Formation of 17β-Alkoxy-16-keto Steroids by Reaction of 16α-Hydroxy-17-keto and 17β-Hydroxy-16-keto Steroids with Trimethylsilyl Iodide in the Presence of Alkyl Alcohols

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Received January 31, 2000; accepted April 15, 2000

16α-Hydroxy-17-keto steroids, 1, 3, and 8, and their 17β-hydroxy-16-keto isomers, 4, 5, and 9, were transformed into the corresponding 17β-alkoxy-16-keto derivatives on treatment with trimethylsilyl iodide (TMSI) in the presence of alkyl alcohol in $CHCl_3$ in poor to high yields.

Key words steroidal D-ring ketol; trimethylsilyl iodide; alkoxylation; alkyl alcohol; 17β-alkoxy-16-keto steroid

Organosilicon reagents are useful in organic synthesis, offering a broad variety of useful functional group transformations.[1] Trimethylsilyl iodide (TMSI), one such reagent, has been used in the reductive deoxygenation of the *tert*-hydroxyl group of α,β-unsaturated γ-*tert*-hydroxy ketones,[2] ketols,[3] and *vic*-diols,[4] as well as in the cleavage of oxygen-containing functional groups such as ethers,[5] lactones,[6] and esters.[6] We have previously reported the regiospecific C-17 deoxygenation of the dihydroxy acetone side- chain of corticoid steroids[7] and the reductive removal of an oxygen function at C-21 of 21-hydroxy-20-keto and 21-alkoxy-20-keto steroids.[8] In addition, reaction of steroidal ring-D 16- and 17β-ketols with TMSI in $CHCl_3$ gives a mixture of the deoxygenated products, 16- and 17-ketones, in which the 17-ketone is the principal product, in poor to excellent yields depending on the A,B-ring structure of the substrate used.[9] We have found that the deoxygenation of the 21-alkoxy-20-ketones with TMSI is accelerated in the presence of MeOH.[8] Thus, we decided to investigate whether alcohol plays such a role in the deoxygenation of steroidal 16,17-ketols. Reaction of the 16,17-ketols with TMSI in the presence of alcohol did not improve the deoxygenation reaction but resulted in the formation of the 17β-alkoxy-16-ketones, as major products.

Results and Discussion

The TMSI-catalyzed deoxygenation reaction of 16α-hydroxy-17-keto steroid **1**, which has a 5α-3-one structure and is known to be a poor substrate for deoxygenation,[9] was carried out in the presence of MeOH (8 mol eq TMSI, 20 mol eq MeOH, 4.5 h, room temperature) in $CHCl_3$ to give the deoxygenated product, 17-ketone **2**, in a similar yield (17%) to that in reaction without MeOH, along with the rearranged product, 17β-ketol **4** (31%) (Chart 1). In contrast, treatment of the 16α-ketol **1** with 8 mol eq TMSI followed by addition of MeOH (20 mol eq) produced 17β-methoxy-16-ketone **6a** in 50% yield as well as the 17-ketone **2** (6%) and the 17β-ketol **4** (25%). 17β-Methoxide **6a** was identical to the authentic sample produced on treatment of the 17β-ketol **4** with MeI and Ag_2O.[9a] The 17β-methoxide **6a** (19%) was also obtained on treatment of the 17β-ketol **4** with TMSI followed by addition of MeOH under the conditions described for the reaction of the 16α-isomer **1**. Furthermore, MeOH was first reacted with TMSI in $CHCl_3$ (8 mol eq TMSI and 20 mol eq MeOH) and then this reaction mixture was added to a solution of the 16α-ketol **1**, yielding the 17β-methoxide **6a** in an improved yield (65%) along with the 17-ketone **2** (10%) and the 17β-ketol **4** (5%).

