Coupling of AB-2 (7) and Dihydro-AB-1 (12). AB-2 (7, 1.2 mg) and dihydro-AB-1 (12, 2.7 mg) were dissolved in methanolic 10 N aqueous hydrochloric acid (2.5:1, v/v, 2.0 mL) and the mixture was stirred under N_2 at room temperature. After 3 days the reaction mixture was worked up in the usual way to afford on orange-yellow powder (3.6 mg). TLC analysis on silica revealed the presence of dihydro-AB-5B (13), unreacted AB-2 (7), dihydro-AB-1 (12), and other minor products.

Reaction of Noracronycine (3) with Methanolic Hydrochloric Acid at Room Temperature. The procedure for this experiment has been described previously.[12] Through TLC analysis, AB-1 (6), AB-3 (8), and AB-5A (10) were detected, as well as unreacted noracronycine (3) and several other minor products. AB-2 (7) and AB-5B (11) were not detected in the reaction mixture.

^{252}Cf Plasma Desorption Mass Spectrometry (^{252}Cf PDMS). A description of the basic operational principles of the ^{252}Cf PD mass spectrometer and the method of mass calibration have been described.[20] The m/z of the ions is measured by the time-of-flight method utilizing a 45-cm path length. The acceleration voltage was ±10 kV: no post acceleration was used. The mass resolution was approximately 450 M/ΔM at full-width half-maximum. At this low resolution, the measured masses closely approximate the chemically averaged masses.[21] The fission fragment flux through the sample was approximately 1500^{-1} cm^{-2}.

Thin solid films of the noracronycine oligomers were prepared by first dissolving the sample in chloroform then diluting with a 50/50 v/v solution of methanol–2-propanol (Burdick and Jackson distilled in glass). The concentrations were estimated to be ≃1 μg/mL. A volume of 25 μL was electrosprayed onto a 1.5-μm-thick aluminized mylar foil (Steiner Film Co.) producing a uniform film 250 nm thick.

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(20) Macfarlane, R. D. *Anal. Chem.*, in press.
(21) McNeal, C. J.; Ogilvie, K. K.; Theriault, N. Y.; Nemer, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 976.

Synthesis of 4-Substituted 5-Amino-2-(β-D-ribofuranosyl)thiazoles and 4-Substituted 5-Amino-2-(β-D-ribofuranosyl)selenazoles and Their Respective Conversion into 2-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidines and 2-(β-D-Ribofuranosyl)selenazolo[5,4-*d*]pyrimidines. A New Synthesis of Tiazofurin and Selenazofurin

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A novel ring closure has been devised to produce fully substituted thiazoles and selenazoles from the condensation of thio- and selenoates with various 2-aminoacetonitrile derivatives. The syntheses of methyl 2,5-anhydroallonothioate (3) and methyl 2,5-anhydroallonoselenoate (4) from methyl 2,5-anhydroallonimidate are described. The condensations of these carboxylates with the appropriate 2-aminoacetonitrile derivatives to give the corresponding 5-amino-2-(β-D-ribofuranosyl)thiazole and -selenazole nucleosides bearing the carboxamide (10 and 13), ethyl carboxylate (11 and 14), and cyano (12) functions at the four positions are reported. Further manipulation of these functionalized thiazoles and selenazoles yielded the corresponding thiazolo- and selenazolo[5,4-*d*]pyrimidine nucleosides (20, 21, and 22), as well as a thiazolo[5,4-*d*][1,2,3]triazine nucleoside (23). New syntheses of tiazofurin (1) and selenazofurin (2) via the reductive dediazotization products of ethyl 5-amino-2-(β-D-ribofuranosyl)-thiazole-4-carboxylate (11) and ethyl 5-amino-2-(β-D-ribofuranosyl)selenazole-4-carboxylate (14) are also reported.

Tiazofurin,[1] 2-(β-D-ribofuranosyl)thiazole-4-carboxamide[2] (1), and selenazofurin,[3] 2-(β-D-ribofuranosyl)selenazole-4-carboxamide[4] (2), are promising antitumor agents currently under study by the National Cancer Institute (NCI). Tiazofurin (1) has been shown to be an effective antitumor agent in animals.[5] Selenazofurin (2) was similarly demonstrated to possess both significant antitumor properties in animals[4] and has been shown to possess broad spectrum antiviral activity[6] in cell culture experiments.

Several modifications of the parent structure of tiazofurin, 1, have been reported. The carboxamido function has been transformed to the thiocarboxamide,[2] the amidine,[7] and the 2-thiazole-4-carboxamide[7] functions. Of

(1) Generic name given to compound 1.
(2) 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.
(3) Generic name given to compound 2.
(4) Srivastava, P. C.; Robins, R. K. *J. Med. Chem.* **1983**, *26*, 445.
(5) Robins, R. K.; Srivastava, P. C.; Narayanan, V. L.; Plowman, J.; Paull, K. D. *J. Med. Chem.* **1982**, *25*, 107.
(6) Kirsi, J. J.; North, J. A.; McKernan, P. A.; Murry, B. K.; Canonico, P. G.; Huggins, J. W.; Srivastava, P. C.; Robins, R. K. *Antimicrob. Agents Chemother.* **1983**, *24*, 353.

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these only the amidine derivative retained slight antitumor activity.[7] Modifications of the thiazole heterocycle have included exchange of the sulfur and nitrogen atoms giving 2-(β-D-ribofuranosyl)thiazole-5-carboxamide[2] and replacement of the sulfur atom with selenium to yield the selenazole **2**.[4] The ribose moiety has been converted into its 5′-deoxy,[2] 3′-deoxy,[8] 2′-deoxy,[9] arabino[10,11] and xylo[11] analogues. Of these only the 3′-deoxy-β-D-ribosyl analogue[10] of **1** retained some activity against P388 leukemia.[11]

In none of these studies has the 5-position of the parent aglycons of **1** and **2** been examined as a modification site leading to potentially active compounds. In the present study incorporation of an amino function at the 5-position of the thiazole ring of **1** and the selenazole ring of **2** was viewed as a versatile point of entry into the synthesis of 5-substituted derivatives of **1** and **2**. The condensation of ethyl 2-amino-2-cyanoacetate with carbon disulfide to produce ethyl 5-amino-2-thiothiazole-4-carboxylate[12] demonstrated that thione containing substrates could be used to form functionalized 5-aminothiazoles.

