Insights into the Synthesis of Steroidal *A*-Ring Olefins

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The classical synthesis, followed by purification of the steroidal *A*-ring Δ^1-olefin, 5α-androst-1-en-17-one (**5**), from the Δ^1-3-keto enone, (5α,17β)-3-oxo-5-androst-1-en-17-yl acetate (**1**), through a strategy involving the reaction of Δ^1-3-hydroxy allylic alcohol, 3β-hydroxy-5α-androst-1-en-17β-yl acetate (**2**), with SOCl$_2$, was revisited in order to prepare and biologically evaluate **5** as aromatase inhibitor for breast cancer treatment. Surprisingly, the followed strategy also afforded the isomeric Δ^2-olefin **6** as a by-product, which could only be detected on the basis of NMR analysis. Optimization of the purification and detection procedures allowed us to reach 96% purity required for biological assays of compound **5**. The same synthetic strategy was applied, using the Δ^4-3-keto enone, 3-oxoandrost-4-en-17β-yl acetate (**8**), as starting material, to prepare the potent aromatase inhibitor Δ^4-olefin, androst-4-en-17-one (**15**). Unexpectedly, a different aromatase inhibitor, the $\Delta^{3,5}$-diene, androst-3,5-dien-17-one (**12**), was formed. To overcome this drawback, another strategy was developed for the preparation of **15** from **8**. The data now presented show the unequal reactivity of the two steroidal *A*-ring Δ^1- and Δ^4-3-hydroxy allylic alcohol intermediates, 3β-hydroxy-5α-androst-1-en-17β-yl acetate (**2**) and 3β-hydroxyandrost-4-en-17β-yl acetate (**9**), towards SOCl$_2$, and provides a new strategy for the preparation of the aromatase inhibitor **12**. Additionally, a new pathway to prepare compound **15** was achieved, which avoids the formation of undesirable by-products.

Introduction. – Among several biological activities, steroidal *A*-ring olefins, with a C(17)=O group, particularly Δ^3- and Δ^4-olefins (*Fig.*) [1][2], were shown to be interesting aromatase inhibitors (AIs). AIs block the biosynthesis of estrogens and offer a therapeutic alternative for the treatment of estrogen-dependent cancers, namely breast cancer [3–5]. This has been attributed to two different factors: the planarity conferred by the C=C bonds, which allows better fitting the enzyme receptor core, and the H-bonding capacity of the C(17)=O O-atom to a receptor residue [1][6][7].

As part of a project on new structure–activity relationships (SAR) of steroidal AIs [1][6][7], we are now interested in synthesizing Δ^1- and Δ^4-olefins **5** and **15**, respectively (*Schemes 1*, *2*, and *3*). Concerning **5**, there are very few references describing its preparation, and the most complete one is a 50 years old reporting the
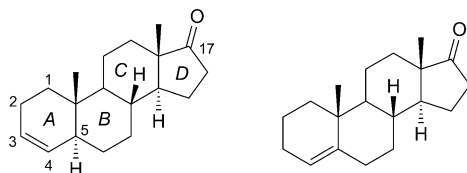
Figure *Steroidal Δ^3- and Δ^4-olefin aromatase inhibitors*

synthesis using the Δ^1-3-keto enone **1** as starting material, and the allylic alcohol **2** as intermediate [8]. In a recent work, we revisited this synthesis [7] and, in the present work, we further explored new insights into the referred strategy. In this study, along with the previously reported Δ^1-olefin **5**, the Δ^2-isomer **6** was identified as a by-product (*Scheme 1*).

