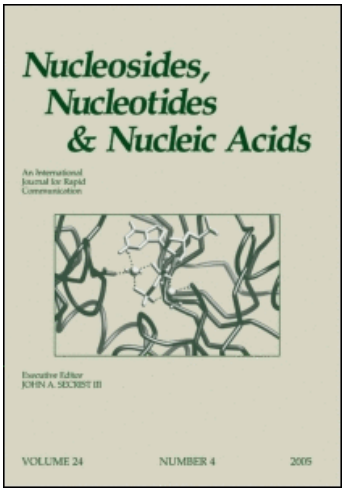

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Ralph H. Baur[a]; David C. Baker[a]
[a] Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama

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Synthesis of 2-(3-Deoxy-β-D-erythropentofuranosyl)-thiazole-4-carboxamide (3'-Deoxytiazofurin)

Ralph H. Baur and David C. Baker*

Department of Chemistry, The University of Alabama, Tuscaloosa, Alabama 35486

Abstract. 2-(3-Deoxy-β-D-erythropentofuranosyl)-thiazole-4-carboxamide was synthesized in four steps from its β-D-ribofuranosyl nucleoside precursor.

INTRODUCTION

2-(β-D-Ribofuranosyl)thiazole-4-carboxamide (tiazofurin, NSC-286193, 1)[1,2] has emerged as a promising new drug that is active against a number of tumors, including i.p.-implanted P388 and L1210 murine leukemias.[3] It is especially effective against Lewis lung carcinoma,[3] an experimental solid tumor that mimics the human metastatic disease.[4] Recent studies have uncovered the fact that tiazofurin (1) acts via the agency of a nicotinamide adenine dinucleotide (NAD) analog in which the thiazole moiety is substituted for the nicotinamide moiety of natural NAD.[5,6] The enzymatic target is believed to be inosine monophosphate dehydrogenase,[7] the inhibition of which leads to decreased levels of guanine nucleotides.

In a program which is centered around the design and evaluation of congeners of active antitumor compounds, our

