A Short Enantioselective Total Synthesis of the Third-Generation Oral Contraceptive Desogestrel

E. J. Corey* and Alan X. Huang

Contribution from the Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138

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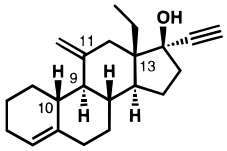
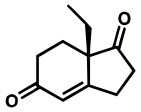
Abstract: Desogestrel (**1**) has been synthesized enantioselectively by a 14-step process from the known and readily available precursor **3**, as outlined in Chart 2. At the heart of this process is the short, convergent, and stereocontrolled method for forming the tetracyclic ring system and the critical 11-exomethylene function, that is, the sequence of steps **6** → **8** → → **12**. All steps of the synthesis proceed in good yield.

Desogestrel (13-ethyl-17α-ethynyl-11-methylenegona-4-en-17β-ol) (**1**) is the most prescribed (worldwide) of the third-generation oral contraceptives with current sales of several hundred million dollars. It is produced commercially by a 24-step partial synthesis from diosgenin, which includes a costly microbial oxidation at C(11).[1] Although the daily dose is tiny (dosage formulation: 0.15 mg of desogestrel plus 0.03 mg of ethynylestradiol), the cost of synthesis is an important consideration, especially for use by developing countries. Despite extensive effort by various research groups to implement an effective total synthesis of **1**,[2] the published synthetic routes are lengthy and far from ideal. The angular ethyl group at C(13) of **1** (i.e., at the C/D ring fusion), which is responsible for a *50-fold* enhancement of biological potency relative to the C(13) methyl analogue, poses a surprisingly great synthetic obstacle in a number of possible synthetic approaches. For example, in our own laboratory the seemingly straightforward transformations outlined in eqs 1 and 2 (Chart 1) could not be realized.[3] In addition, attempts to produce key tetracyclic intermediates by cation−olefin cyclization failed, as shown in eqs 3 and 4 of Chart 1.[4]



1 (Desogestrel)



2

In this paper we describe a successful solution to the challenging problem of developing a concise and stereocontrolled synthetic route to **1**. The starting materials for this synthesis, which is outlined in Chart 2, are the chiral bicyclic diketone **2**, readily available by the Hajos−Parrish−Robinson annulation process,[5] and its sodium borohydride reduction product, **3**.[5] Keto alcohol **3** was efficiently converted to the *tert*-butyldimethylsilyl (TBS) ether **4**.[6] An excellent procedure was developed for the hydridoalkyl cuprate-induced reduction[7a−c] of the α,β-double bond in **4** to form stereoselectively the trans-fused indanone **5** in >90% yield. In this procedure, only a catalytic amount of *t*-BuCu (∼0.3 equiv) is used along with the stoichiometric reductant diisobutylaluminum hydride (2 equiv)−hexamethylphosphoric triamide (HMPA) complex, which is added slowly to the mixture of *t*-BuCu and **4** at −78 °C. Our results on the efficient and stereoselective conversion of **4** to **5** recommend the use of this methodology as an excellent solution to the longstanding problem of trans-fused hydrindanone synthesis.[7d] α-Methoxycarbonylation of **5** with dimethyl carbonate−sodium methoxide−sodium hydride in 1:1 THF−hexane (optimum) proceeded regioselectively (6.3:1) to give the enolic β-keto ester **6**. The regioselectivity of this reaction is lower in THF as sole solvent (4.3:1) than in the 1:1 hexane−THF medium which appears to be the best. Sequential double deprotonation of **6** first by NaH and then by *n*-BuLi (in THF) afforded a metalated enolate which underwent position and stereospecific alkylation by *m*-methoxyphenethyl iodide (**7**)[14]

(1) (a) van den Heuvel, M. J.; Bokhoven, C. W.; de Jongh, H. P.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 331. (b) de Flines, J.; van der Waard, W. F. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 129.

(2) See, for example, the following and references therein: (a) Groen-Piotrowska, E. M.; Groen, M. B. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 627. (b) Schwarz, S.; Ring, S.; Weber, G.; Teichmüller, G.; Palme, H.-J.; Pfeiffer, C.; Undeutsch, B.; Erhart, B.; Grawe, D. *Tetrahedron* **1994**, *50*, 10709. (c) Gao, H.; Su, X.; Li, Z. *Steriods* **1997**, *62*, 398.

(3) Dr. Yong-Jin Wu, unpublished research report, Harvard University, 1994.

(4) Huang, A. X., unpublished research report, Harvard University, 1997.

(5) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612, 1615. (b) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675.

(6) The reaction mixture containing **4** was treated with aqueous acid to convert any enol ether that was present back to α,β-enone.

(7) (a) Daniewski, A. R.; Kiegel, J. *Synth. Commun.* **1988**, *18*, 115. (b) Groth, U.; Taapken, T. *Liebigs Ann. Chem.* **1994**, 669. (c) Daniewksi, A. R.; Piotrowska, E.; Wojciechowska, W. *Liebigs Ann. Chem.* **1989**, 1061. (d) For a recent paper on this subject, see: Satoh, S.; Sodeoka M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 2278.

(8) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(9) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (b) Corey, E. J.; Wess, G.; Xiang, Y. B.; Singh, A. K. *J. Am. Chem. Soc.* **1987**, *109*, 4717.

(10) Turner, R. B.; Buchard, O.; Herzog, E.; Morin, R. B.; Riebel, A.; Sanders, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 1766.

(11) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(12) Midland, M. M.; McLoughlin, J. I.; Werley, R. T., Jr. *Org. Synth.* **1990**, *68*, 14.

(13) Imamoto, T.; Sugiura Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

(14) Prepared in 88% overall yield by the two-step sequence from commercially available 3-methoxyphenylacetic acid: (1) LAH, Et_2O, reflux; (2) PPh_3, imidazole, I_2, CH_2Cl_2. See: (a) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003. (b) Kopach, M. G.; Fray. A. H.; Meyers, A. I. *J. Am. Chem. Soc.* **1996**, *118*, 9876.

