Improved Syntheses of Epristeride, a Potent Human 5α-Reductase Inhibitor

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Two improved syntheses of a potent human 5α-reductase inhibitor, epristeride, SK&F 105657, are described. The first synthesis starts from methyl 3-oxoandrost-4-ene-17β-carboxylate (**1**), which is converted to epristeride (**5**) in four synthetic steps in 44% overall yield. The second synthesis starts from commercially available 3-oxoandrost-4-en-17β-carboxylic acid (**7**), which is converted to epristeride (**5**) in two synthetic steps in 63% overall yield. Both syntheses are suitable for large scale production and have been employed to produce kilograms supplies of epristeride in high purity.

Benign prostatic hyperplasia (BPH) is a progressive disease characterized by a benign enlargement of the prostate gland which affects a large fraction of men over 50 years of age. Typical symptoms include increased frequency or urgency to urinate, which results from increased pressure on the urethra. It has been well established that growth of the prostate is stimulated by androgens, and it now appears that 5α-dihydrotestosterone (DHT) plays a primary role in the trophic support of this organ.[1] Preclinical studies have demonstrated selective retardation of prostate growth by inhibition of human steroid 5α-reductase (SR), an enzyme responsible for the conversion of testosterone (T) into DHT. Thus selective inhibition of SR[2] could offer an alternative therapy for BPH, for which surgery has been the primary treatment.

Epristeride (**5**, SK&F 105657) is a potent uncompetitive (vs T) inhibitor of DHT which belongs to a family of 3-androstene-3-carboxylic acids and is being clinically evaluated for the treatment of BPH. In our role as process development chemists, we sought to develop a cost-effective route for the multikilogram production of epristeride in pure form. Although epristeride was synthesized by Holt[3] and co-workers using an eight-stage procedure starting from pregnenolone, this synthesis was not suitable for large-scale production due to the expense associated with triflic anhydride and multiple required chromatographies. Our initial strategy focused on the preparation of key intermediate **4**, which we reasoned could be converted into epristeride by halogen–metal exchange and carboxylation, or metal-catalyzed carbonylation.

Accordingly, as shown in Scheme 1, methyl 3-oxoandrost-4-ene-17β-carboxylate[4] (**1**) was converted to methyl 3-bromoandrosta-3,5-diene-17β-carboxylate (**2**) in 85% yield by treatment with phosphorus tribromide in glacial acetic acid.[5] Saponification of **2** in methanolic potassium hydroxide afforded **3**, which was further converted to key intermediate **4** in 75% yield by generation of the acid chloride in situ and quenching into excess *tert*-butylamine.

Preliminary attempts to effect halogen–metal exchange and carboxylation by treatment of bromo diene **4** with excess *n*-butyllithium in THF at −78 °C and quenching with carbon dioxide afforded epristeride which was accompanied by a significant amount of **6**, as well as low level *n*-butylated impurities.[6] Attempts to inhibit these byproducts by adding **4** to an excess of *n*-butyllithium were not successful. In an effort to improve the efficiency of this conversion, we reasoned that selective deprotonation of **4** should improve the efficiency of the C-3 carbanion formation. After some study it was found that ethylmagnesium chloride was effective for this purpose. Although the extent of amide deprotonation could be estimated by ^{1}H NMR analysis after quenching a reaction aliquot into deuterium oxide, we found that a more suitable method to establish the extent of deprotonation was by directly examining an aliquot by FT-IR for the absence of the amide carbonyl stretching absorption. We observed that treatment of a THF solution of **4** at 30 °C with 1.5 equiv of ethylmagnesium chloride in THF was required to effect complete deprotonation as judged by FT-IR and ^{1}H NMR analyses. This phenomenon may result from complexation and/or aggregation of the Grignard reagent in solution. Subsequent treatment of the solution of amide anion with 3.3 equiv of *sec*-butyllithium in THF was required to effect efficient bromine–lithium exchange at C-3. Carboxylation of the resulting C-3 carbanion afforded crude epristeride in 78% yield. Crude epristeride was purified and converted to the desired polymorph by heating a suspension in ethyl acetate at reflux.

