suggest that the acetyl group is probably moving faster than the steroid nucleus, since the observed ^{13}C and ^{1}H resonances of the $COCH_3$ side chain are consistently narrower than the ^{13}C frequencies of the rigid ring system or the ^{1}H frequencies of the methyl groups directly attached to it.

The observed differences in mobility between the two steroids in the bilayer can be explained by assuming that the variation in steroid geometry leads to different phospholipid–steroid interactions. We can thus postulate that the inactive Δ^{16}-alphaxalone interacts with the fatty acid chains of phosphatidylcholine bilayer in such a manner that the most stable bilayer geometry is maintained while the interacting steroid is partially immobilized. This interaction may be similar to the interaction of cholesterol with phospholipids, which has been previously described.[9,10] In contrast, the biologically active alphaxalone, because of its slightly different stereochemical features, interacts with the bilayer differently. Presumably, this interaction results in a disruption of the bilayer geometry, which is evidenced by the higher mobility of the incorporated steroid. The perturbation produced by the anesthetic molecule in the lipid region of the membrane could be transmitted to the membrane-associated proteins, resulting in a modification of their functions.[11]

Our results can be used to explain the different biological activities of alphaxalone and Δ^{16}-alphaxalone as anesthetics and as inhibitors of sulfate transport in the red blood cell, both of which are functions associated with a membrane-bound protein. We have recently tested on the phospholipid system described here a number of steroids structurally related to alphaxalone but having widely different anesthetic activity. The results are consistent with the hypothesis that steroid anesthetic activity depends on the ability of the drug to perturb the membrane lipids. This ability appears to be governed by strict geometric requirements.

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Articles

Modified Steroid Hormones. 7. 4-Fluoro-17β-estradiol: Carbon-13 Nuclear Magnetic Resonance, Crystal and Molecular Structure, and Biological Activity[1a,b]

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The 4-fluoro analogue of 17β-estradiol was investigated for estrogenic action in rats by determination of uterine hyperemia and [^{3}H]uridine incorporation and was found to be an active estrogen. Antitumor activity of this analogue was demonstrated against 7,12-dimethylbenz[*a*]anthracene (DMBA) induced rat mammary adenocarcinoma. Its ^{13}C NMR spectrum was determined, and all signals were assigned. A detailed X-ray diffraction investigation of 4-fluoro-17β-estradiol was carried out, and it crystallized in triclinic space group $P\bar{1}$ with two steroids and one methanol in a unit cell of $a = 7.367$ (1), $b = 9.363$ (6), $c = 12.531$ (1) Å, $\alpha = 89.31$ (3), $\beta = 93.38$ (1), $\gamma = 109.62$ (3)°, $V = 812.8$ Å^3, and $Z = 2$. The structure was solved and refined to an R index of 0.062 using 3045 reflections measured on an automated diffractometer. The oxygen atoms at C(3) and C(17) at either ends link the molecules together in a head to tail fashion. The hydroxy groups of the solvent molecules also take part in linking the molecules sideways through the hydroxy groups.

The cancer chemotherapist's armamentarium contains a variety of hormonal agents, such as adrenocorticosteroids, androgens, antiandrogens, estrogens, antiestrogens, antigonadotropic agents, and progestogens.[2,3] The ablation of endocrine glands for removal of endogenous sources of hormones (notably, orchiectomy in prostatic cancer and oophorectomy, adrenalectomy, and hypophysectomy in breast cancer) is practiced, as well as androgen administration in breast cancer, and estrogen administration in breast cancer and in prostatic cancer.[4] The results of

