Synthetic Studies on the Sesquiterpene Antibiotic Verrucarol

By **Ernest W. Colvin,* Swiatoslaw Malchenko, Ralph A. Raphael,** and **James S. Roberts,** Department of Chemistry, University of Glasgow, Glasgow G12 8QQ

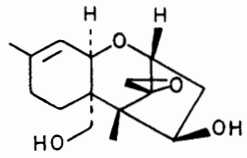
Synthetic investigations on a member of the antibiotic trichothecane group of sesquiterpenes, verrucarol (12,13-epoxytrichothec-9-ene-4β,15-diol) (1) are described.

SINCE our first synthesis [1] of a member of the trichothecane group of sesquiterpenes, synthetic interest in this field has grown considerably.[2] The pharmacological properties of another of the group, verrucarol [3] (1), have recently attracted attention and we now report the results of synthetic approaches to this compound.

The starting material was the cyclohexenone (2), readily available by the interaction of methyl vinyl ketone and ethyl formylsuccinate.[4] Selective attack at the carbonyl group with methylmagnesium chloride gave the tertiary alcohol (3) which, without purification, was hydrolysed with sodium hydroxide. Acidification of the sodium salt with sulphuric acid brought about the desired rearrangement to the *cis*-fused carboxy-γ-lactone † (4). Treatment of this acid with oxalyl chloride gave the corresponding acid chloride, which was then reduced selectively to the hydroxymethyl-γ-lactone (5) with sodium borohydride. This seemingly mundane step entailed considerable practical difficulties and strict adherence to the optimum conditions finally established was found necessary for reproduceability. The expected *cis*-stereochemistry of the lactone (5) was unequivocally confirmed by a direct *X*-ray structural determination.[5]

The free hydroxy-group in (5) was then protected as the methoxymethyl ether (6) by reaction with chloromethyl methyl ether and the protected lactone was treated with lithium di-isopropylamide and methyl iodide. Under these conditions monomethylation proceeded smoothly and stereoselectively, only one homogeneous monomethyl lactone (7) being produced. Although it is likely that methylation of lactone (6) under conditions of kinetic control would proceed from the sterically more accessible convex side of the molecule, thus leading to an α-methyl configuration in (7), no unambiguous assignment could be made spectroscopically.

The use of other hydroxy protecting groups for the hydroxy-lactone (5) was far less straightforward. Attempted *O*-methylation using methyl iodide or methyl fluorosulphate gave mainly the rearranged spirodiene lactones (9). The tetrahydropyranyl (10) and trimethylsilyl (11) ethers were readily prepared but the ensuing *C*-methylation step was found to be non-stereoselective and these protecting groups caused complications at the next stage.



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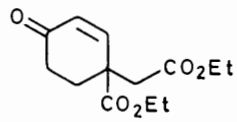

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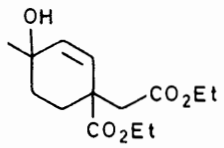

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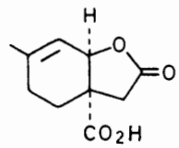

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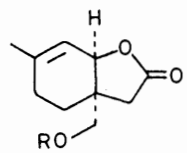
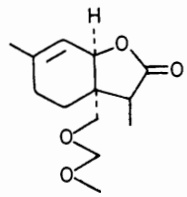


(5) R = H
(6) R = CH_2OCH_3
(8) R = CH_3
(10) R = tetrahydropyran-2-yl
(11) R = $SiMe_3$



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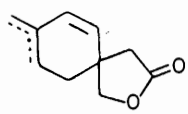


(9)

By contrast the methoxymethyl ether lactone reacted smoothly with the lithium salt of 3,3-diethoxypropyne to give the desired acetylenic hemiacetal (12). Reduc-

† All racemic structures are illustrated by one enantiomer.

[1] E. W. Colvin, S. Malchenko, R. A. Raphael, and J. S. Roberts, *J.C.S. Perkin I*, 1973, 1989.

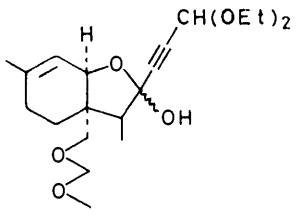
[2] D. J. Goldsmith, A. J. Lewis, and W. C. Still, jun., *Tetrahedron Letters*, 1973, 4807; S. C. Welch and R. Y. Wong, *ibid.*, 1972, 1853; *Synth. Comm.*, 1972, **2**, 291; Y. Fujimoto, S. Yokura, T. Nakamura, T. Morikawa, and T. Tatsuno, *Tetrahedron Letters*, 1974, 2523; N. Masuoka and T. Kamikawa, *ibid.*, 1976, 1691; W. K. Anderson, E. J. LaVoie, and G. E. Lee, *J. Org. Chem.*, 1977, **42**, 1045.

