

A new chiral synthesis of bullfrog bile sterol 5 β -ranol

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(24*R*)-27-Nor-5 β -cholestane-3 α ,7 α ,12 α ,24,26-pentol (5 β -ranol) has been synthesised by the Wittig olefinic coupling of a steroidal module and a side-chain module followed by reduction and deprotection. The steroidal module is derived from cholic acid by a one-carbon degradation of the side chain to produce norcholic acid followed by the loss of a second carbon in an iododecarboxylation and then synthesis of the triphenylphosphonium iodide. The side-chain module is derived from (*S*)-(-)-butane-1,2,4-triol by benzylidene protection of the 2,4-diol followed by Swern oxidation to the aldehyde. This general synthetic scheme could be used to produce a range of bile sterols with the (24*R*)-hydroxy moiety which may have significant hepatoprotective activity against liver damage induced by free radicals or reactive metabolites.

Introduction

A bile alcohol, 5 β -ranol is the major bile constituent of the bullfrog *Rana catesbeiana* and has been shown to be (24*R*)-27-nor-5 β -cholestane-3 α ,7 α ,12 α ,24,26-pentol.¹ Another bile alcohol, 5 β -scymnol (Fig. 1), isolated from shark bile and containing the chiral 24*R* alcohol substituent has been identified as (24*R*)-5 β -cholestane-3 α ,7 α ,12 α ,24,26,27-hexol.² 5 β -Scymnol has been recognised as having a role in the treatment of liver dysfunction and skin complaints,³ and is used in the treatment of acne where it is known to reduce oil production in sebaceous skin glands.⁴ *In vivo* testing has shown 5 β -scymnol is hepatoprotective against acetaminophen,⁵ carbon tetrachloride and the mushroom toxin α -amanitin.⁶ *In vitro*, 5 β -scymnol has potent hydroxyl quenching activity where it is able to markedly inhibit deoxyribose degradation in a ferrous-ascorbate Fenton reaction system.⁵ Because of our interest in the (24*R*)-hydroxy sterols derived from bile, we decided to develop a general method for the synthesis of this class of sterol and for 5 β -ranol **14** in particular.

Scheme 1 shows the retrosynthetic strategy envisaged for the preparation of the required sterol. A side-chain degradation of the C₂₃ and C₂₄ from cholic acid would incorporate the required steroidal ring component. The side-chain module for 5 β -ranol **14** incorporating the correct chirality for the alcohol substituent at the C₂₄ position utilises (*S*)-(-)-butane-1,2,4-triol as starting material.

Results and discussion

In Scheme 2 the conversion of cholic acid **1** into triformylcholic acid **2** (85%) is shown. Treatment of **2** with sodium nitrite in trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) gave the nitrile, which after alkaline hydrolysis pro-