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Table I. Carbon-13 Chemical Shifts, $^{13}C-^{19}F$ and $^{13}C-^{1}H$ Coupling Constants, and Assignments for 4-Fluoro-17β-estradiol (4FE2)

carbon	δ	multiplicity	$J_{^{13}C,^{1}H}$, Hz	$J_{^{13}C,^{19}F}$, Hz	position[g]
1	120.1	d[a]	157.4	3.0	δ
2	114.3	d[a]	160.0	2.6	γ
3	141.8	d[a]	d	12.5	β
4	148.6	d[a]	e	237.4	α
5	123.9	d[a]	f	13.9	β
6	21.9	d[a]	128.0	4.6	γ
7	25.9	t[b,c]	126.6		
8	37.8	d[b]	133.6		
9	43.2	d[b]	130		
10	131.6	d[a]		2.7	γ
11	25.9	t[b,c]	126.6		
12	36.4	t[b]	127.0		
13	42.6	s[b]			
14	49.3	d[b]	122.6		
15	22.7	t[b]	130.6		
16	29.8	t[b]	133.4		
17	79.9	d[b]	138.9		
18	11.1	q[b]	125.5		

[a] In ^{1}H noise-decoupled spectrum. [b] In $^{1}H-^{13}C$ undecoupled spectrum. [c] The signals of C-7 and C-11 were superimposed. [d] J_{CCH} = 7.5 Hz. [e] J_{CCCH} = 8.2 Hz. [f] J_{CCH} = 7.0 Hz. [g] Relative to C-4F.

hormonal therapy of cancer are not fully predictable. Androgens are postulated to counteract estrogens in breast cancer, antiandrogens and estrogens are postulated to counteract androgens in prostatic cancer, antiestrogens are postulated to counteract estrogens in breast and uterine cancer, progestogens are postulated to modify estrogen stimuli in uterine or breast cancer, and antigonadotropic agents are postulated to inhibit stimulation of tumors of primary and secondary sex organs by pituitary gonadotropins.[4] The rationales and mechanisms for treatments of endocrine neoplasms are not well understood.

The rationales for the elucidation of the structural and biophysical determinants of the biological activities (estrogenic and antitumor) of modified estrogens had the following objectives: (a) X-ray crystallographic determination of the structure and stereochemistry of 4-fluoro-1,3,5(10)-estratriene-3,17β-diol (4FE2),[5b,6] (b) determination of the ^{13}C and ^{19}F NMR spectra of 4FE2, and (c) determination of early estrogenic actions of 4FE2 in rats and its antitumor effects on DMBA[5a] induced rat adenocarcinoma,[7] which resembles the human tumor in that it regresses after appropriate ablation therapy, as well as under treatment by androgens or high doses of estrogens, and progresses from hormone dependency toward autonomy.[4,7]

Results and Discussion

Spectral Studies. ^{13}C NMR. 4-Fluoro-17β-estradiol

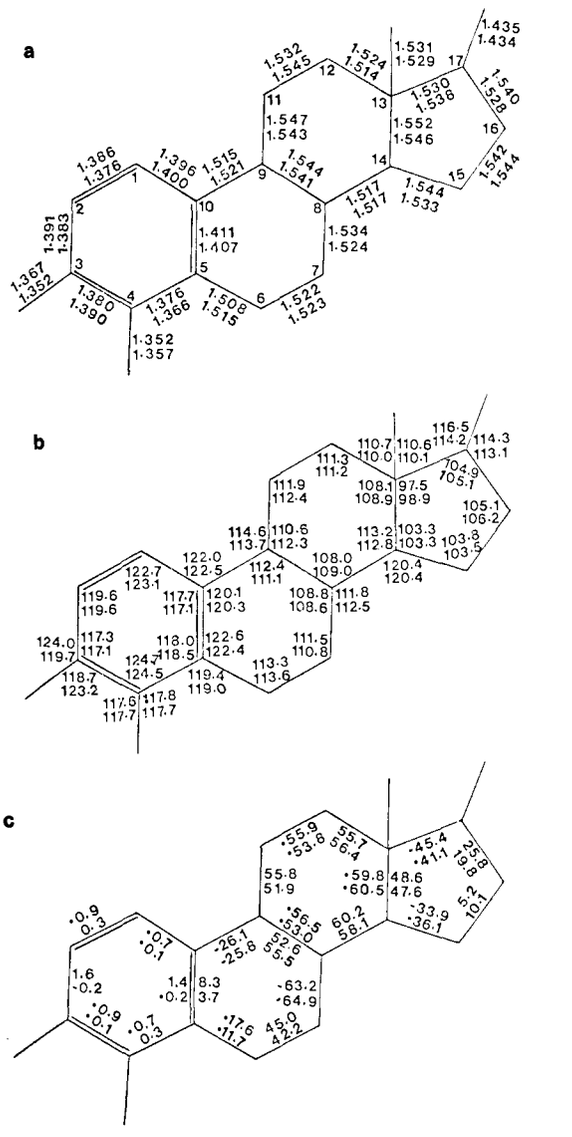

Figure 1. 4-Fluoro-17β-estradiol (a) bond distances (in angstroms), (b) bond angles (in degrees), and (c) torsion angles (in degrees).

