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Practical semisynthesis of equilenin and its derivatives

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ABSTRACT

Equilenin **2** and its derivatives are important intermediates in the synthesis of steroidal drugs. Until now, these estrogens were produced by extraction from pregnant mare's urine due to the lack of efficient synthetic methods. Most reported semisyntheses of equilenin involve expensive raw materials or toxic reagents to suppress undesired epimerization at C/D ring juncture. Herein, we reported a practical synthesis of highly pure equilenin and its derivatives from an easily available raw material **6** with conventional reagents.

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Premarin tablet, a mixture of estrogens extracted from pregnant mare's urine, consists of estrone **1**, equilenin **2**, equilin **3** (Fig. 1) and their derivatives[1] and is widely used as a form of hormone replacement therapy (HRT). Estrone has been produced on an industrial-scale by chemical synthesis for several decades, while equilenin and equilin are still obtained by extraction from pregnant mare's urine. The important physiological properties of these estrogens have created a strong demand for practical preparation from more abundant steroid resources.

Three active ingredients in Premarin were confirmed to be derivatives of equilenin (Fig. 2).[1a] Since the first total synthesis of equilenin was achieved by Bachmann et al. in 1939,[2a,b] numerous total synthetic strategies[2] to construct the aromatic steroidal framework have been developed. However, from the economic and technical points of view, total synthesis is not suitable for the preparation of equilenin and its derivatives on an industrial-scale.

Semisynthesis undoubtedly is more practical to prepare a large quantity of equilenin from inexpensive starting materials. However, an undesired epimerization at C/D ring juncture during B-ring aromatization hampered the development of semisynthesis of equilenin.[3] Although the epimerization can be suppressed under mild reaction conditions,[4] the reported methods are impractical due to the use of expensive equilin **3**(700 \$/g, sigma–aldrich)[4a–d] or toxic selenium reagent.[4e,f]

Another hurdle for the semisynthesis of equilenin is the lack of efficient dehydrogenation methods with high yield and complete conversion. In most cases, the structure and polarity of dehydrogenation products are very similar to those of the unreacted reactant and over-oxidized by-product, which would cause a laborious and inefficient separation procedure to obtain highly pure product.

In our continuous efforts for the chemical synthesis of components of Premarin, we developed a versatile synthesis strategy of steroidal estrogens via retro-aldol reaction from cheap 19-hydroxyandrost-4-ene-3,17-dione **6** (<1000 \$/kg)[5a,b] and an efficient approach to access 17-α-hydroxy steroids under mild conditions.[5c] Encouraged by these results, herein, we presented a practical semisynthesis of equilenin from an easily available raw material **6**. The method featured mild reaction conditions, inexpensive reagents, excellent yield, and highly pure product.

It is known that equilin **3** was readily converted to equilenin **2** under mild conditions without undesired epimerization.[4a–d] We proposed that Δ-6-estrogen **7**, an analogue of equilin **3**, can provide a similar result. Δ-6-Estrogen **7** was easily prepared from 19-hydroxyandrost-4-ene-3,17-dione[6] as our previously reported method.[5a,b] However, the direct dehydrogenation of estrogen **7** with Pd/C as catalyst only occurred at high temperature (>150 °C), which led to significant epimerization (Scheme 1). We rationalized that the equilin **3** was much more active due to the double activation by aromatic A-ring and double bond.

With Δ-6-estrogen **7** as precursor, we tested a series of other oxidants. The dehydrogenation of **7** with chloranil was found to be highly selective and provided equilenin methyl ether **8a** as the only product, albeit with low conversion (Table 1, entry 1).

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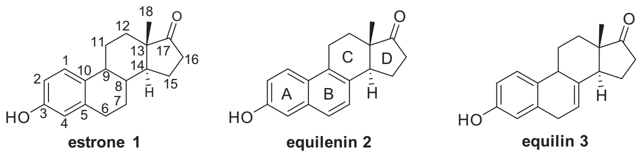


Figure 1. Structures of estrone, equilenin and equilin.

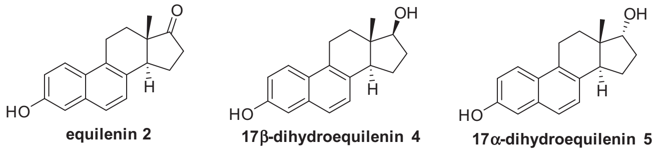
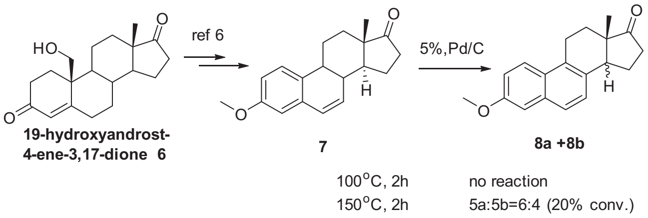


Figure 2. Equilenin and its derivatives in Premarin.



