

## Epoxidation and Reduction of DHEA, 1,4,6-Androstatrien-3-one and 4,6-Androstadien-3 $\beta$ ,17 $\beta$ -diol

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**Abstract:** Dehydroepiandrosterone (DHEA) reacted with *m*-chloroperoxybenzoic acid (*m*-CPBA) to form 3 $\beta$ -hydroxy-5 $\alpha$ ,6 $\alpha$ -epoxyandrostan-17-one (**1**), but it did not react with 30% H<sub>2</sub>O<sub>2</sub>. 1,4,6-Androstatrien-3,17-dione (**2**) was obtained from DHEA and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dioxane. Compound **2** was reacted with 30% H<sub>2</sub>O<sub>2</sub> and 5% NaOH in methanol to give 1 $\alpha$ ,2 $\alpha$ -epoxy-4,6-androstadien-3,17-dione (**3**), which was stereoselectively reduced with NaBH<sub>4</sub> to form 1 $\alpha$ ,2 $\alpha$ -epoxy-4,6-androstadien-3 $\beta$ ,17 $\beta$ -diol (**7**) and reacted with Li metal in absolute ethanol-tetrahydrofuran mixture to give 2-ethoxy-1,4,6-androstatrien-3,17-dione (**8**). Compound **2** was also epoxidized with *m*-CPBA in dichloromethane to afford 6 $\alpha$ ,7 $\alpha$ -epoxy-1,4-androstadien-3,17-dione (**4**), which was reacted with NaBH<sub>4</sub> to synthesize 6 $\alpha$ ,7 $\alpha$ -epoxy-4-androsten-3 $\beta$ ,17 $\beta$ -diol (**9**). Compound **4** was reduced with Li metal in absolute ethanol-tetrahydrofuran mixture to form 7 $\beta$ -ethoxy-6 $\alpha$ -hydroxy-1,4-androstadien-3,17-dione (**10**). Compound **2** was reduced with NaBH<sub>4</sub> in absolute ethanol to form 4,6-androstadien-3 $\beta$ ,17 $\beta$ -diol (**5**), which was reacted with 30% H<sub>2</sub>O<sub>2</sub> to give the original compound, but which reacted with *m*-CPBA to give 4 $\beta$ ,5 $\beta$ -epoxy-6-androsten-3 $\beta$ ,17 $\beta$ -diol (**6**).

**Keywords:** Dehydroepiandrosterone; position selective and reagent selective epoxidation and reduction; H<sub>2</sub>O<sub>2</sub>; *m*-chloroperoxybenzoic acid; sodium borohydride, lithium

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## Introduction

Dehydroepiandrosterone (3 $\beta$ -hydroxyandrost-5-en-17-one, DHEA) is an endogenous steroid synthesized in the adrenal cortex, gonads, brain, and gastrointestinal tract [1,2]. It is known to have chemopreventive and anti-proliferative actions on tumors [3-5]. DHEA is the most abundant steroid in human blood; it is not only an intermediate in the biosynthesis of testosterone and estrogens but it also exerts several physiological effects independent of the sex hormones. It is also an anti-obesity agent for genetically obese and normal animals, but does not affect food intake [6]. It decreases blood cholesterol concentration in several species [7-9], lessens the severity of diabetics in genetically predisposed mice [10], enhances the immune system [11,12], and improves memory in aged mice [13]. Many naturally occurring polyhydroxylated sterols and oxysterols exhibit potent biological activities [14,15]. Some polyhydroxylated sterols showed potent cytotoxicity to cancer cells [16,17], but oxygenated and hydroxylated analogs of DHEA had apparently not been tested for biological activity in animals until recently [18-21]. Several monohydroxylated derivatives of DHEA [4 $\alpha$ ,5 $\alpha$ ,7 $\alpha$ ,7 $\beta$ ,11 $\beta$ ,16 $\alpha$ ,19] and of 5-androsten-3 $\beta$ ,17 $\beta$ -diol were prepared. Among them, 7-hydroxy-DHEA was fully as active as DHEA and 7-oxo-DHEA was more active [18,20]. To search for possible derivatives of DHEA that might have greater biological activity and specificity, we sought to synthesize the corresponding epoxy and hydroxy-DHEA derivatives.

