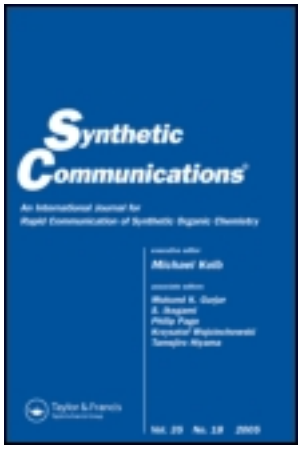

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Improved and Scalable Synthetic Route to the Synthon 17-β-(2-Carboxyethyl)-1,3,5(10)-estratriene: An Important Intermediate in the Synthesis of Bone-Targeting Estrogens

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IMPROVED AND SCALABLE SYNTHETIC ROUTE TO THE SYNTHON 17-β-(2-CARBOXYETHYL)-1,3,5(10)-ESTRATRIENE: AN IMPORTANT INTERMEDIATE IN THE SYNTHESIS OF BONE-TARGETING ESTROGENS

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An improved, highly scalable methodology for the multigram-scale preparation of an important synthon, 17-β-(2-carboxyethyl)-1,3,5(10)-estratriene, is described. Previous approaches have failed to provide useful quantities of the analytically pure product because of facile retro-Michael breakdown of the β-alkoxy carbonyl precursors during workup and isolation operations. The synthetic approach described herein has been designed specifically to sidestep this problematic breakdown process. This new scalable method of preparation overcomes a major hurdle in the exploration of structure–activity relationships centered around novel estradiol derivatives with bone-targeting properties and also provides a scalable process for subsequent developmental work.

Keywords: Bone-targeting; estradiol; retro-Michael addition

INTRODUCTION

Disorders arising from bone resorption constitute a major health concern in the United States and elsewhere in the world. A third of all postmenopausal caucasian women have osteoporosis, and 54% have osteopenia.[1] One of the potentially useful pharmacological actions of the anabolic steroid estradiol (**1**) and its derivatives is that they inhibit the bone resorption that occurs in such disorders. The utility of these steroids is limited, however, because of their nonspecific effects on a number of other physiological systems.

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RESULTS AND DISCUSSION

A few years ago, we explored a prodrug strategy utilizing **1** to selectively target bone tissue.[2] This strategy consisted of conjugating calcium-chelating small molecules, such as the salicylamide derivative **2**, to the 17-β-hydroxy functionality of **1**. Salicylamide derivatives are known to possess a strong affinity for divalent calcium ions.[3] In our previous studies, we have described the interaction of compounds such as **2** with hydroxyapatite in bone tissue, which is advantageous, because large concentrations of hydroxyapatite are usually found in locations of bone tissues that are in the process of undergoing resorption. Two classes of compounds were synthesized: compound **3**, which incorporates succinoyl linker units, and compound **4**, with carboxyethyl linker units (Fig. 1). 17-β-ester-linked compounds such as **3** were found to possess poor hydrolytic stability in vivo, and were cleaved prior to their arrival at the site of action.

It was found that when the labile succinoyl ester bond of **3** was replaced with a carboethoxy linker (as in **4**), the resulting compounds retained targeting and anabolic properties. Additionally, the carboethoxy linker was found to possess high stability toward in vivo hydrolysis. Thus, **4** was chosen as a lead compound for further structure–activity relationship studies.

Synthesis of a library of compounds structurally related to **4** mandated the development of a methodology for the preparation of the key intermediate 17-β-(2-carboxyethyl)-estra-1,3,5(10)-triene (**5**). Analytically pure samples of **5** were required for several studies, including pharmacological testing, toxicity analysis,