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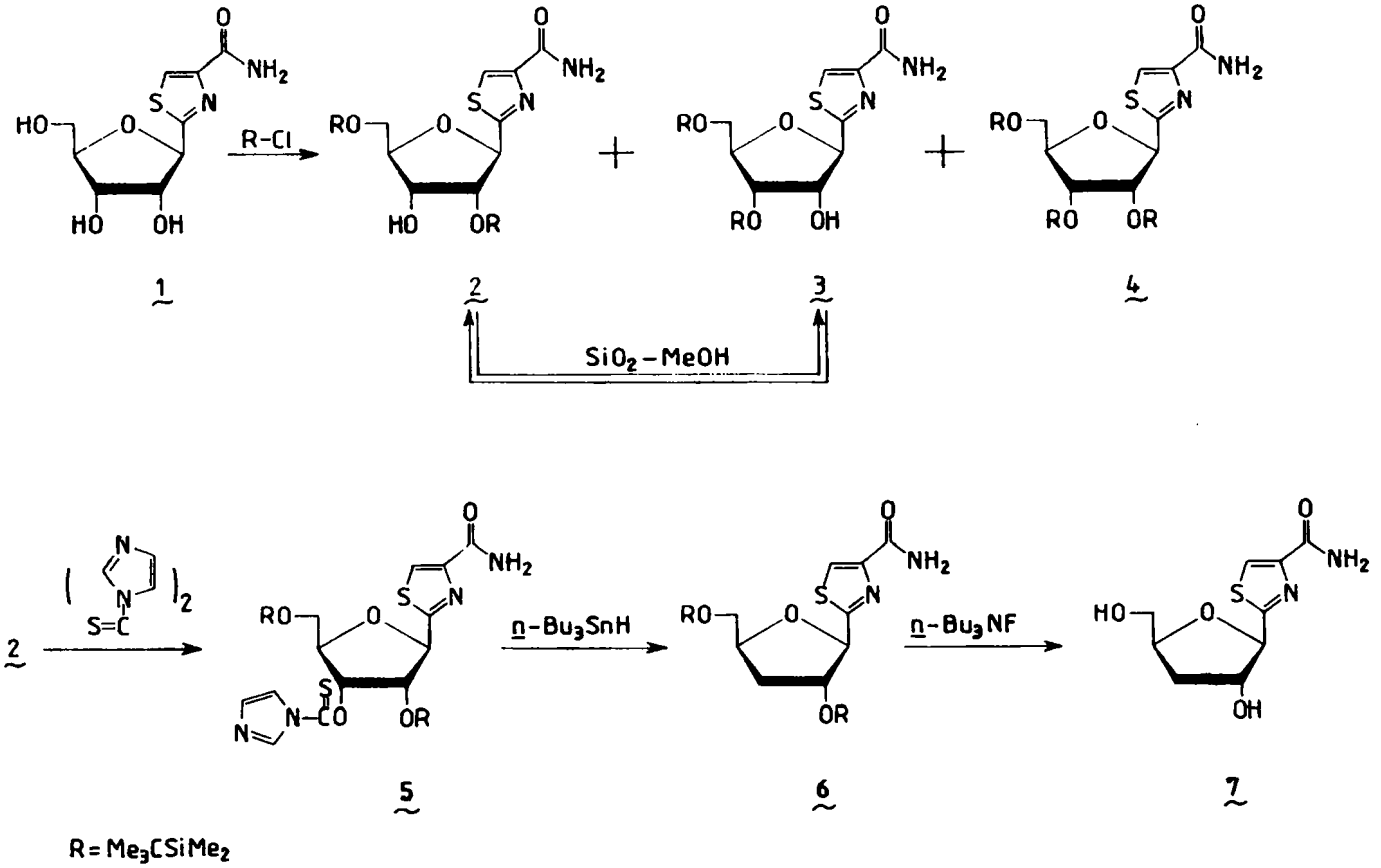
aim was to investigate certain analogs of **1** to hopefully develop a drug that might offer either improvements over, or alternatives to, **1**. Of the nucleosides generally regarded for analog synthesis, the 3'-deoxy-β-D-erythropentofuranosyl derivative was selected. That this 3'-deoxytiazofurin might undergo *in vivo* phosphorylation and subsequent conversion to an analog of NAD is a reasonable possibility based on the known ability of 3'-deoxyadenosine (cordycepin) to undergo most of the enzymatic conversions of adenosine, especially phosphorylation.

RESULTS AND DISCUSSION

Chemistry. A strategy to produce a 3'-deoxynucleoside from its D-*ribo* counterpart necessarily dictates a 2',5'-di-O-protected intermediate that will allow selective derivatization at the 3'-OH position for later deoxygenation. To this end was chosen a relatively non-discriminating reaction of **1** with 2.2 molar equivalents of *tert*-butylchlorodimethylsilane in *N*,*N*-dimethylformamide with imidazole as base to give a mixture of the bis-(silyl)ated, 2',5'-di-O-*tert*-butyldimethylsilyl tiazofurin **2** and its 3',5'-counterpart **3**, as well as the tris(silyl)ated nucleoside **4**, which was separated by column chromatography. (See Scheme I.) Compounds **2** and **3** were shown to equilibrate in methanolic solution, a phenomenon well known with adenosine analogs.[9,10] Furthermore, it was observed that the rate of the equilibration process could be greatly enhanced by the addition of silica gel to a stirring methanolic solution of **2** and **3**, and the ~1:1 equilibrated mixture of **2**:**3** could be separated by column



SCHEME I

chromatography. By a thrice-repeated sequence of equilibration of **3** ⇄ **2**, separation of pure **2**, and recycle of **3**, a total yield amounting to 84% of pure **2**, along with 8% of **3** and 7% of **4** could be obtained from a single silylation reaction. (See Experimental Section.) Thus was achieved a preparative route to the required amounts of pure **2**.

