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Syntheses of (*E*)- and (*Z*)-Volkendousin

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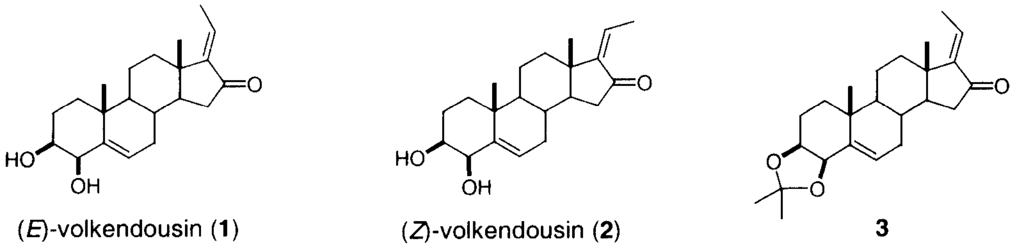
Abstract: The first syntheses of the antitumor agents (*E*)-volkendousin (**1**) and acetonide **3** have been accomplished by efficient routes from readily available dehydroisoandrosterone (**7**) using allylic oxidation with SeO_2 to introduce the 4β-hydroxy group and 16-ketone. This sequence should make these compounds readily available for further biological evaluation.

Melia volensii Gurke is a tree widely distributed in the dry areas of Eastern Africa. A tea prepared from the bark has been used in local folk medicine to alleviate pain and is poisonous in overdoses. McLaughlin and co-workers recently reported the isolation of (*E*)- and (*Z*)-volkendousin (**1** and **2**) from the root bark of this tree collected in Kenya.[1] (*E*)-Volkendousin (**1**) showed significant activity in the brine shrimp lethality test, the yellow fever larvae test, and six human tumor cell lines. The acetonide **3** prepared from **1** showed selectivity for the PC-3 (prostate) cell line at a potency equal to that of adriamycin. (*Z*)-Volkendousin (**2**) showed weaker activity.



(*E*)-volkendousin (**1**) (*Z*)-volkendousin (**2**) **3**

The potent biological activity of **1** and **3** prompted us to develop a route to these compounds from readily available steroid precursors. We envisioned that the 4-hydroxy group could be introduced by allylic oxidation of a 5-double bond with SeO_2, while the 16-ketone could be introduced by allylic oxidation of a 17(20)-double bond with SeO_2. (17*Z*)-Pregan-5,17(20)-dien-3β-ol (**4**) is readily available stereospecifically in high yield by a Wittig reaction on dehydroisoandrosterone (**7**).[2-4] Allylic oxidation with catalytic SeO_2 and *t*BuOOH[5,6] cleanly affords diol **5**, which has previously been prepared by a longer sequence culminating in treatment of 16,17-epoxy-3β-hydroxy-5-pregnen-20-one with hydrazine, which gives 30-40% of **5** as an mixture of double bond stereoisomers.[7-9] Oxidation of crude **5** with MnO_2 in CH_2Cl_2 affords (17*E*)-3β-hydroxypregna-5,17(20)-dien-

