SYNTHESIS OF *N*-SUBSTITUTED 3-OXO-17β-CARBOXAMIDE-4-AZA-5α-ANDROSTANES AND THE TAUTOMERISM OF 3-OXO-4-AZA-5-ANDROSTENES[1]

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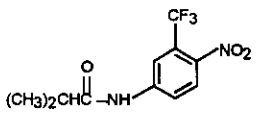
Abstract - An *N*-aryl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide and three *N*-aryl or alkyl substituted 17α-hydroxy-3-oxo-4-aza-5α-androstane-17β-carboxamides were synthesized as antiandrogen candidates from 3-oxoandrost-4-ene-17β-carboxylic acid and androst-4-ene-3,17-dione respectively. The chemo- and stereoselective reduction of 3-oxo-4-aza-5-ene intermediates with formic acid and their tautomerism in a solution of chloroform and methanol were described.

The androgen dihydrotestosterone (DHT), a metabolite of the predominant circulating androgen testosterone (T), has been recognized as a principal mediator of benign prostatic hyperplasia (BPH)[2] and implicated in the etiology of prostatic cancer[3] and several skin disorders such as acne,[4] androgenic alopecia,[5] and hirsutism.[6] Flutamide (**1**) and finasteride (**3**) are two worldwide marketed antiandrogens, which have been used clinically to treat prostate cancer and benign prostatic hyperplacia, respectively. Flutamide exhibits high androgen receptor activity *in vitro*. Its metabolite, hydroxyflutamide (**2**), shows higher receptor-binding affinity and is considered as the active species *in vivo*. In contrast, finasteride is an inhibitor of 5α-reductase, which plays an important function in many androgen-sensitive tissues by converting the major circulating androgenic hormone, testosterone, into the more potent intracellular androgenic metabolite dihydrotestosterone (DHT). Based on the structural features of these two antiandrogens including the metabolite of flutamide, we designed and synthesized four novel *N*-substituted 3-oxo-17β-carboxamide-4-azasteroids (**4** ~ **7**) as antiandrogen candidates.



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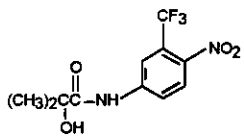

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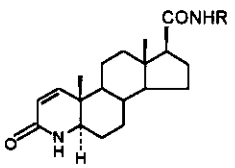
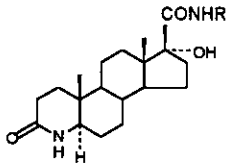


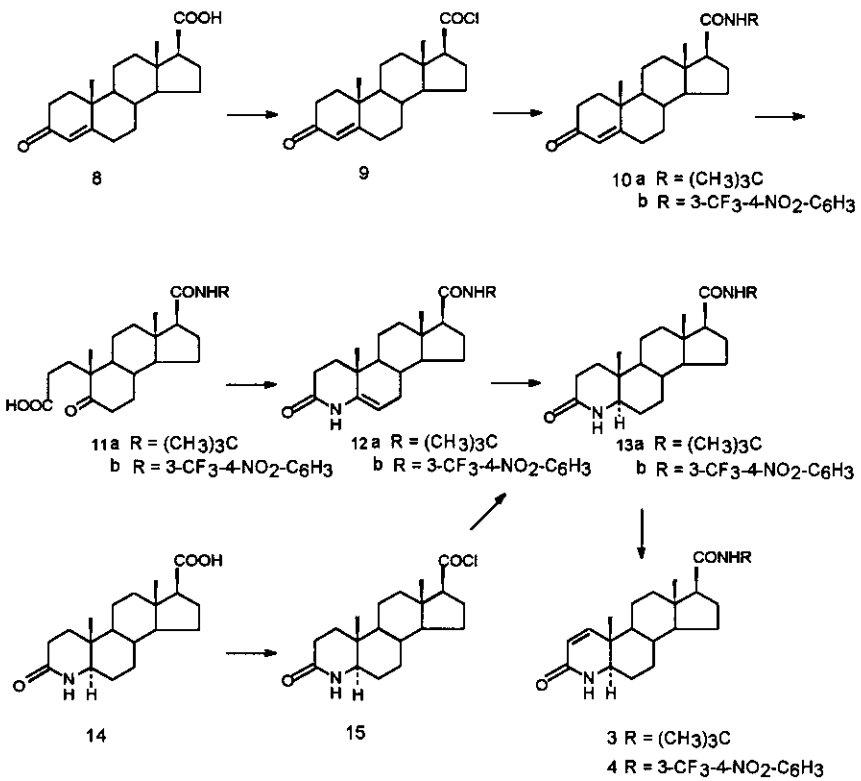
3 R = $C(CH_3)_3$
4 R = 3-CF_3-4-NO_2-C_6H_3



5 R = $C(CH_3)_3$
6 R = 3-CF_3-4-NH_2-C_6H_3
7 R = 3-CF_3-4-NO_2-C_6H_3

N-(3'-Trifluoromethyl-4'-nitrophenyl)-3-oxo-4-azaandrst-1-ene-17β-carboxamide (**4**) was synthesized from 3-oxoandrost-4-ene-17β-carboxylic acid (**8**)7 (Scheme 1). The 17β-carboxylic acid reacted either with oxalyl chloride or with thionyl chloride to give the corresponding acid chloride (**9**), which was further treated *in situ* with *tert*-butylamine and 3-trifluoromethyl-4-nitroaniline, respectively, to afford the 17-carboxamides (**10a**) and (**10b**). The successful chlorination depends on appropriate reaction conditions including reaction medium, concentration of thionyl chloride and reaction temperature (see Experimental section). Compounds (**10a**) and (**10b**) were converted into the ene-lactams (**12a**) and (**12b**) first by oxidative cleavage with $NaIO_4$-$KMnO_4$ in refluxing *tert*-BuOH to seco acids (**11a**) and (**11b**) followed by ring closure with CH_3COONH_4 in acetic acid at high temperature. This ring closure method is simpler than the reported method (with amine in ethylene glycol).7 The reduction of olefins (**12a**) and (**12b**) was completed either by hydrogenation over Pd-C or by reduction with HCOOH-K_2CO_3 in refluxing DMF to afford the corresponding 5α-4-azaandrostanes (**13a**) and (**13b**). The 5α stereoselectivity in catalytic hydrogenation has been reported in several references.7,8 The stereoselectivity of the reduction with HCOOH-K_2CO_3 was clarified by the following facts: (1) Both hydrogenation over Pd-C and reduction with HCOOH-K_2CO_3 gave the same known compound (**13a**) from **12a**, and both 4-azaandrostane products obtained by these two methods were converted into finasteride (**3**) by dehydrogenation with benzeneseleninic anhydride. (2) The reduction product of **12b** with HCOOH-K_2CO_3 coincided with *N*-(3'-trifluoromethyl-4'-nitrophenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (**13b**) prepared from 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (**14**) by converting the 17-COOH into corresponding carboxamide. (3) Both 4-azaandrostane products (**13a**) and (**13b**) obtained by the reaction of **12a** and **12b**, respectively, with HCOOH-K_2CO_3 did not show an NOE effect between C10-CH_3 and 5-H in the ^{1}H-NMR spectra recorded in $CDCl_3$.

