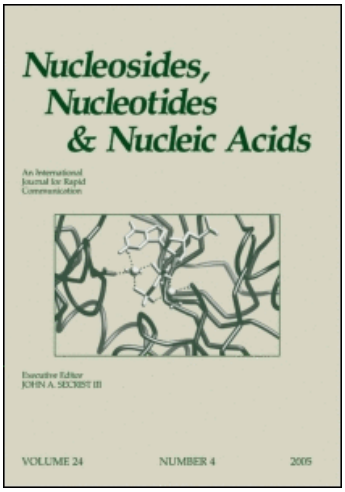

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SYNTHESIS AND STEREOCHEMICAL ASSIGNMENTS FOR 2-(α- AND β-D-ARABINOFURANOSYL)THIAZOLE-4-CARBOXAMIDES

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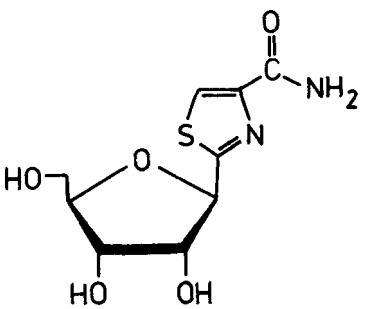
Abstract: Both 2-(α- and β-D-arabinofuranosyl)thiazole-4-carboxamides were synthesized from 2,3,5-tri-O-benzyl-1-O-(p-nitrobenzoyl)-D-arabinofuranose via the 1-cyano- and 1-thioamide sugars. Anomeric assignments were made based on ^{1}H and ^{13}C NMR, as well as on CD spectra.

The thiazole C-nucleoside, tiazofurin [2-(β-D-ribofuranosyl)thiazole-4-carboxamide, **1**],[1,2] has created



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considerable interest among cancer researchers as the compound has demonstrated remarkable antitumor activity, especially against both primary and metastatic Lewis lung carcinoma.[3] The synthesis of **1** is reported[1,2] to proceed smoothly from 2,5-anhydro-3,5,6-tri-O-benzoyl-D-allononitrile[4] (i.e., "2,3,5-tri-O-benzoyl-D-ribofuranosyl cyanide") in a three-step synthesis via the 2,5-anhydro-

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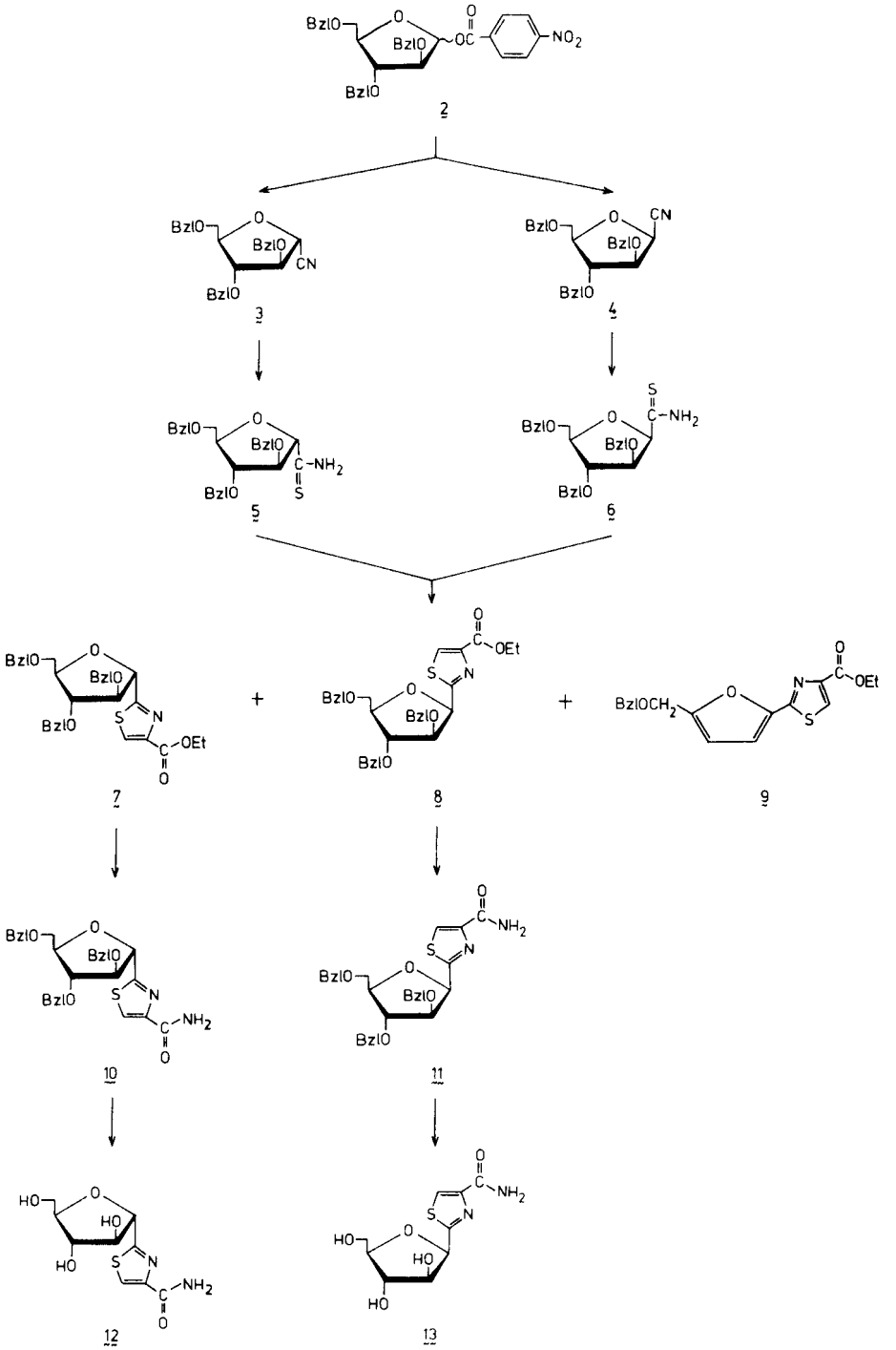
3,5,6-D-allonothioamide,[1,2,5] and the latter reagent's condensation with ethyl α-bromopyruvate, which gives, upon removal of the benzoyl protecting groups, **1** in an acceptable overall yield. Little difficulty is experienced in the synthesis apart from the ring-forming step which gives both α- and β-anomers[6] of the protected C-nucleoside,[2] along with a furan-2-yl by-product.[1,2]

In a program in which we are exploring certain analogues of **1** for possible antitumor activity, a synthesis of the β-D-arabinofuranosyl counterpart to **1** was required. Such synthetic C-glycosyl compounds of the D-arabino configuration, of which only a few examples are known,[7-13,16] in contrast to their D-ribofuranosyl counterparts, can present special problems in both synthesis and anomer assignment. Herein is described the synthesis and structural assignments for both the α- and β-D-arabinofuranosyl analogues to **1** (**12** and **13**), along with complete correlation of their spectral properties with anomeric configuration.

