Novel Rearrangement of 2-α-Isopropyl-8-oxabicyclo[3.2.1]oct-6-ene Producing the Monoterpene 3-Hydroxyphellandral

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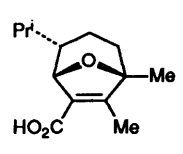
We describe a five-step synthesis of 2-α-isopropyl-8-oxabicyclo[3.2.1]oct-6-ene from 1,1,3,3-tetrabromo-4-methylpentan-2-one, and its unexpected rearrangement to yield *trans*-3-hydroxy-4-isopropylcyclohex-1-enecarbaldehyde (3-hydroxyphellandral).

We have previously described our initial attempts to prepare oxaanalogues **1** of the plant growth-promoting agent helminthosporal **2**.[1] In the event, the closest we came to achieving



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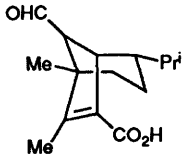

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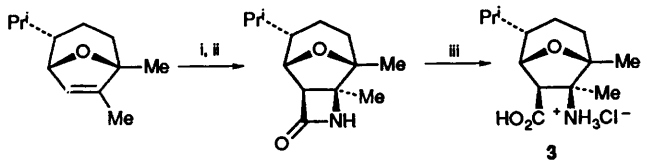
this goal, was the synthesis of the amino acid **3** *via* the route shown in Scheme 1. This compound showed some herbicidal



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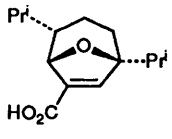
Scheme 1 *Reagents and conditions:* i, $ClSO_2NCO$–ether, −78 °C → room temp.; ii, aq. Na_2SO_3–ether, 0 °C → room temp. (40%); iii, 12% HCl (65%)

activity, and we were encouraged to attempt to prepare the simpler analogue **4** for biological evaluation. However, our efforts were frustrated by the propensity of the bicyclic alkene **5** to rearrange when treated with chlorosulfonyl isocyanate. This unexpected rearrangement is the subject of this paper.

The synthesis of the alkene **5** proceeded without problems (Scheme 2). Reaction of 1,1,3,3-tetrabromo-4-methylpentan-2-



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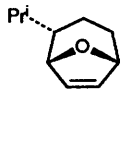

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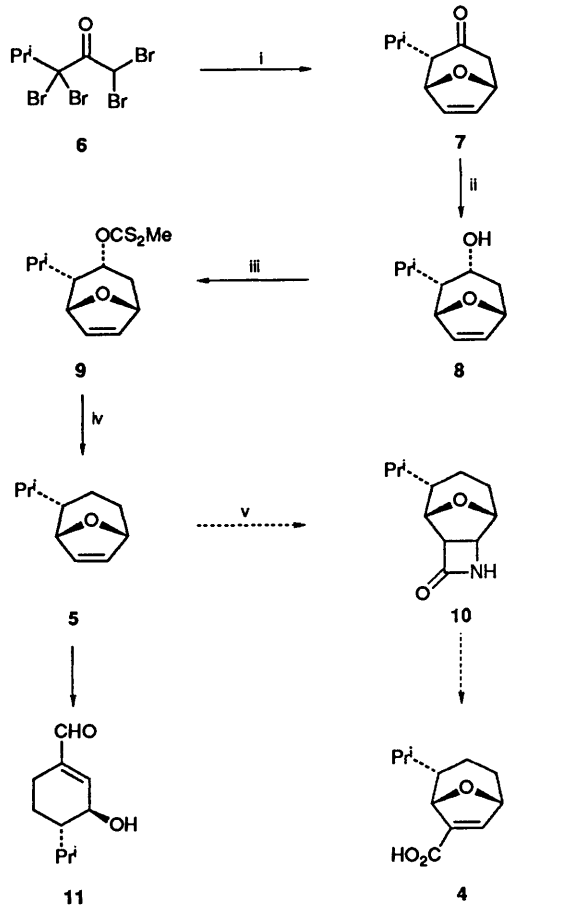
one **6** with furan in the presence of diethylzinc (followed by reductive removal of two bromine atoms) provided the oxabicycle **7** in 55% yield on the 10 mmol scale.[2] Reduction of the ketone **7** with diisobutylaluminium hydride (DIBAH) in CH_2Cl_2 at −24 °C resulted in the formation of the axial alcohol **8** in 95% yield. This was transformed into the xanthate **9** in 80% yield, and thence into the desired bicyclic alkene **5** (90% yield) through reaction with tributyltin hydride and azoisobutyronitrile (AIBN)[3] (benzene, 90 °C, 10 h).



