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5-Amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (1-Deaza-8-azaguanosine) and Certain Related Derivatives[1,2]

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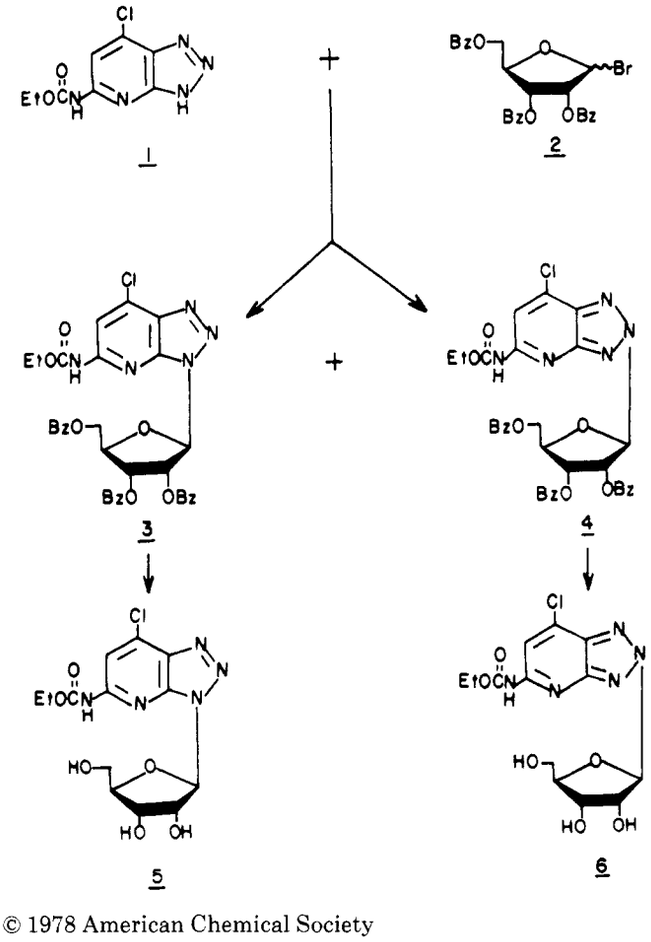
The synthesis of 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (1-deaza-8-azaguanosine) has been accomplished by a condensation of the silyl derivative of ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyridine-5-carbamate and 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide using the mercuric cyanide procedure. The 6-thioguanosine analogue 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-7-thione (1-deaza-8-aza-6-thioguanosine) has been prepared by a nucleophilic displacement of the chloro group from ethyl 7-chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate with sodium hydrogen sulfide, which also effected a concomitant removal of the blocking group from the 5-amino group. A rearrangement of 1-deaza-8-aza-6-thioguanosine was observed under various conditions and has furnished 6-amino-4-(α- and β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[4,5-*c*]pyridine as determined by ultraviolet and ^{1}H NMR spectroscopy. The syntheses of various nucleoside precursors and derivatives of the above compounds are also described. Procedures used to unequivocally determine the site of ribosylation and anomeric configuration are also discussed.

8-Azaguanine was the first purine analogue shown to be incorporated into RNA.[3] The wide spectrum of biological activity exhibited by 8-azaguanine and its nucleoside–nucleotide derivatives[4] influenced investigations which subsequently led to other azapurine analogues.[5] As part of our continuing research efforts involving the synthesis of aza- and deazapurine nucleoside analogues as potential chemotherapeutic agents, we wish to report the synthesis of certain *v*-triazolo[4,5-*b*]pyridines related not only to guanine and guanosine but also to the important chemotherapeutic agents[6] 6-thioguanine and 6-thioguanosine. These types of nucleosides have also been used as valuable biochemical tools for the elucidation of enzyme–substrate specificity.

