Stereospecific Synthesis of 1,6-Dioxadecalins and 2,2′-Linked Ditetrahydrofurans by Rearrangement of Steroidal Spiroacetals

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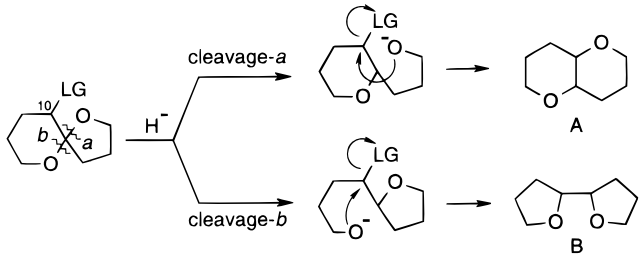
The reduction of steroidal spiroacetal methanesulfonate derivatives, containing the 1,6-dioxaspiro-[4.5]decan-10-yl ring system, with DIBALH promotes a new rearrangement to give steroidal 1,6-dioxadecalin (octahydropyrano[3,2-*b*]pyran) or 2,2′-linked ditetrahydrofuran (octahydro[2,2′]-bifuranyl) derivatives. To study the scope and selectivity of the reaction, several steroidal spiroacetals such as (23*R*,25*R*)-3*β*-methoxy-5α-spirostan-23-yl methanesulfonate (**2**) and its 23*S*-isomer (**5**) and (22*R*,23*R*,25*R*)-3*β*-acetoxy-16*β*,23:23,26-diepoxycholest-5-en-22-yl methanesulfonate (**15**) and its 22*S*-isomer (**19**) have been synthesized. Compound **2** was rearranged with absolute regio- and stereoselectivity to give (22*S*,23*S*,25*R*)-3*β*-methoxy-16*β*,23:22,26-diepoxy-5α-cholestane (**3**) which possesses a *cis*-fused 1,6-dioxadecalin ring system. The reaction of compound **5** gave exclusively (22*S*,23*R*,25*R*)-3*β*-methoxy-23,26-epoxy-5α-furostane (**6**) in which the spiroacetal was converted into a ditetrahydrofuran subunit. The two other isomeric spiroacetals **15** and **19** were also mainly transformed into (22*S*,23*S*,25*R*)-3*β*-acetoxy-16*β*,23:22,26-diepoxycholest-5-ene (**16**) and (22*R*,23*R*,25*R*)-3*β*-acetoxy-23,26-epoxyfurost-5-ene (**20**), respectively. A mechanism is proposed to explain the regio- and sterospecificity observed in the rearrangement.

Introduction

Recently we have described the synthesis of spiroacetals from carbohydrates using an intramolecular hydrogen abstraction reaction promoted by alkoxy radicals.[1] Spiroacetals are present as structural subunits in important metabolites isolated from a large variety of natural sources and have received considerable synthetic attention.[2] During the course of these studies we have envisioned that 1,6-dioxadecalin and 2,2′-linked ditetrahydrofuran ring systems could be effectively constructed through the reductive rearrangement of spiroacetals of the type of 1,6-dioxaspiro[4.5]decan-10-ol shown in Scheme 1.

Many secondary metabolites from a large variety of natural sources exhibit a 1,6-dioxadecalin ring system in their structures.[3] The important biological activity of such compounds and the chemical complexity of their structures have generated a great interest among chemists and biologists.[4] On the other hand, 2,2′-linked ditetrahydrofurans are key structural features of the Annonaceaous acetogenins,[5] a type of natural product with promising pharmacological and plant protection activities. These ditetrahydrofuran units can also be found in some polyether ionophore antibiotics.[6]

Scheme 1



Before either of these transformations of spiroacetals into 1,6-dioxadecalin or 2,2′-linked ditetrahydrofurans

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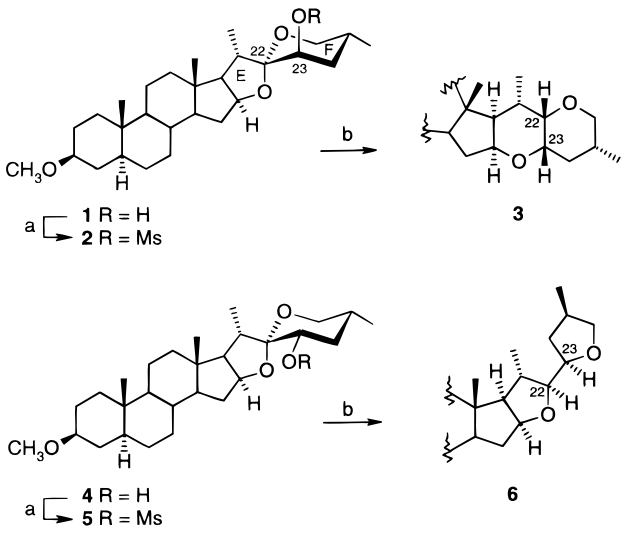
can be synthetically useful, it is necessary to be able to achieve the reduction of the spiroacetal with good regio- and stereoselectivity (Scheme 1). Fortunately, the reduction of acetals and spiroacetals with aluminum, silicon, and boron hydrides is well-documented and in some cases a good selectivity has been achieved.[7] The alcohol at C10 should be transformed into a good leaving group, to be replaced by the alkoxy intermediate. Cleavage of the tetrahydrofuranyl ring via path a should give a 1,6-dioxadecalin system (A) while the fragmentation of the tetrahydropyranyl ring via path b should leave 2,2′-linked ditetrahydrofuran derivatives (B). To test the feasibility of this methodology we have prepared some 1,6-dioxaspiro-[4.5]decan-10-ol derivatives using naturally occurring spirostan sapogenins as starting material.[8] The commercial availability of some of these steroidal substances coupled with their very well-established[9] chemistry and stereochemistry made them attractive substrates to study this rearrangement.

Results and Discussion

The steroidal methanesulfonates **2** and **5**, chosen as models, were prepared from alcohols **1** and **4**, respectively (Scheme 2). A previously described procedure was used to synthesize 3-methoxy-23-oxotigogenin [(25*R*)-3*β*-methoxy-5α-spirostan-23-one], by oxidation of 3-methoxytigogenin with $NaNO_2/BF_3{\cdot}Et_2O$.[10] The reduction of 3-methoxy-23-oxotigogenin with $NaBH_4$/MeOH gave a mixture of alcohols **1** and **4** (91%, 1:17). A somewhat better yield of **1** could be obtained if the reduction of the carbonyl group was made with L-Selectride in THF (72%, 1.6:1) or with H_2/PtO_2 in acetic acid (70%, 1:1.5).

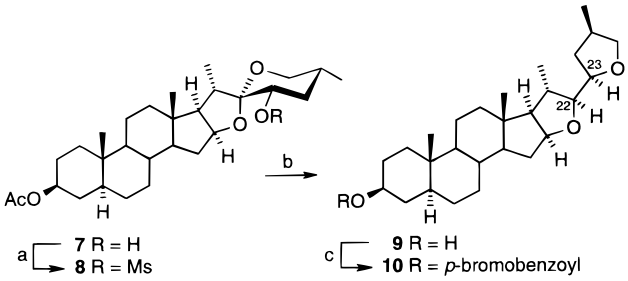
The reduction of methanesulfonate **2** with DIBALH (1 M in toluene, 12 equiv) in dry CH_2Cl_2 (0.02 mmol/mL) at room temperature for 12 h gave the *cis*-1,6-dioxadecalin derivative **3** (87%) with total regio- and stereoselectivity (Scheme 2). The heterocyclic system and the C22 and C23 configurations were deduced from spectroscopic data (COSY, ROESY, HMBC, and HMQC experiments) and confirmed by X-ray analysis[11] of a single crystal of **3**. The *cis*-fused 1,6-dioxadecalin system adopts in crystalline

Scheme 2[a]



[a] Key: (a) MsCl, Py, rt, 2 h, 80−94%; (b) DIBALH, CH_2Cl_2, rt, 8−12 h, 79−87%.

Scheme 3[a]



[a] Key: (a) MsCl, Py, rt, 2 h, 69%; (b) DIBALH, CH_2Cl_2, rt, 5 h, 72%; (c) *p*-bromobenzoyl chloride, CH_2Cl_2/Py, rt, 14 h, 95%.

form a double twist boat conformation. The reductive ring E opening proceeds with inversion of configuration at C22.

Treatment of the epimeric methanesulfonate **5** with DIBALH under similar conditions led us to ditetrahydrofuran **6**, also with total regio- and stereoselectivity in 79% yield (Scheme 2). The structure of compound **6** was also established from spectroscopic data. Of special interest is a strong ion at *m*/*z* 345 [$M^+ - 85$, 81%], indicative of a radical fragmentation of the C22−C23 bond that is observed in its MS spectrum. Since single crystals of **6** were not suitable for X-ray crystallography we prepared the 3-*p*-bromobenzoyl derivative **10**. Since any attempt to deprotect the methoxy group at C3 was unsuccessful, compound **10** was synthesized from the alcohol **7** following the sequence outlined in Scheme 3: mesylation, rearrangement with DIBALH, and subsequent treatment with *p*-bromobenzoyl chloride. Careful examination of the NMR spectra of compounds **6**, **9**, and **10** indicated that they possess identical heterocyclic ring systems. X-ray diffraction analysis[11] of **10** confirmed the proposed stereochemistry indicating that the reaction proceeded in this case by reductive opening of ring F with retention of configuration.

