Synthesis of (25*R*)-5α-Cholestane-3*β*,6*β*,15α,16*β*,26-pentol, a Cytostatic Starfish Steroid†

Irene Izzo, Francesco De Riccardis,* and Guido Sodano*

Dipartimento di Chimica, University of Salerno, Via S. Allende, 84081 Baronissi (SA), Italy

Received February 13, 1998

The synthesis of (25*R*)-5α-cholestane-3*β*,6*β*,15α,16*β*,26-pentol (**1a**), a marine cytostatic steroid, has been achieved in 13 steps (7.8% overall yield) starting from commercially available diosgenin (**2**). A key step in the synthesis was the dimethyldioxirane oxidation of the enolsilane **16** to introduce the 15α-hydroxy group in the D ring.

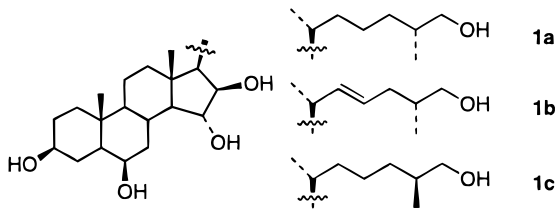
Introduction

Polyhydroxysteroids are naturally occurring steroids present in a wide variety of marine organisms.[1] They have been isolated from soft corals, gorgonians, nudibranchs, sponges, and ophiuroids, but starfishes appear to be the richest source of new polyhydroxysteroids.

Although polyhydroxysteroids do not contain stuctural features commonly associated with cytotoxicity, such as alkylation sites, Michael's acceptors, intercalators, or redox-active quinones, some of them show interesting antiproliferative activity in several tumor cell lines.[2]

Few hypotheses have been made for the activity of steroidal cytotoxins:[3,4] they may interfere with the eucariotic cell membrane,[5] they may be enzyme inhibitors,[6] they may disrupt the cascade of signal transduction.[7] Despite the interesting bioactivities showed by polyhydroxysteroids, few syntheses of these compounds have been reported.[8]

Recently[2a] an investigation of an Antarctic starfish belonging to the Echinasteridae family has led to the isolation of several polyhydroxysteroids and steroidal oligoglycosides, some of them displaying cytotoxic or cytostatic activity. In particular three of them (**1a**−**c**), having a 5α-cholestane-3*β*,6*β*,15α,16*β*,26-pentol framework, showed a cytostatic effect upon human bronchopulmunary non-small-cell lung carcinoma cells (NSCLC-N6), by blocking the cell cycle in phase G_1 (period prior the DNA synthesis).



The fact that insufficient amounts of these compounds were available for further pharmacological studies, coupled with the need to evaluate the mechanism of action, prompted us to undertake the synthesis of one of them: (25*R*)-5α-cholestane-3*β*,6*β*,15α,16*β*,26-pentol (**1a**).

We envisaged diosgenin (**2**) as an useful starting material both for its commercial availability and for the presence of functional groups in position suitable for conversion to **1a**.

Results and Discussion

The synthesis began with the protection of diosgenin (**2**) to give the benzyl ether **3** in 90% yield (eq 1). Treatment of compound **3** with $BH_3{\cdot}SMe_2$, followed by oxidation with alkaline hydrogen peroxide,[9] afforded a mixture of two diasteromeric alcohols (**4** and **5**) in good overall yield (82%) and with a predominance of the trans-fused 6α-alcohol **4** (OH-6α (**4**)/OH-6*β* (**5**), 10.7/1).

The two diastereomers were separated by flash chromatography on silica gel, and the unambiguous assignment of the stereochemistry of the A/B ring junction was determined by comparison of their CH_3-19 ^{1}H and ^{13}C NMR resonances (**4**, trans-A/B ring junction, ^{1}H NMR *δ* 0.79 ppm, ^{13}C NMR *δ* 13.3 ppm; **5**, cis-A/B ring junction, ^{1}H NMR *δ* 1.15 ppm, ^{13}C NMR *δ* 26.0 ppm).[10]

* Authors to whom correspondence should be addressed. Tel.: +39-89-965230. Fax: +39-89-965296. E-mail: guiso@vaxsa.csied.unisa.it.

† Dedicated to the memory of Professor Luigi Minale, deceased May 11, 1997.

(1) (a) Minale, L.; Riccio, R.; Zollo, F. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Spinger-Verlag: New York, 1993; Vol. 62, pp 75−308. (b) D'Auria, M. V.; Minale, L.; Riccio, R. *Chem. Rev.* **1993**, *93*, 1839. (c) Minale, L.; Riccio, R.; Zollo, F. In *Studies in Natural Products Chemistry. Structure and Chemistry (Part C)*; Atta Ur-Rahman, Ed.; Elsevier Science B. V.: Amsterdam, 1995; Vol. 15, pp 43−110.

(2) (a) Iorizzi, M.; De Marino, S.; Minale, L.; Zollo, F.; Le Bert, V.; Roussakis, C. *Tetrahedron* **1996**, *52*, 10997. (b) Andersson, L.; Bohlin, L.; Iorizzi, M.; Riccio, R.; Minale, L.; Moreno-Lopez, W. *Toxicon* **1989**, *27*, 179. (c) Higuchi, R.; Noguchi, Y.; Komori, T.; Sasaki, T. *Liebigs Ann. Chem.* **1988**, 1185. (d) Ganesan, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 611.

(3) (a) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006. (b) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *J. Org. Chem.* **1994**, *59*, 6164.

(4) Mimaki, Y.; Kuroda, M.. Kameyama, A.; Sashida, Y.; Hirano, T.; Oka, K.; Maekawa, R.; Wada, T.; Sugita, K.; Beutler, J. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 633.

(5) Ganesan, A.; Heathcock, C. H. *Chemtracts: Org. Chem.* **1988**, *1*, 311.

(6) Pan, Y.; Merriman, R. L.; Tanzer, R. L.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 967.

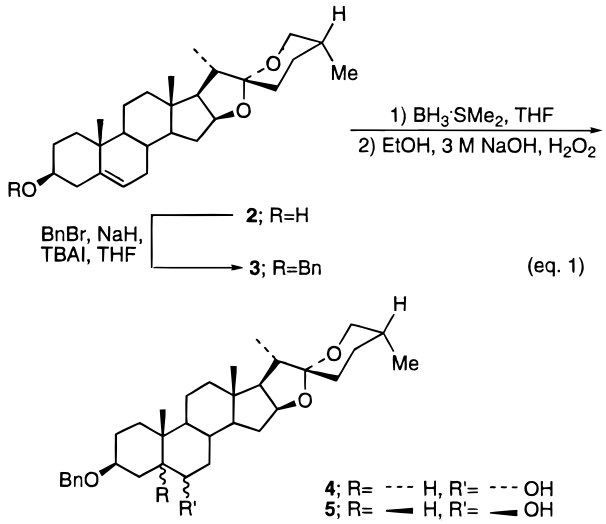
(7) Marx, J. *Science* **1995**, *270*, 232.

(8) (a) Izzo, I.; De Riccardis, F.; Massa, A.; Sodano G. *Tetrahedron Lett.* **1996**, *37*, 4775. (b) Mitome, H.; Miyaoka, H.; Nakano, M.; Yamada, Y. *Tetrahedron Lett.* **1995**, *36*, 8231. (c) Harney, D. W.; Macrides T. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1353.

