A Novel, Practical Synthesis of Estra-1,3,5(10)-triene-3,17β-dicarboxylic Acid 17-*tert*-Butylamide (SK&F 105656) from Estrone, via a Palladium-Catalyzed Methoxycarbonylation of a 3-Fluorosulfonate

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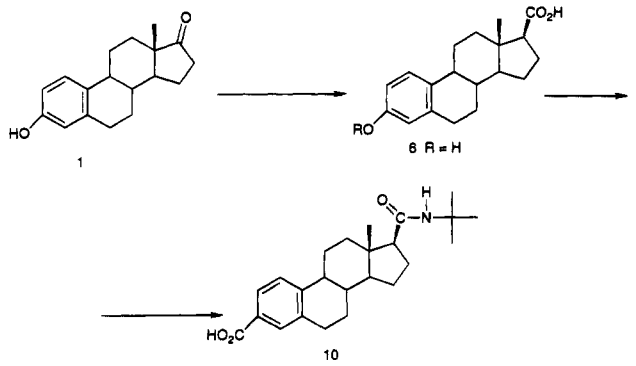
The title compound was prepared in nine steps from estrone in 22% overall yield. Each step was performed on a 50–150 gal scale and 3.5 kg of the title compound was prepared. Estrone was converted to its 3-methanesulfonate with methanesulfonyl chloride. The 17-cyanohydrin was prepared using trimethylsilyl cyanide. Dehydration with phosphorus oxychloride/pyridine followed by Pd/C-catalyzed hydrogenation gave the 17β-cyano-3-hydroxyestra-1,3,5(10),16-tetraen-3-yl methanesulfonate derivative stereoselectively. Hydrolysis with sodium hydroxide in ethylene glycol gave a 3/1 β/α mixture of 17-carboxylic acid isomers. Reaction with Vilsmeier reagent and quenching into *tert*-butylamine, followed by selective crystallization, yielded the desired 3-hydroxyestra-1,3,5-(10)-triene-17β-carboxylic acid *tert*-butylamide. Reaction with fluorosulfonic anhydride yielded the 3-fluorosulfonate. Palladium-catalyzed carbonylation in the presence of methanol gave the 3-carboxylic acid methyl ester, which was saponified to yield SK&F 105656.

Introduction

The 5α-reductase-inhibiting drugs have recently gained much attention both in the scientific literature and in the popular press.[1] In our capacity as process development chemists it became necessary to find a way to make estra-1,3,5(10)-triene-3,17β-dicarboxylic acid 17-*tert*-butylamide (**10**) (SK&F 105656), a leading candidate for 5α-reductase inhibitor development, in a timely, efficient, and economical manner.[2] A previously published synthesis of this compound suffered from two drawbacks.[3] First, the synthesis required the use of more than 2 equiv of relatively expensive triflic anhydride.[4] Second, the synthesis afforded tarry product mixtures upon scaleup, making silica gel chromatography unavoidable. We concluded that a less expensive replacement for the triflate moiety was required. A review by Stang[5] suggested that a fluorosulfonate ester might serve as an economical alternative to triflate in nucleophilic substitution reactions, and we felt it might also serve as a substitute in palladium-catalyzed carbonylation reactions. While we were developing this idea and applying it to the synthesis of SK&F 105656, Roth[6] and co-workers published reports relating to the use of fluorosulfonates as an alternative to triflates in palladium-catalyzed chemistry. We hope to demonstrate in this report that aryl fluorosulfonates can be made and reacted in an efficient and cost effective manner on a 50-gal scale and that the world of palladium-catalyzed coupling *via* triflates, previously inaccessible to the process development chemist due to expense, is now available *via* the chemistry of fluorosulfonates.

