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Highly Diastereoselective Synthesis of 11β,17β-Diaryl-18a-homo-19-nor Steroids

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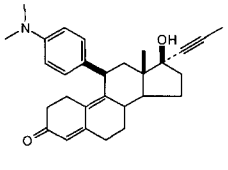
Dedicated to Prof. Dr. Ekkehard Winterfeldt on the Occasion of his 65th Birthday

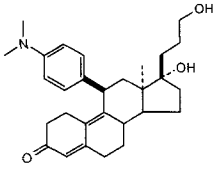
Abstract. In a highly diastereoselective fashion novel 11β, 17β-diaryl steroids **17** and **18** were synthesized *via* Birch-type reduction [1] of styrylic precursors **11** and **15**. Both precursors were readily available by Suzuki-type coupling reactions [2] of aromatic boronic acids [3] and the corresponding enol triflates **6**, **10**, and **14**. Regioselective 17-enol triflate formation in presence of a 11-keto function could be demonstrated in case of steroid **5**. The remarkably high degree of stereoselectivity observed parallels results from the natural series [4] and demonstrated a broader applicability of such single electron transfer reductions in stereoselective transformations on the steroid skeleton.

End of the seventies the newly discovered stereospecific access to 11β-aryl substituted steroids set the basis for the breakthrough [5] in the search for competitive progesterone antagonists. Up to now the key structural feature of all known antigestagens remained the 11β-aryl substitution as indicated unequivocally by the three most prominent representatives RU 38486, ZK 98299 and Org 33628, cp. Scheme A.

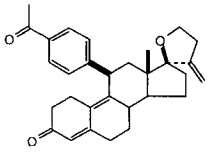
Particularly, since the original route was synthetically limited to 11β-aryl-4,9-diene-3-keto steroids [6] strong efforts have been made in our laboratories to create antigestagens in the androstane as well as the 19-nor-10β-H series. Novel synthetic processes to highly stereoselective 11β-aryl introductions [4] have been elaborated by us providing these antihormones with the desired structural flexibility with regard to the 9,10-region. In continuation of this work we wanted to exploit further the potential of our novel methodology at a different position on the steroid skeleton and to check in more detail on the applicability in a different steroidal setting. Therefore, we turned to the 18a-homo-19-nor series which the most potent synthetic progesterone agonists like Desogestrel and Gestodene (Sche-me B) belong to.



RU 38486

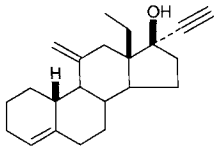


ZK 98299

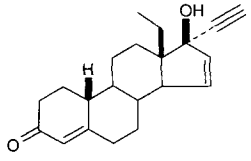


Org 33628

Scheme A



Desogestrel



Gestodene

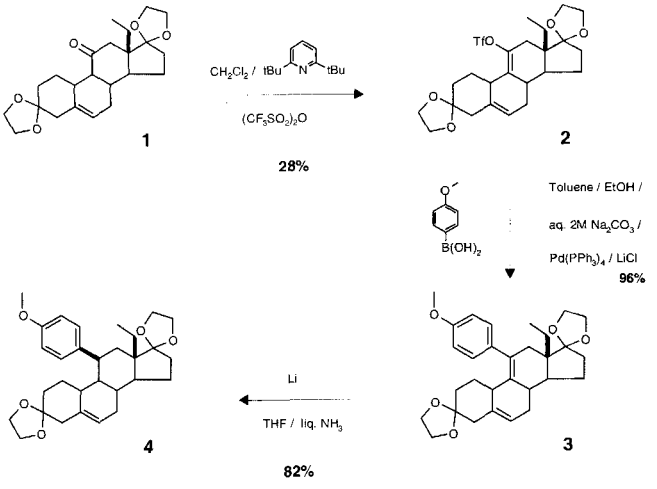
Scheme B

Results and Discussion

In our attempt to investigate the accessibility and biological potency of 11β,17β-diaryl-18a-homo steroids

