temperature. After solvents were removed under a reduced pressure, the residue was distilled at 44 °C (5 mmHg) to afford a mixture of **15** and **16** in 79% yield. Since **15** and **16** were thermally unstable, they were not separated, and the mixture was analyzed: ^{1}H NMR (CCl_4) τ 5.74 (m, 1 H), 7.89 (s, 1 H), 7.8–9.5 [m, 12 H, including 8.89 (d, J = 5.7 Hz) and 8.92 (d, J = 6.3 Hz)]. With the aid of a shift reagent Eu(dpm)$_3$, the absorption at τ 5.74 was separated into two multiplets with widths at half-height of 11 Hz, respectively. With the aid of the shift reagent, the two doublets were shown to include three protons, and the intensity ratio of the doublets at τ 8.89 and 8.92 to be 1.6:1. The coupling constants of the doublets were also determined with the aid of the shift reagent. Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.20. When 20.0 mmol (2.08 mL) of diethylzinc was used, a mixture of **15** and **16** was obtained in 60% yield. ^{1}H NMR spectrum of the mixture showed the ratio of **15** to **16** to be 1:1.7.

Reaction of *cis*-Cyclooctene with Diethylzinc and 1,1-Diiodoethane. Reaction of *cis*-cyclooctene (1.2 mmol, 0.23 g) with diethylzinc (1.5 mmol, 0.15 mL) and 1,1-diiodoethane (2.4 mmol, 0.23 mL) in 3.0 mL of octane at 30 °C for 7 h gave a 1:2.6 mixture of *exo*- and *endo*-9-methyl-*cis*-bicyclo[6.1.0]nonane in 87% yield based on the olefin. The exo isomer: ^{1}H NMR (CCl_4) τ 7.8–10.2 [m, 18 H, including 8.99 (d, 3 H, J = 4.8 Hz)]. Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.60; H, 13.23. The endo isomer: ^{1}H NMR (CCl_4) τ 7.9–9.8 [m, 18 H, including 9.09 (d, 3 H, J = 4.5 Hz)]. Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 86.94; H, 13.02. In the case where 1.5 mmol of ethylzinc methoxide was used instead of diethylzinc, the yield of 9-methyl-*cis*-bicyclo[6.1.0]nonane was <1% when the reaction time was 7 h.

Registry No.—**2,** 14390-23-9; **3,** 62861-98-7; **4,** 62929-18-4; **5,** 62861-99-8; **6,** 62929-19-5; **7,** 62929-20-8; **8,** 62929-21-9; **9,** 4096-38-2; **10,** 62862-00-4; **11,** 62929-22-0; **12,** 62862-01-5; **13,** 62929-23-1; **14,** 822-67-3; **15,** 62862-02-6; **16,** 62862-03-7; diethylzinc, 557-20-0; 1,1-diiodoethane, 594-02-5; *cis*-cyclooctene, 931-87-3; *exo*-9-methyl-*cis*-bicyclo[6.1.0]nonane, 62862-04-8; *endo*-9-methyl-*cis*-bicyclo[6.1.0]nonane, 62929-24-2; ethylzinc methoxide, 15860-82-9.

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(5) The VPC analysis showed the presence of other products in the vicinity of **10** and **11**. However, the amounts of these products were negligible even if they involved the endo,cis and the exo,cis isomers.
(6) Reduction of bicyclo[4.1.0]heptan-2-one with lithium aluminum hydride was reported to give predominantly the trans isomer of 2-hydroxybicyclo[4.1.0]heptane.[2d]
(7) The ^{1}H NMR spectra of *exo*- and *endo*-7-methylbicyclo[4.1.0]heptane showed the absorptions of the methyl protons at τ 9.03 and 9.06, respectively.[1]
(8) For example, the formation of 9-methyl-*cis*-bicyclo[6.1.0]nonanes was extremely slow when ethylzinc methoxide was used instead of diethylzinc in reaction 1 with *cis*-cyclooctene as is given in the Experimental Section.
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Synthesis of Steroidal [16α,17-*b*][1,4]Dioxanes

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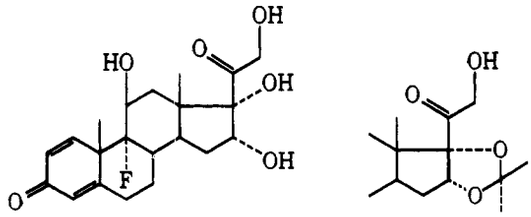
Steroidal [16α,17-*b*][1,4]dioxanes have been prepared for the first time. The key reaction involves the selective functionalization of polyhydroxylated steroids via interaction of 16,17-cycloborates and functionalized diazo compounds to give 16α-alkoxylated 17-hydroxy steroids. Conversion of these intermediates to a variety of substituted dioxanes and dioxins is described. ^{1}H NMR and CD spectra of the products are discussed.

