A THESIS

entitled

"STUDIES IN THE TERPENOID FIELD."

submitted to

The University of Glasgow

for the degree of Doctor of Philosophy

in the Faculty of Science

by

Ian M. S. Thornton, B. Sc.

Chemistry Department.

December 1971

ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

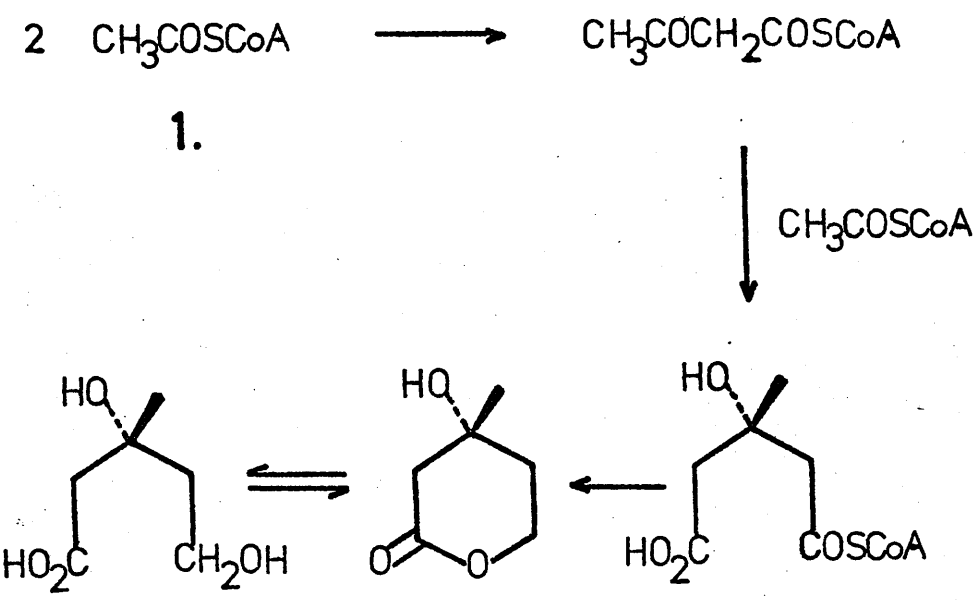
To my parents and Allison.

Acknowledgements

I would like to thank my supervisor Dr. J. D. Connolly for his constant help and encouragement during the course of this research. In addition, I would like to thank Mrs. H. Thomas for the typing of this thesis and the S.R.C. for a maintenance award.

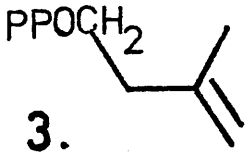
CONTENTS

SCHEME 1

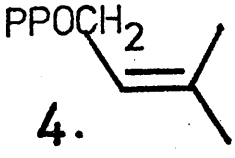


1.

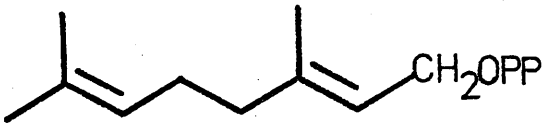
2.



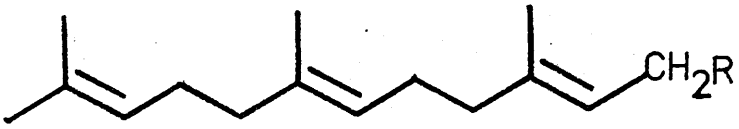
3.



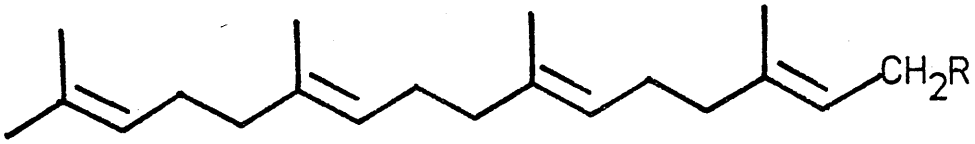
4.



5.



6. R = OH 7. R = OPP

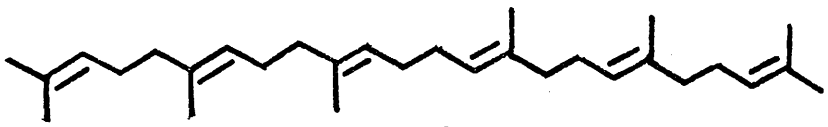


8. R=OH 9. R = OPP

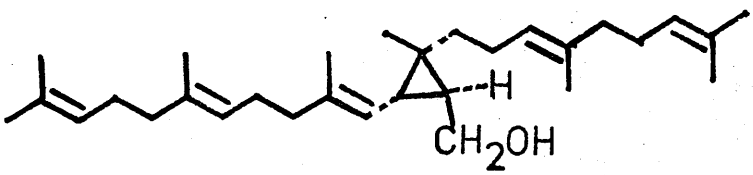
Introduction

The study of natural products has long been a subject of fascination for organic chemists. Indeed, since the last century[1], the biogenetic origin of the terpenoids has been the focal point of intensive research, but it was not until 1921, when Ruzicka formulated the Isoprene Rule, that the relationship between even the most diverse terpene structures could be seen. This recognised that each terpene could be made from a basic "building block" in the form of the isoprene unit joined in a "head to tail" manner. However, further research unearthed compounds which did not conform to this mode of formation and eventually, to overcome this, the Biogenetic Isoprene Rule[2] was conceived. This encompassed the "abnormal" terpenoids and rationalised their formation as proceeding via mechanistically feasible rearrangements of the "regular" polyisoprenoids.

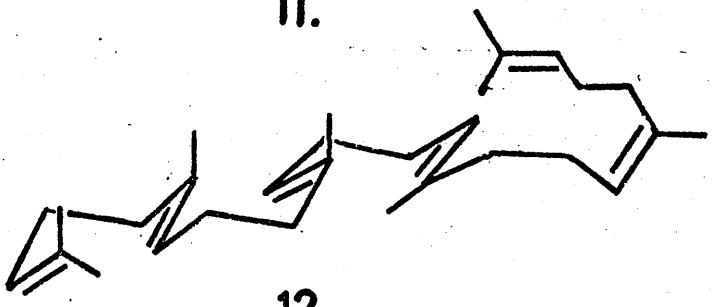
It is now firmly established that the fundamental biogenetic unit is acetic acid in the form of acetyl coenzyme A1, which by condensation reactions gives rise to mevalonic acid 2[3], the immediate precursor of the isoprene unit, (scheme (1)). The active form of the isoprene unit, isopentenyl pyrophosphate 3 and its isomer, dimethylallyl pyrophosphate 4 condense to form geranyl pyrophosphate 5, which can subsequently condense with additional isopentenyl pyrophosphate 3 to give the pyrophosphates of farnesol 6 and geranyl geraniol 8. 7 and 9 are the acyclic precursors of the sesquiterpenoids and diterpenoids respectively.



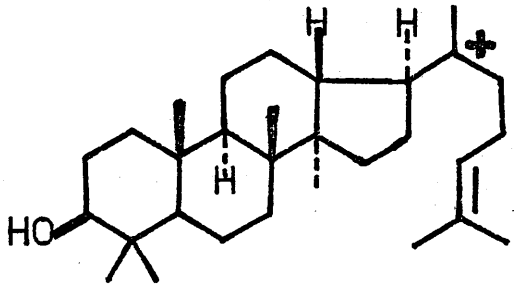
10.



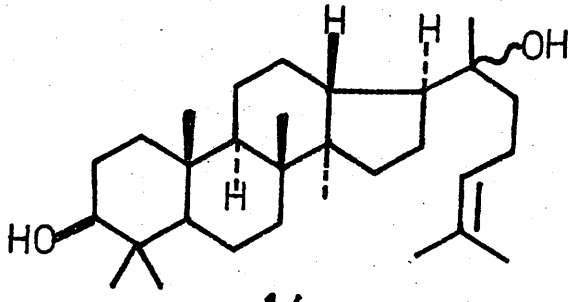
11.



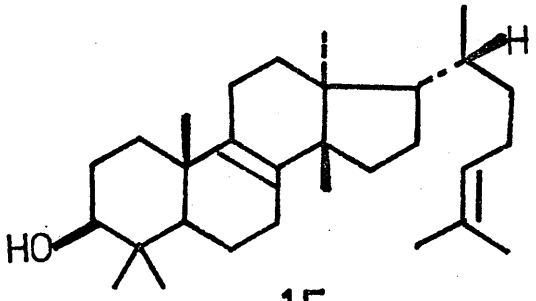
12.



13.



14.



15.

The acyclic precursor of the triterpenoids, squalene 10 has long been known to derive from two farnesyl units joined "head to head". Until recently, the mechanism of this coupling has been the only unknown in the acetate-lanosterol pathway. With the isolation[4] in 1966 of presqualene alcohol 11 and recent structural determination by total synthesis[5], much more information has been obtained about the mode of coupling.

Cyclisation of squalene conforms with the stereochemical postulates of Eschenmoser et al[6] from which the main conclusions derivable are:

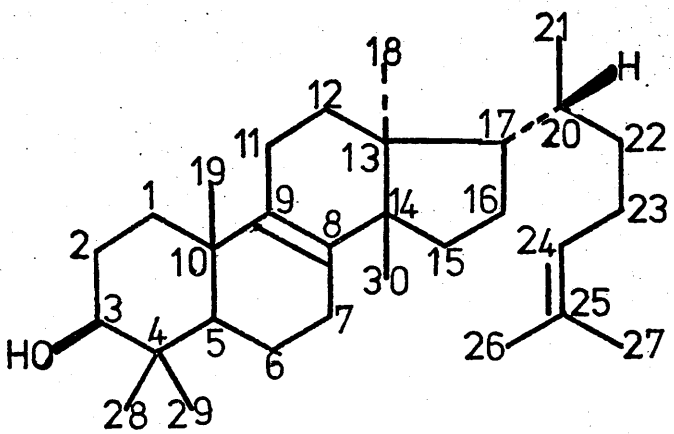
(i) The acyclic precursor is folded at the enzyme surface into a specific conformation.

(ii) Concerted cyclisation occurs by trans-planar additions to the double bond.

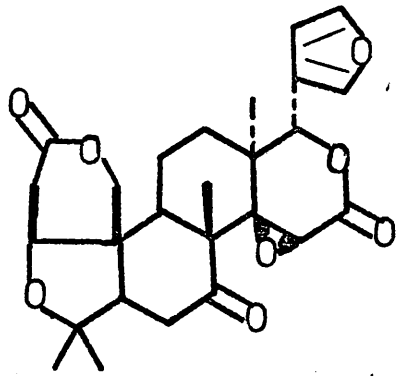
(iii) All subsequent rearrangements and/or eliminations proceed in accordance with optimal stereoelectronic requirements, i.e. the affected groups are trans-antiparallel.

Cyclisation of squalene in the chair, chair, chair, boat, conformation 12 gives rise to the carbonium ion 13 which can undergo extinction to dammarendiol 14 or subsequent rearrangement to the euphol, (or its C-20 epimer, tirucallol) skeleton. Euphol (tirucallol)[7] 15 is the postulated biogenetic precursor of the modified (furanoid) triterpenes. (See numbered skeleton on p. 5).

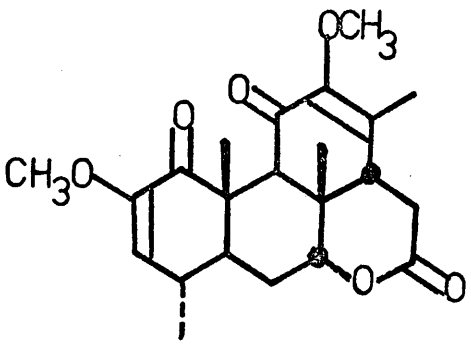
It is not proposed to give a review of the modified triterpenes as this has already been admirably accomplished[8]. However, mention will be


18
21
H
12
17
20
22
11
13
19
1
9
14
16
23
2
8
24
10
15
30
3
25
7
HO
4
5
26
27
6
28
29

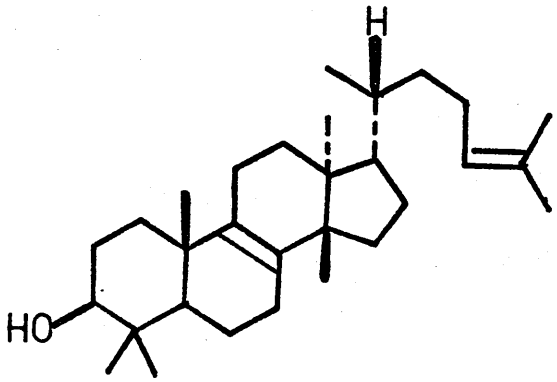
Euphol.



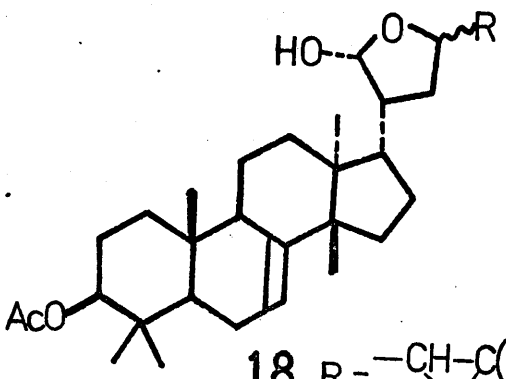
16.

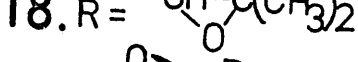


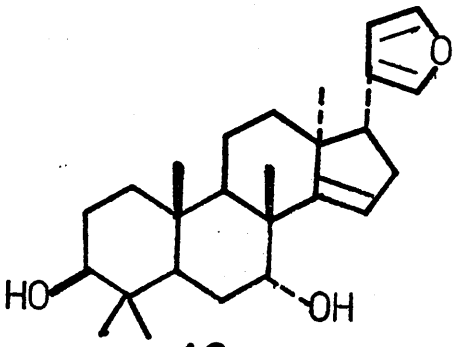
17.



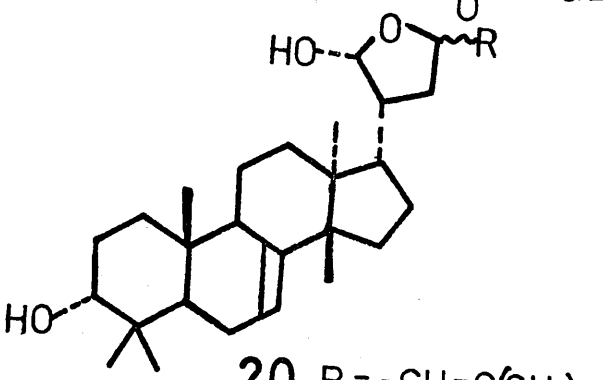
15.



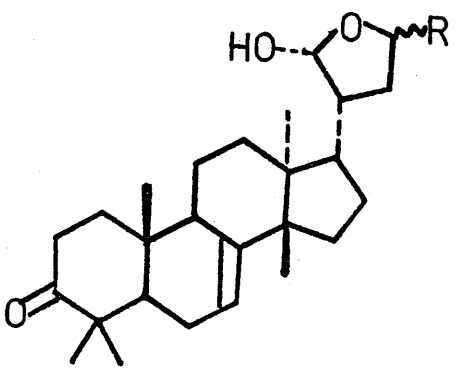
18. R = 

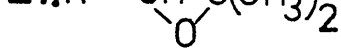


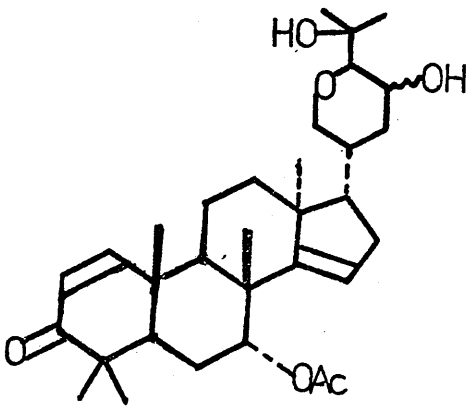
19.



20. R = $-CH=C(CH_3)_2$



21. R = 



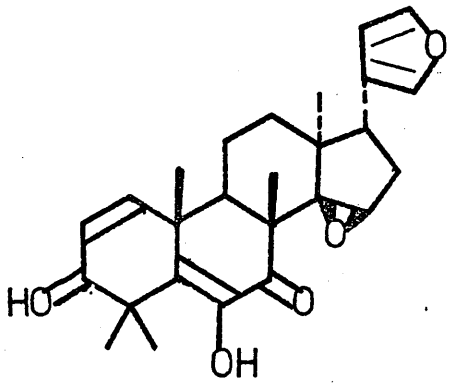
22.

made of their proposed biogenesis and *in vitro* experiments designed to support these theories. The subject of the modified triterpenes can be divided into two main parts; the tetranortriterpenoids, C26 compounds related to limonin 16[9] and C20 compounds related to quassin 17[10].

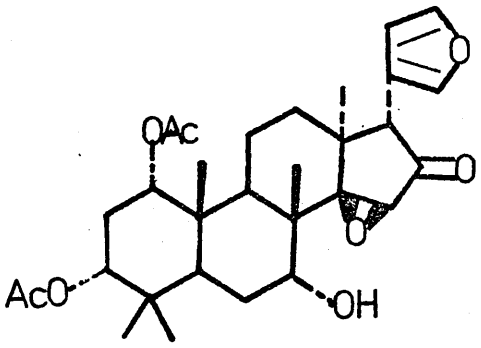
The elucidation of the constitution and configuration of limonin 16 led Arigoni *et al.*[9] to propose a biogenetic derivation for limonoid substances. Thus euphol (tirucallol) 15 a possible precursor can undergo loss of four carbon atoms by cleavage of the C-23 — C-24 bond, formation of the furan ring and skeletal rearrangement, during which one methyl group migrates from C-14 to C-8 with the introduction of oxygenation at C-7, /the apo-euphol (tirucallol) rearrangement/. These processes have now been realised[11] in the laboratory, in the conversion of turreanthin 18 into the diol 19.

The isolation of C30 compounds from Meliaceae, Rutaceae and Simaroubaceae with various stages of side-chain oxygenation lends support for this postulated biogenetic route. Flindissol 20[12], turreanthin 18[13] and melianone 21[14] are all tirucallol derivatives with a potential furan ring in the side chain. Grandifoliolenone 22[15] is particularly interesting since it is the first of a small group of naturally occurring apo-tirucallol derivatives.

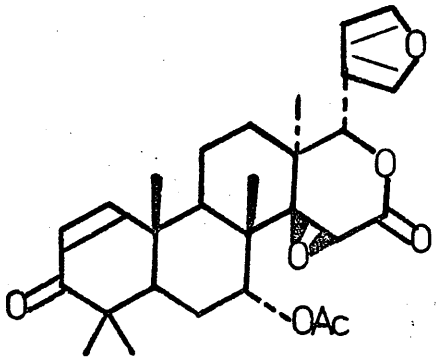
A vast range of tetranortriterpenoids (C26), based on the intact apo-euphol (tirucallol) skeleton has been isolated. The Δ^{14} double bond can be epoxidised as in cedrelone 23[16]. Allylic oxidation can lead to a



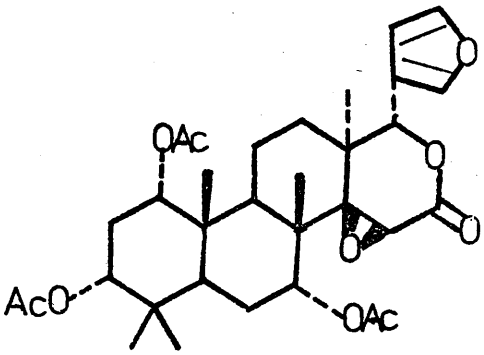
23.



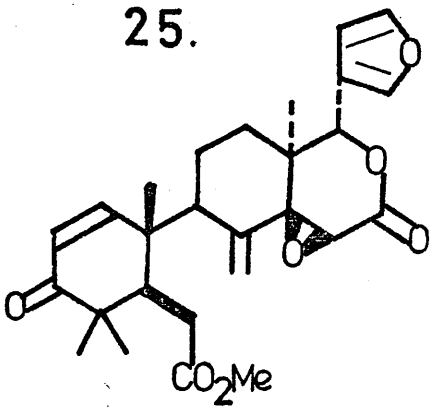
24.



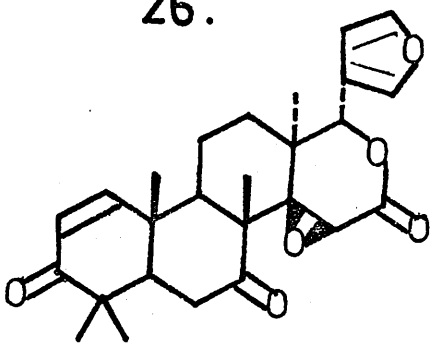
25.



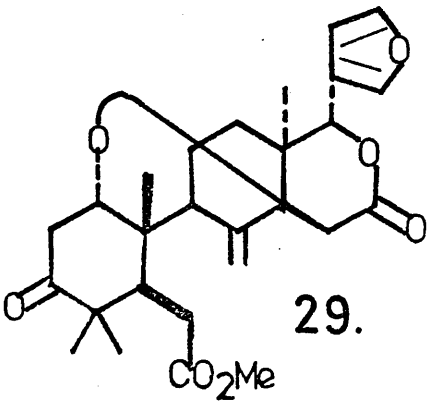
26.



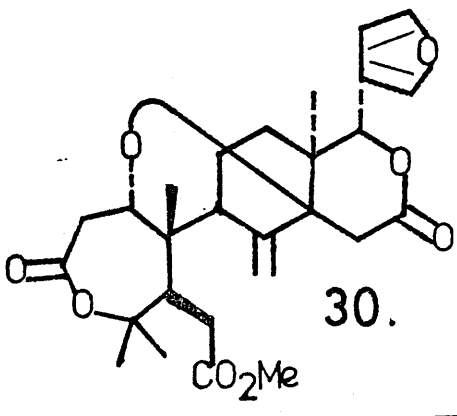
27.



28.



29.

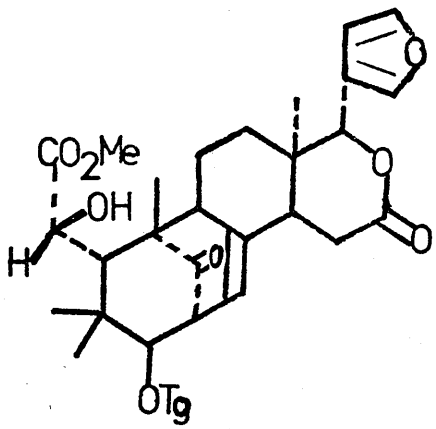


30.

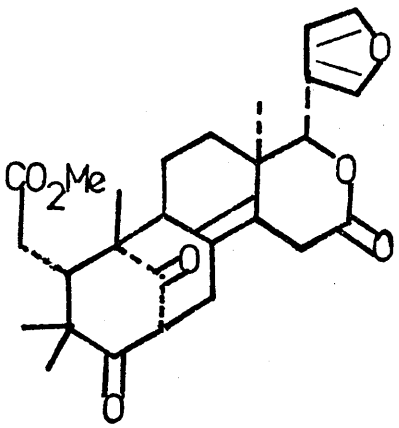
(epoxidised) cyclopentenone as in grandifolione 24[17] which can be further oxidised to the typical αβ-epoxido-δ-lactone structure found in limonin and here exemplified by gedunin 25[18] and khivorin 26[19].

A large number of tetranortriterpenoids arise from cleavage of rings A, B or C of the apo-euphol (tirucallol) skeleton. Limonin 16 provides the classical example of ring-A cleavage. Our interest lies mainly in the group of compounds which arise from cleavage of ring-B. This cleavage can be visualised as arising from a Baeyer-Villiger[20] type oxidation, a reaction which has been used extensively in the in vitro interconversions described later.

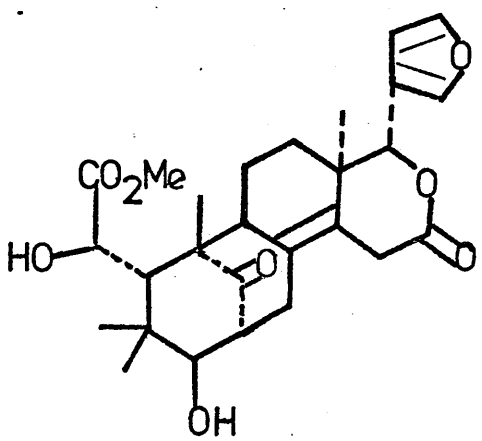
The requisite uncleaved carbonyl compounds occur as natural products and in some cases co-exist with the corresponding ring-B cleaved congener. For example, andirobin 27[21] from the seeds of Carapa guyanensis was isolated with its presumed precursor 7-deacetyl-7-oxo-gedunin 28. Methyl angolensate 29[22] can be considered to arise from 14, 15 deoxyandirobin by β-hydroxylation of the ring-A enone, followed by Michael addition from the β-face of the resulting C-1 hydroxyl to the unsaturated lactone. The isolation of methyl ivorensate 30[23] from Khaya ivorensis (Meliaceae), which can be prepared in low yield by Baeyer-Villiger oxidation of methyl angolensate 29 is of additional interest as it is an exception to the hitherto rigid confinement of ring-A cleaved tetranortriterpenoids to members of the Rutaceae.



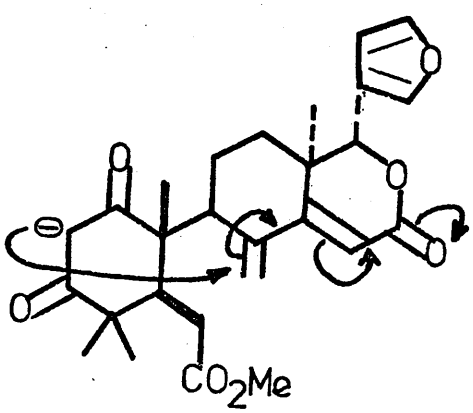
31.



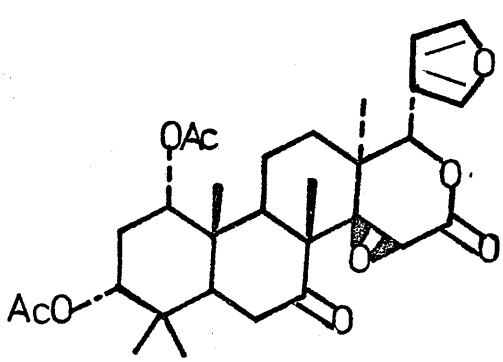
32.



33.



34.



35.

Other members of this group of ring-B cleaved tetranortriterpenoids undergo bond formation between C-2 and C-30 after the initial cleavage, resulting in the formation of the bicyclo [3, 3, 1] nonane system as found in swietenine 31[24] and mexicanolide 32[25]. This modification in structure not surprisingly caused some bewilderment in the initial structure elucidation of these compounds. The complete constitution and stereochemistry of 31 was obtained from an X-ray structure analysis[26] of detigloyl swietenine p-iodobenzoate. Mexicanolide 32 from Cedrela mexicana and swietenolide 33[27] from Swietenia macrophylla are very closely related to swietenine 31, yet differ greatly in their chemical reactivity due to the location of the $\Delta^{8, 14}$ double bond.

In biogenetic terms, mexicanolide 32 can be derived from a precursor of the type 34 which can undergo intramolecular Michael addition (arrows). The first part of this thesis is concerned with successful efforts to emulate in vitro this proposed biogenetic pathway, i.e. the transformation of an intact skeletal type (7-oxo-7-deacetoxy khivorin 35[28]), via a ring-B cleaved derivative into mexicanolide.

References.

1. G. Williams, Chem. News, 2, 206 (1860).

2. L. Ruzicka, Experientia, 9, 357 (1953).

3. K. Folkens, D. E. Wolf, C. H. Hofmann, P. E. Aldrich, H. R. Skeggs and L. D. Wright, J. Amer. Chem. Soc. 78, 4499 (1956).

4. H. C. Rilling, J. Biol. Chem., 241 3233 (1966).

5. (i) L. J. Altman, R. C. Kowerski and H. C. Rilling, J. Amer. Chem. Soc., 93, 1782 (1971).

   (ii) R. M. Coates and W. H. Robinson, J. Amer. Chem. Soc., 93, 1785 (1971).

   (iii) R. V. M. Campbell, L. Crombie and G. Pattenden, Chem. Comm., 218 (1971).

6. A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, Helv. Chim. Acta., 38, 1890 (1955).

7. R. M. Gascoigne and J. J. H. Simes, Quart. Rev. 9, 328 (1955).

8. J. D. Connolly, K. H. Overton and J. Polonsky, "Progress in Phytochemistry", Interscience, Vol. II, p. 385 1970.

9. D. Arigoni, D. H. R. Barton, E. J. Corey, O. Jeger, L. Caglioti, Sukh Dev, P. G. Ferrini, E. R. Glazier, A. Melera, S. K. Pradhan, K. Schaffner, S. Sternhell, J. F. Templeton and S. Tobinga, Experientia, 16, 41 (1960).

