# Regioselective Synthesis Using the Deuterium Isotope Effect[1]

Masateru Miyano

*Department of Medicinal Chemistry, G. D. Searle & Co., Chicago, Illinois 60680*

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Dehydration of **1a** by various procedures invariably produced more exo olefin **2a** than endo olefin **3a**. This could be reversed by introduction of deuterium in the Me-21 group of the starting material. Thus, dehydration of **1b** could afford more endo olefin **3b** than exo olefin **2b** due to the deuterium isotope effect. A regioselective synthesis of 18-oxoprogesterone (**15a**) from 3$\beta$-hydroxypregn-5-en-20-one (**5a**) was carried out taking advantage of the deuterium isotope effect as depicted in Scheme I. The key steps were dehydration of **7b** to predominantly endo olefin **9b** and removal of the deuteriums from 18-oxoprogesterone-*17$\alpha$,21,21,21-$d_4$* (**15b**) to give **15a**.

When a hydrogen in a reactant molecule is replaced by a deuterium, there is often a change in the rate. Such changes have been known as the deuterium isotope effect and have been used for study of the reaction mechanism. Theoretically the deuterium isotope effect might be used for regioselective synthesis of complex organic molecules. This would consist of (1) introduction of a deuterium at the reaction site of the starting molecule, (2) a regioselective reaction due to the isotope effect, and (3) replacement of the deuterium with a hydrogen. The first example of this kind is the subject of this paper.

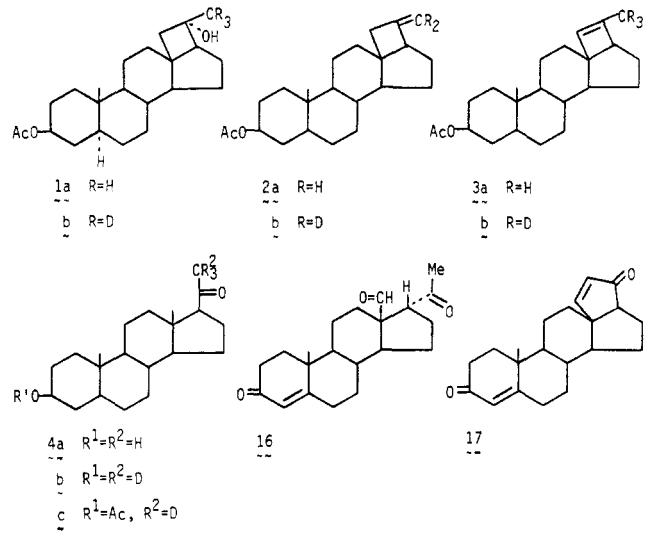
During exploratory work to uncover a novel antihypertensive steroid, it was found[2] that 18$\alpha$-hydroxy-18,20-cyclopregna-4,20(21)-dien-3-one (**13**) had high binding affinity to the rat kidney aldosterone receptor. The key intermediate for synthesis of **13** was **9a**, which in turn was obtained only as a minor product in a conventional dehydration[3] of **7a**. The endo olefin **9a** can also serve as an intermediate for 18-oxoprogesterone (**15a**),[4] a compound having a mild antialdosterone activity. Thus, a new method for the regioselective dehydration of 20$\alpha$-hydroxy-18,20-cyclo steroids (e.g., **7a**) to 18(20)-ene, 18,12-cyclo steroids (e.g., **9a**) was sought. Its successful solution is the central theme of this paper.

## Results and Discussion

**Syntheses.** Jeger and co-workers[3,5] treated (5$\alpha$)-3$\beta$-acetoxy-20$\alpha$-hydroxy-18,20-cyclopregnane (**1a**, Chart I) with phosphorus oxychloride in pyridine on a steam bath and obtained a mixture of the *exo*- and *endo*-cyclobutenes **2a** and **3a**, the former being the major product. We repeated Jeger's work and found that the ratio[6] of **2a** to **3a** was 4:1 based upon gas chromatographic analysis.[7] The *exo*-cyclobutenes appear to be thermodynamically more stable than *endo*-cyclobutenes.[8]

In order to find a condition for regioselective formation of endo olefin **3a**, a number of combinations of chlorides (thionyl chloride, methane sulfonyl chloride, phosphorus oxychloride) and tertiary amines were tested. In our hands none of them produced the endo olefin preferentially.

Chart I




Nevertheless the exo/endo ratio approached 1.0 under certain conditions which are summarized in Table I (entries 2, 4, and 6). Apparently the nature of the tertiary amine was critical. Thus, while thionyl chloride–collidine gave an exo/endo ratio of 1.09 in good yield, thionyl chloride–pyridine gave[9] neither **2a** nor **3a**. Thionyl chloride–DBN (or DBU) produced **2a** as the major product.

