Efficient Route to 7α-(Benzoyloxy)-3-dioxolane Cholestan-24(*R*)-ol, a Key Intermediate in the Synthesis of Squalamine

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Introduction

Squalamine (**1**) is a novel aminosterol isolated from the dogfish shark,[1] which has been shown to possess antiangiogenic and antitumor activity.[2] Until the present time, the only practical way to obtain significant quantities of squalamine was by extraction from shark livers. However, squalamine is obtained in small amounts (0.001−0.002 wt %) at significant expense in time and materials. There have been three published syntheses of squalamine. Two lengthy syntheses (17 steps) begin with 5-cholenic acid, which is expensive and not readily available.[3] In these reports, squalamine was obtained as an equal mixture of C24-stereoisomers. A formal stereoselective synthesis[4] of squalamine was achieved from stigmasterol (**2**). Sixteen steps were required to prepare the steroid **3**, which is of similar complexity to steroid **4** described in this paper (10 steps) (Chart 1).

Methodologies have been developed to prepare less complex analogues of squalamine[5] and to synthesize squalamine from less expensive starting materials.[6] In the latter report, a new stereoselective method of introducing the steroidal side chain on a model system, lacking a C-7 hydroxyl group, was described. We now report the application of this method to the synthesis of the advanced intermediate **4**, which is suitable for synthesis of squalamine. This intermediate contains oxygenation at C-7 and C-24 in the proper orientation, with the C-24 hydroxyl group selectively available for sulfation. Liberation of ketone function at C-3 allows for reductive amination with a protected spermidine reagent. Removal of protecting groups on the polyamine and C-7 hydroxyl would provide squalamine.

Results and Discussion

The synthetic route from the inexpensive plant sterol stigmasterol **2** is depicted in Scheme 1. Allylic oxidation at the C-7 position was accomplished using *N*-hydroxyphthalimide-catalyzed air oxidation with benzoyl peroxide as the free radical initiator.[7] The resulting C-7 hydroperoxide was dehydrated to the ketone with copper(II) chloride in pyridine to afford **5** in good yield. This allylic oxidation method was chosen because of its good yield (82%) and its environmentally friendly nature (no chromium).[3,4] The Δ^5 double bond of **5** was selectively reduced by conjugate reduction with lithium in ammonia. As with previous squalamine syntheses, K-selectride was used to reduce the 7-ketone (**6**) to a 7α-hydroxyl group (**7**).[3,8]

The following step involves selective oxidation of the C-3 hydroxyl group in **7**. Silver carbonate on Celite selectively oxidizes the 3-position of sterols containing other more hindered hydroxyl substituents.[9] The C-7 hydroxy group was protected as a benzoate ester and the C-3 ketone was protected as the 1,3-dioxolane, in preparation for generation of a second carbonyl function. The aldehyde **11** was prepared by ozonolysis of the stigmasterol side chain, followed by reduction with trimethyl phosphite.[10] Wittig olefination with diethyl phosphono 3-methyl-2-butanone **12**[11,12] was achieved in excellent yield without epimerizing the C-21 methyl group to deliver the enone **13**.

The crucial step in the synthesis is the stereoselective reduction of the C-24 ketone to provide the C-24 alcohol with the correct natural orientation. (*R*)-MeCBS reagent has been demonstrated to reduce a cholest-22-en-24-one model system to afford the 24*S*-allylic alcohol (94−98% de), which becomes the 24*R*-saturated alcohol after hydrogenation of the C-22 double bond.[6] Enone **13**, which contains an additional C-7 benzoyloxy group, was also expected to be reduced stereoselectively. Using conditions optimized for the model system, steroid **14** was obtained in 94% yield with a de of 91%. The slightly depressed stereoselectivity is probably due to competition between the benzoate and the enone for binding to the borane−catalyst complex. After hydrogenation of the

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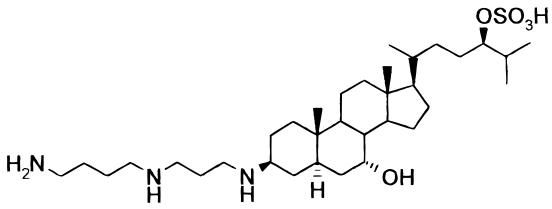
Chart 1



