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ScienceDirect
Tetrahedron 63 (2007) 4630–4635
Tetrahedron

A new route to stereoselective construction of 6β,7β-methylene unit from androst-5-en-7-one

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Received 30 December 2006; revised 16 March 2007; accepted 19 March 2007
Available online 21 March 2007

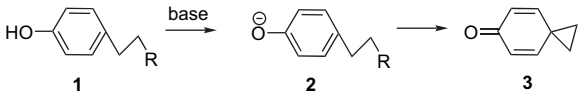
Abstract—By extending the Winstein cyclization method to the steroid system, we developed a simple and efficient method for highly stereoselective construction of 6β,7β-methylene unit. This method involves an initial Grignard reaction with the 7-carbonyl group of 3β,17β-bis(*tert*-butyldimethylsilyloxy)androst-5-en-7-one (**8**) and then stereoselective reduction of the tertiary alcohol followed by a tandem oxidation/cyclopropanation reaction. The excellent yield, high stereoselectivity, and relatively mild reaction conditions should make this an attractive method for the preparation of 6β,7β-methylene derivatives in steroid.

1. Introduction

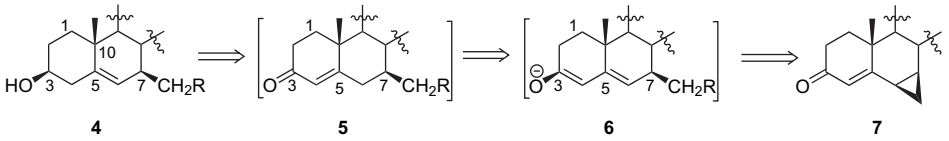
In steroid, 6β,7β-methylene unit represents a key substructure of many biologically active natural products and medicinal entities.[1] Various methods have been developed for the construction of this 6β,7β-methylene unit. Most commonly used are methylenation of the $\Delta^{6,7}$-unsaturated bond with Corey reagent,[2] Simmons–Smith reagent,[3] or diazomethane.[4] Although these developments have allowed accessing to the construction of 6β,7β-methylene structure, few syntheses have been stereoselective, with good yield.

The Winstein cyclization,[5] which represents Ar-3′ spirocyclization of the structure with 2-*p*-hydroxyphenyl-1-ethyl halides under basic condition, has been widely studied and established as an useful method for the construction of the cyclopropylcyclohexadienones[6] (Scheme 1, path A). Based on our earlier studies,[7] we found that it might be possible to extend the Winstein cyclization method to the steroid

Path A: Winstein Cyclization (R=halides):



Path B: Extending of Winstein Cyclization to Steroids (R=halides):



Scheme 1.

Keywords: Winstein cyclization; Stereoselective; Synthesis; 6β,7β-Methylene unit.
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0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.110

system by constructing the 7β-halidemethylene-3,5-diene-3-ol **6** structure as outlined in path B of Scheme 1. Taking into account the instability of the enolate, we expected it to be a tandem reaction by enolization of compound **5**, which was generated in situ, followed by a cyclopropanation reaction. The key intermediate 7β-halidemethyl-5-ene-3-ol **4** could be synthesized by stereoselective reduction of 7-tertiary alcohol. Herein, we report the details of this synthesis.

