Spongian Pentacyclic Diterpenes. Stereoselective Synthesis of Aplyroseol-1, Aplyroseol-2 and Deacetylaplyroseol-2

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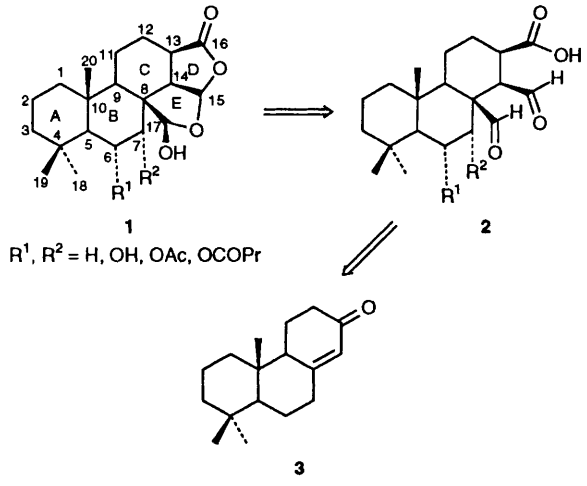
Natural spongian pentacyclic diterpenes aplyroseol-1 **19**, aplyroseol-2 **18** and deacetylaplyroseol-2 **17** have been synthesized in enantiomerically pure form from (+)-podacarp-8(14)-en-13-one **3**. Key intermediate in these syntheses is a suitably substituted acid-dialdehyde **2**, which is prepared from enone **3** by a sequence of transformations involving stereoselective introduction of a C-7 oxygen functionality, photoaddition of acetylene to the C(8)–C(14) double bond to form a cyclobutene ring system, reductive cyanation of the C-13 carbonyl group, hydrolysis of the resulting nitrile group, and ozonolysis of the cyclobutene moiety. An intramolecular participation of the 7α-hydroxy group in the hydrolysis of the 13α-nitrile **8** is set in focus.

A variety of spongian diterpenoids with a common pentacyclic skeleton **1** have been isolated from marine sponges and nudibranches.[1,2] We recently described[3] a general approach for the synthesis of this type of diterpenoids based on the construction of rings D–E by an intramolecular acetalization of a suitably substituted tricyclic acid-dialdehyde **2** (ABC + DE approach) (Scheme 1), which allowed us to synthesize the simplest member of this group, dendrillol-1 **1** ($R^1 = R^2 = H$).



Scheme 1 Synthetic route to spongian pentacyclic diterpenes

In this paper we report the adaptation of this chemistry to the enantioselective synthesis of three compounds of this group which were isolated from the Australian sponge *Aplysilla rosea*[2a] and the Caribbean sponge *Igernella notabilis*:[2b] aplyroseol-1 (**1**; $R^1 = H$, $R^2 = OCOPr$), which has been found to be mildly cytotoxic against lymphocytic leukemia, and related 7-hydroxy **1** ($R^1 = H$, $R^2 = OH$) and 7-O-acetyl **1** ($R^1 = H$, $R^2 = OAc$) analogues.

Results and Discussion

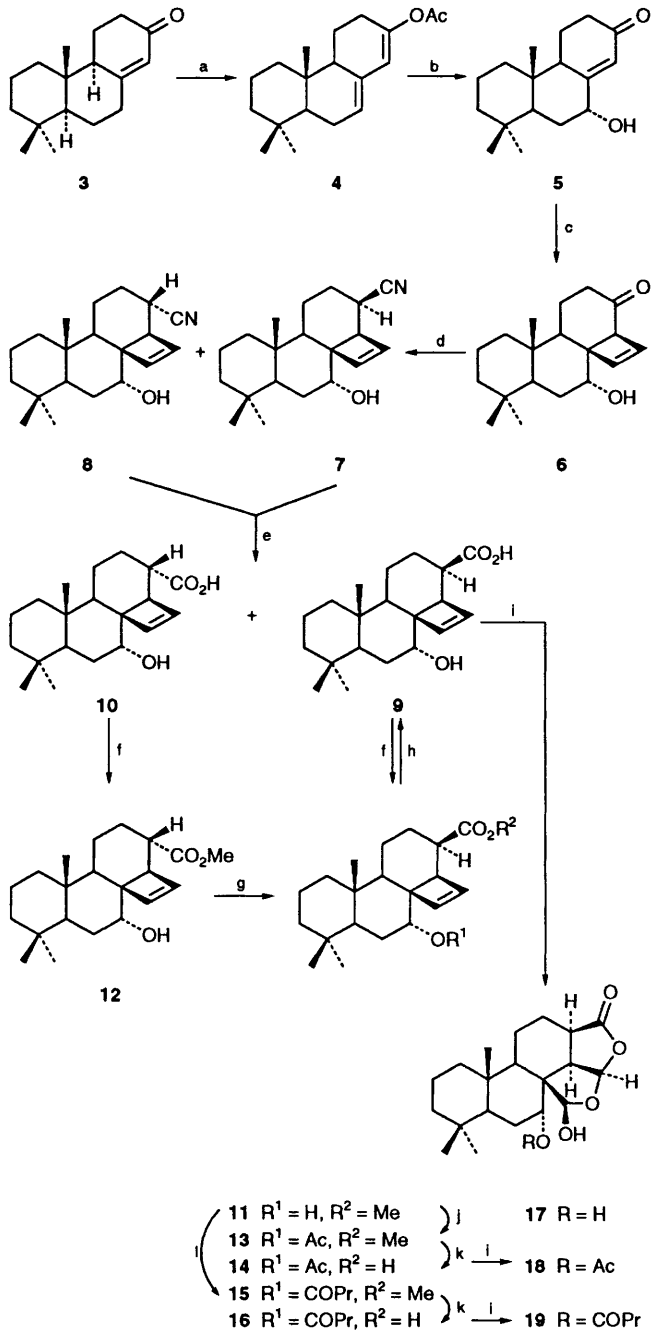
As in the previous synthesis, the easily available podocarpenone (+)-**3**[4] was used as the starting material. The synthesis (Scheme 2) begins with the stereoselective incorporation of a hydroxy function at the 7-position† through the transformation of the enone **3** into the corresponding 7,13-dienyl acetate **4** under standard conditions.[5] Its oxidation with *m*-chloroperbenzoic acid (MCPBA)[6] gave the hydroxy enone **5** in 72% yield from the enone **3**. Assignment of the α-orientation of the 7-OH group in compound **5** may be inferred from its spectroscopic data and in particular from the ^{13}C NMR signals due to C-5 and C-9 which are shifted upfield appreciably in compound **5** with respect to enone **3**, due to the shielding effect (γ-effect) exerted by the OH group on C-5 and C-9.

The conversion of enone **5** into the cyclobutenone **6** was accomplished by photoaddition of acetylene. Thus, irradiation of compound **5** in dry acetone saturated with acetylene at −30 °C, using Pyrex-filtered light from a medium-pressure lamp, resulted in stereoselective formation of the crystalline photoadduct **6** in 63% yield.

