Total Synthesis of (+)-Perrottetianal A

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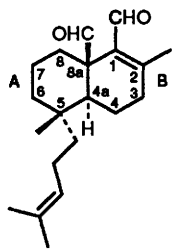
The total synthesis of (+)-perrottetianal A, one of the sacculatane-type diterpenes isolated from liverworts, has been achieved starting from an optically active Wieland–Miescher ketone analogue. The ethylene glycol monoacetal of the starting material was converted into the *trans*-decalone containing the required C-5 and -8a reactant groups *via* an eight-step reaction sequence. After introduction of a methyl group and then transformation of the angular hydroxymethyl functionality to the protected aldehyde group, an additional α,β-unsaturated formyl group was introduced by Nozaki and Yamamoto's method to give the corresponding C-8a monoacetal. Finally, hydrolysis of the acetal furnished (+)-perrottetianal A, which established the absolute configuration as (4a*S*,5*S*,8a*R*).

Recently, various sacculatane-type diterpenes with biological activity have been isolated from the liverworts.†[1,2] (+)-Perrottetianal A (**1**) was isolated as one of the bitter principles from the liverwort *Porella perrottetiana* or *Makinoa crispata* by Asakawa *et al.*[2] and was found to inhibit weakly the germination of rice in the husk.[2] The absolute configuration of compound (**1**) has been tentatively assigned to be (4a*S*,5*S*,8a*R*)‡ by comparison of the CD spectrum with that of a sesquiterpenoid, (−)-polygodial. Here, we report the first total synthesis of (+)-perrottetianal A (**1**) starting from an optically active Wieland–Miescher ketone analogue (*S*)-(+)-(**2**),[3,4] which offers unambiguous proof of the absolute stereochemistry.[5]



(**1**)

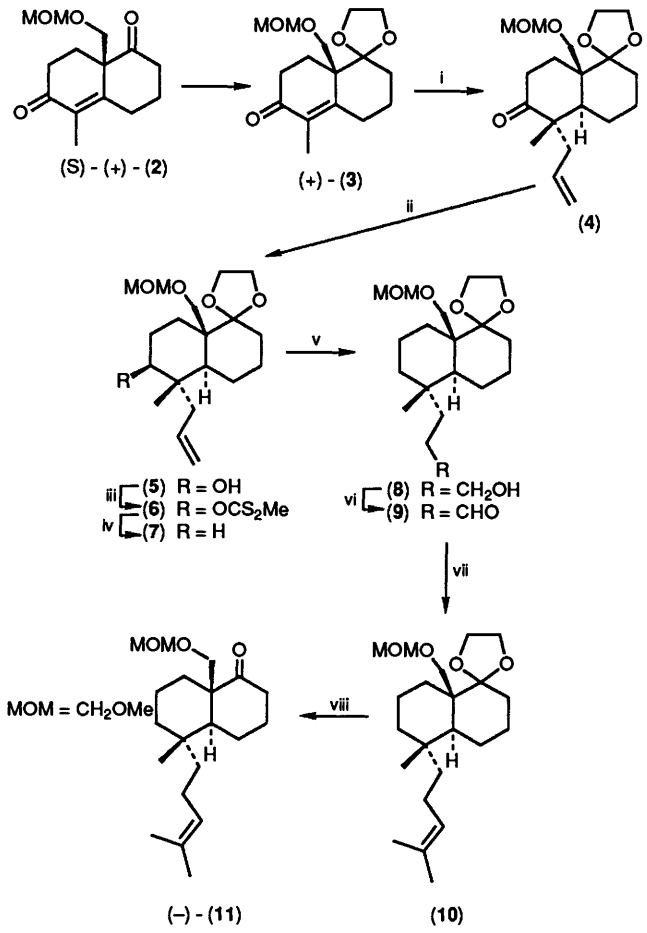
Results and Discussion

Functionalisation of the A *Ring.*—Functionalisation of the ring A of compound (**1**), formation of the *trans*-decalin ring system, and introduction of the homoprenyl side-chain at C-5, was achieved by following the protocol we had previously developed for the synthesis of (+)-dysideapalaunic acid[6] and (−)-sacculatal[7] (Scheme 1). Thus, reductive allylation of the optically pure monoacetal (+)-(**3**)[4] gave the allylated *trans*-decalone (**4**) quantitatively. To reduce the carbonyl group at C-6 of compound (**4**) to the methylene moiety of the decalin (**7**), the ketone (**4**) was stereoselectively reduced with lithium aluminium hydride (LAH) to yield the β-alcohol (**5**) in 81% yield, along with the α-alcohol in 16% yield; the β-alcohol was then converted into the xanthate (**6**) in quantitative yield by successive treatment with butyl-lithium, carbon disulphide, and methyl iodide. The xanthate (**6**) was next reduced with tributylstannane[8] to give the *trans*-decalin (**7**) in 82% yield. All attempts to reduce the carbonyl group of ketone (**4**) directly to the methylene group of the decalin (**7**) by Huang-Minlon procedure or through the toluene-*p*-sulphonylhydrazone were unsuccessful. Elaboration of the homoprenyl side-chain of compound (**7**) was achieved in straightforward manner as follows. Hydroboration of the allylic double bond in compound (**7**) followed by oxidation of the resulting alcohol (**8**) by pyridinium dichromate (PDC) gave the aldehyde (**9**) in 66% overall yield. Wittig reaction of the aldehyde (**9**) with isopropylidenetriphenylphosphorane completed formation of the homoprenyl side-chain to give compound (**10**) in 68% yield, and the product was hydrolysed selectively, yielding the desired *trans*-decalone intermediate (−)-(**11**) in quantitative yield.

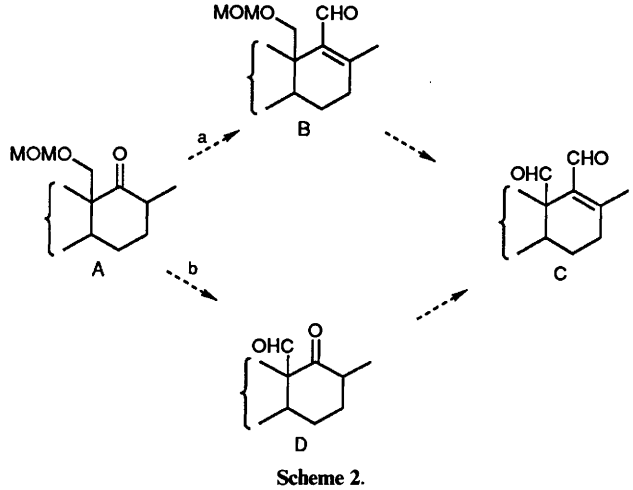
Model Experiments for the Preparation of Dialdehydic Functionality.—For functionalisation of the two aldehyde groups in the final target molecule, there are alternative routes (Scheme 2): path a (A ⟶ B ⟶ C) *via* introduction of an α,β-unsaturated aldehyde group first and then oxidation of the angular, protected hydroxymethyl group to the aldehyde, and path b (A ⟶ D ⟶ C) is the reverse sequence. In order to ascertain the applicability of either route, we examined model experiments on a cyclohexanone analogue (**17**), which was prepared from ethyl 1-methyl-2-oxocyclohexanecarboxylate (**12**) in straightforward manner: acetalisation, reduction, protection, deacetalisation, and methylation (Scheme 3). In this preparation, it should be noted that the direct monomethylation of the keto ether (**16**) to (**17**) was successfully achieved in 76% yield by the use of lithium di-isopropylamide (LDA), hexamethylphosphoric triamide (HMPA), and methyl iodide in tetrahydrofuran (THF) at room temperature. Compound (**17**) consisted of two inseparable stereoisomers. We examined first the functionalisation of ketone (**17**) *via* path a. Reaction of compound (**17**) with dichloromethyl-lithium according to Nozaki and Yamamoto's procedure[9] gave the α,β-unsaturated aldehyde (**18**) in 53% yield. Unfortunately, attempts to deprotect the methoxymethyl group of compound (**18**) were unsuccessful, resulting in decomposition. We then tried the functionalisation of compound (**17**) *via* path b. Deprotection of the methoxymethyl group of compound (**17**)

† Sacculatane is based on (−)-sacculatal, the first compound of this type to be isolated.[1]

‡ Nomenclature and numbering based on the naphthalene nucleus.

