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Synthesis of Epimeric 2-d_1-Dehydroepiandrosterones[1]

Shigeo Ikegawa, Noriko Obatake, Hiroshi Hosoda,[2]
and Toshio Nambara[2a]

Pharmaceutical Institute, Tohoku University[2]

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In order to clarify the metabolic fate of hydrogen at C-2 during microbial transformation of dehydroepiandrosterone into 1α-hydroxy-4-androstene-3,17-dione, the stereospecific synthesis of epimeric 2-d_1-dehydroepiandrosterones have been undertaken. A key intermediate leading to the required substrates, 5α-androst-2-ene-6β,17β-diol 17-*tert*-butyldimethylsilyl ether, was prepared from dehydroepiandrosterone in several steps. Deuterioboration of the Δ^2-olefin and subsequent oxidation of the organoborane afforded the 2α-deuterio-3α-ol. The *trans*-diaxial opening of the 2α,3α-epoxide with lithium aluminum deuteride provided the 2β-deuterio-3α-ol. Being submitted to dehydration with phosphorus oxychloride in pyridine followed by usual elaborations, the C-2 deuterated 6β-hydroxysteroids were converted to the desired 2-d_1-dehydroepiandrosterones.

Keywords——biotransformation mechanism; 5α-androst-2-ene; 2α,3α-epoxy-5α-androstane; deuteriodiborane; lithium aluminum deuteride; *trans*-diaxial opening of epoxide; *tert*-butyldimethylsilyl ether; epimeric 2-d_1-dehydroepiandrosterones; 6β-hydroxy-5α-steroid

The microbial transformation of steroids is of particular interest in connection with the biosynthesis and metabolism of steroid hormones in man. As a series of our studies on the biotransformation mechanism of steroids,[3] elucidation of the steric mechanism for the enzymatic conversion of dehydroepiandrosterone (3β-hydroxy-5-androsten-17-one) into 1α-hydroxyandrostenedione by *Penicillium sp.* (ATCC 12,556)[4] has been attempted. The design of the experiment for the microbial transformation required C_{19} 5-dehydrosteroids labeled with deuterium stereospecifically at the C-2 position as the substrates. The present paper describes the preparation of the titled compounds starting from dehydroepiandrosterone.

As a preliminary experiment toward the final goal we started to establish a synthetic route by which the label can be unambiguously introduced at the desired position. Of the numerous deuteration methods so far available reductive cleavage of the epoxide with lithium aluminum deuteride and deuteration of the double bond appeared to be favorable for the present purpose. In addition, it is sufficiently substantiated that dehydration of the 6β-hydroxy-5α-steroid with phosphorus oxychloride proceeds regiospecifically to give the 5-dehydrosteroid in an excellent yield.[5] An initial effort, therefore, was directed to the preparation of 5α-androst-2-en-6β-ol and its 2α,3α-epoxide as the key intermediates leading to the desired compounds.

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2) Location: *Aobayama, Sendai, 980, Japan*; *a*) To whom any inquiries should be addressed.

