

A Synthesis of 2- β -D-Ribofuranosyl-4-selenazolecarboxamide
(Selenazofurin) and Certain *N*-Substituted Amide Derivatives
Suitable for Large Scale Syntheses

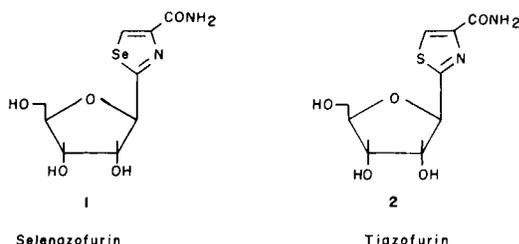
P. Dan Cook* and Dennis J. McNamara

Warner-Lambert/Parke-Davis Pharmaceutical Research
Ann Arbor, Michigan 48105
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A new process suitable for large scale synthesis of the antitumor-antiviral agent, 2- β -D-ribofuranosyl-4-selenazolecarboxamide (selenazofurin, **1**), has been developed. Thus, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (**3**) was converted with cyanotrimethylsilane and stannic chloride to the crystalline 2,5-anhydro-3,4,6-tri-*O*-benzoyl- β -D-allononitrile (**4**) without chromatography. Cyanosugar **4** in ethanol was treated with hydrogen selenide gas to afford stereospecifically the unstable 2,5-anhydro-3,4,6-tri-*O*-benzoyl- β -D-allonoselenoamide (**5**) which was converted *in situ* by ethyl bromopyruvate to the stable ethyl 2-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-4-selenazolecarboxylate (**6**). Selenazole ethyl ester **6** was deprotected with sodium methoxide affording methyl 2- β -D-ribofuranosyl-4-selenazolecarboxylate (**7**) which was aminated with ammonia to provide selenazofurin (**1**) or with other amines to provide *N*-substituted selenazofurin amides.

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2- β -D-Ribofuranosyl-4-selenazolecarboxamide (**1**, CI-935, selenazofurin [1]), the selenium analog of tiazofurin (**2**, CI-909, 2- β -D-ribofuranosyl-4-thiazolecarboxamide [2]), recently synthesized by Srivastava and Robins [3], has pronounced antitumor activity in animals and broad spectrum *in vitro* antiviral activity [4].



Selenazofurin is 5 to 10-fold more dose potent than tiazofurin in several *in vitro* and *in vivo* antitumor screens and in biochemical studies [5], although presumably still acting by an analogous mode as tiazofurin, which is inhibition of inosine monophosphate dehydrogenase (IMPD) *via* the intracellular metabolite, selenazofurin adenosine dinucleotide (SAD) [6].

Larger quantities of selenazofurin were required for further preclinical development and Phase I studies. Although the syntheses of tiazofurin and selenazofurin from Robins' laboratories [2,3] were appropriate for small quantities of the *C*-nucleosides, the general process utilizing as a key step the base catalyzed addition of liquid hydrogen sulfide or hydrogen selenide respectively, to 2,5-anhydro-3,4,6-tri-*O*-benzoyl- β -D-allononitrile in an autoclave, was not suitable for the preparation of kilogram quantities of these compounds.

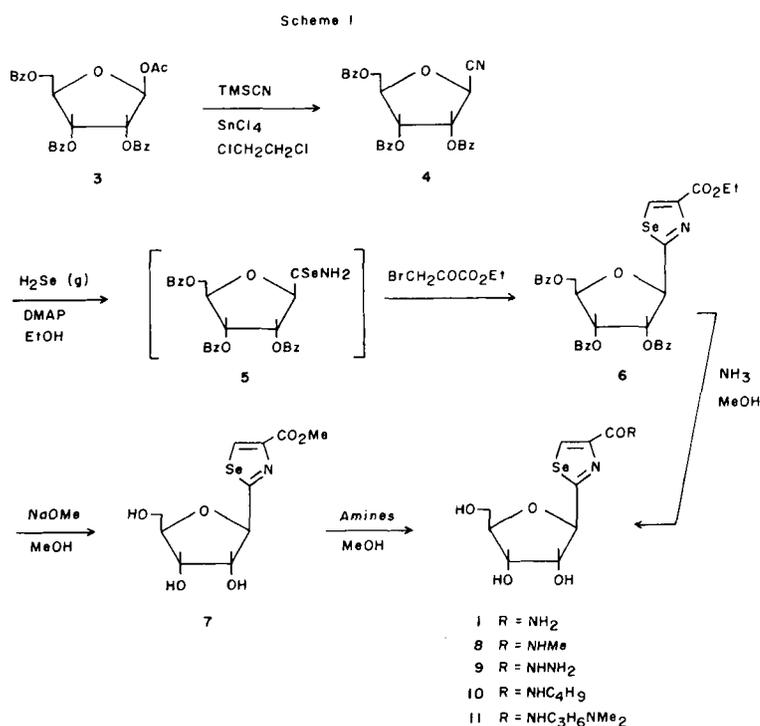
Parsons *et al.* of Starks Associates, Inc. [7] has modified this key step in the preparation of tiazofurin by the use of gaseous hydrogen sulfide in ethanol instead of liquid hy-

