NMR (50 MHz, $CDCl_3$) δ 140.9 (C-5), 121.6 (C-6), 71.8 (C-3), 56.9 (C-14), 55.9 (C-17), 50.4 (C-9), 42.4 (C-13), 42.3 (C-4), 39.8 (C-12), 39.5 (C-24), 37.4 (C-1), 36.6 (C-10), 35.9 (C-22), 35.1 (C-20), 32.1 (C-8), 32.0 (C-7), 31.8 (C-2), 28.0 (C-16), 27.9 (C-25), 24.2 (C-15), 24.0 (C-23), 22.7 (C-27), 22.6 (C-26), 21.2 (C-11), 19.4 (C-19), 18.7 (C-21), 12.2 (C-18).

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Registry No. 1, 84927-48-0; 2, 84927-49-1; 3, 84927-50-4; 4, 14425-92-4; (*Z*)-5, 84985-74-0; (*E*)-5, 84985-75-1; 6, 73668-91-4; 16β-6, 84927-51-5; 7, 84927-52-6; 8, 84927-53-7; 9, 84927-54-8; 10, 84927-55-9; 11, 84927-56-0; 12, 2867-93-8; 13a, 84943-97-5; 13b, 84927-57-1; 14, 84927-58-2; 15, 84927-59-3; 15-ol, 84927-51-5; 16, 84985-76-2; 17, 30270-50-9; 18, 84985-77-3; 19, 84927-60-6; $Ph_3P^+EtBr^-$, 1530-32-1; $Ph_3P^+MeBr^-$, 1779-49-3; $(CH_3)_3CCOCl$, 3282-30-2; PhNCO, 103-71-9; cholesterol, 57-88-5; 20-epicholesterol, 34026-89-6.

Syntheses of [15α-^{2}H]-, [15β-^{2}H]-, and [15-$^2H_2$]Progesterone

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[15α- and 15β-^{2}H]Progesterone and [15-$^2H_2$]progesterone were synthesized, and their deuterium NMR spectra were determined. The chemical shifts of the 15α- and 15β-deuterio isomers were separated by 0.47 ppm.

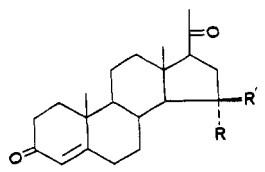
For ongoing biosynthetic studies, we required samples of progesterone stereospecifically labeled with deuterium at C-15. In this paper we describe the synthesis of 15α- and 15β-deuterio- and 15,15-dideuterioprogesterone.

15β-Deuterioprogesterone (**1b**, Chart I) was synthesized as described earlier by us for the synthesis of [15β-^{3}H]-progesterone.[1] Accordingly, 15α-hydroxyprogesterone (**1d**) was converted into the diketal **2a** and treated with *p*-toluenesulfonyl chloride in pyridine to give the 15α-tosylate diketal **2b**. Hydrogenolysis of **2b** with lithium triethylborodeuteride gave [15β-^{2}H]progesterone diketal **2j** which, on acid hydrolysis, provided the desired [15β-^{2}H]progesterone (**1b**). The overall yield was ca. 42%. The assignment of the 15β configuration to the deuterium rests on the proven inversion which occurs in the metal hydride hydrogenolysis of tosyl esters.[2,3]

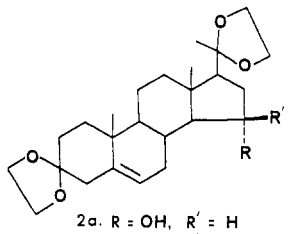
The introduction of deuterium at the 15α-position of progesterone was somewhat more challenging. A logical approach for preparing [15α-^{2}H]progesterone would be via hydrogenolysis of the 15β-tosylate diketal **2d** with lithium triethylborodeuteride. However, exposure of the 15β-alcohol diketal **2c** to *p*-toluenesulfonyl chloride in pyridine led invariably to the dehydration product, pregna-5,14-diene-3,20-dione diethylene diketal (**3a**).[1] Also, the attempted controlled reduction ($LiAlD_4$) of the C-15 tosylhydrazone[4] **2i** failed, and instead the olefin **3a** was obtained. The possibility of introducing the 15α-deuterium by the hydrolysis with propionic acid-*d* of the 15α-alkylborane[5] derived from pregna-5,14-diene-3,20-dione diethylene diketal (**3a**) was considered briefly. However, the approach was abandoned when, in exploratory experiments in which the 15α-alkylborane was refluxed with propionic acid, a mixture of products was obtained, none of which was progesterone.

