Pergamon

Tetrahedron Vol. 51, No. 19, pp. 5563-5572, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00227-8

Synthesis of 14ß-H Antiprogestins

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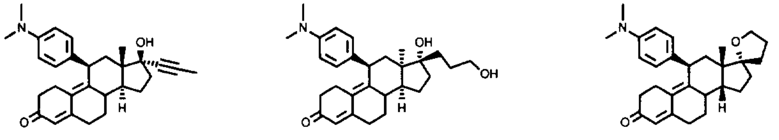
Key Words: antiprogestins; 11β-substituted steroids; 14β-configuration; palladium-catalyzed cross-coupling

Abstract: *An efficient approach to 14β-H antiprogestins is described. The key step of the synthesis is a cleavage of 17-silyl dienol ethers 7 respectively 12, which are generated from the corresponding Δ^{14}-17-ketones, with hydrogen fluoride-pyridine complex. This method gave access to 14β-H analogs of the 11β,19-bridged series (type A) as well as of the 10β-H,11β-aryl series (type B).*

INTRODUCTION

Since the discovery of the first progesterone antagonist[1a,1b] RU 38 486 (Mifepristone) the therapeutic options connected with antigestagens have been demonstrated in a great variety of indications. Apart from early pregnancy termination several other potential applications have been studied like induction of parturition, treatment of endometriosis, contraception, and endocrine tumor therapy.

In addition to antiprogestational activity RU 38 486 shows substantial antiglucocorticoid activity. For long-term use at high doses a more selective antiprogestin would be preferable. Therefore, an intensive search for more potent and more selective antiprogestins was initiated.



RU 38 486
Mifepristone

ZK 98 299
Onapristone

Org 31 376

Figure 1

As a part of these investigations a further class of antigestagens was discovered characterized by the change from trans to cis fusion of rings C and D (13α-series). A representative of this class is Onapristone (ZK 98 299)[2] currently under clinical development for the treatment of mammary carcinoma by Schering AG.

The other possible way to establish cis fusion between rings C and D is to invert stereochemistry at C-14. Such 14β-H compounds, especially Org 31 376, were described by the Organon group as highly dissociated antiprogestins.[3]

Our continued work in the field of antiprogestins has led to a variety of interesting compounds. Among other structural variations the introduction of a methylene bridge between C-10 of the steroid skeleton and the 11β-aryl residue (type A molecules)[4] as well as the successful approach to the 10β-H, 11β-aryl series (type B molecules)[5] have led to potent antiprogestins with greatly reduced antiglucocorticoid side effects.

Consequently, 14β-H analogues of type A and type B molecules appeared to be attractive synthetic targets.

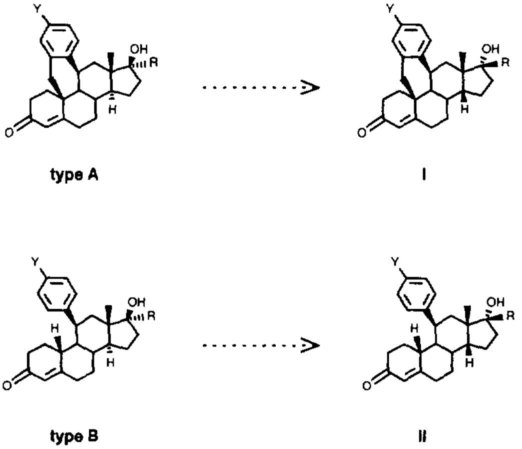
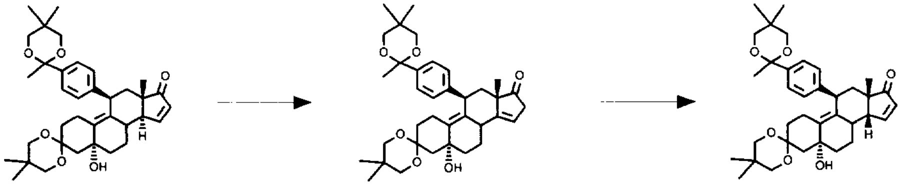


Figure 2

The synthetic route to Org 31 376 and analogs involves inversion of the configuration at C-14 on an early stage starting from estrone methyl ether. With the 14β-H estrone methyl ether in hand the target compounds were prepared analogously to the way developed for RU 38 486 by Roussel Uclaf.[3]

Considering our synthetic approaches to type A[4] and type B molecules[5] this strategy was not considered very promising. It appeared more practical to invert the configuration at C-14 on an advanced stage in the sequence after the aryl substituent had been established.

Previous studies on the synthesis of 14,17-bridged antiprogestins gave access to highly functionalized 14β-H compound **3** (see scheme 1). As published earlier, treatment of **1** with neutral aluminum oxide or silica gel by adding 1% triethylamin to the eluent gave **3** in high yield via 14-unsaturated compound **2**. Under controlled reaction conditions the isolation of **2** was also possible.[6]



1 2 3

Scheme 1

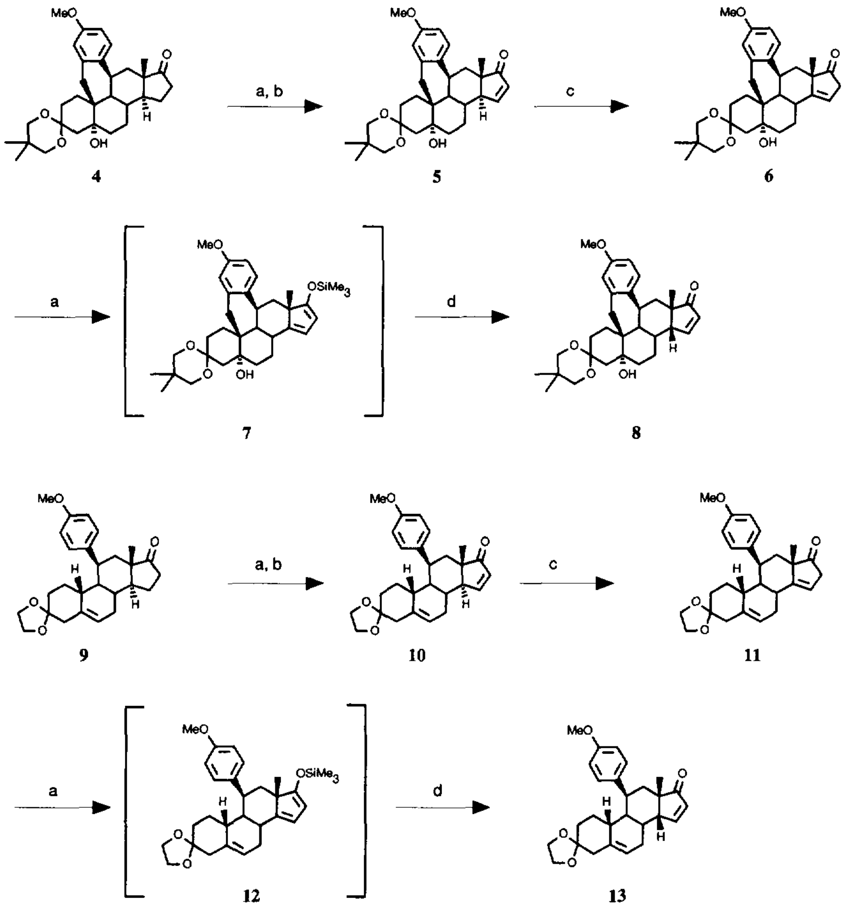
More recent studies showed that the success of this reaction critically depended on the substitution pattern and on the conformational situation of the whole molecule. In case of the 10β-H or the bridged series the inversion at C-14 was generally achieved in low yield only. Due to comparable polarities, chromatographical separation of 14β-H products from starting material turned out to be difficult.