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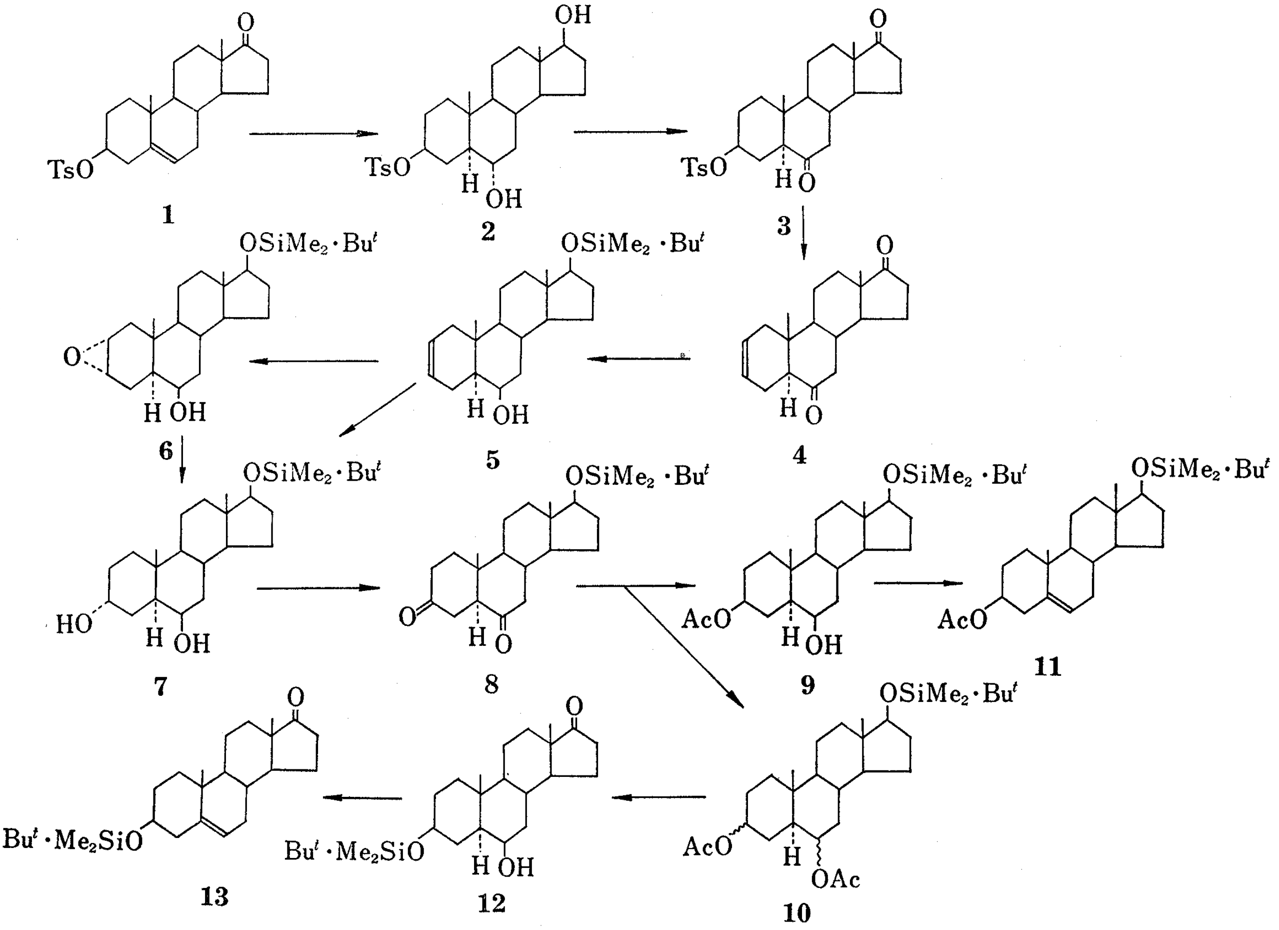

Ac = CH_3CO–, Ts = *p*-$CH_3C_6H_4SO_2$–

Chart 1

Hydration of dehydroepiandrosterone *p*-toluenesulfonate (**1**) with diborane, generated from sodium borohydride and dimethyl sulfate, gave 5α-androstane-3β,6α,17β-triol 3-*p*-toluenesulfonate (**2**) in a satisfactory yield. The structure of this *cis*-adduct was assignable on the basis of nuclear magnetic resonance (NMR) spectral data. Oxidation of **2** with Jones reagent furnished the 6,17-diketone (**3**) as a sole product. Subsequently, elimination of the oxygen function at C-3 was effected by treatment with γ-collidine yielding the Δ^2-olefin (**4**) and a small amount of the 3α,5α-cyclosteroid whose separation was readily attained by column chromatography on silica gel. Reduction of the 6,17-diketone with lithium aluminum hydride provided the 6β,17β-diol accompanied with a small amount of the epimeric 6α,17β-diol. It has previously been demonstrated that the 6β-hydroxyl group is not susceptible to *tert*-butyldimethylsilylation due to the steric hindrance.[6] Accordingly, the epimeric 6,17β-diols were treated with *tert*-butyldimethylsilyl chloride and imidazole in the usual manner. In consequence, 5α-androst-2-ene-6β,17β-diol 17-monosilyl ether (**5**) could be separated with ease by column chromatography on silica gel. The stereochemistry at C-6 was confirmed by the NMR spectrum where the C-6 proton signal appeared at 3.89 ppm as a multiplet. The attack of *m*-chloroperbenzoic acid toward **5** did take place from the less hindered α-side to afford the 2α,3α-epoxide (**6**) as a single product.

Reductive cleavage of the α-epoxide (**6**) with lithium aluminum hydride was then carried out. As was expected the *trans*-diaxial opening of the oxido ring occurred to give the

