hydrofuran (50 mL). The mixture was refluxed for 1 h, the solution cooled, excess NaH filtered off, solvent evaporated at low temperature (~35 °C), and the resulting syrup cleaned by analytical LC (EtOAc–hexanes, 1:2), using a silica gel column, to give **16** in 90% yield: $[\alpha]^{25}{}_D$ +31.2° (*c* 0.52, chloroform); ^1H NMR ($CDCl_3$) δ 7.55–7.02 (12 H, m, aromatic H), 5.42 (1 H, d, $^4J_{1,3}$ = 4 Hz, H-1), 4.58–3.57 (12 H, m, H-2, H-3, H-4, H-5, CH_2O, $CH_2C_6H_4Br$); ^{13}C NMR ($CDCl_3$) 137.59, 137.30, 136.88 (aromatic C-1), 131.92, 131.80 (aromatic C), 107.15 (C-1), 81.88, 80.33 (C-2, C-3), 76.36, 74.97, 73.96, 72.87, 71.75 (C-4, C-5, OCH_2), 71.40 (C-6).

Anal. Calcd for $C_{27}H_{25}Br_3O_5$ (**16**): C, 48.46; H, 3.77. Found: C, 48.30; H, 3.66.

Acknowledgment. This work was supported by a research Grant 5 R01 GM 06168 of the National Institutes of Health, U.S. Public Health Service, which is gratefully acknowledged. Helpful discussions with Drs. Ronald Eby and Hiroshi Ito are also gratefully acknowledged.

Registry No. 2, 20231-36-1; **3**, 75961-95-4; **4**, 75961-96-5; **5**, 67381-27-5; **6**, 73415-94-8; **7**, 73045-61-1; **8**, 75961-97-6; **9**, 73045-58-6; **10**, 75961-98-7; **11**, 75961-99-8; **12**, 75962-00-4; **13**, 75975-13-2; **14**, 75962-01-5; **15**, 75962-02-6; **16**, 75962-03-7; dibutyltin oxide, 818-08-6; allyl bromide, 106-95-6; benzyl chloride, 100-44-7; *p*-bromobenzyl bromide, 589-15-1.

16β-Alkoxy-17aα-hydroxy-*D*-homo-17-oxapregnan-20-ones: Preparation, Chemistry, and X-ray Crystallographic Analysis

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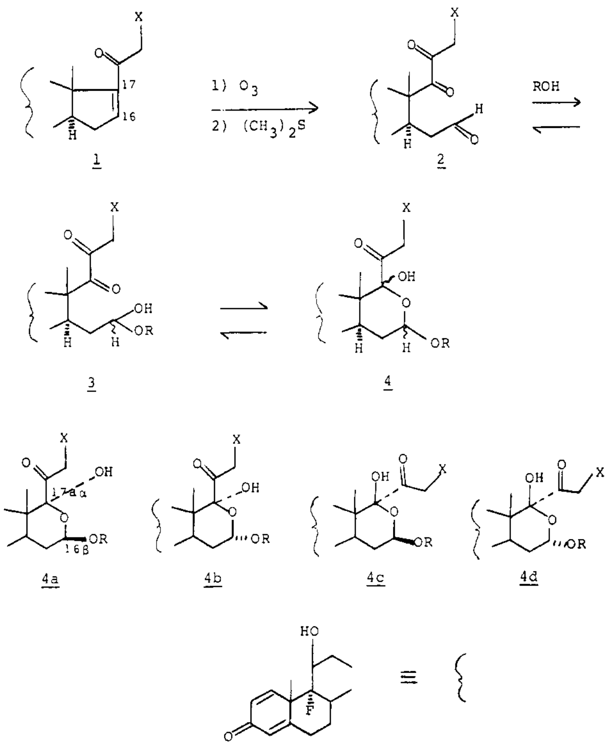
Ozonolysis of certain Δ^{16}-20-oxopregnanes in mixtures of dichloromethane–lower alkanol leads, after reductive workup with dimethyl sulfide, to novel derivatives of the 16β-alkoxy-17aα-hydroxy-*D*-homo-17-oxapregnane system. Under appropriate acidic conditions both the 16β-alkoxyl and 17aα-hydroxyl groups of these compounds can be replaced by alkoxyl groups derived from the solvent. The results of X-ray analysis of the 21-bromo derivative **4a** (X = Br, R = Me) define the stereochemistry as 16β-methoxy-17aα-hydroxy. Comparison of the spectroscopic and physical properties of **4a** (X = Br, R = Me) and the rest of the compounds prepared strongly supports an analogous assignment. X-ray analysis also reveals an unprecedented (solid state) conformation for the C-17a side chain when compared to those of normal pregnan-20-ones.