10. Z. Valenta, S. Papadopoulous and C. Podesva, Tetrahedron, 15, 100 (1961).

11. J. G. St. C. Buchanan and T. G. Halsall, J. Chem. Soc. (C), 2280 (1970).

12. A. J. Birch, D. J. Collins, Sultan Muhammed and J. P. Turnbull, J. Chem. Soc., 2762 (1963).

13. C. W. L. Bevan, D. E. U. Ekong, T. G. Halsall and P. Toft, J. Chem. Soc. (C), 820 (1967).

14. D. Lavie, Mahendra K. Jain and I. Kirson, J. Chem. Soc. (C) 1347 (1967).

15. J. D. Connolly and R. McCrindle, J. Chem. Soc. (C), 1715 (1971).

16. (i) I. J. Grant, J. A. Hamilton, T. A. Hamor, J. M. Robertson and G. A. Sim, J. Chem. Soc., 2506 (1963).

(ii) R. Hodges, S. G. McGeachin and R. A. Raphael, J. Chem. Soc., 2515 (1963).

(iii) K. W. Gopinath, T. R. Govindachari, P. C. Parthasorathy, N. Viswanathan, D. Arigoni and W. C. Wildman, Proc. Chem. Soc., 446 (1961).

17. J. D. Connolly, K. L. Handa, R. McCrindle and K. H. Overton, J. Chem. Soc. (C), 2227 (1968).

18. A. Akisanya, C. W. L. Bevan, T. G. Halsall, J. W. Powell and D. A. H. Taylor, J. Chem. Soc., 3705 (1961).

19. C. W. L. Bevan, T. G. Halsall, M. N. Nwaji and D. A. H. Taylor, J. Chem. Soc., 768 (1962).

20. A. Von Baeyer and V. Villiger, Ber., 32, 3625 (1899).

21. W. D. Ollis, A. D. Ward, H. Meirelles de Oliveira and R. Zelnik, Tetrahedron, 26, 1637 (1970).

22. (i)C. W. L. Bevan, J. W. Powell, D. A. H. Taylor, T. G. Halsall, P. Toft and M. Welford, J. Chem. Soc. (C), 163 (1967).

(ii)W. R. Chan, K. E. Magnus and B. S. Mootoo, J. Chem. Soc. (C), 171 (1967).

23. E. K. Adesogan and D. A. H. Taylor, J. Chem. Soc. (C), 1710 (1970).

24. J. D. Connolly, R. Henderson, R. McCrindle, K. H. Overton and N. S. Bhacca, J. Chem. Soc. 6935 (1965).

25. (i)J. D. Connolly, R. McCrindle and K. H. Overton, Tetrahedron, 24, 1489 (1968).

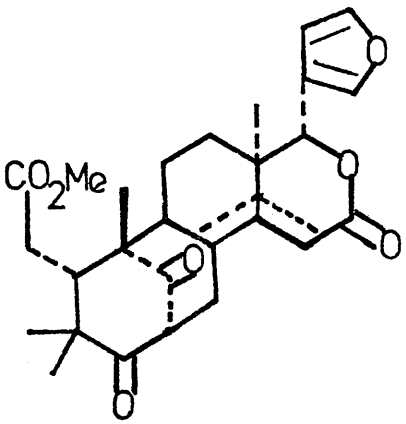
(ii)J. D. Connolly, R. McCrindle and K. H. Overton, Tetrahedron, 24, 1497 (1968).

26. A. T. McPhail and G. A. Sim, J. Chem. Soc. (B), 318 (1966).

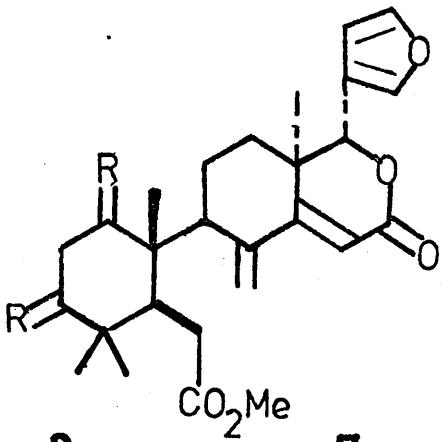
27. (i)T. Chakrabarthy, J. D. Connolly, R. McCrindle, K. H. Overton and J. C. P. Schwarz, Tetrahedron, 24, 1503 (1968).

(ii)J. D. Connolly, R. McCrindle, K. H. Overton and W. D. C. Warnock, Tetrahedron, 24, 1507 (1968).

28. J. D. Connolly, K. L. Handa, R. McCrindle and K. H. Overton, J. Chem. Soc. (C), 2227 (1968).

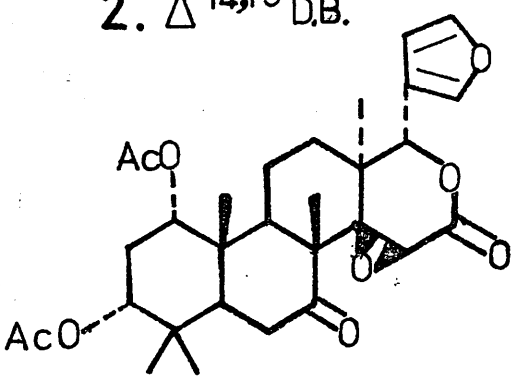


1. $\Delta^{8,14}$ D.B.
2. $\Delta^{14,15}$ D.B.

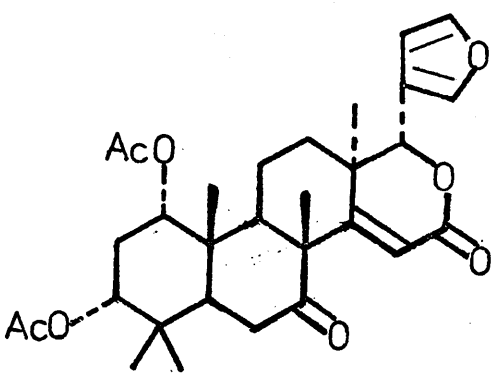


3. R = O

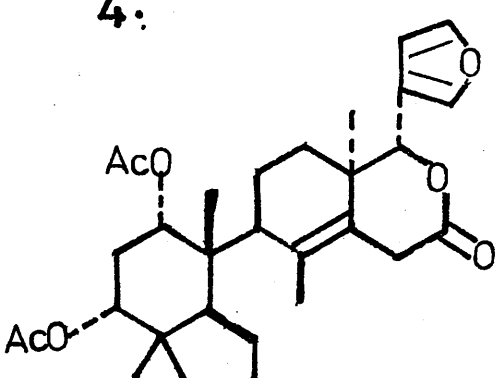
7. R = αOAc, H



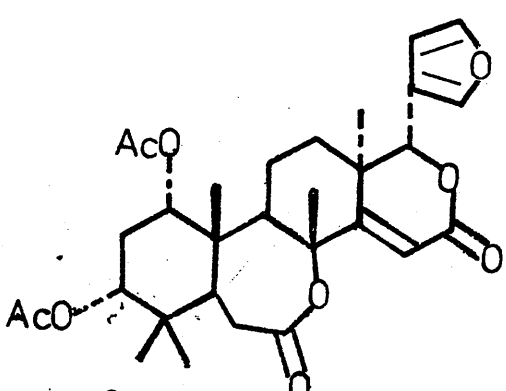
4.



5.



6.

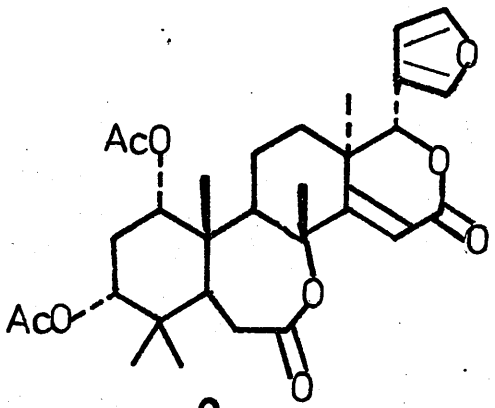


8.

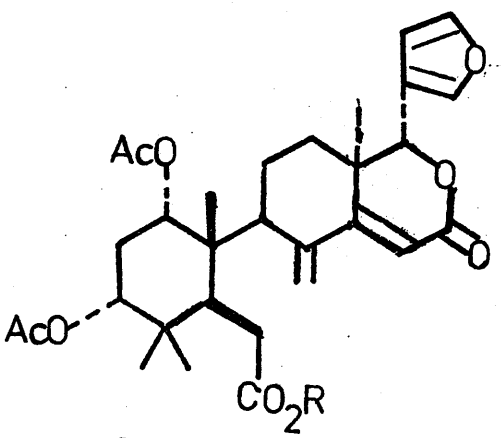
Discussion

As discussed in the introduction (see p.11) the proposed biogenetic precursor of the bicyclononanolide group of tetranortriterpenoids (e.g. mexicanolide 1[1] or its double bond isomer carapin 2[2]) is a compound of the type 3. This, by a Michael-type additon of C-2 to C-30 would give the required bicyclononanolide system. Our aim was to interconvert the intact skeletal type of tetranortriterpenoid as in 7-oxo-7-deacetoxy khivorin 4[3] with the bicyclononanolide in an attempt to emulate in vitro the proposed biogenetic pathway. In a previous attempt[4] at this interconversion, cleavage of ring-B was achieved by treating 14, 15 deoxy-7-oxo-7-deacetoxy khivorin 5 with strong base, under conditions analagous to those employed in the conversion of deoxy-limonin into deoxylimonic acid[5], (cleavage of a vinylogous β-keto lactone). The product formed after esterification with ethereal diazomethane was the βγ-unsaturated lactone 6 which unfortunately could not be transformed into the desired cisoid diene lactone 7.

We preferred to utilise a Baeyer-Villiger[6] oxidation as it had the benefit of giving the required oxidation level. Treatment of 14,15 deoxy-7-oxo-7-deacetoxy khivorin 5 with m-chloro perbenzoic acid gave negligible yields of the desired ε-lactone 8. However, peracetic acid in the presence of anhydrous disodium hydrogen phosphate (as buffer), smoothly converted 5 to the ε-lactone 8 m.p. 289-291°C., [ν_{max} 1730 (δ and ε-lactones) cm^{-1}, (no cyclohexanone)]. Treatment of the

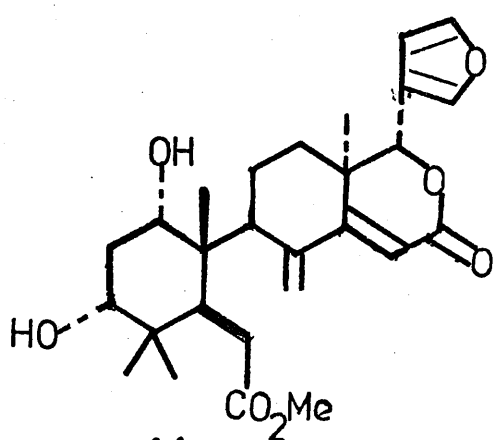


8.

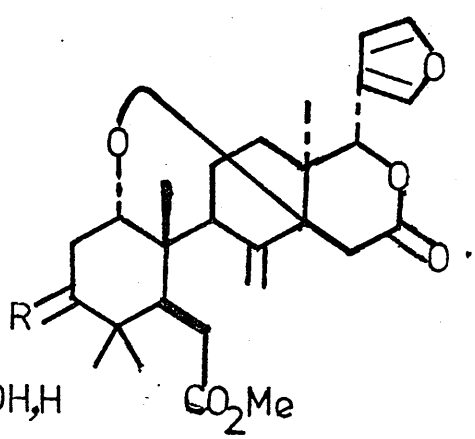


9 . R = H

10 . R = Me



11.

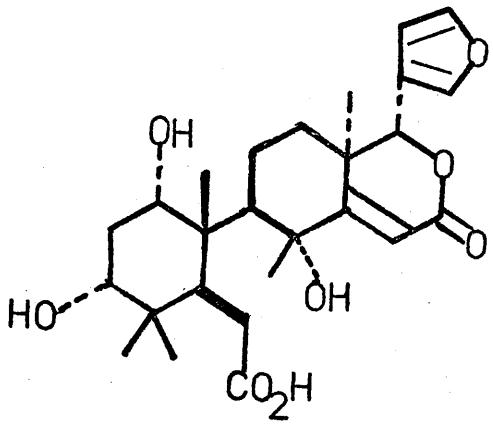


12 . R = αOH,H

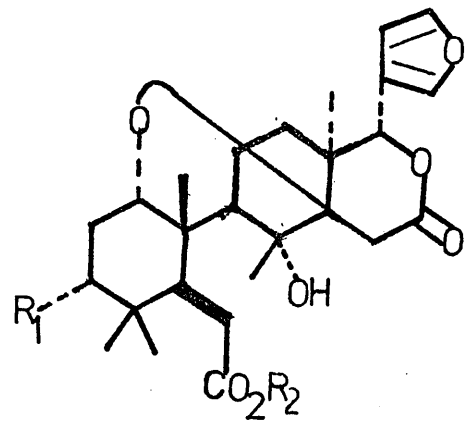
13 . R = O

ε-lactone 8 with either base or acid gave the required ring B-cleaved system, but not without added complications. With a catalytic amount of p-toluene sulphonic acid in refluxing benzene, an equilibrium was set up between starting material and the unsaturated acid 9. No attempts were made to increase yields by altering reaction conditions. The acid 9 m.p. 233-236°C. was purified by preparative TLC and characterised as its methyl ester 10 m.p. 119-124°C., [NMR spectrum showed loss of one tertiary methyl group and introduction of an exomethylene group at τ 4.78, 4.72].

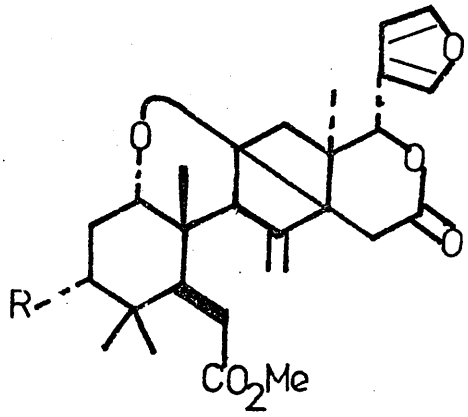
Base hydrolysis of the acetates of 10 in methanol did not give the expected diol 11, but instead gave a compound m.p. 209-212°C. identified as 3α-hydroxy dihydro methyl angolensate 12 [NMR showed loss of acetates and H-15]. This compound 12 is identical with a minor product of reduction of methyl angolensate 13 with aluminium isopropoxide[7] and had resulted from a Michael additon of the C-1 αOH group to the αβ-unsaturated lactone system. Subsequent mild oxidation with Jones[8] reagent of 12 gave methyl angolensate 13 m.p. 201-204°C. (lit.[9] 203-208°C). This series of reactions, transforming a khivorin derivative for which the 1α configuration had been established[10], into methyl angolensate proved that the ether oxygen in methyl angolensate is attached in the 1α configuration, as had been considered most probable.[11]



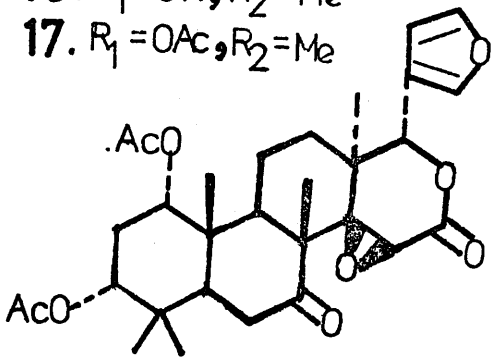
14.



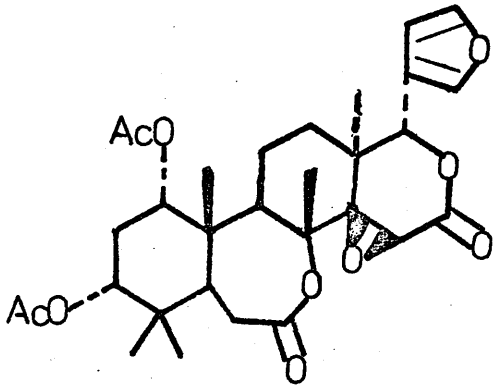
15. $R_1 = OH$, $R_2 = H$
16. $R_1 = OH$, $R_2 = Me$
17. $R_1 = OAc$, $R_2 = Me$



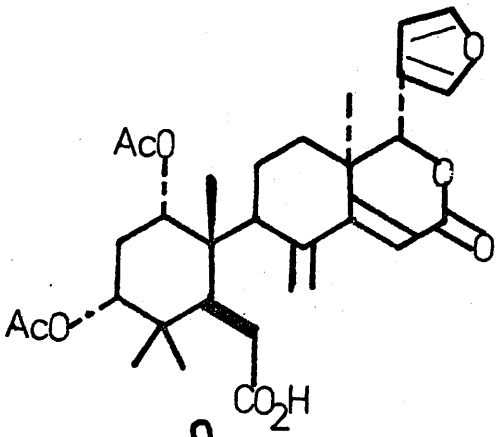
18. R = OAc
12. R = OH



4.



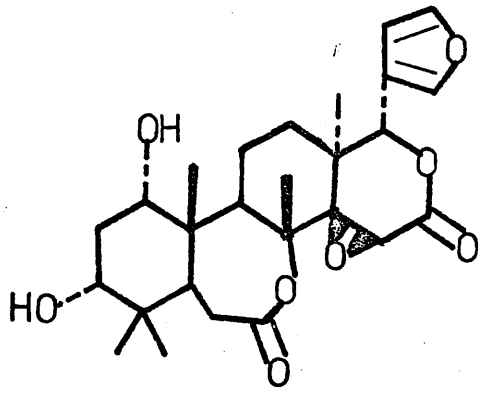
19.



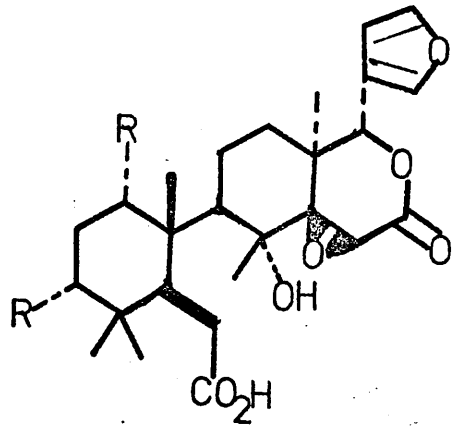
9.

Under basic conditions, the ε-lactone 8 opened to give the trihydroxy acid 14 which underwent the facile Michael addition of the 1 α OH to the ring-D unsaturated lactone giving the acid 15 characterised as its methyl ester 16 m.p. 280°C decomp., [loss of H-15 in the NMR, νmax 3610, 3530 cm^{-1}]. Acetylation of 16 gave the hydroxy acetate 17 m.p. 258-260°C which underwent smooth dehydration with thionyl chloride in pyridine to give the olefin 18 m.p. 224-226°C., 3α-acetoxy dihydro methyl angolensate, identical with the compound from acetylation of 3α-hydroxy dihydro methyl angolensate 12. Dehydration of 17 could in theory give rise to two olefins, the $\Delta^{8,9}$ olefin with a tetrasubstituted double bond, or the $\Delta^{8,30}$ isomer 18 with the exocyclic methylene group. In the event, only the latter was found in detectable amounts.

It was now obvious that removal of the 14,15 epoxide to give the corresponding 14,15 deoxy compound was a step which would have to be carried out later on in the reaction sequence in order to avoid this very ready Michael addition. In a fresh approach, 7-oxo-7-deacetoxy khivorin 4 was transformed under the previously described Baeyer-Villiger conditions to the ε-lactone 19 m.p. 308°C decomp. [$\nu_{max}^{CHCl_3}$ 1730 (acetates, δ and ε-lactones) cm^{-1}, no cyclohexanone]. Attempts to open this epoxy ε-lactone using p-toluene sulphonic acid in refluxing benzene as before, failed. This may be due to the fact that the exomethylene group did not form part of a conjugated system as in 9. However, under basic conditions a variety of compounds could be formed, depending on base used or length of time of reaction.

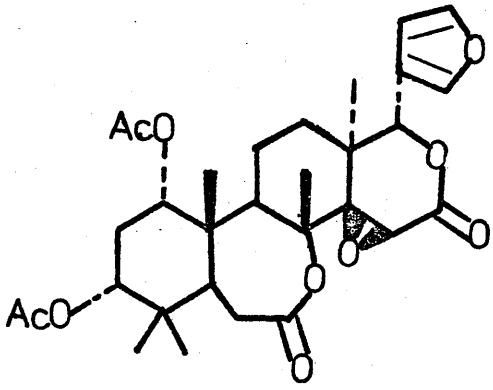


20.

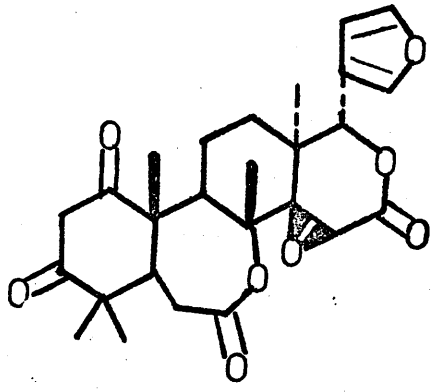


21. R = OAc

22. R = OH



19.

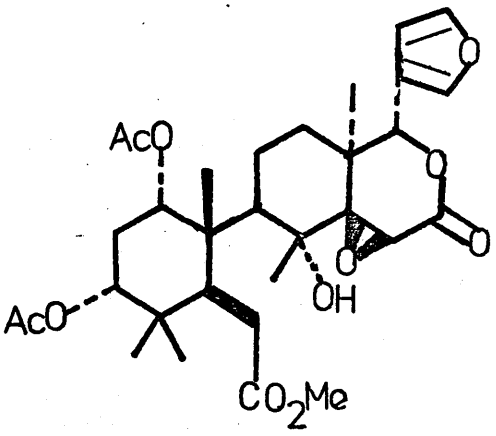


23.

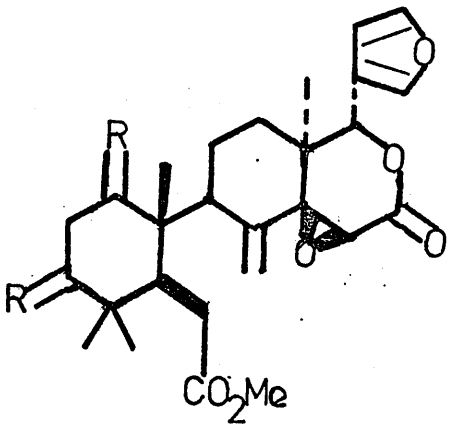
The diol 20 m.p. 250-253°C was obtained in low yield as the minor component of a mixture containing the corresponding diacetoxy hydroxy acid 21. Strangely enough, the latter, if allowed to stand in acidic solution, slowly relactonised to give back the epoxy lactone 19. Under stronger basic conditions (25% NaOH/aqueous methanol), the triol acid 22 was formed. Unfortunately, this very polar compound was accompanied by equal amounts of a compound of similar polarity which could not be utilised in the general reaction scheme. This latter compound will be discussed later, (see p.30).

The NMR spectrum of the diol 20 had broad singlets at τ 8.42, 8.34 which disappeared on shaking with D_2O, in addition to two multiplets at τ 6.34, 6.26 (H-1, H-3), which sharpened correspondingly. Mild oxidation with Jones reagent furnished the β-diketone 23 m.p. 280-284°C $\nu_{max}^{CHCl_3}$ 1740 (lactones), 1710 (β-diketone) cm^{-1}, no hydroxyls; τ 6.55 (singlet, 2 H-2, exchangeable[12] over a period of time with D_2O); λ max 260 nm. shifting to 289 nm. (on addition of base). Attempts to remove the epoxide using chromous chloride were unsuccessful. A large mixture of products was obtained from which the required 14,15 deoxy compound could not be isolated.

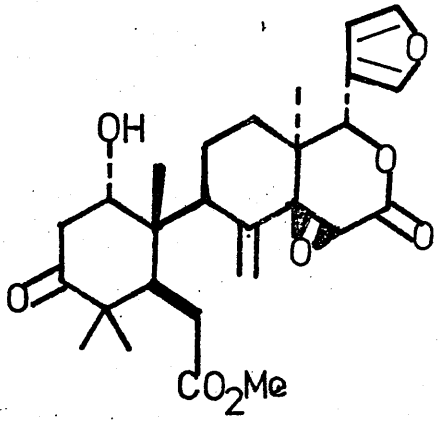
Our attention then turned to the hydroxy acid 21 which could be made in reasonably high yield by treatment of the ε-lactone 19 with potassium carbonate in aqueous methanol. Some hydroxy methyl ester 24 was also



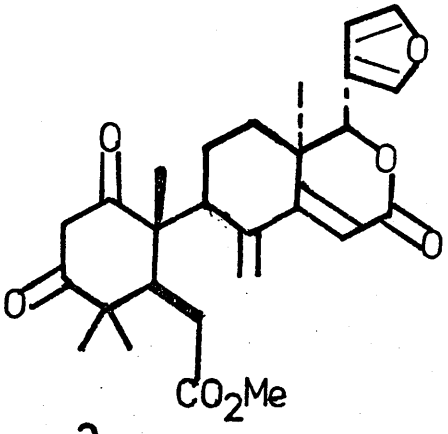
24.



25. R = αOAc, H
26. R = αOH, H
27. R = O



28.

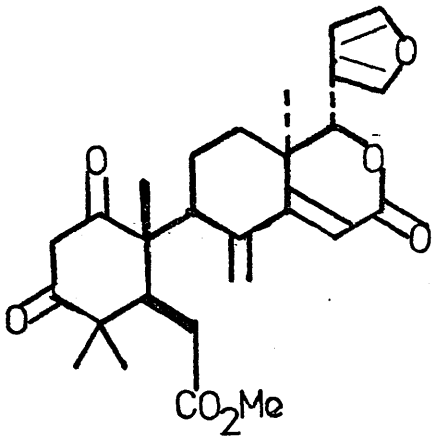


3.

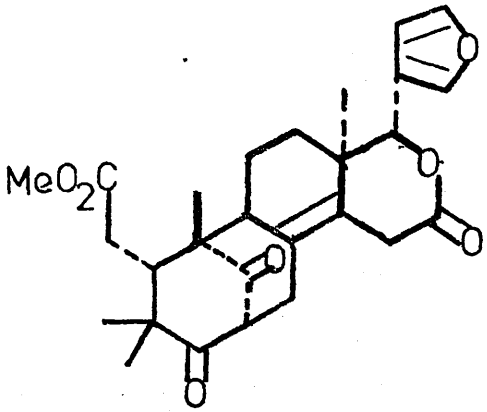
formed. This presumably arises from methanolysis of the ε-lactone. Methylation of this mixture with ethereal diazomethane gave the hydroxy methyl ester 24 m.p. 274-277°C [$\nu_{max}^{CHCl_3}$ 3590 (hydroxyl)cm^{-1}] in good yield. One exchangeable proton [τ 9.00] in the NMR spectrum and the lack of carbinol protons confirmed the presence of a tertiary hydroxyl group.

Dehydration of the hydroxy methyl ester 24 gave the anticipated olefin 25 m.p. 197-198°C [c.f. 17 to 18]. The presence of the exomethylene group was clearly evident from the NMR spectrum [τ 4.93, 4.60 (singlets, each 1H); disappearance of one tertiary methyl group]. Again, no trace of the corresponding $\Delta^{8,9}$ olefin could be detected. Removal of the acetate groups by mild alkaline hydrolysis yielded the non-crystalline diol 26 [τ 6.43, 6.26 (multiplets, H-1, H-3); $\nu_{max}^{CHCl_3}$ 3625, 3600, 3500 (hydroxyls) cm^{-1}]. The β-diketone 27 m.p. 188-192°C was obtained by oxidation of the diol 26 with Jones reagent. It had the expected spectroscopic properties [νmax 1735 (methyl ester, δ-lactone), 1707 (β-diketone) cm^{-1}; τ 6.10 (singlet, 2H-2); λmax 261 n.m. (ε 9,300) moving to 289 n.m. (ε 22,600) on addition of base, returning to 261 n.m. on reacidification]. A second product was the hydroxy ketone, 28, the structure of which will be discussed below (see p.26).

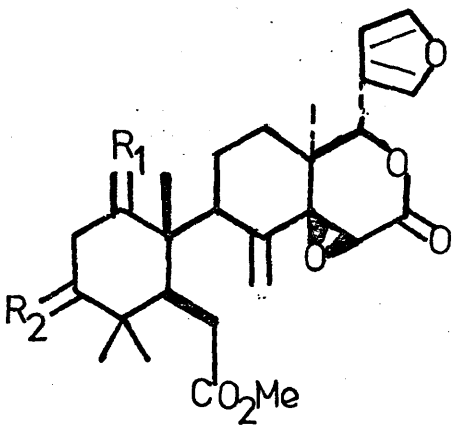
To reach the required cisoid diene-lactone precursor 3 all that remained was to remove the epoxide ring. This was achieved as before with



3.