The structures of both **2** and **3** were determined via study of their ^{1}H NMR spectra. Compound **2** exhibited in DMSO-$\underline{d}_6$ a narrow doublet for H-1' at δ 4.95 ($J_{1',2'}$ = 6 Hz), with H-2' appearing at δ 4.11 as a pseudo triplet. However, H-3' and H-4' were observed as overlapping signals at δ 3.95, and whether H-3' was definitely associated with a carbon bearing a free hydroxy group could not easily be determined. Acetylation of **2**, on the other hand, gave the N-acetyl-2-[3-O-acetyl-2,5-di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (i.e., the N-acetyl-3'-O-acetyl derivative of **2**) in which the H-3' signal was shifted downfield by ~1.3 ppm to show a doublet of doublets at δ 5.24 ($J_{2',3'}$ = 4 Hz, $J_{3',4'}$ = 1 Hz). The other resonances (i.e., the signals for H-1', H-2', H-4' and H-5',5'$_a$) that were not associated with acetylation of the 3'-OH group showed only small shifts from their corresponding resonances in **2**. Similar observations for **3** confirmed that its 2'-OH was indeed free. The ^{1}H NMR spectrum of **3** showed a doublet for H-1' at δ 4.93 ($J_{1',2'}$ = 6 Hz) with both H-2' and H-3' appearing as overlapping signals at ~δ 4.1. Acetylation as for **2** gave N-acetyl-2-[2-O-acetyl-3,5-di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (i.e., the N-acetyl-2'-O-acetyl derivative of **3**) having the H-2' doublet shifted downfield by ~1.1 ppm to δ 5.30 overlapping with H-1'. The

H-3' signal remained relatively unchanged as a pseudo triplet at δ4.41 ($J_{2',3'} = J_{3',4'} = 4.5$ Hz). It is of interest also to point out that for both **2** and its acetylated derivative in which 2',5'-bis(tert-butyldimethylsilyl) groups are present, the resonances for both the tert-butyl and the diastereotopic methyl groups on the silicon appear widely separated and distinct from one another, whereas in the case of the 3',5'-bis(tert-butyldimethylsilyl)ated compound **3** and its 2'-acetate both the tert-butyl resonances and methyl resonances overlap or are separated only by a few hertz. Such signal patterns have been observed in other β-D-ribofuranosyl systems[11] and may well prove to be a ready method for distinguishing such isomers as **2** and **3**.

The 2',5'-bis(tert-butyldimethylsilyl)ated **2** was reacted with 1,1'-thiocarbonyldiimidazole to give in 94% yield 2-[2,5-di-O-(tert-butyldimethylsilyl)-3-O-imidazoylthiocarbonyl-β-D-ribofuranosyl]thiazole-4-carboxamide (**5**), isolated as an amorphous solid by column chromatography. H-3' in **5** was observed to move ~2 ppm downfield from the shift of the H-3' of its precursor **2**, owing to the electron-withdrawing effects of the thiocarbonyl moiety. Deoxygenation of **5** was cleanly carried out using tri-n-butyltin hydride in refluxing toluene with 2,2'-azobis(2-methylpropionitrile) as a promoter as per the general method of Barton and McCombie[12] that has been recently applied to nucleosides.[13] That deoxygenation to 2-[2,5-di-O-(tert-butyldimethylsilyl)-3-deoxy-β-D-erythropentofuranosyl]thiazole-4-carboxamide (**6**) had indeed taken place was shown by the presence of the two H-3',3'$_a$ protons at δ1.93 as a multiplet. It is worthwhile to note that the deoxygenation process described in the foregoing that made

use of the imidazoylthio group was found to be decidedly superior to other methodology including the cyclic thionocarbonate and (methylthio)thiocarbonyl [MeSC(=S)-] derivatives.[12] The former gave ~1:1 mixtures of 2'- and 3'-deoxynucleosides, while attempts to form the latter by reacting the 2',5'-bis(tert-butyldimethylsilyl)ated nucleoside **2** with carbon disulfide and methyl iodide in base resulted in silyl-group migration, with thionoester formation exclusively at the 2'-O-position as determined by ^{1}H NMR spectroscopy. Thus the milder procedure that makes use of 1,1'-thiocarbonyldiimidazole is to be preferred in systems where silyl-group migration is a problem.

