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Convergent stereoselective and efficient synthesis of furanic-steroid derivatives

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ABSTRACT

The stereoselective synthesis of furanic-steroid derivatives involving ring-closing metathesis and catalytic hydrogenation as key steps is described. The synthetic strategy was first illustrated by the synthesis of the furanic-estrane derivative **1** in seven steps starting from estrone and 2-methylene-propane-1,3-diol. This compound initially targeted as a potential inhibitor of 17β-hydroxysteroid dehydrogenase type 1 by a docking experiment was found to inhibit the enzyme. The scope of this new strategy was also extended to furanic-androstane derivatives by synthesizing compound **20**.

1. Introduction

Estrogenic hormones are well known to be involved in the development and progression of estrogen-dependent diseases, such as breast cancer.[1,2] Among the different types of breast tumors, the majority are initially stimulated by estrogens, and estradiol (E_2) plays a crucial role in their growth. Hormonal control is consequently a logical choice in the treatment of hormone-dependent breast cancer (HDBC) and endocrine therapies were developed because they are less toxic than chemotherapy. Antiestrogens (AE) that block off the estrogen receptor (ER), have been designed and their efficiency has been proven by several clinical trials.[3–7] A complementary approach to the treatment of HDBC using an AE consists in lowering the level of E_2 by inhibiting one of the steroidogenic enzymes involved in the biosynthesis of E_2.[8–11] Among these enzymes, 17β-hydroxysteroid dehydrogenase type 1 (17β-HSD1) is responsible for the reduction of the keto group at position 17 of estrone (E_1) to give the most potent of the human estrogens, E_2.[12,13]

Inhibitors of 17β-HSD1 have been reported by several groups, and this field has been reviewed by ourselves[14–16] as well as by others.[17,18] An ongoing program in our laboratory is aimed at the design and synthesis of novel potent inhibitors of 17β-HSD1 for the treatment of HDBC. Our interest in furanic compounds as inhibitors of 17β-HSD1 arose from the result of preliminary docking studies, using the three-dimensional structure of EM-1745,[19] an E_2/adenosine hybrid inhibitor,[20] complexed with 17β-HSD1. The results of these experiments have suggested that the furanic derivative **1** (Scheme 1) might generate favorable interactions with the active site of the enzyme. Furthermore, such a steroid derivative is not expected to be metabolized at positions 16 and 17 because the furanic moiety blocks these two positions, thus avoiding the hydroxylation and glucuronidation reactions,[21] both crucial phase I and phase II steroid metabolism reactions. In fact, with a C17-ether function, which is more stable, rigid, and less estrogenic than the C17-hydroxyl group of E_2, the furanic compound **1** circumvents a drawback of several 17β-HSD1 inhibitors that have been developed until now. Herein, we report a short and efficient strategy to synthesize the furanic-estrane (C18-steroid) derivative **1** using Grubbs metathesis reaction as a key step. The methodology was also extended to androstane (C19-steroid) nucleus by generating compound **20**.

2. Results and discussion

One strategy to obtain the furanic derivative **1** would be to start by an alkylation at position 16 of 17-ketosteroid E_1 with an appropriate secondary bromide properly protected and ending by a cyclization. However, taking into account the considerable time needed to prepare the suitable nucleophile and the well known low reactivity of 17-ketosteroids for the alkylation at C16 using an unactivated bromide,[20,22,23] we instead designed a new strategy for the synthesis of **1**, which is outlined in Scheme 1. Briefly, the chiral furanic compound **1** will be generated by a stereoselective hydrogenation of **2**, which will be obtained by a metathesis of olefin **3** previously generated from alcohol **4** and allylic bromide **5**. Our

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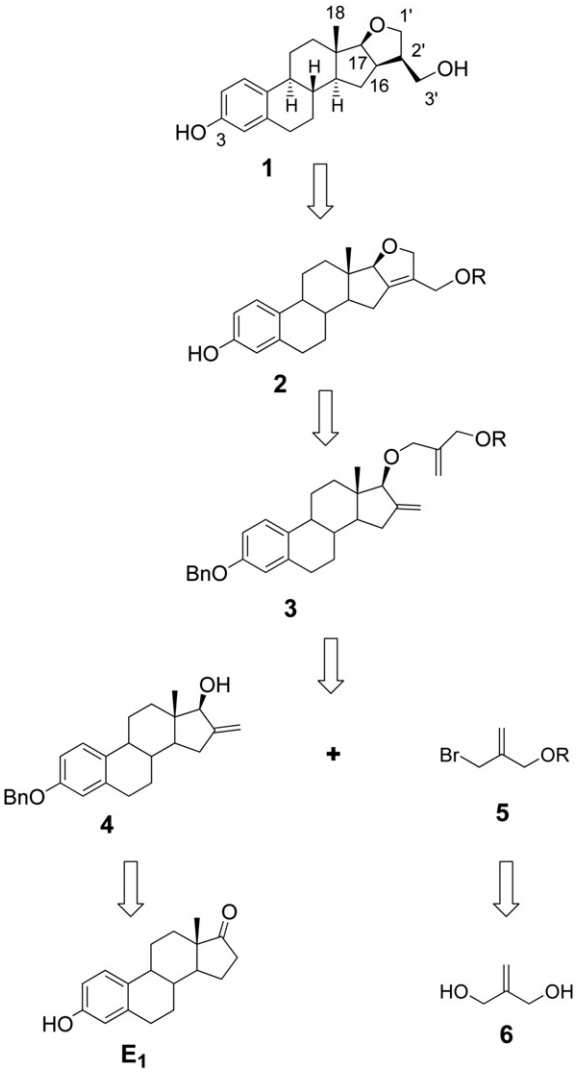


Scheme 1. Retrosynthetic analysis for the synthesis of furanic-estrane derivative **1**.

