product was a mixture of both components, the ratio was determined from NMR analysis using a singlet at δ 2.11 for **14** and a doublet at δ 1.15 for **15** as probe signals. For **14**: exact mass (CI), *m/e* 193.0970 ($C_9H_{18}ClO_2$ (M + H); *m/e* 193.0995); IR ν_{max} 3100–3600, 2930, 2875, 1720, 1460, 1380, 1240 cm^{-1}; NMR δ 0.98 (3 H, t, *J* = 7 Hz), 1.3–1.9 (6 H, m), 2.11 (3 H, s), 2.46 (2 H, dist t), 2.85 (1 H, b), 3.3–3.7 (1 H, m), 3.6–4.1 (1 H, m). For **15**: IR ν_{max} 3100–3600, 2925, 2875, 1460, 1380, 1120 cm^{-1}; NMR δ 0.98 (3 H, t, *J* = 6 Hz), 1.15 (3 H, d, *J* = 7 Hz), 1.3–2.0 (8 H, m), 3.10 (1 H, b s), 3.3–4.1 (3 H, m).

Preparation of 6,7-Epoxy-2-nonanone (21). A crude sample of **14** (142 mg) was dissolved in a methanol solution (7 mL) containing KOH (133 mg), and the solution was refluxed for 15 min. Water was added, and the product was extracted with CH_2Cl_2. The extract was washed with NaCl solution and dried over Na_2SO_4. The evaporation of the solvent followed by preparative TLC (silica gel/AcOEt-*n*-hexane, 1:1) gave almost a pure sample of **21**. GC–MS analysis showed that the product was a mixture of cis (93%) and trans (7%) isomers. Both isomers showed identical mass spectra: MS, *m/e* (relative intensity) 156 (7.3, M), 127 (8.4), 114 (93), 98 (36), 86 (39), 85 (100), 68 (46); NMR (cis–trans mixture) δ 0.97 (3 H, t, *J* = 7 Hz), 1.2–198 (6 H, m), 2.07 (3 H, s), 2.2–2.85 (4 H, m).

Preparation of *exo*-Brevicomin. The crude epoxy ketone **21** containing 93% of the cis isomer obtained from 142 mg of **14** was dissolved in a mixture of acetone (0.9 mL) and water (0.9 mL). To the solution was added H_2SO_4 (245 mg) with cooling by ice–water, and the mixture was stirred for 1 h at room temperature. The solution was neutralized with $NaHCO_3$ solution and shaken with ether. The ether extract was washed with a saturated NaCl solution and dried over Na_2SO_4. The residue (99 mg) left after the evaporation of the solvent was almost pure brevicomin as revealed from GLC and NMR analyses. GC–MS analysis indicated that the product was *exo*-brevicomin accompanied by 6% of endo isomer, each showing mass spectrum identical with the reported datum of the respective isomer.[7] The NMR spectrum of the product was identical with that reported for *exo*-brevicomin.[7]

Registry No. (±)-**6a**, 95694-10-3; (±)-**6b**, 95782-29-9; (±)-**6c**, 95694-11-4; (±)-**6d**, 95694-12-5; **7a**, 95694-13-6; **7b**, 95694-14-7; **7c**, 95694-15-8; **7d**, 95694-16-9; **8a-Cl**, 84098-65-7; **8a-Br**, 95694-17-0; **8a-I**, 95694-19-2; **8a-SCN**, 95694-23-8; **8a-CN**, 95694-18-1; **8a-N_3**, 95694-20-5; **8a-OTs**, 95694-22-7; **8a-OAc**, 95694-21-6; **8b-Cl**, 81505-12-6; **8b-Br**, 95694-24-9; **8c-Br**, 95694-25-0; **8d-Br**, 95694-26-1; (±)-**11a**, 95694-27-2; (±)-**11b**, 95694-28-3; **12a-Cl**, 95694-30-7; **12a-Br**, 95694-29-4; **12a-I**, 95723-90-3; **12b-Cl**, 95694-31-8; **13a**, 95694-32-9; **14**, 95694-33-0; **15**, 95694-34-1; **16a**, 95694-35-2; **16b**, 95694-36-3; **17a**, 95694-37-4; **17b**, 95694-38-5; **18-Cl**, 95694-40-9; **18-Br**, 95694-39-6; (±)-*cis*-**21**, 89188-46-5; (±)-*trans*-**21**, 89188-45-4; (±)-*exo*-**23**, 60018-04-4; (±)-*endo*-**23**, 62532-53-0.

2′-Chloropentostatin,[1] a New Inhibitor of Adenosine Deaminase[2]

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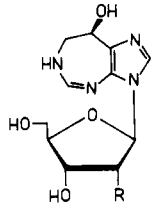
A new inhibitor of adenosine deaminase was isolated from the fermentation broths of an unidentified actinomycete, ATCC 39365. The inhibitor was shown by spectroscopic analysis to be a 2′-chloro analogue of pentostatin. Acetolysis of the glycosylic linkage gave 1,3,5-tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-ribofuranoses, thus establishing the structure of the nucleoside as (8*R*)-3-(2-chloro-2-deoxy-β-D-ribofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol (2′-chloropentostatin). An unambiguous synthesis of the sugar moiety, along with its D-*arabino* isomer, was developed.

Inhibitors of adenosine deaminase (adenosine aminohydrolase, EC 3.5.4.4) have been of interest as possible codrugs to enhance the activity of adenine nucleosides in the treatment of viral diseases and cancer.[3,4] Aside from potentiating the activity of adenosine analogues, these compounds possess potent immunosuppressive activity and represent a new class of agents for modulating the immune function.[4–6] The only compounds of microbial origin known to be potent inhibitors of this enzyme are the nucleosides pentostatin (**1**)[7] and coformycin (**2**),[8] both of which possess the unique 3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepine aglycon. Both compounds, as well as analogues,[9–12] have been the focus of synthetic efforts from these laboratories during the past few years. This report describes the isolation and structure elucidation of the novel component 2′-chloropentostatin (**3**), including the unambiguous synthesis of the carbohydrate moiety.



1: R = -H
2: R = -OH
3: R = -Cl

(1) The chemical name is (8*R*)-3-(2-chloro-2-deoxy-β-D-ribofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol.