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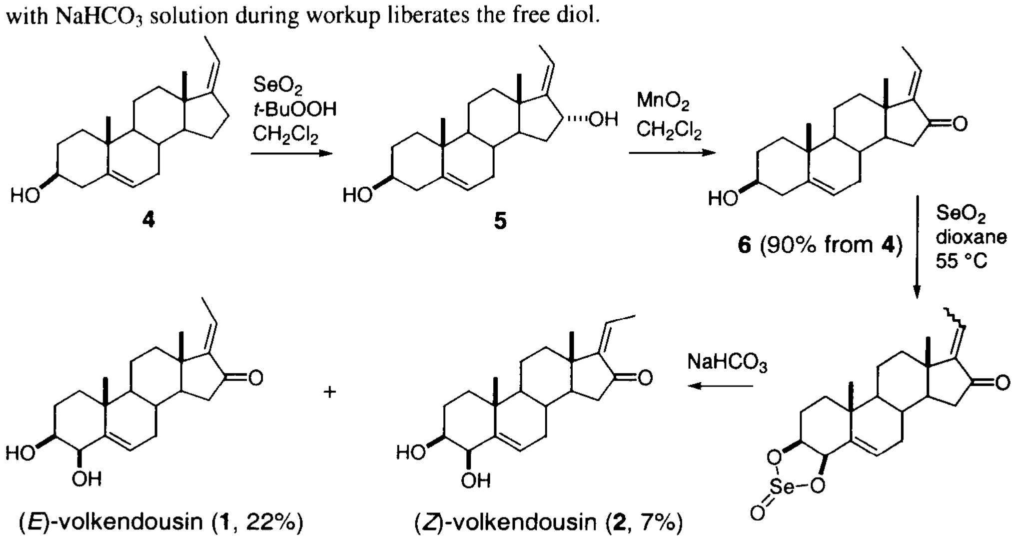
16-one (**6**) in 90% overall yield from **4**. Note that the (17*Z*)-double bond of **4** has the same geometry as the (17*E*)-double bond of **5** and **6**.

4β-Hydroxy groups have been introduced into cholesterol and related steroids by treatment with SeO_2[10-12] or bromine in chloroform followed by treatment with silver acetate and hydrolysis.[13-15] The latter protocol is not compatible with the 17(20)-en-16-one of **6**, which will also react with bromine. Oxidation of **6** with 2 equiv of SeO_2 in dioxane at 55 °C for 2 d provides a 3:1 mixture of **1** and **2** in 30% overall yield from **4**. This oxidation cannot be carried with catalytic SeO_2 and *t*-BuOOH, and even requires excess SeO_2 because the diol reacts with SeO_2 to give a cyclic selenite.[16,17] The NMR spectrum of the crude product shows peaks for the cyclic selenite at δ 5.16 and 4.73 in addition to those for the diol at δ 4.16 and 3.57. The alkene hydrogen absorbs at δ 6.00 in the selenite, downfield from δ 5.60 in the diol. Washing a solution of the cyclic selenite with $NaHCO_3$ solution during workup liberates the free diol.



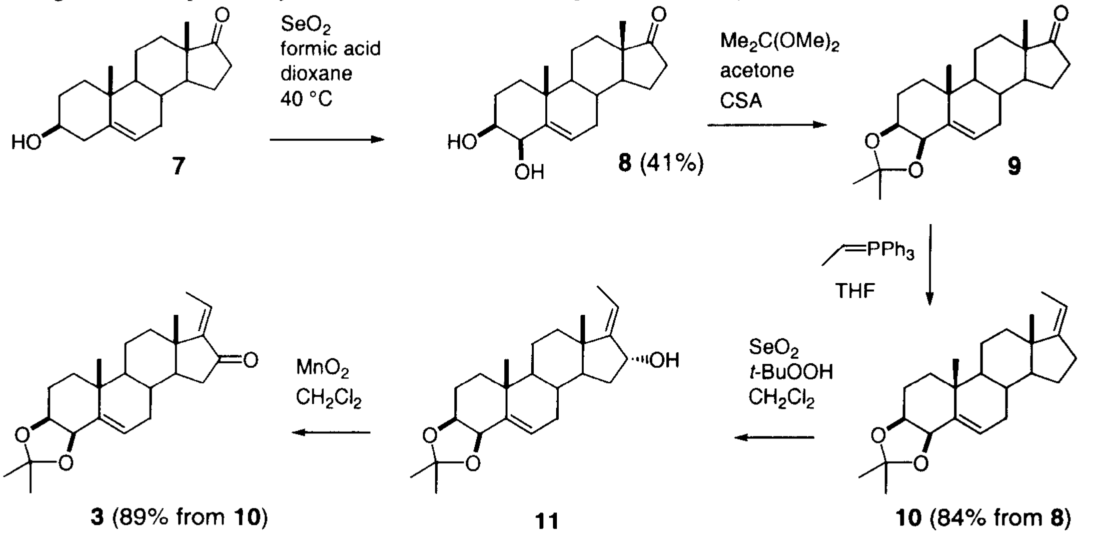
Steroidal (17*E*)- and (17*Z*)-17(20)-en-16-ones are known to be configurationally unstable. Djerassi reported that they equilibrate in diffuse daylight.[18] Trost found that they equilibrate on standing for 2 d.[6] Kessar and Rampal found that they readily equilibrate to a 1:1 mixture of stereoisomers in base.[8] It is therefore not surprising that (*Z*)-volkendousin (**2**) is formed in addition to the desired (*E*)-volkendousin (**1**) during the allylic oxidation of **6**. The two stereoisomers are difficultly separable, but can be purified by chromatography on silica gel and then silver nitrate on silica gel. The data for **1** are identical to those reported. The data for **2** are identical to the spectra provided in the supporting material of reference 1.[19]

