Pergamon

Tetrahedron: *Asymmetry* 14 (2003) 1925–1934

TETRAHEDRON: *ASYMMETRY*

Synthesis of *N*-[2-(2-pyridyl)ethyl]-17a-aza-D-homosteroids and their biomimetic copper-mediated ligand hydroxylations with molecular oxygen

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Received 25 March 2003; accepted 29 April 2003

In memoriam Udo Gräfe

Abstract—Starting with the oximes of 3-*O*-methylestrone and 3-*O*-methyl-13α-estrone we have synthesized 17a-aza steroids as chiral *trans*- and *cis*-fused piperidines via a Beckmann rearrangement. These could then be transformed to the corresponding *N*-[2-(2-pyridyl)ethyl]-17a-aza-steroids. Copper(I) complexes of these bidentate ligands bind and activate molecular oxygen. While the *cis*-azasteroids are inert towards hydroxylation, in the *trans*-series hydroxylation occurs β to the *N*-atom on the ring (C-16) and in the side chain: The former hydroxylation is completely stereoselective with only the (16*R*)-epimer being produced while the latter oxidation occurs with low stereoselectivity. The influence of how the copper(I) complexes were prepared on the oxidation behavior is discussed.

1. Introduction

Copper-containing enzymes are able to hydroxylate selectively different substrates such as tyrosine and dopamine.[1] The mimicking of such activity with simpler copper complexes and molecular oxygen is an interesting goal of bioinorganic and organic chemistry.[2] In most cases, hydroxylation of the ligands has been investigated.[3] It could be shown that β-hydroxylation of benzylic positions is possible using tridentate *N*,*N*-bis[2-(2-pyridyl)ethyl]amino ligands[4] or bidentate *N*-[2-(2-pyridyl)ethyl]amino ligands.[5] With suitable ring compounds possessing a tridentate ligand (2-*N*-substituted indanes), a β-*cis*-hydroxylation of the benzylic position could be demonstrated.[4a] Additionally, β-*cis*-hydroxylation of unactivated CH_2 groups has been recently achieved in racemic form with tridentate ligands.[6]

To investigate such hydroxylations in different chiral environments we have attached similar bi- and tridentate ligands to a steroid core.[7]

We could show that with bidentate 17β-*N*-[2-(2-pyridylethyl) and (2-pyridylmethyl)amino steroid ligands, a β-hydroxylation of an unactivated CH_2 group, i.e. at the 16-position, is possible. The stereochemistry depends on the additional alkyl group at the central amino nitrogen; with *N*-ethyl compounds a *cis*-hydroxylation (16β-OH) takes place, whereas with *N*-methyl compounds both *cis*- and *trans*-hydroxylation (16β- and 16α-OH, ∼1:1) occurs. These results can be attributed to different conformations of the active copper-oxygen complexes.[7] In order to investigate conformational restricted steroid ligands, we decided to synthesize 17a-aza steroids possessing a central amino nitrogen within a ring and in the neighborhood of a tertiary stereogenic carbon atom. Because the configuration of this C-atom (C-13) determines the ring junction between the C and D rings and also strongly influences the steric relations[8] we were interested in synthesizing both 13β- and 13α-17a-aza steroids (type

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0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00362-8

A and B) for comparsion with the known 17β-amino steroids (type C, Fig. 1).

2. Results and discussion

2.1. Synthesis of the 13β,14α- and 13α,14α-ligands

For the synthesis of the 17a-aza-steroids used in this work we employed a Beckmann rearrangement of the known oximes **1**[9] and **7**.[10] It is known that the Beckmann rearrangement of **1** proceeds regio- and stereoselectively to yield compound **2**.[9b,c] We could obtain **2** in 90% yield by a convenient route using *p*-toluenesulfonyl chloride and pyridine[11] for the Beckmann rearrangement[9c] of **1** at room temperature. As a side product, the known olefin **3**[12] was also obtained in small amounts (Scheme 1). Using the same method, the 13α-oxime **7** also reacted regio- and stereoselectively to form the 13α-17a-aza compound **8**[10] in 53% yield. By NMR spectroscopy the known isomeric olefins **3**[12] and **10**[13] and the unknown **9** could be detected as a mixture

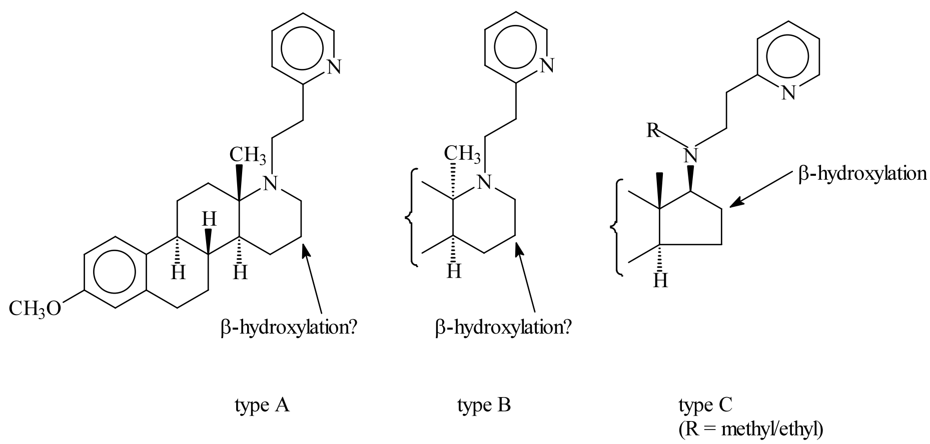
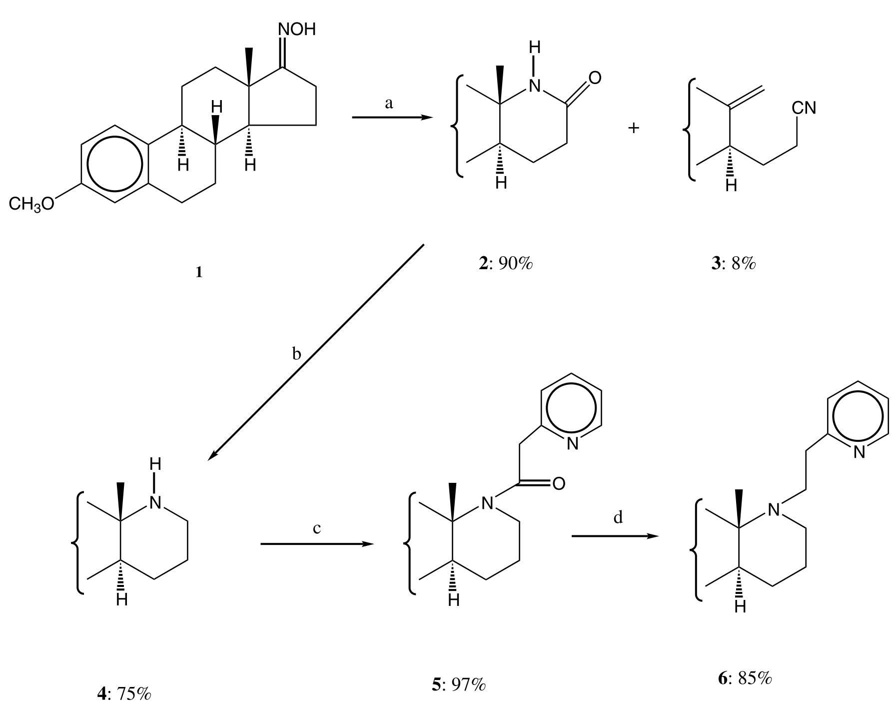
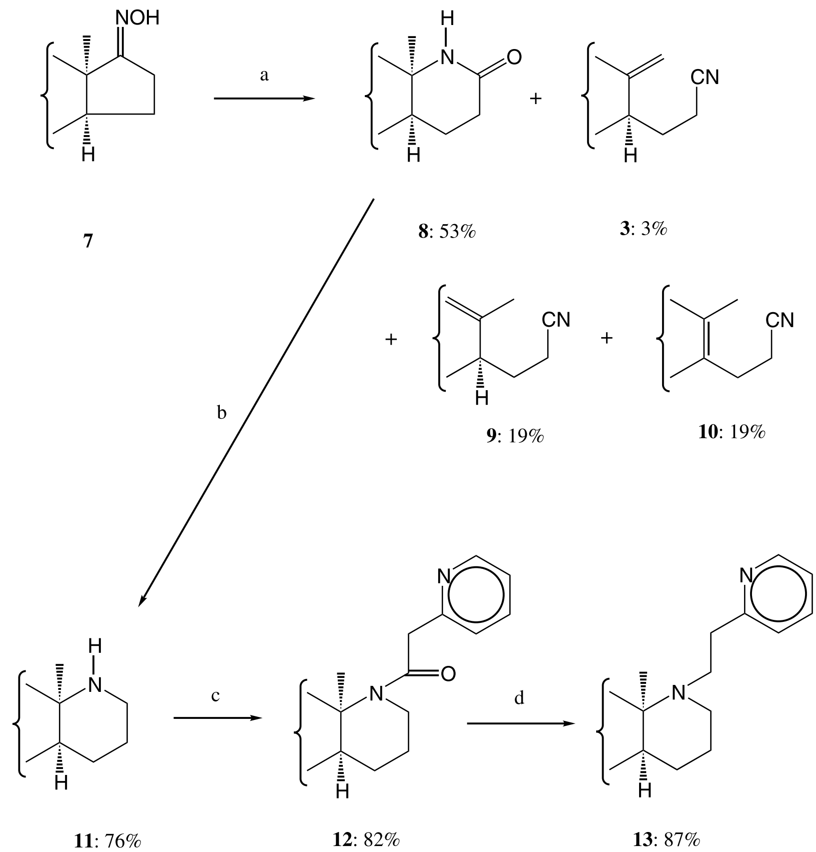