[3] W. O. Godtfredsen and S. Vangedal, *Proc. Chem. Soc.*, 1964, 188; J. Gutzwiller, R. Mauli, H. P. Sigg, and Ch. Tamm, *Helv. Chim. Acta*, 1964, **47**, 2234; A. T. McPhail and G. A. Sim, *Chem. Comm.*, 1965, 350. For antileukaemic activity in the trichothecenes, see S. M. Kupchan, B. B. Jarvis, R. G. Dailey, jun., W. Bright, R. F. Bryan, and Y. Shizuri, *J. Amer. Chem. Soc.*, 1976, **98**, 7092.

[4] H. Plieninger, G. Ege, R. Fischer, and W. Hoffmann, *Chem. Ber.*, 1961, **94**, 2106.

[5] M. Currie, *J.C.S. Perkin II*, 1973, 240.

tion of this product with borohydride readily gave the acetylenic diol (13), the triple bond of which was selectively reduced by sodium in liquid ammonia to give the



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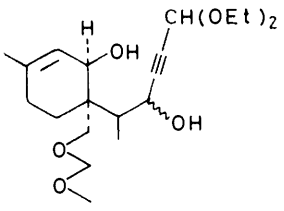

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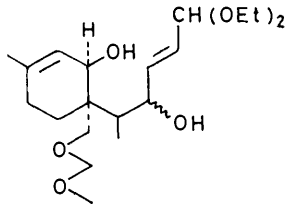

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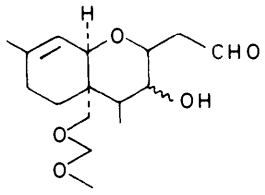

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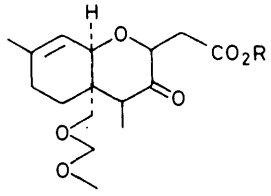
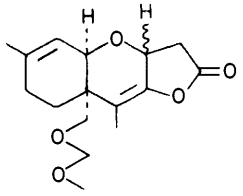
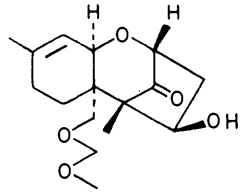


(16) R = H
(17) R = Me



(18) 3β-H
(19) 3α-H



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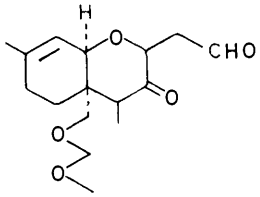

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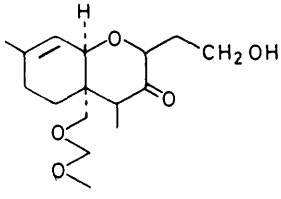

(22)

trans-ethylenic diol (14). Treatment of (11) with buffered acetic acid brought about selective hydrolysis of the acetal function followed by an internal nucleophilic attack of the hydroxy-group on the conjugated double bond to give the *cis*-fused bicyclic hydroxy-aldehyde (15). Oxidation of (15) with Jones reagent gave the unstable oxo-acid (16), which was best isolated and purified by conversion into its methyl ester (17) with diazomethane. Basic hydrolysis of the ester gave the pure acid (16), which was immediately treated with acetic anhydride–sodium acetate to give a separable mixture of the two epimeric enol lactones (18) and (19). On the basis of analogy with the trichodermin synthesis it was hoped that treatment of these enol lactones with lithium hydridotri-t-butoxyaluminate would produce appreciable amounts of the tricyclic hydroxy-ketone (20). In the event the reduction gave only bicyclic products, the oxo-aldehyde (21), the hydroxy-ketone (22), and the hydroxy-aldehyde (15). Variants of the reduction procedure gave no trace of the required tricyclic product. It is thus apparent that completion of this approach to verrucarol is dependent on the development of an alternative effective method of cyclisation to the five-membered ring.

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Pye Unicam SP 1000 or a Perkin-Elmer 225 double-beam spectrophotometer and are for liquid films, unless otherwise stated; u.v. spectra were measured with a Unicam SP 800 instrument. ^{1}H N.m.r. spectra were measured on a Varian T-60 (60 MHz) or a Varian HA 100 (100 MHz) spectrometer, with tetramethylsilane as internal reference. Mass spectra were determined on an A.E.I.–G.E.C. MS12 or MS902S spectrometer.