The conversion of certain 16α,17α-dihydroxy steroids, such as triamcinolone[1] (**1**), to the corresponding "acetonides" [2′2′-dimethyl[16α,17-*d*][1,3]dioxolanes (**2**)] is accompanied by a marked increase in topical antiinflammatory activity.[2] A variety of other fused five-membered ring systems incorporating an additional boron, carbon, phosphorus, or sulfur atom[3–6] have been prepared from **1**; however, none of these modifications has led to a therapeutic agent. We decided to incorporate a second carbon atom into the moiety bridging the 16- and 17-oxygen atoms in **2** and prepare compounds of the type **5** in order to explore the effect on antiinflammatory activity.

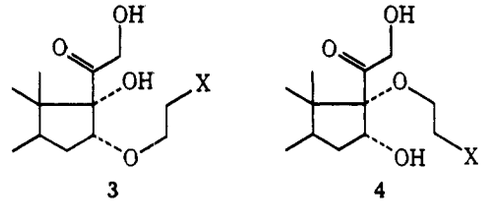
One attractive approach to such compounds appeared to be the cyclization of intermediates of the type **3** or **4**. Conversion of **1** to the penultimate intermediate **3** requires selective functionalization of one of the two most reactive hydroxyl groups in **1**; for conversion to **4**, one of the two least reactive hydroxyls must be alkylated. A simple approach to 16α-alkoxy derivatives such as **3** is provided by the reaction of the 16,17-cycloborate esters of 11β,16α,17,21-tetrahydroxy steroids with diazoalkanes discovered by Fried and Thomas.[8] We have used the reaction of functionalized diazo compounds with cycloborate esters to prepare derivatives of **3** suitable for transformation to various dioxanes, including the parent ring system **5**. At this time, we wish to describe the synthesis of steroidal [16α,17-*b*][1,4]dioxanes; the biologic activity of these compounds will be reported separately.

Results

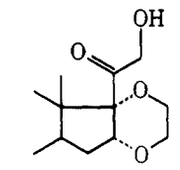
Reaction of 9-fluoro-11β,16α,17,21-tetrahydroxypregn-4-ene-3,20-dione with a large excess of boric oxide in methanol gives cycloborate **6** in excellent yield.[3] When powdered **6** is added to a well-stirred solution of diazoalkene **8a**[9] in ether–methanol at 0 °C nitrogen is evolved and the ether **9a** is produced in 78% yield. It is necessary to use a large excess of diazo compound, since the boron species that is liberated reacts



1 2



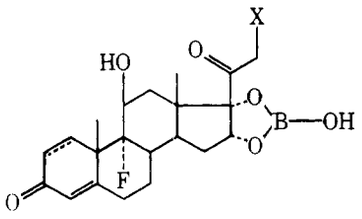
3 4



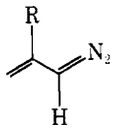
5

rapidly with diazo compounds. We have generally utilized 7–8 mol of the urethane or urea intermediate to the diazo compound for each mole of steroidal borate.

Epoxidation of acetate **10a** with *m*-chloroperbenzoic acid proceeded slowly to give epoxide **12a** (25.6% after 19 h at ambient temperature). Cleavage of **12a** with periodic acid in aqueous tetrahydrofuran gave aldehyde **15a** (53.2%), which existed as the corresponding lactol **21** both in the solid state and in solution (as evidenced by its IR spectrum in KBr and its ^{1}H NMR spectrum in Me_2SO, respectively). This material was converted to the dioxin **18a** (53%) when refluxed for 24 h in benzene with *p*-toluenesulfonic acid (TsOH).