(2) Preliminary details of his work have been presented. See: Schaumberg, J. P.; Hokanson, G. C.; French, J. C. "Abstracts of Papers", 188th National Meeting of the American Chemical Society, Philadelphia, PA, Aug 1984; American Chemical Society: Washington, DC, 1984; CARB-7. Smal, E.; Baker, D. C. *Ibid.*, CARB-8.

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Table I. ^{13}C and ^{1}H NMR Data for 2′-Chloropentostatin (3)[a]

positn	^{13}C[b]	^{1}H (J)[c]
2	134.8 d	7.55 s
5	153.0 d	7.01 s
7	49.9 t	eq, 3.34 dd (13.4, 4.4)
		ax, 3.20 d (13.4)
8	69.5 d	4.97 d (4.4)
9	138.1 s[d]	
10	131.6 s[d]	
1′	90.8 d	5.86 d (7.0)
2′	63.5 d	4.71 dd (7.0, 5.2)
3′	73.3 d	4.33 dd (5.2, 3.4)
4′	87.9 d	4.11 ddd (3.4, 3.4, 2.8)
5′	63.9 t	A, 3.69 dd (12.8, 2.8)
		B, 3.62 dd (12.8, 3.4)

[a] Proton and carbon spectra were measured for solutions in D_2O at 360 and 90.56 MHz, respectively. [b] Chemical shifts referenced to Me_4Si. Multiplicities were determined by off-resonance decoupling. Assignments were made on the basis of chemical shift and selective proton-decoupling experiments. [c] Chemical shifts are referenced to DSS. Assignments are based on chemical shift and homonuclear decoupling experiments. Coupling constants are in hertz. [d] Signals may be interchanged.

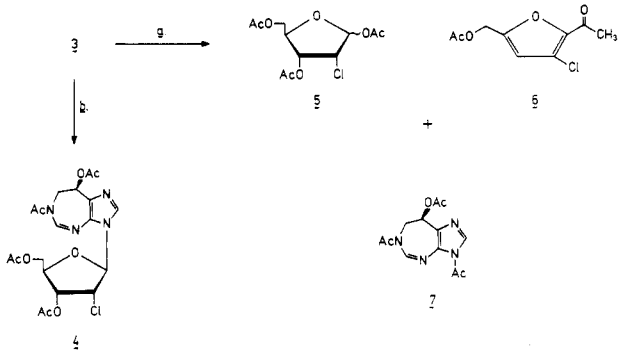
Results and Discussion

Isolation and Characterization of 3. In the course of screening for new adenosine deaminase inhibitors, activity was observed for the culture broths of an as yet unidentified actinomycete (ATCC 39365).[13] Compound **3** was isolated from the fermentation beer filtrates of ATCC 39365 by adsorption onto activated carbon, followed by elution with aqueous acetone. The eluate was concentrated and passed over Dowex 50-X2 [H^+]. The basic components were eluted with aqueous ammonia and subsequently chromatographed over Sephadex G-10. At this point, compound **3** was separated from other components, including **1** and **2**. Fractions containing most of the **3** were lyophilized, and the residue was crystallized from ethanol and recrystallized from water.

While neither electron-impact nor chemical-ionization mass spectrometry of **3** gave a molecular ion, high resolution, fast-atom bombardment mass spectrometry gave an M + H ion at m/z 303.0868 (calcd 303.0860). These data were further supported by elemental microanalysis indicating a molecular formula for **3** of $C_{11}H_{15}ClN_4O_4$. The potent adenosine deaminase inhibitory activity of **3**[14] and the isolation of **1** and **2** from the same culture further suggested a close structural relationship between the novel component and both pentostatin (**1**) and coformycin (**2**). The molecular formula of **3** indicated that a hydroxyl group in **2** had been replaced by a chlorine atom.

The ultraviolet absorption spectra of **3** [λ_{max} (methanol) 284 nm (ϵ 9400) and λ_{max} (HCl–methanol) 266 nm (ϵ 8500)] were the same as those observed for pentostatin (**1**). Comparison of ^{1}H and ^{13}C NMR data (Table I) with published values for **1**, **2**, and analogues[7,9-12] indicated that the chlorine replacement was at C-2′. Specifically, the signals for the protons and carbons of the 3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol ring system could be readily identified[7,10] and the remaining signals could be assigned to a substituted sugar system.[15,16] The latter signals were within the normal values of D-ribonucleosides with the exception of the signal for the 2′-carbon which was shifted upfield by 10–12 ppm in the ^{13}C NMR spectrum as determined by selective, off-resonance proton-decoupling experiments. This observed shift is consistent with the replacement of a hydroxyl group at C-2′ with a chlorine. The position of chlorination was verified by acetylation of **3** to give the tetraacetate **4**. Examination of the ^{1}H NMR spectrum of **4** showed that the chemical shift of the signal for the 2′-proton was virtually unchanged, while the signals for the protons α to the acetoxy groups exhibited the expected downfield shifts. (See Experimental Section.)

Scheme I



[a] Reagents: a, Ac_2O, HOAc, H_2SO_4; *b*, Ac_2O, pyridine.

On the basis of the above data and the structure-activity requirements of this series, which require the 8*R* configuration and a β-D-glycosylic linkage,[10,17] **3** was indicated to be an (8*R*)-3-(2-chloro-2-deoxy-β-D-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol.

Determination of the Stereochemistry of the Sugar Moiety. Having established that the site of chlorine substitution is at the 2′-position in **3**, the problem which remained was to determine the stereochemistry at C-2′ and to firmly establish the overall configuration of the sugar. Examination of the ^{1}H NMR spectrum of **3** revealed a $J_{1',2'}$ = 7.0 Hz. This value, together with the other vicinal coupling constants which are often used to assign sugar stereochemistry, was of little value in the structural assignment for **3**. The $J_{1',2'}$ value was nearly identical with that for both 2′-chloro-2′-deoxyadenosine ($J_{1',2'}$ = 7 Hz)[18,19] and the D-arabino epimer[18] ($J_{1',2'}$ = 6.2 Hz). The assignment of stereochemistry at C-2′ in **3** could then only reliably be established by chemical means. To this end, isolation of the sugar moiety of **3** and comparison with authentic samples of 2-chloro-2-deoxy-D-arabinofuranosyl and D-ribofuranosyl compounds was the established strategy.

