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Synthesis of 4,17-Diazasteroid Inhibitors of Human 5α-Reductase

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Abstract—The synthesis of the 17-aza isomer of finasteride is described. With the side chain amide group of the compound existing in the *Z* configuration the structure is similar to one of the two favored conformations of finasteride. A series of 4.17-diazasteroids was assayed against the isoenzymes of human 5α-reductase. Copyright © 1996 Elsevier Science Ltd

Introduction

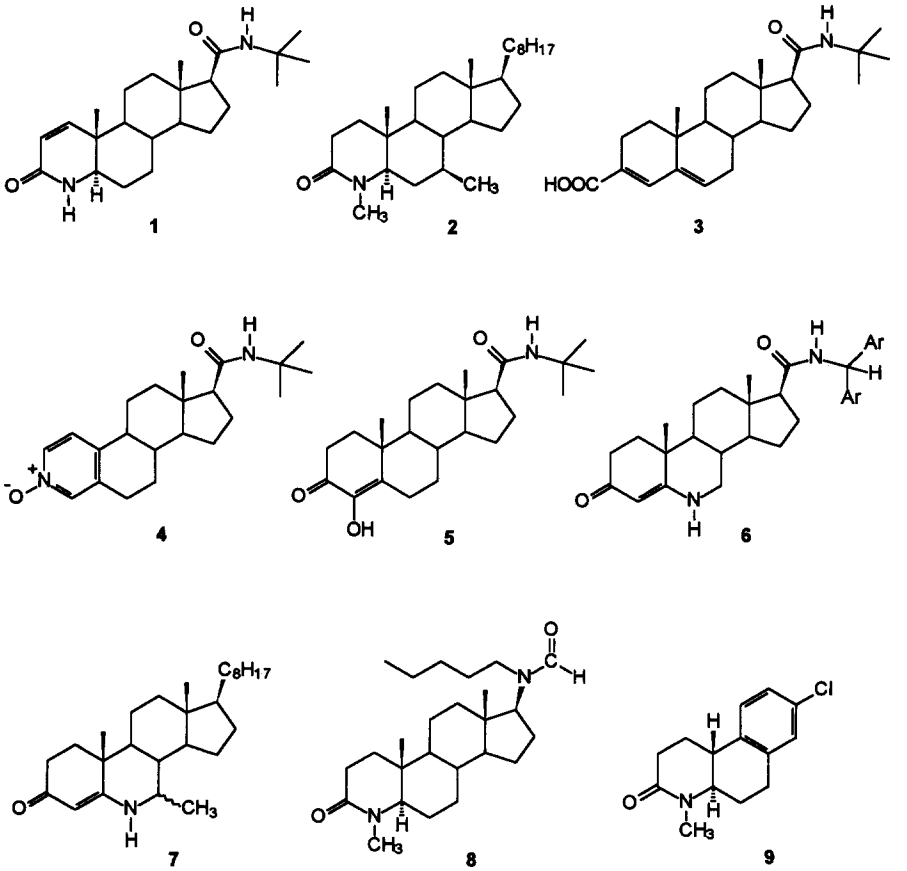
Steroid 5α-reductase (EC 1.3.99.5) is the enzyme responsible for the NADPH-dependent conversion of testosterone to the more potent androgen dihydrotestosterone (DHT). There exist two isoenzymes[1–3] of 5α-reductase, type 1 and type 2, that are differentially expressed in various tissues such as skin, liver, prostate, seminal vesicle, and epididymis.[4] The permissive role of DHT[1,5] in benign prostatic hyperplasia, the most common neoplastic disease of aging men, is well established and DHT is also important in the viability of androgen-responsive cancer cells. These physiological roles for DHT have contributed to the interest in finding potent 5α-reductase inhibitors.

A number of 4-azasteroids, including finasteride **1**, are potent type 2 inhibitors[6,7] but 4,7β-dimethyl-4-azacholestan-3-one (**2**) and related 4-azacholestanes are selective type 1 inhibitors.[8] Epristeride **3**, an unsaturated 3-carboxysteroid, is a potent type 2 5α-reductase inhibitor[9] and is active in models of prostatic cancer.[10] To the same group of type 2 selective inhibitors belong 3-pyridyl-*N*-oxide steroids (e.g., **4**)[11] and 4-substituted-3-oxo-Δ^4-steroids (e.g., **5**).[12] In addition, the latter compounds reduce the DHT-stimulated proliferation of androgen-sensitive Shionogi cells. Recent reports have described dual inhibition of both 5α-reductases by a series of 6-azasteroids (e.g., **6** and **7**).[13,14] *N*-Amyl substituted 17β-formamide **8**[15] has appeared to be one of the most potent inhibitors of human type 1 5α-reductase known so far. Nonsteroidal inhibitors (e.g., **9**) of type 1 5α-reductase have also been described.[16] Probably all compounds mentioned above inhibit the enzyme because of their structural resemblance to the A-ring enol that is a presumed intermediate in the reduction of testosterone.[6,9,17] A common structural feature of the type 2 5α-reductase inhibitors is a 17β-carboxamide side chain substituted by a compact lipophilic residue.