Kieselgel G (Merck) was used for analytical t.l.c.; Kieselgel HF_{254} or GF_{254} (Merck) was used for preparative t.l.c. All organic solutions were dried over anhydrous magnesium sulphate. Solvents were removed on a rotary evaporator.

Ethyl (1-*Ethoxycarbonyl*-4-*oxocyclohex*-2-*enyl*)*acetate* (2).—This compound was prepared by the method of Plieninger *et al.*;[4] b.p. 130—137° at 0.02 mmHg (lit., 126—130° at 0.01 mmHg).

Ethyl (1-*Ethoxycarbonyl*-4-*hydroxy*-4-*methylcyclohex*-2-*enyl*)*acetate* (3).—To a stirred, ice-cold solution of methylmagnesium chloride (29 ml; 3M in tetrahydrofuran; 87 mmol) in ether (200 ml), a solution of the enone ester (2) (20 g, 79 mmol) in ether (20 ml) was added over 1 min. After a further 10 min, saturated aqueous sodium sulphate was added dropwise, and the granular precipitate was filtered off and washed with ether. The combined organic extracts were washed with water and brine and dried, to give, on concentration, the crude tertiary alcohol (3) (21 g), as a viscous mixture of epimers, $\nu_{max.}$ 3 509, 1 730, 1 205, and 1 040 cm^{-1}.

4-*Methyl*-8-*oxo*-7-*oxabicyclo*[4.3.0]*non*-4-*ene*-1-*carboxylic Acid* (4).—The crude alcohol (3) (20.5 g) and sodium hydroxide solution (100 ml; 4N) were stirred vigorously for 13 h at 80 °C; homogeneity was then attained. The mixture was cooled in ice–salt and acidified with dilute sulphuric acid (100 ml; 6N), stirred for 1.5 h, then extracted with ethyl acetate (3 × 100 ml). The organic extracts were combined, washed with brine, and dried. Removal of solvent under pressure followed by trituration with cold ether gave the *lactone acid* (4) (12 g), which crystallised from ethyl acetate as an amorphous powder, m.p. 146—148°,

$\nu_{max.}$ (Nujol) 3 420—2 400, 1 740, 1 705, 1 230, and 970 cm^{-1}, $\delta(CDCl_3)$ 1.8br (3 H, s, CH_3·C=C), 2.62 and 3.13 (2 H, ABq, J_{AB} 18 Hz, CH_2·CO), 5.1 (1 H, m, CH·O), 5.6 (1 H, m, CH=C), and 7.9 (1 H, m, CO_2H). The *methyl ester* crystallised from benzene as plates, m.p. 85—87° (Found: C, 62.7; H, 6.65%; M^+, 210. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7; *M*, 210).

1-*Hydroxymethyl*-4-*Methyl*-7-*oxabicyclo*[4.3.0]*non*-4-*en*-8-*one* (5).—A stirred suspension of the lactone acid (4) (1 g, 5.12 mmol) in dichloromethane (50 ml) was treated with oxalyl chloride (0.7 ml, 1 g, 8 mmol) and *NN*-dimethylformamide (1 drop), and stirring was continued for 12 h. After concentration under reduced pressure and azeotropic removal of the excess of oxalyl chloride with benzene, the corresponding lactone acid chloride was obtained as a moisture-sensitive pale brown solid (1.12 g), $\nu_{max.}$ (Nujol) 1 777 and 1 673 cm^{-1}, which was employed immediately in the subsequent reduction step.

A solution of the lactone acid chloride (1 g, 5.12 mmol) in dioxan (25 ml) was treated with sodium borohydride (1 g, 26.3 mmol). The resulting heterogeneous mixture was stirred for 3 h at 20 °C, then for 0.5 at 85 °C. The mixture was poured on to crushed ice (100 g) and extracted with ethyl acetate (2 × 150 ml). The combined organic extracts were washed with water and brine, and dried. Removal of solvent under reduced pressure, trituration with ether, and crystallisation from benzene gave the *lactone alcohol* (5) as cubes (675 mg), m.p. 82—83°, $\nu_{max.}$ (Nujol) 3 500, 1 745, 1 665, 1 205, and 905 cm^{-1}, $\delta(CDCl_3)$ 1.8br (3 H, d, CH_3·C=C), 2.0 (4 H, m), 2.42br (1 H, OH), 2.3 and 2.65 (2 H, ABq, J_{AB} 17 Hz, CH_2·CO), 3.56 (2 H, s, CH_2·O), 4.67 (1 H, m, CH·O), and 5.54 (1 H, m, CH=C) (Found: C, 65.8; H, 7.7%; M^+, 182. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.75%; *M*, 182).