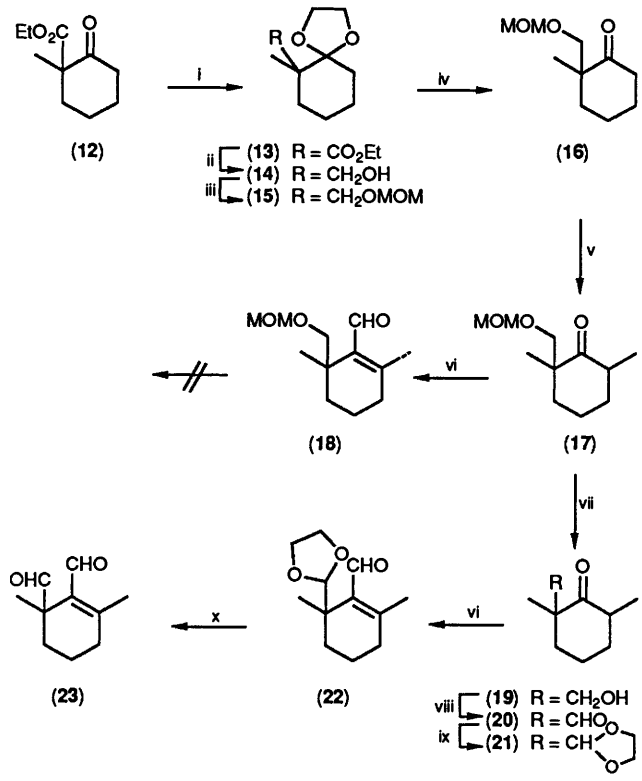


Scheme 1. *Reagents and conditions:* i, Li, liq. NH_3, THF, CH_2=$CHCH_2Br$, water (1 mol equiv.); ii, LAH, Et_2O, 0 °C; iii, BuLi, THF, CS_2, MeI, 0 °C; iv, Bu_3SnH, AIBN, xylene, 150 °C, 6 min; v, BH_3–THF, THF, 0 °C; then NaOH, H_2O_2; vi, PDC, molecular sieves 4 Å, CH_2Cl_2; vii, Ph_3P=$C(Me)_2$, DMSO, Et_2O; viii, PPTS, aq. acetone, reflux.



Scheme 2.

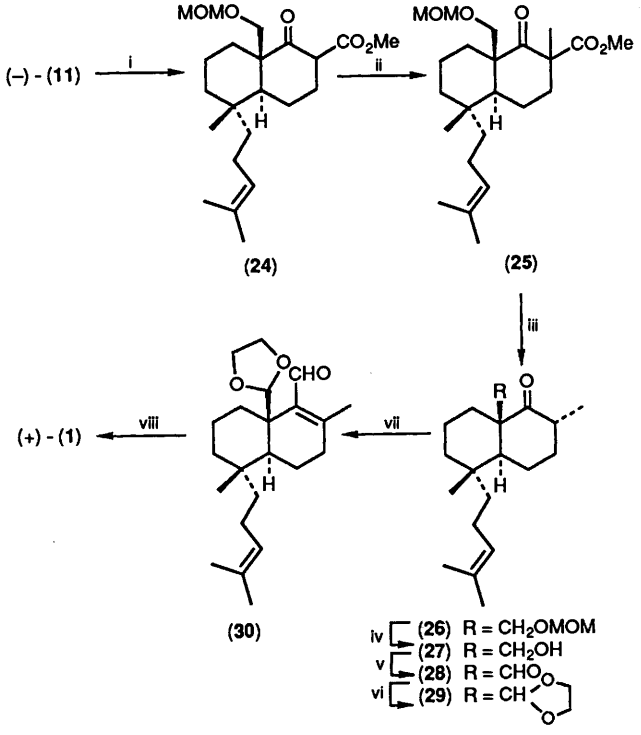
gave equal amounts of two stereoisomeric aldols (**19**) in 80% yield without formation of the fragmentation product by a retro-aldol process. Swern oxidation [10] of both hydroxymethyl ketones (**19**) afforded the corresponding stereoisomeric keto aldehyde (**20**). The aldehyde group of compound (**20**) was selectively protected by treatment with 2-ethyl-2-methyl-1,3-dioxolane to give the keto acetal (**21**) in 84% yield. Treatment of the acetal (**21**) with dichloromethyl-lithium followed by hydrolysis of the acetal of the resulting unsaturated aldehyde (**22**) furnished the dialdehyde (**23**) in 25% overall yield from acetal (**21**). Thus, path b would be suitable for elaboration of the dialdehydic functionality of perrottetianal A (**1**).



Scheme 3. *Reagents and conditions:* i, $(CH_2OH)_2$, PTSA, benzene; ii, LAH, Et_2O, 0 °C; iii, MOMCl, di-isopropylethylamine, CH_2Cl_2; iv, PPTS, aq. acetone, reflux; v, $(MeO)_2CO$, NaH, THF, reflux; NaH, MeI, THF; then LiCl, HMPA, 120 °C or LDA, MeI, HMPA, THF; vi, LDA, CH_2Cl_2; then $LiClO_4$, $CaCO_3$, HMPA, 130 °C; vii, conc. H_2SO_4 (cat), aq. EtOH, reflux; viii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ix, 2-ethyl-2-methyl-1,3-dioxolane, D-camphorsulphonic acid, 40 °C; x, aq. AcOH, 50 °C.

Synthesis of (+)-*Perrottetianal A*.—Based on the results obtained in the model experiments, the same synthetic sequence was employed with the precursor ketone (**11**) (Scheme 4). However, contrary to results with the model compound (**10**), attempted direct methylation of ketone (–)-(**11**) with LDA, sodium amide, or potassium hydride as base resulted in the recovery of starting compound. Thus, in order to activate C-2 of compound (**11**) a methoxycarbonyl group was introduced by reaction with sodium hydride and dimethyl carbonate in the presence of 15-crown-5 to give the keto ester (**24**) in 95% yield. Methylation of compound (**24**) with sodium hydride and methyl iodide in the presence of 4 mol equiv. of HMPA (97%) afforded the two stereoisomeric oily (80%) and crystalline (11%) β-keto esters (**25**). Absence of HMPA gave a lower yield. From the fact that the B part of the AB-type quartet due to the angular methylene group was more shielded in the major isomer than that in the minor isomer in the NMR spectrum (see Experimental section), the orientation of the 2-Me group was assigned to be *cis*-axial to the angular methylene group in the major isomer. Demethoxycarbonylation of the methylated product (**25**) with lithium chloride in HMPA smoothly yielded compound (**26**) in 92% yield. The orientation of the methyl group at C-2 was confirmed to be α-equatorial based on the coupling pattern (d quint, J 12 and 6 Hz) of the proton at C-2 in the NMR

spectrum. Of the two aldehyde groups in the target molecule (**1**), the one at the ring junction was prepared first according to the model experiments. Deprotection of the methoxymethyl group of compound (**26**) with a catalytic amount of conc. H_2SO_4 in refluxing aqueous ethanol (EtOH) to give the aldol (**27**) [62%, 88% based on compound (**25**)]. Longer reaction time or a larger amount of conc. H_2SO_4 decreased the yield considerably. The aldol (**27**) was subjected to Swern oxidation to give the aldehyde (**28**) (91%), which was protected selectively as the acetal (**29**) (86%) by treatment with ethylene glycol bis-trimethylsilyl ether catalysed by trimethylsilyl trifluoromethanesulphonate (TMSOTf),[11] since the use of 2-ethyl-2-methyl-1,3-dioxolane failed, giving rise to a complex mixture of products. Introduction of the α,β-unsaturated aldehyde group was accomplished by Nozaki–Yamamoto procedure in the presence of hex-1-ene, leading to the unsaturated aldehyde (**30**) in 64% yield. Addition of hex-1-ene to the reaction mixture was helpful in getting reproducible yields. Finally, deprotection of the acetal of (**30**) completed the synthesis of (+)-perrottetianal A (**1**) (78%), $[\alpha]_D$ +395° (*c* 0.05, $CHCl_3$) [lit.,[2] +282° (*c* 2.0, $CHCl_3$)], identical (^{1}H NMR, IR, and MS) with the natural material. Thus, the absolute stereochemistry of compound (**1**) was unambiguously established to be (4a*S*,5*S*,8a*R*), as depicted.



