19-Nor-10-azasteroids. 5.[1] A Synthetic Strategy for the Preparation of (+)-17-(3-Pyridyl)-(5β)-10-azaestra-1,16-dien-3-one, a Novel Potential Inhibitor for Human Cytochrome P450$_{17\alpha}$ (17α-Hydroxylase/C$_{17,20}$-lyase)

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Prostatic cancer is the second leading cause of cancer-related mortality in the U.S.A. and Europe. Androgen deprivation by inhibition of human cytochrome P450$_{17\alpha}$ (17α-hydroxylase/C$_{17,20}$-lyase), the enzyme responsible for the conversion of C_{21} steroids to the related C_{19} steroids (androgens),[2] has been devised as a potential therapeutic approach for the treatment of this disease, which frequently exhibits androgen dependence.[3] Therefore, several efforts have been devoted to the synthesis of novel inhibitors of P450$_{17\alpha}$ during the past decade. A broad class of steroid derivatives substituted with heterocyclic rings at C-17 have shown good inhibition of this enzyme.[3,4] Jarman has reported recently the synthesis of Abiraterone and its 4-en-3-one analogue (Figure 1), two steroids belonging to this class, which displayed high inhibitory values toward P450$_{17\alpha}$. It has been suggested that this activity is related to the presence of the 3-pyridyl on the D ring, with the nitrogen lone pair coordinating to the heme iron atom in the active site of the enzyme.[5]

We have recently reported the synthesis of some 19-nor-10-azasteroids, a new class of 5α-reductase enzyme inhibitors.[6] Since 5α-reductase converts testosterone to the more potent androgen dihydrotestosterone in prostatic tissues, cooperative inhibition of 5α-reductase and P450$_{17\alpha}$ might be beneficial in the treatment of prostate cancer.[3,7] Therefore, we reasoned that anchoring a 3-pyridyl moiety on the D ring of 19-nor-10-azasteroids would produce novel steroid derivatives, potentially inhibitors of both 5α-reductase and P450$_{17\alpha}$.

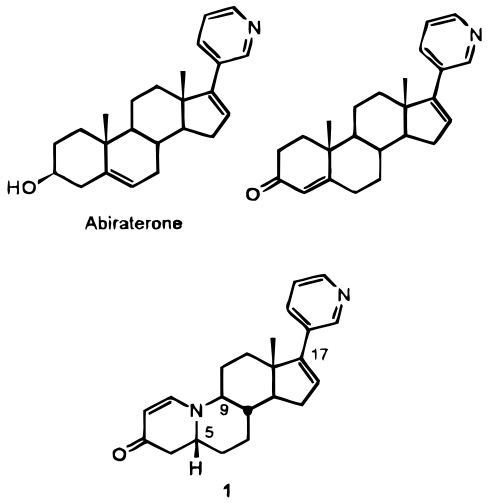
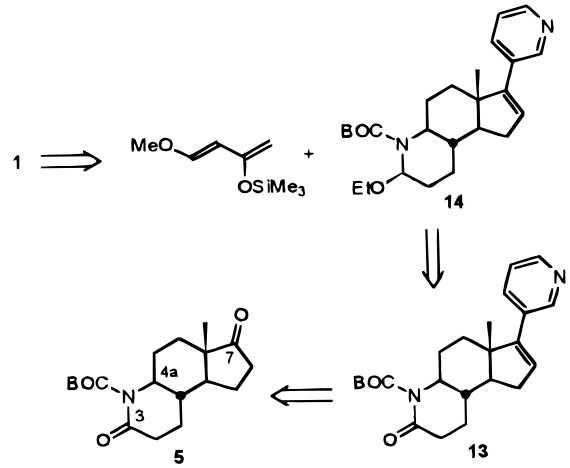


Figure 1.

Scheme 1



To ascertain if the methodology we have reported for the synthesis of 19-nor-10-azasteroids and other related compounds, based on the tandem Mannich−Michael reaction of 3-silyloxy-1,4-dienes with *N*-(acyloxy)iminium ions,[1,8,9] was suitable for the preparation of 17-(3-pyridyl)-19-nor-10-azasteroids, we planned the synthesis of compound **1** (Figure 1) as a first example of this novel class of compounds. Two points in the strategy depicted in Scheme 1 had to be assessed: (a) the compatibility of the pyridyl substituent on the *N*-(acyloxy)iminium ion precursor **14** with cyclization conditions requiring the presence of a Lewis acid; (b) the feasibility of the selective introduction of the pyridyl group on the five-membered ring in **5** in the presence of a *N*-BOC protected lactam.[10]

