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# 1,2-Dehydrogenation of steroidal 6-methylen derivatives. Synthesis of exemestane

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ABSTRACT

The development of an efficient dehydration method of steroidal 4-en-3-ones by using chloranil and BSTFA in the presence of triflic acid in refluxing toluene allowed us, starting from testosterone, to set a large-scale procedure for the synthesis of the anti-cancer drug exemestane in 70% overall yield.



## 1. Introduction

In many clinical situations, estrogens produced in normal or excess quantities play a prominent role in the pathogenesis of various diseases as mammary and ovarian tumours.[1–7] Suppression of estrogen action by inhibition of their biosynthesis at the androstenedione–estrone aromatization step by means of selective inhibitors of the enzyme aromatase, has become an effective therapeutic option for the treatment of hormone-dependent breast cancer.[8]

6-Methylenandrosta-1,4-diene-3,17-dione **1**, an anticancer drug known under the trade name 'exemestane', is the most well known irreversible aromatase inhibitor of the 6-substituted androstane series. It works efficiently as hormonal therapy for postmenopausal patients with advanced breast cancer that has become refractory to standard current hormonal therapies.[9–11] It is orally active and well-tolerated. Exemestane is a highly selective aromatase inhibitor (AI). The irreversibility of its inhibitory action is assigned to the presence of a 1,2-double bond in the molecule; the corresponding 1,2-hydrogenated analogues represent reversible AI. It is these properties rather than pharmacokinetic ones that account for the prolonged action of exemestane on the organism.[12]

Exemestane and its derivatives have been synthesised from testosterone **2a** (Fig. 1), androst-4-ene-3,17-dione (AD) **2b**, or androsta-1,4-diene-3,17-dione (ADD) **3**.[13–32] When AD was used as the starting material, the introduction of the methylene group at position 6 using the method of Annen et al.[33] was followed by 1,2-dehydrogenation and the overall yield of exemestane was rather low (20–25%). The tedious chromatographic purification of the reaction products in both stages prevented application of the method in large scale procedures. The dehydrogenation of steroidal ketones by treatment with 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ) has been studied in depth in the 3-keto-androstane series. The reaction of DDQ with steroidal 4-en-3-ones is catalysed by acids: 1,2-dehydrogenation predominates in the presence of weak acids, as it

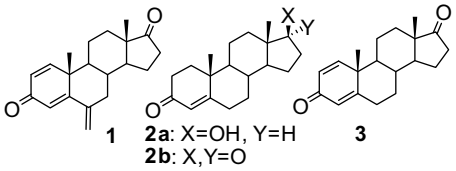


**Figure 1.**

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does in the uncatalysed reaction, whereas strong acids promote the exclusive formation of 6,7-dehydro derivatives. These results can be rationalized in terms of a mechanism involving the oxidation of the alternative enolic forms of the ketone.[34] When DDQ reacted with 3-ethoxy $\Delta^{3,5}$-steroids, a sequence was envisaged as proceeding via hydride abstraction at C-7, loss of a C-2 proton from the oxonium intermediate, followed by hydride loss from C-1 to afford the 1,4,6-trien-3-ones.[35] Furthermore, the DDQ oxidation of silylenol ethers led to the formation of quinone-substrate adducts which afforded enones by thermolysis.[36] The silylation-mediated oxidation of 4-aza-3-ketosteroids with DDQ proceeded via DDQ-substrate adducts and afforded $\Delta^{1}$-4-aza-steroids.[37] This process has been used for the large-scale production of finasteride, the active agent for the treatment of benign prostatic hyperplasia (BHP).[38,39]

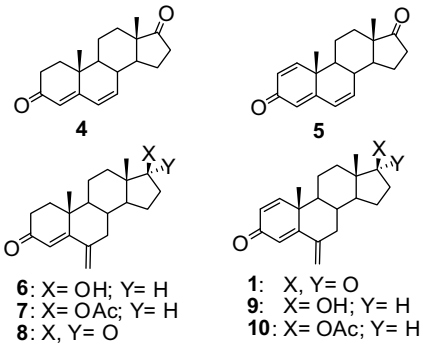



**Figure 2.**

## 2. Results and discussion

With the aim of setting a large-scale procedure for the synthesis of exemestane, we focused our attention on the quinone-promoted 1,2-dehydrogenation reaction of 6-methylenandrost-4-en-3-ones. Our results are summarized in Table 1.