The heterocycle ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyridine-5-carbamate[7,8] (**1**) was chosen as our starting material for the synthetic sequence which should lead to 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (**14**, 1-deaza-8-azaguanosine). The envisaged purpose of using **1** was twofold; ribosylation and subsequent chemical modification[9] of the heterocyclic moiety would eventually furnish a nucleoside [3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine[10]] whose structure had been previously established. This would provide a structure proof, i.e., the site of ribosylation and determination of anomeric configuration, for all nucleosides synthesized in this investigation, and second, the 7-chloro substituent was expected to undergo a facile nucleophilic displacement to afford the desired 5-amino-7-substituted *v*-triazolo[4,5-*b*]-pyridine nucleosides.

The silyl derivative of ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (**1**) (prepared by the reaction of **1** with



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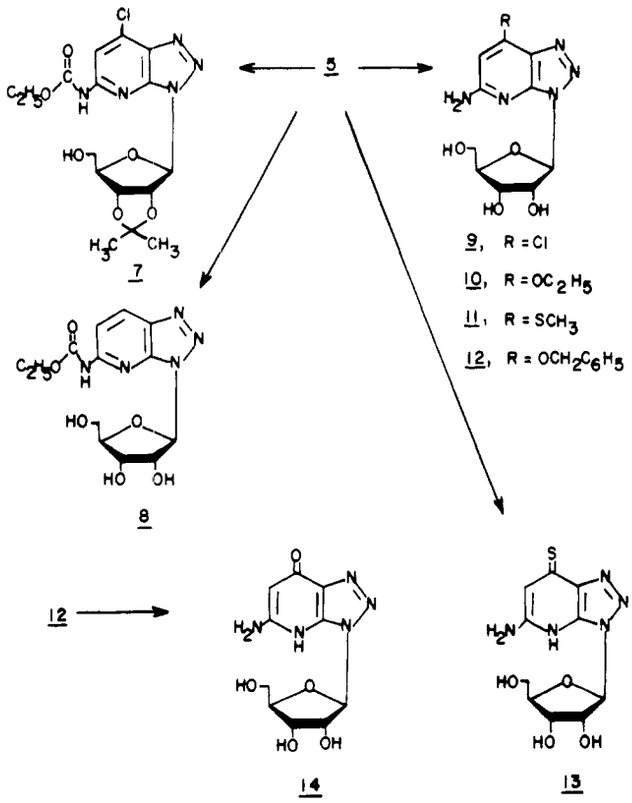
N,O-disilylacetamide in methylene chloride at room temperature) was condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**2**) to furnish a 60% yield of ethyl 7-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (**3**) as the major product. Column chromatography provided some additional **3** and raised the total isolated yield of this nucleoside to 81%. A minor isomer, subsequently assigned as ethyl 7-chloro-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (**4**), was also isolated in 1% yield. The benzoyl blocking groups of both **3** and **4** were removed to furnish **5** and **6**, respectively.

The anomeric configuration of the major nucleoside product (**5**) was assigned on the basis of a study of the ^1H NMR spectra of **5** and the isopropylidene derivative **7**. The anomeric proton of compound **5** was observed as a doublet with a coupling constant of 4.5 Hz. This doublet collapsed to a singlet in the ^1H NMR spectrum of the isopropylidene derivative **7**. This

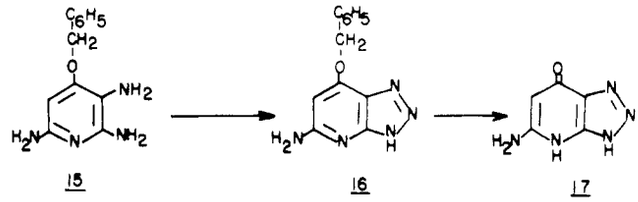


behavior is generally regarded as proof of the β anomeric configuration.[11] Additional corroboration for this assignment was provided[12] by the difference in chemical shifts, $\Delta\delta = 0.17$ ppm, observed between the two isopropylidene methyl groups. The β anomeric configuration of the minor nucleoside product **6** was not proven by the aforementioned method, but was tentatively assigned as β solely on the fact that the formation of α anomers usually does not occur with mercury cyanide catalyzed ribosylation of heterocycles.