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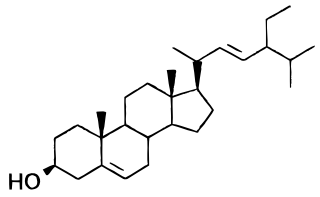

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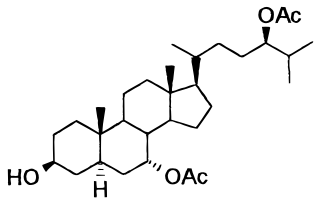

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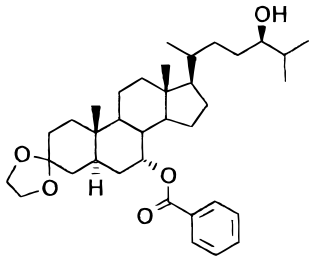


4

C-22 alkene, the 24*R*-alcohol **4** was obtained. The identity and stereochemistry of this entity was confirmed by X-ray crystallography.

In summary, a new stereoselective synthesis of squalamine has been devised, which depends on the advanced intermediate **4**. This key intermediate was prepared efficiently from the inexpensive plant sterol stigmasterol (27% yield), taking advantage of a novel side chain strategy. This approach has made possible the first practical synthesis of squalamine. The conversion of steroid **4** to squalamine will be reported in due course.

Experimental Section

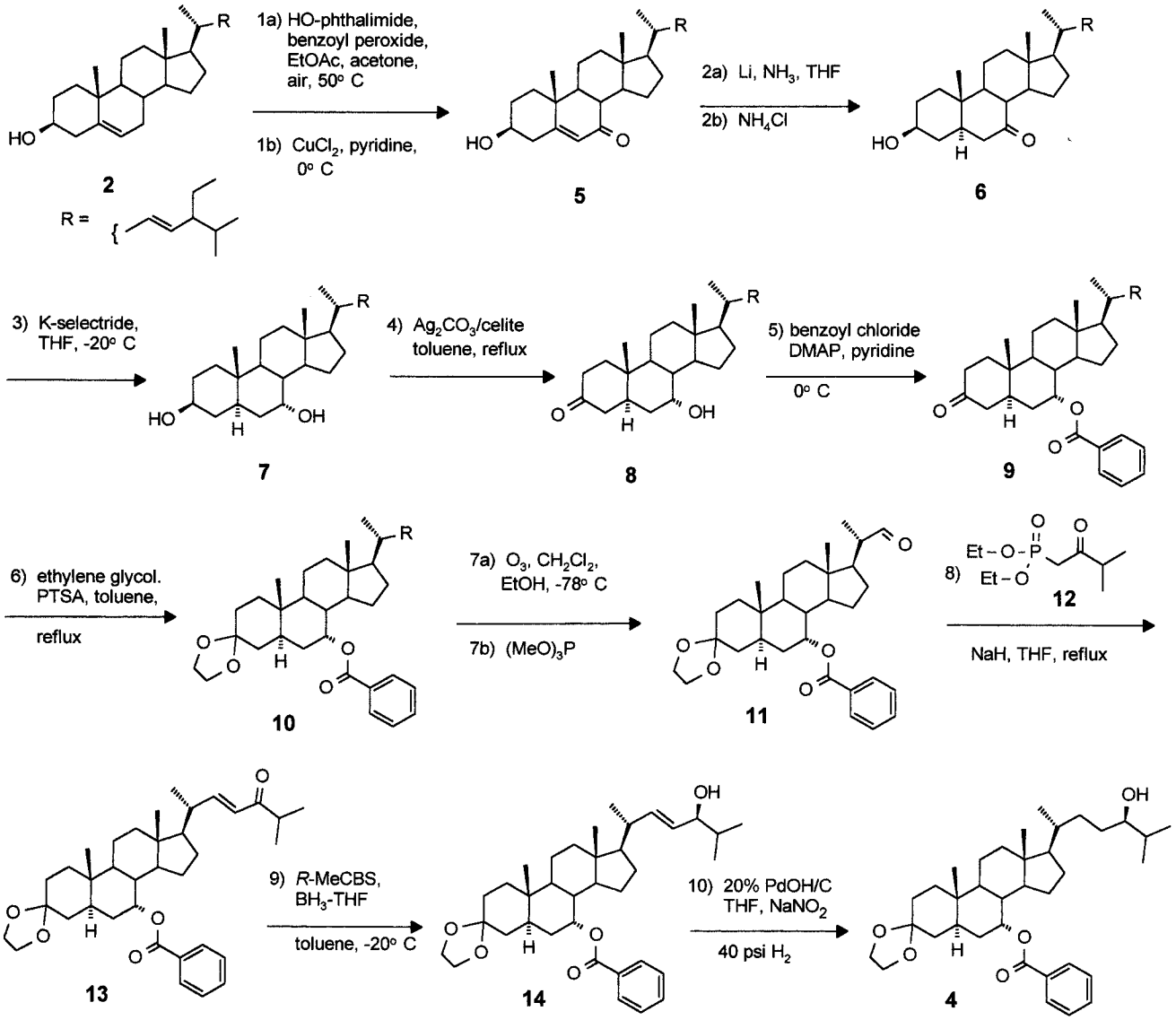
^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 or 400 MHz, and chemical shifts are reported relative to solvent ($\delta_{chloroform}$ = 7.26 ppm, 76.9 ppm). Mass spectra were recorded at the Mass Spectrometry Laboratory at the University of Illinois at Urbana−Champaign. Elemental analyses were performed at Robertson Microlit Laboratories (Madison, NJ). The diastereomeric excess (de) of **14** was determined by reverse phase HPLC. The diastereomers were separable on a Lichrospher 100 RP18 (250 × 4.6) 5 μm column with 75% acetonitrile in water elution. Detection was at 230 nm.

