STEREOSELECTIVE SYNTHESIS OF BRASSINOLIDE AND ITS ANALOGUES: DEVELOPMENT OF NEW METHODOLOGY

A THESIS

SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

BHARAT B. BAHULE

DIVISION OF ORGANIC CHEMISTRY(SYNTHESIS)

NATIONAL CHEMICAL LABORATORY

PUNE - 411 008.

DEDICATED TO MY PARENTS

CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Stereoselective Synthesis of Brassinolide and its Analogues: Development of New Methodology**" submitted by Bharat B. Bahule, was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Date July 6, 1994

National Chemical Laboratory

Pune 411 008

B. P. Hazra

Dr. B. G. Hazra

(Research Guide)

Acknowledgements

I take this opportunity to express a deep sense of gratitude to my Research Guide, Dr. B.G. Hazra. His excellent guidance and encouragement helped me immensely throughout my work.

My sincere thanks are due to Dr. P.L. Joshi, Dr. N.P. Argade, Dr.(Mrs.) V.S. Pore, Dr. M.D. Chordia for their valuable suggestions and help during this work.

I would like to thank Dr. K.N. Ganesh, Head, Organic(Synthesis) Division, for his keen interest in this work and constant encouragement. My special thanks are due to my colleagues, Pavan, Sourav, G. Kumaran, Malay Nandi, L.N. Patkar, K.M. Sathe, Trusar Bagul, Soumen Hazra, Anjan Ghatak, Sanjeev, G. Ravi, Dr. T. Indrasena Reddy, for their cheerful cooperation. Thanks are due to Mr. P.S. Khandekar for his help in day-to-day lab. maintenance. I thank Dr. A.A. Natu, Dr. A. Sarkar, Dr. T. Pathak, Dr. B.M. Bhawal, Dr. A.R.A.S. Deshmukh, Dr. S.V. Pansare, Dr. N.N. Joshi, Dr. (Mrs.) S.P. Maybhate, Dr. A.A. Arbale and all our Divisional members for their constant cooperation and useful suggestions.

Help from Spectroscopic, Microanalytical groups is gratefully acknowledged. In particular, I thank Mr. A.G. Samuel, Mr. V.T. Sathe, Mrs. Usha Phalgune, for their help in recording PMR spectra.

I am indebted to Dr. S. Rajappa, Prof. R.S. Mali, Prof. M.S. Wadia, Dr.(Mrs.) R.S. Kusurkar and Dr. D.D. Dhawale for their constant encouragement.

I am thankful to my dear friends, Arun Dixit, Abhay Chheda, Milind Bhagwat, Dinesh Barawkar, M.Jayaraman and P. Chittari for their cheerful company. I thank my friends, Mr. P.V. Iyer and Mr. T.A.B. Mulla for their typographical help in preparation of this thesis.

I feel very happy to thank my parents, wife and brothers for their love and faith in education.

I thank the CSIR, New Delhi, for financial support.

Finally, I am thankful to Dr. R.A. Mashelkar, Director, National Chemical Laboratory, Pune, for providing me the necessary infrastructure and permitting me to submit this work in the form of a thesis.

Bahule

Bharat B. Bahule

CONTENTS

Chapter 4 **Stereoselective trans-Dichlorination, Dibromination of Alkenes with Tetradecyltrimethylammonium Permanganate- Trimethylchlorosilane, Trimethylbromosilane**

General Remarks

1. All melting points and boiling points are uncorrected.
2. All extracts were finally dried over anhydrous sodium sulphate.
3. All reactions were followed by t.l.c. On glass plate coated with silica gel slurry.
4. IR spectra were recorded on a Perkin-Elmer Spectrophotometer model 599B using NaCl optics. ν_{max} values are given in cm^{-1}.
5. NMR spectra were recorded on Bruker WH-90 or FT-80A or ACF-200 Spectrophotometer using TMS as internal standard. Chemical shifts are given in δ ppm.
6. Mass spectra were taken on Finnigan Mat 1020C Mass Spectrometer at 70 eV.
7. All optical rotations were measured on JASCO-181-digital polarimeter using sodium light (4893 A) source. Concentrations are expressed in g/100 ml of the solution.
8. In the description of NMR signals, the abbreviations s, d, t, q, m, bs, dd, bd mean singlet, doublet, triplet, quarter, multiplet, broad singlet, doublet of a doublet, broad doublet respectively.
9. Pet.ether refers to the fraction boiling between 60-80°C.
10. The number assigned to the compounds, charts and figures in each Chapter of this thesis refer only to that particular chapter.

CHAPTER-I

Stereoselective synthesis of (22R,23R,24S)-3β-hydroxy-5-ene -22,23-dihydroxy-24-methyl-cholestane: A brassinolide intermediate from 16-dehydropregnenolone acetate.

Summary

Chapter I consists of two sections.

Section A

Synthesis of (20S)-3α,5-cyclo-6β-methoxy-5α-pregnane-20-carboxyaldehyde 53.

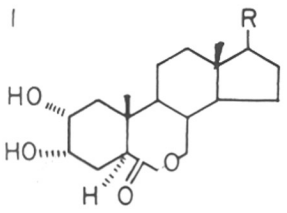
A new synthesis of the important aldehyde[1-7] **53** from easily available 16-dehydropregnenolone acetate **117** in high yield is described. The important feature of this synthesis is stereospecific generation of acetate **126** through ene reaction using three different catalysts. The ene reaction carried out using titaniumtriisopropoxy chloride, trimethylsilyl chloride and *tert*-butyldimethylsilyl chloride generates the natural configuration at C-20. This aldehyde **53** is an important intermediate for the synthesis of a large number of biologically active compounds including brassinolide and its analogues.[1-7] The conversion of 16-dehydropregnenolone acetate **117** to the aldehyde **53** in eleven steps is achieved in 36% overall yield.

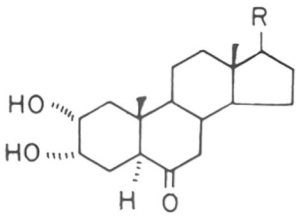
Section B

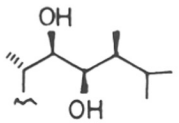
Synthesis of (22R,23R,24S)-3β-hydroxy-5-ene-22,23-dihydroxy-24-methyl-cholestane 116

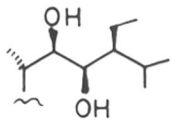
The condensation of aldehyde **53** with 2-lithio-1,3-dithiane gave stereoselectively (22R) alcohol **130** with a small amount of (22S) alcohol in 89% yield [(22R)-:(22S)- = 88:12]. The (22R)-hydroxy group of **130** was acetylated using acetic anhydride and pyridine to get the acetate **131** in 93% yield. The overall yield in these two steps is 83%. The dithiane moiety of compound **131** was deprotected with NBS/$BaCO_3$ in aqueous acetone to furnish compound **132** in 96% yield. The regioselective Wittig reaction on the acetoxy aldehyde **132** with triphenylphosphoniumisobutyl bromide, n-BuLi in tetrahydrofuran yielded **133** in 77% yield [(Z)-:(E)- = 86:14]. The pure (Z)-olefin was obtained after column chromatographic purification on silica gel. The pure (Z)-olefin **133** was epoxidised with *m*-chloroperbenzoic acid, Na_2HPO_4 in methylene chloride to obtain **134** in 95% yield. The 3,5 cyclic ring was opened with *p*-toluenesulfonic acid in aqueous dioxane to afford **135** in almost quantitative yield. The epoxide ring in **135** was opened using trimethylaluminium, n-BuLi in hexane-cyclohexane to obtain **116** in 91% yield. Further elaboration of **116** to the brassinolide **1** is already well established.[3,8] Thus, the above work constitutes a formal total synthesis of brassinolide.

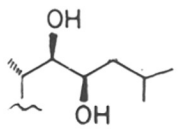
Chart I

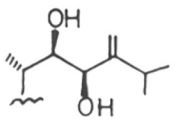


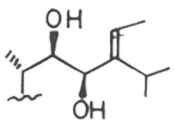


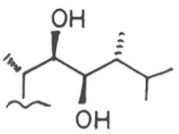
Brassinolide, R =  1

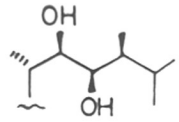
Homobrassinolide, R =  2

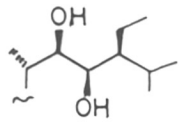
28-Norbrassinolide, R =  3

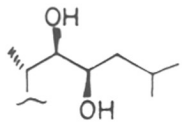
Dolicholide R =  4

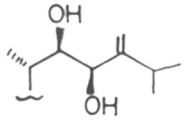
Homodolicholide R =  5

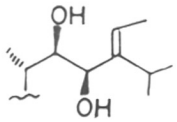
Epibrassirobide R =  6

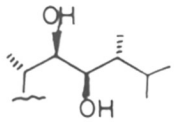
Castasterone R =  7

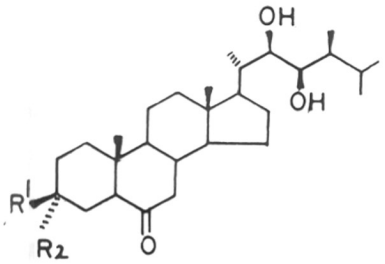
Ethylbrassinone R =  8

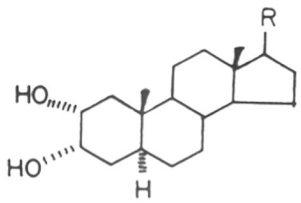
Brassinone R =  9

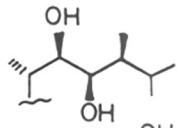
Dolichosterone R =  10

Homodolichosterone R =  11

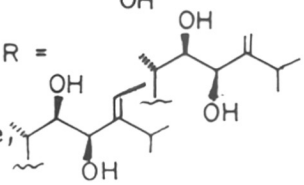
24-Epicastasterone R =  12





2-Deoxycastasterone, R_1 = H ; 6-Deoxycastasterone, R =  15

(Typhasterol) 13 R_2 = OH ; 6-Deoxyclolichosterone, R = 16

Teasterone 14 R_1 = OH ; 6-Deoxyhomodolichosterone, R =  17

R_2 = H

Introduction

Brassinosteroids are a new class of plant growth regulators. In 1979, United States Department of Agriculture Scientists isolated[9] 4 mg. of brassinolide **1**, from 40 kg. of bee collected pollen of the rape plant (*Brassica Napus L.*). It showed a powerful growth accelerating effect when applied to young pinto bean plants. The increase in growth was both due to cell elongation and cell division. Its structure was elucidated as (2R,3S,22R,23R,24S)-2,3,22,23-tetrahydroxy-24-methyl-B-homo-7-oxa-5α-cholestan-6-one by spe- ctroscopic and X-ray crystallography data. It is the first naturally occuring steroid with an unprecedented seven membered B-ring lactone and two vicinal diol functions at ring A and in the side chain. The discovery of brassinolide is the most important discovery of the plant physiologists and biochemists, since the discovery of gibberellic acid.

Because of scarcity, interesting novel structural features and dramatic ability to accelerate the plant growth, much efforts have been devoted in recent years to search for further natural brassinosteroids, to the synthesis of brassinosteroids and to their biological activity and physiological function.

Structure and Occurrence

The first real confirmation of the role of steroids as hormones in higher plants was obtained in 1979 when American scientists established the structure of brassinolide **1**, a powerful growth stimulant, isolated from rape pollen. Subsequently, several brassinosteroids[1,10] were isolated from various sources and identified, and heralded a new group of phytohormones. The number of known naturally occuring brassinosteroids today is close to 30, some of them are given below (**Chart 1**).

Since the discovery of brassinolide **1**, further native brassinosteroids have been found in species of different plant families. Structurally, they exhibit either the 7-membered 7-oxalactone B-ring but differing in the C-24 substitution of the side chain moiety compounds **1-6** or they are the corresponding 6-oxo steroids with a normal 6-membered B-ring compound **7-12**. 6-Deoxycastasterone **15** and 6-deoxydolichosterone **16** lack the B-ring oxygen function. All these brassinosteroids are 2α,3α,22R,23R-tetrols with the exception of 2-deoxycastasterone (typhasterol) **13** and teasterone **14** which show only one 3α- and 3β-hydroxy group in ring A, respectively.

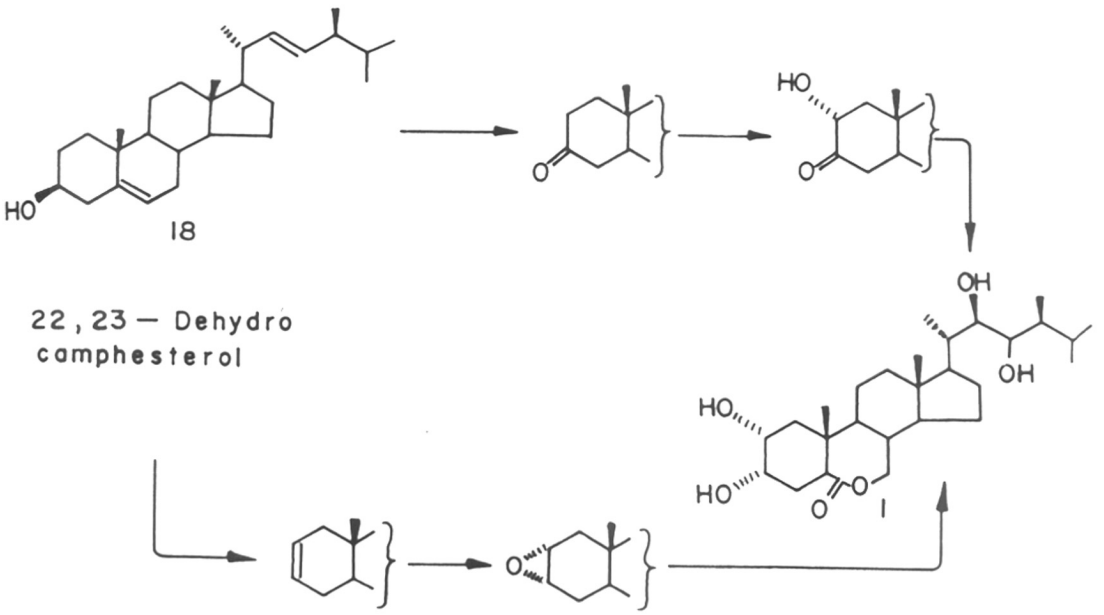
Brassinolide **1** was isolated from pollen of *Brassica napus*. Castasterone **7** is the predominant compound in *Thea sinensis* or *Pharbitis purpurea*, while dolicholide **4** predominates in *Dolichos lablab*. In insect galls of *Distylium racemosum*, the amounts of castasterone **7** and brassinone **9** were found to be higher than in the leaves of the same plant. Insect galls of chestnut tree contain castasterone **7** and 6-deoxycastasterone **15**. All these brassinosteroids are isolated in minute quantities from plant sources. The detected amounts vary from 0.1 ng/kg (ethylbrassinone, **8**, from fruit of *Brassica Campestris* var. *Pekinensis* upto 100 μg/kg (brassinolide, **1**, from pollen of *Brassica napus*. Castasterone **7** is the predominant compound in *Thea Sinensis* and 7.2 μg/kg is the detected amount from the leaves of the plant. Dolicholide **5**, is isolated from the seeds of *Dolichos lablab* in 5 μg/kg amount. Brassinone, **9**, is isolated from the seeds of *Pharbitis purpurea* in 0.2 μg/kg amount. Typhasterol, **13**, is found in pollens of *Pinus thubergii* in 90 μg/kg isolated amount. 6-Deoxycasterone, **15**, isolated from flower buds of *Castanea crenata* in 15-30 μg/kg amount. Teasterone, **14**, is isolated from the leaves of *Thea sinensis* in 0.05 μg/kg amount.

The following structural features are important for a compound to show its brassinosteroidal activity. A trans A/B ring system (5α-hydrogen), a 6-ketone or a 7-oxa-6-ketone system in ring B, *cis* α-oriented hydroxyl groups at C-2 and C-3, *cis* hydroxy groups at C-22 and C-23 as well as methyl or ethyl substituent at C-24.

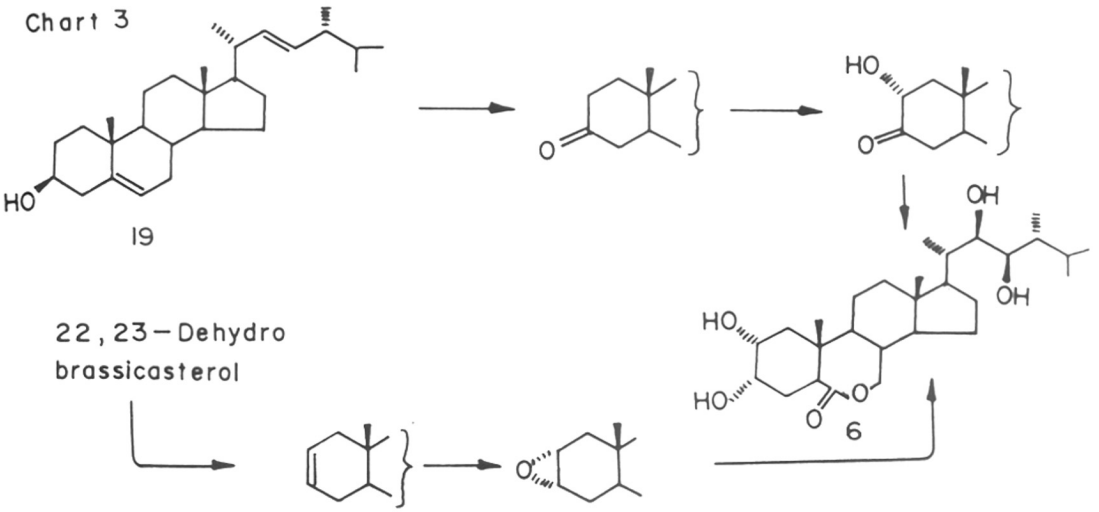
Biosynthesis

No results concerning the biosynthesis of brassinosteroids have been published to date.[11] The structure-activity relationship in brassinolide and its biosynthetic intermediates is an interesting problem still remained to be investigated. One of the most important points in brassinolide biosynthesis is the conversion of 3β-hydroxy group to 2α,3α-dihydroxy group. Possible biosynthetic pathways of the 2α,3α-dihydroxy moiety of brassinolide is given in (**Chart 2**).

Chart 2



The probable biosynthesis starts with the oxidation of 3β-OH group to 3-keto group, followed by hydroxylation at C-2 carbon and reduction of C-3 carbonyl to C-3 hydroxy function. Another biosynthetic pathway deals with dehydration of 3β-OH group to yield Δ^2 ene system, which on oxidation followed by epoxide ring opening gave some intermediate from which the brassinolide **1** is biosynthesised. In a similar manner, the 24-epibrassinolide, **6** probably biosynthesised from 22,23-dehydrobrassicasterol, (**Chart 3**).



The 6-oxotype brassinosteroids are assumed to be biosynthetic precursors of the corresponding 7-oxalactone compounds, especially castasterone, **7**, for brassinolide, **1** and brassinone, **9** for 28-nor-brassinolide, **3**. The 6-deoxo brassinosteroids **15** and **16** have been considered as putative precursors for their respective 6-oxo analogues **7** and **10** respectively, and the 3β-hydroxy compound teasterone, **14** was assumed to be the biosynthetic intermediate to typhasterol, **13** and further to castasterone, **7** and brassinolide, **1** on the basis of their common occurrence in different plant species.

Synthesis of brassinosteroids

In view of extremely low brassinosteroids content in plants C10^{-5} to 10^{-12}%) and the short period in which they have been investigated, it must be assumed that the inventory of natural products of this type is far from complete.[12] Method of isolation from natural raw material cannot be considered as a practical route for brassinosteroids. This explains the wide range of investigations on brassinosteroids synthesis begun in various countries directly after establishment of brassinolide structure. Total synthesis is obviously only the theoretical interest since it requires the formation of the exceptionally complex stereochemistry of these considered compounds which contain 11-13 chiral

centres in the molecule. Even a partial synthesis is an extremely complex task, particularly when forming the polyfunctional side chain. For the chemical synthesis of brassinosteroids starting from a suitable steroidal precursor, the typical A/B ring functionalisation and the construction of the side chain moiety including the asymmetric centres at C-22, C-23 and C-24 are necessary. The later problem has been solved by two different strategies. Either a C-22 aldehyde was used for the possible stereoselective side chain construction or the desired 22,23-diol function was introduced into a precursor with an intact sterol side chain. Thus, any scheme for the synthesis of brassinosteroids may be divided into two parts. (**A**) formation of structural elements of the tetracyclic nucleus characteristic of brassinosteroids and (**B**) construction of the side chain of the molecule.

(A) **Formation of structural elements of the tetracyclic nucleus - A/B ring functionalisation**

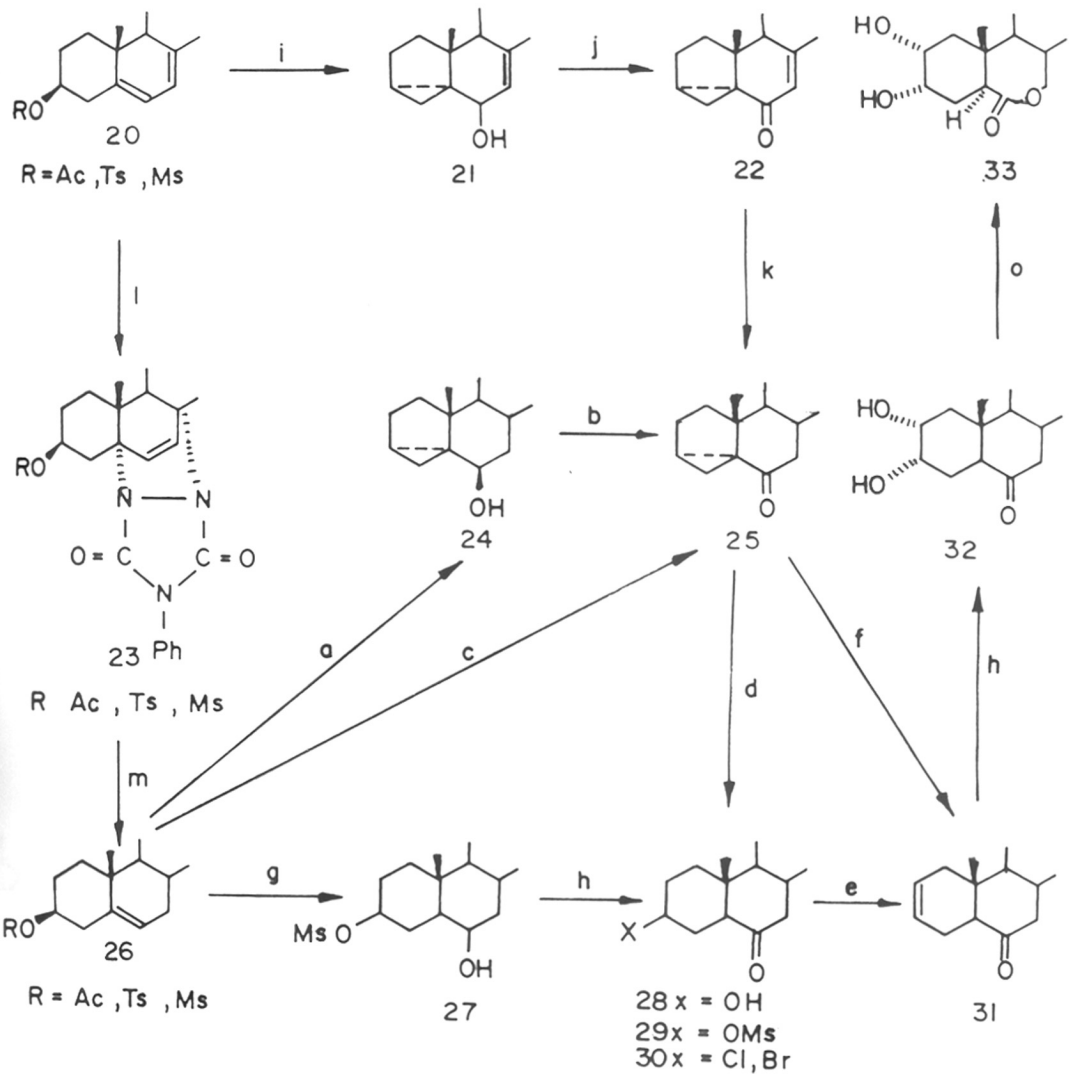
Pathway of A/B ring functionalisation

In nearly all syntheses, a Δ^5-3β-hydroxy starting steroid **26** is transformed into a Δ^2-6-oxo compound **31** representing a suitable intermediate for the synthesis of both 6-oxo and 7-oxolactone type brassinosteroids. This transformation has been achieved via cyclosteroid formation or hydroboration as key reactions (**Scheme 1**). In the first case, a mesylate or tosylate of **26** was solvolysed[13] to the corresponding 3,5-cyclosteroid **24** which gave upon oxidation, e.g. with the CrO_3-pyridine complex or PCC, a 3,5-cyclo-6-oxo-compound **25**. Upon reaction with DMSO-NaOAc the mesylate of **26** could be transformed also directly to **25** in 32% yield. The conversion of **25** to **31** was realised via reaction to the hydroxyketone **28** followed by treatment of a corresponding mesylate **29** or tosylate with Li_2CO_3 or LiBr. A modified sequence to **31** leads via hydrogen halogenide catalysed rearrangement of **25** to **30** and subsequent elimination. Compound **31** was also directly obtained from **25** upon reaction with *p*-TsOH-sulpholane or refluxing **25** in DMF with pyridinium *p*-toluenesulfonate and LiBr in excellent yield.

The second pathway to **31** involves hydroboration of a **26**-mesylate followed by oxidation of the obtained 6β-hydroxy compound **27** with Jones reagent or PCC to **29** and subsequent elimination as described in the case of **29**. With an overall yield of 63% this sequence represents the most superior way to the key intermediate **31**. Also, ergosteryl acetate **20** has been used as starting material for **31** via **25**. Thus, compound **20** was transformed to the corresponding 3,5-cyclosteroid **21** and further oxidised to the Δ^7-6-oxo derivative **22**. Subsequent reduction with Li-liquid NH_3 gave **25**.

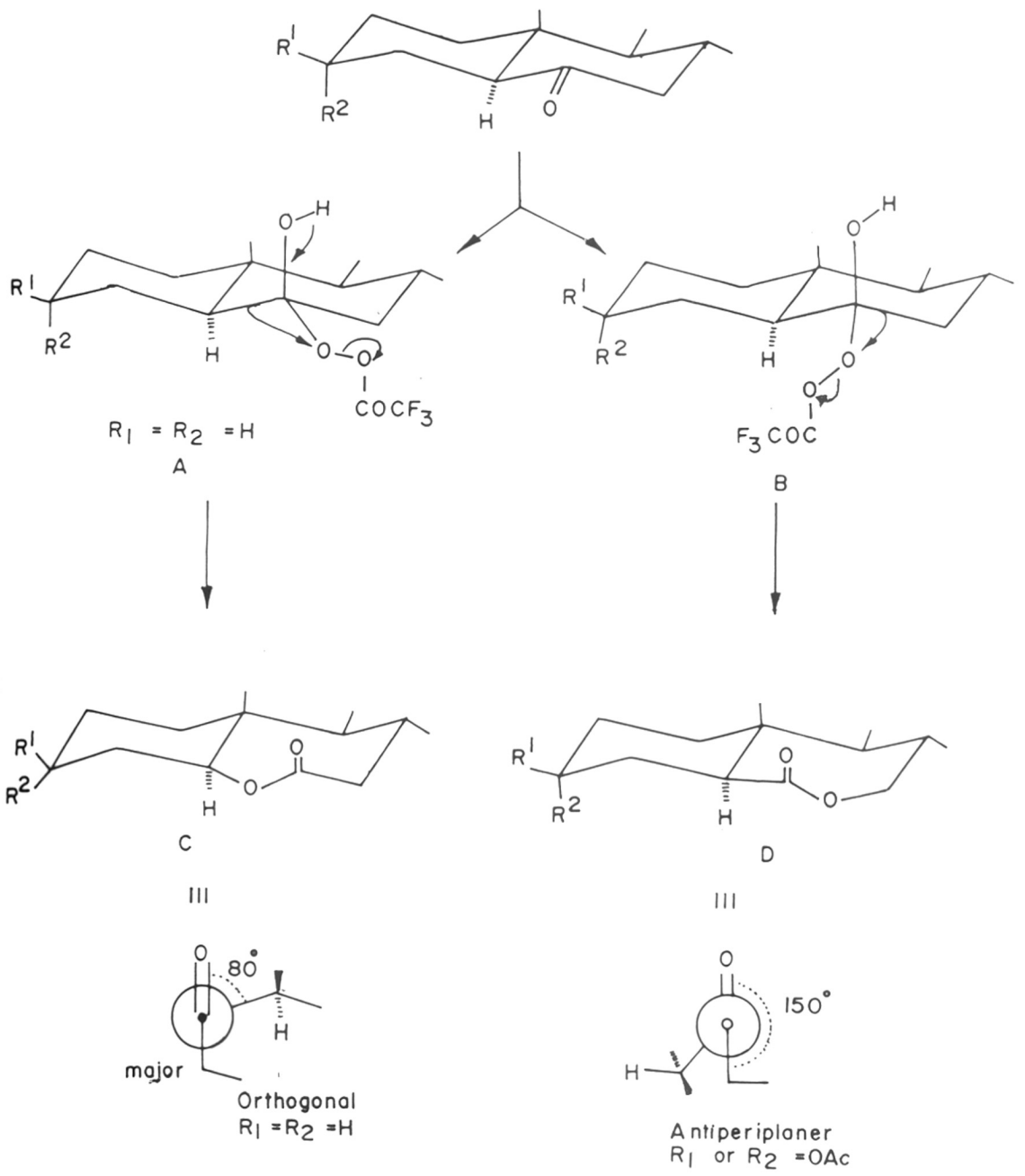
SCHEME I

PATHWAY OF A/B RING FUNCTIONALISATION



a. $KHCO_3/Me_2CO/H_2O$; **b.** Jones reagent; **c.** DMSO/NaOAC; **d.** $ACOH/H_2SO_4/K_2CO_3$, HCl/ACOH, HBr/ACOH; **e.** $LiCO_3/LiBr$; **f.** *p*-TsOH/Sulfolane; **g.** BH_3.THF; **h.** Jones reagent/PCC; **i.** $KHCO_3/Me_2CO/H_2O$; **j.** CrO_3/Py.; **k.** Li/NH_3; **l.** 4-phenyl-1,2,4-triazolin-3,5-dione; **m.** $Li/EtNH_2$; **n.** OSO_4/NMO; **o.** CF_3CO_3H, MCPBA.

Chart 4


R1
R2
H
O
O–H
O–O
COCF3
R1 = R2 = H
A
F3COC
B
C
III
D
III
80°
major
Orthogonal
R1 = R2 = H
150°
Antiperiplaner
R1 or R2 = OAc

On the other hand, reduction of the ergosterol 1,4-cyclo adduct led to the corresponding 3β-hydroxy-Δ^5-compound **26**. Reaction of Δ^2-6-ketones **31** with OsO_4 or OsO_4-NMMNO results in stereospecific hydroxylation to the 2α,3α-dihydroxy-6-oxo compounds **32** thus yielding the typical A/B structural feature of the native brassinosteroids. Subsequent Baeyer-Villiger oxidation of **32** or preferably oxidation of the corresponding 2,3-diacetate and saponification, gives upto 90% of the desired 7-oxalactones **33** with the final A/B-structural features of the lactone-type brassinosteroids. Thus, in the synthesis of 7-oxa-lactones the corresponding 6-oxo type members often occur as intermediates. Huang-Minlon reduction of the 6-oxo precursors **32** with the appropriate side chain led smoothly to 6-deoxocastasterone **15** and 6-deoxodolichosterone **16**, respectively. The commonly used methods for A/B ring functionalisation in the synthesis of brassinosteroid is summarised in (**Scheme 1**).

Baeyer-Villiger oxidation

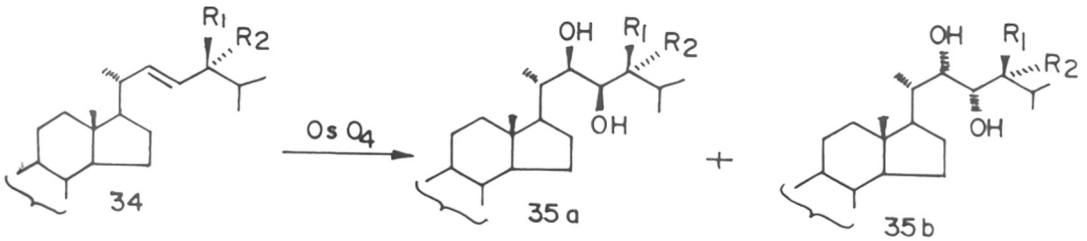
It is well known that in the Baeyer-Villiger oxidation, the migratory aptitude of the alkyl group with retention of configuration falls into the order of reactivity: Bu^t > iso-pro > Et > Me, as expected from their ability to stabilize an electron-deficient transition state.

It was reported[15] that in the case of 5α-cholestan-6-one, this migratory aptitude held to be true, the 6-oxalactone was obtained as a major product on the oxidation. On the other hand, introduction of acetoxyl, hydroxyl, tosyl or halogen at 3β or 3α position affected the regioselectivity[14,15,16] of the Baeyer-Villiger oxidation, and the 7-oxalactones were obtained as major products. The effect of electron-withdrawing substituents at C-1, C-2 or C-3 position on the regioselectivity must come from the conformational factor in the transition state as well as the inductive effect of the substituents and long range effect in a steroid ring system.[16] Ring B with the carbonyl group up, the projected angle between the C(5)-O and C=O bonds in the 6,7-seco lactone is about 150°C, whereas in the 5,6-secolactone, it is about 80°. Therefore, the transition state between the peracid adduct **A** and **C** can form little, if any, stabilization from the developing ester group, whereas migration of C-7 in the intermediate **B** can produce the isomeric lactone **D** directly in a conformation allowing full ester conjugation (**Chart 4**).

(B) **Construction of the side chain**

1) **Synthesis retaining carbon skeleton of the steroid molecule**

SCHEME 2



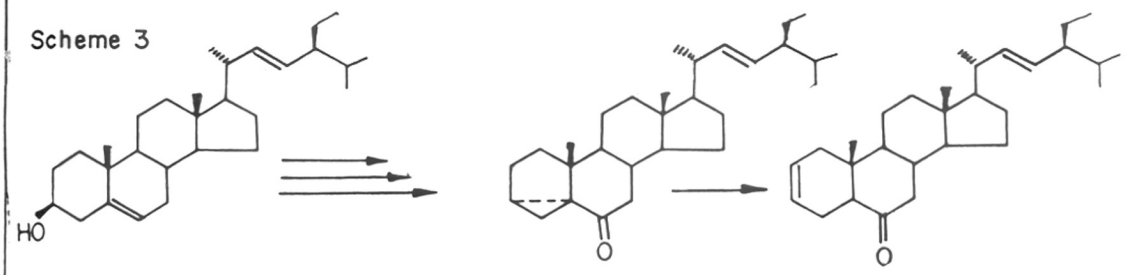
$R_1 = CH_3$, C_2H_5 , $R_2 = H$

$R_2 = CH_3$, $R_1 = H$

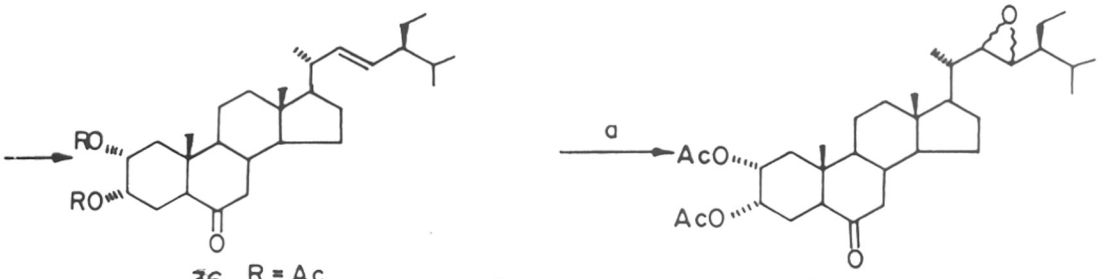
The simplest method of introducing the 22,23-diol in the side chain is hydroxylation of a Δ^{22}-bond with osmium tetroxide. The ratio of both possible diols depends on the size and configuration of the substituent R at C-24. The ratio of isomers, proves to be unfavourable for the synthesis of natural brassinosteroids. This method is used widely in the synthesis of the (22S,23S) analogues of the natural brassinosteroids (**Scheme 2**).

Other stereochemical results were observed in the oxidation of the Δ^{22}-bond with peracids leading to (22R,23R)-epoxide as the main reaction products. The predominant formation of (22R,23R)-epoxides on reaction on Δ^{22}-steroids with peracids enabled a route to be proposed for the synthesis of (22R,23R)-diols which is more efficient than hydroxylation with OsO_4 and is based on a transformation of the epoxide ring.

Scheme 3

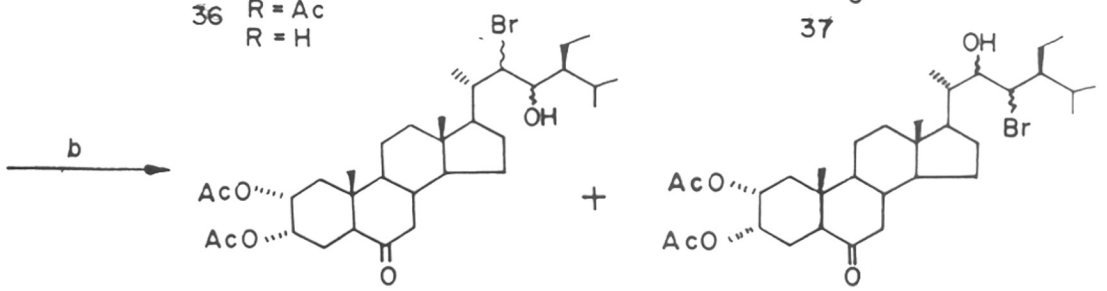


Stigmasterol

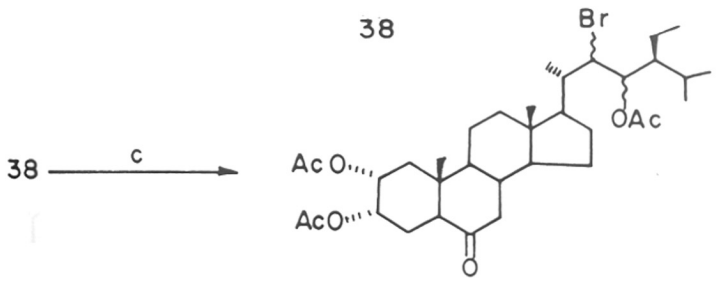


36 R = Ac
R = H

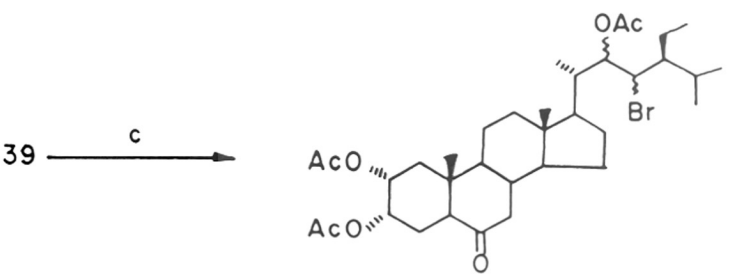
37



38 39

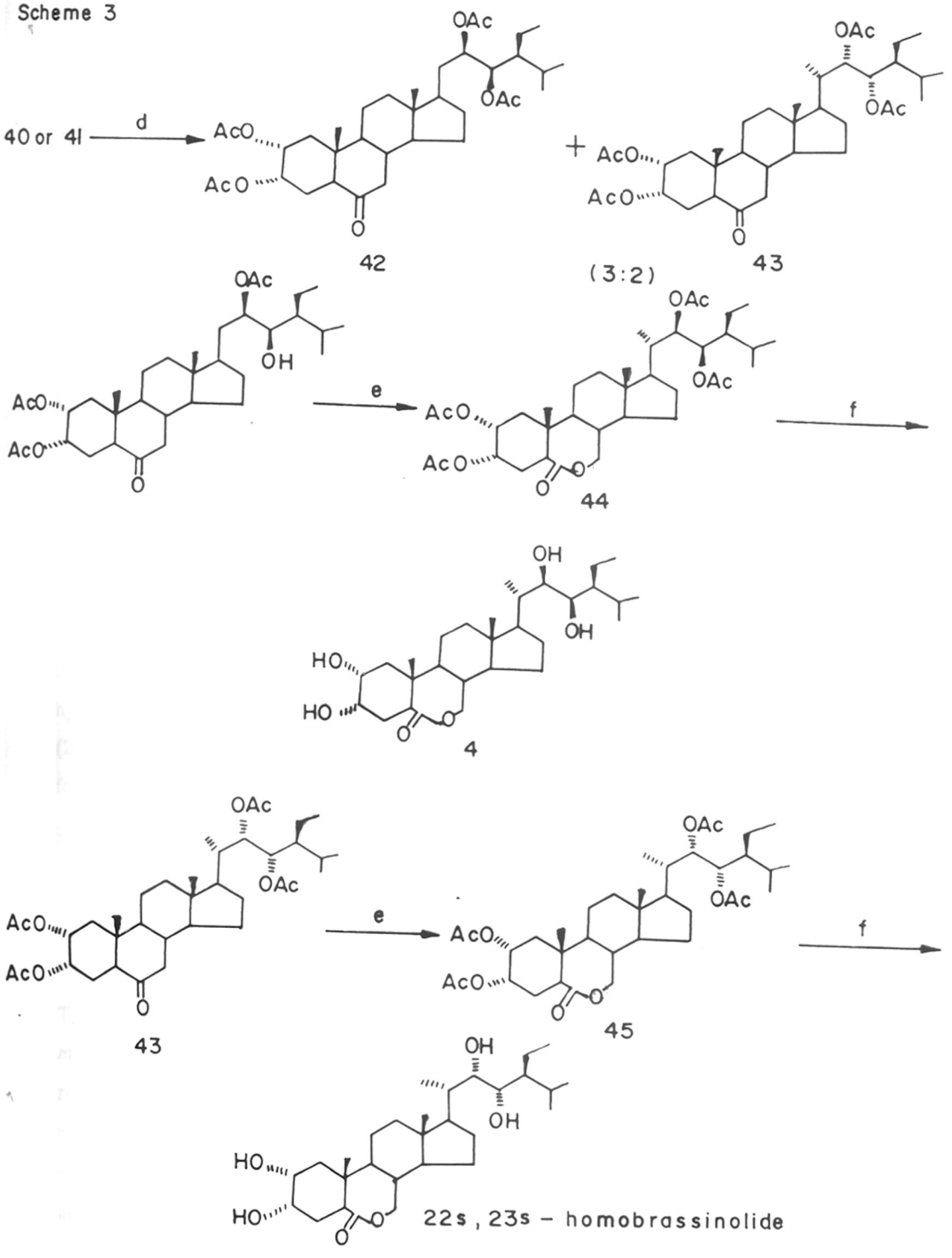


40



41

Scheme 3



a. *m*-CPBA; b. 48% HBr; c. Ac_2O, Py. DMAP; d. 80% aq. AcOH, acetylation; e. CF_3COOH;

f. NaOH, aq. MeOH, dil. HCl

Synthesis of Homobrassinolide

Stigmasterol was converted to (22R,23R)-homobrassinolide utilizing the intact carbon skeleton of stigmasterol side chain by K.Mori.[17] This synthesis provides a practical route for (22R,23R)-homobrassinolide. The reaction sequence for the synthesis of (22R,23R)-homobrassinolide and (22S,23S)-homobrassinolide is given below (**Scheme 3**).

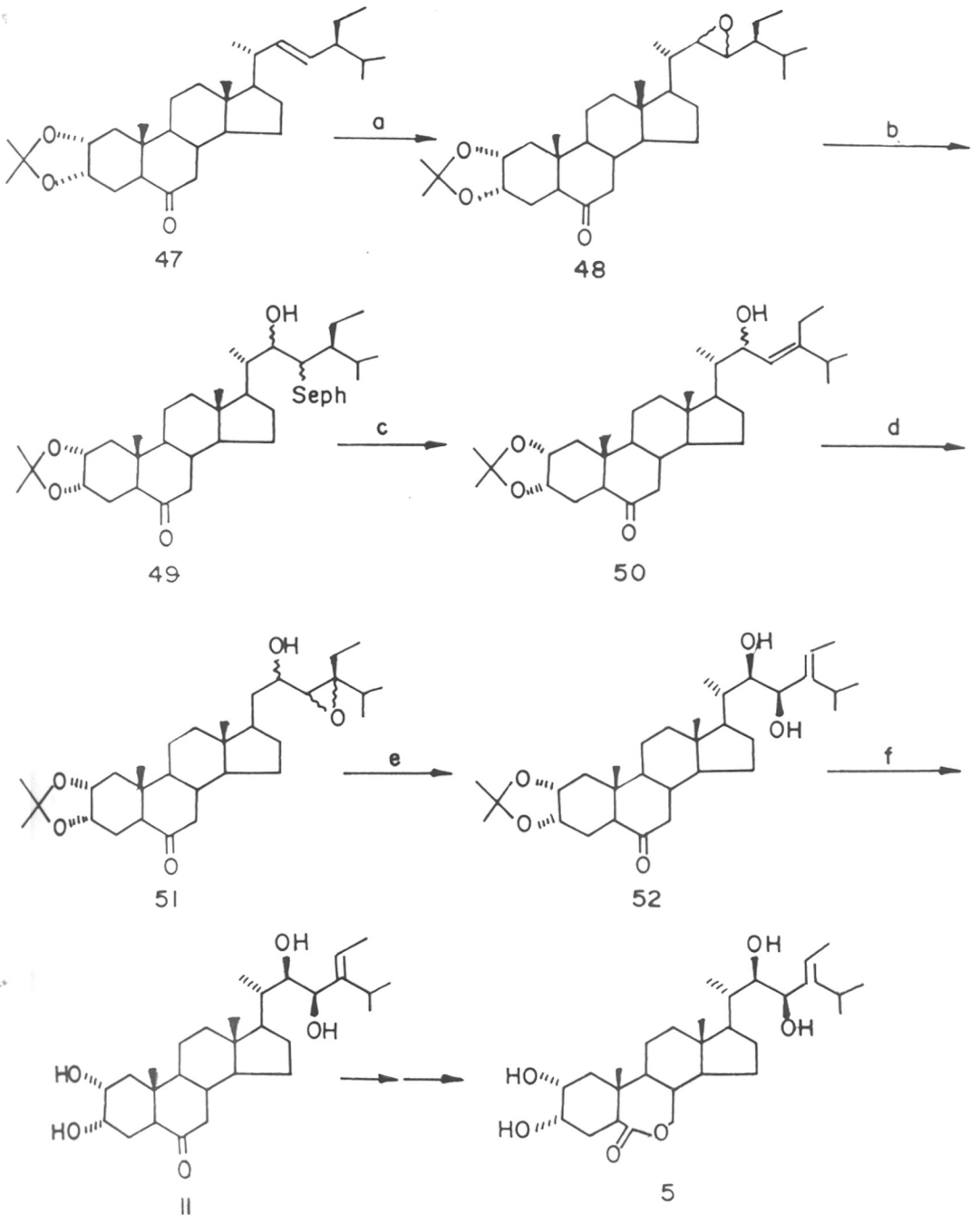
Epoxidation of **36** with m-chloroperbenzoic acid gave an inseparable diastereomeric mixture of epoxides **37** in 94% yield. The mixture was treated with 48% hydrobromic acid resulting regioisomeric mixture of bromohydrins **38** (77% yield), **39** (22% yield). The compound **38** was acetylated with acetic anhydride in pyridine, containing a catalytic amount of 4-dimethylamino-pyridine to give a triacetoxyketone **40** in 91% yield. Hydrolysis of **40** with 80% aqueous acetic acid at 90°C followed by acetylation, gave a mixture of (22R,23R)- and (22S,23S)-tetraacetates **42** and **43**. The more polar bromohydrin **41** was also treated as described above to give **42** and **43** in quantitative yield. Baeyer-Villiger oxidation of **42** with trifluoroperacetic acid in the presence of disodium hydrogen phosphate in methylene chloride followed by column chromatographic purification gave a tetraacetoxy lactone **44** in 79% yield. The tetraacetate **44** was hydrolysed with sodium hydroxide in aqueous methanol and relactonisation with 6N HCl to give (22R,23R)-homobrassinolide **4**. Similarly, compound **43** gave lactone **45** which on hydrolysis followed by relactonisation afforded (22S,23S)-homobrassinolide **46**.

Synthesis of homodolicholide

This synthesis[18] is based upon the epoxide opening with a nucleophile and subsequently its conversion to homodolichosterone utilizing the intact side chain of stigmasterol. The reaction sequence is as follows (**Scheme 4**).

The olefinic ketone **47** was prepared from stigmasterol and it was epoxidised with *m*-chloroperbenzoic acid to give a diastereomeric mixture of epoxides **48** in 86% yield. Epoxide ring opening of **48** with phenylselenyl anion prepared from diphenyl diselenide and sodium borohydride yielded a crude mixture containing **49**. Treatment of this hydroxy phenylselenide **49** with 30% H_2O_2 gave an allylic alcohol **50** and its regioisomers along with small amount of an epoxy alcohol **51** and its regioisomer. The allylic alcohol **50** was epoxidised with *m*-CPBA to give **51**.

Scheme 4



a. *m*-CPBA; b. ph-Se-Se-ph, $NaBH_4$; c. 30% H_2O_2; d. *m*-CPBA; e. Aluminium isopropoxide; f. aq. AcOH

The epoxy alcohol **51** was quite easily rearranged by treatment with aluminium isopropoxide, to furnish an ene diol **52**. Acetonide deprotection of **52** with aqueous acetic acid afforded homodolichosterone **11**. The tetrol can be converted to homodolicholide **5** easily.

2) **Synthesis with the participation of the C-22 centre**

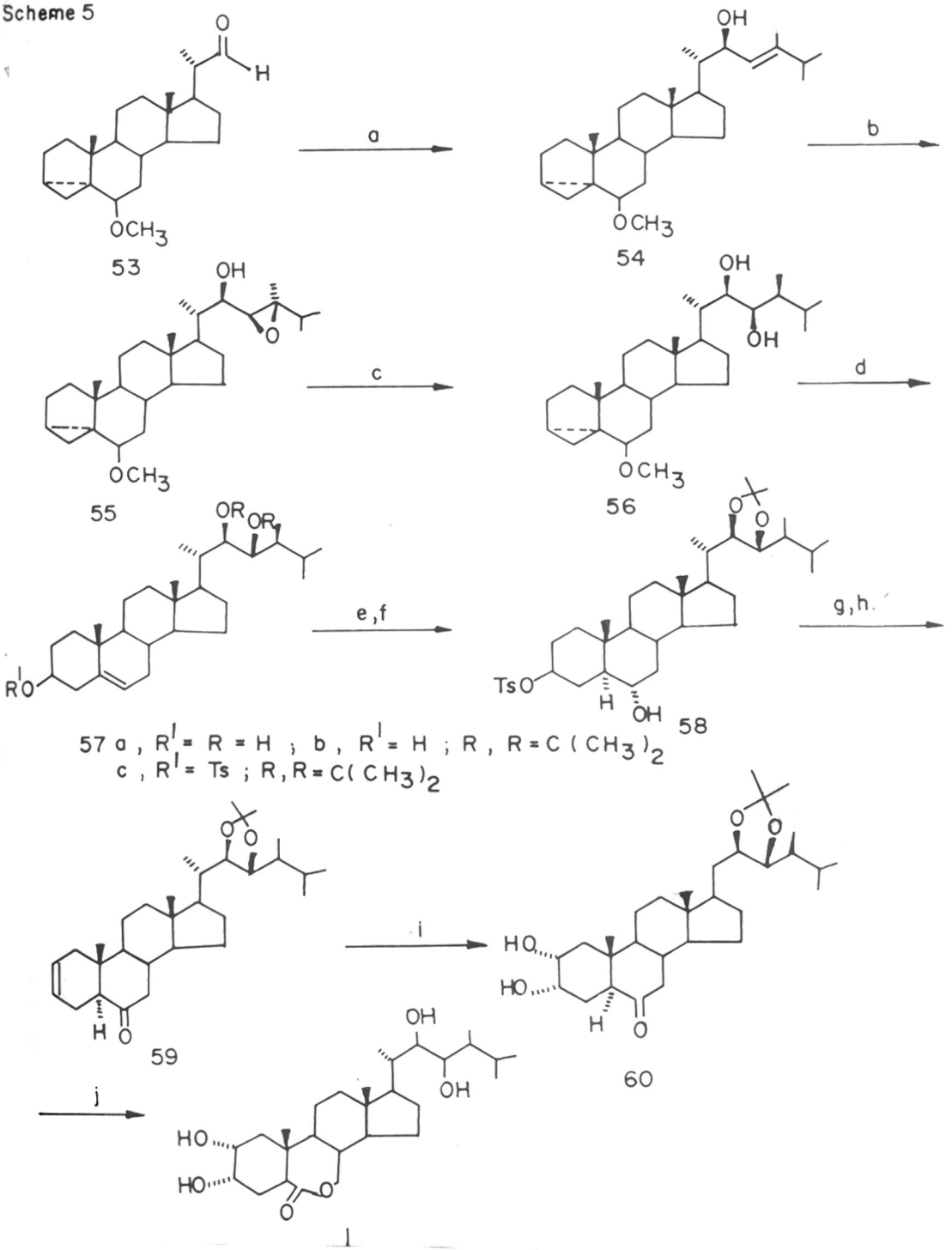
Soon after the structure elucidation of the brassinolide, two groups one at USA by J.B.Siddall[3] and another at Japan by N.Ikekawa[19] have published the first synthesis of brassinolide. J.B.Siddall and co-workers constructed[3] the polyfunctional side chain starting from C-22 aldehyde **53** (**Scheme 5**). They utilized stigmasterols C-20 chiral centre to generate asymmetry first at C-22, which in turn controlled the stereochemistry of C-23 and C-24 during hydroxyl directed epoxidation followed by reduction. Stereoselective alkylation of aldehyde **53** with lithium butyldimethyl (E)-2,3-dimethylbutenylalanate gave the major 22S-allylic alcohol **54**. Hydroxyl directed epoxidation of **54** with *m*-chloroperbenzoic acid furnished epoxide **55**. Completion of the side chain synthesis was carried out by anti-Markovnikov reduction of **55** with inversion at C-24 with $LiBH_4$, BH_3.THF at 50°C, 20h to obtain the vicinal glycol **56**. Proof of the absence of racemisation at C-20 came from $NaIO_4$ cleavage of diol **56** to give aldehyde **53**. The structural elements of the tetracyclic nucleus was then developed from **56** by acid catalysed regeneration of the 3β-hydroxy-5-ene in **57a** protected as the acetonide **57b** to allow tosylation at C-3 to form **57c**. Oxygen was introduced at C-6 by hydroboration-oxidation (BH_3.THF) of **57c** to give **58**, which underwent smooth elimination with Li_2CO_3 in dry dimethylacetamide followed by Jones oxidation to give the 6-ketone **59** after silica gel chromatography. Stereospecific α-face hydroxylation of **59** with osmium tetroxide gave the 2α,3α-diol **60** which was simultaneously deprotected and Baeyer-Villiger oxidised in the final step. Thus, addition of **60** in CH_2Cl_2 to 3 equivalent of ice-cold 0.6M CF_3CO_3H in moist CH_2Cl_2/CF_3CO_2H leads cleanly in 1h. At 22°C to brassinolide **1** in 74% yield.

Stereoselective synthesis of brassinolide from dinorcholenic acid

N.Ikekawa etal[19] has described the total synthesis of brassinolide from the commercially available dinorcholenic acid (**Scheme 6**).

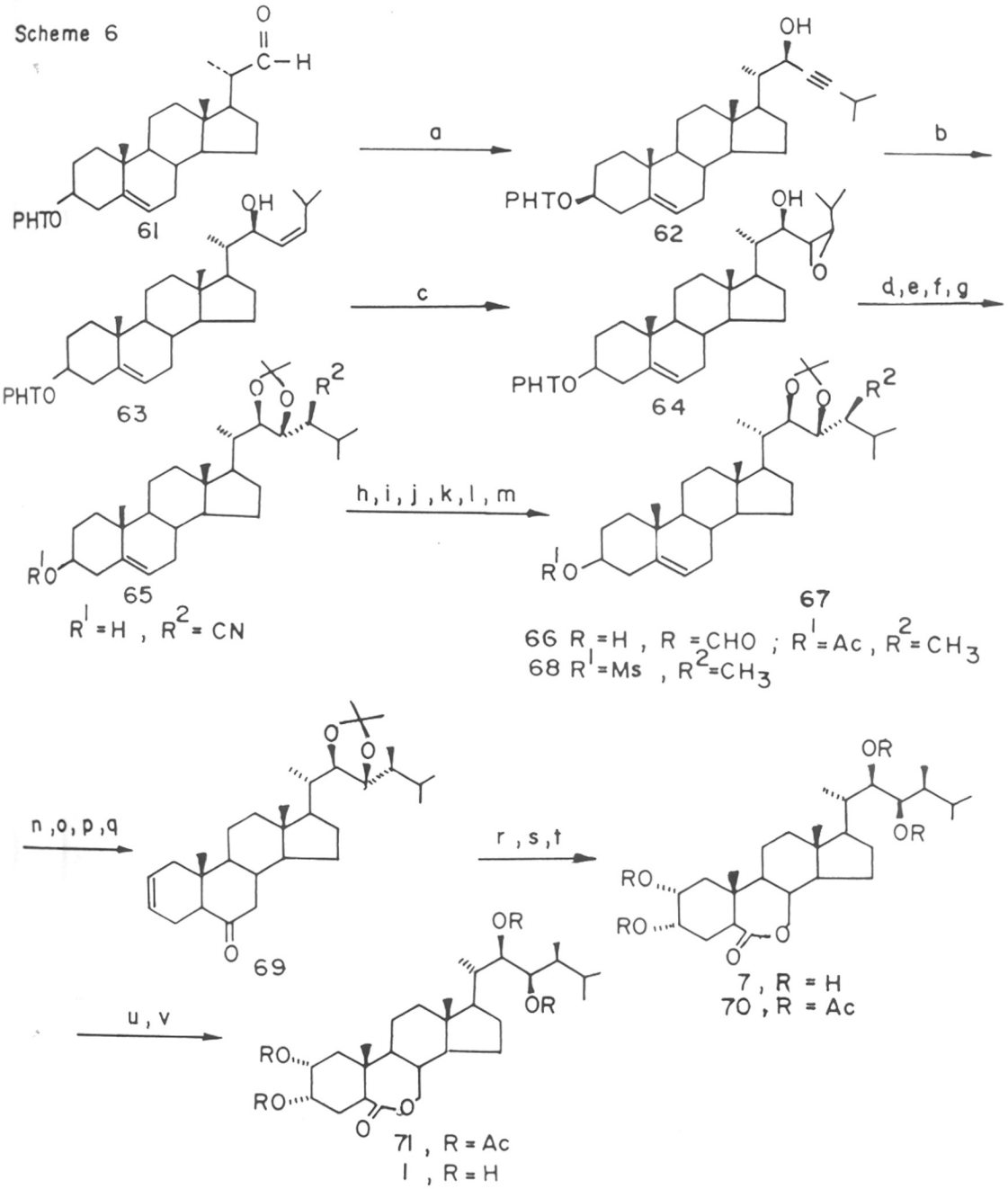
The 22-aldehyde **61** derived from the dinorcholenic acid was treated with 3-methylbut-1-ynyl-lithium in tetrahydrofuran at -78°C to give a 1:1 epimeric mixture of the 22-alcohol, from which the more polar 22R-isomer **62** was isolated in 38% yield. Reduction of **62** with Lindlar

Scheme 5



a. Lithium butyldimethyl (E)-2,3-dimethylbutenylalanate; b. *m*-CPBA; c. $LiBH_4$, BH_3.THF; d. (1) H^+ (2) acetonide formation (3) tosylation; e. BH_3.THF; f. H_2O_2, NaOH; g. Li_2CO_3, dimethylacetamide; h. Jones reagent; i. OsO_4; j. CF_3CO_3H

Scheme 6



a. Li-≡-< ; b. Lindlar catalyst; c. Bu'OOH, oxovanadium acetylacetone; d. Ac_2O, Et_3N; e. HCN-Et_3Al; f. Base; g. Acetone, *p*-TSA, deprotection; h. Dibal-H; i. Ac_2O, Et_3N; j. $NaBH_4$; k. $MeSO_2Cl$, base; l. Iodide substitution; m. Bu_3SnH; n. BH_3.THF; o. Alkaline H_2O_2; p. PCC; q. LiBr, DMF; r. OsO_4, NMO; s. AcOH; t. acetylation; u. CF_3CO_3H, CH_2Cl_2; v. KOH, MeOH, dil. HCl.

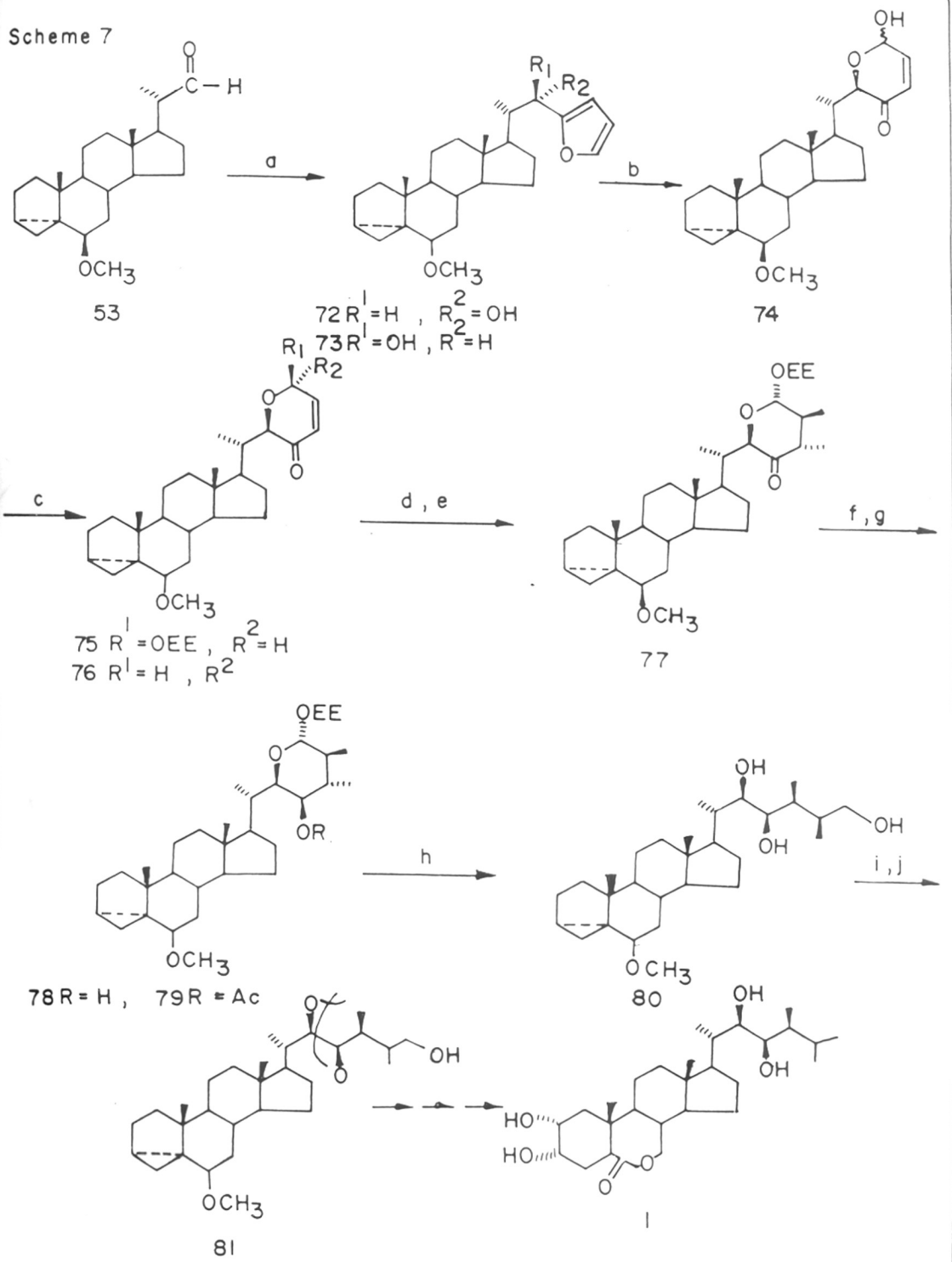
catalyst afforded the *cis*-allylic alcohol **63** in 97% yield. Oxidation of **63** by Sharpless method yield the (23R,24R)-epoxide **64**. The acetate derived from **64** was subjected to hydrocyanation, followed by saponification, acetonide formation, and deprotection to give nitrile **65** in 56% yield. Reduction of **65** with di-isobutyl-aluminium hydride and hydrolysis gave the aldehyde **66** in 65% yield. Transformation of formyl-into the methyl-group was accomplished in a 77% overall yield by the sequence : acetylation, $NaBH_4$ reduction, methanesulphonation, iodide substitution and Bu^n_3SnH reduction, to give acetate **67**. Hydroboration of the methanesulphonate **68** with BH_3-THF in THF and alkaline H_2O_2 oxidation, followed by oxidation with PCC and treatment with LiBr in DMF at reflux, gave the ketone **69** in 65% yield. Treatment of **69** with N-methylmorpholine N-oxide in the presence of a catalytic amount of OsO_4 afforded, after deprotection with 70% acetic acid followed by acetylation, the tetra-acetate **70** in 80% yield. Baeyer-Villiger oxidation of **70** was carried out with an excess of trifluoroperacetic acid in CH_2Cl_2 in the presence of Na_2HPO_4 at 0°C for 3h to give the lactone **71** in 80% yield. Saponification of **71** followed by acidification by dilute HCl produced in 68% yield, brassinolide **1**.

Stereocontrolled synthesis of the brassinolide side chain via a pyranone derivative

T.Kametani et Al.[20] has developed a stereocontrolled synthesis of the brassinolide side chain via a pyranone derivative derived by an addition of 2-lithiofuran to the (20S)-20-carboxyaldehyde, and the oxidation of the adduct with NBS. The pyranone derivative was then converted to the polyfunctional side chain (**Scheme 7**).

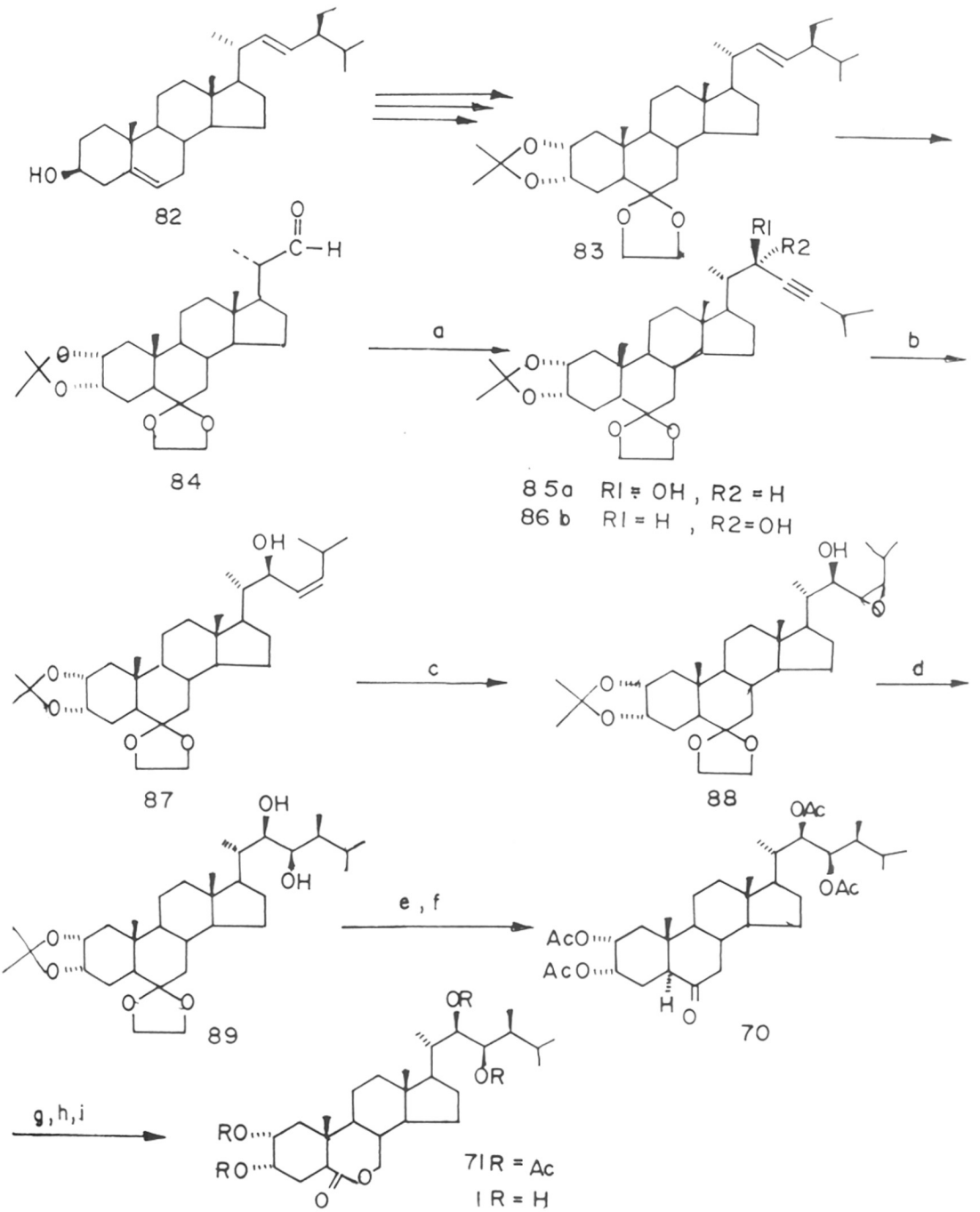
Addition of 2-lithiofuran to the (20S)-20-carboxyaldehyde **53** produced the furylcarbinols **72** and **73** in 96% yield. Conversion of **72** into **73** was achieved employing oxidation of **72** with pyridinium chlorochromate followed by reduction of ketone. Oxidation of the furan **73** with NBS afforded the mixture of lactol **74**. The mixture was converted into α and β-ethoxyethyl ethers **75** and **76** in a ratio of 1:3 in 96% yield. Conjugate addition of lithium-dimethyl cuprate to **76** followed by treatment with lithium diisopropylamide and methyl iodide gave the bis methylated product **77** in 84% yield. Reduction of ketone **77** with $NaBH_4$ followed by treatment with 10% HCl afforded the lactol **78**, which was reduced with $LiAlH_4$ to give the triol **80** in 82% overall yield. Compound **80** was heated with acetic acid to give the acetate, whose treatment with *p*-TsOH in acetone furnished the acetonide **81** in 90% yield. Conversion of **81** into brassinolide **1** was achieved[3] following reported procedure.

Scheme 7



a. 2-lithiofuran; b. NBS; c. ethoxyethylation; d. Lithium dimethyl cuprate; e. LDA, CH_3I; f. $NaBH_4$; g. 10% HCl; h. $LiAlH_4$; i. AcOH, Δ; j. Acetone, *p*-TSA.

