Short-step Stereoselective Synthesis of 2α,3α,22-Triacetoxy-23,24-dinor-5α-cholan-6-one:† Key Intermediate for the Preparation of 24¹-Norbrassinolide, Dolicholide and Dolichosterone‡

Braja G. Hazra,* Vandana S. Pore and Padmakar L. Joshi
National Chemical Laboratory, Pune 411 008, India

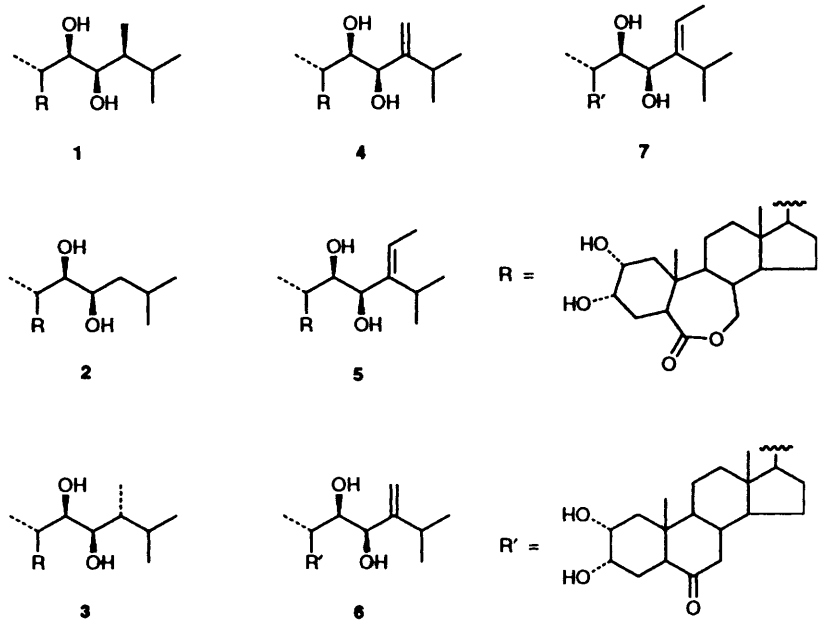
A stereoselective synthesis of 6-oxo-23,24-dinor-5α-cholan-2α,3α,22-triyl triacetate **9** was achieved in 44% overall yield in nine steps starting from 3β-hydroxyandrost-5-en-17-one **8**. The important features of this synthesis are the modified Wittig reaction on the 17-oxo steroid **8** and the stereospecific generation of the chiral centre at C-20 by a resin-catalysed ene reaction on (*Z*)-3β, *p*-tolylsulfonyloxypregna-5,17(20)-diene **11**.