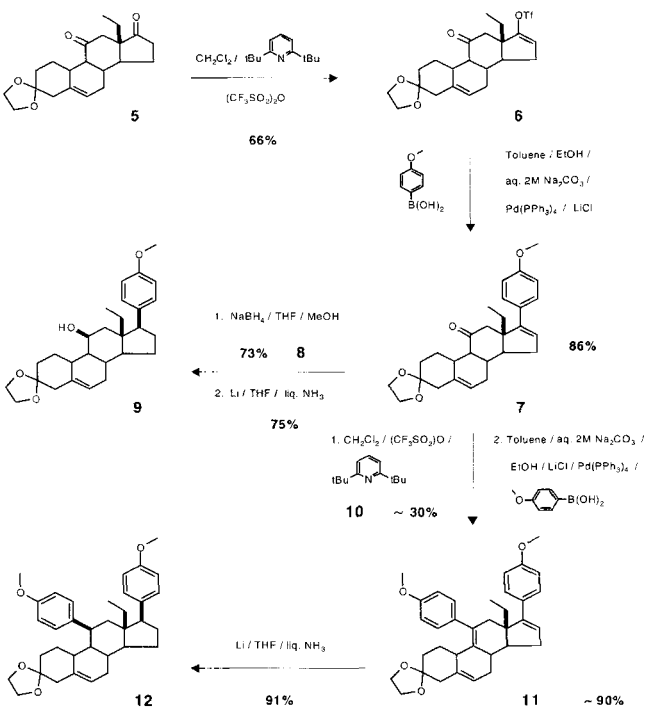
we initiated our synthetic work from readily available ketones **1** and **5**. As published by Su *et al.* [7] starting from 18a-homoestr-4-ene-3,11,17-trione, 11-keto steroid **1** as well as 11,17-diketo steroid **5** is selectively accessible.

Using 11-keto steroid **1** as starting material enol triflate formation under thermodynamic controlled conditions according to Stang *et al.* [8] proceeds only in low yield (28%) contrasting the much higher yield (77%) obtained during the analogous reaction in the natural series [4]. This result clearly demonstrates the strong steric influence of the 18-methyl group on the enol triflate formation. Due to occurring decomposition as indicated by analysis *via* thin layer chromatography, prolonged reaction times did not result in a higher overall yield. Contrary to the enol triflate formation, the aryl coupling reaction using Suzuki-type conditions [2] proceeded well. With styrylic steroid **3** in hand single electron transfer reduction under Birch-type conditions [1] was carried out furnishing stereoselectively 11β-(4-methoxyphenyl) steroid **4**. In analogy to the natural series [4] high diastereoselectivity was observed proving that the 18-methyl substitution does not influence the stereochemical outcome of this reaction.



