SHORT PAPER

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The X-ray crystal structures of ambraketal and 8-*epi*-ambraketal†

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The crystal structures of ambraketal and 8-*epi*-ambraketal, synthesised in five steps from (–)-sclareol, are reported.

Keywords: ambraketal, 8-*epi*-ambraketal, crystal structure

Ambergris, a concretion formed in the intestinal tract of the blue sperm whale, has been used by perfumers since ancient times because of its unique fragrance and fixative properties.[1] Restrictions imposed upon the whaling industry, in an attempt to protect these endangered marine mammals, have forced chemists to make synthetic substitutes for ambergris. Among these synthetic substitutes, the two epimeric bisnorlabdane acetals ambraketal (**1**; amberketal, ambracetal) and 8-*epi*-ambraketal (**2**, *epi*-amberketal, 8-*epi*-ambracetal, iso-ambraketal) have found prominence due to their strong fragrance and fixative properties respectively. Compounds **1** and **2** have also been reported as minor constituents in the bark of the western white pine tree (*Pinus monticola*).[2]

As a consequence of their importance to the fragrance industry, numerous semi-synthetic preparations of **1** and **2**[3–21] and a single stereospecific synthesis of **1**[22] have been reported. The majority of these syntheses proceed *via* the common vinyl ketone intermediate (**3**) obtained through oxidative degradation of labdanes such as manool,[3-11] sclareol,[12-18] larioxol,[19,20] anticopalic acid[11] and the methyl esters of communic acids.[21] It was somewhat surprising, therefore, to find that despite the considerable interest in these compounds their stereochemistries at C-8 and C-13 have only been assigned from ^{1}H NMR data obtained for **1** and **2** and their 12-keto derivatives[4] and nOe experiments performed on **1**.[9] The absolute stereochemistry of neither **1** nor **2** has been unequivocally confirmed through X-ray crystallography and in the course of our semi-synthesis of marine natural products from (–)-sclareol we were eventually able to obtain crystals of both **1** and **2** suitable for X-ray analysis (Figs 1a and b). The structures of **1** and **2** were thus confirmed as (13*S*)-8α,13:13,17-diepoxy-14,15-bisnorlabdane and (13*R*)-8β,13:13,17-diepoxy-14,15-bisnorlabdane respectively.

Vinyl ketone **3**, obtained from (–)-sclareol in three steps and in about 50% yield,[17] was the starting point for our synthesis of **1** and **2** (Scheme 1). In our hands, treatment of **3** with *m*CPBA gave, after semi-preparative normal phase HPLC, the epoxide **4** (71%),[4] sclareolide (**5**; 18%)[24] and the known Baeyer–Villiger oxidation product **6** (3%).[7] Subsequent treatment of **4** with periodic acid gave a mixture of **1** and **2**,[3,4] which were easily separated by normal phase HPLC in yields of 17% and 44% respectively. X-ray quality crystals of ambraketal and 8-*epi*-ambraketal were obtained by slow evaporation from hexane and pentane respectively.

The configurations at C-8, C-9 and C-13 shown in Figure 1 for **1** and **2** were established on the basis of the known stereochemistries at C-5 and C-10. Molecular parameters are in the expected ranges. All six-membered rings in **1** and **2** adopt the chair-conformation while the five-membered rings are both envelopes with the flap at O-20. The crystal structures are maintained by van der Waals interactions only.