Starting from enantiopure alcohol **3** (Scheme 2), easily prepared as already described,[8] *N*-BOC protected compound **5** was obtained in 42% overall yield after Jones

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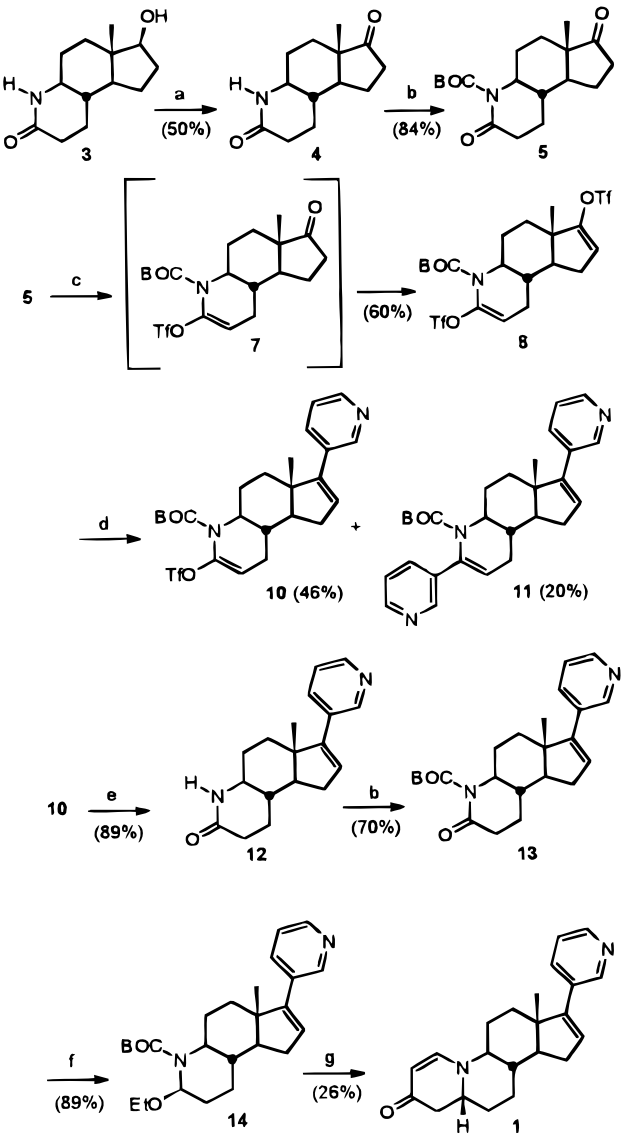
Scheme 2[a]



[a] (a) Jones oxidation; (b) BOC_2O, Et_3N, DMAP, CH_2Cl_2, reflux, 16 h; (c) Tf_2O (3 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (3.6 equiv), CH_2Cl_2, 0 → 25 °C, 12 h; (d) diethyl (3-pyridyl)borane, $(Ph_3P)_2PdCl_2$, 2 M Na_2CO_3, THF-H_2O, 80 °C, 1.5 h; (e) 1 M $TiCl_4$ in CH_2Cl_2, CH_2Cl_2, −25 → 25 °C, 3 h; (f) 1 M $LiEt_3BH$ in THF, THF, −78 °C, 15 min, then 1 M HCl in EtOH, 0 °C, 30 min; (g) 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene, Et_3N, TMSOTf, CH_2Cl_2, 0 → 25 °C, 45 min, then $NaHCO_3$ (satd), 48 h.

oxidation of the hydroxy group and treatment of **4** with di-*tert*-butyl dicarbonate (BOC_2O) as reported for other amides.[8,9] The introduction of the pyridyl moiety at position 7 of compound **5** was first attempted by reaction with 3-pyridyllithium at −78 °C in THF/Et_2O, according to a previous route reported for 17-keto steroids.[11] Unfortunately, the 3-oxo group in **5** reacted much faster with the organolithium compound than the carbonyl at position 7, obtaining, in different experiments, mixtures of products in which 3-hydroxy-3-(3-pyridyl) derivative **6** (Figure 2) was the major component.[10,12]

(10) The protection of an amide N atom as *N*-BOC increases the electrophilic character of the oxo group, which therefore can react more easily with nucleophiles or form enolates with bases. For example, see Posner, G. H.; Cho, C.-G.; Green, J. V.; Zhang, Y.; Talalay, P. *J. Med. Chem*. **1994**, *37*, 170−176 for reactions of *N*-BOC amides with Grignard reagents.