7-Oxostigmasterol (5). Stigmasterol (**2**, 150 g, 363 mmol) and *N*-hydroxyphthalamide (60 g, 368 mmol) were added to a 3000 mL, three-neck, round-bottom flask. A 50/50 mixture of ethyl acetate/acetone (approximately 2500 mL) was added to the flask. The flask was equipped with a glass fritted air inlet and condenser and warmed to approximately 55 °C with magnetic stirring. As the solution warmed, the stigmasterol and *N*-hydroxyphthalamide dissolved. Dibenzoyl peroxide (approximately 250 mg) was then added to the reaction. Air was vigorously bubbled into the reaction vessel, and magnetic stirring was maintained. The temperature of the reaction was kept at 50−55 °C throughout the course of the reaction. Additional 50/50 ethyl acetate/acetone was added to the reaction as needed to replenish what was lost due to air flow through the system. The reaction was followed by TLC on silica gel (40% ethyl acetate in hexane) and judged complete after 48 h. The reaction was worked up by adding the solution to cyclohexane (1000 mL) and allowing to cool. The *N*-hydroxyphthalamide which precipitated was filtered off and the remainder was removed by repetitive sodium carbonate washings, until no orange coloration was observed. The organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the sterol was dissolved in pyridine (500 mL). The pyridine solution was cooled to 0−4 °C and $CuCl_2$ (1 g) was added. The solution was stirred overnight, allowing the solution to warm to room temperature as the ice melted. The pyridine solution was then poured over an ice/water slurry (4000 mL) and the sterol precipitated; the solid was filtered, washed with 0.1 N HCl solution and distilled water, and then recrystallized from methanol (2×) to yield **5** as a white solid (127 g, 298 mmol, 82%, mp 144 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3H), 0.78−0.86 (cm, 9H), 1.02 (d, J = 6.5 Hz, 3H), 1.20 (s, 3H), 3.69 (m, 1H), 4.95−5.26 (m, 2H), 5.71 (s, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 12.0, 12.1, 17.1, 18.8, 20.9, 21.2, 25.2, 26.2, 28.9, 30.8, 31.7, 36.2, 38.1, 38.4, 40.1, 41.6, 42.8, 45.2, 49.7, 49.8, 51.0, 54.5, 70.0, 125.6, 129.3, 137.9, 165.8, 202.5; MS (FD) 426. Anal. Calcd for $C_{29}H_{46}O_2$: C, 80.63; H, 10.87. Found C, 81.77; H, 11.04.