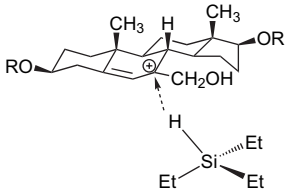


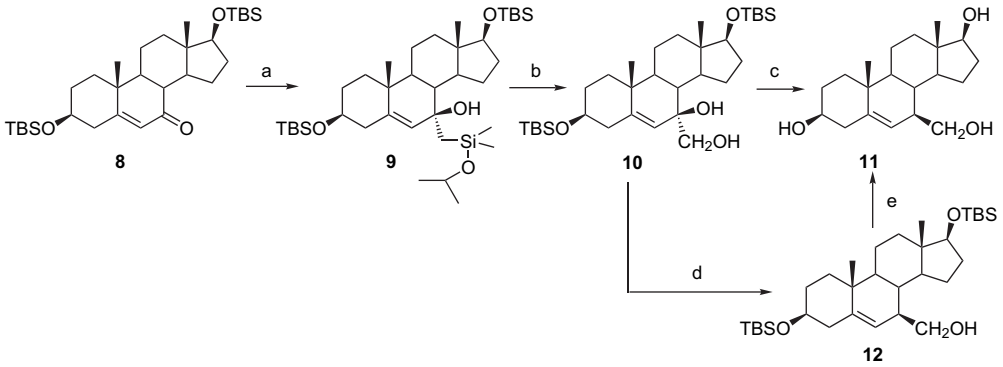
Figure 1. Plausible intermediate for ionic hydrogenation reduction, R=OH or TBS.

2. Results and discussion

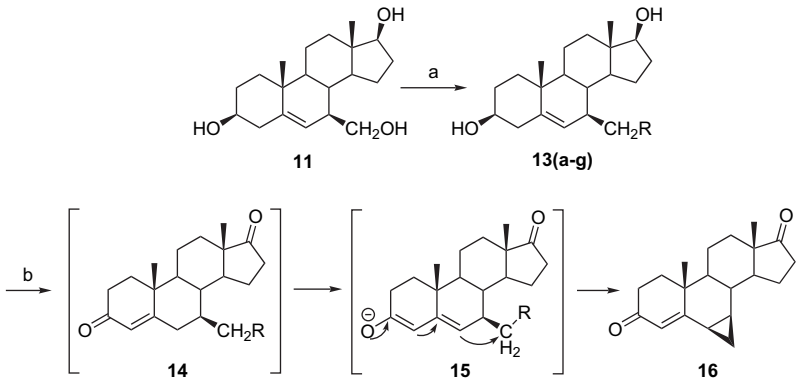
Our synthesis began with the preparation of 7α-hydroxymethyl-5-androsten-7β-ol (**10**), a model tertiary alcohol needed for further stereoselective reduction, using 3β,17β-bis(*tert*-butyldimethylsilyloxy)-5-androsten-7-one (**8**) as the starting material (Scheme 2).[7a] When compound **8** was treated with isopropoxydimethylsilylmethylmagnesium chloride[8] in THF at 0 °C, nucleophilic addition proceeded smoothly providing β-hydroxysilane intermediate **9**, which, without purification, was subjected to oxidative cleavage of the corresponding Si–C bond by potassium fluoride and 30% hydrogen peroxide to give 1,2-diol **10** as a single stereoisomer. We then turned our attention to the stereoselective reduction of 7-tertiary alcohol **10**. Ionic hydrogenation,[9] which was an effective method to reduce tertiary alcohols and has been used in many organic synthetic procedures,[10] was chosen as our first reduction system. Treatment of **10** with $BF_3\cdot Et_2O$ and Et_3SiH in CH_2Cl_2 at 0 °C for 10 min stereoselectively gave 7β-hydroxymethyl-3,17-deprotection compound **11** as the sole product, no byproduct such as 7α-isomer was found. The plausible mechanism may be that the relatively bulky triethylsilane attacking the less hindered α face of the in situ produced 7-carbocation to give the desired 7β-hydroxymethyl-5-androstene (**11**) (Fig. 1).

Considering about the harsh reaction condition utilized in the ionic hydrogenation reduction (incompatible with many groups such as cyclopropane[9a]), we explored another more mild reduction system for stereoselective reduction of 7-tertiary alcohol, which is important for our further research on the synthesis of 6β,7β-methylene derivatives in steroid. The $ZnI_2/NaBH_3CN$ system[11] has been reported as a mild reagent for the reduction of tertiary alcohols. Therefore, we treated our model tertiary alcohol **10** with standard $ZnI_2/NaBH_3CN$ reduction condition. Fortunately, we found that it was a clean and stereoselective reaction giving 3β,17β-bis(*tert*-butyldimethylsilyloxy)-7β-hydroxymethyl-5-androstene **12** as the sole product in 65% isolated yield (98% based on recovered starting material). This reduction condition was mild and compatible with many sensitive groups such as cyclopropane, which should make it a complement to ionic hydrogenation reduction system while the synthesis of 6β,7β-methylene unit in sterid. Deprotection of the TBS group was achieved with TBAF to give **11** in 99% yield.