Based on the above results, we explored the production of 17β-alkoxy-16-keto steroids on treatment of steroidal D-ring 16α- and 17β-ketols with a mixture of TMSI and alkyl alcohol [CH_3OH, C_2H_5OH, C_3H_7OH, $(CH_3)_2CHOH$, or $(CH_3)_2CHCH_2OH$] under various conditions (Table 1). Treatment of the 16α-ketol **1** with a small amount of the reagent mixture (2 mol eq TMSI and 8 mol eq MeOH or EtOH, reagent system B, entry 2 or 4) gave an improved yield of the 17β-methoxide or -ethoxide (**6a** or **6b**) compared with that obtained under the above conditions (reagent system A, entry 1 or 3) (79% *vs.* 65% for MeOH or 48% *vs.* 35% for EtOH). Then the reaction of C_{19} steroids **1**, **3**, **4**, and **5** was studied using the reagent system B which in all cases gave generally better yields of the corresponding 17β-alkoxy-16-keto products than those obtained by the other system (entries 5—19). In contrast, the system A was generally suitable for the reaction of C_{18} steroids **8** and **9**, except for the reactions with MeOH and EtOH. This is due to the presence of a phenolic hydroxyl group at C-3 of the steroids, which consumes another mole of the TMS-alcohol complex formed *in situ* in the reaction mixture. In a series of reactions with the 16α-ketols as substrates, the 17β-alkoxide products were obtained generally in better yields (48—90%) compared with those (35—75%) in reactions with the corresponding 17β-ketols, which are known to be thermodynamically more stable than the 16α-isomers.[10]

Olah and his group have previously reported the TMSI-catalyzed preparation of methoxymethyl ethers of primary and secondary alcohols by reaction with dimethoxy methane.[11] This reaction is thought to proceed through iodination of the dimethoxy compound. Furthermore, treatment of the 17β-ketol **4** with HI in $CHCl_3$ in the presence of MeOH for 45 min produced the 17β-methoxide **6a** (20%). Taken together, it seems likely that the 17β-alkoxide is similarly produced through iodination of the 17β-ketol which is a HI-catalyzed isomerized product in the reaction of the 16α-ketol; displacement of a 17β-hydroxyl group by I^- affords the 17α-iodide **12** which sequentially reacts with RO-TMS initially produced to yield the 17β-alkoxide **6** (Fig. 1, path a). Treatment of the 17β-ketol **5**, which has no oxygen function in the A-ring, with 1 mol eq TMSI for a brief period (15 min), followed by addition of 1 mol eq MeI, did not produce the 17β-methyl ether **7a**, excluding a reaction pathway

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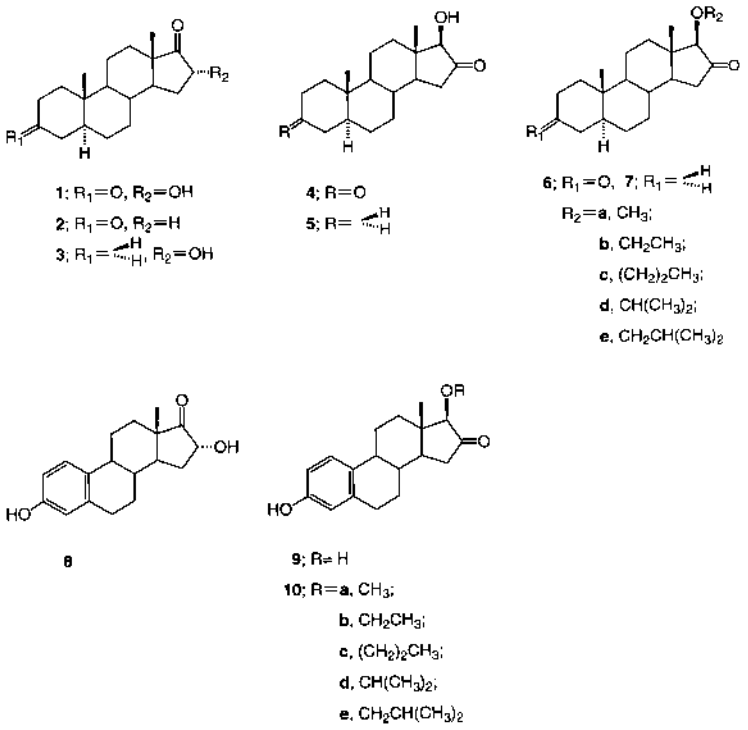

