2.40 (s, 3 H, CH_3); UV 259 (4.2); MS, 236 (36), 129 (100), 107 (12). Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 81.60; H, 4.96.

2,4-Dimethylphenyl phenylpropynoate (3c): mp 104–106 °C; IR 2230 (C≡C), 1730 (C=O, ester); NMR 7.90–7.21 (m, 5 H, C_6H_5), 7.18–6.83 (m, 3 H, $(CH_3)_2C_6H_3$), 2.25 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3); UV 260 (4.4); MS, 250 (7), 129 (100), 121 (7). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.28; H, 5.65.

1-(2-Hydroxy-5-methoxyphenyl)-3-phenylpropynone (4a): mp 85–86 °C; IR 2190 (C≡C), 1630 (C=O); NMR 11.30 (s, 1 H, OH), 7.80–6.68 (m, 8 H, Ar H), 3.83 (s, 3 H, OCH_3); UV 397 (3.8), 306 (4.4), 288 (4.3); MS, 252 (77), 251 (58), 150 (63), 129 (100), 105 (52). Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.06; H, 4.93.

1-(2-Hydroxy-5-methylphenyl)-3-phenylpropynone (4b): mp 57–60 °C; IR 2210 (C≡C), 1630 (C=O); NMR 11.40 (s, 1 H, OH), 8.00–6.81 (m, 8 H, Ar H), 2.42 (s, 3 H, CH_3); UV 370 (3.7), 306 (4.3), 294 (4.2); MS, 236 (100), 235 (36), 134 (98), 129 (5), 105 (18). Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12. Found: C, 80.87; H, 4.93.

1-(3,5-Dimethyl-2-hydroxyphenyl)-3-phenylpropynone (4c): mp 79–80 °C; IR 2210 (C≡C), 1630 (C=O); NMR 11.80 (s, 1 H, OH), 8.00–7.01 (m, 7 H, Ar H), 2.30 (s, 3 H, CH_3), 2.20 (s, 3 H, CH_3); UV 380 (3.7), 309 (4.3), 295 (4.2); MS, 250 (94), 249 (32), 222 (16), 148 (100), 129 (84), 105 (14). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.21; H, 5.93.

1-(2,4-Dimethylphenyl)-2-phenylethyne (7): oil; IR 1580, 1490, 1440; NMR 7.73–6.80 (m, 8 H, Ar H), 2.45 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3); MS, 206 (84), 205 (21), 191 (100).

6,8-Dimethylflavone (8c): mp 163–164 °C; IR 1650 (C=O); NMR 8.50–7.24 (m, 7 H, Ar H), 6.70 (s, 1 H, H at C-3), 2.55 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3); UV 300 (4.2), 211 (4.2), 263 (4.3); MS, 250 (100), 222 (20), 148 (92), 120 (52). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.40; H, 5.69.

(Z)-5,7-Dimethylaurone (9c): mp 114–115 °C; IR 1700 (C=O); NMR 8.22–7.10 (m, 7 H, Ar H), 6.92 (s, 1 H, Ph-CH), 2.48 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3); UV 380 (4.2), 323 (4.4), 308 (4.4), 290 (4.1); MS, 250 (100), 249 (100), 235 (15), 180 (34), 179 (20), 178 (29), 165 (18), 149 (16), 148 (46), 147 (14), 129 (12), 120 (82). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.42; H, 5.66.

Acknowledgment. We thank the CAICYT for financial support (project 1303/83) and for a postgraduate fellowship to S.I.

Registry No. 1, 637-44-5; 1 (acid chloride), 7299-58-3; **2a**, 150-76-5; **2b**, 106-44-5; **2c**, 105-67-9; **3a**, 104213-86-7; **3b**, 20984-26-3; **3c**, 104213-87-8; **4a**, 104213-88-9; **4b**, 104213-89-0; **4c**, 104213-90-3; **5**, 1985-37-1; **6**, 40886-78-0; **7**, 78594-13-5; **8a**, 26964-24-9; **8b**, 29976-75-8; **8c**, 104213-91-4; **9a**, 38216-58-9; **9b**, 37542-10-2; **9c**, 104213-92-5.

