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The Synthesis of an Arylperhydronaphthalenol, an Efficient Chiral Auxiliary

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Abstract

The synthesis of (1*R*,4a*S*,8*S*,8a*S*)-8-(5′-methoxy-2′-methylphenyl)-8-methyldecahydronaphthalen-1-ol from podocarpic acid is described.

Introduction

We recently reported the use of (1*R*,4a*S*,8*S*,8a*S*)-8-(5′-methoxy-2′-methylphenyl)-8-methyldecahydronaphthalen-1-ol (1a) as a highly efficient chiral auxiliary in the Diels–Alder reaction of its acrylate ester and in the diisobutylaluminium hydride reduction of its phenylglyoxylate ester.[1] This auxiliary has features which are expected to restrict the conformations of the aromatic ring, thereby favouring conformations in which the ring and any prochiral element, located within the first few atoms of the group R (1a), occupy approximately parallel planes. These features have led to improved diastereofacial selectivity in the reactions of its derivatives compared with the reactions of the analogous derivatives of 8-phenylmenthol.

The route chosen for the preparation of the perhydronaphthalenol (1a) from podocarpic acid (2) is shown in Scheme 1. It involves decarboxylation with the introduction of a trigonal centre at C4. This then allows the establishment of a three-carbon chain, with control of the stereochemistry at this centre. Ring closure between this side chain and C6, followed by cleavage of the C6a–C7 bond of (B) yields the basic skeleton of the desired chiral auxiliary.

Results and Discussion

The first synthetic target was the aldehyde (4b), from which the three-carbon chain in (A) (Scheme 1) could be readily assembled. The aldehyde (4b) has been synthesized by Cambie and Denny[2] using the boron trifluoride induced rearrangement of the α-epoxide derived from the alkene (3a). The alkene (3b) is now readily available by the radical decarboxylation method.[3,4] Deacetylation

[1] Hamon, D. P. G., Holman, J. W., and Massy-Westropp, R. A., *Tetrahedron: Asymm.*, 1992, **3**, 1533.
[2] Cambie, R. C., and Denny, W. A., *Aust. J. Chem.*, 1969, **22**, 1699.
[3] Pinhey, J. T., Cochrane, E. J., Lazer, S. W., and Whitby, J. D., *Tetrahedron Lett.*, 1989, **30**, 7111.
[4] Pinhey, J. T., and Whitby, J. D., personal communication.

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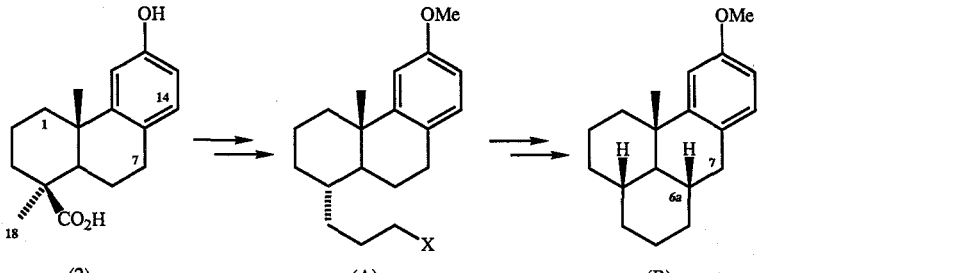
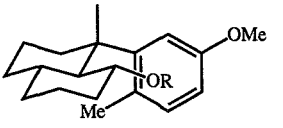
and methylation of alkene (3b) gave the required alkene (3a) in high overall yield from podocarpic acid. As an alternative to the epoxide-rearrangement route, hydroboration/oxidation of alkene (3a) with 9-borabicyclo[3.3.1]nonane followed by Swern[5] oxidation of the resultant alcohol gave the axial aldehyde in good yield. Isomerization of the axial aldehyde to the equatorial aldehyde (4c) with sodium hydroxide in deoxygenated methanol was found to be more efficient than the literature methods.[6]

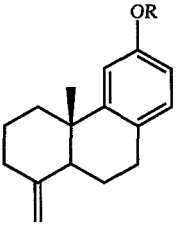


(2) (A) (B)

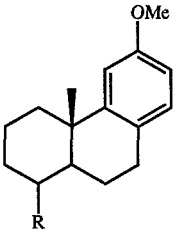


(1a) R = H
(1b) R = Ac

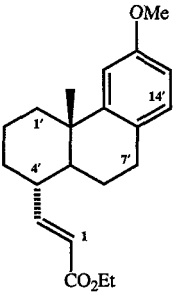
Scheme 1



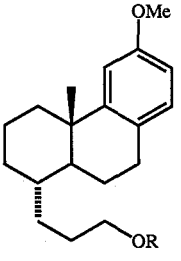
(3a) R = Me
(3b) R = Ac



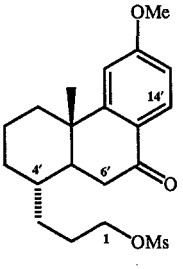
(4a) R = axial CH_2OH
(4b) R = axial CHO
(4c) R = equatorial CHO



(5)



(6a) R = H
(6b) R = Ms



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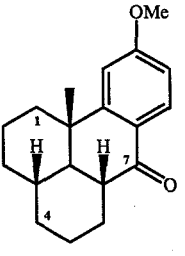


(8)

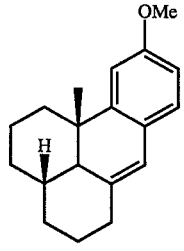
[5] Swern, D., and Omura, K., *Tetrahedron*, 1978, **34**, 1651.
[6] Cambie, R. C., and Palmer, B. D., *Aust. J. Chem.*, 1982, **35**, 601.