drogen sulfide as both solvent and reactant. This modification at the crucial step greatly increases the safety of the process due to the greater ease of manipulation, control, and elimination of the need to use a large excess of hydrogen sulfide in an autoclave. However, a significant advantage in the chemistry of the reaction was not observed since an α,β -anomeric mixture of the desired 2,5-anhydro-3,4,6-tri-*O*-benzoyl- β -D-allonothioamide was obtained as in Srivastava *et al.*'s tiazofurin synthesis [2] as well as Srivastava and Robin's selenazofurin synthesis [3].

In our desire for a synthesis of selenazofurin suitable for the preparation of large quantities, we have sought to eliminate liquid hydrogen selenide but also have attempted to modify the reaction conditions to alleviate the formation of the undesired α -anomer of 2,5-anhydro-3,4,6-tri-*O*-benzoyl- β -D-allonoselenoamide, thus eliminating costly chromatography in early steps.

Chemistry - Results and Discussion.

We have discovered that the rapid addition of one equivalent of hydrogen selenide to a saturated solution of 2,5-anhydro-3,4,6-tri-*O*-benzoyl- β -D-allononitrile (**4**, Scheme I) in ethanol at room temperature in the presence of 4-(dimethylamino)pyridine catalyst rapidly and cleanly produced the desired 2,5-anhydro-3,4,6-tri-*O*-benzoyl- β -D-allonoselenoamide (**5**). There is a short period of time (less than 15 minutes) in which the reaction solution contains only selenoamide sugar **5** but decomposition rapidly takes place producing a mixture of unidentified side products [8]. Tlc indicates in addition to these side products, the reappearance of the initial starting material, cyanosugar **4**, suggesting that it is in equilibrium with selenoamide sugar **5**. In earlier experiments in which the α -anomer of **5** was formed, we had attempted to separate the α -anomer from the β -anomer, **5**, by column chromatography as in the pro-



cedure of Srivastava and Robins [3]. This afforded a rather low yield of **5**, its precursor, cyanosugar **4**, and a red coloration to the column also suggesting that hydrogen selenide is eliminated from **5**. The complete conversion of sugar **4** to the selenamide **5** can be detected by carefully monitoring the reaction by tlc and at this point the reaction is quenched by the addition of an equivalent of ethyl α -bromopyruvate.

The selenazole ring formation is also a rapid reaction cleanly affording ethyl 2-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-4-selenazolecarboxylate (**6**). Parsons *et al.* [7] have used a cation ion exchange resin in their cyclization of 2,5-anhydro-3,4,6-tri-*O*-benzoyl- α,β -allonothioamide with ethyl bromopyruvate to scavenge the liberated hydrogen bromide which was thought to catalyze the anomerization of the resulting ethyl 2-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-4-thiazolecarboxylate. In the case of our synthesis of the selenazole sugar **6**, the immediate presence of hydrogen bromide does not appear to catalyze anomerization or be deleterious to the reaction in other ways. However, the reaction is neutralized on its completion as determined by tlc [10].