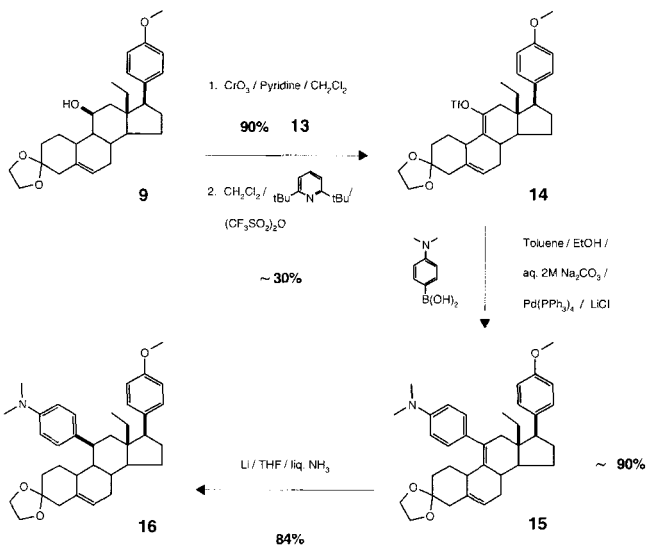
Scheme 1

Starting from steroid **5** [7] enol triflate formation using 1.2 equivalents of trifluoromethanesulfonic anhydride proceeded in moderate yield but with excellent regioselectivity. The sterically less hindered 17-keto function of steroid **5** was selectively converted to the corresponding enol triflate to yield steroid **6**. In an identical fashion as described above enol triflate **6** was coupled in high yield with (4-methoxyphenyl)boronic acid [3] resulting in formation of 17-aryl-16-ene steroid **7**. Ketone **7** was easily converted to 11β-hydroxy steroid **8** *via* reduction with sodium borohydride in methanol/tetrahydrofuran. In addition, steroid **7** was smoothly transformed to 11,17-diaryl-9(11),16-diene steroid **11** by repeating the two step sequence described above. Although the intermediate enol triflate **10** was not isolated the overall yield was low demonstrating again that the 9(11)-enol triflate formation is the problematic step in the 18a-homo series. Experimentally, analysis *via* thin layer chromatography clearly confirmed the limited chemical conversion of steroid **7**. Reduction of the styrylic double bonds in steroids **8** and **11** under Birch-type conditions [1] using lithium in liquid ammonia/tetrahydrofuran resulted uniformly in the highly stereoselective formation of the corresponding β-aryl substituted steroids **9** and **12**. In the ^{1}H NMR spectra a significant upfield shift of the signal of the 18-methyl group was indicative for the β-stereochemistry of the aryl substituents at positions 11 and 17 in these steroids. Remarkably, in case of 11β,17β-aryl steroid **12** the 18-methyl group was found even upfield from the NMR signal for tetramethylsilane at a δ-value of –0.92 ppm.



Scheme 2

As depicted in scheme 3, starting from 11β-hydroxy steroid **9** 11β-[4-(dimethylamino)phenyl] steroid **16** was obtained applying the four step sequence: Ratcliff version of the Sarett oxidation [9], enol triflate formation [8], Suzuki-type coupling [2] and Birch-type reduction [1].



Scheme 3

Deprotection of the 3-keto group under concomitant double bond isomerisation into conjugation furnished steroidal 4-en-3-ones **17** and **18**. Both steroids showed very weak binding affinity at the presterone receptor.

Scheme 4

In summary, the effectiveness of Birch-type reductions of aryl substituted steroidal 9(11)- and 16-double bonds to establish exclusively β-stereochemistry at the site of steroidal aryl substitution has been demonstrated. With regard to the search for more potent antigestagens the process provided access to interesting intermediates in the 18a-homo-19-nor series.

Experimental

Melting points were determined on either a Mettler FP62 melting point instrument or a Kofler hot plate apparatus and are uncorrected. IR spectra were measured on a Bruker FT-IFS 25 spectrometer. ^1H NMR spectra were recorded on a Bruker AC 300 (300 MHz) spectrometer and δ values are given in ppm relative to tetramethylsilane as internal standard. Mass spectra were determined with a Fisons Instruments VG 70–70 E spectrometer at 70 eV ionizing voltage using NH_3 in case of chemical ionization (CI). Optical rotations were determined in a Perkin Elmer polarimeter 241. Microanalytical data were provided by Schering analytical department. TLC analyses were performed on Merck F_{254} silica gel plates. Spots were visualized by soaking the plates with a diethyl ether solution containing vanillin (2.5‰) and sulfuric acid (5%) and heating by means of a heat gun. Column chromatography was carried out on Merck silica gel 60, 70–230 mesh, using ethyl acetate/hexane as eluent. Reactions were run under argon atmosphere. Solvents were reagent grade and dried prior to use. Boronic acids were prepared according to the literature procedure. All other reagents were purchased from commercial suppliers and were used as received.

11-[[(Trifluoromethyl)sulfonyl]oxy]-18a-homoestra-5,9(11)-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (2) (Procedure A: representative procedure for enol triflate formation)

