

An environmentally friendly and cost effective synthesis of estradiol featuring two novel reagents: Si(0)/KF and PMHS/hexamethyldisiloxane/pTSA

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Abstract—Si(0)/KF is introduced as a strong, inexpensive, environmentally friendly, and safe reagent for ‘dissolving metal’-type reduction. PMHS/hexamethyldisiloxane/pTSA is introduced as an inexpensive substitute for Et₃SiH/TFA for ‘ionic hydrogenation’, where the hexamethyldisiloxane functions as a capping agent to block the oligomeric silicone by-product from cross-linking to a gel, rubber, or plastic. An environmentally friendly and cost effective synthesis of estradiol is described which showcases these new reagents.

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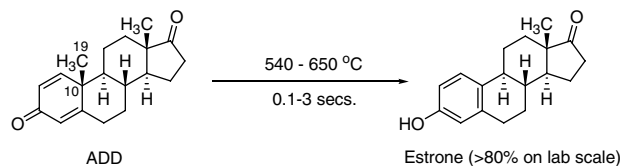
Estradiol-3-bis(2-chloroethyl)carbamate (estramustine) is an antineoplastic agent used for treatment of prostate cancer.¹ Estradiol-3-benzoate and estradiol-17-cyclopentylpropionate are active pharmaceutical ingredients (API's) in hormone replacement treatments. Estradiol itself is an ingredient in animal growth regulation products.² To make these pharmaceuticals available to the worldwide patient population, an efficient synthesis of estradiol is needed.

A number of elegant total syntheses of estradiol have been developed over the years.^{3,4} However, to obtain estradiol in commercial quantity economically, pharmaceutical companies generally employ ‘semisynthetic’ routes that start from androsta-1,4-diene-3,17-dione (ADD)⁵ since ADD is available in one step by microbial degradation of soy sterols^{5c} and can be converted into estrone in one step (Scheme 1).

One drawback of the semisynthetic approach via ADD is that cleavage of the C10–C19 carbon–carbon bond requires harsh conditions. Controlled cracking of ADD in

tetralin (540–650 °C, 0.1–3 s) gives estrone in reported yields of over 80% on laboratory scale, but co-formation of tar and soot render scale up technically challenging (Scheme 1).⁶ Heating ADD-17-ethylene ketal with an alkali metal (Li or Na) and an aromatic hydrocarbon (biphenyl, phenanthrene, etc.) in refluxing THF^{7,8} affords estrone-17-ethylene ketal in 86% yield,⁸ but the difficulties in running Birch-type reactions on commercial scale have been discussed.^{5c} Recently, it has been reported that treatment of ADD with NaH₂Al(OCH₂CH₂OCH₃)₂ (to give the 3,17-diol) followed by 5 equiv *n*-BuLi (PhMe, 100 °C) gives estradiol in 75% yield.⁹

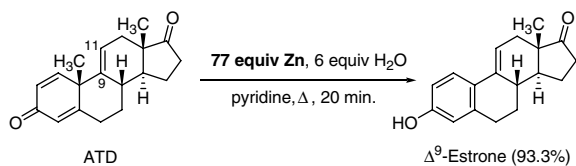
Androsta-1,4,9-triene-3,17-dione (ATD) is readily available from soy sterols by a short series of efficient microbiological¹⁰ and chemical¹¹ steps. In principle, ATD should undergo methyl expulsion under milder conditions than ADD because ATD contains a double bond at 9(11) that is orthogonal to the C10–C19 bond. Indeed, it has been reported that treatment of ATD with the mild reducing agent zinc (pyridine/H₂O, Δ)¹² gives



Scheme 1. Pyrolytic process for synthesis of estrone.

Keywords: Silicon(0); Potassium fluoride; PMHS/hexamethyldisiloxane/pTSA; ATD; Estradiol.

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Scheme 2. Zinc/pyridine reduction of ATD.

Δ^9 -estrone in 93.3% yield without protection of the C17 ketone (Scheme 2). However, an extreme excess of freshly activated zinc dust (77 equiv) is required. Such a large amount of zinc dust is difficult to suspend in organic solvents without resorting to high dilution conditions due to the high density of zinc metal (7.133 g/cm³).