Scheme 8



a. Li≡-< ; b. H_2/P_2-Ni, H_2N-$(CH_2)_2$-NH_2; c. *m*-CPBA; d. Me_3Al, n-BuLi; e. AcOH-H_2O; f. Ac_2O, py, DMAP; g. CF_3CO_3H h. KOH, MeOH; i. HCl.

Improved synthesis of brassinolide

K.Mori and co-workers[21] have published an improved synthesis of brassinolide from stigmasterol, which is given in **Scheme 8.**

Addition of Lic≡CPr^{i} to the aldehyde **84** yielded a diastereomeric mixture of two alkenyl alcohols **85** and **86** in 68% yield. These two isomers **85** and **86** were separable by HPLC. The unwanted alcohol **86** could be converted into **85** by the Mitsunobu reaction. Catalytic hydrogenation of **85** over P-2 Ni in the presence of ethylenediamine gave a enol **87** in 84% yield. The enol **87** was epoxidised with *m*-CPBA to give epoxide **88** in 49% yield. The crucial ring-cleavage of the epoxide **88** was effected with 10 eq. Of Me_3Al in the presence of n-BuLi to get diol **89**. The diol **89** was treated with aqueous AcOH to furnish keto-tetrol; which on acetylation with acetic anhydride, pyridine, DMAP yielded tetraacetate ketone **70**. The tetraacetate ketone **70** on Baeyer-Villiger oxidation with CF_3CO_3H furnished tetraacetate lactone, which after hydrolysis and relactonisation afforded brassinolide **1**.

A Concise synthesis of the brassinolide side chain by T.G.Back and co-workers

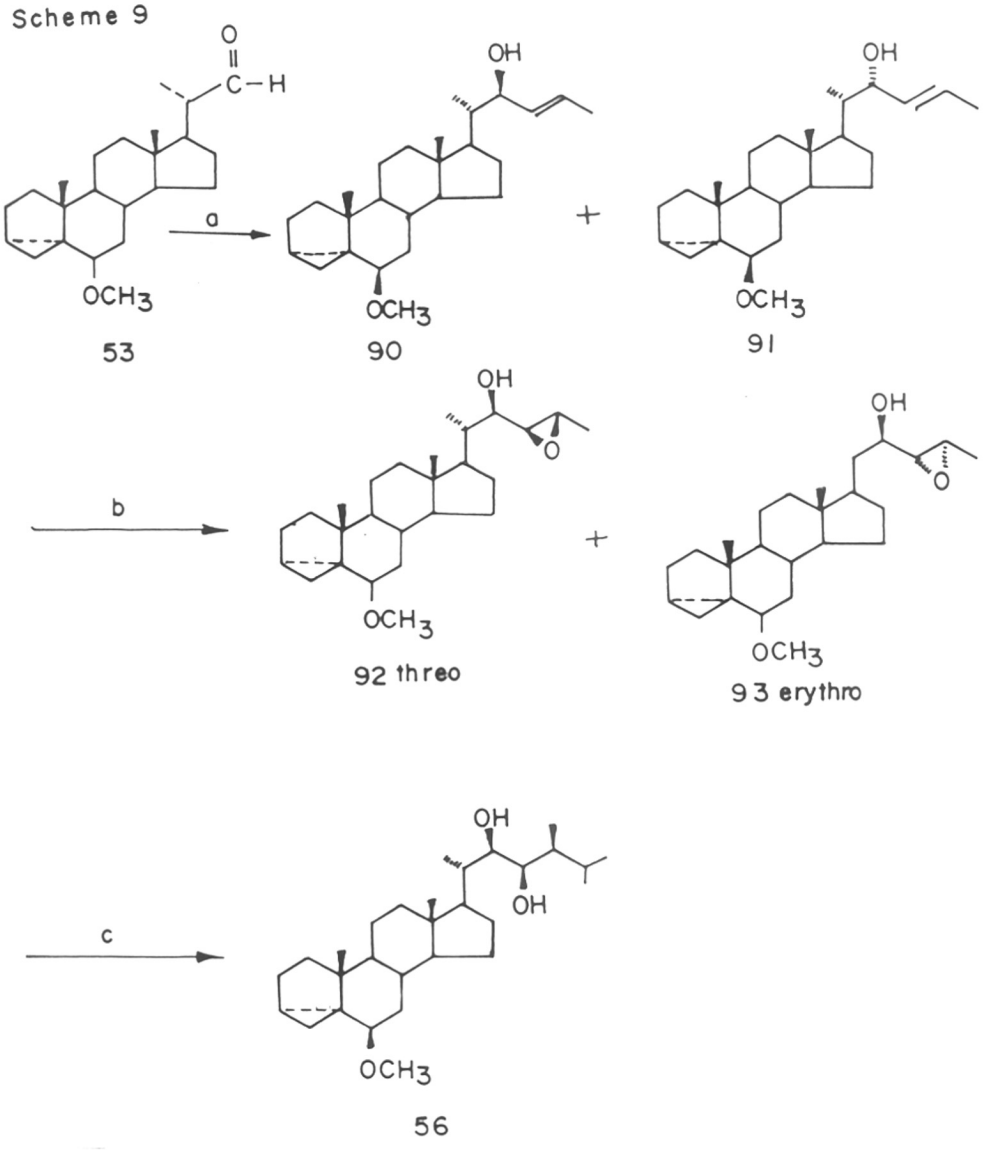
The brassinolide side chain was produced by these authors[2] by the addition of (E)-propenyllithium to the C-22 aldehyde followed by Sharpless epoxidation and epoxide opening with i-$Pr_2CuCNLi_2$ **(Scheme 9).**

Aldehyde **53** was treated with (E)-propenyllithium to afford the alcohols **90** and **91** in 75% yield. These compounds were formed in the ratio 72:28 and were easily separated by flash chromatography on silica gel. The epoxidation of the Cram product **90** by Sharpless epoxidation method afforded the threo:erythro mixture (70:30). The reaction of the unprotected hydroxy epoxide **92** with an excess of the higher order cuprate i-$Pr_2CuCNLi_2$ in ether produced diol **56**. This approach provides short and practical route to the brassinolide side chain.

Study on the synthesis of brassinolide and related compounds by Zhou Wei-Shan et Al.

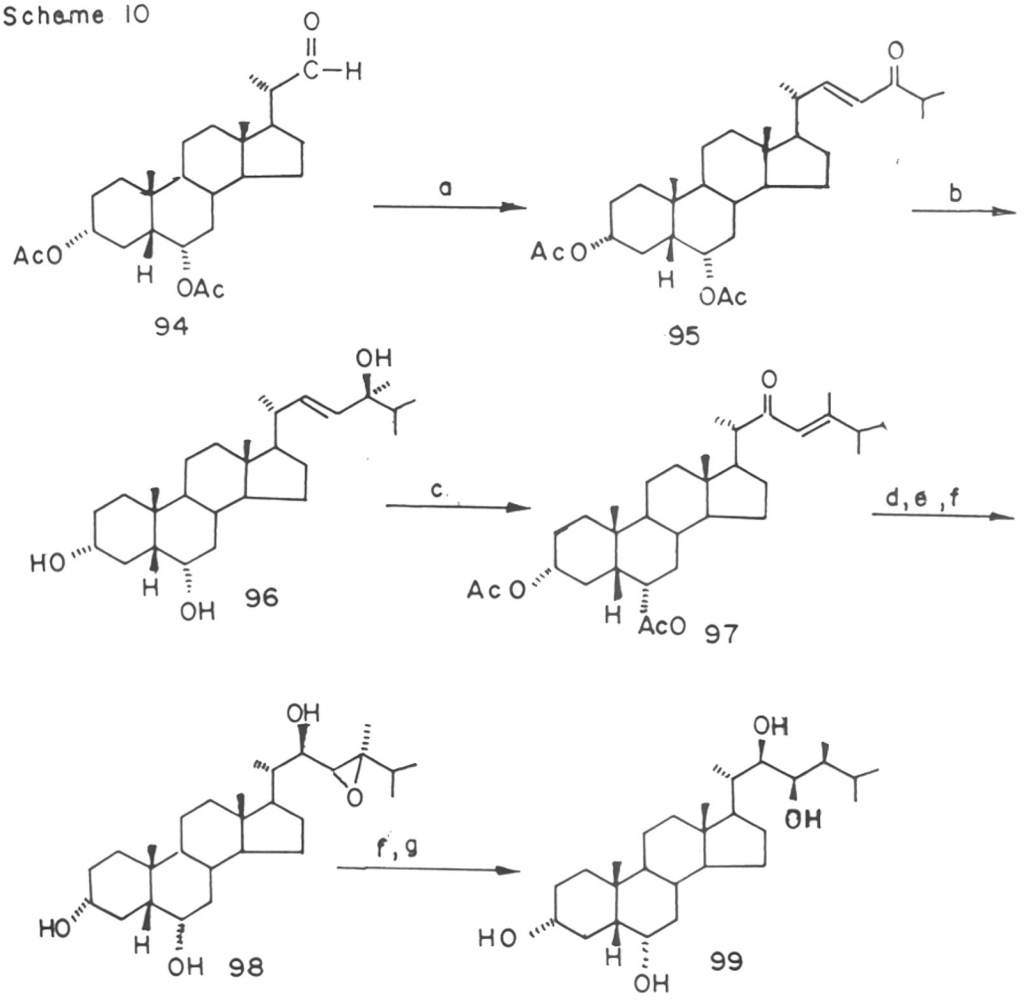
A stereoselective synthesis of the brassinolide side chain by W.S.Zhou Wei-Shan and co-workers[22] involves β-alkylative 1,3-carbonyl transposition of the α,β-unsaturated ketone **95** and its conversion to the intermediate **99**. From **99** typhasterol **13** and brassinolide **1** can be synthesised **(Scheme 10).**

Scheme 9



a. (E)-propenyllithium; b. t-BuOOH, $(i\text{-PrO})_4Ti$, (+)-L-diethyl tartarate, molecular sieves; c. $I\text{-pr}_2CuCBLi_2$, Et_2O.

Scheme 10



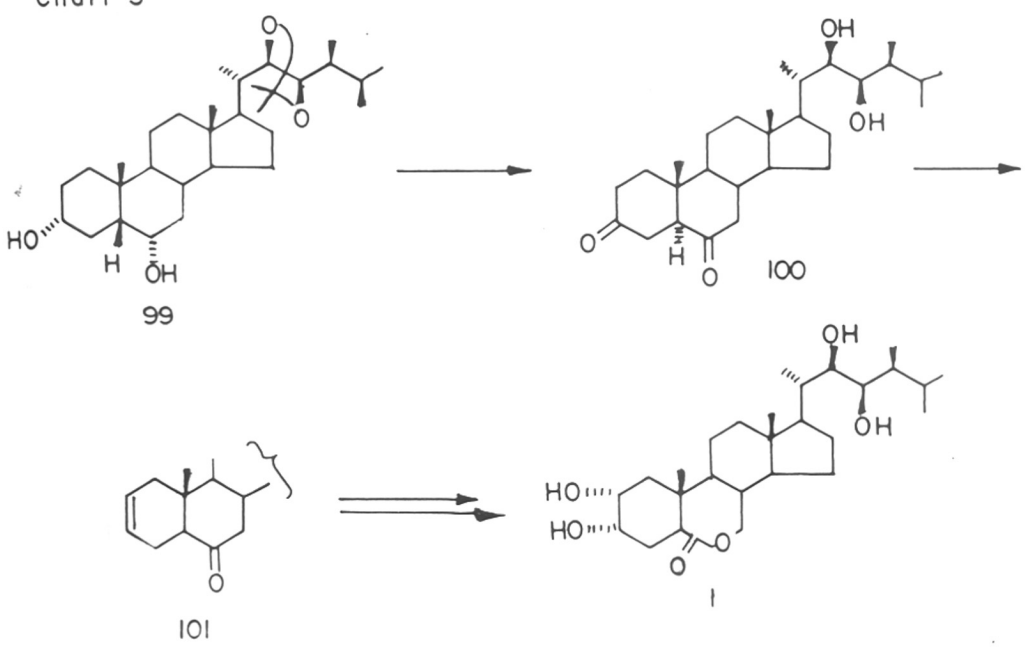
99 — 1 (Brassinolide)
99 — 3 (Typhasterol)

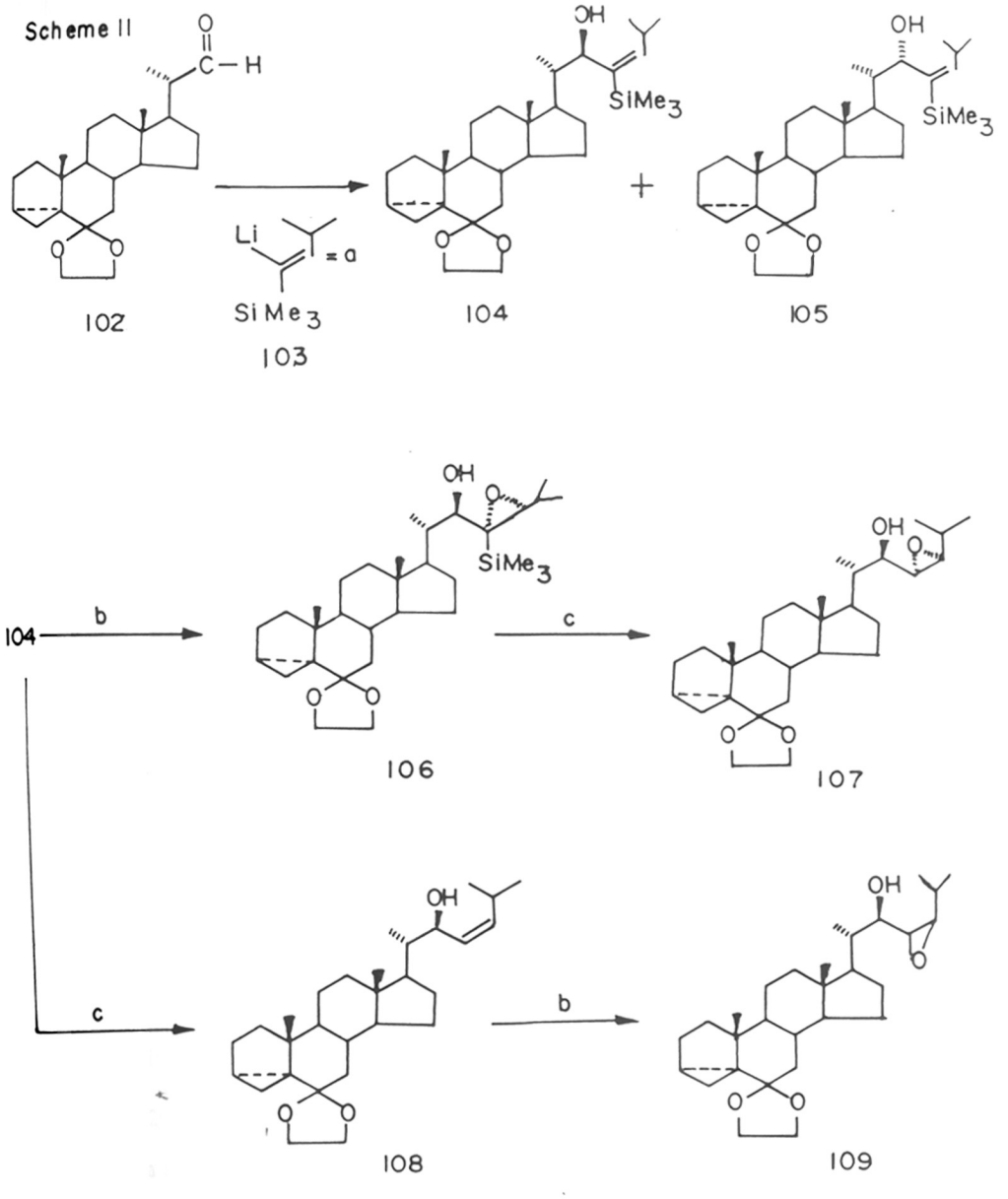
a. isobutyl carbonyl orsonium ylide; b. MeLi; c. Ac_2O, Et_3N, PCC; d. Dibal-H; e. *m*-CPBA; f. $LiBH_4$, BH_3.THF; g. 2,2-dimethoxypropane, *p*-TSA.

The C-20-carboxyaldehyde **94** from hyodeoxycholic acid, was treated with isobutyl carbonyl arsonium ylide' to form α,β-unsaturated ketone **95** in 90% yield. Oxidation of the tertiary allylic alcohol moiety of compound **96** generated by the 1,2-addition of methyl-lithium to the α,β-unsaturated ketone **95** (98%) with pyridinium chlorochromate (PCC) afford β-alkyl-α,β-unsaturated ketone **97** in 93% yield. Stereoselective reduction of enone **97** with di-isobutylaluminium hydride (DIBAL-H) furnished the (22R)-22-hydroxy compound in 95% yield. Hydroxy directed epoxidation of this enol with m-CPBA gave the desired epoxide **98** in 95% yield. The stereo- and regioselective opening of the epoxide **98** with inversion at C-24, followed by treatment with 2,2-dimethoxypropane, *p*-TSA yielded compound **99** in 64% yield in two steps. The A/B ring functionality of typhasterol **13** and brassinolide **1** have been constructed following simple reaction sequence.

The PDC oxidation of **99** followed by acid treatment afforded diketone **100** in 91% yield. Compound **100** was then subjected to a reductive elimination by treatment with chlorotrimethylsilane (TMSCl) and zinc amalgam to give Δ^2-6-keto compound **101**, which on osmylation with catalytic amount of OsO_4-NMMNO followed by Baeyer-Villiger oxidation afforded brassinolide **1** in 34% overall yield in three steps (**Chart 5**).

Chart 5

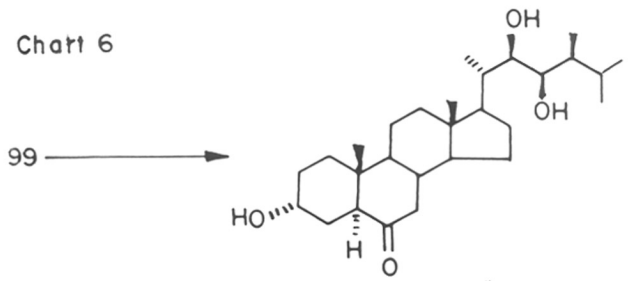




a. 1-lithium-1(trimethylsilyl)-3-methyl-1-butene; b. *m*-CPBA; c. desilylation.

Conversion of compound **99** to typhasterol **13** was achieved in 56% yield in two steps by oxidation with CrO_3-Py and then acid treatment with simultaneous epimerisation of C-5 (**Chart 6**).

Chart 6



13

Highly stereoselective synthesis of steroidal 22α-allylic alcohols via 22-aldehyde and 1-silyl-1-iodo-1-alkenes

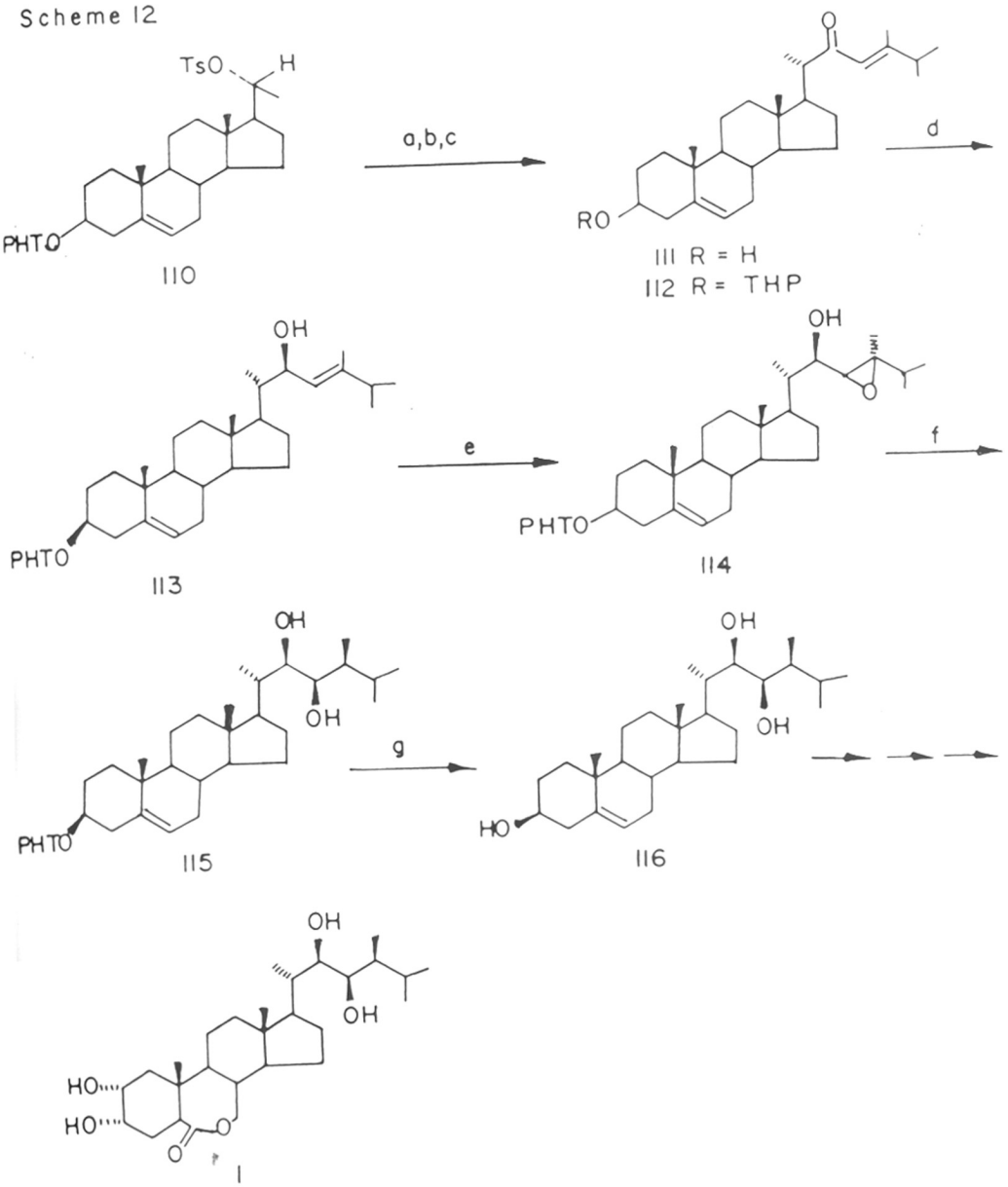
V.A.Khripach et Al.[23] have developed a new efficient route for the side chain construction of the side chain of brassinolide. 1-lithium-1(trimethylsilyl)-3-methyl-1-butene **103** undergoes smooth addition with aldehyde **102** to give 22α-alcohol **104** and 22β-alcohol **105** in 97% yield in the ratio of 10:1. Epoxidation of **104** *m*-CPBA followed by nucleophilic cleavage of Si-C bond in **106** gave epoxide **107** as the main product. Desilylation of **104** afforded **108** and further oxidation of **108** by *m*-CPBA leads to epoxydiol **109** suitable for brassinolide synthesis (**Scheme 11**).

Synthesis with the participation of C-20 centre

The side chain of brassinolide **1** was stereoselectively synthesised[8], in which the 20(S) and the 22(R)-configurations were introduced by the alkylation (SN^2) of the 20(R) tosyloxy steroid **110** with the protected cyanohydrin **111** followed by the stereoselective reduction of the 23-en-22-one **112** with Dibal-H (**Scheme 12**).

The 20β (R)-tosylate **110** was prepared from 3-tetrahydropyranyl ether of pregnenolone following a simple reaction sequence. Alkylation of the protected cyanohydrin with the tosylate **110** and the conversion of the alkylated product to the enone **112** was achieved on treatment with acid (p-TSA) followed by base treatment with 2% NaOH. The overall yield is 83%. The hydride reduction of 22-keto steroids **112** with diisobutyl-aluminium hydride (Dibal-H) and lithium tri-sec-butylborohydride (L-selectride) in THF at -78°C gave the cram product 22β (S)-OH in a ratio

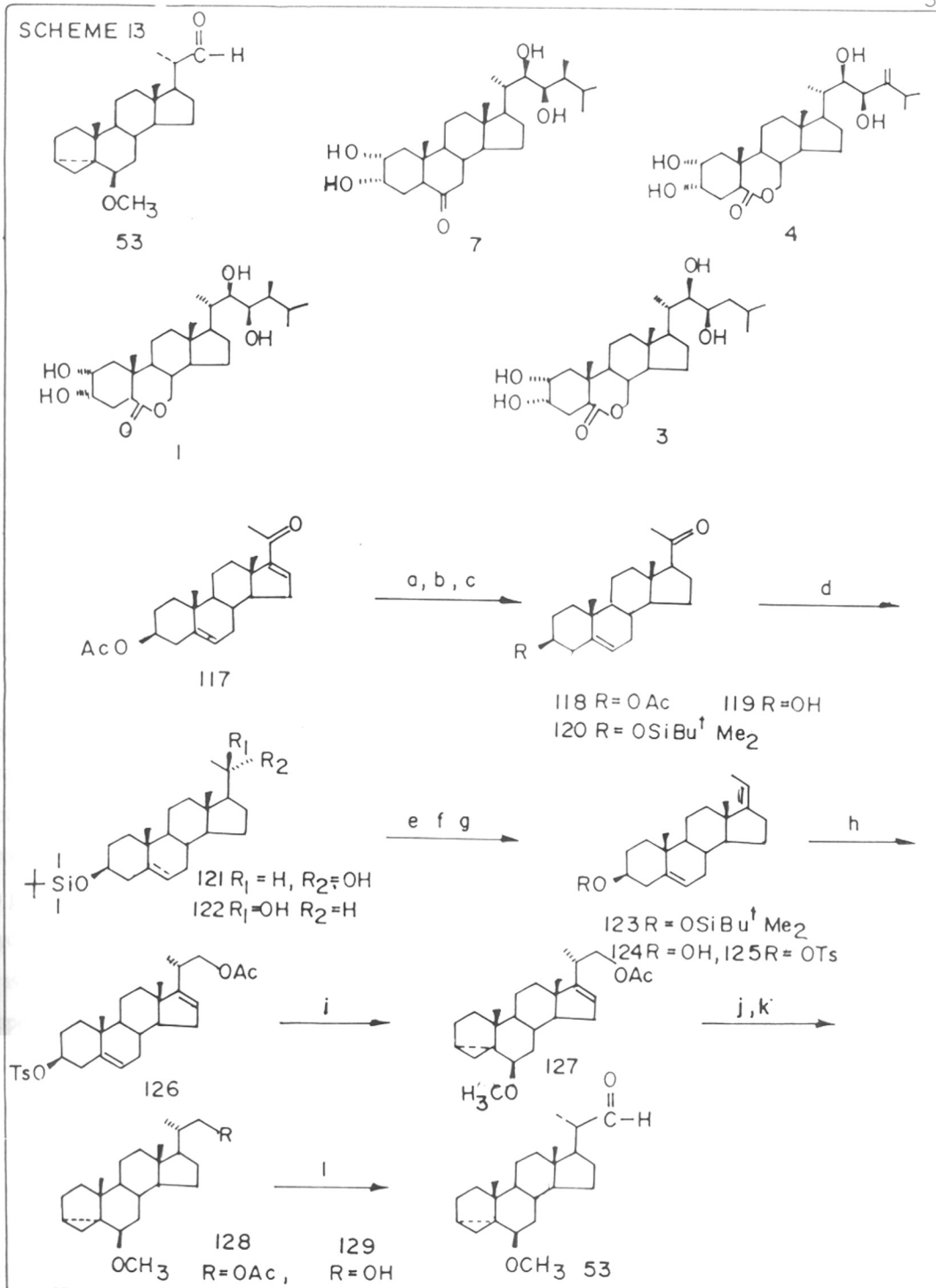
Scheme 12



a. alkylation; b. *p*-TSA; c. 2% NaOH; d, Dibal-H; e. ^{t}BuOOH, Vo (acac)$_2$, benzene; f. AlH_3, ether; g. *p*-TSA, methanol.

of 93:7 (72% yield), while the reduction with Dibal-H in THF at -78°C gave an anti-Cram product 22α(R)-OH **113** in a ratio of 97:3 (85% yield). The stereoselective allylic epoxidation of **113** using the Sharpless method (^{t}BuOOH/VO (acac)$_2$ in benzene at room temperature for 1h) gave the desired epoxide **114** in 79% yield along with its isomer in 7% yield. The stereo and regioselective opening of the epoxide **114** with inversion at C-24 [AlH_3, freshly prepared from $LiAlH_4$ and $AlCl_3$ in ether at room temperature] gave the 22α(R),23α(R)-dihydroxy product **115** in 64% yield and 22(R), 24-dihydroxy product was formed in 17% yield. Hydrolysis of the 3-tetrahydropyranyl ether of **115** with *p*-TSA in methanol gave the triol **116** in 82% yield. Conversion of the 3-hydroxy-5-en-moiety of the triol **116** to the hydroxy lactone portion of brassinolide **1** has been carried out following well established[3] procedure.

SCHEME 13



a. H_2, Pd/C; b. KOH, t-BuOH; c. Me_2SiBu^tCl, DMF, imidazole; d. $LiAlH_4$; e. $POCl_3$, py.; f. Bu_4NF, THF; g. *p*-TSCl, py.; h. $Ti(Oipr)_3Cl$, $(CH_2O)n$, CH_2Cl_2; Ac_2O, py.; i. Me_3SiCl, $(CH_2O)n$, CH_2Cl_2; Ac_2O, py.; j. Me_2SiBu^tCl, CH_2Cl_2, $(CH_2)n$; Ac_2O, py.; k. MeOH, py.; l. Pd/C, EtOH; m. KOH, MeOH; n. PCC.

Present investigation

This mainly deals with the synthesis of C-20 aldehyde 53 starting from 16-Dehydropregnenolone acetate 118, and conversion of this aldehyde 53 to brassinolide intermediate 116.

A) Synthesis of (20S)-3α-5-cyclo-6β-methoxy-5α-pregnane-20-carboxyaldehyde 53

The aldehyde **53** is an important intermediate for the synthesis of a large number of biologically active compound including brassinosteroids.[1-7] Compound **53** has been prepared from stigmasterol in 3 steps[4-7] in varying yields. The aldehyde **53** also has been synthesised from pregnenolone[24], epiandrosterone[25] in recent years. We have successfully synthesised aldehyde **53** from easily available steroidal precursor, 16-dehydropregnenolone acetate **117 (Scheme 13)**. This precursor **117** is available in plenty in India. The plant diascoria which is cultivated in many parts of India, is an abundant source of diosgenin. 16-Dehydropregnenolone acetate is prepared commercially and available in plenty from diosgenin following Marker's procedure.

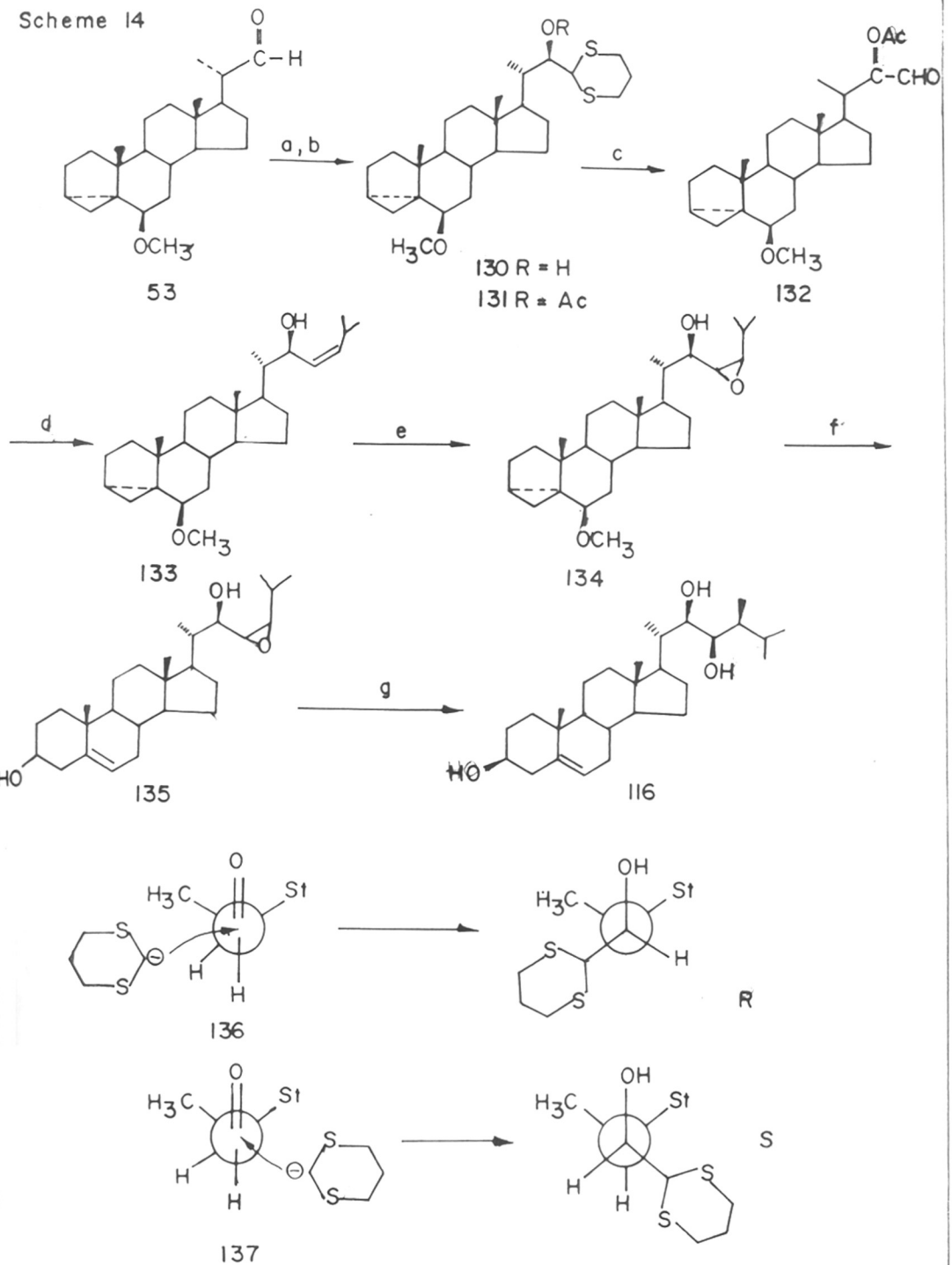
Selective hydrogenation of the steroid **117** using 5% Pd/C in ethyl acetate afforded saturated ketone **118** in 97% yield. The disappearance of the peak at 1680 cm^{-1} for α,β unsaturated carbonyl group in Infrared spectrum indicates the completion of reaction. Hydrolysis of the acetate **118** by potassium hydroxide in aqueous *tert*-butanol gave **119** in 96% yield. The protection of 3β-hydroxy group of **119** was carried out by *tert*-butyldimethylsilyl chloride in DMF in presence of imidazole to give **120** in 92% yield. The reduction of ketone **120** with lithium aluminium hydride in tetrahydrofuran yielded two C-20 epimeric alcohols **121** and **122** in 98% yield. The ratio of 20β:20α was found to be 9:1 from ^{1}H-NMR spectroscopy. The C-21 methyl protons in case of major epimer appear at 1.22 δ while in case of minor epimer they appear at 1.27δ. The required C-17(20) Z olefin **123** was prepared in 88% on dehydration of tertiary alcohol **121** or **122** with phosphorus oxychloride and pyridine. The Z:E ratio was determined by ^{1}H-NMR spectroscopy and was found to be 90:10. The C-20 proton for major olefin appears at 5.04 δ and at 5.15 δ for minor isomer in ^{1}H-NMR spectroscopy. An authentic sample of this compound was prepared for comparison purpose by silylation of a known olefin **124** which was prepared earlier in this laboratory.[25] The spectral data of the two silylated olefins were found to be identical. The desilylation of **123** with n-tetrabutylammonium fluoride in THF furnished the 3β-hydroxy (Z)-17(20)-olefin **124** in 85% yield. This olefin was found to be identical in all respect with the olefin prepared by earlier method.[25]

Tosylate **125** was prepared in 90% yield from alcohol **124** on reaction with *p*-toluenesulfonyl chloride in pyridine. The 22-acetate **126** was obtained in 82% yield by ene reaction on tosylate **125** with paraformaldehyde as an enophile, acetic anhydride and titanium triisopropoxy chloride as a Lewis acid in methylene chloride. To our surprise, the trimethylsilyl chloride and *tert*-butyldimethylsilyl chloride also yielded same 22-acetate **126** in 81% yield and 74% respectively under similar reaction conditions. The ene reaction carried out using titanium triisopropoxy chloride, trimethylsilyl chloride and *tert*-butyldimethylsilyl chloride stereospecifically generates the natural configuration at C-20. This approach makes use of the known preference for attack on the α-face of C-17(20) double bond and the highly ordered transition state of the ene reaction to set the stereochemistry of the C-20 carbon in the natural configuration. All the products were found to be identical in all respects with the acetate prepared according to earlier[25] method. To the best of our knowledge, the use of *tert*-butyldimethylsilyl chloride and trimethylsilyl chloride as a catalyst in ene reaction has not been reported earlier. The 22-acetate **126** was converted to i-methyl ether **127** in 85% yield by refluxing with dry methanol and pyridine, which on hydrogenation using Pd/C in ethanol gave the saturated compound **128** in 98% yield. The transfer of hydrogen from the surface of the catalyst takes place from the less hindered face of the C-16 double bond. The acetate **128** was hydrolysed by potassium hydroxide in methanol to get C-22 alcohol in 96% yield. The alcohol **129** on oxidation with pyridinium chlorochromate, potassium acetate in methylene chloride furnished the aldehyde **53** in 95% yield. The conversion of 16-dehydropregnenolone acetate **117** to the aldehyde **53** in eleven steps has been achieved in 36% overall yield. This constitutes a new synthesis of this important aldehyde **53** starting from 16-dehydropregnenolone acetate **117**.

(B) Synthesis of (22R,23R,24S)-3β-hydroxy-5-ene-22,23 dihydroxy-24-methyl-cholestane 116.

The starting material for most of the brassinolide syntheses is C-22 aldehyde **53**. (20S)-3α-5-Cyclo-6β-methoxy-5α-pregnane-20-carboxyaldehyde **53**, which is obtained from 16-dehydropregnenolone acetate, on condensation with 2-lithio 1,3-dithiane gave stereoselectively the (22R) alcohol **130** with a small amount of (22S) alcohol in 89% yield. The (22R)-:(22S)- ratio was found to be 88:12 from ^{1}H-NMR spectroscopic data. The formation of (22R)-hydroxy isomer **130** as a major product can be explained on the basis of the steric approach control as shown in (**Scheme**

Scheme 14



a. 1,3-dithiane, n-BuLi; b. Ac_2O, py.; c. NBS, $BaCO_3$; d. $Br^-Ph_3P^+CH_2CHMe_2$, n-BuLi, THF; e. *m*-CPBA, CH_2Cl_2; f. *p*-TSA, aq. dioxane; g. Me_3Al, n-BuLi.

14). During the attack of 2-lithio 1,3-dithiane, the path **136** involves less steric interaction hence gave predominantly (22R)-epimer, the Cram product. In path **137** the approach of the anion is hindered by the steroidal D-ring thus resulting the anti-Cram product, (22S)-epimer as a minor product. In the ^{1}H-NMR of the major (22R)-isomer the 22-H shows only a doublet with J=10Hz indicates that it does not couple with C-20H (J=0Hz), on the other hand, in the minor isomer the 22-H shows doublet of a doublet with J=6Hz and 3Hz due to the coupling with C-20H and C-23H. The (22R)-hydroxy group of **130** was acetylated using acetic anhydride and pyridine to get **131** in 93% yield. The overall yield in these two steps is 83%. The aldehyde **132** was obtained on deprotection of dithiane moiety of **131** with NBS/$BaCO_3$ in aqueous acetone in 96% yield. The formation of the aldehyde **132** was confirmed by IR spectroscopy. The acetoxy aldehyde shows a strong absorption at 1740 cm^{-1} for H-C=O and 1750 cm^{-1} for -$OCOCH_3$.

The Wittig reaction on **132** with triphenylphosphoniumisobutyl bromide and n-BuLi in tetrahydrofuran furnished a mixture of olefins in 77% yield. The (Z)-:(E)- ratio is 86:14 from ^{1}H-NMR spectroscopy. The pure (Z)-olefin **133** was obtained after column chromatographic purification. Its spectral as well as analytical data were found to be identical with the known[27] olefin prepared earlier in this laboratory. The olefin **133** was epoxidised with m-chloroperbenzoic acid, Na_2HPO_4 in methylene chloride to obtain the epoxide **134** in 95% yield. The 3,5 cyclic ring was opened with *p*-toluenesulfonyl chloride in aqueous dioxane to yield 3β-hydroxy-5-ene **135** in 98% yield. The epoxide ring of **135** was opened, using trimethylaluminium, n-BuLi in hexane-cyclohexane to afford **116** in 91% yield. Further elaboration of **116** to the brassinolide **1** is already well established.[3,8] Thus, the above work constitutes a total synthesis of brassinolide.

Experimental

Section A

3β-Acetoxy-pregna-5-ene-20-one 118

To a solution of 16-dehydropregnenolone acetate **117** (30.6g, 0.0859 mol) in ethyl acetate (200 ml) was added 1.5g. Pd/C catalyst. The hydrogenation was carried out using Parr apparatus at 45 *psi* pressure and 30°C temperature for 16h. The reaction mixture was filtered and the filtrate was dried under vacuo to obtain the saturated keto- compound **118** (30g, 98%), which was crystallised from ethyl acetate and hexane, m.p. 143°C (lit.[27] 147-147.5°C); IR (nujol) vmax 1740 (O-C=O), 1720 (C=O); ^{1}H-NMR (90 MHz) 0.62 (3H, s, 18-H_3), 1.0 (3H, s, 19-H_3), 2.0 (3H, s, $OCOCH_3$), 2.1 (3H, s, $COCH_3$), 4.6 (1H, m, 3-H), 5.37 (1H, dd, J=1 and 5 Hz, 6-H).

3β-Hydroxy-pregna-5-ene-20-one 119

To a stirred solution of **118** (3.450g, 0.0096 mol) in t-butanol (50 ml) was added KOH (3.1g, 0.055 mol) in H_2O (5 ml). The reaction mixture was stirred at 30°C for 12h, neutralised with 5% HCl solution, t-butanol was removed under vacuo and the residue was extracted with ethyl acetate (3x50 ml). The combined extract was washed with H_2O (2x25 ml), brine (2x25 ml) and finally it was dried over anhydrous Na_2SO_4. Evaporation of solvent yielded **119** (2.914g, 96%), which was crystallised from methanol, m.p. 186°C (lit.[28] 190-191°C); IR (Nujol) vmax 1712 (C=O), 3520 (OH), ^{1}H-NMR (90 MHz), 0.62 (3H, s, 18-H_3), 1.0 (3H, s, 19-H_3), 2.1 (3H, s, $COCH_3$), 3.5 (1H, m, 3-H), 5.33 (1H, d, J=5Hz, 6-H).

3β-tert-Butyldimethylsilyloxy-pregna-5-ene-20-one 120

tert-Butyldimethylsilyl chloride (0.3g, 0.002 mol) was added to a solution of pregnenolone **119** (0.316g, 0.001 mol) in dry DMF (5 ml). Imidazole (0.272g, 0.004 mol) was added to the above solution and the reaction mixture was stirred at 30°C for 10h. The reaction mixture was poured into ice and extracted with ethyl acetate (3x25 ml). The combined extract was washed with H_2O (2x25 ml), brine (2x25 ml) and was dried over anhydrous Na_2SO_4. On evaporation of solvent under vacuo compound **120** (0.398g, 92%) was obtained. The crude product was crystallised from ethyl acetate and hexane, m.p. 160-162°C; IR (Nujol) vmax 1712 (C=O); ^{1}H-NMR (200 MHz) 0.1 (6H, s, $SiMe_2$), 0.62 (3H, s, 18-H_3), 0.9 (9H, s, t-butyl CH_3), 1.05 (3H, s, 19-H_3), 2.1 (3H, s, $COCH_3$), 3.5 (1H, m,

3-H), 5.4 (1H, d, J=5Hz, 6-H); m/z 429 (M^+-1), 415, 374 (100%), 355, 297, 287, 255, 239, 225, 211, 199, 185, 171, 159, 145, 133, 119, 105, 75; Found: C, 75.07; H, 11.00; Calc. for $C_{27}H_{46}O_2Si$, C, 75.34; H, 10.69.

3β-tert-Butyldimethylsilyloxy-20(R), 20(S)-hydroxy-pregna-5-ene 121, 122

To a stirred solution of **120** (1.7g, 0.004 mol) in dry THF (20 ml) was added lithium aluminium hydride (0.2g, 0.005 mol) at 0°C. The reaction mixture was stirred for 10 minutes at 0°C and 2h at 25°C. Excess lithium aluminium hydride was decomposed by adding few drops of ethyl acetate followed by addition of saturated NH_4Cl solution. The reaction mixture was filtered and filtrate was concentrated under vacuo. The concentrated solution was extracted with ethyl acetate (3x50 ml). The combined extract was washed with H_2O (2x25 ml), brine (2x25 ml) and dried over anhydrous Na_2SO_4. The mixture of hydroxy compounds **121** and **122** was obtained after evaporation of solvent under vacuo. From the mixture the major C-20 epimeric alcohol **121** was separated by crystallisation, m.p. 145°C. IR (nujol) vmax 3400 (OH); ^{1}H-NMR (200 MHz) 0.1 (6H, s, $SiMe_2$), 0.82 (3H, s, 18-H_3), 0.95 (9H, s, t-butyl CH_3), 1.05 (3H, s, 19-H_3), 1.22 (3H, d, J=5Hz, 21-H_3), 3.5 (1H, m, 3-H), 3.75 (1H, m, 20-H), 5.4 (1H, d, J=5Hz, 6-H); m/z 432 (M^+), 417, 375, 339, 331, 318, 299, 283, 255, 241, 235, 227, 199, 187, 173, 159, 145, 119, 105, 75 (100%); Found: C; 75.40; H, 11.23; Calc. for C; 75.10; H, 11.11. The minor alcohol **122** m.p. 180°C IR vmax 3420 (OH); ^{1}H-NMR 0.73 (3H, s, 18-H_3), 1.05 (3H, s, 19-H_3), 1.27 (3H, d, J=5Hz, 21-H_3), 3.75 (1H, m, 20-H).

3β-tert-Butyldimethylsilyloxy-(Z)-pregna-5,17(20)-diene 123

To a solution of alcohol **121** (0.1g, 0.00023 mol) in dry pyridine (2 ml) was added $POCl_3$ (0.5 ml, 0.00019 mol) at 0°C. The reaction mixture was stirred for 10 minutes at 0°C and at 25°C for 30h. The reaction mixture was poured into ice water and extracted with ethyl acetate (3x25 ml). The organic layer was washed with H_2O (2x25 ml), brine (2x25 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent under vacuo afforded **123** (0.083g, 88%). The crude product was crystallised from methanol, m.p. 145°C. The minor alcohol **122** under identical conditions yielded same olefin **123**. The compound **123** was compared with an authentic sample prepared by silylation of olefin **124** synthesised by known method[25] and it was found to be comparable in all respects from their mixed melting points as well as spectral data; IR (nujol) vmax 1260, 1200, 980, (Z)-:(E)- = 90:10 from ^{1}H-NMR; ^{1}-H-NMR (200 MHz) 0.1 (6H, s, $SiMe_2$), 0.95 (12H, s, 18-H_3, t-butyl CH_3),

1.06 (3H, s, 19-H_3), 1.52 (3H, s, 21-H_3), 3.52 (1H, m, 3-H), 5.04 (1H, m, 20-H), 5.36 (1H, d, J=5Hz, 6-H); m/z 357 (M^+-57), 287, 253, 213, 171, 161, 145, 133, 121, 105, 91, 79, 75 (100%). The (E)-olefin showed ^{1}H-NMR signals at 5.15 (1H, m) for 20-H.

3β-Hydroxy-(Z)-pregna-5,17(20)-diene 124

To a stirred solution of **123** (0.3g, 0.001 mol) in dry THF (10 ml) was added tetrabutylammonium fluoride (1M solution in THF, 1.5 ml, 0.0015 mol) at 0°C. The reaction mixture was stirred for 5 minutes at 0°C and 2h. At 25°. THF was evaporated off and the residue was extracted with ethyl acetate (3x25 ml). The extract was washed with H_2O (2x25 ml), brine (2x25 ml) and finally dried over anhydrous Na_2SO_4. Evaporation of solvent gave **124** crude (0.215g). The crude product was column chromatographed to obtain **124** (0.184g, 85%), mp. 136-137°C (lit.[25] 136-138°C); IR (nujol) vmax 3280 (OH), 1060; ^{1}H-NMR (200 MHz) 0.88 (3H, s, 18-H_3), 1.04 (3H, s, 19-H_3), 1.6 (3H, dd, J=6Hz, 21-H_3), 3.52 (1H, m, 3-H), 5.04 (1H, m, 20-H), 5.35 (1H, m, 6-H). The (E)-olefin has ^{1}H-NMR signals at 5.15 (1H, m) for C-20.

3β-p-Toluenesulfonoxy-(Z)-pregna-5,17(20)-diene 125

To a solution of **124** (2.53g, 0.0084 mol) in dry pyridine (15 ml) was added *p*-toluenesulfonyl chloride (3g, 0.0158 mol). The reaction mixture was kept in dark for 48h. Then the reaction mixture was poured in ice-cold solution of 5% sodium bicarbonate (200 ml). The compound **125** was isolated by filtration (3.1g, 82%); It was crystallised from diethyl ether and hexane, m.p. 119-120°C (Lit.[25] 119-119.5°C); IR (nujol) vmax 1605, 1200, 1180, 980, 960, 880, 825; ^{1}H-NMR 0.87 (3H, s, 18-H_3), 0.98 (3H, s, 19-H_3), 1.65 (3H, d, J=7Hz, 21-H_3), 2.44 (3H, s, tosyl CH_3), 4.29 (1H, m, 3-H), 5.13 (1H, m, 20-H), 5.32 (1H, bd, 6-H), 7.78 (4H, AB, J=8Hz, aromatic H).

20(S)-3β-p-Toluenesulfonoxy-23,24-dinor-5,16-diene-5α-cholane-22 acetate 126

Method A

A mixture of tosylate **125** (0.454g, 0.001 mol), paraformaldehyde (0.125g, 0.0013 mol), acetic anhydride (0.1 ml) and titanium triisopropoxy chloride (0.115g, 0.0005 mol) in dry methylene chloride (10 ml) was stirred at 25°C for 48h. Methylene chloride was evaporated off and the residue was extracted with ethyl acetate (3x25 ml). The combined extract was washed with H_2O (2x25 ml), brine (2x25 ml) and finally dried over Na_2SO_4 (anhydrous). Evaporation of solvent yielded after

acetylation of OH group with acetic anhydride in pyridine. **126** (0.434g, 82%), crystallised from hexane, mp. 107-108°C (lit.[25] 109-110°C); IR (neat) vmax 1735 (O-C=O); ^{1}H-NMR 0.8 (3H, s, 18-H_3), 0.93 (3H, s, 19-H_3), 1.04 (3H, d, J=7Hz, 21-H_3), 2.02 (3H, s, $OCOCH_3$), 2.42 (3H, s, tosyl CH_3), 3.4-4.2 (3H, m, 3-H, 22-H), 5.30 (2H, m, 6-H, 16-H), 7.29 and 7.76 (4H, AB, J=10Hz, aromatic H).

Method B

A mixture of tosylate **125** (0.114g, 0.00025 mol), paraformaldehyde 0.62 (0.030g, 0.00033 mol), trimethylsilyl chloride (0.035g, 0.00032 mol), acetic anhydride (0.1 ml) in methylene chloride (20 ml) was stirred at 25°C for 4h. The methylene chloride was removed and the residue was extracted with ethyl acetate (3x25 ml). The organic layer was washed with H_2O (2x25 ml), brine (2x25 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent furnished acetate after acetylation of OH group with acetic anhydride in pyridine **126** (0.107g, 81%).

Method C

Tosylate **125** (0.114g, 0.00025 mol), paraformaldehyde (0.056g, 0.00062 mol), *tert*-butyldimethylsilyl chloride (0.077g, 0.0005 mol), acetic anhydride (0.1 ml) were taken in methylene chloride (20 ml). The reaction mixture was stirred at 25°C for 24h. The CH_2Cl_2 was evaporated off and the residue was extracted with ethyl acetate (3x25 ml). The combined extract was washed with H_2O (2x25 ml), brine (2x25 ml) and finally dried over anhydrous Na_2SO_4. After evaporation of solvent, the crude product was dissolved in dry pyridine (5 ml), acetic anhydride (1 ml) was added to it and the mixture was kept at 25°C for 24h. The acetate **126** was obtained after filtration (0.097g, 74%).

(20S)-3α-5-Cyclo-6β-23,24-dinor-5α-cholane-16-ene-22-acetate 127

To a solution of tosylate **126** (1.7g, 0.0032 mol) in dry methanol (15 ml), dry pyridine (1 ml) was added and the reaction mixture was refluxed for 2h. Methanol was evaporated off and the residue was extracted with ether (3x50 ml). The ether extract was washed with H_2O (2x50 ml), brine (2x50 ml) and was dried over anhydrous Na_2SO_4. Evaporation of solvent, after column

chromatographic purification yielded **127** as a thick oil. (1.072g, 86%); IR (neat) νmax 1735 (O-C=O); ^{1}H-NMR 0.8 (3H, s, 18-H_3), 1.04 (3H, s, 19-H_3), 1.07 (3H, d, J=7Hz, 21-H_3), 2.02 (3H, s, $OCOCH_3$), 2.81 (1H, m, 6-H), 3.37 (3H, s, OCH_3), 3.48-4.27 (2H, m, 22-H), 5.24-5.48 (1H, m, 16-H).

(20S)-3α,5-Cyclo-6β-methoxy-23,24-dinor-cholane-22-acetate 128

The compound **127** (1.062g, 0.00275 mol) in ethanol (35 ml) was hydrogenated in Parr hydrogenator using 10% Pd/C (0.150g) for 6h at 30 psi. The catalyst was filtered and solvent was removed under reduced pressure. The compound **128** was obtained as a thick oil, which was crystallised from ethyl acetate-hexane (1.045g, 98%), mp. 123-124°C (lit.[26] 124-125°C); IR (Nujol) νmax 1740 (O-C=O); ^{1}H-NMR 0.67 (3H, s, 18-H_3), 0.93 (3H, d, J=7Hz, 21-H_3), 0.96 (3H, s, 19-H_3), 1.98 (3H, s, $OCOCH_3$), 2.69 (1H, m, 6-H), 3.24 (3H, s, OCH_3), 3.53-4.13 (2H, m, 22-H).

(22S)-3α,5-Cyclo-6β-methoxy-23,24-dinor-5α-cholane-22-ol 129

A solution of potassium hydroxide (0.112g, 0.002 mol) in methanol (10 ml) was added to a solution of **128** (0.378g, 0.00097 mol) in methanol (10 ml). The reaction mixture was stirred at 25°C for 16h. Methanol was removed under reduced pressure. The residue was extracted with ethyl acetate (3x25 ml). The ethyl acetate extract was washed with H_2O (2x25 ml), brine (2x25 ml), dried over anhydrous Na_2SO_4. Evaporation of solvent followed by column chromatographic purification afforded **129** as a thick oil (0.322g, 96%); IR (neat) νmax 3495 (OH); 1460, 1380, 1100, 1020; ^{1}H-NMR 0.84 (3H, s, 18-H_3), 1.00 (3H, d, J=6Hz, 21-H_3), 1.04 (3H, s, 19-H_3), 1.04 (3H, s, 19-H_3), 2.76 (1H, m, 6-H), 3.28 (3H, s, OCH_3), 3.5 (2H, d, J=6Hz, 22-H).

(20S)-3α,5-Cyclo-6β-5α-pregnane-20-carboxyaldehyde 53

To a stirred solution of potassium acetate (0.025g) and pyridinium chlorochromate (0.185g, 0.00086 mol) in methylene chloride (5 ml), a solution of **129** (0.160g, 0.00046 mol) in methylene chloride (1 ml) was added dropwise. The reaction mixture was stirred at 25°C for 1h. The mixture was diluted with diethyl ether (50 ml), filtered and filtrate was washed with H_2O (2x25 ml), brine (2x25 ml), dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude product **53**, which was purified by column chromatography, furnished **53** as a solid (0.151g, 25%); m.p. 82-83°C (lit.[4]

82-83°C); IR (neat) νmax 2700, 1730 (C=O), 1100; ^{1}H-NMR 0.76 (3H, s, 18-H_3), 1.00 (3H, s, 19-H_3), 1.11 (3H, d, J=7Hz, 21-H_3), 2.74 (1H, m, 6-H), 3.29 (3H, s, OCH_3), 9.51 (1H, d, J=3Hz, H-C=O).

Section B

22(R)-22-Hydroxy-3α-5-Cyclo-6β-methoxy-24-nor-5α-cholane-23-al-trimethylene dithioacetal 130

To a stirred solution of 1,3-dithiane (1.5g, 0.0125 mol) in dry THF (30 ml) under nitrogen atmosphere at 0°C was added n-BuLi (15 ml, 1.4M) dropwise. The resulting solution was stirred for 1h at -5°C to 0°C. The solution was further cooled to -20°C and aldehyde **53** (2.2g, 0.0068 mol) dissolved in THF (10 ml) was injected dropwise in 10 minutes and stirred for 2h. To the reaction mixture water (5 ml) was added, stirred for 15 minutes and extracted with ether (3x50 ml). The combine extract was washed with water (2x25 ml), brine (2x25 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded **130** as a thick mass which was purified by column chromatography (2.2g, 89%). The major isomer was crystallised from ethyl acetate and hexane, mp. 163°C, IR ($CHCl_3$) νmax 3460; ^{1}H-NMR 0.3-0.6 (3H, m, cyclopropyl-H), 0.76 (3H, s, 18-H_3), 0.91 (3H, d, J=7Hz, 21-H_3), 1.00 (3H, s, 19-H_3), 2.64 (1H, t, J=3Hz, 6-H), 2.47-3.16 (6H, m, dithiane-H), 3.29 (3H, s, OCH_3), 3.71 (1H, d, J=8Hz, 22-H), 3.87 (1H, d, J=8Hz, 23-H); m/z 464 (M^+), 433, 414, 326, 312, 120; Found: C, 69.92; H, 9.32; S, 13.68; Calc. for $C_{27}H_{44}O_2S_2$ C, 69.83; H, 9.48; S, 13.79.

22(R)-22-Acetoxy-3α-5-Cyclo-6β-methoxy-24-nor-5α-cholane-23-al-trimethylene dithioacetal 131

The alcohol **130** (2.273g, 0.0049 mol) was dissolved in dry pyridine (15 ml) and acetic anhydride (5 ml), the mixture was kept at 25°C for 16h. The reaction mixture was poured into ice cold solution of $NaHCO_3$. The acetate **131** was filtered off (2.35g, 93%) and was crystallised from ethyl acetate and hexane, m.p. 145°C, IR (nujol) νmax 1750 (O-C=O); ^{1}H NMR 0.3-0.6 (3H, m, cyclopropyl-H), 0.76 (3H, s, 18-H_3), 0.96 (3H, d, J= Hz, 21-H_3), 1.02 (3H, s, 19-H_3), 2.36-3.18 (6H, m, dithiane-H), 2.73 (1H, t, J=3Hz, 6-H), 3.29 (3H, s, OCH_3), 3.71 (1H, d, J=10Hz, 23-H), 5.36 (1H, d, J=10Hz,

22-H); m/z 506 (M^+), 447, 415, 159, 119, 59; Found: C, 68.71; H, 9.13; S, 12.53; Calc. for $C_{29}H_{46}O_3S_2$ C, 68.77; H, 9.09; S, 12.65. The 22(S)-acetate showed a ^{1}H-NMR signals at 5.11 (dd, J=6 and 3Hz) for 22-H.

22(R)-22-Acetoxy-3α-5-Cyclo-6β-methoxy-24-norcholane-23-al 132

To a stirred solution of acetoxy dithiane **131** (0.380g, 0.00075 mol) in acetone (15 ml) was added $BaCO_3$ (1.78g, 0.009 mol) at 10°C. NBS solution in aq. acetone (20 ml) was introduced to it and the reaction mixture was stirred at 25°C for 0.5h. Excess NBS was decomposed by using sodium bisulphite solution. The mixture was filtered and filtrate was poured in excess water, extracted with ether (3x50 ml). The combined ether layer was washed with water (3x25 ml), brine (2x25 ml) and dried over anhydrous Na_2SO_4. Evaporation of ether yielded **132** (0.3g, 96%), which was crystallised from ethyl acetate and hexane, mp. 55-56°C; IR νmax 1750 (O-C=O), 1740 (H-C=O); ^{1}H-NMR 0.3-0.6 (3H, m, cyclopropyl-H), 0.77 (3H, s, 18-H_3), 0.97 (3H, d, J=7Hz, 21-H_3), 1.22 (3H, s, 19-H_3), 2.16 (3H, s, $OCOCH_3$), 2.76 (1H, t, J=3Hz, 6-H), 3.28 (3H, s, OCH_3), 5.08 (1H, d, J=2Hz, 22-H), 9.43 (1H, s, O=C-H); m/z 416 (M^+), 384, 213, 145, 105, 55; Found: C, 75.11; H, 9.87. Calc. for $C_{26}H_{40}O_4$ C, 75.00; H, 9.62.

22(R)-22-Hydroxy-3α-5-Cyclo-6β-methoxy-5α-cholane-23-(Z)-ene 133

To a stirred suspension of isobutyl triphenyl phosphonium bromide (1.01g, 0.0025 mol), in THF (5 ml) was added n-BuLi (2.5 ml, 1.4M) in a one lot at 0°C. Aldehyde **53** (0.208g, 0.0005 mol) in THF (5 ml) was added dropwise to the above reaction mixture in 5 minutes. The reaction mixture was left at 25°C for 18h. THF was removed and the residue was dissolved in aqueous methanol, iodomethane (2 ml) was added and the reaction mixture was stirred for 2h at 25°C. Methanol was removed and the residue was poured in excess water, extracted with ethyl acetate (3x25 ml). The combined organic layer was washed with water (2x25 ml), brine (2x25 ml) and was dried over anhydrous Na_2SO_4. Evaporation of solvent followed by column chromatographic purification afforded compound **133** as a thick oil (0.160g, 77%). This on tituration with methanol solidified. The (Z)-olefin **133** was crystallised from methanol, mp. 42-44°C (lit.[29] 42-44°C); ^{1}H-NMR δ0.3-0.6 (3H, m, cyclopropyl-H), 0.71 (3H, s, 18-H_3), 0.96 (3H, s, 19-H_3), 1.00 (6H, d, J=6Hz, 26, 27-H_3),

1.05 (3H, d, J=7Hz, 21-H_3), 2.55 (1H, m, 25-H), 2.75 (1H, m, 6-H), 3.29 (3H, s, OCH_3), 4.51 (1H, d, J=6Hz, 22-H), 5.27 (2H, m, 23-H); 414 (M^+); Found: C, 87.19; H, 11.07. Calc. for $C_{28}H_{46}O_2$ C, 87.10; H, 11.18. The (22E)-olefin showed a ^{1}H-NMR signals at 5.67 (m, 2-H) for 22-H and 23-H.

23,24-Epoxy-(22R)-22-hydroxy-3α-5-cyclo-6β-methoxy-5α-cholestane 134

The alcohol **133** (0.750g, 0.00181 mol), Na_2HPO_4 (0.86g, 0.006 mol), m-CPBA (1.5g, 0.0087 mol) were taken in methylene chloride (20 ml) and the reaction mixture was stirred at 25°C for 6h. The mixture was filtered and the solid was washed with CH_2Cl_2 (3x25 ml). Combined filtrate was washed with 5% NaOH and then with water till alkali free. The organic layer was washed with brine (2x25 ml) and dried over anhydrous Na_2SO_4. The solvent evaporation followed by column chromatographic purification afforded **134** as a foamy solid (0.744g, 95%), was crystallised from ethyl acetate and hexane, mp. 69-70°C; IR (nujol) νmax 3530; ^{1}H-NMR 0.3-0.6 (3H, m, cyclopropyl-H), 0.72 (3H, s, 18-H_3), 1.0 (3H, d, J=7Hz, 21-H_3), 1.02 (3H, s, 19-H_3), 1.11 (6H, d, J=7Hz, 26,27-H_3), 2.70 (1H, dd, J=4 and 4Hz, 24-H), 2.79 (1H, t, J=21Hz, 6-H), 3.08 (1H, dd, J=4 and 5Hz, 23-H), 3.35 (3H, s, OCH_3), 3.62 (1H, d, J=6Hz, 22-H); m/z 430 (M^+); Found: C, 77.99; H, 10.71. Calc. for $C_{28}H_{46}O_3$ C, 78.09; H, 10.77.

23,24-Epoxy-(22R)-22-hydroxy-3β-hydroxy-5α-cholestane-5-ene 135

The mixture of alcohol **134** (0.36g, 0.00083 mol), dioxane (9 ml), water (3 ml), *p*-TSA (0.038g, 0.00024 mol), was heated at 60-65°C for 1.5h. The mixture was neutralised with $NaHCO_3$ and evaporated to dryness. The residue was extracted with CH_2Cl_2 (3x50 ml). The combined organic layer was washed with water (2x50 ml), brine (2x25 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent afforded the crude product **135** (0.344g, 98%), was crystallised from ethylacetate and hexane, mp. 156-157°C; IR νmax 3520; ^{1}H-NMR 0.69 (3H, s, 18-H_3), 0.86 (3H, d, J=6Hz, J=6Hz, 26-H_3), 0.87 (3H, d, J=6Hz, 27-H_3), 0.99 (3H, s, 19-H_3), 1.08 (3H, d, J=7Hz, 21-H_3), 2.67 (1H, dd, J=4 and 5Hz, 23-H), 3.08 (1H, dd, J=4 and 4Hz, 24-H), 3.5 (1H, m, 3-H), 3.60 (1H, d, J=7Hz, 22-H), 5.37 (1H, m, 6-H); m/z 416 (M^+); Found: C, 77.68; H, 10.57. Calc. for $C_{27}H_{44}O_3$ C, 77.83; H, 10.65.

(22R,23R,24S)-3β-Hydroxy-5-ene-22,23-dihydroxy-24-methyl-cholestane 116

Epoxydiol **135** (0.170g, 0.0004 mol) was dissolved in a mixture of cyclohexane and hexane 40 ml (1:1) by boiling and then this was cooled at -70°C to -75°C. To it was added Me_3Al (5 ml, 2.0M) in hexane, followed by n-BuLi (0.6 ml, 1.5M) and the reaction mixture was stirred at 0°C to 10°C for 3h. And at 25°C for 16h. The reaction mixture was cooled to -78°C and 5% HCl (5 ml) was added and it was extracted with ethyl acetate (3x25 ml). The ethyl acetate extract was washed with water (2x25 ml), brine (2x25 ml) and was dried over anhydrous Na_2SO_4. Evaporation of solvent gave the crude product, which was purified by column chromatography to afford **116** (0.160g, 91%), it was crystallised from ethyl acetate and hexane, mp. 217°C (lit.[3,8] 219-220°C); IR νmax 3530; ^{1}H-NMR 0.67 (3H, s, 18-H_3), 0.82 (3H, d, J=6Hz, 21-H_3), 0.87 (3H, d, J=4Hz, 24-H_3), 0.92 (3H, d, J=6Hz, 27-H_3), 0.94 (3H, d, J=6Hz, 26-H_3), 0.98 (3H, s, 19-H_3), 3.6 (1H, m, 3-H), 5.3 (1H, m, 6-H); m/z 430 (M^+); Found: C, 77.51; H, 11.02. Calc. for $C_{28}H_{46}O_3$. C, 77.71; H, 11.18.

References

1. Adam,G.; Marquardt,V. *Phytochemistry* **1986**, 25, 1787-1799.
2. Back,T.G.; Blazecka,P.G.; Krishna,M.V. *Tetrahedron Lett.* **1991**, 32, 4817-4818.
3. Fung,S.; Siddall,J.B. *J.Am.Chem.Soc.* **1980**, 102, 6580-6581.
4. Wiersig,J.R.; Waespe-Sarceric,N.; Djerassi,C. *J.Org.Chem.* **1979**, 44, 3374-3382.
5. Anderson,G.D.; Powers,T.J.; Djerassi,C.; Fayas,J.; Clardy,J. *J.Am.Chem.Soc.* **1975**, 97, 388-394.
6. Hutchins,R.F.N.; Thompson,M.J.; Svoboda,J.A. *Steroids* **1970**, 15, 113-130.
7. Salmond,W.G.; Sobala,M.C.; *Tetrahedron Lett.* **1977**, 20, 1695-1698.
8. Takahashi,T.; Ootake,A.; Yamada,H.; Tsuji,J. *Tetrahedron Lett.* **1985**, 26, 69-72.
9. Grove,M.D.; Spencer,G.F.; Rohwedder,W.K.; Mandava,N.; Worley,J.F.; Warthen,J.D.; Steffens,G.L.; Flippen-Andersen,J.L.; Cook,J.C. Jr. *Nature* **1979**, 281, 216-217.
10. Lakhvich,F.A.; Khripach,V.A.; Zhabinskii,V.N. *Russian Chem.Rev.* **1991**, 60, 658-675.
11. Wada,K.; Marumo,S. *Agric.Biol.Chem.* **1981**, 45, 2579-2585.
12. Japanese P. 6011498; *Chem.Abst.* **1986**, 103, 174038;
    Japanese P. 63255297; *Chem.Abst.* **1989**, 111, 36804.
13. Steele,J.A.; Mosettig,E. *J.Org.Chem.* **1963**, 28, 571-572.
14. Cookson,R.C.; Gandhi,R.P.; Southam,R.M. *J.Chem.Soc.(C)* **1968**, 2494-2500.
15. Takatsuto,S.; Ikekawa,N. *Tetrahedron Lett.* **1983**, 24, 917-920.
16. Ahmad,M.S.; Moinuddin,G.; Khan,I.A. *J.Org.Chem.* **1978**, 43, 162.
17. Sakakibara,M.; Mori,K. *Agric.Biol.Chem.* **1982**, 46, 2769-2779.
18. Sakakibara,M.; Mori,K. *Agric.Biol.Chem.* **1983**, 47, 1407-1408.
19. Takatsuto,S.; Yazawa,N.; Ishiguro,M.; Morisaki,M.; Ikekawa,N. *J.Chem.Soc. Perkin Trans. 1.* **1984**, 139-148; Ishiguro,M.; Takatsuto,s.; Morisaki,M.; Ikekawa,N. *J.Chem.Soc.Chem.Comm.* **1980**, 962-964.

20. Kametani,T.; Keino,K.; Kigawa,M. Tsubuki,M.; Honda,T. *Tetrahedron Lett.* **1989**, 30, 3141-3142.

21. Mori,K.; Sakakibara,M.; Okada,K. *Tetrahedron* **1984**, 40, 1767-1781; Aburatani,M.; Takeuchi,T.; Mori,K. *Agric.Biol.Chem.* **1985**, 49, 3557-3562.

