Efficient Synthesis of IPL576,092: A Novel Anti-Asthma Agent

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Abstract: An enantioseletive synthesis of the novel anti-asthma agent IRL576,092 (**2**) is described. The synthetic route developed involves stereoselective 1,2-reduction of the enone carbonyl functionality of **6** and subsequent hydroboration as the key steps. Starting from the commercially available 5-androsten-3β-ol-17-one **3**, this approach affords IPL576,092 (**2**) in nine steps with overall yields of 25%, employing a limited number of chromatographic steps.

The search for new therapies in the treatment of asthma has focused on many areas, including mechanism-targeted programs: for example, leukotriene D_4 (LTD_4) antagonists, Very Late Antigen-4 (VLA-4) antagonists, and Phosphodiesterase 4 (PDE4) inhibitors. Despite the vast amount of research in this area, there remains a need for new safe, effective treatments for asthma. It was previously reported that contignasterol **1** (Figure 1), a naturally occurring steroid isolated from specimens of the marine sponge *Petrosia contignata* Theile (1899) collected off the coast of Papua New Guinea,[1] possesses biological activity indicative of potential value as a treatment for asthma[2,3] and other inflammatory diseases.[4] However, the structural complexity and potential pharmacokinetic instability led us to undertake in-depth studies to identify an analogue of compound **1** that demonstrated equivalent or better biological activity and would be commercially available through synthetic methodology. This effort has led to the identification of IPL576,092 (**2**), a compound which is structurally less complex and exhibits a better biological activity profile.[5] For example, in a rodent model of allergen-induced lung inflammation, IPL576,092 (**2**) at an oral dose of 5 mg/kg caused an 80% inhibition of the inflammatory response,[5d] whereas contignasterol at an oral dose of 50 mg/kg in this model caused a 60% inhibition of the response.[5e] In

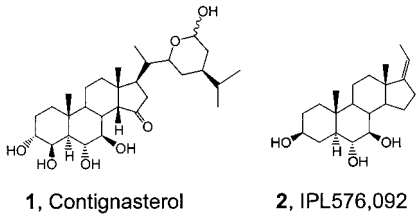
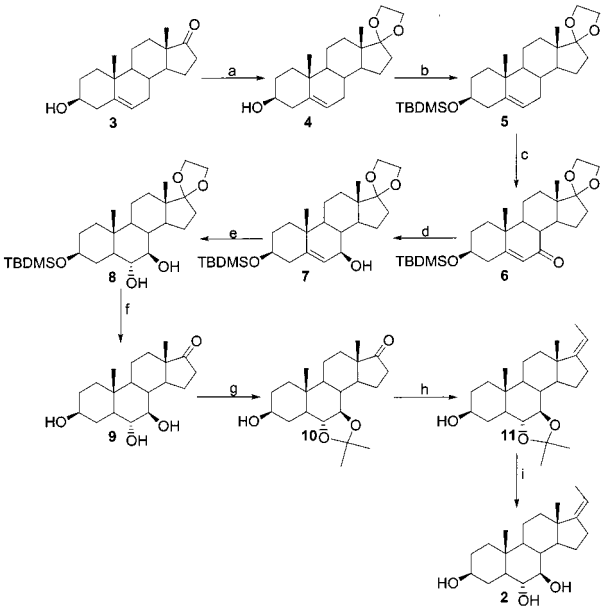


Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (a) $(CH_2OH)_2$, TsOH, benzene, reflux, 99%; (b) TBDMS-Cl, imidazole, DMF, room temperature, 86%; (c) $RuCl_3$, 70% *t*-BuOOH, H_2O, cyclohexane, room temperature, 56% or CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −20 °C; (d) $NaBH_4$, $CeCl_3$, THF−MeOH−$CHCl_3$, room temperature; (e) BH_3, THF, 0 °C, then 30% H_2O_2, NaOH; (f) 80% aqueous AcOH, room temperature, 70%, three steps; (g) 2,2-dimethoxypropane, CSA, room temperature, 85%; (h) $EtPPh_3Br$, *t*-BuOK, toluene, 91%; (i) 80% acetic acid, 98%.

in vitro studies, IPL576,092 showed a significant reduction in the release of mediators of inflammation, including Tumor Necrosis Factor α (TNFα), hexosaminidase, Prostaglandin-D_2 (PGD_2), and Interleukin 5 (IL5). Furthermore, a series of studies demonstrated that IPL576,-092 has a biological profile distinct from glucocorticoids. Currently in phase II human clinical trials, IPL576,092 displays a biological activity profile which justifies the continuation of its evaluation as a potential new treatment for asthma. Herein we report for the first time the structure of IPL576,092 and an efficient, stereochemically controlled synthetic sequence for its preparation.