With 7β-configuration derivative in hand, we set out to realize our intended Winstein cyclization. According to the literature reports,[5,6] we chose chloride as the leaving group. We changed the basic reaction condition of Winstein cyclization into Oppenauer oxidation[12] condition just because it could oxidize the 3-hydroxy group to carbonyl **14**, an important intermediate for our enolation procedure. Selective mesylation of the primary alcohol **11** followed by chlorination with LiCl in refluxing DMF gave **13a** in 82% yield (two steps, Scheme 3). To our satisfaction, the tandem oxidation/cyclopropanation reaction of **13a** was carried out in the presence of $Al(O\text{-}i\text{-}Pr)_3$ and cyclohexanone in refluxing toluene to cleanly afford the desired 6β,7β-methylene-4-androsten-3,17-dione **16** in 58% yield (Table 1, entry 1). We also investigated the influence of some other commonly used leaving groups (R) on the yield of compound **16** (Table 1). To our surprise, we found that when the sulfonates were used as the leaving group (entries 4–6), higher yields of cyclopropanation was obtained and shorter reaction steps were employed than that of halides (entries 1–3). The best result was achieved when the methylsulfonyl group was used as the leaving group (**13d**, entry 4), which gave compound **16** in 78% yield. The relative configuration of **16** was determined by ROESY studies and X-ray crystallography (Fig. 2).



Scheme 2. Reagents and conditions: (a) $Me_2(i\text{-}PrO)SiCH_2Cl$, Mg, THF, 0 °C; (b) KF, $KHCO_3$, 30% H_2O_2, THF, MeOH, rt (84% for two steps); (c) Et_3SiH, $BF_3\cdot Et_2O$, CH_2Cl_2, 0 °C, 96%; (d) ZnI_2, $NaBH_3CN$, 1,2-dichloroethane, rt, 65% (98% based on recovered starting material); (e) TBAF, THF, 99%.



Scheme 3. Reagents and conditions: (a) **13a** (R=Cl): (1) MsCl, collidine, THF, 0 °C; (2) LiCl, DMF, reflux, 82% (two steps); **13b** (R=Br): (1) MsCl, collidine, THF, 0 °C; (2) NaBr, DMF, reflux, 78% (two steps); **13c** (R=I): (1) MsCl, collidine, THF, 0 °C; (2) NaI, acetone, reflux, 87% (two steps); **13d** (R=OMs): MsCl, collidine, THF, 0 °C; 99%; **13e** (R=*p*-TsO–): *p*-TsCl, Py, 0 °C, 98%; **13f** (R=$C_6H_5SO_3$–): benzenesulfonyl chloride, Py, 0 °C, 97%; **13g** (R=OAc): Ac_2O, Py, 0 °C, 98%; (b) Al(O-*i*-Pr)$_3$, cyclohexanone, toluene, reflux.

Table 1. Influence of the leaving group on the course of the cyclopropanation reaction

Entry	Substrate	R (leaving group)	**16** yield[a] (%)
1	**13a**	Cl	58
2	**13b**	Br	62
3	**13c**	I	61
4	**13d**	–OMs	78
5	**13e**	*p*-TsO–	71
6	**13f**	$C_6H_5SO_3$–	68
7	**13g**	–OAc	No **16** was detected

[a] Isolated yield after silica gel chromatography.