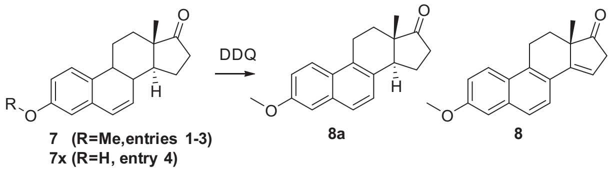
Scheme 1. Reagents and conditions: substrate (0.2 mmol), methylnaphthalene (1 mL), HPLC yield. **8a**: equilenin methyl ether, **8b**: isoequilenin methyl ether.

Alcohol as solvent significantly accelerated the rate of this reaction (entries 1–3). Unfortunately, the attempts to achieve complete conversion of starting material remained unfruitful even with longer reaction time, higher temperature or excess of oxidant (entries 3–5). We proposed that the termination of reaction attributed to a decrease of the oxidation potential of chloranil due to the increase of phenol. However, removal of phenol from the mixture in entry 3 and subsequent reaction with fresh chloranil provided a higher but still incomplete conversion (entry 6). The unreacted estrogen **7** and product **8a** were inseparable by silica gel chromatography. A small quantity of pure **8a** was finally obtained after several recrystallizations, but with unacceptable loss of material (~30% isolated yield with >95% purity).

Encouraged by the high selectivity of chloranil, we turned to examine other quinones. DDQ was found to be more powerful than chloranil and can react with estrogen **7** at room temperature (Table 2). However, the over-oxidation of product **8a** to Δ-14-steroid **8** occurred before complete consumption of the starting material **7** (entry 1). When the oxidant was increased to 2.1 equiv, Δ-14-steroid **8** was obtained in high yield as the sole product (entry 2). The product **8** was proved to be stable in the presence of an excess of oxidant (entry 3). Notably, a similar experiment with Δ-6-estrone **7x** as substrate gave a complex mixture (entry 4), perhaps due to further dehydrogenation or oxidative coupling.

The above exploration provided a route to prepare Δ-14-equilenin with high purity and yield. We next turned our attention to stereoselective reduction of the 14,15-double bond. The direct hydrogenation of ketone **8** in the presence of Pd/C gave low stereoselectivity (Table 3, entry 1). Apparently, increasing the bulk of 17-β-substituent can improve stereoselectivity in favor of 14-α-H-isomer. Urusova and Minailova[7] reported that the hydrogenation of 17-β-acetoxy substrate **9** catalyzed by Raney Ni offered pure product in low yield after recrystallization. However, we found that the reaction only gave moderate stereoselectivity (entry 2). With Pd/C instead of Raney Ni as catalyst, the hydrogenation of substrate **9** can be completed at lower temperature with higher selectivity (entry 3). Unexpectedly, 17-β-hydroxy substrate **10** with less steric hindrance of β-face gave higher selectivity (entry 4). The result implies that steric effect is not the only factor influencing stereoselectivity. Further attempts to improve the

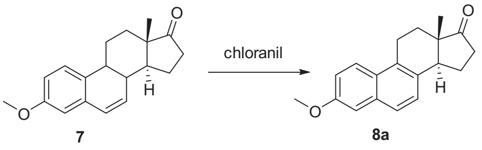
Table 2
Dehydrogenation of Δ6-estrogen **4** with DDQ[a]



Entry	DDQ (equiv)	**7**:**8a**:**8**
1	1.2	19:44:37
2	2.1	0:0:100
3	2.5	0:0:100
4[b]	2.5	Complex

[a] Substrate: 0.2 mmol, solvent: toluene (2 mL), rt, 1 h, NMR yield.
[b] Δ-6-Estrone **7x** as reactant.

Table 1
Dehydrogenation of Δ6-estrogen with chloranil[a]



Entry	Chloranil (equiv)	Solvent	Temp (°C)	Conversion[b] (%)
1	1.2	PhMe	100	22 (32)
2	1.2	Dioxane	100	26 (35)
3	1.2	*i*-Pentanol	100	60 (62)
4	1.2	*i*-Pentanol	120	62
5[c]	**2.0**	***i*-Pentanol**	**100**	**76**
6[d]	1.2 + 1.2	*i*-Pentanol	100	78

[a] Substrate 0.2 mmol, solvent 2.0 ml, 2 h.
[b] HPLC yield. 3 h in bracket.
[c] Optimal condition (in bold).
[d] Chloranil (1.2 equiv) was added into the mixture of **7** and **8a** (2:3).

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