The apparent impasse was overcome by use of the deuterium isotope effect. 3$\beta$-Hydroxypregnan-20-one-*O,21,21,21-$d_4$* (**4b**) was obtained by recrystallization of **4a** from EtOD containing a trace of LiOEt. Hydrogen at 17$\alpha$ was partially replaced by deuterium. A prolonged reflux resulted in complete substitution with deuterium at 17$\alpha$. The presence of the deuterium was confirmed by *m/e* 322 ($M^+$· for **4b**-*17$\alpha$,21,21,21-$d_4$*) and 321 ($M^+$· for **4b**-*21,21,21-$d_3$*)[10] and also demonstrated by the lack of the Me-21 peak at $\delta$ 2.10. Treatment of **4b** with acetic anhydride in pyridine afforded **4c** without loss of deuterium. The latter was then photocyclized in regular ethanol to give **1b**, again without loss of deuterium. As shown in Table I, dehydration of **1b** with thionyl chloride in the presence of proper tertiary bases did give endo olefin **3b** as the major product due to the primary isotope effect. This implies that the rate-determining step involves breakage of the deuterium carbon bond. Since this dehydration is a kinetically controlled reaction, the ratio of **2a** to **3a** given in Table I is equal to $k_{H(exo)}/k_{H(endo)}$, where $k_{H(exo)}$ and $k_{H(endo)}$ are the rates of formation of **2a** and **3a**, respectively.

(1) Part II in the steroid series.
(2) The receptor binding assay was run by Mr. W. F. Pautsch and associates.
(3) Buchschacher, P.; Cereghetti, M.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 2122.
(4) Pappo, R. U.S. Patent 2907758, 1959; *J. Am. Chem. Soc.* **1959**, *81*, 1010.
(5) Cereghetti, M.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1960**, *43*, 354.
(6) Since recrystallization from methanol decreases the exo/endo ratio, the gas chromatographic analysis was carried out on unrecrystallized crude product.
(7) For gas chromatography a 6-ft column of 3% Poly S 179 was used at 220–270 °C. The retention times for **2a** and **3a** were 6.6 and 5.3 min, respectively.
(8) Schrieschein, A. *Trans. N. Y. Acad. Sci.* **1969**, *31*(2), 97.
(9) A dozen peaks were observed in gas chromatography with no major product.
(10) The deuterium on oxygen at C-3 would be immediately replaced with hydrogen in the mass spectrometer and would not show up in the spectrum. The fourth deuterium is apparently at C-17$\alpha$.