Results and Discussion

In this communication we report the synthesis of finasteride isomer **18a** and its derivatives with the amide nitrogen atom on the opposite side (compared with finasteride **1**) of the 20-carbonyl group (i.e., 4,17-diazasteroids). Some 17-azasteroids (such as **10**) have already been described as 'inverted' 5α-reductase inhibitors.[18] These are, however, *N*-methyl-D-homo lactams with an amide side chain at the modified ring A. Our synthesis of 4,17-diazasteroids required prior preparation of 17-aza lactam **11**,[19] which was then reduced with lithium aluminum hydride to the secondary amine **12** followed by *N*-acylation with 3,3-dimethylbutyryl chloride. Oppenauer oxidation of the 3β-hydroxy compound **13** afforded α,β-unsaturated ketone **14**. Further transformations were performed in a way similar to that described for finasteride **1** and its derivatives.[6] Compound **14** was oxidized with $KMnO_4$/$NaIO_4$ to *seco*-acid **15** which was then subjected to ring closure with ammonia at high temperature to give the unsaturated lactam **16**. The reduction of the C(5)—C(6) double bond was achieved by the method recently communicated by our group ($NaBH_4$/*p*-TsOH).[20] The addition of catalytic amounts of *p*-TsOH activates the enamide moiety to the borohydride reduction. The stereoselectivity (>85% of the 5α-H epimer **17a** established by integration of signals in the ^1H NMR spectrum of the crude product) of reduction was as good as in the commonly used hydrogenation[21] over a platinum catalyst. To complete the synthesis of the finasteride isomer **18a** 1-dehydrogenation was performed by silylation-mediated [bis(trimethylsilyl)trifluoroacetamide was used] DDQ oxidation.[22,23] 4-Methyl derivatives of 4,17-diaza lactams (**17b** and **18b**) were also obtained by CH_3I/NaH methylation.

The conformation of the amide side chain needs some comment. Molecular mechanics calculations (MM+ force field)[24] suggest that the finasteride 17-aza isomer



Scheme 1.

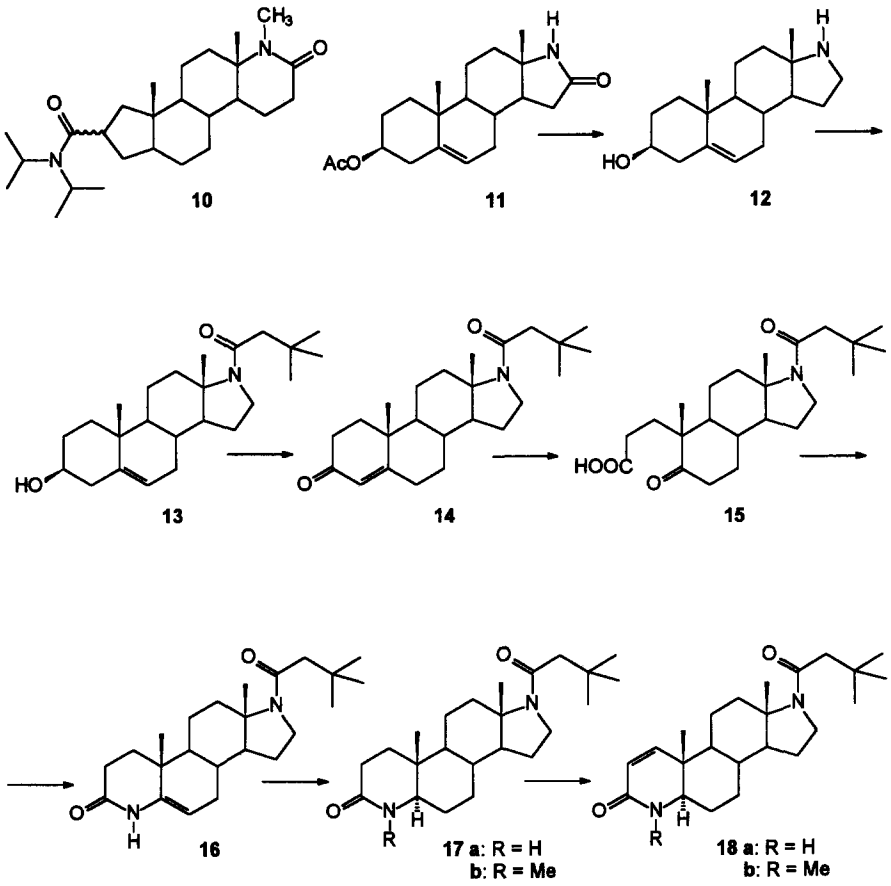
18a preferentially exists in the *Z* configuration with the torsion angle C(13)—N—C(20)—O close to zero (Fig. 1). Significant contribution of this configuration was proved by ^{1}H NMR spectra of compounds **13–18** where 12β-H is strongly deshielded (δ 3.0–3.1 ppm)[25] by the nearby amide carbonyl group. The alternative *E* configuration (Fig. 2) is less stable by 5.7 kcal/mol and is virtually without significance. The preference of the *Z* configuration in **18a** was also confirmed by ^{1}H NOE difference spectroscopy. Upon irradiation of the side chain methylene protons, a 2.2% enhancement of the 16β-H signal at δ 3.53 and a 1.0% enhancement of the 16α-H signal at δ 3.42 were observed. There was also enhancement at δ 1.05 (*t*-butyl protons), but no detectable NOE effect was found for 12β-H. In the ^{1}H 2D NOESY spectrum of **18a** two cross-peaks between the methylene group and both protons at C-(16) were present, whereas no spatial interaction of the side chain protons with 12β-H was found. This excludes the existence of *E* configuration with a short distance between 12β-H and one of the methylene group protons (about 2.05 Å).

