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First synthesis of a steroid containing an unstable 19-nor-androsta-1,5-dien-3-one system

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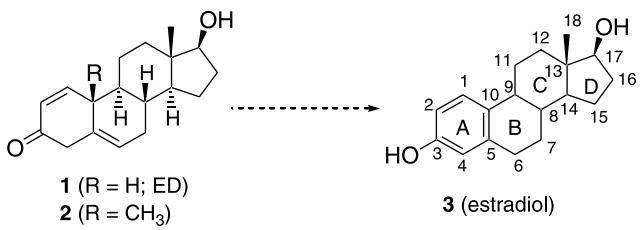
Abstract—Mechanisms involved in the maintenance of human pregnancy and initiation of labour are poorly defined. A novel steroid hormone named estradienolone (ED), and having an unusual 19-nor-androsta-1,5-dien-3-one system, was previously reported. However, ED is scarcely available from urine, placenta and blood of pregnant women. For this reason, we have synthesized ED in order to verify its proposed structure. Although a 1,5-dien-3-one system had already been described for a C19-steroid (androstane) nucleus (no possible aromatization), the synthesis of the 19-nor-analogue is a major challenge because this system is very sensitive to aromatization. We now describe the successful construction and characterization of this unstable system. Starting from nortestosterone, the synthesis of 17β-hydroxy-19-nor-androsta-1,5-dien-3-one (**1**) is based on a protection of the 5,6-double bond, the introduction of the second 1,2-double bond, the careful recovery of the *exo* double bond and a final regioselective oxidation or reduction.

1. Introduction

Mechanisms involved in the maintenance of human pregnancy and initiation of labour are poorly defined. Philip's group isolated a novel steroid hormone, namely estradienolone (ED), which may have the potential to maintain pregnancy.[1] Since the levels of ED in plasma, placenta and urine are high during pregnancy, but markedly decrease both in the placenta and blood at the moment of term or premature labour, this decrease may provide the signal to initiate parturition in humans. This new steroid was identified along with three other low-polarity ligands of sex hormone-binding globulin (SHBG) in pregnant women.[2,3] These included two weakly-bound and well-known steroids, 5α-pregnane-3,20-dione and progesterone, and two strongly-bound substances, 2-methoxyestrone and the new steroid named ED. The identification of the first three ligands was based on chromatographic elution patterns, binding characteristics and gas chromatography–mass spectrometry. The identification of the fourth peak, the new steroid, was based on similar kinds of evidence and, in addition, on ultraviolet absorption spectra and solubility characteristics. Furthermore, ED can transform into estradiol in alkali conditions, suggesting a dearomatized form of the potent estrogenic hormone estradiol. Thus, the proposed structure of ED is 17β-hydroxy-19-nor-androsta-1,5-dien-3-one (**1**), a C18-steroid (estrane) nucleus comprising an unusual and unstable 1,5-dien-3-one system (Scheme 1). Since it is scarcely available from urine, placenta and blood from pregnant women, the low quantity of natural ED thus isolated has not allowed confirming its chemical structure yet. Its chemical synthesis thus seemed an attractive approach for confirming, or invalidating, the proposed structure, as well as for providing a substantial quantity of the hormone for biological studies.



Scheme 1.

Keywords: Steroid; Total synthesis; Nortestosterone; 1,5-Dien-3-one system; Protecting group; NMR.
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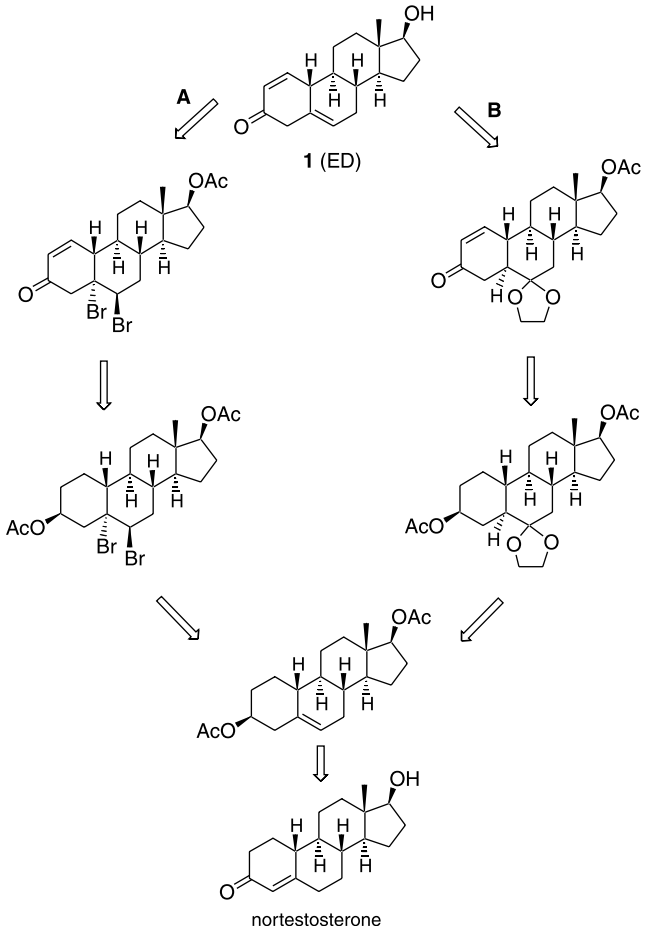
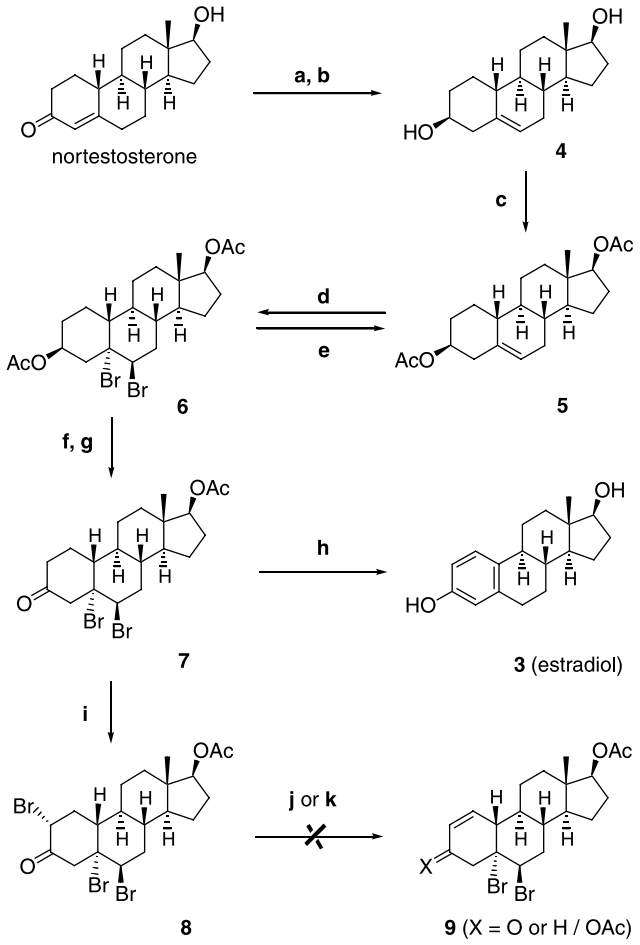
Although the elaboration of 1,5-dien-3-one systems is well documented for C19- and C21-steroids,[4–8] as exemplified by compound **2** in Scheme 1, this is not the case for the C18-steroid derivative **1** (ED), which is expected to be very sensitive to aromatization under an acid or base treatment, giving estradiol (**3**). Contrary to **1**, a steroid like **2** is stable because the aromatization of ring A is not possible with the presence of an angular methyl group at position 10. Considering the serious constraints associated with the instability of the 1,5-dien-3-one system in a C18-steroid (19-nor-androstane), the synthesis of **1** represents an interesting challenge. In this paper, we report the successful chemical synthesis of compound **1** from nortestosterone.