The procedure finally developed was based on the utilization of the 15-^{2}H olefin diketal **3b**. The 15α-hydroxyprogesterone diketal **2a** was oxidized, and the resulting 15-ketone **2h** was reduced with sodium borodeuteride. The obtained 15β-hydroxy[15α-^{2}H]progesterone diketal **2e** was dehydrated (*p*-toluenesulfonyl chloride-

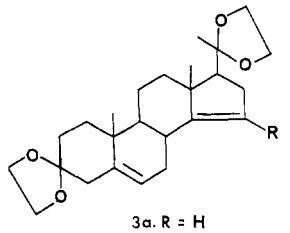
Chart I



1a. R = D, R′ = H
b. R = H, R′ = D
c. R = R′ = D
d. R = OH, R′ = H



2a. R = OH, R′ = H
b. R = OTs, R′ = H
c. R = H, R′ = OH
d. R = H, R′ = OTs
e. R = D, R′ = OH
f. R = OH, R′ = D
g. R = OTs, R′ = D
h. R, R′ = O
i. R, R′ = N_2HTs
j. R = H, R′ = D
k. R = D, R′ = H
l. R = R′ = D



3a. R = H
b. R = D

Table I. Deuterium NMR Spectral Data of 15-Deuterioprogesterone

	chemical shift, ppm	
progesterone	15α-^{2}H	15β-^{2}H
1c	1.66	1.22
1a	1.70	
1b		1.23

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pyridine) to give [15-^{2}H]pregna-5,14-diene-3,20-dione diethylene diketal (**3b**). In some instances, the ketal groups were inadvertently cleaved, and the resulting [15-^{2}H]-pregna-5,14-diene-3,20-dione was reketalized to yield **3b**. Hydroboration of **3b**, followed by oxidation of the alkylborane intermediate (hydrogen peroxide–sodium hydroxide), gave 15α-hydroxy[15β-^{2}H]progesterone diketal **2f** (35%), which was then converted to the [15β-^{2}H]-15α-tosylate diketal **2g**. Hydrogenolysis of **2g** with lithium triethylborohydride gave the expected [15α-^{2}H]progesterone diketal **2k** which, on acid hydrolysis, provided the desired [15α-^{2}H]progesterone (**1a**). As indicated above, the assignment of the 15α configuration to the deuterium rests on the proven inversion which occurs in the metal hydride hydrogenolysis of tosyl esters.[2,3]

Alternatively, hydrogenolysis of **2g** with lithium triethylborodeuteride, followed by acid hydrolysis, gave the [15-$^2H_2$]progesterone (**1c**).

The mass spectra of [15α- and 15β-$^2H_1$]progesterone showed that the samples were ca. 95% monodeuterated. The [15-$^2H_2$]progesterone contained ca. 95% dideuterated species. The ^{2}H NMR spectral data of the three deuterated compounds 1a–c are summarized in Table I. The chemical shift difference between the ^{2}H signals of [15α-^{2}H]progesterone (**1a**, δ 1.70) and [15β-^{2}H]progesterone (**1b** δ 1.23) is 0.47 ppm. The signals of the [15-$^2H_2$]progesterone were separated accordingly (see Table I), but the resolution did not extend to the base line.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer Model 237 spectrometer. NMR spectra were taken on a Varian EM-360 or EM-390. Deuterium NMR spectra were taken at 38.39 MHz on the Bruker WM-250 instrument operating in the FT mode with proton decoupling. Samples for deuterium NMR were dissolved in $CHCl_3$ with $CDCl_3$ as an internal standard (δ 7.25). Mass spectra were determined on a Finnigan Model 1015D updated to a Model 3200. Merck silica gel (HF 254 + 366) was used for TLC. Melting points were taken on a hot stage and are corrected.

3,3:20,20-Bis(ethylenedioxy)pregn-5-en-15α-ol (2a). 15α-Hydroxyprogesterone (**1d**; 1 g, 3.0 mM), ethylene glycol (16 mL), and *p*-toluenesulfonic acid monohydrate (40 mg) were dissolved in dry benzene (140 mL). The solution was refluxed for 18 h under a Dean–Stark apparatus. At the end of the reaction, a saturated solution of $NaHCO_3$ (1 mL) was added, and the mixture was cooled to room temperature and diluted with water (100 mL). The organic layer was separated, and the aqueous phase was then extracted with benzene. After a conventional workup **2a** (1.0 g) was obtained. Crystallization of the product from methanol gave 3,3′:20,20′-bis(ethylenedioxy)pregn-5-en-15α-ol (**2a**): 0.89 g; mp 180–182 °C; ^{1}H NMR δ 0.82 (3 H, s, 18-H), 1.06 (3 H, s, 19-H), 1.3 (3 H, s, 21-H), 3.95 (8 H, s, OCH_2CH_2O), 5.35 (1 H, m, 6-H).