The synthesis of **2** from 5-androsten-3β-ol-17-one (**3**) is summarized in Scheme 1. Treatment (benzene, reflux) of the ketone **3** with ethylene glycol in the presence of *p*-toluenesulfonic acid (TsOH)[6] provided the required ketal **4** (99% yield). Subsequently, the OH group was protected as the TBDMS ether **5** by treatment of the alcohol **4** with *tert*-butyldimethylsilyl chloride (TBDMS-

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Cl) and imidazole in *N*,*N*-dimethylformamide (DMF).[7] The allylic oxidation of the C7 position of the steroidal silyl ether ethylene ketal **5** was achieved using two different methods. In one method, shown in Scheme 1, a mixture of compound **5**, ruthenium chloride hydrate, water, and cyclohexane[8] was treated by the dropwise addition of *tert*-butyl hydroperoxide at room temperature, to give the enone **6** in 56% yield. Another method that was employed in the oxidation of the C7 position involved the use of chromium trioxide−dimethylpyrazole in methylene chloride[9] to afford compound **6** in 65% yield (85% based on recovered starting material). This method, however, uses a 10-fold excess of chromium trioxide−dimethylpyrazole and, therefore, is not scalable. Stereoselective 1,2-reduction of the enone carbonyl function of **6** using sodium borohydride−cerium trichloride in THF−MeOH−$CHCl_3$[10] produced the 7β-alcohol **7**.

Introduction of the 6α-hydroxyl group was achieved by treating compound **7** with a 1.0 M solution of BH_3 in THF, followed by oxidative workup to furnish the diol **8**. Both the ketal and TBDMS protecting groups in steroid **8** were then removed in a one-step process, by treatment with 80% acetic acid over 3 h to give the triol **9** in 70% yield over three steps. The ^{1}H NMR spectrum of compound **9** shows a coupling constant between H-6 (δ 3.16 ppm (dd, J = 8.2, 8.2 Hz)) and H-7 ((δ 3.10 ppm (dd, J = 8.2, 8.2 Hz)) consistent with a trans diaxial relationship between these hydrogens and a 6αOH, 7βOH configuration. Reaction of triol **9** with 2,2-dimethoxypropane in DMF in the presence of camphorsulfonic acid (CSA) produced compound **10** in 85% yield. The 17-keto steroid **10** was converted to (*Z*)-17(20)-ethylidene steroid **11** in 91% yield via the Wittig[11] reaction using toluene as solvent. The use of Wittig olefination in the preparation of (*Z*)-17(20)-ethylidene steroids has been previously demonstrated.[12] A ROESY correlation between the resonances assigned to the methyl group at C21 (δ 1.69) and H12 (δ 2.20) in compound **11** is consistent with the *Z* configuration. Approximately 2% of the C20 *E* isomer is observed in some of the reactions. Ensuring that the addition of compound **10** to the Wittig reagent is carried out at 0 °C using an ice bath minimizes the quantity of *E* isomer. Finally, the acetonide moiety in **11** was hydrolyzed in aqueous 80% acetic acid to afford the desired IPL576,092 (**2**) in 98% yield.