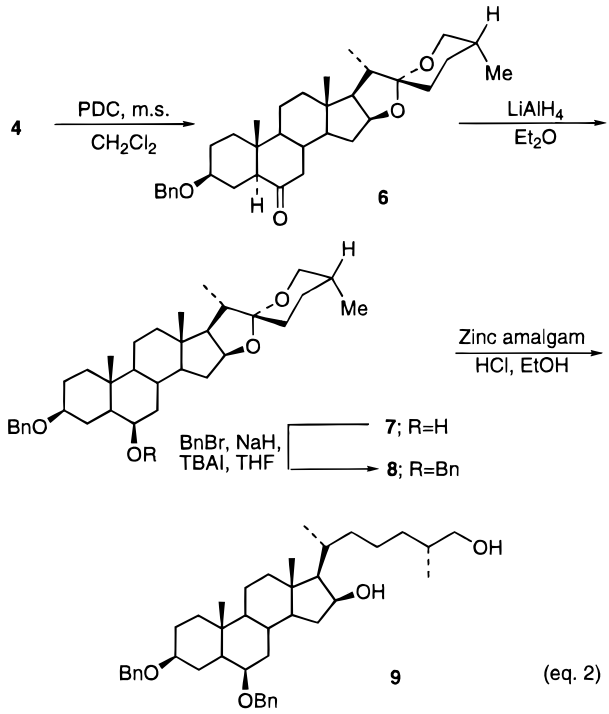
(9) (a) Tavares, R.; Randoux, T.; Braekman, J.-C.; Daloze, D. *Tetrahedron* **1993**, *49*, 5079. (b) Danishefsky, S. J.; Masters, J. J.; Young, W. B., Link, J. T.; Snyder, L. B.; Magee T. V.; Jung D. K.; Isaacs R. C. A.; Bornmann W. G.; Alaimo C. A.; Coburn C. A., Di Grandi M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

(10) Dolle, F.; Hetru, C.; Luu, B. *Tetrahedron* **1991**, *47*, 7059.

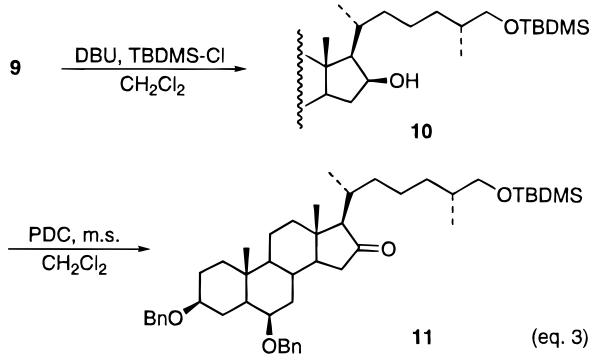
S0022-3263(98)00266-7 CCC: $15.00
Published on Web 06/05/1998



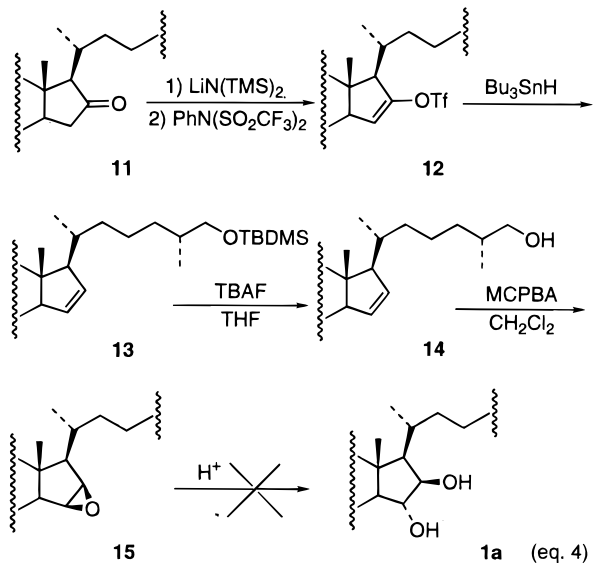
Inversion of the configuration at C-6 of **4** with a two-step procedure (oxidation[11] to ketone **6** and subsequent highly diasteroselective reduction with $LiAlH_4$, eq 2)[8a] furnished alcohol **7** in 95% overall yield. Compound **7** was first protected as benzyl ether (**8**, 75% yield) and then subjected to Clemmensen reduction following Seo's procedure[12] to afford (25*R*)-3*β*,6*β*-bis(benzyloxy)-5α-cholestane-16*β*,26-diol (**9**, 52%).



Chemoselective silylation of diol **9** with *tert*-butyldimethylsilyl chloride (TBDMSCl) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)[13] produced the monoprotected derivative **10** (eq 3). The secondary alcohol at C-16 was then easily oxidated with pyridinium dicromate (PDC) to afford ketone **11** in 78% yield (two steps).



Since the target molecule has a 1,2-*trans*-diol in the D ring, we considered that this moiety could be introduced by opening of a 15,16-epoxide (eq 4). Thus, kinetic enolization of **11** with lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$) and quenching of the enolate with *N*-phenyltrifluoromethanesulfonimide[14] ($PhN(SO_2CF_3)_2$) gave the stable enoltriflate **12**. Deoxygenation of the latter with tributyltin hydride (Bu_3SnH) and tetrakis(triphenylphosphine)palladium(0)[15] afforded (25*R*)-26-[(*tert*-butyldimethylsilyl)oxy]-3*β*,6*β*-bis(benzyloxy)-5α-cholest-15-ene (**13**) in 47% yield (two steps). Desilylation at C-26 with tetra-*n*-butylammonium fluoride (TBAF) and subsequent epoxidation with *m*-chloroperbenzoic acid (MCPBA) furnished compound **15** (31%, two steps). The

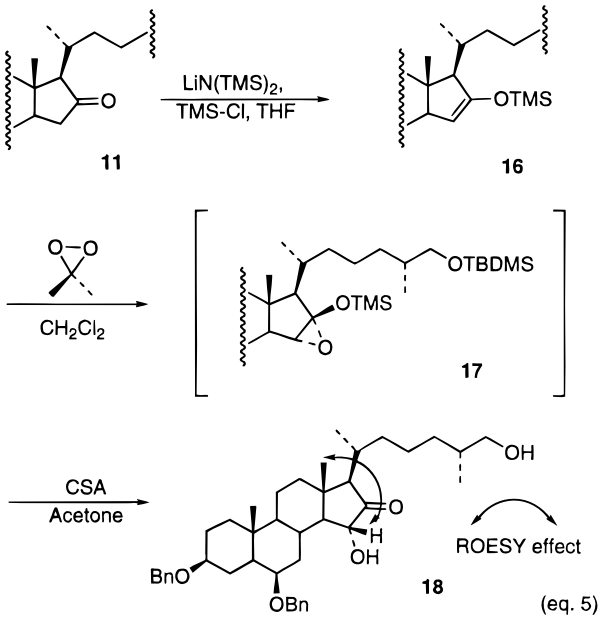


oxirane stereochemistry was indicated by the CH_3-18 1,3-syn deshielding effect compared to that reported for cholesterol (δ_{H-18} cholesterol, 0.68 ppm; δ_{H-18} **15**, 0.92 ppm)[16] and supported by a ROESY[17] experiment which showed dipolar coupling between the signals at δ_H 3.06 (H-15) and δ_H 3.20 (H-16) with the resonance at δ_H 1.05 (H-14α). Unfortunately, attempts to open the oxirane ring in acidic conditions resulted in the formation of an uncharacterized mixture of compounds.

