Effect of a 17α-(3-hydroxypropyl)-17β-acetyl substituent pattern on the glucocorticoid and progestin receptor binding of 11 β-arylestra-4,9-dien-3-ones.

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Experimental:

General Methods. Unless otherwise stated, reagent-grade chemicals and compound **6** were obtained from commercial sources and were used without further purification. Ether and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone ketyl pair under nitrogen. All moisture- and air-sensitive reactions and reagent transfers were carried out under dry nitrogen or argon. Thin layer chromatography (TLC) was performed on EM Science precoated silica gel 60 F-254 plates. Compounds were normally visualized by UV light (254 nm) or para-anisaldehyde spray. Preparative column chromatography employed EM Science silica gel, 60Å (230-400 mesh). Solutions were concentrated by use of a rotoevaporator under water aspirator pressure at ambient temperature. ^{1}H NMR spectra were obtained at 250 MHz on a Bruker AC 250 spectrometer in $CDCl_3$ as solvent with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in units of ppm downfield from TMS. Elemental analyses were performed by Atlantic Microlab Inc., Atlanta, GA

3,3-[1,2-Ethanediylbis(oxy)]-5α,10α-oxidoestr-9(11)-en-17-one (**7**, cf. Cook et al., U.S. Patent 5,962,444). To a solution of 32.0 g (102 mmol) of **6** in 192 mL of CH_2Cl_2 at 0 ^{O}C was added 7.04 mL (50.9 mmol) of hexafluoroacetone trihydrate (Lancaster Synthesis, Inc.) followed by 2.46 g (17.3 mmol) of Na_2HPO_4, and then 8.64 mL (153 mmol) of 50% H_2O_2 was added dropwise to the efficiently stirred mixture (overhead mechanical stirring). Efficient stirring was continued for 18 h, during which time the temperature was allowed to gradually rise to room temperature, then 192 mL of saturated aqueous $Na_2S_2O_3$ was added. After being stirred for 20 min, the mixture was combined with another (32.0 g) batch which had been prepared identically up to this point in parallel. The aqueous layer (bottom) was separated and extracted three times with 80 mL of EtOAc. The combined organic solution was diluted with 240 mL of EtOAc and washed twice with 80 mL of saturated aqueous $NaHCO_3$, twice with 80 mL of brine, dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The yellow solid (76.1 g) was triturated with 320 mL of diethyl ether with magnetic stirring for 12 h in a closed flask. The resulting white slurry was combined with three other batches (3 x 32.0 g) which had been prepared identically (and proportionally) to this point, in parallel, then suction filtered through a coarse-porosity sintered glass funnel, rinsing three times with 40 mL of diethyl ether, then allowed to suck dry for 1.5 h. The resulting white filter cake was gently scraped into a fine white powder and dried *in vacuo* to afford epoxide **7** (89.5 g, 53% yield). ^{1}H NMR δ 0.88 (3, s), 1.32-1.12 (1, m), 2.52-2.44 (2, m), 3.98-3.88 (4, m), 6.06 (1, br s).

11β-[4-(*N*,*N*-Dimethylamino)phenyl]-3,3-[1,2-ethanediylbis(oxy)]-5α-hydroxyestr-9-en-17-one (8). A flask equipped with an overhead mechanical stirrer and charged with 11.6 g (475 mmol) of magnesium turnings was flame-dried under a stream of dry nitrogen. After the apparatus was cooled to room temperature, 400 mL of THF was added, followed by a few crystals of iodine, thus imparting a light brown coloration. To the efficiently stirred mixture was added 35 mL of a solution of 91.4 g (457 mmol) of 4-bromo-*N*,*N*-dimethylaniline in 400 mL of THF. After the mixture was heated to reflux for *ca*. 5 min, the iodine color quickly faded to colorless, at which time the mixture was allowed to cool to room temperature. The remainder of the bromide solution was added dropwise over a period of 2 h. The mixture was cooled in an ice-water bath for 1.8 h, then 18.1 g (183 mmol) of finely powdered CuCl was added in one portion. After the mixture was stirred efficiently for 60 sec, a solution of 60.4 g (183 mmol) of **7** in 453 mL of THF was added (poured in) over 25 sec, causing the formation of a voluminous light yellow precipitate. After 15 min, 300 mL of saturated aqueous NH_4Cl was slowly added, followed by 755 mL of EtOAc. After the mixture was stirred for 10 min, the aqueous layer was separated and extracted three times with 300 mL of EtOAc. The combined organic solution was washed eight times with 300 mL of brine (until the brine washings were relatively low in opacity), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The black viscous oil was dissolved in 30 mL of CH_2Cl_2 and chromatographed on silica gel (elution of aniline reagent by-product with CH_2Cl_2, then elution of product with EtOAc) to afford adduct **8** (75.4 g, 91% yield). ^{1}H NMR δ 0.52 (3, s), 2.91 (6, s), 4.02-3.90 (4, m),), 4.24 (d, 1, J = 7.3 Hz), 4.37 (s, 1), 6.64 (2, d, J = 8.8 Hz), 7.06 (2, d, J = 8.3 Hz).

