Mechanistic Studies of Deoxygenation of Steroidal Ring-D 16,17-Ketols with Trimethylsilyl Iodide

Masao NAGAOKA,* Etsuko NAGASAWA,† Sadao SATO,* and Mitsuteru NUMAZAWA*,#

Tohoku College of Pharmacy,* 4-1 Komatsushima-4-chome, Aoba-ku, Sendai 981–8558, Japan, and Analytical and Metabolic Research Laboratories,# Sankyo Co., Ltd., 2–38 Hiromachi-1-chome, Shinagawaku, Tokyo 140, Japan. Received December 3, 1998; accepted January 13, 1999

Deoxygenation reaction of steroidal 16,17-ketols 1, 2 and 6 as well as their silyl ethers 3 and 7 and 16- and 17-iodoketone analogs 11, 12, and 14 with trimethylsilyl iodide (TMSI) or HI under various conditions was examined. The results indicate that the deoxygenation producing 16- and 17-ketones 9 and 8 proceeds through multiple reaction pathways; a direct iodination of a siloxy group of the ketol silyl ethers by iodide ion to give the iodoketones (path b), addition of TMSI to a carbonyl group of the ketol silyl ethers to yield diiodo derivatives 22 and 23 through iodo-bis-TMS compounds 20 and 21 (path a), and cleavage of ether bond of dimers 15—18 initially produced are, at least, involved. In these sequences, rearrangement of the 16-ketols 1 and 2 to the 17β-ketol 6 also plays a significant role. The yields of the ketones 9 and 8 and their relative amounts would be dependent on the relative importance of each pathway in the reaction.

Key words trimethylsilyl iodide; deoxygenation; 16-hydroxy-17-keto steroid; 17β-hydroxy-16-keto steroid; steroid dimer

Trimethylsilyl iodide (TMSI) is one of the most important organosilicon reagents in organic synthesis, offering a broad variety of useful functional group transformations under mild conditions. Ho3 has reported the usefulness of this silyl reagent in the transformation of α-ketol to ketones. TMSI has also been used in reductive removal of tert-hydroxy group of α,β-unsaturated δ-tert-hydroxy ketones6 and in the deoxygenations of vic-diols,4 epoxides,5 and carbonyl-conjugated allylic ethers.7 We have previously reported the regiospecific deoxygenation at C-17 of the dihydro acetone side chain of corticoid steroids and the corresponding 17-methyl ether7 and the reductive removal of an oxygen function at C-21 of 21-hydroxy-20-keto and 21-alkoxy-20-keto steroids8 with this silyl reagent. Furthermore, treatment of cyclic steroidal α-ketols, 16α- and 16β-hydroxy-17-ketones as well as a 17β-hydroxy-16-ketone with TMSI in CHCl3 gives a mixture of 16- and 17-ketones as the deoxygenated products in which the 17-ketone is a principal product irrespective of the substrate used, the 16-ketols or the 17β-ketol.9 On the basis of this, we report that, in addition to a direct iodination mechanism which involves silylation of a hydroxyl function of the ketol with TMSI followed by displacement of the siloxy group by I and a subsequent reductive deiodination,7 other mechanism(s) is(are) involved in the deoxygenation.

To gain insight into the mechanisms for the deoxygenation of the 16,17-ketols with TMSI, we used three possible 16,17-ketols, 16α-ketol 1, 16β-ketol 2, 17β-ketol 6 for the deoxygenation reaction (Fig. 1). It has previously been reported that on treatment with 3 mol eq of TMSI in CHCl3 at room temperature for 1 h, all the ketols are deoxygenated in good to excellent yields, yielding about 75:25 to 88:12 mixtures of 17-ketone 8 and 16-ketone 9 (Table 1, entries 1, 5, and 8); in contrast, the formation of the deoxygenated compounds is not detected by 1H-NMR analysis in the reaction of 17α-ketol 5 but a complex mixture of products is formed.9 The course of these deoxygenation reactions was carefully monitored by TLC. This indicated that more than two intermediates were formed in the early stages and then disappeared from the reaction mixtures in proportion to the reaction time up to 1 h, being accompanied by the increased production of the deoxygenated products 8 and 9 in each experiment. In order to isolate the intermediates, the 16α-ketol 1 was treated with a decreased amount (1 mol eq) of TMSI for 15 min to 3.5 h (Table 1). Purification of the products with column chromatography afforded two (compounds 15 and 17), three (compounds 15, 17, and 18) or four steroids (compounds 15—18) under the condition with a 15-min, 1-h, or 3.5-h reaction time, respectively, in 1—36% yields, as well as the starting material and/or its rearranged product 6 and the 17- and 16-ketones 8 and 9 (entries 2—4). Under similar conditions, the reaction of the 16β-ketol 2 and the 17β-ketol 6 yielded only compound 15 (21—31%) in addition to the ketones 8 and 9 (entries 6, 7, 9, and 10). However, compounds 15—18 principally did not correspond with the intermediates produced under the condition with 3 mol equivalent of TMSI, based on the TLC analysis.

