with hexane and hexane–0.5% ethanol gave the less polar impurity. Further elution with the same solvent system gave garryfoline azomethine (**12**) as a white solid (1.7 g), which crystallized from acetone in prismatic rods: mp 176–178 °C; $[\alpha]^{25}_D$ −79.8° (*c* 1.0, Et OH). IR (Nujol) ν_{max} 3200, 3070 (OH), 1648 (sh, double bonds) cm^{-1}; ^1H NMR δ 0.81 (3 H, s, C(4) CH_3), 3.38 (2 H, s, NCH_2C), 3.81 (1 H, s, CHOH), 4.96 and 5.06 (each 1 H, s, $C{=}CH_2$) and 7.8 (1 H, s, N=CH). Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.13; H, 9.76; N, 4.66.

A solution of 1.65 g of garryfoline azomethine in ethanol containing 8% HCl was refluxed 30 h when it was completely rearranged to cuauchichicine azomethine (**22**). The usual workup gave a residue (1.6 g) which crystallized from acetone in clusters of needles: mp 135–137 °C; $[\alpha]^{29}_D$ −114.4° (*c* 1.0) (lit.[5] mp 137–138 °C; $[\alpha]_D$ −114°); IR (Nujol) ν_{max} 1740 (C=O), 1650 and 1660 (sh, double bonds); ^1H NMR δ 0.81 (3 H, s, C(4) CH_3), 1.12 (3 H, d, $CHCH_3$), 3.43 and 3.48 (2 H, s, NCH_2C), 7.93 (1 H, br s, N=CH).

Isolation of *ent*-Kaurene from the Extract of *Cryptomeria japonica*. Examination of the crude extract (0.8 g) on an alumina TLC plate showed the presence of several components. Column chromatography of this extract on alumina with petroleum ether–ether (20 mL, 35–60 °C) gave a fraction (0.395 g) which showed mainly one spot on TLC. Crystallization of this fraction from acetonitrile afforded white crystals (0.17 g) of *ent*-kaurene: mp 49–50 °C; $[\alpha]^{26}_D$ −71.4° (*c* 1.0) [lit.[13] mp 51 °C; $[\alpha]^{11}_D$ −72° (*c* 1.0)]. Further elution of this column with more polar solvents gave fractions which showed the absence of *ent*-kaurene on TLC.

Hydrogenation of *ent*-Kaurene. A solution of *ent*-kaurene (0.18 g) in alcohol (70 mL) was hydrogenated at 31 psi of H_2 in the presence of PtO_2 (0.2 g) overnight. The usual workup of this solution afforded a mixture of "α"- and "β"-dihydrokaurenes which on crystallization from acetonitrile afforded long needles of "α"-dihydrokaurene: mp 84.5–85 °C; $[\alpha]^{25}_D$ −34.6° (*c* 0.479) (lit.[13] mp 83–84 °C; $[\alpha]^{21}_D$ −32°). The minor isomer, "β"-dihydrokaurene, could not be isolated in pure state as it was present in too small an amount.

Acknowledgment. This work was supported in part by Grant CA 24180 from the National Cancer Institute, Department of Health, Education, and Welfare. We thank Professor J. MacMillan, University of Bristol, for a sample of an extract of *Cryptomeria japonica* containing *ent*-kaurene and Dr. A. W. Stocklinski of the School of Pharmacy, University of Georgia, for providing the mass spectra. We also thank Dr. D. S. Siegler for collection of some of the plant material.

Registry No. 1A, 68719-14-2; **1B**, 76984-75-3; **2**, 68831-67-4; **3A**, 509-30-8; **3B**, 76984-76-4; **4**, 545-60-8; **5**, 68832-24-6; **8**, 467-92-5; **9**, 7096-94-8; **10**, 74232-41-0; **11**, 74613-52-8; **11**·HCl, 74260-92-7; **12**, 76946-28-6; **14**, 6714-12-1; **15**, 562-28-7; **16**, 1573-40-6; **17**, 467-93-6; **18**, 72580-08-6; **21**, 76946-29-7; **22**, 76915-15-6; **23**, 76900-43-1; **25**, 76900-44-2.

(13) L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, and J. K. Wilmshurst, *J. Chem. Soc.*, 1345 (1963).

Synthesis of Aldosterone

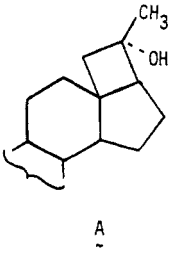
Masateru Miyano

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

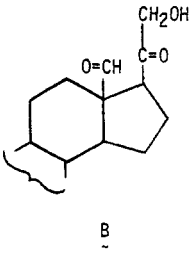
Received September 2, 1980

A convenient synthesis of 11-deoxyaldosterone (**11**) from 3β-acetoxy-20α-hydroxy-18,20-cyclopregn-5-ene (**1**) is described in Scheme I. The key steps were a selective epoxidation of **4** to **6**, base-catalyzed transformation of **6** to an allylic alcohol (**7**), and a selective oxidative cleavage of the 18(20) double bond of the acetate **8** to give 11-deoxyaldosterone acetate (**10**). Aldosterone was synthesized from 3-(ethylenedioxy)-11-oxo-20α-hydroxy-18,20-cyclopregn-5-ene (**16**) as summarized in Scheme II. The critical steps were kinetic addition of phenylselenyl bromide to **19a** followed by oxidative elimination to **20a** and acetate displacement to give **23a**. Subsequent selective oxidative cleavage of the 18(20) double bond of **23b** produced aldosterone acetate (**26a**). An efficient preparation of the starting material **16** is also described.

In connection with other projects, we required a transformation of 20-hydroxy-18,20-cyclo steroids A into 18,20-dioxo-21-hydroxy steroids B. A successful solution of this problem culminated in an efficient synthesis of 11-deoxyaldosterone (**11**) and aldosterone (**26b**).



A



B

Results and Discussion

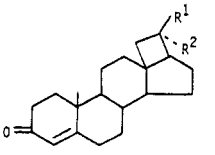
Synthesis of 11-Deoxyaldosterone (11). Pregnenolone acetate was photocyclized by a known procedure[1,2] to 20α-hydroxy-18,20-cyclo steroid **1**, which was dehydrated with phosphorus oxychloride in pyridine[1] to give a 4:1 mixture of exo olefin **2** and endo olefin **3** (Scheme I) as determined by gas chromatography. Saponification of the acetoxy group followed by Oppenauer oxidation afforded a 4:1 mixture of **4** and **5**, which were isolated[3] by a low-pressure column. The exo olefin **4** was epoxidized regioselectively with *m*-chloroperbenzoic acid to give a mixture of α- and β-epoxides **6**.[4] Treatment of **6** (X = H)

(1) Buchschacher, P.; Cereghetti, M.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 2122.

(2) Cereghetti, M.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1960**, *43*, 354.

(3) To the best of my knowledge, neither pure **4** nor **5** has been described in the literature, though these structures were disclosed in: U.S. Patent 3 211 759, 1965.

(4) Two epoxides were formed in comparable amounts and could not be separated by routine procedures. The pure α- and β-epoxides were prepared by indirect methods (see Experimental Section). The reduction of pure α-epoxide with lithium aluminum hydride followed by oxidation with pyridinium chlorochromate gave i, whereas the same treatment of β-epoxide gave ii. The configuration of i and ii has been known (Jeger, O.; et al. *Helv. Chim. Acta* **1960**, *43*, 315; see also related papers).



