Ether formation by intramolecular attack of hydroxy on cyclopropyl rings: a model for the formation of the tetrahydrofuran moiety in the diterpenoid, harringtonolide

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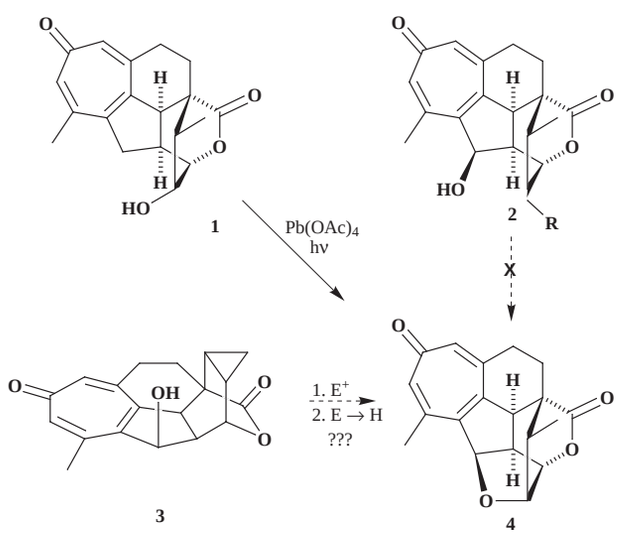
The electrophile induced opening of a cyclopropyl ring with concerted intramolecular addition of a hydroxymethyl group in a number of tricyclo[3.2.2.0^{2,4}]nonene alcohol derivatives has been studied with a view to establishing a procedure for the formation of the tetrahydrofuran ring in the diterpenoid tropone 4. Treatment of the tricyclo[3.2.2.0^{2,4}]nonene diol 15 with H_3PO_4, for example, furnishes diether 19, the structure of which has been determined by X-ray crystallography. This conversion is shown to involve sequential 1,2-bond shifts, rather than direct attack, however, while acid treatment of the saturated diol 16 leads to rearrangement of the carbon skeleton. Nevertheless, mercuric induced opening of the cyclopropyl ring in either 15 or 16 proceeds with direct ether formation as planned and in good yield; mercury is removed from the products by simple stannane reduction.

Introduction

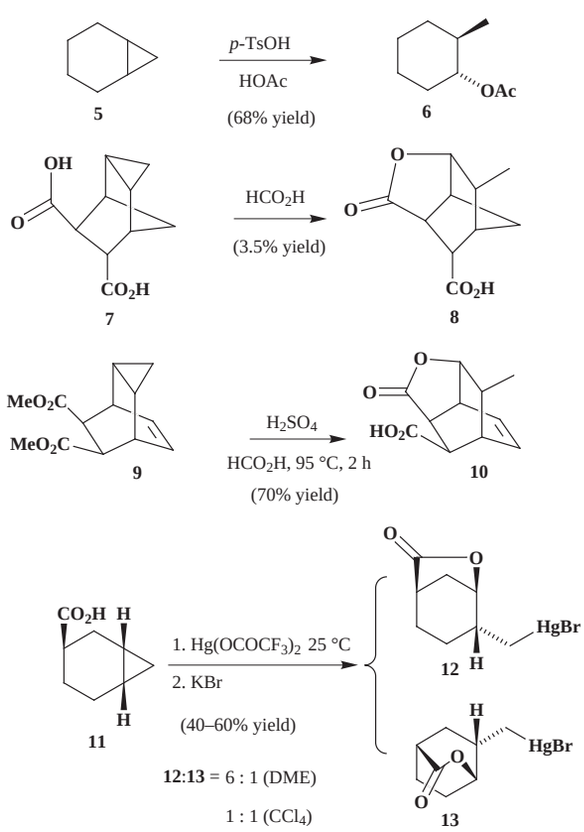
We have recently described the total synthesis[1] of the unusual diterpenoid tropone, hainanolidol (**1**), isolated from the bark of *Cephalotaxus hainanensis*.[2] The preparation of **1** also constitutes a formal synthesis of harringtonolide (**4**), isolated from the same source, and from seeds of *C. harringtonia*,[3] since **1** may be converted into **4** by means of a transannular oxidation with lead tetraacetate.[4] While **1** is biologically inactive, **4** shows promising antiviral and antineoplastic properties, so we have continued to explore alternative approaches to **4** that might be more efficient.[5] It has been possible to prepare lactone **2** (R = H), but the incorporation of a leaving group as in **2** (R = OMs), for example, that would assist in the formation of the 5-membered ether ring, has thus far been frustrated by complications arising from the manipulation of the necessarily densely functionalised C-ring.[6] We have therefore attempted to devise an alternative sequence that would avoid these problems. One such approach, based on the electrophile induced opening of a cyclopropyl ring with intramolecular attack of the D-ring hydroxy (**3** ⟶ **4**), is indicated in Scheme 1. Our studies on a model system designed to test this approach are described in this paper.



