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Synthesis of Epimeric 2-d_1-5β-Pregnane-3,11,20-triones[1]

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In order to clarify the stereochemistry of hydrogen loss from the C-2 position during microbial transformation of 5β-pregnane-3,11,20-trione into the Δ^1-unsaturated compound, the stereospecific synthesis of epimeric C-2 deuterated substrates has been carried out. A key intermediate, 5β-pregn-2-ene-11α,20β-diol diacetate, was obtained from the readily available 11α-hydroxyprogesterone through two synthetic routes. The *trans*-diaxial opening of the 2β,3β-epoxide with lithium aluminum deuteride provided the 2α-d_1-3β-ol. Deuterioboration of the Δ^2-olefin and subsequent oxidation of the organoborane afforded the 2β-d_1-3β-ol. On oxidation with chromium trioxide-pyridine complex, the epimeric 2-d_1-5β-pregnane-3β,11α,20β-triols were converted to the desired 2-d_1-5β-pregnane-3,11,20-triones.

Keywords——biotransformation mechanism; 5β-pregn-2-ene; 2β,3β-epoxy-5β-pregnane; deuteriodiborane; lithium aluminum deuteride; *trans*-diaxial opening of epoxide; epimeric 2-d_1-5β-pregnane-3,11,20-triones

Various microorganisms are capable of introducing a double bond into the 1,2- and 4,5-positions of 5α-, 5β- and Δ^4-3-ketosteroids.[3] The steric mechanism of unsaturation in ring A has been extensively investigated using deuterium-labeled substrates, and the stereoselective loss of axial hydrogen from the α-position of carbonyl group has been reported.[4,5] However, an exception was reported in that C-1,2 dehydrogenation of 5β-pregnane-3,11,20-trione by *Septomyxa affinis* involves the elimination of equatorial 2β-hydrogen.[6] This finding is not necessarily definitive, because only 1α,2α-d_2-5β-pregnanetrione was used as a substrate for the microbial transformation. As part of a series of studies on the bioconversion mechanisms of steroids,[5,7] elucidation of the stereochemistry of hydrogen loss from C-2 during enzymatic dehydrogenation has been undertaken. Our experimental design required epimeric 5β-pregnane-3,11,20-triones labeled with deuterium stereospecifically at the C-2 position as substrates. The present paper describes the preparation of these compounds starting from commercially available 11α-hydroxy-4-pregnene-3,20-dione (11α-hydroxyprogesterone).

As a preliminary experiment, we sought to establish a synthetic route by which the label could be unambiguously introduced at the desired position. In the preceding paper of this series it was demonstrated that stereospecific labeling of deuterium at the C-2 position of

1) Part CXXXXVII of "Studies on Steroids" by T. Nambara; Part CXXXXVI: K. Shimada and T. Nambara, *J. Chromatogr.*, **174**, 440 (1979).
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3) H. Iizuka and A. Naito, "Microbial Transformation of Steroids and Alkaloids," University of Tokyo Press, Tokyo, 1967, pp. 101—138.
4) H.J. Ringold, M. Hayano, and V. Stefanovic, *J. Biol. Chem.*, **238**, 1960 (1963); R. Jerussi and H.J. Ringold, *Biochemistry*, **4**, 2113 (1965).
5) S. Ikegawa and T. Nambara, *Chem. Ind.* (London), **1973**, 230; T. Nambara, S. Ikegawa, and H. Hosoda, *Chem. Pharm. Bull.* (Tokyo), **21**, 2794 (1973); T. Nambara, S. Ikegawa, and C. Takahashi, *ibid.*, **23**, 2358 (1975).
6) Y.J. Abul-Hajj, *J. Biol. Chem.*, **247**, 686 (1972).
7) T. Nambara, S. Ikegawa, and M. Kato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2164 (1975); T. Nambara, S. Ikegawa, H. Ishida, and H. Hosoda, *ibid.*, **25**, 3415 (1977); T. Nambara, S. Ikegawa, T. Hirayama, and H. Hosoda, *ibid.*, **26**, 757 (1978).

5β-androstane-3,17-dione can be attained by deuterioboration of the Δ^2-5β-steroid and by reductive cleavage of the 2β,3β-epoxy-5β-steroid with lithium aluminum deuteride.[8] Our initial effort, therefore, was directed to the preparation of 5β-pregn-2-ene-11α, 20β-diol diacetate as a key intermediate leding to the desired compounds.