was prepared as previously described.[7a,b]

The observed ^{13}C chemical shifts and assignments and the $^{13}C-^{19}F$ coupling constants are given in Table I.

The 18 ^{13}C signals were assigned using ^{13}C chemical shifts, multiplicities, $J_{^{13}C,^{19}F}$ values, and comparisons of chemical shifts to those reported for E2[5c,8a] and 2FE2.[5d,8b] The δ 11.1 for C-18 of 4FE2 is evidence of the 17β-OH stereochemistry.[8c] A comparison of $J_{^{13}C,^{19}F}$ values of the isomeric 2FE2[5d] and 4FE2 showed the following close correspondence (figures in parentheses are for 2FE2[8b]): α, C-4, 237.4 Hz (α, C-2, 229.2); β, C-3, 12.5 (β, C-3, 19.6); β′, C-5, 13.9 (β′, C-1, 19.6); γ, C-10, 2.7 (γ, C-10, 3.8); γ′, C-2, 2.6 (γ′, C-4, not reported); γ″ (ring B), C-6, 4.6; δ, C-1, 3.0 (δ, C-5, 3.8). The ^{13}C chemical shifts of carbons in 4FE2 relative to those in E2[5c,8a] were as follows: α, C-4, Δδ +32.7 ppm; β, C-3, −13.8; β′, C-5, −14.5; γ, C-10, −0.7; γ′, C-2, +0.8; γ″ (ring B), C-6, −17.9; δ, C-1, −6.8. The large shielding

(4) Reference 3, pp 890–895.
(5) (a) DMBA, 7,12-Dimethylbenz[a]anthracene; (b) 4FE2, 4-fluoro-1,3,5(10)-estratriene-3,17β-diol; (c) E2, 1,3,5(10)-estratriene-3,17β-diol; (d) 2FE2, 2-fluoro-1,3,5(10)-estratriene-3,17-diol; (e) 4BrE2, 4-bromo-1,3,5(10)-estratriene-3,17β-diol; (f) P, 4-pregnen-3,20-dione; (g) Ec, ergocornine maleate.
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Table II. 4-Fluoroestradiol Crystal Data

molecular formula	$C_{18}H_{23}O_2F \cdot 0.5CH_3OH$
molecular weight	580.76
crystal system	triclinic
space group	$P\bar{1}$
cell parameters	
a, Å	7.367 (1)
b, Å	9.363 (6)
c, Å	12.531 (1)
α, deg	89.31 (3)
β, deg	93.38 (1)
γ, deg	109.62 (3)
volume, Å^3	812.8
Z	2
density (calcd), g cm^{-3}	1.186
no. of reflections measured	3436
reliability index (for 3045 reflections), %	6.16
μ, cm^{-1}	7.37

of the benzylic C-6 in 4FE2 relative to E2 (−17.9 ppm) had its counterpart in the somewhat lesser shielding (−11.7 ppm) of C-6 in 2FE2[8b] relative to E2.[8a] The doublet centered at 79.9 ppm of C-17 is indicative of the 17β-hydroxy configuration,[8c] confirming the findings of the X-ray crystallography reported in the following paragraph.