Nucleoside **3** was subjected to acetolysis in an acetic acid–acetic anhydride mixture containing sulfuric acid (see Scheme I), and the products were isolated and examined by ^{1}H NMR spectroscopy and mass spectrometry. The sugar component **5**, a product of limited stability, was indicated by MS to be a tri-*O*-acetylchlorodeoxypentofuranose by both m/z and isotopic patterns (M^+ – Ac, m/z 251; M^+ – CH_2OAc, m/z 221). Furthermore, the ^{1}H NMR spectrum of **5** allowed assignment of the sites of acetylation at O-3 and O-5, based on the observed chemical shifts and spin–spin coupling patterns for H-2, H-3, and H-5,5a. (See Experimental Section.) These data, together with the MS data, led to the assignment of a 1,3,5-tri-*O*-acetyl-2-

(13) A description of the organism and fermentation will be reported elsewhere.
(14) Details of adenosine deaminase activity will be reported elsewhere.
(15) Wu, R. T.; Okabe, T.; Namikoshi, M.; Okuda, S.; Nishimura, T.; Tanaka, N. *J. Antibiot.* **1982**, *35*, 379–284.
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(18) Mengel, R.; Wiedner, H. *Chem. Ber.* **1976**, *109*, 433–443.
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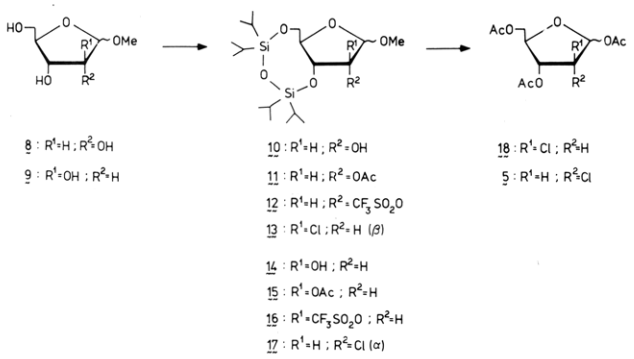
Scheme II



chloro-2-deoxypentofuranose structure for the sugar acetolysis product. Most interestingly, another component, the product of elimination–C-acetylation was identified as the furan **6** based on its MS (M^+, m/z 216; $M^+ - CH_2CO$, m/z 174) and ^1H NMR spectrum through comparison with spectra of known furan derivatives.[20] Knowing the facility with which furan acylates at the α-position,[21] the structure for **6** is not surprising. Along with the carbohydrate products, the unstable peracetylated aglycon **7** was detected by gas chromatography–mass spectrometry (GC/MS) of the crude acetolysis mixture. Its identity was confirmed through comparison, by both GC retention time and MS fragmentation pattern, with the authentic acetylated heterocycle isolated from the acetolysis of **1**.[22]

The first sugar chosen for comparison was the known 1,3,5-tri-*O*-acetyl-2-chloro-2-deoxy-D-arabinofuranose (**18**) reported by Fox and co-workers.[23] Examination of the synthetic route for **18** led to the conclusion that a more straightforward process might well be devised making use of recent advances in simultaneous 3,5-O-protection in D-ribofuranosyl compounds afforded by the 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl) group.[24–26] (See Scheme II). Thus selective 3,5-protection of methyl α,β-D-ribofuranosides (**8**), obtained from D-ribose by the method of Fletcher,[27] was carried out by using dichlorotetraisopropyldisiloxane–imidazole–*N*,*N*-dimethylformamide to give a 1:3 (α/β) anomeric mixture of methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α,β-D-ribofuranosides (**10**). The structure of **10** (whose H-2 resonance was obscured by both H-4 and H-5,5a) was confirmed by acetylation of **10** to give the *O*-acetyl derivative **11**, whereby the H-2 signal in the ^1H NMR spectrum of **11** was observed to shift downfield by ca. 1.3 ppm from that observed in **10**. Both compounds **10** and **11** were further characterized by additional spectroscopic means and by elemental analysis.

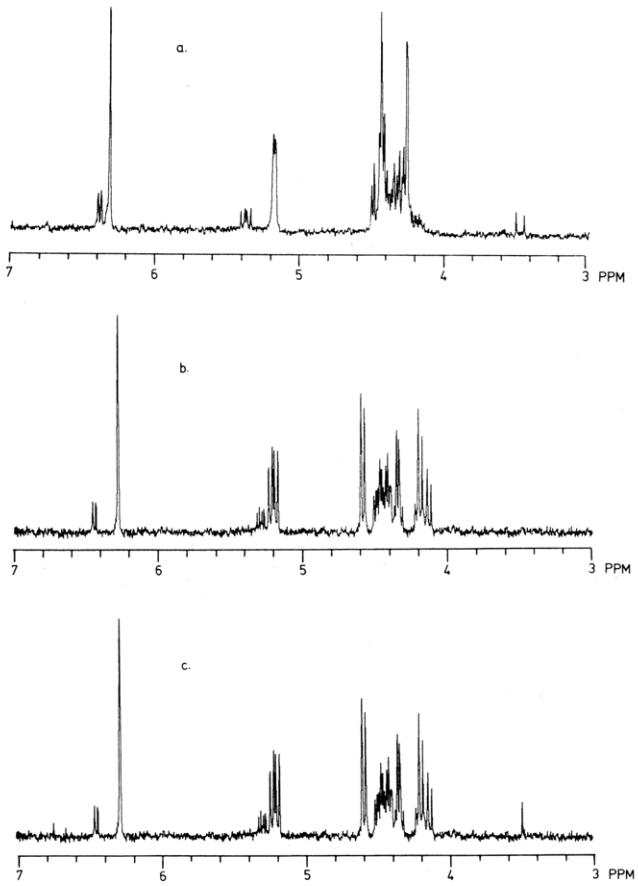
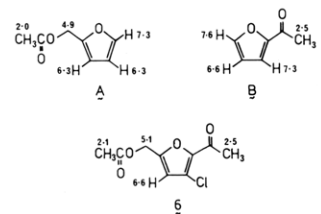


Figure 1. Partial ^1H NMR spectra (200 MHz, $CDCl_3$) for (a) **18** (synthetic), (b) **5** (synthetic), and (c) **5** (from natural product **3**).