6, X = OH
7, X = Cl ($\Delta^{1,4}$-)



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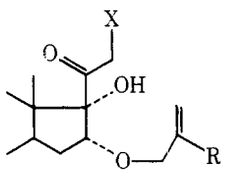
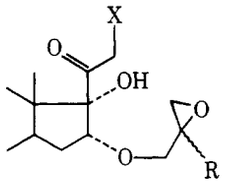
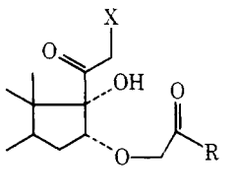


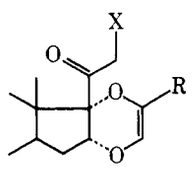
9, X = OH
10, X = OAc
11, X = Cl ($\Delta^{1,4}$-)



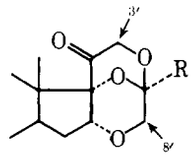
12, X = OAc
13, X = Cl ($\Delta^{1,4}$-)



14, X = OH
15, X = OAc
16, Cl ($\Delta^{1,4}$-)

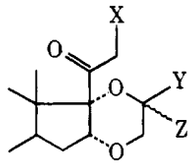


17, X = OH
18, X = OAc
19, X = Cl ($\Delta^{1,4}$-)

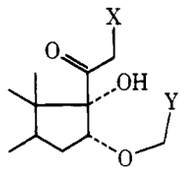


20
a, R = H
b, R = CH_3
c, R = C_6H_5
d, R = $(CH_3)_3C$

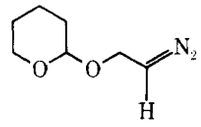
Similar sequences utilizing diazoalkenes **8b–d** provided the corresponding dioxins **18b–c** and **19a–d.** Interestingly, each step of the sequence **10** → **12** → **15** → **18** (21-acetate series) and **11** → **13** → **16** → **19** (21-chloro series) proceeded faster and in better yield with the methyl- and phenyl-substituted derivatives than in the unsubstituted series. This is undoubtedly due to the ability of these substituents to stabilize an adjacent positive charge. In the *tert*-butyl series, epoxidation proceeded rapidly, but the periodic acid cleavage and subsequent cyclization were slower than the unsubstituted case. Thus, the rate enhancement expected for an alkyl substituent is offset by the steric effect of the *tert*-butyl group on nucleophilic attack at the adjacent carbon atom.



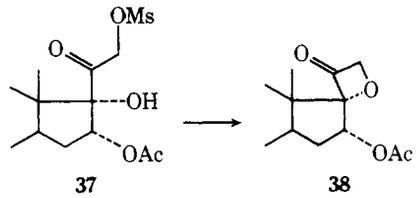
21, X = OAc; Y = OH; Z = H
22, X = OH; Y = OH; Z = H
23, X = OAc; Y = Z = =O
24, X = OH; Y = OEt; Z = H
25, X = OAc; Y = OAc; Z = H
26, X = OAc; Y = Z = H
27, X = Cl ($\Delta^{1,4}$-); Y = Z = H



28, X = OH; Y = $CH(OEt)_2$
29, X = OAc; Y = CH_2OH
30, X = OH; Y = CH_2OThp
31, X = OAc; Y = CH_2OMs
32, X = Cl ($\Delta^{1,4}$-); Y = CH_2OThp
33, X = Cl ($\Delta^{1,4}$-); Y = CH_2OH
34, X = Cl ($\Delta^{1,4}$-); Y = CH_2OMs



$(EtO)_2CHCHN_2$ 35 36



37 38

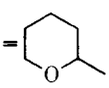
Ms = CH_3SO_2 Thp = 

Table I

Registry no.	Compd	Mp, °C	Anal[a]	C-18	C-19	16α-(OCCCH$_3$)	Solvent
57331-56-3	**11b**	238–240	C, H, Cl, F	0.83	1.47	1.52	D[b]
	13b	193–236	C, H, Cl, F	0.95	1.51	1.27, 1.31[c]	C[d]
57331-58-5	**16b**	226–227	C, H, Cl, F	0.94	1.53	2.00	C
57331-26-7	**19b**	259–260	C, H, Cl, F	1.03	1.48	1.68	D
59648-62-3	**20b**	248–250	C, H, F	1.45	1.55	1.39	C
57331-37-0	**27**	320–321	C, H, Cl, F	0.82	1.45		D
57331-75-6	**33**	226–228	C, H, Cl, F	0.85	1.49		D
4524-39-4	**43**			0.94	1.53		C
	43			0.82	1.48		D

[a] Satisfactory analytical data (±0.4% for C, H, and halogens) reported for all new compounds listed in the table. [b] D = dimethyl-d_6 sulfoxide. [c] Diastereomeric mixture of epoxides. [d] C = chloroform.