X-ray Crystallographic Studies. The steroid nucleus of 4-fluoroestradiol appeared to have an extended structure similar to all estratriene analogues studied crystallographically. Among the closest analogues are the estradiol hemihydrate,[9] estradiol propanol,[10] estradiol urea,[11] and 4-bromoestradiol methanol.[12] Bond distances and angles, as well as torsion angles, are given in Figure 1. Since there are two molecules (A and B) of fluoroestradiol in an asymmetric unit in the crystal, we have two sets of numbers, the top refers to molecule A and the bottom to molecule B. Comparing with the other estratriene analogues mentioned above, the results agree fairly closely. However, there are a few exceptions, such as angles C(2)–C(3)–O(3), O(3)–C(3)–C(4), and C(3)–C(4)–C(5). The angle C(3)–C(4)–C(5) appears to be larger for the steroids that have a substituent at C(4). This is also supported by the data obtained on the torsion angles. Evidently, the substituent at C(4) in bromoestradiol, the bulky bromine atom, does create some distortion in the vicinity due to its size. Another interesting variation is in the angles C(2)–C(3)–O(3) and O(3)–C(3)–C(4), the first being larger than the second for 4-fluoroestradiol (molecule A), 4-bromoestradiol, estradiol hemihydrate, and estradiol propanol, while the reverse is true for estradiol urea and 4-fluoroestradiol (molecule B of this study). As in all other estratriene analogues, the A ring is planar, the B ring has a 7α,8β half chair, the C ring has a chair conformation, and the D-ring conformation is between a 13β envelope and a 13β,14α half chair. The molecules are packed in a head to tail manner and are held together by hydrogen bonds.

Biological Activity. The mean uterine wet weight of 4FE2-treated rats was 185% that of untreated controls, and the ratio of uterine weights of 4FE2/E2 was 1.38; the corresponding figures for uterine [^{3}H]uridine incorporation were 468% and 1.32.

The positive control group (DMBA injection only) showed 10% tumor incidence after 51 days and 100% incidence (a 2.1 average number of tumors and 6.7-g average tumor mass per tumor-bearing rat) after 150 days. The treatments, (a) (1) and (b) (1) with P before and after DMBA, showed, respectively, 80 and 90% tumor incidence, and 1.3 and 1.1 average numbers of tumors per rat after 150 days. In contrast, all the groups, (a) (2) through (a) (5), treated with estrogens E2 or 4FE2 before DMBA, with or without P, showed total inhibition of tumor formation after 150 days. All groups, (b) (2) through (b) (5), treated with estrogens E2 or 4FE2 after DMBA, with or without P, showed significant ($p < 0.001$) inhibition of tumor formation. For example, the 4FE2-treated group, (b) (3), showed a 10% tumor incidence after 78 days, an average of 1.0 tumor per rat, a 0.9-g average tumor mass per tumor-bearing rat, and a 30% tumor incidence 150 days after DMBA injection. In comparison, the corresponding data for E2 treatment, (b) (2), showed a 10% tumor incidence after 78 days, an average of 1.8 tumors per rat (ratio 4FE2/E2 = 0.56), a 5.9-g average mass (ratio 4FE2/E2 = 0.15), and a 50% tumor incidence after 150 days (ratio 4FE2/E2 = 0.6). Tumor formation was completely inhibited during estrogen administration and remained inhibited for 33 days thereafter.

The results of treatment schedules (c) (1) through (c) (5) are shown in Table III. Treatment (1) resulted in reversible tumor regression, with renewed tumor progression after Ec ended. Treatment (5) with Ec and P showed similar reversal of tumor regression after ending Ec administration. In contrast, when Ec administration for 8 days was combined with 4FE2 administration from day 6 through 30 in group (2), tumor regression continued after Ec treatment ended throughout 4FE2 treatment. Thereafter, tumor regression was partially reversed. In group (4), treatment with Ec was continued through day 30, together with 4FE2 and P, and the tumor incidence was as in group (2). Comparison of group (3) with group (5), both of which received Ec for 8 days and P from day 6 through day 30, showed 100% tumor incidence in group (5) without 4FE2 treatment, in contrast to 30% (day 30) and 20% (day 150) incidence in group (3) receiving 4FE2.