Scheme 4. *Reagents and conditions:* i, $(MeO)_2CO$, NaH, 15-crown-5, THF, reflux; ii, NaH, MeI, HMPA; iii, LiCl, HMPA, 130 °C; iv, conc. H_2SO_4 (cat), aq. EtOH, reflux; v, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; vi, $(CH_2OTMS)_2$, TMSOTf, CH_2Cl_2; vii, LDA, CH_2Cl_2, hex-1-ene; then $LiClO_4$, $CaCO_3$, HMPA, 130 °C; viii, PPTS, aq. acetone, 80 °C.

Experimental

All m.p.s were determined with a Mitamura Riken hot-stage apparatus and were uncorrected. IR spectra were recorded on a JASCO A-3 spectrophotometer for solutions in carbon tetrachloride. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with JEOL PS-100 (100 MHz), FX-90Q (90 MHz), and PMX-60 (60 MHz) instruments with tetramethylsilane as internal standard. Mass spectra were run on a JEOL JMS-DX300 spectrometer with a JMA-3500 data system. Optical rotations $[\alpha]_D$ were determined for solutions in chloroform on a JASCO DIP-4S polarimeter at 22 °C. The circular dichroism value was obtained with a JASCO-400X spectropolarimeter. Medium-pressure liquid chromatography (MPLC) was carried out on a JASCO PRC-50 instrument with a silica gel packed column. Anhydrous sodium sulphate was used for the drying of organic extracts. Microanalyses were carried out in the microanalytical laboratory of this Institute. Ether refers to diethyl ether. THF was distilled from LAH before use.

(4a*S*,5*S*,8a*S*)-(+)-3,4,4a,5,8,8a-*Hexahydro*-8a-*methoxymethoxymethyl*-5-*methyl*-5-(*prop*-2-*enyl*)*naphthalene*-1,6(2H,7H)-*dione* 1-*Ethylene Acetal* (**4**).—To a solution of lithium amide [from lithium (119 mg, 17 mmol)] in liquid ammonia (*ca.* 50 ml; distilled from sodium) was added a solution of the acetal enone (**3**)[4] {1.184 g, 4 mmol; 100% optically pure; $[\alpha]_D$ +88.7° (*c* 1.10), m.p. 108–110 °C (from hexane–ether)} in THF (20 ml) containing water (72 μl, 4 mmol) under nitrogen. The resulting solution was warmed under reflux of liquid ammonia for 45 min, and then a solution of 3-bromopropene (3.7 ml, 40 mmol) in THF (4 ml) was added. The blue colour of the solution disappeared during the addition. The solution was refluxed for a further 45 min and then liquid ammonia was evaporated off at room temperature. After the addition of aq. ammonium chloride, extraction with ether followed by column chromatography [eluant hexane–ethyl acetate (2:1)] afforded the *ketone* (**4**) (1.368 g, 100%) as an oil, $[\alpha]_D$ +4.0° (*c* 0.20); ν_{max} 3 080, 1 705, 1 640, 1 440, 1 180, 1 155, 1 110, 1 050, and 920 cm^{-1}; δ(60 MHz) 1.09 (3 H, s, 5-Me), 1.2–2.8 (13 H, m), 3.35 (3 H, s, OMe), 3.72 and 3.84 (each 1 H, AB-type q, *J* 10 Hz, 8a-CH_2O), 3.93 (4 H, s, OCH_2CH_2O), 4.56 (2 H, s, OCH_2O), and 4.77–6.10 (3 H, m, $CH{=}CH_2$) (Found: C, 67.8; H, 8.7. $C_{19}H_{30}O_5$ requires C, 67.4; H, 8.9%).

(4a*S*,5*S*,6*S*,8a*S*)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-6-*hydroxy*-8a-*methoxymethoxymethyl*-5-*methyl*-5-(*prop*-2-*enyl*)-*naphthalen*-1(2H)-*one Ethylene Acetal* (**5**).—To a stirred slurry of LAH (380 mg, 10 mmol) in anhydrous ether (50 ml) at 0 °C under nitrogen was added dropwise a solution of the ketone (**4**) (3.55 g, 10.5 mmol) in ether (50 ml). The mixture was stirred at 0 °C for 25 min, and was then worked up as usual by careful addition of wet ether and then water. Column chromatography and MPLC [eluant hexane–ethyl acetate (1:1)] of the crude product gave the (6S)-*alcohol* (**5**) (2.86 g, 81%) and (4a*S*,5*S*,-6*R*,8a*S*)-3,4,4a,5,6,7,8,8a-octahydro-6-hydroxy-8a-methoxymethoxymethyl-5-methyl-5-(prop-2-enyl)naphthalen-1(2*H*)-one ethylene acetal (574 mg, 16%). The (6S)-alcohol (**5**) had $[\alpha]_D$ −38.7° (*c* 0.50); ν_{max} 3 625, 3 500, 3 075, 1 640, 1 450, 1 150, 1 045, and 920 cm^{-1}; δ(100 MHz) 0.94 (3 H, s, 5-Me), 1.2–2.1 (11 H, m), 2.35 and 2.07 (each 1 H, AB-type q and d, *J* 14, 7 Hz, 5-$CH_2CH{=}CH_2$), 3.38 (3 H, s, OMe), 3.38 (1 H, dd, *J* 15, 8 Hz, 6-H$^{\alpha}$), 3.86 (2 H, s, 8a-CH_2), 3.90 (4 H, br s, OCH_2CH_2O), 4.62 (2 H, s, OCH_2O), 4.96–5.28 (2 H, m, 5-$CH_2CH{=}CH_2$), and 5.64–6.12 (1 H, m, 5-$CH_2CH{=}CH_2$) (Found: C, 67.1; H, 9.7. $C_{19}H_{32}O_5$ requires C, 67.0; H, 9.5%).

The stereoisomeric (6*R*)-alcohol had $[\alpha]_D$ −49.1° (*c* 0.200); ν_{max} 3 600, 3 500br, 3 060, 2 975, 1 635, 1 450, 1 215, 1 180, 1 150, 1 045, 1 000, and 920 cm^{-1}; δ(100 MHz) 0.98 (3 H, s, 5-Me), 1.2–2.2 (13 H, m), 3.34 (3 H, s, OMe), 3.50 (1 H, br s, $w_{\frac{1}{2}}$ 7 Hz, 6-H$^{\beta}$), 3.84 (2 H, s, 8a-CH_2O), 3.90 (4 H, s, OCH_2CH_2O), 4.60 (2 H, s, OCH_2O), 4.9–5.2 (2 H, m, 5-$CH_2CH{=}CH_2$), and 5.8–6.2 (1 H, m, 5-$CH_2CH{=}CH_2$).

(1S,2S,4a*S*,8a*S*)-(−)-5,5-*Ethylenedioxydecahydro*-4a-*methoxymethoxymethyl*-1-*methyl*-1-(*prop*-2-*enyl*)*naphthalen*-2-*yl* S-*Methyl Dithiocarbonate* (**6**).—To a solution of the alcohol (**5**) (683 mg, 2 mmol) in THF (10 ml) was added a solution of BuLi (1.7M in hexane; 2.35 ml, 4 mmol) and then carbon

disulphide (0.36 ml, 6 mmol) was added to the mixture at 0 °C at 10 min intervals under nitrogen. After the addition of methyl iodide (0.37 ml, 6 mmol), the mixture was stirred for 30 min. The reaction was quenched by the addition of aq. ammonium chloride. Extraction with ether followed by MPLC [eluant hexane–ethyl acetate (2:1)] purification gave the *xanthate* (**6**) (824 mg, 96%), $[\alpha]_D$ −40.1° (*c* 1.29); ν_{max} 3 075, 1 640, 1 450, 1 230, 1 150, 1 065, 1 050, and 920 cm^{-1}; δ(90 MHz), 1.12 (3 H, s, 1-Me), 1.2–2.2 (13 H, m), 2.56 (3 H, s, SMe), 3.40 (3 H, s, OMe), 3.88 (2 H, s, 4a-CH_2), 3.92 (5 H, br s, OCH_2CH_2O and 2-H^{α}), 4.64 (2 H, s, OCH_2O), and 4.84–6.12 (3 H, m, $CH{=}CH_2$) (Found: C, 58.8; H, 8.25. $C_{21}H_{34}O_5S_2$ requires C, 58.6; H, 8.0%).