Figure 1. 17a-Aza and 17β-amino steroids as chiral ligands.



Scheme 1. Synthesis of the 13β,14α-ligand **6**. (a) *p*-toluenesulfonyl chloride/pyridine, rt; (b) (i) $Et_3O{\cdot}BF_4/CH_2Cl_2$, rt; (ii) KBH_4/CH_3OH, 0°C; (c) 2-pyridylacetic acid hydrochloride/TEA/$CHCl_3$/*N*,*N′*-carbonyldiimidazole, rt; (d) $BH_3{\cdot}THF$/THF/rt→60°C.



Scheme 2. Synthesis of the 13α,14α-ligand **13**. (a) *p*-toluenesulfonyl chloride/pyridine, rt; (b) $LiAlH_4$/THF, reflux; (c) 2-pyridylacetic acid hydrochloride/TEA/$CHCl_3$/*N*,*N*′-carbonyldiimidazole, rt; (d) BH_3·THF/THF/rt→60°C.

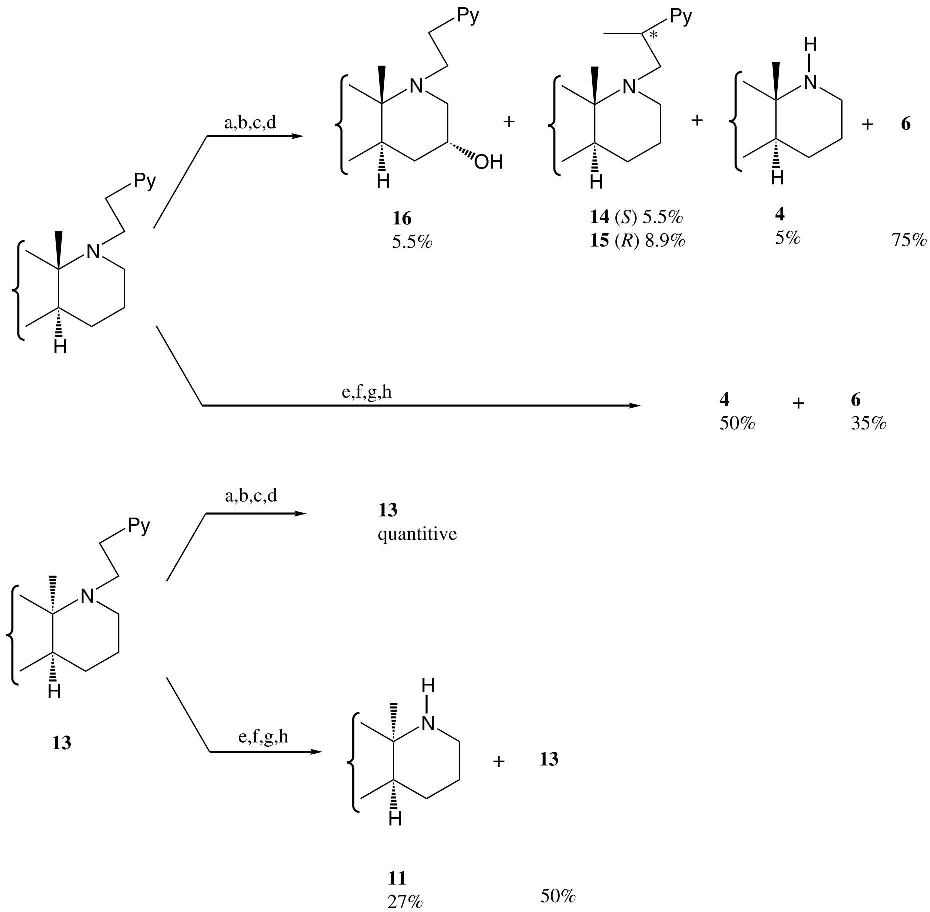
in a yield of 3, 19 and 19% (Scheme 2). The direct reduction of the lactam **2** to the cyclic secondary amine **4** was not successful or yielded only low yields ($LiAlH_4$, BH_3 and other reducing agents).[9c] Compound **4** could be obtained by a two-step procedure using triethyloxonium tetrafluoroborate and KBH_4 as reagents.[14] The iminoether was not isolated, but instead reduced directly. The desired amine as well as some starting material could be obtained in 75% yield after chromatography (Scheme 1). In contrast to this, the direct reduction of the 13α-lactam **8** to the amine **11** in 76% yield was successful with $LiAlH_4$ (Scheme 2).

The last two steps for the introduction of the 2-pyridylethyl group are similar to our previously described procedure.[7a] Acylation of **4** and **11** with 2-pyridylacetic acid and *N*,*N*′-carbonyldiimidazole to the amides **5** and **12** and subsequent reduction with borane in tetrahydrofuran furnished the desired *N*-[2-(2-pyridyl)ethyl]-amino compounds **6** and **13** (Schemes 1 and 2) in good yields. In this manner the bidentate ligands **6** and **13** are available in five to six steps starting with 3-methoxyestra-1,3,5(10)-triene-17-one, a known pharmaceutical.

