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A Scaleable Synthesis of Dutasteride: A Selective 5α-Reductase Inhibitor†

Komati Satyanarayana, Katkam Srinivas, Vurimidi Himabindu,‡ and Ghanta Mahesh Reddy*,§

Department of Research and Development, Dr. Reddy's Laboratories Ltd., Integrated Product Development, Unit-III, Plot No. 116, S.V. Co-Op. Industrial Estate, Bollaram, Jinnaram, Medak Dist-502 325, A.P, India, and Institute of Science and Technology, Center for Environmental Science, J. N. T. University, Kukatpally, Hyderabad-500 072, A.P, India

Abstract:

An improved and scaleable process for Dutasteride (1), a synthetic 4-azasteroid derivative essentially used for the treatment of prostate diseases, is described.

Introduction

Dutasteride (**1**) is a selective inhibitor of the type 1 and type 2 isoforms of steroid 5α-reductase (5 AR),[1] an intracellular enzyme that converts testosterone to 5α-dihydrotestosterone (DHT). Dutasteride (**1**) is currently available in the market as a drug for benign prostatic hyperplasia[2] under the brand name of AVODART and is used for the treatment of prostate diseases such as prostate cancer, acne, male pattern baldness, hirsutism, and prostate gland enlargement.[3] The first reported synthetic method[4a] for this molecule involves a seven-step synthetic sequence (Scheme 1). Oxidation of 3-oxo-4-androstene-17β-carboxylic acid (**2**) and subsequent treatment with aqueous sodium permanganate and sodium periodate at reflux in *tert*-butanol yielded the 5-oxo-a-nor-3,5-secoandrostan-3-oic acid derivative **3**. Reaction of **3** with ammonia in refluxing ethylene glycol yielded 4-aza-androst-5-en-3-one **4**, which was subjected to hydrogenation at 60–70 °C under 40–60 psi pressure in the presence of platinum oxide catalyst to furnish 4-aza-5α-androstan-3-one **5**. Esterification of **5** with methanol and sulphuric acid and subsequent dehydrogenation of the resultant compound **6** using 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) and bis(trimethylsilyl) trifluoroacetamide (BSTFA) afforded steroidal ester **7**. Hydrolysis of **7** with caustic lye in water and methanol mixture yielded dehydrocarboxylic acid intermediate **8**, which was converted to the corresponding acid halide and reacted with 2,5-bis(trifluoromethyl) aniline (**9**) to give Dutasteride **1** in an overall yield of 5.13%.

This process suffers from several disadvantages such as (a) the large number of stages; (b) carryover impurities from compounds **5**, **6**, and **7** leading to several byproducts in subsequent stages; (c) difficulty in controlling the impurities in the active pharmaceutical ingredient (API) obtained from this process; and (d) low overall yield (5.13%). These factors made the process less viable for commercial production. Other reported synthetic procedures have similar drawbacks.[1c,4b,c] Herein we report an economic, efficient, and impurities-free synthesis of Dutasteride that meets regulatory quality requirements[5] with an overall yield of around 40%, involving a new one-pot procedure for the condensation of **10** and **11** by Ullmann–Goldberg-type condensation. Our process involved a shorter synthetic sequence, starting from 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (**5**).

Results and Discussion

In our efforts to develop a robust and scaleable route for Dutasteride **1**, we have chosen 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (**5**), a commercially available compound, as starting material. Thus oxidation[6] of compound **5** with DDQ, BSTFA, and triflic acid in toluene followed by a usual workup and recrystallisation from dichloromethane and methanol directly afforded compound **8** with 99.5 % purity and 85% yield (Scheme 2). Dehydrocarboxylic acid derivative **8** was treated with thionyl chloride in the presence of a catalytic amount of pyridine and further reacted with ammonia to give compound **10** as a crystalline solid powder with 90–92% yield with 99.5% purity (vide HPLC). Condensation of **10** with 2-iodo-1,4-bis(trifluoromethyl) benzene **11**[7] in the presence of potassium carbonate/sodium carbonate/sodium methoxide/sodium hydroxide/potassium hydroxide as a base, in dimethyl formamide/toluene/

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* To whom correspondence should be addressed. E-mail: reddyghanta@yahoo.com.