2. Results and discussion

Two retrosynthetic approaches (A and B) were tested for the synthesis of **1** (Scheme 2). These strategies have in common the double bond deconjugation of nortestosterone, but differ by the nature of the protecting group for the double bond, a 5,6-dibromo or a 6-ketal derivative. In the first approach (A), depicted more comprehensively in Scheme 3, the 4,5-double bond of nortestosterone was first deconjugated with KO-*t*-Bu to form the 5,6-double bond,[9] and the 3-ketone was reduced with $LiAlH_4$ to avoid reconjugation of the double bond.[10] The resulting diol **4**, obtained in 77% yield, was then acetylated in standard conditions to afford the diacetylated compound **5**. The 5,6-double bond of **5** was protected by bromination using Br_2 in acetic acid[11] to give the dibromo compound **6** in 57% yield; this product was found to be quite stable when left for a long time at rt in an inert and dark atmosphere. The double bond deprotection was tested and found satisfactory. In an attempt to recover the 5,6-double bond, it was not possible to use the standard NaI procedure described for the C19-steroids;[11] the C18-steroid **6** was successfully treated instead with $Na_2S{\cdot}H_2O$.[12–14] Thereafter, the 3-acetate group of **6** was hydrolyzed selectively with K_2CO_3 in MeOH and the resulting alcohol submitted to oxidative conditions (PCC/NaOAc, PDC or TPAP/NMO) to obtain ketone **7**. The latter was not very stable, however, being easily converted into estradiol (**3**). Only PCC gave **7** in 95% yield, but this compound cannot be purified by chromatography and is only stable in inert atmosphere and at low temperature in darkness. Using LDA in the presence of PhSeBr or PhSeCl[15] followed by a treatment with H_2O_2 did not allow introducing the 1,2-double bond because **7** was instead transformed into **3**. Alternatively, an additional



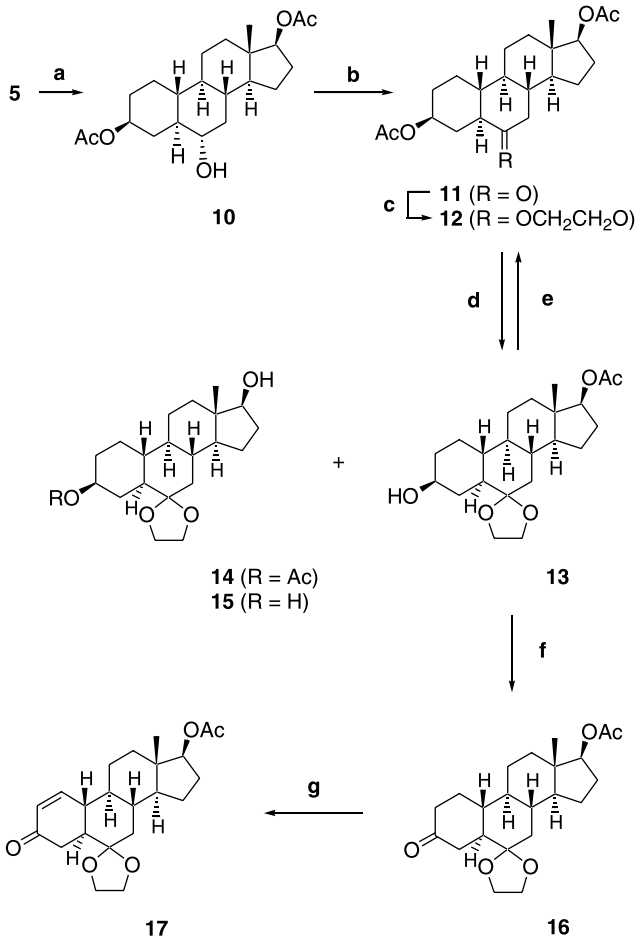
Scheme 2. Two retrosynthetic approaches for the synthesis of ED.



Scheme 3. Reagents and conditions. (a) KO-*t*-Bu, *t*-BuOH, THF, rt, 18 h; (b) $LiAlH_4$, THF, 0 °C, 2.5 h (77%, two steps); (c) Ac_2O, pyridine, DMAP, rt, 3 h (91%); (d) AcOH, Br_2, KOAc, Et_2O, 0 °C, 2 h and rt, 12 h (57%); (e) $Na_2S{\cdot}9H_2O$, DMF, rt, 3 h (99%); (f) K_2CO_3, MeOH, CH_2Cl_2, H_2O, 80 °C, 5 h (59%); (g) PCC, CH_2Cl_2, rt, 3 h (95%); (h) THF, LDA, 0 °C, 10 min; $CDCl_3$, rt, 12 h; or neat, rt, 12 h; (i) AcOH, Br_2, Et_2O, 0 °C, 2 h and rt, 12 h (91%); (j) $CaCO_3$, DMA, 170 °C, 10 min or $CaCO_3$, DMA, C_6H_6, 80 °C, 10 min; (k) (i) $NaBH_4$, MeOH, THF, 0 °C, 1.5 h; (ii) Ac_2O, pyridine, DMAP, rt, 12 h (77%, two steps); (iii) DBU, C_6H_6, rt, 12 h or 80 °C, 8 h.

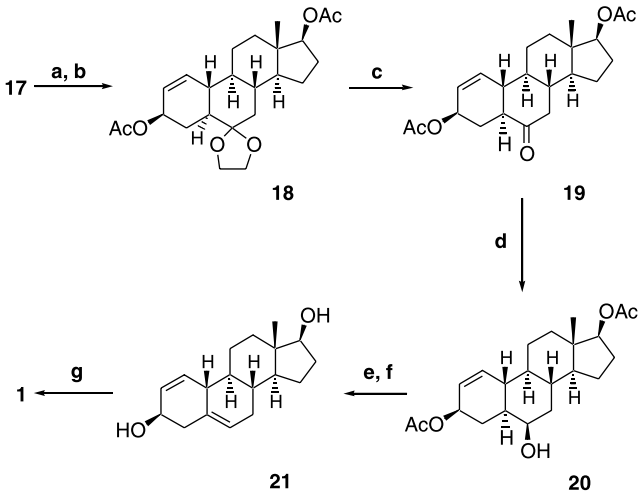
bromide was introduced at position 2 using Br_2 in acetic acid to give the tribromide derivative **8**. Unfortunately, the methods we tried for the dehydrobromination[16–18] failed to provide the enone system of compound **9**.

In the second approach (B), briefly outlined in Scheme 2 and reported in details in Schemes 4 and 5, the 5,6-double bond of **5** was hydroxylated at position 6 using $BH_3 \cdot THF$ and H_2O_2/NaOH at rt.[19] The alcohol **10** was obtained in 62% yield, but two more compounds, deacetylated in C-17 or in C-3, were also observed in 28% yield. Before introducing the 1,2-double bond, **10** was first oxidized into **11** with PCC and then protected as ketal **12** in 96% yield. The regio-deprotection by removal of the 3-acetate group with K_2CO_3 was less selective than previously observed for approach A. Thus, when **12** was treated with K_2CO_3 in MeOH/H_2O, only 15% yield of **13** was obtained after 3 h. A better yield of 51% was, however, obtained with aq $NaHCO_3$. Furthermore, the by-products of this reaction, alcohol **14** and diol **15**, can be recycled by an acetylation step allowing the recovery of **12**.



