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Synthesis of a transmembrane ionophore based on a C_2-symmetric polyhydroxysteroid derivative

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Dedicated to the memory of Professor Guido Sodano

Abstract—The synthesis of the C_2-symmetric bis-(20*S*)-5α-23,24-bisnorchol-16-en-3β,6α,7β-triol-22-terephthaloate (**1**), active as Na^+-transporting transmembrane channel, has been achieved in 16 steps (10% overall yield) starting from the commercially available androst-5-en-3β-ol-17-one (**3**). The straightforward stereospecific functionalization of the side-chain, via the 'ene' reaction, and the successful regioselective terephthaloylation of the C-22 hydroxy group, illustrate the efficiency of the synthetic strategy.

1. Introduction

Transmembrane ion channels play a critical role in transporting ions and molecules through the phospholipid bilayer and the understanding of their function and mechanism is one of the more intensely studied areas of modern biology.[1] The past decade has seen numerous designs for artificial ion channels[2] and most of the synthetic efforts made, for the development of the non-peptidic channels, have been concentrated on bile acids[3] and cholesterol-based scaffolds.[4]

The advantage of using a cholestan all-*trans* ring junction arrangement, instead of the folded AB-*cis* cholic acids framework, resides in the strongly stabilizing contacts between the zig-zag hydrocarbons' conformation of the lipid membrane and the planar α-face of the tetracyclic steroid.[5] Moreover, the study of the mechanism of interaction between lipid bilayer and cholestane derivatives is necessary for understanding the mode of action of the cell damaging natural steroidal oligoglycosides[6] and polyhydroxysteroids.[7]

With the aim of shedding light on these open questions and in an attempt to obtain a prototype of a new class of sterol-based transmembrane channel, we embarked in the synthesis of the C_2-symmetric bis-(20*S*)-5α-23,24-bisnorchol-16-en-3β,6α,7β-triol-22 terephthaloate (**1**) and of the simpler (*Z*)-pregn-17(20)-en-3β,6α,7β-triol (**2**),[8] the latter being useful for model studies (Fig. 1).

Our choice to dimerize a (20*S*)-5α-23,24-bisnorchol-16-en-3β,6α,7β,22-tetrol derivative with the terephthaloate linker was based on the consideration that the incorporation of the

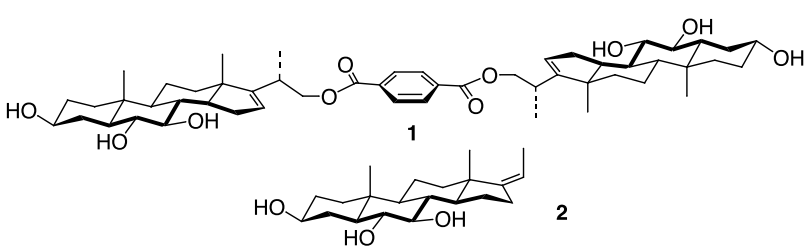

Figure 1. Target molecules.

Keywords: polyhydroxysteroids; ionophores; ene reaction; amphiphiles.
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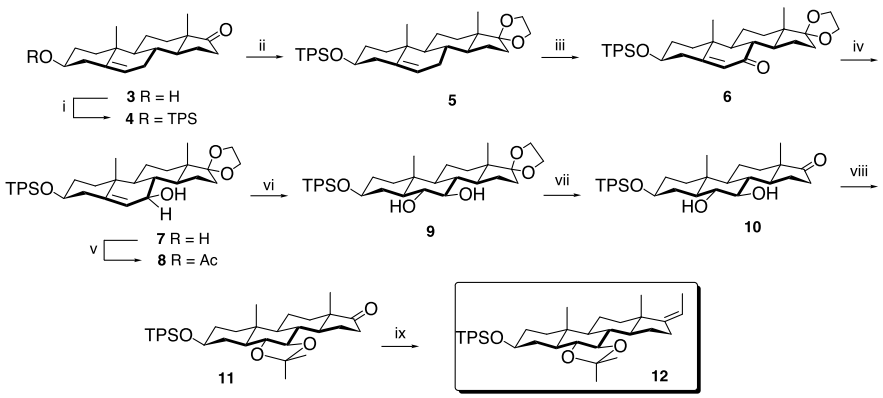


Scheme 1. (i) DBU, TPS-Cl, CH_2Cl_2, rt, 2 h, 95%; (ii) ethylene glycol, $(EtO)_3CH$, *p*-TsOH, CH_2Cl_2, rt, 18 h, 100%; (iii) CrO_3-dimethylpyrazole, CH_2Cl_2, −20°C to >0°C, 4.5 h, 81%; (iv) $CeCl_3$, $NaBH_4$, EtOH/THF (2:1), rt, 1 h, 81%; (v) Py, Ac_2O, DMAP, CH_2Cl_2, rt, 4 h, 98%; (vi) $BH_3{\cdot}SMe_2$, THF, 0°C to rt, 40 min, then NaOH, H_2O_2, 0°C, 2 h 72%; (vii) $Pd(CH_3CN)_2Cl_2$, acetone/H_2O (95:5), 40°C, 4 h, 84%; (viii) PPTS, 2,2-dimethoxypropane, *p*-TsOH, rt, 18 h, 93%; (ix) $EtPPh_3Br$, *t*-BuOK, THF, reflux, 3 h, 92%.

relatively flexible molecule **1** in the lipid bilayer would result in an adoption of an extended conformation having a length of ~42 Å, nearly matching the thickness of the phosphatidylcholine membrane.[9]

2. Results and discussion

The preparation of target compounds **1** and **2** was realized through a stereochemically controlled synthetic sequence, leading to the common key intermediate (*Z*)-3β-[(*tert*-butyldiphenylsilyl)oxy]-6α,7β-[(methylethyldene)-bis-oxy]-pregn-17(20)-ene (**12**, Scheme 1).