Epoxides are among the most frequently occurring functional groups found in natural products and their synthetic analogues. Not only are these compounds easily prepared from variety of starting materials, but the inherent polarity and the strain of their three-membered ring makes them susceptible to reaction with a large number of reagents – electrophiles, nucleophiles, acids, bases, reducing agents, and oxidizing agents [22,23]. Whilst the balance between the various stereoelectronic factors that control the stereochemistry of epoxidation of steroidal alkenes has been thoroughly investigated, there have been relatively few studies of the epoxidation of conjugated steroidal dienes and trienes [24].

In order to investigate the reagent selectivity and position selectivity of different epoxidizing agents towards 1,4,6-androstatrien-3,17-dione and 4,6-androstadien-3 $\beta$ ,17 $\beta$ -diol as examples of trienes and dienes, 30% H<sub>2</sub>O<sub>2</sub> and *m*-chloroperoxybenzoic acid were used. These reagents are easily handled and inexpensive materials that did not require complicated procedures or expensive metal-catalysts, which were mostly used to control the asymmetric epoxidation. In addition, and in order to study the reagent and position selectivity of the resulting epoxy derivatives towards reducing agents, we selected NaBH<sub>4</sub> and Li metal in absolute ethanol-tetrahydrofuran mixture and we tried to compare the selectivity of these reagents for the cleavage of epoxide ring, and reduction of carbonyl groups and double bonds of epoxy unsaturated DHEA derivatives.

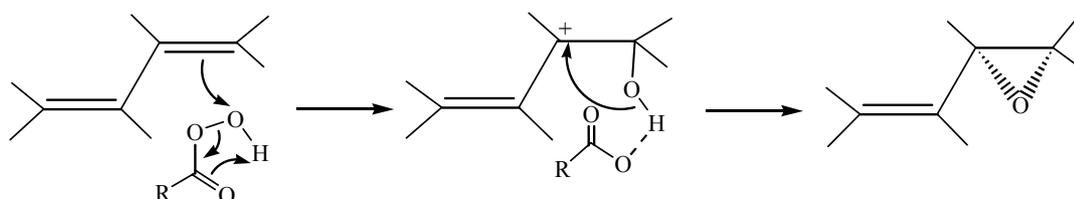
## Results and Discussion

For the synthesis of dehydroepiandrosterone (DHEA) derivatives, commercially available DHEA was used as the starting material. The planned synthetic routes from DHEA are shown in Scheme 1.



in chloroform at room temperature, the 6,7-double bond was epoxidized to form 6 $\alpha$ ,7 $\alpha$ -epoxy-1,4-androstadien-3,17-dione (**4**). Initial attack by a peracid should be directed to a pseudo-axial site on the face opposite to the C-10 methyl group to form  $\alpha$ -epoxide. Allylic interaction between the adjacent double bond and the intermediate in the epoxidation might favour a particular site of attack by stabilizing an adjacent carbocationic intermediate [24] (Scheme 2).