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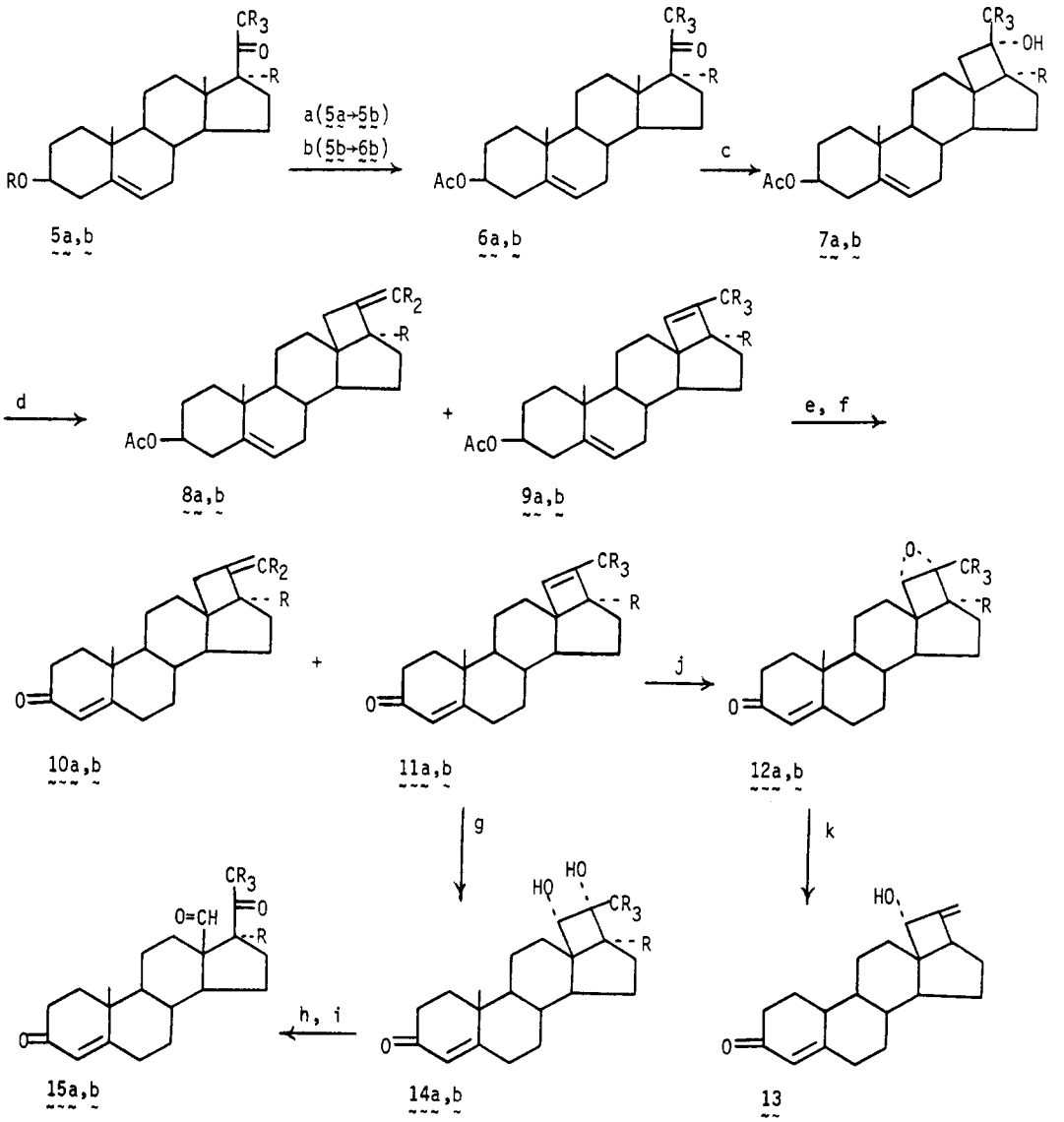
Table I. Dehydration of 1 to 2 and 3

| entry | conditions | starting matl | ratio of 2/3 | deuterium isotope effect |
|---|---|---|---|---|
| 1 | $POCl_3$, pyridine, 100 °C | 1a | 4.0 (2a/3a) | |
| 2 | $SOCl_2$, collidine, −20 °C, in | 1a | 1.09[a] (2a/3a) | |
| 3 | *n*-pentane/$CH_2Cl_2$ | 1b | 0.600,[a] 0.496[b] (2b/3b) | 1.81 |
| 4 | $SOCl_2$, *N*-methylmorpholine, in | 1a | 1.02[a] (2a/3a) | |
| 5 | *n*-pentane/$CH_2Cl_2$, −20 °C | 1b | 0.623,[a] 0.500[b] (2b/3b) | 1.64 |
| 6 | $SOCl_2$, triethylamine, in | 1a | 1.05[a] | |
| 7 | *n*-pentane/$CH_2Cl_2$, −20 °C | 1b | 0.89,[a] 0.643[b] (2b/3b) | 1.18 |

[a] Ratio in the reaction mixture. [b] Ratio after recrystallization from methanol.

Scheme I[a,b]




[a] R = H for the a series, and R = D for the b series. [b] (a) Reflux in EtOD, LiOD; (b) $Ac_2O$, pyridine, 25 °C, 20 h; (c) *hν* in EtOH, $N_2$, 25 °C; (d) $SOCl_2$, collidine, *n*-pentane, $CH_2Cl_2$, −20 to + 25 °C; (e) KOH, MeOH, reflux; (f) *N*-methyl-γ-piperidone, Al(O-*i*-Pr)$_3$, toluene, reflux; (g) *N*-methylmorpholine *N*-oxide, catalytic $OsO_4$; (h) $NaIO_4$; (i) KOAc, EtOH, reflux; (j) *m*-chloroperbenzoic acid, $CH_2Cl_2$; (k) $LiNEt_2$ in THF.

