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Synthesis of 4 –Trifluoromethylsteroids: A Novel Class of Steroid 5α–Reductase Inhibitors

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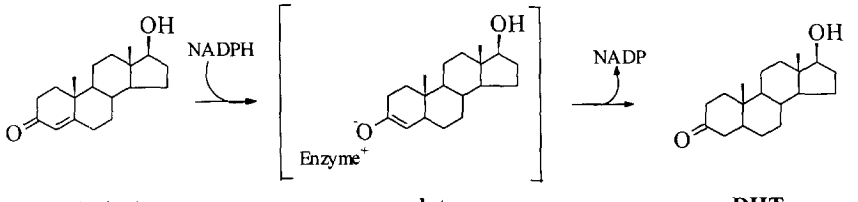
Abstract: A concise synthetic approach to 4–trifluoromethyl steroids, a novel class of steroid 5α–reductase inhibitors, is described. Direct trifluoromethylation of steroid olefinic bromide with methyl fluorosulfonyl-difluoroacetate was used as a key step in the synthesis. The compound **4** exhibited highly inhibitory activity than Finasteride in *in vitro* assay. © 1997 Elsevier Science Ltd.

Steroid 5α–reductase is an enzyme responsible for the NADPH-dependent conversion of testosterone (T) to dihydrotestosterone (DHT) in many androgen sensitive cells (**Scheme 1**).[1] It is well known that excessive accumulation of DHT causes several human endocrine diseases,[2] such as benign prostatic hyperplasia (BPH),[3] prostatic carcinoma,[4] male pattern baldness,[5] acne,[6] alopecia in men[7] and hirsutism in women.[8] Among these diseases, the incidence of BPH in the aging male population is very high, affecting approximately 30% at age 50 and 80% at age 80.[9] Inhibition of steroid 5α–reductase may diminish the formation of DHT in the tissue of human body, thus, steroid 5α–reductase inhibitors can be used as therapeutic agents for these diseases, *e.g.* , 4-aza-5α-androstan-17-carboxamide (Finasteride),[10] 6-azasteroids,[11] 19-nor-10-azasteroids,[12] 4,17-diazasteroids,[13] 3-carboxysteroids,[14] 4-cyanosteroids[15] and nonsteroidal compounds.[16] Since the stable enolate of testosterone binding to 5α–reductase, like that of 4–cyanoprogresterone, is considered to be a key step for preventing the conversion of testosterone to dihydrotestosterone,[15] we envisioned that trifluoromethylated analogues would be interesting candidates because introducion of a trifluoromethyl group to a bioactive molecule often enhances its

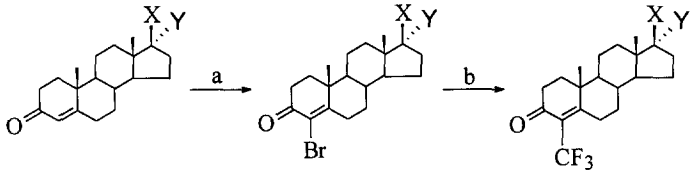


testosterone **enolate** **DHT**

Scheme 1

original pharmacological properties.[17] Thus, we synthesized some trifluoromethyl steroids and examined their biological activities.

Our synthetic approaches to trifluoromethylated steroids were characterized by two points: making use of all possible commercially available steroids as the starting materials and direct trifluoromethylation in the final step with our own trifluoromethylating agents,[18] among which methyl fluorosulfonyldifluoroacetate (MFSDA) $FO_2SCF_2CO_2Me$ was found to be most effective. Our initial studies focused on the synthesis of 4–trifluoromethyl progesterone (**3a**)[19], a counterpart of 4–cyanoprogesterone, by two-step procedures, *i.e.* , bromination of 3–oxo–Δ^4–steroid(**1a**),[20] in AcOH-Et_2O in the presence of collidine followed by trifluoromethylation with MFSDA in the presence of catalytic amounts of CuI. Unfortunately, **3a** did not show any inhibitory activity on 5α–reductase in a preliminary bioassay (**Table 1**). Then, we turned to prepare 4-trifluoromethylandrost-4-en-3,17-dione (**3b**)[21] starting from androst-4-en-3,17-dione (**1b**) as shown in **Scheme 2**. Compound **3b** exhibited remarkable inhibitory activity on 5α–reductase. However, in view of the importance of the C–17 amide side chain which is a common structural feature of many known 5α–reductase inhibitors for biological activity, we further synthesized 4-trifluoromethyl-androsterone-17β-*N*-(*t*-butyl)carboxamide (**4**).