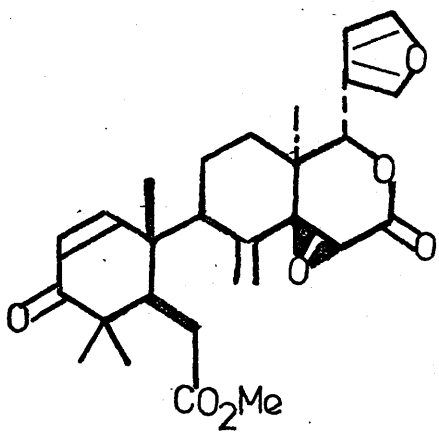


1.

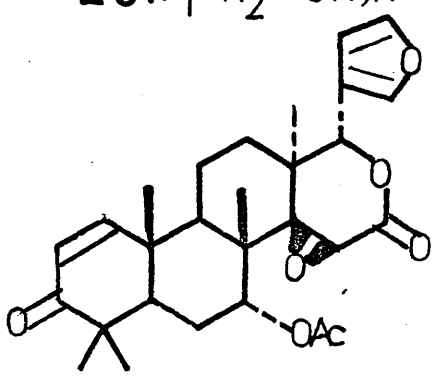


28. R_1 = αOH, H ; R_2 = O

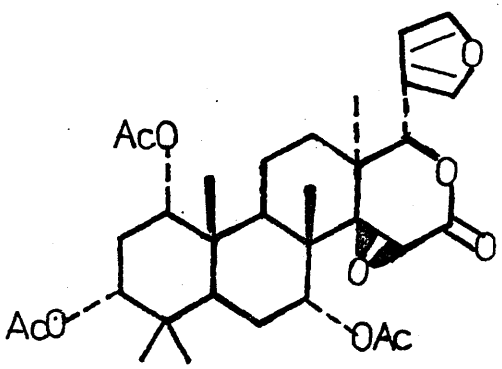
26. R_1 = R_2 = αOH, H



29.



30.

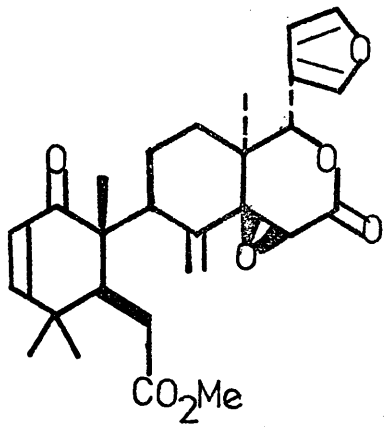


31.

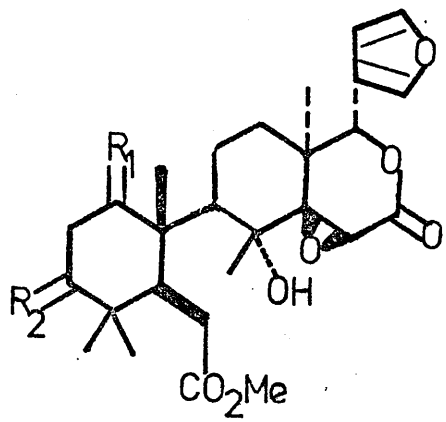
chromous chloride, and produced the surprisingly polar and labile precursor 3 as the major component of a mixture of several compounds. This compound in our hands exhibited a surprising lack of solubility and an amazing urge towards spontaneous cyclisation. Purification by preparative TLC invariably produced a small amount of cyclised product later identified as the long-awaited bicyclononanolide, mexicanolide. The precursor 3 m.p. 193-198°C had H-15 as a sharp singlet at τ4.00 and λmax 262 nm. (ε 9.000). Controlled cyclisation of 3 using a two-phase system of chloroform and aqueous sodium bicarbonate furnished the cyclised product 1 m.p. 221-226°C., $[\alpha]_D$-85°, identified as mexicanolide (lit[1] m.p. 222-227°C., $[\alpha]_D$-90°) identical in all respects to naturally occurring material.

It now remained to clarify the structures of a number of compounds which had arisen in side reactions associated with the main synthetic scheme.

The structure of the hydroxy ketone 28 from partial oxidation of the diol 26 was easily settled by the fact that subsequent dehydration using thionyl chloride in pyridine yielded the known compound andirobin 29[13] m.p. 193-196°C., (lit.[13] m.p. 195-197°C), [identical IR and NMR spectra]. No evidence could be found for the presence of the other possible hydroxy ketone. This type of selective oxidation has been encountered before in analagous systems, i.e. in the interconversion[14] of gedunin 30 and khivorin 31.

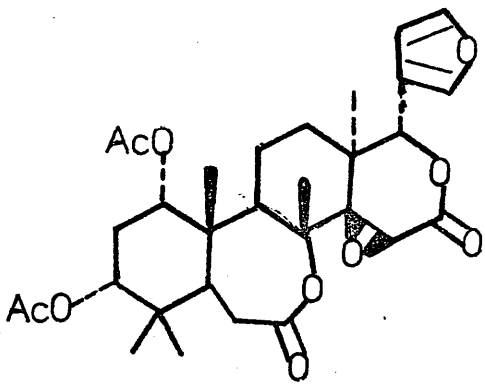


32.

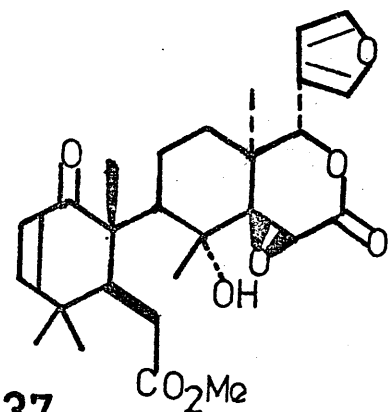


33. $R_1 = R_2 = \alpha OH, H$ 35. $R_1 = O, R_2 = \alpha OH, H$

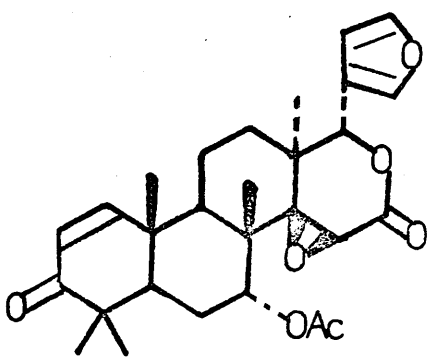
34. $R_1 = R_2 = O$ 36. $R_1 = O, R_2 = \alpha OAc, H$



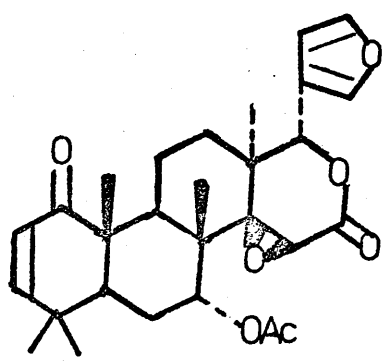
19.



37.



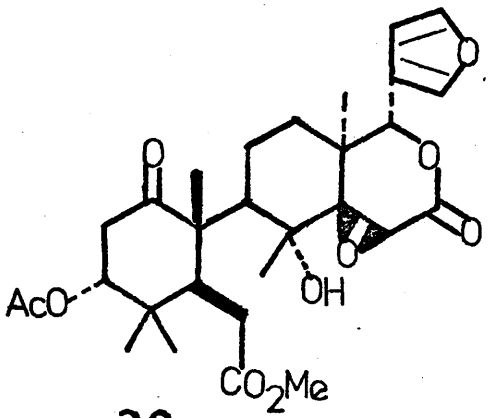
30.



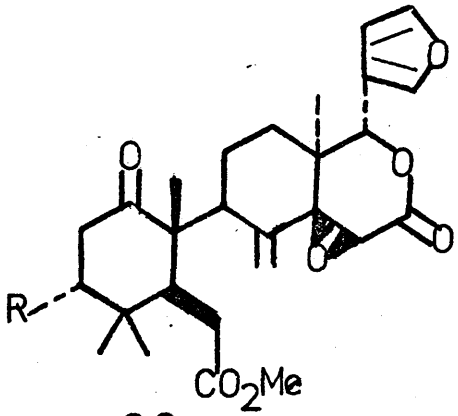
38.

The isomer of andirobin 29 which we shall call isoandirobin 32 was synthesised from yet another of the side products of the general reaction scheme. The triol methyl ester 33 m.p. 236-240°C from prolonged hydrolysis of the ε-lactone 19 was subjected to mild oxidation under Jones conditions. As in the case of the diol 26, two compounds, the β-diketone 34 and the less polar hydroxy ketone 35 were obtained. Acetylation of the latter with acetic anhydride in pyridine led to a mixture of two compounds of very similar polarity. Separation of this mixture proved very difficult. The more polar compound was the expected 3α-acetoxy derivative 36 [τ 7.98 (singlet, acetate), 5.07 (multiplet, H-3); νmax 3600, 3520 (hydroxyl), 1740 (methyl ester, acetate, δ-lactone), 1710 (cyclohexanone) cm^{-1}].

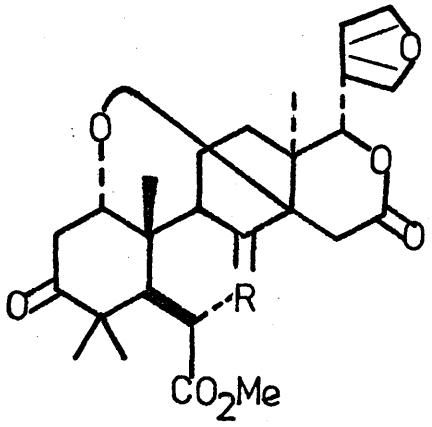
It was apparent from its spectroscopic properties that the less polar compound was the enone 37 m.p. 193-194°C., [νmax 3600, 3520 (hydroxyl), 1740 (methyl ester, δ-lactone), 1675 (cyclohexenone) cm^{-1}; τ 4.14, 3.41 (AB quartet, H-2, H-3, respectively, J = 10 Hz)]. The chemical shifts of the protons on the enone double bond are characteristic[15] of a Δ^2-1-ketone (c.f. gedunin 30 and isogedunin 38) and this confirms the assignment of the 3-hydroxy-1-keto structure to the ketol 35. Dehydration of the tertiary alcohol in the enone 37 using thionyl chloride in pyridine gave as the main product the non-crystalline isoandirobin 32 [$[\alpha]_D$ + 22°, τ 4.74, 4.71, 4.38 (singlets, each 1H,



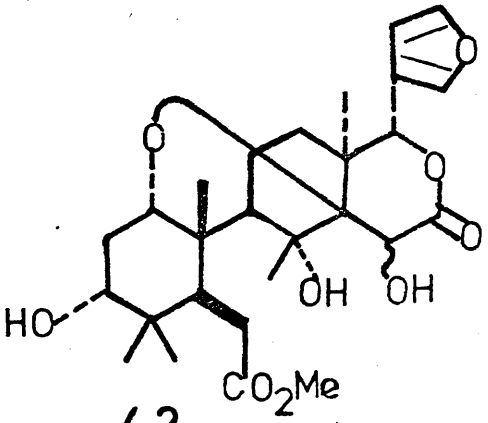
36.



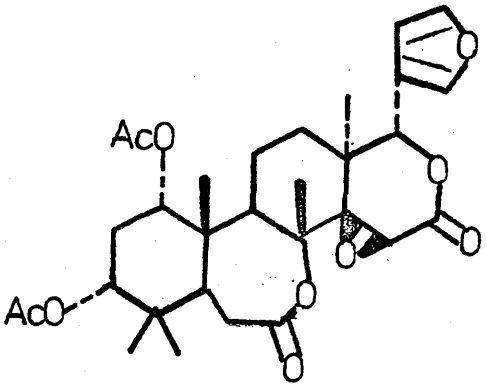
39. R = OAc
40. R = OH



13. R = H
41. R = OH



42.

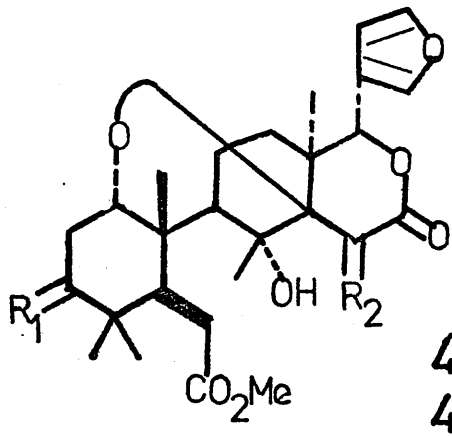


19.

exomethylene protons and H-17, no individual assignments); ν max no hydroxyl 7.

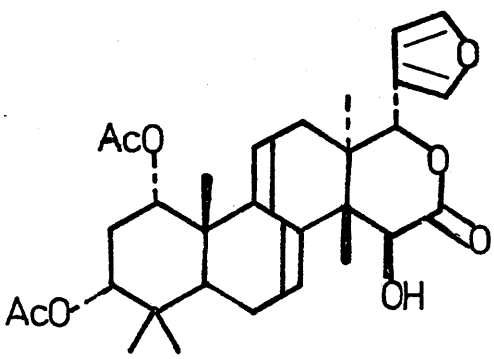
Dehydration of the acetate 36 under the same conditions gave in poor yield the olefin 39, [τ 9.18, 9.08, 8.74 (6H) (singlets, 4 tertiary methyls), 7.89 (singlet, acetate), 6.39 (singlet, methyl ester), 6.10 (singlet, H-15), 5.10 (multiplet, H-3), 4.59, 4.52, 4.38 (singlet, exomethylene, H-17), 3.64, 2.58 (furanic protons); ν max 1740 (methyl ester, acetate, δ-lactone), 1700 (cyclohexanone) cm^{-1}]. The corresponding alcohol 40 "mahoganin" was reputed to have been isolated[16] from Swietenia mahogani. A later investigation[17] showed that "mahoganin" was a mixture of methyl angolensate 13 and 6-hydroxy methyl angolensate 41. Shortage of material prevented hydrolysis of the acetate to form "mahoganin".

The structure of the triol ether 42 m.p. 235-238°C., [$\nu_{max}^{CHCl_3}$ 3460 (hydroxyl), 1735 (methyl ester, δ-lactone) cm^{-1}] from prolonged base treatment of the ε-lactone 19 followed from spectroscopic evidence. Thus the NMR spectrum had significant signals at τ 6.78 (singlet), 6.37 (broad singlet) (each 1H, both exchangeable with D_2O), 6.44, 6.07 (multiplets, the higher field signal sharpening slightly on D_2O addition, H-3, H-1 respectively), 5.52 (multiplet, sharpening to a singlet on D_2O addition, H-15). Confirmation of these assignments came from decoupling experiments. Irradiation at τ 7.86, the C-2 methylene group caused both

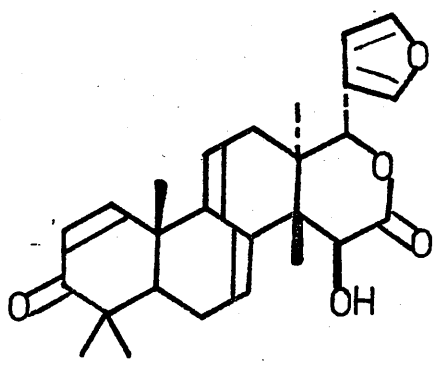


42. R_1 = αOH, H ; R_2 = OH, H

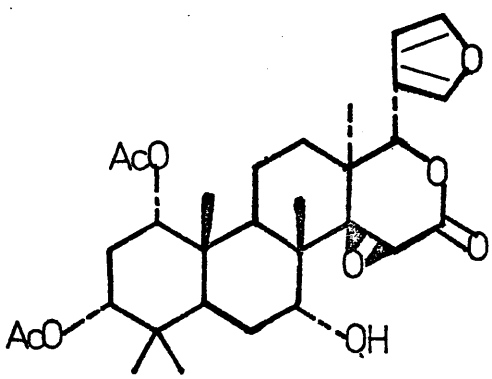
43. R_1 = αOAc, H ; R_2 = OAc, H



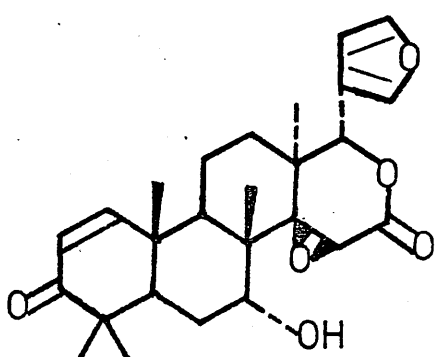
44.



45.



46.

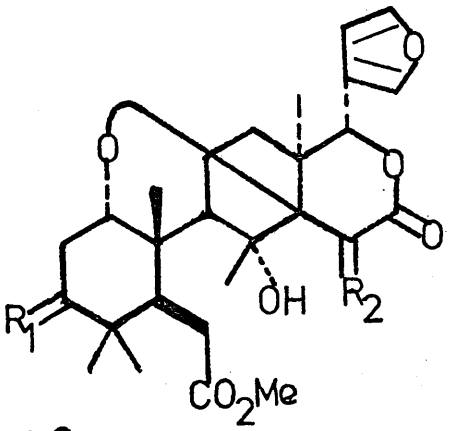


47.

multiplets to collapse to singlets. H-17 appeared at τ 3.79, a remarkably low-field position for this signal.

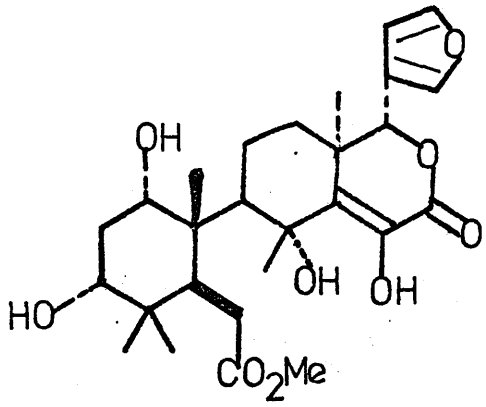
Acetylation of this triol ether 42 gave a diacetoxy alcohol 43 m.p. 173-176°C., λ_{max} 3610, 3490 (hydroxyl), 1770 (δ-lactone), 1740 (methyl ester, acetates) cm^{-1}. The abnormally high value for the δ-lactone is consistent[18] with the presence of an adjacent oxygen substituent, in this case the acetate, causing a direct dipolar interaction with the carbonyl of the δ-lactone. The NMR spectrum had well separated signals at τ 9.20, 9.04, 8.92, 8.73, 8.51 (singlets, 5 tertiary methyls), 8.18, 7.81 (singlets, 2 acetates), 7.14 (1H, singlet, exchangeable with D_2O), 6.33 (singlet, methyl ester), 6.02, 5.35 (multiplets, H-1, H-3 respectively), 4.36 (singlet, H-15), 4.12 (singlet, H-17), 3.41, 2.56, 2.02 (furanic protons). Again, decoupling experiments (irradiation at τ 7.98) demonstrated the correct assignment of H-1, H-3. The change in chemical shift for H-15, (τ 5.52 to τ4.36), on acetylation, agrees well with the values reported by Ekong et al.[19] for compounds of the type 44 and 45 obtained by BF_3 catalysed rearrangement of the 7-hydroxy derivatives related to 7-deacetyl khivorin 46 and 7-deacetyl gedunin 47.

Oxidation of the triol ether 42 with Jones reagent, gave a relatively non-polar compound, which did not crystallise and which decomposed over a period of several days. This compound, λ_{max} 3515 (hydroxyl), 1768 (δ-lactone), 1735 (methyl ester, 15-ketone), 1723

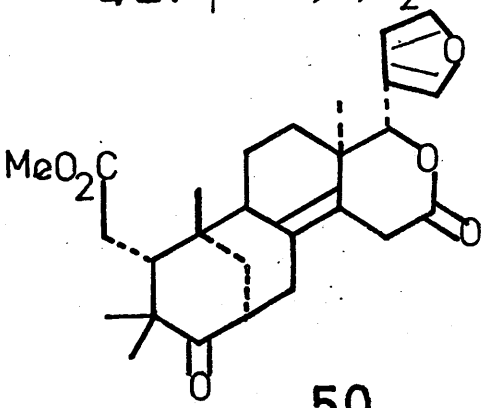


48. $R_1 = R_2 = O$

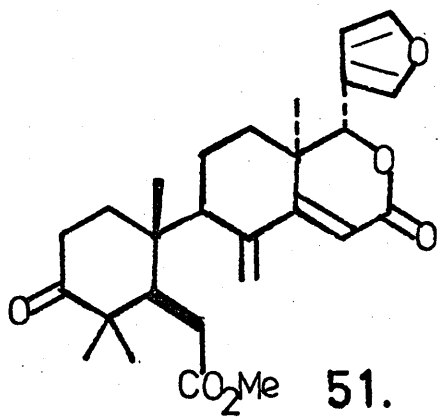
42. $R_1 = \alpha OH, H$; $R_2 = OH, H$



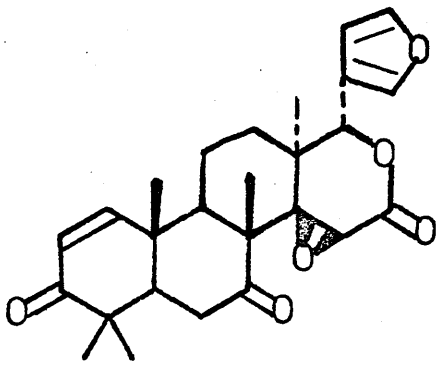
49.



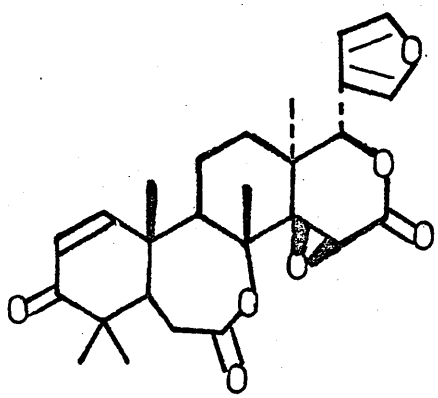
50.



51.



52.



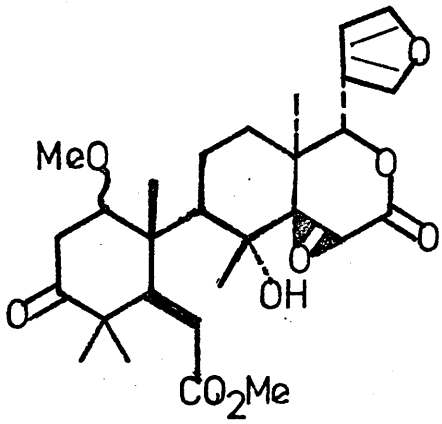
53.

(3-ketone) cm^{-1} 7, had no signals in the NMR spectrum corresponding to H-3 and H-15. It was assigned the diketone structure 48.

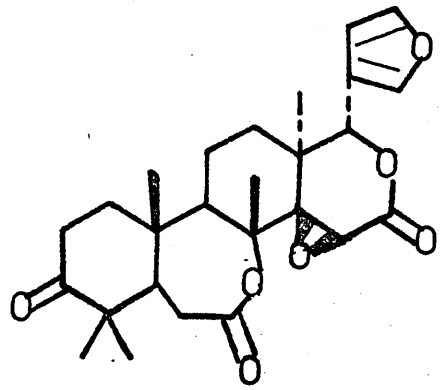
The formation of the triol ether 42 in basic media may be rationalised as follows. Opening of the epoxide ring by α-face attack of hydroxide anion followed by β-elimination of the C-14 hydroxyl would lead to the enol lactone system 49. Subsequent Michael addition of the 1α-OH group, probably under work-up conditions, would give the desired product.

After the successful synthesis of the bicyclononanolide system, attention was centred on the corresponding 1-deoxy system 50 which could arise from a precursor of the type 51 again by Michael addition of C-2 to C-30. The main points of interest were whether cyclisation would occur and under what particular experimental conditions, and whether the predicted product 50, 1 deoxymexicanolide, would be stable under basic conditions.

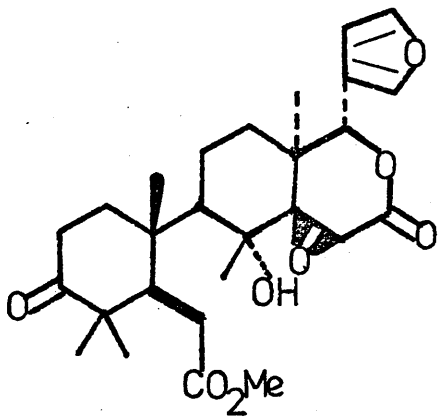
The available starting material, 7-deacetyl-7-keto gedunin 52[20] was subjected to Baeyer-Villiger oxidation using peracetic acid, giving the more polar ε-lactone 53 m.p. 244-246°C., $\nu_{max}^{CHCl_3}$ 1745 (δ and ε - lactones), 1677 (cyclohexenone) 7. Opening of the ε-lactone at this stage was attempted using potassium carbonate in aqueous methanol. However the main product from this reaction was the ring B cleaved Michael adduct 54 from attack by methanol at C-1. It was therefore first of all necessary to remove the $\Delta^{1,2}$ double bond and this was



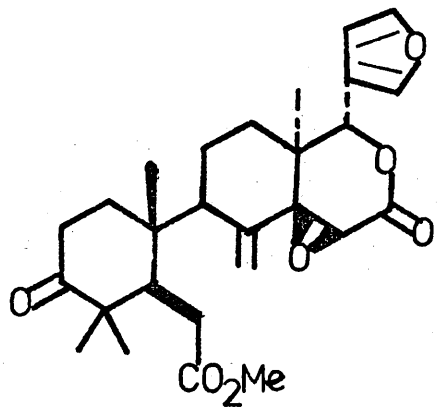
54.



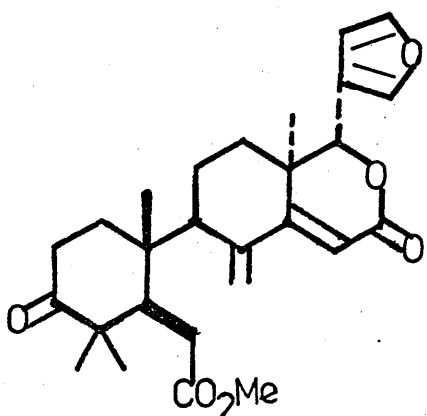
55.



56.



57.



51.

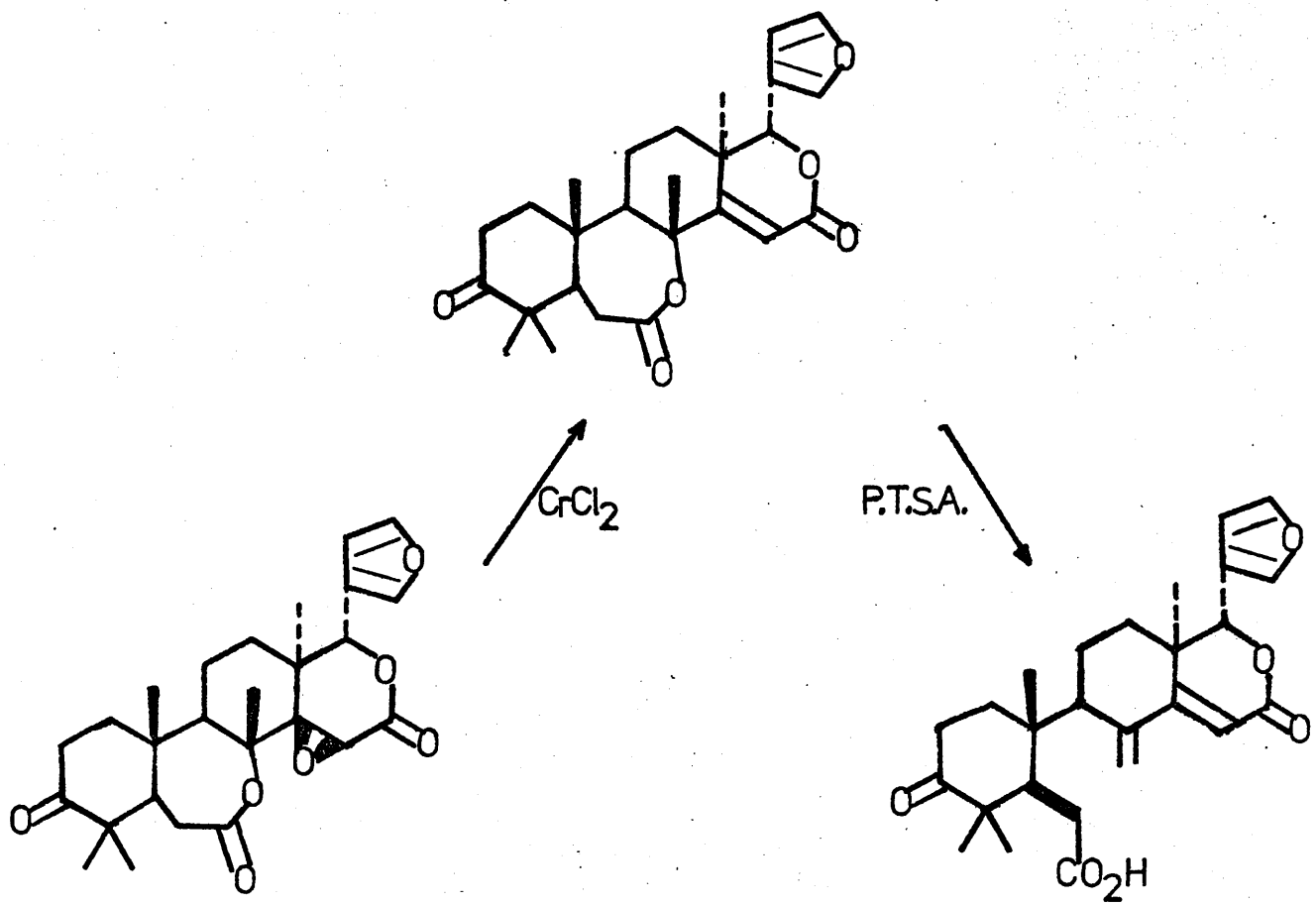
achieved by treatment with excess sodium borohydride, followed by Jones oxidation. This gave mainly the saturated ketone 55 m.p. 287-291°C decomp. [$\nu_{max}^{CHCl_3}$ 1740 (δ and ε-lactones), 1710 (cyclohexanone) cm^{-1}].