22. Zhou,W.S.; Fung,L. *J.Chem.Soc.Perkin Trans.1* **1990**, 1765-1767.

23 Khripach,V.A.; Zhabinskiy,V.N.; Olkhorick,V.K. *Tetrahedron Lett.* **1990**, 31, 4937-4940.

24. Midland,M.M.; Kwon,Y.C. *Tetrahedron Lett.* **1984**, 25, 5981-5984.

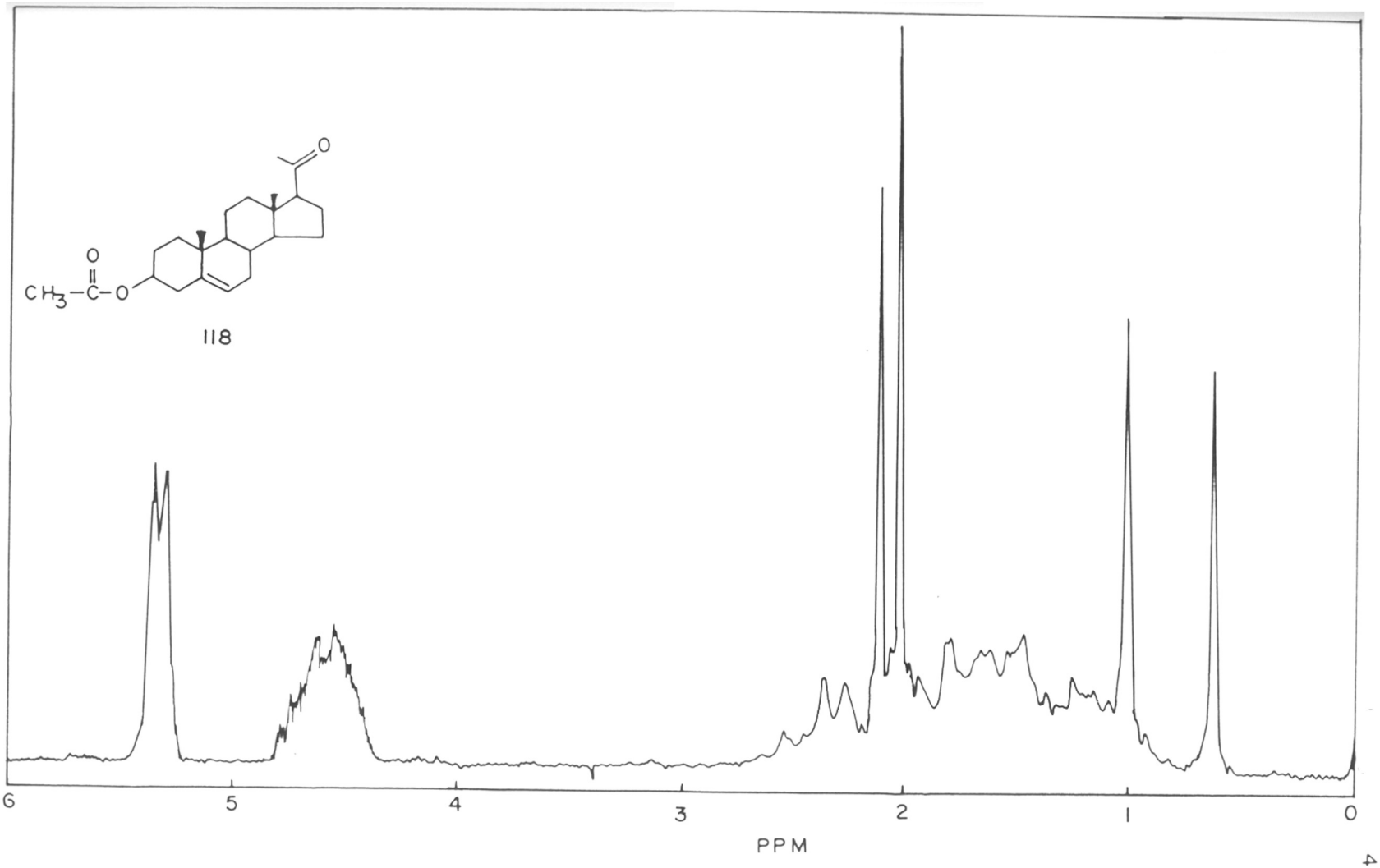
25. Hazra,B.G.; Joshi,P.L.; Pore,V.S. *Tetrahedron Lett.* **1990**, 31, 6227-6230.

26. Hazra,B.G.; Pore,V.S.; Joshi,P.L.; Padalkar,S.N.; Deshpande,S.A.; Rajamohanan,P.R. *Mag.Reson.Chem.* **1993**, 31, 605-608.

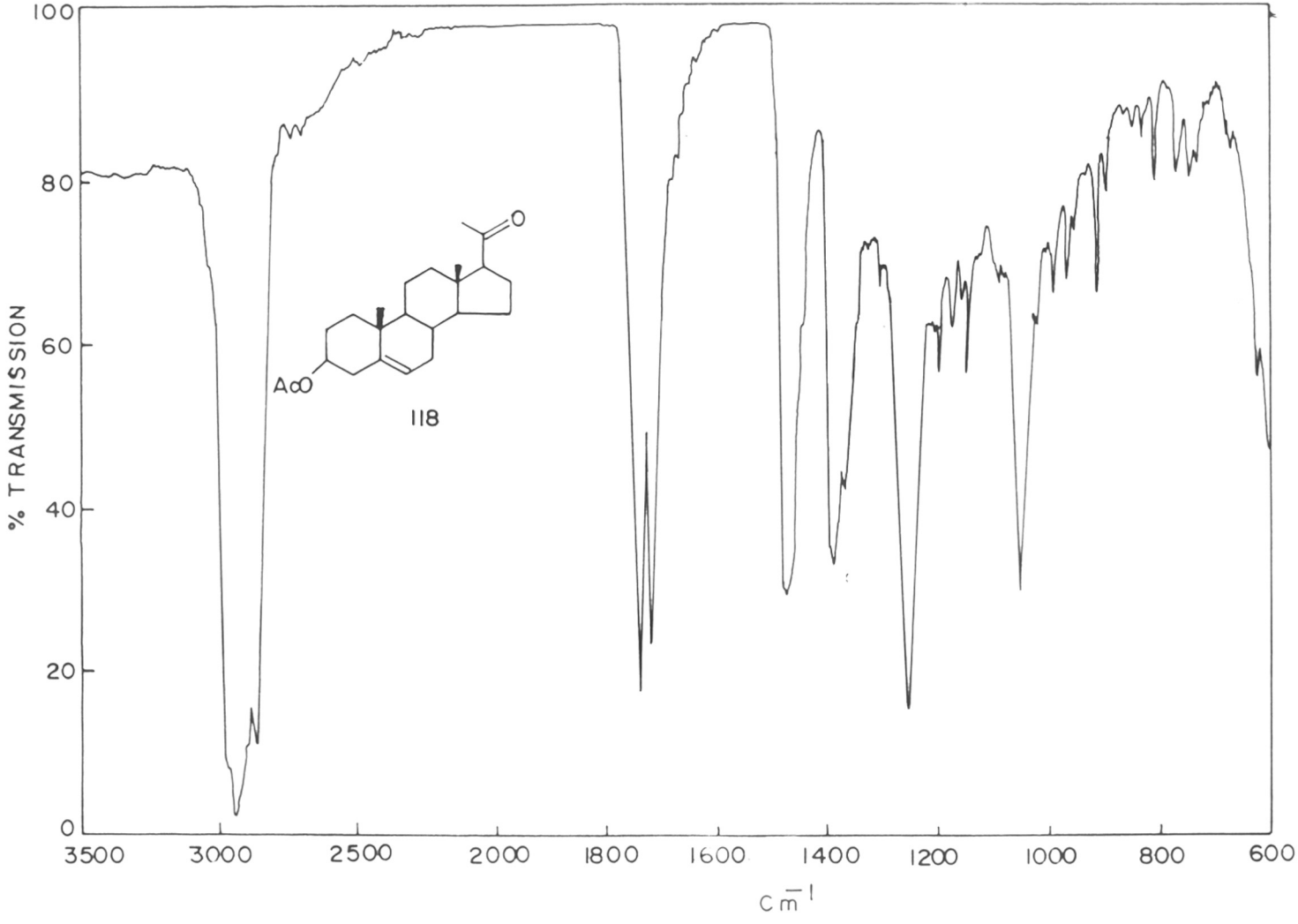
27. Ruzicka,L.; Hofmann,K. *Helv.Chim.Acta.* **1937**, 20, 1291-1297.

28. Danishefsky,S.; Nagasava,K.; Wang,N.J. *J.Org.Chem.* **1975**, 40, 1989-1990.

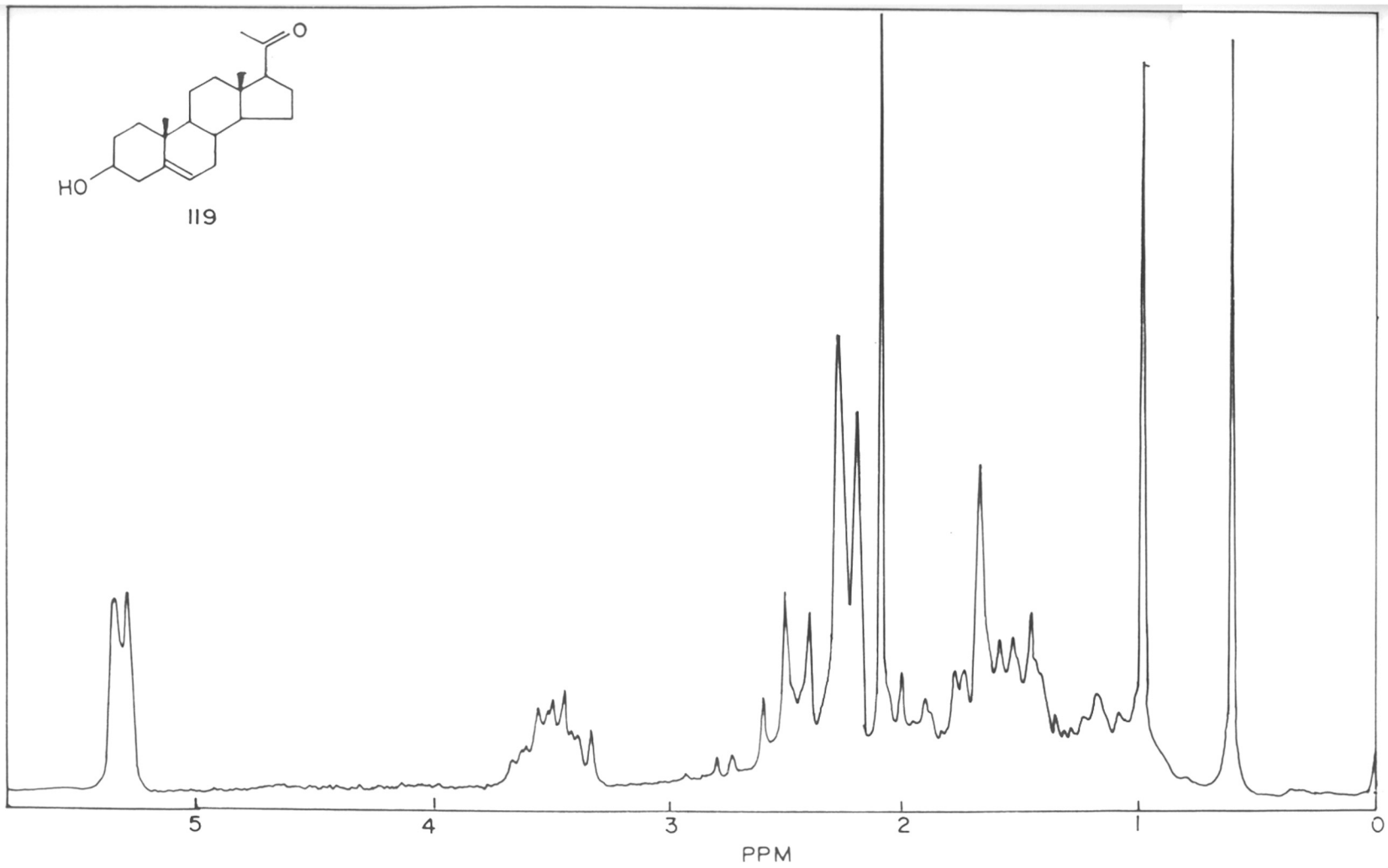
29. Hazra,B.G.; Pore,V.S.; Joshi,P.L. *J.Chem.Soc.Perkin Trans.1* **1993**, 1819-1822.

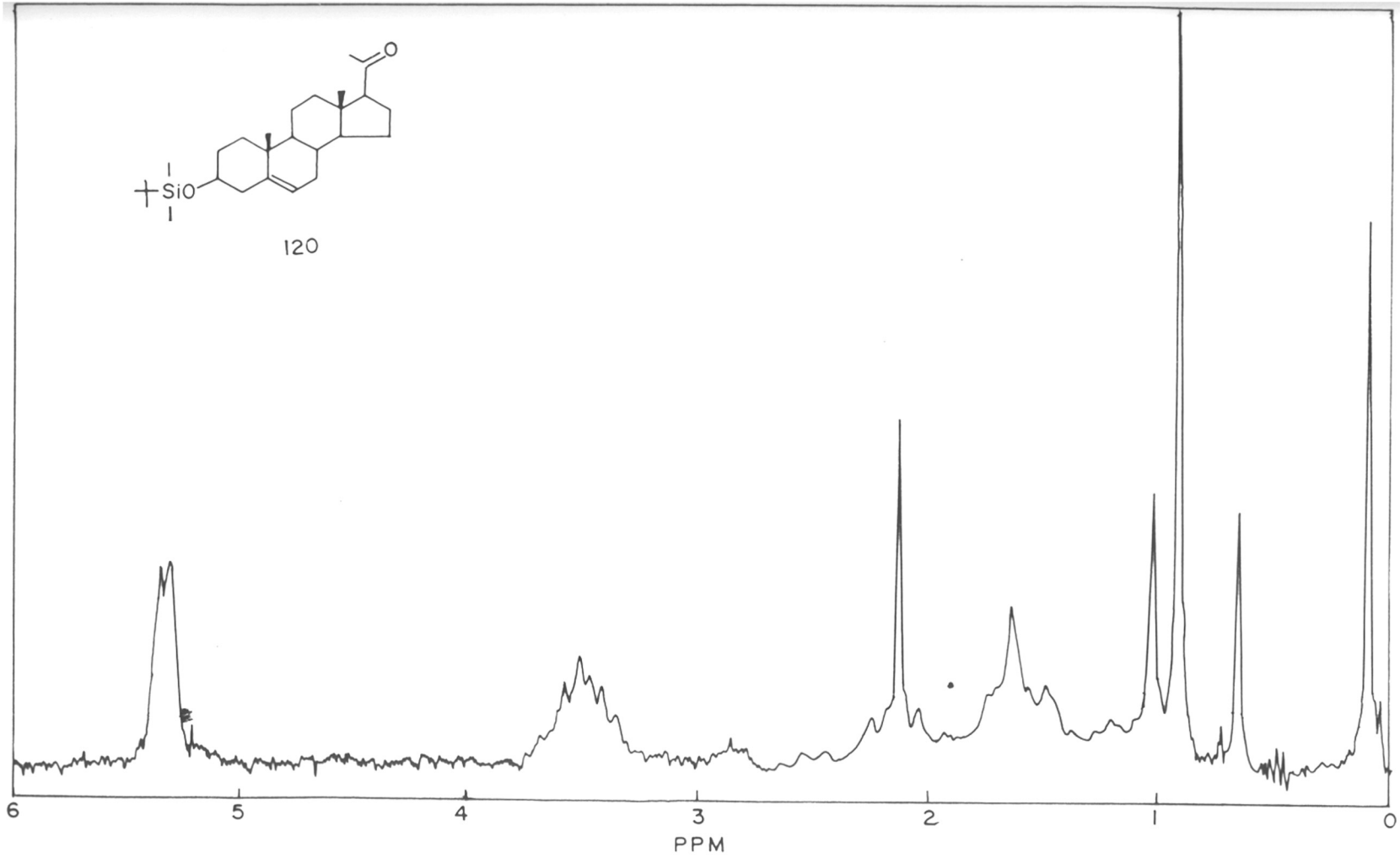


118

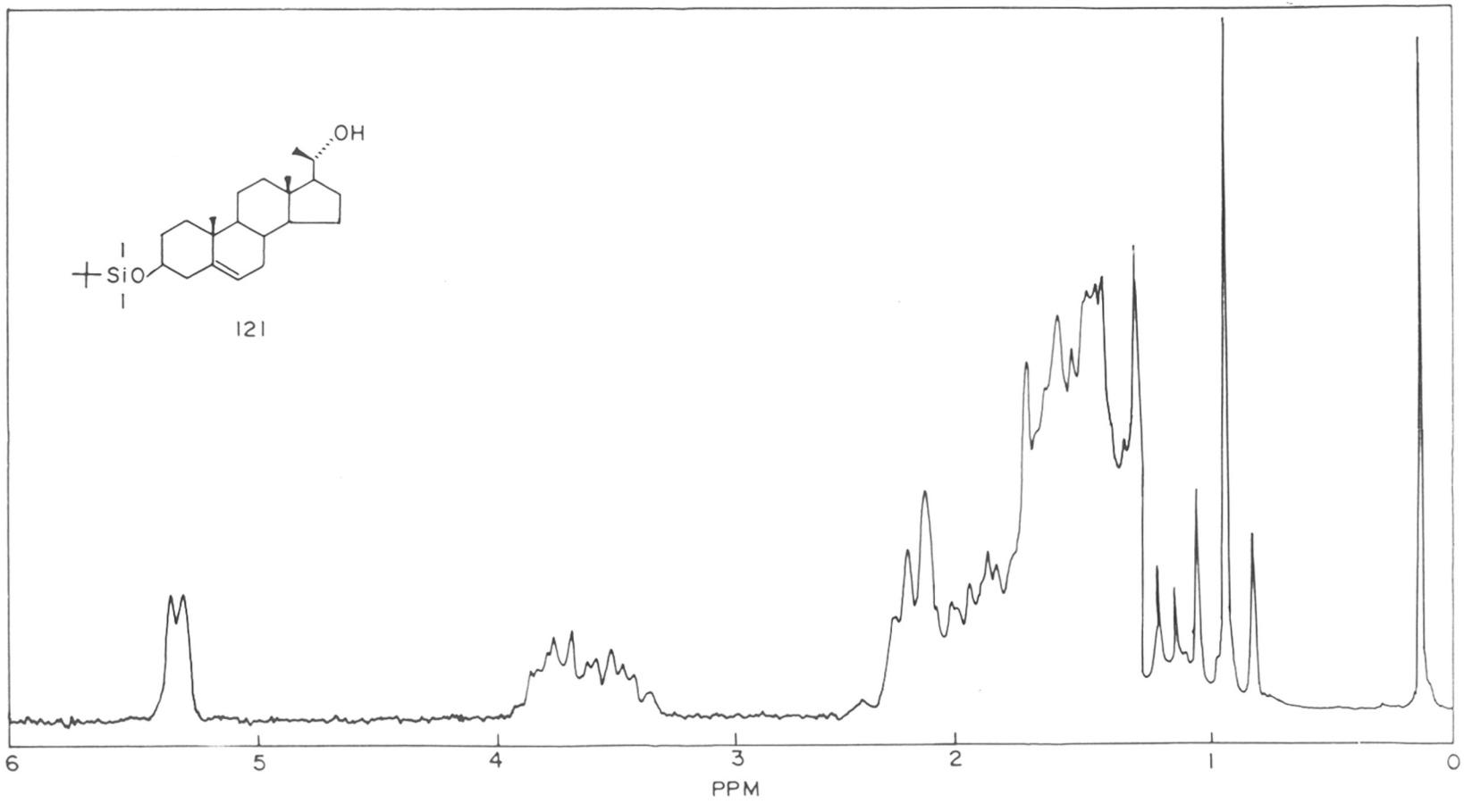

100
80
60
40
20
0
% TRANSMISSION
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
cm⁻¹
AcO
O

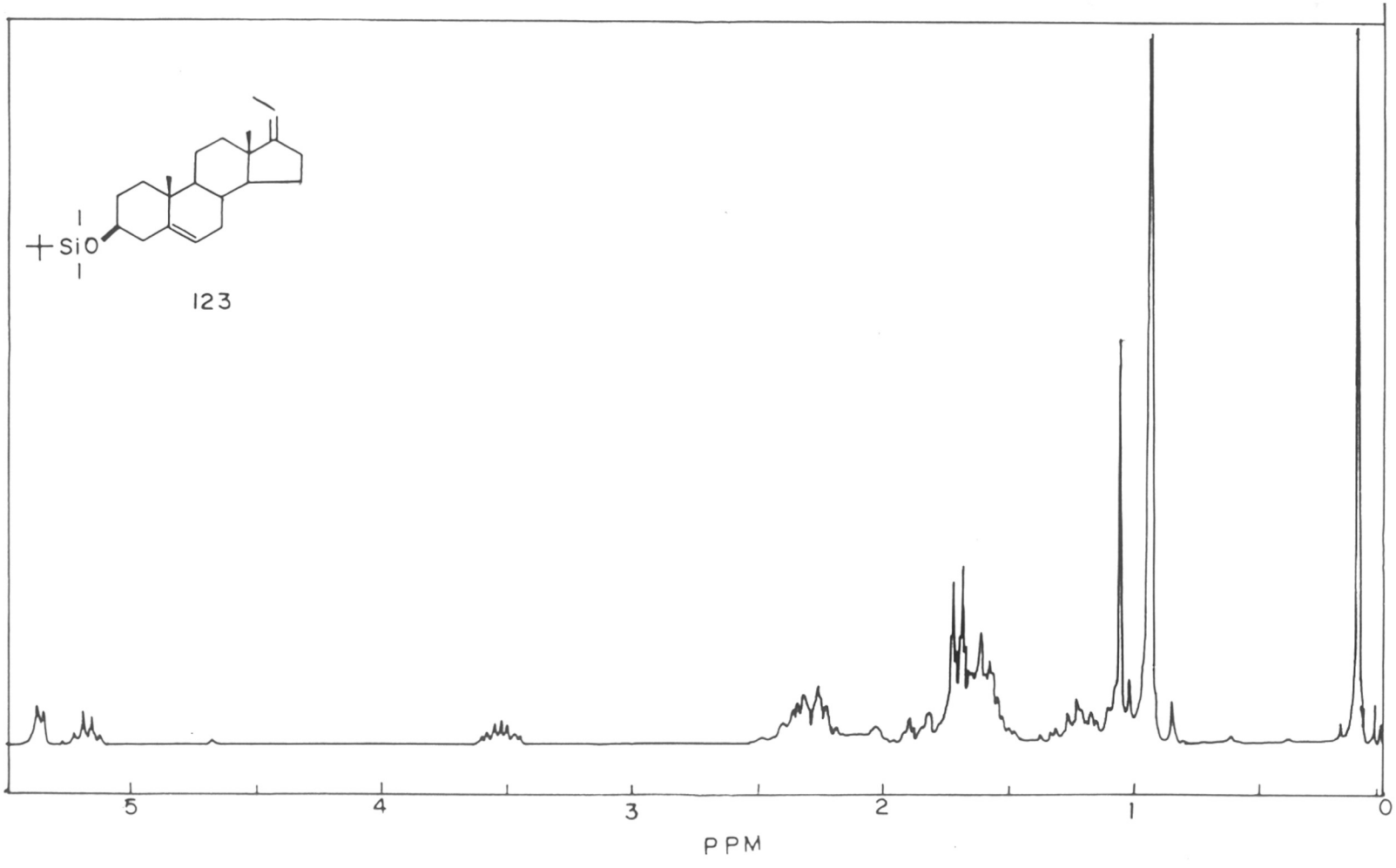
118


HO
O
119
5
4
3
2
1
0
PPM

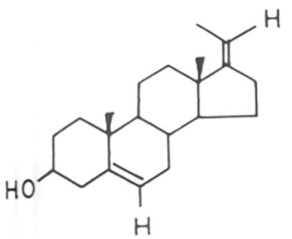


120

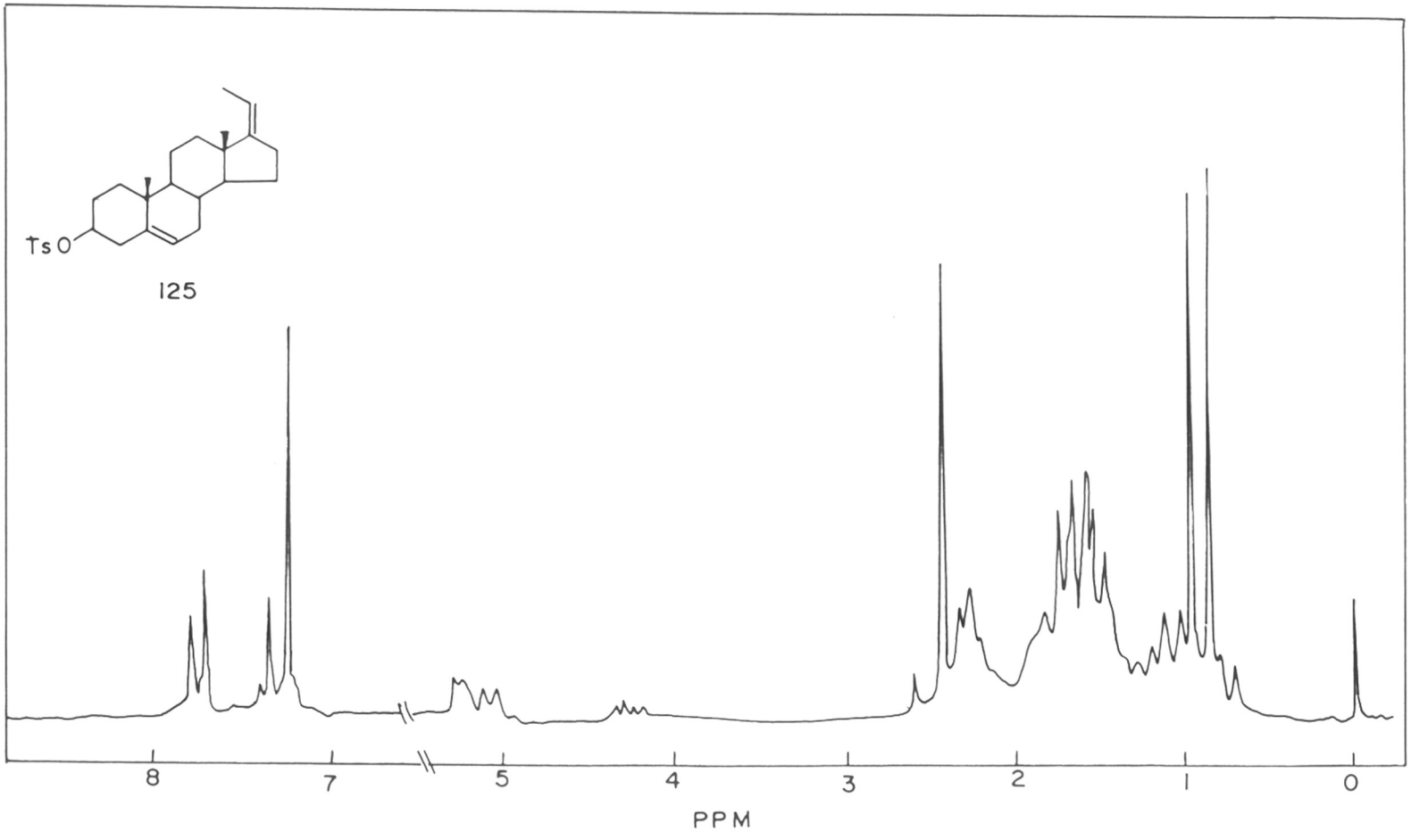

OH
Si
O
121
6
5
4
3
2
1
0
PPM

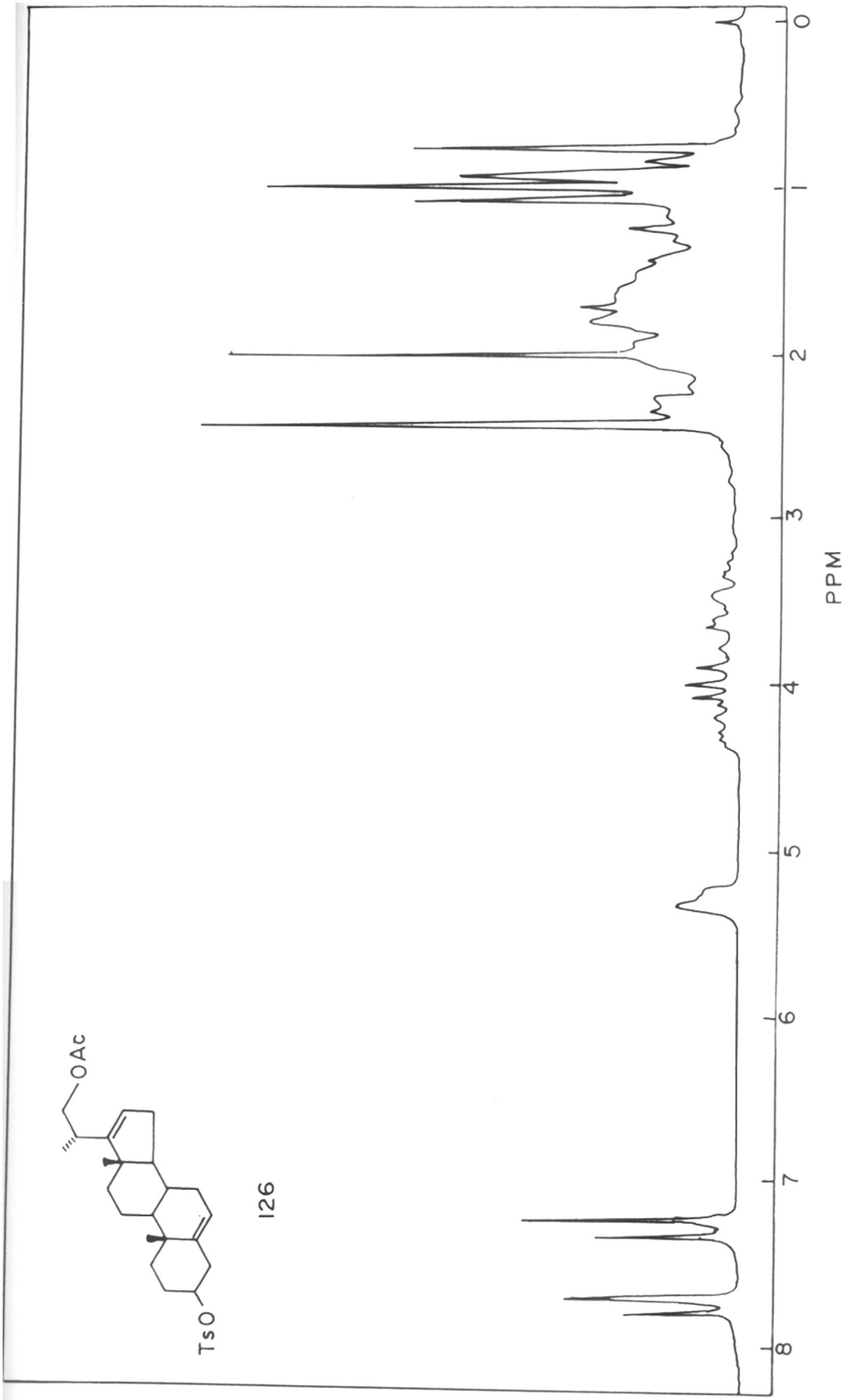


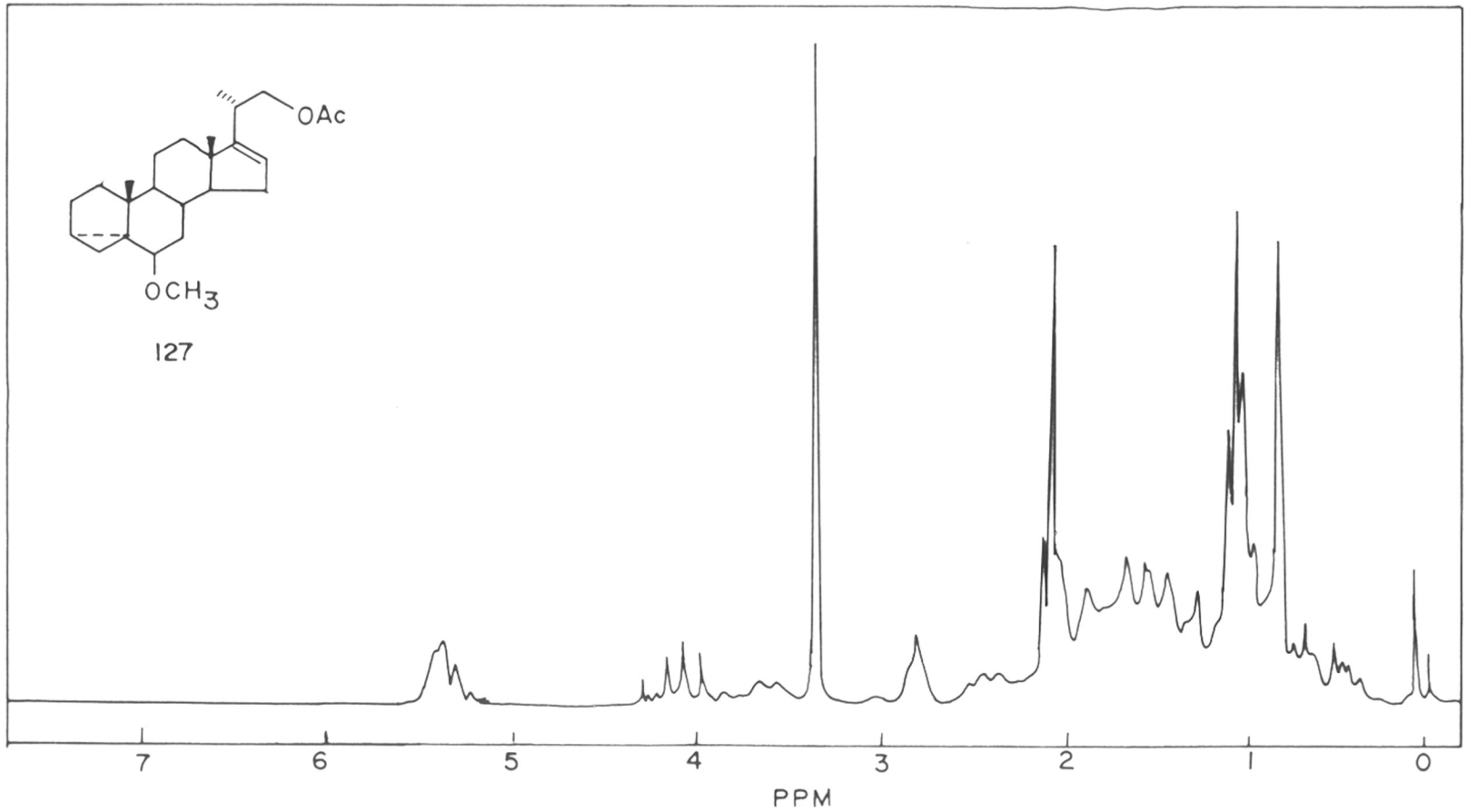
123

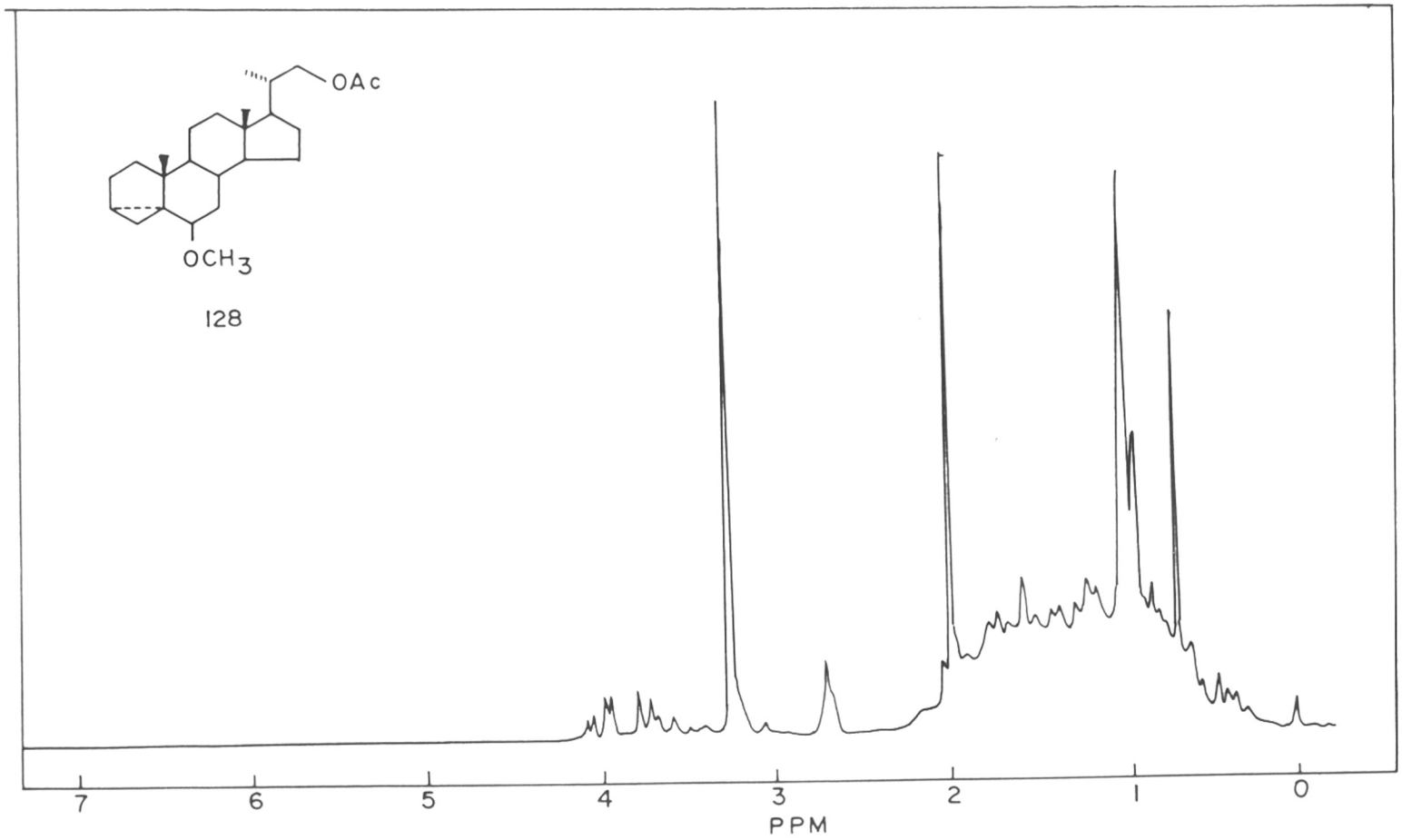


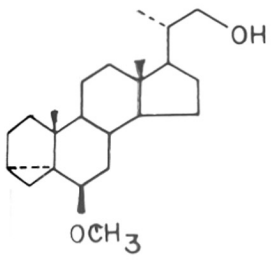
124


TsO
125
8
7
5
4
3
2
1
0
PPM

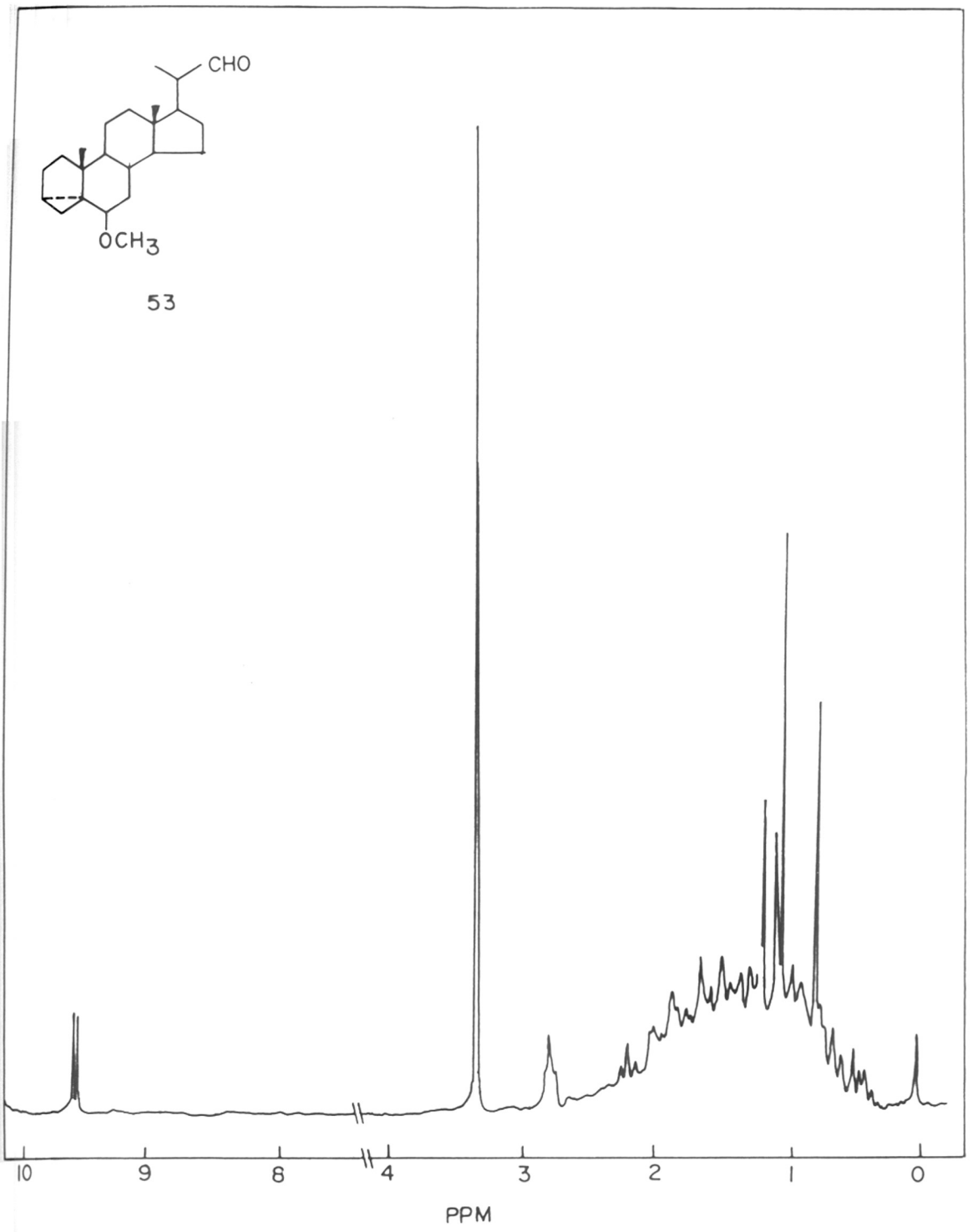

OAc
TsO
126
0
1
2
3
4
5
6
7
8
PPM

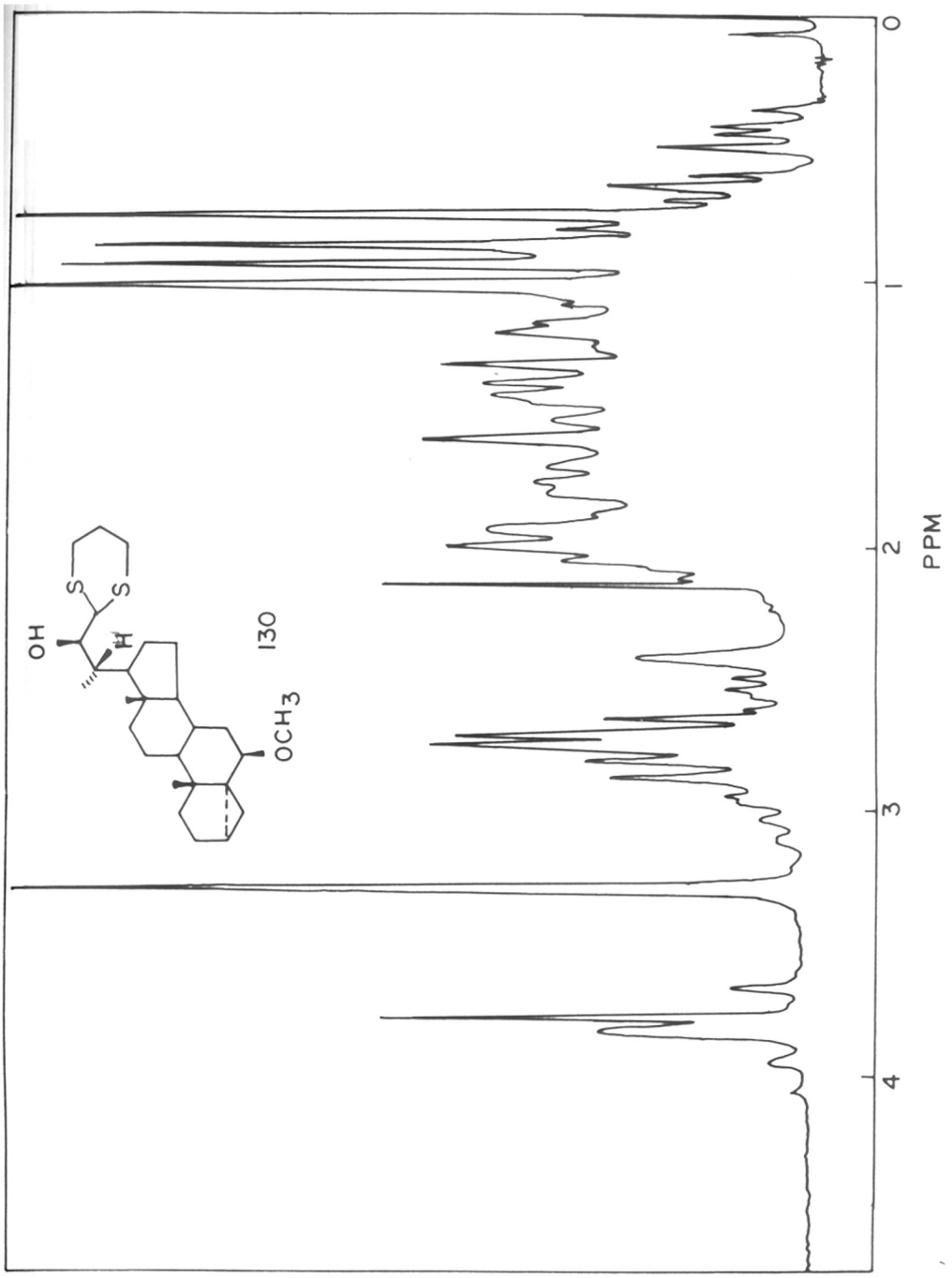

OAc
OCH3
127
7
6
5
4
3
2
1
0
PPM

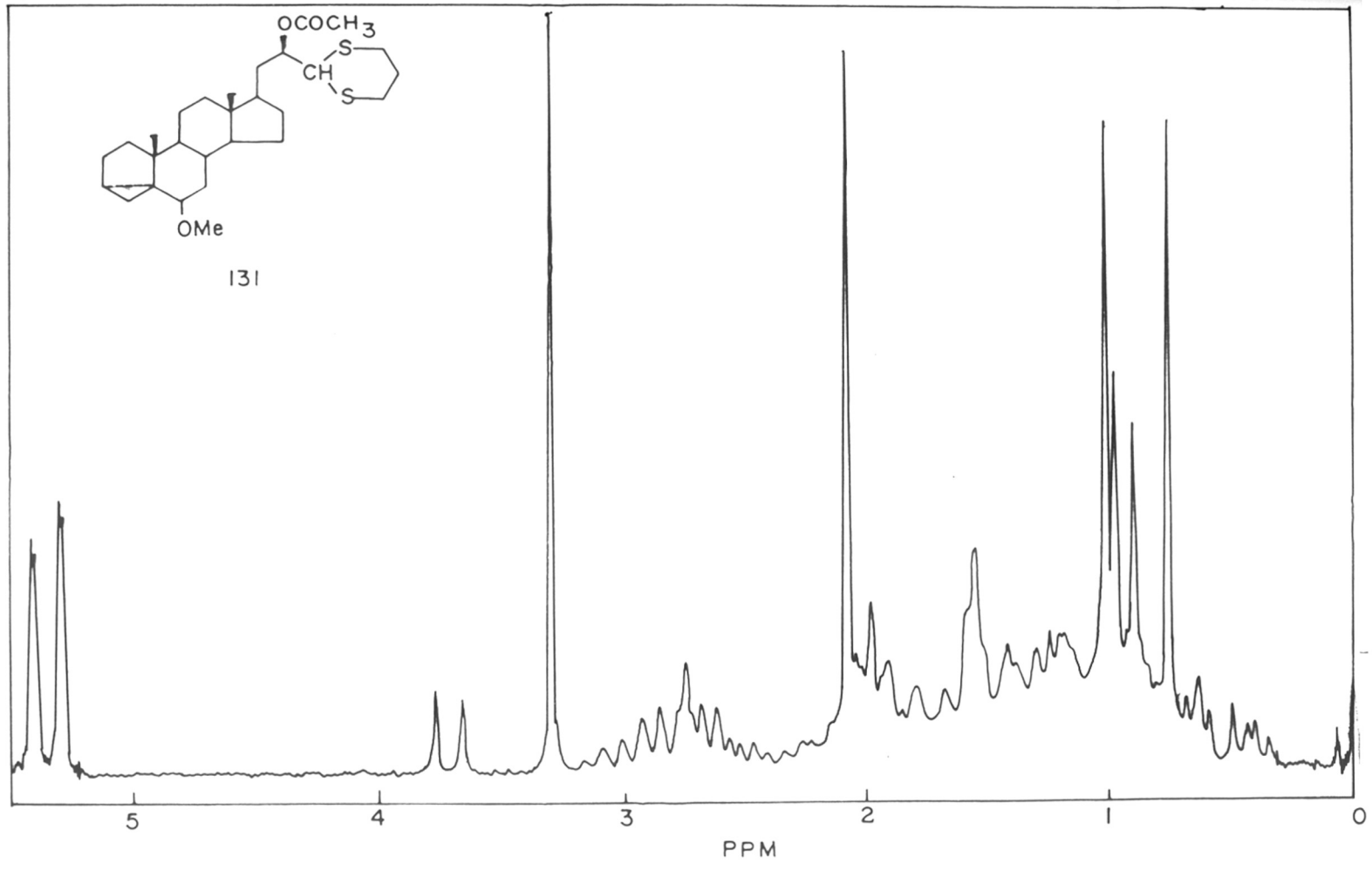

OAc
OCH3
128
7
6
5
4
3
2
1
0
PPM

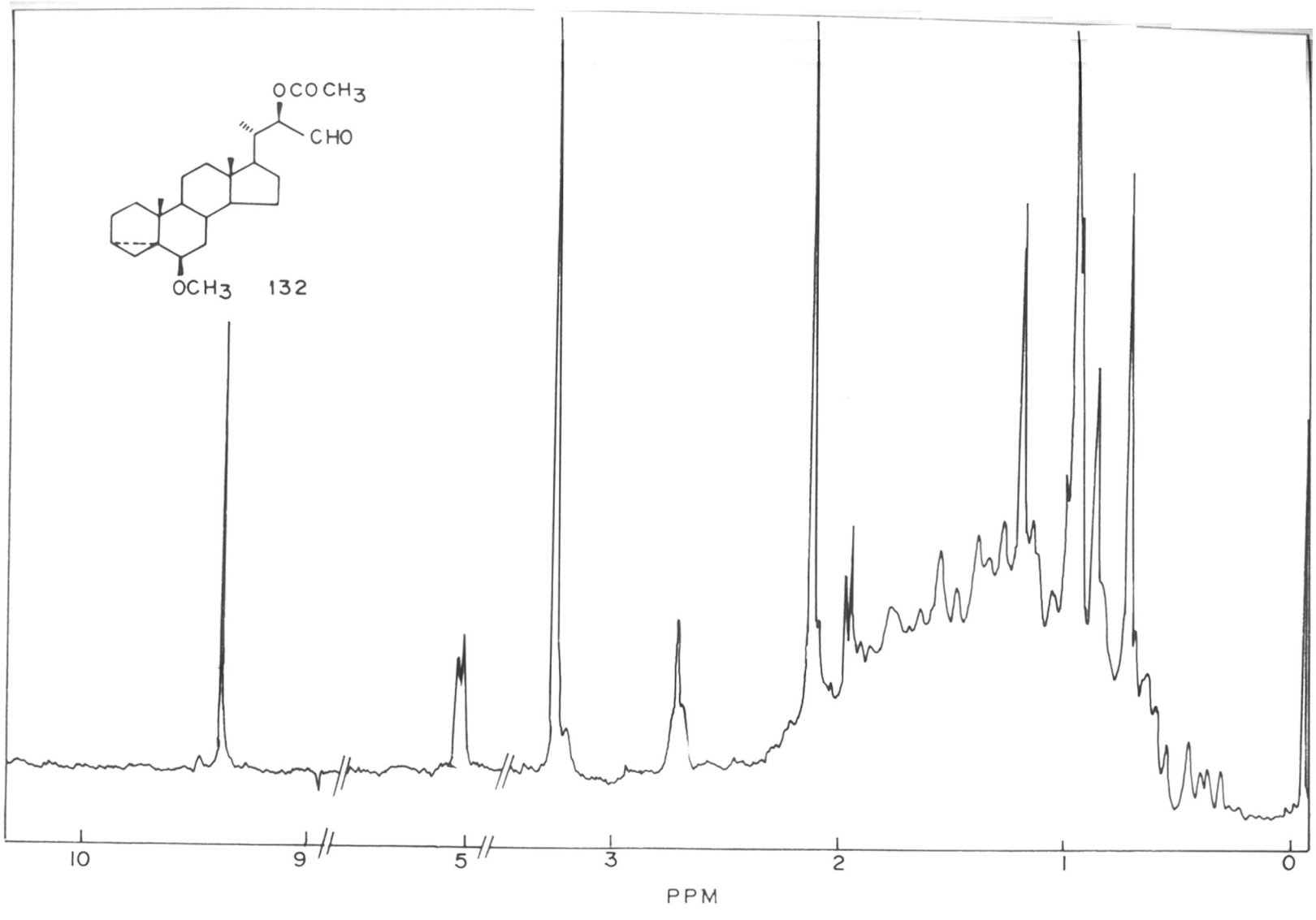


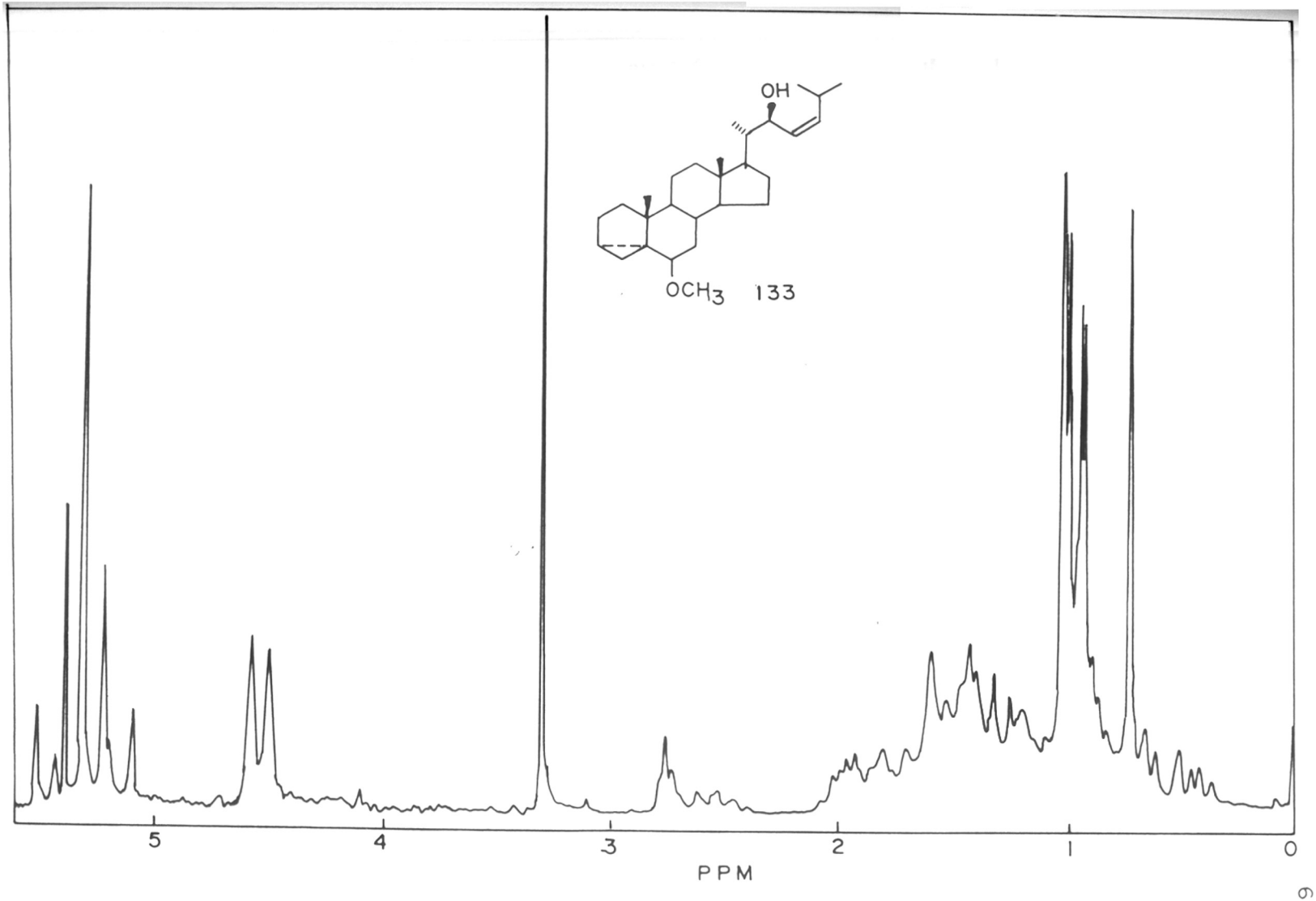
129

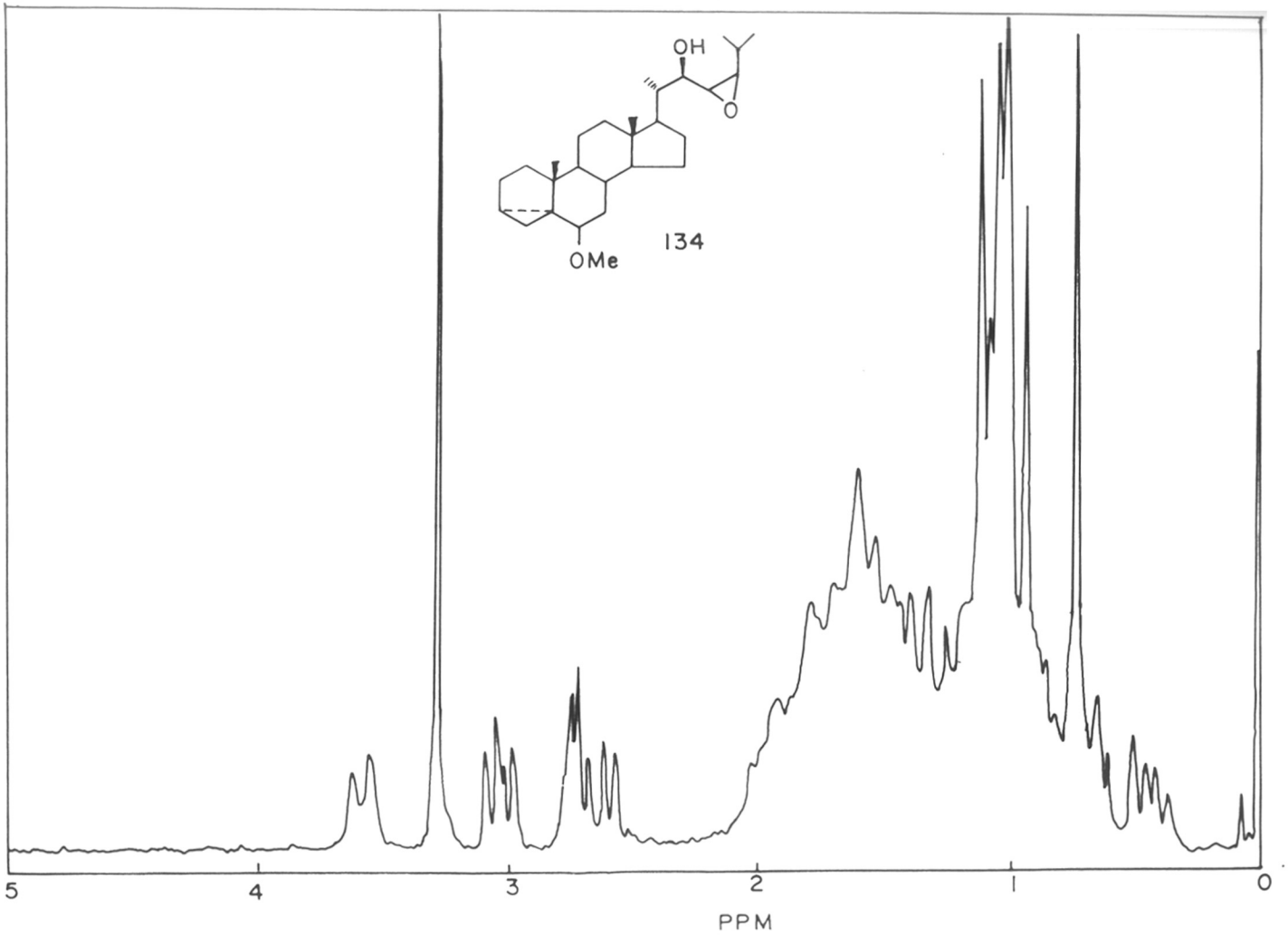

CHO
OCH3
53
10
9
8
4
3
2
1
0
PPM

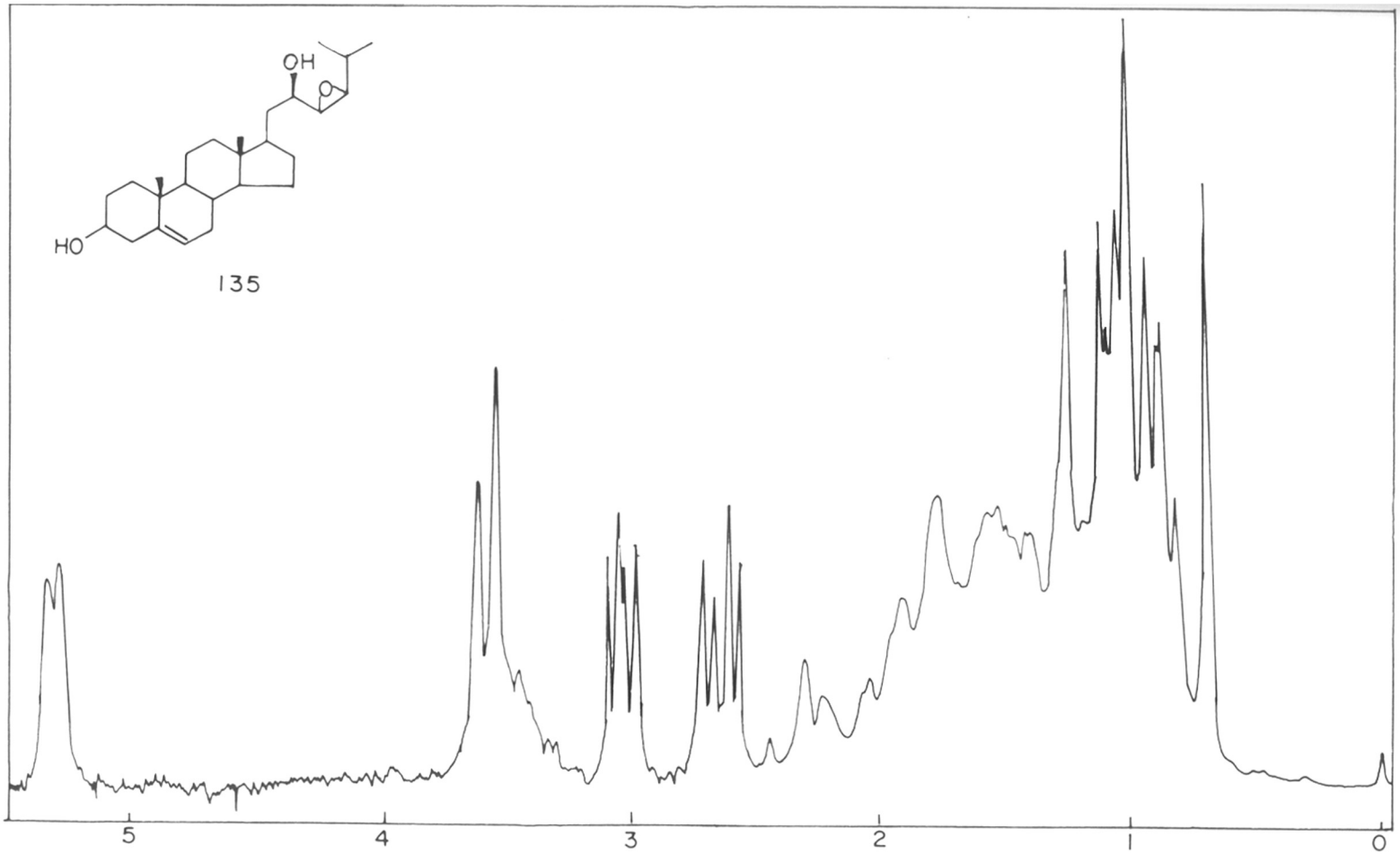

OH
S
S
H
OCH3
130
0
1
2
3
4
PPM

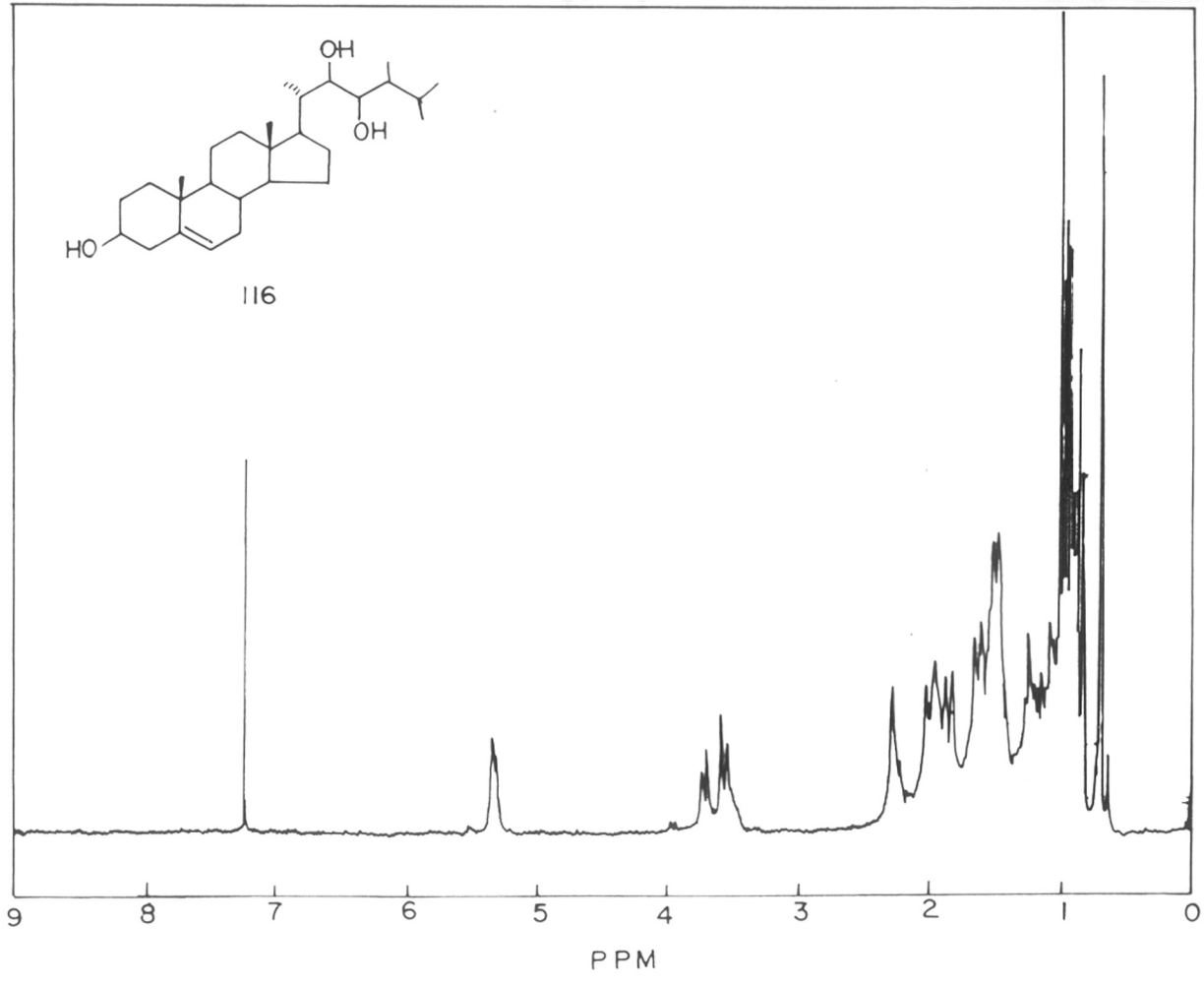

OCOCH3
S
CH
S
OMe
131
5
4
3
2
1
0
PPM


OCOCH3
CHO
OCH3
132
10
9
5
3
2
1
0
PPM


OH
OCH3
133
5
4
3
2
1
0
PPM


OH
O
OMe
134
5
4
3
2
1
0
PPM


OH
O
HO
135
5
4
3
2
1
0



116

CHAPTER II

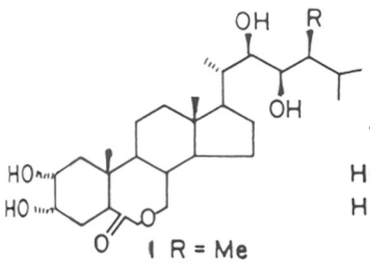
Synthesis of hexanor-20,22-dihydroxy-brassinolide from 16-dehydropregnenolone acetate.

Summary

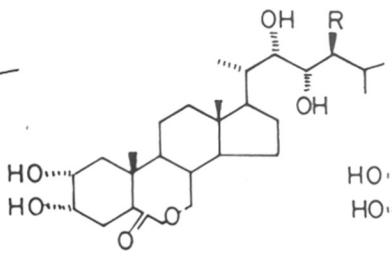
The structure and stereochemistry of brassinolide **1**, a novel plant growth promoting steroidal lactone,[1] isolated from the pollen of rape (*Brassica napus L.*) were determined by physical methods, including X-ray analysis and found to be 2α,3α,22R,23R-tetrahydroxy-24S-methyl-B-homo-7-oxa-5α-cholestan-6-one. Subsequent to the discovery of brassinolide **1**, several other compounds structurally and functionally related to brassinolide, collectively known as brassinosteroids were isolated, synthesised and their structure activity relationship have been studied. Thompson and coworkers[2] were the first to report the synthesis of two 22,23 isomeric brassinosteroids and a non-lactonic steroid (this type of B-ring-6-membered keto brassinosteroid was isolated afterwards from natural sources) with plant growth-promoting activity. A number of brassinosteroids with and without hydroxyl groups or an alkyl substituents in the side chain were synthesised by the same authors.[3] Brassinolide analogues (22S,23S)-28-norbrassinolide **2**, a lactam (6-aza-7-ketoanalogue) **3**, a thiolactam (6-aza-7-thiono analogue) **4** and an isomer (6-oxa-7-keto isomer) **5** of (22S,23S) homobrassinolide **6** were synthesised by Mori and coworkers.[4] The same authors[4] have synthesised several brassinolide analogues with or without the steroidal side chain. In bioassay, all these brassinosteroids are less active in comparison with the parent brassinolide **1**.