Our interest in the chemistry of Δ^{16}-20-oxo steroids[1] led us to examine the ozonolysis of triene 1. After reductive workup, a single product was obtained that we have characterized as a *D*-homo-17-oxapregnane by chemical and spectroscopic means. Confirmation of this assignment, definition of the 17a stereochemistry, and demonstration of an unprecedented C-17a side chain conformation have been provided by X-ray analysis of a 21-bromo derivative. At this time we detail these studies.

Results and Discussion

Preparation and Chemistry. Treatment of 1 (X = AcO) in dichloromethane–methanol (2:1) at −78 °C with 1.1 equiv of ozone, followed by immediate reductive workup[2] with a large excess of dimethyl sulfide, gave a single product (75%) after chromatography on silica gel. Elemental analysis indicated that the elements of O_2 and MeOH had been incorporated. Cursory examination of the ^1H NMR spectrum confirmed the addition of methanol (singlet at 3.23 ppm) to the functionality resulting from oxidation of the Δ^{16}-olefin (since the signals attributable to the $\Delta^{1,4}$-3-ketone moiety were present). At this point we reasoned that a sequence of reactions similar to those of Scheme I had occurred to produce 4 from 1. Further examination of the ^1H NMR spectrum of 4 strongly suggested that the C16 hydrogen was axial (4.80 ppm, broadened d, $J_{15,16}$ = 10 Hz), eliminating structures **4b** and **4d** from consideration and narrowing the possibilities to **4a** or **4c**. Consideration of the "anomeric effect"[3] led us

Scheme I



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[2] P. S. Bailey, "Olefinic Compounds", Vol. I, Academic Press, New York, 1978, p 149.

Table I. Physical and Spectroscopic Properties

no.[a]	X	R	mp, °C	$[M]^{25}_D$,[b]	C-18[c]	C-19[c]	OMe[c]	16α-H[c,d]	17aα-OH[c]
4a	AcO	Me	170–172	−157	1.15	1.46	3.35	4.80	6.85
4a	Cl	Me	181–183	−142	1.11	1.47	3.35	4.80	6.88
4a	Br	Me	193–195	−126	1.11	1.46	3.36	4.80	6.89
4a	Cl	Et	171–173	−165	1.11	1.45		4.91	6.84
4a	Cl	Me_2CH	238–240	−181	1.10	1.46		4.94	6.78
4a	Cl	Me_3C	170–173	−143	1.10	1.46		~5.15[e]	6.78
5a	AcO	Me	225–227	−213	1.12	1.46	3.08, 3.42	4.94	
5a	Cl	Me	228–230	−212	1.12	1.44	3.07, 3.42	4.69	
5a	Cl	Et	218–220	−220	1.11	1.44		~4.70[f]	
5a	Cl	Me_2CH	258–260	−246	1.06	1.43		4.8[f]	

[a] Satisfactory analytical data (±0.3% for C, H, and halogens) reported for all compounds in the table. [b] In degrees; in $CHCl_3$, c = 0.42–0.67. [c] Chemical shifts (parts per million from Me_4Si) in solvent Me_2SO-d_6. [d] Broadened doublet ($J_{15\beta,16\alpha}$ = 9–10 Hz). [e] Overlaps with C11 OH, multiplet. [f] Overlaps with C-21 methylene, multiplet.

provisionally to assign an axial 17a-hydroxyl as depicted in **4a**. The exciting possibility that the novel 17aα-hydroxy-*D*-homo-17-oxapregnan-20-one system preferred to adopt the 17a configuration of "natural" corticosteroids prompted us to seek additional evidence for this assignment.