RESULTS AND DISCUSSION

Chemistry. The synthetic sequence to the desired 2-(β-D-arabinofuranosyl)thiazole-4-carboxamide (**13**) was patterned after that for **1**. (See Scheme I.) The benzyl protecting group was chosen in lieu of ester protecting groups (e.g., benzoyl, as in the synthesis of **1**) as the latter would be expected to give predominantly the α-anomer via neighboring-group participation as in the case of the preparation of the D-allo[14,15] and other C-glycosyl analogues.[16] The requisite cyanosugar, 2,5-anhydro-3,4,6-tri-O-benzyl-D-glucononitrile (**4**) was prepared, along with the D-manno isomer **3** by reacting cyanotrimethylsilane with



SCHEME 1

2,3,5-tri-O-benzyl-1-O-(p-nitrobenzoyl)-D-arabinofuranose (**2**) in the presence of the Lewis acid, trimethylsilyl trifluoromethanesulfonate, in acetonitrile. The products, a mixture of **3** and **4** in a ratio of ~7:3 (97% total yield), could be separated and obtained analytically pure on preparative LC and were spectroscopiclly identical with those obtained by Acton and co-workers by reacting **2** with mercuric cyanide.[7] The present spectroscopic data (See Table 1.) support the original assignments[7] in that the ^{13}C NMR resonance for the cyano group's carbon in the β-anomer **4**, where the cyano group is more sterically compressed, is shown to resonate at higher field ($\Delta\delta$= 1.1 PPM) as expected.[16] The β-anomer **4** exhibited an $[\alpha]_D$ = -9.2°, whereas the α-anomer had an $[\alpha]_D$ = +37.1°. No CN-group absorption was detected in the IR spectra for either **3** or **4**.

Conversion of the α- and β-cyanosugars **3** and **4** to the respective 2,5-anhydro-3,4,6-tri-O-benzyl-D-mannonothioamide (**5**) and the D-gluco isomer **6** was carried out in liquid hydrogen sulfide under catalysis by 4-(dimethylamino)pyridine as generally described for the D-allo analogue.[2,5] No evidence of an α,β-mixture was evident in either **5** or **6** as determined by both TLC and ^1H NMR spectroscopy. The ^1H NMR spectra for **5** and **6** showed, among other resonances, an upfield shift for the H-2 (anomeric) resonance of the trans-α-anomer **5**, relative to that for **6**, as would be expected based on the findings of Nishimura and Shimizu.[17] The H-2 - H-3 spin-spin coupling constants remained small for both **3** and **5** ($J_{2,3}$ = 2.2 and <1 Hz, respectively) and somewhat larger for the cis-oriented **4** and **6** ($J_{2,3}$ = 4.8 and 4.2 Hz, respectively), facts, which taken together with the chemical shift data for H-2,

TABLE 1. Selected Spectroscopic and Optical Roation Data For Compounds 3 - 13.[a]

Compound	Anomeric H	$J_{1',2'}$ or $J_{2,3}$ (Hz)	Aglyconic C[b]	$[\alpha]_D$ (%, Solvent)
3	4.72[c]	2.2	116.9[c]	+37.1° (2, $CHCl_3$)
4	4.73[c]	4.8	115.8[c]	-9.2° (2, $CHCl_3$)
5	4.90[c]	<1.0	204.8[c]	-5.1° (2, $CHCl_3$)
6	5.05[c]	4.2	201.7[c]	+43.0° (1, $CHCl_3$)
7	5.48[c]	2.2	173.5[c]	-7.2° (1, $CHCl_3$)
8	5.56[c]	3.8	169.2[c]	+24.4° (1, $CHCl_3$)
9	--	--	--	0° (1, $CHCl_3$)
10	5.35[c]	2.9	172.3[c]	+15.9° (2, $CHCl_3$)
11	5.41[c]	3.8	168.2[c]	+39.7° (2, $CHCl_3$)
12	4.98[d] 5.19[e]	4.6 5.5	154.9[e]	+12.0° (1, MeOH)
13	5.24[d] 5.49[e]	3.1 4.1	152.2[e]	+63.6° (1, MeOH)

[a] For complete spectral data, see the Experimental section.

[b] C is C-1 for compounds **3 - 6**; C is C-2 of the thiazole moiety for compounds **7 - 13**.

[c] Solvent: chloroform-d. [d] Solvent: methyl sulfoxide-d_6. [e] Solvent: D_2O.

indicate strongly that the stereochemistry at the C-2 (anomeric centers) had remained intact. The ^{13}C NMR resonances for the thiocarbonyl carbons in **5** and **6** appeared at δ 204.8 and 201.7, respectively, which, by analogy with the C-1 resonances for the cyano precursors **3** and **4**, support the assigned anomeric configurations. It is interesting to note, however, that the signs for the optical rotations at the sodium D-line (See Table 1.) reversed in going from **3** → **5** and from **4** → **6**.

