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Novel Stereoselective Synthesis of 7β-Methyl-Substituted 5-Androstene Derivatives

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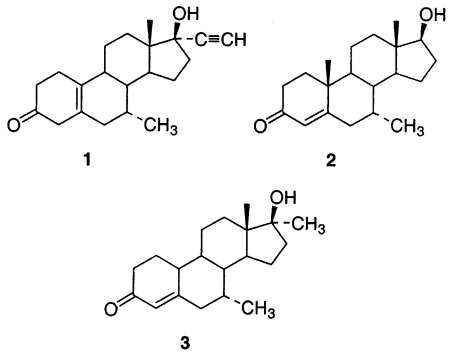
Abstract: The 7β-methyl-5-androstene derivatives **11a**−**c** were prepared in good yield with high stereoselectivities starting from 3β-acetoxyandrost-5-en-17-one **4**. The addition of methylmagnesium iodide to the 7-carbonyl group of **7a**−**c** gave, after hydrolysis, two isomers **9a**−**c** and **10a**−**c**, which were stereoselectively deoxygenated by means of an ionic hydrogenation to afford the compounds **11a**−**c**.

The introduction of methyl at C-7 in steroids has been the subject of several investigations, especially regarding 7α-methyl derivatives. Such compounds have shown significant biological activities, for example, tibolone **1** (therapeutic against tumors, cardiovascular disorders, and osteoporosis),[1] 7α-methyltestosterone **2** (antifertility),[2] and mibolerone **3** (estrus inhibition).[3] However, the synthesis of 7β-methyl derivatives of steroids and their biological activities has not been extensively studied. To explore the effect of such methylation on biological activities, we set out to synthesize 7β-methyl-5-androstene derivatives. Previous reports on the introduction of a 7β-methyl mainly concerned the copper-mediated 1,6-conjugate addition of organometallic reagents to various steroidal 4,6-dien-3-ones.[4,5] Because of the special position of C-7, which features little proximal steric difference between the α-side and β-side, both 7α-and 7β-methyl isomers were obtained. Zeelen et al. reported that 7β-methyl derivatives of steroids could be stereoselectively synthesized using 19-hydroxyandrost-4-ene-3,17-dione 19-acetate as starting material,[6] but the yield was very low (6.0% overall yield in four steps).



Ionic hydrogenation is an effective method to reduce tertiary carbinols.[7] Ionic hydrogenation with triethylsilane has already been used in the stereoselective reduction of hydroxylated and unsaturated estradiol derivatives.[8−10] According to these previous findings, we hypothesized that 7-hydroxy derivatives of steroids, which possessed a tertiary allylic alcohol, would be readily reduced with triethylsilane and boron trifluoride etherate. With regard to the stereochemical result of the reduction, we referred to the literature[9] and anticipated that the approach of relatively bulky triethylsilane to the 7-carbocation would occur from the slightly less hindered α-side, resulting in a predominant product with the methyl function having the desired 7β-configuration.

We report here a novel approach to stereoselective introduction of β-methyl at the C-7 position of steroids in high yield, using 3β-acetoxyandrost-5-en-17-one **4** as starting material (Scheme 1). It involves oxidation at C-7, addition of methyl Grignard to the resulting 7-carbonyl group to give two isomers, and the stereoselective deoxygenation of the 7-hydroxy steroids by means of an ionic hydrogenation. The alkylation/reduction protocol was previously reported by Tedesco et al.[9] The overall yield is 37−62% via five-stage synthesis with 96−99% de.

Androst-5-en-17-one **4** was reduced with KBH_4 and hydrolyzed under basic conditions to give diol **5** in 95% yield. To selectively oxidize the C-7 position, the two hydroxyls of **5** were protected. The acetyl was first selected as the protection group, and oxidation of **6a** with $Na_2Cr_2O_7 \cdot 2H_2O$ gave 3β,17β-diacetoxy-5-androsten-7-one **7a** in 90% yield. The addition of methylmagnesium iodide to **7a** at −40 °C yielded a mixture of the 7α- and 7β-isomers **9a** and **10a**, which could be isolated by column chromatography to afford 23% and 33% of **9a** and **10a**, respectively. Under these conditions, the Grignard reagent also attacked the ester functions, together with other side reactions, which resulted in the relatively low yield. To improve the yield, we used the protecting groups that will not react with the Grignard reagent. The methyl- and TBDMS-protected 5-androstene-7-ones **7b**