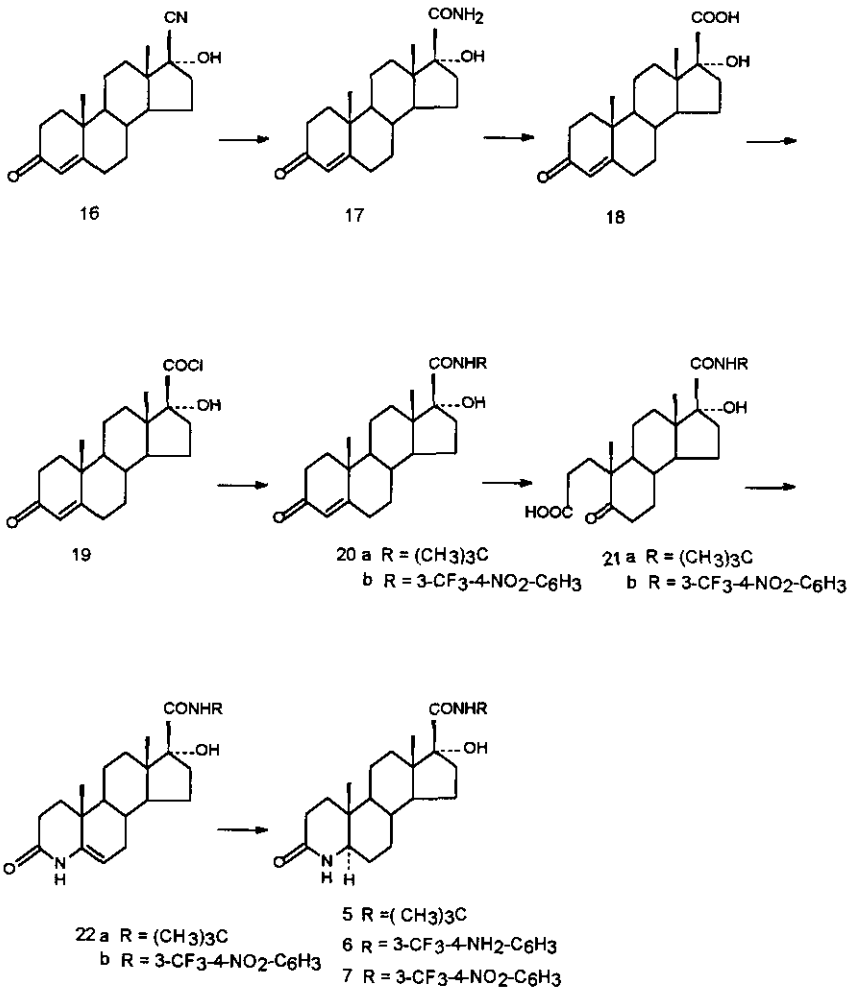
Scheme 1



N-substituted 17α -hydroxy-3-oxo-4-aza-5α -androstane-17β -carboxamides (**5**), (**6**) and (**7**) were synthesized from 17β -cyano-17α -hydroxy-3-oxo-androst-4-ene (**16**)[9] (Scheme 2). Because of poor solubility in many solvents and strong steric hindrance of the cyano group, **16** cannot be easily hydrated to the corresponding 17β -acid directly. Thus, **16** was converted to the corresponding 17α-hydroxy- 17β -carboxylic acid (**18**) in two stages: reaction with concentrated sulfuric acid in acetone followed by hydrolysis to give 17α-hydroxy- 17β-carboxamide (**17**) followed by treatment with $NaNO_2$-H_2SO_4 to obtain the desired **18**. Chlorination of **18** with thionyl chloride gave 17α-hydroxy-17β-acyl chloride (**19**), which reacted *in situ* with *tert*-butylamine or 3-trifluoromethyl-4-nitroaniline to afford the corresponding *N*-substituted-17α-hydroxy-3-oxoandrost-4-ene-17β-carboxamides (**20a**) and (**20b**) respectively. Oxidative cleavage with $NaIO_4$-$KMnO_4$ followed by ring closure with CH_3COONH_4 in acetic acid gave the corresponding 5-ene lactams (**22a**) and (**22b**), respectively, from **20a** and **20b**. Compound (**22a**) could be converted into *N-tert*-butyl-17α -hydroxy-3-oxo-4-aza-5α -androstane-17β -carboxamide (**5**) either by hydrogenation over Pd-C or reduction with HCOOH-K_2CO_3. However, hydrogenation of **22b** over Pd-C gave *N*-(3'-trifluoromethyl-4'-aminophenyl)-17α-hydroxy-3-oxo-4-azaandrostane-17β -carboxamide (**6**), while reduction of **22b** with HCOOH-K_2CO_3 gave *N*-(3'-trifluoromethyl-4'-nitrophenyl)-17α -hydroxy-3-oxo-4-azaandrostane-17β -

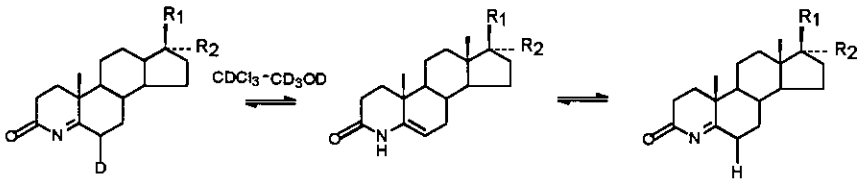
carboxamide (7), with the nitro group retained. These experimental results showed the stereo- and chemoselectivity of the reduction of 3-oxo-4-aza-5-androstene with HCOOH-K_2CO_3.