Chlorination of the 3,5-protected 2-hydroxy compound **10** was effected under a number of conditions. The most direct procedures included (1) the Mitsunobu procedure that uses triphenylphosphine–diethyl azodicarboxylate–benzyl chloride[28] and (2) the procedure reported by Lee and Nolan that uses triphenylphosphine–carbon tetrachloride.[29] While both approaches were successful, a two-step procedure of trifluoromethanesulfonylation of **10** to give **12**, followed by displacement on the latter with lithium chloride in hexamethylphosphoramide (HMPA) to furnish the desired 2-chloro-2-deoxy-D-arabinofuranosyl derivative **13**, routinely gave overall higher yields. However, on account of their convenience, procedures 1 or 2 are recommended for synthesis. Curiously, in all three cases anomerically pure methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranoside (**13**) was the only isomer isolated or observed by ^1H NMR and TLC in the reaction mixture. The anomeric assignment is based on $J_{1,2}$ = 3.17 Hz, a value in line with that expected for a cis 1,2-H arrangement (i.e., the larger of two possible spin–spin couplings). The somewhat skewed ring due to the 3,5-O-protecting group had shown $J_{1,2} \ll 1$ Hz for the trans (α-D) coupling and $J_{1,2}$ = 4.2 Hz for the cis (β-D) coupling in the anomeric mixture **10**, where the anomeric composition is unambiguous. These assignments agree with the general

(20) The following comparisons (chemical shifts indicated) were made with the ^1H NMR spectrum of **6** and those of related furan derivatives **A** and **B** from; "Sadtler Standard Proton NMR Collection"; Sadtler Research Laboratories: Philadelphia, 1982; Nos. 2931 and 14606, respectively, for **A** and **B**.



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(28) Mitsunobu, O. *Synthesis* **1981**, 1–28.

(29) Lee, J. H.; Nolan, T. J. *Can. J. Chem.* **1966**, *44*, 1331–1334.

trends observed in furanose glycosides.[30] Most interestingly the single α-D-anomer ($J_{1,2}$ < 1 Hz) was observed as the chlorination product in the work by Fox et al.[23] where the procedure of Lee and Nolan[29] was employed on methyl 3,5-di-*O*-benzyl-α,β-D-ribofuranosides.

Acetolysis of **13** furnished 1,3,5-tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-arabinofuranoses (**18**) as a 3:1 α/β anomeric mixture whose ^{1}H NMR spectrum[23] was identical to that provided by Dr. J. J. Fox. However, comparison of **18** with the acetolysis product from chloropentostatin **3** (see Figure 1) revealed significant differences. GC/MS on **5** and **18**, while giving nearly identical MS fragmentation patterns, revealed markedly different GC retention times (k' = 17.50 and 18.95, respectively, for **5** and **18**). Thus **3** does not have the 2-chloro-2-deoxy-D-arabinofuranosyl moiety.

A synthetic procedure (see Scheme II) similar to that used for **18** was developed for the synthesis of 1,3,5-tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-ribofuranoses (**5**), a compound herein reported for the first time. Methyl D-arabinofuranoside (**9**)[31] was protected as its 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl) derivative **14** in a manner identical with that for **10**. A byproduct, presumably a 2,5-protected species, was observed by TLC, and its formation could be minimized by short reaction times. Column chromatography afforded pure **14** in 71% yield. The structure of **14** was confirmed by acetylation to give an acetate **15** whose H-2 signal in the ^{1}H NMR spectrum was shifted downfield by ca. 1 ppm from where it was observed in **14**. Both **14** and **15** were fully characterized by ^{1}H NMR spectroscopy and elemental analysis.

Chlorination of **14**, unlike its D-*ribo* counterpart, proved troublesome as both the Mitsunobu[28] and Lee–Nolan[29] procedures failed to give isolable products. Conversion of **14** to the 2-*O*-(trifluoromethanesulfonyl) derivative **16**, followed by reaction with lithium chloride and 1 equiv of HMPA with either acetonitrile or dimethyl sulfoxide (Me_2SO) as solvent, a procedure[32] advocated for such displacements, also failed. Only when anhydrous HMPA was used in excess as solvent was the procedure found successful, giving the desired 2-chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α-D-ribofuranose (**17**) in 81% yield. As was observed for the D-*arabino* isomer **13**, **17** was isolated as a single anomer, the α-anomer being indicated by the large $J_{1,2}$ = 4.0 Hz. None of the corresponding β-anomer was evident by either TLC or ^{1}H NMR analysis of the reaction mixture. Acetolysis of **17** was carried out as for the D-*arabino* isomer **13** to give 1,3,5-tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-ribofuranoses (**5**) as a mixture of α/β-anomers as revealed by ^{1}H NMR spectroscopy. The synthetic product was identical in all respects [i.e., by GC/MS (by both retention time and MS fragmentation pattern), by ^{1}H NMR (see Figure 1), and by optical rotation] with that obtained by the acetolysis of **3**. Both products were unstable, decomposing even upon storage at −20 °C.

Experimental Section

General Data. ^{1}H chemical shifts in deuterium oxide were referenced to internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS), while all others were referenced to internal tetramethylsilane (Me_4Si). Chemical shifts, multiplicities, and J values are apparent, first-order values [d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; ψt, "pseudo" triplet (i.e., a dd where both *J* values are approximately equal)] determined at 200 MHz unless designated otherwise. Optical rotations were measured at the sodium D line in 1-dm cells at ambient temperature in the indicated solvent.

Thin-layer chromatography (TLC) was carried out on **3** by using Analtech silica gel plates (5 × 10 × 0.25 mm) developed with a mobile phase consisting of 40:70:20 chloroform–ethanol–0.5 M pH 5.5 sodium acetate and visualized with iodine vapor (R_f 0.51 for 2′-chloropentostatin). TLC on all other compounds was carried out on E. Merck aluminum-backed silica gel plates (0.20 mm thickness), with detection by anisaldehyde–sulfuric acid spray,[33] visualization being achieved by warming the plates under a hot-air blower. Column chromatography (CC) utilized E. Merck Silica Gel-60 (63–200 μm) at a loading of 1–1.6%.