Chain extension of the equatorial aldehyde (4c) with the anion of triethyl phosphonoacetate in dimethylformamide gave the unsaturated ester (5) in 87% yield. Lower yields were obtained from the analogous phosphorane reaction. Hydrogenation of the unsaturated ester (5) over palladium on carbon, followed by reduction of the saturated ester with lithium aluminium hydride, gave the alcohol (6a) in high yield. The two-proton resonance at δ 3·62 in the ^{1}H n.m.r. spectrum and the hydroxyl absorption at 3628 cm^{-1} in the infrared spectrum were consistent with the terminus of this side chain.

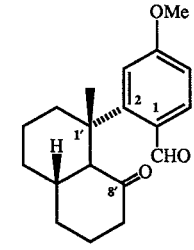
The cyclization required by this route was best achieved by intramolecular alkylation of the ketone (7) which was prepared from the alcohol (6a) by mesylation followed by benzylic oxidation with chromium trioxide in acetic acid. The ^{1}H n.m.r. spectrum of the product confirmed that oxidation had taken place at C 7′ because H 14′ resonated as a doublet at δ 7·98, which is further downfield than usual because of the deshielding effect of the carbonyl group. A doublet of doublets (J 18·2, 4·1 Hz) at δ 2·75 was assigned to the equatorial H 6′ (shifted downfield relative to that in the starting material.)

Cyclization of the 7′-oxo mesylate (7) was achieved by the use of potassium t-butoxide in t-butyl alcohol to give the derivative (8) as a white solid in 92% yield. Spectral and analytical data confirmed the structure (8). While alkylation was expected to occur *trans* to the angular methyl group and equilibration would also favour the stereoisomer shown, the resonance due to H 6a in the ^{1}H n.m.r. spectrum was not sufficiently resolved to allow determination of the stereochemistry at this centre.

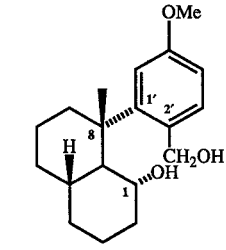
The basic skeleton of the desired alcohol (1a) could now be established by cleavage of the C 6a–C 7 bond in the ketone (8). Reduction of the ketone (8) with sodium borohydride gave the alcohol which was dehydrated directly with acid to give, exclusively, the alkene (9). The ^{1}H n.m.r. spectrum of this alkene (9) showed a triplet (J 2·4 Hz) at δ 6·09 for the vinylic proton H 7. There was no evidence for any isomeric alkenes.



(9)



(10)



(11)

Oxidative cleavage of the C 6a–C 7 bond of alkene (9) was then effected by ozonolysis at −78° in dichloromethane/methanol (1 : 1) followed by workup with dimethyl sulfide which gave keto aldehyde (10) in 95% yield. Absorptions in the infrared spectrum for the ketone and aldehyde carbonyl groups at 1710 and 1690 cm^{-1}, respectively, and an aldehyde C–H stretch at 2748 cm^{-1} were confirmation of the structure. The ^{1}H n.m.r. spectrum showed a doublet (J 11·2 Hz) at δ 3·45 which was assigned to H 8a′. This large coupling establishes that H 8a′ has an axial–axial relationship with H4a′, thus confirming the presence

of the required *trans* ring junction. The proton H6 appeared at δ 7·83 (d, J 8·6 Hz), deshielded by the aldehyde function. A one-proton singlet at δ 10·32 was assigned to the aldehyde proton.

Completion of the synthesis to obtain the required alcohol (1a) involved reduction of the keto aldehyde (10) by sodium borohydride to the diol (11) followed by hydrogenolysis. The stereochemistry of the intermediate diol (11) was confirmed by the ^{1}H n.m.r. spectrum which showed a triplet (J 10·0 Hz) at δ 2·34 which corresponded with H8a being diaxial with respect to H4a and H1. The large coupling observed between H1 and H8a implies that H1 is axial and therefore that the hydroxy group must be equatorial. A doublet of triplets at δ 3·56 (J 10.0, 4·5 Hz) was assigned to the axial H1 which is coupled to H8a (J 10·0 Hz) and to the two H2. The assignments were confirmed when the resonance at δ 2·34 due to H8a was irradiated and the doublet of triplets at 3·56 collapsed to a doublet of doublets. The remaining 10 and 4·5 Hz couplings of the multiplet at δ 3·56 were attributed to the diaxial and axial–equatorial couplings, respectively, to H2. Doublets (each J 11·3 Hz) at δ 4·48 and 5·26 were assigned to an AB quartet due to the geminal benzylic protons. Irradiation of the resonance at δ 5·26 caused a collapse of the doublet at 4·48 to a singlet, thus confirming this assignment. The infrared spectrum of the diol (11) showed two O–H stretches, at 3568 and 3424 cm^{-1}. The diol (11) hydrogenolysed smoothly over palladium on carbon to yield the alcohol (1a). A three-proton singlet at δ 2·62 for the aromatic methyl group in the ^{1}H n.m.r. spectrum confirmed that hydrogenolysis had taken place. In addition, a doublet of triplets at δ 3·53 for H1, similar to that observed for diol (11), confirmed the stereochemistry of the product. The alcohol (1a) was more easily purified via the acetate (1b) which, on reduction with lithium aluminium hydride, gave a product which was pure by 300 MHz ^{1}H n.m.r. spectroscopy, h.p.l.c. analysis and microanalysis.

