A total synthesis of an antibacterial clerodane, 16-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide

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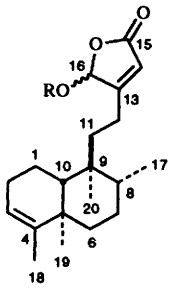
The total synthesis of an antibacterial clerodane, 16-hydroxycleroda-3,13(14)*Z*-dien-15,16-olide, has been achieved and its absolute stereochemistry has been determined.

The wide distribution of clerodane diterpenoids amongst plants and microorganisms makes them an important group of natural products, particularly so since of the 800 known clerodanes[1] a number have significant bioactivity, *e.g.* insect antifeedant, antibiotic or antitumour; nevertheless, the bioactivity of most clerodanes has yet to be explored. In spite of much synthetic effort, there have been only two successful total syntheses of optically active clerodanes so far.[2] 16-Hydroxycleroda-3,13(14)*Z*-dien-15,16-olide† **1** was first isolated by Bohlman *et al.* from *Acritopappus longifolius*[3a] and then from several sources such as *Polyalthia longifolia*,[3b,3d] *Polyalthia viridis*[3c] or *Premna oligotricha*.[4] Although, at the time when Tayur isolated compound **1**, only its antifeedant activity towards casterlooper was known,[3b] Waterman found that it had antibacterial activity comparable to that of streptomycin against a number of Gram-positive bacteria.[4] It is of note that thin twigs of plants containing the compound have been used as chewing sticks while the smoke formed from burning such plants has been used to sterilise milk containers in southern Ethiopia.[4] Although the relative stereochemistry of the acetate **2** was determined by

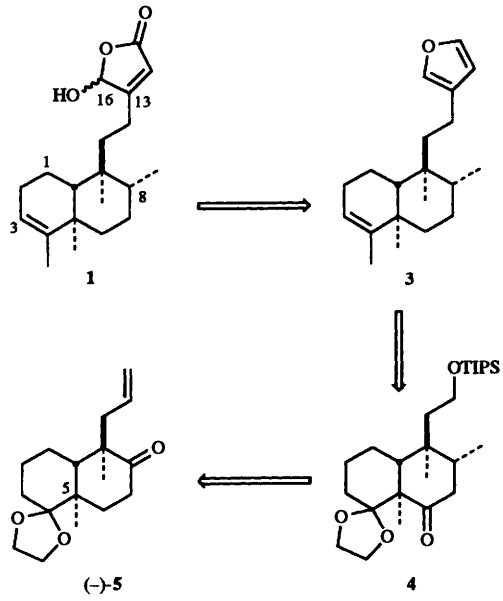


1 R = H
2 R = Ac

X-ray crystallography,[3b] the absolute stereochemistry has not been rigorously established. In view of significance of its biological activity, it was considered of importance to determine the absolute stereostructure of the clerodane **1**, since two enantiomeric series, those arising from clerodane and *ent*-clerodane, occur in natural products. Biologically active compounds from plant sources are attractive targets for total synthesis in view of the difficulty in culturing plant cells. The intriguing bioactivity and lack of assignment of absolute stereochemistry stimulated us to investigate a total synthesis of **1**; herein we delineate such a first total synthesis of **1**,[5] starting from (5*R*,9*R*,10*R*)-(−)-**5** (99% optically pure).

Results and discussion

Our retrosynthetic analysis is described in Scheme 1. There were



Scheme 1

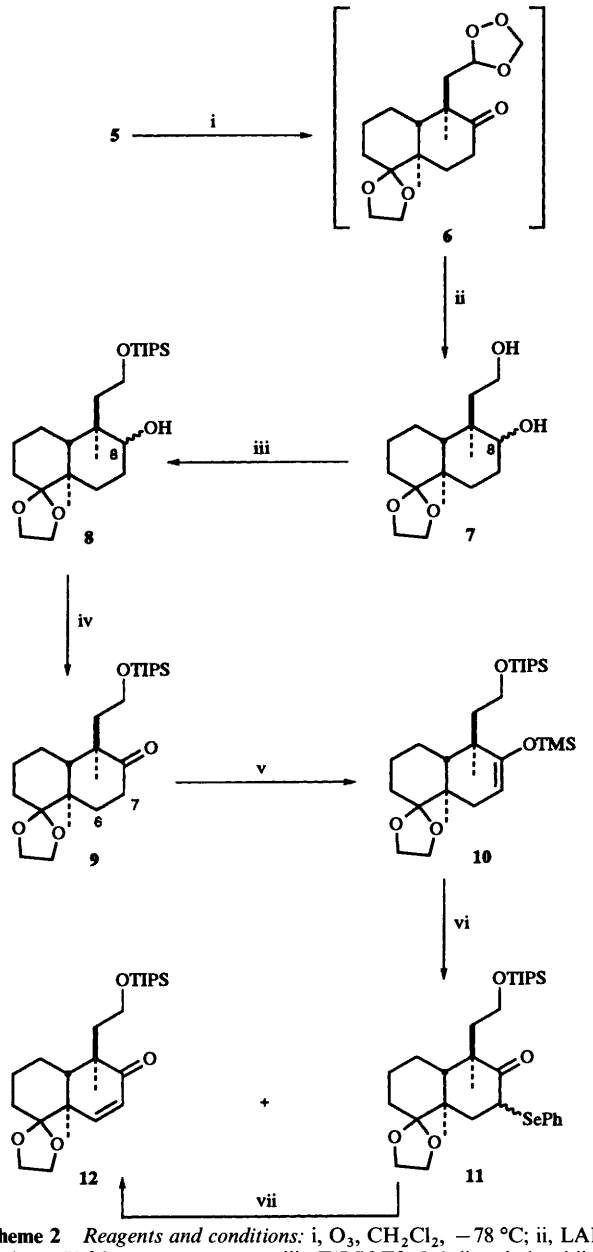
two major problems in the total synthesis of **1**: the first was the construction of the γ-hydroxybutenolide moiety and the second the introduction of four contiguous asymmetric centres in the decalin portion. We envisioned that the γ-hydroxybutenolide moiety of **1** could be generated by photooxygenation of the furan **3** which, in turn, could be derived from the ketal **4** *via* addition of 3-furyllithium. The ketal **4** would be obtained after transposition of the carbonyl group of the decalone (−)-**5** whose enantiomer has been synthesised in stereochemically defined manner and used as a starting point for some biologically active terpenoids in this laboratory.[6]

Although we had no information about the absolute stereochemistry of **1**, (5*R*,9*R*,10*R*)-(−)-**5** was chosen as the starting material in view of what was known about the absolute stereochemistry of other clerodanes and the sign of the optical rotation of **1**.

The decalone (−)-**5** (99% optically pure[6a]) has already three asymmetric centres in line with the four contiguous asymmetric centres of **1**. The fourth asymmetric centre at C-8 was introduced by reduction with lithium in liquid ammonia of the enone **14** formed by enone transposition of the enone **12**.

For introduction of the butenolide moiety at the end of the synthetic pathway, removal of one carbon unit from the side chain was required. Although osmium tetroxide oxidation of the olefin **5** followed by metaperiodate cleavage gave unsatisfactory results, ozonolysis of **5** provided the ozonide **6** which was stable in the presence of dimethyl sulfide, zinc or hot water. However, the ozonide **6** could be reduced with lithium aluminium hydride (LAH) to afford the diol **7** (Scheme 2). The

† Non-systematic numbering is used in this text, except in the Experimental section.



Scheme 2 *Reagents and conditions:* i, O_3, CH_2Cl_2, −78 °C; ii, LAH, Et_2O, −78 °C to room temp.; iii, TIPSOTf, 2,6-dimethylpyridine, CH_2Cl_2, −8 °C; iv, Jones reagent, acetone, −35 to −20 °C, 30 min; v, LDA; HMPA, Me_3SiCl, THF, −78 °C, 5 min; vi, PhSeCl, CH_2Cl_2, −78 °C, 5 min; vii, H_2O_2; pyridine, CH_2Cl_2