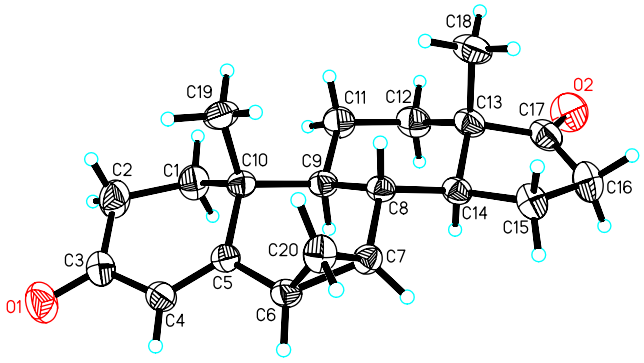


Figure 2. X-ray crystallographic structure of **16**.

3. Conclusions

In conclusion, we have successfully extended the Winstein cyclization method to the steroid system for the construction of 6β,7β-methylene unit, and further developed two methods for stereoselective introduction of β-RCH_2 (R=leaving group) group at the C-7 position of 5-androstene. This method would be applicable to the synthesis of other members of the 6β,7β-methylene family in steroid.

4. Experimental

4.1. General

Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. Elemental analysis was performed on a Carlo Erba 1106 instrument. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco-Dip-181 polarimeter. IR spectra were recorded on a Nicollet Magna FTIR-750 spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were run on a Bruker AM-400 spectrometer using tetramethylsilane as the internal standard (chemical shifts in δ parts per million). Splitting patterns are designated as 's, d, t, q, and m', these symbols indicate 'singlet, doublet, triplet, quartet, and multiplet', respectively. Silica gel 60H (200–300 mesh) manufactured by Qing-dao Haiyang Chemical Group Co. (China) was used for flash chromatography.

4.2. 3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7α-hydroxymethyl-5-androsten-7β-ol (10)[7b]

A solution of **8** (0.533 g, 1.0 mmol) in THF (6.0 mL) was added to the Grignard reagent [prepared from chloromethyldimethylisopropoxysilane (0.627 mL, 3.5 mmol), 1,2-dibromoethane (two drops), and Mg (0.096 g, 4.0 mmol) in THF (4.0 mL) according to the Tamao's procedure[8]] under Ar atmosphere. After stirring at 0 °C for 2 h, the mixture was quenched with an aqueous NH_4Cl solution (10%) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated at 0 °C to give an unstable single adduct as colorless oil. To a stirred mixture of colorless crude adduct, MeOH (5.0 mL), THF (5.0 mL), $KHCO_3$ (0.150 g, 1.5 mmol), and KF (0.282 g, 3.0 mmol) was added H_2O_2 (30%, 0.5 mL, 5.0 mmol) at room temperature. The mixture was stirred at room temperature until starting material disappeared. An aqueous $Na_2S_2O_3$ solution (50%) was added slowly to the mixture and stirred until a negative starch/iodide test was observed. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (25% EtOAc/PE) to provide compound **10** (0.478 g, 84%) as white solid: $[\alpha]_D^{20}$ −28 (*c* 0.93, acetone); mp 148–152 °C (lit.[7b] mp 148–150 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 5.28 (s, 1H), 3.63–3.55 (m,2H), 3.51 (d, *J*=3.6 Hz, 2H), 1.04 (s, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.71 (s, 3H), 0.05 (s, 6H), 0.03 (d, *J*=3.0 Hz, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 142.2, 129.1, 81.8, 73.7, 72.6, 66.6, 46.4,

44.3, 43.9, 42.9, 42.5, 37.5, 37.4, 36.9, 32.5, 31.3, 27.0, 25.8, 21.1, 18.8, 18.2, 18.2, 10.9, −4.6, −4.7, −5.0; IR (KBr) 3429, 2955, 2933, 2856, 1637 cm^{-1}; MS (EI) *m/z* (%) 564 (M^+, <1), 533 (100), 489 (38), 265 (22), 75 (39). Anal. Calcd for $C_{32}H_{60}O_4Si_2$: C, 68.03; H, 10.70. Found: C, 68.09; H, 10.98.

