Synthesis of Locked Half-Chair and Boat δ-Lactones from the Sesquiterpenoid Drimenol

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The half-chair δ-lactone 4α.6β.10,10-tetramethyl-1α*H*-3-oxabicyclo[4.4.0]decan-2-one (1) [≡ (5)] and the epimeric boat δ-lactone 4β,6β.10.10-tetramethyl-1α*H*-3-oxabicyclo[4.4.0]decan-2-one (2) [≡ (6)] have been synthesised from the sesquiterpenoid drimenol *via* the intermediates 1α-(1-acetoxymethylacetonyl)-2β-methoxycarbonylmethyl-1β.3.3-trimethylcyclohexane (7), 1α-acetonyl-2β-methoxycarbonylmethyl-1β,3,3-trimethylcyclohexane (9), 2β-carboxy-1α-[(2*R*)-2-hydroxypropyl]-1β,3.3-trimethylcyclohexane (13), and 2β-carboxy-1α-[(2*S*)-2-hydroxypropyl]-1β.3.3-trimethylcyclohexane (26).

It was our object to synthesise two closely related simple δ-lactones so constituted as to exist one in the half-chair and the other in the boat conformation. Our reason for wishing to procure such lactones was two-fold. We have for some time been interested in the conformational behaviour of δ-lactones and in particular in the relationship between their conformation and i.r. absorption.[1,2] At the same time we have, like others, been impressed by the difficulty of relating the chiroptical properties of δ-lactones to their conformational behaviour, an area in which there has been continued interest but slow progress.[3-8] Access to chiral δ-lactones in fixed and ascertainable half-chair and boat conformations is clearly necessary in both fields of study.

We chose the lactones (1) and (2) for our study, since we expected to be able to obtain them from the naturally occurring sesquiterpenoid drimenol (3),[9] which was available to us in quantity. Models suggest that the lactone (1) will exist in the half-chair conformation (5), whereas the lactone (2), in order to avoid a 1,3,5-triaxial methyl interaction, will exist as the boat (6). Moreover, *trans*-fusion to a cyclohexane ring was expected to confer conformational rigidity on both lactones.

We planned the following synthetic route from drimenyl acetate (4): (i) oxidative double bond cleavage leading to the keto-ester (7): (ii) deformylation of the hydroxy-ketone to the nor-keto-ester (9); (iii) reduction and Barbier–Wieland degradation (or *vice versa*) to the hydroxy-acids (12) and (13), related to the lactones (1) and (2). This is in essence the route which we now describe apart from minor changes in strategy forced on us by unforeseen events.

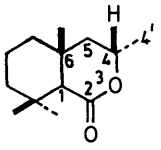
Hydroxylation of drimenyl acetate (4) with osmium tetroxide afforded in 80% yield the triol monoacetates (15) and (16), the former in excess as expected. The configurations were assigned from the H-4 signals in the n.m.r. spectra [for (15) τ 6·44, narrow multiplet, $W_{\frac{1}{2}}$ 4 Hz; for (16) τ 6·72, quartet, J 12 and 5 Hz].

Oxidation of the mixture of (15) and (16) with sodium periodate, Jones oxidation of the unstable keto-aldehyde (17) formed, and methylation of the resulting acid afforded the ester (7) in 50% overall yield from drimenol. The ester (7) was obtained much more conveniently in one step from drimenyl acetate in 65% yield by following a modified Rudloff–Lemieux procedure [10] with potassium periodate and catalytic amounts of potassium permanganate. The major by-product produced during this oxidation was the bisnor-keto-ester (18).

The next step, removal of C-11 of drimenol, proved unexpectedly difficult. Vigorous treatment of the diester (7) with alkali or acid, or pyrolysis of the corresponding hydroxy-ketone (8), afforded the enone (20) as the only major product. Exposure of diester (7) to 1% sulphuric acid in methanol at 20° afforded, in addition to the hydroxy-ester (8) as a major product, the enone (20) and the ε-lactone (21). The latter shows abnormally high frequency i.r. carbonyl bands in carbon tetrachloride at 1759 and 1728 cm^{-1}, possibly the result of an intramolecular field effect. An analogous effect in 1,4-dicarbonyl compounds has been observed.[11] The lactone Cotton effect {$[\theta]_{219}$ (iso-octane) −3150} matches in sign and magnitude that of the lactone (31) discussed later and strongly supports assignment of

[1] K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Comm.*, 1965, 634.
[2] K. H. Overton, N. G. Weir, and A. Wylie, *J. Chem. Soc.* (*C*), 1966, 1482.
[3] J. P. Jennings, W. Klyne, and P. M. Scopes, *J. Chem. Soc.*, 1965, 7211.
[4] G. Snatzke, H. Ripperger, C. Horstmann, and K. Schreiber, *Tetrahedron*, 1966, **22**, 3103.
[5] H. Wolf, *Tetrahedron Letters*, 1966, 5151.
[6] M. Legrand and R. Bucourt, *Bull. Soc. chim. France*, 1967, 2241.
[7] O. Korver, *Tetrahedron*, 1970, **26**, 2391.
[8] F. I. Carroll, A. Sobti, and R. Meck, *Tetrahedron Letters*, 1971, 405.
[9] H. H. Appel, C. J. W. Brooks, and K. H. Overton, *J. Chem. Soc.*, 1959, 3322.
[10] R. U. Lemieux and E. von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701.
[11] Y. Mazur and F. Sondheimer, *Experientia*, 1960, **16**, 181.

similar conformations to the two substances. The observed Cotton effect corresponds well to prediction



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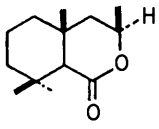

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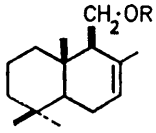
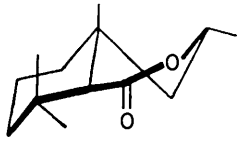


(3) R = H
(4) R = Ac



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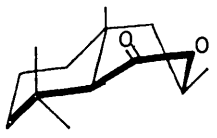

