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Synthesis of 16,17-*seco*-steroids with iminomethyl-2-pyridine and aminomethylene-2-pyridine structures as chiral ligands for copper ions and molecular oxygen activation

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Abstract—Starting from 16-oximino-3-methoxy-estra-1.3.5(10)-trien-17-one, the 16,17-*seco*-13α-carbaldehyde with a 16-nitrile function and its corresponding carboxylic acid have been synthesized via a Beckmann fragmentation. The corresponding 13α-amine is available by Curtius degradation of the carboxylic acid. Condensation of the carboxaldehyde with 2-(aminomethyl)pyridine and the primary amine with pyridine-2-carboxaldehyde gave the corresponding iminomethyl-2-pyridine and the aminomethylene-2-pyridine compounds. Copper-mediated ligand hydroxylations with molecular oxygen were not successful. Reasons for this are discussed.

1. Introduction

Copper-containing enzymes such as dopamine-β-hydroxylase are fascinating models for selective hydroxylations with simpler copper complexes and molecular oxygen.[1–6] The quantitative β-hydroxylation of benzylic positions of tridentate or bidentate ligands possessing a (2-pyridyl)ethylamino unit is possible.[7–11] Hydroxylation of unactivated CH_2 groups in these ligands, however is much more difficult. Réglier et al. have shown that *n*-propyl or cyclopentyl groups can be β-hydroxylated to secondary alcohols in 10 and 13% with tridentate ligands. The main products of this reaction are alcohols formed by β-hydroxylation of the CH_2 group in the neighborhood of the pyridine ring (64 and 42%).[12] In order to investigate the stereochemical requirements for such hydroxylations we have employed a conformationally restricted chiral steroid core possessing tri- and bidentate ligands.[13] With bidentate 17β-*N*-2-(2-pyridylethyl) and (2-pyridylmethyl) amino groups we could achieve β-hydroxylation in the 16-position in yields of 16–33% (Fig. 1).[14] Using 17a-aza-*N*-2-(2-pyridylethyl)amino compounds, β-hydroxylation in the 16α-position (5%) and in the neighborhood of the pyridine ring [(*R*)- and (*S*)-alcohol, 8.5 and 5.5%] took place for the 13β-series (*trans*-fused piperidine, Fig. 1); no β-hydroxylation for the 13α-series (*cis*-fused piperidine) could be found. Moreover, the preparation of the oxidizing complex has an influence on its oxidation behavior.[15]

In order to investigate conformationally more restricted bidentate ligands, we employed the simple to prepare 17-iminoalkyl-2-pyridine steroids (condensation of the 17-ketone with 2-aminoalkylpyridines) in the hydroxylation procedure. For these ligands, a regio- and stereoselective γ-hydroxylation of a nonactivated CH_2 group in 12β-position could be observed in practical yields of 40–50% (Fig. 1).[14] A further advantage of these compounds is the simple hydrolysis of the imino bond after the hydroxylation giving the 12β-hydroxy-17-ketones.

In order to gain further insight into the behavior of such iminoalkylpyridine ligands, we became interested in synthesizing the steroidal 16,17-*seco*-aldehyde **A**

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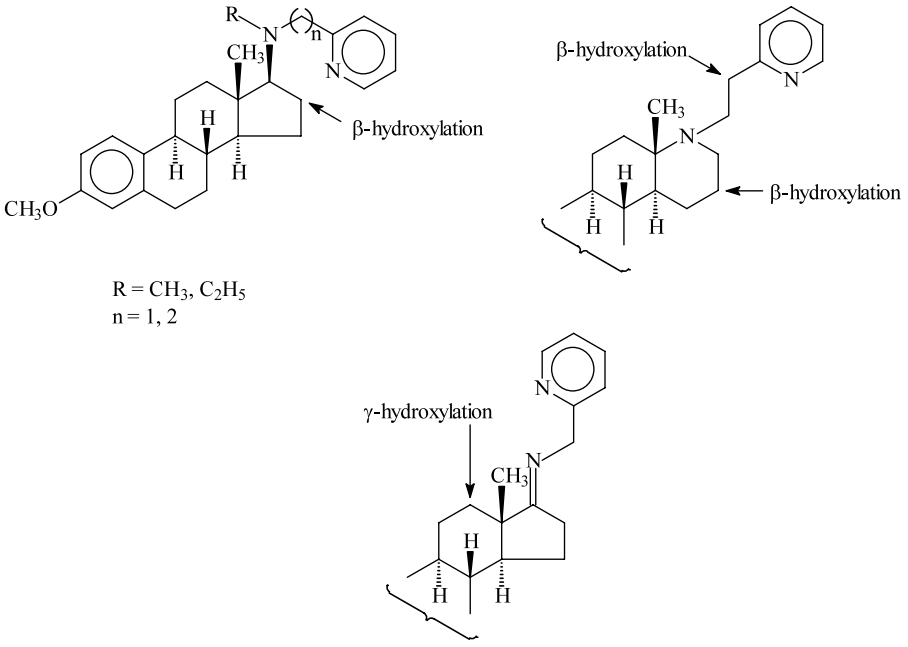


Figure 1. Examples for β- and γ-hydroxylations.

(Fig. 2). Condensation with 2-aminomethylpyridine should then yield the imino ligand **B**. **A** can also be oxidized to give the corresponding carboxylic acid **C**, which possibly can be degradated to the interesting primary 13α-amine **D** which possesses a stereogenic tertiary center. Condensation of **D** with pyridine-2-carboxaldehyde led to another interesting type of aminomethylene pyridine ligands **E**. We now investigate these isomeric ligands in terms of their copper complexation, oxygen activation and ligand hydroxylation.

2. Results and discussion

We then synthesized the desired 16,17-*seco*-17-aldehyde **4** with a 16-nitrile function according to a literature procedure[16,17] starting with 3-*O*-methyl estrone **1**, a known pharmaceutical. Then the thus obtained 16,17-dione 16-oxime **2**[18] was reduced to the 17β-hydroxy compound **3**. Beckmann fragmentation finally furnished the *seco*-17-aldehyde **4**[16,17] (Scheme 1). The carboxylic acid **5** could be obtained in a satisfactory yield by Jones oxidation. The lactone **6** was isolated as a non-polar side product. The structure and absolute configuration of this product was determined by X-ray analysis as a 9α-lactone (Fig. 3). Recently we reported the formation of a similar lactone.[19] **6** is the sole product obtained when an excess of Jones reagent is employed. It could very well be that mixed chromic acid 13α-carboxylic acid anhydride is able to oxidize the 9α-benzylic position in an interesting intramolecular regio- and stereoselective δ-hydroxylation procedure. A few intermolecular reactions using chromyl acetate[20] or chromyl trifluoracetate[21] have been reported in the literature.