We then decided to hydroxylate the ketone **11**. Attempts to obtain the α-hydroxy ketone by treatment of the kinetic enolate of **11** with oxodiperoxymolybdenum-

(11) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561.
(12) Seo, S.; Yoshimura, Y.; Satoh, T.; Uomori, A.; Takeda, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 411.
(13) Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 475.
(14) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
(15) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.
(16) *Dictionary of Steroids*; Hill, R. A., Kirk, D. N., Makin, H. L. J., Murphy, G. M., Eds.; Chapman and Hall: London, 1991; p 169.
(17) Bax, A.; Davis, D. G. *J. Magn. Reson.* **1985**, *63*, 207.

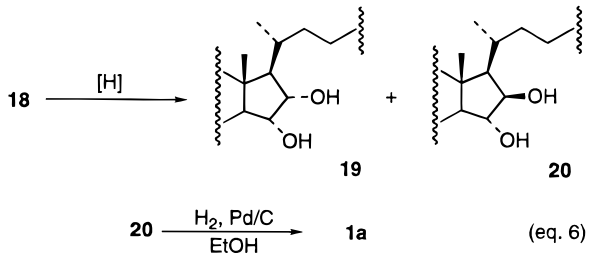
(pyridine)(hexamethylphosphoric triamide) (MoOPH)[18] were also unsuccessful since the unreacted ketone was always recovered. However highly stereoselective hydroxylation at C-15 was accomplished by a three-step sequence involving the preparation of a hydrolitically labile silyloxy epoxide (eq 5). The applied method[19] started from ketone **11** which was selectively enolized under kinetic control (−78 °C) using the bulky base lithium bis(trimethylsilyl)amide. The regioisomeric enolate was then quenched with chorotrimethylsilane (TMSCl), giving the silylenol ether **16**. Dimethyldioxirane[20] epoxidation and opening of the silyloxy epoxide **17** with camphorsulfonic acid (CSA), gave the C-26 desilylated α-hydroxy ketone **18** in good overall yield (71%).



Assignment of the configuration at C-15 was made on the basis of a ROESY[17] experiment which showed a strong cross peak between the β-axial CH_3-18 (δ 0.88 ppm) and the C-15 proton (δ 3.59 ppm), establishing an α stereochemistry for the C-15 hydroxy group.

The penultimate step of the synthesis was the reduction of the C-16 oxo group (eq 6). This seemingly straightforward reaction was unexpectedly difficult to perform with acceptable stereoselectivity. Several hydride based reagents were used in this step. $NaBH_4$ and DIBAL-H gave exclusively the undesired cis isomer **19** in 90% and 86% yields, respectively, while $NaBH_3CN$ and $LiAlH_4$ afforded both **19** and **20** in 1.6/1 (75%) and 1/1.25 (90%) ratio. The $BH_3{\cdot}SMe_2$ reduction procedure, according to Brown and Vogel,[21] afforded exclusively **20** in 58% yield.

Hydrogenolysis (Pd/C) of triol **20** resulted in removal of the benzyl protecting groups to provide (25*R*)-5α-cholestane-3β,6β,15α,16β,26-pentol (**1a**) in quantitative yield. The target compound was identified by comparison of the NMR data with those reported for the natural product.[2a]



Work is in progress to evaluate the cytostatic activity of **1a** in vivo.

Experimental Section

General Procedures. Analytical instrumentation and spectral formats are the same as previously described.[22] All reactions were carried out under a dry argon atmosphere using freshly distilled solvents unless otherwise noted. Tetrahydrofuran was distilled from sodium and benzophenone. 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. Dimethyldioxirane was prepared according ref 20. Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized using UV light, spraying with H_2SO_4−$Ce(SO_4)_2$ solution and drying. Reaction temperatures were measured externally. Flash chromatography was performed on Merck silica gel (60, particle size 0.040−0.063 mm). Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) pure materials. High-resolution mass spectra (electron impact, EIMS; fast ion bombardment, FIBMS) were obtained at 70 eV and 4 kV (Cs^+ ion), respectively, on a Fisons VG Prospec mass spectrometer. The NMR spectra were recorded on a Bruker AM-250, Bruker DRX-400, and Bruker DRX-600 spectrometers. Assignments of ^{1}H and ^{13}C NMR resonances were based on DEPT, COSY, HETCOR, and ROESY[17] experiments.

(25*R*)-3β-(Benzyloxy)spirost-5-ene (3). To a suspension of NaH (0.43 g, 18 mmol) in THF (5 mL) at 0 °C was slowly added a solution of diosgenin (**2**, 5.00 g, 12.0 mmol) in THF (35 mL). After the solution was stirred for 0.5 h at 0 °C, benzyl bromide (BnBr, 2.6 mL, 22.0 mmol) and tetrabutylammonium iodide (TBAI, 0.31 g, 0.84 mmol) were added. The resulting mixture was refluxed for 16 h and then quenched with a saturated solution of NH_4Cl (10 mL), concentrated in vacuo to remove the excess THF, and extracted with diethyl ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. Crystallization from $CHCl_3$/MeOH gave **3** (5.45 g, 90%) as white crystals.

3: mp 134−135 °C; $[\alpha]_D$ −90.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.79 (3 H, s, Me-18), 0.79 (3 H, d, J = 6.7 Hz, Me-27), 0.98 (3 H, d, J = 6.0 Hz, Me-21), 1.04 (3 H, s, Me-19), 3.28 (1 H, m, H-3), 3.37 (1 H, dd, J = 10.6, 10.6 Hz, H-26), 3.48 (1 H, dd, J = 10.6, 2.9 Hz, H′-26), 4.43 (1 H, bdd, J = 14.6, 6.9 Hz, H-16), 4.56 (2 H, s, CH_2Ph), 5.35 (1 H, m, H-6), 7.31 (5 H, m, C$_6H_5$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.5, 16.2, 17.1, 19.4, 20.8, 28.4, 28.7, 30.2, 31.4 (× 2), 31.8, 32.0, 37.0, 37.1, 39.1, 39.7, 40.2, 41.5, 50.0, 56.5, 62.0, 66.8, 69.9, 78.4, 80.7, 109.2, 121.0, 127.3, 127.5 (× 2), 128.3 (× 2), 139.0, 140.9; HR EIMS m/z 504.3633 (calcd 504.3603 for $C_{34}H_{48}O_3$).

(25*R*)-3β-(Benzyloxy)-5α-spirostan-6α-ol (4) and (25*R*)-3β-(Benzyloxy)-5β-spirostan-6β-ol (5). To a solution of **3** (0.70 g, 1.4 mmol) in THF (10 mL) at 0 °C was slowly added $BH_3{\cdot}SMe_2$ (2.8 mL, 2.0 M in THF, 5.6 mmol). After 0.1 h the solution was warmed to room temperature and stirred for a further 20 h. The solution was then cooled at 0 °C, and

(18) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(19) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369.
(20) Adam, W.; Chan, Y. Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800.
(21) Brown, H. C.; Vogel, F. G. M. *Liebigs Ann. Chem.* **1978**, 695.
(22) De Riccardis, F.; Izzo, I.; Di Filippo, M.; Sodano, G.; D'Acquisto, F.; Carnuccio, R. *Tetrahedron* **1997**, *53*, 10871.

absolute ethanol (2.5 mL), a solution of NaOH (3.5 mL, 3.0 M), and H_2O_2 (0.7 mL, 30% in water) were added in succession. The mixture was refluxed for 1 h, concentrated in vacuo to remove the excess of THF, and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 5−40% diethyl ether in petroleum ether) to give **4** (0.54 g, 75%) as a white solid and **5** (0.05 g, 7%) as a colorless oil.