Reduction of the acid chloride could be performed only on a 1—2 g scale, requiring strict adherence to the experimental conditions.

1-*Methoxymethoxymethyl*-4-*methyl*-7-*oxabicyclo*[4.3.0]*non*-4-*en*-8-*one* (6).—Sodium hydride (750 mg, 18.8 mmol) was added rapidly to a stirred solution of the lactone alcohol (5) (1.5 g, 8.3 mmol) in *NN*-dimethylformamide (20 ml) at 65 °C, and stirring was continued for a further 3 min. The vessel was cooled in ice–salt for 5 min, then chloromethyl methyl ether (0.9 ml, 9.5 mmol) added over 1 min. After 10 min, more chloromethyl methyl ether (0.9 ml, 9.5 mmol) was added, and the cooling bath was removed. The mixture was carefully quenched with N-hydrochloric acid–ice, then extracted with ethyl acetate. The extract was washed with dilute sodium hydrogen carbonate solution, water, and brine, and dried. Removal of solvent under reduced pressure followed by chromatography of the residue on alumina (grade I, basic) afforded the *lactone ether* (6) as an oil (955 mg), $\nu_{max.}$ 1 780, 1 680, 1 160, 1 055, and 990 cm^{-1}, $\delta(CDCl_3)$ 1.78 (5 H, m), 2.0 (2 H, m, CH_2·C=C), 2.31 and 2.69 (2 H, ABq, J_{AB} 17.5 Hz,CH_2·CO), 3.39 (3 H, s, MeO), 3.47 (2 H, s, C·CH_2·O), 4.63 (2 H, s, O·CH_2·O), 4.7 (1 H, m, CH·O), and 5.57 (1 H, m, CH=C) (Found: C, 63.65; H, 8.1%; M^+, 226. $C_{12}H_{18}O_4$ requires, C, 63.7; H, 8.0%; *M*, 226).

1-*Methoxymethyl*-4-*methyl*-7-*oxabicyclo*[4.3.0]*non*-4-*en*-8-*one* (8).—Sodium hydride (96 mg, 2.2 mmol) was added to a stirred solution of the lactone alcohol (5) (368 mg, 2.02 mmol) in *NN*-dimethylformamide (10 ml) at 80 °C in an atmosphere of nitrogen, and stirring was continued for 1 h. Methyl iodide (1 ml) was added, and stirring and heating were continued for a further 15 h. The mixture was cooled and extracted with ether. The extract was washed with water and brine, and dried. Removal of solvent *in vacuo* followed by preparative t.l.c. (developing solvent 30% ethyl acetate–light petroleum) of the residue afforded two components in addition to unchanged alcohol (5). The spirolactones (9) were obtained as an oil (171 mg), $\nu_{max.}$ 1 780, 1 180, 1 025, 850, and 750 cm^{-1}, $\lambda_{max.}$ (EtOH) 232 and 264 nm, $\delta(CDCl_3)$ 1.77 (3 H, m, CH_3·C=C), 2.2—2.6br (4 H, m, 2 × CH_2·C=C), 2.47 (4 H, t, *J* 18 Hz, 2 × CH_2·CO), 4.1, 4.2, and 3.99 (4 H, s and ABq, J_{AB} 9 Hz, 2 × CH_2·O), 4.93br (2 H, s, CH_2=C), 5.47 (1 H, m, CH=C), 5.63 and 5.95 (2 H, ABq, J_{AB} 11 Hz, CH=CH), and 5.93 and 6.25 (2 H, ABq, J_{AB} 10 Hz, CH=CH), M^+ 164.

The lactone ether (8) was obtained as an oil (30 mg), $\nu_{max.}$ 1 775, 1 675, 1 200, and 980 cm^{-1}, $\delta(CDCl_3)$ 1.8br (3 H, s, CH_3·C=C), 2.0 (2 H, m, CH_2·C=C), 2.33 and 2.7 (2 H, ABq, J_{AB} 18 Hz, CH_2·CO), 3.3 (2 H, m, CH_2·O), 3.4 (3 H, s, MeO), 4.7 (1 H, m, CH·O), and 5.59 (1 H, m, CH=C), M^+ 196.