Results and Discussion

We successfully accomplished our objective of synthesizing 5-aminothiazole and 5-aminoselenazole C-nucleosides by developing a new ring closure procedure which results in the direct introduction of the 5-amino substituent. For this approach we required substituted 2-aminoacetonitriles and 2,5-allonic acid derivatives capable of acting as thio and selenoacylating agents. The former compounds 2-amino-2-cyanoacetamide (**7**), ethyl 2-amino-2-cyanoacetate (**8**), and ammoniopropanedinitrile 4-methylbenzenesulfonate (**9**) were readily available by reported methods.[13,14] Methyl 2,5-anhydroallonothioate (**3**) and methyl 2,5-anhydroallonoselenoate (**4**), were synthesized[15,16] from the known[17] methyl 2,5-anhydroallonimidate (**5**). Compounds **3** and **4** should prove to be very useful synthetic intermediates in future C glycoside work. No blocking groups were required in the syntheses described herein.

Condensation of methyl 2,5-anhydroallonothioate (**3**) with 2-amino-2-cyanoacetamide (**7**) yielded 5-amino-2-(β-D-ribofuranosyl)thiazole-4-carboxamide (**10**) in 69% yield after purification (Scheme I). Ethyl 2-amino-2-cyanoacetate (**8**) and ammoniopropanedinitrile 4-methylbenzenesulfonate (**9**) were also successfully condensed with methyl 2,5-anhydroallonothioate (**3**) to yield ethyl 5-amino-2-(β-D-ribofuranosyl)thiazole-4-carboxylate (**11**) and 5-amino-4-cyano-2-(β-D-ribofuranosyl)thiazole (**12**), respectively. When methyl 2,5-anhydroallonothioate (**3**) was allowed to react with diethyl aminomalonate (**16**), a new compound was rapidly formed. Proton NMR of the isolated product revealed two ethyl patterns and a methine singlet suggesting a nonring closed product. This was confirmed by the mass spectrum which contained an M + 1 peak at *m/e* 352 (78.6%) and by elemental analysis. The product was therefore identified as diethyl [*N*-(2,5-anhydroallonothioyl)amino]malonate (**17**). The rapid formation and stability of **17** strongly suggests that the reaction pathway leading to the formation of 5-aminothiazole involves the intermediate formation of thiocarboxamides followed by cyclization to give the substituted heterocycles.

Similar condensations of methyl 2,5-anhydroallonoselenoate (**4**) with 2-amino-2-cyanoacetamide (**7**) and ethyl 2-amino-2-cyanoacetate (**8**) were found to be much more rapid than the corresponding ring closures with methyl 2,5-anhydroallonothioate (**3**).

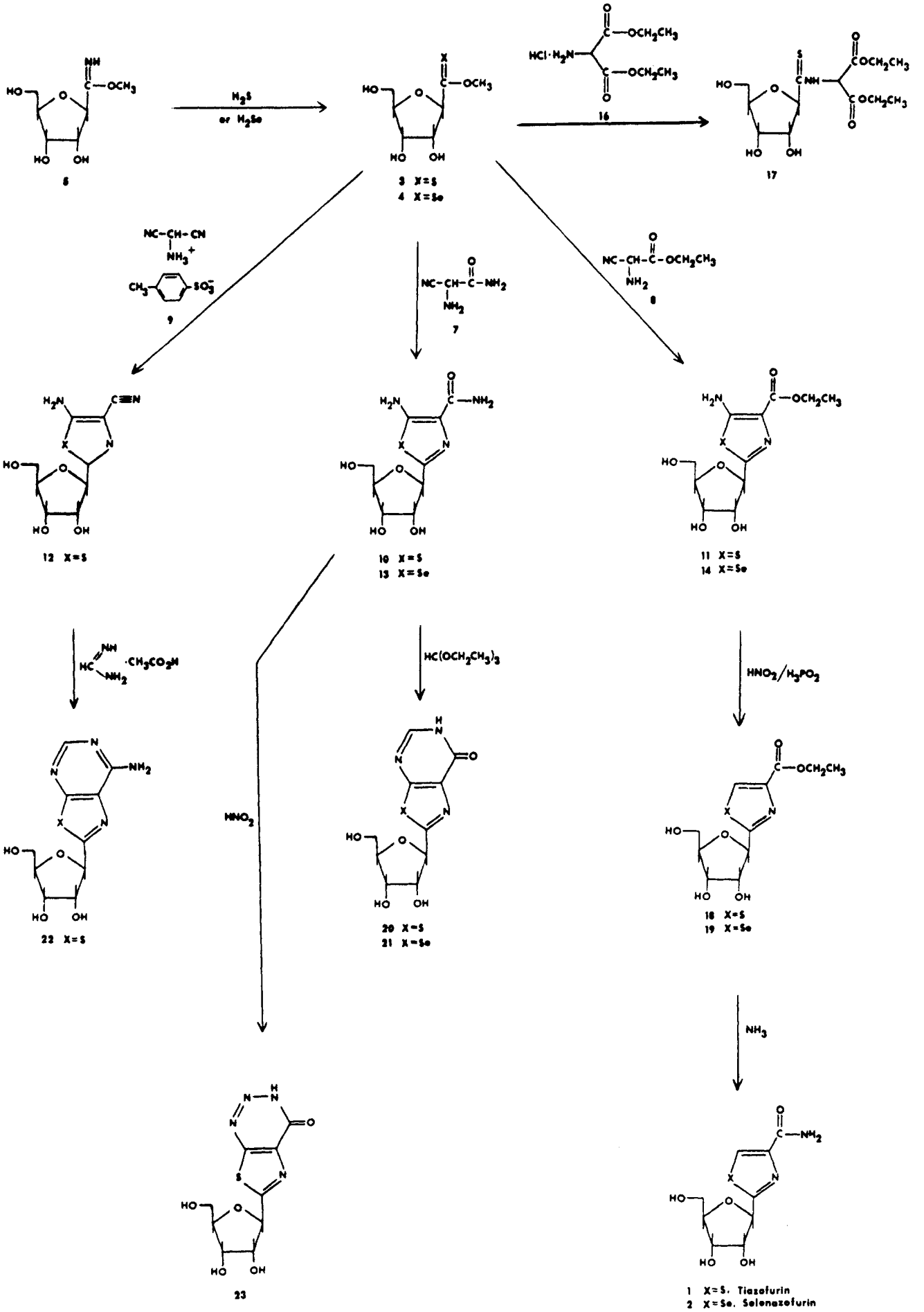
The importance of tiazofurin and selenazofurin (vida supra) justifies the development of new routes to these nucleosides. Consequently, ethyl 5-amino-2-(β-D-ribouranosyl)thiazole-4-carboxylate (**11**) was subjected to reductive dediazotization with sodium nitrite in aqueous hypophosphorus acid which gave ethyl 2-(β-D-ribofuranoyl)thiazole-4-carboxylate (**18**) in 50% yield. The structure of **18** was confirmed by deblocking the previously reported ethyl 2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazole-4-carboxylate[2] with sodium ethoxide in absolute ethanol. The product of the latter reaction was identical with the product obtained by reductive dediazotization. In a similar manner ethyl 5-amino-2-(β-D-ribofuranosyl)selenazole-4-carboxylate (**14**) was converted into ethyl 2-(β-D-ribofuranosyl)selenazole-4-carboxylate (**19**). This product was fully characterized and its structure was confirmed by independent synthesis from ethyl 2-(2′,3′,5′,-tri-*O*-benzoyl-β-D-ribofuranosyl)selenazole-4-carboxylate.[4]