2.2. Copper complexation and reaction with molecular oxygen

In principle, two methods can be used for copper-mediated ligand hydroxylations. From a theoretical point of view, only 50% of the ligand can be hydroxylated when one starts with copper(I) salts, ligands and molecular oxygen because of formation of a binuclear copper(II) complex of the hydroxylated and nonhydroxylated ligand. A quantitative ligand hydroxylation procedure has been described by Fukuzumi et al.[3b,4b] Starting with a copper(II) complex, reduction with an excess of benzoin and triethylamine to the corresponding copper(I) complex and treatment with molecular oxygen gave quantitative hydroxylation of a benzylic position. It should be mentioned that different active copper-oxygen species, depending on the method, have been discussed.[6]

We have investigated the copper-mediated hydroxylation of the bidentate steroid ligands **6** and **13** starting from either copper(I) or copper(II) complexation. A solution of **6** with copper(I) triflate in THF resulted in brown complex solutions. On reaction with pure oxygen, the color changed to a blackish-green. Decomplexation with aqueous ammonia after three days resulted in a mixture of several products. Via chromatography 75% of unchanged **6** could be isolated. Only 5% of **4**, the α-hydroxylation product followed by hydrolytic cleavage of the side chain, was obtained (Scheme 3). Two other products **14** and **15** (Scheme 3), obtained in yields of 5.5 and 8.9%, are diastereomeric side-chain alcohols, formed by β-hydroxylation of the CH_2 group in neighborhood



Scheme 3. Products of hydroxylation procedures. (a) Cu(I)triflate, THF; (b) O_2; (c) NH_4OH; (d) chromatography; (e) Cu(II)triflate, CH_2Cl_2; (f) benzoin, triethylamine; (g) O_2; (h) chromatography.

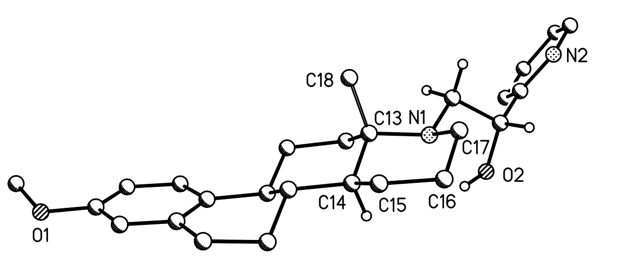


Figure 2. Molecular structure of 3-methoxy-*N*-[2-(2-pyridyl)-2*R*-hydroxyethyl]-17a-aza-D-homoestra-1.3.5(10)-triene **15**.

of the pyridine ring (Scheme 3). The structure of these compounds could be elucidated by a detailed analysis of the ^{1}H and ^{13}C NMR spectra. The configuration of **15** (*R*) was determined from an X-ray structural analysis (Fig. 2).

A further compound **16** (5.5%), proved to be an isomer of **14** and **15** (HRMS). NMR signals at $\delta=3.85$ (^{1}H NMR) and $\delta=65.1$ ppm (^{13}C NMR) confirmed the existence of a CH-OH group. The unchanged side chain indicated a ring hydroxylation product. Selective TOCSY experiments to the signal of $\delta=3.85$ ppm showed five proton signals. Analysis of the coupling constants established a CH_2-C(H)(OH)-CH_2CH system with a central equatorial proton consistent with a 16α-hydroxy group. Compound **16** is the desired product of a β-hydroxylation reaction (see Fig. 1). Despite the low yields obtained, the formation of **14**, **15** and **16** from **6** is interesting in terms of ligand structure and hydroxylation procedures. Stereochemical models show that the formation of both diastereomeric alcohols **14** and **15** can be explained with different side chain conformations and different complex conformations, similar to the 16α- and 16β-hydroxylation of 17β-(*N*-methyl-*N*-2-pyridylalkyl)amino steroids.[7b] The formation of **16** is one of the rare examples of a β-hydroxylation of an unactivated CH_2 group. It is the first known example starting with a copper(I) complex.

Using $Cu(CH_3CN)_4PF_6$ in the place of copper(I) triflate or CH_2Cl_2 instead of THF did not improve the results. Only the unchanged ligand **6** could be isolated. Small amounts of hydroxylation products could be detected by TLC.

Starting with **6** and copper(II) triflate, a green complex solution was obtained in CH_2Cl_2. Reduction with benzoin and triethylamine gave a yellow copper(I) complex solution. Oxidation was performed with pure oxygen for three days. After decomplexation of the dark green complex and chromatography 35% of the unchanged

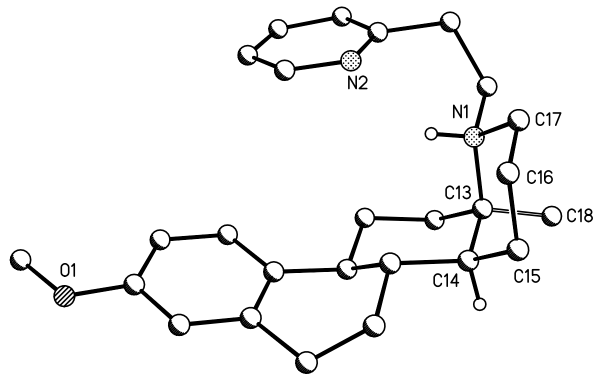


Figure 3. Molecular structure of the HPF_6 salt of 3-methoxy-*N*-[2-(2-pyridyl)ethyl]-17a-aza-13α-D-homoestra-1.3.5(10)-triene **13** (anion omitted).

ligand **6**, 50% of the secondary amine **4** (α-hydroxylation) and small amounts of other oxidation products (MS), could be isolated as mixtures (NMR). These mixtures could be the result of an α-hydroxylation at the ring C atom 17 giving an aminal structure in equilibrium with a reactive amino aldehyde, together with some β-hydroxylations. When THF instead of CH_2Cl_2 was employed similar results were obtained. Comparison of the two hydroxylation procedures confirms the different oxidation behavior of the active copper species. Starting with copper(II), a hydroxylation, especially α-hydroxylation, occurs to a larger amount (nearly 50%). Using copper(I), only 25% of the hydroxylation products could be detected; most of them are products of β-hydroxylation, whereas only 5% of α-hydroxylation product **4** has been formed.

Ligand **13**, which possesses a *cis*-fused piperidine system, could also be complexed with copper(I) and copper(II) in THF, detectable by coloration of the solution. Using the same procedures as reported for ligand **6**, only the unchanged ligand **13** could be isolated in case of copper(I). With copper(II), 50% of the unchanged ligand and 27% of the secondary amine **11** (α-hydroxylation) could be isolated. Only very small amounts of other products were detected. In summary, the 13α,14α-ligand **13** seems to be more difficult to hydroxylate in comparison with the 13β,14α-ligand **6**. An X-ray analysis of the HPF_6 salt of **13** (Fig. 3) shows the different steric relations in comparison to 13β,14α-compounds (Fig. 2), which should be responsible for the different reactivity.