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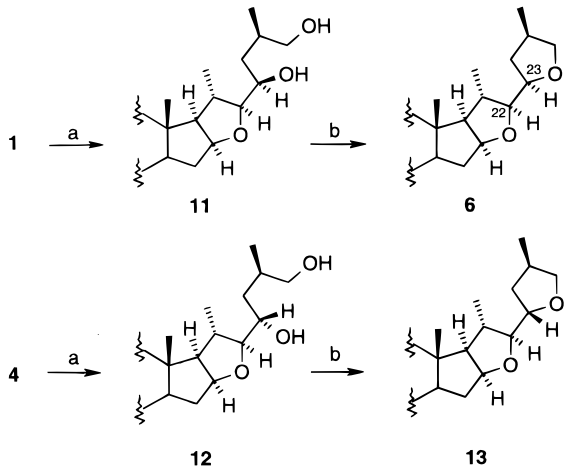
(11) The author has deposited the atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

Scheme 4[a]



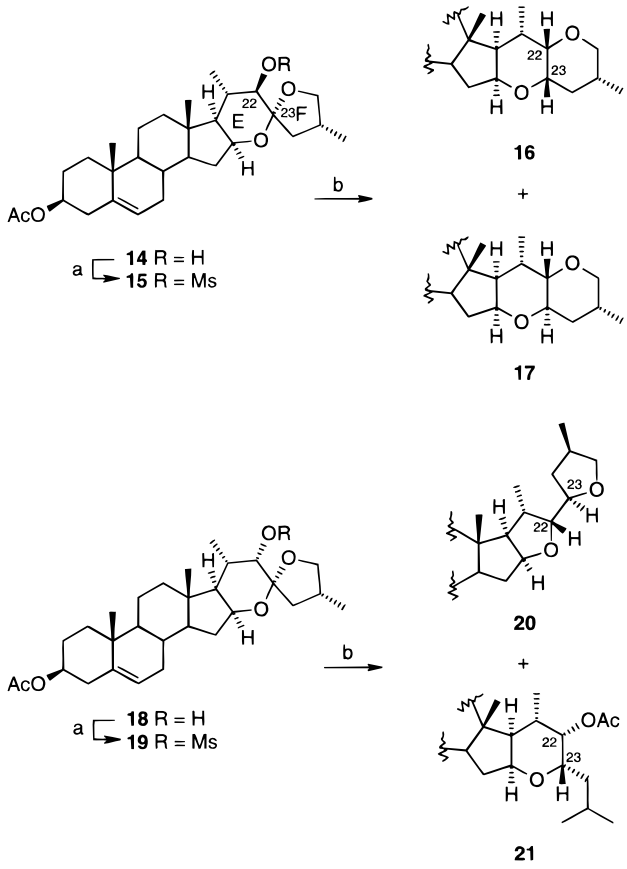
[a] Key: (a) DIBALH, CH_2Cl_2, rt, 28 h, 0−45% or Ph_2SiH_2, $TiCl_4$, 45−90 min, 78%; (b) Ph_3P, imidazole, I_2, toluene, 70 °C, 3.5 h, 63%.

To investigate the influence of the methanesulfonyl group in the regio- and stereoselectivity of the reductive ring opening, alcohol **1** was treated with DIBALH under similar conditions. No reaction was observed, and only starting material was recovered after 24 h at room temperature. However, reduction of alcohol **1** with diphenylsilane (Ph_2SiH_2) as a hydride source in the presence of titanium tetrachloride led to diol **11** in 79% yield, through a ring F opening with retention of configuration (Scheme 4). No products resulting from ring E opening could be detected. The cyclization reaction of diol **11** with the Ph_3P/imidazole/I_2 system[12] gave ditetrahydrofuran **6** in 50% yield, providing confirmation of stereochemical assignments at C22 and C23. This material was identical to compound **6** prepared as described above by rearrangement of the epimeric methanesulfonyl derivative **5**.

The spiroacetal reduction of alcohol **4** with DIBALH was sluggish. A rather moderate chemical yield (45%) of diol **12** was obtained after 28 h with recovery of a substantial amount of starting material (41%). On the contrary, using diphenylsilane and titanium tetrachloride the reaction proceeded smoothly at −25 °C to give diol **12** in 78% yield (Scheme 4). No compounds coming from ring E opening could be isolated in this case either. Analogously to the case of diol **11** compound **12** was cyclized by Ph_3P/imidazole/I_2 to ditetrahydrofuran **13** in 63% yield. It is noteworthy that while methanesulfonyl derivatives **2** and **5** are smoothly reduced with DIBALH little reaction occurs from their respective alcohols **1** and **4**. The formation of an aluminum alkoxy by reaction with the C-23 alcohol may hinder any subsequent attack by another molecule of DIBALH. The regio- and stereoselectivity observed during the reduction of methanesulfonyl derivatives **2** and **5** is also especially noteworthy. These findings can be interpreted by the proposed reaction mechanism (*vide infra*).

To examine the scope of the reaction and to acquire additional insight into its mechanism, we have prepared two new steroidal models, also derivatives of 1,6-dioxaspiro[4.5]decan-10-ol. Methanesulfonates **15** and **19** were prepared from alcohols **14** and **18** respectively

Scheme 5[a]



[a] Key: (a) MsCl, Py, rt, 5−12 h, 80−100%; (b) (i) DIBALH, CH_2Cl_2, rt, 2.5−8 h; (ii) Ac_2O, Py, rt, 12 h.

(Scheme 5), which in turn were obtained by reduction with $NaBH_4$ of the corresponding ketone. This (22*S*,23*R*,-25*R*)-3β-acetoxy-16β,23:23,26-diepoxycholest-5-en-22-one was synthesized in good yield (95%) by Lewis acid-catalyzed rearrangement of 23-oxodiosgenin.[13] The methanesulfonyl derivative **15** was reduced with DIBALH at room temperature for 2.5 h to give, after acetylation, two isomeric 1,6-dioxadecalin compounds **16** and **17** (65%, in an 8.5:1.5 ratio) with good regio- and stereoselectivity. The structure and stereochemistry of these compounds were also established by spectroscopic means and confirmed by X-ray crystallographic analysis.[11] As observed, both compounds have the same configuration at C22 but are epimers at C23. The reductive ring F cleavage then occurs with inversion of configuration in the case of **16** and retention for **17**. The observed conformations of the 1,6-dioxadecalin ring systems deserve some comments. In the case of compound **16** possessing a *cis*-fusion the rings adopt a double twist boat conformation, while the *trans*-fused dioxadecalin system in compound **17** exists in crystalline form as a double chair conformation with both methyl groups in axial disposition.

The treatment with DIBALH of the isomeric methanesulfonate **19** gave, after acetylation, compounds **20** and **21** (62%, in a 1:1 ratio) (Scheme 5). In our preliminary communication we envisioned the structure of **20** presented in that paper as a 1,6-dioxadecalin derivative.[8] On the basis of the proposed mechanism for the DIBALH

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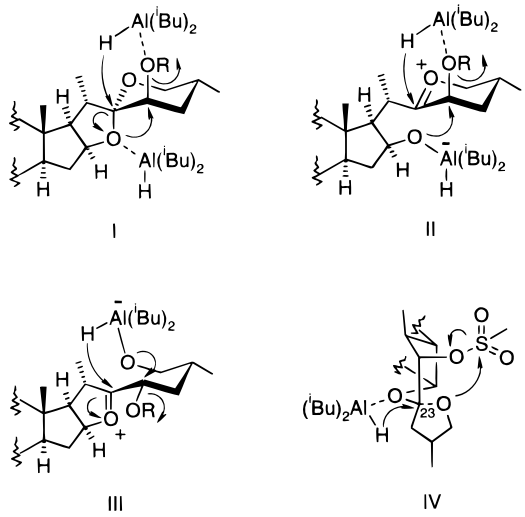

Figure 1. Plausible intermediates in the reduction of α-methanesulfonylspiroacetals with DIBALH.

reduction of α-methanesulfonyl-spiroacetals (*vide infra*) we suspected that the previously reported structure for compound **20** was incorrect and should be revised. X-ray crystallographic analysis[11] confirmed a structure of ditetrahydrofuran for compound **20** with a 22*R*,23*R*-configuration. The reaction would then occur by reductive ring E opening with inversion of configuration at C22 and C23. Note that C22 and C23 stereogenic centers of the ditetrahydrofuran subunits of compounds **13** and **20** are enantiomorphic.

The NMR spectra of compound **21** clearly indicate the presence of an isopropyl group in the molecule and hence the reduction of the O−C26 bond. The observed coupling constants of the low-field protons at C22 and C23 are in good agreement with those calculated over a minimized structure[14] and indicate that the reaction proceeded with inversion of configuration at C23 and retention at C22. This stereochemistry was also confirmed by NOE experiments. As commented below, the formation of compound **21** could be rationalized by admitting an intramolecular transesterification of the secondary methanesulfonyl group and subsequent reduction, with an excess of reagent, of the primary methanesulfonyl group formed.

A number of plausible intermediates for the formation of these products are shown in Figure 1. The results obtained during the study of the reaction with these models led us to two general conclusions. First, the regiochemistry of the spiroacetal cleavage is in all cases controlled by the stereochemistry of the leaving group. The broken C−O bond is always in an *anti*-coplanar disposition with the C−OMs bond. Second, with the exception of compound **6** in which the hydride attack is *syn* to the cleaved C−O bond, the DIBALH reduction always gives products with inversion of configuration. On the basis of previously cited literature, this last result was entirely unexpected, since the reaction of acetals and spiroacetals with alane reducing agents usually proceeds with retention of configuration.

