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Synthesis of 15α-Hydroxytestosterone and Related C_{19} Steroids[1]

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The preparation of 15α-hydroxytestosterone (**5**) and 15α-hydroxyandrostenedione (**11**) was carried out employing 17β-*tert*-butyldimethylsilyloxy-6β-methoxy-3α,5-cyclo-5α-androstan-15α-ol (**1**) as a key intermediate. In a similar fashion the 15α-hydroxylated 5α-androstane derivatives (**20**, **22**, **26**) were also synthesized. The utilization of *tert*-butyldimethylsilylation for protecting the hydroxyl group in the preparation of the desired compounds has been demonstrated.

Keywords——chemical synthesis; *tert*-butyldimethylsilylation; 15α-hydroxytestosterone; 15α-hydroxyandrostenedione; 15α-hydroxydihydrotestosterone; 15α-hydroxyisoandrosterone; 15α-hydroxy-5α-androstanedione

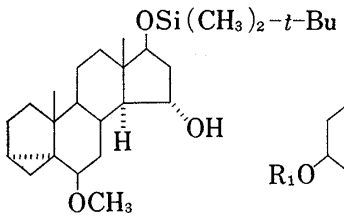
The 15α-hydroxylated C_{18} and C_{19} steroids which have been isolated from human pregnancy and newborn urine,[3] are of particular interest in connection with the biosynthesis of 15α-hydroxyestriol (estetrol).[4] In the preceding papers of this series the synthesis of 15α-hydroxylated estrone, estradiol, dehydroepiandrosterone, and androstenediol has been reported.[5,6] Continuous interests in this field prompted us to prepare the 15α-hydroxy derivatives of testosterone, androstenedione, 5α-dihydrotestosterone, 5α-androstanedione, and isoandrosterone.

An initial effort was focused on the preparation of 15α-hydroxytestosterone (**5**) starting from 17β-*tert*-butyldimethylsilyloxy-6β-methoxy-3α,5-cyclo-5α-androstan-15α-ol (**1**). Treatment of **1** with acetic acid and boron trifluoride in dry ether followed by silylation of the product with *tert*-butyldimethylsilyl chloride and imidazole in dimethylformamide provided 3β-acetoxy-5-androstene-15α,17β-diol disilyl ether (**2**). Saponification with 10% potassium hydroxide in methanol-tetrahydrofuran afforded the 3β,15α,17β-triol 15,17-disilyl ether (**3**), which in turn was led to 15α-hydroxytestosterone bis(*tert*-butyldimethylsilyl) ether (**4**) by Oppenauer oxidation in a fairly good yield. Removal of the silyl groups in **4** was effected by treatment with hydrochloric acid in acetone to furnish the desired 15α-hydroxytestosterone (**5**).

The preparation of 15α-hydroxyandrostenedione (**11**) which possesses a highly susceptible β-ketol system, was undertaken employing 5-androstene-3β,15α,17β-triol 17-monosilyl ether (**6**) as a starting material. Being submitted to Oppenauer oxidation, **6** underwent selective oxidation of the 3β-hydroxyl group and concomitant migration of the double bond yielding the Δ^4-3-ketone (**7**). Acetylation with acetic anhydride and pyridine in the usual manner

1) Part CXXIV of "Studies on Steroids" by T. Nambara; Part CXXIII: M. Numazawa, A. Haryu, K. Kurosaka, and T. Nambara, *FEBS Lett.*, **79**, 396 (1977).
2) Location: *Aobayama, Sendai*; *a*) To whom any inquiries should be addressed.
3) R.A. Anderson, E.M. Chambaz, C. Madani, and G. Defaye, "International Symposium on Sexual Endocrinology of the Perinatal Period," Vol. 32, ed. by M.G. Forest and J. Bertrand, Inserm, Paris, 1974, p. 267; S. Solomon, G. Giannopoulos, E.V. YoungLai, M. Stern, and J.M. Bowman, "Progress in Endocrinology," ICS 184, Excerpta Medica Foundation, Amsterdam, 1969, p. 1119 and references quoted therein.
4) E.V. YoungLai and S. Solomon, *J. Clin. Endocrinol. Metab.*, **28**, 1611 (1968).
5) H. Hosoda, K. Yamashita, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **23**, 3141 (1975).
6) H. Hosoda, K. Yamashita, N. Chino, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **24**, 1860 (1976).

afforded the 15-acetate (**8**), which on treatment with hydrogen chloride in acetone was transformed into 15α-acetoxytestosterone (**9**). Subsequently oxidation with Jones reagent provided 15α-acetoxyandrostenedione (**10**). Hydrolytic cleavage of the 15-acetoxyl group in **10** was attained by exposure to hydrochloric acid in acetone to furnish the desired 15α-hydroxyandrostenedione (**11**) in 80% yield.