4.3. 3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7β-hydroxymethyl-5-androstene (12)

To a solution of **10** (0.113 g, 0.2 mmol) in 1,2-dichloroethane (5.0 mL) at room temperature were added zinc iodide (0.128 g, 0.4 mmol) and sodium cyanoborohydride (0.101 g, 1.6 mmol). The reaction mixture was stirred at room temperature for 12 h, and filtered through a pad of Celite. The Celite was washed with EtOAc. The combined filtrate was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (10% EtOAc/PE) to provide compound **12** (0.071 g, 65%) with recovery of the starting material **10** (0.037 g). Compound **12**: $[\alpha]_D^{24}$ −10 (*c* 0.77, $CHCl_3$); mp 138–139 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.19 (s, 1H), 3.69–3.58 (m, 1H), 3.57–3.39 (m, 3H), 0.98 (s, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.73 (s, 3H), 0.05 (d, *J*=3.9 Hz, 6H), 0.00 (d, *J*=3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.8, 123.0, 81.4, 72.1, 65.5, 51.8, 50.9, 44.3, 44.0, 42.7, 37.3, 37.2, 35.9, 32.4, 32.1, 30.9, 29.7, 25.9, 25.8, 21.2, 19.3, 18.1, 11.6, −4.5, −4.6, −4.8; IR (KBr) 3386, 2929, 2856, 1471 cm^{-1}; MS (EI) *m/z* (%) 548 (M^+, <1), 491 (100), 267 (53), 75 (38); HRMS (EI) calcd for $C_{32}H_{60}Si_2O_3$: 548.4081 (M^+), found: 548.4075.

4.4. 3β,17β-Dihydroxy-7β-hydroxymethyl-5-androstene (11)[7b]

4.4.1. Method A. To a solution of **10** (0.113 g, 0.2 mmol) and Et_3SiH (0.2 mL, 1.2 mmol) in dry CH_2Cl_2 (5.0 mL) was added fresh distilled $BF_3{\cdot}Et_2O$ (1.23 mL, 10.0 mmol) at 0 °C and stirred for 10 min. The mixture was quenched with an aqueous Na_2CO_3 solution (10%) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (EtOAc/PE=3:1) to provide compound **11** (0.061 g, 96%) as white solid.

4.4.2. Method B. To a solution of **12** (0.110 g, 0.2 mmol) in THF (4.0 mL) was added TBAF (1 M in THF, 1.0 mL, 1.0 mmol). The reaction mixture was stirred at room temperature for 12 h and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (EtOAc/PE=3:1) to provide compound **11** (0.063 g, 99%) as white solid. Compound **11**: $[\alpha]_D^{20}$ −15 (*c* 1.13, MeOH); mp 181–183 °C (lit.[7b] mp 181–183 °C); ^1H NMR (CD_3OD, 400 MHz) δ 5.38 (s, 1H), 3.68 (dd, *J*=10.8, 3.2 Hz, 1H), 3.55 (t, *J*=8.0 Hz, 1H), 3.36–3.44 (m, 1H), 3.22 (dd, *J*=7.2, 3.2 Hz, 1H), 1.00 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 143.8, 126.2, 82.7, 72.5, 67.0, 54.1, 52.9, 46.1, 45.3, 43.5, 39.0, 38.8, 37.4, 34.8, 33.0, 31.2, 27.3, 22.9, 20.1, 12.4; IR (KBr) 3311, 2928, 2874, 1635 cm^{-1}; MS (EI) *m/z* (%) 320 (M^+, 4), 302 (4), 289 (76), 271 (100), 253 (82), 159 (48) 91 (35). Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.53; H, 10.19.