This report describes a method which allows the inversion of the stereochemistry at C-14 for both series in high yield by cleavage of 17-silyl-14,16-dienol ethers using hydrogen fluoride-pyridine complex in tetrahydrofuran.

RESULTS AND DISCUSSION

The synthetic approach to 14β-H compounds **8** and **13** is shown in scheme 2. Starting with the known ketones **4**[4] and **9**[5] the 15-unsaturated derivatives **5** and **10** were prepared via modified Saegusa oxidation of the corresponding silyl enol ethers using one equivalent of palladium(II) acetate in acetonitrile.[7] Deconjugation of the 15-double bond was achieved by stirring **5** or **10** with triethylamine and silica gel in a mixture of hexane and ethyl acetate. Under these reaction conditions both Δ^{14} compounds **6** and **11** were obtained in high yield. Small amounts of starting material were easily removed by chromatography. The trimethylsilyl dienol ethers **7** and **12** were produced by conversion of the 14-unsaturated 17-ketones with lithium diisopropyl amide in tetrahydrofuran to the corresponding dienolates and trapping with trimethylchlorosilane at -20 C. After starting material had disappeared on TLC the reaction mixtures were cooled to -70 C and hydrogen fluoride-pyridine complex was added. Under these mild acidic conditions the 14β-H compounds **8** and **13** were produced in high yield by electrophilic attack of H^+ at C-14. Whereas the preparation of silyl dienol ethers **7** and **12** starting from deconjugated ketones **6** and **11** worked without any problems, all attempts for a direct conversion of the conjugated ketones **5** and **10** to **7** and **12** did not succeed. In the latter case complex mixtures were obtained.

The 14β-configuration of compounds **8** and **13** was proven by NOE experiments. In both cases the 14β-protons were assigned by proton-proton correlative spectroscopy (cosy). Irridation on the 14β-H signals in **8** and **13** resulted in enhancemenant of the 13β-CH_3 signal. On the other hand, irridation on the 13β-CH_3 signal also enhanced that of 14β-H. In case of compounds **5** and **10** with natural configuration at C-14 no effects were observed.

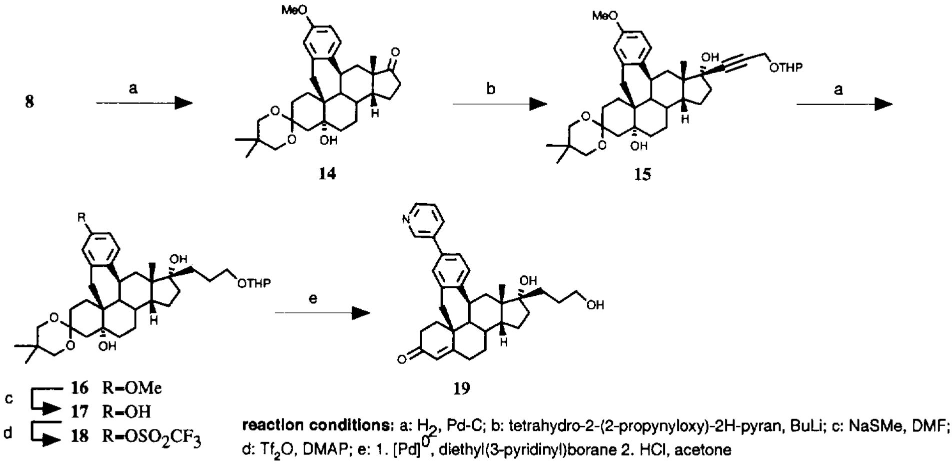


reaction conditions: a: 1. LDA 2. TMS-Cl; b: $Pd(OAc)_2$; c: silica gel, NEt_3; d: HF-pyridine

Scheme 2

Compounds **8** and **13** turned out to be ideal intermediates for the preparation of the desired 14β-H antiprogestins. Scheme 3 demonstrates the preparation of the bridged compound **19**. After hydrogenation of the 15-double bond the saturated 17-ketone **14** was allowed to react with 3-[(tetrahydro-2*H*-pyran-2-yl)-oxy]-1-propynyl lithium. Subsequent hydrogenation of the 17β-side chain gave **16**.

The next step was the introduction of aryl substituents. As we found earlier, replacement of the 4-(dimethylamino) group, which is the substituent of the reference substances RU 38 486, ZK 98 299 and Org 31 376 by several other substituents maintains or enhances antiprogestational activity. The introduction of e.g. acetyl or a number of heterocycles led to equally or in some cases even more potent antiprogestins.[8] Among these heterocycles the 3-pyridinyl group was found to be one of the most active.[9] Therefore this group was chosen as aryl substituent for the first target substance. Cleavage of the aryl methyl ether, without affecting the other functional groups, was performed by heating **16** with sodium methanethiolate in *N,N*-dimethylformamide under reflux.[10] Reaction of **17** with triflic anhydride in the presence of 4-(dimethylamino)pyridine gave the aryltriflate **18**, a suitable intermediate for palladium-catalyzed cross-coupling reactions with organometallics.[11] As shown in scheme 3 cross- coupling of triflate **18** with diethyl(3-pyridinyl)borane[12a,12b] and subsequent cleavage of the protecting groups by treatment with 4 N hydrochloric acid in acetone at 40 C gave compound **19**.