Chart 1

which involves alkylation of the 17β-hydroxyl group of the thermodynamically more stable 17β-ketol. Formation of the 17β-alkoxides from the 17β-ketols is generally less efficient than that from the 16α-ketols in all series of 17β-alkoxylation reactions (Table 1, substrate: **1** *vs.* **4**, **3** *vs.* **5**, and **8** *vs.* **9**). This indicates that, in addition to the iodination pathway (path a), the one which does not involve a 17β-ketol as an intermediate, is involved in the production of the alkoxide from a 16α-ketol.

Reaction of the 16α-ketol **1** with 1 mol eq of HI or TMSI in $CHCl_3$ containing 10 mol eq of MeOH for a short period (45 min) yielded the 17β-methoxide **6a** (22% or 16%) and no detectable amount of the rearranged isomer **4** was produced although substrate **1** was recovered in 47% or 27% yield, respectively. These facts support the involvement of the other pathway which involves addition of HI or MeO–TMS to the 17-carbonyl group of the 16α-ketol. We have previously reported that the deoxygenation of the 16α- and 17β-ketols with TMSI or HI proceeds, in part, through the production of dimers formed at an early stage of the reaction by coupling of various combinations of two molecules, 5α-andorstan-16-one and -17-one, through an ether bond at the 16α-, 16β-, and 17β-positions.[9b] Considering the production mechanisms of dimers of the steroidal D-ring ketols, ether compounds, as well as the previous findings of the production of an ether from a carbonyl compound in alcoholic acidic medium using silane reduction[12] and the TMSI-catalyzed reductive coupling of a carbonyl compound with alkoxysilane,[13] it is presumed that the 17β-alkoxide is also produced through addition of an alkoxide species (RO- or TMS-OR) to the 17-carbonyl group of the 16α-ketol to give the acetal analog **13**, followed by dehydration and subsequent isomerization (Fig. 1, path b).

It was found that 17β-alkoxy-16-ketones were produced

Table 1. Formation of 17β-Alkoxy-16-keto Steroids from 16α- and 17β-Ketols

Entry	Substrate	Conditions			17β-Alkyl ether (yield %)[b]
		Reagents[a]	Alcohol	Time (h)	
1	**1**	A	MeOH	5	**6a** (65)
2		B	MeOH	3.5	**6a** (79)
3		A	EtOH	2	**6b** (35)
4		B	EtOH	1.5	**6b** (48)
5		B	PrOH	2	**6c** (63)
6		B	iso-PrOH	3	**6d** (69)
7		B	iso-BuOH	1	**6e** (81)
8	**4**	B	MeOH	4.5	**6a** (62)
9		B	EtOH	2	**6b** (63)
10		B	PrOH	2.5	**6c** (66)
11		B	iso-PrOH	4	**6d** (35)
12	**3**	B	MeOH	0.83	**7a** (66)
13		B	EtOH	1.33	**7b** (90)
14		B	PrOH	0.83	**7c** (83)
15		B	iso-PrOH	1	**7d** (67)
16	**5**	B	MeOH	0.75	**7a** (52)
17		B	EtOH	2.5	**7b** (65)
18		B	PrOH	2.5	**7c** (75)
19		B	iso-PrOH	4	**7d** (42)
20	**8**	B	MeOH	5	**10a** (3)
21		B	EtOH	7	**10b** (73)
22		A	PrOH	2.5	**10c** (78)
23		A	iso-PrOH	2.5	**10d** (84)
24		A	iso-BuOH	1	**10e** (77)
25	**9**	A	MeOH	1	**10a** (14)
26		A	EtOH	1	**10b** (18)
27		A	PrOH	1	**10c** (65)
28		A	iso-PrOH	1	**10d** (11)

a) Reagent system A: TMSI (8 mol) and alcohol (20 mol) in $CHCl_3$; Reagent system B: TMSI (2 mol) and alcohol (8 mol) in $CHCl_3$. *b*) Isolated yields.