The preference of the *Z* configuration of the amide moiety was found in finasteride **1** [torsion angle O—C(20)—N—C(*t*-butyl) amounts 8.3° and other unsymmetrically substituted side chain amides. There are two favored, almost equally populated conformations about the C(17)—C(20) bond in a series of 20-carboxylic amides (see Table 1). In the case of unsubstituted and monosubstituted amides the amide plane is deviated from the ring D plane by 20–25° for one conformation and by 110–115° for another. The amide group of disubstituted amides may lie in the ring D plane or be perpendicular to it.

As shown in Figure 3, the preferred side chain conformation of the 17-aza isomer is similar to one of the favored finasteride conformations. However, there is more restriction in the side chain rotation in the 17-aza isomer than in the case of finasteride itself.

A series of 4,17-diazasteroids was assayed against both type 1 and type 2 5α-reductase. The methods employed for determining enzyme inhibition data (Table 2) were as previously described.[13]

The finasteride 17-aza isomer **18a** proved to be quite a potent inhibitor of type 2 5α-reductase, although it is less active than finasteride **1** and its congeners. It seems that the conformation found in **18a** is not optimal for the inhibitory activity. Compound **17b** was found to be an inhibitor of both type 1 and type 2 5α-reductases. The results of assays performed show that 4-methylation increases activity in the case of compound **17**, but lowers the inhibition of the type 2 enzyme by the Δ^1 derivative **18**. Compound **16** with a C(5)—C(6) double bond shows only moderate inhibition of human type 2 5α-reductase activity. These results are consistent with general rules established for



Scheme 2.

the 4-azasteroid derivatives.[6] The 4-methyl azasteroids are more active than the unsubstituted analogues when the A ring is saturated, the reverse is true for the Δ^1 derivatives. Unsaturation at C5(6) resulted in reduced 5α-reductase inhibitory activity.

We are pursuing synthetic chemistry towards new azasteroid inhibitors of 5α-reductase.

Experimental

Melting points were determined on a Köffler apparatus of the Boetius type and were uncorrected. NMR spectra were taken with a Bruker AC 200F and a Varian UNITYplus-500 spectrometers using $CDCl_3$ solutions with TMS as the internal standard. IR spectra were recorded on a Specord 75 IR spectrophotometer as chloroform solutions. Mass spectra were obtained at 70 eV with an AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on 70–230 or 230–400 mesh silica gel (Merck). Thin-layer chromatograms were developed on aluminum TLC sheets precoated with silica gel F_{254} and visualized with 50% sulfuric acid after heating. All solvents were dried and freshly distilled prior to use.