The next task, reductive carboxylation at the C-13 carbonyl group of compound **6**, was initially attempted by utilizing the same procedure as in our previous work, based on the reductive cyanation of the C-13 carbonyl group [through the tosylmethylisocyanide (TosMIC) method][7] followed by hydrolysis of the nitrile group. Thus, treatment of ketone **6** with TosMIC and Bu^{t}OK in Bu^{t}OH–DME at room temperature, afforded a 7:3 mixture of nitriles **7** and **8**, respectively, in 32–36% combined yield after column chromatography, which contrasts with the much better yield obtained with the 7-dehydroxylated analogue of ketone **6**.[3] An alternative, and more efficient method, to produce nitriles **7** and **8** involved the initial cyanophosphorylation of ketone **6** followed by reductive elimination of the phosphate moiety.[8] Treatment of ketone **6** with diethyl phosphorocyanidate (DEPC) and lithium cyanide in tetrahydrofuran (THF) at room temperature gave a mixture of epimeric cyano phosphates at C-13 in almost quantitative yield. The crude cyano phosphates reacted with samarium diiodide in the presence of an equimolecular amount of Bu^{t}OH in THF at room temperature to give a 3:7 mixture of β- and α-nitrile, **7** and **8** respectively, in 83% yield from ketone **6** after chromatographic purification.‡ The two C-13 epimeric nitriles

† The numbering system used throughout this paper is the usual in the terpene field. The compounds cited in this paper have been named (see Experimental section) as podocarpane or spongian derivatives, except the compounds that contain the cyclobutene ring system that are named (only in headings) as required by *Chemical Abstract* nomenclature rules.

‡ In contrast with the α/β ratio of nitriles **7** and **8** obtained with the above mentioned TosMIC method, the α/β ratio of both nitriles obtained in this case reflected the kinetic control followed by this process.



11 R^1 = H, R^2 = Me
13 R^1 = Ac, R^2 = Me
14 R^1 = Ac, R^2 = H
15 R^1 = COPr, R^2 = Me
16 R^1 = COPr, R^2 = H

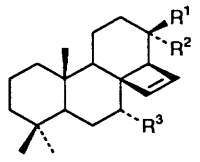
j → **17** R = H
k, i → **18** R = Ac
k, i → **19** R = COPr

l

Scheme 2 Synthesis of compounds **17**–**19**. *Reagents, conditions and yields:* (a) Ac_2O–AcCl, reflux in pyridine (97%); (b) MCPBA in EtOH at 0 °C; then aq. $Na_2S_2O_3$–$NaHCO_3$ (74%); (c) C_2H_2 in acetone at −30 °C, *hv* (63%); (d) $(EtO)_2P(O)CN$–LiCN in THF; then SmI_2–Bu^{t}OH in THF (83%); (e) KOH reflux in $HOCH_2CH_2OEt$; (f) CH_2N_2 in diethyl ether, or Me_2SO_4 in DMF (92% from **7** + **8**); (g) NaOMe in MeOH at 80 °C; (h) KOH in aq. MeOH (99%); (i) O_3 in CH_2Cl_2; then Me_2S (85% for **17**, 73% for **18**; 95% for **19**); (j) Ac_2O and 4-pyrrolidinopyridine in Et_3N (88%); (k) KOH in aq. MeOH (60% for **14** and 84% for **16**); (l) Butyric anhydride and 4-pyrrolidinopyridine in Et_3N (89%).

could be easily separated chromatographically at this stage and identified independently. However, for synthetic purposes, this separation was unnecessary (see below). The assigned stereochemistries at C-13 in both epimers were supported by their NMR data. Particularly significant was the magnitude of the *J*-values of the signal due to 13-H in both epimers, observed at δ 2.92 (ddd, *J* 10.1, 8.8 and 3.8 Hz) and δ 2.89 (ddd, *J* 6.4, 2.4 and 2.4 Hz) for compounds **7** and **8**, respectively. Since the C ring is in a boat conformation, the observed splitting patterns are in agreement with an axial (alpha) orientation of 13-H in the former ($J_{a,a}$, $J_{a,e}$, $J_{a,e}$) and an equatorial (beta) orientation of 13-H in the latter ($J_{e,a}$, $J_{e,e}$, $J_{e,e}$).

Alkaline hydrolysis of both nitriles by treatment with potassium hydroxide in ethylene glycol ethyl ether at reflux afforded, irrespective of the nitrile used, a 40:60 mixture of acid **9** and its 13α-epimer **10**, respectively, in high yield. These results contrast with those previously obtained [3] for the hydrolysis of the analogue nitriles lacking the hydroxy substituent at C-7, **20** and **21**, which were hydrolysed much more slowly under the same conditions to give a 93:7 mixture of acids **22** and **23**, respectively.



20 R^1 = CN, R^2 = R^3 = H
21 R^1 = R^3 = H, R^2 = CN
22 R^1 = CO_2H, R^2 = R^3 = H
23 R^1 = R^3 = H, R^2 = CO_2H
24 R^1 = CO_2H, R^2 = H, R^3 = OMe
25 R^1 = H, R^2 = CO_2H, R^3 = OMe

Although a rigorous kinetic study was not undertaken, monitoring of the changes of concentration of all intervening species with time was carried out in order to provide further insight into the relative rates of both reactions. The concentration–time relationships for each species are illustrated in Figs. 1 and 2. In either case, the shape of the curves is characteristic of two consecutive overall first- or pseudo-first-order reactions.[9] The different rates of the hydrolysis reactions can be clearly appreciated by comparison of both Figs., which shows how the concentrations of both the starting nitriles and the intermediate amides decrease more rapidly when the hydroxy group is present at C-7. In practice, while the hydrolysis of nitriles **7**/**8** was completed in *ca.* 4 h, that of compounds **20**/**21** was somewhat more difficult, requiring more than 15 h to reach completion under the conditions used in this study.

It is apparent from the above data and the different final product ratios obtained in each case that an equilibrium between the 13α- and 13β-nitrile is established rapidly under the alkaline conditions used, but whilst in the case of the nitriles lacking the hydroxy group at C-7 a faster hydrolysis of the 13β-nitrile occurs with the consequent predominant formation of the 13β-acid, the presence of the hydroxy group at C-7 causes a marked rate enhancement on the hydrolysis of the 13α-nitrile, and in spite of this nitrile being the minor isomer at equilibrium, this results in predominant formation of the 13α-acid (see Scheme 3).

This fact can be attributed to a catalytic intramolecular participation of the C-7 hydroxy group in the hydrolysis of the α-nitrile. Since the global rate of these processes is basically controlled by the relative hydrolysis rates of the intermediate amides, the observed rate enhancement must essentially reflect the effectiveness of the intramolecular catalysis in this step.* Intramolecular assistance by the hydroxy group in the elimination of the amide ion,[10a] usually the rate-limiting step in the

* Although there is no effect on the global rate, it is interesting to note that, as a comparison of Figs. 1 and 2 shows, the initial hydrolysis of nitriles **7**/**8** to the corresponding amides is also faster than that of compounds **20**/**21**, so an intramolecular catalysis by the 7-OH group is also operative in the initial hydrolysis of the 13α-nitrile.