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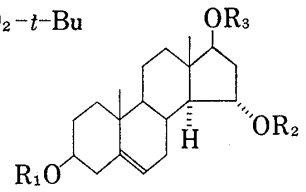
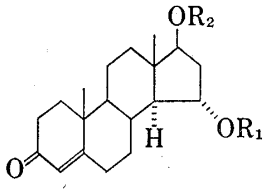
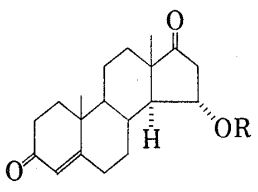


2 : R_1=Ac, R_2=R_3=Si$(CH_3)_2$-*t*-Bu
3 : R_1=H, R_2=R_3=Si$(CH_3)_2$-*t*-Bu
6 : R_1=R_2=H, R_3=Si$(CH_3)_2$-*t*-Bu



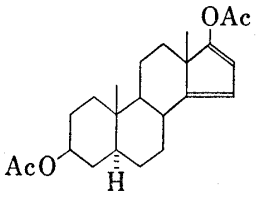
4 : R_1=R_2=Si$(CH_3)_2$-*t*-Bu
5 : R_1=R_2=H
7 : R_1=H, R_2=Si$(CH_3)_2$-*t*-Bu
8 : R_1=Ac, R_2=Si$(CH_3)_2$-*t*-Bu
9 : R_1=Ac, R_2=H



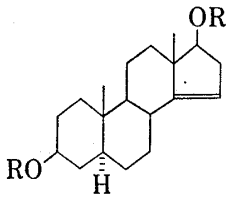
10 : R=Ac
11 : R=H

Chart 1

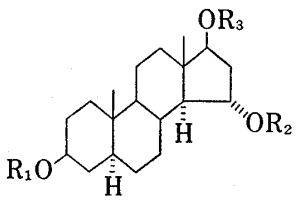
As for the synthesis of 15α-hydroxylated 5α-androstane derivatives, saturation of the 5,6-double bond in the appropriate intermediate described above seems to be feasible. This synthetic route, however, is of disadvantage in that the preparation of the starting material (**1**) is a somewhat tedious work. Therefore, the next effort was directed to the synthesis of 15α-acetoxy-5α-androstane-3β,17β-diol 17-*tert*-butyldimethylsilyl ether (**17**) as a key intermediate. For this purpose 5α-androsta-14,16-diene-3β,17-diol diacetate (**12**) which is readily obtainable from 3β-acetoxy-16α-bromo-5α-androstan-17-one in two steps, was chosen as a starting material. Being treated with sodium borohydride and then with base, **12** was efficiently converted into 14-androstene-3β,17β-diol (**13**). The protection of the hydroxyl function was necessary prior to hydroboration of the 14,15-double bond. It has previously been demonstrated that the presence of the bulky silyloxy group at the 17β-position favored the preferential attack of the reagent from the α-face of a molecule towards the double bond.[5]



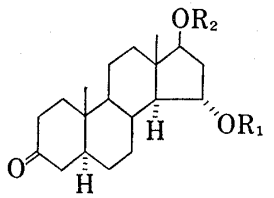
12



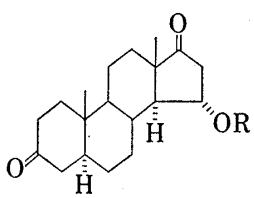
13 : R=H
14 : R=Si$(CH_3)_2$-*t*-Bu



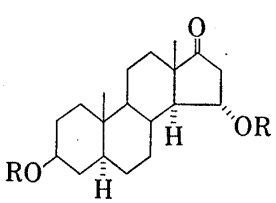
15 : R_1=R_3=Si$(CH_3)_2$-*t*-Bu, R_2=H
16 : R_1=R_3=Si$(CH_3)_2$-*t*-Bu, R_2=Ac
17 : R_1=H, R_2=Ac, R_3=Si$(CH_3)_2$-*t*-Bu
23 : R_1=R_2=Ac, R_3=Si$(CH_3)_2$-*t*-Bu
24 : R_1=R_2=Ac, R_3=H



18 : R_1=Ac, R_2=Si$(CH_3)_2$-*t*-Bu
19 : R_1=Ac, R_2=H
20 : R_1=R_2=H



21 : R=Ac
22 : R=H



25 : R=Ac
26 : R=H

Chart 2

As was expected hydroboration of the 3β,17β-bis(*tert*-butyldimethylsilyl) ether (**14**) and subsequent oxidation of the organoborane with alkaline hydrogen peroxide proceeded to provide the 15α-hydroxy derivative (**15**) in 60% yield. When the 15-acetate (**16**), derivable from **15** in the usual way, was treated with 5N HCl in acetone under mild conditions, elimination of the silyl group occurred predominantly at C-3 to give the 17-monosilyl ether (**17**) in 70% yield.

