Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 1949–1952

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

A Practical Synthesis of 3-Substituted $\Delta^{3,5(6)}$-Steroids as New Potential 5α–Reductase Inhibitor

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Received 3 March 1998; accepted 2 June 1998

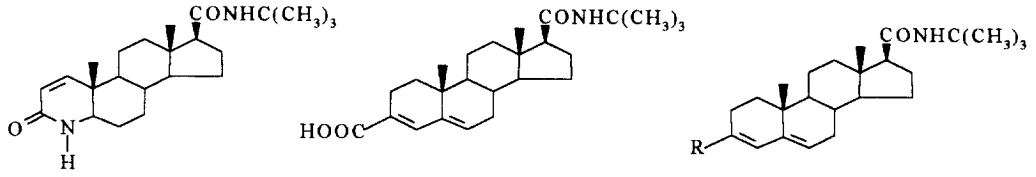
Abstract: A new and practical synthetic approach to 3-substituted $\Delta^{3,5(6)}$-Steroids, as potential 5α–reductase inhibitor, is described. The key step involves Pd-catalyzed coupling reaction of steroid 3-enol 5H-3-oxo-octafluoropentanosulfonates. 3-Phenylacetylenyl substituted $\Delta^{3,5(6)}$-steroid 3g and 3-phosphate substituted $\Delta^{3,5(6)}$-steroid 3f in our synthesized compounds exhibited high 5α–reductase inhibitory activity *in vitro* assay.

Keywords: 5α–Reductase inhibitor, synthesis, coupling reaction.

Steroid 5α–reductase is an enzyme responsible for the NADPH-dependent conversion of testosterone (T) to dihydrotestosterone (DHT).[1] It is well known that excessive accumulation of DHT related to the development of several human endocrine diseases such as benign prostatic hyperplasia(BPH), prostatic carcinoma, male pattern baldness, acne, alopecia in men and hirsutism in women.[2] Inhibition of steroid 5α–reductase can diminish the formation of DHT in the tissue of human body, thus steroid 5α–reductase inhibitor can be used as a pharmacological therapy for these diseases. For this reason, many efforts were made to search for effective 5α–reductase inhibitors. Recently several steroids with the modification of A/B ring, such as 4-aza-5α-androstan-17-carboxamide (Finasteride),[3a] 6-azasteroids,[3b] 19-nor-10-azasteroids,[3c] 4, 17-diazasteroids,[3d] 3-carboxy steroids,[3e] 4-cyanosteroids,[3f] 4-trifluoromethylsteroids[3g] and nonsteroid compounds[3h] as steroid 5α–reductase inhibitors have been reported. Of these, Finasteride has been used as a prescription drug for the treatment of prostatic hyperplasia in many countries. Epristeride (SK&F 105657), one of 3-carboxysteroids, is being clinically evaluated for treatment of BPH. In connection with our interest in 5α–reductase inhibitor and previous work about preparation of steroid 3-enol 5H-3-oxo-octafluoropentanosulfonates, we synthesized some 3-substituted $\Delta^{3,5(6)}$-steroids through the Pd-

0960-894X/98/$ - see front matter
PII: S0960-894X(98)00339-4

catalyzed coupling reaction of steroid 3-enol 5H-3-oxo-octafluoropentanosulfonates and tested their 5α–reductase inhibitory activity preliminarily. These new results will be reported in this communication.

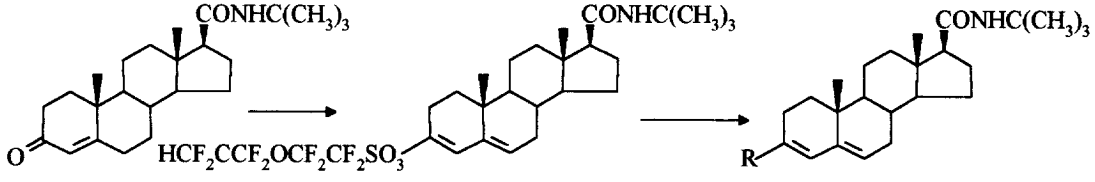


Finasteride 1 Epristeride 2 3

Scheme 1

In steroid 5α–reductase inhibitors, C-17 side chain variation has been extensively examined by Rasmusson.[4] From these studies, 17β-carboxamides exert the greatest positive effect on binding to human 5α–reductase. Holt[3e] and his coworkers observed the activities of a series of 17β-carbamoyl-3-androstene-3-carboxylic acid with varied sites of substitution and unsaturation, and then they considered that the $\Delta^{3,5(6)}$ unsaturation in steroids can enhance 5α–reductase inhibitory activity. A structure activity relationship study about steroid 5α–reductase inhibitors suggested that any steroid-derived structure with a C-3 polar group should possess 5α–reductase inhibitory activity.[5] We therefore believe that other C-3 substituted steroids should be possible to possess 5α–reductase inhibitory activity besides 3-carboxyl steroids.

Our previous studies have shown that the cheap and easily available fluorine-containing chemical, 5H-3-oxo-octafluoropenosulfonyl fluoride can replace the expensive and moisture-sensitive triflic anhydride.[6] However we still interest in the reactivity of 3-enol 5H-3-oxo-octafluoropenosulfonates. According to our previous reported method, steroid 3-ketone -17-carboxamide[3g] 4 was conveniently converted to its 3-enol 5H-3-oxo-octafluoropentano-sulfonate 5. The palladium-catalyzed carbonylation[7] of 5 in dimethylformide and methanol at 70°C produced 3-carboxylate steroid 3a in 90% yield. In the absence of methanol, this reaction can directly gave 3-carboxyl-steroid 3b (Epristeride). The steroids 3c, 3d, 3e, 3f and 3g with a variety of groups at C-3 position in compound 3 have been synthesized from 5 through palladium-catalyzed coupling reaction[8] in 74-92% yields. The results are listed in Table 1.



