Two Novel Approaches toward Stereoselective Introduction of β-Hydroxymethyl Group at the C-7 Position of 5-Androstene

Qin Gu, Yun-Hong Zheng, Yuan-Chao Li*

Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 555 Zu Cong Zhi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, P. R. of China
Fax +86(21)50807288; E-mail: ycli@mail.shcnc.ac.cn

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Abstract: Two novel approaches to stereoselective introduction of 7β-hydroxymethyl group onto 5-androstene have been developed. In the first approach, coupling of benzyloxymethyl chloride with the 7-carbonyl group of **1** mediated by SmI_2 gives, after debenzylation, two isomers **4** and **5** respectively, which are stereoselectively deoxygenated by means of an ionic hydrogenation to afford **6**. The second approach involves the addition of (isopropoxydimethylsilyl)methyl Grignard reagent (Tamao's reagent) to the 7-carbonyl group of **1**, followed by oxidative cleavage of the silicon–carbon bond by hydrogen peroxide giving compound **5**. Stereoselective deoxygenation of **5** via an ionic hydrogenation also affords **6**. The relative configuration of **6** is confirmed by ROESY studies.

Key words: steroids, stereoselective, 7β-hydroxymethyl, 5-androstene, ionic hydrogenation

The introduction of 7α-substituted group in steroids has been widely investigated; especially some 7α-methyl derivatives.[1–3] However, the stereoselective synthesis of 7β-substituted steroids has not been extensively studied. Recently, we have reported novel stereoselective introduction of 7β-methyl substituent in androstenes.[4] Continuous interests in our laboratories prompt us to synthesize some 7β-hydroxymethyl-substituted androstene derivatives.

In 1981, Nickisch et al. reported that 7β-hydroxymethyl derivatives of steroids could be stereoselectively synthesized using 3-(6-chloro-17β-hydroxy-3-oxo-4,6-androstdien-17α-yl)propionic acid γ-lactone as starting material, but the yield was low (16.6% overall yield in four steps).[5] In this paper, we wish to report two simple and highly stereoselective approaches to the introduction of β-hydroxymethyl at the C-7 position of steroids, using 3β,17β-bis(*tert*-butyldimethylsilyloxy)-5-androsten-7-one (**1**) as the starting material. One approach involves the coupling of benzyloxymethyl chloride with the 7-carbonyl group mediated by SmI_2 to give two isomers, followed by debenzylation, and the stereoselective deoxygenation of the 7-hydroxy steroids by means of an ionic hydrogenation. The other approach includes the addition of Tamao's reagent to the 7-carbonyl group to give a single isomer, followed by oxidative cleavage of the corresponding silicon–carbon bond, and the stereoselective deoxygenation of the 7-hydroxy steroid via an ionic hydrogenation.

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The first approach to the stereoselective introduction of 7β-hydroxymethyl in androstene was carried out as shown in Scheme 1. Coupling of benzyloxymethyl chloride, which is a potential hydroxymethylation reagent,[6] with androst-5-en-7-one **1** mediated by SmI_2 afforded **2** and **3** with a stereo ratio of 1:3.53 in 63% overall yield. These two diastereomers could be separated carefully by silica gel column chromatography. Reductive cleavage of the benzyl ether of **2** and **3** with radical anion of biphenyl afforded 7α-OH isomer **4** in 84% yield and 7β-OH isomer **5** in 81% yield, respectively.[7]

The structural assignments of the 7α-OH and 7β-OH isomers were determined by ^{13}C NMR spectra. It has been reported that the chemical shift of the C-7 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.[4,8] The axial 7α-OH isomer **2** and the equatorial 7β-OH isomer **3** showed ^{13}C NMR signals for C-7 at δ = 71.5 and 74.3, respectively. Compounds **4** and **5** showed ^{13}C NMR signals for C-7 at δ = 72.3 and 73.7, respectively.

Ionic hydrogenation with triethylsilane is an effective method to reduce tertiary alcohols and has already been used in the stereoselective reduction of hydroxylated steroids.[9] When a mixture of compound **4** and **5** was treated with triethylsilane and boron trifluoride etherate, the 7-hydroxy group was cleanly reduced affording the desired 7β-hydroxymethyl-5-androstene derivative **6** in 95% yield with 96% de, which was determined by integration of the ^1H NMR of the crude reaction products. The silyl ether groups at C-3 and C-17 of **4** and **5** were also easily removed under the deoxygenation conditions. The relative configuration of **6** at the C-7 position was determined by means of ROESY experiments. From the ROESY spectrum, the cross peaks between 7-H/9-H and 7-H/14-H and the absence of the Overhauser effects between 7-H and 8-H (Figure 1) indicated the β orientation of 7-hydroxymethyl group in compound **6**.