Type 1 and type 2 recombinant human 5α-reductase assays were carried out as previously described.[13]

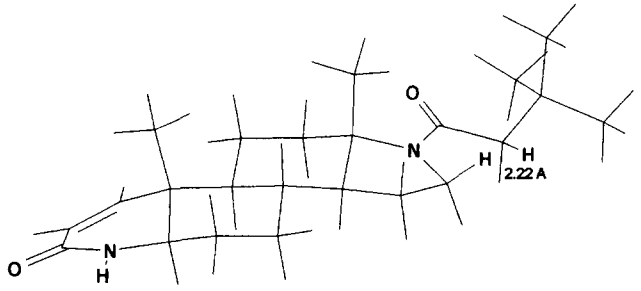


Figure 1. Configuration *Z* of the finasteride 17-aza isomer **18a** with the shortest H—H contact shown.

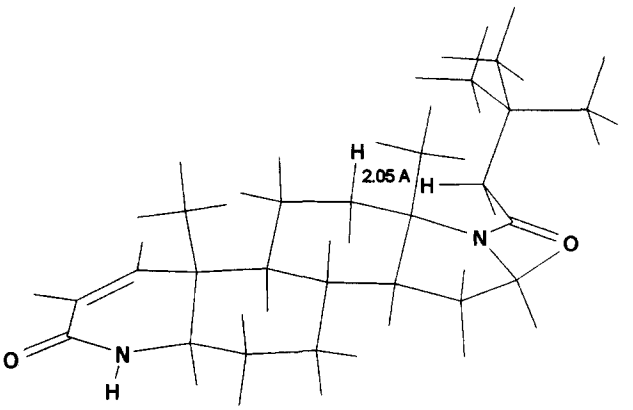


Figure 2. Configuration *E* of the finasteride 17-aza isomer **18a** with the shortest H—H contact shown.

Table 1. Least energy conformations of 5α-reductase inhibitors

	Steric energy of conformation (kcal/mol); torsion angle C(13)—C(17)—C(20)—O		$\Delta E_{(I-II)}$ (kcal/mol)	Human prostatic 5α-reductase[b] IC_{50}/IC_{50} Fin.
	I	II		
$R_1=R_2=H$	27.9; −19.9°	27.5; 115.8°	0.4	151
$R_1=C_2H_5$; $R_2=H$	29.1; −24.1°	28.3; 112.4°	0.8	27
$R_1=C(CH_3)_3$; $R_2=H$ (Fin.)	32.9; −25.9°	31.6; 115.4°	1.3	1
$R_1=C(CH_3)_2CH_2C(CH_3)_3$; $R_2=H$	42.9; −23.1°	41.9; 111.5°	1.0	2.2
$R_1=R_2=C_2H_5$	37.5; −1.7°	37.3; 93.5°	0.2	11
$R_1=R_2=CH(CH_3)_2$	40.5; 0.6°	40.6; 90.7°	−0.1	2.9
Finasteride 17-aza isomer	35.7; −0.9° [a]	41.4; 177° [a]	−5.7	16[b]

[a]Torsion angle C(13)—N—C(20)—O.
[b]Calculated on the basis of type 2 recombinant human 5α-reductase assays.

17-(3,3-Dimethylbutyryl)-17-azaandrost-5-en-3β-ol (13). To a suspension of $LiAlH_4$ (550 mg, 14.5 mmol) in anhydrous dioxane (100 mL), lactam **11** (1.03 g; 3.1 mmol) was added and the reaction mixture was refluxed for 2 days. The reaction was carefully quenched with stoichiometric amount of water (1.05 mL, 58.3 mmol) and to the resulting solution of amine **12**, 3,3-dimethylbutyryl chloride (1.5 mL, 10.7 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature, all inorganic material was filtered off, and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography. Amide **13** (840 mg; 72%) was eluted with benzene:ethyl acetate (3:1) preceded by small amounts of its *O*-3,3-dimethylbutyryl derivative (18 mg; 1%). Amide **13**; mp 214–217°C (hexane:methylene chloride); IR ($CHCl_3$ cm^{-1}): 3610, 3400, 1609, 1403, 1045; ^1H NMR: δ 5.35 (m, 1H, 6-H), 3.33–3.66 (m, 3H, 3α-H and 16-H), 3.06 (m, 1H, 12β-H), 2.06 and 2.10 (AB system, $J=13.9$ Hz, 2H, CH_2-*t*-Bu), 1.15 (s, 3H, 18-H), 1.05 (s, 9H, *t*-Bu), 1.02 (s, 3H, 19-H); ^{13}C NMR: δ 171.0 (C), 141.4 (C), 120.7 (CH), 71.6 (CH), 62.9 (C), 54.8 (CH), 50.2 (CH), 47.8 (CH_2), 47.2 (CH_2), 42.2 (CH_2), 37.4 (CH_2), 37.2 (CH_2), 36.6 (C), 31.6 (C), 31.44 (CH), 31.35 (C), 30.0 ($3\times CH_3$), 29.7 (CH_2), 24.6 (CH_2), 21.9 (CH_2), 19.3 (CH_2), 15.6 (CH_2); MS: *m/z* (rel. int.) 373 (11), 358 (16), 317 (17), 302 (15), 284 (13), 274 (7), 260 (100).