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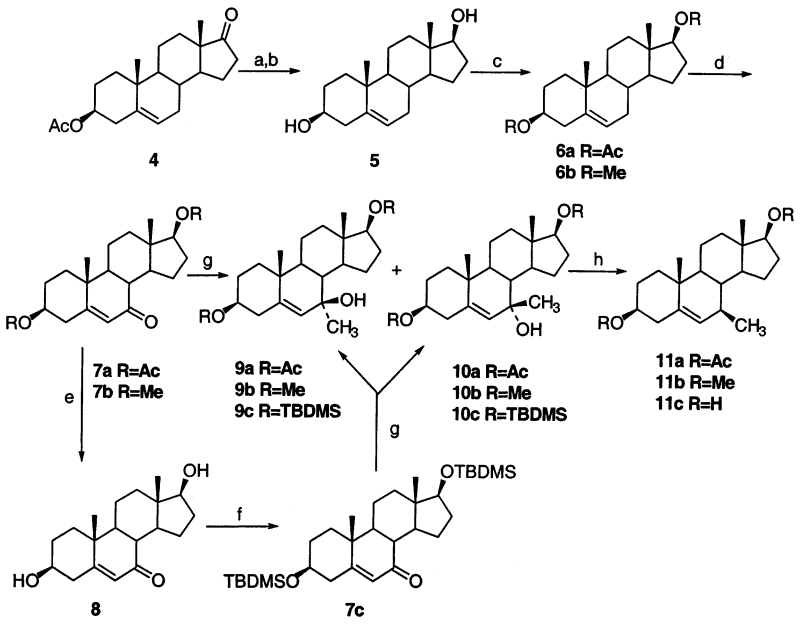
SCHEME 1[a]



[a] Key: (a) KBH_4, MeOH; (b) NaOH, MeOH; (c) Ac_2O, Py for **6a** or MeI, NaH for **6b**; (d) $Na_2Cr_2O_7 \cdot 2H_2O$, NOS, acetone; (e) 10%NaOH, MeOH; (f) imidazole, TBDMSCl, DMF; (g) CH_3MgI, Et_2O, THF; (h) triethylsilane, $BF_3 \cdot Et_2O$.

and **7c** were prepared in 67% yield from **5** and in 83% yield from **7a**, respectively. The addition of methylmagnesium iodide to **7b** at −8 °C and **7c** at 0 °C gave equal amounts of the addition products **9b** and **10b** in 96% overall yield and **9c** and **10c** in 91% overall yield, respectively.

The structural assignments of the 7α- and 7*β*-isomers were determined by ^{13}C NMR. It has been reported that the chemical shift of the carbinyl carbon depends on the orientation of the hydroxyl group; i.e., that an axial hydroxyl group shields the α-carbon atom more than does the corresponding equatorial substituent.[11] The equatorial 7*β*-hydroxy derivative **9a** and the axial 7α-hydroxy derivative **10a** showed ^{13}C NMR signals for C-7 at *δ* 72.8 and 69.5, respectively. Compounds **9b** and **10b** showed ^{13}C NMR signals for C-7 at *δ* 72.9 and 69.9, respectively. Compounds **9c** and **10c** showed ^{13}C NMR signals for C-7 at *δ* 74.0 and 70.0, respectively. In addition, cross-peaks in the NOESY spectrum between H of 7-methyl and H-14 and H-17 in **9a**, **9b**, and **9c** indicated their α-orientation of 7-methyl groups.