In order to prepare the desired 3-keto derivatives **17** was led to the 3-ketone (**18**) by oxidation with chromic anhydride-pyridine complex. Upon exposure to hydrogen chloride in acetone **18** underwent elimination of the silyl group to provide 15α-acetoxydihydrotestosterone (**19**). Saponification with 5% methanolic potassium hydroxide resulted in formation of the desired 15α-hydroxydihydrotestosterone (**20**). 15α-Hydroxyandrostanedione (**22**) could be also obtained from **19** by oxidation with chromic anhydride-pyridine complex followed by acid hydrolysis of the 15-acetate.

The preparation of remaining 15α-hydroxyisoandrosterone (**26**) from **17** was then carried out. Removal of the silyl group in 17β-*tert*-butyldimethylsilyloxy-5α-androstane-3β,15α-diol diacetate (**23**) gave the 3β,15α,17β-triol 3,15-diacetate (**24**), which on chromic anhydride oxidation was converted into the 17-ketone (**25**). Finally, hydrolytic cleavage of both acetoxyl groups at C-3 and C-15 in **25** yielded the desired 15α-hydroxyisoandrosterone (**26**).

It is hoped that the availability of these compounds (**5**, **11**, **20**, **22**, **26**) with more ease will be helpful for obtaining the precise knowledge on the biosynthesis of 15α-hydroxylated steroids in the feto-placental unit.

Experimental[7]

3β-Acetoxy-5-androstene-15α,17β-diol Bis(*tert*-butyldimethylsilyl) Ether (**2**)——To a solution of 17β-*tert*-butyldimethylsilyloxy-6β-methoxy-3α,5-cyclo-5α-androstan-15α-ol[6] (**1**) (100 mg) in anhydrous ether (3 ml)–tetrahydrofuran (5 ml) were added AcOH (2.5 ml) and BF_3-etherate (2.5 ml) and allowed to stand at room temperature for 4 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. To the residue dissolved in dimethylformamide (1.5 ml) were added imidazole (500 mg) and *tert*-butyldimethylsilyl chloride (250 mg) and allowed to stand at room temperature overnight. The resulting solution was diluted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (20: 1) as developing solvent. Recrystallization of the eluate from aq. acetone gave **2** (90 mg) as colorless needles. mp 142.5—143.5°. $[\alpha]_D^{16}$ +4.3° (c=0.24). NMR (CCl_4) δ: 0.03 (12H, s, 15- and 17-$OSi(CH_3)_2$), 0.69 (3H, s, 18-CH_3), 0.87 (18H, s, 15- and 17-OSi-*t*-Bu), 1.01 (3H, s, 19-CH_3), 1.93 (3H, s, 3-$OCOCH_3$), 3.73 (1H, t, J=8 Hz, 17α-H), 3.97 (1H, m, 15β-H), 4.42 (1H, m, 3α-H), 5.36 (1H, m, 6-H). *Anal.* Calcd. for $C_{33}H_{60}O_4Si_2$: C, 68.70; H, 10.48. Found: C, 68.43; H, 10.79.

5-Androstene-3β,15α,17β-triol 15,17-Bis(*tert*-butyldimethylsilyl) Ether (**3**)——To a solution of **2** (25 mg) in MeOH (2 ml)–tetrahydrofuran (3 ml) was added 10% KOH (2 ml) and allowed to stand at room temperature for 1.5 hr. The resulting solution was diluted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (3: 1) as developing solvent. Recrystallization of the eluate from MeOH–acetone gave **3** (17 mg) as colorless needles. mp 162—163°. $[\alpha]_D^{16}$ +9.8° (c=0.20). NMR (CCl_4) δ: 0.03 (12H, s, 15- and 17-$OSi(CH_3)_2$), 0.69 (3H, s, 18-CH_3), 0.86 (18H, s, 15- and 17-OSi-*t*-Bu), 1.00 (3H, s, 19-CH_3), 3.0—4.2 (3H, m, 3α,- 15β- and 17α-H), 5.25 (1H, m, 6-H). *Anal.* Calcd. for $C_{31}H_{58}O_3Si \cdot 1/2H_2O$: C, 68.45; H, 10.93. Found: C, 68.25; H, 10.81.

15α,17β-Dihydroxy-4-androsten-3-one Bis(*tert*-butyldimethylsilyl) Ether (**4**)——A solution of **3** (15 mg) and $Al(iso\text{-}PrO)_3$ (30 mg) in anhydrous benzene (10 ml) was concentrated to its half volume to remove the moisture. After addition of methyl ethyl ketone (1 ml) the reaction mixture was refluxed for 3 hr and concentrated. To this solution was added methyl ethyl ketone (1 ml) in anhydrous benzene (9 ml), refluxed for 5 hr, and then concentrated. The resulting solution was diluted with ether, washed with 25% Rochelle salt and H_2O,

7) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$. Infrared (IR) spectra were run on a JASCO Model IRA-I spectrometer. NMR spectra were recorded on a Hitachi Model R-20A spectrometer at 60 MHz or a JEOL Model PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Abbreviation used s= singlet, d=doublet, t=triplet, sx=sextet, and m=multiplet. For preparative TLC silica gel H (E. Merck AG, Darmstadt) was used as an adsorbent.

dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (7: 1) as developing solvent. Recrystallization of the eluate from MeOH gave **4** (10 mg) as colorless prisms. mp 154—156°. $[\alpha]_D^{20}$ +93.8° (c=0.19). NMR (CCl_4) δ: 0.01 (12H, s, 15- and 17-OSi$(CH_3)_2$), 0.70 (3H, s, 18-CH_3), 0.83 (18H, s, 15- and 17-OSi-*t*-Bu), 1.16 (3H, s, 19-CH_3), 3.69 (1H, t, J=8 Hz, 17α-H), 3.91 (1H, m, 15β-H), 5.53 (1H, s, 4-H). *Anal.* Calcd. for $C_{31}H_{56}O_3Si$: C, 69.87; H, 10.59. Found: C, 69.98; H, 10.84.

15α,17β-Dihydroxy-4-androsten-3-one (15α-Hydroxytestosterone) (5)——To a solution of **4** (17 mg) in acetone (0.5 ml) was added conc. HCl (50 μl) and allowed to stand at room temperature for 1 hr. The resulting solution was diluted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from acetone–hexane gave **5** (6 mg) as colorless needles. mp 194—196°. $[\alpha]_D^{16}$ +152.9° (c=0.09). NMR ($CDCl_3$) δ: 0.82 (3H, s, 18-CH_3), 1.22 (3H, s, 19-CH_3), 3.91 (1H, t, J=8 Hz, 17α-H), 4.12 (1H, sx, J=9, 9, 4 Hz, 15β-H), 5.76 (1H, s, 4-H). *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.76; H, 9.57. Gubler, *et al.* obtained **5** from testosterone by microbial oxidation (lit. mp 102—110°/203—206°).[8]

5-Androstene-3β,15α,17β-triol 17-*tert*-Butyldimethylsilyl Ether (6)——To a solution of 17β-*tert*-butyldimethylsilyloxy-5-androstene-3β,15α-diol diacetate[6] (70 mg) in MeOH (2 ml)–tetrahydrofuran (0.5 ml) was added 30% KOH (0.3 ml) and allowed to stand at room temperature overnight. The resulting solution was diluted with ether–AcOEt (1: 1), washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from MeOH gave **6** (50 mg) as colorless needles. mp 163—164°. $[\alpha]_D^{19}$ −17.0° (c= 0.21). NMR ($CDCl_3$) δ: 0.01 (6H, s, 17-OSi$(CH_3)_2$), 0.70 (3H, s, 18-CH_3), 0.85 (9H, s, 17-OSi-*t*-Bu), 1.00 (3H, s, 19-CH_3), 3.1—4.2 (3H, 3α-, 15β- and 17α-H), 5.30 (1H, m, 6-H). *Anal.* Calcd. for $C_{25}H_{44}O_3Si \cdot 1/4H_2O$: C, 70.62; H, 10.55. Found: C, 70.66; H, 10.66.

15α,17β-Dihydroxy-4-androsten-3-one 17-*tert*-Butyldimethylsilyl Ether (7)——A solution of **6** (328 mg) and Al(iso-PrO)$_3$ (220 mg) in anhydrous benzene (50 ml) was concentrated to its half volume to remove the moisture. After addition of methyl ethyl ketone (10 ml) the reaction mixture was refluxed for 3 hr and concentrated. To this solution was added methyl ethyl ketone (10 ml) in anhydrous benzene (25 ml), refluxed for 4 hr, and then concentrated. The resulting solution was diluted with ether, washed with 25% Rochelle salt and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene–EtOH (13: 1) as developing solvent. Recrystallization of the eluate from aq. acetone gave **7** (200 mg) as colorless needles. mp 169—171.5°. $[\alpha]_D^{18}$ +110.3° (c=0.32). NMR (CCl_4) δ: 0.01 (6H, s, 17-OSi$(CH_3)_2$), 0.70 (3H, s, 18-CH_3), 0.86 (9H, s, 17-OSi-*t*-Bu), 1.18 (3H, s, 19-CH_3), 3.5—4.1 (2H, 15β- and 17α-H), 5.59 (1H, s, 4-H). *Anal.* Calcd. for $C_{25}H_{42}O_3Si$: C, 71.72; H, 10.11. Found: C, 71.64; H, 10.27.