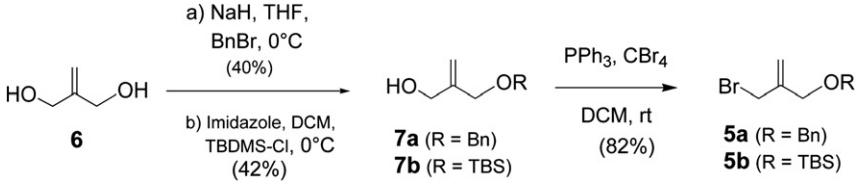
convergent strategy will begin by the preparation of steroid **4** and bromide **5** from E_1 and 2-methylene-propane-1,3-diol (**6**), respectively, both commercially available.

The bromoolefin **5a** was prepared from **6** as shown in Scheme 2. One hydroxyl group of the diol **6** was selectively protected using benzyl bromide (BnBr) and NaH as base to provide **7a**. The latter was then submitted to a bromination of the remaining primary alcohol using triphenylphosphine and carbon tetrabromide to give **5a**. The same sequence of reactions was also performed using TBS-Cl and imidazole as base to provide **7b** and then **5b** after bromination. The use of a TBS group instead of a benzyl (Bn) group allows discrimination between the OH of steroid backbone and the CH_2OH of the furanic moiety. It is thus possible to introduce molecular diversity at both C3 and C3′-positions of **1**.

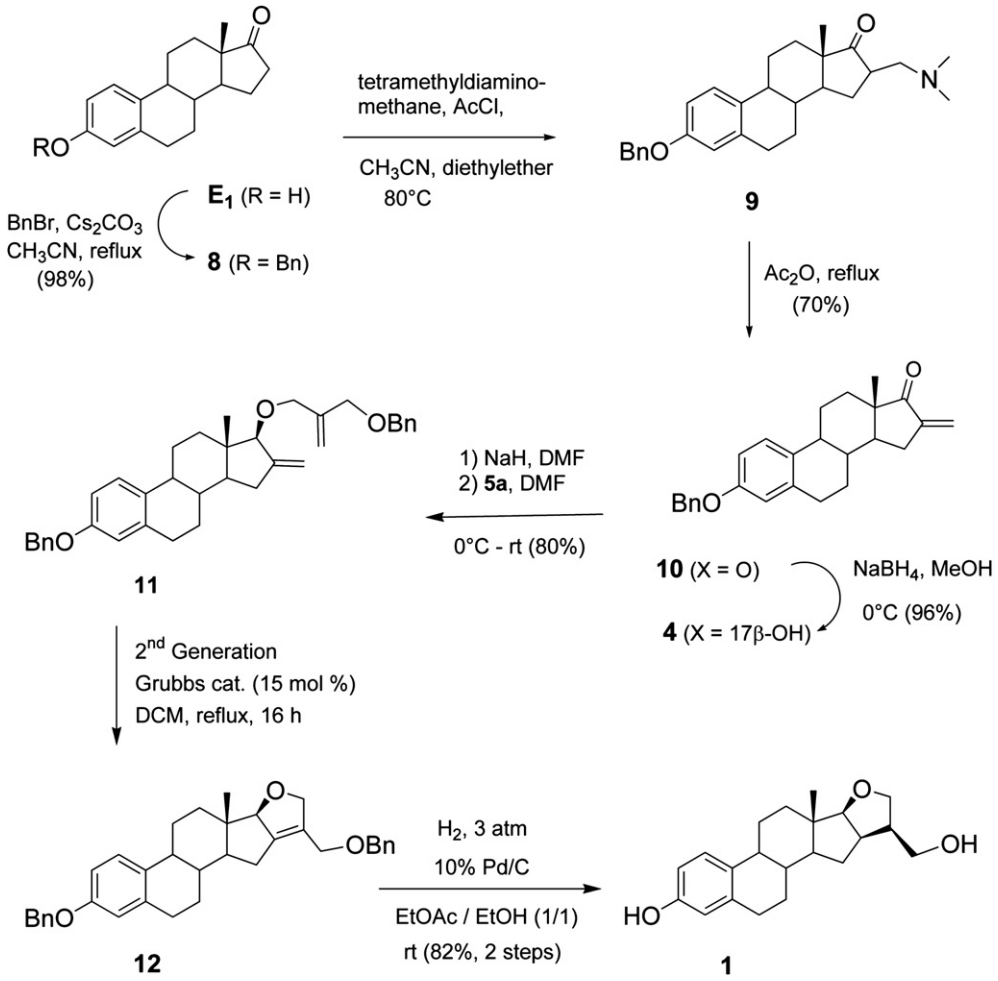
The intermediate **4** was easily synthesized in four steps from E_1 (Scheme 3). After a classical benzylation of E_1 into Bn-E_1 (**8**), the next step involved introducing a methylene group at C16, following known methodology that was previously reported for another E_1 derivative.[24] Bn-E_1 (**8**) is thus transformed to the Mannich base **9**, which in boiling acetic anhydride leads to 16-methylene derivative **10** in 70% yield for two steps. This conjugated ketone was treated with $NaBH_4$ to give 16-methylene-E_2 (**4**) and a small quantity (4–12%) of 16β-methyl-E_2, a side product resulting from both the carbonyl and double bond reductions. However, this amount of side product could be decreased or eliminated by using the Luche reduction conditions ($NaBH_4$, $CeCl_3$).[25] Furthermore, the reduction of the carbonyl at position 17 is well known to proceed stereoselectively due to the presence of the 18-CH_3 group on the β-face of the steroid nucleus.[20,22,23] Consequently, only the 17β-OH isomer **4** was observed.