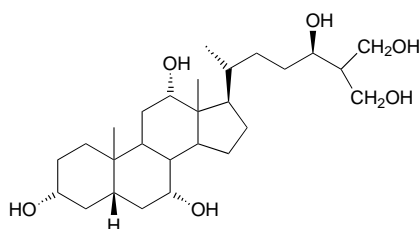
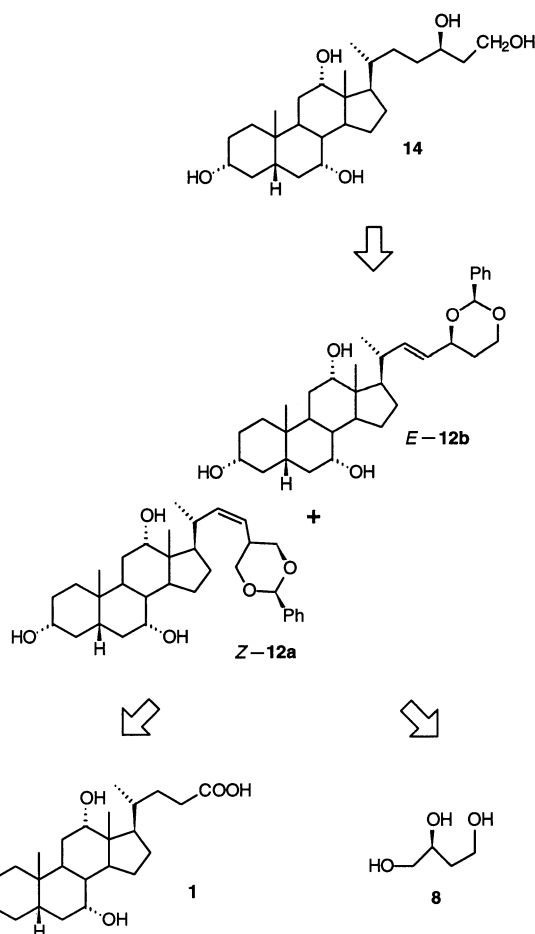
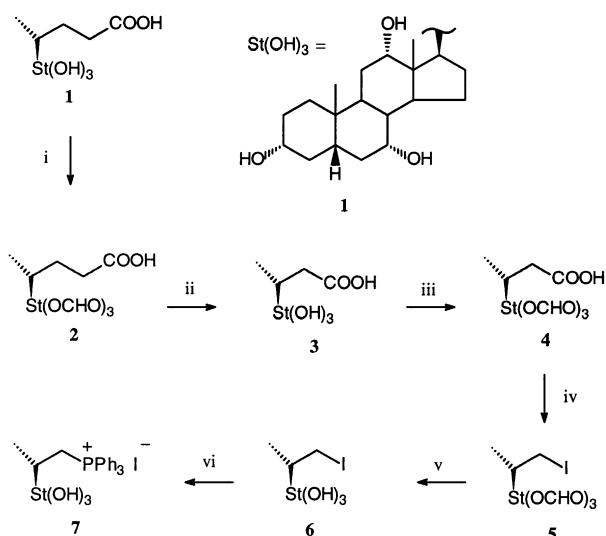


Fig. 1 5 β -Scymnol from shark bile [(24*R*)-5 β -cholestane-3 α ,7 α ,12 α ,24,26,27-hexol]



Scheme 1 General scheme for the preparation of 5 β -ranol

vided norcholic acid **3** (78%).⁷ Treatment of **3** with formic acid in acetic anhydride and perchloric acid provided triformylnorcholic acid **4**.⁸ 3 α ,7 α ,12 α -Triformyloxy-22-iodo-23,24-bisnor-5 β -cholane **5** was prepared from **4** by iododecarboxylation, using a procedure which had previously been successfully employed in the synthesis of 3 α ,7 α ,12 α -triformyloxy-23-iodo-24-nor-5 β -cholane.⁹ The triformate **5** was converted into 3 α ,7 α ,12 α -trihydroxy-22-iodo-23,24-bisnor-5 β -cholane **6** by base-catalysed alcoholysis with methanol and the labile triformyl derivative was easily removed without substantial

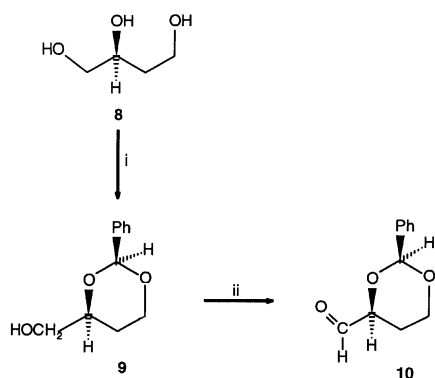


Scheme 2 Reagents and conditions: i, HCO_2H , Ac_2O , HClO_4 (85%); ii, NaNO_2 , TFA, TFAA, KOH (78%); iii, HCO_2H , Ac_2O , HClO_4 (88%); iv, $\text{Pb}(\text{OAc})_4$, I_2 , CCl_4 reflux; (91%); v, NaOMe, MeOH (80%); vi, Ph_3P (5 mol), MeCN, 44 h reflux (68%)

decomposition of the iodide. Preparation of $3\alpha,7\alpha,12\alpha$ -trihydroxy-23,24-bisnor-5 β -cholan-22-yl(triphenyl)phosphonium iodide **7** was carried out by reaction of triphenylphosphine (5 mol equiv.) in acetonitrile under prolonged reflux.¹⁰