Scheme 1. General Approach to SK&F 105656 (10)



Results and Discussion

Scheme 1 outlines our general approach to **10** from estrone. In analyzing our approach to this molecule two possibilities for the synthesis of the key intermediate **6** were explored. In the first case the reaction of tosylmethyl isocyanide with ketones in the presence of potassium *tert*-butoxide to yield nitriles was exploited.[7] Estrone in *tert*-butyl alcohol with 10 equiv of potassium *tert*-butoxide was treated with 1.2 equiv of tosylmethyl isocyanide in DME over 6 h. After workup involving multiple acid/base extractions, the crude product was dissolved in ethylene glycol, treated with 20 equiv of sodium hydroxide, and heated at 160 °C for 4–6 h.[8] This yielded **6** as a 4/1 mixture of C-17β/α isomers. Recrystallization from acetonitrile yielded **6** as the C-17β isomer

† Deceased October 29, 1993.

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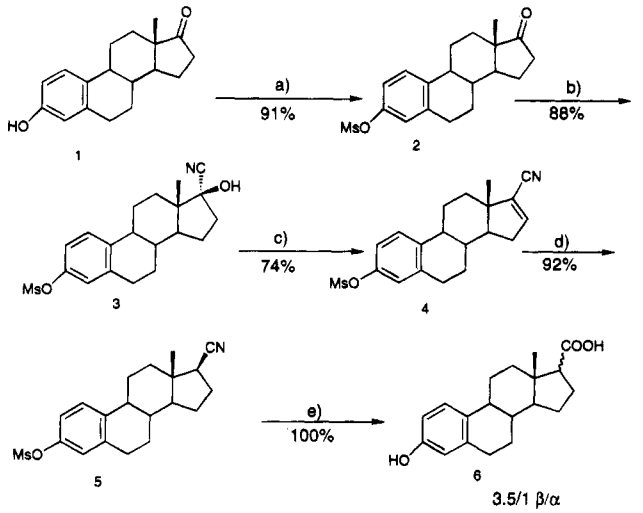
Scheme 2[a]



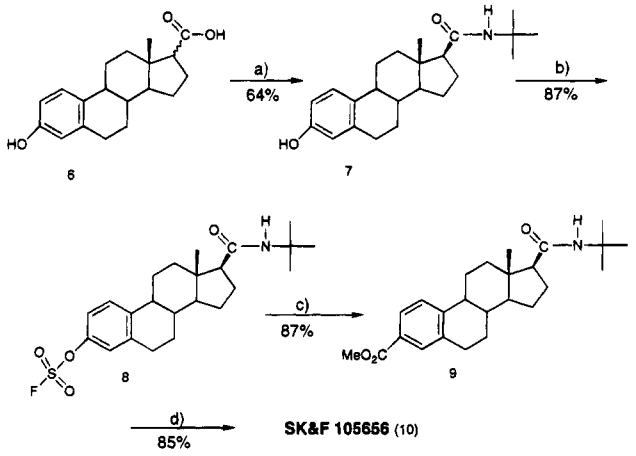
[a] (a) MsCl, TEA, CH_2Cl_2; (b) TMSCN, ZnI_2, CH_2Cl_2; (c) $POCl_3$, pyridine; (d) 10% Pd/C, H_2, CH_2Cl_2; (e) NaOH, ethylene glycol, 160 °C.

in 60% yield from estrone. This method offered a rapid entry into **6** but the high cost of tosylmethyl isocyanide forced us to find a different approach.

A synthesis published by Barton[9] offered a straightforward, high yield, albeit longer approach to **6**, and this is outlined in Scheme 2. The second step of this synthesis was not amenable to large scale work since it involved an acid-catalyzed cyanation using a large excess of potassium cyanide. Cyanation using trimethylsilyl cyanide with zinc iodide catalysis proved to be an excellent alternative.[10] Thus estrone was methanesulfonated in methylene chloride to give **2** in 91% yield. Treatment with trimethylsilyl cyanide/zinc iodide in dichloromethane followed by acidic workup produced cyanohydrin **3** in 88% yield. Dehydration using phosphorus oxychloride/pyridine gave **4** in 74% yield. Hydrogenation of **4** with 10% Pd/C at 26 psig, followed by recrystallization from ethanol, gave **5** as the C-17β isomer in 92% yield. Hydrolysis of **5** with sodium hydroxide in ethylene glycol at 160 °C gave a quantitative yield of **6** as a 3.5/1 mixture of C-17β/α isomers. At this point we were faced with the problem of separating the isomers without losing an unacceptably high amount of product. It was reasoned that by carrying the mixture through to later steps one could eliminate the unwanted C-17α isomer through the recrystallization of a later intermediate.