### 2.1. Dehydrogenation

*2.1.1. The oxidant (quinones)*

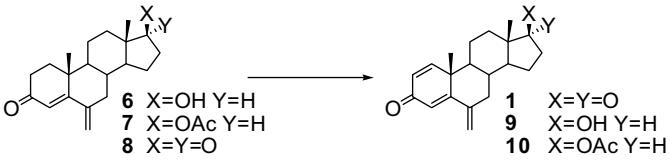
It is well known that treatment of androst-4-ene-3,17-dione **2b** with DDQ[40] in benzene or dioxane under reflux leads to androsta-1,4-diene-3,17-dione **3** as the major product, along with smaller amounts of 4,6-dien- and 1,4,6-trien-3-ones (**4** and **5**, respectively) (Fig. 2). 1,2-Dehydrogenation was more specific in benzene than in dioxane and the best yield (**3**: 84%, **4**: 2%, **5**: 10%) was obtained by treatment of **2** with 1.2 equiv of quinone in refluxing benzene for 15 h.[34] However, when these conditions were applied to **8** (Table 1, entries 1 and 2) no transformation was detected after 48 h, presumably, because of the A-ring deactivation due to the presence of the double bond at C-6. Increasing the amount of oxidant did not give any better results after 7 days of reaction. The same results were obtained with 6-methyl-entestosterone **6** by treatment of the steroid with 1.5 equiv of DDQ in refluxing benzene or dioxane (entries 3 and 4). However, 1,2-dehydrogenation was successfully achieved by reacting **6** with DDQ and the addition of 2 equiv of benzoic acid in refluxing benzene for 5 h. In this case, the 1,2-dehydrogenation product **9** was obtained in 14% isolated yield. The reaction of **6** with DDQ in the presence of 4.2 equiv of bis(trimethylsilyl) trifluoroacetamide (BSTFA) and catalytic *p*-toluenesulphonic acid (0.05 equiv) in toluene at 60 °C, afforded **9** in similar yield (Table 1, entry 6).

However, when DDQ was replaced by chloranil a dramatic improvement of the 1,2-dehydrogenation reaction took place. Treatment of **6** with chloranil in the presence of BSTFA and catalytic triflic acid (0.01 equiv) afforded **9** in 68% isolated yield in only 4 h. (Table 1, entry 8). Analogously, the same reaction conditions applied to 6-methylenandrost-4-ene-3,17-dione **8** afforded **11** in 81% isolated yield. Our best result was obtained by using the testosterone acetate **7**: the reaction took place by treatment of the steroid with chloranil (1.1 equiv), BSTFA (4.2 equiv) and triflic acid (0.1 equiv) in refluxing toluene for 18 h. and allowed us to isolate the dehydrogenated acetate **10** in 85% yield (Table 1, entry 10).

*2.1.2. The silylating reactant*

Different experiments were run to test the relevance of the silyl reagent in the dehydrogenation process; trimethylsilylchloride