1-*Tetrahydropyran*-2-*yloxymethyl*-4-*methyl*-7-*oxabicyclo*-[4.3.0]*non*-4-*en*-8-*one* (10).—A solution of the lactone alcohol (5) (209 mg, 1.15 mmol) and dihydropyran (126 mg, 1.5 mmol) in benzene (10 ml) was treated with phosphoryl chloride (1 drop). After 1.5 h at room temperature, the mixture was poured on to saturated aqueous sodium hydrogen carbonate, and then extracted thoroughly with ether. The combined extracts were washed with water and brine, and dried. Concentration *in vacuo* gave the *tetrahydropyranyl ether* (10) as a viscous oil (260 mg), b.p. (short path) 148—152° at 0.2 mmHg, $\nu_{max.}$ 1 780, 1 675, 1 150, 1 080, 980, and 760 cm^{-1}, $\delta(CDCl_3)$ 2.5 (2 H, m, CH_2·C=C), 2.23 and 2.7 (2 H, ABq, J_{AB} 9.5 Hz, CH_2·CO), 3.7br (2 H, m, CH_2·CH·O), 4.62 (2 H, m, C=C·CH·O and O·CH·O), and 5.54 (1 H, m, CH=C) (Found: C, 67.55; H, 8.5%; M^+, 266. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%; *M*, 266).

1-*Trimethylsilyloxymethyl*-4-*methyl*-7-*oxabicyclo*[4.3.0]-*non*-4-*en*-8-*one* (11).—A solution of the lactone alcohol (5) (172 mg, 0.95 mmol) in acetone (5 ml) was treated with *N*-trimethylsilyldiethylamine (0.4 ml, 3.92 mmol) at room temperature. After 4 h, the solution was concentrated *in vacuo* to furnish the *trimethylsilyl ether* (11) (211 mg), which crystallised from chloroform as cubes, m.p. 80—81°, $\nu_{max.}$ (Nujol) 1 780, 1 675, 1 255, 980, 860, 755, and 697 cm^{-1}, $\delta(CDCl_3)$ 1.66br (3 H, s, CH_3·C=C), 2.0 (2 H, m, CH_2·C=C), 2.3 and 2.65 (2 H, ABq, J_{AB} 18 Hz, CH_2·CO), 3.57 (2 H, s, CH_2·O), 4.7 (1 H, m, CH·O), and 5.53 (1 H, m, CH=C) [Found: C, 61.6; H, 8.85%; *m/e*, 182. $C_{13}H_{22}O_3Si$ requires C, 61.4; H, 8.7%; ($M - C_3H_8Si$), 182].

1-(1-*Methoxymethoxymethyl*)-4,9-*dimethyl*-7-*oxabicyclo*-[4.3.0]*non*-4-*en*-8-*one* (7).—To a stirred solution of diisopropylamine (645 mg, 6.36 mmol) in ether (25 ml) under nitrogen was added n-butyl-lithium (3.16 ml; 2.1M in hexane; 6.65 mmol) at such a rate as to maintain a gentle reflux. The solution was stirred for a further 5 min. A solution of the lactone ether (6) (1.13 g, 5.75 mmol) in ether (10 ml) was added, and stirring was continued for 15 min. Methyl iodide (4 ml) was added, and the mixture was stirred under gentle reflux for 30 min. It was then cooled, water was added, and the mixture was acidified with dilute aqueous sulphuric acid. The layers were separated, the aqueous layer was extracted with ether, and the ethereal extracts were combined, washed with brine, dilute aqueous sodium hydrogen carbonate, and brine, and dried. Removal of solvent under reduced pressure followed by chro-

matography on alumina (Woelm; grade 1 basic) gave the *methylated lactone* (7) as an oil (0.9 g), $\nu_{max.}$ 1 778, 1 675, 1 050, and 990 cm^{-1}, $\delta(CDCl_3)$ 1.17 (3 H, d, *J* 8 Hz, CH_3·CH), 1.73 (5 H, m), 2.0 (2 H, m, CH_2·C=C), 2.59 (1 H, q, *J* 8 Hz, CH_3·C*H*), 3.37 (3 H, s, MeO), 3.42 (2 H, m, C·CH_2·O), 4.6 (2 H, s, O·CH_2O), 4.77 (1 H, m, CH·O), and 5.54 (1 H, m, CH=C) (Found: C, 64.95; H, 8.4%; M^+, 240. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%; *M*, 240).