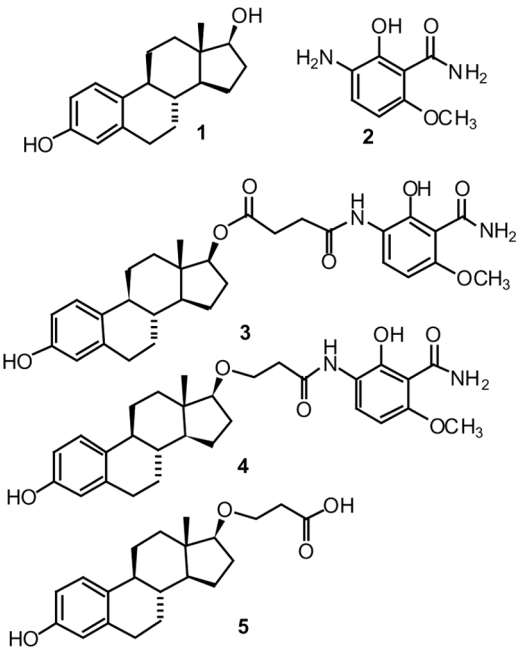
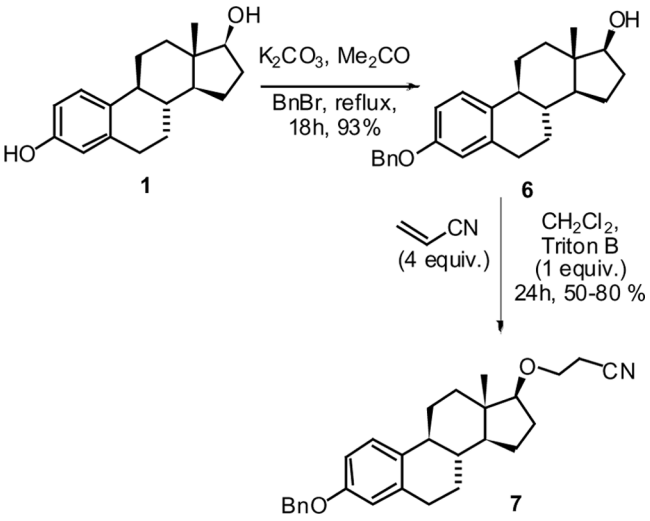


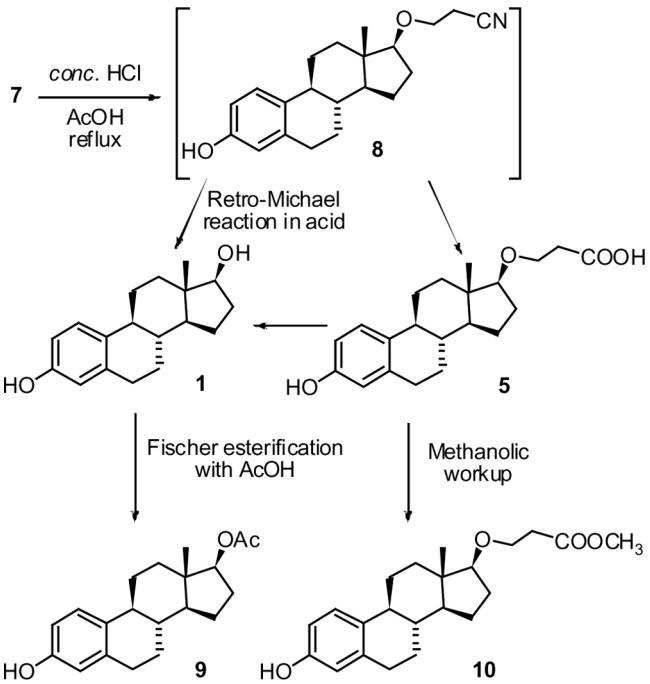
Figure 1. Structures of estradiol (**1**), the calcium chelator 3-amino-6-methoxysalicylamide **2**, and estradiol derivatives **3**–**5**.