‡ J. N. T. University.

§ Present address: Department of Research and Development, Inogent Laboratories Private Limited (a GVK BIO company), 28A, IDA, Nacharam, Hyderabad-500 076, India.

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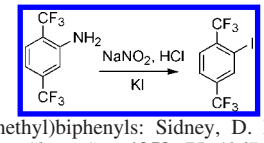
(7) Synthesis of 2-Iodo-1,4-bis(trifluoromethyl) Benzene (11). Diazotization of 1,4-bis(trifluoromethyl) aniline in the presence of sodium nitrite, hydrochloric acid, and water as medium generates diazonium ions, which will react with potassium iodide at 5–10 °C to obtain intermediate **11**.



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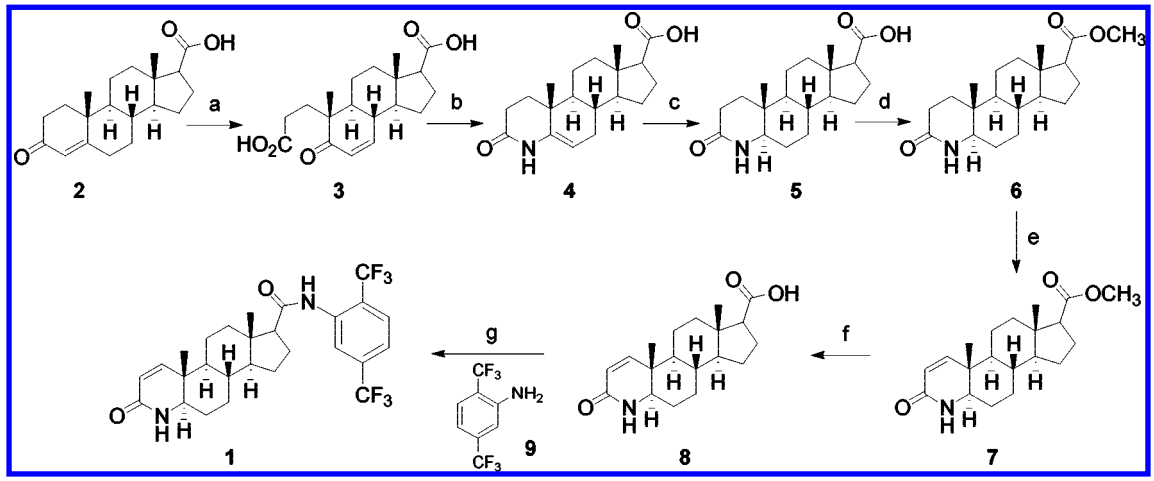
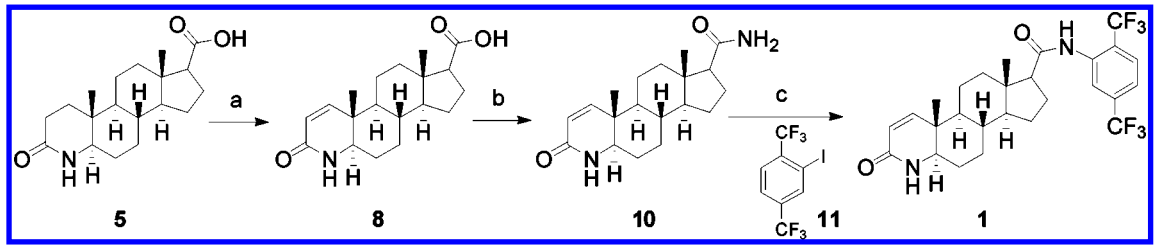
Scheme 1. **Reported synthetic scheme of Dutasteride**[a]



[a] Reagents and conditions: (a) aq $NaMnO_4$, $NaIO_4$, *tert*-butanol, 75 °C, 30–45 min; (b) dry ethylene glycol, NH_3,180 °C, 1 h; (c) CH_3CO_2H, PtO_2, 60–70 °C, 6 h under H_2/50 psi; (d) MeOH, H_2SO_4; (e) DDQ, BSTFA in dioxane, 10–12 h; (f) caustic lye, MeOH, H_2O; (g) SOCl2, toluene/CH_2Cl_2/THF, **9**, 70 °C.