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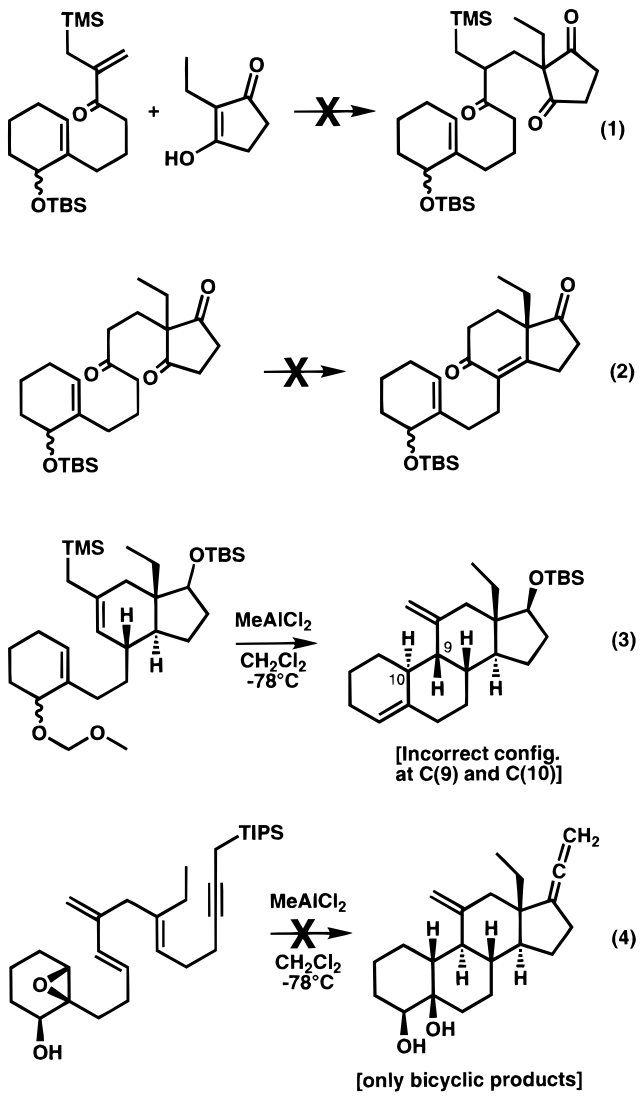
Chart 1



to afford efficiently the tricyclic β-keto ester **8**.[8] The details of this operation, which are critical to success, are fully described in the Experimental Section.

The crucial construction of the tetracyclic framework of desogestrel was accomplished by the cationic cyclization **8** → **9** using 10% CF_3CO_2H in CH_2Cl_2 at 23 °C for 24 h followed by base treatment of the crude product (K_2CO_3 in CH_3OH at 23 °C for 1 h). In the course of this process, the TBS ether function at C(17) is converted to the corresponding trifluoroacetate which is then cleaved by methanolic base to form **9**. The TBS ether was readily reintroduced into **9** by the silylation **9** → **10**. Other acidic catalysts were also studied for the cyclization step (e.g., CH_3SO_3H, Cl_2CHCO_2H, and CH_3CO_2H) but were found to be less satisfactory than CF_3CO_2H. The overall yield of **10** was 73% for the four steps from **6**. Reduction of the tetracyclic ester **10** provided the primary allylic alcohol **11**, which was then subjected to allylic diazine [3,3]-sigmatropic rearrangement[9] to form the desired exomethylene structure **12** stereoselectively and in good yield from **10**.

Birch reduction[10,2b] of **12** gave the corresponding 1-methoxy-1,4-cyclohexadiene, which upon treatment with aqueous acid underwent desilylation and conversion to the α,β-enone **13** in 85% overall yield. Two-step deoxygenation[2b] of the α,β-enone **13** gave hydroxy diene **14** which was oxidized to keto diene **15** in excellent yield by the Dess−Martin periodinane method.[11] Desogestrel (**1**) was synthesized from **15** in 92% yield by treatment with the mixed reagent from ethynyllithium[12] and cerium trichloride[13] in THF solution. Synthetic desogestrel, and also the ketone precursor **15**, made as outlined in Chart 2 were identical with authentic samples generously provided by Dr. Marinus Groen of Akzo Nobel-Organon in Oss, The Netherlands, by the following comparisons: ^{1}H and ^{13}C NMR, infrared, and mass spectra; chromatographic behavior, melting point and mixture melting point; optical rotation.