Very recently, Kerb and coworkers have reported[5] the synthesis of hexanor-brassinolide-22-ethers with plant growth-promoting activity, starting from 20S-acetoxymethyl-5α-pregnane-3,6-dione **45**. The growth promoting activity of these hexanor brassinolide 22-ethers showed typical brassinolide activity in the bean second-internode assay, and the effects are comparable to those of the referred 28-homobrassinolide **17**. With this type of lead regarding activity, shown by hexanor-brassinolide 22-ethers, we decided to synthesise hexanor-brassinolide C-20, C-22-dihydroxy, C-20, C-22 diether as target molecule starting from 16-dehydropregnenolone acetate **50**. This chapter deals with the multistep synthesis of this hexanor-brassinosteroid.

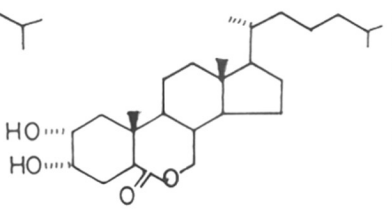
Chart I



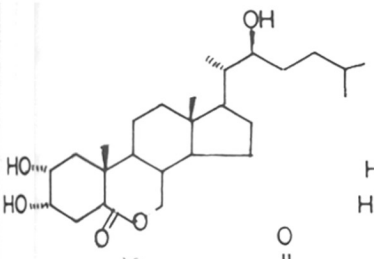
1 R = Me
17 R = Et



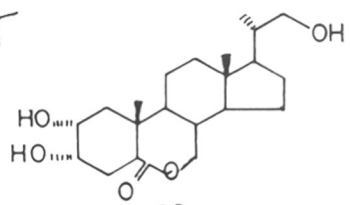
6 R = Et
2 R = H



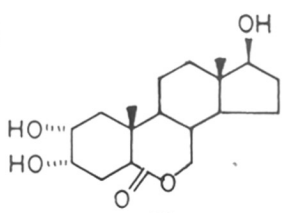
18



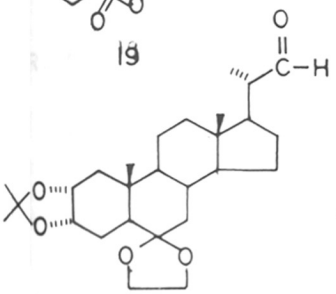
19



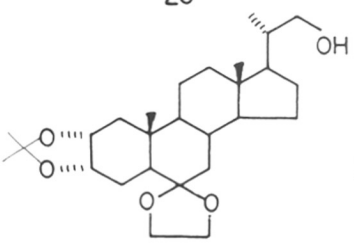
20



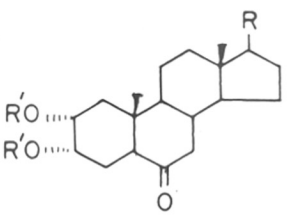
21

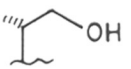


22

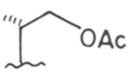


23

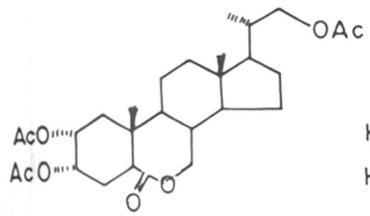


24 R = 

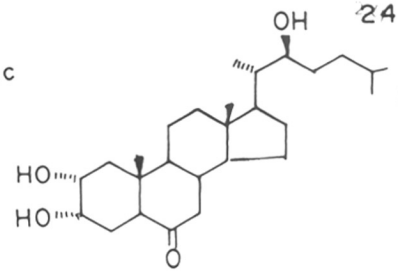
R' = H

R = 

R' = Ac

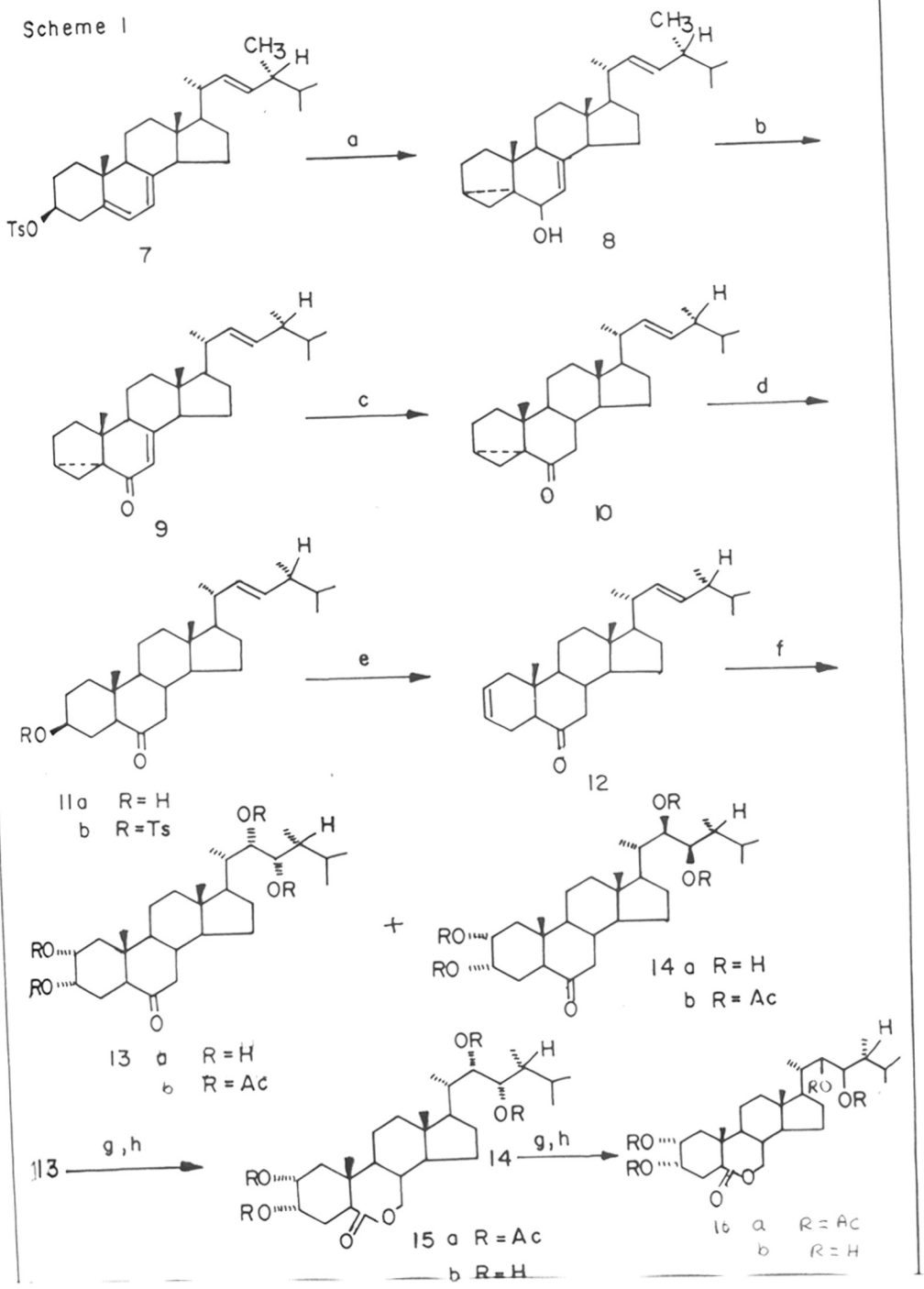


25



26

Scheme I



Reagents and Conditions

a. $NaHCO_3$, Me_2CO, H_2O; b. CrO_3, py.; c. Li/liq. NH_3; d. AcOH-5N H_2SO_4, Δ, NaOH; e. LiBr, DMF, Δ; f. OsO_4, py. Benzene; g. *m*-CPBA, $CHCl_3$; h. K_2CO_3, aq. MeOH.

Introduction

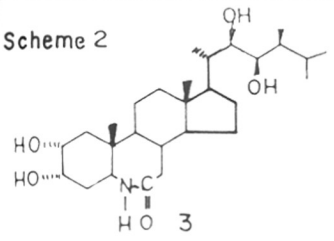
Synthesis of several brassinolide analogues have been reported by Thompson et al[2,3]. They have synthesised 22,23-isomeric brassinosteroids **15b** and **16b**, non-lactonic steroids **14a** with plant growth-promoting activity. In the bean second internode bioassay compound **14a, 15b, 16b** showed brassin activity, a unique biological response of cell elongation and cell division that results in elongation, swelling, and finally splitting of the treated internodes. The ketone **14a** induced more elongation (relative to curvature and swelling), while the ketone **13a** exhibited no brassin activity. The lactones **15b** and **16b** caused marked curvature and swelling in the concentration range 0.01-10μg/plant. In addition, the lactones **15b** and **16b** under certain conditions (1-10μ range) cause an internode splitting response that is a distinguishing characteristic for brassinolide at the 0.1-10μg range. The synthesis of **14**, **15** and **16** is depicted in **Scheme 1**.

Solvolysis of ergosterol 3-β-tosylate **7** gave *i*-ergosterol **8**. Oxidation of **8** to **9** was achieved with chromic acid in pyridine followed by reduction of **9** with lithium and liquid ammonia yielded compound **10**. Acid catalysed rearrangement of **10** by refluxing it in acetic acid/5N H_2SO_4 followed by saponification of the resulting acetate furnish 3β-hydroxy-24β-methyl-5α-cholest-22-en-6-one **11a**. The detosylation of **11b** in DMF, LiBr at refulx temperature yielded **12** in 70% purified yield. Treatment of **12** for 3 days at room temperature in dry benzene containing trace of pyridine and 2 molar equivalent of osmium tetroxide furnished quantitatively 1:1 mixture of **13a** and **14a**. The tetrahydroxy ketones were separated by column chromatography over neutral alumina. A Baeyer-Villiger oxidation of the tetraacetate **13b** and **14b** in $CHCl_3$ with m-CPBA gave lactones **15a** and **16a** respectively.

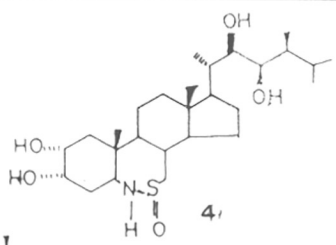
Saponification of **15a** with 4% K_2CO_3 in 70% aq. methanol followed by acidification with dil. hydrochloric acid afforded **15b**. Saponification of **16a** furnished a brassinosteroid **16b** (2α,3α,22α,23α-tetrahydroxy-24β-methyl-B-homo-7-oxa-5α-cholestane-6-one).

The same authors[3] have synthesised brassinosteroids with and without hydroxyl groups or an alkyl substituents in the side chain (**Chart 1**). All these brassinosteroids have been synthesised from stigmasterol, ergosterol, 22,23-dehydrocamphesterol, brassicasterol and cholesterol. Plant growth-promoting activity of all these brassinolide analogues is found to be less as compared to the parent brassinolide **1**.

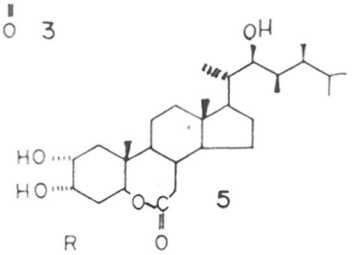
Scheme 2



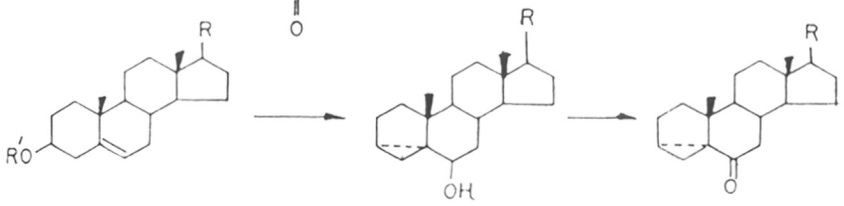
3



4



5



27a R = R'=H 29 R =

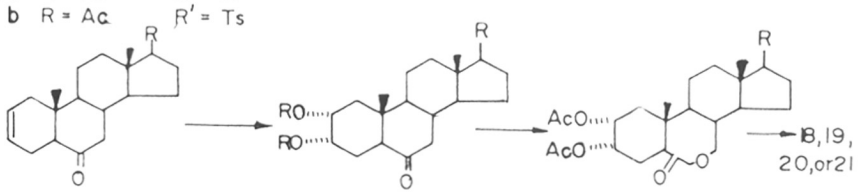
b R = R=Ts 30 R = Ac

28a R = Ac R′ = H

b R = Ac R′ = Ts

31 R =

32 R = Ac



18, 19, 20, or 21

33 R =

34 R = Ac

35a R = R′ = H

b R = R′ = Ac

36a R = R′ = H

b R = R′ = Ac

37a R = R′ = H

b R = R′ = H

38a R = Ac R′ = H

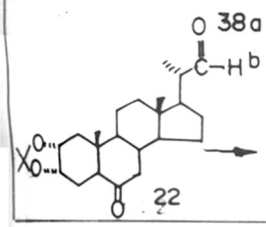
b R = Ac R′ = Ac

39 R =

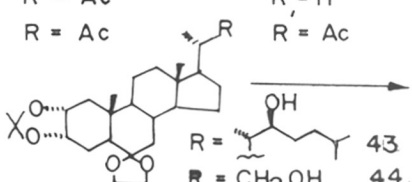
40 R =

41 R =

42 R = OAc



22



R = 43

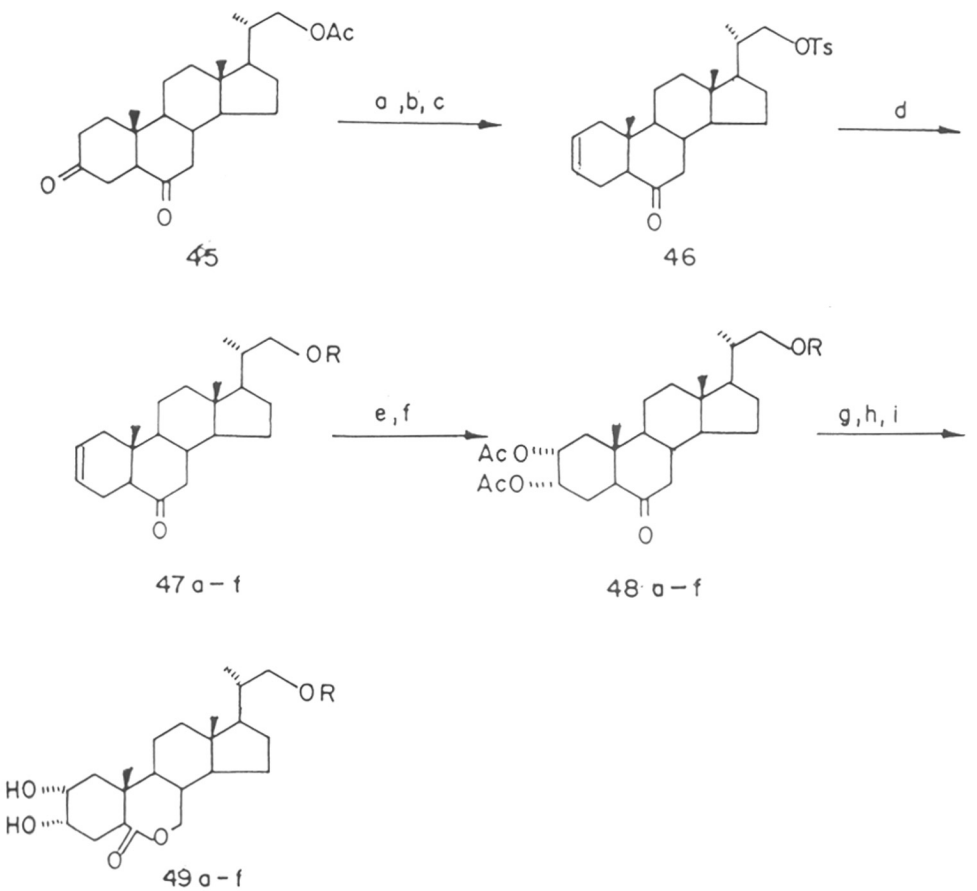
R = CH_2OH 44

36a or 37a

Synthesis of brassinolide analogues substituted with hetero atoms in ring B were reported by Mori et al[4]. The lactam **3** and thiolactam **4** were found to be inactive. This indicates the importance of the ring B-lactone or ketone system. The synthesis of (22R,23R)-homobrassinolide **17**, (22S,23S)-homobrassinolide **6** and (22S,23S)-28-norbrassinolide **2** were reported by Mori and coworkers[4]. A bioassay of these three brassinosteroids revealed that the order of activity is **1> 17> 6> 2>**. In order to define further the structure activity relationship among brassinosteroids, four analogues brassinosteroid **18-21**[4] were synthesised. The biological activity of these analogues was estimated by lamina-inclination test with rice seedlings. The relative activity of these analogues as compared with brassinolide **1** and (22S,23S)-homobrassinolide **6** was **1 : 6 : 18 : 19 : 20 : 21: = 100 : 10 : 1~2 : 2 : 2 : 0.001**. Hence the existance of the steroidal side chain with proper array of the substituents is indispensable for the high plant growth-promoting activity of brassinosteroids. The brassinolide analogues **22-26** were also synthesised[4]. Compound **17** which has the same functional groups of brassinolide on ring A and B and differs only at carbon 24 (Et instead of Me) showed $1/10^{th}$ of the activity of brassinolide **1** in the lamina inclination test on rice seedlings. However, other brassinolide analogues with modified ring A were poorly active, and an analogue with modified ring B, 6-oxa-ketone showed only $1/100^{th}$ of the activity of its 7-oxa-ketone isomer, suggesting the 2α,3α-dihydroxy-7-oxa-6-ketone moiety is one of the requisites for the biological activity. Synthesis of brassinolide analogues with or without the steroidal side chain are presented in **Scheme 2**.

The starting material for the synthesis of **18** is cholesterol **27a**. This was converted by the known procedure to a ketone **31** *via* **27b** and **29**. Treatment of **31** with *p*-toluenesulfonic acid in sulfolane gave **33**. Hydroxylation of **33** with osmium tetroxide and N-methylmorpholine N-oxide yielded a diol **35a**. The corresponding acetate **35b** was subjected to the Baeyer-Villiger oxidation to give a lactone **39**. This was converted to the desired 22,23-bisdeoxy-28-norbrass inolide **18** in the conventional manner. For the synthesis of **19** and **20**, a known aldehyde **22** was employed as a starting material. Addition of isoamylmagnesium bromide to **22** afforded the alcohol **43**. After removing the protective groups, a triol **36a** was obtained. The Baeyer-Villiger oxidation of the corresponding acetate **36b** yielded a lactone **40**. This gave 23-deoxy-28-norbrassinolide **19**, after alkaline hydrolysis and acidification. To synthesise **20**, the aldehyde **22** was reduced with lithium aluminium hydride to get alcohol **44**. Removal of the protecting groups yielding a triol **37a**, whose acetate **37b** was oxidised with CF_3COOOH to give a lactone **41**. After alkaline hydrolysis and

SCHEME 3



(a) R=Me; (b) R=Et; (c) R=n-pr; (d) R=t-Bu; (e) R=CH_2-CH_2OCH_3; (f) R=$CH_2CH_2O^tBu$.

Reagents and conditions:

(a) $(Me)_3SiCl/Zn$ 65%; (b) KOH, MeOH, 92%, (c) TSCl/py 95%; (d) ROK, ROH 95%; (e) NMO/OsO_4 80%; (f) Ac_2O, py 95%; (g) $(CF_3CO)_2O$, 30% H_2O_2, 75%; (h) KOH/MeOH 95%; (i) H_2O, H^+.

relactonisation with dilute HCl yielded triol **20**. The synthesis of **21** was carried out from pregnenolone **28a**. Solvolysis of pregnenolone tosylate **28b** yielded i-alcohol **30**. This after oxidation and acid catalysed rearrangement furnished unsaturated ketone **34**. Oxidation of **34** with osmium tetroxide, followed by Baeyer-Villiger oxidation of triacetate **38b** gave the acetatelactone **42**. This on saponification followed by treatment with acid gave the brassinolide analogue **21**.

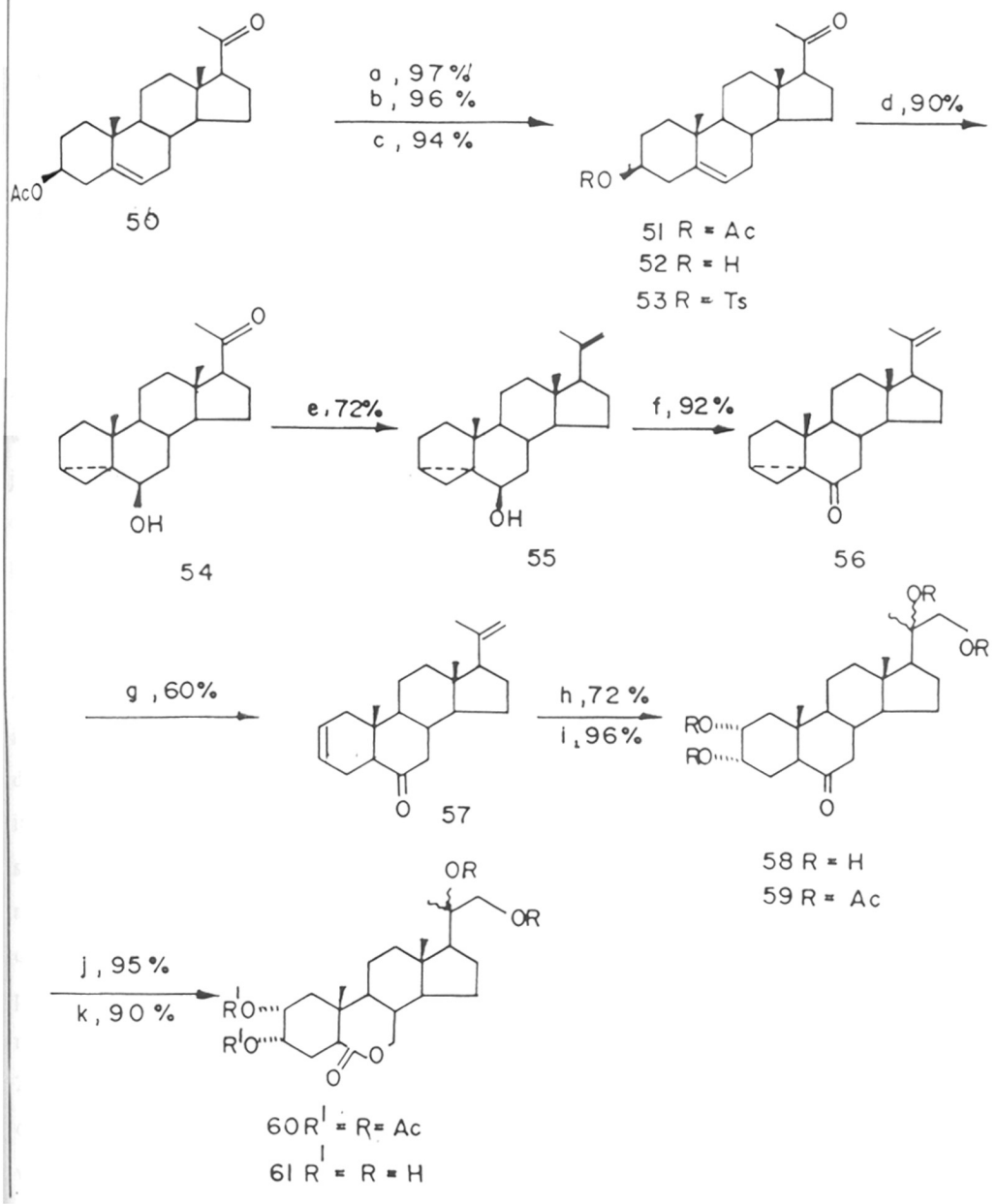
Ikekawa and coworkers[6] have synthesised 28-norbrassinolide (2α,3α,22R,23R-tetrahydroxy-B-homo-7-oxa-5α-cholestan-6-one), which is an analogue of the plant growth promoting steroidal lactone, brassinolide was synthesised *via* 22R,23R-dihydroxycholesterol. Synthesis of other C-22,23 stereoisomers of 22,23-dihydroxycholesterol were also described by these authors.

Recently, Kerb et al.[5] reported the synthesis of hexanorbrassinolide-22-ethers **49a-f** with plant growth promoting activity. These compounds do not possess the three asymmetric centres (C22, C23, C24) of the brassinolide side chain. These compounds **49a-f** were prepared from 20S-acetoxy-5α-pregnane-3,6-dione **45** in few steps, as shown in Scheme 3.

Reduction of **45** with chlootrimethylsilane and zinc gave the Δ^2-6-ketone, which was hydrolysed and tosylated to get **46**. The ether groups were introduced with potassium alcoholates to yield **47a-f**. The 2α,3α-cis dihydroxylation of the Δ^2-double bond with N-methyl morpholine-N-oxide (NMO) and a catalytic amount of osmium tetroxide gave the 2α,3α-diols, which were acetylated to furnish compounds **48a-f**. The synthesis of **49a-f** was completed by Baeyer-Villiger oxidation with trifluoroperacetic acid to the B-ring lactone, hydrolysis and relactonisation.

The plant growth promoting activity of the brassinosteroid derivatives was measured with the Bean-Second-Internode-Bioassay. These hexanor-brassinolide 22-ethers reveals that these compounds showed typical brassinolide activity in the Bean-Second-Internode Assay. With 50μg or 100μg, they showed effects comparable to those of the referred 28-homobrassinolide **17**. The increasing order of the activity for different ethers is **49b** > **49c** > **49a** > **49e**

Scheme 4



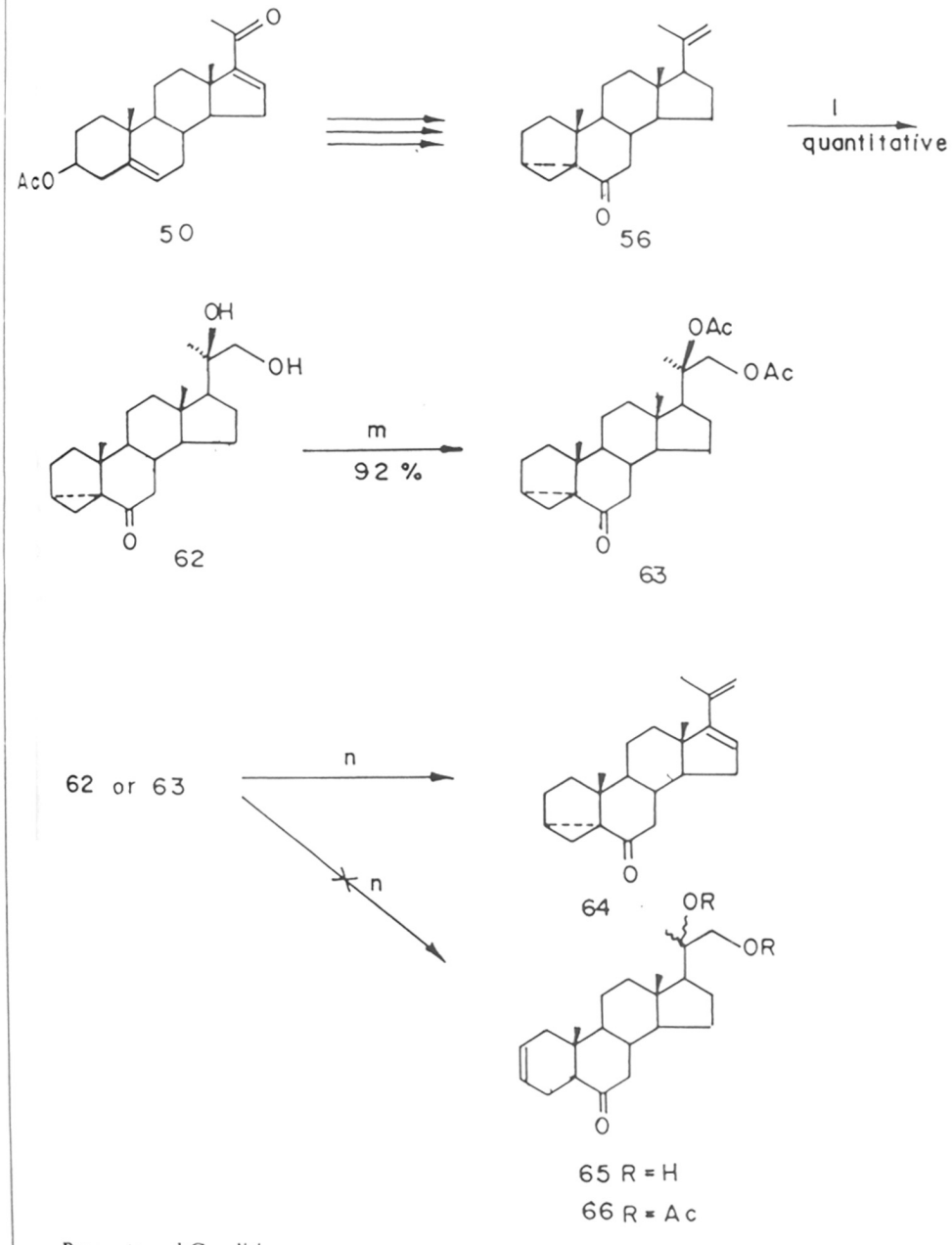
Reagents and conditions: (a) Pd/C, H_2, 45 *psi*, 30°C, 15h. (b) KOH, *tert*-butanol, H_2O, 30°C, 16h. (c) *p*-TSCl, pyridine, 30°C, 24h. (d) CH_3COOK, acetone, H_2O, Δ 20h. (e) KO^{t}Bu, *t*-BuOH, THF, $Ph_3P^+CH_3I^-$, Δ 6h. (f) Jones reagent, 0°-5°C, 10 min. (g) Pyridinium *p*-toluene sulfonate, DMF, LiBr, Δ 3h. (h) OsO_4, benzene, pyridine, 30°C, 52h. (i) acetic anhydride, pyridine, DMAP, 30°C, 16h. (j) $(CF_3CO)_2O$, H_2O_2, CH_2Cl_2, 5-10°C, 2h. 25°C, 20h. (k) K_2CO_3, MeOH, Δ 6h.

Present Investigation

Encouraged by the plant growth-promoting activity of these hexanor-brassinolide 22-ethers **49a-f**, we planed to synthesise hexanor-brassinolide with two hydroxyl groups at C-20 and C-22 position starting from 16-dehydropregnenolone acetate. This chapter reveals in detail the multistep synthetic steps carried out to achieve this goal.The synthesis of hexanor- 20,22-dihydroxy- brassinolide **61** is summarised in **Scheme 4**.

16-Dehydropregnenolone acetate **50** was subjected to partial hydrogenation over Pd/C in ethyl acetate, furnished pregnenolone acetate **51** in quantitative yield. The course of the reaction was followed by IR spectroscopy. The disappearance of IR absorption band at 1670 cm^{-1} for conjugated carbonyl group and its shift towards higher frequency 1712 cm^{-1} indicated the completion of reaction. The hydrolysis of 3β-acetate group of **51** with aqueous KOH in *tert*-butanol afforded pregnenolone **52** in 96% yield. The protection of 3β-hydroxyl group of **52** with *p*-toluenesulfonyl chloride in dry pyridine gave 3β-*p*-toluenesulfonoxy-pregna-5-ene-20-one **53** in 94% yield. The solvolysis of tosylate **53** with potassium acetate in aqueous acetone furnished the ketoalcohol **54** in almost quantitative yield. Wittig reaction on *i*-alcohol **54** with triphenylphosphoniummethyl iodide in THF-*tert*-butanol using $KOBu^t$ as a base yielded the *i*-alcohol **55** in 70% yield. The oxidation of 6β-OH group of **55** with Jones reagent afforded 3α,5-cyclo-pregna-20(22)-ene-6-one **56** in 97% yield. The rearrangement of *i*-ketone **56** with lithium bromide, pyridinium *p*-toluene sulfonate in refluxing DMF gave a crude mixture from which pregna-2,20(22)-diene-6-one **57** was separated by column chromatography on neutral alumina in 60% yield. The dihydroxylation of dienone **57** with catalytic amount of osmium tetroxide with N-methyl-morpholine-N-oxide did not proceed cleanly and the required tetrol **58** was not formed in the reaction. Therefore, we have used molar equivalent of osmium tetroxide to effect this chemical conversion. The dihydroxylation of 2,20(22)-diene-6-one with 2 equivalent of osmium tetroxide in dry benzene and catalytic amount of dry pyridine yielded after column chromatographic purification 72% of tetrol **58**. The tetrol **58** was acetylated using acetic anhydride, pyridine and a catalytic amount of 4-dimethylaminopyridine to obtain tetraacetate ketone **59** which on Baeyer-Villiger oxidation with trifluoroperacetic acid, prepared from trifluoroacetic anhydride and hydrogen peroxide gave the tetraacetate lactone **60** in 95% yield. The hydrolysis of acetate groups of **60** with potassium carbonate in methanol followed

Scheme 5



Reagents and Conditions

l. OsO_4, NMO, THF, *t*-BuOH; m. Ac_2O, py. DMAP; n. LiBr, PPTs, DMF, Δ.

by relactonisation with dilute HCl yielded hexanor-brassinolide-20,22-dihydroxy compound **61** in 90% yield. The absolute stereochemisty at C-20 of compound **61** has not been established conclusively.

Another approach for the total synthesis of hexanor-20,22-dihydroxy brassinolide is given in **Scheme 5.**

The compound 3α,5-cyclo-pregna-20(22)-ene-6-one **56**, obtained from 16-dehydropregnenolone acetate **50** (**Scheme 3**) was dihydroxylated using catalytic amount of osmium tetroxide and N-methyl-morpholine-N-oxide in tetrahydrofuran to afford *i*-keto-20,22-dihydroxy-pregnane **62** in quantitative yield. The diol **62** was acetylated using acetic anhydride, pyridine to obtain diacetate **63** in 80% yield. Attempts for the acid catalysed rearrangement on *i*-keto-20-22-diol **62** as well as *i*-keto-20,22-diacetate **63** using lithium bromide, pyridinium *p*-toluene sulfonate in refluxing DMF did not give neither the expected diol **65** nor the diacetate **66** but the compound **64**. Formation of compound **64** from **62** and **63** is due to the presence of tertiary hydroxyl or acetoxy group which eliminates at elevated temperature (~ 180°C).

Experimental Section

3β-Acetoxy-pregna-5-ene-20-one 51

To a solution of 16-dehydropregnenolone acetate **50** (30.6g, 0.895 mol) in ethyl acetate (200 ml) was added 1.5g. (5%) Pd/C catalyst. The hydrogenation was carried out using Parr apparatus at 45 *psi* pressure and 30°C temperature for 16h. The reaction mixture was filtered and the filtrate was dried under vacuuo to obtain saturated keto compound **51** (30g, 98%), which was crystallised from ethyl acetate and hexane, m.p. 143°C (lit.[7] 147-147.5°C); IR (nujol) ν_{max} 1740 (O-C=O), 1720 (-C=O); ^{1}H-NMR (90 MHz) δ 0.62 (3H, s, 18-H_3), 1.0 (3H, s, 19-H_3), 2.0 (3H, s, $OCOCH_3$), 2.1 (3H, s, $COCH_3$), 4.6 (1H, m, 3H), 5.37 (d, 1H, J=5Hz, 6-H).

3β-Hydroxy-pregna-5-ene-20-one 52

To a stirred solution of acetate **51** (3.450g, 0.096 mol) in *tert*-butanol (50 ml) was added aqueous solution of KOH (3.1g KOH, 0.055 mol in 5 ml H_2O). The reaction mixture was stirred at 30°C for 12h, neutralised with 5% HCl solution. The *tert*-butanol was removed under vacuuo and the residue was extracted with ethyl acetate (3x50 ml). The extract was washed with water (2x50 ml), brine (2x50 ml) and dried over anhydrous sodium sulphate. Evaporation of solvent yielded crude product **52** (2.914g, 96%), which was crystallised from methanol, mp. 186°C (lit.[8] 190-191°C); IR (nujol) ν_{max} 1712 (-C=O), 3520 (-OH); ^{1}H-NMR (90 MHz) δ 0.62 (3H, s, 18-H_3), 1.0 (3H, s, 19-H_3), 2.1 (3H, s, $COCH_3$), 3.5 (1H, m, 3-H), 5.33 (1H, d, J=5Hz, 6-H).

3β-*p*-Toluenesulfonoxy-pregna-5-ene-20-one 53

The alcohol **52** (3g, 0.009 mol) was dissolved in dry pyridine (20 ml) and *p*-toluenesulfonyl chloride (3.0g, 0.015 mol) was added to the solution. The reaction mixture was kept at room temperature (25°C) for 16h. in dark. The reaction mixture was poured into ice-cold saturated aqueous $NaHCO_3$ solution (250 ml) and allowed it to stand for 2h. The product was filtered, washed thoroughly with ice-cold water (3x100 ml) and dried under vacuuo to afford (4.2g, 94%) of tosylate **53**. mp. 128°C; IR (nujol) ν_{max} 1710 (-C=O); ^{1}H-NMR δ 0.62 (s, 3H, 18-H_3), 0.95 (s, 3H, 19-H_3), 2.08 (s, 3H, $COCH_3$), 2.42 (s, 3H, tosylmethyl), 4.35 (m, 1H, 3-H), 5.27 (m, 1H, 6-H), 7.24-7.8 (AB quartet, J=9Hz, aromatic-H); m/z 299, 283, 265, 255, 240, 227, 214, 199, 177, 160, 147, 129, 121, 107, 91(100%).

3α,5-Cyclo-6β-hydroxy-pregnane-20-one 54

Tosylate **53** (3.5g, 0.0074 mol) was dissolved in aqueous acetone (60 ml) and to it was added fused potassium acetate (4.292g, 0.044 mol). The reaction mixture was refluxed on oil bath at 75°C for 20h. Acetone was removed under vacuuo and the residue was extracted with ethylacetate:pet.ether (1:1) 3x50 ml. The organic layer was washed with water (2x50 ml), brine (2x50 ml) and dried over anhydrous sodium sulphate. Evaporation of solvent afforded (2.347g, 99%) of alcohol **54**; m.p. 182°C (pet.ether:ethyl acetate); IR (nujol) ν_{max} 3520 (-OH), 1710 (-C=O); ^{1}H-NMR δ 0.24-0.49 (m, 3H, cyclopropyl-H), 0.68 (s, 3H, 18-H_3), 1.18 (s, 3H, 19-H_3), 2.1 (s, 3H, $COCH_3$), 3.24 (t, 1H, J=5Hz, 6-H); m/z 316 (M^+), 298, 302, 283, 275, 261, 255, 213, 159, 145, 133, 121, 105, 91(100%); Calc. for $C_{21}H_{32}O_2$ C, 79.74%; H, 10.12. Found: C, 79.64%; H, 10.22%; $[\alpha]_D$ +107.4° (C 2.4, $CHCl_3$).

3α,5-Cyclo-6β-hydroxy-pregna-20(22)-ene 55

Potassium *tert*-butoxide (2.12g, 0.018 mol) was prepared by addition of 0.740g. of potassium metal in 10 ml dry *tert*-butanol. To this solution was added triphenylphosphoniummethyl iodide (5.3g, 0.012 mol) with the aid of dry THF (50 ml). The suspension showed intense yellow colour. The mixture was stirred for 45 minutes and ketone **54** (2g, 0.006 mol) was added in dry THF (30 ml) to the above suspension at room temperature. The resultant reaction mixture was refluxed for 5-6 h. The reaction mixture was poured into a mixture of methanol and water (1:1) and the product was isolated by extraction with 1:1 ethyl acetate:pet.ether (3x50 ml). The organic layer was washed with water (2x50 ml), brine (2x50 ml) and dried over anhydrous Na_2SO_4. The evaporation of solvent afforded 4g. of crude gummy material. The crude material was dissolved in methanol and to it methyl iodide (4ml) was added and stirred for 2h. at 30°C. Removal of methanol gave a crude mixture containing triphenylphosphine oxide and phorphorane in addition to the olefin **28**. The further purification of olefin **28** was done by column chromatographic purification over neutral alumina to obtain pure olefin **55** (3.0g, 70%). Oil; IR (nujol) ν_{max} 3450 (-OH), 1655; ^{1}H-NMR δ 0.62 (s, 3H, 18-H_3), 1.04 (s, 3H, 19-H_3), 1.76 (s, 3H, 21-H_3), 3.24 (t, J=5Hz, 1H, 6-H), 4.64 and 4.8 (two bs, 2H, 22-H); m/z 314 (M^+, 100%), 296, 287, 259, 253, 245, 227, 199, 185, 171, 159, 145, 131, 121, 107, 91.

3α,5-Cyclo-pregna-20(22)-ene-6-one 56

To a solution of alcohol **55** (0.470g, 0.014 mol) in acetone (30 ml) was added Jones reagent (8N) (2ml, 0.0047 mol) dropwise at 0°C in two minutes. The resultant solution was stirred at 0°-5°C for 10 minutes. The excess reagent was quenched with methanol and the solvent was removed from the reaction mixture to get a gummy oil. The residue was extracted with 1:1 mixture of pet.ether:ethyl acetate (3x50 ml). The organic layer was washed with water (2x50 ml), brine (2x50 ml) and dried over anhydrous sodium sulphate. The evaporation of solvent afforded the crude product **56** (0.454g, 97%); m.p. 106-108°C (MeOH); IR (nujol)ν_{max} 1710 (-C=O), 1645; ^{1}H-NMR δ 0.63 (s, 3H, 18-H_3), 1.0 (s, 3H, 19-H_3), 1.78 (s, 3H, 21-H_3), 4.64 and 4.8 (two bs, 2H, 22-H); m/z 312 (M^+), 297, 269, 256, 243, 229, 215, 201, 187, 173, 161, 145, 133, 120, 105, 91, 79(100%); $[\alpha]^{25}$ +27.6° (C 1.02, $CHCl_3$); Calc. for $C_{22}H_{32}O$ C, 84.61%, H, 10.25%. Found: C, 84.38%, H, 10.34%.

Pregna-2,20(22)-diene-6-one 57

To a magnetically stirred solution of *i*-ketone **56** (0.196g, 0.0628 mol) in dry DMF (4 ml) was added lithium bromide (0.027g, 0.00031 mol), pyridinium paratoluene sulfonate (0.027g, 0.0001 mol). The reaction mixture was refluxed for 3h. at 175°C. The mixture was cooled and poured into ice water and extracted with pet.ether:ethyl acetate (1:1) (3x25 ml). The organic layer was washed with water (2x25 ml), brine (2x25 ml) and dried over anhydrous sodium sulphate. Evaporation of solvent yielded a mixture containing pregna 2,20(22)-diene-6-one as a major product. Column chromatographic purification gave (0.118g, 60%) of pure pregna-2,20(22)-dien-6-one **57**. m.p. 76-78°C (MeOH); IR (nujol) ν_{max} 1720 (-C=O), 1670, 1655; ^{1}H-NMR δ 0.62 (s, 3H, 18-H_3), 0.75 (s, 3H, 19-H_3), 1.77 (s, 3H, 21-H_3), 4.64 and 4.8 (two bs, 2H, 22-H)); m/z 312 (M^+), 297, 284, 269, 256, 243, 229, 213, 201, 185, 175, 159, 149, 133, 121, 107, 91(100%); Calc. for $C_{22}H_{32}O$ C, 84.61%; H, 10.25%. Found: C, 84.58%; H, 10.58%; $[\alpha]_D$ +11.2° (C 3, $CHCl_3$).

2α,3α,20,22-Tetrahydroxy-pregnane-6-one 58

To a stirred solution of 2,20-diene **57** (0.318g, 0.001 mol) in dry benzene (5 ml) was added osmium tetroxide (0.510g, 0.002 mol), 2-3 drops of pyridine and the reaction mixture was stirred at 25°C for 50h. The reaction mixture was quenched with saturated aqueous sodium bisulphite solution. Benzene was removed under vacuuo and the residue was dissolved in aqueous ethanol, sodium bisulphite was added to it and refluxed for 3h. Filtration followed by evaporation of ethanol gave some residue, which was extracted with ethyl acetate (3x50 ml). The organic layer was washed with water (2x50 ml), brine (2x50 ml) and dried over anhydrous sodium sulphate. Evaporation of

solvent gave crude product, which after column chromatographic purification afforded 0.280g, 72% of tetrol **58**. Crystallised from ethyl acetate:methanol, m.p. 254°C; IR ν_{max} 1712 cm^{-1} (-C=O), 3480 cm^{-1} (-OH); ^{1}H-NMR δ 0.67 (s, 3H, 18-H_3), 0.77 (s, 3H, 19-H_3), 1.22 and 1.27 (s, 3H, 21-H_3), 3.1-3.9 (m, 4H, 2,3,22-H); m/z 380 (M^+), 362, 347, 329, 321, 285, 277, 267, 259, 245, 227, 210, 197, 187, 173, 159, 147, 133, 121, 105, 91(100%). Calc. for $C_{22}H_{36}O_5$ C, 69.4%; H, 9.4%; Found: C, 69.8%; H, 9.8%.

2α,3α,20,22-Tetraacetoxy-pregnane-6-one 59

The tetrol **58** (0.2g, 0.0005 mol) was dissolved in dry pyridine (1.5 ml) and to it acetic anhydride (0.6 ml) was added. Dimethylaminopyridine (DMAP, 5mg) was introduced and the reaction mixture was left at 25°C for 16h. It was poured into the ice-cold solution of aqueous $NaHCO_3$. The product was filtered and dried to obtain tetraacetate **59** (0.225g, 78%). The crude product was purified by column chromatography on silica gel to afford pure tetraacetate **59** (0.2g, 70%); m.p. 128-130°C (C6 H_{14}); IR ν_{max} cm^{-1} 1738, 1558; ^{1}H-NMR 0.88 and 0.91 (s, 3H, 18-H_3), 1.3 (s, 3H, 19-H_3), 1.55 and 1.6 (s, 3H, 21-H_3), 2.02-2.1 (4s, 12-H, $OCOCH_3$), 2.15 (s, 3H, $COCH_3$), 2.6 (m, 1H, 5α-H), 4.14 (m, 2H, 22-H), 4.92 (m, 1H, 2-H), 5.35 (m, 1H, 3-H); m/z 489, 446, 428, 413, 387, 369, 356, 327, 309, 293, 288, 269, 259, 227, 189, 173, 159, 145(100%), 133, 127, 121, 105.

2α,3α,20-22-tetraacetoxy-B-homo-7-oxa-pregnane-6-one 60

Trifluoroperacetic acid, prepared by adding trifluoroacetic anhydride (2 ml) to a solution of H_2O_2 (2 ml) in methylene chloride (2 ml). The addition was done in 10 minutes maintaining the temperature below 5°C and allowed it to warm upto 8-10°C in 0.5h. In a round bottom flask tetraacetate ketone **59** (0.136g, 0.00024 mol) was taken in 5 ml CH_2Cl_2, Na_2HPO_4 (1g.) was added and trifluoroperacetic acid was added dropwise to it in 10 minutes, maintaining the temperature below 5°C. The reaction mixture was allowed to warm upto 25°C (2h.) and stirred overnight (20h.) at 25°C. The reaction mixture was poured into excess of CH_2Cl_2 (25 ml) and was washed with aqueous $NaHCO_3$ solution, water (2x50 ml), brine (2x50 ml) and dried over anhydrous sodium sulphate. Evaporation of solvent afforded tetraacetate lactone **60** (0.132g, 95%). Foamy solid; IR

ν_{max} cm^{-1} 1738, 1558; ^{1}H-NMR δ 0.87 and 1.02 (s, 3H, 18-H_3), 1.22 (s, 3H, 19-H_3), 1.64 (bs, 3H, 21-H_3), 2.02-2.15 (4s, 12H, $OCOCH_3$), 2.2 (s, 3H, $COCH_3$), 3.0 (m, 1H, 5α-H), 4.05 (m, 2H, 22-H), 4.9 (m, 1H, 2-H), 5.4 (m, 1H, 3-H).

2α,3α,20,22-Tetrahydroxy-B-homo-7-oxa-pregnan-6-one 61

Tetraacetoxy lactone **60** (0.1g, 0.00018 mol) was taken in methanol (3 ml) and K_2CO_3 (0.244g.) in 1.5 ml H_2O was added to it. The resulting mixture was refluxed for 6h. Acidification with 5N HCl (pH_3, 10 ml) followed by removal of methanol gave gummy residue; which was extracted with CH_2Cl_2 (3x25 ml). The extract was washed with H_2O (2x25 ml), brine (2x25 ml) and dried over anhydrous sodium sulphate. Evaporation of solvent yielded crude product (0.063g, 90%), which was column chromatographed to obtain pure 2α,3α,20,22-tetrahydroxy-B-homo-7-oxa-pregnane-6-one **61** (0.049g, 69%). Gummy oil; IR ν_{max} cm^{-1} 3409 (-OH), 1698 (-C=O); ^{1}H-NMR δ 0.72 (s, 3H, 18-H_3), 0.78 (s, 3H, 19-H_3), 1.27 (s, 3H, 21-H_3), 3.2 (m, 1H, 5α-H), 3.69 (m, 2H, 2 and 3-H), 4.05 (m, 2H, 22-H).

3α,5-Cyclo-20,22-dihydroxy-pregnane-6-one 62

To a stirred solution of keto olefin **56** (0.5g, 0.0016 mol) in tetrahydrofuran (20 ml) was added osmium tetroxide (0.08g, 0.00031 mol), N-methylmorpholine N-oxide (0.224g, 0.0019 mol), *tert*-butyl alcohol (4 ml) and H_2O (2 ml). The reaction mixture was stirred for 2h. at 30°C and 4h. at 45°C. Saturated aqueous sodium bisulphite solution was added to it and the mixture was stirred for another 1h. at 30°C. The reaction mixture after $NaHSO_3$ treatment was filtered through celite. The filtrate was concentrated under vacuuo and the residue was extracted with chloroform (3x50 ml). The combine extract was washed with H_2O (2x50 ml) and brine (2x50 ml) and dried over anhydrous Na_2SO_4. Evaporation of solvent yielded crude diol **62** (0.552g, 100%); which was further purified by column chromatography over neutral alumina. Gummy oil; IR ν_{max} cm^{-1} 3450 (-OH), 1700 (-C=O), 1550, 1510, 1400, 1050, 945; ^{1}H-NMR δ 0.92 (s, 3H, 18-H_3), 1.02 (s, 3H, 19-H_3), 1.22 (s, 3H, 21-H_3), 3.36-4.06 (m, 2H, 22-H).

3α,5-Cyclo-20,22-diacetoxy-pregnane-6-one 63

To a solution of diol **62** (0.5g, 0.0014 mol) in dry pyridine (10 ml) was added acetic anhydride (5 ml) and 4-dimethylamino pyridine (10 mg). The resultant mixture was kept at 30°C for 16h. The reaction mixture was poured into ice-cold solution of saturated aq. sodium bicarbonate solution

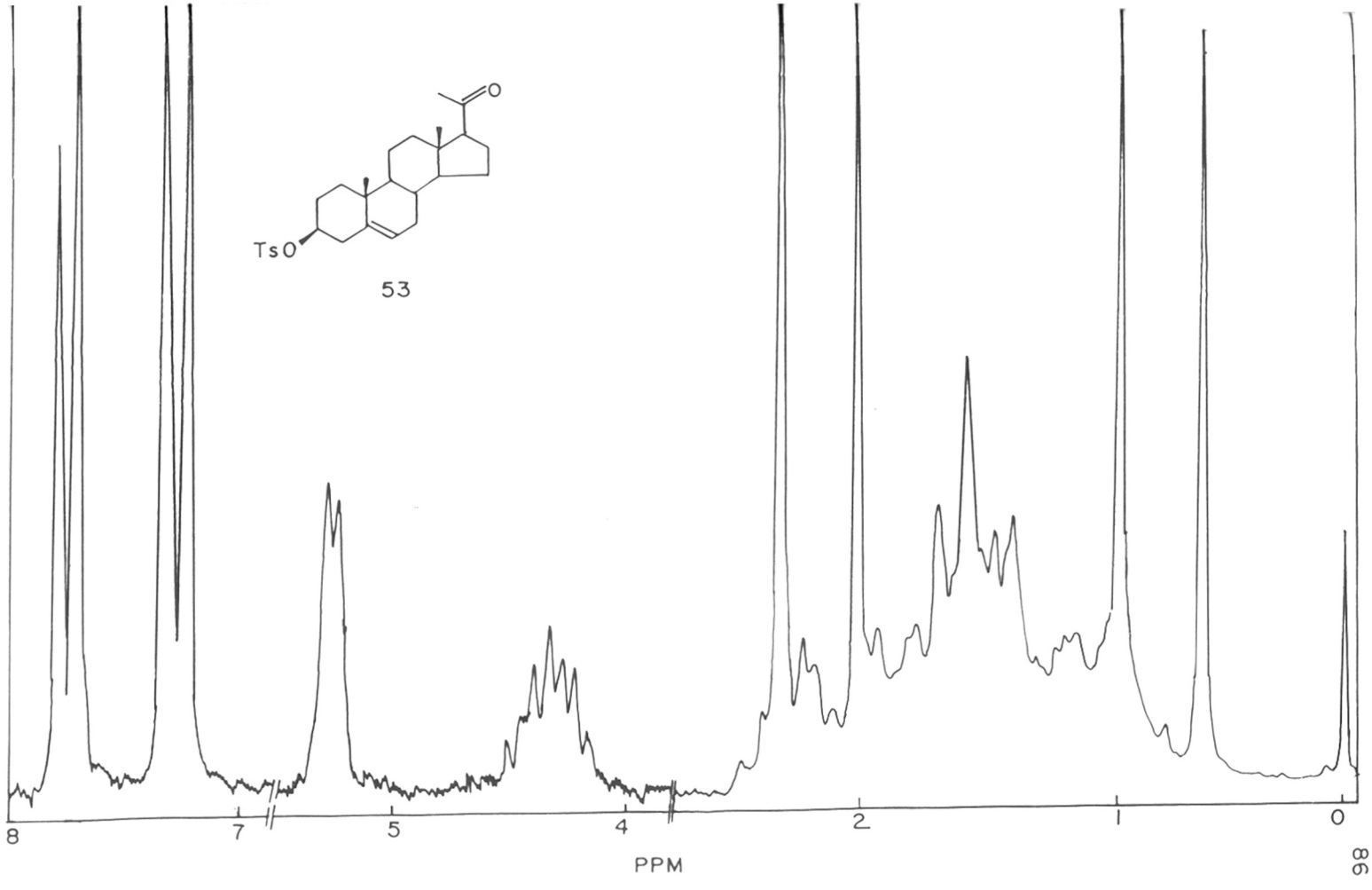
(100 ml) with vigorous stirring. The mixture was extracted with chloroform (3x50 ml). The combine chloroform extract was washed with water (3x50 ml), aq. $CuSO_4$ solution (4x50 ml), water (2x50 ml) and brine (2x50 ml). The extract was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished diacetate **63** (0.570g, 92%). The crude product was purified by column chromatography on neutral alumina to yield pure diacetate **63** (0.495g, 80%). m.p. 185°C (ethyl acetate:pet.ether); IR ν_{max} 1750 (-O-$COCH_3$), 1700 (-C=O), 1620, 1470, 1390, 1060, 930; ^{1}H-NMR δ 0.92 (s, 3H, 18-H_3), 1.02 (s, 3H, 19-H_3), 1.22 (s, 3H, 21-H_3), 2.12 (bs, 6H, O-$COCH_3$), 3.9-4.2 (m, 2H, 22-H); Calc. for $C_{26}H_{38}O_5$; C, 72.55; H, 8.83. Found: C, 72.76; H, 9.2.

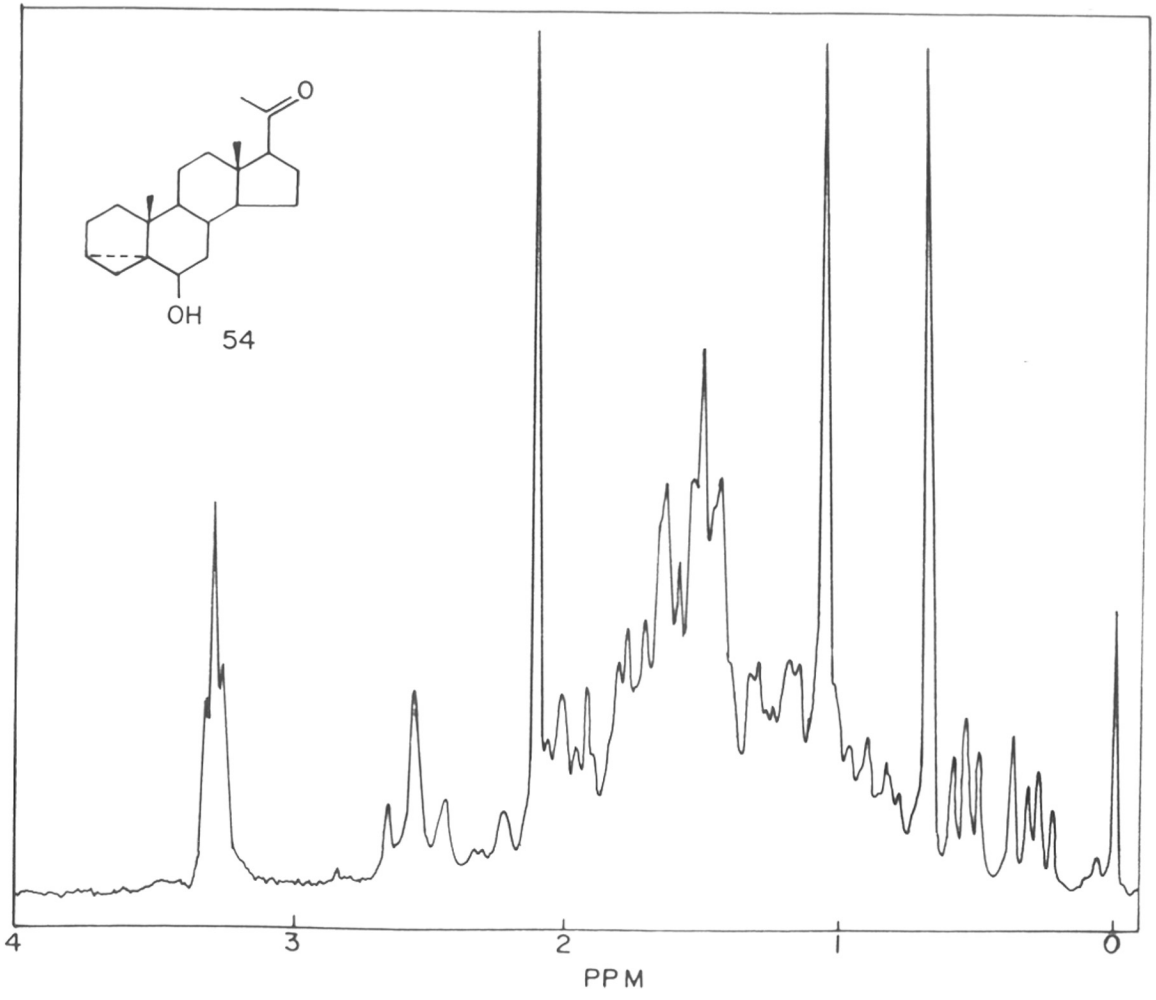
Rearrangement of 3α,5-cyclo-20,22-dihydroxy-pregnane-6-one 62

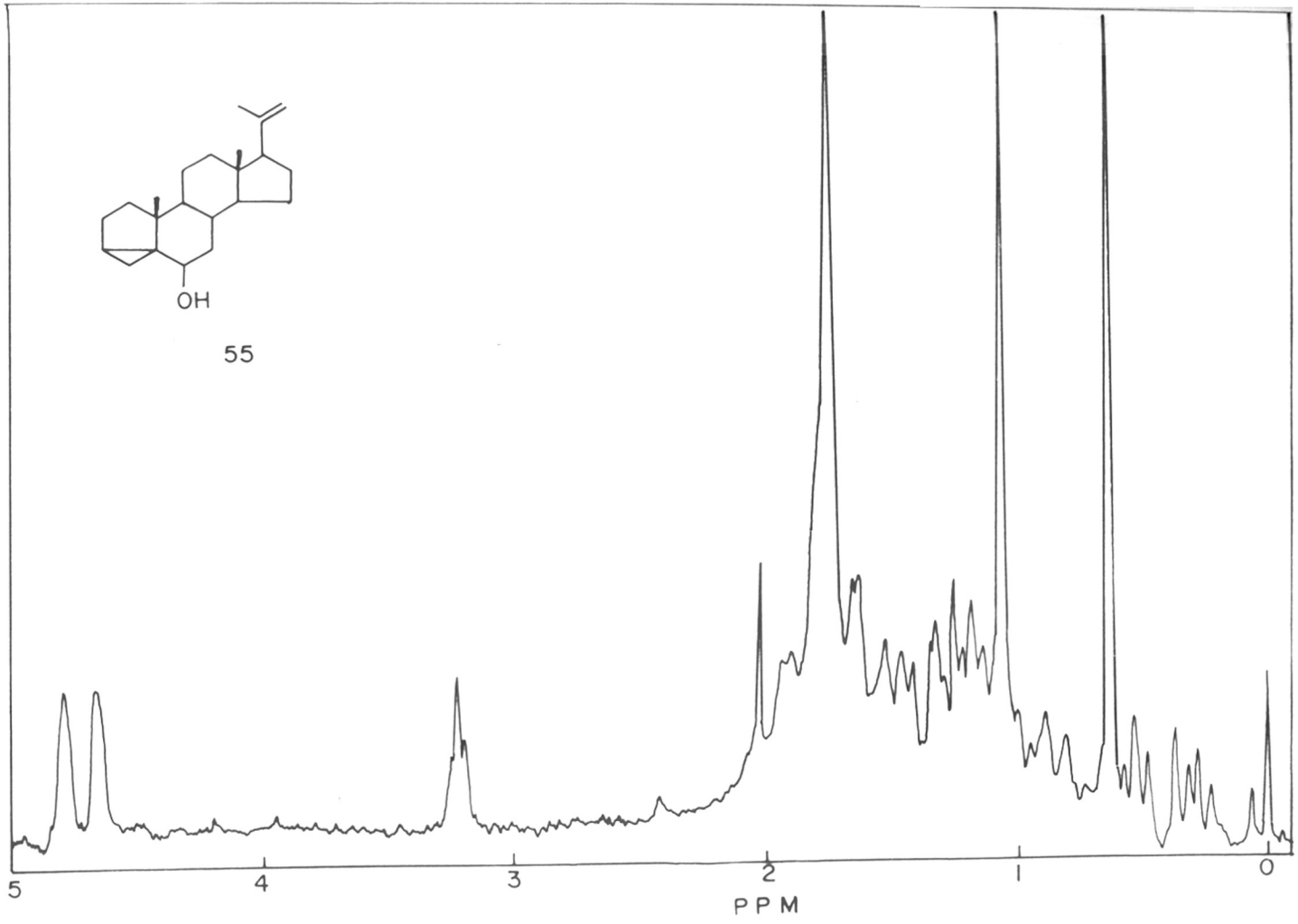
To a solution of diol **62** (0.050g, 0.00014 mol) in dry DMF (1 ml) was added pyridinium *p*-toluene sulfonate (0.008g, 0.0003 mol) and lithium bromide (0.008g, 0.0007 mol). The reaction mixture was refluxed on oil bath at 180°C for 2h. After disappearance of starting material (by tlc), the reaction mixture was poured into crushed ice; extracted with chloroform (3x25 ml). The combine extract was washed well with water (3x25 ml) and brine (3x25 ml); dried over anhydrous Na_2SO_4. Evaporation of solvent afforded crude product, which was purified by column chromatography on neutral alumina furnished single spot compound. From IR, ^{1}H-NMR spectroscopy, it was found that there is no formation of required ene-diol **65**, but dehydration at elevated temperature might have yielded diene **64** as a major product. Similarly, in diacetate **63** attempted rearrangement furnished diene **64** as a major product. Gummy oil; IR ν_{max} 1710 cm^{-1} (-C=O), 1630, 1530, 1450, 1380, 1050, 940, 900; ^{1}H-NMR δ 0.64-0.78 (m, 3H, cyclopropyl-H), 0.78 (s, 3H), 0.97 (s, 3H), 1.9 (s, 3H), 4.92 and 5.1 (two bs), 5.56-6.05 (m).

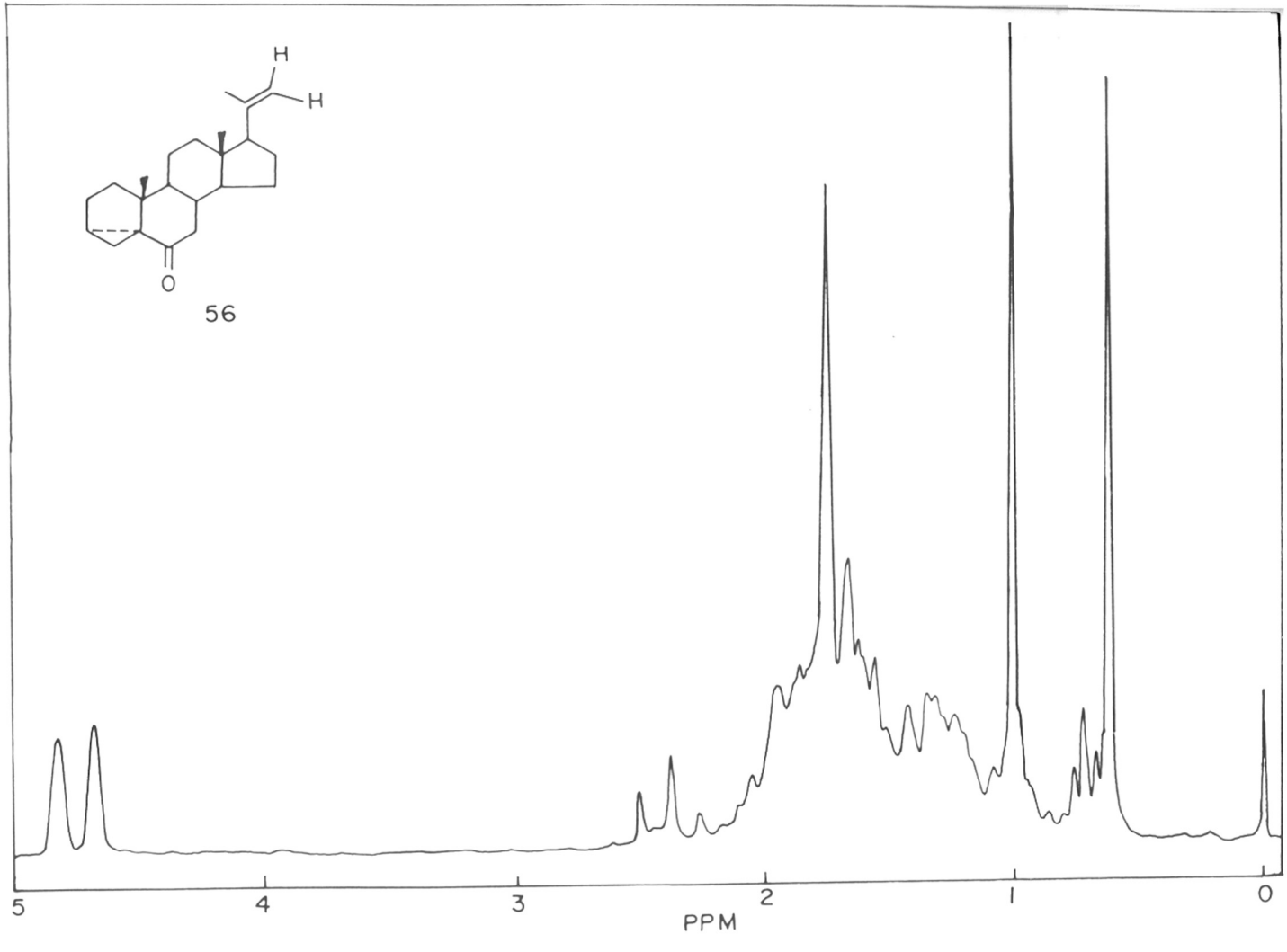
References

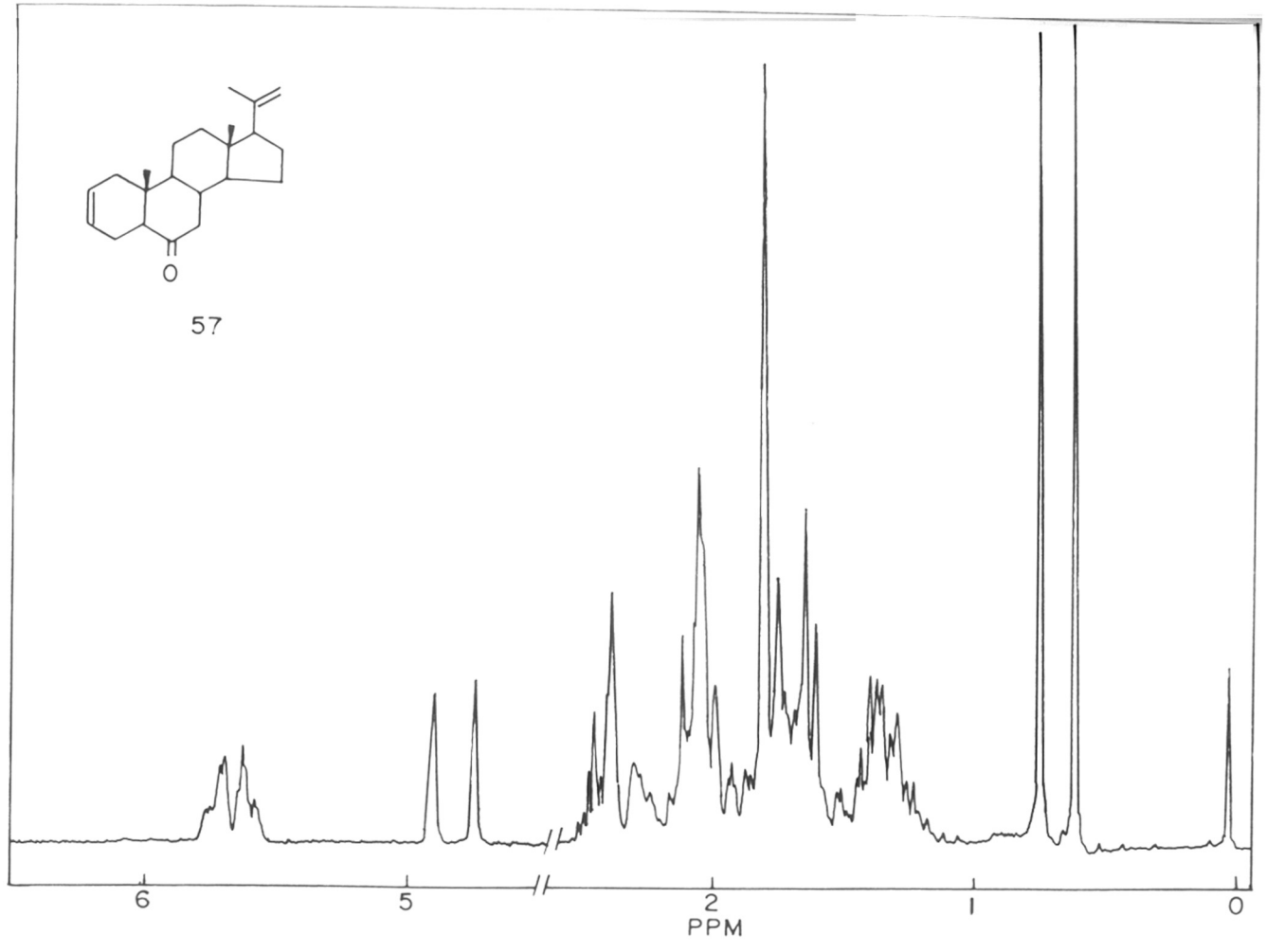
1. Grove, M.D.; Spencer, G.F.; Rohwedder, W.K.; Mandava, N.; Worley, J.F.; Warthen, Jr.,J.D.; Steffens, G.L.; Flippen-Anderson, J.L.; Cook,Jr.,J.C. *Nature*, **1979**, 281, 216-217.
2. Thompson,M.J.; Mandava,N.; Flippen-Anderson,J.L.; Worley,J.F.; Dutky,S.R.; Robbins,W.E.; Lusby,W. *J.Org.Chem.* **1979**, 44, 5002-5004.
3. Thompson,M.J.; Meudt,W.J.; Mandava,N.B.; Dutky,S.R.; Lusby,W.R.; Spaulding,D.W. *Steroids*, **1982**, 39, 89-105.
4. Okada,K.; Mori,K. *Agric. Biol. Chem.* **1983**, 47, 89-95; Kondo,M.; Mori,K. *Agric.Biol.Chem.* **1983**, 47, 97-102.
5. Kerb,U.; Eder,U.; Krahmer,H. *Agric.Biol.Chem.* **1986**, 50, 1359-1360.
6. Takatsuto,S.; Ying, B.; Morisaki, M.; Ikekawa, N. *Chem. Pharm. Bull.* **1981**, 29, 903-905.
7. Ruzicka,L.; Hofmann,K. *Helv.Chim.Acta.* **1937**, 20, 1291-1297.
8. Danishefsky,S.; Nagasava,K.; Wang,N.J. *J.Org.Chem.* **1975**, 40, 1989-1990.