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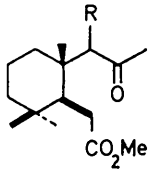
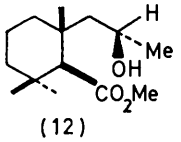


(7) R = CH_2·OAc
(8) R = CH_2·OH
(9) R = H
(10) R = CO_2H
(11) R = CHO



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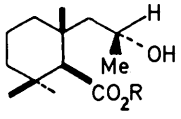
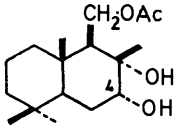


(13) R = H
(14) R = Me



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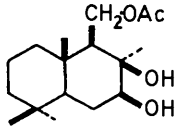

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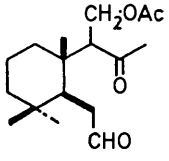

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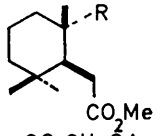
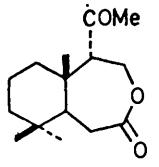


(18) R = CO·CH_2·OAc
(19) R = CO·CH_2·OH
(20) R = C(:CH_2)·COMe

based on the Klyne [3] and Snatzke [4] sector rules for the chair conformation (22) and this conformation also accounts satisfactorily for the small observed vicinal couplings of the ABX system arising from the protons attached to C-5 and C-6 (J_{AB} 14, J_{AX} 4·7, J_{BX} 0·8 Hz). The Cotton effect of the methyl ketone {$[\theta]_{293}$ (isooctane) +2210} accords by the Octant Rule [12] with the expected rotamer conformation in which the carbonyl oxygen system points towards C-1.

Following our failure to retroaldolise the hydroxy-ketone (8), attention was next turned to decarboxylation of the β-keto acid (10). Jones oxidation of the hydroxy-ketone (8) afforded as the only major product the aldehyde (11), which because of its instability was without isolation oxidised with alkaline silver oxide. Methylation of the product afforded the nor-keto-ester (9); not unexpectedly, decarboxylation of the intermediate keto-acid (10) had occurred during the silver oxide oxidation.

Our next task was to reduce the methyl ketone (9) to the methyl carbinols (24) and (29) having the two configurations in the side chain eventually required in the δ-lactones (1) and (2). Sodium borohydride reduction of the ketone (9) afforded the desired methylcarbinols (24) and (29) and in addition the ε-lactone (31). The hydroxy-ester (24) gave the lactone (31) spontaneously when stored at 20°. The lactone (32) corresponding to the carbinol (29) was obtained from the latter by alkaline hydrolysis and dehydration with toluene-*p*-sulphonic acid in benzene with continuous water removal. This lactone was unstable, reverting to (29) spontaneously or, more rapidly, during attempts to purify it by crystallisation or preparative layer chromatography. The configurations were assigned on the following basis. The stable lactone should be that (31) having the 5α-methyl group, since this can exist in the presumably preferred chair conformation [13] (23). The 5β-methyl lactone (32), on the other hand, would



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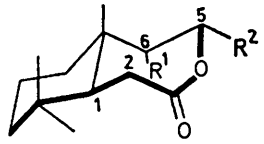
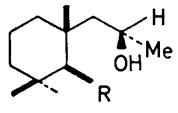
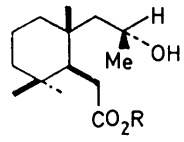


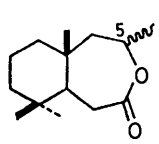
(22) R^1 = COMe, R^2 = H
(23) R^1 = H, R^2 = Me



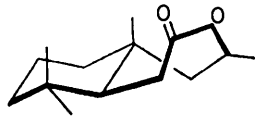


(24) R = CH_2CO_2Me
(25) R = CH_2Bz
(26) R = CO_2H
(27) R = CO_2Me
(28) R = CH(OH)Bz

(29) R = Me
(30) R = H



(31) 5α-Me
(32) 5β-Me



(33)

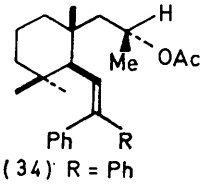
have to exist in a supposedly unfavourable twist-boat conformation (33) which would hasten its hydrolysis to the hydroxy-acid (30).

Analysis of the ABX system for the protons attached

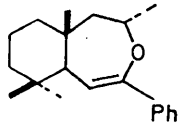
[12] W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, 1961, **83**, 4013.

[13] C. G. Overberger and H. Kaye, *J. Amer. Chem. Soc.*, 1967, **89**, 5646.

to C-1 and C-2 in the two lactones supports these assumptions and predictions. Thus for the stable lactone (23) $J_{AX} = 0{\cdot}5$, $J_{BX} = 10{\cdot}5$ and $J_{AB} = -14$ Hz, and for the unstable lactone (33) $J_{AX} = J_{BX} = 8$, and $J_{AB} = -17$ Hz. In the latter case the boat must be twisted so as to make H-1 lie outside the angle enclosed by the C-2 protons.[14] There is also a striking difference between the i.r. spectra of the hydroxy-esters. Ester (24) (in CCl_4) has normal CO (1740 cm^{-1}) and unbonded OH (3623 cm^{-1}) bands, whereas (29) shows evidence for strong intramolecular H-bonding in both the OH and CO regions [$\nu_{max.}$ (0·03M in CCl_4) 3523 and 1727 cm^{-1}]. These differences are reasonable on conformational grounds and to that extent support the assigned C-5 configurations. Notable differences which further support the foregoing configurational assignments, were also observed when the two hydroxy-esters were treated with phenyl magnesium bromide during the first step of Barbier–Wieland degradation. Thus the hydroxy-ester (29) furnished the expected diphenylethylene acetate (34) when dehydration of the



(34) R = Ph
(35) R = CO_2Me



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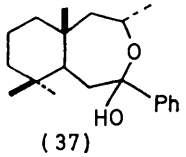

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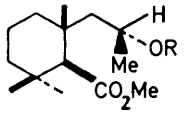
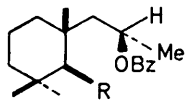


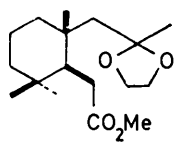
(38) R = Ac
(39) R = H

intermediate diphenylcarbinol was effected with acetic anhydride. However, the isomeric ester (24) or the corresponding lactone (31) under identical conditions afforded instead the enol ether (36). This is clearly formed by the ready dehydration of the hemiacetal (37). The isomeric 5β-methyl hemiacetal would suffer from severe steric congestion, so that instead the open-chain hydroxy-ketone (25) reacts with a second equivalent of Grignard reagent to afford (34). Cleavage of the latter was effected in 50% yield by a modified periodate–ruthenium dioxide procedure;[15] the diester (38) was obtained after methylation. Ozonolysis of (34) followed by methylation gave the phenyl acrylic ester (35) as major product and only a low yield of (38).