**Scheme 2.** Formation of stable allylic carbocationic intermediate by *m*CPBA.



Compound **2** was reduced with NaBH<sub>4</sub> in absolute ethanol to form 4,6-androstadien-3 $\beta$ ,17 $\beta$ -diol (**5**) as 1,2- and 1,4 addition product [29]. Metallic hydrides, such as LiAlH<sub>4</sub> and NaBH<sub>4</sub>, do not in general reduce carbon-carbon double bond, but these reagents may also double bond in conjugated with C=O bonds, as well as reducing the C=O bonds [30,31]. The attack of hydride anion of NaBH<sub>4</sub> to the axial direction of the carbonyl group produced the 3 $\beta$ - and 17 $\beta$ -hydroxy configuration and only the 1,2-double bond of the 1,4,6-triene **2** was reduced. The stereochemistry was established from the NOESY spectrum. No correlation between the hydrogens of the C-10 methyl group on the  $\beta$ -face and H-3, and C-13 methyl hydrogens and H-17 was observed in the NOESY spectrum of **5**, therefore both OH groups on C-3 and C-17 are directed in the  $\beta$ -position. On attempted epoxidation of compound **5** in the presence of 30% H<sub>2</sub>O<sub>2</sub> and 5% NaOH in methanol, only starting material was recovered. Compound **5** reacted with *m*-chloroperoxybenzoic acid to give 4 $\beta$ ,5 $\beta$ -epoxy-androst-6-en-3 $\beta$ ,17 $\beta$ -diol (**6**). In this case, the presence of the 3 $\beta$ -hydroxy group of the allylic alcohol directed the epoxidation exclusively to the  $\beta$ -face of the double bond of the molecule [32,33].

Compounds **3** and **4** were reduced with NaBH<sub>4</sub> and Li metal in absolute ethanol-THF mixture, respectively. Compound **3** reacted with NaBH<sub>4</sub> to give 1 $\alpha$ ,2 $\alpha$ -epoxy-4,6-androstadien-3 $\beta$ ,17 $\beta$ -diol (**7**). NaBH<sub>4</sub> selectively attack the two carbonyl groups of compound **3** to give the corresponding 3 $\beta$ ,17 $\beta$ -diol. This result was similar to the observation by Benn *et al* [34] that 1 $\alpha$ ,2 $\alpha$ -epoxyandrostan-3 $\beta$ ,17 $\beta$ -diol was obtained from 1 $\alpha$ ,2 $\alpha$ -epoxyandrostan-3,17-dione with NaBH<sub>4</sub>. Compound **3** was also reacted with Li metal in absolute ethanol-tetrahydrofuran mixture to form 2-ethoxy-1,4,6-androstatriene-3,17-dione (**8**). In this case, ethoxide anion, formed from Li metal in the solvent, attacked the 2-position of the epoxide ring to form 2 $\beta$ -ethoxy-1 $\alpha$ -hydroxy-4,6-androstadien-3-one as intermediate, and then H<sub>2</sub>O was eliminated to give compound **8**. In the <sup>1</sup>H-NMR spectrum of **8** four double bond hydrogens were identified at 5.93(1H), 6.11(2H), 6.33(1H) ppm and six double bond carbons at 161.8, 150.3, 136.1, 128.1, 124.1, 120.3 ppm and two carbonyl carbons at 219.1, 181.2 ppm were identified in the <sup>13</sup>C-NMR spectrum. Compound **4** was reacted with NaBH<sub>4</sub> to afford 6 $\alpha$ ,7 $\alpha$ -epoxy-4-androsten-3 $\beta$ ,17 $\beta$ -diol (**9**), obtained by 1,2- and 1,4-addition of hydride to the  $\alpha$ , $\beta$ -unsaturated carbonyl group and  $\alpha$ -attack of hydride on the 17-carbonyl group. 7 $\beta$ -Ethoxy-6 $\alpha$ -hydroxy-1,4-androstadien-3,17-dione (**10**) was

obtained from the reaction of **4** with Li metal in absolute ethanol-tetrahydrofuran mixture at room temperature. The  $\beta$ -face attack of ethoxide ion to the 7-position of epoxide ring might be directed to cause cleavage of the epoxide ring. In the  $^1\text{H-NMR}$  spectrum of **10** three double bond hydrogens were observed at 6.16, 6.25, 7.15 ppm and four double bond carbons at 161.7, 157.3, 130.6, 126.8 ppm and two carbonyl carbons at 220.5, 185.9 ppm were identified in  $^{13}\text{C-NMR}$  spectrum, respectively. The structure for **10** was further confirmed by FABMS showing an  $(\text{M}+\text{H}-\text{C}_2\text{H}_5\text{OH})^+$  at 299.1  $m/z$  and  $(\text{M}+\text{H}-\text{C}_2\text{H}_5\text{OH}-\text{H}_2\text{O})^+$  at 281.1  $m/z$ .