Base catalysed opening of the ε-lactone ring in 55 was now possible, and this time, higher yields were obtained using 4N sodium hydroxide instead of potassium carbonate. The hydroxy methyl ester 56 m.p. 198-201°C., [ν_{max} 3600, 3510 (hydroxyl); τ 6.42 (singlet, methyl ester)], underwent facile dehydration with thionyl chloride to the exomethylene derivative 57 m.p. 149-151°C., [τ 4.73, 4.70, 4.54 (singlets, exomethylene and H-17, no individual assignments), loss of one methyl group; $\nu_{max}^{CHCl_3}$ no hydroxyl]. Again, no trace of the $\Delta^{8,9}$ isomer could be found.

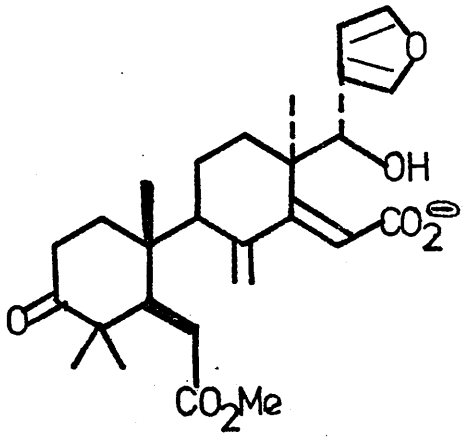
Removal of the epoxide to form the desired diene-lactone system 51 was carried out as usual with chromous chloride. The product 51 m.p. 145-146°C showed the expected shift of H-15 from τ 6.07 to τ 4.10. An alternative route to this precursor 51 involved the reactions shown in scheme (1), identical to those involved in the khivorin-methyl angolensate transformation. However the chromous chloride reduction of the epoxide in 55 failed to proceed to any extent, even with a large excess of chromous chloride present.

Conditions for cyclisation of the precursor 51 were investigated. Using sodium hydroxide in methanol at room temperature, starting material was recovered unchanged after remethylation. Analytical TLC did not provide a good indication of the extent of reaction since the precursor

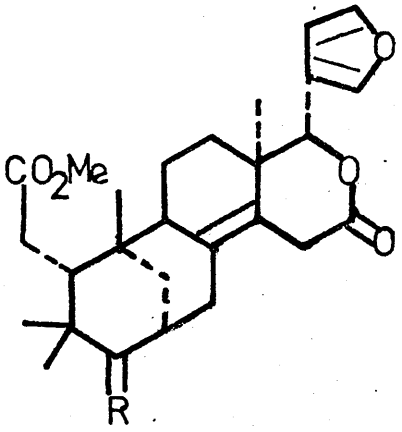
SCHEME 1.



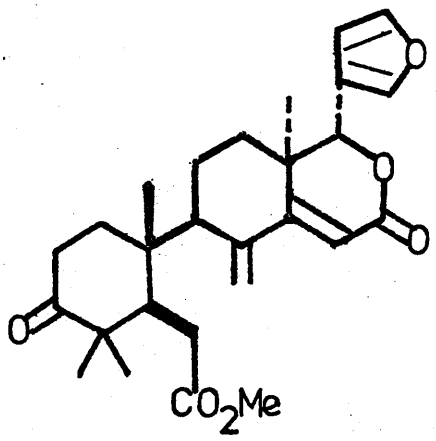
55.



58.



50. R = O
59. R = βOH, H



51.

and the cyclised product had identical polarities. NMR was a much better monitor. The precursor, refluxed in approximately 10% sodium hydroxide/methanol solution for 24 hours tended to cyclise to a small exent (~15%). This could be seen by the introduction of a broad singlet at ~ τ 6.6 corresponding to the C-15 methylene group. Obviously cyclisation was not going as smoothly as had been hoped, due probably to the fact that Michael addition would not occur on the carboxylate anion 58 generated from the δ-lactone in basic media.

With sodium methoxide it was found that after 24 hours at room temperature, all starting material had been consumed. The product, after methylation with ethereal diazomethane and purification by preparative TLC, was the desired 1-deoxymexicanolide 50 $[\alpha]_D$ + 75°. The NMR spectrum had signals at τ 9.08, 9.04, 8.97 (6H) (singlets, 4 tertiary methyls), 6.65 (broad singlet, 2H-15) (c.f. τ 6.54 in mexicanolide), 6.35 (singlet, methyl ester), 4.98 singlet, H-17), 3.56, 2.60, 2.48 (furanic protons). The significant differences between the NMR spectra of the precursor 51 and deoxymexicanolide 50 were loss of signals at τ 4.87, 4.58 (exomethylene) and τ 4.10 (H-15).

Attempts to prepare the corresponding 3β-alcohol 59 by sodium borohydride reduction resulted in an inseparable mixture. Shortage of material prevented further investigation.

Experimental

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 or a Varian H A 100 spectrometer using tetramethylsilane as an internal reference in deuterochloroform.

Ultraviolet (UV) absorption spectra were measured in ethanol solution using a Unicam SP 800 spectrometer. Infrared (IR) solution spectra were obtained on a Perkin-Elmer 225 instrument using carbon tetrachloride as solvent, unless otherwise specified.

Mass spectra were routinely determined on an A.E.I.-G.E.C. M.S.12 mass spectrometer, high resolution spectra being obtained on an A.E.I. M.S. 902S instrument by Mr. I. Jardine. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in chloroform solution. Kieselgel G (Merck) was used for both analytical and preparative thin layer chromatography (TLC). Light petroleum refers to the fraction of boiling point 60-80°C.

Two reactions were frequently employed during the course of this research, the experimental conditions remaining standard. These were:

i) Baeyer-Villiger oxidation using peracetic acid, prepared according to the method of Swern[21]. The acid was added to a stirred solution of the ketone in methylene chloride with anhydrous disodium hydrogen phosphate present as buffer. The weight of buffer added was roughly equal to the weight of ketone used. The reaction was left

for 24 hours, diluted with water and extracted with ethyl acetate.

ii) Chromous chloride reduction of the epoxide ring $\alpha\beta$ to the δ-lactone ring in the tetranortriterpenoids under discussion. The reagent, chromous chloride, was prepared by a modification of the method of Rosencranz et al.[22] whereby amalgamated zinc dust was prepared by vigorously shaking zinc dust (10g.), mercuric chloride (0.8g.), water (10 ml.) and concentrated hydrochloric acid (0.5ml.) for 5 minutes. The supernatent liquid was decanted and water (20ml.) and concentrated hydrochloric acid (2ml.) added. Chromic chloride (5g.) was added portionwise with stirring under an atmosphere of nitrogen. The resultant dark blue solution of chromous chloride was injected into the reaction vessel by means of a syringe. An excess of chromous chloride solution was added, the amount prepared above normally being used for approximately 700 mg. of the required epoxide. Work-up was achieved by dilution with water and subsequent extraction with chloroform.

Chromous chloride reduction of the epoxide 3

7-oxo-7-deacetoxy khivorin 3 (5g.) in acetone (140ml.) and glacial acetic acid (50ml.) was treated with excess chromous chloride solution at 45°C. for 24 hours. Dilution with cold water and extraction with chloroform gave a gum (4.4g.) which by analytical TLC was found to have one major component. Purification by preparative TLC and crystallisation from ethanol gave the 14, 15 deoxy compound 5 as fine needles m.p.

253-257°C.; NMR signals at τ 9.2, 9.00, 8.85, 8.78, 8.47 (singlets, 5 tertiary methyls), 8.03, 7.92 (singlets, 2 acetates), 5.3 (multiplet, (2H), H-1, H-3), 5.03 (singlet, H-17), 3.47 (singlet, H-15), 3.60, 2.58 (furanic protons); νmax 1735 (acetates, δ-lactone), 1715 (cyclohexanone) cm^{-1}.

Baeyer-Villiger oxidation of the deoxy compound 5

Baeyer-Villiger oxidation of the 14,15 deoxy compound 5 (1.8g) in methylene chloride (10 ml.) with peracetic acid gave after work-up a white solid (789 mg.) consisting mainly of the required ε-lactone 8. Purification by preparative TLC and crystallisation from benzene yielded plates m.p. 289-291°C. decomp.; NMR signals at τ 9.13, 9.07, 8.92, 8.86, 8.32 (singlets, 5 tertiary methyls), 8.08 (singlet, (6H), 2 acetates), 5.36 (multiplet, (2H), H-1, H-3), 5.10 (singlet, H-17), 3.59 (singlet, H-15), 3.71, 2.65 (furanic protons); νmax^{CHCl_3} 1730 (acetates, δ and ε-lactones) cm^{-1}.

Mass Analysis: $M^+ = 542.2487$; $C_{30}H_{38}O_9$ requires $M^+ = 542.2516$.

Acid catalysed ring-opening of the ε-lactone 8

The ε-lactone 8 (320 mg.) was dissolved in dry benzene (20 ml.) and refluxed overnight in the presence of a small amount of p-toluene sulphonic acid (20 mg.), after which time it was filtered and the solvent removed. The residue was found to consist of starting material and a polar, acidic

component. Separation by preparative TLC (3% MeOH/$CHCl_3$), gave the acid 9 (116 mg.) characterised as its methyl ester 10 m.p. 119-124°C. (from aqueous ethanol). NMR signals at τ 9.16, 9.00, 8.93, 8.86 (singlets, 4 tertiary methyls), 8.00, 7.94 (singlets, 2 acetates), 6.30 (singlet, methyl ester), 5.22 (multiplet, (2H), H-1, H-3), 4.78, 4.72 (singlets, exomethylene) 4.78 (singlet, H-17), 4.18 (singlet, H-15), 3.53, 2.57, 2.47 (furanic protons); νmax 1735 (acetates, methyl ester), 1720 (δ-lactone) cm^{-1}.

(Found: C, 64.38; H, 7.63%; $C_{31}H_{40}O_9.H_2O$ requires
C, 64.79; H, 7.37%).

3α-hydroxy dihydro methyl angolensate 12

Treatment of the exomethylene compound 10 (70 mg.) in methanol (5 ml.) at room temperature with 4N sodium hydroxide (0.4 ml.) for 20 hours, gave after acidification (dil. HCl), extraction with chloroform and methylation with ethereal diazomethane, 3α -hydroxy dihydro methyl angolensate 12 (61 mg.), m.p. 209-212°C. (from ethanol). NMR signals at τ 9.11, 9.05, 9.03, 8.97 (singlets, 4 tertiary methyls), 6.60 (broad multiplet, (2H), H-1, H-3), 6.26 (singlet, methyl ester), 5.09, 4.83 (singlets, exomethylene), 4.46 (singlet, H-17), 3.55, 2.57, 2.50 (furanic protons); νmax 3550 (hydroxyl), 1740 (δ -lactone, methyl ester), 1660 (exomethylene) cm^{-1}.

(Found: C, 68.50; H, 7.59%; $C_{27}H_{36}O_7$ requires
C, 68.62; H, 7.68%).

Methyl angolensate 13

To the alcohol 12 (30 mg.) in acetone (5 ml.) at 0°C. was added 6 drops of Jones reagent. Dilution with water and extraction with chloroform gave, after removal of the solvent, a solid (24 mg.) which was purified by preparative TLC and recrystallised from ethanol as colourless needles m.p. 201-205°C., $[\alpha]_D$ -41°; (lit.[9] m.p. 203-208°C., $[\alpha]_D$ -43°). This compound was shown to be identical with an authentic sample of methyl angolensate 13 (m.m.p., TLC, IR, NMR). NMR signals at τ 9.12, 9.04, 8.93, 8.79 (singlets, 4 tertiary methyls), 6.49 (multiplet, H-1), 6.28 (singlet, methyl ester), 5.11, 4.87 (singlets, exomethylene), 4.34 (singlet, H-17), 3.62, 2.62, 2.56 (furanic protons); νmax 1735 (methyl ester, δ-lactone), 1715 (cyclohexanone) cm^{-1}. (Found: C, 68.61, H 7.29%; $C_{27}H_{34}O_7$ requires C, 68.92, H, 7.28%).

Base catalysed ring opening of the ε-lactone 8

Treatment of the ε-lactone 8 (53 mg.) in methanol (5 ml.) at room temperature for 12 hours, with 4N sodium hydroxide gave after work-up in the usual manner, a very polar crystalline compound (46 mg.). Methylation with diazomethane and recrystallisation from aqueous methanol gave the diol ether 16 as colourless prisms m.p. 280°C. decomp.; NMR signals at τ 9.07 (6H), 8.98, 8.82, 8.38 (singlets, 5 tertiary methyls), 6.57, 6.33 (multiplets, H-3, H-1 respectively), 6.30 (singlet, methyl ester), 5.90 (broad singlet, 1H, exchangeable with D_2O), 4.20 (singlet,

H-17), 3.60, 2.60 (furanic protons); νmax 3610, 3530 (hydroxyl), 1735 (methyl ester, δ-lactone) cm^{-1}.

(Found: C, 64.09; H, 7.68%; $C_{27}H_{38}O_8.H_2O$ requires C, 63.73; H, 7.93%).

Acetylation of the diol ether 16

To the diol ether 16 (24 mg.) in dry pyridine (1.5 ml.) was added acetic anhydride (0.75 ml.). After 12 hours, water was added and the solution extracted with chloroform. The residue, (23 mg.) was recrystallised from ethanol giving the hydroxy acetate 17 as small prisms, m.p. 258-260°C.; NMR signals at τ 9.20, 9.03, 9.00, 8.93, 8.43 (singlets, 5 tertiary methyls), 8.08 (singlet, acetate), 6.37 (singlet, methyl ester), 6.05 (multiplet, H-1), 5.37 (multiplet, H-3), 4.20 (singlet, H-17), 3.73, 2.63 (furanic protons); νmax 3610, 3410 (hydroxyl), 1740 (acetate, methyl ester, δ-lactone) cm^{-1}.

Mass analysis: $M^+ = 532.2665$; $C_{29}H_{40}O_9$ requires $M^+ = 532.2672$.

Dehydration of the hydroxy acetate 17

Several drops of thionyl chloride were added to the hydroxy acetate 17 (14 mg.) in dry pyridine (1.5 ml.), and almost immediately water was carefully added. Extraction with chloroform gave a residue (11 mg.) consisting of mainly one compound 18. Purification by preparative TLC

and subsequent recrystallisation from methanol gave small cubes m.p. 224-226°C. This compound was identical with the product of acetylation 18, of 3α-hydroxy dihydro methyl angolensate 12. NMR signals at τ 9.21 (9H), 9.03 (singlets, 4 tertiary methyls), 7.94 (singlet, acetate), 6.35 (multiplet, H-1), 6.35 (singlet, methyl ester), 5.32 (multiplet, H-3), 5.17, 4.92 (singlets, exomethylene), 4.26 (singlet, H-17), 3.62, 2.60 (furanic protons); νmax 1740 (acetate, methyl ester, δ -lactone) cm^{-1}.

Mass spectrum: $M^+ = 514$; ($C_{29}H_{38}O_8$ requires $M^+ = 514$).

Baeyer-Villiger oxidation of 7-oxo-7-deacetoxy khivorin 4

Using peracetic acid, 7-oxo-7-deacetoxy khivorin 4 (8 g.) yielded inter alia the ε-lactone 19. Purification by preparative TLC (1% MeOH/$CHCl_3$), gave the pure ε-lactone 19 (2.5 g.) m.p. 308°C. decomp. (from methanol). NMR signals at τ 9.1, 8.97, 8.92, 8.67, 8.63 (singlets, 5 tertiary methyls), 8.03, 7.97, (singlets, 2 acetates), 6.27 (singlet, H-15), 5.27, 5.12 (multiplets, H-1, H-3), 4.63 (singlet, H-17), 3.67, 2.62 (furanic protons); νmax^{CHCl_3} 1730 (acetates, ε and δ- lactones) cm^{-1}.

(Found: C, 64.44; H, 7.02%; $C_{30}H_{38}O_{10}$ requires C, 64.50; H, 6.86%).

Acid catalysed opening of the ε-lactone 19

Treatment of the ε-lactone 19 with p-toluene sulphonic acid in refluxing benzene gave no reaction at all.

Base catalysed ring opening of the ε-lactone 19

Optimum yields of the required product 24 were obtained using potassium carbonate (1 g.) in aqueous methanol at room temperature. From the ε-lactone 19 (1.29 g.) two major compounds were obtained. Methylation of this mixture with diazomethane gave the ring-B cleaved compound 24 (1.12 g.) which was purified by preparative TLC and recrystallised from methanol as transparent prisms m.p. 274-277°C.; NMR signals at τ 9.08, 8.94 (6H), 8.75 (6H). (singlets, 5 tertiary methyls), 9.00 (singlet, exchangeable with D_2O), 7.93 (singlet, 2 acetates), 6.40 (singlet, methyl ester), 6.37 (singlet, H-15), 5.24, 4.78 (multiplets, H-1, H-3), 4.59 (singlet, H-17), 3.61, 2.56 (furanic protons); $\nu_{max}^{CHCl_3}$ 3590 (hydroxyl), 1730 (acetates, methyl ester, δ-lactone) cm^{-1}.

(Found: C, 63.16; H, 7.10%; $C_{31}H_{42}O_{11}$ requires C, 63.03; H, 7.17%).

Dehydration of the alcohol 24

The alcohol 24 (840 mg.) was dehydrated with thionyl chloride in pyridine. The major product 25 (732 mg.) was purified by preparative TLC (½% MeOH/$CHCl_3$), and recrystallised from methanol as colourless plates m.p. 197-199°C.; NMR signals at τ 9.15, 9.07, 8.97, 8.77 (singlets, 4 tertiary methyls), 7.92 (singlet, 6H, 2 acetates), 6.37 (singlet, methyl ester), 6.13 (singlet, H-15), 5.28, 5.07 (multiplets, H-1, H-3),

4.93, 4.60 (singlets, exomethylene), 4.53 (singlet, H-17), 3.65, 2.63 (furanic protons); νmax 1740 (acetates, methyl ester, δ-lactone) cm^{-1}. (Found: C, 65.40 H, 6.94%; $C_{31}H_{40}O_{10}$ requires C, 65.02 H, 7.04%).

Formation of the diol 26

Base hydrolysis of the acetates of 25 (447 mg.) using 4N sodium hydroxide in methanol at room temperature for 6 hours gave inter alia the required diol 26. Methylation and purification by preparative TLC gave a pure sample of the non-crystalline diol (253 mg.). NMR signals at τ 9.05, 9.03, (6H), 8.99 (singlets, 4 tertiary methyls), 6.36 (singlet, methyl ester), 6.43, 6.26 (multiplets, H-1, H-3), 6.08 (singlet, H-15), 4.76, 4.64 (singlets, exomethylene), 4.58 (singlet, H-17), 3.63, 2.58 (furanic protons); νmax 3625, 3600, 3500 (hydroxyl), 1745 (methyl ester, δ-lactone) cm^{-1}.

Mass analysis: $M^+ = 488.2385$; $C_{27}H_{36}O_8$ requires $M^+ = 488.2409$.

Oxidation of the diol 26

Jones oxidation of the diol 26 (170 mg.) in acetone (10 ml) at 0°C. produced two products which were separated by preparative TLC. These were identified as the β-diketone 27 (91 mg.) m.p. 188-192°C. (from methanol); NMR signals at τ 9.10, 9.04 (6H), 8.98 (singlets, 4 tertiary methyls), 6.34 (singlet, methyl ester), 6.27 (singlet, H-15), 6.10

(singlet, 2 H-2), 4.68, 4.46 (singlets, exomethylene), 4.46 (singlet, H-17), 3.64, 2.58 (furanic protons); νmax^{CHCl_3} 1735 (methyl ester, δ-lactone) 1707 (β-diketone) cm^{-1}.; λ max 261 nm. (ε 9,300) rising to 289 nm. (ε 22,600) on addition of base.

(Found: C, 66.83 H, 6.74%; $C_{27}H_{32}O_8$ requires C, 66.92 H, 6.66%).

and the β-hydroxy ketone 28 (20 mg.) m.p. 196-199°C., (from chloroform/ether); NMR signals at τ 9.05, 8.88 (6H), 8.83 (singlets, 4 tertiary methyls), 6.33 (singlet, methyl ester), 6.06 (singlet, H-15), 5.95 (multiplet, H-1), 4.64, 4.49 (singlets, exomethylene), 4.64 (singlet, H-17), 3.64, 2.58 (furanic protons); νmax 3610, 3525 (hydroxyl), 1745 (methyl ester, δ-lactone), 1715 (cyclohexanone) cm^{-1}.

Mass analysis: M^+ = 486.2218; $C_{27}H_{34}O_8$ requires M^+ = 486.2253.

Andirobin 29

Dehydration of the hydroxy ketone 28 (12 mg.) in pyridine with thionyl chloride (3 drops) gave andirobin 29 (9 mg.). Purification by preparative TLC and recrystallisation from methanol produced prisms m.p. 193-196°C., $[\alpha]_D$ 33°; (lit.[13] m.p. 195-197°C., $[\alpha]_D$ 38.5°). NMR signals at τ 9.08, 9.05, 8.94, 8.92 (singlets, 4 tertiary methyls), 6.33 (singlet, methyl ester), 5.98 (singlet, H-15), 4.74, 4.63 (singlets, exomethylene), 4.53 (singlet, H-17), 3.94, 2.83 (AB quartet, H-2, H-1

respectively, J = 10 Hz.), 3.66, 2.59 (furanic protons); νmax 1745 (methyl ester, δ-lactone), 1685 (cyclohexenone) cm^{-1}.

Mass analysis: M^+ = 468.2091; $C_{27}H_{32}O_7$ requires M^+ = 468.2147.

The diene-lactone precursor 3

Treatment of the β-diketone 27 (43 mg.) with excess chromous chloride gave inter alia the polar diene-lactone 3. Purification by preparative TLC afforded a slightly impure sample of the diene-lactone 3 (22 mg.) recrystallised from chloroform ether as small needles m.p. 193-198°C.; NMR signals at τ 9.01, 8.95, 8.84, 8.77 (singlets, 4 tertiary methyls), 6.32 (unsymmetrical singlet, 5H, methyl ester, 2H-2), 4.71, 4.63, 4.53 (singlets, exomethylene, H-17), 4.00 (singlet, H-15), 3.56, 2.55 (furanic protons); $\nu_{max}^{CHCl_3}$ 1720 broad (β-diketone, methyl ester, δ-lactone) cm^{-1}.; λmax 262 nm. (ε 9,000).

Mass spectrum: M^+ = 468; ($C_{27}H_{32}O_7$ requires M^+ = 468).

Mexicanolide 1

The diene-lactone precursor 3 (15 mg.) was stirred in chloroform (2 ml.) in the presence of a few drops of aqueous sodium bicarbonate. After 24 hours the reaction was complete. Acidification and extraction with chloroform gave mexicanolide 1 (13 mg.) recrystallised from methanol as transparent cubes m.p. 221-226°C., $[\alpha]_D$ -85°; (lit.[1] m.p. 222-227°C., $[\alpha]_D$ -90°). NMR signals at τ 9.14, 9.01 (6H), 8.76

(singlets, 4 tertiary methyls), 6.54 (broad singlet, 2H-15), 6.30 (singlet, methyl ester), 4.75 (singlet, H-17), 3.51, 2.59, 2.42 (furanic protons); νmax^{CHCl_3} 1730 (methyl ester, δ-lactone), 1705 (β - diketone) cm^{-1}.

(Found: C, 68.96; H, 6.81%; $C_{27}H_{32}O_7$ requires C, 69.21; H, 6.88%).

Treatment of the ε-lactone 19 with dilute sodium hydroxide.

Treatment of the ε-lactone 19 in methanol with 4N sodium hydroxide for 15 hours at room temperature gave at least four compounds, the relative proportions of which varied with the time of reaction. Methylation of this mixture with diazomethane and separation by preparative TLC afforded pure samples of the alcohol 24; the diol 20 m.p. 250-253°C. (from aqueous methanol); NMR signals at τ 9.18, 9.04, 8.89, 8.70, 8.68 (singlets, 5 tertiary methyls), 8.42, 8.34 (broad singlets, exchangeable with D_2O), 6.34, 6.26 (multiplets, H-1, H-3), 6.29 (singlet, H-15), 4.60 (singlet, H-17), 3.60, 2.58 (furanic protons); νmax^{CHCl_3} 3620, 3480 (hydroxyl), 1740 (ε and δ-lactones) cm^{-1}.

(Found: C, 63.58; H, 6.87%; $C_{26}H_{34}O_8.H_2O$ requires C, 63.40; H, 7.37%);

the triol 33 m.p. 236-240°C. (from methanol); NMR signals at τ 9.05, 9.02, 8.90, 8.79 (6H) (singlets, 5 tertiary methyls), 6.44 (singlet, methyl ester), 6.38 (singlet, H-15), 6.32, 5.87 (multiplets, H-1, H-3),

4.59 (singlet, H-17), 3.61, 2.58 (furanic protons); ν_{max}^{KBr} 3520, 3460 (hydroxyl), 1730 (methyl ester, δ-lactone) cm^{-1}.

(Found: C, 63.79; H, 7.45%; $C_{27}H_{38}O_9$ requires C, 64.01; H, 7.56%) and,

the triol ether 42 m.p. 235-238°C. (from benzene); NMR signals at τ 9.12, 9.09, 9.04, 8.86, 8.67 (singlets, 5 tertiary methyls), 6.78 (singlet, 1H, exchangeable with D_2O), 6.44, 6.07 (multiplets, H-1, H-3), 6.36 (singlet, methyl ester), 5.55 (broad singlet, H-15, sharpening on D_2O addition), 5.37 (broad singlet, 1H, exchangeable with D_2O), 3.79 (singlet, H-17), 3.49, 2.56, 2.52 (furanic protons); $\nu_{max}^{CHCl_3}$ 3460 (hydroxyl), 1735 (methyl ester, δ-lactone) cm^{-1}.

(Found: C, 63.97; H, 7.48%; $C_{27}H_{38}O_9$ requires C, 64.01; H, 7.56%).

Oxidation of the diol 20

Jones oxidation of the diol 20 (50 mg.) in acetone (5 ml.) at 0°C. gave the corresponding β-diketone 23 (41 mg.). It was purified by preparative TLC followed by recrystallisation from ethanol as small prisms m.p. 280 -284°C. decomp.; NMR signals at τ 8.79, 8.75, 8.68 (6H), 8.60 (singlets, 5 tertiary methyls), 6.55 (singlet, 2H-2), 6.33 (singlet, H-15), 4.62 (singlet, H-17), 3.64, 2.59 (furanic protons); $\nu_{max}^{CHCl_3}$ 1740 (ε and δ-lactones), 1710 (β-diketone) cm^{-1}. λmax 260 nm. moving to 289 nm. on addition of base.

Mass spectrum: $M^+ = 470$ ($C_{26}H_{30}O_8$ requires $M^+ = 470$).