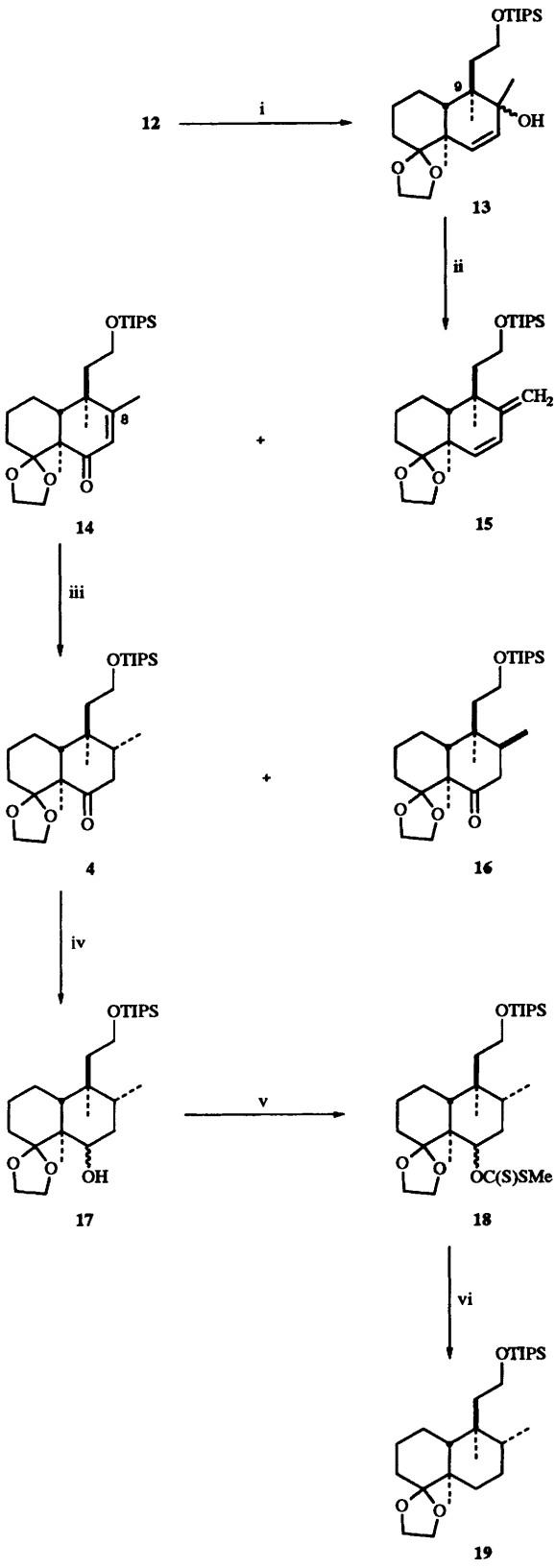
diol **7** was a mixture of epimers (3.5 : 1) and the configuration of the secondary hydroxyl group at C-8 of the major epimer was assigned as equatorial from the half height width of 8-H (δ_H 3.5, $w_{1/2}$ 16 Hz). Selective protection of the diol **7** was successful and gave the silyl ether **8** in 79% overall yield upon treatment with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) at −8 °C. The reactivity of the primary hydroxy group at C-12 was low and attempts to protect it with *tert*-butyldimethylsilyl chloride (TBDMSCl), triethylsilyl chloride (TESCl) or pivaloyl chloride led to recovery of the starting diol **7**. Jones oxidation of the silyl ether **8** at −20 °C gave the ketone **9** in 94% yield. In contrast, pyridinium chlorochromate (PCC) oxidation was slow (38% yield, with recovery of the starting alcohol **8**) probably because C-8 was a neopentyl position. In order to introduce the 6,7-double bond, the ketone **9** was transformed into the silyl enol ether **10** in 92% yield. Palladium-catalysed oxidation [7] of this to give the enone **12** was slow, a large amount of the ketone **9** being recovered. In turn, the silyl enol ether **10** was transformed with phenylselanyl chloride into the selenide **11** in 80% yield, the oxidative elimination of which with hydrogen peroxide gave the enone **12** in 74% yield. Selanylation of the silyl enol ether **10** was clean and instantaneous, in contrast to direct selanylation of the enolate of the ketone **9** which led to large amounts of the starting ketone **9** being recovered.

Introduction of the methyl group at C-8 was accomplished by addition of methyllithium (MeLi) to the enone **12** to afford an epimeric mixture (10 : 1) of the allylic alcohol **13** (98% yield) (Scheme 3). Oxidative rearrangement of the allylic alcohol **13** was performed by employing a large excess of chromium oxide and 3,5-dimethylpyrazole [8] to provide the $\Delta^{7,8}$-enone **14** in 62% yield accompanied by a small amount of the diene **15**. Dissolving metal reduction of the $\Delta^{7,8}$-enone **14** with lithium in liquid ammonia furnished the desired α-methyl decalone **4** and the β-methyl decalone **16** in 65% yield (9 : 1) [9] along with recovery of the enone **14** (29%). Introduction of a proton source after addition of the enone **14** improved the selectivity of the reduction. The relative stereochemistry of the α-methyl group at C-8 of **4** was determined by the coupling constants of 7β-H (δ_H 2.2, dd, *J* 14.4 and 2.8 Hz), 8β-H (δ_H 2.28, dd, *J* 12 and 2.8 Hz) and 7α-H (δ_H 2.46, dd, *J* 14.4 and 12 Hz) in the NMR spectrum. The remaining problem in this series of transformations was removal of carbonyl oxygen at C-6 of the ketone **4**. Since C-6 was a neopentyl position, it was expected to have low reactivity. Thus, the carbonyl group at C-6 was removed by radical deoxygenation. [10] After reduction of the carbonyl group at C-6 of the ketone **4** (93%), the resulting hydroxy group was converted into an *S*-methyldithiocarbonate to give the xanthate **18** which was treated with tributyltin hydride and azoisobutyronitrile (AIBN) to afford the ketal **19** in 89% yield.

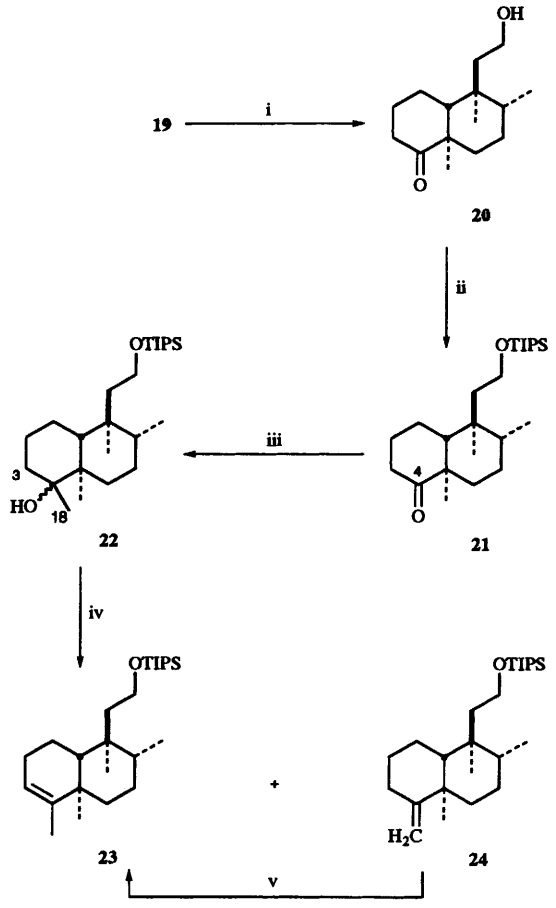
Hydrolysis of the ketal **19** gave the keto alcohol **20** whose primary alcohol function was reprotected to provide the ketone **21** in 91% overall yield (Scheme 4). Selective deprotection of the ketal moiety of the ketal **19** could not be achieved even by pyridinium toluene-*p*-sulfonate. Addition of MeLi gave a diastereoisomeric mixture (4 : 1) of the alcohol **22** quantitatively which was dehydrated with thionyl chloride to give an inseparable mixture of the *exo*-olefin **24** (δ_H 4.51, d, *J* 2 Hz) and the *endo*-olefin (δ_H 5.2, br) **23** (1 : 2) in 74% yield. Refluxing a solution of a mixture of the *exo*-olefin **24** and the *endo*-olefin **23** with a catalytic amount of iodine [11] in xylene completed isomerization of the *exo*-olefin **24** into the *endo*-olefin **23** in 91% yield. According to a molecular mechanics calculation, [12] the *endo*-olefin **23** would be more stable (Δ*E* 1.27 kcal^{-1} mol^{-1} ‡) than the *exo*-olefin **24**.

After several attempts to introduce the γ-hydroxybutenolide moiety of **1**, including alkylation of maleic anhydride derivatives, success was achieved by singlet oxygen oxidation of the furan **3** (Scheme 5). To this end, deprotection of the TIPS ether followed by Swern oxidation provided the aldehyde **26** quantitatively. Addition of 3-furyllithium [13] to the aldehyde **26** gave an epimeric mixture (1 : 1) of the alcohol **27** (97% yield), acetylation (92%) of which followed by reductive removal of the acetate **28** with lithium in liquid ammonia afforded the furan **3** in 89% yield. Finally, photosensitised oxidation of the furan moiety in the presence of Rose Bengal gave a dioxetane precursor which was regioselectively opened by Hunig base [14] to provide 63% yield a total synthesis of the title compound **1**. The spectral data of synthetic **1** were in good agreement with those of the natural product **1** including its optical rotation value {$[\alpha]_D$ −43 × 10^{-1} deg cm^2 g^{-1} (*c* 0.21, $CHCl_3$), lit.,[3] $[\alpha]_D$ −42 × 10^{-1} deg cm^2 g^{-1} (*c* 0.42, $CHCl_3$)}. The ^{1}H NMR

‡ 1 cal = 4.184 J.