Catalytic hydrogenation of 11α,20β-diacetoxy-4-pregnen-3-one (**1**), which is readily obtainable from 11α-hydroxyprogesterone in three steps, with palladium on calcium carbonate in pyridine gave the 5β-3-ketone (**2**) in satisfactory yield. The stereochemistry at C-5 was deduced from the circular dichroism (CD) curve, which exhibited a negative Cotton effect. In addition, the saturated product was converted to the known 5β-pregnane-3α,11α,20β-triol (**3a**)[9] by reduction with sodium borohydride followed by saponification. When the 3-tosylate (**3c**) derivable from **2** was refluxed with lithium chloride in dimethylformamide, elimination of the oxygen function at C-3 was effected, yielding a mixture of the Δ^2- and Δ^3-olefins (**5a**, **5b**). However, difficulties were encountered in the separation of these positional isomers because of the similarity in their chromatographic behavior. Accordingly the crude product was used for subsequent elaboration without further purification. Oxidation with *m*-chloroperbenzoic acid yielded a mixture of the 2,3- and 3,4-epoxides (**6**, **7**) in a ratio of 1 to 6; these could be efficiently separated by column chromatography on silica gel. The configuration

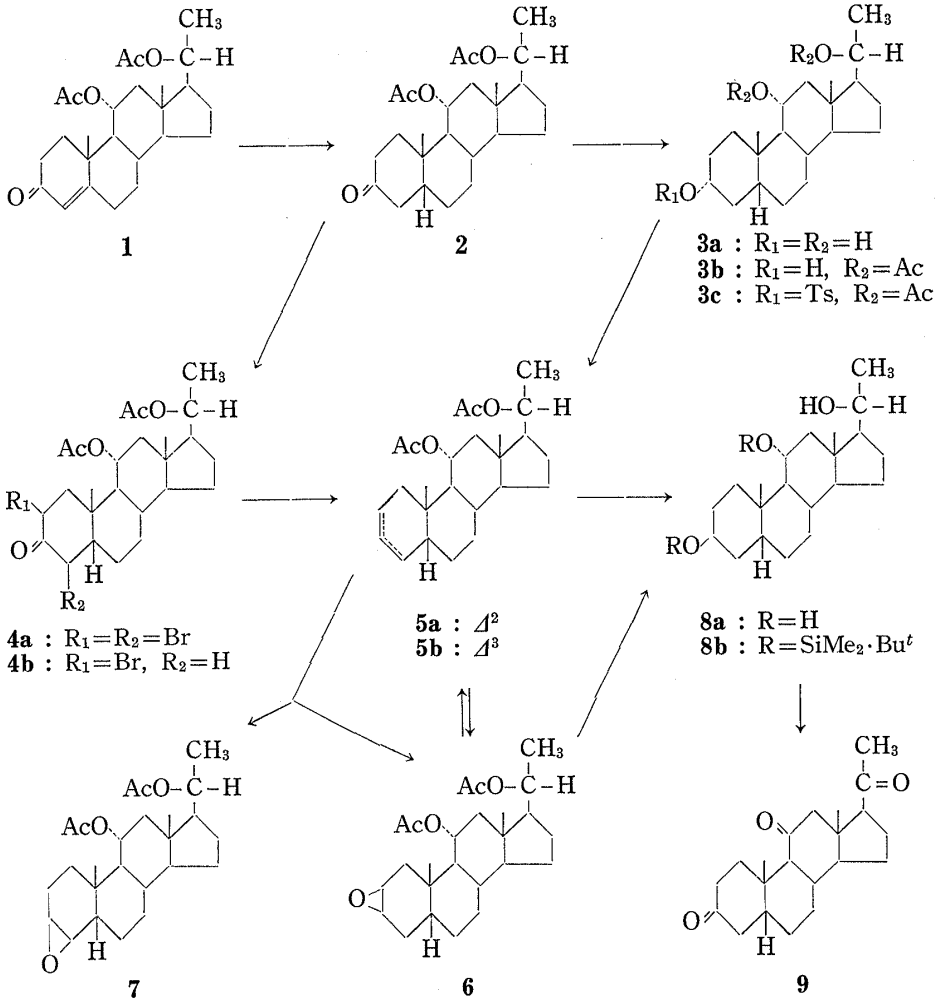

Chart 1

8) T. Nambara, H. Hosoda, T. Anjyo, and S. Ikegawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 2256 (1972).
9) A.H. Nathan and J.H. Hogg, U.S. Patent 2751397 (1956) [*C.A.*, **51**, 1316 (1956)].