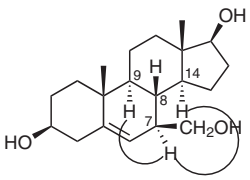
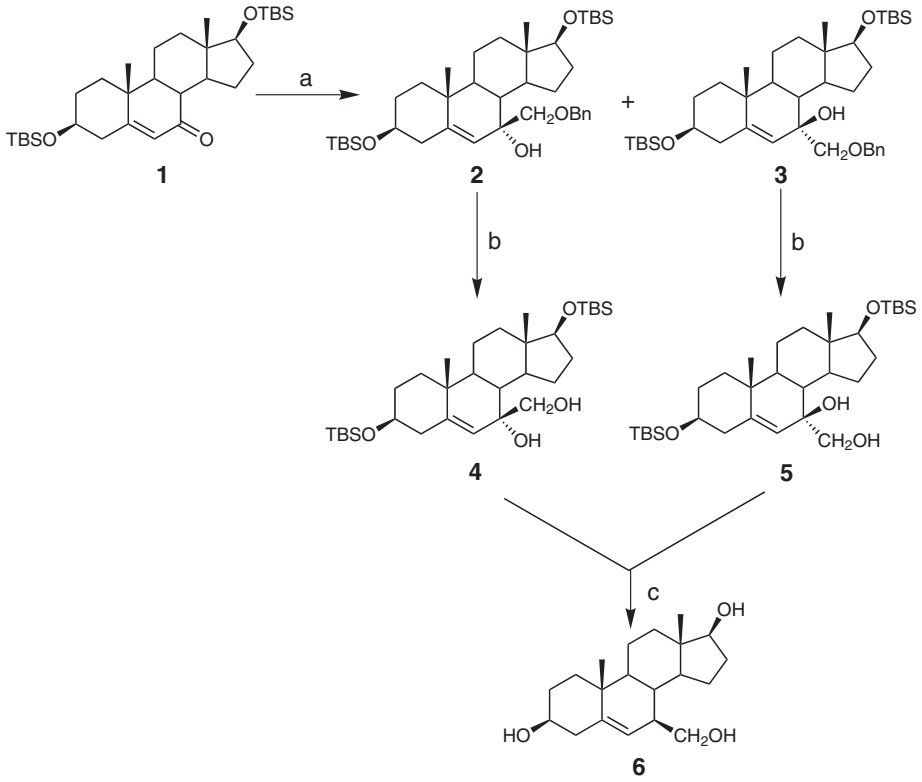


Figure 1 The key ROESY correlations of compound **6**

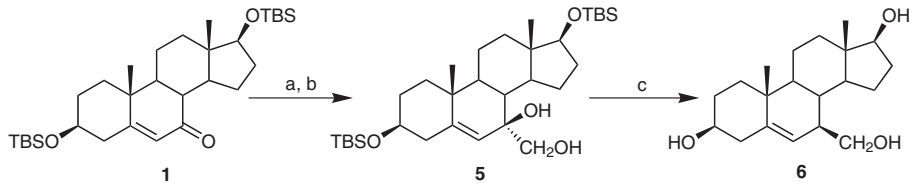


Scheme 1 *Reagents and conditions:* (a) $PhCH_2OCH_2Cl$, SmI_2, THF, r.t.; **2** (14%), **3** (49%); (b) Li, biphenyl, THF, –78 °C; **4** (84%), **5** (81%); (c) triethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 95%.

The second approach towards the stereoselective introduction of 7β-hydroxymethyl in androstene was outlined in Scheme 2. The (isopropoxydimethylsilyl)methyl Grignard reagent was used for the first time as a nucleophilic hydroxymethyl anion equivalent by Tamao et al. in 1984.[10,11] Androst-5-en-7-one **1** was treated with the Grignard reagent in THF at 0 °C to give a single adduct. Without purification, the unstable adduct was subjected to oxidative cleavage of the silicon–carbon bond with hydrogen peroxide to give compound **5** in 84% yield (two steps). Compound **5** was cleanly reduced by treatment with triethylsilane and boron trifluoride etherate, giving compound **6** in 92% yield with 97% de. With regard to the high stereoselectivity in the nucleophilic addition of Tamao's reagent to androst-5-en-7-one **1,** we suggested that the addition of relatively bulky (isopropoxydimethylsilyl)methyl Grignard reagent to the 7-carbonyl group would occur from the slightly less hindered α-side, resulting in a single isomer **5** with the 7-hydroxyl function in the β orientation.