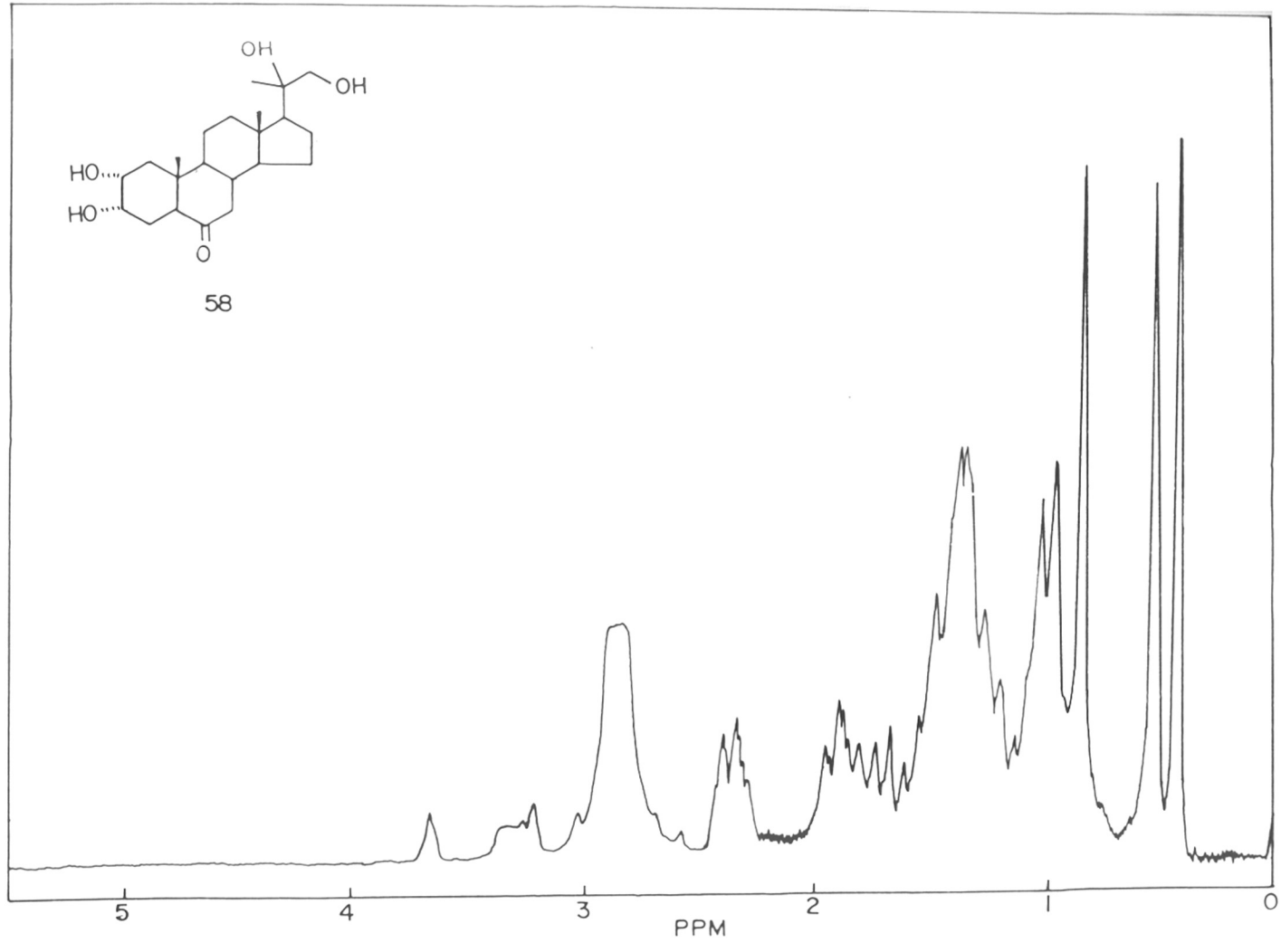

TsO
O
53
8
7
5
4
2
1
0
PPM


O
OH
54
4
3
2
1
0
PPM

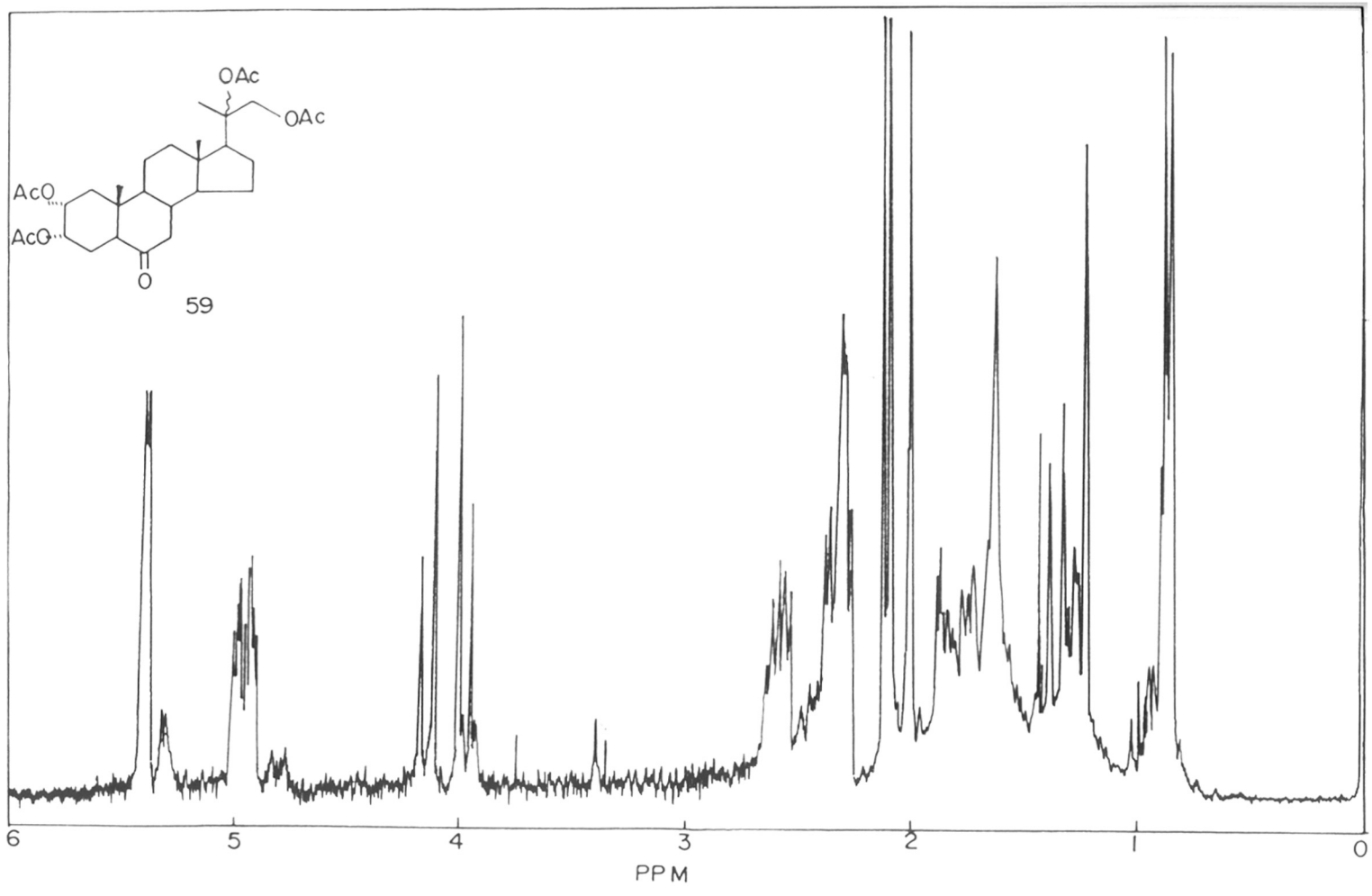

OH
55
5
4
3
2
1
0
PPM

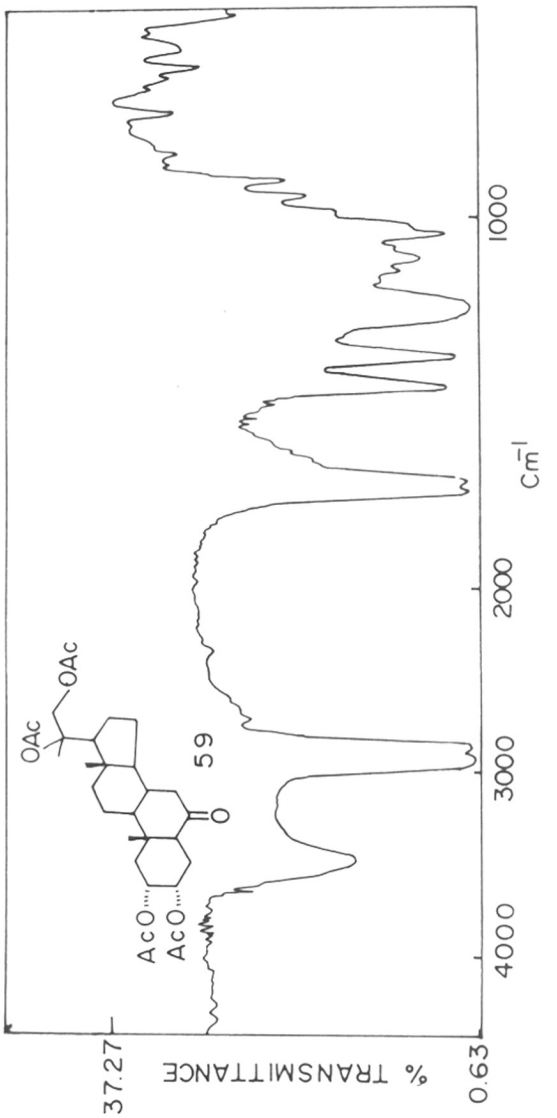

H
H
O
56
5
4
3
2
1
0
PPM

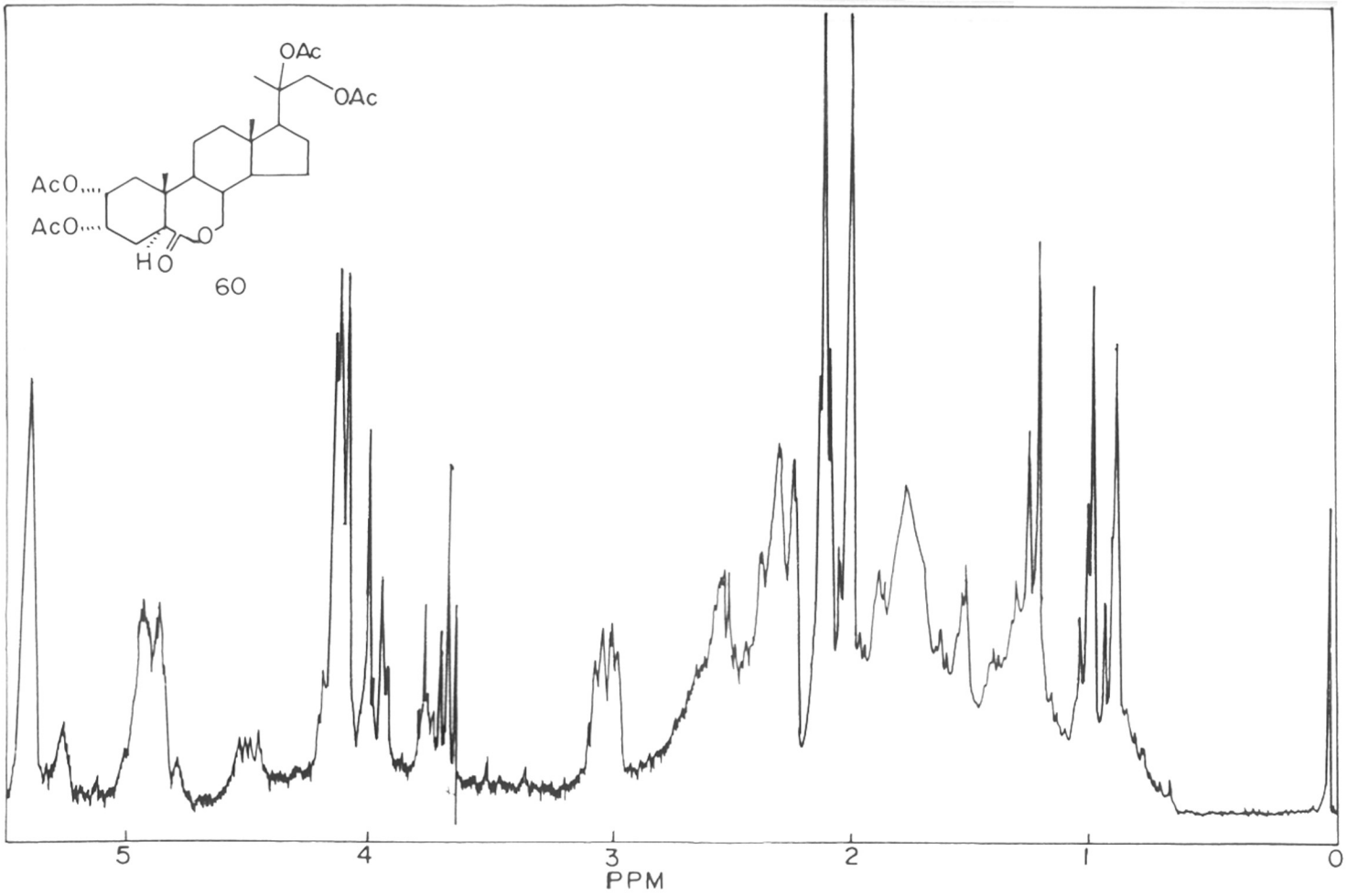

O
57
6
5
2
1
0
PPM

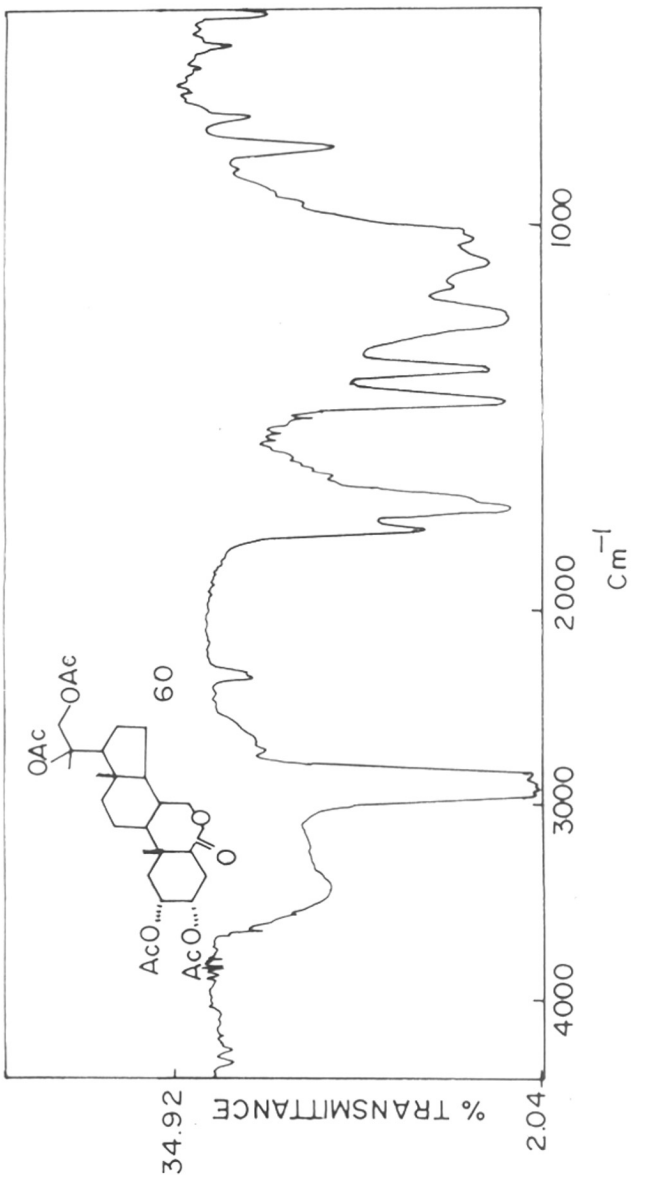


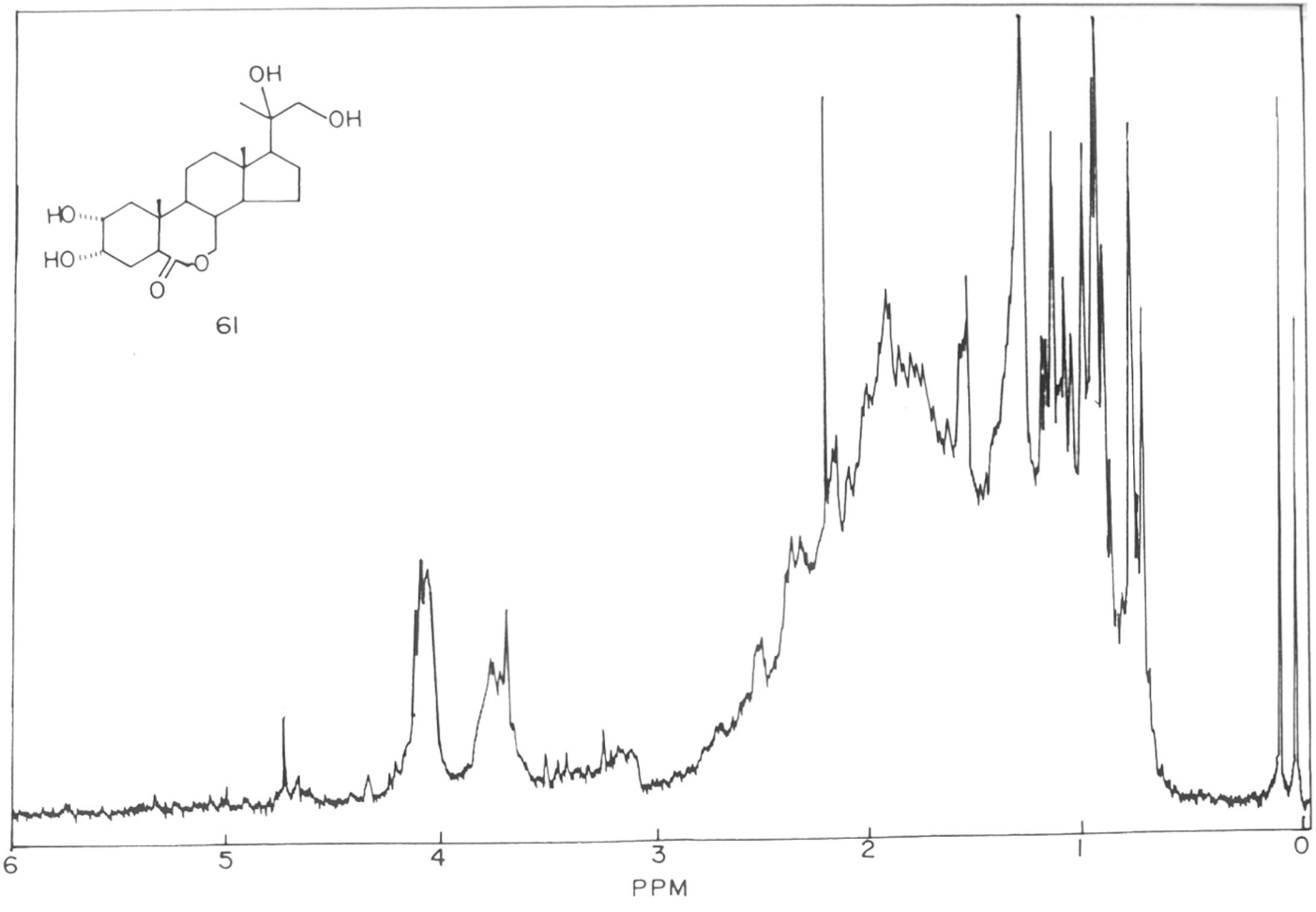
58

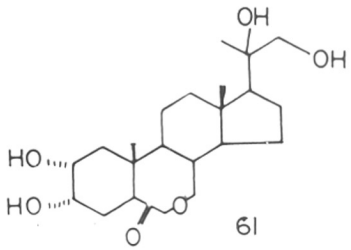

OAc
OAc
AcO
AcO
O
59
6
5
4
3
2
1
0
PPM


37.27
0.63
% TRANSMITTANCE
4000
3000
2000
1000
Cm^{-1}
OAc
OAc
AcO
AcO
O
59

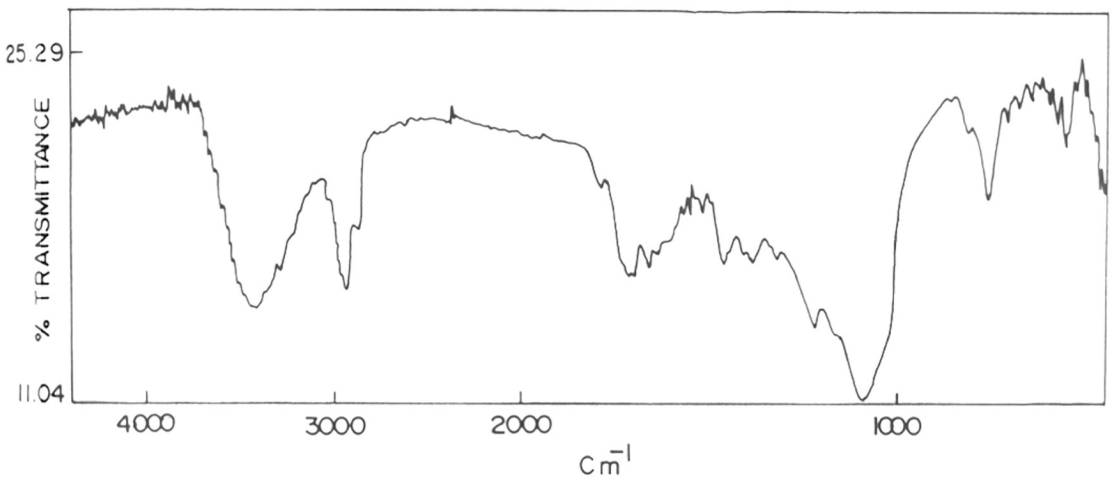

OAc
OAc
AcO
AcO
HO
O
60
5
4
3
2
1
0
PPM

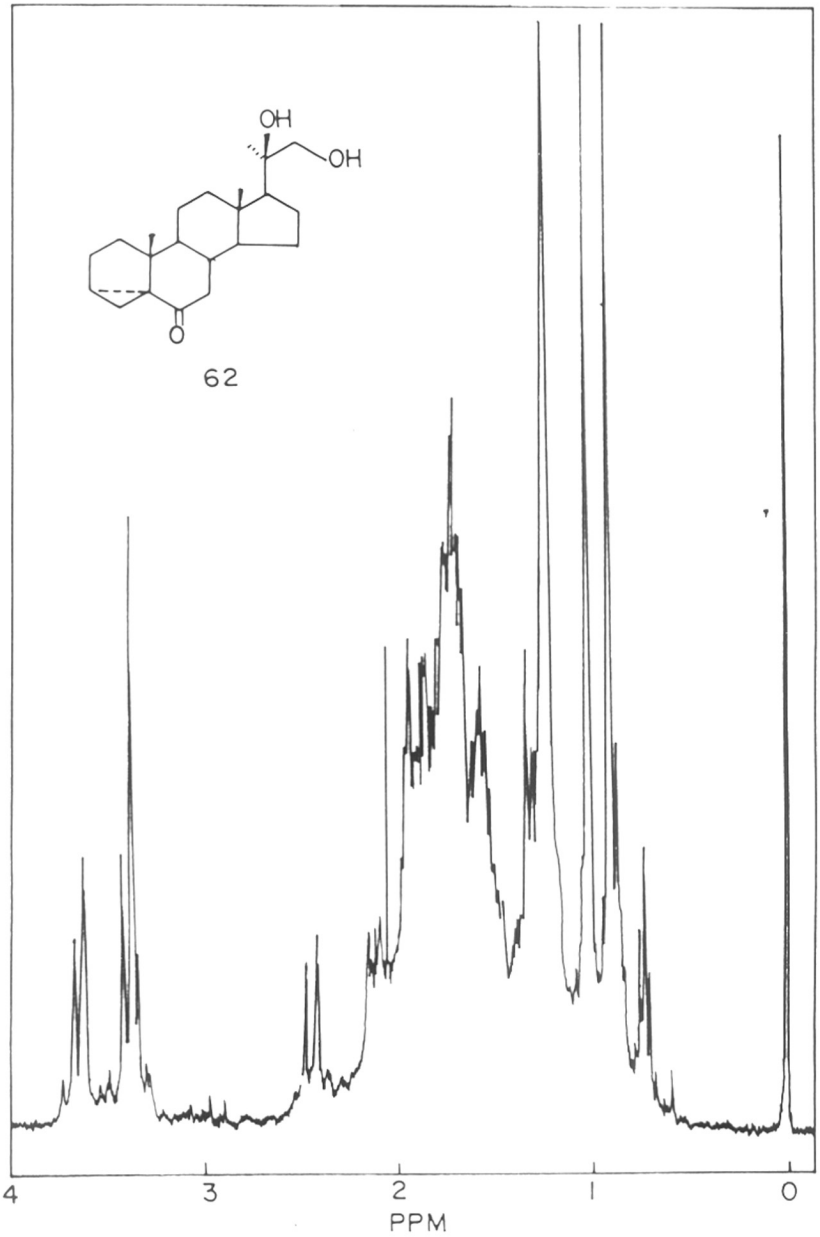

% TRANSMITTANCE
34.92
2.04
4000
3000
2000
1000
cm^{-1}
60
OAc
OAc
AcO
AcO
O
O


OH
OH
HO
HO
O
O
61
6
5
4
3
2
1
0
PPM

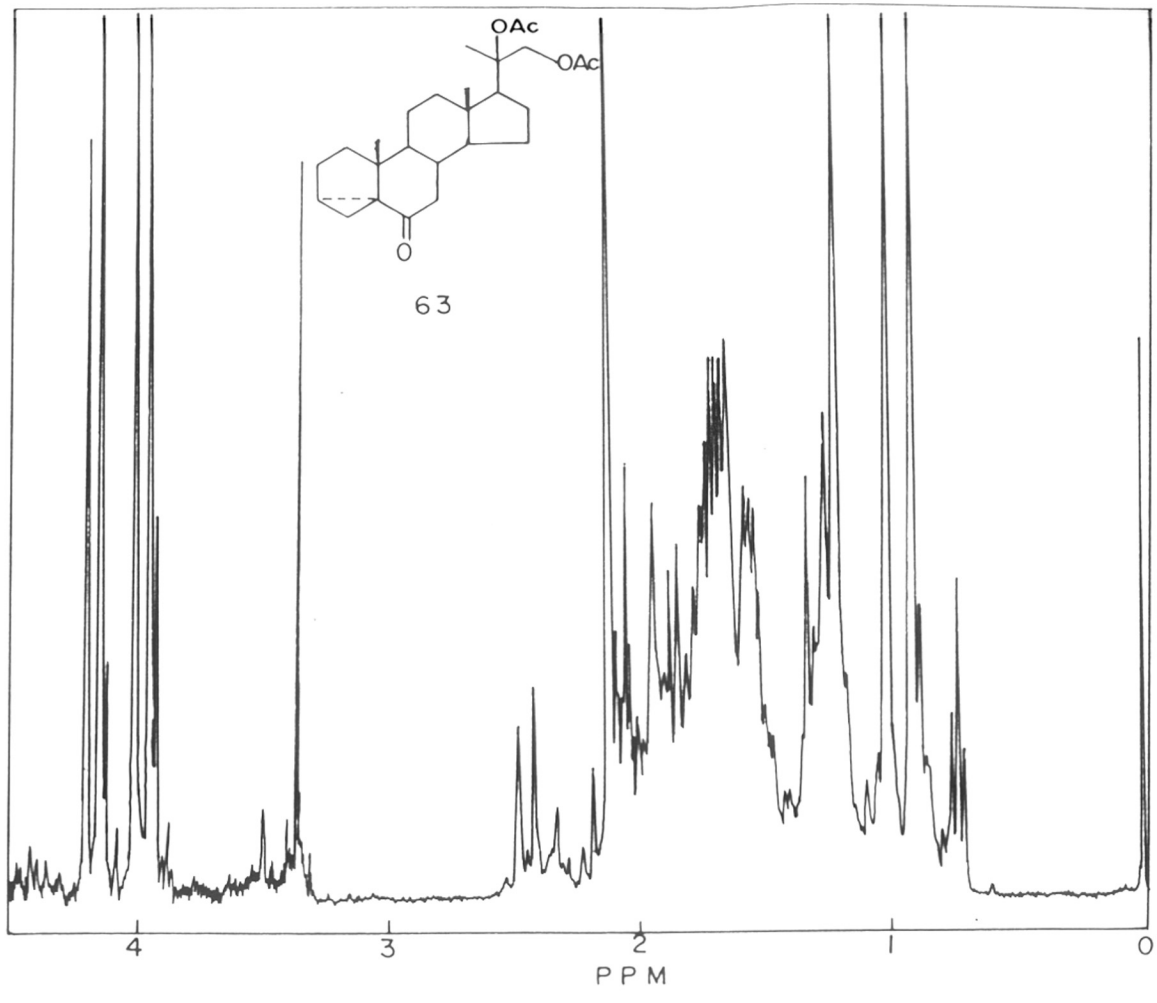

OH
OH
HO
HO
O
O

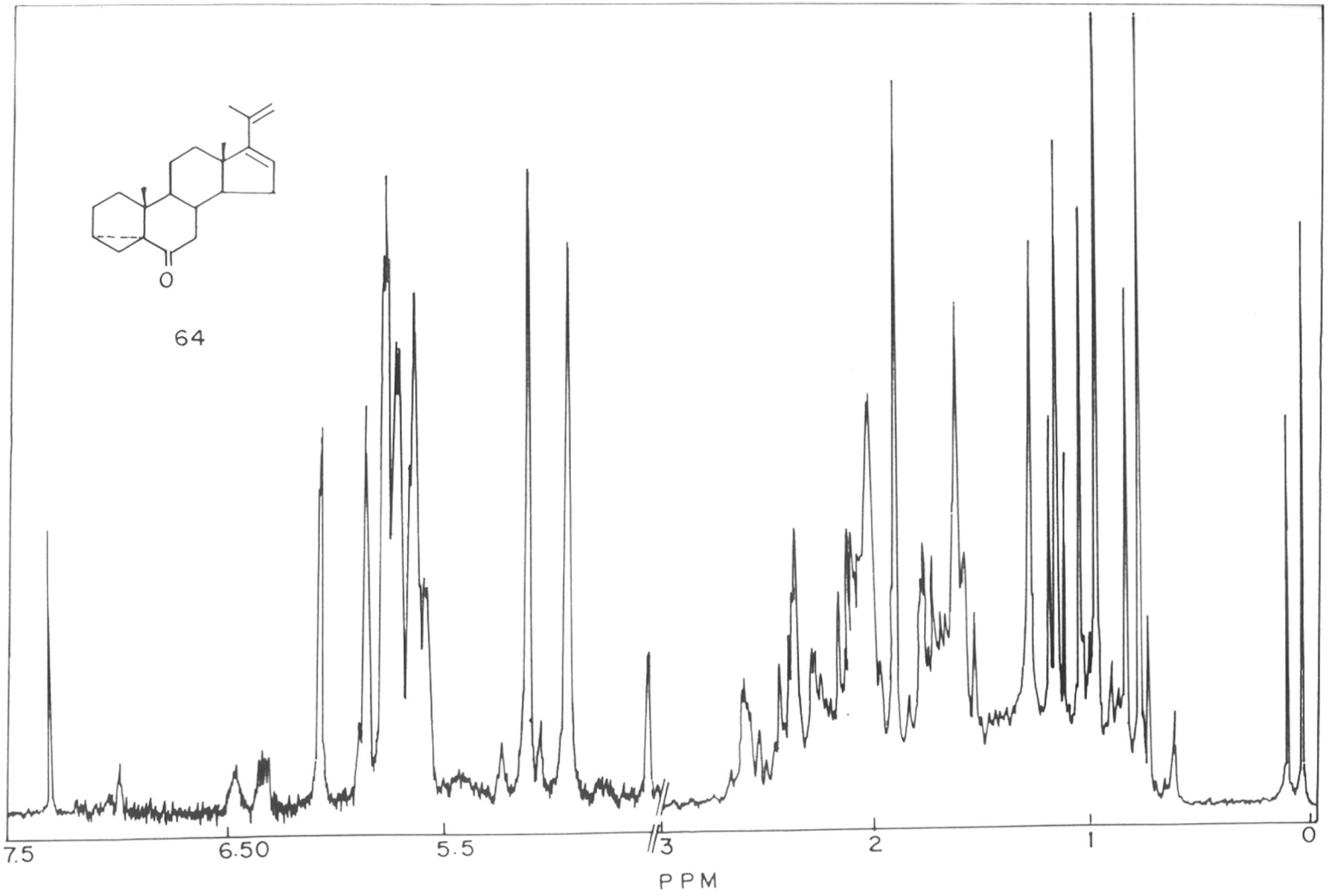
61


25.29
% TRANSMITTANCE
11.04
4000
3000
2000
1000
C m⁻¹



62


OAc
OAc
O
63
4
3
2
1
0
PPM


O
64
7.5
6.50
5.5
3
2
1
0
PPM

CHAPTER-III

cis-Dihydroxylation of olefins with tetradecyltrimethylammonium permanganate (TDTAP) - A new modified potassium permanganate reagent.

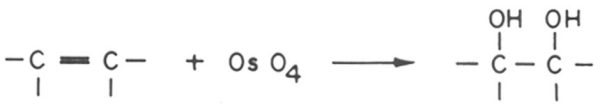
Summary

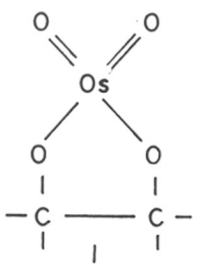
The oxidation of olefins to the corresponding glycols is an important reaction for which several reagents are available.[1] *trans*-Dihydroxylation is usually achieved by organic peracids,[1] by reaction with Prevost's reagent or by the reaction with halogens or hypohalous acids followed by hydrolysis of the halogenated products. *cis*-Dihydroxylation results from oxidation of alkenes with alkaline potassium permanganate[2], osmium tetroxide[2], *tert*-butyl hydroperoxide with traces of osmium tetroxide,[3] or potassium manganate.[4]

The reaction of an olefin with osmium tetroxide is the most reliable method for *cis*-dihydroxylation of a double bonds. Although it is used catalytically along with N-methylmorpholine-N-oxide, its high cost and extreme toxicity have provided the incentive to develop new reagents for *cis*-dihydroxylation. In our attempt to avoid the use of osmium tetroxide for such chemical transformations to improve and modify the reactivity of potassium permanganate, we have prepared tetradecyltrimethylammonium permanganate (TDTAP). This reagent is used for *cis*-dihydroxylation and a number of useful vicinal diols are prepared from the corresponding alkenes in moderate yields (50-71%).

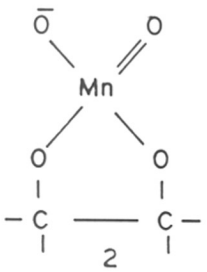
Introduction

There are many reagents which add two -OH groups to a double bond.[1] OsO_4 and alkaline $KMnO_4$ give syn addition, from the less-hindered side of the double bond. Osmium tetroxide adds rather slowly but almost quantitatively. The cyclic ester **1** is an intermediate and can be isolated, but it usually decomposes in solution, with sodium sulphite in ethanol or other reagents.





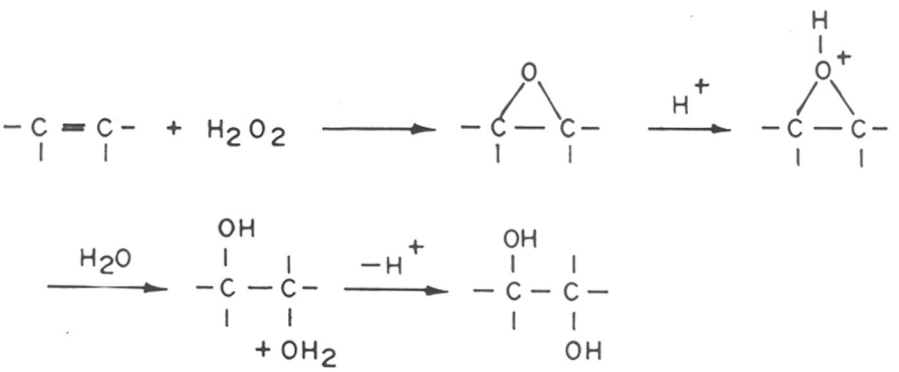
1



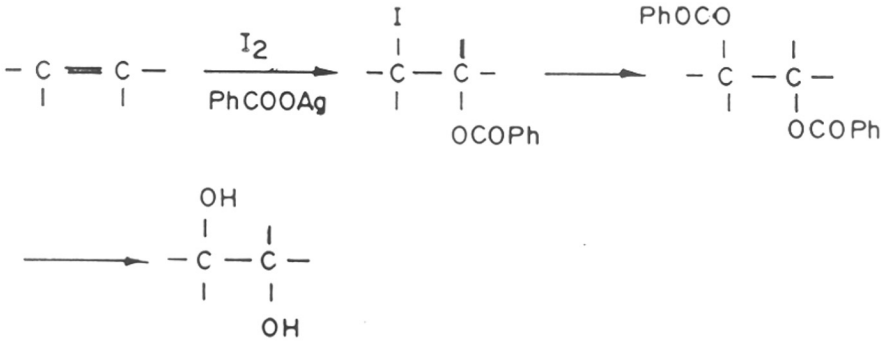
2

OsO_4 is expensive and highly toxic, so its use has been limited to small scale preparations of scarce materials. However, the same result (syn addition) can be accomplished more economically by the use of H_2O_2, with OsO_4 present in catalytic amounts. tert-Butyl hydroperoxide in alkaline solution and N-methylmorpholine-N-oxide[5] have been substituted for H_2O_2 in this procedure. Potassium permanganate is a strong oxidising agent and can oxidise the glycols that are the products of this reaction. In acidic or neutral solution, it always does so; hence it is not feasible to prepare glycols in this manner. Glycols can be prepared with alkaline permanganate, but the conditions must be mild. Even so, yields are seldom above 50%, though they can be improved with phase transfer catalysis[6] or increased stirring.

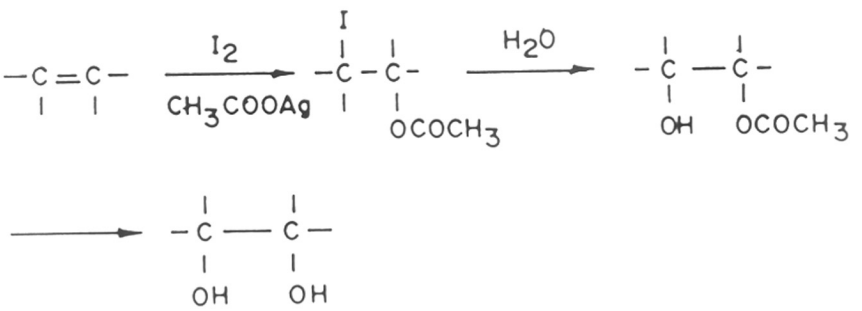
As with OsO_4, it is likely that cyclic esters are intermediates; species believed to be such intermediates have been detected spectrally. This reaction is the basis of the Baeyer test for the presence of double bonds. Anti hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation occurs first, followed by an SN^2 reaction, which results in overall anti-addition.



The same result can be achieved in one step with monopersuccinic acid. Overall anti addition can also be achieved by the method of Prevost. In this method, the olefin is treated with iodine and silver benzoate in a 1 : 2 molar ratio. The initial addition is anti and results in a β-halobenzoate. These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second $PhCOO^-$ group. This is a nucleophilic substitution reaction, and it operates by the neighbouring group participation, so that the groups are still *anti*:



Hydrolysis of the ester does not change the configuration. Woodward's method is similar, but results in overall syn addition. The olefin is treated with iodine and silver acetate in a 1 : 1 molar ratio in acetic acid containing water[7]. Here again, the initial product is a β-halo ester; the addition is anti and a nucleophilic replacement of iodide occurs. However, in the presence of water, neighbouring group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal SN^2 process, so that the monoacetate is *syn*.



Hydrolysis of monoacetate gives the glycol, with overall *syn* addition. In cyclic trisubstituted olefins, both the Woodward and the Prevost methods may give allylic alcohols and ketones rather than the normal products. Although the Woodward method results in overall syn addition, the

product may be different from that with OsO_4 or $KMnO_4$, since the overall syn process is from the more-hindered side of the olefin. Both the Prevost and the Woodward methods have also been carried out in high yields with thalium (I) acetate and thallium (I) benzoate instead of the silver carboxylates. Addition of IOCOMe has also been accomplished with I_2 and peracetic acid and with I_2 and potassium iodate in acetic acid. The resulting β-iodo acetate can then be converted to the diol that is the product of syn addition by treatment with cupric acetate or potassium. By a combination of the I_2-KIO_3 and Cu $(OAc)_2$ or KOAc methods, a double bond can be converted to the diol without the use of expensive silver acetate[8]. Olefins can also be oxidised with metallic acetates such as lead tetraacetate or thallium acetate to give bisacetals of glycols.

Osmium tetroxide: Since this oxidant is expensive and toxic, its use is usually restricted to small scale operations and the oxidation of precious compounds. The applications of the reagent are conveniently considered under non-catalytic and catalytic procedures.

A) **Non-catalytic procedure**:- Reaction of alkene with a stoichiometric quantity of osmium tetroxide,[2] usually in the presence of a tertiary base such as pyridine. It is most effective method for achieving *syn*-dihydroxylation of alkenes.

B) **Catalytic procedures**:-

1. Catalytic dihydroxylation using osmium tetroxide-metal chroate.[2]

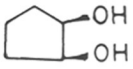
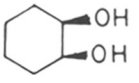
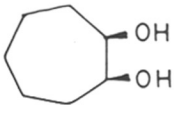
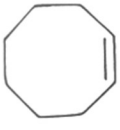
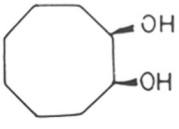
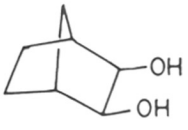
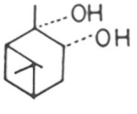
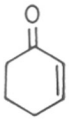
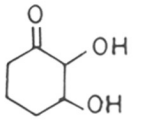
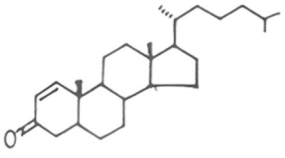
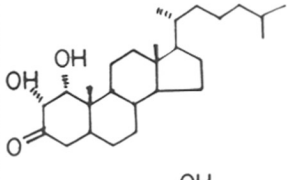
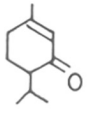
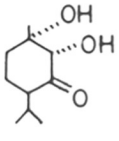
The *syn*-vicinal dihydroxylation of alkenes using catalytic quantities of osmium tetroxide with sodium, potassium, barium, silver chlorates as the primary oxidant has found considerable application. Silver and barium chlorate give better yields of *syn*-vicinal diols and can more easily be removed on completion of the reaction.

2. **Catalytic dihydroxylation using osmium tetroxide-hydrogen peroxide[3,9] (Mila's reagent)**

Syn-Dihydroxylation of alkenes may be effected by a catalytic amount of osmium tetroxide in the presence of hydrogen peroxide in *tert*-butyl alcohol. The disadvantage of the catalytic method

Table 1

Oxidation of alkenes with triphenylmethyl phosphonium permanganate

Substrate	diol	yield %	Reaction time · h	Method used
		58	Instant	—
		20	12	B:15% C:90 % Adipic acid
		55	1	—
		80	0,5	A: 50 % B: 50 %
		80	0,5	A : 15 %
		62	5	A : 18 % C : 40 %
		46	Instant	—
		30	10	—
		40	8	-

is that further oxidation can occur to give carbonyl products, thereby lowering the yield of the vicinal diol. This problem may be alleviated by use of osmium catalysed dihydroxylation procedure using *tert*-butyl hydroperoxide as the oxidant, under alkaline condition.

3. Catalytic dihydroxylation using osmium tetroxide-N-methylmorpholine-N-oxide.[5]

One of the most effective procedure for the osmium tetroxide catalysed *syn*-vicinal dihydroxylation of alkenes uses a tertiary amine N-oxide to regenerate the osmium tetroxide, and allows the reaction to be performed at room temperature with approximately 1 mol % of the catalyst. N-methylmorpholine-N-oxide is generally preferred as the oxidant because it affords a fast reaction rate and can be easily prepared. The procedure is applicable to a range of alkenes of differing complexity, and the superiority of the dihydroxylation method to other *syn*-dihydroxylation procedures has been demonstrated. Compatible functionality includes hydroxyl, ester, lactone, acid, ketone, and electron deficient alkenes such as those conjugated with a carbonyl group. This dihydroxylation method has found applicable in the synthesis of complex natural products. Recently, chloramine-T or alkyl-N-chloro-N-argentocarbamates have been used for effecting catalytic osmium tetroxide *syn*-vicinal dihydroxylation of alkenes.

Potassium permanganate

Potassium permanganate in aqueous solution is a commonly used oxidant in preparative organic synthesis. In case of *cis*-vicinal dihydroxylation of alkenes with potassium permanganate, the yields of *cis*-1,2-diols are very low due to overoxidation. The technique of phase transfer catalyst has improved the permanganate oxidation of alkenes to 1,2-diols or carboxylic acids. A new possibility of the *cis*-dihydroxylation of olefins is described by Zbiral et al.[10]. These authors have used triphenylmethylphosphonium permanganate in dry methylene chloride at -70°C for *cis*-dihydroxylation of alkenes. A large number of olefins are converted to *syn*-diols in moderate yields. The result of *syn*-dihydroxylation by this method are summarised in **Table-1**. Herriott[11] has used the term '*purple benzene*' for the first time which can be obtained more readily using quaternary

ammonium ions with potassium permanganate, and that such solutions are more convenient for effecting oxidations of alkenes. A number of olefins are oxidised with this reagent system and are summarised in **Table-2**.

Table-2

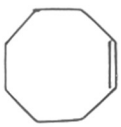
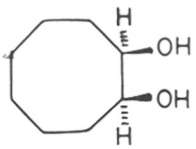
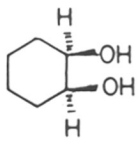
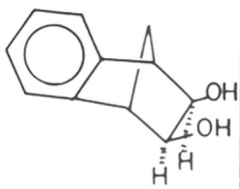
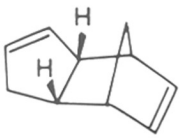
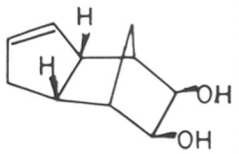
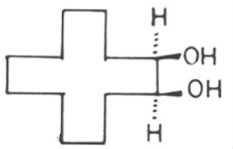
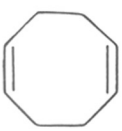
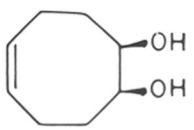
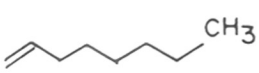
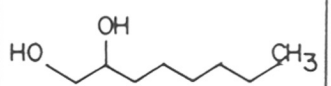
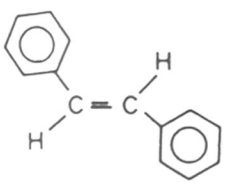
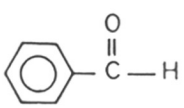
Oxidations with $KMnO_4$ using tricaprylmethylammonium chloride

Olefin	Product	% Yield (isolated)
Ph-C≡N	PhCOOH	86
Ph-CH_2-OH	PhCOOH	92
Ph-CH=CH-Ph (t)	PhCOOH	95
1-Octanol	Octanoic acid	47
1-Octene	Haptanoic acid	81

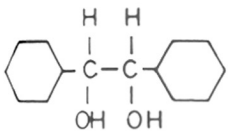
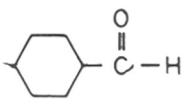
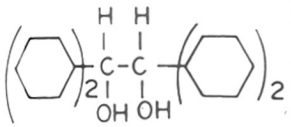
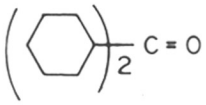
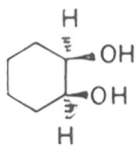
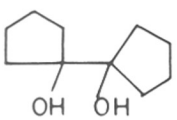
Webber[6] has utilised benzyltriethylammonium chloride as a phase-transfer catalysis for improvement of procedure for the alkaline potassium permanganate oxidation of olefins to *cis*-1,2-glycols. Phase-transfer catalyst (PTC) and crown ethers are two newer methods which have been utilised to make inorganic salts soluble in organic solvents. In the presence of benzyltriethylammonium chloride, potassium permanganate will dissolve in methylene chloride to afford a solution which oxidises alkenes to give a homogeneous dark-brown reaction mixture. From the latter, either 1,2-diols or aldehydes may be isolated, depending upon the pH of the aqueous solution which is used to quench[6] the reaction. Diols are formed if the solution is basic and aldehyde if it is acidic. Recently, Chandrasekaran[12] has improved the permanganate oxidation of alkenes to 1,2-diols or carboxylic acids by using phase-transfer catalyst technique. They prepared cetyltrimethylammonium permanganate (CTAP) for the *cis*-dihydroxylation of number of olefins as shown in **Table-3**, and the yield of diols are found to be comparable to the yield of diols obtained from

Table 3

Oxidation of alkenes and vic-diols with cetyltrimethylammonium permanganate

EDUCT	PRODUCT	method	Reaction time h	yield %	M.P(°C) found	M.P(°C) reported
		B	1	73	78-79	77.5-79 [13]
		B	1	86	97-98	98 [14]
		B	3	73	178-179	177-178.5 [15]
		A	4	86	48-49	48-51 [16]
		A	5	65	157-158	157-158 [17]
		A	1	35	105-106	104.5-106 [18]
		A	2	85	Oil	–
		A	0.5	70	–	–

contd.

EDUCT	PRODUCT	method	Reaction time h	yield %	M.P (°C) found	M.P (°C) reported
		A	0.5	97	—	—
		B	0.5	89	48–49	48.1[18]
	No reaction	A	24	—	—	—
	No reaction	A	24	-	—	—

cis-dihydroxylation of olefins with catalytic osmium tetroxide and N-methylmorpholine-N-oxide.

The reaction of alkenes with iodine and silver acetate in wet acetic acid followed by alkaline hydrolysis of the mixed mono- and di-acetates is a highly satisfactory procedure for the *cis*-dihydroxylation of long chain olefin acid (Woodward's procedure)[19] The reaction occurs in three steps.

1) *trans*-addition of iodine and silver acetate to olefin.

2) Replacement of halogen with -OH group, which may acetylated due to CH_3COOAg in acetic acid.

3) Hydrolysis of mono- and di-acetates.

The number of olefins are dihydroxylated using this method are given in **Table-4**.

Since Woodward's dihydroxylation procedure uses silver salts, which are expensive, a search has been made for alternative, cheap reagents which might achieve the same overall transformation by a similar mechanism. The thallium (I) acetate-iodine combination[20] leads to *syn*- or *anti*-vicinal dihydroxylation of cyclohexene when used in a manner analogous to silver carboxylate-iodine under Woodward or Prevost conditions, respectively. *Syn*-Dihydroxylation of steroidal alkenes with thallium (III) acetate in acetic acid has also been described.[20] Iodine tris (trifluoroacetate) may be prepared by oxidation of iodine with nitric acid in the presence of trifluoroacetic anhydride, oxidises alkenes in pentane to 1,2-bis trifluoroacetates in yields of 50-70%.[21] The oxidation is largely stereospecific. Thus, *cis*- and *trans*-2-butene afford the erythro and threo products in the ratio of 97:3 and 9:91, respectively. The stereoselectivity of the reaction decreases with increasing polarity of solvent and rearrangement can occur. The mechanism of the reaction probably involves electrophilic antiaddition across π-bond to give a 2-iodotrifluoroacetate intermediate, followed by nucleophilic displacement of iodo group by trifluoroacetate anion. Silver nitrate and iodine react in a suitable

Table-4

The *Cis*-hydroxylation of some ethylenic compounds (Woodward's procedure)

Olefin	Crude Product		Pure Product		
	Yield (%)	m.p. (°C)	Yield (%)	m.p. (°C)	m.p. °C (Lit)
Pure Olefins					
Methyl oleate	99	126-128	89	130-132	132
Methyl elaidate	97	92-93	91	93.5-94.5	95
Elaidic acid	89	92-94	85	94-94.5	95
Oleyl alcohol	100	123-125	81	126	126
Elaidyl alcohol	94	82-84	79	82.5-83.5	82
Cyclo-hexane	66	---	41	94-97	98
Acenaphthalene	89	180-204	28	203-208	213
Crude Olefins					
Olive oil	87	---	83	131-132	132
Castor oil	95	---	30	108-111	112
Methyl undecenoate	49	74-77	42	84-87.5	85-87
Methyl hexadecenoate	93	---	62	126-128	129
Methyl linoleate	95	---	14 15	173 163-165	174 164
Oleic acid	95	---	56	123-127	132

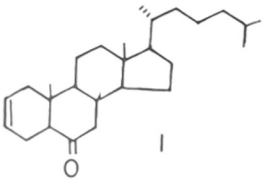
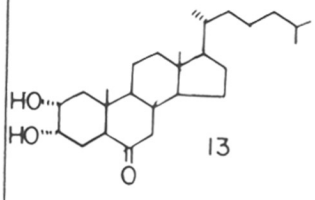
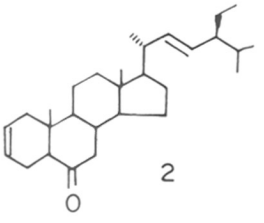
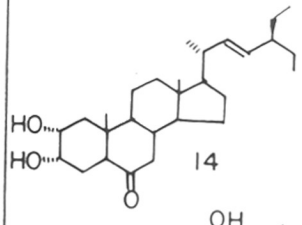
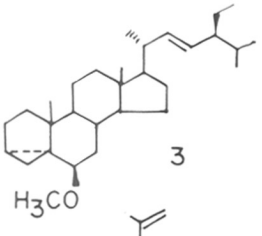
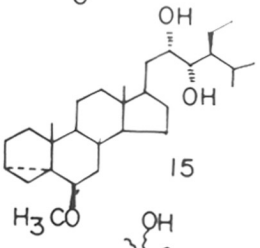
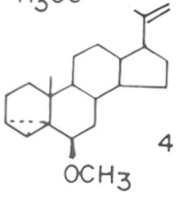
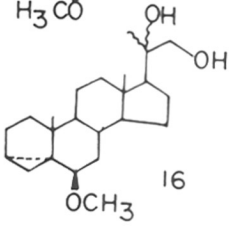
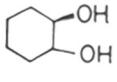
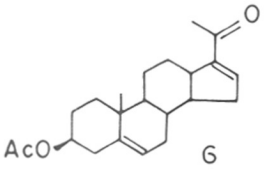
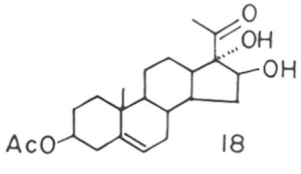
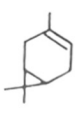
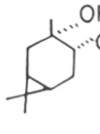
solvent (CH_3CN) to form iodinium nitrate, which may add in anti manner to alkenes to give 2-iodonitrates. Further reaction of the latter compound with silver nitrate leads to replacement of the halogen with inversion, affording by overall *syn*-addition.[22]

Present Investigation

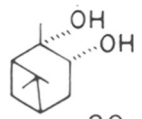
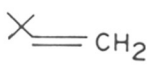
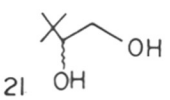
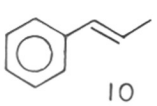
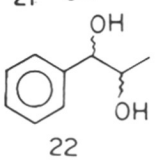
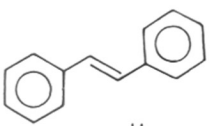
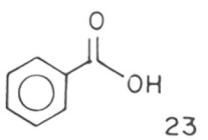
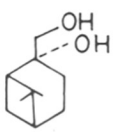
Osmium tetroxide is used as a versatile reagent for *cis*-vicinal dihydroxylation of olefins. The use of stoichiometric amount of osmium tetroxide for the *cis*-vicinal dihydroxylation of olefins is limited to small scale and for the preparation of precious compounds due to its high cost and toxicity. Recently, several methods are available for *cis*-vicinal dihydroxylation of olefins with catalytic amount of osmium tetroxide and primary oxidants. Nowadays, N-methyl-morpholine-N-oxide is widely used with catalytic amount of osmium tetroxide for oxidation of olefins to *cis*-1,2-glycols. It has been shown that under the influence of osmium tetroxide, vanadium pentoxide, chromium trioxide and even ultraviolet light hydrogen peroxide behaves as though it dissociates into two hydroxyl radicals which subsequently add on to carbon-carbon double bond to form glycols which may not oxidise further depending upon the experimental conditions employed. The use of osmium tetroxide and chlorates for the addition of hydroxyl groups to the double bond is limited to aqueous solutions, and, at times to specialised conditions. Similarly, organic peracids which have been used for this purpose are not of general applicability. Woodward's procedure for *cis*-dihydroxylation of olefins requires silver acetate with iodine in wet acetic acid. Since silver salts are costly, it is commercially not useful. Potassium permanganate oxidises olefins but due to overoxidation and other competitive procedures, it is not of practically important for the preparation of *cis*-glycols from alkenes. Potassium permanganate derived reagents such as triphenylmethylphosphonium permanganate is used for dihydroxylation at -70° in moderate yield.

The aim of the present investigation is to provide a cheap, mild, efficient and environment friendly procedure for *cis*-dihydroxylation using tetradecyltrimethylammonium permanganate (TDTAP) reagent. This TDTAP reagent was prepared by mixing an equimolar quantities of the aqueous solutions of potassium permanganate and tetradecyltrimethylammonium bromide. A violet precipitate formed which was filtered and dried. This violet crystalline solid is stable at room temperature for 1 to 2 days. It can be stored at 0°C in brown bottle for months. The solid was characterised by elemental analysis and melting point. The *cis*-vicinal dihydroxylation of a series

Table 5
cis-Dihydroxylation of alkenes with TDTAP reagent

Substrate	Product	Yield (%)	m.p. (°C) (lit °C)
 1	 13	92[a]	202 (206-207)[23]
 2	 14	88[a]	232-234 (235-238)[24]
 3	 15	20	122 (123-123)[25]
 4	 16	71	—
 5	 17	45	96 (98)[26]
 6	 18	50	191 (193-195)[27]
 7	 19	65(70)	68 (70-71)[28]

cont'd

Substrate	Product	Yield (%)	m.p. (°C) (lit. °C)
 8	 20	55	54 (55-56)[29]
 9	 21	28	—
 10	 22	58	58(61-62)[30]
 11	 23	20	120(122)
 12	 24	62	80 (83.5)[31]

a ; Yield based on recovery of starting material

of alkenes has been carried out using this reagent and the *cis*-1,2-diols are obtained in moderate yields (**Table-5**). The reaction is carried out in methylene chloride-*tert*-butanol solvent at ambient temperature. Few potent brassinosteroids intermediates (entry **1-4**) have been prepared from corresponding alkenes. In some cases, the yield of diols are comparable to the yield of diols obtained on treatment of olefins with osmium tetroxide (entry **1**, **2**, **7**). The reaction proceeds smoothly without the formation of unwanted side products. Some terpene and aliphatic olefins have also been dihydroxylated successfully using TDTAP reagent. In case of 16-dehydropregnenolone acetate (entry **6**), the α,β-unsaturated double bond was selectively dihydroxylated in presence of C-5(6) double bond. The diols obtained by this method are similar to those which are obtained by using osmium tetroxide. Hence, this TDTAP reagent can be used for chemo- and stereoselective dihydroxylation of alkenes under mild conditions.

Experimental Section

Tetradecyltrimethylammonium permanganate (TDTAP)

To a stirred solution of potassium permanganate (7.9g, 0.05 mol) in water (250 ml), was added a solution of tetradecyltrimethylammonium bromide (17.5g, 0.052 mol) in water (250 ml), dropwise at 25°C for 30 minutes. A violet colour precipitate formed immediately and the mixture was stirred for 30 minutes more. The violet colour precipitate was filtered, washed thoroughly with water (5x50 ml) and dried in vacuum descicator over P_2O_5 to furnish the salt (17.25g, 92%), m.p. 165-167°C (d); crystallised from CH_2Cl_2. Anal. Calc. for $C_{17}H_{38}NMnO_4$; C, 54.40; H, 10.13; N, 3.73. Found: C, 54.47; H, 10.32; N, 4.01.

A typical procedure for *cis*-dihydroxylation of alkene using tetradecyltrimethylammonium permanganate

To a magnetically stirred solution of tetradecyltrimethylammonium permanganate (0.211g, 0.00075 mol) in methylenechloride (1 ml) and *tert*-butanol (5 ml) was added olefin **1** (0.192g, 0.0005 mol) in CH_2Cl_2 (2 ml) at 10°C with dropping funnel in 5 minutes. The reaction mixture was allowed to attain room temperature (30°C) and was stirred at this temperature for 1h. The saturated aqueous solution of sodium bisulphite (10 ml) was added to the reaction mixture and the mixture was stirred for another 30 minutes. The solvent was evaporated off and the residue was extracted with ethyl acetate (3 times). The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. Evaporation of solvent afforded crude diol **13** containing some starting olefin **1**. This was further purified by column chromatography to get pure diol **13** (0.146g, 90%) and olefin (0.043g, 22%) was recovered back. Similarly, *cis*-dihydroxylation of olefins **2-12** was carried out.

Spectral data

2α,3α-Dihydroxy-5α-cholest-6-one 13

m.p. 202°C (lit.[23] 206-207°C); IR ν_{max} 3380 (-OH), 1720 (-C=O); ^{1}H-NMR δ 0.65 (s, 3H), 0.75 (s, 3H), 0.82 (d, J=2Hz, 3H), 0.88 (d, J=2Hz, 6H).

2α,3α-Dihydroxy-24S-ethyl-5α-cholest-22E-en-6-one 14

m.p. 232-234°C (lit.[24] 235-238°C); IR ν_{max} ~ 3360 (-OH), 1715 (-C=O); ^{1}H-NMR δ 0.7 (s, 3H), 0.76 (s, 3H), 0.79 (d, J=7.5Hz, 3H), 0.8 (t, J=6.4Hz, 3H), 0.86 (d, J=6.4Hz, 3H), 1.02 (d, J=6.5Hz, 3H), 2.2-2.63 (m, 1H), 2.63-2.8 (m, 1H), 3.61-4.27 (m, 2H), 5.04 (t, J=6.5Hz, 2H).

3α,5-Cyclo-6β-methoxy-(22S,23S,24S)-22,23-dihydroxy-24-ethyl-cholestane 15

m.p. 122°C (lit.[25] 122-123°C); IR ν_{max} 3540 (-OH), 1480, 1400, 940; ^{1}H-NMR δ 0.4-0.8 (m, 3H), 0.8 (s, 3H), 0.87-1.1 (m, 15H), 2.82 (t, J=2.6Hz, 1H), 3.37 (s, 3H), 3.35-3.7 (m, 2H).

3α,5-Cyclo-6β-methoxy-(20S),(20R)-20,22-dihydroxypregnane 16

Oil; IR ν_{max} 3410 (-OH), 1390, 1105, 870, 850; ^{1}H-NMR δ 0.9 (s, 3H), 1.05 (s, 3H), 1.28 (s, 3H), 2.82 (t, J=2.6Hz, 1H), 3.36 (s, 3H), 3.25-3.8 (m, 2H); m/z 362 (M^+), 347, 331, 307, 299, 281, 213, 199, 159, 145, 131, 121, 105(100%), 91, 79, 75, 71, 67, 57.

***Cis*-Cyclohexane-1,2-diol 17**

m.p. 96°C (ether) (lit.[26] 98°C); IR ν_{max} 3400 (-OH), 1490, 1480, 1225; ^{1}H-NMR δ 1.05-2.0 (m, 8H), 3.72 (bd, 2H).

3β-Acetoxy-16,17-dihydroxy-5-en-pregna-20-one 18

m.p. 191°C (lit.[27] 193-195°C); IR ν_{max} 3450 (-OH), 1712 (-C=O), 1735 (-O-C=O); ^{1}H-NMR δ 1.02 (s, 3H), 1.24 (s, 3H), 2.06 (s, 3H), 2.33 (s, 3H), 4.02 (m, 1H), 4.62 (m, 1H), 5.37 (m, 1H).

***Cis*-Carane-3,4-diol 19**

68°C (hexane) (lit.[28] 70-71°C); IR ν_{max} 3400 (-OH), 1385, 1080, 1060, 935, 870; ^{1}H-NMR δ 0.9 (s, 3H), 1.0 (s, 3H), 1.22 (s, 3H), 2.05 (m, 1H), 3.18 (dd, J=10, 2Hz, 1H).

***Cis*-Pinane-2,3-diol 20**

54°C (hexane) (lit.[29] 55-56°C); IR ν_{max} 3400 (-OH), 1380, 1230, 1100, 1060, 1030, 960, 920; ^{1}H-NMR 0.93 (s, 3H), 1.26 (s, 3H), 1.29 (s, 3H), 2.65-1.33 (m, 6H), 3.96 (dd, J=9.0 and 5.0Hz, 1H); m/z 152, 149, 136, 126, 117, 108, 107, 79(100%), 77, 71, 55, 51, 43.

3,3-Dimethylpropane-1,2-diol 21

Oil; IR ν_{max} 3400 (-OH), 1375, 1225, 1100, 1050, 1025, 930, 880; ^{1}H-NMR δ 0.91 (s, 9H), 3.47-4.03 (m, 3H).

***Cis*-1-phenyl-1,2-propanediol 22**

58°C (Ether-pet.ether) (lit.[30] 61-62°C); IR ν_{max} 3400 (-OH), 1500, 1460, 1140, 880, 770, 710; ^{1}H-NMR δ 1.16 (d, J=6Hz, 3H), 3.95 (dq, J=1,6Hz, 1H), 4.4 (d, J=7Hz, 1H), 7.36 (s, 5H).

Benzoic acid 23

m.p. 120°C, IR ν_{max} 3400 (-OH), 1700 (-C=O), 1340, 1300, 950.

***Cis*-2,10-Pinanediol 24**

80°C (lit.[31] 83.5°C); IR ν_{max} 3380 (-OH), 1385, 1200, 1185, 1040; ^{1}H-NMR δ 0.91 (s, 3H), 1.22 (s, 3H), 3.17 (s, 2H), 3.5 (s, 2H); m/z 170 (M^+), 152, 139, 121, 109, 93, 83(100%), 69, 55, 41.

References

1. March,J. "*Advanced Organic Chemistry*" 3rd Ed. Wiley Eastern Limited, **1984**, p.732-734.
2. Schroder,M. *Chem.Rev.* **1980**, 80, 187-213; Gunstone,F.D. *Adv.Org.Chem.* **1960**, 1, 103-147.
3. Akashi,K.; Palermo,R.E.; Sharpless,K.B. *J.Org.Chem.* **1978**, 43, 2063-2066.
4. Rigby,W. *J.Chem.Soc.* **1956**, 2452-2454.
5. VanRheenen,V.; Kelly,R.C.; Cha,D.Y. *Tetrahedron Lett.* **1976**, 23, 1973-1976; Ray,R.; Matterson,S. *Tetrahedron Lett.* **1980**, 21, 449-450.
6. Weber,P.W.; Shepherd,J.P. *Tetrahedron Lett.* **1972**, 48, 4907-4908; Ogino,T.; Mochizuki,K. *Chem.Lett.* **1979**, 443.
7. Jasserland,D.; Girard,J.P.; Rosi,J.C.; Gragner,R. *Tetrahedron Lett.* **1976**, 19, 1581-1584.
8. Mangoni,L.; Adinolfi,M.; Barone,G.; Parrilli,M. *Tetrahedron Lett.* **1973**, 45, 4485-4486.
9. Milas,N.A.; Sussman,S. *J.Am.Chem.Soc.* **1936**, 58, 1302-1304; **1937**, 59, 2345-2347.
10. Reischi,W.; Zbrial,E. *Tetrahedron*, **1979**, 35, 1109.
11. Herriott,A.W.; Picker,D. *Tet.Lett.*, **1974**, 16, 1511-1512.
12. Bhushan,V.; Rathore,R.; Chandrasekaran,S. *Synthesis*, **1984**, 431.
13. Cope,A.C.; Fenton,S.W.; Spencer,C.F. *J.Am.Chem.Soc.*, **1952**, 74, 5884.
14. Lloyd,W.D.; Navarette,B.J.; Shaw,M.F. *Synthesis*, **1972**, 610.
15. Tanida,H.; Tsushima,T. *Tet.Lett.*, **1969**, 41, 3647-3650.
16. Ohno,M.; Okamoto,M. *Tet.Lett.*, **1964**, 35, 2423-2426.
17. Jernow,J.W.; Gray,D.; Clossen,W.D. *J.Org.Chem.*, **1971**, 36, 3511-3515.
18. CRC Handbook of *Chemistry and Physics*, 59th Ed. CRC Press Inc., **1978-79**, p. C-200.
19. Woodward,R.B. *J.Am.Chem.Soc.*, **1958**, 80, 209-211.