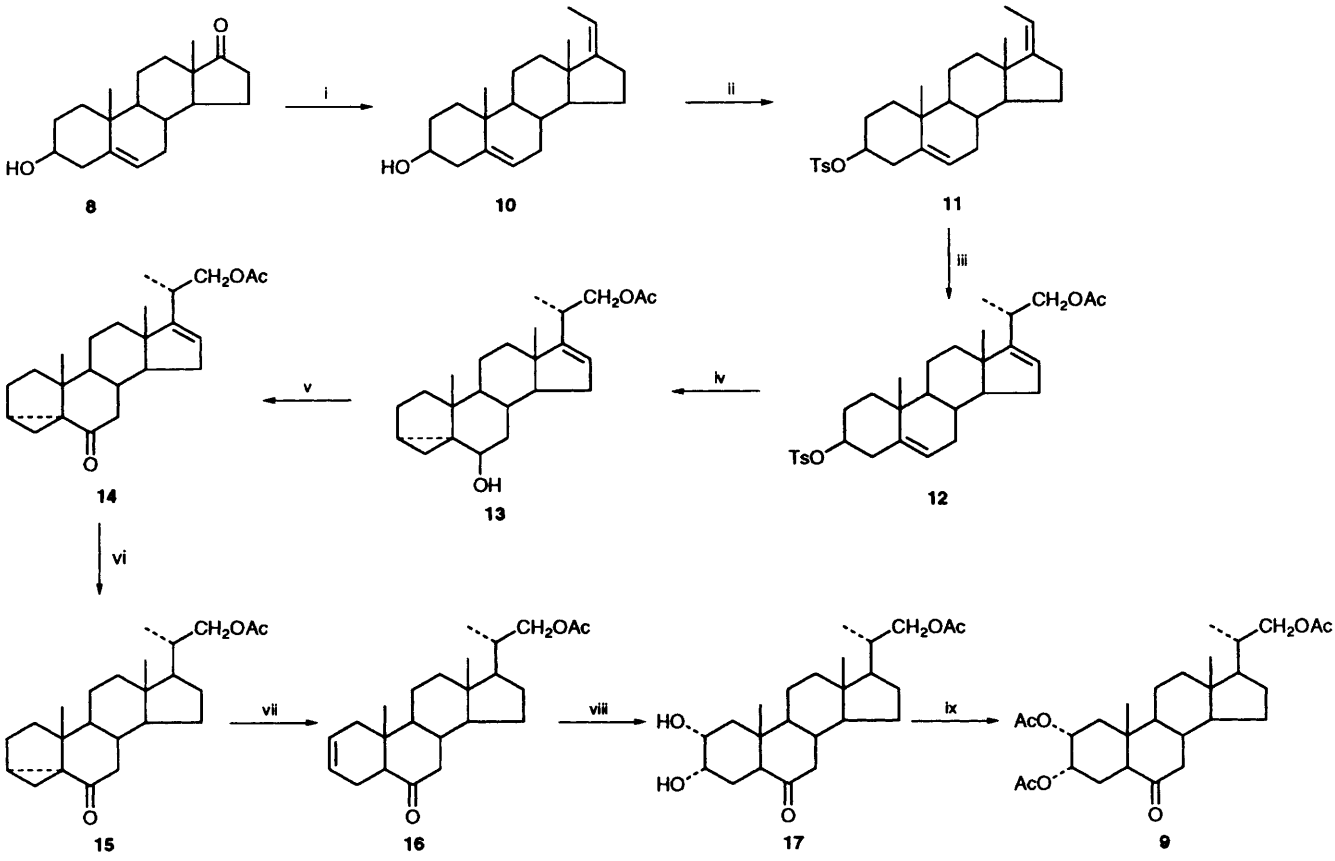
The discovery of brassinolide **1**[1] was a major breakthrough in recent phytochemistry because of its unique structure coupled with remarkable bioactivity in promoting plant growth. Since then a number of new brassinosteroids have been isolated, identified and recognised as a new group of phytohormones. Ikekawa and co-workers[2] have isolated 24[1]-norbrassinolide **2**§ from Chinese cabbage, and also epibrassinolide **3** from the bee pollen made from the broad bean[3] (*Vicia faba* L.). Yokota *et al.* have recently isolated four unsaturated steroids, namely dolicholide **4**,[4] homodolicholide **5**,[5] dolichosterone **6**[6] and homodolichosterone **7**[6] from immature seeds of *Dolichos lablab*. Their low abundance in natural sources, interesting physiological activity, and novel structural features have made brassinosteroids a target of several syntheses.

Syntheses of several brassinosteroids such as 24[1]-norbrassinolide **2**[7,8] 24-epibrassinolide **3**,[9,10] dolicholide **4**[11–14] and dolichosterone **6**[11–14] have already been reported. The synthetic approaches developed for compounds **2**, **4** and **6** are lengthy, consisting of protection and deprotection steps and often requiring exotic reagents. A key intermediate, 2α,3α,22-triacetoxy-23,24-dinor-5α-cholan-6-one **9**, has been converted by Mori *et al.*[11,12] into brassinolide analogues. These investigators have synthesized the triacetate **9** in 11 steps in 6–10% overall yield starting from stigmasterol. Ikekawa and Takatsuto[13,14] have converted this intermediate **9** into the naturally occurring brassinosteroids, namely 24[1]-norbrassinolide **2**, dolicholide **4** and dolichosterone **6**. They have prepared this triacetate **9** from stigmasterol in thirteen steps in 29% overall yield. In continuation of our efforts[15,16] towards the synthesis of brassinosteroids, a simple, efficient, nine-step synthesis of the key intermediate **9** in 44% overall yield, starting from 3β-hydroxyandrost-5-en-17-one **8**, is reported in this paper.