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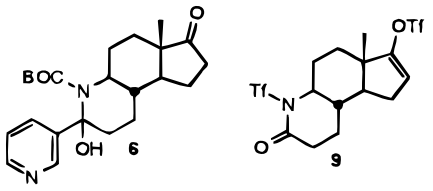

Figure 2.

The apparent higher reactivity of the 3-oxo group toward organometallic reagents convinced us to extend to **5** the methodology described by Jarman for the introduction of a 3-pyridyl on the D ring of steroids, based on the palladium-catalyzed cross-coupling of enol triflates with diethyl (3-pyridyl)borane.[5b] However, when we tried to generate the enol triflate on the five-membered ring in **5** by reaction with 1 equiv of trifluoromethanesulfonic anhydride (Tf_2O) and a slight excess of 2,6-di-*tert*-butyl-4-methylpyridine in CH_2Cl_2, once again the 3-oxo group proved much more reactive, the conversion to triflate **7** (Scheme 2) being quantitative after 6 h at room temperature. The presence of a doublet of doublets (J = 7.7 and 2.9 Hz) at 5.48 ppm (2-H) in the ^{1}H NMR of **7**, and the chemical shift of the methyl group at 0.93 ppm (unchanged with respect to the corresponding signal in **5**) were consistent with the formation of the enol triflate on the six-membered ring.

Given the above results, we reasoned that a possible way to attain the selective introduction of the pyridyl moiety could consist in the preparation and use of double triflate **8,** hoping in a higher reactivity of the *O*-triflate at C-7 under the conditions for the Pd-catalyzed cross-coupling with diethyl (3-pyridyl)borane.[13] Thus, compound **8** was obtained by treatment of **5** with an excess (3 equiv) of Tf_2O and 2,6-di-*tert*-butyl-4-methylpyridine (3.6 equiv) as described above. The use of an excess of Tf_2O was necessary to completely convert **5** to **8**, while even more base was necessary to reduce the formation of *N*-trifluoromethansulfonyl amide **9** (10% yield, Figure 2) derived from initial *N*-BOC deprotection by traces of acidity from triflic anhydride.[14] Some decomposition occurred during the chromatographic purification of the crude reaction mixture, lowering the final yield of **8** to 60%. In the ^{1}H NMR spectrum of **8**, the broad singlet at 5.56 ppm (8-H), the doublet of doublet (J = 7.3 and 2.9 Hz) at 5.46 ppm (2-H), and the shift of the C−6a methyl

(12) Spectroscopic data of **6**: oil; $[\alpha]^{25}_D$ −9.5 (*c* 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.69 (m, 1 H), 8.45 (m, 1 H), 7.73 (m, 1 H), 7.21 (m, 1 H), 3.45 (m, 1 H), 2.60−1.61 (m, 14 H), 1.44 (s, 9 H), 0.84 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 219.1 (s), 156.9 (s), 148.1 (d), 147.9 (d), 140.7 (s), 133.9 (d), 123.2 (d), 80.2 (s), 74.6 (s), 51.0 (d), 47.5 (s), 46.2 (d), 41.3 (d), 35.7 (t), 34.8 (t), 30.1 (t), 29.0 (t), 28.5 (q, 3 C), 21.7 (t), 22.6 (t), 13.3 (q); IR ($CDCl_3$) 3673, 1737 cm^{-1}; MS *m*/*z* 383 (M^+ − 17, 3), 185 (100). Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 68.64; H, 7.90; N, 6.78.

(13) The reactivity of enol triflates derived from *N*-tosyl lactams in Pd-catalyzed coupling reactions with various nucleophiles is known. Thus, a similar reactivity might be expected with the *N*-BOC enol triflate functionality present on the six-membered ring of **8**. For example, see (a) Luker, T.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett*. **1996**, *37*, 8257−8260. (b) Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 3592−3596.

(14) Other methods for preparing enoltriflates are known. For example, Comins' *N*-(5-chloro-2-pyridyl)triflimide has been reported to efficiently trap potassium enolates from *N*-tosyl γ-lactams (ref 13a). In our case the use of Tf_2O and an excess of 2,6-di-*tert*-butyl-4-methylpyridine was successful in converting to enol triflates both a carbonyl group and a *N*-BOC δ-lactam. Moreover, the expensive 2,6-di-*tert*-butyl-4-methylpyridine can be almost quantitatively recovered after the reaction by treatment of the resulting triflate salt with 30% KOH in water and then extraction with pentane.

group signal from ~0.9 to 1.02 ppm are in accordance with the formation of **8**. Concerning compound **9**, the singlet at 171.6 ppm in the ^{13}C NMR spectrum (assignable to the C=O at position 3) and the presence in the ^{1}H NMR spectrum of only one deshielded signal at 5.60 ppm (8-H) are consistent with the assigned structure.