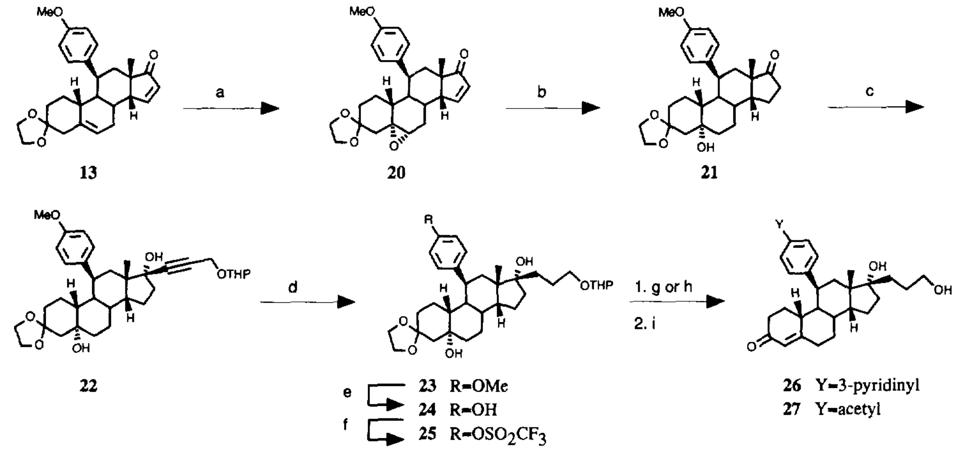


reaction conditions: a: H_2, Pd-C; b: tetrahydro-2-(2-propynyloxy)-2H-pyran, BuLi; c: NaSMe, DMF; d: Tf_2O, DMAP; e: 1. $[Pd]^0$, diethyl(3-pyridinyl)borane 2. HCl, acetone

Scheme 3

Scheme 4 shows the synthetic approach to 10β-H,14β-H compounds **26** and **27**. The protocol leading to 10β-H compounds involves Δ^5-intermediates. Hydrogenation of propargylic side chains in presence of a 5-double bond was described in the literature.[13] In our case previous studies had shown that a selective hydrogenation of the side chain is possible using Pd/C as catalyst in ethyl acetate. However, depending on the reaction time different amounts of starting material respectively material with reduced 5-double bond had to be separated by chromatography. Especially in larger scale preparations (some grams) this separation caused serious problems because of very similar polarity. Therefore we decided to protect the 5-double bond as a 5α-alcohol. Regio- and stereoselective epoxidation of dienone **13** was performed using *m*-nitrotrifluoroacetophenone and hydrogen peroxide in dichloromethane.[14] Reduction of 5,6α-epoxide **20** and concomitant reduction of Δ^{15} and the 17-ketone were achieved by heating **20** with sodium borohydride in ethanol under reflux. Reoxidation of the crude material using Collins' procedure[15] gave the saturated 17-ketone **21**. In analogy to the bridged series the 17-side chain was established in two steps by addition of 3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propynyl lithium and hydrogenation. After cleavage of the aryl ether phenol **24** was converted to aryl triflate **25**. Palladium-catalyzed cross-coupling of **25** either with diethyl(3-pyridinyl)borane or tributyl(1-ethoxyethenyl)stannane[16] followed by cleavage of the protecting groups with 4 N hydrochloric acid in acetone gave compounds **26** and **27**.

In both series the inversion of stereochemistry at C-14 did not lead to further improvement of dissociation between antiprogestational and antiglucocorticoid activities.



reaction conditions: a: H_2O_2, 2,2,2-trifluoro-1-(3-nitrophenyl)ethanone; b: 1. $NaBH_4$ 2. CrO_3/pyridine; c: tetrahydro-2-(2-propynyloxy)-2H-pyran, BuLi; d: H_2/ Pd-C; e: NaSMe, DMF; f: Tf_2O, DMAP; g: $[Pd]^0$, diethyl(3-pyridinyl)borane; h: $[Pd]^0$, tributyl(1-ethoxyethenyl) stannane; i: HCl, acetone

Scheme 4

EXPERIMENTAL

NMR: General Electric QE 300 and Bruker AC 300 spectrometers; δ in ppm rel. to TMS as internal standard. IR: Perkin Elmer PE 621 spectrometer. MS: Finnigan TSQ 700 spectrometer. Combustion analyses were carried out by Schering analytical department. Optical rotations: Perkin Elmer polarimeter mod. 141. Melting points are uncorrected. TLC analyses were performed on Merck 60 F_{254} silica gel plates.

Tetrahydrofuran and diethyl ether were distilled over sodium/benzophenone prior to use. All other solvents were purchased as p.a. (pro analysi) quality and dried over molecular sieves. All reactions were run under positive argon pressure.

