A THESIS ENTITLED

SYNTHETIC AND STRUCTURAL STUDIES IN THE NATURAL PRODUCT FIELD.

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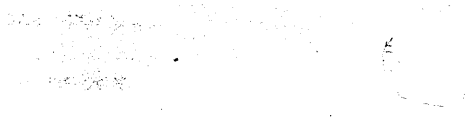


CONTENTS

SUMMARY

This thesis consists of six chapters, the first of which is a General Introduction dealing with (i) the nature of secondary metabolites and (ii) the terpenoids and aromatic constituents of the Hepaticae (liverworts).

Chapter 2 describes the synthesis of conocephalenol, an unusual sesquiterpenoid constituent of the liverwort *Conocephalum conicum*. Michael addition of 5,5-dimethylcyclohexane-1,3-dione to methyl vinyl ketone afforded a triketone which on McMurry reduction using $TiCl_3$/ZnCu, gave 1,6,6-trimethyl-2,3,4,5,6,7-hexahydro-4H-indene-4-one. Hydrogenation of this hydrindenone occurred stereoselectively and furnished the corresponding cis-hydrindanone.

Reaction of this hydrindanone with α-lithio ethoxy vinyl ether afforded, after subsequent hydrolysis of the product in dilute HCl, a mixture of two diastereomeric α-hydroxy ketones. One of these, on dehydration with $SOCl_2$ gave 4-acetyl-1,6,6-trimethyl 2,3,5,6,7,7a hexahydroindene which reacted with MeLi to give conocephalenol. The relative stereochemistry of 1-H and 7a-H in conocephalenol therefore must be trans.

Chapter 3 is concerned with a synthetic approach to the bicyclic system of tamariscol, an unusual sesquiterpenoid alcohol from the liverwort *Frullania tamarisci*. Alkylation of cyclohexane-1,3-dione with methyl vinyl ketone afforded a triketone which was transferred into 1-methyl-2,3,4,5,6,7-hexahydro-4H-inden-4-one using the McMurry reaction. Methylation followed by stereoselective hydrogenation yielded a mixture of dimethylhydrindanones, one of which proved to be identical with a degradation product of tamariscol.

This confirmed the trans relative stereochemistry of 1-H and the adjacent bridgehead proton.

Chapter 4 describes the structural elucidation of pakyonol, a new macrocyclic bisbibenzyl diether from the liverwort *Mannia fragrans*. The structure was assigned on the basis of detailed COSY, NOE and multiple selective irradiation experiments. Pakyonol represents a new bisbibenzyl substitution pattern, the first example to be isolated from the Hepaticae.

The synthesis of 3,5-dimethoxy-4-(3-methyl-2-butenyl)-bibenzyl is described in Chapter 5. The demethoxy derivative occurs in several *Radula* species. A Wittig reaction of 3,5-dimethoxybenzaldehyde and benzylphosphonium chloride afforded a stilbene mixture which on hydrogenation gave 3,5-dimethoxybibenzyl. Alkylation of this with n-BuLi and isoprenyl bromide gave the desired product in good yield.

Chapter 6 describes the structural elucidation of five partially-acetylated derivatives of 1-O-dodecanyl α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranoside, isolated from the stem bark of *Cleistopholis glauca* (Annonaceae). Their structures were elucidated by a combination of COSY, delayed COSY and FAB Mass spectroscopy. The trisaccharide 1-O-dodecanyl α-L-2,3,4-triacetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside was also isolated.

CHAPTER ONE

GENERAL INTRODUCTION

INTRODUCTION

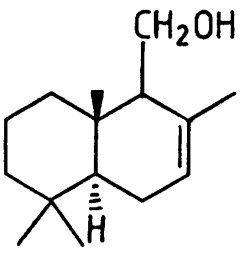
For thousands of years man has made use of natural products to increase quality of life. In the ancient world crude aqueous extractions of certain plants provided medicines, pigments for dyeing, and flavour for food. Stimulants and poisons from natural sources were known, and it was also realised that heating of aromatic plants could provide perfumed distillates. Further progression came in the eighteenth century when rudimentary science began to probe the nature of these substances. Natural product chemistry progressed rapidly in the nineteenth century with the evolution of organic structure theory. Structure elucidation at this time mainly involved degradation procedures which would, with luck, lead to a product of known structure. Thus the scope for discovering new reactions was great and throughout the history of organic chemistry the study of natural products has provided the impetus for great advances.

The development, this century, of physical methods of analysis such as nmr, IR, mass spec., and g.c. has meant that structural elucidation is now possible using only small amounts of material.

Natural products are traditionally divided into two groups, primary and secondary metabolites. The processes involved in primary metabolism synthesise and utilise essential chemical entities such as sugars, fatty acids, nucleic acids etc. Secondary metabolites are often of more interest to the organic chemist. The formation of secondary metabolites appears to involve the use of a non-essential pathway to produce a compound that is not essential for the survival or well-being of the plant. It has been shown that plants and nucro-

organisms can flourish in the absence of many of their normal metabolites, and in the presence of some foreign ones. It has also been suggested[1], however, that apart from being products of waste metabolism, secondary metabolites have somehow played a role in the evolution of plants by maintaining a particular selective advantage. Thus perhaps there is a mechanism for chemical control by particular secondary metabolites in the evolution of plants. There are several areas in which it has been realised that production of certain secondary metabolites can lead to a selective advantage. For example, certain plants contain compounds that can act as either antifeedants or attractants. Development of the plant can also be influenced by the production of metabolites which give the plant an alleopathic advantage over its competitors.

This thesis is concerned with synthetic and structural studies within both fields of primary and secondary metabolism.



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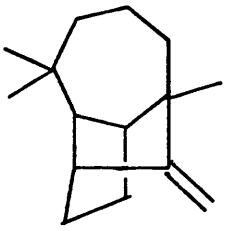

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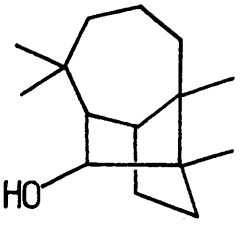

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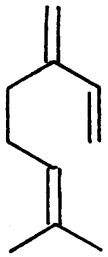
THE HEPATICAE

The Hepaticae (or liverworts) belong to the group Bryophyta, which also contains the classes of Musci (mosses) and Anthocerotae (Hornworts). The bryophytes represent a well defined group of plants. No recognisable link connects them on one hand with the Algae or on the other with the Pteridophytes. Their evolution remains to a greater extent a matter of speculation and the inter-relationships between the different groups are by no means understood. The liverworts are the only class to contain oil bodies, microscopic deposits of oil which occur in the cells and are unconnected with deposits of fatty oil (a widespread food reserve in the bryophytes, as in higher plants). They vary from the massive deposits which occur in certain cells of some thalloid liverworts e.g. *Lunularia* to minute granular bodies (up to twenty per cell) which are found in others e.g. *Jungermanniales*. The reason why liverworts should contain oil bodies has not yet been clarified, but they could be a factor in why so many are unusually resistant to insect and fungal attack.

Liverworts are easily overlooked and economically unimportant. However they have found medicinal use, e.g. *Conocephalum conicum* against gallstones[2]. Muller[3], at the turn of the century, believed that chemical investigation would yield sesquiterpenoids. His assumptions were based on observations on the odour of various species. However it was not until fifty years after his paper that the chemotaxonomy was further investigated, when Fujita[4] reported sesquiterpene hydrocarbons from *Bazzania pompeana*. In 1967 Huneck[5] published the first isolation of a pure terpenoid, (-)-drimenol(1) from *Bazzania trilobata*. Further reports from Huneck



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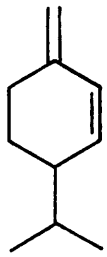

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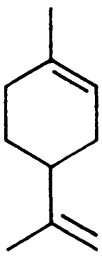

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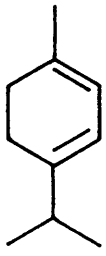

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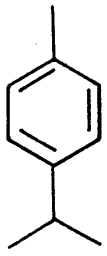

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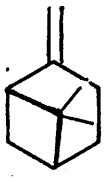

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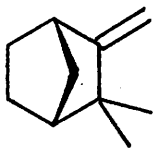

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and Klein[6] concerned the isolation of (-)-longifolene(2) and (-)-longiborneol(3) from *Scapania undulata*. Literature dealing with liverwort chemistry has increased dramatically over the past twenty years, probably due to the fact that analysis of complex mixtures found in the oil bodies has become less of a problem. The discovery of chemically and pharmacologically interesting compounds has also provided a stimulus.

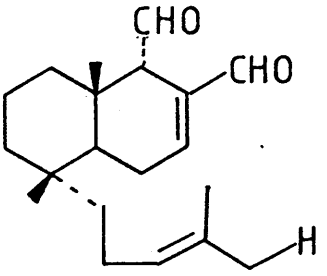
Comprehensive reviews of liverwort constituents have been published by Asakawa[7] and Huneck[8]. A short account of the terpenoid constituents of some European liverworts has also appeared[9].

MONOTERPENOIDS

In the Hepaticae studies have utilised a g.c. or g.c.m.s. approach and except for reports by Asakawa[10], no monoterpenoids have been isolated in a pure state.

The common monoterpenoids reported include mycrene(4), β-phellandrene(5), limonene(6), α-terpinene(7), p-cymene(8), α-pinene(9), β-pinene(10) and camphene(11).

It has been found that some species synthesise only one of the possible enantiomeric forms[11]. Asakawa[10] reported that *C. conicium* contains (-) limonene(ent-6), while *Jungermannia exertifolia*[11] produces the enantiomeric form. Thus, as in higher plants both optical antipodes occur. The chiroptical properties of monoterpenoids found in the Hepaticae have not been clarified and



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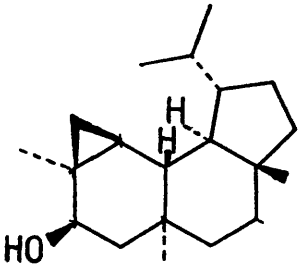

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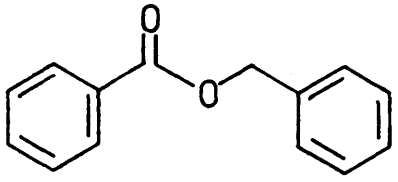

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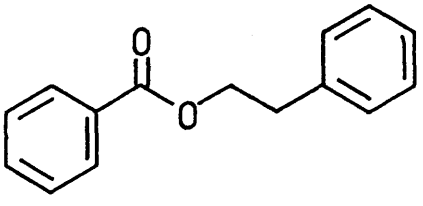

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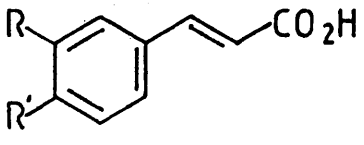


(16) R = H , R' = OH

(17) R = OH , R' = H

much work remains to be done in this field.

SESQUITERPENOIDS

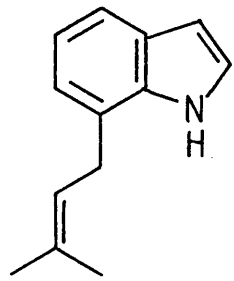
Liverworts are extremely rich in sesquiterpenoids, many of which are enantiomeric to those found in higher plants. The first sesquiterpenoids to be identified were reported in 1967 by Huneck and Klein[6] who isolated (-)-longifolene(2) and (-)-longiborneol (3) from *Scapania undulata*. These sesquiterpenoids are the enantiomers of longifolene and logiloneol found in *Pinus* species.

DITERPENOIDS

These constitute the second largest group of terpenoids in the bryophytes. New types of skeleton that have been found are exemplified by isosacculatal(12), a sacculatane and (-)-neoverrucosan-5β-ol, a verrucosane(13)[7].

AROMATIC COMPOUNDS

Liverworts produce a wide range of aromatic compounds. Benzoic acid derivatives, including benzyl benzoate(14) and β-phenylethyl benzoate(15)[12], have been isolated. Cinnamic acid derivatives are also found, including p- and m-coumaric acids (16) and (17) from Isotachis species[13]. Many bibenzyls and bisbibenzyls have also been isolated. This group will be discussed in detail later in this thesis.



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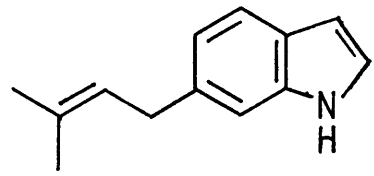

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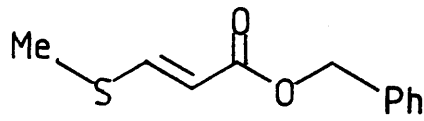

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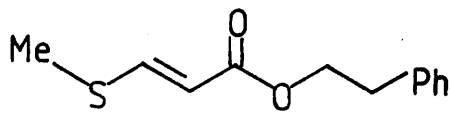

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MISCELLANEOUS

The unusual indole derivatives (18) and (19) have been isolated from *Riccardia* species[14,15]. Two new sulphur acrylates, isotachin A (20) and isotachin B (21) were detected in the liverwort *Isotachis japonica*[16].

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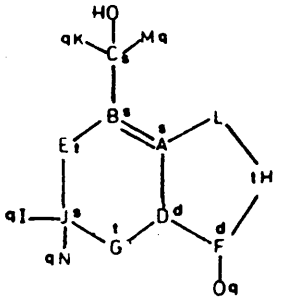
CHAPTER TWO

SYNTHESIS OF CONOCEPHALENOL

Fig. 1 CONOCEPHALENOL

2D INADEQUATE

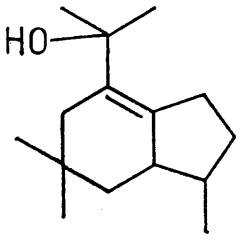


INTRODUCTION

CONOCEPHALENOL AND RELATED COMPOUNDS

Conocephalenol[1] (1) $C_{15}H_{26}O$ [m/z 222 (4%)] $[\alpha]_D = -11^{\circ}$ (C 2.5 in $CHCl_3$), was isolated as an odoriferous oil by Connolly and Harrison from the liverwort *Conacephalum conicum* collected near Loch Katrine. The ^{13}C and ^{1}H nmr parameters revealed the presence of a tertiary hydroxyl [δ_C 74.0 (s)], a tetra-substituted double bond [δ_C 135.9 and 132.7 both (s)], four tertiary methyl groups [δ_H 1.02, 0.99, 0.98 and 0.89 all (s); δ_C 32.9, 30.2, 29.4 and 27.0] and one secondary methyl group [δ_H 1.01 (d, J 7.1 Hz) ; δ_C 18.5]. Information about connectivity was difficult to obtain from the ^{1}H nmr, even at 360 MHz, due to the overlap of resonances and second order effects. The structure was determined as in (1) without stereochemistry, by a 2D INADEQUATE experiment[2], fig.1. This 2D $^{13}C/^{13}C$ correlation technique is the ultimate tool for the structural elucidation of a carbon skeleton. Other compounds isolated from *Conocephalum conicum* include 3-acetoxy-1-octene(2), the aldehyde(3) and the epimeric thujanols (4) and (5).

Although the skeleton of conocephalenol is highly unusual, it is not unique. Extraction of the digestive glands of the sea-hare *Aplysia brasiliana* afforded brasilenol(6), brasilenol acetate(7) and epibrasilenol(8)[3] all of which possess the same non-isoprenoid skeleton as (1). Evidence suggests that compounds (6),(7), and (8) originate from the red algae *Laurencia* which is a foodstuff of *A. brasiliana*. Brasilenol(6) was isolated as a volatile solid, m.p. 55-56°C, with a mild menthol-like odour. High resolution mass spectrometry established the molecular formula as $C_{15}H_{26}O$. The presence of a



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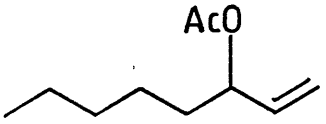

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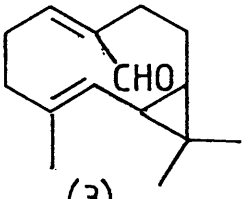

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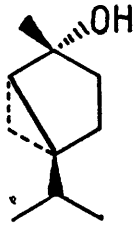

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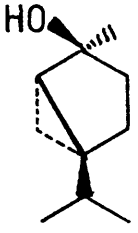

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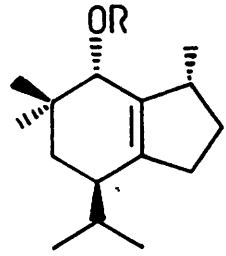
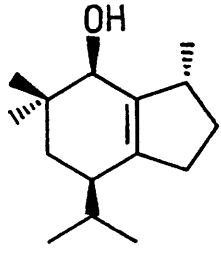


(6) R = H

(7) R = Ac



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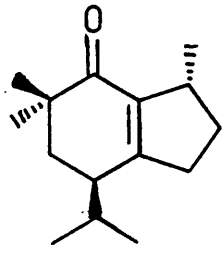


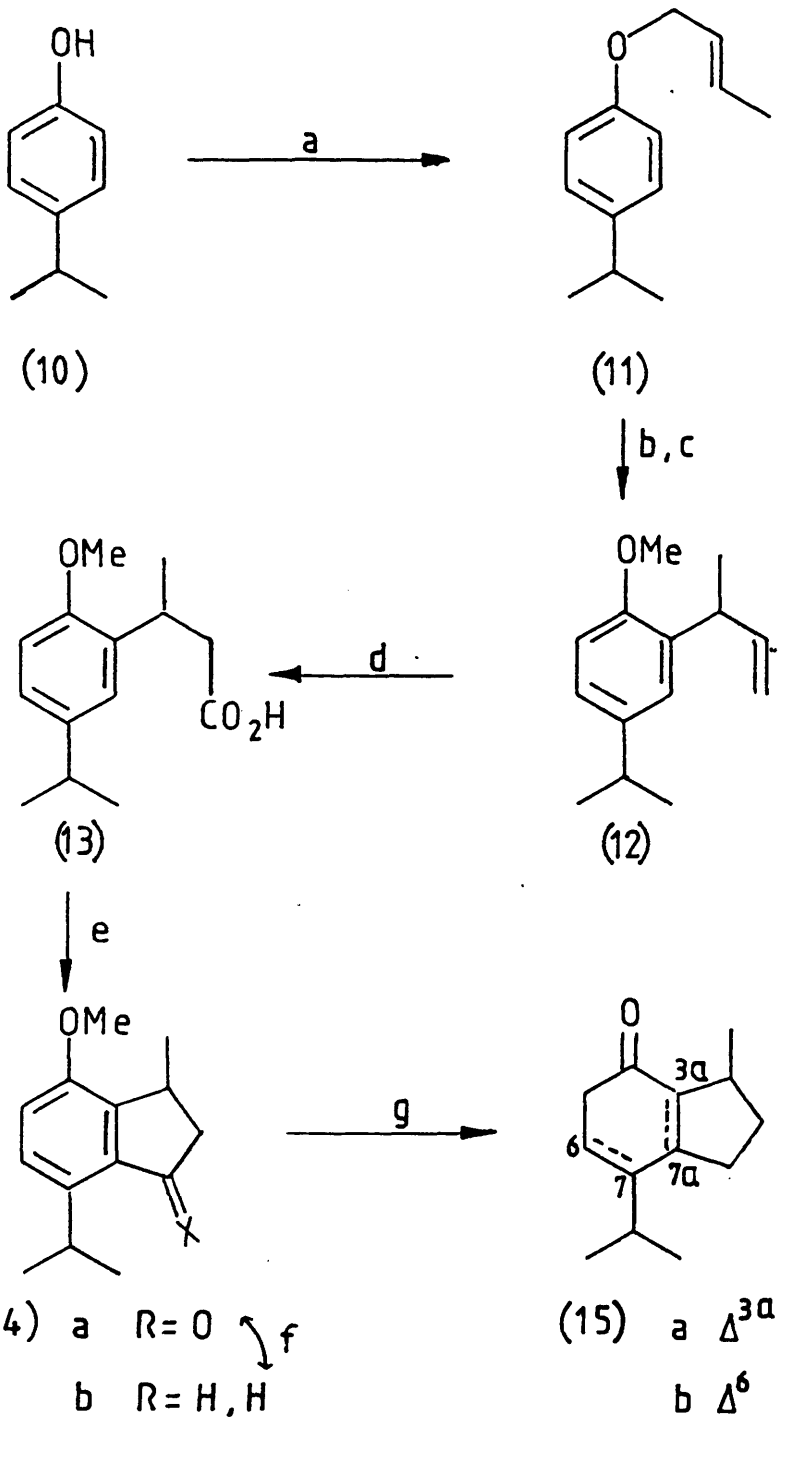
(9)

secondary hydroxyl group [ν_{max} 3650 cm^{-1}; δ_C 77.7] probably allylic, and a tetrasubstituted double bond [δ_C 142.1 and 138.7] was readily revealed. Thus brasilenol(6) is bicarbocyclic. Acetylation of brasilenol afforded the acetate (7) [δ_H 5.36 (dddd, J, 1,3,3,3 Hz] identical with the natural acetate. The ^1H nmr spectrum also revealed the presence of two tertiary [δ_H 0.82 and 1.02] and three secondary [δ_H 0.67, 0.87 and 1.10 (all d, J 7 Hz)] methyl groups. Thus both brasilenol (6) and conocephalenol (1) contain five methyls rather than the more common four methyls (or equivalent) of most sesquiterpenoids. The biosynthesis of this unusual skeleton is not immediately apparent.

Jones oxidation of (6) gave the ketone brasilenone (9) whose spectroscopic properties suggested the presence of a 6-membered α,β-unsaturated ketone. Irradiation of one side of a complex two proton multiplet in (9) at δ_H 2.14 caused the two secondary methyl doublets at δ_H 0.98 and 0.74 to collapse to singlets. This indicated the presence of an isopropyl group. The lack of deshielded protons in (9) suggested that the α carbon must be fully substituted and perhaps the site of a gem-dimethyl group.

Thus brasilenol is a bicyclic sesquiterpene allylic cyclohexanol with gem-dimethyl, secondary methyl and isopropyl substituents and must possess a bicyclo [4.3.0]non-1(6)-ene skeleton since other bridged arrangements of the atoms would violate Bredts rule. The structure of brasilenol as (9) was eventually proved, without stereochemistry, by extensive ^1H nmr double resonance experiments and by the use of the lanthanide shift reagent, Eu $(fod)_3$.

Scheme 1



(14) a R = O ↷ f

b R = H, H

(15) a Δ^{3a} isomer

b Δ^{6} ,,

REAGENTS

a $K_2CO_3/CH_3CH{=}CHCH_2Br$

b Δ

c NaH, CH_3I

d $BH_3; H_2O_2, NaOH; O^x$.

e PPA

f $LiAlH_4$

g Li, CH_3NH_2 $^tC_4H_9OH$

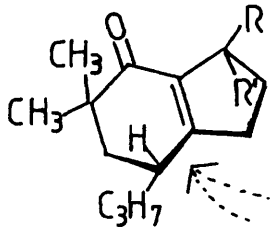
In 1986 Greene and co-workers reported the first synthesis of brasilenol, which confirmed the novel nonisoprenoid bicyclo [4.3.0] nonane skeleton and also the relative stereochemistry of the natural product[4]. In planning the synthesis the authors viewed enone (16) as a potential target which would permit the selective introduction of stereochemistry at the 3-C, 4-C and 7-C allylic centres of brasilenol. It seemed likely that the cis-isomer (16b) would readily equilibrate and thus, if the two isomers (16a) and (16b) could be separated, the generation of the 3-C. 7-C trans isomer, brasilenone (8), would be possible. The subsequent stereoselective reduction of (16a) to brasilenol was deemed possible because inspection of molecular models revealed the face opposite to that of the 3-C and axial 5-C methyl groups to be by far less sterically shielded.

The first stage of the synthesis (Scheme 1) involved the conversion of 4-isopropylphenol (10) to the crotyl ether (11) with trans-crotyl bromide. Subsequent Claisen rearrangement and methylation with iodomethane gave the anisole (12). Hydroboration and oxidation of this olefin yielded a carboxylic acid (13) which was cyclised on heating at 60°C in neat polyphosphoric acid to give the crystalline indanone (14a). Various Birch reductions of the indanone (14a) and the corresponding indane (14b), achieved by stepwise reduction of (14a), resulted in either complete recovery of starting material or over-reduction. Success in the reduction was achieved by treating a solution of either (14a) or (14b) in methylamine-tert-butyl alcohol-tetrahydrofuran at -40°C with a large excess of lithium for 15-30 min. This afforded, after hydrolysis, a separable mixture of enones (15a) and (15b) in an approximate ratio of 1:2. Because the reduction of the indane (14b) was more efficient and more reproducible than that

Scheme 2

(15) a —(h)→

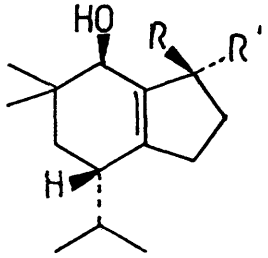
(15) b —(h),(i)→



(16) a R = CH_3 ; R' = H

b R = H ; R' = CH_3

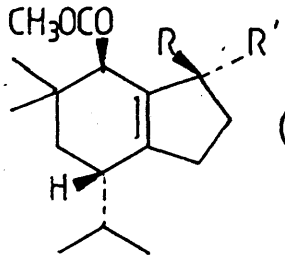
(j) ↓



(6) R = CH_3 ; R' = H

(17) R = H ; R' = CH_3

(k) ↓



(18) a R = CH_3 ; R' = H

b R = H ; R' = CH_3

REAGENTS

(h) L.D.A. , CH_3I

(i) $RhCl_3$, Δ

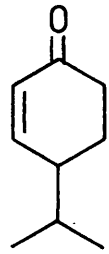
(j) $LiB(C_2H_5)H$

(k) $(CH_3CO_2)O/C_5H_5N$

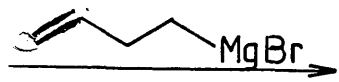
for the indanone (14a), the former was preferred for the synthesis. The target intermediate (16) was achieved by gem-dimethylation of (15a) and also (15b), which was firstly isomerised to (15a) by rhodium chloride catalysis. The stereoisomers (16a) and (16b) were separated by chromatography and spectral comparison revealed that the less polar isomer was racemic brasilenone (9). The trans stereochemistry was assigned to the less polar isomer (16a) solely on the basis of the stereochemistry previously proposed for brasilenone[3]. The more polar enone (16b) was equilibrated with rhodium chloride in ethanol to give another separable mixture of enones (16a) and (16b) (1:1 at equilibrium). Such recycling led to almost complete conversion of the initial enone mixture to pure brasilenone. Treatment of enone (16a) with lithium triethylborohydride in tetrahydrofuran at -78°C produced exclusively racemic brasilenol identical spectroscopically with the natural product. As might be expected corresponding reduction of the isomeric enone was also highly stereoselective and gave essentially a single alcohol. It was suggested that in both the trans- and cis-enones the 5-C axial methyl group exerts the dominant steric effect on the approach of the bulky reducing agent (Scheme 2), and therefore the stereochemistry at 4-C and 7-C must be trans after reduction, giving (6) and (17) which differ only in the relative stereochemistry of 3-C. The relative stereochemistry at 3-C was established by comparing the $Eu(fod)_3$-induced shift data for the alcohols (6) and (17) and the anisotropic shielding effects in the corresponding acetates (7) and (18). Therefore the structure of brasilenol was confirmed by synthesis and is correctly assigned as (6).

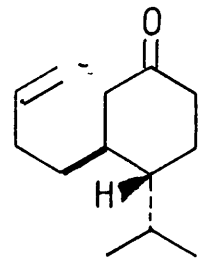
A further communication[5] by the same authors reported efficient syntheses of both racemic and natural forms of brasilenol (Scheme 3).

Scheme 3

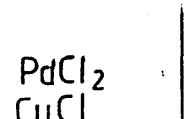


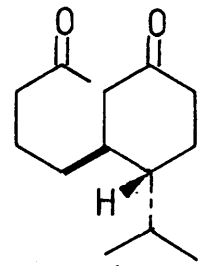
(19)



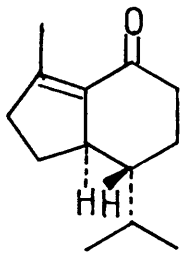


(20)

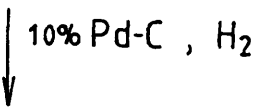


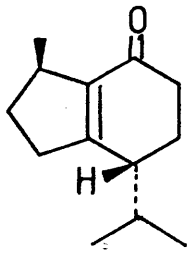


(21)

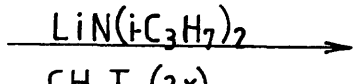


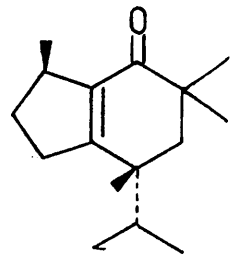
(22)



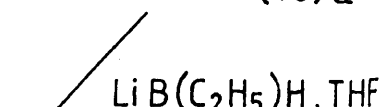


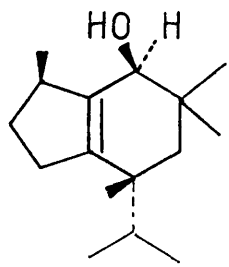
(15)a





(16)a



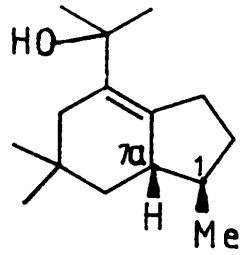


(6)

A more effective approach was taken to racemic brasilenol and synthesis was achieved in seven steps instead of the original thirteen. The first synthesis of natural brasilenol was achieved through an unusual intramolecular transfer of asymmetry. This enantioselective synthesis assigned for the first time the absolute stereochemistry of (+)-brasilenol and also that of (+) 4-epibrasilenol and brasilenol acetate.

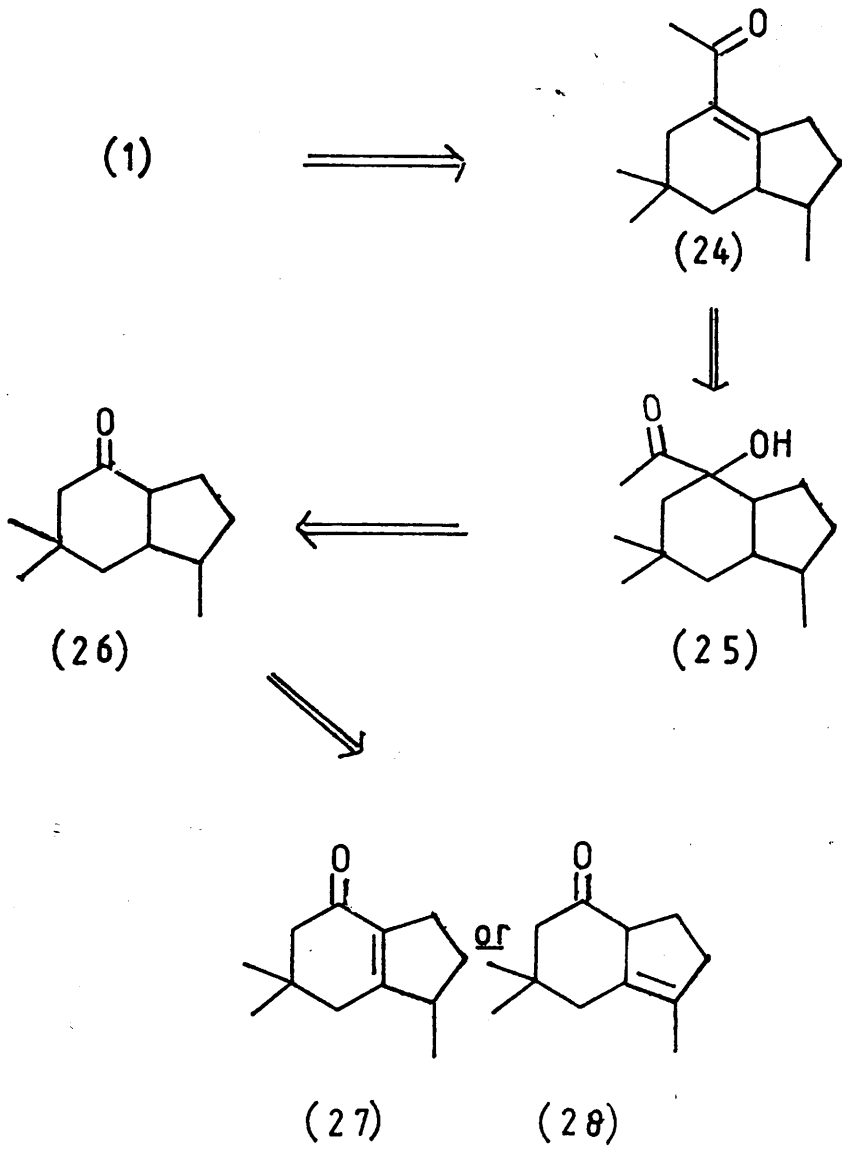
The first step of the synthesis (Scheme 3) involved the conversion of commercially available racemic cryptone (19) to ketone (20) by copper mediated conjugate addition of 3-butenylmagnesium bromide. The formation of (20) was highly stereoselective (> 95% trans). Wacker oxidation of (20) to the diketone (21), followed by aldol condensation using potassium t-butoxide in t-butyl alcohol afforded only the conjugated product (22). Enone (22) underwent a palladium-hydrogen induced migration of the double bond from the Δ^3 to the alternative tetrasubstituted $\Delta^{3a(7a)}$ conjugated position giving enone (15a), an intermediate in the previous synthesis of brasilenol. It is known that the entering and leaving hydrogens are generally co-facial in this type of transformation and, in this case, the Δ^3 to $\Delta^{3a(7a)}$ migration also delivered exclusively the necessary <u>trans</u> relationship at 3-C and 7-C. Therefore the relative stereochemistry generated through the conjugate addition has been transferred to give enone (15a). The synthesis to racemic brasilenol was completed by the same method used previously. This represents a more efficient route to racemic brasilenol.

The same sequence of reactions when applied to (R)-(-)-cryptone (secured from 4-isopropyl-cyclohexanone by using an enantioselective



(23)

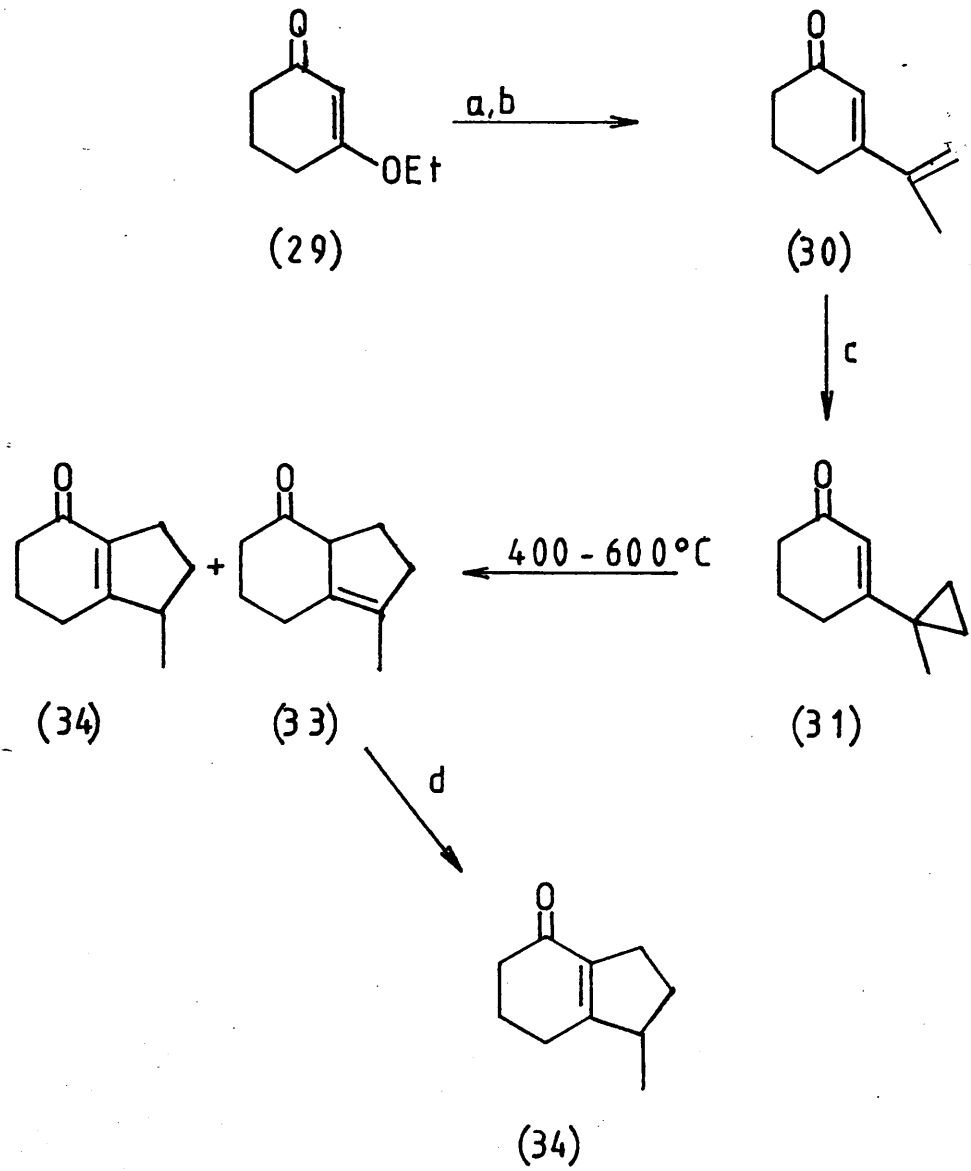
Scheme 4



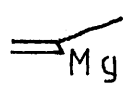
deprotonation-oxidation procedure) produced optically pure (+) brasilenol. Thus (+) brasilenol has the absolute stereochemistry 3R, 4S, 7R.

The complexity of the ^{1}H nmr spectrum of conocephalenol, even at 360 MHz, prevented the determination of the relative stereochemistry of 1-H and 7a-H by the usual methods (coupling constants N.O.Es). The present chapter is concerned with a stereospecific synthesis of the cis isomer (23) which was found to be identical (nmr, IR, MS) with natural concephalenol. Thus the relative stereochemistry of 1-H and 7a-H must be trans.

Scheme 5



REAGENTS

a  (32)

b H^+/H_2O

c Dimethyloxosulphonium methylide

d Na OEt/ Et OH

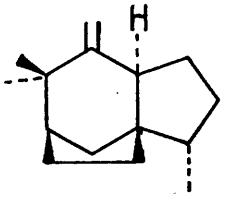
DISCUSSION

Retrosynthetic analysis of the concephalenol skeleton (23), (Scheme 4) suggested the enone (27) or the β,γ unsaturated ketone (28) as possible target synthons. Appropriate hydrogenation of (27) or (28) followed by addition of a suitable acyl anion equivalent to give (25), subsequent dehydration to (24) and finally reaction of (24) with methyl lithium would furnish the desired product (23).

The conversion of the hydrogenated products to conocephalenol appears straight-forward but in reality required considerable effort.

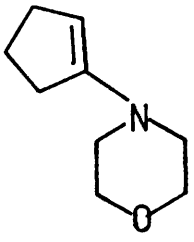
Although (27) is a new compound there are two different syntheses of the related hydrindenone (34). Piers reported[6] the generation of (34) by five membered ring annulation via thermal rearrangement of the β-(1-methylcyclopropyl) enone (31), (Scheme 5). The enone (31) was conveniently prepared by treatment of 3-methoxy-2-cyclohexen-1-one (29) with isopropenyl-magnesium bromide (32) followed by acid hydrolysis of the resultant 1,2 addition product to 3-isopropenyl-2-cyclohexene-1-one (30). This was then allowed to react with dimethyl-oxosulphonium methylide to furnish the cyclopropyl intermediate (31) which on pyrolysis, gave the enone (34) and the β,γ unsaturated ketone (33) in a ratio (34):(33) 7:2. Isomerisation of the mixture in sodium ethoxide yielded the enone (34) (100%) which was employed in the synthesis of (±) zizaene (35)[7].

In 1983 Bhandari and Bhide reported[8] a simpler method to the enone (34) which is a potential synthon for a variety of sesquiterpenoids. Their method (Scheme 6), utilised the alkylation of morpholino-cyclopentene (36) by the acid chloride (37) giving the



(35)

Scheme 6



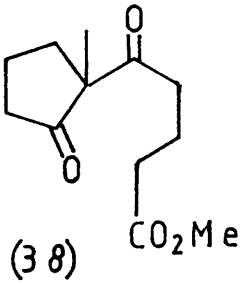
(36)

(37)

a $CH_3C(=O)-(CH_2)_3CO_2Me$

b $H^{\oplus}/H_2O$

c MeI



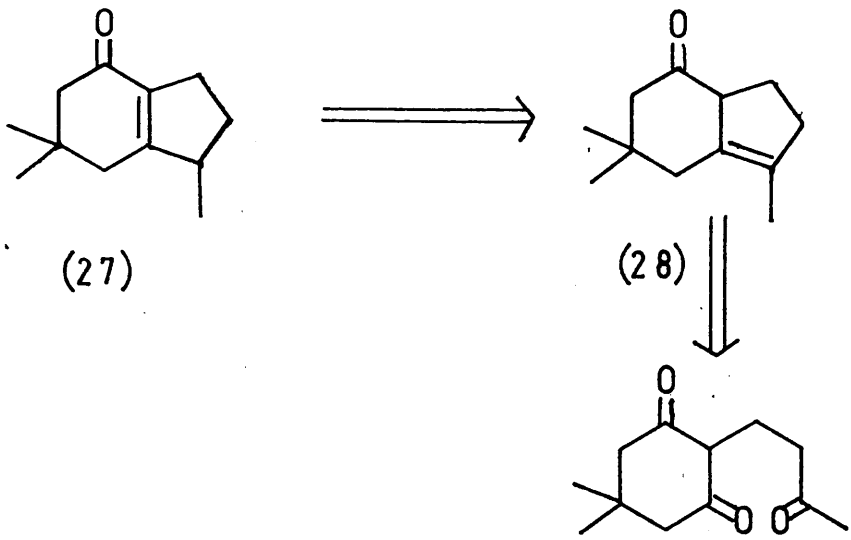
(38)

CO_2Me

NaOEt/EtOH

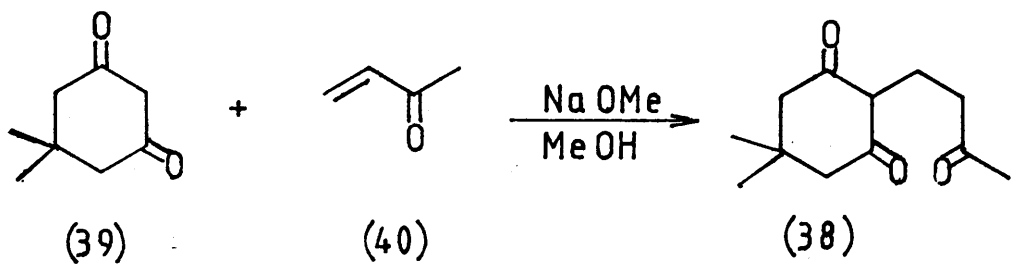
(34)

Scheme 7

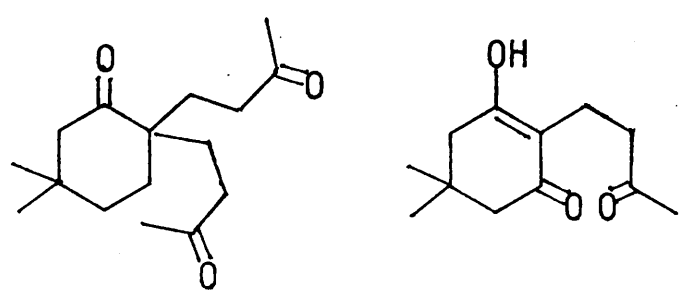


(27) (28) (38)

Scheme 8



(39) (40) (38)



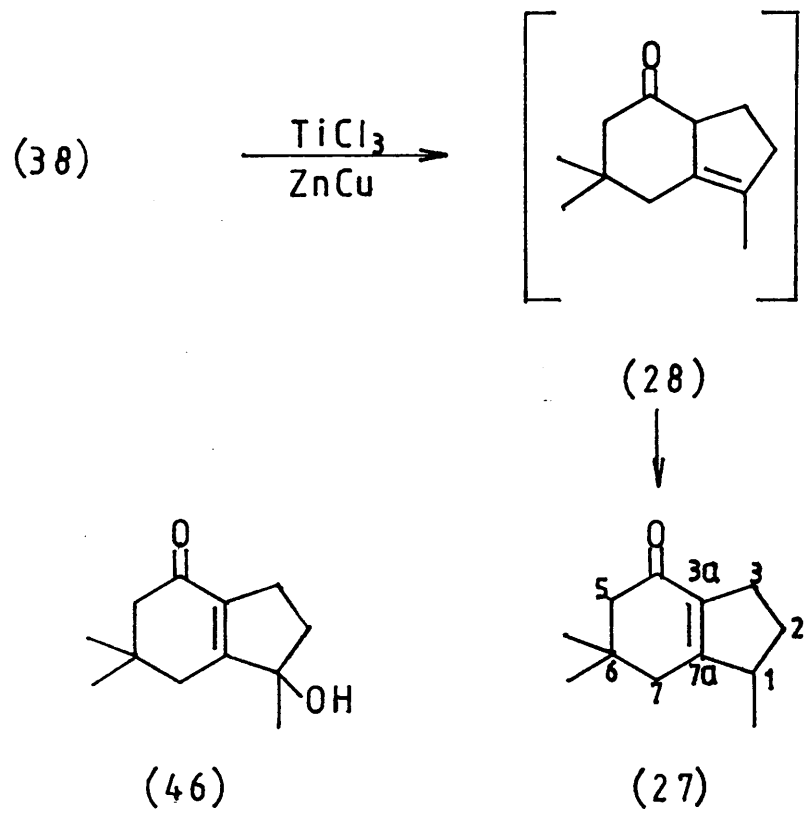
(41) (42)

ester (37) which after methylation and subsequent aldol condensation in potassium t-butoxide/t-butanol afforded (34).