Reaction of the 21-hydroxydioxins **17b–c** (prepared by saponification of the corresponding 21-acetates **18b–c**) with TsOH in refluxing benzene gave the internal ketals **20b–c.** Similar treatment of lactol **22** gave **20a.**

Aldehydes such as **14–16a** proved to be versatile intermediates to substituted dioxanes. Oxidation of **15a** with Fetizon's reagent[10] (Ag_2CO_3/Celite) slowly gave the lactone **23** with no oxidation of the 11β-hydroxyl group. A better preparation of such aldehydes is provided by reaction of borates with diazoacetal **35**[11] followed by acid hydrolysis. Reaction of borate **6** with diazo acetal **35** gave the acetal **28;** hydrolysis of **28** with aqueous acid gave lactol **22,** while treatment with TsOH in benzene gave the cyclic acetal **24.** Acetylation of **22** gave the lactol acetate **25** as a mixture of epimers.

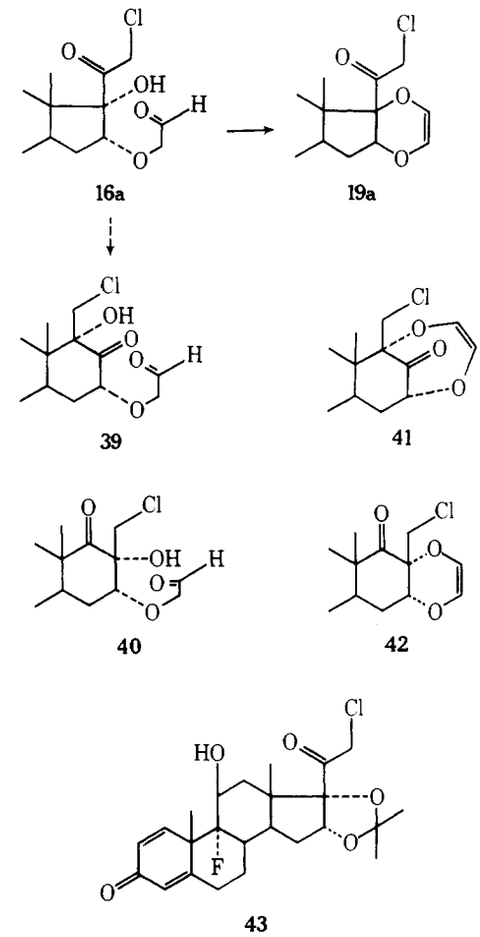
Reduction of **15a** with sodium borohydride in methanol gave the β-hydroxy ether **29** (30%). A better route to **29** involved diazo acetal **36,** prepared from glycolonitrile via the tetrahydropyranyl ether of ethanolamine.[12] Reaction of **6** with **36** gave the tetrahydropyranyl ether **30,** which could be converted to **29** by acetylation followed by hydrolysis with aqueous acetic acid. Treatment of the corresponding mesylate **31** with dry $NaHCO_3$ in Me_2SO[13] gave the parent dioxane **26.** A similar sequence proceeding from borate **7** gave the mesylate **34.** In view of the conversion of **37** to oxetanone **38** with $NaHCO_3$ in Me_2SO,[13] we were concerned that oxetanone formation might intervene in the case of **34** also; however, treatment of **34** smoothly gave dioxane **27.** Apparently the kinetic preference[14] for formation of six- vs. four-membered rings is responsible for this observation.