i R^1=Me, R^2=OH

ii R^1=OH, R^2=Me

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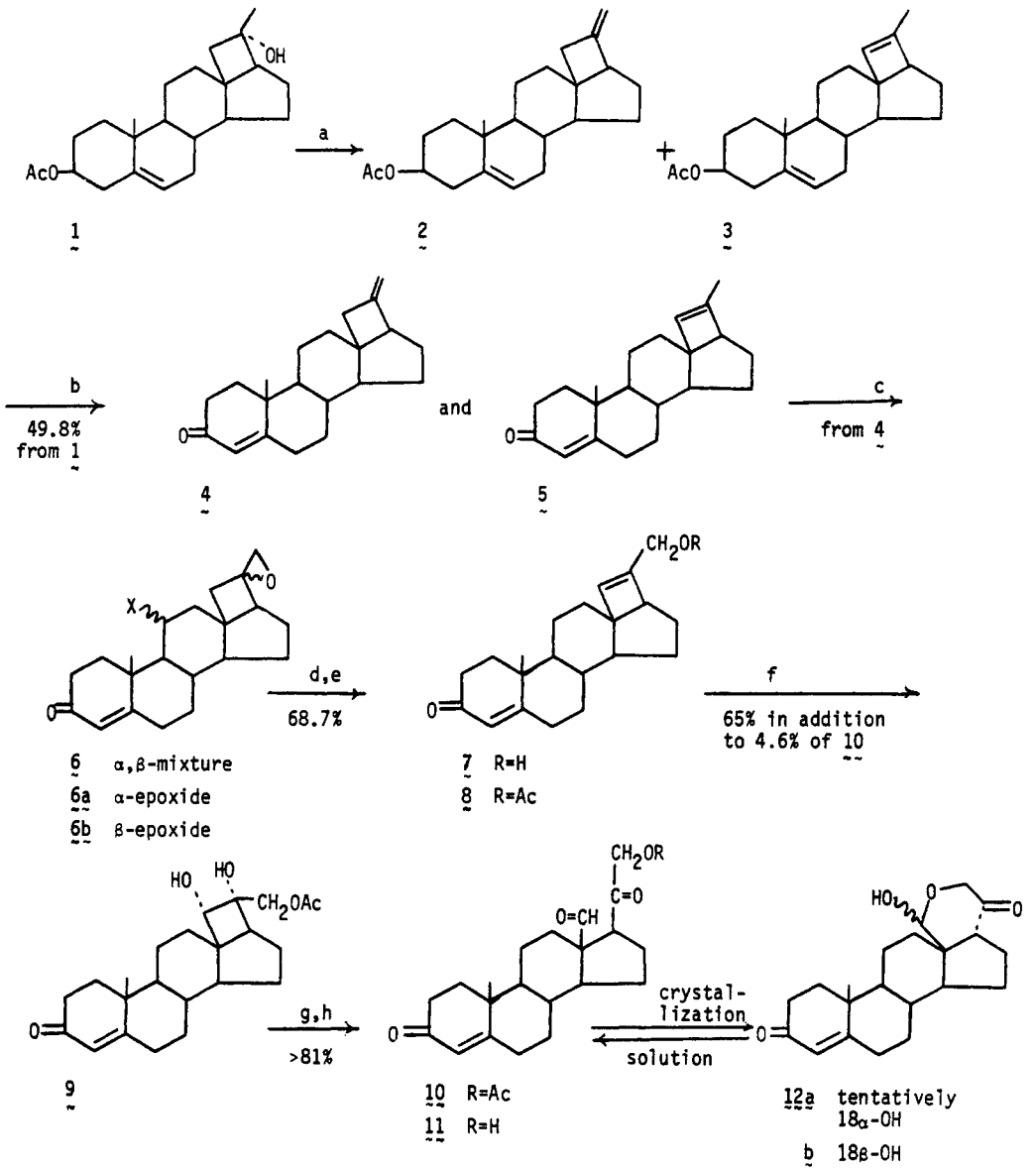
Scheme I[a]

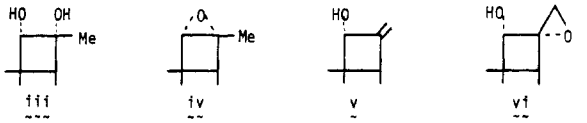


[a] (a) Known; (b) KOH, MeOH; H_3O^+; *N*-methyl-4-piperidone, Al(O-*i*-Pr)$_3$; (c) *m*-chloroperbenzoic acid, CH_2Cl_2, 0 °C; (d) $LiNEt_2$, THF, −78 to 25 °C; (e) Ac_2O, pyridine, 25 °C; (f) *N*-methylmorpholine *N*-oxide, catalytic OsO_4, *t*-BuOH, THF, water, 25 °C; (g) $NaIO_4$, dioxane, water, 25 °C; (h) K_2CO_3, dioxane, water, 25 °C.

with lithium diethylamide in THF gave an allylic alcohol **7** more readily from α- than from β-epoxide, which was acetylated and then selectively hydroxylated[5] to produce an α-glycol **9**.[6] The osmium tetraoxide catalyzed hydroxylation of **8** produced, in addition to 65% of highly crystalline **9**, a minor product in 4–5% yield which turned out to be **10**, the desired material of the next step. When the reaction time was extended by using excess *N*-oxide, **10** became the major product. The unexpected oxidative cleavage was probably due to the strained four-membered ring. Periodate cleavage of **9** gave 21-acetoxy-3,18,20-trioxopregn-4-ene acetate (**10**), which had been earlier obtained by Swiss workers through a different route.[7] The new scheme presented in this paper appears to be more straightforward and easier to execute. The spectral and physical properties of **10** were in good agreement with the published data.[7] The final product (**11**), which was obtained by saponification of **10** under milder conditions, melted at 127.5 °C, more than 12 °C higher than the value in the literature.[7] When the ^1H NMR spectrum was taken immediately after dissolution in deuteriochloroform, 11-deoxyaldosterone existed mostly (~60%) as a hemiacetal

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

(6) The stereochemistry of **9** was assigned on the basis of analogy; that is, under the same conditions, endo olefin **5** produced exclusively an α-glycol (iii) whose stereochemistry was established as follows: epoxidation of **5** with *m*-chloroperbenzoic acid produced exclusively an epoxide (iv), which was reduced with lithium in ethylenediamine to give (5α)-3β,20α-dihydroxy-18,20-cyclopregnane, a Jeger compound, thus establishing the α configuration of iv. Treatment of iv with lithium diethylamide afforded v, which was epoxidized under Sharpless' conditions (*J. Am. Chem. Soc.* **1973**, *95*, 6136) to give vi. The epoxide group of vi was, after protection of the 18-OH with a tetrahydropyranyl group, reductively cleaved with lithium aluminum hydride. Restoration of the 3-oxo group by oxidation with pyridinium chlorochromate followed by removal of the protecting group produced iii.



(7) Biollaz, B.; Schmidlin, J.; Kalvoda, J. *Helv. Chim. Acta* **1975**, *58*, 1433.

(12a). The unusually large geminal coupling constant (J = 18 Hz) of H_2C-21 suggested that the 20-keto group bisected the dihedral angle of the 21-hydrogens. That is, the hemiacetal ring was in a boat form. After 10 min in deuteriochloroform, the ^1H NMR spectrum demonstrated that the free aldehyde form (11) predominated (~60%) in the solution along with two hemiacetals (12a,b).

History. The total synthesis of aldosterone was carried out by Johnson and co-workers[8] and by Heusler and co-workers[9] in the late 1950's. Soon afterward a practical partial synthesis was published by Barton and co-workers[10,11] and by Heusler and collaborators.[12] The stereochemistry of the hemiacetal ring was determined by X-ray crystallography.[13]

Preparation of Key Intermediate: 11β-Hydroxy-18,20-cyclopregna-4,20-dien-3-one (19b). Ringold and co-workers[14] reported that progesterone 3,20-bis(ethylene ketal) (13c), upon exposure to boron trifluoride etherate in benzene, produced selectively 20-keto 3-ketal 14c in 82% yield. Application of Ringold's conditions to the 11α-acetoxy analogue 13a gave rise to a major monoketal which was, to our surprise, the 3-keto 20-ketal, as indicated by the UV maximum at 239.5 nm (ε 16 240), rather than 14a. On the other hand, treatment of 13a with aqueous acetic acid containing tetrahydrofuran afforded the desired monoketal (14a), which was identical with an authentic 14a synthesized by the known procedure,[15a] in 86% yield. Likewise, the selective hydrolysis of 13b with aqueous acetic acid afforded 14b[15b] in 79% yield. It was photocyclized to 15b (45%), which was identical with an authentic specimen[16] prepared by saponification of 15a. The transformation of 15b into the subtitle intermediate 19 is depicted in Scheme II.

Failure of Epoxide Route. The key step of our synthesis of 11-deoxyaldosterone was conversion of 6 (X = H) to 7 by treatment with lithium diethylamide. Unfortunately, it became evident that the epoxides having an 11-substituent (6; X = OH, OAc, ketone, or alkyl) in general produced a miniscule amount (less than 1%) of the corresponding allylic alcohols. No reaction took place under the standard conditions whereas a dozen products were observed at a higher temperature. Replacement of the base with diethylaluminum amide[17] did not improve the yield.

Alternate Route. It has been well documented that phenylselenyl bromide adds to a double bond in the Markovnikov manner under usual conditions. Kinetic (anti-Markovnikov) addition of phenylselenyl bromide in carbon tetrachloride at 0 °C was discovered by Raucher.[18] Addition of phenylselenyl bromide to 19c under the kinetic conditions was instantaneous as indicated by disappearance of the brown color in the reagent. Immediate in situ oxidative elimination of selenium afforded an allylic bromide (20c) and a vinylic bromide (21c) in a 4:1 ratio. The third (last and minor) product obtained from this reaction contained a phenyl group to which structure 22 was tentatively assigned. Treatment of 20c with potassium acetate in boiling ethanol afforded 23c (same as 8) in quantitative yield whereas 21c was recovered unchanged. The overall yield of 23c by the selenium route was comparable to or excelled that of the epoxide route. The kinetic addition of phenylselenyl bromide to 19b followed by in situ oxidative elimination produced 20b and 21b in a 1:2 ratio. Acetate displacement of 20b gave a crystalline acetate (23b). The reversal of regiospecificity caused by the 11β-hydroxy group is probably electronic rather than steric. That is, the phenylselenoxide group tends to be eliminated, forming a double bond away from a nearby standing hydroxy group. The undesirable regioselectivity was successfully overcome, as anticipated, by acetylation of the 11β-hydroxy group prior to kinetic selenium reaction. Thus 19b was acetylated to 19a, which then underwent phenylselenyl bromide addition, in situ oxidative elimination, and finally acetate displacement to afford diacetate 23a (Scheme II). The yield of 23a was 53.2% from 19b. In addition, 10.3% of the starting material (19a) and 14.1% of undesirable vinylic bromide 21a were obtained. Hence, the regioselectivity (allylic/vinylic) was improved to 19:5. Diacetate 23a was saponified to a crystalline dihydroxy compound (24) and then selectively reacetylated in quantitative yield to a crystalline monoacetate (23b) which was identical with the monoacetate obtained directly from 19b (vide supra). Glycolation of 23b with N-methylmorpholine N-oxide in the presence of a catalytic amount of osmium tetraoxide[5] produced a crystalline tetraol monoacetate (25) accompanied by a small amount of 26a. Periodate cleavage of 25 afforded aldosterone 21-acetate (26a) in quantitative yield. The synthetic 26a was indistinguishable (IR, ^1H NMR, melting point) from the authentic compound. The saponification of 26a to a aldosterone (26b) has been well recorded in the literature.[9,10b,19]

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover Uni-Melt capillary apparatus and are uncorrected. A Varian Associates A-60 or FT-80A nuclear magnetic resonance spectrometer was used. A Carlo-Erba Model 1106 was used for carbon and hydrogen analyses. Unless otherwise specified, a low-pressure column was used for all chromatographic separations.

