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Synthesis of 17β-*N*-Substituted 19-Nor-10-azasteroids as Inhibitors of Human 5α-Reductases I and II

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Abstract—The synthesis of 17β-[*N*-(phenyl)methyl/phenyl-amido] substituted 10-azasteroids has been accomplished by either the $TiCl_4$- or TMSOTf-catalysed reaction of carbamates **11** and **12** with Danishefsky's diene. The reaction provided 5α-H isomers **3a**–**5a** and 5β-H isomers **3b**–**5b** depending on the reaction conditions. Both epimers of each compound were tested against human 5α-reductase types I and II. Unexpectedly, 5β-H compounds were found more active than their 5α-H counterparts, the best inhibitors being **3b** (IC_{50} = 279 and 2000 nM toward isoenzyme I and II, respectively) and **5b** (IC_{50} = 913 and 247 nM toward isoenzymes I and II, respectively).

Introduction

The enzyme 5α-reductase plays an important role in androgen metabolism by converting testosterone (T) into dihydrotestosterone (DHT). The enzyme exists in two isoforms, named type I and II, that catalyze the same reaction but in different tissues: type I is mainly expressed in skin, and type II in human prostate. There are many pathologies related to DHT formation, among them the most important is certainly human prostatic hyperplasia (BPH), whose incidence in the aging male population is very high.[1] Acne,[2] alopecia[3] in man and hirsutism[4] in woman are also disorders related to DHT level. It is therefore important the development of inhibitors of 5α-reductase that, lowering the DHT level, can be used as drugs for the pharmacological treatment of the above androgen-dependent pathologies. Among all the inhibitors discovered in recent years,[5] three classes were based on the testosterone skeleton, modified by the introduction of a nitrogen atom in the A ring (4-azasteroids),[6,7] in the B ring (6-azasteroids)[8] and at the bridgehead position 10 (10-azasteroids).[9]

10-Azasteroids are potent in vitro inhibitors of human 5α-reductases I and II, with activity depending on the degree of unsaturation of the A and B rings and substitution on the D ring. The highest activity is observed for the 17β-(*N*-*tert*-butyl)carbamoyl derivative **1** (Fig. 1), which is a dual inhibitor toward type I (IC_{50} 127 nM) and type II (IC_{50} 37 nM) isoenzymes.

We first synthesized 10-azasteroids by a methodology based on the thermal rearrangement of isoxazoline-5-spirocyclopropanes.[9a] More recently we developed a new synthetic route in which the key step, that is the formation of the A ring, is a Lewis acid catalyzed hetero Diels–Alder reaction of silyloxy dienes with *N*-(acyloxy)-iminium ions generated in situ from the corresponding 4-*N*-(*tert*-butoxycarbonyl) 3-ethoxy derivatives (Scheme 1).[10,11] The A ring can be further modified by the introduction of a $\Delta^{1(2)}$ and/or $\Delta^{4(5)}$ double bond. Moreover, we developed a synthetic methodology that afforded either 5α-H or 5β-H epimer simply by changing the order of addition of the reactants in the A-ring formation step.[12]

Since the introduction of polar groups on C-17 is proved to modulate and modify the biological activity of these testosterone-derived inhibitors, we decided to

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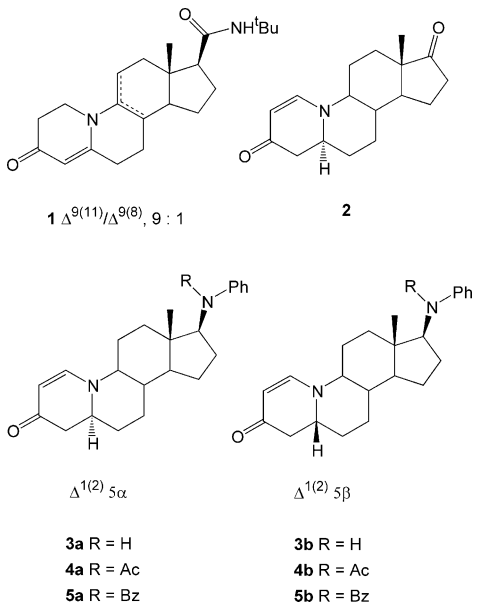


Figure 1.

evaluate whether, analogously to the 17β-carbamoyl groups, the introduction of a 17β-[*N*-(aryl)alkyl/aryl-amido] group determines important variations in the activity of 10-azasteroids. A similar work has been already carried out on 4-azasteroids, in which this kind of substitution resulted in potent and selective type I or dual inhibitors.[13] In the present paper, we thus report on the synthesis of six different 17β-[*N*-(phenyl)methyl/phenyl-amido] substituted 10-azasteroids, as three pairs of 5α-H/5β-H epimers (Fig. 1) and their biological evaluation.

Furthermore, since only the 5α-H epimers, on the basis of the reduction mechanism of 5α-reductase,[9] could be seen as product like inhibitors, we were interested also in seeing how the 5-α/5-β stereochemistry at the A/B ring junction affects the inhibitory potency.