IR spectra of the compounds 15—18 showed a carbonyl absorption at around 1750 cm⁻¹, respectively, and no hydroxy absorption was observed in any spectrum. Mass spec-
of all four compounds showed a molecular ion at m/z 562 in each one, suggesting that these compounds consisted of two molecules of various combinations of ketones 8 and 9 through an ether bond. X-Ray crystallographic analysis of product 18 indicated that this was a dimer produced by coupling of two molecules of the 16-ketone 9 through an ether bond at C-17β of each steroid (Fig. 2). The structures of other compounds 15—17 were established by 1H-NMR spectroscopy using nuclear Overhauser effect (NOE) experiment; there was no significant NOE enhancement of the 18-methyl protons (δ 0.93 and 0.82, respectively) of the 16β-ketol 2 or the 17β-ketol 6 when the 16α-proton (δ 3.94) of compound 2 and the 17α-proton (δ 3.75) of the other were irradiated, whereas significant NOE enhancement (about 10%) of the 18-methyl protons (δ 0.91 and 0.83, respectively) of the 16α-ketol 1 and the 17α-ketol 5 was produced by irradiation of the 16β-proton (δ 4.32) of the former and the 17β-proton (δ 3.39) of the latter, respectively. Then, it was found that compounds 15 and 17 were the coupled products of the 17-ketone 8 with the 16-ketone 9 through an ether bond at C-16β-position of compound 8 and the C-17β position of the other and through an ether bond at C-16α of the former molecule and C-17β of the latter, respectively, whereas compound 16 consisted of two molecules of compound 8 through an ether bond at C-16β and C-16α of each molecule.

To further elucidate the role of these dimers in the deoxygenation reaction, the 16β,17β-dimer 15 was treated with TMSI or HI which is thought to be liberated in the reaction medium during the reaction (Table 2). Treatment of the dimer 15 with TMSI or HI under various conditions gave a 73:27 to 63:37 mixture of the 17- and 16-keto products 8 and 9, respectively, in poor to moderate yields, along with the thermodynamically most stable 17β-ketol 6δ (entries 11—14); the reaction with 1 mol equivalent of TMSI for 0.5 h produced a mixture of the deoxygenated products (36%) (entry 11), whereas the reaction with 1 mol equivalent of HI for the same period did not give the deoxygenation product and only the ketol 6 was isolated. Employment of a large excess (6 mol eq) of TMSI or HI and a longer reaction time (16 h) in the reaction yielded the ketones 8 and 9 in 51 or 65% yield (entry 12 or 14), respectively. This yield is lower than those (90—98%) from the ketols 1, 2, and 6 under the condition with 3 mol eq of TMS and 1-h reaction period (Table 1, entries 5 and 8), indicating that not only the dimer 15 but also other dimers are not obligatory intermediates for the deoxygenation reaction of the 16,17-ketols.

Olah et al.11) and we7,8) have previously shown that a haloketone is quite easily transformed into the corresponding ketone by treatment with TMSI or HI. Thus, we prepared 16α- and 16β-iodo-17-ketones 11 and 12 on treatment of 16α-bromoketone 10 with Nal, whereas treatment of the 16-

Table 1. Deoxygenation and Dimer Formation by the Treatment of Ketols 1, 2, and 6 with TMSIa)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>TMSI mol</th>
<th>Time h</th>
<th>Product (% yield)</th>
<th>Ketone ratio (17- to 16-ketone)b)</th>
<th>Dimers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ketol 17-and 16-Ketonesb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8 and 9 (28)</td>
<td>88:12c)</td>
<td>15 (11), 17 (4)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.25</td>
<td>6 (26)</td>
<td>8 and 9 (28)</td>
<td>90:10</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6 (12)</td>
<td>8 and 9 (46)</td>
<td>93:7</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>3.5</td>
<td>8 and 9 (90)</td>
<td>87:13c)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>6 (46)</td>
<td>8 and 9 (25)</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0.25</td>
<td>6 (30)</td>
<td>8 and 9 (25)</td>
<td>95:5</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>8 and 9 (95)</td>
<td>75:25c)</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>6 (65)</td>
<td>8 and 9 (23)</td>
<td>96:4</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>1</td>
<td>0.25</td>
<td>6 (40)</td>
<td>8 and 9 (23)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>6 (31)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Reactions were carried out in CHCl₃ at room temperature under N₂ atmosphere. b) The product was obtained as a mixture of 17- and 16-ketones. c) The ratio of 17-ketone to 16-ketone was obtained by 1H-NMR or GC analysis. d) Reference 9.
iodoketones served as precursors for the final step of the deoxygenation sequences as previously reported. Based on these results, it seems likely that the iodoketones to 16-ketone was obtained by 1H-NMR or GC analysis.