Further asymmetric syntheses with (1a) as a chiral auxiliary will be published elsewhere.

Experimental

General Methods

^{1}H and ^{13}C n.m.r. spectra were recorded on Bruker ACP 300 or CXP 300 spectrometers, operating at 300 and 75·5 MHz, respectively, in $CDCl_3$ solutions with tetramethylsilane as internal standard. Flash chromatography[7] refers to nitrogen-pressure-driven rapid chromatography with either Amicon Matrex silica (pore diameter 60 Å) or Merck Kieselgel 60 (230–400 mesh). Squat column chromatography refers to 'dry column' flash chromatography[8] with Merck Kieselgel 60 HF_{254} silica on a small scale and Merck Kieselgel 60 (230–400 mesh) on a larger scale. Electron ionization mass spectra (e.i.m.s.) were recorded with an AEI MS-30 at 70 eV. All solvents were distilled before use. Anhydrous diethyl ether and tetrahydrofuran were obtained by distillation from sodium benzophenone ketyl. Drying and purification of other solvents and reagents were accomplished by standard laboratory procedures. Melting points were determined on a Kofler hot-stage under a Reichert microscope and are uncorrected. Elemental analyses were carried out by the Canadian Microanalytical Service Ltd, New Westminster, Canada.

[7] Still, W. C., Kahn, M., and Mitra, A., *J. Org. Chem.*, 1978, **43**, 2923.
[8] Harwood, L. M., *Aldrichimica Acta*, 1985, **18**, 25.

19-Norpodocarpa-4(18),8,11,13-tetraen-12-yl Acetate (3b)

O-Acetylpodocarpic acid[9] was conveerted into (4*R*)-(2-pyridylthio)-18-norpodocarpa-8,11,13-trien-12-yl acetate.[3,4] A solution of magnesium monoperoxyperphthalic acid (16·8 g, 83%, 29 mmol) in water (800 ml) was added to a stirring solution of this acetate (20·2 g, 53 mmol) in ethanol (400 ml) and the solution was stirred at room temperature for 10 min. The reaction mixture was diluted with water (500 ml) and the solution was extracted with dichloromethane. The combined organic extracts were washed with saturated sodium hydrogencarbonate solution, and water, and were dried (Na_2SO_4). The solvent was evaporated under vacuum to yield a colourless oil which was heated at 100° under reduced pressure (20 mm) for 1 h. Chromatography on a silica squat column (ether/hexane gradient) gave (3b) (12·88 g, 90%) as a white solid, m.p. 66–69° (lit.[4] 67–69°). ν_{max} (CCl_4) 1760, 1640, 1600, 1490, 1010 cm^{-1}. ^1H n.m.r. δ 7·05, d, J 8·3 Hz, H 14; 6·98, d, J 2·4 Hz, H 11; 6·82, dd, J 8·3, 2·4 Hz, H 13; 4·85, 4·60, each d, J 1·4 Hz, $(H\,18)_2$; 2·88, m, $(H\,7)_2$; 2·26, s, Ac; 1·00, s, C 10–Me, 2·39–1·53, complex, methylene envelope.

12-Methoxy-19-norpodocarpa-4-(18),8,11,13-tetraene (3a)

A solution of 19-norpodocarpa-4(18),8,11,13-tetraen-12-yl acetate (3b) (26 g, 96 mmol) in methanol (500 ml) containing sodium hydroxide pellets (40 g) was refluxed for 15 min before being cooled and neutralized with dilute hydrochloric acid. The solution was extracted with dichloromethane and the combined organic extracts were washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent yielded 20·8 g (95%) of a red oil which crystallized on standing. The solid was dissolved in dry dimethyl sulfoxide (500 ml), and sodium hydride (2·86 g, 80%, 100 mmol) was added. After stirring for 15 min, iodomethane (12 ml) was added and the mixture was stirred overnight. Water (400 ml) was added and the solution was saturated with sodium chloride before being extracted with ethyl acetate. The combined organic layers were washed with water and brine, and dried (Na_2SO_4). Evaporation of the solvent yielded a yellow oil which was purified on a silica squat column (ether/hexane gradient) to yield 18·77 g (85%) of the alkene (3a) as a colourless, viscous oil. ν_{max} (CCl_4) 1665, 1610, 1500 cm^{-1}. ^1H n.m.r. δ 6·98, d, J 8·4 Hz, H 14; 6·83, d, J 2·8 Hz, H 11; 6·65, dd, J 8·4, 2·8 Hz, H 13; 4·84, 4·59, each m, $(H\,18)_2$; 3·75, s, OMe; 2·82, m, $(H\,7)_2$; 1·00, s, C 10–Me, 2·39–1·54, complex, methylene envelope. The data were identical to those reported.[10]

12-Methoxy-18-norpodocarpa-8,11,13-trien-19-ol (4a)