High-pressure liquid chromatography (HPLC) was carried out on a reversed-phase octadecylsilyl-derivatized (C-18) column (Waters Associates, μBondapak C-18, 300 × 3.9 mm) eluting with a mobile phase of 90:10 (v/v) 0.02 M pH 7.0 sodium phosphate–acetonitrile using a Waters Associates Model 6000A pumping system (1.0 mL/min, a Kratos spectroflow Model 773 absorbance detector (280 nm), and a Shimadzu C-R 18 integrator (retention volume of 2′-chloropentostatin = 5.1 mL). Gas–liquid chromatography (GC) was performed by using a CP Sil 5 CB fused silica wall-coated open tubular capillary column (10 m × 0.32 mm).

Reagents were reagent grade and used as supplied. *N*,*N*-Dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were distilled in vacuo from calcium hydride and stored over 4A molecular sieves; pyridine and dichloromethane were distilled at ambient pressure from calcium hydride and stored over 4A molecular sieves.

Isolation of 2′-Chloropentostatin. A 680-L portion of fermentation beer produced by actinomycete ATCC 39365 was adjusted to pH 6.5, mixed with 31 kg of Celite 545, and filtered through a plate and frame filter press. The filtrate was mixed with 30 kg (4.4% w/v) of Darco G-60 and, after the addition of 15.5 kg of Celite 545, was again filtered. The filter cake was washed with deionized water (185 L) and then eluted with 151 L of 1:1 acetone–water. The eluates, which contained most of the 2′-chloropentostatin (**3**), were combined and concentrated to 21 L.

To 18 L of the above concentrate was added 500 g of Celite 545, and the mixture was filtered. The filtrate was adjusted to pH 5.1 and then passed over 10 L of Dowex 50-X2 [H^+]. The resin was washed with 19 L of deionized water and then eluted with 42 L of 1 N ammonium hydroxide. The ammonium hydroxide eluate was concentrated to 400 mL, applied to a 10-L column of Sephadex G-10, and eluted with deionized water, collecting nine 0.5-L and seven 1-L fractions. Early fractions contained pentostatin (**1**) and coformycin (**2**), with most of the 2′-chloropentostatin (**3**) in fractions 15 and 16. Each of these latter fractions was concentrated to 200 mL and lyophilized to yield 6.3 and 6.0 g, respectively, of crude **3**. The 6.3 g of solid from fraction 15 was dissolved in 50 mL of hot absolute ethanol, affording 3.86 g of crystalline 2′-chloropentostatin upon cooling. Recrystallization from 35 mL of water yielded 2.9 g of pure **3** as colorless needles. Similar treatment of the 6.0 g from fraction 16 afforded an additional 1.55 g of recrystallized **3**: $[\alpha]_D$ +28.5° (*c* 1.26, 0.1 M pH 7.0 phosphate buffer); UV (MeOH) λ_{max} 284 (ε 9380); UV (0.05 M methanolic HCl) λ_{max} 266 (ε 8470); FTIR (KBr) 3350, 1635, 1625, 1198, 1100, 1065 cm^{-1}; for ^{1}H and ^{13}C NMR data, see Table I; HRFABMS (Me_2SO + glycerol), *m/z* (M + H) 303.0868 (calcd for $C_{11}H_{16}ClN_4O_4$ 303.0860). Anal. Calcd for $C_{11}H_{15}ClN_4O_4$: C, 43.64; H, 4.99; Cl, 11.75; N, 18.51. Found: C, 43.83, N, 4.96; Cl, 11.76; N, 18.62.

Acetylation of 3. A solution of 10 mg of **3**, 0.5 mL of anhydrous pyridine, and 0.5 mL of acetic anhydride was stirred at room temperature for 12 h, after which time TLC indicated the absence of starting material. The solution was poured into 20

(30) Stevens, J. D.; Fletcher, H. G., Jr. *J. Org. Chem.* **1968**, *33*, 1799–1805.

(31) The procedure for the preparation of **9** was identical with that used for **8**. (See ref 27.) The product was a 1:3 α:β-anomeric mixture by ^{13}C NMR (50 MHz, Me_2SO-d_6). The ^{13}C NMR chemical shifts were identical with those reported by Beier, R. C.; Mundy, B. P. *J. Carbohydr. Chem.* **1984**, *3*, 253–266. ^{1}H NMR (200 MHz, Me_2SO-d_6) δ 4.604 [s, 1 H, H-1 (α-anomer)], 4.601 [d, *J* = 3 Hz, 1 H, H-1 (β-anomer)].

(32) Su, T. L.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 1790–1792.

(33) The spray consisted of a mixture of 64 mL of anisaldehyde, 87 mL of concentrated sulfuric acid, and 26 mL of acetic acid diluted to 2.5 L with absolute ethanol. The mixture was stored at 0 °C in the dark prior to use.

mL of saturated aqueous sodium bicarbonate and extracted with 3 × 25 mL of ethyl acetate. The organic phase was dried over magnesium sulfate, and the solvent was evaporated. ^{1}H NMR for **4**: (C_6D_6) δ 7.58 (s, 1 H, H-2 or H-5), 6.46 (d, 1 H, $J_{7,8}$ = 2.7 Hz, H-8), 6.18 (d, 1 H, $J_{1',2'}$ = 4.9 Hz, H-1'), 5.35 (ψt, 1 H, $J_{2',3'} = J_{3',4'}$ = 5.3 Hz, H-3'), 4.88 (ψt, 1 H, $J_{1',2'} = J_{2',3'}$ = 5.2 Hz, H-2'), 4.1–4.19 (m, 3 H, H-4', H-5',5'a), 2.3 (d, 1 H, J = 14 Hz, H-7), 1.69, 1.65, 1.61, 1.45 (4s, 12 H, CH_3CO).