As shown in Figure 1 the stereoselectivity found during the rearrangement of compound **2** suggests a concerted mechanism *via* an intermediate such as I. Two molecules of DIBALH, one acting as Lewis acid to activate the tetrahydrofuranyl oxygen and another coordinated with the methanesulfonyl group acting as reducing agent, would be necessary in order to explain the results obtained, especially the inversion of configuration at the reduced center. This mechanism is similar to that proposed by Yamamoto et al. to explain the reduction of acetals with the silane−Lewis acid system.[15] Nevertheless, an analogous mechanism using two DIBALH molecules and a tight oxocarbenium ion-pair intermediate such as II cannot be totally discarded.

In methanesulfonate **5** the β-side of the spiroacetal moiety is highly hindered by the 18-Me group as a consequence of the *cis*-fusion of the two five-membered rings, and no coordination of the organoaluminum at the methanesulfonyl group would be expected in this case. The rearrangement may proceed through the well-established ion-pair intermediate III where one molecule of alane acts at the same time as Lewis acid and reducing agent. In the first step, coordination of the aluminum occurs at the less hindered tetrahydropyranyl oxygen to cleave exclusively the C22−O bond, reduction of the oxocarbenium ion proceeding also exclusively with retention of configuration. In a second step, the formed C26 alkoxy intermediate attacks the C23 to replace the methanesulfonyl substituent *via* an S_N2 reaction with inversion of configuration to give **6**.

The isomeric methanesulfonates **15** and **19** react preferentially through intermediates analogous to I or II to give products **16** and **20**, respectively, by cleavage of the O−C bond *anti*-coplanar to the O−Ms bond and inversion of configuration at the reduced center. In the reaction of **15** minor compound **17** in which the configuration at C23 is retained was also isolated. This can be explained as being formed through an intermediate analogous to III. In this spiroacetal system the methanesulfonyl group is not so hindered as in **5** and the reaction may proceed by both mechanisms. The formation of compound **21** during the reduction of **19** deserves a brief comment. The reaction is considered to proceed through intermediate IV. A transesterification reaction favored by the *cis*-disposition of the methanesulfonyl group and the C23−O(THF) bond gives rise to a more stable primary methanesulfonyl derivative which is afterward reduced by an excess of DIBALH.

In summary, in this work we have shown that the DIBALH-mediated reduction of α-methanesulfonyl-spiroacetals is a convenient method for the stereospecific preparation of 1,6-dioxadecalin and 2,2′-linked ditetrahydrofuran derivatives. The results obtained not only can be a posteriori rationalized but also permit us to establish a possible reaction pathway for these transformations that might have predictive value in the design of key synthetic intermediates with specific stereocenters. To further explore this reaction we are currently preparing other types of conformationally less restricted nonsteroidal spiroacetals.

Experimental Section

General. Melting points were determined with a hot-stage apparatus and are uncorrected. Optical rotation measurements were recorded at room temperature in $CHCl_3$. IR spectra were recorded in CCl_4 solutions unless otherwise

(14) MMX force field as implemented in PCMODEL (v. 4.0), Serena Software, Bloomington IN, 47402-3076.

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indicated. ^{1}H NMR spectra were determined at 200, 400, or 500 MHz for $CDCl_3$ solutions in parts per million from residual $CHCl_3$ (7.26 ppm) as internal reference unless otherwise indicated. Homonuclear coupling constants (J) were confirmed by COSY or single-frequency decoupling experiments. ^{13}C NMR spectra were recorded at 50.3 or 125.7 MHz, and chemical shifts are reported in ppm from the central peak of $CDCl_3$ ($\delta = 77.0$) as internal reference. Signal chemical shift and multiplicity assignments (CH_3, q; CH_2, t; CH, d; C, s) were made from DEPT, HETCOR, and HMBC spectra. Mass spectra were determined at 70 eV. Merck silica gel 60 (0.040−0.063 mm) was used for flash chromatography. Circular layers of 1 mm of Merck silica gel 60 PF_{254} containing gypsum were used on a Chromatotron for centrifugally assisted chromatography. Commercial reagents and solvents were analytical grade or were purified by standard procedures prior to use.[16] All reactions involving air- or moisture-sensitive materials were carried out under a nitrogen atmosphere. The spray reagent for TLC was vanillin (1 g) in H_2SO_4−EtOH (4:1; 200 mL).

(25*R*)-3*β*-Methoxy-5α-spirostan-23-one. To a solution of 3*β*-methoxytigogenin (325 mg, 0.75 mmol) in glacial acetic acid (5 mL) were added $BF_3{\cdot}Et_2O$ (0.45 mL, 3.65 mmol) and $NaNO_2$ (145 mg, 2.04 mmol) in portions every 15 min. After 1 h the mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was solved in hexanes−benzene (90:10) and kept overnight adsorbed on neutral alumina (activity II/III) on a chromatographic column. Elution with hexanes−benzene (30:70) yielded the title compound (227 mg, 0.51 mmol, 68%): mp 227.5−228.5 °C (from *n*-hexane−EtOAc); $[\alpha]_D$ −50 ($c = 0.31$); IR 1734, 1104 cm^{-1}; ^{1}H NMR (200 MHz) 0.77 (3H, s), 0.81 (3H, s), 0.93 (3H, d, $J = 7.3$ Hz), 0.94 (3H, d, $J = 7.2$ Hz), 2.88 (1H, dd, $J = 6.8$, 6.8 Hz), 3.12 (1H, m), 3.34 (3H, s), 3.58 (1H, dd, $J = 11.2$, 4.1 Hz), 3.79 (1H, dd, $J = 11.0$, 11.0 Hz), 4.60 (1H, m); ^{13}C NMR (50.3 MHz) 12.2 (q), 14.3 (q), 16.1 (q), 17.0 (q), 20.9 (t), 27.8 (t), 28.7 (t), 31.6 (t), 32.2 (t), 34.3 (t), 34.7 (d), 35.0 (d), 35.77 (d), 35.82 (s), 36.8 (t), 39.8 (t), 41.0 (s), 44.7 (d), 45.2 (t), 54.3 (d), 55.4 (q), 56.4 (d), 61.7 (d), 65.5 (t), 79.7 (d), 83.3 (d), 109.7 (s), 201.7 (s); MS (EI) *m*/*z* (rel intensity) 444 (M^+, 9), 416 (24), 361 (37), 287 (100). Anal. Calcd for $C_{28}H_{44}O_4$: C, 75.63; H, 9.97. Found: C, 75.81; H, 10.04.

Reduction of (25*R*)-3*β*-Methoxy-5α-spirostan-23-one. Method A. To a stirred solution of (25*R*)-3*β*-methoxy-5α-spirostan-23-one (110 mg, 0.247 mmol) in ethanol (8 mL) was added in small portions $NaBH_4$ (45 mg, 1.19 mmol). The reaction mixture was stirred for 1 h, diluted with water (80 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, and evaporated. Purification of the residue by flash chromatography (hexanes−EtOAc, 90:10) gave the alcohol (23*S*,25*R*)-3*β*-methoxy-5α-spirostan-23-ol (**4**) (95 mg, 86%) and its epimer (23*R*,25*R*)-3*β*-methoxy-5α-spirostan-23-ol (**1**) (6 mg, 5%). Compound **4**: mp 207−209 °C (from *n*-hexane−EtOAc); $[\alpha]_D$ −61 ($c = 0.37$); IR 3587, 1069, 1102 cm^{-1}; ^{1}H NMR (200 MHz) 0.80 (6H, s), 0.82 (3H, d, $J = 6.4$ Hz), 0.94 (3H, d, $J = 7.0$ Hz), 3.12 (1H, m), 3.25 (1H, dd, $J = 11.0$, 11.0 Hz), 3.34 (3H, s), 3.35−3.55 (2H, m), 4.45 (1H, m); ^{13}C NMR (50.3 MHz) 12.2 (q), 14.0 (q), 16.5 (q), 20.9 (t), 27.7 (t), 28.6 (t), 30.7 (d), 31.6 (t), 32.2 (t), 34.2 (t), 34.8 (d), 35.4 (d), 35.8 (s), 36.8 (t), 38.4 (t), 40.0 (t), 40.9 (s), 44.6 (d), 54.3 (d), 55.4 (q), 56.1 (d), 61.6 (d), 65.8 (t), 66.9 (d), 79.7 (d), 81.4 (d), 110.4 (s); MS (EI) *m*/*z* (rel intensity) 446 (M^+, 7), 413 (1), 361 (100), 287 (99). Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.28; H, 10.38. Compound **1**: mp 210−211 °C (from *n*-hexane−EtOAc); $[\alpha]_D$ −77 ($c = 0.16$); IR 3597, 1100 cm^{-1}; ^{1}H NMR (200 MHz) 0.77 (3H, s), 0.79 (3H, d, $J = 6.5$ Hz), 0.80 (3H, s), 1.09 (3H, d, $J = 7.0$ Hz), 3.11 (1H, m), 3.34 (3H, s), 3.42 (1H, dd, $J = 10.6$, 10.9 Hz), 3.46 (1H, m), 3.58 (1H, m), 4.44 (1H, m); ^{13}C NMR (50.3 MHz) 12.3 (q), 16.2 (q), 16.7 (q), 16.8 (q), 20.9 (t), 24.2 (d), 27.8 (t), 28.7 (t), 32.0 (t), 32.2 (t), 34.3 (t), 35.2 (d), 35.9 (s), 36.2 (t), 36.9 (t), 39.7 (t), 40.6 (d), 40.9 (s), 44.7 (d), 54.4 (d), 55.5 (q), 56.4 (d), 64.1 (d), 66.3 (t), 70.7 (d), 79.8 (d), 81.4 (d), 108.4 (s); MS (EI) *m*/*z* (rel intensity) 446 (M^+, 1), 428 (1), 361 (13), 287 (32). Anal. Calcd for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.39; H, 10.54. **Method B.** A solution of (25*R*)-3*β*-methoxy-5α-spirostan-23-one (33 mg, 0.074 mmol) in dry THF (1 mL) was cooled to −20 °C under a nitrogen atmosphere, and L-Selectride 1.0 M in THF (0.37 mL, 0.37 mmol) was added dropwise over 10 min. The solution was stirred for 2 h at −20 °C, diluted with 2 mL of EtOAc, and quenched with 2 mL of 1 N citric acid. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and concentrated. The crude material was purified by chromatotron chromatography (hexanes−EtOAc, 90:10) to give compounds **4** (9 mg, 27%) and **1** (15 mg, 45%). **Method C.** A mixture of (25*R*)-3*β*-methoxy-5α-spirostan-23-one (705 mg, 1.58 mmol) and PtO_2 (460 mg) in glacial acetic acid (90 mL) was stirred under a hydrogen atmosphere at room temperature for 30 h. The mixture was filtered through a pad of Celite, and the residue was washed with EtOAc. The filtrate and the washing were poured into water and extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated. The crude material was purified by flash chromatography on silica gel (hexanes−EtOAc, 90:10) to give starting material (136 mg) and the epimeric alcohols **4** (242 mg, 42%) and **1** (160 mg, 28%).