3-Oxo-18,20-cyclopregna-4,20(21)-diene (4) and 3-Oxo-18,20-cyclopregna-4,18-diene (5). A crude (not recrystallized or chromnatographed) mixture of 3β-acetoxy-18,20-cyclopregna-5,20(21)-diene (2) and 3β-acetoxy-18,20-cyclopregna-5,18-diene (3) prepared from 17 g of 3β-acetoxy-18,20-cyclopregn-5-en-20α-ol (1) by dehydration with phosphorus oxychloride in pyridine[1] was dissolved in 220 mL of methanol and treated with 5 g of KOH in 7.2 mL of water at 50 °C for 90 min. After the mixture cooled, the solvent was removed under reduced pressure, and the residue was diluted with water. Crystals were collected by suction, dried in air (10 g), and then dissolved in 600 mL of toluene. After 30 mL of toluene was removed by distillation, 35 mL of N-methyl-4-piperidone and 10 g of aluminum isopropoxide were added, and the mixture was refluxed for 6 h. The reaction

(8) Johnson, W. S.; Collins, J. C.; Pappo, R.; Rubin, M. B.; Kropp, P. J.; Johns, W. F.; Pike, J. E.; Bartman, W. *J. Am. Chem. Soc.* **1958**, *80*, 2585.

(9) (a) Heusler, K.; Wieland, P.; Wettstein, A. *Helv. Chim. Acta* **1959** *42*, 1586. (b) Schmidlin, J.; Anner, G.; Billeter, J. -R.; Heusler, K.; Ueberwasser, H.; Wieland, P.; Wettstein, A. *Ibid.* **1957**, *40*, 2291.

(10) (a) Barton, D. H. R.; Beaton, J. M.; *J. Am. Chem. Soc.* **1960**, *82*, 2641. (b) *Ibid.* **1961**, *83*, 4083.

(11) Barton, D. H. R.; Basu, N. K.; Day, M. J.; Hesse, R. H.; Pechet, M. M.; Starratt, A. N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2243.

(12) Heusler, K.; Kalvoda, J.; Meystre, C.; Wieland, P.; Anner, G.; Wettstein, A.; Cainelli, G.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1961**, *44*, 502.

(13) Duax, W. L.; Hauptman, H.; Weeks, C. M.; Norton, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 1056.

(14) Bowers, A.; Ibanez, L. C.; Ringold, H. C. *Tetrahedron* **1959**, *7*, 138.

(15) (a) Heusler, K.; Kalvoda, J.; Wieland, P.; Wettstein, A. *Helv. Chim. Acta* **1961**, *44*, 179. (b) Jeger, O.; Arigoni, D.; Wettstein, A.; Anner, G.; Heusler, K.; Meystre, C.; Wieland, P.; Kalvoda, J. U.A. Patent 3 092 625, 1963.

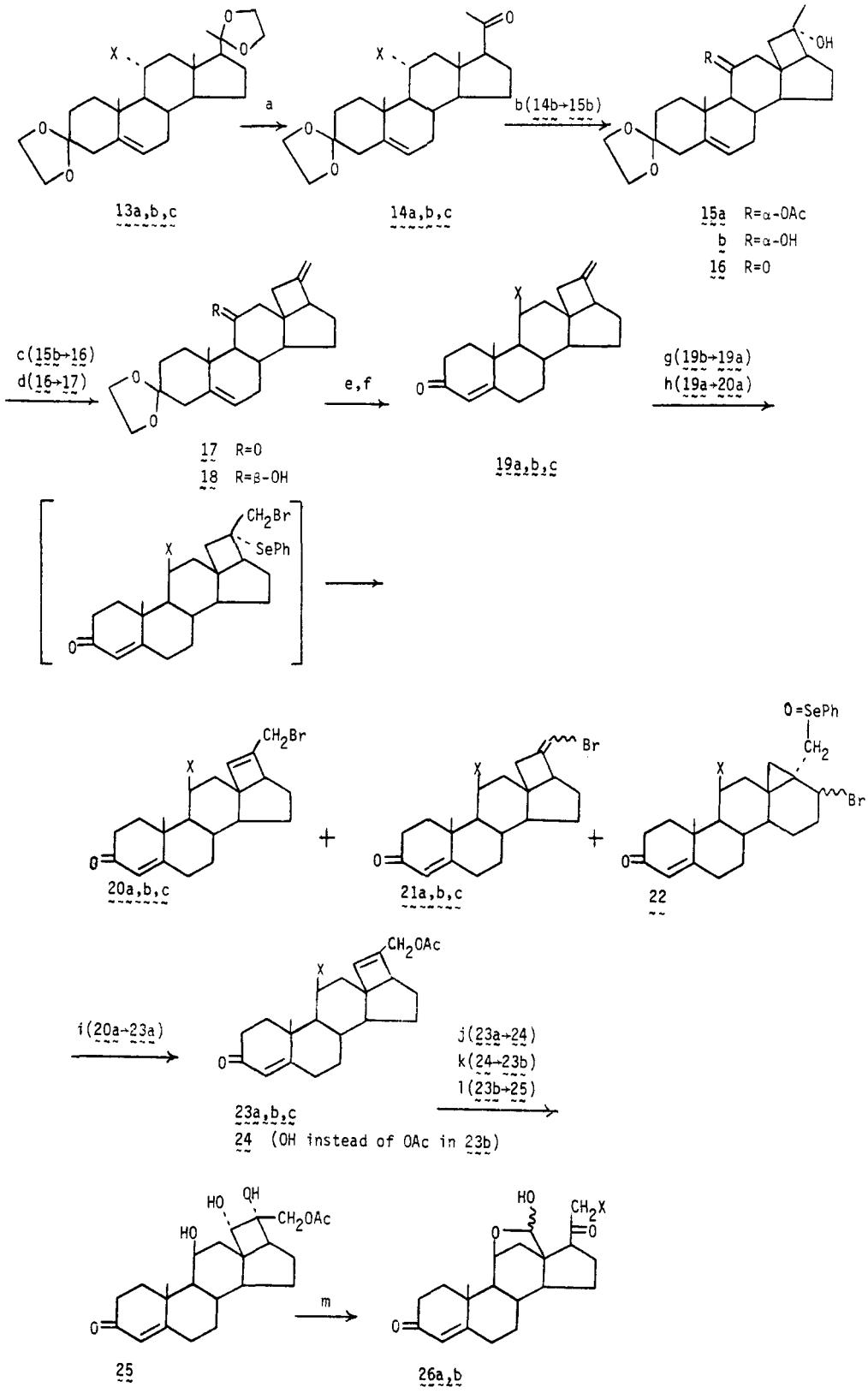
(16) Wehrli, H.; Cereghetti, M.; Schaffner, K.; Urech, J.; Vischer, E. *Helv. Chim. Acta* **1961**, *44*, 1927.

(17) (a) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513. (b) Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *Ibid.* **1977**, *99*, 3864.

(18) Raucher, S. *Tetrahedron Lett.* **1977**, 3909.

(19) Simpson, S. A.; Tait, J. F.; Wettstein, A.; Neher, R.; Euw, J. V.; Schindler, O.; Reichstein, T. *Helv. Chim. Acta* **1954**, *37*, 1163.