Cleavage of 3 by Acetolysis. A solution of 50 mg (0.17 mmol) of **3**, 1 mL of acetic anhydride, 1 mL of acetic acid, and 10 μL of concentrated sulfuric acid was heated gently for 3 h, at the end of which time TLC indicated complete cleavage of the nucleoside. After being cooled, the solution was added dropwise to 50 mL of saturated aqueous sodium bicarbonate at 0 °C and extracted with 4 × 50 mL of chloroform. The combined organic layers were dried ($MgSO_4$), the solvent was evaporated, and the residue was subjected to column chromatography using chloroform as eluant to give 15 mg (30%) of a 1:5 (α/β) anomeric mixture of the acetylated sugar **5** as an oil: $[\alpha]^{22}_D$ +38.4° (*c* 1, chloroform); R_f 0.74 (8:2 chloroform–ethyl acetate); GC/MS (k' = 1.75), *m/z* (relative intensity) 251 (2, M – Ac), 235 (19, M – OAc), 221 (28, M – CH_2OAc), 179 (34), 174 (208, M – 2 HOAc), 115 (65, M – 2HOAc – OAc), 43 (100, Ac); ^{1}H NMR ($CDCl_3$) δ 6.44 [d, $J_{1,2}$ = 4.2 Hz, 1 H, H-1 (α-anomer)], 6.27 [s, 1 H, H-1 (β-anomer)], 5.20 (dd, $J_{3,4}$ = 7.7 Hz, 1 H, H-3), 4.58 (d, $J_{2,3}$ = 5.1 Hz, 1 H, H-2), 4.44 (m, 1 H, H-4), 4.27 [m (AB of ABX, $J_{5,5a}$ = 12.1 Hz, $J_{4,5}$ = 3.4 Hz, $J_{4,5a}$ = 5.2 Hz), 2 H, H-5,5$_a$], 2.10, 2.17 (2s, 9 H, CH_3CO). Anal. Calcd for $C_{11}H_{15}ClO_7$: C, 44.83; H, 5.13; Cl, 12.03. Found: C, 44.93; H, 5.17; Cl, 11.95.

Also isolated from the acetolysis was 7 mg (19%) of a UV-active compound indicated to be the acylated furan **6** based upon MS and ^{1}H NMR data[20] (see Results and Discussion): GC/MS (k' = 10.86), *m/z* (relative intensity) 216 (6, M), 201 (14, M – CH_3), 174 (100, M – CH_2CO), 157 (13, M – OAc), 43 (31, Ac); ^{1}H NMR ($CDCl_3$) δ 6.56 (s, 1 H, ArH), 5.06 (s, 2 H, CH_2OAc), 2.54 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO).

The acetylated heterocycle **7** was detected by GC/MS, only, and was found to be identical with the product obtained from deliberate acetylation of the heterocycle:[22] GC/MS (k' = 88.3), *m/z* (relative intensity) 176 (47, M – Ac – OAc), 134 (100, M – $2CH_2CO$ – HOAc), 81 (38), 43 (20, Ac).

Methyl 3,5-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-α,β-D-ribofuranosides (10). To a solution of 2.91 g (17.7 mmol) of methyl α,β-D-ribofuranoside (**8**)[27] and 5.31 g (78.1 mmol) of imidazole in 70 mL of dry DMF was added dropwise 6.13 mL (19.5 mmol) of dichlorotetraisopropyldisiloxane (Petrarch). After 4 h, excess silylating agent was decomposed by the addition of 10 mL of methanol, which was followed by the addition of 150 mL of ethyl acetate. The solution was poured into 100 mL of saturated aqueous sodium chloride and extracted with 3 × 75 mL of ethyl acetate. The combined organic layers were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the crude material was chromatographed using 9:1 hexane–ethyl acetate to give 4.53 g (63%) of a 1:3 (α/β) anomeric mixture of the desired 3,5-protected sugar **10**: $[\alpha]^{22}_D$ −48.8° (*c* 1, chloroform); R_f 0.75 (8:2 chloroform–ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 4.87 [d, $J_{1,2}$ = 4.2 Hz, 1 H, H-1 (α-anomer)], 4.83 [s, 1 H, H-1 (β-anomer)], 4.50 (ψt, $J_{2,3}$ = 5.3 Hz, 1 H, H-3), 3.74–4.08 (m, 4 H, H-2, H-4, H-5,5$_a$), 3.32 (s, 3 H, OMe), 1.0–1.1 [m, 28 H, $(CH_3)_2CH$]. Anal. Calcd for $C_{18}H_{38}O_6Si_2$: C, 53.16; H, 9.42. Found: C, 53.23; H, 9.42.

Methyl 2-*O*-Acetyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-ribofuranoside (11). To a solution of 81 mg (0.2 mmol) of methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α,β-D-ribofuranosides (**10**) in 4 mL of dry pyridine was added dropwise 0.2 mL (2 mmol) of acetic anhydride. The reaction was kept at room temperature for 8 h, after which time the mixture was added dropwise to 10 mL of saturated aqueous sodium bicarbonate and extracted with 3 × 20 mL of chloroform. The combined organic layers were dried ($MgSO_4$), the solvent was removed, and the residue was chromatographed by using chloroform to give 66 mg (74%) of the desired, anomerically pure β-acetate (the only isomer isolated): $[\alpha]^{22}_D$ −63.0° (*c* 1, chloroform); R_f 0.55 (chloroform); GC/MS (k' = 33.1), *m/z* (relative intensity) 417 (1, M – OCH_3), 405 (3, M – $(CH_3)_2CH$), 345 (10), 277 (100), 116 (27), 43 (11, $(CH_3)_2CH$); ^{1}H NMR ($CDCl_3$) δ 5.23 (d, $J_{2,3}$ = 4.8 Hz, 1 H, H-2), 4.78 (s, 1 H, H-1), 4.53 (dd, $J_{3,4}$ = 6.6 Hz, 1 H, H-3), 3.80–4.08 (m, 3 H, H-4, H-5,5$_a$), 3.33 (s, 3 H, OCH_3), 1.04–1.1 (m, 28 H, $(CH_3)_2CH$). Anal. Calcd for $C_{20}H_{40}O_7Si_2$: C, 53.53; H, 8.99. Found: C, 53.69; H, 9.06.

