Stereoselective Synthesis of the 20-Hydroxyecdysone Side Chain[1,†]

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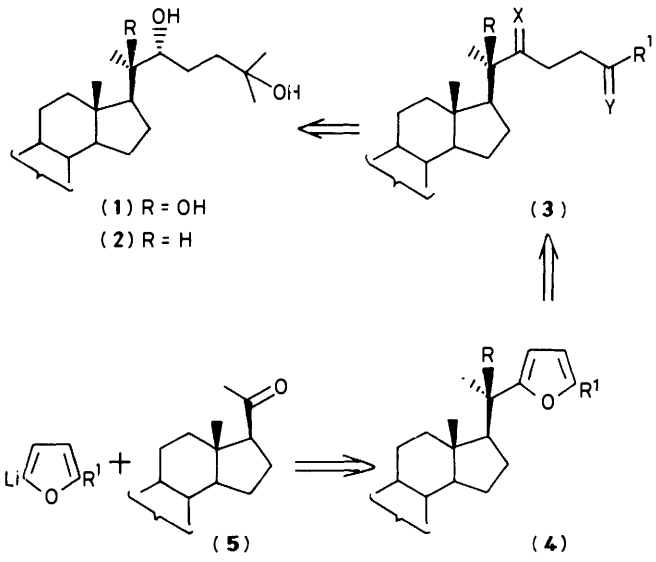
A new procedure for the construction of the 20-hydroxyecdysone-type side chain starting from 20-oxopregnane is described. The stereoselective reduction of the lactone (**15**) as a key reaction to give the δ-lactone (**17**) and the γ-lactone (**18**), under various conditions has also been investigated. A stereoselective synthesis of (20*R*,22*R*)-5α-cholestane-3β,20,22,25-tetraol (**20**) is described.

The stereocontrolled introduction[2] of side chains into steroids has been widely investigated because of the discovery that many steroids with a modified side-chain are physiologically interesting; for example, the ecdysones,[3] the metabolites of vitamin D,[4] withanolides[5] with anti-tumour activity, and the plant growth promoters brassinolide.[6] In a previous paper,[7] we described a simple method for the transformation of a furan derivative (**4**) into a (22*R*)-22,25-dihydroxycholesterol (**2**) with an ecdysone-type side chain (Scheme 1); we have since been investigating the synthesis of compound (**1**) which has a 20-hydroxyecdysone-type side chain containing a (20*R*,22*R*)-20,22-diol functionality.

An important problem in the synthesis of a 20-hydroxyecdysone-type side chain is controlling the stereochemistry at C-20 and C-22. There have been many attempts to solve this problem (Scheme 2), by a Grignard reaction of the (20*R*)-20-formyl-20-hydroxy compound (**6**),[8] reduction of the α-hydroxy ketone (**7**),[9] hydroxylation of the (*E*)-olefin (**8**),[10] alkylation of the epoxy alcohol (**9**),[11] and a [2,3] sigmatropic rearrangement of the sulphoxide (**10**).[12] Here we report a new methodology for a stereoselective synthesis of (20*R*,22*R*)-5α-cholestane-3β,20,22,25-tetraol (**20**), incorporating the required functionality shown in structure (**11**).