Compound **8**, dissolved in a mixture of THF and 2 M Na_2CO_3 aqueous solution, was then heated at 80 °C in the presence of diethyl (3-pyridyl)borane (1.1 equiv) and $(Ph_3P)_2PdCl_2$ (0.1 equiv) as reported.[5b] Monitoring the reaction, we found that the triflate on the five-membered ring reacted faster and, under the best reaction conditions (see the Experimental Section), 7-(3-pyridyl)-substituted compound **10** was obtained in 46% yield after chromatography, besides a lower amount (20%) of 3,7-bis-(3-pyridyl) derivative **11**. The presence of the pyridyl on the five-membered ring of the major compound was easily determined by ^{1}H NMR analysis of **10**: the shift of the 8-H signal from 5.56 to 5.96 ppm (as a broad singlet) and the doublet of doublets (J = 7.3 and 2.9 Hz) attributable to 2-H still at 5.46 ppm are consistent with that structure. In compound **11**, because of the presence of the 3-(3-pyridyl) group, 2-H undergoes a deshielding effect and resonates at 5.65 ppm. To our knowledge, Pd-catalyzed coupling reactions between boranes and enol triflates derived from *N*-BOC lactams, such as that leading to the introduction of the pyridyl group on the six-membered ring in **11**, have never been reported so far.

With compound **10** in hand, we had to restore the amide functionality on the six-membered ring. Acid treatment could serve this purpose, and eventually, we discovered that the use of a Lewis acid such as $TiCl_4$ at −25 °C in CH_2Cl_2 provides **12** in almost quantitative yield. *N*-BOC protection of **12** to give **13** and then reduction by $LiEt_3BH$[8] afforded 3-ethoxy derivative **14** in 89% yield. According to a previous result, the ethoxy group in **14** is equatorial, since the doublet at 5.41 ppm is consistent with the axial position for 3-H.[8]

Finally, the compatibility of the 7-(3-pyridyl) substituent with the conditions for the final cyclization step was established. In fact, a mixture of compound **14**, Danishefsky's diene, and Et_3N, was treated with TMSOTf as reported,[8] obtaining azasteroid **1** in 26% yield after chromatographic purification. The expected 5β stereochemical outcome of the reaction, confirmed by the chemical shift of 5-H at 3.82 ppm, was consistent with that previously reported.[8] The use of $TiCl_4$ instead of TMSOTf as a Lewis acid[1] to promote the *N*-(acyloxy)-iminium ion formation from **14** was unsuccessful. Indeed, the starting material was recovered unreacted when performing the reaction with with 1 equiv of $TiCl_4$, while with 2 equiv of $TiCl_4$, only traces of **1** were detected in the crude mixture. It is possible that the coordination of the pyridyl N lone pair to titanium could occur, thus affecting the reaction course.

In conclusion, we have demonstrated the feasibility of the synthesis of 19-nor-10-azasteroid **1** bearing a 17-(3-pyridyl) substituent. The key step was the selective introduction of the pyridyl group on the desired position, which was realized by exploiting the higher reactivity in compound **8** of the enol triflate a position 7 under Pd-catalyzed cross-coupling conditions. The amide functionality in the six-membered ring from the enol triflate **10** was successfully restored by using $TiCl_4$. With compound **13** as a common intermediate, azasteroids having different subtituents on the A ring could be therefore prepared by using various 2-silyloxy-1,3-dienes in the final cyclization step, provided that TMSOTf is used to promote the reaction.

Experimental Section

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel using flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluant indicated for the column chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.33 MHz, respectively. Mass spectra were carried out in EI at 70 eV ionizing voltage. THF was distilled from sodium/benzophenone. CH_2Cl_2 was distilled from CaH_2. All reactions requiring anhydrous conditions were performed in flame-dried glassware. Compound **3** was prepared as reported.[8]