In attempts to obtain the isomeric hydroxy-acid (26), the enol ether (36) was subjected to both ozonolysis[16] and reaction with *m*-chloroperbenzoic acid,[17] without useful result. However, osmium tetroxide reacted rapidly with (36), furnishing the major aldehyde (40) and the minor ketone (28). The aldehyde (40) resisted both the Jones reagent and alkaline silver oxide, but was oxidised in air to the corresponding acid, which was characterised as the methyl ester (41). A more expeditious route to the hydroxy-esters (39) and (27) was finally devised as follows. The ethylene acetal (42) on



(40) R = CHO
(41) R = CO_2Me



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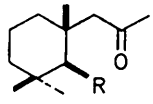

(43) R = $CH{=}CPh_2$
(44) R = CO_2Me

Grignard reaction and dehydration as before furnished the diphenylethylene ketone (43). Double bond cleavage with ruthenium dioxide–periodate and methylation then led to the keto-ester (44). This, upon borohydride reduction, furnished in equal amounts two hydroxy-esters: (i) (39), which on acetylation gave the acetate (38), identical with material previously obtained from (34), and (ii) (14), identical with material obtained by mild hydrolysis of the benzoate (41). Hydrolysis of the hydroxy-esters and acidification finally furnished the desired δ-lactones (1) and (2). The conformations (5) and (6) of lactones (1) and (2), respectively, are supported by their n.m.r. spectra at 100 MHz. In each case the informative part of the spectrum is the $AMNX_3$ system arising from protons attached to C-4, C-5, and C-4'. Lactone (1) [≡ (5)] has signals at τ 5·40 (1H, m, 4-H), 8·67 (3H, d, J 6 Hz, 6'-H_3). Only one 5-proton is visible as a four-line multiplet centred at τ 8·21, collapsing to a doublet (J 13 Hz) on irradiation at τ 5·40. Inspection of the multiplets at τ 5·40 and 8·21 gives the following approximate coupling constants: J_{AX} 6, J_{AM} 5, J_{AN} 13, and J_{MN} −13 Hz, consistent with half-chair conformation (5) but not with the alternative boat conformation for lactone (1). Lactone (2) [≡ (6)] shows signals at τ 5·57 (1H, m, 4-H), 8·69 (3H, d, J 6 Hz, 6'-H_3). In this case six of the eight lines of the MN part can be located by irradiation at τ 5·57. Subspectral analysis gives the following approximate values: J_{AX} 6, J_{AM} 4, J_{AN} 12, J_{MN} −14 Hz, and ($\delta_M - \delta_N = 30$ Hz). These values are confirmed by inspection of the signal for A and are consistent with the boat conformation (6) but not with the alternative chair conformation for lactone (2).

The lactones show in their i.r. solution spectra (CCl_4) the following significant bands: lactone (1), $\nu_{max.}$ 1740s, 1382, 1233, 1214, 1128s, and 1064 cm^{-1}; lactone (2),

[14] R. J. Abraham, *J. Chem. Soc.*, 1963, 806.
[15] H. Nakata, *Tetrahedron*, 1963, **19**, 1959.
[16] U. Schmidt and P. Grafen, *Annalen*, 1962, **97**, 656.
[17] I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *J. Org. Chem.*, 1968, **33**, 2013.

1755s, 1382, 1225, 1204, 1172, 1118s, 1098, and 1070 cm^{-1}.

The o.r.d. and c.d. data for lactones (1) and (2) are recorded in the Experimental section. Their significance will be discussed elsewhere.

Our correlation between the conformations and i.r. carbonyl absorptions of simple δ-lactones has received recent support.[18-21] It has, however, been pointed out [22] that care may be needed in the case of more complex systems.

EXPERIMENTAL

M.p.s were obtained with a Kofler hot-stage apparatus. I.r. solution spectra (in CCl_4 unless otherwise stated) were recorded on a Unicam SP 100 or a Perkin-Elmer 225 double-beam spectrophotometer. N.m.r. spectra were recorded ($CDCl_3$ solution; Me_4Si as internal standard) on a Perkin-Elmer R10, 60 MHz spectrometer or a Varian HA100, 100 MHz spectrometer. The τ values reported are those obtained from the 60 MHz spectrum or from the 100 MHz spectrum after calibration with a Hewlett-Packard electronic counter (5212A). Double-resonance experiments were performed with a Muirhead Oscillator (D-890-A) on the HA100 spectrometer. Mass spectra were obtained on an LKB 900 GCMS or an A.E.I. MS9 or MS12 spectrometer. Microanalyses were performed by Mr. J. M. L. Cameron and his staff. G.l.c. was performed on Pye Argon gas chromatographs (4 m × 4 mm int. diam. packed glass columns). Other g.l.c. was carried out on a Perkin-Elmer F11 gas chromatograph. Merck Kieselgel G was used for analytical t.l.c. and preparative thin layer chromatography (p.l.c.). Petroleum refers to the fraction which boils between 60 and 80° unless otherwise stated. Solutions were dried over anhydrous magnesium sulphate or anhydrous sodium sulphate.