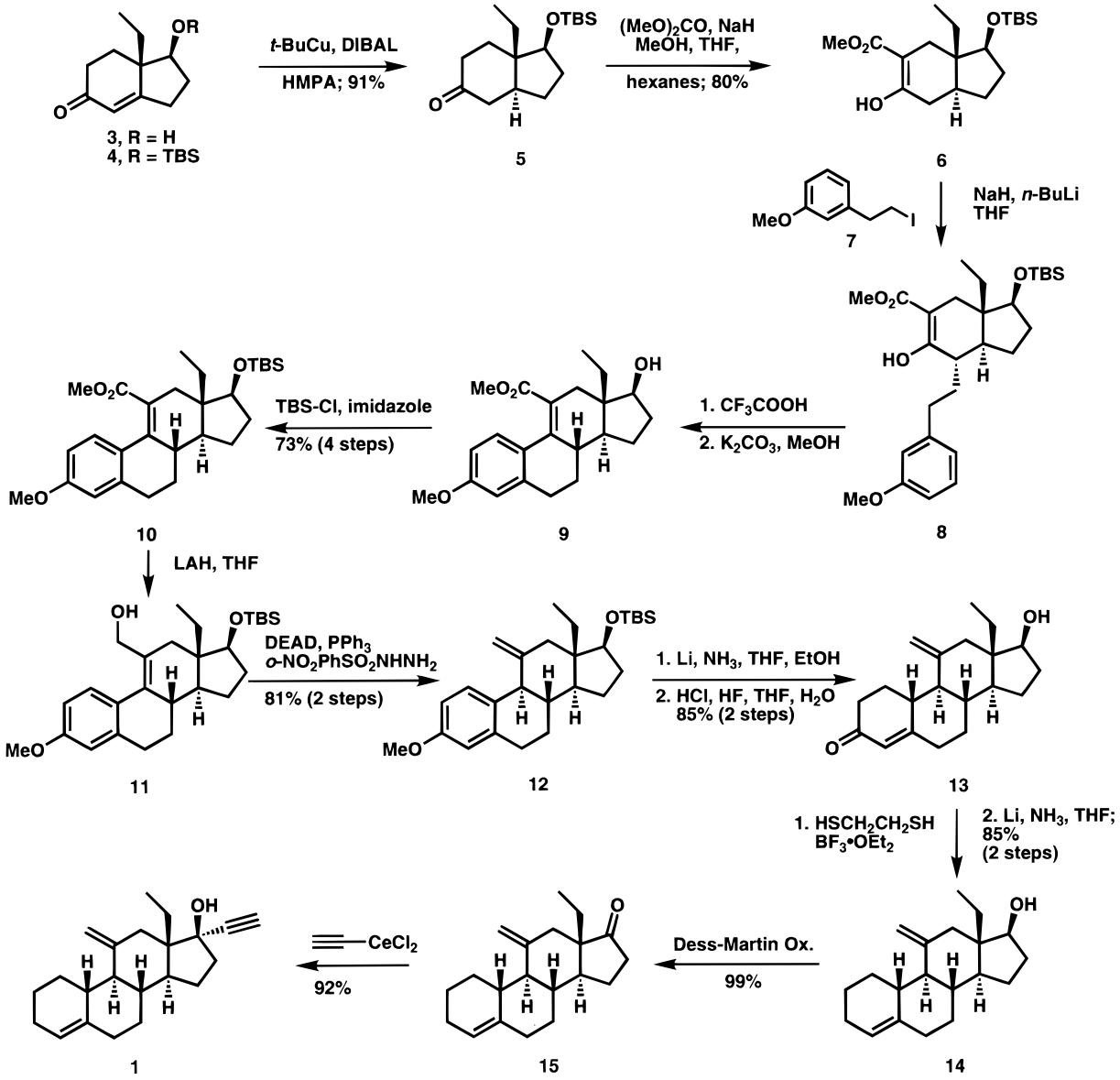
The synthesis outlined in Chart 2 is short and potentially useful for the production of desogestrel. The keys to its success are as follows: (1) the use of readily available chiral starting material; (2) brevity and simplicity of construction of the ring system, especially through the use of cationic cyclization for the closure of ring B; (3) novel synthetic tactic for generation of the 11-exomethylene group and the correct stereochemistry of the C/D and B/C ring fusions; and (4) overall stereo- and regiocontrol.

Experimental Section

(+)-(1*S*,7a*S*)-7,7a-Dihydro-1-(*tert*-butyldimethylsiloxy)-7a-ethyl-5(6*H*)-indanone (4). To a solution of **3** (21.89 g, 0.121 mol) in 75 mL of anhydrous DMF were added *tert*-butyldimethylsilyl chloride (36.78 g, 0.244 mol) and imidazole (16.61 g, 0.244 mol). The mixture was stirred and heated to 50 °C for 6 h. After cooling to 25 °C, 3 M aqueous H_3PO_4 solution was added slowly, followed by 100 mL of hexanes. The layers were separated, and the aqueous layer was extracted twice with 75 mL of hexanes. The organic extract was concentrated in vacuo, and the yellow residue was dissolved in 100 mL of THF. This solution was treated with 50 mL of 0.5 M aqueous HCl and vigorously stirred for 4 h to effect hydrolysis of any silyl enol ether of **4** that was present (assayed by TLC). Solid $NaHCO_3$ was added until gas evolution ceased, and the resulting mixture was concentrated in vacuo to remove THF. The residue was extracted three times with 100 mL of hexanes. The hexane extract was dried over Na_2SO_4 and passed through a column of silica gel (30 g). After elution with 1.0 L of ether, the combined eluent was evaporated and dried under vacuum (0.3 Torr, 45 °C) for 24 h to yield 34.0 g (0.116 mol, 95%) of **4**: $[\alpha]_D^{25}$ +60.4 (*c* 2.1, benzene); >97.5% pure by NMR analysis. A pure sample was obtained by silica gel chromatography (elution with 3−5% EtOAc in hexanes): $[\alpha]_D^{25}$ +64.8 (*c* 0.945, benzene); R_f 0.35 (20% EtOAc in hexanes); FTIR (neat) υ 2956, 2930, 2858, 1674, 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.79 (s, 1H), 3.79 (dd, J = 9.8, 7.8 Hz, 1H), 2.63 (ddt, J = 19.5, 11.8, 2.5 Hz, 1H), 2.50−2.40 (m, 1H), 2.38−2.24 (m, 3H), 1.96 (m, 1H), 1.88−1.75 (m, 2H), 1.65 (dt, J = 13.8, 5.5 Hz, 1H), 1.54 (m, 1H), 1.02 (t, J = 7.6 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 199.6, 175.1, 123.7, 82.6, 77.3, 48.1, 33.8, 32.7, 30.1, 27.4, 25.8, 24.4, 18.0, 11.1; HRMS (CI, M + H$^+$) calculated for $[C_{17}H_{30}O_2Si + H]^+$ 295.2093, found 295.2104.

(+)-(1*S*,3a*S*,7a*S*)-Hexahydro-1-(*tert*-butyldimethylsiloxy)-7a-ethyl-5-indanone (5). A solution of 1.7 M *t*-BuLi (2.79 mL, 4.74 mmol) in pentane was added dropwise to a slurry of 0.885 g (4.30 mmol) of CuBr·Me_2S in 8.5 mL of dry THF at −78 °C. The mixture was warmed to −50 °C and stirred for 15 min to give a tan solution. HMPA (5 mL) was added, and the resulting solution was cooled to −78 °C. A solution of **4** (4.20 g, 14.4 mmol) in 6.3 mL of THF was added via cannula and then a solution of DIBAL (28.7 mmol) in toluene−HMPA (prepared by mixing 28.7 mL of 1.0 M DIBAL in toluene and 14 mL of HMPA at 0 °C) was added dropwise via cannula over a period of 2 h at −78 °C. The dark reaction mixture was warmed to −45 °C and stirred for another 12 h. After addition of 50 mL of hexanes and 40 mL of 2.0 M aqueous HCl solution, the mixture was warmed to room temperature. The two layers were separated, and the aqueous layer was extracted twice with 20 mL of hexanes. The hexane extract was dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude **5** as an oil. Purification by silica gel chromatography (5% EtOAc in hexanes) gave 3.84 g (91%) of the desired product, **5**: $[\alpha]_D^{25}$ +49.5 (*c* 1.17, benzene); R_f 0.48 (20% EtOAc in hexanes); FTIR (neat) υ 2956, 2933, 2880,