Likewise, the ratio of **2b** to **3b** given in Table I is equal to $k_{D(exo)}/k_{D(endo)}$. Ignoring secondary isotope effects, one observes that $k_{H(endo)}$ should be equal to $k_{D(endo)}$. Hence, the isotope effect:

$$k_{H(exo)}/k_{D(exo)} = (\text{ratio of } \mathbf{2a}/\mathbf{3a})/(\text{ratio of } \mathbf{2b}/\mathbf{3b})$$

**Application to Regioselective Synthesis of a Complex Molecule.** Pregnenolone (**5a**) was refluxed in EtOD containing a trace of LiOD and then crystallized out when the mixture cooled to give fully deuterated pregnenolone (**5b**), which was subsequently acetylated to give **6b** (Scheme I). The presence of four deuterium atoms in **6b**

was demonstrated by $m/e$ 302 (M − HOAc). The photocyclization of **6b** produced **7b**. Treatment of **7b** with thionyl chloride in collidine at −20 °C afforded **8b** and **9b** in a 5:8 ratio, the latter being the desired isomer. On the other hand, a dehydration of nondeuterated **7a** under the same conditions produced **8a** and **9a** in a 11:10 ratio. The saponification of a mixture of **8b** and **9b** followed by Oppenauer oxidation and subsequent chromatographic separation produced pure **11b** (predominant product) and **10b**. The presence of four deuteriums in **11b** was confirmed by $m/e$ 300 ($M^{+}\cdot$), which was the most intensive peak, whereas the presence of three deuteriums in **10b** was proven by $m/e$ 299 ($M^{+}\cdot$), which was also the most intensive peak. Osmium tetraoxide catalyzed oxidation[11] of **11b** gave a cis glycol **14b**. Periodate cleavage of **14b** produced 18-oxoprogesterone-$d_4$ (**15b**), which underwent proton exchange on treatment with potassium acetate in refluxing ethanol. TLC and the $^1$H NMR spectrum of the crude product disclosed that it was mostly **15a**; however, it was contaminated by another aldehyde (**16**, ~10%) and a cyclization product (**17**, ~25%).[4]

## Experimental Section

The mass spectra were taken on an AEI Scientific Apparatus MS-30. Gas chromatography was carried out on a Perkin-Elmer 900. Carbon and hydrogen (and deuterium) were analyzed on a Carlo Erba elemental analyzer, Model 1106. The "calculated" figures for $C_mH_xD_yO_n$ were obtained as follows: C was computed as $C_mH_{x+2y}O_n$; H and D were computed as $C_mH_{x+y}O_n$.

**(5α)-3β-Hydroxy-20-oxopregnane-*O,21,21,21-d*$_4$ (4b).** To a suspension of 10 g of allopregnanolone (**4a**) in 100 g of EtOD was added 1 mL of 1.86 M phenyllithium. The mixture was heated close to reflux in order to dissolve the starting material, kept warm for 3 h, and allowed to stand at 25 °C overnight. The reaction mixture was acidified with 1 mL of acetic acid and filtered to collect **4b**, which was washed with EtOD and dried (7.5 g). The second crop (2.1 g) was obtained from the mother liquor upon dilution with water. Both crops were good for the next steps. The first crop was pure **4b**: mp 195 °C; δ ($Me_4Si$, $CDCl_3$) 3.58 (vbr m, 1 H, H-3), 0.80 (s, 3 H), 0.60 (s, 3 H), no peak at δ 2.10; mass spectrum,[10] $m/e$ 322 ($M^{+}\cdot$ for $C_{21}H_{30}D_4O_2$, more intense than 321), 321 ($M^{+}\cdot$ for $C_{21}H_{31}D_3O_2$), 304 (M − 18, more intense than 303), 303 (M − 18).

Anal. Calcd for $C_{21}H_{30}D_4O_2$: C, 78.20; H and D, 10.76. Found: C, 78.44; H and D, 10.58.

**(5α)-3β-Acetoxy-20-oxopregnane-*21,21,21-d*$_3$ (4c).** A suspension of 7.5 g of **4b** in 4.5 mL of acetic anhydride and 60 mL of pyridine was warmed to become homogeneous. After 72 h at 25 °C, the reaction mixture was treated with 5 mL of methanol-*d* for 1 h, diluted with methylene chloride, washed with cold 5% HCl, washed with 0.2% NaCl, and dried over $Na_2SO_4$. The dried solution was concentrated and recrystallized from cyclohexane containing *n*-pentane to give **4c**, mp 146.5 °C (4.8 g). The second crop had the following: mp 145 °C (2.0 g); δ ($Me_4Si$, $CDCl_3$) 4.70 (vbr m, 1 H, H-3), 2.01 (s, 3 H, OAc), 0.83 (s, 3 H), 0.60 (s, 3 H), no peak for Me-21; $m/e$ 364 ($M^{+}\cdot$ for $C_{23}H_{32}D_4O_3$), 363 ($M^{+}\cdot$ for $C_{23}H_{33}D_3O_3$, less intense than 364), 346 (M − $CD_3$), 345 (M − $CD_3$, less intense than 346).

Anal. Calcd for $C_{23}H_{32}D_4O_3$: C, 75.77; H and D, 10.07. Found: C, 75.89; H and D, 10.01.