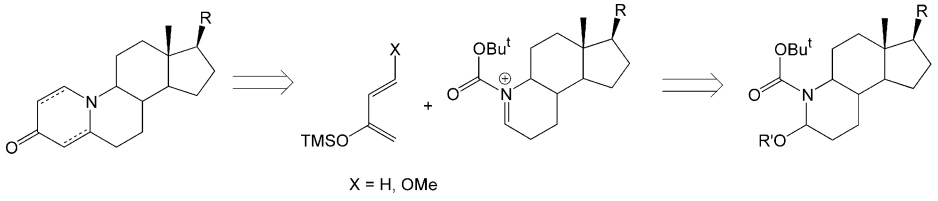
Chemistry

In the synthesis reported by Li et al. the introduction of the 17β-*N*-amido substituent was carried out on the final 4-aza-5α-androstane-3,17-dione product by reductive amination, followed by further *N*-acylation.[13] In our synthesis (Schemes 2 and 3), the transformation of the C-17 carbonyl group into the *N*-phenyl amine group was performed in the initial steps, while the further *N*-acylation was performed either before or after the A-ring formation step (**5a**–**5b** and **4a**–**4b**, respectively).

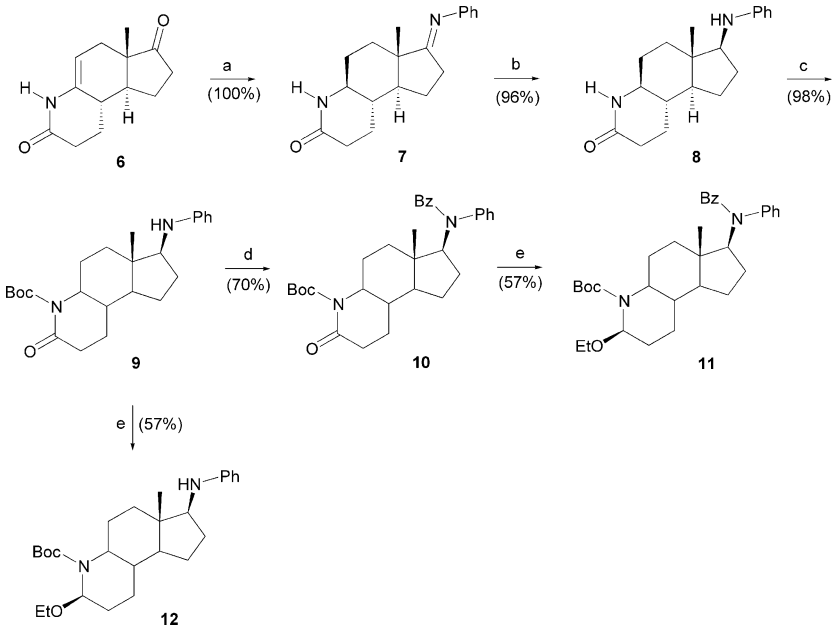
Imine **7** (Scheme 2) was quantitatively obtained from **6**[10] by treatment with aniline and catalytic *p*-TsOH in refluxing toluene over molecular sieves. Crude **7** was reduced to **8** by an excess of $NaBH_3CN$ in MeOH at pH 6, followed by addition of concd HCl up to pH 2–3 (overall yield 96% after chromatographic purification). Alternatively, the quantitative reduction of the imine group in **7** is accomplished by 1.5 equiv $NaBH_4$ in MeOH followed, after isolation of the intermediate, by C–C double bond reduction by $NaBH_3CN$ in MeOH at pH 2 (96%). Even though high yields are obtained with both methods, the former reaction is preferable since it affords the final product **8** in one step. Analogously to earlier observations,[10] both reductions exclusively occurred on the less hindered α face, leading to **8** as a single diastereoisomer with the same stereochemistry of the natural androgens. Lactam **8** was then protected as *N*-Boc derivative **9**, using an excess of Boc_2O in refluxing DCM and catalytic amount of DMAP. It must be highlighted that **9** was obtained as a single product in 98% yield; no reaction at the *N*-phenyl amine group occurred and **9** was used as common precursor for the subsequent steps. Benzoylation of **9**, by benzoyl chloride in anhydrous THF at rt and using anhydrous K_2CO_3 as a base, afforded pure **10** in 70% yield. Noteworthy, benzoylation of **8** under the same reaction conditions occurred on the *N*-phenyl amine group only. However, in the latter reaction perfectly anhydrous conditions are required, because even small traces of water cause benzoylation of the amide group, probably due to the formation of HCl by partial hydrolysis of benzoyl chloride and subsequent protonation of the *N*-phenyl amine group.

Formation of the *N*-Boc ethoxy derivatives **11** and **12** (starting from **10** and **9**, respectively) was obtained by reduction of the carbonyl group with 1.5 equiv $LiBHEt_3$ in THF at −78 °C, followed by treatment with 2 N HCl in abs EtOH. These compounds represent the key intermediates of the whole synthesis and were both obtained in 57% yield as single diastereoisomers. As already reported,[10] this procedure provides the final compounds in higher yields with respect to the $NaBH_4$ reduction, and no traces of over-reduced products were found. In the ^1H NMR spectra of **11** and **12**, 3-H resonates as a sharp doublet at 5.41 ppm ($J = 5.8$ Hz) and 5.39 ppm ($J = 5.8$ Hz), respectively. This suggests an axial–equatorial relationship between 3-H and one of the protons in C-2; the other vicinal J of 3-H is close to zero and cannot be identified. These data are consistent with the equatorial position of the ethoxy group.[10]