Attempts to prepare $3\alpha,7\alpha,12\alpha$ -trihydroxy-22-iodo-23,24-bisnor-5 β -cholane **6** from the triacetate resulted in solvolysis of the iodide during deacetylation. Attempts at reductive deacetylation with a mixture of aluminium chloride and lithium aluminium hydride¹¹ were also unsuccessful.

Scheme 3 shows the synthesis of the side-chain module and



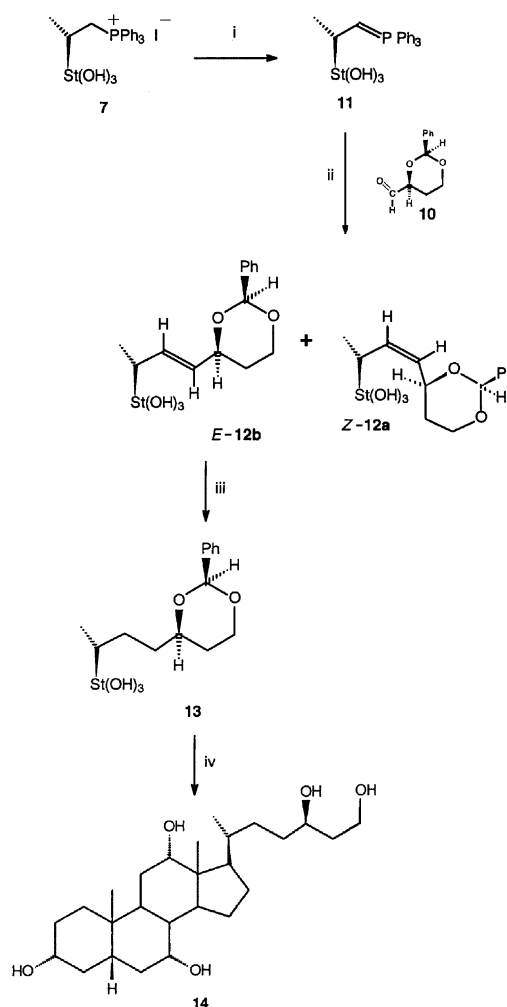
Scheme 3 Reagents and conditions: i, PhCHO , cyclohexane, TSA cat. (72%); ii, -50°C , CH_2Cl_2 , oxalyl chloride, DMSO, Et_3N (50%)

begins with the conversion of (*S*)-(-)-butane-1,2,4-triol **8** into (*2S*-*cis*)-2-phenyl-1,3-dioxane-4-methanol **9** by the general method for chiral aldehydes.¹² Oxidation of alcohol **9** by the Swern procedure¹³ gave (*2S*-*cis*)-2-phenyl-1,3-dioxane-4-carbaldehyde **10** which oligomerises when stored.¹⁴ In refluxing methanol the oligomer was both depolymerised and solubilised prior to its use in the synthesis.

Scheme 4 shows the coupling of the steroidal and side-chain modules by a Wittig reaction using freshly prepared phenyllithium in diethyl ether to give a mixture of *cis*-**12a** and *trans*-**12b** (19%). The olefin mixture of **12a** and **12b** was reduced in the presence of a platinum catalyst to give (*24R*)-24,26-*O*-benzylidene- $3\alpha,7\alpha,12\alpha,24,26$ -pentahydroxy-27-nor-5 β -cholestane **13** (96%). The reduction of the olefin required a second charge of catalyst to initiate reduction and we ascribe this to the presence of sulfur impurities from the Swern oxidation which had poisoned the catalyst. Deprotection of the benzylidene protected diol moiety yielded 5 β -ranol **14** (71%).