## Conclusions

On treatment of 1,4,6-androstatrien-3,17-dione (**2**) with 30%  $\text{H}_2\text{O}_2$ , of the double bonds conjugated with the carbonyl group at position 3 only the 1,2-double bond was selectively transformed into the corresponding  $1\alpha,2\alpha$ -epoxide in 5% NaOH in methanol solution, whereas *m*-CPBA epoxidized the 6,7-double bond of the trienone to form the  $6\alpha,7\alpha$ -epoxide derivative in the presence of the carbonyl group at position 3. On reduction in ethanol in the presence of  $\text{NaBH}_4$ , only the 1,2-double bond and the carbonyl of **2** were reduced to give 4,6-androstadien- $3\beta,17\beta$ -diol (**5**). The  $3\beta$ -hydroxy group of the allylic alcohol of compound **5** directed the subsequent epoxidation by *m*-CPBA exclusively to the  $\beta$ -face of the 4,5-double bond. 30%  $\text{H}_2\text{O}_2$  did not react in the presence of hydroxyl group at position 3. The carbonyl groups at positions 3 and 17 of  $1\alpha,2\alpha$ -epoxy- and  $6\alpha,7\alpha$ -epoxyandrostadien-3,17-dione (**3** and **4**) were selectively reduced by  $\text{NaBH}_4$  to form the  $3\beta,17\beta$ -diol. And reaction of epoxy-dienone in absolute ethanol-tetrahydrofuran mixture in the presence of Li metal resulted in the cleavage of epoxide ring by ethoxide anion without reduction of double bonds and carbonyl groups.

## Acknowledgments

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## Experimental

### General

Reactions were performed under nitrogen gas. Solvents were purified and dried prior to use. Melting points were measured on Thomas-Hoover melting point apparatus in open capillary tubes and are not corrected.  $^1\text{H-}$  and  $^{13}\text{C-NMR}$  spectra were obtained on Gemini 200 MHz or 50MHz spectrometers in  $\text{CDCl}_3$ , chemical shifts  $\delta$  are in ppm are relative to tetramethylsilane, coupling constants  $J$  in Hz. NOESY spectra were measured on Bruker AM-500MHz spectrometer (Rheinstetten, Germany). IR spectra were determined on a Jasco FT-IR 300E spectrometer as KBr pellets. FAB mass spectra were recorded on a tandem mass spectrometer made by Jeol Ltd (Japan). Analytical TLC was performed on Merck precoated silica gel 60  $\text{F}_{254}$  plates. Column chromatography was carried out on Merck silica gel 9385 (230-400 mesh).

*5 $\alpha$ ,6 $\alpha$ -Epoxy-androstan-3 $\beta$ -ol-17-one (1)*

To a solution of androst-5-en-3 $\beta$ -ol (dehydroepiandrosterone, 1 g, 3.47 mmol) in CHCl<sub>3</sub> (50 mL) *m*-chloroperoxybenzoic acid (2 g, 6.93 mmol) was added at room temperature. The mixture was stirred at room temperature for 24 hours. The solution was diluted with CHCl<sub>3</sub>, treated with aqueous sodium sulfite and the aqueous layer was extracted with several portions of CHCl<sub>3</sub>. The combined organic extracts were washed with water, dried with anhydrous MgSO<sub>4</sub>, filtered and evaporated to leave a crude solid, which was column chromatographed with 1:2 ethyl acetate/*n*-hexane as eluent to afford white crystals. Yield: 897 mg (85 %); mp: 208.5-212 °C; IR (cm<sup>-1</sup>): 3520, 2946, 1721, 1440; <sup>1</sup>H-NMR  $\delta$ : 0.82 (3H, s, H-18), 1.26 (3H, s, H-19), 2.94 (1H, d, *J*=3.0Hz, H-6), 3.79-3.96 (1H, m, H-3); <sup>13</sup>C-NMR  $\delta$ : 220.7, 68.4, 65.9, 58.9, 51.9, 47.7, 42.9, 39.8, 35.8, 35.1, 32.5, 31.2, 31.1, 29.6, 27.8, 21.8, 20.1, 16.1, 13.7; FABMS (M+H-H<sub>2</sub>O)<sup>+</sup>: 287.0.