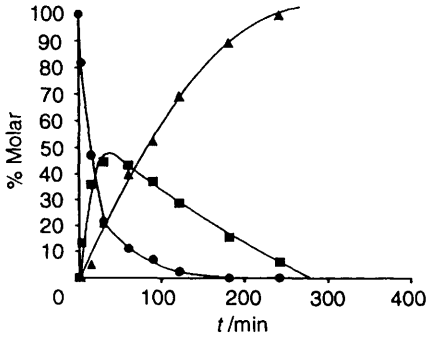


Fig. 1 Alkaline hydrolysis of nitriles **7**/**8**. Relative concentration of nitriles (**7** + **8**) (●), the corresponding amides (■), and acids (**9** + **10**) (▲).

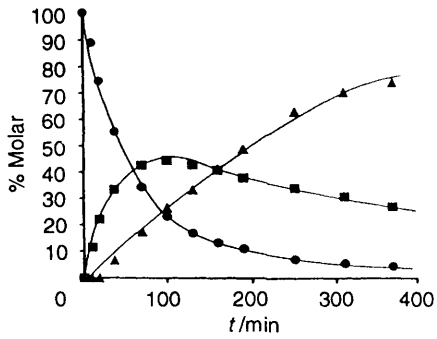
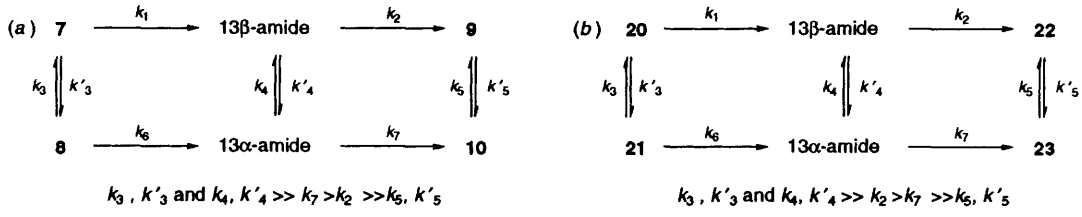


Fig. 2 Alkaline hydrolysis of nitriles **20**/**21**. Relative concentration of nitriles (**20** + **21**) (●), the corresponding amides (■), and acids (**22** + **23**) (▲).

The product obtained by alkaline hydrolysis of the nitriles in an intermediate stage contains the starting nitriles, the initially formed amides, and the corresponding final acids (see Scheme 3). Since a fast equilibrium exists between the epimeric 13α- and 13β-carbonitrile and 13α- and 13β-carboxamide, the plotting of relative concentrations of each epimeric species as a function of time is of little kinetic significance, so the Figs. show only relative total concentrations–time plots for each species.

The concentrations of each species at time *t* were estimated by treatment of an aliquot with hydrochloric acid, followed by extraction with diethyl ether, treatment with an ethereal solution of diazomethane, trimethylsilanization using standard conditions (only in the case of Fig. 1), and finally GLC analysis based on an internal standard.



Scheme 3 Alkaline hydrolysis of nitriles **7**/**8** (*a*) and **20**/**21** (*b*)

basic hydrolysis of amides,[10b] might be considered as the more probable cause of the observed rate enhancement.

Consistent with the above suppositions, protection of the 7-OH group of nitrile **8** as its methyl ether ($CF_3SO_3CH_3$, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, room temp., 16 h; 75%),[11] such that the intramolecular proton transfer is not available, resulted in much slower hydrolysis and the predominant formation of the 13β-acid (a 93:7 mixture of acids **24** and **25** respectively).

In view of the unexpected result obtained in the hydrolysis of nitriles **7**/**8** and in order to achieve a higher proportion of the desired 13β-carboxylic acid **9**, the mixture of acids directly obtained from the above hydrolysis step was treated with ethereal diazomethane and then exposed to methanolic sodium methoxide at 80 °C to effect equilibration, producing a mixture of methyl ester **11** and its 13α-epimer **12** (~ 4:1 ratio).* Chromatographic separation of the C-13 stereoisomers was easily achieved, providing esters **11** and **12** in 58 and 14% yield, respectively, from the mixture of nitriles **7** and **8**. The minor 13α-isomer could be conveniently recycled, thus increasing the yield of compound **11** (~ 70–75% overall yield from ketone **6** to ester **11** after repeated treatment of the 13α-ester **12** with sodium methoxide).

With hydroxy ester **11** in hand we turned our attention to its transformation into the title compounds. The ester **11** was quantitatively saponified back to the acid **9** on treatment with potassium hydroxide in aq. methanol at room temperature. The synthesis of deacetylaplyroseol-2 **17** was finally completed by treatment of the hydroxy acid **9** with ozone at low temperature followed by dimethyl sulfide decomposition of the resultant ozonide. As expected, the initially formed acid-dialdehyde (**2**; R^1 = H, R^2 = OH, see Scheme 1) was not isolated since spontaneous internal lactone-hemiacetal formation took place to give the pentacyclic compound in 85% yield for the overall process, after purification by chromatography.

In order to prepare the related 7-acetyl analogue **18** (aplyroseol-2), the acetate **13** was prepared by treatment of hydroxy ester **11** with two mol equiv. of acetic anhydride and a catalytic amount of 4-pyrrolidinopyridine in dry triethylamine at room temperature for 1 h. Chemoselective saponification of the methyl ester moiety of compound **13** using methanolic KOH at room temperature afforded, albeit in only modest yield (60%), the acid **14**, which was cleanly ozonized under the above stated conditions to give the desired compound **18** in 73% yield after purification by column chromatography.

The synthesis of the third target compound, aplyroseol-1 **19** was carried out by an analogous sequence of steps in good overall yield. Thus, esterification of the hydroxy group at C-7 of ester **11** with butyric anhydride, under similar conditions to that described above for the acetylation of the same compound, afforded butyrate **15** in 89% yield. Treatment of ester **15** with KOH in methanol at room temperature gave selectively the desired acid **16** in 84% isolated yield, which on treatment with excess of ozone and dimethyl sulfide led efficiently to the crystalline spongian pentacyclic diterpenoid aplyroseol-1 **19**.

The spectral properties of these synthetic materials were in complete agreement with those reported earlier for the natural products. Also the m.p.s and specific optical rotations recorded here for these compounds are in good accord with those reported previously.† In particular, the correlation between the

* For synthetic purposes, the isolation of the acids was unnecessary (see Experimental section) since they could be directly transformed into the corresponding methyl ester by *in situ* treatment with dimethyl sulfate and dimethylformamide (DMF).

† The slight difference found between the physical data of synthetic and natural deacetylaplyroseol-2 **17** may probably be due to the lower purity of the latter (only traces of this compound had been isolated from natural sources).

sign of rotations of synthetic and natural products established the absolute configurations of aplyroseol-1, aplyroseol-2, and deacetylaplyroseol-2 as those shown in formule **19**, **18** and **17**, respectively.