A solution of 9-borabicyclo[3.3.1]nonane dimer (4·9 g, 0·02 mol) in dry tetrahydrofuran (100 ml) was added dropwise by syringe to a solution of 12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraene (3a) (10 g, 0·04 mol) in dry tetrahydrofuran (250 ml) and the reaction was stirred overnight. Sodium hydroxide (3 M, 150 ml) was then added, followed by the dropwise addition of 30% hydrogen peroxide (150 ml). After being stirred overnight, the reaction mixture was saturated with potassium carbonate and extracted with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated to yield 8·11 g (78%) of the *alcohol* (4a) as a colourless oil (Found: $M^{+\bullet}$, 260·1788. $C_{17}H_{24}O_2$ requires $M^{+\bullet}$, 260·1776). ν_{max} (CCl_4) 3640, 1612, 1504, 1076 cm^{-1}. ^1H n.m.r. δ 6·94, d, J 8·4 Hz, H 14; 6·78, d, J 2·4 Hz, H 11; 6·65, dd, J 8·4, 2·4 Hz, H 13; 3·75, s, OMe; 3·72–3·66, m, $(H\,19)_2$; 2·82, dd, $(H\,7)_2$; 2·61, br s, OH; 1·03, s, C 10–Me; 2·24–1·39, complex, methylene envelope. ^{13}C n.m.r. δ 157·4, C 12; 149·8, C 9; 129·8, C 14; 127·0, C 8; 110·8, C 11 or C 13; 110·1, C 13 or C 11; 61·0, C 19; 55·0, OMe; 44·2, C 4 or C 5; 43·6, C 5 or C 4; 38·3, C 7; 37·2, C 10; 29·5, C 6; 27·3, C 3; 25·0, C 10–Me; 24·2, C 1; 18·0, C 2. E.i.m.s. *m/z* 260 (M, 100%), 245 ($M - CH_3$, 19), 227 (52).

[9] Cambie, R. C., Grigor, B. A., Hayward, R. C., and Nielson, A. J., *Aust. J. Chem.*, 1974, **27**, 2017.

[10] Cambie, R. C., Hay, M. P., Larsen, L., Rickard, C. E. F., Rutledge, P. S., and Woodgate, P. D., *Aust. J. Chem.*, 1991, **44**, 821.

12-Methoxy-18-norpodocarpa-8,11,13-trien-19-al (4b)

Oxalyl chloride (1·35 g, 10·6 mmol) in dry dichloromethane (50 ml) was added to a dry flask and nitrogen was bubbled through the solution for 10 min. The solution was then cooled to −60° under nitrogen before a deoxygenated solution of dry dimethyl sulfoxide (1·65 g, 21·1 mmol) in dry dichloromethane (25 ml) was added dropwise by syringe. The solution was stirred for 30 min, after which a deoxygenated solution of 12-methoxy-18-norpodocarpa-8,11,13-trien-19-ol (4a) (2·5 g, 9·6 mmol) in dry dichloromethane (50 ml) was added dropwise by syringe and stirring was continued for a further 2·5 h. Deoxygenated dry triethylamine (4·5 g, 44·2 mmol) was then added dropwise and the solution was allowed to warm to room temperature. After 2·5 h stirring at room temperature, water (10 ml) was added and the layers were separated. The organic layer was washed with 5% hydrochloric acid, saturated sodium hydrogencarbonate solution and water. The solution was dried ($MgSO_4$) and the solvent removed under vacuum to yield the aldehyde (4b) (2·3 g, 91%) as a colourless oil which crystallized on standing. ν_{max} (Nujol) 2720, 1710, 1605, 1490, 1022 cm^{-1}. ^1H n.m.r. δ 9·91, s, H19; 6·84, d, J 8·3 Hz, H14; 6·64, d, J 2·5 Hz, H11; 6·54, dd, J 8·3, 2·5 Hz, H13; 3·69, s, OMe; 1·00, s, C10–Me; 2·68–0·66, complex, methylene envelope. The data were identical to those reported by Cambie and Denny.[2]

12-Methoxy-19-norpodocarpa-8,11,13-trien-18-al (4c)

Crushed sodium hydroxide pellets (1·3 g) were added to a solution of 12-methoxy-18-norpodocarpa-8,11,13-trien-19-al (4b) (6·81 g) in dry methanol (70 ml) and the mixture was refluxed for 2·5 h. The solution was cooled, acidified with 10% hydrochloric acid and extracted with dichloromethane. The combined organic extracts were washed with water and dried ($MgSO_4$) and the solvent was evaporated to yield 6·7 g (99%) of the aldehyde (4c) as a white solid, m.p. 87–89° (lit.[2] 88–89°). ν_{max} (CH_2Cl_2) 2712, 1726, 1610, 1504, 1070 cm^{-1}. ^1H n.m.r. δ 9·53, d, J 4·4 Hz, H18; 6·98, d, J 8·5 Hz, H14; 6·83, d, J 2·4 Hz, H11; 6·69, dd, J 2·4, 8·5 Hz, H13; 3·78, s, OMe; 2·82, m, 2H; 2·35, m, 2H; 1·12, s, C10–Me; 1·86–1·26, complex, methylene envelope.