Scheme 1

Discussion

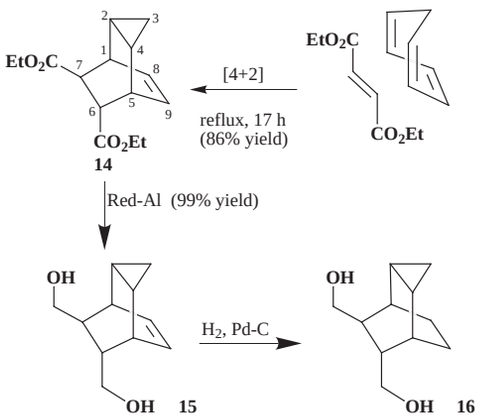
It was not clear from literature precedents (Scheme 2) whether the conversion of **3** into **4** would be successful. Although bicyclo[4.1.0]heptane (**5**) undergoes solvolysis in acetic acid to furnish *trans*-2-methylcyclohexanyl acetate (**6**) in 75% yield,[7] **8** was formed in only 3.5% yield by heating **7** in formic acid.[8] Treatment of tricyclic ester **9** in concentrated H_2SO_4 and formic acid, however, afforded a 70% yield of lactone **10**,[9] while bicyclic acid **11** was converted into lactone **12** in fair yield on



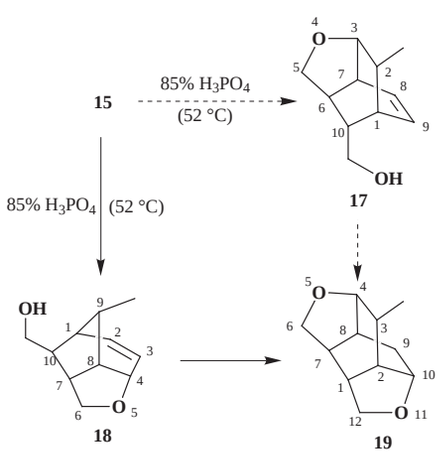
Scheme 2

treatment with mercuric trifluoroacetate, although the regiochemistry of attack was surprisingly solvent dependent.[10]

For our model studies, we chose the tricyclic diols **15** and **16**, which were readily assembled from cycloheptatriene and diethyl fumarate as outlined in Scheme 3.[11] When **15** was heated in 85% H_3PO_4 for 16 hours at 52 °C, a 1:1 mixture of **19** and what we assumed to be the hydroxy alkene **17** was obtained in 80% yield (Scheme 4). On further heating, the proportion of **19** was increased to 4:1, while resubmission of the hydroxy alkene to the cyclisation conditions also afforded additional **19**. The structure of **19** was evident from NMR analysis, but was confirmed by single crystal X-ray crystallography. Although these results were very encouraging, we were surprised that cyclisation onto the alkene bond appeared to be slower than substitution of the cyclopropyl ring. This concern was reinforced when it was found that H_3PO_4 treatment of the saturated diol **16**, afforded no products that corresponded to **17**, but instead, only compounds in which the methyl group was attached to a fully substituted carbon atom (see below).

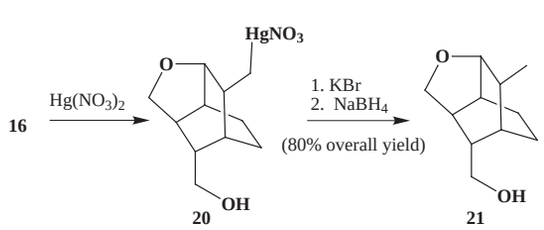


Scheme 3



Scheme 4

With $Hg(NO_3)_2$ as the initiating electrophile, however, **16** underwent cyclisation to **20** in high yield, with subsequent reduction affording the methyl carbinol **21** (Scheme 5). In order to elucidate the puzzling behaviour of the ene diol **15**, cyclisation was induced with $Hg(NO_3)_2$ and, after reduction with sodium borohydride, a 3:1 mixture of hydroxy ether **22** with diether **19** was obtained (Scheme 6), this result being consistent with the general expectation of higher reactivity for the alkene bond towards electrophiles. In one experiment, however, when commercial rather than HPLC grade acetonitrile was employed as the reaction solvent, the reaction did not proceed until a very large excess of $Hg(NO_3)_2$ was added. Under these conditions, the formation of **22** was not observed, but rather a 3:2 mixture of **19** with **17**, the structure of the former product being confirmed by hydrogenation to **21**.