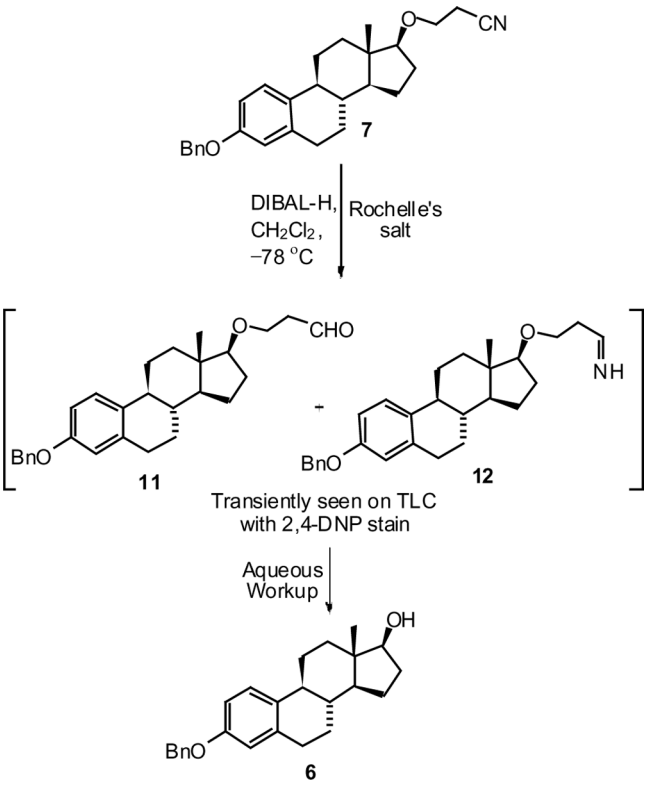
Scheme 1. Synthesis of **7**.

and pharmacokinetic-pharmacodynamic (PK-PD) studies, because **5** is a possible metabolic breakdown product of the final bone-targeting agents.

The β-alkoxy acid functionality of **5** combined with the hindered secondary alcohol at C-17 introduces synthetic challenges, which arise primarily from the

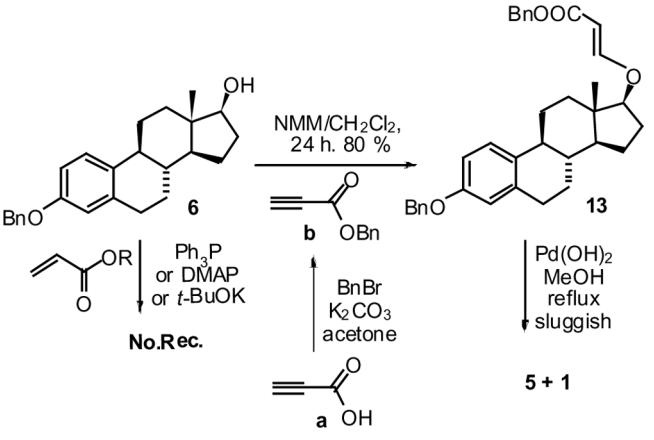


Scheme 2. Acidic hydrolysis of **7**.

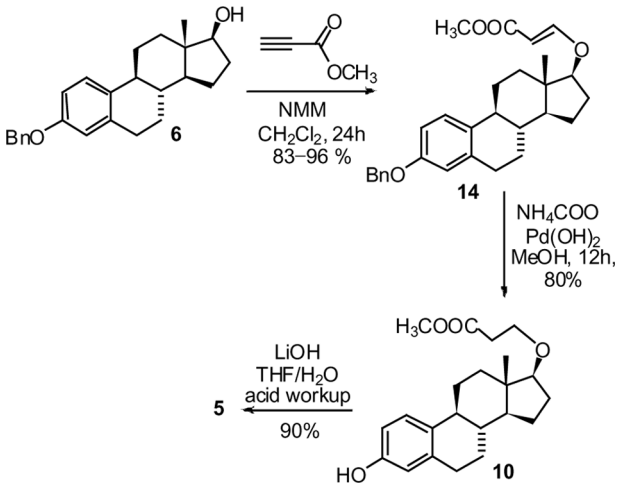


Scheme 3. DIBAL-H reduction of **7**.

tendency of this group to undergo a retro-Michael addition under both acidic and basic conditions. Our initial subgram-scale preparation of this compound involved addition of the 17-β-alkoxide of **6** to acrylonitrile to afford a β-alkoxynitrile that



Scheme 4. Synthesis and hydrogenolysis of **13**.



Scheme 5. Synthesis and hydrogenolysis of **13**.

could be hydrolyzed to the carboxylic acid. We decided to attempt the utilization of this synthetic route for the preparation of multigram quantities of **5**.