of both epoxides was supposed to be β because the reagent should attack preferentially from the less hindered β-side of a steroid molecule having the A/B-*cis* fusion. The splitting pattern of the nuclear magnetic resonance (NMR) signal due to the epoxy proton justified this configurational assignment. On treatment with sodium iodide and zinc dust, the $2\beta,3\beta$-epoxide (**6**) was easily transformed into the desired Δ^2-olefin (**5a**), whose structure was characterized by inspection of the NMR spectra. This synthetic route, however, was unsatisfactory with respect to the yield. Therefore, we next sought an alternative route to the key intermediate.

It is reasonably well substantiated that reductive monodebromination of a 2,4-dibromo-3-ketosteroid occurs preferentially at C-4 rather than at C-2 in the 5β-series while it occurs at C-2 in the 5α-steroid.[10] On treatment with excess bromine in acetic acid under enolizing conditions, **2** was transformed into the $2\beta,4\beta$-dibromo-5β-3-keone (**4a**). Selective debromination of **4a** with freshly prepared chromous acetate proceeded with the expected orientation to provide the 2β-bromo-3-ketone (**4b**) in satisfactory yield. The structure of **4b** was unequivocally established on the basis of spectral data. In the NMR spectra the 2α-proton signal appeared at 4.98—5.36 ppm as a multiplet overlapping with those of the 11β- and 20α-protons. The carbonyl absorption shift (18 cm^{-1}) from the unsubstituted 5β-3-ketosteroid in the infrared (IR) spectra permitted us to assign the structure as having an equatorial bromine at the α-position of the 3-ketone. In addition, the CD curves supported this assignment in that the 2β-bromo compound as well as the parent ketone exhibited a negative Cotton effect with an extremum at 286 nm. Reduction of **4b** with sodium borohydride and subsequent treatment of bromohydrin with zinc dust in acetic acid furnished the 5β-pregn-2-ene (**5a**) in excellent yield. The attack of per acid on **5a** did take place from the less hindered β-side to give the $2\beta,3\beta$-epoxide (**6**) as a sole product. This synthetic route proved to be much more favorable for obtaining **5a** and **6**.

Reductive cleavage of the $2\beta,3\beta$,-epoxide (**6**) with lithium aluminum hydride was then carried out. As expected, *trans*-diaxial opening of the oxido ring occurred to give the 3β-hydroxyl compound (**8a**). The structural assignment was justified by inspection of the NMR spectra, where a multiplet signal ($W_{1/2}$=9 Hz) centered at 4.11 ppm due to the equa-