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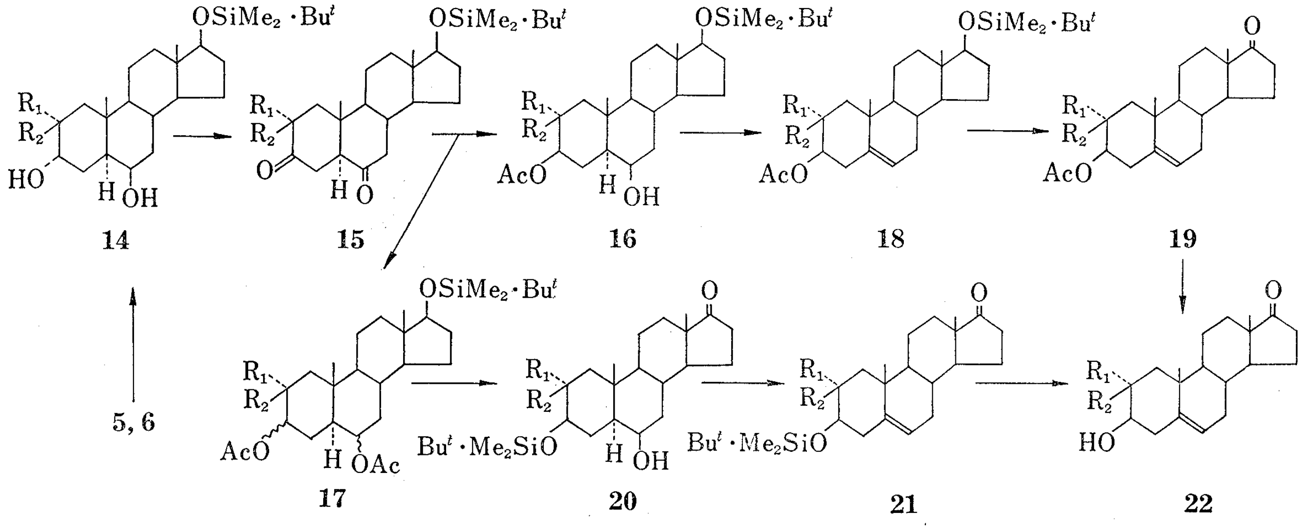
[6] H. Hosoda, C. Iwanuma, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **26**, 2181 (1978).

3α-hydroxyl compound (**7**). The structural assignment of the product was rationalized by inspection of the NMR spectrum where a multiplet signal (W1/2=7 Hz) due to the equatorial 3β-proton was observed. Hydroboration of the Δ^2-olefin (**5**) with diborane and subsequent oxidation of organoborane with alkaline hydrogen peroxide furnished mainly the 3α-hydroxyl compound (**7**) accompanied with the isomeric 2α- and 3β-ols. Among the products the desired 3α-ol could be separated by repeated column chromatography on silica gel. Thus the use of the Δ^2-olefin and 2α,3α-epoxide as the key intermediates proved to be suitable for stereospecific labeling of deuterium at C-2 in 3α-hydroxy-5α-androstane.

Transformation of **7** into dehydroepiandrosterone was also undertaken. Oxidation of the 3α,6β-diol (**7**) with chromium trioxide–pyridine complex under the mild conditions followed by reduction with metal hydride yielded a mixture of the isomeric 3,6-diols. Difficulties were encountered with the separation of these isomers, although they were distinguishable on the thin-layer chromatogram. When the reduction product was submitted to usual acetylation and then to column chromatography on silica gel, the 3β-acetoxy-6β-ol (**9**) was readily separated from the isomeric 3,6-diacetates (**10**). Dehydration of **9** with phosphorus oxychloride in pyridine provided 3β-acetoxy-5-androsten-17β-ol *tert*-butyldimethylsilyl ether (**11**) in a satisfactory yield. Being submitted to desilylation, oxidation, and saponification, successively, **11** can be led to dehydroepiandrosterone.

On the other hand, the mixture of isomeric 3,6-diacetates (**10**) was subjected to the successive reactions involving Jones oxidation, alkaline hydrolysis, and partial silylation. The chromatographic purification of the product afforded 3β,6β-dihydroxy-5α-androstan-17-one 3-*tert*-butyldimethylsilyl ether (**12**). Being treated with phosphorus oxychloride in pyridine, **12** underwent dehydration to yield dehydroepiandrosterone *tert*-butyldimethylsilyl ether (**13**).⁷⁾ The synthetic routes thus established proved to be promising to introduce stereospecifically the deuterium label into the C-2 position of dehydroepiandrosterone.



a : R₁=D, R₂=H **b** : R₁=H, R₂=D

Chart 2

Deuteration of the olefin (**5**) with deuteriodiborane, generated from lithium aluminum deuteride and boron trifluoride etherate, provided a *cis*-addition product, 2α-d_1-5α-androstane-3α,6β,17β-triol 17-*tert*-butyldimethylsilyl ether (**14a**). On the other hand, the preparation of the 2β-deuterated epimer was attained by *trans*-diaxial opening of the 2α,3α-epoxide (**6**) with lithium aluminum deuteride. The two epimeric 2-deuterated 3α-ols were converted to the

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7) H. Hosoda, D.K. Fukushima, and J. Fishman, *J. Org. Chem.*, 38, 4209 (1973).