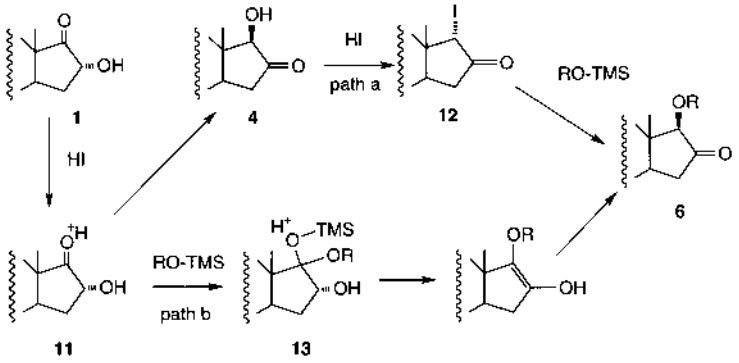

Fig. 1

from the corresponding 17β-hydroxy-16-ketones or 16α-hydroxy-17-ketones on treatment with TMSI or HI-alcohol complex, generally in fair to good yields. Direct iodination of the 17β-ketol along with addition of an alkoxide to the 17-carbonyl group of a 16α-ketol is involved in the reaction.

Experimental

Melting points were measured on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a Perkin Elmer FT-IR 1725X spectrophotometer. ^{1}H-NMR spectra were obtained with a JEOL EX 270 (270 MHz) or a JEOL GX 400 (400 MHz) spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured on a JEOL JMS-DX 303 spectrometer. $CHCl_3$ (EtOH-free) was purified by shaking with conc.-sulfuric acid several times, washing with water until neutral and drying over P_2O_5, followed by distillation. Trimethylsilyl iodide (TMSI) was distilled before use or TMSI, distilled and then stored at -25 °C under N_2 with copper chips in a light-protected bottle, was used.

Reaction of Steroidal Ring-D 16,17-Ketols with TMSI and Alcohols A) Typical reaction conditions are as follows: a mixture of TMSI and alcohol (0.32 and 1.28 mmol or 1.28 and 3.2 mmol, respectively) in $CHCl_3$ (1 ml) was added to a solution of steroid (0.16 mmol) in $CHCl_3$ (2—5 ml) and the reaction mixture was stirred at room temperature for an appropriate period under N_2. Then, the reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, saturated NaCl solution and dried over Na_2SO_4. After evaporation of the solvent, the residue obtained was purified by silica gel column chromatography (hexane–AcOEt) and/or recrystallization.

B) A mixture of compound **1** (50 mg, 0.164 mmol), MeOH (53 μl, 42 mg, 1.3 mmol), TMSI (656 mg, 3.28 mmol) and $CHCl_3$ (2 ml) was stirred at room temperature for 4.5 h and then poured into 10% $Na_2S_2O_3$ solution and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, saturated NaCl solution, and dried over Na_2SO_4. After evaporation of the solvent, the residue obtained was purified by silica gel column chromatography (hexane–AcOEt). The first eluate was recrystallized from acetone to give the 17-ketone **2** (8 mg, 17%), mp 123—126 °C (lit.[14] mp 126—130 °C). The second eluate was recrystallized from MeOH to yield the 17β-ketol **4** (16 mg, 31%), mp 163—165 °C (lit.[15] mp 176—178 °C).