Synthesis of 2-(4′-Amino-4′-deoxy-β-D-ribofuranosyl)thiazole-4-carboxamide, a Carbon-Linked Nucleoside with a Free Pyrrolidine Sugar

Ganesh D. Kini*† and William J. Hennen

Cancer Research Center, Department of Chemistry, Brigham Young University, Provo, Utah 84602

Roland K. Robins

Nucleic Acid Research Institute, Costa Mesa, California 92626

Received March 5, 1986

The first synthesis of a carbon-linked nucleoside containing a 4-amino-4-deoxy-β-D-ribofuranosyl moiety is reported. Methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside (**5**) was activated as its trifluoromethanesulfonate ester **6**. Displacement of **6** with azide ion led to methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**7**). Catalytic reduction of **7** resulted in methyl 4-amino-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**8**) which on treatment with trifluoroacetic anhydride gave the corresponding N-acetylated derivative, methyl 4-deoxy-2,3-*O*-isopropylidene-4-(trifluoroacetamido)-β-D-ribopyranoside (**9**). Acid hydrolysis of **9** with aqueous acetic acid followed by rearrangement and acetylation resulted in 1,2,3,5-tetra-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranose (**10**). Lewis acid catalyzed cyanidation of **10** with trimethylsilyl cyanide gave the corresponding 1,2,3,5-tri-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranosyl cyanide (**11**). Treatment of nitrile **11** with liquid hydrogen sulfide gave the corresponding thioamide, which was subsequently cyclized by reaction with ethyl bromopyruvate to yield ethyl 2-[2′,3′,5′-tri-*O*-acetyl-4′-deoxy-4′-(trifluoroacetamido)-D-ribofuranosyl]thiazole-4-carboxylate (**12**). Ammonolysis of **12** with methanolic ammonia led to 2-(4′-amino-4′-deoxy-β-D-ribofuranosyl)thiazole-4-carboxamide (**3**), the structure of which was confirmed by mass spectral and NMR studies.

We wish to report the first synthesis of a carbon-linked nucleoside containing a 4-amino-4-deoxy-β-D-ribofuranosyl moiety. Previous attempts to form nucleosides[1] or other glycosides[2] containing free pyrrolidine sugars (i.e., 4-amino-4-deoxyfuranose) have been unsuccessful due to the decomposition of the products immediately following deblocking of the amino function, presumably as a consequence of rapid elimination of the heterocyclic base or glycosyl function. The antibiotic anisomycin (**1**) was first isolated by Sobin and Tanner[3] and is active against protozoa and certain fungi and acts as an inhibitor of protein synthesis.[4,5] The structure of anisomycin has been elu-

† Present address: Nucleic Acid Research Institute, Costa Mesa, CA 92626.

(1) Reist, E. J.; Fisher, L. V.; Goodman, L. *J. Org. Chem.* **1967**, *32*, 2541.

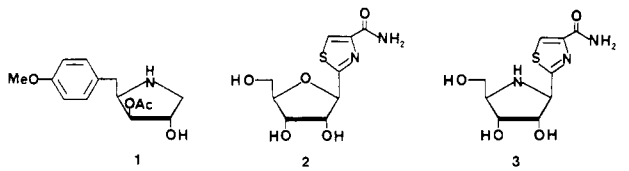
(2) (a) Paulsen, H.; Bruning, J.; Heyns, K. *Chem. Ber.* **1970**, *103*, 1621. (b) Paulsen, H.; Koebernick, H.; Schonherr, H. *Chem. Ber.* **1972**, *105*, 1515.

(3) Sobin, B. A.; Tanner, F. W., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 4053.

(4) Jimenez A.; Vazquez, D. In *Antibiotics*; Hahn, F. E., Ed.; Springer Verlag: Berlin, 1979; p 1 and references cited therein.

0022-3263/86/1951-4436$01.50/0

cidated by X-ray crystallography[6] and proton NMR,[7] and a total synthesis of the antibiotic recently reported.[8]