Scheme II[a,b]



[a] X = OAc for the a series, OH for the b series, and H for the c series. [b] (a) HOAc, water, and THF (20:10:3), 28 °C, 10 min; (b) $h\nu$ in EtOH suspension; (c) pyridinium chlorochromate, NaOAc, CH_2Cl_2; (d) $POCl_3$, pyridine, 100 °C, 2 h; (e) $LiAlH_4$, THF, reflux 20 h; (f) HOAc, water, and THF (20:10:3), 25 °C, 40 h; (g) Ac_2O, *p*-(dimethylamino)pyridine, pyridine, 25 °C; (h) PhSeBr, CCl_4, 0 °C; 30% H_2O_2, pyridine, 0–25 °C; (i) NaOAc, EtOH, reflux; (j) NaOH, MeOH, reflux; (k) Ac_2O, pyridine, 25 °C; (l) *N*-methylmorpholine *N*-oxide, catalytic OsO_4; (m) $NaIO_4$, *t*-BuOH, water.

mixture was cooled, diluted with ether, washed with 1.2 N HCl, washed with 1% NaCl, dried over Na_2SO_4, concentrated, and recrystallized from methanol to give 7 g (49.8% from 1) of an approximately 4:1 mixture of **4** and **5** (mp 120–121 °C) which could be used for further work. Additional material was obtainable upon chromatography of the mother liquor. For pure **4** and **5**, the crude crystalline product was chromatographed on 250 g of Woelm silica gel preconditioned with 7% EtOAc–cyclohexane. Elution with

7% EtOAc–cyclohexane gave exclusively the endo isomer (**5**), which was recrystallized from methanol to give colorless needles: mp 134 °C; λ_{max} ($CHCl_3$) 1670, 1615 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.75 (m, 2 H, H-4 and H-18), 1.62 (m, 3 H, J = 1.2, Me-21), 1.16 (s, 3 H); $[\alpha]^{25}_{589.0}$ +93.3°, $[\alpha]^{25}_{365.0}$ −119.4° (*c* 1.018%, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.86; H, 9.63.

Elution with 9% EtOAc–cyclohexane produced the exo olefin (**4**) which was recrystallized from methanol: mp 112 °C; λ_{max} ($CHCl_3$) 1673, 1618, 882 cm^{-1}; δ (Me_4Si, $CDCl_3$) 5.73 (br s, 1 H), 4.73 (m, 2 H, H_2C-21), 1.12 (s, 3 H); $[\alpha]^{25}_{589.0}$ +193.1°, $[\alpha]^{25}_{365.0}$ +284.9° (*c* 1.008%, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 84.70; H, 9.52.

3-Oxo-20,21-epoxy-18,20-cyclopregn-4-ene (6). To a solution of 836 mg of **4** in 20 mL of methylene chloride at −20 °C was added 0.50 g of *m*-chloroperbenzoic acid all at once. The mixture was stirred at −20 °C for 0.5 h, allowed to warm to 25 °C, and stirred for 4 h. It was washed with 3% Na_2SO_3 solution, washed with K_2CO_3 solution, washed with water, dried over Na_2SO_4, and concentrated. The crude product could be used for the next step. Chromatography on Woelm silica gel (15% EtOAc–cyclohexane) and subsequent recrystallization from ether produced an approximately 1:1 mixture of α- and β-epoxides as colorless needles: 0.30 g; mp 147–149 °C; δ (Me_4Si, $CDCl_3$) 5.76 (br s, 1 H), 2.74 (s, ~1 H, H_2C-21 of β-epoxide), 2.62 (d, ~0.5 H, J = 4.5 H_2C-21 of α-epoxide), 2.54 (d, ~0.5 H, J = 4.5, the other H_2C-21 of α-epoxide), 1.14 (s, 3 H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.50; H, 9.06.

21-Hydroxy-3-oxo-18,20-cyclopregna-4,18(20)-diene (7). Method A. To a solution of 0.40 mL (3.86 mmol) of diethylamine in 25 mL of THF was added 1.5 mL (3.9 mmol) of 2.6 M *n*-butyllithium in hexane at 25 °C. The mixture was cooled in a dry ice/acetone bath, and a solution of 0.16 g (0.51 mmol) of **6** in 5 mL of THF was added. The stirred reaction mixture was allowed to warm slowly to 25 °C. After being stirred at 25 °C for 2 h, the reaction mixture was poured onto ice and extracted with ether. The ethereal extract was washed with water, dried over Na_2SO_4, concentrated, and chromatographed on 15 g of Woelm silica gel. The desired material (0.11 g) was eluted with 15% EtOAc–cyclohexane and recrystallized from methylene chloride–ether to give light tan needles: mp 154 °C; δ (Me_4Si, $CDCl_3$) 6.03 (m, 1 H), 5.74 (br s, 1 H), 4.11 (br s, 2 H), 1.16 (s, 3 H); λ_{max} (MeOH) 240 nm (ϵ 18 400).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.78; H, 9.05.

Method B. For all practical purposes the crude mixture of **4** and **5** (approximately 4:1, recrystallized from methanol but not chromatographed) described above could be used. Epoxidation of 6.8 g of crude **4** with 4.70 g of *m*-chloroperbenzoic acid in 100 mL of methylene chloride as described above (but not chromatographed) gave 9 g of crude oily epoxide **6** which was treated with $LiNEt_2$ in THF as described in method A. Elution from a Woelm silica gel column with 15% EtOAc–cyclohexane gave 0.15 g of **4**, 1.0 g of 18α-hydroxy-18,20-cyclopregna-4,20(21)-dien-3-one (v, footnote 6), and 3.20 g (44.4% from crude **4** or 22.1% from **1**) of crystalline **7**.

20β,21-Epoxy-18,20-cyclopregn-4-en-3-one (6b). Crude **4** (6.8 g) containing ~20% of **5** was epoxidized as described in the preceding paragraph. Without chromatography the oily epoxide was treated with $LiNEt_2$ prepared from 19 mL of diethylamine in 300 mL of THF and 80 mL (0.185 mole) of 2.3 M *n*-BuLi in hexane. The reaction was initiated in a dry ice/acetone bath, allowed to warm to 25 °C, and interrupted while some epoxide **6** was still left (monitored by TLC: 33% EtOAc–toluene, Woelm silica gel plate). The reaction mixture was poured into ice–water and extracted with ether. The ethereal layer was washed with 1% HCl, washed with 0.5% NaCl, dried over Na_2SO_4, and concentrated. Chromatography on a Waters PrepLC/System 500 column packed with 325 g of Porasil using 35% EtOAc–Skelly B gave 0.17 g of **5**, 0.74 g of recovered β-epoxide **6b**, 0.97 g of v, and 2.87 g of **7**. No **6a** was found in the reaction mixture. The β-epoxide **6b** was recrystallized from methylene chloride–ether to give colorless needles: mp 134 °C; δ (Me_4Si, $CDCl_3$) 5.75 (br s, 1 H), 2.74 (s, 2 H, H-21), 1.14 (s, 3 H); λ_{max} ($CHCl_3$) 1668, 1613, 1240, 950, 881, 866 cm^{-1}; $[\alpha]^{25}_{589.0}$ +144.4°, $[\alpha]^{25}_{436.0}$ +286.9° (*c* 1.004, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.76; H, 9.02.

3-Oxo-20α,21-epoxy-18,20-cyclopregn-4-ene (6a). A mixture of 0.33 g of 20α,21-dihydroxy-3-oxo-18,20-cyclopregn-4-ene[20] and 1.0 mL of pyridine in 5 mL of methylene chloride was treated with 0.25 mL of mesyl chloride at 25 °C for 2 h. The reaction mixture was decomposed with 0.5 mL of methanol (25 °C, 0.5 h), diluted with ether, and washed successively with 2% HCl, 2% K_2CO_3, and water. The organic phase was dried over Na_2SO_4, concentrated, and chromatographed on 25 g of Woelm silica gel. Fractions eluted with 15% EtOAc in toluene gave 0.31 g of oily monomeslyate: δ (Me_4Si, $CDCl_3$, 80 MHz) 5.72 (s, 1 H), 4.10 (s, 2 H, H-21), 3.05 (s, 3 H), 1.11 (s, 3 H). A portion (0.10 g) of the monomesylate was dissolved in 10 mL of methanol containing 60 mg of KOH and refluxed for 1 h. The solvent was removed. The residue was taken up in methylene chloride, washed with water, dried over Na_2SO_4, concentrated, and recrystallized from ether to give 51 mg of **6a**. Recrytstallization from methylene chloride–ether produced pure **6a**: mp 167 °C; δ (Me_4Si, $CDCl_3$, 80 MHz) 5.71 (s, 1 H), 2.60 (d, 1 H, J = 5, H-21), 2.52 (d, 1 H, J = 5, H-21), 1.13 (s, 3 H); λ_{max} ($CHCl_3$) 1662, 1610, 951 cm^{-1}; $[\alpha]^{25}_{589.0}$ +162.7°, $[\alpha]^{25}_{365.0}$ +187.3° (*c* 0.529%, $CHCl_3$).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.48; H, 9.06.

21-Acetoxy-3-oxo-18,20-cyclopregna-4,18-diene (8). A solution of 0.36 g of **7** in 15 mL of pyridine was treated with 1.0 mL of acetic anhydride at 25 °C for 5 h. The reaction mixture was treated with 1 mL of methanol (25 °C, 0.5 h), diluted with ether, washed with 2% HCl, washed with water, dried over Na_2SO_4, and concentrated to give 0.37 g of light amber glass (**8**): δ (Me_4Si, $CDCl_3$) 6.04 (m, 1 H), 5.73 (br s, 1 H), 4.52 (br s, 2 H), 2.07 (s, 3 H), 1.15 (s, 3 H).