Scheme 4. Reagents and conditions. (a) (i) $BH_3 \cdot THF$, THF, rt, 2 h; (ii) H_2O_2, NaOH, 0 °C, 0.5 h and rt, 1 h (62%); (b) PCC, CH_2Cl_2, rt, 3 h (97%); (c) ethylene glycol, $HC(OEt)_3$, *p*-TsOH, CH_2Cl_2, rt, 3.5 h (99%); (d) $NaHCO_3$, MeOH, H_2O, 67 °C, 72 h (51%); (e) Ac_2O, pyridine, DMAP, rt, 3 h (99%); (f) PCC, CH_2Cl_2, rt, 3 h (96%); (g) (i) PhSeCl, AcOEt, rt, 3 h; (ii) pyridine, H_2O_2, rt, 15 min then 80 °C, 15 min (70%).

The construction of the 1-en-3-one system was finally achieved by oxidation of the 3-hydroxy group of **13** to its



Scheme 5. Reagents and conditions. (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, MeOH, −78 °C, 1.5 h; (b) Ac_2O, pyridine, DMAP, rt, 3 h (99%, two steps); (c) 1% HCl in acetone, rt, 0.5 h (64%); (d) K-Selectride, THF, −78 °C, 5.5 h (72%); (e) $POCl_3$, pyridine, rt, 1 h; (f) K_2CO_3, MeOH, H_2O, 100 °C, 1 h (63%, two steps); (g) $BaMnO_4/Al_2O_3$ (neutral), $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, rt, 4 h (13%).

corresponding ketone **16**, followed by the double bond introduction giving **17**. Previously, we successfully applied classical methods for the introduction of a double bond, such as LiBr/Li_2CO_3,[20] *N*-bromosuccinimide/DBU,[16] TMSCl/$Pd(OAc)_2$,[21,22] PhSeBr,[15] or $PySO_2CH_3$,[23] to a model compound (19-nor-dihydrotestosterone-17β-*O*-TBDMS), allowing the formation of 1,2-conjugated 3-ketone in 41–61% yields. Unfortunately, these methods were not compatible with the functional group of **16**. The double bond was, however, introduced using Reich's methodology,[15] modified so as not to require LDA.[24] Thus, a sequential treatment of PhSeCl in anhydrous EtOAc and H_2O_2/pyridine at rt and then at reflux yielded the conjugated ketone **17** in 70% yield from **16**.

After successfully elaborating the 1-en-3-one system, the next step was to regenerate the 5,6-double bond carefully in order to avoid the aromatization of ring A. In order to do this, the C-3 carbonyl of **17** was first reduced with $NaBH_4/CeCl_3 \cdot 7H_2O$ and the resulting allylic alcohol protected as diacetate **18** in excellent yield (Scheme 5). The ketal group was next hydrolyzed at rt in acetone and *p*-TsOH (1.4 equiv),[25] but ketone **19** was found to be quite unstable under these conditions, with only 19% isolated. However, carrying out the same reaction using 1% HCl in acetone instead resulted in a mixture of 5α-H and 5β-H isomers in a ratio of 67:33 and a much better yield of 64% for **19** after chromatography. The conditions for the transformation of **19** into **20** were first studied with **11** as a model compound. Indeed, it is known that a 5α-H and a 6β-OH in trans diaxial configuration can be eliminated with $POCl_3$ in pyridine in order to regenerate the 5,6-double bond.[26] When **11** was reduced with $NaBH_4$ in MeOH at 0 °C, the 6α-OH derivative **10** and 6β-OH analogue were obtained in a ratio of 45:55, according to ^1H NMR analysis (3.30 ppm for 6β-CH of 6α-OH derivative **10** and 3.80 ppm for 6α-CH of 6β-OH analogue). When this reduction was performed using $NaBH_4/CeCl_3 \cdot 7H_2O$ in MeOH at −78 °C only the 6α-alcohol **10** was obtained.[27] However, we could

not proceed to the inversion of 6α-OH into 6β-OH because the well known modified Mitsunobu methodology (PPh_3, DEAD and PNBA followed by an ester hydrolysis)[28,29] is not compatible with acetate groups, and accordingly we changed the reductive reagent. Thus, the 6β-OH epimer of **10** was the single isomer isolated using K-Selectride in THF at −78 °C. Finally, the preparation of **21** was completed by (1) a stereoselective reduction of **19** into **20** using the K-Selectride methodology discussed above; (2) a dehydration of the 6β-OH group with $POCl_3$ in pyridine; and (3) a deprotection by removal of diacetate groups with K_2CO_3.

Before the last step in the synthesis of **1**—a compound expected to be very sensitive to usual acid and base conditions—the precursor compound **21** was fully analyzed by NMR spectroscopy. We were especially interested in confirming the 10β-H stereochemistry, because this stereocenter will not be modified in the last step of compound **1** synthesis. Using a combination of NMR experiments (COSY, HSQC, HMBC, and NOESY),[30] all proton and carbon signals were fully identified (see Section 4 and Supporting information). Using the signal at 2.46 ppm (10-CH), the NOESY spectra allowed identifying four interactions of different intensity with 11β-CH (strong), 4β-CH (medium), 8β-CH (weak) and 1-CH (weak) (Fig. 1). Furthermore, no NOE was observed between the hydrogen atoms at positions 10 and 9α. Taken together, these data clearly established the 10β-H stereochemistry in compound **21**.

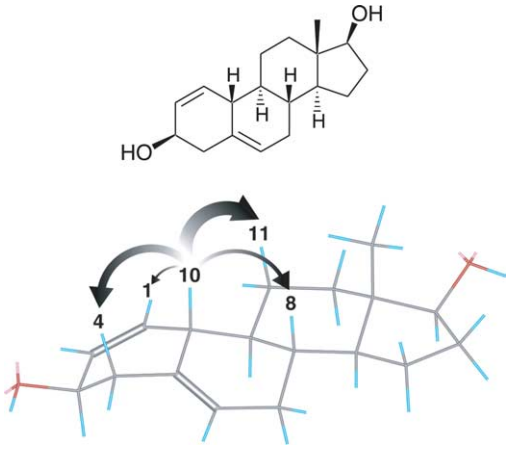
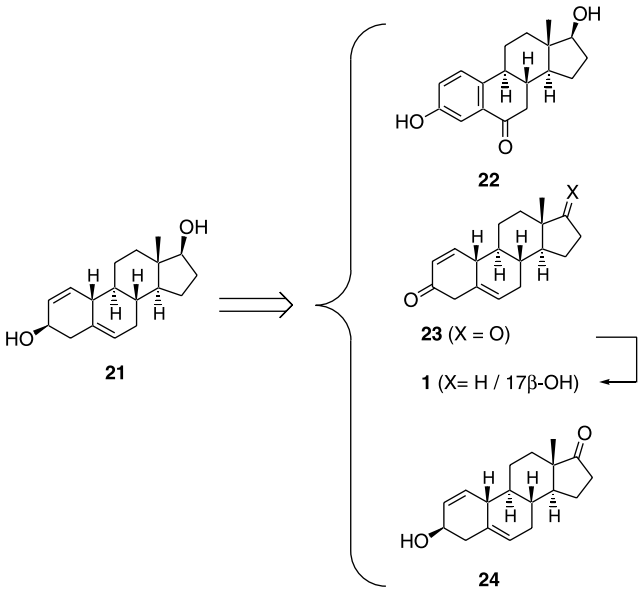


Figure 1. 2D and 3D representations of **21**. The important NOE results are represented by four arrows. The 3D structure was generated with CSChem 3D std 5.0 (Cambridge Soft Corporation, Cambridge, MA). The stereocenters at C-8, 9, 13, 14, and 17 were already fixed in the starting natural steroid and were not affected by the following sequence of reactions.