Scheme 5

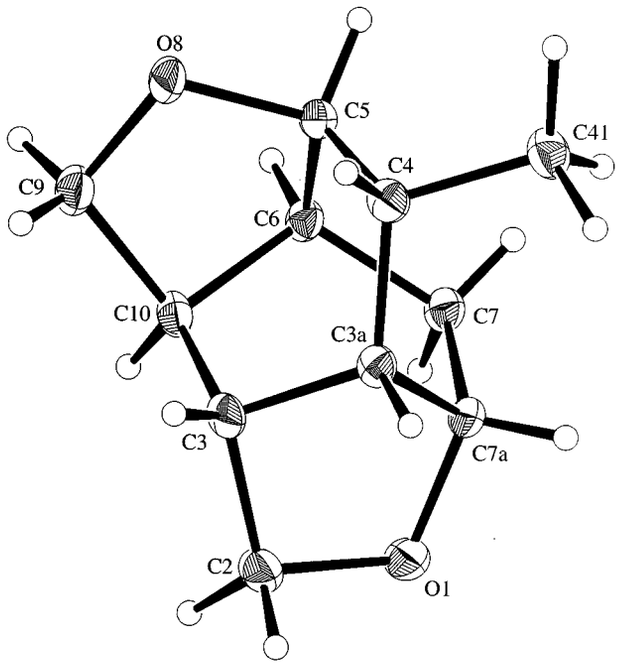
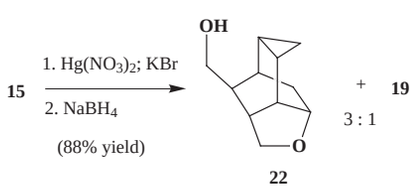
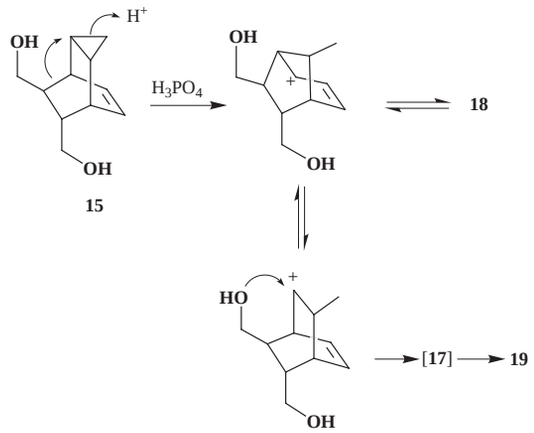


Fig. 1 ORTEP View of diether **19**. Thermal ellipsoids enclose 20% probability levels.

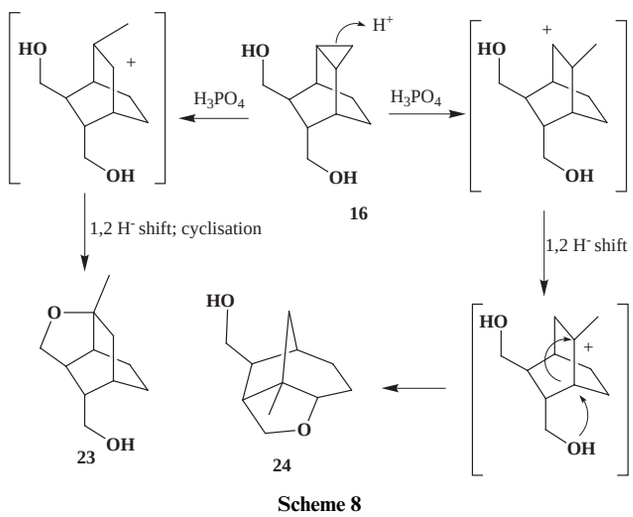


Scheme 6

On closer examination, we determined that the correct structure for the hydroxy alkene formed in the acid catalysed treatment of **15** was not **17**, but **18**. Hydrogenation of **18** afforded a product in which the two methylene carbon resonances were observed at δ 23.3 and 25.5, in sharp contrast to the significantly higher field shifts (δ 12.1 and 15.1) found for C8 and C9 in **21**. Clearly, the two compounds had quite distinct skeletons. Analysis of the ^{1}H NMR spectrum revealed the allylic nature of the ether ring and it was thus possible to deduce the correct structure as **18**. It can be envisaged that this compound would be formed if migration of either C6 or C7 was coupled with opening of the cyclopropyl ring, followed by capture of the resulting allylic cation by the *syn* hydroxymethyl group as outlined in Scheme 7. The *syn* relationship between the 4-methyl group and H4 in **18** was revealed by a NOE effect. By comparison of the NMR spectra of dihydro **18** and of **21** with those of the products formed from H_3PO_4 treatment of the saturated diol **16**, and taking into account the most likely mechanistic pathways (Scheme 8), it was possible to arrive at the probable structures for these compounds, namely **23** (34% yield) and **24** (10% yield).



Scheme 7



Scheme 8

In conclusion, the prospect of forming the tetrahydrofuran moiety in harringtonolide by a process equivalent to **16** ⟶ **21** appears to be excellent. Accordingly, we have initiated the synthesis of an appropriate substrate (either **3** or a close analogue) with a view to the preparation of **4** by such a route.

Experimental

Infrared spectra were recorded on $CDCl_3$ solutions in 0.25 mm NaCl cells on a Perkin-Elmer 683 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini 300 and VXR 300 spectrometers. Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. For proton spectra recorded in deuteriochloroform, the residual peak of $CHCl_3$ was used as the internal reference (7.26 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for ^{13}C spectra. Distortionless enhancement by polarisation transfer (DEPT) and the attached proton test (APT) were used in the assignment of carbon spectra. Low resolution EI mass spectra (70 eV) were recorded on a VG Micromass 7070F double focussing mass spectrometer; the relative intensities of peaks are expressed as percentages of the base peak. Flash chromatography was carried out on Merck Kieselgel 60.