Treatment of ethyl 2-(β-D-ribofuranosyl)thiazole-4-carboxylate (**18**) with methanolic ammonia gave an 86% yield of tiazofurin (**1**) which was identical in all respects with the product previously prepared by the reported procedure.[2] Similarly, ethyl 2-(β-D-ribofuranosyl)selenazole-4-carboxylate (**19**) was treated with methanolic ammonia to give selenazofurin[4] in 87% yield.

The presence of the adjacent amino and carboxamide functions in **10** and **13** and the adjacent amino and cyano functions in **12** provided suitable substrates for formation of fused pyrimidine ring systems. Thus, the 5-amino-2-(β-D-ribofuranosyl)thiazole-4-carboxamide (**10**) was ring closed with hot triethyl orthoformate[18,19] to form 2-(β-D-ribofuranosyl)thiazole[5,4-*d*]pyrimidin-4(5*H*)-one (**20**) in 89% yield. Similarly, 5-amino-2-(β-D-ribofuranosyl)selenazole-4-carboxamide (**13**) produced 2-(β-D-ribofuranosyl)selenazole[5,4-*d*]pyrimidin-4(5*H*)-one (**21**) in 69% yield when heated in triethyl orthoformate. The 4-amino-2-(β-D-ribofuranosyl)thiazole[5,4-*d*]pyrimidine (**22**) was conveniently prepared in 75% yield from 5-amino-4-cyano-2-(β-D-ribofuranosyl)thiazole (**12**) by the action of formamidine acetate in refluxing ethoxyethanol.[20] The UV spectra for the thiazolo[5,4-*d*]pyrimdine nucleosides **20** and **22** were in good agreement with the published data for the parent heterocycles.[19,20] Following a procedure previously devised in our laboratory[22] we were able to effect a controlled diazotization of 5-amino-2-(β-D-ribofuranosyl)thiazole-4-carboxamide (**10**) to obtain 2-(β-

(7) Srivastava, P. C.; Revankar, G. R.; Robins, R. K. *J. Med. Chem.* **1984**, *27*, 266.
(8) Baur, R. H.; Baker, D. C. *Nucleosides Nucleotides* **1984**, *3*, 77.
(9) Jayaram, H. N.; Dion, R. L.; Glazer, R. I.; Johns, D. G.; Robins, R. K.; Srivastava, P. C.; Cooney, D. A. *Biochem. Pharmacol.* **1982**, *31*, 2371.
(10) Jiang, C.; Baur, R. H.; Dechter, J. J.; Baker, D. C. *Nucleosides Nucleotides* **1984**, *3*, 123.
(11) Mao, D. T.; Marquez, V. E. *Tetrahedron Lett.* **1984**, *25*, 2111.
(12) Cook, A. H.; Heilbron, I.; Levy, A. L. *J. Chem. Soc.* **1947**, 1598.
(13) Logemann, F. I.; Shaw, G. *Chem. Ind. (London)* **1980**, 541.
(14) Ferris, J. P.; Sanchez, R. A.; Mancuso, R. W. *Org. Synth.* **1973**, *32*.
(15) Sheithuer, S.; Mayer, R. "Dithiocarboxylic Acids and Their Derivative"; Georg Thieme: Stuttgart, 1979.
(16) Cohen, V. I. *J. Org. Chem.* **1977**, *42*, 2645.
(17) Poonian, M. S.; Nowoswiat, E. F. *J. Org. Chem.* **1980**, *45*, 203.
(18) Ren, W. Y.; Lim, M. I.; Otter, B. A.; Klein, R. S. *J. Org. Chem.* **1982**, *42*, 4633.
(19) Sekiya, M.; Osaki, Y. *Chem. Pharm. Bull.* **1965**, *13*, 1319.
(20) Buchanan, J. G.; Stobie, A.; Wrightman, R. H. *Can. J. Chem.* **1980**, *58*, 2624.
(21) Elion, G. B.; Lange, W. H.; Hitchings, G. H. *J. Am. Chem. Soc.* **1956**, *78*, 2858.
(22) Kawana, M.; Ivanovics, G. A.; Rousseau, R. J.; Robins, R. K. *J. Med. Chem.* **1972**, *15*, 841.

Scheme I


5
3 X=S
4 X=Se
16
17
9
7
8
12 X=S
10 X=S
13 X=Se
11 X=S
14 X=Se
22 X=S
20 X=S
21 X=Se
18 X=S
19 X=Se
23
1 X=S, Tiazofurin
2 X=Se, Selenazofurin

D-ribofuranosyl)thiazole[5,4-*d*]-[1,2,3]triazin-7(6*H*)-one (**23**) in 65% yield.

None of the new nucleosides here reported were superior to tiazofurin or selenazofurin as antitumor agents as judged by cell culture studies against leukemia P-388 and L-1210 and Lewis lung carcinoma.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined at 90 MHz; carbon nuclear magnetic resonance (^{13}C NMR) at 22.5 MHz. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane as an internal standard. The presence of H_2O as indicated by elemental analyses was verified by ^{1}H NMR. Thin-layer chromatography (TLC) was run on aluminum backed silica gel 60 F-254 (EM Reagents) plates. Preparative scale chromatography was conducted by using flash chromatography techniques. J.T. Baker silica gel (~40 μm) or Kiesel gel 60 EM Reagents (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 on TLC was by UV light and with 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with the bath temperature below 35 °C. The cation exchange resin was washed with methanol until the filtrate was clear, air-dried, and finally dried in the presence of phosphorous pentoxide at 100 °C in a vacuum oven for 16 h. No degradation of the resin was observed under these conditions.