We have found that the cleanest reaction of cyanosugar **4** with hydrogen selenide occurs when exactly one equivalent of hydrogen selenide has been added. Most often though, a slight excess of hydrogen selenide is inadvertently introduced into the reaction solution and in these cases an equal excess of ethyl bromopyruvate is added. An immediate precipitation of polymeric selenium is observed and on analysis of the reaction mixture we can detect ethyl

pyruvate. Hydrogen selenide appears to be a strong enough reducing agent to reduce ethyl bromopyruvate to ethyl pyruvate with the formation of selenium and hydrogen bromide. Asinger and Schmitz [11] have noted the unexpected reduction of bromoketones with sodium hydrogen selenide to afford the parent ketones and selenium. Furthermore, sodium hydrogen sulfide reacts with α -chloroketones to provide high yields of α -mercaptoketones whereas the reduction reaction takes precedent if α -bromoketones are used. The use of ethyl α -chloropyruvate may be useful in these *C*-nucleoside formations. In another experiment, we found that addition of gaseous hydrogen selenide to a solution of the cyanosugar **4** and ethyl α -bromopyruvate afforded an immediate heavy red precipitate and tlc examination indicated no selenamide formation. This result indicates the necessity of removing excess hydrogen selenide or adding excess ethyl α -bromopyruvate to obtain a high yield of the selenazole sugar **6**. Addition of an appropriate excess of ethyl α -bromopyruvate is the best procedure since removal of excess hydrogen selenide by reduction of pressure and/or passage of argon through the reaction solution removes little hydrogen selenide and the time required for this operation allows decomposition to take place as noted above.

The one pot reaction leading to the stable selenazole sugar **6**, after neutralization, filtration and extraction procedures, provided crude material containing 75-88% of the desired **6** as determined by its isolation in a pure state *via* a short, rapid chromatography purification procedure. The crude product contains only selenazole sugar **6** and

polymeric material. The α -anomer of **6** cannot be detected by tlc in the crude material.

Selenazole sugar **6**, isolated as described (without chromatography, 75-88% purity), can be treated directly with methanolic ammonia to provide crude selenazofurin (**1**), as reported by Srivastava and Robins [3]. This direct conversion generally requires chromatography to obtain pure material. We have found that deprotecting the crude reaction mixture with sodium methoxide allows easy removal of methyl benzoate and other impurities by decantation or extraction procedures to afford relatively clean methyl 2- β -D-ribofuranosyl-4-selenazolecarboxylate (**7**). This penultimate intermediate can be aminated directly to produce selenazofurin; however a short, rapid column chromatography procedure to obtain pure **7** is useful for large-scale runs. In this manner, pure selenazofurin can be obtained by recrystallization.

Thus, larger quantities of pure selenazofurin can be obtained *via* this three-step synthesis from cyanosugar **4** in 41-47% overall yield.

Our approach to a process suitable for larger scale synthesis of selenazofurin is dependent on the availability of the requisite cyanosugar **4**. Although cyanosugar **4** is not commercially available, its synthesis has been reported from at least five laboratories [12]. Certainly, the most time honored process is its original synthesis from 1-bromo-2,3,5-tri-*O*-benzoyl-D-ribofuranose and mercuric cyanide as reported by Bobek and Farkas [12a] in 1969. Most early *C*-nucleosides as well as tiazofurin [2] and selenazofurin [3] were synthesized from cyanosugar **4** obtained *via* this procedure or slight modifications thereof. The disadvantage of this process for larger scale synthesis is that excess, dry gaseous hydrogen bromide is passed into large volumes of toluene or benzene containing 1-*O*-acetylsugar **3** with careful control of temperature. Solvents are removed by evaporation under controlled temperature and pressure to afford the bromosugar which is not stable, cannot be stored, and must be reacted immediately with excess, toxic mercuric cyanide. After extraction procedures to remove mercuric salts, crude cyanosugar **4** is generally purified by chromatography procedures and even then cyanosugar **4** is often difficult to crystallize.

We have eliminated the intermediacy of the bromosugar and its inherent problems in purification and stability by directly reacting 1-*O*-acetylsugar **3** with cyanotrimethylsilane in the presence of anhydrous stannic chloride to provide cyanosugar **4**. Our conditions, although not optimized, required only several minutes reaction time, a filtration and extraction procedure, and crystallization to provide pure cyanosugar **4** in greater than 80% yield. Several recent reports describe similar reactions in which acetylsugar **3** is converted to cyanosugar **4** with cyanotrimethylsilane and catalysis by Lewis acids [12e,d]. Both of

these procedures are small scale reactions utilizing chromatography to obtain high yields of cyanosugar **4**.