C) To a solution of compound **1** (100 mg, 0.32 mmol) in $CHCl_3$ (4 ml) was added TMSI (510 mg, 2.55 mmol) and the resulting mixture was stirred at room temperature for 1 h. Then, MeOH (256 μl, 203.6 mg, 6.4 mmol) was added and the reaction mixture was stirred for another 1 h, poured into 10% $Na_2S_2O_3$ solution, and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, saturated NaCl solution, and dried over Na_2SO_4. After evaporation of the solvent, the residue obtained was purified by silica gel column chromatography (hexane–AcOEt). The first eluate was recrystallized from acetone to give the 17-ketone **2** (6 mg, 6%), mp 120—124 °C (lit.[14] mp 126—130 °C). The second eluate was recrystallized from acetone to yield the 17β-methoxide **6a** (46 mg, 50%) as colorless prisms, mp 138—141 °C (lit.[9a] mp 139—143 °C). The third eluate was recrystallized from MeOH to give 17β-ketol **4** (25 mg, 25%) as colorless needles, mp 162—165 °C (lit.[15] mp 176—178 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.77 (3H, s, 18-Me), 1.07 (3H, s, 19-Me), 3.80 (1H, s, 17α-H).

D) TMSI (510 mg, 2.55 mmol) was added to a solution of compound **4** (100 mg, 0.32 mmol) in $CHCl_3$ (4 ml) and the reaction mixture was stirred at room temperature for 1 h. Then, MeOH (256 μl, 203.6 mg, 6.4 mmol) was added and the resulting mixture was stirred for 1 h, and poured into 10% $Na_2S_2O_3$ solution. After the same work-up as described above, the oily product obtained was purified by silica gel colunm chromatography (hexane–AcOEt). The first eluate was recrystallized from acetone to give the 17-ketone **2** (58 mg, 62%), mp 124—126 °C (lit. mp[14] 126—130 °C). The second eluate was recrystallized from acetone to give the 17β-methoxide **6a** (20 mg, 19%), mp 139—142 °C (lit.[9a] mp 139—143 °C). The third eluate was recrystallized from MeOH to give the recovered 17β-ketol **4** (16 mg).

17β-Ethoxy-5α-androstane-3,16-dione (6b): mp 154—158 °C (from acetone–hexane). IR (KBr) 1755 and 1710 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, s, 18-Me), 1.05 (3H, s, 19-Me), 1.23 (3H, t, J=7.1 Hz, 17β-OCH_2Me), 3.45 (1H, s, 17α-H), 3.64 and 3.84 (1H each, m, 17β-O$\underline{CH_2}$Me). *Anal.* Calcd for $C_{21}H_{32}O_3$: C, 75.86: H, 9.70. Found: C, 75.39; H, 9.59.

17β-Propoxy-5α-androstane-3,16-dione (6c): mp 136—139 °C (from MeOH). IR (KBr) 1755 and 1715 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, s, 18-Me), 0.93 (3H, t, J=7.2 Hz, 17β-OCH_2CH_2Me), 1.05 (3H, s, 19-Me), 3.43 (1H, s, 17α-H), 3.50 and 3.78 (1H each, m, 17β-O$\underline{CH_2}$–). *Anal.* Calcd for $C_{22}H_{34}O_3$; C, 76.26; H, 9.89. Found: C, 75.14; H, 9.99.

17β-Isopropoxy-5α-androstane-3,16-dione (6d): mp 156—157 °C (from acetone–hexane). IR (KBr) 1750 and 1709 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s, 18-Me), 1.07 (3H, s, 19-Me), 1.12 and 1.25 (3H each, d, J=4.0 Hz, 17β-OCH$\underline{Me_2}$), 3.50 (1H, s, 17α-H), 3.80 (1H, m, 17β-OCH=). *Anal.* Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.52; H, 10.05.