Because of the stereochemical instability of the enone, we examined an alternate route to **1**, in which the carbonyl group will be introduced late in the synthesis. Oxidation of dehydroisoandrosterone (**7**) with two equiv of SeO_2 and two equiv of formic acid in dioxane at 40 °C for 3 d gives 33% (41% based on recovered **7**) of dihydroxy ketone **8**, which has previously been prepared in 30-40% yield by a two-step sequence by bromination in chloroform followed by treatment with silver acetate and hydrolysis.[13,14] Reaction of **8** with 2,2-dimethoxypropane and camphorsulfonic acid in acetone for 3 h at 25 °C gives acetonide **9** in high yield. Reaction of crude **9** with ethylidenetriphenylphosphorane[2-4] in THF affords acetonide diene **10** in overall 84%

yield from **8**. Oxidation of **10** with SeO_2 and *t*-BuOOH[5] in CH_2Cl_2 for 6 h at 0 °C provides crude **11**, which is oxidized with MnO_2 in CH_2Cl_2 to give acetonide enone **3** containing 8% of the (*Z*)-isomer. Flash chromatography yields pure **3** in 89% yield from **10**. The spectral data for **3** are identical to those reported.[1] Acetonide **3** is easily separated from the corresponding (*Z*)-isomer, while (*E*)- and (*Z*)-volkendousins (**1** and **2**) can only be separated with great difficulty. Unfortunately, acidic conditions that cleave the acetonide of **3** in high yield also isomerize the enone affording a 1:1 mixture of **1** and **2**.

Since we were unable to deprotect the ketal of **3** without concomitant isomerization of the enone double bond, we examined more easily cleavable diol protecting groups. Unfortunately, the dimethylsilylene group[20] proved to be too unstable to protect the diol, while the conditions used to deprotect the di-*t*-butylsilylene group[21,22] (TBAF or pyr-HF) isomerize the enone.

In conclusion, we have developed short, efficient routes from readily available dehydroisoandrosterone (**7**) to the antitumor agents (*E*)-volkendousin (**1**) and acetonide **3** that should make these compounds readily available for further biological evaluation. The equilibration of (*E*)-volkendousin (**1**) and (Z)-volkendousin (**2**) during the final step of the synthesis remains an unsolved problem that may be inherent to the structure.



Experimental Section

General. NMR spectra were recorded at 400 MHz in $CDCl_3$. Chemical shifts are reported in δ and coupling constants in Hz. IR spectra are reported in cm^{-1}.