20. Cambie,R.C.; Hayward,J.L. *Org.Synth.*, **1980**, 59, 169.

21. Schmeisser,M.; Dahmen,K. *Chem.Ber.*, **1967**, 100, 1633; Buddrus,J. *Angew.Chem.Int.Ed.Eng.*, **1973**, 12, 163.

22. Morris,L.J. *Chem.Ind.* (London), **1958**, 1291.

23. Thompson,M.J.; Meudt,W.J.; Mandava,N.B.; Dutky,S.R.; Lusby,W.R.; Spaulding,D.W. *Steroids*, **1982**, 39, 89-105.

24. Mori,K.; Sakakibara,M.; Ichikawa,Y.; Veda,H.; Okada,K.; Vmemura,T.; Yabuta,G.; Kuwahara,S.; Kondo,M. *Tetrahedron*, **1982**, 38, 2099-2109.

25. Hazra,B.G.; Pore,V.S.; Joshi,P.L.; Padalkar,S.N.; Deshpande,S.N.; Rajamohanan,P.R. *Mag.Reson.Chem.*, **1993**, 31, 605-608.

26. Smith,W.B. *J.Org.Chem.*, **1979**, 44, 1631-1633.

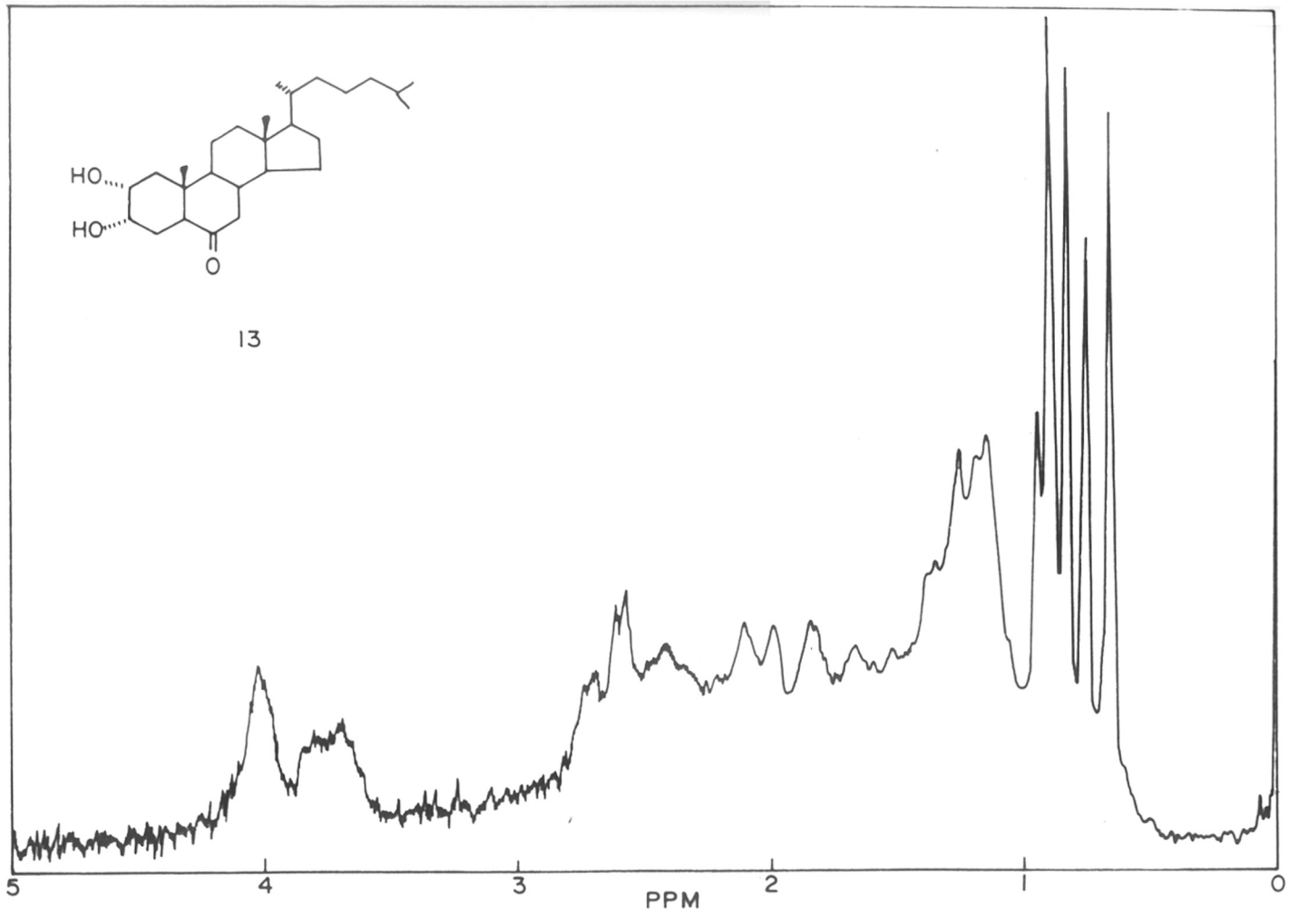
27. Hydorn,A.E.; Korzun,J.N.; Moetz,J.R. *Steroids*, **1964**, 3, 493-494.

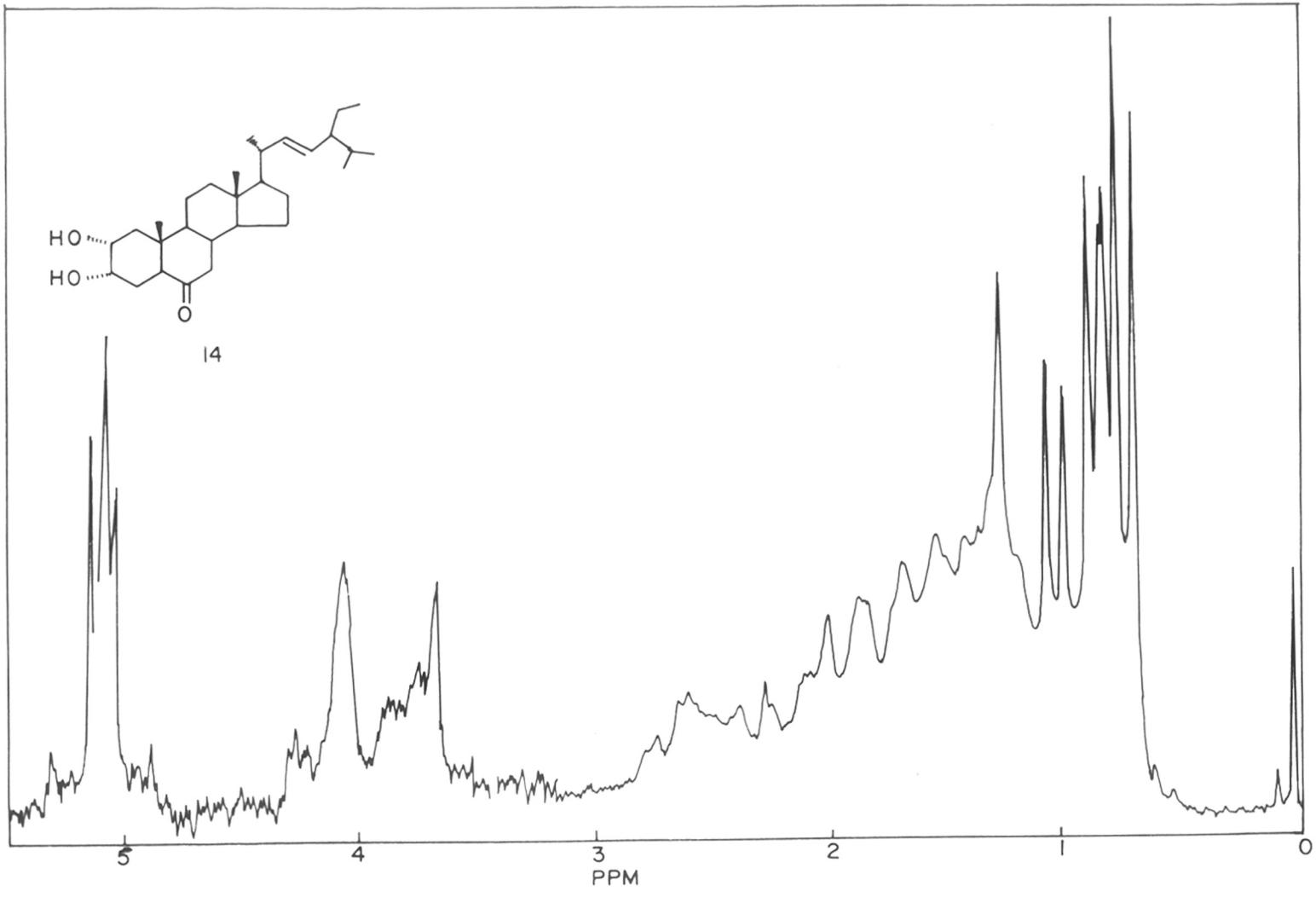
28. Kropp,P.J. *J.Am.Chem.Soc.*, **1966**, 88, 4926-4934.

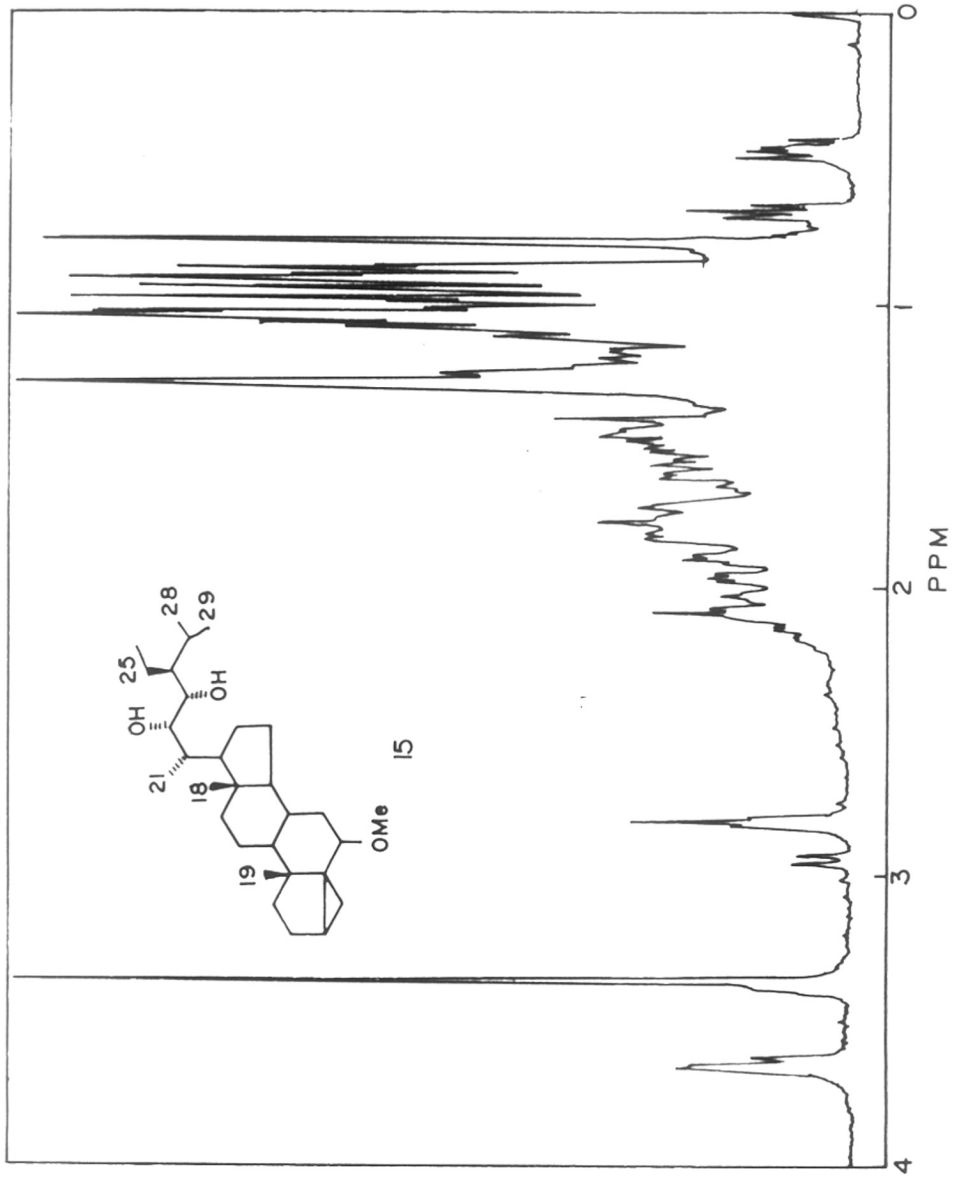
29. Carlson,R.G.; Pierce,J.K. *J.Org.Chem.*, **1971**, 36, 2319-2324.

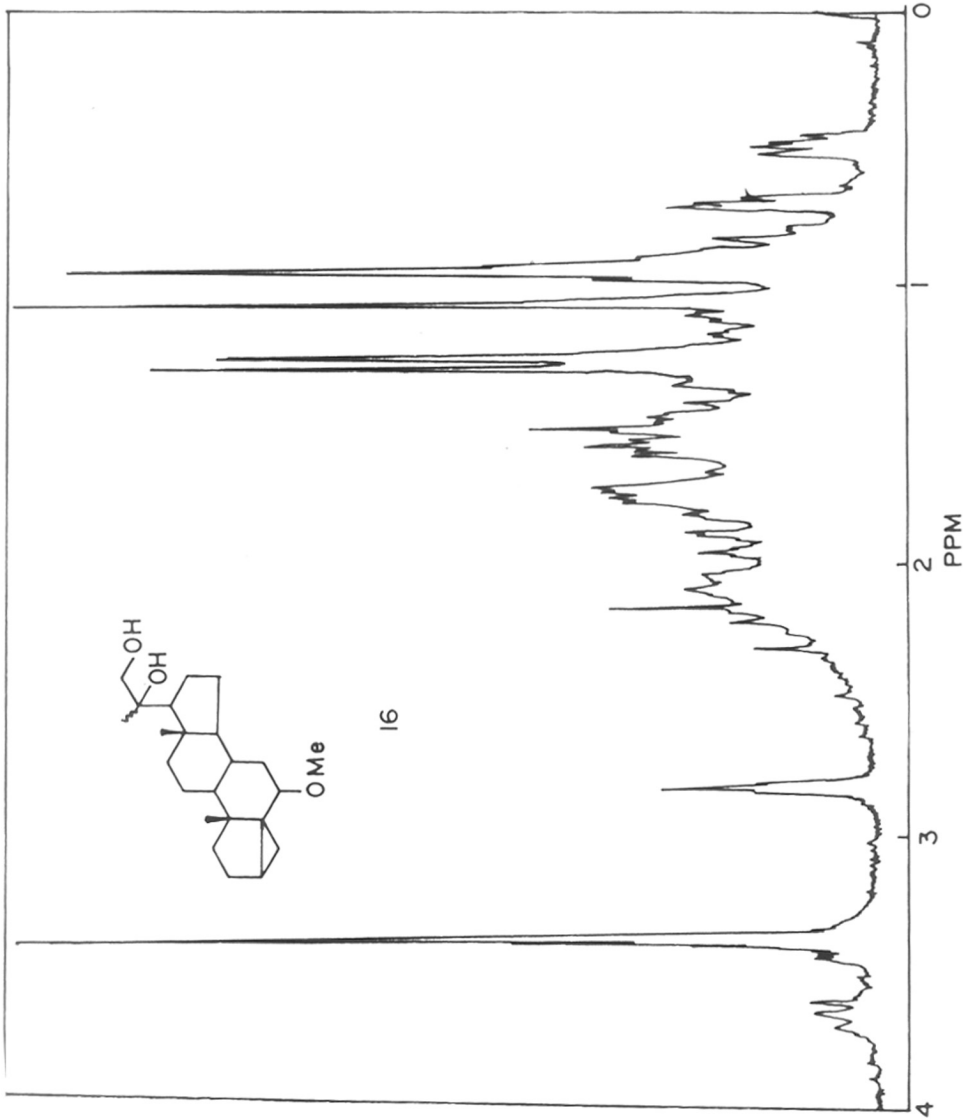
30. Witkop,B.; Foltz,C.M. *J.Am.Chem.Soc.*, **1957**, 79, 197.

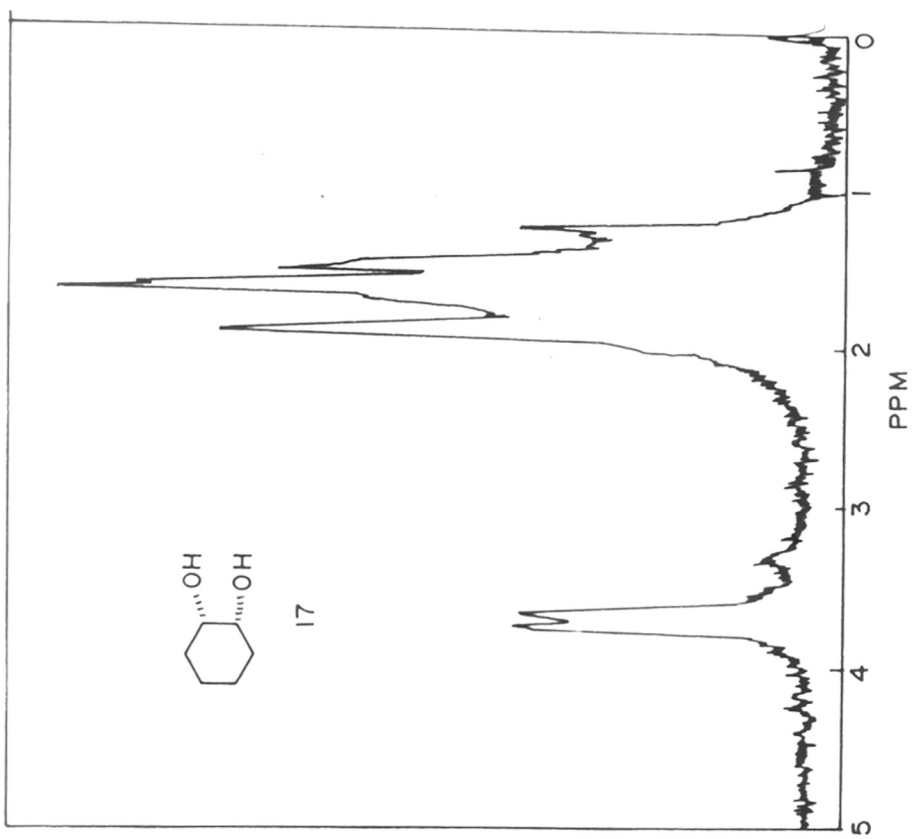
31. Coxon,J.M.; Dansted,E.; Hartshorn,M.P.; Richards,K.E. *Tetrahedron*, **1968**, 24, 1193-1197.

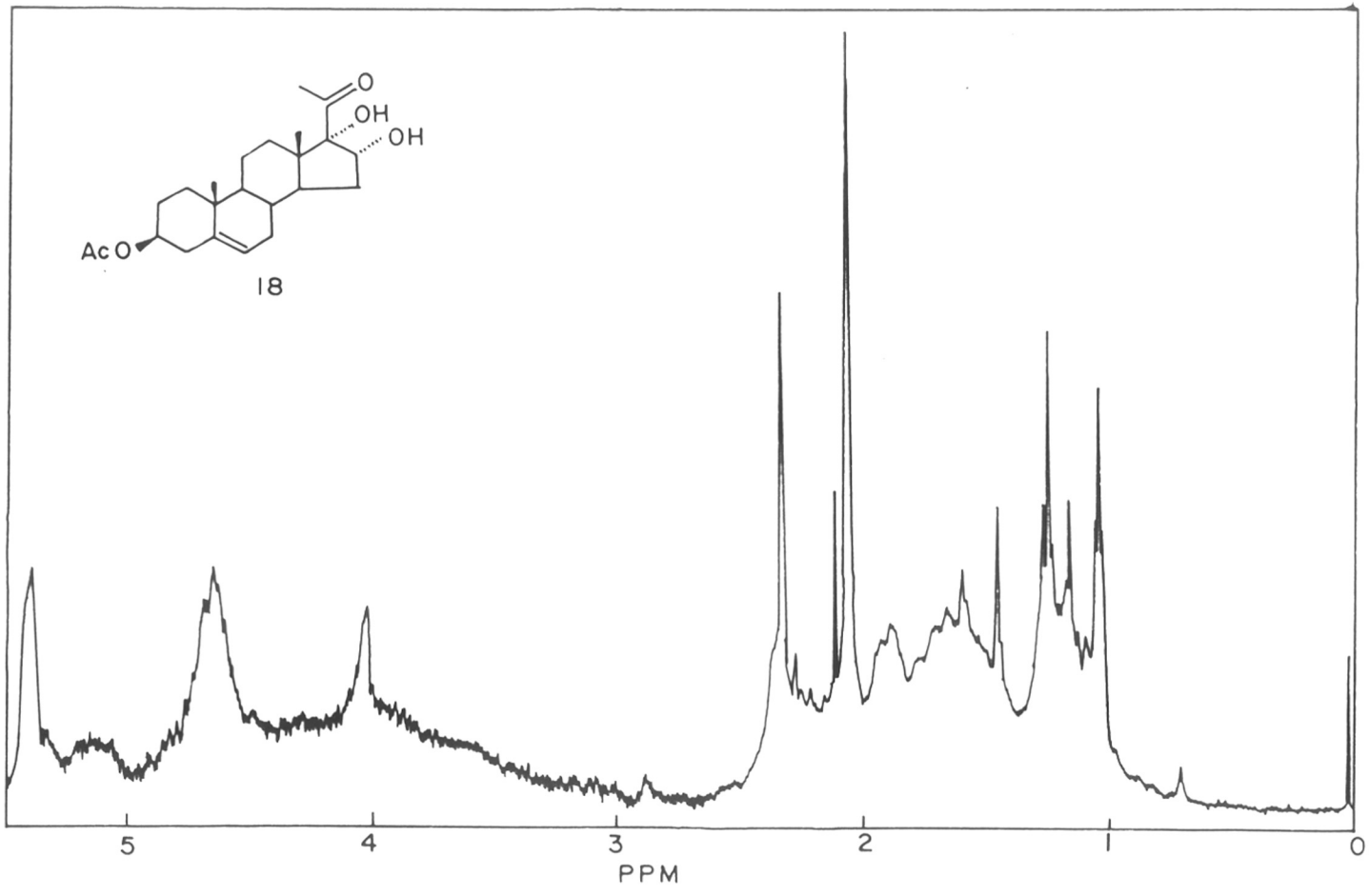

HO
HO
O
13
5
4
3
2
1
0
PPM

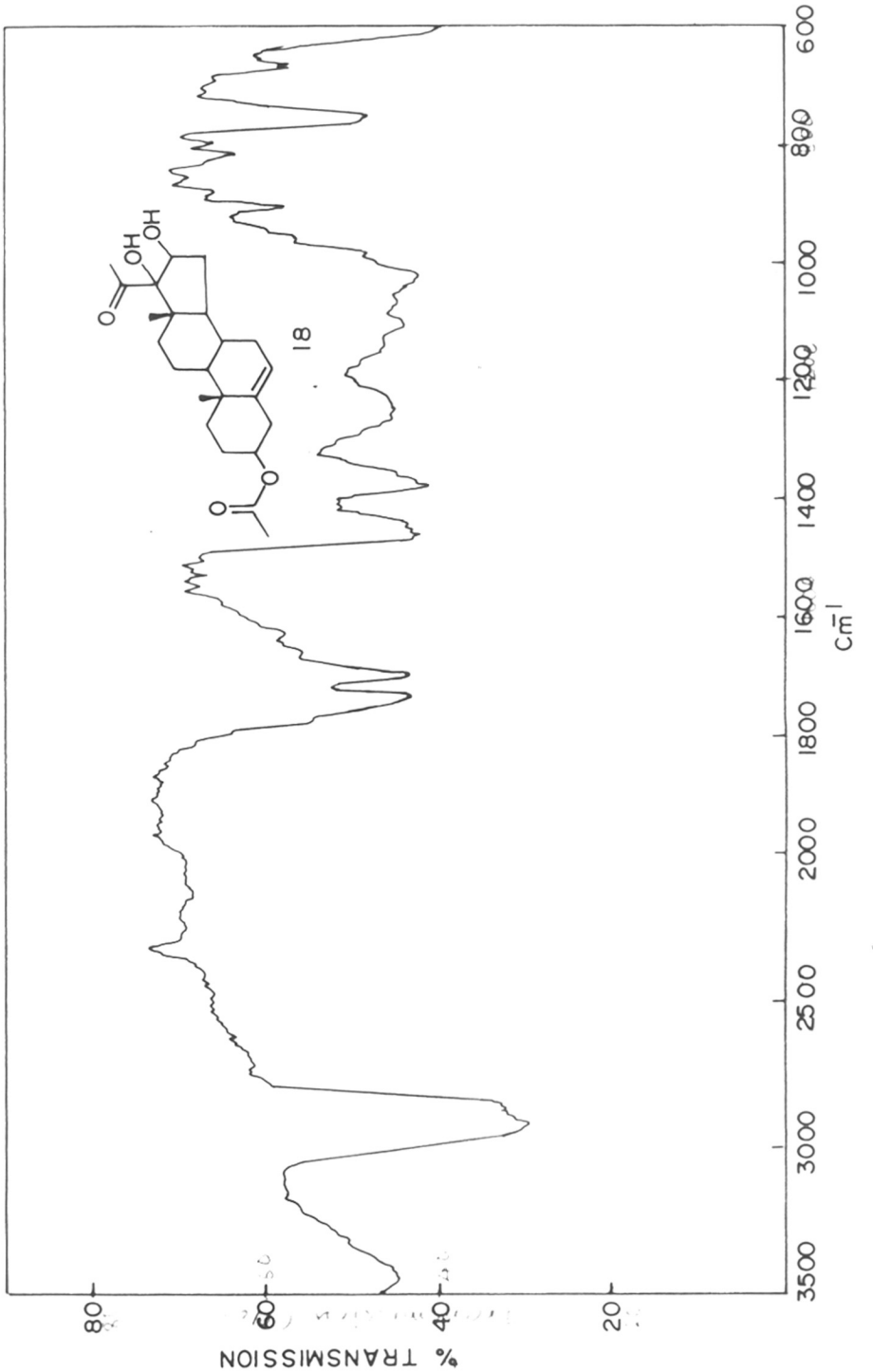

HO
HO
O
14
5
4
3
2
1
0
PPM

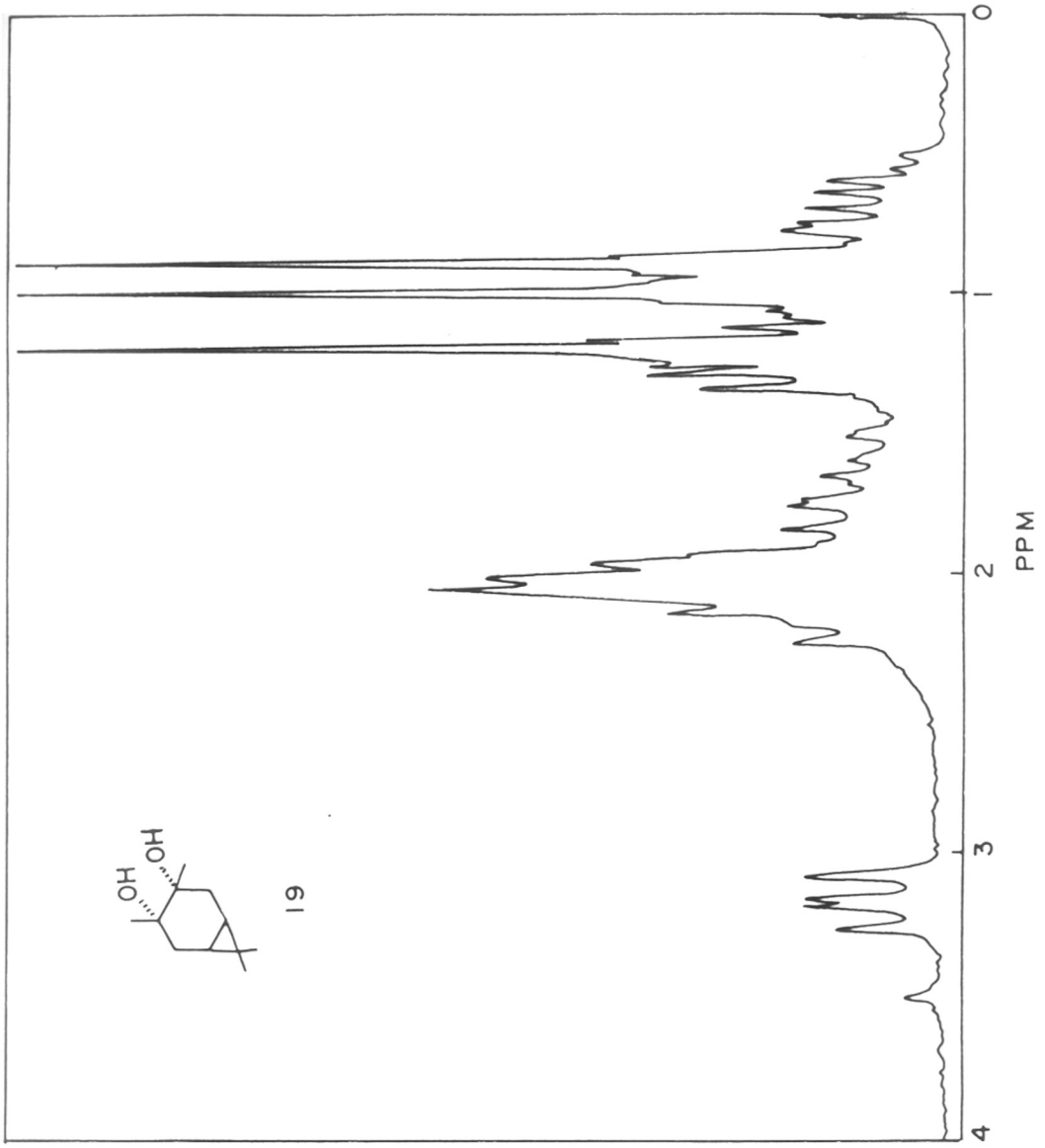

28
29
25
OH
OH
21
18
19
OMe
15
4
3
2
1
0
PPM

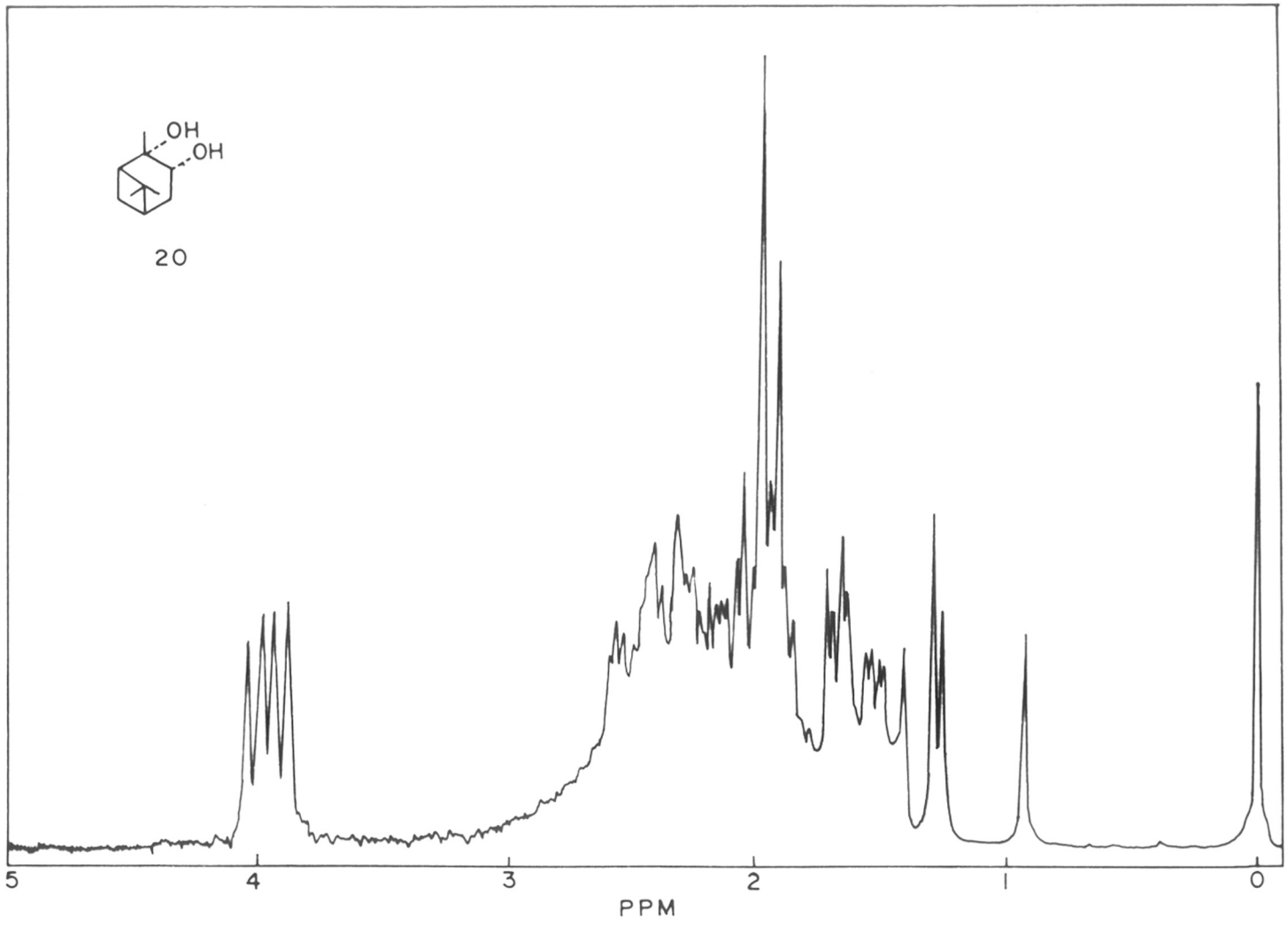

OH
OH
OMe
16
0
1
2
3
4
PPM

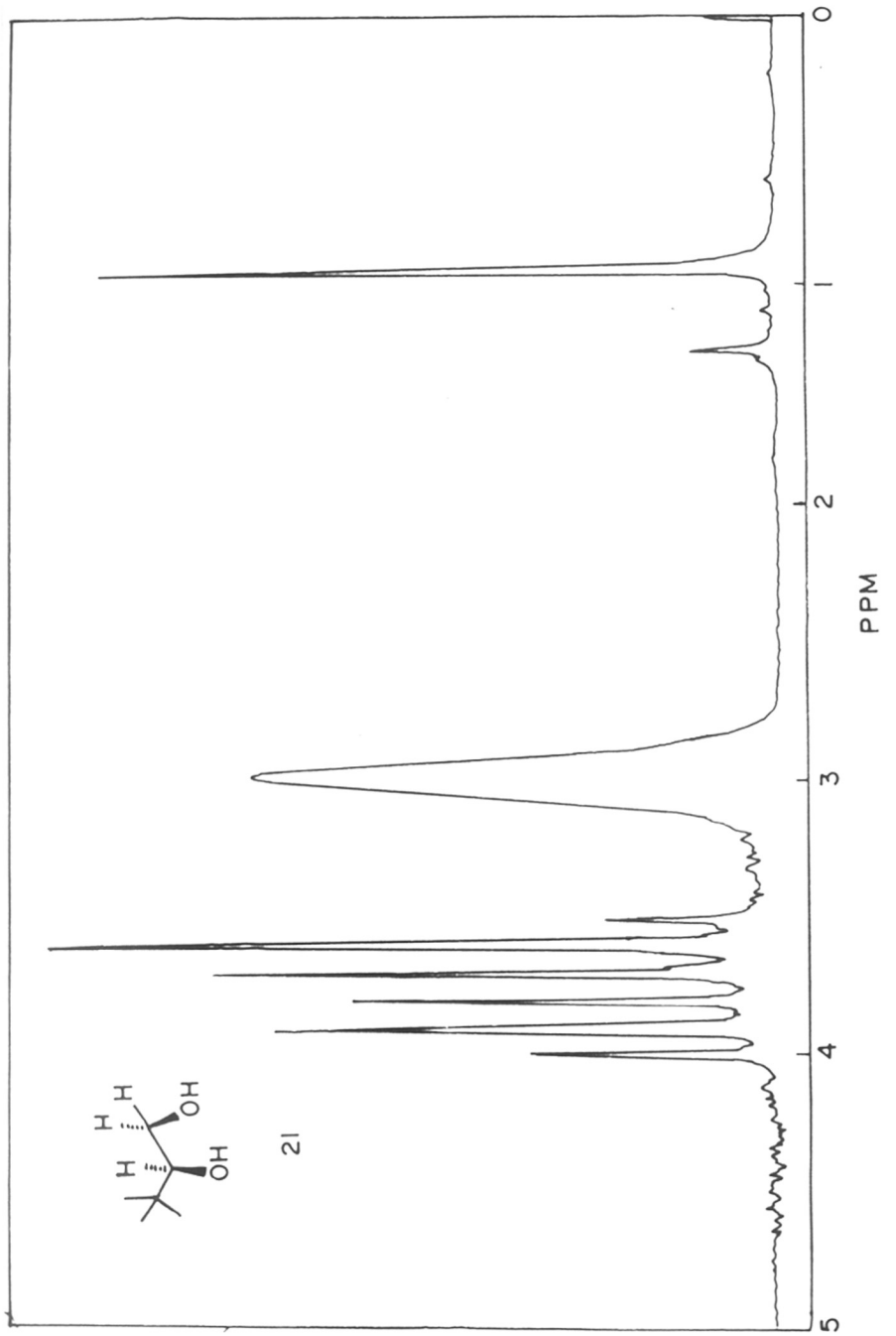

OH
OH
17
0
1
2
3
4
5
PPM

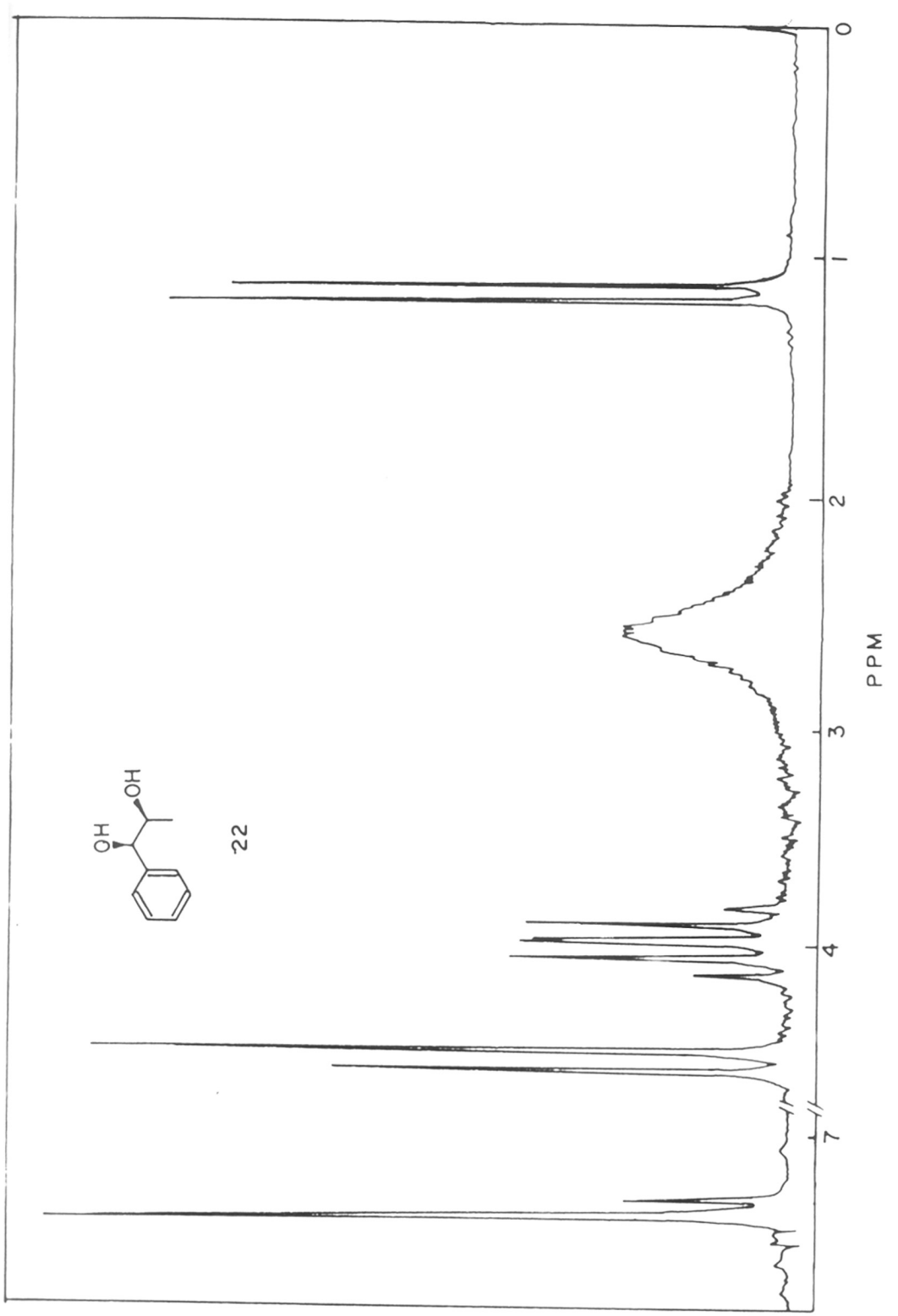

O
OH
OH
Ac O
18
5
4
3
2
1
0
PPM

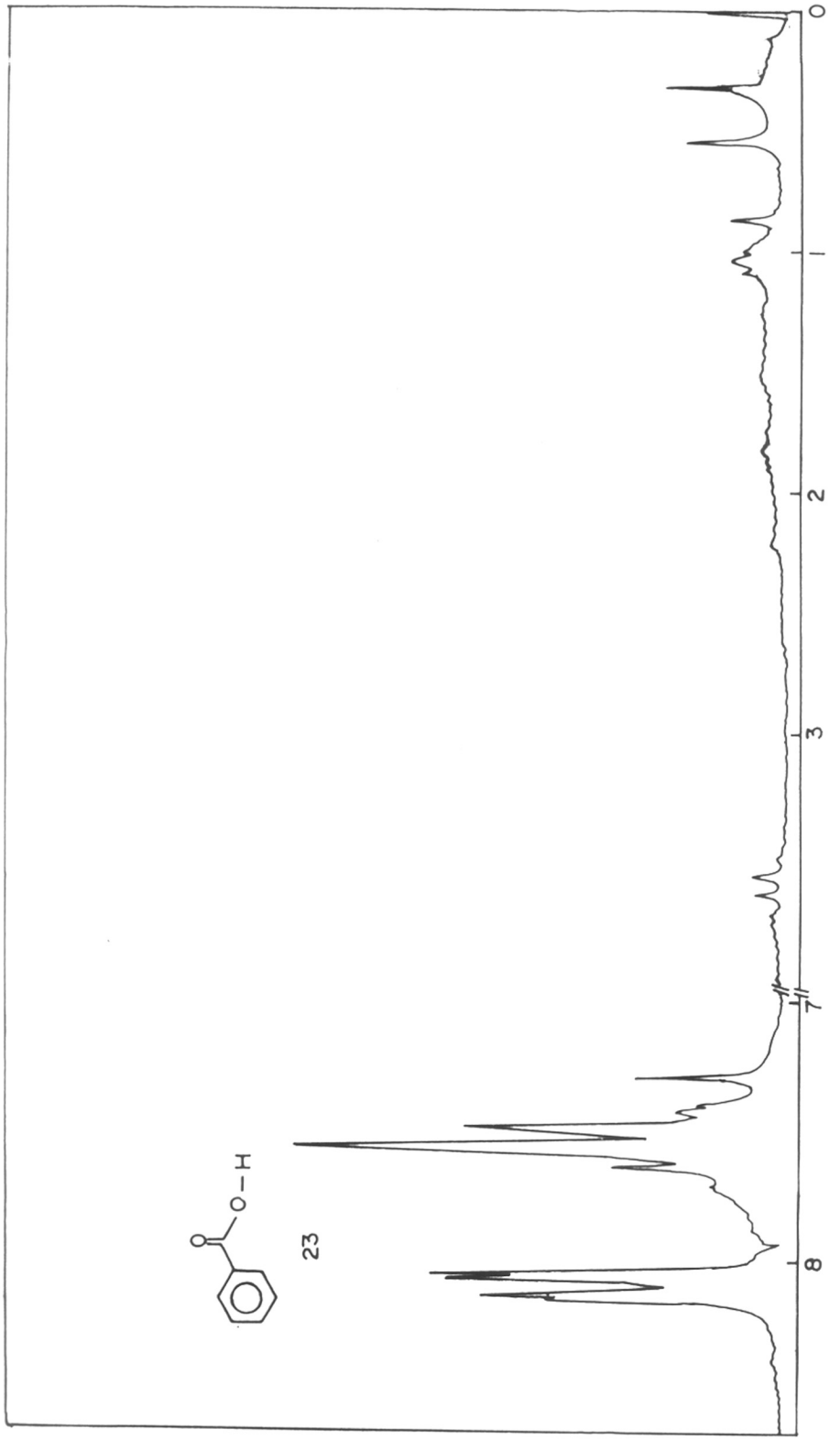

% TRANSMISSION
80
60
40
20
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
cm⁻¹
OH
OH
O
O
O
18

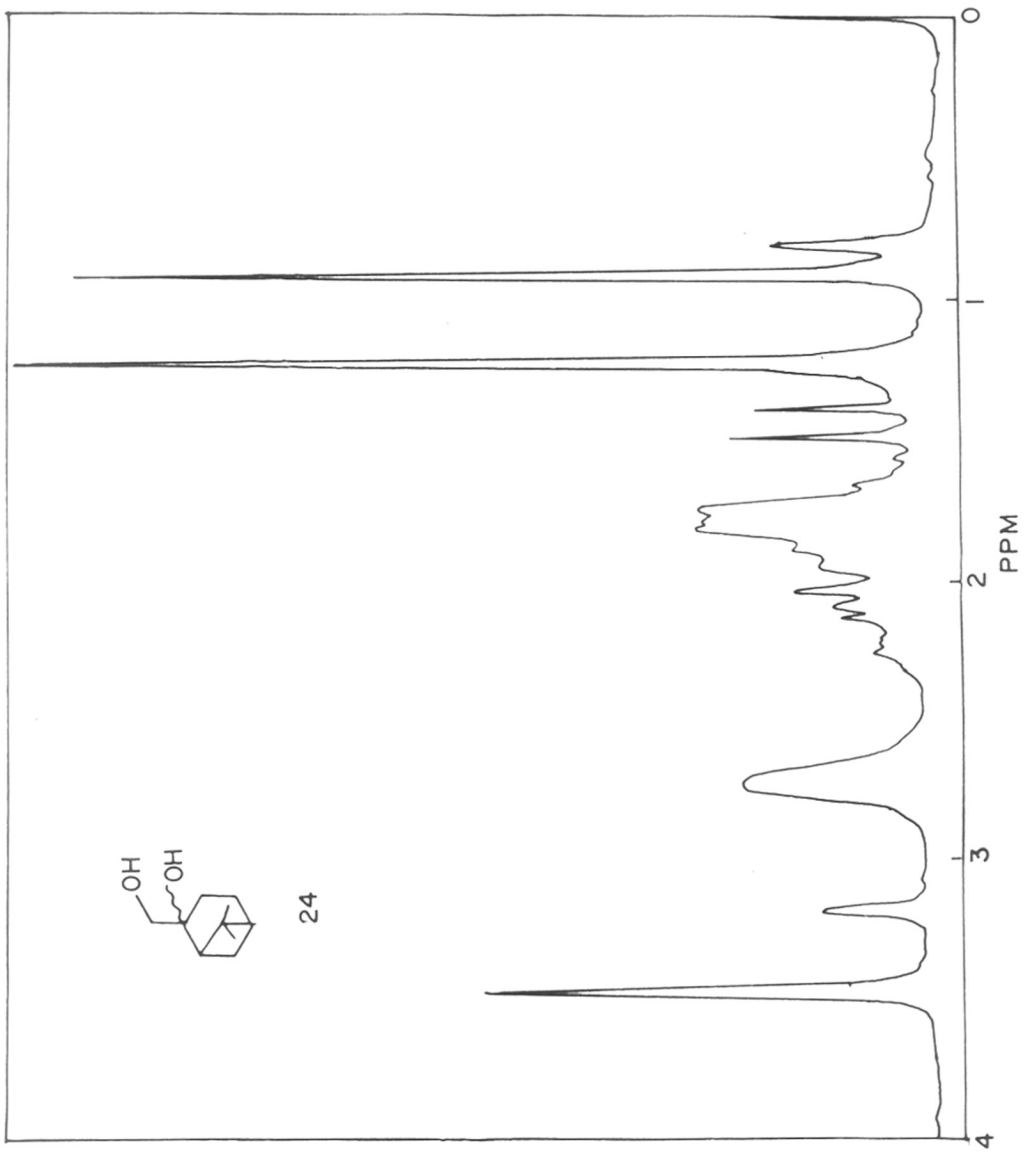

OH
OH
19
0
1
2
3
4
PPM


OH
OH
20
5
4
3
2
1
0
PPM


H
H
OH
H
OH
21
0
1
2
3
4
5
PPM


OH
OH
22
0
1
2
3
4
7
PPM


O-H
O
23
8
7
4
3
2
1
0


OH
OH
24
0
1
2
3
4
PPM

CHAPTER-IV

Stereoselective *trans*-dichlorination, dibromination of alkenes with tetradecyltrimethylammonium permanganate-trimethylchlorosilane, trimethylbromosilane

Summary

This chapter consists of two sections.

Section-A

Stereoselective *trans*-dichlorination of alkenes with tetradecyltrimethylammonium permanganate-trimethylchlorosilane

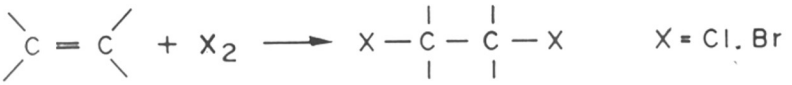
Section-B

Stereoselective *trans*-dibromination of alkenes with tetradecyltrimethylammonium permanganate-trimethylbromosilane

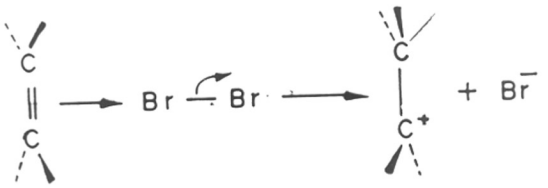
Potassium permanganate exhibits[1] unique reactivity towards olefins. However, its usefulness in organic synthesis has been severely limited by solubility problem. In an attempt to improve and modify the reactivity of potassium permanganate, we have prepared tetradecyltrimethylammonium permanganate (TDTAP). This TDTAP reagent is used for *trans*-dichlorination, dibromination of alkenes in combination with trimethylchlorosilane (TMCS), trimethylbromosilane (TMBS). *trans*-Vicinal dibromination with this type of reagent is achieved for the first time.

Introduction

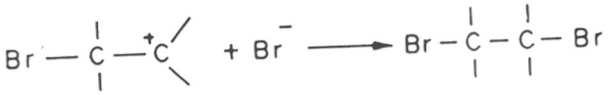
Addition of halogens is an important general reaction of double bonds.



This reaction is rapid and serve as a simple diagnostic method for unsaturation. The reaction can be regarded as a nucleophilic displacement reaction on halogen. The alkene is the nucleophile and halide ion is the leaving group.

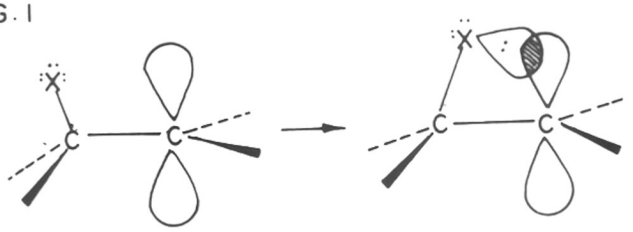


The resulting cation reacts with halide ion to give the observed product.

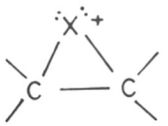


The intermediate cation contains an electron-deficient carbonium ion carbon atom and a halogen atom with nonbonding electron pairs. Consequently, there is a tendency for overlap to produce a cyclic halonium ion, as in **Figure-1.**

FIG. I

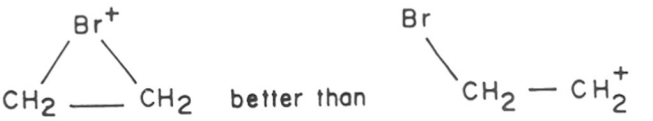


The cyclic halonium ion may be written in Lewis form, as shown below:

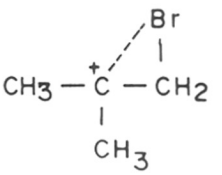


The advantage in terms of energy in forming such a structure is primarily formation of an additional covalent bond. Furthermore, all the atoms now have octet electronic configuration. However, a price is paid for these gains. The angles in the three-membered ring structure are bent far from the desired tetrahedral geometry, and the positive charge is localised on the more electronegative halogen atom rather than on carbon.

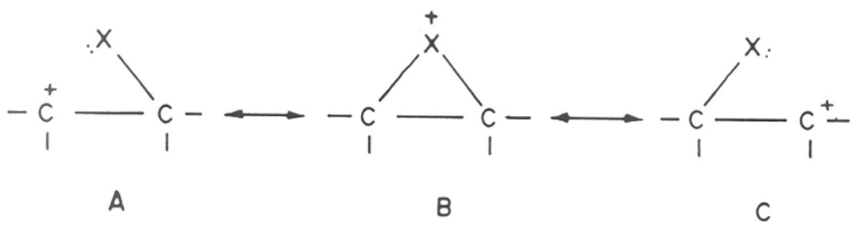
In practice, the tendency of such a cation to exist in the cyclic form depends on the stability of the "*open*" carbonium ion. The intermediate formed from the addition of bromine to ethylene is best described as symmetrical brominium ion having relatively strong C-Br bonds. The alternative open would be a highly unstable primary carbonium ion.



The ion formed by addition of bromine to isobutylene is better described as a tertiary carbonium ion with a long and weak bond to bromine.

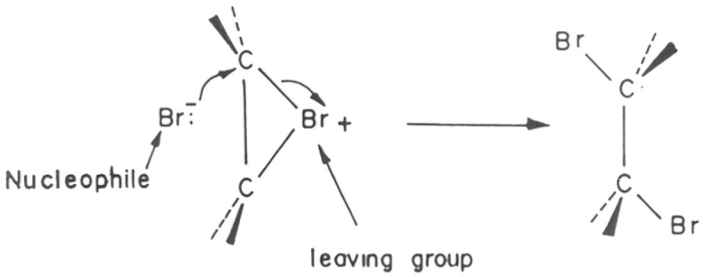


Cations such as these may be described in terms of three resonance structures : The actual ion is hybrid of the three structures **A**, **B** and **C**. If both **A** and **C** correspond to unstable carbonium ions, then structure **B** is more important contributor to the actual structure of the ion.

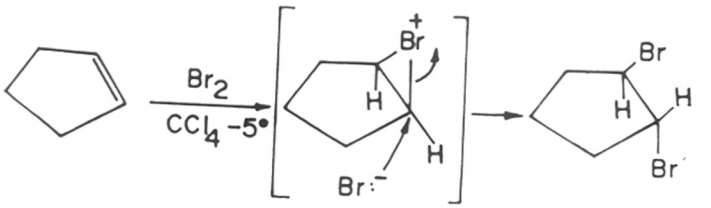


If either **A** or **C** corresponds to a relatively stable carbonium ion, then that structure contributes more and the ion has substantial carbonium ion character without as much halonium ion character.

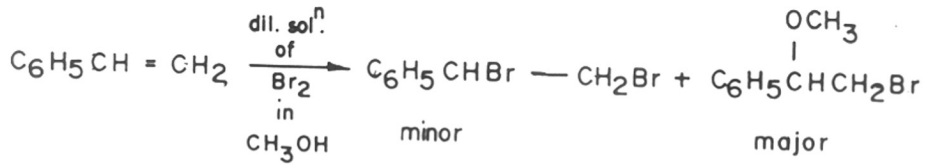
The cyclic halonium ion intermediate has an important effect on the stereochemistry of halogen additions. When halide ion reacts with the cyclic ion, the reaction is a nucleophilic displacement reaction.



Since the nucleophile Br^- must approach carbon to the rear of the leaving group, the net result is *trans* addition of Br_2.



When a solution of bromine is used in an inert solvent such as carbon tetrachloride, the only nucleophilic reagent available for reaction with the intermediate cation is bromide ion. In hydroxylic solvents, the solvent itself is nucleophilic and can react in competition with the bromide ion.

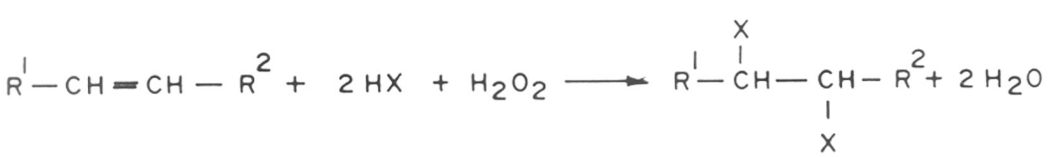


The reactive amounts of dibromide and bromoether produced depend on the concentration. Generally, for dilute solutions, the product is almost exclusively the bromoether.

Several other reagents add Cl_2 to double bonds, among them NCl_3[3], SO_2Cl_2[4], PCl_5[5], $SbCl_5$[6], $MoCl_5$[7] and iodobenzene dichloride $PhICl_2$[8]. A convenient method for the addition of Br_2 to a double bond on a small scale is the commercially available pyridinium bromide perbromide $C_5H_5NH^+Br_3^-$[9]. Br_2 or Cl_2 can also be added with $CuBr_2$ or $CuCl_2$ in the presence of a compound such as acetonitrile, methanol or triphenylphosphine.[10]

Olah et al.[11] has reported a phase transfer catalyst promoted halogenation of alkenes with hydrohalic acid hydrogen peroxide. They used carbon tetrachloride as a solvent and benzyltrimethyl ammonium chloride as a catalyst. These conditions are applicable for the preparation of dichlorides and dibromides from the corresponding olefins in better yields than the conventional halogen addition reactions (**Scheme-1**).

SCHEME 1



A general procedure reported by Olah and co-workers for the halogenation of alkenes is as follows:

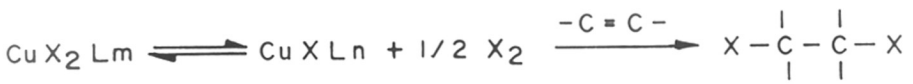
To an ice cooled, magnetically stirred suspension of the alkene (50 mmol), calcium halide (50 mmol), conc. hydrochloric acid (10 ml), carbon tetrachloride (10 ml) and benzyltrimethylammonium chloride (100 mg), is added dropwise 30% H_2O_2 (6 ml). The mixture is then allowed to warm up to room temperature while stirring is continued for 20 min. Dilution with petroleum ether, washing with water, drying and removal of solvent, gives the crude dichloride or dibromide. Purification of the product by vacuum distillation furnished the sample identical in physical and spectral properties which are prepared, using this method are summarised in **Table-1**.

Table-1

Alkene	*vic*-dichloride		Lit. b.p./torr	*vic*-dibromide		Lit. b.p./torr
	Yield(%)	b.p./torr		Yield(%)	b.p./torr	
Cyclohexene	76	90-92°/20	91°/20	95	100-102°/14	101°/14
Cycloheptene	75	68-70°/4.5	93-94°/11-12	95	65-67°/0.35	138-140°/20-25
Cyclooctene	77	90-92°/5	130.5°/25	96	94-97°/1	123-124°/5
1-octene	56	67-71°/4	67-71°/4	92	117-120°/5	118.5°/15

Baird,Jt. et al.[12] has published a new method for halogenation of olefinic bonds with copper(II) halides in the presence of strong co-ordinating species (**Scheme-2**).

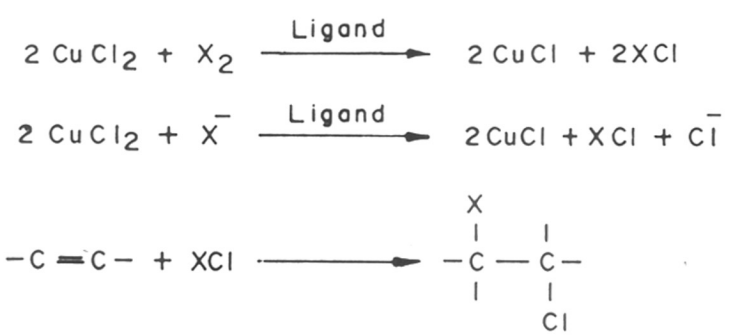
SCHEME 2



L = Ligand

Simple olefins are converted to vicinal dihaloalkanes in good yields. Substitutive halogenation of reactive organic compounds by copper(II) halides has been known for several decades, halogen addition in copper(II) halide-olefin reactions has been observed recently. Ligand induced dissociation of copper(II) halide in the presence of olefin yielded the corresponding halogen addition product. The most beneficial ligands were those derived from nitrogen, phosphorus, sulphur compounds that stabilise copper(I) through strong back donation. Some representative ligands used are acetonitrile, triphenylphosphine, triphenylphosphite, dimethylformamide, thiophene, sulfolane, tetrahydrofuran and methanol. The ligand induced dissociation of copper(II) chloride afforded the *in situ* formation and reaction of interhalogens as iodine and bromide monochloride. The subsequent addition reaction produce vicinal chlorohalides (**Scheme-3**).

SCHEME 3



The chlorohalides are listed in **Table-2**.

Table-2

Halogenation of olefins with copper(II) halides in acetonitrile

	Yield of vicinal dihaloalkane, %				
Olefin	$CuCl_2$	$CuBr_2$	$I_2/CuCl_2$	$Br_2/CuCl_2$	
$2HC=CH_2$	32	57	70	-	
CH_3-CH=CH_2	-	-	85	-	
CH_3-CH=CH-CH_3	-	91	-	-	
$(CH_3)_3CH=CH_2$	17	91	73	-	
$(CH_3)_2C=C(CH_3)_2$	53	91	-	-	
Cyclohexene	73	80	95	85	
$PhCH=CH_2$	-	87	75	-	
norbornene	68	-	-	-	
$CH_2=CH-CH=CH_2$	43	92	90	-	
Cyclopentadiene	-	-	70	-	
$CH_3CH=CHCOOCH_3$	-	49	-	-	
$CH_2=CH-Cl$	-	-	81	-	
$CH_2=CH-CN$	-	32	-	-	
$CH_2=CHOOCCH_3$	-	-	83	-	

Nugent and co-workers[13] have reported *cis*-vicinal dichlorination of olefins by molebdenum (VI)-acetyl chloride. In a typical procedure, 0.73g. (6.48 mmol) *trans*-4-octene was treated with tetrabutylammonium octamolybdate **1**, 3.84g. (14.3 mg - atom Mo) in 50 ml CH_2Cl_2. Fifteen minutes after adding 5 ml acetyl chloride the suspension had turned yellow and homogeneous but no dichloride could be detected by glc. The solution suddenly discharged to red and then green after which stirring was continued for 2h. Ether was added to precipitate Mo-containing products and the solution was washed with 3M NaOH and water. Evaporating and drying organic phase afforded product; purified by column chromatography with pentane afforded 1.08g. (91%) of 4,5-dichlorooctane. Yields of several olefins are summarised in **Table-3**. The stoichiometry of the reaction was described by the following equation (**Scheme-4**).

SCHEME 4

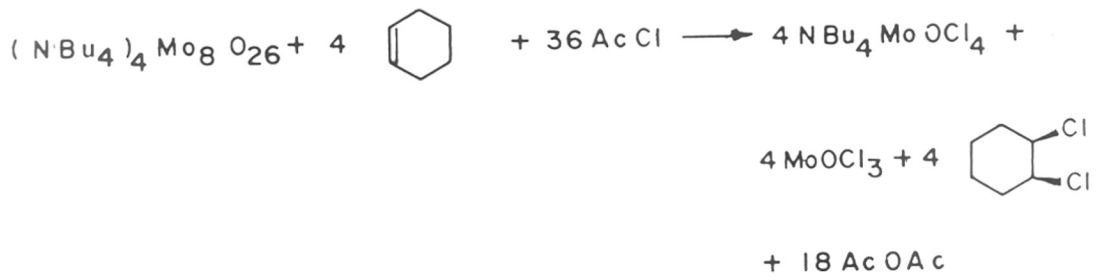


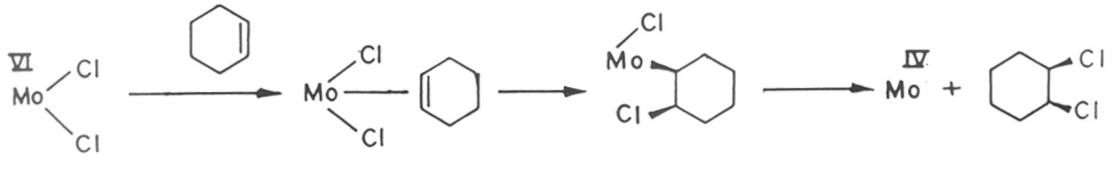
Table-3

cis-Chlorination of alkenes with Mo(VI)-acetyl chloride

Alkene	Product	Yield (%)
1-Hexene	1,2-dichlorohexane	85
1-Octene	1,2-dichlorooctane	86
cis-3-octene	(meso)-3,4-dichlorooctane	91
trans-4-octene	(d,l)-4,5-dichlorooctane	91
Cyclohexene	*cis*-1,2-dichlorocyclohexane	94
Cycloheptene	*cis*-1,2-dichlorocycloheptane	83
Tetramethylethylene	2,3-dichloro-2,3-dimethylbutane	35

These observations are accomodated by a mechanism similar to that proposed by Sharpless for side product formation during chromyl chloride oxidation (**Scheme 5**).

SCHEME 5



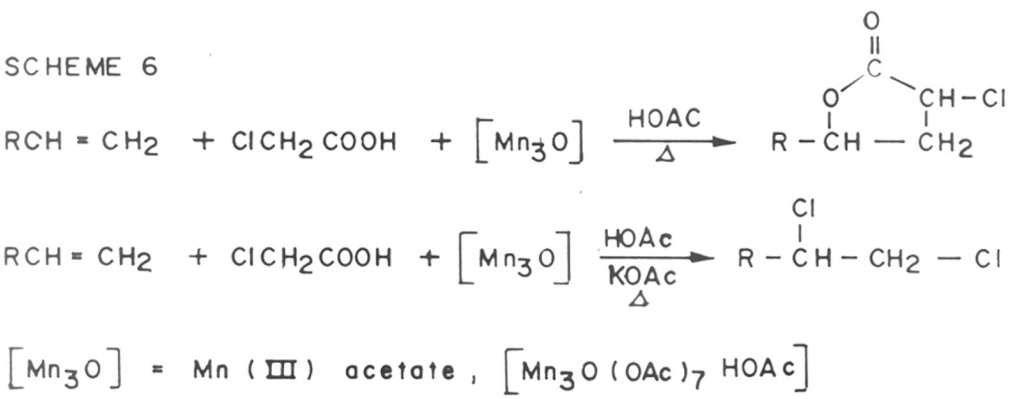
Such a scheme involves formal *cis*-insertion of the olefins into the Mo-Cl bond of polychlorinated Mo^{VI} species followed by reductive elimination. The addition of ether to the product mixture precipitated approximately half of the molybdenum as the complex NBU_4MoOCl_4.

Treatment of the remaining solution with triphenylphosphine oxide allowed isolation of the remaining Mo as $(Ph_3PO)_2MoOCl_3$. The author proposed that the active reagent for *cis*-vicinal dichlorination is a polychlorinated molybdenum species.

Chlorination of alkenes by manganese (III) chloride species was reported by Donnelly et al.[14]

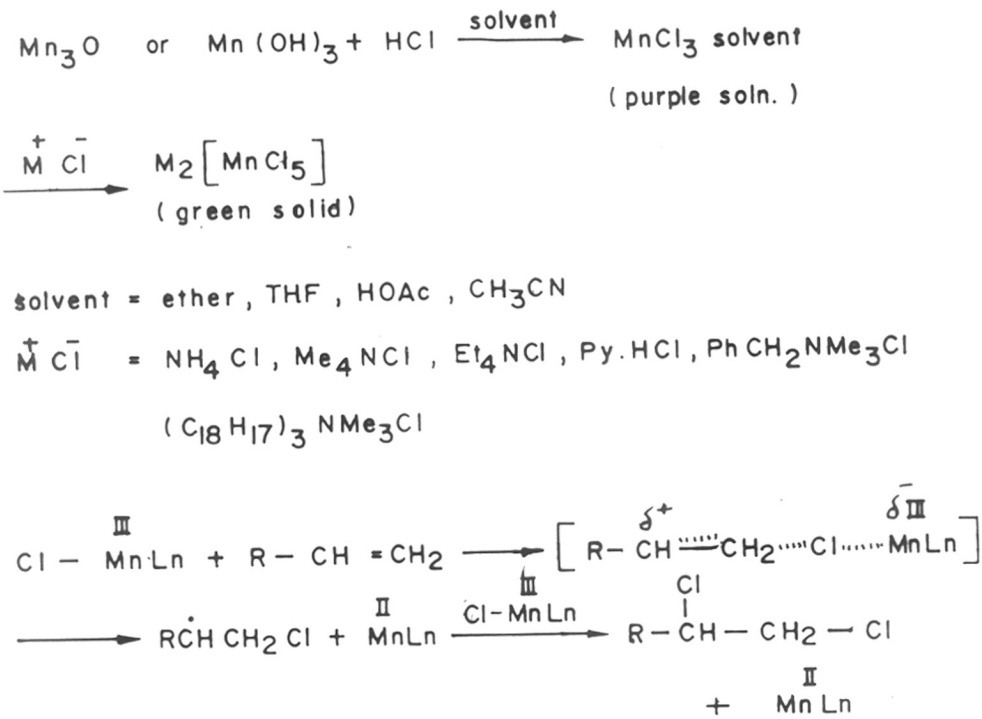
They prepared α-chloro-γ-butyrolactones *via* a Mn(III) acetate lactone annulation reaction employing chloroacetic acid (**Scheme-6**). When potassium acetate was added to the reaction mixture, however, this manifold was completely shut down and the 1,2-dichloride became the exclusive product. They thought that chloride ion was produced by SN^2 displacement by the addition of acetate anion. This chloride ion could have been oxidatively added across the alkene *via* some Mn(III) chloride species eventually resulted in double chloride addition.

SCHEME 6



They mixed alkene, Mn(III) acetate and a chloride salt ($NaCl/CaCl_2$) and heated it to effect the same reaction. The results are given in **Table-4**. The method is very efficient for chlorinating non-conjugated alkenes. The author proposed the possible Mn(III) chloride complexes (**Scheme-7**).

SCHEME 7



All the given salts and solvates proved to be active chlorinating species, however, due to low solubility of all the salts (except $PhCH_2N^+Me_3$ and $(C_{18}H_{17})_3N^+Me_3$) eliminated these species from further practical consideration. Modest to good yields of 1,2-dichloride were obtained.