Scheme 2



To our surprise, in a solution of $CDCl_3$-CD_3OD (3:1), the ^{1}H-NMR spectra of all ene-lactams (3-oxo-4-aza-5-androstenes) (**12a**), (**12b**), (**22a**) and (**22b**) showed two signals for the methyl groups at C_{10} and C_{13} as well as for the three methyls in the *tert*-butyl of **12a** and **22a**. The chemical shift difference between the two signals of each methyl decreased in the order C_{10}-CH_3 > C_{13}-CH_3 > *tert*-butyl, while the integrals of the peak for C_6-H reduced or disappeared. But in the ^{1}H-NMR spectra measured in deuterated pyridine, chloroform or methanol, all these methyl groups exhibited a normal singlet signal. In addition, after the 5-ene of these ene-lactams was saturated, the corresponding 3-oxo-4-azaandrostanes (**13a**), (**13b**), (**5**), (**6**) and (**7**) did not show a

split of these methyl signals even when their ^{1}H-NMR spectra were determined in $CDCl_3$-CD_3OD (3:1). Although the reason for their unexpected ^{1}H-NMR behavior is not completely clear, a reasonable explanation might be the tautomerism of these ene-lactams as shown following:



EXPERIMENTAL

General Details

Melting points were obtained in capillary tubes and uncorrected. The IR spectra were obtained in potassium bromide discs on a Perkin-Elmer 783 spectrophotometer. The ^{1}H-NMR spectra were determined on a JNM-FX-400 spectrometer with TMS as internal reference. The MS spectra were recorded on an HP5989A instrument. Specific rotations were measured on a WZZ-2 instrument. All reactions were monitored by TLC on silica gel plate.

N-tert-Butyl-3-oxoandrost-4-ene-17β-carboxamide (10a)

3-Oxoandrost-4-ene-17β-carboxylic acid (**8**) (1.43 g, 4.52 mmol) was dissolved in 100 mL of dry toluene; 25 mL of toluene was distilled and pyridine (2.43 mL) was added under cooling with an ice-water bath. After stirring a few min, thionyl chloride (0.794 mL, 10.88 mmol) was added dropwise at 5℃. The mixture was stirred at the same temperature for 3 h. After removing excess thionyl chloride by distillation under reduced pressure at 60℃, *tert*-butylamine (4.15 mL, 39.49 mmol) was added at 5℃, then stirred at the same temperature for 0.5 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated to give **10a**, 1.67 g ; mp 198-202 ℃. Recrystallization from acetone gave an analytical sample 1.50 g (89.34%); mp 218-219℃; Anal. Calcd for $C_{24}H_{37}NO_2$: C, 77.58; H, 10.04; N, 3.77. Found: C, 77.37; H, 10.26; N, 3.61; MS: m/z 371(M^+), 271; IR (KBr): 3420, 2920, 1725, 1500 cm^{-1}; ^{1}H-NMR($CDCl_3$): δ 0.72(s, 3H, C_{10}-CH_3), 1.20(s, 3H, C_{13}-CH_3), 5.10(s, 1H, N-H), 5.70(s, 1H, 4-H).

N-(3'-Trifluoromethyl-4'-nitrophenyl)-3-oxoandrst-4-ene-17β-carboxamide (10b)

Compound (**10b**) was prepared in a similar fashion as **10a**. A preparation of **10b** from 500 mg (1.58 mmol) of **8** yielded 570 mg (71.50%) of **10b**; mp 226-228 ℃. Recrystallization from

acetone gave a sample for analysis; mp 226-228℃; Anal. Calcd for $C_{27}H_{31}N_2O_4F_3$: C, 64.27; H, 6.19; N, 5.55; F, 11.30. Found: C, 64.26; H, 6.40; N, 5.27; F, 10.96; MS: m/z 504(M^+), 299(base peak); IR (KBr): 3300, 2940, 1700, 1660, 1520 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.80 (s, 3H, C_{13}-CH_3), 1.25 (s, 3H, C_{10}-CH_3), 5.75(s, 1H, 4-H), 7.90(d, J=8.76Hz, 1H, N-H).

17β-(*N-tert*-Butylaminocarbonyl)-5-oxo-A-nor-3,5-secoandrostan-3-oic acid (11a)

To a solution of **10a** (0.59 g, 1.59 mmol) in a mixture of *tert*-butanol (9.44 mL) and saturated aqueous Na_2CO_3 (3 mL) was added dropwise a solution of $NaIO_4$ (3.4 g, 15.90 mmol) and $KMnO_4$ (19 mg, 0.12 mmol) in water (10 mL) under reflux over 30 min. The reaction mixture was filtered, and the filter cake was washed with a little water. The filtrate was acidified with 6 M HCl to pH 2 and extracted with methylene dichloride (30 mL × 4). The organic phase was washed with water and dried over sodium sulfate. Removal of solvent gave crude product 0.62 g; mp 155-168℃. Recrystallization from ethyl acetate afforded an analytical sample 0.53 g (85.13%); mp 175-177℃; Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.35; H, 9.71; N, 3.34; MS: m/z 391(M^+), 319, 273, 72, 58(base peak); IR (KBr): 3410, 1734, 1695, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.72(s, 3H, 13-CH_3), 1.10(s, 3H, 10-CH_3), 1.31 (s, 9H, $C(CH_3)_3$), 5.11 (s, 1H, 17-NH).