4 5 3

Scheme 2

Table 1 the palladium-catalyzed coupling reaction of compound 5[9]

Entry	reagents	product	yield(%)
1	CO/DMF-CH_3OH	3a, R=$COOCH_3$	90
2	CO/DMF	3b, R=COOH	70
3	HCOOH-DMF	3c, R=H	85
4	CO/DMF-Et_2NH	3d, R=$CONEt_2$	82
5	$EtOCH=CH_2$	3e, R=$COCH_3$	74
6	$HPO(OEt)_2$	3f, R=$PO(OEt)_2$	92
7	PhCCH	3g, R=CCPh	85

The experimental results shown that the enol 5H-3-oxo-octafluoropenosulfonates possess similar reactivity with enol triflates.

The compounds obtained above were examined for their inhibitory effects on rat 5α–reductase. The preliminary results are presented in Table 2.

Table 2. Inhibition of 3-substituted $\Delta^{3,5(6)}$-steroids toward 5α–reductase (Ki Value)[10]

Entry	Isotope Method $[^3H]^T \rightarrow [^3H]$–DHT	Enzymic Kinetics Method NADPH
Finasteride	88.2nM	54.7nM
3c	>>1000nM	>>1000nM
3d	>>1000nM	>>1000nM
3e	>>1000nM	>>1000nM
3f	68.5nM	18.1nM
3g	100.2nM	45.8nM

In a preliminary assay, androst-3-ene-3-phosphate 3f exhibited remarkable activity on rat 5α–reductase. The reason may be that 3f can be considered as a mimic of the putative enolate intermediate of steroid 5α–reductase. On the contrary, 3c without the polar group substitution at C-3 position did not present any inhibitory activity. Although compounds 3d and 3e possess similar polar group at C-3 position, they did not exhibit desired activity. It is very interest that 3-phenylacetylenyl substituted steroid 3g, without the basic structural feature of all of known steroid 5α–reductase inhibitors, presented good activity. It is obvious that this finding provided useful information for searching for new type of steroid 5α–reductase inhibitors.

In conclusion, we provided a new and practical synthetic approach to 3-substituted $\Delta^{3,5(6)}$-steroids involving Pd-catalyzed coupling reaction of steroid 3-enol 5H-3-oxo-octafluoropentanosulfonates. 3-Phenylacetylenyl substituted $\Delta^{3,5(6)}$-steroid 3g and 3-phosphate substituted $\Delta^{3,5(6)}$-steroid 3f in our synthesized compounds exhibited high 5α–reductase inhibitory activity.

Acknowledgement: We thank Prof. Zeng-hong Tu of Shanghai Institute of Materia Medica, Chinese Academy of Sciences for the biological assay of 3-substituted $\Delta^{3,5(6)}$-steroids **3c-3g**.

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[8] Typical procedure: A solution of 5 (680mg, 1.04mmol), diethyl phosphite (200μl, 1.55mmol), triethylamine (680μl, 4.89mmol) and $Pd(PPh_3)_4$ in DMF (4ml) was stirred at 70°C under nitrogen atmosphere over 2 hours. The reaction mixture then was diluted with ether. The etheral solution was washed with aqueous HCl and brine, and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave the crude product, which was purified by flash chromatography on silica gel column to give 3f. m.p. 207.1-207.9°C. $[\alpha]^{20}_D$ -102.89° (c 1.12, $CHCl_3$). ^{1}HNMR(300MHz, $CDCl_3$, TMS) : 0.72 (s, 3H, 18-CH_3), 0.92 (s, 3H, 19-CH_3), 1.31 (m, 2 X CH_3CH_2O), 1.36(s, 9H, $C(CH_3)_3$), 4.07 (m, 4H, 2 X CH_3CH_2O), 5.12 (s, 1H, NH), 5.76(brs, 1H, C_6-H), 6.82 (d, 1H, J = 2.0Hz, C_4-H) ppm. MS m/z: 492 (M^++1), 491 (M^+), 477, 476, 421, 420, 354. IR (film)v: 3350, 2900, 1670, 1540, 1240, 1040-1060cm^{-1}, satisfactory elemental analysis were obtained.

[9] Selective spectra for compound 3g: 3g, a colorless solid, m.p.: 184.9-188.3°C. $[\alpha]^{20}_D$ -144.77° (c 0.63, $CHCl_3$). ^{1}HNMR(300MHz, $CDCl_3$, TMS) : 0.72 (s, 3H, 18-CH_3), 0.97 (s, 3H, 19-CH_3), 1.35(s, 9H, $C(CH_3)_3$), 5.07(s, 1H, NH), 5.53(brs, 1H, C_6-H), 7.43-7.25 (m, 5H, Ar-H) ppm. MS m/z: 456 (M^++1), 455 (M^+, basic peak), 440, 355, 238, 208, 57. IR (film)v: 3350, 2900, 1640, 750, 680cm^{-1}.

[10] The assay of inhibitory activities was performed by professor Tu Zeng-Hong of Shanghai Institute of Material Medica, Chinese Academy of Sciences.