(4aS,5S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-8a-*methoxymethoxymethyl*-5-*methyl*-5-(*prop*-2-*enyl*)*naphthalen*-1(2H)-*one Ethylene Acetal* (**7**).—A solution of the xanthate (**6**) (1.826 g, 4.25 mmol), azoisobutyronitrile (AIBN) (158 mg, 0.96 mmol), and tributylstannane (3.4 ml, 12.8 mmol) in anhydrous xylene (60 ml) was heated at 150 °C for 6 min under nitrogen. The solution changed its colour from orange to black. The resulting solution was poured into water and the product was extracted with ether. Evaporation of the solvents followed by column chromatography [eluant hexane–ethyl acetate (2:1)] afforded the *decalin* (**7**) (1.122 g, 82%). The same procedure was applied to the xanthate prepared from the (6*R*)-alcohol (709 mg, 1.65 mmol), and gave the same *decalin* (**7**) (339 mg, 64%), $[\alpha]_D$ −41.3° (*c* 2.33); ν_{max} 3 075, 1 450, 1 180, 1 150, 1 110, and 920 cm^{-1}; δ(60 MHz) 0.92 (3 H, s, 5-Me), 1.0–2.1 (13 H, m), 1.97 (2 H, d, *J* 7 Hz, 5-$CH_2CH{=}CH_2$), 3.37 (3 H, s, OMe), 3.87 (6 H, s, OCH_2CH_2O and 8a-CH_2O), 4.57 (2 H, s, OCH_2O), and 4.67–6.17 (3 H, m, $CH{=}CH_2$) (Found: C, 70.1; H, 9.9. $C_{19}H_{32}O_4$ requires C, 70.3; H, 9.9%).

(4aS,4S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-5-(3-*hydroxypropyl*)-8a-*methoxymethoxymethyl*-5-*methylnaphthalen*-1(2H)-*one Ethylene Acetal* (**8**).—To a stirred solution of the decalin (**7**) (952 mg, 2.94 mmol) in THF (15 ml) at 0 °C under nitrogen was added a solution of borane–THF complex (1M in THF; 6 ml). After being stirred for 20 min at O °C and for 40 min at room temperature, the mixture was treated successively with water (2 ml), aq. sodium hydroxide (3M; 2 ml), and hydrogen peroxide (30%; 1 ml) at 0 °C. After being stirred for 20 min at 0 °C and then for 30 min at room temperature, the resulting solution was poured into aq. ammonium chloride. Extraction with ether followed by column chromatography [eluant hexane–ethyl acetate (3:1)] gave the *alcohol* (**8**) (755 mg, 75%), $[\alpha]_D$ −34.9° (*c* 2.00); ν_{max} 3 650, 3 500br, 1 460, 1 180, 1 155, 1 120, and 1 050 cm^{-1}; δ(90 MHz) 0.93 (3 H, s, 5-Me), 1.0–2.0 (17 H, m), 3.40 (3 H, s, OMe), 3.60 (2 H, t, *J* 7 Hz, 5-$CH_2CH_2CH_2OH$), 3.88 (2 H, s, 8a-CH_2O), 3.92 (4 H, narrow d, OCH_2CH_2O), and 4.65 (2 H, s, OCH_2O); *m/z* 342 (M^+, 1.2%), 280 (10), 99 (100), 98 (34), 145 (51), 55 (59), and 45 (65) (Found: C, 66.5; H, 10.2. $C_{19}H_{34}O_5$ requires C, 66.6; H, 10.0%).

(−)-3-[(1S,4aS,8aS)-5,5-*Ethylenedioxydecahydro*-4a-*methoxymethoxymethyl*-1-*methylnaphthalen*-1-*yl*]*propanal* (**9**).—To a stirred slurry of PDC (3.205 g, 8.5 mmol) and molecular sieves 4 Å powder[12] (3.22 g) in methylene dichloride (20 ml) at room temperature under nitrogen was added a solution of the alcohol (**8**) (730 mg, 2.14 mmol) in methylene dichloride (15 ml). After being stirred for 30 min, the resulting slurry was passed through an SiO_2 column with the aid of ether. Evaporation of the solvents afforded the *aldehyde* (**9**) (639 mg, 88%), $[\alpha]_D$ −42.8° (*c* 2.03); ν_{max} 2 700, 1 715, 1 450, 1 180, 1 155, 1 115, and 1 050 cm^{-1}; δ(60 MHz) 0.95 (3 H, s, 1-Me), 1.0–2.8 (17 H, m), 3.38 (3 H, s, OMe), 3.86 (2 H, s, 4a-CH_2O), 3.90 (4 H, s, OCH_2CH_2O), 4.60 (2 H, s, OCH_2O), and 9.77 (1 H, m, CHO); *m/z* 340 (M^+, 0.5%), 295 (14), 251 (15), 99 (100), 87 (31), 86 (49), 58 (34), 55 (27), 45 (55), and 43 (98) (Found: M^+, 340.221 91. $C_{19}H_{32}O_5$ requires *M*, 340.224 91).

(4aS,5S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-8a-*methoxymethoxymethyl*-5-*methyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1(2H)-*one Ethylene Acetal* (**10**).—To a stirred slurry of isopropyltriphenylphosphonium iodide (2.684 g, 6.2 mmol) in anhydrous ether (12 ml) at room temperature under nitrogen was added dropwise a solution of BuLi (1.7M in hexane; 3.5 ml, 6 mmol). After addition of dimethyl sulphoxide (DMSO) (2.5 ml), the resulting solution was stirred for a further 1 h to give a deep red solution. A solution of the aldehyde (**9**) (528 mg, 1.55 mmol) in ether (10 ml) was added to the red mixture at −62 °C and the resulting solution was allowed to warm to −20 °C during 45 min. After being stirred at room temperature for 1 h, the reaction mixture was quenched by the addition of aq. ammonium chloride. Extraction with ether followed by MPLC [eluant hexane–ethyl acetate (3:1)] purification gave the *decalin* (**10**) (504 mg, 89%), $[\alpha]_D$ −26.8° (*c* 3.16); ν_{max} 1 720, 1 450, 1 155, 1 110, and 1 050 cm^{-1}; δ(60 MHz) 0.90 (3 H, s, 5-Me), 0.9–2.9 (17 H, m), 1.58 and 1.65 (each 3 H, olefinic Me_2), 3.33 (3 H, s, OMe), 3.87 (6 H, br s, OCH_2CH_2O and 8a-CH_2O), 4.57 (2 H, s, OCH_2O), and 5.03 (1 H, br t, *J* 6 Hz, olefinic H); *m/z* 367 (M^+ + 1, 24%), 366 (M^+, 58), 99 (100), 86 (28), 69 (24), and 45 (44) (Found: C, 72.0; H, 10.6. $C_{22}H_{38}O_4$ requires C, 72.1; H, 10.45%).

(4aS,5S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-8a-*methoxymethoxymethyl*-5-*methyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1(2H)-*one* (**11**).—A solution of the acetal (**10**) (421 mg, 1.15 mmol) and pyridinium toluene-*p*-sulphonate (PPTS)[13] (54 mg) in acetone (10 ml) was refluxed for 26 h. Extraction with ether followed by MPLC [eluant hexane–ethyl acetate (3:1)] purification afforded the *ketone* (**11**) (342 mg, 92%), $[\alpha]_D$ −10.8° (*c* 1.20); ν_{max} 1 720, 1 450, 1 150, and 1 040 cm^{-1}; δ(90 MHz) 0.83 (3 H, s, 5-Me), 1.0–3.0 (17 H, m), 1.58 and 1.67 (each 3 H, s, olefinic Me_2), 3.32 (3 H, s, OMe), 3.86 and 4.03 (each 1 H, AB-type q, *J* 9 Hz, 8a-CH_2O), 4.56 (2 H, s, OCH_2O), and 5.04 (1 H, br t, olefinic H) (Found: M^+, 322.251 56. $C_{20}H_{34}O_3$ requires *M*, 322.250 76).

Ethyl 2,2-*Ethylenedioxy*-1-*methylcyclohexanecarboxylate* (**13**).—A solution of the keto ester (**12**) (16.24 g, 94.4 mmol) and toluene-*p*-sulphonic acid (PTSA) monohydrate (307 mg, 1.62 mmol) in anhydrous benzene (60 ml) was heated under reflux with ethylene glycol (9 ml, 162 mmol) with a Dean–Stark water separator overnight under nitrogen. After cooling to room temperature, the reaction mixture was poured into aqueous sodium hydrogen carbonate–ice, and the product was extracted with ether twice. Evaporation of the solvents afforded almost pure acetal (**13**) (19.22 g, 96%), ν_{max} 1 730, 1 465, 1 260, 1 235, 1 180, 1 130, 1 120, 1 100, and 1 055 cm^{-1}; δ(60 MHz) 1.23 (3 H, s, 1-Me), 1.25 (3 H, t, *J* 7 Hz, OCH_2Me), 1.2–2.8 (8 H, m), 3.90 (4 H, s, OCH_2CH_2O), and 4.15 (2 H, q, *J* 7 Hz, OCH_2Me).