We next explored the reaction of 16α- and 17β-ketol silyl ethers 9 and 18 with TMSI or HI (Table 3). When these silyl ethers were briefly treated with 1 mol eq of TMSI for 10 min, four dimers 15—18 in the case of the 16α-silyl ether 9 (entry 15), and the dimer 15 in the case of the 17β-isomer 7 (entry 18) were produced, respectively. The production of the ketones 8 and 9 increased in a time-dependent manner. On the other hand, treatment of the silyl ethers with 1 mol eq of HI for 1 h resulted in the dimers 15 and 17 and the ketones being produced in each experiment (entries 17 and 20). It is noteworthy that compound 15 is produced as a principal dimer in the reaction of the 17β-silyl ether 7, as seen in the reaction of the 17β-ketol 6.

When a mixture of the 16-iodo-17-ketone 11 and the 17β-silyl ether 7 in CHCl₃ was allowed to stand at room temperature for 12 h, no dimers were observed in the reaction mixture but the steroids used were quantitatively recovered.

Doyle et al.[] reported the synthesis of an ether from a carbonyl compound and an alkoxy silane by silane reduction in acidic medium. Sassaman et al.[] also reported the synthesis of an ether from a carbonyl compound and an alcohol with TMSI as a catalyst. On the basis of these previous reports along with the present results, it was thought that 16β,17β-dimer 15 and the 16α,17β-dimer 17 would be formed from two molecules of the most stable 17β-ketol silyl ether 7 through a sequence shown in Chart 2. Other dimers 16 and 18 could be similarly formed by coupling of 16α-siloxy compound 3 to the 17β-siloxy isomer 7 through a sequence similar to that described above. However, in addition to these coupling reactions, the dimers could also be pro-

ketone 9 with isopropenyl acetate followed by reaction with I₂ gave 17α-iodo-16-ketone 14 (Chart 1). The structures of the iodoketones were determined principally by the 1H-NMR experiments. Treatment of these iodoketones 11, 12 and 14 with TMSI or HI in CHCl₃ for 5 min at room temperature produced quantitatively the corresponding reductively de-

Table 3. Reaction of Silyl Ethers 3 and 7 with TMSI or HI

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reagent mol</th>
<th>Time h</th>
<th>Ketol</th>
<th>17-and 16-Ketones</th>
<th>Ketone ratio (17- to 16-ketone)</th>
<th>Dimers</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>3</td>
<td>TMSI 1</td>
<td>0.15</td>
<td>1</td>
<td>(48), 6 (23)</td>
<td>15 (12), 16 (4), 17 (6), 18 (3)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td>TMSI 1</td>
<td>1</td>
<td>1</td>
<td>(4), 6 (13)</td>
<td>15 (2), 16 (2), 17 (4), 18 (1)</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>HI 1</td>
<td>1</td>
<td>6</td>
<td>(36)</td>
<td>15 (21), 17 (2)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>7</td>
<td>TMSI 1</td>
<td>0.15</td>
<td>6</td>
<td>(84)</td>
<td>15 (5)</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>7</td>
<td>TMSI 1</td>
<td>1</td>
<td>6</td>
<td>(40)</td>
<td>15 (2)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>7</td>
<td>HI 1</td>
<td>1</td>
<td>6</td>
<td>(33)</td>
<td>15 (17), 17 (2)</td>
<td></td>
</tr>
</tbody>
</table>

a) Reactions were carried out in CHCl₃ at room temperature under N₂ atmosphere. b) The product was obtained as a mixture of 17- and 16-ketones. c) The ratio of 17- ketone to 16-ketone was obtained by 1H-NMR or GC analysis.
duced through other coupling combinations of the silyl ethers.

The results obtained by the reaction of the iodoketones and the silyl ethers with TMSI or HI indicate that the deoxygenation reaction of the dimers proceeds in a sequence which involves an initial dimer-cleavage to give the iodoketones and the silyl ethers or the ketols and a subsequent reaction of these products with another mole of the reagent.

