Stereoselective Total Syntheses of (±)-Isoagatholactone and (±)-12α-Hydroxyspongia-13(16),14-diene, Two Marine Sponge Metabolites

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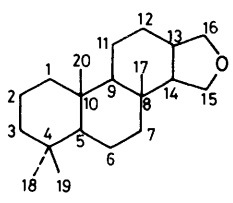
The highly efficient, stereoselective syntheses of (±)-isoagatholactone (1a) and (±)-12α-hydroxyspongia-13(16),14-diene (3e), a fundamental skeleton of spongiadiol (3a) and its related furanoid diterpenes, are described. (±)-Labda-8(20),13-dien-15-oic acid (6), chosen as the starting material, was cyclised to the known tricyclic compound (2b), which after methylation was subjected to photo-oxygenation, yielding the allylic alcohol (7a). Refluxing of the alcohol (7a) with 3.5% sulphuric acid in dioxan afforded the lactone (1b), which after reduction with lithium aluminium hydride led to the diol (2g). Subsequent oxidation of this diol with Collins reagent provided the desired compound (1a). The key precursor for the synthesis of compound (3e) was the allylic alcohol (7a) obtained above. On epoxidation the alcohol (7a) gave the epoxide (13), which by the action with lithium di-isopropylamide led to the α,β-unsaturated γ-lactone (14). Subsequent reduction of this lactone with di-isobutylaluminium hydride afforded the furan (3e).

The family Spongiidae has produced an array of furanoid terpenes.[1] In 1974, Minale *et al.*[2] isolated from the sponge *Spongia officinalis* a new diterpene, named isoagatholactone, and assigned it the structure (1a) on spectral grounds and chemical correlation with grindelic acid. This compound has proved to be the first example of a growing member of tetracyclic diterpenes with the carbon skeleton of isoagathic acid (2a). Since then, a group of nine closely related compounds, spongiadiol † (3a), epispongiadiol (3b), spongiatriol (3c), epispongiatriol (3d), their corresponding di- and tri-acetates,[3] and aplysillin [4] (4), were isolated from several analogous species of the genus *Spongia*. The aim of our present work is to elaborate a new convenient, highly efficient route to the syntheses ‡ of (±)-isoagatholactone (1a) and (±)-12α-hydroxyspongia-13(16),14-diene (3e), a framework of spongiadiol (3a) and its related furanoid diterpenes.

Results and Discussion

In this synthesis we have chosen (±)-labda-8(20),13-dien-15-oic acid § (6) as an ideal starting material since it provides a known tricyclic compound [5] with the required relative stereochemistry by cyclisation.

† The nomenclature of these compounds is based upon the hypothetical skeleton spongian (5).[3]



(5)

‡ For a preliminary communication of this work, see T. Nakano and M. I. Hernández, *Tetrahedron Lett.*, 1982, **23**, 1423.

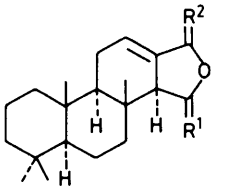
§ This compound occurs as the crystalline racemic form in the trunk resin of *Eperua purpurea* (V. de Santis and J. D. Medina, *J. Nat. Prod.*, 1981, **44**, 340). For the active form, see T. Nakano and C. Djerassi, *J. Org. Chem.*, 1961, **26**, 167; G. Ohloff, *Annalen*, 1958, **617**, 134.

On being refluxed with 88% formic acid for 4 h the acid (6) yielded a single cyclised isomer [5] (2b) ¶ in 70% yield which without isolation was methylated with ethereal diazomethane to the methyl ester (2c). In order to construct a lactonic ring D, we considered it necessary to transform this methyl ester to the allylic alcohol (7a), which by an acid-catalysed allylic rearrangement would provide either compound (2f) or (1b). Photo-oxygenation [6] of compound (2c) in pyridine containing hematoporphyrin as a sensitiser at 20 °C for 72 h yielded three products after a careful chromatography over silica gel. Two of them were the expected allylic alcohols (7a) (25% yield) and (8a) (44% yield). The 12-hydroxy-group in these compounds must be α-oriented since they would be derived from the attack of oxygen from the less hindered α-side of the 12,13-double bond. The third least-polar product was found to be the α,β-unsaturated ketone (8b), the structure of which was confirmed by preparing it from compound (8a) by oxidation.