The carboxylic acid **5** could also be obtained directly from **2** using a Beckmann fragmentation procedure

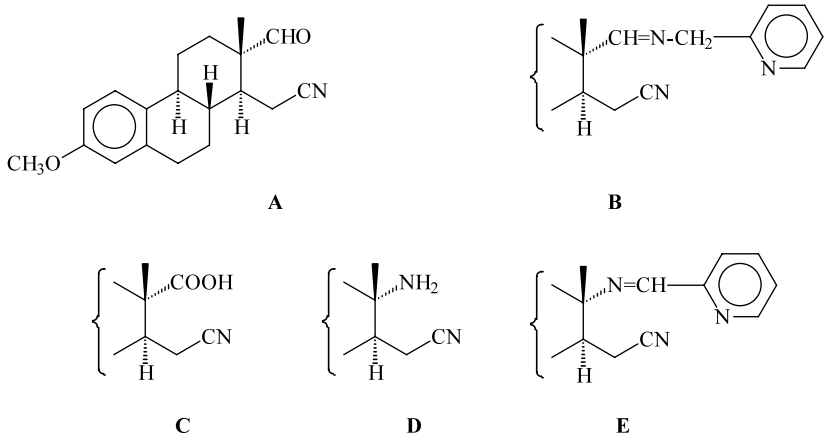
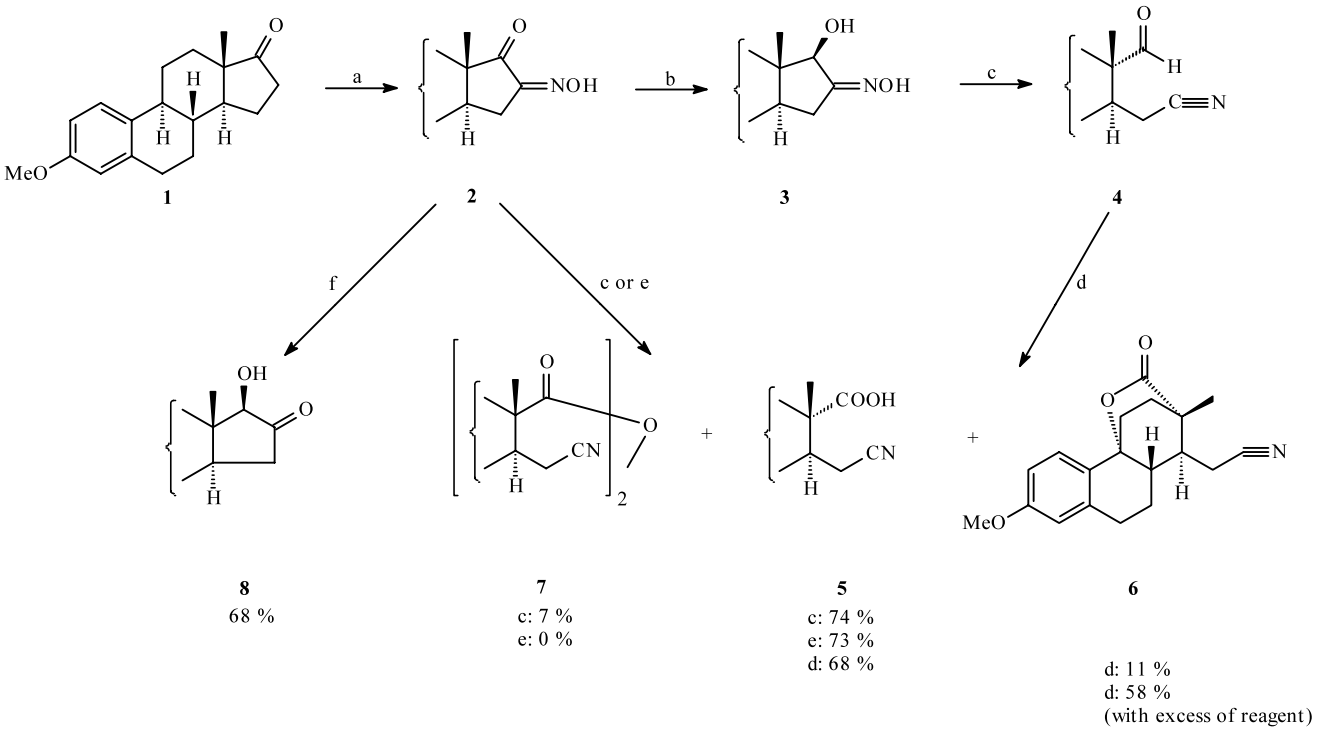


Figure 2. Types of 16,17-*seco* steroids.



Scheme 1. Synthesis of 16,17-*seco*-steroids. *Reagents and conditions*: (a) *i*-amyl nitrite/KO*t*Bu/*t*BuOH; (b) $NaBH_4$/MeOH; (c) *p*TsCl/pyridine; (d) Jones reagent; (e) $TiCl_4/CH_2Cl_2$; (f) $TiCl_3$/HCl/EtOH.

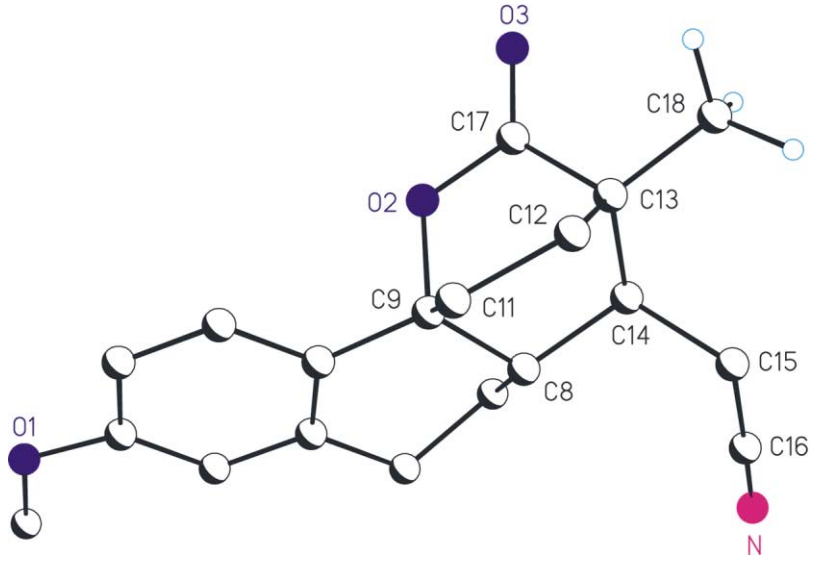


Figure 3. Molecular structure of **6**.

(Scheme 1). Compound **2** could be transformed under heating to **5** (74%) by employing *p*-tosyl chloride and pyridine.[22] The carboxylic acid anhydride **7** could be isolated as a side product (7%). The fragmentation of **2** was also successful with the Lewis acid $TiCl_4$[23] in dichloromethane. This resulted in a yield of 73% for **5**. Reaction of **2** with $TiCl_3$[24] in ethanol gave only the 17β-hydroxy-16-ketone **8** in a yield of 68% (cleavage of the oxime function and reduction of the 17-ketone of **2**). This procedure is a convenient way to synthesize the ketol **8**.[25–28] The structure of **8** was determined by X-ray analysis (Fig. 4).

For the synthesis of the desired primary amine **11**, a one-pot procedure starting from the carboxylic acid **5** with diphenylphosphoryl azide,[29,30] should give the isocyanate **9**, which can then be hydrolyzed to **11** seems to be attractive. Using this Curtius degradation procedure, we could isolate the crystalline isocyanate **9** in 75% yield. A simple reaction with CH_3OH was possible,