Deprotection of the resulting 2',5'-di-O-tert-butyldimethylsilyl-3'-deoxynucleoside **6** was effected with tetra-n-butylammonium fluoride in tetrahydrofuran to give the free nucleoside, 2-(3-deoxy-β-D-erythropentofuranosyl)-thiazole-4-carboxamide (**7**), in near-quantitative yield. It is noteworthy that a total of 48 h were required to fully deprotect **6** in contrast to a relatively short period of time (generally 1-2 h) necessary to achieve similar deblocking on either **2**, **3** or **4**. The participation by a neighboring hydroxy group is suspected in the latter examples. Examination of the ^{1}H NMR spectrum of **7** showed a two-proton multiplet at δ 1.85 for the H-3' protons, a narrow doublet at δ 4.96 ($J_{1',2'}$ = 2.5 Hz) for H-1', as well as other resonances (See Experimental Section.) consonant with the structure assigned for **7**. Compound **7** was further characterized by elemental analysis.

Biological Evaluation of 7. The 3'-deoxytiazofurin (**7**, NSC-366160) was evaluated under standard protocol[14] against L1210 leukemia in mice and found inactive (T/C = 109%, 300 mg/kg). Compound **1**, by contrast, has shown[3] a

T/C = 130 (600 mg/kg) in L1210 leukemia and a T/C = 145 (700 and 800 mg/kg) in i.p.-implanted P388 leukemia on a q.d. 1-9 schedule. Compound 7 is currently undergoing additional testing at higher dosages against L1210 leukemia.

EXPERIMENTAL

General Methods. Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus outfitted with a Cole-Parmer model 8520-50 Digi-Sense thermocouple thermometer with a 8520-55 probe that has been standardized against a set of known mp standards. Ultraviolet spectra (UV) were taken on a Cary-14 spectrophotometer; 200-MHz ^1H nuclear magnetic resonance spectra (^1H NMR) were determined using a Nicolet NT-200 instrument. Chemical shifts are reported as δ units downfield from internal tetramethylsilane; the spin-spin coupling data and peak multiplicities are apparent, first-order values [s, singlet; d, doublet; dd, doublet of doublets; Ψt, "pseudo" triplet (i.e., a doublet of doublets appearing as a triplet); b, broad]. Thin-layer chromatography was carried out on E. Merck aluminum-backed plates (cat. no. 5539) using either eluent system A (toluene - ethyl acetate 1:1) or B (chloroform - methanol 8:2). Preparative column chromatography was done using E. Merck Silica Gel 60 (70 - 230 mesh, cat. no. 7734). All solutions were evaporated at ca. 45 °C under aspirator vacuum. Chemicals and solvents were reagent grade and were used directly except the following: Tetrahydrofuran (THF, distilled under nitrogen from potassium - benzophenone ketyl) and N,N-dimethylformamide (DMF, distilled in vacuo from calcium hydride).

2-[2,5-Di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (2) and 2-[3,5-Di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (3). A mixture of 3.0 g (11.5 mmol) of 2-(β-D-ribofuranosyl)thiazole-4-carboxamide (1),[15] 4.7 g (69 mmol) of imidazole and 3.8 g (25.3 mmol) of tert-butylchlorodimethylsilane in 50 mL of DMF was stirred at room temperature for 2 h, at the end of which time 5 mL of methanol was added, and after stirring for 5 min, the thick syrup was dissolved in 200 mL of ethyl acetate. The solution was washed with conc aqueous sodium chloride (3 x 50 mL), dried over magnesium sulfate and evaporated. The resulting mixture of 2-[2,5-di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (2), 2-[3,5-di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (3) and 2-[2,3,5-tri-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (4) (6.65 g) was separated by column chromatography (150 g of silica gel, 4 cm diameter, 6:4 toluene - ethyl acetate). In the order of elution were obtained: 1.52 g of pure 2, 3.98 g of a mixture of 2 and 3, and 0.4 g of pure 4.

The mixed fraction of 2 and 3 was dissolved in 250 mL of methanol and stirred with 15 g of silica gel (E. Merck cat. no. 7734) overnight at room temperature, and the resulting mixture was separated as in the foregoing by column chromatography. By repeating this process three times, an overall yield of 4.71 g (84%) of 2 (as a colorless oil), along with 0.45 g (8%) of 3 (as an amorphous solid, mp 106 - 107 °C) and 0.40 g (7%) of 4 (as an amorphous solid, mp 127 - 128 °C), was obtained.