To prove the actual site of ribosylation of the nucleoside **5**, an attempt was made to repeat the sequence of chemical conversions which we have used to prove the site of ribosylation of the analogous nucleoside in the imidazo[4,5-*b*]pyridine series.[9] The target compound in this case was 3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine, a nucleoside whose anomeric configuration and site of ribosylation have been rigorously established.[10] The 5-carbamate group of **5** was hydrolyzed to give 5-amino-7-chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine (**9**, 89%). However, repeated attempts to replace the 5-amino group of **9** with a chloro group in a Sandmeyer reaction, under a variety of reaction conditions, failed to provide the desired 5,7-dichloro compound. The failure of this reaction can possibly be attributed to a combination of factors: (1) the low basicity of the 5-amino group, (2) the insolubility of **9** (or its hydrochloride salt) in concentrated hydrochloric acid, and (3) the acid lability of the glycosyl bond of **9**. Therefore, we decided to investigate the use of carbon-13 nuclear magnetic resonance as a means of establishing the specific site of substitution. Several studies[13-15] have used the ^{13}C chemical shift behavior of the aromatic carbon atoms α and β to the site of N-alkylation or N-glycosylation in nitrogenous heterocycles as a basis for assigning the actual site of alkylation or ribosylation. We have determined[2,17] the long-range (2 and 3 bond) ^{13}C–^1H coupling constants for the five aromatic carbon atoms in the *v*-triazolo[4,5-*b*]pyridine ring system, which has allowed us to make unequivocal assignments. It was found[17] that the long-range ^{13}C–^1H coupling constant (^3J) of the aromatic α carbon with the anomeric proton of the carbohydrate moiety provided a reliable diagnostic method for determining the site of glycosylation in this series of nucleosides. These data combined with the α- and β-carbon shifts of the bridgehead carbons made it possible for us to unambiguously assign the actual site of ribosylation for **5** and **6** as N-3 and N-2, respectively.

Unlike the 7-chloro substituent of the isosteric imidazo[4,5-*b*]pyridines,[9] the 7-chloro group of **5** was reactive toward nucleophilic displacement and furnished several 5-amino-7-substituted derivatives in satisfactory yields. For example, when an attempt was made to hydrolyze the 5-carbamate group of **5** under conditions similar to those used for hydrolysis in the imidazo[4,5-*b*]pyridine series, i.e., 0.1 N KOH in ethanol at reflux, a mixture of the desired compound (**9**) and 5-amino-7-ethoxy-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]-pyridine (**10**) was obtained. The reaction of **5** in a more concentrated solution of potassium hydroxide in ethanol (1.0 N) furnished the 7-ethoxy derivative **10** in 77% yield. Treatment of **5** with sodium methyl thiolate (prepared by saturating a solution of sodium ethoxide in ethanol at 0 °C with methyl mercaptan) in ethanol at reflux gave 5-amino-7-methylthio-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine (**11**) in 95% yield.

5-Amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridin-7-one (**14**, 1-deaza-8-azaguanosine)[18] was synthesized from **5** in a two-step reaction sequence. Compound **5** was heated with an excess (10 equiv) of sodium benzylate in benzyl alcohol at 85 °C for 5 h. Column chromatography provided 5-amino-7-benzyloxy-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine (**12**) in 72% yield. Hydrogenolysis of **12** gave 1-deaza-8-azaguanosine (**14**) in 83% yield. A similar hydrogenolysis procedure was employed in the preparation of the heterocyclic aglycon, 5-amino-*v*-triazolo[4,5-*b*]pyridin-7-one (**17**, 1-deaza-8-azaguanine).[18] A solution of 4-benzyloxy-2,3,6-triaminopyridine[19] (**15**) in 1 N hydrochloric acid was treated at 0 °C with 1 equiv