The condensation of either thioamide **5** or **6** with ethyl α-bromopyruvate was carried out at 0 - 23 °C in acetonitrile to give essentially three products, the ethyl 2-(2,3,5-tri-O-benzyl-α-D-arabinofuranosyl)thiazole-4-carboxylate (**7**), its β-D-arabinofuranosyl anomer **8**, and the product of elimination, ethyl 2-(5-benzyloxymethylfuran-2-yl)thiazole-4-carboxylate (**9**). The α:β product ratio was essentially 1:1 (57% overall yield), with ~11% of the furan-2-yl by-product **9**. Compounds **7** and **8**, both syrups, were easily separated by preparative LC; however, considerable amounts of the by-product **9** contaminated **8**, necessitating use of the recycle mode on the LC to obtain pure **8** and **9**. The protected nucleosides **7** and **8** were clearly differentiated on TLC, and their ^{1}H NMR spectra served to indicate their structures. The H-1 proton for the α-anomer **7** appeared as a narrow doublet at δ 5.48 ($J_{1',2'}$ = 2.2 Hz), while the β-anomer **8** gave a broader doublet at δ 5.56 ($J_{1',2'}$ = 3.8 Hz), indicating a probable cis-relationship for the latter, based on the general trends shown for the sequences **3** → **5** → **7** and **4** → **6** → **8** and the generalized relationships previously established.[17] ^{13}C NMR chemical shift data that showed an upfield shift for the heterocyclic C-2 carbon of **8** (δ 169.2) relative to

that for **7** (δ173.5) supported these assignments. The optical rotation data showed negative $[\alpha]_D$-values for both **5** and **7**, and positive values for the β-anomers, **6** and **8**. (See Table 1.)

The by-product **9**, a compound of limited stability, was identified on the basis of its ^{1}H NMR spectrum, elemental analysis and the fact that it had an optical rotation of **Ø**°. An analogous furan-2-yl product was encountered in the synthesis of **1**.[1,2]

The conversion of the nucleoside thiazole carboxylates **7** and **8** to their respective amides, 2-(2,3,5-tri-O-benzyl-α-D-arabinofuranosyl)thiazole-4-carboxamide **1Ø**, and its β-anomer **11**, was accomplished in saturated methanolic ammonia at room temperature. The resulting syrupy nucleosides, purified by column chromatography, were fully characterized by spectroscopy and elemental analysis. (See Table 1 and Experimental section.) The ^{1}H NMR spectra for **1Ø** and **11** showed essentially the same interrelationships as did their precursors, with the H-1' of **1Ø** resonating at slightly higher field than that for **11**, indicating a trans configuration for **1Ø**; however, the H-1' - H-2' spin-spin couplings for **1Ø** and **11** were considered too close to be of interpretative value. The ^{13}C NMR data that showed an upfield shift for the C-2 of **11**, relative to that for **1Ø**, however, strongly supported the indicated assignments. The optical rotation data, while not showing opposite signs for **1Ø** and **11**, did give a value for **1Ø** that was considerably smaller than that for **11**. (See Table 1.) No evidence for anomerization, a potential problem with some C-nucleosides in either acidic[13] or in basic media,[18] was observed.

Debenzylation of the protected nucleosides **1Ø** and **11** was cleanly effected using boron tribromide in anhydrous

dichloromethane,[19] and the free nucleosides, the 2-(α-D-arabinofuranosyl)thiazole-4-carboxamide (**12**) and its β-anomer **13**, were purified by preparative reverse-phase LC to furnish the syrupy products in good yield. While both **12** and **13** were indistinguishable on silica gel TLC, these were readily analyzed on C-18 reverse-phase media, and no evidence of anomerization (i.e., mixtures of **12** and **13**) was evident in the debenzylation of either **10** or **11**. Examination of the ^{1}H NMR spectra for **12** and **13** revealed (See Table 1 and Experimental section.) that the H-1' signal of the proposed α-anomer **12** resonated at higher field in line with that observed with previous examples (i.e., compounds **3**, **5**, **7** and **10**) and in agreement with the predicted[17] position relative to that for **13**. The ^{13}C NMR chemical shift value for C-2 of the thiazole moiety continued to resonate at higher field in the β-anomer **13**.

Structural Assignments for 12 and 13. While the structural assignments for **12** and **13**, as well as those for their precursors, seem reasonably secure based on the spectroscopic data (Table 1) presented in the foregoing discussion, it was deemed desirable, particularly in view of the anomerization encountered in the conversion of **5** and **6** to **7** and **8**, to establish the configurations on a firm basis, preferably based on data from known, closely related examples. This requirement becomes particularly important as one peruses the literature[7-13] of D-arabinofuranosyl C-nucleosides and encounters widely differing, often conflicting, claims for the assignment of anomeric configuration.

The most striking observation[20] was that the ^{1}H NMR spectrum (200 MHz, methyl sulfoxide-d_6) of the α-D-arabinofuranosyl anomer **12** was identical in all respects (i.e., in

chemical shift and spin-spin coupling patterns) to that for the β-D-ribofuranosyl isomer **1**.[21] These data were established visually and confirmed by computer-assigned chemical shift data. Only when the solutions of **12** and **1** were mixed and multiple resonances were observed[22] for the two compounds, was the diastereomeric relationship established between the sample of **12** and that of **1**. Furthermore, a comparison of the ^{1}H NMR data for the β-D-arabinofuranosyl isomer **13** with that published[2] for the α-anomer of **1** revealed a similar, albeit a less striking relationship: δ5.24 ($J_{1',2'}$ = 3.1 Hz) for H-1' of **13**; reported[2] for the α-anomer of **1**: δ5.3 ($J_{1',2'}$ = 3.5 Hz). Thus the β-D-ribofuranosyl system of **1** and the α-D-arabinofuranosyl isomer **12**, both with trans-substitution patterns correlate exactly; also, the cis-substituted pairs (i.e., the α-anomer of **1** and **13**) correlate well. By inspecting Table 1, one sees that the rule established by Nishimura and Shimizu[17] appears to be valid for these examples.

