Available online at www.sciencedirect.com
SCIENCE DIRECT®
Steroids 70 (2005) 690–693
Steroids
www.elsevier.com/locate/steroids

New approach to 3-oxo-4-aza-5α-androst-1-ene-17β-(*N-tert*-butylcarboxamide)

Zhong-Xing Jiang *, Jing-Quan Ye, Li Jiang, Ying-Sheng Zhao

College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, Hubei, PR China

Received 13 December 2004; received in revised form 14 March 2005; accepted 17 March 2005
Available online 17 May 2005

Abstract

We describe the synthesis of 3-oxo-4-aza-5α-androst-1-ene-17β-(*N-tert*-butylcarboxamide) (finasteride) from 4-androstene-3,17-dione (AD) in seven steps in an overall yield of 18.6% via oxidation, ammoniumation, dehydration, and dehydrogenation.

Keywords: Steroid; 4-Androstene-3,17-dione; Finasteride; Synthesis

1. Introduction

3-Oxo-4-aza-5α-androst-1-ene-17β-(*N-tert*-butylcarboxamide), Finasteride (**1**) is an azasteroidal compound that is used in the treatment of benign prostatic hyperplasia (BPH) [1–3], which affects adult males. In addition, finasteride is also used in the treatment of hair loss [4,5] and in the prevention of prostate cancer [6].

The previously reported syntheses of finasteride, which were mostly from 3β-hydroxy-5-pregen-20-one (pregnenolone), usually involved many steps [7], and often used expensive or toxic reagents, such as 2,2-dipyridiyldisulphide and benzeneseleninic anhydride. The highest overall yield has been less than 16% [1,8,9].

Here, we describe (Fig. 1) a convenient and higher yielding approach using the Ritter reaction to introduce 17β-(*N-tert*-butylcarboxamide) [10,11] for the synthesis of finasteride from 4-androste-ene-3,17-dione in seven steps in 18.6% overall yield.

2. Experimental

Melting points were determined on a X-4 Micro Melting Point apparatus and are uncorrected. ^{1}H NMR spectra were determined on a Varian Mercury VX-300 spectrometer with TMS as the internal reference. The IR spectra were obtained in potassium bromide discs on a NICOLET-170SX spectrophotometer, and the data are reported in wavenumbers (cm^{-1}). Specific rotations were measured on a Perkin-Elmer POLARIMETER-341 instrument.

Analytical thin layer chromatography (TLC) was preformed using Merck Silica gel 60 F_{254} plates and visualized with UV light.

2.1. 5,17-Dioxo-A-nor-3,5-secoandrostan-3-oic acid (*3*)

A solution of **2** (4.0 g, 14 mmol) in a mixture of 80 mL *tert*-BuOH and 12 mL of 40% aqueous Na_2CO_3 was treated with a solution of 16.9 g of sodium metaperiodate and 0.54 g of potassium permanganate in 60 mL of water at 60 °C. After addition of the reagents, the mixture was incubated at 60 °C for another 3 h. Then, the reaction mixture was cooled to 30 °C, and after 15 min, the solids were removed by filtration. The solid was washed with water, and the combined filtrates were concentrated under reduced pressure to remove most of the *tert*-BuOH. The aqueous residue was cooled and acidified (pH 2) with 6 mol/L HCl solution. After extraction with CH_2Cl_2, the product was washed with water and dried over Na_2SO_4. Removal of solvent gave **3** (3.7 g, 88.8%) as a colorless oil, and the product was directly used for the next step without

* Corresponding author. Tel.: +86 27 68754827; fax: +86 27 68754827.
E-mail address: ioc@whu.edu.cn (Z.-X. Jiang).