Scheme 1. *Synthesis of (5α)-Androst-1-en-17-one* (**5**) *from (5α,17β)-3-Oxoandrost-1-en-17-yl Acetate* (**1**)
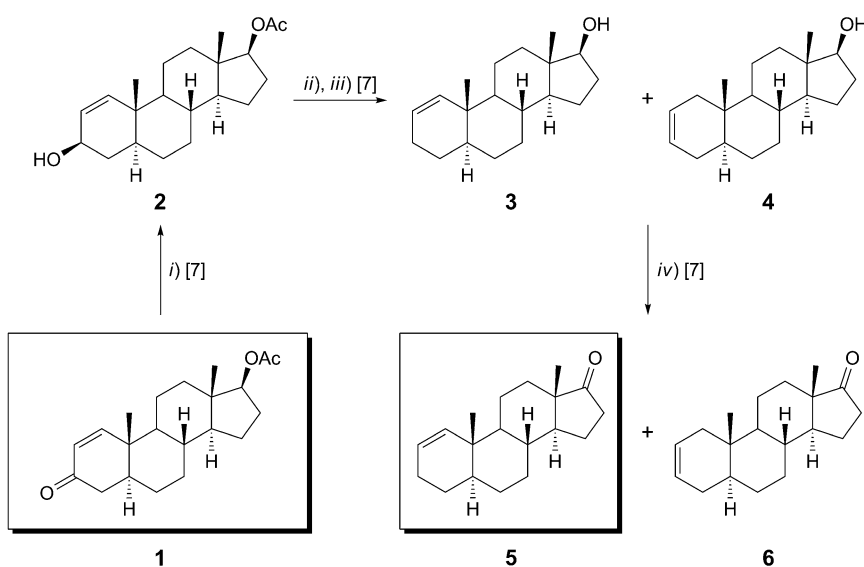
i) Li(*t*-BuO)$_3$AlH, anh. THF, reflux, 3 h; 94%. *ii*) SOCl$_2$, benzene, 5 – 8°, 1 – 2 h. *iii*) LiAlH$_4$, Et$_2$O, reflux, 11 h. *iv*) CrO$_2$. H$_2$SO$_4$. acetone. 0°: 73% of **5/6**.

Furthermore, to achieve an alternative synthetic strategy for the preparation of the Δ^4-olefin **15** [2][7], that avoids the formation of the Δ^4-17β-hydroxylated derivative as well as the Δ^3-olefin as by-products, we applied the same methodology using the Δ^4-3-keto enone **8** as starting material. Unexpectedly, in this case, instead of the desired **15**, another AI, the $\Delta^{3,5}$-diene **12** [9–16], was obtained as the only product (*Scheme 2*). To overcome this problem, another synthetic strategy, using also **8** as starting material, was developed for the preparation of **15** (*Scheme 3*).

Scheme 2. *Formation of Androsta-3,5-dien-17-one* (**12**) *from Testosterone* (**7**)
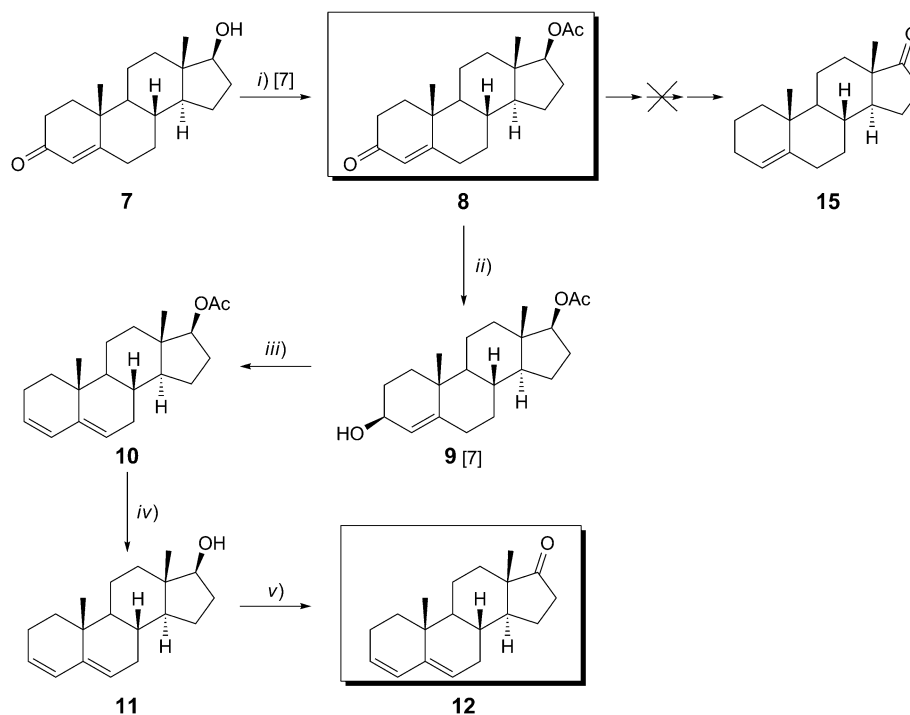
i) Ac$_2$O, dry pyridine, r.t., 21 h 25 min; 84%. *ii*) Li(*t*-BuO)$_3$AlH, anh. THF, reflux, 3 h 30 min. *iii*) SOCl$_2$, benzene, 5 – 8°, 5 h 30 min; 56%. *iv*) LiAlH$_4$, Et$_2$O, reflux, 8 h; 91%. *v*) CrO$_3$, pyridine, r.t., 19 h; 38%.