3,6-diketones (**15a**, **15b**) by oxidation with chromium trioxide under the mild conditions. Subsequent reduction with lithium aluminum hydride and usual acetylation afforded the 3β-acetoxy-6β-ols (**16a**, **16b**) together with the isomeric 3,6-diacetoxy derivatives (**17a**, **17b**). Dehydration of the 6β-hydroxyl function in **16a** and **16b** with phosphorus oxychloride in pyridine yielded solely the Δ^5-unsaturated compounds (**18a**, **18b**). Being subjected to desilylation, Jones oxidation, and alkaline hydrolysis, successively, **18a** and **18b** were transformed into the desired epimeric 2-d_1-dehydroepiandrosterones (**22a**, **22b**). Alternatively, treatment of the mixture of isomeric 3,6-diacetates (**17a**, **17b**) by Jones reagent followed by saponification and silylation provided 2-d_1-3β,6β-dihydroxy-5α-androstan-17-one 3-*tert*-butyldimethylsilyl ethers (**20a**, **20b**). Dehydration and desilylation in the manner as described above yielded the desired 2-d_1-dehydroepiandrosterones (**22a**, **22b**).

The infrared (IR) spectra of non-labeled and deuterated dehydroepiandrosterones were obviously distinguishable each other in the finger print region. Inspection of the molecular ion peak in the mass spectra revealed that the isotopic purity of these deuterium-labeled steroids was more than 98%.

The studies on the steric mechanism of microbial transformation using these labeled substrates will be the subject of a future communication.

Experimental

All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$. IR spectra were obtained on a JASCO Model IRA-1 spectrometer. NMR spectra were recorded on 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. Mass spectra were measured by a JEOL Model JMS-D100 gas chromatograph–mass spectrometer. Isotopic purity of $LiAlD_4$ used was over 98%. All the deuterated compounds obtained were characterized by mixed melting point measurement on admixture with the non-deuterated authentic samples.

5α-Androstane-3β,6α,17β-triol 3-*p*-Toluenesulfonate (2)——To a stirred solution of dehydroepiandrosterone *p*-toluenesulfonate (1) (500 mg) and $NaBH_4$ (480 mg) in anhydrous tetrahydrofuran (THF) (10 ml) was added Me_2SO_4 (5.2 ml) at 0° over a period of 15 min under a stream of N_2 gas, and the reaction mixture was stirred at room temperature for 5 hr. After addition of H_2O the resulting solution was treated with 10% NaOH (5 ml) and 28% H_2O_2 (5 ml) at 0° for 40 min. The reaction mixture was extracted with AcOEt. The organic layer was washed with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, successively, dried over anhydrous Na_2SO_4, and evaporated. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (1: 3) and recrystallization of the eluate from hexane–acetone gave **2** (297 mg) as colorless plates. mp 159—161°. $[\alpha]_D^{26}$ +16.5° (c=0.24). *Anal.* Calcd. for $C_{26}H_{38}O_5S \cdot 1/4H_2O$: C, 66.85; H, 8.20. Found: C, 66.77; H, 8.22. NMR ($CDCl_3$) δ: 0.76 (3H, s, 18-CH_3), 0.84 (3H, s, 19-CH_3), 2.54 (3H, s, Ar–CH_3), 3.73 (1H, t, J=8 Hz, 17α-H), 3.46 (1H, sx, J=11.2, 11.2, 4.8 Hz, 6β-H), 4.53 (1H, m, $W1/2$=24 Hz, 3α-H), 7.48 (2H, d, J=8 Hz, Ar-H), 7.96 (2H, d, J=8 Hz, Ar–H).

3β-Hydroxy-5α-androstane-6,17-dione *p*-Toluenesulfonate (3)——To a solution of **2** (100 mg) in acetone (5 ml) was added Jones reagent (0.5 ml) and the reaction mixture was stirred at room temperature for 20 min. After addition of MeOH to decompose the excess reagent the resulting solution was neutralized with $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product obtained from hexane–CH_2Cl_2 gave **3** (71 mg) as colorless needles. mp 162—164°. $[\alpha]_D^{25}$ +46.6° (c=0.25). *Anal.* Calcd. for $C_{26}H_{34}O_5S$: C, 68.10; H, 7.47. Found: C, 67.66; H, 7.75. NMR ($CDCl_3$) δ: 0.79 (3H, s, 18-CH_3), 0.89 (3H, s, 19-CH_3), 2.51 (3H, s, Ar–CH_3), 4.52 (1H, m, $W1/2$=24 Hz, 3α-H), 7.45 (2H, d, J=8 Hz, Ar-H), 7.91 (2H, d, J=8 Hz, Ar-H).

5α-Androst-2-ene-6,17-dione (4)——A solution of **3** (160 mg) in γ-collidine (1 ml) was refluxed for 30 min. The reaction mixture was diluted with AcOEt, washed with 5% HCl, 5% $NaHCO_3$ and H_2O, successively, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from CH_2Cl_2–MeOH gave **4** (50 mg) as colorless plates. mp 187—190°. $[\alpha]_D^{22}$ +130.7° (c=0.23). *Anal.* Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.58; H, 9.20. NMR ($CDCl_3$) δ: 0.79 (3H, s, 18-CH_3), 0.93 (3H, s, 19-CH_3), 5.67 (2H, m, 2- and 3-H).