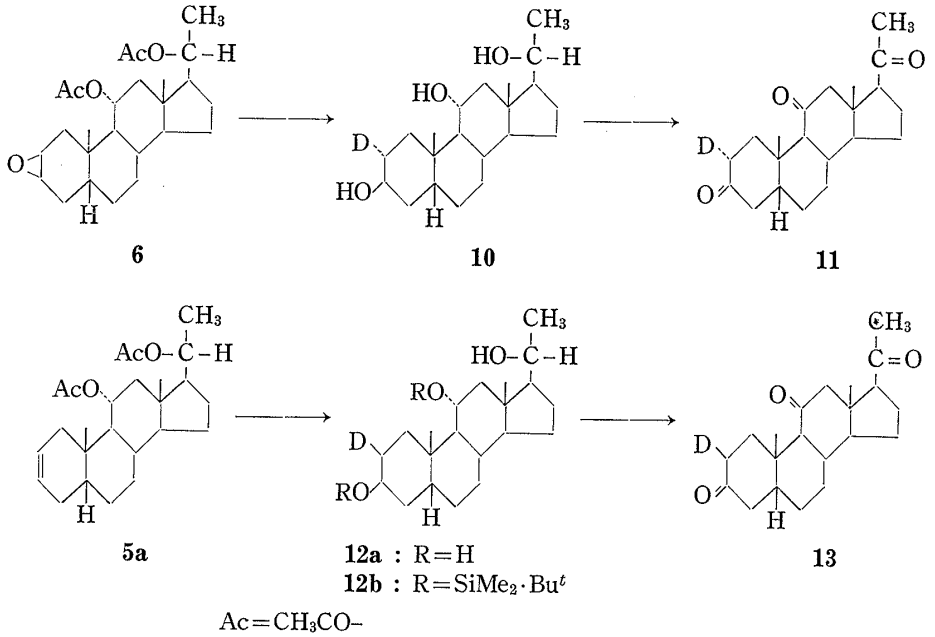

Chart 2

10) K.L. Williamson and W.S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961); J.Y. Satoh, K. Misawa, T.T. Takahashi, M. Hirose, C.A. Horiuchi, S. Tsuji, and A. Hagitani, *Bull. Chem. Soc.* (Japan), **46**, 3155 (1973).

torial 3α-proton was observed. Hydroboration of the Δ^2-olefin (**5a**) with diborane and subsequent oxidation of organoborane with hydrogen peroxide furnished mainly the 3β-hydroxyl compound (**8a**) accompanied by the isomeric 2β- and 3α-ols. Attempts to separate **8a** from the isomers resulted in failure, although they were distinguishable from one another on a thin-layer chromatogram. When the crude product was subjected to *tert*-butyldimethylsilylation[11] followed by column chromatography on silica gel, the 3β,11α,20β-triol 3,11-bis(*tert*-butyldimethylsilyl) ether (**8b**) could be isolated successfully. Upon exposure to 5 N hydrochloric acid in acetone, removal of the silyl groups in **8b** was achieved, yielding the 3β,11α,20β-triol (**8a**). Subsequent oxidation with chromium trioxide-pyridine complex afforded 5β-pregnane-3,11,20-trione (**9**). The synthetic route thus established appeared to be promising for the introduction of a deuterium label stereospecifically at the C-2 position of 5β-pregnane-3,11,20-trione.

The *trans*-diaxial opening of the 2β,3β-epoxide (**6**) with lithium aluminum deuteride gave 2α-d_1-5β-pregnane-3β,11α,20β-triol (**10**). On the other hand, the preparation of the 2β-deuterated epimer (**12a**) was accomplished by deuteration of the Δ^2-olefin (**5a**) with deuteriodiborane, generated from lithium aluminum deuteride and boron trifluoride. Purification of the silyl derivative (**12b**) followed by desilylation furnished the 2β-d_1-3β-ol (**12a**). Oxidation of **10** and **12a** with chromium trioxide under mild conditions provided the desired epimeric 2-d_1-5β-pregnane-3,11,20-triones (**11**, **13**) in reasonable yields.

The IR spectra of non-labeled and deuterated 5β-pregnane-3,11,20-triones were clearly distinguishable from each other in the fingerprint region. Inspection of the molecular ion peak in the mass (MS) spectra indicated that the isotopic purity of these deuterium-labeled steroids was more than 98%.

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

Experimental[12]

11α,20β-Diacetoxy-5β-pregnan-3-one (**2**)——A solution of 11α,20β-diacetoxy-4-pregnen-3-one (**1**)[13] (1 g) in pyridine (5 ml) was stirred with 2% Pd/$CaCO_3$ (1.5 g) at room temperature overnight under a stream of H_2 gas. After removal of the catalyst by filtration, the filtrate was diluted with AcOEt, washed successively with 5% HCl, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from MeOH gave **2** (592 mg) as colorless leaflets. mp 215—216°. $[\alpha]_D^{15}$ −4.1° (c=1.65). *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 72.02; H, 9.34. IR ν_{max} cm^{-1}: 1718, 1730. NMR ($CDCl_3$) δ: 0.72 (3H, s, 18-CH_3), 1.16 (3H, s, 19-CH_3), 1.18 (3H, d, J=6 Hz, 21-CH_3), 1.99, 2.04 (6H, each s, 2×OAc), 4.80 (1H, m, 20α-H), 5.12 (1H, sx, J=5, 10 Hz, 11β-H). CD (c=9.78×10^{-4}, MeOH): $[\theta]_{244}$ 0, $[\theta]_{283}$ −1890, $[\theta]_{327}$ 0.