7-Oxo-5,6-dihydrostigmasterol (6). THF (500 mL) was added to a 2000 mL, three-neck flask equipped with a dry ice condenser, 250 mL addition funnel, and magnetic stir bar. The condenser and a bath surrounding the flask were charged with dry ice/acetone. Ammonia was then collected to a total volume of approximately 1200 mL. Lithium wire (2 g, 288 mmol) was added to the solution with vigorous stirring. Once the lithium was completely dissolved, 25 g (58.6 mmol) of **5** was dissolved in approximately 100 mL of THF and added to the flask in a steady stream from a 250 mL addition funnel. The reaction was stirred for 1 h before being quenched by the addition of NH_4Cl. The reaction was removed from the dry ice bath and the dry ice condenser removed. The ammonia was allowed to evaporate overnight. The solid in the bottom of the flask was then dissolved in 500 mL of toluene/1000 mL of 1 N HCl with vigorous stirring until no solid remained. The entire solution was then poured into a separatory funnel. The aqueous layer was removed, and the organic layer was washed with distilled water and brine. The organic layer was dried over $MgSO_4$, concentrated by rotory evaporation, and recrystallized from 2-propanol to yield steroid **6** (19.4 g, 45.7 mmol, 78%, mp 149 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3H), 0.78−0.86 (cm, 9H), 1.02 (d, J = 6.5 Hz, 3H), 1.10 (s, 3H), 3.52−3.70 (m,1H), 4.92−5.23 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 11.7, 12.1, 18.9, 20.9, 21.2, 21.7, 24.9, 25.2, 28.8, 30.9, 31.7, 35.9, 36.0, 37.7, 38.5, 40.1, 42.3, 46.0, 46.7, 48.8, 49.8, 51.1, 54.8, 55.1, 70.5, 129.3, 138.0, 212.0; MS (FD) 428. Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 80.97; H, 11.20.

7α-Hydroxy-5,6-dihydrostigmasterol (7). Steroid **6** (10 g, 23.4 mmol) was dissolved in dry THF (50 mL) in a 250 mL round-bottom flask under argon. The flask was chilled to −20° C and a solution of 1 M K-Selectride in THF (51.6 mL, 51.6 mmol) was slowly syringed into the flask. The reaction was allowed to stir overnight, warming to room temperature as the ice melted. The reaction was cooled in an ice bath and quenched

Scheme 1



with a 30% H_2O_2 solution until the color disappeared and evolution of gas ceased. (Addition of 1 N NaOH accelerates the destruction of boron compounds remaining after reduction.) Toluene (250 mL) was added to the solution, and the organic layer was washed with distilled water, 1 N HCl solution (2 × 250 mL), sodium bicarbonate solution, and brine. The organic layer was then dried over $MgSO_4$ and the solvent was removed in vacuo. The resulting solid was then chromatographed on silica gel (elution with 60% ethyl acetate in hexanes) to afford **7** as a white solid (9.6 g, 22.4 mmol, 96%, mp 174 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.68 (s, 3H), 0.81−0.86 (cm, 12H), 1.02 (d, J = 6.5 Hz, 3H), 3.52−3.71 (m, 1H), 3.82 (sharp m, 1H), 4.92−5.22 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 11.1, 11.9, 12.1, 18.8, 20.8, 20.9, 23.6, 25.3, 28.7, 31.2, 31.7, 35.4, 36.2, 36.6, 36.9, 37.6, 39.2, 39.4, 40.4, 42.4, 45.7, 50.5, 51.1, 55.8, 67.8, 71.0, 129.2, 138.1; MS (FD) 430. Anal. Calcd for $C_{29}H_{50}O_2$: C, 80.87; H, 11.70. Found: C, 80.62; H, 11.76.