3. Conclusions

A comparison of copper-mediated hydroxylation reactions with molecular oxygen for steroid ligands containing a 17β-*N*-alkyl-*N*-(2-pyridylalkyl)amino group (Fig. 1, type C) as well as ligands containing a central ring nitrogen (**6** and **13**, Fig. 1, types A and B) shows that the structure of the ligand as well as its configuration has a great influence on the reaction behavior. In addition, the preparation of the active copper species is also important and should not be underestimated. For ligands of type C, starting with copper(II), β-hydroxylation in 16-position can be observed (16–33%) together with some α-hydroxylation (formation of 17-ketone and 17β-*sec*-amine). Using the same procedure for the ligands **6** and **13** (types A and B) only α-hydroxylation to differing extents has been found (formation of the secondary amines **4** and **11**). Starting with copper(I), **6** was β-hydroxylated in the side chain {14.4% alcohols (*R*)-**14** and (*S*)-**15**} and at an unactivated CH_2 group of the ring {5.5% (16*R*)-**16**}. Compound **13** remains unchanged under these conditions. The reasons for this difference can probably be attributed to the formation of different active copper–oxygen species with different conformations depending on the ligand structure. Investigations with further ligands currently being designed using both hydroxylation procedures should give more insights into these interesting reactions, especially for the hydroxylation of nonactivated CH_2 groups.

4. Experimental

4.1. General

Melting points were measured on Boëtius micromelting point apparatus (corrected values). Optical rotations were measured in chloroform with a photoelectronic polarimeter Polamat A (Carl Zeiss Jena) at 546 and 578 nm and extrapolated to 589 nm ($c = 1$ g 100^{-1} ml^{-1}). IR spectra were recorded on an Impact 400 spectrometer (NICOLET) by ATR.

^1H and ^{13}C NMR spectra were recorded on Bruker spectrometers DRX 400 instrument (^1H NMR 400 MHz using TMS as internal standard, ^{13}C NMR 100 MHz using $CDCl_3$ triplet as reference, δ 77.0 ppm) in $CDCl_3$ (if not otherwise given). Signals were assigned by DEPT, COSY-DQF, TOCSY and NOESY. Mass spectra were recorded on an AMD 402 Intectra instrument with electron impact (EI), direct electron impact (DEI) und electro spray (ESI) ionization with 70 eV. Elemental analyses were determined on CHNO-Rapid (HERAEUS) or CHNS-932 (LECO) instruments. All reactions were monitored by TLC aluminum sheets, silica gel 60 F_{254} (Merck), 0.2 mm, detection by UV (254 nm) and spraying with a solution of $P_2O_5 \cdot 24MoO_3 \cdot H_2O$ (2.5 g/50 ml 42% H_3PO_4) and heating at 170°C. Solvents were purified and distilled according to conventional methods.

4.2. Crystal structure determination

The intensity data for the compounds were collected on a Nonius Kappa CCD diffractometer, using graphite-monochromated Mo Kα radiation. Data were corrected for Lorentz and polarization effects, and not for absorption effects.[15,16]

The structures were solved by direct methods (SHELXS[17]) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97[18]). For the amine-group N1 of **FO1736** and for the hydroxy-group O2 of **FO1753** the hydrogen atoms were located by difference Fourier synthesis and refined isotropically. All other only hydrogen atoms were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically.[18] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

*Crystal data for **FO1736***:[19] $[C_{26}H_{35}N_2O]^+[PF_6]^-$, M_r = 536.52 g mol^{-1}, colourless prism, size 0.06×0.05×0.03 mm, monoclinic, space group $P2_1$, a = 8.5193(16), b = 12.189(2), c = 12.382(2) Å, β = 103.943(3)°, V = 1247.9(4) Å^3, T = −90°C, Z = 2, ρ_{calcd} = 1.425 g cm^{-3}, μ (Mo Kα) = 1.78 cm^{-1}, F(000) = 562, 5920 reflections in h(−9/9), k(−14/14), l(−14/14), measured in the range 2.38 ≤ Θ ≤ 24.46°, completeness Θ_{max} = 98.3%, 3896 independent reflections, R_{int} = 0.040, 3459 reflections with F_o>4σ(F_o), 328 parameters, 1 restraint, R^1_{obs} = 0.061, wR^2_{obs} = 0.160, R^1_{all} = 0.070, wR^2_{all} = 0.169, GOOF = 1.049, Flack-parameter 0.20(18), largest difference peak and hole: 0.351/−0.307 e Å^{-3}.

*Crystal data for **FO1753***:[19] $C_{26}H_{34}N_2O_2$, M_r = 406.55 g mol^{-1}, colourless prism, size 0.06×0.05×0.04 mm, orthorhombic, space group $P2_12_12_1$, a = 6.5036(1), b = 9.9090(2), c = 33.9789(9) Å, V = 2189.74(8) Å^3, T = −90°C, Z = 4, ρ_{calcd} = 1.233 g cm^{-3}, μ (Mo Kα) = 0.78 cm^{-1}, F(000) = 880, 4812 reflections in h(−8/8), k(−12/12), l(−43/44), measured in the range 2.40° ≤ Θ ≤ 27.47°, completeness Θ_{max} = 98.6%, 4812 independent reflections, 3329 reflections with F_o>4σ(F_o), 275 parameters, 0 restraints, R^1_{obs} = 0.061, wR^2_{obs} = 0.125, R^1_{all} = 0.104, wR^2_{all} = 0.142, GOOF = 1.037, Flack-parameter 0(2), largest difference peak and hole: 0.226/−0.274 e Å^{-3}.

4.3. 3-Methoxy-17a-aza-D-homoestra-1,3,5(10)-trien-17-one 2 and 3-methoxy-13,17-secoestra-1,3,5(10)13(18)-tetraenoic nitrile 3

A solution of *p*-toluenesulfonyl chloride (2.0 g, 10.5 mmol) in abs. pyridine (16 ml) was added dropwise to a solution of the oxime **1** (2.0 g, 6.7 mmol) in abs. pyridine (34 ml) at room temperature. After 12 h the reaction mixture was poured into water and ice mixture (120 ml). After 3 h hydrochloric acid was added for neutralization. The mixture was extracted with CH_2Cl_2, the organic phase was washed with water, dried with Na_2SO_4 and evaporated. Chromatography of the crude product on silica gel with dichloromethane gave the less polar compound **3** (160 mg, 8.0%), then with MeOH/CH_2Cl_2 (5:95) **2** (1.8 g, 90.1%) was obtained.

2: Mp = 223–225°C (MeOH/benzene) [lit.[9c] 222–224°C]; $[\alpha]_D^{20}$ = +102 [lit.[9c] +95, c = 0.776 in dioxane].

3: oil [like lit.[12]]; $[\alpha]_D^{20}$ = +83; MS (EI) m/z (%): 281 (100) $[M]^+$.