As outlined in Scheme 3, the (20*R*)-20-furylsteroid (**13**), prepared from 5α-pregnan-20-one (**12**) by reaction with 2-lithiofuran in tetrahydrofuran at −78 °C, was treated with *m*-chloroperbenzoic acid and sodium acetate in chloroform to give the ketohemiacetal (**14**) [91.4% yield from (**12**)]. It is known that oxidation of the furylcarbinol moiety gives the pyran derivative with retention of the stereochemistry.[13] Oxidation of compound (**14**) with pyridinium chlorochromate and sodium acetate in dry dichloromethane afforded the lactone (**15**) in 91.2% yield. In order to introduce the (22*R*)-22-hydroxy group, the reduction of compound (**15**) was carried out under various conditions to yield the saturated compound (**16**), the γ-hydroxy-δ-lactone (**17**), and the γ-lactone (**18**) formed by rearrangement of (**17**) (Scheme 4). Each compound was prepared almost selectively under the different reaction conditions of hydrogenation or hydride reduction. The results obtained are summarised in the Table. Hydrogenation of compound (**15**) with 10% palladium–carbon in benzene furnished the saturated compound (**16**) in 97.6% yield. With platinum oxide as the catalyst for hydrogenation, reduction of the carbonyl group was observed under one atmosphere to give the δ-lactone (**17**) and the further rearranged γ-lactone (**18**), with the (20*R*,22*R*)-diol functionality, as the main products in 80.1 and 19.8% yields respectively. Of particular interest was the reduction of compound (**15**) with sodium borohydride to give the γ-lactone (**18**) preferentially together with a small amount of the δ-lactone (**17**). The reduction of compound (**16**) with sodium borohydride gave the same result as compound (**15**), that is, the products (**17**)



Scheme 1.

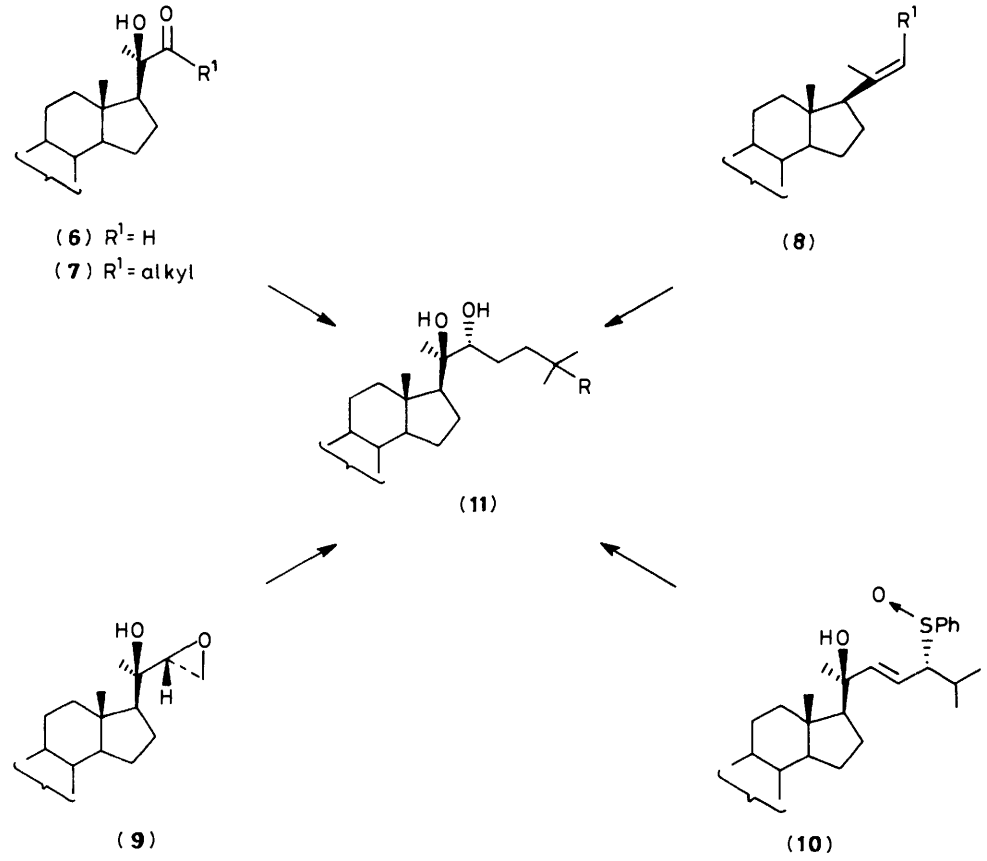
and (**18**) in 4.9 and 79.6% yields, respectively. The structures of compounds (**17**) and (**18**) were deduced from the spectroscopic data, and confirmed together with the detailed stereochemistry by conversion into the known compound (**20**). Treatment of compound (**17**) with methylmagnesium bromide in tetrahydrofuran afforded the triol (**19**) which was subjected to deprotection of the tetrahydropyranyl ether with pyridinium toluene-*p*-sulphonate in ethanol to furnish (20*R*,22*R*)-5α-cholestane-3β,20,22,25-tetraol (**20**) in 94.3% yield. Compound (**18**) was converted in the same way into compound (**20**) in 86.1% yield. This compound obtained was identical with the authentic sample.[14]