17β-*tert*-Butyldimethylsilyloxy-15α-hydroxy-4-androsten-3-one Acetate (8)——A solution of **7** (50 mg) in pyridine (0.6 ml) and Ac_2O (0.3 ml) was allowed to stand at room temperature overnight. The resulting solution was diluted with ice-water and extracted with ether. The organic layer was washed with 10% AcOH, ice-cooled 5% $NaHCO_3$, and H_2O successively, dried over anhydrous Na_2SO_4, and evaporated. Purification of the residue by preparative TLC using hexane–AcOEt (7: 2) as developing solvent gave **8** (40 mg) as colorless oil. NMR (CCl_4) δ: 0.03 (6H, s, 17-OSi$(CH_3)_2$), 0.79 (3H, s, 18-CH_3), 0.88 (9H, s, 17-OSi-*t*-Bu), 1.18 (3H, s, 19-CH_3), 1.90 (3H, s, 15-OCOCH_3), 3.70 (1H, t, J=8 Hz, 17α-H), 4.81 (1H, sx, J=8, 8, 4Hz, 15β-H), 5.53 (1H, s, 4-H).

15α,17β-Dihydroxy-4-androsten-3-one 15-Acetate (9)——To a solution of **8** (40 mg) in acetone (0.5 ml) was added a solution of HCl (150 mg) in acetone (1.5 ml) and allowed to stand at room temperature for 30 min. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene–ether (2: 3) as developing solvent. Recrystallization of the eluate from acetone–hexane gave **9** (28 mg) as colorless needles. mp 226—230°. $[\alpha]_D^{18}$ +108.9° (c=0.20). NMR ($CDCl_3$) δ: 0.83 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 1.97 (3H, s, 15-OCOCH_3), 3.81 (1H, t, J=8 Hz, 17α-H), 4.93 (1H, sx, J=8, 8, 4Hz, 15β-H), 5.70 (1H, s, 4-H). *Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.67; H, 8.90.

15α-Acetoxy-4-androstene-3,17-dione (10)——To a solution of **9** (25 mg) in acetone (3 ml) was added 8 N CrO_3 solution (90 μl) and allowed to stand at 0° for 15 min. After addition of MeOH (2 ml) the resulting solution was diluted with ether, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Purification of the residue by preparative TLC using benzene–ether (4: 1) as developing solvent gave **10** (16 mg) as colorless oil. NMR ($CDCl_3$) δ: 0.99 (3H, s, 18-CH_3), 1.20 (3H, s, 19-CH_3), 2.01 (3H, s, 15-OCOCH_3), 3.15 (1H, dd, J=8, 18Hz, 16ξ-H), 5.22 (1H, m, 15β-H), 5.71 (1H, s, 4-H).

15α-Hydroxy-4-androstene-3,17-dione (15α-Hydroxyandrostenedione) (11)——To a solution of **10** (14 mg) in acetone (2 ml) was added 5 N HCl (1 ml) and allowed to stand at room temperature overnight. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene–ether (1: 2) as developing solvent. Recrystallization of the eluate from acetone–hexane gave **11** (9 mg) as colorless leaflets.

8) A. Gubler and Ch. Tamm, *Helv. Chim. Acta*, **41**, 301 (1958).

mp 193.5—195° (lit. mp 192—198°).[8] NMR ($CDCl_3$) δ: 0.96 (3H, s, 18-CH_3), 1.24 (3H, s, 19-CH_3), 3.02 (1H, dd, J=8, 18 Hz, 16ξ-H), 4.43 (1H, m, 15β-H), 5.74 (1H, s, 4-H). IR spectrum of **11** was entirely identical with that of the sample obtained from 4-androstene-3,17-dione by microbial oxidation.

5α-Androsta-14,16-diene-3β,17-diol Diacetate (12)——To a solution of 3β-acetoxy-16α-bromo-5α-androstan-17-one[9] (3 g) in dimethylacetamide (25 ml) were added LiBr (5.3 g) and Li_2CO_3 (4.5 g) and refluxed for 2.5 hr. The resulting solution was diluted with H_2O and extracted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in benzene (200 ml) and filtered through Al_2O_3 (10 g). After evaporation of the solvent the crystalline product obtained was dissolved in isopropenyl acetate (15 ml) containing *p*-TsOH (200 mg). The solution was refluxed for 1 hr and concentrated to its half volume by slow distillation over 1 hr. An additional 10 ml of isopropenyl acetate was added and the solution was again concentrated to *ca.* 5 ml over another 2 hr. The resulting solution was diluted with ether and washed with ice-cooled 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in benzene and filtered through Al_2O_3 (30 g). After evaporation of the solvent the crystalline product obtained was recrystallized from CH_2Cl_2–MeOH to give **12** (2.1 g) as colorless needles. mp 165—167°. $[\alpha]_D^{18}$ +166.7° (c=0.20). NMR ($CDCl_3$) δ: 0.90 (3H, s, 19-CH_3), 1.02 (3H, s, 18-CH_3), 2.00 (3H, s, 3-OCOCH_3), 2.16 (3H, s, 17-OCOCH_3), 4.65 (1H, m, 3α-H), 5.72 (1H, t, J=2.5 Hz, 15-H), 6.07 (1H, d, J=2.5 Hz, 16-H). *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.87; H, 8.65.