Conclusion

The results of early estrogenic actions of 4FE2 and E2, as expressed by uterine hyperemia and [^{3}H]uridine incorporation, confirmed earlier findings[6c] which had indicated a 4FE2/E2 estrogenic activity ratio of 1.4 in uterotropic tests. Antitumor tests were not reported.[6c] The present results indicate that the early tumor-inhibitory actions of 4FE2 and E2 follow a relative order similar to that of the estrogenic activities, as well as the binding affinities for lamb uterine cytosol estrogen receptor.[6d] This finding is in line with the results of the X-ray crystallographic study, which did not show a major departure in molecular shape of 4FE2 compared to E2,[15] in contrast to 4BrE2 having the bulky 4-bromo substituent. This additional bulk could account for the loss of estrogenic activity by substitution on ring A of E2 with bromo or methyl substituents, particularly adjacent to the 3-OH group,[16]

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(15) Fluorine bonded to sp^2 carbon is capable of p–π interaction, which partly counteracts fluorine's strong inductive electron withdrawal by return of electron density from nonbonding p electrons to the π system; cf. Pople, J. A.; Gordon, M. *J. Am. Chem. Soc.* **1967**, *89*, 4253–4261.

Table III. Effects of Ec, 4FE2, and P on Tumor Incidence, Number, and Mass in DMBA-Treated Rats

treatment	day no.	rats with tumors	total tumors	av tumor no.[a]	av tumor mass,[a] g
control (DMBA)	1	5/10	7	1.4 ± 0.2	0.6 ± 0.4
	6	6/10	9	1.5 ± 0.2	1.4 ± 0.4
	8	7/10	11	1.6 ± 0.2	1.4 ± 0.2
	30	8/10	17	2.1 ± 0.2	1.9 ± 0.3
	150[f]	10/10	21	2.1 ± 0.3	6.7 ± 2.2
(1) Ec	1[b]	5/10	8	1.6 ± 0.2	0.8 ± 0.2
	6	5/10	6	1.2 ± 0.2	0.4 ± 0.3
	8[d]	4/10	5	1.3 ± 0.2	0.4 ± 0.1
	30	9/10	12	1.3 ± 0.3	0.4 ± 0.3
	150[f]	9/10	16	1.9 ± 0.3	1.7 ± 0.3
(2) Ec + 4FE2	1[b]	5/10	6	1.2 ± 0.2	0.4 ± 0.1
	6[c]	5/10	5	1.0 ± 0.0	0.2 ± 0.1
	8[d]	3/10	3	1.0 ± 0.0	0.2 ± 0.0
	30[e]	1/10	1	1.0 ± 0.0	0.3 ± 0.0
	150[f]	3/10	3	1.0 ± 0.0	2.7 ± 1.4
(3) Ec + 4FE2 + P	1[b]	5/10	5	1.0 ± 0.0	0.5 ± 0.3
	6[c]	5/10	7	1.4 ± 0.2	0.8 ± 0.2
	8[d]	4/10	5	1.3 ± 0.2	0.5 ± 0.1
	30[e]	3/10	3	1.0 ± 0.0	0.3 ± 0.2
	150[f]	2/10	5	2.5 ± 0.4	5.0 ± 1.0
(4) Ec + 4FE2 + P	1[b]	5/10	6	1.2 ± 0.2	0.4 ± 0.1
	6[c]	5/10	7	1.4 ± 0.2	0.6 ± 0.6
	8	4/10	6	1.4 ± 0.2	0.6 ± 0.3
	30[d,e]	1/10	1	1.0 ± 0.0	0.5 ± 0.0
	150[f]	3/10	3	1.0 ± 0.0	1.2 ± 0.4
(5) Ec + P	1[b]	5/10	6	1.2 ± 0.2	0.4 ± 0.1
	6[c]	4/10	4	1.0 ± 0.0	0.7 ± 0.2
	8[d]	3/10	4	1.3 ± 0.2	0.9 ± 0.2
	30[e]	10/10	15	1.5 ± 0.3	1.5 ± 0.3
	150[f]	10/10	17	1.7 ± 0.3	4.0 ± 1.2

[a] Per tumor-bearing rat plus or minus standard error. [b] Beginning of Ec treatment (note: day 1 = day 62 after DMBA treatment). [c] Beginning of hormone treatments. [d] End of Ec treatment. [e] End of treatments with hormones. [f] End of observation.

an effect also reflected in the greatly reduced binding to uterine estrogen receptor of ring-A *o*-bromo-17β-estradiols.[6d] Inhibition of tumorigenesis by E2 and 4FE2 administered before DMBA can be attributed to early stimulation of mammary epithelium, and inhibition by estrogen administered after DMBA can be attributed to peripheral inhibition of breast tissue estrogen.[17] The observed pronounced tumor-inhibitory effects of 4FE2 on established DMBA-induced rat mammary adenocarcinoma in the preliminary experiments in series (c) suggest the need for further study of these effects of 4FE2 in comparison to E2, with and without pretreatment with Ec.