5α-Androst-2-ene-6β,17β-diol 17-*tert*-Butyldimethylsilyl Ether (5)——To a solution of **4** (1.9 g) in THF (24 ml) was added $NaBH_4$ (1.8 g) in H_2O (7 ml) and the reaction mixture was stirred at room temperature for 3.5 hr. After addition of AcOH the resulting solution was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue was treated with imidazole (6 g) and *tert*-butyldimethylsilyl chloride (3 g) in dimethylformamide (DMF) (4 ml)–pyridine (2 ml) at room temperature for 3 hr. The reaction mixture was diluted with ether–AcOEt (1: 1), washed with H_2O, dried over anhydrous

Na_2SO_4, and evaporated. The crude product obtained was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (15: 1) and recrystallization of the eluate from MeOH gave **5** (1.7 g) as colorless needles. mp 105—106°. $[\alpha]_D^{22}$ +33.9° (c=0.37). *Anal.* Calcd. for $C_{25}H_{44}O_2Si$: C, 74.20; H, 10.96. Found: C, 74.05; H, 11.19. NMR ($CDCl_3$) δ: 0 (6H, s, –$Si(CH_3)_2$), 0.73 (3H, s, 18-CH_3), 0.86 (9H, s, t-C_4H_9), 0.96 (3H, s, 19-CH_3), 3.62 (1H, t, J=8 Hz, 17α-H), 3.89 (1H, m, 6α-H), 5.67 (2H, m, 2- and 3-H).

2α,3α-Epoxy-5α-androstane-6β,17β-diol 17-*tert*-Butyldimethylsilyl Ether (6)——To a solution of **5** (1.13 g) in $CHCl_3$ (7 ml) was added m-chloroperbenzoic acid (700 mg) and the reaction mixture was stirred at room temperature for 2 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, successively, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from MeOH gave **6** (660 mg) as colorless leaflets. mp 199—202°. $[\alpha]_D^{23}$ +5.6° (c=0.27). *Anal.* Calcd. for $C_{25}H_{44}O_3Si$: C, 71.38; H, 10.54. Found: C, 71.41; H, 10.42. NMR ($CDCl_3$) δ: 0 (6H, s, –$Si(CH_3)_2$), 0.72 (3H, s, 18-CH_3), 0.88 (9H, s, t-C_4H_9), 0.99 (3H, s, 19-CH_3), 3.14—3.20 (2H, m, 2β- and 3β-H), 3.58 (1H, t, J=8 Hz, 17α-H), 3.76 (1H, m, 6α-H). An additional amount of **6** (265 mg) was obtained from the mother liquor.

Reductive Cleavage of 6 with $LiAlH_4$——To a solution of **6** (200 mg) in anhydrous ether (10 ml) was added $LiAlH_4$ (200 mg) and the reaction mixture was refluxed for 6 hr. After addition of moist AcOEt to decompose the excess reagent the resulting solution was diluted with 20% Rochelle salt solution and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (3: 1) and recrystallization of the eluate from MeOH gave 5α-androstane-3α,6β,17β-triol 17-*tert*-butyldimethylsilyl ether (**7**) (162 mg) as colorless leaflets. mp 221—222°. $[\alpha]_D^{22}$ +2.4° (c=0.21). *Anal.* Calcd. for $C_{25}H_{46}O_3Si$: C, 71.03; H, 10.97. Found: C, 70.95; H, 11.04. NMR ($CDCl_3$) δ: 0 (6H, s, –$Si(CH_3)_2$), 0.72 (3H, s, 18-CH_3), 0.89 (9H, s, t-C_4H_9), 1.00 (3H, s, 19-CH_3), 3.61 (1H, t, J=8 Hz, 17α-H), 3.79 (1H, m, 6α-H), 4.20 (1H, m, $W1/2$=7 Hz, 3β-H).

Hydration of 5——To a stirred solution of **5** (100 mg) and $LiAlH_4$ (120 mg) in anhydrous ether (14 ml) was added BF_3-etherate (1 g) in anhydrous ether (6 ml) dropwise at 0° over a period of 10 min under a stream of N_2 gas. 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 THF (10 ml) were added 28% H_2O_2 (3 ml) and 10% NaOH (4 ml) and the reaction mixture was stirred at 0° for 1 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, successively, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (1: 1) and recrystallization of the eluate from ether–MeOH gave **7** (32 mg) as colorless needles. mp 221.5—222.5°. Mixed melting point on admixture with the authentic sample showed no depression and the IR spectra of the two samples were entirely identical in every respect.