Thus we have developed a simple and efficient method for introducing the 20-hydroxyecdysone-type side chain into 20-oxopregnane, the key steps being the conversion of the furylcarbinol (**13**) into the 2*H*-pyran-3(6*H*)-one (**14**) and the stereoselective reduction of compound (**15**), giving the δ-lactone (**17**) and the γ-lactone (**18**). These lactones (**17**) and/or (**18**), which possess the (20*R*,22*R*)-diol functionality, are potentially important intermediates for the synthesis of modified side chains of steroids. We are currently investigating the application of this method to other complicated steroids.

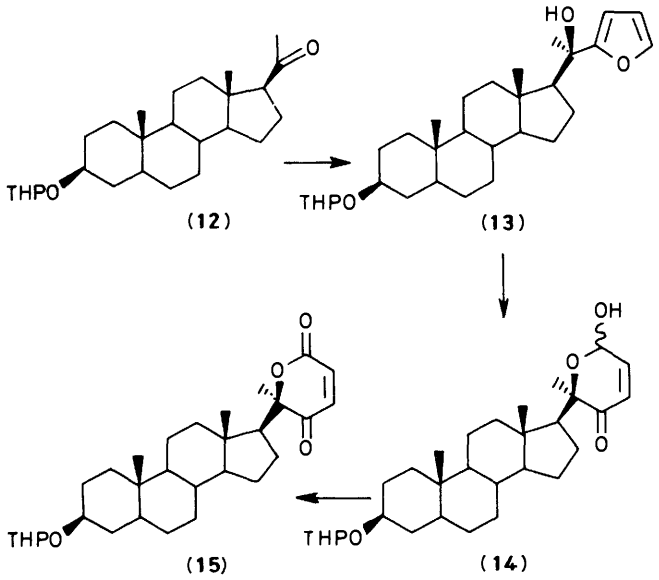
Experimental

M.p.s were measured with a Yanagimoto micro melting point apparatus and are uncorrected. I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer. ^{1}H N.m.r. spectra were obtained for solutions in $CDCl_3$ on a JEOL JMX-60 or JNM

† In the preliminary communication (ref. 1), (20*R*,22*R*)-5α-cholestane-3β,20,22,25-tetraol was wrongly given as the 5β-cholestanetetraol.



Scheme 2.



Scheme 3.

FX-100 instrument, and chemical shifts are reported in p.p.m. on the δ scale from internal Me_4Si. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Column chromatography was carried out on Wakogel C-200 (silica gel).