We have attempted the catalysis of 1-*O*-acetylsugar **3** and cyanotrimethylsilane with trimethylsilyltrifluoromethylsulfonate (TMSTf), which may be the catalyst of choice for Vorbrüggen type glycosylations [13] since its strength as a Lewis acid is just sufficient to promote acyloxonium formation of acyl sugars and it has less tendency to react with silylated heterocycles. Furthermore, a facilitated ease of workup with TMSTf-catalyst is available as compared to stannic chloride catalyst. However, in our case, a complex reaction was obtained which suggests a need for the Lewis acid to complex with cyanotrimethylsilane for cyanide displacement of the 1-*O*-acetoxy group to proceed cleanly.

The novel, penultimate selenazofurin intermediate **7** is also useful for further chemical modifications. As evidence of the utility of **7**, we have reacted it with amines to afford *N*-substituted 2- β -D-ribofuranosyl-4-selenazolecarboxamides. Methyl amine and hydrazine react with **7** to provide crystalline derivatives **8** and **9** whereas *n*-butylamine and *N,N*-dimethyl-1,3-propanediamine derivatives **10** and **11** were not crystalline and were not obtained in an analytically pure state. Reaction of selenazole ester **7** with hydroxylamine hydrochloride or its free base give complex mixtures.

ID₅₀s of selenazofurin amide derivatives **8-11** and their penultimate intermediate **7** against *in vitro* L1210 leukemia cells were greater than 1 mg/ml ($> 10^{-4}$ M) as compared with selenazofurin's ID₅₀ of 10^{-7} M [14]. Selenazofurin amide derivatives **8** and **9** and intermediate **7** were not active against NCI's P388 *in vivo* leukemic mouse model at 200 mg/kg whereas selenazofurin had a % T/C of 170 at 50 mg/kg [5].

In summary, we have described the development of a relatively safe, high yield process to the important antitumor and antiviral agent selenazofurin and certain of its *N*-substituted amides. This process is suitable for larger scale synthesis.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectra were determined on a Finnigan 4000 Mass Spectrometer with INCOS 2300 data system using direct introduction, electron impact at 70 eV and 150°. ¹H nmr spectra were obtained at 200 MHz using a Varian XL-200 or at 90 MHz using a Varian EM-390 with tetramethylsilane as an internal standard. The presence of exchangeable protons was confirmed by the addition of deuterium oxide. Optical rotations were determined using a Perkin-Elmer Model 141 polarimeter with a 10 cm, 1 ml micro cell. Uv spectra were obtained on a Cary C118 uv Vis Spectrophotometer. All compounds had infrared spectra (potassium bromide) consistent with their structure as determined on a Nicolet 250X FT/IR. Elemental analyses were determined by the microanalytical laboratory of this department and by Galbraith Laboratories, Inc., Knoxville, TN. Tlc was performed using E. Merck silica gel 60 F-254 precoated glass plates (0.25 mm). Flash column chromatography was effected using E. Merck silica gel 60, 230-400 mesh.

2,3-Anhydro-3,4,6-tri-*O*-benzoyl- β -D-allononitrile (**4**).

A stirred solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl- β -D-ribofuranose (**3**, 40.3 g, 80 mmoles), 1,2-dichloroethane (100 ml), and cyanotrimethylsilane (15.84 g, 160 mmoles) was treated in one portion *via* a syringe with anhydrous stannic chloride (20.8 g, 9.33 ml, 80 mmoles). The darkening solution was stirred for two minutes then poured into saturated sodium hydrogen carbonate (800 ml), and stirred five minutes (*pH* 7). Chloroform (1 ℓ) was added and the emulsion was filtered through celite. The chloroform layer was separated, dried (magnesium sulfate) and evaporated under reduced pressure (15 torr, 40°) to a light orange syrup [15] which was crystallized from ethanol (charcoal) to afford **4** (30 g from two crops, 80%) as long white needles; mp 77-78° after drying at 0.05 torr, 60° for two hours; $[\alpha]_D^{25} + 24.4^\circ$ (0.5 chloroform).

Anal. Calcd. for $C_{27}H_{21}NO_7$ (471.45): C, 68.78; H, 4.49; N, 2.97. Found: C, 68.77; H, 4.45; N, 2.88.

Caution!

Due to the toxic nature of hydrogen selenide (even more poisonous than hydrogen sulfide), the following reaction and its workup should be performed with great care in a hood with strong, forced ventilation.