3-Oxo-18α,20α-dihydroxy-21-acetoxy-18,20-cyclopregn-4-ene (9). To a solution of 0.20 g of **8** in 4 mL of *t*-BuOH, THF, and water (10:3:1) were added 0.09 g of *N*-methylmorpholine *N*-oxide monohydrate and 0.4 mL of 1% OsO_4 in *t*-BuOH. The mixture was stirred at 25 °C until the starting material had disappeared (~48 h; TLC, Woelm silica gel, 50% EtOAc–benzene). The reaction mixture was diluted with ether and passed through 5 g of Florisil which was washed with ether and then with acetone. The ether solution gave 0.19 g of residue which, upon dissolving in a small amount of ether, produced 0.13 g (60.0%) of crystalline **9** (mp 162.5 °C). The mother liquor (0.06 g of residue) and the acetone washing (0.03 g) were combined and chromatographed on Woelm silica gel preconditioned with 10% EtOAc–toluene. Fractions eluted with 20% EtOAc–toluene produced 16 mg of somewhat impure **10**, and the fractions eluted with 50% EtOAc–toluene produced 10 mg of **9**. Total yield of **9** was 0.14 g (65%) accompanied by 0.01 g (4.6%) of **10**. An analytical specimen of **9**, obtained by recrystallization from methanol, was colorless, stout cubes: mp 166.5 °C; δ (Me_4Si, Me_2SO-d_6) 5.65 (br s, 1 H), 4.04 (d, 1 H, J = 11, H-21), 3.77 (d, 1 H, J = 11, H-21), 3.68 (br d, 1 H, J = 8, turned to s on D_2O exchange, H-18), 2.01 (s, 3 H), 1.10 (s, 3 H); λ_{max} (MeOH) 244.5 nm (ϵ 15 000).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.07; H, 8.35.

3,18,20-Trioxo-21-acetoxypregn-4-ene (10). To a solution of 0.66 g of $NaIO_4$ in 5 mL of water was added a solution of 1.00 g of **9** in 16 mL of dioxane, and the mixture was stirred at 25 °C for 2 h. It was then diluted with water and extracted with ethyl acetate. The organic layer was washed with $KHCO_3$ solution, dried over Na_2SO_4, concentrated, and crystallized immediately from CH_2Cl_2–ether to give 0.81 g (81%) of **10**: mp 147–149 °C;[21] δ (Me_4Si, $CDCl_3$) 9.82 (s, 1 H), 5.74 (br s, 1 H), 4.67 (s, 2 H), 2.15 (s, 3 H), 1.13 (s, 3 H); $[\alpha]^{25}_{589.0}$ +147.2°,[21] $[\alpha]^{25}_{365.0}$ +239.5° (*c* 1.002%, $CHCl_3$).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.70; H, 7.70.

(20) (a) Li, M. P.; Birmingham, K.; Chan, T. H. *J. Org. Chem.* **1976**, *41*, 2552. No stereochemical proof was presented. (b) More conveniently prepared by VanRheenen oxidation of **4**.

(21) Lit.[12] mp 142–147 °C; $[\alpha]_D$ +155 (*c* 0.594, $CHCl_3$).

The second crop (0.05 g) was obtained from chromatography of the mother liquor (0.15 g).

11-Deoxyaldosterone: 3,18,20-Trioxo-21-hydroxypregn-4-ene (11). A solution of 0.148 g of **10** in 3 mL of dioxane was stirred with a solution of 0.138 g of K_2CO_3 in 1 mL of water at 25 °C for 5 h. The reaction mixture was diluted with EtOAc and dried over anhydrous K_2CO_3. Chromatography on 15 g of Woelm silica gel with 20% EtOAc–toluene gave 0.10 g of **11**. Crystallization from EtOAc gave colorless needles: mp 127.5 °C; δ (Me_4Si, $CDCl_3$, immediately after dissolution, 80 MHz) 5.72 (br s, 1 H), 5.30 (d, turned to s on D_2O exchange, H-18 of **12a**), 4.25 (d, J = 18, H-21 of **12a**), 4.02 (d, J = 18, H-21 of **12a**), 1.17 (s, Me-19 of **12a**); δ (10 min after dissolution, 80 MHz) 9.83 (s, H-18 of aldehyde), 5.71 (br s), 5.40 (d, turned to s on D_2O exchange, H-18 of **12b**), 5.30 (H-18 of **12a**), 4.34 (d, J = 17, H-21, of **12b**), 4.25 (d, J = 18, H-21 of **12a**), 4.02 (d, J = 18, H-21 of **12a**), 3.87 (d, J = 17, H-21 of **12b**), 1.20 (s, Me-19 of **12b**), 1.17 (s, Me-19 of **12a**), 1.13 (s, Me-19 of aldehyde **11**).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.11; H, 8.21.

11α-Acetoxy-20-(ethylenedioxy)pregn-4-en-3-one. A solution of 2.0 g of **13a** in 200 mL of benzene–ether (1:1) was treated with 2.0 mL of boron trifluoride etherate at 25 °C for 1 h. The reaction mixture was washed with aqueous K_2CO_3, washed with water, dried over anhydrous K_2CO_3, concentrated, and chromatographed on Woelm silica gel with 5–10% ethyl acetate in toluene. The pure compound was obtained by recrystallization from methanol: mp 184 °C; δ (Me_4Si, $CDCl_3$) 5.76 (br s, 1 H), 5.28 (br m, 1 H), 3.93 (m, 4 H, 20-ketal), 2.01 (s, 3 H), 2.27 (br s, 6 H), 0.88 (s, 3 H); λ_{max} (MeOH) 239.5 nm (ε 16 240).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.44; H, 8.72.

11α-Hydroxy-3,20-bis(ethylenedioxy)pregn-5-ene. To a solution of 200 g of 11α-hydroxyprogesterone[22] in 700 mL of THF were added 330 mL of ethyl orthoformate, 220 mL of ethylene glycol, and 5 small drops of sulfuric acid. The reaction mixture was refluxed for 2 h, cooled to 25 °C, and poured into 8 L of water containing 10 g of $NaHCO_3$. The crystalline material was collected by suction and air-dried. Recrystallization from ethyl acetate–Skelly B gave 230 g (92%) of the first crop, mp 198–212 °C (lit.[12] mp 212–214 °C).

11α-Hydroxy-3-(ethylenedioxy)-20-oxopregn-5-ene (14b). A solution of 30 g of the 3,20-bis(ethylene ketal) in 180 mL of warm THF was diluted with 360 mL of glacial acetic acid and 180 mL of water and allowed to stand at 28 °C for exactly 10 min. The reaction mixture was poured into 2.5 L of cold water containing 450 g of K_2CO_3. Crystals were collected by suction, washed with water, and air-dried to give 35 g of crude **14b**. Recrystallization from methylene chloride–ether gave 21.5 g (80%) of pure **14b**: mp 220–221 °C (lit.[12] mp 204–208 °C); δ (Me_4Si, $CDCl_3$) 5.39 (m, 1 H), 4.03 (br m, 1 H), 3.94 (s, 4 H), 2.12 (s, 3 H), 1.18 (s, 3 H), 0.67 (s, 3 H); λ_{max} ($CHCl_3$) 3595, 1703, 1600 (vw), 1363, 1097 cm^{-1}.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.74; H, 9.21.

11α-Acetoxy-3-(ethylenedioxy)-20-oxopregn-5-ene (14a). The selective hydrolysis of 11α-acetoxy-3,20-bis(ethylenedioxy)pregn-5-ene as described in the previous paragraph afforded **14a** (86.5% after recrystallization from methanol), which was identical with authentic **14a** prepared by the Swiss procedure.[15a]

3-(Ethylenedioxy)-11α,20α-dihydroxy-18,20-cyclopregn-5-ene (15b). A suspension of 10 g of **14b** in 950 mL of ethanol was irradiated with a 200-W, medium-pressure, Hanovia lamp at 20 °C for 7 h under a nitrogen stream. The solvent was removed from the clear solution, and the residue was chromatographed on 250 g of Woelm silica gel with 30–100% ethyl acetate–toluene. The desired substance was found in 50–100% ethyl acetate fractions (4.5 g). Recrystallization from ethyl acetate–cyclohexane gave 3.2 g of pure **15b**, mp 205 °C. This **15b** was identical with the **15b** prepared by a known procedure[16] (saponification of **15a**).

3-(Ethylenedioxy)-11-oxo-20α-hydroxy-18,20-cyclopregn-5-ene (16).[23] A solution of 0.81 g of **15b** in 50 mL of methylene chloride was stirred with 0.80 g of pyridinium chlorochromate and 0.8 g of sodium acetate at 25 °C for 4 h. The reaction mixture was filtered through 5 g of Florisil, which was then washed with methylene chloride. The filtrate and washing gave 1.08 g of residue, which was recrystallized from methanol to give 0.6 g of pure **16**: mp 167 °C; δ (Me_4Si, $CDCl_3$) 5.33 (m, 1 H), 3.92 (s, 4 H), 1.12 (s, 3 H).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.33; H, 8.53.