Crude **6** (Scheme 3) was treated with Vilsmeier reagent[11] and quenched into *tert*-butylamine in methylene chloride to yield **7.** Fortuitously, the C-17β isomer crystallized selectively from the workup mixture and was obtained in 64% yield. Fluorosulfonation of **7** was complicated by the fact that fluorosulfonic anhydride is not presently commercially available.[12] The necessary fluorosulfonic anhydride was prepared by the reaction of fluorosulfonic acid with cyanuric chloride.[13] In certain

Scheme 3[a]



[a] (a) DMF, oxalyl chloride, *tert*-butylamine, CH_2Cl_2; (b) $(FSO_2)_2O$, TEA, CH_2Cl_2; (c) DMSO, MeOH, $Pd(OAc)_2$, dppp, CO, TEA; (d) MeOH/H_2O, NaOH.

cases (simple, substituted phenols) the use of fluorosulfonic anhydride may be avoided by using the Hedayatullah procedure for the synthesis of fluorosulfonates.[14] In this procedure the phenol was treated with sulfuryl chloride to yield a chlorosulfonate, which was reacted with KF in acetic acid to yield the fluorosulfonate. This procedure failed in the fluorosulfonation of **7** due to reaction of sulfuryl chloride with the amide moiety. Fluorosulfonation of **7** with fluorosulfonic anhydride proceeded smoothly in methylene chloride/TEA to yield **8** in 87% yield. Methoxycarbonylation of **8** followed the procedure of Dolle[15] with certain modifications. It was found that although methanol is essential to the reaction, as a source of OMe, the reaction proceeds at a faster rate when about 4–5 equiv of methanol are present. With this decreased amount of methanol the reaction can be run effectively with 0.5–1.0 mol % catalyst, even on a 50-gal scale. Whereas, on a 50-gal scale the reaction was complete in 15 min, on a smaller scale the reaction required 1–4 h to go to completion. The increase in rate is probably related to the superior mixing obtained in a baffled 50-gal vessel. Cooling the reaction mixture to 18 °C caused precipitation of **9** as a white solid in 87% yield. Hydrolysis of **9** in NaOH/MeOH went smoothly, but isolation was a problem due to the product precipitating as an intractable paste upon acidification. Warming the pasty mixture to 60 °C caused granulation to occur and allowed easy isolation. Recrystallization from acetonitrile afforded **10** as a white solid in 85% yield.

Conclusion

We have demonstrated that estrone can be efficiently and inexpensively converted to **10** on a production scale. We have demonstrated that estrone-3-fluorosulfonates are easily methoxycarbonylated on a large scale and the SK&F 105656 produced by this synthesis meets all specifications for purity including limits for heavy metals.[16] Future development in the use of fluorosulfonates

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(11) Bossard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653.
(12) On the basis of an approximate bulk price of $2.00/kg for fluorosulfonic acid, we estimate that fluorosulfonic anhydride can be prepared for less than $20.00/kg.
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(16) Specification for heavy metals is <20 ppm.

in organic synthesis await a dependable source of fluorosulfonic anhydride.

Experimental Section

All commercially obtained solvents and reagents were reagent grade unless otherwise specified and were used without further purification. All water was deionized (DI, 7–15 $\mu\Omega$). Melting points were measured on a capillary melting point apparatus and are uncorrected. HPLC was performed using a Waters C_{18} μ-Bondapak column (10 μ, 3.9 mm × 30 cm).