0039-128X/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2005.03.009

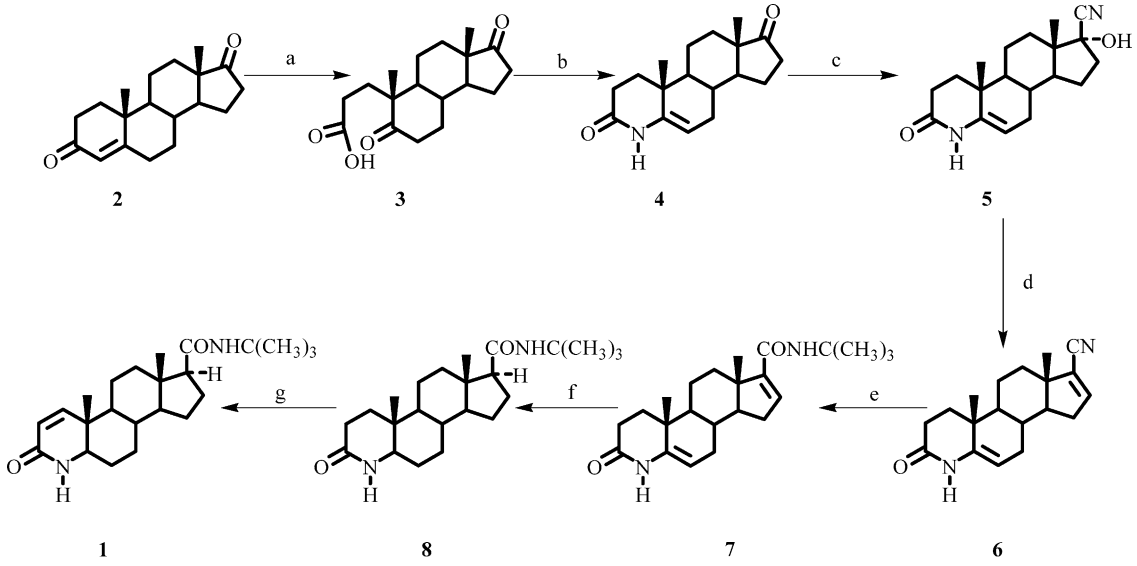

Fig. 1. Synthesis of finasteride (**1**) from 4-androstene-3,17-dione. (a) $NaIO_4$, $KMnO_4$, K_2CO_3; (b) CH_3COONH_4, CH_3COOH; (c) NaCN, CH_2Cl_2, CH_3OH, CH_3COOH; (d) $POCl_3$, pyridine; (e) $(CH_3)_3COH$, CH_3COOH, H_2SO_4; (f) Pd/C, C_2H_5OH, H_2; (g) DDQ, BSTFA, dioxane.

further purification. IR (KBr) (cm^{-1}): 3050–3500, 1736, 1703.

2.2. 4-Aza-5-androstene-3,17-dione (*4*)

A mixture of **3** (3.7 g, 12.1 mmol) and ammonium acetate (2.8 g, 36.7 mmol) in glacial acetic acid (40 mL) was stirred and heated at reflux for 4 h. After removal of the glacial acetic acid under reduced pressure, the residue was poured into water. The precipitate was filtered and washed with water to give **4** (2.7 g, 77.7%) as white crystal needles: mp > 300 °C, Ref. [12] mp = 346–348 °C. IR (KBr) (cm^{-1}): 3187, 3064, 1740, 1676, 1662. ^{1}H MNR ($CDCl_3$), δ (ppm): 7.10 (brs, 1H, NH), 4.82 (m, 1H, H-6), 1.13 (s, 3H, 19-CH_3), 0.92 (s, 3H, 18-CH_3).

2.3. 4-Aza-5-androstene-17α-hydroxy-17β-cyano-3-one (*5*)

Acetic acid (1 mL) was added to a stirred suspension of **4** (2.0 g, 6.97 mmol) and KCN (1.5 g) in MeOH (12 mL) at room temperature. Stirring was continued for 24 h, after which acetic acid (2 mL) and water (80 mL) were added. The precipitate was filtered, washed with water, and dried to give **5** (2.0 g, 91.4%) as white powder, and the product was directly used for the next step without further purification. IR (KBr) (cm^{-1}): 3270, 2227, 1680, 1650.