The synthesis of triacetate **9** starting from dehydroepiandrosterone **8** has not yet been reported. The choice of the ketone **8** as starting material is attractive due to its large-scale availability[17] from microbial degradation of abundant plant sterols and the ease with which it can be further transformed chemically. The formation of the (*Z*)-17(20)-ethylidene steroid **10** from 17-oxo steroid **8** has now been achieved in 89% yield by the Wittig reaction using 2 mol equiv. of $Ph_3(Et)P^+I$ and a simple work-up procedure (Scheme 1). According to an earlier report[18] the ethylidene steroid **10** was prepared from the ketone **8** by using a large excess of $Ph_3(Et)P^+ Br^-$ (6 mol

† *Systematic name:* 6-oxo-23,24-dinor-5α-cholan-2α,3α,22-triyl triacetate.
‡ NCL Communication No. 5652.
§ The 24[1] position is the IUPAC approved numbering for that position also referred to in the literature as 28.





Scheme 1 *Reagents and conditions:* i, $Ph_3P^+Et\ I^-$, KOBu^t, Bu^{t}OH, reflux, 6.5 h (89%); ii, 4-$MeC_6H_4SO_2Cl$, py, 25 °C, 48 h (90%); iii, resin, $(CH_2O)_n$, Ac_2O, CH_2Cl_2, 25 °C, 20 h (96%); iv, KOAc, acetone–water, reflux, 3 h (88%); v, CrO_3, acetone, 10 °C, 0.5 h (86%); vi, Pd/C H_2, EtOH, 25 °C 6 h (98%); vii, PPTS, LiBr, DMF, reflux, 4 h (80%); viii, OsO_4, NMO, Bu^{t}OH, acetone, 25 °C, 1.5 h (98%); ix, py, Ac_2O, 60–65 °C, 8 h (99%).

equiv.), prolonged reaction time, and in lower yield. The ethylidene steroid **10** was transformed into the tosyl ester **11** in 90% yield with toluene-*p*-sulfonyl chloride in pyridine. The use of a cation-exchange resin as a catalyst in performing the ene reaction was demonstrated earlier in our preliminary communication.[15] The (*Z*) olefin **11**, when subjected to the ene reaction with paraformaldehyde and acetic anhydride, with Tulsion T-42 cation-exchange resin as a catalyst, furnished the C-22 acetate **12** in 96% yield. The advantages of this resin-catalysed ene reaction are simple reaction conditions, excellent yields, and the use of cheap, commercially available catalysts which can be easily recovered and reused. This reaction stereospecifically generated the natural configuration at C-20. This approach makes use of the known preference for attack on the α-face of the C-17(20) double bond and the highly ordered transition state of the ene reaction to set the stereochemistry of the C-20 carbon in the natural configuration. This is confirmed by comparison of the spectral data and the mixed m.p. of acetate **12** with those of an authentic compound prepared according to the known[19] route.

The acetate **12** was solvolysed by using potassium acetate in aq. acetone[20] to give 3α,5-cyclo-6-hydroxy steroid **13**. The crude i-alcohol alcohol **13** was oxidised with Jones' reagent to give the corresponding keto compound **14**, which was purified by column chromatography. The keto acetate **14**, when subjected to hydrogenation over 10% Pd/C, afforded the saturated product **15** in 98% yield. The transfer of hydrogen from the surface of the catalyst takes place from the less hindered face of the C-16 double bond. The keto acetate **15** was heated with lithium bromide and pyridinium toluene-*p*-sulfonate (PPTS) in dimethylformamide (DMF)[21] to give a solid product, which, after chromatographic purification on silica gel, afforded the olefin **16** in 80% yield. The double bond in ring A of compound **16** was hydroxylated with a catalytic amount of OsO_4 and an excess of *N*-methylmorpholine *N*-oxide (NMO) in aq. acetone[22] to give the 2α,3α-dihydroxy compound **17** in 98% yield. This dihydroxy acetate **17**, on being heated at 60 °C for 8 h with pyridine and acetic anhydride, was converted into the required triacetate **9** in 99% yield. The transformations of this triacetate **9** into 24[1]-norbrassinolide **2**, dolicholide **4**, dolichosterone **6**[13,14] and the other brassinolide analogues[11,12] have been documented. Our synthesis of triacetate **9** from dehydroepiandrosterone **8** constitutes a formal total synthesis of these compounds. In conclusion, the present procedure is simple and provides a high overall yield (44%) of the triacetate **9** from the 17-oxo steroid **8**.