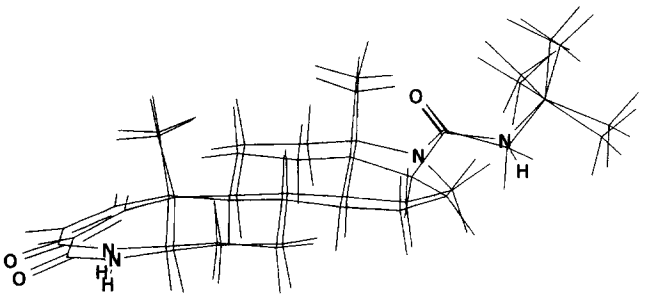


Figure 3. RMS overlay of finasteride **1** (conformation I) and its 17-aza isomer **18a**.

17-(3,3-Dimethylbutyryl)-17-azaandrost-4-en-3-one (14). From a solution of amide **13** (820 mg, 2.2 mmol) in toluene (30 mL) and cyclohexanone (5 mL), ca. 10 mL

Table 2. Inhibition of recombinant type 1 and type 2 human 5α-reductase by 4,17-diazasteroids (IC_{50}s with the standard deviations from the fitted lines in parentheses)

Compound no.	Type 1 5α-reductase IC_{50} (nM)	Type 2 5α-reductase IC_{50} (nM)
16	~7000	52.0 (±7.8)
17a	2200 (±140)	40.1 (±2.8)
17b	28.0 (±2.1)	3.6 (±0.3)
18a	765 (±70)	10.3 (±1.1)
18b	477 (±29)	174 (±42)
4-MA[a]	6.4 (±0.2)	0.4 (±0.04)

[a]*N,N*-Diethyl-3-oxo-4-methyl-4-aza-5α-androstane-17β-carboxamide (**4-MA**) was used as a standard reference.

of the solvent was distilled off and then aluminum tri-*iso*-propoxide (400 mg, 1.96 mmol) in anhydrous toluene (5 mL) was added dropwise. The reaction mixture was gently boiled during 1 h, while another 10 mL of the solvent was distilled off. After cooling, 20 mL of saturated solution of sodium potassium tartrate was added, and the organic solvents were removed by steam distillation. The reaction mixture was diluted with water, extracted with chloroform, and the dried (anhydrous $MgSO_4$) extract was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (elution with 25% ethyl acetate:benzene). Yield of **14**: 675 mg (83%); mp 152–155 °C (hexane:methylene chloride); IR ($CHCl_3$, cm^{-1}): 1700, 1610, 1402, 1196; ^1H NMR: δ 5.74 (m, 1H, 4-H), 3.35–3.63 (m, 2H, 16-H), 3.04 (m, 1H, 12β-H), 2.06 and 2.10 (AB system, $J = 13.9$ Hz, 2H, $C\underline{H}_2$-*t*-Bu), 1.19 (s, 3H, 19-H), 1.17 (s, 3H, 18-H), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR: δ 199.3 (C), 170.3 (2 × C), 124.0 (CH), 62.7 (C), 54.0 (CH), 53.6 (CH), 47.7 (CH_2), 47.1 (CH_2), 38.5 (C), 37.2 (CH_2), 35.6 (CH_2), 34.8 (CH), 33.8 (CH_2), 32.5 (CH_2), 31.44 (CH_2), 31.38 (C), 29.9 (3 × CH_3), 24.4 (CH_2), 21.8 (CH_2), 17.1 (CH_3), 15.6 (CH_3); MS: *m/z* (rel. int.) 371 (16), 356 (15), 315 (33), 301 (18), 272 (4), 258 (100); HRMS: *m/z* calcd for $C_{24}H_{37}O_2N$ $[M]^+$, 371.2824. Found: 371.2822.