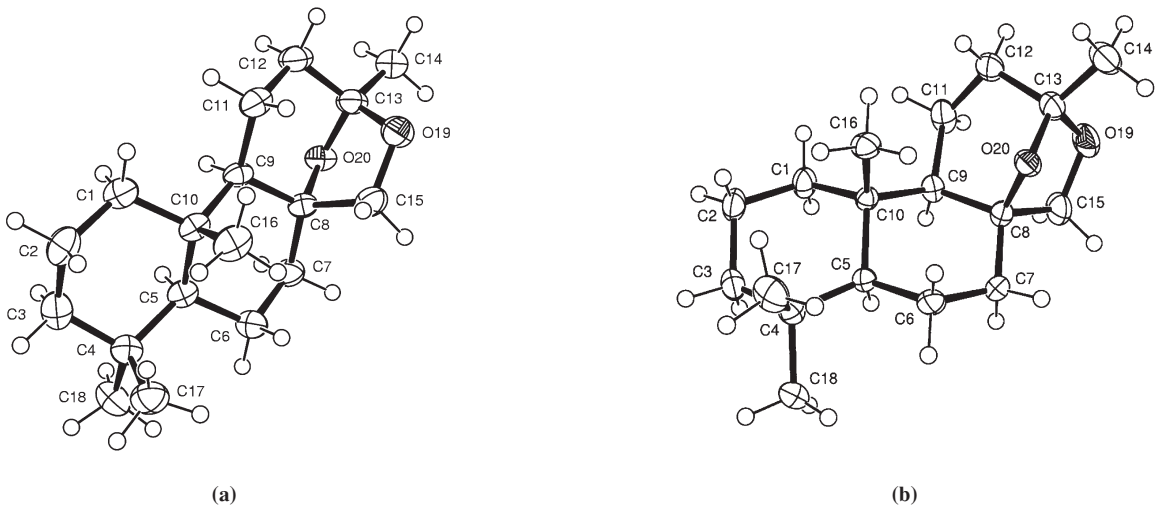

Fig. 1 Views of molecules of ambraketal (a) and 8-*epi*-ambraketal (b) from the crystal structures showing the numbering schemes employed. Anisotropic atomic displacement ellipsoids for the non hydrogen atoms are shown at the 50% probability level.

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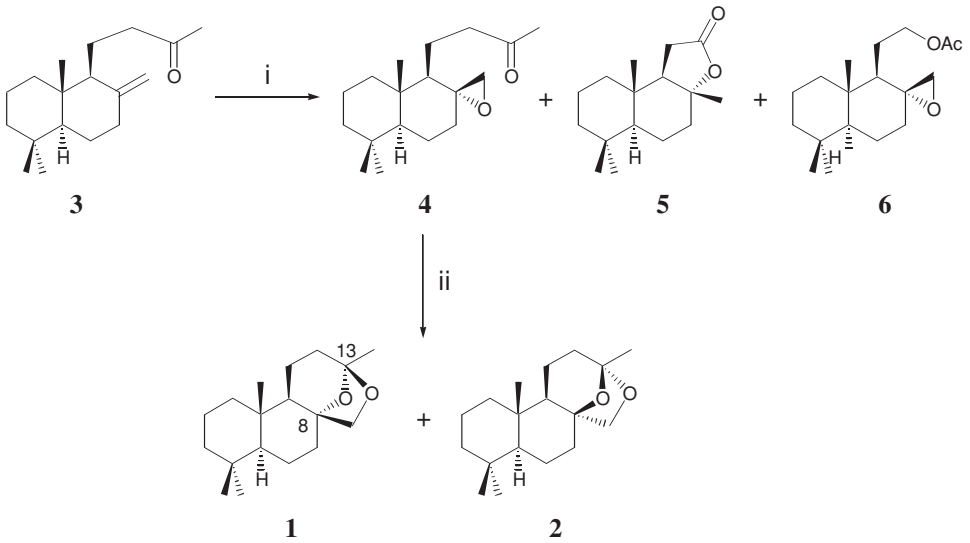

Scheme 1 (i) *m*CPBA (1.2 eq), $CHCl_3$, RT, 19 h; (ii) H_5IO_6 (3.5 eq), Et_2O, 0°C – R.T., overnight.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz Avance NMR spectrometer in $CDCl_3$ and were referenced to residual protonated solvent at δ 7.25 and 77.0 respectively. HRFABMS data were acquired on a Micromass 70-70E spectrometer and the LREI mass spectra (70 eV) were obtained on a Finnegan-Matt GCQ mass spectrometer. IR data for all compounds were obtained from thin films on NaCl discs using a Perkin-Elmer 2000 FTIR spectrometer. All rotations were recorded on a Perkin-Elmer 141 polarimeter as $CHCl_3$ solutions. Melting points were determined using a Reichert hot-stage microscope and are uncorrected. Normal phase semi-preparative HPLC separations were performed on a Whatman Magnum 9 Partisil 10 column with an eluent flow rate of 4 ml/min[1] and eluting fractions detected using a Waters R401 differential refractometer.