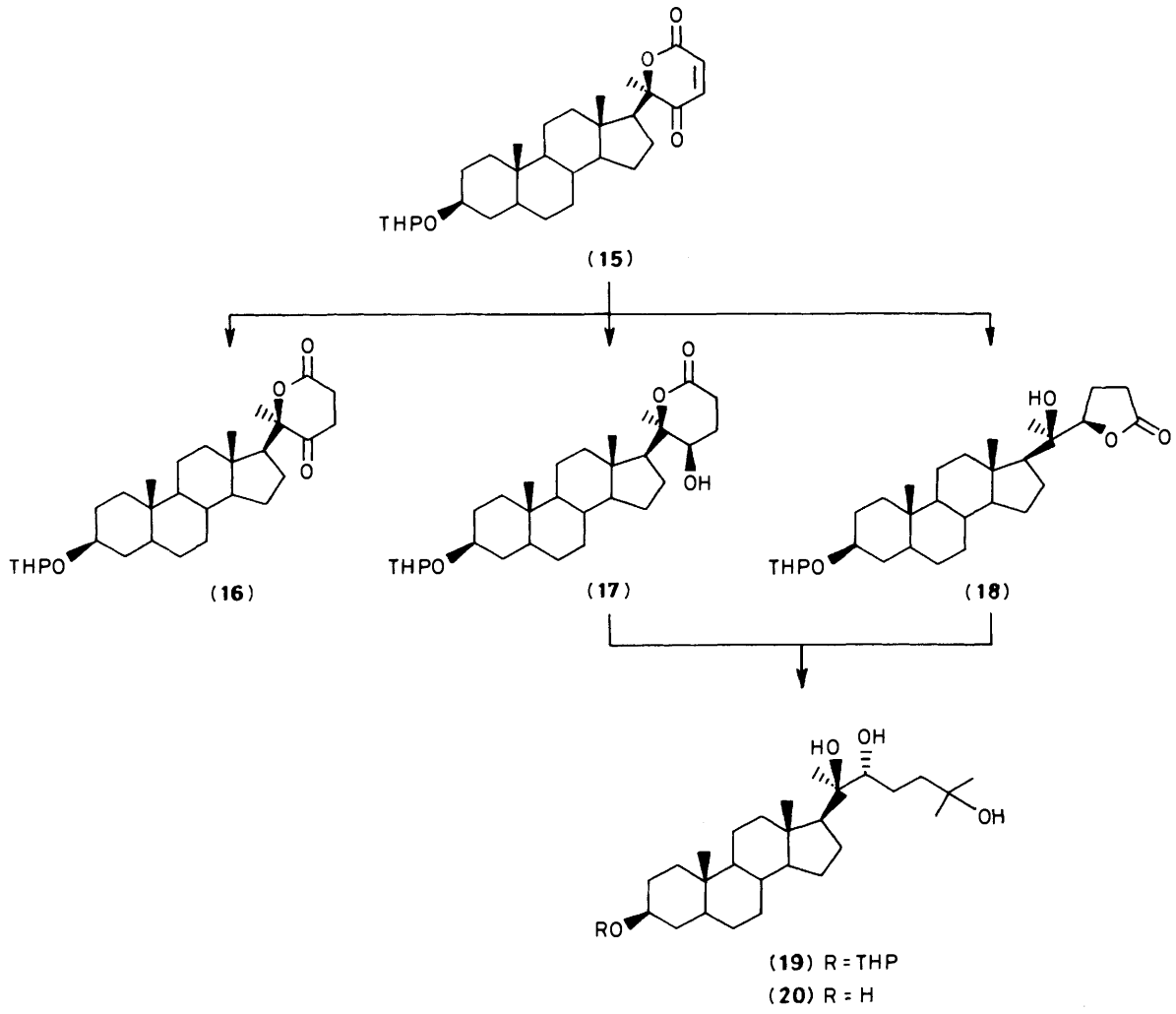
(20R)-20-(2-*Furyl*)-20-*hydroxy*-3β-*tetrahydropyranyloxy*-5α-*pregnane* (**13**).—To a stirred solution of 2-lithiofuran [prepared from furan (0.45 ml, 6.2 mmol) in anhydrous tetrahydrofuran (5 ml) and 2.6M-n-butyl-lithium (2.3 ml)] was added a solution of 3β-tetrahydropyranyloxy-5α-pregnan-20-one (**12**) (1.23 g, 3.1 mmol) in anhydrous tetrahydrofuran (10 ml) at −78 °C under a current of nitrogen and the reaction mixture was stirred for 1 h at room temperature. After quenching with aqueous ammonium chloride, the product was isolated by ethyl acetate extraction to give the *furylcarbinol* (**13**). The crude product was used for the next reaction without further purification because of its instability; $\nu_{max.}(CHCl_3)$ 3 600 and 3 450 cm^{-1}; δ 0.71 (3 H, s, 13-Me), 0.80 (3 H, s, 10-Me), 1.57 (3 H, s, 20-Me), 3.2—4.2 (3 H, m, 3-H and OCH_2CH_2), 4.7 (1 H, br s, $W_{\frac{1}{2}}$ 8 Hz, acetal-H), 6.11 (1 H, d, *J* 3 Hz. 23-H), 6.27 (1 H, dd, *J* 2 and 3 Hz, 24-H), and 7.3 (1 H, d, *J* 2 Hz, 25-H) (Found: M^+, 470.3382. $C_{30}H_{46}O_4$ requires *M*, 470.3394).