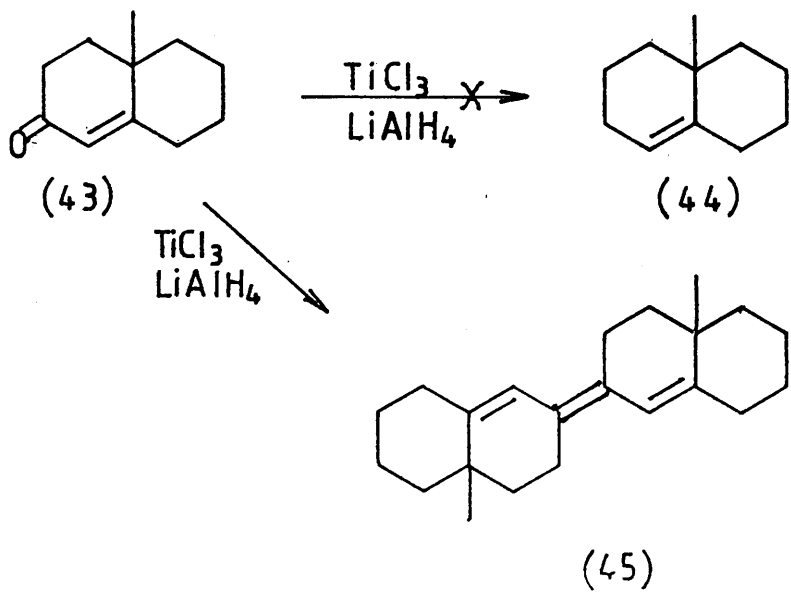
Possible adaptations of the routes outlined in Schemes 5 and 6 were considered for the synthesis of the enone (27). Eventually, however, a new approach was devised. Further retrosynthesis of enone (27), (Scheme 7), revealed the possible intermediacy of the triketone (38)[9]. Subsequent intramolecular McMurry reduction[10] of (38) would give the β,γ unsaturated ketone (28) which could be readily isomerised to the desired enone (27).

The synthesis began, (Scheme 8), with the Michael addition of 5,5-dimethyl-1, 3-cyclohexanedione (dimedone) (39) to 3-buten-2-one (methyl vinyl ketone) (40) in methanol using a catalytic amount of sodium methoxide. The dark oily product from the Michael reaction was dissolved in dilute aqueous base and filtered to remove any non-alkali-soluble material such as the dialkylated by-product (41). The amount of non-alkali-soluble material proved to be negligible and was not characterised. The alkali-soluble portion was acidified, extracted into chloroform and crystallised from acetone/water to give the triketone (38) m.p. 100-102°C. The major impurity present in the crude reaction mixture was dimedone (39). The ^{1}H (90 MHz) nmr of (38) showed the presence of the methine and methylene protons as broad multiplets [δ_H 2.6 - 2.3], the singlet methyl ketone [δ_H 2.15] and the two tertiary methyls as a singlet [δ_H 1.5]. Mass spectrometry confirmed its molecular formula as $C_{12}H_{18}O_3$ [m/z 210.1255]. The presence of the enol tautomer (42) may account for the broad nature of the ^{1}H nmr spectrum.

Scheme 9



Scheme 10



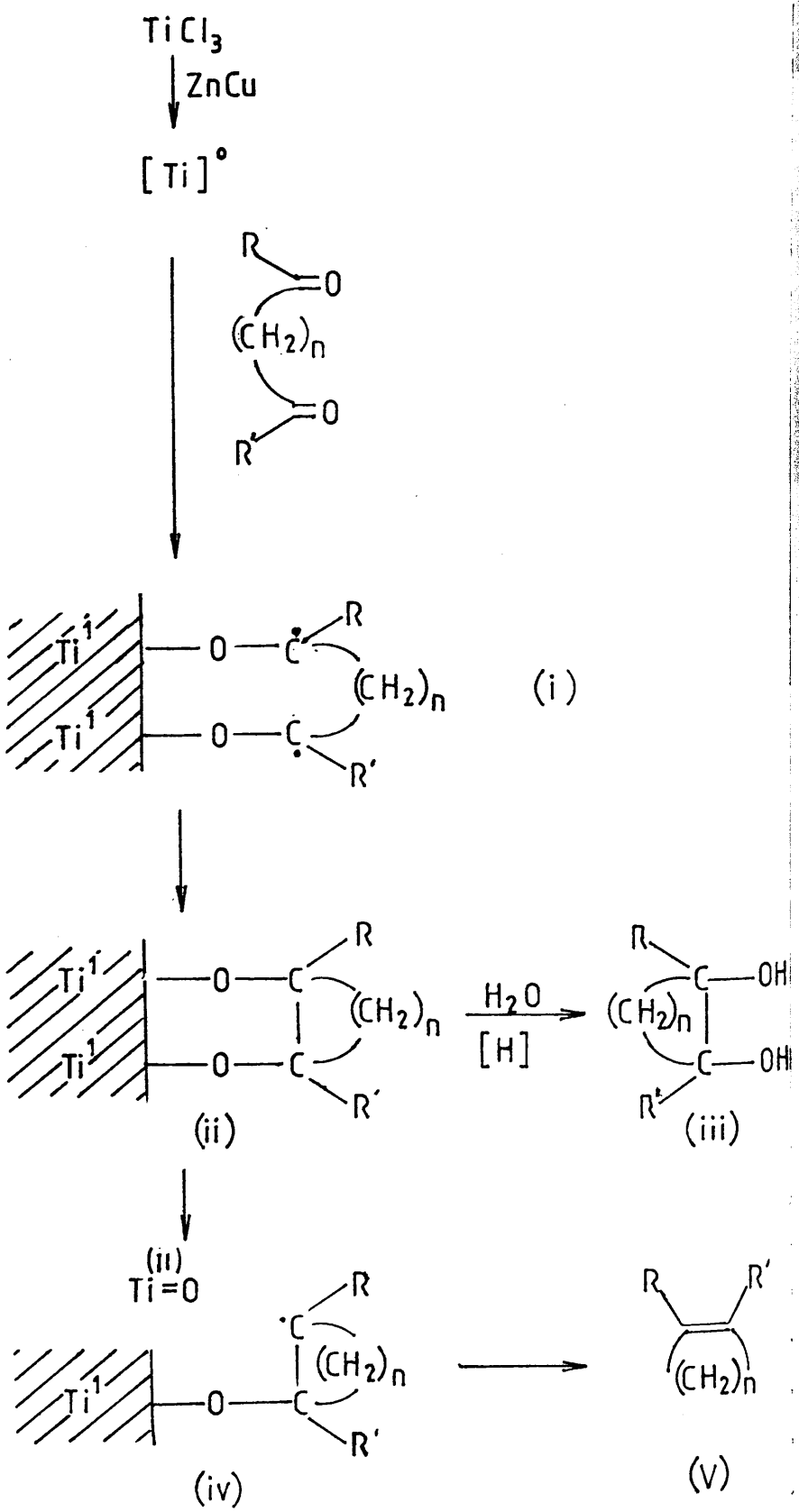
The second stage in the synthesis involved the use of a McMurry reaction for the intramolecular reductive coupling of two carbonyl groups of the symmetrical triketone (38) to give the $\Delta^{3a,7a}$ hydroindene-4-one (27) presumably via the β,γ unsaturated ketone intermediate (28), (Scheme 9). At this point it is appropriate to discuss the scope and mechanism of the McMurry reaction, which has been subject to a recent review[11].

The McMurry reaction was discovered by accident in 1974 when investigation of a possible new ketone deoxygenation method using $TiCl_3/LiAlH_4$ was applied to the enone (43), Scheme 10. Instead of the expected transformation to the olefin (44), a reductive dimerisation occurred to give the triene (45) in 80% yield. It was soon apparent that the reductive coupling was not limited to α,β-unsaturated ketones but was general for a wide variety of ketones and aldehydes. Though many reducing agents can be used with $TiCl_3$ in the reaction the Zn-Cu couple is the most common because of its safety and convenience. Several types of coupling reactions have been reported:

(i) Intermolecular Dicarbonyl Couplings

The reaction can be used to prepare symmetrical olefins by dicarbonyl coupling of identical ketones or aldehydes. The intermolecular dicarbonyl coupling has also been applied to non-identical ketone or aldehyde mixtures. However statistical mixtures of symmetrically and unsymmetrically coupled reaction products render this type of coupling of limited synthetic use.

Scheme 11


TiCl3
ZnCu
[Ti]°
R
O
(CH2)n
O
R'
Ti1
Ti1
O
C
R
(CH2)n
R'
(i)
(ii)
H2O
[H]
OH
OH
(iii)
(ii)
Ti=O
(iv)
(V)

(ii) Intramolecular Dicarbonyl Coupling.

Another type of unsymmetrical coupling is the intramolecular coupling to form cycloalkenes, which can be obtained for a variety of ring sizes (4-22).

(iii) Dicarbonyl Coupling of Keto-Esters.

The titanium-induced dicarbonyl coupling of a keto-ester is a potentially useful synthetic procedure. The product, a cyclic enol ether, can be hydrolysed in situ to afford a cyclic ketone.

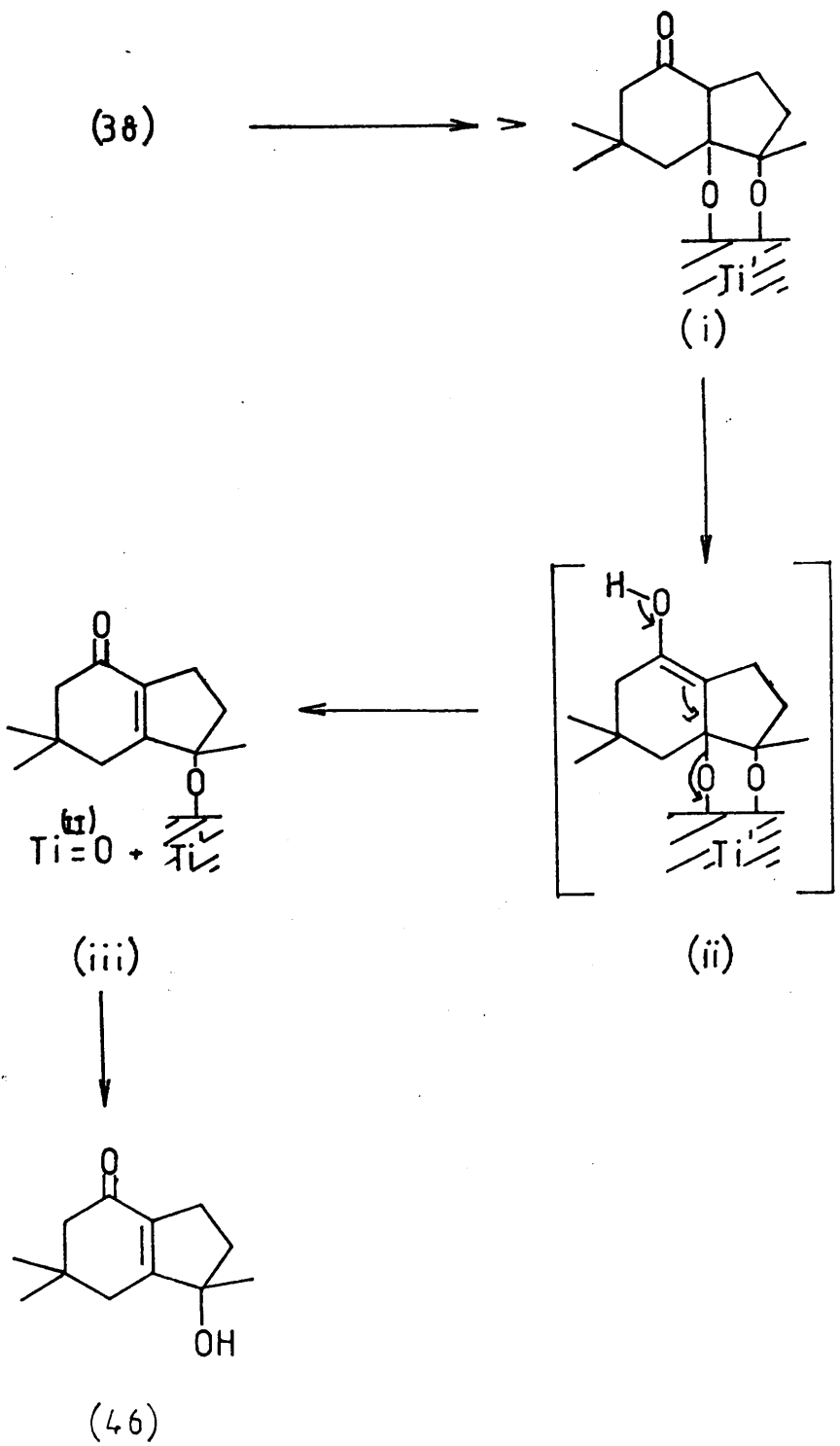
The mechanism of the McMurry reaction has been the subject of investigation by McMurry in 1978[10] and to a further more careful physical study by Geise in 1982[12]. The general mechanism, (Scheme 11), as applied to intramolecular cyclisation, is consistent with all the experimental evidence. In the first step the ketone groups become attached to the low valent titanium and one electron is transferred from the titanium to each ketone giving the organic anion radicals [Species (i), Scheme 11].

Prerequisites of the metal seem to be strong affinity for oxygen and a redox potential exceeding the redox potential of organic ketones. Of the many transition metals that have been tried for the reductive coupling of ketones, only titanium has proved to be successful. The second step involves the reaction of the anion radicals (i). They can either dimerize to the titanium pinocolate (ii) or form alcohols (iii) by the uptake of adsorbed activated hydrogen. The hydrogen source is probably solvent, when Zn-Cu is used as the reducing agent. Reflux of the

low valent titanium reagent prior to the addition of the ketone leads to a great decrease in alcohol production. The majority of anion radicals dimerise under the correct experimental conditions. This dimerisation is the rate determining step, and not the subsequent fission of the C-O bonds, probably because dimerisation requires the statistically unfavourable encounter of two radicals in a correct orientation on neighbouring metal centres. After the formation of the titanium pinacolate (ii), the titanium then withdraws, in consecutive steps, two oxygen atoms from the pinocolate (ii). The resultant olefin (v) remains π bonded to Ti in the post-reaction [Ti = O] complex.

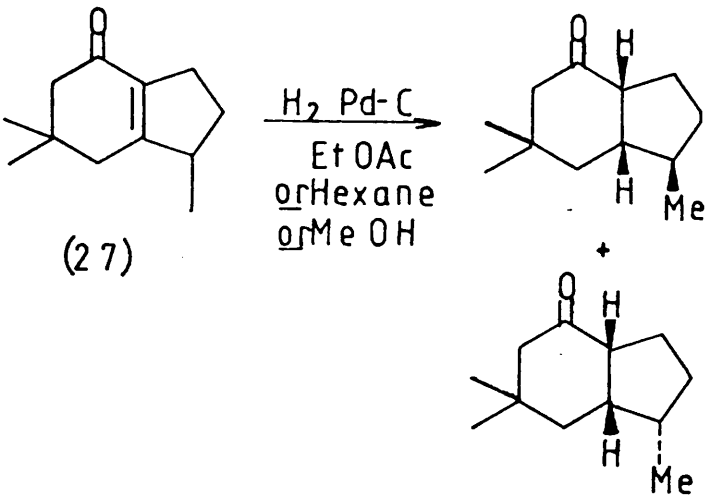
The McMurry reaction was carried out for the triketone (38) in the hope of producing the desired enones (27) or (28) (Scheme 9). Thus titanium trichloride was added to D.M.E under nitrogen quickly followed by Zn-Cu couple which had been prepared by the method in Fieser[13]. The resulting suspension was refluxed under nitrogen for one hour, during which the colour of the reaction mixture changed from violet via blue to green and brown to black, the final colour indicating the formation of the low valent titanium species. The triketone (38) was added in D.M.E solution over a period of 8 hours and the reaction mixture refluxed for 12 hours. More ketone (38) was added over 8 hours, followed by another 12 hour reflux. After filtration of the reagent, workup and chromatography, the enone (27) was obtained in 55% yield. Its structure followed readily from its spectroscopic properties. The ^{1}H nmr spectrum was complex due to second order effects but clearly showed the presence of an AB quartet [δ 2.84 and 2.72 (J_{AB} 12.4 Hz)] which corresponds to the

Scheme 12



methylene protons attached to carbon-5, a secondary methyl group [δ_H 1.06 (d, J 7.1 Hz)] and two tertiary methyl groups [δ_H 1.02, 1.01 (both s)]. The ^{13}C nmr revealed the expected pattern of twelve carbons. Singlets at δ_C 198.2, 167.1 and 135.5, in conjunction with data from the IR [ν_{max} 1665 cm^{-1}] and U.V.[λ_{max} 253 nm(ε10,550)] spectra showed the presence of an enone. The molecular formula $C_{12}H_{18}O$ was established by high resolution mass spectrometry (base peak m/z 178.1357). Thus the expected coupling to the β,γ unsaturated ketone (28) has been followed by <u>in situ</u> isomerisation to the enone (27). This reaction represents the first example of a triketone successfully undergoing dicarbonyl coupling. The major impurity consisted of non-polar material which could not be characterised. When the reaction was carried out at lower temperature (40-50°C) the enone (27) was still formed in good yield (50%), and the percentage of non-polar impurity decreased. The lower reaction temperature was accompanied by an increase in production of an oil with a menthol-like odour, which was shown to be the hydroxyenone (46). Its ^1H nmr spectrum was complex but revealed the presence of two tertiary methyls [δ_H 1.0, 0.98 (both s)] and a tertiary methyl attached to a tertiary-oxygenated carbon [δ_H 1.3 (s)]. The ^{13}C nmr spectrum showed the expected pattern of carbons. Features of this spectrum included the three singlets δ_C 199.3, 162.3 and 137.4 which represent the enone system and a singlet at δ_C 94.8 arising from the tertiary oxygenated carbon. The IR spectra showed hydroxyl and enone absorptions at ν_{max} 3560 and 1660 cm^{-1} respectively. The molecular formula $C_{12}H_{18}O_2$ was established by mass spectrometry (base peak m/z 194). A possible mechanism for the formation of (46) consistent with mechanistic studies by Geise[12], is given (Scheme 12). Activated

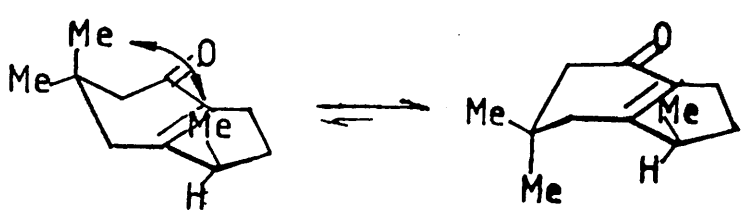
Scheme 13



(27) (47) (48)

(47) : (48) ca. 10 : 1

Scheme 14



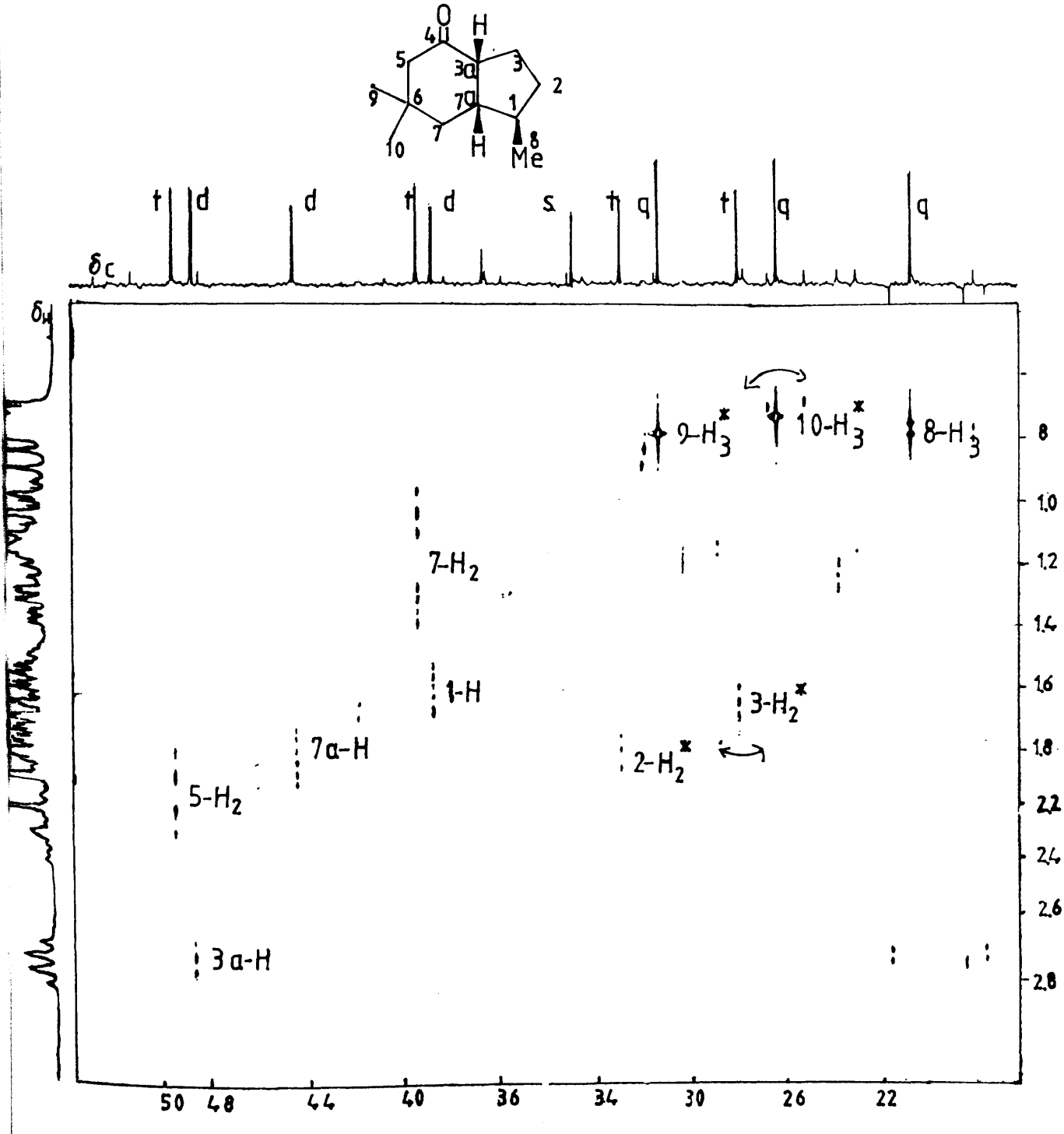
(27a) (27b)

steric interaction

hydrogen present on the catalyst surface could induce enolisation of the carbonyl of the titanium pinocolate [Species (i), Scheme 12] giving species (ii). Elimination of oxygen to give (iii) followed by withdrawal of the titanium reagent would give the hydroxy enone (46). This process is inhibited at reflux temperature of D.M.E (82-85^{o}C).

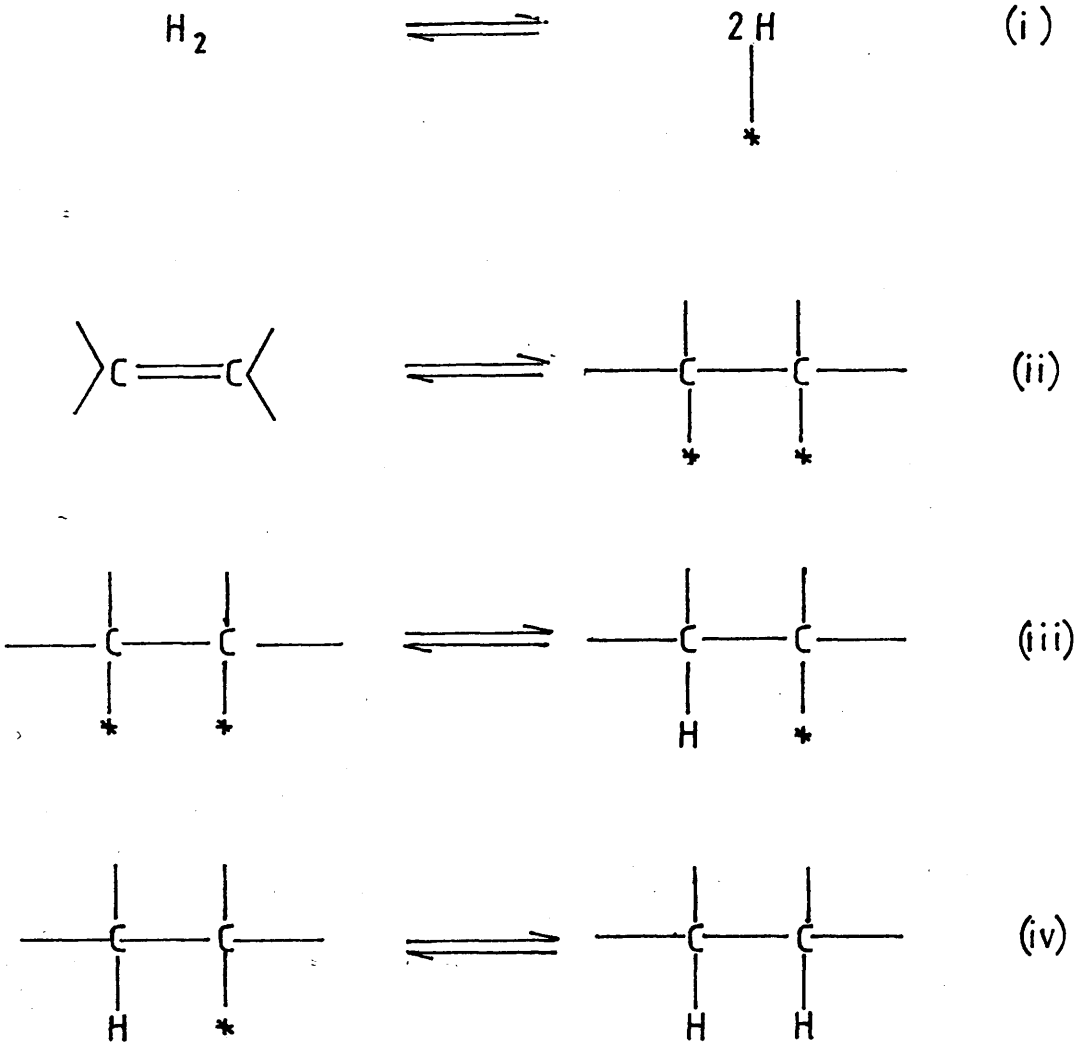
The next stage in the synthesis of conocephalenol involved the appropriate hydrogenation of the hydrindenone (27) (Scheme 13). Filtration of the catalyst and removal of the solvent afforded two products (47), (48) in an approximate ratio of 10:1 (analytical g.c) respectively, which were inseparable by flash chromatography or t.l.c. Confirmation of the presence of two isomers came from inspection of the ^{13}C nmr spectrum which showed the expected pattern of 24 carbons, corresponding to two possible products of hydrogenation. The IR spectrum showed the presence of a saturated ketone at ν_{max} 1710 cm^{-1} and the molecular formula $C_{12}H_{20}O$ was established by high resolution mass spectrometry (base peak m/z 180.1513). The ^{1}H nmr spectrum of the mixture was complex but the bridgehead 3a-H [δ_H 2.62 (ddd, $J_1 \approx J_2 \approx J_3 \approx$ 8.8 Hz)], and the chemical shifts of the tertiary and secondary methyls of the major isomer [δ_H 0.94, 0.88 (both s) ; δ_H 0.92 (d, J 6.9 Hz)] could be identified. A 2D δ_C/δ_H correlation experiment[14] [fig.2] permitted the assignment of the protonated carbons of the major isomer and also revealed the positions of the remaining protons [δ_H 2.19 and 1.99 (ABq, J_{AB} 12.6 Hz 5-H_2), 2.0-1.9 (m, 2-H_2 and 3-H_2), 1.98 (m, 7a-H) and 1.37 (m, 7-H_2)]. Because of the second order nature of the ^{1}H nmr spectrum, the relative stereochemistry of 1-H and 7a-H could not be assigned from coupling information. The major isomer was attributed structure (47) on the basis of conformational analysis and molecular model studies of the hydrogenation. The hydrindenone (27) has two

Fig. 2 $^{1}H/^{13}C$ Correlation of (47)



↔ * May be interchanged

Fig. 3



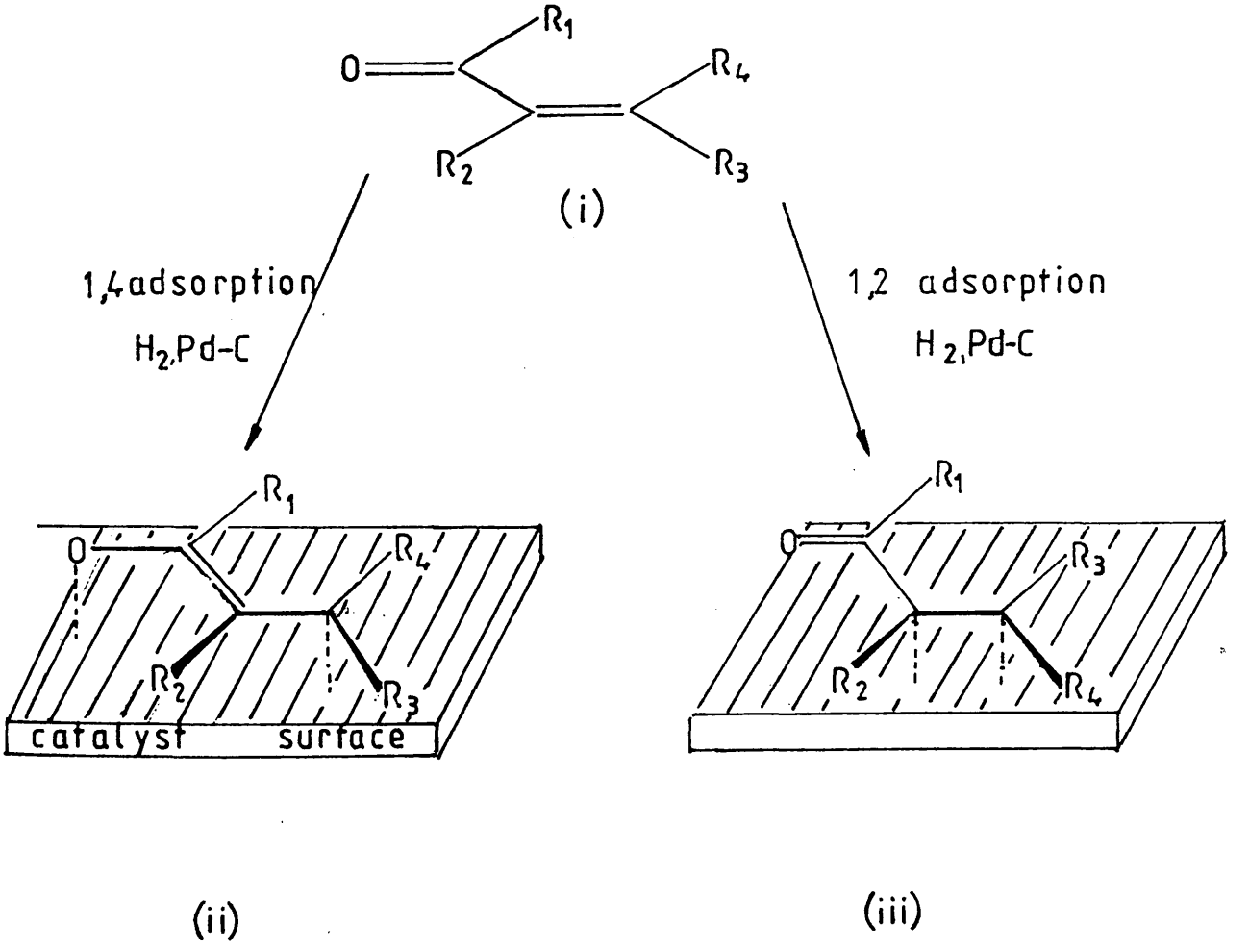
* = Site of adsorption to catalyst

possible conformations (27a) and (27b) (Scheme 14). The axial tertiary methyl is in reasonably close proximity to the secondary methyl of the five membered ring in conformation (27a). The alternative conformation (27b), in which there is no such steric interaction, should be preferred. From molecular models it can be seen that approach to the palladium catalyst would be expected to occur from the face opposite the axial tertiary methyl and, since (27b) seems the more stable conformer, from the same face as the secondary methyl. Such a "steric approach" control of the hydrogenation would give the hydrindanone with stereochemistry as in (47).

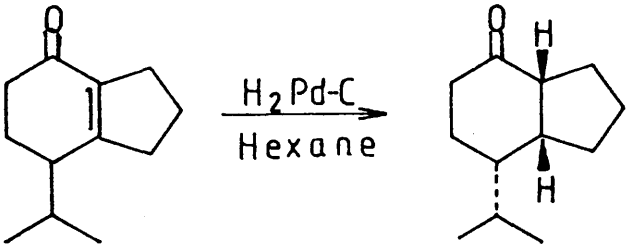
Further support for the assignment of the stereochemistry as in (47) can be obtained by consideration of the hydrogenation mechanism of α,β-unsaturated systems. In a review by Augustine[15] it was suggested that the hydrogenation of these systems basically follows the classic Horriuti-Polyani[16] mechanism [fig. 3] as for olefins, but that product stereochemistry is dependent on the type of solvent, hydrogen availability and pressure. It was shown that if the hydrogenation is carried out in a polar/aprotic solvent such as ethyl acetate, the carbonyl becomes polarised and the enone [Species (i), fig. 4] is adsorbed on the catalyst in a 1,4 fashion [Species (ii), fig. 4]. In non polar/aprotic media the carbonyl group does not react with the solvent and the enone is adsorbed in a 1,2 fashion [Species (iii), fig. 4].

The nature of the adsorbed species is also dependent on hydrogen availability, which can be altered by adjusting the rate of agitation of the reaction mixture and/or the pressure. It has been suggested that, under conditions of low hydrogen availability i.e. atmospheric pressure and moderate stirring level, the product stereo-

Fig. 4

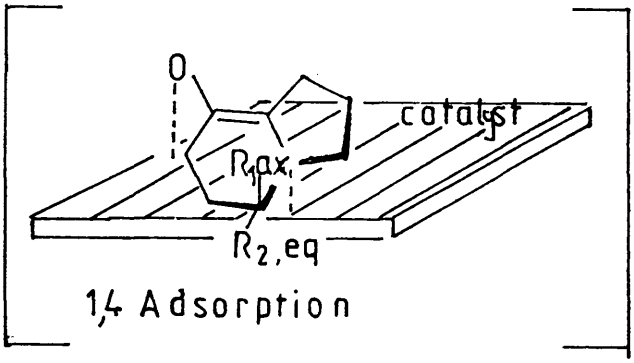

R1
O
R4
R2
R3
(i)
1,4adsorption
H2,Pd-C
1,2 adsorption
H2,Pd-C
R1
O
R4
R2
R3
catalyst surface
R1
O
R3
R2
R4
(ii)
(iii)

Scheme 15



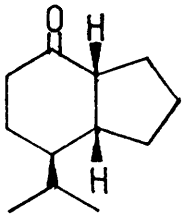
(49) (50)

H_2 Pd-C
EtOAc



(i) R_1 = isopropyl ; R_2 = H

(ii) R_1 = H ; R_2 = isopropyl



(51)

chemistry is determined primarily by the relative stabilities of the half hydrogenated states [equation (iii), Fig. 3], which bind to the catalyst in a tetrahedral fashion. Under conditions of high hydrogen availability i.e. atmospheric pressure, rapid agitation, the product stereochemistry is fixed by the mode of initial adsorption on the catalyst surface [equation (ii), fig.3], and the intermediate species is bound to the catalyst in a trigonal fashion.

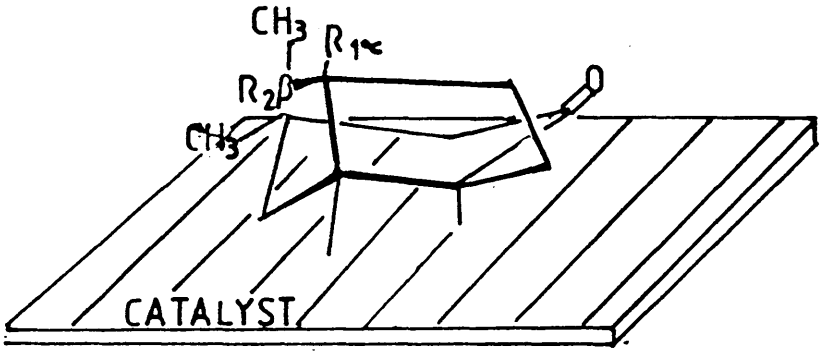
Agosta has shown the dependence of product stereochemistry on solvent in the hydrogenation of the α,β-unsaturated hydrindenone (49), (Scheme 15)[17]. In hexane approach of the catalyst to the less hindered face of the enone gave the saturated product (50). However when ethyl acetate was used as the solvent (51) was formed rather than (50). This is because the presence of an axial isopropyl group in the intermediate [Species (i), Scheme 15] would be very unlikely and therefore the catalyst would approach from the same face as the equatorial isopropyl group [Species (ii), Scheme 15] giving the hydrindanone (51).

The hydrogenation of (27) was therefore carried out separately in methanol, ethyl acetate and hexane, but gave the same product ratio (47):(48) 10:1 in each case, irrespective of the rate of agitation. The mechanisms of hydrogenation in both 1,2 and 1,4 adsorption cases were considered and led to the stereochemistry as assigned in (47).

1,2 Adsorption [fig. 5]

Under conditions of slow stirring, atmospheric pressure and low hydrogen availability, near tetrahedral adsorption of the intermediate species to the catalyst is assumed. Inspection of molecular models,

Fig. 5



(i) $R_1 = CH_3$; $R_2 = H$

(ii) $R_1 = H$; $R_2 = CH_3$

as indicated above, suggests initial adsorption of (27) from the face opposite the axial t-methyl. This leads to a choice of two partially hydrogenated tetrahedral intermediates (i) and (ii).

It is apparent from models that intermediate (i) [fig. 5] would be much less stable than the corresponding isomer (ii), due to strong steric interaction between the secondary methyl and the axial t-methyl. Thus the formation of the isomer (ii) seems much more likely. This would lead to the product stereochemistry as in (47).

1,4 Adsorption (Scheme 16)

Again near tetrahedral adsorption is assumed. Hydrogenation would have to take place from the same face as the axial t-methyl if the half-chair type enolate intermediate (i) is formed. However if the secondary methyl is in the α-position [Species ia, Scheme 16] there would be significant steric strain and the presence of species (ia) would seem unlikely compared to the isomer (ib) with the secondary methyl in the β- position in which there is no steric strain. This would lead to a product with stereochemistry as in (47).

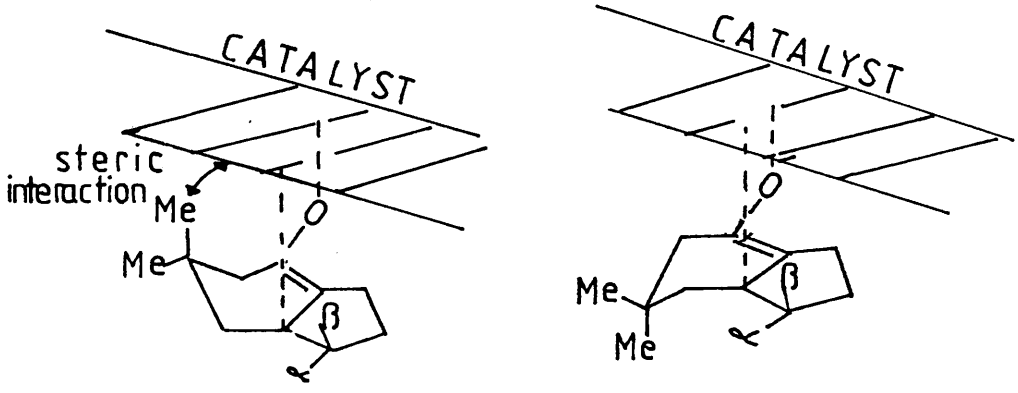
The alternative half-chair conformations (ii) of the enolate can exist in the sterically unlikely species (ii a) if the secondary methyl is in the α- position. Steric strain would be avoided in isomer (ii b), with a β- secondary methyl group. This again leads to product (47).

There are two possible conformations (i) and (ii) of the product hydrindanone (47) (Scheme 17). In 1980 Dana et al undertook a conformational analysis study[18] of substituted 4-hydrindanones and suggested a method, based on the Karplus equation, by which the

Scheme 16

(27)

EtOAc, 10%-Pd-C



(i) a α = Me β = H

b α = H β = Me

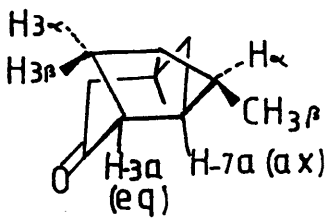
(ii) a α = Me β = H

b α = H β = Me

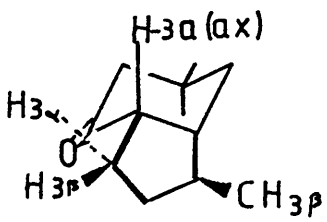
(47)

(47)

Scheme 17



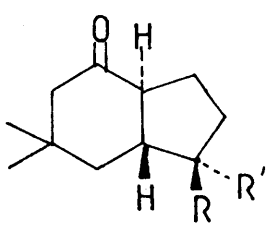
(47 i)



(47 ii)

Scheme 18

(47) + (48) ⇌ (53) (Na OEt)



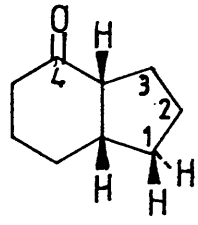
(53) a R = Me ; R' = H

b R = H ; R' = Me

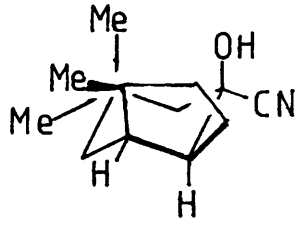
conformation of the parent hydrindanone (52) and related compounds could be deduced. The dihedral angles between (H_{3a} and H_{7a}), (H_{3a} and $H_{3\alpha}$) and (H_{3a} and $H_{3\beta}$) are approximately 30°, 150° and 30° respectively in conformation (i) (Scheme 17). In conformation (ii) the corresponding dihedral angles are 30°, 90° and 30° respectively. Thus, in conformation (i) the equatorial 3a-H should show three equal couplings of ca. 8-9 Hz. The axial 3a-H present in conformation (ii) should show $J_1[(H_{3a}, H_{3\alpha}) \simeq 0$ Hz]. Thus different coupling patterns will be observed depending on whether the bridgehead proton 3a-H is axial or equatorial. It was found that hydrindanone (47) must exist in conformation (i) since the bridgehead proton 3a-H appears as a ddd $[J_1 \approx J_2 \approx J_3 \approx 8.8$ Hz] at δ_H 2.68. Inspection of molecular models supports (i) as the favoured conformation. Treatment of the hydrogenation mixture with ethanolic sodium ethoxide at room temperature afforded an equilibrium mixture of the <u>cis</u> isomer (47) and the <u>trans</u> isomer (53) in the ratio 6:4. This corresponds to a very small free energy difference in favour of the <u>cis</u> isomer.