(+)-1,2,4,4aα,5,6,6a,7,8,9,9aα,9bβ-Dodecahydro-6aβ-methyl-(3*H*)-cyclopenta[f]quinolin-3,7-dione (4). To a solution of **3** (5.6 g, 25.3 mmol) in acetone-dioxane (1:1, 900 mL) cooled at 0 °C was added dropwise a solution prepared dissolving CrO_3 (31.6 g, 316 mmol) and 96% H_2SO_4 (59 mL) in water (421 mL) until the color of reaction mixture turned deep orange. After stirring the reaction mixture for 5 min, water (400 mL) was added and the mixture extracted with CH_2Cl_2. The organic phase was washed with a 5% $NaHCO_3$ aqueous solution, brine, and then dried over Na_2SO_4. After evaporation of the solvent, **4** was obtained (2.8 g, 50%) as a white solid: mp 164 °C; $[\alpha]^{25}_D$ +111.7 (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.66 (br s, 1 H), 2.91 (m, 1 H), 2.53−2.29 (m, 2 H), 2.20−1.20 (m, 12 H), 0.93 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 218.9 (s), 172.1 (s), 58.5 (d), 48.3 (s), 47.6 (d), 37.8 (d), 35.7 (t), 31.0 (t), 29.4 (t), 28.3 (t), 24.4 (t), 20.9 (t), 14.0 (q); IR ($CDCl_3$) 3897, 1733, 1650 cm^{-1}; MS *m*/*z* 221 (M^+, 15), 206 (100). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.37; H, 8.59; N, 6.09.

(+)-4-*N*-(*tert*-Butoxycarbonyl)-1,2,4,4aα,5,6,6a,7,8,9,-9aα,9bβ-dodecahydro-6aβ-methyl-(3*H*)-cyclopenta-[f]quinolin-3,7-dione (**5**). To a solution of lactam **4** (2.73 g, 12.3 mmol) in CH_2Cl_2 (70 mL) were added Et_3N (1.9 mL, 13.5 mmol), DMAP (0.29 g, 2.37 mmol), and BOC_2O (8.0 g, 36.9 mmol), and the reaction mixture was refluxed overnight. Then, a further amount of BOC_2O (2.66 g, 12.3 mmol) and DMAP (0.29 g, 2.37 mmol) were added and the reflux was continued for 4 h to complete the reaction. Water (70 mL) was added, and after separation of the phases, the organic layer was washed with $NaHCO_3$ (satd), $KHSO_4$ (1 M), and brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by eluting through a short layer of silica gel first with CH_2Cl_2 and then with CH_2Cl_2-MeOH, 20:1 affording pure **5** (R_f 0.65) as a brown solid (3.33 g, 84%): mp 155−156 °C; $[\alpha]^{25}_D$ +97.7 (*c* 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.27 (td, J = 11.0, 4.0 Hz, 1 H), 2.56−2.42 (m, 2 H), 2.21−1.72 (m, 12 H), 1.50 (s, 9 H), 0.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 218.6 (s), 170.3 (s), 153.8 (s), 84.0 (s), 62.6 (d), 47.8 (d), 42.5 (s), 37.4 (d), 35.6 (t), 33.2 (t), 29.4 (t), 27.6 (q, 3 C), 26.2 (t), 23.8 (t), 20.9 (t), 14.0 (q); IR ($CDCl_3$) 1739, 1662 cm^{-1}; MS *m*/*z* 265 (M^+-56, 19), 221 (49), 57 (100). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.27; H, 8.47; N 4.36. Found: C, 67.02; H, 8.56; N, 3.97.

(+)-4-*N*-(*tert*-Butoxycarbonyl)-3,7-di[[(trifluoro-methyl)sulfonyl]oxy]-6aβ-methyl-1,4aα,5,6,6a,9,9aα,-9bβ-octahydro-(4*H*)-cyclopenta[f]quinoline (**8**). To a