4: mp 228−231 °C; $[\alpha]_D$ −48.8 (c = 1.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.74 (3 H, s, Me-18), 0.77 (3 H, d, J = 6.7 Hz, Me-27), 0.79 (3 H, s, Me-19), 0.94 (3 H, d, J = 6.0 Hz, Me-21), 3.30 (1 H, m, H-3), 3.34 (1 H, m, H-6), 3.35 (1 H, dd, J = 10.6, 10.6 Hz, H-26), 3.45 (1 H, dd, J = 10.6, 2.9 Hz, H′-26), 4.38 (1 H, bdd, J = 14.6, 6.9 Hz, H-16), 4.50 (1 H, d, J = 11.8 Hz, C*H*Ph), 4.58 (1 H, d, J = 11.8 Hz, C*H*′Ph), 7.30 (5 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.3, 14.4, 16.3, 17.0, 20.8, 27.9, 28.6 (× 2), 30.1, 31.2, 31.6, 33.7, 36.4, 37.1, 39.6, 40.4, 41.4, 41.6, 51.3, 53.6, 55.8, 61.9, 66.6, 68.9, 69.7, 77.8, 80.5, 109.1, 127.2, 127.4 (× 2), 128.2 (× 2), 138.8; HR EIMS m/z 522.3683 (calcd 522.3709 for $C_{34}H_{50}O_4$).

5: $[\alpha]_D$ −27.9 (c = 2.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.78 (3 H, s, Me-18), 0.78 (3 H, d, J = 6.7 Hz, Me-27), 0.96 (3 H, d, J = 6.0 Hz, Me-21), 1.15 (3 H, s, Me-19), 3.35 (1 H, dd, J = 10.6, 10.6 Hz, H-26), 3.45 (1 H, dd, J = 10.6, 2.9 Hz, H′-26), 3.64 (1 H, m, H-3), 3.69 (1 H, bs, H-6), 4.40 (1 H, bdd, J = 14.6, 6.9 Hz, H-16), 4.45 (1 H, d, J = 11.8 Hz, C*H*Ph), 4.55 (1 H, d, J = 11.8 Hz, C*H*′Ph), 7.32 (5 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.5, 16.5, 17.1, 20.6, 24.1, 26.0, 28.7, 30.2, 30.6, 31.3, 31.7, 34.5, 34.8, 40.0, 40.2, 40.4, 40.7, 41.6, 44.2, 56.3, 62.2, 66.8, 68.9, 69.5, 72.8, 73.2, 77.2, 80.8, 109.2, 127.3 (× 2), 128.3 (× 2), 139.2; HR EIMS m/z 522.3745 (calcd 522.3709 for $C_{34}H_{50}O_4$).

(25*R*)-3*β*-(Benzyloxy)-5α-spirostan-6-one (6). To a solution of **4** (0.18 g, 0.34 mmol) in CH_2Cl_2 (2 mL) were added 4 Å molecular sieves (m.s., 0.34 g) and PDC (0.26 g, 0.69 mmol). After 2 h the reaction mixture was diluted with diethyl ether (10 mL). Filtration through a short pad of Celite and $CaSO_4$ (10% in weight) afforded a solution which was concentrated in vacuo to give **6** as a white solid (0.17 g, 95%).

6: mp 178−180 °C; $[\alpha]_D$ −82.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.77 (6 H, s, Me-18, Me-19), 0.78 (3H, d, J = 6.7 Hz, Me-27), 0.97 (3 H, d, J = 6.0 Hz, Me-21), 3.29 (1 H, m, H-3), 3.35 (1 H, dd, J = 10.6, 10.6 Hz, H-26), 3.45 (1 H, dd, J = 10.6, 2.9 Hz, H′-26), 4.40 (1 H, bdd, J = 14.6, 6.9 Hz, H-16), 4.50 (1 H, d, J = 11.8 Hz, C*H*Ph), 4.58 (1 H, d, J = 11.8 Hz, C*H*′Ph), 7.32 (5 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.1, 14.4, 16.4, 17.1, 21.3, 26.3, 27.9, 28.7, 30.2, 31.5, 36.6, 37.2, 39.5, 40.9, 41.2, 41.5, 46.7, 53.8, 56.4, 56.7, 61.9, 66.8, 69.7, 76.9, 80.4, 109.3, 127.4, 127.5 (× 2), 128.3 (× 2), 138.7, 210. 7; HR EIMS m/z 520.3544 (calcd 520.3553 for $C_{34}H_{48}O_4$).

(25*R*)-3*β*-(Benzyloxy)-5α-spirostan-6*β*-ol (7). To a solution of **6** (0.15 g, 0.29 mmol) in diethyl ether (15 mL) was added $LiAlH_4$ (0.43 mL, 1.0 M in THF, 0.43 mmol). The reaction mixture was stirred for 0.2 h and quenched with ethyl acetate (1 mL) and NH_4OH (0.5 mL, 30% aqueous solution). Filtration through a short pad of Celite and concentration in vacuo gave **7** (0.15 g, 100%) as a white solid.

7: mp 194−196 °C; $[\alpha]_D$ −62.3 (c = 1.2, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.77 (3 H, d, J = 6.7 Hz, Me-27), 0.78 (3 H, s, Me-18), 0.95 (3 H, d, J = 6.0 Hz, Me-21), 1.03 (3 H, s, Me-19), 3.35 (1 H, m, H-3), 3.35 (1 H, dd, J = 10.6, 10.6 Hz, H-26), 3.45 (1 H, dd, J = 10.6, 2.9 Hz, H′-26), 3.75 (1 H, bs, H-6) 4.38 (1 H, bdd, J = 14.6, 6.9 Hz, H-16), 4.52 (1 H, d, J = 11.8 Hz, C*H*Ph), 4.57 (1 H, d, J = 11.8 Hz, C*H*′Ph), 7.32 (5 H, m, C_6H_5); ^{13}C NMR (62.5 MHz) δ 14.4, 15.6, 16.4, 17.0, 20.7, 28.1, 28.6, 29.8, 30.1, 31.2, 31.6, 31.9, 35.6, 38.3, 39.6, 39.9, 40.4, 41.4, 47.2, 54.1, 55.9, 62.0, 66.7, 69.7, 71.6, 78.1, 80.6, 109.2, 127.3, 127.4 (× 2), 128.2 (× 2), 138.8; HR EIMS m/z 522.3734 (calcd 522.3709 for $C_{34}H_{50}O_4$).

(25*R*)-3*β*,6*β*-Bis(benzyloxy)-5α-spirostane (8). To a suspension of NaH (0.20 g, 8.52 mmol) in THF (1 mL) at 0 °C was added a solution of **7** (1.75 g, 3.35 mmol) in THF (9 mL). After the solution was stirred for 0.5 h, BnBr (1.2 mL, 10.2 mmol) and TBAI (0.09 g, 0.24 mmol) were added. The resulting mixture was heated at reflux for 16 h, quenched with a saturated solution of NH_4Cl (2 mL), concentrated in vacuo to remove the excess of THF, and extracted with diethyl ether. The organic phase was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was flash chromatographed (silica gel, 5−15% diethyl ether in petroleum ether) to give **8** as a white solid (1.55 g, 75%).