Ozonolysis of **1** (X = Cl) in dichloromethane–methanol (2:1) or dichloromethane–ethanol (2:1) gave, in each case, a single product assigned structure **4a** (X = Cl, R = Me or Et, respectively). Similarly, ozonolysis of **1** (X = Cl) in dichloromethane–*tert*-butyl alcohol (4:1) gave **4a** (X = Cl, R = Me_3C) in 23% yield after extensive purification. Interestingly, careful recrystallization of **4a** (X = Cl, R = Me_3C) from dichloromethane–methanol gave an analytical sample with only slight conversion to **4a** (X = Cl, R = Me). Repeated recrystallization did, however, lead to significant exchange of methanol for *tert*-butyl alcohol (monitored by ^1H NMR).

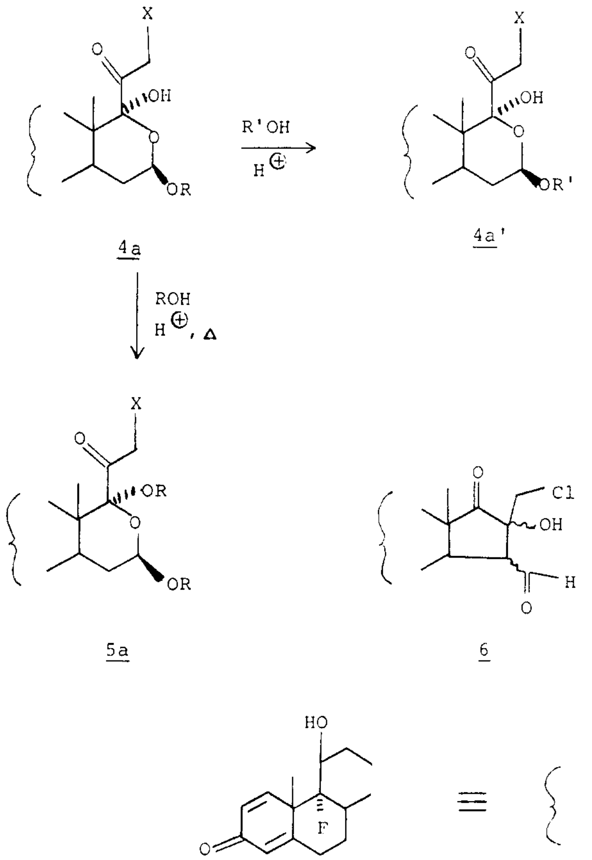
Alkoxyl exchange could be effected preparatively with acid catalysis. Stirring a dilute solution of **4a** (X = Cl, R = Et) in 2-propanol with 0.7 equiv of *p*-toluenesulfonic acid (TsOH; room temperature, 3.5 days) gave a 70% yield of **4a** (X = Cl, R = Me_2CH) in addition to a second component. Elemental analysis of this latter substance suggested the conversion of the hemiketal moiety of **4a** to the mixed ketal **5a** (Scheme II). ^1H NMR indicated its formulation as **5a** (X = Cl, R = Me_2CH) due to the typical appearance of the C16 axial hydrogen. When a more concentrated solution of **4a** (X = Cl, R = Et) in 2-propanol was refluxed with 1.1 equiv of TsOH, **4a** (X = Cl, R = Me_2CH; 17%) and **5a** (X = Cl, R = Me_2CH; 35%) were isolated in addition to a third component (28%). Elemental analysis and spectroscopic properties of this substance are consistent with the simple aldol product **6**.

When a 0.1 M solution of **4a** (X = AcO, R = Me) in methanol was refluxed for 90 min with 0.1 equiv of TsOH, a mixture of compounds was produced. Chromatography, followed by fractional crystallization, gave the major product **5a** (X = AcO, R = Me) in ca. 50% yield.

Similar reactions of **4a** (X = Cl, R = Et) with methanol and ethanol gave single major products assigned structures **5a** (X = Cl, R = Me and Et, respectively). A reaction with phenol gave no indication of ketal formation; the only product isolated was **6**.