The last crucial step in the synthesis of **1** was the regioselective oxidation of the allylic 3-OH versus the 17-OH of diol **21** in neutral and mild conditions avoiding the aromatization of the 1,5-dien-3-one system. Four methods, MnO_2,[16,31–33] Dess–Martin,[34] IBX–polystyrene,[35] and $BaMnO_4$ on alumina,[36,37] were selected to be tested for this transformation (Scheme 6 and Table 1). With MnO_2 in acetone, the transformation of **21** switched toward the aromatized compound **22** (entry 1 of Table 1). The weak basicity (pH 8) and oxidative property of MnO_2 explain the



Scheme 6. The reagents and conditions are reported in Table 1 except for the reduction of **23** into **1** ($NaBH_4$, MeOH, CH_2Cl_2, −35 °C, 13 min).

A-ring aromatization and B-ring oxidation. No reaction was observed when benzene and CH_2Cl_2 were used as aprotic solvents. Diol **21** was next treated with Dess–Martin periodinane (2 equiv), which resulted in the isolation of diketone **23** in 72% yield after 30 min (entry 2). In an attempt to capitalise on the less reactive character of the hindered 17β-OH versus the more reactive allylic 3β-OH, diol **21** was reacted with only 1 equiv of Dess–Martin reagent. A mixture of compounds **21**, **23**, **24**, and **1** was, however, obtained (entry 3), clearly showing the non regioselectivity of this methodology. Furthermore, it was not possible to separate the compounds by chromatography. IBX–polystyrene, a polymer-supported version of iodoxybenzoic acid reported to be selective for allylic alcohol, was also tested for the oxidation of **21**. Considering the low stability expected for compound **1**, we found worthy using this polymer-supported reagent for its mild reactivity, its more hindered nature, and the simple workup (only filtration is needed). Although this reagent is less reactive than hypervalent iodine analogue reagent (Dess–Martin periodinane), a selective oxidation was nonetheless not possible (entries 4–8).

The last reagent tested was a solid mixture of $BaMnO_4$ on basic or neutral alumina and $CuSO_4 \cdot 5H_2O$. We previously obtained promising results with a model diol containing two secondary alcohols. In fact, a mixture of starting material, 3β,17β-dihydroxy-4-androstene, and of the desired compound, 17β-hydroxy-4-androsten-3-one, was obtained in a ratio of 1:2 following the conditions described in the literature (basic alumina, benzene). The same ratio was obtained with CH_2Cl_2, as well as when replacing basic alumina by neutral alumina, a kind of alumina much more compatible with the low stability of **1**. These results prompted us to employ this selective oxidizing agent with diol **21**. In the last two assays (entries 9 and 10), ratios of 60:40 and 63:37 were determined for **21** and **1** by ^1H NMR.

Table 1. Yields (%) under different conditions tested for the regioselective oxidation of **21** into **1**

Entry	Reagents and conditions	**21**	**22**	**23**	**24**	**1**
1	MnO_2 (15 equiv), acetone, rt, 12 h	32[a]	37	0	0	0
2	Dess–Martin (2 equiv), CH_2Cl_2, rt, 30 min	0	0	72	0	0
3	Dess–Martin (1 equiv), CH_2Cl_2, rt, 1 h	*22*[b]	*0*	*23*	*23*	*32*
4	IBX–polystyrene (4 equiv), CH_2Cl_2, rt, 15 min	*65*	*0*	*8*	*13*	*14*
5	IBX–polystyrene (4 equiv), CH_2Cl_2 rt, 30 min	*43*	*0*	*18*	*20*	*19*
6	IBX–polystyrene (2 equiv), CH_2Cl_2, rt, 10 min	*65*	*0*	*13*	*6*	*16*
7	IBX–polystyrene (2 equiv), CH_2Cl_2, rt, 20 min	*62*	*0*	*19*	*3*	*16*
0	IBX–polystyrene (2 equiv), CH_2Cl_2, rt, 45 min	*19*	*0*	*38*	*20*	*23*
9	$BaMnO_4/Al_2O_3$ (neutral), $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, rt, 6 h	*60*	*0*	*0*	*0*	*40*
10	$BaMnO_4/Al_2O_3$ (neutral), $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, rt, 4 h	63 *(63)*	0	0	0	13 *(37)*

[a] Isolated yield (%) after purification by silica gel chromatography (normal characters).
[b] Percentage of compounds as determined by ^1H NMR analysis (italic characters).

In the last assay, ketone **1** was isolated in 13% yield after careful reverse-phase chromatographic steps, which also permitted recovery of the starting diol **21** in 63% yield. This regioselective oxidation remains to be optimized, especially regarding the workup and purification procedures.

As an alternative strategy to obtain **1** more easily, we attempted the regioselective reduction of **23** into **1** (Scheme 6). Indeed, a ketone can be reduced in the presence of a conjugated enone using the conditions reported by Ward et al. ($NaBH_4$ in $MeOH/CH_2Cl_2$ (50/50) at −78 °C).[38] In our case, the ketone at C17 was reduced before the conjugated ketone at C3. No reaction was observed at −78 °C, but the reduction proceeds with a good regioselectivity between −40 and −35 °C. Although the reaction temperature and time appear to be critical for selectivity, an interesting ratio of 41:54:5, for **1**:**23**:**21** was obtained at −35 °C. Compound **1** was thus isolated in a better yield (40%) and much more easily by the regioselective reduction than by the regioselective oxidation.

Compounds **23** and **1** were analysed by ^1H and ^{13}C NMR to confirm the formation of the 1,5-estradien-3-one system. We had previously assessed the stability of **23** at rt during a period of 1 month when dissolved in various deuterated solvents (Fig. 2).

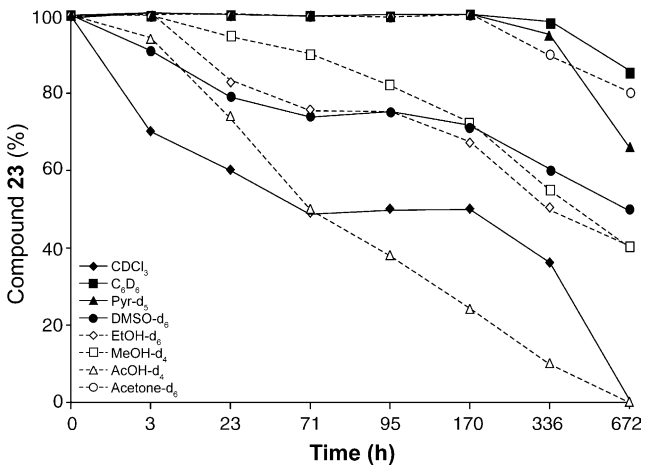
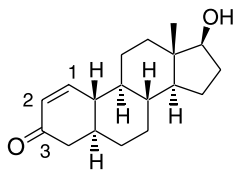


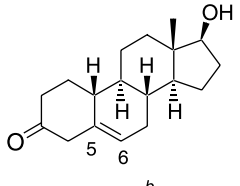
Figure 2. Stability of **23** (1 mg) at rt when dissolved in deuterated solvents as determined by NMR analysis.