Diethyl (1*RS*,2*RS*,4*SR*,5*SR*,6*SR*,7*SR*)-tricyclo[3.2.2.0^{2,4}]non-8-ene-6,7-dicarboxylate 14

A mixture of cycloheptatriene (13 cm^3, 0.125 mol) and diethyl fumarate (4.75 cm^3, 0.029 mol) was heated at reflux for 41 h. The excess of cycloheptatriene was then removed by rotary evaporation and the residue subjected to Kugelrohr distillation to afford adduct **14** (5.2 g, 68%), bp 130–150 °C/0.1 mm Hg (Found: C, 68.3; H, 8.0. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%); ν_{max}(film)/cm^{-1} 3052, 2980, 2906, 1730, 1302, 1275, 1242, 1186 and 1036; δ_H(300 MHz; $CDCl_3$) 0.05–0.13 (2 H, m, 3-H), 0.83–0.90 (1 H, m), 1.00–1.09 (1 H, m), 1.21 (3 H, t, *J* 7.1, Me), 1.27 (3 H, t, *J* 7.1, Me), 2.90 (1 H, br dd, *J* 4.8 and 2.6, 6-H or 7-H), 3.19–3.28 (3 H, m), 4.09 (2 H, q, *J* 7.1, CO_2CH_2), 4.15–4.20 (2 H, m, CO_2CH_2), 5.70 (1 H, m, 8-H or 9-H) and 5.87 (1 H, m, 8-H or 9-H); δ_C(75 MHz; $CDCl_3$) 2.9 (C3), 6.1, 9.6 (C2, C4), 14.2, 14.3 (2 × Me), 33.9, 34.1 (C1, C5), 45.9, 46.7 (C6, C7), 60.6, 60.7 (2 × CH_2O), 127.4, 129.4 (C8, C9) and 173.6, 174.1 (2 × CO_2Et); *m*/*z* 265 (M$^+$, 70%), 219 (85), 190 (58), 173 (25), 161 (19), 145 (55), 127 (40), 117 (69), 92 (100), 77 (21) and 65 (24).

(1*RS*,2*RS*,4*SR*,5*SR*,6*SR*,7*SR*)-7-Hydroxymethyltricyclo-[3.2.2.0]non-8-en-6-ylmethanol 15

A solution of diester **14** (15.0 g, 56.7 mmol) in benzene (450 cm^3) was cooled to 0 °C and treated with Red-Al (50.0 cm^3 of a 3.4 M solution in toluene, 170 mmol) over a period of 90 min. The mixture was stirred at room temp for 18 h before the addition of EtOH (30 cm^3), saturated aq. NH_4Cl (30 cm^3) and H_2O (300 cm^3). The solution was extracted with EtOAc and the combined organic layers washed with brine, dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford diol **14** as a colourless solid (10.0 g, 98%), mp 87 °C (Found: C, 73.3; H, 9.25. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%); ν_{max}(KBr)/cm^{-1} 3238, 3046, 3016, 2939, 2868, 2843, 1101, 1086, 1063, 1035 and 1005; δ_H(300 MHz; $CDCl_3$) 0.05 (1 H, td, *J* 7.4 and 5.3, 3-H), 0.15 (1 H, dt, *J* 5.3 and 3.6, 3-H′), 0.82–0.90 (1 H, m), 0.94–1.01 (1 H, m), 1.42 (1 H, dtd, *J* 9.8, 5.0 and 2.1, 6-H or 7-H), 1.68 (1 H, dtd, *J* 9.8, 5.0 and 2.1, 6-H or 7-H), 2.70–2.77 (2 H, m, 1-H, 5-H), 2.94 (2 H, br s, 2 × OH), 3.15 (1 H, t, *J* 9.8, C*H*H′OH), 3.59 (1 H, dd, *J* 9.8 and 5.0, C*H*H′OH), 3.68 (1 H, t, *J* 9.8, CH*H*′OH), 3.77 (1 H, dd, *J* 9.8 and 5.4, CH*H*′OH), 5.63 (1 H, br t, *J* 7.1, 8-H or 9-H) and 5.86 (1 H, br t, *J* 7.1, 8-H or 9-H); δ_C(75 MHz; $CDCl_3$) 2.3 (C3), 5.6, 10.2 (C2, C4), 33.1, 33.4 (C1, C5), 46.2, 47.2 (C6, C7), 65.5, 67.1 (2 × CH_2O) and 126.7, 130.1 (C8, C9); *m*/*z* 180 (M$^+$, 2%), 162 (3), 149 (10), 131 (89), 117 (61), 105 (43), 92 (100), 77 (17) and 65 (17).