An interesting feature of the ^1H NMR spectra of the ethoxy derivatives **4a** and **5a** (X = Cl, R = Et) is the complex appearance of the methylene groups (CH_3CH_2O), This can be clearly seen in **4a** (X = Cl, R = Et) where a quartet of quartets is observed between 3.36 and 4.00 ppm. Calculations utilizing a chemical shift difference of 31 Hz between the diastereotopic methylene hydrogens (with J_{gem} = −10.1 Hz and J_{vic} = 7.1 Hz) reproduce this pattern quite well. This region of the spectrum in **5a** (X = Cl, R = Et) is more complex, suggesting magnetic nonequivalence of both sets of methylene hydrogens. This phenomenon has been noted previously and analyzed in the same manner as indicated here.[4]

Scheme II



17a Stereochemistry. The ^1H NMR data of Table I suggest that both hemiketals **4** and mixed ketals **5** belong to the same stereochemical series. The molecular rotation data of Table I are not inconsistent with this conclusion. In an attempt to provide more convincing evidence for the stereochemical assignment at C-17a, we have examined the CD spectra of **4a** and **5a** (X = Cl, R = Et). Both compounds exhibit small negative maxima close to 300 nm in methanol (**4a**, [Θ] −346 at 298 nm; **5a**, [Θ] −573 at 303 nm). 17β-Pregnan-20-ones usually exhibit large positive maxima ([Θ] ~10 000) at 300 nm while 17α-pregnan-20-ones exhibit similarly large negative maxima in the same region.[5]

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(3) B. Capon, *Chem. Rev.*, **69**, 407 (1969).

(4) F. Kaplan and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 4666 (1961).

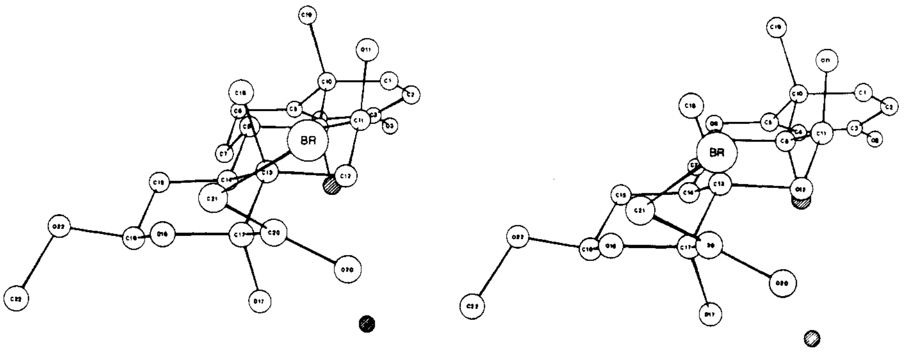

Figure 1. Stereoview of **4a** (X = Br, R = Me) illustrating the C-17a side chain conformation.

Table II. Dihedral Angles of the Pyranose Ring and Its Substitutents

atoms	angle, deg	atoms	angle, deg
C13-C14-C15-C16	-54	C13-C17-C20-O20	-86
C14-C15-C16-O16	55	C13-C17-C20-C21	101
C15-C16-O16-C17	-57	O20-C20-C21-Br	33
C16-O16-C17-C13	60	C17-C20-C21-Br	-156
O16-C17-C13-C14	-56	O16-C17-C20-O20	153
C17-C13-C14-C15	54	O16-C17-C20-C21	-20
C8-C14-C13-C17	179	C17-O16-C16-O22	-172
C8-C14-C15-C16	-177	C14-C15-C16-O22	167
C12-C13-C17-O16	-178	C15-C16-O22-C22	171
C12-C13-C17-C20	65	O16-C16-O22-C22	-71
C12-C13-C17-O17	-61	C16-O16-C17-O17	-58
C14-C13-C17-C20	-172	C16-O16-C17-C20	-178
C14-C13-C17-O17	62	O17-C17-C20-O20	37
C18-C13-C17-O16	60	O17-C17-C20-C21	-135
C18-C13-C17-C20	-57		
C18-C13-C17-O17	177		

Unable to make a clear assignment by CD spectroscopy, we prepared a derivative for X-ray analysis. Ozonolysis of 1 (X = Br) in dichloromethane–methanol gave a single product assigned structure **4a** (X = Br, R = Me). This assignment is supported by the ^{1}H NMR and molecular rotation data of Table I that show marked similarity for **4a** (R = Me, X = AcO, Cl, and Br).