Oxidation of the triol 33

Jones oxidation of the triol 33 (313 mg.) in acetone (25 ml.) at 0°C. gave a mixture of mainly two compounds. These were the non-crystalline β-diketone 34 (124 mg.); NMR signals at τ 9.00, 8.87, 8.85, 8.72, 8.69 (singlets, 5 tertiary methyls), 6.62 (singlet, 2H-2), 6.36 (singlet, H-15), 6.33 (singlet, methyl ester), 4.62 (singlet, H-17), 3.64, 2.60 (furanic protons); νmax 3600, 3460 (hydroxyl), 1740 (methyl ester, δ-lactone), 1705 (β -diketone) cm^{-1}; λmax 261 nm. moving to 290 nm. on additon of base;

and the β-hydroxy ketone 35 (92 mg.) as a gum; NMR signals at τ 9.03, 8.91, 8.79 (6H), 8.62 (singlets, 5 tertiary methyls), 6.62 (broad singlet, 1H, exchangeable with D_2O), 6.35 (singlet, methyl ester), 6.31 (singlet, H-15), 6.21 (multiplet, H-3), 4.53 (singlet, H-17), 3.59, 2.54 (furanic protons); νmax^{CHCl_3} 3600, 3510 (hydroxyl), 1735 (methyl ester, δ-lactone), 1715 (cyclohexanone) cm^{-1}.

Mass analysis: $M^+ = 504.2332$; $C_{27}H_{36}O_9$ requires $M^+ = 504.2359$.

Acetylation of the β-hydroxy ketone 35

Acetylation of the β-hydroxy ketone 35 (61 mg.) using acetic anhydride in pyridine gave the corresponding acetate 36 (14 mg.) (impure); NMR signals at τ 9.13, 8.73 (9H), 8.60 (singlets, 5 tertiary methyls), 7.98 (singlet, acetate), 6.35 (singlet, 4H, methyl ester, H-15),

5.07 (multiplet, H-3), 4.60 (singlet, H-17), 3.65, 2.63 (furanic protons); νmax 3600, 3520 (hydroxyl), 1740 (methyl ester, δ-lactone), 1710 (cyclohexanone) cm^{-1};

and a close-running component, the enone 37 (23 mg.) m.p. 193-194°C. (from ether/petrol); NMR signals at τ 9.00, 8.88, 8.79, 8.72, 8.64 (singlets, 5 tertiary methyls), 6.40 (singlet, 4H, methyl ester, H-15), 4.61 (singlet, H-17), 4.14, 3.41 (AB quartet, H-2, H-3 respectively, J = 10 Hz.), 3.64, 2.61 (furanic protons); νmax 3600, 3525 (hydroxyl), 1740 (methyl ester, δ-lactone), 1675 (cyclohexenone) cm^{-1}.

Mass spectrum: M^+ = 486; ($C_{27}H_{34}O_8$ requires M^+ = 486).

Dehydration of the acetate 36

Dehydration of the acetate 36 (10 mg.) with thionyl chloride in pyridine gave inter alia "mahoganin acetate" 39 (7 mg.). Purification by preparative TLC failed to give a completely pure sample of 39 which did not crystallise. NMR signals at τ 9.18, 9.08, 8.74 (6H) (singlets, 4 tertiary methyls), 7.89 (singlet, acetate), 6.39 (singlet, methyl ester), 6.10 (singlet, H-15), 5.10 (multiplet, H-3), 4.59, 4.52, 4.38 (singlets, exomethylene, H-17), 3.64, 2.58 (furanic protons); νmax 1740 (methyl ester, acetate, δ-lactone), 1705 (cyclohexanone).

Mass analysis: M^+ = 528.2357; $C_{29}H_{36}O_9$ requires M^+ = 528.2359.

Isoandirobin 32

Dehydration of the enone 37 (15 mg.) gave a mixture, with one major component. Purification by preparative TLC yielded isoandirobin 32 (7 mg.), $[\alpha]_D$ + 22° which resisted all attempts at crystallisation. NMR signals at τ 9.60, 8.96 (6H), 8.77 (singlets, 4 tertiary methyls), 6.33 (singlet, methyl ester), 6.12 (singlet, H-15), 4.74, 4.71, 4.38 (singlets, exomethylene, H-17), 4.09, 3.38 (AB quartet, H-2, H-3 respectively, J = 10 Hz.), 3.65, 2.60 (furanic protons); νmax 1745 (methyl ester, δ-lactone), 1675 (cyclohexenone) cm^{-1}.

Mass analysis: M^+ = 468.2097; $C_{27}H_{32}O_7$ requires M^+ = 468.2147.

Acetylation of the triol ether 42

The triol ether 42 (15 mg.) after treatment at room temperature for 2 days with acetic anhydride in pyridine afforded the diacetate 43 (13 mg.), recrystallised from chloroform/ether as small cubes m.p. 173-176°C.; NMR signals at τ 9.20, 9.04, 8.92, 8.73, 8.51 (singlets, 5 tertiary methyls), 8.18, 7.81 (singlets, 2 acetates), 7.14 (singlet, 1H, exchangeable with D_2O), 6.33 (singlet, methyl ester), 6.02 (multiplet, H-1), 5.35 (multiplet, H-3), 4.36 (singlet, H-15), 4.12 (singlet, H-17), 3.41, 2.56, 2.02 (furanic protons); νmax 3610, 3490 (hydroxyl), 1770 (δ-lactone), 1740 (methyl ester, acetates) cm^{-1}.

Mass spectrum: M^+ = 580 ($C_{31}H_{32}O_{11}$ requires M^+ = 580).

Oxidation of the triol ether 42

Jones oxidation of the triol ether 42 (18 mg.) gave inter alia the non-crystalline diketone 48 (9 mg.); NMR signals at τ 9.13, 8.97, 8.89, 8.74 (6H) (singlets, 5 tertiary methyls), 6.29 (singlet, methyl ester), 6.10 (multiplet, H-1), 3.39 (singlet, H-17), 3.50, 2.50, 2.33 (furanic protons); νmax 3515 (hydroxyl), 1768 (δ -lactone), 1735 (methyl ester, 15-ketone), 1723 (3-ketone) cm^{-1}.

Mass spectrum: $M^+ = 502$ ($C_{27} H_{34} O_9$ requires $M^+ = 502$).

Baeyer-Villiger oxidation of 7-deacetoxy-7-keto gedunin 52

The starting material 52 was not pure, but was one component (~40%) of a binary mixture containing mexicanolide (~60%). The polarities of these two compounds were identical, so separation by TLC was not possible. The ε-lactone 53 (870 mg.) was obtained from oxidation of the mixture (5 g.) and subsequent separation by preparative TLC from unreacted mexicanolide. Recrystallisation from methanol gave needles m.p. 244-246°C.; NMR signals at τ 8.93, 8.78, 8.74, 8.69, 8.60 (singlets, 5 tertiary methyls), 6.25 (singlet, H-15), 4.57 (singlet, H-17), 4.04, 2.91 (AB quartet, H-2, H-1 respectively, J = 11 Hz.), 3.59, 2.54 (furanic protons); $\nu_{max}^{CHCl_3}$ 1745 (δ and ε-lactones), 1677 (cyclohexenone) cm^{-1}.

(Found: C, 68.55; H, 6.73%; $C_{26} H_{30} O_7$ requires C, 68.70; H, 6.65%).

The dihydro ε-lactone 55

Removal of the $\Delta^{1,2}$ double bond was achieved by reduction of the ε-lactone 53 (721 mg.) in ethyl acetate (30 ml.) using excess sodium borohydride at room temperature for 4 hours. Addition of dilute hydrochloric acid and extraction with ethyl acetate gave a mixture which was oxidised using excess Jones reagent in acetone at 0°C. After the normal work-up procedure, one main compound was formed, the required 3-ketone 55 (580 mg.). Purification by preparative TLC and recrystallisation from methanol/chloroform gave small prisms m.p. 287-291°C. decomp. ; NMR signals at τ 8.97, 8.90, 8.82, 8.69, 8.62 (singlets, 5 tertiary methyls), 6.28 (singlet, H-15), 4.60 (singlet, H-17), 3.60, 2.56 (furanic protons); $\nu_{max}^{CHCl_3}$ 1740 (δ and ε-lactones), 1710 (cyclohexanone) cm^{-1}.

(Found: C, 68.20; H, 7.13%; $C_{26}H_{32}O_7$ requires
C, 68.40; H, 7.07%).

The alcohol 56

Opening of the ε-lactone ring was found to proceed smoothly with dilute sodium hydroxide. Thus treatment of the dihydro ε-lactone 55 (327 mg.) in methanol (15 ml.) with 4N sodium hydroxide (1 ml), gave the hydroxy acid (305 mg.) which was methylated with ethereal diazomethane to give the corresponding hydroxy ester 56. Recrystallisation from methanol/chloroform gave small cubes m.p. 198-201°C.; NMR signals at τ 8.98, 8.86 (6H), 8.78, 8.68 (singlets, 5 tertiary methyls),

6.42 (singlet, methyl ester), 6.38 (singlet, H-15), 4.60 (singlet, H-17), 3.63, 2.58 (furanic protons); νmax 3610, 3510 (hydroxyl), 1740 (methyl ester, δ-lactone), 1715 (cyclohexanone) cm^{-1}.

(Found: C, 66.42; H, 7.51%; $C_{27}H_{36}O_8$ requires
C, 66.37; H, 7.43%).

Chromous chloride treatment of the dihydro ε-lactone 55

The dihydro ε-lactone 55 failed to react with excess chromous chloride under the normal reaction conditions, and was recovered unchanged.

Dehydration of the alcohol 56

The alcohol 56 (192 mg.) was dehydrated with thionyl chloride in pyridine to give the exomethylene derivative 57 (157 mg.). Purification by preparative TLC (2% petrol/chloroform), and subsequent recrystallisation from ethanol yielded prisms m.p. 149-151°C.; NMR signals at τ 9.08, 9.04, 8.93, 8.89 (singlets, 4 tertiary methyls), 6.36 (singlet, methyl ester), 6.07 (singlet, H-15), 4.73, 4.70, 4.54 (singlets, exomethylene, H-17), 3.64, 2.58 (furanic protons); $\nu_{max}^{CHCl_3}$ no hydroxyl, 1735 (methyl ester, δ-lactone), 1705 (cyclohexanone) cm^{-1}.

(Found: C, 69.18; H, 7.42%; $C_{27}H_{34}O_7$ requires
C, 68.92; H, 7.28%).

Chromous chloride reduction of 57

Treatment of the exomethylene derivative 57 (95 mg.) with excess chromous chloride solution gave the required diene-lactone precursor 51 (87 mg.). Purification by preparative TLC and recrystallisation from ethanol produced fine needles m.p. 145-146°C.; NMR signals at τ 9.01, 8.96, 8.90, 8.86 (singlets, 4 tertiary methyls), 6.35 (singlet, methyl ester), 4.87, 4.58 (singlets, exomethylene), 4.81 (singlet, H-17), 4.10 (singlet, H-15), 3.52, 2.54, 2.44 (furanic protons); $\nu_{max}^{CHCl_3}$ 1715 broad (methyl ester, δ-lactone, cyclohexanone) cm^{-1}.

(Found: C, 71.17; H, 7.36; $C_{27}H_{34}O_6$ requires C, 71.34; H, 7.54%).

Deoxymexicanolide 50

Cyclisation of the precursor 51 occurred to a small extent with sodium hydroxide in methanol under gentle reflux. Use of sodium methoxide at room temperature for 24 hours gave, from starting material 51 (43 mg.) the required cyclised product as the major component of a mixture. Methylation and purification by preparative TLC yielded 1-deoxymexicanolide 50 as a gum (26 mg.), $[\alpha]_D$ + 75° which failed to crystallise. NMR signals at τ 9.08, 9.04, 8.97 (6H) (singlets, 4 tertiary methyls), 6.65 (broad singlet, 2 H-15), 6.35 (singlet, methyl ester), 4.98 (singlet, H-17), 3.56, 2.60, 2.48 (furanic protons); νmax 1740 (methyl ester, δ-lactone), 1708 (cyclohexanone) cm^{-1}.

Mass spectrum: M^+ = 454 ($C_{27}H_{34}O_6$ requires M^+ = 454).

Attempted reduction of 1-deoxymexicanolide 50

Attempts were made at reducing the 3-ketone in 1-deoxymexicanolide 50 using sodium borohydride in ethanol. However, no matter how carefully quantities were measured out, the formation of a multitude of products was unavoidable. Due to shortage of material, this reaction could not be carried out on a large enough scale to isolate a realistic amount of the required alcohol 59.

References.

1. (i) J. D. Connolly, R. McCrindle and K. H. Overton, Tetrahedron, 24, 1489 (1968).

(ii) J. D. Connolly, R. McCrindle and K. H. Overton, Tetrahedron, 24, 1497 (1968).

2. (i) C. W. L. Bevan, J. W. Powell and D. A. H. Taylor, J. Chem. Soc., 980 (1963).

(ii) E. O. Arene, C. W. L. Bevan, J. W. Powell and D. A. H. Taylor, Chem. Comm., 302 (1965).

3. J. D. Connolly, K. L. Handa, R. McCrindle and K. H. Overton, Chem. Comm., 867 (1966).

4. W. D. C. Warnock, Ph.D. Thesis, Glasgow, 1967.

5. D. H. R. Barton, S. K. Pradham, S. Sternhell and J. F. Templeton, J. Chem. Soc., 255 (1961).

6. A. Von Baeyer and V. Villiger, Ber., 32, 3625 (1899).

7. D. A. H. Taylor, unpublished results.

8. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 39 (1946).

9. (i) C. W. L. Bevan, J. W. Powell, D. A. H. Taylor, T. G. Halsall, P. Toft and M. Welford, J. Chem. Soc. (C), 163 (1967).

(ii) W. R. Chan, K. E. Magnus and B. S. Mootoo, J. Chem. Soc. (C), 171 (1967).

10. E. K. Adesogan, J. W. Powell and D. A. H. Taylor, J. Chem. Soc. (C), 554 (1967).

11. E. K. Adesogan and D. A. H. Taylor, J. Chem. Soc. (C), 1974 (1968).

12. R. Caputo and L. Mangoni, Gazzetta, 96, 220 (1966).

13. W. D. Ollis, A. D. Ward, H. Meirelles de Oliveira and R. Zelnik, Tetrahedron, 26, 1637 (1970).

14. A. Akisanya, E. O. Arene, C. W. L. Bevan, D. E. U. Ekong, M. N. Nwaji, J. I. Okogun, J. W. Powell and D. A. H. Taylor, J. Chem. Soc. (C), 506 (1966).

15. W. R. Chan and D. R. Taylor, Chem. Comm., 720 (1967).

16. D. P. Chakraborty, K. C. Das and C. F. Hammer, Tetrahedron Letters, 5015 (1968).

17. D. A. H. Taylor, Chem. Comm., 58 (1969).

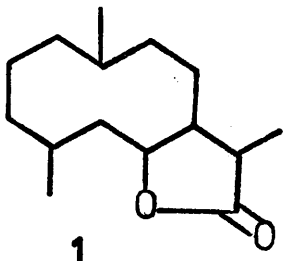
18. L. J. Bellamy, "Advances in Infra-red Group Frequencies", Methuen, P141 (1968).

19. D. E. U. Ekong and M. D. Selema, Chem. Comm., 783 (1970).

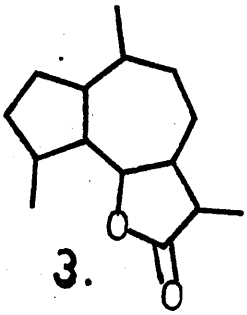
20. C. W. L. Bevan, J. W. Powell and D. A. H. Taylor, J. Chem. Soc., 980 (1963).

21. D. Swern, Org. Reactions, 7, 378 (1953).

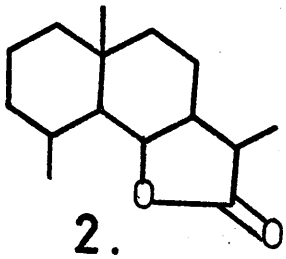
22. G. Rosencranz, O. Mancera, J. Gatica and C. Djerassi, J. Amer. Chem. Soc., 72, 4077 (1950).



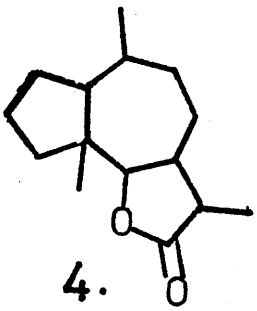
1.



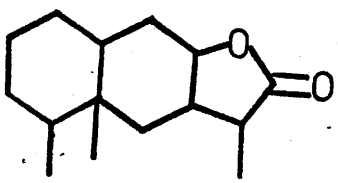
3.



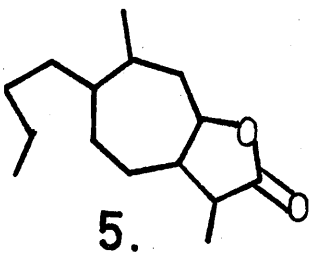
2.



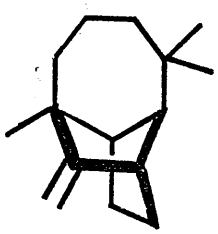
4.



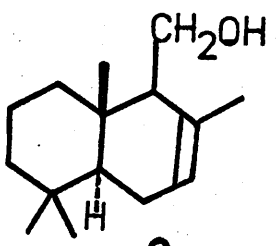
6.



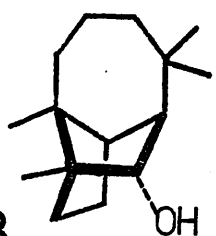
5.



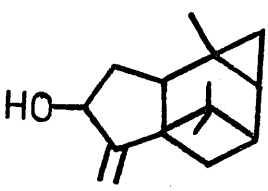
7.



9.



8.



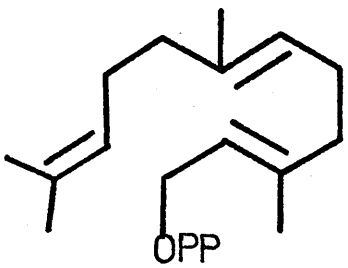
10.

Introduction

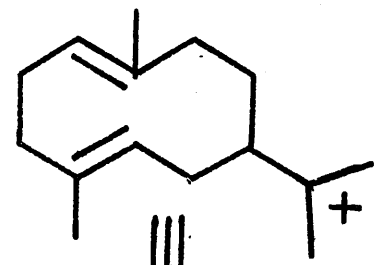
Recent studies in chemotaxonomy have shown that the Compositae, possibly the largest of all plant families, are rich in "secondary metabolites", especially essential oils, sesquiterpenes, other terpenoids and flavanoids. The possibilities of using these phytochemical characters for taxonomic studies have been recently reviewed by Hegnauer[1].

In particular, attention[2] has been centred on those sesquiterpenes which are regarded as typical members of their class, namely the germacranolide 1, eudesmanolide 2, guaianolide 3, pseudoguaianolide (ambrosanolide[3]) 4, xanthanolide 5 and eremophilanolide 6 classes of sesquiterpene lactones, a group of compounds that appear to be formed by closely allied biosynthetic processes[4].

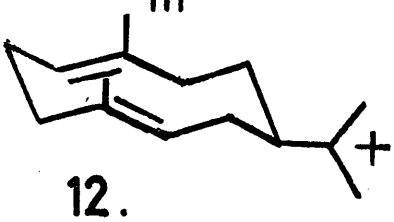
Sesquiterpene lactones have only been found to a small extent outside the Compositae, e.g. in liverworts (Hepaticae). Recent research[5] into the allergenic activity of species of Frullania, a genus of liverworts has shown that this activity is probably due to the presence of certain of these sesquiterpene lactones. Other investigations[6] of liverworts have yielded inter alia longifolene 7, longiborneol 8 and drimenol 9 and an interesting tetracyclic sesquiterpene alcohol 10 from Mylia taylorii[7]. Since liverworts occur widely in the West of Scotland, it was decided to carry out an investigation into the terpenoid content of a number of species. Three of these, Lepidozia pinnata, Nardia compressa and Marsupella emarginata gave no evidence of any terpenoid constituents.



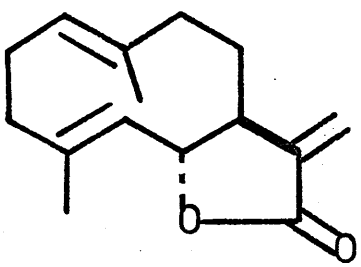
11.



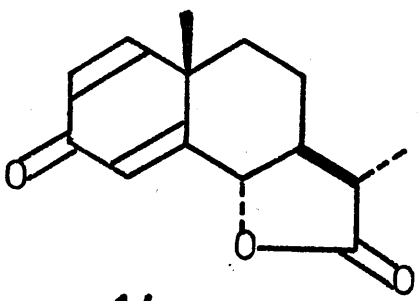
III



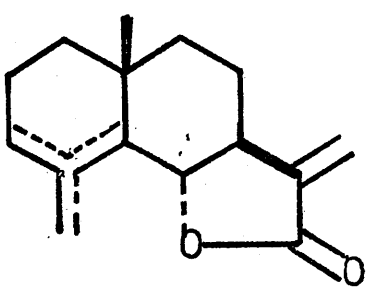
12.



13.



14.



15. $\triangle^{3,4}$ D.B.

16. $\triangle^{4,15}$ D.B.

17. $\triangle^{4,5}$ D.B.

However, in the case of Frullania tamascifolia, several sesquiterpene lactones of the germacranolide and eudesmanolide types were isolated. These closely related sesquiterpenes can be considered to arise[4] from cyclisation of trans-farnesyl pyrophosphate 11 to the carbonium ion 12, which can undergo oxidative modification to the ten-membered ring sesquiterpenes with the germacrane skeleton, a good example of which is costunolide 13[8]. Due to the relative position of the two double bonds in the carbonium ion 12, facile transannular cyclisation can occur to the eudesmane skeleton of which perhaps the best known is santonin 14[9].

Interconversions of germacranolides with eudesmanolides have recently[10] been achieved in vitro, in the transformation of costunolide 13 into the corresponding α15, β16 and γ17 cyclocostunolides. In the chloroform extract of Frullania tamascifolia were found costunolide 13 and three compounds of the cyclocostunolide (eudesmanolide) type.

References

1. R. Hegnauer, "Chemotaxonomie der Pflanzen", Vol III Birkhäuser, Basel, 1964.

2. (i) T. A. Geissman and M. A. Irwin, Pure and Appl. Chem., 21, 167 (1970).

(ii) T. A. Geissman and M. A. Irwin, Phytochem., 10, 637 (1971), and references cited therein.

3. F. Sorm and L. Dolejs, "Guaianolides and Germacranolides" Hermann, Paris, 1965.

4. W. Parker, R. Ramage and J. S. Roberts, Quart. Rev., 21, 331 (1967).

5. J. C. Mitchell, B. Fritig, B. Singh and G. H. N. Towers, J. Invest. Derm., 54, 233 (1970).

6. A. Matsuo, M. Nakazoma and S. Hayashi, Phytochemistry, 10, 430 (1971) and references cited therein.

7. V. Benesova, P. Sedmera, V. Herout and F. Sorm, Tetrahedron Letters, 2679 (1971).

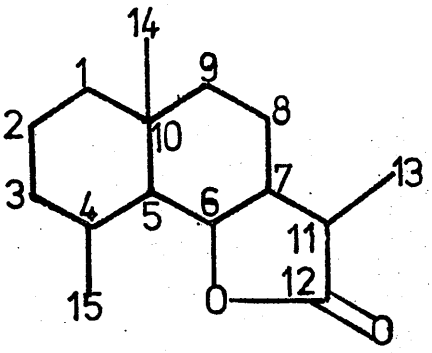
8. A. S. Rao, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron, 9, 275 (1960).

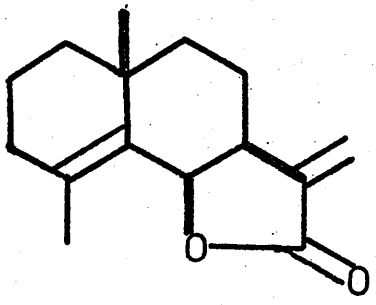
9. (i) M. Nakazaki and H. Arakawa, Proc. Chem. Soc., 151 (1962).

(ii) J. D. M. Asher and G. A. Sim, Proc. Chem. Soc., 335 (1962).

10. (i) T. C. Jain and J. E. McCloskey, Tetrahedron Letters, 4525 (1969).

(ii) R. W. Doskotch and F. S. El-Feraby, J. Org. Chem., 35, 1928 (1970).



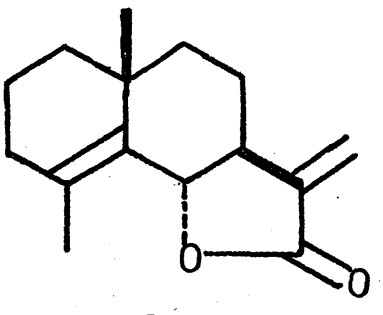


1.

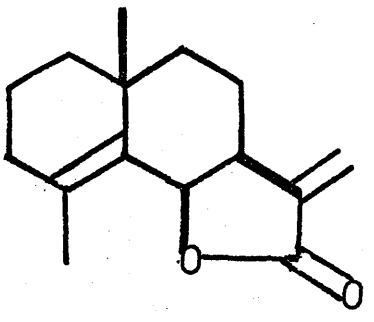
Discussion

The first and most abundant compound isolated from Frullania tamascifolia was the cis-lactone 1 m.p. 74-76°C.; $[\alpha]_D$ -109° which showed NMR signals at τ 8.93 (singlet, tertiary methyl), 8.25 (singlet, vinyl methyl), 7.03 (broad multiplet, H-7), 4.77 (doublet, H-6, J = 5Hz), 4.42, 3.84 (doublets, exomethylene, J = 1 Hz) and a strong band in the IR at 1770 (γ-lactone) cm^{-1}.

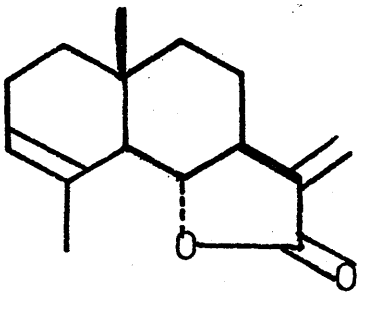
The assignment of structure was made on the basis of decoupling experiments (see 1). Irradiation at H-6 (τ 4.77) changed the signal for H-7 (τ 7.03) from a broad multiplet to a broad triplet (Jobs. = 9 Hz.) consistent with the presence of an adjacent methylene group. The reverse experiment caused H-6 to collapse to a broad singlet. The residual broadening in H-6 is due to homoallylic coupling[1] with the C-4 methyl group, and this was demonstrated by irradiating at H-6 (τ 4.77), whereupon the intensity of the C-4 methyl signal increased. From the size of this homoallylic coupling, (<1 Hz.) the stereochemistry of the lactone ring junction was deduced as cis, as in 1. Additional evidence came from comparison of the observed coupling between H-6 and H-7 (5 Hz.) with the value predicted by the Karplus[2] relationship on the basis of a dihedral angle between H-6 and H-7 of 40°, (5 Hz.). The shift to lower field than normal of the signals for the exomethylene protons Ha and Hb confirmed the presence of conjugation with the γ-lactone carbonyl group.



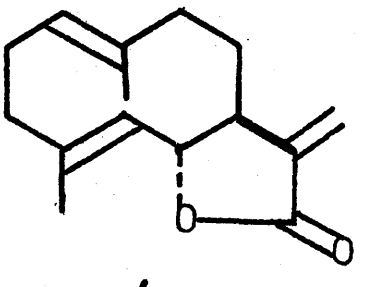
2.



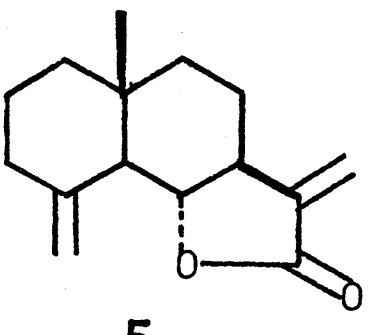
1.



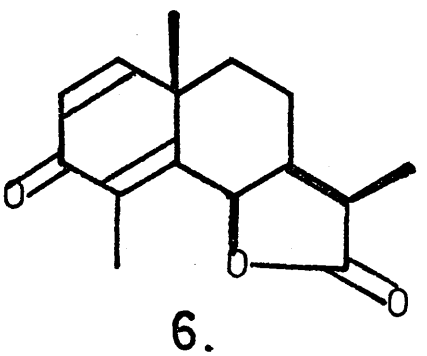
3.



4.



5.