D-Ring Structure. D-Homoannelation of 17α-hydroxy-20-keto steroids under acidic or basic conditions is well documented.[15] All of the conditions utilized for ring closure in this work, therefore, had the potential for first D-homoannelating the steroid, as illustrated in Scheme I for **16a,** to eventually form either a dioxepin (**41**) or a rearranged dioxin (**42**), rather than the normal dioxin **19a.** The ^{1}H NMR spectrum of **19a** exhibits a coupling constant of 18 Hz between the magnetically nonequivalent C-21 methylene hydrogens (4.50 and 4.71 ppm), indicating that the C-20 carbonyl group is still adjacent to this methylene group[16] as it is in **16a** (J = 16 Hz, 4.28 and 4.99 ppm). The coupling constant anticipated for the C-21 methylene group of **41** or **42** is ca. 12 Hz; further, the chemical shift of this group would be expected ca. 0.6 ppm upfield[17] from that in normal 21-chloro-20-ketones. Similar coupling constants (16–18 Hz) are exhibited by **18c, 20b,** and **26.**

Further evidence for the normal D-ring structure of these compounds is provided by CD spectra. Compounds **19d** and **27** exhibit the expected[18] positive maxima at ca. 300 nm ($[\theta]_{306}$ = +15 900 and $[\theta]_{304}$ = +10 500, respectively). For comparison, dioxolane **43** exhibits $[\theta]_{300}$ = +12 080.

The IR, UV, and NMR spectra of these compounds were all in accord with the assigned structures. Table I illustrates the effect of selected substitutions on C-18 and C-19 chemical shifts as compared with the dioxolane **43.** Only in the case of bicyclo[3.3.1]nonane derivatives such as **20b** is the C-18 resonance affected in any major way; the restricted conformation of the C-4′ carbonyl is responsible for this downfield shift of 0.51 ppm.

Scheme I



Summary

A novel class of annelated steroids has been prepared for the first time and characterized. The reaction of steroidal cycloborates with diazoalkanes discovered by Fried and Thomas has been utilized as the key step in a regioselective alkylation of 11β,16α,17,21-tetrahydroxy steroids. Conversion of these intermediates to steroidal [16α,17-b]dioxanes may be effected in a variety of ways. The integrity of the D ring of the resultant compounds was demonstrated by NMR and CD spectroscopy.

Experimental Section

All boiling points and melting points are uncorrected. Melting points were determined on a Thomas-Hoover capillary apparatus. NMR spectra were obtained on a Perkin-Elmer R-12B in either Me_2SO-d_6 or $CDCl_3$. CD spectra were determined on a Cary 60 in dioxane (c 0.022–0.066). IR spectra were determined on a Perkin-Elmer 621 in KBr. Column chromatography was performed with dry packed columns of J. T. Baker silica gel, 60–200 mesh.

21-Chloro-9-fluoro-11β,16α,17-trihydroxypregna-1,4-diene-3,20-dione 16,17-Cycloborate (7). A solution of 15.0 g of 21-chloro-9-fluoro-11β,16α,17-trihydroxypregna-1,4-diene-3,20-dione[10] and 60 g of boric oxide in 750 mL of methanol was refluxed for 1 h, cooled to 30 °C, and diluted with 1.5 L of water. The resulting solid was filtered and dried in vacuo to give 13.85 g (86.5%) of borate **7**.

Anal. Calcd for $C_{21}H_{25}BClFO_6$: B, 2.56. Found: B, 2.37.

3-Diazo-2-phenylpropene (8c) and 3-Diazo-2-*tert*-butylpropene (8d). Utilizing the general procedure of ref 9, 3-bromo-2-phenylpropene[20] and 2-bromomethyl-3,3-dimethyl-1-butene[21] were converted into **8c** and **8d**, respectively.

16α-(Allyloxy)-9-fluoro-11β,17,21-trihydroxypregn-4-ene-3,20-dione (9a). A total of 11.8 g (0.028 mol) of **6** was added in portions to a stirred solution of 3-diazopropene (**8a**) in 250 mL of ether (prepared from 0.22 mol of ethyl *N*-allylcarbamate[9]) to which 50 mL of methanol had been added at 0 °C. After nitrogen evolution ceased the solvent was removed in vacuo, the residue was dissolved in chloroform–hexane (4:1) and chromatographed on a 220-g silica gel column. Elution with chloroform gave 9.5 g (78%) of TLC pure **9a** after crystallization from acetone–hexane. Recrystallization of a similar sample from acetone–hexane gave the analytical sample, mp 199–201 °C.

Anal. Calcd for $C_{24}H_{33}FO_6$: C, 66.04; H, 7.62; F, 4.35. Found: C, 65.82; H, 7.83; F, 4.24.