One- and two-dimensional NMR experiments were used to assign the carbon and hydrogen resonances associated with the intermediates, including compound **11** and the final product IPL576,092 (**2**). COSY and TOCSY experiments were used to identify the hydrogen spin systems within the molecule, and direct and long-range hydrogen−carbon connectivities were determined using HSQC and HMBC experiments. The relative stereochemistry of the hydroxyl groups and the geometry of the double bond were determined using coupling constants and ROESY experiments. The stereochemistry at C3 is not modified during the synthetic process. Therefore, IPL576,092 (**2**) has the same 3βOH configuration as the starting material androstenolone. The complex resonance at δ 3.48 ppm in the ^{1}H NMR spectrum assigned to the hydrogen attached to C3 is consistent with the 3βOH configuration. The coupling constants for the resonances in the ^{1}H NMR spectrum of IPL576,092 (**2**) assigned to H6 (δ 3.13 ppm, dd, J = 8.6, 10.7 Hz) and H7 (δ 3.01 ppm, dd, J = 8.6, 10.6 Hz) are consistent with trans diaxial relationships between H5 and H6, H6 and H7, and H7 and H8. Thus, the configuration of the hydroxyl groups at C6 and C7 can be assigned as α and β, respectively. An observed ROESY correlation between the resonance at δ 1.66 (C21) and the resonance assigned to one of the C12 methylene hydrogens (δ 2.28) supports the *Z* configuration of the 17(20) double bond.

In conclusion, we have described a highly efficient synthesis of the novel anti-asthma agent IPL576,092 (**2**), with stereoselective 1,2-reduction of the enone carbonyl functionality of **6** and subsequent hydroboration as the key steps. Starting from the 5-androsten-3β-ol-17-one **3**, this approach affords IPL576,092 in nine steps with overall yields of 25% and only involves three column chromatography purifications. The synthesis described herein provides the basis for developmental efforts toward the commercial-scale synthesis of this potential new treatment of asthma.

Experimental Section

General Considerations. THF, toluene, and Et_2O were dried by distillation over Na/benzophenone under an argon atmosphere. CH_2Cl_2 was dried over CaH_2 and distilled before use. $EtPPh_3Br$ was dried by azeotropic distillation with benzene. The starting material 5-androsten-3β-ol-17-one (**3**) was obtained from Sigma-Aldrich Fine Chemicals. Unless otherwise noted, all other starting materials and solvents were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR, ROESY, TOCSY, COSY, HSQC, and HMBC spectra were obtained using a Varian Mercury 300 instrument. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F_{254} plates, and flash chromatography was performed on 230−240 mesh silica gel.

5-Androsten-3β-ol-17-one Ethylene Ketal (4). 5-Androsten-3β-ol-17-one (**3**; 20.07 g, 69.37 mmol), *p*-TsOH (501.3 mg, 2.64 mmol), ethylene glycol (20 mL), and benzene (200 mL) were refluxed under a Dean−Stark trap for 4.5 h. The mixture was cooled to room temperature, diluted with ether (200 mL), and washed with saturated $NaHCO_3$ solution (2 × 100 mL) and saturated NaCl solution (2 × 100 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness, giving **4** (22.80 g, 99%) as a white solid: R_f = 0.25 (2:1 hexanes−ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 1H), 3.88 (m, 4H), 3.52 (m, 1H), 2.34−2.16 (m, 2H), 2.00 (m, 2H), 1.82 (m, 2H), 1.78−1.17 (m, 12H), 1.02 (m, 2H), 1.01 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 121.6, 119.6, 71.8, 65.3, 64.7, 50.7, 50.1, 45.9, 42.4, 37.4, 36.7, 34.4, 32.3, 31.8, 31.4, 30.7, 22.9, 20.6, 19.6, 14.4. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.00; H, 9.84.

5-Androsten-3β-ol-17-one Ethylene Ketal *tert*-Butyldimethylsilyl Ether (5). 5-Androsten-3β-ol-17-one ethylene ketal (**4**; 22.50 g, 67.77 mmol), imidazole (11.25 g, 165.4 mmol), DMF (120 mL), and CH_2Cl_2 (120 mL) were treated with *tert*-butyldimethylsilyl chloride (15.75 g, 104.5 mmol) for 6 h. The mixture was diluted with ether (675 mL) and washed with 5% aqueous HCl solution (2 × 135 mL), saturated $NaHCO_3$ solution (2 × 135 mL), and saturated NaCl solution (2 × 135 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residue was then crystallized from methanol−ethyl acetate (3:2, 165 mL) and afforded **5** (25.84 g, 86%) as a white solid: R_f = 0.30 (19:1