Scheme 3 *Reagents and conditions:* i, MeLi, Et_2O, 0 °C, 15 min; ii, CrO_3, 2,3-dimethylpyrazole, CH_2Cl_2; iii, Li, liq. NH_3, THF, EtOH, −78 °C to reflux, 1 h; iv, LAH, Et_2O, −78 to −70 °C, 1.5 h; v, BuLi, CS_2, MeI, THF, 0 °C; vi, Bu_3SnH, AIBN, xylene, 150 °C, 15 min



Scheme 4 *Reagents and conditions:* i, PTSA, 80% aq. acetone, reflux, 3 h; ii, TIPSOTf, 2,6-dimethylpyridine, CH_2Cl_2, 0 °C, 1 h; iii, MeLi, Et_2O, 0 °C, 10 min; iv, $SOCl_2$, pyridine, 0 °C, 1.5 h; v, I_2, xylene, reflux, 2 h

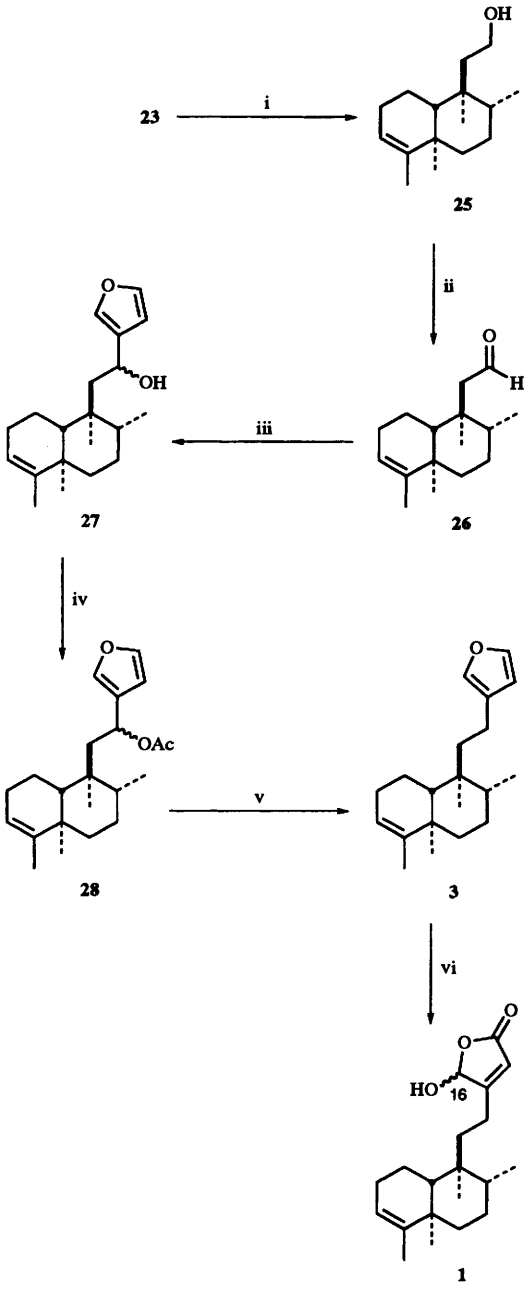
spectra of both natural and synthetic **1** indicated the presence of two C-16 epimers in equal ratio.[15] Thus, the absolute stereochemistry of **1** was established as 5*R*,8*R*,9*R*,10*R*.

Experimental

All mps were determined with a Mitamura Riken hot-stage apparatus and are uncorrected. IR spectra were recorded on a JASCO A-3 or FT/IR-8300 spectrophotometer for solutions in carbon tetrachloride unless otherwise indicated. ^1H NMR spectra were obtained for solutions in deuteriochloroform with JEOL-FX 90Q (90 MHz) and JEOL-GX 400 (400 MHz) instruments with tetramethylsilane as internal standard. *J* Values are given in Hz. Mass spectra were run on a JEOL JMS-DX300 spectrometer with a JMA-3500 data system. Specific rotations, $[\alpha]_D$, were determined on a JASCO DIP-370 polarimeter for solutions in chloroform, and are given in 10^{-1} deg cm^2 g^{-1}. Medium-pressure liquid chromatography (MPLC) was carried out on a JASCO PRC-50 instrument with a silica gel packed column. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether refers to diethyl ether. Anhydrous sodium sulfate was used for drying organic extracts. THF was distilled from sodium diphenyl ketyl prior to use. Upon typical work-up, the product was extracted with solvent (2 × 20 cm^3 for 1–10 mmol scale reaction). The organic layer was washed with water once and brine once. After being dried over sodium sulfate, the solvent was evaporated under reduced pressure.

(4a*R*,5*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-6-hydroxy-5-(2′-hydroxyethyl)-5,8a-dimethylnaphthalen-1(2*H*)-one ethylene ketal 7

Ozone (10% in oxygen) was bubbled through a stirred solution of the olefin **5** (5.966 g, 21.4 mmol) in dichloromethane (150 cm^3)



Scheme 5 *Reagents and conditions:* i, TBAF, THF, room temp., 7 h; ii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 to −20 °C; iii, 3-lithiofuran, THF, −78 °C, 15 min; iv, acetic anhydride, pyridine; v, Li, liq. NH_3, THF, −78 to reflux, 2 h; vi, O_2, tungsten lamp, Rose Bengal, diisopropylethylamine, CH_2Cl_2, −70 to −55 °C

at −70 °C for 15 min. The resulting solution was flushed with nitrogen and evaporated to dryness at room temperature. The residue had δ_H 1.07 (3 H, s), 1.25 (3 H, s), 1.2–2.8 (13 H, m), 3.9 (4 H, m), 5.03–5.24 (3 H, m) and was dissolved in anhydrous diethyl ether (100 cm^3). After addition of LAH (2.41 g, 63.5 mmol) to the solution at −78 °C, the resulting slurry was stirred for 5 h and allowed to warm to room temperature. Aq. ammonium chloride was carefully added to the mixture which was then filtered to remove aluminium hydroxide and evaporated to leave the *diol* **7** as an oil (5.28 g), a part of which was purified by MPLC for spectral data. The less polar minor (6*S*) isomer had mp 143–145 °C; $[\alpha]_D$ +30 (*c* 0.25) (Found: C, 67.7; H, 9.9. $C_{16}H_{28}O_4$ requires C, 67.7; H, 9.9%); ν_{max}/cm^{-1} 3421, 1457, 1384, 1335, 1283, 1234, 1177, 1128, 1104, 1047, 1012 and 950; δ_H(90 MHz) 0.85 (3 H, s, Me), 1.09 (3 H, s, Me), 1.2–2.04 (13 H, m), 2.81–2.95 (2 H, br, OH) and 3.61–4.01 (7 H, m, OCH_2CH_2O, 6-H and 2′-H); *m/z* 284 (M^+, 8%), 266 (7), 194 (8), 125 (8), 113 (9), 112 (12), 109 (9), 100 (15), 99 (100), 87 (22) and 86 (36).

The more polar major (6*R*) isomer had mp 108–111 °C; $[\alpha]_D$ +14 (*c* 0.25) (Found: C, 67.3; H, 9.8. $C_{16}H_{28}O_4$ requires C, 67.6; H, 9.9%); ν_{max}/cm^{-1} 3270, 1452, 1383, 1335, 1280, 1177, 1128, 1104, 1066 and 949; δ_H(90 MHz) 0.85 (3 H, s, Me), 1.09 (3 H, s, Me), 1.39–1.99 (13 H, m), 2.67 (2 H, br s, OH), 3.50 (1 H, m, $w_{1/2}$ 16, 6-H), 3.73 (2 H, dd, *J* 8 and 7, 2′-H) and 3.85–3.96 (4 H, m, OCH_2CH_2O); *m/z* 284 (M^+, 10%), 266 (6), 222 (11), 194 (8), 178 (4), 125 (7), 113 (9), 100 (20), 99 (100), 87 (19), 86 (31) and 55 (15).