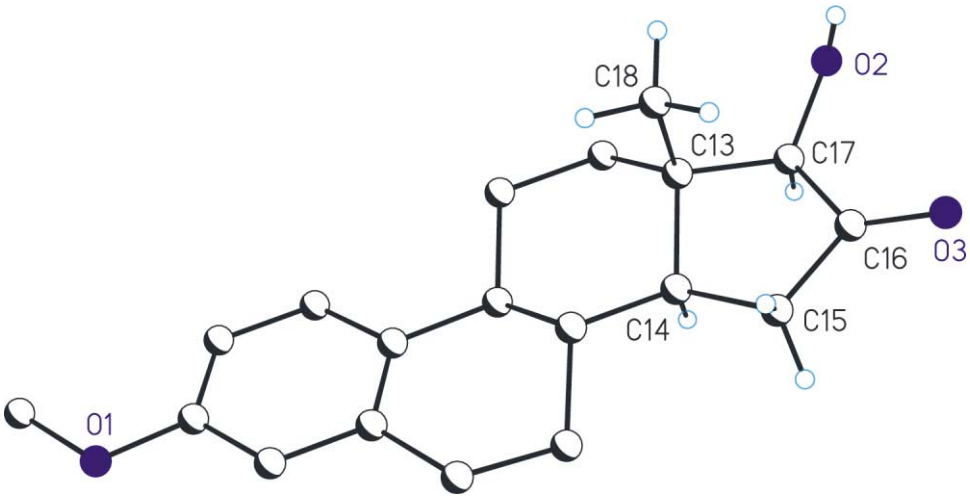
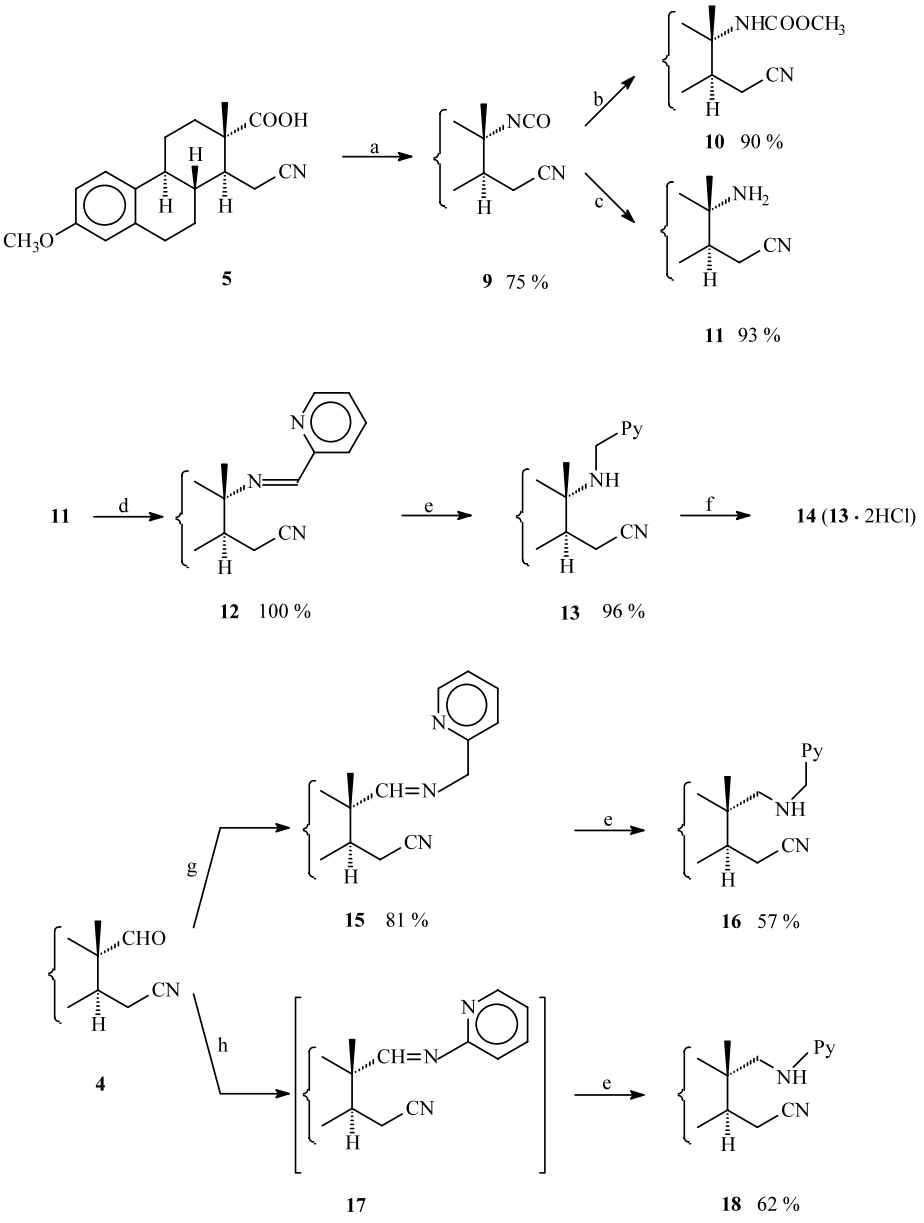


Figure 4. Molecular structure of **8**.

which led to the urethane **10** in a high yield. In contrast to this, the hydrolysis of **9** to **11** was problematic.[31,32] Quite a few products were detected by TLC in both acidic and alkaline conditions. It seems that the nitrile group is involved in the reaction. Several intramolecular cyclisation reactions are possible. We finally succeeded in transforming of **9** into **11** in a nearly quantitative yield by a direct reaction with concentrated hydrobromic acid followed by treatment with sodium hydroxide (Scheme 2). In summary, **5** can be conveniently employed to obtain the interesting primary amine **11** which contains a stereogenic tertiary center and an additional nitrile function.

The aldehyde **4** and the primary amine **11** are starting materials for the synthesis of chiral ligands (Scheme 2) suitable for the binding of copper ions. **4** was condensed with 2-(aminomethyl)pyridine in order to obtain the iminomethyl-2-pyridine compound **15**. The *E*-configuration of the C=N bond was determined by NMR-NOESY experiments and by X-ray analysis (Fig. 5). The secondary amine **16** with a pyridylmethyl group could be obtained by reduction with $NaBH_4$. Condensation of **4** with 2-aminopyridine was successful using $BF_3{\cdot}OEt_2$ in CH_2Cl_2. Direct reduction of **17** with $NaBH_4$ yielded the secondary 2-aminopyridine **18**. Starting with the primary amine **11**, the aminomethylene-2-pyridine compound **12** could be obtained quantitatively by reaction with pyridine-2-carboxaldehyde. The *E*-configuration of the C=N double bond was also determined by NMR-NOESY experiments. By reduction with $NaBH_4$, the pyridylmethylamino compound **13** was obtained as an oil in a high yield. The bis-hydrochloride **14** is a crystalline compound. We then investigated the ability of the aminomethylene-2-pyridine compound **12** and the iminomethyl-2-pyridine compound **15** to complex with copper(I) ions. These complexes were then tested to see if they react with molecular oxygen. The chelating part of **15** resembles the ring-imino compound (see Fig. 1) and therefore could possibly induce an interesting γ-hydroxylation in the positions 12, 14 and 18, depending on the conformation of the active complex.[14] The X-ray structure of **15** shows a conformation that would result in a preference for a 18-hydroxylation (13β-CH_3 group). The chelating part of the iminomethylene-2-pyridine compound **12** is isomeric with the corresponding functionality in **15**. The C=N double bond is conjugated with the pyridine ring. Only the 15-position (CH_2 group in neighborhood to the CN group) is close enough for a γ-hydroxylation. The influence of the cyano group is difficult to estimate. It could activate the neighboring CH_2 group (C-15) for hydroxylation; on the other hand, participation in the complexation of copper could prevent the binding and activation of molecular oxygen.

Compound **15** was reacted with $Cu(I)(CH_3CN)_4PF_6$ in CH_2Cl_2 to obtain a yellow complex. Reaction with O_2 then resulted in a green solution. After three days, decomplexation was carried out with aqueous ammonia. The isolated mixture was investigated with spectroscopic methods, especially with mass spectroscopy (ESI). Main peaks at 406 (**15**+H_2O+H) and 315 (**4**+NH_3+H) and a further peak at 388 (**15**+H) indicated partial hydrolysis and ammonolysis of the imino group and the cyano group but not to hydroxylated products. After chromatography the unchanged ligand **15** (34%) and the hydrolyzed ligand **4** (12%) were isolated, as the only products. More polar fractions furnished mixtures of unseparable compounds. The same procedure with **12** gave a brown copper(I) complex solution, which was changed to a green–brown slurry upon exposure to O_2. In this case, main peaks at 396 (**12**+Na), 374 (**12**+H) and 295 (**11**+H) could be detected by MS (ESI). After preparative TLC, **12** (56%) could be isolated as the only product. The results demonstrated that the 16-nitrile function of 16,17-*seco* steroids has some disadvantages in copper-mediated hydroxylation procedures. It is not fully stable under the used conditions and can also prevent a successful hydroxylation procedure.