17-Cyano-11β-[4-(N,N-dimethylamino)-phenyl]-3,3-[1,2-ethanediylbis(oxy)]-5α-hydroxyestr-9-ene (9). Following the procedure described by Yoneda et al. (1989), **8** (0.83 g, 1.8 mmol) was dissolved in 40 mL of THF at room temperature. Diethyl cyanophosphonate (0.83 mL, 5.5 mmol) was added, followed by a solution of LiCN in DMF (0.50 M, 11.0 mL, 5.5 mmol). The reaction mixture was stirred for 30 min and then diluted with 50 mL of water. The organic phase was extracted with EtOAc-hexane (1:1, 2 x 75 mL). The combined organic extracts were washed with brine (2 x 75 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford the intermediate cyanophosphate as a brown oil which was kept under vacuum (~1.0 torr) for 2 h before using for the subsequent step.

The intermediate cyanophosphate was dissolved in 20 mL of THF containing 0.18 mL (1.83 mmol) of t-BuOH and added to a 0.1 M solution of samarium(ll) iodide in THF (82.5 mL, 8.25 mmol). The reaction

mixture was stirred for 3.5 h and then 10% NH_4Cl solution (50 mL) was added. The organic phase was separated and the aqueous layer was extracted with ether (2 x 150 mL). The combined organic extracts were washed with 5% $Na_2S_2O_3$ solution (50 mL) and then with brine (2 x 50 mL), dried over anhydrous $MgSO_4$ and filtered. The solvents were evaporated under reduced pressure to afford crude **9** as a brown solid. The crude compound was further purified by column chromatography with EtOAc-hexane (1:2) as eluent to afford cyano compound **9** (0.58 g) as a 3:2 mixture of α:β isomers in 69% yield.

17-Cyano-3,3-[1,2-ethanediylbis(oxy)]estra-5(10),9(11)-diene (11). Method A. Following a procedure described by Yoneda et al., (1989), ketal **6** (3.0 g, 9.6 mmol) was dissolved in 180 mL of THF at room temperature followed by diethylcyanophosphonate (2.54 mL, 16.8 mmol) and then a 0.50 M solution of LiCN in DMF (33.6 mL, 16.8 mmol LiCN). The reaction mixture was stirred for 30 min and then diluted with 150 mL of water. The organic phase was extracted with EtOAc-hexane (1:1, 2 x 250 mL). The organic extracts were combined, washed with brine (2 x 150 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford the intermediate cyanophosphate as a brown oil which was kept under vacuum (~1.0 torr) for 2 h before using for the subsequent step.

The intermediate cyanophosphate was dissolved in 150 mL of THF containing 1.42 mL (19.1 mmol) of t-BuOH and added to a 0.10 M solution of samarium(ll) iodide in THF (430 mL, 43 mmol). After the mixture was stirred for 3.5 h, 10% NH_4Cl solution (250 mL) was added. The organic phase was separated and the aqueous layer extracted with ether (2 x 150 mL). The organic extracts were combined, washed with 5% $Na_2S_2O_3$ solution (200 mL), with brine (2 x 150 mL), dried over anhydrous $MgSO_4$ and filtered. The solvents were evaporated under reduced pressure to afford crude **11** as a white sticky solid (3.04 g) in 98% yield. The crude compound was further purified by column chromatography with EtOAc-hexane (1:2) as eluent to afford **11** (2.5 g) as a 3:2 mixture of α:β isomers in 79% yield. ^{1}H NMR δ 0.82 (s, minor isomer), 0.92 (s, major isomer), 1.18-1.52 (3, m), 1.59-2.71 (16, m), 3.99 (4, s), 5.59 (1, s).