(4a*R*,5*R*,6*S* or 6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-6-hydroxy-5,8a-dimethyl-5-(2′-triisopropylsiloxyethyl)-naphthalen-1(2*H*)-one ethylene ketal 8

To a solution of the diol **7** (5.28 g, 18 mmol) and 2,6-dimethylpyridine (3.15 cm^3, 27 mmol) in dichloromethane (25 cm^3) was added a solution of TIPSOTf (4.85 cm^3, 18 mmol) in dichloromethane (5 cm^3) over 1 h at −8 °C. After the reaction mixture had been stirred for 4 h, the reaction was quenched by addition of aq. sodium hydrogen carbonate to the mixture. After separation of the organic layer, the aqueous layer was extracted with ethyl acetate (×2). The combined extracts were washed with brine and evaporated to dryness. The residue was purified by column chromatography on silica gel [eluent: hexane–ethyl acetate (5:1)] to give the *silyl ether* **8** (7.47 g, 79% overall), a part of which was separated by MPLC for spectral data. The less polar minor (6*S*) isomer had $[\alpha]_D$ +14 (*c* 0.37) (Found: C, 68.1; H, 11. $C_{25}H_{48}O_4Si$ requires C, 68.1; H, 11%); ν_{max}/cm^{-1} 3483, 1463, 1384, 1339, 1283, 1210, 1187, 1137, 1104, 1068, 1034, 997, 952 and 911; δ_H(90 MHz) 0.83 (3 H, s, Me), 1.05 (3 H, s, Me), 1.07 (18 H, s, *Me*CH × 6), 1.0–2.07 (16 H, m), 3.56–3.67 (1 H, m, OH), 3.75–4.0 (6 H, m, OCH_2CH_2O and 2′-H) and 4.19 (1 H, br d, *J* 4, 6-H); *m/z* 440 (M^+, 10%), 397 (39), 336 (29), 335 (48), 266 (19), 249 (35), 223 (13), 205 (15), 188 (28), 187 (79), 175 (15), 162 (12), 161 (12), 161 (38) and 99 (100).

The more polar major (6*R*) isomer had $[\alpha]_D$ +5 (*c* 1.16) (Found: C, 68.3; H, 11. $C_{25}H_{48}O_4Si$ requires C, 68.1; H, 11%); ν_{max}/cm^{-1} 3416, 1463, 1383, 1335, 1281, 1199, 1177, 1128, 1097, 1068, 1014 and 962; δ_H(90 MHz) 0.85 (3 H, s, Me), 1.06 (3 H, s, Me), 1.08 (18 H, s, *Me*CH × 6), 1.37–1.78 (16 H, m), 3.33–3.55 (1 H, m, 6-H), 3.74–3.97 (6 H, m, OCH_2CH_2O and 2′-H) and 4.38 (1 H, d, *J* 3); *m/z* (M^+, 13%), 397 (46), 336 (27), 335 (43), 266 (15), 249 (29), 223 (22), 205 (18), 162 (32), 161 (100), 145 (17), 131 (23), 119 (20) and 99 (97).

(4a*R*,5*R*,8a*R*)-3,4,4a,5,8,8a-Hexahydro-5,8a-dimethyl-5-(2′-triisopropylsiloxyethyl)naphthalene-1,6(2*H*,7*H*)-dione ethylene ketal 9

To a stirred solution of alcohol **8** (2.30 g, 5.22 mmol) in acetone (15 cm^3) was added Jones reagent dropwise at −35 °C until an orange colour persisted. After 10 min, the reaction was quenched by addition of isopropyl alcohol to the mixture and the product was extracted with ethyl acetate (×2). Evaporation of the combined extracts followed by column chromatography of the residue on silica gel [eluent hexane–ethyl acetate (5:1)] provided the *ketone* **8** (2.14 g, 94%), $[\alpha]_D$ +16 (*c* 1.01) (Found: C, 68.7; H, 10.6. $C_{25}H_{46}O_4Si$ requires C, 68.4; H, 10.3%); ν_{max}/cm^{-1} 1742, 1705, 1463, 1382, 1239, 1184, 1128, 1103, 1047, 1013, 949 and 884; δ_H(90 MHz) 1.04 (3 H, s, Me), 1.06 (18 H, s, *Me*CH × 6), 1.01–1.12 (3 H, m), 1.18 (3 H, s, Me), 1.41–2.37 (13 H, m), 3.64 (2 H, dd, *J* 9 and 2, 2′-H) and 3.84–4.0 (4 H, m, OCH_2CH_2O); *m/z* 438 (M^+, 1%), 396 (34), 395 (100), 333 (13), 323 (10), 247 (18), 213 (21), 201 (39), 187 (17), 185 (21), 145 (11), 131 (11), 113 (10) and 99 (76).

(4a*R*,5*R*,8a*R*)-3,4,4a,5,8,8a-Hexahydro-5,8a-dimethyl-5-(2′-triisopropylsiloxyethyl)-6-trimethylsiloxynaphthalen-1(2*H*)-one ethylene ketal 10

To a stirred solution of lithium diisopropylamide prepared from diisopropylamine (219 mm^3, 1.56 mmol) in THF (2 cm^3) and butyllithium (1.6 mol dm^3 in hexane; 0.8 cm^3, 1.25 mmol) was added a solution of the ketone **9** (341.6 mg, 0.78 mmol) in THF (5 cm^3) at −78 °C. After the mixture had been stirred for 20 min, HMPA (0.54 cm^3, 3.1 mmol) followed by a solution of trimethylsilyl chloride (0.4 cm^3, 3.12 mmol) in THF (1 cm^3) were added to it. Stirring was continued for 10 min after which the reaction was quenched by the addition of aq. sodium hydrogen carbonate to the mixture. The mixture was extracted with ether (×2) and the combined extracts were evaporated to afford an oil which was purified by MPLC [eluent hexane–ethyl acetate 5:1)]; this gave the *enol ether* **10** (365 mg, 92%); ν_{max}/cm^{-1} 1743, 1670, 1464, 1375, 1344, 1253, 1186 and 846; δ_H(90 MHz) 0.18 (9 H, s), 0.9 (3 H, s, Me), 1.05 (18 H, s, *Me*CH × 6), 1.05 (3 H, s, Me), 1.01–1.12 (3 H, m), 1.47–2.33 (11 H, m), 3.64 (2 H, t like, *J* 8, 2′-H), 3.82–3.97 (4 H, m, OCH_2CH_2O) and 4.67 (1 H, dd, *J* 7 and 2, 7-H).

(4a*R*,5*R*,8a*R*)-3,4,4a,5,8,8a-Hexahydro-5,8a-dimethyl-7-phenylselanyl-5-(2′-triisopropylsiloxyethyl)naphthalene-1,6(2*H*,7*H*)-dione ethylene ketal 11

To a stirred solution of the enol ether **10** (260 mg, 0.5 mmol) in dichloromethane (1.5 cm^3) was added a solution of phenylselanyl chloride (112 mg, 0.58 mmol) in dichloromethane (2 cm^3) in one portion. After the reaction mixture had been stirred for 5 min aq. sodium hydrogen carbonate was added to it to quench the reaction. The mixture was extracted with ethyl acetate (×2) and evaporation of the combined extracts left residue which was purified by MPLC [eluent hexane–ethyl acetate (5:1)] to afford the *selenide* **11** (272 mg, 80%) and the enone **12** (23 mg, 9% from **9**); for **11**, $[\alpha]_D$ +120 (*c* 1.17) (Found: C, 62.7; H, 8.3. $C_{31}H_{50}O_4SiSe$ requires C, 62.7; H, 8.5%); ν_{max}/cm^{-1} 1705, 1464, 1438, 1384, 1184, 1098, 1071, 1001 and 690; δ_H(90 MHz) 1.07 (18 H, s, *Me*CH × 6), 1.11 (3 H, s, Me), 1.16 (3 H, s, Me), 1.02–1.18 (3 H, m), 1.4–2.26 (11 H, m), 3.54–3.92 (6 H, m, OCH_2CH_2O and 2′-H), 4.42 (1 H, dd, *J* 12 and 8, 7-H), 7.21–7.36 (3 H, m, ArH) and 7.48–7.63 (2 H, m, ArH); *m/z* 594 (M^+, 7%), 592 (4), 553 (20), 552 (26), 551 (69), 549 (38), 547 (14), 394 (15), 393 (25), 333 (22), 332 (11), 331 (13), 201 (25), 197 (17), 185 (27), 183 (16), 176 (12), 157 (11), 147 (11), 131 (12), 115 (13), 103 (12) and 99 (100).