Scheme 2. Synthesis of amino- and imino-*seco*-steroids. *Reagents and conditions*: (a) diphenylphosphoryl azide, NEt_3, toluene; (b) CH_3OH/KOH; (c) conc. HBr, NaOH; (d) pyridine-2-carboxaldehyde, CH_3OH; (e) $NaBH_4$, CH_3OH; (f) HCl, ether; (g) 2-(aminomethyl)pyridine, CH_3OH/THF; (h) 2-aminopyridine, CH_2Cl_2, $Et_2O{\cdot}BF_3$.

3. Conclusions

Comparison of the conformationally restricted 17-iminomethyl-2-pyridine ligand[14] (Fig. 1, regio- and stereoselective copper-mediated 12β-hydroxylation with molecular oxygen[14]) with the more flexible 17-iminomethyl-2-pyridine ligand **15** of the 16,17-secosteroid series [Scheme 2, no hydroxylation could be observed starting with Cu(I) or Cu(II) complexes] shows that a predefined arrangement for the C–H bond and the active copper–oxygen complex is important for a successful hydroxylation procedure. In addition, the 13α-aminomethylene-2-pyridine ligand **12** of the 16,17-secosteroid series (Scheme 2) could not be hydroxylated. It should also be pointed out that the ligands **12** and **15** possess a nitrile function in the neighborhood of the complexing moiety, which could possibly prevent oxygen activation. Further studies with similar ligands which do not contain a nitrile function are necessary to give more insight into these interesting reactions.

4. Experimental

4.1. General

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

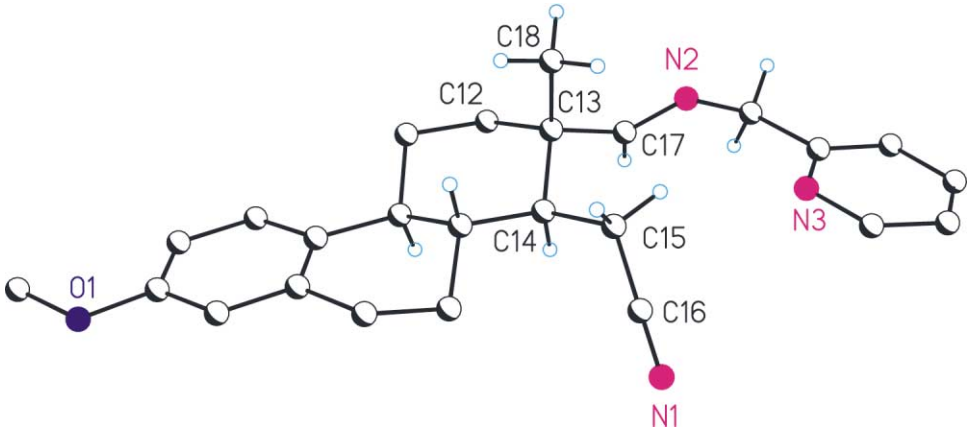


Figure 5. Molecular structure of **15**.

spectra were recorded on an Impact 400 spectrometer (NICOLET) by ATR.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer DRX 400 (^{1}H 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) and 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 dried, purified and distilled according to conventional methods.

4.2. Crystal structure determination

The intensity data for the compounds were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated Mo–K_α radiation. Data were corrected for Lorentz and polarization effects, but not for absorption effects.[33,34]

The structures were solved by direct methods (SHELXS[35]) and refined by full-matrix least-squares techniques against F_o^2 (SHELXL-97[36]). For compound **6** and for the hydroxy-group O2 of **8**, the hydrogen atoms were located by difference Fourier synthesis and refined isotropically. All other hydrogen atoms were included at calculated positions with fixed thermal parameters. All nonhydrogen atoms were refined anisotropically.[36] XP (SIEMENS Analytical X-ray Instruments, Inc.) was used for structure representations.

Crystal data for **6**:[37] $C_{19}H_{21}NO_3$, $M_r = 311.37$ g mol^{-1}, colourless prism, size 0.18×0.12×0.10 mm^3, monoclinic, space group $P2_1$, $a = 7.1427(2)$, $b = 7.7100(3)$, $c = 14.9150(5)$ Å, $\beta = 100.535(2)°$, $V = 807.53(5)$ Å^3, $T = -90$°C, $Z = 2$, $\rho_{calcd} = 1.281$ g cm^{-3}, μ (Mo–K_α) = 0.86 cm^{-1}, $F(000) = 332$, 3112 reflections in $h(-8/8)$, $k(-10/9)$, $l(-19/19)$, measured in the range $3.63° \le \Theta \le 27.45°$, completeness $\Theta_{max} = 96.5\%$, 3112 independent reflections, 2934 reflections with $F_o > 4\sigma(F_o)$, 292 parameters, 1 restraint, $R^1_{obs} = 0.037$, $wR^2_{obs} = 0.096$, $R^1_{all} = 0.040$, $wR^2_{all} = 0.098$, GOOF = 1.049, Flack-parameter −0.1(11), largest difference peak and hole: 0.171/−0.137 e Å^{-3}.

Crystal data for **8**:[37] $C_{19}H_{24}O_3$, $M_r = 300.38$ g mol^{-1}, colourless prism, size 0.04×0.04×0.03 mm^3, monoclinic, space group $P2_1$, $a = 6.9232(2)$, $b = 8.1608(3)$, $c = 13.9745(6)$ Å, $\beta = 91.866(1)°$, $V = 789.12(5)$ Å^3, $T = -90$°C, $Z = 2$, $\rho_{calcd} = 1.264$ g cm^{-3}, μ (Mo–K_α) = 0.84 cm^{-1}, $F(000) = 324$, 3050 reflections in $h(-8/8)$, $k(-9/10)$, $l(-18/18)$, measured in the range $2.92° \le \Theta \le 27.48°$, completeness $\Theta_{max} = 99.2\%$, 3050 independent reflections, 2549 reflections with $F_o > 4\sigma(F_o)$, 203 parameters, 1 restraint, $R^1_{obs} = 0.039$, $wR^2_{obs} = 0.094$, $R^1_{all} = 0.053$, $wR^2_{all} = 0.1024$, GOOF = 1.013, Flack-parameter 0.2(12), largest difference peak and hole: 0.162/−0.145 e Å^{-3}.

Crystal data for **15**:[37] $C_{25}H_{29}N_3O$, $M_r = 387.51$ g mol^{-1}, colourless prism, size 0.04×0.03×0.03 mm^3, monoclinic, space group $P2_1$, $a = 11.2252(5)$, $b = 8.1233(4)$, $c = 12.0500(5)$ Å, $\beta = 106.830(3)°$, $V = 1051.72(8)$ Å^3, $T = -90$°C, $Z = 2$, $\rho_{calcd} = 1.224$ g cm^{-3}, μ (Mo–K_α) = 0.75 cm^{-1}, $F(000) = 416$, 7571 reflections in $h(-13/14)$, $k(-10/10)$, $l(-14/15)$, measured in the range $2.94° \le \Theta \le 27.39°$, completeness $\Theta_{max} = 98.9\%$, 4661 independent reflections, $R_{int} = 0.053$, 3177 reflections with $F_o > 4\sigma(F_o)$, 262 parameters, 1 restraint, $R^1_{obs} = 0.077$, $wR^2_{obs} = 0.119$, $R^1_{all} = 0.129$, $wR^2_{all} = 0.147$, GOOF = 1.085, Flack-parameter 4(3), largest difference peak and hole: 0.255/−0.267 e Å^{-3}.