Chart 2



2860, 1714, 1467, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.70 (t, J = 8.4 Hz, 1H), 2.40−2.17 (m, 5H), 2.00 (m, 1H), 1.80−1.32 (m, 6H), 1.21 (m, 1H), 1.08 (t, J = 7.5 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 212.0, 82.5, 45.7, 43.6, 42.6, 37.7, 32.0, 31.4, 25.9, 25.0, 18.1, 16.7, 9.7, −4.6, −4.8; HRMS (EI, M^+) calculated for $[C_{17}H_{32}O_2Si]^+$ 296.2172, found 296.2167.

Two byproducts were also isolated. The first one was found to be (+)-(1*S*,3a*R*,7a*S*)-hexahydro-1-(*tert*-butyldimethylsiloxy)-7a-ethylindan-5-one: yield 0.12 g (2.8%); $[\alpha]_D^{25}$ +52.0 (*c* 1.35, benzene); R_f 0.57 (20% EtOAc in hexanes); FTIR (neat) υ 2946, 2874, 1717, 1461, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.85 (dd, J = 5.3, 3.7 Hz, 1H), 2.43 (dd, J = 14.9, 6.2 Hz, 1H), 2.30 (m, 2H), 2.24−2.07 (m, 2H), 2.00−1.82 (m, 2H), 1.77 (m, 1H), 1.67 (m, 1H), 1.60−1.47 (m, 2H), 1.41 (m, 1H), 1.20 (m, 1H), 0.89 (t, J = 7.5 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 213.5, 78.2, 45.9, 42.7, 42.0, 36.8, 32.3, 28.5, 27.0, 25.8, 23.9, 18.0, 9.0, −4.0, −5.0; HRMS (CI, M + NH_4^+) calculated for $[C_{17}H_{32}O_2Si + NH_4]^+$ 314.2515, found 314.2524.

The second one was identified as (+)-(1*S*,5*S*,7a*S*)-5,6,7,7a-tetrahydro-1-(*tert*-butyldimethylsiloxy)-7a-ethylindan-5-ol: yield 38 mg (0.9%); $[\alpha]_D^{25}$ +18.8 (*c* 0.24, benzene); R_f 0.20 (20% EtOAc in hexanes); FTIR (neat) υ 3328, 2956, 2933, 2898, 2879, 2858, 1467, 1254 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.39 (m, 1H), 4.20 (m, 1H), 3.58 (t, J = 8.8 Hz, 1H), 2.38 (m, 1H), 2.09−1.80 (m, 4H), 1.70−1.60 (m, 5H), 1.21 (dt, J = 13.3, 4.0 Hz, 1H), 0.93 (t, J = 9.5 Hz, 3H), 0.85 (s, 9H), −0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 148.9, 123.1, 82.4, 68.0, 46.5, 31.1, 30.1, 29.6, 26.5, 25.9, 24.5, 18.1, 10.6, −4.5, −4.8.

(+)-(1*S*,3a*S*,7a*S*)-3a,4,7,7a-Tetrahydro-1-(*tert*-butyldimethylsiloxy)-6-carbomethoxy-7a-ethyl-5-hydroxyindane (6). To a stirred suspension of NaH (1.36 g, 57 mmol) in 11 mL of THF and 14 mL of hexanes at 23 °C were added 2.39 mL (2.55 g, 28 mmol) of dimethyl carbonate and 0.11 mL (0.090 g, 2.8 mmol) of anhydrous methanol via syringe. The mixture was heated to reflux. A solution of 4.20 g (14 mmol) of **5** in 3 mL of THF was added dropwise via cannula over a period of 1 h, and the resulting mixture was heated at reflux for 1 h. After cooling to 0 °C, 4.0 g (67 mmol) of acetic acid was added slowly. Dilution with 50 mL of hexanes, filtration through a pad of Celite, and concentration in vacuo afforded crude **6** as an oil. Silica gel chromatography (3% EtOAc in hexanes) gave 4.01 g (80%) of **6** as a colorless oil, which solidified upon cooling: mp 51−52 °C; $[\alpha]_D^{25}$ +81.6 (*c* 2.20, benzene); R_f 0.36 (10% EtOAc in hexanes); FTIR (neat) υ 2956, 2933, 1654, 1609, 1287, 1261 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.72 (s, 1H), 3.75 (s, 3H), 3.75 (t, J = 8.2 Hz, 1H), 2.72 (d, J = 15.5 Hz, 1H), 2.28 (ddd, J = 17.0, 5.9, 1.3 Hz, 1H), 2.15 (ddd, J = 18.3, 11.7, 2.3 Hz, 1H), 1.96 (m, 1H), 1.69−1.56 (m, 4H), 1.39 (m, 2H), 1.13 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.5, 172.6, 96.8, 83.1, 51.5,

43.5, 40.8, 32.0, 31.6, 30.9, 25.9, 25.0, 18.1, 17.2, 10.4, −4.5, −4.8; HRMS (EI, M^+) calculated for $[C_{19}H_{34}O_4Si]^+$ 354.2226, found 354.2225.