Ethyl (E)*-(12-Methoxy-19-norpodocarpa-8,11,13-trien-18-ylidene)acetate (5)*

Sodium hydride (0·63 g, 80%, 21 mmol) was added to a solution of triethyl phosphonoacetate (4·89 g, 21·8 mmol) in dry dimethylformamide (250 ml) and the solution was stirred for 10 min under nitrogen. A solution of 12-methoxy-19-norpodocarpa-8,11,13-trien-18-al (4c) (5·63 g, 21·8 mmol) in dry dimethylformamide (50 ml) was added and the reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere. Water (100 ml) was then added and the solution was extracted with ether (2×50 ml). The aqueous layer was saturated with sodium chloride and extracted with ether. Standard workup and flash chromatography (ethyl acetate/hexane, 1:9) yielded the *ester* (5) (6·0 g, 87%) as a colourless viscous oil (Found: C, 76·29; H, 8·39, $C_{21}H_{28}O_3$ requires C, 76·79; H, 8·59%). ν_{max} (CH_2Cl_2) 1710, 1650, 1610, 1504, 1068 cm^{-1}. ^1H n.m.r. δ 6·97, d, J 8·4 Hz, H14; 6·84, d, J 2·6 Hz, H11; 6·79, dd, J 15·6, 6·0 Hz, H18; 6·68, dd, J 8·4, 2·6 Hz, H13; 5·84, d, J 15·6 Hz, $CHCO_2Et$; 4·20, q, OCH_2CH_3; 3·78, s, OMe; 2·77, m, $(H7)_2$; 1·30, t, OCH_2CH_3; 1·13, s, C10-Me; 2·28–1·02, complex, methylene envelope. ^{13}C n.m.r. δ 166·7, C=O; 157·6, C12; 153·4, $CHCO_2Et$; 148·7, C9; 129·9, C14; 127·4, C8; 121·2, C18; 111·0, C11 or C13; 110·5, C13 or C11; 60·2, OCH_2CH_3; 55·2, OMe; 45·8, C4; 41·9, C5; 37·5, C7; 37·0, C10; 32·8, C6; 28·4, C3; 22·9, C1; 22·5, C2; 21·3, C10–Me; 14·2, OCH_2CH_3. E.i.m.s. m/z 328 (M, 100%), 313 (10).

2-(12′-Methoxy-19′-norpodocarpa-8′,11′,13′-trien-18′-yl)ethanol (6a)

(i) A mixture of ethyl (12-methoxy-19-norpodocarpa-8,11,13-trien-18-ylidene)acetate (5) (5·68 g) in ethyl acetate (100 ml) and 5% palladium on carbon (0·25 g) was stirred under a slight positive pressure of hydrogen overnight. Filtration through Kenite, solvent removal and flash chromatography (ethyl acetate/hexane, 1:9) gave *ethyl (12-methoxy-19-norpodocarpa-8,11,13-trien-18-yl)acetate* (5·34 g, 95%) as a colourless viscous oil (Found: $M^{+\bullet}$, 330·2205. $C_{21}H_{30}O_3$ requires $M^{+\bullet}$, 330·2195). ν_{max} (CH_2Cl_2) 1728, 1608, 1504, 1038 cm^{-1}. ^1H n.m.r.

δ 6·97, d, J 8·4 Hz, H 14; 6·84, d, J 2·6 Hz, H 11; 6·67, dd, J 8·4, 2·6 Hz, H 13; 4·13, q, J 7·2 Hz, OCH_2CH_3; 3·77, s, OMe; 2·78, m, $(H\,7)_2$; 1·26, t, J 7·2 Hz, OCH_2CH_3; 1·09, s, C 10–Me; 2·36–0·92, complex, methylene envelope. ^{13}C n.m.r. δ 179·9, C=O; 164·9, C 12; 157·2, C 9; 129·4, C 14; 127·1, C 8; 110·4, C 11 or C 13; 110·2, C 13 or C 11; 59·9, OCH_2CH_3; 54·8, OMe; 46·1, C 5; 37·6, C 7; 37·3, C 10; 35·3, C 4; 31·4 (t); 30·9 (t); 28·3 (t); 28·2 (t); 22·2, C 10–**Me**; 21·5 (t); 20·6 (t); 13·9, OCH_2CH_3. E.i.m.s. *m/z* 330 (M, 100%), 315 (M – Me, 6).

(ii) Ethyl (12-methoxy-19-norpodocarpa-8,11,13-trien-18-yl)acetate (4·77 g) was refluxed with lithium aluminium hydride (1 g) in dry ether (150 ml) for 3 h. Ice was added, the solution was acidified with dilute hydrochloric acid (10 ml) and then extracted with ethyl acetate. Standard workup gave the *alcohol* (6a) (4·03 g, 97%) as a colourless viscous oil (Found: $M^{+\bullet}$, 288·2072. $C_{19}H_{28}O_2$ requires $M^{+\bullet}$, 288·2089). ν_{max} ($CHCl_3$) 3628, 1610, 1504, 1040 cm^{-1}. ^1H n.m.r. δ 6·96, d, J 8·4 Hz, H 14′; 6·84, d, J 2·5 Hz, H 11′; 6·66, dd, J 2·5, 8·4 Hz, H 13′; 3·77, s, OMe; 3·62, t, J 6·0 Hz, $(H\,1)_2$; 2·75, m, $(H\,7)_2$; 1·09, s, C 10′–Me; 2·22–0·90, complex, methylene envelope. ^{13}C n.m.r. δ 157·4, C 12′; 149·5, C 9′; 129·6, C 14′; 127·5, C 8′; 110·6, C 11′; 110·5, C 13′; 63·4, C 1; 55·1, OMe; 46·4, C 5′; 37·9, C 7′; 37·5, C 10′; 35·8, C 4′; 32·0 (t); 29·4 (t); 29·2 (t); 28·6 (t); 22·5, C 10′–**Me**; 21·9 (t); 20·9 (t). E.i.m.s. *m/z* 288 (M, 100%), 273 (M – CH_3, 31), 260 (M – CO, 62), 227 (92).