4.4. 3-Methoxy-17a-aza-D-homoestra-1,3,5(10)-triene 4

A solution of triethyloxonium tetrafluoroborate (380 mg, 2.0 mmol) and amide **2** (299 mg, 1.0 mmol) in dichloromethane (10 ml) was stirred overnight at rt under an argon atmosphere. CH_2Cl_2 was removed at reduced pressure and the residue was dissolved in methanol (20 ml). Potassium borohydride (300 mg) was added in portions to the stirred solution at 0°C. Stirring was continued for 3 h at rt. The solution was poured onto ice/water (40 ml) and extracted three times with dichloromethane. The combined extracts were washed with NaCl solution. The organic solvent was dried over Na_2SO_4 and evaporated to give a solid residue (325 mg). Chromatography on silica gel with MeOH/CH_2Cl_2 (1:9) and conc. NH_4OH/MeOH (1:99) yielded amide **2** (47 mg, 16%) and **4** (214 mg, 75%). Mp 135–137°C (Et_2O) [lit.[9c] 135–136°C]; $[\alpha]_D^{20}$ = +73; ^{1}H NMR: δ = 1.07 (s, 3H, 18-H_3), 3.77 (s, 3H, OMe), 6.62 (d, J = 2.1 Hz, 1H, 4-H), 6.71 (dd, J = 8.6 and 2.1 Hz, 1H, 2-H), 7.20 (d, J = 8.6 Hz, 1H, 1-H) ppm; ^{13}C NMR: δ = 16.9 (C-18), 52.8 (C-13), 55.2 (OMe), 111.5 (C-2), 113.5 (C-4), 126.2 (C-1), 132.8 (C-10), 137.9 (C-5), 157.5 (C-3) ppm; IR (ATR): 3243, 2927, 2866, 1728, 1611 cm^{-1}; MS (ESI) m/z (%): 286 (100) $[M+H]^+$; HRMS m/z: found 286.21634 $[M+H]^+$, calcd. 286.21709 ($C_{19}H_{28}NO$).

4.5. 3-Methoxy-*N*-[(2-pyridyl)acetyl]-17a-aza-D-homoestra-1,3,5(10)-triene 5

A solution of *sec*-amine **4** (100 mg, 0.4 mmol) in abs. chloroform (1.0 ml) was added to a stirred mixture of 2-pyridylacetic acid hydrochloride (243 mg, 1.4 mmol), abs. chloroform (2 ml), triethylamine (141 mg, 0.3 ml, 1.4 mmol) and *N*,*N'*-carbonyldiimidazole (227 mg, 1.4 mmol). After stirring at rt overnight, water was added and the mixture was stirred for 2 h. The organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated. Column chromatography on silica gel with ethyl acetate yielded **5** (138 mg, 97%). Mp 123–125°C (CH_2Cl_2/*n*-heptane); $[\alpha]_D^{20}$ = +89; ^{1}H NMR: δ = 1.43 (s, 3H, 18-H_3), 2.81 (m, 2H, 6-H_2), 3.75 (s, 3H, OMe), 3.88–3.97 (AB part, 2H, CH_2-Py), 6.58 (d, J = 2.6 Hz, 1H, 4-H), 6.68 (dd, J = 8.7, 2.6 Hz, 1H, 2-H); 7.15 (m, 2H, 1-H and 5-H_{Py}), 7.32 (d, J = 7.8 Hz, 1H, 3-H_{Py}), 7.63 (td, J = 7.8, 1.8 Hz, 1H, 4-H_{Py}), 8.50 (d, J = 4.8 Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: δ = 16.7 (C-18), 55.3 (OMe), 60.4 (C-13), 111.6 (C-2), 113.4 (C-4), 121.7 and 123.4 (C_{Py}-5 and -3), 126.4 (C-1), 132.4 (C-10), 136.6 (C_{Py}-4), 137.5 (C-5), 149.2 (C_{Py}-6), 156.5 (C_{Py}-2), 157.5 (C-3), 169.7 (C=O) ppm; IR (ATR): 1746 (C=O) cm^{-1}; MS (ESI) m/z (%): 427 (100%) $[M+Na]^+$, 405 (66%) $[M+H]^+$; HRMS m/z: found 427.23521 $[M+Na]^+$, calcd. 427.23615 ($C_{26}H_{32}NaN_2O_2$).

4.6. 3-Methoxy-*N*-[2-(2-pyridyl)ethyl]-17a-aza-D-homoestra-1,3,5(10)-triene 6

To a stirred solution of BH_3·THF (1 M in THF, 5.6 ml) a solution of steroid amide **5** (162 mg, 0.4 mmol) in abs. tetrahydrofuran (20 ml) was slowly added. After stirring at rt for 2 h, the solution was heated to 60°C for 4 h. 6 N HCl (6 ml) was added to the mixture and heated to 60°C for 1 h. After cooling to rt, aq. KOH was added and the alkaline mixture was extracted three times with ether. The combined organic phases were washed with water, dried (Na_2SO_4) and evaporated. The oily residue was chromatographed on silica gel with $MeOH/CH_2Cl_2$ (1:9) and conc. NH_4OH/MeOH (1:99) affording amine **6** (132 mg, 85%). Mp 65–67°C (CH_2Cl_2/petroleum ether); $[\alpha]_D^{20}=+148$; ^{1}H NMR: $\delta=$ 0.87 (s, 3H, 18-H_3), 2.20–2.40 (m, 3H, N-CH and 2H), 2.47 (td, $J=12.5$ and 3.1 Hz, 1H, 17-H), 2.74–3.05 (m, 5H, 6-H_2 and 17-H′ and CH_2-Py), 3.24 (m, 1H, N-CH′), 3.75 (s, 3H, OMe), 6.59 (d, $J=2.8$ Hz, 1H, 4-H), 6.68 (dd, $J=8.7$ and 2.8 Hz, 1H, 2-H), 7.09 (m, 1H, 5-H_{Py}), 7.17 (m, 2H, 1-H and 3-H_{Py}), 7.57 (td, $J=7.6$ and 1.8 Hz, 1H, 4-H_{Py}), 8.51 (d, $J=4.9$ Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: $\delta=9.9$ (C-18), 22.9 (C-15), 26.5 (C-16), 26.6 (C-7), 27.6 (C-11), 30.5 (C-6), 38.5 (C-12), 39.0 ($\underline{C}H_2$-Py), 40.2 (C-8), 43.3 (C-9), 47.6 (C-17), 50.1 (N-$\underline{C}H_2$), 50.3 (C-14), 55.6 (OMe), 58.2 (C-13), 112.0 (C-2), 113.8 (C-4), 121.5 (C_{Py}-5), 124.0 (C_{Py}-3), 126.7 (C-1), 133.4 (C-10), 136.5 (C_{Py}-4), 138.2 (C-5), 149.5 (C_{Py}-6), 157.9 (C-3), 161.4 (C_{Py}-2) ppm; IR (ATR): 3015, 2952, 1610 cm^{-1}; MS (ESI) m/z (%): 391 (100%) $[M+H]^+$; HRMS m/z: found 391.27613 $[M+H]^+$, calcd. 391.27494 ($C_{26}H_{35}N_2O$).

4.7. 13α-Estrone 3-methylether oxime 7[10]

A solution of 13α-estrone-3-methylether (400 mg, 1.4 mmol), $NH_2OH\cdot HCl$ (336 mg, 4.7 mmol), sodium acetate (606 mg, 4.7 mmol) in ethanol (12 ml) was refluxed for 48 h. The reaction mixture was cooled and treated with 30 ml water. The precipitate was filtered, washed with water and dried yielding 408 mg (97%) oxime **7**. It was purified on silica gel column (*t*-butyl methyl ether) to give oxime **7** (380 mg, 91%). Mp 139–141°C (CH_2Cl_2/petroleum ether) [lit.[10] 138–141°C]; $[\alpha]_D^{20}=+1.6$ [lit.[10] +5 (dioxane, $c=1$)]; ^{1}H NMR (500 MHz): $\delta=$ 1.11 (s, 3H, 18-H_3), 2.79 (m, 2H, 6-H_2), 3.74 (s, 3H, OMe), 6.57 (d, $J=2.6$ Hz, 1H, 4-H), 6.66 (dd, $J=8.6$ and 2.6 Hz, 1H, 2-H), 7.16 (d, $J=8.6$ Hz, 1H, 1-H), 9.2 (br s, 1H, C=N-O$\underline{H}$) ppm; ^{13}C NMR: $\delta=28.5$ (C-18), 45.9 (C-13), 51.7 (C-14), 55.2 (3OMe), 111.6 (C-2), 113.5 (C-4), 126.8 (C-1), 132.4 (C-10), 138.1 (C-5), 157.5 (C-3), 168.3 (17-C) ppm; IR (ATR): 3272 (O-H), 2955, 1609, 1579 cm^{-1}; MS (DEI) m/z (%): 300 (22) $[M+H]^+$, 299 (100) M^+.