The synthesis of **1** was performed in three steps starting from **4** (Scheme 3). The steroid **11** was first obtained in excellent yield by O-alkylation of the hydroxy group of **4** in presence of bromide **5a** and NaH. The unsaturated five-membered ring compound **12** was next generated from olefin **11** by a ring-closing metathesis (RCM).[26–28] In fact, producing a tetrasubstituted carbon–carbon double bond by RCM represents a challenge, but new ruthenium catalysts were recently reported to form tetrasubstituted olefins with increased efficacy.[29,30] We isolated the dihydrofuran **12** in 66% yield by using the commercially available second generation Grubbs catalyst. However, we found that it was more convenient to proceed with the double bond saturation rapidly. During this last step in the synthesis of **1**, the tetrasubstituted double bond of **12** was stereoselectively reduced and the two benzyl ether groups were cleaved using the same catalytic hydrogenation conditions (H_2, 3 atm). Thanks to the axial 18-CH_3 group on the steroid β-face, the two hydrogen atoms add to the double bond by the less hindered steroid α-face, thus providing the compound **1** with 16*R* and 2′*R*-configuration.

The 16*R* and 2′*R*-stereochemistry of furanic compound **1** was confirmed by NMR spectroscopy (NOESY) after establishing the assignment of key protons and carbons by COSY, HSQC, and HMBC experiments,[31] and comparison of data reported in literature for steroid compounds.[32,33] The *S*-configuration of H17 (α-H in steroid nomenclature) and *S*-configuration of C13 (β-orientation of CH_3-18) being well known, both NMR signals were used as starting point for structure elucidation using a NOESY experiment (Fig. 1). The NOESY spectrum showed an interaction between H17 and H16, thus setting the α-stereochemistry of H16. The *R*-configuration of H2′ was next confirmed by the presence of a NOE signal between H16 and H2′. These two protons are thus clearly on the same side of the furanic ring (α-steroid side) as expected by the mechanism of Pd-catalyzed hydrogenation. We also observed a NOE signal between the C18 and one methylenic H of 1′-CH_2O (1′β-H) and a NOE signal between 1′α-H and H2′. All the results discussed above confirm without a doubt the 2′*R*-stereochemistry and the presence of the 3′-CH_2OH group on the same β-steroid



Scheme 2. Synthesis of bromoolefin **5**.



Scheme 3. Synthesis of furanic compound **1**.

side than the CH_3-18. Interestingly, this isomer is the one, which was predicted to interact favorably with the enzyme in our preliminary docking study.

Furanic-estrane derivative **1** was evaluated for its ability to inhibit the transformation of labeled E_1 into E_2 catalyzed by 17β-HSD1. According to an established procedure using homogenized HEK-293 cells overexpressing the enzyme,[34] compound **1** was tested at two concentrations (0.1 and 1 μM) and showed inhibition of 55 and 70%, respectively. It was thus a more effective inhibitor than the natural substrate E_1 and the first generation of 17β-HSD1 inhibitor EM-251,[35] which gave 40 and 45% of inhibition at 0.1 μM, respectively. A docking experiment showed the presence of two key interactions between **1** and the enzyme (Fig. 2). Indeed, two hydrogen bonds are clearly apparent between the 3-OH and His_{221} and the 17β-O and Tyr_{155}, thus supporting the inhibitory activity produced by **1**.

To expand the scope of the straightforward sequence of reactions providing **1**, a different steroid scaffold was next tested. We selected androsterone (ADT), a C19-androstane nucleus previously reported as a lead compound for 17β-HSD3 inhibitors.[36,37] We therefore used the same chemical route as for the synthesis of **1** to afford the furanic-androstane derivative **20** with the desired 2′*R*-configuration (Scheme 4). The 16-methylene-3-*O*-TBS-ADT (**14**) was prepared from ADT similarly as described for **4** in 54% yield. This yield is lower than expected but is explained by the formation of 16-methylene-3-*O*-Ac-ADT (**15**) in 25% yield during the treatment in refluxing acetic anhydride. This side product was however easily transformed to **14** after hydrolysis of acetate and protection as a TBS ether. Reduction of **14** with $NaBH_4$ gave a 90% yield of the alcohol **16**. The next steps involve the 17-O-alkylation of **16** with primary bromide **5a** to give **17**, the ring-closing metathesis to obtain the unsaturated dihydrofuran **18**, and the catalytic hydrogenation to afford exclusively the isomer **19**. Finally, after cleavage of the TBS ether protective group in acidic solution, the chiral furanic-androstane compound **20** was successfully obtained. As described above for **1**, the NMR analysis of **20** demonstrated the *R*-configuration at C16 and C2′.

3. Conclusion

We have developed an efficient strategy for the preparation of furanic-steroid derivatives in three steps from a 16-methylenic steroid with an overall yield of 29%. Ring-closing metathesis and catalytic hydrogenation are the key steps in this synthesis. When using two different protective groups, the synthetic strategy allows us to introduce a molecular diversity at both C3 and C3′-positions, which are two locations playing a crucial role in maximizing interactions between steroidal derivatives and targeted enzymes, such as 17β-HSD1.[38,39] The strategy could also be used for the preparation of additional steroidal or non-steroidal furanic derivatives, thus extending our methodology to other families of therapeutic agents.