(1*RS*,2*RS*,4*SR*,5*SR*,6*SR*,7*SR*)-7-Hydroxymethyltricyclo-[3.2.2.0]nonan-6-ylmethanol 16

A solution of alkene **15** (1.00 g, 5.55 mmol) in EtOAc (50 cm^3) was treated with 10% Pd on carbon and the mixture stirred overnight at room temp. under an atmosphere of hydrogen. The suspension was then filtered through Celite and the filtrate concentrated to afford diol **16** (833 mg, 82%), mp 103 °C (from Et_2O) (Found: C, 72.15; H, 10.25. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%); ν_{max}(KBr)/cm^{-1} 3232, 3013, 2937, 2909, 2869, 1079, 1050, 1029 and 1008; δ_H(300 MHz; $CDCl_3$) 0.33 (1 H, td, *J* 7.7, 7.7 and 5.9, 3-H), 0.65 (1 H, dt, *J* 5.9, 3.6 and 3.6, 3-H′), 0.84 (1 H, m), 0.95 (1 H, m), 1.14–1.45 (4 H, m), 1.56–1.74 (2 H, m), 1.86–1.94 (2 H, m), 3.52 (2 H, br s, 2 × OH), 3.52–3.64 (2 H, m, 2 × C*H*H′OH), 3.66 (1 H, dd, *J* 9.8 and 4.8, CH*H*′OH), 3.74 (1 H, dd, *J* 9.8 and 5.0, CH*H*′OH); δ_C(75 MHz; $CDCl_3$) 3.5 (C3), 10.3, 15.7 (C2, C4), 18.9 (C9), 25.3 (C8), 27.3, 27.4 (C1, C5), 45.7, 47.6 (C6, C7) and 67.1, 67.3 (2 × CH_2O); *m*/*z* 182 (M$^+$, 6%), 164 (76), 151 (12), 146 (21), 133 (56), 119 (31), 105 (61), 91 (84), 79 (100), 67 (57).

Cyclisation of diol 15 in phosphoric acid: preparation of (1*RS*,2*RS*,3*RS*,4*SR*,7*RS*,8*SR*,10*SR*)-3-methyl-5,11-dioxa-tetracyclo[5.5.0.0^{2,10}.0^{4,8}]dodecane 19

A solution of alkene **15** (1.00 g, 5.55 mmol) in 100% H_3PO_4 (100 cm^3) was heated at 50 °C under an atmosphere of nitrogen for 7 h. The mixture was then poured into ice–water (700 cm^3) and extracted with CH_2Cl_2 (3 × 800 cm^3). The combined organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a red oil. Chromatography on silica gel (hexane–EtOAc 2:1) afforded diether **19** (340 mg, 34%) as a solid, mp 71 °C

(Found: C, 73.1; H, 9.2. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%); ν_{max}(KBr)/cm^{-1} 2961, 2939, 2915, 2893, 2861, 2847, 1080, 1042, 1012, 998, 976 and 950; δ_H(300 MHz; $CDCl_3$) 0.99 (3 H, d, *J* 7.7, 3-Me), 1.63 (1 H, dd, *J* 15.3 and 4.0, 9-H), 1.82–1.93 (2 H, m), 2.02–2.05 (4 H, m), 3.60–3.70 (3 H, m), 3.89–3.93 (2 H, m) and 4.10 (1 H, br t, *J* 5.8, 5-H or 10-H); δ_C(75 MHz; $CDCl_3$) 18.6 (3-Me), 28.0 (C9), 33.3, 36.1, 39.3 (C2, C3, C8), 43.2, 43.8 (C1, C7), 71.8 (C10), 75.3, 75.6 (C12, C6) and 80.1 (C12); *m*/*z* 180 (M^+, 100%), 165 (13), 149 (23), 135 (22), 121 (37), 105 (40), 93 (51), 81 (43) and 69 (32).

Further elution gave (1RS,4SR,7RS,8SR,9SR,10SR)-(9-*Methyl*-5-*oxatricyclo*[5.2.1.0^{4,8}]*dec*-2-*en*-10-*yl*)*methanol* **18** (360 mg, 36%) as an oil (Found: C, 72.8; H, 9.3. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%; Found: M^+, 180.1152. $C_{11}H_{16}O_2$ requires M^+, 180.1150); ν_{max}(film)/cm^{-1} 3407, 3028, 2930, 2874, 1071, 1043, 1020 and 1005; δ_H(300 MHz; $CDCl_3$) 1.03 (3 H, d, *J* 6.6, 9-Me), 1.90 (1 H, dt, *J* 1.8 and 8.0), 2.16–2.27 (3 H, m), 2.34 (1 H, m), 2.46 (1 H, m), 3.48–3.53 (3 H, m, C*H*$_2$OH + C*H*H′O), 4.12 (1 H, t, *J* 8.6, C*H*H′O), 4.54 (1 H, br dd, $J_{4,8}$ 6.0 and $J_{4,3}$ 3.6, 4-H), 5.52 (1 H, ddd, $J_{3,2}$ 9.4, $J_{3,4}$ 3.6 and $J_{3,1}$ 1.2, 3-H) and 6.00 (1 H, ddd, $J_{2,3}$ 9.4, $J_{2,1}$ 7.0 and $J_{2,4}$ 1.3, 2-H); δ_C(75 MHz; $CDCl_3$) 12.4 (9-Me), 37.9, 41.2 (C8, C1), 44.6, 50.4 (C7, C10), 58.3 (C9), 65.1 (C10), 73.6 (C6), 76.7 (C4) and 125.0, 134.5 (C2, C3); *m*/*z* 180 (M^+, 45%), 162 (18), 149 (52), 131 (29), 119 (77), 105 (44), 91 (100), 79 (59), 69 (62) and 57 (28).