Epoxidation of (+)-14,15-bisnorlabd-8(16)-en-13-one (**3**): Vinyl ketone **3** (198 mg, 0.76 mmol) and *m*CPBA (158 mg, 0.92 mmol, 1.2 eq) were stirred in $CHCl_3$ (10 ml) at RT for 19 h and the reaction mixture then washed with 1 M NaOH (5 ml) and H_2O (2 × 5 ml). Drying ($MgSO_4$) and concentration of the resulting organic fraction yielded a colourless oil (188 mg) that was subjected to NP HPLC in 9:1 hexane/EtOAc to give (in order of elution) (+)-8α,17-epoxy-13,14,15,16-tetranorlabdan-12-yl acetate (**6**; 7 mg, 0.02 mmol, 3%), (+)-sclareolide (**5**; 33 mg, 0.13 mmol, 17%) and (+)-8α,17-epoxy-14,15-bisnorlabdan-13-one (**4**; 141 mg, 0.51 mmol, 67%).

(+)-8α,17-epoxy-14,15-bisnorlabdan-13-one (**4**):[4] Colourless oil; $[\alpha]_D^{32}$ +7.7 (*c* 3.00 $CHCl_3$), lit.[4] +9; IR ν_{max} 2868, 1715, 1462, 1386, 1205, 1040, 893 cm^{-1}; ^1H and ^{13}C NMR data consistent with published values;[18,23] EIMS *m/z* (rel. int.) 278 [M^+] (4), 245 (43), 177 (46), 149 (44), 123 (63), 82 (100); HRFABMS obsd. 279.2324 [$(M + H)^+$], $C_{18}H_{31}O_2$ requires 279.2324.

(+)-Sclareolide (**5**):[24] White solid; m.p. 125–126 °C, lit.[24] 123–124 °C; $[\alpha]_D^{34}$ +39.3 (*c* 0.267, $CHCl_3$), lit.[24] +45.9; IR, ^1H and ^{13}C NMR data consistent with published values;[18,25] EIMS *m/z* (rel. int.) 250 [M^+] (5), 235 (86), 207 (88), 150 (65), 109 (89), 67 (100); HRFABMS obsd. 251.2011 [$(M + H)^+$], $C_{16}H_{27}O_2$ requires 251.2011.

(+)-8α,17-epoxy-13,14,15,16-tetranorlabdan-12-yl acetate (**6**):[7] Colourless oil; $[\alpha]_D^{32}$ +6.8 (*c* 0.278); IR ν_{max} 2863, 1739, 1367, 1245, 1036, 895 cm^{-1}; ^1H NMR data consistent with published values;[7] ^{13}C NMR δ 171.1 (s), 65.6 (t), 58.7 (s), 55.0 (d), 50.6 (t), 50.4 (d), 41.9 (t), 40.0 (s), 39.0 (t), 36.3 (t), 33.5 (q), 33.4 (s), 21.8 (t), 21.6 (q), 21.5 (t), 21.1 (q), 18.6 (t), 14.6 (q); EIMS *m/z* (rel. int.) 290 (14), 219 (33), 191 (39), 177 (100), 107 (52), 82 (81); HRFABMS obsd. 295.2275 [$(M + H)^+$], $C_{18}H_{31}O_3$ requires 295.2273.

Treatment of (+)-8α,17-epoxy-14,15-bisnorlabdan-13-one (**4**) *with periodic acid*: Epoxide **4** (49 mg, 0.18 mmol) in Et_2O (1 ml) was added to a solution of H_5IO_6 (144 mg, 0.63 mmol, 3.5 eq) in Et_2O (3 ml) at 0°C and the mixture stirred for 6 h before being allowed to warm to room temperature and stir overnight. The reaction was quenched with sat. $NaHCO_3$ (4 ml) and extracted with Et_2O (3 × 5 ml). The combined organic fractions were then washed with sat. $NaHCO_3$ (10 ml), H_2O (5 ml) and sat. brine (5 ml), dried ($MgSO_4$) and concentrated to give a white cloudy oil (42 mg). NP HPLC of this oil in 9:1 hexane/EtOAc yielded (in order of elution) 8-*epi*-ambraketal (**2**; 22 mg, 0.08 mmol, 44%) and ambraketal (**1**; 9 mg, 0.03 mmol, 17%). Ketals **1** and **2** were obtained as needles through slow evaporation of hexane and pentane solutions respectively.