8-(3,3-*Diethoxyprop*-1-*ynyl*)-1-*methoxymethoxymethyl*-4,9-*dimethyl*-7-*oxabicyclo*[4.3.0]*non*-4-*en*-8-*ol* (12).—n-Butyllithium (4.25 ml; 2.1M in hexane; 8.9 mmol) was added to a stirred solution of 1,1-diethoxypropyne (1.14 g, 8.9 mmol) in ether (25 ml) at −78 °C in an atmosphere of nitrogen. Stirring was continued at −78 °C for a further 20 min. A solution of the lactone (7) (1.29 g, 5.94 mmol) in ether (10 ml) was added, the cooling bath was removed, and the mixture was stirred for 1 h. Saturated aqueous sodium sulphate was added dropwise, and the granular precipitate was filtered off and washed with ether. The combined organic extracts were concentrated under reduced pressure to give an oil, which was azeotropically distilled several times with carbon tetrachloride to furnish the crude *hemiacetal* (12) as a thermally unstable gum (2.25 g), $\nu_{max.}$ 3 440, 1 670, and 1 100—1 000 cm^{-1}, $\delta(CDCl_3)$ 1.08 (3 H, d, *J* 7 Hz, CH_3·CH), 1.2 (6 H, t, *J* 6 Hz, 2 × CH_3·CH_2·O), 1.72br (3 H, s, CH_3·C=C), 3.4 (3 H, s, MeO), 3.3—4.0br (6 H, m, CH_3·CH_2·O and C·CH_2·O·CH_2), 4.43 (1 H, m, CH·O), 4.57—4.93br (3 H, m), 5.3br (1 H, s, CH·C≡C), and 5.53 (1 H, m, CH=C) [Found: *m/e*, 350.210 6. $C_{20}H_{30}O_5$ (*M* − H_2O) requires 350.209 3].

6,6-*Diethoxy*-2-(2-*hydroxy*-1-*methoxymethoxymethyl*-4-*methylcyclohex*-3-*enyl*)*hex*-4-*yn*-3-*ol* (13).—A solution of the crude acetylenic hemiacetal (12) (2.1 g) and sodium borohydride (2 g) in ethanol (5 ml) and water (5 ml) was stirred at room temperature for 2 h. Dilution with water, followed by thorough extraction with ethyl acetate, washing of the combined extracts with water and brine, and drying gave, on concentration, the *diol* (13) as a thermally unstable oil (2.07 g), $\nu_{max.}$ 3 360, 1 674, and 1 200—1 050 cm^{-1}, $\delta(CDCl_3)$ 1.19 (3 H, d, *J* 7.5 Hz, CH_3·CH), 1.22 (6 H, t, *J* 6.5 Hz, 2 × CH_3·CH_2·O), 1.7br (3 H, s, CH_3·C=C), 1.5—2.46br (5 H, m), 3.37 (3 H, s, MeO), 3.2—4.1br (7 H, m), 4.59 (2 H, s, O·CH_2·O), 4.92br (1 H, s, CH·O), 5.32br (1 H, s, CH·C=C), and 5.59 (1 H, m, CH=C) [Found: *m/e*, 307.196 2. $C_{18}H_{27}O_4$(*M* − H_2O − C_2H_5O) requires 307.190 9].

(E)-6,6-*Diethoxy*-2-(2-*hydroxy*-1-*methoxymethoxymethyl*-4-*methylcyclohex*-3-*enyl*)*hex*-4-*en*-3-*ol* (14).—Sodium (320 mg, 13.9 mmol) was added to ammonia (100 ml; distilled from sodium) and the blue solution was stirred for 15 min. A solution of the diol (13) (1.7 g, 4.6 mmol) in tetrahydrofuran (10 ml) was added over 5 min, after which stirring was continued for a further 5 min, then absolute ethanol (0.5 ml) was added. Decolourisation ensued rapidly, and the ammonia was allowed to evaporate. The residue was partitioned between ethyl acetate and water, the aqueous layer was re-extracted with ethyl acetate, and the organic extracts were combined, washed with water and brine, and dried to give, on concentration *in vacuo*, the (*E*)-alkene (14) as a thermally labile gum (1.4 g). A sample purified by preparative t.l.c. (developing solvent 60% ethyl acetate–light petroleum) showed $\nu_{max.}$ 3 400, 1 675, and 1 200—1 100 cm^{-1}, $\delta(CDCl_3)$ 0.85 (3 H, d, *J* 7.5 Hz, CH_3·CH), 1.11 (6 H, t, *J* 7 Hz, 2 × CH_3·CH_2·O), 1.61br (3 H, s, CH_2·C=C), 3.27 (3 H, s, MeO), 4.5 (2 H, s, O·CH_2·O), 4.87 [1 H, d, *J* 3 Hz, C*H*$(OEt)_2$], 5.5br (2 H, m, 2 × CH=C), and 5.7 (1 H, dd, *J* 16 and 3 Hz, O·CH=CH·O). High resolution mass spectroscopy did not allow characterisation of this alkene.