Scheme 3. *Preparation of Androst-4-en-17-one* (**15**) *from (17β)-3-Oxoandrost-4-en-17-yl Acetate* (**8**)
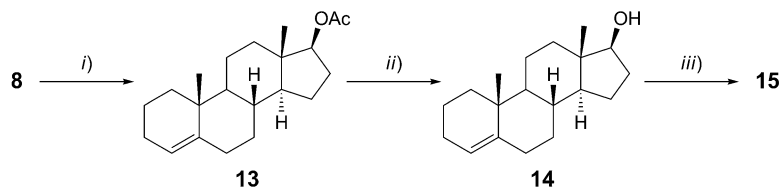
i) NaBH$_4$, CF$_3$COOH, AcOH, MeCN, CH$_2$Cl$_2$, r.t., 3 h 30 min; 99%. *ii*) KOH, H$_2$O, dioxane, r.t., 2 – 3 d; 99%. *iii*) CrO$_3$, H$_2$SO$_4$, H$_2$O, acetone, 0°, 5 min; 75%.

^{1}H-NMR Spectroscopy turned out to be the most adequate technique for the detection of the Δ^2-olefin **6**, as well as of its precursors, and the 2D-COSY experiment allowed us to unequivocally identify the precursor **10** of the $\Delta^{3,5}$-diene **12**.

Results and Discussion. – The Δ^1-olefin **5** was prepared as described in [7][8] (*Scheme 1*). Briefly, reduction of enone **1** gave allylic alcohol **2**, which afforded an

untractable crude (TLC, NMR, and LC/MS control) after treatment with $SOCl_2$. Reaction of this crude with $LiAlH_4$ and conventional workup furnished a mixture (one TLC spot) of the isomers **3** and **4** in similar amounts (NMR analysis). To isolate the desired compound **3**, the isomeric mixture was subjected to column chromatography using neutral alumina and hexane/CH_2Cl_2. However, the isolated fractions, subjected to ^{1}H-NMR analysis, always turned out to be mixtures **3/4** with variable compositions (from 1:3 to 9:1). Given the impossibility of obtaining the pure compound **3**, the next oxidative step was performed with the the 9:1 mixture of **3/4** using *Jones* reagent, which allowed, after a laborious column chromatography purification process of the obtained crude, isolation of the Δ^1-olefin **5** in the required purity for further biological studies (96% by LC/MS control) (*Scheme 1*).

Although the formation of the Δ^2-isomer **6** has not been reported before, our results revealed that migration of the C=C bond from the C(1) to the more stable C(2) occurred to a considerable extent. In fact, the Δ^1- and Δ^2-isomers **5** and **6**, respectively, possessed similar physico-chemical properties, exhibiting the same R_f values with several chromatography solvents and similar crystallization conditions. Accordingly, it is very difficult to distinguish the two isomers. Facing these difficulties, the complete diagnosis of the C=C bond position in this kind of compounds could only be achieved by ^{1}H-NMR spectroscopy. The Δ^1-isomer **5** presents two signals at 5.52 ppm (H–C(2)) and 5.83 ppm (H–C(1)) for the olefinic H-atoms, whereas the Δ^2-isomer **6** displays only one common typical *multiplet* around 5.9 ppm for both olefinic H-atoms, allowing the accurate identification of both compounds **5** and **6**. Therefore, the NMR analysis appears to be the most adequate technique to disclose the nature of the compounds isolated after column chromatography.

To obtain the Δ^4-olefin **15**, the above-mentioned synthetic strategy was further applied to the Δ^4-3-keto enone **8** (prepared from **7** [7]) as starting material (*Scheme 2*). In this case, instead of **15** we obtained the $\Delta^{3,5}$-diene **12**. Treatment of **8** with Li(*t*-BuO)$_3$AlH, under the conditions previously described, led to Δ^4-3β-hydroxy allylic alcohol **9** with traces of its 3α-isomer. Treatment of this compound with $SOCl_2$ in benzene, contrarily to what was expected, gave the $\Delta^{3,5}$-diene precursor **10**. Then, **10** was treated with $LiAlH_4$ to afford the $\Delta^{3,5}$-diene derivative **11**, which, after oxidation with CrO_3 in pyridine [10], led to **12**. This approach opens a new way to prepare compound **12**, which is also an AI [9].