Table 1 5 β -ranol **14** side-chain ^{13}C NMR chemical shifts compared with reported values¹

Carbon no.	24 <i>S</i>	24 <i>R</i>	Synthetic ranol 14
20	36.2	36.2	36.3
21	18.1	18.0	18.0
22	32.5	32.4	32.5
23	35.3	35.2	35.2
24	70.5	70.1	70.1
25	40.7	40.7	40.7
26	60.4	60.4	60.4



Scheme 4 Reagents and conditions: i, PhLi -diethyl ether, 0°C , 10 min, room temp., 1 h; ii, **10** in diethyl ether added, 20 h room temp. (19%); iii, PtO_2 , MeOH, 24 h room temp. (96%); iv, TSA cat., MeOH, 24 h, room temp. (71%)

Pure product was recovered only after chromatographic removal of toluene-4-sulfonic acid catalyst which had an R_F value similar to 5 β -ranol **14**.

The ^{13}C NMR data for the synthetic ranol product **14** was compared with the literature values¹ and is summarised in Table 1.

The C_{24} chemical shift differentiates the two isomers. ^{13}C NMR indicated that the 5 β -ranol prepared was the *24R* isomer and from the signal to noise ratio in the region of the (*24S*) isomer at 70.5, it was calculated that the *24S* isomer was present in <5% by weight.

Experimental

^1H NMR spectra were recorded on a Varian Gemini-200 (200 MHz) instrument using deuteriochloroform (or other indicated solvents) as reference or an internal deuterium lock. The

multiplicity of the signal is indicated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, etc. and *J* values are expressed in Hz. ¹³C NMR spectra were recorded on a Varian Gemini-200 (50.28 MHz) instrument using an internal deuterium lock and proton decoupling. The chemical shift data is given in units of δ relative to tetramethylsilane (TMS), where δ (TMS) = 0. When required, COSY, APT, DEPT and spin decoupling were used to assist in NMR peak assignments. High resolution fast atom bombardment (FAB) mass measurements were performed on a JOEL JMS-DX 300 instrument by Mr Stuart Thomson of the Victorian College of Pharmacy, Monash University, Melbourne, Australia using a matrix of 3-nitrobenzyl alcohol. Novel steroidal compounds were characterised by mass spectral analysis. Microanalysis was not used for characterisation since our experience shows that steroids often retain significant traces of solvent, despite long periods of vacuum stripping. Analytical TLC was carried out on pre-coated 0.25 mm thick Merck Kieselgel 60 F₂₅₄ silica plates. Visualisation was by absorption of UV light and/or by spraying with 5% phosphomolybdic acid and 7.5% sulfuric acid in acetic acid followed by thermal development. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Mps are uncorrected. Reagents were purified and dried by standard techniques.¹⁵ THF and diethyl ether were dried from sodium using benzophenone ketyl as indicator. Ether refers to diethyl ether. Light petroleum refers to the fraction boiling in the range 60–80 °C. All reactions were performed under an atmosphere of dry nitrogen unless indicated to the contrary. All reagents were analytical grade and were purchased from regular commercial sources.