3-Oxo-7α-hydroxy-5,6-dihydrostigmasterol (8). Silver carbonate on Celite was prepared by dissolving $AgNO_3$ (8.3 g, 49 mmol) in 250 mL of deionized water. Celite (6.7 g) was added to the solution, which was stirred vigorously to suspend the Celite. A large excess of pH 11 carbonate buffer was then slowly added to the slurry. Silver carbonate precipitated out onto the Celite as a yellow-green solid. The solution was filtered, washed with deionized water, and then dried in a foil-covered vacuum desiccator overnight. The 3β-hydroxy sterol **7** (7.0 g, 16.3 mmol) was dissolved in toluene (600 mL) in a 1000 mL round-bottom flask equipped with a Dean−Stark trap. The silver carbonate was added to the flask and the solution was refluxed for 8 h. The reaction mixture was allowed to cool and was worked up by filtration through Florosil, eluting with ethyl acetate. The solvent was removed in vacuo to yield **8** (6.4 g, 92%, mp 174−175 °C). The sterol appeared pure by TLC and NMR analyses, but was discolored (light yellow), due to elution of a trace of silver impurity from the Florosil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.69 (s, 1H), 0.82−0.93 (cm, 9H), 1.00 (s, 3H), 1.02 (d, J = 6.5 Hz, 3H), 3.84 (sharp m, 1H), 4.92−5.23 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 10.3, 11.9, 12.1, 18.9, 21.0, 23.6, 25.3, 28.8, 31.8, 35.6, 36.4, 38.0, 38.9, 39.2, 39.3, 40.4, 42.4, 44.0, 45.1, 50.4, 51.1, 55.8, 67.4, 129.3, 138.0, 211.6; MS (FD) 428. Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.17; H, 11.49.

7α-Benzyloxy-3-oxo-5,6-dihydrostigmasterol (9). The silver carbonate oxidation product **8** (5.0 g, 12 mmol) was dissolved in pyridine (100 mL). The solution was cooled using an ice water bath before the dropwise addition of benzoyl chloride (6.8 mL, 58 mmol). DMAP (200 mg) was then added to the reaction vessel, which was allowed to warm to room temperature and stirred for approximately 8 h. The reaction mixture was poured over ice and allowed to stand overnight. The resulting solution was filtered, leaving the sterol behind as a thick waxy solid. The sterol was dissolved in toluene and washed with 1 N HCl (2×) and then sodium bicarbonate to ensure complete removal of excess pyridine, DMAP, and benzoic acid. The resulting solution was then dried over $MgSO_4$ and the solvent was removed by rotory evaporation. The residue was chromatographed on silica gel, eluting with a gradient of ethyl acetate in toluene. The

desired benzoate **9** was isolated as a white solid (5.33 g, 86%, mp 155 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70−0.85 (m, 12H), 1.04 (d, J = 6.5 Hz, 3H), 1.09 (s, 3H), 4.92−5.24 (m, 3H), 7.40−7.63 (m, 3H), 7.99−8.04 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 10.3, 11.7, 12.0, 18.7, 20.9, 21.0, 23.5 25.1, 28.5, 31.6, 33.3, 35.4, 37.8, 38.0, 38.3, 39.0, 40.1, 40.3 42.3, 43.6, 46.8, 50.4, 50.9, 55.5, 71.0, 128.2, 129.2, 129.3, 130.4, 132.7, 137.8, 165.3, 210.8; MS (FD) 532. Anal. Calcd for $C_{36}H_{52}O_3$: C, 81.15; H, 9.84. Found: C, 80.98; H, 9.89.

7α-Benzyloxy-3-dioxolane-5,6-dihydrostigmasterol (10). Steroid **9** (4.0 g, 7.5 mmol) was dissolved in toluene (250 mL) in a 500 mL round-bottom flask. *p*-Toluenesulfonic acid (250 mg) and ethylene glycol (5 mL, large excess) were added. The flask was equipped with a Dean−Stark trap, and the reaction was brought to reflux. The reaction was refluxed for 2 h before being allowed to cool. The reaction was treated with approximately 2 g of anhydrous sodium carbonate, followed by water. The organic layer was washed (2×) with sodium bicarbonate, deionized water, and brine and dried over Na_2SO_4. The solvent was removed by rotory evaporation to yield the ketal **10** (4.1 g, 7.1 mmol, 95%, mp 74 °C) as a light yellow waxy solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70−0.81 (m, 12H), 0.89 (s, 3H), 1.01 (d, J = 6.5 Hz, 3H), 3.87 (sharp m, 4H), 4.92−5.23 (m, 3H), 7.40−7.63 (m, 3H), 8.04−8.14 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 10.4, 11.8, 12.1, 18.8, 21.0, 23.6, 25.3, 28.7, 31.1, 31.7, 33.1, 35.4, 35.6, 37.1, 37.2, 38.5, 39.3, 40.4, 42.5, 47.1, 50.7, 51.1, 55.6, 64.0, 71.8, 108.9, 128.3, 129.2, 129.5, 130.9, 132.6, 138.0, 165.8; MS (FD) 576. Anal. Calcd for $C_{38}H_{56}O_4$: C, 79.12; H, 9.78. Found: C, 78.89; H, 9.75.