17-(3,3-Dimethylbutyryl)-4-nor-3,5-*seco*-5-oxo-17-aza-androstan-3-oic acid (15). To a stirred solution of compound **14** (660 mg, 1.78 mmol) in *tert*-butanol (10 mL) was added 1.5 mL of hot aqueous solution of sodium carbonate (0.3 g). The reaction mixture was heated at reflux,[26] while a warm aqueous solution (1.5 mL) of $NaIO_4$ (3.2 g, 14.96 mmol) and $KMnO_4$ (40 mg, 0.25 mmol) was added portionwise. After addition of the last portion of the oxidizing agents, the reaction was refluxed for another 1 h. All inorganic material was filtered off, and washed with water and chloroform. The filtrate was acidified with diluted hydrochloric acid and extracted with chloroform. The solvent was removed from the dried (anhydrous $MgSO_4$) extract in vacuo and the residue was purified by silica gel column chromatography. *seco*-Acid **15** (497 mg, 71%) was eluted with benzene:ethyl acetate (1:9); mp 58–60° C (hexane:benzene); IR ($CHCl_3$, cm^{-1}): 1692, 1614, 1403, 1201; ^1H NMR: δ 7.55 (bs, 1H, COOH), 3.35–3.65 (m, 2H, 16-H), 3.04 (m, 1H, 12β-H), 2.54 (m, 1H, 2-H), 2.15 and 2.19 (AB system, $J = 13.9$ Hz, 2H, $C\underline{H}_2$-*t*-Bu), 1.20 (s, 3H, 19-H), 1.12 (s, 3H, 18-H), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR: δ 200.3 (C), 178.1 (C), 171.8 (C), 63.5 (C), 54.0 (CH), 50.2 (C), 47.9 (CH_2), 47.7 (CH), 46.8 (CH_2), 37.6 (CH_2), 36.9 (CH_2), 34.1 (CH), 31.8 (C), 30.6 (CH_2), 30.0 (3 × CH_3), 29.1 (CH_2), 28.9 (CH_2), 24.3 (CH_2), 22.2 (CH_2), 20.1 (CH_3), 15.8 (CH_3); MS: *m/z* (rel. int.) 391 (12), 376 (15), 335 (23), 320 (4), 303 (9), 278 (100); HRMS: *m/z* calcd for $C_{23}H_{37}O_4N$ $[M]^+$, 391.2723. Found: 391.2723.

17-(3,3-Dimethylbutyryl)-4,17-diazaandrost-5-en-3-one (16). To a stirred suspension of *seco*-acid **15** (440 mg, 1.13 mmol) in ethylene glycol (6 mL) liquid ammonia (2 mL) was added dropwise. The homogeneous solution was then gradually heated (3 °C/min) to 180 °C and held at 180 °C for 15 min. After cooling, the mixture was acidified with diluted hydrochloric acid and extracted with chloroform. The extract was washed three times with water, dried (anhydrous $MgSO_4$), and evaporated in vacuo. The crude product **16** was purified by silica gel column chromatography (elution with 3% methanol:chloroform). Yield 326 mg (78%); mp 222–225 °C (benzene); IR ($CHCl_3$ cm^{-1}): 3408, 1662, 1631, 1416, 1210; ^1H NMR: δ 8.58 (*s*, 1H, NH), 4.93 (m, 1H, 6-H), 3.32–3.60 (m, 2H, 16-H), 3.06 (m, 1H, 12β-H), 2.47 (m, 2H, 2-H), 2.06 and 2.10 (AB system, $J = 13.8$ Hz, 2H, $C\underline{H}_2$-*t*-Bu), 1.17 (s, 3H, 19-H), 1.10 (s, 3H, 18-H), 1.05 (s, 9H, *t*-Bu); ^{13}C NMR: δ 171.1 (C), 170.0 (C), 140.2 (C), 102.8 (CH), 68.4 (C), 62.8 (C), 54.4 (CH), 47.9 (CH), 47.7 (CH_2), 47.1 (CH_2), 37.0 (CH_2), 34.1 (C), 31.4 (CH_2), 31.0 (CH), 29.9 (3 × CH_3), 29.1 (CH_2), 28.2 (CH_2), 24.4 (CH_2), 21.6 (CH_2), 18.5 (CH_3), 15.6 (CH_3); MS: *m/z* (rel. int.) 372 (18), 357 (10), 316 (18), 301 (42), 273 (6), 259 (100); HRMS: *m/z* calcd for $C_{23}H_{36}O_2N_2$ $[M]^+$, 372.2777. Found: 372.2777.