Elaboration of **12** started from the commercially available androst-5-en-3β-ol-17-one (**3**). This was protected at C-3[10] and C-17[11] with known procedures, to give silylated acetal **5** in 95% overall yield. Allylic oxidation at C-7[12] afforded the α,β-unsaturated steroid **6**, which was reduced, under Luche conditions,[13] to give the 7β-alcohol **7** as a single detectable isomer. An almost quantitative acetylation[14] and a highly stereoselective hydroboration–oxidation reaction[15] gave the 6α,7β-diol **9** in 46% overall yield from **5**.

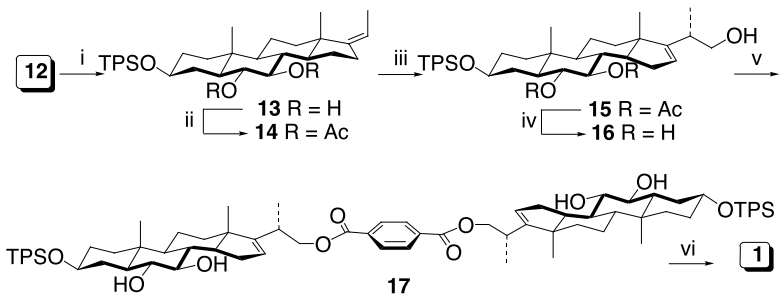
Attachment of the ethylidene side-chain was achieved in a three step sequence involving a Pd(II)-mediated[16] restoration of the C-17 carbonyl, a 6α,7β-diol acetonide protection[17] and a highly stereoselective Wittig olefination.[18] The key intermediate **12** was thus obtained in a satisfying 72% overall yield from **9**.

With **12** in our hands, we were ready for the preparation of target compound **1**. Transformation of the (*Z*)-17(20)-ethylidene moiety to the (20*S*)-22-hydroxy side-chain was achieved through a boron trifluoride catalyzed stereospecific 'ene' reaction (Scheme 2).[19]

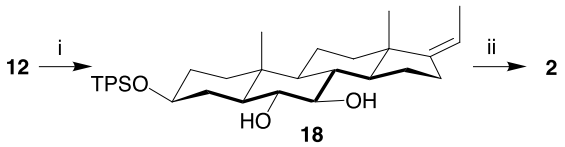
Unfortunately this reaction proved to be incompatible with the C-6,7 acetonide[20] but gave good results protecting the B-ring hydroxyl groups as acetates. KOH-induced acetyl hydrolysis gave the 3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorchol-16-en-6α,7β,22-triol (**16**). This was subjected to a rt DMAP activated regioisomeric bis-acylation, in the presence of terephthaloyl chloride, giving, to our delight, the bis-adduct **17** in 70% yield. HF induced[21] desilylation of terephthaloate **17** provided the expected bis-(20*S*)-5α-23,24-bisnorchol-16-en-3β,6α,7β-triol-22-terephthaloate (**1**).

(*Z*)-Pregn-17(20)-en-3β,6α,7β-triol (**2**) was obtained from **12** in 70% overall yield, through the straightforward two-step deprotection route shown in Scheme 3.

Preliminary results[22] show that, while **2** behaves as a very poor ionophore, **1** self-assemble in a trimeric form inside the phosphatidylcholine membrane, leading to a functional ionophore with a Na^+-transporting activity comparable to



Scheme 2. (i) $Pd(CH_3CN)_2Cl_2$, Acetone/H_2O (95:5), rt, 3 h, 92%; (ii) Ac_2O, Py, DMAP, 48 h, 96%; (iii) paraformaldehyde, $BF_3{\cdot}Et_2O$, 0°C, 1.5 h, 79%; (iv) KOH, MeOH, rt, 12 h, 86%; (v) terephthaloyl chloride, DMAP, CH_2Cl_2, rt, 48 h, 70%; (vi) HF, Py, rt, 80%.



Scheme 3. (i) TBAF, THF, rt, 12 h, 90%; (ii) $Pd(CH_3CN)_2Cl_2$, acetone/H_2O (95:5), 40°C, 4 h, 78%.

that of natural occurring antifungal polyene macrolide amphotericin B.[23]

3. Conclusions

In conclusion, we have reported a synthetic route illustrating the advantage of using the straightforward chemistry of polyhydroxysteroids for the construction of a new class of steroid scaffold, active as ion transporters.

4. Experimental

4.1. General methods

All reactions were carried out under a dry argon atmosphere using freshly distilled and dried solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from $LiAlH_4$. Toluene, methylene chloride and diethyl ether were distilled from calcium hydride. Glassware was flame-dried (0.05 Torr) prior to use. When necessary, compounds were dried in vacuo over P_2O_5 or by azeotropic removal of water with toluene under reduced pressure. Starting materials and reagents purchased from commercial suppliers were generally used without purification. Reaction temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light or spraying with $H_2SO_4/Ce(SO_4)_2$ solution and drying.