8: mp 54−56 °C; $[\alpha]_D$ −69.5 (c = 1.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.81 (3 H, s, Me-18), 0.82 (3H, d, J = 6.7 Hz, Me-27), 1.00 (3 H, d, J = 6.0 Hz, Me-21), 1.10 (3 H, s, Me-19), 3.35 (1 H, dd, J = 10.6, 10.6 Hz, H-26), 3.39 (1 H, m, H-3), 3.45 (1 H, dd, J = 10.6, 2.9 Hz, H′-26), 3.46 (1 H, m, H-6), 4.34 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.43 (1 H, bdd, J = 14.6, 6.9 Hz, H-16), 4.58 (2 H, bs, CH_2Ph), 4.60 (1 H, d, J = 12.2 Hz, C*H*′Ph), 7.34 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.5, 15.7, 16.4, 17.1, 20.8, 28.2, 28.7, 30.2, 30.4, 31.3, 31.7, 32.4, 35.1, 36.0, 38.3, 39.9, 40.6, 41.6, 47.7, 54.4, 55.9, 62.2, 66.8, 69.7, 71.1, 78.4, 79.1, 80.7, 109.1, 126.9 (× 3), 127.3, 127.5 (× 2), 128.1 (× 2), 128.2 (× 2), 139.1, 139.6; HR EIMS m/z 612.4137 (calcd 612.4179 for $C_{41}H_{56}O_4$).

(25*R*)-3*β*,6*β*-Bis(benzyloxy)-5α-cholestane-16*β*,26-diol (9). To a suspension of zinc amalgam, freshly prepared from $HgCl_2$ (0.30 g, 1.10 mmol), and zinc powder (3.20 g, 48.9 mmol) were added **8** (0.094 g, 0.186 mmol), dissolved in absolute ethanol (12 mL), and concentrated hydrochloric acid (3 mL, 37%, aqueous solution). The mixture was heated at reflux for 1.6 h, cooled to room temperature, filtered, and concentrated under reduced pressure. The crude material was diluted with chloroform, washed with water, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue on silica gel (0−1% MeOH in $CHCl_3$) gave **9** (0.049 g, 52%) as a white solid.

9: mp 94−96 °C; $[\alpha]_D$ −12.1 (c = 1.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.87 (3 H, s, Me-18), 0.90 (3 H, d, J = 6.7 Hz, Me-27), 0.97 (3 H, d, J = 6.0 Hz, Me-21), 1.06 (3 H, s, Me-19), 3.36 (1 H, m, H-3), 3.44 (3 H, m, H-6, H_2-26), 4.32 (1 H, m, H-16), 4.33 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.56 (2 H, s, CH_2Ph), 4.59 (1 H, d, J = 12.2 Hz, −C*H*′Ph), 7.34 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.3, 15.7, 16.6, 18.1, 20.6, 23.7, 28.2, 29.6, 30.4, 32.4, 33.3, 34.9, 35.6, 35.9, 36.0, 36.6, 38.3, 40.0, 42.5, 47.8, 53.8, 54.5, 61.6, 68.4, 69.7, 71.1, 72.4, 78.4, 79.2, 126.9 (× 3), 127.3, 127.5 (× 2), 128.1 (× 2), 128.3 (× 2), 139.1, 139.7; HR EIMS m/z 616.4461 (calcd 616.4492 for $C_{41}H_{60}O_4$).

(25*R*)-26-[(*tert*-Butyldimethylsilyl)oxy]-3*β*,6*β*-bis(benzyloxy)-5α-cholestan-16*β*-ol (10). To a solution of **9** (0.640 g, 1.04 mmol) in CH_2Cl_2 (5 mL) were added 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU, 0.28 mL, 1.9 mmol) and TBDMSCl (0.250 g, 1.66 mmol). The reaction was stirred for 1.5 h before being diluted with CH_2Cl_2 (15 mL), sequentially washed with 0.1 M HCl (10 mL) and with a saturated solution of $NaHCO_3$ (10 mL) and water, dried (Na_2SO_4), and concentrated in vacuo. The residue (0.760 g), a colorless oil, was used in the next step without purification.

10: $[\alpha]_D$ −11.8 (c = 1.5, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04 (6 H, s, $(CH_3)_2$−Si), 0.86 (3 H, s, Me-18), 0.89 (9 H, s, $(CH_3)_3$−C), 0.90 (3 H, d, J = 6.7 Hz, Me-27), 0.97 (3 H, d, J = 6.0 Hz, Me-21), 1.06 (3 H, s, Me-19), 3.40−350 (4 H, m, H-3, H-6 and H_2-26), 4.32 (1 H, m, H-16), 4.32 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.55 (2 H, s, CH_2Ph), 4.57 (1 H, d, J = 12.2 Hz, C*H*′Ph), 7.32 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.3 (× 2) 13.3, 15.7, 16.7, 18.1, 18.4, 20.6, 23.7, 25.6, 26.0 (× 3), 28.2, 29.8, 30.4, 32.4, 33.6, 34.9, 35.8, 36.0, 36.2, 36.5, 38.4, 40.0, 42.5, 47.8, 54.5, 61.5, 68.5, 69.7, 71.1, 72.5, 78.4, 79.2, 126.9 (× 3), 127.3, 127.6 (× 2), 128.1 (× 2), 128.3 (× 2), 139.1, 139.8; EIMS m/z 730 (M^+).

(25*R*)-26-[(*tert*-Butyldimethylsilyl)oxy]-3*β*,6*β*-bis(benzyloxy)-5α-cholestan-16-one (11). To a solution of **10** (0.760 g, 1.04 mmol) in CH_2Cl_2 (5 mL) were added 4 Å molecular sieves (1.40 g) and PDC (0.782 g, 2.18 mmol). After 2 h the reaction mixture was diluted with diethyl ether (10 mL). Filtration through a short pad of Celite and $CaSO_4$ (10% in weight) afforded a solution which was concentrated in vacuo and purified by flash chromatography (silica gel, 5−10% diethyl ether in petroleum ether) to give **11** as a colorless oil (0.59 g, 78% two steps).

11: $[\alpha]_D$ −55.5 (c = 2.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.04 (6 H, s, $(CH_3)_2$−Si), 0.81 (3 H, s, Me-18), 0.87 (3H, d, J = 6.7 Hz, Me-27), 0.89 (9 H, s, $(CH_3)_3$−C), 0.96 (3 H, d, J = 6.0 Hz, Me-21), 1.09 (3 H, s, Me-19), 3.34 (1 H, dd, J = 10.9, 6.5 Hz, H-26), 3.36 (1 H, m, H-3), 3.45 (1 H, dd, J = 10.9, 5.8 Hz, H′-26), 3.46 (1 H, bs, H-6), 4.37 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.54 (1 H, d, J = 12.2, C*H*′Ph), 4.56 (2 H, s, CH_2Ph), 7.32 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.4 (× 2) 13.8, 15.7, 16.7, 18.6, 20.4, 24.6, 25.9 (× 3), 28.2, 29.7, 31.2, 32.3, 33.3, 35.2, 35.7, 35.9, 36.0, 38.1, 38.9, 39.1, 43.3, 47.7, 50.4, 54.3, 68.2, 68.5, 69.8, 71.4, 78.3, 79.2, 126.9 (× 3), 127.1, 127.3, 127.5 (× 2), 128.1 (× 2), 128.3 (× 2), 139.1, 139.6, 218.7; EIMS m/z 728 (M^+).