3,3:20,20-Bis(ethylenedioxy)pregn-5-en-15α-ol *p*-Toluenesulfonate (2b). *p*-Toluenesulfonyl chloride (freshly recrystallized from $CHCl_3$; 0.71 g, 3.7 mmol) was added to a solution of 15α-hydroxydiketal **2a** (0.8 g, 1.9 mmol) in dry pyridine (12 mL) at 0 °C, and the mixture was stored at 5 °C for 15 h. Cold water (50 mL) was then added, and the product was recovered with $CHCl_3$ and processed in the usual way to yield 15α-tosylate **2b** (1.1 g). An aliquot (100 mg) was crystallized from methanol-CH_2Cl_2: mp 122–124 °C; ^{1}H NMR δ 0.8 (3 H, s, 18-H), 1.03 (3 H, s, 19-H), 1.25 (3 H, s, 21-H), 2.47 (3 H, s, 4′-H), 3.93 (8 H, s, OCH_2CH_2O), 4.78 (1 H, m, 15β-H), 5.21 (1 H, m, 6-H), 7.57 (4 H, AB q, δ_{AB} = 26 Hz, J_{AB} = 8 Hz, aromatic H).

[15β-^{2}H]Progesterone (1b). To a stirred (under argon) solution of the 15α-tosylate diketal **2b** (1.0 g, 1.7 mmol) in dry THF (5 mL), was added 6 mL of lithium triethylborodeuteride (1 M, in THF), and the solution was stirred for 24 h at room temperature. The excess reagent was destroyed by the dropwise addition of 2.5 N NaOH (1 mL), water (10 mL) was added, and the mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to give [15β-^{2}H]progesterone diketal **2j** (0.7 g). A mixture of **2j** and *p*-toluenesulfonic acid (100 mg) in acetone (10 mL) was refluxed for 15 h. Water (20 mL) was added, the mixture was extracted with ethyl acetate, and the extract was processed in the conventional manner to give a residue (0.59 g). The crude product was purified by preparative TLC [silica gel, hexane–EtOAc (2:1)] to give solid **1b** (0.42 g) which was recrystallized from acetone: mp 128–130 °C; ^{1}H NMR δ 0.67 (3 H, s, 18-H), 1.17 (3 H, s, 19-H), 2.1 (3 H, s, 21-H), 5.7 (1 H, s, 4-H); ^{2}H NMR δ 1.23 (1-^{2}H, s, 15β-^{2}H); mass spectrum, *m/e* 315 (M^+ 95% d_1).

3,3:20,20-Bis(ethylenedioxy)pregn-5-en-15-one (2h). A solution of 15α-hydroxy diketal **2a** (0.75 g, 1.8 mmol) in dry pyridine (2 mL) was treated with a solution of chromium trioxide (0.7 g) in pyridine (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 48 h, methanol (1 mL) was added, and the mixture was diluted with benzene (100 mL). The mixture was poured onto a short column of silica gel, and the column was washed with benzene (500 mL). The eluate was evaporated to give the expected 15-keto diketal **2h** in quantitative yield. Crystallization from methanol–ether gave 3,3′:20,20′-bis(ethylenedioxy)pregn-5-en-15-one (**2h**): 0.7 g; mp 191–193 °C; IR ν_{max} 1735 cm^{-1} (C-15, C=O); ^{1}H NMR δ 0.87 (3 H, s, 18-H), 1.05 (3 H, s, 19-H), 1.38 (3 H, s, 21-H), 3.95 (8 H, s, OCH_2CH_2O), 5.38 (1 H, m, 6-H).

15β-Hydroxy[15α-^{2}H]progesterone Bis(ethylene ketal) (2e). Sodium borodeuteride (100 mg) was added portionwise to a stirred solution of the 15-ketone **2h** (0.69 g, 1.66 mM) in methanol (10 mL) at 0 °C. The reaction was stirred at room temperature for 24 h, and then the methanol was removed under reduced pressure. Water (20 mL) was added to the residue, and the product was recovered (ethyl acetate) and processed to give **2e** (0.65 g). A sample of **2e** was crystallized from ethyl acetate–hexane: mp 169–170 °C; ^{1}H NMR δ 1.08 (6 H, s, 18-H and 19-H), 1.33 (3 H, s, 21-H), 3.95 (8 H, s, OCH_2CH_2O), 5.36 (1 H, m, 6-H).