*1,4,6-Androstatrien-3,17-dione (2)*

A solution of DHEA (5 g, 17.36 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (11.8 g, 52.08 mmol) in dioxane (100 mL) was refluxed for 24 hours according to the procedure reported by Furst *et al.* [35]. The reaction mixture was cooled down and the resulting precipitate was filtered off and washed with dichloromethane. The filtrate was rotary evaporated to dryness and the dark brown residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane=1:3) to afford white crystals. Yield: 2.98 g (61 %); mp : 165-166 °C; IR (cm<sup>-1</sup>): 2977, 2937, 1739, 1649, 1602; <sup>1</sup>H-NMR  $\delta$ : 1.01 (3H, s, H-18), 1.23 (3H, s, H-19), 6.08 (2H, t, H-6, H-7), 6.24-6.36 (2H, m, H-2, H-4), 7.06 (1H, d, *J*=10.0Hz, H-1); <sup>13</sup>C-NMR  $\delta$ : 186.1, 161.7, 152.4, 135.7, 128.6, 128.4, 124.3, 49.0, 48.6, 48.0, 41.2, 37.7, 35.7, 31.4, 21.5, 21.8, 20.9, 14.0; FABMS (M+H)<sup>+</sup>: 283.0.

*1 $\alpha$ ,2 $\alpha$ -Epoxy-4,6-androstadien-3,17-dione (3)*

According to a procedure of Pelc *et al.* [27], to a solution of the trienone **2** (600 mg, 2.1 mmol) in methanol (30 mL) was added a mixture of 5 % NaOH-MeOH (0.4 mL) and 30 % H<sub>2</sub>O<sub>2</sub> (1.2 mL). The reaction mixture was stirred at room temperature for 22 hours, at which time TLC indicated reaction completion, and then extracted with dichloromethane. The organic layers were combined and washed with brine and H<sub>2</sub>O, dried over anhydrous MgSO<sub>4</sub>, filtered, and concentrated to leave a crude solid. Column chromatography on silica gel, eluting with 1:2 ethyl acetate/*n*-hexane gave pure white crystals of epoxide **3**. Yield: 1.65 g (78 %); mp: 220-223 °C; IR (cm<sup>-1</sup>): 2946, 1740, 1671, 1664, 1615, 1440; <sup>1</sup>H-NMR  $\delta$ : 1.00 (3H, s, H-18), 1.23 (3H, s, H-19), 3.45-3.49 (1H, m, H-1), 3.61 (1H, d, *J*=4.0Hz, H-2), 5.69 (1H, s, H-4), 6.09-6.23 (2H, m, H-6, H-7); <sup>13</sup>C-NMR  $\delta$ : 194.7, 158.1, 137.7, 128.9, 120.3, 63.2, 62.5, 59.6, 55.0, 48.9, 48.1, 46.5, 37.1, 35.9, 31.4, 21.8, 20.9, 18.8,14.0; FABMS (M+H)<sup>+</sup>: 299.0.