4.8. 3-Methoxy-17a-aza-13α-D-homoestra-1,3,5(10)-trien-17-one 8, 3-methoxy-13,17-secoestra-1,3,5-(10)13(18)-tetraenoic nitrile 3, 3-methoxy-13,17-secoestra-1,3,5(10)12(13)-tetraenoic nitrile 9, and 3-methoxy-13,17-secoestra-1,3,5(10)13(14)-tetraenoic nitrile 10

A solution of *p*-toluenesulfonyl chloride (898 mg, 4.7 mmol) in abs. pyridine (5 ml) was added dropwise to the solution of oxime **7** (898 mg, 3.0 mmol) in abs. pyridine (10 ml) and stirred overnight at rt. The reaction mixture was poured onto ice (50 ml)/H_2SO_4 (8 ml). The precipitate was filtered and dried, yielding a solid residue (950 mg). The chromatography of the mixture on silica gel with CH_2Cl_2 and $MeOH/CH_2Cl_2$ (1:9) gave in one fraction a mixture of the secosteroids **3**,[12] **9**, **10**[13] (348 mg; 3, 19, and 19%, respectively) and as a more polar product **8** (479 mg, 53%).

8: Mp 235–237°C (CH_2Cl_2/petroleum ether) [lit.[10] 228–231°C]; $[\alpha]_D=-17.1$ [lit.[10] −2 (dioxane, $c=1$)]; ^{1}H NMR: $\delta=1.33$ (s, 3H, 18-H_3), 2.84 (m, 2H, 6H_2), 3.76 (s, 3H, OMe), 6.10 (br s, 1H, CON$\underline{H}$), 6.61 (d, $J=2.6$ Hz, 1H, 4-H), 6.70 (dd, $J=8.6$ and 2.6 Hz, 1H, 2-H), 7.16 (d, $J=8.6$ Hz, 1H, 1-H) ppm; ^{13}C NMR: $\delta=31.9$ (C-18), 54.5 (C-13), 55.2 (OMe), 111.7 (C-2), 113.4 (C-4), 126.4 (C-1), 131.8 (C-10), 137.7 (C-5), 157.6 (C-3), 172.5 (C-17) ppm; MS (DEI) m/z (%): 299 (100) $[M]^+$, 284 (85), 173 (18), 162 (25), 147 (13).

3+**9**+**10** mixture: pale yellow oil; ^{1}H NMR: $\delta=1.67$ (s, 3H, 18-CH_3, **9**), 1.73 (s, 3H, 18-CH_3, **10**), 4.57 (s, 0.14H, 18-H, **3**), 4.87 (s, 0.14H, 18-H′, **3**), 5.72 (d, $J=$Hz, 1H, **9**) ppm; MS (DEI), m/z (%): 282 (24) $[M+H]^+$, 281 (96) $[M]^+$.

4.9. 3-Methoxy-17a-aza-13α-D-homoestra-1,3,5(10)-triene 11

To a stirred solution of lactam **8** (299 mg, 1.0 mmol) in abs. THF (30 ml) was added LAH/THF (1 M, 6.0 ml, 6.0 mmol) dropwise under argon. The mixture was heated for 24 h and then cooled with ice. Some drops of aq. tetrahydrofuran and water (6 ml) was added under stirring. The precipitate was filtered through silica pad and the filtrate was concentrated in vacuo yielding amine **11** (265 mg, 93%). The chromatographic separation on silica gel ($MeOH/CH_2Cl_2$, 1:9 and conc. NH_4OH/MeOH 1:99) yielded **11** (211 mg, 76%). Mp 247–250 ($CHCl_3$); $[\alpha]_D=+65$; ^{1}H NMR: $\delta=1.27$ (s, 3H, 18-H_3), 2.81 (m, 2H, 6-H_2), 2.91 (dd, $J=12.9$ and 5.1 Hz, 1H, 17-H), 3.01 (td, $J=12.9$ and 3.7 Hz, 1H, 17-H′), 3.75 (s, 3H, OMe), 6.59 (d, $J=2.7$ Hz, 1H, 4-H), 6.68 (dd, $J=8.6$ and 2.7 Hz, 1H, 2-H), 7.18 (d, $J=8.6$ Hz, 1H, 1-H) ppm; ^{13}C NMR: $\delta=25.8$ (C-18), 51.9 (C-13), 55.2 (3-OMe), 111.6 (C-2), 113.3 (C-4), 126.5 (C-1), 132.7 (C-10), 138.1 (C-5), 157.4 (C-3) ppm; IR (ATR): 2922, 1610, 1499 cm^{-1}; MS (ESI) m/z (%): 286 (100) $[M+H]^+$; HRMS m/z: found 286.21693 $[M+H]^+$, calcd. 286.21709 ($C_{19}H_{28}NO$).

4.10. 3-Methoxy-*N*-[(2-pyridyl)acetyl]-17a-aza-13α-D-homoestra-1,3,5(10)-triene 12

A solution of *sec*-amine **11** (571 mg, 2.0 mmol) in abs. chloroform (6 ml) was added to a stirred mixture of 2-pyridylacetic acid hydrochloride (1.39 g, 8.0 mmol), abs. chloroform (10 ml), triethylamine (1.8 ml, 2.0 mmol) and *N*,*N*′-carbonyldiimidazole (1.3 g, 2.0 mmol). After stirring overnight at rt, water was added and the mixture was stirred for another 2 h. The organic phase was separated, washed with water, dried (Na_2SO_4) and evaporated. Column chromatography on silica gel with EtOAc yielded **12** (664 mg, 82%). Mp 116–118°C (CH_2Cl_2/petroleum ether); $[\alpha]_D^{20}=+74$; ^{1}H NMR: $\delta=$ 1.39 (s, 3H, 18-H_3), 2.80 (m, 2H, 6-H_2), 3.77 (s, 3H, OMe), 3.81–3.90 (m, 3H, 3.86: C$\underline{H}_2$-Py and 1H), 6.63 (d, $J=2.8$ Hz, 1H, 4-H), 6.72 (dd, $J=8.6$ and 2.8 Hz, 1H, 2-H); 7.07 (m, 1H, 5-H_{Py}), 7.21 (d, $J=8.6$ Hz, 1H, 1-H), 7.23 (d, $J=7.6$ Hz, 1H, 3-H_{Py}), 7.45 (td, $J=7.6$ and 1.8 Hz, 1H, 4-H_{Py}), 8.43 (d, $J=4.9$ Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: $\delta=23.6$ (C-18), 47.6 (C-14), 55.2 (OMe), 59.5 (C-13), 111.4 (C-2), 113.3 (C-4), 121.6 and

123.8 (C_{Py}-5 and -3), 126.4 (C-1), 133.4 (C-10), 136.7 (C_{Py}-4), 137.7 (C-5), 148.7 (C_{Py}-6), 156.2 (C_{Py}-2), 157.5 (C-3), 172.0 (C=O) ppm; IR (ATR): 3059, 2937, 1727, 1658 (C=O), 1503 cm^{-1}; MS (ESI) *m*/*z* (%): 427 (100%) $[M+Na]^+$, 405 (56%) $[M+H]^+$; HRMS *m*/*z*: found 427.23563 $[M+Na]^+$, calcd. 427.23615 ($C_{26}H_{32}NaN_2O_2$); $C_{26}H_{32}N_2O_2$ (404.56) calcd. C 77.19, H 7.97, N 6.92%; found C 76.81, H 8.27, N 6.34%.