4.3. 3-Methoxy-16,17-secoestra-1,3,5(10)-trien-16-nitrile-17-oic acid 5

(a) Aldehyde **4** (3.41 g, 11.5 mmol) was dissolved in acetone (250 ml) and cooled to 0°C. To this stirred solution, Jones reagent (11.5 ml, 8N CrO_3 solution in conc. H_2SO_4) was added dropwise. After 20 min, a

small amount of *i*-propanol was added and stirring was continued for further 10 min. H_2O/ice (250 ml) was then poured onto the reaction mixture and it was extracted with CH_2Cl_2. The combined organic phases were washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent afforded a mixture of **5** and **6** (3.27 g). Chromatography on silica gel with 5 and 10% *t*-butyl methyl ether/CH_2Cl_2 yielded the lactone **6** (0.39 g, 11%) as the less polar compound and **5** (2.44 g, 68%). **5** Mp 160–165°C (methanol): $[\alpha]_D^{20}=+78$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H, 18-H_3), 2.91 (m, 2H, 6-H_2), 3.77 (s, 3H, OMe), 6.63 (d, $J=2.6$ Hz, 1H, 4-H), 6.72 (dd, $J=8.6$, 2.6 Hz, 1H, 2-H), 7.17 (d, $J=8.6$ Hz, 1H, 1-H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1 (C-18), 18.5 (C-15), 47.1 (C-13), 55.2 (3-OMe), 112.0 (C-2), 113.6 (C-4), 118.8 (C-16, C≡N), 126.3 (C-1), 131.0 (C-10), 137.4 (C-5), 157.9 (C-3), 182.3 (C-17, COOH) ppm; IR (ATR): 2245 (C≡N), 1695 (acid C=O) cm^{-1}; MS (ESI) *m*/*z* (%): 368 (15) [M+Na+MeOH]$^+$, 336 (100) [M+Na]$^+$; HRMS *m*/*z*: found 336.15616 [M+Na]$^+$, calcd: 336.15756 for $C_{19}H_{23}NO_3Na$. Anal. calcd for $C_{19}H_{23}NO_3$ (313.40): C, 72.82; H, 7.40; N, 4.47. Found: C, 73.44; H, 7.14; N, 4.24%.

9α-Hydroxy-3-methoxy-16,17-secoestra-1,3,5(10)-trien-16-nitrile-17-oic acid 9,17-lactone 6

Mp 235–242°C (acetone): $[\alpha]_D^{20}=+92$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 3H, 18-H_3), 2.82 (m, 2H, 6-H_2), 3.77 (s, 3H, OMe), 6.63 (d, $J=2.5$ Hz, 1H, 4-H), 6.80 (dd, $J=8.8$, 2.6 Hz, 1H, 2-H), 7.43 (d, $J=8.8$, 1H, 1-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.4 (C-15), 18.3 (C-18), 40.0 (C-13), 55.3 (3-OMe), 113.2 (C-4 and C-2), 118.2 (C-16, C=N), 126.3 (C-10), 129.1 (C-1), 138.9 (C-5), 159.8 (C-3), 176.2 (C-17, COO) ppm; IR (ATR): 2253 (C≡N), 1739 (lactone C=O) cm^{-1}; MS (EI) *m*/*z* (%): 311 (45) M$^+$. Anal. calcd for $C_{19}H_{21}NO_3$ (311.38): C, 73.29; H, 6.80; N, 4.50. Found: C, 73.29; H, 7.10; N, 4.34%.

(b) A solution of *p*-toluenesulfonyl chloride (575 mg, 3.02 mmol) in abs. pyridine (2.5 ml) was added dropwise to a solution of **2** (575 mg, 1.84 mmol) in abs. pyridine (5.5 ml) at 60°C. After 36 h, the reaction mixture was poured into 50 ml of diluted H_2SO_4. It was extracted with CH_2Cl_2, the organic phase was washed with water, dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica gel with CH_2Cl_2 until the less polar part **7** (53 mg, 10%) was eluted, then with MeOH/CH_2Cl_2 (1:9) to obtain **5** (429 mg, 74%). The resulted compound **5** was identical with the product of the Jones oxidation of **4** (see above).

3-Methoxy-16,17-secoestra-1,3,5(10)-trien-16-nitrile-17-oic acid anhydride 7

Mp 175–177°C (CH_2Cl_2/*n*-hexane): $[\alpha]_D^{20}=+77$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.36 (s, 6H, 2×18-H_3), 2.92 (m, 4H, 2×6-H_2), 3.77 (s, 6H, 2×OMe), 6.64 (d, $J=2.7$ Hz, 2H, 2×4-H), 6.72 (dd, $J=8.7$, 2.7 Hz, 2H, 2×2-H), 7.16 (d, $J=8.7$ Hz, 2H, 2×1-H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 15.2 (C-18), 18.4 (C-15), 48.8 (C-13), 55.2 (3-OMe), 112.1 (C-2), 113.6 (C-4), 118.6 (C-16, C=N), 126.2 (C-1), 130.6 (C-10), 137.3 (C-5), 158.0 (C-3), 173.3 (C-17, COO) ppm; IR (ATR): 2246 (C≡N), 1803, 1739, 1609 cm^{-1}; MS (ESI) *m*/*z* (%): 631 (100) [M+Na]$^+$. Anal. calcd for $C_{38}H_{44}O_5N_2$ (608.78): C, 74.97; H, 7.29; N, 4.60. Found: C, 74.64; H, 7.16; N, 4.50%.

(c) **2** (223 mg, 0.7 mmol) was dissolved in abs. dichloromethane (5 ml) under argon at 0°C and $TiCl_4$ (0.2 ml, 2.1 mmol) was added. The solvent became dark brown. It was stirred for 8 h at rt and refluxed for 10 h. Wet ether (1 ml) and water (10 ml) was added to the cold reaction mixture, which was extracted three times with CH_2Cl_2, dried (Na_2SO_4) and concentrated in vacuo to yielding crude **5** (214 mg, 96%). Preparative TLC (silica gel) with methanol/dichloromethane (1:9) affording **5** (163 mg, 73%), which is identical with the product of the Jones oxidation of aldehyde **4** (see above).

4.4. 9α-Hydroxy-3-methoxy-estra-1,3,5(10)-trien-16-nitrile-17-oic acid 9,17-lactone 6

Compound **4** (100 mg, 0.34 mmol) was dissolved in acetone (83 ml). To the stirred solution, Jones reagent (1 ml, 8N CrO_3 solution in conc. H_2SO_4) was added dropwise at rt. After 20 min, a few drops of *i*-propanol was added and stirring was continued for further 10 min. H_2O/ice (10 ml) was poured onto the reaction mixture and it was extracted three times with CH_2Cl_2. The combined organic phases were washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent afforded 95.6 mg product (91%; the conversion to **6** was total according to the TLC). Chromatography on silica gel with *t*-butyl methyl ether/CH_2Cl_2; 5:95 yielded 60.8 mg of **6** (58%), identical with the side product described above (see Section 4.3.a).

4.5. 3-Methoxy-17β-hydroxy-estra-1,3,5(10)-trien-16-one 8

Compound **2** (223 mg, 0.7 mmol) was dissolved in ethanol (30 ml) under argon. Ethanol/hydrochloric acid (1:1, 6 ml), and aq. $TiCl_3$ (15%, 2.8 ml, 3.1 mmol) was added. The violet solution became a white slurry. It was first stirred for 8 h at rt and then refluxed for 10 h. The mixture was poured onto water (100 ml), extracted three times with CH_2Cl_2, dried (Na_2SO_4) and evaporated. The residue (194 mg) was chromatographed on silica gel with *t*-butyl methyl ether/CH_2Cl_2 (1:9) yielding **8** (145 mg, 68%) as a white solid. Mp 168–169°C [169.5–171°C, lit.[28]]; $[\alpha]_D^{20}=-134$ (*c* 1, $CHCl_3$) [−88, ethanol. lit.[28]]; IR (ATR): 3420 (OH), 2935, 2867, 1734 (C=O), 1499, 1040 cm^{-1}; MS (ESI) *m*/*z* (%):355 (100) [M+Na+MeOH]$^+$, 323 (80) [M+Na]$^+$, 15 [M+H]$^+$; HRMS *m*/*z*: found 323.16150 [M+Na]$^+$, calcd: 323.16231 for $C_{19}H_{24}NaO_3$.