3-(Ethylenedioxy)-11-oxo-18,20-cyclopregna-5,20(21)-diene (17). A. By Phosphorus Oxychloride. To a solution of 0.11 g of **16** in 3.5 mL of pyridine was added 0.80 mL of $POCl_3$, and the mixture was heated on a steam bath for 2 h. After cooling, the reaction mixture was poured onto ice and extracted with ether. The ethereal phase was washed with cold aqueous HCl, washed with 0.5% NaCl, and dried over Na_2SO_4. According to gas chromatographic analysis the crude product contained 69.37% of exo isomer **17** and 9.27% of endo olefin.

B. By Thionyl Chloride. To a solution of 0.14 g of **16** in 15 mL of 1:1 methylene chloride–*n*-pentane at −20 °C were added 2 mL of collidine and 0.55 mL of 10% $SOCl_2$ in methylene chloride. The reaction mixture was stirred at −20 to 0 °C for 2 h then at 25 °C for 2 h. The workup procedure was the same as for part A. The gas chromatographic analysis showed that the crude product contained 75.94% of exo isomer **17** and 19.24% of endo olefin. The crude product was dissolved in benzene and passed through a column of 2 g of Florisil which was then washed with 17% ethyl acetate–benzene. The benzene fraction was recrystallized from cyclohexane: the first crop (mp 165 °C) was an exo/endo mixture (ratio 4.82), the second crop (mp 173 °C) had an exo/endo ratio of 5.42, and the third crop (mp 175 °C) had an exo/endo ratio of 6.21 based on gas chromatographic analysis. The second crop was used for analysis: δ (Me_4Si, $CDCl_3$) 5.47 (m, ≪1 H, H-18 of endo), 5.33 (m, ~1 H, H-6), 4.75 (m, ~2 H, H-21 of exo), 3.93 (s, 3 H), 1.20 (s, Me-19 of endo), 1.15 (s, Me-19 of exo).

Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.65; H, 8.52.

For the gas chromatography a 6-ft column of 3% Poly S 179 was used at 220–270 °C. The retention time for the exo and endo compounds was 6.74 and 5.62 min, respectively.

3-(Ethylenedioxy)-11β-hydroxy-18,20-cyclopregna-5,20-diene (18). A solution of 0.38 g of crude **17** and 0.30 g of lithium aluminum hydride in 100 mL of THF was refluxed for 20 h. The reaction mixture was decomposed with 1 mL of water, filtered to remove inorganic material, and concentrated. The crystalline residue could be used for the next step without purification. For an analytical specimen, crude **18** was dissolved in methylene chloride, and the mixture was passed through a column of 3 g of Florisil, concentrated, and recrystallized from ether to give pure **18**: mp 157 °C; δ (Me_4Si, $CDCl_3$, 80 MHz) 5.24 (m, 1 H), 4.66 (m, 2 H, H-21), 4.42 (m, 1 H), 3.94 (s, 4 H), 1.26 (s, 3 H); λ_{max} ($CHCl_3$) 3610, 1670 ($\Delta^{20,21}$), 1600 (vw, $\Delta^{5,6}$), 1100, 1015 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.57; H, 9.00.

11β-Hydroxy-18,20-cyclopregna-4,20-dien-3-one (19b). The crude lithium aluminum hydride reduction product (**18**) described above was dissolved in 40 mL of HOAc, water, and THF (20:10:3) and allowed to stand for 40 h. The solvent was removed in vacuo. The residue, which crystallized slowly (~7 days), was triturated with toluene and filtered to collect the first crop (0.08 g of **19b**). The filtrate was concentrated and chromatographed on 80 g of Woelm silica gel with 17% ethyl acetate–toluene. The less polar fractions gave 0.02 g of crystalline endo olefin 11β-hydroxy-18,20-cyclopregna-4,18(20)-dien-3-one: mp 162.5 °C; δ (Me_4Si, $CDCl_3$, 80 MHz) 5.85 (m, 1 H), 5.67 (s, 1 H), 4.43 (m, 1 H), 1.61 (s or m, 3 H, Me-21), 1.42 (s, 3 H); λ_{max} ($CHCl_3$) 3615, 1667, 1620, 1140, 1036, 870 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_2 \cdot {}^1/_4H_2O$: C, 79.57; H, 9.06. Found: C, 79.66; H, 9.08.

The more polar fractions gave 0.08 g of **19b**: mp 143 °C; δ (Me_4Si, $CDCl_3$, 80 MHz) 5.67 (s, 1 H), 4.68 (m, 2 H), 4.39 (m, 1

(22) Inexpensive industrial intermediate purchased from the Upjohn Co. For total synthesis see: Johnson, W. S.; Brinkmayer, R. S.; Kapoor, V. M.; Yarnell, T. *J. Am. Chem. Soc.* **1977**, *99*, 8341.

(23) Jeger, O. German Patent 1 125 919, 1962; *Chem. Abstr.* **1963**, *58*, 2492.

H), 1.42 (s, 3 H); λ_{max} ($CHCl_3$) 3615, 1670, 1620, 1150, 1035, 880 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_2 \cdot {}^1/_3Et_2O$: C, 79.56; H, 9.36. Found: C, 79.54; H, 9.26.

21-Bromo-18,20-cyclopregnan-4,18-dien-3-one (20c). To a solution of 0.30 g of phenylselenyl bromide in 5 mL of carbon tetrachloride stirred in a ice–water bath was added a solution of 0.30 g of **4** in 5 mL of carbon tetrachloride. After being stirred at 0 °C for 5 min, the almost colorless reaction mixture was treated with 1 mL of pyridine and 1.25 mL of 30% hydrogen peroxide. The temperature was allowed to rise to 25 °C in 2 h. The reaction mixture was diluted with methylene chloride, washed with cold 2% HCl, washed with 1% NaCl, dried over Na_2SO_4, and concentrated. Chromatography on 12 g of Woelm silica gel with 8% ethyl acetate–cyclohexane gave 0.13 g of pure **20c**, 0.05 g of crude **20c** containing **21c**, 0.04 g of **21c**, and 0.04 g of selenium containing a substance (possibly **22**) in this order. The oily allylic bromide **20c** had the following: δ (Me_4Si, $CDCl_3$) 6.14 (m, 1 H, H-18), 5.73 (br s, 1 H), 3.88 (br s, 2 H, H-21), 1.18 (s, 3 H). The vinylic bromide (**21c**, semicrystalline): δ (Me_4Si, $CDCl_3$) 5.75 (m, 2 H, H-4 and H-21), 1.12 (s, 3 H).

21-Acetoxy-18,20-cyclopregna-4,18-dien-3-one (23c). To a solution of 0.20 g of phenylselenyl bromide in 3 mL of carbon tetrachloride was added at 0 °C 0.30 g of **4** in 3 mL of carbon tetrachloride. The mixture was stirred at 0 °C for 10 min and then treated with 1 mL of pyridine and 1.2 mL of 30% hydrogen peroxide. The temperature was allowed to rise to 25 °C. The mixture was diluted with methylene chloride, washed with 2% aqueous HCl, washed with water, dried over Na_2SO_4, and concentrated. The residue was dissolved in 10 mL of ethanol and refluxed in the presence of 1.0 g of KOAc for 1 h. The solvent was removed. The residue was taken up with methylene chloride, washed with aqueous 1% NaCl, dried over Na_2SO_4, concentrated, and chromatographed on 12 g of Woelm silica gel. Fractions eluted with 7% ethyl acetate–cyclohexane gave ~0.05 g of **4** containing **21c**. Fractions of 10% ethyl acetate-cyclohexane gave 0.02 g of semicrystalline **21c** and then 0.18 g of **23c**. The latter was identical with authentic **8** prepared by the epoxide route.

11β-Hydroxy-21-acetoxy-18,20-cyclopregna-4,18-dien-3-one (23b) Directly from 19b. Starting from 0.13 g of **19b**, essentially the same procedure as for **23c** was used. Chromatographic separation on 15 g of Woelm silica with 10% ethyl acetate–toluene gave ~10 mg of a mixture of the recovered starting material and one isomer of **21b** (*E* or *Z*), then ~30 mg of the other **21b** (*Z* or *E*), and finally 16.9 mg of oily **23b**, which crystallized spontaneously. The recovered starting material found in the first fraction was endo olefin 11β-hydroxy-18,20-cyclopregna-4,18-dien-3-one which was free from exo olefin **19b** as confirmed by comparison of ^1H NMR spectra. The NMR spectrum of **21b** was as follows: δ (Me_4Si, $CDCl_3$, 80 MHz) 5.69 (m, 2 H, H-4 and H-21), 4.43 (m, 1 H, H-11α), 1.39 (s, 3 H). For the spectral data and analysis of **23b**, see the section for the preparation of the same compound by selective acetylation of **24**.

11β-Acetoxy-18,20-cyclopregna-4,20-dien-3-one (19a). A solution of 2.69 g of **19b**, 0.04 g of *p*-(dimethylamino)pyridine, and 15 mL of acetic anhydride in 75 mL of pyridine was allowed to stand overnight. The reaction mixture was decomposed with 10 mL of methanol while cooling in an ice–water bath for 15 min and then was diluted with methylene chloride. It was washed successively with iced 5% HCl, water, and 0.1% $KHCO_3$ and dried over Na_2SO_4. Upon evaporation, 3.26 g (~115%) of **19a** was obtained which showed a single spot of R_f 0.45 on TLC (33% EtOAc–toluene, silica gel plate): δ (Me_4Si, $CDCl_3$, 80 MHz) 1.22 (s, 3 H, Me-19), 2.03 (s, 3 H, OAc), 4.67 (m, 2 H, H-21), 5.45 (m, 1 H, H-11α), 5.66 (br s, 1 H, H-4). This substance was used without further purification.