The ^{13}C NMR chemical shift data for the aglyconic carbons (i.e., C-1 of **3** - **6** and C-2 of the thiazole moiety of **7** and **8** and **10** - **13**) for **12**, **13** and their precursors consistently show upfield shifts for the β-anomers, a fact in line with observations of others, both on D-arabinofuranosyl-[16] and on cis-α-D-ribofuranosyl compounds.[18] In order to establish precisely what other C-atoms might reflect the effects of anomeric differences, much as was done for the D-ribofuranosyl analogues in the classical studies of Moffatt and co-workers,[18] a reliable ^{13}C chemical shift assignment was necessary for all of the sugar ring carbons, especially C-1' and C-2'. To this end was carried out a two-dimensional NMR experiment (See Experimental section.) which permitted an exact C-atom

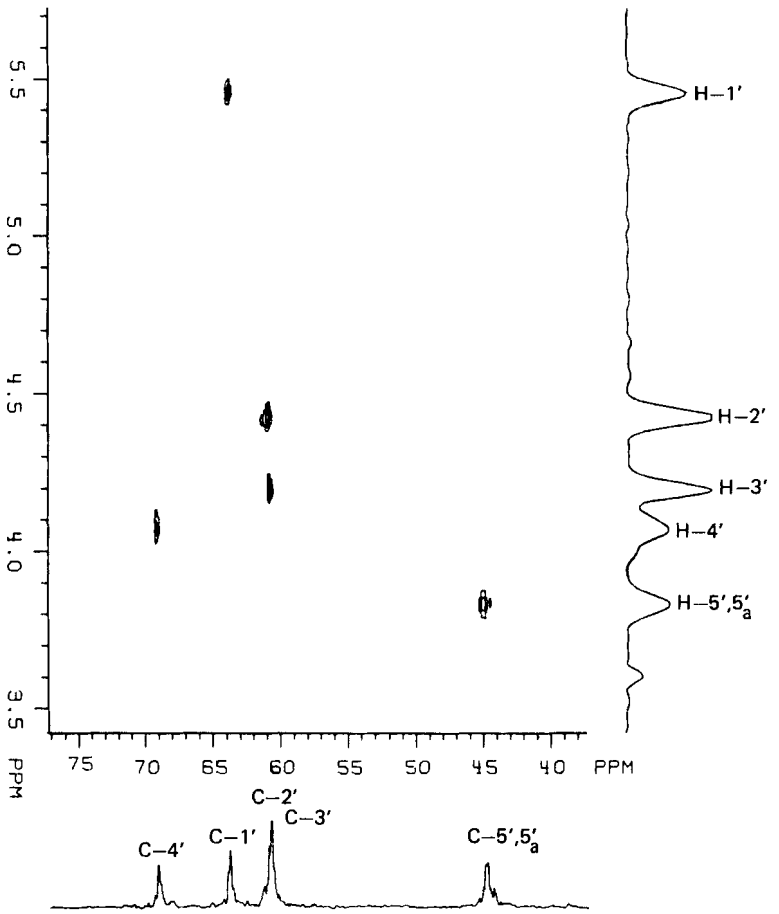


FIG. 1: 2DFT NMR Heteronuclear Shift Correlation Spectrum

The ^{1}H and ^{13}C NMR spectra are correlated through one-bond scalar couplings. A contour plot of the two-dimensional dataset is shown. The projection onto the ordinate yields the ^{1}H spectrum, while the projection onto the abscissa yields the ^{13}C spectrum.

assignment, based on the unambiguous assignments for all of the protons in the ^{1}H NMR of **13**. (See Fig. 1. Note the otherwise possible confusion among C-1', C-2', C-3' and C-4'.) By analogy, the carbon assignments were made for **12**, with some uncertainty existing in the assignments for C-1' and C-2', which differ by only **Ø**.1 PPM. The combined data for **12** and **13** (See Tables 1 and 2.) then show that for the

TABLE 2. ^{13}C NMR Chemical Shift Data for Compounds 12 and 13.[a]

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-4	C-5	C=O
12[b]	64.82[c]	64.72[c]	59.53	67.79	44.23	131.3	109.2	148.2
13[d]	63.86	60.91	60.77	69.06	44.88	131.0	109.5	148.6

[a] For C-2 shift data, see Table 1.

[b] Assignments made through comparison with those for 13.

[c] Assignments may be reversed between C-1' and C-2'.

[d] Assignments based on two-dimensional NMR experiment.

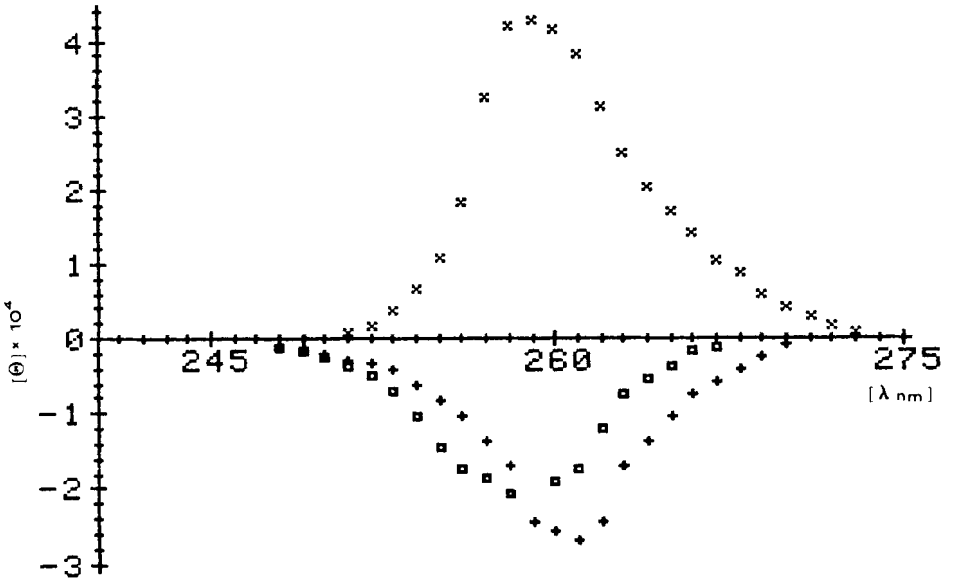


FIG. 2: CD Spectra for Compounds 1, 12 and 13

(+) = 1; (x) = 12; (□) = 13.

β-anomer **13**, in which both C-1', C-2' and the C-2 of the thiazole ring are sterically compressed by the cis-substituents, the resonances appear at distinctly higher field, a fact that is analogous to that observed in a set of D-ribofuranosyl C-nucleoside precursors where the α-anomers showed these upfield shifts.[18] It is likely that this trend would apply to the precursors if reliable assignments were available for them.