In summary, we have developed two novel approaches to 7β-hydroxymethyl-substituted 5-androstene derivative **6** in 96–97% de, starting with 3β,17β-bis(*tert*-butyldimethylsilyloxy)-androsten-7-one (**1**). These two methods will be applicable for stereoselective synthesis of other 7β-hydroxymethyl-substituted steroids.

All melting points were determined on a Büchi 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 FT-IR-750 spectrometer as KBr pellets. ^1H and ^{13}C NMR spectra were run on a Bruker AM-400 spectrometer using tetramethylsilane as the internal standard (chemical shifts in δ ppm). Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. Elemental analysis was performed at a Carlo Erba 1106 instrument. 3β,17β-Bis(*tert*-butyldimethylsilyloxy)-5-androsten-7-one (**1**) was prepared according to literature.[4] Silica gel 60H (200–300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for flash chromatography. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C.



Scheme 2 *Reagents and conditions:* (a) (isopropoxydimethylsilyl)methyl chloride, Mg, THF, 0 °C; (b) H_2O_2, $KHCO_3$, KF, MeOH, THF, r.t., 84% (for 2 steps); (c) triethylsilane, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 92%.

3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7β-benzyloxymethylandrost-5-en-7α-ol (2) and 3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7α-benzyloxymethylandrost-5-en-7β-ol (3)

Powdered samarium (1.22 g, 8.11 mmol) was added to a dry 150-mL round-bottomed flask equipped with a stirring bar. The flask was simultaneously flushed with argon and flamed dry. Anhyd THF (75 mL) was added to the cooled flask. The vigorously stirred slurry of samarium metal in THF was cooled to 0 °C, and neat diiodomethane (0.61 mL, 7.57 mmol) was added. The green slurry was stirred at 0 °C for 30 min, then allowed to warm to r.t., and vigorously stirred for an additional hour. A mixture of **1** (1.00 g, 1.88 mmol) and chloromethyl benzyl ether (0.52 mL, 3.74 mmol) in anhyd THF (15 mL) was added dropwise to the resulting deep blue solution of 0.1 M SmI_2 at r.t. After the initial dark blue color of the SmI_2 solution turned yellow, the reaction was quenched with 0.1 N HCl (30 mL), and then extracted with EtOAc (3 × 80 mL). The combined extracts were washed sequentially with aq sat. $Na_2S_2O_3$, aq sat. $NaHCO_3$, and brine, dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was chromatographed using PE–EtOAc (25:1) as eluent to give **2** (0.17 g, 14%) as a colorless oil and **3** (0.60 g, 49%) as a white solid, which was recrystallized from *n*-hexane.

2

Oil; $[\alpha]_D^{20}$ –23.8 (*c* = 2.20, *n*-hexane).

IR (KBr): 3471, 2955, 2856, 1664 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.01 [(d, 6 H, *J* = 3.6 Hz, $(CH_3)_2Si$], 0.06 [s, 6 H, $(CH_3)_2Si$], 0.69 (s, 3 H, 18-CH_3), 0.87 [s, 9 H, $(CH_3)_3CSi$], 0.89 [s, 9 H, $(CH_3)_3CSi$], 0.94 (s, 3 H, 19-CH_3), 3.20 (d, 1 H, *J* = 9.2 Hz, 7-CH_2OBn), 3.49 (d, 1 H, *J* = 9.2 Hz, 7-CH_2OBn), 3.49–3.57 (m, 2 H, 3-H, 17-H), 4.53 (s, 2 H, CH_2Ph), 5.48 (s, 1 H, 6-H), 7.29–7.37 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.8, –4.6, –4.5, 11.3, 17.9, 18.1, 18.2, 20.9, 25.8, 25.9, 27.0, 30.7, 32.0, 36.5, 36.7, 37.1, 37.8, 42.4, 43.7, 44.4, 45.9, 71.5, 71.8, 73.3, 76.4, 81.3, 126.2, 127.6, 127.6, 128.3, 138.3, 144.5.

MS (EI): *m*/*z* (%) = 654 (M^+, 2), 636 ([M – H_2O]$^+$, 22), 533 (100), 515 (20), 401 (16), 91 (39), 73 (27).

HRMS (EI): *m*/*z* calcd for $C_{39}H_{66}O_4Si_2$ [M]$^+$: 654.4500; found: 654.4463.

3

Mp 114–116 °C; $[\alpha]_D^{20}$ –32.1 (*c* = 1.90, *n*-hexane).