4-*Hydroxy*-5,9-*dimethyl*-6-*methoxymethoxymethyl*-2-*oxabicyclo*-[4.4.0]*dec*-9-*en*-3-*ylethanal* (15).—A mixture of the (*E*)-olefin (14) (1.4 g), sodium acetate trihydrate (27 g), acetic acid (12 g), and water (20 ml) was stirred vigorously for 18 h, diluted with water, and extracted thoroughly with ether. The extracts were combined, washed well with dilute sodium hydrogen carbonate and brine, and dried. Removal of solvent *in vacuo* gave the bicyclic *hydroxy-aldehyde* (15) as a viscous oil (1.12 g). A sample purified by preparative t.l.c. (developing solvent 60% ethyl acetate–light petroleum) showed $\nu_{max.}$ 3 440, 2 740, 1 720, 1 674, and 1 150—1 100 cm^{-1}, $\delta(CDCl_3)$ 1.0 (3 H, d, *J* 7.5 Hz, CH_3·CH), 2.73 (2 H, m, CH_2·CHO), 3.37 (3 H, s, MeO), 4.5 (1 H, m, C=C·CH·O), 4.62 (2 H, s, O·CH_2·O), 5.33 (1 H, m, CH=C) and 10.7 (1 H, t, *J* 2.5 Hz, CHO) [Found: *m/e*, 266.151 4. $C_{15}H_{22}O_4$ (*M* − CH_3CHO) requires 266.151 8].

5,9-*Dimethyl*-6-*methoxymethoxymethyl*-4-*oxo*-2-*oxabicyclo*-[4.4.0]*dec*-9-*en*-3-*enylacetic Acid* (16).—A solution of the hydroxy-aldehyde (15) (1.12 g) in acetone (10 ml) was treated with Jones reagent at 0 °C in the usual manner for 0.75 h. The mixture was poured on to a slight excess of saturated aqueous sodium hydrogen carbonate, and extracted with ether. The extract was discarded. The basic solution was carefully acidified with N-hydrochloric acid, and extracted with ethyl acetate (2 × 50 ml). The combined organic extracts were washed with brine, dried, and concentrated *in vacuo* to give the oxo-acid (16) as an unstable gum. This was treated immediately with diazomethane to give the stable *methyl ester* (17), which on preparative t.l.c. (developing solvent 75% ether–light petroleum) was obtained as prisms (334 mg), m.p. 52—55°, $\nu_{max.}$ (Nujol), 1 735, 1 720, 1 670, 1 150, and 925 cm^{-1}, $\delta(CDCl_3)$ 1.0 (3 H, d, *J* 7 Hz, CH_3·CH), 1.73br (3 H, s, CH_3·C=C), 1.88—2.1br (2 H, m, CH_2·C=C), 2.49 (1 H, A of ABX, J_{AB} 17, J_{AX} 7 Hz, C*H*·CO_2Me), 2.71 (1 H, q, *J* 7 Hz, CO·C*H*·CH_3), 2.89 (1 H, B of ABX, J_{BA} 17, J_{BX} 7 Hz, C*H*·CO_2Me), 3.27 and 3.34 (2 H, ABq, J_{AB} 9 Hz, C·CH_2·O), 3.28 (3 H, s, MeO), 4.47br [2 H, t, CO·C*H*·CH_2 and C=C·CH·O (obscured)], 4.5 (2 H, s, O·CH_2·O), and 5.48 (1 H, m, CH=C) (Found: M^+, 326.172 1. $C_{17}H_{26}O_6$ requires *M*, 326.172 9).

9-*Methoxymethoxymethyl*-8,12-*dimethyl*-2,6-*dioxatricyclo*-[$7.4.0^{3,7}$]*trideca*-7,12-*dien*-5-*one* [(18), (19)].—A solution of the oxo-ester (17) (334 mg, 1 mmol) in methanol (4 ml) and sodium hydroxide solution (10 ml; 4N) was stirred for 3 h at 50 °C, cooled, then extracted with ether. The remaining basic aqueous layer was acidified with N-sulphuric acid, then saturated with sodium chloride and thoroughly extracted with ethyl acetate; these organic extracts were combined, washed with brine, and dried. Removal of solvent gave the unstable oxo-acid (16) as an oil (318 mg), which was used directly in the next step.