Ethyl 2-(2,3,5-Tri-*O*-benzoyl- β -D-ribofuranosyl)-4-selenazolecarboxylate (**6**).

A mixture of **4** (612 g, 1.30 moles), 4-(dimethylamino)pyridine (12 g, 98 mmoles) and absolute ethanol (6.0 ℓ) was warmed to 45° with stirring to obtain a complete solution [16,17]. Argon was dispersed through the solution as it was cooled with a water bath to 20°. The cooling bath was removed and the resulting suspension was treated with gaseous hydrogen selenide (approximately 30 minutes, 108 g, 1.33 moles) *via* the argon dispersion tube [18,19]. During the hydrogen selenide treatment, cyanide sugar **4** gradually dissolved and the reaction exotherms to 23°. Tlc of the greenish-yellow solution indicates a complete and clean conversion of cyanide sugar to the selenocarboxamide sugar **5** [20]. The hydrogen selenide flow was replaced with argon and the solution was immediately treated with ethyl α -bromopyruvate (293 g of 90% purity, 1.33 moles) causing a red precipitate to form. This mixture was stirred for 0.5 hours, neutralized to *pH* 7 with saturated sodium hydrogen carbonate solution (2 ℓ) and filtered through a bed of celite. The cake was washed with ethanol and then chloroform. The reddish-yellow filtrate [21] was evaporated under reduced pressure to a thick red syrup (15 torr, 50-60°) which was dissolved in chloroform (2 ℓ) and washed with saturated sodium hydrogen carbonate (1 ℓ), water (1 ℓ), and dried with magnesium sulfate. Evaporation of the dried chloroform solution (15 torr, 60-70°) provided 826 g (98%) of the crude, blocked selenazole nucleoside, **6**, as a thick red syrup.

A portion of the dried syrup (12.8 g) was dissolved in a minimum amount of toluene-ethyl acetate (10:1) and placed on a column of silica gel (130 g, 70-230 mesh, packed in toluene-ethyl acetate, 10:1). Elution (4 ml/minute) with toluene-ethyl acetate (10:1) provided the tlc pure [22] product in 500 ml of eluent following 500 ml of forerun. The fractions containing pure material were evaporated under reduced pressure (15 torr, 60°) to afford 10.1 g (79%) of **6** as a light yellow syrup. A sample dried at 0.05 torr and 100° for one hour provided a hard light yellow foam, $[\alpha]_D^{25} - 34.7^\circ$ (1.07 methanol); λ max (methanol): 229 nm (ϵ 39,917), 259 (7322); pmr (deuteriodimethylsulfoxide): δ 8.85 (s, 1, C_5H).

Anal. Calcd. for $C_{32}H_{27}NO_9Se$ (648.51): C, 59.26; H, 4.20; N, 2.16. Found: C, 59.44; H, 4.21; N, 1.89.

2- β -D-Ribofuranosyl-4-selenazolecarboxamide (**1**).

Method A.

A solution of syrup **6** from the previous reaction (93 g, 79% purity, 114 mmoles) and methanol (250 ml) [23] was saturated at 0° with ammonia and then heated in a Parr pressure vessel in a steam bath for six hours. The bomb was cooled, vented and the resulting solution evaporated under reduced pressure (15-20 torr, 60°). The residue was coevaporated two times with methanol and the dark brown syrup was dissolved in hot

water (50°, 150 ml) and extracted with ethyl acetate (3 \times 100 ml) [24]. The aqueous layer was treated with charcoal (10 g) and filtered through a bed of celite. The light yellow filtrate was evaporated under reduced pressure (15-20 torr, 60°) to provide a light yellow foam (29 g, 83%) [25] which was dissolved in methanol (50°, 200 ml), absorbed on silica gel (50 g, 70-230 mesh), and placed on a column of silica gel (250 g, 70-230 mesh, packed in chloroform, 7 \times 15 cm). Rapid elution (10 ml/minute) with chloroform-methanol (4:1) provided the majority of the product in two liters of eluent [26] which was evaporated under reduced pressure (15 torr, 60°). The resulting light yellow residue (27 g) was crystallized from 2-propanol [27] to afford 25.0 g (71%) [28] of 2- β -D-ribofuranosyl-4-selenazolecarboxamide (**1**), as faint yellow crystals, mp 130-131°; $[\alpha]_D^{25} - 20.8^\circ$ (1.01 water); pmr (deuteriodimethylsulfoxide): 8.75 (s, 1, C_5H), 7.58 (bs, 2, CONH₂); (deuteriodimethylsulfoxide-deuterium oxide): 4.88 δ (d, 1, H_1 , $J = 5.0$ Hz); λ max (95% EtOH) 259 nm (ϵ 6263).