Reagents: Estrone (99.6%) was obtained from Schering AG. Methanesulfonyl chloride (99%) was obtained from Atochem Corp. Triethylamine (98%) (TEA) was obtained from K. K. Grelx Corp. Trimethylsilyl cyanide (96%) was obtained from Fluka Chem. Zinc iodide (98%) was obtained from BDH Corp. Pyridine (99%) was obtained from Synthetic Chemicals Ltd. Phosphorus oxychloride (reagent) was obtained from Albright and Wilson. Sodium chloride was obtained from ICI. Sodium hydroxide (98.4%) was obtained from Mallinkrodt. Dimethylformamide (DMF) (99%) was obtained from Aldrich. Oxalyl Chloride (98%) was obtained from Raylo. *tert*-Butylamine (98%) was obtained from Aldrich. Carbon monoxide (99.5%) was obtained from Union Carbide. Palladium on carbon (10%) and palladium acetate (48.2% Pd) were obtained from Engelhard. 1,3-Bis(diphenylphosphino)propane (dppp) was obtained from Lancaster Synthesis.

Solvents: Dichloromethane (reagent) was obtained from ICI. Methanol and hydrochloric acid (36–38%) were obtained from Hays Corp. Dimethyl sulfoxide was obtained from Spectrum Chemicals. Ethylene glycol (99.9%) was obtained from Union Carbide. Ethanol (99%) was obtained from Hayman Ltd. Ethyl acetate (99%) was obtained from Alcohols Ltd. Acetonitrile (99.9%) was obtained from Spectrum Chemicals. Tetrahydrofuran (THF) (HPLC Reagent) was obtained from Baker.

Preparation of 3-[(Methanesulfonyl)oxy]estra-1,3,5-(10)-trien-17-one (2). A solution of **1** (15.9 kg, 58.88 mol) and triethylamine (16.1 kg, 159.41 mol) in dichloromethane (87.5 L) was cooled to 0–5 °C and treated with methanesulfonyl chloride (15.1 kg, 131.82 mol) over 1 h while maintaining the temperature between 0–5 °C. The mixture was stirred for 3 h, after which time HPLC assay (60% acetonitrile/40% 0.05 M TFA, 220 nm) indicated <0.5% area estrone. The solution was quenched with 40 L of water with stirring. The organic phase was separated and washed with 3 N hydrochloric acid (40 L), followed by water (40 L). The organic phase was subjected to vacuum distillation (the pot temperature was maintained below 40 °C) and dichloromethane (40 L) was removed. Methanol (40 L) was added, and the solution was again subjected to vacuum distillation so as to remove another 40 L of solvent. Crystallization occurred during this concentration. Methanol (40 L) was added and the resulting suspension was cooled to 0–5 °C and stirred for 2 h. The crystalline product was isolated by centrifugation and washed with cold methanol (8 L, 0–5 °C). The product was dried under vacuum to afford **2** (18.6 kg, 91%) as a crystalline white solid. The product was identical to previously reported **2**.[9]

Preparation of 17α-Cyano-3,17β-dihydroxyestra-1,3,5-(10)-triene 3-Methanesulfonate (3). A solution of **2** (18.4 kg, 52.87 mol) and zinc iodide (0.50 kg, 1.57 mol) in dichloromethane (11.8 L) was treated at 20–30 °C with trimethylsilyl cyanide (7.84 kg, 79.02 mol). The solution was heated to reflux for 25 min, cooled to 20–25 °C, and stirred for 2 h, 35 min. HPLC assay (60% acetonitrile/40% 0.05 M TFA, 220 nm) indicated <0.5% area of remaining **2**. The reaction solution was quenched with concd hydrochloric acid (7.82 L) and was heated to reflux for 30 min, during which time a thick slurry formed. [Note: HCN is evolved. Take appropiate precautions!] An additional 14 L of dichloromethane and 7.8 L of water were added, and the heating was continued until the solids dissolved. The organic layer was separated. The aqueous phase was extracted with dichloromethane (7.8 L). The organic phases were combined and distilled under vacuum, maintaining the pot temperature below 40 °C. The methylene chloride was replaced with methanol by addition of methanol and distillation of the azeotrope. The resulting slurry was cooled to 0–5 °C. The solid product was isolated by centrifugation and was washed with cold methanol (0–5 °C, 7.6 L). The product was dried under vacuum and **3** (17.5 kg, 88% yield) was obtained as a white crystalline solid. The product was identical to previously reported **3**.[9]