11β,21-Dihydroxy-18,20-cyclopregna-4,18-dien-3-one Diacetate (23a). Crude acetate (**19a**), prepared from 0.83 g (2.46 mmol) of **19b** as described above, was dissolved in 40 mL of carbon tetrachloride, cooled in an ethanol–ice bath (−20 °C), and treated with 1.2 g of phenylselenyl bromide. The bath was replaced with an ice–water bath, and the reaction mixture was stirred for 20 min. Then 2.5 mL of pyridine and 4.2 mL of 30% hydrogen peroxide were added. The mixture was stirred at 0 °C for 1 h and then at 25 °C for 2 h. The reaction mixture was diluted with methylene chloride, washed with cold 2% HCl, washed with 0.2% NaCl, dried over Na_2SO_4, and concentrated. The residue was dissolved in 60 mL of ethanol and heated with 3.5 g of NaOAc under reflux for 2 h. Water (50 mL) was added to the reaction mixture and ethanol was removed under reduced pressure. The residue was diluted with water and extracted with methylene chloride. The organic extract was washed with water, dried over Na_2SO_4, and concentrated (1.43 g). Low-pressure column chromatography on 80 g of Woelm silica gel with 10% ethyl acetate–toluene gave 0.09 g (10.3% from **19b**) of recovered **19a**, 0.15 g (0.346 mmol, 14.1% from **19b**) of (*E*)- and (*Z*)-vinyl bromide **21a**, and 0.54 g (1.31 mmol, 53.2% from **19b**) of diacetate **23a**. The yield of **23a** amounted to 59.4% based upon recovered **19a**. For the oily **23a**: δ (Me_4Si, $CDCl_3$, 80 MHz) 1.24 (s, 3 H, Me-19), 2.04 (s, 3 H, AcO-11), 2.07 (s, 3 H, AcO-21), 4.48 (br s, 2 H, H-21), 5.50 (m, 1 H, H-11α), 5.66 (br s, 1 H, H-4), 5.97 (m, 1 H, H-18); λ_{max} ($CHCl_3$) 1737, 1670, 1620, 1377, 1256, 1023 cm^{-1}; λ_{max} (MeOH) 234 nm (ε 16 550).

Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.61; H, 7.85.

11β,21-Dihydroxy-18,20-cyclopregna-4,18-dien-3-one (24). A solution of 0.46 g of **23a** in 60 mL of ethanol was treated with 10 mL of 20% aqueous NaOH, and the mixture was refluxed under nitrogen for 2.5 h. The saponification mixture was concentrated under reduced pressure, diluted with 20 mL of water, and extracted with methylene chloride. The organic phase was washed with 0.5% NaCl, dried over Na_2SO_4, and concentrated to give 0.30 g of pale yellow crystalline residue. For analytical purposes a portion of crude **24** was dissolved in methylene chloride and chromatographed (regular column, no pressure) on Florisil. Elution with 10–20% ethyl acetate–methylene chloride afforded colorless crystals which were recrystallized from ethyl acetate to give pure **24**: mp 210 °C; δ (Me_4Si, CD_3OD, 80 MHz) 1.44 (s, 3 H, Me-19), 3.95 (m, 2 H, H-21), 4.38 (m, 1 H, H-11α), 5.62 (br s, 1 H, H-4), 6.12 (m, 1 H, H-18); λ_{max} (MeOH) 242 nm (ε 14 600); λ_{max} (KBr) 3435, 3310, 1641, 1610 cm^{-1}.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.28; H, 8.68.

11β-Hydroxy-21-acetoxy-18,20-cyclopregna-4,18-dien-3-one (23b) by Selective Acetylation of 24. A solution of 0.60 g of **24** and 0.456 mL of acetic anhydride in 9.3 mL of pyridine was allowed to stand at 25 °C for 1.75 h. The reaction mixture was diluted with methylene chloride, washed with iced 5% HCl, washed with water, dried over Na_2SO_4, and concentrated to give crystalline residue (0.65 g). The crude product showed essentially one spot on TLC (R_f 0.62, 50% ethyl acetate–toluene, silica gel plate) and could be used without further purification. For an analytical specimen a portion of crude **23b** was dissolved in methylene chloride and chromatographed on Florisil (regular column, no pressure). Pure **23b** was eluted with 5–10% ethyl acetate–methylene chloride: mp 126 °C (recrystallization from ether did not change the melting point); δ (Me_4Si, $CDCl_3$, 80 MHz) 1.42 (s, 3 H, Me-19), 2.07 (s, 3 H, AcO), 4.48 (m, 3 H, H-21 and H-11α), 5.66 (br s, 1 H, H-4), 6.13 (m, 1 H, H-18); λ_{max} (MeOH) 242 nm (ε 15 130); λ_{max} ($CHCl_3$) 3620, 1742, 1672, 1620, 1252, 1038 cm^{-1}; $[\alpha]^{25}_{589.0}$ +134.0°, $[\alpha]^{25}_{365.0}$ +74.1° (*c* 1.019%, $CHCl_3$).

Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.32; H, 8.30.

11β,18α,20α-Trihydroxy-21-acetoxy-18,20-cyclopregn-5-en-3-one (25). A solution of 0.10 g of **23b**, 0.045 g of *N*-methylmorpholine *N*-oxide, and 1 mg of OsO_4 in 10 mL of *t*-BuOH–THF–H_2O (10:3:1) was allowed to stand for 3 h (the reaction was about 70% complete at this point) and was then kept in a refrigerator overnight. The reaction mixture, which no longer contained **23b**, was diluted with methylene chloride, washed with cold 1% HCl, washed with 0.5% NaCl, dried over Na_2SO_4, and concentrated. The residue, which showed two spots (R_f 0.45 and 0.14) on TLC (75% ethyl acetate–toluene, silica gel plate), could, for all practical purposes, be used for the next step without separation or purification. For analysis this mixture was dissolved in methylene chloride and chromatographed (regular column, no pressure) on 2 g of Florisil. The less polar product (**26a**, 0.01 g, crystalline) was eluted with 5% ethyl acetate–methylene chloride, 0.015 g of a mixture (**25** and **26a**) was eluted with 10% ethyl acetate–methylene chloride, and finally 0.08 g of the more polar product (**25**) was eluted with 20% ethyl acetate–methylene chloride. The latter was recrystallized from ethyl acetate to give

pure **25**: mp 199–200 °C; δ (Me_4Si, DMF-d_7, 80 MHz) 1.43 (s, 3 H, Me-19), 2.04 (s, 3 H, AcO), 5.60 (br s, 1 H, H-4); λ_{max} (MeOH) 241.5 nm (ε 14 700); λ_{max} (KBr) 3380, 3230, 1738, 1698, 1673 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.04; H, 8.07.

Aldosterone Acetate (26a). The mixture of **25** and **26a** mentioned above (17.4 mg, prepared from 16.9 mg of **23**) was dissolved in 1.0 mL of *t*-BuOH and treated with 8.0 mg of $NaIO_4$ in 0.21 mL of water. After being stirred at 25 °C for 30 min, the reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. Recrystallization from methylene chloride–ether gave 12 mg of **26a**: mp 197 °C (lit.[11] mp 196.5–198 °C; lit.[12] mp 192–195 °C); δ^{24} (Me_4Si, $CDCl_3$, 80 MHz) 5.71 (s, 1 H), 5.42 (s, 1 H), 4.78 (m, ~2 H), 4.16 (d, ~1 H, J = 10), 3.98 (d, ~1 H, J = 10), 2.13 (s, ≪3 H, acetoxy of one isomer), 2.10 (s, ~3 H, acetoxy of another isomer), 1.30 (s, ~3 H, Me-19), 1.26 (s, ≪3 H, Me-19); λ_{max} ($CHCl_3$)[9a,b] 3570, 1743, 1665, 1612, 1453 cm^{-1}.

18α,20α-Dihydroxy-18,20-cyclopregn-4-en-3-one (iii). A suspension of 1.73 g of **5**, 0.95 g of *N*-methylmorpholine *N*-oxide monohydrate, and 30 mg of OsO_4 in 30 mL of *t*-BuOH–THF–water (10:3:1) was warmed to 35–40 °C in order to obtain a homogeneous solution and was stirred at 25 °C for 96 h. The reaction mixture was diluted with methylene chloride, washed successively with 1% HCl, 1% NaCl, and 2% $KHCO_3$, dried over Na_2SO_4, and concentrated. The residue (3.8 g) was chromatographed on 250 g of Woelm silica gel with 25% ethyl acetate–toluene to give 1.62 g of pure iii (recrystallization from methylene chloride–ether): mp 167.5 °C; δ (Me_4Si, $CDCl_3$) 5.74 (br s, 1 H), 3.60 (d, became s on D_2O exchange, 1 H, J = 9, H-18β), 3.13 (d, 1 H, J = 9.5, OH-18α, replaced with D_2O), 1.17 (s, 3 H), 1.14 (s, 3 H); λ_{max} ($CHCl_3$) 3620, 3545, 1673, 1620, 1103 cm^{-1}; λ_{max} (MeOH) 241 nm (ε 15 500).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.30; H, 9.25.