To a solution of 5 g (12.9 mmol) 18a-homoestr-5-ene-3,11,17-trione cyclic 3,17-bis(1,2-ethanediyl acetal) (**1**) in a mixture of 5.8 ml 2,6-di-*tert*-butylpyridine (25.7 mmol, 2 equiv.) and 78 ml dichloromethane 2.94 ml trifluoromethanesulfonic anhydride (17.5 mmol, 1.2 equiv.) were slowly added. After stirring for 24 hours at room temperature the reaction mixture was carefully poured into saturated sodium bicarbonate solution and stirred for 30 minutes. The aqueous phase was extracted with dichloromethane and the combined organic layers were dried over sodium sulfate. Removal of the solvent under vacuum furnished 10.8 g of crude product suitable for intended coupling reactions. A representative sample (200 mg) was analysed by column chromatography yielding 44 mg (47%) of starting material 18a-homoestr-5-ene-3,11,17-trione cyclic 3,17-bis(1,2-ethanediyl acetal) **1** and 35 mg (28%) of 11-[[(trifluoromethyl)sulfonyl]oxy]-18a-homoestra-5,9(11)-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) **2** as a yellowish foam. – IR (KBr): 2950 s (C-H), 2880 s (C-H), 1655 s (C=C), 1385 vs (S=O), 1215 vs (S=O). – ^1H NMR (300 MHz, $CDCl_3$): δ 5.64 (d br, J = 5.5 Hz,1H), 4.02–3.80 (m, 8H), 2.94 (d br, J = 11.5 Hz, 1H), 2.75 (d tr, J = 4.5 and 15.5 Hz, 1H), 2.48 (d q, J = 4.5, 7.5 and 12.5 Hz, 1H), 1.08 (tr, J = 7.5 Hz, 3H). – MS (CI, *m/z*): 538 (13%, $[MH+NH_3]^+$), 521 (27%, $[MH]^+$).

$C_{24}H_{31}F_3O_7S$ (520.56) Calcd.: C 55.38, H 6.00, F 10.95, S 6.16, Found: C 55.22, H 5.93, F 10.61, S 6.05.

17-[[(Trifluoromethyl)sulfonyl]oxy]-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) (**6**)

Following procedure A 10.4 g crude 17-[[(trifluoromethyl) sulfonyl]oxy]-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) **6** were obtained starting from 5 g (14.5 mmol) 18a-methylestr-5-ene-3,11,17-trione cyclic 3-(1,2-ethanediyl acetal) **5**. Analysis of a representative sample (200 mg) by column chromatography furnished 33 mg (33%) starting material **5** and 88 mg (66%) 17-[[(trifluoromethyl) sulfonyl]oxy]-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) **6** as a white solid (*m.p.* 128 °C from diisopropyl ether). – $[\alpha]_D^{22}$= +76° (c=0.535, $CHCl_3$). – IR (KBr): 2970 s (C-H), 2940 s (C-H), 2940 s (C-H), 1710 vs (C=O), 1625 s (C=C), 1420 vs (S=O), 1205 vs (S=O). – ^1H NMR (300 MHz, $CDCl_3$): δ 5.77 (m,1H), 5.48 (d br, J = 5.5

Hz,1H), 4.02–3.88 (m, 4H), 2.73 (d, J = 12.5 Hz, 1H), 2.52 (d, J = 12.5 Hz, 1H), 0.93 (tr, J = 7.5 Hz, 3H).
$C_{22}H_{27}F_3O_6S$ (476.51) Calcd.: C 55.45, H 5.71, F 11.96, S 6.73, Found: C 55.31, H 5.66, F 11.81, S 6.55.

11-(4-Methoxyphenyl)-18a-homoestra-5,9(11)-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (3) (Procedure B: representative procedure for Suzuki-type coupling reaction)

10,6 g crude enol triflate **2** (12.9 mmol) was heated at reflux together with 1.11 g lithium chloride (26.2 mmol, 2 equiv.), 2.22 g (4-methoxyphenyl)boronic acid (14.6 mmol, 1.1 equiv.), 0.75 g tetrakis(triphenylphosphine)palladium(0) (0.64 mmol, 0.05 equiv.), and 17 ml aqueous sodium carbonate solution (2M) in 100 ml toluene and 40 ml ethanol for 1 hour. The reaction mixture was poured into saturated sodium bicarbonate solution, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate, and the organic portions were combined, washed with brine, dried over sodium sulfate, filtered, and evaporated. Column chromatography of the residue afforded 2.2 g (44%) of starting material 18a-homoestr-5-ene-3,11,17-trione cyclic 3,17-bis(1,2-ethanediyl acetal) **1** and 1,84 g (27%) of 11-(4-methoxyphenyl)-18a-homoestra-5,9(11)-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) **3** as a white solid (*m.p.* 150 °C from ethyl acetate). – IR (KBr): 2940 vs (C-H), 2880 vs (C-H), 1605 s (C=C), 1510 vs (C=C). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.65 (d br, J = 5.5 Hz,1H), 4.00–3.73 (m, 11H), 3 (d br, J = 11.5 Hz, 1H), 2.74 (d tr br, J = 3.5 and 15.5 Hz, 1H), 0.92 (tr, J = 7.5 Hz, 3H).
$C_{30}H_{38}O_5$ (478.63) Calcd.: C 75.28, H 8.00, Found: C 75.33, H 8.05.