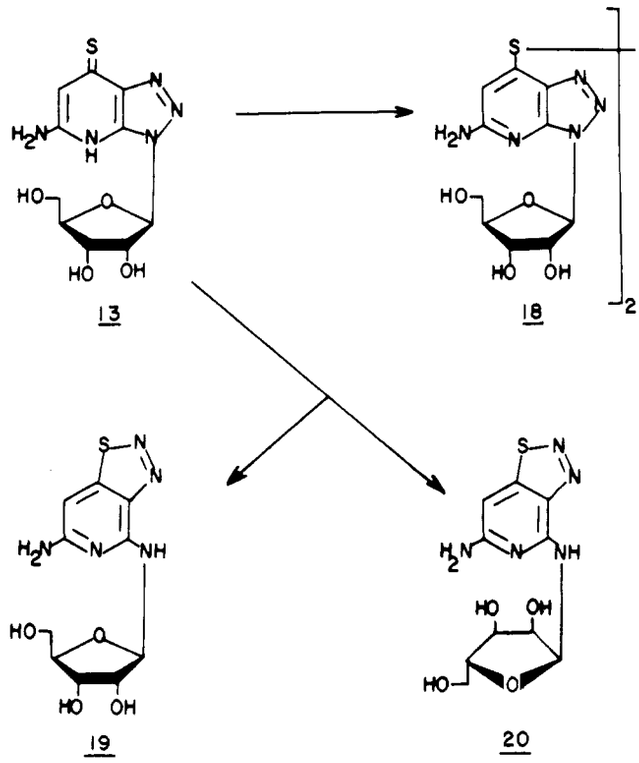
of sodium nitrite to furnish the ring-closed product, 5-amino-7-benzyloxy-*v*-triazolo[4,5-*b*]pyridine (**16**). Treatment of **16** with 5% Pd/C in a hydrogen atmosphere furnished the desired 1-deaza-8-azaguanine (**17**, 94%).

The synthesis of 5-amino-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-7-thione (**13**, 1-deaza-8-aza-6-thioguanosine) was accomplished by the thiation of ethyl 7-chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (**5**) with sodium hydrogen sulfide in dimethylformamide. Due to the strong nucleophilic nature of the complex formed be-

tween sodium hydrogen sulfide and DMF, the thiation of **5** was accomplished at room temperature over a 24-h period to give a 65% yield of 1-deaza-8-aza-6-thioguanosine (**13**). Actually, the major product formed in the initial exploratory reaction was presumably ethyl 3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-7-thione-5-carbamate on the basis of TLC, UV, and ^{1}H NMR. However, in the preparative-scale reaction, the isolation of this intermediate nucleoside was circumvented by treating the reaction mixture with 1 N aqueous potassium hydroxide at reflux, which hydrolyzed the 5-carbamate function to provide **13**.

A major concern in this synthesis was the possibility of a rearrangement since rearrangements have been reported[16,20,21] for certain closely related ring systems; e.g., *v*-triazolo[4,5-*b*]pyridine-7-thione and *v*-triazolo[4,5-*c*]pyridine-4-thione undergo a rearrangement on heating in various solvents to afford 4-amino-1,2,3-thiadiazolo[4,5-*c*]pyridine and 4-amino-1,2,3-thiadiazolo[5,4-*b*]pyridine, respectively,[22] with the triazole–thiadiazole product ratio being dependent on the solvent employed. This type of rearrangement was recently observed[23] with 1-deaza-8-aza-6-thioguanine (**21**) in dimethylacetamide.