(17*E*)-Pregna-5,17(20)-diene-3β,16α-diol (5). A mixture of SeO_2 (11 mg, 0.1 mmol) and *tert*-butyl hydroperoxide (90%, 88 μL, 0.8 mmol) in CH_2Cl_2 was stirred at 25 °C for 1 h and cooled to 0 °C. A solution of **4** (122 mg, 0.4 mmol) in 2 mL of CH_2Cl_2 was added and the reaction mixture was stirred at 0 °C for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in 2 mL of MeOH. $NaBH_4$ (8 mg, 0.2 mmol) was added immediately to the MeOH solution, which was stirred until it became clear (5 min). Water (4 mL) was added and the mixture was extracted quickly with three portions of ether. The combined organic layers were dried over Na_2SO_4 and concentrated to give 130 mg of crude **5**, which was used for the next step. Flash chromatography on silica gel (2:1 hexanes/EtOAc) gave pure **5**: mp 188-189 °C (lit.[8] 192.5-193 °C); ^{1}H NMR 5.60 (td, 1, *J* = 7.0, 1.2), 5.36 (br, 1), 4.44 (br, 1), 3.54 (dddd, 1, *J* = 10, 10, 5, 5), 2.34-2.20 (m, 3), 2.00 (dddd, 1, J = 17.5, 5, 5, 2.7), 1.88-1.82 (m, 2), 1.75 (d, 3, *J* = 7.0), 1.68-1.45 (m, 8), 1.36 (br, 1), 1.14-1.00 (m, 2), 1.03 (s, 3), 0.89 (s, 3); ^{13}C NMR 155.3, 140.8, 121.5, 119.7, 74.4, 71.7, 52.7, 50.1, 44.2, 42.3, 37.17, 37.14, 36.6, 35.1, 31.6, 31.6, 30.8, 21.1, 19.3, 17.3, 13.2; $[\alpha]^{25}_D$ -76.1° (*c* 0.51, MeOH) [lit.[8] $[\alpha]^{25}_D$ -83° (EtOH)].

(17*E*)-3β-Hydroxypregna-5,17(20)-dien-16-one (6). A mixture of 130 mg of crude **5** and MnO_2 (580 mg, 8 mmol) in CH_2Cl_2 was stirred at reflux for 8 h. The solution was filtered and the filtrate was concentrated to give 132 mg of crude **6**. Flash chromatography of the residue on silica gel (4:1 hexanes/EtOAc) gave 120 mg (90% from **4**) of **6**: mp 170-171 °C (lit.[8] 172-172.5 °C); ^{1}H NMR 6.51 (q, 1, *J* = 7.4), 5.36 (br, 1), 3.54 (dddd, 1, *J* = 10, 10, 5, 5), 2.36-2.24 (m, 3), 2.22 (dd, 1, J = 17.4, 7.0), 2.02 (dd, 1, J = 17.4, 14.6), 2.00 (m, 1), 1.90-1.83 (m, 2), 1.86 (d, 3, J = 7.4), 1.75-1.50 (m, 6), 1.46 (ddd, 1, *J* = 14.0, 10.4, 6.7), 1.15-1.07 (m, 2), 1.06 (s, 3), 1.05 (s, 3); ^{13}C NMR 206.3, 147.7, 141.0, 129.3, 120.9, 71.6, 50.2, 49.8, 43.0, 42.2, 37.9, 36.9, 36.6, 36.1, 31.6, 31.5, 30.6, 20.7, 19.4, 17.3, 13.2; $[\alpha]^{25}_D$ -201.5° (*c* 0.92, MeOH) [lit.[8] $[\alpha]^{25}_D$ -208° (EtOH)].

(*E*)-Volkendousin (1) and (Z)-Volkendousin (2). A solution of crude **6** (680 mg) from 610 mg (2.0 mmol) of **4** and SeO_2 (220 mg, 2 mmol) in 16 mL of dioxane was stirred at 55 °C for 24 h. Additional SeO_2 (220 mg, 2 mmol) was added and the mixture was stirred at 55 °C for 24 h and cooled to 25 °C. Water (15 mL) and ether (15 mL) were added and the mixture was extracted with three portions of ether. The combined organic layers were washed with saturated $NaHCO_3$ aqueous solution, dried over Na_2SO_4 and concentrated to give 630 mg of a residue containing **1** and **2**. Flash chromatography of the residue on silica gel (1:1 hexanes/EtOAc) gave 190 mg (30% from **4**) of a 90% pure 3:1 mixture of **1** and **2** as determined by ^{1}H NMR spectroscopic analysis. Careful flash chromatography on wet (1-2% water) silica gel (5:5:1, 2:2:1 then 2:1:2, hexanes/CH_2Cl_2/EtOAc) gave 25 mg of a 1:8 mixture of **1** and **2**, followed by 48 mg of a 3.5:1 mixture of **1** and **2**, 46 mg of a 16:1 mixture of **1** and **2**, and 55 mg of 65% pure **1** containing an unknown impurity.