It was somewhat surprising to observe that compound (7a) did not undergo an allylic rearrangement to compound (2f) with 3.5% sulphuric acid in dioxan at room temperature. However, heating of compound (7a) at reflux temperature in the same acidic medium led to a lactone (1b) in 83% yield. The structure of this compound was determined on the basis of spectroscopic evidence. It gave a molecular ion peak at *m/z* 302 in the mass spectrum. The presence of a γ-lactone ring D was clearly demonstrated by the i.r. spectrum (1 770 cm^{-1}). The n.m.r. spectrum showed a one-proton singlet at δ 2.73 (14-H), a two-proton multiplet at 4.58 (16-H), and a one-proton multiplet at 5.66 (12-H). On reduction with lithium aluminium hydride this lactone afforded in 95% yield the diol (2g).

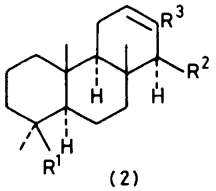
At this stage we also thought that the diol (2g) might conveniently be derived from compound (2c), *viz.* through reduction to the alcohol (2d), photo-oxygenation to the allylic alcohol (7b), followed by an allylic rearrangement. Reduction of compound (2c) with lithium aluminium hydride afforded in 98% yield the alcohol (2d). This alcohol, after conversion into the tetrahydropyranyl ether (2e), was submitted to photo-oxygenation under the same conditions as before. The crude product isolated was chromatographed over silica gel and

¶ All compounds we synthesised are racemic modifications although only one enantiomer is depicted in the drawings.



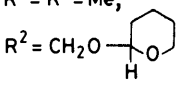
(1)

a; $R^1 = H_2$, $R^2 = O$
b; $R^1 = O$, $R^2 = H_2$
c; $R^1 = R^2 = H_2$

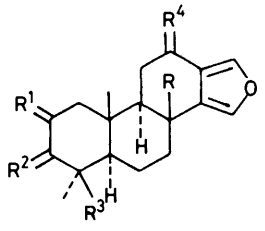


(2)

a; $R^1 = R^2 = CO_2H$, $R^3 = Me$
b; $R^1 = R^3 = Me$, $R^2 = CO_2H$
c; $R^1 = R^3 = Me$, $R^2 = CO_2Me$
d; $R^1 = R^3 = Me$, $R^2 = CH_2OH$
e; $R^1 = R^3 = Me$,



f; $R^1 = Me$, $R^2 = CO_2Me$, $R^3 = CH_2OH$
g; $R^1 = Me$, $R^2 = R^3 = CH_2OH$



(3)

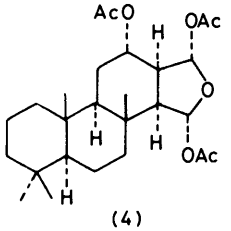
a; $R^1 = O$, $R^2 =$  , $R^3 = CH_2OH$, $R^4 = H_2$, $R^5 = Me$

b; $R^1 = O$, $R^2 =$  , $R^3 = CH_2OH$, $R^3 = H_2$, $R^5 = Me$

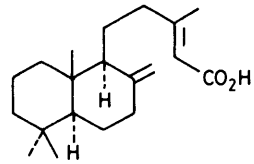
c; $R^1 = O$, $R^2 =$  , $R^3 = R^5 = CH_2OH$, $R^4 = H_2$

d; $R^1 = O$, $R^2 =$  , $R^3 = R^5 = CH_2OH$, $R^4 = H_2$

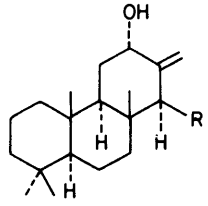
e; $R^1 = R^2 = H_2$, $R^3 = R^5 = Me$, $R^4 =$ 



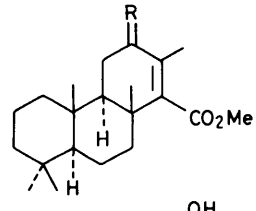
(4)



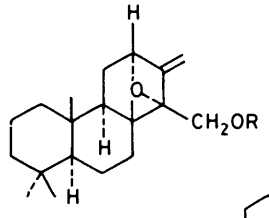
(6)

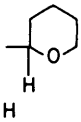


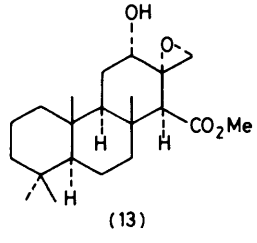
(7) a; $R = CO_2Me$
b; $R = CH_2OH$



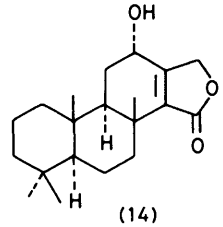
(8) a, $R =$ 
b; $R = O$



(9) a; $R =$ 
b; $R = H$



(13)