(+)-(1*S*,3a*S*,4*S*,7a*S*)-hexahydro-1-(*tert*-butyldimethylsiloxy)-4-carbomethoxy-7a-ethyl-5-indanone (0.41 g, 8%) was also isolated: mp 98.6−99.2 °C; $[\alpha]_D^{25}$ +8.7 (*c* 2.49, benzene); R_f 0.12 (10% EtOAc in hexanes); FTIR (neat) υ 2956, 2933, 2874, 1749, 1712, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75 (t, J = 8.4 Hz, 1H), 3.70 (s, 3H), 2.40 (d, J = 13.6 Hz, 1H), 2.41−2.26 (m, 3H), 2.10 (dt, J = 13.0, 7.2 Hz, 1H), 2.02 (m, 1H), 1.68 (m, 2H), 1.55 (m, 1H), 1.49−1.28 (m, 3H), 1.08 (t, J = 7.5 Hz, 3H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 205.9, 169.9, 82.1, 58.6, 52.0, 47.8, 43.7, 37.6, 31.7, 31.2, 25.9, 23.6, 18.1, 17.8, 9.8, −4.6, −5.9; HRMS (CI, M + NH_4^+) calculated for $[C_{19}H_{34}O_4Si + NH_4]^+$ 372.2570, found 372.2557.

(+)-(1*S*,3a*S*,4*S*,7a*S*)-3a,4,7,7a-Tetrahydro-1-(*tert*-butyldimethylsiloxy)-6-carbomethoxy-7a-ethyl-5-hydroxy-4-(2-(3-methoxyphenyl)-ethyl)indane (8). To a stirred suspension of 87 mg of NaH (60% suspension in mineral oil, 2.2 mmol) in 3.0 mL of THF was added dropwise a solution of **6** (500 mg, 1.4 mmol) in 2.0 mL of THF. The resulting mixture was heated to 45 °C for 30 min and then cooled to −78 °C. A 1.6 M solution of *n*-BuLi in hexanes (1.19 mL, 1.90 mmol) was added dropwise. The mixture was warmed slowly to 0 °C over a 1-h period and maintained at that temperature for 30 min. To the resulting orange solution was added **7**[14] (388 mg, 1.48 mmol) via syringe at −78 °C. The resulting mixture was stirred at −45 °C for 12 h and slowly warmed to 0 °C over a 4-h period. The reaction mixture was treated with 0.30 mL of acetic acid, 15 mL of hexanes, and 2 g of Celite, and the whole was passed through a short silica gel column, which was further eluted with 4:1 hexanes−ethyl acetate. The eluent was evaporated in vacuo to give crude **8** as an oil, which was used without further purification in the subsequent reaction. A pure sample was obtained by preparative TLC: $[\alpha]_D^{25}$ +2.10 (*c* 2.42, benzene); R_f 0.24 (10% EtOAc in hexanes); FTIR (neat) υ 2943, 2872, 1728, 1612, 1460, 1360, 1252 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.37 (s, 1H), 7.17 (t, J = 7.8 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 6.74−6.70 (m, 2H), 3.80 (t, J = 8.5 Hz, 1H), 3.78 (s, 6H), 2.76 (d, J = 15.5 Hz, 1H), 2.68−2.45 (m, 2H), 2.41 (m, 1H), 2.10 (m, 1H), 1.99 (m, 1H), 1.85−1.53 (m, 5H), 1.50−1.28 (m, 2H), 1.18 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 174.9, 173.7, 159.7, 144.4, 129.2, 120.9, 114.2, 111.1, 97.3, 83.2, 55.1, 51.6, 44.9, 43.4, 41.4, 32.2, 31.5, 31.2, 30.9, 25.9, 24.1, 18.1, 17.9, 10.5, −4.6, −5.8; HRMS (EI, M^+) calculated for $[C_{28}H_{44}O_5Si]^+$ 488.2958, found 488.2948.

11-Carbomethoxy-13-ethyl-3-methoxygona-1,3,5(10),9(11)-tetraen-17β-ol (9). To a stirred solution of the alkylation product **8** obtained as above in 15 mL of CH_2Cl_2 at 23 °C was added 1.5 mL of trifluoroacetic acid (2.2 g, 19.5 mmol). The solution was protected from light (aluminum foil) and stirred for 24 h. The resulting tan solution was evaporated in vacuo to yield a brown residue containing **9** and corresponding trifluoroacetate. Treatment of this mixture in methanol (15 mL) with 585 mg of anhydrous K_2CO_3 at 23 °C for 1 h effected cleavage of the trifluoroacetate. Evaporation in vacuo, addition of 6.5 mL of 1.0 M aqueous HCl, and extractive workup with ethyl acetate gave crude **9**, which was dried azeotropically with toluene and directly used in the next step. A pure sample of **9** was obtained by preparative TLC: mp 156−157 °C; $[\alpha]_D^{25}$ +219.6 (*c* 1.45, benzene); R_f 0.34 (40% EtOAc in hexanes); FTIR (neat) υ 3470, 2942, 2869, 1702, 1605, 1487, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.03 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 6.59 (s, 1H), 3.86 (t, J = 8.8 Hz, 1H), 3.75 (s, 3H), 3.59 (s, 3H), 3.09 (d, J = 17.5 Hz, 1H), 2.96−2.78 (m, 2H), 2.13 (m, 3H), 2.03 (br, 1H), 1.92 (dd, J = 17.5, 2.6 Hz, 1H), 1.79 (m, 1H), 1.65 (m, 1H), 1.58−1.22 (m, 5H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.4, 159.4, 142.7, 138.7, 129.3, 127.4, 122.9, 113.1, 111.6, 83.5, 55.2, 51.7, 48.8, 43.1, 39.8, 38.0, 30.8, 28.9, 28.9, 23.7, 17.8, 10.5; HRMS (CI, M + H^+) calculated for $[C_{22}H_{28}O_4 + H]^+$ 357.2066, found 357.2075.