Scheme 2. **Synthetic scheme of Dutasteride**[a]



[a] Reagents and conditions: (a) DDQ, BSTFA, triflic acid, toluene,10–12 h, 85%; (b) $SOCl_2$, pyridine, toluene, NH_3, 90–92%; (c) Cu powder, K_2CO_3, *o*-xylene, 140–150 °C, 50–52 h, 52.61%.

dimethyl acetamide/dimethyl sulfoxide/dimethyl imidazole as solvent medium, at high temperatures were unsuccessful. When the reaction was conducted[8–16] using copper powder and potassium carbonate without using any solvent (neat reaction), the reaction proceeded but formation of impurities was very high. However, when the reaction was conducted by using copper powder and potassium carbonate in *o*-xylene solvent medium at a temperature of 140–150 °C, **1** was obtained in 63% crude yield. Recrystallisation from acetonitrile and hydrochloric acid and a second recrystallization from a tetrahydrofuran/water mixture resulted in substantial purification of **1**. Further purification of **1** by dissolving in methanol followed by carbon treatment, filtration, and dilution of the filtrate with water, furnished Dutasteride **1** having >99.8% purity. Compounds **12**, **13**, and **14** were observed as impurities in Dutasteride **1** synthesized by our process. They were isolated and fully characterized.[17] Overoxidation[18] of **5** led to an impurity **12**, and impurity **13** was formed from traces of **5** in the amidation reaction of corresponding dehydroderivative **8**. Traces of the 5β-isomer of **5** present in **5** leads to the formation of the corresponding 5β-isomer[19,20] of Dutasteride, **14** (Scheme 3). A robust purification method was developed to control all of these impurities in **1**, so that they were at less than 0.01% levels in the pharma (vide HPLC), thus fulfilling all regulatory specifications. The overall yield and purity of the Dutasteride obtained from this process at scale-up level are summarized in Table 1.

Conclusion

We have provided an industrially viable manufacturing process for Dutasteride, which is substantially free from impurities and meets the regulatory requirements.

Experimental Section

A Waters model alliance 2695 separation module equipped with a Waters 2996 photo diode array UV detector was used in recording HPLC. Mass spectra were obtained using a Shimadzu QP-8000α mass spectrometer with an electron energy set to 1.5 kV. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$

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Scheme 3. **Synthetic scheme of Dutasteride impurities**