(23*R*,25*R*)-3*β*-Methoxy-5α-spirostan-23-yl Methanesulfonate (2). To a stirred solution of compound **1** (74 mg, 0.161 mmol) in dry pyridine (2 mL) was added at room temperature methanesulfonyl chloride (40 μL, 0.48 mmol). After 2 h, the mixture was poured over an aqueous solution of HCl (10%) and extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, filtered, and evaporated under reduced pressure to give compound **2** (70 mg, 80%): mp 190 °C (from MeOH); $[\alpha]_D$ −61 ($c = 0.16$); IR 1372, 1344, 1182, 1172 cm^{-1}; ^{1}H NMR (500 MHz) 0.78 (3H, s), 0.80 (3H, s), 0.81 (3H, d, $J = 5.5$ Hz), 1.08 (3H, d, $J = 6.8$ Hz), 3.04 (3H, s), 3.11 (1H, m), 3.33 (3H, s), 3.44 (1H, dd = 11.2, 11.2 Hz), 3.54 (1H, m), 4.48 (1H, m), 4.62 (1H, s); ^{13}C NMR (50.3 MHz) 12.3 (q), 16.1 (q), 16.1 (q), 16.5 (q), 20.8 (t), 24.2 (d), 27.8 (t), 28.7 (t), 31.9 (t), 32.2 (t), 34.3 (t), 34.5 (t), 35.2 (d), 35.9 (s), 36.9 (t), 38.7 (q), 39.4 (t), 40.5 (d), 41.0 (s), 44.7 (d), 54.4 (d), 55.5 (q), 56.4 (d), 64.1 (d), 66.3 (t), 78.6 (d), 79.8 (d), 82.0 (d), 106.4 (s); MS (EI) *m*/*z* (rel intensity) 428 ($[M - 96]^+$, 2), 361 (14), 287 (23). Anal. Calcd for $C_{29}H_{48}O_6S$: C, 66.38; H, 9.22; S, 6.11. Found: C, 66.37; H, 9.30; S, 6.21.

(22*S*,23*S*,25*R*)-3*β*-Methoxy-16*β*,23:22,26-diepoxy-5α-cholestane (3). To a stirred solution of compound **2** (14 mg, 0.026 mmol) in CH_2Cl_2 (1.5 mL) at room temperature under nitrogen was added DIBALH in toluene (0.4 mL, 0.4 mmol). The solution was stirred at room temperature for 12 h, and the reaction was quenched by careful addition of saturated aqueous NH_4Cl. The mixture was filtered through filter paper, and the residue was washed with CH_2Cl_2. The combined filtrates were washed with brine, dried, and concentrated. The residue was purified by chromatotron chromatography (benzene−EtOAc, 97:3) to give compound **3** (10 mg, 0.023 mmol, 87%): mp 172−175 °C (from MeOH); $[\alpha]_D$ +2 ($c = 0.21$); IR 1102, 1074 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 0.72 (3H, s), 0.79 (3H, d, $J = 6.8$ Hz), 0.93 (3H, s), 1.24 (3H, d, $J = 6.8$ Hz), 3.04 (1H, m), 3.13 (1H, dd, $J = 4.8$, 2.3 Hz), 3.24 (3H, s), 3.33 (1H, dd, $J = 10.3$, 8.0 Hz), 3.53 (1H, dd, $J = 10.3$, 6.6 Hz), 3.75 (1H, ddd, $J = 7.7$, 7.7, 4.9 Hz), 4.42 (1H, m); ^{13}C NMR (125.7 MHz, C_6D_6) 12.1 (q), 14.8 (q), 18.2 (q), 18.8 (q), 21.1 (t), 25.7 (d), 28.2 (t), 28.8 (t), 29.6 (d), 31.1 (t), 32.2 (t), 34.1 (t), 34.6 (t), 34.9 (d), 35.7 (s), 36.9 (t), 40.5 (t), 41.7 (s), 44.6 (d), 52.6 (d), 54.0 (d), 54.5 (d), 55.0 (q), 70.8 (d), 72.0 (t), 72.6 (d), 75.6 (d), 79.7 (d); MS (EI) *m*/*z* (rel intensity) 430 (M^+, 2), 415 (41). Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 77.86; H, 11.01. The structure of **3** was determined by X-ray crystallography.

(23*S*,25*R*)-3*β*-Methoxy-5α-spirostan-23-yl Methanesulfonate (5). A stirred solution of compound **4** (90 mg, 0.2

(16) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1988.

mmol) in dry pyridine (3 mL) was treated for 2 h at room temperature with methanesulfonyl chloride (50 μL, 0.6 mmol), in a manner similar to that described for the preparation of **2**, to give compound **5** (100 mg, 94%): mp 173−176 °C dec (from *n*-hexane−EtOAc); $[\alpha]_D$ −37 (c = 0.33); IR 1368, 1345, 1178 cm^{-1}; ^{1}H NMR (200 MHz) 0.80 (3H, s), 0.83 (3H, s), 0.85 (3H, d, J = 7.4 Hz), 0.98 (3H, d, J = 7.0 Hz), 3.01 (3H, s), 3.12 (1H, m), 3.34 (3H, s), 3.35 (1H, dd, J = 10.0, 10.0 Hz), 3.42 (1H, m), 4.45 (1H, m), 4.61 (1H, dd, J = 5.0, 11.4 Hz); ^{13}C NMR (50.3 MHz) 12.1 (q), 13.8 (q), 16.1 (q), 16.2 (q), 20.8 (t), 27.7 (t), 28.6 (t), 31.0 (d), 31.5 (t), 32.1 (t), 34.2 (t), 35.0 (d), 35.1 (t), 35.7 (d), 35.7 (s), 36.7 (t), 38.7 (q), 39.8 (t), 41.1 (s), 44.6 (d), 54.2 (d), 55.4 (q), 56.2 (d), 61.3 (d), 65.3 (t), 74.5 (d), 79.6 (d), 81.4 (d), 107.7 (s); MS (EI) m/z (rel intensity) 428 ([M − 96]$^+$, 12), 361 (98), 287 (77). Anal. Calcd for $C_{29}H_{48}O_6S$: C, 66.38; H, 9.22; S, 6.11. Found: C, 66.22; H, 9.59; S, 5.98.

(22*S*,23*R*,25*R*)-3*β*-Methoxy-23,26-epoxy-5α-furostane (6). A stirred solution of compound **5** (46 mg, 0.087 mmol) in CH_2Cl_2 (4 mL) was treated at room temperature under nitrogen with DIBALH in toluene (0.8 mL, 0.8 mmol), in a manner similar to that described for the preparation of **3**. The residue was purified by chromatotron chromatography (benzene−EtOAc, 97:3) to give compound **6** (30 mg, 0.07 mmol, 79%): mp 98.5−100.5 °C (from MeOH); $[\alpha]_D$ −2 (c = 0.22); IR 1101, 1048 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6), 0.68 (3H, s), 0.85 (3H, d, J = 6 Hz), 0.85 (3H, s), 1.24 (3H, d, J = 6.7 Hz), 3.02 (1H, m), 3.24 (3H, s), 3.33 (1H, dd, J = 7.8, 7.8 Hz), 3.51 (1H, dd, J = 7.4, 7.4 Hz), 3.81 (1H, dd, J = 7.8, 7.8 Hz), 4.06 (1H, ddd, J = 8.3, 6.6, 6.6 Hz), 4.35 (1H, ddd, J = 4.9, 7.7, 7.7 Hz); ^{13}C NMR (125.7 MHz, C_6D_6) 12.1 (q), 16.4 (q), 17.3 (q), 20.1 (q), 20.9 (t), 28.1 (t), 28.8 (t), 32.2 (t), 32.4 (t), 34.2 (d), 34.6 (t), 35.2 (d), 35.7 (s), 37.0 (d), 37.0 (t), 38.7 (t), 39.6 (t), 41.0 (s), 44.7 (d), 54.5 (d), 55.0 (q), 56.8 (d), 66.1 (d), 74.6 (t), 79.6 (d), 81.8 (d), 83.5 (d), 92.5 (d); MS (EI) m/z (rel intensity) 431 ([M + 1]$^+$, 1), 345 (81), 287 (100), 85 (58); HRMS calcd for $C_{23}H_{37}O_2$ 345.2794, found 345.2805. Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.32; H, 10.86.