2-*Hydroxymethyl*-2-*methylcyclohexanone Ethylene Acetal* (**14**).—To a stirred suspension of LAH (3.00 g, 81 mmol) in anhydrous ether (100 ml) at 0 °C under nitrogen was added dropwise a solution of the acetal ester (**13**) (19.22 g, 90.7 mmol) in anhydrous ether (100 ml) during 20 min. The resulting solution was stirred for 30 min at room temperature and then quenched by the addition of wet ether and then water. Filtration, evaporation of the ether, and column chromatography [eluant hexane–ethyl acetate (3:1)] of the residue afforded the *acetal alcohol* (**14**) [11.84 g, 70% in two steps from the keto ester (**12**)], ν_{max} 3 550, 1 470, 1 420, 1 185, 1 130, 1 100, 1 040, and 950 cm^{-1}; δ(60 MHz) 1.02 (3 H, s, 2-Me), 1.58 (8 H, br s), 3.08 (1 H, br s, OH), 3.63 (2 H, br s, CH_2OH), and 4.07 (4 H, s,

OCH_2CH_2O) (Found: C, 64.5; H, 9.8. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

2-Methoxymethoxymethyl-2-methylcyclohexanone Ethylene Acetal (**15**).—A solution of the acetal alcohol (**14**) (6.558 g, 35.6 mmol), di-isopropylethylamine (12 ml, 70 mmol), and methoxymethyl chloride (5.4 ml, 70 mmol) in methylene dichloride (5 ml) was stirred at room temperature overnight under nitrogen. After addition of ice, the product was extracted with ether to give, after work-up, the methoxymethyl compound (**15**) (7.43 g), ν_{max} 1 460, 1 450, 1 180, 1 150, 1 100, 1 090, 1 050, 950, and 915 cm^{-1}; δ(60 MHz) 1.03 (3 H, s, 2-Me), 1.55 (8 H, br s), 3.35 (4 H, s, includes A part of AB-type q, OMe and 2-CH*H*O), 3.53 (1 H, B part of AB-type q, *J* 4 Hz, 2-C*H*HO), 3.90 (4 H, s, OCH_2CH_2O), and 4.62 (2 H, s, OCH_2O); *m/z* 230 (M^+, 1%), 215 (7), 185 (20), 169 (29), 113 (17), 99 (100), 86 (18), 73 (16), 55 (37), and 45 (66).

2-Methoxymethoxymethyl-2-methylcyclohexanone (**16**).—A solution of the crude acetal (**15**) (7.43 g) and PPTS (1.62 g, 6.45 mmol) in acetone (100 ml) was heated under reflux overnight. After evaporation of the acetone under reduced pressure, the residue was extracted with ether, and column chromatography [eluant hexane–ethyl acetate (3:1)] afforded the *ketone* (**16**) [3.45 g, 58% in two steps from the acetal alcohol (**14**)], ν_{max} 1 710, 1 470, 1 455, 1 155, 1 120, 1 050, and 925 cm^{-1}; δ(60 MHz) 1.13 (3 H, s, 2-Me), 1.3–2.2 (6 H, m), 2.2–2.6 (2 H, m, 6-H_2), 3.33 (3 H, s, OMe), 3.57 (2 H, s, 2-CH_2O), and 4.57 (2 H, s, OCH_2O); *m/z* 186 (M^+, 0.4%), 141 (9), 124 (11), 95 (12), 55 (18), and 45 (100) (Found: C, 64.4; H, 9.8. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%).

2-Methoxymethoxymethyl-2,6-dimethylcyclohexanone (**17**).—*Method I:* To a stirred slurry of sodium hydride (50%; 1.15 g; washed with hexane three times, 24 mmol) in dimethyl carbonate (2.5 ml, 30 mmol) and THF (5 ml) under nitrogen was added a solution of the keto ether (**16**) (1.866 g, 10 mmol) in THF (15 ml). The resulting slurry was heated under reflux for 3 h. The reaction was quenched by the addition of ice to the mixture at 0 °C and dil. HCl was added (to pH 2). The product was extracted with ether and the extract was washed with water until neutral to litmus. Evaporation of the ether followed by column chromatography [eluant hexane–ethyl acetate (3:1)] of the residue gave methyl 3-methoxymethoxymethyl-3-methyl-2-oxocyclohexanecarboxylate (2.197 g, 90%), ν_{max} 1 750, 1 710, 1 650, 1 610, 1 440, 1 365, 1 290, 1 245, 1 190, 1 150, 1 110, and 1 045 cm^{-1}; δ(60 MHz) 1.23 (3 H, s, 3-Me), 1.4–2.6 (8 H, m), 3.45 (3 H, s, CH_2OCH_2OMe), 3.47 and 3.90 (each 1 H, AB-type q, *J* 9 Hz, 3-CH_2O), 3.85 (3 H, s, CO_2Me), and 4.70 (2 H, s, OCH_2O).

To a stirred slurry of sodium hydride (50%; 520 mg; washed with hexane three times, 10.8 mmol) in THF (3 ml) at 0 °C under nitrogen was added a solution of the keto ester prepared above (2.197 g, 9.00 mmol) in THF (7 ml). After being stirred at 0 °C for 30 min, the mixture was treated with methyl iodide (1.1 ml, 18 mmol). The mixture was stirred for 40 min at 0 °C and then at room temperature overnight. The reaction was quenched by the addition of ice. Extraction with ether followed by column chromatography [eluant hexane–ethyl acetate (3:1)] afforded an inseparable stereoisomeric mixture of methyl 3-methoxymethoxymethyl-1,3-dimethyl-2-oxocyclohexanecarboxylate (1.181 g) and a pure sample of the more polar stereoisomer (468 mg, 71% total). Another stereoisomer was obtained by MPLC separation. The less polar stereoisomer had δ(60 MHz) 1.07 and 1.30 (each 3 H, s, 1- and 3-Me), 1.2–2.8 (6 H, m), 3.36 and 3.70 (1 H, each, AB-type q, *J* 9 Hz, 3-CH_2O), 3.35 (3 H, s, CH_2OCH_2OMe), 3.70 (3 H, s, CO_2Me), and 4.60 (2 H, s, OCH_2O). The more polar stereoisomer had ν_{max} 1 740, 1 710, 1 460, 1 245, 1 155, 1 115, and 1 055 cm^{-1}; δ(60 MHz) 1.13 and 1.35 (each 3 H, s, 1- and 3-Me), 1.2–3.0 (6 H, m), 3.2–3.8 (overlaps with δ 3.33 and 3.38, 2 H, AB-type q, 3-CH_2O), 3.33 (3 H, s, CH_2OCH_2OMe), 3.68 (3 H, s, CO_2Me), and 4.55 (2 H, s, OCH_2O).

A stirred solution of the above keto ester (762 mg, 2.95 mmol) and lithium chloride (635 mg, 15 mmol) in HMPA (3 ml) was heated at 120 °C for 2 h. After addition of ice and water, the product was extracted with ether and the extract was evaporated. The residue was separated by MPLC [eluant hexane–ethyl acetate (3:1)] to give an inseparable stereoisomeric mixture of the dimethyl ketone (**17**) (233 mg, 40%; 76% based on the consumed starting material) and recovered starting keto ether (**16**) (204 mg, 48%).