Benzylation of the 3-OH function of **1** was carried out with benzyl bromide in acetone/K_2CO_3.[4] This transformation could be carried out on a 30-g scale in 93–95% yields.

Excess benzyl bromide was removed from the product **6** by triturating with hexanes followed by crystallization of the resulting residue from EtOAc/hexanes. On smaller scales, the product **6** was purified by chromatography. Scale-up of the Michael addition of **6** with acrylonitrile proved to be difficult. This transformation was initially carried out with 5 equiv. of Triton B as the base in CH_2Cl_2, employing a large excess (typically 40-fold molar excess) of acrylonitrile, which was necessary to ensure completion of the reaction. It was noticed that acrylonitrile undergoes extensive degradation when treated with Triton B alone; thus, we attempted to lower the quantity of this base. After several trials, the reaction proceeded to completion with just 4 equiv. of acrylonitrile, provided the quantity of Triton B was no more than 1.0 equiv. Column chromatography could be avoided by triturating the resulting brown-black residue with diethyl ether, followed by precipitation of the product from cold MeOH, to afford an analytically pure sample of the β-alkoxynitrile derivative, **7**. The isolated yields of **7**, however, varied widely (50–80%).

Unfortunately, concomitant deprotection of the 3-*O*-benzyl function and nitrile hydrolysis did not result in the formation of appreciable amounts of **5**. Heating a mixture of **7** in AcOH and conc. HCl resulted in varied and complex product mixtures across several runs. One prominent side product was **1** itself, which likely arises from retro-Michael breakdown of the β-alkoxynitrile derivative. Absence of the 3-benzylated **6** in the product mixture indicated that benzyl deprotection is the first step during the acid-mediated breakdown of **7**. Other side products observed were 17-acetyl estradiol (**9**) and a significant quantity of the debenzylated product **8**, which was significant especially when shorter reaction times were utilized.

Attempts to precipitate **8** from the reaction mixture by partial evaporation of the solvent followed by addition of MeOH resulted in rapid esterification of **5** (present in small quantities) to the methyl ester, **10**. Treatment of **7** with anhydrous HCl in MeOH resulted in the formation of the 3-*O*-debenzylated derivative **8**, but no further reaction was observed, even when the reaction mixture was heated. Stirring **7** in AcOH and conc. HCl at ambient temperature also led to **8** as the sole product.

Attempts to oxidize nitrile **7** to the corresponding carboxylic acid with sodium peroxides with alcoholic potassium hydroxide (KOH)[5] failed because of immediate retro-Michael breakdown of **7**. Therefore, we concluded that intermediate **7** is unstable in the harsh acidic or basic conditions that are generally required for nitrile hydrolysis.

In a final attempt at utilizing nitrile **7**, we carried out a diisobutylaluminum hydride (DIBAL-H) reduction at $-78\,^{\circ}C$ in CH_2Cl_2.[6] Although an aldehyde intermediate was seen transiently by thin-layer chromatographic (TLC) monitoring of the reaction, we could not obtain this product after quenching the reaction mixture with Rochelle's salt. Instead, 3-*O*-benzylated estradiol **6** was isolated in nearly quantitative yields after removal of a brown polymeric material. This indicated that, as with **7**, the β-alkoxy aldehyde **11**, or imine **12** is likely susceptible to retro-Michael breakdown.

In all of these cases, it was not possible to obtain an analytically pure sample of the required acid **5**, even in small quantities. Among the aforementioned side products, the methyl ester **10** could be isolated in an analytically pure form. A carefully controlled basic hydrolysis with one equiv. of LiOH in 4:1 THF/H_2O, followed by acidic workup, was found to yield pure **5**. We therefore focused our efforts at obtaining **10** through a synthetic route that avoided harsh acidic or basic conditions.

Michael addition of **6** to methyl, ethyl, or *t*-butyl acrylate was attempted, under base, dimethylaminopyridine (DMAP), or Ph_3P catalysis. Unfortunately, we did not see any evidence of a desired product in these reactions. In all cases, a polymeric material was obtained, which formed even in the absence of **6**. It was therefore concluded that this Michael addition reaction is either not possible under these reaction conditions or is slower than the rate of base-catalyzed degradation of alkyl acrylates. In fact, Christain and Hixon[7] reported that hindered secondary alcohols are poor substrates for reaction with alkyl acrylates because of facile base-catalyzed retro-Michael reactions.