This is not unexpected since <u>cis</u>-hydrindanes are generally more stable than their corresponding <u>trans</u> isomers[19].

N.O.E. difference experiments were used in an effort to confirm the relative stereochemistry of (47). The second order nature of the ^1H nmr spectrum, however, made irradiation of individual multiplets difficult and thus accurate analysis of N.O.E. enhancements was impossible.

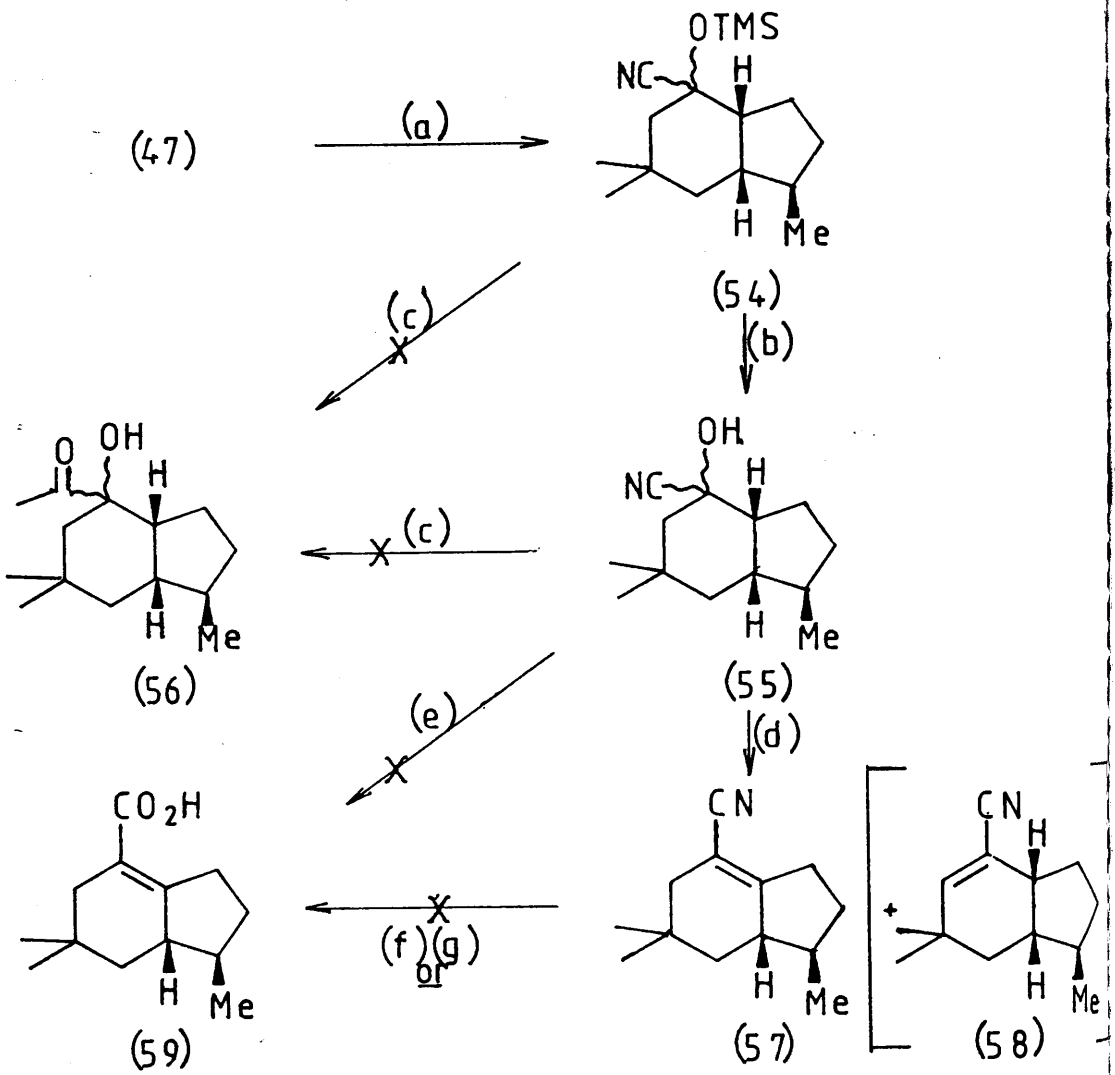


(52)



(56i)

Scheme 19



REAGENTS

a	TMS-CN / $ZnCl_2$	e	conc HCl ,RT 3Hrs, Reflux 12 Hrs
b	3N HCl	f	conc HCl Reflux 12 Hrs
c	(i)MeMgI (ii)H^+/H_2O	g	NaOH/H_2O Reflux
d	$POCl_3$/Py		

Several strategies were employed in an effort to convert the hydrindane (47) to conocephalenol.

STRATEGY 1 (Schème 19)

The first stage involved the almost quantitative generation of the trimethylsilyl-cyanohydrin from reaction of the hydrindanone (47) with trimethylsilylcyanide at room temperature using $ZnCl_2$ as the catalyst[20]. T.l.c. of the crude product (54) showed only one spot so no further purification was carried out. The ^1H (90 MHz) nmr spectrum was complex but showed the presence of the bridgehead 3a-H at δ_H 2.6 and three methyls at δ_H 1.05 - 1.00 and the o-trimethylsilyl group at δ_H 0.3 (s). High resolution mass spectrometry confirmed the molecular formula $C_{16}H_{29}ONSi$ (m/z 279)

Hydrolysis of the silylcyanohydrin (54) in 3N HCl followed by preparative t.l.c. purification using chloroform:hexane, 10:1, as the eluent afforded the cyanohydrin (55) in good yield, as essentially one diastereoisomer. The IR spectrum showed hydroxyl (3590 cm^{-1}) and nitrile (2220 cm^{-1}) bands while ^1H (90 MHz) nmr spectrum featured inter alia hydroxyl resonance at δ_H 3.2 (br s). The ^{13}C (25 MHz) nmr spectrum confirmed the presence of only one diastereoisomer, with the expected pattern of 13 carbons including a cyano group at δ_C 122.3 (s) and an oxygenated tertiary carbon at δ_C 69.3 (s).

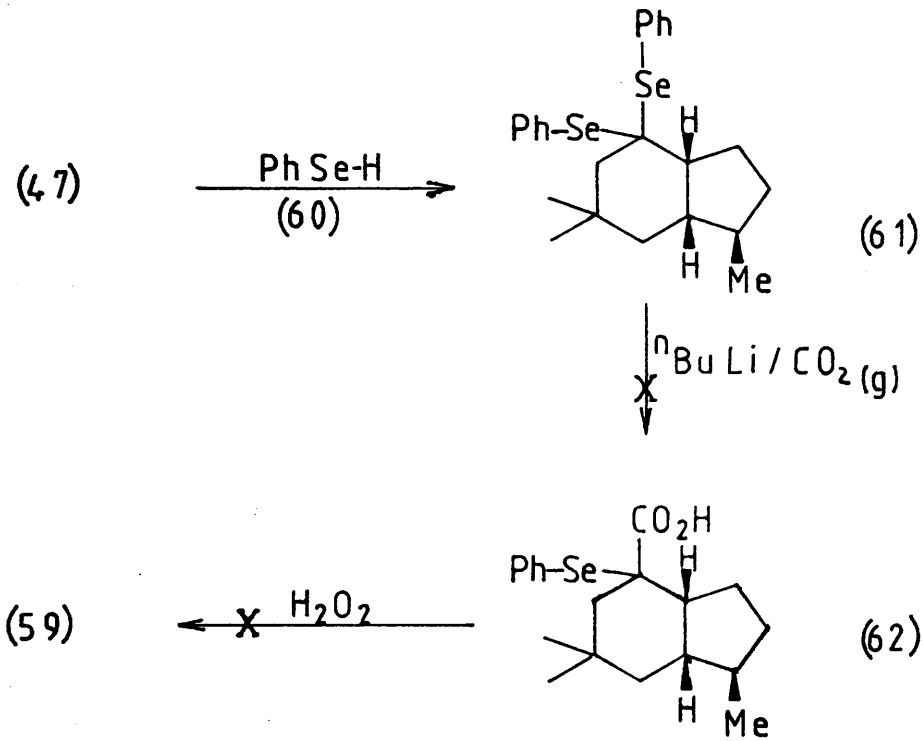
The next stage involved attempted Grignard reaction of the cyanohydrin (55) to give the α-hydroxy ketone (56), using MeMgI. Even after long periods of reflux and the use of a large excess of Grignard reagent no ketone (56) was produced and only starting material was recovered. Similarly, Grignard reaction of the silylcyanohydrin

(54) failed to yield the desired ketone (56) and gave only the cyanohydrin (55), following the acidic workup of the reaction mixture.

The failure of this reaction led us to abandon this route in favour of dehydration of (55) to the unsaturated nitrile (57) and then hydrolysis to (59), a useful intermediate for conversion to conocephalenol (23). Dehydration of (55) was carried out in refluxing pyridine containing $POCl_3$. After workup t.l.c showed two U.V active spots. Purification by flash chromatography gave the nitrile (57), an oil, as the major product. The ^1H (90 MHz) nmr spectrum was again complex but showed no vinyl proton resonance, thus supporting the formation of a tetrasubstituted double bond as in (57). The structure of (57) was confirmed by the ^{13}C nmr spectrum which showed a nitrile at δ_C 164.1 (s) and the tetrasubstituted double bond with singlets at δ_C 112.6, δ_C 101.7. The IR spectrum showed the nitrile at ν_{max} 2200 cm^{-1} and the molecular formula $C_{13}H_{19}N$ was established by mass spectrometry (m/z 189). The other product from the crude reaction mixture, presumed to be the tri-substituted isomer (58) was not characterised.

The formation of (57) as the major product suggests an anti-relationship between the bridgehead proton - 3a and the hydroxyl and therefore the stereochemistry of the cyanohydrin as in (56i). Attempted hydrolysis of the nitrile (57) in 40% aqueous sodium hydroxide at reflux for up to 12 hours failed to produce any acidic product (59). The unsaturated nitrile (57) was recovered unchanged. Attempted acidic hydrolysis of (57) to (59) in refluxing concentrated sulphuric acid also failed to produce (59). No starting material was recovered in this case and characterisation of the darkly coloured reaction mixture

Scheme 20



Ph–Se–Se–Ph

(63)

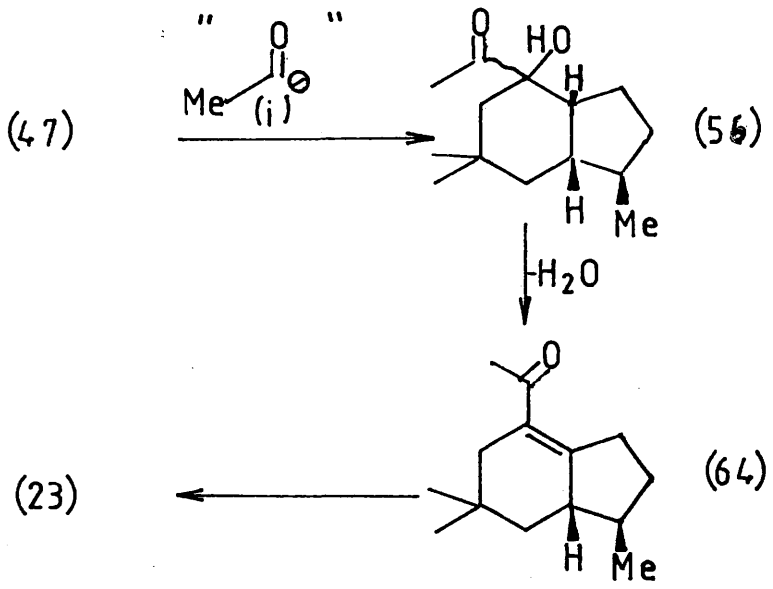
not undertaken. Strategy 1, involving the use of the cyanohydrin (55) was therefore abandoned.

Strategy 2. (Scheme 20)

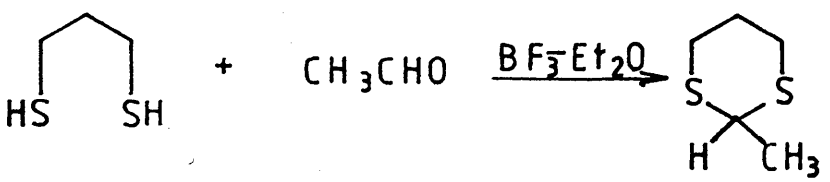
Due to its electronegative character, selenium has the useful property of stabilising negative charge at a neighbouring carbon. Selenium-stabilised carbanions are versatile synthetic intermediates and can react with a variety of electrophiles producing potentially useful compounds[22]. Thus it was planned to synthesise (59) via the selenoacetal (61). Reaction of the hydrindanone (47) with benzeneselenol (60) should give the selenoacetal (61) which, on reaction with BuLi, would undergo PhSe/Li exchange giving the α-lithio selenide which could be quenched with CO_2 (g) to furnish the α-carboxy-selenide (62). Subsequent -Se-Ph elimination from (62) with hydrogen peroxide could give the desired intermediate (59).

The hydrindanone (47) was stirred in CCl_4 with two equivalents of benzeneselenol (60) for 3 hours. After evaporation of the solvent in vacuo, a crystalline solid was formed which was found to be a mixture of the selenoacetal (61) and diphenyldiselenide (63). Treatment of the crude mixture with $LiAlH_4$ to remove the major impurity (63), followed by purification by flash chromatography yielded the selenoacetal (61) as an oil. Its ^1H nmr spectrum showed the presence of one major diastereoisomer with two phenyl groups [δ_H 7.4 - 7.1 (m)] two tertiary methyls [δ_H 1.2, 0.82 (both s)], and a secondary methyl [δ_H 0.89 (d, J 7.1 Hz)]. The IR spectrum showed bands at ν_{max} 2950 (Se-C stretch) and 1620 (phenyl stretch) cm^{-1}. The molecular formula $C_{24}H_{30}{}^{80}Se_2$ was confirmed by mass spectrometry

Scheme 21

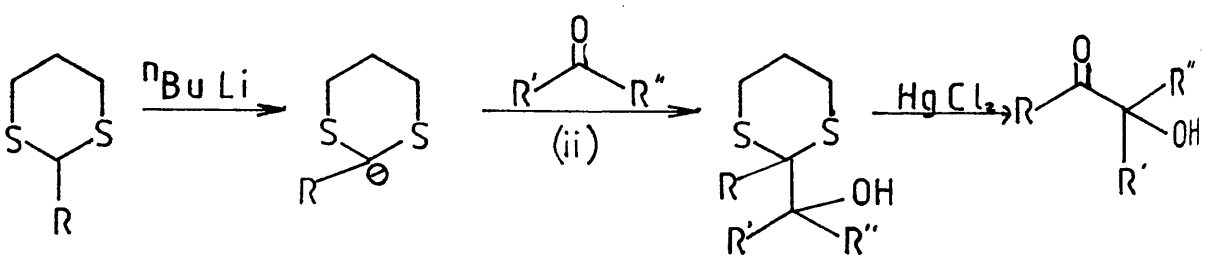


Scheme 22



(65) (66) (67)

Scheme 23



(68) (69) (70) (71)

R = Alkyl or Allyl

(m/z 320) which showed the expected isotopic selenium distribution.

The next stage involved the attempted formation of the α-carboxy selenide (62) by Se/Li exchange and reaction with CO_2. The presence of only starting material suggested that Se/Li exchange was not taking place, probably due to steric factors.

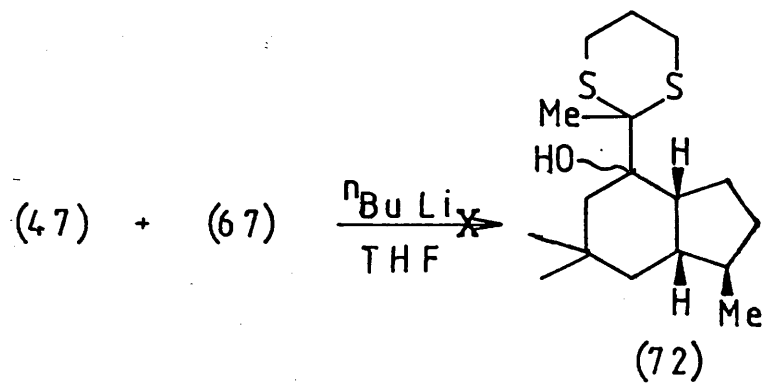
Investigation of synthetic routes to the unsaturated acid (59) was therefore abandoned.

The remaining strategies 3-6, involved routes to the synthesis of the α,β-unsaturated ketone (64), from the hydrindanone (47). Methyl lithium reaction of (64) should lead to conocephalenol. The concept of Umpolung[21] suggests the reaction of a suitable acyl anion equivalent [(i), Scheme 21] with (47) to form the α-hydroxyketone (56) which can lose water to give (64). There are many acyl anion equivalents which could be used as reagents in this sequence.[23] Strategies 3, 4, 6 describe approaches based on the use of acyl anion equivalents, while strategy 5 is based on the use of a formyl anion equivalent.

Strategy 3, (Scheme 22)

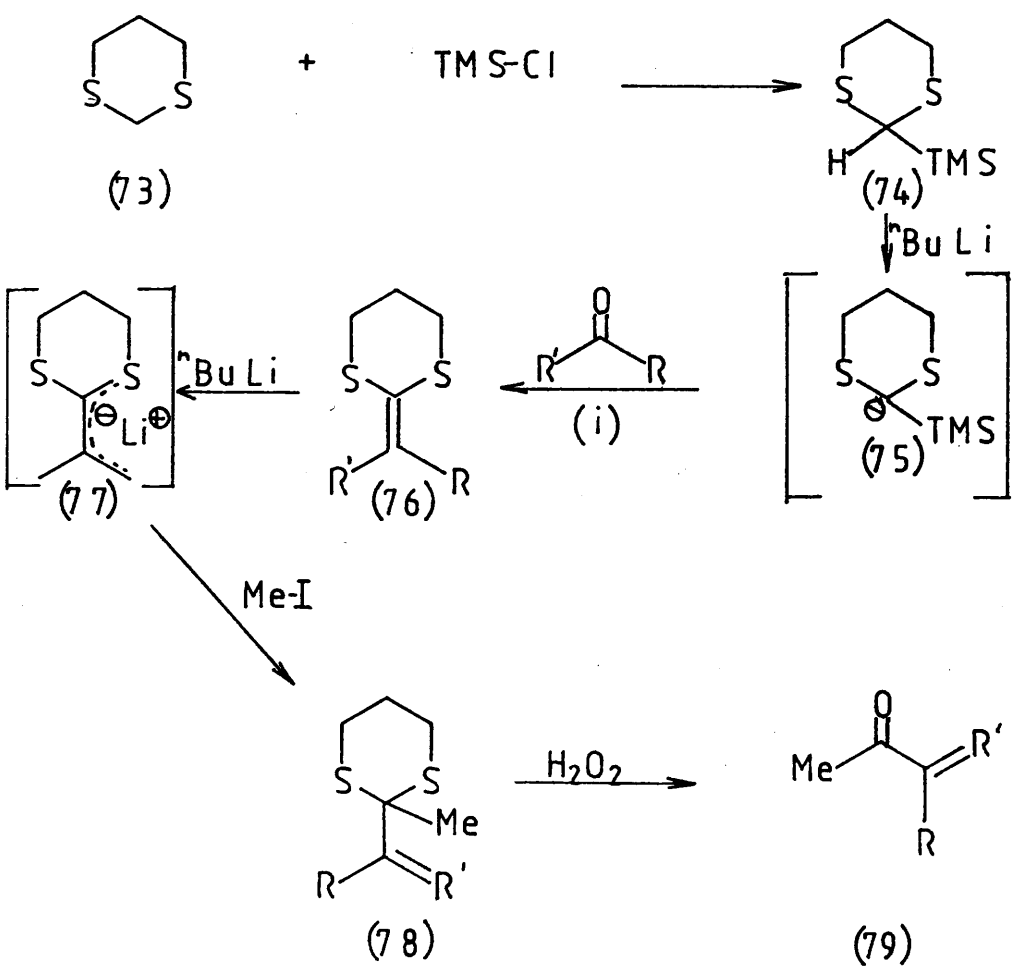
This involved the use of 2-methyl-1,3-dithiane (67) as the acyl anion equivalent. It was readily prepared from reaction of 1,3-propanedithiol (65) with acetaldehyde (66) at room temperature, using BF_3-etherate as the Lewis acid catalyst. Distillation gave the dithiane (67). [ν_{max} 2900 and 1430 cm^{-1}] in good yield. Its ^1H nmr spectrum showed expected resonances for 2-H [δ_H 4.15 (q, J 6.7 Hz)], 6-H_2 [δ_H 2.9 (m)], 5-H_2 [δ_H 2.0 (m)] and the secondary methyl [δ_H 1.45 (d J 6.7 Hz)] while the mass spectrum showed a base peak at m/z 134,

Scheme 24



(72)

Scheme 25



confirming the molecular formula $C_5H_{10}S_2$.

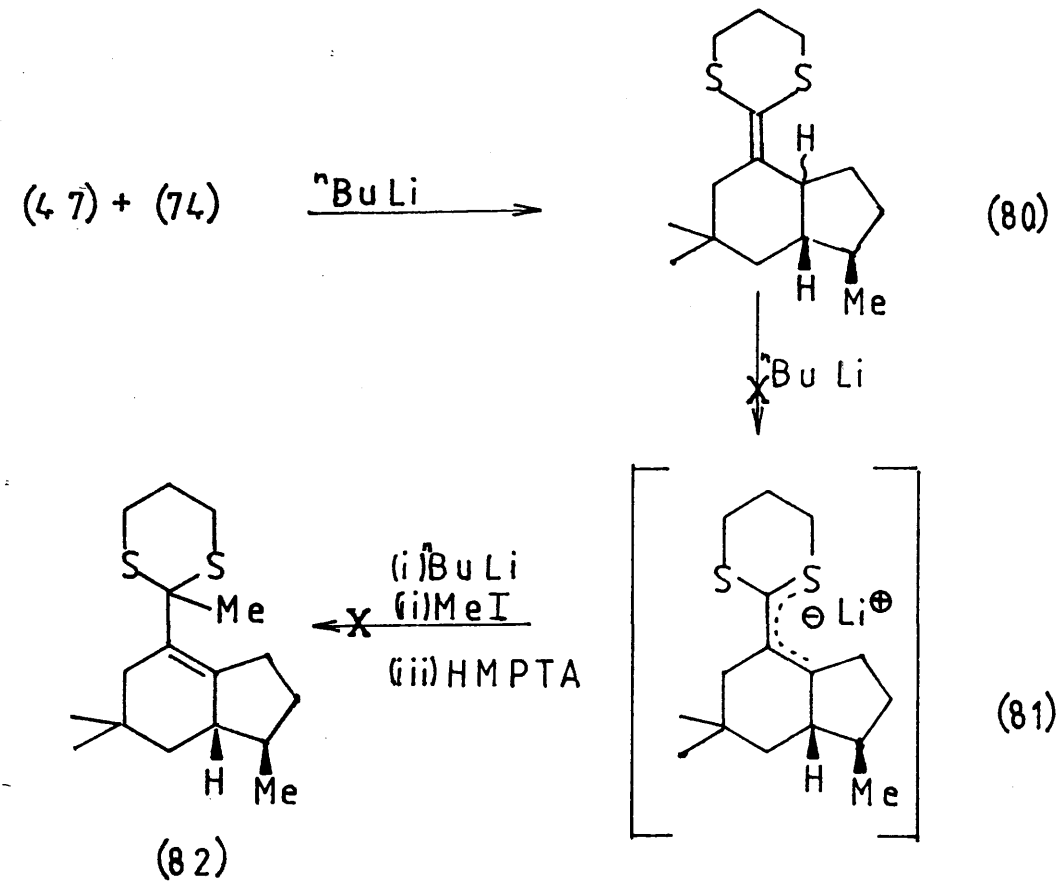
2-Substituted-1,3-dithianes of the type (68) (Scheme 23) readily deprotonate to give the equatorial 2-lithio-1,3-dithiane (69) on reaction with ^{n}BuLi, (Scheme 22). Alkylation of (69) with a carbonyl species (ii) gives an α-hydroxydithiane which can be hydrolysed with mercuric chloride to give an α-hydroxyketone (71).

The 1,3-dithiane (67) was dissolved in THF, stirred under dry nitrogen at -20°C and 1.3 equivalents of ^{n}BuLi added dropwise, (Scheme 24). The mixture was stirred for 2 hours before the temperature of the bath was reduced to -78°C and the ketone added. The reaction mixture was kept at 0°C for a week and then worked up. The crude product consisted mainly of the starting materials (47) and (67) with no trace of (72). The reasons for this failure are unclear but it may be due to steric-hindrance between the ketone (47) and the α-lithio derivative (67).

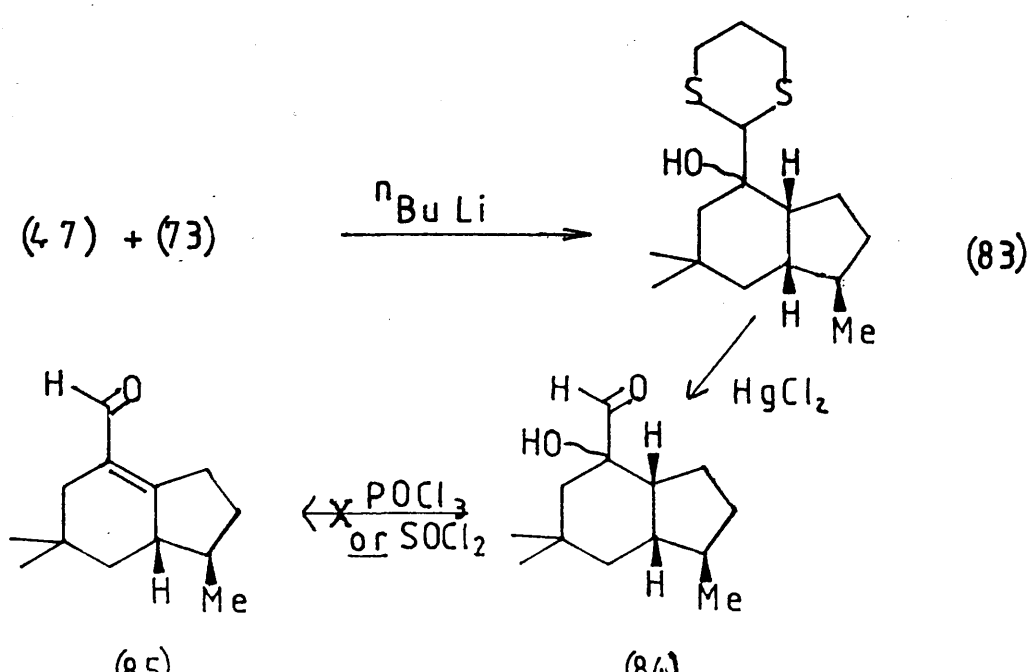
Strategy 4, (Scheme 25)[25].

Another approach, using 2-trimethylsilyl-1,3-dithiane (74) was attempted in an effort to prepare the α,β-unsaturated ketone (64). It is known that reaction of 1,3-dithiane (73) with TMS-Cl yields the TMS-dithiane (74). Subsequent addition of ^{n}BuLi should give the α-lithio derivative (75) which can react with a carbonyl species (i) via the Peterson olefination[26] reaction to furnish the ketene equivalent (76). Alkyl lithium addition across the double bond provides the more stable anion (77), α to the sulphur atom. This can be reacted with methyl iodide to give the unsaturated dithiane (78) which, on hydrolysis, affords the α,β-unsaturated ketone (79). The overall process (74) to (79) is equivalent to acyl anion addition to a carbonyl

Scheme 26



Scheme 27



species followed by dehydration.

2-Trimethylsilyl-1,3-dithiane (74) was prepared by addition of ^{n}BuLi to a stirred solution of 1,3-dithiane (73) followed by subsequent addition of neat TMS-Cl. Workup and distillation furnished a good yield of (74), b.p. 51-52^{o}C (0.1 mm Hg) [lit.[25] 54.7^{o}C (0.17 mm Hg)]. The ^{1}H (90 MHz) nmr spectrum featured signals for the methine [δ_{H} 3.85 (s)] and the trimethylsilyl group [δ_{H} 0.25 (s)]. ^{n}BuLi and the ketone (47) were added consecutively to (74) at -23^{o}C and the reaction left overnight at 0^{o}C. Workup afforded the thioketene acetal (80) (Scheme 26) as an inseparable mixture of diastereoisomers (3:2). Its ^{1}H nmr spectrum was complex but clearly showed resonances for six tertiary methyls and two secondary methyls at δ_{H} 1.1 - 0.8. The presence of two diastereoisomers was confirmed by the ^{13}C nmr which showed the expected distribution of 32 carbons including the tertiary olefinic carbons at δ_{C} 145.4 and 117.1 in the major isomer and δ_{C} 146.2 and 118.1 in the minor isomer. The molecular formula $C_{16}H_{26}S_{2}$ was established by mass spectrometry (base peak m/z 282). The presence of two diastereoisomers may be explained by the epimerisation under the strongly basic conditions. The reaction was repeated with less α-lithio reagent (1 equiv) but still afforded a (3:2) mixture of diastereoisomers.

The next stage involved attempted methylation of (80) to (82) with methyl iodide. Addition of BuLi to (80) in HMPTA/THF at -78^{o}C under nitrogen formed a deep red solution which seemed to indicate the formation of the corresponding anion (81). However addition of methyl iodide and workup gave only starting materials. Because of the problems associated with the production of a diastereomeric

mixture of (80) and its failure to alkylate, this route was abandoned.

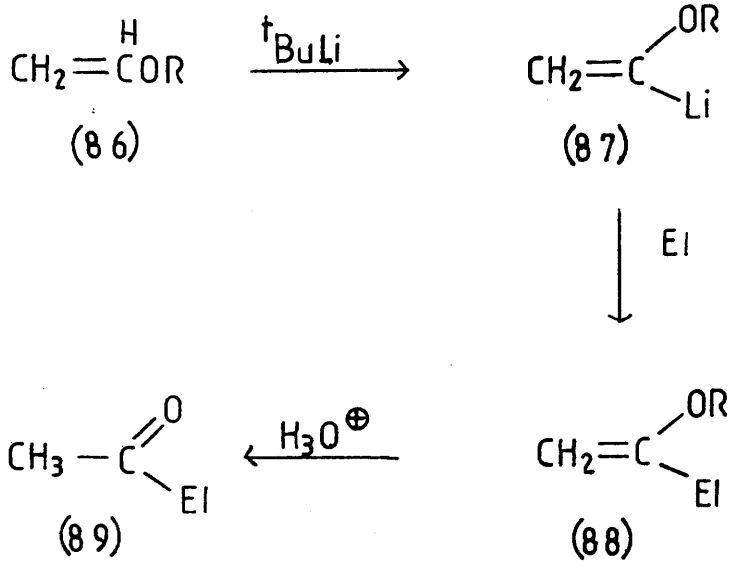
Strategy 5, (Scheme 27)[24]

Using experimental methods developed for previous strategies, we persevered with reagents derived from 1,3-dithiane analogues. In an attempt to produce (84), the equivalent of formyl anion addition to hydrindanone (47), we successfully prepared the α-hydroxyldithiane intermediate (83) by reaction of the ketone (47) with the α-lithio derivative of 1,3-dithiane (73). Purification of the crude reaction mixture by flash chromatography afforded a product (83) which was only partially characterised due to the complexity of its nmr spectrum.

Hydrolysis of (83) was carried out under reflux in a suspension of $HgCl_2/CaCO_3$ in aqueous acetonitrile. The product, a diastereomeric mixture (2:1), had bands in its IR spectrum for hydroxyl (3580 cm^{-1}) and an aldehyde (1750 cm^{-1}) absorbtions. Its nmr spectra revealed aldehyde resonances for both the major [δ_H 9.46 (s); δ_C 204.8 (d)] and minor [δ_H 9.45 (s) ; δ_C 203.2 (d)] isomers in addition to the t-hydroxyl resonances [δ_H 3.2 - 3.1 (br s) ; δ_C 79.1 and 79.5 (both s)]. The molecular formula $C_{13}H_{22}O_2$ was established by mass spectrometry, (m/z 210).

The next stage involved attempted dehydration of the α-hydroxyaldehyde (84) to the α,β-unsaturated aldehyde (85), a useful intermediate in the synthesis of conocephalenol. However it proved impossible to find suitable conditions for the dehydration. Addition of $POCl_3$ or $SOCl_2$ to a solution of (84) in pyridine at ice-temperature resulted in the formation of a very dark solution from which no product

Scheme 28

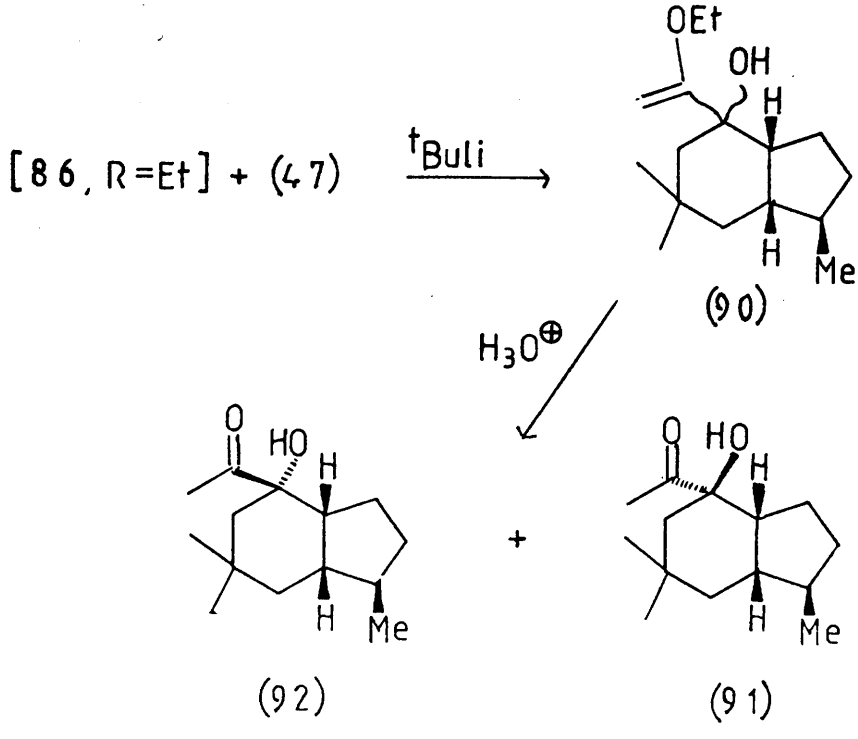


R=Et or Me

El= R'–X ; X=Cl,Br,I.

$= \begin{matrix} R'' \\ R''' \end{matrix} \!\!>\!\!=O$

Scheme 29



could be obtained.

The use of 1,3-dithiane analogues as reagents in the synthesis of conocephalenol was abandoned in favour of strategy 6.

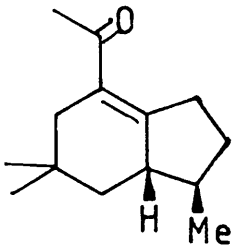
Strategy 6, (Schemes 28-31)[27]

In 1974 Baldwin discovered that methyl vinyl ether (86; R = Me) can be deprotonated with ^{t}BuLi at -65°C to give the corresponding acyl anion equivalent (87, R = Me) which can react with a wide variety of electrophiles (El) including alkyl halides and carbonyls. The resultant ethoxyvinyl ethers (88) can be hydrolysed in situ to give ketones or α-hydroxyketones (as (89)).

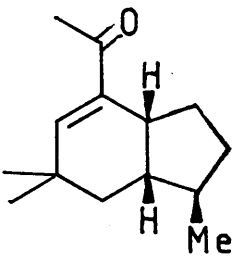
Ethyl vinyl ether (86; R = Et) can also be used in this reaction and it was hoped that the lithio-derivative (87; R = Et) would react with the hydrindane (47) to yield the α-hydroxy vinyl ether (90) which upon hydrolysis would afford the desired α-hydroxy ketones (91), (92).

Ethyl vinyl ether (86; R = Et), used instead of methyl vinyl ether because of its greater convenience, was stirred in THF at -65°C and ^{t}BuLi added. Removal of the cooling bath and warming to 0°C resulted in the initial deep yellow solution becoming clear. This indicates the formation of the vinyllithium. The mixture was then re-cooled to -65°C and the ketone (47) added. Workup yielded (90) as a mixture of 2 diastereoisomers. The IR spectrum showed hydroxyl (3600 and 3200 cm^{-1}) and vinyl (1610 cm^{-1}) absorptions. The ^{1}H (90 MHz) nmr spectrum showed the vinyl protons at δ_H 4.2 (m), the methylene protons of the ethoxy ethers at δ_H 3.7 and 3.4 both q, J(6.9 Hz) and the secondary and tertiary methyls between δ_H 0.9 and 1.1.

Scheme 30

(92) $\xrightarrow[0°C]{SOCl_2}$  (64)

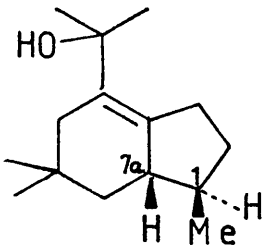
+

 (93)

Scheme 31

(91) $\xrightarrow[0°C]{SOCl_2}$ (93)

Scheme 32

(64) $\xrightarrow[0°C]{MeLi}$ 

(23)

The molecular formula $C_{16}H_{28}O_2$ was established by mass spectrometry (m/z 252). The 2 diastereoisomers were not separated or characterised further.

The next stage of the synthesis involved hydrolysis of (90) with 0.02M HCl, which yielded, after workup, a diastereomeric mixture of (91) and (92) in a ratio ca. 1:2. The diastereoisomers were separated by flash chromatography giving (92) as an oil and (91) as a crystalline solid, m.p. 87-89°C (ex ether). The major, less polar ketol is likely to have the stereochemistry as in (92), because attack of the ethoxy vinyl lithium should come from the less hindered side of the hydrindanone. The results of dehydration experiments (see below) confirmed this view.

The oily ketol (92) [ν_{max} 3300, 1690 cm^{-1}] showed the expected proton resonances for a hydroxyl group [δ_H 3.80 (s)], the bridgehead 3a-H [δ_H 2.60 (m)], the methyl ketone [δ_H 2.12 (s)], two tertiary methyls [δ_H 0.95, 0.91 (both s)] and a secondary methyl [δ_H 0.92 (d, J 6.7 Hz)]. The ^{13}C nmr spectrum showed the expected number and distribution of carbon atoms, including the ketone at δ_C 212.5 (s) and the tertiary oxygenated carbon δ_C 81.8 (s). The molecular formula $C_{14}H_{34}O_2$ was confirmed by mass spectrometry (m/z 224).

The crystalline, more polar ketol (91) [ν_{max} 3500, 1690 cm^{-1}] had similar spectroscopic properties (see Experimental). Its molecular formula was confirmed as $C_{14}H_{34}O_2$ by mass spectrometry.

The next stage involved appropriate dehydration of the less polar ketol (92) in thionyl chloride at 0°C, (Scheme 30), which led to a mixture of two U.V. active products in a ratio of 4:3. The major

product was readily identified as (64) by analysis of its spectroscopic properties. Its IR spectrum showed an unsaturated ketone at 1670 cm^{-1}, while its spectrum lacked a vinyl proton resonance. The identifiable features of the spectrum included an allylic methylene group [δ_H 2.7 (m)], a methyl ketone [δ_H 2.2 (s)], two tertiary methyls [δ_H 1.0, 0.92 (both s)] and a secondary methyl [δ_H 0.95 (d, J 7.1 Hz)]. The ^{13}C nmr spectrum confirmed the presence of an enone system with resonances at δ_C 200.7 (s), 158.3 (s) and 128.0 (s). The mass spectrum gave the parent ion as the base peak at m/z 206.1670 ($C_{14}H_{22}O$).

The more polar compound (93) m.p. 60-62°C showed similar IR and high resolution mass spectra to those of (64) but clearly revealed the presence of an enone with a trisubstituted double bond in both its ^1H [δ_H 6.03 (t, J 1.2 Hz)] and ^{13}C [δ_C 200.5 (s) ; 149.4 (d) ; 140.5 (s)] nmr spectra. As expected, dehydration of ketol (91) with $SOCl_2$ yielded only the trisubstituted enone (93), (Scheme 31).

The final stage in the synthesis of conocephalenol involved reaction of the enone (64) at 0°C in THF with methyl lithium. Workup and purification by preparative t.l.c yielded a product (23) which was identical with natural conocephalenol [^1H, ^{13}C nmr spectra, t.l.c]. This synthesis resolves the residual uncertainty in the structure of conocephalenol in the relative stereochemistry of 1-H and 7a-H. These two protons are <u>trans</u> and the stereochemistry of conocephalenol is as shown (23).

TABLE (1)

COMPOUND (47)

CARBON	δ(ppm) ($CDCl_3$)
1	40.7 (d)
*2	32.8 (t)
*3	27.8 (t)
3a	50.7 (d)
4	215.2 (s)
5	51.5 (t)
6	34.9 (s)
7	41.3 (t)
7a	46.5 (d)
8	20.7 (q)
9, 10	31.3 (q), 26.2 (q)

* may be interchanged.

GENERAL EXPERIMENTAL

Melting-points (m.p) which are uncorrected, were determined on a Kofler hot-stage apparatus. Infrared (IR) spectra were recorded in CCl_4 solution unless otherwise stated on either Perkin Elmer 580 or 257 instruments. Mass spectra (M.S) were recorded using an MS12 instrument (low resolution) and an MS9025 instrument (high resolution). Unless otherwise stated, nuclear magnetic resonance (nmr) spectra were recorded for $CDCl_3$ solutions using a Bruker WP200SY or AM200SY instrument (^1H, 200 MHz, ^{13}C 50.32 MHz). Lowfield spectra were recorded at 90 MHz on a Perkin Elmer R32 instrument, or on a Varian XL100 (^1H 100 MHz, ^{13}C 25.16 MHz) instrument. Chemical shifts were measured using the δ scale with tetramethylsilane as internal standard or relative to $CHCl_3$ at δ_H 7.25 or $CDCl_3$ at δ_C 77.0 unless otherwise stated. Column chromatography was carried out on Merck silica HF_{254}. Kieselgel G F_{254} was used for preparative thin layer chromatography. Analytical t.l.c. plates were visualised using U.V. light (254 or 350 nm) and by spraying with ceric sulphate/H_2SO_4. Eluents for column chromatography were increasing percentages of diethyl ether in hexane. All solvents and reagents used were of analytical grade except for column chromatography when bulk solvents were used. Solvents were removed using a Buchi rotary evaporator and water aspirator. Organic solutions were dried over anhydrous magnesium sulphate. "Normal workup" refers to extraction of the reaction mixture with ether, washing with water, brine and water, drying and evaporation of the solvents under reduced pressure.

EXPERIMENTAL

2-(3-Oxybutyl)-5,5-dimethylcyclohexane-1,3-dione (38).[9]

5,5-Dimethyl-1,3-cyclohexanedione (39) (10g, 90 mmol) was dissolved in methanol (50 ml) and potassium hydroxide (1g) in methanol (10 ml) added. Finally methyl vinyl ketone (40) (6.3g, 90 mmol) was added and the solution refluxed for 3 hours. After cooling, (aq) sodium hydroxide (25 ml, 2.5M) was added and the resulting coloured solution filtered and acidified to pH4 by conc. H_2SO_4. The acidic solution was then extracted into chloroform (3 x 50ml), and the combined organic layers washed with water (3 x 100 ml) and dried. Evaporation of the chloroform under reduced pressure and then crystallisation of the crude reaction mixture from acetone/water afforded the triketone (38) (11.3g, 60%), m.p. 100-102°C. ν_{max} (KBr): 3400 and 1600 cm^{-1} ; δ_H (90MHz) : 2.6 - 2.3 (4 H, m), 2.15 (s, $-\overset{O}{\overset{\|}{C}}-\underline{CH}_3$), 1.5 (s, 6H, two tertiary methyls); M.S. : m/z 210.1255 ($C_{12}H_{18}O_3$ requires 210.1256).