This synthesis offers significant advantages over its prototype. It uses cheap, readily available reagents and proceeds in high overall yield without the use of chromatography. This synthesis was successfully employed for the production of over 45 kg of epristeride for preclinical testing.

With the commercial availability of 3-oxoandrost-4-en-17β-carboxylic acid (**7**), we were able to further improve

† Deceased October 29, 1993.

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(1) Levy, M. A.; Brandt, M.; Sheedy, K. M.; Dinh, J. T.; Holt, D. A.; Garrison, L. M.; Bergsma, D. J.; Metcalf, B. W. *J. Steroid Biochem. Molec. Biol.* **1994**, *48*, 197–206.

(2) Metcalf, B. W.; Levy, M. A.; Holt, D. A. *Trends Pharmacol. Sci.* **1989**, *10*, 491–495.

(3) Holt, D. A.; Levy, M. A.; Oh, H.-J.; Erb, J. M.; Heaslip, J. I.; Brandt, M.; Lan-Hargest, H.-Y.; Metcalf, B. W. *J. Med. Chem.* **1990**, *33*, 943–950.

(4) Johnston, D. B. R. U.S. Patent 4 179 453, 1979.

(5) Ross, J. A.; Martz, M. D. J. *Org. Chem.* **1964**, *29*, 2784–2785.

(6) HPLC analysis indicated the presence of several low level impurities, whose LC-MS analyses were consistent with *n*-butylated and C-3 butylated byproducts.

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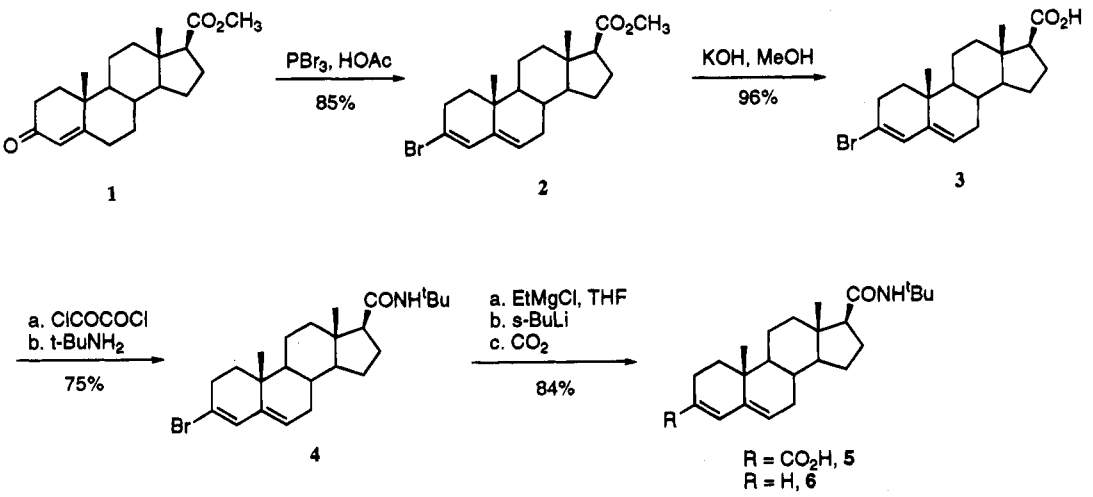
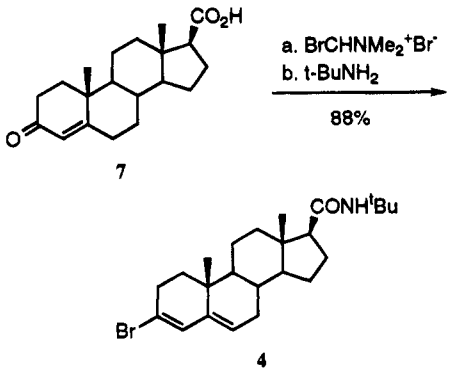
Scheme 1



Scheme 2



the synthesis of epristeride by designing an efficient two-stage process, shown in Scheme 2. Acid **7** was treated with 2.5 equiv of a suspension of (bromomethylene)-dimethylammonium bromide[7] in dichloromethane, prepared in situ from oxalyl chloride, dimethylformamide, and hydrogen bromide, followed by quenching into an excess of *tert*-butylamine to afford pure crystalline **4** in 88% yield. Key intermediate **4** was converted to epristeride, as described above. This synthesis constitutes a very efficient, cost-effective approach to the manufacture of pure epristeride and has been successfully used for the production of over 80 kg of pure epristeride for clinical testing.

