Elaboration of Sclareol by Claisen Rearrangement

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Transetherification of sclareol (labd-14-ene-8,13-diol) (1) with triethyl orthoacetate and subsequent rearrangement gave (*E*)- and (*Z*)-ethyl 8-hydroxylabd-13-en-15-ylacetate (2) and (3) (R = CO_2Et). Products of cyclisation of these esters with tin(IV) chloride in benzene were characterised. Similar reactions with sclareol monoacetate (11) are described and stereochemical implications are discussed.

SCLAREOL (1) is a readily available diterpene, the conversion of which into higher terpenoids has been investigated.[1] In these studies [1] methods for development of the side-chain to give polycyclic and hence triterpenoid systems were based upon oxidative degradations. A novel alternative approach is the development of the side-chain by extension of the vinyl group. The allyl alcohol system is capable of elaboration by Claisen rearrangement to give bicyclic products of type (2) and (3), which might be useful as intermediates for formation of the tricyclic structure (4). This system (4) incorporates much of the sesterterpene skeleton of cheilanthane (5), of which a representative (6) has been found [2] recently. Further, the intermediate (4) is suitable for elaboration into the skeletons of limonoid bitter principles,[3] *e.g.* azadirone (7) and gedunin (8). We describe here progress in synthesising intermediates of type (4).

It would be expected that for sclareol, being a tertiary allylic alcohol containing the added complication of a further tertiary alcohol centre, difficulty in obtaining satisfactory conditions for selective transetherification and subsequent rearrangement would be encountered. A number of approaches have been examined.

Attempted reactions of 2,2-dimethoxypropane [4] or ethyl vinyl ether [4] with sclareol (1) using a variety of catalysts proved unsatisfactory. Only low yields of enol ethers were obtained.

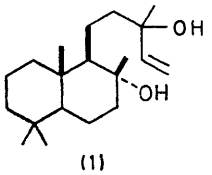
[1] M. S. Hadley and T. G. Halsall, *J.C.S. Perkin I*, 1974, 1334; N. A. J. Rogers and J. A. Barltrop, *Quart. Rev.*, 1962, **16**, 117.

[2] H. Khan, A. Zaman, G. L. Chetty, A. S. Gupta, and S. Dev, *Tetrahedron Letters*, 1971, 4443.

[3] D. L. Dreyer, *Fortschr. Chem. Org. Naturstoffe*, 1968, **26**, 190.

[4] D. J. Faulkner, *Synthesis*, 1971, **2**, 175.

Attention was then focused on transetherification with triethyl orthoacetate.[4,5] Reaction in xylene with propionic acid as catalyst gave, after chromatographic separation, a hydroxy-ester in 52% yield. Spectra (hydroxy- and ester i.r. absorptions, a vinylic proton n.m.r. signal at τ 4·92, and a molecular ion at *m/e* 378) indicated that the ester must be bicyclic. Several



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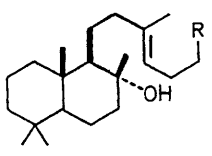

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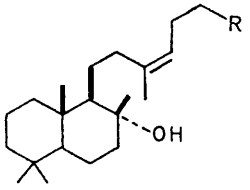

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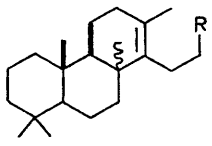

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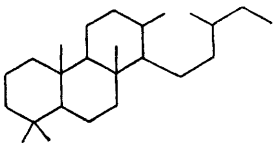
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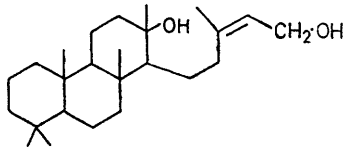

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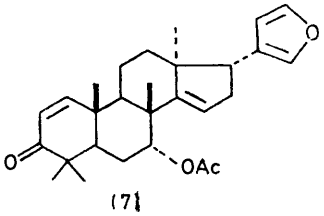

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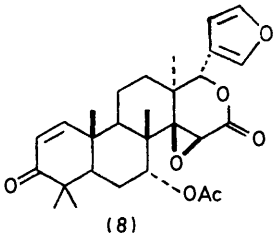