Table. Reduction of compound (**15**)

Reaction conditions	Products (%) (**16**)	(**17**)	(**18**)
H_2–10% Pd/C, benzene	97.6		
H_2–Pt, benzene	17.4	Trace[a]	80.6
H_2–Pt, AcOEt		80.1	19.8
$NaBH_4$, MeOH–CH_2Cl_2		4.9	78.3

[a] A small amount of the compound was detected on t.l.c.

(20R)-20,25-*Epoxy*-25-*hydroxy*-3-*tetrahydropyranyloxy*-25-*homo*-5α-*chol*-23-*en*-22-*one* (**14**).—To a suspension of the crude product (**13**) (1.45 g) and sodium acetate (0.5 g, 6.1 mmol) in



Scheme 4.

$CHCl_3$ (15 ml) was added dropwise a solution of *m*-chloroperbenzoic acid (1.58 g, 6.4 mmol) in $CHCl_3$ (15 ml) at 0 °C and the reaction mixture was stirred for 1.5 h at the same temperature. The product was extracted by diethyl ether and the organic layer was washed with 10% sodium hydroxide solution, saturated sodium thiosulphate solution, and saturated sodium chloride solution and dried (Na_2SO_4). Evaporation of the solvent gave the crude product which was purified by column chromatography on silica gel ($CHCl_3$) to afford the ketone (**12**) (0.125 g) and the *hemiacetal* (**14**) [1.221 g, 91.4% from (**12**)], m.p. 139—143 °C ($CHCl_3$–hexane); $\nu_{max.}$($CHCl_3$) 3 595, 3 360, and 1 690 cm^{-1}, δ 0.82 (6 H, s, 10- and 13-Me) 1.58 (3 H, s, 20-Me), 3.2—4.2 (3 H, m, 3-H and OCH_2CH_2), 4.72 (1 H, br s, $W_{\frac{1}{2}}$ 7 Hz, acetal-H), 5.55—5.8 (1 H, m, 25-H), 6.02 (1 H, distorted d, *J* 10 Hz, 24-H), and 6.83 (1 H, dd, *J* 3 and 10 Hz, 23-H) (Found: C, 73.6; H, 9.7. $C_{30}H_{46}O_5$ requires C, 74.05; H, 9.55%).

(20R)-22-*Oxo*-3β-*tetrahydropyranyloxy*-25-*homo*-5α-*chol*-23-*eno*-25,20-*lactone* (**15**).—To a stirred suspension of pyridinium chlorochromate (0.913 g, 4.2 mmol) and sodium acetate (0.35 g, 4.2 mmol) in dry dichloromethane (10 ml) was added rapidly a solution of the hemiacetal (**14**) (1.029 g, 2.1 mmol) in dry dichloromethane (12 ml) at room temperature. The reaction mixture was stirred for 2 h and then diluted with anhydrous ether (30 ml). The product was isolated by decantation using anhydrous ether. The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvent afforded the residue which was purified by column chromatography on silica gel (CH_2Cl_2) to give the *lactone* (**15**) (0.935 g, 91.2%) as colourless needles, m.p. 202—203 °C (acetone); $\nu_{max.}$($CHCl_3$) 1 720 and 1 695 cm^{-1}, δ 0.81 (3 H, s, 13-Me), 0.83 (3 H, s, 10-Me), 1.62 (3 H, s, 20-Me), 3.2—4.2 (3 H, m, 3-H and OCH_2CH_2), 4.7 (1 H, br s, $W_{\frac{1}{2}}$ 7 Hz, acetal-H), 6.62 (1 H, d, *J* 10 Hz, 24-H), and 6.88 (1 H, d, *J* 10 Hz, 23-H) (Found: C, 74.1; H, 9.25. $C_{30}H_{44}O_5$ requires C, 74.35; H, 9.15%).