Methyl 2,5-Anhydroallonothioate (3). To a solution of methyl 2,5-anhydroallonimidate (**5**) (4.0 g, 20.9 mmol) in dry methanol (100 mL) was added dried cation exchange resin (Dowex 50W-X8, H^+, 8 g, 40 mequiv). The rapidly stirred mixture was cooled in an ice bath [at temperatures above 4 °C the reaction mixture was found to be contaminated with 2,5-anhydroallonthiocarboxamide (**6**), a compound previously reported by Garcia-Lopez et al.[23]] and treated with gaseous hydrogen sulfide for 1 h. The resin was removed by filtration and washed with dry methanol (2 × 15 mL). The filtrate and washings were evaporated in vacuo to yield 4.03 g (93%) of **3** as a slowly crystallizing chromatographically pure syrup which was used without further purification, mp 50–54 °C. For Analysis the residue was recrystallized from ethyl acetate–hexane which raised its melting point to 58–60 °C: $[\alpha]^{22}_D$ −106.4 (*c* 1, CH_3OH); ^{1}H NMR (Me_2SO-d_6) δ 3.60–3.76 (m, 2), 3.92–4.08 (m, 2), 4.08–4.22 (m, 1), 4.24 (s, 3), 4.60 (d, 1, J = 4.2 Hz, H-2), 4.5–5.20 (m, 3); ^{13}C NMR (Me_2SO-d_6) δ 59.3, 62.1, 71.5, 76.2, 84.8, 89.5, 221.5; TLC (20% CH_3OH in $CHCl_3$) R_f 0.47. Anal. Calcd for $C_7H_{12}O_5S$: C, 40.38; H, 5.81; S, 15.40. Found: C, 40.44; H, 5.98; S, 15.66.

Methyl 2,5-Anhydroallonoselenoate (4). A solution of methyl 2,5-anhydroallonimidate (**5**) (4.0 g, 20.9 mmol) in dry methanol (100 mL) containing dried cation exchange resin (Dowex 50W-X8, H^+, 8 g, 40 mmol) was rapidly stirred and purged with dry nitrogen gas. The mixture was cooled to −22 °C in a carbon tetrachloride/dry ice slush bath and treated with hydrogen selenide gas for 10 min, after which the solution was stirred for 1 h at −22 °C. The resin was removed by filtration and washed with dry methanol (2 × 25 mL). The filtrate and washings were evaporated in vacuo to yield 5.57 g (ca. 100%) of **4** as a yellow syrup which retained some unreacted hydrogen selenide. Because of instability, the product was used directly without further purification: ^{1}H NMR (Me_2SO-d_6) δ 3.33 (s, 3), 3.50–3.72 (m, 2), 3.84–4.00 (m, 1), 4.00–4.28 (m, 2), 4.34 (d, 1, J = 5.8 Hz, H-2), 4.80–5.60 (bd, 3); ^{13}C NMR (Me_2SO-d_6) δ 5.19, 62.0, 71.3, 74.1, 81.5, 84.7, 171.9; TLC (20% CH_3OH in $CHCl_3$) R_f 0.39.

5-Amino-2-(β-D-ribofuranosyl)thiazole-4-carboxamide (10). To a solution of methyl 2,5-anhydroallonothioate (**3**) (4.03 g, 19.3 mmol) in a mixture of dry methanol (100 mL) and dry pyridine (20 mL) was added 2-amino-2-cyanoacetamide[10] (2.8 g, 28.3 mmol). After the solution was stirred at room temperature for 16 h the solvents were removed in vacuo and the residue was azeotroped with toluene (2 × 100 mL). The residue was dissolved in methanol and silica gel (60–200 mesh, 22 g) was added. The methanol was evaporated in vacuo leaving a dry powder which was placed on top of a 40 mm × 90 mm column of silica gel and eluted with a mixture of chloroform and methanol (6:1, 500 mL followed by 3:2, 2 L). The product fractions were pooled to give 5.56 g of syrup. The syrup was dissolved in warm methanol–water (2:1, 125 mL) and treated with charcoal (2 g). After hot filtration through a Celite pad and evaporation of the methanol, the crystalline product was collected, washed with water, and dried in vacuo over phosphorus pentoxide at 100 °C for 24 h to yield 3.83 g (69%) of **10** as a hydrate: mp 152–153 °C; $[\alpha]^{22}_D$ −43.1 (*c* 1, CH_3OH); ^{1}H NMR (Me_2SO-d_6) δ 3.36 (s, H_2O), 3.42–3.60 (m, 2), 3.70–4.10 (m, 3), 4.68 (d, 1, J = 5.5 Hz, H-1′), 4.81 (t, 1), 4.99 (d, 1), 5.22 (d, 1), 6.99 (br s, 2, amide NH_2), 7.14 (s, 2, NH_2-4); ^{13}C NMR (D_2O) δ 62.1, 71.6, 76.5, 81.8, 85.0, 121.7, 150.6, 157.2, 166.8; IR cm^{-1} 1640, 1578; UV λ_{max} (pH 1) 273 nm (ϵ 10460), λ_{max} (pH 11) 273 (ϵ 10050); MS, *m/e* 275, 172, 169, 150; TLC (20% CH_3OH in $CHCl_3$) R_f 0.19, (solvent E) R_f 0.38. Anal. Calcd for $C_9H_{13}N_3O_5S$·H_2O: C, 36.86; H, 5.15; N, 14.33; S, 10.93. Found: C, 36.95; H, 5.47; N, 14.07; S, 11.22.

Ethyl 5-Amino-2-(β-D-ribofuranosyl)thiazole-4-carboxylate (11). To a stirred solution of methyl 2,5-anhydroallonothioate (**3**) (3.25 g, 15.6 mmol) in dry methanol (75 mL) was added ethyl 2-amino-2-cyanoacetate[10] (2.0 g, 15.6 mmol) dissolved in dry pyridine (15 mL). After 16 h at room temperature, the solvents were removed in vacuo and the residue was azeotroped with toluene (2 × 75 mL). The residue was dissolved in methanol and silica gel (60–200 mesh, 15 g) was added. After evaporation in vacuo the dry powder residue was added to a 40 mm × 150 mm silica gel column. The column was eluted with chloroform (300 mL) followed by 10% methanol in chloroform. The product fractions were pooled and evaporate in vacuo to yield 4.0 g of light yellow syrup which crystallized on standing. Recrystallization from 95% ethanol yielded 2.48 g (50.7%) of **11** as its hemihydrate: mp 75–76 °C; $[\alpha]^{22}_D$ −52.8 (*c* 1, CH_3OH); ^{1}H NMR (Me_2SO-d_6) δ 1.29 (3, J = 7.1 Hz), 3.40–3.72 (m, 2), 3.75–4.08 (m, 3), 4.25 (q, 2, J = 7.1), 4.31 (d, 1, J = 4.7 Hz, H-1′), 4.85 (t, 1), 5.02 (d, 1), 5.31 (d, 1), 7.34 (s, 2, NH_2); ^{13}C NMR (D_2O) δ 62.1, 71.5, 76.5, 81.8, 85.0, 119.0, 151.2, 161.1, 163.9; IR cm^{-1} 1670, 1590; UV λ_{max} (pH 1) 273 (ϵ 10408), λ_{max} (pH 11) 277 (ϵ 10712); MS, *m/e* 304, 259, 215, 201, 169, 155; TLC (20% CH_3OH in $CHCl_3$) R_f 0.42, (solvent E) R_f 0.46. Anal. Calcd for $C_{11}H_{16}N_2O_6S$·$^1/_2H_2O$: C, 42.16; H, 5.46; N, 8.94; S, 10.23. Found: C, 42.39; H, 5.58; N, 8.61; S, 10.12.