(4*R*,4a*R*,8a*R*)-4a,5,6,7-Tetrahydro-4,8a-dimethyl-4-(2′-triisopropylsiloxyethyl)naphthalene-3,8(4*H*,8a*H*)-dione 8-ethylene ketal 12

To a stirred solution of the selenide **11** (1.911 g, 1 mmol) and pyridine (0.16 cm^3, 1.98 mmol) in dichloromethane (8 cm^3) was added hydrogen peroxide (30 wt%; 0.3 cm^3, 9.8 mmol) at 0 °C. After the reaction mixture had been stirred for 1.5 h at 0 °C aq. sodium hydrogen carbonate was added to it to quench the reaction. The product was extracted with ether (×2) and the combined extracts were evaporated to dryness. The residue was purified by MPLC to give the *enone* **12** (541.3 mg, 74%); $[\alpha]_D$ +31 (*c* 1.58) (Found: C, 69.0; H, 10.0. $C_{25}H_{44}O_4Si$ requires C, 68.8; H, 10.2%); ν_{max}/cm^{-1} 1672, 1464, 1387, 1276, 1249, 1186, 1106, 1068, 996, 950 and 884; δ_H(90 MHz) 1.03 (18 H, s, *Me*CH × 6), 1.06 (3 H, s, Me), 1.0–1.1 (3 H, m), 1.25 (3 H, s, Me), 1.47–2.63 (9 H, m), 3.61 (2 H, br t, *J* 7, 2′-H), 3.94–4.03 (4 H, m, OCH_2CH_2O), 5.94 (1 H, d, *J* 10, 7-H) and 7.02 (1 H, d, *J* 10, 8-H); *m/z* 436 (M^+, 5%), 394 (16), 393 (47), 333 (11), 332 (33), 331 (100), 289 (10), 247 (12), 235 (24), 175 (21), 161 (14), 115 (45) and 99 (36).

(4*R*,4a*R*,8a*R*)-3,4,4a,5,6,7-Hexahydro-3-hydroxy-3,4,8a-trimethyl-4-(2′-triisopropylsiloxyethyl)naphthalen-8(8a*H*)-one ethylene ketal 13

To a stirred solution of the enone **12** (27 mg, 0.062 mmol) in ether (1 cm^3) was added MeLi (1 mol dm^3 in hexane; 0.11 cm^3, 0.13 mmol) at 0 °C under nitrogen. After the reaction mixture had been stirred for 20 min, aq. ammonium chloride was added to it to quench the reaction. The product was extracted with diethyl ether (×2) and the combined extracts were evaporated to dryness. MPLC purification of residue [eluent hexane–ethyl acetate (5:1)] afforded two diastereoisomers of **13** (27.3 mg, 98%). The less polar, major diastereoisomer had $[\alpha]_D$ −12 (*c* 2.0) (Found: C, 68.8; H, 10.85. $C_{26}H_{48}O_4Si$ requires C, 69; H, 10.7%); ν_{max}/cm^{-1} 3432, 1464, 1375, 1335, 1238, 1186, 1128, 1079, 949 and 884; δ_H(90 MHz) 0.96 (3 H, s, Me), 1.07 (18 H, s, *Me*CH × 6), 1.15 (3 H, s, Me), 1.0–1.17 (3 H, m), 1.36 (3 H, s, Me), 1.49–2.19 (9 H, m), 3.49 (1 H, s, OH), 3.83–4.03 (6 H, m, OCH_2CH_2O and 2′-H) and 5.52 (2 H, d, *J* 1, olefinic H); *m/z* 452 (M^+, 0.6%), 434 (2), 419 (4), 409 (8), 347 (8), 261 (28), 234 (25), 233 (100), 199 (27), 173 (14), 147 (11), 131 (15), 115 (18), 114 (14), 113 (13), 112 (21), 99 (75) and 86 (24).

The more polar, minor diastereoisomer had $[\alpha]_D$ +20 (*c* 0.58) (Found: C, 69.05; H, 10.9. $C_{26}H_{48}O_4Si$ requires C, 69; H, 10.7%); ν_{max}/cm^{-1} 3417, 1463, 1375, 1240, 1186, 1092, 1072, 994, 949, 915 and 884; δ_H(90 MHz) 0.8 (3 H, s, Me), 1.07 (18 H, s, *Me*CH × 6), 1.13 (3 H, s, Me), 1.0–1.17 (3 H, m), 1.23 (3 H, s, Me), 1.35–1.84 (7 H, m), 2.37–2.58 (2 H, m), 3.49 (1 H, s, OH), 3.68–4.01 (6 H, m, OCH_2CH_2O and 2′-H), 5.55 (1 H, B part of AB type quartet, *J* 10, olefinic H) and 5.75 (1 H, A part of AB type quartet, *J* 10, olefinic H); *m/z* 452 (M^+, 1%), 408 (19), 393 (10), 347 (15), 278 (16), 262 (119), 261 (52), 235 (13), 234 (12), 233 (26), 201 (11), 199 (51), 175 (12), 173 (28), 169 (25), 159 (13), 147 (15), 133 (13), 131 (18), 119 (13), 115 (29), 114 (16), 113 (17), 112 (23), 105 (11), 103 (13), 99 (100) and 86 (29).

(4a*R*,5*R*,8a*R*)-3,4,4a,5-Tetrahydro-3,4,8a-trimethyl-4-(2′-triisopropylsiloxyethyl)naphthalene-1,8(2*H*,8a*H*)-dione ethylene ketal 14

To a stirred solution of chromic anhydride (99.9 mg, 1 mmol) in dichloromethane (1 cm^3) was added 3,5-dimethylpyrazole (88.7 mg, 1 mmol) at −20 °C under nitrogen. After the mixture had been stirred for 20 min, a solution of the diastereoisomeric mixture of alcohols **13** (22.9 mg, 0.05 mmol) in dichloromethane (3 cm^3) was added and stirring was continued for 20 min. The resulting solution was neutralized with aq. sodium hydroxide (1 mol dm^3) and extracted with ethyl acetate (×2). Evaporation of the combined extracts followed by MPLC purification of the residue gave the enone **14** (14.2 mg, 62%) together with a small amount of the diene **15**. The enone **14** had $[\alpha]_D$ −23 (*c* 1.27) (Found: C, 69.4; H, 10.2. $C_{26}H_{46}O_4Si$ requires C, 69.3; H, 10.3%); ν_{max}/cm^{-1} 1742, 1675, 1636, 1464, 1377, 1287, 1241, 1183, 1111 and 883; δ_H(90 MHz) 1.04 (18 H, s, *Me*CH × 6), 1.09 (3 H, s, Me), 0.98–1.13 (3 H, m), 1.28 (3 H, s, Me), 1.42–1.84 (7 H, m), 1.91 (3 H, d, *J* 1, 6-Me), 2.35–2.52 (2 H, m), 3.52 (1 H, dd, *J* 7 and 7, 2′-*H*H), 3.58 (1 H, dd, *J* 7 and 5, 2′-H*H*), 3.8–4.35 (4 H, m, OCH_2CH_2O) and 5.74 (1 H, d, *J* 1, 7-H); *m/z* 450 (M^+, 15%), 407 (13), 363 (16), 251 (21), 250 (100), 249 (25), 189 (12), 161 (12), 131 (10), 114 (19), 113 (18), 99 (42) and 86 (52). The diene **15** had ν_{max}/cm^{-1} 1464, 1382, 1187, 1093, 1008, 949, 914, 884 and 681; δ_H(90 MHz) 0.82–2.02 (12 H, m), 1.05 (21 H, s), 1.17 (3 H, s, Me), 3.61 (2 H, br t, *J* 8), 3.91–3.99 (4 H, m), 4.97 (2 H, d, *J* 7) and 6.98 (2 H, quartet like, *J* 9).

(4a*R*, 5*R*,6*R*,8a*R*)-3,4,4a,5,6,7-Hexahydro-5,6,8a-trimethyl-5-(2′-triisopropylsiloxyethyl)naphthalene-1,8-(2*H*,8a*H*)-dione ethylene ketal 4

To a stirred solution of the enone **14** (68.4 mg, 0.152 mmol) in THF (5 cm^3) and liquid ammonia (30 cm^3) was added lithium

(8.9 mg, 1.27 mmol) at −78 °C under nitrogen. After the mixture had been refluxed for 20 min at room temperature, ethanol (0.1 cm^3, 1.37 mmol) was added to it at −78 °C. The resulting solution was then allowed to warm to room temperature during 2.5 h after which aq. ammonium chloride was added to it to quench the reaction. The product was extracted with ether (×2) and the combined extracts were washed with brine and evaporated. MPLC separation afforded the (6S)-*methyl derivative* **4** (40.2 mg, 58.5%) and (4aR,5R,6S,8aR)-(+)-3,4,4a,5,6,7-*hexahydro*-5,6,8a-*trimethyl*-5-(2′-*triisopropylsiloxyethyl*)*naphthalene*-1,8(2H,8aH)-*dione ethylene ketal* **16** (4.6 mg, 6.7%) along with recovered enone **14** (20.1 mg, 29.4%).