The 7-hydroxy-5-androstene derivatives **9a**−**c** and **10a**−**c** were cleanly reduced by treatment with triethylsilane and boron trifluoride etherate, giving the desired 7*β*-methyl-5-androstene derivatives **11a**−**c** in high yields with 99%, 96%, and 98% de, respectively, which were determined by integration of the ^1H NMR of the crude reaction products. The silyl ether groups at C-3 and C-17 of **9c** and **10c** were easily removed under deoxygenation conditions. The ^1H NMR chemical shifts of the 7*β*-methyl group of **11a**−**c** appeared at *δ* 0.94 (d, $J = 6.95$ Hz, 3H), *δ* 0.91 (d, $J = 6.97$ Hz, 3H), and *δ* 0.95 (d, $J = 6.59$ Hz, 3H), respectively, which are similar to that [*δ*0.98 (d, $J = 7$ Hz, 3H)] of the 7*β*-methyl group of a related 5-androstene derivative.[4] In addition, single-crystal X-ray diffraction analysis confirmed that **11c** is the 7*β*-isomer (Figure S1, Supporting Information).

In conclusion, we have developed a novel approach to 7*β*-methyl-substituted 5-androstene derivatives in 96−99% de, starting with 3*β*-acetoxyandrost-5-en-17-one **4**. This method will make 7*β*-alkyl-substituted derivatives more easily obtainable than before. The availability of 7*β*-alkylated steroids will provide the opportunities to study their structure−activity relationship and possibility to develop potent new drugs for clinical use.

Experimental Section

3*β*,17*β*-Dihyroxyandrost-5-ene (5). A stirring suspension of **4** (10.05 g, 30.41 mmol) in methanol (300 mL) was heated to 36 °C. KBH_4 (1.04 g, 19.29 mmol) was added in portion in 7 min, and the mixture was stirred at 36 °C for 40 min. After the addition of glacial acetic acid (4.0 mL), most of the methanol was evaporated, and the crude mixture of 3*β*-acetoxy-17*β*-hydroxyandrost-5-ene and **5** was precipitated by the addition of water (400 mL). The residue was collected by filtration. The residue was dissolved in methanol (250 mL), and then 20% NaOH (15 mL) was added. After the mixture was stirred at room temperature for 1 h, glacial acetic acid (5.0 mL) was added to the mixture. The mixture was poured into water (800 mL). The solid was collected by filtration and dried to give 8.40 g (95% yield) of **5**. A sample was recrystallized from ethyl acetate: mp 181 °C (lit.[12] mp 180.5 °C).

3*β*,17*β*-Diacetoxyandrost-5-ene (6a). A mixture of **5** (8.00 g, 27.54 mmol), *p*-toluenesulfonic acid monohydrate (0.15 g, 0.78 mmol), Ac_2O (5.5 mL, 59.21 mmol), and Py (7.5 mL) was stirred at room temperature for 1 h and then heated to 95 °C for 3.5 h. After the mixture was cooled to room temperature, 400 mL of water was added. The solid was collected by filtration and dried to give 10.00 g (97% yield) of **6a**. Recrystallization from ethyl acetate afforded white crystals: mp 158−160 °C (lit.[13] mp 153−155 °C).

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3β,17β-Dimethoxyandrost-5-ene (6b). To a solution of **5** (0.83 g, 2.86 mmol) in dry THF (20 mL) was added NaH (0.44 g, 10.90 mmol). The mixture was stirred for 30 min, and then MeI (1.2 mL, 19.30 mmol) was added. After continued stirring for 1.5 h, 0.6 mL of glacial acetic acid and 10 mL of water were added to the mixture. The aqueous layer was extracted with 10 mL of ethyl acetate three times. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give the yellow solid. Recrystallization from acetone afforded white crystals of **6b** (0.88 g, 97%yield): mp 137−139 °C; $[\alpha]^{20}_D$ −69.0 (*c* 0.92, $CHCl_3$); IR ν_{max} (KBr) 2941, 1664, 1452 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 0.99 (s, 3H), 3.05 (m, 1H), 3.22 (t, J = 8.43 Hz, 1H), 3.34 (d, J = 1.29 Hz, 6H), 5.34 (d, J = 5.13 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.4, 19.4, 20.7, 23.3, 27.6, 27.9, 31.5, 31.6, 36.9, 37.1, 37.8, 38.6, 42.6, 50.2, 51.5, 55.6, 57.8, 80.2, 90.7, 120.2, 140.9; MS (*m*/*z*) 318 $[M]^+$ (67), 286 $[M - CH_3OH]^+$ (100). Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.37; H, 10.74.