1 **2** **3**

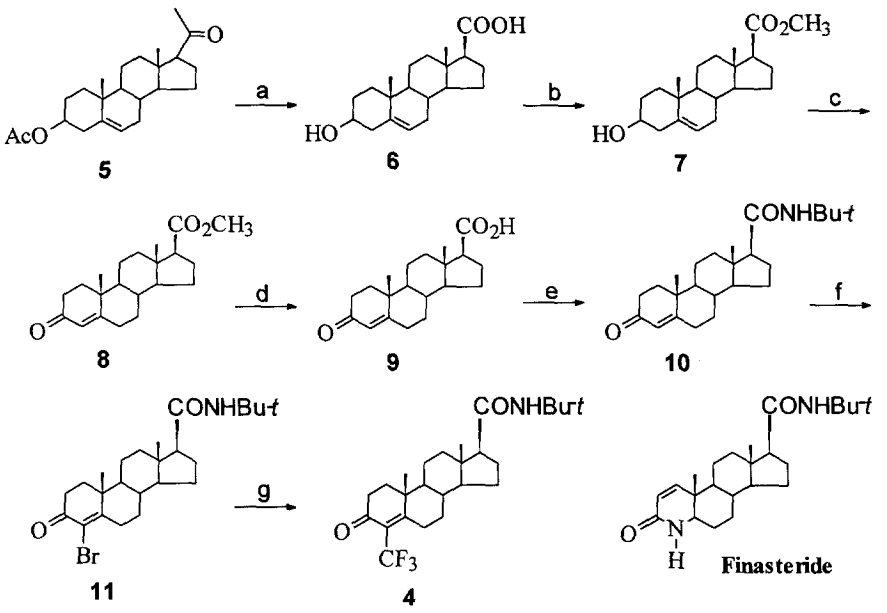
2a X= CH_3CO , Y= H (70%). **3a** X= CH_3CO , Y= H (74%)

2b X ,Y = O (80%) **3b** X ,Y = O (83%)

Reagents and conditions: a. Br_2, collidine, AcOH, Et_2O. b. MFSDA, CuI, DMF, 75°C

Scheme 2

We took commercially available prognenolone acetate (**5**) as the starting material, which was first submitted to haloform reaction to produce steroid 20-carboxylic acid **6**.[22] The conversion of **6** to the corresponding methyl ester (**7**) was carried out in refluxing methanol in the presence of TsOH for 5h. Oppenaur oxidation of **7** afforded methyl 3-oxo-androst-4-ene-17β-carboxylate (**8**),[23] which was then hydrolyzed to **9**. Compound **9** was easily converted further to 17-amide **10** in high yield. Bromination of **10** followed by trifluoromethylation afforded **4** .[21] The overall yield of **4** from **5** is 42 % (**Scheme 3**).



Reagents and conditions: a. i.NaOBr, dioxane, H_2O, <10°C, ii. conc. HCl, 91% b. TsOH, MeOH, 5h, 82% c. Al(*i*-PrO)$_3$, cyclohexanone, toluene, 87%. d. 10% KOH/H_2O, EtOH, 95%. e. i. oxalyl chrolide, py, toluene, 1h. ii. *t*-BuNH_2, toluene, 1h, 94%. f. Br_2, collidine, AcOH, Et_2O, 79%. g. MFSDA, CuI, DMF, 91%.

Scheme 3

In *in vitro* assay, 4-trifluoromethyl-*N*-(*t*-butyl)-4-androsten-17β-carboxamide (**4**) exhibited higher activity than Finasteride did, the latter has been used as an effective cure for BPH (**Table 1**)[24]. The synthesis and biological evaluation of other trifluoromethylsteroids are in progress.

Table 1. Inhibition of 4-trifluoromethylsteroids toward 5α–reductase (Ki Value)[24]

Compound	Isotope Method $[^3H]^T \rightarrow [^3H]$–DHT	Enzymic Kinetics Method NADPH
Finasteride	88.2nM	54.7nM
3a	>>1000nM	>>1000nM
3b	95.2nM	28.8nM
4	20.9nM	20.2nM

In conclusion, a novel class of steroid 5α–reductase inhibitors possessing a 4-trifluoromethyl group has been synthesized by a concise method involving direct trifluoromethylation of steroid olefinic bromides with methyl fluorosulfonyldifluroacetate.