2-(12′-Methoxy-19′-norpodocarpa-8′,11′,13′-trien-18′-yl)ethyl Methanesulfonate (6b)

Methanesulfonyl chloride (1·63 g, 14·2 mmol) was added to a stirring solution of 2-(12′-methoxy-19′-norpodocarpa-8′,11′,13′-trien-18′-yl)ethanol (6a) (3·72 g, 12·9 mmol) and triethylamine (1·44 g) in dichloromethane (150 ml) at 0°. After addition, the reaction was warmed to room temperature and stirred overnight. The reaction mixture was washed with dilute hydrochloric acid, water and brine and dried ($MgSO_4$). Evaporation of the solvent yielded 4·27 g (90%) of the *mesylate* (6b) as a colourless oil (Found: $M^{+\bullet}$, 366·1856. $C_{20}H_{30}O_4S$ requires $M^{+\bullet}$, 366·1865). ν_{max} (CCl_4) 1612, 1504, 1046 cm^{-1}. ^1H n.m.r. δ 6·98, d, J 8·4 Hz, H 14′; 6·84, d, J 2·7 Hz, H 11′; 6·67, dd, J 8·4, 2·7 Hz, H 13′; 4·23, t, J 6·3 Hz, $(H\,1)_2$; 3·78, s, OMe; 3·01, s, $MeSO_3$; 2·80, m, $(H\,7')_2$; 1·10, s, C 10′–Me; 2·24–0·90, complex, methylene envelope. ^{13}C n.m.r. δ 157·4, C 12′; 149·1, C 9′; 129·6, C 14′; 127·2, C 8′; 110·6, C 11′ or C 13′; 110·3, C 13′ or C 11′; 70·6, C 1; 55·0, OMe; 46·2, C 5′; 37·8, C 7′; 37·4, C 10′; 37·1, OMs; 35·5, C 4′; 31·8 (t); 29·6 (t); 28·4 (t); 25·7 (t); 22·4, C 10′–**Me**; 21·7 (t); 20·8 (t). E.i.m.s. *m/z* 366 (M, 100%).

2-(12′-Methoxy-7′-oxo-19′-norpodocarpa-8′,11′,13′-trien-18′-yl)ethyl Methanesulfonate (7)

A solution of chromium trioxide (2·17 g) in 80% aqueous acetic acid (170 ml) was added dropwise to an ice cooled solution of 2-(12′-methoxy-19′-norpodocarpa-8′,11′,13′-trien-18′-yl)ethyl methanesulfonate (6b) (4·0 g) in acetic acid (800 ml) and the mixture was stirred at 5° for 3 days. Water (500 ml) was added and the solution was extracted with dichloromethane. The combined organic extracts were washed with saturated sodium hydrogencarbonate solution and water and dried ($MgSO_4$). The solvent was evaporated to yield a yellow oil which was purified by flash chromatography. Elution (ethyl acetate/hexane, 6:4) yielded 3·8 g (92%) of the *ketone* (7) as a colourless viscous oil (Found: $M^{+\bullet}$, 380·1647. $C_{20}H_{28}O_5S$ requires $M^{+\bullet}$, 380·1657). ν_{max} (CH_2Cl_2) 1674, 1600, 1499, 1180 cm^{-1}. ^1H n.m.r. δ 7·98, d, J 8·7 Hz, H 14′; 6·88, d, J 2·3 Hz, H 11′; 6·81, dd, J 8·7, 2·3 Hz, H 13′; 4·22, t, J 6·3 Hz, $(H\,1)_2$; 3·86, s, OMe; 3·04, s, $MeSO_3$; 2·75, dd, J 18·2, 4·1 Hz, H 6′*eq*; 2·40–2·24, complex, 2H; 1·17, s, C 10′–Me; 1·88–0·90, complex, methylene envelope. ^{13}C n.m.r. δ 196·7, C 7′; 163·9, C 12′; 156·9, C 9′; 129·8, C 14′; 124·6, C 8′; 111·3, C 11′ or C 13′; 109·3, C 13′ or C 11′; 70·1, C 1; 55·2, OMe; 45·3, C 5′; 38·0, C 6′; 37·4, C 10′; 37·1, OMs; 36·5 (t); 35·9, C 4′; 31·0 (t); 28·3 (t); 25·5 (t); 21·6, C 10′–**Me**; 21·3 (t). E.i.m.s. *m/z* 380 (M, 100%), 365 (M – CH_3, 14).

*(3a*R*,6a*R*,11b*S*,11c*R*)-10-Methoxy-11b-methyl-1,2,3,3a,4,5,6a,11b,11c-decahydro-7*H*-benz*[de]*anthracen-7-one (8)*

Potassium t-butoxide (4·93 g, 44 mmol) was added to a solution of 2-(12′-methoxy-7′-oxo-19′-norpodocarpa-8′,11′,13′-trien-18′-yl)ethyl methanesulfonate (7) (3·8 g, 10 mmol) in dry

t-butyl alcohol (200 ml) and the mixture was refluxed for 1·5 h. Water (100 ml) was added to the cooled reaction mixture and the solution was extracted with dichloromethane. The organic extracts were dried ($MgSO_4$), and the solvent was removed under vacuum to yield *ketone* (8) as a red oil which crystallized on standing. Recrystallization from ethanol/water gave 2·61 g (92%) of the product as white plates, m.p. 100–101° (Found: C, 80·16; H, 8·65%; $M^{+\bullet}$, 284·1780. $C_{19}H_{24}O_2$ requires C, 80·24; H, 8·51%; $M^{+\bullet}$, 284·1776). ν_{max} (CH_2Cl_2) 1668, 1598, 1488, 1072 cm^{-1}. ^1H n.m.r. δ 8·04, d, J 8·7 Hz, H8; 6·87, d, J 2·3 Hz, H11; 6·80, dd, J 8·7, 2·3 Hz, H9; 3·86, s, OMe; 2·48, br d, 1H; 2·2–2·4, complex 2H; 1·24, s, C11b–Me; 1·81–0·90, complex, methylene envelope. ^{13}C n.m.r. δ 198·5, C7; 163·7, C10; 156·8, C11a; 130·3, C8; 124·3, C7a; 111·4, C9 or C11; 109·2, C11 or C9; 55·3, OMe; 51·2, C6a; 45·5, C11c; 37·3, C6; 36·6, C11b; 36·2, C3a; 33·8 (t); 33·7 (t); 27·5 (t); 25·1, C3; 22·1, C11b–**Me**; 21·5, C1. E.i.m.s. *m/z* 284 (M, 100%), 269 ($M-CH_3$, 19), 241 (7).