Experimental Section

Unless stated elsewhere, experiments were performed under a slight static pressure of nitrogen. 3-Oxoandrost-4-en-17β-carboxylic acid (**7**) is available from Berlichem, Wayne, NJ. Tetrahydrofuran was used as reagent grade from J.T.Baker without further purification. Phosphorus tribromide was technical grade from Aldrich Chemical Co. Nuclear magnetic resonance spectra were obtained on a Bruker AM 400 using tetramethylsilane as a reference. Infrared spectra were measured on a Perkin-Elmer Model 1320 infrared spectrophotometer. FT-IR spectra were measured using CaF_2 cells on Nicolet 20SXB or Perkin-Elmer 983G FT-IR spectrometers equipped with triglycine sulfate (TGS) detectors. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C CHN Analyzer.

(7) Arnold, Z.; Holy, A. *Collect. Czech. Chem. Commun.* **1961**, *26*, 3059. We have also found this reagent is effective for converting β-diketones to β-bromo enones. See: Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30*, 3753–3755.

Preparation of Methyl 3-bromoandrosta-3,5-diene-17β-carboxylate (2). Methyl 3-oxoandrost-4-ene-17β-carboxylate[4] (500 g, 1.5 mol) was dissolved in glacial acetic acid (2.5 L) by stirring at room temperature. Phosphorus tribromide (615 g, 2.27 mol) was added over 45 min at room temperature. The dark mixture was stirred at room temperature for 21 h, during which time product precipitated from solution. HPLC assay (C_{18} μ-Bondapak, 10 μm, 3.9 mm × 30 cm; mobile phase 80% acetonitrile, 20% 0.05 M aqueous sodium perchlorate adjusted to pH 2.7 with perchloric acid; 240 nm; 1.0 mL/min, 0.1 AUFS) indicated complete consumption of the starting material. The solid product was collected by filtration and washed with 500 mL of cold glacial acetic acid, followed by 3 × 450 mL portions of chilled methanol. The product was dried under vacuum at 40–50 °C to afford 502 g (85%) of pure methyl 3-bromoandrosta-3,5-diene-17β-carboxylate (**2**): mp 180-182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 6.27 (1H, bs), 5.40 (1H, bs), 3.67 (3H, s), 0.96 (3H, s), 0.69 (3H, s); IR (Nujol, cm^{-1}) 1725, 1610. Anal. Calcd for $C_{21}H_{29}BrO_2$: C, 64.12; H, 7.43; Br, 20.31. Found: C, 63.99; H, 7.56; Br, 20.20.

Preparation of 3-Bromoandrosta-3,5-diene-17β-carboxylic acid (3). Methyl 3-bromoandrosta-3,5-diene-17β-carboxylate (**2**) (495.4 g, 1.26 mol) was added to a solution made from 86% potassium hydroxide pellets (494.3 g, 8.82 mol) and methanol (4.45 L), and the mixture was heated at reflux until the starting material was <0.5% area by HPLC assay (C_{18} μ-Bondapak, 10 μm, 3.9 mm × 30 cm; mobile phase 80% acetonitrile, 20% 0.05 M aqueous sodium perchlorate adjusted to pH 2.7 with perchloric acid; 240 nm; 1.0 mL/min, 0.1 AUFS; this typically takes about 24 h). The resulting clear solution was cooled to 60 °C and the desired product was precipitated by acidifying the stirred solution with 1300 mL of 3 N HCl, 360 mL of 6 N HCl, and 150 mL of concd HCl. Dilute acid was initially used to avoid gumming. The final pH was 1.5 by paper. The suspension was stirred in an ice–water bath for 2 h. The product was collected by filtration and washed with 500 mL of cold water. The product wet cake was slurried in 6 L of water at room temperature for 1 h and was collected by filtration. The product was washed with 1 L of water and dried under vacuum at 60–80 °C to afford 463 g (96%) of 3-bromoandrosta-3,5-diene-17β-carboxylic acid (**3**): mp 250–251 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 6.27 (1H, bs), 5.40 (1H, bs), 0.97 (3H, s), 0.77 (3H, s); IR (Nujol, cm^{-1}) 3233, 1725, 1696, 1614. Anal. Calcd for $C_{20}H_{27}BrO_2$: C, 63.33; H, 7.17; Br, 21.07. Found: C, 63.44; H, 7.12; Br, 21.37.

