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Protecting group effect on the 1,2-dehydrogenation of 19-hydroxysteroids: a highly efficient protocol for the synthesis of estrogens

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ABSTRACT

19-O-Acylation was found to be indispensable for 1,2-dehydrogenation of 19-hydroxyandrost-4-ene-3,17-dione **1a** with DDQ as an oxidant after exploring a variety of C-19 substituents. 1,2-Dehydrogenation in combination with subsequent A-ring aromatization via retro-aldol reaction provided a flexible and efficient protocol for the synthesis of estrogens. To demonstrate the utility of the protocol, pharmaceutically attractive estrogens were synthesized from easily available 19-hydroxy-4-ene-3-keto steroids.

The important physiological properties of estrogens have created a strong demand for practical preparation of this type of compounds from more abundant steroid resources.[1] Recently, new biological discoveries[2] have renewed the interest in the exploration of their structure diversity aiming at SAR study and drug development. So far, diversity-oriented synthesis (DOS) of estrogens has been problematic with conventional method such as structural modification of estrone[3] or expulsion of the 19-angular methyl groups of 1,4-diene-3-keto steroids via pyrolytic aromatization,[4] or reductive aromatization[5] with Zn or Li, and development of a flexible strategy for the synthesis of estrogens with structural diversity is therefore needed.

The key step in the synthesis of estrogens is the aromatization of A ring. A route via retro-aldol-type fragmentation reaction of 19-hydroxyandrost-1,4-diene-3-ones **2** seemed particularly attractive (Scheme 1).[6] The advantages of this protocol are (1) starting material is easily available from an important industrial intermediate, which is prepared from abundant dehydroepiandrosterone (DHEA);[7] (2) non-aromatic starting materials are easily amendable for DOS; (3) retro-aldol reaction is favored due to the stabilization after aromatization.

However, this promising method was rarely used as an efficient approach to prepare estrogens due to the difficulties in the preparation of retro-aldol reaction precursors **2** from **1**. Conventional oxidants (such as SeO_2 and DDQ[8]) for the 1,2-dehydrogenation of androst-4-ene-3-ones often lead to low yield for 19-hydroxyl-substituted substrates **1**.[6] In our studies, we found that the success of the 1,2-dehydrogenation of 19-hydroxy-4-ene-3-keto steroids depended crucially on the nature of 19-O-protecting group. 1,2-Dehydrogenation of 19-hydroxy-4-ene-3-keto steroids combined with subsequent A-ring aromatization via retro-aldol reaction provided a flexible and efficient protocol for the synthesis of estrogens. A variant of the protocol provided an unprecedented approach to synthesize estrone 3-alkyl ethers without using toxic alkylating reagents.

Initially, we examined the direct dehydrogenation of 19-hydroxyandrost-4-ene-3,17-dione **1a**. Conventional reagents, SeO_2 and DDQ, did not provide the desired dehydrogenation or aromatization product (Table 1, entry 1). Considering the success of 1,2-dehydrogenation of 19-methyl-androst-4-ene-3,17-dione,[8b] we envisioned that the protection of 19-hydroxyl group may facilitate the reaction. However, methoxymethyl ether **1b** and tetrahydropyranyl ethers **1c** did not react with DDQ at all; and the starting materials remained intact in various solvents (entries 2 and 3). Less hindered methyl ether **1d** also is inactive (entry 4). The use of benzyl- and silyl-protecting group did not improve the reactivity (entries 5–7).

Interestingly, treatment of 19-acetoxyandrost-4-ene-3,17-dione **1h** with DDQ resulted in a complete conversion in less than 3 h (entry 8). It is notable that all acylated substrates can be dehydrogenated smoothly with DDQ (entries 9–13), albeit with a slower reaction rate compared to 19-acetoxyandrost-4-ene-3,17-dione. Trace of 6,7-dehydrogenation by-product can be removed

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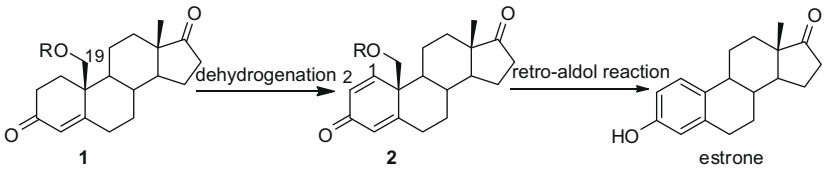
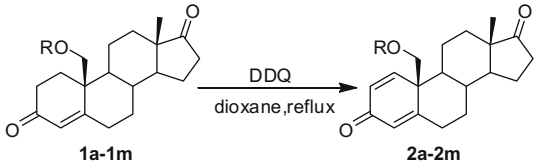


Scheme 1. Synthetic strategy via retro-aldol reaction.