*6 $\alpha$ ,7 $\alpha$ -Epoxy-1,4-androstadien-3,17-dione (4)*

*m*-Chloroperoxybenzoic acid (1.95 g, 11.33 mmol) was added to a solution of trienone **2** (1.6 g, 5.66 mmol) in CHCl<sub>3</sub> (80 mL) at room temperature. The reaction mixture was stirred at the same temperature until no starting material could be detected by TLC. The mixture was stirred with H<sub>2</sub>O and extracted with dichloromethane. The extract was dried over anhydrous MgSO<sub>4</sub>, filtered, and evaporated to obtain pale yellow precipitate. Column chromatography on silica gel, eluting with 1:5 ethyl acetate/*n*-hexane gave the pure white crystals of epoxide **4**. Yield: 1.35 g (64 %); mp: 199-202 °C; IR (cm<sup>-1</sup>): 2942, 1743, 1662, 1454; <sup>1</sup>H-NMR  $\delta$ : 1.00 (3H, s, H-18), 1.25 (3H, s, H-19), 3.50 (1H, d, *J*=2.2Hz, H-6), 3.72 (1H, d, *J*=3.8Hz, H-7), 6.25 (1H, dd, *J*=1.8Hz, 10.0Hz, H-4), 6.51 (1H, d, *J*=1.2Hz, H-2), 7.02 (1H, d, *J*=10.2Hz, H-1); <sup>13</sup>C-NMR  $\delta$ : 219.0, 185.2, 159.2, 153.1, 131.4, 128.0, 53.0, 51.8, 47.9, 46.7, 41.1, 38.7, 35.7, 35.2, 31.2, 21.5, 21.4, 20.8, 13.9; FABMS (M+H)<sup>+</sup>: 299.0.

*1,4-Androstadien-3 $\beta$ ,17 $\beta$ -diol (5)*

To a solution of compound **2** (1 g, 3.55 mmol) in absolute ethanol (100 mL), NaBH<sub>4</sub> (537 mg, 14.2 mmol) was added at room temperature. The resulting mixture was stirred overnight at same temperature, and then was concentrated by rotary evaporation to afford white solid. It was stirred with water for 30 minutes, then extracted with dichloromethane from the aqueous layer. The organic layer was washed with aqueous sodium hydrogen carbonate, water and dried with anhydrous MgSO<sub>4</sub>, filtered, and concentrated to give a residue, which was recrystallized from 1:2 ethyl acetate/*n*-hexane to afford white crystals of the title compound. Yield: 1.37 g (63 %); mp: 155-158.5 °C; IR (cm<sup>-1</sup>): 3400, 2960, 1670, 1460; <sup>1</sup>H-NMR  $\delta$ : 0.83 (3H, s, H-18), 1.01 (3H, s, H-19), 3.62-3.66 (1H, m, H-3), 4.36 (1H, m, H-17), 5.58 (1H, s, H-4), 5.60 (1H, d, *J*=9.8Hz, H-6), 5.96 (1H, dd, *J*=2.4Hz, 10.0Hz, H-7); <sup>13</sup>C-NMR  $\delta$ : 159.1, 148.3, 126.7, 123.2, 58.7, 54.5, 48.5, 47.7, 40.5, 36.2, 34.7, 30.5, 29.5, 27.8, 25.8, 22.0, 21.2, 19.0, 13.8; FABMS (M+H-H<sub>2</sub>O)<sup>+</sup>: 271.1.