In chloroform, **23** underwent only aromatization of the steroidal A-ring giving estrone (100%) after 4 weeks, while it was fully degraded in acetic acid. The formation of aromatized and degraded compounds gradually occurred in methanol, ethanol, or dimethylsulfoxide, but ~70 and 40% of **23** still remained after 1 and 4 weeks. However, the 1,5-dien-3-one system was fully stable in benzene, pyridine, or acetone until 14 days and few degradation (15–34%) was observed at the end of the experiment. We then selected C_6D_6 for our NMR analysis, and data for ketone **1**, diketone **23**, and model compounds **25** and **26** are reported in Table 2. Clearly the CH-1 and CH-2 signals of **1** and **23** are close to the corresponding signals observed for model compound **25**. The same conclusion was also obtained for the C-5 and CH-6 signals of **1** and **23** when compared to the *exo* 5,6-double bond of **26**. Taken together these data clearly confirmed the 1,5-dien-3-one system of **23** and **1**.

Table 2. Characteristic NMR signals (ppm) in C_6D_6 observed for compounds **25**, **26**, **23**, and **1**



25[a]



26[b]

Carbon number	**25**[a] H, C	**26**[b] H, C	**23** H, C	**1** H, C
1	6.48, 150.6	—	6.24, 149.4	6.33, 149.8
2	6.02, 129.7	—	5.99, 128.9	6.00, 128.7
3	—, 198.0	—, 206.8	—, 196.4	—, 196.7
5	—	—, 135.7	—, 132.4	—, 132.2
6	—	5.20, 122.2	5.16, 122.8	5.18, 123.2

[a] Compound **25** was obtained by treatment of 19-nor-dihydrotestosterone-17β-*O*-TBDMS with $Pd(OAc)_2$ followed by a TBDMS hydrolysis.
[b] Compound **26** was obtained as an intermediate during the synthesis of **4**.

3. Conclusion

The successful synthesis of **23** and **1**, two dearomatized forms of potent estrogenic hormones estrone and estradiol, respectively, was described starting from nortestosterone. To the best of our knowledge, the synthesis of a steroidal 1,5-dien-3-one system without a methyl 19 group at position 10 had never been reported before. This unusual chemical

arrangement explains the low stability of **23** and **1** that complicated the chemical synthesis. In fact a careful planning of the sequence of reactions was necessary to overcome the synthetic difficulty associated with the high reactivity of a 19-nor-androsta-1,5-dien-3-one system toward acids and bases. As reported for natural ED,[3] **1** was treated with 3 N NaOH in acetone at rt giving as expected the aromatized compound **3** (estradiol) in 70% yield. However, **1** may not be identical to natural ED since a biological assay has shown its potency to be lower (20% of that of natural ED). LC/MS analysis and Sephadex chromatography also confirmed the non-identity of **1** and natural ED. They nonetheless have in common certain unstable properties and it is possible that both compounds contain the same unusual 1,5-dien-3-one system. Preliminary studies also determined the range of stability of this 19-nor-androsta-1,5-dien-3-one system under different solvents.

4. Experimental

4.1. General remarks

Anhydrous reactions were performed in oven-dried glassware under positive argon pressure using commercially available anhydrous solvents, except THF, which was distilled from sodium/benzophenone ketyl under argon. Flash chromatography was performed on Silicycle 60 230–400-mesh silica gel. Thin-layer chromatography (TLC) was performed on 0.25-mm silica gel 60 F_{254} plates and compounds were visualized by exposure to UV light (254 nm), a solution of ammonium molybdate/sulphuric acid/water and/or a solution of *para*-anisaldehyde/sulphuric acid/acetic acid/ethanol (plus heating). Infrared (IR) spectra were obtained from a thin film of the solubilized compound on NaCl pellets (usually in CH_2Cl_2) or in a KBr pellets containing the solid compound. Only significant bands are reported (in cm^{-1}). ^1H and ^{13}C spectra were recorded, respectively, at 300 and 75.5 MHz or at 400 (^1H) and 100 (^{13}C) MHz. The chemical shifts (δ) are expressed in ppm and referenced to chloroform (7.26 and 77.0 ppm), methanol (3.31 and 49.0 ppm) or benzene (7.16 and 128.0 ppm) for ^1H and ^{13}C, respectively. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy. Melting points were recorded on an Electrothermal IA9300 SERIES Digital Melting Point Apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained with a dual spray ESI source on positive mode.

4.2. Synthesis of compounds 1 and 23

4.2.1. Synthesis of 3β,17β-dihydroxy-19-nor-androst-5-ene (4).[39] A mixture of nortestosterone (15.00 g, 54.74 mmol) and KO-*t*-Bu (13.82 g, 136.85 mmol) in *t*-BuOH (260 mL) and THF (150 mL) was stirred under nitrogen for 18 h at rt and then quenched by the rapid addition of 10% aq AcOH (930 mL) to the resulting slurry. Saturated aq $NaHCO_3$ was added and the product was isolated by an extraction with diethyl ether. The combined organic layer was washed with excess aq $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude unconjugated ketone was added to a stirred solution of $LiAlH_4$ (2.29 g, 60.21 mmol) in dry THF (675 mL) at 0 °C. After being stirred at 0 °C for 2.5 h, the reaction mixture was quenched with saturated aq NH_4Cl (100 mL) and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 80:20) to afford diol **4** (11.68 g, 77% yield) as a white solid. IR (film) ν 3362 (OH); ^1H NMR (300 MHz, MeOH-d_4) δ 0.76 (s, 18-CH_3), 0.80–2.05 (m, 19H, CH and CH_2 of steroid skeleton), 2.40 (m, 1H), 3.40 (m, 3α-CH), 3.58 (t, J=8.5 Hz, 17α-CH), 5.44 (dd, J_2=5.7 Hz, J_1=1.5 Hz, 6-CH); ^{13}C NMR (75 MHz, MeOH-d_4) δ 11.5 (C18), 24.1, 28.0, 30.6, 31.4, 31.6, 36.1, 37.8, 38.0, 44.1, 44.2, 45.7, 47.2, 51.7, 71.8 (C3), 82.5 (C17), 122.1 (C6), 138.8 (C5); HRMS calcd for $C_{18}H_{29}O_2$ $[M+H]^+$ 277.21621, found 277.21689.

4.2.2. Synthesis of 3β,17β-diacetoxy-19-nor-androst-5-ene (5).[39] To a stirred solution of **4** (11.68 g, 42.32 mmol) in CH_2Cl_2 (640 mL) were added pyridine (7.50 mL), Ac_2O (6.83 mL) and a catalytic amount of DMAP. The reaction mixture was stirred under nitrogen for 3 h at rt, poured into ice cold aq 1 M HCl (230 mL), and extracted with EtOAc. The combined organic layer was washed with saturated aq $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude product was purified by chromatography (hexanes/EtOAc, 90:10) to afford **5** (13.86 g, 91% yield) as a white solid. IR (film) ν 1732 (C=O, esters); ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 18-CH_3), 0.80–2.10 (m, 19H, CH and CH_2 of steroid skeleton), 2.02 (s, 2×$OCOCH_3$), 2.50 (m, 1H), 4.59 (m, 3α-CH and 17α-CH), 5.46 (dd, J_2=5.7 Hz, J_1=1.5 Hz, 6-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9 (C18), 21.1 (OCO*CH*$_3$), 21.4 (OCO*CH*$_3$), 23.3, 26.5, 27.4, 30.0, 30.2, 31.5, 36.1, 36.5, 40.7, 42.6, 42.7, 45.2, 49.9, 73.2 (C3), 82.7 (C17), 122.2 (C6), 136.1 (C5), 170.5 (O*CO*CH$_3$), 171.2 (O*CO*CH$_3$); HRMS calcd for $C_{22}H_{33}O_4$ $[M+H]^+$ 361.23734, found 361.23767.