Anal. Calcd. for $C_9H_{12}N_2O_5Se$ (307.19): C, 35.19; H, 3.94; N, 9.12. Found: C, 35.38; H, 3.94; N, 9.12.

Method B.

A solution of 168 g (521 mmoles) of the methyl ester **7** in 2.0 ℓ of methanol was cooled to approximately 10° and treated with anhydrous ammonia gas for eight hours. The solution was allowed to stand at room temperature overnight. The tlc (silica gel, dichloromethane-methanol, 5:1) indicated complete conversion to the desired product. A very small amount of a red solid was removed by filtration. The filtrate was evaporated under reduced pressure and the residue was recrystallized from 2-propanol and dried at 40° under 0.5 atmospheres to give 136 g (85%) of the product, mp 128-130°.

Tlc (silica gel, dichloromethane-methanol, 4:1) showed this material to be homogenous, $R_f = 0.2$. The nmr of this material was consistent with the assigned structure and matched that in the literature [3]; ¹H nmr (deuteriodimethylsulfoxide): δ 3.5-4.1 (m, 5, H-5', H-5'', H-4', H-3', H-2'), 4.80 (d, $J_{H-1':H-2'} = 4.6$ Hz, 1, H-1'), 4.86 (t, $J = 5.4$ Hz, 1, 5'-OH, deuterium oxide exchangeable), 5.01 (d, $J = 5.2$ Hz, 1, 2'-OH or 3'-OH, deuterium oxide exchangeable), 5.35 (d, $J = 5.6$ Hz, 1, 2'-OH or 3'-OH, deuterium oxide exchangeable), 8.77 (s, 1, H-5); $[\alpha]_D^{25} - 20.7$ (c 1.07, water); uv (methanol): max 215, 259 (ϵ 17500, 5700) min 240 (ϵ 4290); ms: m/e 309 ($M^+ + H$).

Anal. Calcd. for $C_9H_{12}N_2O_5Se$ (307.2): C, 35.19; H, 3.94; N, 9.12; Se, 25.71. Found: C, 35.07; H, 3.94; N, 9.04; Se, 25.84.

Methyl 2- β -D-Ribofuranosyl-4-selenazolecarboxylate (**7**).

A gummy suspension of 206.3 g (75.0% pure by hplc, 239 mmoles) of the blocked ethyl ester **6** in 700 ml of methanol was heated and stirred on the steam bath until solution occurred. The solution was allowed to cool to room temperature during which time a finely dispersed oily suspension formed. To this suspension was added 17.2 g (318 mmoles) of sodium methoxide. The addition was slightly exothermic and resulted in a brown solution. The solution was stirred at room temperature overnight. Tlc (silica gel, toluene-ethyl acetate, 10:1) indicated that no starting material remained. To the reaction solution was added 100 g of Dowex 50 W \times 4 resin (H⁺) (washed with methanol) and the suspension was stirred for one hour. The resin was filtered off, washed well with methanol, and discarded. The filtrate and washings were evaporated under reduced pressure to give a two phase mixture. The upper, more liquid phase (mainly methyl benzoate) was decanted. The remaining brown viscous gum was triturated twice with ether. (The methyl benzoate was combined with the ether triturates and upon standing yielded some desired product as a solid). The brown viscous gum was treated with approximately 1 ℓ of warm ethanol and triturated. A dark brown material was filtered from the suspension. Tlc (silica gel; dichloromethane-methanol, 10:1) indicated that the dark brown material was mostly slower moving impurities in the filtrate and was discarded. To the ethanol solution of the product was added 250 g of flash silica gel (230-400 mesh) and the ethanol was removed under reduced pressure to give a solid.

The above reaction was carried out three other times with 185.1 g, 246.0 g, and 189.0 g of ethyl 2-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)-4-

selenazolecarboxylate (**6**, 75.0% purity) as the starting material. The only difference between these four reactions was the amount of sodium methoxide required to maintain the molar ratio above.