5-Amino-4-cyano-2-(β-D-ribofuranosyl)thiazole (12). To a stirred solution of methyl 2,5-anhydroallonothioate (**3**) (3.15 g, 15.1 mmol) in dry pyridine was added ammoniopropanedinitrile 4-methylbenzenesulfonate[11] (4.42 g, 17.4 mmol). After 24 h the pyridine was evaporated in vacuo and the residual pyridine was removed by azeotroping with toluene (2 × 75 mL). The residue was dissolved in methanol and silica gel (60–200 mesh, 15 g) was added. After evaporation in vacuo the residual powder was added on top of a 24 mm × 90 mm column of silica gel. The column was eluted with a mixture of chloroform–methanol (6:1). The product crystallized spontaneously in the collection tubes to give 1.13 g of **12**. Attempted recrystallization of **12** resulted in decomposition. Rechromatography of the impure fractions yielded an additional 0.63 g for a total of 1.76 g (45.2%) of **12**: mp 171–172 °C; $[\alpha]^{22}_D$ −65.3 (*c* 1, CH_3OH); ^{1}H NMR (Me_2SO-d_6) δ 3.42–3.64 (m, 2), 3.76–4.08 (m, 3), 4.65 (d, 1, J = 5.04 Hz, H-1′), 5.00 (bd s, 3), 7.35 (bd s, 2, NH_2); ^{13}C NMR (D_2O) δ 61.9, 71.5, 76.4, 81.7, 85.2, 100.6, 115.9, 154.1, 162.2; IR cm^{-1} 2212, 1609, 1525, 1508; UV λ_{max} (pH 1) 280 (sh, ϵ 8438), 253 (ϵ 8901), λ_{max} (pH 11) 280 (sh, ϵ 9056), 254 (ϵ 9519); MS, *m/e* 257, 168, 154, 138; TLC (20% CH_3OH in $CHCl_3$) R_f 0.22, (solvent E) R_f 0.55. Anal. Calcd for $C_9H_{11}N_3O_4S$: C, 42.01; H, 4.31; N, 16.33; S, 12.46. Found: C, 42.08; H, 4.60; N, 16.07; S, 12.11.

5-Amino-2-(β-D-ribofuranosyl)selenazole-4-carboxamide (13). To a stirred solution of methyl 2,5-anhydroallonoselenoate (**4**) (5.57 g, 20.9 mmol) in dry methanol (100 mL) was added 2-amino-2-cyanoacetamide[10] (2.4 g, 24.2 mmol). After 0.5 h the reaction mixture was filtered through a Celite pad to remove the colloidal selenium which had formed. The filtrate was concentrated in vacuo to yield a yellow syrup. The syrup was dissolved in methanol (25 mL) and the solution diluted with water (25 mL)

(23) Garcia-Lopez, M. T.; Herranz, R.; Mendez-Castrillon, P. P. *Nucleosides Nucleotides* **1982**, *1*, 127.

to yield 3.64 g of **13** as red needles. The product was recrystallized from a mixture of methanol and water (2:1, v:v), with simultaneous treatment with charcoal to yield 2.90 g (43%) of **13** as white needles: mp 182–183 °C; $[\alpha]^{22}_D$ −48.6 (*c* 1, CH_3OH); ^1H NMR (Me_2SO-d_6) δ 3.44–3.60 (m, 2), 3.75–4.07 (m, 3), 4.62 (d, 1, *J* = 4.5 Hz, H-1′), 4.84 (t, 1), 4.97 (d, 1), 5.23 (d, 1), 6.91 (br s, 2, amide NH_2), 7.51 (br s, 2, NH_2); ^{13}C NMR (D_2O) δ 62.1, 71.6, 76.8, 84.0, 84.8, 122.5, 156.5, 163.4, 167.4; IR cm^{-1} 1635, 1575; UV λ_{max} (pH 1) 275 nm (ε 8780) 225 (ε 9955), λ_{max} (pH 11) 272 (ε 8585), 225 (ε 9775); MS, *m/e* (^{80}Se) 323, 220; TLC (20% CH_3OH in $CHCl_3$) R_f 0.18, (solvent E) R_f 0.39. Anal. Calcd for $C_9H_{13}N_3O_5Se$: C, 33.55; H, 4.07; N, 13.04; Se, 24.51. Found: C, 33.34; H, 4.10; N, 13.04; Se, 24.43.

Ethyl 5-Amino-2-(β-D-ribofuranosyl)selenazole-4-carboxylate (14). To a stirred solution of methyl 2,5-anhydroallonoselenoate (**4**) (1.37 g, 5.4 mmol) in dry methanol (50 mL) was added ethyl 2-amino-2-cyanoacetate[10] (1.0 g, 7.8 mmol) dissolved in methanol (5 mL). After 0.5 h the reaction mixture was filtered to remove the colloidal selenium which had formed. Silica gel (60–200 mesh, 6 g) was added. The methanol was removed in vacuo leaving a dry powder which was added to the top of a 24 mm × 100 mm silica gel column. The column was eluted with chloroform (400 mL) followed by 4% methanol in chloroform. The product fractions were combined and evaporated in vacuo. The residue was recrystallized from absolute ethanol to yield, after seedng, 320 mg (17%) of **14**: mp 154–155 °C; $[\alpha]^{22}_D$ −40.6 (*c* 0.5, CH_3OH); ^1H NMR (Me_2SO-d_6) δ 1.26 (t, 3, *J* = 7.1 Hz), 3.35–3.62 (m, 2), 3.70–4.04 (m, 3), 4.20 (q, 2, *J* = 7.1 Hz), 4.61 (d, 1, *J* = 4.2 Hz, H-1′), 4.84 (t, 1), 4.91 (d, 1), 5.29 (d, 1), 7.66 (bd s, 2, NH_2); ^{13}C NMR (D_2O) δ 61.9, 71.2, 76.7, 84.1, 84.5, 119.9, 156.4, 164.2, 167.3; IR cm^{-1} 1670, 1660, 1590; UV λ_{max} (pH 1) 295 (sh, ε 6673), 272 (ε 8289), 228 (ε 9834), λ_{max} (pH 11) 276 (ε 8289), 227 (ε 10747); MS, *m/e* (^{80}Se) 352, 249; TLC (20% CH_3OH in $CHCl_3$) R_f 0.40 (solvent E) R_f 0.48. Anal. Calcd for $C_{11}H_{16}N_2O_6Se$: C, 37.62; H, 4.59, N, 7.98; Se, 22.48. Found: C, 37.85; H, 4.80; N, 7.69; Se, 22.10.