4.2.3. Synthesis of 3β,17β-diacetoxy-6α-hydroxy-19-nor-5α-androstane (10). To a solution of **5** (16.32 g, 45.33 mmol) in dry THF (620 mL) was added 1 M BH_3 in THF (91 mL) dropwise at 0 °C, and the mixture was stirred for 2 h at rt. Then 3 N NaOH (40 mL) and H_2O_2 (33% w/v, 15 mL) were added at 0 °C, and the mixture was stirred 0.5 h at 0 °C and 1 h at rt. The mixture was poured into H_2O (500 mL). The aq phase was extracted with CH_2Cl_2, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. Purification by flash chromatography (hexanes/EtOAc, 70:30) afforded **10** (10.62 g, 62%) as a white solid. Mp 199–200 °C (Et_2O/MeOH); IR (film) ν 3528 (OH), 1736 and 1709 (C=O, esters); ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (m, 1H), 0.75 (s, 18-CH_3), 0.78–2.20 (m, 19H, CH and CH_2 of steroid skeleton), 1.98 (s, $OCOCH_3$), 2.00 (s, $OCOCH_3$), 2.40 (m, 1H), 3.24 (m, 6β-CH), 4.55 (t, J=8.4 Hz, 17α-CH), 4.66 (m, 3α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (C18), 21.2 (OCO*CH*$_3$), 21.4 (OCO*CH*$_3$), 23.3, 25.2, 27.4, 28.0, 31.5, 34.5, 36.6, 38.6, 39.7, 42.7, 43.9, 47.2, 48.2, 49.5, 72.7 (C3 or C6), 73.7 (C6 or C3), 82.7 (C17), 170.6 (O*CO*CH$_3$), 171.2 (O*CO*CH$_3$); HRMS calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.22985, found 401.22938.

4.2.4. Synthesis of 3β,17β-diacetoxy-6-oxo-19-nor-5α-androstane (11). A solution of **10** (18.40 g, 48.67 mmol) and PCC (26.16 g, 121.69 mmol) in dry CH_2Cl_2 (270 mL)

was stirred for 3 h at rt. Celite was then poured into the mixture and the resulting suspension was filtered through a cake of Celite and silica gel. The filter cake was washed with hexanes/EtOAc, 50:50 (1.5 L), and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 70:30) to afford **11** (17.70 g, 97% yield) as a white solid. Mp 187–188 °C (Et_2O/MeOH); IR (film) ν 1736 and 1708 (C=O, esters and ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 18-CH_3), 1.10–2.38 (m, 21H, CH and CH_2 of steroid skeleton), 2.03 (s, $OCOCH_3$), 2.05 (s, $OCOCH_3$), 4.65 (t, J=8.4 Hz, 17α-CH), 4.70 (m, 3α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9 (C18), 21.1 ($OCOCH_3$), 21.3 ($OCOCH_3$), 23.1, 25.2, 27.3, 29.0, 30.8, 31.0, 36.3, 42.2, 43.0, 45.8, 47.2, 47.4, 50.3, 52.3, 72.3 (C3), 82.3 (C17), 170.6 ($OCOCH_3$), 171.2 ($OCOCH_3$), 209.7 (C6); HRMS calcd for $C_{22}H_{33}O_5$ $[M+H]^+$377.23225, found 377.23253.

4.2.5. Synthesis of 3β,17β-diacetoxy-6,6-ethylenedioxy-19-nor-5α-androstane (12). A mixture of **11** (17.70 g, 47.07 mmol), triethyl orthoformate (28.5 mL), ethylene glycol (26 mL), and a catalytic amount of *p*-TSA in CH_2Cl_2 (1 L) was stirred for 3.5 h at rt. The reaction was quenched by addition of H_2O, then the organic phase was washed with H_2O, dried over $MgSO_4$, and evaporated to afford **12** (19.60 g, 99%) as a white solid. Mp 135–136 °C (Et_2O/pentane); IR (film) ν 1732 (C=O, esters); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (m, 1H), 0.79 (s, 18-CH_3), 0.90–2.20 (m, 20H, CH and CH_2 of steroid skeleton), 2.01 (s, $OCOCH_3$), 2.02 (s, $OCOCH_3$), 3.93 (m, OCH_2CH_2O), 4.58 (t, J=8.4 Hz, 17α-CH), 4.68 (m, 3α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (C18), 21.1 ($OCOCH_3$), 21.4 ($OCOCH_3$), 23.2, 25.1, 27.4, 28.5, 29.8, 31.3, 36.7, 37.5, 39.6, 42.6, 42.8, 47.4, 47.7, 49.5, 64.9 (OCH_2), 65.3 (OCH_2), 73.1 (C3), 82.7 (C17), 109.2 (C6), 170.5 ($OCOCH_3$), 171.2 ($OCOCH_3$); HRMS calcd for $C_{24}H_{37}O_6$ $[M+H]^+$421.25847, found 421.25801.

4.2.6. Synthesis of 17β-acetoxy-6,6-ethylenedioxy-3β-hydroxy-19-nor-5α-androstane (13). Compound **12** (9.80 g, 23.44 mmol) was dissolved in MeOH (290 mL) and a solution of $NaHCO_3$ (1.97 g, 23.44 mmol) in H_2O (96 mL) was added. The resulting mixture was warmed at 67 °C for 72 h. Then, the mixture was extracted with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 70:30 to 50:50) to afford **13** (4.49 g, 51% yield) as a white amorphous solid. In addition to **13**, purification yielded **12** (1.86 g, 19% yield), **14** (0.74 g, 8% yield) and **15** (1.94 g, 25% yield), all as white solids. Data are reported only for **13**. IR (film) ν 3434 (OH), 1736 (C=O, ester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (m, 1H), 0.81 (s, 18-CH_3), 0.80–2.20 (m, 20H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 3.60 (m, 3α-CH), 3.95 (m, OCH_2CH_2O), 4.60 (t, J=8.4 Hz, 17α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (C18), 21.2 ($OCOCH_3$), 23.2, 25.2, 27.4, 28.8, 33.7, 35.2, 36.7, 37.5, 39.8, 42.6, 42.8, 47.6, 47.9, 49.6, 65.0 (OCH_2), 65.4 (OCH_2), 70.6 (C3), 82.7 (C17), 109.5 (C6), 171.2 ($OCOCH_3$); HRMS calcd for $C_{22}H_{35}O_5$ $[M+H]^+$379.24790, found 379.24827.

4.2.7. Synthesis of 17β-acetoxy-6,6-ethylenedioxy-3-oxo-19-nor-5α-androstane (16). A solution of **13** (8.16 g, 21.70 mmol) and PCC (11.66 g, 54.25 mmol) in dry CH_2Cl_2 (140 mL) was stirred for 3 h at rt. Then Celite was poured into the mixture and the resulting suspension was filtered through a cake of Celite and silica gel. The filter cake was washed with hexanes/EtOAc, 50:50 (0.5 L), and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 70:30) to afford **16** (7.80 g, 96% yield) as a white solid. Mp 136–138 °C (Et_2O); IR (film) ν 1736 (C=O, ester), 1720 (C=O, ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (m, 1H), 0.83 (s, 18-CH_3), 1.05–1.90 (m, 14H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.10–2.50 (m, 6H, CH and CH_2 of steroid skeleton), 3.85 (m, 1H of OCH_2CH_2O), 3.95 (m, 3H of OCH_2CH_2O), 4.60 (t, J=8.4 Hz, 17α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (C18), 21.1 ($OCOCH_3$), 23.2, 25.3, 27.4, 30.3, 36.6, 37.4, 39.3, 39.6, 40.8, 42.3, 42.8, 47.2, 49.4, 49.6, 64.9 (OCH_2), 65.4 (OCH_2), 82.6 (C17), 108.9 (C6), 171.1 ($OCOCH_3$), 212.2 (C3); HRMS calcd for $C_{22}H_{33}O_5$ $[M+H]^+$377.23225, found 377.23210.