Preparation of 17-Cyano-3-hydroxyestra-1,3,5(10),16-tetraene 3-Methanesulfonate (4). A solution of **3** (16.42 kg, 43.78 mol) in pyridine (67.68 kg, 856.71 mol) was treated with phosphorus oxychloride (27.0 kg, 176.09 mol) and heated to reflux for 9.5 h. After 9 h, HPLC assay (60% acetonitrile/40% 0.05 M TFA, 220 nm) indicated the reaction was complete. The reaction was cooled to about 70 °C and was quenched into well-stirred 0–5 °C 6 N hydrochloric acid (140 L), while maintaining the temperature below 35 °C. The solution was treated with ethyl acetate (346.0 L) and deionized water (381 L), and the mixture was stirred for 5 min. The aqueous phase was separated and extracted with ethyl acetate (100 L). The organic phases were combined and washed with brine (60 L). The organic phase was distilled under vacuum, keeping the pot temperature below 40 °C. The methylene chloride was removed by azeotropic distillation with absolute ethanol. The resulting slurry was cooled to 0–5 °C and stirred for 3 h. The solid product was isolated by centrifugation and was washed with 30 L of cold (0–5 °C) absolute ethanol. The product was dried under vacuum to afford **4** (11.5 kg, 74% yield) as a white crystalline solid. The product was identical to previously reported **4**.[9]

Preparation of 17β-Cyano-3-hydroxyestra-1,3,5(10)-triene 3-Methanesulfonate (5). A suspension of **4** (10.8 kg, 30.25 mol) and 10% palladium on carbon (1.1 kg) in dichloromethane (108.0 L) was hydrogenated at about 26 psig for a total of 3.5 h. The solution was then cooled to room temperature and stirred for 2 h and 15 min. HPLC assay (60% acetonitrile/40% 0.05 M TFA, 220 nm) indicated < 0.5% of **4** remained. The mixture was filtered to remove the catalyst, and the filtrate was vacuum distilled to a volume of 54 L while maintaining the pot temperature below 40 °C. The methylene chloride was replaced by azeotropic distillation with ethanol. The resulting suspension was cooled to 5 °C and stirred for 2 h. The solid product was isolated by centrifugation and was washed with cold ethanol (0–5 °C, 10 L). The product was dried under vacuum to afford **5** (9.97 kg, 92% yield) as a white crystalline solid. The product was identical to previously reported **5**.[9]

3-Hydroxyestra-1,3,5(10)-triene-17-carboxylic acid (6). A solution of sodium hydroxide (35.4 kg, 885 mol) in ethylene glycol (208.0 L) was charged with **5** (10.3 kg, 28.69 mol) and the mixture was heated to 155–160 °C for 7.5 h, after which HPLC assay (60% acetonitrile/40% 0.05 M TFA, 220 nm) indicated the reaction was complete. The solution was cooled to about 110 °C and was treated with DI water (208 L) and enough hydrochloric acid (85.35 kg) to adjust the pH to 1.5. The resulting suspension was cooled to 0–10 °C and stirred for 1 h, 10 min. The solid product was isolated by centrifugation and was washed with DI water. The product was dried under vacuum to afford **6** (8.58 kg, 100% yield). HPLC assay indicated 74.6% of the C17-β isomer of **6** and 21.1% of the C17-α isomer. mp 275–277 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (s, 1 H), 8.95 (s, 1 H), 7.02 (d, J = 8.5 Hz, 1 H), 6.48 (dd, J = 8.4 Hz, 2.53 Hz, 1 H), 6.41 (d, J = 2.41 Hz, 1 H), 2.69 (br s, 2 H), 2.40–2.19 (m, 2 H), 2.18–1.88 (m, 3 H), 1.85–1.60 (m, 3 H), 1.50–1.17 (m, 6 H), 0.64 (s, 3 H); IR (KBr) 1715, 1608 cm^{-1}. MS ($C_{19}H_{24}O_3$) calcd 300.1725, found 300.1715.