17-(3,3-Dimethylbutyryl)-4,17-diaza-5α-androstan-3-one (17a). A stirred solution of diazasteroid **16** (180 mg, 0.48 mmol) in THF (20 mL) was treated with concd sulfuric acid (0.08 mL, 1.52 mmol) and $NaBH_4$ (600 mg, 15.8 mmol). Borohydride was added portionwise during 5 h and stirring was continued for another 1 h. The reaction was quenched with water and extracted with chloroform. The solvent was evaporated from the dried (anhydrous $MgSO_4$) extract and the residue was chromatographed on a silica gel column. The pure product **17a** (96 mg; 53%) was eluted with 3% methanol:chloroform preceded by fraction (23 mg) containing **17a** and its 5β-epimer; mp 285–288 °C (benzene); IR ($CHCl_3$, cm^{-1}): 3406, 1640, 1621, 1396; ^1H NMR: δ 6.00 (bs, 1H, NH), 3.32–3.60 (m, 2H, 16-H), 3.06 (m, 2H, 5α-H and 12β-H), 2.40 (m, 2H, 2-H), 2.06 and 2.10 (AB system, $J = 13.8$ Hz, 2H, $C\underline{H}_2$-*t*-Bu), 1.13 (s, 3H, 18-H), 1.05 (s, 9H, *t*-Bu), 0.90 (s, 3H, 19-H); ^{13}C NMR: δ 172.4 (C), 170.9 (C), 63.1 (C), 60.6 (CH), 54.0 (CH), 51.3 (CH), 47.7 (CH_2), 47.1 (CH_2), 37.3 (CH_2), 35.6 (C), 34.3 (CH), 33.2 (CH_2), 31.4 (C), 29.9 (3 × CH_3), 29.1 (CH_2), 28.5 (CH_2), 27.0 (CH_2), 24.3 (CH_2), 21.9 (CH_2), 15.7 (CH_3), 11.2 (CH_3); MS: *m/z* (rel. int.) 374 (10), 359 (11), 318 (28), 303 (8), 275 (4), 261 (100); HRMS: *m/z* calcd for $C_{23}H_{38}O_2N_2$ $[M]^+$, 374.2933. Found: 374.2931.

17-(3,3-Dimethylbutyryl)-4,17-diaza-5α-androst-1-en-3-one (18a). A stirred solution of compound **17a** (87 mg, 0.23 mmol) in anhydrous dioxane (1 mL) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (60 mg; 0.26 mmol) and bis(trimethylsilyl)trifluoroacetamide (0.3 mL, 1.11 mmol) under N_2. The reaction mixture was stirred at room temperature for 4 h and then at 110 °C for 18 h. The resulting dark solution was diluted with methylene chloride, washed with 2% aqueous sodium bisulfite solution, 2 N hydrochloric acid, water, dried (anhydrous $MgSO_4$) and evaporated.

The crude product **18a** was purified by silica gel column chromatography (elution with 3% methanol: chloroform). Yield 66 mg (76%), mp 245–248°C (benzene); IR ($CHCl_3$, cm^{-1}): 3432, 1671, 1624, 1412; ^1H NMR: δ 6.79 (d, $J=10.0$ Hz, 1H, 1-H), 5.90 (broad signal, 1H, NH), 5.81 (dd, $J=10.0$ Hz, 1.9 Hz, 1H, 2-H), 3.53 (t, $J=9.5$ Hz, 1H, 16β-H), 3.42 (ddd, $J=9.7$ Hz, 9.5 Hz, 7.5 Hz, 1H, 16α-H), 3.35 (dd, $J=11.5$, 4.6 Hz, 1H, 5α-H), 3.09 (m, 1H, 12β-H), 2.06 and 2.11 (AB system, $J=13.7$ Hz, 2H, $C\underline{H}_2$-*t*-Bu), 1.14 (s, 3H, 18-H), 1.05 (s, 9H, *t*-Bu), 0.98 (s, 3H, 19–H); ^{13}C NMR: δ 171.1 (C), 166.6 (C), 150.7 (CH), 123.1 (CH), 63.1 (C), 59.6 (CH), 54.0 (CH), 47.7 (CH_2 and CH), 47.2 (CH_2), 39.4 (C), 37.4 (CH_2), 34.6 (CH), 31.4 (C), 30.0 ($3\times CH_3$), 29.1 (CH_2), 25.8 (CH_2), 24.4 (CH_2), 22.1 (CH_2), 15.8 (CH_3), 11.9 (CH_3); MS: *m/z* (rel. int.) 372 (10), 357 (12), 316 (31), 301 (24), 273 (4), 259 (100); HRMS: *m/z* calcd for $C_{23}H_{36}O_2N_2$ $[M]^+$, 372.2777. Found: 372.2777; Anal. calcd for $C_{23}H_{36}O_2N_2$: C, 74.15; H, 9.74; N, 7.52. Found: C, 74.04; H, 9.79; N, 7.56.

