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Mettilda Lourdusamy [a], Fernand Labrie [a] & Shankar M. Singh [a]

[a] Medicinal Chemistry Division, Laboratory of Molecular Endocrinology, CHUL Research Center, Québec City, Québec, GIV 4G2, Canada

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Synthesis of Atamestane (SH 489): An Aromatase Inhibitor

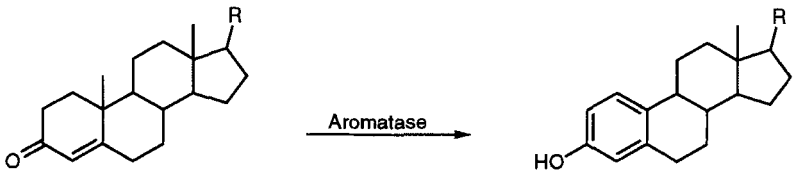
Mettilda Lourdusamy, Fernand Labrie, and Shankar M. Singh*

Medicinal Chemistry Division, Laboratory of Molecular Endocrinology, CHUL Research Center, Québec City, Québec GIV 4G2, Canada

ABSTRACT: Atamestane (SH 489) was synthesized from 17β-Acetoxy-1α-methyl-5α-androstan-3-one. Thus dibromination followed by dehydrobromination of the A-ring gave dienone (5) in good yield, which was hydrolyzed and oxidized to give the title compound in 60% overall yield.

Recently, aromatase inhibitors have attracted much attention due to their potential use in the treatment of several estrogen-dependent diseases, especially breast cancer[1] and benign prostatic hyperplasia (BPH).[2] Aromatase[3] catalyzes the formation of estrone and estradiol from androstenedione or testosterone respectively (Scheme 1). Many derivatives of androstenedione function as inhibitors of estrogen biosynthesis both in vitro and in vivo.[1,2,4] Out of these, (1-Methyl-1,4-androstadiene-3,17-dione) atamestane **1** has been characterized as a potent competitive inhibitor of estrogen biosynthesis in

*To whom correspondence should be addressed.



R = O, Androstenedione

R = 17β-OH, Testosterone

R = O, Esterone

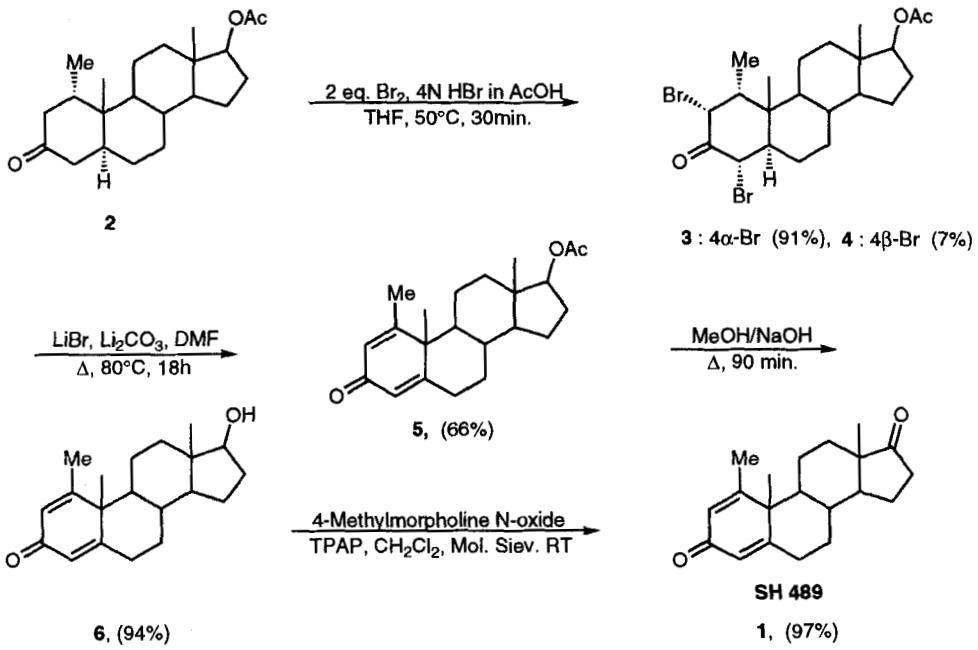
R = 17β-OH, Estradiol

Scheme 1

several model systems, both in vitro and in vivo.[5] In in vivo studies, atamestane has been found to reduce serum estrogen levels in female rats, the aromatization of testosterone or androstenedione in monkeys[5-7] and the peripheral levels of estrogens in healthy volunteers.[8] It has also been reported to reduce prostate weight in the monkey.

A number of approaches have been patented to synthesize atamestane utilizing testosterone and androstenedione derivatives as starting materials.[9] A key step in the above synthesis is the halogenation of 2,3-enol silyl or acetyl ether of the 4-en-3-one system. Herein, we describe the synthesis of atamestane from 1α-Methyl-17β-acetoxy-5α-androstan-3-one via dibromination and dehydrobromination of the A-ring.