21-(Acetyloxy)-9-fluoro-11β,17-dihydroxy-16α-(oxiranylmethoxy)pregn-4-ene-3,20-dione (12a). A solution of 6.44 g (0.013 mol) of **10a** (mp 189–191 °C, prepared by acetylation of **9a** with acetic anhydride–pyridine) in 150 mL of dichloromethane was stirred with 2.88 g (0.0143 mol) of *m*-chloroperbenzoic acid for 19 h at room temperature. The resulting solution was washed with a mixture of 10% potassium carbonate solution and 10% sodium sulfite solution, dried, and evaporated in vacuo. The residue was dissolved in dichloromethane and chromatographed on a 125-g silica gel column. Elution with chloroform and chloroform–ethyl acetate mixtures gave successively 3.5 g of unreacted starting material and 1.7 g (25.6%) of TLC pure **12a**. Two recrystallizations from acetone–hexane gave the analytical sample, mp 191–192.5 °C.

Anal. Calcd for $C_{26}H_{35}FO_8$: C, 63.15; H, 7.13; F, 3.84. Found: C, 63.17; H, 6.84; F, 3.64.

21-(Acetyloxy)-9-fluoro-5′ε,11β-dihydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,20-dione (21). A solution of 20.1 g of crude **12a** in 300 mL of tetrahydrofuran was stirred with a solution of 30 g of periodic acid in 75 mL of water for 6.75 h. The solution was diluted with water and extracted with chloroform. The chloroform extract was washed with 5% sodium bicarbonate solution, dried, and evaporated in vacuo to give 18.2 g of crude product. This material was dissolved in 60 mL of dichloromethane and chromatographed on a 450-g silica gel column. Fractions of 250 mL were collected as the column was eluted successively with 3 L each of dichloromethane, chloroform, and 19:1 chloroform–ethyl acetate. Fractions 17–21 were combined and evaporated in vacuo to give 4.4 g of recovered **10a**. Fractions 23–31 were combined and evaporated in vacuo to give 8.1 g of slightly impure **21** (53.2%). A portion of this material was recrystallized from acetone–hexane and then from acetonitrile to give the analytical sample, mp 205–208 °C.

Anal. Calcd for $C_{25}H_{33}FO_8$: C, 62.10; H, 7.50; F, 3.93. Found: C, 62.22; H, 7.28; F, 3.69.

21-(Acetyloxy)-9-fluoro-2′,3′-dihydro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxin-3,20-dione (18a). A slurry of 100 mg of TsOH in 250 mL of benzene was distilled to a volume of 200 mL and 1.0 g (0.0021 mol) of **15a** added. The resulting solution was refluxed with a Dean–Stark trap filled with Linde 4A molecular sieves for 24 h under nitrogen. The solution was then cooled, diluted with chloroform, washed with 5% sodium bicarbonate solution, and dried. The residue obtained on solvent removal in vacuo was chromatographed on a 20-g silica gel column. Elution with 1:1 dichloromethane–chloroform gave 510 mg (53%) of TLC pure **18a**. Two recrystallizations from acetone–hexane gave the analytical sample, mp 231–240 °C dec.

Anal. Calcd for $C_{25}H_{31}FO_7$: C, 64.92; H, 6.76; F, 4.11. Found: C, 64.64; H, 6.54; F, 3.90.

9-Fluoro-11β-hydroxy-1′α-methylandrost-4-eno[17β,16α-*e*]-2,7,9-trioxabicyclo[3.3.1]nonane-3,4′-dione (20b). A slurry of 150 mg of TsOH in 600 mL of benzene was distilled to a volume of 500 mL, Linde 4A molecular sieves added to the trap, and the solution refluxed for 30 min. The solution was cooled and 775 mg of **17b** (prepared in 96% yield by hydrolysis of **18b** with 10% aqueous potassium carbonate in methanol) added. The resulting slurry was refluxed for 1 h and the benzene evaporated in vacuo. The residue was dissolved in chloroform, washed with 5% sodium bicarbonate solution and water, dried, and evaporated in vacuo. The residue was dissolved in chloroform and chromatographed on a 40- g silica gel column. Elution with chloroform gave 580 mg (74.8%) of material that was recrystallized twice from acetone–hexane to give the analytical sample of **20b** (375 mg), mp 248–256 °C dec.

Anal. Calcd for $C_{24}H_{31}FO_6$: C, 66.34; H, 7.19; F, 4.37. Found: C, 66.06; H, 7.18; F, 4.18.