The Isomeric Triol Monoacetates (15) *and* (16).—Drimenyl acetate (0·586 g) in ether (10 ml) and osmium tetroxide (0·5 g) in ether (10 ml) and pyridine (0·5 ml) were mixed. Brown crystalline osmate separated after a few min. After 24 h the solvents were removed *in vacuo*, the residue was dissolved in benzene, and hydrogen sulphide passed for several minutes to complete precipitation of osmium sulphide. Filtration and solvent removal left a semi-solid mixture (0·603 g) of acetates (15) and (16), which were separated by p.l.c. (ethyl acetate–petroleum 1 : 1). The less mobile 2β-*acetoxymethyl*-1β,3β,7,7-*tetramethyl*-6αH-*bicyclo*[4.4.0]*decane*-3α,4α-*diol* (15) (0·256 g) had m.p. 136·5—137·5° (from petroleum–chloroform), $[\alpha]_D$ −46·5° (*c* 1·46), $\nu_{max.}$ 3635, 3584, 3563, 1753, 1737, 1724, and 1241 cm^{-1}, τ 9·21, 9·16, 9·13, 8·87, and 8·00 (3H, s each), 7·06 and 6·46 (1H, s each, D_2O-exchangeable), 6·44 (1H, m, $W_{\frac{1}{2}}$ 4 Hz), and 5·80 (2H, m) (Found: C, 68·55; H, 10·45. $C_{17}H_{30}O_4$ requires C, 68·4; H, 10·15%). The more mobile 2β-*acetoxymethyl*-1β,3α,7,7-*tetramethyl*-6αH-*bicyclo*[4.4.0]*decane*-3β,4β-*diol* (16) (0·148 g) had m.p. 122·5—123·5° (from petroleum–chloroform), $[\alpha]_D$ +29° (*c* 0·62), $\nu_{max.}$ (CCl_4) 3630, 3582, 1741, 1233, and 1017 cm^{-1}, τ 9·17, 9·12, 9·04, 8·76, and 8·02 (3H, s each), 7·88 and 7·72 (1H, s each, D_2O-exchangeable), 6·72 (1H, q, *J* 12 and 5 Hz), and 5·74 (2H, m) (Found: C, 68·4; H, 10·1%).

The Keto-aldehyde (17) *and Keto-ester* (7).—The mixture of diols (15) and (16) (89 mg) in methanol (10 ml) was added to sodium periodate (114 mg) in water (10 ml) and stored for 20 h at 20°. Removal of methanol *in vacuo*, addition of water (10 ml), extraction into ethyl acetate, washing with brine, and evaporation left the keto-aldehyde (17) (84 mg), m.p. 139·5—140·5°, $\nu_{max.}$ 2714, 1746, 1717, 1225, and 1020 cm^{-1}, τ 9·1 (9H, s), 8·06 and 7·88 (3H, s each), and 0·2 (1H, d). To the aldehyde (53 mg) in acetone (5 ml) Jones reagent was added dropwise and with cooling until in excess. After 10 min, the acidic product (30 mg) was recovered as usual and methylated with ethereal diazomethane to afford 1α-(1-*acetoxymethylacetonyl*)-2β-*methoxycarbonylmethyl*-1β,3,3-*trimethylcyclohexane* (7), m.p. 75—76° (from petroleum), $\nu_{max.}$ 1742, 1717, 1233, and 1014 cm^{-1}, τ 9·12, 9·07, 9·03, 8·00, 7·78, and 6·30 (3H, s each), 7·60 (2H, d), 7·05 (1H, q), and 5·55 (2H, m) (Found: C, 66·2; H, 9·05. $C_{18}H_{30}O_5$ requires C, 66·25; H, 9·25%).

The Keto-ester (7) *directly from Drimenyl Acetate*.—Drimenyl acetate (4) was oxidised in four 2 g lots as follows. The acetate (2 g) in AnalaR dioxan (80 ml) was added to potassium permanganate (0·5 g) and potassium periodate (26·4 g) in water (1300 ml), and the pH was adjusted to 8·0 with potassium carbonate. The mixture was vigorously stirred for 2 days, acidified with conc. hydrochloric acid, and extracted into ether. Solvent removal from the brine-washed ether extracts afforded (from 8 g) a green oil (9·5 g) which crystallised spontaneously. Separation in the usual way furnished a semi-solid acidic fraction (7·32 g) and a neutral fraction (2·0 g) which did not contain drimenyl acetate and was not further investigated. Methylation of the acid fraction afforded a 10 : 1 mixture (g.l.c. on 1% SE30 at 150°) of the keto-esters (7) and (18), separated by p.l.c. (ethyl acetate–petroleum, 3 : 10). The major acetate was identical (g.l.c., t.l.c., i.r., mixed m.p.) with acetate (7) already prepared. The minor acetate (18) was hydrolysed to 1α-*glycoloyl*-2β-*methoxycarbonylmethyl*-1β,3,3-*trimethylcyclohexane* (19) (1% H_2SO_4–MeOH; 20°; 16 h), which after sublimation (80°, 0·5 mmHg) had m.p. 51—53°, $\nu_{max.}$ 3490, 3380, 1740, and 1697 cm^{-1}; τ 9·11 (6H, s), 8·80 and 6·42 (3H, s each), 8·20—7·40 (3H, m), 5·59 (2H, q), and 7·15br (1H, s, D_2O-exchangeable) (Found: C, 65·75; H, 9·3. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·45%).

Hydrolysis of the Keto-acetate (7).—The keto-acetate (7) (9·00 g) was stored in methanol (1000 ml) containing 1% sulphuric acid at 20° for 16 h. Solid sodium carbonate was added to neutralise the acid and the methanol was removed *in vacuo*. Addition of brine and extraction into ether afforded a green oil (7·3 g), showing one major and two minor components on t.l.c. (ethyl acetate–petroleum, 3 : 5). The major 1α-(1-*hydroxymethylacetonyl*)-2β-*methoxycarbonylmethyl*-1β,3,3-*trimethylcyclohexane* (8) (5·5 g) was obtained by crystallisation from petroleum and had m.p. 87°, $[\alpha]_D$ −52° (*c* 1·0), $\nu_{max.}$ 3638, 3580, 3515 (unchanged on dilution), 1737, and 1715 cm^{-1}, τ 9·11 and 7·78 (3H, s each), 9·05 (6H, s), 8·05 (1H, t), 7·61 (2H, d), 7·23 (1H, q), and 6·10 (2H, m) (Found: C, 67·35; H, 9·65. $C_{16}H_{28}O_4$ requires C, 67·55; H, 9·95%).