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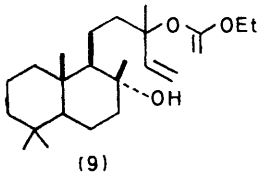

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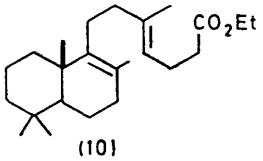


(10)

structures are possible. Reaction of sclareol (1) with triethyl orthoacetate might be expected to give the intermediate (9) by reaction at the sterically less hindered hydroxy-group, and subsequent rearrangement could lead to structures (2) and (3) (R = CO_2Et). Under the acidic conditions, isomerisation leading to loss of stereochemical integrity at C-8, or less probably at C-9, might also occur. These possibilities are reinforced by isolation of a second ester, *m/e* 360, assigned structure (10) on the basis of n.m.r. methyl signals at τ 8·35 and 8·42 and a single vinyl proton signal at 4·95. The composition of the hydroxy-ester fraction was clarified by a variety of techniques. Although t.l.c. showed a single spot, high-pressure liquid chromatography showed the presence of at least two esters. Further, although the 100 MHz n.m.r. spectrum (solvent $CDCl_3$) did not indicate two components, addition of the shift reagent $Eu(fod)_3$ led to splitting of the $CO_2{\cdot}CH_2{\cdot}CH_3$ signal into two quartets (a single sharp quartet was observed in the absence of shift reagent). Methyl signals remained sharp. There are two possible explanations for the separation of the methylene resonances. Either two closely related esters are present or the consequence of complex formation is a discrimination between the two diastereotopic CH_2 protons. The latter possibility receives support from recent studies [6] with chiral shift reagents. However, as two *quartets* are observed, whereas a more complex pattern would be expected, the former possibility appears the more likely. The failure to observe additional methyl resonances on addition of the shift reagent indicates that stereochemical integrity has not been lost at C-8 or C-9. We tentatively suggest that both esters (2) and (3) (R = CO_2Et) are formed.

This view is further confirmed by study of the analogous reaction with sclareol monoacetate [7] (11). Treatment with triethyl orthoacetate gave an ester fraction which again showed a single spot on t.l.c. Addition of a shift reagent led to the splitting of the $CO_2{\cdot}CH_2{\cdot}CH_3$ n.m.r. signal into two quartets, yet only a single OAc resonance was observed. It is probable that the respective ester fractions are mixtures of (2) and (3) and of (12) and (13).

In the light of subsequent transformations, the distinction between formation of a single ester (2) or (3), or formation of a mixture, is not important. There is no loss of stereochemistry at C-8 or C-9, and the extension of the sclareol side-chain proceeds with reasonable efficiency. Acid-catalysed cyclisation of (2) or (3) might be expected to give the same product (4). Cyclisation with tin(IV) chloride in benzene gave an unsaturated ester fraction, *m/e* 360, in 81% yield. Further chromatography failed to separate components of this fraction but n.m.r. analysis suggested the presence of a mixture of esters having tri- and tetra-substituted double bonds, for which a number of structural assignments are possible. Hydrogenation gave only dihydro-products; hence the esters are tricyclic. This mixture was further analysed after hydrolysis.

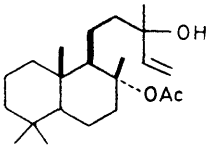
Hydrolysis and chromatographic purification afforded the tricyclic acid (14) and other minor non-crystalline acid fractions. The gross structure of (14) was established by mass and n.m.r. spectra (absence of a vinyl proton resonance and observation of a methyl resonance at τ 8·45). Preservation of the stereochemical integrity

[5] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Peterson, *J. Amer. Chem. Soc.*, 1970, **92**, 741.

[6] M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Amer. Chem. Soc.*, 1974, **96**, 1038.