3 α ,7 α ,12 α -Triformyloxy-24-nor-5 β -cholan-5 β -oic acid 4

Norchoic acid **3** (5.75 g, 14.6 mmol) was dissolved in 88% formic acid (26 cm³) and 70% perchloric acid (0.25 cm³) and heated at 50–60 °C for 1.5 h. The mixture was cooled to room temperature and acetic anhydride (19 cm³ in total) was added portionwise to it. The exothermic reaction was maintained at 50–60 °C until bubbles (CO) were produced. The reaction mixture was then allowed to stand at 60 °C for a further 15 min, after which it was immediately poured into a well stirred ice-water mixture (250 cm³). Crystals developed on storage of the mixture and after 30 min were filtered off, and washed well with water to give the *title compound 4* which was air-dried to afford a white crystalline solid (6.11 g, 88%); mp 112.5–116.5 °C (as isolated); *R*_F 0.6 (5:95, MeOH–CH₂Cl₂); δ_{H} (200 MHz; CD₃OD) 1.01 (3 H, s, 18-H), 1.10 (3 H, d, *J* 5.0, 21-H), 1.16 (3 H, s, 19-H), 4.85 (1 H, br m, *w*/2 10, 3- β H), 5.22 (1 H, m, *w*/2 10, 7- β H), 5.43 (1 H, m, *w*/2 8, 12- β H), 8.20 (1 H, s, CHO), 8.30 (1 H, s, CHO) and 8.37 (1 H, s, CHO).

3 α ,7 α ,12 α -Triformyloxy-22-iodo-23,24-bisnor-5 β -cholane 5

A dry flask was charged with triformylnorchoic acid **4** (2.30 g, 4.81 mmol) and lead tetraacetate (2.75 g, 6.2 mmol) in dry CCl₄ (100 cm³) and the mixture was stirred under N₂ at reflux while being irradiated with an Atlas 275 W IR lamp. Iodine (1.32 g, 5.2 mmol) dissolved in CCl₄ (70 cm³) was added to the above refluxing mixture and heated at reflux for a further 1.5 h. The reaction mixture was then allowed to cool to room temperature after which the resulting precipitate was filtered off and washed with CCl₄ (70 cm³). The combined filtrate and washings were washed with 10% aqueous sodium thiosulfate, water, saturated aqueous sodium hydrogen carbonate and finally with more water. The solution was then dried (MgSO₄), filtered and concentrated on a rotary evaporator to give the *title compound 5* (2.45 g, 91%); mp 81–84 °C (as isolated); δ_{H} (200 MHz; CDCl₃) 0.77 (3 H, s, 18-Me), 0.91–0.92 (6 H, m, 21-H and 19-H), 3.05–3.2 (2 H, m, 22-CH₂), 4.7 (1 H, br m, *w*/2 20, 3- β H), 5.05 (1 H, m, *w*/2 10, 7- β H), 5.22 (1 H, m, *w*/2 8, 12- β H), 8.0 (1 H, s, CHO), 8.08 (1 H, s, CHO) and 8.18 (1 H, s, CHO)

[Found (FAB) (M⁺ – 3HCOOH), 423.155 29. C₂₂H₃₂I requires 423.154 88].

3 α ,7 α ,12 α -Trihydroxy-22-iodo-23,24-bisnor-5 β -cholane 6

To a solution of sodium (56 mg, 2.4 mmol) in dry methanol (48 cm³) stirred under N₂ was added triformyl iodide **5** (1.10 g, 1.96 mmol) in one portion. The stirred mixture was allowed to react at room temperature for 24 h, after which time saturated aqueous ammonium chloride (25 cm³) was added to it and methanol was removed by rotary evaporation at 30 °C (caution, this procedure causes excessive foaming). The reaction mixture was extracted with dichloromethane (3 \times 50 cm³) and the combined extracts were washed with 20% aqueous sodium chloride (8 cm³), dried (Na₂SO₄) and evaporated to yield the crude product. Purification by column chromatography using a stepwise elution of 1, 2, 3 and 5% methanol in dichloromethane gave fractions which were monitored by TLC. *Title compound 6* was isolated as a white crystalline solid (744 mg, 80%); mp softens 108 °C and melts 116.5 °C; *R*_F 0.47 (MeOH–CH₂Cl₂, 10:90); δ_{H} (200 MHz; CDCl₃) 0.69 (3 H, s, 18-H), 0.85 (3 H, s, 19-H), 1.10 (3 H, d, *J* 6.0, 21-H), 3.13 (1 H, dd *J* 9.6 and 5.7, 22-CH₂), 3.33 (1 H, dd, *J* 9.6 and 2.4, 22-CH₂), 3.43 (1 H, br m, *w*/2 13, 3- β H), 3.84 (1 H, m, *w*/2 8, 7- β H) and 3.95 (1 H, m, *w*/2 8, 12- β H) [Found (FAB) (M⁺ – 3H₂O), 423.155 67. C₂₂H₃₂I requires 423.154 88].