7α-Benzyloxy-3-dioxolane Cholestan-22-al (11). Sterol **10** (3.5 g, 6.1 mmol) was dissolved in methylene chloride/ethanol (250 mL of 2/1). The Welsbach ozonolyzer was purged with oxygen at 7 psi, 1 mL/min, and the water was turned on. The sterol solution was then chilled in a dry ice/ethanol bath. The ozonolyzer was set at 90 V and switched on. Ozone was bubbled into the magnetically stirred, chilled flask until a blue coloration was observed. The power was switched off, and oxygen was bubbled into the flask until the color dissipated. Trimethyl phosphite (5 mL) was added to the reaction vessel. The ice bath was removed and the reaction mixture was allowed to warm to room temperature. The solvent was removed by rotory evaporation and the flask was placed under high vacuum overnight to remove any remaining trimethyl phosphate. The resulting white solid was chromatographed on silica gel, eluting with a gradient of ethyl acetate in toluene, to give the desired product **11** (2.7 g, 5.5 mmol, 90%, mp 166−168 °C) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (d, J = 2.4 Hz, 1H), 8.06 (d, J = 7 Hz, 2H), 7.60 (t, J = 7 Hz, 1H), 7.49 (t, J = 7 Hz, 2H), 5.17 (m, 1H), 3.88 (m, 4H), 2.35 (m, 1H), 2.0−1.1 (m, 21H), 1.11 (d, J = 6.9 Hz, 3H), 0.89 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 10.4, 12.0, 13.3, 20.9, 23.8, 26.7, 31.1, 33.1, 35.3, 35.5, 37.0, 37.1, 38.4, 39.0, 43.2, 47.1, 49.3, 49.9, 50.7, 64.0, 71.6, 108.8, 128.3, 129.5, 130.7, 132.7, 165.8, 204.8.

7α-Benzyloxy-3-dioxolane 24-Ketocholest-22-ene (13). A solution of 1-bromo-3-methyl-2-butanone[11] (10 g, 60 mmol) and triethyl phosphite (10.3 mL, 60 mmol) was heated to 120 °C under nitrogen for 3 h with the removal of ethyl bromide by distillation. The cooled reaction mixture was placed under high vacuum and then distilled to afford diethylphosphono-3-methyl-2-butanone (**12**, 8.0 g, 60%, bp 127−130 °C, 3 mm):[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (p, J = 7 Hz, 4H), 3.14 (d, J = 22.5 Hz, 2H), 2.87 (heptet, 7 Hz, 1H), 1.34 (t, J = 7 Hz, 6H), 1.13 (d, J = 7 Hz, 6H).

Sodium hydride (60%, 44 mg, 1.1 mmol) was washed with heptane (2 mL) and hexane (2 × 2 mL) and evaporated with a nitrogen flow. Anhydrous THF (2 mL), diethylphosphono-3-methyl-2-butanone (**12**, 0.34 mL, 1.5 mmol), and a solution of **11** (486 mg, 0.982 mmol) in THF (3 mL) were added. The reaction mixture was heated to reflux for 1 h, cooled to room temperature, and treated with water (25 mL). The aqueous layer was extracted with ethyl acetate (3 × 50 mL), which was in turn washed with brine (3 × 50 mL) and water (2 × 50 mL) and dried over sodium sulfate. After removal of the solvent, the product was dissolved in methanol (5 mL) containing 4 drops of pyridine and dropped into water (100 mL) with shaking. The resulting solid was filtered, washed with water (3 × 20 mL), and dried under vacuum at 50 °C to give pure **13** (499 mg, 0.89 mmol, 90%, mp 85−121 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.4 Hz, 2H), 7.59 (t, J = 7.1 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 6.65 (d of d, J = 15.6 and 9 Hz, 1H), 6.02 (d, J = 15.6 Hz, 1H), 5.15 (br s, 1H), 3.88 (br s, 4H), 2.80 (hept, J = 6.7 Hz, 1H), 2.25 (m, 1H), 2.0−1.0 (m, 21H), 1.08 (d, 3H), 1.06 (d, J = 6.9 Hz, 6H), 0.89 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.0, 12.5, 13.9, 18.9, 19.1, 19.8, 21.5, 24.1, 28.5, 31.7, 33.7, 36.0, 36.2, 37.7, 37.8, 38.7, 39.1, 39.8, 40.4, 43.5, 47.7, 51.1, 55.3, 64.6, 64.7, 72.3, 109.5, 126.8, 128.9, 130.1, 131.4, 133.3, 152.8, 166.4, 205.0; MS (+FAB) 563.3 (M + 1). Anal. Calcd for $C_{36}H_{50}O_5 \cdot 0.2H_2O$: C, 76.34; H, 8.97. Found: C, 76.26; H, 9.13.