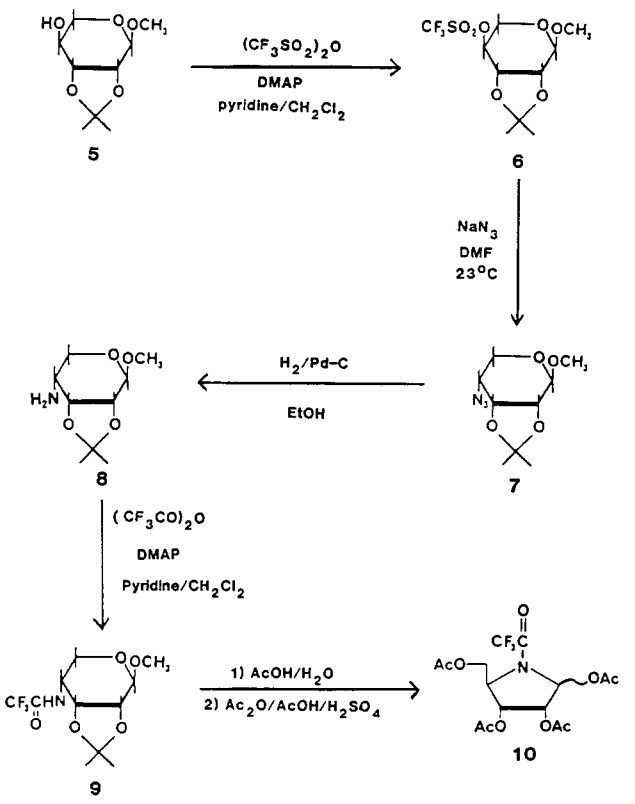


1 2 3

Inspection of structure 1 suggests that a carbon-linked nucleoside containing the 4-amino-4-deoxy-β-D-ribofuranosyl moiety as in 3 should be a stable entity since elimination at C_1 should be prevented due to the carbon–carbon linkage. Our interest in the synthesis of 2-(4′-amino-4′-deoxy-β-D-ribofuranosyl)thiazole-4-carboxamide (3) is prompted by the significant biological activity of 2-(β-D-ribofuranosyl)thiazole-4-carboxamide (2), tiazofurin,[9] first prepared in our laboratory in 1977 and shown to be active against Lewis lung carcinoma in mice.[10] Tiazofurin is presently in phase II clinical trials against a variety of human tumors in a multicentered study sponsored by the National Cancer Institute. For a summary of the chemistry, biochemistry and animal studies with tiazofurin, the reader is referred to a recent review.[11] The synthesis of 3, the subject of the present report, was prompted by a desire to examine the potential effects of replacing the furanose ring oxygen of tiazofurin with an amino function.

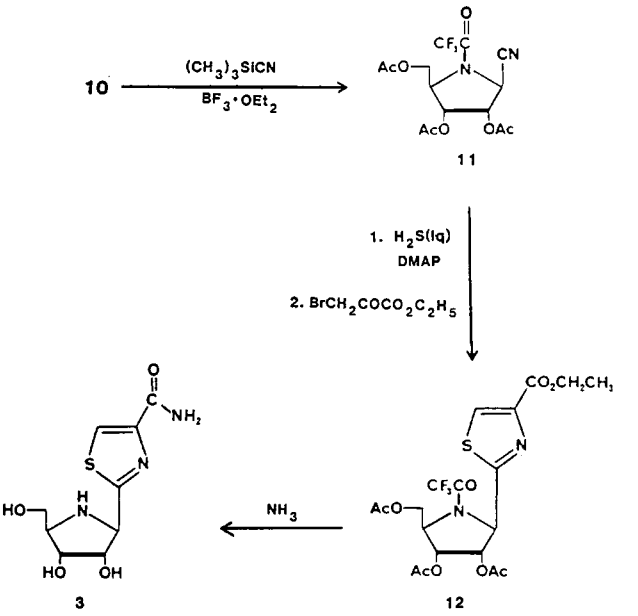
The synthesis of the pyrrolidine sugar derivative, 1,2,3,5-tetra-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribose (10) is outlined in Scheme I. The free hydroxyl group in methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside (5)[12] was activated as its trifluoromethanesulfonate ester 6, which was subsequently displaced with azide ion in dimethylformamide at room temperature for 2–3 h to provide a 54% yield of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (7). In contrast, the reported displacement of the corresponding *p*-toluenesulfonate ester[13] required a high temperature and a long reaction time to yield 39% of 7. The azide 7 was catalytically reduced with hydrogen and 5% palladium-on-carbon to give methyl 4-amino-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (8) in nearly quantitative yield. The trifluoroacetamido derivative 9 was prepared to provide acid-stable, base-labile[14,15] protection of the amino function. Treatment of 8 with trifluoroacetic anhydride led to methyl 4-deoxy-2,3-*O*-isopropylidene-4-(trifluoroacetamido)-β-D-ribopyranoside (9) in 90% yield. Acidic cleavage of the acetyl functions in 9 with aqueous acetic acid followed by rearrangement and acetylation gave a 70% yield of 1,2,3,5-tetra-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranose (10) as a 45:55 mixture of α and

Scheme I



5 6 7 8 9 10

Scheme II



11 12 3

β anomers. The anomeric ratio of 10 was determined from its ^{1}H NMR spectrum, which was closely analogous to the ^{1}H NMR spectrum of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose.[16] The overall yield of 10 from 5 was 33%.