Physical data for 2: R_f = 0.56 (A); $[\alpha]_D^{20}$ = -8.8° (c 1, chloroform); UV (methanol) 232 nm (ε 8100); ^{1}H NMR (DMSO-

d$_6$, 10% D_2O): δ -0.06 (s, 6H, 2'-OSiCH_3), 0.08 (s, 6H, 5'-OSiCH_3), 0.81 (s, 9H, t-Bu), 0.87 (s, 9H, t-Bu), 3.76 (m, 2H, H-5',5'$_a$), 3.95 (m, 2H, H-3', H-4'), 4.11 (ψt, 1H, H-2', $J_{1',2'} = J_{2',3'} = 4$ Hz), 4.95 (d, 1H, H-1'), 7.43 (bs, 1H, NH), 7.62 (bs, 1H, NH), 8.25 (s, 1H, H-5). Anal. Calcd for $C_{21}H_{40}N_2O_5SSi_2$ (MW 488.7): C, 51.61; H, 8.25; N, 5.73. Found: C, 51.77; H, 8.28; N, 5.69.

N-Acetyl-2-[3-O-Acetyl-2,5-di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (N-Acetyl-3'-O-acetyl Derivative of **2**): ^{1}H NMR (DMSO-d$_6$): δ-0.19 (s, 3H, 2'-OSiCH_3), -0.01 (s, 3H, 2'-OSiCH_3), 0.10 (s, 6H, 5'-OSiCH_3), 0.75 (s, 9H, t-Bu), 0.87 (s, 9H, t-Bu), 2.10 (s, 3H, OAc), 2.39 (s, 3H, NAc), 3.81 (m, 2H, H-5',5'$_a$), 4.25 (m, 2H, H-2', H-4'), 4.99 (d, 1H, H-1', $J_{1',2'}$ = 7.8 Hz), 5.24 (m, 1H, $J_{2',3'}$ = 4 Hz, $J_{3',4'}$ = 1 Hz, H-3'), 8.68 (s, 1H, H-5), 10.02 (s, 1H, NH).

Physical data for **3**: R_f = 0.51 (A); $[\alpha]_D^{20}$ -16.1° (c 1, chloroform); UV (methanol) 234 nm (ε8600); ^{1}H NMR (DMSO-d$_6$, 10% D_2O): δ 0.09 (s, 6H, OSiCH_3), 0.10 (s, 6H, OSiCH_3), 0.87 (s, 9H, t-Bu), 0.89 (s, 9H, t-Bu), 3.71 (m, 2H, H-5',5'$_a$), 3.95 (m, 1H, H-4'), 4.10 (m, 2H, H-2', H-3', $J_{1',2'}$ = 6 Hz), 4.93 (d, 1H, H-1'), 7.58 (bs, 1H, NH), 7.68 (bs, 1H, NH), 8.23 (s, 1H, H-5). Anal. Calcd for $C_{21}H_{40}N_2O_5SSi_2$ (MW 488.7): C, 51.61; H, 8.25; N, 5.73. Found: C, 51.69; H, 8.26; N, 5.70.

N-Acetyl-2-[2-O-Acetyl-3,5-di-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]thiazole-4-carboxamide (N-Acetyl-2'-O-acetyl derivative of **3**): ^{1}H NMR (DMSO-d$_6$): δ 0.04 (m, 6H, OSiCH_3), 0.84 (s, 9H, t-Bu), 0.87 (s, 9H, t-Bu), 2.09 (s, 3H, 2'-OAc), 2.38 (s, 3H, NAc), 3.79 (m, 2H, H-5',5'$_a$), 4.01 (m, 1H, H-4'), 4.41 (ψt, 1H, $J_{2',3'}$ = 4.5 Hz, H-3'), 5.30 (m, 2H, H-1', H-2'), 8.65 (s, 1H, H-5), 10.18 (s, 1H, N-H).