17β-Hydroxy-5α-androstane-3,6-dione *tert*-Butyldimethylsilyl Ether (8)——To a stirred solution of **7** (100 mg) in pyridine (0.5 ml) was added 10% CrO_3-pyridine complex (1: 10, w/v) (1 ml) and the reaction mixture was allowed to stand at room temperature for 18 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. Recrystallization of the crude product from MeOH gave **8** (62 mg) as colorless needles. mp 182.5—183.5°. $[\alpha]_D^{22}$ −2.1° (c=0.23). *Anal.* Calcd. for $C_{25}H_{42}O_3Si$: C, 71.72; H, 10.11. Found: C, 71.39; H, 10.10. NMR ($CDCl_3$) δ: 0 (6H, s, –$Si(CH_3)_2$), 0.71 (3H, s, 18-CH_3), 0.88 (9H, s, t-C_4H_9), 0.94 (3H, s, 19-CH_3), 3.62 (1H, t, J=8 Hz, 17α-H).

Reduction of 8 with $LiAlH_4$——To a solution of **8** (40 mg) in anhydrous ether (4 ml) was added $LiAlH_4$ (20 mg) and the reaction mixture was refluxed for 1 hr. After addition of moist AcOEt to decompose the excess reagent the resulting solution was diluted with 20% Rochelle salt solution and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. To the residue dissolved in pyridine (1.8 ml)–benzene (0.4 ml) was added Ac_2O (0.4 ml) and the reaction mixture was allowed to stand at room temperature for 2 hr. After addition of H_2O the resulting solution was extracted with AcOEt. The organic layer was washed with 10% AcOH, 5% $NaHCO_3$ and H_2O, successively, dried over anhydrous Na_2SO_4, and evaporated. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (7: 2) gave a mixture of epimeric 3,6-diacetoxy-5α-androstan-17β-ol *tert*-butyldimethylsilyl ethers (**10**) (25 mg) which was submitted to further elaboration without purification. Further elution and recrystallization of the more polar eluate from MeOH gave 3β-acetoxy-5α-androstane-6β,17β-diol 17-*tert*-butyldimethylsilyl ether (**9**) (22 mg) as colorless leaflets. mp 188.5—189°. $[\alpha]_D^{18}$ −19.0° (c=0.21). *Anal.* Calcd. for $C_{27}H_{48}O_4Si$: C, 69.78; H, 10.41. Found: C, 70.01; H, 10.49. NMR ($CDCl_3$) δ: 0 (6H, s, –$Si(CH_3)_2$), 0.73 (3H, s, 18-CH_3), 0.89 (9H, s, t-C_4H_9), 1.06 (3H, s, 19-CH_3), 2.63 (3H, s, –$OCOCH_3$), 3.56 (1H, t, J=8 Hz, 17α-H), 3.79 (1H, m, 6α-H), 4.72 (1H, m, 3α-H).

Dehydration of 9——To a solution of **9** (4 mg) in anhydrous pyridine (0.5 ml) was added $POCl_3$ (0.3 ml) and the reaction mixture was allowed to stand at room temperature for 40 hr. After addition of moist ether to decompose the excess reagent the resulting solution was extracted with ether. The organic layer was washed with 10% AcOH, 5% $NaHCO_3$ and H_2O, successively, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from MeOH gave 3β-acetoxy-5-androsten-17β- ol *tert*-butyldimethylsilyl ether (**11**) (2 mg) as colorless plates. mp 130.5—131.5°. Mixed melting point on admixture with the authentic sample8) showed no depression and the IR spectra of the two samples were entirely identical.

3β,6β-Dihydroxy-5α-androstan-17-one 3-*tert*-Butyldimethylsilyl Ether (12)——To a solution of **10** (78 mg) in acetone (2 ml) was added conc. H_2SO_4 (0.05 ml) and the reaction mixture was allowed to stand at room temperature for 1 hr. To the resulting solution was added Jones reagent (0.1 ml) and the reaction mixture was allowed to stand at room temperature for 15 min. After addition of MeOH to decompose the excess reagent the resulting solution was evaporated to its half volume under the reduced pressure and extracted with AcOEt. 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 MeOH (2 ml) was added 30% KOH (0.22 ml) and the resulting solution was allowed to stand at 37° for 40 hr. The reaction mixture was diluted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. To the residue dissolved in DMF (0.1 ml)–pyridine (0.05 ml) were added imidazole (100 mg) and *tert*-butyldimethylsilyl chloride (50 mg) and the reaction mixture was stirred at room temperature for 40 min. The resulting solution was diluted with AcOEt–ether (1: 1), washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (2: 1) and recrystallization of the eluate from MeOH gave **12** (26 mg) as colorless needles. mp 229.5—231°. $[\alpha]^{14}_{D}$ +44.7° (c=0.19). *Anal.* Calcd. for $C_{25}H_{44}O_3Si$: C, 71.38; H, 10.54. Found: C, 71.48; H, 10.66. NMR ($CDCl_3$) δ: 0.08 (6H, s, $-Si(CH_3)_2$), 0.92 (12H, s, t-C_4H_9 and 18-CH_3), 1.08 (3H, s, 19-CH_3), 3.72 (1H, m, 3α-H), 3.96 (1H, m, 6α-H).