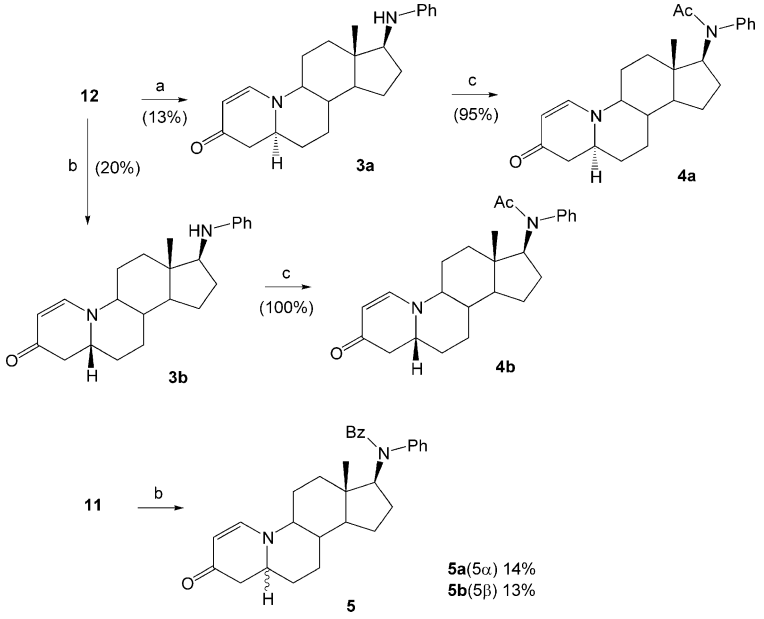
N-Boc ethoxy compound **12** was used in the next A-ring formation step, with Danishefsky's diene as a partner of



Scheme 1.



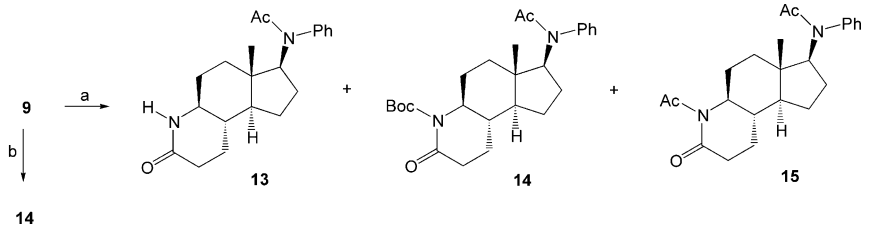
Scheme 2. (a) $PhNH_2$, toluene, reflux, 16 h; (b) $NaBH_3CN$, MeOH, pH 6→2, 24 h; (c) Boc_2O, Et_3N, DMAP 0.1 equiv, DCM, reflux, 12 h; (d) PhCOCl, K_2CO_3, THF, rt, 12 h; (e) (i) $LiBHEt_3$, THF, −78 °C, 15 min; (ii) 2 N HCl, EtOH, −78→0 °C, 30 min.



Scheme 3. (a) 1-Methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene, then $TiCl_4$, 0→25 °C, 1 h; then $NaHCO_3$ satd, 25 °C, 30 min; (b) 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene, Et_3N, TMSOTf, DCM, 0→25 °C, 45 min; then $NaHCO_3$ satd, 25 °C, 36 h; (c) Ac_2O, pyridine, rt, 24 h.

the reaction (Scheme 3). As already reported,[12] we verified that the stereochemical outcome at C-5 can be chosen by using different reaction conditions. Addition of TMSOTf to a mixture of diene, Et_3N and **12** in anhydrous DCM, followed by a 36 h $NaHCO_3$ treatment, results in **3b**, with 5β-H stereochemistry, in 20% yield after chromatographic purification. On the contrary, addition of Danishefsky's diene to a mixture of **12** and $TiCl_4$ affords **3a**, in 13% yield but with opposite 5α-H stereochemistry. These yields are consistent with those already reported for analogous reactions.[12] Surprisingly, applying to **11** the same reaction conditions employed for the synthesis of **3b** leads to **5** as a 1.5:1 5α-H (**5a**)/5β-H (**5b**) diastereoisomeric mixture. After chromatography, the two diastereoisomers **5a** and **5b** were obtained in 14 and 13% yield, respectively.

Further functionalisation at position 17 of **3a** and **3b** was quantitatively achieved by acetylation with Ac_2O in pyridine and catalytic DMAP, affording pure **4a** and **4b**, respectively. It must be noticed that acetylation of **9**, using the same reaction conditions, resulted in a mixture of products composed by deprotected amide **13**, monoacetylated compound **14** (analogue to **10**) and diacetylated compound **15** (Scheme 4). On the other hand, acetylation conditions analogue to those used for the



Scheme 4. (a) Ac_2O, pyridine, rt, 24 h; (b) AcCl, K_2CO_3, THF, rt, 12 h.

synthesis of **10**, that is acetyl chloride in THF and anhydrous K_2CO_3 as a base, afforded the expected **14**. However, whereas **10** could be obtained in high yield, in the case of **14** conversions were never quantitative (independently on the acetyl chloride equivalents employed) and the yields were lower than 50%. Therefore, we preferred using the methodology reported in Schemes 2 and 3. The stereochemistry at C-5 can be determined by analysis of the ^{1}H NMR spectra. In fact 5-H resonates at different chemical shifts depending on its α or β orientation. Analogously to the 10-azasteroids already synthesized,[9,10a] the downfield shifted signals can be assigned at a 5β-H.[10a] According to this, in **3b** 5β-H resonates at 3.78 ppm, while in **3a** 5α-H resonates at 2.65 ppm. The same assignment applies to **5**, where 5α-H resonates at 2.69 ppm and 5β-H at 3.76 ppm. Obviously, since compounds **4a** and **4b** directly derive from **3a** and **3b** by acetylation, the C-5 stereochemistry is identical to that of their precursors. In the ^{1}H NMR spectrum, 5-H resonates at 2.60 and 3.76 ppm for the α (**4a**) and β (**4b**) epimer, respectively.