1,6,6-Trimethyl-2,3,4,5,6,7-hexahydro-4H-indene-4-one (27)

Distilled D.M.E. (250 ml) was added to a three-necked round-bottom flask and purged with dry nitrogen. Titanium trichloride (6.2g, 40 mmol) was added quickly,followed by Zn-Cu couple (5.2g, 40 mmol) (prepared by the method in Fieser[13]). The resulting suspension was stirred and refluxed under dry nitrogen for 1 hour. The triketone (38) (420mg, 2 mmol) dissolved in D.M.E. (30 ml) was added over an 8 hour period via a syringe pump, followed by a 12 hour reflux. Further triketone (420mg, 2 mmol) in D.M.E. (30 ml) was added over 8 hours, followed by another 12 hour reflux. After cooling the reaction mixture was filtered through celite and the D.M.E. evaporated. Normal workup and purification by flash chromatography afforded the enone (27) (390mg, 55%) as a clear oil ; ν_{max} 1665 cm^{-1}, λ_{max} 253 nm, ε10,550. Several other minor products were also present (T.l.c). One of them was identified as the hydroxyenone (46).

(i) the enone (27)

δ_H: 2.84 and 2.72 (ABq, J_{AB} 12.4 Hz, 5-H_2), 2.23 (m,5H), 1.14 (m, 2H), 1.06 (d, J 7.1 Hz, secondary methyl), 1.02 and 1.01(both s, tertiary methyls)

δ_C : 198.2 (s), 167.1 (s), 135.5 (s), 51.7 (t), 43.8 (d), 39.0 (t), 31.2 (t), 29.7 (s), 28.7 (q), 28.3 (q), 27.3 (t), 18.0 (q)

M.S.: m/z 178.1357 ($C_{12}H_{18}O$ requires 178.1357).

(ii) hydroxyenone (46)

ν_{max} 3560 and 1660 cm^{-1}

δ_H : 2.5 - 1.3 (m, 8H), 1.3 (s, hO - C -CH_3), 1.0, 0.98 (both s, tertiary methyls)

δ_C : 199.3 (s), 162.3 (s), 137.4 (s) 94.8 (s), 51.8 (t), 36.3 (t), 35.0 (s), 33.6 (t), 28.3 (q), 27.3 (q), 25.8 (t), 20.7 (q)

M.S.: m/z 194 ($C_{12}H_{18}O_2$ requires m/z 194).

1,6,6-Trimethyloctahydroinden-4-one (47).

The enone (27) (500mg, 2.8 mmol) was dissolved in methanol (30 ml) and 10% Pd-C (50mg) was added. The mixture was rapidly stirred under an atmosphere of hydrogen for 3 hours then filtered through a pad of celite, dried, and the solvent removed under reduced pressure. Analysis of the hydrogenation mixture [λ_{max} 1710 cm^{-1}] by analytical g.c. and n.m.r. showed the presence of the two hydrogenated products (47) (91%) and (48) (9%). Flash chromatography failed to separate these isomers.

The above procedure was repeated using both hexane and ethylacetate as solvents and gave essentially the same ratio of respective diastereoisomers (47) and (48).

(i) the major isomer (47)

δ_H : The proton resonances were assigned by carrying out a $^1H/^{13}C$ correlation (Fig. 2)[2] 2.62 (ddd, $J_1 \approx J_2 \approx J_3 \approx$ 8.8 Hz, 3a-H), 2.19 and 1.99 (ABq, J_{AB} 12.6 Hz, 5-H_2), 2.0 - 1.9 (m, 2-H_2 and 3-H_2), 1.98 (m, 7a-H), 1.37 (m, 7-H_2), 0.94 and 0.86 (both s, tertiary methyls), 0.92 (d, J 6.9 Hz, secondary methyl)

δ_C : see Table 1 (page 71).

M.S.: m/z 180.1513 ($C_{12}H_{20}O$ requires 180.1514)

(ii) the minor isomer (48)

δ_H : 1.03 and 0.87 (both s, tertiary methyls)

δ_C : 214.6 (s), 50.6 (t), 43.9 (d), 38.7 (d), 34.7 (t), 30.4 (t), 27.8 (t), 25.2 (q), 53.4 (d), 32.1 (q), 28.1 (q), 14.8 (q).

Epimerisation of 1,6,6-trimethyloctahydroinden-4-one (47).

A catalytic amount of sodium was added to absolute ethanol (1 ml). After the hydrogen evolution had ceased, the hydrindanone (47) (20 mg) in absolute ethanol was added and the reaction mixture was stirred for 48 hours at room temperature. The solution was then diluted with water (5 ml) and extracted with pentane (3 x 5 ml). The combined pentane extracts were washed with (aq) NH_4Cl (1 x 10ml), aq $NaHCO_3$ (1 x 10 ml), brine (1 x 10 ml), dried, and the solvent evaporated under reduced pressure. Examination of the reaction mixture by analytical g.c. and n.m.r showed a mixture of two main products (47) and (53a) in a ratio of 6:4 respectively and also minor products (48) and (53b) in a ratio of 4:1 respectively.

ν_{max} 1710 cm^{-1}

M.S. : m/z 180.1514 ($C_{12}H_{20}O$ requires 180.1514)

(i) the major trans isomer (53a)

δ_H : 2.25 (m, 3a-H), 0.96 (d, J 7.1 Hz, secondary methyl), 0.91, 0.87 (both s, tertiary methyls)

δ_C : 211.2 (s), 57.8 (d), 55.0 (t), 51.6 (d), 42.8 (t), 40.4 (d), 32.2 (q), 31.6 (t), 31.4 (s), 26.8 (q), 20.7 (t), 18.8 (q)

(ii) the minor trans isomer (53b)

δ_C : (The 3 singlets were not observed), 55.8 (d), 50.1 (t), 45.3 (t), 40.3 (d), 39.0 (t), 33.1 (t), 25.2 (q), 23.0 (q), 15.1 (q).

1,6,6-Trimethyl-4-cyano-4-trimethylsiloxyoctahydroindene (54).

The ketone (47) (0.5g, 2.8 mmol) in dichloromethane (30 ml) was stirred at room temperature for 12 hours with trimethylsilylcyanide (0.3g, 3 mmol) in the presence of a catalytic amount of zinc chloride. The solvent was removed under reduced pressure to yield (54) as an oil (0.78g) which was analysed without purification. ν_{max} 2930 and 1300 cm^{-1}.

δ_H (90 MHz) CCl_4 : 2.6 (m, 3a-H), 1.05-1.00 (9H, 3 x CH_3), 0.3 (12 H, $-Si-(CH_3)_4$).

M.S : m/z 279 ($C_{16}H_{29}OHSi$ requires m/z 279)

Attempted preparation of 1,6,6-trimethyl-4-acetyloctahydroinden-4-ol (56)

The trimethylsilylcyanohydrin (630mg, 2.3 mmol) (54) in 40 ml dry ether was added dropwise to a stirred solution of methyl magnesium iodide (40 ml, 0.12M in ether) at room temperature. Stirring was continued for a further two hours at reflux after the addition was complete. The reaction mixture was cooled in an ice bath, poured into 5g of crushed ice containing 20 ml of conc. H_2SO_4 and left for periods of up to 24 hours before workup. Spectroscopic analysis of the product showed the presence of some cyanohydrin (55).

1,6,6-Trimethyl-4-cyano-octahydroinden-4-ol (55).

The crude trimethylsilylcyanohydrin (54) (780mg, 2.7 mmol) was added to 15 ml of 3N HCl and stirred at room temperature for 1 hour. Normal workup and purification by preparative t.l.c using chloroform/hexane (10:1) as the eluent, gave the cyanohydrin (55) (0.44g, 79%) as the major product, ν_{max} 3590 and 2220 cm^{-1}.

δ_H (90 MHz) : 3.2 (s,OH), 1.05-1.00 (9H, 3 x $-CH_3$)

δ_C (25 MHz) : 122.3 (s), 69.3 (s), 53.2 (d), 49.4 (t), 43.1 (t), 43.0 (d), 42.1 (d), 33.6 (t), 32.1 (s), 31.2 (t), 27.9 (q), 22.5 (q), 18.3 (q).

M.S. : m/z 207 (base peak, 3.2%), ($C_{13}H_{21}OH$ requires m/z 207)

1,6,6-Trimethyl-4-cyano-2,3,4,5,6,7,7a-hexahydroindene (57).

The cyanohydrin (55) (100mg, 0.48 mmol) was refluxed for 8 hours in pyridine (10 ml) containing xs. phosphorus oxychloride (2 ml). After cooling, the dark solution was poured into ice containing 5N HCl (10 ml) and extracted into ether (3 x 25 ml). Normal workup and purification by flash chromatography gave the unsaturated nitrile (57), an oil (38mg, 42%), as the major product, ν_{max} 2200 and 1420 cm^{-1}.

δ_H (90 MHz) : complex multiplets, no vinyl protons

δ_C (25 MHz) : 164.1 (s), 112.6 (s), 101.7 (s), 43.7 (d), 41.0 (d), 40.3 (t), 39.7 (t), 31.0 (t), 32.3 (q), 31.5 (s), 29.7 (t), 26.0 (q), 17.8 (q).

M.S. : m/z 189 (base peak, 47%), $C_{13}H_{19}N$ requires m/z 189.

Attempted preparation of 1,6,6-trimethyl-4-carboxy-2,3,5,6,7,7a-hexahydroindene (59).

The unsaturated nitrile (57) was subjected to both basic and acidic hydrolysis procedures. However even after long reaction times (>12 hours), there was no sign of the unsaturated acid (59).

1,6,6-Trimethyl-4,4-bis-[phenylseleno]-octahydroindene (61).

The hydrindanone (47) (120mg, 0.67 mmol) was slowly added under nitrogen to a stirred suspension of anhydrous $ZnCl_2$ (45mg, 0.3 mmol) in a solution of phenylselenol (0.15ml, 1.3 mmol) in CCl_4 (30 ml). The mixture was stirred at room temperature for 3 hours and diluted with ether (50ml). The solution was washed with 5% (aq) HCl (2 x 50 ml), aqueous $NaHCO_3$ (2 x 50ml) and water (3 x 50 ml). The organic phase was dried and the solvents evaporated. The residual gem-bis[phenyl-seleno]-alkene (61) containing some diphenylselenide (63) was dissolved in ether (30 ml) and the solution gradually added to a stirred suspension of excess $LiAlH_4$ (1.5g) in ether (30 ml). The mixture was refluxed for 30 minutes, cooled to 0^oC and carefully treated with the minimum amount of 50% (aq) potassium hydroxide until hydrogen evolution had ceased. The mixture was then immediately filtered through celite, the filtercake washed with ether (30 ml). Normal workup and purification by column chromatography, afforded the selenoacetal (61) (98 mg, 46%), ν_{max} (CCl_4) 2950, 1620 cm^{-1}.

δ_H : 7.4 - 7.1 (10H, m, Se-Ph), 2.45 (m, 3a-H), 1.2, 0.82 (both s tertiary methyls, 0.89 (d, J 7.1 Hz, secondary methyl).

M.S. : m/z 320 ($C_{24}H_{30}{}^{80}Se_2$ requires m/z 320).

Attempted preparation of 1,6,6-trimethyl-4-carboxy-4-phenylseleno-octahydroindene (62).

To a solution of the gem-bis-[phenylseleno]-alkene (61) (98mg, 0.3 mmol) in THF (10ml) was added (at $0^{o}C$ under N_2) $^{n}BuLi$ (0.5ml, 0.33 mmol, 1.5M in hexane) and the solution stirred for up to 3 hours at $0^{o}C$. Excess CO_2 (g) was then allowed to react with this solution for 2 hours at $0^{o}C$ followed by 1 hour at room temperature. However only starting material was present after usual workup.

2-Methyl-1,3-dithiane (67).

Acetaldehyde (66) (1.5ml, 27 mmol) was stirred in $CHCl_3$ (30ml) at room temperature for 1 hour with an equimolar amount of propane-1,3-dithiol (65) (4.9ml). The solution was then cooled to ice temperature and BF_3-etherate (3.4 ml, 8 mmol) added. After further stirring at this temperature for 1 hour the solution was allowed to warm to room temperature and was washed with water (1 x 30ml), 10% aqueous KOH (1 x 30 ml) water (3 x 30ml), dried and the chloroform evaporated under reduced pressure. The residue, an oil, was distillated to give (67) (2.5g, 70%) as an oil (b.p. 50-52° 1.1 torr, lit.[24] 53-54° 1.1 torr), ν_{max} 2900 and 1430 cm^{-1}.

δ_H (90 MHz): 4.15 (q, J 6.7 Hz, 2-H), 2.9 (m, 4-H_2, 6-H_2), 2.0 (m, 5-H_2), 1.45 (d, J 6.7 Hz, secondary methyl).

M.S. : m/z 134 ($C_5H_{10}S_2$ requires 134).

Attempted reaction of ketone (47) with 2-methyl-1,3-dithiane (67).

The 1,3-dithiane (67) (90mg, 0.67 mmol) was dissolved in THF (50ml), stirred under dry nitrogen at -20°C and ^{n}BuLi (0.5ml, 0.75 mmol, 1.5M in hexane) added dropwise. The mixture was stirred for 2 hours and the temperature was reduced to -78°C. The ketone (47) (85mg, 0.5 mmol) in THF (20ml) was added over 30 minutes. After a further 30 minutes the cold bath was removed. The reaction mixture, left for up to 1 week under nitrogen at 0°C, proved on workup to contain mainly starting materials (47) and (67).

2-Trimethylsilyl-1,3-dithiane[25] (74)

^{n}BuLi (2ml, 3.3 mmol, 1.58M in hexane) was added to a stirred solution of 1,3-dithiane (73) (400mg, 3.3 mmol) in dry THF (30ml) under nitrogen and the reaction stirred at ice/salt bath temperature for 2 hours. The solution was cooled to -25°C and neat trimethylsilyl chloride (0.42ml, 3.3 mmol) added over 30 minutes. The solution was warmed to room temperature, water added (10ml) and most of the THF removed under reduced pressure. Normal workup and distillation of the crude product gave 2-trimethylsilyl-1,3-dithiane (74) (70.6%), b.p. 51-52° (0.1mm Hg), [lit.[25] 54.7°C (0.17mm Hg)]

δ_H (90MHz) : 3.85 (s, -C-H), 2.8 (4H,m), 2.1 (2H,m), 0.25 (9H, $-SiMe_3$).

Formation of Compound (80).

2-Trimethylsilyl-1,3-dithiane (74) (390mg, 2.0 mmol) was dissolved in dry THF (20ml) and stirred under dry nitrogen with ^{n}BuLi (1.5ml, 2.2 mmol, 1.5M in hexane) at -23°C for 1 hour. The ketone (47) (358mg, 2.0 mmol) was added dropwise in THF (10ml) and the reaction mixture left overnight at 0°C and then warmed to room temperature. Water was added (10ml) and most of the THF evaporated under reduced pressure. Normal workup and purification by flash chromatography using ether/hexane as the eluent gave an inseparable diastereomeric mixture (3:2) of the ketene thio acetal (80) (153g, 27%), as an oil, ν_{max} (CCl_4) 2980 and 1450 cm^{-1}.

δ_H : 3.45 (m, 2 x 3a-H), 2.95-2.65 (8H,m), 2.2-1.1 (m), 1.1 - 0.8 (methyls).

δ_C : 146.2 (s), 145.4 (s), 118.1 (s), 117.4 (s), 44.9 (d), 44.0 (d), 42.7 (t), 42.0 (d), 41.4 (d), 40.5 (2 x t), 40.3 (t), 40.0 (d), 38.2 (d), 35.2 (t), 33.2 (s), 33.0 (s), 32.3 (q), 32.1 (q), 30.6 (2 x t), 30.5 (3 x t), 28.8 (t), 27.4 (t), 25.5 (t), 25.4 (t), 24.0 (2 x q), 22.6 (q) 15.2 (q).

M.S: m/z 282 ($C_{16}H_{26}S_2$ requires 282).

Attempted methylation of ketene thioacetal (80).

The ketene thioacetal (80) (200mg, 0.7 mmol) was dissolved in dry THF (20ml) and stirred under dry N_2 at -78°C with H.M.P.T.A. . ^{n}BuLi (0.66ml, 0.77 mmol, 1.58M in hexane) was added and the temperature of the reaction mixture raised to room temperature. Within periods of 2 to 3 hours the coloured solution was cooled to -78°C, methyl iodide (100mg, 0.7 mmol) added and the reaction mixture stirred for 2 hours. After warming to room temperature and further stirring for up to 2 hours

the solution was subjected to workup. N.m.r. analysis showed only the presence of starting material.

Formation of Compound (83).

^{n}BuLi (1.4ml, 2.1 mmol, 1.5M) was added dropwise to a stirred solution of 1,3-dithiane (73) (225mg, 1.8 mmol) in dry THF (30ml) at -10°C (ice-salt bath) under dry nitrogen and the mixture stirred for 2 hours. The ketone (47) (311mg, 1.8 mmol) in dry THF (5ml) was added dropwise. After further stirring at -10° for 1 hour the reaction mixture was left overnight at 0°C. Water was added (20ml) and most of the THF evaporated under vacuum. Normal workup and purification by column chromatography using hexane/ether as the eluent, the hydroxydithiane (83) as a colourless oil (170mg, 33%), ν_{max} 3600, 2980 and 1310 cm^{-1}.

δ_H (90MHz) : 4.1 (s, S-CH), 2.9 (m), 2.3 -1.5 (m).

M.S.: m/z 300 ($C_{16}H_{28}OS_2$ requires 300).

1,6,6-Trimethyl-4-formyl-octahydroindane-4-ol (84).

A solution of the dithiane (83), (110mg, 0.37 mmol) in (aq) 80% acetonitrile (10ml) was added at 25°C to an effectively stirring solution of $HgCl_2$ (250mg, 0.9mmol) in the same solvent mixture. Ca CO_3 (400mg) was added to buffer the reaction mixture near pH.7. The mixture was stirred and heated for 5 hours and then left to cool. After filtration in which the filtercake was washed with aq. NH_4Cl (1 x 10ml), water (1 x 10ml), the reaction mixture was extracted with $CHCl_3$ (3 x 30ml). The combined organic layers were washed with

water (3 x 30ml), dried and the solvent removed under reduced pressure. Purification by flash chromatography afforded the α-hydroxyaldehyde (84) as an inseparable mixture of diastereomers (2:1), m/z 210, ($C_{13}H_{22}O_2$ requires m/z 210) , ν_{max} (CCl_4) 3580 and 1750 cm^{-1}. δ_H : 9.46 (s, major -CHO), 9.45 (s, minor -CHO), 3.2 - 3.1 (2H, two hydroxyls), 1.06 - 0.95 (methyls)

δ_C : (i) the major diastereomer : 204.84 (d), 79.1 (s), 44.6 (d), 41.5 (d), 40.9 (t), 38.6 (t), 37.7 (d), 34.0 (q), 31.4 (t), 30.2 (s), 28.5 (q), 24.7 (t), 22.6 (q).

(ii) the minor diastereoisomer : δ_C : 203.2 (s), 79.5 (s), 47.7 (d), 38.6 (d), 38.4 (t), 36.4 (d), 34.4 (q), 33.7 (t), 30.1 (s), 29.8 (t), 26.6 (q), 23.8 (t), 15.0 (q).

Attempted dehydration of α-hydroxyaldehyde (84).

The attempted dehydration of (84) was carried out as reported for the dehydration of the α hydroxyketone (64) p 86 . Neither the expected product (77) not the starting material (76) could be detected.

1,6,6-Trimethyl-4-[1-ethoxy-1-ethenyl]-octahydroindene-4-ol (90).

^{t}BuLi (0.84ml, 1.4 mmol, 1.7M in hexane) was added dropwise to a solution of ethyl vinyl ether (86; R=Et) (2.3ml, 0.23 mmol) in dry THF (10ml) at -65°C under dry nitrogen. After removal of the cooling bath, the solution was heated to 0°C and stirred at this temperature for 30 minutes, until the colour of the solution changed - formation of the anion. The solution of the anion was cooled to

-65°C and the ketone (47) (0.254mg, 1.41 mmol) added dropwise in THF (2ml). The reaction was stirred at -65°C for 1 hour and then heated to 0°C. 20% (aq) ammonium chloride solution (10ml) was added and a precipitate formed. Most of the THF was evaporated at the pump, the reaction mixture extracted with ether (3 x 25ml) and the combined organic layers washed with water (1 x 50ml), brine (1 x 50ml) water (1 x 50ml), dried and the solvent evaporated under reduced pressure. The crude reaction product was purified by flash chromatography giving a mixture of two diastereomeric α-hydroxyvinyl ethers (90) (256mg, 72%) ν_{max} 3600, 3200, 1610 cm^{-1}.

δ_H (90 MHz): 4.2 (m, vinyl protons), 3.7, 3.45 (q, J 6.9Hz, 2 x -O-CH_2-CH_3), 2.6 (m, 3a-H), 1.1 - 0.9 (secondary and tertiary methyls).

M.S : m/z 252 ($C_{16}H_{28}O_2$ requires m/z 252).

1,6,6-Trimethyl-4-acetyloctahydroinden-4-ol (91)., (92).

The enol ether (90) (250mg, 0.99 mmol) was stirred in methanolic 0,02M HCl (50ml) for 30 minutes at room temperature. The methanol was evaporated under reduced pressure and the reaction mixture extracted with ether (3 x 25ml). The combined organic layers were washed with $NaHCO_3$ (1 x 25ml), brine (1 x 25ml), water (3 x 25ml), dried and the solvent removed under reduced pressure. Purification by flash chromatography yielded two diastereomeric α-hydroxyketones (91) and (92) (2:3, 76% overall yield).

(i) the more polar ketol (91) (65mg) m.p. 87-89°C (ex ether) ν_{max} 3500 and 1690 cm^{-1}.

δ_H : 2.87 (s, -OH), 2.19 (s, methyl ketone), 2.00-1.65 (6H,m), 1.45 - 1.3 (2H, m), 1.24 - 1.2 (3H,m), 1.09, 0.9 (both s, tertiary methyls),

0.93 (d, J 7.2 Hz, secondary methyl).

δ_C : 212.9 (s), 80.8 (s), 45.4 (d), 41.5 (d), 41.1 (t), 40.0 (t), 38.3 (d), 34.3 (q), 31.1 (t), 30.6 (s), 26.6 (q), 26.2 (t), 25.0 (q), 22.7 (q).

M.S. : m/z 224 ($C_{14}H_{34}O_2$ requires m/z 224).

(ii) the less polar ketol (92): an oil (104mg), ν_{max} 3300 and 1690 cm^{-1}.

δ_H : 3.80 (s, -OH), 2.60 (m, 3a-H), 2.35 - 2.15 (m, 4H), 2.12 (s, methyl ketone), 2.02 - 1.05 (m, 6H), 0.95, 0.91 (both s, tertiary methyls), 0.92 (d J 6.7 Hz, secondary methyl).

δ_C : 212.5 (s), 81.8 (s), 45.5 (t), 43.0 (d), 42.0 (d), 41.6 (d), 39.0 (t), 34.7 (t), 33.6 (q), 31.0 (q), 29.5 (s), 24.5 (t), 23.5 (q), 18.5 (q).

M.S. : m/z 224 ($C_{14}H_{34}O_2$ requires m/z 224).

1,6,6-Trimethyl-4-acetyl-2,3,5,6,7,7a-hexahydroindene (64) and 1,6,6-Trimethyl-4-acetyl-2,3,3a,6,7,7a-hexahydroindene (93).

To a stirred, ice cold solution of the alcohol (92) (200mg, 0.9 mmol), in dry pyridine (4ml) was added freshly distilled thionyl chloride (12 drops). After 5 minutes the mixture was allowed to come to room temperature and poured into ice-cold $NaHCO_3$ solution (15ml). Normal workup and purification by flash chromatography gave the two enones (64) and (93).

(i) the more polar enone (64) (80mg), an oil, ν_{max} 1670 cm^{-1}.

δ_H : 2.7 (2H, m), 2.22 (s, methyl ketone), 2.0 - 1.1 (9H, m), 1.0, 0.92 (both s, tertiary methyls), 0.95 (d, J 7.1 Hz, secondary methyl).

δ_C : 200.7 (s), 158.3 (s), 128.0 (s), 57.8 (s), 48.9 (d), 40.8 (d), 40.7 (t), 39.1 (t), 33.2 (t), 32.1 (q), 31.9 (t), 29.9 (s), 29.7 (q), 26.2 (q), 17.8 (q).

M.S : m/z 206.1670 ($C_{14}H_{22}O$ requires m/z 206.1670).

(ii) the less polar enone (93) (60mg), m.p. 60-62°C, (ex ether), ν_{max} (CCl_4) 1670 cm^{-1}

δ_H : 6.05 (t, J 1.2 Hz, 5-H), 2.80 (m, 3a-H), 2.26 (s, methyl ketone), 2.2 - 1.3 (8H, m), 1.07, 1.00 (both s, tertiary methyls), 1.00 (d, J 6.8 Hz, secondary methyl).

δ_C : 200.5 (s), 149.4 (d), 140.5 (s), 42.0 (d), 40.4 (t), 39.7 (d), 36.4 (d), 33.8 (s), 33.0 (t), 31.6 (t), 30.4 (q), 27.4 (q), 25.7 (q), 22.0 (q).

M.S : m/z 206.1670 ($C_{14}H_{22}O$ requires m/z 206.1670).

1,6,6-Trimethyl 4-[2-hydroxy-2-propyl]-2,3,5,6,7,7a-hexahydroindene, Conocephalenol (23).

Excess methyl lithium (0.2ml, 1.5M) was added to a stirred solution of the unsaturated methyl ketone (64) (32mg, 0.17 mmol) in dry ether (2ml) under N_2 at 0°C. Stirring was continued at this temperature for a further 1 hour and then (aq) ammonium chloride (2ml) added. The ether layer was washed with water (3 x 2ml), dried and the solvent evaporated *in vacuo* giving conocephalenol (24mg, 65%) as an oil, after preparative t.l.c, using hexane : chloroform (1:5). The synthetic product was identical spectroscopically (^1H and ^{13}C n.m.r, IR, MS) with the natural product (23). ν_{max} 3640 cm^{-1}, 1620 cm^{-1}

δ_H ; 2.59 (1H, m), 1.9 - 1.8 (4H, m), 1.7 - 1.5 (5H, m), 1.26 (s, two tertiary methyls), 1.0 (d, J 6.7 Hz, secondary methyl), 0.89 (s, tertiary methyl).

δ_C (C_6H_6) : 135.9 (s), 132.7 (s), 74.0 (s), 48.2 (d), 41.5 (t), 40.7 (d), 40.5 (t), 34.1 (t), 32.5 (q), 30.2 (q), 30.0 (s), 29.5 (t), 29.3 (q), 26.6 (q), 18.2 (q).

M.S : m/z 222.1983 ($C_{15}H_{26}O$ requires 222.1983).

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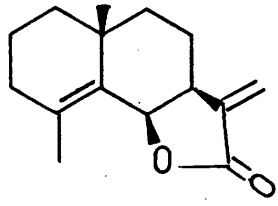
CHAPTER 3.

A SYNTHETIC APPROACH TO THE SESQUITERPENOID TAMARISCOL.



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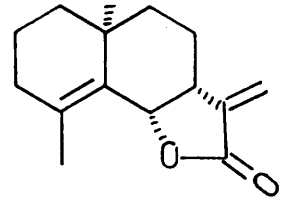

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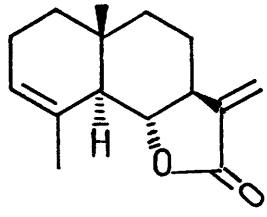

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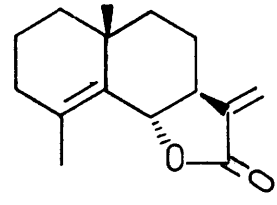

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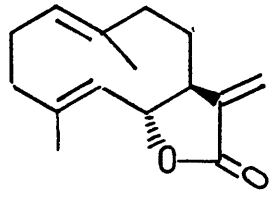

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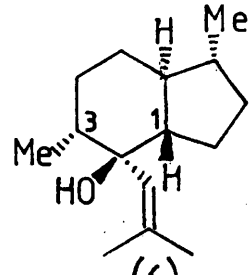

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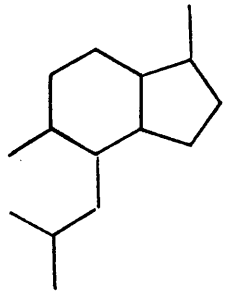

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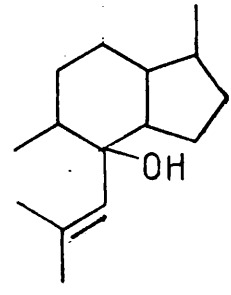

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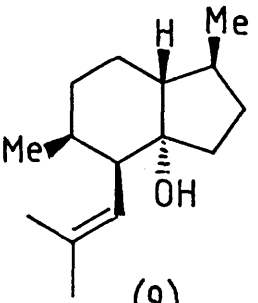
INTRODUCTION

The liverwort *Frullania tamarisci* grows on walls and on the bark of trees and has been implicated in the high incidence of contact dermatitis which affects lumberjacks in France, Canada and the U.S.A. Of the many species of *Frullania* known eleven have been reported to be contact sensitising.[1] Interest in the biological activity of liverwort compounds began with the pioneering work on the allergens of *F. tamarisci* by Ourisson[2] in 1972. The allergenic compounds obtained from this plant include (-)-frullanolide (1) whose structure was deduced from its spectral properties[3] and confirmed by total synthesis.[4] Surprisingly the enantiomeric (+)-frullanolide (2) was subsequently isolated from *F. dilatata*.[2]

In 1973 Connolly and Thornton[5] reported isolation of (+)-α-cyclocostunolide (3) and (+)-γ-cyclocostunolide (4) from *F. tamarisci*, along with (+)-costunolide (5) and (-)-frullanolide (1).

Reinvestigation of the liverwort in 1984 by Connolly and Harrison[6] yielded the above compounds apart from (3). However the major constituent was identified as tamariscol (6), a pungent oil, $C_{15}H_{16}O$ (m/z 222.), $[\alpha]_D$ + 19.7° (C, 1.1 in $CHCl_3$), [ν_{max} 3620], which has a trisubstituted double bond [δ_H 5.07 (m, J 1.3 Hz) ; δ_C 121.9 (d) and 136.4 (s)], a tertiary alcohol [δ_C 79.0 (s)] two vinyl methyls [δ_H 1.88 (d, J 1.2 Hz), 1.75 (d, J 1.5 Hz); δ_C 20.3 (q) and 28.5 (q)] and two secondary methyls [δ_H 0.92 (d, J 6.6 Hz), 0.88 (d, J 6.6 Hz) ; δ_C 15.4 (q), 19.2 (q)] which together with four methine and four methylene groups constitute a bicarboxyclic system. A 2D-INADEQUATE experiment established the basic carbon skeleton as (7) and hence the gross structure of the alcohol is (8).



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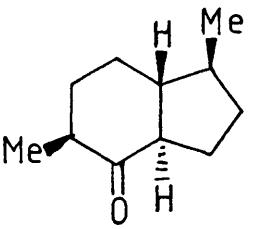
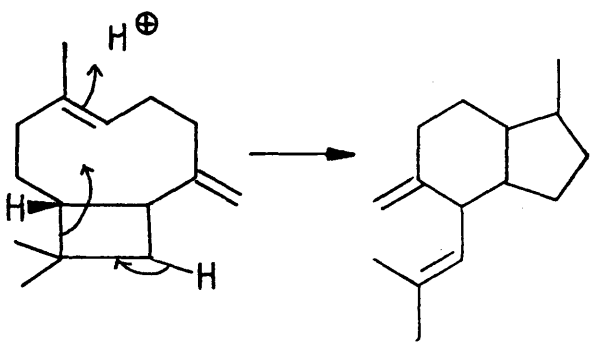
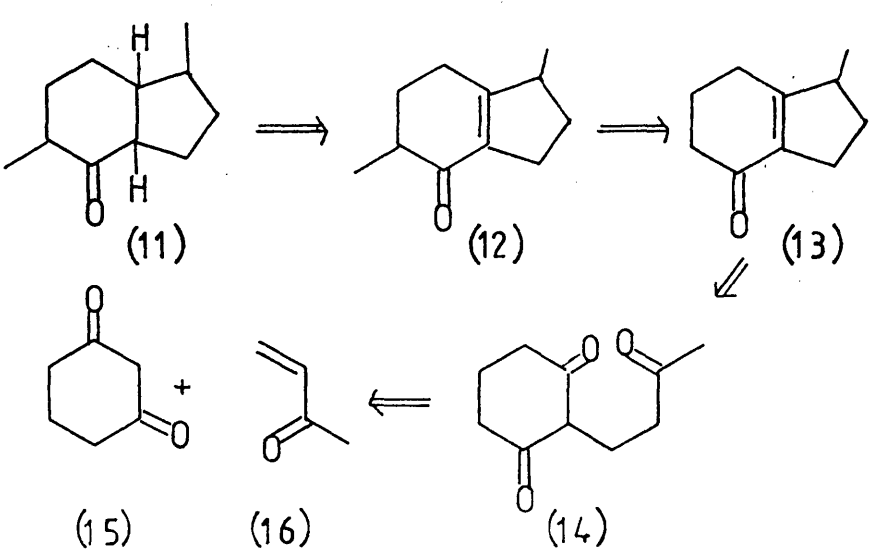


(10)

Scheme 1



Scheme 2



(11) (12) (13)

(15) (16) (14)

The 360 MHz ^{1}H n.m.r spectrum of (6) is not adequately resolved to allow the stereochemistry to be determined. The relative stereochemistry follows from coupling data in the $Eu(fod)_3$ shifted proton spectrum. The C-3 methyl group, the vinyl proton, and H-3 and H-1 all move downfield significantly. H-3 (ddq, J 4.5, 12.0, 6.5 Hz) has a large coupling to an axial proton on C-4 and is therefore axial (α). The C-3 methyl group is equatorial (β). The tertiary hydroxyl group must be equatorial to account for the large shift of H-3. The large couplings of the ring junction proton H-1 (dt, J 8.0, 11.0 Hz) indicate that it is axial and that the ring junction is trans. The configuration of the C-7 methyl group is β, as in pacifigorgiol[7] (9) (isolated from the marine organism *Pacifigorgia adamsii*), because of the virtual identity of the ^{13}C n.m.r chemical shifts of this methyl group in both compounds. The structure and stereochemistry of (9) was determined by X-ray analysis.

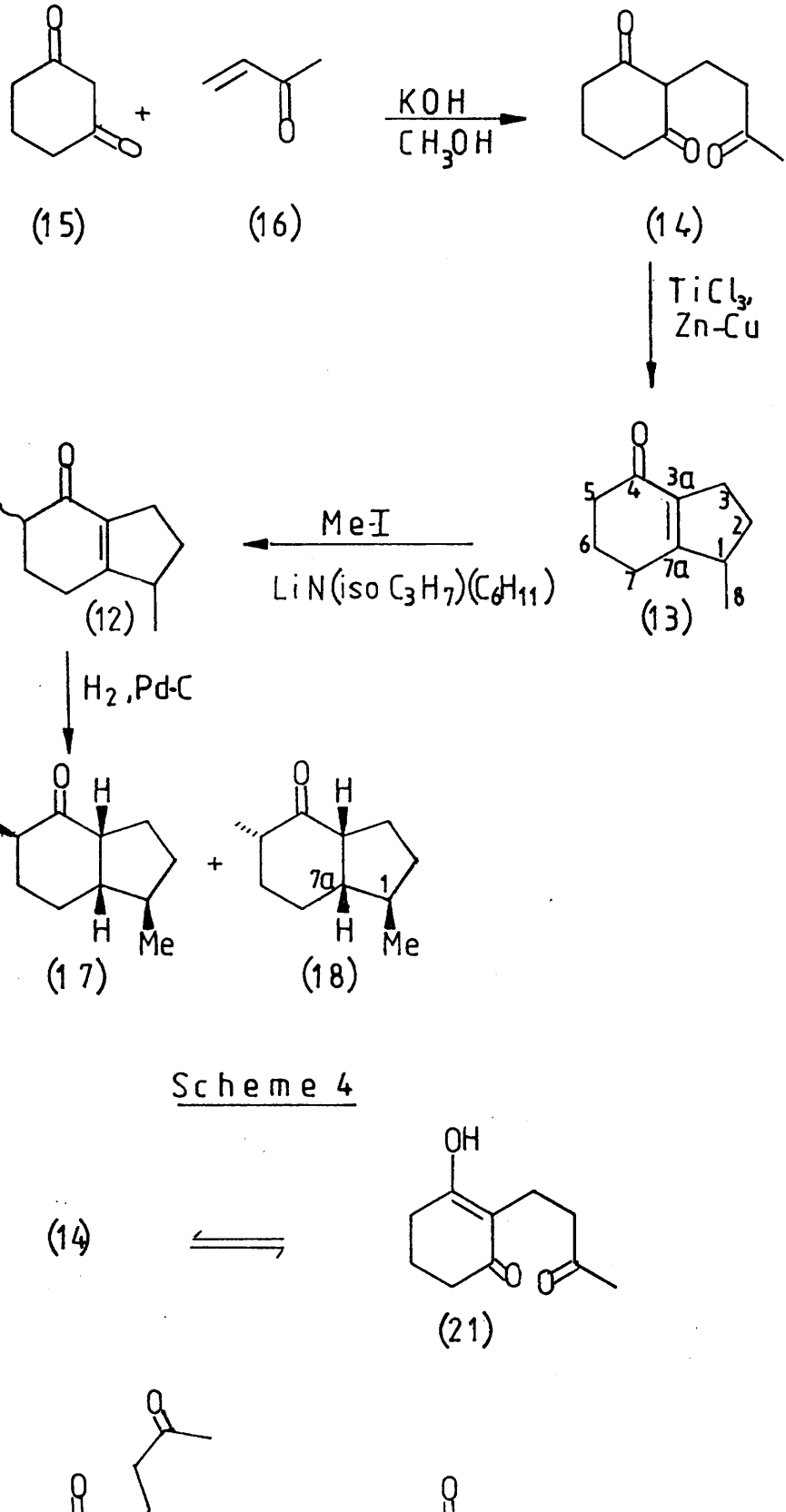
The occurrence of similar unusual terpenoids found in both the liverworts and marine organisms perhaps has some significance in terms of the evolutionary origin of liverworts.

Biogenesis of Tamariscol

Tamariscol (6) possesses an unusual carbon skeleton of which (9) is the only other example recorded. No suggestion has been made in the literature concerning the biogenesis of the novel carbon framework of (9). However the skeleton is easily derived from rearrangement of a caryophyllene derivative (Scheme 1). This pathway is supported by the presence of β-caryophyllene in the Frullaniaceae[8], although it has not been observed in *F. tamarisci*.

Work by Connolly and Wickremesinghe[9] revealed that ruthenium tetroxide/periodate oxidation of tamariscol afforded the ketone (10) with the relative configuration as shown. This chapter is concerned with a synthetic approach to the bicyclic system of tamariscol.

Scheme 3



Scheme 4

DISCUSSION

Retrosynthesis (Scheme 2) suggested the ketone (11) as an intermediate in the synthesis of the bicyclic system of tamariscol (6). Subjection of the triketone (14) produced by reaction of 1,3-cyclohexanedione (15) with methyl vinyl ketone (16) to the McMurry reaction (see page 34) was expected to give the enone (13). Methylation should give two products : the cis and trans isomers of (12). It was difficult to predict the results of hydrogenation of (12). In the event, the hydrogenation exhibited considerable stereoselectivity and interpretation was facilitated by comparison with authentic tamariscol degradation products.

The first stage in the synthesis involved a Michael addition of 1,3-cyclohexanedione (15) to methyl vinyl ketone under basic conditions to give the monoalkylated product (14). T.l.c. showed the presence of a less polar product which proved very difficult to purify. Spectroscopic methods failed to reveal its identity. The dialkylated product (19) or the product of an internal aldol condensation (20) seem most likely candidates.

The dark orange solution from the Michael reaction was dissolved in sodium hydroxide and filtered, which removed some of the impurity. Workup and purification by flash chromatography yielded the triketone (14), m.p. 109-110°.

The n.m.r spectra of (14) were very broad and difficult to interpret. The presence of a tautomeric mixture of (14) and (21), (Scheme 4) would account for such spectra.

The ^{1}H n.m.r showed the presence of an enolic hydroxyl at

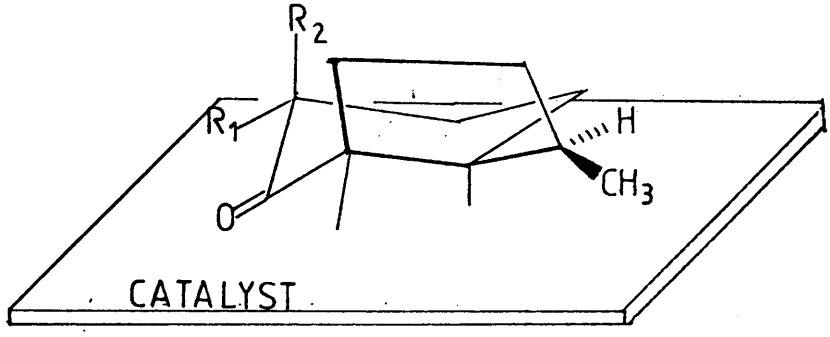
δ_H 9.7 (br) and a methyl ketone at δ_H 2.14 (s) as well as other broadened multiplets at δ_H 2.7, 2.32, 1.89 and 1.87. Its ^{13}C n.m.r confirmed the presence of a tautomeric mixture and featured both saturated and unsaturated ketones at δ_C 211.9 and 198.5 respectively, along with an olefinic system at δ_C 113.7 and 110.1. The IR spectrum showed a hydroxyl at 3300 cm^{-1}, along with a ketone at 1700 cm^{-1} and an enone at 1645 and 1620 cm^{-1}. Mass spectrometry gave the molecular ion as the base fragment (m/z 182 $C_{10}H_{14}O_3$).

A McMurry reaction (see page **34**) was used to couple reductively the two carbonyl groups in (14) to give the hydroinden-4-one (13) [ν_{max} 1660, 1635 cm^{-1}] whose structure followed readily from its spectroscopic properties. Its mass spectrum confirmed the molecular formula with the base peak at m/z 150 ($C_{10}H_{14}O$). The ^1H n.m.r spectrum was complex due to second order effects but included resonances for H-1 [δ_H 1.09(d, J 7.1 Hz)]. The ^{13}C n.m.r showed the expected distribution of carbons including the enone system [δ_C 198.4, 169.0 and 136.8 (all s)].

The hydroinden-4-one (13) was methylated using lithium N-isopropylcyclohexylamine and methyl iodide in THF at 0^oC to give an inseparable 1:1 mixture of <u>cis</u> and <u>trans</u> diastereoisomers of (12). Capillary g.c. of the methylated product showed only one peak but it was clear from both the ^1H and ^{13}C n.m.r spectra that two diastereoisomers were formed. In the ^1H spectrum signals for four secondary methyls were apparent [δ_H 1.13, 1.12, 1.09 and 1.08, (all d, J 7 Hz)].

The last stage in the construction of the bicyclic ring system of tamariscol was the hydrogenation of the double bond of (12).

Fig.1



(17) $R_1 = CH_3$; $R_2 = H$

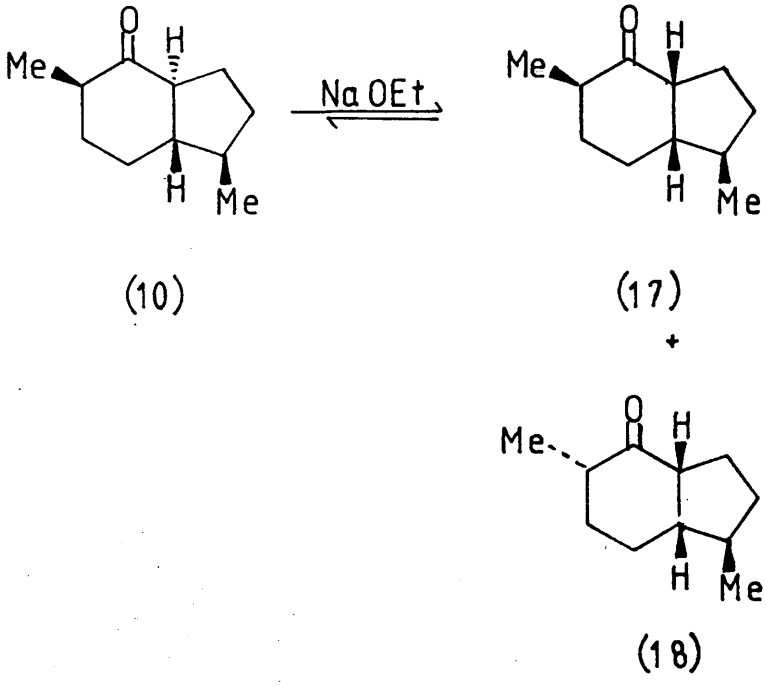
(18) $R_1 = H$; $R_2 = CH_3$

The hydrogenation of α,β-unsaturated enones , see Chapter 2 page 41 is dependent on the stability of the tetrahedral intermediate, attached in either a 1,2 or 1,4 fashion to the catalyst, at slow rates of agitation and atmospheric pressure. In the case of (12) it was difficult to predict which face of the molecule would be initially adsorbed on the catalyst. However, from molecular models, it can be seen that the isomer attached tetrahedrally to the catalyst with the secondary methyl group of the cyclopentane on the adsorbed face would suffer less steric conjestion than that in which the same methyl was on the opposite face, irrespective of whether the methyl at C-5 was cis or trans. It is therefore reasonable to suggest that isomers (17) and (18) would be produced. Fig. 1 shows isomers (17) and (18) attached to the catalyst surface in one of the two possible conformations.