Hydrogenation of hydroxy alkene 18: (1*RS*,4*SR*,7*RS*,8*SR*,9*SR*,10*SR*)-(9-methyl-5-oxatricyclo[5.2.1.0^{4,8}]decan-10-yl)methanol

A solution of alkene **18** (150 mg, 0.84 mmol) in EtOAc (75 cm^3) was treated with 10% Pd on carbon (40 mg, 0.038 mmol) and the mixture stirred at room temp. under an atmosphere of hydrogen for 16 h. The catalyst was then removed by filtration and the filtrate concentrated to dryness. Chromatography on silica gel (hexane–EtOAc 1 : 1) afforded the title compound (112 mg, 74%) as an oil (Found: M^+, 182.1310. $C_{11}H_{18}O_2$ requires *M*, 182.1307); ν_{max}(film)/cm^{-1} 3385, 2928, 2873 and 1045; δ_H(300 MHz; $CDCl_3$) 1.11 (3 H, d, *J* 7.1, 9-Me), 1.47–1.58 (2 H, m), 1.69 (1 H, td, *J* 7.9 and 3.6), 1.75–1.82 (2 H, m), 1.94 (1 H, tdd, *J* 11.3, 6.6 and 1.2), 2.02–2.11 (3 H, m), 2.46 (1 H, m), 3.49–3.52 (2 H, m, 10-C*H*$_2$OH), 3.79 (1 H, dd, *J* 8.4 and 1.4, 6-C*H*H′O), 3.84 (1 H, dd, *J* 8.4 and 4.8, 6-CH*H*′O) and 4.26 (1 H, ddd, $J_{4,3}$ 8.4, $J_{4,8}$ 5.7 and $J_{4,3}$ 1.8, 4-H); δ_C(75 MHz; $CDCl_3$) 13.3 (9-Me), 23.3 (t), 25.5 (t), 35.0 (d), 39.1 (d), 47.1 (d), 49.1 (d), 56.5 (d), 66.3 (t), 73.4 (t) and 76.5 (d); *m*/*z* 182 (M^+, 49%), 164 (33), 151 (40), 134 (82), 107 (69), 93 (92), 79 (72), 69 (100) and 55 (61).

Cyclisation of diol 16 in phosphoric acid

A solution of diol **16** (400 mg, 2.19 mmol) in 85% H_3PO_4 (40 cm^3) maintained under a nitrogen atmosphere was heated at 52 °C for 16 h. The mixture was then cooled to room temp., poured into saturated aq. $NaHCO_3$ (500 cm^3) and treated with solid $NaHCO_3$ until the pH measured 6. The solution was then extracted with Et_2O (2 × 200 cm^3) and EtOAc (1 × 200 cm^3) and the combined organic layers washed with brine (1 × 100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel (hexane–EtOAc 2 : 1) afforded two products:

24 (40 mg, 10%) (Found: C, 72.2; H, 9.9. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%); ν_{max}(film)/cm^{-1} 3386, 2929, 2867, 1086 and 1046; δ_H(300 MHz; $CDCl_3$) 1.14 (3 H, s, Me), 1.34–1.53 (4 H, m), 1.57–1.67 (3 H, m), 1.77 (1 H, br s, OH), 1.79–1.89 (1 H, m), 1.99 (1 H, br dd, *J* 8.8 and 4.5), 3.47–3.53 (2 H, m, 10-C*H*$_2$OH), 3.76 (2 H, br d, *J* 8.3, 6-C*H*H′O), 3.81 (1 H, dd, *J* 8.3 and 3.5, 6-CH*H*′O) and 3.89 (1 H, m, 4-H); δ_C(75 MHz; $CDCl_3$) 24.07 (8-Me), 24.1, 26.8 (C2, C3), 34.4 (C1), 36.2 (C9), 50.1 (C8), 53.4, 58.6 (C7, C10), 66.5 (10-CH_2OH), 71.9 (C6) and 85.7 (C4); *m*/*z* 182 (M^+, 21%), 164 (16), 151 (24), 134 (100), 121 (46), 107 (78), 93 (77), 83 (69) and 79 (45).

23 (136 mg, 34%) (Found: C, 73.0; H, 10.4. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%; Found: M^+, 182.1312. $C_{11}H_{18}O_2$ requires *M*, 182.1307); ν_{max}(film)/cm^{-1} 3407, 2926, 2869, 1058 and 1013; δ_H(300 MHz; $CDCl_3$) 1.28 (3 H, s, Me), 1.45–1.82 (10 H, m), 2.12 (1 H, br s, OH), 3.38 (1 H, d, *J* 7.4, 5-H), 3.62 (2 H, d, *J* 8.1, 10-C*H*$_2$OH), 3.76 (1 H, dd, *J* 7.4 and 4.0, 5-H′); δ_C(75 MHz; $CDCl_3$) 15.9, 19.3 (C8, C9), 24.6 (2-Me), 24.8, 39.9, 40.5, 46.1 (C1, C6, C7, C10), 44.9 (C2), 46.1 (d), 65.6 (10-CH_2OH), 73.9 (C5) and 80.3 (C3); *m*/*z* 182 (M^+, 76%), 164 (47), 151 (46), 134 (76), 121 (80), 107 (75), 93 (98), 79 (100), 69 (70) and 55 (55).