17β-(*tert*-Butyldimethylsiloxy)-11-carbomethoxy-13-ethyl-3-methoxygona-1,3,5(10),9(11)-tetraene (10). To a solution of the crude product **9** obtained as above in 5 mL of anhydrous DMF were added 425 mg (2.8 mmol) of *tert*-butyldimethyl chloride and 240 mg of (3.53 mmol) imidazole. The resulting solution was stirred at 50 °C for 12 h. Most of the DMF was removed by evaporating the mixture at 0.3 Torr and 50 °C. The residue was treated with 10 mL of water. Extractive workup with ethyl acetate afforded a residue which was purified by silica gel chromatography (5% EtOAc in hexanes) to give 482 mg of pure **10** (73% for four steps) as a colorless oil which solidified upon cooling: mp 93−94 °C; $[\alpha]_D^{25}$ +201.1 (*c* 0.945, benzene); R_f 0.46 (20% EtOAc in hexanes); FTIR (neat) υ 2946, 2860, 1710, 1608, 1499, 1463, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.05 (d, J = 8.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 3.77 (t, J = 8.3 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 3.00 (d, J = 18.1 Hz, 1H), 2.95−2.80 (m, 2H), 2.13 (m, 2H), 1.98 (m, 1H), 1.87 (dd, J = 17.5, 2.7 Hz, 1H), 1.77 (m, 1H), 1.63 (m, 1H), 1.56−1.42 (m, 2H), 1.39 (dq, J = 12.0, 5.6 Hz, 1H), 1.33 (m, 1H), 1.22 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 173.7, 159.4, 142.1, 138.7, 129.3, 127.6, 123.4, 113.1, 111.6, 83.6, 55.2, 51.7, 48.4, 43.2, 39.8, 38.4, 31.5, 29.0, 25.9, 25.9, 23.9, 18.2, 18.1 10.4, −4.5, −4.7; HRMS (CI, M + H^+) calculated for $[C_{28}H_{42}O_4Si + H]^+$ 471.2931, found 471.2925.

17β-(*tert*-Butyldimethylsiloxy)-13-ethyl-11-(hydroxymethyl)-3-methoxygona-1,3,5(10),9(11)-tetraene (11). To a solution of **10** (650 mg, 1.38 mmol) in 7.0 mL of THF at 0 °C was slowly added 79 mg (2.07 mmol) of lithium aluminum hydride powder. The mixture was warmed to 23 °C and stirred for 2 h. After dilution with 30 mL of Et_2O, the reaction mixture was cooled to 0 °C, and 0.80 g of finely ground $Na_2SO_4 \cdot 10H_2O$ powder was added slowly, followed by 1 g of Celite. The resulting mixture was stirred at 23 °C for 16 h, and the whole was passed through a short column of silica which had been washed with 5% Et_3N in Et_2O. The column was further eluted with 50 mL of 5% Et_3N in Et_2O. The combined eluent was concentrated in vacuo to give 580 mg (95%) of **11** as a white foam, which was pure and used in the next step without further purification: mp 127−128 °C; $[\alpha]_D^{25}$ +198.4 (*c* 2.91, benzene); R_f 0.34 (20% EtOAc in hexanes); FTIR (neat) υ 3419, 2940, 2868, 1601, 1473, 1376, 1252 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz) δ 7.56 (d, J = 8.5 Hz, 1H), 6.73 (dd, J = 8.5, 2.7 Hz, 1H), 6.70 (s, 1H), 4.34 (d, J = 10.9 Hz, 1H), 3.97 (d J = 10.9 Hz, 1H), 3.74 (t, J = 8.5 Hz, 1H), 3.37 (s, 3H), 2.96 (d, J = 17.2 Hz, 1H), 2.79−2.62 (m, 2H), 2.07 (m, 1H), 1.89 (m, 2H), 1.79 (dd, J = 17.2, 2.6 Hz, 1H), 1.62−1.50 (m, 3H), 1.37 (m, 2H), 1.23 (t, J = 7.5 Hz, 3H), 1.19 (m, 1H), 1.33 (m, 1H), 1.03 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (C_6D_6, 101 MHz) δ 159.4, 139.2, 136.3, 130.9, 129.3, 129.1, 113.7, 111.3, 84.3, 64.4, 54.7, 49.0, 43.8, 39.9, 38.9, 31.8, 29.8, 29.3, 26.2, 24.3, 18.4, 18.3, 10.9, −4.4, −4.6.

17β-(*tert*-Butyldimethylsiloxy)-13-ethyl-11-methylene-3-methoxygona-1,3,5(10)-triene (12). To a solution of 534 mg (2.07 mmol) of PPh_3 in 5 mL of THF at −15 °C was added 326 μL of diethyl azodicarboxylate (361 mg, 2.07 mmol) dropwise. The resulting yellow solution was stirred at −15 °C for 15 min and cooled to −40 °C. A solution of **11** prepared above in 3 mL of THF was added via cannula, followed by a solution of *o*-nitrobenzenesulfonylhydrazide (420 mg, 1.93 mmol) in 5 mL of THF 5 min later. The resulting solution was warmed to −15 °C over a period of 1 h, stirred at −15 °C for 1 h, and finally warmed to 23 °C and stirred for 12 h. The mixture was evaporated in vacuo to give an orange residue, which was dissolved in minimal amount of CH_2Cl_2 and passed through a silica gel column. The column further was eluted with 100 mL of CH_2Cl_2. The eluent was concentrated, and the resulting residue was purified by silica gel chromatography (1% EtOAc in hexanes) to give 478 mg (85%) of **12** as a colorless oil which solidified upon cooling: mp 71−72 °C; $[\alpha]_D^{25}$ +256.0 (*c* 2.65, benzene); R_f 0.42 (5% EtOAc in hexanes); FTIR (neat) υ 3065, 2939, 2871, 1611, 1477, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, J = 8.7 Hz, 1H), 6.70 (dd, J = 8.6, 2.7 Hz, 1H), 6.63 (d, J = 2.6 Hz, 1H), 4.96 (s, 1H), 4.85 (s, 1H), 3.82 (t, J = 9.0 Hz, 1H), 3.78 (s, 3H), 2.99 (d, J = 10.5 Hz, 1H), 2.91 (d, J = 12.1 Hz, 1H), 2.83 (dt, J = 12.5 3.7 Hz, 1H), 2.71 (m, 1H), 2.00 (m, 1H), 1.79 (m, 1H), 1.72 (d J = 12.1 Hz, 1H), 1.68−1.53 (m, 2H), 1.48−1.36 (m, 1H), 1.33 (m, 3H), 1.36−1.23 (m, 3H), 1.04 (t, J = 7.4 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 157.3, 147.9, 139.3, 131.1, 128.0, 113.7, 111.4, 108.8, 83.3, 55.2, 51.8, 51.5, 47.2, 44.8, 41.7, 31.8, 31.0, 27.0, 26.0, 22.2, 19.2, 18.1 9.1−4.6, −4.7; HRMS (EI, M^+) calculated for $[C_{27}H_{42}O_2Si]^+$ 426.2954, found 426.2951.