solution of **5** (3.11 g, 9.71 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (7.39 g, 36.1 mmol) in CH_2Cl_2 (86 mL) cooled at 0 °C was added dropwise Tf_2O (5.2 mL, 30.9 mmol), the mixture was stirred for 15 min and then allowed to warm to room temperature. After 12 h, the pyridinium triflate salt was filtered off and the solvent evaporated, obtaining the crude triflate as a brown oil. This was purified by chromatography eluting with CH_2Cl_2-petroleum ether, 1:1.5. Pure triflate **8** (R_f 0.4) was obtained as a colorless oil (1.87 g, 60%). A fraction containing the *N*-triflate **9** (R_f 0.18) was also collected (471 mg, 10%). **8**: $[\alpha]^{25}_D$ +41.8 (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.56 (m, 1 H), 5.46 (dd, J = 7.3, 2.9 Hz, 1 H), 3.17 (m, 1 H), 2.43−2.38 (m, 1 H), 2.17−2.05 (m, 5 H), 1.78−1.73 (m, 4 H), 1.45 (s, 9 H), 1.02 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.8 (s), 153.4 (s), 141.4 (s), 118.4 (q, J_{C-F} = 320 Hz, 2 C) 116.2 (d), 109.4 (d), 82.9 (s), 65.9 (d), 52.2 (d), 45.6 (s), 39.0 (d), 31.9 (t), 27.9 (q, 3 C), 26.9 (t), 25.5 (t), 15.5 (q); IR ($CDCl_3$) 1715, 1414 cm^{-1}; MS *m*/*z* 485 (M^+-100, 3), 69 (100). Anal. Calcd for $C_{20}H_{25}NO_8F_6S_2$: C, 41.02; H, 4.30; N 2.39. Found: C, 40.76; H, 4.56, N, 2.09. **9**: oil; $[\alpha]^{25}_D$ +135.7 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.60 (m, 1 H), 3.73 (m, 1 H), 2.99−2.87 (m, 2 H), 2.65−2.57 (m, 2 H), 2.55 (m, 2 H), 2.27−2.05 (m, 2 H), 1.83−1.40 (m, 4 H), 1.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.6 (s), 158.1 (s), 118.9 (q, J_{C-F} = 324 Hz), 118.4 (q, J_{C-F} = 321 Hz), 114.5 (d), 67.9 (d), 50.9 (d), 44.9 (s), 38.3 (d), 35.5 (t), 31.1 (t), 28.0 (t), 27.8 (t), 21.9 (t), 15.4 (q); IR ($CDCl_3$) 1732, 1400 cm^{-1}. Anal. Calcd for $C_{15}H_{17}NO_6S_2F_6$: C, 37.11; H, 3.53; N, 2.89. Found: C, 36.80; H, 3.84; N, 2.71.

(+)-4-*N*-(*tert*-Butoxycarbonyl)-3-[[(trifluoromethyl)sulfonyl]oxy]-6aβ-methyl-1,4aα,5,6,6a,9,9aα,9bβ-octahydro-7-(3-pyridyl)-(4*H*)-cyclopenta[f]quinoline (**10**). Diethyl (3-pyridyl)borane (521 mg, 3.54 mmol) was added to a stirred solution of **8** (1.80 g, 3.1 mmol) in THF (18 mL), containing bis(triphenylphosphine)palladium (II) chloride (215.8 mg, 0.3 mmoli). A 2 M aqueous solution of Na_2CO_3 (11.8 mL) was then added and the mixture stirred for 1.5 h after having put the reaction flask in an oil bath heated at 80 °C. Monitoring the reaction by TLC (CH_2Cl_2-MeOH, 40:1) revealed that after this time the starting material was almost completely consumed and two new spots (at the UV light) were visible on the TLC plate. The reaction mixture was thus partitioned between Et_2O and H_2O, the organic phase was dried over Na_2SO_4, concentrated, and purified by chromatography eluting with CH_2Cl_2-MeOH, 40:1 through a short layer of silica gel. Pure **10** (R_f 0.4, 733 mg, 46%) and **11** (R_f 0.1, 240 mg, 20%) were thus obtained. **10**: $[\alpha]^{25}_D$ +58.0 (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.57 (m, 1 H), 8.44 (dm, J = 4.8 Hz, 1 H), 7.60 (dm, J = 8.5 Hz, 1 H), 7.18 (m, 1 H), 5.96 (m, 1 H), 5.46 (dd, J = 7.3, 2.9 Hz, 1 H), 3.22−3.10 (m, 1 H), 2.44−2.38 (m, 1 H), 2.36−2.14 (m, 4 H), 1.99−1.57 (m, 5 H), 1.45 (s, 9 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.5 (s), 151.3 (s), 148.1 (d), 147.8 (d), 141.2 (s), 133.7 (d), 132.5 (s),128.8 (d), 123.1 (d), 118.3 (q, J_{C-F} = 320 Hz), 109.7 (d), 82.7 (s), 66.1 (d), 55.2 (d), 48.3 (s), 39.9 (d), 33.8 (t), 30.9 (t), 27.9 (q, 3 C), 27.5 (t), 26.2 (t), 16.9 (q); IR ($CDCl_3$) 1714, 1414 cm^{-1}; MS *m*/*z* 414 (M^+-100, 100). Anal. Calcd for $C_{24}H_{29}N_2O_5SF_3$: C, 56.02; H, 5.68; N, 5.44. Found: C, 56.30; H, 6.02; N, 5.79. **11**: mp 60 °C; $[\alpha]^{25}_D$ +74.9 (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.58 (m, 2 H), 8.43 (m, 2 H), 7.59 (m, 2 H), 7.19 (m, 2 H), 5.96 (m, 1 H), 5.65 (m, 1 H), 3.36 (m, 1 H), 2.69 (m, 1 H), 2.24−2.13 (m, 4 H), 1.92−1.69 (m, 5 H), 1.05 (s, 9 H), 1.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.4 (s), 152.0 (s), 149.3 (s), 148.1 (d), 147.8 (d), 147.6 (d), 146.3 (d), 138.2 (s), 136.9 (s), 134.4 (d), 133.6 (d), 128.9 (d), 123.1 (d), 122.8 (d), 119.1 (d), 80.7 (s), 65.9 (d), 55.7 (d), 48.4 (s), 41.0 (d), 34.0 (t), 30.8 (t), 28.8 (t), 27.4 (q, 3 C), 27.1 (t), 17.0 (q); IR ($CDCl_3$) 1691 cm^{-1}; MS *m*/*z* 387 (M^+-56, 17), 57 (100). Anal. Calcd for $C_{28}H_{33}N_3O_2$: C, 75.82; H, 7.50; N, 9.47. Found: C, 76.04; H, 7.36; N, 9.54.