IR (KBr): 3440, 2956, 2856, 1667 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.01 [s, 6 H, $(CH_3)_2Si$], 0.08 [s, 6 H, $(CH_3)_2Si$], 0.69 (s, 3 H, 18-CH_3), 0.88 [s, 9 H, $(CH_3)_3CSi$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 1.05 (s, 3 H, 19-CH_3), 3.42 (d, 1 H, *J* = 9.0 Hz, 7-CH_2OBn), 3.46–3.55 (m, 2 H, 3-H, 17-H), 3.56 (d, 1 H, *J* = 9.0 Hz, 7-CH_2OBn), 4.52 (d, 1 H, *J* = 12.6 Hz, CH_2Ph), 4.60 (d, 1 H, *J* = 12.6 Hz, CH_2Ph), 5.31 (s, 1 H, 6-H), 7.30–7.38 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.5, –4.2, –4.1, 11.1, 18.4, 18.5, 19.3, 21.0, 26.2, 26.2, 27.0, 31.1, 32.3, 36.7, 37.6, 37.6, 42.2, 42.7, 43.9, 44.5, 46.4, 72.7, 73.7, 74.3, 74.6, 81.6, 127.6, 127.8, 127.9, 128.6, 138.6, 143.2.

MS (EI): *m*/*z* (%) = 654 (M^+, 1), 636 ([M – H_2O]$^+$, 20), 533 (100), 401 (16), 91 (33), 73 (23).

Anal. Calcd for $C_{39}H_{66}O_4Si_2$: C, 71.50; H, 10.15. Found: C, 71.35; H, 10.38.

3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7β-hydroxymethylandrost-5-en-7α-ol (4)

Freshly activated lithium wire (2–3 cm) was added to a solution of biphenyl (1.10 g, 7.13 mmol) in anhyd THF (20 mL) at 0 °C under argon. The solution was vigorously stirred at 0 °C for 1.5 h. The resulting green solution was cooled to –78 °C, and then **2** (200 mg, 0.31 mmol) in anhyd THF (3 mL) was added dropwise at the same temperature. After stirring the mixture for 1 h at –78 °C, aq sat. NH_4Cl solution (40 mL) was added. The organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed using PE–EtOAc (10:1) as eluent to give **4** (145 mg, 84%), which was recrystallized from *n*-hexane to give an analytical sample: white solid; mp 80–82 °C; $[\alpha]_D^{20}$ –29.8 (*c* = 0.80, acetone).

IR (KBr): 3433, 2933, 2856, 1632 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.05 [d, 6 H, *J* = 3.6 Hz, $(CH_3)_2Si$], 0.06 [s, 6 H, $(CH_3)_2Si$], 0.76 (s, 3 H, 18-CH_3), 0.89 [s, 9 H, $(CH_3)_3CSi$], 0.90 [s, 9 H, $(CH_3)_3CSi$], 0.98 (s, 3 H, 19-CH_3), 2.84 (br s, 1 H, 7-OH), 3.31 (d, 1 H, *J* = 10.5 Hz, 7-CH_2OH), 3.41 (d, 1 H, *J* = 10.5 Hz, 7-CH_2OH), 3.51–3.63 (m, 2 H, 3-H, 17-H), 5.34 (s, 1 H, 6-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = –5.0, –4.7, –4.7, –4.6, 11.5, 18.0, 18.3, 21.4, 25.9, 27.1, 31.3, 32.7, 36.9, 37.3, 37.5, 37.6, 43.1, 44.1, 45.2, 46.5, 69.1, 72.3, 72.4, 82.1, 128.6, 144.3.

MS (EI): *m*/*z* (%) = 563 ([M – 1]$^+$, 2), 533 (100), 489 (10), 401 (12), 75 (16).

Anal. Calcd for $C_{32}H_{60}O_4Si_2$: C, 68.03; H, 10.70. Found: C, 68.52; H, 10.68.

3β,17β-Bis(*tert*-butyldimethylsilyloxy)-7α-hydroxymethylandrost-5-en-7β-ol (5)

Method A: Under similar conditions as above, **3** (200 mg, 0.31 mmol) was debenzylated to afford a residue which was chromatographed on silica gel. Elution with PE–EtOAc (10:1) gave **5** (140 mg, 81%), which was recrystallized from *n*-hexane to give an analytical sample; white solid; mp 148–150 °C; $[\alpha]_D^{20}$ –28.0 (*c* = 0.93, acetone).