As the ^{1}H-NMR did not allow unequivocal elucidation of the position of the diene C=C bonds in the *A/B*-ring system, a 2D-COSY analysis of **10** was performed. The most relevant signals in the COSY spectrum were those of the three olefinic H-atoms at 5.9, 5.6, and 5.4 ppm, of the H_α–C(17) at 4.5 ppm, and of the Me(18) and Me(19) groups at 0.82 and 0.95 ppm, respectively. The H_α–C(17) correlates with Me(18) (^3J) which resonates at 0.82 ppm; therefore, the resonance at 0.95 ppm is due to Me(19). Focusing on the three olefinic H-atoms, of the $\Delta^{3,5}$-diene isomer **10**, the H–C(4) will correlate strongly with the H–C(3) and weakly with the H–C(6). In fact, we observed that an olefinic H-atom absorbing at 5.9 ppm strongly correlates with an olefinic H-atom at 5.6 ppm (^3J); the same olefinic H-atom (at 5.9 ppm) has a very weak correlation with an olefinic H-atom absorbing at 5.4 ppm (^4J), and there is no observable correlation between the olefinic H-atom signals at 5.6 ppm and 5.4 ppm (^5J). Therefore, the signal

at 5.6 ppm corresponds to H–C(3), the signal at 5.9 ppm to H–C(4), and the signal at 5.4 ppm to H–C(6), which is in agreement with the structure of compound **10**.

To obtain the Δ^4-olefin **15**, an alternative synthetic strategy was developed from the same starting material **8** (*Scheme 3*). In this case, reaction of **8** with a mixture of $NaBH_4$ in CF_3COOH (TFA), glacial AcOH, and MeCN was performed in a controlled environment [17], to yield compound **13** in 99% yield. This compound was then submitted to a base-catalyzed hydrolysis to give quantitatively compound **14**, which was then subjected to *Jones* oxidation to furnish the desired **15** in 75% yield. The above-mentioned strategy avoided the formation of the Δ^4-17β-hydroxylated derivative as well as the Δ^3-olefin isomer as by-products.

In summary, the preparation of Δ^1-olefin **5** from the Δ^1-3-keto enone **1** according to the revisited protocol takes place with the formation of the Δ^2-isomer **6** as a by-product, which can only be detected by NMR analysis. However, an adequate sequential purification procedure by column chromatography, assisted by ^{1}H-NMR control of the separated fractions, allows the isolation of the AI **5** in 96% purity, which is an adequate purity for compounds to proceed to biochemical assays.

The potent AI Δ^4-olefin **15** cannot be obtained from the Δ^4-3-keto enone **8** by the reported strategy. Instead, another important aromatase inhibitor, the $\Delta^{3,5}$-diene **12**, is formed. This achievement offers a new synthetic way to compound **12**. From these data, presented for the first time, to the best of our knowledge, it is possible to establish the unequal reactivity of steroidal Δ^1- and Δ^4-3-hydroxy allylic alcohol intermediates **2** and **9**, respectively, towards the elimination reactions by treatment with $SOCl_2$ (*Schemes 1* and *2*). Indeed, while the Δ^1-isomer **2** renders the mixture of olefins **3/4** by the expected elimination process, followed by isomerization of the C=C bond, the Δ^4-isomer **9** embarks in an additional elimination of a H–C(6) H-atom, followed by the migration of the C=C bond with the formation of the $\Delta^{3,5}$-diene derivative **10**.

The preparation of the AI **15** can be achieved by a new method, using also the Δ^4-3-keto enone **8** as starting material, by a sequence involving the reduction at C(3), followed by the hydrolysis of the AcO group at C(17) of **13**, and subsequent oxidation of the resulting OH group, which precludes the formation of undesirable by-products.