(+)-1,2,3,4aα,5,6,6a,9,9aα,9bβ-Decahydro-6aβ-methyl-7-(3-pyridyl)-(4*H*)-cyclopenta[f]quinolin-3-one (**12**). To a solution of **10** (530 mg,1.03 mmol) in CH_2Cl_2 (25 mL), cooled at −25 °C, was slowly added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (3 mL, 3 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for 3 h. An aqueous saturated solution of $NaHCO_3$ (10 mL) was then added, and after separation of the phases, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered, and evaporated, affording **12** as a white solid (260 mg, 89%): mp 282 °C; $[\alpha]^{25}_D$ +6.9 (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.57 (m, 1 H), 8.44 (m, 1 H), 7.59 (m, 1 H), 7.18 (m, 1 H), 5.98 (m, 1 H), 5.63 (br s, 1 H), 2.98 (m, 1 H), 2.47 (m, 2 H), 2.22−1.64 (m, 10 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.2 (s), 151.3 (s), 148.2 (d), 147.9 (d), 133.6 (d), 132.5 (s), 129.0 (d), 123.1 (d), 58.8 (d), 53.5 (d), 48.2 (s), 37.0 (d), 33.3 (t), 31.3 (t), 30.7 (t), 29.0 (t), 25.4 (t), 16.8 (q); IR ($CDCl_3$) 3395, 1656 cm^{-1}; MS *m*/*z* 282 (M^+, 10), 84 (100). Anal. Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.94; H, 7.44; N, 9.74.

(+)-4-*N*-(*tert*-Butoxycarbonyl)-1,2,3,4aα,5,6,6a,9,9aα,9bβ-decahydro-6aβ-methyl-7-(3-pyridyl)-(4*H*)-cyclopenta[f]quinolin-3-one (**13**). To a solution of **12** (210 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) were added BOC_2O (245 mg, 1.11 mmol), Et_3N (104 μL, 0.74 mmol) and DMAP (13 mg, 0.1 mmol). The reaction mixture was heated to reflux and additional BOC_2O up to 6 equiv was added at 4 h intervals. After 16 h, the reaction mixture was cooled to room temperature, water (20 mL) was added, and after separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with 1 M $KHSO_4$ (10 mL), $NaHCO_3$ (satd) (10 mL), and dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **13** was obtained. Purification by chromatography (CH_2Cl_2, then CH_2Cl_2-MeOH, 20:1) afforded **13** (R_f 0.25) as a white solid (200 mg, 70%): mp 48 °C; $[\alpha]^{25}_D$ +38.7 (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.57 (m, 1 H), 8.44 (dm, J = 4.8 Hz, 1 H), 7.60 (dm, J = 8.5 Hz, 1 H), 7.18, (m, 1 H), 5.97 (m, 1 H), 3.32 (m, 1 H), 2.56−2.48 (m, 2 H), 2.22−1.57 (m, 10 H), 1.45 (s, 9 H), 1.07 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 170.7 (s), 153.8 (s), 151.2 (s), 148.3 (d), 147.8 (d), 133.6 (d), 132.5 (s), 128.8 (d), 123.1 (d), 83.9 (s), 62.7 (d), 53.8 (d), 47.7 (s), 36.7 (d), 33.5 (t), 33.3 (t), 30.8 (t), 27.7 (q, 3 C), 26.8 (t), 25.0 (t), 16.8 (q); IR ($CDCl_3$) 1738, 1666 cm^{-1}; MS *m*/*z* 382 (M^+, 3), 277 (100), 84 (100). Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.43; H, 8.00; N, 7.11.