Inhibition Activity

Compounds **3a**–**b**, **4a**–**b** and **5a**–**b** were tested against human recombinant 5αR-I and II, according to the reported procedures,[14] and their inhibition data are reported as IC_{50} in Table 1, including **1** and **2** (Fig. 1) for comparison. For a few compounds, the value of IC_{50} could not be determined. In these cases, we reported the data related to the percentage of inhibition obtained when these compounds were tested at the defined concentration of 10 μM.

Table 1. In vitro activities of 19-nor-10-azasteroids 17β-[*N*-(phenyl)] and 17β-[*N*-(phenyl)methyl/phenyl-amido] substituted

Inhibitor	IC_{50} (μM)	
	Human type I 5αR	Human type II 5αR
	CHO 1827	CHO 1829
1	0.127±0.012[a]	0.037±0.007[b]
2	n.d.[c]	46.0±18.4[b]
3a	0.580±0.115	31%[d]
3b	0.279±0.083	2.000±0.646
4a	24%[d]	9%[d]
4b	65%[d]	45%[d]
5a	4.7±1.1	5.6±1.2
5b	0.913±0.284	0.247±0.078

[a]Determined in DU-145 cells.[8a]
[b]Determined in human prostate homogenate.[8a]
[c]Not determined.
[d]Percentage values refer to inhibition obtained by the specified compound at 10 μM concentration.

In general, compounds **3**–**5** were less active than 17β-carbamoyl substituted 10-azasteroid **1**. This is not unexpected since we have already shown as $\Delta^{4(5)}$ unsaturated compounds, like **1**, are by far more active than $\Delta^{1(2)}$ 19-nor-10-azasteroids, such as **3**–**5**. In the series of $\Delta^{1(2)}$ 5α-H derivatives **3a**, **4a** and **5a** the introduction of the 17β-*N*-acyl group decreases the activity toward 5αR-I: in fact, *N*-phenyl amine **3a** (IC_{50} = 0.580 μM) is nearly ten times more potent than **5a** (IC_{50} = 4.7 μM), that bears a benzoyl group, and more potent than **4a** (bearing an acetyl), which shows a 24% inhibition when tested at 10 μM concentration. Different results can be observed considering the activity of the cited compounds against 5αR-II. In this case, only the introduction of the *N*-benzoyl moiety determines the maintenance of the activity toward the enzyme: in fact, **5a** (IC_{50} = 5.6 μM) proved to be a better inhibitor than both **3a** and **4a**, that, at 10 μM concentration, inhibit the enzyme only by 31 and 9%, respectively. Furthermore, only compound **5a** showed a higher potency than the corresponding 5α-H 17-oxo 10-azasteroid **2** (5.6 μM vs 46 μM).

As for the $\Delta^{1(2)}$ 5β-H series, all compounds **3b**, **4b** and **5b** resulted more active than their corresponding 5α-H epimers, even though the behavior within the single series is similar. In fact, looking at the 5αR-I inhibition data, the less potent inhibitor resulted the *N*-acetyl derivative **4b** (65% inhibition at 10 μM concentration), whereas the 17β-*N*-phenyl amino substituted **3b** (IC_{50} = 0.279 μM) was still more active than **5b** (IC_{50} = 0.913 μM), even if the difference in potency is not as remarkable as for **3a** and **5a**.

In the case of type II enzyme, the data are consistent with the behavior of the homologous α series. Compound **5b** (IC_{50} = 0.247 μM) is 10 times more potent than **3b** (IC_{50} = 2.0 μM), and more potent than **4b**, that inhibits the enzyme by 45% at 10 μM concentration.

While azasteroid **1** is a dual inhibitor (IC_{50} = 0.127 and 0.037 μM against 5αR-I and 5αR-II, respectively),[9a] all compounds tested in this work were more active against 5αR-I. The only exception is represented by **5b**, that is roughly 4 times more potent against isoenzyme II. Our results are consistent with the data reported by Li et al. for an homologous series of 4-azasteroids.[13] In that paper, almost all 17β-*N*-amido compounds were more active against 5αR-I.

However, an unexpected result was obtained in this work: for the first time it was found that, in the same series, the 5β-H isomers are more potent than the corresponding 5α-H compounds.

These data seem to be in contrast with the transition state model previously reported,[9a,15] which includes a partial bond formation on the α face of the steroid by the attack of NADPH on C-5. According to this model, compounds **3a**, **4a** and **5a** are product-like transition state analogues and therefore were expected to be the most potent inhibitors.

Therefore, it is surprising that the 5β-H compounds were up to 20 times more active than the corresponding azasteroids having 5α stereochemistry. Currently, we are unable to explain this result. However, we have already shown[9b] that the presence of the bridgehead nitrogen atom at 10 position confers a high degree of flexibility to the A and B ring moiety of the azasteroids, thus making the *cis* fusion in the 5β epimers less drastically different from the normal *trans* fusion of a steroid-like structure. To the best of our knowledge, compounds **3b** and **5b** represent the first examples of potent aza-steroidal inhibitors of the enzyme 5α-reductase having 5β-H stereochemistry.

Finally, it is noteworthy that, within the 5β-H series, the selectivity of the inhibitors against 5αR-I and 5αR-II can be reversed by the introduction of the benzoyl group, being the *N*-phenyl amino substituted compound **3b** more potent toward 5αR-I and its *N*-benzoyl derivative **5b** more potent toward 5αR-II.