Silicon(0) should be an ideal commercial scale reducing agent because it is inexpensive (150 USD/kg for –325 mesh powder from Aldrich), safe to handle,¹³ generates silicate by-products of relatively low toxicity, has a sufficiently low density (2.33 g/cm³) to be easily suspendable in organic solvents, and has a reduction potential (–0.8 V) more negative than that of zinc (–0.497 V) so that, thermodynamically, silicon(0) is a stronger reducing agent than zinc (Table 1).¹⁴

On treatment of ATD with 5 equiv silicon(0) (–325 mesh powder) in 2/1 diethyleneglycol monoethyl ether ('DEGME')/ethylene glycol (EG) at 120 °C for 2 h, no reaction occurred. Thus, just as zinc requires activation by pyridine, silicon(0) requires activation to function as a reducing agent. Ferrosilicon is inert to water but reacts with 20% aqueous sodium hydroxide at 100 °C to generate hydrogen gas at a rapid rate.¹⁵ Sodium hydroxide activates the ferrosilicon by increasing its reduction potential (Table 1) and/or by dissolving a silicon dioxide overlayer to expose surface silicon atoms.¹⁶ Our interest was to investigate whether the electrons from the silicon(0) could be intercepted by ATD to give Δ^9 -estrone rather than reduce water to give hydrogen.

Treatment of ATD with 5 equiv silicon(0) powder (–325 mesh) and 5 equiv sodium hydroxide or potassium carbonate in 2/1 DEGME/EG (120 °C, 2.5 h) gave mainly hydrogen gas (identified by Raman spectroscopy) along with minor amounts of Δ^9 -estrone. The silicon clumped up during the reaction, presumably due to coating of its surface with sodium silicate (so-called 'silicate cement'¹⁷). By including a small amount of water (5 vol %) and doubling the amounts of silicon and potassium carbonate, it was possible to attain a yield of 52–53% of Δ^9 -estrone, but clumping was still a problem.

Table 1. Reduction potentials of zinc and silicon¹⁴

Electrochemical equation	Reduction potential
$\text{ZnO} + 2\text{H}^+ + 2\text{e}^- \rightleftharpoons \text{Zn} + \text{H}_2\text{O}$	–0.497 V
$\text{SiO} + 2\text{H}^+ + 2\text{e}^- \rightleftharpoons \text{Si} + \text{H}_2\text{O}$	–0.8 V
$\text{SiF}_6^{2-} + 4\text{e}^- \rightleftharpoons \text{Si} + 6\text{F}^-$	–1.24 V
$\text{SiO}_3^{2-} + 3\text{H}_2\text{O} + 4\text{e}^- \rightleftharpoons \text{Si} + 6\text{OH}^-$	–1.697 V

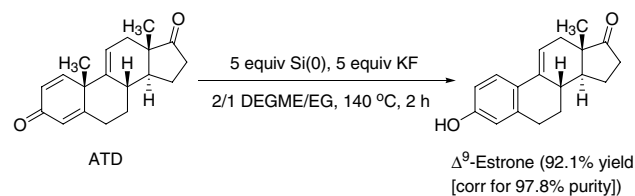
In order to avoid the waste of electrons to hydrogen formation as well as the formation of 'silicate cement', fluoride was investigated as silicon activator under anhydrous conditions. Fluoride increases the reduction potential of silicon(0) only slightly less than hydroxide (Table 1). Treatment of ATD with 5 equiv silicon powder and 5 equiv potassium fluoride in 2/1 DEGME/EG¹⁸ (140 °C, 2 h) afforded, after extractive workup and crystallization, Δ^9 -estrone in 92.1% yield (Scheme 3). The reaction mixture remained easily stirrable throughout the course of the reaction.

The evolved gas from the reaction was collected and analyzed by Raman spectroscopy. It was found to consist of a mixture of hydrogen and methane (identified by characteristic peaks at 2917, 3020, and 3072 cm^{–1}). The amounts were not quantitated. The source of the hydrogen atom that is abstracted by the expelled methyl group to give methane was not determined.

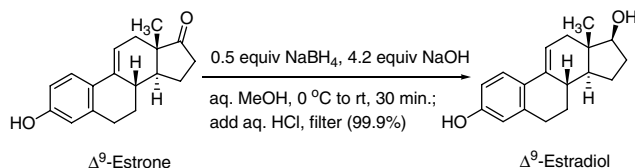
To complete the synthesis, first the C17 ketone was reduced with sodium borohydride. The reduction is conveniently carried out using commercially available 12% NaBH₄/40% NaOH solution in methanolic caustic as solvent, as these conditions are safer than using solid sodium borohydride and permit higher throughput (Scheme 4). The reduction is highly stereoselective (0.9% 17-*epi*).