2.4. 4-Aza-androst-5,16-diene-17-cyano-3-one (*6*)

A suspension of **5** (2.0 g, 6.36 mmol) in a mixture of $POCl_3$ (4 mL) and pyridine (20 mL) was refluxed for 15 min. After cooling to about 60–70 °C, the reaction mixture was dropped with vigorous stirring into a mixture of ice-water (350 mL) and 37% aqueous HCl (20 mL), stirring was continued for another 40 min. The precipitate was filtered, washed with water and dried, yielding crude **6** (1.4 g, 74.3%) as a brown powder. This product was directly used for the next step without further purification. IR (KBr) (cm^{-1}): 3412, 3204, 2212, 1693, 1659.

2.5. 3-Oxo-4-azaandrosta-5,16-diene-17-(N-tert-butylcarboxamide) (*7*)

A solution of **6** (1.4 g, 4.73 mmol), acetic acid (15 mL), and *tert*-BuOH (5 mL) cooled in an ice-bath was treated with concentrated sulfuric acid (3 mL) while stirring in order to keep the temperature below 40 °C during the addition and subsequent reaction for 3 h. The reaction mixture was poured onto 200 g of ice, and the product was filtered and dried. Recrystallization from acetone afforded **7** (1.4 g, 79.9%) as white crystal needles: mp = 265–269 °C, Ref. [13] mp = 266–269 °C. IR (KBr) (cm^{-1}): 3425, 3211, 1695, 1675, 1655, 1593, 1506, 1391, 1364, 1217. ^{1}H MNR ($CDCl_3$) δ (ppm): 1.04 (s, 3H, 18-CH_3), 1.14 (s, 3H, 19-CH_3), 1.38 (s, 9H, $C(CH_3)_3$), 2.52 (m, 2H, H-2), 4.92 (s, 1H, H-6), 5.47 (brs, 1H, 4-NH), 6.19 (s, 1H, H-16), 7.79 (brs, 1H, 17-CONH).

2.6. 3-Oxo-4-aza-5α-androstane-17β-(N-tert-butylcarboxamide) (*8*)

7 (1.0 g, 2.7 mmol) in C_2H_5OH (50 mL) was hydrogenated in the presence of 0.5 g of 10% Pd/C at 10 kPa at 50 °C for 8 h. The catalyst was removed, and the solution was concentrated to dryness. Recrystallization from ethyl acetate afforded **8** (0.71 g, 70.3%, β: α < 2%) as white crystal needles: mp = 276–277 °C, Ref. [14] mp = 277–278 °C. $[\alpha]_D^{14}$ +59.02 (c = 2.425, CH_3OH). IR (KBr) (cm^{-1}): 3425, 1698, 1670, 1502, 1367. ^{1}H MNR ($CDCl_3$) δ (ppm): 5.39 (s, 1H, 4-NH), 5.07 (s, 1H, 17-CONH), 3.04 (m, 1H, 5α-H), 1.35 (s, 9H, $C(CH_3)_3$), 0.91 (s, 3H, 18-CH_3), 0.69 (s, 3H, 19-CH_3).

2.7. 3-Oxo-4-aza-5α-androst-1-ene-17β-(N-tert-butylcarboxamide) (1)

A 50 mL three neck round bottom flask equipped with a nitrogen inlet, reflux condenser, magnetic stirrer, and a septum inlet was charged with **8** (1.0 g, 2.67 mmol), DDQ (1.0 g) and dioxane (7 mL). BSTFA (3 mL) was added to this suspension with a syringe while stirring. Heating the mixture at reflux for 10 min yielded a clear solution. The solution was refluxed for 18 h at the end of which complete disappearance of starting material was observed by TLC. The suspension was cooled to room temperature and added to a mixture of 30 mL CH_2Cl_2 and 6 mL of 1% aqueous sodium bisulfite solution, precipitating the hydroquinone, which was separated by filtration. The CH_2Cl_2 layer of the filtrate was separated, extracted twice with 25 mL of 5% $NaHSO_3$, concentrated to thick oil, and triturated with diethyl ether (50 mL). The solid was isolated and dried, yielding white analytical sample **1** (0.70 g, 70.5%): mp = 253–255 °C, Ref. [1] mp = 252–254 °C. IR (KBr) (cm^{-1}): 3429, 3240, 3114, 2967, 2936, 1687, 1668, 1599, 1450, 1383, 1364, 1255, 1219, 1127, 814. ^{1}H MNR ($CDCl_3$) δ (ppm): 6.78 (d, 2H, 2-H), 5.80 (dd, 2H, 1-H), 5.37 (brs, 1H, 4-NH), 5.07 (brs, 1H, 17-CONH), 3.32 (m, 1H, 5α-H), 2.14 (dd, 1H, H-17), 1.35 (s, 9H, $C(CH_3)_3$), 0.97 (s, 3H, 19-CH_3), 0.69 (s, 3H, 18-CH_3).