Conclusions

In this paper we have described the synthesis of novel 17β-[*N*-(phenyl)-methyl/phenyl]-amido substituted 19-nor-10-azasteroids and their evaluation as inhibitors against both the isoforms of human 5α-reductase. We applied a hetero Diels–Alder reaction based methodology in order to obtain each compound as 5α and 5β epimer. We found that, surprisingly, the 5β-H compounds were more active than their transition state analogue counterparts 5α-H. These are the first examples of 5β-H inhibitors having steroidal structure of the enzyme 5α-reductase. Furthermore, the presence of the substituent at C-17 can modulate the selectivity toward 5α-reductase type I and II.

Experimental

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 column chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 50.33 MHz, respectively. EI mass spectra were carried out at 70 eV ionizing voltage. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. All reactions requiring anhydrous conditions were performed in flame-dried glassware. (+)-1,2,4,6,6a,7,8,9,9aα,9bβ-Decahydro-6aβ-methyl-(3*H*)-cyclopenta[*f*]quinoline-3,7-dione (**6**) was prepared as already described.[10]

(−)-1,2,4,4aα,5,6a,7,8,9aα,9bβ-Dodecahydro-6aβ-methyl-7β-(*N*-phenylamino)-(3*H*)-cyclopenta[*f*]quinoline-3-one (8). Enelactame **6** (3.00 g, 13.7 mmol), aniline (12.5 mL, 137 mmol) and *p*-TsOH (24 mg, 0.14 mmol) were dissolved in toluene (90 mL) in a Dean–Stark apparatus, and the resulting solution refluxed for 16 h. After removal of the solvent, crude imine **7** was obtained and used without purification in the next step. **7**: ^{1}H NMR ($CDCl_3$, δ ppm): 7.78 (s, 1H), 7.17–7.09 (m, 2H), 6.68–6.59 (m, 3H), 4.81 (m, 1H), 3.55 (m, 2H), 2.53–1.87 (m, 7H), 1.66–1.38 (m, 4H), 0.81 (s, 3H).

Crude imine **7** was suspended in MeOH (160 mL) and the pH adjusted to 6 by adding concd HCl. After cooling to 0 °C, $NaBH_3CN$ (2.66 g, 41.1 mmol) was then slowly added and the resulting solution stirred for 30 min. Concd HCl was then added (pH 2) and further $NaBH_3CN$ (0.98 g, 15.1 mmol) was slowly added and the solution left under stirring at rt. After 12 h, the suspension was poured into water (160 mL), NaOH (satd) was added up to pH 10 and the product extracted with DCM (3×200 mL). The organic layer was first washed with brine and then dried over Na_2SO_4. After filtration and evaporation of the solvent, crude **8** was obtained as a red oil. Purification by flash chromatography, eluting first with CH_2Cl_2 and then with CH_2Cl_2–MeOH, 10:1 (R_f = 0.47), afforded pure **8** (3.93 g, 96%) as a white solid. **8**: mp 186–187 °C; $[\alpha]_D^{25}$ −9.99 (*c* 0.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ ppm): 7.20–7.12 (m, 2H), 6.80–6.60 (m, 3H), 5.82 (s, 1H), 3.40 (m, 1H), 2.97–2.82 (m, 1H), 2.60–2.35 (m, 2H), 2.35–1.07 (m, 13H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 172.3 (s), 147.9 (s), 129.1 (d, 2 C), 117.1 (d), 113.3 (d, 2 C), 63.1 (d), 58.6 (d), 49.1 (d), 44.3 (d), 38.4 (t), 35.7 (d), 31.2 (t), 29.9 (t), 28.7 (t), 25.1 (t), 22.5 (t), 12.2 (q); MS *m*/*z* (%): 298 (M^+, 23), 132 (100), 86 (60), 84 (91); IR ($CDCl_3$): 2942, 2870, 2244, 1653, 1599, 1501 cm^{-1}. Elem. Anal. calcd for $C_{19}H_{26}N_2O$: C, 76.45; H, 8.78; N, 9.43. Found: C, 76.42; H, 9.09; N, 9.04.

(+)-1,2,4,4aα,5,6a,7,8,9aα,9bβ-Dodecahydro-4-*N*-(*tert*-butoxycarbonyl)-6aβ-methyl-7β-(*N*-phenylamino)-(3*H*)-cyclopenta[f]quinoline-3-one (9). To lactame **8** (500 mg, 1.68 mmol), dissolved in anhydrous CH_2Cl_2 (10 mL), were added Et_3N (259 μL, 1.85 mmol), Boc_2O (1.48 g, 6.72 mmol) and DMAP (30 mg, 0.15 mmol), and the resulting solution refluxed for 12 h. Water (10 mL) was then added and, after separation of the phases, the organic layer was washed with 1 M $KHSO_4$ (10 mL), satd $NaHCO_3$ (10 mL), brine and then dried over Na_2SO_4. After removal of the solvent and purification of the crude oil by flash chromatography (eluant: first CH_2Cl_2 and then CH_2Cl_2–MeOH, 40:1, R_f = 0.53), pure **9** (6.56 g, 98%) was obtained as a white solid. **9**: mp 67–70 °C; $[\alpha]_D^{25}$ +11.9 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ ppm): 7.15–7.07 (m, 2H), 6.67–6.58 (m, 3H), 3.50–3.41 (m, 1H), 3.27 (td, *J* = 10.3, 3.7 Hz, 1H), 2.58–2.39 (m, 2H), 2.37–2.25 (m, 1H), 1.90–1.55 (m, 6H), 1.51–1.23 (m, 6H), 1.50 (s, 9H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 170.6 (s), 154.0 (s), 148.1 (s), 129.1 (d, 2 C), 117.0 (d), 113.4 (d, 2 C), 83.8 (s), 62.9 (d), 62.6 (d), 49.4 (d), 44.0 (d), 38.1 (t), 36.0 (t), 33.2 (t), 30.0 (t), 27.6 (q, 3 C), 26.8 (t), 24.6 (t), 22.6 (t), 12.1 (q); MS *m*/*z* (%): 398

(M^+, 4), 298 (9), 297 (3), 132 (100), 106 (14), 77 (8); IR ($CDCl_3$): 2876, 1740, 1662, 1601, 1147 cm^{-1}. Elem. Anal. calcd for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03. Found: C, 71.87; H, 8.47; N, 6.85.