The desired (6*S*)-methyl ketone **4** had $[\alpha]_D$ −21 (*c* 2.09) (Found: C, 69.0; H, 10.6. $C_{26}H_{48}O_4Si$ requires C, 69.0; H, 10.7%); ν_{max}/cm^{-1} 1717, 1675, 1464, 1378, 1339, 1279, 1182, 1088, 1038, 884 and 682; δ_H(400 MHz) 0.98 (3 H, d, *J* 6.8, 6-Me), 1.0 (3 H, s, Me), 1.03–1.1 (3 H, m), 1.07 (18 H, s, *Me*CH × 6), 1.33 (3 H, s, Me), 1.39–1.79 (9 H, m), 2.2 (1 H, dd, *J* 14.4 and 2.8, 7β-H), 2.28 (1 H, dd, *J* 12, 2.8, 8β-H), 2.46 (1 H, dd, *J* 14.4 and 12, 7α-H), 3.75–3.94 (4 H, m, OCH_2CH_2O and 2′-H) and 4.06 (2 H, m, OCH_2CH_2O); *m/z* 453 (M^+ + 1, 18%), 452 (M^+, 49), 409 (23), 365 (27), 321 (27), 267 (12), 252 (19), 196 (35), 191 (11), 183 (14), 175 (10), 131 (16), 114 (12), 113 (62), 112 (81), 103 (16), 100 (11), 99 (100), 87 (21) and 86 (44).

The (6*R*)-methyl ketone **16** had $[\alpha]_D$ +16 (*c* 0.5) (Found: C, 68.9; H, 10.7. $C_{26}H_{48}O_4Si$ requires C, 69; H, 10.7%); ν_{max}/cm^{-1} 1717, 1464, 1384, 1240, 1188, 1100, 1046, 951, 884 and 682; δ_H(400 MHz) 0.9 (3 H, s, Me), 0.9 (3 H, d, *J* 6.4, 6-Me), 1.05–1.11 (3 H, m), 1.06 (18 H, s, *Me*CH × 6), 1.32 (3 H, s, Me), 1.45–1.7 (9 H, m), 2.03–2.12 (2 H, m), 2.52 (1 H, dd, *J* 14 and 14), 3.65 (2 H, m, 2′-H), 3.86–3.95 (2 H, m, OCH_2CH_2O), 4.05–4.1 (1 H, m, OCH_2CHHO) and 4.18–4.25 (1 H, m, OCH_2CHHO); *m/z* 453 (19%), 452 (M^+, 52), 409 (22), 365 (24), 321 (32), 252 (22), 233 (13), 196 (31), 175 (12), 173 (15), 131 (22), 114 (15), 113 (55), 112 (70), 103 (18), 99 (100), 87 (19), 86 (48) and 75 (26).

(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-8-hydroxy-5,6,8a-trimethyl-5-(2′-triisopropylsiloxyethyl)naphthalen-1(2*H*)-one ethylene ketal 17

To a stirred solution of the ketone **4** (208.9 mg, 0.461 mmol) in ether (3 cm^3) was added LAH (18.2 mg, 0.48 mmol) at −78 °C under nitrogen. After the mixture had been stirred for 1.5 h, water was added to it to quench the reaction. The aluminium hydroxide was filtered off and the filtrate evaporated to leave an oil which was purified by MPLC [eluent hexane–ethyl acetate (5:1)] to give the *alcohol* **17** (194.2 mg, 93%); $[\alpha]_D$ +6 (*c* 0.84) (Found: C, 69.0; H, 11.0. $C_{26}H_{50}O_4Si$ requires C, 68.7; H, 11.1%); ν_{max}/cm^{-1} 3539, 1464, 1386, 1355, 1302, 1175, 1103, 1068, 1014, 951, 884 and 681; δ_H(90 MHz) 0.72 (3 H, s, Me), 0.87 (3 H, d, *J* 6, 6-Me), 1.07 (18 H, s, *Me*CH × 6), 1.11 (3 H, s, Me), 1.43–2.55 (16 H, m), 3.63 (2 H, br t, *J* 8, 2′-H), 3.72 (1 H, s, 8-H) and 3.94–4.09 (4 H, m, OCH_2CH_2O); *m/z* 454 (M^+, 49%), 412 (31), 411 (95), 349 (36), 268 (14), 267 (17), 254 (14), 237 (24), 219 (13), 201 (26), 191 (15), 175 (38), 163 (14), 159 (22), 131 (26), 121 (19), 99 (100), 95 (23) and 86 (29).

***O*-[(4a*R*,5*R*,6*R*,8a*R*)-1-Ethylenedioxydecahydro-5,6,8a-trimethyl-1-oxo-5-(2′-triisopropylsiloxyethyl)-8-naphthyl] *S*-methyl dithiocarbonate 18**

To a stirred solution of the alcohol **17** (12.6 mg, 0.028 mmol) in THF (1 cm^3) was added butyllithium (1.6 mol dm^3 in hexane; 0.085 cm^3, 0.14 mmol) at 0 °C under nitrogen. Stirring was continued for 30 min at 0 °C and for 1 h at room temperature. After this, carbon disulfide (12 mm^3, 0.2 mmol) was added at 0 °C to the mixture which was then stirred for 30 min. Iodomethane (23 mm^3, 0.37 mmol) was then added to the mixture and stirring was continued for 20 min. The reaction was quenched by addition of aq. ammonium chloride to the mixture which was then extracted with ethyl acetate (×2). The combined extracts were evaporated to dryness and the residue was purified by MPLC to provide the *xanthate* **18** (15.4 mg, quant); $[\alpha]_D$ +12 (*c* 0.99) (Found: C, 61.5; H, 9.5. $C_{28}H_{52}O_4S_2Si$ requires C, 61.7; H, 9.6%); ν_{max}/cm^{-1} 1464, 1386, 1242, 1177, 1110, 1048, 961, 884 and 681; δ_H(90 MHz) 0.75 (3 H, s, Me), 0.87 (3 H, d, *J* 6, 6-Me), 1.06 (18 H, s, *Me*CH × 6), 1.29 (3 H, s, Me), 1.4–2.01 (14 H, m), 2.29–2.35 (1 H, m), 2.51 (3 H, s, MeS), 3.72–4.11 (6 H, m, OCH_2CH_2O and 2′-H) and 4.88–5.05 (1 H, m, 8-H); *m/z* 501 ($M^+ - Pr^i$, 1%), 438 (33), 437 (93), 263 (34), 237 (13), 221 (13), 201 (52), 176 (16), 175 (100), 159 (14), 145 (15), 131 (19), 119 (13), 99 (84), 95 (13), 87 (35) and 73 (34).

(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-5,6,8a-trimethyl-5-(2′-triisopropylsiloxyethyl)naphthalen-1(2*H*)-one ethylene ketal 19

A solution of the xanthate **18** (254.9 mg, 0.47 mmol), butyltin hydride (0.25 cm^3, 0.93 mmol) and AIBN (15.5 mg, 0.094 mmol) in xylene (5 cm^3) was heated at 150 °C for 15 min. After the mixture had been cooled to room temperature, xylene was removed by flash column chromatography (eluent hexane). Elution with ethyl acetate followed by evaporation to dryness and purification of the residue by MPLC gave the *ketal* **19** (182.7 mg, 89%); $[\alpha]_D$ +5 (*c* 1.78) (Found: C, 71.0; H, 11.4. $C_{26}H_{50}O_3Si$ requires C, 71.2; H, 11.5%); ν_{max}/cm^{-1} 1463, 1383, 1335, 1279, 1240, 1180, 1091, 980, 938, 884 and 681; δ_H(90 MHz) 0.69 (3 H, s, Me), 0.82 (3 H, d, *J* 5, 6-Me), 1.02 (3 H, s, Me), 1.05 (18 H, s, *Me*CH × 6), 1.24–1.68 (17 H, m), 3.66 (2 H, dd, *J* 7 and 7, 2′-H) and 3.83–3.98 (4 H, m, OCH_2CH_2O); *m/z* 440 (9), 439 (31), 438 (M^+, 84%), 396 (32), 395 (100), 238 (20), 221 (32), 203 (75), 193 (49), 177 (95), 176 (49), 175 (75), 133 (20), 131 (28), 121 (29), 109 (29), 99 (78), 95 (40) and 86 (22).

(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-5-(2′-hydroxyethyl)-5,6,8a-trimethylnaphthalen-1(2*H*)-one 20

A solution of the ketal **19** (78 mg, 0.178 mmol) and a catalytic amount of PTSA in 80% aq. acetone (5 cm^3) was heated under reflux for 3 h. After addition of aq. sodium hydrogen carbonate to the mixture, the product was extracted with ethyl acetate (×2). The combined extracts were evaporated after which MPLC purification of the residue afforded the *hydroxy ketone* **20** (42.3 mg, quant); mp 87–89 °C; $[\alpha]_D$ +34 (*c* 0.90) (Found: C, 75.8; H, 11. $C_{15}H_{26}O_2$ requires C, 75.6; H, 11%); ν_{max}/cm^{-1} 3503, 1709, 1453, 1385, 1313, 1254, 1115, 1025, 950 and 669; δ_H(90 MHz) 0.81 (3 H, s, Me), 0.84 (3 H, d, *J* 6, 6-Me), 1.12 (3 H, s, Me), 1.09–2.77 (14 H, m) and 3.44–3.72 (3 H, m, OH and 2′-H); *m/z* 238 (M^+, 15%), 223 (28), 220 (62), 205 (44), 193 (96), 192 (47), 176 (53), 175 (95), 149 (24), 137 (56), 124 (33), 123 (30), 121 (40), 111 (67), 110 (37), 109 (69), 107 (30), 97 (29), 96 (88), 95 (78), 83 (59), 81 (89), 67 (75), 55 (100) and 41 (90).