3 α ,7 α ,12 α -Trihydroxy-23,24-bisnor-5 β -cholan-22-yl(triphenyl)phosphonium iodide 7

To a solution of the iodo compound **6** (3.00 g, 6.29 mmol) in anhydrous acetonitrile (65 cm³) was added triphenylphosphine (8.25 g, 31.5 mmol) and the resulting mixture was refluxed under N₂ for 44 h; it was then evaporated to give a pale yellow solid. The crude reaction product was broken up, washed with dry ether (3 \times 25 cm³) and filtered. Purification of the crude product by flash chromatography using a stepwise elution of 1, 2.5, 5, 10 and 15% methanol in dichloromethane gave fractions which were monitored by TLC. *Title compound 7* was isolated as a pale yellow crystalline solid (3.15 g, 68%); mp 176–178 °C; *R*_F 0.40 (MeOH–CH₂Cl₂, 12.5:87.5); δ_{H} (200 MHz; CDCl₃) 0.49 (3 H, s, 18-H), 0.80 (3 H, s, 19-H), 1.08 (3 H, d, *J* 6.6, 21-H), 2.3–2.5 (1 H, m, 20-CH), 2.9–3.2 (1 H, t, 22-CH₂), 3.32 (1 H, br m, *w*/2 22, 3- β H), 3.76 (1 H, m, *w*/2 11, 7- β H), 3.79 (1 H, m, *w*/2 10, 12- β H), 3.95–4.12 (1 H, m, 22-CH₂) and 7.6–7.9 (15 H, m, ArH) [Found (FAB) (M⁺ – I), 611.367 53. C₄₀H₅₂O₃P requires 611.365 42].

(2*S*-*cis*)-2-Phenyl-1,3-dioxane-4-methanol 9

To a solution of (*S*)-butane-(–)-1,2,4-triol **8** (1.06 g, 10 mmol) in cyclohexane (100 cm³) was added benzaldehyde¹⁶ (1.07 g, 10 mmol) and toluene-4-sulfonic acid hydrate (20 mg, 0.11 mmol). The resulting mixture was heated under Dean–Stark conditions for 7 h after which it was diluted with ether (30 cm³). The ether extract was immediately washed with 1 M aqueous sodium carbonate (10 cm³) and water (5 cm³), dried (Na₂SO₄) and evaporated to give the crude product as an oil, purification of which by flash chromatography (ethyl acetate–hexane, 1:2) furnished *title compound 9* as a colourless oil (1.40 g, 72%); *R*_F 0.40 (MeOH–CH₂Cl₂, 2:98); δ_{H} (200 MHz; CDCl₃)¹³ 1.37 (1 H, d, *J* 13.3, CH_{eq}), 1.83 (1 H, ddt, 13.3, 12.3 and 5.25, CH_{ax}), 2.9 (1 H, s, OH), 3.6 (2 H, m, CH₂OH), 3.8–4.0 (2 H, m, OCH_{ax}, OCH_{eq}), 4.24 (1 H, ddd, *J* 11.4, 5.2 and 1.3, OCH_{eq}), 5.48 (1 H, s, ArCH), 7.25–7.4 (3 H, m, ArH) and 7.4–7.5 (2 H, m, ArH).