Methyl 2-Chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranoside (13). A. Via the Mitsunobu Reaction. To a solution of 812 mg (2 mmol) of methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α,β-D-ribofuranosides (**10**) and 576 mg (2 mmol) of triphenylphosphine in 10 mL of dry toluene was added 2.68 mL (2.2 mmol) of diethyl azodicarboxylate. The resulting deep orange solution was stirred for 10 min at room temperature prior to adding 2.52 mL (2.2 mmol) of benzyl chloride. The solution was then heated under reflux for 24 h, keeping the reaction free from moisture. The solvent was evaporated, and the residue was chromatographed with toluene to give 390 mg (46%) of anomerically pure **13** (α-anomer not observed): $[\alpha]^{22}_D$ +0.5° (*c* 1, chloroform); R_f 0.75 (8:2 toluene–chloroform); GC/MS (k' = 17.9), *m/z* (relative intensity) 381 (8, M – $(CH_3)_2CH$), 349 (1), 321 (39), 275 (20), 249 (100); ^{1}H NMR ($CDCl_3$) δ 4.96 (d, $J_{1,2}$ = 3.2 Hz, 1 H, H-1), 4.28 (ψt, $J_{2,3} = J_{3,4}$ = 7.8 Hz, 1 H, H-3), 4.06 (dd, $J_{2,3}$ = 7.1 Hz, 1 H, H-2), 3.99 (m, 2 H, H-5,5$_a$), 3.86 (m, 1 H, H-4), 3.41 (s, 3 H, OMe), 1.02–1.1 [m, 28 H, $(CH_3)_2CH$]. Anal. Calcd for $C_{18}H_{37}ClO_5Si_2$: C, 50.85; H, 8.77; Cl, 8.34. Found: C, 51.03; H, 8.80; Cl, 8.45.

B. Via Triphenylphosphine–Carbon Tetrachloride. A solution of 203 mg (0.5 mmol) of methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α,β-D-ribofuranosides (**10**) and 262 mg (1 mmol) of triphenylphosphine in 50 mL of anhydrous carbon tetrachloride was heated under reflux for 12 h, after which time the solvent was evaporated and the residue was chromatographed with toluene to give 125 mg (59%) of **13**, identical by ^{1}H NMR spectroscopy and TLC with the product obtained under A.

C. Via the Triflate 12. A solution of 203 mg (0.5 mmol) of methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α,β-D-ribofuranosides (**10**) in 0.2 mL of anhydrous pyridine and 2 mL of anhydrous dichloromethane was cooled to −15 °C, and a solution of 0.1 mL (0.6 mmol) of trifluoromethanesulfonic anhydride in 2 mL of dry dichloromethane was added over 5 min, taking care to exclude moisture from the reaction. After 3 h, 0.5 mL of methanol was added to the reaction, and the solvent was removed in vacuo. The triflate **12** was purified by column chromatography (1:1 hexane–toluene) and used immediately in the next step.

To a solution of the above-prepared triflate **12** in 2 mL of HMPA was added, under dry conditions, 105 mg (2.5 mmol) of dry lithium chloride. After 1 h the solution was poured into 10 mL of water and extracted with 3 × 25 mL of chloroform. The organic layers were combined and dried over $MgSO_4$, and the solvent was evaporated. The crude material was chromatographed by using toluene to afford 134 mg (63%) of **13**, identical with the sample prepared under **A** by ^{1}H NMR spectroscopy and TLC.

1,3,5-Tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-arabinofuranoses (18). A solution of 100 mg (0.24 mmol) of methyl 2-chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranoside (**13**) in 2 mL of acetic anhydride and 2 mL of acetic acid was allowed to stir for 1 h, at the end of which time 20 μL of concentrated sulfuric acid was added. After 10 h the solution was added dropwise to 75 mL of saturated aqueous sodium bicarbonate and extracted with 3 × 50 mL of chloroform. The combined organic layers were dried ($MgSO_4$), the solvent was evaporated, and the crude material was chromatographed with chloroform to yield 67 mg (92%) of a 3:1 (α/β) anomeric mixture of **18**: $[\alpha]^{22}_D$ +23.4° (*c* 1, chloroform); R_f 0.68 (8:2 chloroform–ethyl acetate); GC/MS (k' = 18.95), *m/z* (relative intensity) 235 (16, M – OAc), 221 (19, M – CH_2OAc), 179 (15), 174 (14, M – 2HOAc), 115 (50, M – 2HOAc – OAc), 43 (100, Ac); ^{1}H NMR ($CDCl_3$) δ 6.39 [d, $J_{1,2}$ = 4.5 Hz, 1 H, H-1 (β-anomer)], 6.30 [s, 1 H, H-1 (α-anomer)], 5.17 (m, 1 H, H-3), 4.25–4.50 (m, 4 H, H-2, H-4, H-5,5$_a$), 2.11, 2.13, (2s, 9 H, CH_3CO). Anal. Calcd for $C_{11}H_{15}ClO_7$: C, 44.83; H, 5.13; Cl, 12.03. Found: C, 44.93; H, 5.17; Cl, 12.17.

Methyl 3,5-*O*-(Tetraisopropyldisiloxane-1,3-diyl)-α,β-D-arabinofuranosides (14). A 2.91-g (17.7-mmol) sample of methyl α,β-D-arabinofuranosides (**9**)[31] was protected with 6.13 mL (19.5 mmol) of dichlorotetraisopropyldisiloxane (Petrarch) following the procedure described for **10**. By limiting the reaction time to 1 h, byproducts were minimized, giving 5.1 g (71%) of the desired product **14** (1:4 α/β-anomers) after chromatography using 9:1 hexane–ethyl acetate: $[\alpha]^{22}_D$ +51.2° (*c* 1, methanol); R_f 0.68 (8:2

chloroform–ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 4.80 [s, 1 H, H-1 (α-anomer)], 4.75 [d, 1 H, $J_{1,2}$ = 4.4 Hz, H-1 (β-anomer)], 4.10–4.25 (m, 2 H, H-2, H-3), 3.7–3.99 (m, 3 H, H-4, H-5,5$_a$), 3.40 (s, 3 H, OCH_3), 1.04–1.1 (m, 28 H, $(CH_3)_2CH$). Anal. Calcd for $C_{18}H_{38}O_6Si_2$: C, 53.16; H, 9.42. Found: C, 53.02; H, 9.47.