11α,20β-Diacetoxy-5β-pregnan-3α-ol (**3b**)——To a solution of **2** (185 mg) in tetrahydrofuran (THF) (5 ml) was added $NaBH_4$ (206 mg) in H_2O (3 ml) under ice-cooling and the solution was allowed to stand at room temperature for 10 min. After addition of 10% AcOH to decompose excess reagent 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 crude product from hexane–acetone gave **3b** (139 mg) as colorless needles. mp 201—202°. $[\alpha]_D^{15}$ −12.7° (c=0.71). *Anal.* Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Found: C, 71.36; H,

11) E.J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972); H. Hosoda, K. Yamashita, H. Sagae, and T. Nambara, *Chem. Pharm. Bull.* (Tokyo), **23**, 2118 (1975).

12) All melting points were taken on a micro hot-stage apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ unless otherwise specified. IR spectra were obtained in KBr discs on a JASCO Model IRA-1 spectrometer. CD curves were measured with a JASCO Model ORD/UV-5 spectropolarimeter. NMR spectra were recorded on a JEOL Model PS-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard. Abbreviations: s=singlet, d=doublet, sx=sextet, and m=multiplet. MS spectra were measured with a Hitachi Model M-52G spectrometer. The isotopic purity of $LiAlD_4$ used was over 98%. All the deuterated compounds obtained were characterized by mixed melting point measurement on admixture with non-labeled authentic samples. For preparative TLC, silica gel H (E. Merck AG, Darmstadt) was used as an adsorbent.

13) K. Heusler, J. Kalvoda, P. Wieland, and A. Wettstein, *Helv. Chim. Acta*, **44**, 179 (1961).

9.36. NMR ($CDCl_3$) δ: 0.64 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 1.12 (3H, d, J=6 Hz, 21-CH_3), 1.94, 1.99 (6H, each s, 2×OAc), 3.68 (1H, m, $W_{1/2}$=20 Hz, 3β-H), 4.76 (1H, m, 20α-H), 5.00 (1H, sx, J=5, 10 Hz, 11β-H). Additional **3b** (20 mg) was obtained from the mother liquor.

5β-Pregnane-3α,11α,20β-triol (**3a**)——**3b** (35 mg) was dissolved in 5% methanolic KOH (3 ml) and heated at 60° for 1 hr. The reaction mixture was diluted with AcOEt, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from acetone gave **3a** (22 mg) as colorless leaflets. mp 186—187° (reported 197—199°).[9]

11α,20β-Diacetoxy-5β-pregnan-3α-ol *p*-Toluenesulfonate (**3c**)——To a solution of **3b** (1.4 g) in pyridine (10 ml) was added *p*-toluenesulfonyl chloride (2 g) under ice-cooling and the solution was stirred at room temperature overnight. To the reaction mixture was added 5% HCl and the resulting solution was extracted with AcOEt. The organic layer was washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crystalline product (1.85 g) was used for further elaboration without purification. A portion of the crude product was recrystallized from acetone to give **3c** as colorless needles. mp 162.5—164°. $[\alpha]_D^{15}$ +16.0° (c=0.28). *Anal.* Calcd. for $C_{32}H_{46}O_7S$: C, 66.87; H, 8.07. Found: C, 66.49; H, 8.11. NMR ($CDCl_3$) δ: 0.64 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 1.16 (3H, d, J=6 Hz, 21-CH_3), 1.92, 2.01 (6H, each s, 2×OAc), 2.48 (3H, s, Ar-CH_3), 4.48 (1H, m, 3β-H), 4.80 (1H, m, 20α-H), 5.00 (1H, sx, J=5, 10 Hz, 11β-H), 7.32, 7.77 (4H, d, J=8 Hz, Ar-H).