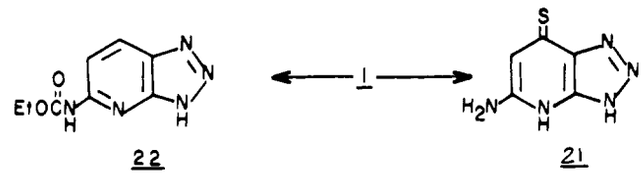
We have now established that 1-deaza-8-aza-6-thioguanosine (**13**) also undergoes a similar rearrangement to afford 6-amino-4-(β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[4,5-*c*]pyridine[2] (**19**). However, we have found that two additional



minor components were also formed during this rearrangement. These components were subsequently identified as the disulfide compound **18** and presumably the α anomer (**20**) of **19**. When **13** was dissolved in dimethyl-d_6 sulfoxide (Me_2SO-d_6) and heated for 30 s, we observed a mixture [~4 (β):1(α)] of the α- and β-thiadiazolo nucleosides. The ^{1}H NMR spectrum of this anomeric mixture exhibits two doublets centered at δ 8.29 (**19**) and 7.66 (**20**) ($J_{4,1'}$ = 10 Hz) which are attributed to the N-4 protons and two quartets at δ 5.96 (**19**) and 6.10 (**20**) ($J_{1',2'}$ = 4.5 Hz, $J_{1',4}$ = 10 Hz) which are assigned to the anomeric protons. A small amount of **18** is also visible (δ 6.76, H-6) in this spectrum. Presumably, the formation of **18** results from Me_2SO oxidation of 1-deaza-8-aza-6-thioguanosine (**13**) since dimethyl sulfoxide is an excellent reagent[24] for the oxidation of thiols to disulfides.

When 1-deaza-8-aza-6-thioguanosine (**13**) was dissolved in Me_2SO-d_6 without heating, the ^{1}H NMR spectrum revealed a predominance of **13**. On standing at room temperature, the rearrangement as well as the formation of **18** slowly takes place over a 24-h period. After 72 h, little change in the relative amounts of the three products **18**, **19**, and **20** was observed. These data imply that the rearrangement, in this particular case, is not an equilibrium process. If the process was reversible, an increase in the oxidation product (**18**) and a decrease in the thiadiazolo nucleosides should have been observed, and judging from the ^{1}H NMR spectral evidence this is not the case. In fact, when a solution of **13** in dimethylformamide-d_7 (DMF-d_7) was allowed to stand at room temperature for a period of 7 days, only the appearance of **19** and **20** was observed in the ^{1}H NMR spectra. It is worthwhile mentioning that an aqueous solution of **13** was relatively stable, and no appreciable rearrangement products were detected (TLC).

The heterocycle 1-deaza-8-aza-6-thioguanine (**21**) was synthesized directly from ethyl 7-chloro-*v*-triazolo[4,5-*b*]-pyridine-5-carbamate (**1**) by treatment with sodium hydrogen sulfide/DMF. Unlike the nucleoside derivative (**5**), thiation of **1** required heating at 95 °C for 12 h in order for a reaction to occur. Although **21** has been reported[23] to undergo a rearrangement, we found it to be relatively stable in DMF. Only after prolonged heating in this solvent was the thiadiazolo



product observed. It was determined that we needed ethyl *v*-triazolo[4,5-*b*]pyridine-5-carbamate (**22**) and ethyl 3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (**8**) for use in determining the site of glycosylation of this series of *v*-triazolo[4,5-*b*]pyridine nucleosides. Dehalogenation of **1** and **5** furnished a good yield of the desired compounds **22** and **8**, respectively.