The hydrogenation of (12), carried out in methanol, hexane or ethyl acetate afforded two products (17), (18) by capillary g.c. hence confirming that the hydrogenation was stereoselective and occurred on only one face of the molecule. The ^{1}H n.m.r spectrum was complex and could not be used to confirm the stereochemical assignments made for (17) and (18), but clearly showed the presence of four secondary methyls at [δ_H 1.05, 0.98, 0.93 and 0.87 (all d, J 7.1 Hz)]. The ^{13}C confirmed that only two diastereoisomers were present with 2 singlet, 8 doublet, 8 triplet and 4 quartet resonances. The IR spectrum showed a saturated ketone absorption at 1708 cm^{-1} and the molecular formula was confirmed by mass spectrometry (m/z 166 $C_{11}H_{18}O$).

Work on tamariscol carried out simultaneously by Connolly and Wickremesinghe[9] further supported the claim that hydrogenation

Scheme 5



(10) (17) + (18)

does occur as indicated to give (17), (18). A sample of tamariscol was oxidised by ruthenium tetroxide and periodate to yield (10) with the relative configuration shown. ^{1}H, ^{13}C n.m.r and capillary g.c confirmed (10) as the only product. Equilibration of (10) in base for two days afforded two major compounds, one of them unchanged (10), and a minor compound. It is known that for hydrindanones the cis-fused ring system is generally more stable, thus the cis-isomer (17) (Scheme 5) should be the other major product of equilibration of (10). A CO-injection of the base-equilibrated product of (10) and compounds (17) and (18) was carried out. This showed an overlap of one of the main peaks of the equilibrated mixture i.e. structure (17, Scheme 5) with one of the products from the hydrogenation reaction. Confirmation of the presence of (17) in both the equilibrated mixture of the tamariscol oxidation product (10) and the hydrogenated synthetic mixture was obtained by comparison of their ^{13}C n.m.r spectra. These chemical shifts are listed in Table 1. It is clear that the equilibrated mixture contains both the original trans isomer (10) and the more stable cis-isomer (17). The cis-isomer (17) is also clearly present in the hydrogenation mixture along with a second product which should have structure (18).

The trans stereochemical assignment of H-7a and H-1a in compound (10) supports ^{1}H n.m.r evidence that these protons are trans in natural tamariscol.

TABLE 1.

m	(10)	Equilibration of (10) (17) cis	(10) trans	Hydrogenated Product (17)	(18)
s	212.4	214.0	212.5	213.9	216.5
d	58.0	53.2	58.1	53.1	54.6
	57.1	51.2	57.2	51.2	48.8
	47.7	44.8	44.8	44.8	40.6
	40.5	34.9	40.5	34.9	38.6
t	37.7	32.1	37.3	32.0	34.3
	31.7	31.8	31.7	31.8	30.3
	29.2	29.7	29.2	29.7	28.0
	20.9	24.3	20.9	24.2	21.8
q	18.2	18.4	18.2	18.4	15.0
	14.1	14.7	14.1	14.7	14.6

EXPERIMENTAL

2-(3-oxo-butanyl)-cyclohexane-1,3-dione (14)

Cyclohexane-1,3-dione (15) (5g, 45mmol) was dissolved in methanol (30 ml) and potassium hydroxide (0.4g) in methanol and finally methyl vinyl ketone (16) (4.4 ml, 55 mmol) added and the solution refluxed for 3 hours. Basification with sodium hydroxide (10ml, 2.5M) afforded a dark green solution which was filtered and acidified to pH4 by bench hydrochloric acid (5M). The acidic solution was extracted into chloroform (3 x 50ml), washed with water (3 x 50ml) dried, filtered and the solvent evaporated under vacuum. Flash chromatography using chloroform/ methanol as eluent yielded the triketone (14) (3.2g, 40%), m.p. 109-110°C. ν_{max} 3300, 1700, 1645 and 1620 cm^{-1}.

The n.m.r spectra were broad and difficult to interpret because of the presence of both the triketone (14) and its tautomer (21).

δ_H : 9.7 (s, -OH), 2.70 (br s), 2.32 (br) 2.14 (s, $-C-CH_3$), 1.89 (br), 1.87 (br).

δ_C : 211.9 (s), 198.5 (s), 174.3 (s), 113.7 (s), 110.1 (s), 42.2 (t), 35.1 (t), 31.2 (t), 29.0 (t), 28.5 (q), 20.0 (t).

M.S : m/z^+ 182, 19.9% ($C_{10}H_{14}O_3$ requires 182).

1-Methyl-2,3,4,5,6,7-hexahydro-4H-indene-4-one (13)

Distilled D.M.E. (250ml) was added to a three neck round bottom flask purged with dry nitrogen. Titanium trichloride (6.2g, 40mmol) was added, quickly follwed by one equivalent of Zn-Cu (6.1g). The suspension was refluxed under dry nitrogen for one hour. Triketone (14) (0.35g, 2 mmol) in D.M.E. (30ml) was added over an 8 hour period via a syringe pump and the reaction refluxed for 12 hours. Additional tricarbonyl compound (2 mmol) in D.M.E (30ml) was added over 8 hours followed by a further 12 hour period of reflux. The reaction mixture was then cooled to room temperature, filtered and the D.M.E. evaporated under vacuum.

The residual oil was added to water (50ml), extracted with chloroform (3 x 50ml). The chloroform solution washed with water (1 x 50ml), brine (1 x 50ml) and water (1 x 50ml), and dried. Removal of solvent afforded an oil which was purified by flash chromatography to give the hydrindenone (13) (280mg, 48%) as an oil ν_{max} 1660 and 1635 cm^{-1}.

δ_H : 2.81 (m, -CH-CH_3), 1.09 (d, J 7.1 Hz, -CH-CH_3)

δ_C : 198.4 (s), 169.0 (s), 136.8 (s), 43.6 (d), 37.6 (t), 31.0 (t), 27.6 (t), 24.6 (t), 23.5 (t), 18.3 (q).

M.S : m/z 150, 53.4% base peak, ($C_{10}H_{14}O$ requires 150).

1,5-Dimethyl-2,3,4,5,6,7-hexahydro-4H-inidene-4-one (12)[10]

To a stirred solution of N-isopropylcyclohexylamine (0.51ml, 3.1 mmol) in THF (25ml) at -78°C (dry ice/acetone) under dry nitrogen was added BuLi (2.2ml, 3.1 mmol, 1.5M in hexane) and the solution stirred for 30 minutes. The hydroindene (13) (0.47g, 3.1 mmol) was added to give a yellow solution. The solution was allowed to warm to room temperature, excess methyl iodide added and the reaction left to stir overnight. Water (10ml) was added and most of the THF evaporated under vacuum. The organic product was extracted into chloroform and the usual workup followed by purification by flash chromatography afforded an inseparable mixture of the enones (12) (0.37g, 73%) ν_{max} 1667, 1638 cm^{-1} as a volatile oil.

δ_H : The spectrum shows four secondary methyl doublets due to the two diastereomeric products at 1.13, 1.12, 1.09 and 1.00 (J = 7.0 Hz)

δ_C : 167.6 (s), 136.2 (s), 44.0 (d), 43.4 (d), 41.2 (d), 41.1 (d), 31.6 (t), 31.5 (t), 31.3 (t), 31.2 (t), 27.7 (t), 27.68 (t), 24.3 (t), 23.5 (t), 18.4 (q), 18.3 (q), 15.2 (q), 15.0 (q).

M.S : m/z 164 ($C_{11}H_{16}O$ requires 164).

G.C. Capillary G.C was unable to separate the diastereomers and only one peak was observed.

1,5-Dimethyl-4-hydrindanone (17), (18).

The enone (12) (40mg, 0.25 mmol) was dissolved in hexane (10 ml) and 10% Pd-C (4mg) added. The mixture was slowly stirred under a hydrogen atmosphere for 2 hours. Filtration and evaporation afforded the hydrindanones(17) and (18) as an inseparable mixture (0.38mg, 96%) ν_{max} 1708 cm^{-1}.

The experiment was repeated using methanol and ethyl acetate as solvents and the rate of agitation was also altered, but in each case the same product distribution was observed.

δ_H : 1.05, 0.98, 0.93, 0.87 (four secondary methyls, J 7.1 Hz).

δ_C : 216.5 (s), 213.9 (s), 54.6 (d), 53.1 (d), 51.2 (d), 48.8 (d), 44.8 (d), 40.6 (d), 38.6 (d), 34.9 (d), 34.3 (t), 32.0 (t), 31.8 (t), 30.3 (t), 28.0 (t), 24.2 (t), 21.8 (t), 21.9 (t), 18.1 (q), 15.0 (q), 14.7 (q), 14.6 (q).

The ^{13}C n.m.r shifts could be assigned to two isomers (17), (18) by comparison with the shifts of the equilibrated ketone (10) see Table 1.

M.S : m/z 166 ($C_{11}H_{18}O$ requires 166).

Equilibration of the 1,5-dimethyl-4-hydrindanone (10) obtained from the oxidation of tamariscol[9] (6).

A catalytic amount of sodium was added to absolute ethanol (1 ml). After the hydrogen evolution had ceased, the hydrindanone (10) (20mg) in absolute ethanol (2 ml) was added and the reaction mixture stirred for 48 hours at room temperature. It was then diluted with water (5 ml) and extracted with pentane (3 x 10 ml). The combined organic layers were washed with aqueous NH_4Cl (1 x 30 ml), aqueous $NaHCO_3$ (1 x 30 ml), brine (1 x 30 ml), dried and the solvent evaporated under vacuum to give an inseparable mixture of the trans (10) and cis (17) diastereomers in a ratio (10) : (17) of 2:3.

δ_H : 1.01, 0.98, 0.93, 0.89 (four secondary methyls J 7.0 Hz).

δ_C (see Table 1).

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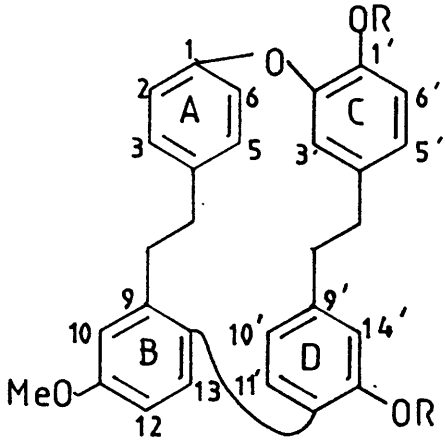
CHAPTER 4

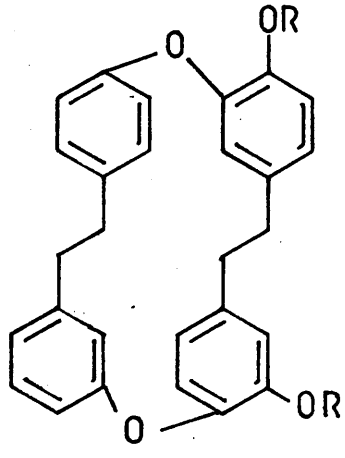
PAKYONOL, A MACROCYCLIC BISBIBENZYL DIETHER FROM THE LIVERWORT *Mannia fragrans*.



(1) R=H

(2) R=Ac

(3) R=Me



(4) R=H

(5) R=Ac

(6) R=Me

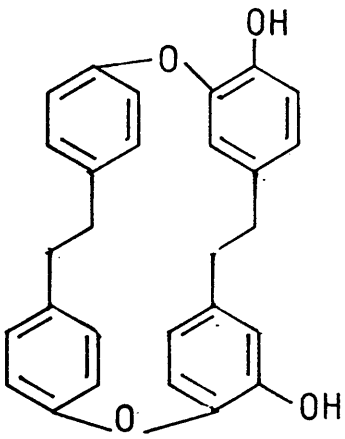
INTRODUCTION

Bisbibenzyls from the Hepaticae

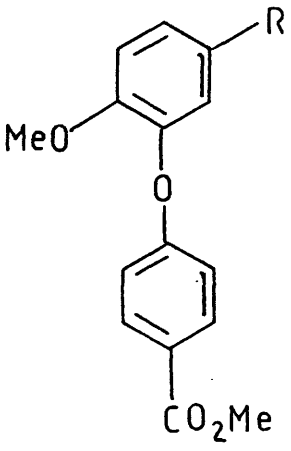
Several new classes of bisbibenzyls have recently been isolated from the orders of the Marchantiales and Metzgeriales Hepaticae. In the course of investigation of the chemical constituents of *Marchantia* (Marchantiales) and *Riccardia* (Metzgeriales) species, Asakawa and co-workers found that some of these species produced characteristic cyclic bis(bibenzyls) as major constituents.

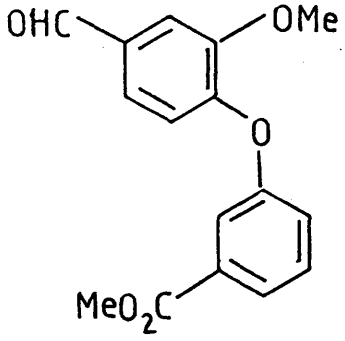
THE RICCARDINS

In 1983 two structurally unique cytotoxic cyclic bis(bibenzyls) riccardin A (1) and riccardin B (4a) were isolated from *Riccardia multifida*.[1] The former, $C_{29}H_{26}O_4$ (m/z 438.2) ν_{max} 1605, 1560 and 1500 cm^{-1}; λ_{max} 238 nm had ^1H n.m.r resonances for four benzylic methylenes, a methoxyl group, two phenolic hydroxyls, three meta coupled protons (H-3', H-10, H-14'), one of which (H-3') was shielded strongly by ring A, three sets of ortho protons in which three (H-5', H-10' and H-12) were coupled to meta protons (H-3', H-14' and H-10) and an additional two sets of ortho protons (H-2 , H-3 , H-5 and H-6). The presence of the phenolic hydroxyls were confirmed by acetylation to give (2). Since the IR spectrum of the trimethyl ether (3) showed no carbonyl absorption the fourth oxygen had to be an ether. N.O.E experiments on (3) revealed 15% enhancements between the C-1' methoxyl group and H-6', the C-13' methoxyl group and H-14', and the C-11 methoxyl group and H-10 and H-12. The structure of riccardin A was eventually established as (1) by X-ray analysis of the acetate (2). Spectroscopic and chemical evidence showed that riccardin B (4a) was a cyclic bisbibenzyl with two phenolic hydroxyl groups and two bibenzyls linked



(4 b)





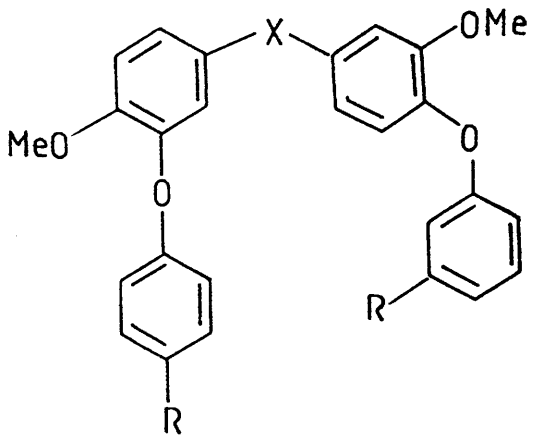
(8)

(7) R = CHO

(9) R = CH_2OH

(10) R = CH_2Br

(11) R = $CH_2^{\oplus}PPh_3^{\ominus}Br$



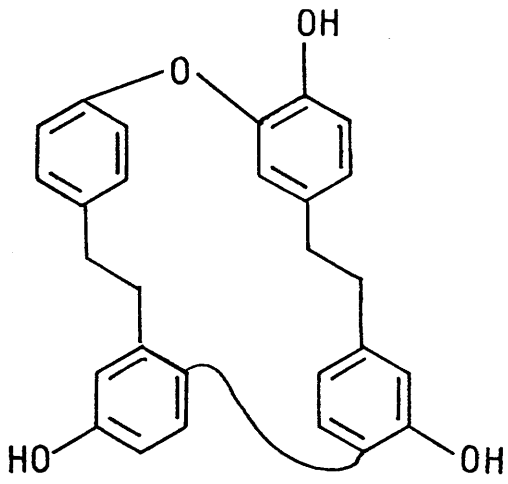
(12) X = CH=CH R = CO_2Me

(13) X = CH_2CH_2 R = CH_2OH

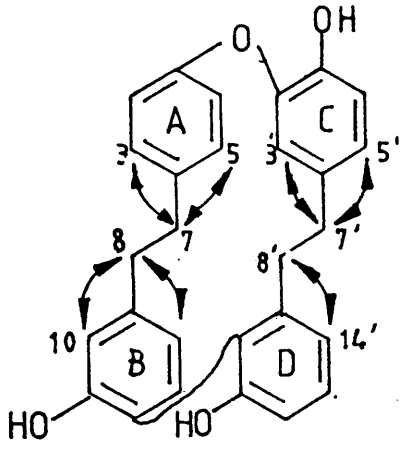
(14) X = CH_2CH_2 R = CH_2Br

through ether oxygens. Double resonance experiments, long-range coupling and N.O.E. experiments indicated the presence of two 1,2,4 trisubstituted benzene rings along with meta and para disubstituted benzene rings. Since ^{1}H n.m.r spectra of (4a), its acetate (5) and its methyl ether (6) resembled those of riccardin A it was suggested that the additional ether oxygen might be linked between C-12' and C-14 in place of the biphenyl bond in (1). The alternative structure (4b) also fits the spectroscopic data. The constitution as in (4a) was preferred for riccardin B on the basis of its co-existence with riccardin A. Synthesis of the dimethyl ether (6) by Nógrádi and co-workers proved constitution (4a) to be correct.[2] In the synthesis, Ullman coupling of methyl 4-bromobenzoate and isovanillin dimethyl ether in pyridine in the presence of CuO gave, after hydrolysis, the diphenyl ether (7). Similar coupling of methyl 3-bromobenzoate and vanillin dimethyl acetal provided (8). Reduction of the aldehyde with $NaBH_4$ gave the alcohol (9) which, on treatment with HBr, yielded the benzyl bromide (10). This was converted to the Wittig salt (11) by refluxing with Ph_3P. Wittig reaction of (11) and (8) gave a mixture of stilbenes (12) which after hydrogenation and $LiAlH_4$ reduction gave diol (13). This was treated with PBr_3 to give the dibromide (14). Intramolecular Wurtz reaction of (14) gave a product which was identical with riccardin B di-o-methyl ether (6).

A further cytotoxic bisbibenzyl in this series, riccardin C (15), was isolated from the Japanese liverwort *Reboulia hemisphaerica* (Marchantiales).[3] The trimethyl ether (3) was identical with the

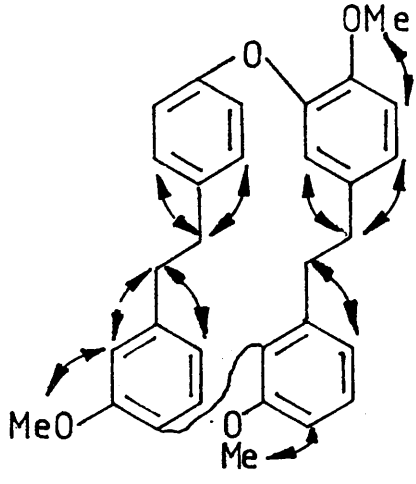


(15)



N.O.E.s

(16)



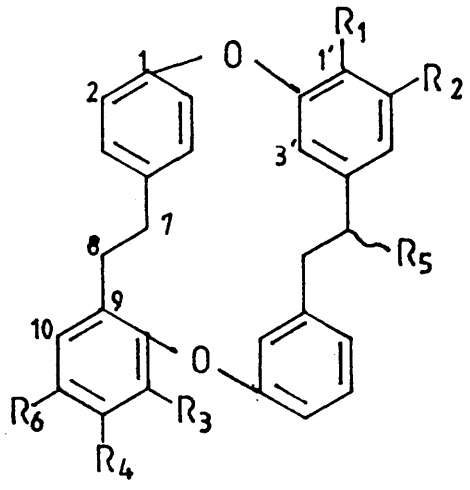
(17)

dimethoxy derivative of riccardin A. Thus riccardin C is the dimethoxy derivative of riccardin A.

The isomeric isoriccardin C (16) was isolated from the Indian *Marchantia palmata*.[4] Chemical and spectral data indicated that isoriccardin C was a cyclic bisbibenzyl possessing three phenolic hydroxyls, a biphenyl ether and a biphenyl linkage as in riccardins A (1) and C (15). The arrangement of the substituents on the four benzene rings was established by a combination of N.O.E experiments on (16), and the trimethoxy derivative (17). Thus in (16) N.O.E's were observed between (i) H-7 and H-3, -5 (ii) H-8 and H-10, -14 (iii) H-7' and H-3', H-5' and (iv) H-8' and H-14'. N.O.E experiments on (17) assigned the position of the phenolic hydroxyls. N.O.E's were observed between (i) the C-11 methoxyl group and H-10 (ii) the C-1 methoxyl group and H-6' and (iii) the C-11' methoxyl group and H-12'.

THE MARCHANTINS

Of the three Marchantiaceae genera *Dumortiera, Pressia* and *Marchantia*, it is only from the last that cyclic bisbibenzyls have been isolated. Asakawa reported the isolation of several Marchantins in 1983.[5] The structure of marchantin A (18) from *M. polymorpha, M. paleacea* and *M. tosana* was established by both chemical degradation and X-ray crystallographic analysis of the corresponding trimethyl ether (19). Unfortunately these techniques cannot be used for other members of this class because they tend to be non-crystalline and present only in small amounts. The structural elucidation of the marchantins in general was carried



(18) $R_1 = R_2 = R_3 = OH$ $R_4 = R_5 = R_6 = H$

(19) $R_1 = R_2 = R_3 = OMe$ $R_4 = R_5 = R_6 = H$

(20) $R_1 = R_2 = R_3 = R_4 = OH$ $R_5 = R_6 = H$

(21) $R_1 = R_3 = OH$ $R_2 = R_4 = R_5 = R_6 = H$

(22) $R_1 = R_2 = R_3 = OMe$ $R_4 = R_6 = H$ $R_5 = OH$

(23) $R_1 = R_3 = R_4 = OH$ $R_2 = R_5 = R_6 = H$

(24) $R_1 = OH$ $R_6 = OMe$ $R_2 = R_3 = R_4 = R_5 = H$

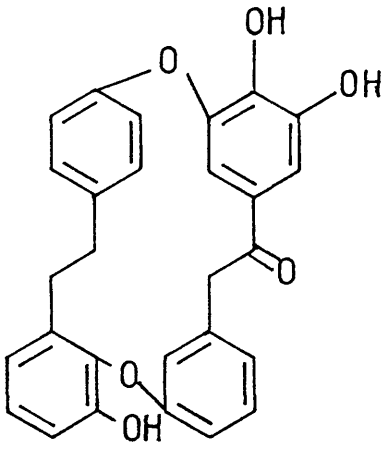
(25) $R_1 = R_2 = R_3 = OH$ $R_4 = R_6 = H$ $R_5 = OMe$

out by the complete assignment of the ^{1}H and ^{13}C n.m.r spectra using N.O.E. difference experiments, ^{13}C-^{1}H correlation and long-range proton selective decoupling (LSPD) experiments.

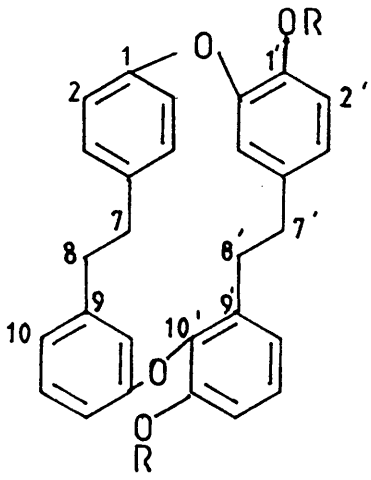
The assignment of the ^{1}H n.m.r spectrum of marchantin A (18) was carried out using double resonance and N.O.E. experiments. As in the riccardin series the most characteristic signal, H-3', is strongly shielded by ring A. In (18) this occurs at δ 5.13 (d, J = 2 Hz), with the other protons being identified from the ^{13}C-^{1}H correlation spectrum. The aromatic and benzylic protons were assigned using LSPD experiments.

The three *Marchantia* species that yielded marchantin A (18) as the major component also contained marchantins B (20), C (21) and D (22) as minor products. Marchantins H (23) and I (24) were isolated from *Plagiochasma intermedium* and *Riccardia multifida* respectively. Structural elucidation was carried out by the combination of techniques discussed above. Marchantins E (25) and G (26)[5] were isolated from both *M. polymorpha* and *M. palmata* species.

A further addition to the series, isomarchantin C (27), was isolated by Asakawa in 1987.[4] The spectroscopic data of (27) and its methyl ether (28) were similar to those of marchantin C (21), though the substitution pattern appeared to be different. Significantly the H-3' resonance, normally strongly shielded, was shifted downfield by 0.5 ppm to δ_H 6.08 ppm. The substitution pattern of the rings was established in a similar manner to that for isoriccardin C (16) and its trimethyl ether (17) by use of extensive double resonance and N.O.E experiments.

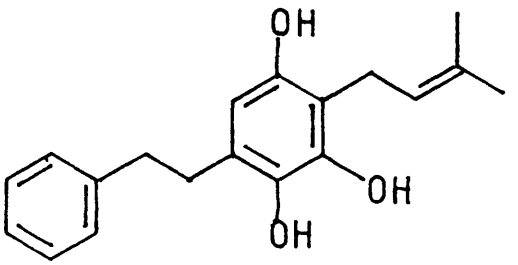


(26)

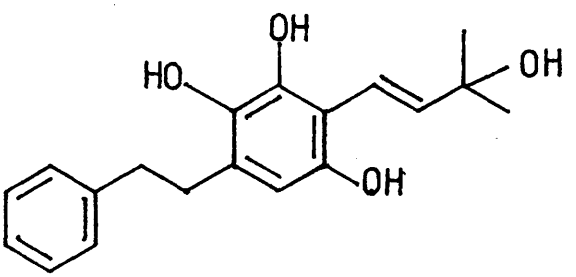


(27) R=H

(28) R=Me



(29)



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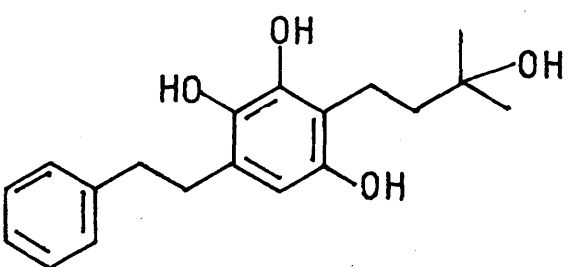

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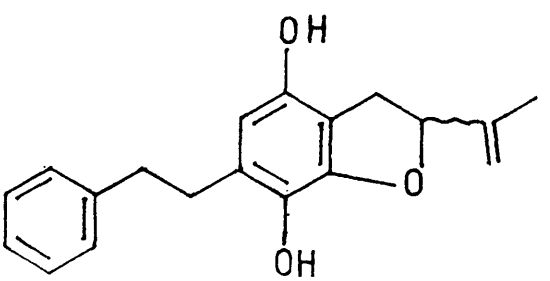


(32)

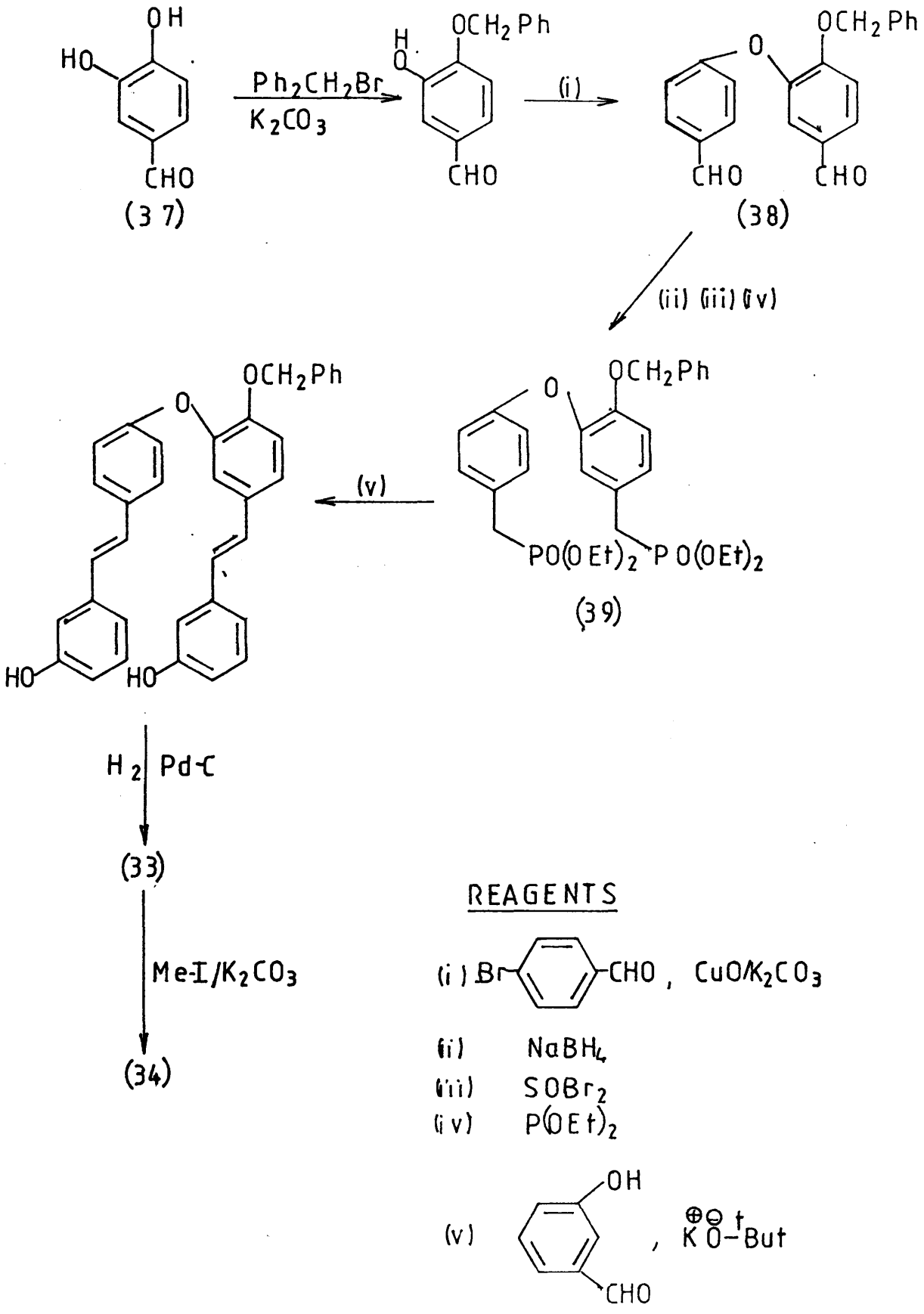
THE PERROTTETINS

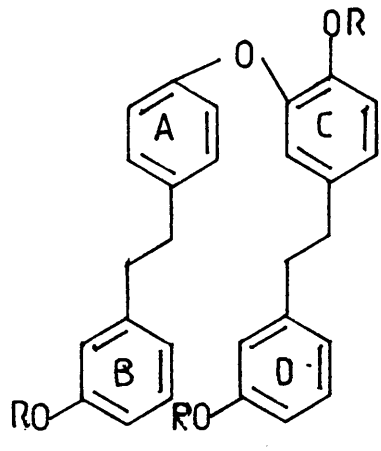
Perrottetins A-D (29)-(32), four novel prenyl bibenzyls from *Radula perrotteti* were isolated in 1982.[6] Further work permitted the full characterisation of cytotoxic bisbibenzyl ethers, perrottetins E (33), F (35) and G (36). A total synthesis of perrottetin E was reported in 1985.[7]

The ^{1}H n.m.r spectrum of (33), $C_{28}H_{26}O_4$, was similar to those of the macrocyclic marchantin series but the degree of unsaturation of (33) was one fewer than that of marchantin A (18). Decoupling and N.O.E. experiments revealed the presence of four benzene rings, one 1,4-disubstituted, one 1,2,4 trisubstituted and two 1,3 disubstituted. N.O.E. experiments on the methyl ether (34) were used to assign the position of the phenolic hydroxyl groups. However, the results were difficult to explain. When the higher field benzylic protons were irradiated N.O.E s were observed which could account for both substitution patterns (I) and (II) of ring C, (Fig. 1).

In order to determine the correct structure a total synthesis of (33) was undertaken (Scheme 1). Mono protection of 3,4 dihydroxy benzaldehyde (37) with benzyl bromide followed by Ullman coupling, in the presence of CuO, with p-bromobenzaldehyde produced the dialdehyde ether (38). The diphosphonate (39), prepared in several steps, was condensed in a Wittig reaction with m-hydroxy-benzaldehyde to give the stillbene ether (40). Hydrogenation afforded perrottetin E, identical to the natural product. From the ^{1}H n.m.r spectrum of perrottetin F (35) it was apparent that one of the benzene rings (C) contained an additional hydroxyl group

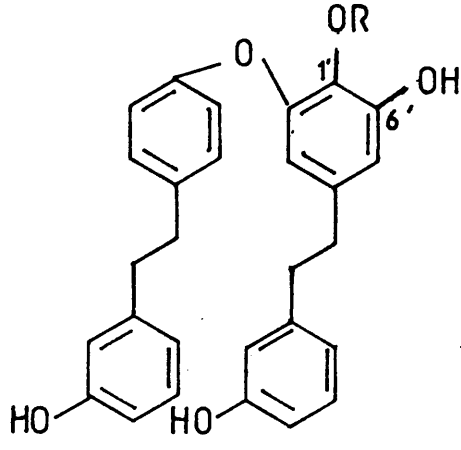
Scheme 1


OH
HO
CHO
(37)
Ph2CH2Br
K2CO3
OCH2Ph
H
O
CHO
(i)
OCH2Ph
O
CHO
CHO
(38)
(ii) (iii) (iv)
OCH2Ph
O
PO(OEt)2
PO(OEt)2
(39)
(v)
OCH2Ph
O
HO
HO
H2 Pd-C
(33)
Me-I/K2CO3
(34)
REAGENTS
(i) Br
CHO
, CuO/K2CO3
(ii) NaBH4
(iii) SOBr2
(iv) P(OEt)2
(v)
OH
CHO
, K O-But



(33) R = H

(34) R = Me



(35) R = H

(36) R = Me

relative to perrottetin E. Double resonance and N.O.E experiments revealed that the 1' and 6' positions were hydroxylated, since irradiation of the benzylic methylenes gave enhancements of the mutually coupled protons H-3' (d, J = 2 Hz) and H-5' (d J = 2 Hz).

The related bisbibenzyl perrottetin G (36), contained a methoxyl group. Permethylation afforded a product identical with the methyl ether derivative of perrottetin F (35). The position of the methoxyl group was established as C-1' by N.O.E. experiments (no enhancements).

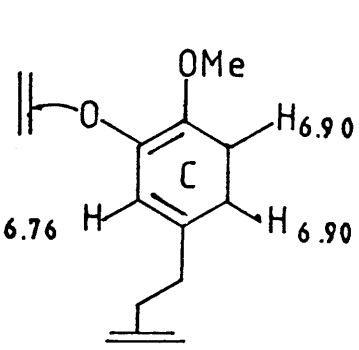
TAXONOMY

On the basis of the presence of common cyclic bisbibenzyls it has been suggested that the three *Marchantia* species, *M. polymorpha* *M. paleacea* and *M. tosana*[5,8] are quite similar. Thus the chemical results support the morphological classification.[9] Recently it has also been suggested that two genera from the Marchantiaceae, *Dumortia* and *Pressia* are not closely allied to *Marchantia* species and that, based on comparative flavanoid chemistry, *Dumortia* belongs to the Wiesnorellaceae.[10] The lack of cyclic bisbibenzyls in *Dumortia* and *Pressia* lend further support to these proposals.

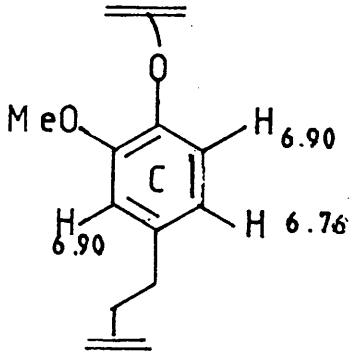
The two genera of the Riccardiaceae, *Aneura* and *Riccardia* do not share similar compounds, the former containing pinguisane-type sesquiterpenoids and the latter the two cyclic bisbibenzyls riccardins A (1) and B (4). These data support the separation, on morphological grounds, of the two genera. Riccardin C (15) has

Fig. 1

Ring C, Compound (34)

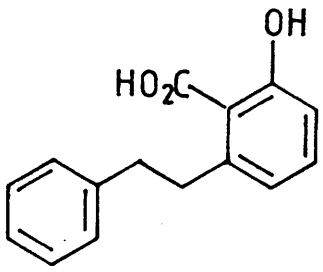


(i)

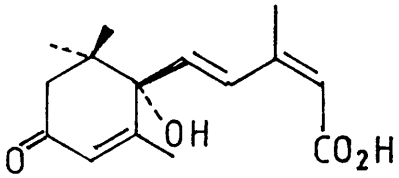


(ii)

[δ's in p.p.m.]

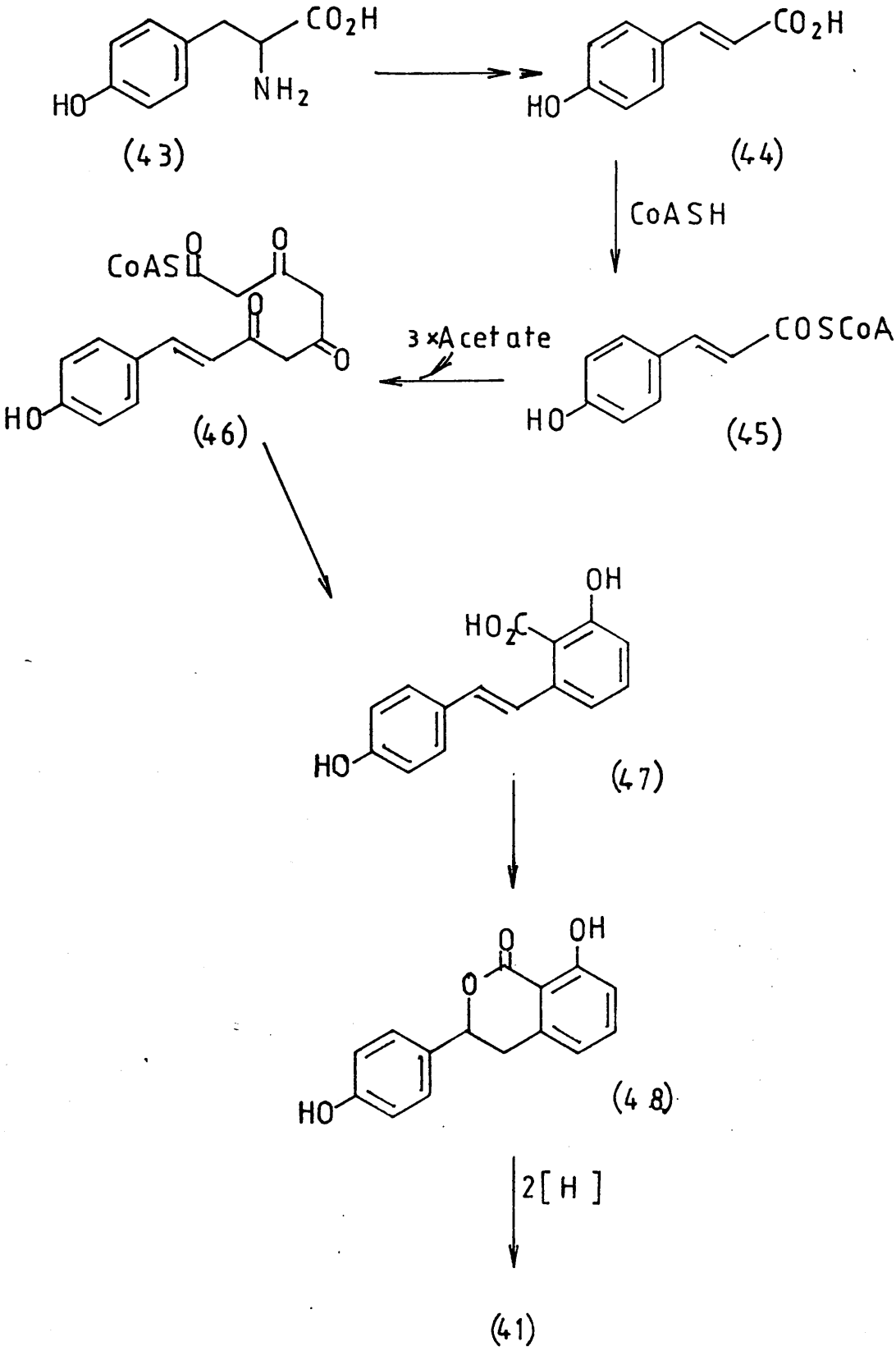


(41)



(42)

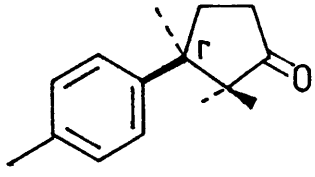
Scheme 2


CO2H
NH2
HO
(43)
CO2H
HO
(44)
CoASH
CoAS
O
O
O
O
HO
(46)
3×Acetate
COSCoA
HO
(45)
OH
HO2C
HO
(47)
OH
O
O
HO
(48)
2[H]
(41)

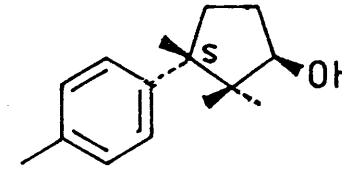
been found in *Reboulia hemisphaerica* (Grimaldiaceae) belonging to the Marchantinales, indicating perhaps some chemical similarity between *Marchantia* and *Riccardia* species.

BIOSYNTHESIS

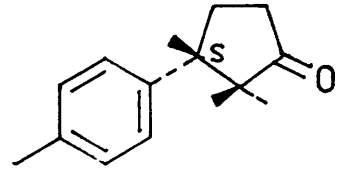
Little work has been done on the biosynthesis of liverwort metabolites. However bisbibenzyls may be synthesised from lunularic acid (41) which is found in abundance in the leafy and thalloid liverworts.[11] Lunularic acid appears to act as a growth regulator in the liverworts, having a similar effect to that of abscisic acid (42) in higher plants. Lunularic acid is probably derived from mixed biosynthetic origins incorporating biogenetic sub-units from both the shikimate and acetate pathways. The biosynthesis (Scheme 2) involves the stereospecific anti elimination of ammonia from tryosine (43) to yield cinnamic acid (44). The reaction if believed to involve an amino acid-ammonium catyla se. After conversion to p-coumaryl-SCoA (45) and condensation with three acetate units the keto compound (46) is further condensed to yield the stilbene (47). Reduction to lunularic acid (41) is presumed to be via intermediate (48). Decarboxylation of (41) followed by phenolic coupling, with another bibenzyl and methylation etc., seems a probable route for the formation of the bisbibenzyl derivatives.