3. Results and discussion

4-Androstene-3,17-dione **2** is an important intermediate for the synthesis of steroid since it is commercially available in high purity. Oxidation of 4-androsten-3,17-dione has been reported to yield 5,17-dioxo-A-nor-3,5-secoandrostan-3-oic acid **3** via two methods: (1) oxidation with Von Rudloff solution in 81.5% yield [15] and (2) ozonolysis with ozone in 93.0% yield [16]. For large-scale manufacture, we chose method (1) to oxidize **2** for the synthesis of **3**. The ring closure of **3** was carried out with ammonium acetate in acetic acid at high temperature to give 4-azaandrost-5-ene-3,17-dione **4**, which was simpler than the previously reported methods [1,12].

In order to introduce 17β-(*N-tert*-butylcarboxamide), we chose the Ritter reaction by using α,β-unsaturated carbonitrile to react with *tert*-BuOH in concentrated sulfuric and acetic acids [10,11]. Since Gasc and Nedelec reported the successful introduction of the 17β-cyano-17α-hydroxyl group in 3,3-ethylene-dioxy-19-norandtosta-5(10),9(11)-dien-17-one [17], the cyanohydrin reaction has been thoroughly investigated [18,19]. In our approach, **4** was selectively converted to 4-aza-5-androstene-17α-hydroxy-17β-cyano-3-one **5** in 91.4% yield. Dehydration of **5** with $POCl_3$ in pyridine at 120 °C gave 4-aza-androst-5,16-diene-17-cyano-3-one **6**, a small difference as described in Ref. [20]. The warm mixture was cooled to about 60–70 °C, then dropped with vigorous stirring into a mixture of ice-water and 37% aqueous HCl, and the precipitate was stirred until it hydrolyzed to jelly, the yield was 74.3%. Subsequently, this product was reacted with *tert*-BuOH in concentrated sulfuric and acetic acids, and **6** was converted to 3-oxo-4-azaandrosta-5,16-diene-17-(*N-tert*-butylcarboxamide) **7** in 79.9% yield. The introduction of 17β-(*N-tert*-butyl-carboxamide) was convenient and gave a higher yield.

Subsequently, the reduction of **7** was carried out over Pd/C in C_2H_5OH in the presence of hydrogen to give 3-oxo-4-aza-5α-androstane-17β-(*N-tert*-butylcarboxamide) **8**. Under these conditions, with the steric hindrance of the 19-CH_3 group, the 16-ene-17-(*N-tert*-butylcarboxamide) was nearly reduced to 17β-(*N-tert*-butylcarboxamide), and the reduction of the 5-ene had high selectivity for the 5α-H (5β-H: 5α-H < 2%). Finally, dehydrogenation of **8** was carried out by treatment with a suitable dehydrogenating agent, such as chloranil, benzeneseleninic anhydride, or dichlorodicyanobenzoquinone (DDQ), in an anhydrous solvent, such as chlorobenzene, dioxane, xylene, toluene, or benzene, and optionally, in the presence of BTSFA [bis(trimethylsilyl)trifluoro acetamide]. To optimize the yield, we chose DDQ and BSTFA in dioxane to dehydrogenate **8** in order to give finasteride **1** in 70.5% yield [21]. Using this sequence, finasteride was synthesized from 4-androstene-3,17-dione in 18.6% overall yield.