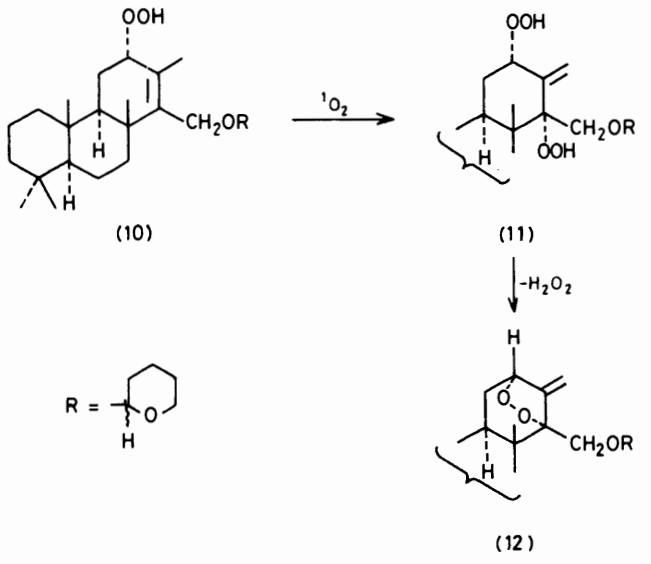


(14)

then hydrolysed with hydrochloric acid in acetone, whereupon two alcohols were obtained. The most polar one was the expected diol (7b) (31% yield) and the less polar was found to be the cyclised ether (60% yield). The latter was formulated as (9b) from the following spectroscopic data. It gave a molecular ion at *m/z* 304 in the mass spectrum. The n.m.r. spectrum lacked a signal due to the proton at C-14, but showed the presence of a primary hydroxy-group (δ 3.76, 2 H, ABq, *J* 11 Hz, 15-H_2), an exocyclic double bond (5.06 and 5.20, each 1 H, s, 16-H_2), and a hydrogen (4.40, t, 12-H) attached to the carbon bearing an ether linkage. This product may be formed *via* the following reaction sequence (see Scheme). It is evident that compound (2e) would, at first, yield the peroxide (10) with absorption of 1 mol equivalent of singlet oxygen. This intermediate peroxide would, subsequently, take up a further 1 mol equivalent of singlet oxygen to form the di-peroxide (11), which would then cyclise with loss of 1 mol equivalent of hydrogen peroxide to the *endo*-peroxide (12). This *endo*-peroxide, after the usual work-up with sodium iodide, would eventually lead to the epoxide (9a).

The diol (7b) also resisted the acid-catalysed rearrangement to an isomeric diol (2g). On treatment with 3.5% sulphuric acid in dioxan at room temperature it was recovered unchanged. Refluxing in the same acidic medium for 24 h resulted in the formation of the cyclised ether (1c). This compound gave, besides a molecular ion at *m/z* 288, a fragment ion at *m/z* 192 as the base peak in the mass spectrum. The same fragment ion, $[C_{14}H_{24}]^+$, was also observed in the mass spectra of compounds (1a) and (1b) with the relative abundances of 100 and 69%, respectively, and hence it apparently originates from the retro-Diels–Alder cleavage of ring c. The n.m.r. spectrum showed signals for four tertiary methyl groups (δ 0.93, 0.87, 0.84, and 0.77, each 3 H, s), an olefinic proton (5.50, m, 12-H), coupled with allylic methylene (2.00, bm, 11-H_2) and an allylic methine proton (2.37, bm, 14-H), and two methylene groupings bearing the oxygen linkage (2 × 1 H triplets, both with *J* 9 Hz, at δ 3.51 and 3.95, 15-H_2 and a 2 H multiplet at δ 4.20, 16-H_2).

The next step was the oxidation of the diol (2g). For this



Scheme

purpose the two primary hydroxy-groups were located at especially favourable positions. We expected that the allylic 16-hydroxy-group would be more susceptible to oxidation than the 15-hydroxy-group and hence the resulting C-16 hemiacetal would be oxidised *in situ* to the desired α,β-unsaturated lactone (1a). In fact, the diol (2g), on oxidation with Collins reagent [7] in methylene chloride, furnished in one-step the objective (±)-isoagatholactone * (1a) in 59% yield. The i.r., n.m.r., and mass spectral data of this synthetic material were identical with those [2] reported for (+)-isoagatholactone.