Experimental Part

General. Testosterone (**7**) was purchased from *Pharmacia & Upjohn Company*, Kalamazoo, Michigan (USA), and *(5α,17β)-3-oxoandrost-1-en-17-yl acetate* (**1**) and *(5α)-androst-2-en-17-one* (**6**) were purchased from *Steraloids, Inc.* (Newport RI, USA). Other reagents and solvents were used as obtained from the suppliers without further purification, with the exception of CH_2Cl_2, which was dried through reflux and distilled from CaH_2 [18]. M.p.: *Reichert Thermopan* hot-block apparatus; uncorrected. IR Spectra: *Jasco 420FT/IR* spectrometer. ^{1}H- and ^{13}C-NMR spectra: *Varian* 600 MHz spectrometer, using a 3-mm broadband NMR probe; chemical shifts in ppm downfield from TMS used as an internal standard; all *J* values in Hz. ESI- and LC-MS: mass spectrometer *QIT-MS Thermo Finningan*, model *LCQ Advantage MAX*, coupled to a liquid chromatograph of high performance *Thermo Finningan* (column: *C18*; reversed phase (RP); H_2O/MeCN 40:60).

(3β,5α,17β)-3-Hydroxyandrost-1-en-17-yl Acetate (**2**). See [7].

(5α,17β)-Androst-1-en-17-ol (**3**) *and (5α,17β)-Androst-2-en-17-ol* (**4**). Prepared as described in [7]. ^{1}H-NMR Analysis of the obtained crude product revealed a mixture **3/4** 1:1. The crude product was purified by column chromatography (CC) (neutral Al_2O_3; hexane/CH_2Cl_2 80:20) to give a white solid (one TLC spot). ^{1}H-NMR Analysis of this solid indicated an enriched mixture of **3** (90%) with **4** (10%).

Data of **3**. ^{1}H-NMR ((D$_6$)DMSO; selected signals): see [7].

Data of **4**. ^{1}H-NMR ((D$_6$)DMSO; selected signals): 0.63 (*s*, Me(18)); 0.71 (*s*, Me(19)); 3.42 (*ddd*, $J(17\alpha,16\alpha) = 9.0, J(17\alpha,16\beta) = 9.0, J(17\alpha,OH) = 5.0$, H$_\alpha$–C(17)); 4.42 (*d*, $J(OH,17\alpha) = 5.0$, HO$_\beta$–C(17)); 5.53–5.59 (*m*, H–C(2), H–C(3)).

(5α)-Androst-1-en-17-one (**5**) *and (5α)-Androst-2-en-17-one* (**6**). Prepared as described in [7]. The obtained crude product was crystallized from MeOH/H$_2$O to give white crystals (one TLC spot). ^{1}H-NMR Analysis of these crystals revealed the presence of a mixture **5** (83%)/**6** (17%). Purification by CC (hexane/Et$_2$O), followed by consecutive recrystallizations from MeOH, gave **5** in 96% purity (LC/MS analysis) with a small amount of isomer **6**.

Data of **5**. ^{1}H-NMR (CDCl$_3$): see [7].

Data of **6**. ^{1}H-NMR (CDCl$_3$; selected signals): 0.78 (*s*, Me(19)); 0.87 (*s*, Me(18)); 5.55–5.62 (*m*, H–C(2), H–C(3)).

(17β)-3-Oxoandrost-4-en-17-yl Acetate (**8**). To a soln. of **7** (2.0 g, 6.93 mmol) in dry pyridine (48 ml), Ac$_2$O (7.9 ml, 83.9 mmol) was added, and the mixture was stirred for 21 h 25 min at r.t. (20°), until all the starting material was consumed (TLC control). Then, CH$_2$Cl$_2$ (250 ml) was added, and the org. layer was washed with 10% NaHCO$_3$ (3 × 150 ml), 10% HCl (3 × 150 ml), and H$_2$O (3 × 150 ml), dried (anh. MgSO$_4$), filtered, and concentrated to dryness. Crystallization of the obtained residue from AcOEt gave pure **8** (1.92 g, 84%). M.p.: 141–142° ([19]: 139–140°). IR (CHCl$_3$): 3018 (=CH), 1736 (C=O), 1675 (C=C), 1248 (C–O). ^{1}H-NMR (CDCl$_3$; selected signals): 0.82 (*s*, Me(18)); 1.18 (*s*, Me(19)); 2.03 (*s*, MeCOO); 4.58 (*dd*, $J(17\alpha,16\alpha) = 9.0, J(17\alpha,16\beta) = 8.0$, H$_\alpha$–C(17)); 5.71 (*s*, H–C(4)). ^{13}C-NMR (150 MHz, CDCl$_3$): 12.0 (C(18)); 17.4 (C(19)); 20.5; 21.1; 23.4; 27.4; 31.4; 32.7; 33.9; 35.4; 35.7; 36.6; 38.6; 42.4; 50.2; 53.7; 82.4 (C(17)); 123.9 (C(4)); 170.9 (C(5)); 171.1 (OC=O); 199.4 (C(3)).