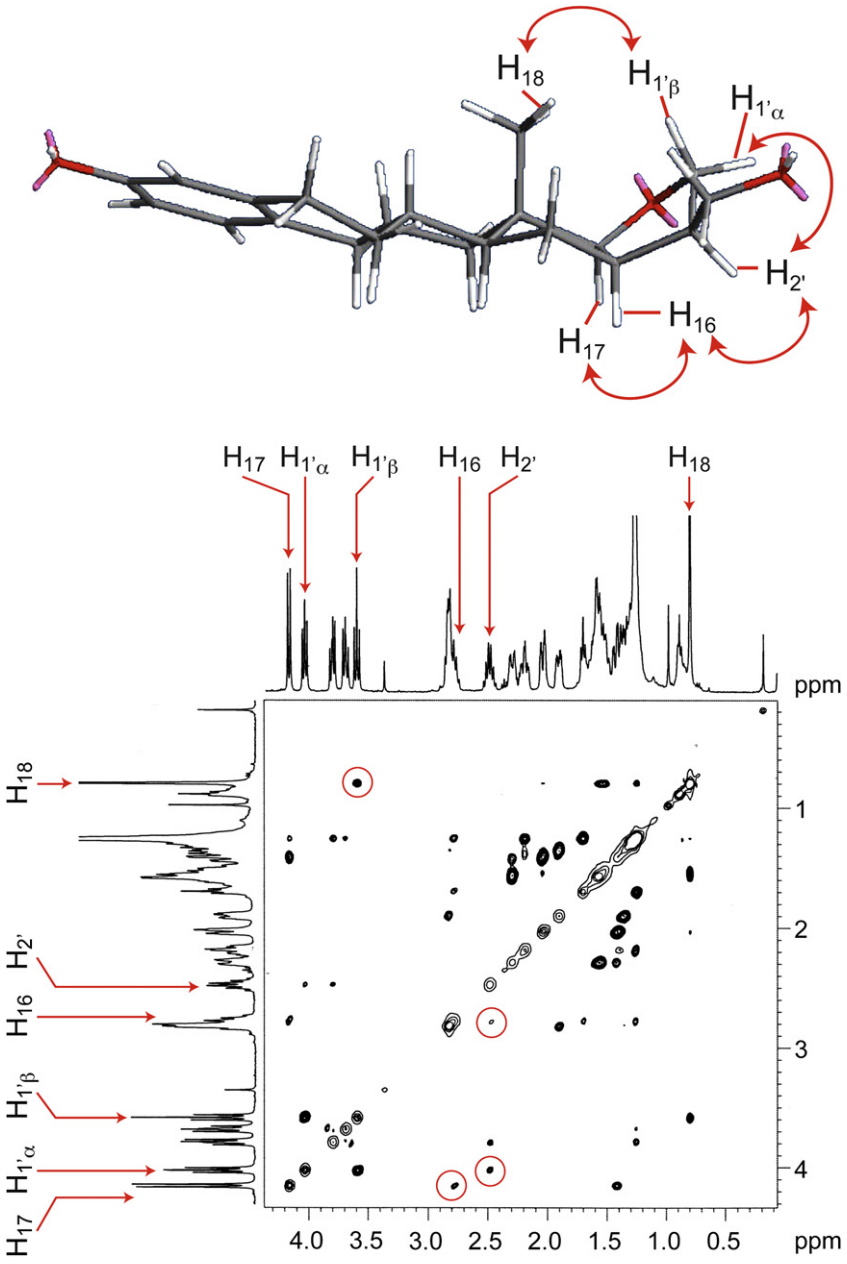


Fig. 1. Partial NOESY spectrum (0–4.3 ppm) obtained for **1** dissolved in $CDCl_3$.

4. Experimental

4.1. General remarks

Reagents were obtained from Sigma–Aldrich Canada Co. (Oakville, ON, Canada). Usual solvents were obtained from Fisher Scientific and VWR (Montréal, Qc, Canada) and were used as received. Anhydrous solvents were purchased from Aldrich and VWR in SureSeal bottles, which were conserved under positive argon pressure. All anhydrous reactions were performed in oven-dried glassware under positive argon pressure. Thin-layer chromatography (TLC) was performed on 0.25-mm silica gel 60 F_{254} plates (Whatman, Maidstone, England), and compounds were visualized by exposure to UV light (254 nM) and/or with a solution of ammonium heptamolybdate tetrahydrate (with heating). Flash chromatography was performed on Silicycle 60 (Québec, Qc, Canada) 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded with a Bruker AVANCE 400 spectrometer at 400 MHz. The chemical shifts (δ) are expressed in parts per million and referenced to chloroform (centered at 7.26 and 77.00 ppm), acetone (centered at 2.07 and 206.26 ppm) or dimethyl sulfoxide (centered at 2.49 and 39.50 ppm) for ^1H and ^{13}C, respectively. Low-resolution mass spectra (LRMS) were recorded with an LCQ Finnigan apparatus (San Jose, CA, USA) equipped with an atmospheric pressure chemical ionization (APCI) source on positive or negative mode. High-resolution mass spectra (HRMS) were provided by Pierre Audet from the Deptartment of Chemistry at Laval University (Québec, Qc, Canada).

4.2. Selective benzylation of diol 6 to give 7a

To a cooled solution of 2-methylene-propane-1,3-diol (**6**) (0.12 mmol) in dry THF (60 mL) was added NaH (60% in oil,

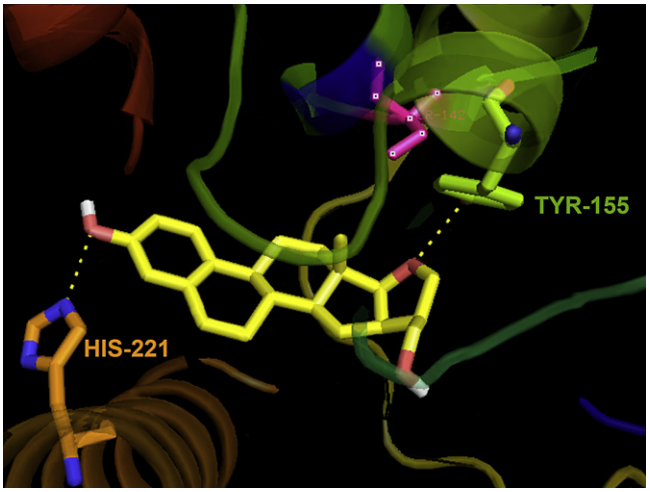


Fig. 2. Docking result obtained for furanic-estrane compound **1**.