Preparation of 3-Bromo-*N*-(1,1-dimethylethyl)androsta-3,5-diene-17β-carboxamide (4). A suspension of 3-bromoandrosta-3,5-diene-17β-carboxylic acid (**3**) (400 g, 1.05 mol) in toluene (4 L) was heated to reflux, and the solution was dried by removing 250 mL of toluene by distillation. The solution was chilled to 3–5 °C and the resulting suspension was treated over 20 min with oxalyl chloride (226 mL, 2.58 mol) while maintaining the temperature below 10 °C. The mixture was warmed to room temperature and stirred for 3–4 h. HPLC

analysis[8] of an aliquot of the resulting clear solution indicated that no starting material remained. The solvent was removed under vacuum (to remove excess oxalyl chloride) while maintaining a pot temperature between 35 and 40 °C. The residue was dissolved in fresh toluene (2 L), and the solution was cooled to 15–20 °C and treated dropwise with *tert*-butylamine (400 mL, 3.80 mol) while maintaining the temperature below 25 °C. The mixture was warmed to room temperature and stirred for 30 min. Water (500 mL) was added, and the two-phase mixture was filtered to remove any solids. The aqueous phase was separated and extracted with toluene (2 × 500 mL). The combined organic extracts were washed with 10% aqueous sodium hydroxide (200 mL) and brine (200 mL). The organic phase was dried over magnesium sulfate and concentrated under vacuum while maintaining the temperature below 45 °C. The resulting residue was triturated with *tert*-butyl methyl ether (500 mL), and the resulting suspension of product was stirred at 0–5 °C for 2 h. The solid product was collected by filtration and washed with cold *tert*-butyl methyl ether (100 mL) and hexane (500 mL). The product was dried under vacuum at 40 °C to afford 339 g (75%) of pure 3-bromo-*N*-(1,1-dimethylethyl)androsta-3,5-diene-17β-carboxamide (**4**) as a white solid: mp 184–186 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) 6.27 (1H, bs), 5.40 (1H, bs), 5.09 (1H, bs), 1.35 (9H, s), 0.97 (3H, s), 0.71 (3H, s); IR (Nujol, cm^{-1}) 3450, 3415, 1650. Anal. Calcd for $C_{24}H_{36}BrNO$: C, 66.35; H, 8.35; Br, 18.39. Found: C, 66.60; H, 8.40; Br, 18.60.

Preparation of 17β-[[(1,1-Dimethylethyl)amino]carbonyl]androsta-3,5-diene-3-carboxylic Acid (Epristeride, 5). A solution of 3-bromo-*N*-(1,1-dimethylethyl)androsta-3,5-diene-17β-carboxamide (**4**) (12.0 kg, 27.6 mol) in tetrahydrofuran (266 kg) was warmed to 31 °C under a nitrogen atmosphere. Ethylmagnesium chloride (15.0 kg, 24.5% w/w in THF, Chemetall, 41.4 mol) was added and the solution was stirred at 30–40 °C for 54 min. FT-IR assay of an aliquot indicated complete deprotonation (as evidenced by the complete disappearance of the carbonyl stretch at 1676 cm^{-1}). The solution was cooled to −10 °C and *sec*-butyllithium (48.2 kg, 12.1% w/w in cyclohexane, 91.2 mol) was added over 42 min while maintaining the reaction temperature below 0 °C. The reaction mixture was stirred at 0–5 °C for 15 min and was gassed with an dry carbon dioxide (30.4 kg, 691 mol) over 36 min with cooling. The mixture was warmed to room temperature and was quenched with a solution made of 38.7 kg of concd HCl and 88 L of water. The organic phase was separated and washed with water (200 L and 133 L). Water (100 L) was added, and the organic phase was removed under vacuum. The resulting slurry was dissolved by adding 2-butanone (95 kg). The organic phase was separated and washed twice with demineralized water (120 L). The organic phase was filtered through Celite, rinsed with 25 kg of 2-butanone, and concentrated under vacuum (to remove approximately 100 L of distillate). The solution was cooled to 0–5 °C and stirred for 1 h. Petroleum ether (60–80 °C, 196 L) was added to induce cystallization. The suspension was stirred at 0–5 °C for 1 h. The solid product was collected by filtration and washed with cold petroleum ether (74 L). The product was dried under vacuum at 50 °C to afford 9.3 kg (84%) of 17β-[[(1,1-dimethylethyl)amino]carbonyl]androsta-3,5-diene-3-carboxylic acid (epristeride, **5**) as a white solid.