Preparative t.l.c. of the mother liquors from the foregoing crystallisation afforded the least mobile 6α-*acetyl*-

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7β,11,11-*trimethyl*-4-*oxabicyclo*[5.4.0]*undecan*-3-*one* (21), m.p. (from petroleum) 143—145°, $\nu_{max.}$ 1759 and 1728 cm^{-1}, τ 9·23, 9·02, 8·92, and 7·80 (3H, s each), 7·57 (1H, d, *J* 4 Hz), 7·4 (3H, m), and 5·52 (2H, m), c.d. (EtOH) $[\theta]_{293}$ +2210, $[\theta]_{219}$ −3150 (Found: C, 71·3; H, 9·35. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%).

The most mobile oily 2β-*methoxycarbonylmethyl*-1β,3,3-*trimethyl*-1α-(1-*methyleneacetonyl*)*cyclohexane* (20) was microdistilled (80° at 0·5 mmHg), and then had $[\alpha]_D$ −33° (*c* 0·9), $\nu_{max.}$ 3010, 1740, 1689, and 1606 cm^{-1}, τ 9·17, 9·06, 8·91, 7·69, and 6·43 (3H, s each), 7·77 (3H, m), 7·39 (1H, t), and 4·24 (2H, d) (Found: C, 71·85; H, 9·95. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·95%).

Attempted Retroaldolisation of the Acetoxy-ketone (7) *and the Hydroxy-ketone* (8).—The acetate (7) was subjected to a variety of acidic and basic conditions. Mild acid generally afforded the hydroxy-ketone (8); more vigorous acid conditions, *e.g.* sulphuric acid in dioxan at reflux afforded the enone (20). Even mild conditions (Na_2CO_3–MeOH) gave high yields of enone (20). Vapour phase pyrolysis of the hydroxy-ketone (8) gave mostly the enone (20).

The Keto-aldehyde (11).—(i) The hydroxy-ketone (8) (25 mg), dimethyl sulphoxide (0·33 ml), dry benzene (0·33 ml), pyridine (0·008 ml), trifluoroacetic acid (0·008 ml), and dicyclohexylcarbodi-imide (62 mg) were stirred at 20° for 16 h. Benzene (2 ml) was then added and the dicyclohexylurea formed was filtered off. T.l.c. disclosed formation of the more mobile aldehyde (11), but this was obtained more efficiently as follows.

(ii) To the hydroxy-ketone (8) (9·0 g) in ice-cooled AnalaR acetone (1·2 l) Jones reagent (16 ml) was added dropwise and with stirring. After 6 min, excess of oxidant was destroyed by addition of methanol. Dilution with brine (4 l) and extraction with ether (6 l) afforded an oil (8·7 g), showing one major component, the aldehyde (11), by t.l.c., $\nu_{max.}$ (film) 1730 and 1700 cm^{-1}, $\lambda_{max.}$ (EtOH) 212 nm, $\lambda_{max.}$ (EtOH–NaOH) 295 nm with increased ε. The aldehyde rapidly decomposed and was therefore oxidised as follows.

The Keto-ester (9).—The foregoing aldehyde (4·0 g) in ethanol (300 ml) was added dropwise and with stirring to aqueous sodium hydroxide (50 ml; 20%) and silver nitrate (3·8 g in 50 ml) and then stirred on a steam-bath for 1·5 h; the flask became internally coated by silver. The solution was diluted with water (100 ml), filtered through Celite, and carefully acidified with conc. hydrochloric acid; the product was extracted into ether. Methylation with diazomethane afforded the oily 1α-*acetonyl*-2β-*methoxycarbonylmethyl*-1β,3,3-*trimethylcyclohexane* (9) (3·5 g), 85% by g.l.c. (1% SE 30, 125°). A sample purified by p.l.c. and microdistillation (75° at 0·04 mmHg) had $[\alpha]_D$ +40° (*c* 1·0), $\nu_{max.}$ 1739, 1709, and 1161 cm^{-1}, τ 9·13, 9·10, 8·97, 7·87, and 6·31 (3H, s each), 8·12 (1H, t, *J* 0 and 4 Hz), 7·65 (2H, s), and 7·67 (2H, d, *J* 4 Hz) (Found: C, 70·05; H, 11·1. $C_{15}H_{26}O_3$ requires C, 70·25; H, 11·0%).

Sodium Borohydride Reduction of the Keto-ester (9).—The keto-ester (2·35 g, 0·01 mol) and sodium borohydride (200 mg, 0·005 mol) in ethanol were stirred at 20° for 16 h. Dilute hydrochloric acid was carefully added (to pH 3) to destroy excess of borohydride. Ethanol was removed *in vacuo* and replaced by brine. Extraction with ether afforded an oil (2·2 g) consisting (t.l.c.) of three components slightly less mobile than the starting material. The mixture was separated by p.l.c. (5 plates 100 × 20 × 0·05 mm; multiple elution with ethyl acetate–petroleum, 1 : 4). The most mobile product was 5α,7β,11,11-*tetramethyl*-1αH-4-*oxabicyclo*[5.4.0]*undecan*-3-*one* (31) (769 mg), m.p. 117° (from petroleum), $\nu_{max.}$ 1738, 1273, and 1117 cm^{-1}, τ 9·11, 8·94, and 8·93 (3H, s each), 8·63 (3H, d, *J* 6 Hz), 7·4 (2H, m), and 5·35 (1H, m), c.d. (iso-octane) $[\theta]_{224}$ −2795 (Found: C, 75·15; H, 11·15. $C_{14}H_{24}O_2$ requires C, 74·95; H, 10·8%). The least mobile product was the oily 1α-[(2S)-2-*hydroxypropyl*]-2β-*methoxycarbonylmethyl*-1β,3,3-*trimethylcyclohexane* (24), which was microdistilled (80° at 0·03 mmHg) and then had $\nu_{max.}$ 3623, 3400—3550, and 1740 cm^{-1}, τ 9·18, 9·12, 9·06, and 6·36 (3H, s each), 8·85 (3H, d, *J* 6 Hz), 8·26 (1H, t, *J* 5 Hz), 7·72 (2H, d, *J* 5 Hz), and 5·92 (1H, m) (Found: C, 70·05; H, 11·25. $C_{15}H_{28}O_3$ requires C, 70·25; H, 11·0%). The third product, the oily 1α-[(2R)-2-*hydroxypropyl*]-2β-*methoxycarbonylmethyl*-1β,3,3-*trimethylcyclohexane* (29) (773 mg), was microdistilled (80° at 0·03 mmHg) and then had $[\alpha]_D$ −31° (*c* 0·8), $\nu_{max.}$ 3623, 3523, 1727, and 1739sh cm^{-1}, τ 9·25, 9·15, 8·97, and 6·30 (3H, s each), 8·80 (3H, d, *J* 6 Hz), 8·04 (1H, t, *J* 6 Hz), 7·63 (2H, d, *J* 6 Hz), and 5·92 (1H, m) (Found: C, 70·05; H, 11·1%).