Method B. Following a procedure described by Bull and Tuinman (1975), compound **6** (5.0 g, 0.0159 mol) was dissolved in 300 mL of anhydrous dimethoxyethane (DME) and 10 mL of t-BuOH was added to the solution. The mixture was stirred for 5 min after which t-BuOK (17.9 g, 0.159 mol) was added in one portion. The reaction mixture was stirred vigorously for 5 min. A mixture of tosylmethylisocyanide (TosMIC, 6.22 g, 31.9 mmol) in 80 mL of anhydrous DME and 10 mL of t-BuOH (to increase solubility of TosMIC) was added via an addition funnel over a period of 1.5 h and stirring was continued for 1 h after the addition was complete. The reaction mixture was quenched with 10% NH_4Cl solution and brought to pH 7, followed by extraction with EtOAc (2 x 150 mL). The combined organic extracts were washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford crude **11** in quantitative yield. Further purification was carried out by column chromatography with methylene chloride as the eluent to afford **11** (3.67 g) as a 3:2 mixture of α:β isomers in 71% yield. ^{1}H NMR data were consistent with the material from Method A.

3,3-[1,2-Ethanediylbis(oxy)]-19-norpregna-5(10),9(11)-dien-20-one (12). Cyano compound **11** (3.6 g, 11 mmol) was dissolved in 30 mL of THF and a solution of methylmagnesium bromide (1.00 M in 3:1 toluene-THF, 32.3 mL, 32.3 mmol) was added at room temperature. The resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and a saturated solution of ammonium chloride was added until the aqueous layer was slightly acidic. The organic phase was separated and the aqueous phase extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (2 x 25 mL), dried over anhydrous $MgSO_4$, filtered and the solution evaporated under reduced pressure to afford crude **12** as a brown sticky solid. Further purification was accomplished by column chromatography with 5% EtOAc in CH_2Cl_2 as eluent to afford **12** (1.13 g) in 51% yield. ^{1}H NMR δ 0.59 (s, major), 0.90 (s, minor), 1.21-2.68 (28, m), 3.99 (4, s), 5.56 (1, s).

3,3-[1,2-Ethanediylbis(oxy)]-17-formylestra-5(10),9(11)-diene (13). Compound **11** (2.00 g, 6.16 mmol) was dissolved in 20 mL of toluene and the solution was cooled to –78 ^{O}C. A solution of diisobutylaluminum hydride (DIBAL-H, 1.00 M in hexanes, 24.6 mL, 24.6 mmol) was added dropwise over a period of 15 min via an addition funnel. The reaction mixture was stirred at –78 ^{O}C for 30 min. A saturated solution of NH_4Cl was added with the bath at –78 ^{O}C until the aqueous layer was slightly acidic. The cooling bath was removed and the mixture was stirred for 2 h. The reaction mixture was further diluted with 250 mL of water and extracted with diethyl ether (3 x 200 mL). The combined organic extracts were washed with brine (2 x 75 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford crude **13**. Further purification was done by column chromatography with EtOAc-hexane (1:2) as eluent to afford **13** (1.25 g) in 62% yield as a white solid. ^{1}H NMR δ 0.75 (s, major), 0.91 (s, minor), 1.23-1.48 (3, m), 1.77-2.36 (16, m), 3.99 (4, s), 9.71 (d, J = 3.6 Hz, minor), 9.80 (d, J = 1 Hz, major).