Scheme 2 outlines our synthetic approach using 17β-Acetoxy-1α-methyl-5α-androstan-3-one as starting material, which was obtained from commercially available dihydrotestosterone (DHT) following the method of Westermann et al.[10] Dibromination of 1α-methylandrostan-3-one **2** with 2 eq. of bromine in 4N HBr in acetic acid[11] gave 91% of 2α,4α-dibromo compound **3**, along with 7% of 2α,4β-dibromo compound **4**. The structures of both isomers were confirmed by NMR spectroscopy.[12] Thus, for compound **3**, the 4α-configuration of the dibromide was established by coupling of the 4β-H (axial)



Scheme 2

with the 5α-H (axial) which was 12 Hz, and in the case of compound **4**, the 4β-configuration was determined by coupling of the 4α-H (equatorial) with the 5α-H (axial) leading to a *J* value of 5 Hz. Dehydrobromination of isomers **3** and **4** with $CaCO_3$[13] gave many unidentified compounds. Reaction with MgO[9] also failed to give 1,4-diene **5**. However, when anhydrous Li_2CO_3 and LiBr were used as dehydrobrominating agents,[14] 1,4-diene-3-one **5** was obtained, the best yield (66%) being obtained when the reaction was carried out at 80°C. Hydrolysis under usual conditions gave 17β-hydroxy steroid **6**, which was then oxidized with tetra-n-propylammonium perruthenate[15] to give 1-methylandrosta-1,4-diene-3,17-dione (**1**) in quantitative yield.

In conclusion, synthesis of atamestane was achieved by simple dibromination and dehydrobromination, and with bench top reagents with an overall yield of 60%.[16]

EXPERIMENTAL PROCEDURE

General. Unless otherwise mentioned, materials obtained from commercial suppliers were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. All reactions except those involving acetic acid as solvent were carried out under an argon atmosphere. Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. IR spectra were recorded in KBr pellets with a Perkin-Elmer 1600 Series FT Infrared Spectrometer. ^1H NMR spectra were obtained in $CDCl_3$ solutions with a Brucker Aspect - 3000 (300 MHz) and are reported as ppm downfield from Me_4Si. ^{13}C NMR spectra were measured at 75.14 MHz with a Bruker Aspect - 3000. High resolution mass spectra were measured at the Department of Chemistry, University of Montreal, Montreal, Quebec.

17β-Acetoxy-2α,4α-dibromo-1α-methyl-5α-androstan-3-one (3) and 17β-Acetoxy-2α,4β-dibromo-1α-methyl-5α-androstan-3-one (4). To a solution of 1α-methylandrostan-3-one **2** (2.913 g, 8.44mmol) in AcOH (25 ml) was added bromine (2.646 g, 1.96 eq) in AcOH (2 ml) at 50°C with vigorous stirring fallowed by 4N HBr in AcOH (2.5 ml) and the reaction mixture was stirred at rt for 30 min. After extraction with CH_2Cl_2 (3 X 200 ml), and several washings of the organic layer with saturated $NaHCO_3$ and water, the organic layer was dried and evaporated to afford a white crystalline solid, which was purified by a flash chromatography using hexane/acetone (gradient 0-10%) as an eluent to give

2α,4α-dibromide **3** (3.807 g, 91%); mp 190°C. IR (KBr, cm^{-1}) 1745,1724,1255. ^1H NMR ($CDCl_3$) δ 0.79 (s, 3 H), 0.93 (d, 3 H, J = 7 Hz), 1.26 (s, 3 H), 2.01 (s, 3 H), 4.56 (d, 1 H, J = 13 Hz), 4.57 (t, 1 H, J = 8 Hz), 5.2 (d, 1 H, J = 4.6 Hz). ^{13}C NMR ($CDCl_3$) δ 192.2, 171, 82.3, 60.2, 58.1, 50.3, 49.6, 49.5, 49.1, 42.8, 42.7, 36.5, 34.9, 30.5, 27.4, 27.3, 23.3, 21.1, 20.1, 16.4, 12.1, 9.3. EI-MS m/s (relative intensity) 505 (M^+, 40), 504 (22), 445 (30), 425 (12), 154 (75), 137 (100). HRMS Calcd for $C_{22}H_{33}O_3Br_2$, 503.0818; found 503.0796, and 2α,4β-dibromide **4** (292 mg, 7% yield); mp 145°C. IR (KBr, cm^{-1}) 1739, 1727 1255. ^1H NMR ($CDCl_3$) δ 0.79 (s, 3 H), 0.93 (d, 3 H, J = 7 Hz), 1.47 (s, 3 H), 2.02 (s, 3 H), 4.35 (d, 1 H, J = 5 Hz), 4.57 (t, 1 H, J = 8 Hz), 5.8 (d, 1 H, J = 4.6 Hz) ^{13}C NMR ($CDCl_3$) δ 195.3, 171.1, 82.4, 56.2, 53.9, 50.6, 49.3, 42.8, 42.7, 41.5, 36.4, 34.7, 30.8, 27.4, 26.6, 23.4, 22.6, 21.1, 19.2, 16.3, 12.1, 8.9. EI-MS m/s (relative intensity) 504 (M^+, 26), 504 (12), 445 (18), 363 (16), 307 (80), 289 (50), 154 (100). HRMS Calcd for $C_{22}H_{33}O_3Br_2$, 503.0818; found 503.0796.