(+)-1,2,4,4aα,5,6a,7,8,9aα,9bβ-Dodecahydro-4-*N*-(*tert*-butoxycarbonyl)-6aβ-methyl-7β-[(*N*-phenyl)benzamido]-(3*H*)-cyclopenta[*f*]quinoline-3-one (10). To a mixture of **9** (2.00 g, 5.02 mmol) and anhydrous K_2CO_3 (1.53 g, 11.0 mmol) in anhydrous THF (37 mL), benzoyl chloride (700 μL, 6.02 mmol) was added dropwise and the suspension left under stirring in nitrogen atmosphere at rt for 24 h. The precipitate was then filtered off and the solvent evaporated. Satd $NaHCO_3$ (30 mL) was added to the residue and the product extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over Na_2SO_4. After removal of the solvent and purification of the crude oil by flash chromatography (eluant: CH_2Cl_2–MeOH, 30:1, R_f = 0.38), pure **10** (1.77 g, 70%) was obtained as a yellowish solid. **10**: $[\alpha]_D^{25}$ +55.8 (*c* 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$, δ ppm): 7.19–6.95 (m, 10H), 4.78 (m, 1H), 3.36–3.14 (m, 1H), 2.60–2.30 (m, 3H), 1.95–1.18 (m, 11H), 1.51 (s, 9H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 172.8 (s), 170.4 (s), 153.4 (s), 141.7 (s), 137.5 (s), 131.1 (d, 2 C), 128.7 (d), 128.4 (d, 2 C), 127.7 (d, 2 C), 127.4 (d, 2 C), 127.1 (d), 83.6 (t), 65.4 (d), 62.5 (d), 48.8 (d), 45.7 (d), 37.7 (d), 36.0 (t), 33.0 (t), 27.5 (q, 3 C), 26.8 (t), 25.0 (t), 24.4 (t), 22.1 (t), 13.8 (q); MS *m*/*z* (%): 403 (M^+-101, 0.27), 297 (5), 197 (5), 105 (100), 77 (33); IR ($CDCl_3$): 3001, 2984, 1758, 1642, 1347, 1246, 1146 cm^{-1}.

1,2,4,4aα,5,6a,7,8,9aα,9bβ-Dodecahydro-4-*N*-(*tert*-butoxycarbonyl)-3β-ethoxy-6aβ-methyl-7β-[(*N*-phenyl)benzamido]-(3*H*)-cyclopenta[*f*]quinoline-3-one (11). To a solution of **10** (1.67 g, 3.32 mmol) in anhydrous THF (13 mL), cooled at −78 °C, was added dropwise a 1 M $LiBHEt_3$ solution in THF (5.0 mL, 5.00 mmol). After 15 min, 2 N HCl in abs EtOH was added up to pH 3, immediately followed by further abs EtOH (10 mL) and the solution warmed up to 0 °C and left under stirring for 30 min. After dilution with CH_2Cl_2 (130 mL), the organic phase was washed with satd $NaHCO_3$ (100 mL), H_2O (100 mL), brine (100 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent afforded crude **11** (1.01 g, 57%), in sufficiently pure form to be used in the next reaction without further purification. **11**: ^1H NMR ($CDCl_3$, δ ppm): 7.20–7.04 (m, 10H), 5.41 (d, *J* = 5.8 Hz, 1H), 4.83–4.70 (m, 2H), 3.60–3.48 (m, 1H), 3.45–3.33 (m, 1H), 3.13–3.02 (m, 1H), 2.23–2.12 (m, 1H), 1.84–1.13 (m, 15H), 1.45 (s, 9H), 0.87 (s, 3H).

1,2,4,4aα,5,6a,7,8,9aα,9bβ-Dodecahydro-4-*N*-(*tert*-butoxycarbonyl)-3β-ethoxy-6aβ-methyl-7β-(*N*-phenylamino)-(3*H*)-cyclopenta[*f*]quinoline-3-one (12). Prepared as described for **11**, starting from **9** (2.00 g, 5.02 mmol) and obtaining crude **12** (1.23 g, 57%) in sufficiently pure form to be used in the next reaction without further purification. **12**: ^1H NMR ($CDCl_3$, δ ppm): 7.19–7.05 (m, 2H), 6.70–6.55 (m, 3H), 5.39 (d, *J* = 5.8 Hz, 1H), 3.63–3.47 (m, 2H), 3.44–3.29 (m, 2H), 3.68 (m, 1H), 2.35–2.10 (m, 2H), 1.95–1.50 (m, 6H), 1.44 (s, 9H), 1.35–1.10 (m, 5H), 0.84 (s, 3H).