Flash chromatography of the 25 mg of the 1:10 mixture of **1** and **2** on 20% $AgNO_3$-impregnated silica gel (1:1 hexanes/CH_2Cl_2, then 1:1 hexanes/EtOAc) gave 10.2 mg of a 1:4 mixture of **1** and **2** preceded by 9.6 mg of pure **2**: mp 197-198 °C (lit.[1] 194-197 °C); ^{1}H NMR 5.74 (q, 1, *J* = 7.4), 5.69 (dd, 1, *J* = 4.9, 2.4), 4.16 (d, 1, *J* = 3.8), 3.57 (dddd, 1, *J* = 9, 9, 4, 4), 2.21 (dd, 1, *J* = 17.1, 7.3), 2.12-2.00 (m, 2), 2.09 (d, 3, *J* = 7.4), 1.94 (ddd, 1, *J* = 13, 13, 3.7), 1.92-1.83 (m, 2), 1.75 (dddd, 1, *J* = 10, 10, 10, 5.0), 1.71-1.53 (m, 4), 1.44-1.32 (m, 2), 1.24 (s, 3), 1.15-1.01 (m, 2), 0.94 (s, 3); ^{13}C NMR 208.3, 148.0, 143.0, 130.4, 127.9, 77.1, 72.4, 50.1, 49.9, 43.0, 39.4, 36.7, 36.2, 35.5, 31.7, 30.8, 25.3, 21.0, 20.2, 19.4, 14.1; $[\alpha]^{25}_D$ -219.8° (*c* 0.32, MeOH) [lit.[1] $[\alpha]^{25}_D$ -812.5° (*c* 0.008, MeOH)]. The ^{1}H and ^{13}C NMR spectra are identical to those published.[19]

Similarly, flash chromatography on 20% $AgNO_3$-impregnated silica gel of the 46 mg of the 16:1 mixture of **1** and **2** gave 20 mg of a 7:1 mixture of **1** and **2**, followed by 20 mg of pure **1**: mp 182-183 °C (lit.[1] 193-196 °C); the ^{1}H and ^{13}C NMR spectra are identical to those previously reported;[1] $[\alpha]^{25}_D$ -204.0° (*c* 0.88, MeOH) [lit.[1] $[\alpha]^{25}_D$ -163.5° (*c* 0.34, MeOH)].

3β,4β-Dihydroxyandrost-5-en-17-one (8). Dehydroisoandrosterone (**7**) (1.152 g, 4.0 mmol), SeO_2 (880 mg, 8.0 mmol) and formic acid (280 μL, 8.0 mmol) in 15 mL of dioxane were stirred at 40 °C for 3 d. Ether (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL) were added slowly. The mixture was extracted with 3 portions of ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated to give 962 mg of residue. Flash chromatography of the residue on silica gel (1:1 hexanes/EtOAc) gave 402 mg (33%, 41% based on recovered **7**) of **8** and 215 mg (20%) of recovered **7**: mp 202-203 °C (lit.[13,14] 204-205 °C); the ^{1}H NMR spectrum is identical to those previously reported;[14] ^{13}C NMR 221.0, 142.9, 127.8, 77.1, 72.3, 51.9, 50.3, 47.5, 36.8, 36.1, 35.8, 31.4, 31.3, 30.9, 25.2, 21.8, 21.0, 19.8, 13.5; $[\alpha]^{25}_D$ -17.4° (*c* 0.87, MeOH) [lit.[13] $[\alpha]^{25}_D$ -28.5° (*c* 0.23, $CHCl_3$)].