Unless noted otherwise, usual work-up means quenching of the reaction mixture with sodium chloride solution, extraction with ethyl acetate, washing of the organic layer with either sodium bicarbonate solution or dilute hydrochloric acid and sodium chloride solution, drying over sodium sulfate, and evaporation of the solvent. Purification of crude materials was performed by chromatography on silica gel (Merck silica gel 60, 70-230 mesh) using ethyl acetate/hexane as eluents.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-5-hydroxy-6'-methoxy-4'*H*-naphth-[3',2',1':10,9,11]-5α-estra-9(11),15-dien-17-one (5): Diisopropylamine (2.1 mL, 15.2 mmol) was dissolved in 45 mL tetrahydrofuran (THF) and cooled to -78 C. Butyllithium (9.5 mL, 15.2 mmol, 1.6 M in hexane) was added and the mixture was stirred for 30 min at 0 C. Afterwards it was cooled to -78 C and a solution of 3 g (6.06 mmol) **3,3-[2,2-dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-5-hydroxy-6'-methoxy-4'*H*-naphth[3',2',1':10,9,11]-5α-estr-9(11)-en-17-one (4)** in 25 mL THF was added dropwise. After 1 h of stirring at -78 C chlorotrimethylsilane (1.93 mL, 15.2 mmol) was added. The mixture was warmed to 25 C and stirred for another 30 min. The reaction mixture was added to a saturated aqueous solution of sodium bicarbonate and worked-up further as usual. The crude silyl enol ether (3.4 g) was suspended in 40 mL acetonitrile. Palladium(II) acetate (2 g, 9.03 mmol) was added and the solution was stirred at room temperature for 12 h. Afterwards the reaction mixture was filtered through Celite®. Evaporation and purification yielded 2.24 g (75%) **5**. **IR** (KBr, cm^{-1}): 3480, 2950, 1720. **^1H NMR** (300 MHz, $CDCl_3$): δ= 7.51 ppm dd (J=6, 1 Hz, 1H, H-15), 7.30 d (J=10 Hz, 1H, aryl), 6.73 dd (J=10, 2.5 Hz, 1H, aryl), 6.58 d (J=2.5 Hz, 1H, aryl), 5.97 dd (J=6, 3 Hz, 1H, H-16), 4.50 s (1H, OH), 3.79 s (3H, OMe), 3.50-3.65 m (4H, ketal), 3.22 ddbr (J=6, 5 Hz, 1H, H-11), 3.10 d (J=18 Hz, 1H, H-19), 2.72 dbr (J=15 Hz, 1H, H-12β), 2.69 d (J=18 Hz, 1H, H-19'), 2.51 dbr (J=10 Hz, 1H, H-14), 1.93 dd (J=15, 5 Hz, 1H, H-12α), 1.00 s (3H, Me-ketal), 0.95 s (3H, Me-ketal), 0.60 s (3H, H-18). **MS** (EI) m/z: 492 (M^+, 12), 474 (M^+-H_2O, 31), 388 (11), 331 (64), 171 (30), 141 (100), 69 (29), 55 (27). $C_{31}H_{40}O_5$ calcd. C 75.58; H 8.18, found C 75.52; H 8.14 %.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-5-hydroxy-6'methoxy-4'*H*-naphth-[3',2',1':10,9,11]-5α-estra-9(11),14-dien-17-one (6): Compound **5** (2.24 g, 4.55 mmol) was dissolved in 250 mL of a 9:1 mixture of ethyl acetate and hexane. Triethylamine (25 mL) and silica gel (100 g) were added. The reaction mixture was stirred for 60 h at room temperature. After filtration, evaporation, and purification 1.62 g (72%) **6** and 337 mg (15%) starting material **5** were isolated. **IR** (KBr, cm^{-1}): 3480, 2950, 1740. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ= 7.38 d (J=10 Hz, 1H, aryl), 6.74 dd (J=10, 2.5 Hz, 1H, aryl), 6.61 d (J=2.5 Hz, 1H, aryl), 5.54 m (1H, H-15), 4.48 s (1H, OH), 3.80 s (3H, OMe), 3.50-3.65 m (4H, ketal), 3.14 d (J=18 Hz, 1H, H-19), 3.10 m (1H, H-11), 3.00 ddd (J=22, 4, 1.5 Hz, 1H, H-16), 2.81 dt (J=22, 1 Hz, H-16'), 2.68 d (J=18 Hz, 1H, H-19'), 1.00 s (3H, H-18), 0.96 s (3H, Me-ketal), 0.70 s (3H, Me-ketal). **MS** (EI) m/z: 492 (M^+, 8), 474 (M^+-H_2O, 15), 388 (8), 331 (32), 171 (30), 141 (10), 69 (20), 55 (19). $C_{31}H_{40}O_5$ calcd. C 75.58; H 8.18, found C 75.67; H 8.23%.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-5-hydroxy-6'-methoxy-4'*H*-naphth-[3',2',1':10,9,11]-5α,14β-estra-9(11),15-dien-17-one (8): Compound **6** (1.62 g, 3.29 mmol) was converted into silyl dienol ether **7** with diisopropylamine (1.13 mL, 8.2 mmol), butyllithium (5.1 mL, 8.2 mmol, 1.6 M in hexane) and chlorotrimethylsilane (1.04 mL, 8.2 mmol) in the same manner as described for the preparation of **5**. After starting material had disappeared on TLC (30 min) it was cooled to -78 C and 1.4 mL of hydrogen fluoride-pyridine complex was added. The reaction mixture was stirred for another 2 h at -78 C and then poured into saturated sodium bicarbonate solution and further worked-up as usual. Purification gave 1.23 g (76%) **8**. **IR** (KBr, cm^{-1}): 3420, 2940, 1700. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ= 7.80 dd (J=6, 2.5 Hz, 1H, H-15), 7.07 d (J=10 Hz, 1H, aryl), 6.72 dd (J=10, 2.5 Hz, 1H, aryl), 6.54 d (J=2.5 Hz, 1H, aryl), 6.31 dd (J=6, 1 Hz, 1H, H-16), 4.36 s (1H, OH), 3.78 s (3H, OMe), 3.43-3.54 m (4H, ketal), 2.96 d (J=18 Hz, 1H, H-19), 2.86 ddd (J=11, 10, 6 Hz, 1H, H-11), 2.68 m (1H, H-14), 2.47 d (J=18 Hz, 1H, H-19'), 1.02 s (3H, H-18), 0.99 s (3H, Me-ketal), 0.87 s (3H, Me-ketal). **MS** (EI) m/z: 492 (M^+, 27), 474 (M^+-H_2O, 20), 388 (10), 187 (19), 171 (12), 141 (100), 69 (22), 55(19). $C_{31}H_{40}O_5$ calcd. C 75.58; H 8.18, found C 75.62, H 8.23 %.

3,3-[1,2-Ethanediylbis(oxy)]-11β-(4-methoxyphenyl)estra-5,15-dien-17-one (10): Compound **10** (7.05 g, 78%) was prepared from 9 g (21.30 mmol) **3,3-[1,2-ethanediylbis(oxy)]-11β-(4-methoxyphenyl)estr-5-en-17-one (9)**, diisopropylamine (4.42 mL, 32 mmol), butyllithium (20 mL, 32 mmol, 1.6 M in hexane), chlorotrimethylsilane (4.1 mL, 32 mmol) and oxidation of the isolated crude silyl enol ether with palladium(II) acetate (7.03 g, 31.74 mmol) following the procedure described for the preparation of compound **5**. **IR** (KBr, cm^{-1}): 3450, 2940, 1715, 1510. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ= 7.53 dd (J=6, 1 Hz, 1H, H-15), 7.25 d (J=10 Hz, 2H, aryl), 6.80 d (J=10 Hz, 2H, aryl), 5.98 dd (J=6, 3 Hz, 1H, H-16), 5.57 dbr (J=5 Hz, 1H, H-6), 3.87-4.00 m (4H, ketal), 3.79 s (3H, OMe), 3.51 ddbr (J= 6, 5 Hz, 1H, H-11), 2.42 dbr (J=10 Hz, 1H, H-14), 0.90 s (3H, H-18). **MS** (EI) m/z: 420 (M^+, 6), 319 (3), 134 (17), 121 (15), 99(100), 55 (11). $C_{27}H_{32}O_4$: calcd. C 77.11; H 7.67, found C 77.05; H 7.61 %.