(23*S*,25*R*)-3*β*-Acetoxy-5α-spirostan-23-yl Methanesulfonate (8). A stirred solution of (23*S*,25*R*)-3*β*-acetoxy-5α-spirostan-23-ol (**7**) (60 mg, 0.13 mmol) in dry pyridine (2 mL) was treated at room temperature for 2 h with methanesulfonyl chloride (35 μL, 0.42 mmol), in a manner similar to that described for the preparation of **2**, to give compound **8** (50 mg, 69%): mp 176−178 °C dec (from MeOH); $[\alpha]_D$ −41 (c = 0.3); IR 1732, 1178 cm^{-1}; ^{1}H NMR (200 MHz) 0.83 (6H, s), 0.85 (3H, d, J = 8.0 Hz), 0.97 (3H, d, J = 7.0 Hz), 2.01 (3H, s), 3.01 (3H, s), 3.34 (1H, dd, J = 10.0, 10.0 Hz), 3.44 (1H, m), 4.44 (1H, m), 4.60 (1H, dd, J = 5.0, 11.4 Hz), 4.62 (1H, m); ^{13}C NMR (50.3 MHz) 12.2 (q), 13.8 (q), 16.2 (q), 16.3 (q), 20.9 (t), 21.4 (q), 27.4 (t), 28.4 (t), 31.1 (d), 31.6 (t), 32.1 (t), 34.0 (t), 35.1 (d), 35.2 (t), 35.5 (s), 35.9 (d), 36.7 (t), 38.9 (q), 39.8 (t), 41.2 (s), 44.6 (d), 54.1 (d), 56.2 (d), 61.4 (d), 65.4 (t), 73.6 (d), 74.7 (d), 81.5 (d), 107.8 (s), 170.6 (s); MS (EI) m/z (rel intensity) 456 ([M − 96]$^+$, 100); HRMS calcd for $C_{29}H_{44}O_4$ 456.3276, found 456.3240. Anal. Calcd for $C_{30}H_{48}O_7S$: C, 65.19; H, 8.75; S, 5.80. Found: C, 65.36; H, 8.58; S, 5.71.

(22*S*,23*R*,25*R*)-23,26-Epoxy-5α-furostan-3*β*-ol (9). A stirred solution of compound **8** (37 mg, 0.067 mmol) in CH_2Cl_2 (1 mL) was treated at room temperature under nitrogen for 5 h with DIBALH in toluene (1.1 mL, 1.1 mmol), in a manner similar to that described for the preparation of **3**. The residue was purified by chromatotron chromatography (benzene−EtOAc, 97:3) to give compound **9** (20 mg, 0.048 mmol, 72%): mp 142−144 °C (from MeOH); $[\alpha]_D$ +1 (c = 0.46); IR 3620, 1039 cm^{-1}; ^{1}H NMR (500 MHz), 0.78 (3H, s), 0.81 (3H, s), 1.04 (3H, d, J = 6.6 Hz), 1.06 (3H, d, J = 6.7 Hz), 1.75 (1H, m), 1.93 (1H, m), 2.00 (1H, m), 2.13 (1H, m), 2.31 (1H, m), 3.34 (1H, dd, J = 8.2, 8.2 Hz), 3.43 (1H, dd, J = 5.5, 8.4 Hz), 3.59 (1H, m), 3.88 (1H, dd, J = 8.2, 8.1 Hz), 3.93 (1H, ddd, J = 5.8, 5.8, 9.1 Hz), 4.35 (1H, dd, J = 5.1, 5.1, 7.8 Hz); ^{13}C NMR (125.7 MHz) 12.3 (q), 16.5 (q), 17.3 (q), 19.8 (q), 20.8 (t), 28.6 (t), 29.7 (t), 32.2 (2 × t), 34.3 (d), 35.3 (d), 35.5 (s), 36.0 (d), 36.8 (t), 37.0 (t), 38.2 (t), 39.6 (t), 41.1 (s), 44.8 (d), 54.3 (d), 56.8 (d), 65.5 (d), 71.2 (d), 74.7 (t), 81.2 (d), 83.7 (d), 91.3 (d); MS (EI) m/z (rel intensity) 416 (M$^+$, 0.1), 331 ([M − 85]$^+$, 45); HRMS calcd for $C_{27}H_{44}O_3$ 416.3290, found 416.3295. Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.84; H, 10.64. Found: C, 77.71; H, 10.72.

(22*S*,23*R*,25*R*)-23,26-Epoxy-5α-furostan-3*β*-yl *p*-Bromobenzoate (10). To a stirred solution of compound **9** (12 mg, 0.03 mmol) in CH_2Cl_2 (0.7 mL) and pyridine (15 μL) was added *p*-bromobenzoyl chloride (20 mg, 0.09 mmol). The solution was stirred at room temperature for 14 h, and then the mixture was poured over an aqueous solution of HCl (10%) and extracted with EtOAc. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and evaporated under reduced pressure to give compound **10** (17 mg, 0.028 mmol, 95%): mp 179.5−181.5 °C (from EtOAc); ^{1}H NMR (500 MHz) 0.75 (3H, s), 0.83 (3H, s), 1.00 (3H, d, J = 6.6 Hz), 1.03 (3H, d, J = 6.7 Hz), 3.30 (1H, dd, J = 8.2, 8.2 Hz), 3.39 (1H, dd, J = 6.0, 8.0 Hz), 3.84 (1H, dd, J = 7.4, 7.4 Hz), 3.92 (1H, m), 4.32 (1H, ddd, J = 7.7, 7.7, 7.7 Hz), 4.88 (1H, m), 7.54 (2H, d, J = 6.8 Hz), 7.86 (2H, d, J = 6.7 Hz); ^{13}C NMR (50.3 MHz, C_6D_6) 12.3 (q), 16.7 (q), 17.6 (q), 20.4 (q), 21.1 (t), 27.8 (t), 28.7 (t), 32.3 (t), 32.7 (t), 34.4 (t), 34.6 (d), 35.4 (d), 35.6 (s), 36.8 (t), 37.3 (d), 39.1 (t), 39.8 (t), 41.3 (s), 44.7 (d), 54.3 (d), 56.9 (d), 66.4 (d), 74.6 (d), 75.0 (t), 82.2 (d), 83.8 (d), 92.9 (d), 165.1 (s), aromatic carbons not observed. Anal. Calcd for $C_{34}H_{47}BrO_4$: C, 68.10; H, 7.90. Found: C, 68.24; H, 7.83. The structure of **10** was determined by X-ray crystallography.

(22*S*,23*R*,25*R*)-3*β*-Methoxy-5α-furostane-23,26-diol (11). To a solution of **1** (72 mg, 0.16 mmol) in dry CH_2Cl_2 (2 mL) were added diphenylsilane (75 μL, 0.40 mmol) and titanium tetrachloride (45 μL, 0.40 mmol). The mixture was stirred for 45 min at room temperature. The reaction was quenched by addition of 5 mL of 1 N HCl, and the resultant solution was extracted with $CHCl_3$. The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated under vacuum. Chromatotron chromatography (hexanes−EtOAc, 70:30) of the residue gave compound **11** (57 mg, 79%): mp 144.5−146.5 °C (from *n*-hexane−EtOAc); $[\alpha]_D$ −12 (c = 0.16); IR ($CHCl_3$) 3570, 3400, 1095 cm^{-1}; ^{1}H NMR (500 MHz) 0.77 (3H, s), 0.78 (3H, s), 0.90 (3H, d, J = 6.8 Hz), 1.04 (3H, d, J = 6.7 Hz), 3.09 (1H, m), 3.30 (3H, s), 3.33 (1H, dd, J = 8.3, 4.1 Hz), 3.38 (1H, dd, J = 10.8, 7.4 Hz), 3.56 (1H, dd, J = 10.8, 4.3 Hz), 3.87 (1H, m), 4.32 (1H, ddd, J = 7.8, 7.8, 5.2 Hz); ^{13}C NMR (50.3 MHz) 12.3 (q), 16.5 (q), 18.0 (q), 20.6 (q), 20.8 (t), 27.8 (t), 28.7 (t), 32.1 (t), 32.2 (t), 32.5 (d), 34.3 (t), 34.7 (t), 35.1 (d), 35.9 (s), 36.9 (t), 38.5 (t), 39.5 (t), 41.4 (s), 44.8 (d), 54.4 (d), 55.5 (q), 56.8 (d), 66.0 (d), 68.7 (t), 71.6 (d), 79.8 (d), 83.3 (d), 92.8 (d); MS (EI) m/z (rel intensity) 345 ([M − 103]$^+$, 40), 287 (100); HRMS calcd for $C_{23}H_{37}O_2$ 345.2793, found 345.2774. Anal. Calcd for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 74.93; H, 10.82.