(−)-17β-(*N*-phenylamino)-(5α)-10-azaestr-1-en-3-one (3a). To a solution of **12** (429 mg, 1.0 mmol) and 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (585 μL, 3.0 mmol) in anhydrous CH_2Cl_2 (5 mL) cooled at 0 °C, $TiCl_4$ (330 μL, 3.0 mmol) was added dropwise and the solution left under stirring 1 h at 25 °C. Satd $NaHCO_3$ (5 mL) was then added and the resulting mixture stirred vigorously for 30 min. After separation of the phases, the product was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers dried over Na_2SO_4. Filtration and evaporation of the solvent afforded crude **3a**, which was purified by flash chromatography, eluting with acetone–petroleum ether, 1:1. Pure **3a** was obtained (R_f = 0.50) as a brown solid (46 mg, 13%). **3a**: mp 69–70 °C; $[\alpha]_D^{25}$ −112.3 (*c* 0.26, $CHCl_3$). ^1H NMR ($CDCl_3$, δ ppm): 7.19–7.08 (m, 3H), 6.68–6.58 (m, 3H), 4.96 (d, *J* = 7.6 Hz, 1H, 2-H), 3.43 (t, *J* = 8.2 Hz, 2H), 2.65 (m, 1H, 5-H), 2.64 (dd, *J* = 17.2, 6.6 Hz, 1H) 2.30 (m, 3H), 1.97–1.55 (m, 6H), 1.55–1.11 (m, 6H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 192.0 (s), 149.5 (d), 148.2 (s), 129.8 (d, 2 C), 117.5 (d), 113.6 (d, 2 C), 98.0 (d), 66.2 (d), 62.8 (d), 59.0 (d), 51.0 (d), 43.5 (s), 42.3 (d), 41.0 (t), 36.1 (t), 29.8 (t), 28.8 (t), 28.2 (t), 24.6 (t), 22.1 (t), 11.9 (q); MS *m*/*z* (%): 350 (M^+, 15), 236 (42), 218 (36), 137 (32), 132 (100), 91 (98); IR ($CDCl_3$): 3001, 1629, 1601, 1579 cm^{-1}.

(+)-17β-(*N*-phenylamino)-(5β)-10-azaestr-1-en-3-one (3b). To a solution of **12** (570 mg, 1.33 mmol), 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (518 μL, 2.66 mmol) and Et_3N (408 μL, 2.93 mmol) in anhydrous CH_2Cl_2 (9 mL) cooled at 0 °C was added dropwise TMSOTf (411 μL, 2.13 mmol). The solution was allowed to warm to rt and left under stirring for 45 min. Satd $NaHCO_3$ (9 mL) was then added and the mixture vigorously stirred for 36 h. After separation of the phases, the product was extracted with CH_2Cl_2 (3×9 mL) and the combined organic layers dried over Na_2SO_4. Filtration and evaporation of the solvent afforded crude **3b**, which was purified by flash chromatography, eluting with CH_2Cl_2–MeOH, 30:1. Pure **3b** was obtained (R_f = 0.69) as a pale yellow solid (94 mg, 20%). **3b**: mp 98–100 °C; $[\alpha]_D^{25}$ +103.2 (*c* 0.76, $CHCl_3$). ^1H NMR ($CDCl_3$, δ ppm): 7.22–7.09 (m, 3H), 6.70–6.61 (m, 3H), 4.91 (d, *J* = 7.4 Hz, 1H, 2-H), 3.78 (m, 1H, 5-H), 3.55 (s br, 1H), 3.43 (t, *J* = 8.4 Hz, 1H), 3.23 (m, 1H), 2.30 (m, 1H), 2.03 (m, 2H), 1.95–1.10 (m, 13H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 191.1 (s), 149.5 (s), 148.1 (d), 129.1 (d, 2 C), 117.0 (d), 113.1 (d, 2 C), 96.5 (d), 62.7 (d), 59.6 (d), 53.1 (d), 52.2 (d), 43.3 (t), 42.3 (t), 36.0 (t), 35.7 (d), 29.9 (t), 26.2 (t), 25.6 (t), 23.7 (t), 22.6 (t), 11.9 (q); MS *m*/*z* (%): 350 (M^+, 38), 284 (8), 132 (100), 105 (11), 77 (21); IR ($CDCl_3$): 3695, 2930, 2855, 1600, 1253 cm^{-1}. Elem. Anal. calcd for $C_{23}H_{30}N_2O$: C, 78.82; H, 8.63; N, 7.99. Found: C, 78.50; H, 9.12; N, 7.26.

17β-[(*N*-phenyl)benzamido]-10-azaestr-1-en-3-one (5). Prepared as described for **3b**, starting from **11** (799 mg, 1.5 mmol) but obtaining **5** as a 1.5:1 mixture of **5a**(5α)/**5b**(5β) diastereoisomers. Purification of the mixture by flash chromatography (eluant: acetone) afforded pure **5a** (R_f = 0.58; 95 mg, 14%) and **5b** (R_f = 0.29; 89 mg, 13%). **5a**: mp 109–110 °C; $[\alpha]_D^{25}$ −20.6 (*c* 0.04, $CHCl_3$).