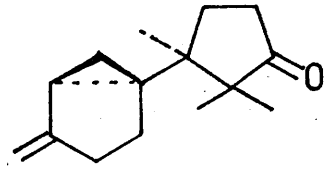
(49)



(50)



(51)



(52)

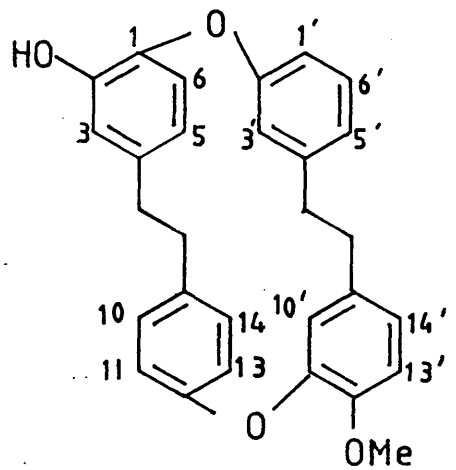
Mannia fragrans

The genus *Mannia* (Marchantiales) in Central Europe consists of three species, *M. pilosa*, *M. tiandra* and the most abundant *M. fragrans*. This intensely scented miniature liverwort was first investigated in 1975 by Huneck and Schreiber[12] who isolated the principal odoriferous component, $C_{15}H_{22}O$ and named it grimaldone, after the old genus name *Grimaldia*. However it was Benesova[13] in 1976 who reported the isolation of (R)-(-)-α-cuparenone (49) from *M. fragrans*. It was identical with (+)-α-cuparenone (51), from the wood of *Thuja orientalis*[14] and also with the oxidation product of α-cuparenol (50) from *Biota orientalis*[15] except in sign of rotation. Thus the ketone (49), $[\alpha]_D^{20}$ - 169.9°, from the liverwort *M. fragrans* is the optical antipode of (+)-α-cuparenone, $[\alpha]_D^{30}$ + 177°.

The structure of grimaldone (52) was reported in 1988[16]. It was isolated from *M. fragrans* collected in Outer Mangolia. The structural elucidation was carried out by means of a single crystal X-ray analysis. Thus grimaldone is (-)-6S, 8R-cyclo-5R-cupar-9 (15) en-2-one (52) a derivative of ent-cuparane.

These two sesquiterpenoids (49), (52) provide further evidence of the ability of liverworts to produce sesquiterpenoids enantiomerically related to those found in higher plants.

In the following discussion the structural elucidation of pakyonol (53) a novel macrocyclic bisbibenzyl diether from *M. fragrans* will be considered.[17] The liverwort, collected by Siegfried Huneck in the Peoples Republic of Korea in the autumn of 1986, lacked the intense scent of grimaldone and is probably of a different

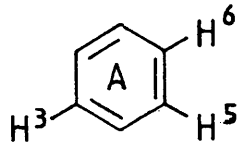


(53)

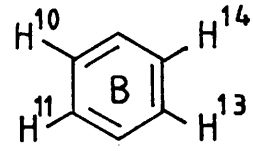
chemotype. From the small amount of plant that was available only one pure constituent was isolated. It was named pakyonol after the place of collection.

DISCUSSION

Chromatography of the ether extract of *M. fragrans* and crystallisation afforded pakyonol (53), m.p. 185-186°C, $C_{29}H_{26}O_4$ [m/z 438.1846 (100%)]. Similarity to a bisbibenzyl diether was apparent after initial inspection of the 200 MHz ^1H and 50 MHz ^{13}C n.m.r spectra. These showed the presence of a phenolic hydroxyl [δ_H 5.28 (exchangeable with D_2O) ; ν_{max} 3565 cm^{-1}], a methoxy group (δ_H 3.91 ; δ_C 56.1), four methylene groups [δ_H 3.07 (4H, br s) and 2.47 (4H, br s) ; δ_C 35.0, 35.4, 39.8 and 40.0] and the remaining fourteen protons distributed round the four aromatic rings. The lack of coupling between the two methylene broad singlets indicated that there must be two independently substituted 1,2 ethanes present and that pakyonol consists of two substituted bibenzyl moieties joined by two ether oxygens to form a macrocyclic structure. As already indicated in the introduction, previous work on the structural elucidation of related compounds relied heavily on X-ray analysis N.O.E. experiments and synthetic confirmation of structure. It was decided, however to utilise a 2D delayed COSY experiment[18] to determine the substitution pattern of pakyonol (53). Such an experiment is useful for detecting small, long-range couplings. This technique had not been applied previously in the structure elucidation of bibenzyls and represents perhaps the most convenient method of obtaining the coupling information needed to determine the substitution



(54)



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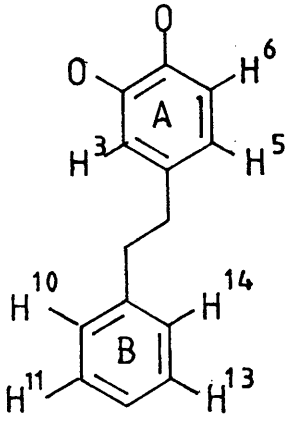

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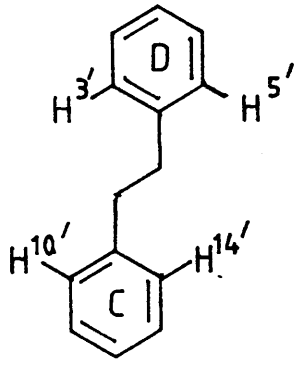

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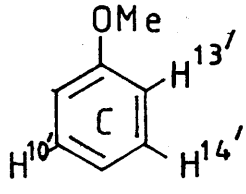

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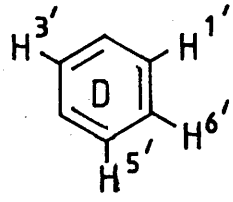


(58)

pattern. A contour plot of the 2D delayed COSY is shown in Figures 2,3. Correlations in ring A (54) were observed between H-3 [δ_H 6.92 (d, J 2.1 Hz)], H-5[δ_H 6.53 (dd, J 8.2 and 2.1 Hz)] and H-6[δ_H 6.79 (d, J 8.2 Hz)] which indicated 1,2,4 trisubstitution of the benzene ring. In ring B (55) which contains the AA'XX' spin system, correlations were noted between H-10, -14 [δ_H 7.12 (J+J' 8.7 Hz)] and H-11, -13 [δ_H 6.96(J+J' 8.7 Hz)] which suggested 9,12 disubstitution. In ring C (57), H-10' [δ_H 6.18 (d, J 2.0 Hz)] H-13' [δ_H 6.83 (d, J 8.1 Hz)] and H-14' [δ_H 6.72 (dd, J 8.1 and 2.0 Hz)] were correlated indicating 9',11', 12' trisubstitution. In ring D (58) correlations were observed between H-1' [δ_H 7.01 (ddd, J 8.3, 2.6 and 1.1 Hz)], H-3' [δ_H 6.15 dd, J 2.6 and 1.5 Hz)], H-5' [δ_H 6.82 (ddd, J 7.3, 1.5 and 1.1 Hz)] and H-6' [δ_H 6.79 (d, J 8.2 Hz)] indicating 2', 4' disubstitution. In addition to this information the delayed COSY also showed correlations between the methylene group at δ_H 3.07 (s) and the aromatic protons H-3, H-5, H-10 and H-14, allowing the assignment of the bibenzyl unit (A-B) (56). The second pair of methylene groups δ_H 2.77 (s), did not show any correlation with the aromatic protons. The methoxyl group δ_H 3.91 was shown to be attached to ring C by its strong correlation with H-13'. No correlation was observed for any other proton, therefore it may be assumed the methoxy is attached to carbon 12'. Thus the delayed COSY has provided sufficient information to permit the assignment of moieties (56), (57) and (58). The location of the phenolic hydroxyl could not be detected by this experiment.

Fig. 2 DELAYED COSY (53)

[6.1 - 7.3 ppm]

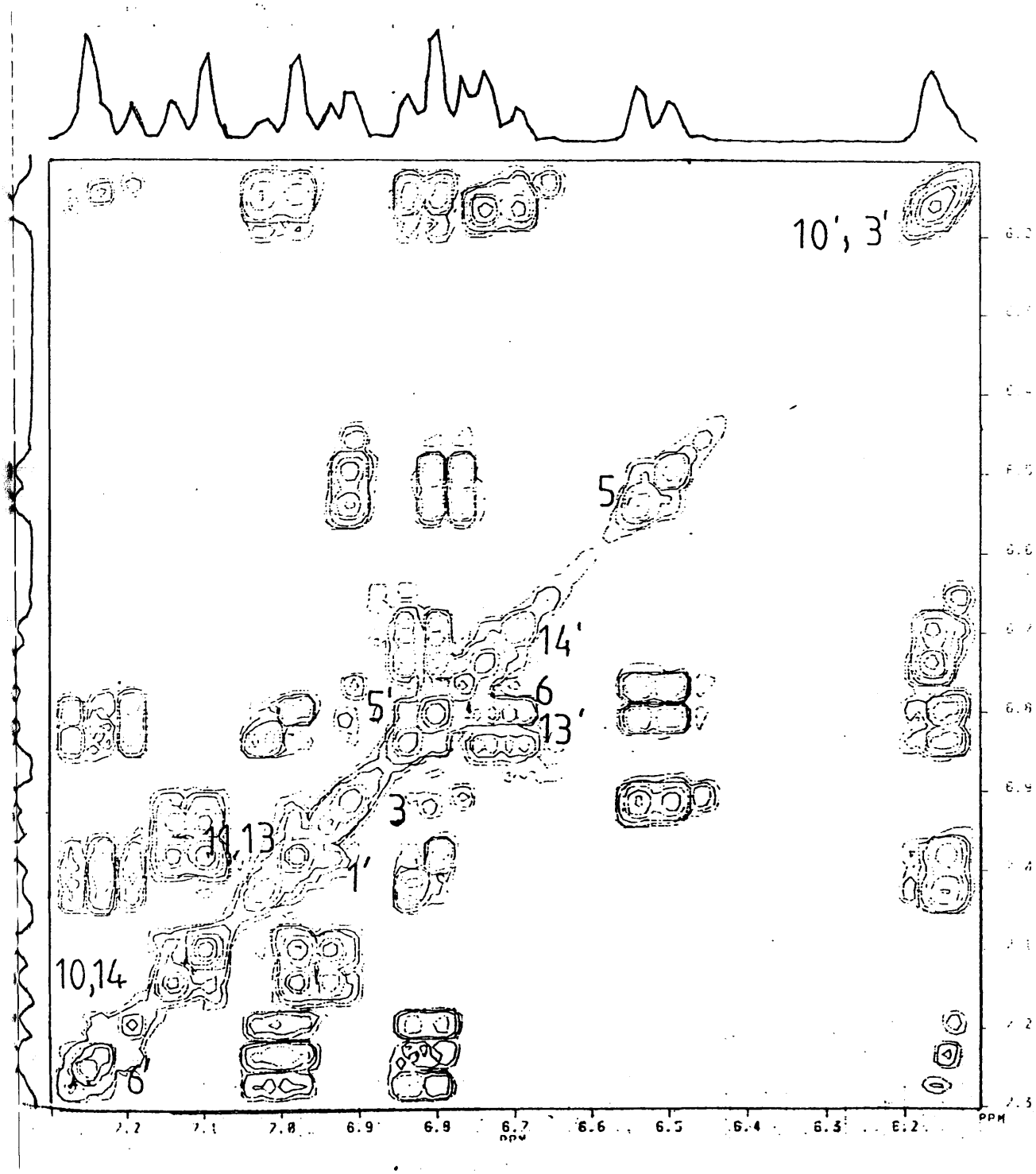
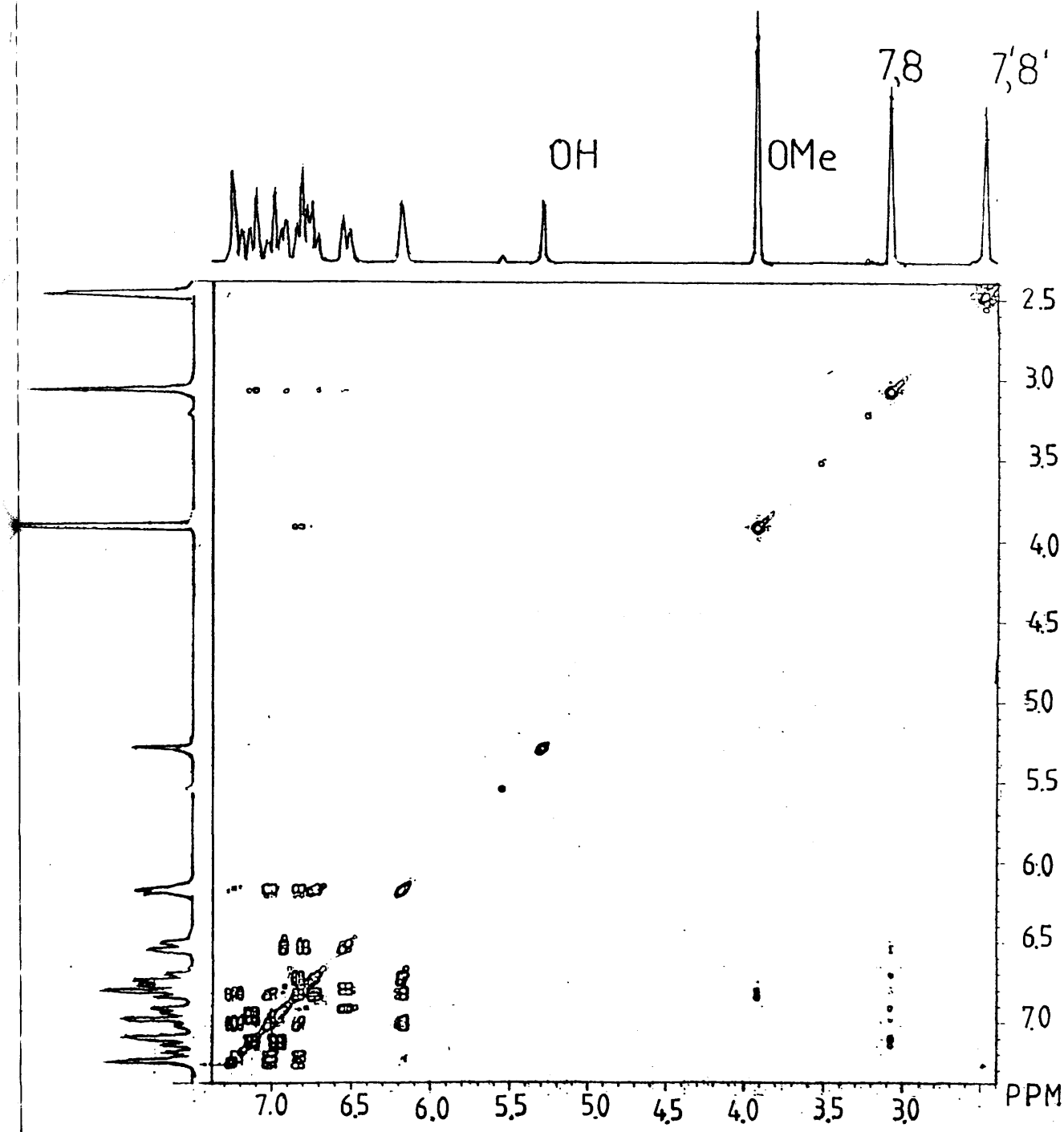
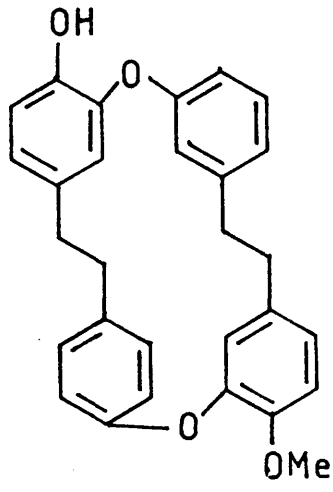


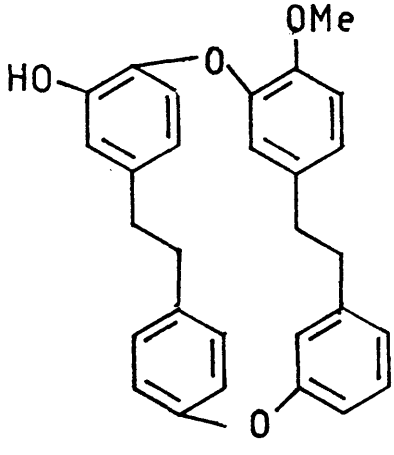
Fig.3 DELAYED COSY (53)

[2.5 - 7.3 ppm]

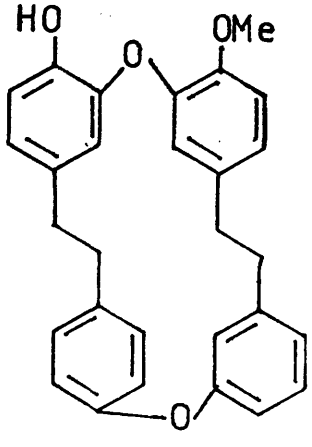




(60)



(61)



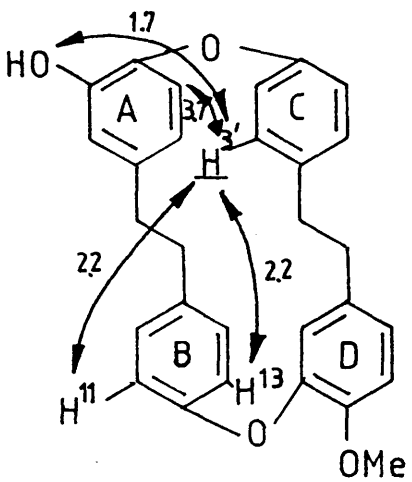
(62)

N.O.E.'s were used to determine the structure of the other bibenzyl moiety (59) and also to confirm the structure of (56). Thus when the methylene signal at δ_H 2.47 (s) was irradiated N.O.E's (%) were detected at H-14' (11.3), H-3' (17.9), H-10' (18.5) and H-5' (14.5) indicating that the second bibenzyl unit was (C-D) (59). When the other methylene signal at δ_H 3.07 was irradiated N.O.E's were observed at H-5 (13.6), H-3 (16.9) and H-10, H-14 (14.0). This confirms structure (56) from the delayed COSY experiment.

From the delayed COSY and initial N.O.E experiments there are four possible structures (53), (60), (61) and (62). In principle it should be possible to distinguish between them by measuring N.O.E's across the ether oxygens. However since conventional techniques involve irradiation at the centre of a multiplet, frequency discrimination is lost in the case of overlapping multiplets. Unfortunately H-3' and H-10' are partially overlapping. In 1984 Sanders and Kinns[19] proposed multiple selective irradiation in which each line in a multiplet is irradiated consecutively, improving the frequency selectivity. Applied to pakyonol (53) (Figure 4) this technique allowed sufficient discrimination to be achieved between the overlapping H-3' and H-10' multiplets, although complete selectivity was not possible. When H-3' was irradiated the N.O.E's (%) at H-6 and -OH were 3.7 and 1.7 respectively, and larger than when H-10' was irradiated (1.5 and 0.8 respectively). However when H-10' was irradiated the N.O.E's at H-11 and H-13 were 2.5 and larger than when H-3' was irradiated (2.2). Thus

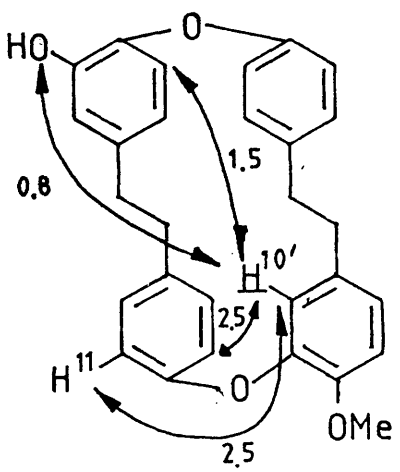
Fig. 4

(i) 3'-H Irradiation



(53)

(ii) 10'-H Irradiation



(53)

N.O.E.s (%)

[See spectum, overleaf]

Fig.4 (Cont.)

NOE EXPERIMENTS ON (53)

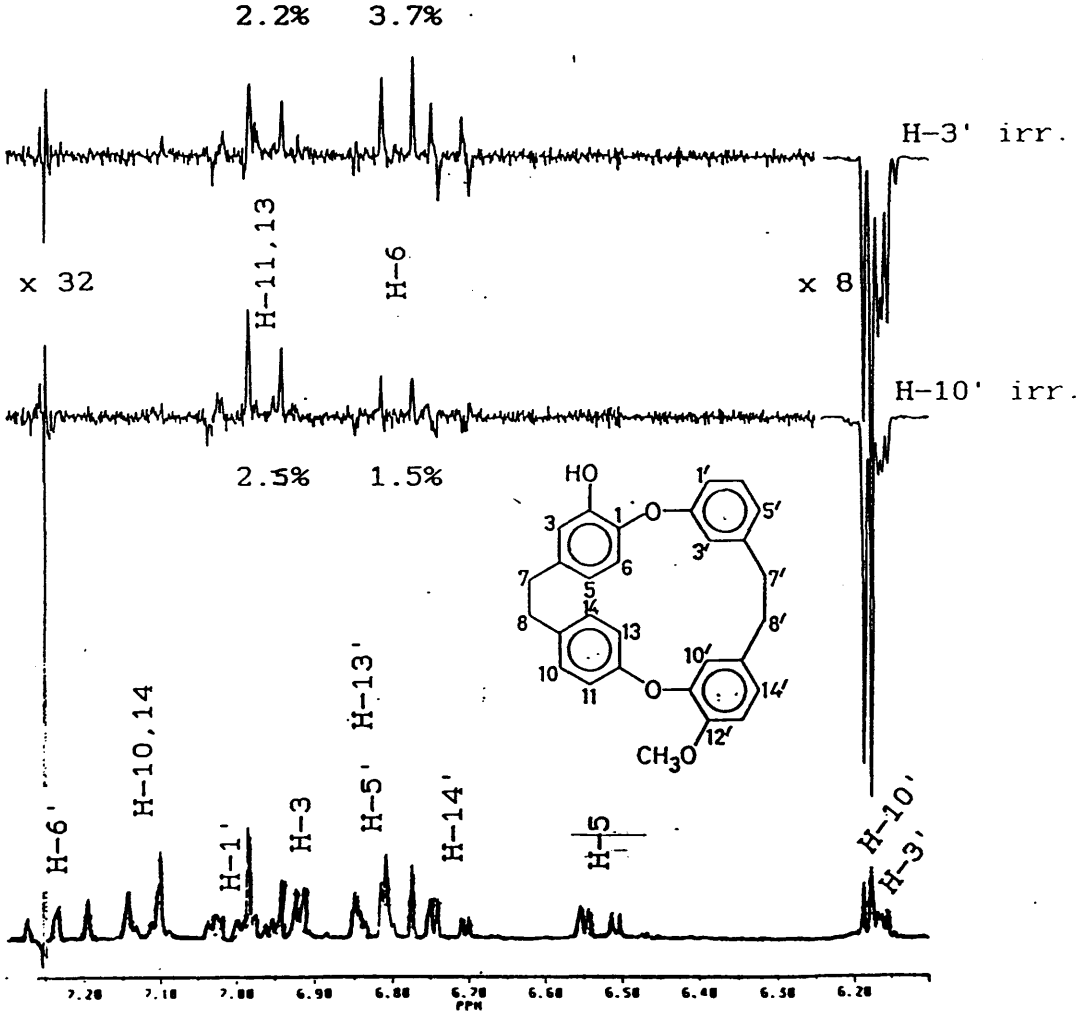
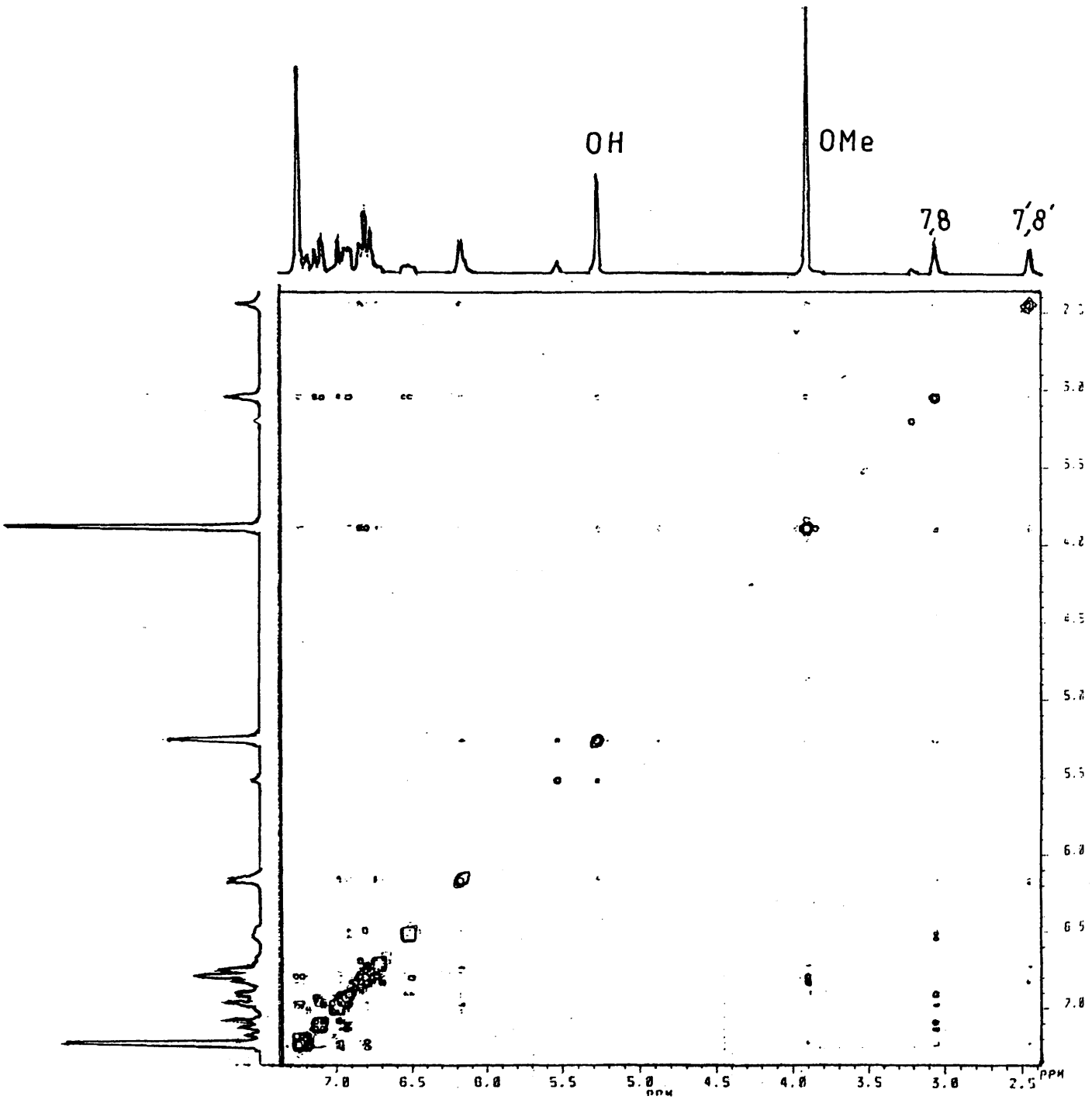


Fig. 5

2D NOESY (53)



the larger N.O.E's across the ether oxygens of rings A to D and B to C support the order of the rings as ABCD and not ABDC.

These results led unambiguously to structure (53) for pakyonol. In the mass spectrum the expected double benzylic cleavage led to major fragments m/z^+ 227 (60%) and 211 (31%).

2D NOESY EXPERIMENTS

The 2-D NOESY experiment[20] can offer a means of determining either chemical exchange pathways or spatial relationships in certain situation. Pairs of nuclei which would show a N.O.E in a 1D experiment may also show crosspeaks in this 2-D experiment. Thus NOESY is the 2-D equivalent of the transient N.O.E. 2-D NOESY experiments are usually run for large, slowly tumbling molecules, such as proteins, where N.O.E. effects are negative.

Because relatively few NOESY experiments have been obtained for smaller molecules it was decided to carry out this experiment on pakyonol (Figure 5). Crosspeaks were observed between the methylene protons at δ_H 3.07 and the aromatic protons H-3, H-5, H-10 and H-14 thus allowing the assignment of the bibenzyl unit (A-B) (56). It was not possible to see the crosspeaks which would have defined the ether links and the other bibenzyl unit.

EXPERIMENTAL

Isolation

A sample of pakyonol (53) was provided by Siegfried Huneck, Institute of Plant Biochemistry of the Academy of Sciences of the G.D.R, Halle/Saale, G.D.R. It was isolated from *Mannia fragrans* collected near a waterfall at Pakyon, Kaesong City, Democratic Peoples Republic of Korea. It was dried at room temperature for 20 days, pulverised (50g), and extracted with ether to give a residue (1.1g) which was chromatographed over silica gel, using n-hexane-Et_2O as the eluant, which yielded complex mixtures in the early fractions. n-Hexane-Et_2O (9:1) (500ml) eluted a resin which after further chromatography and crystallisation from methanol, gave pakyonol (53) in prisms, m.p. 185-186°C ν_{max} (KBr) 3430 cm^{-1}.

N.M.R

The delayed COSY-45-2D spectrum was run with a delay of 80 ms before and after the 45° pulse. The digital resolution was 2 Hz per data point in both dimensions (acquisition time 0.5S. , recycle delay 2S, 256 increments of 1 ms, sine bell squared window function in both dimensions, magnitude mode presentation). 2D NOESY experiments were run with mixing times 1.5 and 1.0 S (in $CDCl_3$ solution) and the longitudinal relaxation times were ca. 1.5S for methylene protons.

δ_H 2.47 (s, H-7', -8'), 3.07 (s, H-7, -8), 3.91 (s, OMe), 5.28 (OH, exchangeable with D_2O), 6.15 (dd, J 2.6 and 1.5 Hz, H-3'), 6.18 (d, J 2.0 Hz, H-10'), 6.53 (dd, J 8.2 and 2.1 Hz, H-5), 6.72 (dd, J 8.1 and 2.0 Hz, H-14'), 6.79 (d, J 8.2 Hz, H-6'), 6.79 (d, J 8.2 Hz, H-6),

6.82 (ddd, J 7.3, 1.5 and 1.1 Hz, H-5'), 6.83 (d, J 8.1 Hz, H-13'), 6.92 (d, J 2.1 Hz, H-3), 6.96 (J+J' 8.7 Hz, H-10, -14), 7.01 (ddd, J 8.3, 2.6 and 1.1 Hz, H-1'), 7.12 (J+J' 8.7 Hz, H-11, -13) ; δ_C 158.4, 153.2, 149.0, 147.3, 144.6, 139.5, 138.5, 136.5, 135.2 (all s), 130.1 (s), 129.9, 121.8, 121.6, 121.2 (2), 120.9, 120.7 116.3, 115.7, 115.2, 114.1, 111.8 (all d), 56.1 (OMe), 40.9, 39.8, 35.4, 35.0 (all t).

Found : m/z^+ 438.1846. $C_{29}H_{26}O_4$ requires m/z^+ 438.1831.

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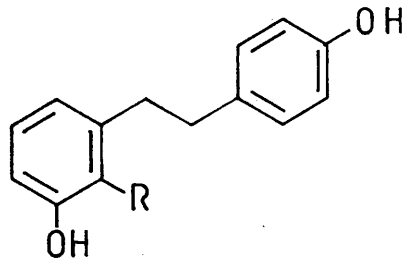
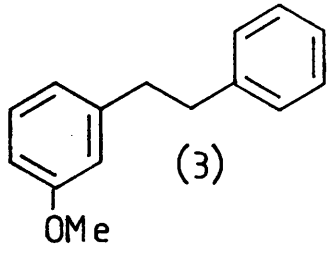
CHAPTER 5

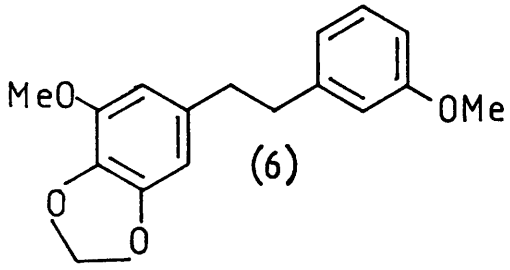
SYNTHESIS OF 3,5-DIMETHOXY-4-(3-METHYL BUT-2-ENYL)-BIBENZYL



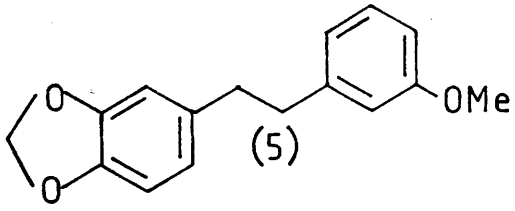
(1) R=CO_2H
(2) R=H
(4) R=OH



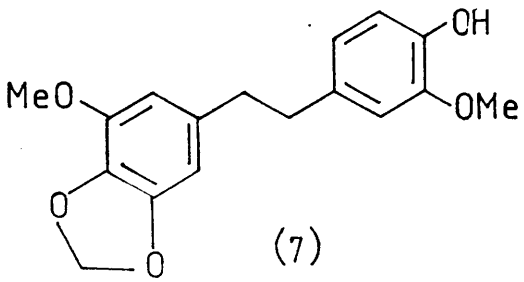
(3)



(6)



(5)



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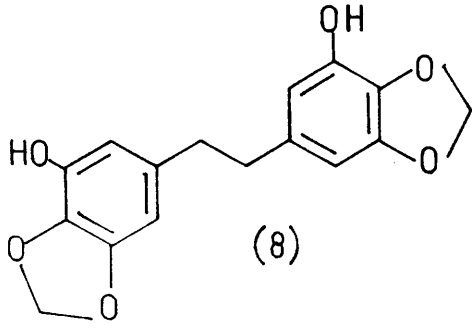


(8)

INTRODUCTION

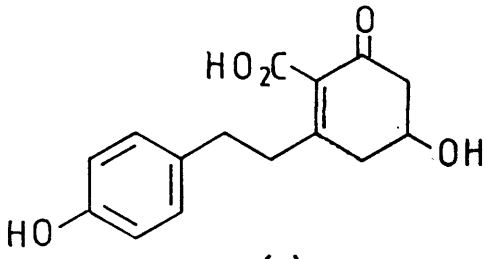
Bibenzyls in the Hepaticae

The first representative of this large group, Lunularic acid (3,4'-dihydroxybibenzyl-2-carboxylic acid)(1) was isolated by Valio et al[1] in 1969 from *Lunularia cruciata*. Lunularic acid and the corresponding decarboxylated derivative lunularin (2) have been detected[2] in many species of the Hepaticae, but do not occur in the Anthrocerotae or algae.

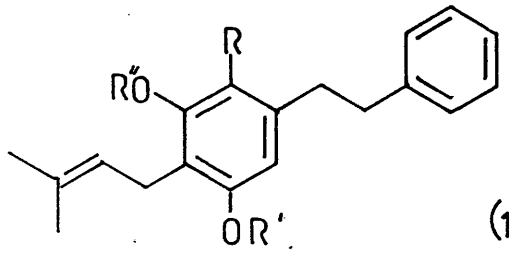
Numerous other bibenzyls have been reported from liverwort species. 3-Methoxybibenzyl (3)[3] was isolated from *F. dilatata* while 2,3,4'-trihydroxybibenzyl (4)[4] was isolated from *P. endiviifolia* and its structure proved by synthesis.[5] More recently Asakawa[6] has found four new related bibenzyls (5) - (8) from three *Frullania* species. The structure of compound (5) was also confirmed by synthesis.[7]

The most significant compound in this series, prelunularic acid (pre-LNA) (9)[8] was obtained from a suspension of cultured cells of *Marchantia polymorpha*. Compound (9) can be converted to lunularic acid by acid or base. For example ca. 0.3% of preLNA (9) was converted to (1) in one day at room temperature, and 9% on boiling for thirty minutes. The isolation of (9) is significant in terms of biosynthesis of (1) and of bibenzyls in general. Bibenzyl biosynthesis is discussed in Chapter 4, page 129 .

Asakawa et al reported[9] three isoprenoid-substituted bibenzyls from *Radula complanta*, 3-methoxy-5-hydroxy-4-(3-methylbut-2-enyl)-bibenzyl (10), 3,5-dihydroxy-4-(3-methyl-but-2-enyl)-bibenzyl (11) and 3,5-dihydroxy-6-carboxy-4-(3-methyl-but-2-enyl)-bibenzyl (12) in



(9)

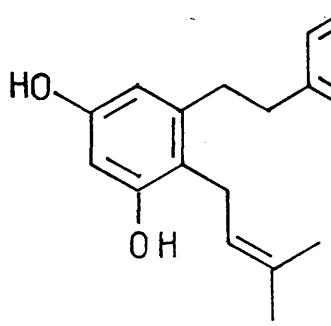


(10) R= H R'= Me R''= H

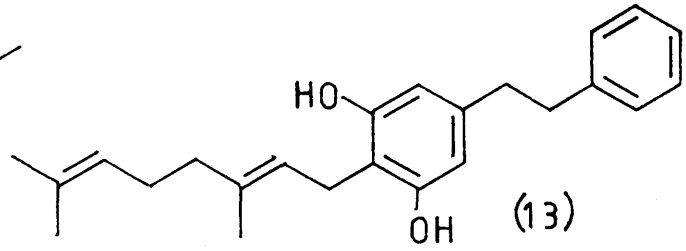
(11) R = H R'= H R''= H

(12) R = CO_2H R'= H R''= H

(15) R = H R'= Me R''= Me



(14)



(13)

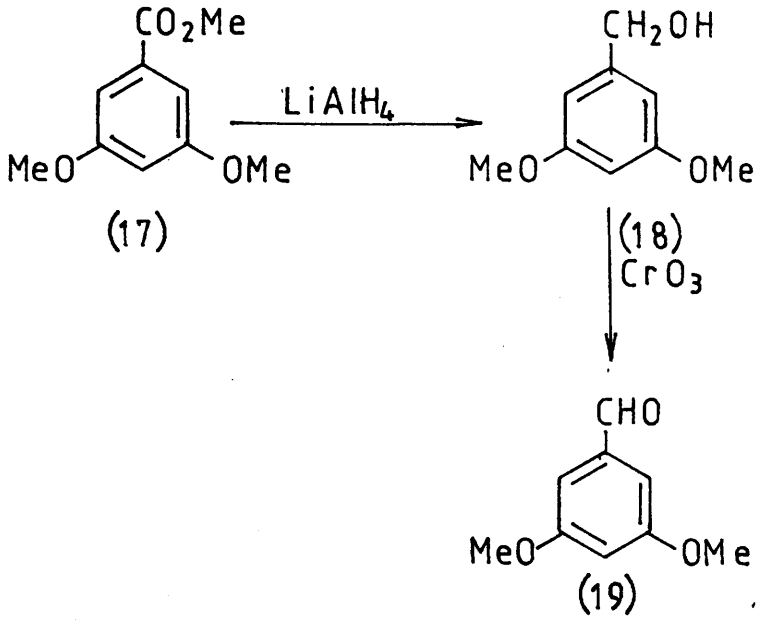
addition compound (13). Connolly[10] isolated 3,5-dihydroxy-2-(3-methyl-but-2-enyl) (14) from *Radula boryana* and confirmed its structure by synthesis.

Asakawa's original evidence for (11)[11] was based on the ^{1}H n.m.r data, in particular the apparent equivalence of 2-H and 6-H. These protons were no longer equivalent in the derived diacetate and hence Asakawa had isolated the 2-prenylbibenzyl (14), whose structure had previously been confirmed by synthesis.[10]

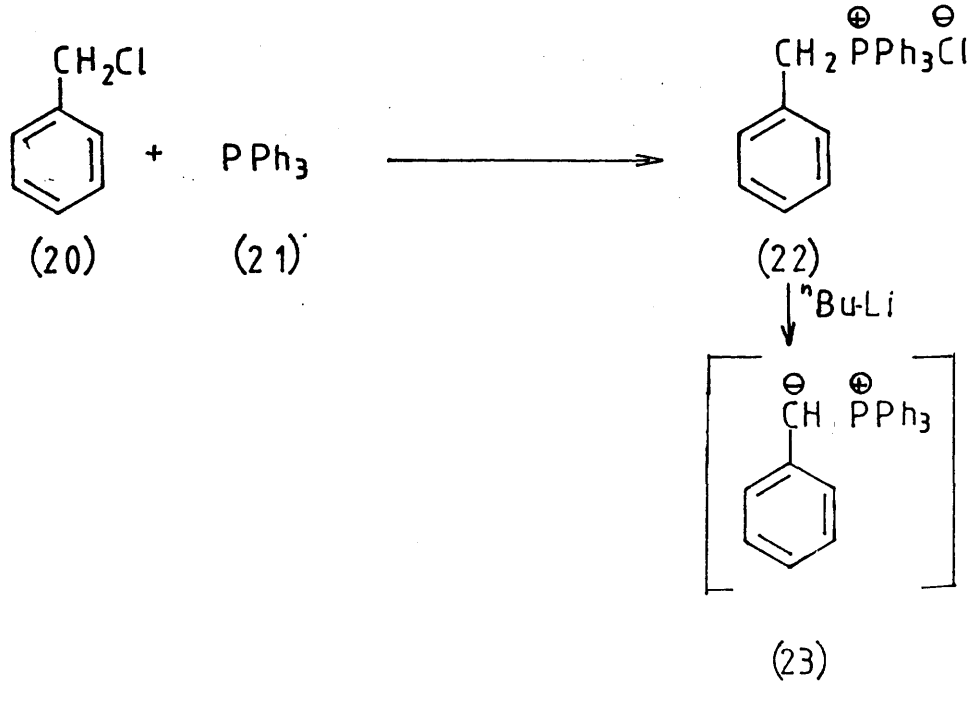
The present chapter is concerned with the synthesis of the dimethyl ether of (11) whose symmetrical ^{1}H and ^{13}C n.m.r spectra confirmed its structure.

Subsequently Asakawa also isolated (11) from *Radula complanta*.[9]

Scheme 1



Scheme 2



DISCUSSION

Our aim was to synthesise 3,5, dimethoxy-4-(3-methyl-but-2-enyl) (15). The approach involved construction of the bibenzyl system using a Wittig reaction and introduction of the isoprenyl group via appropriate alkylation of the dimethoxy bibenzyl (16).

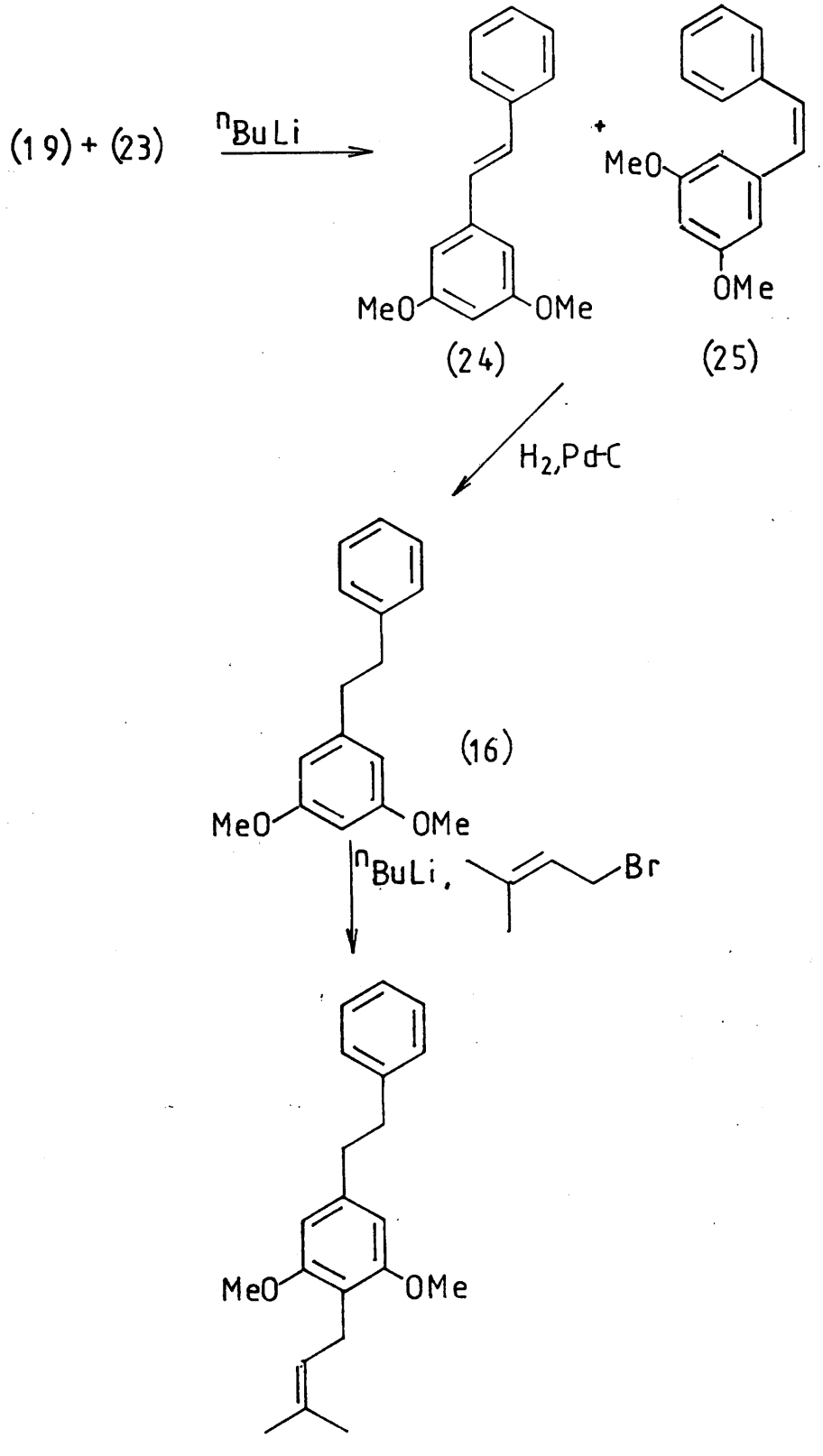
Methyl-3,5-dimethoxybenzoate (17) (Scheme 1) was easily reduced to the corresponding alcohol (18) using lithium aluminium hydride in dry ether. The ^{1}H n.m.r spectrum of the product (ν_{max} 3390 cm^{-1}) showed loss of the methyl ester and the appearance of a two proton singlet at δ_H 4.5 due to the benzylic methylene group. Oxidation of (18) with CrO_3/pyridine gave the aldehyde (19) ν_{max} 1690 cm^{-1} in good yield. Its ^{1}H n.m.r spectrum showed the loss of the hydroxyl group and the appearance of an aldehyde at δ_H 9.9 (s) ν_{max} 1690 cm^{-1}.