(3aR,11bS,11cR)-10-Methoxy-11b-methyl-2,3,3a,4,5,6,11b,11c-octahydro-1H-benz[de]*-anthracene (9)*

A solution of (3a*R*,6a*R*,11b*S*,11c*R*)-10-methoxy-11b-methyl-1,2,3,3a,4,5,6a,11b,11c-decahydro-7*H*-benz[*de*]anthracen-7-one (8) (282 mg) and sodium borohydride (71 mg) in methanol (60 ml) was stirred overnight before water (20 ml) was added and the mixture was acidified with dilute hydrochloric acid. The mixture was extracted with ether, and the combined ether extracts were washed with water, dried ($MgSO_4$) and concentrated to yield a yellow oil which was refluxed with oxalic acid (32 mg) in ethanol (30 ml) for 1 h. Water (30 ml) was added to the cooled reaction mixture and the solution was extracted with dichloromethane. Workup and flash chromatography (ethyl acetate/hexane, 1:9) yielded 167 mg (68%) of the *alkene* (9) as a colourless oil (Found: $M^{+\bullet}$, 268·1837. $C_{19}H_{24}O$ requires $M^{+\bullet}$, 268·1827). ν_{max} (CH_2Cl_2) 1600, 1496, 1040 cm^{-1}. ^1H n.m.r. δ 6·88, d, J 8·2 Hz, H8; 6·77, d, J 2·7 Hz, H11; 6·62, dd, J 8·2, 2·7 Hz, H9; 6·09, t, J 2·4 Hz, H7; 3·77, s, OMe; 2·50, br d, 1H; 2·1–2·3, complex, 2H; 1·02, s, C11b–Me; 1·9–0·9, complex, methylene envelope. ^{13}C n.m.r. δ 158·3, C10; 147·0, C11a; 137·2, C7a; 126·6, C6a; 126·2, C7; 120·7, C8; 109·5, C9 or C11; 109·4, C11 or C9; 54·8, OMe; 49·6, C11c; 37·0, C11b; 35·4 (t); 34·9, C3a; 34·5 (t); 32·6 (t); 32·2 (t); 24·4 (t); 22·1 (t); 20·1, C11b–**Me**. E.i.m.s. *m/z* 268 (M, 71%), 253 ($M-CH_3$, 100).

(1'S,4a'S,8a'S)-4-Methoxy-2-(1'-methyl-8'-oxodecahydronaphthalen-1'-yl)benzaldehyde (10)

A stream of ozone in oxygen was bubbled through a solution of (3a*R*,11b*S*,11c*R*)-10-methoxy-11b-methyl-2,3,3a,4,5,6,11b,11c-octahydro-1*H*-benz[*de*]anthracene (9) (1·6 g) in dichloromethane/methanol (1:1, 150 ml) at −75°. After the disappearance of the starting material by t.l.c., dimethyl sulfide (2 ml) was added, the mixture was allowed to warm to room temperature and stirring was continued overnight. The solvent was then evaporated, water was added and the mixture was extracted with ether. The combined ethereal extracts were washed with water and dried ($MgSO_4$), and the solvent was evaporated to yield 1·71 g (95%) of the *keto aldehyde* (10) as an unstable yellow oil. Flash chromatography (ethyl acetate/hexane, 3:7) gave a colourless oil which turned yellow on prolonged exposure to air (Found: $M^{+\bullet}$, 300·1720. $C_{19}H_{24}O_3$ requires $M^{+\bullet}$, 300·1725). ν_{max} (CCl_4) 2748, 1710, 1690, 1602, 1046 cm^{-1}. ^1H n.m.r. δ 10·32, s, CHO; 7·83, d, J 8·6 Hz, H6; 7·12, d, J 2·4 Hz, H3; 6·80, dd, J 8·6, 2·4 Hz, H5; 3·85, s, OMe; 3·45, d, J 11·2 Hz, H8a'; 1·64, s, C1'–Me; 2·23–0·90, complex, methylene envelope. ^{13}C n.m.r. δ 210·3, C8'; 192·1, CHO; 163·2, C4; 155·4, C2; 138·2, C6; 127·8, C1; 115·6, C3; 109·5, C5; 60·4, C8a'; 55·2, OMe; 43·0, C7'; 41·0, C1'; 40·3, C2'; 40·2, C4a'; 33·7 (t); 33·5 (t); 25·8 (t); 21·8, C1'–**Me**; 21·3 (t). E.i.m.s. *m/z* 300 (M, 100%).