3-Hydroxyestra-1,3,5(10)-triene-17β-carboxylic Acid *tert*-Butylamide (7). A solution of 4.15 kg DMF (4.15 kg, 56.77 mol) in dichloromethane (105.3 L) was stirred under nitrogen and cooled to 0 °C. The reaction mixture was treated with oxalyl chloride (7.21 kg, 56.80 mol) over a 20 min period, while keeping the reaction temperature below 10 °C. The mixture was stirred for 1.25 h and the temperature was lowered to 2 °C, after which **6** (4.25 kg, 14.2 mol) was added. The mixture was stirred at 10 °C for 4 h, at which time HPLC analysis (65% acetonitrile/35% 0.05 M TFA, 220 nm) indicated

that the reaction was complete. The reaction mixture was quenched into a solution of *tert*-butylamine (10.4 kg, 142.2 mol) in dichloromethane (35 L). After 1.0 h, deionized water (37 L) was added and the mixture was cooled to 0–10 °C for 1.0 h. The solid was isolated by centrifugation and was washed with DI water (160 L). The product was dried under vacuum to afford **7** (3.21 kg , 63.5% yield) as a white crystalline solid: mp 305–307 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (s, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 6.87 (s, 1 H), 6.49 (dd, J = 8.3 Hz, 2.4 Hz, 1 H), 6.41 (d, J = 2.3 Hz, 1 H), 2.76–2.65 (m, 2 H), 2.29–2.16 (m, 2 H), 2.15–1.97 (m, 2 H), 1.87–1.44 (m, 5 H), 1.39–1.17 (m, 5 H), 1.25 (s, 9 H), 0.57 (s, 3 H); IR (KBr) 1637, 1582, 1252 cm^{-1}. Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.89; H, 9.46; N, 3.91.

3-[(Fluorosulfonyl)oxy]estra-1,3,5(10)-triene-17β-carboxylic Acid *tert*-Butylamide (8). A slurry of **7** (6.35 kg, 17.86 mol) and triethylamine (3.64 kg, 36.04 mol) in dichloromethane (115.0 L) was cooled to −8 °C under nitrogen. The mixture was treated with fluorosulfonic anhydride (4.70 kg, 25.54 mol) over 15.5 min. After 0.5 h HPLC analysis (80% acetonitrile/20% water, 220 nm) indicated the reaction was complete. After 1.5 h the reaction mixture was treated with deionized water (30 L) and the layers were allowed to separate. The organic layer was separated and the solvent was removed by azeotropic distillation with deionized water. When the process temperature reached 100 °C the distillation was stopped and the mixture was cooled to 60 °C. The aqueous slurry was treated with DMSO (143.0 L) and heated to reflux. The mixture was cooled to 20 °C for 1.0 h and the solid was isolated by centrifugation. The product was washed with deionized water (65.0 L) and dried under vacuum to afford **8** (6.7 kg, 86.5% yield) as a white crystalline solid: mp 138–141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.7 Hz, 1 H), 7.08 (dd, J = 8.6 Hz, 2.36 Hz, 1 H), 7.04 (s, 1 H), 5.12 (s, 1 H), 2.95–2.84 (m, 2 H), 2.39–2.04 (m, 5 H), 1.99–1.90 (m, 1 H), 1.83–1.73 (m, 2 H), 1.63–1.27 (m, 6 H), 1.37 (s, 9 H), 0.72 (s, 3 H); IR (KBr) 1675, 1501, 1392, 1365 cm^{-1}; MS (DCI/methane) m/z 438 (M + H)$^+$, 354 (M^+ − FSO_2), 338 (M^+ − FSO_3). Anal. Calcd for $C_{23}H_{32}FNO_4S$: C, 63.13; H, 7.37; F, 4.34; N, 3.20; S, 7.33. Found: C, 62.97; H, 7.38; F, 4.24; N, 3.02; S, 7.41.