(1*RS*,2*RS*,3*SR*,6*RS*,7*SR*,10*SR*)-(2-Methyl-4-oxatricyclo-[4.3.1.0^{3,7}]decan-10-yl)methanol 21

Diol **16** (120 mg, 0.66 mmol) was dissolved in dimethoxyethane (10 cm^3) and treated with acetonitrile (25 cm^3) (dropwise) and $Hg(NO_3)_2$·H_2O (300 mg, 0.88 mmol). The mixture was stirred at room temp. for 2.5 h before the addition of 2 M KBr (2 cm^3). Stirring was continued for a further 30 min and then the solution diluted with EtOAc and washed with 3% aq. $KHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless gum. This was dissolved in THF (20 cm^3) and 3 M NaOH (20 cm^3), and treated with $NaBH_4$ (2.0 cm^3 of a 0.53 M solution in 3 M NaOH), resulting in precipitate formation. The mixture was then extracted with ether and the combined organic layers washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography on silica gel (hexane–EtOAc 1 : 1) afforded carbinol **21** (75 mg, 63%) as an oil which solidified on standing, mp 52–54 °C (Found: C, 72.2; H, 10.0. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%); ν_{max}(film)/cm^{-1} 3406, 2920, 2869, 1062 and 1037; δ_H(300 MHz; $CDCl_3$) 0.99 (3 H, d, *J* 7.2, 2-Me), 1.27–1.40 (2 H, m), 1.51–1.66 (5 H, m), 1.70 (1 H, m), 1.88 (1 H, m), 2.16 (1 H, br s, OH), 3.45 (1 H, d, *J* 7.3, 5-H), 3.57 (1 H, br d, *J* 5.3, 3-H), 3.65 (2 H, d, *J* 7.8, 10-C*H*$_2$OH) and 3.73 (1 H, dd, *J* 7.3 and 3.8, 5-H′); δ_C(75 MHz; $CDCl_3$) 12.1, 15.1 (C8, C9), 17.1 (2-Me), 28.7, 35.4, 37.9, 41.7, 47.5 (C1, C2, C6, C7, C10), 65.3 (10-CH_2OH), 75.5 (C5) and 81.3 (C3); *m*/*z* 182 (M^+, 100%), 164 (16), 149 (25), 134 (39), 121 (22), 107 (11), 93 (22), 79 (14), 69 (10) and 55 (11).

(1*RS*,2*SR*,3*SR*,5*SR*,6*RS*,8*SR*,11*SR*)-9-Oxatetracyclo-[4.4.1.0^{2,8}.0^{3,5}]undecan-11-ylmethanol 22

Diol **15** (500 mg, 2.77 mmol) in dimethoxyethane (42 cm^3) and acetonitrile (HPLC grade, 105 cm^3) was treated with $Hg(NO_3)_2$·H_2O (1.20 g, 3.50 mmol) and the mixture stirred for 4 h at room temp. A solution of 2 M KBr (8.3 cm^3) was added, and the resulting suspension poured into EtOAc. After washing with 3% aq. $KHCO_3$ (2 × 100 cm^3), brine (100 cm^3), the organic layer was dried ($MgSO_4$) and concentrated to dryness. Reduction of the resultant organomercurial intermediate [dissolved in THF (170 cm^3) and 3 M NaOH (170 cm^3)] with $NaBH_4$ (340 mg in 18 cm^3 of 3 M NaOH) afforded, after chromatography on silica gel (hexane–EtOAc 2 : 1), starting material **15** (42 mg, 8% recovery), diether **19** (84 mg, 18% at 92% conversion) and hydroxy ether **22** (231 mg, 50% at 92% conversion) (Found: M^+, 180.1149. $C_{11}H_{16}O_2$ requires *M*, 180.1150); ν_{max}(film)/cm^{-1} 3386, 3011, 2933, 2873, 1087, 1067, 1033, 1004 and 987; δ_H(300 MHz; $CDCl_3$) 0.25 (1 H, dt, $J_{4\beta,4\alpha}$ 5.9, $J_{4\alpha,3}$ 3.7 and $J_{4\alpha,5}$ 3.7, 4α-H), 0.36 (1 H, td, $J_{4\beta,3}$ 7.8, $J_{4\beta,5}$ 7.8 and $J_{4\beta,4\alpha}$ 5.9, 4β-H), 0.85–1.03 (2 H, m, 3-H, 5-H), 1.15 (1 H, m, 7-H), 1.66–1.82 (3 H, m), 1.80 (1 H, br s, OH), 2.08 (1 H, m), 2.30 (1 H, m), 3.56 (1 H, d, *J* 7.7, 7-C*H*H′O), 3.66 (1 H, dd, *J* 10.4 and 7.6, 11-C*H*H′O), 3.77–3.85 (2 H, m, 6-CH*H*′O, 10-CH*H*′O) and 3.87 (1 H, br dd, *J* 7.1 and 5.5, 8-H); δ_C(75 MHz; $CDCl_3$) 5.1 (C4), 5.5, 8.3 (C3, C5), 23.1 (C6), 35.6 (C7), 36.7, 37.4 (C2, C11), 49.1 (C7), 64.7 (11-CH_2OH), 74.8 (C8) and 74.7 (C10); *m*/*z* 180 (M^+, 33%), 162 (21), 149 (28), 131 (35), 119 (71), 105 (55), 91 (100), 79 (92) and 69 (52).