Finally, the question of chiroptical properties vs. structure was resolved by the CD spectra shown in Fig. 2. While a general trend of a larger, more dextrorotatory specific optical rotation for the β-anomer at the sodium D-line was consistently noted in each pair of those compounds with a definite aglyconic chromophore (i.e., compounds **5** - **13**, excluding **3** and **4** where the contribution of the weakly absorbing -CN group is outweighed by O-benzyl), the fact

that the β-anomer **13** and tiazofurin **1** both show powerfully negative CD's while the α-anomer **12** exhibits a strongly positive curve adds to the similarities between the two series.

Conclusions. In summary, the D-arabinofuranosyl compounds presented generally conform to the various spectroscopic "rules" or "trends" established for D-ribofuranosyl compounds in general. While no ^{1}H NMR "Δδ" rules for 1,2-O-isopropylidene derivatives[23] are possible, and "geometry-only" methods require 3',5'-cyclic phosphate derivatives,[24] which can present a problem for D-arabinofuranosyl compounds, both the time-honored ^{1}H NMR chemical shift data for anomeric protons[17] and the steric compression phenomenon between C-1' and C-2' substituents that gives rise to upfield shifts[16,18] in the cis-substituted examples for C-1', C-2' and the aglyconic carbon, seem operative, based on a firm comparison with the β-D-ribofuranosyl derivative **1**.

EXPERIMENTAL

General Methods. Solvents were evaporated at aspirator vacuum at ~40 °C, and the syrupy products were dried at 25 - 60 °C (<0.1 torr). Melting points were determined using a Thomas-Hoover "Unimelt" capillary melting point apparatus equipped with a Cole-Parmer model 8520-50 Digi-sense digital thermometer/8520-55 thermocouple combination that was calibrated with known standards. Infrared (IR) spectra were recorded on a Perkin-Elmer model 710B spectrophotometer. Ultraviolet (UV) spectra were recorded in 1-cm cells on a Varian Associates DMS-100 UV-VIS specrophotometer. Optical rotations were measured on a Perkin-Elmer model 241 digital spectropolarimeter using a 1-dm cell.

^{1}H NMR (at 200 MHz) and ^{13}C NMR (at 50.3 MHz) spectra were determined using a Nicolet NT-200 instrument. Chemical shifts are reported in δ-units downfield from internal tetramethylsilane; "*" indicates that the signal disappears upon addition of D_2O. Multiplicities are first-order values (in Hz) and are indicated thusly: d, doublet; dd, doublet of doublets; m, multiplet; q, quartet; s, singlet; t, triplet; ψt, "pseudo-triplet". Solutions were typically ~0.1% for ^{1}H NMR and ~10% for ^{13}C NMR. The 2DFT heteronuclear shift correlation spectrum (Fig. 1) was obtained with ^{13}C decoupling during the evolution period (via a 180° pulse) and ^{1}H decoupling during detection.[25] The pre- and post-mixing pulse delays were 3.3 and 1.7 msec, respectively. The proton 90° pulse was applied through the decoupler and was 40 μsec. The proton frequency was set to 3.4 PPM, and the step size of the evolution period was 1 msec corresponding to a ±500 Hz sweep window in the proton dimension. A total of 128 spectra of 512 real datapoints were collected. The data was processed with 10 Hz of artificial line broadening applied in both dimensions and with zero-filling in the ^{1}H dimension. The power spectrum of the proton dimension was obtained.

Adsorption chromatography was carried out using E. Merck silica gel-60 products: (a) TLC on 0.2 mm aluminum-backed plates (catalog no. 5760); (b) open-column chromatography using 70-200 μm silica gel (catalog no. 7734). Analytical HPLC was conducted on an Altex-Beckman unit using 254 nm UV detection and a 0.5 x 40-cm column of Spherisorb C-18 (packed in-house); solvent: 1:9 methanol - water (pH 6.86); flowrate = 2.0 mL min^{-1}. Preparative LC was carried out using a Waters Associates Prep-500A

instrument either (a) in the adsorption mode using two Prep-Pak-500/Silica Gel cartridges or (b) in the reverse-phase mode using one Prep-Pak-500/C-18 cartridge. Solvents include: A. 3:7 ethyl acetate - hexane; B. 95:5 chloroform - ethyl acetate; C. 9:1 chloroform - methanol; D. water - methanol 9:1; E. 7:3 chloroform - methanol. All solvents and reagents were "reagent grade" unless otherwise noted.

2,5-Anhydro-3,4,6-tri-O-benzyl-D-mannononitrile (3) and 2,5-Anhydro-3,4,6-tri-O-benzyl-D-gluconononitrile (4). To 40 g (70 mmol) of 2,3,5-tri-O-benzyl-1-O-(p-nitrobenzoyl)-D-arabinofuranose (**2**, Pfanstiehl Laboratories) in 300 mL of dry acetonitrile was added dropwise during 0.5 h 20.8 g (210 mmol) of cyanotrimethylsilane (Petrarch), followed by the dropwise addition of 33 mL of a 0.22 M solution (7.2 mmol) of trimethylsilyl trifluoromethanesulfonate (Fluka) in dichloromethane during 10 min. The mixture was stirred for 5 h at room temperature, at the end of which time 200 mL of saturated aqueous sodium bicarbonate was added to the yellow solution. The mixture was extracted with 3 x 300 mL of ether, and the combined organic layers were dried over magnesium sulfate and concentrated to provide a yellow syrup which was rapidly chromatographed over a short (125-g) column of silica gel slurry-packed in and eluted with chloroform to provide, upon evaporation of the solvent, a crude mixture of **3** and **4** that was suitable for conversion directly to **5** and **6**.

The mixture of **3** and **4** was separated into the pure components by preparative LC over silica gel using 95:5 hexane - ethyl acetate as eluent giving 20 g (67%) of pure **3** in 55 min and 10 g (33%) of pure **4** in 75 min (flowrate 250 mL min^{-1} at ~225 psi).

Physical data for **3**: Syrup; R_f 0.38 (A); IR (chloroform) 1100(s), 1360(m), 1450(m), 2830(m) cm^{-1}; UV

(methanol) 257 nm (ε830); ^{1}H NMR (chloroform-d) δ 3.58 (2H, m, H-6,6$_a$), 4.05 [1H, m (width 6.6 Hz) H-5], 4.31 (2H, m, H-3, H-4), 4.52 (6H, m, PhC$\underline{H}_2$), 4.72 (1H, d, $J_{2,3}$ = 2.2 Hz, H-2), 7.32 (15H, m, Ph$\underline{H}$); ^{13}C NMR (chloroform-d) δ 69.02, 83.06, 83.54, 86.54 (sugar ring C's), 69.02, 70.41, 72.43, 73.40 (C-6 and PhC$\underline{H}_2$) and 116.9 (CN).