**(5α)-3β-Acetoxy-20α-hydroxy-18,20-cyclopregnane-*21,21,21-d*$_3$ (1b) and (5α)-3β-Acetoxy-20β-hydroxy-18,20-cyclopregnane-*21,21,21-d*$_3$.** A stirred suspension of 8.5 g of **4c** in 900 mL of 3A ethanol was irradiated with a 200-W, Hanovia, medium-pressure lamp under nitrogen at 25 °C until the starting material disappeared (8.5 h). The reaction mixture was concentrated in vacuo and chromatographed on Woelm neutral alumina. The 20β-carbinol was eluted with 10% ethyl acetate–benzene that was closely followed by the α-carbinol (**1b**). The 20β-hydroxy compound was recrystallized from cyclohexane: mp 171 °C; δ ($Me_4Si$, $CDCl_3$) 4.77 (vbr m, 1 H, H-3), 2.00 (s, 3 H, OAc), 0.73 (s, 3 H, Me-19); compared with the nondeuterated compound, a singlet at δ 1.35 (3 H, Me-21) was conspicuously missing.

Anal. Calcd for $C_{23}H_{32}D_4O_3$: C, 75.77; H and D, 9.95. Found: C, 75.90; H and D, 9.80.

The pure 20α-hydroxy compound (**1b**) was obtained by recrystallization from cyclohexane: mp 142.5 °C; δ ($Me_4Si$, $CDCl_3$) 4.66 (vbr m, 1 H, H-3), 2.00 (s, 3 H, OAc), 0.75 (s, 3 H, Me-19).

**Dehydration of 1a to 2a and 3a. A. Thionyl Chloride and Collidine.** To a stirred solution of 1.18 g of **1a** in 130 mL of *n*-pentane–methylene chloride (1:1) in an ethanol–ice bath (−20 °C) were added 1.5 mL of collidine and 0.45 mL of $SOCl_2$. The mixture was stirred for 3 h at −20 to 0 °C and stirred for an additional 1.5 h without a cooling bath. The reaction mixture was poured into water and extracted with ether. The ethereal layer was washed with a 0.2% NaCl solution, dried over $MgSO_4$, and concentrated. The **2a** (46.2%) to **3a** (42.4%) ratio was 1.09.[6,7] The crude material (1.0 g) was recrystallized from 30 mL of methanol to give 0.27 g of a first crop which was a 40.28% **2a**/59.28% **3a** mixture (exo/endo ratio of 0.68): $^1$H NMR δ ($Me_4Si$, $CDCl_3$) 5.73 (m, H-18 of **3a**), 4.70 (m, H-21 of **2a**), 2.01 (s, 3 H, OAc), 0.795 (s, Me-19 of **3a**), 0.77 (s, Me-19 of **2a**).

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.87; H, 10.13.

**B. Thionyl Chloride and *N*-Methylmorpholine.** The procedure was similar to that of part A: 0.29 g of **1a** 0.36 mL of *N*-methylmorpholine, and 0.11 mL of thionyl chloride in 32 mL of *n*-pentane–methylene chloride (1:1). The crude product contained 39.3% of **2a** and 38.5% of **3a** (exo/endo ratio 1.02).[6,7]

**C. Thionyl Chloride and Triethylamine.** The procedure was similar to that of part A: 0.36 g of **1a**, 0.3 mL of triethylamine, and 0.12 mL of thionyl chloride in 40 mL of *n*-pentane–methylene chloride (1:1). The crude product contained 45.4% of **2a** and 42.5% of **3a** (exo/endo ratio 1.05).[6,7]

**Dehydration of 1b to 2b and 3b. Method A.** A solution of 0.15 g of **1b** in 15 mL of *n*-pentane–methylene chloride (1:1) was treated with 0.20 mL of collidine and 0.06 mL of thionyl chloride at −20 to 0 °C for 3 h. The reaction mixture was stirred at 25 °C for 1 h, poured into water, extracted with ether, washed with 0.2% NaCl, dried over $Na_2SO_4$, and concentrated. The crude product crystallized spontaneously. It contained 31.4% of **2b** and 52.3% of **3b** (exo/endo ratio 0.60).[6,7] The crude product was recrystallized from 1 mL of methanol to give a first crop which contained 32.52% of **2b** and 65.28% of **3b** (exo/endo ratio 0.50), and the mother liquor had an exo/endo ratio of 1.37. The first crop was used for analysis.

Anal. Calcd for $C_{23}H_{31}D_3O_2$: C, 79.94; H and D, 10.01. Found: C, 79.71; H and D, 10.09.