4.5. 3β,17β-Dihydroxy-7β-methanesulfonyloxymethyl-5-androstene (13d)

At 0 °C, fresh distilled collidine (0.089 mL, 0.669 mmol) was added to a solution of **11** (0.107 g, 0.334 mmol) in THF (3.0 mL) followed by the addition of methanesulfonyl chloride (0.031 mL, 0.401 mmol). The reaction mixture was allowed to warm up slowly to room temperature and stirred for 2 h. The mixture was treated with saturated aqueous solution of Na_2CO_3 and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (EtOAc/PE=3:1) to provide compound **13d** (0.132 g, 99%) as white solid: $[\alpha]_D^{22}$ +23 (*c* 1.05, MeOH); mp 102–103 °C; ^1H NMR (acetone-d_6, 400 MHz) δ 5.28 (s, 1H), 4.38–4.33 (dd, *J*=9.6, 3.1 Hz, 1H), 4.00–3.95 (dd, *J*=9.7, 6.7 Hz, 1H), 3.58–3.53 (dd, *J*=9.3, 8.3 Hz, 1H), 3.44–3.36 (m, 1H), 3.07 (s, 1H), 1.00 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (acetone-d_6, 100 MHz) δ 144.5, 122.3, 80.8, 73.7, 70.6, 52.3, 51.2, 44.1, 42.5, 41.8, 37.5, 37.3, 36.8, 36.2, 33.4, 32.0, 30.4, 25.8, 21.5, 19.0, 11.4; IR (KBr) 3475, 3251, 2933, 2866, 1657, 1466 cm^{-1}; MS (EI) *m/z* (%) 398 (M^+, <1), 380 (6), 302 (100), 284 (86), 271 (56); HRMS (EI) calcd for $C_{21}H_{34}O_5S$: 398.2127 (M^+), found: 398.2145.

4.6. 3β,17β-Dihydroxy-7β-chloromethyl-5-androstene (13a)

To a solution of **13d** (0.100 g, 0.251 mmol) in DMF (3.0 mL) was added LiCl (0.046 g, 0.754 mmol). The resulting suspension was refluxed for 2 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (50% EtOAc/PE) to provide compound **13a** (0.071 g, 83%) as white solid: $[\alpha]_D^{25}$ +2 (*c* 0.85, $CHCl_3$); mp 135–136 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.26 (s, 1H), 3.70–3.58 (m, 2H), 3.57–3.39 (m, 2H), 1.00 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.0, 123.1, 81.0, 70.9, 51.5, 50.3, 49.5, 43.5, 41.7, 36.8, 36.5, 35.6, 34.0, 31.3, 30.1, 26.7, 25.5, 20.9, 18.8, 11.1; IR (KBr) 3365, 2939, 1716, 1668 cm^{-1}; MS (EI) *m/z* (%) 338 (M^+, 13), 320 (30), 271 (100), 253 (60); HRMS (EI) calcd for $C_{20}H_{31}ClO_2$: 338.2013 (M^+), found: 338.2015.

4.7. 3β,17β-Dihydroxy-7β-bromomethyl-5-androstene (13b)

To a solution of **13d** (0.100 g, 0.251 mmol) in DMF (3.0 mL) was added NaBr (0.078 g, 0.754 mmol). The resulting suspension was refluxed for 2 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (50% EtOAc/PE) to provide compound **13b** (0.076 g, 79%) as white solid: $[\alpha]_D^{24}$ +4 (*c* 0.56, $CHCl_3$); mp 146–147 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.20 (s, 1H), 3.68–3.58 (m, 1H), 3.57–3.42 (m, 2H), 3.39–3.30 (m, 1H), 1.01 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.1, 123.8, 81.0, 70.9, 51.5, 50.3, 43.6, 43.2, 41.7, 36.9, 36.6, 35.7, 35.3, 31.4, 30.1,

26.7, 25.5, 21.0, 18.9, 11.1; IR (KBr) 3396, 2937, 1718, 1666 cm^{-1}; MS (EI) *m/z* (%) 382 (M^+, 7), 364 (5), 285 (100), 271 (67), 267 (46), 253 (43); HRMS (EI) calcd for $C_{20}H_{31}BrO_2$: 382.1508 (M^+), found: 382.1516.