Dehydration of 12——**12** (5 mg) was treated with $POCl_3$ and pyridine in the manner as described with **9**. Recrystallization of the crude product from MeOH gave dehydroepiandrosterone *tert*-butyldimethylsilyl ether (**13**) (3 mg) as colorless leaflets. mp 142—144°. Mixed melting point on admixture with the authentic sample7) showed no depression.

2α-d_1-5α-Androstane-3α,6β-17β-triol 17-*tert*-Butyldimethylsilyl Ether (14a)——To a stirred solution of **5** (1.11 g) and $LiAlD_4$ (800 mg) in anhydrous ether (70 ml) was added BF_3-etherate (6 g) in anhydrous ether (26 ml) dropwise at 0° over a period of 20 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 THF (40 ml) were added 28% H_2O_2 (20 ml) and 10% NaOH (20 ml) and the reaction mixture was stirred at 0° for 1 hr. The resulting solution was diluted with AcOEt, washed with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, successively, dried over anhydrous Na_2SO_4, and evaporated. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (1: 2) and recrystallization of the eluate from MeOH gave **14a** (410 mg) as colorless needles. mp 222—222.5°.

2α-d_1-17β-Hydroxy-5α-androstane-3,6-dione *tert*-Butyldimethylsilyl Ether (15a)——Oxidation of **14a** (406 mg) with 10% CrO_3-pyridine complex (1: 10, w/v) (4.9 ml) was carried out in the usual manner. The crude product (384 mg) was submitted to further elaboration without purification. A portion of the crude product was recrystallized from MeOH to give **15a** as colorless needles. mp 182—183°.

Reduction of 15a with $LiAlH_4$——Reduction of **15a** (384 mg) with $LiAlH_4$ followed by usual acetylation was carried out in the manner as described with **8**. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (3: 1) gave a mixture of epimeric 2α-d_1-3,6-diacetoxy-5α-androstan-17β-ol *tert*-butyldimethylsilyl ethers (**17a**) (172 mg) as colorless oil which was submitted to further elaboration without purification. Further elution and recrystallization of the more polar eluate from MeOH gave 2α-d_1-3β-acetoxy-5α-androstane-6β,17β-diol 17-*tert*-butyldimethylsilyl ether (**16a**) (149 mg) as colorless plates. mp 189.5—190°.

2α-d_1-3β-Acetoxy-5-androsten-17β-ol *tert*-Butyldimethylsilyl Ether (18a)——Dehydration of **16a** (150 mg) with $POCl_3$ and pyridine was carried out in the manner as described with **9**. The crude product (144 mg) was submitted to further elaboration without purification. A portion of the crude product was recrystallized from MeOH to give **18a** as colorless needles. mp 132—133°.

2α-d_1-3β-Acetoxy-5-androsten-17-one (19a)——To a solution of **18a** (143 mg) in acetone (4 ml) was added conc.H_2SO_4 (0.1 ml) and the reaction mixture was allowed to stand at room temperature for 35 min. To this solution was added Jones reagent (0.3 ml) and the solution was stirred at room temperature for 20 min. After addition of MeOH to decompose the excess reagent the resulting solution was neutralized with 5% $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from MeOH gave **19a** (62 mg) as colorless needles. mp 165—166°.

2α-d_1-3β,6β-Dihydroxy-5α-androstan-17-one 3-*tert*-Butyldimethylsilyl Ether (20a)——Treatment of **17a** (172 mg) with Jones reagent and then with methanolic KOH followed by silylation was carried out in the manner as described with **10**. The crude product was submitted to column chromatography on silica gel.

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8) H. Hosoda, K. Yamashita, S. Ikegawa, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), 25, 2545 (1977).

Elution with hexane–AcOEt (2: 1) and recrystallization of the eluate from MeOH gave **20a** (57 mg) as colorless leaflets. mp 230—231.5°.

2*α*-d_1-Dehydroepiandrosterone *tert*-Butyldimethylsilyl Ether (21a)——Dehydration of **20a** (57 mg) with $POCl_3$ and pyridine was carried out in the manner as described with **9**. The crude product (54 mg) was submitted to further elaboration without purification. A portion of the crude product was recrystallized from MeOH to give **21a** as colorless leaflets. mp 142—144°.