17-(4-Methoxyphenyl)-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) (**7**)

Following procedure B 10,2 g of crude enol triflate **6** (14.5 mmol) was coupled with 2.45 g (4-methoxyphenyl)boronic acid (16 mmol, 1.1 equiv.). After work up and column chromatography 3,96 g (57%) 17-(4-methoxyphenyl)-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) **7** were obtained as a white solid (*m.p.* 130 °C from diisopropyl ether). In addition, 1.43 g (29%) of starting material 18a-homoestr-5-ene-3,11,17-trione cyclic 3-(1,2-ethanediyl acetal) (**5**) were isolated. – IR (KBr): 2940 s (C-H), 2870 vs (C-H), 1705 vs (C=O), 1605 m (C=C), 1510 vs (C=C). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.03 (m, 1H), 5.52 (d br, J = 5.5 Hz,1H), 4.03–3.90 (m, 4H), 3.81 (s, 3H), 2,97 (d, J = 11.5 Hz, 1H), 2.72 (d, J = 11.5 Hz, 1H), 0.70 (tr, J = 7.5 Hz, 3H).
$C_{28}H_{34}O_4$ (434.58) Calcd.: C 77.39, H 7.89, Found: C 77.28, H 7.94.

11β-(4-Methoxyphenyl)-18a-homoestr-5-ene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (4) (Procedure C: representative procedure for Birch-type reduction)

A solution of 479 mg (1 mmol) 11-(4-methoxyphenyl)-18a-homoestra-5,9(11)-diene-3,17-dione cyclic bis(1,2-ethanediyl acetal) (**3**) dissolved in 60 ml tetrahydrofuran was added to liquid ammonia (approx. 40 ml) at –78 °C. Then, 70 mg lithium wire (10 mmol, 10 equiv.) was added. After 1 hour at –78 °C the mixture was cautiously treated with water until decolouration occurred, the ammonia was evaporated, the residue was diluted with water, and the aqueous layer was extracted with ethyl acetate. The organic portions were combined, washed with water and with brine, dried over sodium sulfate, filtered and evaporated. The obtained white solid was recrystallized from diisopropyl ether to yield 247 mg (52%) pure compound **4** (*m.p.* 218 °C under decomposition). Column chromatography of the mother liquor resulted in an additional 143 mg (30%) of product **4**. – IR (KBr): 2940 vs (C-H), 2880 vs (C-H), 1610 s (C=C), 1510 vs (C=C). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (s br, 2H), 6.78 (d br, J = 8.5 Hz, 2H), 5.52 (d br, J = 5 Hz,1H), 4.02–3.73 (m, 11H), 3.37 (tr br, J = 5 Hz, 1H), 0.10 (tr, J = 7.5 Hz, 3H).
$C_{30}H_{40}O_5$ (480.65) Calcd.: C 74.97, H 8.39, Found: C 74.93, H 8.45.

17-(4-Methoxyphenyl)-11-[[(trifluoromethyl)sulfonyl]oxy]-18a-homoestra-5,9(11),16-triene-3-one cyclic (1,2-ethanediyl acetal) (**10**)

Following procedure A 2.2 g crude 17-(4-methoxyphenyl)-11-[[(trifluoromethyl)sulfonyl]oxy]-18a-homoestra-5,9(11),16-triene-3-one cyclic (1,2-ethanediyl acetal) **10** were obtained starting from 1 g (2.3 mmol) 17-(4-methoxyphenyl)-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) (**7**). The crude material was used for the next step without further purification.