3β,17β-Diacetoxy-5-androsten-7-one (7a). To a solution of **6a** (23.23 g, 0.062 mol) in acetone (200 mL) were added *N*-hydroxysuccinimide (28.23 g, 0.24 mol) and $Na_2Cr_2O_7 \cdot 2H_2O$ (21.24 g, 0.071 mol). The mixture was heated to 40 °C and stirred for 48 h. The reaction was quenched with saturated sodium sulfite (100 mL), and the mixture was poured into water (2500 mL). The solid was collected by filtration, washed thoroughly with water, and dried. Crystallization from methanol gave **7a** (21.68 g, 90% yield), mp 224−225 °C (lit.[14] mp 225 °C).

3β,17β-Dimethoxy-5-androsten-7-one (7b). To a suspension of **6b** (8.62 g, 0.027 mol) in acetone (250 mL) were added *N*-hydroxysuccinimide (10.62 g, 0.092 mol) and $Na_2Cr_2O_7 \cdot 2H_2O$ (10.03 g, 0.034 mol). The mixture was heated to 50 °C and stirred for 36 h. The reaction was quenched with saturated sodium sulfite (50 mL), and the mixture was poured into water (2000 mL). The precipitate was filtered off, washed thoroughly with water, and dried. Chromatography with cyclohexane/ethyl acetate 10/1, followed by crystallization from diethyl ether, gave **7b** (6.20 g, 69% yield): mp 142−143 °C; $[\alpha]^{20}_D$ −150.8 (c 0.85, $CHCl_3$); IR ν_{max} (KBr) 2975, 2863, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 1.18 (s, 3H), 3.19 (m, 2H), 3.33 (s, 3H), 3.37 (s, 3H), 5.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.6, 17.3, 20.8, 25.6, 27.5, 36.2, 36.6, 38.7, 43.2, 45.0, 50.0, 55.9, 57.8, 78.9, 89.7, 125.9, 165.6, 202.0; MS (*m*/*z*) 332 $[M]^+$ (100), 317 $[M - CH_3]^+$ (6), 300 $[M - CH_3OH]^+$ (22). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.08; H, 9.63.

3β,17β-Dihydroxy-5-androsten-7-one (8). Sodium hydroxide (10%, 60 mL) was added to the suspension of **7a** (20.13 g, 0.052 mol) in methanol (500 mL). After the mixture was stirred at room temperature for 2 h, glacial acetic acid (26 mL) was added. Most of the methanol was evaporated, and a white solid was precipitated by the addition of water (1500 mL). The solid was collected by filtration and dried to give **8** (14.09 g, 89% yield). Crystallization from methanol afforded an analytical sample: mp 201−204 °C (lit.[15] mp 201 °C).

3β,17β-Bis(*tert*-butyldimethylsilyloxy)-5-androsten-7-one (7c). Imidazole (4.20 g, 0.062 mol) and *tert*-butyldimethylsilyl chloride (6.29 g, 0.042 mol) were added to a solution of **8** (4.00 g, 0.013 mol) in dry DMF (200 mL). The mixture was stirred at room temperature for 20 h and then poured into water (800 mL). The precipitate was collected by filtration to give **7c** (6.54 g, 93% yield). Recrystallization from acetone afforded an analytical sample: mp 185−186 °C; $[\alpha]^{20}_D$ −82.6 (*c* 1.15, $CHCl_3$); IR ν_{max} (KBr) 2950, 2856, 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.0015 (s, 6H), 0.05 (s, 6H), 0.71 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.19 (s, 3H), 3.56 (m, 2H), 5.66 (d, J = 1.28 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.7, −4.5, 11.3, 17.3, 18.1, 20.9, 25.8, 30.9, 31.7, 36.0, 36.4, 38.4, 42.6, 43.6, 44.5, 45.3, 50.2, 71.2, 80.9, 125.6, 166.3, 202.4; MS (*m*/*z*) 532 $[M]^+$ (4), 475 $[M - t\text{-}Bu]^+$ (100), 399 (96). Anal. Calcd for $C_{31}H_{56}Si_2O_3$: C, 69.86; H, 10.59. Found: C, 69.94; H, 10.45.