Flash cromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) pure materials. The NMR spectra were recorded at rt on a Bruker DRX 400 spectrometer (400 MHz) or a Bruker AMX (250 MHz). Chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ=7.26, $^{13}CDCl_3$: δ=77.0). Electron impact (EIMS) spectra (EI, 70 eV) were performed on a VG TRIO 2000 mass spectrometer. Fast ion bombardment, (FABMS) were obtained at 4 kV (Cs^+ ion) on a Fisons VG Prospec mass spectrometer. Mps were measured on a digital Electrothermal 9100. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

4.2. Procedures described in Scheme 1

4.2.1. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-androst-5-en-17-one (4). To a solution of 5-androsten-3β-ol-17-one (0.500 g, 1.97 mmol) CH_2Cl_2 (5.0 ml) were added 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 0.460 ml, 3.0 mmol) and *tert*-butylchlorodiphenylsilane (TPS-Cl, 0.762 g, 2.70 mmol). The reaction mixture was stirred for 2 h, at rt, quenched with a saturated solution of NH_4Cl (2.5 ml) and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was flash chromatographed (silica gel, 10–15% ethyl acetate in petroleum ether) to give **4** (0.857 g, 95%) as a white solid.

Compound **4**. Mp 119–121°C. R_f: 0.37 (10% diethyl ether in petroleum ether). $[\alpha]_D^{20}=-8.2$ (c=2.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.86 (3H, s, CH_3-18), 1.02 (3H, s, CH_3-19), 1.08 (9H, s, –C(CH_3)$_3$), 3.55 (1H, m, H-3), 5.16 (1H, m, H-6), 7.40 (6H, m, Ar-*H*), 7.68 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.9, 19.0, 19.3, 20.1, 21.7, 26.5 (×2), 26.9 (×3), 30.6, 31.3, 31.7, 35.7, 36.5, 37.0, 42.4, 47.4, 50.0, 51.6, 72.9, 120.3, 127.4 (×3), 127.5, 129.4 (×2), 134.6, 134.8 (×2), 135.6 (×2), 142.3, 221.2. EIMS, *m/z* (%): 526 M^+. Calcd for $C_{35}H_{46}O_2Si$: C, 79.79; H, 8.80. Found: C, 79.69; H, 8.76.

4.2.2. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-17,17-(ethylenedioxy)-androst-5-ene (5). To a solution of **4** (10.0 g, 190 mmol) in CH_2Cl_2 (30.0 ml) were added ethylene glycol (16.6 ml, 190 mmol), triethyl orthoformate (15.8 ml, 95.0 mmol) and *p*-TsOH·H_2O (0.543 g, 28.0 mmol). The reaction mixture was stirred overnight, at rt, quenched by addition of triethylamine (3.0 ml) then water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was flash chromatographed (silica gel, 10% diethyl ether in petroleum ether) to give **5** (11.0 g, quant.) as a white solid.

Compound **5**. Mp 120–122°C. R_f: 0.73 (10% diethyl ether in petroleum ether). $[\alpha]_D^{20}=-57.8$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.89 (3H, s, CH_3-18), 1.05 (3H, s, CH_3-19), 1.12 (9H, s, –C(CH_3)$_3$), 3.62 (1H, m, H-3), 3.80–3.90 (4H, m, –OCH_2CH_2O–), 5.19 (1H, m, H-6), 7.40 (6H, m, Ar-*H*), 7.70 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.2, 18.4, 19.5, 21.8, 26.5 (×5), 29.6, 30.2, 30.9, 31.2, 33.2, 35.5, 36.2, 41.5, 44.7, 48.9, 49.6, 63.5, 64.1, 72.2, 118.5, 120.0, 126.5 (×5), 128.5, 133.8, 134.8 (×5), 140.2. EIMS, *m/z* (%): 570 M^+. Calcd for $C_{37}H_{50}O_3Si$: C, 77.84; H, 8.83. Found: C, 77.90; H, 8.77.

4.2.3. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-17,17-(ethylenedioxy)-androst-5-en-7-one (6). CrO_3 (175.2 g, 1.75 mol) was finely ground and dried for 2 h in vacuo over P_2O_5. In an argon purged flask to a suspension of CrO_3 in CH_2Cl_2 (1.0 L) at −20°C was added dimethylpyrazole (168.42 g, 1.75 mol). The dark-red solution was stirred at −20°C for 0.5 h. Compound **5** (50.0 g, 0.088 mol) was added, the reaction mixture was stirred at −20°C for 4 h, quenched by addition of a solution of 5 M NaOH (0.5 L) and then stirred at 0°C for 0.5 h. Et_2O (300 ml) was added and the mixture was filtered through a path of silica gel (0.063–0.200 mm) and $CaSO_4$ (10% in weight), dried (Na_2SO_4) and concentrated in vacuo. The residue was flash chromatographed (silica gel, 20–40% diethyl ether in petroleum ether) to give **6** (41.5 g, 81%) as a white solid.

Compound **6**. Mp 159–160°C. R_f: 0.28 (10% diethyl ether in petroleum ether). $[\alpha]_D^{20}=-113.7$ (c=1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.84 (3H, s, CH_3-18), 1.07 (9H, s, –C(CH_3)$_3$), 1.16 (3H, s, CH_3-19), 3.63 (1H, m, H-3), 3.80–3.90 (4H, m, –OCH_2CH_2O–), 5.46 (1H, bs, H-6), 7.42 (6H, m, Ar-*H*),

7.65 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 14.3, 17.3, 19.0, 20.6, 25.0, 26.9 (×3), 29.6, 31.4, 34.1, 36.2, 38.2, 42.1, 44.3, 45.2, 46.1, 49.7, 64.4, 65.1, 71.8, 118.6, 125.6, 127.5 (×4), 129.6, 129.7, 134.0, 134.2, 135.6 (×4), 166.0, 201.6. EIMS, *m/z* (%): 584 M^+. Calcd for $C_{37}H_{48}O_4Si$: C, 75, 98; H, 8, 27. Found: C, 75.89; H, 8.30.