Experimental

All m.p.s were measured on a Campbell Electronics (Bombay) m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer model 599B, using NaCl optics. ^1H NMR spectra were run in $CDCl_3$ on a Bruker MSL 90 spectrophotometer with $SiMe_4$ as internal standard, and *J* values are given in Hz. All optical rotations were measured on a JASCO-181 digital polarimeter using a sodium light (5893 Å) source, and $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a Finnigan Mat 1020C mass spectrometer at 70 eV. For column chromatography, ACME silica gel 100–200 mesh size was used. TLC was performed using Merck precoated aluminium sheets of silica gel 60 F_{254} (0.2 mm thickness). Elemental analyses were carried out in the analytical section of the department. Methylene dichloride was freshly distilled over calcium hydride. Tetrahydrofuran (THF) used

was freshly distilled over lithium aluminium hydride (LAH). Light petroleum refers to the fraction boiling in the range 60–80 °C, which was distilled prior to use. Cation-exchange resin Tulsion, T-42(H), strongly acidic cation exchanger was procured from Tulsi Fine Chemicals, Pune, India. DMF and acetic anhydride were freshly dried and distilled. All other reagents were purchased from commercial sources and were purified by standard methods as required.

(Z)-*Pregna*-5,17(20)-*dien*-3β-*ol* **10**.—Potassium *tert*-butoxide (7.68 g, 68.6 mmol) was prepared by dissolution of potassium metal (2.68 g) in *tert*-butyl alcohol (43 cm^3) by heating under reflux for 1.5 h. The mixture was cooled to room temperature and $(C_6H_5)_3P^+Et\ I^-$ (28.7 g, 68.6 mmol) and THF (40 cm^3) were added. The mixture was stirred for 0.5 h and a solution of dehydroepiandrosterone **8** (9.88 g, 34.31 mmol) in THF (40 cm^3) was added. The reaction mixture was then refluxed for 6.5 h and was then cooled to room temperature. To the reaction mixture was added 50% methanol in water (150 cm^3). The mixture was stirred for 20 min and then extracted with hexane (3 × 100 cm^3), and the combined extracts were washed successively with water (2 × 50 cm^3) and brine (50 cm^3). The organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, a gummy compound was obtained (16.2 g). To this gummy mass was added methanol (50 cm^3) and the mixture was warmed to give a clear solution. This solution was cooled to room temperature, treated with methyl iodide (8 cm^3), and kept overnight at room temperature. This procedure converted[23] any excess of triphenylphosphine, if present, into methyltriphenylphosphonium iodide, which can then be easily removed by chromatography or aqueous extraction. The mixture was concentrated under reduced pressure and filtered to give (*Z*)-pregna-5,17(20)-dien-3β-ol **10** (6.75 g). From the mother liquor a further crop of diene **10** was obtained by column chromatography over silica gel, combined yield 9.28 g (89%); m.p. 136–137 °C (lit.,[23] 136–138 °C); R_f 0.4 (30% ethyl acetate–light petroleum; ν_{max}(Nujol)/cm^{-1} 3280 (OH) and 1060; δ_H 0.88 (3 H, s, 18-H_3), 1.04 (3 H, s, 19-H_3), 1.6 (3 H d, *J* 6, 21-H_3), 3.52 (1 H, m, 3-H), 5.04 (1 H, m, 20-H) and 5.28 (1 H, m, 6-H).

(Z)-*Pregna*-5,17(20)-*dien*-3β-*yl Toluene*-p-*sulfonate* **11**.—To a solution of the alcohol **10** (2.53 g, 8.4 mmol) in pyridine (15 cm^3) was added toluene-*p*-sulfonyl chloride (3 g, 15.8 mmol). The reaction mixture was kept in the dark for 48 h and was then poured into ice-cooled, 5% aq. sodium hydrogen carbonate (200 cm^3). Compound **11** was isolated by filtration. It was crystallised from diethyl ether–light petroleum, (3.4 g, 90%); m.p. 119–120 °C (lit.,[19] 119–119.5 °C); R_f 0.55 (10% ethyl acetate in light petroleum); ν_{max}(Nujol)/cm^{-1} 1605, 1200, 1180 and 1110; δ_H 0.87 (3 H, s, 18-H), 0.98 (3 H, s, 19-H_3), 1.65 (3 H, d, *J* 7, 21-H_3), 2.44 (3 H, s, *Me*Ar), 4.29 (1 H, m, 3-H), 5.13 (1 H, m, 20-H), 5.32 (1 H, br d, 6-H) and 7.33 and 7.78 (4 H, AB pattern, *J* 8 ArH).