17β-[(*N*-3'-Trifluoromethyl-4'-nitrophenyl)aminocarbonyl]-5-oxo-A-nor-3,5-secoandrostan-3-oic acid (11b)

Compound (**11b**) was prepared in a similar fashion as **11a**. A preparation of **11b** from 0.5 g (0.99 mmol) of **10b** yielded 0.52 g of **11b**; mp 198-220℃. Recrystallization from ethanol gave an analytical sample (0.33 g, 63.55%); mp 240-242 ℃; Anal. Calcd for $C_{26}H_{31}N_2O_6F_3$: C, 59.54; H, 5.96; N, 5.34; F, 10.87. Found: C, 59.26; H, 5.71; N, 5.17; F, 10.75; MS: m/z 524(M^+), 506, 319, 273(base peak); IR (KBr): 1725, 1700, 1685, 1545, 1525, 1320 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.82(s, 3H, 13-CH_3), 1.14 (s, 3H, 10-CH_3), 7.62(s, 1H, 17-NH), 7.94-8.00(m, 3H, Ar-H).

***N-tert*-Butyl-3-oxo-4-azaandrst-5-ene-17β-carboxamide (12a)**

A mixture of **11a** (1.96 g, 5.01 mmol) and ammonium acetate (1.18 g, 15.31 mmol) in glacial acetic acid (40 mL) was stirred and heated at reflux for 4 h. After removal of glacial acetic acid under reduced pressure, the residue was poured into water. The precipitate was filtered and washed with water to give **12a** 1.81 g; mp 292-298℃. Crystallization from methanol gave an analytical sample 1.67 g (89.47%); mp 297-298℃; Anal. Calcd for $C_{23}H_{36}N_2O_2$: C,74.15; H,

9.74; N, 7.52. Found: C, 74.01; H, 9.93; N, 7.37; MS: m/z 373(M^+ + 1), 372(M^+, base peak), 357, 272, 58, 57; IR(KBr): 3420, 3190, 2940, 1670, 1500, 1390, 1360, 1220 cm^{-1}; ^{1}H-NMR(C_5D_5N): δ 0.95(s, 3H, C_{13}-CH_3), 1.14(s, 3H, C_{10}-CH_3), 1.55(s, 9H, *tert*-Bu), 2.62(m, 1H, 17-H), 5.19(m, 1H, 6-H); ^{1}HNMR($CDCl_3$): δ 0.72(s, 3H, C_{13}-CH_3), 1.10(s, 3H, C_{10}-CH_3), 1.36(s, 9H, *tert*-Bu), 2.50(m, 1H, 17-H), 4.85(m, 1H, 6H), 5.09(s, 1H, 4-NH), 7.89(s, 1H, 17-CONH-); ^{1}H-NMR(CD_3OD): δ 0.88(s, 3H, C_{13}-CH_3), 1.40(s, 3H, C_{10}-CH_3), 1.54(s, 9H, *tert*-Bu), 4.83(s, 1H, 4-NH), 5.17(m, 1H, 6-H), 7.15(s, 1H, 17-CONH-); ^{1}H-NMR($CDCl_3$: CD_3OD 3:1): δ 0.68 and 0.71(two s, C_{13}-CH_3), 0.79 and 0.84(two s, C_{10}-CH_3), 1.30 and 1.31(two s, *tert*-Bu).

_N_-(3'-Trifluoromethyl-4'-nitrophenyl)-3-oxo-4-azaandrst-5-ene-17β-carboxamide (12b)

A suspension of **11b** (1.5 g, 2.86 mmol) in ethylene glycol (90 mL) was treated with a slow stream of NH_3 gas for 1 h at − 15℃ and stirred at rt for 15 min, then the temperature was raised to 180℃ at the rate of 0.5℃ a minute and stirring continued at this temperature for 15 min. After cooling, the reaction mixture was poured into water. Filtration and water wash gave the crude product 1.46 g; mp 110-140℃. Crystallization afforded an analytical sample 0.91 g (62.94%); mp 267-269℃; Anal Calcd for $C_{26}H_{30}N_3O_4F_3$: C, 61.77; H, 5.98; N, 8.31; F, 11.27; Found: C, 61 .63; H, 6.13; N, 8.24; F, 11.20; MS: m/z 506(M^+ + 1), 505(M^+), 490, 475, 300, 274; IR (KBr): 1670, 1650, 1540, 1520, 1340 cm^{-1}; ^{1}H-NMR (C_5D_5N): δ 1.08(s, 3H, C_{13}-CH_3), 1.15(s, 3H, C_{10}-CH_3), 2.75(m, 1H, 17-H), 5.20(m, 1H, 6-H), 8.20-8.65(m, 3H, Ar-H), 10.36(s, 1H, 4-NH), 11.20(s, 1H, 17-CONH-); ^{1}H-NMR (C_5D_5N-D_2O): δ 1.05(s, 3H, C_{13}-CH_3), 1.08(s, 3H, C_{10}-CH_3), 3.00(m, 1H, 17-H), 5.31(m, 1H, 6-H), 8.25-8.89(m, 3H, Ar-H); ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1): δ 0.78 and 0.82 (two s, C_{13}-CH_3), 1.04 and 1.12(two s, C_{10}-CH_3), 4.9(m, 1H, 6-H), 7.95-8.20(m, 3H, Ar-H).

***N*-*tert*-Butyl-3-oxo-4-aza-5α-andrstane-17β-carboxamide (13a)**

Procedure A: (Hydrogenation of **12a** with H_2 - Pd/C)

1.00 g (2.68 mmol) of **12a** was dissolved in 50mL of HOAc and hydrogenated in the presence of 2.43g of 10% Pd-C at 70-80℃ and 3.65 atm of hydrogen for 7 h. Removal of the catalyst by filtration and the solvent by evaporation under reduced pressure gave the crude product. It was dissolved in methylene chloride, washed with saturated aqueous Na_2CO_3 (15 mL × 3) and dried over anhydrous Na_2SO_4. Removal of solvent gave a crystalline **13a** (0.88 g); mp 266-267℃.