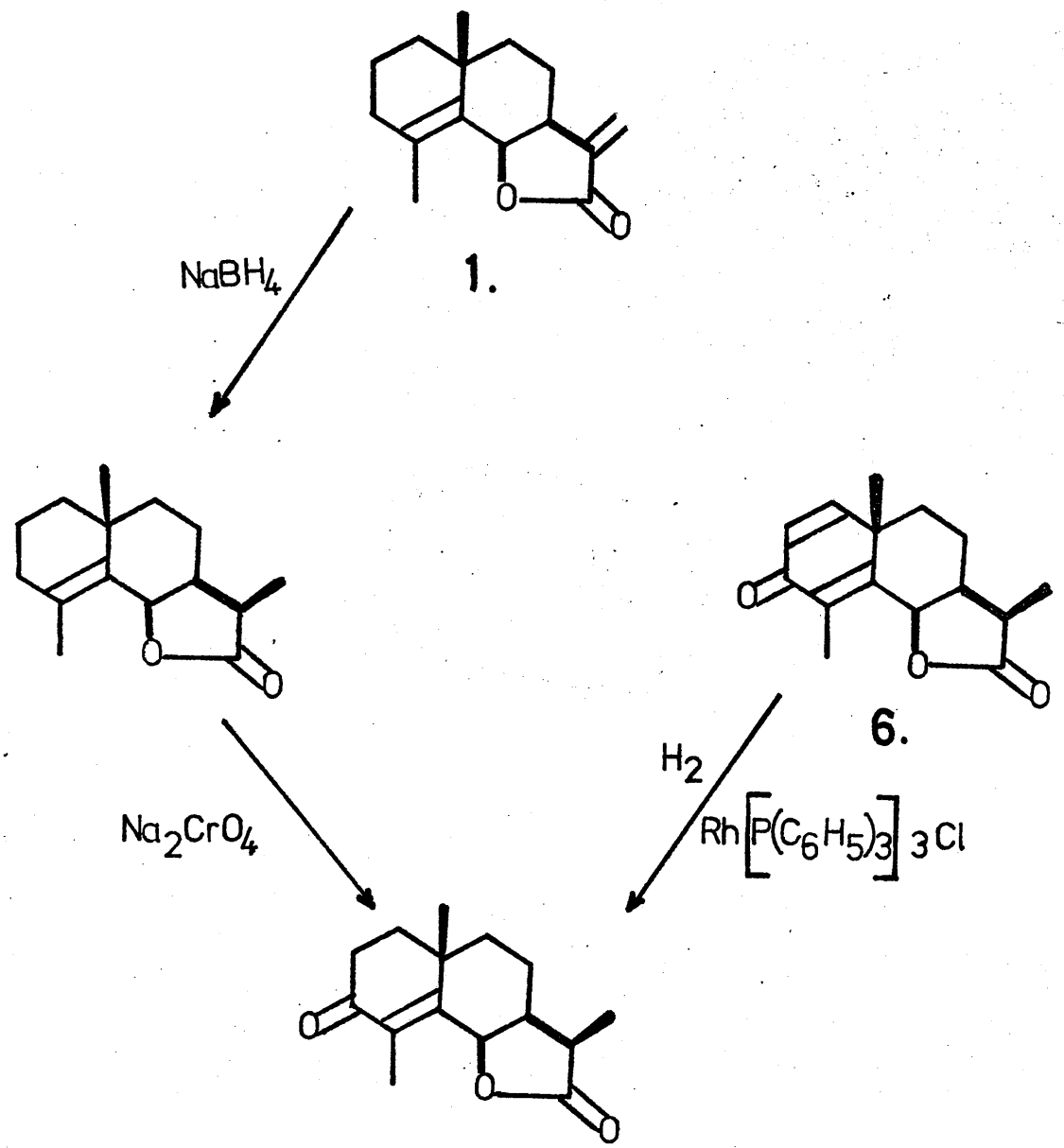
6.

The other naturally occurring sesquiterpene lactones showed similarities in their NMR spectra. Thus the second compound 2 m.p. 86-87°C.; $[\alpha]_D$ + 27°, had in the NMR, signals at τ 8.92 (singlet, tertiary methyl), 8.16 (broad singlet, vinyl methyl), 7.4 (broad multiplet, H-7), 5.46 (diffuse doublet, H-6, Jobs. = 12 Hz.), 4.57, 3.87 (doublets, exomethylene, J = 3 Hz.), and a strong band in the IR spectrum at 1780 (γ-lactone) cm^{-1}.

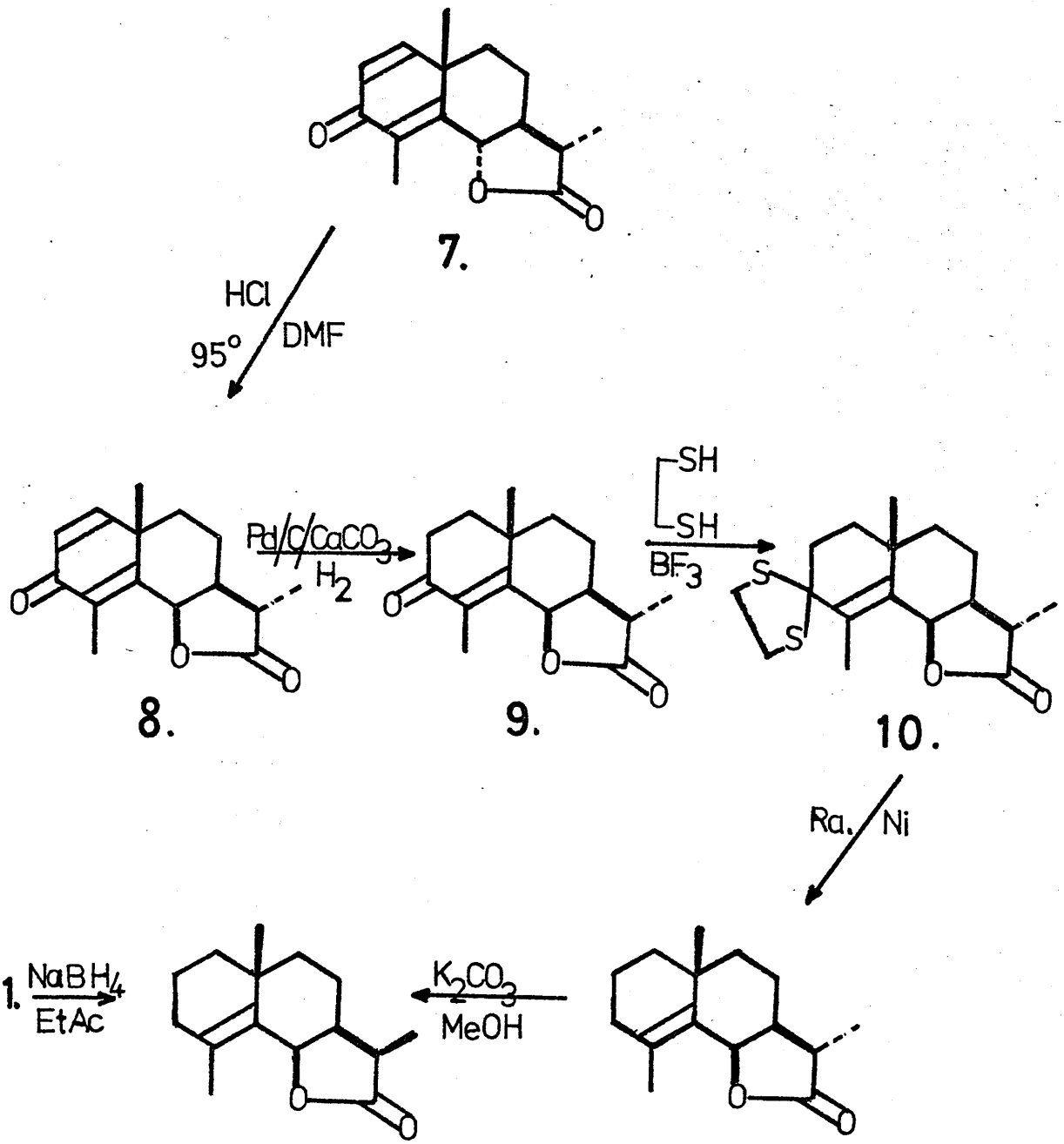
The main difference in the spectra of 1 and 2 was the signal for H-6 which in the case of 2 was a diffuse doublet further upfield at τ 5.46. However, irradiation at H-6 (τ 5.46) sharpened the broad singlet at τ 8.16 (C-4 vinyl methyl) by removal of a relatively large homoallylic coupling, showing that the lactone ring in this case was in a trans configuration as in 2. This is, in fact, a known compound, γ-cyclocostunolide[3] (arbusculin B[4]). The two remaining sesquiterpene lactones were identified as α-cyclocostunolide[5] 3 and costunolide[6] 4 respectively. The compounds 2 and 3 were compared with authentic samples prepared by cyclising[3] authentic costunolide (from Saussurea lappa[6]) to α 3, β 5 and γ 2 cyclocostunolide. No trace in the extract was found of β-cycloscostunolide 5[7]. That α and γ-cyclocostunolide were probably not artefacts followed from the failure of costunolide to give these products when subjected to the isolation procedure.

The cis-lactone 1 has recently been isolated in both enantiomeric forms by Ourisson[8], from Frullania species and its structure inter-related with a known sesquiterpene, 11β-6-epi-santonin 6[9] as in scheme (1).

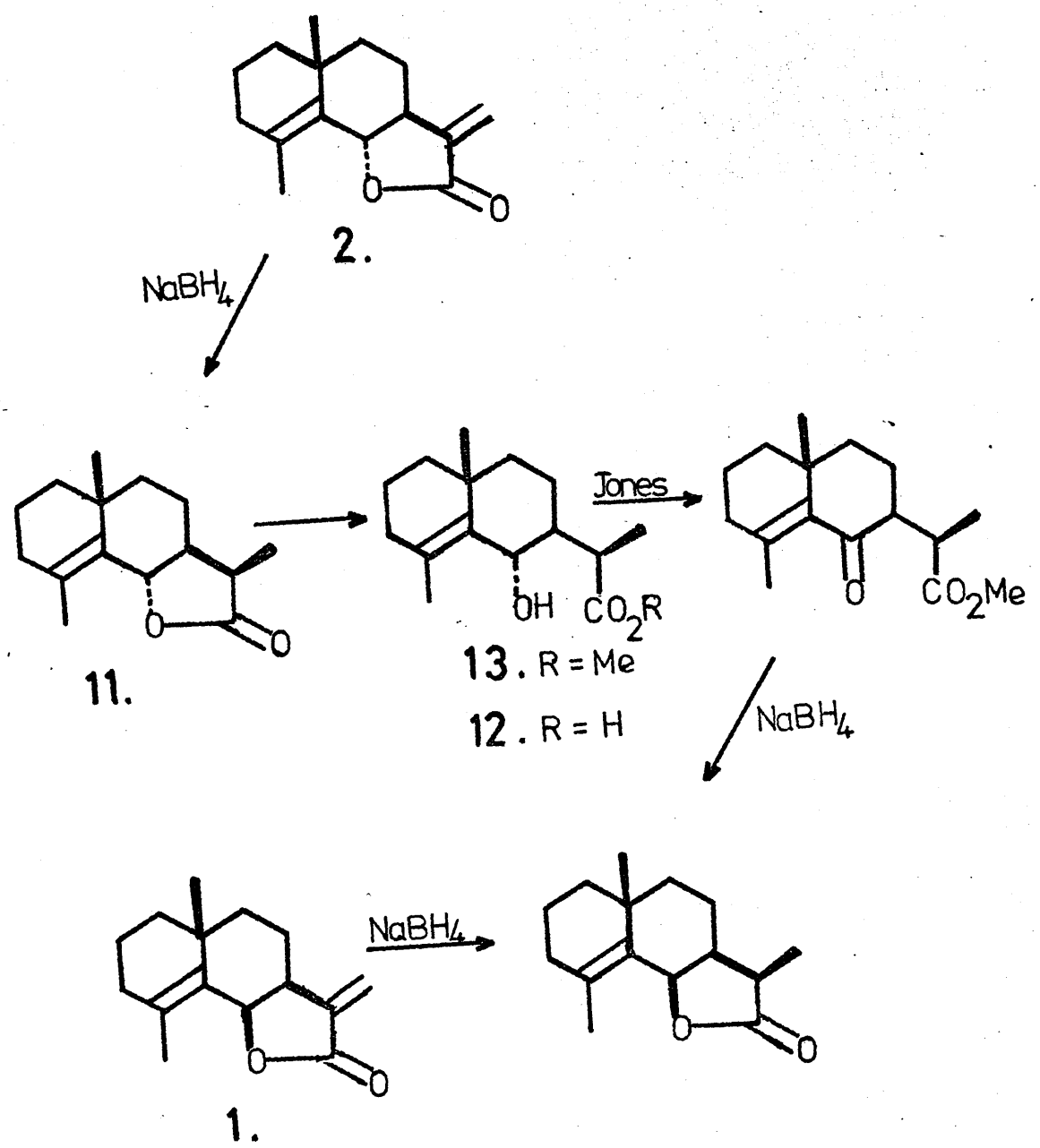
SCHEME 1.



SCHEME 2.


7.
HCl
95°
DMF
8.
Pd/C/CaCO3
H2
9.
SH
SH
BF3
10.
Ra. Ni
1. NaBH4
EtAc
K2CO3
MeOH

SCHEME 3.



The corresponding trans-isomer, γ-cyclocostunolide 2 has been discovered naturally-occurring in the species Artemesia arbuscula (Compositae) by Geissman[4].

Our attempts to inter-relate 11α-santonin[10] 7 with the cis-lactone 1 failed. The proposed synthetic route is shown in scheme (2). Difficulty was encountered in obtaining high yields and pure samples of 8 and 9. When at last the thioketal 10 was formed, treatment with Raney nickel produced a vast mixture of products.

Attempts at interconverting γ-cyclocostunolide 2 with the cis-lactone 1 also were of no avail. The intended route, shown in scheme (3) foundered at the initial γ-lactone ring opening stage where very low yields of the hydroxy methyl ester 13 were obtained. Subsequent attempts at oxidising the C-6 secondary hydroxyl group met with no success.

Experimental

The liverwort Frullania tamascifolia was collected in the West of Scotland. After drying, it was finely ground and extracted with chloroform in a Soxhlet apparatus. Large scale chromatography over alumina (grade H deactivated) followed by preparative TLC furnished four closely related sesquiterpenes, three of which were known compounds.

The cis-lactone 1

The most abundant component, the cis-lactone 1 was recrystallised from methanol as needles m.p. 74-76°C.; $[\alpha]_D$ -109° (lit.[8] m.p. 77°C.; $[\alpha]_D$ -113°). NMR signals at τ 8.93 (singlet, tertiary methyl), 8.25 (singlet, vinyl methyl), 7.03 (broad multiplet, H-7), 4.77 (doublet, H-6, J = 5 Hz.), 4.45, 3.88 (broad singlets, exomethylene), νmax 1768 (γ-lactone) cm^{-1}.

Mass spectrum: M^+ = 232 ($C_{15}H_{20}O_2$ requires M^+ = 232).

Costunolide 4

This was the most polar compound isolated and tended to polymerise. Recrystallisation from methanol yielded needles m.p. 103-105°C.; $[\alpha]_D$ + 121° (lit.[6] m.p. 106-107°C.; $[\alpha]_D$ + 128°). NMR signals at τ 8.57, 8.30 (broad singlets, 2 vinyl methyls), 5.33 (multiplet, (3H), H-5, H-6, H-10), 4.47, 3.77 (doublets, exomethylene, J = 3 Hz.), νmax 1773 (γ-lactone) cm^{-1}.

Mass spectrum: M^+ = 232 ($C_{15}H_{20}O_2$ requires M^+ = 232).

γ-cyclocostunolide 2

Recrystallisation of γ-cyclocostunolide 2 from methanol, gave needles m.p. 86-87°C.; $[\alpha]_D$ + 27°, (lit.[3] m.p. 87-88°C.; $[\alpha]_D$ + 22°). NMR signals at τ 8.92 (singlet, tertiary methyl), 8.16 (singlet, vinyl methyl), 5.46 (diffuse doublet, H-6, Jobs = 12 Hz.), 4.57, 3.87 (doublets, exomethylene, J = 3 Hz.), νmax 1780 (γ-lactone) cm^{-1}.
Mass spectrum: M^+ = 232 ($C_{15}H_{20}O_2$ requires M^+ = 232).

α-cyclocostunolide 3

α-cyclocostunolide 3 was recrystallised from methanol as needles m.p. 82-83°C.; $[\alpha]_D$ + 108°, (lit.[5] 83-84°C.; $[\alpha]_D$ + 118°). NMR signals at τ 9.14 (singlet, tertiary methyl), 8.20 (broad singlet, vinyl methyl), 6.16 (triplet, H-6, Jobs. = 12 Hz.), 4.65 (diffuse doublet, (2H), exomethylene proton, H-3), 3.97 (doublet, exomethylene proton, J = 3 Hz.), νmax 1780 (γ-lactone) cm^{-1}.
Mass spectrum: M^+ = 232 ($C_{15}H_{20}O_2$ requires M^+ = 232).

Cyclisation of costunolide 4

Costunolide 4 (200 mg.) was allowed to stand in chloroform (50 ml.) containing thionyl chloride (0.1 ml.) according to the method of Doskotch et al.[3]. Removal of the solvent left a residue consisting of three components. Separation by preparative TLC afforded pure samples of α 3 β 5 and γ 2-cyclocostunolide.

Epimerisation of 11α-santonin 7

11α-santonin 7 (500 mg.) was heated at 95°C. in 5% HCl/dimethyl formamide according to the method of Cocker et al.[9]. The reaction did not go, if concentrated HCl was used in making up the 5% solution. However when dry HCl gas from a generator was passed at a steady rate for 45 seconds through the solution, and then heated to 95°C. for six hours, an 80% conversion to the 6-epi form 8 was obtained. This was not obtained pure. NMR signals at τ 8.70 (singlet, tertiary methyl), 8.60 (doublet, secondary methyl, J = 8 Hz.), 7.93 (singlet, vinyl methyl), 4.40 (doublet, H-6, J = 5 Hz.), 3.73, 3.15 (AB quartet, H-2, H-1, J = 10 Hz.), νmax 1785 (γ-lactone), 1668 (dienone) cm^{-1}.

Hydrogenation of 6-epi-santonin 8

Hydrogenation in ethyl acetate of 8 using 1% palladium/charcoal poisoned with calcium carbonate gave disappointingly small yields of the Δ' dihydro compound 9 isolated as a mixture containing some tetrahydro compound. NMR signals at τ 8.73 (singlet, tertiary methyl), 8.63 (doublet, secondary methyl, J = 8 Hz.), 8.08 (singlet, vinyl methyl), 4.55 (doublet, H-6, J = 5 Hz.), νmax 1785 (γ-lactone), 1680 (enone) cm^{-1}.

The thioketal 10

To the Δ' dihydro compound 9 (70 mg.) dissolved in ether (5 ml.) was added ethane dithiol (5 drops) and BF_3 etherate (5 drops). This was left for 12 hours, water added and extracted into chloroform. Any

excess ethane dithiol present was removed by preparative TLC. The non-crystalline thioketal 10 (34 mg.) was obtained pure. NMR signals at τ 8.90 (singlet, tertiary methyl), 8.68 (doublet, secondary methyl, J = 8 Hz.), 7.93 (singlet, vinyl methyl), 6.67 (multiplet, (4H), thioketal), 4.65 (doublet, H-6, J = 5 Hz.), νmax, 1780 (γ-lactone) cm^{-1}.

Desulphurisation of the thioketal 10

The thioketal 10 (27 mg.) in acetone (8 ml.) was refluxed overnight in the presence of Raney nickel (~50 mg.). Filtration and removal of the solvent left a residue consisting of an intractable mixture of compounds.

11, 13 dihydro γ-cyclocostunolide 11

Treatment of γ-cyclocostunolide 2 (19 mg.) in ethyl acetate (3 ml.) with excess sodium borohydride produced the dihydro derivative 11 (14 mg.) as a gum. NMR signals at τ 8.88 (singlet, tertiary methyl), 8.86 (doublet, secondary methyl, J = 8 Hz.), 8.17 (broad singlet, vinyl methyl), 5.47 (multiplet, H-6), νmax 1785 (γ-lactone) cm^{-1}. Mass spectrum: $M^+ = 234$ ($C_{15} H_{22} O_2$ requires $M^+ = 234$).

Attempted opening of the γ-lactone 11

(i) Treatment of the γ-lactone 11 with aqueous sodium hydroxide in methanol followed by addition of a vast excess of ethereal diazomethane did not produce any of the desired hydroxy methyl ester 13.

(ii) Formation of the silver salt of the ring-opened hydroxy acid 12 and subsequent addition of methyl iodide to this produced a mixture containing the desired hydroxy methyl ester 13 as the minor component and the relactonised compound 11. The hydroxy methyl ester had ν_{max} 3590 (hydroxyl), 1785 (γ-lactone), 1738 (methyl ester) cm^{-1}.

Attempted oxidation of the hydroxy methyl ester 13

The above mixture was treated with two drops of Jones reagent in acetone at 0°C. The product, one spot on TLC had, ν_{max} 1785 (γ-lactone), (no ketone) cm^{-1}, indicative of the γ-lactone 11.

References.

1. S. Sternhell, Pure and Appl. Chem., 14, 15 (1964).

2. M. Karplus, J. Amer. Chem. Soc., 85, 2870 (1963).

3. R. W. Doskotch and F. S. El-Feraby, J. Org. Chem., 35, 1928 (1970).

4. T. A. Geissman and M. A. Irwin, Phytochemistry, 8, 2411 (1969).

5. G. H. Kulkarmi, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron, 20, 2639 (1964).

6. A. S. Ras, G. R. Kelkar and S. C. Bhattacharyya, Tetrahedron, 9, 275 (1960).

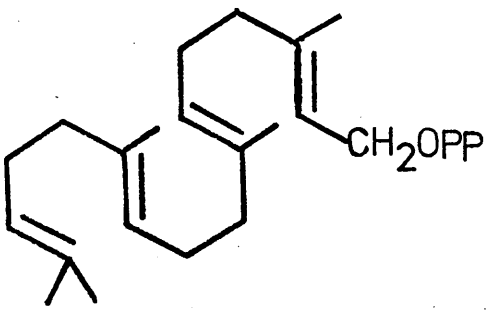
7. T. C. Jain and J. E. McCloskey, Tetrahedron Letters, 2917 (1969).

8. H. Knoche, G. Ourisson, G. W. Perold, J. Foussereau and J. Maleville, Science, 166, 239 (1969).

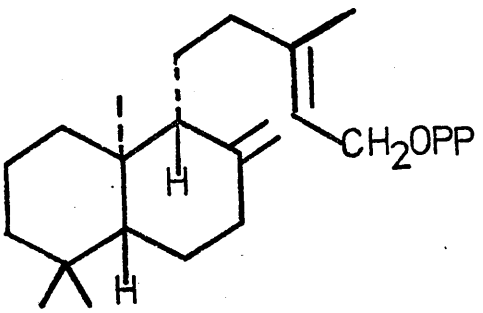
9. W. Cocker, H. Gobinsingh, T. B. H. McMurray and M. A. Nisbet, J. Chem. Soc., 1432 (1962).

10. (i) M. Nakazaki and H. Arakawa, Proc. Chem. Soc., 151 (1962).

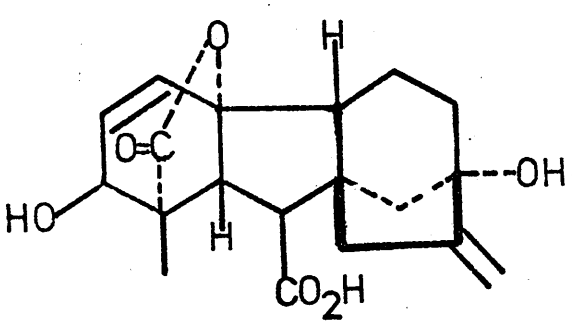
(ii) J. D. M. Asher and G. A. Sim, Proc. Chem. Soc., 335 (1962).



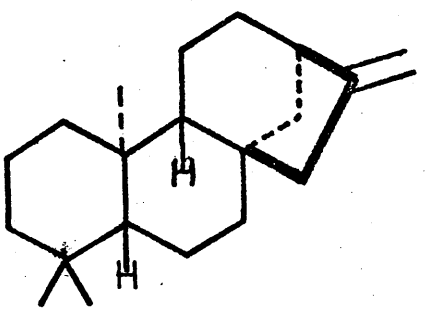
1.



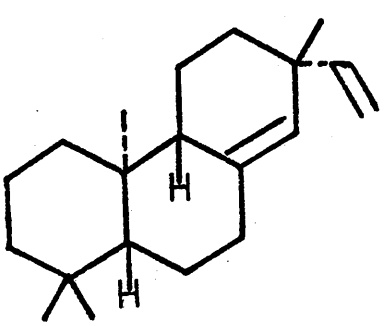
2.



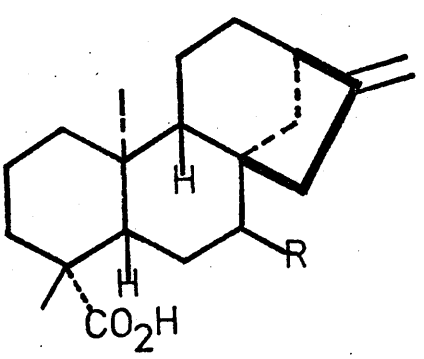
3.



4.



5.



6. R = H
7. R = OH

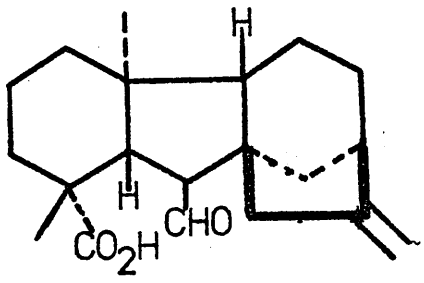
Introduction

Investigation of the liverwort Solenostoma triste resulted in the isolation of four tetracyclic diterpenoids which were shown by chemical and spectroscopic means to be ent.-kaurene derivatives. An account of the structural determination of these diterpenoids is given in the ensuing discussion (see p.89).

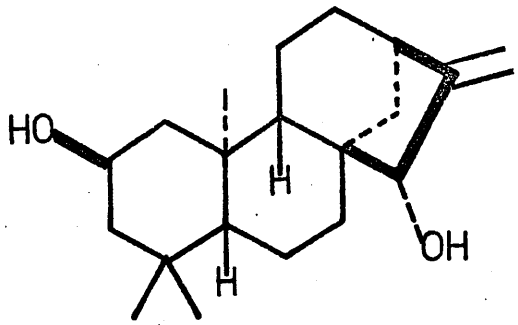
Of all the diterpenes found in nature, perhaps most interest has been directed recently to the group of tetracyclic diterpenoids containing the phyllocladene - kaurene derivatives. The reason for this primarily is the importance of the gibberellins[1], plant growth hormones, derived from a rearranged ent.-kaurane skeleton.

Gibberellin biosynthesis is thought to proceed by cyclisation of geranyl geranyl pyrophosphate 1[2,3] to the labdadienol 2[2]. This dienol 2 has been shown[4] to be incorporated (as its pyrophosphate) during the biosynthesis of gibberellic acid 3. The incorporation of labdadienol 2 occurs by formation of ent.-kaurene[5] 4 possibly via the (−) pimaradiene precursor 5, although as yet, no tricyclic intermediates have been isolated[4].

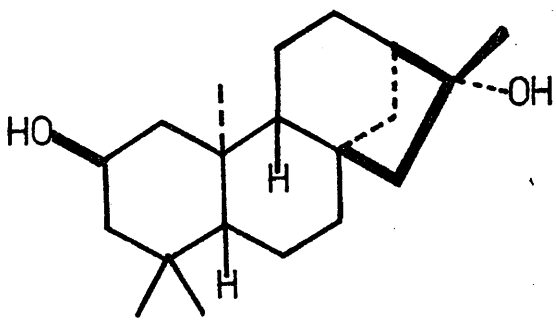
The subsequent modification of ent.-kaurene 4 to the gibberellins involves oxidation and contraction of ring-B to a cyclopentane carboxylic acid. It has been demonstrated[6] that this conversion takes place through the successive formation of ent.-kaur-16-en-19-oic acid 6 and 7 β-hydroxy


H
H
CHO
CO_2H

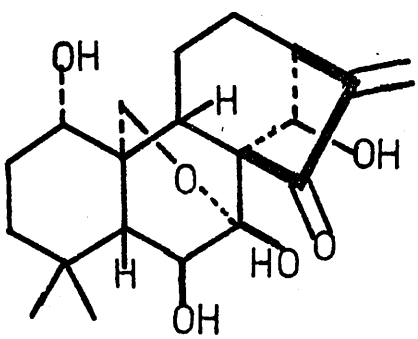
8.


HO
H
OH
H

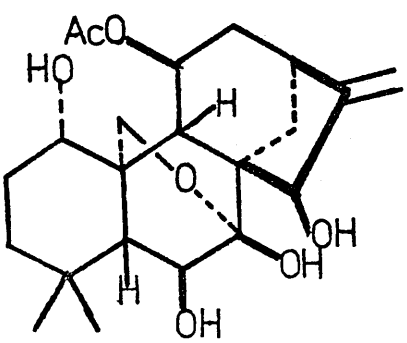
9.