3β,17β-Diacetoxy-7α-methylandrost-5-en-7β-ol (9a) and 3β,17β-Diacetoxy-7β-methylandrost-5-en-7α-ol (10a). A solution of methylmagnesium iodide prepared from magnesium (0.46 g, 0.019 mol), methyl iodide (1.2 mL, 0.019 mol), and anhydrous ether (20 mL) was cooled to −40 °C, and at this temperature, a solution of **7a** (0.50 g, 1.29 mmol) in dry THF (25 mL) was added dropwise over 15 min. Stirring was continued at −40 °C for 1 h. The reaction was quenched with saturated ammonium chloride (15 mL) and the mixture partitioned between water and ether. The aqueous layer was extracted with ethyl acetate (6 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude mixture was chromatographed with cyclohexane/ethyl acetate 8/1 to give **9a** (0.12 g, 23% yield), which was recrystallized from diisopropyl ether to give an analytical sample [mp 125−126 °C; $[\alpha]^{20}_D$ −58.8 (*c* 0.79, $CHCl_3$); IR ν_{max} (KBr) 3496, 2971, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 1.05 (s, 3H), 1.12 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 4.59 (m, 2H), 5.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.7, 19.0, 20.4, 21.1, 21.3, 23.6, 26.3, 27.6, 36.2, 36.9, 37.2, 37.4, 42.6, 43.0, 44.6, 46.5, 72.8, 73.3, 82.4, 132.0, 139.1, 170.5, 171.2; MS (*m*/*z*) 404 $[M]^+$ (<1), 344 (41), 329 (92), 149 (100). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.24; H, 9.19] and **10a** (0.17 g, 33% yield), which was recrystallized from diisopropyl ether to give an analytical sample: mp 151−152 °C; $[\alpha]^{20}_D$ −84.2 (*c* 0.80, $CHCl_3$); IR ν_{max} (KBr) 3510, 2944, 1733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.95 (s, 3H), 1.21 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 4.59 (m, 2H), 5.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.1, 17.9, 20.6, 21.1, 21.3, 27.1, 27.5, 27.6, 30.3, 36.4, 36.6, 36.8, 37.5, 42.1, 42.9, 44.8, 45.9, 69.5, 73.1, 82.5, 131.5, 141.4, 170.4, 171.2; MS (*m*/*z*) 404 $[M]^+$ (<1), 344 (71), 329 (100), 149 (30). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.26; H, 8.97. Found: C, 71.43; H, 8.88.

3β,17β-Dimethoxy-7α-methylandrost-5-en-7β-ol (9b) and 3β,17β-Dimethoxy-7β-methylandrost-5-en-7α-ol (10b). A solution of methylmagnesium iodide prepared from magnesium (0.69 g, 0.028 mol), methyl iodide (1.8 mL, 0.029 mol), and anhydrous ether (30 mL) was cooled to −8 °C, and at this temperature, a solution of **7b** (2.35 g, 7.07 mmol) in dry THF (30 mL) was added dropwise over 20 min. Stirring was continued at −8 °C for 1 h. The reaction was quenched with saturated ammonium chloride (25 mL) and the mixture partitioned between water and ether. The aqueous layer was extracted with ethyl acetate (15 mL × 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed with chloroform/methanol 250/1 to give **9b** (1.13 g, 46% yield), which was recrystallized from ethyl acetate to give an analytical sample [mp 140−141 °C; $[\alpha]^{20}_D$ −56.1 (*c* 1.68, $CHCl_3$); IR ν_{max} (KBr) 3467, 2969, 2931, 2819, 1677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3H), 1.03 (s, 3H), 1.12 (s, 3H), 3.06 (m, 1H), 3.22 (t, J = 7.69 Hz, 1H), 3.34 (s, 6H), 5.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.3, 19.0, 20.7, 23.6, 26.2, 27.7, 27.9, 37.2, 37.3, 37.6, 38.1, 43.0, 43.3, 45.2, 46.8, 55.6, 57.8, 72.9, 80.0, 90.2, 131.2, 140.3; MS (*m*/*z*) 348 $[M]^+$ (2), 333 $[M - CH_3]^+$ (100); Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 76.07; H, 10.53] and **10b** (1.23 g, 50% yield) as a white powder: $[\alpha]^{20}_D$ −71.5 (*c* 0.63, $CHCl_3$); IR ν_{max} (KBr) 3508, 3382, 2935, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 0.92 (s, 3H), 1.21 (s, 3H), 3.06 (m, 1H), 3.21 (t, J = 8.06 Hz, 1H), 3.33 (s, 6H), 5.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.6, 18.0, 20.8, 27.1, 27.6, 27.9, 30.5, 36.9, 37.0, 37.4, 38.1, 42.0, 43.3, 45.3, 46.2, 55.6, 57.8, 69.9, 79.6, 90.3, 130.6, 142.7; MS (*m*/*z*) 348 $[M]^+$ (8), 333 $[M - CH_3]^+$ (100); HRMS calcd for $C_{22}H_{36}O_3$ 348.26649, found 348.26650.