17β-Acetoxy-1-methyl-1,4-androstadiene-3-one (5). Dibromide **3** (200 mg, 0.397mmol) in absolute DMF (25 ml) was heated at 80°C with anhydrous Li_2CO_3 (177 mg, 6.1 eq) and anhydrous LiBr (203 mg, 5.9 eq) over a period of 16 h under an atmosphere of argon. After cooling, the mixture was poured into water and extracted with CH_2Cl_2 (3 X 75 ml). The organic layer was washed with water and dried. The product was purified by a flash column chromatography using hexane/acetone (gradient 0-13%) as an eluent to give 1,4-diene **5** (88 mg, 66%); mp 135°C. IR (KBr, cm^{-1}) 1717, 1728, 1664, 1240. ^1H NMR ($CDCl_3$) δ 0.83 (s, 3 H), 1.33 (s, 3 H), 2.02 (s, 3 H), 2.1 (s, 3 H), 4.54 (t, 3 H J = 8 Hz), 6.06 (s, 1 H), 6.16 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 186, 171, 170, 165.8, 129.3, 123.8, 82.3, 57.1, 50, 48.1, 42.1, 36.7, 35.3, 34.3, 33.1, 27.3, 25.1, 23.9, 23.6, 21.1, 16.3, 11.9. EI-MS m/s (relative intensity) 342 (18), 300 (8), 267 (6). HRMS Calcd for $C_{22}H_{30}O_3$, 342.2190; found 342.2194.

17β-Hydroxy-1-methyl-1,4-androstadiene-3-one (6). To the 17β-acetoxy compound **5** (880 mg, 2.5 mmol) in MeOH (50 ml) were added NaOH (100 mg, 1 eq.) and water (0.5 ml). The reaction mixture was refluxed for 90 min, MeOH was evaporated and the product was extracted with CH_2Cl_2 (3 X 150 ml). The organic layer was washed with 2N aq. HCl and water, and then dried to obtain 1,4-diene-3-one **6** (725 mg, 94%); mp 120°C. IR (KBr, cm^{-1}) 3404, 1665, 1605. ^1H NMR ($CDCl_3$) δ 0.77 (s, 3 H), 1.31 (s, 3 H), 2.03 (s, 1 H), 2.09 (s, 3 H), 3.56 (t, 3 H, J = 8 Hz), 6.04 (s, 1 H), 6.14 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 186, 170.5, 166.3, 129.1, 123.5, 81.3, 57.4, 50.2, 48.2, 42.4, 36.4, 35.4, 34.4, 33.1, 30.1, 25.2, 23.7, 23.6, 16.2, 11. EI-MS m/s (relative intensity) 300 (54), 272 (12), 187 (18), 161 (42). HRMS Calcd for $C_{20}H_{28}O_2$, 300.2077; found 300.2089.

1–Methyl-1,4-androstadiene-3,17-dione (1). Solid tetra-n-propylammonium perruthenate (121 mg, 5 mol %) was added to a stirring mixture of alcohol **6** (725 mg, 2.42 mmole), 4-methylmorpholine N-oxide (425 mg, 1.5 eq) and powdered 4A° molecular sieves (1.210 g, 500 mg/mmol) in CH_2Cl_2 (50 ml) at rt under argon. The mixture was stirred for 30 min and filtered through a bed of silica gel and eluted with a mixture of CH_2Cl_2/acetone (4/1). The filtrate was evaporated and the residue was filtered through a bed of silica gel using hexane/acetone (gradient 0-10%) as an eluent to give 1,4-diene-3,17-dione **1** (699 mg, 97%); mp 165°C (lit[9b] mp 165-166°C). IR (KBr, cm^{-1}) 1735, 1662, 1621. ^1H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 1.31 (s, 3 H), 2.07 (s, 3 H), 6.03 (s, 1 H), 6.12 (s,1 H). ^{13}C NMR ($CDCl_3$) δ 219.7, 185.6, 169.4, 165.4, 129.3, 123.8, 57, 50.4, 47.8, 46.9, 35.4, 34.9, 33.4, 32.7, 31.1, 24.6, 23.5, 22, 16.1, 13.5. EI-MS m/s (relative intensity) 298 (42), 270 (9), 255 (11), 159 (65), 136 (100). HRMS Calcd for $C_{20}H_{26}O_2$, 298.1926; found 298.193.

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