The results of this X-ray analysis confirm the initial assignment of structure **4a** to this series of compounds and by extension support the analogous formulation of the mixed ketals as **5a**.

X-ray Results. Several features of the structure of **4a** (X = Br, R = Me) deserve comment. Interest was focused on the trans-fused pyranose ring and its substituents which are present in this *D*-homo-17-oxa steroid rather than the usual trans-fused five-membered carbocyclic D ring of other steroids. As the hemiketal hydroxyl (O17) has the α configuration, with the C17 side chain in the usual β configuration, the structure may be compared directly with the many other structures of pregnane derivatives which have been reviewed[6] (Figure 1).

The pyranose ring exists in a chair conformation (torsional angles are given in Table II) in which all but the α-O17 and β-C18 substituents are equatorial. Of particular interest is the unusual conformation of the C17 side chain. In most pregnanes, O20 is directed *over* ring D, resulting in a positive, essentially orthogonal C13–C17–C20–O20 torsional angle (average of many structures having 17α-OH substituents = 89°).[6] Virtually the opposite side-chain conformation (C13–C17–C20–O20 = -86°; an -175° rotation about the C17–C20 bond) occurs in **4a** (X = Br, R = Me). This conformation, in which the bulkier C21 methylene group replaces O20, is expected to be more stable in a *D*-homo-17-oxa steroid than in other steroids, in view of the larger ring size and the absence of the usual axial C16 hydrogen atom adjacent to C17.[7]

The equatorial β-methoxyl group (O22–C22) of the acetal moiety imposes no *intra*molecular steric restraint on the conformation of the C17 side chain. The structural features of rings A–C and their substituents are similar to those observed in 9-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.[8]

Both hydroxyl groups appear to be hydrogen bonded to other oxygens. O11 is *inter*molecularly H bonded to O22 (2.71 Å) while O17 is probably H bonded to either O3 (*inter*molecular O–O distance = 2.86 Å, C17–O17–O3 angle = 137°) or O20 (*intra*molecular O–O distance = 2.71 Å). In any case, the unusually oriented side chain carbonyl group is not involved in any *inter*molecular H bonds. Solution conformations similar to the solid-state conformation noted here have been inferred from infrared studies[9] of 17α-hydroxy-20-oxo steroids unsubstituted at C21 and from ^{13}C NMR studies[10] of the 21-hydroxy-20-oxo steroid deoxycorticosterone.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 621 (KBr). ^{1}H NMR spectra were determined in Me$_2$SO-d_6 on Varian T-60 or Perkin-Elmer R12B spectrometers with Me$_4$Si as internal standard. Optical rotations were recorded in ethanol on a Perkin-Elmer 141 polarimeter. CD spectra were recorded in methanol on a Carey 60 (*c* 0.58–0.64 mg/mL).

General Procedure for Ozonolysis. Preparation of Hemiketals 4a. A solution of triene 1 (0.001–0.01 mol) in a mixture of 30–150 mL of dichloromethane-alcohol [MeOH plus EtOH (2:1), Me$_3$COH (4:1)] was cooled to -78 °C and a stream of 1.1 equiv of ozone in oxygen passed through. Excess ozone was removed with a stream of nitrogen and a large excess (2–5 mL) of Me$_2$S added. The solution was allowed to warm to ambient temperature and then evaporated in vacuo after 2–17 h. A solution of the residue in CHCl$_3$ was washed with water, dried (Na$_2$SO$_4$), and evaporated. The residue was either crystallized directly or after filtration through a silica gel column (ca. 20 g/g of residue) to remove polar byproducts. Yields and spectral and physical

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(7) A 16β-bromo-substituted pregnane was found to have C13–C17–C20–O20 = -5°: J. M. Ohrt, B. Hanes, A. Cooper, and D. A. Norton, *Acta Crystallogr., Sect. B*, **B24**, 312 (1968).