**Table 1**
1,2-Dehydogenations of 6-methylenandrost-4-en-3-ones




| Entry | Starting material | Quinone (equiv) | Silylating agent (equiv) | Acid (equiv) | Solvent | Temperature | Time | Product | Yield % |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **8** | DDQ (1.0) | — | — | Benzene | Reflux | 50 h | — | — |
| 2 | **8** | DDQ (2.2) | — | — | Benzene | Reflux | 7 days | — | — |
| 3 | **6** | DDQ (1.5) | — | — | Benzene | Reflux | 18 h | — | — |
| 4 | **6** | DDQ (1.4) | — | — | 1,4-Dioxane | Reflux | 17 h | — | — |
| 5 | **6** | DDQ (1.5) | — | PhCOOH (1.9) | Benzene | Reflux | 5 h | **9** | 14% |
| 6 | **6** | DDQ (1.1) | BSTFA (4.21) | *p*-TsOH (0.05) | Toluene | 60 °C | 41 h | **9** | 12% |
| 7 | **6** | Chloranil (1.1) | BSTFA (3.21) | $H_2SO_4$ (0.5) | Toluene | Reflux | 15 h | **9** | 65% |
| 8 | **6** | Chloranil (1.1) | BSTFA (4.21) | TfOH (0.01) | Toluene | Reflux | 4 h | **9** | 68% |
| 9 | **8** | Chloranil (1.1) | BSTFA (4.21) | TfOH (0.1) | Toluene | Reflux | 45 min | **1** | 81% |
| 10 | **7** | Chloranil (1.1) | BSTFA (4.21) | TfOH (0.1) | Toluene | Reflux | 30 min | **10** | 85% |
| 11 | **7** | Chloranil (1.1) | TMSCl (4.21) | TfOH (0.1) | Toluene | Reflux | 32 h | — | |
| 12 | **7** | Chloranil (1.1) | BSA (4.21) | TfOH (0.1) | Toluene | Reflux | 4.0 days | — | — |
| 13 | **7** | Chloranil (1.1) | BSU (4.21) | TfOH (0.1) | Toluene | Reflux | 3.0 days | **10** | 16% |
| 14 | **7** | Chloranil (1.1) | TMSIm (4.21) | TfOH (0.1) | Toluene | Reflux | 2.5 days | **10** | 4% |
| 15 | **7** | Chloranil (1.1) | TMSIm (4.21) | TfOH (0.1) | Toluene | 50 °C | 3.5 days | **10** | 3% |
| 16 | **7** | DDQ (1.1) | BSTFA (4.21) | TFA (0.2) | Toluene | 60° | 32 h | **10** | 49% |
| 17 | **7** | Chloranil (1.1) | BSTFA (4.21) | TFA (0.2) | Toluene | Reflux | 48 h | **10** | 82% |
| 18 | **7** | Chloranil (1.1) | BSTFA (3.2) | $H_2SO_4$ (0.5) | Toluene | Reflux | 15 h | **10** | 83% |

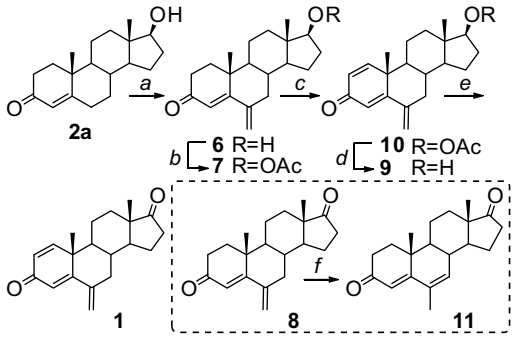
(TMSCl), bis(trimethylsilyl)acetamide (BSA), bis(trimethylsilyl)urea (BSU) and trimethylsilylimidazol were studied (Table 1, entries 10–14), but all these alternatives resulted to be far less efficient than BSTFA (Table 1, entries 11–15).

*2.1.3. The catalyst (acid)*

Benzoic, *p*-toluenesulphonic, triflic, sulphuric and trifluoroacetic acids were used under different conditions. Among them, triflic acid has shown to be the most efficient catalyst of the dehydrogenation process. However, because of its easier handling in large-scale processes, sulphuric or trifluoroacetic acid can also be used, although in these cases, the reaction times were longer (Table 1, entries 16–18).

### 2.2. Synthesis of exemestane

With the dehydrogenation results in our hands, the synthesis of exemestane was straightforward (Scheme 1). The direct introduction of a methylene group at 6-position of a 3-oxo-4-ene steroid is a known process.[22,25] Our synthesis exploited the 6-methylenation of testosterone by treatment of the steroid with triethylorthoformate in tetrahydrofuran–EtOH at 40 °C in the presence of *p*-toluenesulphonic acid. The formation of the intermediate ethyl $\Delta^{3,5}$-enolether was followed by treatment with *N*-methylaniline and aqueous formaldehyde at 40 °C. Isolation of 6-methylentestosterone was achieved after HCl-promoted elimination of *N*-methylaniline by quaternization of the Mannich precursor in 89% isolated yield after precipitation.




**Scheme 1.** (a) TEOF, *p*-TsOH, THF/EtOH, *N*-methylaniline, HCHO, HCl, 40 °C (89%); (b) $Ac_2O$/Pyr, DCM, rt, (99%); (c) chloranil, BSTFA, TfOH, Toluene, Δ, (85%); (d) 1 M NaOH, MeOH, rt, (95%); (e) Jones, acetone, −20 °C (100%); (f) 5% Pd/C, cyclohexene, NaAcO·$3H_2O$ (93%).