One way of overcoming the reversibility of this reaction is to replace the enone electrophile by an alkyne (i.e., by employing an alkyl/aryl propiolate),[8] because the elimination of alcohols from enol-ethers is not as facile as that in a β-alkoxy ester. Benzyl propiolate was prepared by the alkylation of propiolic acid with benzyl bromide in acetone/K_2CO_3.[9] Addition of **6** to benzyl propiolate and *N*-methyl morpholine in CH_2Cl_2 proceeded without event to yield **13** in 80% yield after chromatography. Unfortunately, we were unable to achieve an efficient and clean concomitant hydrogenolysis of the two benzyl groups and reduction of the alkene moiety of **13**. The longer reaction times necessary for complete consumption of **13** resulted in the formation of large amounts of **1**, which could not be completely removed from the product mixture.

We finally attempted the utilization of methyl propiolate instead of benzyl propiolate. Treatment of **6** with methyl propiolate and *N*-methyl morpholine in CH_2Cl_2

resulted in complete consumption of the starting material within 24 h, affording the enol ether **14** in 83–96% yield. This reaction was reproducible when carried out on a 30-g scale. Although initially isolated by chromatography, **14** could be purified by filtering the reaction mixture through a short silica plug, evaporating to dryness, and crystallizing the resulting residue from hot methanol (MeOH). An attempted catalytic hydrogenation of **14** with $Pd(OH)_2$ under H_2 was found to be too slow to be of any practical value. We therefore attempted a catalytic-transfer hydrogenation with ammonium formate as the hydrogen source. This reaction proceeded to completion within 24 h, with 10 equiv. of ammonium formate and 10% w/w of catalyst (Pd/C) loading. Surprisingly, traces of **1** were observed in the crude product mixture, indicating that even a weak acid–base catalyst such as ammonium formate is capable of mediating breakdown of the product, **10**. Methyl ester **10** could be rendered free from traces of **1** by suspension in hexanes and filtering, followed by recrystallization from hot hexanes. LiOH hydrolysis then afforded the desired acid **5**, which could then be purified by crystallization from CH_2Cl_2 and hexanes.

CONCLUSIONS

We have thus accomplished the development of a scalable and reliable synthetic route for the preparation of **5** in an analytically pure form. During the course of these studies, an alternative sequence for the conversion of a hindered secondary alcohol to a β-alkoxy ester that bypasses intermediates labile toward retro-Michael breakdown was developed.

EXPERIMENTAL

Tetrahydrofuran (THF) and ether were distilled over THF/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Chloroform was distilled from potassium hydroxide (KOH) pellets and stored over KOH. Hexanes were used as received. All other chemicals were used without purification. Silica gel (60 Å ICN Silica Tech) was used for flash chromatography. NMR spectra were recorded (in $CDCl_3$) on a Varian 300-MHz instrument, and chemical shifts are reported in parts per million (ppm). Gas chromatography–mass spectrometry (GC-MS) were recorded on an Agilent 6890 GC incorporating an Agilent 7683 autosampler and an Agilent 5973 MSD. Elemental analysis was performed by Atlantic Micro Labs. Compounds **6** and **b** (Scheme 4) were prepared according to previously reported method.[4,9]

3-Benzyloxy-17-β-1-(2-carboxybenzyloxyethylenyl)-1,3,5(10)-estratriene (13)