Epristeride (5) was converted to the desired polymorph by heating a slurry in six volumes (w/v) of ethyl acetate at reflux for 2 h, cooling, and collecting by filtration. Pure epristeride was dried under vacuum at 50–60 °C and was isolated with 85% recovery: ^{1}H NMR ($CDCl_3$, 400 MHz) 9.50 (1H, bs), 7.16 (1H, bs), 5.87 (1H, bs), 5.12 (1H, bs), 1.36 (9H, s), 0.92 (3H, s), 0.73 (3H, s); IR (Nujol, cm^{-1}) 3439, 1678, 1661, 1632, 1605, 1499, 1290, 1277. Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.33; N, 3.51; Found: C, 75.12; H, 9.34; N, 3.49. $[\alpha]^{25}_D$ = −127.9° (*c* = 1, MeOH).

Preparation of 3-bromo-*N*-(1,1-dimethylethyl)androsta-3,5-diene-17β-carboxamide (4) from 30Oxoandrost-4-en-17β-carboxylic Acid (7). A mixture of dimethylformamide (144 g, 1.98 mol) and dichloromethane (2.5 L) was cooled to 0–5 °C. The mixture was carefully treated with oxalyl chloride (244 g, 1.98 mol) while maintaining the reaction temperature between 0 and 5 °C. Some foaming occurred, and the resulting white suspension was stirred for 1 h. The suspension was gassed with hydrogen bromide (442 g, 5.15 mol) while maintaining the reaction temperature between 5 and 10 °C. A clear solution was formed. Dichloromethane (1.25 L) was removed under vacuum, and fresh dichloromethane (1.25 L) was added. This distillation/fill procedure was repeated to remove excess HBr and HCl from the reaction. The resulting white suspension was treated with 3-oxoandrost-4-en-17β-carboxylic acid (**7**) (250 g, 0.79 mol) and stirred at room temperature. The suspension changed to a clear solution, and after 3 h the reaction was quenched into a stirred cold solution of *tert*-butylamine (577 g, 7.89 mol) in dichloromethane (1.25 L) while maintaining the quench temperature between 10 and 15 °C. The mixture was stirred for 30 min and water (1 L) was added. The two-phase mixture was filtered through Celite. The aqueous phase was separated and washed with dichloromethane (200 mL). The combined organic phases were concentrated to half their volume under vacuum and restored to their original volume with acetone. This concentration/fill procedure was repeated to ensure complete replacement of dichloromethane. The final volume of the acetone solution was adjusted to 4 L. Water (1.0 L) was added with stirring, and the resulting suspension was cooled at 0–5 °C for 2 h. The solid product was isolated by filtration and was washed with cold 50% aqueous acetone (500 mL). The product was dried under vacuum at 50 °C to afford 307 g (88%) of pure 3-bromo-*N*-(1,1-dimethylethyl)androsta-3,5-diene-17β-carboxamide (**4**).

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(8) About ten drops of the aliquot are quenched with 10 drops of methanol containing an equal volume of triethylamine. The mixture is allowed to stand for 5 min, and 6–8 drops are diluted with about 10 mL of mobile phase; C_{18} μ-Bondapak, 10 m, 3.9 mm × 30 cm; mobile phase 80% acetonitrile, 20% 0.05 M aqueous sodium perchlorate adjusted to pH 2.7 with perchloric acid; 240 nm; 1.0 mL/min, 0.1 AUFS.