We now proceed to the synthesis of (±)-12α-hydroxyspongia-13(16),14-diene (3e). This furanoid spongian skeleton is commonly encountered in spongiadiol (3a) and its seven related diterpenes. We assumed that the furan ring D in this framework would possibly be constructed by utilizing the allylic alcohol (7a) as a key precursor, transforming it to the epoxide (13), and cyclising the latter to the α,β-unsaturated γ-lactone (14). Once this lactone was formed, reduction with di-isobutylaluminium hydride would then provide the desired furanoid derivative (3e). On epoxidation with *m*-chloroperbenzoic acid in methylene chloride compound (7a) gave in 99% yield solely the α-epoxy-ester (13). The approach of the peracid from the less hindered α-side of the 13,16-double bond was greatly facilitated by the presence of the adjacent 12α-hydroxy-group.[8]

When the epoxy-ester (13) was treated with lithium di-isopropylamide in tetrahydrofuran, the β-elimination and lactonisation took place in one-step, and the lactone (14) was obtained in 50% yield. Reduction [9] of this lactone with di-isobutylaluminium hydride in tetrahydrofuran afforded in 19% yield the furan (3e), the spectral data of which were in accord with the proposed structure. The mass spectrum gave, as expected, a molecular ion peak at *m/z* 302. The n.m.r. spectrum showed a one-proton multiplet at δ 4.90, readily assignable to the hydrogen at C-12, and two signals at 7.06 and 7.36 (each 1 H, d, both with *J* 1 Hz), characteristic of α-furan protons.

* After we had completed our present work, a similar synthesis appeared (P. M. Imamura, M. G. Sierra, and E. A. Ruveda, *J. Chem. Soc., Chem. Commun.*, 1981, 734).

Experimental

M.p.s were measured on a Kofler hot-stage apparatus and are uncorrected. Unless otherwise specified, i.r. spectra were recorded for potassium bromide discs with a Perkin-Elmer 337 spectrometer. N.m.r. spectra were obtained for solutions in $CDCl_3$ on a Varian EM 3940 spectrometer. Chemical shifts are reported in p.p.m. downfield from internal $SiMe_4$. Mass spectra were determined on a DuPont 21-492B (Data System 21-094B) at 70 eV using a direct inlet system. The relative abundances of the ions are indicated in parentheses as a percentage of the base peak. All peaks are reported with the *m/z* values more than 135 and with the relative abundances greater than 10% of the base peak. For column chromatography silica gel 60 (Merck, 70-230 mesh) was used. Thin layer chromatograms were prepared on silica gel G or silica gel GF_{254}60 (Merck) and the spots were observed by exposure to iodine vapour or u.v. light. All organic extracts were dried over anhydrous sodium sulphate or magnesium sulphate and evaporated under reduced pressure below 60 °C. Microanalyses were carried out by A. Bernhardt microanalytical laboratory, 5251 Elbach über Engelskirchen, West Germany.

Cyclisation of (±)-*Labda*-8(20),13-*dien*-15-*oic Acid* [5] (6).—The acid (1 g) was refluxed with 88% formic acid (60 ml) for 4 h. After concentration of the solution under reduced pressure, the tricyclic acid (2b) was obtained as a solid (700 mg). It was methylated in a mixture of chloroform and ether with ethereal diazomethane to yield the methyl ester (2c) (670 mg), m.p. 75—80 °C; *m/z* 318 (M^+) (55), 304 (12), 303 (44), 287 (18), 272 (13), 271 (53), 260 (11), 259 (48), 258 (19), 243 (19), 231 (11), 194 (12), 193 (20), 192 (65), 191 (54), 189 (17), 180 (16), 179 (24), 178 (17), 177 (59), 175 (17), 173 (11), 167 (26), 166 (17), 165 (51), 163 (19), 161 (18), 159 (11), 153 (22), 151 (11), 150 (10), 149 (31), 148 (13), 147 (25), 145 (13), 139 (24), 138 (21), 137 (77), 136 (38), and 135 (58); $\nu_{max.}$ 1 720 cm^{-1} (CO_2Me), δ 0.83, 0.86, 0.90, 0.95 (each 3 H, s, Me), 1.60 (3 H, s, 16-Me), 2.93 (1 H, m, 14-H), and 3.66 (3 H, s, OMe).