Scheme 2 *Reagents:* 1, Et_2Zn, furan, benzene; Zn/Cu, MeOH–NH_4Cl (50–55%); ii, DIBAH, CH_2Cl_2 (95%); iii, NaH, imidazole, CS_2, MeI, 80%; iv, Bu_3SnH, AIBN (95%); v, CSI, 20%

We then tried the reaction with chlorosulfonyl isocyanate (CSI), which had been successful in our earlier work. In the event, treatment of **5** with CSI[4] (1.5 molar equiv.) at room temperature yielded no products after 2 days, but a complex mixture was obtained following the addition of a further aliquot (1.5 molar equiv.) of CSI, and a further reaction period of 6 days. Careful column chromatography provided one major product in 20% isolated yield, but this was not the anticipated β-lactam **10**. It was instead the rare monoterpene 3-hydroxyphellandral **11**.

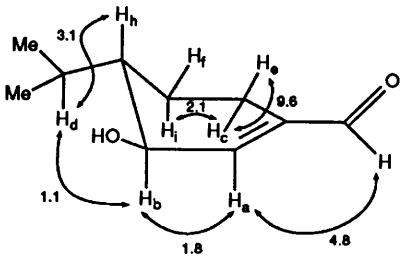
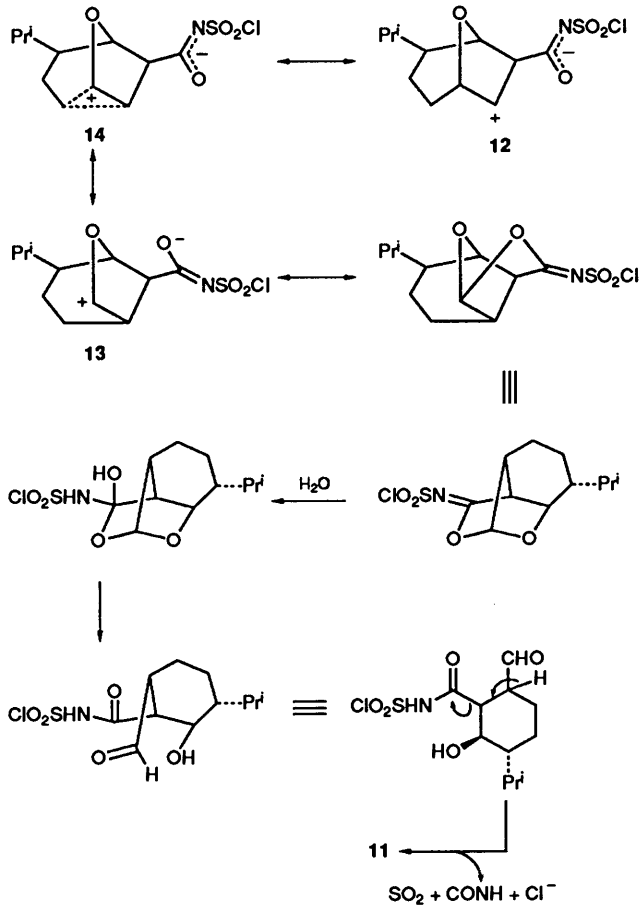


Fig. 1 Some NOE data for aldehyde **11**

The structure of **11** was confirmed by spectroscopic analysis; ν_{max}/cm^{-1} 3403 (OH), 2870 and 2700 (CHO), 1689 (unsaturated carbonyl); and key features of the NMR spectrum δ 0.86 and 0.90 (2 d, J 6.9 Hz, Pr^i), 6.64 (dt, $J_1 = J_2$ 2.5 and J_3 0.8 Hz, =CH) and 9.49 (s, CHO). The stereochemistry was assigned using the NOE data shown in Fig. 1.

In order to account for the unexpected formation of **11**, we



Scheme 3 Proposed mechanism of formation for aldehyde **11**

propose the mechanism shown in Scheme 3, whereby the initial carbocation **12** is converted into carbocation **13** *via* the non-classical carbocation **14**. We have, at present, no idea of the generality of this chemistry, but given the ease of formation of 8-oxabicyclo[3.2.1]oct-6-enes,[2] this transformation offers the possibility of facile access to highly substituted cyclohexenes.