Recrystallization from acetone afforded an analytical sample (0.76 g, 75.71%), white needle crystals; mp 277-278 ℃. Anal. Calcd for $C_{23}H_{38}N_2O_2$: C, 73.75; H, 10.23; N, 7.48; Found: C, 73.71; H, 10.31; N, 7.38; MS: m/z 375(M^+ + 1), 374(M^+, base peak), 359, 274, 58, 57; IR (KBr): 3420, 3190, 1695, 1500, 1365 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.68(s, 3H, C_{13}-CH_3), 0.90(s, 3H, C_{10}-CH_3), 1.34(s, 9H, *tert*-Bu), 3.06(m, 1H, 5-H), 5.10(s, 1H, 17-CONH-), 6.36(s, 1H, 4-NH); ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1) δ 0.50(s, 3H, C_{13}-CH_3), 0.73(s, 3H, C_{10}-CH_3), 1.19(s, 9H, *tert*-Bu), 2.89(m, 1H, 5-H), $[\alpha]_D^{14}$ +59.98° (c 2.484, CH_3OH).

Procedure B: (Reduction of **12a** with HCOOH-K_2CO_3)

To a solution of **12a** (0.50 g, 1.34 mmol) in DMF (60 mL) were added HCOOH (88%, 30 mL) and K_2CO_3 (6.92 g, 50.07 mmol) under stirring. The reaction mixture was heated at reflux for 6 h. After dilution with water and extraction with methylene chloride, the organic phase was washed with saturated aqueous Na_2CO_3 solution (15 mL × 3) and water, dried over anhydrous Na_2SO_4 and filtered. Removal of solvent gave needle crystals **13a** (0.46 g); mp 269-270 ℃. Recrystallization from acetone gave an analytical sample (0.40 g, 79.69%); mp 277-278 ℃. Anal. Calcd for $C_{23}H_{38}N_2O_2$: C, 73.75; H, 10.23; N, 7.48; Found: C, 73.63; H, 10.38; N, 7.38; MS: m/z 375(M^+ + 1), 374(M^+), 359, 274, 58, 57; IR (KBr): 3420, 3190, 1695, 1500, 1365 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.68(s, 3H, C_{13}-CH_3), 0.90(s, 3H, C_{10}-CH_3), 1.34(s, 9H, *tert*-Bu), 3.06(m, 1H, 5-H), 5.09(s, 1H, 17-NH), 5.80(s, 4-NH) and no NOE between 5-H and C_{13}-CH_3; ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1): δ 0.52(s, 3H, C_{13}-CH_3), 0.75(s, 3H, C_{10}-CH_3), 1.20(s, 9H, *tert*-Bu), 2.91(m, 1H, 5-H); $[\alpha]_D^{14}$ +57.2° (c 0.0918, CH_3OH).

Procedure C: (14 → 13a)

To a suspension of **14** (100 mg, 0.31 mmol) in methylene chloride (3 mL) was added dry pyridine (0.01 mL), the mixture was stirred at rt for a few minutes and thionyl chloride (0.025 mL, 0.34 mmol) was added. After stirring for additional 1 h, *tert*-butylamine (0.054 mL, 0.51 mmol) was added. The mixtutre was stirred for another 1 h, poured into water then extracted with methylene chloride. The organic phase was washed with 0.1 M aqueous HCl and water and dried with anhydrous Na_2SO_4. Filtration and evaporation gave crude product (100 mg). Flash chromatography (silica gel, CH_2Cl_2 : acetone, gradient elution) and recrystallization from acetone gave an analytical sample(90 mg, 77.51%); mp 277-279 ℃, which coincided with the product obtained from procedures A and B. Anal. Calcd for $C_{23}H_{38}N_2O_2$: C, 73.75; H, 10.23; N, 7.48; Found: C, 73.62; H, 10.37; N, 7.39; MS: m/z 375(M^+ + 1), 374(M^+), 359, 274, 58, 57; IR

(KBr): 3420, 3190, 1695, 1500, 1365 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.68(s, 3H, C_{13}-CH_3), 0.90(s, 3H, C_{10}-CH_3), 1.34(s, 9H, *tert*-Bu), 3.06(m, 1H, 5-H), 5.09(s, 1H, 17-NH), 5.80(s, 4-NH) and no NOE between 5-H and C_{13}-CH_3.

N-(3'-Trifluoromethyl-4'-nitrophenyl)-3-oxo-4-aza-5α-androstane-17β-carboxamide (13b)

Procedure A: Reduction of **12b** with HCOOH-K_2CO_3

To a suspension of **12b** (50 mg, 0.10 mmol) in DMF (6 mL) were added HCOOH (88%, 2 mL, 38.24 mmol) and K_2CO_3 (0.44 g, 3.18 mmol) with stirring. The reaction mixture was heated at reflux for 8 h. Dilution with water (100 mL) and filtration gave the crude product (45 mg); mp 205-207℃. Twice recrystallization from methanol gave an analytical sample (38.7 mg, 76.25%); mp 288-292℃. Anal. Calcd for $C_{26}H_{32}N_3O_4F_3$: C, 61.53; H, 6.36; N, 8.28; F, 11.23; Found: C, 61.48; H, 6.51; N, 8.20; MS: m/z 505(M^+ − 2), 477, 302, 274; IR (KBr): 3470, 3220, 2940, 2870, 1700, 1645, 1525, 1490, 1250 cm^{-1}; ^{1}H-NMR (C_5D_5N): δ 0.90(s, 3H, C_{13}-CH_3), 1.02(s, 3H, C_{10}-CH_3), 3.05(m, 1H, 5-H), 8.05-8.35(m, 3H, Ar-H), 8.65(s, 1H, 4-NH), 11.19(s, 1H, 17-CONH-); ^{1}H-NMR ($CDCl_3$): δ 0.78(s, 3H, C_{13}-CH_3), 0.92(s, 3H, C_{10}-CH_3), 3.10(m, 1H, 5-H), 5.65(s, 1H, 4-NH), 7.54(s, 1H, 17-CONH-), 7.92-8.09(m, 3H, Ar-H) and no NOE between 5-H and C_{10}-CH_3; ^{1}H-NMR (CD_3OD): δ 0.98(s, 3H, C_{13}-CH_3), 1.10(s, 3H, C_{10}-CH_3), 3.30(m, 1H, 5-H), 4.78(br s, 1H, 4-NH), 8.22-8.46(m, 3H, Ar-H); ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1): δ 0.60(s, 3H, C_{13}-CH_3), 0.72(s, 3H, C_{10}-CH_3), 2.90(m, 1H, 5-H), 7.78-7.98(m, 3H, Ar-H); $[\alpha]_D^{14}$ + 113.2° (c 0.00053, CH_3OH).