5α-Androst-14-ene-3β,17β-diol (13)——To a solution of **12** (2.3 g) in EtOH (150 ml) was added $NaBH_4$ (3.5 g) in tetrahydrofuran (15 ml)–H_2O (20 ml) at 0° and stirred at room temperature for 2 hr. Then 40% KOH (5 ml) was added and stirred for another 1 hr. After addition of 10% AcOH to decompose the excess reagent the resulting solution was concentrated under the reduced pressure and diluted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from MeOH gave **13** (1.4 g) as colorless leaflets. mp 137—139° (lit. mp 141—142°).[10]

5α-Androst-14-ene-3β,17β-diol Bis(*tert*-butyldimethylsilyl) Ether (14)——To a solution of **13** (1.3 g) in dimethylformamide (30 ml) were added imidazole (10 g) and *tert*-butyldimethylsilyl chloride (3.5 g) and allowed to stand at room temperature overnight. The resulting solution was diluted with ether, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from MeOH gave **14** (1.45 g) as colorless needles. mp 127—128°. $[\alpha]_D^{18}$ +31.3° (c=0.08). NMR (CCl_4) δ: 0.04 (12H, s, 3- and 17-OSi$(CH_3)_2$), 0.75—0.95 (24H, 18-CH_3, 19-CH_3, 3- and 17-OSi-*t*-Bu), 3.45 (1H, m, 3α-H), 3.85 (1H, t, J=8 Hz, 17α-H), 4.95 (1H, m, 15-H). *Anal.* Calcd. for $C_{31}H_{58}O_2Si_2$: C, 71.75; H, 11.27. Found: C, 71.51; H, 11.29.

Hydroboration of 14——To a stirred solution of **14** (1.4 g) and $LiAlH_4$ (3 g) in anhydrous ether (35 ml) was added BF_3-etherate (10 g) in anhydrous ether (20 ml) dropwise at 0° over a period of 30 min under a N_2 gas stream. The ice-bath was then removed and the reaction mixture was stirred at room temperature for 1 hr. After addition of moist ether to decompose the excess reagent the resulting solution was extracted with ether. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. To the residue dissolved in tetrahydrofuran (30 ml) were added 30% H_2O_2 (20 ml) and 10% NaOH (30 ml), and stirred at 0° for 1 hr. The resulting solution was diluted with H_2O and extracted with ether. The organic layer was washed with 5% $NaHSO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (10: 1) as developing solvent. Recrystallization of the major product from MeOH gave 5α-androstane-3β,15α,17β-triol 3,17-bis(*tert*-butyldimethylsilyl) ether (**15**) (830 mg) as colorless leaflets. mp 84—87°. $[\alpha]_D^{20}$ +47.3° (c=0.13). NMR (CCl_4) δ: 0.04 (12H, s, 3- and 17-OSi$(CH_3)_2$), 0.70 (3H, s, 18-CH_3), 0.82 (3H, s, 19-CH_3), 0.88 (18H, s, 3- and 17-OSi-*t*-Bu), 3.3—4.2 (3H, 3α-, 15β- and 17α-H). *Anal.* Calcd. for $C_{31}H_{60}O_3Si_2 \cdot 1/2H_2O$: C, 68.19; H, 11.26. Found: C, 67.78; H, 11.09. The minor product obtained from the less polar fraction was recrystallized from MeOH to give 5α,14β-androstane-3β,15β,17β-triol 3,17-bis(*tert*-butyldimethylsilyl) ether (150 mg) as colorless needles. mp 155—157°. $[\alpha]_D^{18}$ +25.5° (c=0.22). NMR (CCl_4) δ: 0—0.07 (12H, 3- and 17-OSi$(CH_3)_2$), 0.76 (3H, s, 19-CH_3), 0.83, 0.88 (each 9H, s, 3- or 17-OSi-*t*-Bu), 0.95 (3H, s, 18-CH_3), 3.45 (1H, m, 3α-H), 3.48 (1H, d, J=5 Hz, 17α-H), 4.05 (1H, m, 15α-H). *Anal.* Calcd. for $C_{31}H_{60}O_3Si_2$: C, 69.34; H, 11.26. Found: C, 69.18; H, 11.48.