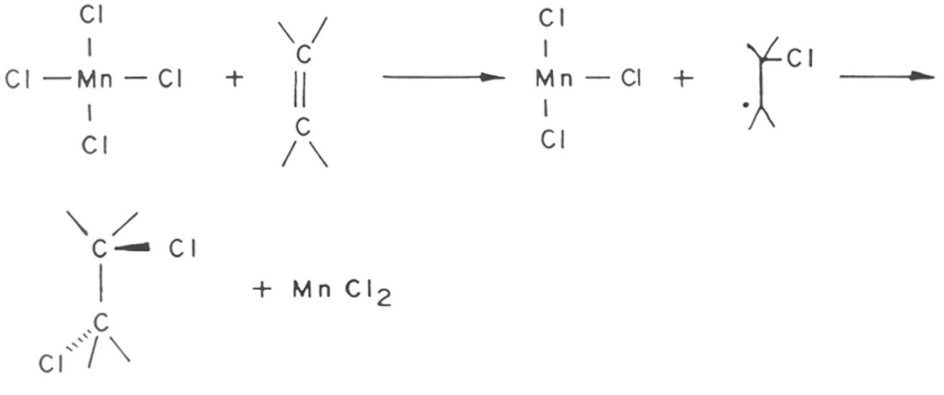
Table-4

Manganese (III) chlorination of alkenes

Alkene	$[Mn_3O(OAc)_7HOAc]/CaCl_2$ 1,2-dichloride, %	$MnCl_3$/HOAc 1,2-dichloride, %
1-Hexene	81	52
1-Octene	79	72
trans-4-Octene	91 (2.2:1; meso:dl)	71 (11:1; meso:dl)
Cyclohexene	61 (*trans*)	48 (*trans*)
Cyclooctene	83 (3:1; *trans*:*cis*)	85 (1.3:1; *trans*:*cis*)
Methylcyclohexene	74	14
α-Methylstyrene	0	62
Methyl Cinnamate	47 (erythro)	63 (63:1; erythro:threo)

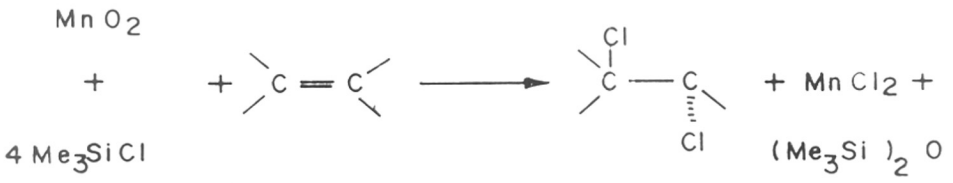
The observations can be rationalised by participation of Mn (IV) chloride species. During the reduction, therefore, the MnO_2TMCS reagent apparently inserts two chlorine atoms stepwise. The great selectivity towards the addition must be taken as evidence of a negligible involvement of a free chlorine atoms. They have proposed a radical mechanism, as shown in **Scheme-8.**

SCHEME 8



Dichlorination of alkenes with manganese dioxide-trimethylchlorosilane (TMCS) was reported by Bellesia et al.[15] The title reagent system (MnO_2-TMCS) gives rise to a smooth and high yield chlorination of unconjugated olefins, without isomerisation occuring. The *trans-vic*-dichloro derivatives are obtained from cyclic substrates with high stereoselectivity. The results are summarised in **Table-5**. When the deep violet colour, developed after the addition of TMCS to the suspension of MnO_2 in THF, has faded out the reagents have been transformed into $MnCl_2$ as the only inorganic solid and hexamethyldisiloxane virtually as the only observed (gc, ms, tlc) organic reaction product (besides the 1,2-dichloroderivatives) (**Scheme-9**).

SCHEME 9



The participation of chlorine gas can be ruled out from the results of parallel experiments with molecular chlorine, which are characterised by comparatively low yields and by a variety of by-products which are virtually absent when MnO_2-TMCS system is used. The observations can be rationalised by participation of a manganese (IV) chloride species. During its reduction, therefore, the MnO_2-TMCS reagent apparently inserts two chlorine atoms stepwise. The great selectivity towards the addition must be taken as evidence of a negligible involvement of free chlorine atoms. Thus, the addition product can derive from a collision between the alkene and the chloro-carrier in solution, involving a non-chain radical mechanism.

More recently, the same authors[16] (Bellesia et al.) have achieved chlorination of alkenes with MnO_2-$MnCl_2$-Acetyl chloride in DMF. A Mn(III) intermediate and ligand transfer processes are

Table – 5

trans – Dichlorination of Olefins with manganese dioxide – trimethylchlorosilane

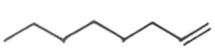
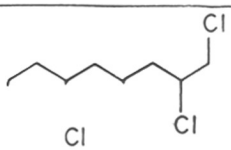
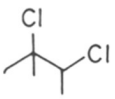
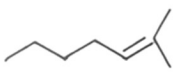
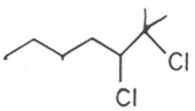
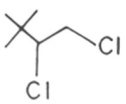
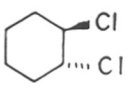
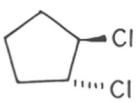
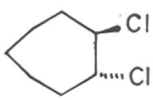
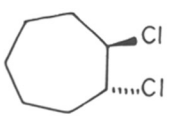
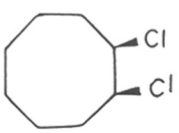
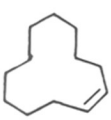
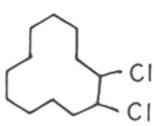
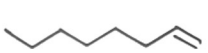
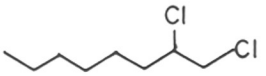
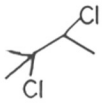
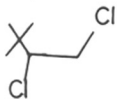
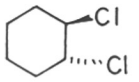
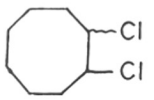
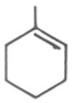
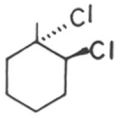
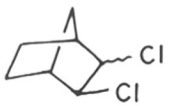
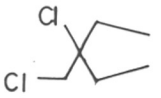
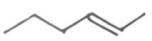
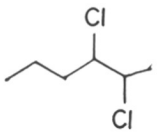
OLEFIN	PRODUCT	YIELD %	b.p (°C) / torr
		95	67-71/4
		87	126-128
		85	105-120/10
		96	91-92/70
		96	59-65/14
		94	53-55/27
		91	98-104/2
		72	105-119/10
		19	105-119/10
		91	158-158/1.5

Table 6

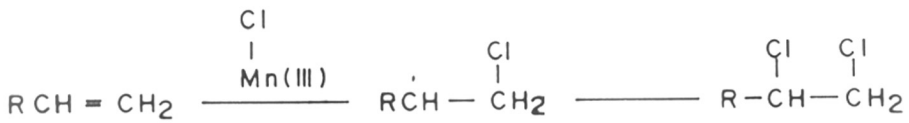
trans--Dichlorination of Olefins with manganese dioxide- TMCS

ALKENE	PRODUCT	REACTION TIME (h)	YIELD %	b.p(°C)/torr
		6	84	67-71/4
		2	93	126-128
		4	94	92-94/70
		4	96	59-65/14
		3	92	105-109/10
		2	94	86-89/1.5
		1	93	92-98/18
		4	92	172-174
		4	95	162-165

suggested. On substituting AcCl for TMCS as chloride carrier, the main transformation was the opening of THF heterocyclic ring. In dimethylformamide (DMF), instead, the MnO_2-AcCl system smoothly halogenates the alkenes without side reactions. The peculiar ability of DMF to solubilize $MnCl_2$, the end product of the MnO_2 reduction, should enable the comproportionation reaction according the equilibrium Mn(II) + Mn(IV) $\rightleftharpoons$ Mn(III) + Mn(III).

In a typical procedure, the acetyl chloride (60 mmol) is poured into a mixture of MnO_2 (15 mmol), $MnCl_2$ (10 mmol) and alkene (10 mmol) in DMF at 30°C. A strong dark green colour developes immediately and then fades at a rate depending upon the substrate structure. Vicinal dichloro compounds are prepared in high yields (**Table-6**) under mild conditions and with cheap reagents, from differently alkyl substituted olefins. A halogenation through molecular chlorine from MnO_2-AcCl is ruled out by results obtained from norbornylene, which is good olefinic probe for free chlorine in reactionw with metal chlorides. When indeed, this substrate is treated with Cl_2 in DMF, a significantly different products distribution is observed, with a great amount of nortricyclyl chloride. As alkyl tri and gemdi substituted alkenes give no allylic substitution products, and norbornylene and neohexane do not undergo molecular rearrangement the carbonium ion formation is ruled out and a non-chain radical process, in which Mn(III)-Cl acts like donor of Ci has been proposed. This is depicted in **Scheme-10**.

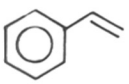
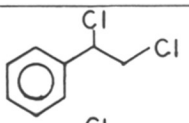
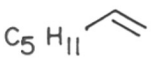
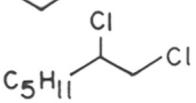
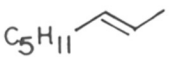
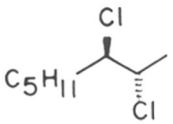
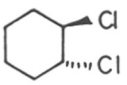
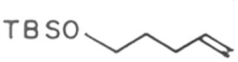
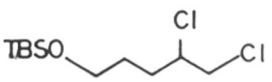
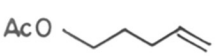
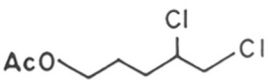
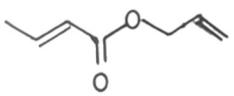
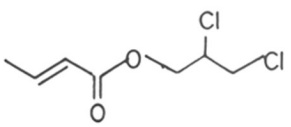
SCHEME 10



Marko and co-workers[17] have used benzyltriethylammonium permanganate and oxalyl chloride for *trans*-dichlorination of alkenes. A CH_2Cl_2 solution of benzyltriethylammonium permanganate, prepared by stirring benzyltriethylammonium chloride with $KMnO_4$. This solution was

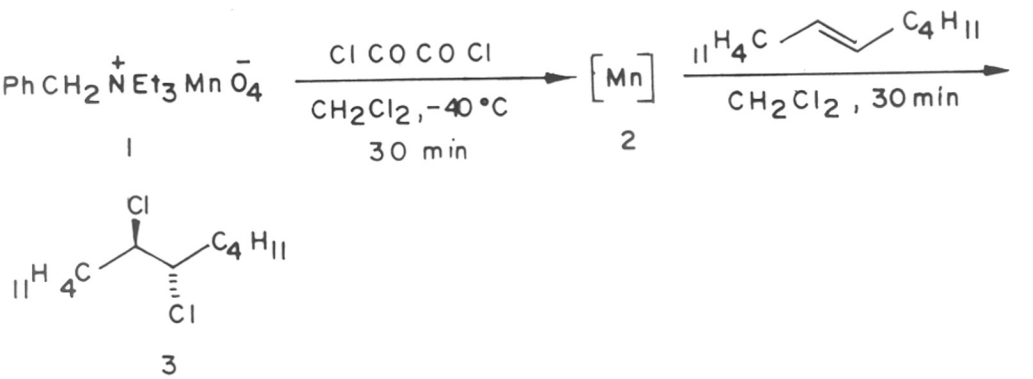
Table 7

Stereospecific trans-dichlorination of alkenes with benzyltriethyl ammonium permanganate-axalyl chloride

OLEFIN	trans 1,2 – dichloride	YIELD %
		98
		75
		69
		80
		87
		85
		96

treated at -40°C with two equivalents of oxalyl chloride, a vigorous gas evolution took place and a brown-coloured solution formed. After stirring for 30 minutes at that temperature (E)-5-decene was added. A beautiful emerald-green colour developed. Working up the reaction mixture using sodium thiosulphate produced two clear colourless organic and aqueous layers. Removal of solvent afforded in high yield and purity, the corresponding *trans*-vicinal dichloride 3, (**Scheme-11**).

SCHEME II



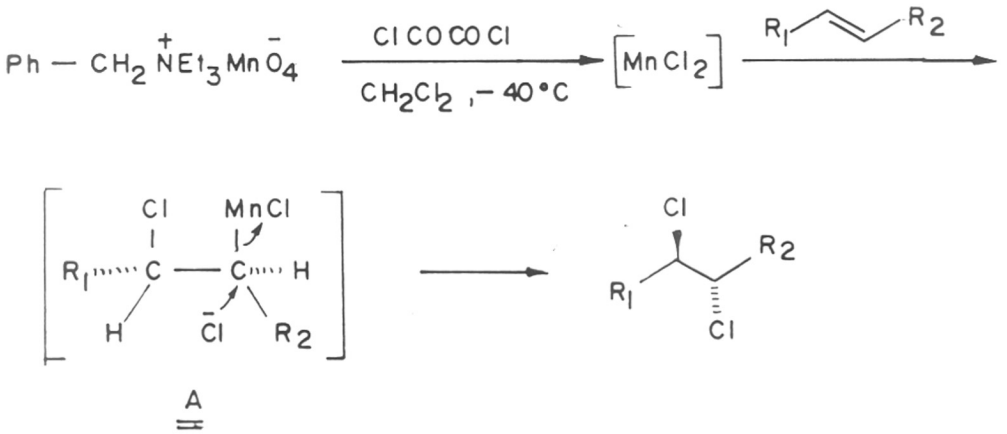
1 2 3

This reaction appears to be general and a number of olefins were converted to the corresponding dichloride, (**Table-7**). Terminal, internal and trisubstituted olefins were found to be suitable substrate for this reagent. The reagent tolerate protecting groups as *tert*-butyldimethylsilyl and acetyl. The chlorinating species generated *in situ* from benzyltriethylammonium permanganate-oxalyl chloride is unstable above -35°C.

In a subsequent publication, Marko and coworkers[18] have demonstrated that the *trans*-dichlorination of olefins mediated by manganese species, generated from oxalyl chloride and benzyltriethylammonium permanganate is not involving the participation of chloronium cation intermediate. They have rationalised their results by postulating the intermediacy of an organo-manganese species **A**, which could arise by insertion of the carbon-carbon double bond into a Mn-Cl

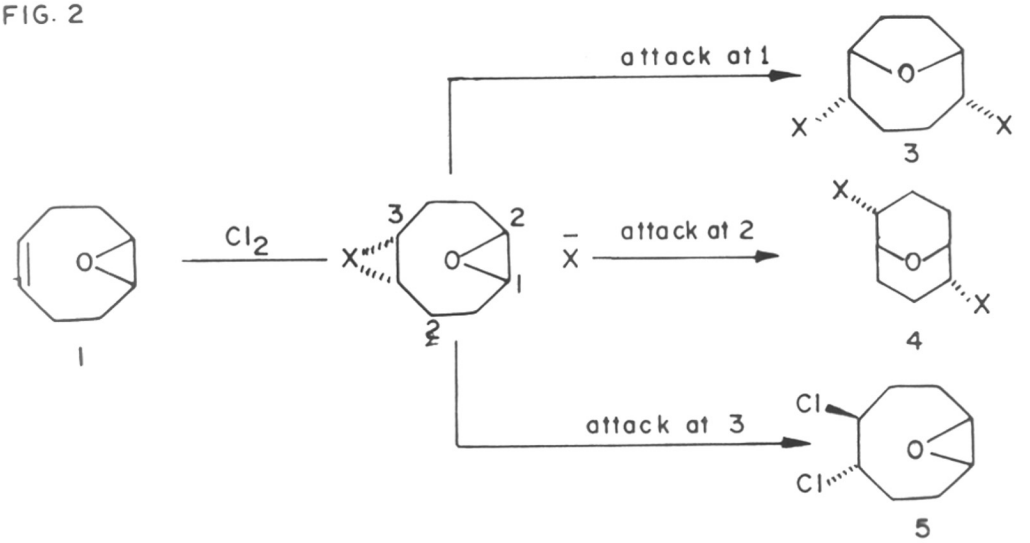
bond, followed by nucleophilic displacement of the manganese moiety by an external chloride ion. (**Scheme-12**).

SCHEME 12



Chlorination of **1** (**Figure-2**) is a messy reaction - as are most chlorinations using molecular chlorine - but out of the numerous products formed, the two dichloro-bicyclic ethers **3** and **4** predominated. In sharp contrast, the reaction using the manganese catalyst was particularly clean, affording the dichloroepoxide **5** as the major component of the reaction mixture, in almost quantitative yield (**Figure-2**). These observations rule out any significant chloronium ion participation in the manganese-mediated halogenation.

FIG. 2



Present Investigation

This consists of two sections.

Section A

Stereoselective *trans*-dichlorination of alkenes with tetradecyltrimethylammonium permanganate-trimethylchlorosilane

Although a number of methods available[2] for the addition of halogens to alkenes, reaction of halogens, especially that of gaseous chlorine presents a potential environmental hazard and their quantitative utilisation is often hard to work out. Metal mediated *cis*-vicinal dichlorination of olefins by molybdenum (VI-acetyl chloride by Nugent[13] and and manganese (III) acetate-calcium chloride by Donnelly et al.[14] have been reported. Metal mediated *trans*-vicinal dichlorination of alkenes with manganese dioxide-trimethylchlorosilane, MnO_2-$MnCl_2$-acetyl chloride and acetal chlorination with MnO_2-trimethylchlorosilane have been published by Bellesia et al.[15,16] Marko and coworkers[17,18] described *trans*-dichlorination of olefins mediated by manganese species generated from oxalyl chloride and benzyltriethylammonium permanganate. The permanganate reagent, prepared *in situ* from benzyltriethylammonium chloride and $KMnO_4$ in CH_2Cl_2 solution. To this solution they have added two equivalents of oxalyl chloride at -40°C and after 30 minutes, olefin was added at this temperature (-40°C) for getting *trans*-vicinal dichloride. The chlorinating species prepared by using benzyltriethylammonium permanganate and oxalyl chloride is unstable above -35°C. Moreover, the main disadvantage of benzyltriethylammonium permanganate is its instability. The benzyl radical easily formed from this, initiates a chain reaction, during drying or when this reagent is handled neat. This reagent has also been reported[19] to detonate during drying.

Potassium permanganate exhibits[1] unique reactivity towards olefins. However, its usefulness in organic synthesis has been severely limited by solubility problems. In an attempt to improve and modify the reactivity of potassium permanganate, we have prepared tetradecyltrimethylammonium

permanganate. In this new reagent, we have replaced benzyl group by a long chain hydrocarbon radical, eg. tetradecyl, to give rise to increase stability and solubility. Indeed, our reagent tetradecyltrimethylammonium permanganate (TDTAP) proved to be the case.

Tetradecyltrimethylammonium permanganate (TDTAP) is a violet crystalline solid stable at room temperature for a few days and can be stored at 0°C in a brown bottle for months. This new reagent can be prepared easily by mixing equimolar amounts of aqueous solutions of potassium permanganate and tetradecyltrimethylammonium bromide to give a violet precipitate. It was filtered and fully characterised.

$C_{14}H_{29}N^{+}Me_3Br^{-}$ + $K^{+}MnO_4^{-}$ ---> $C_{14}H_{29}N^{+}Me_3\ MnO_4^{-}$

Aqueous solution Aqueous solution Violet crystalline solid

+ $K^{+}Br^{-}$

The dichlorination reaction can be monitored by colour changes. Thus a violet coloured solution of TDTAP in methylene chloride at 0°C changed immediately to brown on treatment with trimethylchlorosilane (TMCS). On addition of olefin to this mixture at 0 to 3°C, the colour changed slowly to dark green during 1 h. indicating completion of the reaction. A number of olefins were dichlorinated using this TDTAP-TMCS reagent system. The results are summarised in **Table-8**.

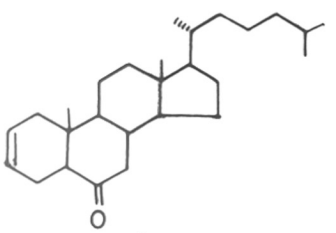
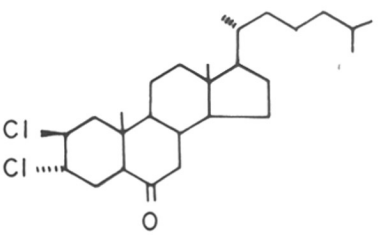
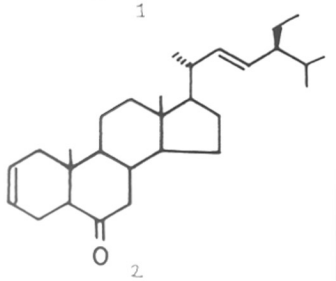
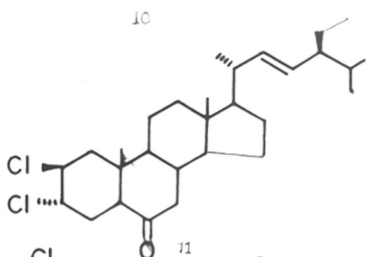
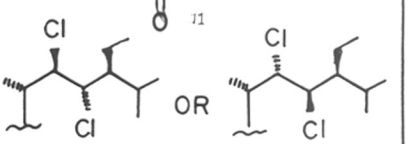
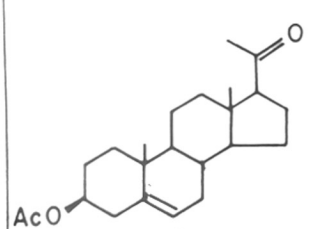
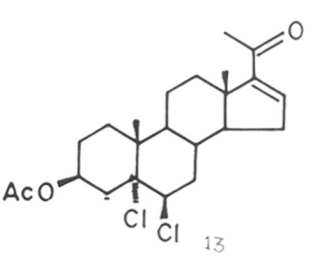
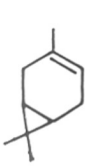
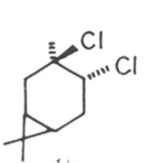
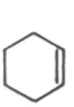
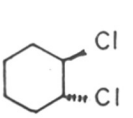
Cholest-2-en-6-on **1** was prepared from cholesterol in four steps in 66% overall yield. This compound **1** was dichlorinated using TDTAP-TMCS reagent to furnish the dichlorinated product **10** in 96% yield. The detail dichlorination procedure and spectral characterisation of the product is included in the Experimental Section. This TDTAP-TMCS reagent displays high chemoselectivity as evidenced by no reaction of the α,β-unsaturated double bond at C-16 of pregnenolone acetate **3** and the electron deficient double bond of coumarin **9**. The reaction of the C-5(6) double bond with TDTAP-TMCS reagent to form 5α,6β-dichloropregnenolone acetate **13**, from pregnenolone acetate **3**, was confirmed by IR and ^{1}H-NMR spectroscopic studies. Compound **13** exhibits strong IR absorption bond at 1730 cm^{-1} (*OCO*CH_3) and 1668 cm^{-1} (α,β-unsaturated keto carbonyl). The IR spectrum of the starting 16-dehydropregnenolone acetate **3**, shows strong absorption at 1738

cm^{-1} (*-OCOCH*$_3$) and 1670 cm^{-1} (α, β-unsaturated carbonyl). As there is no change in IR absorption bond for α, β-unsaturated carbonyl (1668 cm^{-1}) after chlorination reaction, indicates no reaction of the α, β-unsaturated double bond of pregnenolone acetate **3**. The ^{1}H-NMR spectrum of 5α,6β-dichloropregnenolone acetate **13** shows signals at 4.40 (m, 1H, 6-H), and 6.75 (m, 1H, 16-H), whereas in starting 16-dehydropregnenolone acetate **3**, the ^{1}H-NMR exhibits signals at 5.28 (m, 1H, C6-H) and 6.64 (m, 1H, 16-H). The disappearance of ^{1}H-NMR peak at 5.28 and appearance of new signal at 4.40 for C6-H attached with a chlorine atom to it indicates the reaction of C5(6) double bond. The C-16 double bond, however, remains in tact. Stigmasterol derivative **2** furnished (2S,3S)-2,3-dichloro-stigmast-6-one **11** (0 to 3°C, 1h). In this substrate **2**, the 22E-double bond is sterically crowded by 24-ethyl and D ring of steroid thus hindering the approach of chlorinating species and 22E-double bond remains in tact. The yield of tetrachlorinated product **12** is found to be less (49%) even with 2 equivalents of TDTAP and 4.2 equivalents of trimethylchlorosilane and extended reaction time (18h, at 28°C). β-Methylstyrene **8**, afforded a mixture of *trans*- and *cis*-chlorinated product **18** in the ratio 7:3, as found from the ^{1}H-NMR shows signals at 1.73 (d, J=7Hz, β-chloro CH_3), 4.92 (d, J=7Hz, benzylic H) for *trans*-dichloride and signals at 1.45 (d, J=5Hz, β-chloro CH_3), 5.02 (d, J=5Hz, benzylic H) for *cis* dichloride. Formation of this mixture can be explained, due to the presence of benzyl group in the substrate; some form of cationic character is developing leading to the loss of stereochemical integrity and formation of *trans*- and *cis*-dichloro compounds **18**.

The probable pathway for the *trans*-dichlorination of alkenes with TDTAP-TMCS reagent is depicted in **Scheme-13**.

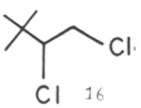
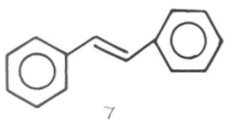
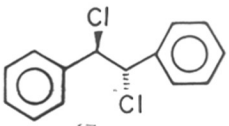
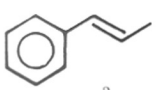
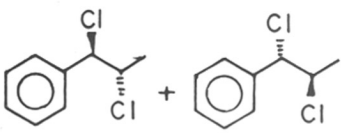
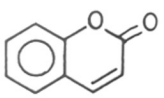
-Table 8

trans- Dichlorination of Alkenes using TDTAP-TMCS

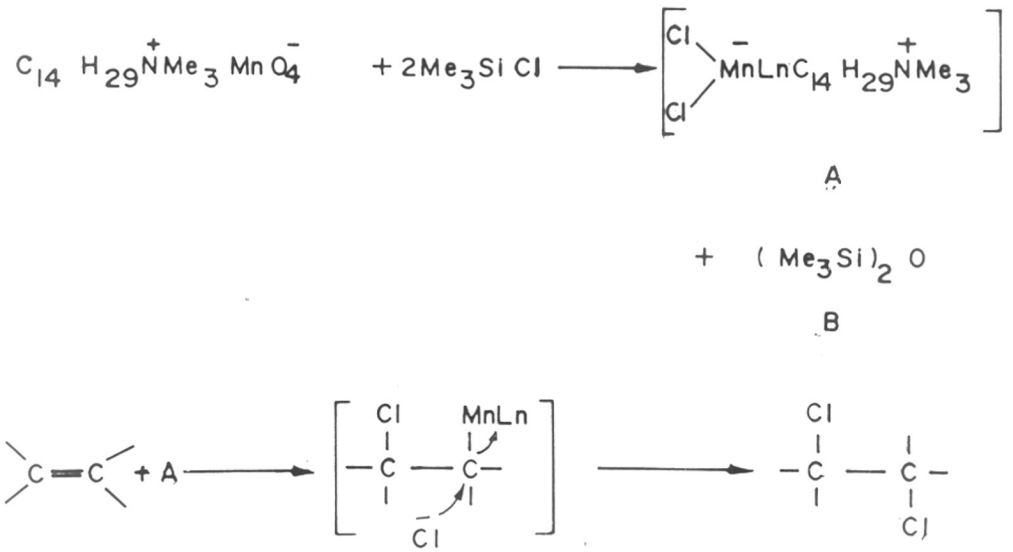
ALKENE	PRODUCT	YIELD (%)	M.P(°C) / b.p (°C) / torr (lit)
 1	 10	96	134 (131)[22]
 2	 11	86	181 – 182
	 12	49	208 – 210
 3	 13	87	157 – 158
 4	 14	84	oil
 5	 15	92	68/10 (59–65/14)[18]

Contd.

T.

ALKENE	PRODUCT	YIELD (%)	M.P (°C) / b.p (°C) / torr (lit)
 6	 16	90	80/40 (91/70)[15]
 7	 17	77	191 (191-193)[15]
 8	 18	88	70-75 / 0.6
 9	No reaction	—	—

SCHEME 13



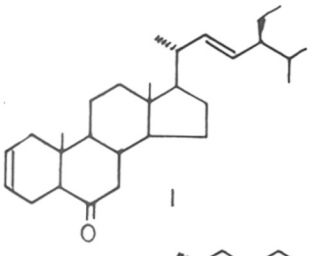
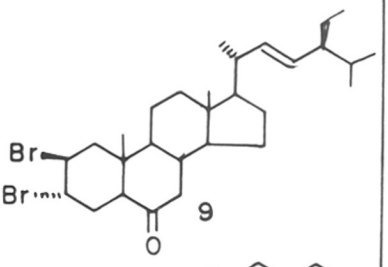
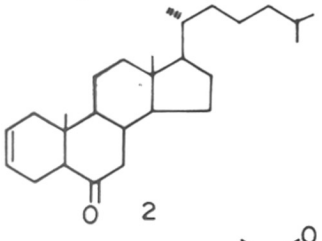
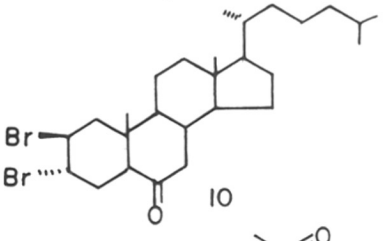
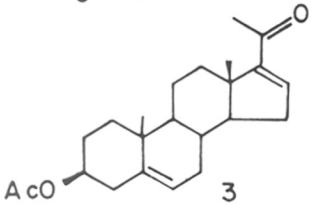
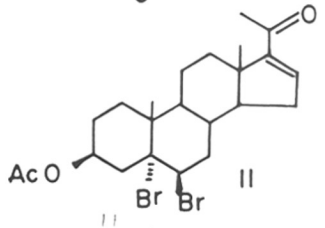
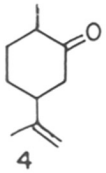
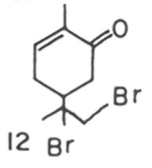
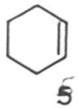
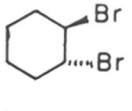
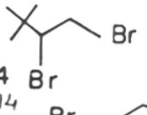
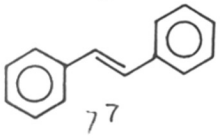
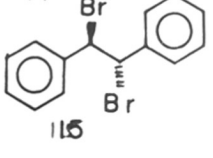
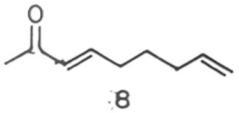
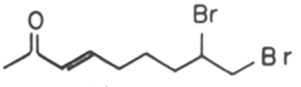
The observed colour change of violet permanganate species to the brown chlorinating species can be rationalised by the formation of an intermediate manganese chloride species **A**. This species apparently inserts two chlorine atoms in stepwise manner and eventually turned to lower valnet manganese. The vicinal-dichlorinated products, compound **10-18** (**Table-8**) were obtained in excellent yield. We have also isolated hexamethyldisiloxane **B**. The reaction of different olefins in methylene chloride gave a mixture of products from which the dichlorinated product was isolated in poor yields; and thereby ruling out the participation of chlorine as the dichlorinating agent.

Section B

Stereoselective *trans*-dibromination of alkenes with tetradecyltrimethylammonium permanganate-trimethyl bromosilane

Olefins are usually treated with a solution of bromine in carbon tetrachloride, chloroform, carbon disulphide, acetic acid, ether or ethyl acetate to form 1,2-dibromides[2], although commercially available pyridinium bromide perbromide is convenient for the addition of bromine to a double

Table 9
trans-Dibromination of Alkenes using TDTAP-TMBS

Alkenes	Product	Yield%	m.p (°C)/b.p (°C)/ torr (lit)
 1	 9	91	194–195
 2	 10	85	134 (132)[22]
 3	 11	89	119 (121)[23]
 4	 12	73	65–70/0.3 (40/0.04)[24]
 5	 13	79	98/8 (101/14)[25]
 6	 14	62	88–90/9 (91–92/14)[26]
 7	 15	60	235 (237)[27]
 8	 16	60	125–130/ 0.075

bond on a small scale,[8] Copper(II) bromide also reacts readily with olefins in the presence of acetonitrile, methanol or triphenylphosphine to furnish[9] exclusively vicinal dibromoalkanes in high yields. Anion-exchange resins act as a bromine carrier and hydrobromic acid, hydrogen peroxide, benzyltriethylammonium chloride in carbon tetrachloride[10,11] have been used to brominate alkenes. Whilst potassium permanganate exhibits[1] unique reactivity towards olefins, its limited solubility has curtailed its use in organic synthesis. In an attempt to overcome this problem, we have prepared tetradecyltrimethylammonium permanganate (TDTAP), a reagent which in combination with trimethylbromosilane (TMBS) provides a simple and mild method for stereo- and chemo-selective *trans*-dibromination of alkenes. *trans*-vicinal dibromination with this reagent is reported here for the first time.

A violet coloured solution of TDTAP in methylene dichloride at 0° to 3°C changed immediately to deep brown on treatment with trimethylbromosilane (TMBS). The olefin in methylene chloride was added to this mixture which was then stirred at 0-1.5h. The results are summarised in **Table-9**.

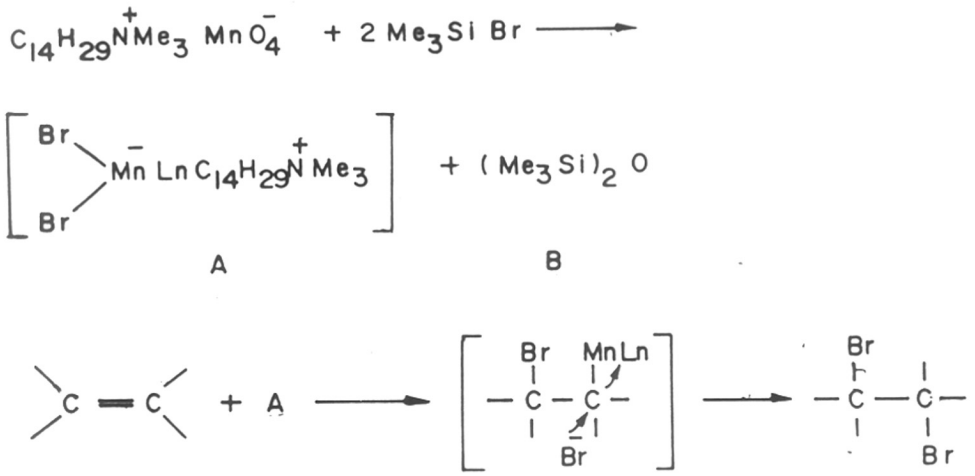
This TDTAP-TMBS reagent displays high chemoselectivity as evidenced by no reaction of the α,β-unsaturated double bond at C-16 of pregnenolone acetate **3**. This was confirmed on the basis of ^{1}H-NMR and IR spectroscopic studies. The starting 16-dehydropregnenolone acetate **3** shows strong IR absorption at 1738 cm^{-1} (acetate >C=O) and 1670 cm^{-1} (α,β-unsaturated >C=O) while the dibrominated compound **11** exhibited IR absorption at 1740 cm^{-1} (acetate >C=O) and 1672 cm^{-1} (α,β-unsaturated >C=O). The presence of α,β-unsaturated >C=O in the product **11** clearly indicates no reaction of the α,β-unsaturated double bond. The only C5(6) double bond has undergone bromination reaction with TDTAP-TMBS system. The ^{1}H-NMR of the starting 16-dehydropregnenolone acetate shows signals at 5.28 (m, 1H, 6-H) and 6.64 (m, 1H, 16-H) for olefinic protons. The 5α,6β-dibromopregnenolone acetate **11** shows ^{1}H-NMR signals at 5.47 (m, 6H), C-6 proton

having bromine atom attached and 6.72 (m, 1H, 16-H), indicates no bromination of C-16 double bond. The C5(6) double bond has been selectively brominated to furnish the dibrominated product **11**.

The electron deficient double bond of carvone **4** is in tact, and the isolated double bond has been brominated selectively gave the dibromide **12**. The carvone **4** shows IR absorption at 1670 cm^{-1} for α, β-unsaturated >C=O group, whereas the dibromide **12** shows IR absorption at 1680 cm^{-1}. This suggests no reaction of conjugated double bond with TDTAP-TMBS reagent. The carvone **4** shows ^{1}H-NMR signals at 4.75-4.85 (m,2H) and 6.7 (m, 1H, 6-H) for olefinic protons. The *trans*-9,10-dibromo carvone **12** shows ^{1}H-NMR peaks at 3.82-4.02 (m, 2H, CH_2-Br) and 6. (m, 1H, 6-H). The disappearance of the signal at 4.75-4.85 for isolated olefin proves the formation of dibromide **12**. In nona-3,8-dien-2-one **8**, the only product formed is *trans*-8,9-dibromo-nona-3-ene-2-one **16**. This is confirmed by IR and ^{1}H-NMR spectroscopy. The starting nona-3,8-diene-2-one **8** shows IR absorption at 1680 cm^{-1}, while the dibromide **16** exhibits IR absorption at 1685 cm^{-1} for α, β-unsaturated >C=O group. This indicates no reaction of the α, β-unsaturated double bond with TDTAP-TMBS reagent. The nona-3,8-diene-2-one **8** exhibits ^{1}H-NMR signals at 5.05 (m, 2H), 5.8 (m, 1H) for isolated double bond and 6.08 (m, 1H), 6.82 (m, 1H) for α, β-unsaturated double bond. The ^{1}H-NMR have new chemical shift values at 4.14-4.25 (m, 1H), 3.58-3.9 (m, 2H) and no absorption due to isolated double bond at 5.05 and 5.8. From this data, the formation of dibromide **16** can be explained. In the stigmasterol derivative **1**, the 22E-double bond is sterically crowded by the (24S)-ethyl and D ring of the steroid, thus hindering the approach of the brominating species. The only product isolated is 2,3-dibromide **9** in 91% yield.

The probable pathway for the *trans*-vicinal dibromination of alkenes with TDTAP-TMBS can be represented as follows (**Scheme-14**).

SCHEME 14



The observed colour change from violet of TDTAP in methylene dichloride to that of the dark brown brominating reagent can be rationalised in terms of formation of an intermediate manganese dibromide species **A**. This species apparently inserts two bromine atoms in a stepwise manner giving, eventually, lower valent manganese; we have isolated hexamethyldisiloxane **B**. The reaction of pregnenolone acetate **3** in methylene chloride at 0° to 3°C with one molequivalent of bromine in methylene dichloride is instantaneous. The product isolated after 3 min is the 5α, 6β, 16β, 17α- tetrabromide (21%); m. p. 165-167°C, starting pregnenolone acetate **3** (76%) with no traces of the 5α,6β-dibromide **11**. The stigmasterol derivative **1** on reaction with 1 mole equiv. of bromine in methylene dichloride at 0°-3°C for 5 minutes furnished a complex mixture of products from which a small amount of 2β,3α,22,23-tetrabromide (6%; m.p. 218-221°C) was isolated. With 2 mole equiv. of bromine at 0°-3°C for 1.5 h. a similar complex mixture formed containing a little amount of the same tetrabromide. With TDTAP-TMBS formation of the dibrominated compound **11** and **9** as a single product and in good yield strongly suggests that *trans*-dibromination occurs by a different pathway and clearly ruling out the possibility of generation of molecular bromine in the reaction medium as the brominating species.

Experimental

Preparation of tetradecyltrimethylammonium permanganate (TDTAP)

To a stirred solution of potassium permanganate (7.9g, 0.05 mol) in water (250ml), was added a solution of tetradecyltrimethylammonium bromide (17.5g, 0.052 mol) in water (250ml), dropwise at 25°C for 30 min. A violet colour precipitate was formed immediately and the mixture was stirred for 30 min more. The violet color precipitate was filtered , washed thoroughly with water (5 50ml) and dried in vacuum descicator over P_2O_5 to furnish the salt (17.25g,92%), m.p. 165-167°C (d); crystallised from CH_2Cl_2. Anal. Calc. for $C_{17}H_{38}NMnO_4$; C,54.40; H,10.13; N, 3.73. Found C, 54.47; H, 10.32; N, 4.01.

Preparation of cholest-2-ene-6-one 1

To a solution of cholesterol (19.5g, 0.05 mol) in dry pyridine (150 ml) was added *p*-toluenesulfonyl chloride (14.25g, 0.075 mol), and the mixture was kept in dark for 48h. Usual work up afforded cholesteryl tosylate 24.3g. in 90% yield. The tosylate (25g, 0.046 mol) was dissolved in acetone (600 ml), water (150 ml) was added to this solution. To this mixture fused potassium acetate (30g, 0.30 mol) was added, and the mixture was refluxed on water bath (20h.). The usual work up furnished *i*-cholesterol 16g. in 90% yield. To a cooled (10°C) solution of *i*-cholesterol (1.6g, mol) in acetone (20 ml) was added Jones reagent (8N, 1.1 ml) dropwise in 5 minutes. The resultant mixture was stirred vigorously for another 10 minutes at 10°C. The reaction mixture on usual work up gave cholesterol *i*-ketone 1.543g. in 95% yield. The 3α,5-cyclocholest-6-one (1.152g, 0.003 mol) was taken in dry DMF (12 ml). To this solution was added LiBr (0.130g, 0.0015 mol), pyridinium *p*-toluene sulfonate (0.200g, 0.0008 mol). The reaction mixture was refluxed on oil bath (170°C) for 3h. Usual work up followed by column chromatography on silica gel (60-120 mesh) yielded 1.0g, 86% of cholest-2-en-6-one **1**. m.p. 103-104°C (lit.[20] 104-105°C); IR ν_{max} 1715 cm^{-1}; ^{1}H-NMR 0.7 (s, 3H), 0.76 (s, 3H), 0.92 (d, J=7 Hz, 3H), 0.97 (d, J=7 Hz,3H), 2.4 (dd, J=2, 12 Hz,1H), 5.67 (m, 2H)

***trans*-Chlorination of Alkenes : A Typical Procedure**

To a magnetically stirred violet colour solution of TDTAP (0.376g, 0.001 mol) in CH_2Cl_2 (20 ml) was added trimethylchlorosilane (0.229g, 0.002 mol) in CH_2Cl_2 (2ml) at 0°C. A brown coloured solution resulted immediately. To this cholest-2-ene-6-one **1** (0.384g, 0.001 mol) in CH_2Cl_2 (5 ml) was added dropwise over 5 minutes. The homogeneous mixture was then stirred at 0°-5°C for 1h. It was then stirred with a 10% aqueous solution of sodium bisulphite (10 ml) and was brought to room temperature (30°C) to give a colourless reaction mixture. From the reaction mixture CH_2Cl_2 was removed on a rotary evaporator and it was extracted with ethyl acetate (3x50 ml). The ethyl acetate extract was washed with water (2x30 ml), brine (2x30 ml) and finally dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude product which on crystallisation from hexane-diethyl ether furnished pure dichlorinated product **10** (0.437g, 96%). Compounds **2** to **9** were chlorinated in a similar manner.

Spectral data

Section A

2*s*, 3*s*- 2, 3- Dichloro- cholestane- 6- one 10

Cholest-2-ene-6-one **1** (0.192g, 0.0005 mol) in CH_2Cl_2 (3ml), tetradecyltrimethylammonium permanganate (0.188g, 0.0005 mol) in CH_2Cl_2 (10ml) and trimethylchlorosilane (0.108g, 0.001 mol) in CH_2Cl_2 (2ml) at 0 to 3°C furnished 0.217g of the dichlorinated product **10** in 96% yield. The m.p.134°C (lit.[22] 131°C); IR ν_{max} 1712 (-C=O), 650; ^{1}H-NMR δ 0.75 (s, 3H, 18-H_3), 0.94 (d, 6H, J=7.0Hz, 26-H_3, 27-H_3), 1.0 (d, 3H, J=7.0Hz, 21-H_3), 1.12 (s, 3H, 19-H_3), 2.9 (dd, 1H, J=2.0Hz, 12Hz, 5-H), 4.43-4.65 (m, 2H, 2,3-H0; m/z 454 and 456 (M^+), 439, 418, 403, 384, 367, 341, 247, 191, 107, 93(100%); $[\alpha]_D$ = +34.9°C (C 1.7, $CHCl_3$).

2*s*,3*s*-2,3-Dichloro-stigmast-22(23)-ene-6-one 11

The starting material, stigmast-2-ene-6-one **2** prepared from stigmasterol. A mixture of stigmasterol (22.5g, 0.055 mol), pyridine (300 ml) and *p*-toluenesulfonyl chloride (26.8g, 0.14 mol) was kept in dark for 36 h. It was worked up in usual way to afford 3β-stigmasteryl tosylate 29.1g., 94%. The stigmasteryl tosylate (28.9g, 0.051 mol) was solvolysed using fused potassium acetate (28.9g, 0.295 mol) in acetone (600 ml) and water (140 ml), by refluxing the mixture for 20 h. The usual work up afforded *i*-stigmasterol 20.6g, 98%. The *i*-stigmasterol (20.6g, 0.05 mol) on oxidation with Jones reagent (8N, 13.8 ml, 0.05 mol) in acetone (350 ml) at 0-10°C furnished on usual work up 3α,5-cyclo-stigmast-6-one, 20g, 98%. This *i*-ketone (18.9g, 0.046 mol) on acid catalysed rearrangement with LiBr (1.97g, 0.022 mol), pyridinium-*p*-toluene sulfonate (1.97g, 0.0078 mol) in dry DMF (190 ml), by refluxing the mixture at 165°C for 4 h, gave crude stigmast-2-ene-6-one **2**. Column purification on silica gel furnished pure stigmast-2-ene-6-one **2**, 9.58g, 52%. The m.p. 111°C (lit.[21] 111-112°C); IR ν_{max} 1712; ^{1}H-NMR 0.73- 0.87 (m, 12H), 0.90 (s, 3H), 1.1 (d, J= 7Hz, 3H), 2.43 (dd, J=2, 12 Hz, 1H), 5.1 (m, 2H), 5.63 (m, 2H).

Stigmast-2,22(23)-diene-6-one **2** (0.205g, 0.0005 mol) in CH_2Cl_2 (2 ml), TDTAP (0.188g, 0.0005 mol) in CH_2Cl_2 (10 ml) and trimethylchlorosilane (0.108g, 0.001 mol) in 2 ml CH_2Cl_2 at 0-3°C furnished 0.212g of the dichlorinated product **11** in 88% yield. The m.p. 181-182°C; IR ν_{max} 1718 (-C=O), 650; ^{1}H-NMR δ 0.75 (s, 3H, 18-H_3), 0.82 (t, 3H, J=5Hz, 29-H_3), 0.87 (d, 6H, J=6Hz, 26,27-H_3), 1.18 (d, 3H, J=7Hz, 21-H_3), 1.2 (s, 3H, 19-H_3), 2.85 (dd, 1H, J=2,12Hz, 5-H), 4.38-4.55 (m, 2H, 2,3-H), 5.12 (m, 2H, 22,23-H); m/z 481 and 483 (M^+-1), 437, 411, 367, 341, 313, 271, 245, 231, 191, 177, 149, 97, 83, 69, 55(100%); Found: C, 72.03; H, 9.34; Cl, 15.01. Calc. for $C_{29}H_{46}Cl_2O$ C, 72.32; H, 9.63; Cl, 14.72; $[\alpha]_D$ = +21.8°C (C 1.3, $CHCl_3$).

2s,3s,22,23-Tetrachloro-stigmastane-6-one 12

Stigmast-2,22(23)-diene-6-one **2** (0.205g, 0.0005 mol) in CH_2Cl_2 (2 ml), TDTAP (0.375g, 0.001 mol) in CH_2Cl_2 (15 ml) and trimethylchlorosilane (0.216g, 0.002 mol) in 3 ml at 0-3°C in CH_2Cl_2 afforded 0.178g. of the tetrachlorinated product **13** in 49% yield; m.p. 208-210°C; IR ν_{max} 1720 (-C=O), 655; ^{1}H-NMR δ 0.75 (Two s, 3H, 18-H_3), 0.97-1.06 (Five s, 9H, 26,27,29-H_3), 1.08 (s, 3H, 19-H_3), 1.22 (d, 3H, J=7Hz, 21-H_3), 2.85 (d, 1H, J=14Hz, 5-H), 4.1-4.35 (m, 2H, 22,23-H), 4.42-4.58 (m, 2H, 2,3-H); m/z 552 (M^+), 515, 494, 478, 467, 458, 411, 375, 361, 333, 321, 279(100%), 171, 107, 95, 81, 55; Found: C, 62.99; H, 8.48; Cl, 25.81. Calc. for $C_{29}H_{46}Cl_4O$, C, 63.04; H, 8.39; Cl, 25.67; $[\alpha_D$ = +22.7° (C, 2.3, $CHCl_3$).

3β-Acetoxy, 5α,6β-dichloro-pregna-16-ene-20-one 13

16-Dehydropregnenolone acetate **3** (0.356g, 0.001 mol) in CH_2Cl_2 (5 ml), TDTAP (0.375g, 0.001 mol) in CH_2Cl_2 (15 ml) and trimethylchlorosilane (0.216g, 0.002 mol) in 4 ml CH_2Cl_2 at 0-3°C yielded 0.370g of the dichlorinated product **13** in 87% yield. The m.p. 157-158°C; 1730 (-O-C=O), 1668 α,β-unsaturated (>C=O), 660; ^{1}H-NMR 0.96 (s, 3H, 18-H_3) 1.44 (s, 3H, 19-H_3), 2.08 (s, 3H, 21-H_3), 2.3 (s, 3H, $OCOCH_3$), 4.40 (m, 1H, 6-H), 5.4 (m, 1H, 3-H), 6.75 (m, 1H, 16-H); m/z 426 and 428 (M^+), 411, 383, 315, 296(100%), 287, 279, 251, 157, 145, 105, 91, 81, 55; Found: C, 64.40; H, 7.59; Cl, 16.27. Calc. for C, 64.63; H, 7.55; Cl, 16.59; $[\alpha]_D$ = -62.9° (C 1.2, C_6H_6).

***trans*-3,4-Dichloro carane 14**

Δ^3-carene **4** (0.204g, 0.0015 mol) in CH_2Cl_2 (1 ml), TDTAP (0.565g, 0.0015 mol) CH_2Cl_2 (20 ml) and trimethylchlorosilane (0.324g, 0.003 mol) in 4 ml CH_2Cl_2 at 0-3°C afforded 0.250g. of the dichlorinated product **14** in 84% yield. Thick oil; IR ν_{max} 680, 630; ^{1}H-NMR δ 0.99 (s, 3H), 1.01 (s, 3H), 1.64 (s, 3H), 3.93 (m, 1H); m/z 206 and 208 (M^+), 171, 155, 135, 127, 119, 107, 93(100%), 77, 67, 53.

***trans*-1,2-dichloro-cyclohexane 15**

Cyclohexene **5** (0.328g, 0.004 mol) in CH_2Cl_2 (2 ml), TDTAP (1.5g, 0.004 mol) in CH_2Cl_2 (25 ml) and trimethylchlorosilane (0.864g, 0.008 mol) in 5 ml CH_2Cl_2 at 0-3°C furnished 0.664g. (92%) of the dichlorinated product **15**, b.p. 68/10mm (59-65/14mm)[15]; IR ν_{max} 1450, 985, 910, 700, 670, 620; ^{1}H-NMR δ 1.42 (m, 2H), 1.77 (m, 4H), 2.35 (m, 2H), 4.15 (m, 2H).

***trans*-1,2-dichloro-3,3-dimethyl-butane 16**

3,3-Dimethyl-1-butene **6** (0.850g, 0.010 mol) in CH_2Cl_2 (2 ml), TDTAP (3.75g, 0.010 mol) in CH_2Cl_2 (30 ml) and trimethylchlorosilane (2.16g, 0.020 mol) in 5 ml CH_2Cl_2 at 0-3°C furnished 1.8g. (90%) of the dichlorinated product **16**, b.p. 80/40 mm (91/70mm)[15]; IR ν_{max} 1490, 1480, 1440, 1410, 1380, 1340, 1290, 1275, 1250, 1185, 685; ^{1}H-NMR δ 1.11 (s, 9H), 3.61 (dd, 1H, J=2,12Hz), 3.92 (dd, 2H, J=2,12Hz); m/z 153 and 155 (M^+-1), 137, 125, 110, 103, 93, 76, 67, 65, 57(100%).

***meso*-1,2-dichloro stilbene 17**

trans-stilbene **7** (0.180g, 0.001 mol) in CH_2Cl_2 (2 ml), TDTAP (0.375g, 0.001 mol) in CH_2Cl_2 (10 ml) and trimethylchlorosilane (0.216g, 0.002 mol) in 2 ml CH_2Cl_2 at 0-3°C afforded 0.192g (77%) of the dichlorinated product **17**; m.p. 191 (191-193)[15]; IR ν_{max} 1590, 1190, 1170, 1080, 920, 680, 620; ^{1}H-NMR δ 5.27 (s, 2H), 7.42-7.54 (m, 10H); m/z 250 and 252 (M^+), 215, 178, 165, 152, 127, 125(100%), 89, 76.

1-phenyl-1,2-dichloropropane 18

β-Methylstyrene **8** (0.472g, 0.004 mol) in CH_2Cl_2 (2 ml), TDTAP (1.5g, 0.004 mol) in CH_2Cl_2 (15 ml) and trimethylchlorosilane (1.0g, 0.0092 mol) in CH_2Cl_2 (5 ml) at 0-3°C yielded 0.539g. (71%) of the dichlorinated product **18**; b.p. 70-75/0.6mm; IR ν_{max} 1600, 1495, 1455, 1380, 1200, 675; ^{1}H-NMR δ 1.45-1.73 (Two d, 3H, J=5,7Hz), 4.38 (m, 1H), 4.95 (m, 1H), 7.38 (m, 5H); m/z 188 and 190 (M^+), 153, 127, 125(100%), 117, 105, 91, 77, 63; Found: C, 56.88; H, 5.45; Cl, 37.21. Calc. for $C_9H_{10}Cl_2$, C, 57.17; H, 5.33; Cl, 37.50.

Section B

***trans*-Bromination of Alkenes : A Typical Procedure**

To a magnetically stirred solution of TDTAP (0.188g, 0.0001 mol) in CH_2Cl_2 (20 ml) was added trimethylbromosilane (0.191g, 0.0002 mol) in CH_2Cl_2 (2 ml) at 0-3°C. A dark brown solution resulted immediately. To this stigmast-2,22-diene-6-one **1** (0.205g, 0.0005 mol) in CH_2Cl_2 (5 ml) was added dropwise during 3 minutes. The reaction mixture was stirred at 0-10°C for 2h. It was then stirred with a 10% solution of aqueous sodium bisulphite (10 ml) and was brought to room temperature (30°C) to give a colourless reaction mixture. From this reaction mixture CH_2Cl_2 was removed on a rotary evaporator and it was extracted with ethyl acetate (3x50 ml). The ethyl acetate extract was washed with water (2x30 ml), brine (2x30 ml) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to afford a solid compound. This on recrystallisation from hexane:methylene chloride gave the pure dibrominated product **9** (0.260g, 91%). In a similar manner, compound **2** to **8** were brominated.

Spectral data

2s,3s-2,3-Dibromo-stigmast-22(23)-ene-6-one 9

Stigmast-2,22(23)-diene-6-one **1** (0.205g, 0.0005 mol) in CH_2Cl_2 (2 ml), TDTAP (0.188g, 0.0005 mol) in CH_2Cl_2 (10 ml) and trimethylbromosilane (0.150g, 0.001 mol) in CH_2Cl_2 (2 ml) at 0-3°C afforded (0.260g, 91%) of the dibrominated product **9**; m.p. 194-195°C; IR ν_{max} 1720 (-C=O); ^{1}H-NMR 0.7 (s, 3H, 18-H_3), 0.82 (d, 6H, J=1Hz, 26,27-H_3), 0.87 (t, 3H, J=5Hz, 29-H_3), 1.04 (d, 3H, J=5Hz, 21-H_3), 1.12 (s, 3H, 19-H_3), 2.92 (dd, 1H, J=2,12Hz, 5-H), 4.7-4.9 (m, 2H, 2,3-H), 5.12 (m, 2H, 22,23-H); Found: C, 60.95; H, 8.13. Calc. for $C_{29}H_{46}Br_2O$ C, 61.05; H, 8.07; $[\alpha]_D$ = +39.7°C (C 0.99, $CHCl_3$).

2s,3s-2,3-Dibromo-cholestane-6-one 10

Cholest-2-ene-6-one **2** (0.192g, 0.0005 mol) in CH_2Cl_2 (2 ml), TDTAP (0.188g, 0.0005 mol) in CH_2Cl_2 (10 ml) and trimethylbromosilane (0.150g, 0.0010 mol) in 3 ml CH_2Cl_2 at 0-3°C yielded 0.231g (88%) of the dibrominated product **10**; m.p. 137°C (132)[22]; IR ν_{max} 1720, 620; ^{1}H-NMR δ 0.7 (s, 3H, 18-H_3), 0.9 (d, 6H, J=8Hz, 26,27-H_3), 0.95 (d, 3H, J=8Hz, 21-H_3), 1.14 (s, 3H, 19-H_3), 2.92 (dd, 1H, J=2,12Hz, 5-H), 4.68-4.94 (m, 2H, 2,3-H); m/z 544 (M^+), 529, 431, 384, 369, 356, 309, 281, 247, 229, 149, 121, 107, 93, 55(100%); $[\alpha]_D$ = +42.9° (C 1.3, $CHCl_3$).

3β-Acetoxy-5α,6β-dibromo-pregna-16-ene-20-one 11

16-Dehydropregnenolone acetate **3** (0.178g, 0.0005 mol) in CH_2Cl_2 (2 ml), TDTAP (0.188g, 0.0005 mol) in CH_2Cl_2 (10 ml) and trimethylbromosilane (0.150g, 0.001 mol) in 2 ml CH_2Cl_2 at 0-3°C afforded (0.230g, 89%) of the dibrominated product **11**; m.p. 119°C (121°C)[23]; IR ν_{max} 1740 (O-C=O), 1680 (-C=O); ^{1}H-NMR 0.95 (s, 3H, 18-H_3), 1.5 (s, 3H, 19-H_3), 2.06 (s, 1H, $OCOCH_3$), 2.29 (s, 1H, $COCH_3$), 4.87 (m, 1H, 3-H), 5.47 (m, 1H, 6-H), 6.72 (m, 1H, 16-H).

***trans*-9,10-Dibromo carvone 12**

Carvone **4** (0.150g, 0.001 mol) in CH_2Cl_2 (2 ml), TDTAP (0.390g, 0.0011 mol) in CH_2Cl_2 (15 ml) and trimethylbromosilane (0.638g, 0.004 mol) in CH_2Cl_2 (5 ml) at 0-3°C furnished *trans*-9,10-Dibromo carvone **12** (0.227g, 73%); b.p. 65-70°C/0.3mm (40°C/0.05mm)[24]; IR ν_{max} 1680 (-C=O), 1445, 1125, 1100, 1055, 915, 680; ^{1}H-NMR δ 1.80 (bd, 3H, J=1.5Hz, 1-H_3), 1.92 (s, 3H, 8-H_3), 3.82-4.02 (m, 2H, CH_2-Br), 6.77 (m, 1H, 6-H).

***trans*-1,2-Dibromocyclohexane 13**

Cyclohexene **5** (0.164g, 0.002 mol) in CH_2Cl_2 (2 ml), TDTAP (0.760g, 0.002 mol) in CH_2Cl_2 (20 ml) and trimethylbromosilane (0.6g, 0.004 mol) in 4 ml CH_2Cl_2 at 0-3°C yielded 0.380g (79%) of the *trans*-1,2-dibromocyclohexane **13**; b.p. 98°C/8mm (101°C/14mm)[25]; IR ν_{max} 1460, 1415, 1350, 1270, 1190, 1015, 915, 875, 825, 700, 675; ^{1}H-NMR δ 1.28-2.0 (m, 6H0, 2.24-2.66 (m, 2H), 4.46 (m, 2H, CHBr).

***trans*-1,2-Dibromo-3,3-dimethyl-butane 14**

3,3-Dimethyl-1-butene **6** (0.169g, 0.002 mol) in CH_2Cl_2 (2 ml), TDTAP (0.768g, 0.002 mol) in CH_2Cl_2 (15 ml) and trimethylbromosilane (0.6g, 0.004 mol) in 5 ml CH_2Cl_2 at 0-3°C furnished the dibrominated product **14** (0.3g, 62%); b.p. 88-90°C/9mm (91-92°C/14mm)[26]; IR ν_{max} 1480, 1435, 1380, 1270, 1240, 1145, 1070, 910, 855, 780, 675, 625; ^{1}H-NMR 1.14 (s, 9H, *t*-Butyl CH_3), 3.42-4.2 (m, 3H, CH-Br and CH_2-Br).

***meso*-1,2-Dibromostilbene 15**

trans-stilbene **7** (0.180g, 0.001 mol) in CH_2Cl_2 (2 ml), TDTAP (0.378g, 0.001 mol) in CH_2Cl_2 (10 ml), trimethylbromosilane (0.459g, 0.003 mol) in 2ml CH_2Cl_2 at 0-3°C afforded the dibrominated product **15** (0.204g, 60%); m.p. 235 (237)[27]; IR ν_{max} 635; ^{1}H-NMR 6.04 (s, 2H), 7.18-7.69 (m, 10H); m/z 340 (M^+), 260, 180, 171, 165, 152, 115, 102, 89.

***trans*-8,9-Dibromo-nona-3-ene-2-one 16**

Nonane-3,8-diene-2-one **8** (0.280g, 0.002 mol) in CH_2Cl_2 (2 ml), TDTAP (0.750g, 0.002 mol) in CH_2Cl_2 (10 ml) and trimethylbromosilane (0.638g, 0.004 mol) in 5 ml CH_2Cl_2 at 0-3°C furnished 0.358g (60%) of the dibrominated product **16**; b.p. 125-130°C/0.075mm; IR ν_{max} 1685 cm^{-1} (-C=O); ^{1}H-NMR δ 1.84 (m, 2H), 2.12-2.35 (m, 7H), 3.8-4.15 (m, 2H, CH_2-Br), 4.14-4.25 (m, 1H, CH-Br), 6.07-6.87 (two m, 2H).

References

1. Fatiadi,A.J. *Synthesis*, **1987**, 85.

2. House,H.O. "*Modern Synthetic Reactions*", 2nd Ed.; Benjamin,W.A. Inc. **1972**, p.422; Larock,R.C. "*Comprehensive Organic Transformations*", VCH Publishers, Inc., **1989**, p.319.

3. Field,K.W.; Kovacic,P. *Synthesis*, **1969**, 135; Strand,J.W.; Kovacic,P. *Synth.Commun.* **1972**, 2, 129-137.

4. Kharasch,M.S.; Brown,H.C. *J.Am.Chem.Soc.* **1939**, 61, 3432-3434.

5. Spiegler,L.; Tinker,J.M. *J.Am.Chem.Soc.* **1939**, 61, 940-942.

6. Uemura,S.; Onoe,A.; Okano,M. *Bull.Chem.Soc.Jpn.* **1974**, 47, 692-697; Heasley,V.L.; Rold,K.D.; Titterington,D.R.; Leach,C.T.; Gipe,B.T.; Mckee,D.B. *J.Org.Chem.* **1976**, 41, 3997-4001.

7. Uemura,S.; Onoe,A.; Okano,M. *Bull.Chem.Soc.Jpn.* **1974**, 47, 3121-3124; Filippo,Jr.,J.S.; Sowinski,A.F.; Romano,L.J. *J.Am.Chem.Soc.* **1975**, 97, 1599-1600.

8. Tanner,P.D.; Gidley,G.C. *J.Org.Chem.* **1968**, 33, 38-43; Masson,S.; Thuillier,A. *Bull.Chem.Soc.Fr.* **1969**, 4368-4377; Lasne,M.C.; Thuillier,a. *Bull.Chem.Soc.Fr.* **1969**, 249-252.

9. Fieser,L.F.; Fieser,M. "*Reagents for Organic Synthesis*" **1967**, 1, 967-970, Wiley,J. and Sons, Inc., New York.

10. Koyano,T. *Bull.Chem.Soc.Jpn.* **1970**, 43, 1439-1443; Koyano,T. *Bull.Chem.Soc.Jpn.* **1970**, 43, 3501-3504; Koyano,T.; Watanabe,O. *Bull.Chem.Soc.Jpn.* **1971**, 44, 1378-1381; Uemura,S.; Kimura,Y.; Ichikawa,K. *Bull.Chem.Soc.Jpn.* **1971**, 44, 1973-1975.

11. Ho,T.; Gupta,B.G.B.; Olah,G.A. *Synthesis*, **1977**, 676.

12. Baird,Jr.,W.C.; Surridge,J.H.; Buza,M. *J.Org.Chem.* **1971**, 36, 3324-3330.

13. Nugent,W.A. *Tetrahedron Lett.* **1978**, 37, 3427-3430.

14. Donnelly,K.D.; Fristad,W.E.; Gellerman,B.J.; Peterson,J.R. Selle,B.J. *Tetrahedron Lett.* **1984**, 25, 607-610.

15. Bellesia,F.; Ghelfi,F.; Pagnoni,U.M.; Pinneti,A.J. *J.Chem.Research*(S), **1989**, 108.

16. Bellesia,F.; Ghelfi,F.; Pagnoni,U.M.; Pinneti,A.J. *Synth.Commun.* **1991**, 21, 489; Bellesia,F.; Boni,M.; Ghelfi,F.; Grandi,R.; Pagnoni,U.M.; Pinetti,A. *Tetrahedron* **1992**, 48, 4579-4586.

17. Marko,I.E.; Richardson,P.F. *Tetrahedron Lett.* **1991**, 32, 1831-1834.

18. Richardson,P.F.; Marko,I.E. *Synlett.* **1991**, 733.

19. Jager,H.; Lutolf,J.; Meyer,M.W. *Angew.Chem.Int.Ed.Engl.* **1979**, 18, 786; Schmidt,H.J.; Schafer,H.J. *Angew.Chem.Int.Ed.Engl.* **1979**, 18, 787.

20. Cerny, V.; Kasal, A.; Sorn, F. *Coll. Czech. Chem. Commun.* **1970**, 35, 1235-1254.

21. Mori, K.; Sakakibara, M.; Ichikawa, Y.; Ueda, H.; Okada,K.; Uemura, T.; Yabuta, T.; Kuwahara, S.; Kondo,M. *Tetrahedron*, **1982**, 38, 2099-2109.

22. Shoppee,C.W.; Summer,G.H.R. *J.Chem.Soc.* **1952**, 3374.

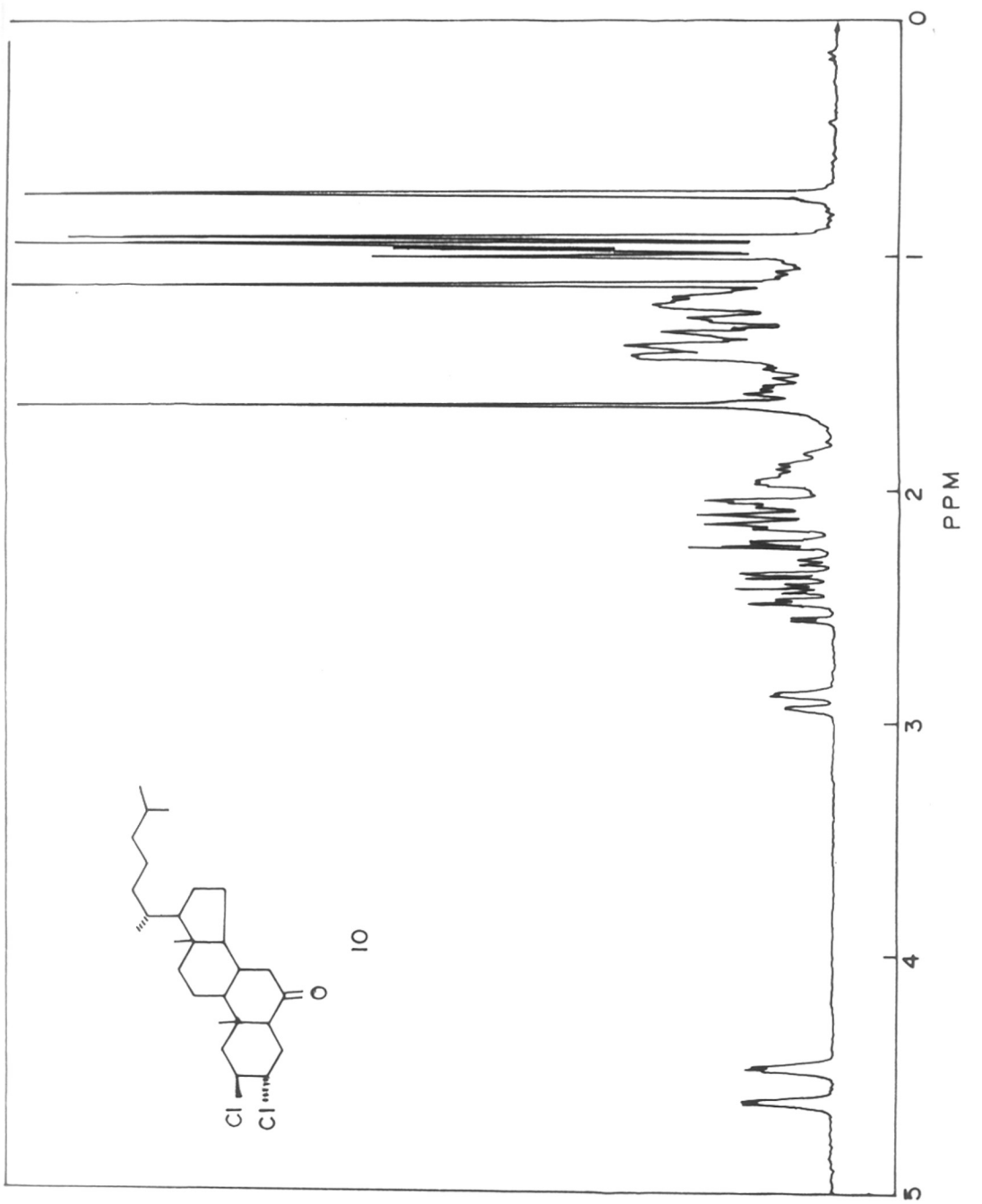
23. Solo,A.J.; Singh,B. *J.Org.Chem.* **1965**, 30, 1658.