(1R,4aS,8S,8aS)-8-(2'-Hydroxymethyl-5'-methoxyphenyl)-8-methyldecahydronaphthalen-1-ol (11)

Sodium borohydride (10 mg, 0·26 mmol) was added to a stirring solution of (1'*S*,4a'*S*,8a'*S*)-4-methoxy-2-(1'-methyl-8'-oxodecahydronaphthalen-1'-yl)benzaldehyde (10) (84 mg, 0·28 mmol)

in dry methanol (15 ml) and the reaction was stirred overnight. Water (10 ml) was then added and the mixture was acidified with dilute hydrochloric acid before being extracted with ether. The combined ether extracts were washed with saturated sodium hydrogencarbonate solution and water and dried ($MgSO_4$). Evaporation of the solvent yielded 74 mg (87%) of the *diol* (11) as a colourless oil which crystallized on standing, m.p. 140–145° (Found: $M^{+\bullet}$, 304·2030. $C_{19}H_{28}O_3$ requires $M^{+\bullet}$, 304·2038). ν_{max} (CH_2Cl_2) 3568, 3424, 1606, 1040 cm^{-1}. ^1H n.m.r. δ 7·30, d, J 8·3 Hz, H3′; 7·03, d, J 2·5 Hz, H6′; 6·73, dd, J 8·3, 2·5 Hz, H4′; 5·26 and 4·48, AB, J 11·3 Hz, CH_2OH; 3·79, s, OMe; 3·56, dt, J 4·5, 10·0 Hz, H1; 2·34, br t, J 10·0 Hz, H8a; 1·51, s, C8–Me; 2·0–0·90, complex, methylene envelope. ^{13}C n.m.r. δ 159·5, C5′; 151·0, C1′; 135·8, C3′; 131·0, C2′; 113·6, C4′; 109·9, C6′; 72·7, C1; 64·1, CH_2OH; 55·1, OMe; 54·7, C8a; 42·7 (t); 41·9, C8; 37·1, C4a; 35·7 (t); 34·5 (t); 33·8 (t); 23·6 (t); 22·2 (t); 20·4, C8–**Me**. E.i.m.s. m/z 304 (M, 67%), 286 ($M - H_2O$, 100).

(1R,4aS,8S,8aS)-8-(5′-Methoxy-2′-methylphenyl)-8-methyldecahydro-1-naphthalenol (1a)

(1*R*,4a*S*,8*S*,8a*S*)-8-(2′-Hydroxymethyl-5′-methoxyphenyl)-8-methyldecahydro-1-naphthalenol (11) (314 mg) in ethyl acetate (100 ml) was hydrogenolysed overnight with 5% palladium on carbon (10 mg). The reaction mixture was then filtered through Kenite and the solvent evaporated to yield a colourless oil. Flash chromatography (ethyl acetate/hexane, 3:17) yielded 249 mg (84%) of the alcohol (1a) as a colourless viscous oil. The alcohol was most easily purified via the acetate. A solution of the alcohol (1a) (266 mg, 0·92 mmol) in acetic anhydride (5 ml), triethylamine (0·13 ml, 0·92 mmol) and 4-dimethylaminopyridine (2 mg) was stirred for 24 h under nitrogen. Methanol (5 ml) was added and the mixture was stirred for 30 min. Standard workup and flash chromatography (ethyl acetate/hexane, 1:9) gave 275 mg (90%) of *(1R,4aS,8S,8aS)-8-(5′-methoxy-2′-methylphenyl)-8-methyldecahydronaphthalen-1-yl acetate* (1b) as a colourless oil which crystallized on standing, m.p. 58–60° (Found: $M^{+\bullet}$, 330·2195. $C_{21}H_{30}O_3$ requires $M^{+\bullet}$, 330·2195). ν_{max} (CH_2Cl_2) 1720, 1606, 1044 cm^{-1}. ^1H n.m.r. δ 6·98, d, J 8·3 Hz, H3′; 6·83, d, J 2·6 Hz, H6′, 6·54, dd, J 8·3, 2·6 Hz, H4′; 4·69, dt, J 10·6, 4·6 Hz, H1; 3·72, s, OMe; 2·58, s, 4H, ArMe, H8a; 1·40, s, C8–Me; 1·08, s, Ac; 2·2–1·0, complex, methylene envelope. E.i.m.s. m/z 330 (M, 100%), 270 ($M - CH_3CO_2H$, 47), 255 (79). Lithium aluminium hydride (50 mg) reduction of pure acetate (1b) (95 mg) in dry ether (10 ml) was done overnight and then under reflux for 1 h. Workup and flash chromatography (ethyl acetate/hexane, 3:17) gave the *alcohol* (1a) as an oil which was homogeneous by 300 MHz ^1H n.m.r. spectroscopy and h.p.l.c. $[\alpha]_D^{20}$ −35·7° (*c*, 0·51 in EtOH) (Found: C, 78·94; H, 9·62%; $M^{+\bullet}$, 288·2084. $C_{19}H_{28}O_2$ requires C, 79·12; H, 9·78%, $M^{+\bullet}$, 288·2089). ν_{max} (CH_2Cl_2) 3572, 1606, 1488, 1048 cm^{-1}. ^1H n.m.r. δ 7·06, d, J 8·3 Hz, H3′; 7·05, d, J 2·7 Hz, H6′; 6·65, dd, J 8·3, 2·7 Hz, H4′; 3·76, s, OMe; 3·53, dt, J 10·0, 4·2 Hz, H1; 2·62, s, ArMe; 1·53, s, C8–Me; 2·4–0·9, complex, methylene envelope. ^{13}C n.m.r. δ 158·0, C5′; 149·2, C1′; 134·8, C3′; 127·9, C2′; 113·4, C6′; 110·0, C4′; 72·8, C1; 55·0, OMe; 52·0, C8a; 41·5, C8; 39·0, C2; 37·0, C4a; 35·5, C3, C6 or C7; 34·8, C6, C3 or C7; 33·5, C7, C3 or C6; 23·6, ArMe; 23·4, C4 or C5; 22·1, C5 or C4; 20·4, C8–**Me**. E.i.m.s. m/z 288 (M, 100%), 271 ($M - OH$, 55).