Method II: To a stirred solution of di-isopropylamine (2.0 ml, 14.3 mmol) in THF (10 ml) at 0 °C under nitrogen was added BuLi (1.5M in hexane; 9.6 ml, 14.4 ml). After the mixture had been stirred for 10 min, a solution of the keto ether (**16**) (2.177 g, 11.7 mmol) in THF (5 ml) was added to the mixture at −40 °C. The mixture was stirred for 25 min and then HMPA (8.4 ml) and methyl iodide (1.0 ml, 16.1 mmol) were added successively to the mixture at −30 °C. The resulting solution was stirred at room temperature for 2 days. The reaction was quenched by addition of aq. ammonium chloride and the product was extracted with ether. Purification by column chromatography and MPLC [eluant hexane–ethyl acetate (3:1)] afforded a stereoisomeric mixture of *dimethyl ketones* (**17**) (1.782 g, 76%), ν_{max} 1 710, 1 460, 1 155, 1 120, and 1 060 cm^{-1}; δ(60 MHz) 0.95, 1.07, 1.12, and 1.18 (6 H total, 2- and 6-Me), 1.2–3.0 (7 H, m), 3.30 and 3.35 (3 H total, 2 × s, 2-CH_2OCH_2OMe) [3.43 and 3.64 (*J* 10 Hz), 3.52 and 3.91 (*J* 9 Hz) (2 H total, 2 × AB-type q), 2-CH_2O], and 4.57 and 4.62 (2 H total, 2 × s, OCH_2O); *m/z* 200 (M^+, 5%), 169 (22), 155 (30), 138 (75), 110 (38), 109 (37), 95 (100), 82 (41), 81 (43), and 69 (52) (Found: C, 65.7; H, 10.0. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.1%).

6-Methoxymethoxymethyl-2,6-dimethylcyclohex-1-enecarbaldehyde (**18**).—To a stirred solution of di-isopropylamine (140 μl, 1 mmol) in THF (1 ml) at 0 °C under nitrogen was added BuLi (1.5M in hexane; 0.67 ml, 1 mmol). After the mixture had been stirred for 10 min, the solution of LDA was cannulated into a solution of the ketone (**17**) (102 mg, 0.5 mmol) in methylene dichloride (1 ml) at −92 °C. The temperature was raised gradually to −20 °C during 2 h, and then the solution was heated under reflux for 1 h, when the solution became black. After evaporation of the solvents at 0 °C under reduced pressure, HMPA (2 ml), anhydrous lithium perchlorate (109 mg, 1 mmol), and calcium carbonate (125 mg, 1.25 mmol) were added to the residue, and the resulting mixture was heated at 130 °C for 1.5 h. Extractive work-up with ether followed by MPLC [eluant hexane–ethyl acetate (3:1)] purification afforded the unsaturated aldehyde (**18**) (57 mg, 53%), ν_{max} 2 775, 1 680, 1 620, 1 145, 1 115, and 1 055 cm^{-1}; δ(60 MHz) 1.17 (3 H, s, 6-Me), 1.3–2.5 (6 H, m), 2.15 (3 H, s, 2-Me), 3.28 (3 H, s, OMe), 3.42 and 3.91 (each 1 H, AB-type q, *J* 9 Hz, 6-CH_2O), 4.53 (2 H, s, OCH_2O), and 10.12 (1 H, s, CHO); *m/z* 212 (M^+, 7%), 180 (24), 153 (100), 152 (32), 107 (35), 45 (65), and 43 (41).

2-Hydroxymethyl-2,6-dimethylcyclohexanone (**19**).—A solution of the methoxymethyl ether (**17**) (209 mg, 1.05 mmol) and conc. sulphuric acid (2 drops) in ethanol (2 ml) was heated under reflux for 3 h. Extractive work-up with ether followed by MPLC [eluant hexane–ethyl acetate (2:1)] purification afforded two isomeric *aldols* (**19**) (63 mg and 67 mg in the order of elution, 80%). The less polar isomer had b.p. 50–55 °C (0.15 mmHg); ν_{max} 3 560, 1 690, 1 460, 1 320, 1 130, 1 060, and 1 010 cm^{-1}; δ(90 MHz) 1.00 (3 H, d, *J* 6.3 Hz, 6-Me), 1.20 (3 H, s, 2-Me), 1.2–3.0 (7 H, m), 2.66 (1 H, dq, *J* 10.8 and 5.4 Hz, 6-H), and 3.47 (2 H, br s, CH_2OH) (Found: C, 69.2; H, 10.2. $C_9H_{16}O_2$

requires C, 69.2; H, 10.3%). The more polar isomer had b.p. 70–80 °C (0.15 mmHg); ν_{max} 3 450, 1 705, 1 455, 1 380, 1 320, 1 130, 1 060, and 1 040 cm^{-1}; δ(90 MHz) 1.04 (3 H, d, *J* 6.5, 6-Me), 1.10 (3 H, s, 2-Me, 1.0–2.2 (6 H, m), 2.60 (1 H, dq, *J* 10.8 and 5.4 Hz, 6-H), and 3.56 and 3.89 (each 1 H, AB-type q, *J* 10.9 Hz, CH_2OH); *m/z* 156 (M^+, 4%), 138 (25), 95 (21), 83 (100), 74 (36), 71 (33), 69 (37), and 55 (69) (Found: C, 69.1; H, 10.2%).

1,3-*Dimethyl*-2-*oxocyclohexanecarbaldehyde* (**20**).—To a stirred solution of oxalyl dichloride (0.23 ml, 2.6 mmol) in methylene dichloride (1 ml) at −100 °C under nitrogen was added a solution of DMSO (0.37 ml, 5.2 mmol) in methylene dichloride (1 ml). After the mixture had been stirred for 10 min, a solution of the more polar aldol (**19**) (81 mg, 0.52 mmol) in methylene dichloride (2 ml) was added, and the mixture was stirred for 30 min (temperature rose to −72 °C). A white precipitate appeared on addition of triethylamine (1.8 ml, 13 mmol) and the mixture was stirred for a further 1 h (temperature to −20 °C). The reaction was quenched by the addition of ether and water. Extractive work-up with ether followed by MPLC [eluant hexane–ethyl acetate (4:1)] purification gave the keto aldehyde (**20**) (76 mg, 95%), ν_{max} 2 700, 1 730, 1 710, 1 455, 1 130, and 915 cm^{-1}; δ(60 MHz) 1.05 (3 H, d, *J* 6 Hz, 3-Me), 1.35 (3 H, s, 1-Me), 1.2–3.0 (7 H, m), and 9.72 (1 H, s, CHO). The keto aldehyde (**20**) obtained from the less polar aldol by the same procedure had δ(60 MHz) 1.05 (3 H, d, *J* 6 Hz, 3-Me), 1.20 (3 H, s), 1.2–3.0 (7 H, m), and 9.47 (1 H, s, CHO).

1,3-*Dimethyl*-2-*oxocyclohexanecarbaldehyde Ethylene Acetal* (**21**).—A solution of the keto aldehyde (**20**) (26 mg, 0.17 mmol) in 2-ethyl-2-methyl-1,3-dioxolane (5 ml) containing D-camphorsulphonic acid (5 mg) was warmed at 40 °C for 5 h under nitrogen. Addition of aq. sodium hydrogen carbonate quenched the reaction. Extractive work-up with ether and MPLC [eluant hexane–ethyl acetate (3:1)] purification afforded the *keto acetal* (**21**) (28 mg, 84%), ν_{max} 1 715, 1 460, 1 125, and 1 100 cm^{-1}; δ(60 MHz) 1.00 (3 H, s, 1-Me), 1.00 (3 H, d, *J* 6 Hz, 3-Me), 1.0–3.0 (7 H, m), 3.87 (4 H, br s, OCH_2CH_2O), and 5.13 (1 H, s, OCHO) (Found: M^+, 198.125 45. $C_{11}H_{18}O_3$ requires *M*, 198.125 55).

1,3-*Dimethylcyclohex*-2-*ene*-1,2-*dicarbaldehyde* 1-*Ethylene Acetal* (**22**).—To a stirred solution of LDA prepared, at 0 °C, from di-isopropylamine (65 μl, 0.46 mmol) and BuLi (1.5M in hexane; 0.3 ml, 0.45 mmol) in THF (1 ml) under nitrogen at −100 °C was added a solution of the keto acetal (**21**) (46 mg, 0.23 mmol) in methylene dichloride (1 ml). The resulting solution was stirred for 2 h (temperature rose to −10 °C) and was then heated under reflux for 1 h. After evaporation of the solvents under reduced pressure at 0 °C, lithium perchlorate (50 mg, 47 mmol), calcium carbonate (59 mg, 0.59 mmol), and HMPA (1 ml) were added to the residue, and the resulting slurry was heated at 120–130 °C for 1 h. After cooling to room temperature, the product was extracted with ether. MPLC [eluant hexane–ethyl acetate (2:1)] purification afforded the *unsaturated aldehyde* (**22**) (22 mg, 45%), ν_{max} 1 675, 1 620, and 1 150 cm^{-1}; δ(60 MHz) 1.28 (3 H, s, 1-Me), 1.0–2.5 (6 H, m), 2.15 (3 H, br s, 3-Me), 3.88 (4 H, br s, OCH_2CH_2O), 5.42 (1 H, s, OCHO), and 10.12 (1 H, s, CHO); *m/z* 210 (M^+, 2%), 73 (100), and 45 (16) (Found: M^+, 210.124 17. $C_{12}H_{18}O_3$ requires *M*, 210.125 57).