The ε-*Lactone* (32).—The hydroxyester (29) (30 mg) was refluxed with 2% potassium hydroxide in aqueous methanol (1 : 1) for 2 h. Acidification and extraction into ether afforded the hydroxy-acid (30) (28 mg), which was taken up in dry benzene (25 ml) and refluxed with toluene-*p*-sulphonic acid (15 mg) for 10 min, water being removed with a Dean–Stark attachment. The ice-cooled benzene solution was washed with cold sodium hydrogen carbonate solution and brine. Drying and solvent removal afforded mainly the lactone (32) (19 mg) (one major non-polar material and some acid at base line on t.l.c.). The acidic material increased when purification was attempted by crystallisation or p.l.c., thus making it impossible to obtain a satisfactory analysis; $\nu_{max.}$ 1730, 1275, 1190, and 1142 cm^{-1}, τ 9·2, 9·1, and 8·9 (3H, s each), 8·75 (3H, d, *J* 6 Hz), 7·4 (2H, m), and 5·45 (1H, m).

The Diphenylethylene (34).—The hydroxy-ester (29) (600 mg) in ether (16 ml) was added with stirring during 10 min to phenylmagnesium bromide [from bromobenzene (4·5 ml) and magnesium turnings (640 mg)] in ether (32 ml). The mixture was refluxed for 2 h and stirred for 16 h at 20°. Saturated ammonium chloride (10 ml) was added dropwise, the ether was decanted, and the salts were washed with ether. The diphenylcarbinol (1·5 g) [one major component by t.l.c.; $\nu_{max.}$ (film) 3400br, 3050, 2910, 1590, 740, and 690 cm^{-1}] obtained from the ether was dehydrated without isolation. It was dissolved in glacial acetic acid (12 ml) and acetic anhydride (24 ml) and refluxed for 4 h. Removal of solvents *in vacuo* and chromatography of the residue over silica gel (100 g) afforded (with benzene–petroleum) 1α-[(2R)-2-*acetoxypropyl*]-2β-(2,2-*diphenylvinyl*)-1β,3,3-*trimethylcyclohexane* (34), needles (400 mg) from petroleum, m.p. 117—118°, $[\alpha]_D$ +86° (*c* 0·6), $\nu_{max.}$ 3084, 2930, 1744, 1606, and 1250 cm^{-1}, τ 9·19 (3H, s), 8·9 (6H, s), 8·87 (3H, d, *J* 6 Hz), 8·17 (1H, d, *J* 11 Hz), 8·06 (3H, s), 5·0 (1H, m), 3·80 (1H, d, *J* 11 Hz), and 2·72 (10H, m) (Found: C, 82·95; H, 8·9. $C_{28}H_{38}O_2$ requires C, 83·1; H, 8·95%). Elution with ether–benzene afforded a crystalline substance (200 mg), $\nu_{max.}$ 1744, 1605, and 1240 cm^{-1}, τ 9·27 (3H, s), 9·06 (6H, s), 8·93 (3H, d, *J* 6 Hz), 8·03 (3H, s), 4·95 (1H, m), 2·6 (3H, m), and 2·0 (2H, m).

The Enol Ether (36).—(i) The ε-lactone (31) (200 mg) and phenylmagnesium bromide [from bromobenzene (1·5 ml) and magnesium turnings (220 mg)] were refluxed under nitrogen for 4 h. The mixture was decomposed as in the work-up

leading to the diphenylethylene (34). Dehydration as before with acetic acid–acetic anhydride and p.l.c. afforded *5α,7β,11,11-tetramethyl-3-phenyl-1αH-4-oxabicyclo*[5.4.0]-*undec-2-ene* (36) (200 mg), which after microdistillation (80° at 0·03 mmHg) had $\nu_{max.}$ 3080, 2933, 1648, 1496, 1380, 1118, 1063, and 1038 cm^{-1}, τ 9·07 (6H, s), 8·97 (3H, s), 8·65 (3H, d, *J* 6 Hz), 7·75 (1H, d, *J* 6 Hz), 6·10 (1H, m), 4·37 (1H, d, *J* 6 Hz), and 2·5 (5H, m) (Found: C, 84·05; H, 10·15. $C_{20}H_{28}O$ requires C, 84·45; H, 9·9%).

(ii) Reaction of the hydroxy-ester (24) as for the ε-lactone (31) with phenylmagnesium bromide afforded the same major product (36).