[7] G. Buchi and K. Biemann, *Croat. Chem. Acta*, 1957, **29**, 163; P. F. Vlad, A. G. Russo, and K. F. Chang, *Zhur. obshchei Khim.*, 1969, **39**, 451.

at C-9 is assumed and has adequate precedent.[8] Concerted displacement at C-8 would be expected to lead to structure (15), but a non-concerted displacement leading to structure (16) is possible. A distinction between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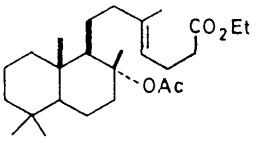
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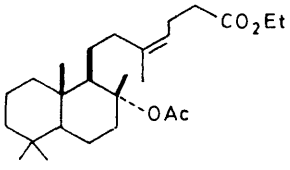
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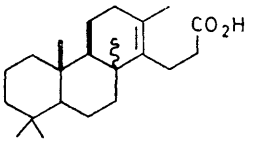
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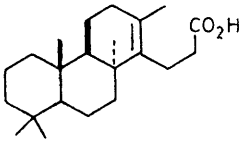
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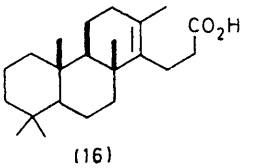
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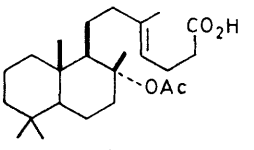
(17)

structures (15) or (16) is not justified at this stage. In view of the ready availability of other diterpenes, *e.g.* manool, which might permit attack at C-8 from either face, and of analogues of sclareol oxygenated in rings A and B, this synthetic approach (Claisen–Copere arrangement followed by cationic cyclisation) offers considerable flexibility, and possible scope for synthesis of both cheilanthanes and triterpenoids.

EXPERIMENTAL

I.r. spectra were measured for solutions in chloroform with a Unicam SP 200 spectrophotometer. N.m.r. spectra were measured for solutions in deuteriochloroform with a Varian HA-100 spectrometer. As shift reagent tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)-europium [Eu(fod)$_3$] was used. Mass spectra were determined with an A.E.I. MS 12 spectrometer. Organic solvents were dried (Na_2SO_4) before evaporation and light petroleum refers to the fraction of b.p. 40—60° unless otherwise stated. T.l.c. was carried out on Merck silica gel (Stahl) on 1 mm thick plates, column chromatography on Grace Kieselgel (100—200 mesh), and high-pressure liquid chromatography (h.p.l.c.) on an ALC 202 Waters Associates apparatus (8 ft column packed with Porosil A; cyclohexane–chloroform as mobile phase).

Reaction of Sclareol (1) *with Triethyl Orthoacetate.*—Sclareol (1) (5 g), triethyl orthoacetate (26 g), and propionic acid (1 ml) were heated under reflux in xylene (225 ml) under nitrogen for 40 h. Solvents were removed under reduced pressure and the residue was chromatographed on silica gel. Elution with ether–light petroleum (1 : 9) afforded *ethyl labda-8,13-dien-15-ylacetate* (10) (0·5 g), $\nu_{max.}$ 1730, 1603, and 916 cm^{-1} (Found: M^+, 360·3014. $C_{24}H_{40}O_2$ requires M, 360·3028); *m/e*, 360, 345, 273, 258, 205, and 189; τ 4·95 (1H, t, J 6·5 Hz), 5·90 (2H, q, J 7 Hz), 8·35 (3H, s), 8·42 (3H, s), 9·18 (3H, s), and 9·26 (6H, s). Further elution with ether–light petroleum (1 : 2) afforded a hydroxy-ester fraction (*ethyl 8-hydroxylabd-13-en-15-ylacetate*) [(2) and/or(3)] (2·6 g), $\nu_{max.}$ 3485, 1732, 1471, 1391, 1190, and 950 cm^{-1}; *m/e* 378 (M^+), 360, 345, 333, 223, and 205 [Found: *m/e*, 345·2779. $C_{23}H_{37}O_2$ requires 345·2793 for $M - (CH_3 + H_2O)$]; τ 4·92 (1H, t, J 6·5 Hz), 5·95 (2H, q, J 7 Hz), 8·48 (3H, s), 8·98 (3H, s), 9·21 (3H, s), and 9·29 (6H, s). Although (10) was homogeneous to t.l.c. and h.p.l.c., the hydroxy-ester fraction was partly resolved by h.p.l.c. The possibility of equilibration of (2) and (3) has not been eliminated. Addition of shift reagent caused the resonance formerly at τ 5·95 to separate into two quartets.