Diethyl [*N*-(2,5-Anhydroallonothioyl)amino]malonate (17). To a solution of methyl 2,5-anhydroallonothioate (**3**) (2.0 g) in 50 mL of dry pyridine was added diethyl aminomalonate hydrochloride (2.4 g) and the mixture was stirred for 16 h at room temperature. The pyridine was evaporated in vacuo and the residue azeotroped twice with methanol. The hygroscopic residue was absorbed into 8 g of silica gel (60–200 mesh) and added to the top of a 2.4 cm diameter flash chromatography column containing 90 mL of silica gel (40–63 μm) packed in dichloromethane. The title compound was eluted with 1–5% methanol in dichloromethane; pooling and evaporation of the fractions containing pure **17** yielded 2 g (55.5%) of a syrup after being dried at 40 °C (0.2 torr) over phosphorus pentoxide: ^1H NMR ($CDCl_3$) δ 1.28 (t, 3, *J* = 7.5 Hz), 1.32 (t, 3, *J* = 7.5 Hz), 3.42 (s, 1, H_2O), 3.88 (dd, 2 *J* = 3.0 Hz), 4.25 (q, 2, *J* = 7.5 Hz), 4.26 (q, 2, *J* = 7.5 Hz), 4.00–4.40 (m, 7), 4.72 (d, 1, *J* = 4.1 Hz, H-2′), 5.73 (s, 1 H, H-2); MS, *m/e* 352 (m + 1), 306, 250, 249, 176; Anal. Calcd for $C_{13}H_{21}NO_8S \cdot {}^1/_2H_2O$: C, 43.33; H, 6.15; N, 3.89. Found: C, 43.52; H, 6.12; N, 3.76.

Ethyl 2-(β-D-Ribofuranosyl)thiazole-4-carboxylate (18). Method A. To a stirred ice-cold solution of ethyl 5-amino-2-(β-D-ribofuranosyl)thiazole-4-carboxylate (**11**) (634 mg, 2 mmol) in 20 mL of an 18:12:31 mixture of concentrated hydrochloric acid–water–50% aqueous hypophosphorus acid was slowly added sodium nitrite (207 mg, 3 mmol) dissolved in a small amount of water. After 15 min an additional portion of sodium nitrite (70 mg, 1 mmol) dissolved in a small amount of water was slowly added. After the addition was complete the ice bath was removed and the reaction was allowed to gradually warm to room temperature. After 1 h the reaction mixture was again cooled to 0 °C and made slightly alkaline by dropwise addition of 50% aqueous sodium hydroxide (approximately 8.2 mL). The excess hydroxide was destroyed by addition of 4 mL of acetic acid. Silica gel (60–200 mesh, 5 g) was added and the solvents removed in vacuo at 30 °C. The resulting dry granular residue was added to the top of a 22 mm × 150 mm column of silica gel and the column was eluted with 10% methanol in chloroform. The product fractions were combined and evaporated to yield 300 mg (50%) of **18**. Crystallization of the product from 2-propanol–diethyl ether gave white crystals: mp 78–79.5 °C; $[\alpha]^{22}_D$ −4.7 (*c* 2, MeOH); ^1H NMR (Me_2SO-d_6) δ 1.31 (t, 3, *J* = 7.0 Hz) , 3.46–3.64 (m, 2), 3.80–4.12 (m, 3), 4.30 (q, 2, *J* = 7.0), 4.84 (t, 1), 4.94 (d, 1, *J* = 4.5, H-1′), 5.04 (d, 1), 5.40 (d, 1), 8.49 (s, 1, H-5); ^{13}C NMR (Me_2SO-d_6) δ 14.1, 60.7, 61.8, 71.2, 77.0, 82.1, 85.0, 129.2, 146.0, 160.8, 172.9); IR cm^{-1} 1710; UV λ_{max} (pH 1) 237 (ε 9923), λ_{max} (pH 11) 237 (ε 8679); MS, *m/e* 290, 244, 200, 186, 154, 140; TLC (20% CH_3OH in $CHCl_3$) R_f 0.50. Anal. Calcd for $C_{11}H_{15}NO_6S$: C, 45.67; H, 5.23; N, 4.84; S, 11.08. Found: C, 45.78; H, 5.31; N, 4.94; S, 11.26.

Method B. To a solution of 0.20 g of sodium metal in 30 mL of absolute ethanol was added 3.0 g (5.0 mmol) of ethyl 2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)thiazole-4-carboxylate.[2] After stirring at room temperature for 20 h, the solution was neutralized by addition of 2.2 g of Dowex 50W × 8 (H^+) with stirring. The solution was filtered, 4.5 g of silica gel (60–200 mesh) was added, and the ethanol evaporated in vacuo. The dry residue was added to the top of a 1.5 cm diameter flash chromatography column containing 50 mL of silica gel (40–63 μm) and the column eluted with 100 mL of chloroform followed by 10% methanol in chloroform. The product fractions were pooled and evaporated to dryness. The residue was recrystallized from 2-propanol–ether to yield 790 mg (55%) of **18**: mp 78–80 °C, identical with that obtained by method A.

2-(β-D-Ribofuranosyl)thiazole-4-carboxamide (1). Ethyl 2-(β-D-ribofuranosyl)-4-carboxylate (**18**) (1.0 g) was treated with saturated methanolic ammonia at 22 °C for 24 h. After evaporation of the volatile components, the residue was recrystallized from 2-propanol to give in two crops (800 mg) of **1** which was identical in all respects with a sample of **1** prepared by the published procedure:[2] ^{13}C NMR (Me_2SO-d_6) δ 61.9, 71.4, 76.9, 81.8, 85.0, 124.3, 150.2, 162.4, 172.1; MS, *m/e* 261, 260, 171, 157, 140.