(2*S*-*cis*)-2-Phenyl-1,3-dioxane-4-carbaldehyde 10

A solution of oxalyl chloride (0.91 g, 7.17 mmol) in dichloromethane (10 cm³) was stirred and cooled to –50 °C after which DMSO (1.01 g, 12.9 mmol) was added to it, the temperature being kept constant. The complex was allowed to form over 20 min after which time compound **9** (1.01 g, 5.23 mmol) in dry dichloromethane (12 cm³) was added to it over 8 min at –50 °C.

Stirring was continued for a further 20 min after which time triethylamine (3.27 g, 32.3 mmol) was added over 5 min to the mixture which was then stirred and allowed to warm to room temperature during 1 h. The mixture was poured into water (20 cm³) and the dichloromethane layer was separated and washed with 20% aqueous sodium chloride (2 × 10 cm³), dried (MgSO₄) and evaporated to give an oil. Purification of this by flash chromatography, using a stepwise elution of 15, 20, 30 and 100% dichloromethane in light petroleum afforded from column fractions the CH₂Cl₂-light petroleum, 3:7 eluted with the *title compound* **10**¹³ initially as an oil before oligomerisation occurred (502 mg, 50%); δ_H(200 MHz; CDCl₃) 1.35–2.2 (2 H, m), 3.6–4.6 (3 H, m), 5.3–5.7 (1 H, m) and 9.7 (0.5 H, s, CHO), partially oligomerised.

(24R)-24,26-O-Benzylidene-3α,7α,12α,24,26-pentahydroxy-27-nor-5β-cholest-22(Z)-ene 12a and 22(E)-ene 12b

A solution of triphenylphosphonium iodide **7** (719 mg, 0.97 mmol) in anhydrous ether (35 cm³) was stirred under N₂ and cooled to 4 °C after which 1.37 M phenyllithium (5.1 cm³, 7 mmol) in dry ether was added to it and the temperature kept constant for 10 min. Stirring was continued for a further 1 h at room temperature during which time the mixture turned a deep orange colour, indicating formation of phosphorane. In a second flask a solution of the carbaldehyde **11** (215 mg, 1.12 mmol) in dry ether (5 cm³) was prepared and stirred under N₂. The orange phosphorane solution was pressure siphoned with N₂ into the aldehyde **11** solution and a thick white slurry resulted with the orange colour fading rapidly. The mixture was stirred for a further 20 h after which time it was diluted with dichloromethane (100 cm³) and worked up by washing with water (2 × 15 cm³). The organic extract was dried (Na₂SO₄) and evaporated to yield the crude product, purification of which by flash chromatography using a stepwise elution of 1, 2, 3, 3.5, 4 and 5% methanol in dichloromethane afforded from column fractions 21–27 (3.5% methanol) the *E*-olefin **12b** (56.8 mg, 11%). Fraction 30 was further chromatographed on a silica gel plate to give *E*-olefin **12b** (2.6 mg); R_F 0.63 (MeOH–CH₂Cl₂, 10:90) and *Z*-olefin **12a** (5.2 mg); R_F 0.57 (MeOH–CH₂Cl₂, 10:90). *Title compounds* **12a** and **12b** from fractions 28–36 were obtained as glassy solids (67.1 mg, 8%).

Data for *Z*-olefin **12a**: δ_H(200 MHz; CDCl₃) 0.7 (3 H, s, 18-H), 0.88 (3 H, s, 19-H), 1.04 (3 H, d, J 6.6, 21-H), 3.40 (1 H, br m, w/2 22, 3-βH), 3.77–4.14 (3 H, m, 7-βH, 12-βH, OCH_{ax}), 4.2–4.37 (1 H, m, OCH_{eq}), 4.58–4.77 (1 H, m, OCH=CH=), 5.34 (1 H, d, J 4, 22-CH=CH), 5.37 (1 H, s, 23-CH=CH) and 7.26–7.6 (5 H, m, ArH) [Found (FAB) (M⁺ – ArCO) 419.318 15. C₂₆H₄₃O₄ requires 419.316 13].