*4 $\beta$ ,5 $\beta$ -epoxyandrost-6-en-3 $\beta$ ,17 $\beta$ -diol (6)*

*m*-Chloroperoxybenzoic acid (611 mg, 3.55 mmol) was added to a solution of dienol **5** (500 mg, 1.77 mmol) in CHCl<sub>3</sub> (50 mL) at room temperature and the reaction mixture was then treated in a manner similar to that described for the synthesis of compound **1**. The pure compound **6** was obtained as white crystals by column chromatography on silica gel (elution with 1:3 ethyl acetate/*n*-hexane=). Yield: 678 mg (64 %); mp: 146-149 °C; IR (cm<sup>-1</sup>): 3405, 2933, 1455; <sup>1</sup>H-NMR  $\delta$ : 0.85 (3H, s, H-18), 1.22 (3H, s, H-19), 3.57-3.80 (2H, m, H-3, H-17), 4.17 (1H, d, *J*=3.2Hz, H-4), 5.32 (1H, dd, *J*=2.2Hz, 6.4Hz, H-7), 5.64 (1H, d, *J*=2.2Hz, H-6); <sup>13</sup>C-NMR  $\delta$ : 125.3, 121.7, 69.3, 63.6, 58.2, 53.2, 47.5, 46.2, 39.9, 36.2, 35.1, 30.7, 30.0, 28.8, 27.5, 22.0, 21.1, 19.0, 14.0; FABMS (M+H)<sup>+</sup>: 305.1, (M+H-H<sub>2</sub>O)<sup>+</sup>: 287.1

*1 $\alpha$ ,2 $\alpha$ -Epoxy-1,4--androstadien-3 $\beta$ ,17 $\beta$ -diol (7)*

To a solution of compound **3** (500 mg, 1.68 mmol) in absolute ethanol (100 mL) NaBH<sub>4</sub> (237 mg, 6.27 mmol) was added at room temperature. The resulting mixture was stirred overnight at the same temperature and then was concentrated by rotary evaporation to afford a white solid which was stirred with water and *d*-HCl solution for 30 minutes, then extracted with dichloromethane from the aqueous layer. The organic layer was washed with water and dried with MgSO<sub>4</sub>, filtered, and concentrated to give a white solid, which was purified by column chromatography (1:3 ethyl acetate/ *n*-hexane). Yield: 706 mg (69 %); mp : 139-142 °C; IR (KBr) cm<sup>-1</sup> : 3407, 2931, 2859, 1672, 1453; <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.81 (3H, s, H-18), 1.00 (3H, s, H-19), 3.33 (1H, m, *J*=9.6Hz, H-1), 3.54 (1H, t, H-2), 3.63-3.75 (1H, m, H-3), 4.53 (1H, br s, H-17), 5.21 (1H, s, H-4), 5.60 (1H, d, *J*=6.2Hz, H-6), 5.95 (1H, d, *J*=9.6Hz, H-7); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 140.0, 130.7, 128.1, 121.1, 81.2, 65.7, 58.9, 56.0, 48.8, 45.8, 43.5, 36.9, 36.6, 36.4, 30.2, 23.6, 21.0, 17.4, 11.2; FABMS (M+H)<sup>+</sup>: 303.1.

*2-Ethoxy-1,4,6-androstatrien-3,17-dione (8)*

To a solution of **3** (500 mg, 1.68 mmol) in absolute ethanol (50 mL) lithium metal (400 mg) was added slowly and the resulting mixture was vigorously stirred at the room temperature for 18 hours. The reaction mixture was cooled down to 0°C and water was slowly added with stirring until a clear solution was obtained. The mixture was evaporated to remove the ethanol, and then the aqueous layer was extracted several times with ethyl acetate. The combined organic layer was washed with H<sub>2</sub>O and dried over anhydrous MgSO<sub>4</sub>, filtered and evaporated to give a crude oil, which was purified by column chromatography on silica gel (1:3 ethyl acetate/*n*-hexane). Yield: 372 mg (73 %); mp :175-178 °C; IR (KBr) cm<sup>-1</sup>: 2930, 2870, 1735, 1649, 1456, 1191; <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 1.01 (3H, s, H-18), 1.24 (3H, s, H-19), 1.44 (3H, t, OCH<sub>2</sub>CH<sub>3</sub>), 3.86 (2H, q, OCH<sub>2</sub>CH<sub>3</sub>), 5.93 (1H, s, H-4), 6.11 (2H, d, *J*=12.4Hz, H-6, H-1), 6.33 (1H, dd, *J*=1.2Hz, *J*=9.8Hz, H-7); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 219.1, 181.2, 161.8, 150.3, 136.1, 128.1, 124.1, 120.3, 63.4, 49.6, 49.0, 48.0, 41.3, 37.7, 35.8, 31.4, 29.9, 22.2, 21.8, 21.5, 14.5, 14.0; FABMS (M+H)<sup>+</sup>: 327.1.