Anal. Calcd. for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.35; N, 3.25. Found: C, 75.37; H, 6.38; N, 3.22.

Physical data for **4**: Syrup; R_f 0.33 (A); IR (chloroform) 1100(s), 1360(m), 1450(m), 2830(m) cm^{-1}; UV (MeOH) 257 nm (ε742); ^{1}H NMR (chloroform-d) δ 3.61 (2H, m, H-6,6$_a$), 4.06 [1H, m (width 6 Hz), H-5], 4.16 (2H, m, H-3, H-4), 4.59 (6H, m, PhC$\underline{H}_2$), 4.73 (1H, d, $J_{2,3}$ = 4.8 Hz, H-2), 7.30 (15H, m, Ph), ^{13}C NMR (chloroform-d) δ 69.42, 82.41, 82.47, 83.39 (sugar ring C's), 69.65, 71.98, 72.70, 73.44 (C-6 and PhC$\underline{H}_2$) and 115.8 (CN).

Anal. Calcd. for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.35; N, 3.25. Found: C, 75.31; H, 6.39; N, 3.20.

2,5-Anhydro-3,4,6-tri-O-benzyl-D-mannonothioamide (5). A mixture of (18.0 g, 42.0 mmol) of 2,5-anhydro-3,4,6-tri-O-benzyl-D-mannononitrile (**3**), 0.4 g (3.3 mmol) of 4-(dimethylamino)pyridine and 20 g (0.59 mol) of liquid hydrogen sulfide was shaken in a sealed stainless steel bomb (capacity 150 mL) at room temperature for 24 h. At the end of this time, the excess hydrogen sulfide was vented into saturated aqueous sodium carbonate, the syrupy residue was dissolved in 200 mL of dichloromethane, and the extract was washed with 2 x 100 mL of water. The combined organic extracts were dried over magnesium sulfate, and the solvent was evaporated to give 18.2 g of **5** as a light yellow syrup that was purified by column chromatography over 200 g of silica gel using 98:2 chloroform - methanol

as eluent; yield 15.9 g (82%) of pure **5** after drying under high vacuum; R_f Ø.23 (B); IR (chloroform) 11ØØ(s), 1595(s), 285Ø(m), 3234(m), 3268(m) cm^{-1}; UV (methanol) 268 nm (ε 12,3ØØ); ^1H NMR (chloroform-d) δ 3.59 (2H, m, H-6,6_a), 3.87 (1H, m, H-5), 4.28 - 4.9Ø (9H, m, H-2, H-3, H-4 and $PhCH_2$), 7.26 (15H, m, Ph), 7.7Ø, 8.14 (2H, 2bs, NH); ^{13}C NMR (chloroform-d) δ 69.89, 83.42, 85.1Ø, 87.26, 89.55, (sugar ring C's), 71.42, 71.64, 73.35 ($PhCH_2$), 2Ø4.8 (C=S).

Anal. Calcd. for $C_{27}H_{29}NO_4S$: C, 69.95; H, 6.31; N, 3.Ø2; S, 6.92. Found: C, 69.82; H, 6.33; N, 3.ØØ; S, 6.85.

2,5-Anhydro-3,4,6-tri-O-benzyl-D-gluconothioamide (6). By the same procedure used for **5**, 9.Ø g (21 mmol) of **4**, Ø.2Ø g (1.7 mmol) of 4-(dimethylamino)pyridine and 13 g (Ø.37 mol) of liquid hydrogen sulfide was reacted to give, after workup and chromatography, 8.8 g (9Ø%) of pure **6** as a light yellow syrup; R_f Ø.28 (B); IR (chloroform) 11ØØ(s), 1595(s) 285Ø(m), 3234(m), 3268(m) cm^{-1}; UV (methanol) 267 nm (ε12,3ØØ); ^1H NMR (chloroform-d) δ 3.61 (2H, m, H-6,6_a), 3.86 (1H, m, H-5), 4.24 - 4.71 (8H, m, H-3, H-4 and PhCH), 5.Ø5 (1H, d, $J_{2,3}$ = 4.2 Hz, H-2), 7.28 (15H, m, Ph), 7.48, 8.13 (2H, 2bs, 2NH); ^{13}C NMR (chloroform-d) δ 69.72, 82.54, 83.37, 83.82, 87.43 (sugar ring C's), 71.51, 73.1Ø, and 73.48 ($PhCH_2$), 2Ø1.7 (C=S).

Anal. Calcd. for $C_{27}H_{29}NO_4S$: C, 69.95; H, 6.31; N, 3.Ø2; S, 6.92. Found: C, 69.72; H, 6.34; N, 2.97; S, 6.84.

Condensation of 2,5-Anhydro-3,4,6-tri-O-benzyl-D-gluconothioamide (6) with Ethyl α-Bromopyruvate. Synthesis of the Nucleosides 7, 8 and 9. A cold (Ø °C) solution of 6.1 mL (8.5 g, 44 mmol) of ethyl α-bromopyruvate (9Ø% reagent, Aldrich) in 1Ø mL acetonitrile was added with stirring to an ice-cold solution of 7.5 g (16 mmol) 2,5-anhydro-3,4,6-tri-O-benzyl-D-gluconothioamide (**6**) in 1ØØ mL

of dry acetonitrile, and the mixture was stirred for Ø.5 h at Ø °C, then for 15 h at room temperature. At the end of that time, the solvent was evaporated leaving a brown oil to which was added 1ØØ mL of saturated aqueous sodium bicarbonate. The mixture was extracted with 3 x 2ØØ mL of ether, and the combined organic layers were washed with 3ØØ mL of water, dried over magnesium sulfate and evaporated at 2Ø °C/1-2 torr to give a yellow-orange oil which was subsequently passed over a short, 2ØØ-g column of silica gel (chloroform as both packing solvent and eluent). The product obtained upon evaporation of the solvent was a light yellow oil that showed three major zones by TLC; R_f Ø.23, Ø.26 and Ø.31 (A) for **9**, **8** and **7**, respectively. The mixture was separated by preparative LC on silica gel using chloroform as eluent (2ØØ mL/min^{-1}, 225 psi).