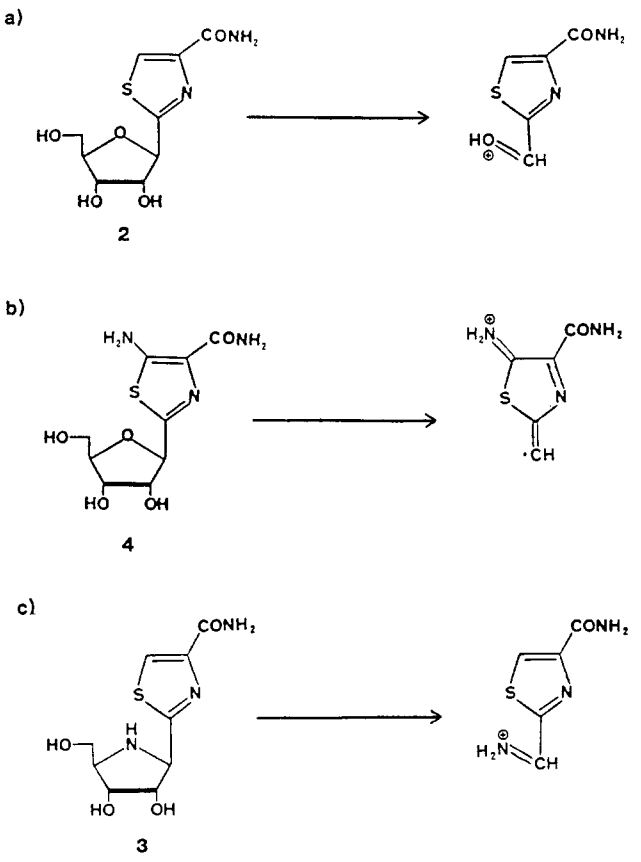
The sequence of reactions involved in the synthesis of the nucleoside 3 from 10 is outlined in Scheme II. Incorporation of the nitrile function by reacting 1,2,3,5-tetra-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranose (10) with trimethylsilyl cyanide in dry nitromethane, using boron trifluoride etherate as the catalyst was accomplished in 52% yield. The product, 2,3,5-tri-*O*-acetyl-4-deoxy-

(5) Grollman, A. P. *J. Biol. Chem.* **1967**, *242*, 3226.
(6) Beereboom, J. J.; Butler, K.; Pennington, F. C.; Solomons, I. A. *J. Org. Chem.* **1968**, *30*, 2334.
(7) Schaefer, J. P.; Wheatley, P. J. *Chem. Commun.* **1967**, 578; *J. Org. Chem.* **1968**, *33*, 166.
(8) Buchanan, J. G.; Maclean, K. A.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1463.
(9) Srivastava, P. C.; Pickering, M. V.; Allen, L. B.; Streeter, D. G.; Campbell, M. T.; Witkowski, J. T.; Sidwell, R. W.; Robins, R. K. *J. Med. Chem.* **1977**, *20*, 256.
(10) Robins, R. K.; Srivastava, P. C.; Narayanan, V. L.; Plowman, J.; Paull, K. D. *J. Med. Chem.* **1982**, *25*, 107.
(11) Robins, R. K.; Revankar, G. R. *Med. Res. Rev.* **1985**, *3*, 273.
(12) Bobek, M.; Whistler, R. L. In *Methods in Carbohydrate Chemistry*; Whistler, R. L.; BeMiller, J. N., Eds.; Academic: New York, 1972; Vol. VI, p 292.
(13) Reist, E. J.; Gueffroy, D. E.; Blackford, R. W.; Goodman, L. *J. Org. Chem.* **1966**, *31*, 4025.
(14) Whistler, R. L.; Anisuzzaman, A. K. M. *Methods in Carbohydrate Chemistry*, **1980**, *8*, 297.
(15) Wolfrom, M. L.; Conigliaro, P. *J. Carbohydr. Res.* **1969**, *11*, 63.
(16) Townsend, L. B. In *Synthetic Procedures in Nucleic Acid Chemistry*; Zorbach, W. W.; Tipson, R. S., Eds.; Wiley: New York, 1973; Vol. II, p 325.