Experimental Section

Proton magnetic resonance (^{1}H NMR) spectra were obtained with Jeol C60H, Varian A56/60, and Varian XL-100/15 spectrometers (solution in dimethyl-d_6 sulfoxide or dimethylformamide-d_7) with chemical shift values reported in δ, parts per million, relative to an internal standard (sodium 2,2-dimethyl-2-silapentane-5-sulfonate or tetramethylsilane). Ultraviolet spectra were recorded on a Beckman Acta CIII spectrophotometer, and infrared spectra were recorded on a Beckman IR8 spectrophotometer. Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Thin-layer chromatography was run on glass plates coated (0.25 mm) with silica gel (SilicAR 7GF, Mallinckrodt) unless otherwise stated. Compounds of interest were detected by either an ultraviolet lamp (Mineralight, 254 nm) or treatment with sulfuric acid followed by heating. Open-bed column chromatography was carried out on SilicAR CC7 (Mallinckrodt) using gravity flow. The columns were dry-packed and preequilibrated with the elution solvent. Low-pressure column chromatography was performed using Altex columns dry-packed with Silica 60 (EM Laboratories) adsorbent. Elution solvent was delivered by an FMC fluid metering pump equipped with low-volume fittings. The sample solution was introduced to the column through a three-way valve in-line between the solvent reservoir and the pump. All solvent proportions are given by volume. Evaporations were performed under reduced pressure (in vacuo) at 40 °C with a rotary evaporator unless otherwise stated. All compounds were dried under reduced pressure over phosphorus pentoxide at room temperature for 12 h unless otherwise noted. The presence of water of crystallization in the elemental analyses was verified by ^{1}H NMR.

Ethyl 7-Chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (3) and Ethyl 7-Chloro-2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazolo-[4,5-*b*]pyridine-5-carbamate (4). *N,O*-disilylacetamide (30 mL) was added to a suspension of ethyl 7-chloro-*v*-triazolo[4,5-*b*]pyri-

dine-5-carbamate[7,8] (1; 26g, 0.11 mol) in methylene chloride (500 mL), and the mixture was stirred at room temperature until complete solution had occurred (2 h). The solution was evaporated in vacuo and the residual syrup dissolved in dry benzene (800 mL). Mercuric cyanide (53 g) was added, and the mechanically stirred mixture was heated to reflux temperature. A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**2**, prepared from 61 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose) in dry benzene (200 mL) was added to the reaction mixture, and the mixture was heated at reflux for 1 h. Methanol (100 mL) was added to the cooled reaction mixture, the mixture was evaporated in vacuo, and the residual syrup was dissolved in chloroform (500 mL). The insoluble material was removed by filtration, and the filtrate was washed with 30% KI solution (3 × 150 mL) and then water (3 × 150 mL). The organic phase was dried over anhydrous sodium sulfate. The chloroform solution was concentrated to 200 mL, hexane was added to the cloud point, and the solution was allowed to stand at 5 °C for 12 h. The resulting white, crystalline precipitate was collected by filtration, washed with hexane/EtOAc (1:1), and air-dried to give 36 g of **3**. The filtrate was concentrated in vacuo to the cloud point and again allowed to stand at 5 °C for 12 h to give an additional 15 g of **3**.

The filtrate was evaporated in vacuo, and the residual syrup was dissolved in hexane/EtOAc (150 mL 1:1). This solution was applied to an open-bed silica gel column (3.5 × 60 cm), and the column was eluted with hexane/EtOAc (2:1). The fractions containing the major product [TLC, R_f 0.65 (hexane/EtOAc, 3:2)] were evaporated to dryness in vacuo (additional yield of **3**, 9g). The fractions containing a mixture of **3** and a second nucleoside product [4; TLC, R_f 0.55 (hexane/EtOAc, 3:2)] were evaporated in vacuo. The residual foam was dissolved in hexane/EtOAc (50 mL, 2:1), and the sample solution was introduced onto a low-pressure column system (column, 2.5 × 95 cm; flow rate, 5 mL/min) using a mixture of hexane/EtOAc (4:1) as the elution solvent. The fractions containing **3** were evaporated in vacuo to afford an additional 2.4 g of product. The combined yield of the major product was recrystallized from ethanol to afford pure ethyl 7-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (**3**; 60 g, 81%), mp 163–165 °C. Anal. Calcd for $C_{34}H_{28}N_5O_9Cl$: C, 59.52; H, 4.11; N, 10.21. Found: C, 59.72; H, 4.16; N, 10.29.