4.6. 13α-Isocyanato-3-methoxy-16,17-*seco*-17-nor-estra-1,3,5(10)-trien-16-nitrile 9

Compound **5** (0.63 g, 2.00 mmol), diphenylphosphoryl azide (0.6 ml, 2.8 mmol) and triethylamine (0.4 ml, 2.86 mmol) in abs. toluene (50 ml) were refluxed for 3.5 h. The mixture was diluted with toluene, washed with aq. K_2CO_3, dried ($MgSO_4$) and filtered through silica gel. The solvent was evaporated yielding the crude product (0.83 g). Crystallization from diethyl ether yields **9** (465 mg, 75%) as a white solid. Mp 92–95°C (Et_2O); $[\alpha]_D^{20}=+246$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (s, 3H, 18-H_3), 2.59 (A part of an ABX-system, dd, $J=17.4$, 4.0 Hz, 1H, 15-H), 2.69 (B part of an ABX-system, dd, $J=17.4$, 5.3 Hz, 1H, 15-H′), 2.91 (m, 2H, 6-H_2), 3.76 (s, 3H, OMe), 6.63 (d, $J=2.8$ Hz, 2H, 4-H), 6.71 (dd, $J=8.7$, 2.8 Hz, 2H, 2-H), 7.15 (d, $J=8.7$ Hz, 2H, 1-H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.4 (C-15), 21.9 (C-18), 55.2 (3-OMe), 61.7 (C-13), 112.0 (C-2), 113.5 (C-4), 118.7 (C-16, C≡N), 123.8 (NCO), 126.3 (C-1), 130.5 (C-10), 137.2 (C-5), 157.9 (C-3) ppm; IR (ATR): 2240 (-C≡N), 2170 (-NCO) cm^{-1}; MS (ESI) *m*/*z* (%): 365 (60) [M+Na+MeOH]$^+$, 333 (100) [M+Na]$^+$; HRMS *m*/*z*: found 333.15773 [M+Na]$^+$, calcd: 333.15790 for $C_{19}H_{22}NaN_2O_2$. Anal. calcd for $C_{19}H_{22}N_2O_2$ (310.40): C, 73.52; H, 7.14; N, 9.02. Found: C, 74.16; H, 7.32; N, 9.06%.

4.7. 13α-(*N*-Methoxycarbonyl)amido-3-methoxy-16,17-*seco*-17-nor-estra-1,3,5(10)-trien-16-nitrile 10

Isocyanate **9** (310 mg, 1.0 mmol) was stirred in 5% KOH/MeOH (20 ml) for 20 min. After addition of water (50 ml), the mixture was extracted three times with ether. The combined organic phases were washed with aq. NaCl solution, dried (Na_2SO_4) and evaporated under vacuo. The product (340 mg, 99%) was crystallized from Et_2O yielding **10** (308 mg, 90%). Mp 81–84°C (Et_2O); $[\alpha]_D^{20}=+169$ (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.23 (s, 3H, 18-H_3), 2.89 (m, 2H, 6-H_2), 3.61 (s, 3H, NHCOOMe), 3.76 (s, 3H, OMe), 4.68 (br s, 1H, N-H), 6.62 (d, $J=2.8$ Hz, 1H, 4-H), 6.70 (dd, $J=8.6$, 2.8 Hz, 1H, 2-H), 7.17 (d, $J=8.6$ Hz, 1H, 1-H) ppm; ^{13}C NMR: δ 15.5 (C-16), 20.6 (C-18), 55.2 (3-OMe), 56.6 (C-13), 111.9 (C-2), 113.4 (C-4), 119.3 (C-16, C≡N), 126.4 (C-1), 131.3 (C-10), 137.4 (C-5), 154.9 (NHCO), 157.7 (C-3) ppm; IR (ATR): 2246 (C≡N), 1635 (C=O) cm^{-1}; MS (ESI) *m*/*z* (%): 381 (42) [M+K]$^+$, 365 (100) [M+Na]$^+$; HRMS *m*/*z*: found 365.18349 [M+Na]$^+$, calcd: 365.18411 for $C_{20}H_{26}N_2O_3Na$. Anal. calcd for $C_{20}H_{26}N_2O_3$ (342.44): C, 70.15; H, 7.65; N, 8.18. Found: C, 70.97; H, 8.29; N, 8.82%.

4.8. 13α-Amino-3-methoxy-16,17-*seco*-17-nor-estra-1,3,5(10)-trien-16-nitrile 11

To the isocyanate **9** (1.1 g, 3.5 mmol), conc. HBr (9.0 ml) was added cautiously. After gas evolution, the clear solution was treated with 10% aq. NaOH to pH 9. The mixture was extracted with ether and the combined organic phases was washed with aq. NaCl, dried (Na_2SO_4) and evaporated. The crude glassy product (975 mg, 98%) was crystallized from Et_2O to yield pure **10** (937 mg, 93%). Mp 97–99°C (CH_2Cl_2/heptane); $[\alpha]_D^{20}=+94$ (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.04 (s, 3H, 18-H_3), 2.68 (A part of an ABX-system, dd, $J=17.4$, 4.6 Hz, 1H, 15-H), 2.79 (B part of an ABX-system, dd, $J=17.4$, 4.9 Hz, 1H, 15-H′), 2.90 (m, 2H, 6-H_2), 3.76 (s, 3H, OMe), 5.95 (br s, 1H, N-H), 6.62 (d, $J=2.8$ Hz, 1H, 4-H), 6.70 (dd, $J=8.6$, 2.8 Hz, 1H, 2-H), 7.17 (d, $J=8.6$ Hz, 1H, 1-H) ppm; ^{13}C NMR: δ 15.2 (C-15), 20.78 (C-18), 27.4 (C-7), 28.1 (C-11), 30.0 (C-6), 41.3 (C-8), 42.9 (C-9), 45.4 (C-12), 49.3 (C-14), 51.9 (C-13), 55.2 (3-OMe), 111.9 (C-2), 113.4 (C-4), 120.3 (C-16, C≡N), 126.4 (C-1), 131.4 (C-10), 137.5 (C-5), 157.7 (C-3), ppm; IR (ATR): 3353 (N-H), 2242 (-C≡N) cm^{-1}. MS (ESI) *m*/*z* (%): 307 (15) [M+Na]$^+$, 285 (100) [M+H]$^+$, 268 (24). HRMS *m*/*z*: found 285.19532 [M+H]$^+$, calcd: 285.19669 for $C_{18}H_{25}N_2O$.