17-(3,3-Dimethylbutyryl)-4-methyl-4,17-diaza-5α-androstan-3-one (17b) and its 1-dehydro derivative 18b. A solution of diazasteroid (**17a** or **18a**; 37 mg, 0.1 mmol) in anhydrous DMF (3 mL) was treated with NaH (60% suspension in oil; 10 mg, 0.25 mmol). The reaction mixture was stirred at room temperature for 15 min, then methyl iodide (0.2 mL, 3.21 mmol) was added and stirring was continued for 1 h at 40 °C. The mixture was poured into water, acidified and extracted with chloroform. The crude products (**17b** or **18b**) were purified by silica gel column chromatography (elution with 3–4% methanol:chloroform). Yield of **17b** 35 mg (92%), mp 199–203 °C (hexane:methylene chloride); IR ($CHCl_3$, cm^{-1}): 1623, 1431; ^1H NMR: 3.32–3.60 (m, 2H, 16-H), 3.05 (m, 2H, 5α-H and 12β-H), 2.93 (m, 3H, N—CH_3), 2.45 (m, 2H, 2-H), 2.06 and 2.10 (AB system, $J=13.85$ Hz, 2H, $C\underline{H}_2$-*t*-Bu), 1.13 (s, 3H, 18-H), 1.05 (s, 9H, *t*-Bu), 0.89 (s, 3H, 19-H); ^{13}C NMR: δ 171.0 (C), 170.7 (C), 65.6 (CH), 63.1 (C), 54.0 (CH), 51.9 (CH), 47.8 (CH_2), 47.1 (CH_2), 37.4 (CH_2), 36.4 (C), 33.6 (CH), 32.8 (CH_2), 31.4 (C), 30.0 ($3\times CH_3$), 29.8 (CH_2), 29.1 (CH_3), 29.0 (CH_2), 25.2 (CH_2), 24.3 (CH_2), 21.9 (CH_2), 15.7 (CH_3), 12.2 (CH_3); MS: *m/z* (rel. int.) 388 (12), 373 (13), 332 (28), 317 (10), 289 (4), 275 (100). HRMS: *m/z* calcd for $C_{24}H_{40}O_2N_2$ $[M]^+$, 388.3090. Found: 388.3091. Yield of **18b** 34 mg (89%); mp 169–172 °C (hexane:methylene chloride); IR ($CHCl_3$, cm^{-1}): 1658, 1620, 1417, 1203, 1102; ^1H NMR: δ 6.66 (d, $J=$ 9.8 Hz, 1H, 1-H), 5.83 (d, $J=$ 9.8 Hz, 1H, 2-H), 3.30–3.60 (m, 3H, 5α-H and 16-H), 3.05 (m, 1H, 12β-H), 2.93 (s, 3H, N—CH_3), 2.06 and 2.10 (AB system, $J=13.8$ Hz, 2H, $C\underline{H}_2$-*t*-Bu), 1.11 (s, 3H, 18-H), 1.01 (s, 9H, *t*-Bu), 0.89 (s, 3H, 19-H); ^{13}C NMR: δ 171.0 (C), 165.5 (C), 140.4 (CH), 123.2 (CH), 63.6 (CH), 62.9 (C), 53.8 (CH), 47.8 (CH), 47.6 (CH_2), 47.0 (CH_2), 39.5 (C), 37.3 (CH_2), 33.9 (CH), 31.4 (C), 29.9 ($3\times CH_3$), 29.5 (CH_2), 27.6 (CH_3), 24.3 (CH_2), 24.2 (CH_2), 22.0 (CH_2), 15.7 (CH_3), 12.0 (CH_3); MS: *m/z* (rel. int.) 386 (14), 371 (12), 330 (29), 315 (29), 287 (5), 273 (100); HRMS: *m/z* calcd for $C_{24}H_{38}O_2N_2$ $[M]^+$, 386.2933. Found: 386.2933.

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24. Molecular modeling was performed with HyperChem™ Release 4 from Hypercube, Inc. Minimizations employed the MM+ force field (Polak-Ribiere algorithm). RMS Overlay was done with ChemPlus™ extension.

25. The signal was unequivocally assigned to the 12β-proton by considering its coupling pattern and connectivities established by a ^{1}H 2D COSY spectrum, as well as the through-space proximity data obtained from a ^{1}H 2D NOESY spectrum.

26. Oxidation of unsaturated ketones is usually performed at room temperature (e.g., Kasal, A.; Starka, L.; Hampl, R.; Kohout, L. *Collect. Czech. Chem. Commun.* **1983**, *48*, 2040). However, the reaction of compound **14** with $KMnO_4/NaIO_4$ works better at higher temperature.

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