0.12 mmol). After 2 h at 0 °C, benzyl bromide (0.15 mmol) was added and the mixture was stirred for 4 h at 0 °C. The reaction was then quenched at 0 °C with a saturated NH_4Cl aqueous solution and the mixture was extracted with EtOAc. The organic layers were combined and washed with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by flash chromatography (hexanes/EtOAc) to afford **7a**.

*4.2.1. 2-(Benzyloxymethyl)prop-2-en-1-ol (**7a**).* Yield=40%. ^{1}H NMR ($CDCl_3$): 2.20 (s, OH), 4.10 (s, CH_2OBn), 4.19 (s, CH_2OH), 4.52 (s, OCH_2Ph), 5.16 and 5.21 (2s, C=CH_2), 7.28–7.38 (m, OCH$_2$*Ph*). ^{13}C NMR ($CDCl_3$): 64.4, 71.7, 72.2, 113.5, 127.7 (4C), 128.4, 137.9, 144.9. LRMS for $C_{11}H_{15}O_2$ $(M+H)^+$: 178.9 *m*/*z*.

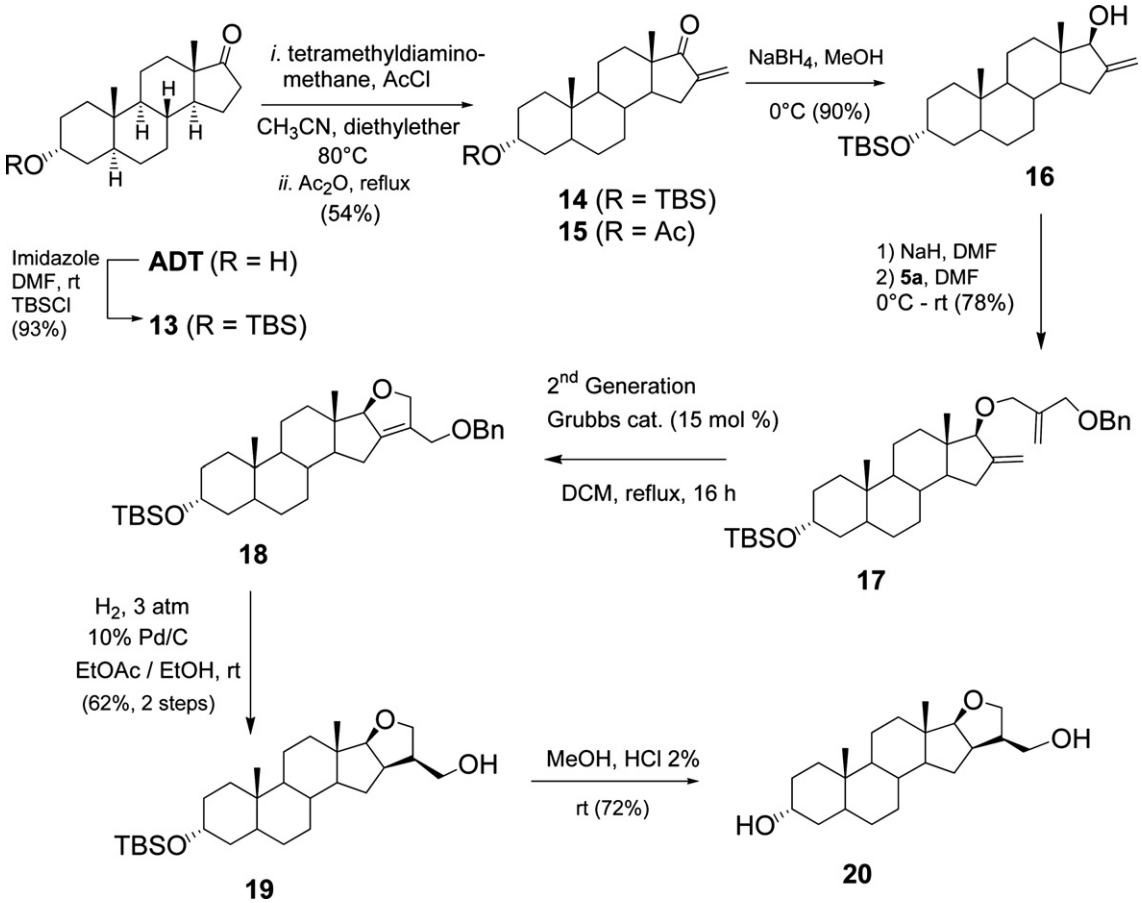
4.3. Bromination of 7a to give 5a

A solution of the alcohol **7a** (0.56 mmol), PPh_3 (1.11 mmol), and CBr_4 (1.11 mmol) in dry CH_2Cl_2 (15 mL) was stirred at 0 °C under argon. The reaction was monitored by TLC and was completed after 3 h. The crude mixture was purified by flash chromatography (hexanes/EtOAc) to give the bromide **5a**.

*4.3.1. ((2-(Bromomethyl)allyloxy)methyl)benzene (**5a**).* Yield=82%. ^{1}H NMR (acetone-d_6): 4.18 (s, CH_2Br, and CH_2OBn), 4.55 (s, OCH_2Ph), 5.32 and 5.43 (2s, C=CH_2), 7.30–7.50 (m, OCH$_2$*Ph*). ^{13}C NMR ($CDCl_3$): 33.0, 70.3, 72.4, 117.2, 127.7 (4C), 128.4, 137.9, 142.3. LRMS for $C_{11}H_{12}O^{79}Br$ $(M-H)^-$: 239.0 *m*/*z*. HRMS calcd for $C_{11}H_{12}{}^{79}Br$ $(M-[OH])^+$: 375.2319, found 375.2332.