Experimental Section

The ^{13}C NMR Fourier transform ^{1}H noise-decoupled spectrum was recorded on a Varian XL-100 spectrometer at 25.2 MHz, employing dimethyl-d_6 sulfoxide as solvent (concentration: 59 mg in 0.4 mL) and tetramethylsilane as internal reference in a 5-mm diameter tube spun at 11 rps at 29 °C, with the following parameters: flip angle, 65°; acquisition time, 0.727 s, pulse delay, 1.0; number of transients, 4.184×10^3; points, 8K; time constant, 0.5 s, decoupled from ^{1}H offset, 45 691 Hz; and noise bandwidth, 1.5 kHz. For the ^{13}C–^{1}H undecoupled spectrum (under conditions of gated decoupling), the parameters were the same, except for the number of transients (34.387×10^3) and the time constant (0.3 s).

The crystallographic parameters and diffraction data were measured on an Enraf-Nonius CAD-4 automated diffractometer and are summarized in Table II. Data to a Bragg angle of 75° were collected using nickel-filtered Cu radiation and converted to structure amplitude by applying Lorentz and polarization as well as an empirical absorption correction. Of 3436 unique reflections measured, intensities of 3045 reflections were greater than $2\sigma(I)$, and the structure was determined and refined using these reflections.

Virgin female Sprague–Dawley rats were housed at 24 °C and given laboratory animal chow and water ad libitum. Estrogenic activity of 4FE2, in comparison to E2, was determined by subcutaneous administration to groups of 15 rats ovariectomized at age 31 days. The estrogen was administered subcutaneously at a dose of 1.0 μg per rat, and determination of [5-^{3}H]uridine incorporation and uterine hyperemia was made by the method of Miller and Emmens.[13] Antitumor activity of 4FE2 and E2, alone or in combination with progesterone (P), and of 4FE2 with ergocornine maleate (Ec) or with both P and Ec was determined in groups of 10 rats given a single intravenous injection of DMBA (5.0 mg in a lipid emulsion) at age 55 days. Control groups were treated with DMBA only (positive control) or received no treatment (negative control, which developed no tumors). The following treatment schedules were employed: daily intramuscular injections, beginning (a) 25 days before DMBA injection and continuing for 70 days, or (b) beginning 15 days after DMBA injection and continuing for 30 days, of (1) P (4.0 mg), (2) E2 (20 μg), (3) 4FE2 (20 μg), (40) E2 (20 μg) + P (4.0 mg), and (5) 4FE2 (20 μg) + P (4.0 mg), and (c) beginning 62 days after DMBA injection ("day 1"), when 50% of rats had palpable breast tumors, of (1) Ec (0.4 mg from day 1 through 8), (2) Ec (0.4 mg from day 1 through 8) + 4FE2 (20 μg from day 6 through 30), (3) Ec (0.4 mg from day 1 through 8) + 4FE2 (20 μg from day 6 through 30)

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+ P (4.0 mg from day 6 through 30), (4) Ec (0.4 mg from day 1 through 30) + 4FE2 (20 μg from day 6 through 30) + P (4.0 mg from day 6 through 30), and (5) Ec (0.4 mg from day 1 through 8) + P (4.0 mg from day 6 through 30).