2β,3β-Epoxy-5β-pregnane-11α,20β-diol Diacetate (**6**), **3β,4β-Epoxy-5β-pregnane-11α,20β-diol Diacetate** (**7**)——To a solution of **3c** (1.74 g) in dimethylformamide (DMF) (15 ml) was added LiCl (2 g) and the solution was refluxed for 5 hr. The resulting solution was diluted with H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (5: 1) gave a mixture of Δ^2- and Δ^3-olefins (**5a**, **5b**) (1.02 g). To a solution of the mixture (750 mg) in $CHCl_3$ (10 ml) was added *m*-chloroperbenzoic acid (1 g) and the solution was stirred at room temperature overnight. The resulting solution was diluted with AcOEt, washed successively with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (7: 1) and recrystallization of the less polar eluate from MeOH gave **7** (415 mg) as colorless plates. mp 207—208°. $[\alpha]_D^{14}$ −19.5° (c=0.74). *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.93; H, 9.58. NMR ($CDCl_3$) δ: 0.69 (3H, s, 18-CH_3), 0.93 (3H, s, 19-CH_3), 1.14 (3H, d, J=6 Hz, 21-CH_3), 1.97 (6H, s, 2×OAc), 2.84, 3.20 (2H, m, 3α- and 4α-H), 4.50—5.30 (2H, m, 11β- and 20α-H). Further elution and recrystallization of the more polar eluate from MeOH gave **6** (65 mg) as colorless needles. mp 234—236°. $[\alpha]_D^{15}$ −27.3° (c=0.79). *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.56; H, 9.17. NMR ($CDCl_3$) δ: 0.65 (3H, s, 18-CH_3), 1.00 (3H, s, 19-CH_3), 1.14 (3H, d, J=6 Hz, 21-CH_3), 1.99, 2.00 (6H, each s, 2×OAc), 2.95—3.36 (2H, m, 2α- and 3α-H), 4.50—5.26 (2H, m, 11β- and 20α-H).

11α,20β-Diacetoxy-2β,4β-dibromo-5β-pregnan-3-one (**4a**)——To a solution of **2** (500 mg) in AcOH (2.5 ml) was added Br_2 (0.5 ml) in AcOH (1 ml) and the solution was stirred at room temperature for 5 hr. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (2: 1) and recrystallization of the eluate from hexane–acetone gave **4a** (465 mg) as colorless needles. mp 193—194.5°. $[\alpha]_D^{14}$ +5.2° (c=0.96). *Anal.* Calcd. for $C_{25}H_{36}Br_2O_5$: C, 52.10; H, 6.30. Found: C, 52.20; H, 6.29. IR ν_{max} cm^{-1}: 1730, 1738. NMR ($CDCl_3$) δ: 0.72 (3H, s, 18-CH_3), 1.16 (3H, d, J=6 Hz, 21-CH_3), 1.23 (3H, s, 19-CH_3), 2.02, 2.16 (6H, each s, 2×OAc), 4.80 (1H, m, 20α-H), 4.92—5.32 (3H, m, 2α-, 4α- and 11β-H). CD (c=9.00×10^{-4}, MeOH): $[\theta]_{242}$ 0, $[\theta]_{268}$ −2640, $[\theta]_{320}$ −73.

2β-Bromo-11α,20β-diacetoxy-5β-pregnan-3-one (**4b**)——To a solution of **4a** (230 mg) in $CHCl_3$ (1 ml)–AcOH (2 ml) was added freshly prepared chromous acetate (1 g) and the solution was stirred at room temperature for 1 hr. The reaction mixture was diluted with AcOEt, washed with 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was subjected to column chromatography on silica gel. Elution with benzene–ether (4: 1) and recrystallization of the eluate from hexane–acetone gave **4b** (156 mg) as colorless needles. mp 178—179.5°. $[\alpha]_D^{12}$ −25.0° (c=1.0). *Anal.* Calcd. for $C_{25}H_{37}BrO_5$: C, 60.36; H, 7.50. Found: C, 60.07; H, 7.39. IR ν_{max} cm^{-1}: 1730, 1736. NMR ($CDCl_3$) δ: 0.70 (3H, s, 18-CH_3), 1.15 (3H, s, 19-CH_3), 1.18 (3H, d, J=6 Hz, 21-CH_3), 2.03, 2.16 (6H, each s, 2×OAc), 4.81 (1H, m, 20α-H), 4.98—5.36 (2H, m, 2α- and 11β-H). CD (c=9.42×10^{-4}, MeOH): $[\theta]_{248}$ 0, $[\theta]_{286}$ −2837, $[\theta]_{336}$ 0.