(8) L. Dupont, O. Dideberg, and H. Campsteyn, *Acta Crystallogr., Sect. B*, **B30**, 514 (1974).

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(10) N. S. Bhacca, D. G. Giannini, W. S. Jankowski, and M. E. Wolff, *J. Am. Chem. Soc.*, **95**, 8421 (1973).

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Table III. Fractional Atomic Coordinates and Estimated Errors

atom	*x*	*y*	*z*
Br	−0.0422 (3)	0.5622 (2)	0.4748 (3)
F	−0.1164 (0)	0.0060 (0)	0.4737 (0)
O3	−0.195 (1)	−0.2748 (9)	0.673 (1)
O11	−0.059 (1)	0.1796 (9)	0.681 (1)
O16	0.091 (1)	0.3132 (9)	0.286 (1)
O17	−0.084 (1)	0.2506 (9)	0.260 (1)
O20	−0.162 (1)	0.3981 (12)	0.374 (1)
O22	0.256 (0)	0.2610 (0)	0.212 (0)
C1	−0.129 (2)	−0.034 (1)	0.705 (2)
C2	−0.189 (2)	−0.116 (1)	0.720 (2)
C3	−0.142 (2)	−0.201 (1)	0.663 (2)
C4	−0.033 (2)	−0.195 (2)	0.598 (2)
C5	0.025 (2)	−0.114 (2)	0.581 (1)
C6	0.132 (2)	−0.105 (1)	0.525 (2)
C7	0.109 (2)	−0.028 (1)	0.431 (2)
C8	0.076 (2)	0.066 (1)	0.494 (1)
C9	−0.043 (2)	0.050 (1)	0.551 (1)
C10	−0.015 (2)	−0.022 (1)	0.645 (2)
C11	−0.103 (2)	0.141 (2)	0.584 (2)
C12	−0.118 (2)	0.212 (1)	0.487 (2)
C13	−0.001 (2)	0.231 (1)	0.435 (2)
C14	0.060 (1)	0.136 (1)	0.392 (1)
C15	0.164 (2)	0.158 (2)	0.335 (2)
C16	0.145 (1)	0.228 (1)	0.246 (2)
C17	−0.013 (2)	0.296 (1)	0.338 (2)
C18	0.085 (2)	0.284 (1)	0.516 (2)
C19	0.077 (2)	0.008 (1)	0.731 (1)
C20	−0.054 (2)	0.395 (1)	0.369 (2)
C21	0.029 (2)	0.473 (1)	0.375 (2)
C22	0.245 (2)	0.322 (2)	0.106 (2)

properties are listed in Table I.

General Preparation of Mixed Ketals 5a. A solution of 0.001–0.01 mol of hemiketal **4a** in 50–150 mL of alcohol was refluxed for 60–90 min with 10–15% TsOH by weight. The solution was cooled and poured into >10 volumes of cold water, and the product was isolated either by extraction with ethyl acetate or by filtration. Crystallization of the solid obtained either directly or by evaporation of the dried ethyl acetate solution gave mixed ketals **5a** except as noted in the Results and Discussion (see also below).

21-Chloro-9-fluoro-11β,17a-dihydroxy-16β-(1-methylethoxy)-*D*-homo-17-oxapregna-1,4-diene-3,20-dione (4a; X = Cl, R = Me_2CH). A solution of 1.63 g of **4a** (X = Cl, R = Et) in 400 mL of 2-propanol was stirred for 3.5 days with 500 mg of TsOH. The solution was poured into 2 L of water and extracted with ethyl acetate to give 1.61 g of residue. Trituration with dichloromethane gave 782 mg of TLC-homogeneous material [silica gel, chloroform–ethyl acetate (3:1) development, UV visualization]. This was combined with a further 400 mg, obtained by chromatography of the mother liquors, and recrystallized from methanol to give 844 mg of the title compound (physical and spectroscopic properties are listed in Table I).