13-Ethyl-17β-hydroxy-11-methylenegona-4-en-3-one (13). Anhydrous NH_3 (7.5 mL) was distilled into a flask containing a solution of **12** (200 mg, 0.47 mmol) in 2.5 mL of THF and 0.25 mL of absolute EtOH at −78 °C. The resulting slurry (**12** had precipitated out of solution) was stirred under a nitrogen atmosphere. Small pieces of Li ribbon (45 mg, 6.48 mmol) were added portionwise over a period of 3 h, carefully avoiding the disappearance of the blue color. After stirring at −78 °C for another 1 h, solid NH_4Cl (0.5 g) was added to the mixture slowly, followed by 5 mL of hexanes. Ammonia was allowed to evaporate as the mixture slowly warmed to room temperature. Another 10 mL of hexanes and 5 mL of water were added. The two layers were separated, and the aqueous layer was extracted two times with 5 mL of hexanes. The combined organic extract was evaporated in vacuo to give a colorless oil, which was directly used in the next step.

To a solution of the crude product obtained above in 15 mL of THF in a plastic reaction vessel were added 5 mL of 1.0 M aqueous HCl and 2.0 mL of 48% aqueous HF. The resulting solution was stirred at 23 °C for 20 h. After the reaction mixture was diluted with 10 mL of water and 10 mL of ether, solid $NaHCO_3$ was added slowly until gas evolution ceased. The resulting mixture was filtered and evaporated in vacuo. Extractive workup of the aqueous residue with EtOAc afforded a yellow paste, which was purified by silica gel chromatography (15% EtOAc in hexanes) to give 120 mg (85%) of **13** as a white solid: mp 152−153 °C; $[\alpha]_D^{25}$ +180.6 (*c* 0.53, benzene); R_f 0.32 (40% EtOAc in hexanes); FTIR (neat) υ 3420, 2941, 2875, 1658, 1441, 1348, 1262 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83 (s, 1H), 4.98 (s, 1H), 4.76 (s, 1H), 3.79 (t, J = 8.4 Hz, 1H), 2.82 (d, J = 12.4 Hz, 1H), 2.61−2.04 (m, 7H), 1.95 (br s, 1H), 1.76 (m, 1H), 1.59 (d, J = 12.3 Hz, 1H), 1.58−1.18 (m, 9H), 1.02 (m, 1H), 1.01 (t, J = 9.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 200.2, 166.8, 146.1, 125.6, 108.6, 82.9, 54.1, 52.2, 46.6, 44.4, 41.6, 37.6, 36.9, 35.4, 30.9, 30.1, 28.3, 22.1, 18.6, 8.9; HRMS (EI, M^+) calculated for $[C_{20}H_{28}O_2]^+$ 300.2089, found 300.2095.

13-Ethyl-11-methylenegona-4-en-17β-ol (14). To a solution of **13** (210 mg, 0.70 mmol) in 2.0 mL of MeOH were added 88 μL of 1,2-ethanedithiol (99 mg, 1.05 mmol) and 52 μL of BF_3•Et_2O (60 mg, 0.42 mmol). The solution was stirred at 23 °C for 2 h. Saturated aqueous $NaHCO_3$ was added, and the resulting mixture was stirred for 30 min at 23 °C. Extractive workup of the aqueous phase with EtOAc gave a white solid, which was dissolved in EtOAc and passed through a short column of silica gel. The eluent was evaporated at 0.3 Torr for 12 h to give 265 mg (100%) of 13-ethyl-3,3-(ethylenedithio)-11-methylenegona-4-en-17β-ol as a white solid, which was pure and used directly in the next step.

To a two-necked flask equipped with dry ice condenser was added Li ribbon (26.7 mg, 3.85 mmol) under a nitrogen atmosphere. The flask was cooled in a −40 °C bath, while anhydrous NH_3 (6 mL) was distilled into it. A solution of 145 mg (0.38 mmol) of 13-ethyl-3,3-(ethylenedithio)-11-methylenegona-4-en-17β-ol in 2 mL of THF was added dropwise to the deep blue ammonia solution via cannula over a 10-min period. The cooling bath was removed, and the reaction mixture was kept at reflux for 30 min. Solid NH_4Cl (0.5 g) was added to the mixture slowly, and ammonia was allowed to evaporate as the mixture slowly warmed to room temperature. Water (5 mL) was added to the reaction mixture. Extractive workup with EtOAc gave crude **14** as a colorless oil, which was purified by silica gel chromatography (5% EtOAc in hexanes) to give 94 mg (85%) of pure **14** as a colorless oil, which solidified upon cooling.

Analytical data for 13-ethyl-3,3-(ethylenedithio)-11-methylenegona-4-en-17β-ol: $[\alpha]_D^{25}$ +142.3 (*c* 0.98, benzene); R_f 0.19 (20% EtOAc in hexanes); FTIR (neat) υ 3431, 2930, 2875, 1642, 1470, 1439, 1357, 1272 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.62 (s, 1H), 4.94 (s, 1H), 4.72 (s, 1H), 3.79 (t, J = 8.5 Hz, 1H), 3.34 (m, 3H), 3.22 (m, 1H), 2.79 (d, J = 12.2 Hz, 1H), 2.28 (m, 1H), 2.25−1.17 (m, 3H), 2.10 (m, 1H), 2.06 (m 1H), 1.93 (m, 1H), 1.69, (br s, 1H), 1.64 (m, 1H), 1.59 (d, J = 12.2 Hz, 1H), 1.51−1.39 (m, 2H), 1.39−1.12 (m, 7H), 1.02 t, J = 7.5 Hz, 3H), 0.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.7, 141.6, 126.1, 108.3, 83.0, 65.7, 54.5, 52.3, 46.6, 44.4, 41.9, 40.5, 40.0, 39.6, 35.8, 34.9, 31.1, 30.9, 28.6, 22.1, 18.5, 9.0; HRMS (EI, M^+) calculated for $[C_{22}H_{32}O_2S_2]^+$ 376.1895, found 376.1904.