3,3-[1,2-Ethanediylbis(oxy)]-11β-(4-methoxyphenyl)estra-5,14-dien-17-one (11): As described above 7.05 g (16.76 mmol) of **10** was reacted with silica gel and triethylamine in a 9:1 mixture of ethyl acetate and hexane. After purification 5.22 g (74%) **11** and 916 mg (13%) starting material **10** were isolated. **IR** (KBr, cm^{-1}): 3460, 2960, 1740, 1510. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ= 7.33 d (J=10 Hz, 2H, aryl), 6.83 d (J= 10 Hz, 2H, aryl), 5.60 m (2H, H-6, H-15), 3.90-4.01 m (4H, ketal), 3.80 s (3H, OMe), 3.39 ddbr (J= 7, 5 Hz, 1H, H-11), 3.05 ddd (J=22, 4, 1.5 Hz, 1H, H-16), 2.78 dt (J=22, 1 Hz, 1H, H-16'), 0.80 s (3H, H-18). **MS** (EI) m/z: 420 (M^+, 8), 134 (9), 121 (13), 99 (100), 55 (7). $C_{27}H_{32}O_4$ calcd. C 77.11; H 7.67, found C 77.03; H 7.64 %.

3,3-[1,2-Ethanediylbis(oxy)]-11β-(4-methoxyphenyl)-14β-estra-5,15-dien-17-one (13): Following the procedure described for the preparation of **8** compound **11** (5.22 g, 12.4 mmol) was treated with diisopropylamine (2.56 mL, 18.6 mmol), butyllithium (11.57 mL, 18.6 mmol, 1.6 M in hexane), chlorotrimethylsilane (2.36 mL, 18.6 mmol) and 3 mL hydrogen fluoride-pyridine complex. After purification 3.86 g (74%) **13** was isolated. **IR** (KBr, cm^{-1}): 3450, 2920, 1705, 1510. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ=7.78 dd (J=6, 2 Hz, 1H, H-15), 7.02 d (J=10 Hz, 2H, aryl), 6.77 d (J=10 Hz, 2H, aryl), 6.36 dd (J= 6, 1.5 Hz, 1H, H-16), 5.50 m (1H, H-6), 3.78-3.95 m (4H, ketal), 3.67 s (3H, OMe), 2.85 ddd (J=11.5, 10.5, 6 Hz, 1H, H-11), 2.72 m (1H, H-14), 1.10 s (3H, H-18). **MS** (EI) m/z:. 420 (M^+, 4), 134 (7), 121 (13), 99 (100), 55 (15). $C_{27}H_{32}O_4$ calcd. C 77.11; H 7.67, found C 77.06; H 7.60 %.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-5-hydroxy-6'-methoxy-4'*H*-naphth-[3',2',1':10,9,11]-5α,14β-estr-9(11)-en-17-one (14): Compound **8** (1.23 g, 2.50 mmol) was dissolved in 50 mL ethanol and hydrogenated over Pd-C (120 mg, 10%). Afterwards the slurry was filtered through Celite® and the filtrate evaporated in vacuo. After purification 1.05 g (85%) **14** was obtained. **IR** (KBr, cm^{-1}): 3480, 2960, 1740. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ= 7.31 d (J=10 Hz, 1H, aryl), 6.72 dd (J=10, 2.5 Hz, 1H, aryl), 6.58 d (J=2.5 Hz, 1H, aryl), 4.47 s (1H, OH), 3.76 s (3H, OMe), 3.50-3.62 m (4H, ketal), 3.09 d (J=18 Hz, 1H, H-19), 3.03 m (1H, H-11), 2.69 d (J=18 Hz, 1H, H-19'), 1.00 s (3H, Me-ketal), 0.98 s (3H, Me-ketal), 0.67 s (3H, H-18). **MS** (EI) m/z: 494 (M^+, 5), 476 (M^+-H_2O, 12), 390 (10), 333 (10), 186 (16), 171 (15), 141 (100), 69 (45), 55 (35). **$C_{31}H_{42}O_5$** calcd. C 75.27; H 8.56, found C 75.35; H 8.63 %.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-6'methoxy-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propynyl]-4'*H*-naphth[3',2',1':10,9,11]-5α,14β-estr-9(11)-en-5,17α-diol (15): To a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (3 mL, 21.21 mmol) in 50 mL THF was added butyllithium (13.2 mL, 21.12 mmol, 1.6 M in hexane) at 0 C. After 0.5 h a solution of 1.05 g (2.12 mmol) **14** in 20 mL THF was added and the mixture was stirred for 3 h at 0 C. Afterwards it was poured into saturated ammonium chloride solution and further worked-up as usual. After purification 1.107 g (82%) **15** was obtained. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3480, 2950, 1620, 1500. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=7.30 d (J= 10 Hz, 1H, aryl), 6.70 dd (J=10, 2.5 Hz, 1H, aryl), 6.56 d (J= 2.5 Hz, 1H, aryl), 4.78 m (1H, THP), 4.40 s (1H, OH), 4.28 m (2H, CH_2OTHP), 3.80 m (1H, THP), 3.77 s (3H, OMe), 3.48-3.60 m (5H, ketal+THP), 3.09 d (J=18 Hz, 1H, H-19), 3.04 m (1H, H-11), 2.63 d (J=18 Hz, 1H, H-19'), 1.00 s (3H, Me-ketal), 0.97 s (3H, Me-ketal), 0.71 s (3H, H-18). **MS** (EI) m/z: 616 (M^+-H_2O, 15), 598 (M^+-$2H_2O$, 3), 532 (M^+-$C_5H_{10}O_2$, 5), 514 (10), 313 (10), 235 (15), 211 (17), 186 (60), 171 (30), 141 (90), 85 (100), 69 (63), 55(95). **$C_{39}H_{54}O_7$** calcd. C 73.79; H 8.57, found C 73.74, H 8.51 %.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-6'-methoxy-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl]-4'*H*-naphth[3',2',1':10,9,11]-5α,14β-estr-9(11)-en-5,17α-diol (16): As described above 1.107 g (1.74 mmol) **15** was hydrogenated over Pd-C (110 mg, 10%) in ethanol. After work-up and purification 557 mg (50%) **16** was obtained. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3480, 2950, 1620, 1500. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=7.30 d (J=10 Hz, 1H, aryl), 6.71 dd (J=10, 2.5 Hz, 1H, aryl), 6.55 d (J= 2.5 Hz, 1H, aryl), 4.59 m (1H, THP), 4.41 s (1H, OH), 3.83 m (1H, THP), 3.77 s (3H, OMe), 3.72 m (1H, THP), 3.40-3.60 m (6H, ketal+CH_2OTHP), 3.10 d (J=18 Hz, 1H, H-19), 3.07 m (1H, H-11), 2.63 d (J=18 Hz, 1H, H-19'), 0.99 s (3H, Me-ketal), 0.96 s (3H, Me-ketal), 0.50 s (3H, H-18). **MS** (EI) m/z: 620 (M^+-H_2O, 4), 553 (5), 535 (10), 518 (6), 186 (20), 171 (14), 141 (63), 85 (100), 69 (34), 55 (63). **$C_{39}H_{58}O_7$** calcd. C 73.32; H 9.15 %, found C 73.38; H 9.20 %.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)-oxy]propyl]-4'*H*-naphth[3',2',1':10,9,11]-5α,14β-estr-9(11)-en-5,6',17α-triol (17): A solution of 557 mg (0.87 mmol) **16** and sodium methanethiolate (243 mg, 3.48 mmol) in 10 mL *N,N*-dimethylformamide was heated under reflux for 2 h. Afterwards the reaction mixture was poured into ice-water and further worked-up as usual. After purification 474 mg (87%) **17** was isolated. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3500, 2950. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=7.22 d (J=10 Hz, 1H, aryl), 6.63 dd (J=10, 2.5 Hz, 1H, aryl), 6.51 d (J=2.5 Hz, 1H, aryl), 4.60 m (1H, THP), 4.41 s (1H, OH), 3.83 m (1H, THP), 3.70 m (1H, THP), 3.40-3.60 m (6H, ketal+CH_2OTHP), 3.05 d (J=18 Hz, 1H, H-19), 3.00 m (1H, H-11), 2.53 d (J=18 Hz, 1H, H-19'), 0.96 s (3H, Me-ketal), 0.94 s (3H, Me-ketal), 0.49 s (3H, H-18). **MS** (EI) m/z: 522 (M^+-$C_5H_{10}O_2$, 8), 504 (522-H_2O, 5), 418 (5), 171 (15), 157 (20), 141 (100), 97 (25), 85 (95), 69 (40), 55 (60). **$C_{38}H_{56}O_7$** calcd. C 73.04; H 9.03, found C 73.11; H 9.07 %.