Methyl 2-*O*-Acetyl-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-β-D-arabinofuranoside (15). By the same procedure as described for **11**, 81 mg (0.2 mmol) of methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α,β-D-arabinofuranosides (**14**) was acetylated with 0.2 mL (2 mmol) of acetic anhydride in 4 mL of dry pyridine to yield 63 mg (70%) of the β-acetate **15** (the only anomer isolated): $[\alpha]^{22}_D$ −54.9° (*c* 1, chloroform); R_f 0.50 (chloroform); GC/MS (k' = 32.8), *m/z* (relative intensity) 417 (4, M − OCH_3), 405 (4, M − $(CH_3)_2CH$), 345 (4), 291 (12), 277 (100), 116 (30), 43 (19, $(CH_3)_2CH$); ^{1}H NMR ($CDCl_3$) δ 5.16 (dd, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 5.3 Hz, 1 H, H-2), 4.77 [d, 1 H, H-1 (β-anomer)], 4.31 (ψt, $J_{2,3} = J_{3,4}$, 1 H, H-3), 3.92–4.02 (m, 3 H, H-4, H-5,5a), 3.38 (s, 3 H, OCH_3), 2.1 (s, 3 H, CH_3CO), 1.0–1.1 (m, 28 H, $(CH_3)_2CH$). Anal. Calcd for $C_{20}H_{40}O_7Si_2$: C, 53.53; H, 8.99. Found: C, 53.70; H, 9.06.

Methyl 2-Chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α-D-ribofuranoside (17). A 203-mg (0.5-mmol) sample of methyl 3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α,β-D-arabinofuranosides (**14**) was transformed to 172 mg (81%) of methyl 2-chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α-D-ribofuranoside (**17**) via the triflate **16**, following the procedure described under **13-C**: $[\alpha]^{22}_D$ +11.6° (*c* 1, chloroform); R_f 0.71 (8:2 chloroform–toluene); GC/MS (k' = 18.7), *m/z* (relative intensity) 381 (28, M − $(CH_3)_2CH$), 349 (16), 321 (39), 249 (100); ^{1}H NMR ($CDCl_3$) δ 5.08 (d, $J_{1,2}$ = 4.0 Hz, 1 H, H-1), 4.39 (ψt, $J_{2,3} = J_{3,4}$ = 6.4 Hz, 1 H, H-3), 4.30 (dd, J = 6.3 Hz, H-2), 4.08 [m, (width 15 Hz), 1 H, H-4], 3.96 [m, 2 H, (AB of ABX, $J_{5,5a}$ = 12.6 Hz, $J_{4,5}$ = 3.0 Hz, $J_{4,5a}$ = 5.4 Hz), H-5,5a], 3.50 (s, 3 H, OMe), 1.03–1.08 [m (4 lines), 28 H, $(CH_3)_2CH$]. Anal. Calcd for $C_{18}H_{37}ClO_5Si_2$: C, 50.85; H, 8.77. Found: C, 50.97; H, 8.77.

1,3,5-Tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-ribofuranoses (5). 1,3,5-Tri-*O*-acetyl-2-chloro-2-deoxy-α,β-D-ribofuranoses (**5**) were obtained in 89% yield (62 mg) from the acetolysis of 100 mg (0.24 mmol) of methyl 2-chloro-2-deoxy-3,5-*O*-(tetraisopropyldisiloxane-1,3-diyl)-α-D-ribofuranoside (**17**), performed in a similar fashion as described for **13**. The spectroscopic, chromatographic and optical rotation {$[\alpha]^{22}_D$ +35.8° (*c* 1, chloroform)} data were found to be identical with those obtained for the product from the acetolysis of **3**. (For a comparison of ^{1}H NMR spectra, see Figure 1.)

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A ^{13}C NMR Study of Electronic Effects in the Hydrogen Bonding of Trifluoroacetic Acid with Substituted Benzenes, 1- and 2-Substituted Naphthalenes, and 9-Substituted Anthracenes in Chloroform

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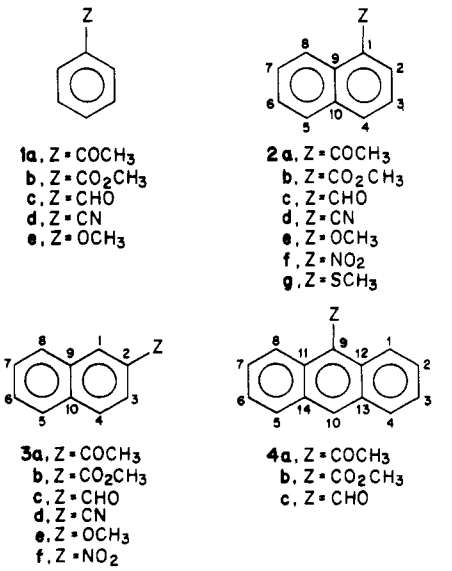
Considerable changes are produced in the ^{13}C chemical shifts of monosubstituted benzenes, 1- and 2-substituted naphthalenes, and 9-substituted anthracenes bearing the $COCH_3$, CO_2CH_3, CHO, OCH_3, and CN substituents on titrating with trifluoroacetic acid in deuteriochloroform. These shift displacements are interpreted in the light of electronic and steric effects associated with the formation of hydrogen bonds.

Titrating the weak bases, **1–4**, with trifluoroacetic acid (hereafter TFA) in deuteriochloroform causes considerable displacements of their ^{13}C NMR signals as a result of hydrogen bonding. In a previous paper[1] methods were described for using such changes in shift to calculate the values of equilibrium constants corresponding to the formation of various hydrogen-bonded aggregates. It is the purpose of the present work to try to gain some insight into the electronic and steric factors associated with the formation of hydrogen bonds in these systems through a more detailed analysis of their ^{13}C NMR shifts.

Earlier studies have shown[2,3] that the ^{13}C chemical shifts of carbonyl and methoxy substituents in aromatic systems are not the same for the in-plane as for the out-of-plane geometries. Therefore, differences in the average conformations of many of the basic substituents of the series **1–4** in solution may be readily recognized by observing the relative positions of their ^{13}C resonances. As seen in Table I the carbonyl shifts of formyl, acetyl, and methyl carboxylate substituents, as well as the methyl shifts of these



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