HO
OH
H
H

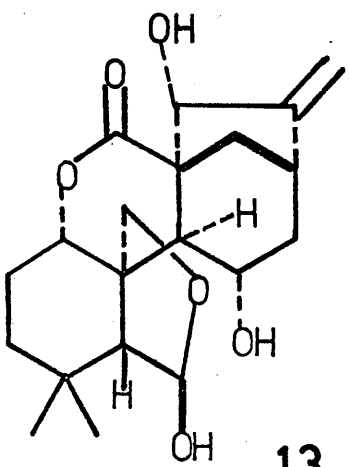
10.


OH
H
OH
O
HO
O
H
OH

11.


AcO
HO
H
O
OH
OH
H
OH

12.


OH
O
O
H
O
OH
H
OH

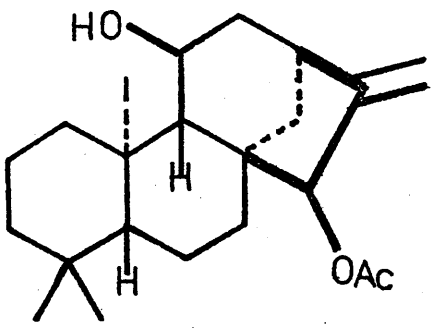
13.

ent.-kaur-16-en-19-oic acid 7 followed by ring contraction to the gibbane aldehyde 8. Various hydroxylations and oxidations of this aldehydo-acid 8 yield the bewildering variety of C_{19} and C_{20} gibberellins found in nature.[7,8]

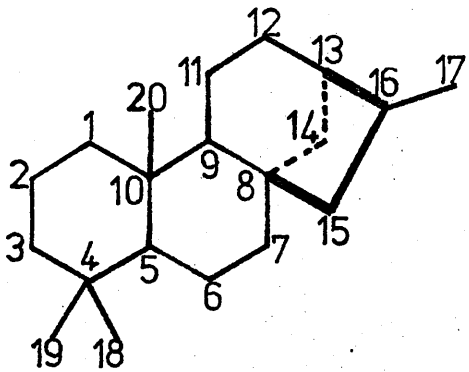
Although gibberellic acid and its related compounds have been isolated from ferns[9], it was not until quite recently that ent.-kaurenoids have been isolated from this source. The compounds 9 and 10 were isolated by Chen et al[10] from Pteris cretica. Studies on Isodon species (Labiatae) have unearthed several polyoxygenated ent.-kaurenoids which together form a very interesting biogenetic pattern. Thus oridonin 11 has been isolated from two Isodon species[11,12] and sodoponin 12 and epinodosinol 13 have both been obtained[13] from Isodon japonicus.

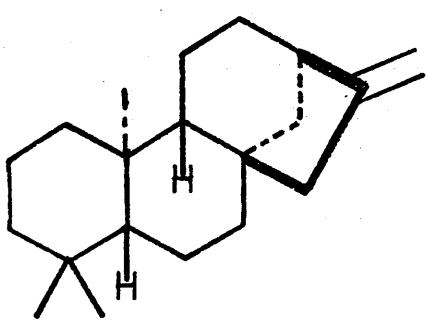
References.

1. J. F. Grove, Quart. Rev., 15, 56 (1961) and references therein.
2. J. D. Bu'lock, "Biosynthesis of Natural Products", McGraw-Hill, 1965, p. 46.
3. J. R. Hanson and A. F. White, J. Chem. Soc. (C), 981 (1969).
4. J. R. Hanson and A. F. White, Chem. Comm., 103 (1969).
5. B. E. Cross, R. H. B. Galt and J. R. Hanson, J. Chem. Soc., 295 (1964).
6. J. R. Hanson and A. F. White, Chem. Comm., 410 (1969).
7. B. E. Cross, K. Norton, and J. C. Stewart, J. Chem. Soc. (C), 1054 (1968).
8. J. R. Hanson and B. Achilladelis, Perfum. essent. Oil Rec., 802 (1968).
9. L. Reinhold and Y. Liwschitz, "Progress in Phytochemistry", Vol I, Interscience, 1968, p. 645.
10. C. M. Chen and T. Murakarri, Tetrahedron Letters, 1121 (1971).
11. T. Kubota and I. Kubo, Bull. Chem. Soc. Japan, 42, 1778 (1969).
12. E. Fujita, T. Fujita, H. Katayama, M. Shibuya and T. Shingu, J. Chem. Soc. (C), 1674 (1970).
13. E. Fujita, T. Fujita, M. Taoka, H. Katayama and M. Shibuya, Tetrahedron Letters, 421 (1970).

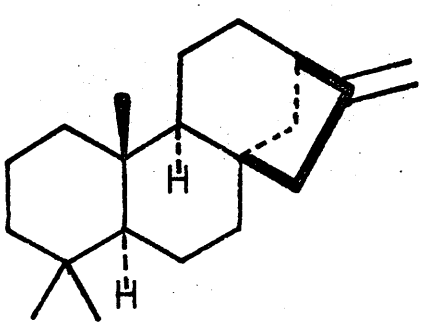


1.





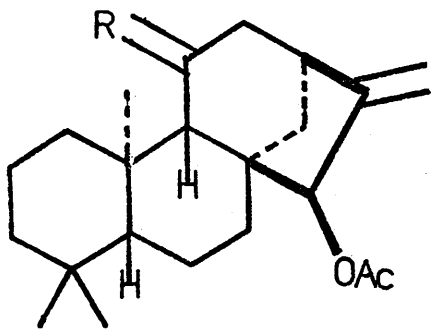
2.



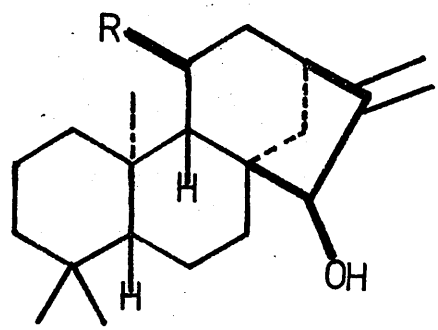
3.

Discussion

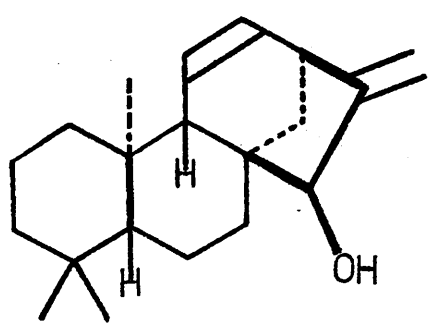
The first compound was the hydroxy acetate 1, $C_{22}H_{34}O_3$ m.p. 118-120°C; $[\alpha]_D$ -89°, ν_{max} 3590 (hydroxyl), 1750 (acetate), 1660 (exomethylene) cm^{-1}. The NMR spectrum had signals at τ 9.10, 9.04, 8.99 (singlets, 3 tertiary methyls), 7.75 (singlet, acetate), 7.40 (broad singlet, 1H, exchangeable with D_2O), 7.28 (multiplet, H-13), 6.20 (multiplet, H-11) 5.07, 4.88 (multiplets, each 1H, exomethylene), 4.72 (triplet, H-15, Jobs = 2Hz.). This data suggested that the basic skeleton was that of a tetracyclic diterpene hydrocarbon of the kaurene 2[1] or phyllocladene 3[2] type. Decoupling experiments confirmed the relative positioning of the secondary acetate and exomethylene group (as 1) in ring-D. Irradiation at the centre of the multiplet at τ 7.28 (H-13) led to simplification of the exomethylene proton signals, which were reduced to doublets, (J = 2 Hz., 3 Hz.) by removal of a small coupling. This coupling was due to allylic coupling between H-13 and the exomethylene protons. No effect was noticed on the carbinol proton (H-11), nor on the secondary acetate proton (H-15). That the remaining coupling to the exomethylene protons was due to H-15 was shown by irradiating at τ 5.07, the upfield exomethylene signal, whereupon the signal at τ 4.72 (H-15) collapsed to a doublet, J = 3 Hz., by removal of a coupling of 2 Hz..



1. R = αH, βOH
4. R = O
5. R = αH, βOAc
7. R = αH, βOTs



6. R = OH
8. R = H



9.

Jones oxidation of the hydroxy acetate 1 gave the keto acetate 4 m.p. 120-122°C. [νmax 1700 (cyclohexanone) cm^{-1}]. Acetylation of the hydroxy acetate yielded the nicely-crystalline diacetate 5 m.p. 156-159°C., [τ 8.12, 7.86 (singlets, 2 acetates)]. The latter reaction, using acetic anhydride in pyridine was very slow at room temperature but increased markedly on gentle heating. Removal of the acetate functions with lithium aluminium hydride, afforded the diol 6 m.p. 192-194°C., later found to be identical with one of the more-polar natural products isolated from Solenostoma triste.

In order to determine the skeletal type of the hydroxy acetate, it was necessary to remove the secondary hydroxyl function. Kaurane[3] and phyllocladane[4] derivates, functionalised in the 15 position are well known, and so a straightforward comparison would then be possible. Tosylation, using p-toluene sulphonyl chloride in pyridine was an extremely slow reaction at room temperature, but despite this, a small amount of the desired tosylate 7 was isolated. The tosylate was subjected to gentle reflux in ether, in the presence of lithium aluminium hydride. The main product from this reaction was not the expected deoxy compound 8, but the diene 9. Evidence for placing the cis-disubstituted double bond in the Δ^{11} position was again derived from decoupling studies. The prominent features in the NMR spectrum of 9 (fig. 1), were signals at τ 7.17 (multiplet, H-13), 5.20, 5.14 (doublet, Jobs. = 3 Hz.), broad singlet, respectively; exomethylene,

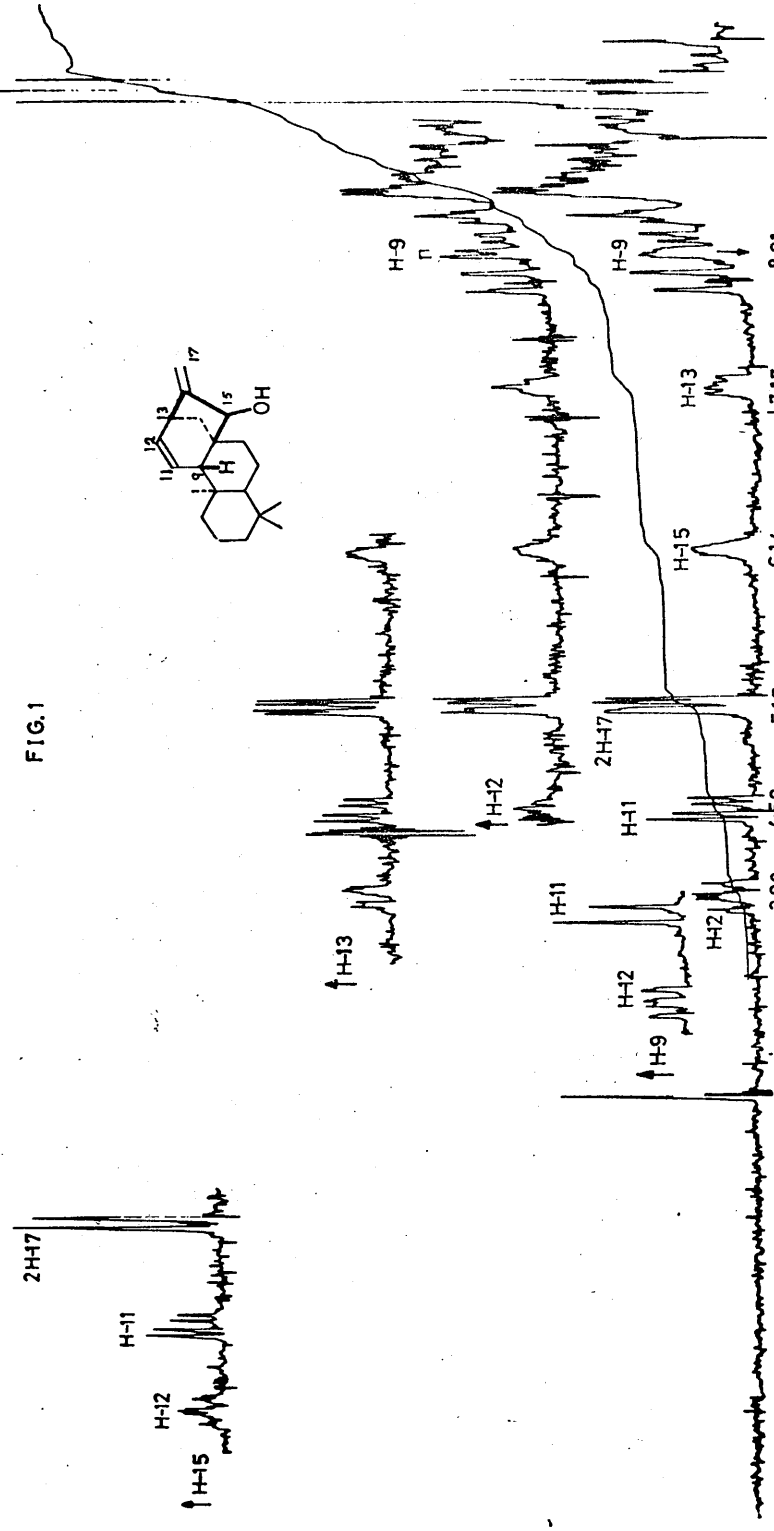

2H-17
H-11
H-12
H-15
H-13
H-12
H-11
H-12
H-9
H2
2H-17
H-11
H-15
H-13
H-9
H-9
3·98
4·50
5·17
6·14
7·17
8·01
OH

FIG. 1

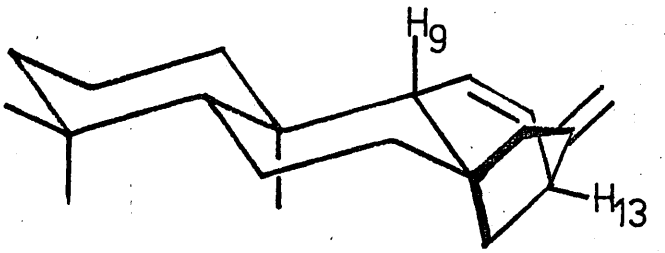
4.50 (double doublet, ABMX system, H-11, Jobs.$_{BA}$ = 10 Hz., Jobs.$_{BX}$ = 4 Hz., Jobs.$_{BM}$ = 0 Hz.), 3.98 (diffuse triplet, ABMX system, H-12, Jobs.$_{AB}$ = 10 Hz., Jobs.$_{AM}$ = 8 Hz., Jobs.$_{AX}$ = 2 Hz.).

Irradiation at H-13 (τ 7.17), removed a small allylic coupling from the exomethylene signals and reduced the diffuse triplet centred at τ 3.98 (H-12) to a diffuse doublet (Jobs = 10 Hz.), by removing the vicinal coupling between them. The remaining coupling to H-12 was vicinal coupling to H-11 (Jobs = 10 Hz.) and allylic coupling to H-9 (Jobs. = 2 Hz.).

Similarly, irradiation at a broad singlet at τ 8.02 (H-9), reduced the quartet at τ 4.50 (H-11) to a clean doublet, one leg of an AB system (J_{AB} = 10 Hz.). Thus H-11 showed no obvious allylic coupling. In addition, the main coupling to the exomethylene protons, (Jobs. = 3 Hz.), could be removed by irradiating at τ 6.14 (H-15), reducing them to sharp singlets. The coupling constant values expected from the Karplus[5] relationshp by consideration of Fieser models of both the kaurene and phyllocladene skeletons are shown in fig. 2. It was not possible to distinguish between α H-15 and β H-15 protons on the basis of the

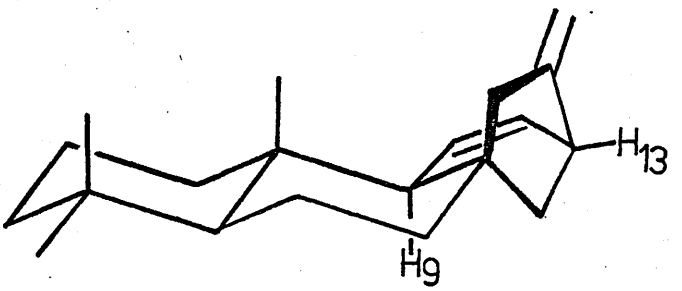
++ The NMR spectrum (fig.1) of the diene 9 was interpreted on a first-order basis. This was justified, as perturbation of the signals involved had not occurred to any great extent. ++

FIG 2.



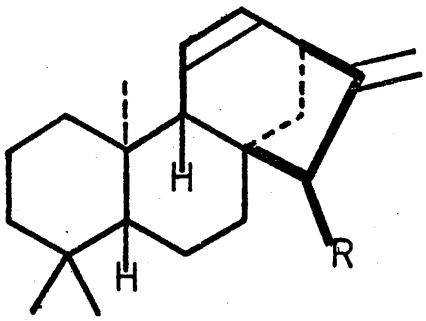
Kaurene Skeleton

	OBS.	THEOR.
$J_{H_9,H_{11}}$	4 Hz.	~3 Hz. *
$J_{H_{12},H_{13}}$	8 Hz.	~8 Hz.

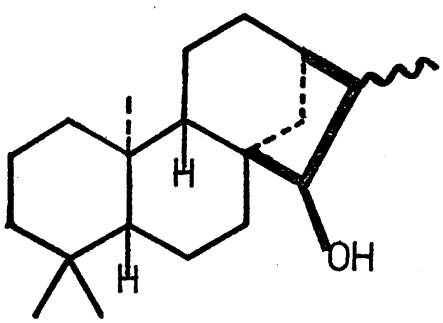


Phyllocladene Skeleton

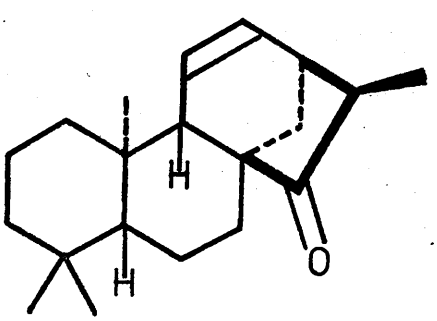
	OBS.	THEOR.
$J_{H_9,H_{11}}$	4 Hz.	~0·5 Hz. *
$J_{H_{12},H_{13}}$	8 Hz.	~8 Hz.



9. R = OH
10. R = OAc



11.

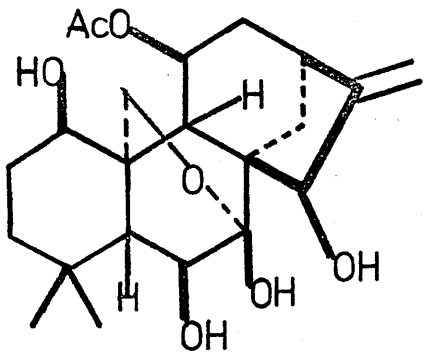


12.

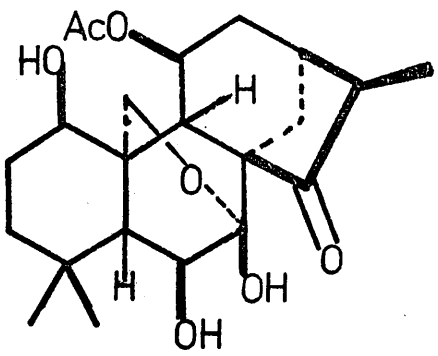
magnitude of the observed allylic coupling between H-15 and the exomethylene group. Thus the configuration of the C-15 oxygenated substituent could not be predicted. These results, however, unequivocally place the double bond at 11, 12 and hence the original secondary hydroxyl group, (neglecting unforeseen skeletal rearrangements in tosylate formation and elimination), must be either at 11 or 12.

In an effort to increase the rate of tosylate formation, the reaction mixture was heated gently. This led directly to the formation of the acetoxy diene 10 which, with lithium aluminium hydride gave the diene 9 in slightly better yields than before. The diene 9, was hydrogenated over 10% palladium/charcoal for 30 minutes. The product was not the expected tetrahydro product 11 but instead the ketone 12, m.p. 124-125°C., ν_{max} 1740 (cyclopentanone) cm^{-1}, (no hydroxyl); τ 8.96 (doublet, secondary methyl, J = 6 Hz.), loss of H-15 7. The NMR spectrum clearly showed the loss of the exomethylene group, with the retention of the Δ^{11} double bond.

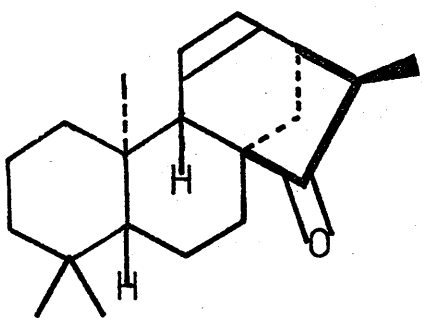
It was obvious that under catalytic hydrogenation conditions, the diene 9 had undergone a facile Garryfoline - Cuauchichicene rearrangement.[3,6] Normally this rearrangement affects only 15 β-hydroxy kaurenols and requires dilute mineral acid. Subsequent to our observation, another example[7] has been published. Thus the kaurenoid derivative 13



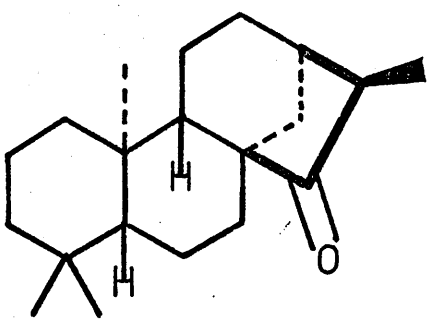
13.



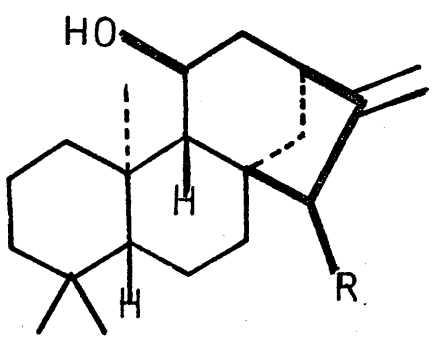
14.



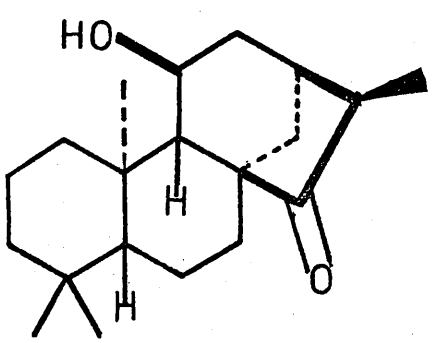
12.



15.



6. R = OH
1. R = OAc



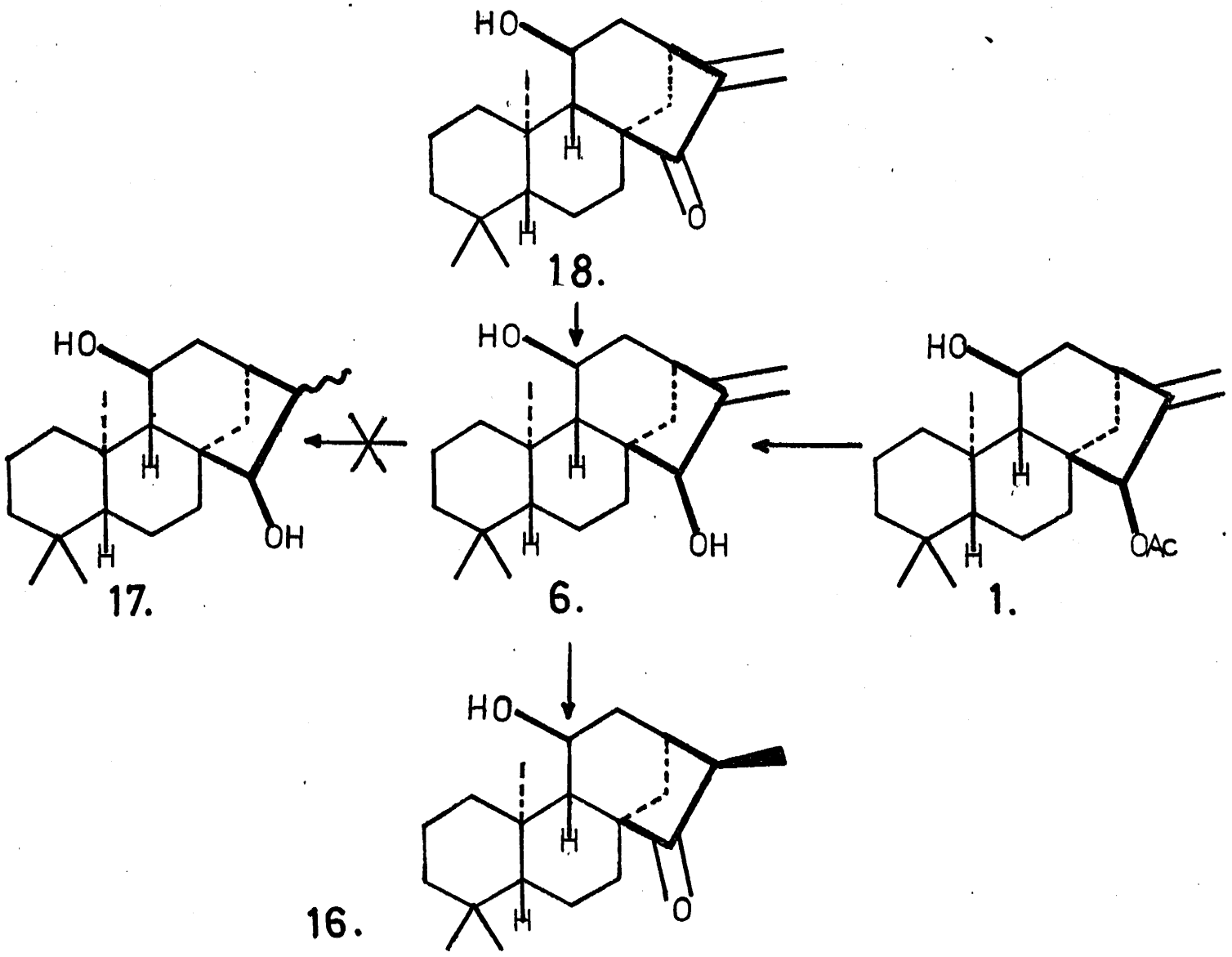
16.

rearranges to 14 under catalytic hydrogenation conditions. This reaction is stereospecific[3] and defines the stereochemistry of the product as in 12 (16β-Me). Further hydrogenation of the unsaturated ketone 12 over 10% palladium/charcoal catalyst for 48 hours furnished ent. kauran-15-one 15 m.p. 147-149°C., $[\alpha]_D$ -87°; (lit.[3] m.p. 150°C., $[\alpha]_D$ -81°).

This degradation to the kauranone system of known absolute configuration established the basic skeleton and the position and stereochemistry of the acetate (15β-OAc.) in the original hydroxy acetate 1. The position and configuration of the secondary hydroxyl group remained to be settled.

It is convenient at this stage to discuss the other products isolated from the extract. Separation by preparative TLC of the more-polar fractions of the extract afforded what appeared by normal analytical TLC to be one compound. However the NMR spectrum showed it to be a mixture of two compounds in roughly equal proportions. Use of silver nitrate impregnated TLC plates (20% w/w), allowed separation of this mixture into two close-running components. The less polar was the hydroxy ketone 16, m.p. 186-188°C., $[\alpha]_D$ -85°; [ν_{max} 3615, 3510 (hydroxyl), 1735 (cyclopentanone) cm^{-1}]. The more polar component, the diol 6, m.p. 192-194°C., $[\alpha]_D$ -62° was identical with the product from the reaction of lithium aluminium hydride on the hydroxy acetate 1.

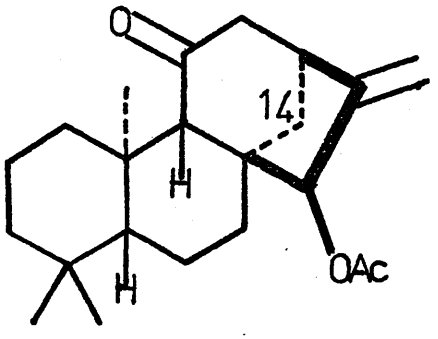
SCHEME 1



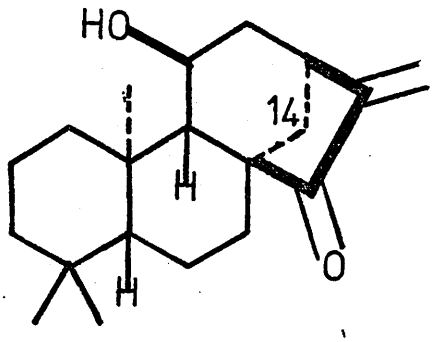
Thus the naturally occurring diol had the same oxygenation pattern and stereochemistry as the hydroxy acetate. On catalytic hydrogenation, the diol was converted to the hydroxy ketone 16 and not to the dihydro compound 17. Thus the Garryfoline-Cuauchichicene rearrangement once again was preferred to straightforward hydrogenation. The ease with which this rearrangement occurs raises the possibility that the hydroxy ketone 16 is an artefact. The diol 6 however appeared to be stable under extraction conditions.