Photo-oxygenation of the Tricyclic Methyl Ester (2c).—The ester (3 g) in dry pyridine (150 ml) was irradiated at 20 °C in the presence of hematoporphyrin (90 mg) with a 200-W tungsten and three 32-W fluorescent lamps placed near the vessel while oxygen was bubbled through the reaction mixture. After 72 h, the brown solution was evaporated under reduced pressure and the resultant peroxide was treated with sodium iodide (18 g) in ethanol (250 ml) containing acetic acid (9 ml) at room temperature for 48 h. After concentration of the solution under reduced pressure, a dark brown oil was obtained, which after addition of water was extracted with ether. The ether solution was washed with aqueous sodium thiosulphate, then water, dried, and evaporated. The crude product was chromatographed over silica gel and elution with 5% ether in hexane yielded recovered starting material (1.2 g). Elution with hexane–ether (10 : 1.5) gave the less-polar *alcohol* (7a) (0.47 g), m.p. 183—185 °C; *m/z* 334 (M^+) (0.3), 316 (23), 301 (14), 205 (10), 192 (29), 191 (46), 190 (19), 179 (12), 178 (19), 177 (22), 175 (10), 165 (17), 164 (12), 163 (12), 159 (10), 149 (14), 147 (12), 145 (11), 138 (13), 137 (39), 136 (13), and 135 (18), $\nu_{max.}$ 3 550 (OH), 1 725 (CO_2Me), and 1 655 cm^{-1} (terminal C=C); δ 0.80 (3 H, s, Me), 0.86 (6 H, s, 2 × Me), 1.01 (3 H, s, Me), 3.33 (1 H, s, 14-H), 3.63 (3 H, s, OMe), 4.36 (1 H, m, 12-H), 4.83 (1 H, m, 16-H), and 5.03 (1 H, m, 16-H) (Found: C, 75.65; H, 10.0. $C_{21}H_{34}O_3$ requires C, 75.40; H, 10.25%)

Further elution with hexane–ether (10 : 2) afforded the *alcohol* (8a) (0.81 g), m.p. 146—148 °C; *m/z* 334 (M^+) (14), 319 (13), 303 (15), 302 (12), 287 (13), 275 (33), 259 (22), 257

(16), 192 (28), 191 (16), 179 (10), 178 (20), 177 (57), 175 (19), 173 (13), 165 (13), 163 (25), 161 (12), 159 (26), 151 (17), 150 (10), 149 (30), 147 (14), 145 (19), 143 (52), 142 (80), 138 (11), 137 (52), 136 (21), and 135 (36); $\nu_{max.}$ 3 470 (OH) and 1 692 cm^{-1} (α-β-unsaturated ester); δ 0.80, 0.83, 0.86 (each 3 H, s, Me), 1.16 (3 H, s, 17-Me), 1.73 (3 H, s, 16-Me), 3.73 (3 H, s, OMe), and 4.00 (1 H, t, 12-H) (Found: C, 75.15; H, 10.4. $C_{21}H_{34}O_3$ requires C, 75.40; H, 10.25%).

In some cases a small amount of the α,β-*unsaturated ketone* (8b) [55 mg from compound (2c) (0.7 g)] was isolated as the third product. This compound was more polar than the alcohol (7a), and was eluted with hexane–ether (10 : 1). It had m.p. 104—106 °C, *m/z* 332 (M^+) (0.8), 273 (42), 182 (16), 175 (11), 161 (11), 149 (25), 141 (35), 137 (28), 136 (25), and 135 (100); $\nu_{max.}$ 1 730 (CO_2Me), 1 675 (α,β-unsaturated CO), and 1 630 cm^{-1} (conjugated C=C) (Found: C, 75.45; H, 9.5. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%). The structure of this compound was confirmed by preparing it from the alcohol (8a) by oxidation with pyridinium dichromate [10] in methylene chloride.