IR (KBr): 3429, 2955, 2933, 2856, 1637 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.03 [d, 6 H, *J* = 3.0 Hz, $(CH_3)_2Si$], 0.05 [s, 6 H, $(CH_3)_2Si$], 0.71 (s, 3 H, 18-CH_3), 0.87 [s, 9 H, $(CH_3)_3CSi$], 0.88 [s, 9 H, $(CH_3)_3CSi$], 1.04 (s, 3 H, 19-CH_3), 3.51 (d, 2 H, *J* = 3.6 Hz, 7-CH_2OH), 3.55–3.63 (m, 2 H, 3-H, 17-H), 5.28 (s, 1 H, 6-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = –5.0, –4.7, –4.6, 10.9, 18.2, 18.2, 18.8, 21.1, 25.8, 27.0, 31.3, 32.5, 36.9, 37.4, 37.5, 42.5, 42.9, 43.9, 44.3, 46.4, 66.6, 72.6, 73.7, 81.8, 129.1, 142.2.

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.

Method B: Under N_2, a portion (2 mL) of a solution of (isopropoxydimethylsilyl)methyl chloride (1.70 mL, 9.44 mmol) in anhyd THF (10 mL) was added to Mg turnings (0.24 g, 10.00 mmol). To the stirred mixture was added a few drops of 1,2-dibromoethane at r.t. and an exothermic reaction started in several min. The remaining solution was added dropwise over 30 min at such a rate as to maintain a gently exothermic reaction. After the addition was complete, the grey mixture was refluxed for 45 min and then cooled to 0 °C. A solution of **1** (1.00 g, 1.88 mmol) in anhyd THF (15 mL) was added dropwise at the same temperature over 30 min. The mixture was stirred at 0 °C for another 2 h, and aq sat. NH_4Cl solution (30 mL) was added at the same temperature. The organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 60 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give an unstable single adduct as a colorless oil; R_f 0.47 (PE–EtOAc, 15:1). To a stirred mixture of colorless crude adduct, MeOH (10 mL), THF (10 mL), $KHCO_3$ (0.28 g,

2.80 mmol) and KF (0.33 g, 5.68 mmol), was added 30% aq H_2O_2 solution (1.10 mL, 9.71 mmol) dropwise at r.t. The mixture was stirred at r.t. for 7 h until no starting material remained. Aq sat. $Na_2S_2O_3$ solution (25 mL) was added with stirring over 15 min until a negative starch-iodide test was observed. The mixture was extracted with EtOAc (3 × 80 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give a residue which was chromatographed on silica gel. Elution with PE–EtOAc (10:1) gave **5** (0.89 g, 84% for two steps).

3β,17β-Dihydroxy-7β-hydroxymethylandrost-5-ene (6)

Method A: A mixture of **4** and **5** (200 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. To the solution was added Et_3SiH (0.35 mL, 2.17 mmol), and then $BF_3{\cdot}OEt_2$ (0.45 mL, 3.55 mmol) was added dropwise. After stirring the mixture for 1 h, aq 10% Na_2CO_3 (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed with PE–EtOAc (3:1) to give **6** (108 mg, 95%), which was recrystallized from acetone to give an analytical sample; white solid; mp 181–183 °C; $[\alpha]_D^{20}$ –15.1 (*c* = 1.13, MeOH).

IR (KBr): 3311, 2928, 2874, 1635 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.76 (s, 3 H, 18-CH_3), 1.00 (s, 3 H, 19-CH_3), 3.22 (dd, 1 H, *J* = 7.2, 3.2 Hz, 7-CH_2OH), 3.36–3.44 (m, 1 H, 3-H), 3.55 (t, 1 H, *J* = 8.0 Hz, 17-H), 3.68 (dd, 1 H, *J* = 10.8, 3.2 Hz, 7-CH_2OH), 5.38 (s, 1 H, 6H).

^{13}C NMR (100 MHz, CD_3OD): δ = 12.4, 20.1, 22.9, 27.3, 31.2, 33.0, 34.8, 37.4, 38.8, 39.0, 43.5, 45.3, 46.1, 52.9, 54.1, 67.0, 72.5, 82.7, 126.2, 143.8.

MS (EI): *m*/*z* (%) = 320 (M^+, 4), 302 ([M – H_2O]$^+$, 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.

Method B: Under similar conditions as above, **5** (200 mg, 0.35 mmol) was reacted with Et_3SiH and $BF_3{\cdot}OEt_2$ to afford a residue, which was chromatographed on silica gel. Elution with PE–EtOAc (3:1) gave **6** (104 mg, 92%).

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