Ambraketal (**1**): [3,4] Needles from hexane; m.p. 113–115 °C, lit.[4] 115–116 °C; $[\alpha]_D^{34}$ +25.3 (*c* 0.162, $CHCl_3$), lit.[4] +31; IR ν_{max} 2946, 1449, 1385, 1194, 1020, 866 cm^{-1}; ^1H and ^{13}C NMR data consistent with published values;[18,21] EIMS *m/z* (rel. int.) 278 [M^+] (3), 218 (100), 203 (56), 175 (76), 147 (33), 120 (58), 106 (32); HRFABMS obsd. 279.2326 [$(M + H)^+$], $C_{18}H_{31}O_2$ requires 279.2324.

8-epi-Ambraketal (**2**): [3,4] Needles from pentane; m.p. 121–122 °C, lit.[4] 121–122 °C; $[\alpha]_D^{34}$ –3.0 (*c* 0.902, $CHCl_3$), lit.[4] –9; IR ν_{max} 2977, 1458, 1384, 1026, 860 cm^{-1}; ^1H and ^{13}C NMR data consistent with published values;[4,18] EIMS *m/z* (rel. int.) 278 [M^+] (2), 218 (100), 203 (59), 175 (69), 120 (56), 105 (35); HRFABMS obsd. 279.2324 [$(M + H)^+$], $C_{18}H_{31}O_2$ requires 279.2324.

X-ray analysis of ambraketal (**1**): Intensity data were collected on a Nonius Kappa CCD diffractometer at 173(2)K. The structure was solved using SHELXS-97[26] and refined by full-matrix least-squares using SHELXL-97[27]. All H atoms were located in difference electron density maps but were included in idealised positions in a riding model with U_{iso} = 1.2 times those of their parent atoms. All non-H atoms were refined anisotropically.

Crystal data: $C_{18}H_{30}O_2$, plate, 0.41 x 0.32 x 0.06 mm^3, *M* = 278.42, monoclinic, space group *C2*, *a* = 13.916(2), *b* = 6.013(1), *c* = 19.703(4)Å, β = 108.223(5)°, *V* = 1566.1(5) $Å^3$, *Z* = 4, D_c = 1.181 Mg m^{-3}, μ(MoKα) = 0.074 mm^{-1}, *F*(000) = 616.

Data collection: Crystal-to-detector distance 43 mm, ϕ-and ω-scan combinations (0.5°), 6737 integrated reflections of which 2093 unique, 1532 observed ($I > 2\sigma(I)$).

Structure refinement: Number of parameters = 185, *R1* = 0.051, *wR2* = 0.1152, *S* = 1.11.

X-ray analysis of 8-epi-ambraketal (**2**): Analogous procedures to those above were followed. Intensity data were collected at 203(2)K.

Crystal data: $C_{18}H_{30}O_2$, prism, 0.30 x 0.30 x 0.32 mm^3, *M* = 278.42, orthorhombic, space group $P2_12_12_1$, *a* = 5.9749(1), *b* = 15.3187(1), *c* = 17.2227(2)Å, *V* = 1576.35(3) $Å^3$, *Z* = 4, D_c = 1.173 Mg m^{-3}, μ(MoKα) = 0.074 mm^{-1}, *F*(000) = 616.

Data collection: Crystal-to-detector distance 33 mm, ϕ-and ω-scan combinations (1.0°), 34273 integrated reflections of which 3730 unique, 3523 observed ($I > 2\sigma(I)$).

Structure refinement: Number of parameters = 185, *R1* = 0.030, *wR2* = 0.0827, *S* = 1.01.

The crystal structures of **1** and **2** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 200244 and 200245 respectively).

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