4-(trifluoroacetamido)-D-ribofuranosyl cyanide (11) was obtained as a 2:3 mixture of α and β anomers as shown by its ^1H and ^{13}C NMR spectra. The similar reaction of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose with trimethylsilyl cyanide leads exclusively to the β anomer[17,18] (1,2-trans orientation of the nitrile and 2-acetyl groups). Hence, the 4-trifluoroacetamido function must be competing with the 2-acetyl function in the stabilization of the transition state leading from **10** to **11**, resulting in the observed loss of stereospecificity in the above reaction. The anomeric mixture of **11** was homogeneous on TLC and hence carried through subsequent steps without separation of the anomers. Treatment of **11** with liquid hydrogen sulfide in the presence of 4-(dimethylamino)pyridine quantitatively converted the nitrile to the thioamide which was immediately cyclized with ethyl bromopyruvate[9] to give ethyl 2-[2′,3′,5′-tri-*O*-acetyl-4′-deoxy-4′-(trifluoroacetamido)-D-ribofuranosyl]thiazole-4-carboxylate (**12**) in 30% overall yield as an unseparated mixture of anomers. Treatment of the blocked nucleoside **12** with methanolic ammonia (previously saturated at 0 °C) for 3 days yielded 2-(4′-amino-4′-deoxy-β-D-ribofuranosyl)thiazole-4-carboxamide (**3**) in 40% yield after chromatography. The ^1H and ^{13}C NMR spectra of **3** revealed only a single set of absorptions corresponding to the β anomer.[19] No significant portion of the α anomer of **3** was isolated in any of the reactions run under the above conditions. The high-resolution fast atom bombardment mass spectrum of **3** established the molecular weight for the MH^+ ion to be 260.0704, compared to a calculated value of 260.0706.

The electron-impact mass spectrum (70 eV) of 2-(4′-amino-4′-deoxy-β-D-ribofuranosyl)thiazole-4-carboxamide (**3**) showed the base + 30 fragment as a dominant peak recorded at 93% of the base peak intensity. The characteristic base peak observed for C-nucleosides has been the base + 30 peak[20] arising as shown in Scheme IIIa for tiazofurin (**2**). The only exceptions we have previously observed to the above rule have been in the cases of the electron impact mass spectra of 5-aminothiazole and 5-aminoselenazole C-nucleosides.[21] In these cases the base peak [shown in Scheme IIIb for the 5-amino-2-(β-D-ribofuranosyl)thiazole-4-carboxamide (**4**) case] was a base + 13 fragment.

Scheme III



Experimental Section

General Methods. Proton nuclear magnetic resonance (^1H NMR) spectra were determined at 90 MHz with a JEOL FX-90Q spectrometer. Carbon nuclear magnetic resonance (^{13}C NMR) were determined at 22.5 MHz on the same instrument. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. Electron impact mass spectra (MS) were obtained on a Hitachi Perkin-Elmer RMU-6E instrument at an ionizing voltage of 70 eV. Optical rotations were recorded on a Perkin-Elmer 241 automatic polarimeter. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Thin-layer chromatography (TLC) was run on aluminum-backed silica gel 60 F-254 (EM Reagents) plates. Preparative-scale chromatography was conducted with flash chromatography techniques. J. T. Baker silica gel (40 μm) or EM Reagents Kiesel gel 60 (40–63 μm) was used for flash chromatography. Solvent E is the saturated upper phase of a 4:1:2 mixture of ethyl acetate–1-propanol–water. Detection of components of TLC was by UV light and with 10% H_2SO_4 in MeOH spray followed by heating. Standard workup procedure for organic extracts of acidic solutions employed was washing with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl in succession followed by drying over anhydrous Na_2SO_4. Evaporations were carried out under reduced pressure with the bath temperature below 35 °C.