Ozonolysis of the Diphenylethylene (34).—The diphenylethylene (34) (500 mg) in AnalaR ethyl acetate (250 ml) was ozonised at 20° for 5 h. Acetic acid (50 ml) and hydrogen peroxide (5 ml; 30%) were added and the solution was stored at 20° for 16 h. Recovery of the acidic reaction product, by continuous extraction of the acidified sodium carbonate extract with ether, afforded an oil (260 mg) which was methylated and then separated by p.l.c. (ethyl acetate–petroleum, 1 : 4). The more mobile product was *1α-[(2R)-2-acetoxypropyl]-2β-methoxycarbonyl-1β,3,3-trimethylcyclohexane* (38) (50 mg), homogeneous by g.l.c. (1% QF1, 100°; 1% SE30, 100°) and after microdistillation had $[\alpha]_D$ +19° (*c* 1·1), $\nu_{max.}$ 1735, 1239, and 1138 cm^{-1}, τ 9·09, 8·90, 8·85, 8·00, and 6·35 (3H, s each), 8·82 (3H, d, *J* 6 Hz), 7·90 (1H, s), and 4·90 (1H, m) (Found: C, 67·8; H, 9·9. $C_{16}H_{28}O_4$ requires C, 67·6; H, 9·95%). The less mobile product was *1α-[(2R)-2-acetoxypropyl]-2β-(2-methoxycarbonyl-2-phenylvinyl)-1β,3,3-trimethylcyclohexane* (35) (70 mg), m.p. 108—109° (from petroleum), $\nu_{max.}$ 3040, 2930, 1736, 1720, 1240, and 700 cm^{-1}, τ 9·24 and 8·06 (3H, s each), 8·95 (6H, s), 8·84 (3H, d, *J* 6 Hz), 8·24 (1H, d, *J* 12 Hz), 6·27 (3H, s), 5·0 (1H, m), 2·79 (1H, d, *J* 12 Hz), and 2·70 (5H, m) (Found: C, 74·7; H, 8·9. $C_{24}H_{34}O_5$ requires C, 74·55; H, 8·85%).

Unchanged diphenylethylene (34) (300 mg) was recovered from the neutral fraction.

Ruthenium Tetroxide Oxidation of the Diphenylethylene (34).—Ruthenium dioxide (12 mg) was added to a stirred aqueous solution of sodium periodate (1·3 ml; 5%), followed by the diphenylethylene (34) (60 mg) in acetone (5 ml). When the solution turned black after 15 min the yellow colour was restored by adding sodium periodate (100 mg) and this was repeated twice during the following 24 h. Excess of ruthenium tetroxide was destroyed by adding propan-2-ol (1 ml) and the solvents were removed *in vacuo*. The acidic product (32 mg), recovered as usual, was methylated with ethereal diazomethane affording the methyl ester acetate (38) (29 mg), identical (t.l.c., g.l.c., and i.r.) with the material obtained by ozonolysis.

Cleavage of the Enol Ether (36).—(i) *Ozonolysis*. The enol ether (36) (25 mg) in ethanol (10 ml) was ozonised at 0° for 1·5 h. Ethanol was removed *in vacuo*, and the residue taken up in hydrogen peroxide (0·5 ml; 30%) and acetic acid (2·5 ml) and stored for 16 h. T.l.c. of the product then showed mainly unchanged (36).

(ii) *Osmium tetroxide cleavage*. The enol ether (36) (200 mg) and osmium tetroxide (220 mg) were stored in dry ether (10 ml) and pyridine (0·25 ml) for 3 days in the dark at 20°. The solvents were removed *in vacuo* and replaced with benzene, hydrogen sulphide was passed through, and osmium sulphide was filtered off through Celite. The product (208 mg) was separated by p.l.c. (ethyl acetate–petroleum, 1 : 4). The least mobile fraction was resolved by p.l.c. into a minor (3 mg) unidentified substance and *2β-[benzoyl(hydroxy)methyl]-1α-[(2S)-2-hydroxypropyl]-1β,3,3-trimethylcyclohexane* (28) (20 mg), m.p. 107—108° (from petroleum), $\nu_{max.}$ 3620, 3455, and 1702 cm^{-1}, τ 9·33 (3H, d, *J* 6 Hz), 8·98 (6H, s), 8·90 (3H, s), 7·45 (1H, s, sharpens on irradiation at τ 7·45 and on exchange with D_2O), and 2·65br (5H, s) (Found: C, 75·4; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·4; H, 9·5%). The second product recovered from the chromatoplate was the aldehyde (40) (67 mg), obtained as an unstable oil, $\nu_{max.}$ 3060, 3015, 2840, 2740, 1730, 1275, and 1110 cm^{-1}, τ 9·04, 8·81, and 8·75 (3H, s each), 8·68 (3H, d, *J* 6 Hz), 8·17 (1H, d, *J* 6 Hz), 4·52 (1H, m), 1·89 (2H, q), 2·48 (3H, m), and −0·74 (1H, d, *J* 6 Hz). On storage in air the above aldehyde (60 mg) was oxidised to the acid, which was transformed into *1α-[(2S)-2-benzoyloxypropyl]-2β-methoxycarbonyl-1β,3,3-trimethylcyclohexane* (41) (30 mg). After p.l.c. and microdistillation (80° at 0·05 mmHg) this had $[\alpha]_D$ +51° (*c* 1·26), $\nu_{max.}$ 2530, 1736, 1718, and 1270 cm^{-1}, τ 9·09, 8·88, and 8·82 (3H, s each), 8·71 (3H, d, *J* 6 Hz), 7·81 (1H, s), 6·34 (3H, s), 4·60 (1H, m), 2·49 (3H, m), and 1·97 (2H, m) (Found: C, 72·7; H, 8·75. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·75%).

Unchanged enol ether (25) (61 mg) was also recovered from the chromatoplate.

Attempts to oxidise the aldehyde (40) with Jones reagent or alkaline silver oxide were unsuccessful, unchanged starting material resulting with the former and a mixture of unidentified products with the latter.

Reaction of the Ethylene Acetal (42) *with Phenylmagnesium Bromide.—The ethylene acetal* (42). The keto-ester (9) (750 mg), ethylene glycol (2 ml), toluene-*p*-sulphonic acid (15 mg), and benzene (50 ml) were refluxed under a Dean–Stark separator. Conversion was complete in 24 h (t.l.c.) and the usual work-up then afforded the oily acetal (800 mg) (single peak on 1% SE30 at 140°), $\nu_{max.}$ (film) 1740, 1200, 1100, and 1045 cm^{-1}, τ 9·2, 9·1, 9·0, and 8·68 (3H, s each), 6·33 (4H, m), 6·1 (3H, s), and 7·7 (3H, m). This acetal was not isolated but was subjected at once to Grignard reaction.