4.2.4. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-17,17-(ethylenedioxy)-androst-5-en-7β-ol (7). To a solution of **6** (40.0 g, 0.068 mol) in EtOH/THF (1.2 L, 2:1) at 0°C were added $CeCl_3$ (12.7 g, 0.037 mol) and $NaBH_4$ (5.17 g, 0.137 mol). The reaction mixture was stirred for 1 h at rt, quenched by addition of water, concentrated in vacuo to remove the excess of EtOH and THF and then extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was flash chromatographed (silica gel, 20% diethyl ether in petroleum ether) to give **7** (32.1 g, 81%) as a white solid.

Compound **7**. Mp 188–189°C. R_f: 0.13 (10% diethyl ether in petroleum ether). $[\alpha]_D^{20}=-43.9$ (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.84 (3H, s, CH_3-18), 1.02 (3H, s, CH_3-19), 1.05 (9H, s, –C(CH_3)$_3$), 3.55 (1H, m, H-3), 3.78 (1H, bd, J=8.5 Hz, H-7), 3.80–3.90 (4H, m, –OCH_2CH_2O–), 5.03 (1H, bs, H-6), 7.41 (6H, m, Ar-*H*), 7.66 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 14.2, 19.1 (×2), 20.3, 24.9, 26.9 (×3), 30.1, 31.7, 34.2, 36.5, 36.8, 41.0, 41.8, 46.0, 47.9, 49.8, 64.5, 65.1, 72.7, 73.4, 118.9, 125.1, 127.5 (×4), 129.5 (×2), 134.6 (×2), 135.7 (×4), 143.8. EIMS, *m/z* (%): 586 M^+. Calcd for $C_{37}H_{50}O_4Si$: C, 75.72; H, 8.59. Found: C, 75.67; H, 8.50.

4.2.5. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-17,17-(ethylenedioxy)-7β-acetoxy-androst-5-ene (8). To a solution of **7** (0.141 g, 0.240 mmol) in CH_2Cl_2 and pyridine (1.0 ml, 9:1) were added Ac_2O (0.091 ml, 0.96 mmol) and catalytic amounts of DMAP. The reaction mixture was stirred for 4 h, at rt, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 5% ethyl acetate in petroleum ether) to give **8** (0.149 g, 98%) as a white solid.

Compound **8**. Mp 124–126°C. R_f: 0.37 (15% ethyl acetate in petroleum ether). $[\alpha]_D^{20}=-2.6$ (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.85 (3H, s, CH_3-18), 1.07 (9H, s, –C(CH_3)$_3$), 1.07 (3H, s, CH_3-19), 2.00 (3H, s, COCH_3), 3.54 (1H, m, H-3), 3.80–390 (4H, m, –OCH_2CH_2O–), 4.97 (1H, bd, J=8.5 Hz, H-7), 5.02 (1H, bs, H-6), 7.39 (6H, m, Ar-*H*), 7.66 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 14.1, 19.0 (×2), 20.3, 21.5, 23.7, 26.9 (×3), 29.9, 31.6, 34.0, 36.4, 36.6 (×2), 41.8, 45.9, 47.7, 49.3, 64.4, 65.1, 72.5, 75.7, 118.6, 120.8, 127.4 (×4), 129.5 (×2), 134.6 (×2), 135.6 (×4), 145.6, 170.9. EIMS, *m/z* (%): 628 M^+. Calcd for $C_{39}H_{52}O_5Si$: C, 74.48; H, 8.33. Found: C, 74.56; H, 8.46.

4.2.6. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-17,17-(ethylenedioxy)-5α-androstan-6α,7β-diol (9). To a solution of **8** (5.38 g, 8.55 mmol) in THF (32.0 ml) was added $BH_3{\cdot}SMe_2$ (21.4 ml, 2 M in THF, 42.8 mmol) at 0°C. After 10 min the solution was warmed to rt and stirred for a further 30 h. The solution was then cooled at 0°C, and absolute ethanol (170 ml), a solution of 3 M NaOH (59.0 ml) and H_2O_2 (60 ml, 30% in water) were added. The mixture was stirred for 2 h concentrated in vacuo to remove the excess of THF, and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was flash chromatographed (silica gel, 20% ethyl acetate in petroleum ether) to give **9** (3.71 g, 72%) as a white solid.

Compound **9**. Mp 177–178°C. R_f: 0.56 (40% ethyl acetate in petroleum ether). $[\alpha]_D^{20}=-2.8$ (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.84 (3H, s, CH_3-18), 1.05 (9H, s, –C(CH_3)$_3$), 1.05 (3H, s, CH_3-19), 3.05 (1H, dd, J=10.0, 8.6 Hz, H-6 or H-7), 3.17 (1H, dd, J=11.1, 8.6 Hz, H-7 or H-6), 3.55 (1H, m, H-3), 3.80–3.90 (4H, m, –OCH_2CH_2O–), 7.38 (6H, m, Ar-*H*), 7.67 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.5, 14.4, 19.0, 20.5, 25.3, 26.9 (×3), 30.1, 31.2, 32.1, 34.1, 35.6, 37.2, 40.9, 46.4, 47.5, 49.6, 51.6, 64.4, 65.1, 72.4, 74.7, 80.7, 118.6, 127.4 (×4), 129.4 (×2), 134.5, 134.7, 135.7 (×4). EIMS, *m/z* (%): 604 M^+. Calcd for $C_{37}H_{52}O_5Si$: C, 73.47; H, 8.66. Found: C, 73.55; H, 8.72.