18α,20α-Epoxy-18,20-cyclopregn-4-en-3-one (iv). A solution of 0.42 g of **5** in 15 mL of methylene chloride was cooled to −20 °C. It was treated with 0.40 g of *m*-chloroperbenzoic acid, and the mixture was stirred at −20 °C for 30 min, allowed to warm to 25 °C, and stirred at 25 °C for 4 h. The reaction mixture was washed with aqueous Na_2SO_3, washed with aqueous K_2CO_3, dried over Na_2SO_4, and concentrated. The crystalline residue was recrystallized from methylene chloride–ether to give iv as stout needles: mp 200 °C; δ (Me_4Si, $CDCl_3$) 5.74 (br s, 1 H), 3.63 (d, 1 H, J = 3.5, H-18β), 1.39 (s, 3 H), 1.22 (s, 3 H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.41; H, 9.02.

18α-Hydroxy-3-oxo-18,20-cyclopregna-4,20-diene (v). Lithium diethylamide was prepared from 9.5 mL (6.7 g, 92 mmol) of diethylamine and 38.5 mL (0.10 mol in hexane) of 2.6 M *n*-BuLi in 300 mL of THF at 25 °C. The solution was cooled in a dry ice/acetone bath, and a solution of 3.8 g of iv in 30 mL of THF was added. After the mixture was stirred for 0.5 h, the dry ice/acetone bath was removed, and the stirring was continued for 2 h. The reaction mixture was poured into water and extracted with ether. The ethereal layer was washed with water, dried over Na_2SO_4, concentrated, and chromatographed on 250 g of Woelm GF silica gel with 20% EtOAc in toluene. Recrystallization from cyclohexane gave pure v: mp 168 °C; δ (Me_4Si, $CDCl_3$) 5.76 (br s, 1 H), 5.12 (t, 1 H, J = 2, H-21), 4.91 (t, 1 H, J = 2, H-21), 4.45 (m, 1 H, H-18β), 1.18 (s, 3 H); λ_{max} ($CHCl_3$) 3605, 1673, 1620, 897 (*exo*-methylene) cm^{-1}; λ_{max} (MeOH) 241.5 nm (ε 16 800).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.93; H, 9.15.

18α-Hydroxy-3-oxo-20α,21-epoxy-18,20-cyclopregn-4-ene (vi). A solution of 1.05 g of v, 25 mg of $VO(acac)_2$, and 0.55 mL of 90% *tert*-butyl hydroperoxide in 50 mL of toluene was stirred at 45 °C for 2.5 h. The reaction mixture was diluted with toluene, washed with 2% Na_2SO_3, washed with 1% NaCl, and dried over Na_2SO_4. Evaporation and recrystallization of the residue from methylene chloride–ether gave 0.84 g of pure vi: mp 149 °C; δ (Me_4Si, $CDCl_3$) 5.76 (br s, 1 H), 4.26 (br d, 1 H, J = 8, H-18β, became s on D_2O exchange), 2.82 (d, 1 H, J = 4, H-21), 2.74 (d, 1 H, J = 4, H-21), 1.18 (s, 3 H).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.70; H, 8.56.

Transformation of vi to iii. A. Tetrahydropyranyl Ethers of vi. A solution of 200 mg of vi and 0.40 mL of dihydropyran in 2 mL of methylene chloride was treated with 1 mg of toluenesulfonic acid at 25 °C for 5 h. The reaction mixture was washed with 5% $KHCO_3$, dried over Na_2SO_4, and concentrated. Chromatography on 40 g of Woelm silica gel with 10% EtOAc–toluene separated the two tetrahydropyranyl ethers. For the less polar oily tetrahydropyranyl ether: δ (Me_4Si, $CDCl_3$) 5.75 (br s, 1 H), 4.43 (m, 2 H, H-18β and acetal H), 2.60 (s, 2 H, H-21), 1.15 (s, 3 H). The more polar tetrahydropyranyl ether was recrystallized from ether: mp 172 °C; δ (Me_4Si, $CDCl_3$) 5.73 (br s, 1 H), 4.51 (m, 1 H, acetal H), 4.14 (m, 1 H, H-18β), 2.62 (s, 2 H, H-21), 1.11 (s, 3 H).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found (for less polar ether): C, 74.63; H, 8.94. Found (for more polar ether): C, 75.40; H, 8.81.

B. Hydrogenolysis, Reoxidation, and Hydrolysis to iii. A 0.25-g mixture of the above two tetrahydropyranyl ethers (R_f values on Woelm silica gel with 33% EtOAc in toluene were 0.65 and 0.60, respectively) was treated with 0.15 g of lithium aluminum hydride in 50 mL of boiling THF for 6 h. The reaction mixture was diluted with 50 mL of ether containing 0.3 mL of water and filtered. The filtrate containing 3,18α,20α-trihydroxy-18,20-cyclopregn-4-ene 18-*O*-tetrahydropyranyl ethers (R_f 0.53 and 0.49 with 33% EtOAc in toluene on a silica gel plate) was concentrated, dissolved in 10 mL of methylene chloride, and treated with 0.30 g of pyridinium chlorochromate and 0.30 g of NaOAc at 25 °C. After 2 h the reaction mixture was adsorbed on 5 g of Florisil and eluted with 10% EtOAc in methylene chloride. The earlier fractions (crystalline) containing 18α,20α-dihydroxy-3-oxo-18,20-cyclopregn-4-ene 18-*O*-tetrahydropyranyl ethers (R_f 0.59 and 0.55) were combined and dissolved in 1 mL of THF and then diluted with 20 mL of HOAc–water (2:1). After 24 h the reaction mixture was concentrated and chromatographed on Woelm silica gel with 25% EtOAc in toluene. The less polar product, probably hydroxyvaleraldehyde, was discarded. The more polar, major product was crystallized from ether; mp 168 °C, no depression upon admixture with iii prepared by glycolation of **5**.

Acknowledgment. I thank Mr. M. Stealey and Mr. C. Dorn for technical assistance. I am also grateful to Mr. E. Zielinski and associates for microanalyses, Mr. A. J. Damascus and associates for obtaining the spectral data, and Mr. B. Smith and associates for low-pressure column chromatographies. I thank Professor A. I. Meyers, Professor P. A. Grieco, Dr. F. Colton, and Dr. G. Lenz for helpful discussion and Ms. Lydia Swenton for interpretation of some ^1H NMR spectra. Finally I thank Ken E. Miyano for correcting the English.

Registry No. **1**, 76831-50-0; **2**, 76773-50-7; **3**, 76773-52-9; **4**, 76807-06-2; **5**, 76807-07-3; **6a**, 76807-08-4; **6b**, 76831-54-4; **7**, 76807-09-5; **8**, 76822-60-1; **9**, 76807-10-8; **10**, 56896-22-1; **11**, 56896-23-2; **12a**, 76807-11-9; **12b**, 76807-12-0; **13a**, 76807-13-1; **13b**, 3386-06-9; **14a**, 70165-46-7; **14b**, 76807-14-2; **15a**, 76807-36-8; **15b**, 76807-15-3; **16**, 76807-16-4; **17**, 76807-17-5; *endo*-**17**, 76807-18-6; **18**, 76807-19-7; **19a**, 76807-20-0; **19b**, 76807-21-1; **20c**, 76807-22-2; (*E*)-**21a**, 76807-23-3; (*Z*)-**21a**, 76807-24-4; (*E*)-**21b**, 76807-25-5; (*Z*)-**21b**, 76807-26-6; **21c**, 76807-27-7; **23a**, 76807-28-8; **23b**, 76807-29-9; **24**, 76807-30-2; **25**, 76807-31-3; **26a** (isomer 1), 76831-55-5; **26a** (isomer 2), 36030-57-6; iii, 76807-32-4; iii THP ether (isomer 1), 76822-53-2; iii THP ether (isomer 2), 76847-26-2; iv, 76822-54-3; v, 76807-35-7; vi, 76807-33-5; vi THP ether (isomer 1), 76807-34-6; vi THP ether (isomer 2), 76945-58-9; 20α,21-dihydroxy-3-oxo-18,20-cyclopregn-4-ene, 59055-10-6; 11α-acetoxy-20-(ethylenedioxy)pregn-4-en-3-one, 20853-67-2; 11α-hydroxyprogesterone, 80-75-1; 11β-hydroxy-18,20-cyclopregna-4,18(20)-dien-3-one, 76807-37-9; **26a** (isomer 2), 36030-57-6; 3,18α,20α-trihydroxy-18,20-cyclopregn-4-ene 18-*O*-THP (isomer 1), 76807-38-0; 3,18α,20α-trihydroxy-18,20-cyclopregn-4-ene 18-*O*-THP (isomer 2), 76807-39-1.

(24) Wieland, P.; Heusler, K.; Wettstein, A. *Helv. Chim. Acta* **1960**, *43*, 2066.