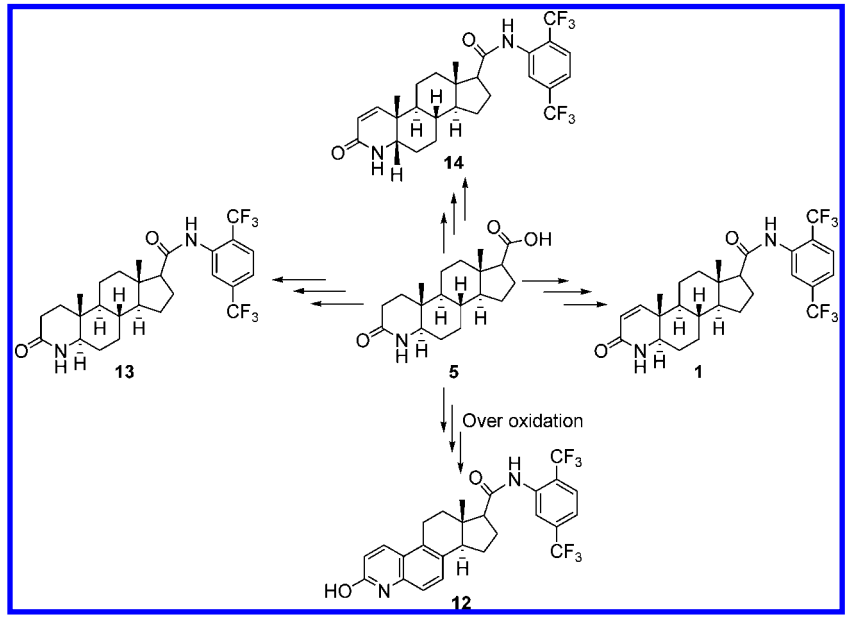

Table 1. **Impurities in Dutasteride (1) by HPLC**

no.	purity	desmethyl (**12**)	dihydro impurity (**13**)	β-isomer (**14**)	overall yield (%)
01	99.89	0.01	ND[a]	ND	40.3
02	99.91	ND	ND	0.01	40.8
03	99.93	ND	ND	0.01	40.0

[a] ND = not detected.

and DMSO-d_6, using 200 and 50 MHz, respectively, on a Varian Gemini 200 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS.

3-Oxo-4-aza-5α-androst-1-ene-17-β-carboxylic Acid (8). A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (85.3 g, 0.375 mol) in dry toluene (1500.0 mL) was heated to azeotropic reflux for 2 h. The reaction mixture was cooled to 25–35 °C, and 3-oxo-4-aza-5α-androstane-17β-carboxylic acid (100 g, 0.313 mol), bis(trimethylsilyl) trifluoroacetamide (322.2 g, 1.25 mol) and triflic acid (1.6 mL, 0.018 mol) were added. The reaction mixture was heated to 105–108 °C for 10–12 h under nitrogen atmosphere. After the reaction mixture was cooled to 50–60 °C, water (250 mL) was added, and the obtained solid was filtered. The wet material was then taken into water (100 mL), heated to 50–60 °C, and stirred for 30 min. The obtained solid was filtered under reduced pressure. The same process was repeated, and the filtered solid was washed with water (100 mL). The wet solid was added to acetone (500 mL), which was then heated to reflux temperature for 20–30 min. The resulting reaction mixture was cooled to 25–35 °C and maintained for 30–45 min. The obtained solid was filtered under reduced pressure and washed with acetone (50.0 mL). The filtered wet compound was added into a mixture of methylene chloride and methanol (600 mL), in the ratio of 8:2, which was stirred at 25–35 °C for 20–30 min. Then 80% of the solvent was distilled off under reduced pressure. After the reaction mass cooled to 25–35 °C, methanol (300 mL) was added. The solvent around 100 mL was again distilled off under reduced pressure. The reaction mixture was cooled to 25–35 °C and maintained for about 30 min. The obtained solid was filtered and washed with methanol (100 mL) and dried at 60–70 °C under reduced pressure to give the title compound. Yield 85 g (85.5%); mp 295–297 °C; M/S m/z 318 $M^+ + H$; purity by HPLC 99.5%; ^{1}H NMR ($CDCl_3$) δ 6.79 (d, J = 10.0 Hz, 1H), 5.82 (d, J = 10.0 Hz, 1 H), 5.7 (s, 1H), 3.35 (t, 1H), 1.63 (m, 2H), 1.08 (m, 2H), 1.50 (m, 1H), 1.75 (m, 2H), 2.13 (m, 2H), 1.26 (m, 1H), 1.40 (m, 2H), 1.90 (m, 2 H), 2.37 (t, 1H), 0.80 (s, 3H), 0.99 (s, 3H), 7.51 (s, br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 13.4, 21.1, 21.1, 23.6, 24.1, 25.7, 29.3, 35.3, 37.8, 39.3, 44.8, 47.5, 55.7, 58.3, 123.0, 150.7, 166.7, 171.3. Anal. Calcd for $C_{19}H_{27}NO_3$: C 71.89, H 8.57, N 4.41, O 15.12. Found: C 71.92, H 8.53, N 4.46, O 15.16. DSC: 315.09 and 336.7 °C.