11,17-Bis(4-methoxyphenyl)-18a-homoestra-5,9(11),16-trien-3-one cyclic (1,2-ethanediyl acetal) (**11**)

Following procedure B 2,2 g of crude enol triflate **10** (2.3 mmol) was coupled with 385 mg (4-methoxyphenyl)boronic acid (2.5 mmol, 1.1 equiv.). After work up and column chromatography 340 mg (28%) triene **11** were obtained as a white foam. – IR (KBr): 2930 s (C-H), 1605 s (C=C), 1510 vs (C=C). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.10 (m, 1H), 5.70 (d br, J = 5.5 Hz, 1H), 3.98-3.75 (m, 10H), 3.04 (d br, J = 12.5 Hz, 1H), 2.91 (d tr, J = 4 and 15 Hz, 1H), 0.77 (tr, J = 7.5 Hz, 3H).
$C_{35}H_{40}O_4$ (524.70) Calcd.: C 80.12, H 7.68, Found: C 79.98, H 7.63.
In addition, 621 mg (62%) of starting material 17-(4-methoxyphenyl)-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) (**7**) were recovered.

11β,17β-Bis(4-methoxyphenyl)-18a-homoestr-5-en-3-one cyclic (1,2-ethanediyl acetal) (**12**)

Following procedure C 327 mg (0.62 mmol) triene **11** were reduced. After work up 325 mg (99%) crude steroid **12** were obtained. The crude product was recrystallized from diisopropyl ether to yield 225 mg (69%) pure compound **12** as white crystals. Column chromatography of the mother liquor resulted in an additional 72 mg (22%) of product **12** (*m.p.* 223 °C under decomposition). – IR (KBr): 2940 s (C-H), 1610 s (C=C), 1510 vs (C=C). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (s br, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 8.5 Hz,

2H), 6.69 (d, J = 8.5 Hz, 2H), 5.53 (d br, J = 5.5 Hz, 1H), 4.03–3.84 (m, 4H), 3.74 (s, 3H), 3.73 (s, 3H), 3.36 (tr br, J = 4 Hz, 1H), 2.6 (tr br, J = 7.5 Hz, 1H), -0.92 (tr, J = 7.5 Hz, 3H).

$C_{35}H_{44}O_4$ Calcd.: C 79.51, H 8.39,
(528.73) Found: C 79.28, H 8.35.

11β,17β-Bis(4-methoxyphenyl)-18a-homoestr-4-en-3-one (17) (Procedure D: representative procedure for acidic ketal cleavage)

To a solution of 200 mg (0.38 mmol) steroid **12** in 20 ml acetone 4 ml aqueous hydrogen chloride solution (4M) were added. After stirring for 12 hours at room temperature the reaction mixture was poured onto saturated sodium bicarbonate solution, the aqueous phase extracted with ethyl acetate and the organic layers combined. Drying over anhydrous sodium sulfate and evaporation of the solvent furnished 198 mg crude product. Column chromatography on silica gel yielded 178 mg (97%) pure steroid **17** as a white foam – IR (KBr): 2930 s (C-H), 1670 s (C=O), 1610 m (C=C), 1510 vs (C=C), 1250 s (C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (s br, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.76 (tr, J = 8.5 Hz, 4H), 5.87 (s br, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.30 (tr br, J = 6.5 Hz, 1H), -0.87 (tr, J = 7.5 Hz, 3H).

$C_{33}H_{40}O_3$ Calcd.: C 81.78, H 8.32,
(484.68) Found: C 81.68, H 8.25.