Experimental

All m.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a Schmidt Haensch Polartronic D polarimeter using a 5-cm path-length cell. $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured as KBr pellets or liquid films on a Perkin-Elmer 281 spectrophotometer. NMR spectra were measured on a Varian Unity 300 at 299.95 MHz (^{1}H) and at 75.43 MHz (^{13}C), and a Varian Unity 400 at 399.95 MHz (^{1}H). The signal of the deuteriated solvent ($CDCl_3$) was taken as the reference (the singlet at δ 7.24 for ^{1}H and the triplet centered at δ_C 77.00 for ^{13}C NMR data). Complete assignments of most of the products were made on the basis of a combination of homonuclear COSY, DEPT and inverse-detected heteronuclear multiple quantum coherence (HMQC) experiments. In all compounds, NMR assignments are given with respect to the numbering scheme shown in structure **1**. Mass spectra were run on a Perkin-Elmer 5988A spectrometer at 70 eV for both electron impact (EI) and chemical ionization (CI) (CH_4 as a reagent gas). Elemental analyses were performed by Servicio de Semimicroanálisis del CSIC (Barcelona). Column chromatography refers to flash chromatography and was performed on Merck silica gel 60, 230–400 mesh. All non-aqueous reactions were carried out under an inert atmosphere in oven-dried glassware. Solvents were dried and distilled fresh by standard methods. Organic solutions were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure using a rotary evaporator. The enone **3** was obtained from abietic acid or commercial colophony following the procedure previously described by us.[4b]

13-*Acetoxypodocarpa*-7,13-*diene* **4**.—To a solution of the enone **3** (520 mg, 2.11 mmol) in acetic anhydride (11.2 cm^3)–acetyl chloride (4.5 cm^3) was added pyridine (0.5 cm^3). The mixture was heated at reflux for 3 h. The acetic anhydride and acetyl chloride were removed by distillation under reduced pressure and the dark brown residue was filtered through a pad of silica gel with hexane–ethyl acetate (9:1) as eluent to give the dienyl acetate **4** as a pale yellow oil (589 mg, 97%); $[\alpha]_D^{23}$ −231 (*c* 0.9, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3030, 2860–3000, 1760, 1670, 1640, 1220 and 1125; δ_H(400 MHz) 5.74 (1 H, d, *J* 2.4, 14-H), 5.49 (1 H, m, 7-H), 2.40 (1 H, br t, *J* 14.7, 12α-H), 2.14 (1 H, ddd, *J* 14.7, 5.0 and 2.3, 12β-H), 2.12 (3 H, s, AcO), 2.12 (1 H, m, 6-H), 1.96 (1 H, m, 6-H′), 1.26 (1 H, dd, *J* 11.9 and 4.5, 5-H), 1.18 (1 H, ddd, *J* 13.5, 13.5 and 4.5, 3α-H), 1.02 (1 H, ddd, *J* 12.3, 12.3 and 4.0, 1α-H), 0.91 (3 H, s, 4β-Me), 0.86 (3 H, s, 4α-Me) and 0.79 (3 H, s, 10β-Me); δ_C see Table 1.

7α-*Hydroxypodocarp*-8(14)-*en*-13-*one* **5**.—A solution of 85% MCPBA (578 mg, 3.35 mmol) in 96% ethanol (6 cm^3) was added dropwise during 30 min to a stirred solution of the above dienyl acetate **4** (527 mg, 1.83 mmol) in 96% ethanol (7 cm^3) at 0 °C. The reaction mixture was stirred for 3 h at room temperature, treated with a solution of sodium thiosulfate (2 g) and sodium hydrogen carbonate (1.5 g) in the minimum amount of water (~3 cm^3), and stirred for a further two hours. The solution was poured into cold water and extracted with dichloromethane. The extracts were washed successively with aq. sodium hydrogen carbonate and brine, dried, and then evaporated to dryness to give an oily residue which, after column chromatography with hexane–ethyl acetate (7:3) as eluent, gave the *hydroxy enone* **5** (356 mg, 74%) as a solid, m.p. 165–166 °C (from hexane–diethyl ether) (Found: C, 78.1; H, 10.0. $C_{17}H_{26}O_2$ requires C, 77.82; H, 9.99%); $[\alpha]_D^{20}$ −77 (*c* 5.1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3470, 3010, 2840–3000, 1680, 1130 and 870; δ_H(300 MHz) 5.96 (1 H, br s, 14-H), 4.38 (1 H, t, *J* 2.9, 7-H), 2.49 (1 H, ddd, *J* 9.5, 5.5 and 2.2, 9-H), 2.41 (1 H, ddd, *J* 15.4, 4.4 and 4.4, 12β-H), 2.25 (1 H, ddd, *J* 15.4, 14.3 and 4.8, 12α-H), 2.03 (1 H, dddd, *J* 13.2, 5.5, 4.8 and 4.4, 11α-H), 0.93 (3 H, s, 4α-Me), 0.87 (3 H, s, 4β-Me) and 0.79 (3 H, s, 10β-Me); δ_C see Table 1; *m*/*z* (CI) 264 (M^+ + 2, 0.5%), 263 (M^+ + 1, 4), 262 (M^+, 19), 246 (0.5), 245 (3), 244 (16), 229 (16), 218 (7), 161 (11), 126 (82), 125 (73), 124 (96), 123 (100), 97 (56) and 41 (62).

[3aS-(3aα,5aR,7aα,11aβ,11bα)]-(+)-1,6,7,7a,8,9,10,11,11a,11b-*Decahydro*-6α-*hydroxy*-8,8,11a-*trimethyl*-2H-*cyclobuta*[j]-*phenanthren*-3(3aH)-*one* **6**.—A solution of the podocarpenone **5** (100 mg, 0.38 mmol) in dry acetone (160 cm^3) saturated with acetylene was irradiated between −40 and −30 °C for 2 h, such as is described in ref. 3 for the 7-dehydroxylated (podocarpane numbering) analogue of compound **6**. Chromatography of the residue obtained after evaporation of the solvent, with hexane–ethyl acetate (6:4) as eluent, afforded *photoadduct* **6** (69.3 mg, 63%) as a solid, m.p. 213–214 °C (from hexane–CH_2Cl_2) (Found: C, 78.5; H, 10.0. $C_{19}H_{28}O_2$ requires C, 79.12; H, 9.78%); $[\alpha]_D^{21}$ +12 (*c* 1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3410, 3050, 2840–3000, 1680, 1075, 1050 and 825; δ_H(300 MHz) 6.38 (1 H, dd, *J* 2.8 and 0.5, 17-H), 6.11 (1 H, dd, *J* 2.8 and 1.3, 15-H), 3.88 (1 H, dd, *J* 2.9 and 2.9, 7-H), 3.18 (1 H, m, 14-H), 2.62 (1 H, dddd, *J* 19.1, 5.3, 2.0 and 1.0, 12β-H), 2.21 (1 H, dddd, *J* 19.1, 10.9, 7.8 and 1.7, 12α-H), 1.23 (1 H, ddd, *J* 13.7, 13.7 and 4.5, 3α-H), 1.03 (1 H, ddd, *J* 12.6, 12.6 and 4.0, 1α-H), 0.88 (3 H, s, 4α-Me), 0.85 (3 H, s, 10β-Me) and 0.84 (3 H, s, 4β-Me); δ_C see Table 1; *m*/*z* (CI) 289 (M^+ + 1, 0.4%), 288 (M^+, 1.5), 273 (1), 270 (11), 260 (8), 255 (9), 245 (7), 242 (6), 227 (9), 186 (17), 123 (100), 91 (55), 55 (72) and 41 (69).