[15-^{2}H]Pregna-5,14-diene-3,20-dione Bis(ethylene ketal) (3b). The [15α-^{2}H]-hydroxy diketal **2e** (0.6 g, 1.4 mmol) was treated with *p*-toluenesulfonyl chloride in pyridine in the manner described for **2b**. The resulting product was crystallized from methanol to give **3b**: 0.4 g; mp 149–151 °C; ^{1}H NMR δ 1.06 (6 H, s, 18-H and 19-H), 1.36 (3 H, s, 21-H), 3.91 (8 H, s, OCH_2CH_2O), 5.34 (1 H, m, 6-H); the absence of a signal for the olefinic C-15 hydrogen is in accordance with the structure **3b**.

3,3:20,20-Bis(ethylenedioxy)[15β-^{2}H]pregn-5-en-15α-ol (2f). To a stirred (under argon) solution of **3b** (400 mg, 1.0 mmol) in dry THF (5 mL) maintained at -10 °C was added dropwise over 15 min a solution of borane in THF (1.0 M, 0.83 mL, 0.83 mmol). The reaction mixture was stirred at room temperature for 2 h, water (1 mL) was then added dropwise, followed by 3 M NaOH (1 mL) and 30% hydrogen peroxide (2 mL), and the stirring was continued for 2 h. The mixture was diluted with water and extracted with ether; the extract was washed with water, dried (Na_2SO_4), and evaporated. The main product (**2f**, 167 mg) was isolated by preparative TLC [silica gel, hexane–EtOAc (2:1)] and crystallized from methanol: mp 180–182 °C; ^{1}H NMR δ 0.82 (3 H, s, 18-H), 1.06 (3 H, s, 19-H), 1.3 (3 H, s, 21-H), 3.95 (8 H, s, OCH_2CH_2O), 5.35 (1 H, m, 6-H).

3,3:20,20-Bis(ethylenedioxy)[15β-^{2}H]pregn-5-en-15α-ol p-Toluenesulfonate (2g). The [15β-^{2}H]-15α-ol **2f** (160 mg, 0.38 mmol) was treated with *p*-toluenesulfonyl chloride in pyridine as described above for **2b**. The resulting **2g** (200 mg) was chromatographically homogeneous and was not further purified. A portion of the product was crystallized from methanol–CH_2Cl_2: mp 122–124 °C; ^{1}H NMR δ 0.8 (3 H, s, 18-H), 1.02 (3 H, s, 19-H), 1.25 (3 H, s, 21-H), 2.47 (3 H, s, 4′-H), 3.93 (8 H, s, OCH_2CH_2O), 5.21 (1 H, m, 6-H), 7.57 (4 H, AB q, δ_{AB} = 26 Hz, J_{AB} = 8 Hz, aromatic H). As expected for (**2g**) there was no signal for the 15β-H.

[15α-^{2}H]Progesterone (1a). Hydrogenolysis of **2g** (130 mg, 0.23 mmol) with lithium triethylborohydride (1 M in THF) was carried out in the manner as described with **2b**. The expected 15α-deuterio diketal **2k** (70 mg) was then hydrolyzed with *p*-toluenesulfonic acid in acetone to give the [15α-^{2}H]progesterone **1a** (45 mg). The product was purified by preparative TLC [silica gel, hexane–EtOAc (2:1)] and crystallized from acetone: 30 mg; mp 127–130 °C; ^{1}H NMR δ 0.68 (3 H, s, 18-H), 1.17 (3 H, s, 19-H), 2.1 (3 H, s, 21-H), 5.7 (1 H, s, 4-H); ^{2}H NMR δ 1.70 (1-^{2}H, s, 15α-^{2}H); mass spectrum, *m/e* 315 (M^+) (95% d_1).

[15-$^2H_2$]Progesterone (1c). Hydrogenolysis of **2g** (70 mg, 0.12 mmol) with lithium triethylborodeuteride, followed by acid hydrolysis as described above, gave **1c**. The **1c** was purified by preparative TLC and crystallized from acetone: 16 mg; mp 126-128 °C; ^1H NMR δ 0.68 (3 H, s, 18-H), 1.17 (3 H, s, 19-H), 2.1 (3 H, s, 21-H), 5.7 (1 H, s, 4-H); ^2H NMR δ 1.22 (1-^2H, s, 15β-^2H), 1.66 (1-^2H, s, 15α-^2H); mass spectrum m/e 316 (M^+, 95% d_1).