17-Cyano-3,3-[1,2-ethanediylbis(oxy)]-17-ethylestra-5(10),9(11)-diene (14). Diethylamine (0.286 mL, 2.77 mmol) was dissolved in 2 mL of THF and the solution cooled to –78 ^{O}C. n-BuLi (2.5 M in hexane, 0.83 mL, 2.1 mmol) was added dropwise to this solution via syringe and the resulting mixture stirred at –78 ^{O}C for 30 min. A solution of **13** (450 mg, 1.38 mmol) in 3 mL of THF was added dropwise over a

period of 30 min. The reaction mixture turned bright orange and a thick slurry formed, which was stirred for another 30 min at –78 ^{O}C. Ethyl iodide (860 mg, 5.5 mmol) was added dropwise and stirring was continued at –78 ^{O}C for 20 min and then at room temperature for 1 h. The reaction mixture was extracted with EtOAc (2 x 15 mL). After addition of 10 mL of water, the combined organic extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford crude **14**. Purification of the crude product by column chromatography with EtOAc-hexane (1:4) as eluent afforded **14** in 66% yield (316 mg) as an off-white solid. ^{1}H NMR δ 0.73 (s, minor isomer), 1.06 (s, major isomer), 1.12 (3, t, J = 7.2 Hz), 1.24-2.71 (20, m), 3.99 (4, s), 5.58 (1, s).

3,3-[1,2-Ethanediylbis(oxy)]-17-ethyl-17-formylestra-5(10),9(11)-diene (15). Compound (**13**)**14** (316 mg, 0.890 mmol) was dissolved in 50 mL of toluene and the solution was cooled to –30 ^{O}C. A solution of DIBAL-H (1.00 M in hexanes, 1.80 mL, 1.80 mmol) was added dropwise over a period of 15 min via a syringe. The reaction mixture was stirred at –30 ^{O}C for 1 h. Saturated NH_4Cl solution was added at –30 ^{O}C until the pH of the aqueous layer was slightly acidic. The cooling bath was removed and the mixture stirred for 2 h. The reaction mixture was further diluted with 150 mL of water and was extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with brine (2 x 30 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford crude **15**. Further purification was done by column chromatography with EtOAc-hexane (1:3) as eluent to afford **15** (189 mg) in 60% yield as a white solid. ^{1}H NMR δ 0.71-0.81 (6, m), 1.26-2.61 (20, m), 3.99 (4, s), 5.56 (1, s), 9.55 (s, major isomer), 9.70 (s, minor isomer).

3,3-[1,2-Ethanediylbis(oxy)]-17-ethyl-20-hydroxy-19-norpregna-5(10),9(11)-diene (16). Compound **15** (189 mg, 0.530 mmol) was dissolved in 4 mL of THF and the resulting solution cooled to –78 ^{O}C. A solution of MeLi (1.20 M in diethyl ether, 1.04 mL, 1.25 mmol) was added dropwise via syringe. The reaction mixture was stirred at –78 ^{O}C for 30 min and then slowly warmed to room temperature. After the mixture was stirred for 30 min at room temperature, 15 mL of 10% ammonium chloride solution was added. The mixture was extracted with ethyl acetate (2 x 15 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and the solvents removed on a rotary evaporator to afford crude **16**. Further purification was done by column chromatography with EtOAc-hexane (1:2) as eluent to afford **16** (122 mg) as a mixture of epimers at C-20 in 62% yield. ^{1}H NMR δ 0.80 (s, minor isomer), 0.86 (s, major isomer), 0.98 (3, t, J = 7.5 Hz), 1.14 (3, d, J = 6.4 Hz), 3.99 (4, br s), 5.56 (1, s).

3,3-[1,2-Ethanediylbis(oxy)]-17α-ethyl-19-norpregna-5(10),9(11)-dien-20-one (17). Compound **16** (20.0 mg, 0.050 mmol) was dissolved in 2.5 mL of CH_2Cl_2 at room temperature. Pyridinium dichromate (40.5 mg, 0.107 mmol) was added to this solution in one portion and the mixture stirred for 6-7 h. The reaction mixture was diluted with diethyl ether-hexane (1:1, 10 mL) and passed through a small pad of Celite. The last traces of chromium salts were removed by passing the resulting solution through a pad of anhydrous $MgSO_4$. Solvents were removed by evaporating under reduced pressure to afford **17** (17.1 mg) in 86% yield. ^{1}H NMR δ 0.63 (3, s), 0.75 (3, t, J = 7.4 Hz), 1.18-2.67 (23, m), 3.99 (4, s), 5.59 (1, s).