4.9. 3-Methoxy-13α-*N*[(2-pyridyl)methylene]amino-16,17-*seco*-17-nor-estra-1,3,5(10)-trien-16-nitrile 12

Amine **11** (284 mg, 1.0 mmol) and pyridine-2-carbaldehyde (0.1 ml, 1.0 mmol) was refluxed in abs. methanol (10 ml) for 24 h. The solvent was evaporated yielding **12** as an oil (373 mg, 100%). The substance was subsequently used without further purification. $[\alpha]_D^{20}=+157$ (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.29 (s, 3H, 18-H_3), 2.57 (A part of an ABX-system, dd, $J=17.4$, 4.2 Hz, 1H, 15-H), 2.68 (B part of an ABX-system, dd, $J=17.4$, 5.4 Hz, 1H, 15-H′), 2.94 (m, 2H, 6-H_2), 3.77 (s, 3H, OMe), 6.62 (d, $J=2.7$ Hz, 1H, 4-H), 6.72 (dd, $J=8.6$, 2.7 Hz, 1H, 2-H), 7.21 (d, $J=8.6$ Hz, 1H, 1-H), 7.32 (ddd, $J=7.5$, 4.8, 1.2 Hz, 1H, 5-H_{Py}), 7.75 (ddd, $J=7.9$, 7.5, 1.7 Hz, 1H, 4-H_{Py}), 8.04 (ddd, $J=7.9$, 7.5, 1.7 Hz, 1H, 3-H_{Py}), 8.45 (s, 1H, N=CH-Py), 8.63 (ddd, $J=4.8$, 1.7, 0.9 Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: δ 15.9 (C-15), 18.6 (C-18), 55.2 (3-OMe), 62.2 (C-13), 111.9 (C-2), 113.5 (C-4), 120.0 (C≡N), 120.9 (C_{Py}), 124.8 (C_{Py}), 126.4 (C-1), 131.4 (C-10), 136.6 (C_{Py}), 137.5 (C-5), 149.4 (C_{Py}-6), 155.1 (C_{Py}-2), 157.8 (C-3), 158.6 (N=CH) ppm; IR (ATR): 2242 (C≡N) cm^{-1}; MS (ESI) *m*/*z* (%): 412 (8) [M+K]$^+$ 396 (100) [M+Na]$^+$, 374 (10) [M+H]$^+$; HRMS *m*/*z*: found 396.20515 [M+Na]$^+$, calcd: 396.20518 for $C_{24}H_{27}NaN_3O$.

4.10. 3-Methoxy-13α-*N*[(2-pyridyl)methyl]amino-16,17-*seco*-17-nor-estra-1,3,5(10)-trien-16-nitrile 13

To a solution of the imine **12** (373 mg, 1.0 mmol) in methanol (10 ml), $NaBH_4$ (373 mg, 9.9 mmol) was added in small portions at 0°C. After 10 min, the reaction mixture was treated with water. The white precipitate was filtered to yield 360 mg (96%) of the *sec*-amine **16** as a glassy product. Mp 45–47°C, $[\alpha]_D^{20}=+59$ (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.09 (s, 3H, 18-H_3), 2.70 (dd, $J=17.1$, 4.3 Hz, 1-H, 15-H), 2.80–3.00 (m, 3H, 6-H_2 and 15-H′), 3.76 (s, 3H, OMe), 6.63 (d, $J=2.7$ Hz, 2H, 4-H), 6.71 (dd, $J=8.6$, 2.7 Hz, 1H, 2-H), 7.16 (m, 2H, 1-H and 5-H_{Py}), 7.33 (d, $J=7.9$ Hz, 1H, 3-H_{Py}), 7.64 (td, $J=7.9$, 1.8 Hz, 1H, 4-H_{Py}), 8.53 (m, 1H, 6-H_{Py}) ppm; ^{13}C NMR: δ 14.9 (C-15), 19.7 (C-18), 55.2 (3-OMe), 55.4 (C-13), 111.9 (C-2), 113.5 (C-4), 120.5 (C-16, C≡N), 121.9 and 122.3 (C_{Py}-3 and -5), 126.4 (C-1), 131.5 (C-10), 136.5 (C_{Py}-4), 137.5 (C-5), 149.1

(C_{Py}-6), 157.8 (C-3), 160.2 (C_{Py}-2) ppm; IR (ATR): 2927, 2240 (C≡N), 1610, 1500, 1237, 754 cm^{-1}; MS (ESI) m/z (%): 398 (48) $[M+Na]^+$, 376 (100) $[M+H]^+$; HRMS m/z: found 376.23878 $[M+H]^+$, calcd: 376.23889 ($C_{24}H_{30}N_3O$). Anal. calcd for $C_{24}H_{29}N_3O$ (375.52): C, 76.77; H, 7.78; N, 11.19. Found: C, 76.25; H, 7.80; N, 10.80%.

4.11. Bis-hydrochloride of 13: 14

A solution of the amine **13** (96 mg, 0.26 mmol), 10 ml of ether and 1 ml of CH_3OH) was saturated with HCl gas at 0°C. The resulting bis-hydrochloride **14** crystals were filtered, washed with cold ether and dried. Yield of **14**: 104 mg (99%). Mp 174–175°C, $[\alpha]_D^{20}=+45$ (c 1, $CHCl_3$); ^1H NMR (250 MHz, DMSO): δ 1.10 (s, 3H, 18-H_3), 2.87 (m, 3H), 3.68 (s, 3H, OMe), 4.98 (AB part, 2H, N-C$\underline{H}_2$-Py), 6.66 (m, 2H), 7.06 (m, 1H), 7.53 (m, 2H), 7.95 (m, 2H), 8.65 (d, $J=5.2$, 1H), 9.49 (br s, 1H), 9.98 (br s, 1H) ppm; ^{13}C NMR: δ 15.4 (C-18), 54.5 (3-OMe), 69.3 (C-13), 111.2 (C-2), 113.1 (C-4), 125.6 (C-1), 143.5 (C_{Py}-4), 154.2 (C_{Py}-6), 157.2 (C-3), 169.3 (C_{Py}-2) ppm; IR (ATR): 2916, 2620, 2338, 1615, 1500, 1236, 771 cm^{-1}; MS (ESI) m/z (%): 376 (100) $[M-2HCl+H]^+$; HRMS m/z: found 376.23892 $[M-2HCl+H]^+$, calcd: 376.23889 ($C_{24}H_{30}N_3O$). Anal. calcd for $C_{24}H_{31}N_3OCl_2$ (448.44): C, 64.28; H, 6.97; N, 9.37. Found: C, 63.77; H, 7.03; N, 8.97%.

4.12. (17*E*)-3-Methoxy-17-*N*[(2-pyridyl)methyl]imino-16,17-secoestra-1,3,5(10)-trien-16-nitrile 15

Aldehyde **4** (1.49 g, 5.00 mmol) and 2-(aminomethyl)pyridine (0.5 ml, 5.0 mmol) were refluxed in methanol (100 ml) and THF (30 ml) for 2 h. After stirring overnight at rt, the solvents were removed and the product **15** was crystallized from ethanol (1.57 g, 81%). Mp 102–104°C (methanol); $[\alpha]_D^{20}=+62$ (c 1, $CHCl_3$); ^1H NMR: δ 1.18 (s, 3H, 18-H_3), 2.57 (dd, $J=17.6$, 5.0 Hz, 1H, 15-H), 2.90 (m, 2H, 6-H_2), 3.76 (s, 3H, OMe), 4.73 (AB part, 2H, N-C$\underline{H}_2$-Py), 6.63 (d, $J=2.7$ Hz, 1H, 4-H), 6.71 (dd, $J=8.6$, 2.7 Hz, 1H, 2-H), 7.18 (m, 2H, 1-H and 5-H_{py}), 7.35 (d, $J=7.9$ Hz, 1H, 3-H_{py}), 7.66 (m, 2H, 4-H_{py} and -$\underline{H}$C=N-), 8.55 (m, 1H, 6-H_{py}) ppm; ^{13}C NMR: δ 16.0 (C-18), 17.2 (C-15), 29.9 (C-6), 43.6 (C-13), 55.2 (3-OMe), 66.5 (N-$\underline{C}H_2$-Py), 112.0 (C-2), 113.5 (C-4), 119.9 (C-16, C≡N), 126.4 (C-1), 131.4 (C-10), 136.7 (C_{Py}-4), 137.5 (C-5), 149.3 (C_{Py}-6), 157.8 (C_{Py}-2), 158.8 (C-3), 173.3 (C-17, -C=N-) ppm; IR (ATR): 2235 (C≡N) cm^{-1}; MS (ESI) m/z (%): 410 (100) $[M+Na]^+$, 388 (15) $[M+H]^+$; HRMS m/z: found 388.23961 $[M+H]^+$, calcd: 388.23888 for $C_{25}H_{30}N_3O$. Anal. calcd for $C_{25}H_{29}N_3O$ (387.53): C, 77.50; H, 7.54; N, 10.84. Found: C, 77.63; H, 7.15; N, 10.42%.