(25*R*)-26-[(*tert*-Butyldimethylsilyl)oxy]-3*β*,6*β*-bis(benzyloxy)-5α-cholest-15-en-16-yl Triflate (12). To a solution of **11** (0.250 g, 0.340 mmol) in THF (4 mL) at −78 °C was added $LiN(TMS)_2$ (0.77 mL, 1.0 M in THF, 0.77 mmol). After 1 h *N*-phenyltrifluoromethanesulfonimide (0.235 g, 0.660 mmol) was added, and after an additional 0.3 h, the reaction mixture was warmed to room temperature. The reaction was then quenched by addition of water, concentrated in vacuo to remove the excess of THF, and extracted with diethyl ether. The organic layer was washed with a saturated solution of NH_4Cl, dried (Na_2SO_4), and concentrated in vacuo. The residue was flash chromatographed (silica gel, 0−10% diethyl ether in petroleum ether) to give **12** as a colorless oil (0.274 g, 94%).

12: $[\alpha]_D$ −8.22 (c = 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.08 (6 H, s, $(CH_3)_2$−Si), 0.91 (3 H, d, J = 6.7 Hz, Me-27), 0.94 (9 H, s, $(CH_3)_3$−C), 0.96 (3 H, s, Me-18), 1.04 (3 H, d, J = 6.0 Hz, Me-21), 1.12 (3 H, s, Me-19), 3.39 (1 H, m, H-3), 3.40 (1 H, dd, J = 9.7, 6.5 Hz, H-26), 3.44 (1 H, J = 9.7, 5.9 Hz, H′-26), 3.51 (1 H, bs, H-6), 4.41 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.59 (2 H, s, CH_2Ph), 4.63 (1 H, d, J = 12.2 Hz, C*H*′Ph), 5.72 (1 H, bs, H-15), 7.33 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.4 (× 2), 13.6, 15.5, 16.6, 19.2, 20.2, 25.0, 25.9 (× 3), 27.3, 28.1, 31.5, 32.3, 33.3, 35.0, 35.7, 36.0, 36.1, 36.1, 36.4, 38.0, 47.9, 50.5, 54.5, 56.4, 60.4, 68.4, 69.8, 71.6, 78.2, 79.0, 116.2, 118.4 (q), 126.9 (× 2), 127.1, 127.3, 127.5 (× 2), 128.1 (× 2), 128.3 (× 2), 139.0, 139.5, 153.1; HR EIMS m/z 860.4648 (calcd 860.4693 for $C_{48}H_{71}F_3O_6SSi$).

(25*R*)-26-[(*tert*-Butyldimethylsilyl)oxy]-3*β*,6*β*-bis(benzyloxy)-5α-cholest-15-ene (13). To a solution of **12** (0.038 g, 0.045 mmol) in THF (2 mL) were added LiCl (0.008 g, 0.200 mmol), $Pd(PPh_3)_4$ (0.002 g, 0.002 mmol), and Bu_3SnH (0.018 mL, 0.062 mmol). The reaction mixture was refluxed for 16 h, then quenched with water (1 mL), concentrated in vacuo to remove the excess of THF, and extracted with petroleum ether. The organic layer was washed with a solution of NH_4OH (10% in water), and then with brine and finally dried (Na_2SO_4) and concentrated in vacuo. The residue was flash chromatographed (silica gel, 0−1% diethyl ether in petroleum ether) to give **13** as a colorless oil (0.016 g, 50%).

13: $[\alpha]_D$ −6.5 (c = 1.8, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (6 H, s, $(CH_3)_2$−Si), 0.77 (3 H, s, Me-18), 0.88 (3 H, d, J = 6.7 Hz, Me-27), 0.91 (9 H, s, $(CH_3)_3$−C), 0.92 (3 H, d, J = 6.0 Hz, Me-21), 1.10 (3 H, s, Me-19), 3.36 (1 H, m, H-3), 3.37 (1 H, dd, J = 9.7, 6.5 Hz, H-26), 3.47 (1 H, J = 9.7, 5.9 Hz, H′-26), 3.49 (1 H, bs, H-6), 4.35 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.57 (2 H, s, CH_2Ph), 4.65 (1 H, d, J = 12.2 Hz, C*H*′Ph), 5.79 (1 H, bd, J = 6.2 Hz, H-15 or H-16), 5.83 (1 H, bd, J = 5.8 Hz, H-15 or H-16), 7.35 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.3 (× 2), 12.8, 15.6, 16.7, 18.3, 18.5, 20.8, 23.8, 26.0 (× 3), 28.0, 28.3, 32.2, 32.5, 33.5, 35.2, 35.7, 36.1, 36.5, 37.7, 38.3, 48.1, 49.6, 55.1, 61.5, 62.4, 68.5, 69.8, 71.3, 78.5, 79.3, 126.9 (× 2), 127.1, 127.3, 127.5 (× 2), 128.1 (× 2), 128.3 (× 2), 130.8, 133.8, 139.2, 139.7; HR EIMS m/z 712.5238 (calcd 712.5251 for $C_{47}H_{72}O_3Si$).

(25*R*)-3*β*,6*β*-Bis(benzyloxy)-5α-cholest-15-en-26-ol (14). To a solution of **13** (0.037 g, 0.052 mmol) in THF (0.5 mL) was added Bu_4NF (0.1 mL, 1 M in THF, 0.1 mmol). After 16 h the reaction mixture was quenched with water (1 mL), concentrated in vacuo to remove the excess of THF, and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated in vacuo, and the residue was flash chromatographed (silica gel, 5−20% ethyl acetate in petroleum ether) to give **14** as a colorless oil (0.017 g, 54%).

14: $[\alpha]_D$ −27.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (3 H, s, Me-18), 0.90 (3 H, d, J = 6.7 Hz, Me-27), 0.92 (3 H, d, J = 6.0 Hz, Me-21), 1.08 (3 H, s, Me-19), 2.20 (1 H, bd, J = 13.7 Hz, H-7*β*), 3.39 (1 H, m, H-3), 3.42 (1 H, dd, J = 9.7, 6.7 Hz, H-26), 3.47 (1 H, bs, H-6), 3.49 (1 H, J = 9.7, 5.9 Hz, H′-26), 4.35 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.56 (2 H, s, CH_2Ph), 4.64 (1 H, d, J = 12.2 Hz, C*H*′Ph), 5.74 (1 H, bd, J = 6.2 Hz, H-15 or H-16), 5.81 (1 H, bd, J = 5.8 Hz, H-15 or H-16), 7.29 (10 H, m, C_6H_5); ^{13}C NMR δ (100 MHz, $CDCl_3$) 12.8, 15.6, 16.5, 18.4, 20.7, 23.8, 28.0, 28.2, 32.1, 32.4, 33.5, 35.1, 35.8, 36.1, 36.4, 37.7, 38.2, 48.0, 49.6, 55.0, 61.5, 62.3, 68.5, 69.7, 71.2, 78.4, 79.2, 126.8 (× 2), 127.0, 127.3, 127.6 (× 2), 128.1 (× 2), 128.3 (× 2), 130.9, 133.7, 139.1, 139.7; HR EIMS m/z 598.4377 (calcd 598.4386 for $C_{41}H_{58}O_3$).