(22*S*,23*R*,25*R*)-3*β*-Methoxy-23,26-epoxy-5α-furostane (6). A mixture of compound **11** (25 mg, 0.05 mmol), triphenylphosphine (22 mg, 0.08 mmol), imidazole (12 mg, 0.17 mmol), and iodine (21 mg, 0.08 mmol) in toluene (2 mL) was vigorously stirred at 70 °C for 3 h. The reaction mixture was cooled and quenched by addition of a saturated aqueous solution of $NaHCO_3$ (2 mL), and the mixture was stirred for 5 min. Iodine was added in portions. When the toluene phase remained iodine-colored it was stirred for an additional 10 min. Excess iodine was removed by addition of aqueous sodium thiosulfate. The organic layer was diluted with toluene, washed with water, dried over Na_2SO_4, and evaporated under vacuum. Chromatotron chromatography (hexanes−EtOAc, 93:7) of the residue gave a product in all aspects identical to compound **6** (12 mg, 50%) prepared from **5**.

(22*S*,23*S*,25*R*)-3*β*-Methoxy-5α-furostane-23,26-diol (12). Method A. Compound **4** (56 mg, 0.125 mmol) in dry CH_2Cl_2 (2 mL) was treated at room temperature for 28 h with a 1 M solution of DIBALH in toluene (2.38 mL, 2.38 mmol), in a manner similar to that described for the preparation of **3**. Chromatotron chromatography (hexanes−EtOAc, 70:30) of the residue gave starting material **4** (23 mg, 41%) and compound **12** (25 mg, 45%): mp 83−84 °C (from *n*-hexane−EtOAc); $[\alpha]_D$ −14 (c = 0.15); IR ($CHCl_3$) 3580, 3444, 1102 cm^{-1}; ^{1}H NMR (500 MHz) 0.79 (3H, s), 0.80 (3H, s), 0.96 (3H, d, J = 6.9 Hz),

1.04 (3H, d, J = 6.8 Hz), 3.12 (1H, m), 3.32 (1H, dd, J = 5.0, 8.2 Hz), 3.34 (3H, s), 3.50 (1H, dd, J = 10.8, 6.6 Hz), 3.56 (1H, dd, J = 10.8, 4.6 Hz), 3.75 (1H, m), 4.36 (1H, ddd, J = 7.8, 7.8, 5.1 Hz); ^{13}C NMR (50.3 MHz) 12.3 (q), 16.4 (q), 17.4 (q), 19.7 (q), 20.8 (t), 27.8 (t), 28.7 (t), 32.2 (2 × t), 32.5 (d), 33.7 (d), 34.3 (t), 35.2 (d), 35.9 (s), 36.9 (t), 38.6 (t), 39.5 (t), 41.3 (s), 44.8 (d), 54.4 (d), 55.5 (q), 56.8 (d), 65.6 (d), 67.6 (t), 69.8 (d), 79.8 (d), 83.6 (d), 92.6 (d); MS (EI) m/z (rel intensity) 430 ([M − 18]$^+$, 2), 345 (18), 287 (100); HRMS calcd for $C_{28}H_{46}O_3$ 430.3447, found 430.3423. Anal. Calcd for $C_{28}H_{48}O_4$: C, 74.95; H, 10.78. Found: C, 75.31; H, 11.01. **Method B.** To a solution of **4** (43 mg, 0.096 mmol) in dry CH_2Cl_2 (1 mL) were added at −25 °C diphenylsilane (45 μL, 0.24 mmol) and titanium tetrachloride (27 μL, 0.24 mmol). The mixture was stirred for 1.5 h at this temperature. The reaction was quenched by addition of 5 mL of 1 N HCl, and the resultant solution was extracted with $CHCl_3$. The organic layers were combined, washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated under vacuum. Chromatotron chromatography (hexanes−EtOAc, 70:30) of the residue gave compound **12** (34 mg, 78%).

(22*S*,23*S*,25*R*)-3β-Methoxy-23,26-epoxy-5α-furostane (13). A mixture of compound **12** (49 mg, 0.11 mmol), triphenylphosphine (42 mg, 0.16 mmol), imidazole (23 mg, 0.38 mmol), and iodine (39 mg, 0.15 mmol) in toluene (2 mL) was vigorously stirred at 70 °C for 3.5 h in a manner similar to that described above for **6**. Chromatotron chromatography (hexanes−EtOAc, 93:7) of the residue gave compound **13** (30 mg, 63%): mp 108−109.5 °C (from *n*-hexane); $[\alpha]_D$ −9 (c = 0.17); IR 1100 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) 0.74 (3H, s), 0.90 (3H, d, J = 6.8 Hz), 1.04 (3H, s), 1.06 (3H, d, J = 6.8 Hz), 3.08 (1H, m), 3.30 (3H, s), 3.35 (1H, dd, J = 7.8, 6.3 Hz), 3.38 (1H, dd, J = 11.6, 3.1 Hz), 4.08 (1H, dd, J = 7.8, 6.6 Hz), 4.18 (1H, ddd, J = 8.8, 5.9, 3.1 Hz), 4.35 (1H, ddd, J = 7.8, 7.8, 5.2 Hz); ^{13}C NMR (125.7 MHz, C_6D_6) 12.1 (q), 16.4 (q), 17.8 (q), 18.9 (q), 20.9 (t), 28.1 (t), 28.8 (t), 32.3 (t), 32.4 (t), 33.1 (d), 33.4 (d), 34.6 (t), 35.1 (d), 35.8 (s), 36.7 (t), 37.0 (t), 39.9 (t), 41.4 (s), 44.7 (d), 54.5 (d), 55.0 (q), 56.8 (d), 65.6 (d), 75.2 (t), 77.4 (d), 79.6 (d), 83.2 (d), 93.3 (d); MS (EI) m/z (rel intensity) 415 ([M − 15]$^+$, <1), 345 (50), 287 (100); HRMS calcd for $C_{27}H_{43}O_3$ 415.3212, found 415.3197. Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 78.08; H, 10.98.

(25*R*)-3β-Acetoxyspirost-5-en-23-one. To a solution of (25*R*)-3β-acetoxyspirost-5-ene (diosgenin acetate) (6.2 g, 13.6 mmol) in glacial acetic acid (114 mL) were added BF_3·Et_2O (4 mL, 32.6 mmol) and $NaNO_2$ (3.91 g, 56.7 mmol) in portions every 15 min. After 2 h the mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residue was dissolved in hexanes−benzene (1:1) and kept adsorbed on neutral alumina (activity II/III) on a chromatographic column for 3 h. Elution with benzene gave the title compound (3.85 g, 8.19 mmol, 60%): mp 187.5−189 °C (from MeOH); $[\alpha]_D$ −94 (c = 0.24); IR ($CHCl_3$) 3020, 1727, 1253 cm^{-1}; ^{1}H NMR (200 MHz) 0.75 (3H, s), 0.88 (3H, s), 0.91 (3H, s), 0.99 (3H, s), 1.99 (3H, s), 2.84 (1H, m), 3.54 (1H, dd, J = 4.3, 11.1 Hz), 3.75 (1H, dd, J = 11.0, 11.0 Hz), 4.45−4.63 (2H, m), 5.32 (1H, m); ^{13}C NMR (50.3 MHz) 14.35 (q), 16.0 (q), 17.1 (q), 19.3 (q), 20.7 (t), 21.4 (q), 27.7 (t), 31.3 (d), 31.8 (t), 32.0 (t), 34.7 (d), 35.8 (d), 36.7 (s), 36.9 (t), 38.1 (t), 39.5 (t), 40.7 (s), 45.2 (t), 49.9 (d), 56.5 (d), 61.6 (d), 65.6 (t), 73.9 (d), 83.3 (d), 109.8 (s), 122.1 (d), 139.8 (s), 170.4 (s), 201.7 (s); MS (EI) m/z (rel intensity) 471 ([M + H]$^+$, 9), 442 (80), 387 (100), 327 (98), 253 (100); HRMS calcd for $C_{29}H_{42}O_5$ 470.3032, found 470.3030. Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 74.14; H, 9.04.

(22*S*,23*R*,25*R*)-3β-Acetoxy-16β,23:23,26-diepoxycholest-5-en-22-one. To a solution of (25*R*)-3β-acetoxyspirost-5-en-23-one (23-oxodiosgenin acetate) (46 mg, 0.099 mmol) in dry CH_2Cl_2 (2 mL) was slowly added at room temperature under nitrogen $TiCl_4$ (0.027 mL, 0.247 mmol) and stirred for 30 min at this temperature. The reaction was poured into an aqueous saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Chromatotron chromatography (hexanes−EtOAc, 90:10) of the residue yielded the title compound (44 mg, 0.094 mmol, 95%): mp 161−163 °C (from MeOH); $[\alpha]_D$ +44 (c = 0.342); IR 1736, 1243, 1033 cm^{-1}; ^{1}H NMR (200 MHz) 0.98 (3H, s), 1.04 (3H, s), 1.04 (3H, d, J = 6.6 Hz), 1.09 (3H, d, J = 6.4 Hz), 2.02 (3H, s), 2.79 (1H, m), 3.53 (1H, dd, J = 8.6, 8.6 Hz), 4.12 (1H, dd, J = 7.5, 7.5 Hz), 4.37 (1H, ddd, J = 8.0, 8.0, 8.0 Hz), 4.58 (1H, m), 5.36 (1H, m); ^{13}C NMR (50,3 MHz) 12.8 (q), 14.4 (q), 16.4 (q), 19.2 (q), 20.7 (t), 21.2 (q), 27.5 (t), 31.3 (d), 31.8 (t), 32.8 (t), 33.2 (d), 36.4 (s), 36.7 (t), 37.9 (t), 39.4 (t), 39.7 (d), 42.4 (s), 43.7 (t), 49.6 (d), 53.0 (d), 57.2 (d), 72.6 (d), 73.6 (d), 75.1 (t), 107.7 (s), 122.0 (d), 139.5 (s), 170.2 (s), 212.8 (s); m/z (rel intensity) 471 ([M + H]$^+$, 3), 440 (2), 282 (100), 253 (38); HRMS calcd for $C_{28}H_{40}O_4$ 440.2928 found 440.2927. Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 73.96; H, 9.10.