N-Methyl morpholine (3.62 mL, 2.0 equiv.) was added dropwise to a solution of 3-benzyloxy-17-β-hydroxy-estra-1,3,5-triene (6.0 g, 16.57 mmol) and benzyl propiolate (5.30 g, 2.0 equiv) in CH_2Cl_2 (80 mL). The resulting amber solution was stirred at ambient temperature overnight (24 h) before being filtered through a plug of silica. The plug was washed with EtOAc (3×100 mL), and the combined filtrates were evaporated to afford a brown solid, which was dissolved in $CHCl_3$ (ca. 2 mL) and loaded on a silica-gel plug (20 g, packed with hexanes). The plug was

eluted with hexanes/diethyl ether (24:1, 12:1, 6:1, ca. 200 mL of each). The product was isolated in the last 200 mL of eluent, evaporation of which furnished pure **13** as a white solid (1.60 g, 79.7%); $R_f = 0.52$ (diethyl ether/hexanes; 9:13); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, $J = 12.6$ Hz, 1H), 7.46–7.31 (m, 10H), 7.19 (d, $J = 8.4$ Hz, 1H), 6.79 (dd, $J = 8.4$ and 2.7 Hz, 1H), 6.72 (d, $J = 2.7$ Hz, 1H), 5.32 (d, $J = 12.6$ Hz, 1H), 5.17 (s, 2H), 5.04 (s, 2H), 3.97 (t, $J = 8.4$ Hz, 1H), 2.86 (m, 2H), 2.24 (m, 3H), 2.00–1.22 (m, 10H), 0.83 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 165.9, 163.2, 157.8, 156.9, 138.0, 137.4, 136.7, 132.6, 128.8, 128.7, 128.6, 128.3, 128.2, 127.6, 126.5, 115.0, 112.5, 104.3, 97.1, 91.5, 70.2, 66.6, 65.8, 50.0, 44.1, 44.0, 38.8, 37.4, 30.1, 27.9, 27.5, 26.4, 23.6, 12.2 ppm. EI-MS m/z 522. Elemental analysis (**13**) calculated for $C_{35}H_{38}O_4$: C, 80.43%; H, 7.33%. Found: C, 80.40%; H, 7.12%.

3-Benzyloxy-17-β-1-(2-carboxymethylethylenyl)-1,3,5(10)-estratriene (14)

N-Methyl morpholine (3.62 mL, 2.0 equiv.) was added dropwise to a solution of 3-benzyloxy-17-β-hydroxy-estra-1,3,5-triene (**6**, 6.0 g, 16.57 mmol) and methyl propiolate (2.76 mL, 2.0 equiv) in CH_2Cl_2 (80 mL). The resulting amber solution was stirred at ambient temperature overnight before being filtered through a plug of silica; the plug was then washed with EtOAc (3 × 100 mL). The combined filtrates were evaporated to afford a brown solid, which was suspended in 400 mL of methanol; this mixture was boiled for 15 min. Cooling of the resulting solution afforded white needles, which were removed by filtration and washed with chilled MeOH (2 × 50 mL) before being dried in air (7.10 g, 96%). Mp 125–127 °C; $R_f = 0.45$ (petroleum ether [bp 35–60 °C]/diethyl ether; 7:3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, $J = 12.3$ Hz, 1H), 7.48–7.35 (m, 5H), 7.24 (d, $J = 8.4$ Hz, 1H), 6.82 (dd, $J = 8.4$ and 2.4 Hz, 1H), 6.76 (d, $J = 2.4$ Hz, 1H), 5.32 (d, $J = 12.3$ Hz, 1H), 5.06 (s, 2H), 3.99 (t, $J = 8.4$ Hz, 1H), 3.74 (s, 3H), 2.89 (m, 2H), 2.36–2.08 (m, 3H), 2.02–1.22 (m, 10H), 0.87 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 162.9, 156.9, 138.0, 137.4, 132.6, 128.7, 128.0, 127.6, 126.5, 115.0, 112.4, 97.0, 91.5, 70.0, 51.2, 49.8, 43.9, 43.8, 38.6, 37.2, 29.8, 27.7, 27.3, 26.2, 23.3, 11.9 ppm. EI-MS m/z 446. Elemental analysis (**14**) calculated for $C_{29}H_{34}O_4$: C, 78.00%; H, 7.67%. Found: C, 78.03%; H, 7.70%. Subsequent runs of this reaction of **6** produced yields ranging from 83 to 96%.