3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7α-methylandrost-5-en-7β-ol (9c) and 3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7β-methylandrost-5-en-7α-ol (10c). A solution of methylmagnesium iodide prepared from magnesium (4.0 g, 0.16 mol), methyl iodide (10 mL, 0.16 mol), and anhydrous ether (130 mL) was cooled to 0 °C, and at this temperature, a solution of **7c** (6.54 g, 0.012 mol) in dry THF (100 mL) was added dropwise over 30 min. Stirring was continued at 0 °C for 1 h. The reaction was quenched with saturated ammonium chloride (100 mL) and the mixture partitioned between water and ether. The aqueous layer was extracted with ethyl acetate (70 mL × 3). The

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combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The crude mixture was chromatographed with cyclohexane/ethyl acetate 50/1 to give **9c** (2.98 g, 44% yield), which was recrystallized from diisopropyl ether to give an analytical sample [mp 111 °C; $[\alpha]^{20}_D$ −27.8 (*c* 1.13, $CHCl_3$); IR ν_{max} (KBr) 3527, 2956, 2854 cm^{-1}; ^1H NMR (CD_3OD) δ −0.09 (d, J = 3.30 Hz, 6H), −0.10 (d, J = 1.46 Hz, 6H), 0.59 (s, 3H), 0.73 (s, 18H), 0.91 (s, 3H), 0.94 (s, 3H), 3.34 (m, 1H), 3.44 (t, J = 8.05 Hz, 1H), 4.97 (d, J = 1.46 Hz, 1H); ^{13}C NMR (CD_3OD) δ −4.1, −3.9, −3.7, 12.2, 19.5, 19.9, 22.4, 24.1, 26.9, 27.9, 32.6, 33.7, 38.5, 38.9, 39.0, 43.9, 44.2, 45.1, 46.5, 48.9, 74.0, 74.3, 83.4, 133.5, 141.7; MS (*m*/*z*) 548 $[M]^+$ (2), 533 $[M - CH_3]^+$ (36), 491 $[M - C(CH_3)_3]^+$ (33), 473 (100). Anal. Calcd for $C_{32}H_{60}Si_2O_3$: C, 70.00; H, 11.02. Found: C, 70.07; H, 11.00] and **10c** (3.17 g, 47% yield) as a white powder: $[\alpha]^{20}_D$ −41.6 (*c* 1.15, $CHCl_3$); IR ν_{max} (KBr) 3479, 2956, 2856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (d, J = 2.93 Hz, 6H), 0.03 (s, 6H), 0.71 (s, 3H), 0.86 (s, 18H), 0.94 (s, 3H), 1.21 (s, 3H), 3.53 (m, 2H), 5.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ -4.8, −4.6, −4.4, 11.3, 18.0, 18.1, 18.2, 20.8, 25.9, 27.4, 30.6, 30.9, 32.0, 36.8, 37.3, 42.3, 42.4, 43.7, 44.7, 46.3, 70.0, 71.9, 81.4, 130.2, 143.5; MS (*m*/*z*) 548 $[M]^+$ (<1), 491 $[M - C(CH_3)_3]^+$ (54),473 (100); HRMS calcd for $C_{32}H_{60}Si_2O_3$ 548.40927, found 548.40940.