References

[1] Rasmusson GH, Reynolds GF, Utne T, Jobson RB, Primka RL, Berman C, et al. Azasteroids as inhibitors of rat prostatic 5α-reductase. J Med Chem 1984;27(12):1690–701.
[2] Rasmusson GH, Reynolds GF, Steinberg NG, Walton E, Patel GF, Liang T, et al. Azasteroids: structure–activity relationships for inhibition of 5α-reductase and of androgen receptor binding. J Med Chem 1986;29:2298–315.
[3] Rasmusson GH, Reynolds GF. 17beta-substituted-4-aza-5alpha-androstenones and their use as 5alpha-reductase inhibitors. Merck & Co. Inc., USA. Europe Patent 85-155096, 18 September 1985.
[4] Heinzl S. Androgenetic alopecia: finasteride treated hair loss. Med Monatsschr Pharm 1999;22(4):124–7.
[5] Tosti A, Piraccini BM. Finasteride and the hair cycle. J Am Acad Dermatol 2000;42(5 Pt 1):848–9.
[6] Coltman CA, Thompson IM, Feigl P. Prostate cancer prevention trial (PCPT) update. Eur Urol 1999;35(5–6):544–7.
[7] Li XJ, Chen LG, Fang F, Wang XJ. Graphical synthetic routes of finasteride. Chin J Pharm 2001;32(5):245–7.
[8] Zheng JH, Xu F, Liao QJ. New synthesis of finasteride. Chin J Pharm 2003;34(3):105–7.
[9] Zheng JH, Xu F, Liao QJ. Synthesis of finasteride, a new drug for the treatment of begin prostatic hyperplasia. Chin J Med Chem 1996;6(3):203–6.
[10] Ritter JJ, Minieri PP. A new reaction of nitriles. I. Amides from alkenes and mono-nitriles. J Am Chem Soc 1948;70:4045–8.
[11] Plaut H, Ritter JJ. A new reaction of nitriles. VI. Unsaturated amides. J Am Chem Soc 1951;73:4076–7.
[12] Solomons WZ, Doorenbos NJ. Synthesis and antimicrobial properties of 17-β-amino-4-aza-5α-androstane and derivatives. J Pharm Sci 1974;63(1):19–23.
[13] Zoltan T, Judit H, Janos S, Laszlo K, Gabor B. Novel process for preparing 17β-substituted-4-azaandrostane derivatives. Richter

Gedeon Vegyeszeti Gyar Rt, USA. International Patent 95-00531, 5 January 1995.

[14] Xia P, Yang ZY, Xia Y, Zhang HB, Zhang KH, Sun X, et al. Synthesis of *N*-substituted 3-oxo-17β-carboxamide-4-aza-5α-androstanes and the tautomerism of 3-oxo-4-aza-5-androstenes. Heterocycles 1998;47(2):703–16.

[15] Piniella JF, Estape J, Lupon P, Merino L, Puig M, Bonet JJ, et al. Photochemical reactions. 21. Sensitized photooxygenation of *N*-methylated 4-aza-5-androsten-3-one and 4-aza-5-androstene steroidal systems. Bull Chem Soc Jpn 1987;60(8):3011–6.

[16] Yang YY, Haino T, Usui S, Fukazawa Y. Shielding effect of ether C–O bond obtained from proton chemical shifts of 4-aza-5α- and 4-oxa-5β-androstan-17-ones. Tetrahedron 1996;52(7):2325–36.

[17] Gasc JC, Nedelec L. New approach to corticoid total synthesis. Tetrahedron Lett 1971;22:2005–8.

[18] Carruthers NI, Garshasb S. Synthesis of corticoids from 9α-hydroxyandrost-4-ene-3,17-dione. J Org Chem 1992;57:961–5.

[19] Batist JN, Barendse NC, Marx AF. The chemistry of 9α-hydroxysteroids. 3. Methods for selective formation and dehydrations of 17β-cyano-9α,17α-dihydroxyandrost-4-en-3-one. Steroids 1990;55(3):109–13.

[20] Achille P, Enrico DS, Marcella N. 17β-Substituted-4-aza-5α-androstan-3-one derivatives and process for their preparation. Farmitalia Carlo Erba, Milan, Italy. US patent 92-5155107, 13 October 1992.

[21] Bhattacharya A, Douglas AW, Grabowski EJ, Dolling UH. Dehydrogenation process and intermediates. Merck & Co. Inc., NJ, USA. European Patent 89-0298652, 11 January 1989.