4.2.8. Synthesis of 17β-acetoxy-6,6-ethylenedioxy-3-oxo-19-nor-5α-androst-1-ene (17). Phenylselenyl chloride (2.49 g, 13.10 mmol) was added to **16** (7.80 g, 10.42 mmol) in dry EtOAc (110 mL) and the resulting reaction mixture was stirred for 3 h at rt. Pyridine (3.14 mL) was then added to the reaction mixture cooled at 0 °C, followed by the addition of H_2O_2 (33% w/v, 2.66 mL) over a period of 6 min. The reaction mixture was stirred at rt for 15 min, then refluxed for 15 min, cooled, and diluted with EtOAc (110 mL). The organic layer was washed with brine (25 mL) and saturated aq $NaHCO_3$ (25 mL), dried over $MgSO_4$, and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 75:25) to afford **17** (5.40 g, 70% yield) as a white solid. Mp 137–139 °C (Et_2O); IR (film) ν 1709 (C=O, ester), 1664 (C=O, conjugated ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 18-CH_3), 0.80–2.35 (m, 16H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.60 (dd, J_2=16.4 Hz, J_1=2.6 Hz, 4-CH), 3.95 (m, OCH_2CH_2O), 4.63 (t, J=8.0 Hz, 17α-CH), 5.99 (dd, J_2=10.2 Hz, J_1=2.2 Hz, 2-CH), 7.07 (dd, J_2=10.2 Hz, J_1=1.6 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (C18), 21.1 ($OCOCH_3$), 23.1, 24.9, 27.4, 36.5, 36.8, 38.0, 39.1, 42.9, 43.2, 45.1, 47.8, 49.4, 65.2 (OCH_2), 65.4 (OCH_2), 82.4 (C17), 108.2 (C6), 129.3 (C2), 151.2 (C1), 171.2 ($OCOCH_3$), 199.9 (C3); HRMS calcd for $C_{22}H_{31}O_5$ $[M+H]^+$375.21660, found 375.21681.

4.2.9. Synthesis of 3β,17β-diacetoxy-6,6-ethylenedioxy-19-nor-5α-androst-1-ene (18). $NaBH_4$ (21 mg, 0.555 mmol) in EtOH (2.5 mL) was added to a cooled (−78 °C) solution of **17** (176 mg, 0.473 mmol) and $CeCl_3 \cdot 7H_2O$ (194 mg, 0.520 mmol) in MeOH (6 mL) over a period of 0.25 h. After the mixture was stirred for 1.5 h, the reaction was quenched by addition of a saturated aq NH_4Cl solution and the extraction was performed with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to dryness. To obtain the protected C-3 alcohol, the crude product (176 mg) was dissolved in dry CH_2Cl_2 (2 mL), and pyridine (50 μL), Ac_2O (50 μL) and a catalytic amount of DMAP were added. The reaction mixture was stirred under nitrogen for 3 h at rt, poured into an ice-cold aq 1 M HCl (2 mL), and extracted with CH_2Cl_2. The combined organic layer was washed with

saturated aq $NaHCO_3$, dried over Na_2SO_4, and evaporated. Purification of the crude compound by flash chromatography (hexanes/EtOAc, 75:25) afforded **18** (195 mg, 99% yield) as a white amorphous solid. IR (film) ν 1736 (C=O, esters); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (m, 1H), 0.82 (s, 18-CH_3), 1.05–2.35 (m, 16H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.05 (s, $OCOCH_3$), 3.95 (m, OCH_2CH_2O), 4.61 (t, J=8.4 Hz, 17α-CH), 5.42 (m, 3α-CH), 5.60 (d app, J=10.3 Hz, 2-CH), 5.97 (d app, J=10.3 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (C18), 21.1 ($OCO\mathit{CH_3}$), 21.3 ($OCO\mathit{CH_3}$), 23.2, 24.9, 27.2, 27.4, 36.6, 38.3, 39.5, 42.8, 43.0, 46.3 (2×), 49.5, 65.2 (OCH_2), 65.3 (OCH_2), 71.2 (C3), 82.6 (C17), 108.9 (C6), 127.2 (C2), 132.3 (C1), 170.7 ($O\mathit{CO}CH_3$), 171.1 ($O\mathit{CO}CH_3$); HRMS calcd for $C_{24}H_{34}O_6Na$ $[M+Na]^+$ 441.22476, found 441.22587.

4.2.10. Synthesis of 3β,17β-diacetoxy-6-oxo-19-nor-5α-androst-1-ene (19). A solution of **18** (12 mg, 0.032 mmol) in acetone (1 mL) was treated with concentrated HCl (0.01 mL). The resulting mixture was stirred at rt for 0.5 h. The reaction was neutralized with saturated aq $NaHCO_3$ and the crude product was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4. The crude ketone was a 67:33 mixture of 5α-CH and 5β-CH diastereomers. Purification of this mixture by flash chromatography (hexanes/EtOAc, 90:10) afforded the 5α-CH diastereomer **19** (7.0 mg, 64% yield) and the 5β-CH analogue (3.0 mg, 27% yield) as white solids. Data are reported only for **19**. Mp 201–203 °C (Et_2O); IR (film) ν 1736 and 1708 (C=O, esters and ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 18-CH_3), 1.10–2.50 (m, 17H, CH and CH_2 of steroid skeleton), 2.05 (s, $OCOCH_3$), 2.06 (s, $OCOCH_3$), 4.65 (t, J=8.4 Hz, 17α-CH), 5.42 (m, 3α-CH), 5.64 (d app, J=10.3 Hz, 2-CH), 6.00 (d app, 1H, J=10.3 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (C18), 21.2 ($OCO\mathit{CH_3}$), 21.3 ($OCO\mathit{CH_3}$), 23.1, 25.0, 27.3, 27.7, 36.2, 42.7, 43.1, 45.5, 46.3, 46.8, 50.2, 50.6, 70.3 (C3), 82.2 (C17), 128.2 (C2), 130.9 (C1), 170.8 ($O\mathit{CO}CH_3$), 171.2 ($O\mathit{CO}CH_3$), 209.0 (C6); HRMS calcd for $C_{22}H_{30}O_5Na$ $[M+Na]^+$ 397.19855, found 397.19885.

4.2.11. Synthesis of 3β,17β-diacetoxy-6β-hydroxy-19-nor-5α-androst-1-ene (20). To a solution of **19** (1.23 g, 3.28 mmol) in dry THF (30 mL) under argon atm at −78 °C was added 1 M K-Selectride in THF (4.93 mL, 4.93 mmol). The mixture was stirred for 5.5 h at −78 °C, and then quenched by addition of a saturated aq NH_4Cl solution. The aq phase was extracted with CH_2Cl_2, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 90:10 to 80:20) to afford **19** (0.15 g, 12% yield) and **20** (0.89 g, 72%) as a white solid. Mp 123–125 °C (Et_2O); IR (film) ν 3474 (OH), 1732 (C=O, esters); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 18-CH_3), 0.80–2.30 (m, 17H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.06 (s, $OCOCH_3$), 3.90 (br s, 6α-CH), 4.60 (t, J=8.4 Hz, 17α-CH), 5.46 (m, 3α-CH), 5.56 (d app, J=10.3 Hz, 2-CH), 6.00 (d app, J=10.3 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (C18), 21.2 ($OCO\mathit{CH_3}$), 21.4 ($OCO\mathit{CH_3}$), 23.2, 24.8, 27.4, 32.6, 35.0, 36.6, 37.7, 38.8, 42.9, 43.3, 46.9, 49.5, 70.1 (C3), 71.5 (C6), 82.7 (C17), 126.7 (C2), 132.8 (C1), 171.0 ($O\mathit{CO}CH_3$), 171.3 ($O\mathit{CO}CH_3$); HRMS calcd for $C_{22}H_{32}O_5Na$ $[M+Na]^+$ 399.21420, found 399.21367.