(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-5,6,8a-trimethyl-5-(2′-triisopropylsiloxyethyl)naphthalen-1(2*H*)-one 21

To a stirred solution of the hydroxy ketone **20** (24.0 mg, 0.101 mmol) and 2,6-dimethylpyridine (35 mm^3, 0.30 mmol) in dichloromethane (1 cm^3) was added TIPSOTf (54 mm^3, 0.20 mmol) at 0 °C. After the reaction mixture had been stirred for 1 h, aq. sodium hydrogen carbonate was added to it to quench the reaction. The product was extracted with ether (×2) and the combined extracts were evaporated to dryness. The residue was purified by MPLC [eluent hexane–ethyl acetate (5:1)] to give the *silyl ether* **21** (36.3 mg, 91%); $[\alpha]_D$ +21 (*c* 0.64) (Found: C, 73.2; H, 11.9. $C_{24}H_{46}O_2Si$ requires C, 73; H, 11.75%); ν_{max}/cm^{-1}

1709, 1463, 1384, 1254, 1094, 1014, 950, 920, 884 and 682; δ_H(90 MHz) 0.8 (3 H, s, Me), 0.84 (3 H, d, *J* 7, 6-Me), 1.04 (18 H, s, *Me*CH × 6), 1.12 (3 H, s, Me), 1.25–2.62 (17 H, m) and 3.6 (2 H, td, *J* 7 and 2, 2'-H); *m/z* 394 (M^+, 1%), 351 (42), 203 (52), 177 (100), 175 (39), 133 (21), 131 (19), 121 (27), 109 (23), 107 (21), 95 (36) and 75 (26).

(4a*R*,5*R*,6*R*,8a*R*)-Decahydro-1-hydroxy-1,5,6,8a-tetramethyl-5-(2'-triisopropylsiloxyethyl)naphthalene 22

To a solution of the ketone **21** (53.3 mg, 0.135 mmol) in ether (1.5 cm^3) was added MeLi (1 mol dm^3 in hexane; 0.25 cm^3, 0.25 mmol) at 0 °C under nitrogen. The reaction was quenched by addition of aq. ammonium chloride to the mixture. The mixture was then extracted with ether (× 2) and the combined extracts were evaporated to leave an oil which was purified by MPLC [eluent hexane–ethyl acetate (5:1)] to give the *alcohol* **22** (56.6 mg, quant). The less polar, minor isomer had $[\alpha]_D$ +11 (*c* 0.41) (Found: C, 73.3; H, 12.3. $C_{25}H_{50}O_2Si$ requires C, 73.1; H, 12.3%); ν_{max}/cm^{-1} 3627, 1463, 1385, 1249, 1184, 1086, 994, 915, 884 and 681; δ_H(90 MHz) 0.8 (3 H, s, Me), 0.84 (3 H, d, *J* 7, 6-Me), 0.95 (3 H, s, Me), 1.04 (18 H, s, *Me*CH × 6), 1.12 (3 H, s, Me), 1.25–2.62 (18 H, m) and 3.60 (2 H, td, *J* 7 and 2, 2'-H); *m/z* 410 (M^+, 2%), 367 (4), 349 (8), 220 (15), 219 (82), 193 (25), 191 (48), 177 (15), 175 (19), 163 (52), 149 (57), 137 (29), 135 (25), 131 (24), 123 (69), 121 (24), 119 (21), 109 (100), 107 (24), 103 (21), 97 (18), 83 (25), 81 (42), 75 (36) and 69 (46).

The more polar, major isomer had $[\alpha]_D$ +6 (*c* 0.58) (Found: C, 73.2; H, 12.5. $C_{25}H_{50}O_2Si$ requires C, 73.1; H, 12.3%); ν_{max}/cm^{-1} 3621, 1463, 1384, 1313, 1247, 1179, 1093, 997, 884 and 682; δ_H(90 MHz) 0.73 (3 H, s, Me), 0.85 (3 H, d, *J* 5, 6-Me), 1.03 (3 H, s, Me), 1.07 (18 H, s, *Me*CH × 6), 1.27 (3 H, s, Me), 1.34–1.79 (18 H, m) and 3.67 (2 H, t like, *J* 7, 2'-H); *m/z* 410 (M^+, 4%), 368 (33), 367 (100), 235 (26), 217 (62), 191 (39), 177 (19), 131 (20), 123 (20), 109 (35), 103 (18), 95 (36), 81 (19), 75 (26) and 43 (18).

(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-1,5,6,8a-tetramethyl-5-(2'-triisopropylsiloxyethyl)naphthalene 23

To a stirred solution of the diastereoisomeric mixture of the alcohols **22** (31.4 mg, 0.07 mmol) in pyridine was added thionyl chloride (0.08 cm^3, 1.09 mmol) at 0 °C under nitrogen. After the mixture had been stirred for 1.5 h, ice was added to it to quench the reaction. The product was extracted with ethyl acetate (× 2) and the combined extracts were evaporated. MPLC purification of residue provided the *endo*-olefin **23** and the *exo*-olefin **24** (20.1 mg, 74%) in a 1:2 ratio.

A solution of the mixture of *endo*- and *exo*-olefins **23** and **24** (20.1 mg, 0.5 mmol) and iodine (2 mg) in xylene (3 cm^3) was heated under reflux for 2 h and then cooled to room temperature. Aq. sodium hypochlorite was added to the mixture which was then stirred until it was colourless. The organic layer was separated, diluted with hexane and passed through short column of silica gel. Elution with ethyl acetate followed by evaporation of solvent left an oil which was chromatographed by MPLC [eluent hexane] to give the endo-*olefin* **23** (18.2 mg, 91%); $[\alpha]_D$ −23 (*c* 0.44); ν_{max}/cm^{-1} 1463, 1383, 1092, 1014, 884 and 688; δ_H(90 MHz) 0.72 (3 H, s, Me), 0.86 (3 H, d, *J* 7, 6-Me), 0.98 (3 H, s, Me), 1.05 (18 H, s, *Me*CH × 6), 1.57 (3 H, d, *J* 1, 1-Me), 1.24–2.25 (15 H, m), 3.64 (2 H, t like, *J* 7, 2'-H) and 5.2 (1 H, br s, 2-H); *m/z* 392 (M^+, 7%), 350 (25), 349 (73), 218 (25), 217 (100), 191 (63), 189 (18), 161 (19), 147 (18), 121 (27), 119 (36), 109 (36), 107 (34) and 95 (52) (Found: M^+, 392.3474. $C_{25}H_{48}OSi$ requires *M*, 392.3474).

(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-5-(2'-hydroxyethyl)-1,5,6,8a-tetramethylnaphthalene 25

A solution of the olefin **23** (56.2 mg, 0.143 mmol) in THF (1 cm^3) and tetrabutylammonium fluoride (TBAF) (1.0 mol dm^3 in THF; 0.7 cm^3, 0.7 mmol) was stirred at room temperature for 7 h and then diluted with water and extracted with ethyl acetate (× 2). Evaporation of the combined extracts followed by MPLC purification of the residue gave the *alcohol* **25** (34.1 mg, quant); $[\alpha]_D$ −47 (*c* 0.57); ν_{max}/cm^{-1} 3630, 1458, 1383, 1024, 999 and 795; δ_H(90 MHz) 0.74 (3 H, s, Me), 0.86 (3 H, d, *J* 6, 6-Me), 0.99 (3 H, s, Me), 1.58 (3 H, s, 1-Me), 1.04–1.79 (11 H, m), 1.92–2.1 (2 H, m), 3.5–3.76 (2 H, m, 2'-H) and 5.2 (1 H, br d, *J* 1, 2-H); *m/z* 236 (M^+, 23), 221 (11), 203 (11), 194 (17), 193 (100), 192 (14), 191 (59), 177 (13), 175 (17), 163 (20), 149 (33), 147 (12), 136 (37), 135 (28), 133 (14), 123 (61), 122 (39), 121 (47), 119 (18), 109 (36), 108 (20), 107 (75), 105 (29), 95 (71), 93 (44), 91 (28), 81 (43), 79 (27), 69 (32) and 55 (37) (Found: M^+, 236.2140. $C_{16}H_{28}O$ requires *M*, 236.2140).