11β-Hydroxy-17-(4-methoxyphenyl)-18a-homoestr-5,16-dien-3-one cyclic 3-(1,2-ethanediyl acetal) (**8**)

To a solution of 3 g (6.9 mmol) 17-(4-methoxyphenyl)-18a-homoestra-5,16-diene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) **7** in 66 ml tetrahydrofuran and 34 ml methanol 564 mg (14.9 mmol, 6.6 equiv.) sodium borohydride was added at 0 °C. The reaction was stirred overnight and quenched with aqueous saturated ammonium chloride solution. The aqueous phase was extracted with ethyl acetate, the organic layers combined, washed with brine, dried over sodium sulfate and concentrated under vacuum furnishing 2,95 g of crude 11β-hydroxy steroid **8**. The crude product was purified by column chromatography on silica gel yielding 2.17 g (73%) pure product **8** as a white solid (*m.p.* 164 °C from diisopropyl ether). – IR (KBr): 3470 m (O-H), 2930 s (C-H), 2900 s (C-H), 1605 m (C=C), 1510 vs (C=C), 1250 s (C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.93 (tr, J = 2.5 Hz, 1H), 5.5 (d br, J = 5 Hz, 1H), 4.30 (m, 1H), 4.05–3.90 (m, 4H), 3.78 (s, 3H), 2.58 (dd, J = 2 and 14.5 Hz, 1H), 0.74 (tr, J = 7.5 Hz, 3H).

$C_{28}H_{36}O_4$ Calcd. C 77.03, H 8.31,
(436.59) Found. C 76.88, H 8.24.

11β-Hydroxy-17β-(4-methoxyphenyl)-18a-homoestr-5-ene-3-one cyclic 3-(1,2-ethanediyl acetal) (**9**)

Following procedure C 1.75 g (4 mmol) diene **8** were reduced. After work up 1.84 g crude compound **9** were obtained. The crude white product was recrystallized from diisopropyl ether to yield 1.32 g (75%) pure 11β-hydroxy-17β-(4-methoxyphenyl)-18a-homoestr-5-ene-3-one cyclic 3-(1,2-ethanediyl acetal) (**9**) (*m.p.* 183 °C). – IR (KBr): 3490 m (O–H), 2940 vs (C-H), 2880 s (C-H), 1610 m (C=C), 1510 vs (C=C), 1250 s (C-O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.48 (d br, J = 5 Hz, 1H), 4.18 (m, 1H), 4.05-3.9 (m, 4H), 3.78 (s, 3H), 2.67 (tr, J = 18.5 Hz, 1H), 2.42 (dd, J = 2.5 and 14.5 Hz, 1H), 0.19 (tr, J = 7.5 Hz, 3H).

$C_{28}H_{38}O_4$ Calcd.: C 76.68, H 8.73,
(438.61) Found: C 76.44, H 8.65.

Following procedure C 436 mg (1 mmol) ketone **7** was directly reduced to compound **9**. After work up 423 mg crude product were obtained yielding after column chromatography on silica gel 345 mg of pure **9** as a white solid.

17β-(4-Methoxyphenyl)-18a-homoestr-5-ene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) (**13**)

At 0 °C 1.86 g (5.8 mmol) chromium trioxide was added in portions to a solvent mixture of 6 ml pyridine and 50 ml dichloromethane. Subsequently, a solution of 1.3 g (3 mmol) 11β-hydroxy-17β-(4-methoxyphenyl)-18a-homoestr-5-ene-3-one cyclic 3-(1,2-ethanediyl acetal) **9** in 30 ml dichloromethane was added dropwise, and the reaction stirred for 1 hour. For work up, the reaction mixture was poured onto aqueous saturated sodium bicarbonate solution and the aqueous phase extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under vacuum. The crude product was purified by column chromatography on silica gel yielding 1.16 g of compound **13** as a slightly yellow solid (*m.p.* 161 °C from diisopropyl ether). – IR (KBr): 2940 s (C-H), 2880 s (C-H), 1705 vs (C=O), 1610 m (C=C), 1510 vs (C=C), 1250 vs (C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.48 (d br, J = 5 Hz, 1H), 4.05–3.89 (m, 4H), 3.80 (s, 3H), 2.95 (tr, J = 18.5 Hz, 1H) 2.73 (d, J = 11 Hz, 1H), 0.13 (tr, J = 7.5 Hz, 3H).

$C_{28}H_{36}O_4$ Calcd.: C 77.03, H 8.31,
(436.59) Found: C 76.97, H 8.21.