4.4. General procedure for the synthesis of 16-methylene derivative of estrone and androsterone (compounds 10 and 14)

To a solution of *N*,*N*,*N*′,*N*′-tetramethyldiaminomethane (11.6 mmol) in diethylether (14.6 mL) was added, dropwise, a solution of acetyl chloride (11.6 mmol) in diethylether (11 mL). After 30 min of stirring, the precipitate was rapidly filtered off and suspended in acetonitrile (15 mL). Addition of 3-*O*-benzylestrone (**8**)[40] or 3-*O*-*tert*-butyldimethylsilyl androsterone (**13**)[41] (2.0 g) was followed by stirring at 80 °C for 12 h. After cooling, the solvent was evaporated under reduced pressure, the residue taken up in 1 N HCl (100 mL), and the mixture was extracted with diethylether. A



Scheme 4. Synthesis of furanic-androstane derivative **20**.

solution of 2 N NaOH was added dropwise (pH=11) and the mixture was extracted with diethylether. The solvent was evaporated under reduced pressure and the crude Mannich base was dissolved in acetic anhydride (6 mL) and refluxed at 140 °C for 12 h. After cooling, the reaction mixture was carefully dropped into a saturated $NaHCO_3$ solution (100 mL), stirred for another 15 min at 25 °C, and extracted with CH_2Cl_2. The organic layers were combined and washed with water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude material was purified by flash chromatography (hexanes/EtOAc) to give **10** or **14**.

*4.4.1. 3-(Benzyloxy)-16-methylideneestra-1(10),2,4-trien-17-one (**10**).* Yield=70%. ^{1}H NMR ($CDCl_3$): 0.94 (s, 18-CH_3), 1.30–2.50 (unassigned CH and CH_2), 2.70 (dd, J_1=6.2 Hz, J_2=15.5 Hz, 15α-CH), 2.91 (m, 6-CH_2), 5.05 (s, OCH_2Ph), 5.42 and 6.11 (2s, C=CH_2), 6.75 (d, J=2.3 Hz, 4-CH), 6.81 (dd, J_1=2.4 Hz, J_2=8.6 Hz, 2-CH), 7.22 (d, J=8.6 Hz, 1-CH), 7.30–7.45 (m, OCH_2*Ph*). ^{13}C NMR ($CDCl_3$): 14.2, 25.9, 26.7, 29.0, 29.6, 31.6, 37.8, 43.9, 47.7, 48.1, 69.9, 112.4, 114.9, 118.8, 126.3 (2C), 127.5, 127.9 (2C), 128.5, 132.3, 137.2, 137.7, 144.4, 156.9, 208.6. LRMS for $C_{26}H_{29}O_2$ $(M+H)^+$: 373.1 *m*/*z*. HRMS calcd for $C_{26}H_{29}O_2$ $(M+H)^+$: 373.2162, found 373.2161.

*4.4.2. (3α,5α)-3-{[tert-Butyl(dimethyl)silyl]oxy}-16-methylideneandrostan-17-one (**14**).* Yield=54%. ^{1}H NMR ($CDCl_3$): 0.01 (s, Si(CH_3)$_2$), 0.76 (s, 19-CH_3), 0.85 (s, 18-CH_3, and SiC(CH_3)$_3$), 0.80–2.20 (unassigned CH and CH_2), 2.52 (dd, J_1=6.4 Hz, J_2=15.5 Hz, 15α-CH), 3.93 (t, J=2.5 Hz, 3β-CH), 5.31 and 6.01 (2s, C=CH_2). ^{13}C NMR ($CDCl_3$): −4.9 (2C), 11.3, 14.1, 18.0, 20.0, 25.8 (3C), 28.3, 29.1, 29.6, 31.0, 31.5, 32.2, 34.5, 36.1, 36.6, 39.0, 47.9, 48.6, 54.3, 66.6, 118.2, 144.6, 208.8. LRMS for $C_{26}H_{45}O_2Si$ $(M+H)^+$: 417.0 *m*/*z*. HRMS: calcd for $C_{20}H_{29}O$ $(M-[TBSO])^+$: 285.2218, found 285.2220.

4.5. General procedure for the reduction of 17-ketone into 17β-hydroxy group (synthesis of 4 and 16)

$NaBH_4$ (0.85 mmol) was added to a cooled (0 °C) solution of **10** or **14** (0.5 mmol) in MeOH (12.7 mL) and CH_2Cl_2 (2.5 mL). After the mixture was stirred for 3–4 h at 0 °C, the reaction was quenched by addition of water and extraction was performed with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude material was purified by flash chromatography (hexanes/EtOAc) to afford **4** or **16** containing a small quantity (4 and 12% by NMR, respectively) of the product of double bond reduction (16-CH_3).

*4.5.1. (17β)-3-(Benzyloxy)-16-methylideneestra-1(10),2,4-trien-17-ol (**4**).* Yield=96%. ^{1}H NMR ($CDCl_3$): 0.73 (s, 18-CH_3), 1.20–2.40 (unassigned CH and CH_2), 2.50 (dd, J_1=7.5 Hz, J_2=16.5 Hz, 15α-CH), 2.88 (m, 6-CH_2), 4.01 (s, 17α-CH), 5.06 (s, OCH_2Ph), 5.10 and 5.21 (2s, C=CH_2), 6.75 (d, J=2.4 Hz, 4-CH), 6.82 (dd, J_1=2.6 Hz, J_2=8.5 Hz, 2-CH), 7.24 (d, J=8.5 Hz, 1-CH), 7.30–7.50 (m, OCH_2*Ph*). ^{13}C NMR ($CDCl_3$): 10.9, 26.3, 27.3, 29.7, 30.5, 36.4, 38.1, 43.3, 43.9, 46.8, 69.9, 83.9, 107.8, 112.2, 114.8, 126.2 (2C), 127.4, 127.8 (2C), 128.5, 132.7, 137.2, 137.8, 153.1, 156.7. LRMS for $C_{26}H_{31}O_2$ $(M+H)^+$: 375.2 *m*/*z*. HRMS calcd for $C_{26}H_{31}O_2$ $(M+H)^+$: 375.2319, found 375.2332.