Reduction of Compound (**15**).—(*a*) *Hydrogenation of compound* (**15**) *with* 10% Pd–C. A suspension of compound (**15**) (10 mg, 0.02 mmol) and 10% palladium–carbon (2 mg) in benzene (1 ml) was shaken in a hydrogen atmosphere for 2 h. After removal of the catalyst, the solvent was evaporated off to give the residue which was purified by column chromatography on silica gel ($CHCl_3$) to give (20R)-22-*oxo*-3β-*tetrahydropyranyloxy*-25-*homo*-5α-*cholano*-25,20-*lactone* (**16**) (9.8 mg, 97.6%) as colourless needles, m.p. 187—190 °C (acetone), $\nu_{max.}$($CHCl_3$) 1 740 and 1 725 cm^{-1}; δ 0.82 (3 H, s, 13-Me), 0.86 (3 H, s, 10-Me), 1.55 (3 H, s, 20-Me), 2.77 (4 H, br s, $W_{\frac{1}{2}}$ 3 Hz, 23- and 24-H), 3.2—4.2 (3 H, m, 3-H and OCH_2CH_2), and 4.66 (1 H, br s, $W_{\frac{1}{2}}$ 7 Hz, acetal-H) (Found: C, 74.1; H, 9.75. $C_{30}H_{46}O_5$ requires C, 74.05; H, 9.55%).

(*b*) *Hydrogenation of compound* (**15**) *using* PtO_2. A suspension of compound (**15**) (260 mg, 0.54 mmol) and platinum oxide (30 mg) in ethyl acetate was shaken in a hydrogen atmosphere for

2.5 h. The reaction mixture was worked up in the same manner as described above. Purification of the crude product by column chromatography on silica gel ($CHCl_3$) afforded (20R,22R)-20-*hydroxy*-3β-*tetrahydropyranyloxy*-25-*homo*-5α-*cholano*-25,22-*lactone* (**18**) (less polar; 52 mg, 19.8%) as colourless plates, m.p. 222—224 °C ($CHCl_3$—acetone), $\nu_{max.}$($CHCl_3$) 3 580 and 1 765 cm^{-1}; δ 0.82 (6 H, s, 10- and 13-Me), 1.21 (3 H, s, 20-Me), 3.2—4.2 (3 H, m, 3-H and OCH_2CH_2), 4.52 (1 H, t, *J* 8 Hz, 22-H), and 4.79 (1 H, br s, $W_{\frac{1}{2}}$ 7 Hz, acetal-H); *m/z* 488 (M^+) (Found: C, 73.05; H, 10.05. $C_{30}H_{48}O_5 \cdot 0.25H_2O$ requires C, 73.05; H, 9.9%), and (20R,22R)-22-*hydroxy*-3β-*tetrahydropyranyloxy*-25-*homo*-5α-*cholano*-25,20-*lactone* (**17**) (more polar, 210 mg, 80.1%) as colourless needles, m.p. 211—212 °C (ethyl acetate), $\nu_{max.}$($CHCl_3$) 3 420 and 1 720 cm^{-1}; δ 0.74 (3 H, s, 13-Me), 0.81 (3 H, s, 10-Me), 1.38 (3 H, s, 20-Me), 3.2—4.2 (4 H, m, 3-, 22-H, and OCH_2CH_2), and 4.69 (1 H, br s, $W_{\frac{1}{2}}$ 7 Hz, acetal-H) (Found: C, 73.75; H, 10.1. $C_{30}H_{48}O_5$ requires C, 73.75; H, 9.9%). The hydrogenation of compound (**15**) (80 mg, 0.17 mmol) using platinum oxide (10 mg) in benzene (5 ml) for 2 h was performed as described above. The products were chromatographed on silica gel ($CHCl_3$) to afford the products (**16**) and (**18**) in 17.4 and 80.6% yields, respectively.