3,3-[2,2-Dimethyl-1,3-propanediylbis(oxy)]-9,11α-dihydro-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)-oxy]-propyl]-6'-[[(trifluoromethyl)sulfonyl]oxy]-4'*H*-naphth[3',2',1':10,9,11]-5α,14β-estr-9(11)-en-5,17α-diol (18): To a solution of **17** (474 mg, 0.76 mmol) and 4-(dimethylamino)pyridine (464 mg, 3.8 mmol) in 10 mL methylene chloride at -78 C was slowly added triflic anhydride (0.17 mL, 1.00 mmol). After stirring for 1.5 h at that temperature the reaction mixture was added to 20 mL of saturated aqueous sodium bicarbonate solution. It was stirred for another 30 min at 25 C, extracted with methylene chloride and worked-up as usual. Purification gave 390 mg (71%) **18**. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3480, 2960. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=7.70 d (J=10 Hz, 1H, aryl), 7.21 dd (J=10, 2.5 Hz, 1H, aryl), 7.13 d (J=2.5 Hz, 1H, aryl), 4.81 m (1H, THP), 4.68 s (1H, OH), 4.04 m (1H, THP), 4.00 m (1H, THP), 3.60-3.80 m (6H, ketal+CH_2OTHP), 3.36 d (J=18 Hz, 1H, H-19), 3.30 m (1H, H-11), 2.88 d (J=18 Hz, 1H, H-19'), 1.03 s (3H, Me-ketal), 1.00 s (3H, Me-ketal), 0.48 s (3H, H-18). **MS** (EI) m/z: 738 (M^+-H_2O, 3), 654 (M^+-$C_5H_{10}O_2$, 23), 636 (M^+-H_2O-$C_5H_{10}O_2$, 12), 613 (19), 521 (15), 183 (10), 141 (82), 85 (100), 69 (28), 55 (19). **$C_{39}H_{55}F_3O_9S$** calcd. C 61.89; H 7.32, found C 61.95; H 7.35 %.

9,11α-Dihydro-17α-hydroxy-17β-(3-hydroxypropyl)-6'-(3-pyridinyl)-4'*H*-naphth-[3',2',1':10,9,11]-14β-estra-4,9(11)-dien-3-one (19): A solution of **18** (390 mg, 0.54 mmol), diethyl(3-pyridinyl)borane (112 mg, 0.76 mmol), tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol), lithium chloride (46 mg, 1.09 mmol) and 0.35 mL of a 2 N aqueous sodium carbonate solution in 5.5 mL toluene and 2 mL ethanol was heated under reflux for 1h. The usual work-up gave the crude cross-coupling product which was diluted in 15 mL acetone. After addition of 1.2 mL 4 N hydrochloric acid the mixture was stirred for 30 min at 40 C. Afterwards the reaction mixture was added to 20 mL of saturated aqueous sodium bicarbonate solution. The usual work-up and purification gave 160 mg (65%) **19**. **IR** (KBr, cm^{-1}): 3420, 2940, 1670. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ=8.88 m (1H py), 8.58 m (1H, py), 7.88 dbr (J=7.5 Hz, 1H, py), 7.58 d (J=10 Hz, 1H, aryl), 7.42 dd (J=10, 2.5 Hz, 1H, aryl), 7.31 m (1H, py), 7.32 d (J=2.5 Hz, 1H, aryl), 5.90 sbr (1H, H-4), 3.60-3.80 m (2H, CH_2OH), 3.38 m (1H, H-11), 3.32 d (J=18 Hz, 1H, H-19), 2.81 (J=18 Hz, 1H, H-19'), 0.60 s (3H, H-18). **MS** (EI) m/z: 497 (M^+, 5), 479 (M^+-H_2O, 13), 378 (16), 184 (45), 146 (16), 127 (15), 115 (16), 97 (100), 79 (20), 69 (18) 55 (57). $C_{33}H_{39}NO_3$ calcd. C 79.64; H 7.90; N 2.81, found C 79.67; H 7.97; N 2.84 %.