Experimental

IR spectra were recorded with a Perkin-Elmer 881 double beam grating spectrophotometer. NMR spectra were recorded with Perkin-Elmer R34 (220 MHz) instrument, a Bruker WH 250 (250 MHz) or with a Bruker WH 400 spectrometer (400 MHz) at the University of Warwick, using tetramethylsilane as internal standard. All J values are given in Hz. Mass spectra were obtained at the University of Swansea using a VG ZAB-E high resolution spectrometer. Flash chromatography was performed using Crosfield Sorbil C60 (40–60 μm). Solvents were purified according to Perrin,[5] and light petroleum refers to the fraction with b.p. 40–60 °C, ether refers to diethyl ether.

1,1,3,3-*Tetrabromo-4-methylpentan-2-one* **6**.—A two-necked 250 cm^3 flask was fitted with a dropping funnel and an air condenser. Bromine (25.8 cm^3, 0.5 mol) was added dropwise to a stirred solution of 4-methylpentan-2-one (10 g, 0.1 mol) and phosphorus tribromide (1 cm^3), maintaining the temperature around 0 °C. After complete addition of bromine, the mixture was allowed to warm to room temperature and stirred overnight. The flask was then flushed with nitrogen and CH_2Cl_2 (500 cm^3) was added. The resultant solution was washed with water (80 cm^3), $NaHCO_3$ (saturated aq.; 2 × 80 cm^3), $Na_2S_2O_5$ (sat., 2 × 50 cm^3), brine (80 cm^3) and dried ($MgSO_4$). After concentration under reduced pressure the required polybromoketone was obtained, 92.8% yield (38.5 g, 92.8 mmol) as a pale yellow oil; ν_{max}(thin film)/cm^{-1} 3010, 2950, 2920, 2735, 1470, 1405, 1385, 1210, 1110 and 830; δ_H(220 MHz; $CDCl_3$) 1.21 (d, 6 H, J 6.5, 2 × CH_3), 2.67 (hept, 1 H, J 6.5, $CHMe_2$) and 6.82 (s, 1 H, $CHBr_2$).

2α-*Isopropyl-8-oxabicyclo*[3.2.1]*oct-6-en-3-one* **7**.—To an ice-cooled stirred solution of 4-methyl-1,1,3,3-tetrabromopentan-3-one (4.15 g, 10 mmol) and furan (12.5 cm^3, ~200 mmol) in dry benzene (200 cm^3) was added diethylzinc in hexane (1 mol dm^{-3}; 10 cm^3, 10 mmol). The mixture was stirred at 0 °C for 2 h and at room temperature for a further 6 h. The reaction was quenched by addition of ethyl acetate (200 cm^3) and a saturated solution of Na_2EDTA (60 cm^3). The two layers were separated and the organic phase was washed with Na_2EDTA solution (2 × 40 cm^3), brine (40 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to leave a brown residue. This residue was dissolved in methanol saturated with NH_4Cl (80 cm^3) and to this solution was added Zn/Cu couple (6.54 g, 0.1 mol) portionwise. The resultant mixture was stirred at room temperature for 6 h before removal of the solids by filtration through a Celite pad. The filtrate was diluted with CH_2Cl_2 (200 cm^3) and extracted with saturated Na_2EDTA (3 × 30 cm^3), washed (brine, 30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to afford a brown oil. This oil was purified by flash chromatography on silica gel using light petroleum–diethyl ether (3:1) as eluent, to yield 848 mg (5.1 mmol, 51%) of the required product as a pale yellow oil; R_f 0.2 (light petroleum–ether, 3:1); ν_{max}(thin film)/cm^{-1} 3079, 2960, 2871, 1710, 1580, 1468, 964 and 725; δ_H(250 MHz; $CDCl_3$) 0.87 (d, 3 H, J 6.8, CH_3), 1.06 (d, 3 H, J 6.8, CH_3), 2.03 (oct, 1 H, J 6.8, $CHMe_2$), 2.20 (dd, 1 H, J_1 16.8, J_2 1.7, 4_{endo}-H), 2.57 (dd, 1 H, J_1 = 6.8, J_2 = 4.5, 2-H), 2.67 (dd, 1 H, J_1 16.8, J_2 = 4.5, 4_{exo}-H), 4.94 (dt, 1 H, J_1 4.5, $J_2 = J_3$ 1.4, 5-H), 4.99 (dd, 1 H, J_1 4.5, J_2 1.4, 1-H) and 6.17 and 6.21 (2 dd, 1 H each, J_1 6.1, J_2 1.4, 6-H and 7-H); δ_C(62.5 MHz; $CDCl_3$) 19.92, 22.33, 24.51, 46.04, 63.80, 77.80, 79.53, 132.28, 133.58 and 205.95; m/z (%, CI NH_3) 151 (15), 123 (8), 84 (25), 69 (100) and 43 (25) (Found: C, 72.3, H, 8.5; $[M+1]^+$, 167.1072. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%; $[M+1]^+$, 167.1072).