(25*R*)-3*β*,6*β*-Bis(benzyloxy)-15*β*,16*β*-epoxy-5α-cholestan-26-ol (15). To a solution of **14** (0.007 g, 0.012 mmol) in methylene chloride (0.5 mL) at 0 °C was added MCPBA (0.004 g, 0.024 mmol). After 5 h the reaction mixture was quenched with a saturated solution of Na_2SO_3 (1 mL), extracted with methylene chloride, dried (Na_2SO_4), and concentrated in vacuo. The residue was flash chromatographed (silica gel, 0−2% methanol in methylene chloride) to give **15** as a colorless oil (0.004 g, 57%).

15: $[\alpha]_D$ −19.7 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (3 H, s, Me-18), 0.93 (6 H, d, J = 7.0 Hz, Me-27 and Me-21), 1.05 (1 H, d, J = 11.6 Hz, H-14), 1.08 (3 H, s, Me-19), 2.26 (1 H, bd, J = 13.7 Hz, H-7*β*), 3.06 (1 H, bs, H-15 or H-16), 3.20 (1 H, d, J = 3.2 Hz, H-15 or H-16), 3.36 (1 H, m, H-3), 3.44 (1 H, dd, J = 10.4, 6.7 Hz, H-26), 3.50 (1 H, bs, H-6), 3.51 (1 H, J = 10.4, 6.0 Hz, H′-26), 4.43 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.55 (2 H, s, CH_2Ph), 4.59 (1 H, d, J = 12.2 Hz, C*H*′Ph), 7.29 (10 H, m, C_6H_5); ^{13}C NMR δ (100 MHz, $CDCl_3$) 15.2, 16.4, 18.5, 20.3, 23.9, 27.2, 28.2, 29.6, 32.3 (× 2), 33.3, 35.3, 35.7, 36.1, 36.9, 37.2, 38.1, 48.0, 53.7, 54.7, 58.8, 59.3 (× 2), 64.1, 68.4, 69.8, 71.6, 78.3, 79.4, 126.9 (× 2), 127.0, 127.3, 127.5 (× 2), 128.1 (× 2), 128.3 (× 2), 139.1, 139.8; HR EIMS m/z 614.4306 (calcd 614.4335 for $C_{41}H_{58}O_4$).

(25*R*)-26-[(*tert*-Butyldimethylsilyl)oxy]-3*β*,6*β*-bis(benzyloxy)-16-[(trimethylsilyl)oxy]-5α-cholest-15-ene (16). To a solution of **11** (0.200 g, 0.275 mmol) in THF (2 mL) at −78 °C was added $LiN(SiMe_3)_2$ (0.55 mL, 1.0 M in THF, 0.55 mmol). After 1 h Me_3SiCl (0.10 mL, 0.83 mmol) was added, and after additional 0.3 h, the mixture was allowed to warm to room temperature. The reaction was then quenched by addition of water, concentrated in vacuo to remove the excess of THF, and extracted with petroleum ether. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give crude **16** as a colorless oil (0.240 g). **16** was used in the next step without further purification.

16: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (6 H, s, $(CH_3)_2$−Si), 0.24 (9 H, s, $(CH_3)_3$−Si), 0.91 (3 H, s, Me-18), 0.92 (3 H, d, J = 6.7 Hz, Me-27), 0.95 (9 H, s, $(CH_3)_3$−C), 1.09 (3 H, d, J = 6.0 Hz, Me-21), 1.18 (3 H, s, Me-19), 3.37 (1 H, m, H-3), 3.38 (1 H, dd, J = 9.8, 6.7 Hz, H-26), 3.48 (1 H, dd, 9.8, 5.9 Hz, H′-26), 3.49 (1 H, bs, H-6), 4.39 (1 H, d, J = 12.2 Hz, C*H*Ph), 4.58 (1 H, s, CH_2Ph), 4.61 (1 H, bs, H-15), 4.66 (1 H, d, J = 12.2 Hz, C*H*′Ph), 7.33 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ −5.3 (× 2), −5.4 (× 3), 13.6, 15.6, 16.7, 18.3, 19.4, 20.4, 22.6, 25.2, 26.0 (× 3), 28.1, 28.3, 32.1, 32.4, 33.7, 35.3, 35.9, 36.1, 36.7, 36.9 38.1, 48.1, 49.1, 54.8, 56.6, 61.3, 68.6, 69.8, 71.4, 78.5, 79.5, 101.2, 126.9 (× 2), 127.0, 127.3, 127.5 (× 2), 128.1 (× 2), 128.3 (× 2), 139.1, 139.8, 158.7.

(25*R*)-3*β*,6*β*-Bis(benzyloxy)-5α-cholestane-15α,26-diol-16-one (18). To a solution of **16** (0.220 g 0.275 mmol) in CH_2Cl_2 at 0 °C was added dimethyldioxirane (3.3 mL 0.1 M in acetone, 0.33 mmol). After 1 h the mixture was concentrated in vacuo, and the residue was dissolved in acetone (4 mL). Camphorsulfonic acid (0.01 g, 0.04 mmol) was added, and the mixture was left at 4 °C for 16 h. The reaction mixture was then diluted with water (2 mL), concentrated in vacuo to remove the excess of acetone, extracted with chloroform, dried (Na_2SO_4), and concentrated in vacuo. The crude residue was

purified by flash chromatography (0−1% methanol in chloroform) to give **18** (0.123 g, 71%, overall yield) as a white solid.

18: mp 53−55 °C; $[\alpha]_D$ −31.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 0.88 (3 H, s, Me-18), 0.92 (3 H, d, *J* = 6.7 Hz, Me-27), 1.01 (3 H, d, *J* = 6.0 Hz, Me-21), 1.12 (3 H, s, Me-19), 3.37 (1 H, m, H-3), 3.39 (1 H, dd, *J* = 9.8, 6.7 Hz, H-26), 3.49 (1 H, dd, *J* = 9.8, 5.9 Hz, H′-26), 3.50 (1 H, bs, H-6), 3.59 (1 H, d, *J* = 11.5 Hz, H-15), 4.39 (1 H, d, *J* = 12.2 Hz, C*H*Ph), 4.57 (2 H, bs, CH_2Ph), 4.63 (1 H, d, *J* = 12.2 Hz, C*H*′Ph), 7.33 (10 H, m, C_6H_5); ^{13}C NMR (62.5 MHz) *δ* 15.7, 15.8, 16.5, 19.3, 20.3, 24.4, 28.1, 29.8, 31.2, 32.2, 33.1, 34.9, 35.1, 35.5, 36.0, 38.1, 39.1, 39.7, 47.4, 53.9, 56.1, 64.5, 68.1, 69.7, 71.3, 76.6, 77.2, 78.2, 79.1, 126.8 (× 2), 127.2, 127.4 (× 2), 128.0 (× 2), 128.2 (× 2), 139.0, 139.8, 213.1; HR EIMS *m*/*z* 630.4256 (calcd 630.4284 for $C_{41}H_{58}O_5$).

(25*R*)-3*β*,6*β*-Bis(benzyloxy)-5α-cholestane-15α,16α,26-triol (19) and (25*R*)-3*β*,6*β*-Bis(benzyloxy)-5α-cholestane-15α,16*β*,26-triol (20). (a) Reduction with $LiAlH_4$. To a solution of **18** (0.042 g, 0.67 mmol) in diethyl ether (2 mL) at 0 °C was added $LiAlH_4$ (0.2 mL, 1.0 M in THF, 0.2 mmol). The reaction mixture was stirred for 0.2 h and quenched with ethyl acetate (0.5 mL) and NH_4OH (0.2 mL, 30% aqueous solution). Filtration through a short pad of Celite and concentration in vacuo gave a crude residue which was purified by flash chromatography (0−1% methanol in chloroform) to give **19** as colorless oil (0.017 g, 40%) and **20** (0.021 g, 50%) as white solid.