2*α*-d_1-Dehydroepiandrosterone (22a)——i) To a solution of **19a** (62 mg) in MeOH (5 ml) was added 30% KOH (0.56 ml) and the reaction mixture was stirred at room temperature for 1 hr. The resulting solution was diluted with H_2O, concentrated to its half volume under the reduced pressure, and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from MeOH gave **22a** (53 mg) as colorless plates. mp 137—139°. MS *m/e*: 289 (M^+) (98% d_1).

ii) To a solution of **21a** (54 mg) in acetone (2.5 ml) was added 5 N HCl (0.2 ml) and the reaction mixture was allowed to stand at room temperature for 15 min. The resulting solution was neutralized with 5% $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was submitted to column chromatography on silica gel using hexane–AcOEt (1: 1) as an eluent. Recrystallization of the eluate from MeOH gave **22a** (40 mg) as colorless plates. mp 136—137°. The IR spectra of the two samples obtained in i) and ii) were entirely identical in every respect.

2*β*-d_1-5*α*-Androstane-3*α*,6*β*,17*β*-triol 17-*tert*-Butyldimethylsilyl Ether (14b)——To a solution of **6** (77 mg) in anhydrous ether (20 ml) was added $LiAlD_4$ (400 mg) and the reaction mixture was refluxed for 5 hr. After addition of moist AcOEt to decompose the excess reagent the resulting solution was diluted with 20% Rochelle salt solution and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product obtained was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (1: 1) and recrystallization of the eluate from MeOH gave **14b** (551 mg) as colorless needles. mp 222—222.5°.

2*β*-d_1-17*β*-Hydroxy-5*α*-androstane-3,6-dione *tert*-Butyldimethylsilyl Ether (15b)——Oxidation of **14b** (521 mg) with 10% CrO_3–pyridine complex (1: 10, w/v) (5.3 ml) was carried out in the usual manner. The crude product (490 mg) was submitted to further elaboration without purification. A portion of the crude product was recrystallized from MeOH to give **15b** as colorless needles. mp 182.5—183.5°.

Reduction of 15b with $LiAlH_4$——Reduction of **15b** (520 mg) with $LiAlH_4$ followed by usual acetylation was carried out in the manner as described with **8**. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (3: 1) gave a mixture of epimeric 2*β*-d_1-3,6-diacetoxy-5*α*-androstan-17*β*-ol *tert*-butyldimethylsilyl ethers (**17b**) (233 mg) as colorless oil which was submitted to further elaboration without purification. Further elution and recrystallization of the more polar eluate from MeOH gave 2*β*-d_1-3*β*-acetoxy-5*α*-androstane-6*β*,17*β*-diol 17-*tert*-butyldimethylsilyl ether (**16b**) (226 mg) as colorless plates. mp 189—190°.

2*β*-d_1-3*β*-Acetoxy-5-androsten-17*β*-ol *tert*-Butyldimethylsilyl Ether (18b)——Dehydration of **16b** (197 mg) with $POCl_3$ and pyridine was carried out in the manner as described with **9**. The crude product (190 mg) was submitted to further elaboration without purification. A portion of the crude product was recrystallized from MeOH to give **18b** as colorless needles. mp 130.5—131.5°.

2*β*-d_1-3*β*-Acetoxy-5-androsten-17-one (19b)——Treatment of **18b** (190 mg) with conc. H_2SO_4 and then with Jones reagent was carried out in the manner as described with **18a**. Recrystallization of the crude product from MeOH gave **19b** (135 mg) as colorless needles. mp 165—166°.

2*β*-d_1-3*β*,6*β*-Dihydroxy-5*α*-androstan-17-one 3-*tert*-Butyldimethylsilyl Ether (20b)——Treatment of **17b** (231 mg) with Jones reagent and then with methanolic KOH followed by silylation was carried out in the manner as described with **10**. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (2: 1) and recrystallization of the eluate from MeOH gave **20b** (122 mg) as colorless leaflets. mp 230—231.5°.

2*β*-d_1-Dehydroepiandrosterone *tert*-Butyldimethylsilyl Ether (21b)——Dehydration of **20b** (114 mg) with $POCl_3$ and pyridine was carried out in the manner as described with **9**. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (6: 1) and recrystallization of the eluate from MeOH gave **21b** (103 mg) as colorless needles. mp 145.5—146.5°.

2*β*-d_1-Dehydroepiandrosterone (22b)——i) **19b** (97 mg) was hydrolyzed with 3% methanolic KOH in the manner as described with **19a**. Recrystallization of the crude product from MeOH gave **22b** (88 mg) as colorless leaflets. mp 137—139°. MS *m/e*: 289 (M^+) (98% d_1).

ii) **21b** (54 mg) was hydrolyzed with 5 N HCl in the manner as described with **21a**. The crude product was submitted to column chromatography on silica gel. Elution with hexane–AcOEt (1: 1) and recrystallization of the eluate from MeOH gave **21b** (39 mg) as colorless plates. mp 137—139°. The IR spectra of the two samples were entirely identical in every respect.

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