17β-Isobutoxy-5α-androstane-3,16-dione (6e): mp 124—127 °C (from MeOH). IR (KBr) 1752 and 1712 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, s, 18-Me), 0.90 and 0.93 (3H each, d, J=5.0 Hz, 17β-OCH_2CH$\underline{Me_2}$), 1.05 (3H, s, 19-Me), 3.40 (1H, s, 17α-H), 3.26 and 3.65 (1H each, m, 17β-O$\underline{CH_2}$–). *Anal.* Calcd for $C_{23}H_{36}O_4$: C, 76.62; H, 10.06. Found: C, 76.38; H, 10.26.

17β-Methoxy-5α-androstan-16-one (7a): mp 87—90 °C (from acetone–hexane). IR (KBr) 1750 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, s, 19-Me), 0.83 (3H, s, 18-Me), 3.41 (1H, s, 17α-H), 3.59 (3H, s, 17β-OMe). *Anal.* Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 79.02; H, 10.87.

17β-Ethoxy-5α-androstan-16-one (7b): An oily substance. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, s, 19-Me), 0.81 (3H, s, 18-Me), 1.23 (3H, t, J=6.9 Hz, 17β-OCH_2Me), 3.44 (1H, s, 17α-H), 3.64 and 3.82 (1H each, m, 17β-O$\underline{CH_2}$Me). Exact MS: Calcd for $C_{21}H_{34}O_2$ (M^+) 318.2523. Found 318.2541.

17β-Propoxy-5α-androstan-16-one (7c): mp 32—34 °C (from ethyl ether). IR (KBr) 1753 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, s, 19-Me), 0.81(3H, s, 18-Me), 0.93 (3H, t, J=7.4 Hz, 17β-OCH_2CH_2Me), 3.42 (1H, s, 17α-H), 3.50 and 3.76 (1H each, m, 17β-O$\underline{CH_2}$–). *Anal.* Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.93. Found: C, 79.20; H, 11.14.

17β-Isopropoxy-5α-androstan-16-one (7d): mp 55—56 °C (from ethyl ether). IR (KBr) 1743 (CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, s, 19-Me), 0.83 (3H, s, 18-Me), 1.13 and 1.27 (3H each, d, J=4.0 Hz, 17β-OCH$\underline{Me_2}$), 3.53 (1H, s, 17α-H), 3.83 (1H, m, 17β-OCH=). *Anal.* Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.93. Found: C, 79.61; H, 10.75.

3-Hydroxy-17β-methoxyestra-1,3,5(10)-trien-16-one (10a): mp 267—270 °C (from acetone). IR (KBr) 3450 (OH), 1740 (CO) and 1620 (C=C) cm^{-1}. UV λ_{max} (EtOH) 281 nm (ε=1.8×10^3). ^{1}H-NMR ($CDCl_3$) δ: 0.83 (3H, s, 18-Me), 3.52 (1H, s, 17α-H), 3.58 (3H, s, 17β-OMe), 6.58 (1H, d, J=2.7 Hz, 4-H), 6.65 (1H, dd, J=2.7 and 8.3 Hz, 2-H), 7.16 (1H, d,

J=8.3 Hz, 1-H). *Anal.* Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found; C, 75.71; H, 8.10.

3-Hydroxy-17β-ethoxyestra-1,3,5(10)-trien-16-one (10b): mp 236—239 °C (from MeOH). IR (KBr) 3450 (OH), 1740 (CO) and 1620 (C=C) cm^{-1}. UV λ_{max} (EtOH) 281 nm (ε=2.1×10^3). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-Me), 1.26 (3H, t, J=6.9 Hz, 17β-OCH$_2$Me), 3.54 (1H, s, 17α-H), 3.68 and 3.87 (1H each, m, 17β-OCH$_2$CH$_3$), 6.58 (1H, d, J=2.9 Hz, 4-H), 6.65 (1H, dd, J=2.9 and 8.3 Hz, 2-H), 7.16 (1H, d, J=8.3 Hz, 1-H). *Anal.* Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.31: H, 8.50.