Ethyl 2-(β-D-Ribofuranosyl)selenazole-4-carboxylate (19). Method A. Ethyl 5-amino-2-(β-D-ribofuranosyl)selenazole-4-carboxylate (**14**) (655 mg, 1.8 mmol) was subjected to the same reaction conditions as those used for the preparation of **18** to yield 250 mg (40%) of **19**. Crystallization from a mixture of ethyl acetate and hexane yielded an analytical sample: mp 98–101 C; $[\alpha]^{22}_D$ −17.7 (*c* 1.0, CH_3OH); ^1H NMR (Me_2SO-d_6) δ 1.31 (t, 3, *J* = 7.1), 3.52–3.70 (m, 2), 3.81–4.09 (m, 3), 4.29 (q, 2, *J* = 7.1), 4.86 (d, 1, *J* = 4.0, H-1′), 9.09 (s, H-5); ^{13}C NMR (Me_2SO-d_6) δ 14.1, 60.6, 61.5, 71.0, 77.0, 84.4, 84.7, 136.3, 147.0, 161.0, 180.9; IR cm^{-1}; UV λ_{max} (pH 1) 257 (ε 6790), 216 (ε 18177) λ_{max} (pH 11) 256 (ε 6616), 216 (ε 18455); MS *m/e* (^{80}Se) 337, 292, 234; TLC (20% CH_3OH in $CHCl_3$) R_f 0.49. Anal. Calcd for $C_{11}H_{15}NO_6Se$: C, 39.30; H, 4.50; N, 4.17; Se, 23.49. Found: C, 39.65; H, 4.59; N, 4.21; Se, 23.70.

Method B. Ethyl 2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)selenazole-4-carboxylate[4] (2.0 g) was treated with a solution of sodium metal (0.20 g) in 30 mL of absolute ethanol. The reaction mixture was processed as described above (see method B for compound **18**) to yield 602 mg (56%) of ethyl 2-(β-D-ribofuranosyl)selenazole-4-carboxylate (**19**) which was identical in all respects with that prepared by method A.

2-(β-D-Ribofuranosyl)selenazole-4-carboxamide (2). The same procedure used to prepare **1** from **18** was used to convert ethyl 2-(β-D-ribofuranosyl)selanazole-4-carboxylate (**19**) (750 mg) to **2** (600 mg, 87%). The product was identical in all respects with that previously reported:[4] ^{13}C NMR (Me_2SO-d_6) δ 61.7, 71.3, 76.9, 84.2, 84.7, 131.0, 151.1, 162.7, 180.3.

2-(β-D-Ribofuranosyl)thiazolo[5,4-*d*]pyrimidin-4(5*H*)-one (20). A stirred suspension of 5-amino-2-(β-D-ribofuranosyl)-thiazole-4-carboxamide (**10**) (1.0 g, 3.63 mmol) and crushed 4 Å molecular seives (750 mg) in freshly distilled triethyl orthoformate was heated at 95–100 °C for 48 h. After filtration, the volatile components were evaporated in vacuo. The residue was dissolved in a mixture of methanol and 0.1 N aqueous hydrochloric acid (1/1, v/v). After stirring overnight the solution was evaporated in vacuo and the residue treated with saturated methanolic ammonia overnight. The solvent was evaporated to dryness and the residue adsorbed onto silica gel (60–200 mesh, 3 g) as previously described. The powder was added to the top of a 24 × 125 mm silica gel column and the column was eluted with solvent E. The product fractions were combined and evaporated in vacuo to yield 930 mg (89%) of **20** as a chromatographically pure powder. Recrystallization of the residue from absolute ethanol yielded an

analytical sample of **20**: mp 245–248 °C; $[\alpha]^{22}_D$ +27.4 (*c* 0.5, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 3.39–3.64 (m, 2), 3.77–4.14 (m, 3), 4.90 (d, 1, *J* = 5.4 Hz, H-1′), 4.70–5.50 (br, 3 H), 8.15 (s, 1, H-6); ^{13}C NMR (Me_2SO-d_6) δ 61.7, 71.4, 77.0, 82.5, 85.2, 137.8, 146.7, 155.78, 161.4, 169.4; IR cm^{-1} 1770, 1570; UV λ_{max} (pH 1) 282 nm (ε 4857), 261 (ε 5714), 254 (ε 5514), 215 (ε 14857), λ_{max} (pH 11) 289 (ε 5485), 263 (ε 5700), 257 (ε 5914), 225 (ε 11457); MS, *m/e* 285, 249, 232, 220, 196, 182; TLC (solvent E) R_f 0.26. Anal. Calcd for $C_{10}H_{11}N_3O_5S$: C, 42.10; H, 3.89; N, 14.73; S, 11.24. Found: C, 42.08; H, 4.07; N, 14.52; S, 11.04.

2-(β-D-Ribofuranosyl)selenazolo[5,4-*d*]pyrimidin-4-(5*H*)-one (21). The same procedure used to prepare **20** was also used to prepare **21**. Thus 5-amino-2-(β-D-ribofuranosyl)selenazole-4-carboxamide (**13**) (1.0 g, 3.1 mmol) yielded 720 mg (69%) of **21**: mp 232–235 °C; $[\alpha]^{22}_D$ +20.0 (*c* 0.5, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 3.50–3.65 (m, 2), 3.82–4.12 (m, 3), 4.84 (d, 1, *J* = 4.5, H-1′), 8.15 (s, 1, H-6); ^{13}C NMR (Me_2SO-d_6) δ 61.7, 71.5, 77.3, 84.8, 85.2, 140.7, 145.7, 156.3, 167.7, 177.7; IR cm^{-1} 1675; UV λ_{max} (pH 1) nm 290 (ε 5769), 258 (sh, ε 4192), 233 (ε 18077), λ_{max} (pH 11) 295 (ε 6538), 263 (sh, ε 5000), 238 (ε 14115); MS, *m/e* (^{80}Se) 333, 297, 280, 268, 244, 230; TLC (solvent E) R_f 0.26. Anal. Calcd for $C_{13}H_{11}N_3O_5Se \cdot {}^1/_2H_2O$: C, 35.20; H, 3.55; N, 12.32. Found: C, 35.57; H, 3.54, N, 12.17.