**Method B** is similar to method A: 0.15 g of **1b**, 0.18 mL of *N*-methylmorpholine, and 0.06 mL of thionyl chloride in 15 mL of *n*-pentane–methylene chloride gave a crystalline crude product which contained 31.8% of **2b** and 51.0% of **3b** (exo/endo ratio 0.623). It was recrystallized from 1 mL of methanol to give crystals containing 32.98% of **2b** and 65.97% of **3b** (exo/endo ratio 0.50).

**Method C.** Use of triethylamine resulted in a crude material of exo/endo ratio 0.89. Recrystallization from methanol produced crystals of exo/endo ratio 0.643.

**Pregnenolone-*17α,21,21,21-d*$_4$ (5b).** To 500 g of EtOD containing 5 g of $D_2O$ was added 10 mL of 1.8 M phenyllithium in benzene. Pregnenolone (60 g) was added, and the mixture was heated to reflux for 30 min. After cooling, the reaction mixture was placed in a refrigerator for 2 h and then treated with 10 g of glacial acetic acid. The crystals were filtered by suction, washed with $H_2O$, and dried in air to give 58 g of **5b**: mp 193 °C; δ ($Me_4Si$, $CDCl_3$) 5.37 (m, 1 H), 3.48 (br m, 1 H), 1.03 (s, 3 H), 0.65 (s, 3 H), methyl ketone peak was missing.

Anal. Calcd for $C_{21}H_{28}D_4O_2$: C, 78.69; H and D, 10.19. Found: C, 78.42; H and D, 10.08.

**Pregnenolone-*17α,21,21,21-d*$_4$ Acetate (6b).** A suspension of 55 g of **5b** in 40 mL of acetic anhydride and 240 mL of pyridine was warmed to 40 °C in order to obtain a homogeneous solution and allowed to stand at 25 °C for 18 h. The reaction mixture was decomposed with 20 mL of MeOD at 25 °C for 1 h and concentrated in vacuo. The crystalline residue was taken up in methylene

(11) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(12) The melting point was higher than that of the nondeuterated compound (112 °C for **10a**).

chloride, washed with cold 3% HCl, washed with 0.5% brine, dried over $Na_2SO_4$, concentrated, and crystallized by addition of Skelly B to give 38.4 g of **6b**: mp 149.5 °C; *m/e* 302 (M - HOAc); δ ($Me_4Si$, $CDCl_3$) 5.38 (m, 1 H), 4.58 (br m, 1 H, H-3α), 2.00 (s, 3 H), 1.02 (s, 3 H), 0.63 (s, 3 H).

Anal. Calcd for $C_{23}H_{30}D_4O_3$: C, 76.20; H and D, 9.54. Found: C, 75.92; H and D, 9.42.

**3β-Acetoxy-20α-hydroxy-18,20-cyclopregn-5-ene-*17,21,21,21-d*$_4$ (7b).** A suspension of 30 g of **6b** in 900 mL of ethanol (not EtOD) was irradiated with a Hanovia, medium-pressure mercury lamp at 22–28 °C under nitrogen until the starting material had disappeared (9 h). The clear colorless solution was concentrated and chromatographed on two Waters columns (System 500) each containing 325 g of Porasil. Elution with 15% EtOAc–Skelly B afforded a 5.29 g mixture of **7b** and the corresponding 20β-hydroxy isomer and then 5.73 g of **7b**. The latter was recrystallized from methylene chloride–cyclohexane to give pure **7b**: mp 148 °C; *m/e* 302 (M - HOAc), 284 (302 - $H_2O$), 283 (302 - DHO); δ ($Me_4Si$, $CDCl_3$) 5.37 (m, 1 H), 4.58 (br m, 1 H), 2.00 (s, 3 H), 0.92 (s, 3 H).

Anal. Calcd for $C_{23}H_{30}D_4O_3$: C, 76.20; H and D, 9.56. Found: C, 76.26; H and D, 9.72.

**3-Oxo-18,20-cyclopregna-4,18-diene-*17,21,21,21-d*$_4$ (11b) and 3-Oxo-18,20-cyclopregna-4,20(21)-diene-*17,21,21-d*$_3$ (10b).**

**A. 3β-Acetoxy-18,20-cyclopregna-5,18-diene (9b) and 3β-Acetoxy-18,20-cyclopregna-5,20(21)-diene (8b).** A solution of 4.9 g of **7b** and 70 mL of collidine in 500 mL of methylene chloride–*n*-pentane (1:1) was cooled to −10 °C and treated all at once with 2.0 mL of thionyl chloride under vigorous mechanical stirring. The mixture was stirred at −10 to 17 °C for 5 h, poured into ice–water, and extracted with ether. The ethereal layer was washed with cold 10% aqueous HCl, washed twice with 0.5% NaCl, dried over $Na_2SO_4$, and concentrated to leave 6 g of gum. According to gas chromatographic analysis[7] this product contained 51.83% of **9b** and 32.72% of **8b** (exo/endo ratio of 0.63) and was used for the next step without purification.