Preparation of 3-(Methoxycarbonyl)estra-1,3,5(10)-triene-17β-carboxylic Acid *tert*-Butylamide (9). A solution of 66.4 kg of DMSO (73.1 L), triethylamine (3.40 kg, 33.66 mol), methanol (2.64 kg, 82.5 mol), and dppp (0.063 kg, 0.152 mol) was stirred under nitrogen. The solution was treated with **8** (6.70 kg, 15.31 mol) and was stirred until a solution was obtained. The cloudy solution was treated with palladium acetate (0.03429 kg, 0.153 mol). The reactor was sealed and evacuated to a vacuum of 20 in. Hg and pressurized to 7 psi with CO. The process was repeated. The reaction mixture was slowly heated to 75 °C. At 60 °C carbon monoxide uptake began and an exotherm was observed. After 15 min carbon monoxide uptake slowed and the reaction was stirred under 7 psi carbon monoxide at 75 °C for 1.5 h. At that time HPLC analysis (80% acetonitrile/20% 0.05% TFA, 220 nm) indicated the reaction was complete and the mixture was cooled to 18 °C for 2.0 h. The solid product was isolated by centrifugation[17] and was washed with deionized water (114.0 L) and then dried under vacuum to yield **9** (5.31 kg, 87.2% yield) as a white crystalline solid: mp 157–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 1 H), 7.75 (s, 1 H), 7.34 (d, J = 8.1 Hz, 1 H), 5.14 (s, 1 H), 3.89 (s, 3 H), 2.95–2.85 (m, 2 H), 2.43–2.05 (m, 5 H), 1.98–1.88 (m, 1 H), 1.84–1.70 (m, 2 H), 1.67–1.28 (m, 6 H), 1.37 (s, 9 H), 0.72 (s, 3 H); IR (KBr) 1716, 1676, 1610, 1501, 1394, 1364 cm^{-1}; MS (DCI/methane) m/z 398 (M + H)$^+$, 366 (M + H − CH_3OH)$^+$.

Preparation of Estra-1,3,5(10)-triene-3,17β-dicarboxylic Acid 17-*tert*-Butylamide (10). A solution of sodium hydroxide (1.58 kg, 39.50 mol) in 50/50 methanol/water (52 L) was stirred for 0.5 h. The solution was treated with **9** (5.1 kg, 12.83 mol) and heated to reflux. After 45 min HPLC analysis (70% acetonitrile/30% 0.05 M TFA, 220 nm) indicated the reaction was complete. The reaction was filtered through supercell and the pad was washed with hot water (30 L). The reaction mixture was distilled under atmospheric pressure to a pot temperature of 101 °C. The reaction mixture was cooled to 69 °C and quenched into 1.5 M HCl (52 L). The mixture was stirred at 60 °C for 2 h and filtered. The product was isolated by centrifugation and was washed with 750 L of water. The crude product was recrystallized from 20/1 acetonitrile/THF (100 L) and was isolated by centrifugation. The product was dried under vacuum to yield **10** (4.1 kg, 85%) as a white crystalline solid: mp 238–240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.66 (d, J = 8.1 Hz, 1 H), 7.62 (s, 1 H), 7.38 (d, J = 8.2 Hz, 1 H), 6.90 (s, 1 H), 2.85 (br s, 2 H), 2.39–2.14 (m, 3 H), 2.12–1.97 (m, 1 H), 1.89–1.78 (m, 2 H), 1.75–1.20 (m, 8 H), 1.25 (s, 9 H), 0.58 (s, 3 H); ^{13}C NMR (90.54 MHz, $CDCl_3$) δ 171.3, 169.6, 145.4, 136.2, 129.8, 126.5, 126.3, 124.5, 76.6, 76.3, 75.9, 56.9, 54.6, 50.4, 50.3, 48.7, 43.8, 43.2, 37.9, 37.5, 28.5, 28.2, 26.6, 25.5, 23.3, 22.6, 12.3; IR (KBr) 1686, 1660, 1610, 1571, 1512 cm^{-1}; $[\alpha]_D$ +61.0° (c 0.026, MeOH). Anal. Calcd for $C_{24}H_{33}NO_3$: C, 75.16; H, 8.67; N, 3.65. Found: C, 74.89; H, 8.79; N, 3.74.

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(17) No attempt was made to recover the palladium from the mother liquor.