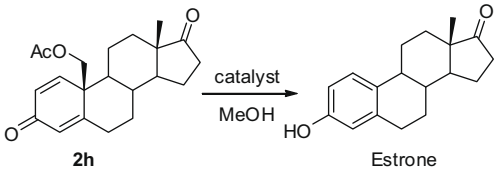
Table 1
Dehydrogenation of protected 19-hydroxyandrost-4-ene-3,17-dione[a]



Entry	Substrate	R=	Time (h)	Product	Yield[b] (%)
1	**1a**	H	—	**2a**	NR
2	**1b**	MOM	—	**2b**	NR
3	**1c**	THP	—	**2c**	NR
4	**1d**	Me	—	**2d**	NR
5	**1e**	Bn	—	**2e**	Complex
6	**1f**	TMS	—	**2f**	NR
7	**1g**	TBS	—	**2g**	NR
8	**1h**	Ac	3	**2h**	88 (77[c])
9	**1i**	$COCF_3$	4	**2i**	83[d]
10	**1j**	COOMe	5	**2j**	88
11	**1k**	Piv	3	**2k**	82
12	**1l**	Bz	4	**2l**	85
13	**1m**	C(O)H	3	**2m**	87

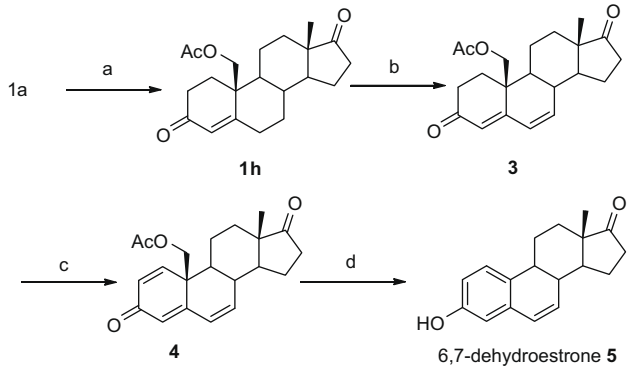
[a] Conditions: substrate (0.5 mmol), DDQ (1.2 equiv), dioxane (5 mL), 110 °C.
[b] NMR yield.
[c] Isolated yield on gram-scale after treatment with *m*-CPBA.
[d] Unstable **2i** cannot be separated.

Table 2
Retro-aldol reaction of 19-hydroxyandrost-1,4-diene-3,17-dione[a]



Entry	Catalyst (equiv)	Temp (°C)	Time	Yield[b] (%)
1	NaOH (4)	rt	3 min	90
2	K_2CO_3 (4)	rt	5 min	88
3	TsOH (4)	rt	5 h	91
4	TsOH (0.1)	Reflux	7 h	90

[a] Conditions: substrate (~0.5 mmol), methanol (5 mL).
[b] Isolated yield.



Scheme 2. Reagents and conditions: (a) Ac_2O, DMAP, rt, 20 min; (b) chloranil, *t*-BuOH, reflux, 2 h; (c) DDQ, dioxane, reflux, 3 h; (d) TsOH, MeOH, rt, 5 h, (69% over four steps).

by treatment with *m*-CPBA.[9] The preparation of **2h** on up to gram-scale has been performed with no drop in efficiency.

The data listed in Table 1 provided useful information for DDQ dehydrogenation. Inductive effect of electron-withdrawing acyl group seemed to be responsible for the successful dehydrogenation. An additional evidence is that 19-mesyloxyandrost-4-ene-3,17-dione can be dehydrogenated with DDQ in high yield.[10] Steric effect was found not to be crucial after comparing reaction rate of formyl ester **1m**, acetyl ester **1h**, and pivaloyl ester **1k** (entries 8, 11, and 13).