**B. From 9b and 8b to 11b and 10b.** The **9b,8b** mixture described above was dissolved in 100 mL of methanol and treated with 2 g of KOH in 3 mL of water. The mixture was gently heated on a steam bath for 2 h. Most methanol was removed in vacuo, and the residue was diluted with cold water. The solid product was filtered, washed with water, and air-dried to give 4.4 g of 3-hydroxy 5-enes. It was taken up in 300 mL of toluene and filtered to remove a small amount of insoluble material. The filtrate was mixed with 16 mL of *N*-methyl-4-piperidone, and the solution was boiled to distill 35 mL of solvent. Aluminum isopropoxide (5 g) was added, and the mixture was refluxed for 6 h. After cooling, the reaction mixture was diluted with 500 mL of ether, washed with 1.2 N aqueous HCl, and washed with 0.5% NaCl. The organic phase was dried over $Na_2SO_4$, concentrated (4 g), and chromatographed on 250 g of Woelm silica gel. Fractions eluted with 5% ethyl acetate–cyclohexane afforded the endo isomer **11b** (1.50 g), and fractions eluted with 10% ethyl acetate–cyclohexane gave the exo isomer **10b** (0.85 g). Pure **11b** (1.19 g) was obtained by recrystallization from methanol: mp 133–135 °C; *m/e* 300 ($M^{+\cdot}$); δ ($Me_4Si$, $CDCl_3$) 5.76 (s, 1 H, H-18), 5.73 (br s, 1 H), 1.15 (s, 3 H).

Anal. Calcd for $C_{21}H_{24}D_4O$: C, 83.94; H and D, 9.52. Found: C, 84.28; H and D, 9.47.

Pure **10b** (0.54 g) was obtained by recrystallization from methanol: mp 116–118 °C;[12] *m/e* 299 ($M^{+\cdot}$); δ ($Me_4Si$, $CDCl_3$) 5.73 (br s, 1 H), 1.13 (s, 3 H).

Anal. Calcd for $C_{21}H_{25}D_3O$: C, 84.22; H and D, 9.52. Found: C, 84.38; H and D, 9.42.

**18α,20α-Dihydroxy-18,20-cyclopregn-4-en-3-one-*17α,21,21,21-d*$_4$ (14b).** A solution of 1.84 g of **11b**, 1.2 g of *N*-methylmorpholine *N*-oxide monohydrate, and 6 mg of osmium tetraoxide in 40 mL of *t*-BuOH/THF/water (10:3:1) was stirred at 25 °C. After the starting material had disappeared, the reaction mixture was diluted with methylene chloride, washed with cold 1% HCl, washed with 1% $KHCO_3$, dried over $Na_2SO_4$, and concentrated. The residue was dissolved in methylene chloride and chromatographed on 20 g of Florisil (regular column, no pressure). Fractions eluted with 10–20% ethyl acetate–methylene chloride were combined and recrystallized from methylene chloride–ether, producing 1.47 g of **14b**, which could be used without further purification. An analytical specimen was obtained by recrystallization from methylene chloride–ether: mp 169–170 °C; δ ($Me_4Si$, $CDCl_3$, 80 MHz) 1.16 (s, 3 H, Me-19), 3.56 (d, 1 H, *J* = 8 Hz, became singlet upon $D_2O$ exchange, H-18β), 5.70 (br s, 1 H, H-4), no peak corresponding to Me-21; *m/e* 332 (M - 2), 316 (M - 18), 315 (M - 19), 304 (M - 30), 286 (M - 48), 270 (M - 64, the most intense peak).

Anal. Calcd for $C_{21}H_{26}D_4O_3$: C, 75.40; H and D, 9.15. Found: C, 75.38; H and D, 9.18.

**18-Oxoprogesterone-*17α,21,21,21-d*$_4$ (15b).** To a solution of 1.0 g of **14b** in 24 mL of dioxane was added a solution of 0.90 g of $NaIO_4$ in 7.5 mL of water. After being stirred at 25 °C for 2.5 h, the reaction mixture was diluted with water and extracted with ether. The ethereal extract was washed with 2% $KHCO_3$, dried over $Na_2SO_4$, concentrated, and recrystallized from ether to give 0.68 g of **15b**: mp 148–149 °C; δ ($Me_4Si$, $CDCl_3$, 80 MHz) 1.14 (s, 3 H, Me-19), 5.69 (br s, 1 H, H-4), 9.83 (s, 1 H, H-18), no peak corresponding to Me-21; *m/e* 332 ($M^{+\cdot}$), 304, 286 (M - 46).