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Structure-Activity Relationships of Synthetic Antibiotic Analogues of Anisomycin[1,2]

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A general synthetic sequence was used to synthesize a series of analogues of anisomycin, and the biological activities of the new synthetic analogues as antiprotozoals, antifungals, and antibacterials were evaluated. The synthetic antibiotics included 3β-acetoxy-4α-hydroxy-2β-(*p*-methylbenzyl)pyrrolidine (**1b**), 3β-acetoxy-2β-benzyl-4α-hydroxypyrrolidine (**1c**), 3β-acetoxy-4α-hydroxy-2β-(*m*-methoxybenzyl)pyrrolidine (**1d**), 3β-acetoxy-4α-hydroxy-2β-(*o*-methoxybenzyl)pyrrolidine (**1e**), 3β-acetoxy-4α-hydroxy-2β-(α-methyl-*p*-methoxybenzyl)pyrrolidine (**1f**), and 3β-acetoxy-4α-hydroxy-2β-(α-phenyl-*p*-methoxybenzyl)pyrrolidine (**1g**). The anisomycin analogues showed activity against protozoa and fungi, but this activity was restricted primarily to the *p*-methylbenzyl and benzyl analogues **1b** and **1c**. The activities dropped dramatically as the methoxy substituent was moved to the meta or ortho positions of the benzyl group (**1d** and **1e**) or a methyl or phenyl group was attached at the α-benzyl carbon (**1f** and **1g**).

Anisomycin (**1a**),[3] which exhibits a remarkably selective inhibition of peptide chain elongation on 60S eukaryotic ribosomes,[4] has become a valuable tool in molecular biology. Because of this mode of action, anisomycin exhibits selective activity against several strains of fungi and protoza.[5] The antibiotic has been shown to be useful in clinical trials for the treatment of amoebic dysentery[6] and vaginitis[7] and in field applications as a plant fungicide.[8] In an effort to search for a more effective anisomycin antibiotic and to establish structure–activity relationships, we recently developed an efficient, stereospecific total synthesis of (±)-anisomycin (**1a**) and demonstrated the utility of the synthesis by preparing two closely related analogues, **1b** and **1c**.[1b] Herein, this general synthetic sequence was used to prepare new anisomycins, **1d–g**, and subject the entire series **1a–g** to biological evaluation.

Chemistry. The first phase of the synthesis was to elaborate the entire carbon skeleton of anisomycin, which is embodied in the 2-benzylpyrroles **2a–g**, by utilizing our tandem alkylation–reduction techniques.[1a] The second phase of the synthetic sequence was the stereospecific synthesis of the *syn*-epoxides **7a–g**. The last phase then involved the regioselective, stereospecific ring opening of these *syn*-2-benzyl-3-pyrrolidine epoxides **7a–g** and subsequent selective manipulations to convert the resultant 3β,4α-dihydroxy-2β-benzylpyrrolidines **8a–g** by a protection–acetylation–deprotection sequence to the anisomycins **1a–g**. The entire synthesis is outlined in Scheme I.

In our original total synthesis of anisomycin (**1a**) and the analogues **1b** and **1c**, the benzyloxycarbonyl (Cbz) group had been used to protect the secondary amine group at two crucial stages of the synthesis.[1b] N-Protection was necessary during the generation of the halohydrin **5** and during the selective acylation of the *trans*-diol **9**, and for these purposes the *N*-Cbz group performed this task admirably. However, when the *N*-Cbz protecting group was employed in the **d–g** series, the protecting group could *not* be removed by catalytic hydrogenation from the *N*-Cbz derivatives of the *syn*-2-benzyl-3-pyrrolidine epoxides **7d–g**. We subsequently discovered, to our chagrin, that this is a rather general phenomenon for a sterically hindered Cbz protecting group. Medium-pressure (45 psi) catalytic hydrogenation or HBr/HOAc conditions destroyed the epoxide. A procedure,[9] of limited success, was to reflux the *N*-Cbz derivatives (R_2 = Cbz) of the *syn*-epoxides **7e** and **7g** in triethylsilane containing a catalytic amount of $PdCl_2$ and Et_3N to yield the corresponding deprotected *syn*-epoxides **7e** and **7g** in ca. 70% yields. The procedure failed for the *N*-Cbz derivatives (R_2 = Cbz) of the *syn*-epoxides **7d** and **7f**. The best solution to this problem was to change to 2,2,2-trichloroethoxycarbonyl (TCE) as the N-protecting group, which could be removed

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