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hexanes−ethyl acetate); mp 121−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (m, 1H), 3.88 (m, 4H), 3.48 (m, 1H), 2.33−2.12 (m, 2H), 1.99 (m, 2H), 1.85−1.16 (m, 13H), 0.99 (m, 2H), 0.98 (s, 3H), 0.88 (s, 9H), 0.85 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 121.1, 119.6, 72.6, 65.3, 64.7, 50.7, 50.1, 45.9, 42.9, 37.5, 36.8, 34.4, 32.3, 32.2, 31.4, 30.7, 26.1, 22.9, 20.6, 19.6, 18.4, 14.4, −4.2. Anal. Calcd for $C_{27}H_{46}O_3Si$: C, 72.59; H, 10.38. Found: C, 72.89; H, 10.61.

5-Androsten-7,17-dione-3*β*-ol 17-Ethylene Ketal *tert*-Butyldimethylsilyl Ether (6). Method a. Chromium trioxide (10.2 g, 0.102 mol) was ground with a mortar and pestle before use and then added to an argon-purged flask, followed by CH_2Cl_2 (60 mL). The mixture was stirred and cooled to −20 °C. 3,5-Dimethypyrazole (9.81 g, 0.102 mmol) was added, and the mixture was stirred at −20 °C for 1.5 h. 5-Androsten-3*β*-ol-17-one ethylene ketal *tert*-butyldimethylsilyl ether (**5**; 4.56 g, 0.0102 mol) was added, and the thick, dark mixture was stirred under argon at −20 °C for 16 h. The mixture was diluted with diethyl ether (500 mL) and filtered through a pad of Celite to remove the muddy brown-red precipitate. The filtrate was washed with water (2 × 200 mL), dried ($MgSO_4$), and evaporated to dryness. The resulting residue was chromatographed (gradient: 49:1, 9:1, 4:1 hexanes−ethyl acetate) to give enone **6** (3.05 g, 65%) as a white solid and starting material **5** (0.91 g, 20%).

Method b. To the mixture of **5** (17.04 g, 38.12 mmol), ruthenium chloride hydrate (59.7 mg, catalytic), and water (10.2 mL) in cyclohexane (68 mL) was added dropwise 70% *t*-BuOOH (42.6 mL) with stirring, and the resulting mixture was stirred at room temperature overnight. The mixture was poured into ethyl acetate (400 mL) and washed with 25% $Na_2S_2O_3$ solution (2 × 200 mL) and saturated NaCl solution (2 × 200 mL). The organic phase was dried with $MgSO_4$ and evaporated to dryness. The residue was recrystallized from hot ethyl acetate (53 mL) to give ketone **6** (7.96 g) as a white solid. A second crop was obtained by recrystallization of the mother liquor from hot ethyl acetate (6.2 mL) and gave ketone **6** (1.88 g). The two crops were combined and gave an overall yield of 9.84 g (56%) of **5**: R_f = 0.25 (17:3 hexanes−ethyl acetate); mp 224−226 °C; IR (film) 2951, 1665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (s, 1H), 3.89 (m, 4H), 3.60 (m, 1H), 2.53−2.16 (m, 4H), 2.07−1.37 (m, 13H), 1.18 (s, 3H), 0.90 (s, 9H), 0.86 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 166.3, 125.9, 118.8, 71.4, 65.3, 64.6, 50.1, 46.3, 45.5, 44.5, 42.7, 38.5, 36.6, 34.3, 31.9, 29.8, 26.0, 25.2, 20.8, 18.3, 17.6, 14.6, −4.30, −4.27. Anal. Calcd for $C_{27}H_{44}O_4Si$: C, 70.39; H, 9.63. Found: C, 70.46; H, 9.59.

5-Androsten-3*β*,7*β*-diol-17-one Ethylene Ketal 3-*tert*-Butyldimethylsilyl Ether (7). 5-Androsten-7,17-dione-3*β*-ol 17-ethylene ketal *tert*-butyldimethyl silyl ether (**6**; 47.61 g, 103.3 mmol) was dissolved in THF (380 mL). A solution of $CeCl_3 \cdot 7H_2O$ (57.75 g, 155.0 mmol) in methanol (115 mL) and chloroform (230 mL) were added to the THF solution and the mixture cooled to 0 °C for 30 min. This mixture was treated with $NaBH_4$ (8.10 g, 214.2 mmol), which was added in portions over 30 min. The reaction mixture was removed from the ice bath and stirred for another 2.5 h. The mixture was cautiously quenched with 5% aqueous HCl solution (150 mL) and then placed into ethyl acetate (1.5 L) and washed with 5% aqueous HCl solution (150 mL), saturated $NaHCO_3$ solution (400 mL), and saturated NaCl solution (400 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness, affording the crude steroid **7** (47.40 g). No purification was attempted on this crude compound.