1,3-*Dimethylcyclohex*-2-*enedicarbaldehyde* (**23**).—A solution of the unsaturated aldehyde (**22**) (21 mg, 0.1 mmol) in acetic acid (0.8 ml) and water (0.2 ml) was heated at 50 °C for 30 min. The resulting solution was diluted with ether and poured into aq. sodium hydrogen carbonate. Extractive work-up with ether followed by MPLC [eluant hexane–ethyl acetate (3:1)] purification gave the dialdehyde (**23**) (9.5 mg, 50%); ν_{max} 2 700, 1 730, 1 670, 1 630, 1 380, 1 300, and 1 275 cm^{-1}; δ(90 MHz) 1.0–2.1 (6 H, m), 1.29 (3 H, s, 1-Me), 2.24 (3 H, s, 3-Me), and 9.41 and 10.06 (each 1 H, s, 2 × CHO); *m/z* 166 (M^+, 3%), 138 (100), 137 (37), 109 (94), 95 (37), 81 (31), 67 (59), and 55 (24).

(2ξ,4aS,5S,8aS)-(−)-*Methyl Decahydro*-8a-*methoxymethoxymethyl*-5-*methyl*-5-(4-*methylpent*-3-*enyl*)-1-*oxonaphthalene*-2-*carboxylate* (**24**).—To a stirred slurry of sodium hydride (60%; 471 mg, washed with hexane 3 times; 11.8 mmol) in THF (2 ml) under nitrogen were added successively a solution of the ketone (**11**) (627 mg, 1.95 mmol) in THF (7 ml), 15-crown-5 (1.5 ml, 8 mmol), and dimethyl carbonate (1.6 ml, 19 mmol). The resulting slurry was heated under reflux for 5 h and the reaction was quenched by the addition of aq. ammonium chloride to the mixture at 0 °C. Extractive work-up with ether followed by MPLC [eluant hexane–ethyl acetate (1:1)] purification gave the *keto ester* (**24**) (907 mg, 95%); $[\alpha]_D$ −15.5° (*c* 1.99); ν_{max} 1 750, 1 720, 1 175, 1 150, 1 105, and 1 040 cm^{-1}; δ(90 MHz) 0.83 (3 H, s, 5-Me), 1.0–2.5 (16 H, m), 1.58 and 1.68 (each 3 H, s, olefinic Me), 3.38 (3 H, s, CH_2OCH_2OMe), 3.74 (3 H, s, CO_2Me), 3.84 and 4.03 (each 1 H, AB-type q, *J* 9 Hz, 8a-CH_2O), and 5.04 (1 H, br t, *J* 6 Hz, olefinic H); *m/z* 380 (M^+, 8%), 305 (25), 266 (22), 69 (54), 55 (25), 45 (100), and 41 (36) (Found: M^+, 380.252 89. $C_{22}H_{36}O_5$ requires *M*, 380.256 19).

(2ξ,4aS,5S,8aS)-(+)-*Methyl Decahydro*-8a-*methoxymethoxymethyl*-2,5-*dimethyl*-5-(4-*methylpent*-3-*enyl*)-1-*oxonaphthalene*-2-*carboxylate* (**25**).—To a stirred slurry of sodium hydride (60%; 180 mg; washed with hexane 3 times; 4.5 mmol) under nitrogen was added a solution of the keto ester (**24**) (707 mg, 1.86 mmol) in THF (7 ml) containing HMPA (1.3 ml, 7.48 mmol). After the mixture had been stirred for 15 min at room temperature, methyl iodide (1.1 ml, 17.7 mmol) was added and the mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of aq. ammonium chloride, and extractive work-up with ether followed by MPLC [eluant hexane–ethyl acetate (3:1)] separation afforded oily (583 mg, 80%) and crystalline (82 mg, 11%) *alkylation products* (**25**). The oily, less polar stereoisomer had $[\alpha]_D$ +40.1° (*c* 2.04); ν_{max} 1 745, 1 715, 1 455, 1 155, 1 115, and 1 055 cm^{-1}; δ(90 MHz) 0.90 (3 H, s, 5-Me), 1.0–2.5 (15 H, m), 1.34 (3 H, s, 2-Me), 1.61 and 1.68 (each 3 H, s, olefinic Me), 3.31 (3 H, s, CH_2OCH_2OMe), 3.71 (3 H, s, CO_2Me), 3.72 and 3.89 (each 1 H, AB-type q, *J* 9.7 Hz, 8a-CH_2O), 4.52 (2 H, s, OCH_2O), and 5.06 (1 H, br t, *J* 6 Hz, olefinic H); *m/z* 394 (M^+, 27%), 363 (35), 319 (63), 150 (62), 186 (77), 121 (50), 108 (45), 135 (45), 122 (43), 121 (49), 109 (44), 95 (40), 93 (44), 81 (43), 69 (89), 55 (47), 45 (100), and 41 (72) (Found: M^+, 394.269 41. $C_{23}H_{38}O_5$ requires *M*, 394.271 81).

The crystalline, more polar stereoisomer had $[\alpha]_D$ +52.4° (*c* 0.82); m.p. 72–73 °C; ν_{max} 1 735, 1 710, 1 250, 1 170, 1 110, and 1 050 cm^{-1}; δ(60 MHz) 0.85 (3 H, s, 5-Me), 1.0–3.0 (15 H, m), 1.33 (3 H, s, 2-Me), 1.58 and (each 3 H, s, olefinic Me), 3.30 (3 H, s, CH_2OCH_2Me), 3.63 (3 H, s, CO_2Me), 3.69 and 4.03 (each 1 H, AB-type q, *J* 10 Hz, 8a-CH_2O), 4.47 (2 H, s, OCH_2O), and 5.07 (1 H, br t, olefinic H); *m/z* 394 (M^+, 7%), 259 (27), 161 (15), 93 (16), 69 (52), 45 (100), and 41 (38).

(2ξ,4aS,5S,8aS)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-8a-*methoxymethoxymethyl*-2,5-*dimethyl*-5-(4-*methylpent*-3-*enyl*)-*naphthalen*-1(2H)-*one* (**26**).—A solution of the keto ester (**25**) (582 mg, 1.48 mmol) and lithium chloride (318 mg, 7.4 mmol) in HMPA (8 ml) was heated at 130 °C for 2 h. After the addition of ice–water, the resulting solution was extracted with ether. Evaporation of the solvent followed by MPLC [eluant hexane–ethyl acetate (3:1)] purification gave the *ketone* (**26**) (457 mg, 92%), $[\alpha]_D$ +2.59° (*c* 1.97); ν_{max} 1 715, 1 450, 1 380, 1 160, 1 110, 1 050, and 915 cm^{-1}; δ(90 MHz) 0.83 (3 H, s, 5-Me), 1.00 (3 H, d,

J 6.3 Hz, 2-Me), 0.8–2.2 (15 H, m), 1.56 and 1.66 (each 3 H, s, olefinic Me), 2.71 (1 H, m, 2-H), 3.30 (3 H, s, OMe), 3.84 and 4.05 (each 1 H, AB-type q, *J* 9.2 Hz, 8a-CH_2O), 4.55 (2 H, s, OCH_2O), and 5.03 (1 H, br t, *J* 6 Hz, olefinic H); *m/z* 336 (M^+, 23%), 222 (100), 178 (61), 176 (91), 109 (60), 107 (58), 95 (66), 93 (62), 82 (62), 81 (67), 69 (88), 55 (55), 45 (89), and 41 (63) (Found: M^+, 336.267 24. $C_{21}H_{36}O_3$ requires *M*, 336.266 44).