[3R-(3aα,5aS,7aα,11aβ,11bα)]-(+)-1,3,3a,6,7,7a,8,9,10,11,11a,11b-*Dodecahydro*-6α-*hydroxy*-8,8,11a-*trimethyl*-2H-*cyclobuta*[j]*phenanthrene*-3β-*carbonitrile* **7** *and* [3S-(3aα,5aS,7aα,11aβ,11bα)]-(−)-1,3,3a,6,7,7a,8,9,10,11,11a,11b-*Dodecahydro*-6α-*hydroxy*-8,8,11a-*trimethyl*-2H-*cyclobuta*[j]*phenanthrene*-3α-*carbonitrile* **8**.—To a mixture of ketone **6** (42 mg, 0.15 mmol) and LiCN (14.4 mg, 0.44 mmol) in THF (2.8 cm^3) at 0 °C was added dropwise DEPC (70 mm^3, 0.44 mmol), and the mixture was stirred for 15 min. Water was added, and the mixture was then extracted with diethyl ether. The extracts were washed with brine, dried, and evaporated.

A solution of the crude product thus obtained in THF (2 cm^3) was added to a solution of SmI_2, prepared from Sm (164.4 mg, 0.58 mmol) and ICH_2CH_2I (5 ml) in THF (5 cm^3) at room temperature. A solution of Bu^{t}OH (0.2 mmol) in THF (0.2 cm^3) was then added and the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with diethyl ether and washed successively with dil. hydrochloric acid, 5% aq. $Na_2S_2O_3$, and brine. Drying and evaporation of the diethyl ether afforded a solid residue, which was purified by chromatography on silica gel with hexane–ethyl acetate (8:2) as eluent. The first eluted compound was the 13β-*nitrile* **7** (10 mg, 23%) followed by the 13α-*nitrile* **8** (26 mg, 60%).

13β-Nitrile **7** was a solid, m.p. 179–182 °C (from hexane–CH_2Cl_2) (Found: C, 79.95; H, 9.9; N, 4.6. $C_{20}H_{29}NO$ requires C, 80.22; H, 9.76; N, 4.68%); $[\alpha]_D^{23}$ +19 (*c* 1.88, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3480, 3060, 2840–3000, 2240, 1045 and 1030; δ_H(300 MHz) 6.30 (1 H, dd, *J* 3.0 and 0.9, 15-H), 6.27 (1 H, d, *J* 3.0, 17-H), 3.82 (1 H, dd, *J* 2.8 and 2.8, 7-H), 2.99 (1 H, br d, *J* 3.8, 14-H), 2.92 (1 H, ddd, *J* 10.1, 8.8 and 3.8, 13-H), 1.91 (2 H, m, 12-H_2), 1.71 (1 H, dd, *J* 13.0 and 5.9, 9-H), 1.67 (2 H, m, 6-H_2), 1.18 (1 H, ddd, *J* 13.7, 13.7 and 4.3, 3α-H), 0.91 (1 H,

Table 1 ^{13}C Chemical shifts (δ in ppm from $SiMe_4$) of compounds **4–9** and **11–19**[a]

	4	**5**	**6**	**7**	**8**	**9**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
C-1	39.34	39.15	38.60	38.21	37.97	38.26	38.27	38.12	38.33	38.29	38.33	38.34	38.55	38.84	38.86
C-2	18.81	18.75	18.46	18.42	18.42	18.49	18.48	18.53	18.45	18.42	18.45†	18.45‡	18.43	18.71	18.70
C-3	42.33	41.77	41.95	41.88	41.85	41.95	41.94	41.91	41.92	41.87	41.95	41.95	41.55	41.77	41.81
C-4	32.92	32.95	32.83	32.80	32.82	32.77	32.76	32.78	32.66	32.65	32.69	32.70	32.41	32.70	32.73
C-5	50.13	46.54	47.10*	47.39	47.34	47.37	47.43	47.05	48.45*	48.42*	48.49*	48.49†	47.86*	48.47*	48.49*
C-6	24.06	29.56	27.32	27.82	27.32	27.36	27.52	26.42	24.83	24.79	24.92	24.90	27.15	24.56	24.64
C-7	124.21	71.72	73.12	74.00	73.96	74.59	74.50	74.03	77.50	77.43	77.08	77.06	69.00	72.99	72.61
C-8	148.66*	164.12	57.60	54.05	54.45	54.41	54.45	54.91	52.61	52.56	52.67	52.67	51.24	50.86	50.88
C-9	49.64	47.16	47.81*	43.96	43.63	44.42	44.41	44.17	45.60	45.60	45.69	45.72	46.83*	49.50*	49.56*
C-10	34.96	39.60	38.28	38.40	38.62	38.34	38.34	38.57	38.06	38.04	38.06	38.07	37.71	37.95	37.94
C-11	22.31	20.29	17.44	15.29	14.76	15.52	15.58	15.44	15.55	15.45	15.52	15.47	15.80	16.12	16.13
C-12	28.20	36.74	40.38	21.62	20.67	20.08	20.32	20.49	20.40	20.20	20.30	20.17	23.23	23.29	23.32
C-13	132.82*	200.60	211.88	25.92	25.80	40.04	40.13	39.08	40.13	39.63	40.10	39.85	37.41	37.58	37.59
C-14	117.93	127.54	59.79	47.98	47.80	48.20	48.41	46.89	48.27*	48.05*	48.34*	48.13†	41.27	42.21	42.20
C-15			134.60	136.65	136.74	138.33	138.45	137.60	139.17	138.90	139.08	138.90	104.41†	104.34†	104.35†
C-16				122.22	123.58	181.05	176.16	178.75	175.90	*b*	175.87	180.34	177.42	177.03	177.09
C-17			145.04	144.36	144.96	143.01	143.03	143.34	141.70	141.89	141.74	141.92	103.82†	103.60†	103.59†
C-18	33.29	33.33	33.14	33.24	33.12	33.22	33.27	33.13	33.21	33.20	33.19	33.20	32.64	33.05	33.02
C-19	21.89	21.93	21.52	21.66	21.68	21.68	21.66	21.81	21.47	21.45	21.48	21.48	21.02	21.17	21.18
C-20	13.70	14.74	14.51	13.94	14.03	13.99	13.96	14.15	14.03	14.01	14.03‡	14.04*	14.92	15.26	15.28
O*C*OMe	169.22								170.43	170.44				170.32	
CO*Me*	21.07								21.43	22.63				21.39	
CO_2Me							51.48	52.32	51.52		51.50				
O*C*OCH$_2$CH$_2$Me											172.93	172.93			172.92
OCO*C*H$_2$CH$_2$Me											36.92	36.91			36.67
OCOCH$_2$*C*H$_2$Me											18.81†	18.81‡			18.68
OCOCH$_2$CH$_2$*Me*											13.76‡	13.79*			13.81

[a] At 75.4 MHz in $CDCl_3$. The signals with the same superscript may be interchanged within the same column. [b] Carbonyl carbon signal not observed due to small sample size.

ddd, *J* 13.0, 13.0 and 3.9, 1α-H), 0.86 (3 H, s, 4α-Me), 0.82 (3 H, s, 4β-Me) and 0.80 (s, 3 H, 10β-Me); δ_C see Table 1; *m/z* (EI) 300 ($M^+ + 1$, 0.7%), 299 (M^+, 3), 285 (1), 284 (5), 282 (3), 281 (7), 280 (6), 271 (5), 266 (33), 238 (9), 162 (17), 123 (100), 91 (44), 79 (56), 69 (72) and 41 (71).