4.2.7. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-5α-androstan-6α,7β-diol-17-one (10). To a solution of **9** (0.100 g, 0.165 mmol) in acetone and water (3.0 ml, 95:5) was added $Pd(MeCN)_2Cl_2$ (0.009 g, 0.03 mmol). The reaction mixture was heated at 40°C, stirred for 4 h, at rt, and then concentrated in vacuo. The residue was flash chromatographed (silica gel, 40% diethyl ether in petroleum ether) to give **10** (0.078 g, 84%) as a white solid.

Compound **10**. Mp 160–161°C. R_f: 0.18 (40% ethyl acetate in petroleum ether). $[\alpha]_D^{20}=+55.0$ (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.86 (3H, s, CH_3-18), 1.05 (3H, s, CH_3-19), 1.05 (9H, s, –C(CH_3)$_3$), 3.12 (1H, m, H-6 or H-7), 3.19 (1H, m, H-6 or H-7), 3.54 (1H, m, H-3), 7.40 (6H, m, Ar-*H*), 7.66 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.6, 14.0, 19.1, 20.5, 24.7, 26.9 (×3), 31.2, 31.3, 32.1, 35.8, 35.9, 37.1, 40.2, 47.7, 48.2, 51.0, 51.9, 72.3, 74.9, 80.0, 127.4 (×2), 127.5 (×2), 129.5 (×2), 134.5, 134.6, 135.7 (×4), 221.3. FABMS *m/z* (%): 583 $[M+Na]^+$. Calcd for $C_{35}H_{48}O_4Si$: C, 74.95; H, 8.63. Found: C, 74.99; H, 8.69.

4.2.8. (*Z*)-3β-[(*tert*-Butyldiphenylsilyl)oxy]-6α,7β-[(methylethyldene)-bis-oxy]-5α-androstan-17-one (11). To a solution of **10** (1.98 g, 3.54 mmol) in 2,2-dimethoxypropane (10.0 ml) was added pyridinium *p*-toluenesulfonate (PPTS, 0.089 g 0.35 mmol). The reaction mixture was stirred overnight at rt, quenched by addition of triethylamine and concentrated in vacuo. The residue was flash chromatographed (silica gel, 15% diethyl ether in petroleum ether) to give **11** (1.98 g, 93%) as white solid.

Compound **11**. Mp 104–105°C. R_f: 0.30 (silica gel, 10% ethyl acetate in diethyl ether). $[\alpha]_D^{20}=+46.3$ (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.87 (3H, s, CH_3-18), 0.90 (3H, s, CH_3-19), 1.03 (9H, s, –C(CH_3)$_3$), 1.36 (3H, s, –CCH_3), 1.40 (3H, s, –CCH_3), 3.01 (1H, dd, J=10.0, 8.6 Hz, H-6 or H-7), 3.22 (1H, dd, J=11.1, 8.6 Hz, H-6 or H-7), 3.59 (1H, m, H-3) 7.38 (6H, m, Ar-*H*), 7.67 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.8, 14.7, 19.1, 20.3, 23.6, 26.9 (×3), 27.1 (×2), 31.2, 31.4, 32.6, 35.7, 37.0, 37.2, 38.6, 45.9, 47.5, 50.1, 52.6, 71.9, 78.3, 84.8, 109.1, 127.4 (×4), 129.4 (×2), 134.3, 134.8, 135.7 (×4), 220.8. EIMS, *m/z* (%): 600 M^+. Calcd for $C_{38}H_{52}O_4Si$: C, 75.95; H, 8.72. Found: C, 75.87; H, 8.64.

4.3. Procedures described in Scheme 2

4.3.1. (*Z*)-3β-[(*tert*-Butyldiphenylsilyl)oxy]-6α,7β-[(methylethyldene)-bis-oxy]-5α-pregn-17(20)-ene (12). To a solution of $EtPPh_3Br$ (8.43 g, 22.7 mmol) in THF (36.5 ml) was added *t*BuOK, (2.33 g, 20.8 mmol). The suspension was stirred for 10 min, then a solution of **11** (3.98 g, 6.63 mmol) in THF (10.0 ml) was added. The reaction mixture was heated at reflux for 3 h, cooled to rt, quenched by addition of a saturated solution of NH_4Cl, concentrated in vacuo to remove the excess of THF, and extracted with diethyl ether. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 10–30% diethyl ether in petroleum ether) to give **12** (3.76 g, 92%) as a white solid.

Compound **12**. Mp 72–74°C. R_f: 0.90 (10% ethyl acetate in petroleum ether). $[\alpha]_D^{20}=+24.1$ ($c=1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.88 (6H, s, C*H*$_3$-18 and C*H*$_3$-19), 1.04 (9H, s, $-C(CH_3)_3$), 1.35 (3H, s, $-CCH_3$), 1.39 (3H, s, $-CCH_3$), 1.62 (3H, bd, $J=7.0$ Hz, C*H*$_3$-21) 2.97 (1H, dd, $J=10.0$, 8.6 Hz, H-6 or H-7), 3.21 (1H, dd, $J=11.1$, 8.6 Hz, H-6 or H-7), 3.60 (1H, m, H-3), 5.12 (1H, bq, $J=7.0$ Hz, H-20), 7.38 (6H, m, Ar-*H*), 7.66 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.1, 14.7, 16.9, 19.1, 21.2, 26.2, 26.9 (×3), 27.1 (×2), 31.3, 31.6, 32.7, 37.0 (×2), 37.2, 38.5, 40.5, 44.2, 45.9, 52.6, 54.8, 72.1, 78.4, 85.1, 108.7, 113.6, 127.4 (×4), 129.4 (×2), 133.6 (×2), 135.8 (×4), 149.5. EIMS, *m/z* (%): 612 M^+. Calcd for $C_{40}H_{56}O_3Si$: C, 78.38; H, 9.21. Found: C, 78.42; H, 9.13.