21-Chloro-9-fluoro-11β-hydroxy-16β,17a-bis(1-methylethoxy)-*D*-homo-17-oxapregna-1,4-diene-3,20-dione (5a; X = Cl, R = Me_2CH). A solution of 1.85 g of **4a** (X = Cl, R = Et) in 50 mL of 2-propanol was refluxed for 30 min with 180 mg of TsOH. The solution was diluted with water and extracted with ethyl acetate to give a mixture of **4a** and **5a** (X = Cl, R = Me_2CH) and **6**. Chromatography on silica gel gave 713 mg of highest R_f material characterized as **5a** (Table I) after crystallization from methanol, 328 mg of **4a**, identical with material prepared above, and 515 mg of the compound with lowest R_f. Crystallization of this last compound from CH_2Cl_2–methanol gave 462 mg of **6** (X = Cl): mp 258–260 °C; IR (Nujol) 5.70, 5.80, 6.01, 6.24 μm; $[\alpha]^{25}_D$ +101° (*c* 0.067, $CHCl_3$); ^1H NMR (Me_2SO-d_6) 1.23 (3 H, s, C-18 CH_3), 1.53 (3 H, s, C19 CH_3), 3.63 (2 H, dd, *J* = 10 Hz, CH_2Cl), 9.60 ppm (1 H, d, *J* = 3 Hz, CHO).

Anal. Calcd. for $C_{21}H_{24}ClFO_5$: C, 61.39; H, 5.89; Cl, 8.63; F, 4.63. Found: C, 61.43; H, 5.88; Cl, 8.28; F, 4.90.

X-ray Analysis of 4a (X = Br, R = Me). The unit cell constants (a = 11.881 (3), b = 14.368 (4), c = 12.344 (3) Å), space group $P2_12_12_1$, and measured crystal density (1.53 g/cm^3) are consistent with one molecule ($C_{22}H_{28}BrFO_6$) per asymmetric unit. The calculated density based on four molecules in the unit cell was 1.536 g/cm^3. Small crystal size (crystals grown from CH_2Cl_2–MeOH) limited the number of observable intensities. Thus, although 1679 reflections were measured diffractometrically (Cu Kα, λ 1.5418 Å) by using the θ–2θ variable scan rate technique ($2\theta_{max}$ = 115°), only 642 were "observed" with $I > 2.5$. Errors were assigned according to $\sigma = r(C + 100(B_1 + B_2))^{1/2}$ where r is the variable scan rate and B_1, B_2, and C are the background and net counts, respectively. Background counts at both ends of the scan range were measured for $^1/_{10}$ of the total scan time.

The positions of all the nonhydrogen atoms were readily obtained by Patterson and Fourier methods. However, the severely limited number of observed intensities precluded a precise definition of the atomic parameters.

The atomic coordinates given in Table III were obtained through least-squares refinements in which the quantity minimized was $\sum w(F_o^2 - F_c^2)^2$ with $w = \sigma^{-2}$. These refinements of coordinates and anisotropic temperature parameters converged after only a few cycles to $R = \sum||F_o| - |F_c||/\sum F_o = 0.078$. A final difference map showed diffuse residual densities corresponding to some of the hydrogen atoms but no other significant peaks. Atomic scattering factors were taken from the literature.[8]

Acknowledgment. The authors are indebted to their colleagues Dr. A. I. Cohen and associates for analytical and spectroscopic data. The CD spectra were obtained through the courtesy of Dr. J. Fried.

Registry No. 1 (X = AcO), 1250-85-7; 1 (X = Cl), 69283-83-6; 1 (X = Br), 75961-82-9; **4a** (X = AcO; R = Me), 69291-31-2; **4a** (X = Cl; R = Me), 69283-57-4; **4a** (X = Br; R = Me), 75961-83-0; **4a** (X = Cl; R = Et), 69283-56-3; **4a** (X = Cl; R = Me_2CH), 69503-79-3; **4a** (X = Cl; R = Me_3C), 69283-63-2; **5a** (X = AcO; R = Me), 69283-62-1; **5a** (X = Cl; R = Me), 69283-59-6; **5a** (X = Cl; R = Et), 69283-58-5; **5a** (X = Cl; R = Me_2CH), 69283-64-3; **6**, 75961-84-1.