13α-Nitrile **8** was a solid, m.p. 122–123 °C (from hexane) (Found: C, 80.0; H, 10.0; N, 4.6%); $[\alpha]_D^{22}$ −41 (*c* 1.4, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3490, 3040, 2820–3000, 2240, 1045 and 1030; δ_H(400 MHz) 6.29 (1 H, d, *J* 2.9, 17-H), 6.05 (1 H, dd, *J* 2.9 and 0.9, 15-H), 3.78 (1 H, m, 7-H), 3.01 (1 H, m, 14-H), 2.89 (1 H, ddd, *J* 6.4, 2.4 and 2.4, 13-H), 2.19 (1 H, dd, *J* 13.8 and 5.9, 9-H), 1.98 (1 H, dddd, *J* 14.5, 10.5, 6.4 and 5.3, 12-H), 1.88 (1 H, ddddd, *J*14.5, 10.8, 3.9, 2.4 and 1.6. 12-H'), 1.75 (1 H, ddd, *J* 13.8, 2.6 and 2.6, 6α-H), 1.64 (1 H, ddd, *J* 13.8, 13.8 and 2.6, 6β-H), 1.51 (1 H, dd, *J* 13.8 and 2.6, 5-H), 1.21 (1 H, ddd, *J* 12.6, 12.6 and 4.0, 3α-H), 1.01 (1 H, ddd, *J* 13.0, 13.0 and 4.0, 1α-H), 0.87 (3 H, s, 4α-Me) and 0.82 (6 H, s, 4β- + 10β-Me); δ_C see Table 1.

[3R-(3aα,5aS,7aα,11aβ,11bα)]-(+)-*Methyl* 1,3,3a,6,7,7a,8,9,10,11,11a,11b-*Dodecahydro*-6α-*hydroxy*-8,8,11a-*trimethyl*-2H-*cyclobuta*[j]*phenanthrene*-3β-*carboxylate* **11** *and* [3S-(3aα,5aS,7aα,11aβ,11bα)]-(−)-*Methyl* 1,3,3a,6,7,7a,8,9,10,11,11a,11b-*Dodecahydro*-6α-*hydroxy*-8,8,11a-*trimethyl*-2H-*cyclobuta*[j]*phenanthrene*-3α-*carboxylate* **12**.—To a solution of the 3:7 mixture of nitriles **7** and **8** (60 mg, 0.2 mmol) obtained from the above reaction in ethylene glycol monoethyl ether (0.8 cm^3) was added aq. KOH 0.2 cm^3 of a solution of 1.5 g in 1 cm^3) and the mixture was stirred and heated under reflux for 3 h. The mixture was allowed to cool to room temperature and then dimethylformamide (DMF) (1 cm^3) and Me_2SO_4 (382 mm^3, 4 mmol) were added. After being stirred at room temperature for 1 h the reaction mixture was poured into cold, dil. hydrochloric acid and extracted with hexane (× 5). The extracts were washed with brine, dried, and then evaporated to dryness to give an oily residue, which was purified by chromatography, with hexane–ethyl acetate (from 95:5 to 90:10) as eluent. The first material eluted (36 mg, 55%) was identified as the 13α-*ester* **12**, a solid, m.p. 104–105 °C (from hexane) (Found: C, 76.0; H, 9.7. $C_{21}H_{32}O_3$ requires C, 75.86; H, 9.70%); $[\alpha]_D^{20}$ −51 (*c* 3.1, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3480, 3040, 2820–3000, 1705, 1220, 1050 and 990; δ_H(400 MHz) 6.21 (1 H, d, *J* 2.9, 17-H), 6.12 (1 H, dd, *J* 2.9 and 1.0, 15-H), 3.84 (1 H, dd, *J* 2.4 and 2.4, 7-H), 3.75 (3 H, s, CO_2Me), 2.98 (1 H, br s, 14-H), 2.70 (1 H, ddd, *J* 7.8, 2.4 and 2.4, 13-H), 1.91–2.09 (2 H, m, 12-H_2), 1.78 (1 H, ddd, *J* 13.4, 2.4 and 2.4, 6α-H), 1.20 (1 H, ddd, *J* 12.5, 12.5 and 3.8, 3α-H), 0.87 (3 H, s, 4α-Me) and 0.81 and 0.79 (6 H, 2 s, 4β- + 10β-Me); *m/z* (EI) 332 (M^+, 0.4%), 317 (0.3), 314 (7), 299 (22), 271 (3), 267 (3), 255 (5), 239 (12), 176 (10), 123 (37), 117 (45) and 41 (100); δ_C see Table 1.

The second material eluted (25.4 mg, 38%) was identified as the 13β-*ester* **11**, an amorphous solid (Found: C, 76.0; H, 9.7%); $[\alpha]_D^{20}$ +9.5 (*c* 2.5, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3500, 3040, 2820–3000, 1725, 810 and 750; δ_H(400 MHz) 6.23 (1 H, dd, *J* 2.9 and 1.0, 15-H), 6.19 (1 H, d, *J* 2.9, 17-H), 3.82 (1 H, dd, *J* 2.6 and 2.6, 7-H), 3.65 (3 H, s, CO_2Me), 2.92 (1 H, ddd, *J* 3.7, 1.0 and 1.0, 14-H), 2.81 (1 H, ddd, *J* 12.7, 6.1 and 3.7, 13-H), 1.19 (1 H, ddd, *J* 13.9, 13.9 and 4.2, 3α-H), 0.86 (3 H, s, 4α-Me) and 0.82 and 0.80 (6 H, 2 s, 4β- + 10β-Me); *m/z* (EI) 333 ($M^+ + 1$, 1%), 332 (M^+, 3), 314 (1), 299 (2), 239 (4), 208 (9), 176 (11), 123 (33), 79 (39), 55 (59) and 41 (100); δ_C see Table 1.

Sodium Methoxide-catalysed Equilibration of Esters **11** *and* **12**.—A 2:3 mixture of esters **11** and **12** obtained in the above reaction (53.2 mg) was treated with 2% sodium methoxide in MeOH (2 cm^3) at 80 °C in a sealed tube for 1 h. The reaction mixture was poured into cold, dil. hydrochloric acid and extracted with ethyl acetate. The extracts were washed with brine, dried, and concentrated to give a mixture of epimeric methyl esters **11** and **12** (53.1 mg, 100%) in the ratio 4:1 (^{1}H NMR analysis). The two esters were separated by chromatography as above to afford 13β-ester **11** (42.8 mg, 74% from the mixture of nitriles **7** and **8**) and 13α-ester **12** (10.3 mg, 17% from the mixture of nitriles **7** and **8**).