15α-Acetoxy-5α-androstane-3β,17β-diol 3,17-Bis(*tert*-butyldimethylsilyl) Ether (16)——A solution of **15** (800 mg) in pyridine (5 ml) and Ac_2O (2.5 ml) was allowed to stand at room temperature overnight. The resulting solution was diluted with ice-water and extracted with ether. The organic layer was washed with 10% AcOH, ice-cooled 5% $NaHCO_3$, and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from MeOH gave **16** (800 mg) as colorless prisms. mp 114—115°. $[\alpha]_D^{20}$ +44.9° (c=0.22). NMR (CCl_4) δ: 0.04 (12H, s, 3- and 17-OSi$(CH_3)_2$), 0.75 (3H, s, 18-CH_3), 0.82 (3H, s, 19-CH_3), 0.86 (18H, s, 3- and 17-OSi-*t*-Bu), 1.92 (3H, s, 15-OCOCH_3), 3.45 (1H, m, 3α-H), 3.72 (1H, t, J=8 Hz, 17α-H), 4.78 (1H, m, 15β-H). *Anal.* Calcd. for $C_{33}H_{62}O_4Si_2$: C, 68.46; H, 10.80. Found: C, 68.59; H, 10.72.

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15α-Acetoxy-5α-androstane-3β,17β-diol 17-*tert*-Butyldimethylsilyl Ether (17)——To a solution of **16** (600 mg) in acetone (20 ml) was added 5 N HCl (500 μl) and stirred at room temperature for 30 min. The resulting solution was neutralized with 5% $NaHCO_3$, concentrated under the reduced pressure, and extracted with ether. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Purification of the residue by preparative TLC using benzene–ether (2: 1) as developing solvent gave **17** (340 mg) as colorless oil. NMR (CCl_4) δ: 0.04 (6H, s, 17-OSi$(CH_3)_2$), 0.75 (3H, s, 18-CH_3), 0.82 (3H, s, 19-CH_3), 0.86 (9H, s, 17-OSi-*t*-Bu), 1.92 (3H, s, 15-OCOCH_3), 3.50 (1H, m, 3α-H), 3.70 (1H, t, J=8 Hz, 17α-H), 4.80 (1H, m, 15β-H).

17β-*tert*-Butyldimethylsilyloxy-15α-hydroxy-5α-androstan-3-one Acetate (18)——To a solution of **17** (500 mg) in pyridine (2 ml) was added CrO_3-pyridine complex (10% w/v) (6 ml) and allowed to stand at room temperature for 4 hr. The resulting solution was diluted with ether, washed with 10% AcOH, 5% $NaHCO_3$, and H_2O successively, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (5: 1) as developing solvent. Recrystallization of the eluate from MeOH gave **18** (340 mg) as colorless needles. mp 137—139°. $[\alpha]_D^{19}$ +52.5° (c=0.20). NMR (CCl_4) δ: 0.04 (6H, s, 17-OSi$(CH_3)_2$), 0.75 (3H, s, 18-CH_3), 0.86 (9H, s, 17-OSi-*t*-Bu), 1.02 (3H, s, 19-CH_3), 1.92 (3H, s, 15-OCOCH_3), 3.70 (1H, t, J=8 Hz, 17α-H), 4.78 (1H, m, 15β-H). *Anal.* Calcd. for $C_{27}H_{46}O_4Si$: C, 70.08; H, 10.21. Found: C, 69.83; H, 10.11.

15α,17β-Dihydroxy-5α-androstan-3-one 15-Acetate (19)——To a solution of **18** (70 mg) in acetone (1 ml) was added a solution of HCl (300 mg) in acetone (4 ml) and allowed to stand at room temperature for 2 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from acetone–hexane gave **19** (52 mg) as colorless needles. mp 207—209°. $[\alpha]_D^{19}$ +72.9° (c=0.10). NMR ($CDCl_3$) δ: 0.81 (3H, s, 18-CH_3), 1.02 (3H, s, 19-CH_3), 1.98 (3H, s, 15-OCOCH_3), 3.81 (1H, t, J=8 Hz, 17α-H), 4.90 (1H, sx, J=9, 9, 3.5 Hz, 15β-H). *Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.10; H, 9.27.

15α,17β-Dihydroxy-5α-androstan-3-one (15α-Hydroxy-5α-dihydrotestosterone) (20)——To a solution of **19** (30 mg) in MeOH (2 ml) was added 5% KOH (1 ml) and allowed to stand at room temperature for 1 hr. The resulting solution was diluted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from acetone gave **20** (18 mg) as colorless prisms. mp 218—221°. $[\alpha]_D^{18}$ +76.5° (c=0.10). NMR ($CDCl_3$) δ: 0.76 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 3.85 (1H, t, J=8 Hz, 17α-H), 4.04 (1H, m, 15β-H). *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.48; H, 9.94.

15α-Acetoxy-5α-androstane-3,17-dione (21)——To a solution of **19** (40 mg) in pyridine (0.5 ml) was added CrO_3-pyridine complex (10% w/v) (2 ml) and allowed to stand at room temperature for 3 hr. The resulting solution was diluted with ether, washed with 10% AcOH, 5% $NaHCO_3$, and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Purification of the residue obtained by preparative TLC using benzene–ether (3: 1) as developing solvent gave **21** (30 mg) as colorless oil. NMR ($CDCl_3$) δ: 0.96 (3H, s, 18-CH_3), 1.02 (3H, s, 19-CH_3), 2.02 (3H, s, 15-OCOCH_3), 3.15 (1H, dd, J=7, 19 Hz, 16ξ-H), 5.20 (1H, m, 15β-H).