General Conditions for the Deoxygenation of 9a−c and 10a−c (11a−c). A mixture of **9** and **10** (1.0 mmol) was dissolved in methylene chloride (20 mL) and cooled to 0 °C. Triethylsilane (1.0 mL, 6.00 mmol) was added to the solution, and then boron trifluoride etherate (1.2 mL, 10.00 mmol) was added dropwise. After the mixture was stirred for 10 min, 10% sodium carbonate (10 mL) was added. The aqueous layer was extracted with methylene chloride. The combined methylene chloride was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo to afford a residue from which **11a−c** were obtained after chromatography.

3*β*,17*β*-Diacetoxy-7*β*-methylandrost-5-ene (11a) was isolated by chromatography with cyclohexane/ethyl acetate 20/1: white powder (79% yield); $[\alpha]^{20}_D$ −26.4 (*c* 0.85, $CHCl_3$); IR ν_{max} (KBr) 2952, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3H), 0.94 (d, J = 6.95 Hz, 3H), 0.96 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 4.57 (m, 2H), 5.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.4, 19.4, 21.1, 21.3, 21.6, 22.7, 26.4, 27.9, 28.1, 31.1, 36.1, 36.3, 37.1, 38.0, 39.6, 43.4, 50.8, 51.9, 73.8, 82.8, 130.1, 138.4, 170.7, 171.4; MS (*m*/*z*) 388 $[M]^+$ (<1), 328 $[M - CH_3OOH]^+$ (100); HRMS calcd for $C_{24}H_{36}O_4$ 388.25806, found 388.25770.

3*β*, 17*β*-Dimethoxy-7*β*-methylandrost-5-ene (11b) was isolated by chromatography with cyclohexane/ethyl acetate 80/1: white powder (85% yield); $[\alpha]^{20}_D$ −17.6 (*c* 1.31, $CHCl_3$); IR ν_{max} (KBr) 2946, 2875, 1677 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3H), 0.91 (d, J = 6.97 Hz, 3H), 0.94 (s, 3H), 3.02 (m, 1H), 3.16 (t, J = 7.33 Hz, 1H), 3.34 (s, 6H), 5.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.8, 19.3, 21.2, 22.7, 26.1, 27.8, 28.1, 36.2, 37.2, 38.1, 38.5, 39.5, 43.5, 51.0, 52.4, 55.5, 57.8, 80.0, 90.6, 129.1, 139.4; MS (*m*/*z*) 332 $[M]^+$ (12), 317 $[M - CH_3]^+$ (4), 300 $[M - CH_3OH]^+$ (100); HRMS calcd for $C_{22}H_{36}O_2$ 332.27177, found 332.27180.

3*β*,17*β*-Dihydroxy-7*β*-methylandrost-5-ene (11c). The residue was chromatographed with cyclohexane/ethyl acetate 3/1, followed by crystallization with ethyl acetate to give the white crystal (99% yield): mp 185−187 °C; $[\alpha]^{20}_D$ −5.1 (*c* 1.23, $CHCl_3$); IR ν_{max} (KBr) 3266, 2935, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3H), 0.95 (d, J = 6.59 Hz, 3H), 0.97 (s, 3H), 3.51 (m, 1H), 3.61 (t, J = 8.42 Hz, 1H), 5.07 (t, J = 2.20 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.2, 19.4, 21.1, 22.6, 26.2, 30.6, 31.8, 35.8, 36.3, 36.9, 37.2, 39.7, 42.1, 43.5, 50.9, 52.0, 71.5, 81.7, 129.2, 139.3; MS (*m*/*z*) 304 $[M]^+$ (12), 286 $[M - H_2O]^+$ (100). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.05; H, 10.48.

Supporting Information Available: The X-ray diffraction analytical data and an ORTEP diagram of **11c** and the proton NMR spectra of **6a**, **7a−c**, **10a−c**, and **11a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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