*6 $\alpha$ ,7 $\alpha$ -Epoxy-androst-4-en-3 $\beta$ ,17 $\beta$ -diol (9)*

To a solution of **4** (500 mg, 1.68 mmol) in absolute ethanol (100 mL) NaBH<sub>4</sub> (177 mg, 4.70 mmol) was added and the mixture stirred at room temperature until the starting material had disappeared in a TLC test. The reaction mixture was evaporated to a dry solid and H<sub>2</sub>O was added to the residue with stirring. The aqueous layer was extracted with ethyl acetate, and the organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered, concentrated to give a crude precipitate. The purified product was obtained by column chromatography on silica gel (1:3 ethyl acetate/*n*-hexane). Yield: 390 mg (76 %); mp: 138-141 °C; IR (KBr) cm<sup>-1</sup>: 3401, 2935, 1452; <sup>1</sup>H-NMR (CDCl<sub>3</sub>)  $\delta$ : 0.78 (3H, s, H-18), 1.16 (3H, s, H-19), 3.70 (1H, t, H-7), 3.83 (1H, s, H-6), 4.19-4.28 (1H, m, H-3), 5.44 (1H, s, H-4); <sup>13</sup>C-NMR (CDCl<sub>3</sub>)  $\delta$ : 151.3, 145.4, 68.9, 66.3, 59.2, 53.3, 46.7, 45.4, 43.1, 42.2, 39.5, 37.8, 34.9, 30.4, 22.2, 21.3, 19.4, 14.0; FABMS (M+H)<sup>+</sup> : 305.1.

*7β-Ethoxy-6α-hydroxy-1,4-androstadien-3,17-dione (10)*

To a solution of **4** (500 mg, 1.68 mmol) in absolute ethanol (50 mL) lithium metal (300 mg) was added slowly and the mixture vigorously stirred at room temperature until the starting material had disappeared in a TLC test. The workup was as described in the preparation of compound **8**. The purified product was obtained as white crystals by column chromatography on silica gel (1:3 ethyl acetate/*n*-hexane). Yield: 450 mg (78 %); mp: 210-211 °C; IR (KBr)  $\text{cm}^{-1}$ : 3407, 2922, 1739, 1657, 1453, 1105;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 0.96 (3H, d,  $J=5.4\text{Hz}$ , H-18), 1.19 (3H, t,  $\text{OCH}_2\text{CH}_3$ ), 1.76 (3H, s, H-19), 3.35-3.54 (2H, m,  $\text{OCH}_2\text{CH}_3$ ), 3.91 (1H, d,  $J=13.0\text{Hz}$ , H-6), 4.05 (1H, m, H-7), 6.19 (1H, d,  $J=1.8\text{Hz}$ , H-4), 6.24 (1H, s, H-2), 7.05 (1H, d,  $J=9.4\text{Hz}$ , H-1);  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 220.5, 185.8, 161.7, 157.3, 130.6, 126.8, 85.2, 71.3, 64.6, 47.6, 45.2, 43.7, 43.5, 35.8, 35.3, 31.1, 21.7, 21.6, 19.3, 15.2, 13.8; FABMS ( $\text{M}+\text{H}$ ) $^+$ : 345.1, ( $\text{M}+\text{H}-\text{C}_2\text{H}_5\text{OH}$ ) $^+$ : 299.1, ( $\text{M}+\text{H}-\text{C}_2\text{H}_5\text{OH}-\text{H}_2\text{O}$ ) $^+$ : 281.1.

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*Sample Availability:* Samples of compounds **1**, **2**, **3**, **4** and **5** are available from MDPI. For other samples contact the authors.