(3β,17β)-3-Hydroxyandrost-4-en-17-yl Acetate (**9**). To a soln. of **8** (2.0 g, 6.05 mmol) in anh. THF (75 ml) under N$_2$, Li(*t*-BuO)$_3$AlH (2.0 g, 7.86 mmol) was added, and the mixture was heated under reflux for 2 h, then an excess of Li(*t*-BuO)$_3$AlH (500.1 mg, 1.97 mmol) was added. The reaction proceeded until complete transformation of the starting material (3½ h). After removal of the solvent under vacuum, H$_2$O (200 ml) was added, and the aq. layer was extracted with CH$_2$Cl$_2$ (3 × 200 ml). The org. layer was then washed with H$_2$O (200 ml), dried (anh. Na$_2$SO$_4$), filtered, and concentrated to dryness to give 1.97 g of a crude material mainly composed of **9**. ^{1}H-NMR ((D$_6$)DMSO; selected signals): 0.76 (*s*, Me(18)); 0.99 (*s*, Me(19)); 1.98 (*s*, MeCOO); 3.88–3.92 (*m*, H$_\alpha$–C(3)); 4.49 (*dd*, $J(17\alpha,16\alpha) = 9.0, J(17\alpha,16\beta) = 8.0$, H$_\alpha$–C(17)); 4.54 (*d*, $J(OH,3\alpha) = 5.5$, HO$_\beta$–C(3)); 5.19 (br. *s*, H–C(4)). ^{13}C-NMR (150 MHz, (D$_6$)DMSO): 11.8 (C(18)); 18.4 (C(19)); 20.0; 20.8; 22.9; 27.0; 28.9; 31.4; 32.2; 35.1; 35.2; 36.2; 36.7; 41.9; 49.7; 53.8; 65.8 (C(3)); 81.8 (C(17)); 125.5 (C(4)); 143.9 (C(5)); 170.2 (OC=O).

(17β)-Androsta-3,5-dien-17-yl Acetate (**10**). A soln. of crude **9** (500.4 mg) in benzene (10 ml) was kept at 5–8° under N$_2$, treated with SOCl$_2$ (0.5 ml, 6.72 mmol), and the mixture was stirred for 2 h 25 min. Then, an excess of SOCl$_2$ (0.1 ml, 1.38 mmol) was added. The reaction did not proceed to the complete transformation of the starting material (5½ h). Benzene was evaporated under vacuum at r.t. giving an oily residue, to which solid NaHCO$_3$ (500 mg) was added, followed by 10% NaHCO$_3$ (100 ml). The aq. layer was extracted with CH$_2$Cl$_2$ (3 × 100 ml), and the resulting org. layer was washed with H$_2$O (3 × 100 ml), dried (anh. MgSO$_4$), filtered, and concentrated to dryness to give a white solid residue. This residue was purified by CC (silica gel *60*; PE (60–80°)/AcOEt) to afford 263.4 mg of **10** as a white crystalline residue in an overall yield of 56% from **8**. Recrystallization from PE 60–80°/AcOEt. M.p. 116–119°. IR (CHCl$_3$): 3018 (=CH), 1736 (C=O ester), 1648 (C=C), 1244 (C–O). ^{1}H-NMR (CDCl$_3$; selected signals): 0.83 (*s*, Me(18)); 0.96 (*s*, Me(19)); 2.04 (*s*, MeCOO); 4.61 (*dd*, $J(17\alpha,16\alpha) = 9.0, J(17\alpha,16\beta) = 8.0$, H$_\alpha$–C(17)); 5.37–5.38 (*m*, H–C(6)); 5.58–5.60 (*m*, H–C(3)); 5.91–5.93 (*m*, H–C(4)). ^{13}C-NMR (150 MHz, CDCl$_3$): 12.0 (C(18)); 18.8 (C(19)); 20.4; 21.2; 22.9; 23.5; 27.5; 31.3; 31.6; 33.7; 35.2; 36.8; 42.5; 48.3; 51.2; 82.8 (C(17)); 122.6 (C(6)); 125.1 (C(3)); 128.8 (C(4)); 141.5 (C(5)); 171.2 (OC=O). ESI-MS: 315.1 (76, $[M + H]^+$).