17α-Allyl-17β-cyano-3,3-[1,2-ethanediylbis-(oxy)]estra-5(10),9(11)-diene (18). Diethylamine (1.01 mL, 9.7 mmol) was dissolved in 12 mL of THF and the solution cooled to –78 ^{O}C. n-BuLi (2.50 M in hexane, 2.9 mL, 7.3 mmol) was added dropwise to this solution via syringe and the resulting mixture stirred at –78 ^{O}C for 30 min. A solution of **11** (1.58 g, 4.90 mmol) in 12 mL of THF was added rapidly via syringe. The reaction mixture in some instances turned bright orange and a thick slurry formed or remained as a yellow solution, which was stirred for another 30 min at –78 ^{O}C. Allyl bromide (1.81 mL, 20.9 mmol) was added dropwise to the reaction mixture and stirring was continued at –78 ^{O}C for 10 min. The reaction mixture was extracted with EtOAc (2 x 25 mL). After addition of 30 mL of water, the combined organic extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Purification of the crude product by column chromatography with EtOAc-hexane (1:3) as eluent afforded **18** in 73% yield (1.31 g) as an off-white solid. ^{1}H NMR δ 1.07 (3, s), 3.99 (4, s), 5.15-5.26 (2, m), 5.59 (1, s), 5.85-5.98 (1, m).

17α-Allyl-3,3-[1,2-ethanediylbis(oxy)]-17β-formylestra-5(10),9(11)-diene (19). The above compound (1.98 g, 5.43 mmol) was dissolved in 65 mL of toluene and the solution was cooled to –42 ^{O}C. A solution of DIBAL-H (1.00 M in hexanes, 11 mL, 10.9 mmol) was added dropwise over a period of 15 min via a syringe. The reaction mixture was stirred at –42 ^{O}C for 1 h. Super saturated NH_4Cl solution was added at –42 ^{O}C until the pH of the aqueous layer was slightly acidic. The cooling bath was removed and the mixture stirred vigorously for 2-3 h. The reaction mixture was further diluted with 150 mL of water and was extracted with diethyl ether (3 x 75 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure. Further purification was done by column chromatography with EtOAc-hexane (1:3) as eluent to afford **19** (1.56 g) in 78% yield as a white solid. ^{1}H NMR δ 0.75 (3, s), 3.99 (4, s), 5.02-5.08 (2, m), 5.4-5.57 (2, m), 9.6 (1, s).

17α-Allyl-3,3-[1,2-ethanediylbis(oxy)]-20-hydroxy-19-norpregna-5(10),9(11)-diene (20). The above compound (1.56 g, 4.2 mmol) was dissolved in 20 mL of THF and the resulting solution cooled to –78 ^{O}C.

A solution of MeLi (1.4 M in diethyl ether, 6.03 mL, 8.5 mmol) was added rapidly via syringe. The reaction mixture was stirred at –78 ^{O}C for 15 min and then slowly warmed to room temperature. After the mixture was stirred for 15 min at room temperature, 20 mL of 10% ammonium chloride solution was added. The mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered and the solvents removed under vacuum. The crude product was used in the subsequent step without purification.

17α-Allyl-3,3-[1,2-ethanediylbis(oxy)]-19-norpregna-5(10),9(11)-dien-20-one (21). A 2.0 M solution of oxalyl chloride in CH_2Cl_2 was cooled in a -60 °C bath (dry ice-$CHCl_3$) and 2.5 mL of CH_2Cl_2 was added. A solution of 0.46 mL (6.5 mmol) of dimethyl sulfoxide (DMSO) in 2.0 mL of CH_2Cl_2 was added dropwise (gas evolution) and the mixture was stirred for 10 min. A solution of alcohol **20** in 30 mL of CH_2Cl_2 was added dropwise and the mixture was stirred for 15 min before the addition of 2.1 mL (19.9 mmol) of triethylamine. The reaction mixtured was allowed to warm to room temperature and was stirred until TLC analysis (SiO_2; hexane-EtOAc, 2:1) showed that the starting material had been consumed. The mixture was quenched with water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine and dried ($MgSO_4$). The solvent was removed under vacuum after filtration, and the residue purified by chromatography with hexane-EtOAc (1:2) as eluent to afford 371 mg (72% yield) of **21** as a white solid. ^{1}H NMR δ 0.65 (3, s), 2.10 (3, s), 3.99 (4, s), 5.04-5.10 (2, m), 5.46-5.58 (2, m).