With 19-acetoxyandrost-1,4-diene-3,17-dione in hand, we attempted to synthesize estrone via retro-aldol reaction. As expected, removal of acetyl group with NaOH or K_2CO_3 rapidly afforded estrone in excellent yield under mild condition (Table 2, entries 1 and 2). Deprotection with acid also provided estrone in excellent yield but with a much slower rate (entries 3 and 4). In all cases, no 19-hydroxyandrost-1,4-diene-3,17-dione intermediate was detected, which indicated that the retro-aldol reaction is very fast and the deprotection step is rate-determining step.

The synthesis of 6,7-dehydroestrone **5** demonstrated the efficiency and generality of the new protocol (Scheme 2). Conventional synthesis of 6,7-dehydroestrone **5** requires five steps to introduce 6,7-double bond from estrone,[11] namely, protection of phenol and 17-carbonyl group, oxidation at 6-position, elimination, and deprotection. In contrast, our protocol can directly introduce the double bond with chloranil as oxidant.[12] With **1a** as starting material, the 6,7-dehydrogenation with chloranil provided dienone in 70–80% yield.[13] Notably, acetylation of 19-hydroxyl group also facilitated 6,7-dehydrogenation, and dienone **3** was obtained quantitatively under otherwise identical conditions. The 1,2-dehydrogenation of dienone **3** with DDQ was accomplished smoothly and provided 1,4,6-trien-3-one **4** as the precursor of retro-aldol reaction. Finally, 6,7-dehydroestrone was synthesized from **1a** in four steps and 69% overall yield.[14]

Our protocol provided an unprecedented approach to produce 3-etherified estrogens without the use of toxic alkylating agents. 3-Etherified estrogens, such as mestranol, quinestrol, and promestriene, have been commercially available as long-acting oral drug or biologically inactive prodrug (Fig. 1), which were generally synthesized by alkylation of estrone.[15] However, electrophilic alkylating agents, such as MeI and Me_2SO_4, are often very toxic.

The stability of **2h** under acidic condition (Table 2, entries 3 and 4) prompted us to explore a new synthetic approach to estrone 3-alkyl ethers, via a retro-ene reaction (Scheme 3). To our delight, treatment of **2h** with trimethyl orthoformate and TsOH (10 wt %) provided the desired estrone 3-methyl ether **6a** in 82% yield within an hour (Table 3, entry 1).[16] The efficiency of this process was surprising because no by-product formed. The analogous reaction with triethyl orthoformate proceeded smoothly to afford ethyl

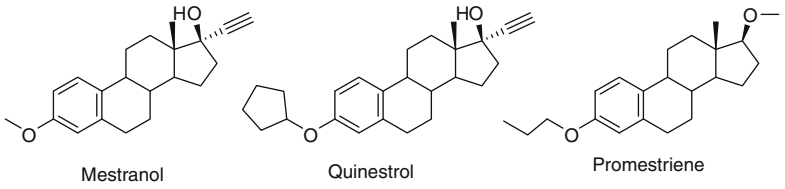
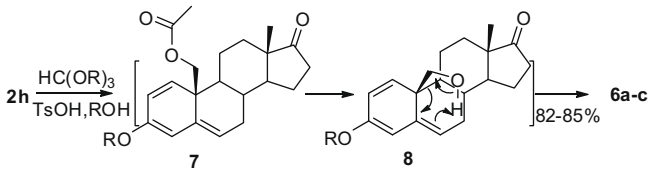
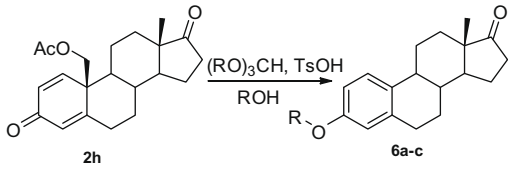


Figure 1. 3-Etherified estrogenic drugs.



Scheme 3. Proposed retro-ene mechanism.

Table 3
Synthesis of 3-etherified estrogens[a]



Entry	R	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	Me	MeOH	60	1	82
2	Et	EtOH	70	2.5	84
3	^{i}Pr	^{i}PrOH	80	5	NR
4[b]	^{i}Pr	^{i}PrOH[b]	80	17	85

[a] Conditions: substrate (200 mg, 0.58 mmol), orthoester (1 mL), solvent (3 mL), TsOH (10 wt %).
[b] TsOH (50 wt %).

ether **6b** in 84% yield (entry 2). However, bulky isopropyl orthoformate did not react with dienone **2h** with TsOH (10 wt %) as catalyst. Fortunately, increasing the amount of TsOH to 50 wt % accelerated the reaction and afforded the desired product **6c** in 85% yield (entry 4). Rapid retro-ene aromatization resulted in no observable formation of intermediates **7** and **8**.