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19. General procedure for preparation of 4–trifluoromethylsteroids: *4-Trifluromethyl-pregn-4-ene-3,20-dione–(3a)* A solution of 105mg (0.275mmol) pregnenedione **2a**, 30mg (0.157 mmol) CuI and 0.4ml MFSDA in dry DMF (10ml) was stirred at 75°C under nitrogen for 7 hr. After the completion of the reaction , the reaction mixture was diluted by ether(20ml) and filtered. The filtrate was poured into water (20ml) and then extracted with ether (4×25ml). The combined extracts were washed with water (3×5ml) and dried over anhydrous $MgSO_4$. The residue upon evaporation of the solvent was chromatographyed on silical gel with petroleum ether–ethyl acetate as elution solvent (4/1, v/v) to give 85mg (83%) **3a** as a white solid. m.p.: 124.5~125.5°C. $[\alpha]^{25}_D$=182.9°(c 1.36, $CHCl_3$). IR (KBr): 2950, 2800, 1700, 1600, 1460, 1364, 1120cm^{-1}. ^1H NMR (300MHz, TMS, in $CDCl_3$) δ: 0.68 (s, 3H,C_{18}–H), 1.26 (s, C_{19}–H), 2.21 (s, C_{21}–H), 3.05 (d, br, *J*=14.65Hz, 1H) ppm. ^{19}F NMR (60MHz, CF_3CO_2H, in $CDCl_3$) δ: -21.3 (s) ppm. MS m/z: 382 (M^+, 6), 367 (M^+-Me, 11), 364 (4), 339 (4), 192 (50), 190 (59), 173 (27), 147 (64), 133 (37), 43 (100). Elemental Analysis for $C_{22}H_{29}O_2F_3$ Calcd: C: 69.09, H:7.64 Found: C: 69.00, H: 8.11.

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21. Selective Spectra for compoud **3b** and **4:** **3b,** a white solid, m.p.: 150.0~151.0°C. $[\alpha]^{25}_D$= -10.0°(c 0.33, $CHCl_3$) IR (KBr): 3000, 1750, 1600, 1350, 1160, 1120cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ: 0.93 (s, 3H,C_{18}–H), 1.29 (s, C_{19}–H), 3.12 (d, br, *J*=14.82Hz, 1H) ppm. ^{19}F NMR (60MHz, $CDCl_3$) δ: -21.7 (s) ppm. MS

m/z: 355 (M^++1, 7), 354 (M^+, 30), 339 (M^+-CH_3, 8), 310 (16), 285 (M^+-CF_3, 25), 268 (16), 241 (18), 192 (100), 107 (79), 69 (18). Elemental Analysis: $C_{20}H_{25}O_2F_3$ Calcd: C: 67.78, H: 7.11 Found: C: 67.54, H: 7.37; **4** a white solide . m.p.: 158.0~159.0°C. $[\alpha]^{25}_D$= 108.5° (c 0.363, $CHCl_3$) IR (KBr): 3499 (br, N-H), 2900, 1680 (br), 1590, 1510, 1450, 1360, 1260, 1230, 1120cm^{-1}. ^1H NMR (300MHz, $CDCl_3$) δ: 0.74 (s, C_{18}–H), 1.26 (s,C_{19}-H), 1.35 (s, t-Bu), 5.08 (s, N–H) ppm. ^{19}F NMR (60MHz, $CDCl_3$) δ: -20.8 (s) ppm. MS m/z: 439 (M^+, 31), 424 (M^+-CH_3, 12), 404 (23), 384 (11), 368 (8), 339 (8), 248 (20), 149 (52), 69 (64), 57 (100). Elemental Analysis for $C_{25}H_{36}O_2NF_3$ Calcd: C: 68.31, H: 8.25, N: 3.19. Found: C: 68.22, H: 8.31, N: 2.98.

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24. The assay of inhibitory activities was performed by Professor Zeng-Hong Tu of Shanghai Institute of Material Medica, Chinese Academy of Sciences.

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