Methyl 4-Azido-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside[13] (**7**). In a flame-dried three-necked 1-L round-bottomed flask fitted with two 125-mL addition funnels were placed dry dichloromethane (350 mL), dry pyridine (11.5 mL), and 4-(dimethylamino)pyridine (70 mg, 0.5 mmol). The solution was cooled to −20 °C in a dry ice–carbon tetrachloride bath and trifluoromethanesulfonic anhydride (13.3 mL, 149 mmol) added dropwise with stirring. The resulting suspension was stirred at −20 °C for 20 min, and a solution of methyl 2,3-*O*-isopropylidene-α-L-lyxopyranoside (10 g, 49 mmol) in dry dichloromethane (90 mL) added dropwise over a period of 1 h. The pale yellow solution was stirred at −20 °C for 15 min and poured into ice–water (600 mL). The organic phase was separated and the aqueous phase extracted with dichloromethane (3 × 100 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was dissolved in dry dimethylformamide (750 mL), and sodium azide (21 g, 724 mmol) and tetramethylurea (4 mL) were added. The suspension was stirred for 3 h at room temperature and concentrated in vacuo. The residue was dissolved in water (300 mL) and the aqueous solution extracted with chloroform (3 × 200 mL). The combined organic extracts were washed, dried, and concentrated in vacuo, and the residue was chromatographed over silica gel with 5% ethyl acetate in benzene as eluent to yield 6.0 g (53%) of **7** as an oil: ^1H NMR ($CDCl_3$) δ 1.4 (s, 3), 1.56 (s, 3), 3.44 (s, 3), 3.8 (br s 2), 4 (m, 2), 4.4–4.8 (m, 2); ^{13}C NMR ($CDCl_3$) δ 24.70, 26.11, 54.10, 55.37, 59.34, 72.30, 74.76, 100.04, 109.88; TLC (4:1 benzene–ethyl acetate) R_f 0.57.

Methyl 4-Amino-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**8**). A solution of methyl 4-azido-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**7**) (5.9 g, 25.8 mmol) in ab-

(17) Reetz, M. T.; Chatziiofidis, I.; Kunzer, H.; Muller-Starke, H. *Tetrahedron* **1983**, *39*, 961.
(18) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967.
(19) Chu, C. K.; El-Kabbani, F. M.; Thompson, B. B. *Nucleosides Nucleotides* **1984**, *3*, 1.
(20) Rice, J. M.; Dudek, G. O. *Biochem. Biophys. Res. Commun.* **1969**, *35*, 383.
(21) Hennen, W. J.; Hinshaw, B. C.; Riley, T. A.; Wood, S. G.; Robins, R. K. *J. Org. Chem.* **1985**, *50*, 1741.

solute ethanol (150 mL), to which $NaHCO_3$ (4 g, 47.6 mmol) and 5% palladium-on-charcoal (1.2 g) were added, was hydrogenated at 50 psi for 16 h. The mixture was filtered through Celite and the filtrate concentrated in vacuo to yield 5 g (95.6%) of **8** as an oil. This product was used without further purification: ^1H NMR ($CDCl_3$) δ 1.16 (s, 3), 1.22 (s, 3), 3.3 (m, 1), 3.48 (s, 3), 3.7 (m, 1), 4.0 (m, 1), 4.4 (m, 2), 4.7 (br s, 1); ^{13}C NMR ($CDCl_3$) δ 24.93, 26.74, 46.15, 55.49, 64.32, 74.74, 75.02, 100.99, 108.75; TLC (6:1 chloroform–methanol) R_f 0.35.

Methyl 4-Deoxy-2,3-*O*-isopropylidene-4-(trifluoroacetamido)-β-D-ribopyranoside (9). A solution of methyl 4-amino-4-deoxy-2,3-*O*-isopropylidene-β-D-ribopyranoside (**8**) (11.0 g, 53.9 mmol), 4-(dimethylamino)pyridine (100 mg, 0.74 mmol), and dry pyridine (10.7 mL) in dry dichloromethane (250 mL) was cooled to 0 °C in an ice–salt bath. Trifluoroacetic anhydride (10.8 mL, 76.5 mmol) was added dropwise with stirring. The mixture was stirred at 0 °C for 3 h and at room temperature overnight. The solution was washed, dried, and concentrated in vacuo. The residue was chromatographed over silica gel with 20% ethyl acetate in benzene to yield 14.5 g (90%) of **9** as an oil: $[\alpha]^{22}$ −22.87° (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.4 (s, 3), 1.56 (s, 3), 3.5 (s, 3), 3.54 (m, 1), 3.84 (m, 1), 4.1 (m, 1), 4.4–4.8 (m, 3), 6.6 (br d, 1, NH); ^{13}C NMR ($CDCl_3$) δ 24.93, 26.46, 44.91, 55.78, 59.62, 71.28, 74.57, 99.98, 110.23, 115.55 (J = 192.16 Hz), 156.72 (J = 37.8 Hz); TLC (6:1 benzene–ethyl acetate) R_f 0.4. Anal. Calcd for $C_{11}H_{16}NO_5F_3$: C, 44.17; H, 5.34; N, 4.68; F, 19.06. Found: C, 43.97; H, 5.61; N, 4.44; F, 19.24.