3,3-[1,2-Ethanediylbis(oxy)]-11β-(4-methoxyphenyl)-5,6α-epoxy-5α,14β-estr-15-en-17-one (20): Hydrogen peroxide (3.9 mL of a 30% aqueous solution, 37.9 mmol) was added slowly to a solution of **13** (3.86 g, 9.18 mmol) and 2,2,2-trifluoro-1-(3-nitrophenyl)ethanone (1.02 g, 4.65 mmol) in a mixture of 40 mL methylene chloride and 3 mL saturated aqueous sodium bicarbonate at 0 C. The mixture was stirred for 60 h at 25 C. Afterwards the solution was cooled to 0 C and saturated aqueous sodium thiosulfate (15 mL) was added. The layers were separated and the aqueous layer was extracted with methylene chloride. The combined organic layers were washed with 5 % aqueous sodium hydroxide and worked-up further as usual. After purification 2.12 g (53%) **20** and 1.31 g (34%) starting material **13** were isolated. **IR** (KBr, cm^{-1}): 3460, 2910, 1700, 1510. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ=7.72 dd (J=6, 2 Hz, 1H, H-15), 7.06 d (J=10 Hz, 2H, aryl), 7.78 d (J=10 Hz, 2H, aryl), 6.38 dd (J=6, 1.5 Hz, 1H, H-16), 3.80-3.97 m (4H, ketal), 3.78 s(3H, OMe), 2.94 dbr (J=4.5 Hz, 1H, H-6), 2.76 ddd (J=11.5, 6 Hz, 1H, H-11), 2.68 m (1H, H-14), 1.04 s (3H, H-18). **MS** (EI) m/z: 436 (M^+, 12), 408 (5), 149 (8), 134 (10), 121 (12), 99 (80), 85 (10), 55 (15), 28 (100). $C_{27}H_{32}O_5$ calcd. C 74.29; H 7.39, found C 74.25; H 7.33 %.

3,3-[1,2-Ethanediylbis(oxy)]-5-hydroxy-11β-(4-methoxyphenyl)-5α,14β-estran-17-one (21): Sodium borohydride (919 mg, 24.3 mmol) was added to a solution of 2.12 g (4.86 mmol) **20** in 50 mL ethanol at room temperature. It was heated under reflux for 1 h and then cooled to room temperature. The reaction mixture was poured into water. It was extracted with methylene chloride and further worked-up as usual. The crude reduction product (2.07 g, 100%) was used without purification: Chromium(VI) oxide (2.9 g, 29 mmol) was carefully added to a mixture of 10 mL pyridine and 75 mL methylene chloride at 0 C. After stirring for 20 min a solution of the crude reduction product in 15 mL methylene chloride was added. The reaction mixture was stirred for another 2 h at 0 C. The usual work-up and purification yielded 1.80 g (84%) **21**. **IR** (KBr, cm^{-1}): 3470, 2950, 1730, 1510. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ= 7.31 d (J=10 Hz, 2H, aryl), 6.78 d (J=10 Hz, 2H, aryl), 3.85-4.00 m (4H, ketal), 3.80 s (3H, OMe), 3.10 ddbr (J=7, 6 Hz, 1H, H-11), 0.76 s (3H, H-18). **MS** (EI) m/z: 440 (M^+, 24), 422 (M^+-H_2O, 7), 268 (25), 174 (15), 159 (13), 121 (60), 99 (100), 55 (17). $C_{27}H_{36}O_5$ calcd. C 73.61; H 8.24, found C 73.54, H 8.20 %.

3,3-[1,2-Ethanediylbis(oxy)]-11β-(4-methoxyphenyl)-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propynyl]-5α,14β-estra-5,17α-diol (22): As described above **21** (1.80 g, 4.09 mmol) was treated with tetrahydro-2-(2-propynyloxy)-2*H*-pyran (5.8 mL, 40.9 mmol) and butyllithium (25.5 mL, 40.8 mmol, 1.6 M in hexane) in THF. After purification 2.31 g (97%) **22** was isolated. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3500, 2950, 1510. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ=7.33 d (J=10 Hz, 2H, aryl), 6.79 d (J=10 Hz, 2H, aryl), 4.78 m (1H, THP), 4.28 m (2H, CH_2OTHP), 3.85-4.00 m (5H, ketal+THP), 3.81 s (3H, OMe), 3.50 m (1H, THP), 3.15 ddbr (J=7, 6 Hz, 1H, H-11), 0.83 s (3H, H-18). **MS** (EI) m/z: 562 (M^+-H_2O, 5), 544 (M^+-2 H_2O, 5), 478 (M^+-$C_5H_{10}O_2$, 3), 460 (M^+-H_2O-$C_5H_{10}O_2$, 15), 174 (13), 161 (15), 134 (45), 121 (78), 99 (100), 85 (46), 55 (27). $C_{35}H_{48}O_7$ calcd. C 72.39; H 8.33, found C 72.48; H 8.39 %.

3,3-[1,2-Ethanediylbis(oxy)]-11β-(4-methoxyphenyl)-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-propyl]-5α,14β-estra-5,17α-diol (23): As described above, 2.31 g (3.96 mmol) **22** was hydrogenated over Pd-C (230 mg, 10%) in ethanol. After purification 2.186 g (94%) **23** was isolated. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3470, 2950, 1600. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ=7.31 d (J=10 Hz, 2H, aryl), 6.78 d (J=10 Hz, 2H, aryl), 4.58 m (1H, THP), 3.70-3.95 m (6H, ketal+THP), 3.80 s (3H, OMe), 3.35-3.55 m (2H, CH_2OTHP), 3.16 ddbr (J=7, 5 Hz, 1H, H-11), 0.65 s (3H, H-18), 0.63 s (3H, H-18, THP-isomer). **MS** (EI) m/z: 566 (M^+-H_2O, 5), 548 (M^+-2 H_2O, 3), 482 (M^+-$C_5H_{10}O_2$, 10). 464 (M^+-H_2O-$C_5H_{10}O_2$, 8), 313 (25), 134 (25), 121 (60), 99 (72), 85 (100), 55 (24). $C_{35}H_{52}O_7$ C 71.89; H 8.96, found C 71.81; H 8.90 %.

