Two Novel Approaches toward Stereoselective Introduction of \(\beta\)-Hydroxy-methyl Group at the C-7 Position of 5-Androstene

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Abstract: Two novel approaches to stereoselective introduction of \(\beta\)-hydroxy-methyl group onto 5-androstene have been developed. In the first approach, coupling of benzylxymethyl chloride with the 7-carbonyl group of 1 mediated by SmI\(_2\) gives, after debenzylatation, two isomers 4 and 5 respectively, which are stereoselectively deoxygenated by means of anionic 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, \(\beta\)-hydroxy-methyl, 5-androstene, ionic hydrogenation

The introduction of \(\alpha\)-substituted group in steroids has been widely investigated; especially some \(\alpha\)-methyl derivatives.\(^1\)\(^-\)\(^3\) However, the stereoselective synthesis of \(\beta\)-substituted steroids has not been extensively studied. Recently, we have reported novel stereoselective introduction of \(\beta\)-methyl substituent in androstenes.\(^4\) Continuous interests in our laboratories prompt us to synthesize some \(\beta\)-hydroxy-methyl-substituted androstene derivatives.

In 1981, Nickisch et al. reported that \(\beta\)-hydroxy-methyl derivatives of Nickisch could be stereoselectively synthesized using 3-(6-chloro-1\(\beta\))-hydroxy-3-oxo-4,6-androstadien-17\(\alpha\)-yl)propionic acid \(\gamma\)-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 \(\beta\)-hydroxy-methyl at the C-7 position of steroids, using \(\beta\)-17\(\beta\)-bis(tert-butylidimethylsilyloxy)-5-androsten-7-one (1) as the starting material. One approach involves the coupling of benzylxymethyl 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 anionic 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.

The first approach to the stereoselective introduction of \(\beta\)-hydroxy-methyl in androstene was carried out as shown in Scheme 1. Coupling of benzylxymethyl chloride, which is a potential hydroxymethylation reagent,\(^6\) with androst-5-en-7-one 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 \(\alpha\)-OH isomer 4 in 84% yield and \(\beta\)-OH isomer 5 in 81% yield, respectively.\(^7\)

The structural assignments of the \(\alpha\)-OH and \(\beta\)-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 \(\alpha\)-carbon atom more than does the corresponding equatorial substituent.\(^4\)\(^,\)\(^8\) The axial \(\alpha\)-OH isomer 2 and the equatorial \(\beta\)-OH isomer 3 showed \(^{13}\)C NMR signals for C-7 at \(\delta = 71.5 \) and 74.3, respectively. Compounds 4 and 5 showed \(^{13}\)C NMR signals for C-7 at \(\delta = 72.3 \) 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 \(\beta\)-hydroxy-methyl-5-androstene derivative 6 in 95% yield with 96% de, which was determined by integration of the \(^1\)H 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 \(\beta\) orientation of 7-hydroxy-methyl group in compound 6.

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Figure 1 The key ROESY correlations of compound 6
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)-5-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 13C 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 1  Reagents and conditions: (a) PhCH₂OCH₂Cl, SmI₂, THF, r.t.; 2 (14%), 3 (49%); (b) Li, biphenyl, THF, −78 °C; 4 (84%), 5 (81%); (c) triethylsilane, BF₃·Et₂O, CH₂Cl₂, 0 °C, 95%.

Scheme 2  Reagents and conditions: (a) (isopropoxydimethylsilyl)methyl chloride, Mg, THF, 0 °C; (b) H₂O₂, KHCO₃, KF, MeOH, THF, r.t., 84% (for 2 steps); (c) triethylsilane, BF₃·Et₂O, CH₂Cl₂, 0 °C, 92%.

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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 flame-dried. 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 dimethyl ether (75 mL) was added to the cooled flask. The vigorously stirred slurry was stirred at 0 °C for another 2 h, and aq sat. NH₄Cl solution (30 mL) was added. The aqueous layer was separated. The aqueous layer was extracted with EtOAc (3 × 80 mL). The combined extracts were washed with brine, dried (Na₂SO₄), and evaporated in vacuo. The residue was chromatographed using PE–EtOAc (25:1) as eluent to give 4 (145 mg, 84%), which was recrystallized from n-hexane to give an analytical sample: white solid; mp 148–150 °C; [α]ᵣᵈ [387] = 564 (M*+, <1), 533 (100), 489 (38), 265 (22), 75 (39).

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2.80 mmol) and KF (0.33 g, 5.68 mmol), was added 30% aq H2O2 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. Na2S2O3 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 (Na2SO4), 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 CH2Cl2 (10 mL) and cooled to 0 °C. To the solution was added Et3SiH (0.35 mL, 2.17 mmol), and then BF3·OEt2 (0.45 mL, 3.55 mmol) was added dropwise. After stirring the mixture for 1 h, aq 10% Na2CO3 (5 mL) was added and the aqueous layer was extracted with CH2Cl2. The combined CH2Cl2 layers were washed with brine, dried (Na2SO4), 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; [α]D20 –15.1 (c = 1.13, MeOH).

**MS (EI):** m/z (%) = 320 (M+, 4), 302 ([M – H2O]+, 4), 289 (76), 271 (100), 253 (82), 159 (48), 91 (35).

**Anal. Calcd for C20H32O3: 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 Et3SiH and BF3·OEt2 to afford a residue, which was chromatographed on silica gel. Elution with PE–EtOAc (3:1) gave 6 (104 mg, 92%).

**References**