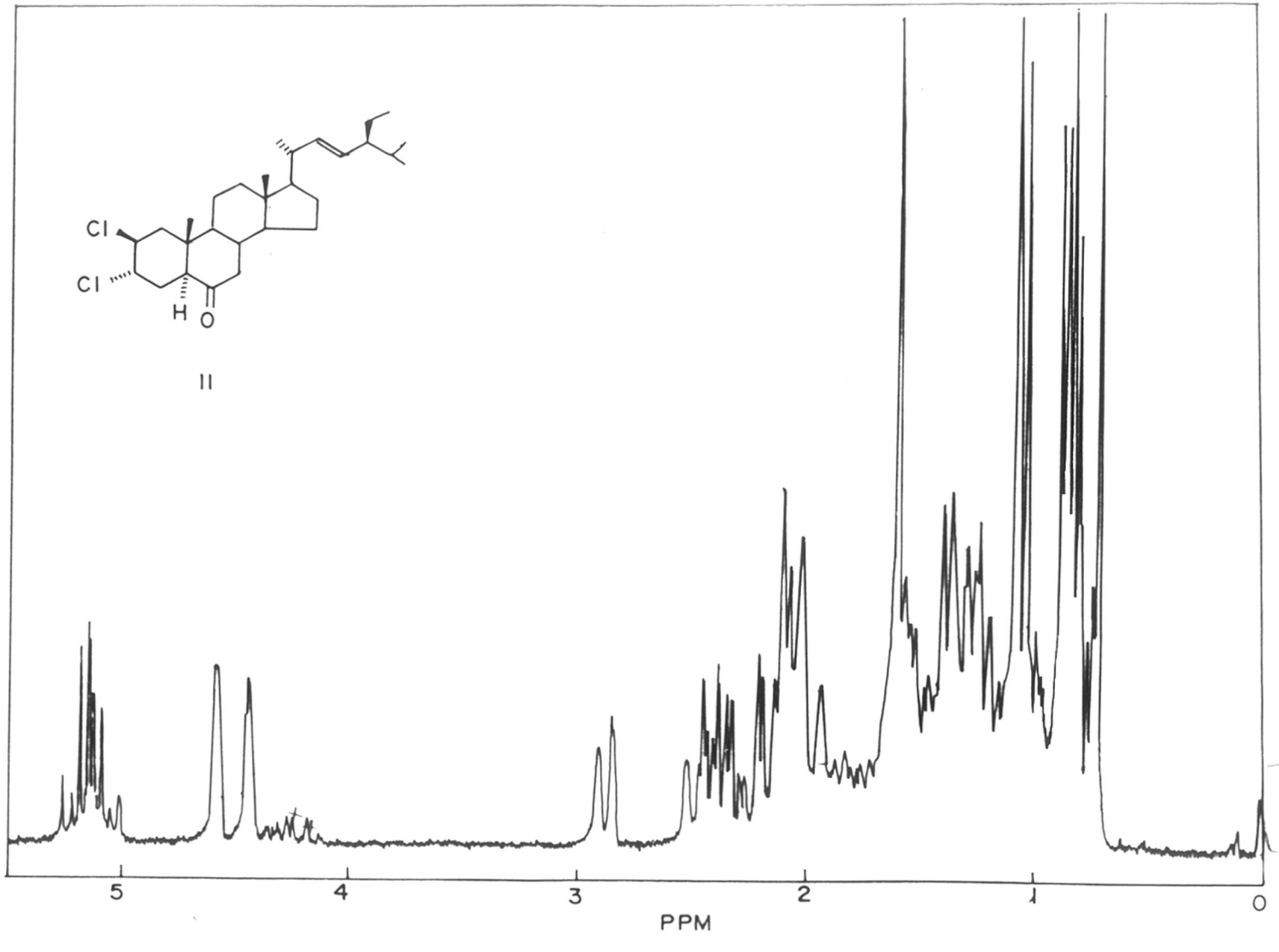
24. Kato,T.; Ichinose,I. *J.Chem.Soc.Perkin Trans.1* **1980**, 1051-1056.

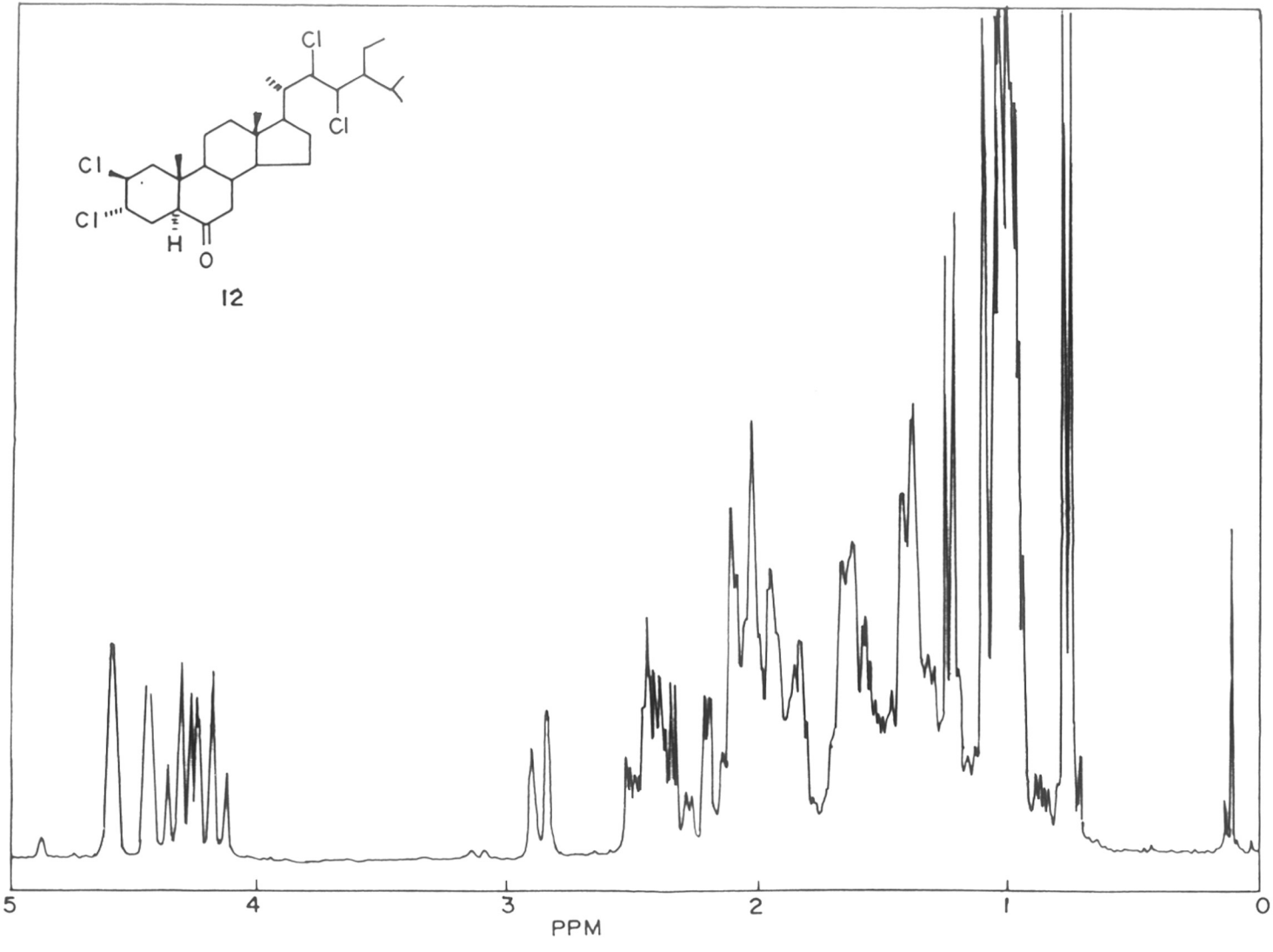
25. Snyder,H.R.; Brooks,L.A. *Org.Syn.Coll.* Vol.**2**, p.171.

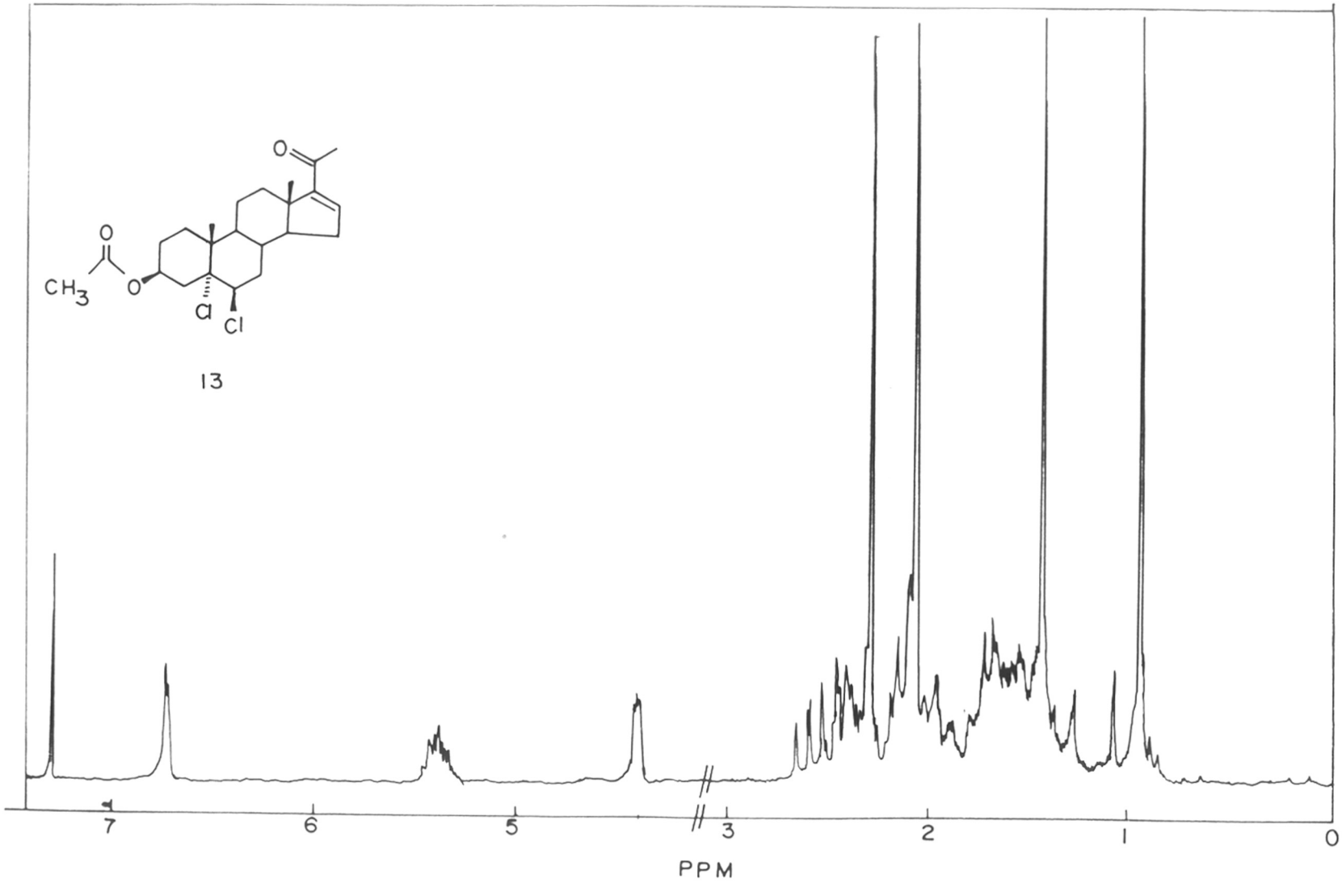
26. Leonard,N.J.; Gelfand,S. *J.Am.Chem.Soc.* **1955**, 77, 3272.

27. Hartshorn,M.P.; Opie,M.C.A.; Vaughan,J. *Aust.J.Chem.* **1973**, 26, 917.

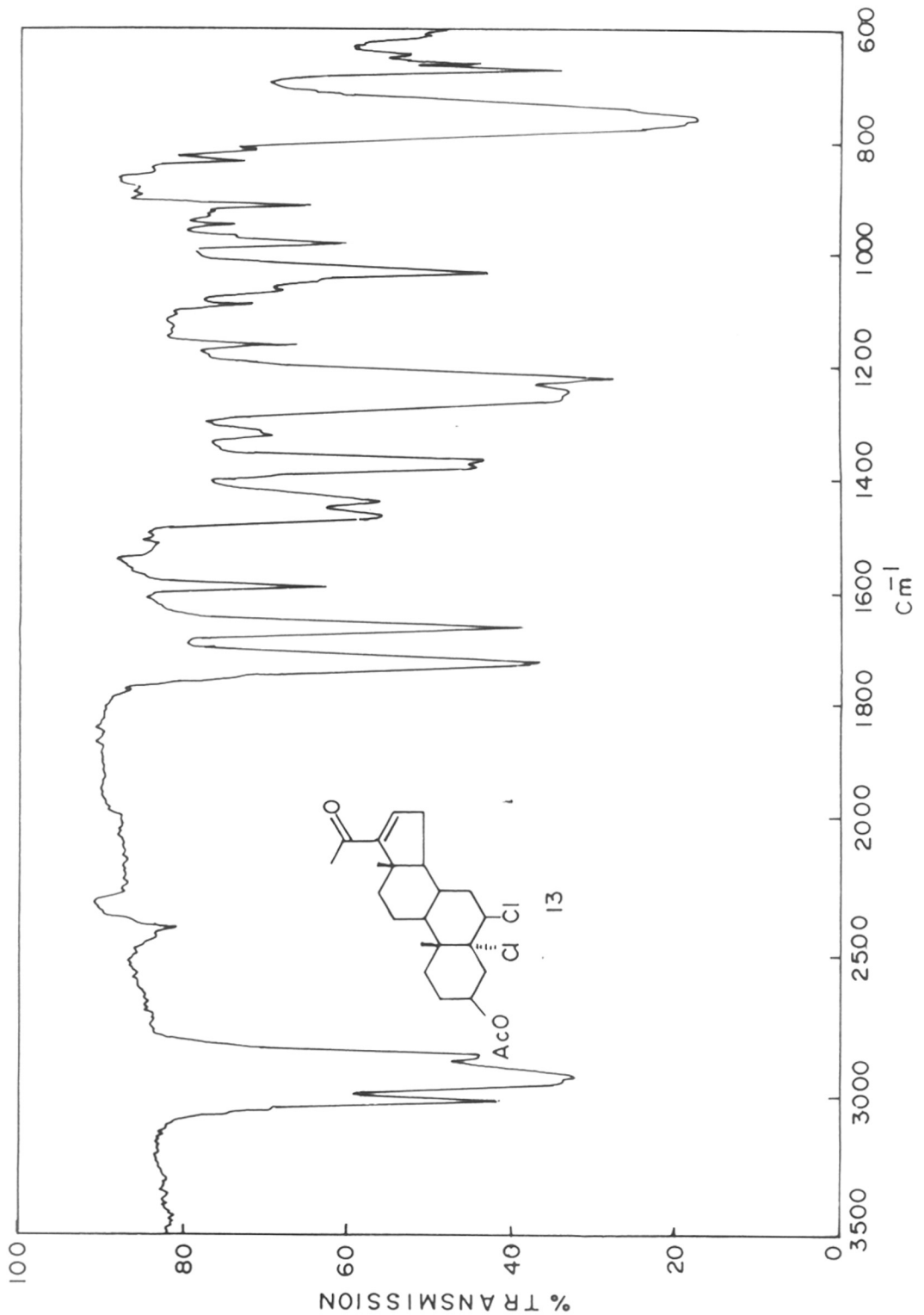

Cl
Cl
O
10
0
1
2
3
4
5
PPM

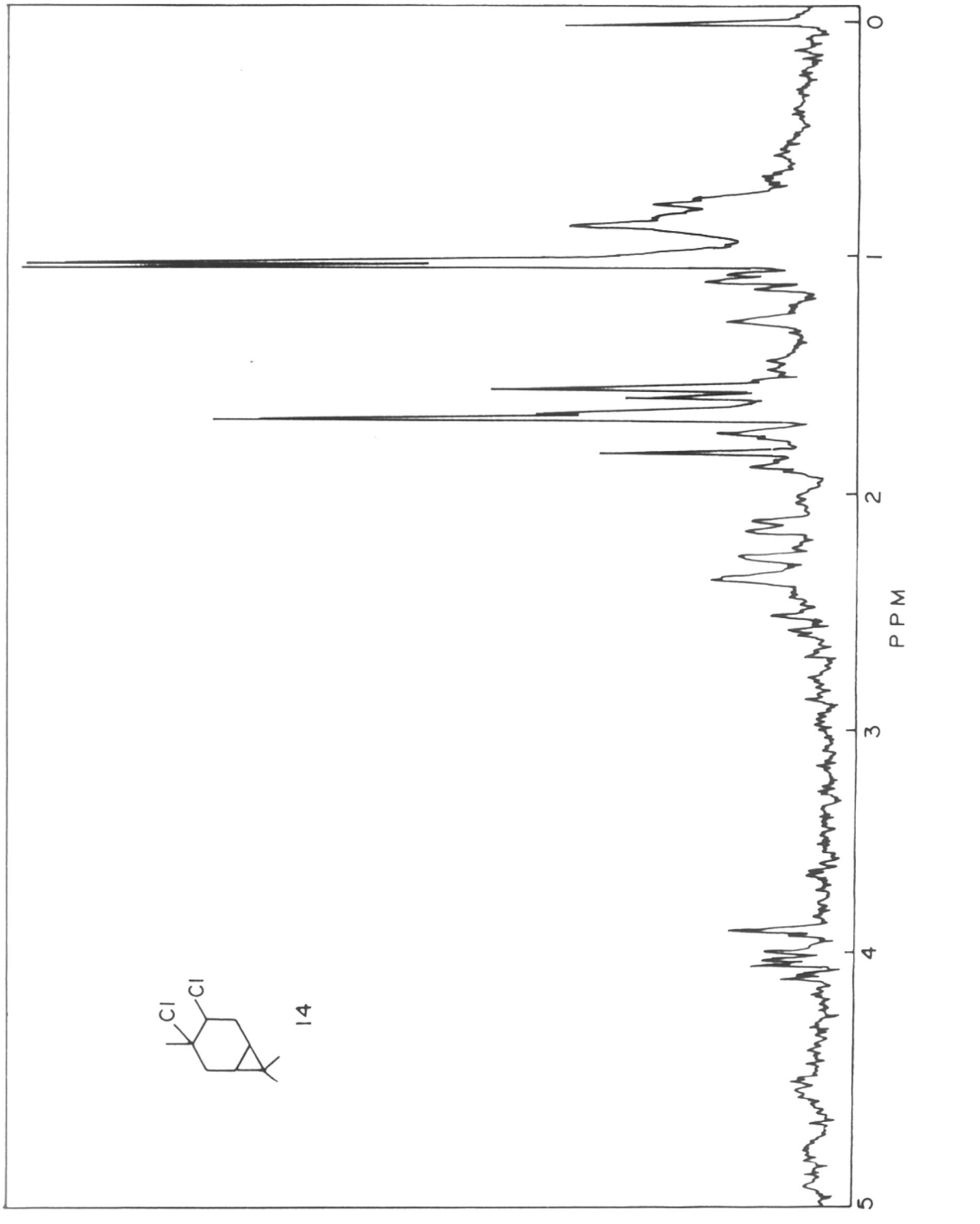

Cl
Cl
H
O
II
5
4
3
2
1
0
PPM

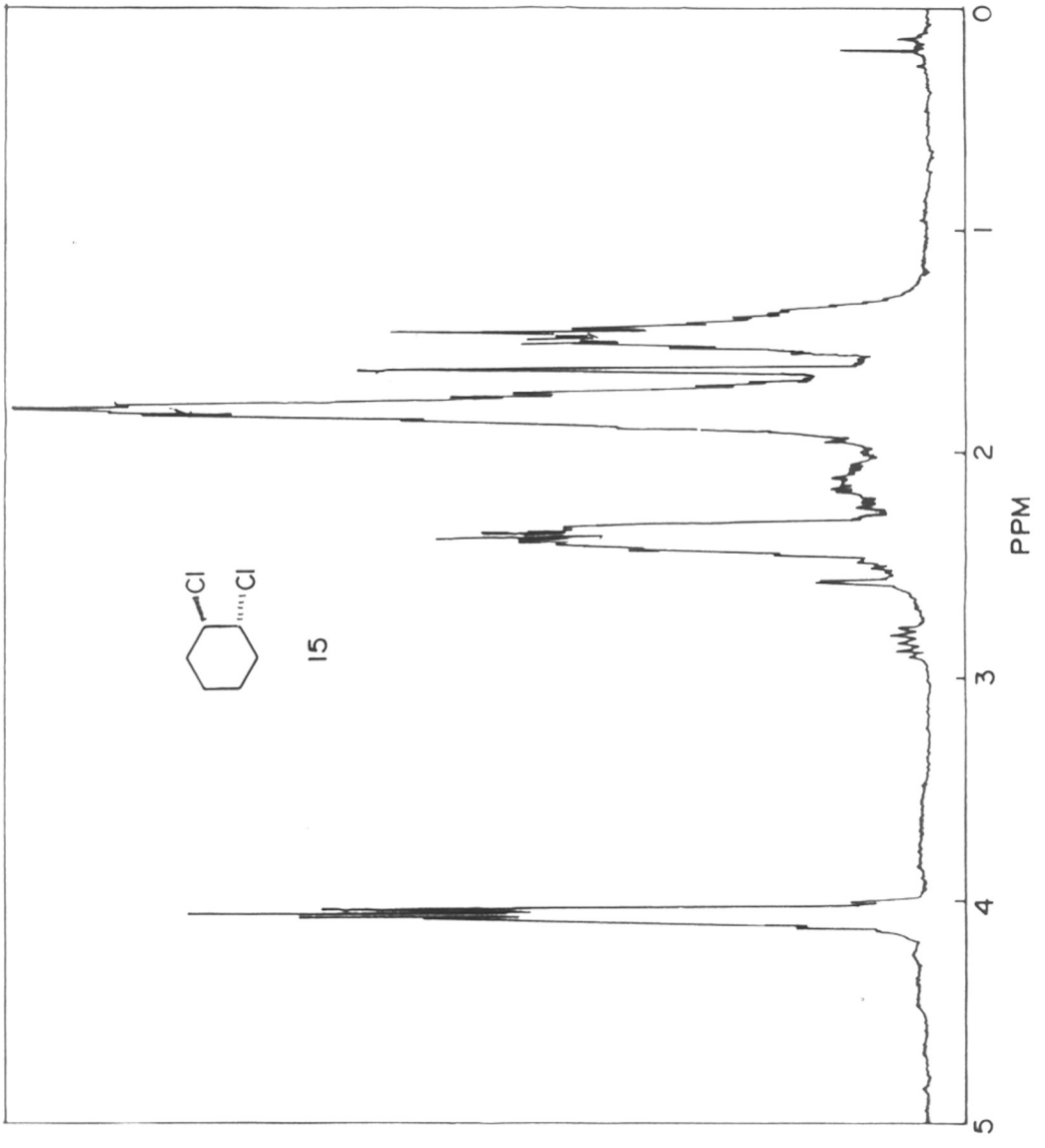

Cl
Cl
Cl
Cl
H
O
12
5
4
3
2
1
0
PPM

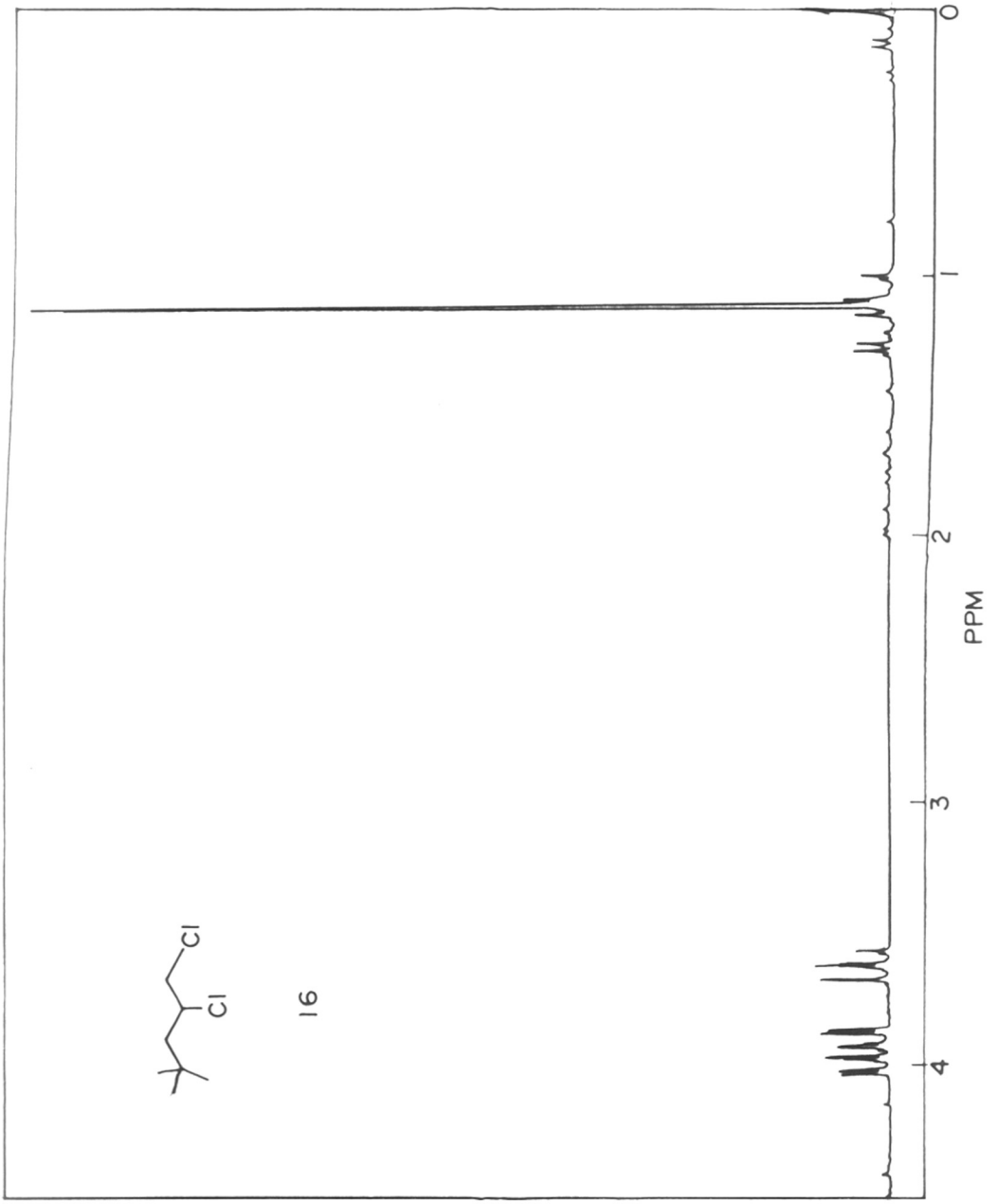


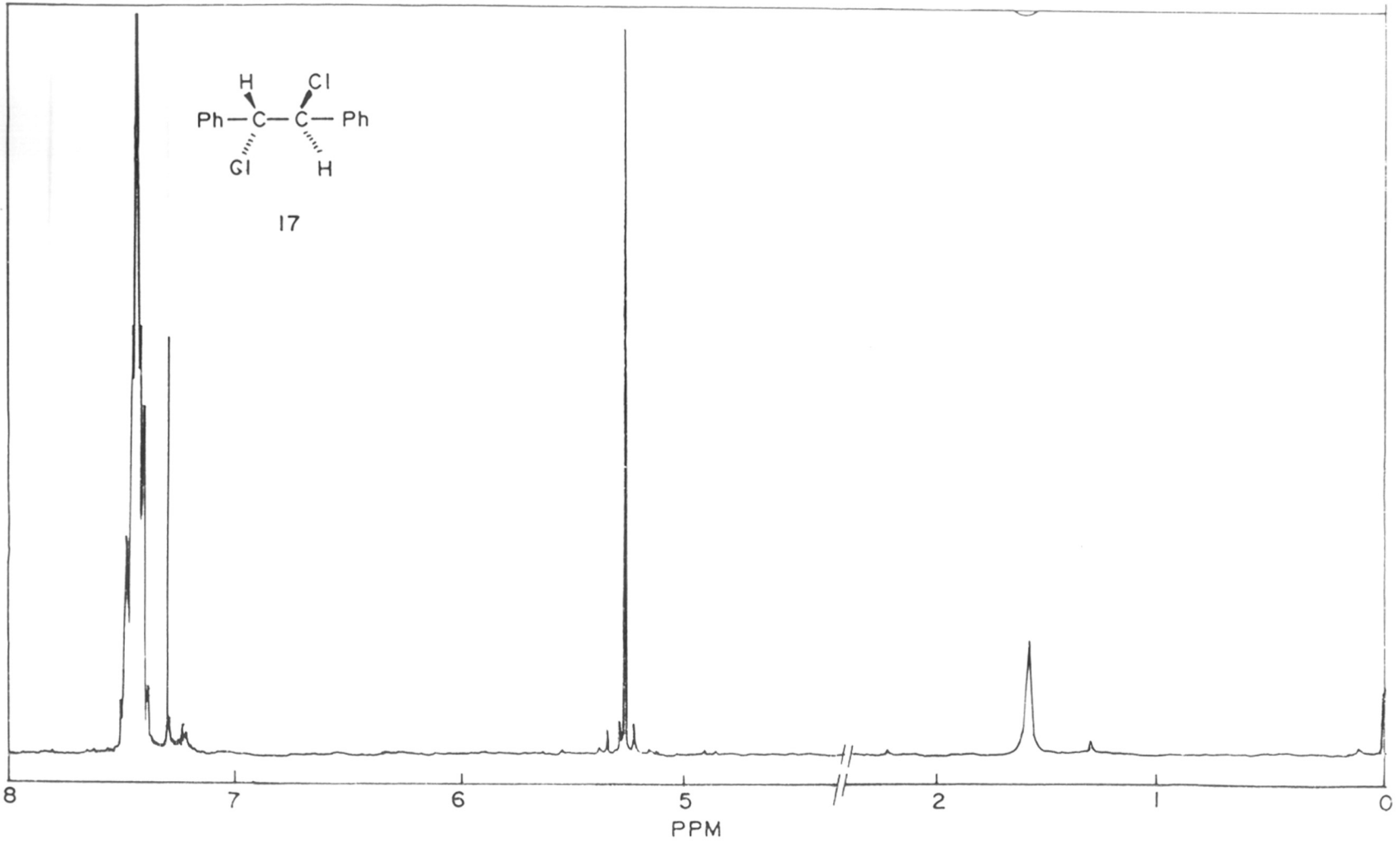
13


% TRANSMISSION
100
80
60
40
20
0
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
cm⁻¹
AcO
Cl
Cl
O
13

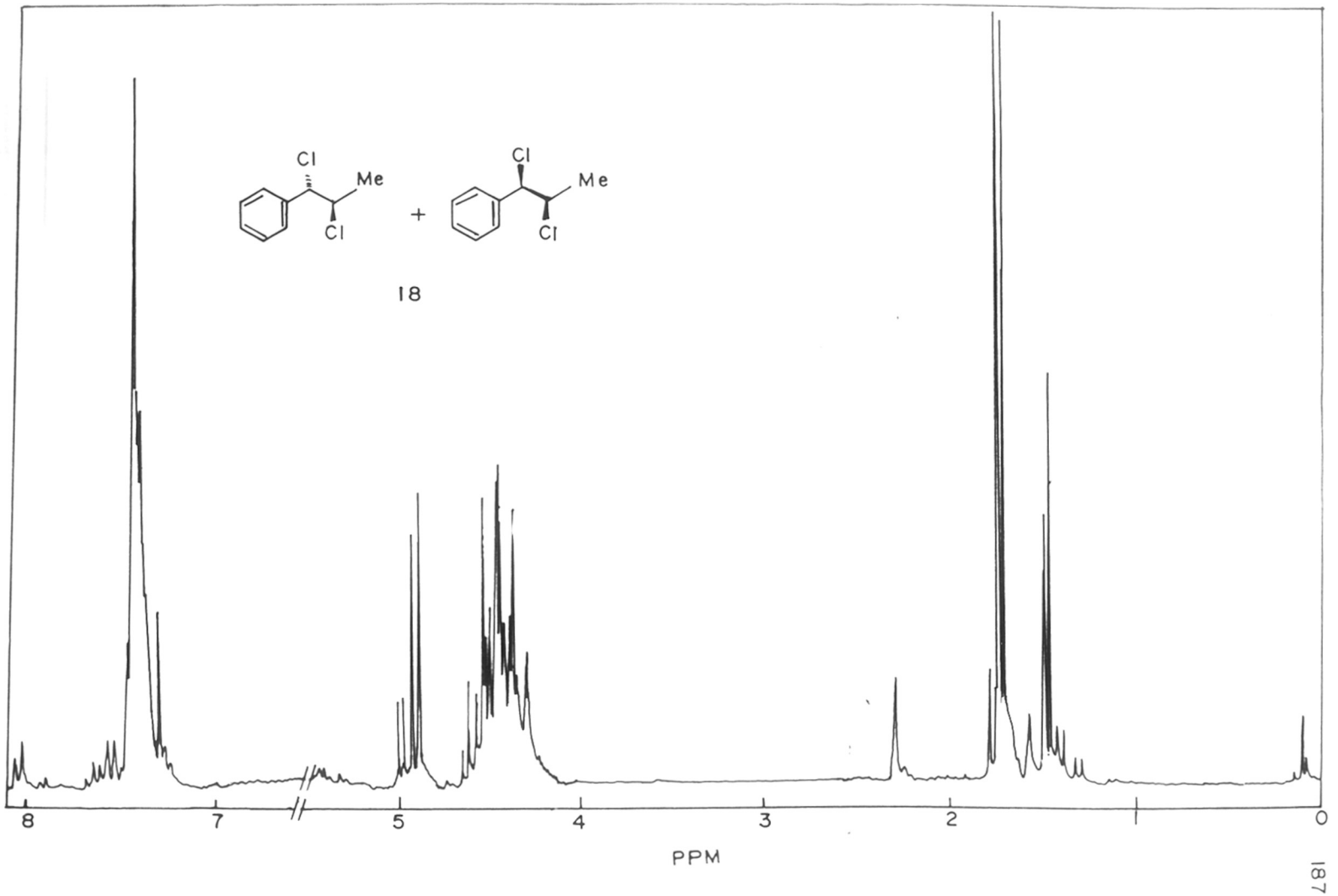

Cl
Cl
14
0
1
2
3
4
5
PPM

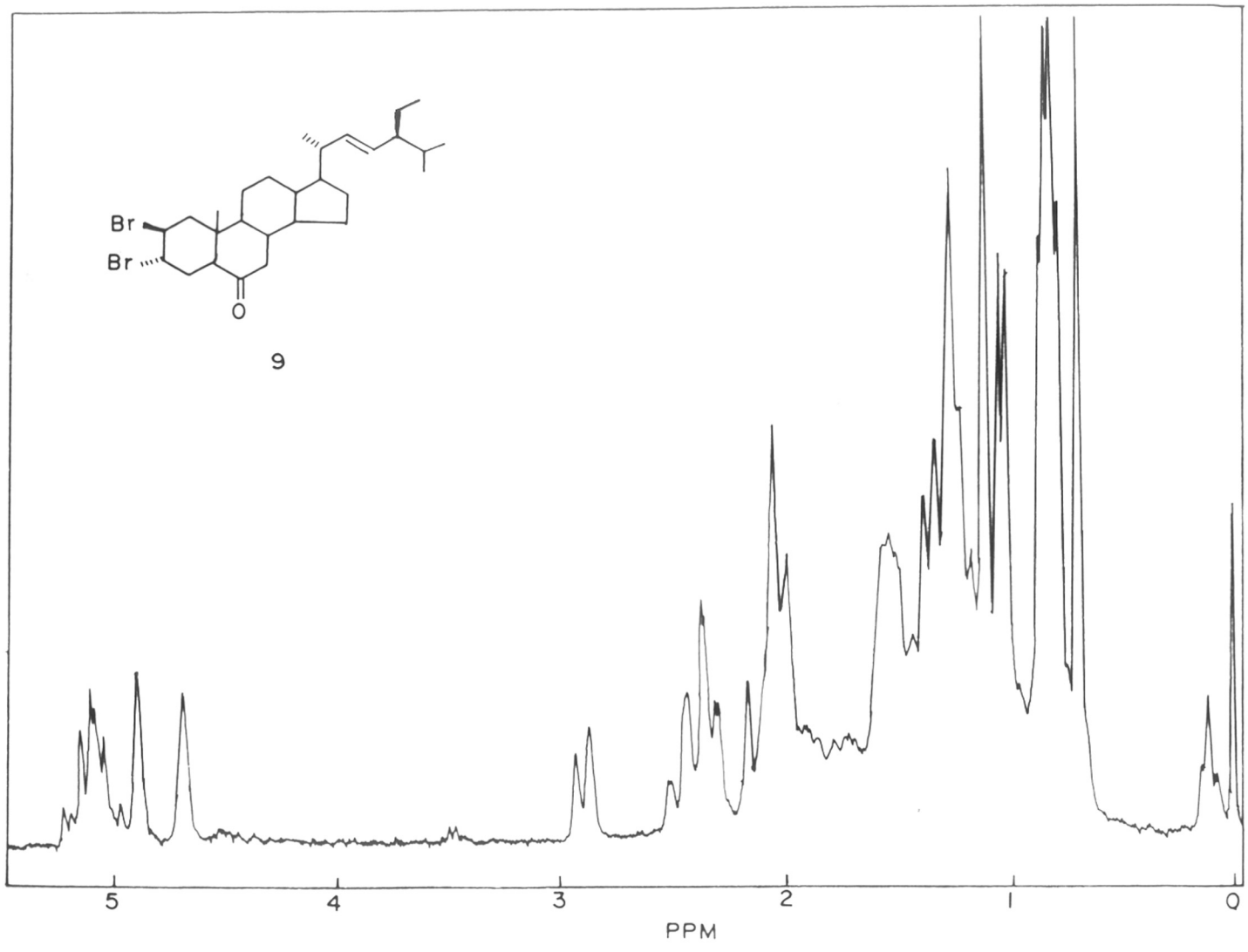

Cl
Cl
15
0
1
2
3
4
5
PPM

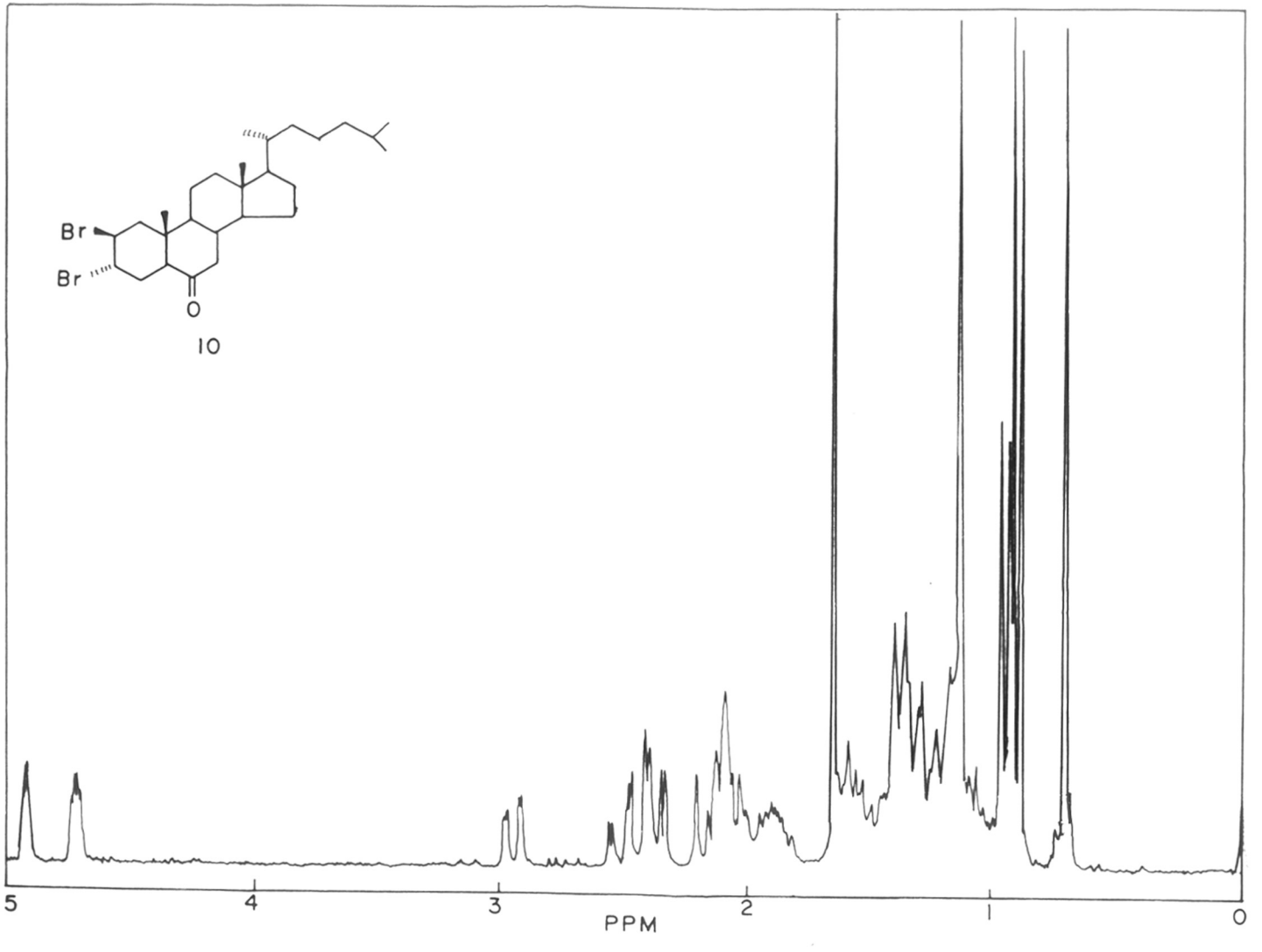

Cl
Cl
16
0
1
2
3
4
PPM

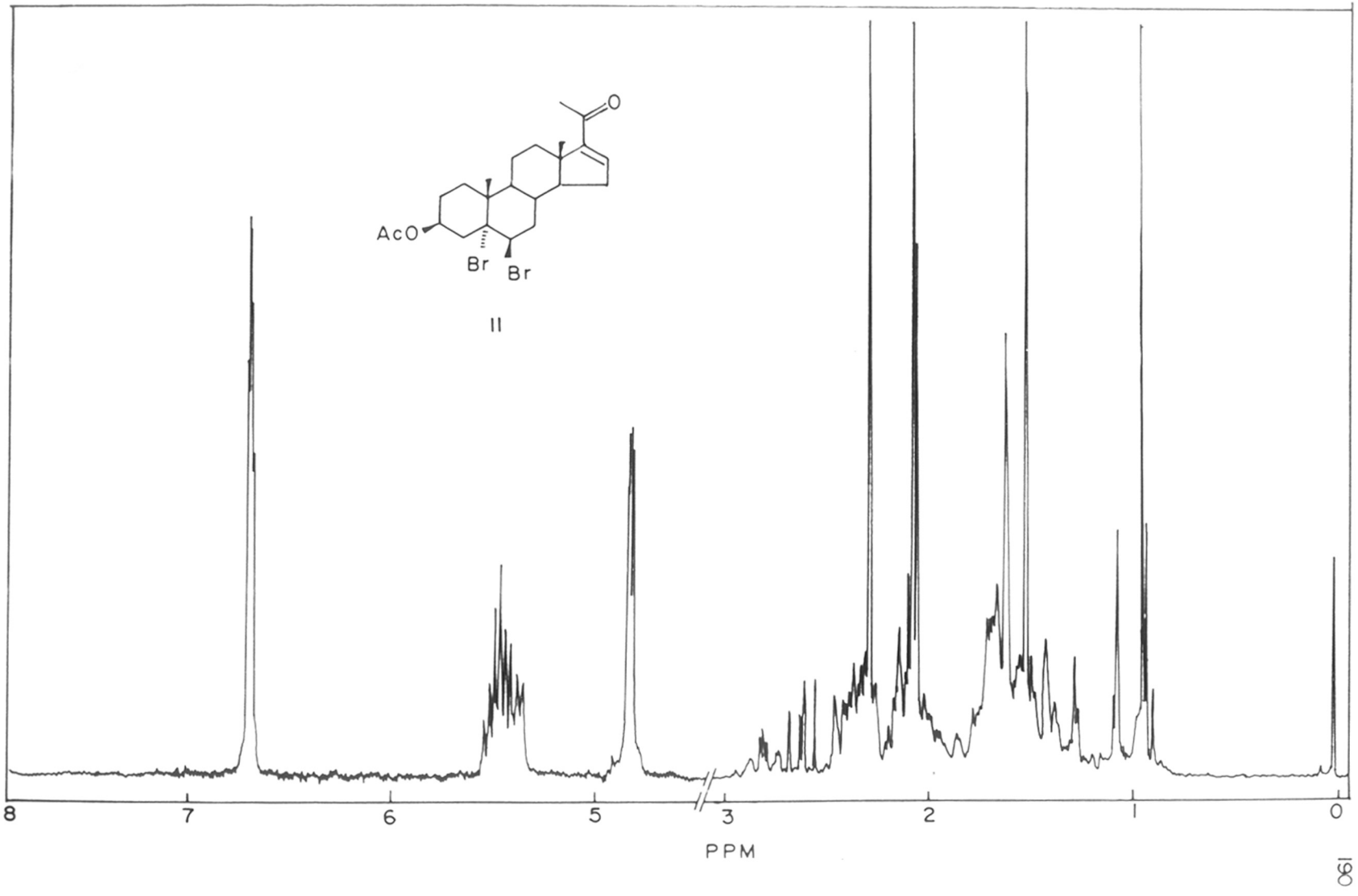


17

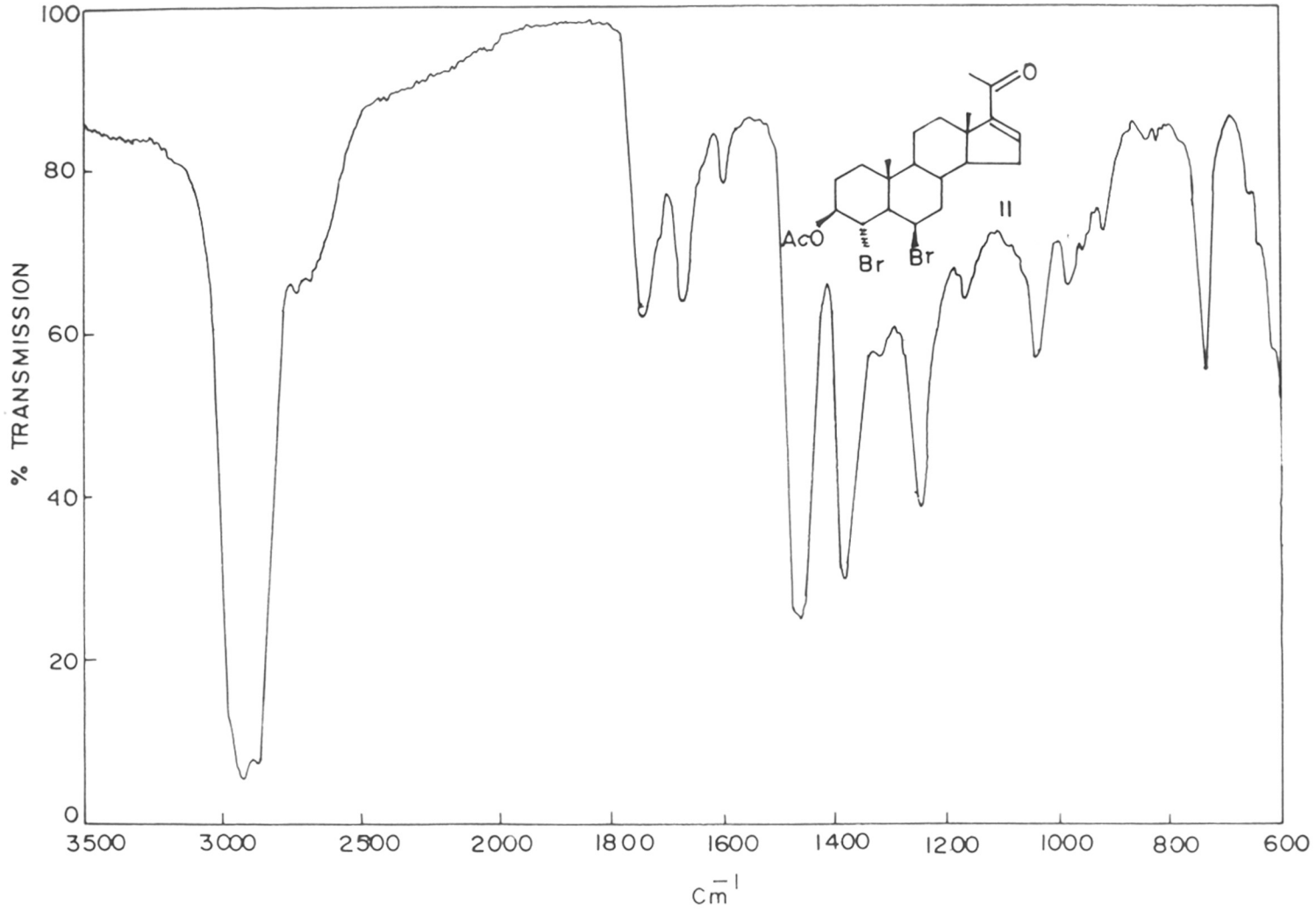

Cl
Me
Cl
+
Cl
Me
Cl
18
8
7
5
4
3
2
0
PPM

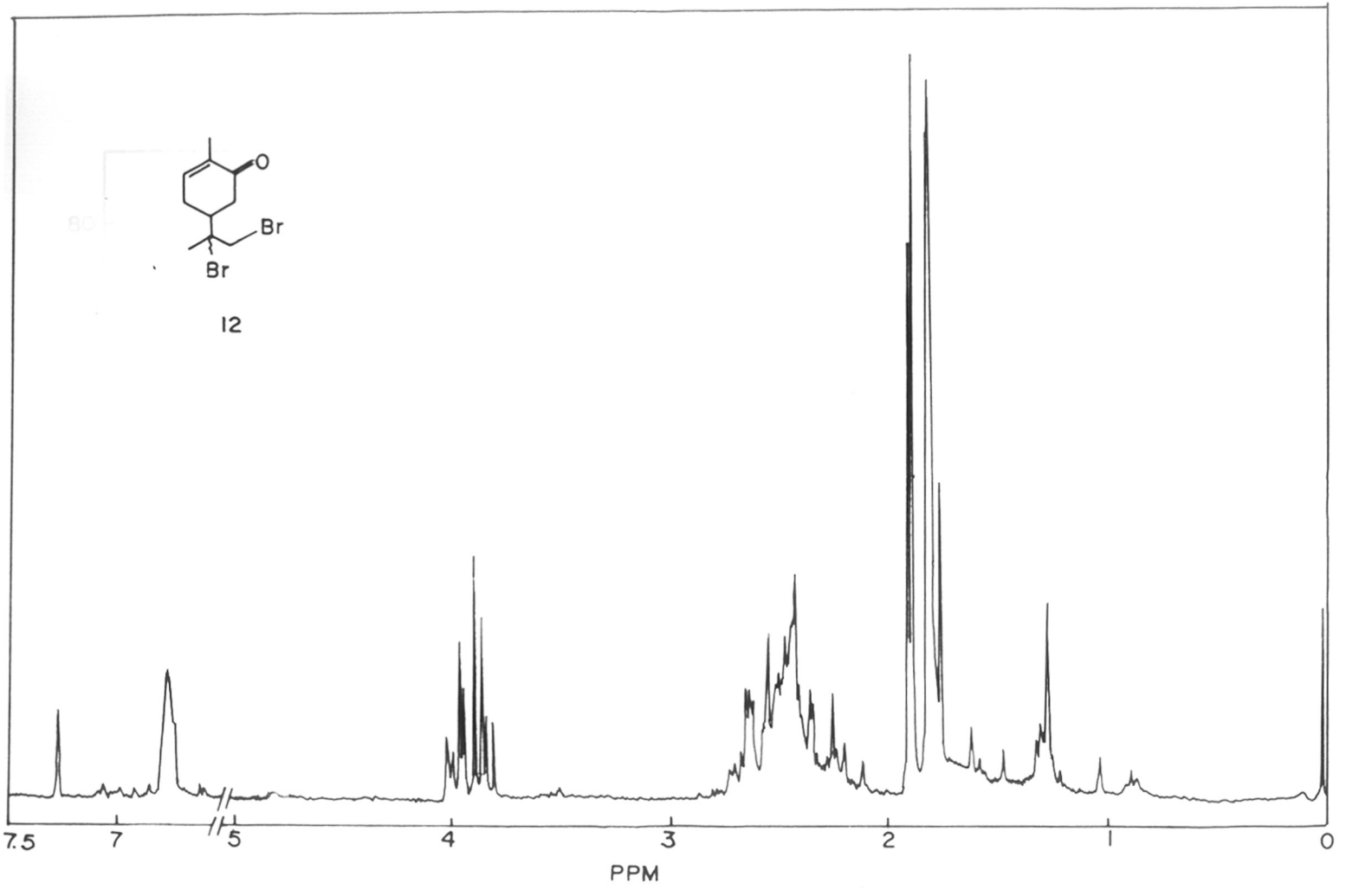

Br
Br
O
9
5
4
3
2
1
0
PPM

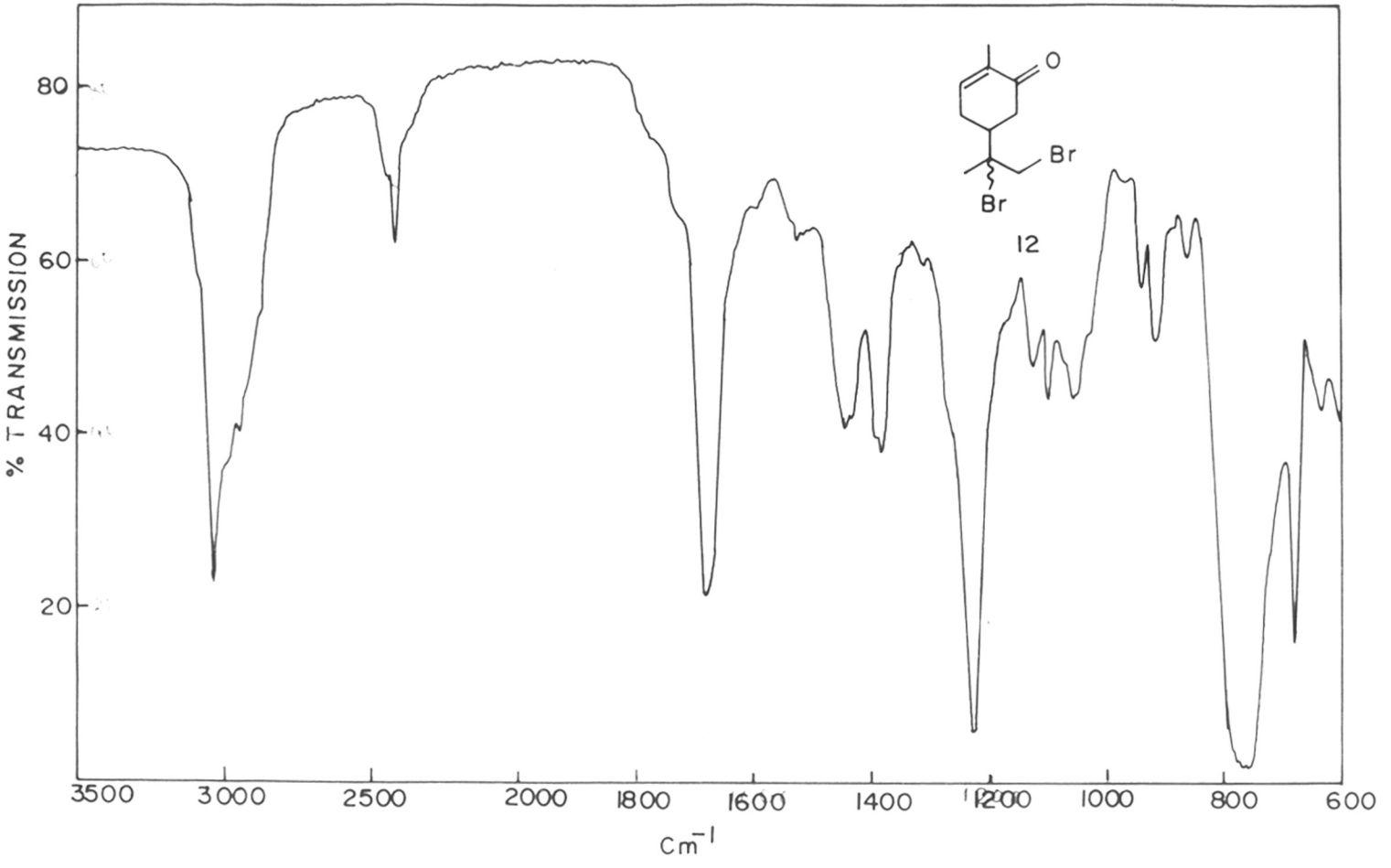

Br
Br
O
10
5
4
3
2
1
0
PPM

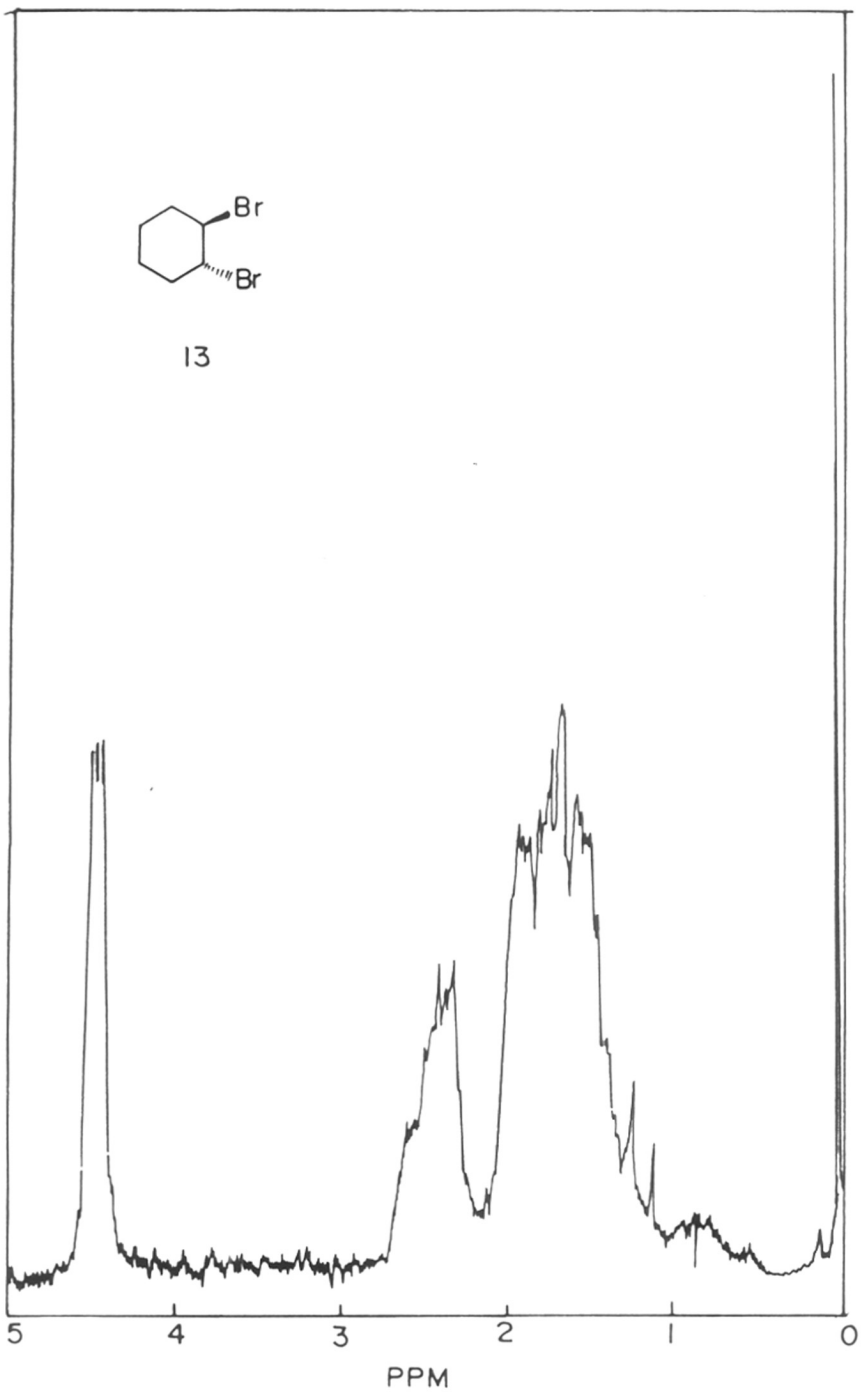


11

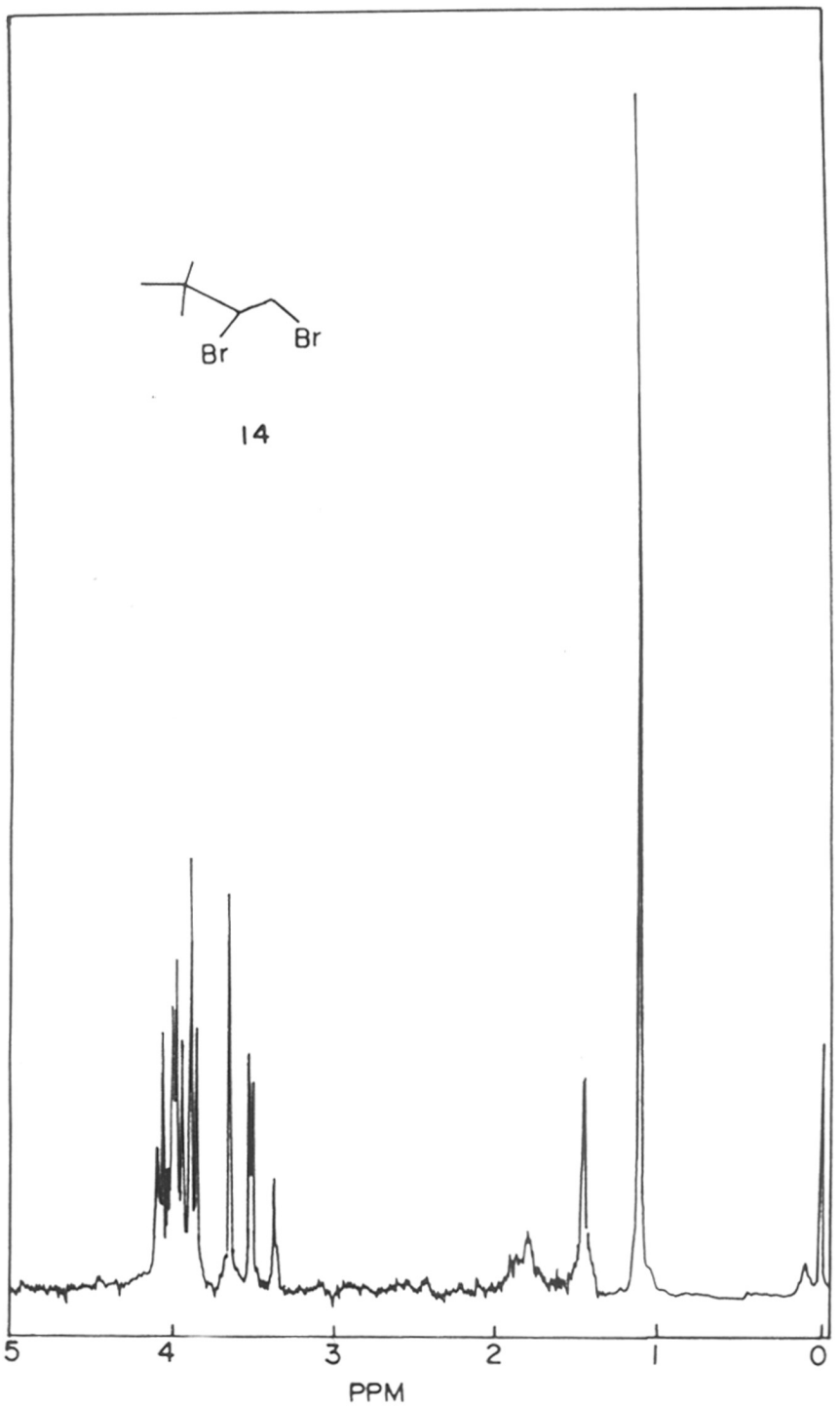

100
80
60
40
20
0
% TRANSMISSION
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Cm⁻¹
O
AcO
Br
Br
II


O
Br
Br
12
7.5
7
5
4
3
2
1
0
PPM

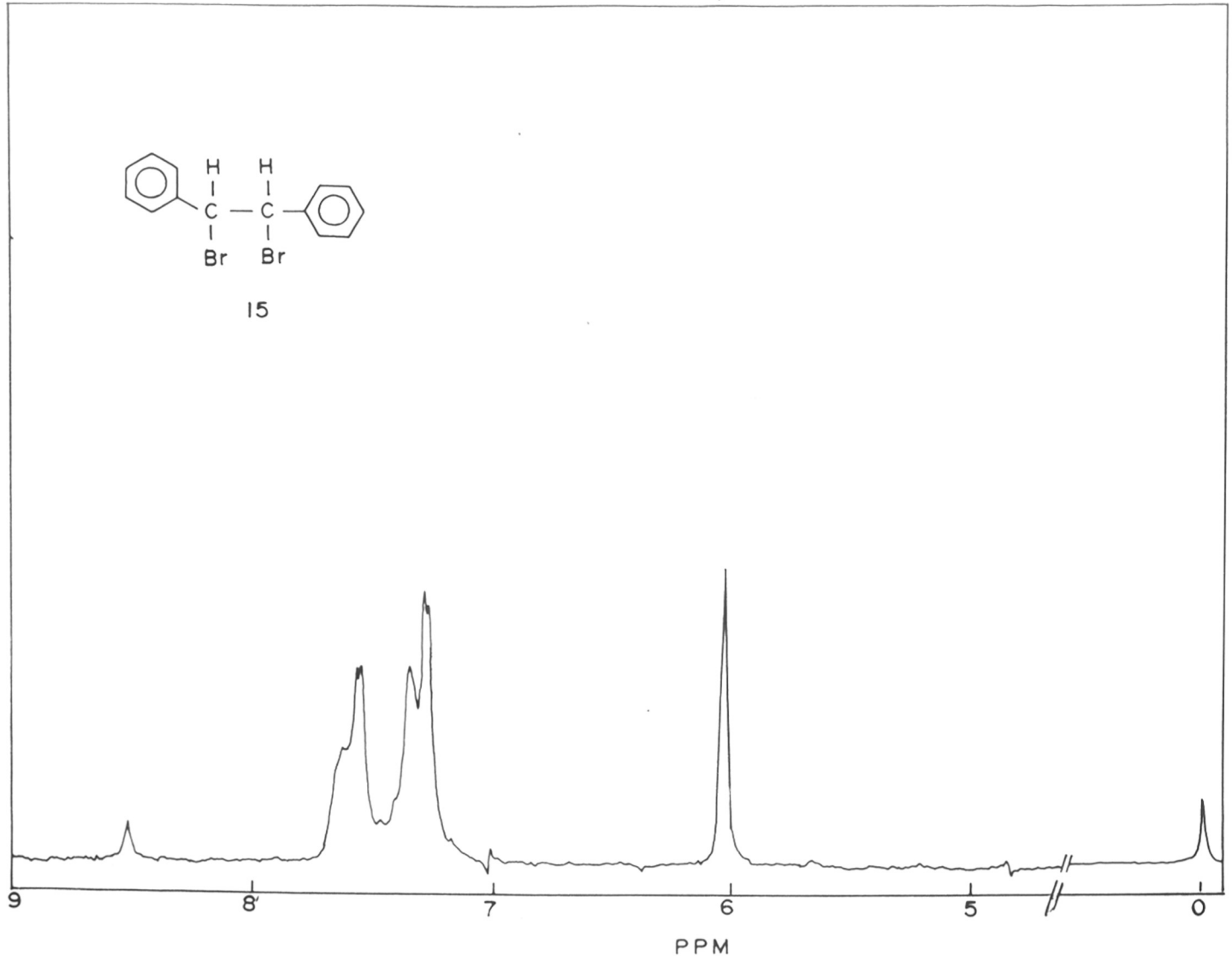

% TRANSMISSION
80
60
40
20
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Cm⁻¹
O
Br
Br
12



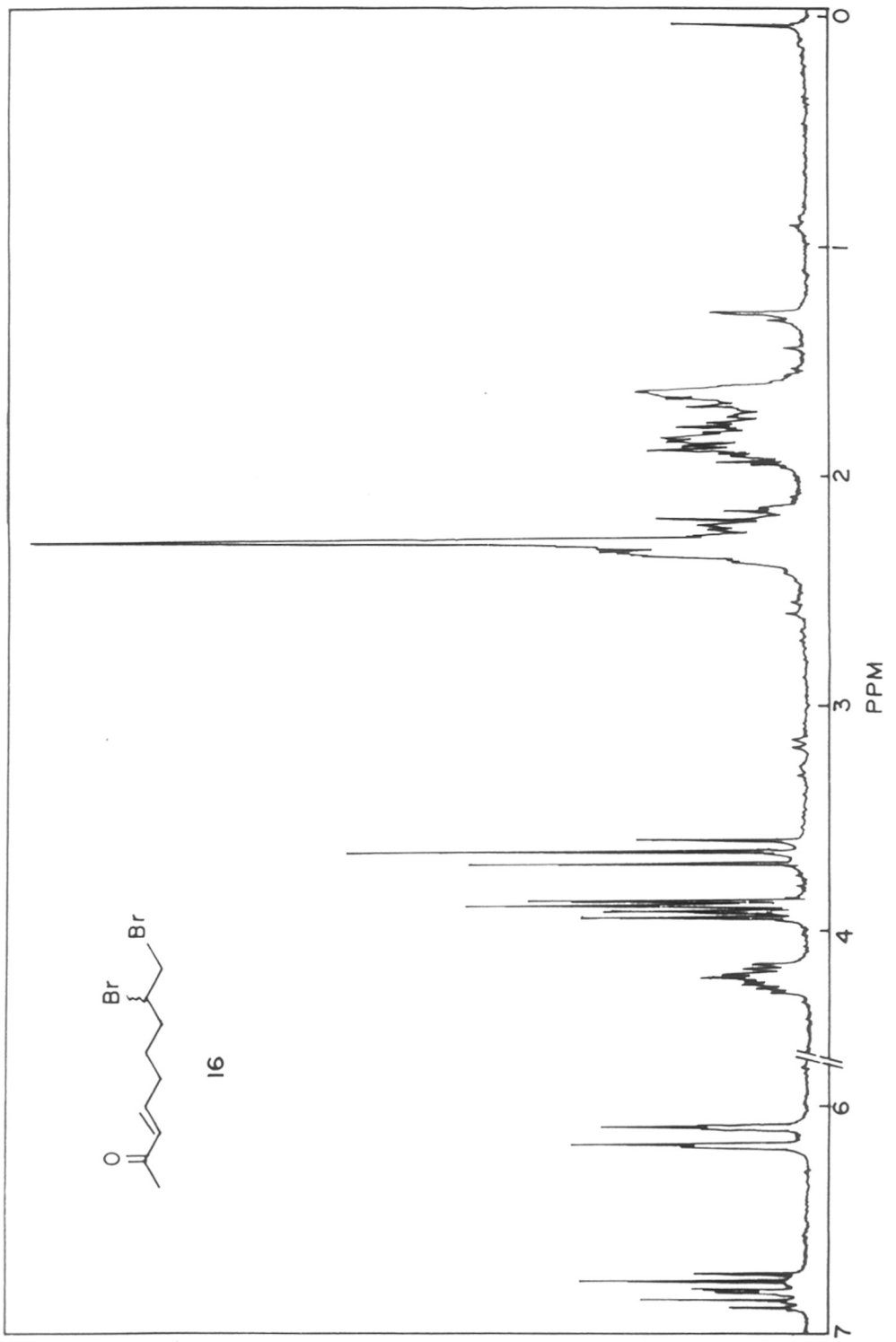
13



14



15


Br
Br
O
16
0
1
2
3
4
6
7
PPM

% TRANSMISSION
80
60
40
20
3500
3000
2500
2000
1800
1400
1000
600
cm⁻¹
Br
Br
O
16

List of Publications

1. Stereoselective synthesis of (22R, 23R, 24S)-3β-Hydroxy-5-ene-22,23-dihydroxy-24-methyl-cholestane: A Brassinolide Intermediate from 16-Dehydropregnenolone Acetate
   B.G.Hazra, P.L.Joshi, B.B.Bahule,N.P.Argade, V.S.Pore and M.D.Chordia
   Tetrahedron **1994**, 50, 2523-2532.

2. Manganese-mediated novel dibromination of olefins with tetradecyltrimethylammonium Permanganate and Trimethylbromosilane
   B.G.Hazra, M.D.Chordia, B.B.Bahule, V.S.Pore and S.Basu
   J.Chem.Soc. Perkin Trans.1 **1994** (in press).