(17β)-Androsta-3,5-dien-17-ol (**11**). To a soln. of **10** (100.8 mg, 0.32 mmol) in Et$_2$O (15 ml), LiAlH$_4$ (76.2 mg, 2.01 mmol) was added cautiously under N$_2$, and the mixture was heated under reflux for 8 h. Then, a sat. soln. of sodium potassium tartrate (150 ml) was added, and the mixture was extracted with Et$_2$O (4 × 100 ml). The org. layer was then washed with H$_2$O (4 × 100 ml), dried (anh. MgSO$_4$), filtered, and concentrated to dryness to give pure **11** (79.4 mg, 91%). White solid. Recrystallization from AcOEt/

hexane. M.p. 140–142°. IR (CHCl$_3$): 3302 (OH), 3021 (=CH), 1646 (C=C), 1054 (C–O). ^{1}H-NMR ((D$_6$)DMSO; selected signals): 0.67 (*s*, Me(18)); 0.89 (*s*, Me(19)); 3.45 (*ddd*, *J*(17α,OH) = 5.0, *J*(17α,16α) = 9.0, *J*(17α,16β) = 9.0, H$_a$–C(17)); 4.45 (*d*, *J*(OH,17α) = 5.0, HO$_β$–C(17)); 5.33–5.35 (*m*, H–C(6)); 5.56–5.58 (*m*, H–C(3)); 5.87–5.89 (*m*, H–C(4)). ^{13}C-NMR (150 MHz, (D$_6$)DMSO): 11.2 (C(18)); 18.5 (C(9)); 20.1; 22.4; 22.9; 29.8; 30.8; 31.4; 33.2; 34.6; 36.3; 42.3; 48.0; 50.9; 79.9 (C(17)); 122.6 (C(6)); 124.5 (C(3)); 128.8 (C(4)); 140.8 (C(5)). ESI-MS: 271.2 (100, [*M* – H]$^+$).

Androsta-3,5-dien-17-one (**12**). To a soln. of **11** (62.0 mg, 0.23 mmol) in pyridine (3 ml), a pyridine soln. (2.3 ml) of CrO$_3$ (98.0 mg, 0.98 mmol) was added at 0°. The mixture was stirred at r.t. for 19 h until total transformation of the starting material (TLC control). The mixture was then diluted with Et$_2$O (150 ml) and poured into H$_2$O (50 ml). The org. phase was washed with brine (6 × 150 ml) and H$_2$O (3 × 200 ml), dried (anh. MgSO$_4$), filtered, and concentrated to dryness giving a yellow residue which was purified by CC (neutral Al$_2$O$_3$; PE (40–60°)) to furnish pure **12** (9.0 mg, 38%). M.p. 81–83° ([20]: 80–82°). IR (CHCl$_3$): 3018 (=CH), 1739 (C=O), 1652 (C=C). ^{1}H-NMR (CDCl$_3$; selected signals): 0.91 (*s*, Me(19)); 0.97 (*s*, Me(18)); 5.39–5.41 (*m*, H–C(6)); 5.59–5.62 (*m*, H–C(3)); 5.92–5.94 (*m*, H–C(4)). ^{13}C-NMR (150 MHz, CDCl$_3$): 13.7 (C(19)); 18.8 (C(18)); 20.2; 21.8; 22.9; 30.6; 31.3; 31.4; 33.7; 35.3; 35.8; 47.7; 48.5; 51.9; 122.1 (C(6)); 125.3 (C(3)); 128.7 (C(4)); 141.6 (C(5)); 221.0 (C(17)). ESI-MS: 269.1 (99, [*M* – H]$^+$).

(17β)-Androst-4-en-17-yl Acetate (**13**). NaBH$_4$ (566.2 mg, 14.97 mmol) was added in small portions under stirring and cooling to a previously cooled mixture of CF$_3$COOH (3.5 ml), glacial AcOH (3.5 ml), and MeCN (3.5 ml). A soln. of **8** (1.0 g, 3.03 mmol) in dry CH$_2$Cl$_2$ (18 ml) was added to the mixture. Then, the mixture was let to react at r.t. under magnetic stirring and N$_2$, until consumption of all the starting material (3½ h; TLC control). The mixture was then neutralized with a soln. of 10% NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (4 × 100 ml). The org. layer was washed with H$_2$O (4 × 100 ml), dried (anh. MgSO$_4$), filtered, and concentrated to dryness to give **13** (945.0 mg, 99%). White solid. Recrystallization from CH$_2$Cl$_2$/hexane/EtOH. M.p. 95–99°. IR (CHCl$_3$): 3024 (=CH), 1737 (C=O), 1663 (C=C), 1043 (C–O). ^{1}H-NMR (CDCl$_3$; selected signals): 0.80 (*s*, Me(18)); 1.01 (*s*, Me(19)); 2.03 (*s*, MeCOO); 4.58 (*dd*, *J*(17α,16α) = 9, *J*(17α,16β) = 8, H$_a$–C(17)); 5.29–5.30 (*m*, H–C(4)). ^{13}C-NMR (150 MHz, CDCl$_3$): 12.0 (C(18)); 19.2 (C(19)); 19.4; 20.9; 21.2; 23.5; 25.7; 32.4; 32.8; 35.8; 36.9; 37.1; 37.8; 42.5; 50.5; 54.4; 82.8 (C(17)); 119.3 (C(4)); 144.7 (C(5)); 171.2 (OC=O).