(20S)-23,24-*Dinorchola*-5,16-*diene*-3β,22-*diyl* 22-*Acetate* 3-(*Toluene*-p-*sulfonate*) **12**.—A solution of tosyl compound **11** (0.23 g, 0.56 mmol) in methylene dichloride (5 cm^3) was added to a stirred mixture of paraformaldehyde (0.05 g, 0.56 mmol), Tulsion T-42 cation-exchange resin (1.15 g, 5 parts) and acetic anhydride (0.1 cm^3, 1.12 mmol) in methylene dichloride (5 cm^3). The mixture was stirred at 25 °C for 20 h, the resin was filtered off, and the filtrate was treated with water and extracted with methylene dichloride (3 × 50 cm^3). The combined extracts were washed successively with water (3 × 25 cm^3), saturated aq. sodium hydrogen carbonate (2 × 25 cm^3), water (2 × 25 cm^3) and finally with brine, and were then dried over anhydrous Na_2SO_4. Removal of solvent afforded title compound **12**, which was crystallised from hexane (0.253 g, 96%); m.p. 107–108 °C (lit.,[19] 109–110 °C); R_f 0.35 (15% ethyl acetate in light petroleum); $[\alpha]_D^{20}$ −36.1 (*c* 2, $CHCl_3$) (lit.,[19] $[\alpha]^{20}$ −36.9); ν_{max}(Nujol)/cm^{-1} 1740 (OAc), 1605 and 1375; δ_H 0.76 (3 H, s, 18-H_3), 0.93 (3 H, s, 19-H_3), 1.04 (3 H, d, *J* 6, 21-H_3) 2.02 (3 H, s, OAc), 2.44 (3 H, s, *Me*Ar), 3.4–4.2 (2 H, m, 22-H_2), 4.27 (1 H, m, 3-H), 5.2–5.4 (2 H, m, 6- and 16-H) and 7.29 and 7.76 (4 H, AB pattern, *J* 10 ArH).

(20S)-6β-*Hydroxy*-3α,5-*cyclo*-23,24-*dinor*-5α-*chol*-16-*en*-22-*yl Acetate* **13**.—To a solution of acetate **12** (2.0 g, 3.8 mmol) in acetone (40 cm^3) were added potassium acetate (1.0 g, 10.2 mmol) and water (10 cm^3). The reaction mixture was refluxed on a water-bath for 3 h. The solvent was then removed under reduced pressure and the residue was extracted with light petroleum. This extract was washed successively with water (2 × 50 cm^3) followed by brine, and was dried over anhydrous Na_2SO_4. The solvent was evaporated off and the residue was purified by column chromatography on silica gel (12% ethyl acetate in light petroleum) to afford *title compound* **13** as a thick liquid (1.29 g, 88%), R_f 0.35 (15% ethyl acetate in light petroleum) (Found: C, 77.2; H, 9.6. $C_{24}H_{36}O_3$ requires C, 77.37; H, 9.74%); *m*/*z* 372, 324, 310 (100%), 295, 269 and 173; ν_{max}(Nujol)/cm^{-1} 3460 (OH), 1750 (OAc), 1235 and 1020; δ_H 0.84 (3 H, s, 18-H_3), 1.09 (3 H, s, 19-H_3), 1.13 (3 H, d, *J* 7, 21-H_3), 2.04 (3 H, s, OAc), 3.27 (1 H, t, *J* 2, 6-H), 3.64–4.18 (2 H, m, 22-H_2) and 5.42 (1 H, br s, 16-H).