The final challenge was to reduce the 9(11) double bond stereoselectively. In the final step of Torgov's classic synthesis of estradiol, Δ^8 -estradiol is stereoselectively reduced to estradiol by treatment with Et₃SiH/TFA (PhH, rt, 3 h; 96% yield after workup with hydroxide).²⁰ However, one drawback of this process is that both triethylsilane and trifluoroacetic acid are relatively expensive. Also triethylsilanol and silyl ether by-products complicate product isolation/purification.²¹

Although Et₃SiH/TFA is the 'most frequently reported'²² reagent used for 'ionic hydrogenation', polymethylhydrosiloxane ('PMHS'; Me₃SiO(HSiMeO)_n-SiMe₃, where *n* ~ 35) is 'most economically favored



Scheme 3. ATD Si(0)/KF reduction protocol.¹⁹



Scheme 4. Borohydride reduction step.

for large-scale reductions'.²² Applications of PMHS in organic synthesis have been reviewed.²³ However, one disadvantage of PMHS is that, under both acidic and basic conditions, the oligomeric chains tend to cross-link to form a polymer that separates from the reaction mixture as a gel, rubber, or plastic.^{23a,d,24} This precipitate could render a plant reactor inoperable or, at best, very difficult to clean. This longstanding problem has limited applications of PMHS on commercial scale.

Attempted reduction of Δ^9 -estradiol by treatment with 3.0 equiv PMHS²⁵ and 4.0 equiv anhyd pTSA²⁶ (CH_2Cl_2 , MeOH, $-20^\circ\text{C}\rightarrow\text{rt}$) gave estradiol cleanly, but the silicone by-product formed a solid crust that covered the surface of the reaction mixture. It is known that $(\text{HSiMeO})_5$ equilibrates with $(\text{Me}_3\text{Si})_2\text{O}$ in the presence of acid to give the monomer $(\text{Me}_3\text{SiO})_3\text{SiMeH}$.²⁷ Thus, it was speculated that, if the above Δ^9 -estradiol reduction experiment were run with added $(\text{Me}_3\text{Si})_2\text{O}$, the silicone by-product would equilibrate to the monomer $(\text{Me}_3\text{SiO})_2\text{SiMeOMe}$, which would remain in solution.

Indeed, on treatment of Δ^9 -estradiol with 3.0 equiv PMHS and 4.0 equiv anhyd pTSA in the presence of 1.1 equiv²⁸ $(\text{Me}_3\text{Si})_2\text{O}$ (CH_2Cl_2 ,²⁹ 6.1 equiv MeOH, -25 to 38°C , 1 h), the double bond underwent smooth reduction to give estradiol with high stereoselectivity ($9\alpha/\beta \sim 94/6$). As the reaction progressed, the reaction mixture divided into two liquid phases: a colorless upper phase consisting of the neat silicone by-product (presumably $(\text{Me}_3\text{SiO})_2\text{MeSiOMe}$ and higher oligomers) and a lower $\text{CH}_2\text{Cl}_2/\text{MeOH}$ phase containing estradiol, 9-*epi*-estradiol, and pTSA. When the reaction was complete, the reaction mixture was quenched into aq potassium carbonate. This extracts the pTSA and essentially all the methanol out of the CH_2Cl_2 layer, thus reducing the solubility of the estradiol, causing it to crystallize out, leaving essentially all of the 9-*epi*-estradiol as well as the silicone by-product in the filtrate. After recrystallization from acetone/water, crystalline estradiol hemihydrate was obtained in 72.8% yield (Scheme 5). The yield was 67.0% (overall from ATD).^{30,31}

In summary, an environmentally friendly and cost effective synthesis of estradiol is described. The synthesis starts with a readily available steroidal raw material (ATD). The C19 methyl group is expelled by treatment with $\text{Si}(0)/\text{KF}$, the C17 ketone is reduced by treatment with NaBH_4 , then the 9(11) double bond is reduced by treatment with PMHS in the presence of pTSA and

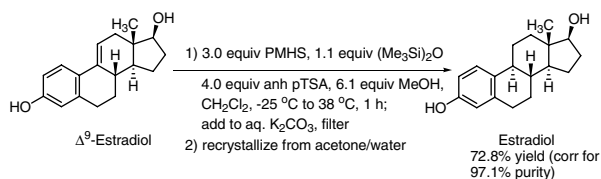
$(\text{Me}_3\text{Si})_2\text{O}$, which functions as a capping agent to block the oligomeric silicone by-product from cross-linking to a gel, rubber, or plastic. The synthesis is environmentally friendly because the silicon-containing by-products have low toxicity.

Acknowledgements

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Scheme 5. 'Ionic hydrogenation' of Δ^9 -estradiol with PMHS/ $(\text{Me}_3\text{Si})_2\text{O}/\text{pTSA}$.