*4.5.2. (3α,5α,17β)-3-{[tert-Butyl(dimethyl)silyl]oxy}-16-methylideneandrostan-17-ol (**16**).* Yield=90%. ^{1}H NMR ($CDCl_3$): 0.01 (s, Si(CH_3)$_2$), 0.65 (s, 18-CH_3), 0.76 (s, 19-CH_3), 0.88 (s, SiC(CH_3)$_3$), 0.80–2.00 (unassigned CH and CH_2), 2.33 (dd, J_1=7.5 Hz, J_2=16.4 Hz, 15α-CH), 3.87 (s, 17α-CH), 3.95 (t, J=2.4 Hz, 3β-CH), 5.00 and 5.12 (2s, C=CH_2). ^{13}C NMR ($CDCl_3$): −4.8 (2C), 11.0, 11.4, 18.1, 20.4, 25.9 (3C), 28.5, 29.7, 30.8, 31.7, 32.3, 35.0, 36.1, 36.5, 36.7, 39.0, 43.1, 47.9, 54.5, 66.8, 84.1, 107.4, 153.6. LRMS for $C_{26}H_{47}O_2Si$ $(M+H)^+$: 419.2 *m*/*z*. HRMS calcd for $C_{26}H_{47}O_2Si$ $(M+H)^+$: 419.3340, found 419.3331.

4.6. General procedure for O-alkylation of methylenic steroids (synthesis of 11 and 17)

To a cooled solution of alcohol **4** or **16** (0.267 mmol) in dry DMF (1 mL) was added NaH (60% in oil, 0.4 mmol). After 1 h at 0 °C, the solution of **5a** (0.267 mmol) in dry DMF (1.2 mL) was added and the mixture was stirred for 3 h at 0 °C. The reaction was then quenched at 0 °C with a saturated NH_4Cl aqueous solution and extracted with EtOAc. The organic layers were combined and washed with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was purified by flash chromatography (hexanes/EtOAc) to yield **11** or **17**.

*4.6.1. (17β)-3-(Benzyloxy)-17-({2-[(benzyloxy)methyl]prop-2-en-1-yl}oxy)-16-methylideneestra-1(10),2,4-triene (**11**).* Yield=80%. ^{1}H NMR ($CDCl_3$): 0.81 (s, 18-CH_3), 1.25–2.40 (unassigned CH and CH_2), 2.45 (dd, J_1=7.4 Hz, J_2=16.4 Hz, 15α-CH), 2.88 (m, 6-CH_2), 3.84 (s, 17α-CH), 4.14 (s, CH_2OBn), 4.22 and 4.33 (2d, J=12.5 Hz, OCH_2C=CH_2), 4.57 (s, OCH_2Ph of side chain), 5.06 (s, OCH_2Ph at position 3), 5.06 and 5.21 (2s, C=CH_2 at C16), 5.28 and 5.32 (2s, C=CH_2 of side chain), 6.75 (d, J=2.4 Hz, 4-CH), 6.82 (dd, J_1=2.6 Hz, J_2=8.6 Hz, 2-CH), 7.23 (d, J=8.6 Hz, 1-CH), 7.30–7.50 (m, 2×CH_2*Ph*). ^{13}C NMR ($CDCl_3$): 11.7, 26.5, 27.2, 29.7, 30.4, 38.0, 38.1, 43.6, 43.7, 47.1, 69.9, 70.9, 71.8, 72.2, 90.5, 108.5, 112.3, 114.3, 114.8, 126.2 (2C), 127.4 (2C), 127.6, 127.7 (2C), 127.8, 128.3 (2C), 128.5, 132.7, 137.3, 137.9, 138.3, 143.1, 150.3, 156.7. LRMS for $C_{37}H_{41}O_3$ $(M-H)^-$: 533.6 *m*/*z*.

*4.6.2. (3α,5α,17β)-17-({2-[(Benzyloxy)methyl]prop-2-en-1-yl}oxy)-3-{[tert-butyl(dimethyl)silyl] oxy}-16-methylideneandrostane (**17**).* Yield=78%. ^{1}H NMR ($CDCl_3$): 0.06 (s, Si(CH_3)$_2$), 0.76 (s, 19-CH_3), 0.80 (s, 18-CH_3), 0.93 (s, SiC(CH_3)$_3$), 0.90–2.00 (unassigned CH and CH_2), 2.33 (dd, J_1=7.4 Hz, J_2=16.6 Hz, 15α-CH), 3.74 (s, 17α-CH), 4.00 (s, 3β-CH), 4.12 (s, CH_2OBn), 4.18 and 4.30 (2d, J=12.5 Hz, OCH_2C=CH_2), 4.54 (s, OCH_2Ph of side chain), 5.01 and 5.16 (2s, C=CH_2), 5.25 and 5.29 (2s, C=CH_2 of side chain), 7.25–7.40 (m, CH_2*Ph*). ^{13}C NMR ($CDCl_3$): −4.8 (2C), 11.3, 11.7, 18.0, 20.5, 25.8 (3C), 28.4, 29.6, 30.6, 31.6, 32.3, 34.8, 36.0, 36.7, 38.0, 39.0, 43.4, 48.0, 54.2, 66.7, 70.8, 71.7, 72.1, 90.5, 108.1, 114.1, 127.5, 127.6 (2C), 128.3 (2C), 138.2, 143.1, 150.6. LRMS for $C_{37}H_{59}O_3Si$ $(M+H)^+$: 579.2 *m*/*z*.