Benzyl chloride (20) (Scheme 2) was transformed into the Wittig reagent (22) by treatment with triphenylphosphine (21) under anhydrous conditions in toluene. The ^{1}H n.m.r spectrum of (22) showed the expected coupling of the benzylic methylene protons with phosphorus [δ_H 5.4 (d, J_{PH} 14 Hz)].

The first step of the Wittig reaction involves the formation of a ylid (23) by deprotonation of the phosphonium chloride (22) using $^{n}BuLi$. The ylid (23) is a good nucleophile and should react easily with the aldehyde (19) to form two isomeric products (24) and (25) as shown in Scheme 3.

On addition of $^{n}BuLi$ to the phosphonium chloride (22) a deep-red colour appeared, presumably indicating the formation of the ylid (23).

Scheme 3


(19) + (23)
nBuLi
MeO
OMe
(24)
MeO
OMe
(25)
H2,Pd-C
(16)
MeO
OMe
nBuLi,
Br
MeO
OMe

(15)

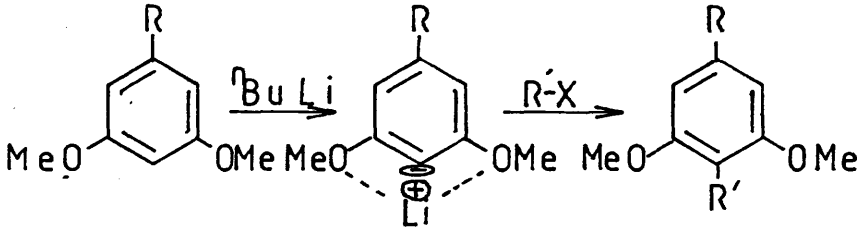
Reaction of the aldehyde (19) with the ylid (23) gave the desired stilbene as a mixture of E- (24) and Z - (25) isomers. The ^{1}H (90 MHz) n.m.r spectrum was complex and the ratio of Z:E could not be determined. The mass spectrum of the dimethoxy stilbene mixture confirmed the molecular formula (m/z 242).

The mixture (24), (25) was converted to the corresponding bibenzyl (16), by hydrogenation in methanol over 10% Pd-C. Filtration of the catalyst and removal of the solvent in vacuo afforded the 3,5-dimethoxybibenzyl (16) in high overall yield. The structure accorded with ^{1}H n.m.r spectrum which shows the loss of olefinic protons and the appearance of a broad singlet at δ_H 2.9 arising from the four benzylic methylene protons.

The final stage in the synthesis involved appropriate alkylation of compound (15) with isoprenyl bromide. It is known[12] in aromatic systems that a negative charge can be stabilised on the carbon between two meta-methoxyls. Thus when an aromatic species such as (26) is reacted with ^{n}BuLi at low temperature the carbanion (27) is formed as the only product. Subsequent reaction of (27) with an alkyl or allyl halide gives (28) as the sole product of alkylation (28).

When the bibenzyl (16) was reacted with ^{n}BuLi a deep red colour formed, presumably indicating the formation of the carbanion. On addition of isoprenyl bromide to the reaction mixture the colour faded, signifying alkylation. Workup and purification by flash chromatography afforded the isoprenylated bibenzyl (16) (ν_{max} 1680 cm^{-1}). The symmetrical nature of the molecule followed from its ^{1}H and ^{13}C n.m.r spectra which showed that protons 2-H and 6-H are equivalent [δ_H 6.4 (s); δ_C 104.1] as are the methoxyls [δ_H 3.82 (s); δ_C 55.7]. The presence

Scheme 4



(26) (27) (28)

R' = Alkyl or Allyl

X = Cl, Br, I

of the isoprenyl group was apparent from resonances for the vinyl proton [δ_H 5.25 (tq, J 7.4, 1.4 Hz)], the allylic methylene group [δ_H 3.38 (brd, 7.2 Hz)] and the two downfield tertiary methyls [δ_H 1.82, 1.71; δ_C 25.8, 17.7]. The remaining aromatic protons and the benzylic protons appear at δ_H 7.3 (m, 5H) and 2.90 (br s) respectively. The two methoxyls appear as a singlet [δ_H 3.82 ; δ_C 55.7]. The molecular formula was established by high resolution mass spectrometry as $C_{21}H_{26}O_2$ (m/z 310.1941).

EXPERIMENTAL

3,5 Dimethoxybenzyl alcohol (18)

To a stirred suspension of $LiAlH_4$ in ether (30 ml) was added methyl 3,5 dimethoxybenzoate (17) (8.5g) in ether (30 ml) at such a rate that the mixture refluxed gently. Gentle refluxing was continued for 3 hours. The reaction was worked up by adding aqueous sodium sulphate, followed by hydrochloric acid (5N, 10ml). The aqueous phase was extracted thoroughly with ether, and the combined organic layers washed with 5% sodium bicarbonate and dried to afford the crude product as a colourless oil which crystallised from ether to give the pure alcohol (18) (6g, 81%) as needles m.p. 49-51°C [lit.[13] 47-50°C]

ν_{max} 3290 cm^{-1}.

δ_H (90 MHz) : 6.4 (d, J 1.2 Hz, H-2, H-6), 6.2 (d, J 1.2 Hz, H-4), 4.5 (s, $-CH_2OH$), 3.7 (s, exchangeable with D_2O), 3.65 (s, 2 x -OMe).

M.S : m/z 168 ($C_9H_{12}O_3$ requires 168).

3,5 Dimethoxybenzaldehyde (19)

To the cold stirred slurry from CrO_3 (10 g) and pyridine (100ml) was added the alcohol (18) (6g) in pyridine (20ml) and the mixture allowed to stand at room temperature for 2 hours. After addition of methanol (50 ml) the mixture was kept for 2 hours then diluted with 5% NaOH (200 ml) and ether (200 ml). The aqueous layer was re-extracted with ether (200 ml) and the combined colourless extracts washed with water (1 x 400 ml), 5% H_2SO_4 (3 x 400 ml), water (1 x 400 ml). brine (1 x 400 ml), dried and evaporated under vacuum leaving a colourless oil which crystallised from pentane as colourless cubes

(4.5g, 77%) m.p. 46-48°C [lit.[14] 45-48°C] ν_{max} 1690 cm^{-1}

δ_H (90 MHz) : 9.9 (s, -CHO), 7.0 (d, J 1.2 Hz, H-2, H-6), 6.7 (br s, H-3), 3.8 (s, 2 x -OMe).

M.S : m/z 166 ($C_9H_{10}O_3$ requires 166).

Benzyltriphenylphosphonium chloride (22).

Benzyl chloride (20) (12g) and triphenylphosphine (21) (20.5g) were stirred and heated in anhydrous toluene (150 ml) at 90°C for 60 hours. The precipitated salt (12.6g) was separated by filtration and washed with petroleum ether and anhydrous ether. Crystallisation from chloroform-hexane gave the product (22) (9.4g, 25%) m.p. > 330°

δ_H (90 MHz): 7.8 (m), 7.1 (m), 5.4 (d, J 14 Hz).

3,5 Dimethoxystilbene (24), (25).

To benzyltriphenyl phosphonium chloride (22) (9.4g) in dry THF (50 ml) was added ^nBuLi (20 ml, 1.5M) and the mixture stirred under nitrogen at -78°C for 1 hour. 3,5-Dimethoxybenzaldehyde (19) (4g) in THF (15 ml) was added and the stirring was continued for 2 hours at room temperature. Water was added (20 ml) and most of the THF evaporated at the pump. Normal workup gave a dark oil which after purification by flash chromatography, using hexane : ethyl acetate as the eluant, afforded a mixture of stilbenes (24), (25) (3.4g, 58%). ν_{max} 1620 cm^{-1}.

δ_H (90 MHz) : 7.28 (br s), 6.8 - 6.3 (Ar-H, vinyl-H), 3.8 (-OMe), 3.6)-OMe).

M.S : m/z 242 ($C_{16}H_{18}O_2$ requires 242).

3,5 Dimethoxybibenzyl (16).

The stilbene mixture containing (24) and (25) (3.4g) was dissolved in methanol (20 ml) and a catalytic amount of 10% Pd-C was added; the mixture was then stirred under a hydrogen atmosphere for 2 hours. The solution was filtered through celite and the solvent evaporated. Purification by flash chromatography afforded the bibenzyl (16) (2.9g, 85%) ν_{max} 3100 cm^{-1}.

δ_H (90 MHz) : 7.2 (s, 5H), 6.3 (s, 3H), 3.7 (s, 6H), 2.9 (s, 4H).

M.S : m/z 244 ($C_{16}H_{20}O_2$ requires 242).

3,5-Dimethoxy-4-(3-methyl-2-butenyl)-bibenzyl (15).

The bibenzyl (16) (0.96g, 4 mmol) was stirred in THF (15 ml) at -78°C under dry nitrogen and n-BuLi (3.0 ml, 4.4 mmol, 1.5M in hexane) added. Stirring was continued at this temperature for 1 hour and then prenyl bromide (0.6g, 4 mmol) in THF (5 ml) was added dropwise and the mixture allowed to stir for a further hour at -78°C. Water (5 ml) was added and most of the THF evaporated at the pump. Normal workup, and purification by flash chromatography, afforded the isoprenylated-bibenzyl (15) (0.58g, 47%) as an oil, ν_{max} 1680 cm^{-1}.

δ_H : 7.3 (m, 5H), 6.4 (s, 2H), 5.25 (tq, J 7.4, 1.4 Hz, vinyl -H), 3.82 (2 x -OMe), 3.38 (br d, J 7.2 Hz, vinyl $-CH_2$), 2.90 (br s, 2 x $-CH_2$), 1.82, 1.71 (d, J 1.09, 2 x t $-CH_3$).

δ_C : 157.9 (2 x s), 141.8 (s), 140.6 (s), 130.8 (s), 128.4 (2 x d), 128.3 (2 x d), 125.9 (d), 123.2 (d), 115.9 (s), 104.1 (2 x d), 55.7 (2 x q), 38.5 (t), 38.0 (t), 25.8 (q), 22.1 (t), 17.7 (q).

M.S : m/z 310.1941 (M^+, base peak) ($C_{21}H_{26}O_2$ requires 310.1933).

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CHAPTER 6

PARTIALLY-ACETYLATED DODECANYL TRI- AND TETRA-RHAMNOSIDE DERIVATIVES FROM *Cleistopholis glauca* (ANNONACEAE)

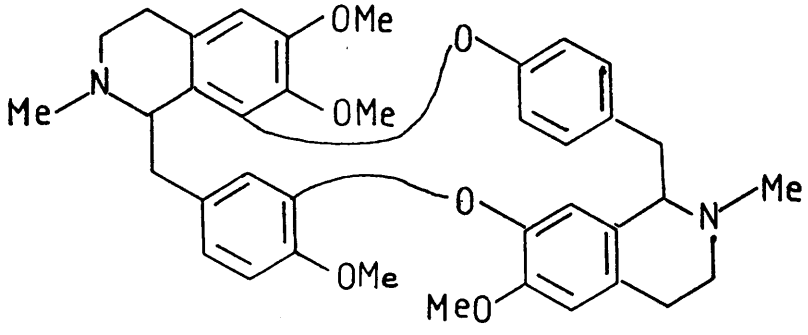
INTRODUCTION

Chemistry of the Annonaceae

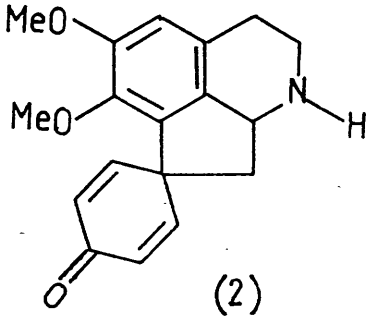
The Annonaceae constitute a large family of more than 2000 species contained within about 120 genera. They are included within the order Magnioliales (Annonales) and belong with the most primitive families of angiosperms.[1] Annonaceous species tend to be evergreen trees or shrubs, sometimes climbers and are often recognisable by the glaucosus or metallic sheen of their leaves. They have many archaic features which have somehow escaped extinction and are what Darwin called "living fossils". Most species are found in tropical or sub-tropical regions, mainly in the rain forests, with only one species being found in the temperate zone.[2]

Economically the plants are of importance as sources of edible fruits. Berries are usually produced but in a few genera, particularly the *Annona*, the berries have coalesced producing an edible fleshy fruit. Soaps, alcohol and edible oils have also been manufactured from certain species. The fragrant flower of the ylang-ylang (*Cananga orodata*) has been used in perfumery and many species have found use in folk medicine.

Until about twenty years ago little other than pioneering work had been done in the chemical investigation of this family. Much of this work indicated the general occurrence of alkaloids in the family. The plants however are not readily accessible and even after more than a decade of intensive investigation it was pointed out by Waterman in 1978[3] that "for its size the Annonaceae is perhaps one of the chemically least known families". The phytochemistry of the Annonaceae has been reviewed on several occasions. The first



(1)



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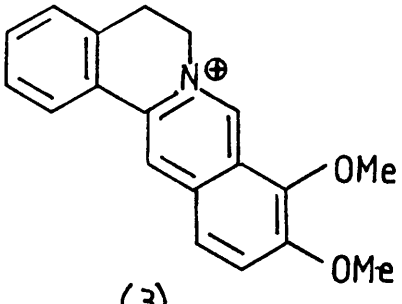

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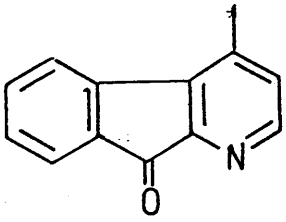

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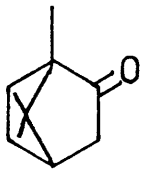

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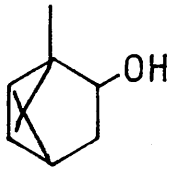

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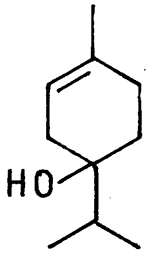

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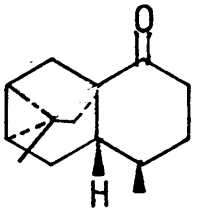

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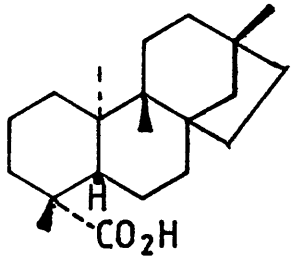

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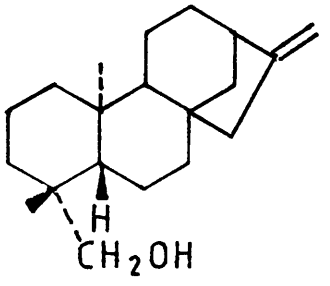
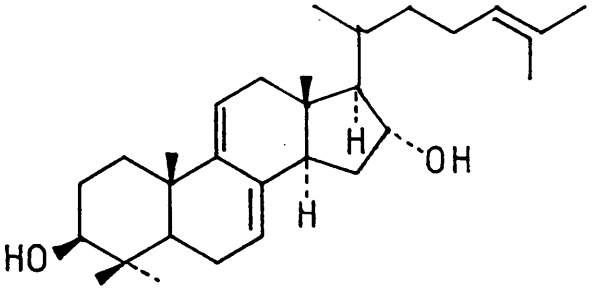
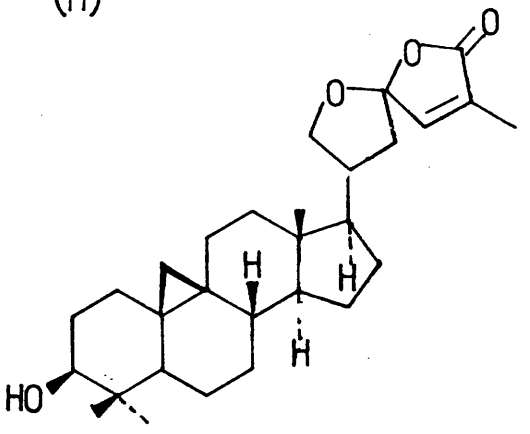


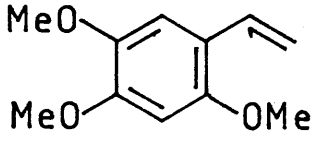
(10)


HO
H
OH
H

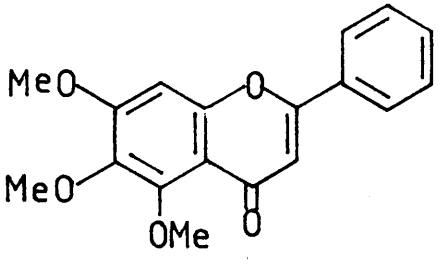
(11)


O
O
O
H
H
H
HO

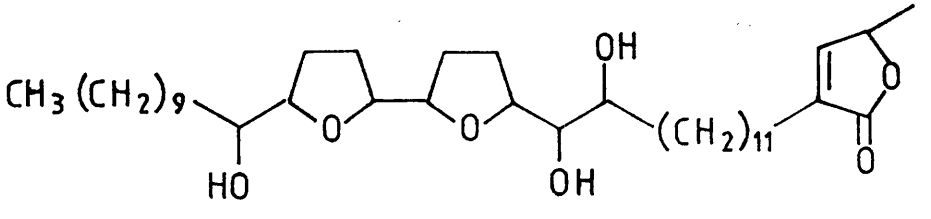
(12)


MeO
MeO
OMe

(13)


MeO
MeO
OMe
O
O

(14)


CH3(CH2)9
HO
O
O
OH
OH
(CH2)11
O
O

(15)

review[4] in 1982 by Cave and co-workers dealt mainly with alkaloids. More recent reviews[5,6] have concentrated on the presence of a wide variety of non-alkaloidal products.

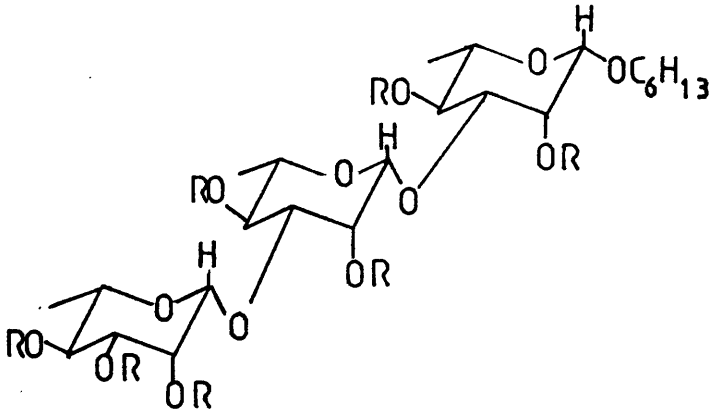
ALKALOIDS

Isoquinoline-derived alkaloids are widespread in the Annonaceae. Several classes including bisbenzyltetraisoquinolines[7] (1), proaporphinoids[8] (2) and protoberberines[9] (3) are common. Among several examples of non-isoquinoline alkaloids is onychine[10] (4), probably derived via a combination of the phenylalanine and mevalonate pathways.

Non-Alkaloidal Constituents

Some Annonaceae are fragrant due to the presence of essential oils which contain common monoterpenes such as camphor (5), borneol (6) and terpen-4-ol (7). The presence of sesquiterpenoids is much rarer and those that have been isolated such as ishwarone[11] (8) are somewhat unusual. Diterpenes appear to be narrowly distributed within the Annonaceae and are found mainly in the species of *Annona* and *Xylopia*. Most of the diterpenes isolated belong to the kauranes, such as xylopic acid (9) and (-)-kaur-16-en-19-ol (10).[6] The search for triterpenes has been rather unrewarding. The only two compounds of interest are polycorpol (11)[12] and uvariastrol (12).[13]

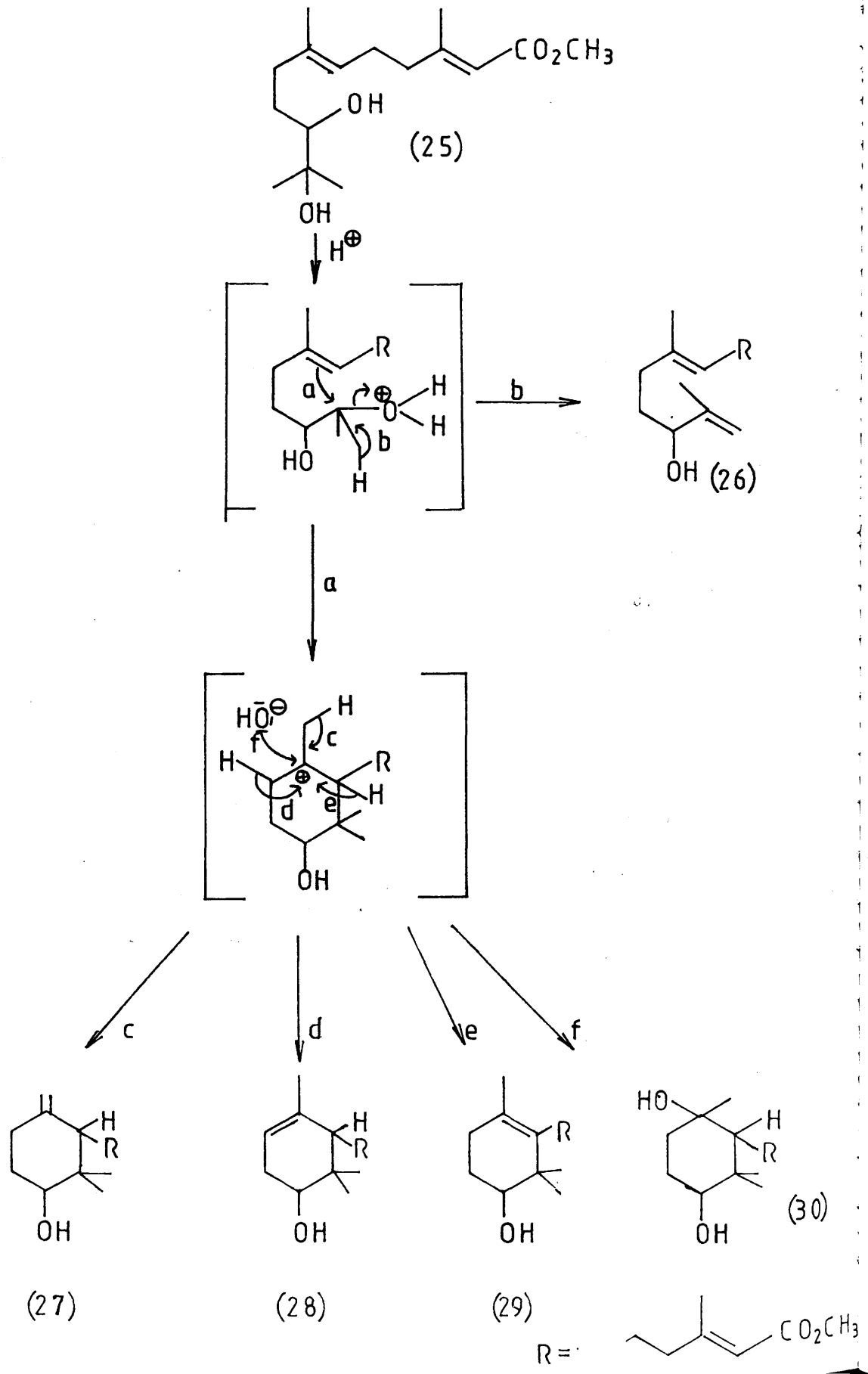
Aromatic compound isolated range from simple cinnamyl alcohol derivatives such as (13)[14] to flavones typified by baicalein trimethyl ether (14).[3]



R = H, Ac, COC_7H_{15}

(16)

Scheme 1


CO2CH3
OH
OH
(25)
H⊕
R
a
H
O
H
b
HO
H
b
R
OH
(26)
a
HO⊖
H
f
c
H
R
d
e
H
OH
c
d
e
f
H
R
OH
(27)
H
R
OH
(28)
R
OH
(29)
HO
H
R
OH
(30)
R =
CO2CH3

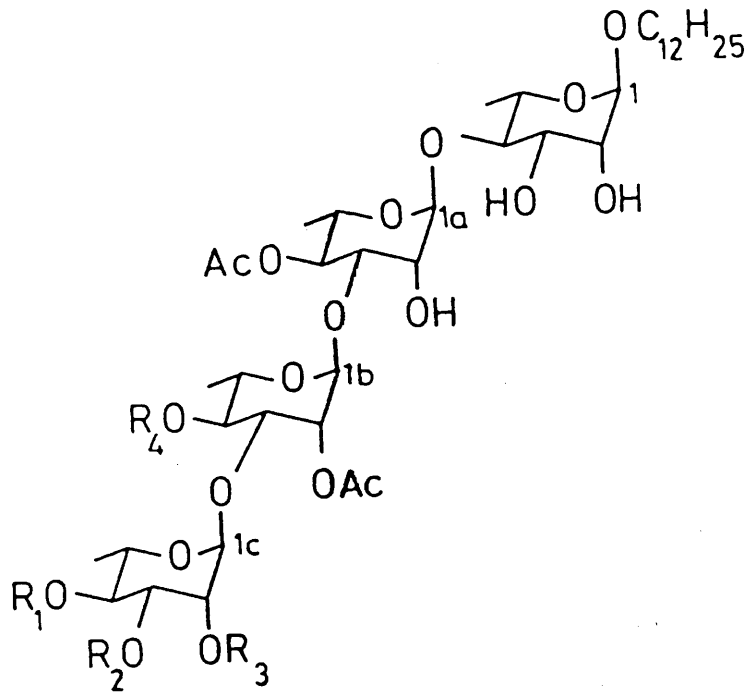
Several C_{37} acetogenins such as (15)[15] have been isolated from species of the Annonaceae. Such compounds are characterised by a wide spectrum of biological activity and are certainly among the most interesting found in this family.

Carbohydrates

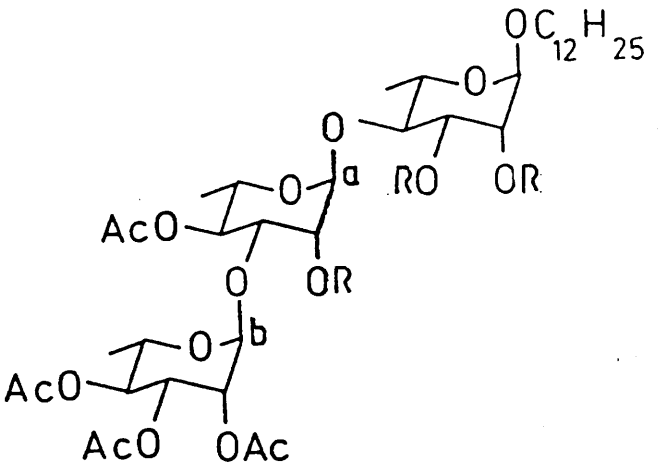
Reports[4] have indicated the presence of simple sugars such as glucose, fructose and sucrose in some Annonaceous plants. Polysaccharides including galactams and xylans have also been isolated. Waterman has suggested[16] the presence of a range of seven 1,3 linked trirhammosides with O-octyl, O-hexyl and between two and four O-acetyl substituents (general structure 16). The positions of some substituents are tentative and await confirmation from appropriate highfield n.m.r experiments.

In this chapter we report the isolation of five new partially acetylated derivatives (17) - (21) of 1-O-dodecanyl α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→3)-α-L-rhamnopyranosyl-(1→4)-α-L-rhamnopyranoside from the stem bark of *Cleistopholis glauca* (Annonaceae) and discuss their structural elucidation using COSY, delayed COSY and N.O.E experiments and FAB Mass spectroscopy. The novel trisaccharide 1-O-dodecanyl α-L-2,3,4-triacetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside (22) was also isolated.[17]

Previous work on *Cleistopholis glauca* has reported only sesquiterpenoids[18] (25)-(30), (Scheme 1) shows the possible derivation



	R_1	R_2	R_3	R_4
(17)	H	H	H	H
(18)	H	H	H	Ac
(19)	Ac	H	H	Ac
(20)	H	H	Ac	Ac
(21)	Ac	Ac	H	Ac
(23)	PERACETATE			



(22) R=H

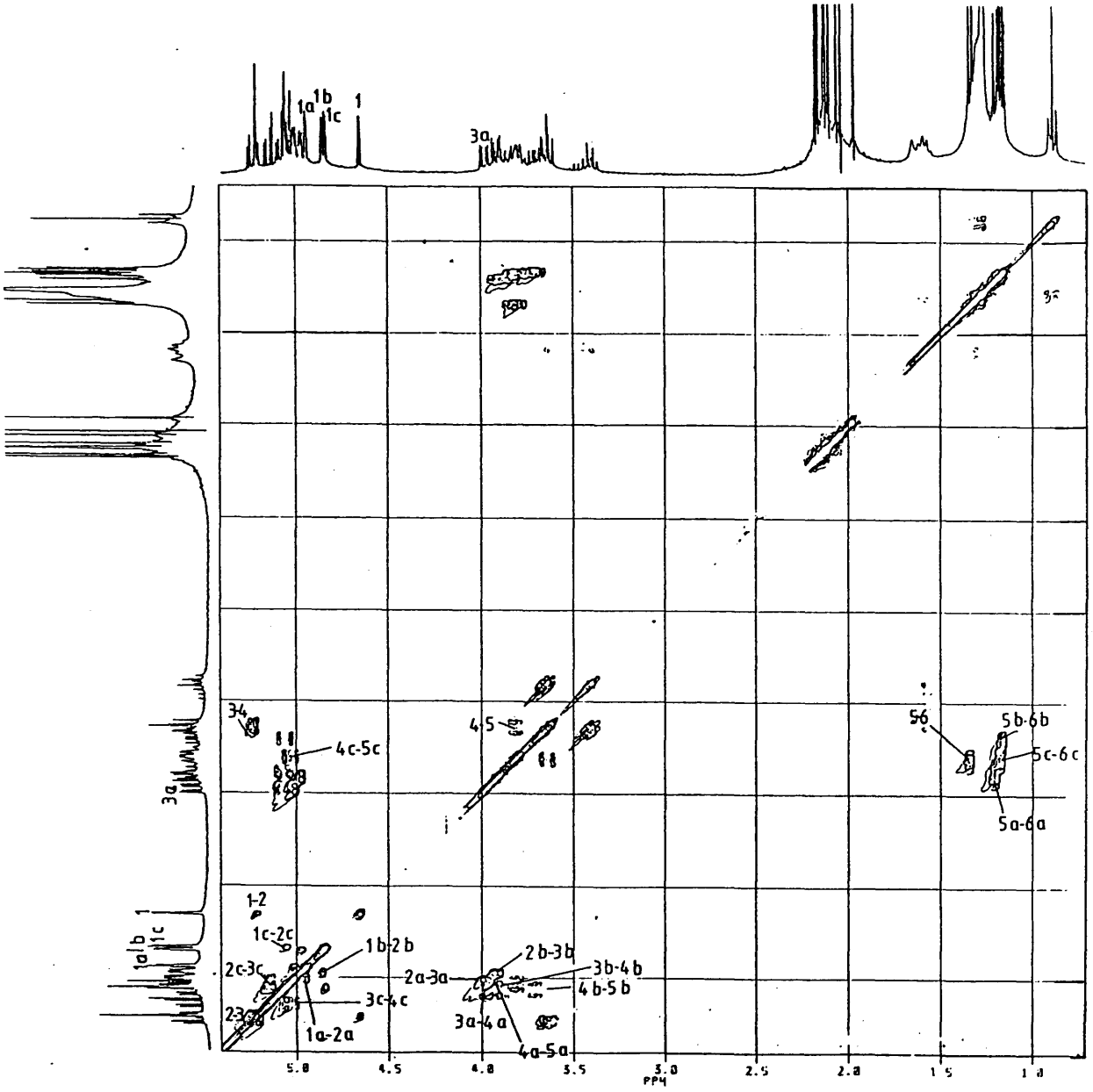
(24) R=Ac

sesquiterpenoids (26)-(30) by acid-catalysed reaction of (25).

DISCUSSION

Column chromatography of the chloroform extract of the stem bark of *Cleistopholis glauca* (Annonaceae) afforded six new compounds (17) - (21). The structure elucidation was simplified by the fact that compounds (17) - (20) afforded the same peracetate, m.p. 140 - 143°C, $[\alpha]_D$ = -31.5° (C 0.6 in $CHCl_3$), after reflux in pyridine/acetic anhydride. Initial 360 MHz ^1H and ^{13}C n.m.r revealed that the compounds were all partially acetylated tri/tetrarhamnoses with a terminal acetal involving a long chain alcohol. Thus, as would be expected, a typical coupling pattern emerged (Table 9) showing the anomeric 1-H as a doublet (J ca. 2Hz); 2-H as a doublet of doublets (J ca. 3.5, 2.0 Hz); 3-H as a doublet of doublets (J ca 10, 3.5 Hz); 4-H as a triplet (J ca 10 Hz); 5-H as a doublet of doublets (J 10, 6.3 Hz) and $6\text{-}H_3$ as a doublet (J 6.3 Hz). These coupling data were in accord with those of α-L-rhamnose. The problem of assigning each proton to its respective rhamnose unit was solved using a 2D COSY experiment (Figure 1) of the peracetate (23). The chemical shift and the coupling data are shown in Table 9. Any non-acetylated positions on the rhamnose rings in the peracetate (23) at 1-H, 2-H, 3-H and 4-H must involve points of linkage to the next ring. These positions can be readily identified by the fact they have a relative upfield shift compared to the other acetylated protons. Thus the upfield shifts of 3-H [δ_H 3.98 (dd, J 9.8, 3.2 Hz)], 3-H [δ_H 3.92 (dd, J 9.9, 3.4 Hz)] and 4-H [δ_H 3.64 (t, J 9.3 Hz)]

Fig.1 COSY (23)

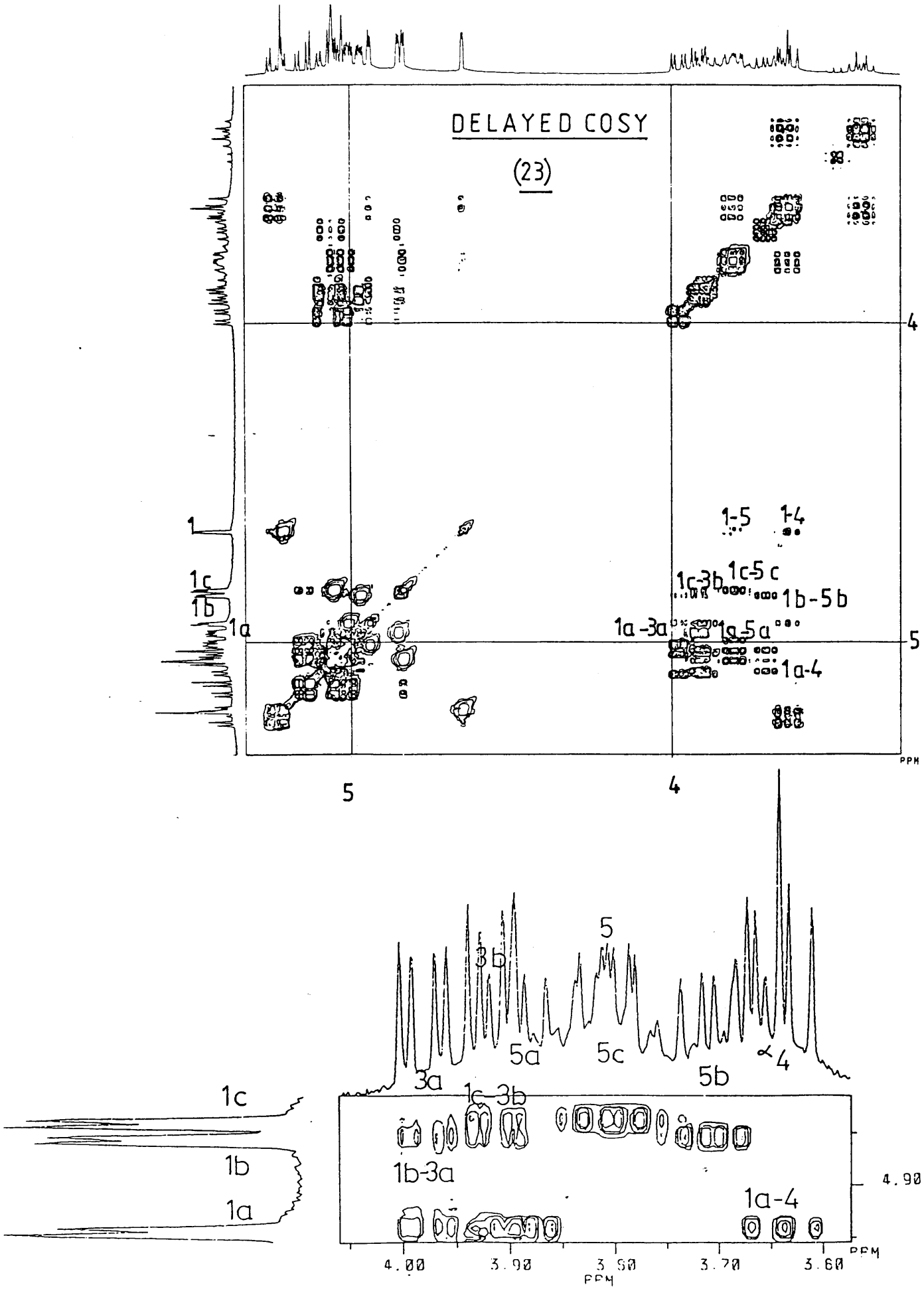

1a
1b
1c
1
3a
3-4
4-5
5-6
4c-5c
5b-6b
5c-6c
5a-6a
1-2
1c-2c
1b-2b
2c-3c
2b-3b
2a-3a
3b-4b
4b-5b
3c-4c
2-3
3a-4a
1a-2a
4a-5a
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM

indicated that the rings are joined by two (1→3) and (1→4) links. The protons of the oxygenated methylene groups [δ_C 6.82 (t)] of the alkyl chain resonate at δ_H 3.64 (dt, J 10.2, 6.8 Hz).

Fast Atom Bombardment[19] (F.A.B) mass spectrometry was used for each compound to determine the molecular weight and hence to confirm the number of rhamnose units and acetates present. F.A.B is a soft ionisation technique which has been successfully applied in determining the precise molecular weights of thermolabile and non-volatile polar compounds with high molecular weights. Fragmentation appeared to occur in a predictable fashion and with hindsight it was possible to identify the sequence of the partially acetylated units present in some of the tri/tetrarhamnoses. The dodecanyl nature of the alkyl chain was determined by acidic hydrolysis of (17) which fortuitously afforded 1-O-dodecanyl α-rhamnopyranoside (31). Analysis of the F.A.B. mass spectrum of (31) showed the parent ion $(M+Na)^+$ at m/z 355. The major fragment ions at $C_{12}H_{25}O$ (m/z 185) and $C_6H_{11}O_4$ (m/z 147) corresponded to cleavage at the acetal bond. Sequential cleavage of the acetals also occurred in the F.A.B mass spectrum of the peracetate (23) which showed $(M+H)^+$ at m/z 1149 and fragment ions at m/z 963, 733, 503 and 273. This also confirmed the dodecanyl nature of the alkyl chain. In most compounds a series of small peaks attributable to a bis-homologue (tetradecanyl) was also observed.

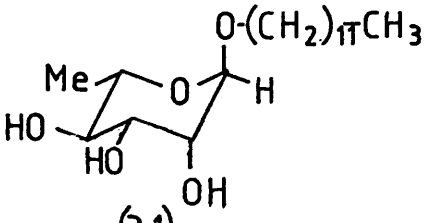
To determine the relative order of the sugar units of the peracetate (23) it was necessary to observe correlations across the acetal linkages between each unit. This was not observed in the normal COSY (Figure 1). However the method which readily solved

Fig. 2

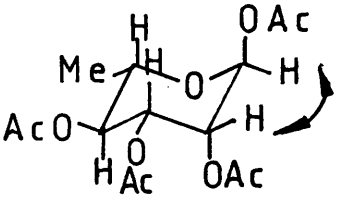

DELAYED COSY
(23)
1
1c
1b
1a
4
5
1-5
1-4
1c-3b
1c-5c
1b-5b
1a-3a
1a-5a
1a-4
PPM
5
4
5
3b
5a
5c
5b
α4
3a
1c-3b
1b-3a
1a-4
4.90
4.00
3.90
3.50
3.70
3.60
PPM

the order of the rhamnose units in (23) was a delayed COSY (Figure 2), with very long delays (eg. 250 ms) before and after the mixing pulse. This method has recently been used effectively in the structure elucidation of triterpenoid saponins such as (32) from alfalfa.[20] In the COSY (Figure 1) of (23) correlations were observed between the anomeric protons 1, 1a, 1b and 1c and other protons on their respective rings. However, with the longer delays used in the delayed COSY (Figure 2) correlations were also observed across the acetal links, between the anomeric protons and a proton on the adjacent sugar units. Thus 1a-H showed a correlation to 4-H, 1b-H to 3a-H, and 1c-H to 3b-H. Therefore the glycosidic links are clearly 1a→4, 1b→3a, and 1c→3b. Correlations of 1-H with the methylene protons of the dodecanyl chain were not observed under the conditions of the experiment. These results lead unequivocally to structure (23), the peracetate, with the exception of the anomeric configurations.