S-*Methyl* 2α-*Isopropyl-8-oxabicyclo*[3.2.1]*oct-6-en-3-yl Dithiocarbonate* **9**.—To a stirred solution of compound **7** (1.61 g, 9.7 mmol) in CH_2Cl_2 (25 cm^3) held at −24 °C and under nitrogen atmosphere, a solution of DIBAH (1 mol dm^{-3} in hexane; 11 cm^3, 11 mmol) was added slowly. The resultant solution was stirred at −24 °C for 2 h and at room temperature for another 2 h before addition of saturated NH_4Cl (30 cm^3)

and Na_2EDTA (sat., 30 cm^3). The product was then extracted with $CHCl_3$ (3 × 60 cm^3), and the combined organic extracts were washed with water (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to leave the required alcohol **8** (1.55 g) as an orange oil that crystallized on standing.

A solution of this crude alcohol **8** in dry THF (12 cm^3), was added to a suspension of NaH (60% dispersion in mineral oil, washed with light petroleum twice, 1.1 g, ~23 mmol) and imidazole (80 mg) in THF (15 cm^3), under nitrogen atmosphere. The mixture was refluxed for 3.5 h (the oil bath was kept at 70–80 °C) and after that time it had turned into a pale tan colour. On addition of CS_2 (2.85 cm^3, 47 mmol) and refluxing for 35 min, the mixture became very dark brown. MeI (3 cm^3, 47 mmol) was then added and the mixture turned into a dark yellow colour. After stirring at 70–80 °C for 2 h the reaction mixture was worked up by slow addition of a cold saturated solution of NH_4Cl (50 cm^3) and $CHCl_3$ (50 cm^3). The two layers were separated and the aqueous phase was extracted with $CHCl_3$ (3 × 50 cm^3). The combined organic extract was washed with $Na_2S_2O_3$ (10%, 40 cm^3), brine (60 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure to afford a dark brown oil. This oil was purified by flash chromatography (4:1, light petroleum–ether) to afford the required product as an orange oil, in an overall yield of 80% (2.00 g, 7.77 mmol). This product consisted of a mixture of two isomers, with the axial one being the major one (>92%); R_f 0.15 (1:1, light petroleum–diethyl ether); ν_{max}(thin film)/cm^{-1} 3075, 2956, 2868, 1625w, 1267, 1229, 1195, 1051, 967 and 881; δ_H(220 MHz; $CDCl_3$) 0.80 (d, 3 H, *J* 6.0, Me), 1.01 (d, 3 H, *J* 6.0, Me), 1.50–1.70 (m, 1 H, $CHMe_2$), 1.85–2.05 (m, 2 H, 4_{exo}-H and 2-H), 2.18 (ddd, 1 H, J_1 16.9, J_2 5.5, J_3 4, 4_{endo}-H), 4.70 (br s, 1 H, 1-H), 4.83 (br s, 1 H, 5-H), 5.85 (br t, 1 H, *J* 5, 3-H), 6.22 (dd, 1 H, J_1 6, J_2 1.5, 6-H) and 6.35 (dd, 1 H, J_1 6, J_2 1.5, 7-H) (Found: M^+, 258.0748. $C_{12}H_{18}S_2O_2$ requires *M*, 258.0748; *m/z* (%) 211 (8), 183 (10), 151 (100), 123 (40), 107 (25), 91 (58), 83 (85), 67 (48), 55 (95) and 43 (35).