3-Oxo-4-aza-5α-androst-1-ene-17-β-carboxamide (10). A solution of 3-oxo-4-aza-5α-androst-1-ene-17β-carboxylic acid (50.0 g, 0.157 mol) and toluene (750 mL) was heated at azeotropic reflux condition for 30–60 min. The resulting solution was cooled to 25 to 35 °C under nitrogen atmosphere. Pyridine (6.3 mL, 0.077 mol) was added to the cooled solution, which was then stirred for about 15 min. Then, thionyl chloride (14.0 mL, 0.188 mol) was added slowly for over a period of 20 min. The resulting reaction mixture was maintained at 25–35 °C for 2–3 h, and then ammonia gas was passed through the reaction mixture till the reaction was completed (8–10 h). After the completion, the reaction mixture was filtered and washed with toluene (100 mL). The resulting solid was dried for 1–2 h. The resultant solid was slurried in water (500 mL), and the solid was filtered and washed with water (50.0 mL) to get the reaction mass pH up to 6.5–7.5. The obtained solid was dried at 70–75 °C to yield 50.0 g, which was dissolved in a mixture of methylene chloride and methanol (8:2, 2250 mL)

and stirred for 30 min at 25–35 °C. Insoluble material was removed by filtration, and the organic solution was washed with 2% aqueous sodium hydroxide solution (3 × 63.0 mL). The solvent was distilled off about 70–80% at below 50 °C under reduced pressure. Methanol (150.0 mL) was added to the reaction mass, and about 50–60% of the solvent was distilled off under reduced pressure. After the reaction mass was stirred for 10–20 min at 25–35 °C, the obtained solid was filtered, washed with methanol (100.0 mL), and dried at 60–70 °C. Yield 45.0 g (90.28%), mp 298–302; M/S *m/z* 317 $M^+ + H$; ^{1}H NMR ($CDCl_3$) δ 6.79 (d, J = 10.0 Hz, 1H), 5.82 (d, J = 10.0 Hz, 1H), 5.7 (s, 1H), 3.35 (t, 1H), 1.63 (m, 2H), 1.08 (m, 2H), 1.50 (m, 2H), 1.75 (m, 2H) 2.13 (m, 2H),1.26 (m, 1H), 1.40 (m, 2H), 1.90 (m, 2H), 2.37 (t, 1H), 0.80 (s, 3H), 0.99 (s, 3H), 7.51 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 13.4, 21.1, 21.1, 23.6, 24.1, 25.7, 29.3, 35.3, 37.8, 39.3, 44.8, 47.5, 55.7, 58.3,123.0, 150.7, 166.7, 171.3. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C 72.12, H 8.92, N 8.85, O 10.11. Found: C 72.22, H 8.90, N 8.89, O 10.14. DSC: 362.71 °C.

2-Iodo-1,4-bis(trifluoromethyl)benzene (11). A mixture of water (250 mL) and hydrochloric acid (2385 mL, 26.2 mol) was taken into a round bottom flask and cooled to 0–5 °C. 2,5-Bis(trifluoromethyl) aniline (250 g, 1.09 mol) was added at 0–5 °C, and the resulting solution was stirred for 10 min. A solution of sodium nitrite (94.1 g, 1.36 mol) in water (415 mL) was added slowly to the reaction mass over a period of 30 min at the same temperature. The reaction mixture was stirred for 10 min, followed by addition of a solution of potassium iodide (225 g, 1.36 mol) in water (585 mL), for 30 min. After the resulting reaction mixture was heated to 60–70 °C for about 3–4 h, it was cooled to 25–35 °C and extracted with methylene chloride (2 × 250 mL). The combined organic layer was washed with 5% sodium thiosulfite solution (2 × 250 mL). Finally, the organic layer was washed with water (2 × 250 mL), and the separated organic layer was distilled off under reduced pressure to give the title compound. Yield 352.61 g (95%); purity by HPLC 98.5%; bp 89–92 °C; MS *m/z* 341 $M^+ + H$; ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 120.3, 121.7, 124.4, 124.8, 126.7, 135.0.