17β-(4-Methoxyphenyl)-11-[[(trifluoromethyl)sulfonyl] oxy]-18a-homoestra-5,9(11)-diene-3-one cyclic (1,2-ethanediyl acetal) (**14**)

Following procedure A 2.9 g of crude compound **14** were obtained starting from 1.18 g (2.7 mmol) 17β-(4-methoxyphenyl)-18a-homoestra-5-ene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) (**13**). The crude material was used for the next step without further purification.

11-[4-(Dimethylamino)phenyl]-17β-(4-methoxyphenyl)-18a-homoestra-5,9(11)-diene-3-one cyclic (1,2-ethanediyl acetal) (**15**)

Following procedure B 2,9 g of crude enol triflate **14** (2.7 mmol) was coupled with 500 mg [4-(dimethylamino)phenyl]boronic acid (2.5 mmol, 1.1 equiv.). After work up and column chromatography 360 mg (25%) product **15** were obtained as a white foam. – IR (KBr): 2930 s (C-H), 1610 s (C=C), 1510 vs (C=C), 1250 s (C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J = 8.5 Hz, 2H), 7.03 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 5.61 (d br, J = 5.5 Hz, 1H), 3.98–3.80 (m, 4H), 3.75 (s, 3H), 3.01 (d br, J = 7.5 Hz, 1H), 2.92 (s, 6H), 2.49 (d tr, J = 3.5 and 15 Hz,

1H), 0.15 (tr, J = 7.5 Hz, 3H).
$C_{36}H_{45}NO_3$ Calcd.: C 80.11, H 8.40 N 2.60,
(539.76) Found: C 79.87, H 8.29, N 2.47.
In addition, 713 mg (60%) of starting material 17β-(4-methoxyphenyl)-18a-homoestr-5-ene-3,11-dione cyclic 3-(1,2-ethanediyl acetal) (**13**) were recovered.

11β-[4-(Dimethylamino)phenyl]-17β-(4-methoxyphenyl)-18a-homoestr-5-en-3-one cyclic (1,2-ethanediyl acetal) (**16**)

Following procedure C 300 mg (0.56 mmol) of diene **15** were reduced. After work up 295 mg crude steroid **16** were obtained. The crude product was purified by column chromatography on silica gel yielding 254 mg (84%) of **16** as a white foam. – IR (KBr): 2935 s (C-H), 1610 m (C=C), 1510 vs (C=C), 1250 s (C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13 (m, 4H), 6.75 (d, J = 8.5 Hz, 2H), 6.55 (d, J = 8.5 Hz, 2H), 5.52 (m, 1H), 3.97–3.84 (m, 4H), 3.73 (s,3H), 3.31 (tr br, J = 6.5 Hz, 1H), 2.83 (s, 6H), 2.60 (tr, J = 10 Hz, 1H), –0.88 (tr, J = 7.5 Hz, 3H).
$C_{36}H_{47}NO_3$ Calcd.: C 79.81, H 8.74, N 2.59
(541.77) Found: C 79.76, H 8.65, N 2.46.

11β-[4-(Dimethylamino)phenyl]-17β-(4-methoxyphenyl)-18a-homoestr-4-en-3-one (**18**)

Following procedure D 200 mg (0.37 mmol) ketal **16** were cleaved. After work up 165 mg crude compound **18** were obtained. The crude product was purified by column chromatography on silica gel yielding 112 mg (61%) of **18** as a slightly yellow foam. – IR (KBr): 2930 s (C-H), 1680 vs (C=O), 1610 s (C=C), 1510 vs (C=C), 1250 s (C–O). – ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.2 (m br, 2H), 7.13 (d, J = 8.5 Hz, 2H), 6.76 (tr, J = 8.5 Hz, 2H), 6.58 (tr, J = 8.5 Hz, 2H), 5.86 (s br, 1H), 3.75 (s, 3H), 3.23 (tr br, J = 6.5 Hz, 1H), 2.84 (s, 6H), 2.74 (m, 1H), –0.84 (tr, J = 7.5 Hz, 3H).
$C_{34}H_{43}NO_2$ Calcd.: C 82.05, H 8.71, N 2.81
(497.72) Found: C 81.93, H 8.62, N 2.64.

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