Reduction of (22*S*,23*R*,25*R*)-3β-Acetoxy-16β,23:23,26-diepoxycholest-5-en-22-one. To a solution of (22*S*,23*R*,25*R*)-3β-acetoxy-16β,23:23,26-diepoxycholest-5-en-22-one (888 mg, 1.89 mmol) in ethanol (65 mL) was added $NaBH_4$ (286 mg, 7.56 mmol). After 10 min of stirring at room temperature the mixture was poured into aqueous HCl 10% and extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Chromatotron chromatography (benzene−EtOAc, 90:10) of the residue gave (22*R*,23*R*,25*R*)-3β-acetoxy-16β,23:23,26-diepoxycholest-5-en-22-ol (**14**) (588 mg, 1.24 mmol, 66%) and (22*S*,23*R*,25*R*)-3β-acetoxy-16β,23:23,26-diepoxycholest-5-en-22-ol (**18**) (167 mg, 0.354 mmol, 19%). Compound **14**: mp 196.5−199 °C (from MeOH); $[\alpha]_D$ −96 (c = 0.236); IR 3620, 3554, 1733, 1243 cm^{-1}; ^{1}H NMR (200 MHz) 0.84 (3H, s), 1.01 (3H, d, J = 6.4 Hz), 1.03 (3H, s), 1.04 (3H, d, J = 7.2 Hz), 2.02 (3H, s), 2.60 (1H, dd, J = 8.4, 12.8 Hz), 3.43 (1H, dd, J = 8.2, 10.4 Hz), 3.53 (1H, dd, J = 1.7, 11.9 Hz), 3.90 (1H, dd, J = 7.4, 7.4 Hz), 4.20 (1H, ddd, J = 5.3, 7.7, 7.7 Hz), 4.59 (1H, m), 5.36 (1H, m); ^{13}C NMR (50.3 MHz) 14.8 (q), 15.9 (q), 16.9 (q), 19.3 (q), 20.7 (t), 21.4 (q), 27.7 (t), 31.0 (d), 31.3 (d), 31.9 (t), 33.6 (t), 34.8 (d), 36.6 (s), 37.0 (t), 38.1 (t), 39.9 (t), 40.4 (t), 41.5 (s), 50.0 (d), 53.7 (d), 60.1 (d), 71.6 (d), 73.4 (t), 73.9 (d), 76.0 (d), 112.2 (s), 122.3 (d), 139.7 (s), 170.5 (s); MS (EI) m/z (rel intensity) 472 (M$^+$, 1), 454 (2), 412 (18); HRMS calcd for $C_{29}H_{44}O_5$ 472.3189, found 472.3181. Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.51; H, 9.34. Compound **18**: mp 185−186 °C (from MeOH); $[\alpha]_D$ −104 (c = 0.14); IR 3554, 1732, 1244 cm^{-1}; ^{1}H NMR (200 MHz) 0.80 (3H, s), 1.03 (3H, d, J = 6.4 Hz), 1.04 (3H, s), 1.15 (3H, d, J = 6.8 Hz), 2.03 (3H, s), 3.04 (1H, s), 3.46 (1H, d, J = 1.6 Hz), 3.56 (1H, dd, J = 7.5, 10.1 Hz), 3.98 (1H, dd, J = 7.5, 7.5 Hz), 4.33 (1H, ddd, J = 5.5, 7.7, 7.7 Hz), 4.60 (1H, m), 5.38 (1H, m); ^{13}C NMR (50.3 MHz) 14.6 (q), 15.5 (q), 17.9 (q), 19.3 (q), 20.7 (t), 21.3 (q), 27.7 (t), 29.4 (d), 31.3 (d), 31.9 (t), 33.6 (t), 33.8 (d), 36.6 (s), 36.9 (t), 38.0 (t), 39.9 (t), 40.9 (s), 45.1 (t), 50.0 (d), 52.9 (d), 53.1 (d), 73.1 (d), 73.8 (d), 74.0 (t), 76.2 (d), 108.2 (s), 122.3 (d), 139.6 (s), 170.3 (s); MS (EI) m/z (rel intensity) 473 ([M + H]$^+$, 37), 472 (M$^+$, 4), 454 (2), 412 (62); HRMS calcd for $C_{29}H_{44}O_5$ 472.3188, found 472.3148. Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.53; H, 9.44.

(22*R*,23*R*,25*R*)-3β-Acetoxy-16β,23:23,26-diepoxycholest-5-en-22-yl Methanesulfonate (15). A solution of the β-alcohol **14** (140 mg, 0.297 mmol) in dry pyridine (4 mL) was treated at room temperature for 12 h with methanesulfonyl chloride (0.069 mL, 0.189 mmol), in a manner similar to that described for the preparation of **2**, to give compound **15** (163 mg, 0.296 mmol, 100%): mp 173.5−174.5 °C (from MeOH); $[\alpha]_D$ −97 (c = 0.18); IR 1734, 1366, 1180, 1244 cm^{-1}; ^{1}H NMR (200 MHz) 0.84 (3H, s), 1.03 (3H, s), 1.04 (3H, d, J = 6.2 Hz), 1.10 (3H, d, J = 6.6 Hz), 2.02 (3H, s), 2.60 (1H, dd, J = 8.9, 13.2 Hz), 3.04 (3H, s), 3.43 (1H, dd, J = 8.5, 10.4 Hz), 3.91 (1H, dd, J = 7.7, 7.7 Hz), 4.23 (1H, ddd, J = 5.2, 7.8, 7.8 Hz), 4.48 (1H, d, J = 12.1 Hz), 4.61 (1H, m), 5.36 (1H, m); ^{13}C NMR (50.3 MHz) 14.6 (q), 16.0 (q), 16.5 (q), 19.2 (q), 20.6 (t), 21.3 (q), 27.6 (t), 30.8 (d), 31.2 (d), 31.8 (t), 33.3 (t), 34.0 (d), 36.5 (s), 36.8 (t), 38.0 (t), 38.4 (q), 39.7 (t), 41.1 (t), 41.6 (s), 49.8 (d), 53.6 (d), 59.7 (d), 71.7 (d), 73.2 (t), 73.7 (d), 86.3 (d), 109.8 (s), 122.1 (d), 139.6 (s), 170.4 (s); MS (EI) m/z (rel intensity)

490 (2), 454 (18), 412 (2), 394 (4), 313 (52), 253 (100); HRMS calcd for $C_{29}H_{42}O_4$ 454.3083, found 454.3074. Anal. Calcd for $C_{30}H_{46}O_7S$: C, 65.42; H, 8.42; S, 5.82. Found: C, 65.61; H, 8.57; S, 6.07.