Procedure B: (14 → 13b)

To a suspension of **14** (100 mg, 0.31 mmol) in methylene chloride (3 mL) was added dry pyridine (0.01 mL), the mixture was stirred at rt for a few min and thionyl chloride (0.025 mL, 0.34 mmol) was added. After stirring for an additional 1.5 h, 3-trifluoromethyl-4-nitroaniline (105 mg, 0.51 mmol) was added. The mixture was stirred for another 1 h, poured into water, then extracted with methylene chloride. The organic phase was washed with 0.5 M aqueous HCl and water and dried over anhydrous Na_2SO_4. Filtration and evaporation gave a white solid crude product. Flash chromatography (silica gel, CH_2Cl_2 : acetone, gradient elution) afforded **13b** (130 mg); mp 282-284℃. Recrystallization from methanol gave an analytical sample(120 mg, 76.27%); mp 288-290 ℃. Anal. Calcd for $C_{26}H_{32}N_3O_4F_3$: C, 61.53; H, 6.36; N, 8.28; F, 11.23; Found: C, 61.48; H, 6.30; N, 8.23; F, 11.20; MS: m/z 507 (M^+), 477, 302, 274; ^{1}H-NMR ($CDCl_3$): δ 0.78(s, 3H,

C_{13}-CH_3), 0.92(s, 3H, C_{10}-CH_3), 3.10(m, 1H, 5-H), 5.60(s, 1H, 4-NH), 7.54(s, 1H, 17-CONH-), 7.92-8.09(m, 3H, Ar-H); ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1): δ 0.60(s, 3H, C_{13}-CH_3), 0.72(s, 3H, C_{10}-CH_3), 2.90(m, 1H, 5-H), 7.78-7.98(m, 3H, Ar-H); $[\alpha]_D^{14}$ + 122.73° (c 0.0011, CH_3OH).

N-tert-Butyl-3-oxo-4-aza-5α-andrst-1-ene-17β-carboxamide (3)

A solution of **13a** (500 mg, 1.33 mmol) and $[C_6H_5Se(O)]_2O$ (696.3 mg, 1.93 mmol) in chlorobenzene (12.5 mL) was stirred and heated at reflux for 10 h. After removal of solvent by distillation at reduced pressure, the residue was dissolved in methylene chloride (50 mL). The solution of methylene chloride was washed with saturated aqueous Na_2CO_3 (10 mL × 3) and water (20 mL × 2), then dried over anhydrous Na_2SO_4. Filtration and evaporation gave a crude product, which was purified by flash chromatography (silica gel, methylene chloride : acetone, gradient elution) to give **3** (330 mg); mp 248-254 ℃. Recrystallization from acetone obtained an analytical sample (200 mg, 40.36%); mp 253-354 ℃. Anal.. Calcd for $C_{23}H_{36}N_2O_2$: C, 74.15; H, 9.74; N, 7.52; Found: C, 74.09; H, 9.92; N, 7.36; MS: m/z 373(M^+ + 1), 372(M^+), 357, 272, 58, 57; IR (KBr): 3430, 3310, 3190, 2920, 1669, 1590, 1520, 1440, 1380, 1355, 1245, 1210 cm^{-1}; ^{1}H-NMR (C_5D_5N): δ 0.96(s, 3H, C_{13}-CH_3), 1.01(s, 3H, C_{10}-CH_3), 1.59(s, 9H, *tert*-Bu), 3.36(m, 1H, 5-H), 6.15(dd, J=2.1 and 9.85 Hz, 1H, 1-H), 6.68(d, J=10.0 Hz, 1H, 2-H), 7.00(s, 1H, 17-CONH-), 8.25(s, 1H, 4-NH).

_N_-(3'-Trifluoromethyl-4'-nitrophenyl)-3-oxo-4-aza-5α-andrst-1-ene-17β-carboxamide (4)

Compound (**4**) was prepared in a similar fashion as **3**. A preparation of **4** from 330 mg (0.65 mmol) of **13b** yielded 160 mg of **4**. Recrystallization from methanol gave an analytical sample (137.6 mg, 41.87%); mp 288-291 ℃. Anal. Calcd for $C_{26}H_{30}N_3O_4F_3$: C, 61.77; H, 5.98; N, 8.31; F, 11.27; Found: C, 61.64; H, 5.93; N, 8.14; F, 11.35; MS: m/z 505(M^+), 475, 300, 272; IR (KBr): 3390, 3250, 2920, 1660, 1590, 1515, 1230 cm^{-1}; ^{1}H-NMR (C_5D_5N): δ 1.00(s, 3H, C_{13}-CH_3), 1.05(s, 3H, C_{10}-CH_3), 3.36(dd, J=3.4 and 3.8 Hz, 1H, 5-H), 6.13(dd, J=2.1 and 9.85 Hz, 1H, 1-H), 6.75(d, J=10.0 Hz, 1H, 2-H), 8.20-8.35(m, 3H, Ar-H), 8.63(s, 1H, 17-CONH-), 11.20(s, 1H, 4-NH).

17α-Hydroxy-3-oxo-androst-4-ene-17β-carboxamide (17)

Portions of **16** (60 g, 0.19 mol) were added slowly to a mixture of conc. H_2SO_4 (300 mL) and THF (300 mL) at 5 ℃ under stirring, then stirred at 18 ℃ for 12 h and at 40 ℃ for 10 h. The

reaction mixture was poured into ice water (2 L). Filtration and water wash gave a crude product (59.62 g). Recrystallization from CH_2Cl_2-CH_3OH gave an analytic sample(44.12 g, 70.06%); mp 282-284℃. Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23; Found: C, 72.26; H, 8.83, N, 4.08; MS: m/z 331(M^+), 287; IR (KBr): 3420, 2920, 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 0.80(s, 3H, C_{13}-CH_3), 1.20(s, 3H, C_{10}-CH_3), 5.75(s, 1H, 4-H), 5.40 and 6.40(br s, NH and OH).