4.7. General procedure for the ring-closing metathesis and catalytic hydrogenation (synthesis of 1 and 19)

To a solution of diene **11** or **17** (0.80 mmol) in dry CH_2Cl_2 (12 mL) was added second generation Grubbs catalyst (tricyclohexylphosphine[1,3-bis(2,4,6-tri-methylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidine] ruthenium(IV)dichloride) (0.12 mmol). This mixture was refluxed overnight, then filtered through Celite and the solvent evaporated under reduced pressure to give the crude alkene **12** or **18**. A suspension of crude **12** or **18** (0.37 mmol) and 10% Pd–C (0.07 mmol) in EtOAc/EtOH: 1/1 (14 mL) was hydrogenated at 3–4 atm for 16 h. After filtration through Celite, the solvent was removed under reduced pressure and purification by flash chromatography (hexanes/EtOAc) afforded **1** or **19**.

*4.7.1. (4bS,6aS,6bS,9R,9aR,10aS,10bR)-9-(hydroxymethyl)-6a-methyl-5,6,6a,6b,8,9,9a,10,10a,10b,11,12-dodecahydro-4bH-naphtho[2′,1′:4,5]indeno[1,2-b]furan-2-ol (**1**).* Yield=82%. ^{1}H NMR ($CDCl_3$): 0.79 (s, 18-CH_3), 1.20–2.35 (unassigned CH and CH_2), 2.46 (m, 2′-CH), 2.80 (m, 6-CH_2, and 16-CH), 3.58 (t, J=8.8 Hz, 1′α-CH), 3.68 and 3.79 (2m, 3′-CH_2O), 4.02 (dd, J_1=7.4 Hz, J_2=8.7 Hz, 1′β-CH), 4.15 (d, J=9.0 Hz, 17α-CH), 4.80 (br, OH), 6.55 (d, J=2.6 Hz, 4-CH), 6.63 (dd, J_1=2.7 Hz, J_2=8.4 Hz, 2-CH), 7.14 (d, J=8.4 Hz, 1-CH). ^{13}C NMR

($CDCl_3$): 12.4, 25.4, 26.6, 27.8, 29.6, 37.9, 38.3, 43.3, 43.6, 44.3, 44.6, 53.5, 62.0, 72.8, 93.6, 112.7, 115.2, 126.5, 132.7, 138.1, 153.3. LRMS for $C_{21}H_{29}O_3$ $(M+H)^+$: 329.2 *m/z*. HRMS calcd for $C_{21}H_{29}O_3$ $(M+H)^+$: 329.2111, found 329.2113.

*4.7.2. [(2R,4aS,4bS,6aS,6bS,9aR,9R,10aS,10bR,12aS)-2-{[tert-Butyl(dimethyl)silyl]oxy}-4a,6a-dimethyloctadecahydro-1H-naphtho[2′,1′:4,5]indeno[1,2-b]furan-9-yl]methanol (**19**).* Yield=62%. ^1H NMR ($CDCl_3$): 0.01 (s, $Si(CH_3)_2$), 0.73 (s, 19-CH_3), 0.75 (s, 18-CH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.90–2.35 (unassigned CH and CH_2), 2.40 (m, 2′-CH), 2.70 (m, 16-CH), 3.55 (t, *J*=8.4 Hz, 1′α-CH), 3.63 and 3.74 (2m, 3′-CH_2O), 3.94 (s, 3β-CH), 3.98 (t, *J*=8.4 Hz, 1′β-CH), 4.05 (d, *J*=9.0 Hz, 17α-CH). ^{13}C NMR ($CDCl_3$): −5.0 (2C), 11.3, 12.3, 18.0, 20.6, 25.8 (3C), 26.1, 28.4, 29.6, 32.2, 34.5, 34.7, 35.9, 36.6, 38.3, 38.9, 43.2, 44.0, 44.5, 54.1, 54.4, 61.6, 66.7, 72.8, 93.6. LRMS for $C_{28}H_{51}O_3Si$ $(M+H)^+$: 463.3 *m/z*.

4.8. Hydrolysis of silylated ether 19 (synthesis of 20)

The silylated ether **19** was dissolved in a methanolic solution of HCl (2%, v/v) and the mixture was stirred at room temperature for 3 h. Water was added, the methanol evaporated under reduced pressure and the residue extracted with EtOAc. The organic layers were combined and washed with a saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography (hexanes/EtOAc) to give the furanic-androstane product **20**.

*4.8.1. (2R,4aS,4bS,6aS,6bS,9aR,9R,10aS,10bR,12aS)-9-(Hydroxymethyl)-4a,6a-dimethyloctadeca hydro-1H-naphtho[2′,1′:4,5]indeno[1,2-b]furan-2-ol (**20**).* Yield=72%. ^1H NMR (DMSO-d_6): 0.65 (s, 19-CH_3), 0.72 (s, 18-CH_3), 0.80–2.35 (unassigned CH and CH_2), 2.55 (m, 16-CH), 3.36 (m, 1′α-CH and 1H of 3′-CH_2O), 3.47 (m, 1H of 3′-CH_2O), 3.80 (m, 1′β-CH and OH), 3.88 (d, *J*=9.0 Hz, 17α-CH), 4.16 (d, *J*=2.3 Hz, 3β-CH), 4.47 (t, *J*=4.6 Hz, OH). ^{13}C NMR (DMSO-d_6): 11.2, 12.5, 20.3, 25.3, 28.3, 28.7, 32.0, 32.1, 34.3, 35.8 (2C), 38.1, 38.6, 43.0, 43.7, 44.1, 53.9, 54.0, 59.9, 64.1, 72.6, 92.8. LRMS for $C_{22}H_{37}O_3$ $(M+H)^+$: 349.1 *m/z*. HRMS calcd for $C_{22}H_{36}O_3Na$ $(M+Na)^+$: 371.2557, found 371.2577.

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Supplementary data

^1H NMR, COSY, APT, and HSQC spectra of furanic-estrane **1**, NMR spectra of furanic-androstane **20**, and NMR spectra of intermediate compounds **7a**, **5a**, **10**, **14**, **4**, **16**, **11**, **17**, and **19**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.01.083.

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