(b) Reduction with BH_3·SMe_2. To a solution of **18** (0.022 g, 0.35 mmol) in THF (3 mL) at 0 °C was added BH_3·SMe_2 (0.055 mL, 2 M in THF, 0.11 mmol). After 2 h the mixture was quenched with 0.1 M HCl, concentrated in vacuo to remove the excess of THF, extracted with chloroform (6 mL), and washed with a saturated solution of NaCl. The organic phase was then dried (Na_2SO_4) and concentrated to give a crude residue which was purified by flash chromatography (0−1% methanol in chloroform) to give **20** (0.013 g, 58%).

19: $[\alpha]_D$ −6.3 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.70 (3 H, s, Me-18), 0.91 (3 H, d, *J* = 7.0 Hz, Me-27), 0.95 (3 H, d, *J* = 6.6 Hz, Me-21), 1.07 (3 H, s, Me-19), 2.43 (1 H, bd, *J* = 14.3 Hz, H-7*β*), 3.36 (1 H, m, H-3), 3.47 (3 H, m, H-6 and H_2-26), 3.64 (1 H, dd, *J* = 8.2, 8.0 Hz, H-15), 3.80 (1 H, dd, *J* = 7.2, 7.0 Hz, H-16), 4.37 (1 H, d, *J* = 12.2 Hz, C*H*Ph), 4.56 (2 H, m, CH_2Ph), 4.60 (1 H, d, *J* = 12.2 Hz, C*H*′Ph), 7.33 (10 H, m, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 15.3, 15.8, 16.6, 19.2, 20.5, 23.8, 28.3, 30.2, 32.4, 33.5, 33.9, 35.2, 35.6, 35.7, 36.0, 38.5, 39.8, 40.3, 47.5, 54.2, 59.8, 63.6, 68.4, 69.8, 71.4, 72.8, 74.8, 78.4, 79.4, 126.9 (× 3), 127.4, 127.6 (× 2), 128.1 (× 2), 128.3 (× 2), 139.1, 139.9; HR FABMS *m*/*z* 633.4492 (calcd 633.4519 for $C_{41}H_{61}O_5$, $[M + H]^+$).

20: mp 61−63 °C; $[\alpha]_D$ −1.5 (*c* = 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.88 (3 H, s, Me-18), 0.89 (3 H, d, *J* = 7.0 Hz, Me-27), 0.95 (3 H, d, *J* = 6.6 Hz, Me-21), 1.07 (3 H, s, Me-19), 2.29 (1 H, bd, *J* = 14.3 Hz, H-7*β*), 3.36 (1 H, m, H-3), 3.45 (3 H, m, H-6 and H_2-26), 3.75 (1 H, dd, *J* = 10.0, 1.6 Hz, H-15), 4.06 (1 H, dd, *J* = 7.4, 1.6 Hz, H-16), 4.37 (1 H, d, *J* = 12.2 Hz, C*H*Ph), 4.55 (2 H, bs, CH_2Ph), 4.60 (1 H, d, *J* = 12.2 Hz, C*H*′Ph), 7.33 (10 H, m, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 14.6, 15.8, 16.7, 17.9, 20.6, 23.5, 28.2, 29.3, 30.2, 32.3, 33.2, 35.1, 35.4, 35.8, 35.9, 38.4, 40.2, 43.8, 47.5, 54.2, 58.6, 59.9, 68.3, 69.7, 71.4, 78.3, 79.3, 82.4, 83.9, 126.9 (× 2), 127.0, 127.3, 127.5 (× 2), 128.1 (× 2), 128.3 (× 2), 139.1, 139.9; HR FABMS *m*/*z* 633.4487 (calcd 633.4519 for $C_{41}H_{61}O_5$, $[M + H]^+$).

(25*R*)-5α-Cholestane-3*β*,6*β*,15α,16*β*,26-pentol (1a). To a solution of **20** (0.068 g, 0.107 mmol) in absolute ethanol (2.5 mL) was added palladium on activated carbon (7 mg). The flask was evacuated (20 Torr) and flushed with hydrogen three times. The reaction mixture was then stirred vigorously under an atmosphere of hydrogen for 5 h. The reaction mixture was filtered through a pad of silica gel and concentrated to give **1a** (0.048 g, 0.104 mmol, 100%).

1a: mp 133−135 °C; $[\alpha]_D$ +29.5 (*c* = 2.3, MeOH); ^{1}H NMR (400 MHz, CD_3OD_3) *δ* 0.93 (3 H, d, *J* = 6.9 Hz, Me-27), 0.95 (3 H, s, Me-18), 0.99 (3 H, d, *J* = 6.6 Hz, Me-21), 1.07 (3 H, s, Me-19), 2.18 (1 H, bd, *J* = 14.3 Hz, H-7*β*), 3.36 (1 H, dd, *J* = 10.5, 6.8 Hz H-26), 3.44 (1 H, *J* = 10.5, 5.9 Hz H′-26), 3.57 (1 H, m, H-3), 3.77 (1 H, bs, H-6), 3.78 (1 H, dd, overlapped with H-6, H-15), 4.00 (1 H, dd, *J* = 7.6, 2.0 Hz, H-16), 4.37 (1 H, d, *J* = 12.2 Hz, C*H*Ph), 4.55 (1 H, bs, CH_2Ph), 4.60 (1 H, d, *J* = 12.2 Hz, C*H*′Ph), 7.33 (10 H, m, C_6H_5); ^{13}C NMR (100 MHz, CD_3OD_3) *δ* 15.0 (C-18), 16.3 (C-19), 17.1 (C-27), 18.6 (C-21), 21.9 (C-11), 24.8 (C-23), 30.9 (C-20), 31.2 (C-8), 32.2 (C-2), 34.7 (C-24), 36.3 (C-4), 36.6 (C-10), 36.9 (C-25), 37.3 (C-22), 39.8 (C-1), 40.6 (C-7), 41.8 (C-12), 44.7 (C-13), 48.8 (C-5), 55.7 (C-9), 60.0 (C-17), 61.1 (C-14), 68.6 (C-26), 72.4 (C-3), 72.5 (C-6), 82.9 (C-16), 85.0 (C-15); HR FIBMS *m*/*z* 453.3577 (calcd 453.3580 for $C_{27}H_{49}O_5$, $[M + 1]^+$).

Acknowledgment. This work has been supported by the European Commission, MAST-III program (contract no. MAS3-CT95-0032), by MURST (40%), and by CNR (Rome). The mass spectra were obtained from the "Servizio di Spettrometria di Massa del CNR e dell'Università di Napoli" and from the CRIAS (Centro Interdipartimentale di Analisi Strumentale) dell'Università di Napoli "Federico II"; the staffs are gratefully acknowledged.

Supporting Information Available: ^{1}H NMR spectra of compounds **1a** and **3**−**20**, ^{13}C NMR spectra of compounds **1a**, **3**−**11**, **13**−**15**, and **18**−**20**, and two-dimensional spectra of compounds **15**, **18**, and **19** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO980266C