^{1}H NMR ($CDCl_3$, δ ppm): 7.22–6.95 (m, 11H), 4.97 (d, J = 7.8 Hz, 1H, 2-H), 4.78 (m, 1H), 3.40 (m, 1H, 9-H), 2.69 (m, 1H, 5-H), 2.56 (dd, J = 17.2, 6.2 Hz, 1H), 2.29 (dd, J = 16.2, 8.8 Hz, 1H), 2.02–1.19 (m, 14H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 191.8 (s), 173.1 (s), 148.8 (d), 141.8 (d), 137.7 (s), 131.3 (d, 2 C), 128.9 (d), 128.6 (d, 2 C), 127.9 (d, 2 C), 127.6 (d, 2 C), 127.3 (d), 98.6 (d), 66.5 (d), 65.4 (d), 59.0 (d), 50.2 (d), 45.4 (s), 42.6 (d), 40.9 (t), 36.3 (t), 30.5 (t), 28.7 (t), 25.3 (t), 24.8 (t), 22.2 (t), 13.7 (q); MS m/z (%): 454 (M^+, 2), 349 (3), 105 (65), 84 (100), 77 (22); IR ($CDCl_3$): 1708, 1636, 1579, 1466 cm^{-1}. **5b**: mp 92–93 °C; $[\alpha]_D^{25}$ +73.4 (c 0.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ ppm): 7.25–6.95 (m, 11H), 4.91 (d, J = 7.6 Hz, 1H, 2-H), 4.78 (t, J = 9.9 Hz, 1H), 3.76 (m, 1H, 5-H), 3.26 (td, J = 10.6, 4.4 Hz, 1H, 9-H), 2.50–2.20 (m, 2H), 2.10–1.90 (m, 2H), 1.90–1.00 (m, 12H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 198.0 (s), 173.1 (s), 149.6 (d), 141.8 (s), 135.7 (s), 131.3 (d, 2 C), 128.9 (d), 128.6 (d, 2 C), 128.0 (d, 2 C), 127.6 (d, 2 C), 127.3 (d), 96.6 (d), 65.3 (d), 59.5 (d), 53.2 (d), 51.8 (d), 45.3 (s), 42.5 (d), 36.3 (t), 35.5 (t), 30.9 (t), 26.3 (t), 25.7 (t), 23.6 (t), 22.2 (t), 13.7 (q); MS m/z (%): 454 (M^+, 12), 105 (100), 77 (32); IR ($CDCl_3$): 1709, 1631, 1571, 1355 cm^{-1}.

(−)-17β-[(*N*-phenyl)acetamido]-(5α)-10-azaestr-1-en-3-one (4a). To a solution of **3a** (15 mg, 0.04 mmol) in pyridine (750 μL) cooled at 0 °C was added dropwise Ac_2O (30 μL, 0.27 mmol). The solution was allowed to warm to rt and left under stirring for 18 h. Water was added (5 mL) and the product extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were then washed with 5% citric acid (10 mL), 10% $NaHCO_3$ (10 mL), H_2O (10 mL) and dried over Na_2SO_4. Filtration and evaporation of the solvent afforded **4a** (15 mg, 95%). **4a**: mp 72–74 °C; $[\alpha]_D^{25}$ −114.3 (c 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ ppm): 7.35 (m, 3H), 7.18 (d, J = 7.9 Hz, 1H, 1-H), 6.98 (m, 2H), 4.96 (d, J = 7.9 Hz, 1H, 2-H), 4.59 (t, J = 9.7 Hz, 1H), 3.40 (m, 1H, 9-H), 2.60 (m, 1H, 5-H), 2.63 (dd, J = 16.5, 6.6 Hz, 1H), 2.28 (dd, J = 16.5, 8.8 Hz, 1H), 1.94 (m, 1H), 1.80–1.00 (m, 13H), 1.71 (s, 3H), 0.70 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 191.8 (s), 172.4 (s), 148.8 (d), 141.7 (s), 131.2 (d), 130.5 (d), 129.2 (d, 2 C), 128.1 (d), 98.5 (d), 66.1 (d), 64.2 (d), 59.0 (d), 50.1 (d), 45.2 (s), 42.6 (d), 41.3 (t), 36.5 (t), 34.1 (t), 29.7 (t), 25.5 (t), 22.6 (t), 22.3 (q), 22.1 (t), 14.0 (q); MS m/z (%): 392 (M^+, 34), 132 (100), 83 (44); IR ($CDCl_3$): 1715, 1640, 1585 cm^{-1}.

(+)-17β-[(*N*-phenyl)acetamido]-(5β)-10-azaestr-1-en-3-one (4b). As described for **4a**, starting from **3b** (7 mg, 0.02 mmol) and obtaining **4b** (8 mg, quantitative) as a pale yellow solid. **4b**: mp 95–96 °C; $[\alpha]_D^{25}$ +150.0 (c 0.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ ppm): 7.35–6.95 (m, 6H), 4.91 (d, J = 7.3 Hz, 1H, 2-H), 4.58 (t, J = 9.8 Hz, 1H), 3.76 (m, 1H, 5-H), 3.20 (m, 1H, 9-H), 2.40–2.00 (m, 4H), 1.71 (s, 3H), 1.90–0.75 (m, 12H), 0.66 (s, 3H); ^{13}C NMR ($CDCl_3$, δ ppm): 195.6 (s), 172.4 (s), 149.6 (d), 141.6 (s), 130.5 (d, 2 C), 129.2 (d, 2 C), 128.1 (d), 96.5 (d), 64.1 (d), 59.4 (d), 53.2 (d), 51.7 (d), 43.3 (s), 42.4 (d), 36.1 (t), 35.4 (t), 29.7 (t), 26.1 (t), 25.4 (t), 23.6 (t), 22.1 (t), 19.1 (q), 13.3 (q); MS m/z (%): 392 (M^+, 1), 149 (8), 86 (59), 84 (100); IR ($CDCl_3$): 3692, 1639, 1574 cm^{-1}.

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