In order to elucidate whether enediol bis-silyl ether 19 is involved in the deoxygenation reaction, this ether was prepared from the silyl ethers 3 or 7 on treatment with TMSI in Et₃N at room temperature for 5 d in almost quantitative yield (Chart 3). The spectral data of compound 19 obtained was consistent with the assigned structure. Reaction of compound 19 with TMSI (1 mol eq, 1 h) gave the 17β-ketol 6 in 90% yield, accompanied by a small amount of the 17β-silyl ether 7 (5%). Reaction of these products with another mole of TMSI gave the 17β-iodoketone 14 or its 17β-isomer 24 and the 16-iodoketone 11 or 12 which is efficiently converted into the corresponding deoxygenated product 9 or 8, respectively. The cleavage of the ether bond of the dimers 15—18 principally produced through compounds 3 and 7 would also be involved in the reaction. The relative importance of each sequence in the deoxygenation should be one of the factors affecting not only the yield of deoxygenated products but also the relative amount of the 16- to 17-ketone.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were determined on a Shimadzu IR-430 or a Perkin Elmer FT-IR 1725X spectrophotometer. ¹H-NMR spectra were obtained with a JEOL PMX 60 (60 MHz) or a JEOL GX 400 (400 MHz) spectrometer and ¹³C-NMR were obtained on JEOL GX 400 (100 MHz) using tetramethylsilane as an internal standard. Mass spectra were measured on a JEOL JMS-DX 303 spectrometer. GC was carried out using a Shimadzu GC-7AG equipped with a hydrogen flame ionization detector. TMSI and CHCl₃ were purified as described in the previous work. The 16,17-ketols 1, 2, and 6 were synthesized according to the methods previously reported.

16α-Iodo-5α-androstan-17-one 11 and 16β-Iodo-5α-androstan-17-one (12) A mixture of 16α-bromo-5α-androstan-17-one 8 and 9 was synthesized according to the methods previously reported.

In conclusion, the deoxygenation reaction of the 16,17-ketols 1, 2, and 6 with TMSI was found to proceed not solely through the direct iodination pathway (path b) but through multiple sequences (Chart 4). The addition of TMSI to the silyl ether 3 or 7 initially gives the adducts 21 and 20 (path a) of which further reaction with another mole of TMSI yields the diiodo derivative 23 and 22, respectively, and dehydriodination of the diiodo compound followed by ketonization produces the 17-iodoketone 14 or its 17β-isomer 24 and the 16-iodoketone 11 or 12 which is efficiently converted into the corresponding deoxygenated product 9 or 8, respectively. The cleavage of the ether bond of the dimers 15—18 principally produced through compounds 3 and 7 would also be involved in the reaction. The relative importance of each sequence in the deoxygenation should be one of the factors affecting not only the yield of deoxygenated products but also the relative amount of the 16- to 17-ketone.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were determined on a Shimadzu IR-430 or a Perkin Elmer FT-IR 1725X spectrophotometer. ¹H-NMR spectra were obtained with a JEOL PMX 60 (60 MHz) or a JEOL GX 400 (400 MHz) spectrometer and ¹³C-NMR were obtained on JEOL GX 400 (100 MHz) using tetramethylsilane as an internal standard. Mass spectra were measured on a JEOL JMS-DX 303 spectrometer. GC was carried out using a Shimadzu GC-7AG equipped with a hydrogen flame ionization detector. TMSI and CHCl₃ were purified as described in the previous work. The 16,17-ketols 1, 2, and 6 were synthesized according to the methods previously reported.
mmol) and sodium iodide (1.3 g, 8.67 mmol) in aceton (20 ml) was heated under reflux for 4 h. The reaction mixture was then diluted with AcOEt, washed with water, and dried over Na2SO4. After evaporation of the solvent, the residue obtained was chromatographed on silica gel (hexane-AcOEt = 100:1). The first eluate was recrystallized from ethyl ether to give compound 12 (189 mg, 21%) as colorless needles, mp 129—131 °C. 1-H-NMR (CDCl3) δ: 0.80 (3H, s, 19-Me), 1.13 (3H, s, 18-Me), 4.37 (1H, t, J = 9.0 Hz, 16-H). The second eluate was recrystallized from MeOH to give compound 11 (227 mg, 25%) as colorless needles, mp 171—174 °C (lit.19) mp 163—165 °C. 1-H-NMR (CDCl3) δ: 0.77 (3H, s, 19-Me), 0.83 (3H, s, 18-Me), 4.83 (1H, s, 16-H).