17α-Hydroxy-3-oxo-androst-4-ene-17β-carboxylic acid (18)

Compound **17** (10 g, 30.17 mmol) was dissolved in 50%(v/v) H_2SO_4 (125 mL) at 0℃. To this reaction mixture, a solution of $NaNO_2$ (5.20 g, 75.36 mmol) in H_2O (20 mL) was added dropwise at 5-8℃ over 30 min, stirred for an additional 10 min, then poured into 1 L of ice-water. Urea (2.5 g, 41.63mmol) was then added. Filtration and water wash gave crude product as a pale brown solid (6.78 g). Flash chromatography (silica gel, methylene chloride : methanol, gradient elution) and recrystallization from methylene chloride-methanol gave an analytical sample 5.56 g, 55.44%); mp 234-236℃. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; Found: C, 72.11; H, 8.45; MS: m/z 332(M^+, base peak); IR (KBr): 3500, 2940, 1710, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.80(s, 3H, C_{13}-CH_3), 1.20(s, 3H, C_{10}-CH_3), 5.75(s, 1H, 4-H); $[\alpha]_D$ - 91.6° (c 1.0, $CHCl_3$).

***N-tert*-Butyl-17α-hydroxy-3-oxoandrost-4-ene-17β-carboxamide (20a)**

A suspension of **18** (5 g, 15.04 mmol) in dry toluene (420 mL) was distilled and about 40 mL of toluene was collected. Then cooled to rt and dry pyridine (3.13 mL) was added. After addition of thionyl chloride (1.62 mL, 22.21 mmol) dropwise, the mixture was stirred at 22℃ for 3.5 h. *tert*-Butylamine (20 mL, 190.32 mmol) was added dropwise in a period of 40 min, then stirred for additional 2 h and stood overnight. The reaction mixture was washed with diluted aqueous 6% HCl and water then with saturated aqueous $NaHCO_3$ and water. Drying over anhydrous Na_2SO_4 and evaporation gave **20a** (2.64 g). Recrystallization from ethanol afforded a pure sample (2.32 g, 39.80%); mp 266-267℃. HRMS: Calcd for $C_{24}H_{37}NO_3$: 387.2773; Found: 387.2774; MS: m/z 387(M^+), 359, 287, 58; IR (KBr): 3380, 3420, 1670, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.77(s, 3H, C_{13}-CH_3), 1.19(s, 3H, C_{10}-CH_3), 1.37(s, 9H, *tert*-Bu), 5.74(s, 1H, 4-H), 6.32(s, 1H, OH).

***N*-(3'-Trifluoromethyl-4'-nitrophenyl)-17α-hydroxy-3-oxoandrost-4-ene-17β-carboxamide (20b)**

Reaction of **18** as above for **20a** gave **20b** with the substitution of 3-trifluoromethyl-4-nitroaniline for *tert*-butylamine, in the yield of 65.53%, mp 229-231 ℃. HRMS: Calcd for $C_{27}H_{31}N_2O_5F_3$: 520.2185; Found: 520.2158; MS: m/z 520(M^+), 258, 287, 57; IR (KBr): 3620, 3360, 1685, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.85(s, 3H, C_{13}-CH_3), 1.20(s, 3H, C_{10}-CH_3), 5.75(s, 1H, 4-H), 7.98-8.08(m, 3H, Ar-H).

17α-Hydroxy-17β-(*N-tert*-butyl-aminocarbonyl)-5-oxo-A-nor-3,5-secoandrostan-3-oic acid (21a)

To a solution of **20a** (2 g, 5.16 mmol) in *tert*-BuOH (30 mL) was added 20% aqueous Na_2CO_3 (5 mL). Under stirring at reflux, a solution of $NaIO_4$ (5.33 g, 24.92 mmol) and $KMnO_4$ (33 mg, 0.21 mmol) in water (20mL) was added over 5 min. After cooling to rt, the mixture was filtered. The *tert*-BuOH was removed from filtrate by evaporation at reduced pressure. The left aqueous solution was acidified with 6 M aqueous HCl to pH 2-3 and extracted with CH_2Cl_2(30 mL × 3). The organic layer was washed with water and dried over anhydrous Na_2SO_4. Removal of solvent gave crude product (2.23 g). Chromatography (silica gel, methylene : methanol, gradient elution) gave an oily solid, which was treated with diisopropyl ether to give pure **21a** as a white powder (1.66g, 78.93%); mp 224-225 ℃. Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44; Found: C, 67.65; H, 9.32; N, 3.31; MS: m/z 407(M^+), 307, 58; IR (KBr): 3430, 3390, 3220, 1700, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.79(s, 3H, C_{13}-CH_3), 1.13(s, 3H, C_{10}-CH_3), 1.36(s, 9H, *tert*-Bu), 6.35(s, 1H, OH).

17α-Hydroxy-17β-[(*N*-3'-trifluoromethyl-4'nitrophenyl)carbamino]-5-oxo-A-nor-3,5-secoandrostan-3-oic acid (21b)

Reaction of **20b** as for **21a** above gave **21b** in the yield of 93.84%, mp 264-266 ℃; Anal. Calcd for $C_{26}H_{31}N_2O_7F_3$: C, 57.77; H, 5.78; N, 5.18; F, 10.55. Found: C, 57.62; H, 5.95; N, 5.06; F, 10.47; MS: m/z 540(M^+), 176; IR (KBr): 3430, 3350, 3285, 1737, 1695, 1685 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.69(s, 3H, C_{13}-CH_3), 1.05(s, 3H, C_{10}-CH_3), 5.75(s, 1H, OH), 8.19-8.55(m, 3H, Ar-H), 10.31(s, 1H, -CONH-), 11.99(s, 1H, -COOH).