The oxo-acid (16) (318 mg, 1 mmol) was heated under reflux with acetic anhydride (10 ml) and anhydrous sodium acetate (240 mg, 3 mmol) for 2 h in nitrogen. The solution was then concentrated *in vacuo* three times with toluene, and the residue purified directly by preparative t.l.c. (developing solvent 40% ethyl acetate–light petroleum). A difficult separation afforded two compounds, assigned the epimeric structures (18) and (19); the proportions of these were variable. In the case at hand, the less polar *enol lactone* was obtained as an oil (81.6 mg), $\nu_{max.}$ 1 810, 1 725, 1 670, 1 250—1 000, 970, and 860 cm^{-1}, $\delta(CDCl_3)$ 1.62 (3 H, d,

J 2 Hz, CH_3·C=C·O), 1.85br (3 H, s, CH_3·C=C), 2.55 (1 H, A of ABX, J_{AB} 16, J_{AX} 10 Hz, CH·CO·O), 2.72 (1 H, B of ABX, J_{BA} 16, J_{BX} 7 Hz, CH·CO·O), 3.35 (3 H, s, MeO), 3.41 and 3.6 (2 H, ABq, J_{AB} 9 Hz, C·CH_2·O), 4.15br (1 H, C=CH·C*H*·O), 4.62 (2 H, s, O·CH_2·O), 4.65 (1 H, m, C=C·CH·O), and 5.3 (1 H, m, CH=C) (Found: M^+, 294.146 4. $C_{16}H_{22}O_5$ requires M, 294.146 5).

The more polar *enol lactone* was also obtained as an oil (47.5 mg), $\nu_{max.}$ 1 810, 1 730, 1 675, 1 130, 1 050, 960, and 870 cm^{-1}, $\delta(CDCl_3)$ 1.66 (3 H, d, J 2 Hz, CH_3·C=C·O), 1.68br (3 H, s, CH_3·C=C), 2.57 (1 H, A of ABX, J_{AB} 17.5, J_{AX} 9.5 Hz, CH·CO·O), 2.77 (1 H, B of ABX, J_{BA} 17.5, J_{BX} 11.5 Hz), 3.4 (3 H s, CH_3·O), 3.42 and 3.52 (2 H, ABq, J_{AB} 10 Hz), 4.15 1 H, C=CH·C*H*·O), 4.6 (2 H, s, O·CH_2·O), 4.65 (1 H, m, C=C·CH·O), and 5.6 (1 H, m, CH=C) (Found: M^+, 294.146 5).

Attempted Reductive Cyclisations of the Enol Lactones (18) *and* (19).—These experiments were performed on each separate epimer, and also on the epimeric mixtures originally obtained.

(*a*) To a stirred suspension of lithium hydridotri-t-butoxyaluminate [from lithium aluminium hydride (3.3 mg, 0.086 mmol) and t-butyl alcohol (17.7 mg, 0.24 mmol)] in ether (2 ml) at −78 °C in an atmosphere of nitrogen was added a solution of the enol lactone (18) or (19) (18 mg, 0.061 mmol) in ether (1 ml). The cooling bath was removed, and stirring was continued for a further 45 min; the mixture was then treated dropwise with saturated aqueous sodium sulphate, and the granular precipitate was filtered off and washed with ether. The combined organic extracts were concentrated *in vacuo*.

(*b*) To a stirred solution of the enol lactone (18) or (19) (53 mg, 0.18 mmol) in tetrahydrofuran (5 ml) at −78 °C in nitrogen was added di-isobutylaluminium hydride (0.3 ml; 0.9M in hexane; 0.27 mmol), and stirring continued for 30 min. The cooling bath was removed, and stirring continued for a further 2.5 h; the mixture was then poured on to brine, and extracted with ethyl acetate. The organic extract was washed with brine, dried, and concentrated *in vacuo*.

In each case, the products consisted of varying amounts of starting enol lactone, the oxo-aldehyde (21) and its two reduction products, the hydroxy-ketone (22), and the hydroxy-aldehyde (15). No crude reaction mixture, nor any of the individual components, showed the high i.r. carbonyl stretching frequency, $\nu_{max.}$ 1 760 cm^{-1}, associated with bicyclo[3.2.1]octan-8-ones, nor did n.m.r. spectroscopy indicate any grounds for optimism.

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