Reduction of (22*R*,23*R*,25*R*)-3*β*-Acetoxy-16*β*,23:23,26-diepoxycholest-5-en-22-yl Methanesulfonate (15). The *β*-mesyl derivative **15** (50 mg, 0.091 mmol) in dry CH_2Cl_2 (3 mL) was treated at room temperature for 2.5 h with a 1 M solution of DIBALH in toluene (0.637 mL, 0.637 mmol), in a manner similar to that described for the preparation of **3**. The residue was treated with acetic anhydride (0.5 mL) and pyridine (2 mL) and stirred at room temperature for 12 h. The mixture was then poured into an aqueous solution of 10% HCl and extracted with CH_2Cl_2. The organic layer was washed with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, and evaporated under vacuum. Chromatotron chromatography (benzene−EtOAc, 99:1) of the residue gave (22*S*,23*S*,25*R*)-3*β*-acetoxy-16*β*,23:22,26-diepoxycholest-5-ene (**16**) (23 mg, 0.05 mmol, 55%) and (22*S*,23*R*,25*R*)-3*β*-acetoxy-16*β*,23:22,26-diepoxycholest-5-ene (**17**) (4.1 mg, 0.009 mmol, 10%). Compound **16**: mp 166−169 °C (from MeOH); $[\alpha]_D$ −57 (*c* = 0.14); IR 1732, 1245 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) 0.79 (3H, d, *J* = 6.6 Hz), 0.89 (3H, s), 0.91 (3H, s), 1.23 (3H, d, *J* = 6.8 Hz), 1.75 (3H, s), 3.10 (1H, dd, *J* = 2.1, 4.7 Hz), 3.33 (1H, dd, *J* = 8.0, 10.2 Hz), 3.51 (1H, dd, *J* = 6.7, 10.2 Hz), 3.72 (1H, ddd, *J* = 4.8, 7.6, 7.6 Hz), 4.38 (1H, ddd, *J* = 7.1, 7.1, 7.1 Hz), 4.83 (1H, m), 5.29 (1H, m); ^{13}C NMR (50.3 MHz, C_6D_6) 14.5 (q), 18.1 (q), 19.0 (q), 19.3 (q), 20.7 (t), 21.4 (q), 25.8 (d), 27.7 (t), 29.2 (d), 30.6 (t), 31.2 (d), 32.0 (t), 33.9 (t), 36.7 (s), 36.9 (t), 38.1 (t), 40.0 (t), 41.4 (s), 50.0 (d), 52.5 (d), 53.3 (d), 70.8 (d), 72.3 (t), 73.0 (d), 73.9 (d), 75.6 (d), 122.4 (d), 139.7 (s), 170.5 (s); MS (EI) *m*/*z* (rel intensity) 456 (M^+, 1), 455 (3), 396 (71), 381 (22), 288 (15); HRMS calcd for $C_{27}H_{40}O_2$ 396.3028, found 396.3047. Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.32; H, 9.82. The structure of **16** was determined by X-ray crystallography. Compound **17**: mp 171−176 °C (from MeOH); IR 1736, 1246 cm^{-1}; ^1H NMR (200 MHz) 0.89 (3H, s), 1.04 (3H, s), 1.09 (3H, d, *J* = 7.1 Hz), 1.10 (3H, d, *J* = 7.2 Hz), 2.02 (3H, s), 3.27 (1H, dd, *J* = 5.7, 9.7 Hz), 3.47 (1H, ddd, *J* = 4.7, 10.9, 10.9 Hz), 3.56 (1H, dd, *J* = 2.3, 11.0 Hz), 3.65 (1H, d, *J* = 11.1 Hz), 4.21 (1H, ddd, *J* = 3.7, 7.6, 7.6 Hz), 4.60 (1H, m), 5.36 (1H, m); ^{13}C NMR (50.3 MHz) 15.4 (q), 16.0 (q), 17.5 (q), 19.3 (q), 20.3 (t), 21.4 (q), 27.7 (t), 29.2 (d), 30.0 (d), 31.3 (d), 31.8 (t), 33.8 (t), 35.8 (t), 36.8 (s), 37.0 (t), 37.4 (t), 38.1 (t), 42.0 (s), 50.6 (d), 54.0 (d), 60.0 (d), 65.4 (d), 72.6 (t), 73.9 (d), 75.6 (d), 79.4 (d), 122.4 (d), 139.8 (s), 170.5 (s); MS (EI) *m*/*z* (rel intensity) 455 ($[M - H]^+$, 1), 396 (100), 381 (11); HRMS calcd for $C_{27}H_{40}O_2$ 396.3028, found 396.3043. Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.21; H, 9.68. The structure of **17** was determined by X-ray crystallography.

(22*S*,23*R*,25*R*)-3*β*-Acetoxy-16*β*,23:23,26-diepoxycholest-5-en-22-yl Methanesulfonate (19). A solution of the α-alcohol (**18**) (110 mg, 0.233 mmol) in dry pyridine (3 mL) was treated at room temperature for 5 h with methanesulfonyl chloride (0.072 *μ*L, 0.932 mmol), in a manner similar to that described for the preparation of **2**. Chromatotron chromatography (hexanes−EtOAc, 90:10) of the residue gave compound **19** (103 mg, 0.187 mmol, 80%): mp 168−169 °C (from MeOH); $[\alpha]_D$ −86 (*c* = 0.14); IR 1734, 1353, 1175, 1240 cm^{-1}; ^1H NMR (200 MHz) 0.79 (3H, s), 1.02 (3H, s), 1.02 (3H, d, *J* = 6.4 Hz), 1.15 (3H, d, *J* = 6.7 Hz), 2.02 (3H, s), 3.09 (3H, s), 3.53 (1H, dd, *J* = 8.1, 9.9 Hz), 3.95 (1H, dd, *J* = 7.4, 7.4 Hz), 4.27 (1H, ddd, *J* = 5.5, 7.6, 7.6 Hz), 4.57 (1H, d, *J* = 1.7 Hz), 4.59 (1H, m), 5.36 (1H, m); ^{13}C NMR (50.3 MHz) 14.5 (q), 15.5 (q), 17.5 (q), 19.3 (q), 20.7 (t), 21.4 (q), 27.7 (t), 29.3 (d), 31.3 (d), 31.9 (t), 33.4 (t), 33.4 (d), 36.6 (s), 36.9 (t), 38.0 (t), 38.9 (q), 39.7 (t), 41.1 (s), 45.9 (t), 49.9 (d), 53.0 (d), 53.4 (d), 73.2 (d), 73.8 (d), 74.2 (t), 87.3 (d), 107.1 (s), 122.2 (d), 139.7 (s), 170.4 (s); MS (EI) *m*/*z* (rel intensity) 490 (6), 454 (69), 439 (4), 313 (98), 253 (100); HRMS calcd for $C_{29}H_{42}O_4$ 454.3083, found 454.3083. Anal. Calcd for $C_{30}H_{46}O_7S$: C, 65.42; H, 8.42; S, 5.82. Found: C, 65.65; H, 8.60; S, 5.95.

Reduction of (22*S*,23*R*,25*R*)-3*β*-Acetoxy-16*β*,23:23,26-diepoxycholest-5-en-22-yl Methanesulfonate (19). The α-mesyl derivative **19** (90 mg, 0.164 mmol) in dry CH_2Cl_2 (3 mL) was treated at room temperature for 8 h with a 1 M solution of DIBALH in toluene (1.4 mL, 1.4 mmol), in a manner similar to that described for the preparation of **3**. The residue was treated with acetic anhydride (0.5 mL) and pyridine (2 mL) and stirred at room temperature for 12 h. The mixture was then poured into an aqueous solution of 10% HCl and extracted with CH_2Cl_2. The organic layer was washed with an aqueous saturated solution of $NaHCO_3$, dried over Na_2SO_4, and evaporated under vacuum. Chromatotron chromatography (benzene−EtOAc, 97:3) of the residue gave (22*R*,23*R*,25*R*)-3*β*-acetoxy-23,26-epoxyfurost-5-ene (**20**) (23.2 mg, 0.051 mmol, 31%) and (22*S*,23*S*)-3*β*,22-diacetoxy-16*β*,23-epoxycholest-5-ene (**21**) (25.4 mg, 0.051 mmol, 31%). Compound **20**: mp 157−160 °C (from MeOH); $[\alpha]_D$ −35 (*c* = 0.1); IR 1737, 1246 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) 0.86 (3H, s), 0.87 (3H, d, *J* = 6.2 Hz), 0.88 (3H, s), 1.23 (3H, d, *J* = 7.0 Hz), 1.72 (1H, dd, *J* = 8.5, 8.5 Hz), 1.75 (3H, s), 1.90 (1H, dd, *J* = 4.8, 8.1 Hz), 1.98−2.12 (2H, m), 2.39−2.45 (2H, m), 2.48 (1H, br dd, *J* = 3.0, 12.6 Hz), 3.35 (1H, dd, *J* = 8.2, 8.2 Hz), 3.82 (1H, dd, *J* = 7.4, 7.4 Hz), 3.92 (1H, ddd, *J* = 2.0, 8.0, 8.0 Hz), 4.00 (1H, dd, *J* = 1.7, 7.7 Hz), 4.81−4.87 (2H, m), 5.28 (1H, m); ^{13}C NMR (50,3 MHz) 14.6 (q), 16.8 (q), 17.4 (q), 19.3 (q), 20.7 (t), 21.4 (q), 27.7 (t), 31.0 (d), 32.1 (t), 33.8 (t), 34.3 (d), 34.6 (d), 36.7 (s), 37.0 (t), 37.2 (t), 38.1 (t), 39.4 (t), 40.9 (s), 50.1 (d), 55.5 (d), 65.0 (d), 73.9 (d), 74.6 (t), 80.1 (d), 83.3 (d), 86.8 (d), 122.4 (d), 139.6 (s), 170.5 (s); MS (EI) *m*/*z* (rel intensity) 457 ($[M + H]^+$, 2), 396 (28), 371 (50), 313 (100), 253 (69); HRMS calcd for $C_{27}H_{40}O_2$ 396.3028, found 396.3038. Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.35; H, 9.69. The structure of **20** was determined by X-ray crystallography. Compound **21**: mp 157.5−160 °C (from MeOH); $[\alpha]_D$ −42 (*c* = 0.07); IR 1742, 1249 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 0.84 (3H, s), 0.93 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 0.98 (3H, d, *J* = 7.2 Hz), 1.05 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 4.00 (1H, dd, *J* = 6.2, 6.2 Hz), 4.55−4.69 (2H, m), 5.05 (1H, ddd, *J* = 4.0, 6.0, 9.4 Hz), 5.38 (1H, m); ^{13}C NMR (200 MHz) 14.7 (q), 16.2 (q), 19.3 (q), 20.7 (t), 21.4 (q), 21.6 (q), 22.1 (q), 23.3 (q), 24.5 (d), 27.7 (t), 31.0 (d), 32.0 (t), 33.6 (t), 34.8 (d), 36.7 (s), 37.0 (t), 38.1 (t), 39.5 (t), 40.9 (t), 50.0 (d), 55.5 (d), 64.9 (d), 72.5 (d), 73.8 (d), 83.2 (d), 84.8 (d), 122.3 (d), 139.7 (s), 170.5 (s), 170.6 (s); the C-13 (s) could not be observed; MS (EI) *m*/*z* (rel intensity) 501 ($[M + H]^+$, 4), 440 (45), 397 (26), 380 (27), 371 (100), 313 (100), 253 (100). Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66. Found: C, 74.38; H, 9.74.

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Supporting Information Available: Supporting Information Available: X-ray structural data for compounds **3**, **10**, **16**, **17**, and **20**, including tables of atomic coordinates, bond lengths, and bond angles (32 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.

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