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Registry No. **1a**, 85098-39-1; **1b**, 85098-40-4; **1c**, 85115-79-3; **1d**, 600-73-7; **2a**, 24377-04-6; **2b**, 24377-10-4; **2e**, 85098-41-5; **2f**, 85098-42-6; **2g**, 85098-43-7; **2h**, 24377-05-7; **2j**, 85098-44-8; **2k**, 85098-45-9; **3b**, 85098-46-0; ethylene glycol, 107-21-1.

Studies on a Convergent Route to Side-Chain Analogues of Vitamin D: 25-Hydroxy-23-oxavitamin D_3[1]

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Permanganate oxidation of vitamin D_3 affords the 7,8-diol **4a**, which was successively silylated to **4b** and then oxidatively cleaved and reduced to afford **3c**. The latter was converted in several steps to phosphine oxide **3b**, a useful A-ring fragment for analogue synthesis. The readily available diol **2** was selectively alkylated to give **6a**, which was easily transformed to **6b** and **9c**. Horner-Wittig coupling of **3b** with **6b** followed by deprotection afforded **8a**, which upon oxymercuration-demercuration afforded the 23-oxavitamin **1b** in low yield. By contrast, coupling of **9c** and **3b** followed by deprotection afforded **1b** in satisfactory yield.

In the vitamin D field,[2] there is a continuing need for side-chain analogues that might serve as biochemical research tools for metabolism studies. For example, analogues of 25-hydroxyvitamin D_3 (**1a**) (Chart I) possessing side-chain carbons that cannot be hydroxylated or further oxidized are of considerable interest. Since C_{23} oxidation of **1a** appears at least in part to be involved in its catabolism,[3] blocking of this position was expected to make this metabolite more resistant to degradation. Accordingly, the 23-oxa analogue **1b** was targeted for synthesis since the 23-position is blocked and the replacement of a methylene unit by an ether oxygen was not expected to impart significant steric perturbation.[4]

Since **1b** represents only one example of a family of analogues that are of interest in this laboratory, we have devoted some of our recent efforts toward utilizing the readily available Inhoffen-Lythgoe diol **2**[5] as a basic building block in convergent syntheses of analogues. Once appropriate fragments are available, the convergent approach would appear to be more versatile and efficient than the classical photochemical approach to a family of analogues needed for systematic structure-activity studies. Since **1b** possesses the simple, unmodified A ring of readily available vitamin D_3, application of Lythgoe's method[6] for attaching the phosphine oxide **3a** to an appropriate C/D

Chart I

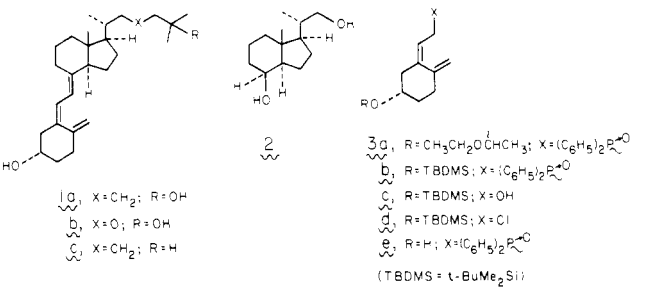
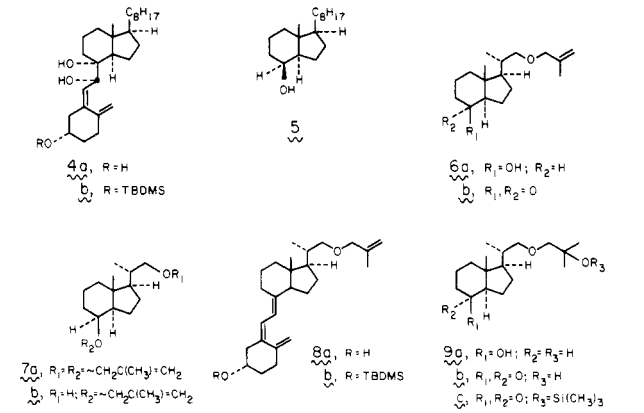


Chart II



(1) This is paper 25 in the series Studies on Vitamin D (Calciferol) and Its Analogues. For paper 24, see: Haces, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6105.

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