4.13. 3-Methoxy-17-*N*[(2-pyridyl)methyl]amino-16,17-secoestra-1,3,5(10)-trien-16-nitrile 16

To a solution of the imine **15** (388 mg, 1.0 mmol) in methanol (10 ml), $NaBH_4$ (388 mg, 10.3 mmol) was added in small portions at 0°C. After 10 min, the reaction mixture was treated with water. The white precipitate was filtered (380 mg) and recrystallized from ether to yield the *sec*-amine **16** (222 mg, 57%). Mp 174–177°C (ether), $[\alpha]_D^{20}=+39$ (c 1, $CHCl_3$); ^1H NMR: δ 0.91 (s, 3H, 18-H_3), 2.37–2.64 (m, 4H, 15-H_2 and 17-H_2), 2.88 (m, 2H, 6-H_2), 3.76 (s, 3H, OMe), 3.89 (AB part, 2H, N-C$\underline{H}_2$-Py), 6.61 (d, $J=2.7$ Hz, 1H, 4-H), 6.70 (dd, $J=8.6$, 2.7 Hz, 1H, 2-H), 7.16 (m, 2H, 1-H and 5-H_{Py}), 7.30 (d, $J=7.8$ Hz, 1H, 3-H_{Py}), 7.64 (td, $J=7.8$, 1.8 Hz, 1H, 4-H_{Py}), 8.55 (d, $J=4.9$ Hz, 1H, 6-H_{Py}) ppm; ^{13}C NMR: δ 15.6 (C-15), 17.9 (C-18), 30.0 (C-6), 37.8 (C-13), 55.2 (3-OMe), 56.0 (N-$\underline{C}H_2$-Py), 60.1 (17-C), 111.8 (C-2), 113.4 (C-4), 120.0 (C-16, C≡N), 122.0 (C_{Py}-5), 122.3 (C_{Py}-3), 126.3 (C-1), 131.9 (C-10), 136.4 (C_{Py}-4), 137.5 (C-5), 149.3 (C_{Py}-6), 157.7 (C-3), 159.9 (C_{Py}-2) ppm; IR (ATR): 2914, 2241 (C≡N), 1609, 1500, 758 cm^{-1}; MS (ESI) m/z (%): 412 (48) $[M+Na]^+$, 390 (100) $[M+H]^+$; HRMS m/z: found 390.25565 $[M+H]^+$, calcd: 390.25454 for $C_{25}H_{32}N_3O$. Anal. calcd for $C_{25}H_{31}N_3O$ (389.55): C, 77.08; H, 8.02; N, 10.79. Found: C, 76.53; H, 7.96; N, 10.79%.

4.14. 3-Methoxy-17-*N*(2-pyridyl)amino-16,17-secoestra-1,3,5(10)-trien-16-nitrile 18

Aldehyde **4** (297 mg, 1.0 mmol) and 2-aminopyridine (94 mg, 1.0 mmol) were dissolved in dichloromethane (5 ml) under argon and 1 drop of $Et_2O{\cdot}BF_3$ was added at 0°C. The solution became dull. It was then heated to 50°C for 1 h. To the cold slurry, methanol (5.0 ml) and $NaBH_4$ (297 mg, 7.9 mmol) were added in small portions at 0°C and stirred for 1 h. Water was added to the mixture, which was extracted three times with ether, washed with NaCl and dried (Na_2SO_4) to afford **18** (369 mg, 98%) as a pale yellow oil. It was purified through HCl salt forming. **18** was dissolved in ether (20 ml) and treated with HCl gas. The solvent was decanted from the sticky precipitate. The precipitate was dissolved in methanol and treated with 10% NaOH, diluted with water, extracted with ether and dried (Na_2SO_4) to afford pure **18** (233 mg, 62%) as an oil. $[\alpha]_D^{20}=+27$ (c 1, $CHCl_3$); ^1H NMR: δ 0.90 (s, 3H, 18-H_3), 2.50 (dd, $J=17.7$, 3.7 Hz, 1-H, 15-H), 2.62 (dd, $J=17.7$, 5.5 Hz, 1-H, 15-H′), 2.89 (m, 2H, 6-H_2), 3.34 (d, $J=11.2$ Hz, 1H, 17-H), 3.54 (d, $J=11.2$ Hz, 1H, 17-H′), 3.76 (s, 3H, OMe), 4.43 (br s, 1H, NH), 6.47 (d, $J=8.3$ Hz, 1H, 3-H_{Py}), 6.62 (m, 2H, 4-H and 5-H_{Py}), 6.70 (dd, $J=8.6$, 2.7 Hz, 1H, 2-H), 7.19 (d, $J=8.6$ Hz, 1H, 1-H), 7.40 (m, 1H, 4-H_{Py}), 8.03 (m, 1H, 6-H_{Py}) ppm; ^{13}C NMR: δ 15.5 (C-15), 16.1 (C-18), 55.2 (3-OMe), 71.0 (C-17), 108.7 and 111.8 and 113.3 and 114.0 (C-4 and -2 and CPy-3 and -5), 120.0 (C-16, C≡N), 126.4 (C-1), 131.8 (C-10), 137.5 and 137.8 (C-5 and C_{Py}-4), 147.9 (C_{Py}-6), 157.6 (C-3), 158.3 (C_{Py}-2) ppm; IR (ATR): 2915, 2243 (C≡N), 1607, 1500, 1043, 773 cm^{-1}; MS (ESI) m/z (%): 398 (100) $[M+Na]^+$, 376 (10) $[M+H]^+$; HRMS m/z: found 376.23963 $[M+H]^+$, calcd: 376.23889 ($C_{24}H_{30}N_3O$).

4.15. Copper complexation and O_2 activation with 15

The steroid ligand **15** (775 mg, 2.0 mmol) was dissolved in abs. CH_2Cl_2 (100 ml) under argon. The solution was degassed 3 times and $Cu^I(CH_3CN)_4PF_6$ (745 mg, 2

mmol) was added under argon. The resulting yellow solution was stirred for 20 h. The flask was degassed and filled three times with pure O_2. This resulted in an oily green mixture. The mixture was kept for 3 days under O_2 and then extracted three times with conc. NH_4OH (stirred for 30 min with conc. NH_4OH, the blue aqueous phase was separated), the brown organic phase was dried (Na_2SO_4) and evaporated giving an oily product (760 mg). MS (ESI) m/z (%): 426 (12) [**15**+K]$^+$, 406 (78) [**15**+19]$^+$, 388 (30) [**12**+H]$^+$, 315 (100) [**4**+18]$^+$, 297 (18). HRMS: 406, $C_{25}H_{32}N_3O_2$ (**15**+H_2O+H); 315, $C_{19}H_{27}N_2O_2$ (**4**+NH_3+H).

The resulting mixture was chromatographed on silica gel with CH_2Cl_2, MeOH/CH_2Cl_2 (1:9) and NH_4OH/MeOH (5:95) yielding **4** (72 mg, 12%), **15** (256 mg, 34%) and a fraction (150 mg) of a nonseparable mixture.

4.16. Copper complexation and O_2 activation with 12

The steroid ligand **12** (187 mg, 0.5 mmol) was dissolved in abs. CH_2Cl_2 (28 ml) under argon. Reaction with $Cu^1(CH_3CN)_4PF_6$ (186 mg, 0.5 mmol), O_2 and conc. NH_4OH as described for **15** (4.15.) gave an oily product (154 mg). MS (ESI) m/z (%): 396 (100) [**12**+Na]$^+$, 374 (80) [**12**+H]$^+$, 295 (58) [**11**+H]$^+$. Preparative TLC with t-butyl methyl ether/CH_2Cl_2 (1:9) gave **12** (105 mg, 56%).

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37. CCDC 210986–210988 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 deposit@ccdc.cam.ac.uk).