3,3-[1,2-Ethanediylbis(oxy)]-17α-(3-hydroxypropyl)-19-norpregna-5(10),9(11)-dien-20-one (22). Disiamylborane was generated by stirring BH_3•THF (1.0 M, 62.8 mL, 62.8 mmol) and 2-methyl-2-butene (2.0 M, 62.8 mL, 125.7 mmol) at ice-bath temperature for 2 h. Compound **17** (8.0 g, 20.9 mmol) in 75 mL of THF was added dropwise to this solution over a period of 45 min. The reaction mixture was stirred at ambient temperature overnight. The solution was cooled to –5 ^{O}C in an ice-salt bath. A 2 N solution of NaOH (20 mL) was added at such a rate that the temperature did not rise above 0 ^{O}C. Hydrogen peroxide (35% solution in water, 20 mL) was then added dropwise at such a rate that the temperature did not exceed 10 ^{O}C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was washed with 10% $Na_2S_2O_3$ solution. The organic phase was extracted with EtOAc, and the EtOAc was back extracted with brine and dried over anhydrous $MgSO_4$. The dried extract was filtered and evaporated under reduced pressure to afford crude **22**. The crude mixture was purified by column chromatography with EtOAc-hexane (2:1) as eluent to afford **22** (7 g) in 83% yield. ^{1}H NMR δ 0.63 (3, s), 2.12 (3, s), 3.39-3.64 (2, m), 3.99 (4, s), 5.56 (1, s).

3,3-[1,2-Ethanediylbis(oxy)]-17α-(3-hydroxypropyl)-5,10-oxido-19-norpregn-9-en-20-one (23). Compound **22** (792 mg, 198 mmol) was dissolved in 3 mL of CH_2Cl_2. Hexafluoroacetone (152 μL, 1.08 mmol), H_2O_2 (35%, 184 μL, 5.94 mmol) and 10 μL of 2 mg/10 mL Na_2HPO_4 was added. The reaction mixture was stirred vigorously for 72 h. The organic phase was extracted with CH_2Cl_2 (2 x 10 mL), washed with 10% $Na_2S_2O_3$ solution (10 mL), dried over Na_2SO_4 and the solvent evaporated to afford crude 5,10-epoxide (mixture of epimers) as a white foam (775 mg, 98% yield).

11β-[4-(N,N-Dimethylamino)phenyl]-3,3-[1,2-ethanediylbis(oxy)]-5α-hydroxy-17α-(3-hydroxypropyl)-19-norpregn-9-en-20-one (24a). To a 1 M solution (30 mL, 30 mmol) of freshly prepared Grignard reagent of 4-bromo-N,N-dimethylaniline was added solid CuBr•Me_2S (6.8 g, 33 mmol) at room temperature and the reaction mixture was stirred for 30 min. The solution of organocuprate was cooled to 0 ^{O}C and a solution of **23** (2.3 g, 6 mmol) in 30 mL of THF was added dropwise. The resulting mixture was warmed to room temperature and stirred for 30 h, after which 30 mL of saturated NH_4Cl was added and the mixture stirred for 15 min. The reaction mixture was extracted with Et_2O (3 x 25 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried over $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford a crude mixture which was purified by column chromatography with 30% acetone and 10% EtOAc in CH_2Cl_2 as eluent to afford **24a** (504 mg) in 16% yield. ^{1}H NMR δ 0.29 (3, s), 2.11 (3, s), 2.9 (6, s), 3.6 (2, br, s), 3.95-4.00 (4, m), 4.24 (1, d), 4.3 (1, s), 6.63 (2, d), 7.04 (2, d).

11β-[4-N,N-Dimethylamino)phenyl]-17α-(3-hydroxypropyl)-19-norpregna-4,9-diene-3,20-dione (25a). Compound **24a** from above was dissolved in 10 mL of acetone and the solution cooled to 0 ^{O}C in an ice bath. A catalytic amount of p-TsOH was added and the reaction mixture was warmed to ambient temperature and stirred for 5 h. The pH of the solution was made slightly basic by adding 1 N NaOH. The organic phase was extracted with EtOAc (2 x 10 mL) dried over Na_2SO_4 and the solvent evaporated to afford 118 mg (26% yield) of **25a** after purification by column chromatography (hexane-EtOAc, 2:1). ^{1}H NMR δ 0.36 (3, s), 2.04 (3, s), 2.91 (6, s), 3.6 (2, br, s), 4.10 (2, d), 5.75 (1,s), 6.64 (2, d), 7.0 (2, d). Anal Calcd. For $C_{31}H_{41}NO_3$•0.75 H_2O: C, 76.2; H, 8.46; N, 2.86. Found C, 76.1; H, 8.63; N, 2.55.