4.3.2. (*Z*)-3β-[(*tert*-Butyldiphenylsilyl)oxy]-5α-pregn-17(20)-en-6α,7β-diol (13). To a solution of **12** (0.100 g, 0.163 mmol) in acetone and water (3.0 ml, 95:5) was added $Pd(MeCN)_2Cl_2$ (0.002 g, 0.008 mmol). The reaction mixture was heated at 40°C, stirred for 3 h and then concentrated in vacuo. The residue was flash chromatographed (silica gel, 10% diethyl ether in petroleum ether) to give **13** (0.086 g, 92%) as a white solid.

Compound **13**. Mp 98–99°C. R_f: 0.40 (20% ethyl acetate in petroleum ether). $[\alpha]_D^{20}=+28.0$ ($c=1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.84 (3H, s, C*H*$_3$-18), 0.87 (3H, s, C*H*$_3$-19), 1.05 (9H, s, $-C(CH_3)_3$), 1.62 (3H, bd, $J=7.0$ Hz, C*H*$_3$-21), 3.04 (1H, dd, $J=10.0$, 8.6 Hz, H-6 or H-7), 3.19 (1H, dd, $J=11.1$, 8.6 Hz, H-6 or H-7), 3.56 (1H, m, H-3), 5.13 (1H, bq, $J=7.0$ Hz, H-20), 7.40 (6H, m, Ar-*H*), 7.66 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.1, 13.5, 16.9, 19.0, 21.4, 26.9 (×3), 27.2, 31.2, 32.0, 32.2, 35.6, 36.8, 37.1, 40.5, 44.9, 47.6, 52.0, 55.6, 72.5, 74.8, 80.2, 113.7, 127.4 (×4), 129.4 (×2) 134.5, 134.8, 135.7 (×4), 149.1. EIMS, *m/z* (%): 572 M^+. Calcd for $C_{37}H_{52}O_3Si$: C, 77.57; H, 9.15. Found: C, 77.65; H, 9.19.

4.3.3. (*Z*)-6α,7β-(Diacetoxy)-3β-[(*tert*-butyldiphenylsilyl)-oxy]-5α-pregn-17(20)-ene (14). To a solution of **13** (4.00 g, 6.99 mmol) in CH_2Cl_2 (20.0 ml) were added pyridine (5.5 ml, 68 mmol), Ac_2O (5.16 ml, 54.7 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at rt for 48 h and concentrated in vacuo. The residue was flash chromatographed (silica gel, 10% diethyl ether in petroleum ether) to give **14** (4.39 g, 96%) as a white solid.

Compound **14**. Mp 88–89°C. R_f: 0.76 (20% ethyl acetate in petroleum ether). $[\alpha]_D^{20}=+24.2$ ($c=1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.86 (3H, s, C*H*$_3$-18), 0.94 (3H, s, C*H*$_3$-19), 1.04 (9H, s, $-C(CH_3)_3$), 1.62 (3H, bd, $J=7.1$ Hz, C*H*$_3$-21), 1.87 (3H, s, $COCH_3$), 1.95 (3H, s, $COCH_3$), 3.53 (1H, m, H-3), 4.68 (1H, dd, $J=10.0$, 8.6 Hz, H-6 or H-7), 4.78 (1H, dd, $J=11.0$, 8.6 Hz, H-6 or H-7), 5.12 (1H, bq, $J=7.1$ Hz, H-20), 7.37 (6H, m, Ar-*H*), 7.64 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.2, 13.4, 16.9, 19.1, 20.7, 21.5 (×2), 25.4, 27.0 (×3), 31.1, 31.8, 32.2, 35.8, 36.6, 37.0, 38.7, 45.0, 46.0, 51.9, 54.7, 72.1, 74.6, 77.8, 113.9, 127.5 (×4), 129.5 (×2), 134.5, 134.6, 135.7 (×4), 148.6, 170.7, 171.0. EIMS, *m/z* (%): 656 M^+. Calcd for $C_{41}H_{56}O_5Si$: C, 74.96; H, 8.59. Found: C, 74.86; H, 8.50.

4.3.4. 6α,7β-(Diacetoxy)-3β-[(*tert*-butyldiphenylsilyl)-oxy]-5α-23,24-bisnorchol-16-en-22-ol (15). To solution of **14** (0.263 g, 0.400 mmol) in CH_2Cl_2 (24.0 ml) were added paraformaldehyde (0.058 g, 1.95 mmol) and $BF_3{\cdot}OEt_2$ (5 μl, 0.039 mmol). The reaction mixture was stirred for 1.5 h, at rt, quenched with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo and the residue was flash chromatographed (silica gel, 20% ethyl acetate in petroleum ether) to give **15** (0.217 g, 79%) as a white solid.