The diphenylethylene (43). The acetal (670 mg) in dry ether (35 ml) was added to phenylmagnesium bromide [from bromobenzene (3·5 ml) and magnesium (630 mg)] in ether (17 ml). After 3 h at reflux and 16 h at 20°, the diphenylcarbinol was liberated with ammonium chloride solution and then dehydrated with acetic acid–acetic anhydride as for the diphenylethylene acetate (34). Column chromatography of the product (1·0 g) on silica gel (80 g) afforded (with benzene–petroleum, 2 : 98) an oil (121 mg), $\nu_{max.}$ (film) 3050, 2910, 1670, 1595, 740, and 690 cm^{-1}, which was not further investigated, and then (with benzene–petroleum, 1 : 4), *1α-acetonyl-2β-(2,2-diphenylvinyl)-1β,3,3-trimethylcyclohexane* (43) (270 mg). After microdistillation (100° at 0·05 mmHg) this had $\nu_{max.}$ 3070, 3050, 3010, 2940, 2920, 1710, 1595, and 695 cm^{-1}, τ 9·14, 8·93, 8·80, and 8·01 (3H, s each), 7·39 (1H, d, *J* 14 Hz), 3·80 (1H, d, *J* 14 Hz), and 2·7 (10H, m) (Found: C, 86·65; H, 9·2. $C_{26}H_{32}O$ requires C, 86·6; H, 8·95%).

The Keto-ester (44).—Ruthenium dioxide (60 mg) was added with stirring to aqueous sodium periodate (6·5 ml; 5%), followed by the diphenylethylene (43) (200 mg) in acetone (30 ml). The oxidation was continued for 24 h with regeneration of osmium tetroxide by further additions of sodium periodate, as in the oxidation of the diphenylethylene (34). Work-up and recovery of the acidic product (70 mg) as usual, followed by methylation, afforded one

principal product (t.l.c.). P.l.c. and microdistillation (80° at 0·1 mmHg) afforded the oily 1α-*acetonyl*-2β-*methoxycarbonyl*-1β,3,3-*trimethylcyclohexane* (44) (52 mg), $\nu_{max.}$ 2920, 1734, 1705, 1158, and 1140 cm^{-1}, τ 9·10, 8·90, 8·80, 7·92, and 6·37 (3H, s each), 7·66 (2H, s), and 7·57 (1H, s) (Found: M^+, 240·1723. $C_{14}H_{24}O_3$ requires M, 240·1725).

The Hydroxy-esters (39) *and* (14).—The keto-ester (44) and sodium borohydride (10 mg) in ethanol (4 ml) were stirred during 6 h at 20°, then excess of reducing agent was destroyed by dropwise addition of dilute hydrochloric acid (to pH 3). Work-up as usual afforded a mixture (64 mg) of the hydroxy-esters (39) and (14) which were separated by p.l.c. (ethyl acetate–petroleum, 1 : 9; multiple elution). The more mobile ester (39) (18 mg) on acetylation afforded the previously obtained acetate (38) and had $\nu_{max.}$ 3612, 3565, 1732, 1715sh, 1700 (less intense than 1732 band), and 1136 cm^{-1}, τ 9·13, 8·92, and 8·90 (3H, s each), 8·88 (3H, d, J 0·6 Hz), 8·20 (1H, s, D_2O-exchangeable), 7·76 (1H, s), 6·39 (3H, s), and 6·05 (1H, m).

The less mobile ester (14) (18 mg) was identical with that formed by mild hydrolysis of the benzoate (41), and had $\nu_{max.}$ 3615, 1733, 1715sh, and 1136 cm^{-1}, τ 9·11, 8·88, and 8·81 (3H, s each), 8·87 (3H, d, J 6 Hz), 7·5br (1H, s, D_2O-exchangeable), 7·84 (1H, s), 6·39 (3H, s), and 6·00 (1H, m).

The δ-*Lactones* (1) *and* (2).—(i) The hydroxy-ester (14) (18 mg) was refluxed for 3 h with methanolic potassium hydroxide (20 ml; 2%). Recovery after acidification of neutral material (15 mg) and purification by p.l.c. and microdistillation afforded 4α,6β,10,10-*tetramethyl*-1αH-3-*oxabicyclo*[4.4.0]*decan*-2-*one* (1) (9 mg) as an oil, homogeneous on g.l.c. on 1% SE30, 1% PEGA, and 10% APL; τ 8·87 (6H, s), 8·78 (3H, s), 8·06 (1H, s), 8·67 (3H, d, J 0·6 Hz), and 5·40br (1H, m) (Found: M^+, 210·16186. $C_{13}H_{22}O_2$ requires M, 210·16197), o.r.d. (MeOH) $[\phi]_{217}$ −4320, $[\phi]_{239}$ +1620, c.d. (EtOH) $[\theta]_{225}$ +4600.

(ii) The methyl ester acetate (38) (30 mg) was hydrolysed as above. Acidification afforded neutral material (21 mg) which on p.l.c. and microsublimation afforded 4β,6β,10,10-*tetramethyl*-1αH-3-*oxabicyclo*[4.4.0]*decan*-2-*one* (2), m.p. 36—38°, homogeneous on 1% SE30, 1% PEGA, 5% APL, τ 8·92, 8·89, and 8·74 (3H, s each), 8·69 (3H, d, J 6 Hz), 7·83 (1H, s), and 5·57br (1H, m) (Found: C, 74·05; H, 10·6%), o.r.d. (MeOH) $[\phi]_{212}$ −10,400, $[\phi]_{236}$ +6520, c.d. (EtOH) $[\theta]_{223}$ +9170.

We thank the S.R.C. and the Salters' Institute of Industrial Chemistry for Scholarship support, and Professor W. Klyne (London) and Dr. G. Snatzke (Bonn), respectively, for o.r.d. and c.d. measurements.

[2/2117 *Received, 8th September,* 1972]