(+)-4-*N*-(*tert*-Butoxycarbonyl)-3β-ethoxy-1,2,3,-4aα,5,6,6a,9,9aα,9bβ-decahydro-6aβ-methyl-7-(3-pyridyl)-(4*H*)-cyclopenta[f]quinoline (**14**). To a solution of amide **13** (161 mg, 0.42 mmol) in THF (2.0 mL) cooled at −78 °C was added dropwise a 1 M solution of $LiEt_3BH$ in THF (0.5 mL) over 5 min. The reaction mixture was stirred at −78 °C for 15 min and then 1 M HCl in anhydrous EtOH was added dropwise until pH 3−4 was reached, immediately followed by the addition of 4 mL of EtOH. The mixture was allowed to warm to 0 °C, and

after 30 min stirring, was diluted with CH_2Cl_2 (4 mL); the organic layer was washed with water (4 mL), $NaHCO_3$ (satd) (4 mL), and brine (4 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent, **14** was obtained (89%) as an oil sufficiently pure to be used in the next step without purification: $[\alpha]^{25}_D$ +32.3 (*c* 0.90, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.57 (m, 1 H), 8.44 (m, 1 H), 7.60 (m, 1 H), 7.18 (m, 1 H), 5.97 (m, 1 H), 5.41 (d, J = 9.0 Hz, 1 H), 3.64−3.27 (m, 2 H), 3.17 (m, 1 H), 2.58−1.50 (m, 12 H), 1.41 (s, 9 H), 1.17 (t, J = 7.2 Hz, 3 H), 1.09 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.5 (s), 149.8 (s), 147.8 (d), 147.3 (d), 132.1 (d), 132.0 (s), 129.5 (d), 123.0 (d), 81.0 (d), 79.8 (s), 61.9 (t), 61.3 (d), 58.3 (d), 55.9 (d), 48.2 (s), 34.0 (t), 33.8 (t), 30.5 (t), 29.0 (t), 28.3 (q, 3 C), 21.9 (t), 16.7 (q), 14.5 (q); IR ($CDCl_3$) 1680 cm^{-1}; MS *m*/*z* 311 (M^+-101), 57 (100). Anal. Calcd for $C_{25}H_{36}N_2O_3$: C, 72.78; H, 8.80; N, 6.79. Found: C, 72.53; H, 8.91; N, 6.84.

(+)-17-(3-Pyridyl)-(5*β*)-10-azaestra-1,16-dien-3-one (**1**). To a solution of **14** (144 mg, 0.35 mmol), 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (136 μL, 0.70 mmol), and Et_3N (110 μL, 0.79 mmol) in CH_2Cl_2 (3 mL), cooled at 0 °C, was slowly added TMSOTf (135 μL, 0.70 mmol). The mixture was allowed to warm to room temperature and left under stirring for 45 min. Then $NaHCO_3$ (satd) was added (2 mL) and the resulting reaction mixture was stirred for 48 h at room temperature. After separation of the phases, the product was extracted with CH_2Cl_2 and the organic layer dried over Na_2SO_4. After filtration the solution was concentrated under reduced pressure and the resulting residue was purified by chromatography (CH_2Cl_2-MeOH, 20:1) to give **1** (R_f 0.12) as a yellowish oil (30 mg, 26%): $[\alpha]^{20}_D$ +88.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.58 (m, 1 H), 8.45 (m, 1 H), 7.60 (dm, J = 8.5 Hz, 1 H), 7.25 (m, 1 H), 7.20 (d, J = 7.4 Hz, 1 H), 5.99 (m, 1 H), 4.92 (d, J = 7.4 Hz, 1 H), 3.82 (m, 1 H), 3.30 (m, 1 H), 2.42−1.19 (m, 15 H), 1.04 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 191.2 (s), 151.5 (s), 149.3 (d), 148.2 (d), 147.8 (d), 133.6 (d), 129.2 (d), 129.1 (s), 123.4 (d), 96.7 (d), 59.6 (d), 56.7 (d), 53.2 (d), 47.1 (s), 42.5 (d), 34.2 (t), 33.6 (t), 30.8 (t), 26.4 (t), 25.7 (t), 23.4 (t), 16.5 (q); IR ($CDCl_3$) 1572 cm^{-1}; MS *m*/*z* 334 (M^+, 26), 267 (40), 156 (42), 149 (68), 91 (44), 86 (64), 84 (100). Anal. Calcd for $C_{22}H_{26}N_2O$: C, 78.99; H, 7.84; N, 8.38. Found: C, 78.86; H, 7.64; N, 8.18.

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