The four crude reaction products adsorbed onto silica gel were pooled and placed on a column of 2600 g of flash silica gel (230-400 mesh) packed with dichloromethane. The column was eluted with dichloromethane containing gradually increasing amounts of methanol (first dichloromethane-methanol, 50:1, then 40:1, 30:1, 20:1, 10:1, 5:1, and finally 2:1). The appropriate fractions were combined and concentrated to give 262 g (85%) of product as a solid. Recrystallization from ethyl acetate gave 168 g (55%) of the product. Tlc (silica gel, dichloromethane-methanol, 10:1) showed this material to be homogenous, $R_f = 0.3$.

Recrystallization of 2.00 g of slightly impure material from 50 ml of ethyl acetate, and then drying the resulting solid at 60° at reduced pressure gave 1.51 g (76%) of the product as a cream solid, mp 113-115°; ¹H nmr (deuteriodimethylsulfoxide): δ 3.4-4.0 (m, 5, H-5', H-5'', H-4', H-3', H-2'), 3.78 (s, 3, CH₃), 4.80 (d, $J_{H-1'H-2'}$ = 4.6 Hz, 1, H-1'), 4.89 (t, $J = 5.4$ Hz, 1, 5'-OH, deuterium oxide exchangeable), 5.01 (d, $J = 5.0$ Hz, 1, 2'-OH or 3'-OH, deuterium oxide exchangeable), 5.42 (d, $J = 6.0$ Hz, 1, 2'-OH or 3'-OH, deuterium oxide exchangeable), 9.08 (s, 1, H-5); $[\alpha]_D^{25} - 14.4^\circ$ (c 1.18, water); uv (methanol): max 214, 260 (ϵ 14400, 5300) min 237 (ϵ 3730).

Anal. Calcd. for C₁₀H₁₃NO₆Se (322.17): C, 37.28; H, 4.07; N, 4.35. Found: C, 37.23; H, 4.06; N, 4.23.

N-Methyl-2-β-D-ribofuranosyl-4-selenazolecarboxamide (**8**)

Gaseous monomethylamine was bubbled into an ice bath-cooled solution of **7** (2.00 g, 6.21 mmoles) in 100 ml of methanol for 15 minutes. The solution was stirred at 0° for three hours and then concentrated under reduced pressure. The resulting syrup solidified on standing and was recrystallized from 2-propanol. The solid was dried at 60° over phosphorus pentoxide at 0.01 torr to give 1.34 g (67%) of the product as a cream solid, mp 152-154°; nmr (deuteriodimethylsulfoxide): δ 2.75 (d, J_{CH_3-NH} = 5 Hz, 3, CH₃, coalesces to singlet upon addition of deuterium oxide), 3.5-4.1 (m, 5, H-5', H-5'', H-4', H-3', H-2'), 4.81 (d, $J_{H-1'H-2'}$ = 4 Hz, 1, H-1'), 4.84 (m, 1, OH, deuterium oxide exchangeable), 5.0 (m, 1, OH, deuterium oxide exchangeable), 5.3 (d, $J = 6$ Hz, 1, OH, deuterium oxide exchangeable), 8.15 (br q, 1, NH, deuterium oxide exchangeable), 8.72 (s, 1, H-5).

Anal. Calcd. for C₁₀H₁₄N₂O₅Se (322.17): C, 37.39; H, 4.39; N, 8.72. Found: C, 37.67; H, 4.65; N, 8.56.

2-β-D-Ribofuranosyl-4-selenazolecarboxylic Acid, Hydrazone (**9**)

To a solution of **7** (2.00 g, 6.21 mmoles) in 50 ml of methanol was added 1.24 ml (39.1 mmoles) of anhydrous hydrazine and the solution was stirred at room temperature for five hours. The solution was concentrated under reduced pressure to give a gummy residue. The residue was dissolved in methanol, treated with 10 g of flash silica gel, and the methanol was removed *in vacuo*. The resulting powder was placed on a column of 100 g of flash silica gel packed with dichloromethane/methanol (4:1). Flash chromatography using the same solvent mixture gave 1.5 g of a foam which was recrystallized from ethanol. The solid was dried at 60° over phosphorus pentoxide at 0.01 mm to give 1.2 g (60%) of the product as a cream solid, mp 161-163°; ¹H nmr (deuteriodimethylsulfoxide): δ 3.4-4.1 (m, 5, H-5', H-5'', H-4', H-3', H-2'), 4.40 (s, 2, NH₂, deuterium oxide exchangeable), 4.73 (d, $J_{H-1'H-2'}$ = 5 Hz, 1, H-1'), 4.78 (m, 1, OH, deuterium oxide exchangeable), 4.90 (d, $J = 5$ Hz, 1, OH, deuterium oxide exchangeable), 5.27 (d, $J = 6$ Hz, 1, OH, deuterium oxide exchangeable), 8.63 (s, 1, H-5), 9.30 (br s, 1, NH).