4.8. 3β,17β-Dihydroxy-7β-iodomethyl-5-androstene (13c)

To a solution of **13d** (0.100 g, 0.251 mmol) in acetone (8.0 mL) was added NaI (0.141 g, 0.754 mmol). The resulting suspension was refluxed for 2 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (50% EtOAc/PE) to provide compound **13c** (0.095 g, 88%) as white solid: $[\alpha]_D^{25}$ +17 (*c* 0.52, $CHCl_3$); mp 163–164 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.09 (s, 1H), 3.64–3.57 (t, *J*=8.6 Hz, 1H), 3.56–3.46 (m, 1H), 3.37–3.31 (dd, *J*=9.4, 2.4 Hz, 1H), 3.20–3.26 (dd, *J*=9.5, 5.7 Hz, 1H), 1.05 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.0, 125.5, 81.2, 71.0, 51.4, 50.2, 43.6, 42.4, 41.7, 37.4, 36.9, 36.6, 35.9, 31.4, 30.2, 25.4, 21.0, 19.2, 17.9, 11.2; IR (KBr) 3377, 2935, 1637, 1452 cm^{-1}; MS (EI) *m/z* (%) 430 (M^+, 10), 303 (30), 285 (100), 267 (75), 81 (63); HRMS (EI) calcd for $C_{20}H_{31}IO_2$: 430.1369 (M^+), found: 430.1359.

4.9. 3β,17β-Dihydroxy-7β-*p*-toluenesulfonyloxymethyl-5-androstene (13e)

At 0 °C, to a solution of **11** (0.107 g, 0.334 mmol) in pyridine (3.0 mL) was added *p*-toluenesulfonyl chloride (0.077 g, 0.401 mmol). The reaction mixture was allowed to warm up slowly to room temperature and stirred for 2 h. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (50% EtOAc/PE) to provide compound **13e** (0.155 g, 98%) as white solid: $[\alpha]_D^{26}$ +29 (*c* 0.53, $CHCl_3$); mp 97–98 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79–7.72 (d, *J*=8.4 Hz, 2H), 7.38–7.31 (d, *J*=8.4 Hz, 2H), 5.08 (s, 1H), 4.12–4.04 (dd, *J*=9.7, 2.8 Hz, 1H), 3.79–3.70 (dd, *J*=9.3, 6.8 Hz, 1H), 3.61–3.51 (dd, *J*=17.1, 8.2 Hz, 1H), 3.51–3.42 (m, 1H), 2.45 (s, 1H), 0.93 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.6, 143.3, 132.6, 129.6, 129.6, 127.7, 127.7, 121.6, 80.8, 73.1, 70.6, 51.3, 50.2, 43.4, 41.6, 40.9, 36.7, 36.4, 35.4, 32.7, 31.2, 29.9, 25.1, 21.4, 20.8, 18.7, 11.1; IR (KBr) 3396, 3251, 2937, 1599, 1460, 1358 cm^{-1}; MS (ESI) *m/z* (%) 497 ([M+Na]$^+$, 100); HRMS (ESI) calcd for $C_{27}H_{38}O_5SNa$: 497.2338 ([M+Na]$^+$), found: 497.2341.

4.10. 3β,17β-Dihydroxy-7β-benzenesulfonyloxymethyl-5-androstene (13f)

At 0 °C, to a solution of **11** (0.107 g, 0.334 mmol) in pyridine (3.0 mL) was added *p*-toluenesulfonyl chloride (0.064 mL, 0.502 mmol). The reaction mixture was allowed to warm up slowly to room temperature and stirred for 3 h. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (50% EtOAc/PE) to provide compound **13f** (0.149 g, 97%) as white solid: $[\alpha]_D^{26}$ +33 (*c* 0.50, $CHCl_3$); mp 97–98 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94–7.85 (d, *J*=8.1 Hz, 2H), 7.71–7.62 (dt, *J*=8.2, 0.9 Hz, 1H), 7.61–7.52 (t, *J*=8.1 Hz, 2H), 5.06 (s, 1H), 4.14–4.08 (dd, *J*=9.3, 2.5 Hz, 1H), 3.82–3.75 (dd, *J*=9.1, 6.7 Hz, 1H), 3.61–3.52 (t, *J*=8.2 Hz, 1H), 3.52–3.41 (m, 1H), 0.92 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.4, 135.6, 133.6, 129.1, 129.1, 127.7, 127.7, 121.5, 80.8, 73.3, 70.7, 51.4, 50.2, 43.4, 41.7, 40.9, 36.7, 36.5, 35.4, 32.7, 31.3, 29.9, 25.1, 20.8, 18.7, 11.1; IR (KBr) 3396, 2937, 2874, 1448, 1360 cm^{-1}; MS (ESI) *m/z* (%) 483 ([M+Na]$^+$, 100); HRMS (ESI) calcd for $C_{26}H_{36}O_5SNa$: 483.2181 ([M+Na]$^+$), found: 483.2192.