5α-Androstan-17-one-3*β*,6α,7*β*-triol Ethylene Ketal 3-*tert*-Butyldimethylsilyl Ether (8). 5-Androsten-3*β*,7*β*-diol-17-one ethylene ketal 3-*tert*-butyldimethyl silyl ether (**7**; 47.40 g, 102.4 mmol) was dissolved in THF (350 mL) and cooled to 0 °C. To this solution was added slowly 300 mL of a 1.0 M BH_3 in THF solution. The mixture was warmed to room temperature over 2.5 h and then cautiously quenched with a 10 N NaOH aqueous solution (61 mL), followed by the slow addition of a 30% H_2O_2 aqueous solution (61 mL). The mixture was then vigorously stirred for 16 h, poured into a saturated solution of NaCl (1600 mL), and extracted with CH_2Cl_2 (4 × 1000 mL). The organic layers were combined, dried with $MgSO_4$, and evaporated to dryness to afford the crude **8** (46.80 g), which was used in the next reaction without further purification.

5α-Androstan-17-one-3*β*,6α,7*β*-triol (9). The crude compound **8** (46.80 g), acetic acid (320 mL), and water (80 mL) were stirred at room temperature for 3 h. The mixture was then concentrated in vacuo and azeotroped to dryness with methanol (2 × 200 mL). To this residue was added diethyl ether (400 mL), and the mixture was vigorously stirred for 1 h. The resulting white precipitate was collected by filtration, giving the compound **9** (16.87 g) as a white solid. The filtrate was then chromatographed over a silica gel column with ethyl acetate as eluent (1000 mL), followed by a 85:15 ethyl acetate−methanol solution (2000 mL), to afford additional compound **9** (6.40 g). The precipitate (16.87 g) and the compound purified by chromatography (6.40 g) were combined. The overall yield for the conversion of **6** to **9** was 70%: R_f = 0.05 (ethyl acetate); ^{1}H NMR (300 MHz, CD_3OD) δ 3.47 (m, 1H), 3.16 (dd, J = 8.2, 8.2 Hz, 1H), 3.10 (dd, J = 8.2, 8.2 Hz, 1H), 2.40 (dd, J = 8.1, 19.5 Hz, 1H), 2.35−0.95 (m), 0.90 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 224.3, 80.9, 75.8, 71.7, 53.5, 52.6, 49.3, 41.9, 38.5, 36.9, 36.8, 33.2, 32.7, 31.8, 25.8, 21.8, 14.4, 13.8. Anal. Calcd for $C_{19}H_{30}O_4 \cdot H_2O$: C, 70.39; H, 9.63. Found: C, 70.46; H, 9.59.

5α-Androstan-17-one-3*β*,6α,7*β*-triol 6,7-acetonide (10). 5α-Androstan-3*β*,6α,7*β*-triol-17-one (**9**; 11.13 g, 0.0345 mol), (1*S*)-(+)-10-camphorsulfonic acid (445.7 mg, catalytic), and 2,2-dimethoxypropane (445 mL) were stirred at room temperature for 2 h. The mixture was diluted with ethyl acetate (890 mL) and washed with saturated $NaHCO_3$ solution (2 × 445 mL) and saturated NaCl solution (2 × 445 mL). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The residue was chromatographed over silica gel (126 g) with 5:1 hexanes−ethyl acetate (650 mL), which was discarded, and then with 1:1 hexanes−ethyl acetate (1.6 L). The second fraction was evaporated to dryness, affording the acetonide **10** (10.6 g, 85%) as a white solid: R_f = 0.20 (1:1 hexanes−ethyl acetate); mp 201−202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (m, 1H), 3.23 (dd, 1H, J = 8.1, 10.8 Hz), 3.11 (dd, 1H, J = 8.7, 10.2 Hz), 2.42 (m, 1H), 2.21−1.98 (m, 4H), 1.90−1.63 (m, 8H), 1.63−1.00 (m), 1.41 (s), 1.39 (s), 0.92 (s, 3H), 0.90 (s, 3H), 0.84 (m); ^{13}C NMR (75 MHz, CD_3OD) δ 221.0, 109.5, 85.0, 78.4, 70.6, 52.9, 50.3, 47.7, 46.1, 38.8, 37.4, 37.3, 35.9, 32.8, 31.6, 30.9, 27.3, 27.3, 23.8, 20.6, 14.8, 14.0. Anal. Calcd for $C_{22}H_{34}O_4 \cdot 0.25H_2O$: C, 72.00; H, 9.48. Found: C, 72.01; H, 9.45.