Acetylation of the hydroxy function of **6** by treatment of the steroid with acetic anhydride in pyridine afforded the acetate **7** in quantitative yield. Dehydrogenation of **7** took place, as already shown, by treatment of the acetate with BSTFA (4.2 equiv), chloranil (1.1 equiv) and triflic acid (0.1 equiv) in refluxing toluene for 18 h (Table 1, entry 10) and afforded the $\Delta^{1,3}$-3-keto steroid **10** in 85% yield. Saponification of the acetate **10** by reaction with methanolic sodium hydroxide at room temperature led to isolation of the hydroxy derivative **9** in 95% yield. This compound was also obtained by dehydrogenation of **6** under standard conditions in 68% yield (Table 1, entry 7). Jones oxidation of **9** in acetone at −20 °C led to exemestane **1** in quantitative yield.

Interest in preparing reference samples of possible secondary products of the synthetic route for analytical control in plant production prompted us to prepare the double conjugated ketone **11**. This was successfully achieved by reaction of **8** with 5% Pd on carbon and cyclohexene in the presence of sodium acetate trihydrate in refluxing ethanol. Isolation of **11** was achieved by precipitation in 93% yield.

## 3. Conclusion

The use of chloranil and BSTFA in the presence of catalytic amounts of triflic acid in refluxing toluene is the most efficient method for the 1,2-dehydrogenation of 6-methylenandrost-4-en-3-ones under acid catalysis. We have developed a large-scale procedure to transform testosterone into exemestane by application of a 5-step sequence in 70% overall yield.

## 4. Experimental

### 4.1. General experimental methods

Melting points are uncorrected. $^1$H NMR spectra were measured at either 200 or 400 MHz and $^{13}$C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS ($^1$H) or solvent ($^{13}$C), except where indicated otherwise. IR spectra were recorded for $CHCl_3$ solution samples on NaCl plates, unless otherwise noted, on a FT-IR instrument. HRMS determinations (EI) were recorded at the Mass Spectrometry Service of the University of Salamanca, Spain. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for handling of air-sensitive materials. Chemicals and solvents were obtained from commercial sources and used as received with the exception of benzene, toluene and dioxane which were distilled from sodium and benzophenone. Yields reported are for chromatographic pure isolated products unless mentioned otherwise.

### 4.2. 7β-Hydroxy-6-methylenandrost-1,4-diene-3-one (9)

*4.2.1. Synthesis of **9** from **6***

A 50 ml two neck round bottom flask equipped with an Argon inlet, reflux condensed, magnetic stirrer, and a septum was charged with **6** (0.29 g, 1.00 mmol), chloranil (0.27 g, 1.1 mmol), toluene (26 ml) and a catalytic amount of trifluoromethanesulphonic acid (0.008 ml, 0.1 mmol). The reaction mixture developed a yellow color. BSTFA (1.2 ml, 4.21 mmol) was added dropwise via syringe while stirring. The solution was refluxed for 4 h, at the end of which complete disappearance of starting material was observed by TLC. The suspension was cooled to room temperature and diluted with EtAcO (20 ml). The organic layer was consecutively washed with 5% $Na_2SO_3$, (2×15 ml), 2% NaOH (3×15 ml) and saturated NaCl (3×15 ml). The organic phase was dried ($Na_2SO_4$) and evaporated to afford a residue that was fractionated by chromatography on silica gel. Elution with 1:1 hexane/ethyl acetate gave 0.19 g (68%) of **9**. Mp: 131 °C; $[\alpha]_D^{20}$ +144.9 (*c* 14.34, $CHCl_3$); IR ($CHCl_3$), $\nu$ ($cm^{-1}$): 860, 1255, 1619, 1722, 1730, 2851, 2923, 3383; $^1$H NMR ($CDCl_3$), $\delta$ (ppm): 0.81 (s, 3H), 1.14 (s, 3H), 0.8–2.6 (m. 13H), 3.66 (t, *J*=10.0 Hz, 1H), 4.93 (s, 1H), 5.00 (s, 1H), 6.14 (d, *J*=10.0 Hz, 1H), 6.24 (dd, $J_1$=10.0 Hz, $J_2$=2.0 Hz, 1H), 7.08 (d, *J*=10.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$), $\delta$ (ppm): 11.1, 19.6, 22.4, 23.3, 30.2, 35.7, 36.2, 40.0, 43.0, 43.8, 50.0, 50.4, 81.2, 111.8, 122.3, 127.5, 145.8, 154.6, 168.0, 186.5; HRMS-EI (M+Na) calcd for $C_{20}H_{26}O_2Na$ 321.1825, found 321.1843.