Hydrolysis of Methyl Ester **11** *to Acid* **9**.—To a solution of methyl ester **11** (41.5 mg, 0.125 mmol) in MeOH (3.6 cm^3) was added aq. KOH (120 mg in 0.43 cm^3) and the mixture was stirred at room temperature for 24 h. Water was added, and the mixture was acidified with dil. hydrochloric acid and extracted with ethyl acetate. The extracts were washed with brine, dried, and then evaporated to dryness to give spectroscopically pure *hydroxy acid* **9** (39.5 mg, 99.4%) as a solid, m.p. 201–203 °C (from hexane–diethyl ether); $[\alpha]_D^{20}$ +12.4 (*c* 2.9, $CHCl_3$) (Found: C, 75.4; H, 9.5. $C_{20}H_{30}O_3$ requires C, 75.43; H, 9.49%); ν_{max}(KBr)/cm^{-1} 3415, 2500–3600, 3040, 2820–3000, 1695, 1035 and 800; δ_H(400 MHz) 6.25 (1 H, dd, *J* 2.9 and 0.7, 15-H), 6.20 (1 H, d, *J* 2.9, 17-H), 3.85 (1 H, dd, *J* 2.8 and 2.8, 7-H), 2.96 (1 H, br d, *J* 3.7, 14-H), 2.84 (1 H, ddd, *J* 12.2, 6.6 and 3.7, 13-H), 1.20 (1 H, ddd, *J* 13.3, 13.3 and 4.7, 3α-H), 0.86 (3 H, s, 4α-Me) and 0.82 and 0.81 (6 H,2 s, 4β- + 10β-Me); δ_C see Table 1.

(−)-7α,17β-*Dihodroxy*-15β,17-*epoxyspongian*-16-*one* (*Deacetylaplyroseol*-2) **17**.—A solution of hydroxy acid **9** (16.5 mg, 0.052 mmol) in CH_2Cl_2 (2.5 cm^3) was cooled to −78 °C. The mixture was ozonolysed until its colour became slightly bluish (a few minutes). The solution was purged with argon, and then Me_2S (0.5 cm^3) was added. The solution was allowed to reach room temperature while being stirred overnight. After 18 h the solvent was removed under reduced pressure and the resulting residue was purified by chromatography, with hexane–ethyl acetate (1:1) as eluent, to give deacetylaplyroseol-2 **17** (15.4 mg, 85%) as a solid, m.p. 225–228 °C (decomp.) (from MeOH) (lit.,[2b] 199–204 °C); $[\alpha]_D^{18}$ −53 (*c* 1.36, MeOH) (lit.,[2b] −21.7°); ν_{max}(KBr)/cm^{-1} 3490, 3380, 2840–3000, 1760 and 970; δ_H(300 MHz) 6.09 (1 H, d, *J* 6.1, 15-H), 5.40 (1 H, s, 17-H), 3.54 (1 H, br s, 7-H), 3.52 (1 H, dd, *J* 11.1 and 6.1, 14-H), 2.78 (1 H, dd, *J* 11.1 and 7.3, 13-H), 2.34 (1 H, m, 12β-H), 1.95 (1 H, dddd, *J* 12.1, 12.1, 12.1 and 4.0, 11β-H), 0.92 (3 H, s, 10β-Me), 0.84 (3 H, s, 4α-Me) and 0.83 (3 H, s, 4β-Me); δ_C see Table 1.

[3R-(3aα,5aS,7aα,11aβ,11bα)]-(+)-*Methyl* 6α-*Acetoxy*-1,3,3a,6,7,7a,8,9,10,11,11a,11b-*dodecahydro*-8,8,11a-*trimethyl*-2H-*cyclobuta*[j]*phenanthrene*-3β-*carboxylate* **13**.—To a solution of the hydroxy ester **11** (16.9 mg, 0.051 mmol) and a catalytic amount of 4-pyrrolidinopyridine in dry triethylamine (125 mm^3) at 0 °C was added, dropwise, acetic anhydride (9.6 mm^3, 0.102 mmol). After being stirred at the same temperature for 45 min the reaction mixture was poured into hexane. The organic layer was washed successively with dil. hydrochloric acid, aq. sodium hydrogen carbonate, and brine, dried, and concentrated to give the crude product, which was purified by chromatography with hexane–ethyl acetate (95:5) as eluent to afford the acetate **13** (16.7 mg, 88%) as an oil, $[\alpha]_D^{19}$ +3.6 (*c* 3.3, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3020, 2840–3000, 1735, 1240, 1170, 1025, 945 and 810; δ_H(300 MHz) 6.24 (1 H, dd, *J* 2.9 and 1.0, 15-H), 6.19 (1 H, d, *J* 2.9, 17-H), 4.94 (1 H, dd, *J* 2.7 and 2.7, 7-H), 3.65 (3 H, s, CO_2Me), 2.75 (1 H, ddd, *J* 12.2, 6.8 and 3.7, 13-H), 2.70 (1 H, br d, *J* 3.7, 14-H), 2.06 (3 H, s, OAc), 1.31 (1 H, dd, *J* 12.5 and 2.1, 5-H), 1.16 (1 H, ddd, *J* 13.4, 13.4 and 4.4, 3α-H), 0.92 (1 H, ddd, *J* 12.1, 12.1 and 3.5, 1α-H) and 0.81, 0.80 and 0.78 (9 H, 3, s, 4α-, 4β- + 10β-Me); δ_C see Table 1.

Hydrolysis of Methyl Ester **13** *to Acid* **14**.—A solution of methyl ester **13** (11.1 mg, 0.0297 mmol) and KOH (60 mg) in MeOH–water (9:1) (2 cm^3) was stirred at room temperature

until analysis (TLC) of the reaction mixture showed no starting material (*ca.* 8 h). Work-up as described for the hydrolysis of compound **11**, followed by chromatography with hexane–ethyl acetate (8:2) as eluent, gave *acids* **14** (6.4 mg, 60%) and **9** (3.8 mg, 40%). Data for the acid **14**, δ_H(400 MHz) 6.24 (1 H, dd, *J* 2.9 and 1.0, 15-H), 6.19 (1 H, d, *J* 2.9, 17-H), 4.93 (1 H, dd, *J* 2.9 and 2.9, 7-H), 2.77 (1 H, ddd, *J* 12.5, 6.4 and 3.7, 13-H), 2.73 (1 H, br d, *J* 3.7, 14-H), 2.05 (3 H, s, OAc), 1.29 (1 H, dd, *J* 12.4 and 2.2, 5-H) and 0.80, 0.78 and 0.77 (9 H, 3 s, 4α-, 4β- + 10β-Me); *m/z* (EI) 318 (0.7%), 301 (2), 300 (8), 285 (7), 231 (5), 176 (7), 131 (12), 117 (25), 55 (26) and 43 (100); δ_C see Table 1.