1,2,3,5-Tetra-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranose (10). Methyl 4-deoxy-2,3-*O*-isopropylidene-4-(trifluoroacetamido)-β-D-ribopyranoside (**9**) (3.47 g, 8.4 mmol) was dissolved in 50% aqueous acetic acid (35 mL) and the solution heated at 68 °C with stirring for 2.5 h. Solvent was removed in vacuo, and the residue dissolved in ethanol (25 mL). This solution was evaporated to dryness in vacuo and the residue dissolved in a 1:1 mixture of glacial acetic acid and acetic anhydride (35 mL). The solution was cooled to 0 °C in an ice–salt bath and concentrated H_2SO_4 (0.9 mL) added dropwise with stirring. After being stirred at 0 °C for 1 h, the solution was kept at 4 °C for 2 days. Sodium acetate (10 g) was added and the mixture stirred at room temperature for 30 min and poured into ice–water (100 mL). The aqueous solution was extracted with chloroform (3 × 100 mL), and the combined organic extracts were washed and dried. Solvent was removed in vacuo and the resulting oil chromatographed over silica gel with 6:1 benzene–ethyl acetate as the eluent to yield 3.35 g (70%) of pure **10** as an oil: $[\alpha]^{22}$ −15.7° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.0 (m, 12), 4–4.8 (m, 3), 5.3–5.7 (m, 2), 6.48 (s, α-H1), 6.72 (d, β-H1); TLC (4:1 benzene–ethyl acetate) R_f 0.37. Anal. Cald for $C_{15}H_{18}O_9NF_3$: C, 43.58; H, 4.36; N, 3.39; F, 13.80. Found: C, 43.29; H, 4.65; N, 3.45; F, 13.53.

2,3,5-Tri-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranosyl Cyanide (11). A solution of 1,2,3,5-tetra-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranose (**10**) (9.75 g, 23.61 mmol) in dry nitromethane (125 mL) was heated to 38 °C. Freshly distilled trimethylsilyl cyanide (14.36 mL, 107.7 mmol) and boron trifluoride etherate (9.67 mL, 78.6 mmol) were added, and the mixture was stirred for 1 h at 35–40 °C. The volatile components (Caution: excess trimethylsilyl cyanide) were removed in vacuo, and the residue was partitioned between dichloromethane (250 mL) and saturated aqueous $NaHCO_3$ (150 mL). The organic phase was separated, the aqueous phase was extracted with dichloromethane (2 × 100 mL), and the combined organic extracts were washed, dried, and concentrated in vacuo to yield an oil, which was chromatographed on silica gel with 6:1 benzene–ethyl acetate as the eluent to yield 4.62 g (52%) of **11** as an oil: $[\alpha]^{22}$ +16.32° (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.1 (m, 9), 4.4 (m, 3), 4.72 (d, α-H2), 4.96 (s, β-H2), 5.6 (d, 1), 5.8 (m, 1); ^{13}C NMR ($CDCl_3$) δ 113.62, 114.98 (CN, α,β); TLC (4:1 benzene–ethyl acetate) R_f 0.44. Anal. Calcd for $C_{14}H_{15}N_2F_3O_7$: C, 44.21; H, 3.95; N, 7.37; F, 15.00. Found: C, 44.44; H, 4.09; N, 7.37; F, 14.89.