4.2.12. Synthesis of 3β,17β-dihydroxy-19-nor-androsta-1,5-diene (21). $POCl_3$ (1.45 mL) was added to a solution of **20** (545 mg, 1.45 mmol) in pyridine (14 mL) under argon atm at rt. After the mixture was stirred for 1 h, the reaction was diluted with CH_2Cl_2 (50 mL), quenched by addition of aq 1 M HCl, and extracted with CH_2Cl_2. The combined organic layer was washed with saturated aq $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness. The crude alkene (534 mg) was dissolved in MeOH (20 mL) and a solution of K_2CO_3 (1.00 g, 7.24 mmol) in H_2O (6.5 mL) was added. The resulting mixture was refluxed for 1 h. Then, the mixture was extracted with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 70:30) to afford **21** (250 mg, 63% yield) as a white solid. Mp 150–151 °C (Et_2O); IR (film) ν 3364 (OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 18-CH_3), 0.85 (ddd, J_3=22.0 Hz, J_2=10.6 Hz, J_1=4.5 Hz, 9α-CH), 1.01 (m, 14α-CH), 1.14 (td, J_2=12.9 Hz, J_1=3.9 Hz, 12α-CH_2), 1.26 (m, 11β-CH_2 and 15β-CH_2), 1.40–1.70 (m, 7β-CH_2, 8β-CH, 15α-CH_2 and 16β-CH_2), 1.84 (dt, J_2=12.3 Hz, J_1=3.2 Hz, 12β-CH_2), 1.95–2.20 (m, 4β-CH_2, 7α-CH_2, 11α-CH_2 and 16α-CH_2), 2.46 (d app, J=9.8 Hz, 10β-CH), 2.64 (ddd, J_3=11.8 Hz, J_2=5.9 Hz, J_1=1.2 Hz, 4α-CH_2), 3.66 (t, J=8.5 Hz, 17α-CH), 4.25 (m, 3α-CH), 5.50 (s app, 6-CH), 5.68 (d app, J=10.1 Hz, 2-CH), 5.84 (d app, J=10.1 Hz, 1-CH); ^{13}C NMR (75 and 100 MHz, $CDCl_3$) δ 11.0 (C18), 23.1 (C15), 26.1 (C11), 30.2 (C7), 30.4 (C16), 36.3 (C12), 36.7 (C8), 42.5 (C4 and C10), 42.9 (C13), 44.0 (C9), 50.4 (C14), 69.2 (C3), 81.8 (C17), 122.0 (C6), 130.6 (C1), 131.2 (C2), 134.3 (C5); HRMS calcd for $C_{18}H_{26}O_2Na$ $[M+Na]^+$ 297.18250, found 297.18303.

4.2.13. Synthesis of 19-nor-androsta-1,5-dien-3,17-dione (23). Dess–Martin periodinane (37 mg, 0.088 mmol) was added to a solution of **21** (12 mg, 0.044 mmol) in dry CH_2Cl_2 (4.5 mL) under argon atm at rt. After the mixture was stirred for 30 min, the reaction was diluted with CH_2Cl_2 (50 mL), quenched by addition of H_2O, and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, and evaporated to dryness. The crude diketone was purified with a preparative silica gel TLC (hexanes/EtOAc, 50:50) to afford **23** (8.5 mg, 72% yield) as a white solid. Mp 161–163 °C (Et_2O/MeOH); IR (film) ν 1734, 1676 (C=O, ketones); ^{1}H NMR (400 MHz, C_6D_6) δ 0.58 (s, 18-CH_3), 0.49–2.09 (m, 14H, CH and CH_2 of steroid skeleton), 2.84 (dd, J_2=16.5 Hz, J_1=1.5 Hz, 4-CH), 3.05 (d app, J=16.5 Hz, 4-CH), 5.16 (dd, J_2=5.2 Hz, J_1=2.3 Hz, 6-CH), 5.99 (dd, J_2=10.1 Hz, J_1=2.8 Hz, 2-CH), 6.24 (dd, J_2=10.1 Hz, J_1=1.9 Hz, 1-CH); ^{13}C NMR (75 MHz, C_6D_6) δ 13.5 (C18), 21.4, 25.7, 29.1, 31.6, 35.4, 36.0, 42.8, 43.3, 47.4, 47.9, 50.3, 122.8 (C6), 128.9 (C2), 132.4 (C5), 149.4 (C1), 196.4 (C3), 217.5 (C17); HRMS calcd for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.16926, found 271.16866.

4.2.14. Synthesis of 17β-hydroxy-19-nor-androsta-1,5-dien-3-one (1). *Method A* (*from* **21**). To a mixture of $BaMnO_4$ (192 mg, 3.36 mmol) and neutral Al_2O_3 (94 mg, 0.94 mmol) in dry CH_2Cl_2 (1.6 mL) under argon atm was added $CuSO_4\cdot 5H_2O$ (15 mg, 0.06 mmol) and **21** (35 mg, 0.128 mmol). After 4 h at rt, the adsorbed reagent was removed by filtration on Celite and washed with CH_2Cl_2. The filtrate was evaporated and the crude product was purified with three reverse-phase (C18 silica gel) column chromatographies

[(CH_3CN/H_2O, 4:3)/MeOH, 91:9]. The organic layer of chromatographic tubes was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to afford **1** (4.6 mg, 13% yield).

Method B (*from* **23**). $NaBH_4$ (10.2 mg, 0.268 mmol) was added to a solution of **23** (18.0 mg, 0.067 mmol) in dry CH_2Cl_2/MeOH (1/1) (0.5 mL) under argon at −78 °C. The resulting mixture was then stirred for 13 min at −35 °C, quenched by addition of H_2O at −35 °C, and the crude products isolated by an extraction with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The mixture was purified with a preparative silica gel TLC (hexanes/EtOAc, 50:50) to afford the starting material **23** (9.8 mg, 54% yield) and **1** (7.3 mg, 40% yield).

White solid. Mp 137–139 °C (Et_2O); IR (film) ν 1665 (C=O, ketone); ^{1}H NMR (400 MHz, C_6D_6) δ 0.67 (s, 18-CH_3), 0.54–2.09 (m, 14H, CH and CH_2 of steroid skeleton), 2.94 (dd, J_2=16.5 Hz, J_1=1.4 Hz, 4-CH), 3.06 (d app, J=16.5 Hz, 4-CH), 3.36 (t, J=8.5 Hz, 17α-CH), 5.18 (dd, J_2=5.3 Hz, J_1=2.3 Hz, 6-CH), 6.00 (dd, J_2=10.1 Hz, J_1=3.0 Hz, 2-CH), 6.33 (dd, J_2=10.1 Hz, J_1=2.0 Hz, 1-CH); ^{13}C NMR (75 MHz, C_6D_6) δ 11.1 (C18), 23.2, 26.2, 29.9, 30.7, 36.5, 36.7, 42.9, 43.1, 43.5, 47.9, 50.2, 81.4 (C17), 123.2 (C6), 128.7 (C2), 132.2 (C5), 149.8 (C1), 196.7 (C3); HRMS calcd for $C_{18}H_{25}O_2$ $[M+H]^+$ 273.18491, found 273.18418.

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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.2006.02.063. NMR experimental data (COSY, HSQC, HMBC, and NOESY) for **21**, as well as ^{1}H and ^{13}C NMR spectra of **21**, **23**, and **1**.

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