4.11. 3-Methoxy-*N*-[2-(2-pyridyl)ethyl]-17a-aza-13α-D-homoestra-1,3,5(10)-triene 13

To a stirred solution of BH_3·THF (1 M in THF, 5.6 ml) a solution of steroid amide **12** (162 mg, 0.4 mmol) in abs. tetrahydrofuran (20 ml) was slowly added. After stirring at rt for 2 h, the solution was heated to 60°C for 4 h. 6 N HCl (6 ml) was added to the mixture and heated to 60°C for 1 h. After cooling to rt, aq. KOH was added and the basic mixture was extracted three times with ether. The combined organic phases were washed with water, dried and evaporated. The oily residue was chromatographed on silica gel with MeOH/CH_2Cl_2 (1:9) and conc. NH_4OH/MeOH (1:99) affording amine **13** (135 mg, 87%). Mp 153–155°C (EtOAc); $[\alpha]_D^{20}=-29$; ^1H NMR: $\delta=0.97$ (s, 3H, 18-H_3), 2.48 (td, *J*=11.9 and 3.8 Hz, 1H, 17-H), 2.74–2.93 (m, 5H, 6-H_2 and 17-H′ and CH_2-Py), 3.10 (m, 1H, N-CH), 3.77 (s, 3H, OMe), 6.60 (d, *J*=2.7 Hz, 1H, 4-H), 6.68 (dd, *J*=8.6 and 2.7 Hz, 1H, 2-H), 6.93 (m, 1H, 5-H_{Py}), 7.06 (m, 2H, 1-H and 3-H_{Py}), 7.37 (td, *J*=7.6 and 1.8 Hz, 1H, 4-H_{Py}), 8.42 (d, *J*=4.9 Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: $\delta=17.9$ (C-18), 47.7 (C-14), 55.2 (3-OMe), 55.5 (C-13), 111.1 (C-2), 113.1 (C-4), 120.9 (C_{Py}-5), 123.7 (C_{Py}-3), 126.4 (C-1), 133.8 (C-10), 135.9 (C_{Py}-4), 138.1 (C-5), 149.0 (C_{Py}-6), 157.3 (C-3), 161.3 (C_{Py}-2) ppm; IR (ATR): 2925, 2798, 1610, 1589 cm^{-1}; MS (ESI) *m*/*z* (%): 391 (100%) $[M+H]^+$; HRMS *m*/*z*: found 391.27641 $[M+H]^+$, calcd. 391.27494 ($C_{26}H_{35}N_2O$).

4.12. Hydroxylation procedures with steroid ligand 6

A: The steroid ligand **6** (280 mg, 0.7 mmol) was dissolved in abs. tetrahydrofuran (28 ml) under argon and a solution of $Cu(CF_3SO_3)(C_6H_6)_{0.5}$ (361 mg, 1.4 mmol) in abs. tetrahydrofuran (13 ml, brown solution) was added dropwise. The resulting dark brown solution was stirred for 3 h. Pure O_2 was bubbled through the mixture for 15 min. The color changed to black-green. The mixture was allowed to stand for 3 days in O_2 atmosphere. Diethylether was added to the solution, which was extracted three times with conc. NH_4OH, the ochre organic phase was washed with brine, dried (Na_2SO_4) and evaporated yielding 284 mg yellow oil. Separation by preparative TLC [conc. NH_4OH/MeOH/ethyl acetate (1:10:90)] yielded **14** (16 mg, 5.5%), **15** (26 mg, 8.9%), **6** (210 mg, 75%), **16** (16 mg, 5.5%) and **4** (15 mg, 5%). The ratio of **14**:**15**=0.52:1 by NMR. The isolated ratio of **14**:**15**:**16**=0.62:1:0.62.

4.12.1. 3-Methoxy-*N*-[2-(2-pyridyl)-2*S*-hydroxylethyl]-17a-aza-D-homoestra-1,3,5(10)-triene 14. White solid, mp 148–150°C (MeOH/H_2O); $[\alpha]_D^{20}=+15$; ^1H NMR: $\delta=0.95$ (s, 3H, 18-H_3), 2.23–2.34 (m, 3H, N-CH and 2H), 2.75–2.86 (m, 2H, 6-H_2), 3.37–3.45 (m, 1H, N-CH′), 3.76 (s, 3H, OMe), 4.66 (t, *J*=6.6 Hz, 1H, HO-C<u>H</u>-Py), 6.60 (d, *J*=2.1 Hz, 1H, 4-H), 6.69 (dd, *J*=8.6 and 2.1 Hz, 1H, 2-H), 7.11–7.19 (m, 2H, 1-H and 5-H_{Py}), 7.53 (d, *J*=7.6 Hz, 1H, 3-H_{Py}), 7.66 (m, 1H, 4-H_{Py}), 8.51 (d, *J*=4.9 Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: $\delta=10.3$ (C-18), 22.3 (C-15), 26.2 (C-11), 27.0 (C-16), 29.0 (C-7), 30.3 (C-6), 38.8 (C-12), 39.9 (C-8), 43.0 (C-9), 50.0 (C-17), 50.4 (C-14), 55.2 (3-OMe), 56.1 (N-CH_2), 57.5 (C-13), 71.5 (HO-<u>C</u>H-Py), 111.8 (C-2), 113.7 (C-4), 120.2 (C_{Py}-5), 122.2 (C_{Py}-3), 126.4 (C-1), 132.9 (C-10), 136.6 (C_{Py}-4), 138.0 (C-5), 148.8 (C_{Py}-6), 157.8 (C-3), 163.9 (C_{Py}-2) ppm; IR (ATR): 3282 (O-H), 3061 (O-H), 2923, 1727, 1610 cm^{-1}; MS (ESI) *m*/*z* (%): 429 (8%) $[M+Na]^+$, 407 (100%) $[M+H]^+$, 298 (16%) $[M-(Py\text{-}CHOH)]^+$; HRMS *m*/*z*: found 407.27010 $[M+H]^+$, calcd. 407.26985 ($C_{26}H_{35}N_2O_2$).