Compound **15**. Mp 102–104°C. R_f: 0.58 (40% diethyl ether in petroleum ether). $[\alpha]_D^{20}=+7.3$ ($c=1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.76 (3H, s, C*H*$_3$-18), 0.95 (3H, s, C*H*$_3$-19), 0.98 (3H, d, $J=6.9$ Hz, C*H*$_3$-21), 1.03 (9H, s, $-C(CH_3)_3$), 1.87 (3H, s, $COCH_3$), 1.96 (3H, s, $COCH_3$), 3.54 (3H, m, H-3, H-22 and H′-22), 4.67 (1H, dd, $J=10.0$, 8.6 Hz, H-6 or H-7), 4.79 (1H, dd, $J=11.1$, 8.6 Hz, H-6 or H-7), 5.34 (1H, bs, H-16), 7.37 (6H, m, Ar-*H*), 7.63 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.3, 16.0, 18.2, 19.0, 20.6, 20.9, 21.4, 26.9 (×3), 31.1, 32.0, 32.1, 34.2, 34.9, 36.0, 36.8, 37.9, 46.4, 47.8, 52.0, 54.8, 66.5, 72.0, 74.2, 77.6, 122.8, 127.4 (×4), 129.5 (×2), 134.5 (×2), 135.7 (×4), 156.2, 170.6, 170.7. EIMS, *m/z* (%): 686 M^+. Calcd for $C_{42}H_{58}O_6Si$: C, 73.43; H, 8.51. Found: C, 73.37; H, 8.48.

4.3.5. 3β-[(*tert*-Butyldiphenylsilyl)oxy]-5α-23,24-bisnorchol-16-en-6α,7β,22-triol (16). Compound **15** (0.226 g, 0.330 mmol) was dissolved in 5% KOH methanol solution (3.0 ml). The reaction mixture was stirred overnight, at rt, quenched by addition of chloroform, filtered through a pad of Celite® and concentrated in vacuo. The residue was flash chromatographed (silica gel, 0–3% methanol in chloroform) to give **16** (0.171 g, 86%) as a white solid.

Compound **16**. Mp 184–186°C. R_f: 0.47 (50% ethyl acetate in petroleum ether). $[\alpha]_D^{20}=+11.3$ ($c=1.0$, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.78 (3H, s, C*H*$_3$-18), 0.88 (3H, s, C*H*$_3$-19), 1.02 (3H, d, $J=6.8$ Hz, C*H*$_3$-21), 1.08 (9H, s, $-C(CH_3)_3$), 3.03 (1H, dd, $J=10.0$, 8.6 Hz, H-6 or H-7), 3.20 (1H, dd, $J=11.0$, 8.6 Hz, H-6 or H-7), 3.57 (3H, m, H-3, H-22 and H′-22), 5.41 (1H, bs, H-16), 7.39 (6H, m, Ar-*H*), 7.67 (4H, m, Ar-*H*); ^{13}C NMR ($CDCl_3$) δ: 13.5, 16.1, 18.2, 19.0, 20.9, 26.9 (×3), 31.2, 32.2, 33.8, 34.5, 34.8, 35.7, 36.9, 39.6, 47.5, 47.9, 52.1, 56.0, 66.4, 72.5, 74.5, 80.0, 123.3, 127.3 (×4), 129.3 (×2), 134.4, 134.7, 135.6 (×4), 156.2. FABMS *m/z* (%): 625 $[M+Na]^+$. Calcd for $C_{38}H_{54}O_4Si$: C, 75.70; H, 9.03. Found: C, 75.80; H, 9.11.

4.3.6. Bis-(20*S*)-3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-23,24-bisnorchol-16-en-6α,7β-diol-22-terephthaloate (17). To a solution of **16** (0.515 g, 0.855 mmol) in CH_2Cl_2 (3.0 ml) were added DMAP (0.313 g, 0.257 mmol) and terephthaloyl chloride (0.087 g, 0.427 mmol) in CH_2Cl_2 (1.0 ml). The reaction mixture was stirred for 48 h, at rt, quenched by the addition of water and extracted with chloroform. The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was flash chromatographed (silica gel, 1–2% methanol in chloroform) to give **17** (0.401 g, 70%) as a white solid.

Compound **17**. Mp 177–178°C. R_f: 0.53 (40% ethyl acetate in petroleum ether). $[\alpha]_D^{20}$=+20.8 (c=1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.77 (6H, s, CH_3-18), 0.87 (6H, s, CH_3-19), 1.05 (18H, s, –C(CH_3)$_3$), 1.12 (6H, d, J=6.7 Hz, CH_3-21), 3.04 (2H, dd, J=10.0, 8.6 Hz, H-6 or H-7), 3.21 (2H, dd, J=11.1, 8.6 Hz, H-6 or H-7), 3.55 (2H, m, H-3), 4.20 (2H, dd, J=10.2, 8.3 Hz, H-22), 4.39 (2H, dd, J=10.2, 6.4 Hz, H′-22), 5.49 (2H, bs, H-16), 7.38 (12H, m, Ar-*H*), 7.69 (8H, m, Ar-*H*), 8.05 (4H, s, –CO–C$_6H_4$–CO–); ^{13}C NMR ($CDCl_3$) δ: 13.6, 16.2, 18.8, 19.1, 20.9, 26.9 (×3), 31.2, 31.4, 32.1, 33.9, 34.5, 35.9, 37.0, 39.7, 47.8, 47.9, 52.1, 55.7, 69.2, 72.5, 74.7, 80.2, 123.5, 127.4 (×4), 129.3 (×4), 134.4, 134.7, 135.7 (×5), 155.4, 165.7. FABMS m/z (%): 1357 $[M+Na]^+$. Calcd for $C_{84}H_{110}O_{10}Si_2$: C, 75.52; H, 8.30. Found: C, 75.62; H, 8.25.