Physical data for **4**: R_f = Ø.69 (A); $[\alpha]_D^{2Ø}$ -2Ø.4° (c 1, chloroform); UV (methanol) 233 nm (ε8ØØØ); ^{1}H NMR (DMSO-d_6): δ -Ø.2Ø (s, 3H, 2'-OSiCH_3), -Ø.Ø9 (s, 3H, 2'-OSiCH_3), Ø.12 (12H, 3',5'-OSiCH_3), Ø.81 [m, 9H, 2'-t-Bu], Ø.86, [m, 18H, 3',5'-t-Bu], 3.77 (m, 2H, H-5',5'$_a$), 4.Ø1 (m, 1H), 4.13 (m, 2H), 4.99 (d, 1H, H-1'), $J_{1',2'}$ = 7 Hz). Anal. Calcd for $C_{27}H_{54}N_2O_5Si_3$ (MW 6Ø3.1): C, 53.78; H, 9.Ø3; N, 4.64. Found: C, 53.9Ø; H, 9.Ø5; N, 4.6Ø.

2-[2,5-Di-O-(tert-butyldimethylsilyl)-3-O-imidazoylthiocarbonyl-β-D-ribofuranosyl]thiazole-4-carboxamide (5): 3.14 g (6.43 mmol) of **2** and 2.Ø9 g (11.6 mmol) of 1,1'-thiocarbonyldiimidazole were stirred in 5Ø mL of DMF for 18 h at room temperature, at the end of which time 25Ø mL of ethyl acetate was added, and the solution was extracted with saturated aqueous sodium chloride (4 x 5Ø mL). The organic layer was dried over magnesium sulfate and evaporated to yield 3.85 g (quant.) of crude **5**, which was chromatographed (2ØØ g of silica gel, 4 cm diameter, 6:4 toluene - ethyl acetate) to give 3.61 g (94%) of pure **5** as an amorphous colorless solid: mp 116 - 117 °C; R_f = Ø.49 (A); $[\alpha]_D^{2Ø}$ = -71.6° (c 1, chloroform); UV (methanol) 273 nm (ε 8ØØØ), 242 (11,4ØØ); ^{1}H NMR (DMSO-d_6): δ-Ø.24 (s, 3H, 2'-OSiCH_3), -Ø.Ø9 (s, 3H, 2'-OSiCH_3), Ø.Ø3 (s, 3H, 5'-OSiCH_3), Ø.16 (s, 3H, 5'-OSiCH_3), Ø.66 (s, 9H, t-Bu), Ø.92 (s, 9H, t-Bu), 3.9Ø (m, 2H, H-5',5'$_a$), 4.41 (m, 1H, H-2'), 4.57 (m, 1H, H-4'), 5.24 (d, 1H, H-1', $J_{1',2'}$ = 5 Hz), 6.Ø3 (m, 1H, H-3', $J_{2',3'}$ = 4 Hz), 7.14 (s, 1H, imidazole), 7.43 (bs, 1H, NH), 7.66 (bs, 1H, NH), 7.87 (s, 1H, imidazole), 8.49 (s, 1H, H-5), 8.59 (s, 1H, imidazole): Anal. Calcd for $C_{25}H_{42}N_4O_5S_2Si_2$ (MW 599.Ø): C, 5Ø.13; H, 7.Ø7; N, 9.35. Found: C, 5Ø.22; H, 7.Ø8; N, 9.34.

2-[2,5-Di-O-(tert-butyldimethylsilyl)-3-deoxy)-β-D-erythropentofuranosyl]thiazole-4-carboxamide (6): A mixture of 2.50 g (4.18 mmol) of 5, 3.0 mL (11.2 mmol) tri-n-butyltin hydride and 1.2 g (7.3 mmol) 2,2'-azobis(2-methylpropionitrile) was refluxed in 125 mL of toluene under nitrogen for 1.3 h. The resulting colorless solution was allowed to cool, and then it was passed through a column of silica gel (250 g, 4 cm diameter, 1.5 L of toluene, then 7:3 toluene - ethyl acetate). Upon eluting with the more polar solvent, **6** was obtained as a thick syrup which partially solidified. In order to separate traces of tin-containing compounds, the syrup was triturated with 50 mL of pentane to yield 1.82 g (92%) of 6 as an amorphous colorless solid: mp 114 - 115 °C; R_f = 0.69 (A); $[\alpha]_D^{20}$ = -21.7° (c 1, chloroform); UV (methanol) 230 nm (ε8900); ^{1}H NMR (DMSO-d_6, 10% D_2O): δ 0.05 (m, 12H, $SiCH_3$), 0.86 (m, 18H, t-Bu), 1.93 (m, 2H, H-3'), 3.73 (m, 2H, H-5',5'$_a$), 4.35 (m, 1H, H-4'), 4.50 (m, 1H, H-2', $J_{1',2'}$ = 4 Hz), 4.92 (d, 1H, H-1'), 7.45 (bs, 1H, NH), 7.65 (bs, 1H, NH), 8.24 (s, 1H, H-5). Anal. Calcd for $C_{21}H_{40}N_2O_5SSi_2$ (MW 472.8): C, 53.35; H, 8.53; N, 5.93. Found: C, 53.09; H, 8.54; N, 5.89.