Attempted Acid-catalysed Allylic Rearrangement of the Alcohol (7a).—The alcohol (0.1 g) in a mixture (10 ml) of dioxan and 3M-sulphuric acid (13 : 1) was stirred at room temperature. Since, after 12 h, no reaction took place (as demonstrated by t.l.c.) the solution was heated under reflux for 24 h. Water was then added and the product extracted with ether and chromatographed over silica gel. Elution with hexane–chloroform (10 : 1) gave the *lactone* (1b) (75 mg), m.p. 142 °C, *m/z* 302 (M^+) (39), 287 (26), 205 (15), 193 (13), 192 (63), 191 (37), 179 (17), 178 (24), 177 (50), 166 (13), 165 (18), 164 (22), 163 (19), 152 (34), 151 (40), 150 (22), 249 (33), 145 (15), 138 (13), 137 (52), 136 (21), and 135 (20); $\nu_{max.}$ 1 770 cm^{-1} (γ-lactone); δ 0.83 (6 H, s, 2 × Me), 0.86 and 0.89 (each 3 H, s, Me), 2.73 (1 H, s, 14-H), 4.58 (2 H, m, 16-H), and 5.66 (1 H, m, 12-H) (Found: C, 79.25; H, 9.85. $C_{20}H_{30}O_2$ requires C, 79.42; H, 10.00%).

Reduction of the Lactone (1b) *with Lithium Aluminium Hydride*.—To a stirred solution of the lactone (100 mg) in anhydrous ether (10 ml) was added lithium aluminium hydride (150 mg); the mixture was then allowed to stand at room temperature for 6 h under an atmosphere of nitrogen. The excess of reagent and the complex were then decomposed by addition of aqueous sodium hydroxide. Anhydrous sodium sulphate was then added and the solution was filtered and evaporated, yielding the *diol* (2g) (96 mg), m.p. 149—151 °C; *m/z* 306 (M^+) (0.4), 258 (20), 205 (19), 193 (12), 192 (40), 191 (37), 178 (11), 177 (42), 163 (15), 151 (13), 150 (14), 149 (22), 145 (13), 139 (11), 138 (11), 137 (33), 136 (21), and 135 (23); δ 0.73, 0.80 (each 3 H, s, Me), 0.86 (6 H, s, 2 × Me), 3.86 (2 H, bm, 15-CH_2OH), 4.16 (2 H, ABq, *J* 12 Hz, 16-CH_2OH), and 5.76 (1 H, m, 12-H) (Found: C, 78.15; H, 10.9. $C_{20}H_{34}O_2$ requires C, 78.38; H, 11.18%).

Reduction of the Tricyclic Methyl Ester (2c) *with Lithium Aluminium Hydride*.—The ester (350 mg) in anhydrous ether (30 ml) was reduced with lithium aluminium hydride (250 mg) in the same way as described for the lactone (1b). The *alcohol* (2d) was obtained as a semisolid (323 mg); *m/z* 290 (M^+) (10), 259 (32), 257 (22), 192 (46), 191 (36), 177 (38), 149 (16), 147 (10), 137 (49), 136 (16), and 135 (22); δ 0.81 (6 H, s, 2 × Me), 0.84, 0.87 (each 3 H, s, Me), 1.78 (3 H, s, 16-Me), 3.90 (2 H, m, CH_2OH), and 5.50 (1 H, t, 12-H) (Found: 82.35; H, 11.55. $C_{20}H_{34}O$ requires C, 82.69; H, 11.80%).

The alcohol (2d) (1 g) in dihydropyran (20 ml) was stirred with toluene-*p*-sulphonic acid (2 mg) at room temperature for 35 min. Anhydrous potassium carbonate (1 g) was added and the solution was stirred for an additional 2 min. Water was then added, and the product was extracted with ether and chromatographed over silica gel. Elution with hexane yielded the tetrahydropyranyl ether (2e) as an oil (1.02 g); *m/z* 272 ($M^+ - C_5H_{10}O_2$) (18), 191 (25), 190 (15), 136 (11), 135 (13), 123 (10), 121 (13), 119 (12), 109 (13), 107 (12), 105 (12), 95 (16), 93 (13), 91 (13), 86 (10), and 85 ($C_5H_{10}O_2$ − OH) (100); δ 0.81 (6 H, s, 2 × Me), 0.85 (3 H, s, Me), 0.88 (3 H, s, Me), 3.60 (4 H, m, 15-H_2, 2′-H_2), 4.56 (1 H, t, 6′-H), and 5.43 (1 H, t, 12-H).