2-[(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-1,5,6,8a-tetramethyl-5-naphthyl]ethanal 26

To a stirred solution of oxalyl dichloride (14 mm^3, 0.16 mmol) in dichloromethane (1 cm^3) was added DMSO (23 mm^3, 0.32 mmol) at −60 °C under nitrogen. After the mixture had been stirred for 30 min, a solution of the alcohol **25** (7.7 mg, 0.033 mmol) in dichloromethane (3 cm^3) was added to it and stirring was continued for 45 min. Triethylamine (45 mm^3, 0.32 mmol) was then added to the mixture and the resulting slurry was stirred for 1 h at −20 °C. The mixture was then diluted with water and the product was extracted with dichloromethane (× 2). The combined extracts were evaporated to dryness to afford an oil which was purified by MPLC [eluent hexane–ethyl acetate (5:1)] to give the *aldehyde* **26** (9.0 mg, quant); $[\alpha]_D$ −30 (*c* 0.39); ν_{max}/cm^{-1} 2863, 2725, 1719, 1459, 1383, 1245, 1175, 1128, 1101, 1075, 1045, 1001 and 980; δ_H(90 MHz) 0.82 (3 H, s, Me), 0.95 (3 H, d, *J* 6, 6-Me), 0.99 (3 H, s, Me), 1.57 (3 H, d, *J* 2, 1-Me), 1.11–1.83 (8 H, m), 1.92–2.11 (2 H, m), 2.39 (2 H, t, *J* 3.5, 2'-H), 5.2 (1 H, br s, 2-H) and 9.67 (1 H, t, *J* 3.5, CHO); *m/z* 234 (M^+, 10%), 191 (11), 190 (35), 176 (11), 175 (65), 147 (15), 121 (20), 119 (15), 107 (17), 105 (17), 95 (15), 93 (16), 91 (16), 81 (16), 79 (14), 69 (14), 58 (30), 55 (16), 43 (100) and 41 (29) (Found: M^+, 234.1982. $C_{16}H_{26}O$ requires *M*, 234.1984).

3-{1-Hydroxy-2-[(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-octahydro-1,5,6,8a-tetramethyl-5-naphthyl]ethyl}furan 27

To a stirred solution of 3-bromofuran (21 mm^3, 0.23 mmol) in THF (1 cm^3) was added *tert*-butyllithium (1.5 mol dm^3 in hexane; 0.15 cm^3, 0.23 mmol) at −78 °C under nitrogen. After the mixture had been stirred for 30 min, a solution of the aldehyde **26** (10.9 mg, 0.047 mmol) in THF (4 cm^3) was added to it and the resulting solution was stirred for 25 min at −70 °C. The reaction was quenched by addition of aq. ammonium chloride to the mixture which was then extracted with ethyl acetate (× 2). The combined extracts were evaporated to dryness and the residue was purified by MPLC [eluent hexane–ethyl acetate (3:1)] to afford a diastereoisomeric mixture of the *alcohols* (1:1 ratio) **27** (13.7 mg, 97%); ν_{max}/cm^{-1} 3613, 1501, 1458, 1450, 1383, 1161, 1128, 1101, 1044, 1023, 999, 875 and 601; δ_H(90 MHz) 0.73 (3 H, s, Me), 0.91 (3 H, d, *J* 6, 6-Me), 1.0 (3 H, s, Me), 1.57 (3 H, d, *J* 2, 1-Me), 1.25–2.12 (13 H, m), 4.75–4.93 (1 H, m, 1'-H), 5.19 (1 H, br s, 2-H), 6.41 (1 H, br s, furan) and 7.37–7.41 (2 H, m, furan); *m/z* 302 (M^+, 2%), 285 (24), 284 (100), 190 (44), 175 (62), 161 (97), 148 (46), 147 (37), 133 (34), 121 (83), 119 (54), 108 (68), 107 (58), 105 (41), 95 (43), 91 (34), 85 (32), 83 (46), 81 (47) and 55 (31) (Found: $M^+ - H_2O$, 284.2140. $C_{20}H_{28}O$ requires *m/z* 284.2140).

3-{1-Acetoxy-2-[(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-octahydro-1,5,6,8a-tetramethyl-5-naphthyl]ethyl}furan 28

A solution of the alcohol **27** (24.3 mg, 0.08 mmol) in acetic anhydride (1 cm^3) and pyridine (1 cm^3) was stirred at room

temperature overnight under nitrogen. The solution was evaporated to dryness under reduced pressure and the residue was purified by MPLC [eluent hexane–ethyl acetate (5:1)] to provide the acetate **28** (25.5 mg, 92%); ν_{max}/cm^{-1} 1742, 1505, 1438, 1371, 1236, 1162, 1024, 951, 875 and 602; δ_H(90 MHz) 0.72 (3 H, s, Me), 0.89 (3 H, d, *J* 6, 6-Me), 0.98 (3 H, s, Me), 1.53 (3 H, s, 1-Me), 1.99 (3 H, s, Ac), 1.25–2.32 (12 H, m), 5.18 (1 H, br s, 1-H), 5.85–6.03 (1 H, m, 1'-H), 6.40 (1 H, br s, furan) and 7.35–7.44 (2 H, m, furan); *m/z* 285 (22%), 284 (M^+ – AcOH, 100), 269 (21), 190 (42), 175 (55), 161 (77), 148 (37), 147 (33), 133 (32), 121 (77), 119 (47), 108 (60), 107 (55), 105 (44), 95 (47), 93 (39), 91 (35), 81 (47), 55 (34) and 43 (42) (Found: M^+ – AcOH, 284.2139. $C_{20}H_{28}O$ requires *m/z* 284.2140).

3-{2-[(4a*R*,5*R*,6*R*,8a*R*)-3,4,4a,5,6,7,8,8a-Octahydro-1,5,6,8a-tetramethyl-5-naphthyl]ethyl}furan 3

To a stirred solution of lithium (1.7 mg, 0.24 mmol) in liquid ammonia (15 cm^3) was added a solution of the acetate **28** (6.6 mg, 0.019 mmol) in THF (5 cm^3) at −78 °C under nitrogen. The resulting solution was refluxed for 1.5 h after which liquid ammonia was removed by evaporation overnight at room temperature. Aq. ammonium chloride was added to the mixture and the product was extracted with ether (×2). Evaporation of the combined extracts followed by MPLC purification (eluent hexane) of the residue gave the *furan* **3** (4.9 mg, 89%); $[\alpha]_D$ −58 (*c* 0.36, $CHCl_3$); ν_{max}/cm^{-1} 1457, 1383, 1162, 1066, 1026, 874, 668 and 600; δ_H(90 MHz) 0.75 (3 H, s, Me), 0.83 (3 H, d, *J* 5, 6-Me), 1.00 (3 H, s, Me), 1.59 (3 H, d, *J* 2, 1-Me), 1.27–2.47 (14 H, m), 5.20 (1 H, br s, 1-H), 6.27 (1 H, br s, furan), 7.22 (1 H, br s, furan) and 7.37 (1 H, t, *J* 2, furan); *m/z* 287 (6%), 286 (M^+, 27), 271 (17), 191 (18), 121 (14), 107 (19), 96 (15), 95 (48), 81 (25), 58 (58), 43 (100) and 32 (69) (Found: M^+, 286.2297. $C_{20}H_{30}O$ requires *M*, 286.2297).

(5*R*,8*R*,9*R*,10*R*)-16-Hydroxycleroda-3,13(14)*Z*-dien-15,16-olide 1§

Anhydrous oxygen was passed through a solution of the furan **3** (9.2 mg, 0.032 mmol), diisopropylethylamine (56 mm^3, 0.32 mmol) and a catalytic amount of Rose Bengal in dichloromethane (6 cm^3) irradiated with a tungsten lamp and held at −78 to −55 °C for 1.5 h. The resulting solution was diluted with a mixture of hexane and ethyl acetate and passed through short column of silica gel to remove Rose Bengal. Evaporation of solvent followed by MPLC purification [eluent hexane–ethyl acetate (3:1)] gave the butenolide **1** (6.4 mg, 63%); $[\alpha]_D$ −43 (*c* 0.21, $CHCl_3$) and −46 (*c* 0.21, MeOH); ν_{max}/cm^{-1} 3336br, 1752, 1647, 1456, 1132, 957 and 761; δ_H(400 MHz) 0.77 (3 H, s, 20-Me), 0.81 and 0.82 (3 H total, d, *J* 6.4, 17-Me), 1.00 (3 H, s, 19-Me), 1.15–1.57 (6 H, m), 1.59 (3 H, d, *J* 1.2, 18-Me), 1.63–1.75 (4 H, m), 1.99–2.43 (4 H, m), 3.99 (1 H, br s), 5.19 (1 H, br s, 3-H), 5.85 (1 H, s, 14-H) and 6.00 (1 H, s, 16-H); *m/z* 318 (M^+, 34%), 303 (14), 285 (33), 191 (62), 190 (62), 189 (100), 175 (18), 135 (40), 123 (79) and 107 (83) (Found: M^+, 318.2194. $C_{20}H_{30}O_3$ requires M, 318.2195).

§ Non-systematic numbering is used in this part. See text.

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