2-(3-Deoxy-β-D-erythropentofuranosyl)thiazole-4-carboxamide (7): To 1.76 g (2.49 mmol) of **6** dissolved in 20 mL of THF was added 10 mL of a 1 N solution of tetra-n-butylammonium fluoride in THF, and the mixture was stirred at room temperature for 48 h. The solvent was evaporated, and the crude product was chromatographed (50 g of silica gel, 2.5 cm diameter, 9:19 chloroform - methanol) to yield 0.90 g (99%) of 7 as a thick syrup which was triturated with ether - methanol to give 0.68 g (75%) of pure **7** as a

colorless, amorphous solid: mp 114 - 115 °C; R_f = 0.33 (B); $[\alpha]_D^{20}$ = -6.40° (c 1, methanol); UV (methanol) 228 nm (ε 11,000); ^{1}H NMR (DMSO-d_6, 10% D_2O): δ 1.85 (m, 2H, H-3'), 3.57 (m, 2H, H-5',5'$_a$), 4.32 (m, 1H, H-4'), 4.43 (m, 1H, H-2', $J_{1',2'}$ = 2.5 Hz), 4.96 (d, 1H, H-1'), 8.15 (m, 1H, H-5). Anal. Calcd for $C_9H_{12}N_2O_4S$ (MW 244.3): C, 44.25; H, 4.95; N, 11.47. Found: C, 44.19; H, 4.99; N, 11.45.

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REFERENCES

1. Fuertes, M.; García-López, T.; García-Muñoz, G.; Stud, M. J. Org. Chem. **1976**, 41, 4074 - 4077.

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 - 262.

3. Robins, R. K.; Srivastava, P. C.; Narayanan, V. L.; Plowman, J.; Paull, K. D. J. Med. Chem. **1982**, 25, 107 - 108.

4. Hanna, N.; Fidler, I. J. Cancer Res. **1981**, 41, 438 - 444.

5. Cooney, D. A.; Jayaram, H. N.; Gebeyehu, G.; Betts, C. R.; Kelley, J. A.; Marquez, V. E.; Johns, D. G. Biochem. Pharmacol. **1982**, 31, 2133 - 2136.

6. Gebeyehu, G.; Marquez, V. E.; Kelley, J. A.; Cooney, D. A.; Jayaram, H. N.; Johns, D. G. J. Med. Chem. **1983**, 26, 922 - 925.

7. Robins, R. K. Nucleos. Nucleot. **1982**, 1, 35 - 44.

8. Suhadolnik, R. J. "Nucleosides as Biological Probes"; Wiley-Interscience: New York, NY, 1979; pp. 118 - 135.

9. Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. Can. J. Chem. **1978**, 56, 2768 - 2780.

10. Köhler, W.; Pfleiderer, W. Justus Liebigs Ann. Chem. **1979**, 1855 - 1871.

11. Baker, D. C.; Crews, R. P., unpublished observations.

12. Barton, D. H. R.; McCombie, S. W. J. Chem. Soc. Perkin Trans. **1975**, 1574 - 1585.

13. Ogilvie, K. K.; Hakimelahi, G. H.; Proba, Z. A.; Usman, N. Tetrahedron Lett. **1983**, 24, 865 - 868.

14. Geran, R. L.; Greenburg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. Cancer Chemother. Rep., Part 3 **1972**, 3, 7 - 9.

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