(−)-7α-*Acetoxy*-17β-*hydroxy*-15β,17-*epoxyspongian*-16-*one* (*Aplyroseol*-2) **18**.—The hydroxy acid **14** (3.2 mg, 0.009 mmol) was ozonolysed in the same manner as described for compound **9**. The residue obtained after removal of the solvent and the excess of Me_2S was purified by chromatography with hexane–ethyl acetate (8:2) as eluent to afford aplyroseol-2 **18** (2.5 mg, 73%) as an oil which solidified on storage (the natural aplyroseol-2 had been reported as both a solid [2b] of m.p. 114–117 °C and an oil; [2a] however, we did not attempt its recrystallization because of the very limited amount of synthetic sample available); $[\alpha]_D^{18}$ −23 (*c* 0.6, $CHCl_3$) (lit.,[2b] −35°); ν_{max}(NaCl)/cm^{-1} 3420, 3060, 2820–3000, 1780, 1730, 1245, 865 and 735; δ_H(300 MHz) 5.98 (1 H, d, *J* 6.0, 15-H), 5.41 (1 H, s, 17-H), 4.69 (1 H, dd, *J* 2.7 and 2.7, 7-H), 2.82 (1 H, dd, *J* 11.5 and 6.0, 14-H), 2.70 (1 H, br dd, *J* 11.5 and 7.1, 13-H), 2.32 (1 H, m, 12β-H), 2.09 (3 H, s, OAc), 1.92 (1 H, dddd, *J* 12.8, 12.8, 12.8 and 4.0, 11β-H), 1.81 (1 H, ddd, *J* 15.1, 3.0 and 3.0, 6α-H), 0.87 (3 H, s, 10β-Me) and 0.75 and 0.72 (6 H, 2 s, 4α- + 4β-Me); δ_C see Table 1.

[3R-(3aα,5aS,7aα,11aβ,11bα)]-(−)-*Methyl* 6α-*Butyroxy*-1,3,3a,6,7,7a,8,9,10,11,11a,11b-*dodecahydro*-8,8,11a-*trimethyl*-6α-2H-*cyclobuta*[j]*phenanthrene*-3β-*carboxylate* **15**.—This compound was prepared from hydroxy ester **11** (25.4 mg, 0.076 mmol) in the same manner as compound **13** except that butyric anhydride (25.5 mm^3, 0.153 mmol) was used to afford, after purification by chromatography with hexane–ethyl acetate (95:5) as eluent, the butyrate **15** (27.4 mg, 89%) as an oil, $[\alpha]_D^{20}$ −1.3 (*c* 6.3, $CHCl_3$); ν_{max}(NaCl)/cm^{-1} 3040, 2840–3000, 1730, 1190, 1170 and 805; δ_H(300 MHz) 6.21 (1 H, dd, *J* 2.7 and 0.7, 15-H), 6.18 (1 H, d, *J* 2.7, 17-H), 4.94 (1 H, dd, *J* 2.9 and 2.9, 7-H), 3.62 (3 H, s, CO_2Me), 2.72 (1 H, ddd, *J* 12.5, 6.3 and 3.7, 13-H), 2.67 (1 H, br d, *J* 3.7, 14-H), 2.28 (2 H, t, *J* 7.6, $COCH_2$), 1.65 (2 H, sextet, *J* 7.6, $COCH_2CH_2$), 1.29 (1 H, dd, *J* 12.7 and 2.2, 5-H), 1.14 (1 H, ddd, *J* 13.9, 13.9 and 4.3, 3α-H), 0.95 (3 H, t, *J* 7.6, $COCH_2CH_2Me$) and 0.80, 0.78 and 0.75 (9 H, 3 s, 4α-, 4β- + 10β-Me); *m/z* (EI) 332 (2.7%), 315 (3.5), 314 (15), 299 (11), 255 (6), 245 (6), 239 (8), 190 (8), 143 (11), 117 (34), 71 (54), 49 (75) and 43 (100); δ_C see Table 1.

Hydrolysis of Methyl Ester **15** *to Acid* **16**.—A solution of methyl ester **15** (21.9 mg, 0.054 mmol) in MeOH (3.7 cm^3) was treated with aq. KOH (120 mg in 0.4 cm^3) during 15 h at room temperature. Work-up as described for the hydrolysis of ester **11**, followed by chromatography with hexane–ethyl acetate (8:2) as eluent, gave the corresponding acid **16** (17.8 mg, 84%) as an amorphous solid, $[\alpha]_D^{19}$ +2.2 (*c* 3.6, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3600–2500, 3050, 1725, 1700, 1170 and 800; δ_H(300 MHz) 6.25 (1 H, dd, *J* 2.9 and 0.7, 15-H), 6.21 (1 H, d, *J* 2.9, 17-H), 4.98 (1 H, dd, *J* 2.9 and 2.9, 7-H), 2.78 (1 H, ddd, *J* 12.5, 6.3 and 3.7, 13-H), 2.74 (1 H, m, 14-H), 2.30 (2 H, t, *J* 7.6, $COCH_2$), 1.68 (2 H, sextet, *J* 7.6, $COCH_2CH_2$), 0.97 (3 H, t, *J* 7.6, $COCH_2CH_2Me$) and 0.82, 0.80 and 0.78 (9 H, 3 s, 4α-, 4β- + 10β-Me); δ_C see Table 1.

Further elution with ethyl acetate afforded the hydroxy acid **9** (2.8 mg, 16%), formed by hydrolysis of both ester moieties of diester **15**.

(−)-7α-*Butyroxy*-17β-*hydroxy*-15β,17-*epoxyspongian*-16-*one* (*Aplyroseol*-1) **19**.—This compound was prepared in the same manner as compound **17** except that the acid **16** (17.2 mg, 0.044 mmol) was used to afford product **19** (17.7 mg, 95%), after purification by chromatography with hexane–ethyl acetate (8:2) as eluent. Aplyroseol-1 **19** was a solid, m.p. 197–199 °C (from hexane–diethyl ether) (lit.,[2a] 190–192 °C; lit.,[2b] 197–198 °C); $[\alpha]_D^{18}$ −47 (*c* 4.1, $CHCl_3$) (lit.,[2a] −52.8°; lit.,[2b] −37.2°); ν_{max}(KBr)/cm^{-1} 3350, 3020, 2820–3000, 1775, 1710, 950 and 865; δ_H(300 MHz) 6.04 (1 H, d, *J* 6.0, 15-H), 5.48 (1 H, s, 17-H), 4.76 (1 H, dd, *J* 2.9 and 2.9, 7-H), 2.86 (1 H, dd, *J* 11.4 and 6.0, 14-H), 2.74 (1 H, br dd, *J* 11.4 and 6.8, 13-H), 2.38 (1 H, m, 12-H), 2.37 (2 H, t, *J* 7.7, $COCH_2$), 1.98 (1 H, dddd, *J* 12.5, 12.5, 12.5 and 3.9, 11β-H), 1.85 (1 H, ddd, *J* 15.1, 2.9 and 2.9, 6α-H), 1.30 (1 H, dd, *J* 13.2 and 2.9, 5-H), 0.99 (3 H, t, *J* 7.7, $COCH_2CH_2Me$), 0.93 (3 H, s, 10β-Me) and 0.81 and 0.77 (6 H, 2 s, 4α- + 4β-Me); δ_C see Table 1.

Acknowledgements

Financial support from CICYT (Grant No. 89-0528) is gratefully acknowledged. M. L. M. thanks Conselleria de Educación y Ciencia de la Generalitat de Valencia for a grant. We also thank Dr. Donald Craig for the revision of the manuscript.

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Paper 3/01933K
Received 5th *April* 1993
Accepted 22nd *April* 1993