17β-*N*-[2,5-Bis(trifluoromethyl)phenyl]carbamoyl-4-aza-5α-androst-1-ene-3-one (Dutasteride). A mixture of potassium carbonate (11 g, 0.079 mol) and xylene (125 mL) was heated to azeotropic reflux temperature for 2 h to remove water azeotropically. The xylene mixture was cooled to about 30–40 °C, and 3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (25 g, 0.079 mol), copper powder (15.1 g, 0.237 mol), and 2-iodo-1,4-bis(trifluoromethyl) benzene (81 g, 0.238 mol) were added. Then, the resulting mixture was heated to 140–150 °C for 50–52 h. The reaction mixture was cooled to 25–35 °C, maintained for 3–4 h at the same temperature, and filtered, and the solid was washed with *o*-xylene (12.5 mL) and dried for 2 h under reduced pressure. The dried solid was added to ethyl acetate (750 mL), which was then heated to reflux for 30 min. The refluxed acetate solution was filtered to remove insoluble impurities with the help of an additional 500 mL of ethyl acetate. The filtrate was washed with aqueous ammonium chloride solution (5.0 g of NH_4Cl dissolved in 100 mL of water) at 60–65 °C, followed by water (2 × 125 mL) at 50–60 °C. The solvent was distilled off 70–75% under reduced pressure, and the remaining solution was cooled to 25–35 °C. The separated solid was filtered, washed with ethyl acetate (25 mL), and dried at 65–70 °C under reduced pressure. The obtained solid was added to a mixture of acetonitrile and hydrochloric acid (95.0 mL acetonitrile/5.0 mL of HCl), heated to 55–60 °C, cooled to 5–10 °C, filtered, and washed with same mixture (10.0 mL). The obtained solid was taken into a 1:1 mixture of tetrahydrofuran and water (375 mL), which was then heated to reflux for dissolution. After refluxing for 15 min, the hot solution was filtered. The filtrate was cooled to 25–35 °C and maintained for 2 h. The precipitated solid was filtered, washed with a (1:1) mixture of tetrahydrofuran and water (25 mL), and dissolved in methanol (175 mL), followed by carbon treatment (1.2 g). The filtrates were added to water (438 mL) at 25–35 °C for 20–30 min. Further, the reaction mass was maintained at the same temperature for 30–60 min, filtered, and washed with water (50.0 mL). The product was dried at 80–90 °C. Yield 22.0 g (52.61%); purity 99.89%; mp 254–258 °C; Cu-content not detected, heavy metals <10 ppm; MS *m/z* 529 $M^+ + H$; ^{1}H NMR, ($CDCl_3$) δ 6.79 (d, J = 10.0 Hz, 1H), 5.82 (d, J = 10.0 Hz, 1 H), 5.70 (s, br, 1H), 3.35 (t, 1H), 1.63 (m, 2H), 1.08 (m, 2H), 1.50 (m, 1H), 1.75 (m, 2H), 2.13 (m, 2H), 1.26 (m, 1H), 2.29 (m, 2H), 2.37 (t, 1H), 0.80 (s, 3H), 0.99 (t, 3H), 7.51 (s, 1H), 8.77 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 13.4, 21.1 23.6 24.1, 25.7, 29.3, 35.3, 37.8, 39.3, 44.8, 47.5, 55.7, 58.3, 59.5, 120.3,121.7, 123.0, 126.7, 126.7, 136.3, 150.7, 166.7, 171.3. Anal. Calcd for $C_{27}H_{30}F_6N_2O_2$: C 61.36, H 5.72, N 5.30, O 27.62. Found: C 61.35, H 5.68, N 5.27, O 27.60. DSC: 250.36 °C.

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