*4.2.2. Synthesis of **9** from **10***

To a solution of **10** (0.23 g, 0.7 mmol) in methanol (4 ml) was added 1 N NaOH (1.4 ml) at room temperature. After 6 h, the reaction mixture was poured into brine and extracted with EtAcO (3×15 ml). The combined organic layers were dried ($Na_2SO_4$) and evaporated to afford **9** (0.19 g, 95%).

### 4.3. 6-Methylenandrost-1,4-diene-3-one 17β-acetate (10)

Compound **7** (0.27 g, 0.8 mmol) was dehydrogenated as described above (compound **9** from **6**) for 18 h. The residue was cromatographed on silica gel and eluted with 8:2 hexane/ethyl acetate

to afford **10** (0.23 g, 85%). $[\alpha]_D^{20}$ +92.7 (*c* 21.35, $CHCl_3$); IR ($CHCl_3$) $\nu$ ($cm^{-1}$): 918, 1041, 1255, 1379, 1658, 1735, 2858, 2942; $^1H$ NMR ($CDCl_3$), $\delta$ (ppm): 0.85 (s, 3H), 1.14 (s, 3H), 2.04 (s, 3H), 1.0–2.6 (m, 13H), 4.62 (t, *J*=8.0 Hz, 1H), 4.94 (s, 1H), 5.01 (s, 1H), 6.14 (d, *J*=2.0 Hz, 1H), 6.28 (dd, $J_1$=10.0 Hz, $J_2$=2.0 Hz, 1H), 7.06 (d, *J*=10.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$), $\delta$ (ppm): 12.0, 19.6, 21.0, 22.2, 23.4, 27.3, 35.5, 36.4, 39.9, 42.6, 43.6, 49.8, 50.2, 82.1, 111.9, 122.5, 127.6, 145.7, 154.3, 167.6, 170.9, 186.5; HRMS-EI (M+Na) calcd for $C_{22}H_{28}O_3Na$ 363.1931, found 363.1921.

### 4.4. 6-Methylenandrost-1,4-diene-3,17-dione (1). Exemestane

#### *4.4.1. Synthesis of exemestane (**1**) from **9***

A two neck round bottom flask equipped with an Argon inlet, an addition funnel, magnetic stirrer, and a septum inlet was charged with **9** (0.11 g, 0.4 mmol) solved in methanol and cooled to −20 °C. Jones reagent was poured dropwise into the reaction vessel to the point of a persistent orange colour. The excess of the reagent was destroyed with isopropyl alcohol, and the reaction mixture was poured into brine at 0 °C. The steroid was extracted with EtAcO and washed with saturated $NaHCO_3$. The organic phase was dried ($Na_2SO_4$) and evaporated to afford **1** (0.11 g, 100%). Mp: 196 °C; $[\alpha]_D^{20}$ +280.6 (*c* 13.79, $CHCl_3$); IR ($CHCl_3$), $\nu$ ($cm^{-1}$): 729, 813, 909, 1027, 1277, 1453, 1647, 1734, 2941; $^1H$ NMR ($CDCl_3$), $\delta$ (ppm): 0.94 (s, 3H), 1.17 (s, 3H), 1.2–2.7 (m, 13H), 5.00 (s, 1H), 5.06 (s, 1H), 6.17 (d, *J*=2.0 Hz, 1H), 6.25 (dd, $J_1$=10.0 Hz, $J_2$=2.0 Hz, 1H), 7.08 (d, *J*=10.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$), $\delta$ (ppm): 13.3, 19.2, 21.4, 21.6, 30.7, 34.9, 35.1, 38.8, 43.2, 47.2, 49.5, 50.3, 112.0, 122.2, 127.3, 144.8, 153.7, 167.0, 185.9, 219.0; HRMS-EI (M+Na) calcd for $C_{20}H_{24}O_2Na$: 319.1668, found 319.1650.

#### *4.4.2. Synthesis of exemestane (**1**) from **8***

Compound **8** (1.06 g, 3.54 mmol) was dehydrogenated as described above (compound **9** from **6**) for 45 min. The residue was cromatographed on silica gel and eluted with 1:1 hexane/ethyl acetate to achieve **1** (0.85 g, 81%) pure.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.094.

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