9-Fluoro-5′ε,11β,21-trihydroxypregn-4-eno[16α,17-*b*][1,4]-dioxane-3,20-dione (22). A solution of 1.6 g (0.0031 mol) of **28** in 200 mL of tetrahydrofuran was refluxed with 20 mL of 1 N hydrochloric acid for 3 h. The solution was cooled, evaporated in vacuo to one-third the original volume, and diluted with water. The resulting solid was filtered and dried in vacuo to give 800 mg (58.9%) of product. Recrystallization from methanol gave 350 mg of **22**, mp 260–262 °C dec.

Anal. Calcd for $C_{23}H_{31}FO_7$: C, 63.00; H, 7.13; F, 4.33. Found: C, 62.96; H, 7.07; F, 4.48.

21-(Acetyloxy)-9-fluoro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,5′,20-trione (23). A solution of 1.2 g (0.0025 mol) of **21** in 250 mL of toluene, slurried with 22 g of Fetizon's reagent,[10] was distilled to a volume of 200 mL. The resulting slurry was refluxed under nitrogen for 12.5 h, cooled, and filtered, and the solid washed well with chloroform. The filtrate and washings were combined and evaporated in vacuo, and the residue was chromatographed on a 40-g silica gel column. Elution with chloroform gave 270 mg (22.6%) of oil, which crystallized from acetone–hexane to give 181 mg of TLC pure solid. Recrystallization from acetone–hexane gave the analytical sample of **23**, mp 217–220 °C dec.

Anal. Calcd for $C_{25}H_{31}FO_8$: C, 62.75; H, 6.53; F, 3.97. Found: C, 62.61; H, 6.53; F, 3.73.

5′ε-Ethoxy-9-fluoro-11β,21-dihydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,20-dione (24). A slurry of 100 mg of TsOH in 250 mL of benzene was distilled to 200 mL and Linde 4A molecular sieves added to the trap. After 30 min at reflux, the solution was cooled and 2 g (0.0039 mol) of **28** added. The resulting slurry was refluxed for 2 h under nitrogen, cooled, diluted with chloroform, washed with 5% sodium bicarbonate solution and water, dried, and evaporated. The crude residue (2.25 g) was dissolved in chloroform and chromatographed on a 100-g silica gel column. Elution with chloroform and 4:1 chloroform–ethyl acetate gave a total of 1.33 g (73.5%) of TLC pure material. Two recrystallizations from acetone–hexane (the last with charcoal) gave the analytical sample of **24**, mp 248–250 °C dec.

Anal. Calcd for $C_{25}H_{35}FO_7$: C, 64.64; H, 7.16; F, 4.10. Found: C, 64.75; H, 7.02; F, 3.95.

5′,21-Bis(acetyloxy)-9-fluoro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,20-dione (25). A solution of 1.3 g of **22** in 10 mL of pyridine was kept for 4 h at ambient temperature with 5 mL of acetic anhydride. The solvent was removed in vacuo and the residue dissolved in chloroform, washed with dilute hydrochloric acid, and dried. The solvent was removed in vacuo and the residue dissolved in chloroform and chromatographed on a silica gel column. Elution with chloroform gave 506 mg of TLC pure material. Recrystallization from acetone–hexane gave the analytical sample of **25**, mp 195–197 °C.

Anal. Calcd for $C_{27}H_{35}FO_9$: C, 62.42; H, 6.21; F, 3.66. Found: C, 62.37; H, 6.44; F, 3.61.

21-(Acetyloxy)-9-fluoro-11β-hydroxypregn-4-eno[16α,17-*b*][1,4]dioxane-3,20-dione (26). A solution of 521 mg (0.000 93 mol) of **31** (prepared as described below for **34** by reaction of **6** with **36** followed by acetylation, hydrolysis, and mesylation) in 40 mL of dimethyl sulfoxide was stirred at 110 °C under nitrogen for 2 h with 600 mg of sodium bicarbonate (dried at 110 °C in vacuo). The solution was cooled, poured into 5% hydrochloric acid, and extracted with chloroform. The chloroform extract was washed twice with 2% hydrochloric acid, dried, and evaporated in vacuo to give 421 mg of oil. This material was chromatographed on a 20-g silica gel column. Elution with chloroform gave 331 mg (76.6%) of TLC pure material which solidified. Recrystallization from acetone–hexane gave 215 mg, mp 275–280 °C dec.