3-Hydroxy-17β-propoxyestra-1,3,5(10)-trien-16-one (10c): mp 188—191 °C (from MeOH). IR (KBr) 3350 (OH), 1740 (CO) and 1620 (C=C) cm^{-1}. UV λ_{max} (EtOH) 281 nm (ε=2.2×10^3). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, s, 18-Me), 0.95 (3H, t, J=7.4 Hz, 17β-OCH$_2$CH$_2$Me), 3.52 (1H, s, 17α-H), 3.54 and 3.80 (1H each, m, 17β-OCH$_2$CH$_2$Me), 6.58 (1H, d, J=2.6 Hz, 4-H), 6.65 (1H, dd, J=2.6 and 8.3 Hz, 2-H), 7.16 (1H, d, J=8.3 Hz, 1-H). *Anal.* Calcd for $C_{21}H_{28}O_3$: C, 76.56; H, 8.87. Found: C, 76.61; H, 8.85.

3-Hydroxy-17β-isopropoxyestra-1,3,5(10)-trien-16-one (10d): mp 210—213 °C (from MeOH). IR (KBr) 3347 (OH), 1740 (CO) and 1620 (C=C) cm^{-1}. UV λ_{max} (EtOH) 281 nm (ε =2.3×10^3). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, s, 18-Me), 1.19 and 1.25 (3H each, d, J=6.3 Hz, 17β-OCHMe$_2$), 3.59 (1H, s, 17α-H), 3.83 (1H, m, 17β-OCH=), 6.58 (1H, d, J=2.7 Hz, 4-H), 6.65 (1H, dd, J=2.7 and 8.6 Hz, 2-H), 7.16 (1H, d, J=8.6 Hz, 1-H). *Anal.* Calcd for $C_{21}H_{28}O_3$: C, 76.56; H, 8.87. Found: C, 76.78; H, 8.80.

3-Hydroxy-17β-isobutoxyestra-1,3,5(10)-trien-16-one (10e): mp 233—236 °C (from MeOH). IR (KBr) 3425 (OH), 1742 (CO) and 1621 (C=C) cm^{-1}. UV λ_{max} (EtOH) 281 (ε =2.1×10^3). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, s, 18-Me), 0.92 and 0.94 (3H, d, J=5.6 Hz, 17β-OCH$_2$CHMe$_2$), 3.30 and 3.67 (1H each, m, 17β-OCH$_2$CHMe$_2$), 3.50 (1H, s, 17α-H), 6.58 (1H, d, J=2.6 Hz, 4-H), 6.65 (1H, dd, J=8.6 and 2.6 Hz, 2-H), 7.16 (1H, d, J=8.6 Hz, 1-H). *Anal.* Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.42; H, 8.99.

Reaction of The 16α- or 17β-Ketol 1 or 4 with Hydriodic Acid and MeOH A 9 w/v% solution of HI in $CHCl_3$ was prepared from 55% aqueous HI solution and P_2O_5 according to the method[16] reported previously and its concentration was determined by titration with 0.06 mol/l KIO_3 solution.[8]

A 9 w/v% solution (0.23 ml, 21 mg, 0.164 mmol) of HI in $CHCl_3$ and MeOH (52.6 mg, 1.64 mmol) were separately added to solutions of **1** and **4** (50 mg, 0.164 mmol) in 2 ml of $CHCl_3$. The mixture was stirred at room temperature for 45 min under N_2, poured into 10% $Na_2S_2O_3$ solution, and extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ solution, H_2O, and dried over Na_2SO_4. Evaporation of the solvent gave an oily substance which was purified by silica gel column chromatography (hexane–AcOEt). The crude products obtained were purified by silica gel TLC to afford the 17β-methoxide **6a** (12 mg, 22%), and 16α-ketol **1** (24 mg, 47%) in the reaction with **1** and the 17β-methoxide **6a** (10 mg, 20%) and the recovered ketol **4** (30 mg) in the experiment with **4**, respectively.

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