The most polar compound to be isolated was the unsaturated hydroxy ketone 18 m.p. 121-124°C., $[\alpha]_D$ -118°; νmax 3608, 3450 (hydroxyl), 1730 (cyclopentenone), 1650 (exomethylene) cm^{-1}; λ max 238 nm. (ε7,100); τ 6.90 (multiplet, H-13), 5.90 (multiplet, H-11), 4.71, 4.11 (singlets, exomethylene conjugated with a carbonyl group)[7]. It was readily interrelated with the diol 6 by reduction with lithium aluminium hydride. The stereochemistry of the secondary hydroxyl group was thus the same as in the other natural products. These results are summarised in Scheme (1).

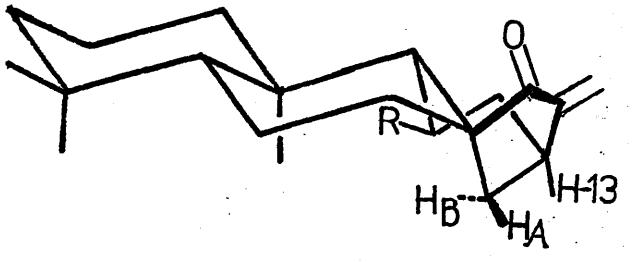
A closer examination of the NMR spectra of the above compounds, together with decoupling experiments, and the use of benzene shifts[8] and Eu $(DPM)_3$ induced shifts[9] allowed us to settle the position and configuration of the secondary hydroxyl group.



4.



18.

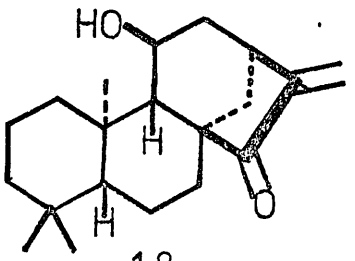


19. R = OH

A doublet at approximately τ 7.6 appeared in several compounds, including the keto acetate 4 and the unsaturated hydroxy ketone 18. This doublet, undoubtedly one leg of an AB quartet (J_{AB} = 12 Hz.) was assigned to one of the bridge protons at C-14 (see 19). The other proton resonated at approximately τ 8.5 but was hidden in the methylene envelope. Irradiation at approximately τ 8.6 (H_A-14) in the unsaturated ketone 18, reduced this doublet, centred at τ 7.63 (H_B-14) to a singlet, and also removed coupling from the multiplet at τ 6.90 (H-13), ($W_{\frac{1}{2}}$ 12 Hz. to $W_{\frac{1}{2}}$ 8 Hz.). No effect was observed on the carbinol proton H-11 (τ 5.90).

Irradiation at H-13 sharpened up the doublet at τ 7.63 (H_B-14) very slightly, caused a change in the spectrum at ~τ 8.6, had no effect on the carbinol proton (H-11) and little or no effect on the exomethylene protons, which were sharp singlets. Fieser models show that the dihedral angle Φ between H-13 and H_A-14 is approximately 40°, and that between H-13 and H_B-14 is approximately 80-90°. This requires coupling constants of ~5 Hz. and ~0Hz. respectively, irrespective of ring C being in a boat or chair conformation. This is in agreement with the results observed above.

Thus H-13 couples only to one of the bridge (C-14) protons and to an insignificant extent to the exomethylene protons. To account for the remaining coupling of H-13 ($W_{\frac{1}{2}}$ ~8 Hz.), there must be vicinal coupling to other protons. Since there is no observable coupling with the carbinol proton at τ 5.90 (H-11), then there must be a methylene



18

TABLE 1

	>C=CH$_2$	H-11	H-13	H$_A$-14	H$_B$-14	H-9	3^y METHYLS	>C$_{12}$-H$_2$
18 in $CDCl_3$	4·11 4·71 s.^{s}	5·90 m.	6·90 m.	~8·60 b.d.	~7·60 b.d.	—	9·06 8·98 8·87 s.^{s}	~8·8
18 in $CDCl_3$ + $Eu(DPM)_3$	2·43 3·60 s.^{s}	−0·84 m.	5·24 m.	6·97 b.d.	5·88 b.d.	3·13 b.s.	8·97 8·90 7·92 s.^{s}	5·78 4·02 b.d.^{s} J=12 Hz.

b.=broad. d.=doublet. m.=multiplet. s.=singlet.

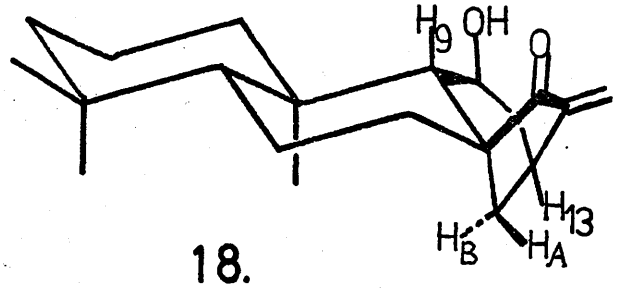
group at C-12. Hence the hydroxyl group must be at C-11.

Further evidence was obtained from the NMR spectrum of 18 using decoupling studies in conjunction with the pseudo-contact shift reagent $Eu(DPM)_3$. This reagent forms a complex with some suitable functionality in a molecule and usually[10] causes a downfield shift in the resonances of protons in its environment. The magnitude of the shift follows an inverse relationship[11] with the distance between proton and metal ion. Difficulties were encountered using this reagent, due to its relative insolubility in deuterochloroform and also to the fact that it causes line broadening to a certain extent. However, using a 4:3 ratio by weight of reagent to compound, an appreciable shift in the spectrum was obtained* (see Table 1).

The carbinol proton (H-11), as expected, moved downfield to the greatest extent. Other signals in the shifted spectrum of 18 were assigned primarily on decoupling considerations, and these were compared to assignments predicted on the basis of changes in chemical shift. One of the main features of the shifted spectrum was the fact that H-9 had moved out of the methylene envelope and appeared as a broad singlet at τ 3.13.

* All τ values are approximate, as, after a period of time, the signals began to drift, probably due to decomposition of the shift reagent.*

FIG 3



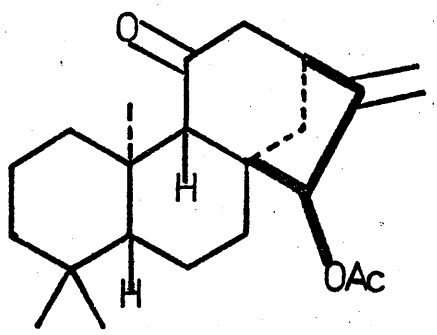
18.

	OBS.	THEOR.
$J_{H_9,\alpha H_{11}}$	0 Hz.	~0 Hz.
$J_{\alpha H_{11},\alpha H_{12}}$	~4 Hz	~5 Hz.
$J_{\alpha H_{11},\beta H_{12}}$	0 Hz.	~0 Hz.
$J_{H_{13},\alpha H_{12}}$	~3 Hz.	~2 Hz.
$J_{H_{13},\beta H_{12}}$	~3 Hz.	~2 Hz.

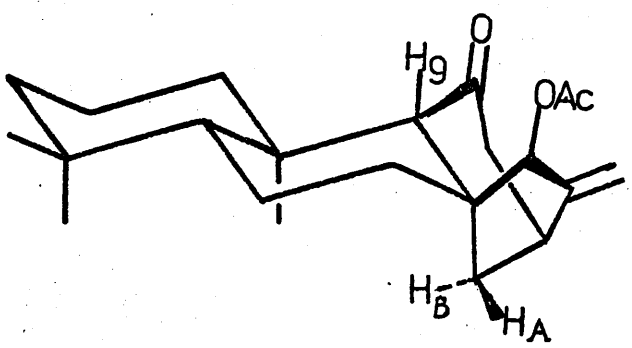
Irradiation at τ -0.84 (H-11) caused a change in the signal at τ 5.78 (α H-12) but not in the signal for β H-12 (τ 4.02) to any noticeable extent. No change occurred in H-9 (τ 3.13). Irradiation at τ 4.02 (βH-12) reduced the signal for αH-12 (τ 5.78) to a broad singlet by removal of geminal coupling, and removed a small coupling from H-13 (τ 5.24).

Subsequent irradiation at H-13 (τ 5.24) increased the intensities of the exomethylene signals, removed a small coupling from the C-12 protons and sharpened the diffuse doublet at τ 6.97 (H_A-14) considerably. In the reverse experiment, decoupling at τ 6.97 (H_A-14) reduced the signal for H-13 to a broad singlet ($W_{\frac{1}{2}} \sim 7$ Hz.), reduced the doublet at τ 5.88 (H_B-14) to a singlet and sharpened H-9 (τ 3.13) slightly (possibly due to removal of "W" coupling[12]).

These results lead to the same conclusions as before but with a few important additions. H-13 has its main coupling (Jobs.$\sim$ 5 Hz.) to H_A-14 and minor couplings to the C-12 protons and to the exomethylene protons. The conformation of ring C which fits these values is that of a slightly flattened chair. In this conformation, the dihedral angle Φ between H-13 and H_B-14 is $\sim 90^\circ$ and between H-13 and H_A-14 is $\sim 45^\circ$, leading to J values of about 0 Hz., 5 Hz. respectively. With the 11-hydroxyl in the β-configuration and ring-C in a flattened chair, there is good agreement with other observed J values (see fig. 3). This contrasts with the



4.



20.

predicted values for an 11α -hydroxyl group, with ring C in either a boat or chair conformation, which requires a relatively large coupling between H-9 and βH-11 and between the latter and one of the C-12 protons.

Strong support for the 11β configuration of the hydroxyl group was obtained from the Eu $(DPM)_3$ shifted spectrum. H-9 and βH-12 are equatorial and cis to the complexed 11β-hydroxyl group and both showed large shifts (see Table 1). The αH-12 proton is trans to the 11β - hydroxyl group and did not experience such a large change in chemical shift. One tertiary methyl group (C-10 Me) moved approximately 1 τ unit further downfield than the other two. A much larger shift of this signal would have been expected for an 11α -hydroxy derivative.

Addition of benzene to the $CDCl_3$ solution of the keto acetate 4 caused the signal for H-9 to move from under the acetate resonance at τ 7.88. This signal, a slightly broadened singlet, showed long-range coupling with H_A-14 (τ 8.60). Thus, irradiation at τ 8.60 caused it to sharpen. Simultaneously, the doublet at τ 7.60 (H_B-14) collapsed to a singlet and H-13 also sharpened. The "W" conformation between H_A-14 and H-9, necessary for this long-range coupling is only possible if ring-C of the keto acetate 4 is in a chair conformation (see 20).

Experimental

The liverwort Solenostoma triste was collected in the Renfrewshire hills. It was finely ground and extracted with chloroform in a Soxhlet apparatus. After removal of the solvent, the residual extract was subjected to chromatography on alumina (grade H deactivated). Subsequent separation and purification by preparative TLC afforded four closely related natural products.

The hydroxy acetate 1

Crystallisation of the hydroxy acetate 1 from methanol furnished needles m.p. 118-120°C. $[\alpha]_D$ -89°; NMR signals at τ 9.10, 9.04, 8.99 (singlets, 3 tertiary methyls), 7.75 (singlet, acetate), 7.40 (broad singlet, 1H, exchangeable with D_2O), 7.28 (multiplet, H-13), 6.20 (multiplet, H-11), 5.07, 4.88 (multiplets, exomethylene), 4.72 (triplet, H-15, Jobs. = 3 Hz.); νmax 3590 (hydroxyl), 1750 (acetate), 1660 (exomethylene) cm^{-1}.

Mass spectrum: M^+ = 346 ($C_{22}H_{34}O_3$ requires M^+ = 346).

Found: C, 75.76; H, 9.65%; $C_{22}H_{34}O_3$ requires C, 76.26; H, 9.89%).

The hydroxy ketone 16

The hydroxy ketone 16 crystallised from ethanol as needles m.p. 186-188°C., $[\alpha]_D$ -85°; NMR signals at τ 9.24, 9.17, 9.06 (singlets, 3 tertiary methyls), 8.79 (doublet, secondary methyl, J = 6 Hz.), 6.09

(diffuse doublet, H-11); νmax 3615, 3510 (hydroxyl), 1735 (cyclopentanone) cm^{-1}.

Mass spectrum: M^+ = 304 ($C_{20}H_{32}O_2$ requires M^+ = 304).

Mass analysis: M^+ = 304.2399; $C_{20}H_{32}O_2$ requires M^+ = 304.2402.

The diol 6

The diol 6 crystallised from ethanol as needles m.p. 192-194°C., $[\alpha]_D$-62°; NMR signals at τ 9.19, 9.12, 9.06 (singlets, 3 tertiary methyls), 7.40 (multiplet, H-13), 6.28 (multiplet, H-11), 6.02 (diffuse doublet, H-15), 5.02, 4.92 (broad singlets, exomethylene); νmax 3605, 3480 (hydroxyl) cm^{-1}.

Mass spectrum: M^+ = 304 ($C_{20}H_{32}O_2$ requires M^+ = 304).

Mass analysis: M^+ = 304.2402; $C_{20}H_{32}O_2$ requires M^+ = 304.2402.

The unsaturated hydroxy ketone 18

Recrystallisation from methanol yielded the unsaturated hydroxy ketone 18 as needles m.p. 121-124°C., $[\alpha]_D$-118°; NMR signals at τ 9.06, 8.98, 8.87 (singlets, 3 tertiary methyls), 6.90 (multiplet, H-13), 5.90 (multiplet, H-11), 4.71, 4.11 (singlets, exomethylene in conjugation with a carbonyl); νmax 3608, 3450 (hydroxyl), 1730 (cyclopentenone), 1650 (exomethylene) cm^{-1}; λmax 238 nm. (ε 7,100).

Mass spectrum: M^+ = 302 ($C_{20}H_{30}O_2$ requires M^+ = 302).

Mass analysis: M^+ = 302.2187; $C_{20}H_{30}O_2$ requires M^+ = 302.2245.

The keto acetate 4

To the hydroxy acetate 1 (15 mg.) in acetone (3 ml.) at 0°C. was added excess Jones reagent. The reaction mixture was diluted with water and extracted with chloroform. Removal of the solvent left a residue which was purified by preparative TLC to give the keto acetate 4 (7 mg.), recrystallised from methanol as needles m.p. 120-122°C.; NMR signals at τ 9.16, 9.11, 8.94 (singlets, 3 tertiary methyls), 7.88 (singlet, acetate), 7.10 (multiplet, H-13), 5.14, 5.04 (multiplets, exomethylene), 4.86 (multiplets, H-15); νmax 1730 (acetate), 1698 (cyclohexanone) cm^{-1}.

Mass spectrum: M^+ = 344 ($C_{22}H_{32}O_3$ requires M^+ = 344).

Mass analysis: M^+ = 344.2339; $C_{22}H_{32}O_3$ requires M^+ = 344.2351.

The diacetate 5

The hydroxy acetate 1 (10 mg.) was dissolved in dry pyridine (0.5 ml.). To this was added acetic anhydride (0.5 ml.) and the resultant solution heated on a steam bath for 6 hours. Addition of water and extraction with chloroform gave the crude diacetate 5 (9 mg.), which was purified by preparative TLC (10% ethyl acetate/ petrol) and recrystallised from methanol as fine needles m.p.

156-159°C.; NMR signals at τ 9.18, 9.12, 9.01 (singlets, 3 tertiary methyls), 8.12, 7.86 (singlets, acetates), 7.38 (multiplet, H-13), 5.23, 5.15 (broad singlets, exomethylene, 5.03 (multiplet, H-11), 4.88 (triplet, H-15, Jobs. = 2 Hz.); ν max 1735 (acetates), 1664 (exomethylene) cm^{-1}.

Mass spectrum: M^+ = 388 (C_{24} H_{36} O_4 requires M^+ = 388).

Mass analysis: M^+ = 388.2573; C_{24} H_{36} O_4 requires M^+ = 388.2613.

Hydride reduction of the hydroxy acetate 1

The hydroxy acetate 1 (18 mg.) in dry ether (3 ml.) was treated with excess lithium aluminium hydride for 30 minutes. Addition of saturated sodium sulphate solution and extraction with chloroform gave the diol 6 (12 mg.), identical with natural material. [NMR, TLC, IR, m.p., m.m.p.].

Hydride reduction of the unsaturated hydroxy ketone 18

Treatment of the unsaturated hydroxy ketone 18 (18 mg.) in ether (4 ml.) at room temperature with excess lithium aluminium hydride gave the diol 6 (8 mg.) identical with natural material. [NMR, TLC, IR, m.p., m.m.p.].

Catalytic hydrogenation of the diol 6

The diol 6 (10 mg.) in ethyl acetate was stirred under hydrogen with 10% palladium/charcoal catalyst for 30 minutes. Filtration and removal of solvent left a gum (9 mg.), crystallised as needles from ethanol, the hydroxy ketone 16 m.p. 186-188°C., identical with naturally occurring material. [NMR, IR, TLC, m.p., m.m.p.].

The tosylate 7

To the hydroxy acetate 1 (25 mg.) in pyridine (0.5 ml.) at 0°C. was added p-toluene sulphonyl chloride (30 mg.) in pyridine (0.5 ml.). The reaction proceeded very slowly, and after two weeks, approximately 60% conversion had occurred. Addition of ice and subsequent extraction with chloroform gave a mixture of two compounds, the tosylate 7, and unreacted starting material. Separation by preparative TLC gave the tosylate 7 (5 mg.) as a gum. NMR signals at τ 9.10, 9.04, 8.97 (singlets, 3 tertiary methyls), 7.92 (singlet, acetate), 7.51 (singlet, aromatic methyl), 5.20 (multiplet, H-11), 5.13, 5.04 (multiplets, exomethylene), 4.82 (multiplet, H-15), 2.70, 2.24 (aromatic A_2B_2 system).

Reduction of the tosylate 7

A crude reaction mixture, containing tosylate 7 and starting material, the hydroxy acetate 1 was refluxed overnight in the presence of excess lithium aluminium hydride in ether. The residue contained

the diol 6 and the diene 9 which were separated by preparative TLC. The diene 9 failed to crystallise. NMR signals at τ 9.14, 9.07, 9.00 (singlets, 3 tertiary methyls), 7.17 (multiplet, H-13), 6.14 (broad singlet, H-15), 5.20, 5.14 (doublet (Jobs. = 3 Hz.), singlet, exomethylene), 4.50 (double doublet, H-11, ABMX system, J_{BA} obs = 10 Hz., J_{BX} obs = 4 Hz., J_{BM} obs = 0 Hz.), 3.98 (diffuse triplet, H-12, ABMX system, J_{AB} obs = 10 Hz., J_{AM} obs = 8 Hz., J_{AX} obs. = 2 Hz.); νmax 3610 (hydroxyl) cm^{-1}.

Mass spectrum: M^+ = 286 ($C_{20}H_{30}O$ requires M^+ = 286).

Mass analysis: M^+ = 286.2315; $C_{20}H_{30}O$ requires M^+ = 286.2297.

Catalytic hydrogenation of the diene 9

The diene 9 (8 mg.) in ethyl acetate (10 ml.) was stirred with 10% palladium/charcoal for 30 minutes under hydrogen. Filtration and removal of the solvent gave a residue (8 mg.), the unsaturated ketone 12, which was crystallised from methanol as fine needles m.p. 124-125°C.; NMR signals at τ 9.21, 9.13, 9.07 (singlets, 3 tertiary methyls), 8.96 (doublet, secondary methyl, J = 6 Hz.), 4.43 (double doublet, H-11, ABMX system), 3.97 (diffuse triplet, H-12, ABMX system); νmax 1740 (cyclopentanone), 1660 (Δ" double bond) cm^{-1}.

Mass spectrum: M^+ = 286 ($C_{20}H_{30}O$ requires M^+ = 286).

Mass analysis: M^+ = 286.2305; $C_{20}H_{30}O$ requires M^+ = 286.2297.

Kauran-15-one. 15

The unsaturated ketone 12 (6 mg.) in ethyl acetate (10 ml.) was stirred in the presence of 10% palladium/charcoal under hydrogen for 2 days. Filtration and removal of the solvent gave 16β -methyl kauran-15-one 15 (6 mg.) recrystallised from methanol as fine needles m.p. 147-149°C., $[\alpha]_D$-87°; (lit.[3] m.p. 150°C., $[\alpha]_D$-81°); NMR signals at τ 9.20, 9.15, (6H) (singlets, 3 tertiary methyls), 8.91 doublet, secondary methyl, J = 6 Hz.); νmax 1735 (cyclopentanone) cm^{-1}.

Mass spectrum: M^+ = 288 ($C_{20}H_{32}O$ requires M^+ = 288).

Mass analysis: M^+ = 288.2450; $C_{20}H_{32}O$ requires M^+ = 288.2453.

References

1. C. Djerassi, P. Quitt, E. Mosettig, P. C. Cambie, R. S. Rutledge and L. H. Briggs, J. Amer. Chem. Soc., 83, 3720 (1961).

2. P. K. Grant and R. Hodges, Tetrahedron, 8, 261 (1960).

3. M. F. Barnes and J. MacMillan, J. Chem. Soc. (C), 361 (1967).

4. L. H. Briggs, R. C. Cambie and P. S. Rutledge, J. Chem. Soc., 5374 (1963).

5. M. Karplus, J. Amer. Chem. Soc., 85, 2870 (1963).

6. C. Djerassi, C. R. Smith, A. E. Lippman, S. K. Figdor and J. Herran, J. Amer. Chem. Soc., 77, 4801 (1955).

7. E. Fujita, T. Fujita, M. Taoka, H. Katayama and M. Shibuya, Tetrahedron Letters, 421 (1970).

8. J. D. Connolly and R. McCrindle, Chem. and Ind., 379 (1965).

9. J. K. M. Sanders and D. H. Williams, Chem. Comms., 422 (1970).

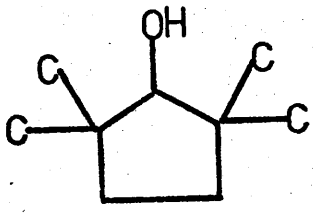
10. B. L. Shapiro, J. R. Hlubucek, G. R. Sullivan and L. F. Johnson, J. Amer. Chem. Soc., 93, 3281 (1971).

11. H. J. Keller and K. E. Schwartzhaus, Angew. Chem. Internat Edn., 9, 196 (1970).

12. M. Barfield, J. Chem. Phys., 41, 3825 (1964).

Introduction

The liverwort *Gymnomitrium obtusum*, collected at Ben Lawers, yielded 5 related tricyclic sesquiterpenoids which appear to be of a new structural type.



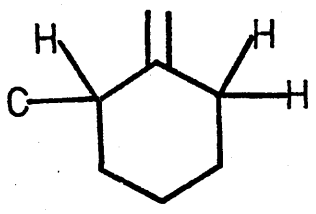
1.

Discussion

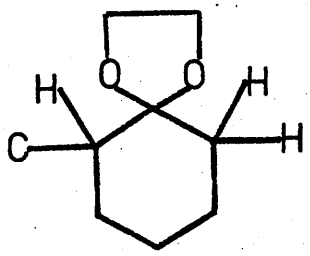
The most abundant compound present in the chloroform extract of Gymnomitrium obtusum was an alcohol, $C_{15}H_{24}O$ [νmax 3625 (hydroxyl), 1640 (exomethylene) cm^{-1}]. The NMR spectrum showed signals at τ 9.09, 8.95, 8.80 (singlets, 3 tertiary methyls), 8.48 (singlet, 1H, exchangeable with D_2O), 7.69 (singlet, 1H), 6.31 (singlet, carbinol proton), 5.39, 5.37 (singlets, exomethylene). The most revealing features of the NMR spectrum were the two singlets at τ 7.69 (possibly allylic in nature) and τ 6.31 (carbinol proton) neither of which showed any coupling.

Acetylation of the alcohol produced the corresponding acetate, [νmax 1740 (acetate), 1640 (exomethylene) cm^{-1}; τ 9.16, 8.96, 8.88 (singlets, 3 tertiary methyls), 7.98 (singlet, acetate), 7.64 (singlet, 1H), 5.30 (multiplet, exomethylene), 5.26 (singlet, > CHOAC)] identical with one of the other natural products obtained.

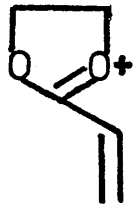
Oxidation of the alcohol produced the expected ketone, [νmax, 1745 (cyclopentanone), 1640 (exomethylene) cm^{-1}; τ 9.23, 9.15, 9.13 (singlets, 3 tertiary methyls), 7.42 (singlet, 1H), 5.31, 5.29 (singlets, exomethylene)]. In addition, the ketone did not incorporate any deuterium atoms when heated under nitrogen in dry dioxan/sodium deuteroxide, and when treated with lithium aluminium hydride reformed the original alcohol only. The conclusions drawn from this evidence is that the secondary hydroxyl group in the original alcohol is contained in a five-membered ring and has the environment shown in part structure 1.



2.

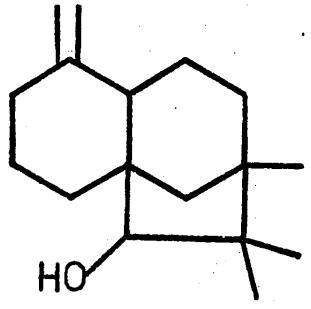


3.



4.

$\frac{m}{e} = 99$



5.

Ozonolysis of the above ketone cleanly produced a diketone by cleavage of the exomethylene group. [νmax 1748 (cyclopentanone), 1710 (cyclohexanone) cm^{-1}; τ 9.13, 9.02, 8.97 (singlets, 3 tertiary methyls), 7.52 (multiplet, 2H), 7.09 (singlet, 1H); UV (end absorption)]. This diketone incorporated 3 deuterium atoms and the conclusions drawn from these results is that the environment of the exomethylene group is that shown in part structure 2. Further support for part structure 2 was derived from the mass spectral breakdown of the ethylene ketal of the nor keto-acetate. This had a base peak at m/e 99 corresponding to the fragment 4.

From consideration of the total evidence accumulated, it would appear that the structure could be similar to 5, with a bicyclo [3, 2, 1] system. The other compounds isolated were the parent hydrocarbon $C_{15}H_{24}$ and two di-oxygenated compounds. Lack of time prevented further investigation.

Experimental

The liverwort Gymnomitrium obtusum was collected at Ben Lawers. It was finely ground, extracted with chloroform in a Soxhlet apparatus and the crude extract subjected to large-scale chromatography over alumina. Repeated purification by preparative TLC produced pure samples of five closely related sesquiterpenes, only two of which; the alcohol, $C_{15}H_{24}O$ ($M^+ = 220$) and the acetate, $C_{17}H_{26}O_2$ ($M^+ = 262$) were investigated to any extent (see p 119).

The hydrocarbon

The hydrocarbon was obtained as a non-polar gum, present as a minor component. NMR signals at τ 9.18, 9.12, 8.98 (singlets, 3 tertiary methyls), 7.88 (singlet, 1H), 5.43 (multiplet, exomethylene).
Mass spectrum: $M^+ = 204$ ($C_{15}H_{24}$ requires $M^+ = 204$).

The ketone

Jones oxidation of the alcohol (15 mg.) produced the non-crystalline ketone (10 mg.). NMR signals at τ 9.23, 9.15, 9.13 (singlets, 3 tertiary methyls), 7.42 (singlet, 1H), 5.31, 5.29 (singlets, exomethylene); νmax 1745 (cyclopentanone), 1640 (exomethylene) cm^{-1}.
Mass spectrum: $M^+ = 218$ ($C_{15}H_{22}O$ requires $M^+ = 218$).

The diketone

The ketone (20 mg.) was dissolved in ethyl acetate (8 ml.) and cooled to -70°C. Ozone was passed through for three hours after which time a blue colouration remained. The solvent was removed by blowing with nitrogen and zinc dust and acetic acid added. After stirring for twelve hours the solution was filtered and removed, leaving the diketone (13 mg.) as a gum. NMR signals at τ 9.13, 9.02, 8.97 (singlets, 3 tertiary methyls), 7.52 (multiplet, 2H), 7.09 (singlet, 1H); ν_{max} 1748 (cyclopentanone), 1710 (cyclohexanone) cm^{-1}.

Mass spectrum: $M^+ = 220$ ($C_{14}H_{20}O_2$ requires $M^+ = 220$).

Deuteration of the diketone

Treatment of the diketone (3 mg.) in dry dioxan (5 ml.) with D_2O (3 ml.) and sodium metal (50 mg.) under nitrogen at 60°C. for 96 hours, according to the method of Connolly et al.[1] produced a compound, $M^+ = 223$ ($C_{14}H_{17}D_3O_2$ requires $M^+ = 223$).

References.

1. J. D. Connolly, D. M. Gunn, R. McCrindle, R. D. H. Murray and K. H. Overton, J. Chem. Soc. (C), 668 (1967).