(20S)-6-*Oxo*-3α,5-*cyclo*-23,24-*dinor*-5α-*chol*-16-*en*-22-*yl Acetate* **14**.—Standard 2.67 mol dm^{-3} Jones' reagent was prepared by dissolution of chromium(VI) trioxide (2.67 g) in conc. sulfuric acid (2.3 cm^3) diluted with water to a volume of 10 cm^{-3}. To a stirred and cooled (10 °C) solution of the alcohol **13** (1.4 g, 3.76 mmol) in acetone (45 cm^3) was added Jones' reagent (1.4 cm^3, 2.67 mol dm^{-3}) dropwise, while the temperature was kept below 15 °C. After the addition, the reaction mixture was stirred for a further 5 min and then methanol was added to destroy excess of Jones' reagent. Solvent was removed completely under reduced pressure and the residue was extracted with diethyl ether (3 × 75 cm^3). The combined extracts were washed successively with water (2 × 25 cm^3), saturated aq. sodium hydrogen carbonate (2 × 25 cm^3), water (2 × 25 cm^3) and finally with brine. The extract was dried over anhydrous Na_2SO_4 and, after evaporation of the solvent, afforded the ketone **14** as a thick oil. This was chromatographed over silica gel (10% ethyl acetate in light petroleum) to afford pure *ketone* **14** (1.2 g, 86%); R_f 0.6 (15% ethyl acetate in light petroleum) (Found: C, 77.6; H, 9.1. $C_{24}H_{34}O_3$ requires C, 77.80; H, 9.25%); *m*/*z* 310 (100%), 295, 269, 173, 161, 145, 123 and 105; ν_{max}(film)/cm^{-1} 1740 (OAc) and 1685 (CO); δ_H 0.8 (3 H, s, 18-H_3), 1.04 (3 H, s, 19-H_3), 1.13 (3 H, d, *J* 7, 21-H_3), 2.04 (3 H, s, OAc), 2.47 (2 H, d, *J* 10, 7-H_2), 3.84–4.29 (2 H, m, 22-H_2) and 5.42 (1 H, br s, 16-H).

(20S) 6-*Oxo*-3α,5-*cyclo*-23,24-*dinor*-5α-*cholan*-22-*yl Acetate* **15**.—Olefin **14** (0.5 g, 1.35 mmol) in ethanol (20 cm^3) was hydrogenated in a Parr apparatus using 10% Pd/C (0.1 g) for 6 h at 30 psi pressure. The catalyst was filtered off and the solvent was removed under reduced pressure to give *compound* **15** as a solid, homogeneous on TLC (0.493 g, 98%); a small portion was crystallised, m.p. 127–128 °C (from diethyl ether–light petroleum); R_f 0.6 (15% ethyl acetate–light petroleum); $[\alpha]_D^{31}$ + 35.4 (*c* 0.9, $CHCl_3$) (Found: C, 77.2; H, 9.7. $C_{24}H_{36}O_3$ requires C, 77.37; H, 9.74%); *m*/*z* 372 (100%), 354, 344, 314, 297, 269, 136, 121, 91 and 79; ν_{max}(Nujol)/cm^{-1} 1735 (OAc) and 1690 (CO); δ_H 0.76 (3 H, s, 18-H_3), 0.93 (3 H, d, *J* 7, 21-H_3), 1.0 (3 H, s, 19-H_3), 2.04 (3 H, s, OAc), 2.44 (2 H, d, *J* 10, 7 H_2) and 3.6–4.29 (2 H, m, 22-H_2).

(20S)-6-*Oxo*-23,24-*dinor*-5α-*chol*-2-*en*-22-*yl Acetate* **16**.—Ketone **15** (0.280 g, 0.75 mmol), lithium bromide (0.028 g, 0.32

mmol) and PPTS (0.028 g, 0.11 mmol) were refluxed in DMF (5 cm^3) for 4 h. The reaction mixture was cooled to room temperature, treated with cold water, and then extracted with ethyl acetate. The extract was washed successively with water (2 × 25 cm^3), saturated aq. sodium hydrogen carbonate (2 × 25 cm^3), water (2 × 25 cm^3) and finally with brine. After being dried over anhydrous Na_2SO_4, the solvent was distilled off to furnish a crude product (0.298 g), which was chromatographed on a silica gel column. Elution with 5% ethyl acetate–light petroleum gave *compound* **16** as a solid (0.224 g, 80%); m.p. 75 °C (from diethyl ether–light petroleum); R_f 0.65 (15% ethyl acetate in light petroleum); $[\alpha]_D^{25}$ +31.3 (*c* 2.8, $CHCl_3$) (Found: C, 77.2; H, 9.6. $C_{24}H_{36}O_3$ requires C, 77.37; H, 9.74%); *m/z* 372 (M^+), 375, 344, 297, 229, 175, 159, 133, 121, 107, 93 (100%), 79, 67 and 55; ν_{max}(Nujol)/cm^{-1} 1738 (OAC), 1708 (CO) and 1240; δ_H 0.71 (3H, s, 18-H_3), 0.73 (3 H, s, 19-H_3), 1.02 (3 H, d, *J* 7, 21-H_3), 2.04 (3 H, s, OAc), 3.6–4.29 (2 H, m, 22-H_2) and 5.58 (2 H, m, 2- and 3-H).