3β,4β-Methylethylidenebis(oxy)-androst-5-en-17-one (9). A solution of **8** (153 mg, 0.50 mmol), 2,2-dimethoxypropane (500 μL, 4.0 mmol) and camphorsulfonic acid (1.1 mg, 0.0050 mmol) in 2 mL of dry acetone was stirred at 25 °C for 3 h. The solvent was removed under reduced pressure to give 178 mg of 98% pure **9** as determined by ^{1}H-NMR spectroscopic analysis, which was used for the next step. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave pure **9**: mp 146-147 °C; ^{1}H NMR 5.84 (dd, 1, *J* = 4.3, 2.7), 4.43 (d, 1, *J* = 6.2), 4.12 (ddd, 1, *J* = 7, 7, 6.2), 2.48 (dd, 1, *J* = 19.4, 8.6), 2.26 (ddd, 1, *J* = 17.2, 5.7, 5.7), 2.10 (ddd, 1, *J* = 19.4, 9.1, 9.1), 1.96 (ddd, 1, *J* = 11.7, 8.6, 6.2), 1.89-1.55 (m, 8), 1.54 (s, 3), 1.46 (dddd, 1, *J* = 13, 13, 13, 4), 1.36 (s, 3), 1.36-1.22 (m, 2), 1.20 (s, 3), 1.16 (ddd, 1, *J* = 14.2, 10.1, 4.7), 1.01 (ddd, 1, *J* = 12.5, 10.9, 4.7), 0.91 (s, 3); ^{13}C NMR 220.8, 138.6, 129.9, 108.1, 80.5, 75.5, 52.0, 48.6, 47.6, 36.3, 35.8, 32.6, 31.4, 31.3, 30.8, 28.0, 25.8, 25.7, 21.8, 21.4, 20.1, 13.7; IR (KBr) 2951, 1742, 1452, 1372, 1363, 1244, 1218, 1052, 879; $[\alpha]^{25}_D$ 69.4° (*c* 1.45, MeOH). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.32; H, 9.60.

3β,4β-Methylethylidenebis(oxy)-(17Z)-pregna-5,17(20)-diene (10). A mixture of ethyltriphenylphosphonium bromide (224 mg, 0.60 mmol) and potassium *tert*-butoxide (74 mg, 0.60 mmol) in 5 mL of dry THF was stirred at 25 °C under N_2 for 1 h. Crude **9** (178 mg) in 2 mL of dry THF was added dropwise, and the resulting solution was stirred at 25 °C for 2 d. Ice (1 g) was added to the mixture, which was extracted with three portions of EtOAc. The combined organic layers were dried over Na_2SO_4, and concentrated. Flash chromatography of the residue on silica gel (20:1 hexanes/EtOAc) gave 150 mg (84% from **8**) of **10** containing 4% of the (*Z*)-isomer, as determined by ^{1}H-NMR spectroscopic analysis, as a white solid: mp 167-168 °C; ^{1}H NMR 5.82 (dd, 1, *J* = 4.6, 2.2), 5.14 (qdd, 1, *J* = 7.3, 2.1, 2.1), 4.42 (d, 1, *J* = 5.5), 4.11 (ddd, 1, *J* = 6, 6, 5.5), 2.39 (m, 1), 2.30 (m, 1), 2.25-2.12 (m, 2), 1.74 (ddd, 1, *J* = 12.8, 5.5, 3.7), 1.70-1.1.58 (m, 6), 1.66 (d, 3, *J* = 7.3), 1. 57-1.45 (m, 2), 1.54 (s, 3), 1.36 (s, 3), 1.30-1.11 (m, 3), 1.18 (s, 3), 0.98 (ddd, 1, J = 11, 11, 4.3), 0.91 (s, 3); ^{13}C NMR ($CDCl_3$) 150.1, 138.4, 130.8, 113.5, 108.0, 80.6, 75.6, 56.8, 48.6, 44.2, 37.0, 36.2, 32.7, 31.8, 31.4, 31.2, 28.0, 25.9, 25.7, 24.4, 21.4, 21.0, 16.8, 13.1; IR (KBr) 2940, 1444, 1380, 1367, 1244, 1217, 1044, 972, 880; $[\alpha]^{25}_D$ -62.6° (*c* 0.92, $CHCl_3$).