Photo-oxygenation of the Tetrahydropyranyl Ether (2e).—The tetrahydropyranyl ether (1.02 g) was photo-oxygenated under the same conditions as described for the tricyclic methyl ester (2c). The crude product obtained was chromatographed over silica gel and elution with hexane gave recovered starting material (100 mg). Elution with 10% ether in hexane yielded three fractions. The least-polar fraction contained the *cyclised ether* (9a), which was hydrolysed with a mixture of 3M-hydrochloric acid and acetone (1 : 3) at room temperature. After work-up, the *ether-alcohol* (9b) (492 mg) was crystallised and had m.p. 197—200 °C; *m/z* 304 (M^+) (7), 274 (13), 273 (60), 192 (10), 191 (33), 177 (10), 163 (10), 149 (17), 145 (10), 137 (27), 136 (10), and 135 (17); $\nu_{max.}$ 3 430 cm^{-1} (OH); δ 0.79, 0.85 (each 6 H, s, 2 × Me), 3.76 (2 H, ABq, *J* 11 Hz, CH_2OH), 4.40 (1 H, t, 12-H), 5.06 (1 H, s, 16-H), and 5.20 (1 H, s, 16-H) (Found: C, 78.6; H, 10.3. $C_{20}H_{32}O_2$ requires C, 78.89; H, 10.59%).

The second less-polar fraction, after hydrolysis with hydrochloric acid–acetone, gave a small amount of solid (78 mg), which was not investigated further. The third most-polar fraction, after hydrolysis, afforded the *diol* (7b) (219 mg), m.p. 208—210 °C (in a sealed tube); *m/z* 288 ($M^+ - H_2O$) (26), 286 (13), 271 (11), 270 (17), 255 (17), 193 (12), 192 (55), 191 (40), 190 (24), 187 (10), 185 (12), 175 (11), 173 (16), 171 (11), 159 (22), 157 (11), 150 (13), 149 (17), 147 (17), 146 (11), 145 (21), 143 (11), 137 (26), 136 (22), and 135 (30); δ 0.70 (3 H, s, Me), 0.80 (6 H, s, 2 × Me), 0.85 (3 H, s, Me), 2.46 (1 H, m, 14-H), 3.80 (2 H, m, CH_2OH), 4.38 (1 H, m, 12-H), 0.48 (1 H, s, 16-H), and 5.13 (1 H, s, 16-H) (Found: C, 78.15; H, 10.9. $C_{20}H_{34}O_2$ requires C, 78.38; H, 11.18%).

Attempted Acid-catalysed Rearrangement of the Diol (7b).—The diol (65 mg) in a mixture (5 ml) of 3M-sulphuric acid and dioxan (1 : 13) was stirred at room temperature for 26 h. Since, after this time, no reaction had taken place (as demonstrated by t.l.c.) the solution was heated under reflux for 24 h. The product isolated on work-up, was chromatographed over silica gel. Elution with 10% chloroform in hexane yielded the *cyclised ether* (1c) (15 mg), m.p. 116—118 °C, *m/z* 288 (M^+) (27), 193 (20), 192 (100), 191 (27), 178 (10), 177 (64), 149 (20), 137 (26), 136 (20), and 135 (20) (Found: C, 83.0; H, 10.85. $C_{20}H_{32}O$ requires C, 83.27; H, 11.18%).

Oxidation of the Diol (2g).—The diol (70 mg) in dichloromethane (20 ml) was stirred with freshly prepared Collins reagent (700 mg) at room temperature for 3 h. The reaction mixture was then poured into a column containing silica gel and eluted with hexane–ether (1 : 1) to yield the lactone (1a) (41 mg), m.p. 140—142 °C; *m/z* 302 (M^+) (0.5), 287 (11), 193 (22), 192 (100), 191 (49), 178 (23), 177 (77), 164 (18), 163 (13), 149 (27), 137 (41), 136 (29), and 135 (15), $\nu_{max.}$ 1 760 (α,β-unsaturated γ-lactone) and 1 685 cm^{-1} (conjugated C=C), δ 0.75, 0.81, 0.86, 0.93 (each 3 H, s, Me), 2.20 (2 H, bm, 11-H_2), 2.70 (1 H, bm, 14-H), 4.03 (1 H, t, *J* 9 Hz, 15-H), 4.36 (1 H, t, *J* 9 Hz, 15-H), and 6.86 (1 H, q, *J* 3 Hz, 12-H) (Found: C, 79.2; H, 9.65. $C_{20}H_{30}O_2$ requires C, 79.42; H, 10.00%).