Ethyl 2-(2,3,5-Tri-O-benzyl-α-D-arabinofuranosyl)-thiazole-4-carboxylate (7). The fraction which eluted in a zone of retention time of 5.5 min [R_f Ø.31 (A)] on the preparative LC described in the previous paragraph was evaporated at 2Ø °C/1-2 torr to give 2.6 g (29%) of a yellow syrup: IR (chloroform) 11Ø5(s), 122Ø(m), 173Ø(s), 291Ø(m) cm^{-1}; UV (methanol) 235 nm (ε848Ø); ^1H NMR (chloroform-d) δ 1.42 (3H, t, CH_3CH_2); 3.65 (2H, m, H-5',5'$_a$), 4.1Ø [1H, m (width 4.6 Hz), H-4'], 4.38 - 4.78 (1ØH, m, H-2', H-3', $PhCH_2$, CH_3CH_2), 5.48 (1H, d, $J_{1',2'}$ = 2.2 Hz, H-1'), 7.28 (15H, m, Ph), 8.11 (1H, s, H-5); ^{13}C NMR (chloroform-d) δ14.39 (CH_3CH_2), 69.89, 81.97, 83.68, 83.98 (sugar ring C's), 71.49, 72.Ø9, 73.38 ($PhCH_2$), 146.5 (C-4), 161.5 (C=O); 173.5 (C-2).

Anal. Calcd. for $C_{32}H_{33}NO_5S$: C, 68.67, H, 5.94; N, 2.5Ø; S, 5.73. Found: C, 68.39; H, 6.Ø4; N, 2.46; S, 5.68.

Ethyl 2-(2,3,5-Tri-O-benzyl-β-D-arabinofuranosyl)-thiazole-4-carboxylate (8). The next peak to emerge (retention time 7.5 min) on preparative LC [R_f Ø.26 (A)] was collected, and the solvent was evaporated as for **7** to give 2.5 g (28%) of pure **8** as a light yellow syrup: IR (chloroform) 1105(s), 1220(m), 1730(s), 2910(m) cm^{-1}; UV (methanol) 236 nm (ε 8360); ^1H NMR (chloroform-d) δ 1.41 (3H, t, CH_3CH_2), 3.70 (2H, m, H-5',5'a), 4.11 (1H, m, H-4'), 4.21 - 4.60 (10H, m, H-2', H-3', $PhCH_2$, CH_3CH_2), 5.56 (1H, d, $J_{1'2'}$ = 3.8 Hz, H-1'), 7.3 (15H, m, Ph), 8.18 (1H, s, H-5); ^{13}C NMR (chloroform-d) δ 14.44 (CH_3CH_2), 61.38 (CH_3CH_2), 70.16, 81.39, 83.14, 83.65, 84.06 (sugar ring C's), 71.62, 72.15, 73.38 ($PhCH_2$), 146.5 (C-4), 161.5 (C=O) and 169.2 (C-2).

Anal. Calcd for $C_{32}H_{33}NO_5S \cdot 0.5\ H_2O$: C, 67.59; H, 6.02; N, 2.46; S, 5.63. Found: C, 67.43; H, 5.95; N, 2.43; S, 5.59.

Ethyl 2-(5-Benzyloxymethylfuran-2-yl)thiazole-4-carboxylate (9). The last component to elute (recycle mode) on preparative LC [R_f Ø.23 (A)],upon evaporation of the solvent, gave 1.0 g (18%) of **9** as a yellow syrup: IR (chloroform) 1100(s), 1220(m), 1720(s), 2900(m) cm^{-1}; UV (methanol) 309 nm (5750), 228 (8000); ^1H NMR (chloroform-d) δ 1.43 (3H, t, CH_3CH_2), 4.44 (2H, q, CH_2CH_3), 4.55, 4.60 (2H, 2H, s, s, H-5',5'a or $PhCH_2$-), 6.48 (1H, d, $J_{2',3'}$ = 3.3 Hz, H-3'), 7.14 (1H, d, H-2'), 7.34 (5H, m, Ph); 8.14 (1H, s, H-5).

Anal. Calcd for $C_{18}H_{17}NO_4S \cdot 0.8\ H_2O$: C, 60.59; H, 5.19; N, 3.82. Found: C, 60.77; H, 5.41; N, 3.50.

2-(2,3,5-Tri-O-benzyl-α-D-arabinofuranosyl)thiazole-4-carboxamide (10). Under dry conditions ammonia was passed into a solution of 4.2 g (7.5 mmol) of **7** in 20 mL of

methanol in a 150-mL stainless steel bomb at -78 °C until saturation was complete. The mixture was then shaken for 2 d at room temperature, at the end of which time the solvent and ammonia were evaporated, and the residual syrup was purified by chromatography over 200 g of silica gel (packed in chloroform, eluent C) to give 3.20 g (80%) of syrupy **10**: R_f 0.65 (C); IR (chloroform) 1095(s), 1360(m), 1570(m), 1670(s), 2850(m), 3400, 3500(d,m) cm^{-1}; UV (methanol) 237 nm (ε7460); ^1H NMR (chloroform-d) δ 3.66 (2H, d, H-5',5'$_a$), 4.15 [1H, (3 lines), H-4'], 4.41 - 4.73 (8H, m, H-2', H-3', PhC$\underline{H}_2$), 5.35 (1H, d, $J_{1',2'}$ = 2.9 Hz, H-1'), 7.30 (15H, m, Ph), 8.10 (1H, s, H-5); ^{13}C NMR (chloroform-d) δ 69.61, 82.72, 83.16, 84.18, 88.09 (sugar ring C's), 71.60, 71.99, 73.23 (Ph$\underline{C}H_2$), 149.7 (C-4), 163.5 ($\underline{C}$=O), 172.3 (C-2).

Anal. Calcd. for $C_{30}H_{30}N_2O_5S \cdot 0.5\ H_2O$: C, 66.77; H, 5.79; N, 5.19; S, 5.93. Found: C, 66.71; H, 5.99; N, 5.07; S, 5.97.