4.11. 3β,17β-Dihydroxy-7β-acetoxymethyl-5-androstene (13g)

Ac_2O (0.041 mL, 0.435 mmol) was added to a solution of **11** (0.107 g, 0.334 mmol) in anhydrous pyridine (3.0 mL) under Ar. The mixture was stirred at 0 °C for 5 h, and then extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (50% EtOAc/PE) to provide compound **13g** (0.119 g, 98%) as white solid: $[\alpha]_D^{26}$ +28 (*c* 0.85, $CHCl_3$); mp 97–98 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.25 (s, 1H), 4.32–4.26 (dd, *J*=11.1, 3.5 Hz, 1H), 3.73–3.64 (dd, *J*=10.6, 8.0 Hz, 1H), 3.64–3.58 (m, 1H), 3.57–3.46 (m, 1H), 2.04 (s, 3H), 0.98 (s, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 142.5, 122.8, 81.0, 70.7, 67.5, 51.6, 50.4, 43.4, 41.7, 40.6, 36.9, 36.6, 35.5, 33.3, 31.3, 30.0, 25.4, 20.9, 20.8, 18.8, 11.1; IR (KBr) 3412, 2937, 2848, 1740, 1720, 1452, 1385 cm^{-1}; MS (ESI) *m/z* (%) 385 ([M+Na]$^+$, 16), 363 ([M+H]$^+$ 31); HRMS (ESI) calcd for $C_{22}H_{34}O_4Na$: 385.2355 ([M+Na]$^+$), found: 385.2350.

4.12. 6β,7β-Methylene-4-androsten-3,17-dione (16)

4.12.1. General procedure. To a solution of **13** (0.2 mmol) in dry toluene (5.0 mL) were added cyclohexanone (0.2 mL, 2.0 mmol) and Al(O-*i*-Pr)$_3$ (0.248 g, 0.3 mmol). The mixture was refluxed for 1 h. After cooling to room temperature, the reaction mixture was extracted with EtOAc and washed with diluted sulfuric acid and brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (EtOAc/PE=1:2) to provide compound **16** as white solid: $[\alpha]_D^{21}$ −123 (*c* 0.19, MeOH); mp 185–187 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.02 (s, 1H), 1.10 (s, 3H), 0.90 (s, 3H), 0.85–0.79 (dd, *J*=10.4, 4.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 219.9, 197.8, 170.9, 125.7, 51.5, 51.0, 48.0, 37.2, 37.1, 35.6, 34.9, 33.8, 31.0, 21.9, 20.4, 19.1, 18.9, 18.3, 17.7, 13.6; IR (KBr) 3444, 2942, 2854, 1732, 1657 cm^{-1}; MS (EI) *m/z* (%) 298 (M^+, 100), 283 (18), 254 (60), 149 (43), 91 (47); HRMS (EI) calcd for $C_{20}H_{26}O_2$: 298.1933 (M^+), found: 298.1918.

4.13. X-ray structural analysis of 16

Crystallographic data (excluding structural factors) for compound **16** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 637078. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road,

Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

We thank Zhejiang Shenzhou Pharmaceutical Co., Ltd. for providing original starting materials.

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