Reaction of Sclareol 8-Acetate (11) *with Triethyl Orthoacetate.*—Sclareol 8-acetate (11) (3 g), triethyl orthoacetate (15·2 g), and propionic acid (3 ml) were heated under reflux in benzene (440 ml) for 40 h under nitrogen. Solvents were removed under reduced pressure and the residue was chromatographed. Elution with ether–light petroleum (1 : 4) afforded the esters (12) and/or (13) as an oil (1 g), $\nu_{max.}$ 1725br, 1470, 1398, 1373, 1255, 1187, 1132, and 1023 cm^{-1}; τ 4·94 (1H, t, J 6·5 Hz), 5·92 (2H, q, J 7 Hz), 8·01 and 8·07 (3H, two singlets), 8·41 and 8·48 (3H, two singlets), 8·65 (3H, s), and 9·23, 9·27, and 9·31 (9H, three singlets).

The esters (0·9 g) were heated under reflux in methanol–water (3 : 2; 16 ml) with potassium hydroxide (0·2 g) under nitrogen for 20 h. Work up as previously described afforded an acid fraction purified by preparative t.l.c. [ether–light petroleum (1 : 1)] to give crystalline *8-acetoxylabd-13-en-15-ylacetic acid* (17), m.p. 120°, $\nu_{max.}$ 3490—3100, 1726br, 1472, 1392, 1372, 1269, 1125, 1086, 1021, and 950 cm^{-1}; τ 4·96 (1H, t, J 6·5 Hz), 8·06 (3H, s), 8·32 (3H, s), 8·55 (3H, s), 9·23 (3H, s), 9·27 (3H, s), and 9·32 (3H, s); *m/e* 332, 317, 243, 220, and 205 (Found: *m/e* 332·2710. $C_{22}H_{36}O_2$ requires 332·2715 for $M - CH_3{\cdot}CO_2H$).

Reaction of the Esters (2) *and* (3) (R = CO_2Et) *with Tin*(IV) *Chloride.*—Tin(IV) chloride (1·71 g) was added dropwise to a stirred solution of esters (2) and (3) (R = CO_2Et) (2·6 g) in benzene (20 ml) at 5°. After 30 min at 5° the solution was poured with stirring into ice–water. The dried organic phase was evaporated under reduced pressure to leave a pale yellow oil (2·37 g). Preparative t.l.c. [ether–light petroleum (6 : 94)] afforded a tricyclic ester fraction (2·12 g), $\nu_{max.}$ 1726, 1460, 1378, 1173, and 1037 cm^{-1}; τ 4·50 (<1H, m) and 5·90 (2H, q, J 7 Hz) (discrete methyl resonances were not clearly observed) (Found: M^+, 360·3018. Calc. for $C_{24}H_{40}O_2$: M, 360·3028); *m/e* 360, 345 ($M - CH_3$), 315 (M — OEt), 259, 223, and 189. Hydrogenation over PtO_2 in ethyl acetate afforded an ester fraction, *m/e* 362 (M^+). No further purification was effected by t.l.c., and h.p.l.c. failed to separate the ester mixture.

Hydrolysis of the Tricyclic Esters.—A portion (1 g) of the

[8] W. S. Johnson, *Accounts Chem. Res.*, 1968, **1**, 1.

fraction obtained by cyclisation with tin(IV) chloride was hydrolysed in ethanol–water (8 : 2; 10 ml) with added potassium hydroxide (0·78 g). The solution was heated under reflux under nitrogen for 20 h and cooled. After extraction with ether, the aqueous phase was acidified to pH 3 with 2N-sulphuric acid and extracted with chloroform. The chloroform extract afforded acids (1·05 g), purified by further preparative t.l.c. Elution with ether–light petroleum afforded crystalline *3-(13-methyl-8ξ-podocarp-13-en-14-yl)propionic acid* (14), m.p. 136°, $\nu_{max.}$ 3500—3000, 1710, 1480, 1398, 1316, 1132, and 988 cm^{-1} (Found: M^+, 332·2717. $C_{22}H_{36}O_2$ requires M, 332·2715); *m/e* 332, 317 ($M - CH_3$), 287 ($M - CO_2H$), 259, 223, 189, 175, and 141; τ 7·70 (2H), 8·45 (3H, s), 9·08 (3H, s), and 9·20 (6H, s).

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