5α-Progest-17(20)-ene-3*β*,6α,7*β*-triol 6,7-Acetonide (11). A flask was charged with $EtPPh_3Br$ (23.66 g, 21.24 mmol), *t*-BuOK (7.15 g, 63.72 mmol), and a stir bar under argon. Toluene (150 mL) was added via syringe, and the suspension was stirred for 1 h at room temperature. The reaction mixture was cooled to 0 °C with an ice bath, and a solution of the ketone **10** (7.70 g, 21.24 mmol) in toluene (150 mL) was added. The ice bath was removed, and the reaction mixture was stirred at room temperature under argon for 24 h. Water (150 mL) was added slowly, and the product was extracted with EtOAc (900 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Chromatography over silica gel with 2:1 hexane−ethyl acetate gave compound **11** as a white solid (7.20 g, 91%): R_f = 0.20 (7:3 hexanes−ethyl acetate); mp 156−157 °C; ^{1}H NMR (300 MHz, benzene-d_6) δ 5.23 (m, 1H), 3.34 (m, 1H), 3.32 (dd, 1H, J = 8.9, 11.5 Hz), 3.05 (dd, 1H, J = 8.9, 10.7 Hz,), 2.51−2.10 (m, 4H), 1.66−0.49 (m), 1.69 (m, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 0.85 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, benzene-d_6) 149.5, 114.0, 109.1, 85.6, 78.9, 70.5, 55.2, 52.9, 46.5, 44.5, 39.1, 37.6, 37.5, 37.2, 33.4, 32.2, 31.5, 27.7, 27.5, 27.0, 21.6, 17.1, 14.8, 13.6. Anal. Calcd for $C_{24}H_{38}O_3 \cdot 0.75H_2O$: C, 74.28; H, 10.26. Found: C, 74.36; H, 10.47.

5α-Progest-17(20)-ene-3*β*,6α,7*β*-triol (2). 5α-Progest-17(20)-ene-3*β*,6α,7*β*-triol 6,7-acetonide (**11**; 1.44 g, 3.87 mmol), acetic acid (18.2 mL), and water (4.6 mL) were stirred at room temperature for 3 h. The mixture was then concentrated in vacuo and triturated in EtOAc and methyl *tert*-butyl ether to afford pure compound **2** (1.25 g, 98%) as a white solid: R_f = 0.40 (9:1 ethyl acetate/methanol); mp 183−184 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 5.12 (m, J = 7.2 Hz, 1H), 3.48 (m, 1H), 3.13 (dd, J = 8.3, 10.7, 1H), 3.01 (t, J = 9.2 Hz, 1H), 2.31 (m, 2H), 2.16 (m, 2H), 1.95 (m, 1H), 1.751−1.26 (m, 10H), 1.64 (bd, J = 7.2 Hz, 3H), 1.12 (m, 2H), 0.92 (s, 3H), 0.88 (s, 3H), 0.85 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 150.7, 114.6, 80.9, 75.9, 71.7, 57.6, 53.7, 49.3, 46.1, 41.8, 38.5, 38.4, 36.7, 33.2, 31.8, 28.3, 22.8, 17.6, 13.9, 13.7. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.49; H, 10.28.

Supporting Information Available: Spectrometric information (^{1}H and ^{13}C NMR) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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