(17β)-Androst-4-en-17-ol (**14**). Compound **13** (945.0 mg, 2.99 mmol) was added to a mixture dioxane/H$_2$O 85:15 (90 ml) with 2% NaOH (18 ml), at r.t. The mixture was let to react until total transformation of the starting material (52 h; TLC control) and then neutralized with an aq. soln. of 5% HCl. The dioxane was evaporated under vacuum leading to a white solid residue that was diluted with H$_2$O (200 ml) and extracted with AcOEt (4 × 100 ml). The org. layer was then washed with H$_2$O (4 × 100 ml), dried (anh. MgSO$_4$), filtered, and concentrated to dryness to afford **14** (819.0 mg, 99%). White solid. Recrystallization from hexane/AcOEt. M.p. 143–146°. IR (CHCl$_3$): 3278 (OH), 2959 (=CH), 1651 (C=C). ^{1}H-NMR ((D$_6$)DMSO): 0.65 (*s*, Me(18)); 0.97 (*s*, Me(19)); 3.43 (*ddd*, *J*(17α,16α) = 9.0, *J*(17α,16β) = 9.0, *J*(17α,OH) = 5.0, H$_a$–C(17)); 4.43 (*d*, *J*(OH,17α) = 5.0, HO$_β$–C(17)); 5.23–5.25 (*m*, H–C(4)). ^{13}C-NMR (150 MHz, (D$_6$)DMSO): 11.2 (C(18)); 18.8 (C(19)); 19.1; 20.6; 23.0; 25.1; 29.8; 31.9; 32.5; 35.5; 36.4; 36.5; 37.2; 42.4; 50.3; 54.1; 79.9 (C(17)); 118.7 (C(4)); 144.2 (C(5)).

Androst-4-en-17-one (**15**). *Jones* reagent (2.7 ml) was added dropwise to a soln. of **14** (839.8 mg, 3.06 mmol) in acetone/dioxane 60:10 (190 ml), at 0° under magnetic stirring, until a persistent brown coloration was obtained. Then, the excess of the oxidant was destroyed with the addition of ^{i}PrOH until the soln. turned greenish. The dioxane and acetone were evaporated under vacuum. To the remaining residue, H$_2$O (200 ml) was added, and the aq. phase was extracted with AcOEt (4 × 100 ml). The org. layer was then washed with 10% NaHCO$_3$ (3 × 100 ml) and H$_2$O (3 × 100 ml), dried (anh. MgSO$_4$), filtered, and concentrated to dryness to give a white solid residue (129.3 mg) after the addition of some drops of Et$_2$O. This residue was then purified by CC (SiO$_2$; hexane/AcOEt 97:03) to afford pure **15** (624.2 mg, 75%). White crystalline solid. Recrystallization from hexane/AcOEt. M.p. 74–76°. IR (CHCl$_3$): 3018 (=CH), 1738 (C=O), 1657 (C=C). ^{1}H-NMR (CDCl$_3$; selected signals): 0.88 (*s*, Me(18)); 1.03 (*s*, Me(19)); 5.31–5.33 (*m*, H–C(4)). ^{13}C-NMR (150 MHz, CDCl$_3$): 13.7 (C(18)); 19.2 (C(19)); 19.4; 20.6; 21.8; 25.7; 31.5; 32.1; 32.3; 35.5; 35.8; 37.1; 37.8; 47.7; 51.2; 54.5; 119.6 (C(4)); 144.3 (C(5)); 221.3 (C(17)). ESI-MS: 271.0 ([*M* – H]$^+$, 50%).

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