Anal. Calcd. for C₉H₁₃N₃O₅Se (322.18): C, 33.55; H, 4.07; N, 13.04. Found: C, 33.70; H, 4.29; N, 13.06.

REFERENCES AND NOTES

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- [8] Tlc examination of the reaction mixture clearly shows that the α-anomer of **5** is not present. The major decomposition product, being less polar than **5**, is likely the benzoate elimination product, ethyl 2-[5-[(benzoyloxy)methyl]furan-2-yl]-4-selenazolecarboxylate. Ethyl 2-[5-[(benzoyloxy)methyl]furan-2-yl]-4-thiazolecarboxylate is a major decomposition product in previous tiazofurin syntheses [2,9].
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- [10] In several experiments the reaction, after treatment with ethyl bromopyruvate, was filtered through filter aid prior to neutralization without any apparent loss in the yield in the isolated β-anomer **6**.
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- [15] Tlc, silica gel/toluene-ethyl acetate (5:1), indicates a very clean and complete conversion of **3** to **4**. Spots were detected by anisaldehyde:methanol:sulfuric acid spray (0.1:10:1) followed by heating; on charring in this manner 1-*O*-acetylsugar **3** is a brownish-red spot and cyanide sugar **4** is a blue spot.
- [16] Considerable volume reduction may be realized by using a suspension of cyanide sugar **4** in ethanol; the reaction appears to proceed satisfactorily as such. Passing hydrogen selenide through a solution of **4** at 35° provides a major side product, possibly the furan-2-yl-selenazole elimination product [2,9].
- [17] A 12-liter, round-bottom flask was equipped with an air stirrer, inlet dispersion tube, outlet dispersion tube and thermometer, and septum for sampling. The outlet dispersion tube vented exhaust gases through a 4-liter filter flask of ice water (3 l). Hydrogen selenide is quite soluble in cold water (3.77 g in 1 ml of 4° water). (Trapping hydrogen selenide in an alkaline solution is not practical due to the extreme tendency for alkali metal selenides to clog the outlet tubes). After the gas has been trapped in ice water, the red suspension (polymeric selenium?) is made basic with 50% sodium hydroxide solution and placed in waste bottles.
- [18] Hydrogen selenide (2 × 14 ml, MLB lecture bottle, 350 valve outlet, 0.5 pound) was purchased from Synthatron Corporation, Parsippany, New Jersey.
- [19] Argon flow was stopped during hydrogen selenide treatment. Under these conditions, hydrogen selenide was completely absorbed in the ethanol is noted by the lack of decomposed hydrogen selenide (red color) in the exhaust line and ice water trap. From a safety point of view,

it is certainly desirable to contain all hydrogen selenide in the reaction solvent.

[20] Silica gel/chloroform-ethyl acetate (10:1) tlc was used. During several runs, a rather heavy precipitate of selenocarboxamide **5** was formed.

[21] Refiltration through celite may be required at this stage to remove additional polymeric selenium.

[22] Silica gel/chloroform-ethyl acetate (10:1) tlc was used.

[23] The methanol was heated to approximately 50° to solubilize the syrup. The ammonolysis of selenazole **6** to selenazofurin (**1**) may also be realized by keeping the pressure vessel at ambient temperature for 48-72 hours.

[24] Deblocking of selenazole **6** under these conditions provides *both*

benzamide and methyl benzoate as side products which are essentially completely removed by the extraction procedure.

[25] It should be possible to purify this foam at this stage by crystallization, however on a relatively small run as this, a short column procedure before crystallization is desirable.

[26] An impurity which chars lightly, is not detected by ultraviolet light, but is visible in iodine vapor, appears just below the major product in the tlc.

[27] 2-Propanol-methanol (10:1) is a more appropriate solvent system for recrystallization of larger amounts of crude material.

[28] This yield is based on the 79% purity of the starting syrup material.