Analytical data for **14**: mp 91−92 °C; $[\alpha]_D^{25}$ +134.8 (*c* 1.0, benzene); R_f 0.23 (20% EtOAc in hexanes); FTIR (neat) υ 3391, 3367, 2923, 2872, 2849, 1446 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44 (s, 1H), 4.93 (s, 1H), 4.73 (s, 1H), 3.79 (t, J = 8.5 Hz, 1H), 2.78 (d, J = 12.2 Hz, 1H), 2.27−2.14 (m, 3H), 2.09 (m, 1H), 1.92 (br, 3H), 1.65−1.45 (m, 4H), 1.58 (d, J = 11.8 Hz, 1H), 1.66−1.16 (m, 8H), 1.09 (m, 1H), 1.02 (t, J = 7.5 Hz, 3H), 0.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 147.3, 140.0, 121.4, 108.3, 83.4, 55.2, 52.7, 46.8, 44.7, 42.3, 36.7, 35.6, 31.8, 31.2, 29.2, 25.7, 22.2, 22.0, 18.6, 9.1; HRMS (CI, M^+) calculated for $[C_{20}H_{30}O + NH_4]^+$ 304.2640, found 304.2636.

13-Ethyl-11-methylenegona-4-en-17-one (15). To a stirred solution of **14** (100 mg, 0.35 mmol) in 3.5 mL of CH_2Cl_2 at 23 °C was added the Dess−Martin periodinane (222 mg, 0.52 mmol). The resulting mixture was stirred at 23 °C for 1 h. Saturated aqueous $NaHCO_3$ (3 mL) and 10% aqueous $Na_2S_2O_3$ (3 mL) were added, and the mixture was stirred for 2 h at 23 °C. The aqueous phase was extracted three times with 10 mL of CH_2Cl_2. The combined CH_2Cl_2 extract was dried over anhydrous Na_2SO_4 and passed through a short silica gel column. The column was further eluted with 50 mL of CH_2Cl_2. The combined eluent was evaporated at 0.3 Torr for 4 h to give 98 mg (99%) of pure **15** as a colorless oil which solidifies upon cooling; mp 92−93 °C; $[\alpha]_D^{25}$ +170.4 (*c* 1.15, chloroform); R_f 0.44 (20% EtOAc in hexanes); FTIR (neat) υ 2961, 2922, 2879, 2850, 1737, 1641, 1447 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.47 (s, 1H), 4.90 (d, J = 1.0 Hz, 1H), 4.81 (s, 1H), 2.55 (d, J = 12.7 Hz, 1H), 2.39 (dd, J = 18.9, 9.2 Hz, 1H), 2.30−2.13 (m, 3H), 2.09 (dt, J = 19.1, 8.7 Hz, 1H), 2.00−1.83 (m, 4H), 1.81 (d, J = 12.6 Hz, 1H), 1.76 (dq, J = 12.4, 3.3, 1H), 1.68−1.50 (m, 4H), 1.47−1.30 (m, 3H), 1.24 (m, 1H), 1.11 (m, 1H), 0.94 (m, 1H), 0.74 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 218.7, 146.0, 139.3, 121.7, 110.0, 55.1, 52.9, 52.3, 41.5, 39.6, 36.5, 36.1, 35.3, 31.0, 29.1, 25.6, 21.8, 20.8, 18.1, 7.2; HRMS (EI, M^+) calculated for $[C_{20}H_{28}O]^+$ 284.2141, found 284.2146.

Desogestrel (1). Acetylene gas was bubbled through 3.0 mL of THF at −78 °C for 30 min. Nitrogen was blown over the surface of the solution to purge any residual acetylene gas that might be remaining in the flask. A 1.6 M solution of *n*-BuLi (0.587 mL, 0.94 mmol) in hexane was slowly added along the side of the flask over 15 min. The resulting clear solution of monolithium acetylide was stirred at −78 °C for another 15 min. A suspension of anhydrous cerium(III) chloride (232 mg. 0.94 mmol) in 3.0 mL of THF, precooled to −78 °C, was added via cannula. The resulting yellow suspension was stirred at −78 °C for 1 h. A solution of **15** (89 mg, 0.31 mmol) in 3.0 mL of THF, precooled to −78 °C was added via cannula. The resulting mixture was stirred at −78 °C for 1 h, −40 °C for 1 h, and finally at 0 °C for 12 h. A 0.2 M aqueous solution of HCl (10 mL) was added, and the resulting mixture was filtered through a pad of Celite. The filtrate was evaporated in vacuo to remove THF. The aqueous residue was extracted three times with 10 mL of CH_2Cl_2. The combined CH_2Cl_2 extract was washed once with 10 mL of saturated aqueous $NaHCO_3$, once with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to give crude **1** as a colorless oil, which was purified by silica gel chromatography (5% EtOAc in hexanes) to give 89 mg (92%) of pure **1** as a white solid: mp 106−107 °C; $[\alpha]_D^{25}$ +53.6 (*c* 0.96, benzene); R_f 0.37 (20% EtOAc in hexanes); FTIR (neat) υ 3462, 3435, 3300, 2924, 2878, 2853, 1442 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.44 (s, 1H), 4.96 (d, J = 1.0 Hz, 1H), 4.76 (s, 1H), 2.59 (d, J = 12.3 Hz, 1H), 2.58 (s, 1H), 2.33 (ddd, J = 15.7, 9.7, 6.0 Hz, 1H), 2.25 (d, J = 12.2 Hz, 1H), 2.25−2.14 (m, 3H), 2.08 (ddd, J = 15.5, 11.9, 3.6 Hz, 1H), 1.93 (br, 3H), 1.83−1.73 (m, 2H), 1.67−1.55 (m, 3H), 1.50−1.20 (m, 6H), 1.12 (m, 1H), 1.02 (t, J = 7.4 Hz, 3H), 0.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 147.6, 140.0, 121.4, 108.6, 87.9, 81.2, 74.1, 54.7, 52.5, 50.5, 42.7, 40.7, 39.9, 36.7, 35.6, 31.8, 29.2, 25.8, 22.01, 21.97, 19.9, 9.2; HRMS (EI, M^+) calculated for $[C_{22}H_{30}O]^+$ 310.2297, found 310.2296.

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