2α,3α-*Dihydroxy*-6-*oxo*-23,24-*dinor*-5α-*cholan*-22-*yl Acetate* **17**.—A solution of OsO_4 (0.008 g) in Bu'OH (0.4 cm^3) was added to a solution of **16** (0.227 g, 0.83 mmol) in acetone (13 cm^3). Then NMO (0.227 g) and water (0.5 cm^3) were added. The reaction was stirred under nitrogen for 1.5 h, and a solution of sodium hydrogen sulfite (0.1 g) in water (1 cm^3) was then added. The mixture was stirred for 0.5 h and was then filtered through Celite. The filtrate was evaporated to dryness. The residue was extracted with chloroform, and the extract was washed successively with water (2 × 50 cm^3) and with brine. After being dried over anhydrous Na_2SO_4, the chloroform was evaporated off to afford the *diol* **17** as a solid, homogeneous on TLC (0.244 g, 98%); a portion of this was recrystallised, m.p. 170–171 °C (from MeOH); $[\alpha]_D^{24}$ +0.662 (*c* 2.72, $CHCl_3$) (Found: C, 70.7; H, 9.3. $C_{24}H_{38}O_5$ requires C, 70.90, H, 9.42%); *m/z* 406 (M^+), 391, 346, 328, 304 (100%), 286, 277, 272, 263, 245, 175, 133, 121, 107, 93 and 81; ν_{max}(Nujol)/cm^{-1} 3580br (OH), 1735 (OAc), 1705 (CO) and 1270; δ_H 0.67 (3 H, s, 18-H_3), 0.76 (3 H, s, 19-H_3), 0.93 (3 H, d), *J* 7, 21-H_3), 1.82 (2 H, br s, OH, exch. with D_2O), 2.04 (3 H, s, OAc), 2.64 (1 H, dd, *J* 4 and 13, 5-H), 3.6–4.29 (2 H, m, 22-H_2); 3.6–3.89 (1 H, m, 2-H) and 3.93–4.09 (1 H, m, 3-H).

6-*Oxo*-23,24-*dinor*-5α-*cholane*-2α,3α,22-*triyl Triacetate* **9**.—A stirred mixture of diol **17** (0.208 g, 0.51 mmol), pyridine (1.2 cm^3), acetic anhydride (0.8 cm^3) and 4-(dimethylamino)pyridine (0.048 g) was heated at 60–65 °C for 8 h, poured into water, and extracted with diethyl ether (3 × 50 cm^3). The combined extracts were washed successively with water (1 × 25 cm^3), 2% HCl (2 × 25 cm^3), water (1 × 25 cm^3), saturated sodium hydrogen carbonate (2 × 25 cm^3), water (2 × 25 cm^3) and finally with brine. The extract was dried over anhydrous Na_2SO_4, and after evaporation gave a gummy mass, homogeneous on TLC (0.250 g, 99%). On trituration with methanol the whole mass solidified. A small portion of this was recrystallised from methanol to give compound **9**, m.p. 205 °C (lit.,[11] 182–185 °C; lit.,[13,14] 212 °C); R_f 0.7 (2.5% MeOH in $CHCl_3$) (Found: C, 68.35; H, 8.5. $C_{28}H_{42}O_7$ requires C, 68.54, H, 8.63%); $[\alpha]_D^{28}$ −4.58 (*c* 1.44, $CHCl_3$); *m/z* 430 (M − AcOH), 388, 370, 355 (100%), 326, 311, 295, 266, 227, 175, 105, 93, 81, 67 and 55; ν_{max}(Nujol)/cm^{-1} 1745 (OAc), 1720 (CO), 1240 and 1050; δ_H 0.69 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 0.96 (3 H, d, *J* 7, 21-H_3), 1.96 (3 H, s, OAc), 2.02 (3 H, s, OAc), 2.07 (3 H, s, OAc), 3.6–4.31 (2 H, m, 22-H_2), 4.89 (1 H, m, 2-H) and 5.31 (1 H, m, 3-H).

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