3,3-[1,2-Ethanediylbis(oxy)-11β-(4-hydroxyphenyl)-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-propyl]-5α,14β-estra-5,17α-diol (24): The procedure used was the same as for compound **17**: From methyl ether **23** (2.186 g, 3.73 mmol), sodium methanethiolate (1.04 g, 14.9 mmol) in *N,N*-dimethylformamide, phenol **24** (1.664 g, 78%) was obtained. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3500, 2940. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ=7.25 d (J=10 Hz, 2H, aryl), 6.70 d (J=10 Hz, 2H, aryl), 4.59 m (1H, THP), 3.68-3.97 m (6H, ketal+THP), 3.35-3.55 m (2H, CH_2OTHP), 3.13 m (1H, H-11), 0.63 s (3H, H-18), 0.62 s (3H, H-18, THP-isomer). **MS** (EI) m/z: 552 (M^+-H_2O, 3), 534 (M^+-2 H_2O, 3), 468 (M^+-$C_5H_{10}O_2$, 38), 450 (M^+-H_2O-$C_5H_{10}O_2$, 50), 406 (15), 314 (32), 299 (77), 107 (25), 99 (53), 85 (100), 55 (26). $C_{34}H_{50}O_7$ calcd. C

71.55; H 8.83, found C 71.61; H 8.90 %.

3,3-[1,2-Ethanediylbis(oxy)]-17β-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]propyl]-11β-[4-[[(trifluoromethyl)sulfonyl]oxy]phenyl]-5α,14β-estra-5,17α-diol (25): Triflate **25** (1.495 g, 73%) was prepared from 1.664 g (2.91 mmol) **24**, 1.78 g (14.55 mmol) 4-(dimethylamino)pyridine and 0.65 mL (3.8 mmol) triflic anhydride in methylene chloride. (Mixture of THP-isomers): **IR** (KBr, cm^{-1}): 3470, 2950. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=7.49 d (J=10 Hz, 2H, aryl), 7.15 d (J=10 Hz, 2H, aryl), 4.58 m (1H, THP), 3.70-3.98 m (6H, ketal+THP), 3.33-3.55 m (2H, CH_2OTHP), 3.24 m (1H, H-11), 0.61 s (3H, H-18), 0.60 s (3H, H-18, THP-isomer). **MS** (EI) m/z: 600 (M^+-$C_5H_{10}O_2$, 25), 582 (M^+-H_2O-$C_5H_{10}O_2$, 18), 556 (20), 538 (26), 455 (26), 329 (15), 99 (40), 85 (100), 55 (18). $\mathbf{C_{35}H_{49}F_3O_9S}$ calcd. C 59.81; H 7.03, found C 59.90; H 7.05 %.

17α-Hydroxy-17β-(3-hydroxypropyl)-11β-[4-(3-pyridinyl)phenyl]-14β-estr-4-en-3-one (26): The procedure used was the same as for compound **19**: Aryl triflate **25** (750 mg, 1.06 mmol) was cross-coupled with diethyl(3-pyridinyl)borane (220 mg, 1.49 mmol) in the presence of tetrakis(triphenylphosphine)palladium(0) (137 mg, 0.12 mmol), lithium chloride (90 mg, 2.14 mmol) and 0.7 mL of a 2 N aqueous sodium carbonate solution in 10 mL toluene and 4 mL ethanol. The crude cross-coupling product was deprotected and dehydrated with 2.4 mL 4 N hydrochloric acid in 30 mL acetone. After purification 357 mg (69%) **26** was obtained. **IR** (KBr, cm^{-1}): 3410, 2940, 1660. **^{1}H NMR** (300 MHz, $CDCl_3$): δ= 8.87 sbr (1H, py), 8.58 dbr (J=4 Hz, 1H, py), 7.87 dt (J=7, 5 Hz, 1H, py), 7.53 m (4H, aryl), 7.37 dd (J=7.5, 4 Hz, 1H, py), 5.83 sbr (1H, H-4), 3.60-3.78 m (2H, CH_2OH), 3.45 ddbr (J=7.5, 5 Hz, 1H, H-11), 0.77 s (3H, H-18). **MS** (EI) m/z: 485 (M^+, 52), 467 (M^+-H_2O, 22), 384 (43), 370 (25), 316 (20), 208 (25), 182 (55), 169 (100). $\mathbf{C_{32}H_{39}NO_3}$ calcd. C 79.14; H 8.09; N 2.88, found C 79.20; H 8.19; N 2.90 %.

11β-(4-Acetylphenyl)-17α-hydroxy-17β-(3-hydroxypropyl)-14β-estr-4-en-3-one (27): A solution of **25** (745 mg, 1.06 mmol), tributyl(1-ethoxyethenyl)stannane (0.48 mL, 1.41 mmol), tetrakis-(triphenylphosphine)palladium(0) (62 mg, 0.05 mmol), lithium chloride (91 mg, 2.13 mmol) and pyridine (0.12 mL, 1.52 mmol) in 10 mL dioxane was heated under reflux for 2 h. The solution was filtered through Celite®. The usual work-up gave the crude cross-coupling product which was diluted with 30 mL acetone. After addition of hydrochloric acid (2.4 mL, 4 N) the mixture was stirred for 30 min at 40 C and worked-up as usual. After purification 305 mg (64%) **27** was obtained. **IR** (KBr, cm^{-1}): 3440, 2960, 1670. **^{1}H NMR** (300 MHz, $CDCl_3$): δ=7.90 d (J=10 Hz, 2H, aryl), 7.54 (J=10 Hz, 2H, aryl), 5.83 sbr (1H, H-4), 3.60-3.77 m (2H, CH_2OH), 3.45 ddbr (J=9, 5 Hz, 1H, H-11), 2.60 s (3H, acetyl), 0.72 s (3H, H-18). **MS** (EI) m/z: 450 (M^+, 25), 432 (M^+-H_2O, 30), 349 (32), 239 (25), 173 (27), 147 (30), 134 (35), 110 (60), 97 (100). $\mathbf{C_{29}H_{38}O_4}$ calcd. C 77.30; H 8.50, found C 77.32; H 8.54 %.

Acknowledgement - The technical assistance of Mrs. Hue-Quan Lao, Mr. Frank Halwaß and Mr. Jörg Lorenz is gratefully acknowledged.

REFERENCES AND NOTES

This paper is dedicated to Professor Helmut Vorbrüggen on the occasion of his 65th birthday.

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(*Received in Germany* 20 *February* 1995; *accepted* 20 *March* 1995)