3β,4β-Methylethylidenebis(oxy)-(17*E*)-pregna-5,17(20)-diene-16α-ol (11). A solution of SeO_2 (3.0 mg, 0.025 mmol) and *tert*-butyl hydroperoxide (5 M in hexane, 40 μL, 0.2 mmol) in CH_2Cl_2 was stirred at 25 °C for 0.5 h. Alkene **10** (36 mg, 0.1 mmol) was added at 0 °C and the solution was stirred at 0 °C for 6 h. The solvent was removed under reduced pressure. The residue was dissolved in 3 mL of MeOH. $NaBH_4$ (3 mg, 0.07 mmol) was added immediately to the MeOH solution, which was stirred for 5 min until it became clear. Water (5 mL) was added and the mixture was extracted quickly with three portions of ether. The combined organic layers were dried over Na_2SO_4 and concentrated to give 46 mg of crude **11** containing 5% of the (*Z*)-isomer as determined by ^{1}H-NMR spectroscopic analysis, which was used for the next step. Flash chromatography on silica gel (3:1 hexanes/EtOAc) gave pure **11**: mp 199-201 °C; ^{1}H NMR 5.82 (dd, 1, *J* = 4.8, 2.3), 5.60 (qd, 1, *J* = 7.3, 1.2), 4.45 (br, 1), 4.42 (d, 1, *J* = 6.1), 4.11 (ddd, 1, *J* = 6.1, 6, 6), 2.30 (m, 1), 2.15 (dddd, 1, *J* = 12.8, 10, 10, 4.3), 1.75 (d, 3, J = 7.3), 1.76-1.48 (m, 10), 1.54 (s, 3), 1.36 (s, 3), 1.33 (d, 1, J = 4.3), 1.19 (s, 3), 1.15 (ddd, 1, J = 12.8, 10.4, 4.9), 1.04 (m, 1), 0.90 (s, 3); ^{13}C NMR ($CDCl_3$) 155.2, 138.3, 130.6, 119.7, 108.0, 80.6, 75.6, 74.4, 53.0, 48.5, 44.3, 37.2, 36.2, 35.0, 32.6, 31.6, 30.6, 28.0, 25.8, 25.7, 21.4, 20.9, 17.4, 13.2; IR (KBr) 3504, 2951, 1450, 1377, 1242, 1216, 1052, 883; $[\alpha]^{25}_D$ -68.3° (c 0.42, MeOH). Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 76.95; H, 9.80.

3β,4β-Methylethylidenebis(oxy)-(17*E*)-pregna-5,17(20)-diene-16-one (3). A mixture of crude **11** (46 mg) and MnO_2 (145 mg, 2 mmol) in CH_2Cl_2 was stirred at reflux for 8 h. The solution was filtered and the filtrate was concentrated to give 42 mg of crude **3** containing 8% of the (*Z*)-isomer as determined by ^{1}H-NMR spectroscopic analysis. Flash chromatography on silica gel (5:1 hexanes/EtOAc) gave 33 mg (89% from **10**) of pure **3**: mp 213-215 °C (lit.[1] 171-173 °C); the ^{1}H and ^{13}C NMR spectra are identical to those previously reported;[1] $[\alpha]^{25}_D$ -184.8° (c 0.15, MeOH), [lit.[1] $[\alpha]^{25}_D$ -16.7° (c 0.006, MeOH)].

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