2-(2,3,5-Tri-O-benzyl-β-D-arabinofuranosyl)thiazole-4-carboxamide (11). By the same procedure used for **10**, 4.2 g (7.5 mmol) of **8** was converted to 3.3 g (85%) of **11**: R_f 0.65 (C); IR (chloroform) 1095(s), 1360(m), 1570(m), 1670(s), 2850(m), 3400, 3500 (d, m) cm^{-1}; UV (methanol) 237 nm (ε 7890); ^1H NMR (chloroform-d) δ 3.71 (2H, m, H-5', H-5'$_a$), 4.07 - 4.69 (9H, m, H-2', H-3', H-4', PhC$\underline{H}_2$), 5.41 (1H, d, $J_{1',2'}$ = 3.8 Hz, H-1'), 7.3 (15H, m, Ph), 8.15 (1H, s, H-5); ^{13}C NMR (chloroform-d) δ 70.03, 82.95, 83.53, 83.70, 83.71 (sugar ring C's), 71.53, 71.89, 73.38 (Ph$\underline{C}H_2$), 136.9 (C-4), 163.2 ($\underline{C}$=O), 168.2 (C-2).

Anal. Calcd for $C_{30}H_{30}N_2O_5S$: C, 66.77; H, 5.79; N, 5.19; S, 5.93. Found: C, 66.94; H, 5.94; N, 4.87; S, 5.64.

2-(α-D-Arabinofuranosyl)thiazole-4-carboxamide (12). To an ice-cold solution of 3.Ø g (5.7 mmol) of **1Ø** in 5Ø mL of dry dichloromethane under a dry nitrogen atmosphere was added 24 mL (24 mmol) of a 1 M solution of boron tribromide in dichloromethane (Aldrich), and the mixture was stirred for 3Ø min at Ø °C, then at room temperature for 5 h. The solvent was then evaporated at 2Ø °C to give a brown syrup to which 3 x 2ØØ mL of dry methanol was repeatedly evaporated. To the residue, dissolved in 5Ø mL of dry methanol, was added 6Ø mL of a cold, saturated solution of ethylene oxide in ether, which effectively neutralized the solution. The solvent was evaporated at 2Ø °C to give a golden yellow syrup that was purified on reverse-phase LC using eluent D. The appropriate fractions were partially evaporated, then lyophilized to give 1.Ø g (68%) of **12** as a white glass: mp 89 - 91 °C; R_f Ø.4 (E); T_r (HPLC) = 13 min; IR (KBr) 1Ø4Ø (s), 138Ø (m), 166Ø (s), 285Ø (m) and 33ØØ (s) cm^{-1}; UV (water) 238 nm (ε755Ø); ^1H NMR (methyl sulfoxide-d_6) δ 3.57 (2H, m, H-5',5'$_a$), 3.98 (2H, m, H-3', H-4'), 4.18 (1H, d, H-2'), 4.93 (1H, m, 5'-OH*), 4.98 (1H, d, $J_{1',2'}$ = 4.6 Hz, H-1'), 5.25 (1H, d, 2'-OH*), 5.68 (1H, d, 3'-OH*), 7.58, 7.72 (2H, bs, NH*) and 8.2Ø (1H, s, H-5); ^1H NMR (D_2O) δ3.84 (2H, m, H-5',5'$_a$), 4.22 (2H, m, H-3', H-4'), 4.44 (1H, m, H-2'), 5.19 (1H, d, $J_{1',2'}$ = 5.5 Hz, H-1') and 8.25 (1H, s, H-5).

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.53; H, 4.65; N, 1Ø.77; S, 12.32. Found: C, 41.45; H, 4.73; N, 1Ø.57; S, 12.13.

2-(β-D-Arabinofuranosyl)thiazole-4-carboxamide (13). By the procedure as for **12**, 3.Ø g (5.7 mmol) of **11** was converted to 1.Ø5 g (71%) of glassy **13**: mp 93 - 95 °C; R_f

Ø.4 (E); T_r (HPLC) = 14 min; IR (KBr) 1Ø4Ø (s), 138Ø (m), 166Ø (s), 285Ø (m), 33ØØ (s) cm^{-1}; UV (water) 237 nm (ε 83ØØ); ^1H NMR (methyl sulfoxide-$\underline{d}_6$) δ 3.61 (2H, m, H-5',5'$_a$), 3.84 [1H, (3 lines), H-4'], 4.Ø3 (2H, m, H-2', H-3'); 5.1Ø (1H, t, 5'-O$\underline{H}$*), 5.24 (1H, d, $J_{1',2'}$ = 3.1 Hz, H-1'), 5.33 (1H, d, 3'-O$\underline{H}$*), 5.44 (1H, d, 2'-O$\underline{H}$*), 7.52, 7.68 (2H, bs, N$\underline{H}$*), 8.17 (1H, s, H-5); ^1H NMR (D_2O) δ 3.85 (2H, m, H-5',5'$_a$), 4.1Ø [1H, m, 4 lines (width 5 Hz), H-4'], 4.22 (1H, m, H-3'), 4.45 (1H, ψt, $J_{2',3'}$ = ~3 Hz, H-2'), 5.49 (1H, d, $J_{1',2'}$ = 4.1 Hz, H-1') and 8.27 (1H, s, H-5).

Anal. Calcd for $C_9H_{12}N_2O_5S \cdot Ø.5\ H_2O$: C, 4Ø.15; H, 4.87; N, 1Ø.4Ø; S, 11.91. Found: C, 4Ø.Ø8; H, 4.75; N, 1Ø.18; N, 11.83.

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6. The term "anomer," although restricted in the classical sense to glycosides and thioglycosides (i.e., O- and S-glycosyl compounds) is employed throughout this paper for the analogous configurational relationships in C-glycosyl compounds, including C-nucleosides. For compounds **2** - **4**, the carbohydrate numbering system is used; for **5** - **13**, nucleoside numbering (i.e., heterocycle: non-primed numbers, glycosyl moiety: primed numbers) is used.

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20. The authors are indebted to F. L. Boyd, Jr. who pointed out this fact.

21. Compound **1** (NSC-286193) was obtained from the Drug Synthesis and Chemistry Branch of the National Cancer Institute. The structure of **1** (refs. 1 and 2) is firmly established.

22. Presumably the observed multiplicity of signals observed on admixture of **12** and **1** is due to a diastereomeric interaction between the two nucleosides.

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