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- A mixed solvent of DEGME and EG was chosen because it was found to insure dispersability of both the silicon(0) powder and the silicate by-products.
- Experimental procedure: A mixture of ATD (10.0 g, 35.4 mmol, 1 equiv), silicon(0) powder (–325 mesh; 4.97 g, 177 mmol, 5 equiv), potassium fluoride (10.3 g, 177 mmol, 5 equiv), diethylene glycol monoethyl ether (140 mL) and ethylene glycol (70 mL) was heated to 90 °C, at which point mild gas evolution began to occur. When the temperature reached 120 °C, an exotherm to 140 °C occurred. After 2 h, the reaction was judged complete by TLC. The mixture was cooled to rt, poured into 1000 mL 1 N HCl (aq) and 500 mL THF, and the layers separated. The organic layer was filtered through a pad of magnesol on a glass frit (coarse porosity). The filtrate was concentrated to remove THF, causing solids to precipitate. The slurry was filtered and the solids dried by nitrogen stream overnight to give a solid identified as Δ^9 -estrone by ¹³C NMR, ¹H NMR, HPLC retention time, and UV ($\lambda_{\text{max}} = 263$ nm) comparison with an authentic reference standard. Weight: 8.95 g (92.1% yield [corrected for 97.8% purity]). ¹³C NMR (100 MHz, pyridine-*d*₅): δ 220.4 (s); 158.1 (s); 138.1 (s); 136.2 (s); 126.2 (s); 126.1 (d); 116.1 (d); 116.0 (d); 115.0 (d); 47.9 (d); 46.3 (s); 38.6 (d); 36.3 (t); 34.4 (t); 30.1 (t); 28.1 (t); 22.6 (t); 14.6 (q). ¹H NMR (400 MHz, pyridine-*d*₅): δ 7.71 (1H, d, *J* = 8.6 Hz); 7.12 (1H, dd, *J* = 2.5 Hz, 8.6 Hz); 7.00 (1H, d, *J* = 2.0 Hz); 6.16 (1H, t, *J* = 2.6 Hz); 5.18 (1H, br s); 2.84 (2H, m); 2.41 (2H, m); 2.20 (3H, m); 1.97 (2H, m); 1.52 (2H, m); 1.36 (1H, dd, *J* = 5.6 Hz, 12.7 Hz); 0.89 (3H, s). MS (CI, positive ion): 269 (P⁺+H); MS (CI, negative ion): 267 (P⁺-H).
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- Experimental procedure: To a mixture of Δ^9 -estradiol (30 g, 0.111 mol, 1 equiv), hexamethyldisiloxane (HMDSO; 27 g, 0.13 mol, 1.1 equiv), and polymethylhydrosiloxane (PMHS; 20 g, 0.33 mol, 2.8 equiv) in methanol (12.8 mL, 0.316 mol, 3 equiv) and methylene chloride (120 mL) was added a solution of anhyd pTSA (77 g, 0.45 mol, 4.0 equiv) in methanol (12.3 mL, 0.30 mol, 2.7 equiv) and methylene chloride (75 mL) while maintaining the pot temperature at –30 to –25 °C. The pTSA solution was rinsed in with methanol (2.5 mL, 0.063 mol, 0.56 equiv) and methylene chloride (2.5 mL). The mixture was warmed to 38 °C and stirred 1 h. The resulting two phase mixture was then added to a mixture of potassium carbonate (44 g, 0.32 mol, 2.9 equiv) and water (300 mL), rinsing with 30 mL methylene chloride (30 mL). The resulting slurry was cooled to 15 °C and filtered. The cake was washed with water (320 mL) and methylene chloride (142 mL) and dried to afford crude estradiol (weight: 25.6 g). A portion of the solids (25.0 g, from 0.108 mol Δ^9 -estradiol) was dissolved in acetone (275 mL) and water (6.25 mL) at 58 °C. The solution was concentrated by atmospheric distillation to a volume of 137 mL. Water (21 mL) was added and the mixture was concentrated by atmospheric distillation to a volume of 78 mL. The mixture was cooled to –12.5 °C and the solids collected by vacuum filtration, washed with a cold (–8 °C) mixture of acetone (23 mL), and water (23 mL), and dried to afford a solid identified as estradiol hemihydrate by ¹³C NMR and ¹H NMR comparison with a reference standard. The product contained 3.29% water by KF and was 97.1% pure by quantitative HPLC comparison with a reference standard. Weight: 22.8 g (22.0 g on anhydrous basis, 72.8% yield [purity corrected]).
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