17α,5α-androst-16-one (14) To a solution of 9 (458 mg, 1.67 mmol) in 10 ml of isopropyl acetate was added 0.3 ml of a catalyst solution (0.10 mmol of isopropyl acetate containing 0.2 ml of concentrated sulfuric acid). After the slow distillation of about half the solvent over 5 h, an additional 5 ml of isopropyl acetate and 0.3 ml of the catalyst solution were added and the slow distillation was continued for another 5 h. The solution was cooled, diluted with ethyl ether, and washed with 5% NaHCO3 solution and then with water, and dried over Na2SO4. After evaporation of the solvent, the residue obtained was chromatographed on silica gel (hexane-ethyl ether = 1:1) to give 5α-androst-16-en-16-y1 acetate (13) (279 mg, 42%) as colorless prisms, mp 106—109 °C. 1-H-NMR (CDCl3) δ: 0.82 (3H, s, 18-Me), 1.20 (6H, s, 19-Me), 1.28 (IH, s, 18-Me), 2.80 (1H, s, 19-Me), 4.55 (1H, dd, J = 7.0, 17.0 Hz). IR (KBr) cm⁻¹: 1750 (C=O). Anal. Calcd for C19H30O2: C, 72.87; H, 10.39. Found: C, 72.80; H, 10.50.

17β-androst-16-one (16) (1.0 g, 3.44 mmol) in 15 ml of CHCl3 was treated with TMSI (689 mg, 3.44 mmol) at room temperature for 3.5 h. The same workup as described above afforded an oily product which was chromatographed on silica gel. Elution with hexane–benzene gave a solid (435 mg, 46%). Elution with hexane–benzene and recrystallized from AcOEt gave compound 17 (10 mg, 1%) as colorless plates, mp 288.5—290 °C. 1-H-NMR (CDCl3) δ: 0.80 (12H, s, 18- and 19-Me), 4.36 (2H, s, 17-Me). GC conditions and retention times were as follows: 3% SE-30 Chromosorb WAW DMCS 80/100, 3 × 3.5 mm i.d. column temperature 220 °C, Injection port and detector temperature 250 °C, N2 30 ml/min, tR: 18.72 min; 18.4 min.

Isolation of 16β-(16-Oxo-5α-androst-17β-yloxy)-5α-androst-17-one (15), 16β-(17-Oxo-5α-androst-17β-yloxy)-5α-androst-17-one (16), 16β-(16-Oxo-5α-androst-17β-yloxy)-5α-androst-17-one (17), and 17β-(16-Oxo-5α-androst-17β-yloxy)-5α-androst-17-one (18) The solution of compound 1 (1.0 g, 3.44 mmol) in aceton at room temperature for 3.5 h.

General Procedure for Reaction of 16,17-Ketols with TMSI A solution of the ketol substrate (0.3 mmol) and TMSI in CHCl3 (alcohol free, 1 ml) was stirred at room temperature for an appropriate time under N2, and then the reaction mixture was poured into 5% Na2S2O3 solution (10 ml) and extracted with AcOEt (50 ml). The organic layer was washed with 5% NaHCO3 solution and saturated NaCl solution, and dried over Na2SO4. After evaporation of the solvent, the residue was purified by silica gel thin layer chromatography or column chromatography (hexane-AcOEt) or recrystallization to give the deoxygenated 16- and 17-ketones, the dimer products, and the recovered and/or rearranged ketols. The ratios of 16-hydroxy-17-ke- tone to 17β-hydroxy-16-ketone were determined by 1-H-NMR (60 MHz) spectroscopy (methine signals at C-16 or C-17) without separation. The ratios of 17- to 16-ketols, the deoxygenated product, were determined by 1-H-NMR (400 MHz) spectroscopy (the 18- and 19-angular methyl signals) or GC.
April 1999 553

22.05, 22.07, 26.70, 28.67, 28.69, 28.91, 28.94, 29.59, 31.12, 31.88, 34.32, 34.42, 36.34, 36.43, 36.46, 36.65, 37.25, 38.30, 38.38, 38.54, 42.49, 44.99, 45.31, 46.97, 46.99, 47.17, 53.63, 55.01, 80.92, 91.14, 214.73, 216.65. IR (KBr) cm⁻¹: 1750 (C=O). MS m/z (rel. int. %): 562 (M⁺, 22), 547 (5), 274 (100), 259 (90), 218 (60). Anal. Calcd for C₃₈H₅₈O₃: C, 81.12; H, 10.20. Elution with benzene–ethyl ether (4 : 1) and re-crystallization from acetone afforded compound 7 (81 mg, 97%).

Crystal Structure Determination for Dimer 18. Data was collected on a Rigaku AFC-5R diffractometer, C₃₈H₅₈O₃, F. W. = 562.9, a=7.098 (1), b=

References