4-Amino-2-(β-D-ribofuranosyl)thiazolo[5,4-*d*]pyrimidine (22). To a solution of 5-amino-4-cyano-2-(β-D-ribofuranosyl)-thiazole (**12**) (150 mg, 0.58 mmol) in ethoxyethanol (10 mL) was added formamidine acetate (200 mg, 1.92 mmol) and the mixture was refluxed for 30 min. The solution was allowed to cool to room temperature followed by evaporation in vacuo. The residue spontaneously crystallized. The product purified by recrystallization from absolute ethanol (2x) to give 124 mg (75%) of **22**: mp 208–211 °C; $[\alpha]^{22}_D$ +73.2 (*c* 0.5, Me_2SO); ^1H NMR (Me_2SO-d_6) δ 3.52–3.68 (m, 2), 3.88–4.44 (m, 3), 4.91 (t, 1, *J* = 5.4 Hz), 5.0 (d, 1, *J* = 6.3 Hz, H-1′), 5.06–5.12 (m, 1), 5.42 (d, 1, *J* = 5.4 Hz), 7.65 (br s, 2, NH_2), 8.29 (s, 1, H-6); ^{13}C NMR (Me_2SO-d_6) δ 61.7, 71.4, 77.0, 82.6, 85.6, 129.7, 154.2, 156.9, 162.2, 168.7; IR cm^{-1} 1570; UV λ_{max} (pH 1) 268 nm (ε 11857), 222 (ε 21714), λ_{max} (pH 11) 290 (sh, ε 5571), 265 (ε 9857), 226 (ε 14857); MS, *m/e* 284, 195, 181; TLC (solvent E) R_f 0.38. Anal. Calcd for $C_{10}H_{12}N_4O_4S$: C, 42.25; H, 4.25; N, 19.71; S, 11.28. Found: C, 42.22; H, 4.46; N, 19.44; S, 11.18.

2-(β-D-Ribofuranosyl)thiazolo[5,4-*d*][1,2,3]triazin-7-(6*H*)-one (23). To a cold (−22 °C, CCl_4/dry ice slush bath) stirred solution of 5-amino-2-(β-D-ribofuranosyl)thiazole-4-carboxamide (**10**) (300 mg, 1.09 mmol) in 6 N aqueous hydrochloric acid (5.5 mL) was added sodium nitrite (230 mg, 3.27 mmol) dissolved in water (2 mL). After 30 min the solution was made slightly basic (pH 8) by addition of cold concentrated ammonium hydroxide (2.18 mL). After silica gel (60–200 mesh, 1 g) had been added the red solution was evaporated in vacuo. The dry powder was added to the top of a 24 mm × 175 mm silica gel column and the column was eluted with solvent E. Evaporation of the product fractions yielded 200 mg (65%) of **23** as a crystalline solid: mp 178 °C dec with gas evolution; ^1H NMR (Me_2SO-d_6) δ 3.48–3.68 (m, 2), 3.86–4.23 (m, 3 H), 5.05 (d, 1, *J* = 4.5, H-1′), exchangeable protons were observed as broad undefined absorptions; ^{13}C NMR (D_2O) δ 61.5, 71.4, 77.1, 82.6, 85.1, 139.1, 152.9, 156.3, 177.4; IR cm^{-1} 1700; UV λ_{max} (pH 1) 295 nm (ε 5507), 223 (ε 13590), λ_{max} (pH 11) 310 (ε 6795), 258 (ε 4220), 230 (ε 12088); MS, *m/e* 286, 257, 243, 204, 197, 185, 171, 149, 129, 97, 69; TLC (solvent E) R_f 0.51. Anal. Calcd for $C_9H_{10}N_4O_5S$: C, 37.76; H, 3.52; N, 19.57; S, 11.20. Found: C, 37.81; H, 3.72; N, 19.31; S, 11.46.

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Registry No. **1**, 60084-10-8; **2**, 83705-13-9; **3**, 95936-45-1; **4**, 95936-46-2; **5**, 62404-62-0; **7**, 6719-21-7; **8**, 32683-02-6; **9**, 5098-14-6; **10**, 95936-47-3; **11**, 95936-48-4; **12**, 95936-49-5; **13**, 95936-50-8; **14**, 95936-51-9; **16**, 13433-00-6; **17**, 95936-52-0; **18**, 95936-53-1; **19**, 95936-54-2; **20**, 95936-55-3; **21**, 95936-56-4; **22**, 95936-57-5; **23**, 95936-58-6; ethyl 2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-thiazole-4-carboxylate, 60084-09-5; ethyl 2-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)selenazole-4-carboxylate, 83705-11-7; triethyl orthoformate, 122-51-0; formamidine acetate, 3473-63-0.

Notes

Hydrogen–Deuterium Exchange of Weak Carbon Acids under Phase-Transfer Catalysis Conditions

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Phase-transfer catalysis (PTC) enables the chemist to maintain a concentration of substances from an aqueous reservoir in an organic phase which contains an organic substrate.[1] The mechanism of this process has been the subject of much discussion[1c] and study.[1a] An extraction mechanism has been considered by Starks in which the nucleophile is extracted from the aqueous reservoir into the organic phase with the aid of a quaternary ammonium or phosphonium ion (quat).[2-4] Makosza proposed an alternative mechanism for alkylation and carbene addition in which proton abstraction by the hydroxide ion occurs in the interface.[5,6] In the latter case, the quat has the role of removing the resulting organic anion from the interface into the bulk organic phase for subsequent reaction. The critical component of PTC reactions is the catalyst, and it has recently been shown that the choice of this parameter may lead to favorable results.[7] Hydroxide ion initiated reactions performed under PTC conditions provide unique advantages in the laboratory and industry due to the employment of an aqueous base instead of the classical alkoxides and hydrides in strictly dry media.

Proton exchange in compounds of low acidity is often difficult in a practical method because of high kinetic barriers associated with removal of the hydrogen. Toluene and toluene derivatives were shown by Streitwieser to

(1) (a) Heriott, A.; Picker, D. *J. Am. Chem. Soc.* **1975**, *97*, 2345. (b) Weber, W. P.; Gokel, G. "Phase Transfer Catalysis in Organic Synthesis"; Springer-Verlag: Berlin, 1977. (c) Dehmlow, E.; Dehmlow, S. "Phase Transfer Catalysis"; Verlag Chemie: Weinheim, 1980.
(2) Starks, C. *J. Am. Chem. Soc.* **1971**, *93*, 195.
(3) Starks, C.; Owens, R. *J. Am. Chem. Soc.* **1973**, *95*, 3613.
(4) The extraction mechanism has been characterized by comprehensive studies, e.g.: (a) Landini, D.; Maia, A.; Montanari, F. *J. Chem. Soc., Chem. Commun.* **1975**, 950. (b) Landini, D.; Maia, A.; Montanari, F. *J. Am. Chem. Soc.* **1978**, *100*, 2796.
(5) Makosza, M. *Pure Appl. Chem.* **1975**, *43*, 439.
(6) Makosza, M.; Bialecka, E. *Tetrahedron Lett.* **1977**, 183.
(7) (a) Halpern, M.; Sasson, Y.; Rabinovitz, M. *Tetrahedron* **1982**, *38*, 3183. (b) Halpern, M.; Sasson, Y.; Rabinovitz, M. *J. Org. Chem.* **1983**, *48*, 1022.

0022-3263/85/1950-1746$01.50/0