3-Hydroxy-17-β-1-(2-carboxymethylethyl)-1,3,5(10)-estratriene (10)

$Pd(OH)_2$ (20% on carbon, 50% wet, 0.25 g, 10%w/w) and ammonium formate (5.00 g, excess) were added to a solution of **14** (2.50 g, 5.60 mmol) in THF/MeOH (1:2, 70 mL). The reaction was stirred at 60 °C for 12 h before being filtered through celite and evaporated to afford a white solid residue, which was mostly **10** (98% by GC analysis) with traces of estradiol (**1**). This residue was dissolved in $CHCl_3$ (ca. 2 mL) and loaded onto a silica-gel plug (20 g, packed with hexanes). The plug was eluted with hexanes/EtOAc (24:1 → 12:1 → 6:1, ca. 200 mL of each). The product was eluted in the last 200 mL of eluent, evaporation of which furnished pure **10** as a white solid (1.60 g, 80%). With larger scale runs (20 g) the reaction mixture was

filtered through celite, evaporated, and the residue was suspended in hot hexanes. Filtration of this mixture followed by cooling led to the crystallization of pure **10**. $R_f = 0.55$ (diethyl ether/hexanes; 9:13); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, $J = 8.4$ Hz, 1H), 6.65 (dd, $J = 8.4$ and 2.7 Hz, 1H), 6.58 (d, $J = 2.7$ Hz, 1H), 3.86–3.71 (m, 2H), 3.73 (s, 3H), 3.42 (t, $J = 8.7$ Hz, 1H), 2.81 (m, 2H), 2.60 (t, $J = 6.6$ Hz, 2H), 2.29–1.13 (m, 14H), 0.77 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 153.7, 138.3, 132.5, 126.6, 115.4, 112.8, 89.6, 65.6, 51.9, 50.3, 44.0, 43.4, 38.7, 38.0, 35.5, 29.8, 28.1, 27.3, 26.6, 23.2, 11.7 ppm. GC-MS m/z 358. Elemental analysis (**10**) calculated for $C_{22}H_{30}O_4$: C, 73.71%; H, 8.44%. Found: C, 73.53%; H, 8.32%.

3-Hydroxy-17-β-1-(2-carboxyethyl)-1,3,5(10)-estratriene (5)

A solution of LiOH (150 mg, 2.1 equiv.) in water (10 mL) was added slowly to a stirred solution of **10** (1.32 g, 2.95 mmol) in THF (20 mL). The resulting pale pink solution was heated to reflux for 1 h before being cooled to ambient temperature and neutralized with conc. HCl. The THF was removed under reduced pressure, and the aqueous layer (pH = 1) was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to afford a white solid. This white solid was dissolved in hot chloroform (ca. 20 mL), and hot hexanes (ca. 20 mL) were added portionwise to the chloroform solution until a slight turbidity persisted. A few drops of chloroform were then added to clarify the solution, and the solution was allowed to cool to ambient temperature, during which time large white crystals were formed. The mixture was chilled in the freezer and then filtered. The filter cake was washed with chilled $CHCl_3$/hexanes (1:1) 2 × 20 mL. Drying in air yielded **5** as a white solid (1.13 g, 90%). Mp = 151–152 °C; $R_f = 0.40$ ($CHCl_3$/MeOH; 19:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, $J = 8.7$ Hz, 1H), 6.63 (dd, $J = 8.7$ and 2.7 Hz, 1H), 6.57 (d, $J = 2.7$ Hz, 1H), 3.78 (m, 2H), 3.45 (t, $J = 8.0$ Hz, 1H), 2.81 (m, 2H), 2.65 (t, $J = 8.0$ Hz, 2H), 2.28–2.00 (m, 5H), 1.87–1.13 (m, 10H), 0.78 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 153.4, 138.4, 132.7, 126.7, 115.5, 112.8, 89.9, 65.3, 50.3, 44.1, 43.5, 38.7, 38.0, 35.4, 29.8, 28.1, 27.4, 26.6, 23.3, 11.9 ppm. EI-MS m/z 344. Elemental analysis (**5**) calculated for $C_{21}H_{28}O_4$. 0.33 H_2O: C, 71.97%; H, 8.24%. Found: C, 72.23%; H, 8.09%.

ACKNOWLEDGMENTS

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