(*c*) *Sodium borohydride reduction of compound* (**15**). To a stirred solution of compound (**15**) (100 mg, 0.21 mmol) in methanol (2 ml) and CH_2Cl_2 (2 ml) was added sodium borohydride (8 mg, 0.21 mmol) at 0 °C. Stirring was continued for 8 h at room temperature. After quenching with water (0.5 ml), the resulting mixture was extracted by ethyl acetate. The organic layer was washed with aqueous ammonium chloride and dried (Na_2SO_4). Evaporation of the solvent gave the residue which was purified by column chromatography on silica gel ($CHCl_3$) to afford the products (**17**) and (**18**) in 4.9 and 78.3% yields, respectively.

Sodium Borohydride Reduction of (**16**).—Compound (**16**) (20 mg, 0.04 mmol) was reduced with sodium borohydride (2 mg, 0.05 mmol) in methanol (1 ml) and CH_2Cl_2 (1 ml) for 2 h as described above. The products were separated by column chromatography on silica gel ($CHCl_3$) to afford compound (**17**) and (**18**) in 4.9 and 79.6% yields, respectively.

Synthesis of (20R,22R)-5α-*Cholestane*-3β,20,22,25-*tetraol* (**20**).—(*a*) *From* (20R,22R)-22-*hydroxy*-3β-*tetrahydropyranyloxy*-25-*homo*-5α-*cholano*-25,20-*lactone* (**17**). To a stirred solution of the lactone (**17**) (40 mg, 0.08 mmol) in dry tetrahydrofuran (3 ml) was added dropwise 1M-methylmagnesium bromide (0.8 ml) at −78 °C under N_2 and stirring was continued for 0.5 h at −78 °C and then for 0.5 h at room temperature. After addition of water (1 ml), the mixture was extracted with ethyl acetate, washed with aqueous ammonium chloride, dried (Na_2SO_4), and concentrated to give a white solid. The crude product was used for the next reaction without further purification. A small amount of the product was purified by column chromatography on silica gel ($CHCl_3$—MeOH, 99: 1 v/v) to afford (20R,22R)-3β-*tetrahydropyranyloxy*-5α-*cholestane*-20,22,25-*triol* (**19**) as colourless prisms, m.p. 203—205 °C (MeOH–ethyl acetate); $\nu_{max.}$($CHCl_3$) 3 400 cm^{-1}; δ 0.80 (3 H, s, 13-Me), 0.84 (3 H, s, 10-Me), 1.22 (s, 3H, 20-Me), 3.1—4.2 (4 H, m, 3-, 22-H, and OCH_2CH_2), and 4.68 (1 H, br s, $W_{\frac{1}{2}}$ 7 Hz, acetal-H) (Found: C, 73.5; H, 11.0. $C_{32}H_{56}O_5$ requires C, 73.8; H, 10.5%).

A mixture of the crude product (44 mg) and pyridinium toluene-*p*-sulphonate (2 mg, 0.008 mmol) in EtOH (1 ml) and tetrahydrofuran (1 ml) was heated for 2 h at 55 °C. Evaporation of the solvent gave the residue which was purified by column chromatography on silica gel (MeOH–$CHCl_3$, 2:98 v/v) to afford (20R,22R)-5α-*cholestane*-3β,20,22,25-*tetraol* (**20**) (34 mg, 94.3%). This compound was identical with the authentic sample.[14]

(*b*) *From* (20R,22R)-20-*hydroxy*-3β-*tetrahydropyranyloxy*-25-*homo*-5α-*cholano*-25,22-*lactone* (**18**). Methylation of the lactone (**18**) was performed as described above, and the resulting triol ether was subjected to hydrolysis to give the tetraol (**20**) in 86.1% yield.

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