(1*SR*,2*RS*,3*SR*,6*RS*,7*SR*,10*SR*)-(2-Methyl-4-oxatricyclo-[4.3.1.0^{3,7}]dec-8-en-10-yl)methanol 17

Diol **15** (700 mg, 3.88 mmol) in dimethoxyethane (58 cm^3) and

acetonitrile (commercial grade, 146 cm^3) was treated with $Hg(NO_3)_2 \cdot \frac{1}{2}H_2O$ (6.78 g, 20.3 mmol) and the mixture stirred for 20 h at room temp. A solution of 2 M KBr (47 cm^3) was added, the resulting suspension poured into EtOAc and the product processed as in the previous experiment. Chromatography on silica gel (hexane–EtOAc 1:1) gave diether **19** (184 mg, 26% yield), followed by hydroxy ether **17** (112 mg, 16%) (Found: C, 73.5; H, 9.3. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%); ν_{max}(film)/cm^{-1} 3406, 3049, 2928, 2870, 1067, 1037 and 990; δ_H(300 MHz; $CDCl_3$) 0.70 (3 H, d, *J* 7.3, 2-Me), 1.55 (1 H, dq, *J* 3.2, 7.3, 2-H), 1.62–1.70 (2 H, m), 2.58 (1 H, br s, OH), 2.45 (1 H, m), 2.80 (1 H, m), 3.25 (1 H, *A*BX, *J* 7.1, 10.4, 10-C*H*H′OH), 3.29 (1 H, A*B*X, *J* 8.4, 10.4, 10-CH*H*′OH), 3.45 (1 H, d, *J* 5.1, 3-H), 3.53 (1 H, d, *J* 7.6, 5-H), 3.75 (1 H, dd, *J* 4.0, 7.6, 5-H′) and 5.98–6.10 (2 H, m, 4-H, 9-H); δ_C(75 MHz; $CDCl_3$) 18.0 (2-Me), 36.6, 38.5, 41.4, 43.9, 50.7 (C1, C2, C6, C7, C10), 65.3 (10-CH_2OH), 74.1 (C5), 81.5 (C3), 126.1, 132.7 (C8, C9); *m*/*z* 180 (M^+, 60%), 149 (28), 135 (18), 118 (52), 105 (86), 91 (79), 79 (100), 71 (48), 65 (30) and 58 (34).

Crystal data for diether 19

$C_{11}H_{16}O_2$, $M = 180.25$, $T = 296(1)$ K, monoclinic, space group $P2_1/a$, $a = 11.237(1)$, $b = 7.611(2)$, $c = 11.704(2)$ Å, $\beta = 114.932(8)°$, $U = 907.7(3)$ $Å^3$, D_c ($Z = 4$) = 1.319 g cm^{-3}, $F(000) = 392$, μ(Cu-K_α) = 7.10 cm^{-1}, semi-empirical absorption correction; 1472 unique data ($2\theta_{max} = 120.1°$), 979 with $I > 3\sigma(I)$; $R = 0.046$, $wR = 0.050$, GOF = 2.98. Data were measured on a Rigaku AFC6R rotating anode diffractometer (graphite crystal monochromator, $\lambda = 1.541\ 80$ Å). Cell parameters were obtained using 25 accurately centered reflections in the range $50.71 < 2\theta < 77.56°$. Data acquisition utilised the ω-2θ scan technique. A semi-empirical absorption correction using azimuthal psi scans[12] was applied, resulting in transmission factors ranging from 0.87 to 1.00. Data were corrected for Lorentz and polarization effects. No decay correction was necessary.

Structure analysis and refinement. The structure was solved by direct methods[13] and expanded using Fourier techniques.[14] Non-hydrogen atoms were refined anisotropically while the rest were refined isotropically. Refinement was by full-matrix least-squares analysis on *F* using the TEXSAN Structure analysis Software of Molecular Structure Corporation.[15] The weighting scheme used was $w = [\sigma^2(F_o) + 0.000\ 16F_o^2]^{-1}$. The final difference synthesis revealed no peaks lying outside the range −0.21 to 0.19 e $Å^{-3}$. Computations were performed on a Silicon Graphics Power Challenge Supercomputer at the Australian National University. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC Web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/202.

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Paper 8/00099I
Received 5*th January* 1998
Accepted 26*th February* 1998