5β-Pregn-2-ene-11α,20β-diol Diacetate (**5a**)——i) To a solution of **6** (15 mg) in AcOH (0.1 ml) were added a solution of NaI (50 mg) and AcONa (50 mg) in H_2O (0.2 ml) and Zn dust (50 mg), and the suspension was stirred at room temperature for 2 hr. After removal of the precipitate by filtration the filtrate was diluted with ether, washed successively with H_2O, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from MeOH gave **5a** (10 mg) as colorless plates. mp 172.5—174°. $[\alpha]_D^{14}$ −31.5° (c=0.90). *Anal.* Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.32; H, 9.80. NMR ($CDCl_3$) δ: 0.68 (3H, s, 18-CH_3), 1.08 (3H, s, 19-CH_3), 1.16 (3H, d, J=6 Hz, 21-CH_3), 2.04 (6H, s, 2×OAc), 4.64—5.20 (2H, m, 11β- and 20α-H), 5.68 (2H, m, 2- and 3-H).

ii) To an ice-cooled solution of **4b** (1.5 g) in THF (10 ml) was added $NaBH_4$ (1 g) in H_2O (2 ml) and the solution was stirred at room temperature for 1 hr. After addition of 10% AcOH to decompose excess reagent, 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 AcOH (10 ml) was added Zn dust (3 g) and the suspension was stirred at 100° for 4 hr. After removal of the precipitate by filtration the filtrate was diluted with AcOEt, washed successively with H_2O, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was subjected to column chromatography on silica gel. Elution with hexane–AcOEt (6: 1) and recrystallization of the eluate from MeOH gave **5a** (855 mg) as colorless plates. mp 172—174°. Mixed melting point on admixture with the sample obtained in i) showed no depression.

Epoxidation of 5a——To a solution of **5a** (10 mg) in $CHCl_3$ (1 ml) was added *m*-chloroperbenzoic acid (10 mg) and the solution was stirred at room temperature for 1 hr. The reaction mixture was diluted with AcOEt, washed successively with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. Recrystallization of the crude product from MeOH gave **6** (7 mg) as colorless needles. mp 231—233.5°. Mixed melting point on admixture with an authentic sample showed no depression.

Reductive Cleavage of 6 with $LiAlH_4$——To a solution of **6** (57 mg) in anhydrous THF (5 ml) was added $LiAlH_4$ (200 mg) and the reaction mixture was refluxed for 5 hr. After addition of moist AcOEt to decompose 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 subjected to column chromatography on silica gel. Elution with $CHCl_3$–MeOH (10: 1) and recrystallization of the eluate from aq. MeOH gave 5β-pregnane-3β,11α,20β-triol (**8a**) (21 mg) as colorless prisms. mp 228—229°. $[\alpha]_D^{19}$ −10.2° (c=0.69, MeOH). *Anal.* Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.71; H, 10.96. NMR(CD_3OD) δ: 0.79 (3H, s, 18-CH_3), 1.12 (3H, s, 19-CH_3), 1.14 (3H, d, J=6 Hz, 21-CH_3), 3.48—4.00 (2H, m, 11β- and 20α-H), 4.11 (1H, m, $W_{1/2}$=9 Hz, 3α-H).

Hydration of 5a——To a stirred solution of **5a** (55 mg) and $LiAlH_4$ (100 mg) in anhydrous ether (12 ml) was added BF_3-etherate (3 ml) in anhydrous ether (4 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 AcOEt to decompose excess reagent, the resulting solution was 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 THF (1 ml) were added 28% H_2O_2 (1.5 ml) and 10% NaOH (1 ml), and the solution was stirred at 0° for 1 hr under a stream of N_2 gas. The resulting solution was extracted with AcOEt. The organic layer was washed successively with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue was treated with *tert*-butyldimethylsilyl chloride (150 mg) and imidazole (400 mg) in DMF (0.4 ml)–pyridine (0.15 ml) at room temperature overnight. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was subjected to column chromatography on silica gel. Elution with hexane–benzene (1: 1) gave 5β-pregnane-3β,11α,20β-triol 3,11-bis(*tert*-butyldimethylsilyl) ether (**8b**) (32 mg) as semicrystals. $[\alpha]_D^{12}$ −3.4° (c=1.16). *Anal.* Calcd. for $C_{33}H_{64}O_3Si_2$: C, 70.15; H, 11.42. Found: C, 70.27; H, 11.14. NMR ($CDCl_3$) δ: 0.02, 0.08 (12H, each s, 2×Si(CH_3)$_2$), 0.67 (3H, s, 18-CH_3), 0.89 (18H, s, 2×*tert*-C_4H_9), 1.08 (3H, s, 19-CH_3), 1.09 (3H, d, J=6 Hz, 21-CH_3), 3.49—4.06 (2H, m, 11β- and 20α-H), 4.20 (1H, m, $W_{1/2}$=9 Hz, 3α-H). Treatment of **8b** (26 mg) with 5 N HCl (0.1 ml)–acetone (1 ml) followed by recrystallization of the hydrolysate from aq. MeOH gave **8a** (10 mg) as colorless prisms. mp 228—229°. Mixed melting point on admixture with an authentic sample showed no depression. IR spectra of the two samples were identical.