(2R,4aS,5S,8aS)-(−)-3,4,4a,5,6,7,8,8a-*Octahydro*-8a-*hydroxymethyl*-2,5-*dimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalen*-1(2H)-*one* (**27**).—A stirred solution of the keto ether (**26**) (123 mg, 0.367 mmol) and conc. sulphuric acid (1 drop) in ethanol (12 ml) containing water (1.2 ml) was heated under reflux for 24 h. During reflux, conc. sulphuric acid (1 drop) was added 3 times at 2 or 3 h intervals. Evaporation of the ethanol under reduced pressure and extraction with ether followed by MPLC [eluant hexane–ethyl acetate (3:1)] separation afforded the *hydroxy ketone* (**27**) (69 mg, 62%; 88% on consumed starting material) and the starting keto ether (**26**) (36 mg, 29% recovery. The *hydroxy-ketone* (**27**) had $[\alpha]_D$ −21.6° (*c* 1.07); ν_{max} 3 450br, 1 715, 1 455, 1 380, and 1 025 cm^{-1}; δ(60 MHz) 0.80 (3 H, s, 5-Me), 0.98 (3 H, d, *J* 6 Hz, 2-Me), 1.0–2.5 (15 H, m), 1.57 and 1.65 (each 3 H, s, olefinic Me), 2.77 (1 H, d quint, *J* 12, 6 Hz, 2-H), 4.05 (2 H, br AB-type q, 8a-CH_2OH), and 4.98 (1 H, br t) (Found: M^+, 292.240 75. $C_{19}H_{32}O_2$ requires *M*, 292.240 25).

(1S,4aS,6R,8aS)-(−)-*Decahydro*-1,6-*dimethyl*-1-(4-*methylpent*-3-*enyl*)-5-*oxonaphthalene*-4a-*carbaldehyde* (**28**).—To a stirred solution of oxalyl dichloride (0.47 ml, 5.39 mmol) in methylene dichloride (1 ml) at −80 °C under nitrogen was added a solution of DMSO (0.76 ml) in methylene dichloride (1 ml). After the mixture had been stirred for 10 min, a solution of the keto alcohol (**27**) (209 mg, 1.08 mmol) in methylene dichloride (5 ml) was added and the solution was stirred for 1 h at between −75 and −54 °C. After addition of triethylamine (3.7 ml. 26.6 mmol), the mixture was stirred for 2 h at between −54 and 0 °C. The resulting slurry was poured into water and the product was extracted with ether. MPLC [eluant hexane–ethyl acetate (4:1)] purification afforded the *keto aldehyde* (**28**) (195 mg, 93%); $[\alpha]_D$ −156° (*c* 0.475), ν_{max} 2 725, 1 735, 1 705, 1 450, 1 385, 1 220, 1 100, and 910 cm^{-1}; δ(60 MHz) 0.82 (3 H, s, 1-Me), 1.0–3.0 (19 H, m), 1.57 and 1.67 (each 3 H, s, olefinic Me), 5.00 (1 H, br s, *J* 6 Hz, olefinic H), and 9.95 (1 H, s, CHO); *m/z* 290 (M^+, 21%), 178 (46), 167 (42), 149 (97), 81 (34), 69 (54), 57 (39), and 40 (100) (Found: M^+, 290.226 31. $C_{19}H_{30}O_2$ requires *M*, 290.224 61).

(1S,4aS,6R,8aS)-(−)-*Decahydro*-1,6-*dimethyl*-1-(4-*methylpent*-3-*enyl*)-5-*oxonaphthalene*-4a-*carbaldehyde Ethylene Acetal* (**29**).—To a solution of the keto aldehyde (**28**) (195 mg, 0.671 mmol) in methylene dichloride (2 ml) at −58 °C under nitrogen was added a solution of ethylene glycol bistrimethylsilyl ether (418 mg, 2.0 mmol) in methylene dichloride (1 ml) containing TMSOTf (65 μl, 0.34 mmol). After being stirred for 2 h at between −58 and −12 °C, the resulting solution was poured into aq. sodium hydrogen carbonate and extracted with ether. MPLC [eluant hexane–ethyl acetate (3:1)] purification gave the *acetal* (**29**) (131 mg, 86%) which crystallised spontaneously in a freezer, $[\alpha]_D$ −52.3° (*c* 0.409); m.p. 61–62 °C; ν_{max} 1 715, 1 455, 1 380, and 1 110 cm^{-1}; δ(60 MHz) 0.95 (3 H, d, *J* 6 Hz, 6-Me), 0.97 (3 H, s, 1-Me), 1.0–2.5 (15 H, m), 1.57 and 1.63 (each 3 H, s, olefinic Me), 2.77 (1 H, d quint, *J* 12, 6 Hz, 6-H), 3.62 (4 H, m, OCH_2CH_2O), 5.02 (1 H, br t, olefinic H), and 5.23 (1 H, s, OCHO); *m/z* 334 (M^+, 38%), 250 (50), 178 (30), 93 (31), 81 (35), 74 (86), 69 (93), 67 (41), 55 (67), 45 (100), and 41 (94) (Found: M^+, 334.250 99. Calc. for $C_{21}H_{34}O_3$ requires *M*, 334.250 79).

(4aS,5S,8aR)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-2,5-*dimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalene*-1,8a-*dicarbaldehyde* 8a-*Ethylene Acetal* (**30**).—To a stirred solution of di-isopropylamine (38 μl, 0.27 mmol) in THF (0.5 ml) at 0 °C under nitrogen was added BuLi (1.5M in hexane; 0.18 ml, 0.27 mmol). After the mixture had been stirred for 10 min, a solution of the ketone (**29**) (31.2 mg, 0.093 mmol) in methylene dichloride (1.5 ml) was added to the mixture at −93 °C, the mixture was stirred for 2 h at between −93 and −20 °C, and hex-1-ene (0.5 ml) was added. The solvents were evaporated off under reduced pressure at −10 °C and HMPA (4 ml), lithium perchlorate (32 mg, 0.30 mmol), and calcium carbonate (29 mg, 0.29 mmol) were added. The resulting slurry was heated at 130 °C for 1 h and cooled. Addition of water followed by extractive work-up (with ether) and MPLC [eluant hexane–ethyl acetate (3:1)] purification gave the unsaturated aldehyde (**30**) (21 mg, 64%), $[\alpha]_D$ +164° (*c* 0.845); ν_{max} 1 690, 1 615, 1 380, 1 240, and 1 120 cm^{-1}; δ(60 MHz) 0.92 (3 H, s, 5-Me), 1.0–2.6 (15 H, m), 1.58 and 1.67 (each 3 H, s, olefinic Me), 1.95 (3 H, s, 2-Me), 3.67 (4 H, m, OCH_2CH_2O), 5.03 (1 H, br t, olefinic H), 5.37 (1 H, s, OCHO), and 9.70 (1 H, s, CHO); *m/z* 346 (M^+, 36%), 273 (11), 139 (11), 105 (12), 91 (16), 73 (100), 69 (42), 45 (27), and 41 (33).

(4aS,5S,8aR)-(+)-3,4,4a,5,6,7,8,8a-*Octahydro*-2,5-*dimethyl*-5-(4-*methylpent*-3-*enyl*)*naphthalene*-1,8a-*dicarbaldehyde*, (+)-*Perrottetianal A* (**1**).—A solution of the acetal (**30**) (33.4 mg, 0.097 mmol) and PPTS (15.6 mg) in acetone (2.5 ml) containing a drop of water was heated at 80 °C for 3 h. After cooling to room temperature, the resulting solution was poured into water and extracted with ether. MPLC [eluant hexane–ethyl acetate (3:1)] purification afforded (+)-perrottetianal A (**1**) (22.6 mg, 78%), m.p. 67–69 °C (from hexane) (lit.,[2] 68–69 °C); $[\alpha]_D$ +395° (*c* 0.005) [lit.,[2] +282° (*c* 2.0)]; ν_{max} 2 750, 1 715, 1 670, and 1 620 cm^{-1}; Δε −1.75 (243 nm) and +6.14 (304 nm) [lit.,[2] −1.35 (243 nm) and +6.14 (304 nm)]; λ_{max} 245 (ε 8 300) and 204 nm (7 370) [lit.,[2] 245 (ε 6 480) and 204 nm (6 290)]; δ(90 MHz) 0.71 (3 H, s, 5-Me), 1.60 and 1.68 (each 3 H, s, olefinic H), 2.15 (3 H, s, 2-Me), 1.0–3.0 (15 H, m), 5.08 (1 H, t, *J* 5.3 Hz, olefinic H), and 9.86 and 10.08 (each 1 H, s, CHO); *m/z* 274 (M^+ − CO, 100%), 255 (32), 191 (37), 161 (35), 148 (35), 145 (34), 133 (62), 131 (37), 130 (39), 119 (53), 109 (56), 107 (61), 105 (61), 91 (56), 81 (75), 77 (58), 73 (41), and 67 (51).

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