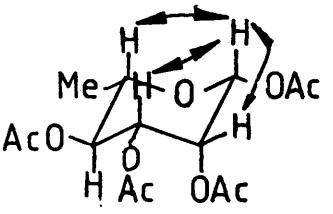
The first step in the determination of the anomeric configurations of (17) - (22) was to examine the situation in rhamnose itself. α-L-Rhamnose was acetylated with acetic anhydride/pyridine and the chemical shift and coupling constant of 1-H measured for both anomers (33) and (34). The coupling constant of 1-H of the α- and β-rhamnose derivatives is not a reliable indication of configuration. In the mixture of anomers obtained, 1-H of the α-isomer appears at δ_H 5.92 (dd, J 1.9, 0.6 Hz) while 1-H of the β isomer is at δ_H 5.76 (d, J 1.2 Hz). It seemed likely that NOE experiments sould provide valid distinction between the α- and β-anomers. Irradiation of 1-H of the α-anomer of L-rhamnose tetraacetate (33) resulted in a substantial enhancement only at 2-H while irradiation of 1-H of the β-anomer (34) gave substantial N.O.E s at 2-H, 3-H, and 5-H. For the


O-(CH2)11CH3
Me
O
H
HO
HO
OH

(31)

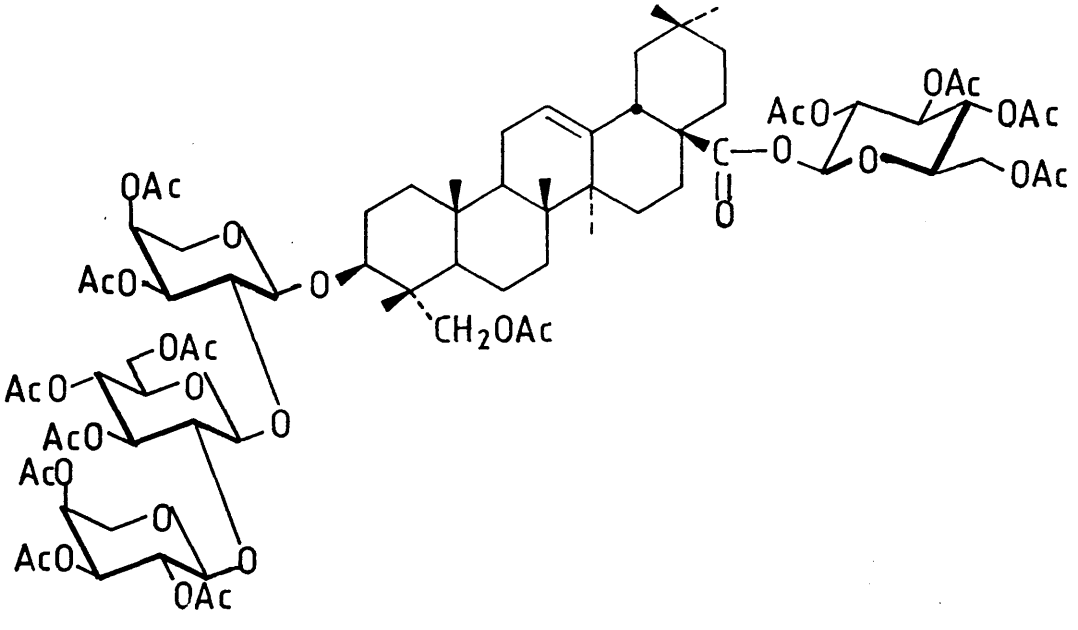

H
OAc
Me
H
O
H
AcO
H
O
H Ac
OAc

(33)


H
H
Me
H
O
OAc
AcO
H
O
H Ac
OAc

(34)

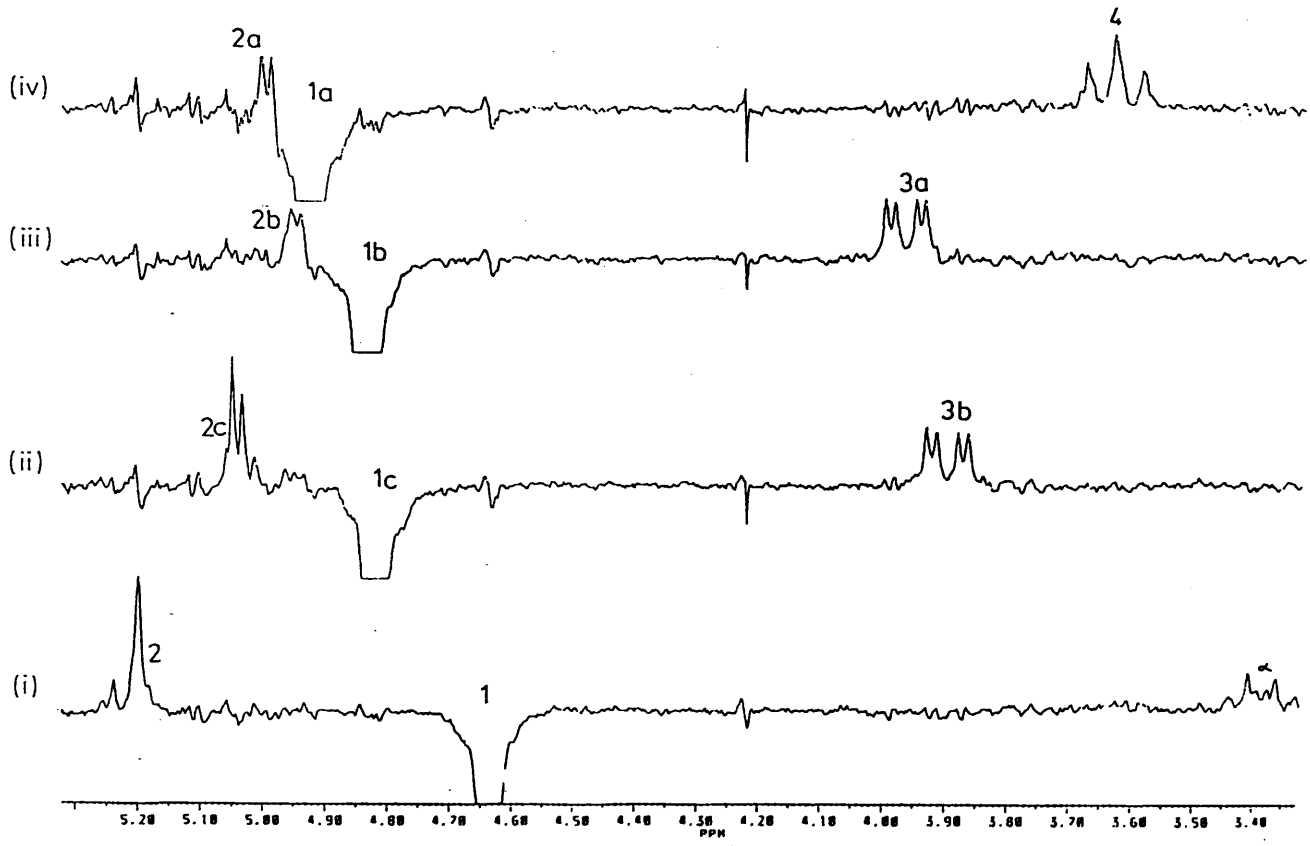
N.O.E.


OAc
AcO
OAc
OAc
C
O
O
O
OAc
O
AcO
O
CH2OAc
OAc
AcO
O
AcO
O
AcO
O
AcO
O
OAc

(32)

Fig.3

NOE EXPERIMENTS ON (23)



peracetate (23) (at 200 MHz) (Figure 3), irradiation at 1-H resulted in N.O.E's at 2-H (δ_H 5.21, 3%), and at one of the resonances (δ_H 3.38, 3%) of the terminal methylene group of the dodecanyl unit. When 1a-H (δ_H 4.94) was irradiated N.O.E's at 2a-H (δ_H 5.01, 5%) and also at 4-H (δ_H 3.64, 5%) were observed. Irradiation of resonances 1b-H (δ_H 4.85) and 1c-H (δ_H 4.84) resulted in N.O.E's at the corresponding protons 2b-H (δ_H 4.79, 3%) and 2c-H (δ_H 5.05, 4%) and also at 3a-H (δ_H 3.98, 5%) and 3b-H (δ_H 3.92, 5%) respectively. These results establish unambiguously the presence of α-rhamnose units as in (23) and also confirm the assignment of the glycosidic links provided by the delayed COSY spectrum.

The absolute configuration was established by hydrolysis of the peracetate (23) in trifluoroacetic acid. This yielded L-(+)-rhamnose {$[\alpha]_D$ + 11.5°(C, 0.54 in MeOH); lit.[21] $[\alpha]_D$ + 8.2°(C, 10 in H_2O)}. The structural elucidation of compounds (17) - (21) was carried out using a similar combination of COSY and delayed COSY. The most polar of the tetrarhamnoside-containing fractions yielded the diacetate (17), m.p. 117 - 120°C, $[\alpha]_D$ = -65.6° (C, 1.5 in MeOH). The F.A.B. mass spectrum did not show the expected molecular ion peaks at $(M+H)^+$ or $(M+Na)^+$. Acetal fragmentation, however, showed the presence of a terminal rhamnose residue, containing two acetates at m/z 205 ($M+Na^+$) with the remainder of the molecule represented by a peak at m/z 649 $(M+Na)^+$. The ^1H n.m.r spectrum of (17) was broad in $CDCl_3$ at room temperature. In CD_3OD at 34°C the spectra were much sharper and the appropriate COSY and delayed COSY correlations were observed. The acetates at δ_H 2.29 and 2.25 ppm were assigned to positions 4a-C, and 2b-C because of the downfield shifts of protons 4a-H [δ_H 5.27 (t, J 10.0 Hz)], and 2b-H [δ_H 5.17 (dd, J 3.5,

Fig. 4 COSY (16)

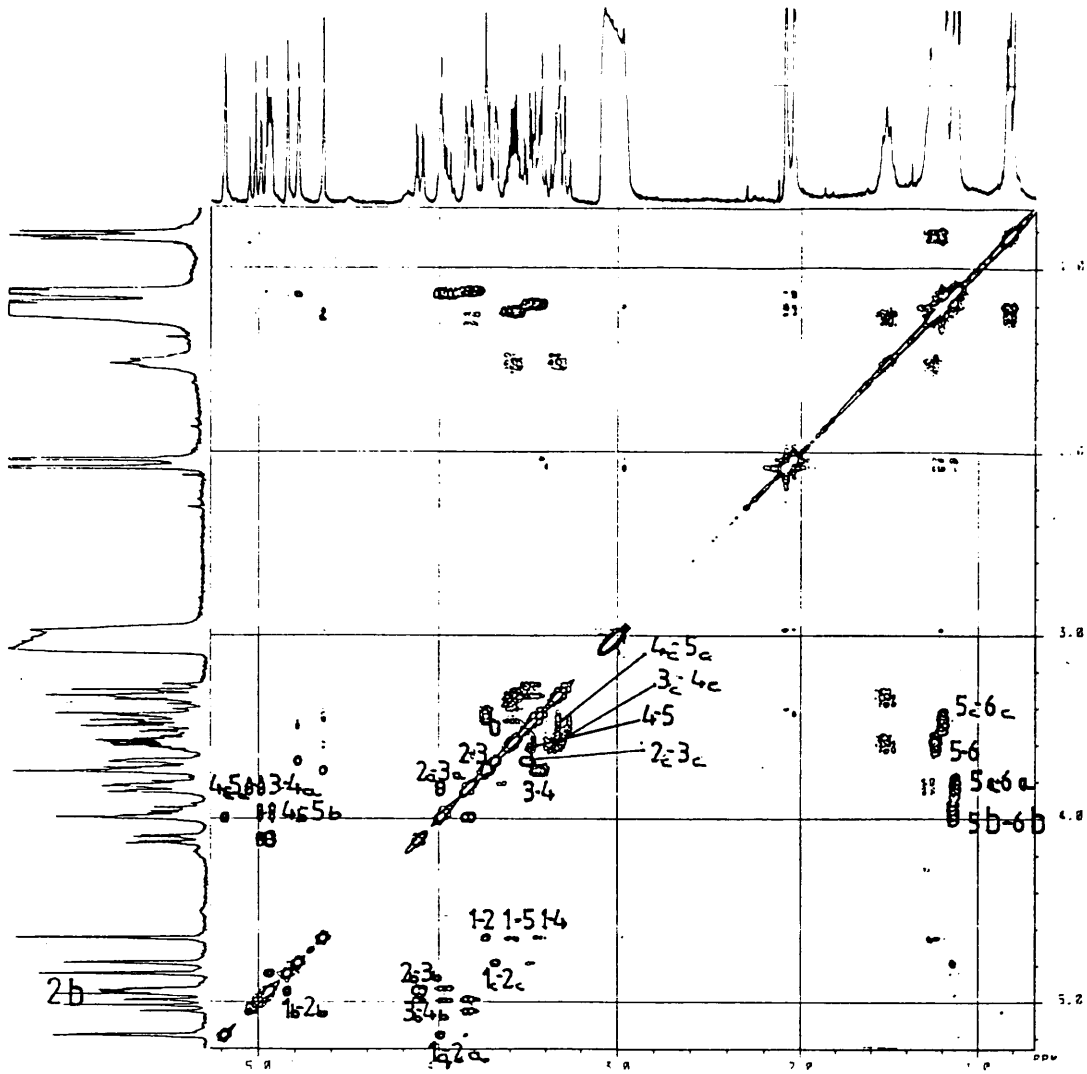
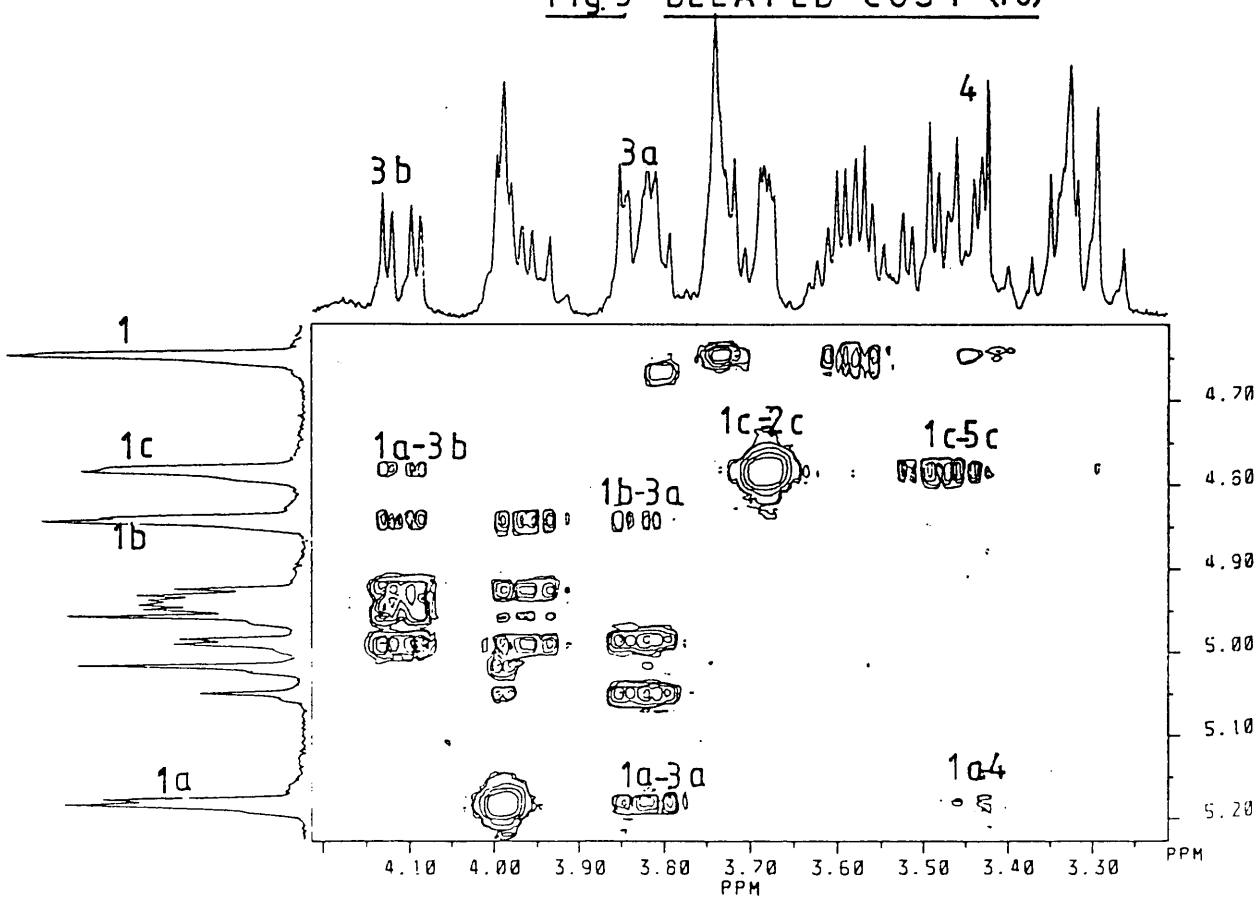


Fig. 5 DELAYED COSY (18)



1.7 Hz)] respectively. Thus the structure was assigned as in (17).

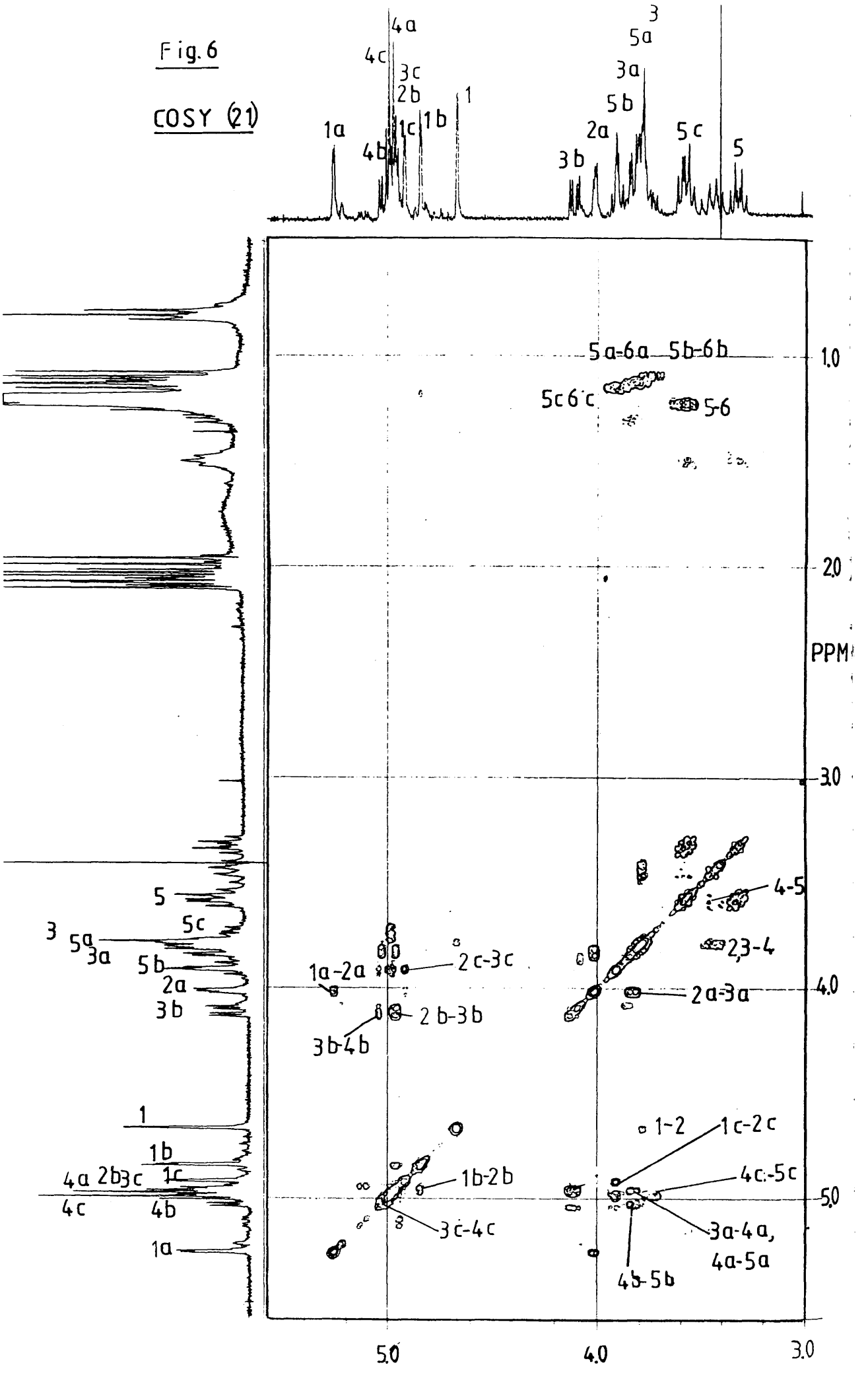
The triacetate (18), m.p. 107 - 109°C, $[\alpha]_D$ = -67.8°(C, 1.82 in MeOH), showed a molecular ion m/z at 920 $(M+Na^+)$. Fragmentation about the acetal linkages which could have provided information about the distribution of the acetates was not as clear as with the corresponding peracetate (23) and no further information could be derived from the mass spectrum. The three acetates [δ_H 2.19(2), 2.04] were assigned by COSY and delayed COSY (Figures 4 and 5) to 2b-C, 4b-C and 4a-C in accord with the ^1H shifts of 4a-H [δ_H 5.02, (t, J 9.7 Hz)], 2b-H [δ_H 4.94 (dd, J 3.3, 1.7 Hz)], and 4b-H [δ_H 4.95, (t, J 9.9 Hz)]. The spectroscopic evidence thus led to the structure (18).

The tetraacetate (19), m.p. 105 - 107°, $[\alpha]_D$ = -41.5° (C, 0.6 in MeOH), showed a molecular ion m/z at 961 $(M+Na)^+$ and fragment ions at m/z 801, 571 and 383 all $(M+Na)^+$ corresponding to sequential cleavage of the acetal bonds. A major peak at m/z 189 $(M+H)^+$ clearly indicated that there was an acetate on the terminal rhamnose unit. Again the acetates [δ_H 2.13, 2.12, 2.09 and 2.08] were assigned to positions 4a-C, 2b-C, 4b-C and 4c-C from the COSY spectrum at 360 MHz to accommodate the downfield shifts of 4a-H [δ_H 5.02 (t, J 9.8 Hz)], 2b-H [δ_H 4.95 (Ndd, J Obsc.)], 4b-H [δ_H 4.80 (t, J 9.7 Hz)], and 4c-H [δ_H 5.03 (t, J 9.7 Hz)]. Thus the structure (19) was established.

The tetraacetate (20), m.p. 98 - 100°C, $[\alpha]_D$ = -44.5° (C, 0.51 in MeOH) showed a mutual cleavage pattern with the isomeric tetraacetate (19) in the F.A.B mass spectrum, indicating that the distribution of acetates must be similar. The ^1H shifts at 4a-H [δ_H 4.98 (t, J 9.8 Hz)], 2b-H [δ_H 4.90 (dd, J 3.2, 1.7 Hz)], 4b-H [δ_H 4.94 (t, J 9.8

Fig. 6

COSY (21)

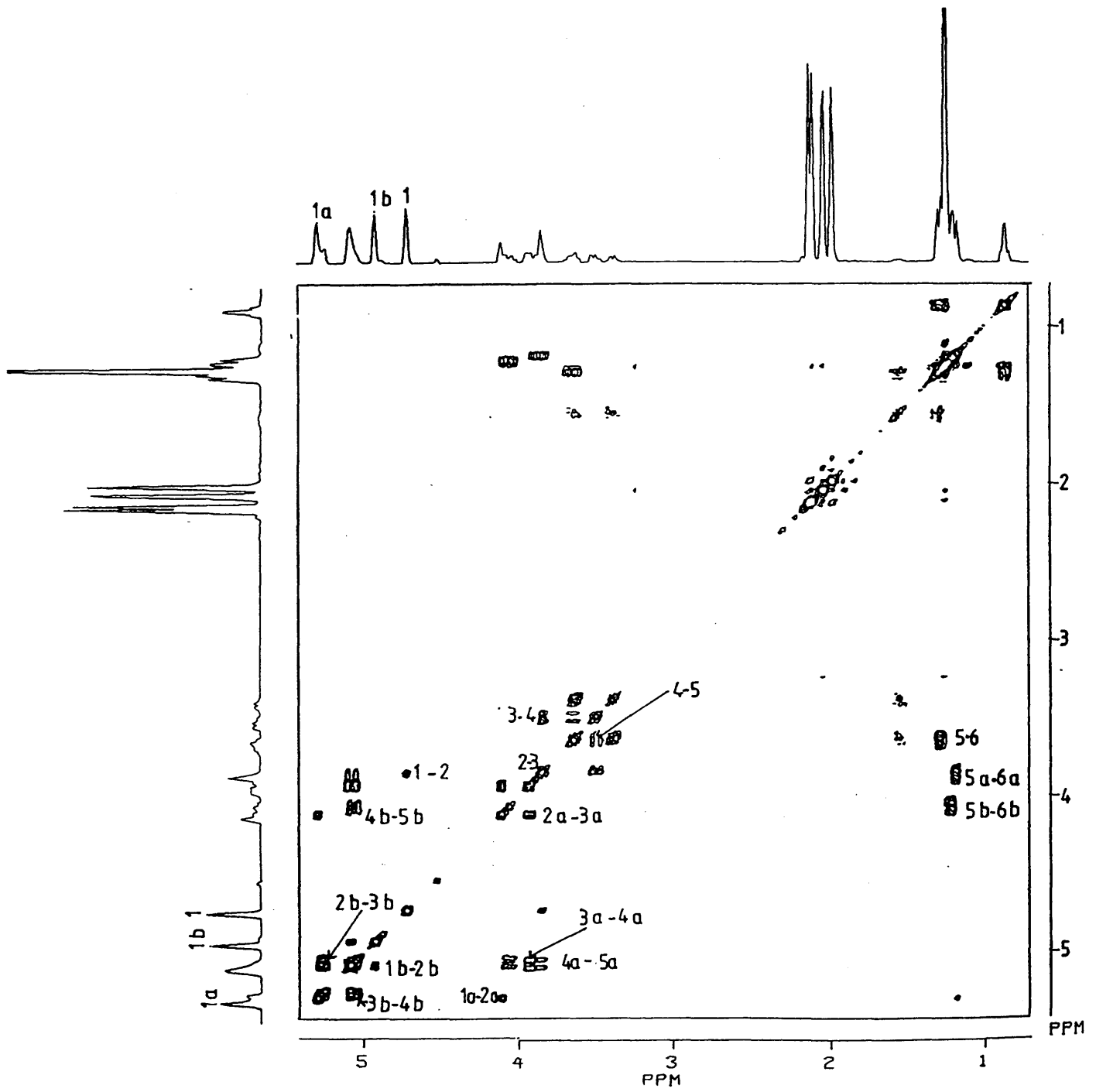

4a
4c
3c
2b
1
1a
1c
1b
4b
3
5a
3a
5b
2a
5c
3b
5
5a-6a
5b-6b
5c 6c
5-6
1.0
2.0
PPM
3.0
4-5
2,3-4
2a-3a
1a-2a
2c-3c
2b-3b
3b-4b
1-2
1c-2c
1b-2b
4c-5c
3c-4c
3a-4a,
4a-5a
4b-5b
5.0
4.0
3.0

Hz)], and 2c-H [δ_H 4.78 (d, J 1.5 Hz)] placed the acetate groups [δ_H 2.08 (x2), 2.06 and 2.04], at 4a-C, 2b-C, 4b-C and 2c-C. Thus the tetraacetate has structure (20).

The pentaacetate (21) m.p. 90-93° $[\alpha]_D$ -54.4 (C, 0.75 in MeOH), showed molecular ions at m/z 1003 $(M+Na)^+$ for the dodecanyl pentaacetate (21) and m/z 1031 $(M+Na)^+$ for the corresponding bis-homologue (tetradecanyl). Sequential cleavage of the acetal bonds in (21) showed fragment ions at m/z 773, 543 and 339 $(M+Na)^+$. Other peaks at m/z 801, and 571 $(M+Na)^+$ correspond to fragmentations of the bis-homologue. The reasons for the increased clarity of the cleavage patterns in (21), are not apparent. It does appear, however, that in the F.A.B. mass spectra of (17) - (24), interpretation becomes simpler as more acetates are added. The ^1H shifts indicated acetylated positions to be at 4a-H [δ_H 4.99 (t, J 9.9 Hz)], 2b-H [δ_H 4.96 (d, J 1.7 Hz)], 4b-H [δ_H 5.00 (t, J 9.9 Hz)], 3c-H [δ_H 4.98 (dd, J Obsc., 1.7 Hz)], and 4c-H [δ_H 4.98 (t, J 10.0 Hz)] (Figure 6) and led to structure (21).

Compound (22) has m.p. 64 - 67°C, $[\alpha]_D$ -35.7°(C, 0.82 in MeOH). Initial 360 MHz ^1H and 90 MHz ^{13}C n.m.r showed that it was a trirhamnose derivative containing a dodecanyl alkyl chain and four acetates. The F.A.B mass spectrum showed the molecular ion at m/z 815 $(M+Na)^+$. Fragmentation suggested that 3 of the acetates are located on the terminal ring m/z 273 $(M+Na)^+$ and one on the central ring m/z 461 $(M+Na)^+$. The four acetylated positions were identified by the ^1H n.m.r chemical shifts of the deshielded protons 2-H [δ_H 5.06 (br)], 3-H [δ_H 5.27 (dd J 10.2, 3.3 Hz)], 4-H [δ_H 5.07 (t, J 9.3 Hz)], and 4-H [δ_H 5.05 (t, J 9.3 Hz)] as 1 x 2-C, 1 x 3-C,

Fig. 7 COSY (22)


1a
1b 1
1b 1
1a
1-2
2a-3a
3a-4a
4a-5a
1a-2a
1b-2b
2b-3b
3b-4b
4b-5b
4-5
5-6
5a-6a
5b-6b
PPM
5
4
3
2
1
PPM

and 2 x 4-C. A COSY experiment confirmed the presence of 2,3,4-triacetylated and 4 monoacetylated rhamnose residues (Figure 7). Acetylation with Ac_2O/pyridine yielded a heptaacetate (24), $[\alpha]_D$ -28.6° (C, 0.59 in $CHCl_3$), three protons, 2 x 2-H [δ_H 5.03 (br) and 4.87 (br)] and 1 x 3-H [δ5.13 (dd, J 9.3, 3.4 Hz)] were deshielded downfield relative to (22). Thus the peracetate (24) has gained additional acetates at positions 2 x 2-C and 1 x 3-C. These results lead unambiguously to structure (22), 1-O-dodecanyl α-L-2,3,4-triacetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside.

TABLE 1.

^{1}H n.m.r Chemical Shifts (ppm) of (17)

	1-H dd, J(Hz)	2-H (dd)
	4.81 bs.	3.90 bs.
a	5.39 (1.7)	4.23 (3.0, 1.9)
b	5.11 (1.6)	5.17 (3.5, 1.7)
c	5.00 (1.5)	4.05 (3.3, 1.7)

	3-H (dd)	4-H (t)
	3.92 (9.6, 3.4)	3.62 (10.4)
a	4.05 (9.3, 3.7)	5.27 (10.0)
b	4.14 (9.0, 3.3)	3.65 (9.7)
c	3.75 (9.4, 3.4)	3.55 (9.2)

	5-H (dq)	6-H_3 (d)
	3.80 (9.2, 6.2)	1.45 (ObSc)
a	4.03 (10.2, 6.3)	1.44 (6.2)
b	4.04 (9.9, ObSc.)	1.30 (6.3)
c	3.68 (10.4, 6.7)	1.38 (6.2)

ACETATES δ_H 2.29, and 2.25 both (s)

$-OCH_2-$ δ_H 3.82, 4.02 [dt (J 9.6, 6.6 Hz)]

^{t}METHYL δ_H 1.06, [t (6.5 Hz)]

TABLE 2.

^{1}H n.m.r Chemical Shifts (ppm) of (18).

	1-H dd, J(Hz)	2-H (dd)
	4.65 bs.	3.73 bs.
a	5.17 d(1.9)	3.99 t(2.6)
b	4.84 d(1.4)	4.94 dd(3.7, 1.7)
c	4.87 bs.	4.87 bs.

	3-H (dd)	4-H (t)
	3.72 Obsc.	3.42 (11.2)
a	3.84 (9.7, 2.8)	5.02 (9.7)
b	4.11 (10.0, 3.3)	4.95 (9.9)
c	3.50 (9.4, 3.3)	3.30 (9.4)

	5-H (dq)	6-H_3 (d)
	3.59 (9.6, 6.0)	1.25 (6.2)
a	3.82 (Obsc., 6.1)	1.12 (6.2)
b	3.96 (9.8, 6.3)	1.14 (6.2)
c	3.46 (Obsc.)	1.19 (Obsc.)

ACETATES δ_H 2.19 (x2), 2,04, all (s)

$-OCH_2-$ δ_H 3.59, [dt(9.6, 6.8 Hz)]
δ_H 3.35

^{t}METHYL δ_H 0.83, [t(6.5 Hz)]

TABLE 3.

^{1}H n.m.r Chemical Shifts (ppm) of (19)

	1-H (S)	2-H (br s)
	4.69	3.77
a	4.88	4.95
b	5.01	3.83
c	5.28	4.07

	3-H (dd)	4-H (t)
	3.78 (8.6, 3.2)	3.49 (Obsc.)
a	4.23 (10.0, 3.0)	5.02 (9.8)
b	3.67 (9.7, 3.3)	4.8 (9.7)
c	3.86 (Obsc., 3.2)	5.02 (9.8)

	5-H (dq)	6-H (d)
	3.6 (Obsc.)	1.20 (7.0)
a	4.00 (9.6, 6.5)	1.19 (6.2)
b	3.64 (Obsc., 6.3)	1.09 (6.2)
c	3.86 (Obsc., 5.7)	1.17 (6.2)

ACETATES δ_H 2.13, 2.12, 2.09, 2.08, all (s)

$-OCH_2-$ δ_H 3.35 [dt(9.7, 6.5 Hz)]
δ_H 2.79

^{t}METHYL δ_H 0.82 [t(6.4 Hz)]

TABLE 4.

^{13}C n.m.r Chemical Shifts (ppm) of (19).

$CH_3-\overset{O}{\overset{\|}{C}}$ (s)	1-C (d)	CH_2-O (d)
171.70	100.95	67.76
171.10	100.85	
170.41	99.53	
170.33	99.01	

CH-O (d)	ALKYL CHAIN(t)	$CH_3-\overset{O}{\overset{\|}{C}}-$ (q)
79.70	31.78	20.96
77.55	29.52	20.81
75.44	29.45	20.74 (x2)
74.48	29.36	
72.35	29.31	
72.17	29.20	
72.00 (x2)	22.54	
70.72		
70.65		
69.20		
67.20		
67.10		
66.70		
66.22		

6-C (q)	^{t}METHYL (q)
17.98	13.95
17.24	
16.98	
16.92	

TABLE 5.

^{1}H n.m.r Chemical Shifts (ppm) of (20)

	1-H (d), J (Hz)	2-H (dd)
	4.62 (Nd)	3.71 (Ndd)
a	5.13 (1.7)	3.97 t (2.7)
b	4.79 (Nd)	4.90 (3.2, 1.7)
c	4.75 (1.3)	4.78 Nd (1.5)

	3-H (dd)	4-H (t)
	3.70 (Obsc., 3.4)	3.41 (9.1)
a	3.80 (9.7, 3.3)	4.98 (9.9)
b	4.09 (9.9, 3.4)	4.94 (9.9)
c	3.64 (9.6, 3.5)	3.30 (Obsc.)

	5-H (dq)	6-H_3 (d)
	3.56 (9.5, 6.1)	1.20 (6.6)
a	3.80 (9.8, Obsc.)	1.10 (6.2)
b	3.94 (9.9, 6.3)	1.12 (6.6)
c	3.46 (9.4, 6.2)	1.18 (6.6)

ACETATES δ_H 2.08, 2.06, 2.04, all (s)

$-OCH_2-$ δ_H 3.30 [dt (9.6, 6.9 Hz)]

δ_H 3.49

^{t}METHYL δ_H 0.81, [t (6.46 Hz)]

TABLE 6

^{13}C n.m.r Chemical Shifts (ppm) of (20)

$CH_3-\overset{O}{\overset{\|}{C}}$ (s)	1-C (d)	CH_2-O (t)
170.96	100.76	67.80
170.76	99.45	
170.61	99.34	
170.53	98.87	

CH-O (d)	ALKYL CHAIN (t)	$CH_3-\overset{O}{\overset{\|}{C}}$ (q)
79.94	31.79	20.80 (x2)
77.84	29.52	20.68 (x2)
74.71	29.34	
72.66	29.30	
72.31	29.21	
72.19	25.98	
72.05 (x2)	22.55	
71.87		
71.41		
70.67		
69.25		
68.97		
67.19 (x2)		
66.23		

6-C (q)	^{t}METHYL (q)
17.98	13.96
17.23	
17.09	
17.04	

TABLE 7

^{1}H n.m.r Chemical Shifts (ppm) of (21)

	1-H (d) J(Hz)	2-H (dd)
	4.67 (bs)	3.78 (bs)
a	5.26 (1.8)	4.01 t(2.2)
b	4.84 (1.6)	4.96 (1.7)
c	4.92 (1.7)	3.91 (1.6)

	3-H (dd)	4-H (t)
	3.78 (Obsc.)	3.43 (9.2)
a	3.82 (9.8, 2.9)	4.99 (9.9)
b	4.11 (9.9, 3.4)	5.00 (9.9)
c	4.98 (Obsc., 1.6)	4.98 (10.0)

	5-H (dq)	6-H_3 (d)
	3.58 (9.6, 6.7)	1.23 (6.2)
a	3.82 (Obsc.6.8)	1.12 (6.7)
b	3.91 (9.4, 6.7)	1.15 (6.5)
c	3.74 (9.8, 6.4)	1.09 (6.4)

ACETATES δ_H 2.10, 2.07, 2.03, 1.99, 1.96 all (s)

$-OCH_2-$ δ_H 3.30, [dt(9.6, 6.8 Hz)]

δ_H 3.57

t_{METHYL} δ_H 0.82 [t(6.5 Hz)]

TABLE 8

^{1}H n.m.r Chemical Shifts (ppm) of (22)

	1-H	J(Hz)	2-H	
	4.71	s	3.82	s
a	5.28	s	5.06	s
b	4.92	d	(1.8) 4.11	d (2.7)

	3-H	(dd)	4-H	(t)
	3.79	(Obsc., 3.4)	3.49	(9.0)
a	5.27	(10.2, 3.3)	5.05	(9.7)
b	3.92	(9.7, 3.6)	5.07	(9.3)

	5-H	(dq)	6-H_3	(d)
	3.62	(9.4, 6.7)	1.28	(6.2)
a	4.06	(9.7, 6.3)	1.21	(6.3)
b	3.85	(9.4, 6.7)	1.18	(6.3)

ACETATES δ_H 2.12, 2.10, 2.04, 1.98 all (s)

$-OCH_2-$ δ_H 3.37 [dt(9.7, 6.7 Hz)]
δ_H 3.63

^{t}METHYL δ_H 0.86, [t(6.8 Hz)]

TABLE 9

^{1}H n.m.r Chemical Shifts (ppm) of (23).

	1-H (d) J (Hz)	2-H (dd)
	4.66 (1.4)	5.21 (3.4, 1.6)
a	4.94 (1.9)	5.01 (3.1, 2.0)
b	4.85 (1.7)	4.97 (3.4, 1.7)
c	4.84 (1.8)	5.05 (3.5, 1.9)

	3-H (dd)	4-H (t)
	5.24 (9.4, 3.4)	3.64 (9.3)
a	3.98 (9.8, 3.2)	5.07 (9.8)
b	3.92 (9.9, 3.4)	5.06 (9.7)
c	5.15 (10.2, 3.3)	5.02 (10.0)

	5-H (dq)	6-H$_3$ (d)
	3.80 (9.3, 6.2)	1.34 (6.2)
a	3.89 (9.8, 6.3)	1.22 (6.4)
b	3.71 (9.7, 6.3)	1.16 (6.3)
c	3.81 (9.6, 6.3)	1.17 (6.3)

ACETATES δ_H 2.18, 2.17, 2.13(x2), 2.10, 2.06, 2.04, 1.97 all (s).

$-OCH_2-$ δ_H 3.64, [dt(9.6, 6.8)]

δ_H 3.40

t_{METHYL} δ_H 0.88, [t(7.0)]

TABLE 10.

^{13}C n.m.r Chemical Shifts (ppm) of (23)

$CH_3-\overset{O}{\overset{\|}{C}}$ (s)	1-C (d)	CH_2-O (t)
170.30	99.13	68.18
169.89	99.03	
169.85	98.72	
169.80	97.21	
169.76		
169.73		
169.38		

CH-O (d)	ALKYL CHAIN (t)	$CH_3-\overset{O}{\overset{\|}{C}}$ (q)
79.33	31.172	20.74
75.17	29.43 (x3)	20.69
74.65	29.33	20.61 (x2)
72.03	29.19	20.54 (x2)
71.79	29.13	20.52
71.61	25.87	20.40
71.44	22.47	
71.32		
70.76		
70.16		
69.96		
68.47		
67.41		
67.27		
67.04		
66.54		

6-C (q)	^{t}METHYL (q)
17.91	13.87
17.02	
16.97	
16.93	

TABLE 11

^1H n.m.r Chemical Shifts (ppm) of (24).

1-H (d)	J(Hz)	2-H (d)	
5.21	(1.6)	5.03	(1.5)
5.20	(1.7)	4.95	(1.9)
4.64	(1.5)	4.87	(1.7)

3-H (dd)		4-H (t)	
5.23	(10.2, 3.3)	5.08	(10.3)
5.13	(9.3, 3.4)	5.02	(9.3)
3.99	(9.7, 3.3)	3.63	(9.8)

5-H (dq)		$6\text{-}H_3$ (d)	
3.89	(9.9, 6.3)	1.25	(6.3)
3.82	(9.5, 6.3)	1.20	(6.3)
3.80	(9.2, 6.3)	1.16	(6.3)

ACETATES δ_H 2.16, 2.12 (x2), 2.10, 2.06, 2.03, 1.96, all (s)

$-OCH_2-$ δ_H 3.63 [dt (9.3, 6.7 Hz)]
δ_H 3.39

^{t}METHYL δ_H 0.87 [t(6.6 Hz)]

EXPERIMENTAL

The crude chloroform extract, which had been subjected to preliminary chromatography, of the stem bark of *Cleistopholis glauca* (Annonaceae), was provided by Johnson F. Ayafor, Dept. of Chemistry University of Yaounde, Cameroon. Repeated column chromatography over silical gel using $CHCl_3$-MeOH as the eluant followed by preparative T.L.C. using 7% MeOH-$CHCl_3$ as the eluant yielded six new compounds (17) - (22).

(i) 1-O-dodecanyl α-L-rhamnopyranosyl-(1→3)-α-L-2-acetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside (17)

The diacetate (17) has m.p. 117 - 120°C $[\alpha]_D$ = -65.6° (C, 1.5 in MeOH), m/z 649.

δ_H : see table 1.

(ii) 1-O-dodecanyl α-L-rhamnopyranosyl-(1→3)-α-L-2,4-diacetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside (18)

The triacetate (18) has m.p. 107 - 109°C, $[\alpha]_D$ = -67.8° (C, 1.82 in MeOH), m/z 920 $(M+Na)^+$.

δ_H : see table 2.

(iii) 1-O-dodecanyl α-L-4-acetylrhamnopyranosyl-(1→3)-α-L-2,4-diacetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside (19)

The tetraacetate (19) has m.p. 105 - 107°C, $[\alpha]_D$ = -41.5° (C, 0.6 in MeOH), m/z 961 $(M+Na)^+$

δ_H : see table 3.

δ_C : see table 4.

(iv) 1-O-dodecanyl α-L-2-acetyrhamnopyranosyl-(1→3)-α-L-2,4-diacetyl-rhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamno-pyranoside (20)

The tetraacetate (20) has m.p. 98 - 100°C, $[\alpha]_D$ = -44.5° (C, 0.5 in MeOH), m/z 961 $(M+Na)^+$.

δ_H : see table 5

δ_C : see table 6

(v) 1-O-dodecanyl-α-L-3,4-diacetylrhamnopyranosyl-(1→3)-α-L-2,4-diacetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside (21).

The pentaacetate (21) has m.p. 90 - 93°C, $[\alpha]_D$ = -54.4° (C, 0.75 in MeOH), m/z 1003 $(M+Na)^+$

δ_H : see table 7.

(vi) 1-O-dodecanyl α-L-2,3,4-triacetylrhamnopyranosyl-(1→3)-α-L-4-acetylrhamnopyranosyl-(1→4)-α-L-rhamnopyranoside (22)

The tetraacetate (22) has m.p. 64 - 67°C, $[\alpha]_D$ = -35.7° (C, 0.82 in MeOH), m/z 815 $(M+Na)^+$.

δ_H : see table 8

(vii) 1-O-dodecanylα-L-2,3,4-triacetylrhamnopyranosyl-(1→3)-α-L-2,4-diacetylrhamnopyranosyl-(1→3)-α-L-2,4-diacetylrhamnopyranosyl-(1→4)-α-L-2,3-diacetylrhamnopyranoside (23).

The peracetate (23) has m.p. 140 - 143°C $[\alpha]_D$ =-31.5°(C, 0.61 in $CHCl_3$), m/z 1149 $(M+H)^+$.

δ_H : see table 9

δ_C : see table 10.

(viii) 1-O-dodecanylα-L-2,3,4-triacetylrhamnopyranosyl-(1→3)-α-L-2,4-diacetylrhamnopyranosyl-(1→4)-α-L-2,3-diacetylrhamnopyranoside (24).

The peracetate (24) has m.p. 50-52°C $[\alpha]_D$ = -28.6°(C, 0.59 in $CHCl_3$), m/z 941 $(M+Na)^+$.

δ_H : see table 11.

1-O-dodecanyl α-L-rhamnopyranoside (32)

A small portion of the triacetate (18) was subjected to alkaline hydrolysis in Yaounde, Cameroon. Normal acidic workup fortuitiously afforded the rhamnoside (32) as a sticky solid, $[\alpha]_D$ = 8.2° (C, 0.12 in $CHCl_3$), m/z 355 $(M+Na)^+$

δ_C (25 MHz) : d : 99.7 (C-1), 73.0, 71.9, 71.2, 67.8

t : 31.9, 26.5 (5), 29.5 (3), 26.1, 22.7

q : 17.5 (C-6), 14.1

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