15α-Hydroxy-5α-androstane-3,17-dione (15α-Hydroxy-5α-androstanedione) (22)——To a solution of **21** (42 mg) in acetone (4 ml) was added 5 N HCl (3 ml) and allowed to stand at room temperature for 5 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene–ether (3: 1) as developing solvent. Recrystallization of the eluate from acetone–hexane gave **22** (15 mg) as colorless plates. mp 164—166°. $[\alpha]_D^{18}$ +128.2° (c=0.08). NMR ($CDCl_3$) δ: 0.90 (3H, s, 18-CH_3), 1.03 (3H, s, 19-CH_3), 2.96 (1H, dd, J=8, 17 Hz, 16ξ-H), 4.35 (1H, m, 15β-H). *Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.74; H, 9.38.

3β,15α-Diacetoxy-5α-androstan-17β-ol *tert*-Butyldimethylsilyl Ether (23)——A solution of **17** (58 mg) in pyridine (1 ml) and Ac_2O (0.5 ml) was allowed to stand at room temperature overnight. The resulting solution was diluted with ice-water and extracted with ether. The organic layer was washed with 10% AcOH, ice-cooled 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the residue from MeOH gave **23** (60 mg) as colorless needles. mp 165.5—167°. $[\alpha]_D^{20}$ +43.0° (c=0.13). NMR (CCl_4) δ: 0 (6H, s, 17-OSi$(CH_3)_2$), 0.72 (3H, s, 18-CH_3), 0.80 (3H, s, 19-CH_3), 0.84 (9H, s, 17-OSi-*t*-Bu), 1.89 (6H, s, 3- and 15-OCOCH_3), 3.68 (1H, t, J=8 Hz, 17α-H), 4.2—5.1 (2H, 3α- and 15β-H). *Anal.* Calcd. for $C_{29}H_{50}O_5Si$: C, 68.73; H, 9.95. Found: C, 68.92; H, 10.27.

5α-Androstane-3β,15α,17β-triol 3,15-Diacetate (24)——To a solution of **23** (55 mg) in acetone (1 ml) was added a solution of HCl (200 mg) in acetone (2.5 ml) and allowed to stand at room temperature for 2 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$, and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using hexane–AcOEt (1: 1) as developing solvent. Recrystallization of the eluate from acetone–hexane gave **24** (47 mg) as colorless plates. mp 170—171°. $[\alpha]_D^{15}$ +26.0° (c=0.10). NMR ($CDCl_3$) δ: 0.75 (3H, s, 18-CH_3), 0.81 (3H, s, 19-CH_3), 1.99 (6H, s, 3- and 15-OCOCH_3), 3.80 (1H, t, J=8 Hz, 17α-H), 4.3—5.1 (2H, 3α- and 15β-H). *Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.43; H, 9.42.

3β,15α-Diacetoxy-5α-androstan-17-one (25)——To a solution of **24** (37 mg) in pyridine (0.5 ml) was added CrO_3-pyridine complex (10% w/v) (2 ml) and allowed to stand at room temperature for 4 hr. The resulting solution was diluted with ether, washed with 10% AcOH, 5% $NaHCO_3$, and H_2O successively, dried over

anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene–ether (5: 1) as developing solvent. Recrystallization of the eluate from acetone–hexane gave **25** (25 mg) as colorless plates. mp 151—153°. $[\alpha]_D^{15}$ +86.7° (c=0.10). NMR ($CDCl_3$) δ: 0.83 (3H, s, 19-CH_3), 0.92 (3H, s, 18-CH_3), 2.00 (6H, s, 3- and 15-$OCOCH_3$), 3.11 (1H, dd, J=8, 19 Hz, 16ξ-H), 4.65 (1H, m, 3α-H), 5.15 (1H, m, 15β-H). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.12; H, 9.16.

3β,15α-Dihydroxy-5α-androstan-17-one (15α-Hydroxyisoandrosterone) (26)——To a solution of **25** (20 mg) in acetone (3 ml) was added 5 N HCl (1.2 ml) and allowed to stand at room temperature overnight. The resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was purified by preparative TLC using benzene–ether (2: 3) as developing solvent Recrystallization of the eluate from aq. acetone gave **26** (7 mg) as colorless needles. mp 198—201°. $[\alpha]_D^{20}$ +124.9° (c=0.05). NMR ($CDCl_3$) δ: 0.86 (3H, s, 19-CH_3), 0.91 (3H, s, 18-CH_3), 3.00 (1H, dd, J=8, 17 Hz, 16ξ-H), 3.60 (1H, m, 3α-H), 4.40 (1H, m, 15β-H). *Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.00; H, 10.00.

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