2-[2′,3′,5′-Tri-*O*-acetyl-4′-deoxy-4′-(trifluoroacetamido)-D-ribofuranosyl]thiazole-4-carboxylate (12). To a mixture of 2,3,5-tri-*O*-acetyl-4-deoxy-4-(trifluoroacetamido)-D-ribofuranosyl cyanide (**11**) (2.0 g, 5.26 mmol) and 4-(dimethylamino)pyridine (90 mg, 0.7 mmol) in a Teflon-lined 125-mL steel reaction vessel was added liquid hydrogen sulfide (50 mL), the reaction vessel was sealed, and the contents were stirred at room temperature for 2 days. After cooling in an acetone–dry ice bath, the reaction vessel was opened and the hydrogen sulfide allowed to evaporate. The residue was dissolved in ethyl acetate (50 mL) and the organic solution washed with saturated aqueous sodium chloride. After the mixture was dried over anhydrous sodium sulfate, solvent was removed in vacuo to yield the corresponding thioamide (2.2 g, ca. 100%) as a syrup. The syrup (2.15 g, 5.2 mmol) was immediately dissolved in dry acetonitrile (30 mL), cooled to 0 °C in an ice–salt bath, and treated with a solution of ethyl bromopyruvate (1.8 mL, 12.9 mmol) in acetonitrile (10 mL) dropwise over a period of 30 min. The mixture was stirred at 0 °C for 1 h and at room temperature overnight. Solvent was removed in vacuo and the residue dissolved in ethyl acetate (50 mL). The organic solution was washed and dried and solvent removed in vacuo, resulting in an oil, which was chromatographed over silica gel with benzene–ethyl acetate (4:1) as eluent to yield 0.8 g (30%) of **12** as an oil: $[\alpha]^{22}$ +5.79° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.4 (t, 3), 2.1 (3 s, 9), 4–4.6 (m, 6), 5.6 (m, 2), 8.2 (s, 1). ^{13}C NMR ($CDCl_3$) δ 128.4, 127.9 (C-1, α, β), 146.8, 146.3 (C-5, α, β), 160.6, 160.4 (C-4, α, β); TLC (4:1 benzene–ethyl acetate) R_f 0.2. Anal. Calcd for $C_{19}H_{21}N_2O_9SF_3$: C, 44.71; H, 4.12; N, 5.49; F, 11.18. Found: C, 44.91; H, 4.40; N, 5.28; F, 11.30.

2-(4′-Amino-4′-deoxy-β-D-ribofuranosyl)thiazole-4-carboxamide (3). To a solution of **12** (0.58 g, 1.1 mmol) in dry methanol (5 mL) in a pressure bottle was added a solution of methanol saturated at 0 °C with dry ammonia gas (25 mL), the bottle sealed, and the solution stirred at room temperature for 5 days. The solution was concentrated in vacuo and the residue dissolved in dry methanol (25 mL) and treated with Norit-A decolorizing carbon (1 g) for 1 h. The carbon was filtered off and the filtrate concentrated in vacuo to yield an oil, which was chromatographed over silica gel with solvent E as eluent to yield **3** (100 mg, 40%) as an oil. This oil was dissolved in H_2O and lyophilized to yield a foam: $[\alpha]^{22}$ +9.83° (*c* 0.2, CH_3OH); ^1H NMR (Me_2SO-d_6) δ 3.2 (m, 2), 4.3 (s, 1), 4.8 (d, 1), 7.5 (br d, 2), 8.1 (s, 1); ^{13}C NMR (Me_2SO-d_6) δ 63.67, 64.46, 72.45, 77.82, 123.84, 150.33, 162.78, 178.17; TLC (solvent E) R_f 0.2. Anal. Calcd for $C_9H_{13}N_3SO_4 \cdot CH_3OH$: C, 41.23; H, 5.84; N, 14.43; S, 10.99. Found: C, 40.85; H, 5.50; N, 14.20; S, 11.10. The (+) fast atom bombardment (FAB) high-resolution mass analysis of **3** gave a measured mass of 260.0704 (MH^+). This was in agreement with the empirical formula $C_9H_{14}O_4N_3S$ (theoretical molecular mass 260.0706). The sample was prepared by dissolving approximately 100 μg in 10 μL of methanol and combining this solution with an equal volume of glycerol. The sample was peak matched against the 259 of glycerol at a mass spectral resolution of 10 000 on a Varian MAT 731 mass spectrometer. The instrument was operated at an accelerating voltage of 8 kV with a xenon potential of 6 kV.

Acknowledgment. We thank the American Cancer Society (Grant CH 276) for its support of this work. We also than Professor James McClosky and Dr. Elliot M. Rachlin of the University of Utah's mass spectrometry facility for their assistance in obtaining the high-resolution mass spectra of compound **3**.

Registry No. **3**, 104575-51-1; **5**, 2495-99-0; **7**, 3964-10-1; **8**, 104575-45-3; **9**, 104575-46-4; α-**10**, 104575-47-5; β-**10**, 104575-48-6; **11**, 104575-49-7; **12**, 104575-50-0; $BrCH_2COCOOEt$, 70-23-5.