2α-Isopropyl-8-oxabicyclo[3.2.1]*oct-6-ene* **5**.—To a stirred solution of the dithiocarbonate **9** (1.8 g, 6.98 mmol) and AIBN (100 mg) in dry benzene (25 cm^3), under nitrogen atmosphere, was added Bu_3SnH (1.89 cm^3, 7.0 mmol). The reaction flask was transferred to an oil bath at 80–90 °C, and stirred for 10 h, after which the solvent was removed with a stream of nitrogen and the yellow oil obtained was purified by flash chromatography (7:1, light petroleum–ether) to afford the required product as a pale yellow oil, 95% yield (1.00 g, 6.63 mmol). The product was distilled at 120 °C; 40 mmHg to afford a colourless oil; R_f 0.20 (7:1, light petroleum–diethyl ether); ν_{max}(thin film)/cm^{-1} 3074, 2941, 2872, 1647, 1387/1370, 1052, 890 and 710; δ_H(250 MHz; $CDCl_3$) 0.83 (d, 3 H, *J* 6.5, Me), 0.92 (d, 3 H, *J* 6.5, Me), 1.00–1.80 (mult, 6 H, 2-H, 3-CH_2, 4-CH_2 and C*H*Me_2), 4.67 and 4.75 (2 d, 1 H each, *J* 3.1, 1-H and 5-H) and 6.12 (s, 2 H, 6-H and 7-H); δ_C(62.5 MHz; $CDCl_3$) 20.44, 20.57, 21.56, 24.53, 30.71, 42.61, 79.31, 81.08, 130.71 and 131.11; *m/z* (%) 137 (5), 109 (20), 95 (25), 81 (100) and 68 (75) (Found: C, 78.8, H 10.6; M^+, 152.1201. $C_{10}H_{10}O$ requires C, 78.90, H, 10.59%, *M*, 152.1201).

3β-Hydroxy-4α-isopropylcyclohex-1-enecarbaldehyde **11**.—To a stirred solution of the 8-oxabicyclo[3.2.1]oct-6-ene **5** (0.65 g, 4.3 mmol) in dry CH_2Cl_2 (3.0 cm^3), kept under nitrogen and at room temperature, was added CSI (0.56 cm^3, 6.4 mmol). After 2 days stirring at room temperature, TLC analysis of the mixture showed only starting material. A further amount of CSI (0.56 cm^3, 6.4 mmol) was added and the resultant mixture stirred at room temperature for 6 more days. After that time TLC analysis showed that all starting material was consumed and a complex mixture was formed, with two major components. The mixture was quenched with saturated aq. $Na_2S_2O_3$ (10 cm^3) and 10% NaOH (pH 8–9). After stirring for 2 h the product was extracted into ether (5 × 30 cm^3), the combined organic extract was dried ($MgSO_4$) and concentrated under reduced pressure to leave a brown oil. This oil was purified by flash chromatography on silica gel (1:1, light petroleum–diethyl ether) to afford several compounds, but only one was obtained in a pure form as an orange oil, and was identified as the aldehyde **11** (159 mg, 0.95 mmol, 22% yield); R_f = 0.15 (1:1, light petroleum–ether); ν_{max}(thin film)/cm^{-1} 3403br, 2957, 2870/2700, 1689, 1560, 1468, 1233, 1183, 1039 and 910; δ_H(400 MHz; $CDCl_3$) 0.86 (d, 3 H, *J* 6.9, Me), 0.99 (d, 3 H, *J* 6.9, Me), 1.20–1.32 (m, 1 H, H_i), 1.36–1.43 (m, 1 H, H_h), 1.76–1.83 (m, 2 H, H_f and OH), 1.98–2.11 (m, 2 H, H_d and H_e), 2.34–2.41 (dm, 1 H, $J_{c,e} \simeq 18$, H_C), 4.20–4.32 (m, 1 H, H_b), 6.64 (dt, 1 H, $J_1 \simeq J_2 \simeq 2.5$, $J_3 \simeq 0.8$, H_a) and 9.48 (s, 1 H, CHO); δ_C(100 MHz; $CDCl_3$) 16.59, 19.98, 20.82, 21.47, 26.48, 47.55, 69.13, 141.79, 151.39 and 193.94 (Found $[M + 1]^+$, 169.1228. $C_{10}H_{17}O_2$ requires $[M + 1]$, 169.1229); *m/z* 168 (M^+, 68), 151 100), 139 (50), 125 (60), 107 (40), 97 (65) and 79 (40).

Acknowledgements

L. C. de A. B. thanks the RSC for a research grant towards the purchase of chemicals.

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Paper 2/05371C
Received 7th October 1992
Accepted 30th November 1992