Epoxidation of the Alcohol (7a).—The alcohol (230 mg) in dichloromethane (50 ml) was treated with *m*-chloroperbenzoic acid (227 mg) at room temperature for 3 h. The solution was filtered on a column containing alumina (Merck, standardised, activity II—III) to remove both the excess of reagent and *m*-chlorobenzoic acid. Evaporation of the solvent gave the *epoxy-ester* (13) (238 mg), m.p. 196—198 °C; *m/z* 350 (M^+) (0.3), 205 (20), 193 (11), 192 (28), 191 (85), 190 (25), 189 (12), 177 (26), 175 (15), 167 (10), 163 (18), 161 (15), 159 (12), 153 (10), 151 (11), 150 (11), 149 (26), 147 (22), 146 (82), 145 (27), 144 (14), 141 (15), 138 (14), 137 (60), 136 (23), and 135 (29); $\nu_{max.}$ 3 480 (OH) and 1 730 cm^{-1} (CO_2Me); δ 0.80 (3 H, s, CH_3), 0.85 (6 H, s 2 × Me), 1.11 (3 H, s, Me), 2.66 (1 H, d, *J* 5 Hz, 16-H), 3.21 (1 H, s, 14-H), and 3.58 (3 H, s, OMe). A one-proton doublet (*J* 5 Hz, 16-H) and one-proton multiplet (12-H) were superimposed at δ 3.50. However, upon addition of the lanthanide shift-reagent Eu(fod)$_3$, these signals were resolved, both shifting downfield (Found: C, 71.65; H, 9.5. $C_{21}H_{34}O_4$ requires C, 71.96; H, 9.78%).

Treatment of the Epoxy-ester (13) *with Lithium Di-isopropylamide in Tetrahydrofuran.*—To a solution of di-isopropylamine (0.1 ml) in anhydrous tetrahydrofuran (10 ml) was added at −70 °C in small portions n-butyl-lithium (0.6 ml; 1.13M-solution in hexane) under an atmosphere of nitrogen; the solution was then stirred for 15 min. The epoxy-ester (300 mg) in anhydrous tetrahydrofuran (10 ml) was then added dropwise to the above solution and stirring was continued at −70 °C for 1 h. The reaction mixture was neutralised with cold aqueous hydrochloric acid, treated with sodium chloride, and extracted with ether. The crude product obtained was chromatographed over silica gel. Elution with hexane–chloroform (1 : 1) yielded recovered starting material (200 mg). Further elution with chloroform afforded the *lactone* (14) (45 mg), m.p. 263—265 °C; *m/z* 318 (M^+) (16), 303 (30), 285 (17), 203 (23), 192 (13), 191 (26), 177 (13), 171 (10), 169 (11), 168 (84), 167 (41), 166 (10), 163 (10), 161 (18), 159 (16), 152 (14), 151 (50), 150 (25), 149 (34), 145 (12), 137 (27), 136 (10), and 135 (19); $\nu_{max.}$ 3 370 (OH) and 1 735 cm^{-1} (α,β-unsaturated γ-lactone); δ 0.83, 0.86, 0.90, 1.10 (each 3 H, s, Me), 2.60 (1 H, dm, *J* 12 Hz, 7β-H), 4.42 (1 H, m, 12-H), and 4.70 (2 H, ABq, *J* 17 Hz, 16-H_2) (Found: C, 75.25; H, 9.25. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.50%).

Reduction of the Lactone (14) *with Di-isobutylaluminium Hydride.*—Di-isobutylaluminium hydride (0.4 ml; 1M-solution in hexane) was added at −13 °C in two portions (0.2 ml each) to a stirred solution of the lactone (130 mg) in anhydrous tetrahydrofuran (25 ml) at intervals of 30 min under an atmosphere of nitrogen. Stirring was continued at room temperature for an additional 2 h. The reaction mixture was then treated with 10% aqueous sulphuric acid (20 ml) and the product was extracted with ether. Elution with 5% ether in hexane yielded the *furan* (3e) as an amorphous solid (23 mg); *m/z* 302 (M^+) (44), 287 (14), 205 (11), 193 (16), 192 (63), 191 (38), 179 (17), 178 (26), 177 (57), 166 (15), 165 (19), 164 (26), 163 (19), 152 (16), 151 (32), 150 (26), 149 (36), 147 (11), 145 (18), 138 (15), 137 (53), 136 (25), and 135 (22), δ 0.83, 0.86, 0.90, 1.15 (each 3 H, s, Me), 4.90 (1 H, m, 12-H), 7.06 (1 H, d, *J* 1 Hz, 15-H or 16-H), and 7.36 (1 H, d, *J* 1 Hz, 16-H or 15-H) (Found: C, 79.25; H, 9.8. $C_{20}H_{30}O_2$ requires C, 79.42; H, 10.00%). Further elution with ether gave recovered starting material (50 mg).

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