***N-tert*-Butyl-17α-hydroxy-3-oxo-4-azaandrost-5-ene-17β-carboxamide (22a)**

A mixture of **21a** (0.5 g, 1.23 mmol) and CH_3COONH_4 (0.5 g, 6.49 mmol) in glacial acetic acid (10 mL) was heated at reflux for 4 h. After removal of AcOH, the residue was poured into water. Filtration gave crude product (**22a**) (0.43 g). Recrystallization from CH_2Cl_2-CH_3OH obtained an

analytical sample (0.38 g, 79.51%) as plate crystals; mp > 310℃. Anal. Calcd for $C_{23}H_{36}N_2O_3$: C, 71.10; H, 9.34; N, 7.21; Found: C, 70.60; H, 9.56; N, 7.39; MS: m/z 388(M^+), 370, 288, 270; IR (KBr): 3400, 3340, 3320, 1670, 1660, 1645 cm^{-1}; ^{1}H-NMR (C_5D_5N): δ 1.08(s, 3H, C_{13}-CH_3), 1.18(s, 3H, C_{10}-CH_3), 1.49(s, 9H, *tert*-Bu), 5.19(m, 1H, 6-H); ^{1}H-NMR ($CDCl_3$: CD_3OD 3:1): δ 0.69 and 0.73(two s, 3H, C_{13}-CH_3), 1.01 and 1.10(two s, 3H, C_{10}-CH_3), 1.35 and 1.36(two s, 9H, *tert*-Bu).

_N_-(3'-Trifluoromethyl-4'-nitrophenyl)-17α-hydroxy-3-oxo-4-azaandrost-5-ene-17β-carboxamide (22b)

Reaction of **21b** as for **22a** above gave **22b**, in the yield of 67.93%, mp > 310℃. HRMS: Calcd for $C_{26}H_{30}N_3O_5F_3$: 521.2137; Found: 521.2136; MS: m/z 521(M^+), 288; IR(KBr): 3369, 3320, 3200, 1680, 1640 cm^{-1}; ^{1}H-NMR (C_5D_5N): δ 1.12(s, 3H, C_{13}-CH_3), 1.16(s, 3H, C_{10}-CH_3), 4.99(s, 1H, OH), 5.19(m, 1H, 6-H), 8.22-8.83(m, 3H, Ar-H), 10.36 and 10.79(2H, two CONH); ^{1}H-NMR ($CDCl_3$: CD_3OD 3:1): δ 0.78 and 0.82(two s, 3H, C_{13}-CH_3), 1.03 and 1.12(two s, 3H, C_{10}-CH_3), 8.00-8.29(m, 3H, Ar-H).

***N-tert*-Butyl-17α-hydroxy-3-oxo-4-azaandrostane-17β-carboxamide (5)**

Hydrogenation at 70-80℃ of **22a** (0.5 g, 1.29 mmol) in HOAc (30 mL) in the presence of 10% Pd-C (1.25 g) at 2.76 atm for 9 h gave, after filtration and evaporation under reduced pressure, the crude product. It was dissolved in methylene chloride (150 mL), washed with saturated aqueous $NaHCO_3$ (15 mL × 3) and water, then dried over anhydrous Na_2SO_4. Removal of solvent gave crude product **5** (0.40 g). Recrystallization from CH_2Cl_2-CH_3OH afforded an analytical sample(0.36 g, 71.45%), mp > 300℃. Anal. Calcd for $C_{23}H_{38}N_2O_3$: C,70.73; H, 9.81; N, 7.17; Found: C, 70.58; H, 10.09; N, 7.08; MS: m/z 390(M^+), 290, 58; IR (KBr): 3400, 3360, 3230, 1680, 1365 cm^{-1}; ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1) δ 0.71(s, 3H, C_{13}-CH_3), 0.90(s, 3H, C_{10}-CH_3), 1.35(s, 9H, *tert*-Bu).

_N_-(3'-Trifluoromethyl-4'-aminophenyl)-17α-hydroxy--3-oxo-4-azaandrostane-17β-carboxamide (6)

Hydrogenation at 40-50℃ of **22b** (0.5 g, 0.96 mmol) in HOAc (30 mL) in the presence of 10% Pd-C (0.58 g) at 9.87 atm for 9 h gave, after filtration and evaporation under reduced pressure, the crude product, which was purified by flash chromatography (silica gel, chloroform : methanol, gradient elution) to give *N*-(3'- trifluoromethyl- 4'-aminophenyl)- 17α - hydroxy-3-

oxo-4-azaandrost-5-ene-17β -carboxamide (0.26 g) and the compound (**6**) (0.19 g, 40.10%), mp 264-266℃ . MS: m/z 493(M^+), 290, 176; IR (KBr): 3480, 3370, 3240, 1660, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1) δ 0.78(s, 3H, C_{13}-CH_3), 0.90(s, 3H, C_{10}-CH_3), 6.82-7.65(m, 3H, Ar-H).

_N_-(3'-Trifluoromethyl-4'-nitrophenyl)-17α-hydroxy-3-oxo-4-azaandrostane-17β-carboxamide (7)

To a suspension of **22b** (0.6 g, 1.15 mmol) in DMF (60 mL) were added HCOOH (88%, 18 mL, 344.16 mmol) and K_2CO_3 (4.2 g, 30.39 mmol) under stirring. The reaction mixture was heated at reflux for 7.5 h. Dilution with ice-water and filtration gave crude product (0.58 g). Flash chromatography (silica gel, chloroform : methanol, gradient elution) and recrystallization from ethanol gave an analytical sample (0.49 g, 81.38%); 312-314 ℃ (decomp); Anal. Calcd for $C_{26}H_{32}N_3O_5F_3$: C, 59.65; H, 6.16; N, 8.03; F, 10.89. Found: C, 59.47; H, 6.02; N, 7.94; F, 10.85; MS: m/z 523(M^+), 505, 299; ^{1}H-NMR ($CDCl_3$:CD_3OD 3:1): δ 0.79(s, 3H, C_{13}-CH_3), 0.91(s, 3H, C_{10}-CH_3), 7.98-8.22(m, 3H, Ar-H).

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