7α-Benzyloxy-3-dioxolane Cholest-22-en-24(*R*)-ol (14). An argon-blanketed flask was charged with 1 M *R*-MeCBS in toluene (0.92 mL, 0.92 mmol) and 1 M borane−THF complex in THF (2.3 mL, 2.3 mmol). The reaction mixture was stirred at room temperature for 2 h, cooled to −20 °C, and treated with a solution of **13** (520 mg, 0.92 mmol) in anhydrous toluene (15 mL) over 1.5 h. After 1 h, the reaction mixture was treated with solid ammonium chloride and water (2 mL), warmed to room temperature, diluted with more water (20 mL), and extracted into toluene (2 × 80 mL). The toluene layer was washed with saturated ammonium chloride (3 × 50 mL), dried with magnesium sulfate, and evaporated to give a solid, which was recrystallized from ethyl acetate in hexane to give **14** in two crops (491 mg, 0.87 mmol, 94%, mp 196−199 °C, 91% de): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7 Hz, 2H), 7.59 (t, J = 7 Hz, 1H), 7.48 (t, J = 7 Hz, 2H), 5.35 (m, 2H), 5.16 (br s, 1H), 3.88 (br s, 4H), 3.67 (t, J = 6.2, 1H), 2.1−1.0 (m, 23H), 1.03 (d, J = 6.3 Hz, 3H), 0.89 (m, 6H), 0.82 (d, J = 6.6 Hz, 3H), 0.70 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.7, 12.2, 18.4, 18.6, 20.6, 21.3, 23.9, 28.8, 31.5, 33.5, 34.1, 35.7, 35.9, 37.4, 37.5, 38.8, 39.6, 40.2, 42.9, 47.4, 51.0, 55.6, 64.3, 64.4, 72.0, 78.8, 109.2, 128.6, 128.8, 129.9, 131.2, 133.0, 139.8, 166.1,; MS (+FAB) 565.3 (M + 1). Anal. Calcd for $C_{36}H_{52}O_5$-$0.2H_2O$: C, 76.07; H, 9.29. Found: C, 75.93; H, 9.14.

7α-Benzyloxy-3-dioxolane Cholestan-24(*R*)-ol (4). A solution of **14** (2.7 g, 4.8 mmol) in THF (30 mL) was treated with sodium nitrite (89 mg, 1.3 mmol), 20% palladium hydroxide on carbon (0.5 g, Pearlman's catalyst), and 40 psi of hydrogen in a Parr apparatus. After 16 h, the reaction mixture was filtered through Celite and concentrated to obtain crude material, which was recrystallized from dichloromethane in hexane (15 mL) to afford pure **4** (2.13 g, 3.76 mmol, 78%, mp 205−208 °C): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 5.16 (br s, 1H), 3.88 (m, 4H), 3.28 (m, 1H), 2.0−1.0 (m, 27H), 0.93−0.90 (m, 9H), 0.89 (s, 3H), 0.69 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 11.0, 12.2, 17.7, 19.1, 19.4, 21.5, 24.1, 28.5, 31.0, 31.7, 32.4, 33.7, 33.9, 35.9, 36.1, 37.6, 37.8, 39.0, 39.9, 43.2, 47.6, 51.1, 56.3, 64.6, 64.7, 72.4, 77.3, 109.5, 128.9, 130.2, 131.5, 133.3, 166.5; MS (+FAB) 567.5 (M + 1). Anal. Calcd for $C_{36}H_{54}O_5$-$0.3H_2O$: C, 75.56; H, 9.62. Found: C, 75.29; H, 9.04.

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Supporting Information Available: X-ray information for compound **4** (13 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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