4.3.7. Bis-(20*S*)-5α-23,24-bisnorchol-16-en-3β,6α,7β-triol-22-terephthaloate (1). To a solution of **17** (0.049 g, 0.037 mmol) in pyridine (2.0 ml) a solution of hydrogen fluoride-pyridine (0.275 ml) was added. The reaction mixture was stirred overnight at rt and concentrated with a flux of nitrogen. The residue was flash chromatographed (silica gel, 5% methanol in chloroform) to give **1** (0.025 g, 80%) as a white solid.

Compound **1**. Mp 106–107°C. R_f: 0.50 (40% methanol in dichloromethane). $[\alpha]_D^{20}$=+48.2 (c=1.0, $CHCl_3$). ^{1}H NMR (400 MHz, CD_3OD) δ: 0.84 (6H, s, CH_3-18), 0.92 (6H, s, CH_3-19), 1.18 (6H, d, J=6.9 Hz, CH_3-21), 2.15 (2H, m, H-4$_{eq}$), 2.22 (2H, m, H-15), 2.31 (2H, m, H′-15), 2.62 (2H, m, H-20), 3.04 (2H, dd, J=10.0, 8.9 Hz, H-6 or H-7), 3.16 (2H, dd, J=11.1, 8.9 Hz, H-6 or H-7), 3.51 (2H, m, H-3), 4.24 (2H, dd, J=10.6, 7.6 Hz, H-22), 4.45 (2H, dd, J=10.6, 6.5 Hz, H′-22), 5.57 (2H, bs, H-16), 8.10 (4H, s, Ar-*H*); ^{13}C NMR (100 MHz, CD_3OD) δ: 13.9, 16.7, 19.3, 22.4, 31.8, 32.8, 33.2, 35.0, 36.0, 36.9, 38.4, 41.2, ~49.0 (×2, overlapping with ^{13}CD$_3$OD), 53.9, 57.8, 70.4, 71.8, 75.9, 81.0, 125.0, 130.6 (×2), 135.5, 156.9, 167.0. FABMS m/z (%): 881$[M+Na]^+$. Calcd for $C_{52}H_{74}O_{10}$: C, 72.70; H, 8.68. Found: C, 72.67; H, 8.66.

4.4. Procedures described in Scheme 3

4.4.1. (*Z*)-6α,7β-[(Methylethyldene)-bis-oxy]-5α-pregn-17(20)-en-3β-ol (18). To a solution of **12** (0.269 g, 0.439 mmol) in THF (1.0 ml) Bu_4NF (1.31 ml, 1 M in THF, 1.31 mmol). The reaction mixture was stirred overnight, quenched by addition of water, concentrated in vacuo to remove the excess of THF and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated in vacuo and the residue was flash chromatographed (silica gel, 10% ethyl acetate in petroleum ether) to give **18** (0.149 g, 90%) as a white solid.

Compound **18**. Mp 106–107°C. R_f: 0.30 (30% ethyl acetate in petroleum ether). $[\alpha]_D^{20}$=+56.7 (c=1.0, in $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.87 (3H, s, CH_3-18), 0.88 (3H, s, CH_3-19), 1.35 (3H, s, –CCH_3), 1.37 (3H, s, –CCH_3), 1.62 (3H, d, J=7.2 Hz, CH_3-21) 3.02 (1H, dd, J=10.0, 8.6 Hz, H-6 or H-7), 3.20 (1H, dd, J=11.1, 8.6 Hz, H-6 or H-7), 3.59 (1H, m, H-3), 5.11 (1H, bq, J=7.0 Hz, H-20); ^{13}C NMR ($CDCl_3$) δ: 13.1, 14.6, 16.8, 21.3, 26.2, 27.1 (×2), 30.7, 31.6, 32.7, 37.0 (×2), 37.2, 38.5, 44.1, 46.0, 52.7, 54.8, 70.4, 78.3, 85.1, 108.8, 113.6, 149.4. EIMS, m/z (%): 374 M^+. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.94; H, 10.20.

4.4.2. (*Z*)-5α-Pregn-17(20)-en-3β,6α,7β-triol (2). To a solution of **18** (0.193 g, 0.516 mmol) in acetone and water (3.0 ml, 95:5) was added $Pd(MeCN)_2Cl_2$ (0.004 g, 0.015 mmol). The reaction mixture was stirred overnight and then concentrated in vacuo. The residue was flash chromatographed (silica gel, 2% methanol in chloroform) to give **2** (0.135 g, 78%) as a white solid.

Compound **2**. Mp 177–178°C. R_f: 0.50 (14% methanol in dichloromethane). $[\alpha]_D^{20}$=+66.2 (c=1.0, in $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.87 (3H, s, CH_3-18), 0.90 (3H, s, CH_3-19), 1.62 (3H, d, J=7.2 Hz, CH_3-21) 3.14 (1H, dd, J=10.0, 8.9 Hz, H-6 or H-7), 3.27 (1H, dd, J=11.1, 8.9 Hz, H-6 or H-7), 3.57 (1H, m, H-3), 5.16 (1H, bq, J=7.0 Hz, H-20); ^{13}C NMR ($CDCl_3$) δ: 13.1, 13.6, 17.1, 21.6, 27.4, 30.6, 32.0, 32.5, 35.7, 36.7, 37.2, 40.5, 44.9, 47.9, 52.1, 55.8, 70.9, 74.7, 79.9, 113.7, 149.2. FABMS m/z (%): 357 $[M+Na]^+$. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.38; H, 10.23.

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