3,3-[1,2-Ethanediylbis(oxy)]-11β-{4-{1,1-[1,2-ethanediylbis(oxy)]ethyl}phenyl}-5α-hydroxy-17α-(3-hydroxypropyl)-19-norpregn-9-en-20-one (24b). Prepared following the procedure described for compound **24a** using the following amounts of reagents: Grignard reagent 1 M solution (51.7 mL, 51.7 mmol) of 1-(4-bromophenyl)-2,2-[1,2-ethanediylbis(oxy)] acetone, epoxide **23** (2.7 g, 6.5 mmol), CuBr•Me_2S (11.3 g, 54.9 mmol). Compound **24b** was isolated as a white solid (530 mg, 15% yield) after column chromatography with 30% acetone and 10% EtOAc in CH_2Cl_2 as eluent.

^{1}H NMR δ 0.23 (3, s), 2.1 (3, s), 3.6 (2, br s), 4.3 (2, d), 7.16 (2, d), 7.33 (2, d).

3,3-[1,2-Ethanediylbis(oxy)]-5α-hydroxy-17α-(3-hydroxypropyl)-11β-(4-methylthio-phenyl)-19-norpregn-9-en-20-one (24c). Prepared following the procedure described for compound **24a** using the following amounts of reagents: Grignard reagent 1 M solution (30 mL, 30 mmol) of 4-bromothioanisole, CuBr•Me_2S (6.8 g, 33 mmol), epoxide **23** (2.5 g, 6 mmol) in 50 mL THF. Compound **24c** was obtained as a white foam after purification by column chromatography (540 mg, 17% yield). ^{1}H NMR δ 0.26 (3, s), 2.07 (3, s), 2.45 (3, s), 3.6 (2, m), 4.0 (1, d), 4.1 (1, s), 6.8 (4, s).

17α-(3-Hydroxypropyl)-11β-(4-methylthio-phenyl)-19-norpregna-4,9-diene-3,20-dione (25c). Compound **25c** (540 mg, 0.99 mmol) was dissolved in 10 mL of acetone and the solution cooled to 0 °C in an ice bath. Catalytic p-TsOH was added and reaction mixture warmed to ambient temperature and stirred for 5 h. The pH of the solution was made slightly basic by adding 1 N NaOH. The organic phase was extracted with EtOAc (2 x 10 mL), dried over Na_2SO_4 and the solvent evaporated to afford **25c** as a white foam (110 mg, 23% yield) after purification by column chromatography. ^{1}H NMR δ 0.33 (3, s), 2.23 (3, s), 2.38 (3, s), 3.6 (2, m), 4.39 (1, d), 5.7 (1, s), 7.08 (2,), 7.16 (2, d). Anal. Calcd. for $C_{30}H_{38}O_3S$•0.25 H_2O: C, 74.5; H, 7.93; S, 6.40. Found: C, 74.6; H, 8.05; S, 6.50.

11β-(4-Acetylphenyl)-17α-(3-hydroxy-propyl)-19-norpregna-4,9-diene-3,20-dione (25b). Prepared from ketal **24b** following the procedure for **24c** to afford **25b** as a white foam (120 mg, 27% yield) after column chromatography with 30% acetone, 5% EtOAc, 5% hexane in CH_2Cl_2 as eluent. ^{1}H NMR δ 0.29 (3, s), 1.76 (3, s), 2.28 (3, s), 3.36-3.32 (2, m), 4.19 (1, d), 5.49 (1, s), 6.98 (2, d), 7.58, (2, d). Anal. Calcd. for $C_{31}H_{38}O_4$•0.5 H_2O: C, 77.0; H, 8.13. Found: C, 77.0, H, 8.13.

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