In summary, our study demonstrates that the acylation of 19-hydroxyandrost-4-ene-3-ones significantly facilitated 1,2-dehydrogenation with DDQ as oxidant. The efficient dehydrogenation in combination with subsequent retro-aldol-type aromatization provides a practical protocol for the synthesis of estrogens from easily available 19-hydroxyandrost-4-ene-3,17-dione **1a**. Based on the current protocol, pharmaceutically attractive estrogens were efficiently synthesized. Further synthetic application is in progress.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.070.

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9. *General procedure for the preparation of* **2h**: (Warning: Most of the steroids are biologically active. The materials, reaction, and its work-up should be handled with special care!) A mixture of steroid **1h** (7.90 g, 22.9 mmol) and DDQ (6.25 g, 27.5 mmol) in dry dioxane (50 mL) was refluxed at 110 °C for 3 h. After completion of the reaction (monitored with ^{1}H NMR), the solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (100 mL). The insoluble portion was removed by filtration and washed with CH_2Cl_2 (3×20 mL). The combined filtrates were washed with aqueous $NaHSO_3$ and water, dried ($MgSO_4$), filtered, and concentrated. The residue was filtered through a short silica column to afford 6.90 g of crude **2h** as a light brown oil. Crude **2h** (500 mg) was solved in 10 mL of $CHCl_3$ and *m*-CPBA (85%, 140 mg, 0.70 mmol) was sequentially added to $CHCl_3$ (10 mL). The solution was vigorously stirred for 12 h at room temperature, upon which it was diluted with CH_2Cl_2 (20 mL) and washed with Na_2SO_3 solution (20 mL), and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography to afford pure **2h** (438 mg, 77% for two steps from **1h**).
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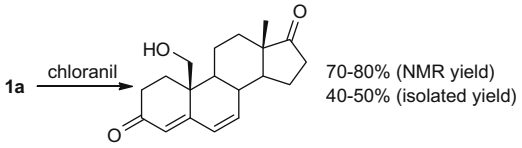
13. Direct oxidation of **1a** formed a by-product, which can only be removed by recrystallization and resulted in decrease of isolated yield (40–50%).



14. *Preparation of 6,7-dehydroestrone*: According to the previous procedure, 300 mg of **1a** (1 mmol) provided crude acetyl ester **1h** (390 mg), which was used without further purification.
The mixture of crude acetyl ester **1h** (390 mg) and chloranil (417 mg, 1.70 mmol) in *t*-BuOH (10 mL) was refluxed for 2 h, then the solvent was removed under reduced pressure and the residue was dissolved in MeOH

(30 mL). The insoluble portion was removed by filtration and washed with MeOH (3 × 10 mL). Solvent removal afforded the acetyl ester **4** (550 mg) as a yellow oil, which was used without further purification. According to the previous procedure, dehydrogenation of crude **4** with DDQ and subsequent acid-catalyzed hydrolysis provided 6,7-dehydroestrone (184 mg, 69% from **1a**) as a white powder after purification by column chromatography.

According to the previous procedure, dehydrogenation of crude **4** with DDQ and subsequent acid-catalyzed hydrolysis provided 6,7-dehydroestrone (184 mg, 69% from **1a**) as a white powder after purification by column chromatography.

15. (a) Kanojia, R. M.; Allen, G. O.; Killinger, J. M.; Mcguire, J. L. *J. Med. Chem.* **1979**, *22*, 1538; (b) Ercoli, A.; Gardi, R. *Chem. Ind.* **1961**, 1037.
16. *General procedure for the preparation of compound* **6a**: To a solution of steroid **2h** (200 mg, 0.58 mmol) and TsOH (20 mg, 0.10 mmol) in dry MeOH (3 mL), trimethyl orthoformate (1 mL) was added slowly. The mixture was heated for 1 h (60 °C). After completion (monitored with TLC), the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography to afford estrone 3-methyl ether **6a** (136 mg, 82%).