Oxidation of 8a with CrO_3-Pyridine Complex——To a solution of **8a** (5 mg) in pyridine (0.1 ml) was added 10% CrO_3–pyridine complex (1: 10 w/v) (0.2 ml) and the solution was allowed to stand at room temperature for 24 hr. The reaction mixture was diluted with AcOEt, washed successively with 10% AcOH, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by preparative TLC using hexane–AcOEt (1: 1) as a developing solvent. Recrystallization of the eluate from hexane–acetone gave 5β-pregnane-3,11,20-trione (**9**) (3 mg) as colorless plates. mp 155—158°. Mixed melting point on admixture with an authentic sample showed no depression. IR spectra of the two samples were identical.

2α-d_1-5β-Pregnane-3β,11α,20β-triol (10)——To a solution of **6** (310 mg) in anhydrous THF (10 ml) was added $LiAlD_4$ (500 mg) and the reaction mixture was refluxed for 7 hr. After addition of moist AcOEt to decompose 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 subjected to column chromatography on silica gel. Elution with $CHCl_3$–MeOH (10: 1) and recrystallization of the eluate from aq. MeOH gave **10** (193 mg) as colorless prisms. mp 228—229°. IR ν_{max} cm^{-1}: 2160 (C–D). MS m/e: 319 (M^+−18) (98% d_1).

2α-d_1-5β-Pregnane-3,11,20-trione (11)——Oxidation of **10** (140 mg) with 10% CrO_3–pyridine complex (1: 10 w/v) (4 ml) was carried out in the usual manner. The crude product was purified by preparative TLC using hexane–AcOEt (1: 1) as a developing solvent. Recrystallization of the eluate from hexane–acetone gave **11** (114 mg) as colorless plates. mp 158—158.5°. MS m/e: 331 (M^+) (98% d_1).

2β-d_1-5β-Pregnane-3β,11α,20β-triol (12a)——To a stirred solution of **5a** (800 mg) and $LiAlD_4$ (1 g) in anhydrous ether (50 ml) was added BF_3-etherate (6 g) in anhydrous ether (20 ml) dropwise at 0° over a period of 20 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 AcOEt to decompose excess reagent, the resulting

solution was 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 THF (20 ml) were added 28% H_2O_2 (10 ml) and 10% NaOH (10 ml), and the solution was stirred at 0° for 1 hr under a stream of N_2 gas. The resulting solution was diluted with AcOEt, washed successively with 5% $NaHSO_3$, 5% $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The residue was treated with *tert*-butyldimethylsilyl chloride (1.5 g) and imidazole (3 g) in DMF (4.2 ml)–pyridine (1.4 ml) at room temperature overnight. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The crude product was subjected to column chromatography on silica gel. Elution with hexane–benzene (1: 1) gave 2β-d_1-5β-pregnane-3β,11α,20β-triol 3,11-bis(*tert*-butyldimethylsilyl) ether (**12b**) (488 mg). **12b** was treated with 5 N HCl (2 ml) in acetone (10 ml) at room temperature for 2.5 hr. 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 crystalline product (300 mg) was used for further elaboration without purification. A portion of the crude product was recrystallized from aq. MeOH to give **12a** as colorless prisms. mp 227—228°. IR ν_{max} cm^{-1}: 2160 (C–D). MS *m/e*: 319 (M^+-18) (98% d_1).

2β-d_1-5β-Pregnane-3,11,20-trione (13)——Oxidation of **12a** (300 mg) with 10% CrO_3–pyridine complex (10 ml) was carried out in the usual manner. The crude product was subjected to column chromatography on silica gel. Elution with benzene–ether (2: 3) and recrystallization of the eluate from hexane–acetone gave **13** (242 mg) as colorless plates. mp 157—158°. MS *m/e*: 391 (M^+) (98% d_1).

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