4.12.2. 3-Methoxy-*N*-[2-(2-pyridyl)-2*R*-hydroxylethyl]-17a-aza-D-homoestra-1,3,5(10)-triene 15. White solid, mp 176–180°C (EtOAc); $[\alpha]_D^{20}=+101$; ^1H NMR: $\delta=0.89$ (s, 3H, 18-H_3), 2.46 (dd, *J*=12.7 and 4.5 Hz, 1H, N-CH), 2.56 (td, *J*=12.5 and 3.4 Hz, 1H, 17-H), 2.77–2.95 (m, 4H, 6-H_2, N-CH′ and 17-H′), 3.75 (s, 3H, OMe), 4.71 (dd, *J*=10.1 and 4.1 Hz, 1H, HO-C<u>H</u>-Py), 6.60 (d, *J*=2.8 Hz, 1H, 4-H), 6.68 (dd=8.4 and 2.8 Hz, 1H, 2-H), 7.16 (m, 2H, 1-H and 5-H_{Py}), 7.56 (d, *J*=7.6 Hz, 1H, 3-H_{Py}), 7.69 (td, *J*=7.6 and 1.8 Hz, 1H, 4-H_{Py}), 8.51 (d, *J*=4.9 Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: $\delta=10.6$ (C-18), 22.5 (C-15), 26.2 (C-11), 26.4 (C-16), 27.2 (C-7), 30.2 (C-6), 38.6 (C-12), 39.8 (C-8), 43.0 (C-9), 46.3 (C-17), 50.4 (C-14), 55.1 (N-CH_2), 55.2 (3-OMe), 57.1 (C-13), 69.2 (HO-<u>C</u>H-Py), 111.7 (C-2), 113.4 (C-4), 120.2 (C_{Py}-3), 122.1 (C_{Py}-5), 126.2 (C-1), 132.7 (C-10), 136.7 (C_{Py}-4), 137.8 (C-5), 148.7 (C_{Py}-6), 157.6 (C-3), 162.9 (C_{Py}-2) ppm; IR (ATR): 3369 (O-H), 1737, 1612 cm^{-1}; MS (ESI) *m*/*z* (%): 429 (10%) $[M+Na]^+$, 407 (100%) $[M+H]^+$, 298 (12%) $[M-(Py\text{-}CHOH)]^+$; HRMS *m*/*z*: found 407.27161 $[M+H]^+$, calcd. 407.26985 ($C_{26}H_{35}N_2O_2$).

4.12.3. 16α-Hydroxy-3-methoxy-*N*-[2-(2-pyridyl)ethyl]-17a-aza-D-homoestra-1,3,5(10)-triene 16. Pale yellow oil; $[\alpha]_D^{20}=+49$; ^1H NMR: $\delta=0.84$ (s, 3H, 18-H_3), 2.70–2.95 (m, 6H, 6-H_2 and CH_2-Py and 2H), 3.25 (m, 1H, N-CH′), 3.74 (s, 3H, OMe), 3.85 (m, 1H, C<u>H</u>-OH), 6.58 (d, *J*=2.7 Hz, 1H, 4-H), 6.67 (dd, *J*=8.5 and 2.7 Hz, 1H, 2-H), 7.11 (m, 3H, 1-H and 3-H_{Py} and 5-H_{Py}), 7.59 (td, *J*=7.6 and 1.8 Hz, 1H, 4-H_{Py}), 8.53 (d, *J*=4.9 Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: $\delta=8.36$ (C-18), 55.2 (3-OMe), 57.3 (C-13), 65.1 (CH-OH), 111.7 (C-2), 113.4 (C-4), 121.2 and 123.5 (C_{Py}-3 and C_{Py}-5), 126.0 (C-1), 132.6 (C-10), 136.2 (C_{Py}-4), 137.8 (C-5), 149.2 (C_{Py}-6), 157.4 (C-3), 160.8 (2-C_{Py}) ppm; IR (ATR): 3305 (O-H), 3063, 1726, 1609 cm^{-1}; MS (ESI) *m*/*z* (%): 407 (100%) $[M+H]^+$, 314 (15%) $[M-(Py\text{-}CH_2)]^+$; HRMS *m*/*z*: found 407.26913 $[M+H]^+$, calcd. 407.26985 ($C_{26}H_{35}N_2O_2$).

B: The steroid ligand **6** (114 mg, 0.3 mmol) was dissolved in abs. CH_2Cl_2 (10 ml) and a solution of $Cu(CF_3SO_3)_2$ (105 mg, 0.3 mmol) in abs. MeOH (5 ml) was added dropwise. The resulting green solution was stirred for 1 h. The solvent was removed and a green oil was obtained. It was solved in abs. CH_2Cl_2 (20 ml) and the solution was bubbled with argon. Benzoin (123 mg, 0.6 mmol) and Et_3N (0.1 ml, 0.6 mmol) were added under argon and stirred for 20 h (after 14 h the mixture was yellow and cloudy). Pure O_2 was bubbled through the mixture for 15 min. The color changes to darkgreen. It was allowed to stand for 3 days in an oxygen atmosphere. The solution was extracted three times with conc. NH_4OH, the brown organic phase was washed with brine, dried (Na_2SO_4) and evaporated yielding 240 mg black oil. Column chromatography with CH_2Cl_2, MeOH/CH_2Cl_2 (15:85), MeOH and NH_4OH/MeOH (5:95) gave the following products: 1) 18 mg of a mixture, MS (ESI): 405 (100) [**6**+15]$^+$, 406 (30) [**6**+16]$^+$, 391 (30) [**6**+H]$^+$, 312 (15) [**6**+16–92]$^+$, 298 (12) [**6**–92]$^+$; HRMS: found 405.25289, calcd. 405.25158 ($C_{26}H_{33}N_2O_2$); 2) 10 mg of a mixture, MS (ESI): 425 (20) [**6**+34]$^+$, 407 (100) [**6**+16+1]$^+$, 391 (20) [**6**+H]$^+$, 389 (6). HRMS: found 407.26872, calcd. 407.26759 ($C_{26}H_{35}N_2O_2$); 3) unchanged ligand **6** (40 mg, 35%); 4) *sec*-amine **4** (42 mg, 50%).

4.13. Hydroxylation procedures with steroid ligand 13

A: The reaction with $Cu(CF_3SO_3)(C_6H_6)_{0.5}$ (129 mg, 0.5 mmol) in the 13α-series (**13**, 100 mg, 0.25 mmol) was carried out as well as by the ligand **6**. No oxidations products could be found, only starting ligand **13** (98 mg, 98%) was found, and purification by preparative TLC with conc. NH_4OH/MeOH/CH_2Cl_2 (1:10:90) yielded **13** (81 mg, 81%).

B: The steroid ligand **13** (160 mg, 0.4 mmol) was dissolved in abs. tetrahydrofuran (14 ml) and a solution of $Cu(CF_3SO_3)_2$ (147 mg, 0.4 mmol) in abs. tetrahydrofuran (7 ml) was added dropwise. The resulting dark green solution was stirred for 1 h. The mixture was through-bubbled with argon. Benzoin (173 mg, 0.8 mmol) and Et_3N (0.1 ml, 0. 8 mmol) were added under argon and stirred for 3.5 h (the mixture was ochre-yellow and cloudy). Pure O_2 was bubbled through the mixture for 15 min. The color changed in 1 h to green. It was allowed to stand for 3 days in O_2 atmosphere. Diethyl ether was added to the solution and the mixture was extracted three times with conc. NH_4OH, the brown organic phase was washed with brine, dried (Na_2SO_4) and evaporated yielding 280 mg dark brown oil. After chromatography on preparative TLC with conc. NH_4OH/MeOH/CH_2Cl_2 (0.5/10/90) starting ligand **13** (80 mg, 50%) and *sec*-amine **11** (32 mg, 27%) were isolated.

Acknowledgements

We gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 436), the Thuringian Ministry for Science, Research and Arts, the Fonds der Chemischen Industrie, and the Schering AG for the gift of steroids.

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19. CCDC 205992 and 205993 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).