Anal. Calcd for $C_{25}H_{33}FO_7$: C, 64.64; H, 7.16; F, 4.09. Found: C, 64.59; H, 7.21; F, 3.98.

16α-(2,2-Diethoxyethoxy)-9-fluoro-11β,17,21-trihydroxy-

pregn-4-ene-3,20-dione (28). A solution of 2,2-diethoxy-1-diazoethane (prepared[11] from 0.0935 mol of *N*-2,2-diethoxyethylurea) in 300 mL of 3:2 ether–pentane was diluted with 100 mL of methanol and stirred at 0 °C. A total of 5.5 g (0.013 mol) of **6** was added in portions until nitrogen evolution stopped. The solvent was removed in vacuo and the residue recrystallized from methanol to give 3.4 g (51%) of slightly impure material. This was dissolved in chloroform and chromatographed on an 80-g silica gel column. Elution with chloroform gave 2.95 g, which was recrystallized from acetone–hexane to give the analytical sample (2.6 g), mp 208–210 °C.

Anal. Calcd for $C_{21}H_{41}FO_8$: C, 63.26; H, 8.07; F, 3.71. Found: C, 63.03; H, 7.86; F, 3.79.

21-Chloro-9-fluoro-11β,17-dihydroxy-16α-(2-mesyloxyethoxy)pregna-1,4-diene-3,20-dione (34). Reaction of **7** with **36** as described for **6** and **8a** gave **32** (mp 168–170 °C, 51.8%). Hydrolysis of **32** was effected by stirring a 5% solution in acetic acid–water (2:1) for 6 h, diluting with water, and recrystallizing the resulting solid from acetone–hexane to give the alcohol **33** (mp 226–228 °C, 53%).

A solution of 1.5 g (0.003 28 mol) of **33** in 25 mL of pyridine was cooled to 0 °C and 0.6 mL of methanesulfonyl chloride added. After 2 h the mixture was poured into cold dilute hydrochloric acid and extracted with chloroform. The chloroform solution was dried and evaporated in vacuo to 2.0 g of crude mesylate **34.**

21-Chloro-9-fluoro-11β-hydroxypregna-1,4-dieno[16α,17b][1,4]dioxane-3,20-dione (27). A solution of 2.0 g of crude **34** in 100 mL of dimethyl sulfoxide was stirred at 110 °C under nitrogen with 2.0 g of sodium bicarbonate (dried at 110 °C in vacuo). After 1 h the slurry was cooled, poured into 2 L of 2.5% hydrochloric acid, and extracted with chloroform. The chloroform solution was washed twice with dilute hydrochloric acid, dried, and evaporated in vacuo to give 1.4 g of crude product. This material was dissolved in chloroform and chromatographed on a 100-g silica gel column. Elution with chloroform gave 880 mg (62%) of material which crystallized from methanol–chloroform to give 405 mg of the analytical sample of **27,** mp 320–321 °C dec.

Anal. Calcd for $C_{23}H_{28}ClFO_5$: C, 62.94; H, 6.43; Cl, 8.08; F, 4.33. Found: C, 62.73; H, 6.20; Cl, 8.27; F, 4.27.

16α-(Acetyloxy)-9-fluoro-17,21-epoxy-11β-hydroxypregna-1,4-diene-3,20-dione (38). A solution of 3.0 g (0.0058 mol) of **37** (prepared by mesylation of triamcinolone 16-acetate[17]) in 70 mL of dimethyl sulfoxide was stirred at 130 °C under nitrogen for 2 h with 3.0 g of sodium bicarbonate (dried at 110 °C in vacuo). The reaction mixture was cooled, poured into cold 5% hydrochloric acid, and extracted with chloroform. The chloroform extract was dried and evaporated to give 4.2 g of oil. This was chromatographed on a 110-g silica gel column. Elution with 9:1 chloroform–hexane gave 1.1 g (45.2%) of TLC pure solid. Two recrystallizations from acetone–hexane gave the analytical sample of **38,** IR (KBr) 1810 cm^{-1}, mp 286–287 °C dec.

Anal. Calcd for $C_{23}H_{27}FO_6$: C, 66.01; H, 6.54; F, 4.54. Found: C, 65.78; H, 6.64; F, 4.33.

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