Anal. Calcd for $C_{21}H_{24}D_4O_3$: C, 75.86; H and D, 8.59. Found: C, 75.65; H and D, 8.57.

**18-Oxoprogesterone (15a).** A solution of 0.60 g of **15b** and 14 g of NaOAc in 200 mL of 3A ethanol was refluxed under nitrogen for 5 h. The reaction mixture was concentrated in vacuo, dissolved in 50 mL of water, and extracted with methylene chloride. The organic layer was washed with water, dried over $Na_2SO_4$, and concentrated (0.60 g). The $^1H$ NMR spectrum of the residue disclosed that it was a mixture of **15a** (~65%), **16** (~10%), and **17** (~25%). Triturated with 1 mL of ether, the oily mixture gave 0.38 g of crystals which were somewhat enriched with **17**. The mother liquor (0.22 g) was dissolved in methylene chloride and chromatographed on 5 g of Florisil (regular, no pressure). Early fractions eluted with methylene chloride gave **16** (recrystallization from ether): mp 147 °C (crystalline form changed at 144 °C); $R_f$ 0.35 (15% ethyl acetate–methylene chloride, silica gel plate), 0.41 (5% THF–methylene chloride); δ ($Me_4Si$, $CDCl_3$, 80 MHz), 1.12 (s, 3 H, Me-19), 2.19 (s, 3 H, MeCO), 3.12 (m, 1 H, H-17β), 5.68 (br s, 1 H, H-4), 9.71 (s, 1 H, aldehyde).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 77.02; H, 8.82.

Later fractions eluted with 10% ethyl acetate–methylene chloride gave **15a** (recrystallized from methylene chloride–ether): mp 147 °C; δ ($Me_4Si$, $CDCl_3$, 80 MHz) 1.12 (s, 3 H, Me-19), 2.12 (s, 3 H, MeCO), 5.67 (br s, 1 H, H-4), 9.83 (s, 1 H, aldehyde), distinctly different from **16** and identical with authentic **15a**.

**Conversion of 15a to 15b.** A solution of 0.10 g of **15a** and 1 g of KOAc in 8 mL of MeOD was refluxed under nitrogen for 14 h, diluted with water, and extracted with methylene chloride. The organic layer was washed with water, dried over $Na_2SO_4$, and concentrated. $^1H$ NMR spectrum of the crude product was as follows: δ ($Me_4Si$, $CDCl_3$, 80 MHz) 1.14 (s, 3 H, Me-19), no peak at around 2.13, proving that COMe was converted to $COCD_3$, 5.71 (br s, 1 H, H-4), 7.72 (s, ~0.2 H, H-18 of 17-*21-d*), 9.72 (s, ~0.1, aldehyde of **16**-*17β-21,21,21-d*$_4$), 9.83 (s, ~0.7 H, aldehyde of **15b**).

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**Registry No.** **1a**, 76773-45-0; **1b**, 76773-46-1; **2a**, 2458-81-3; **2b**, 76806-99-0; **3a**, 76793-65-2; **3b**, 76793-66-3; **4a**, 516-55-2; **4b**, 76793-67-4; **4c**, 76773-47-2; **5a**, 145-13-1; **5b**, 61574-54-7; **6b**, 76773-48-3; **7a**, 76831-50-0; **7b**, 76773-49-4; **8a**, 76773-50-7; **8b**, 76793-68-5; **9a**, 76773-52-9; **9b**, 76773-51-8; **10b**, 76793-69-6; **11b**, 76793-70-9; **14b**, 76793-61-8; **15a**, 15181-71-2; **15b**, 76773-53-0; **16**, 76821-81-3; **16**-*17β,21,21,21-d*$_4$, 76821-82-4; **17**, 76773-54-1; **17**-*21-d*, 76773-55-2; (5α)-3β-acetoxy-20β-hydroxy-18,20-cyclopregnane-*21,21,21-d*$_3$, 76773-56-3; 3β,20β-dihydroxy-18,20-cyclopregn-5-ene-*17,21,21,21-d*$_4$, 76773-57-4; 3β-hydroxy-18,20-cyclopregna-5-20(21)-diene, 76773-58-5; 3β-hydroxy-18,20-cyclopregna-5,18-diene, 76773-59-6; deuterium, 7782-39-0.