Data for *E*-olefin: **12b** 0.69 (3 H, s, 18-H), 0.87 (3 H, s, 19-H), 1.08 (3 H, d, J 6.6, 21-H), 3.40 (1 H, br m, w/2 22, 3-βH), 3.85 (1 H, m, w/2 8, 7-βH), 3.90–4.05 (2 H, m, 12-βH, OCH_{ax}), 4.2–4.35 (2 H, m, OCH_{eq}, OCH=CH=), 5.46 (1 H, dd, J 15.5 and 5.7, 22-CH=CH), 5.52 (1 H, s, ArCH), 5.58 (1 H, dd, J 15.5 and 7.7, 23-CH=CH), 7.25–7.53 (5 H, m, ArH) [Found (FAB) (M⁺ – ArCO), 419.317 05. C₂₆H₄₃O₄ requires 419.316 13].

(24R)-24,26-O-Benzylidene-27-nor-5β-cholestane-3α,7α,12α,24,26-pentol 13

A mixture of platinum oxide catalyst (45 mg) in methanol (10 cm³) was flushed and stirred under an atmosphere of hydrogen for 20 min. The *E*-**12b** and *Z*-**12a** olefin mixture (55.6 mg, 0.106 mmol) in methanol (2 cm³) was then added to the catalyst mixture and stirred for 24 h under an atmosphere of hydrogen. A further charge of platinum oxide (39 mg) was added to the mixture and stirring continued under hydrogen for 24 h after which the reaction mixture was filtered through Celite and evaporated to afford *title compound* **13** as a glassy solid (53.5 mg, 96%); R_F 0.63 (MeOH–CH₂Cl₂, 10:90); δ_H(200 MHz;

CDCl₃) 0.66 (3 H, s, 18-H), 0.85 (3 H, s, 19-H), 0.97 (3 H, d, J 5.6, 21-H), 3.40 (1 H, br m, w/2 22, 3-βH), 3.5–4.05 (4 H, m, 7-βH, OCH_{ax}, 12-βH, OCH=CH=), 4.06–4.32 (1 H, m, OCH_{eq}), 5.48 (1 H, s, ArCH) and 7.27–7.54 (5 H, m, ArH) [Found (FAB) (M⁺ + 1), 527.375 80. C₃₃H₅₁O₅ requires 527.373 66].

(24R)-27-Nor-5β-cholestane-3α,7α,12α,24,26-pentol 14

A mixture of reduced benzylidene **13** (48.2 mg, 0.09 mmol) and toluene-4-sulfonic acid hydrate (4.7 mg, 0.009 mmol) in methanol (9 cm³) was stirred at room temperature for 24 h. The reaction was quenched by addition of potassium carbonate (9 mg, 0.065 mmol) and evaporated to afford a crude solid. The crude material was redissolved in a little methanol to which silica (2 g) was then added; methanol was again removed by evaporation. The silica was added to the top of a silica column and the reaction product purified by flash chromatography using a stepwise elution of 5, 10, 15 and 20% methanol in dichloromethane. *Title compound* **14** was eluted in 15% methanol and was contaminated with some toluene-4-sulfonic acid which was washed out by dissolving in ethyl acetate-butanol (1:1) (5 cm³) and washing with potassium carbonate (3 × 0.5 cm³) and water (5 cm³). The organic phase was dried (MgSO₄) and evaporated to give pure ranol **14** (28.5 mg, 71%) as a crystalline solid; R_F 0.35 (15:85, MeOH–CH₂Cl₂); δ_H(200 MHz; [2H₅]pyridine) 0.85 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 1.27 (3 H, d, J 5.4, 21-H), 3.77 (1 H, br m, w/2 18, 3-βH), 4.12 (1 H, m, w/2 11, 7-βH), 4.25 (2 H, t, 26-CH₂OH) and 4.29 (1 H, m, w/2 12, 12-βH)

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