Fractions containing the second nucleoside product were evaporated to dryness in vacuo, and the solid was recrystallized from ethanol to afford 0.7 g (1%) of the N-2 isomer **4**, mp 152–154 °C. Anal. Calcd for $C_{34}H_{28}N_5O_9Cl$: C, 59.52; H, 4.11; N, 10.21. Found: C, 59.32; H, 4.17; N, 10.21.

Ethyl 7-Chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (5). A solution of sodium methoxide (1.6 g, 30 mmol) in methanol (400 mL) was added to a solution of **3** (20 g, 29 mmol) in tetrahydrofuran (100 mL), and the solution was stirred at room temperature for 2 h. The pH of the solution was adjusted (pH 6, paper) with Amberlite IRC-50(H^+) resin (20 g), and the resin was removed by filtration. The filtrate was evaporated to dryness in vacuo and the residual syrup triturated with ethyl ether (3 × 100 mL). The resulting solid was recrystallized from ethanol/water (9:1) to afford 11.0 g (97%) of **5** (monohydrate): mp 195–197 °C; UV λ_{max} (ε) (pH 1) 310 sh (16 800), 302 (21 000), 274 (11 000), 265 (11 100) nm; (pH 11) UV λ_{max} (ε) 310 sh (17 600), 303 (18 700), 274 (9800), 266 (10 000) nm; ^1H NMR (Me_2SO-d_6) δ 10.85 (broad singlet, 1, 5-NH), 8.15 (s, 1, H-6), 6.24 (d, 1, H-1′, $J_{1',2'}$ = 4.5 Hz), 4.24 (q, 2, CH_2CH_3), 1.30 (t, 3, CH_2CH_3). Anal. Calcd for $C_{13}H_{16}N_5O_6Cl \cdot H_2O$: C, 39.85; H, 4.63; N, 17.88. Found: C, 40.11; H, 4.94; N, 17.82.

Ethyl 7-Chloro-2-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (6). A solution of sodium methoxide (40 mg, 0.7 mmol) in methanol (40 mL) was added to a solution of **4** (0.5 g, 0.7 mmol) in tetrahydrofuran (10 mL). The solution was then stirred at room temperature for 2 h. The solution was neutralized (pH 6, paper) with Amberlite IRC-50(H^+) resin (1 g), and the resin was removed by filtration. The filtrate was evaporated to dryness in vacuo and the residue triturated with ethyl ether (3 × 10 mL). The solid was collected by filtration and then recrystallized from ethanol/water (9:1) to give 0.26 g (95%) of pure **6**: mp 171–173 °C; UV λ_{max} (ε) (pH 1) 310 (8700), 262 (7300) nm; UV λ_{max} (ε) (pH 11) 311 (8200), 260 (8700) nm; ^1H NMR (Me_2SO-d_6) δ 10.68 (s, 1, 5-NH), 8.25 (s, 1, H-6), 6.51 (d, 1, H-1′, $J_{1',2'}$ = 3.0 Hz), 4.25 (a, 2, CH_2CH_3), 1.33 (t, 3, CH_2CH_3). Anal. Calcd for $C_{13}H_{16}N_5O_6Cl$: C, 41.77; H, 4.32; N, 18.74. Found: C, 41.49; H, 4.49; N, 18.61.

Ethyl 7-Chloro-3-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine-5-carbamate (7). Acetone dimethyl acetal (0.2 mL) and 70% perchloric acid (0.3 mL) were added to dry acetone (150 mL), and the solution was allowed to stir for 5 min. Anhydrous **5** (0.2 g of the monohydrate of **5** was dissolved in 50 mL of boiling ethanol and evaporated to dryness in vacuo at 80 °C) was added and the solution stirred at room temperature for 24 h. A solution of concentrated ammonium hydroxide (5 mL) in water (25 mL) was added, the solution was concentrated in vacuo to 30 mL, and the mixture was allowed to stand at 5 °C for 12 h. The crystalline precipitate was collected by filtration, washed with water (20 mL), and air-dried to afford 0.16 g (75%) of the isopropylidene derivative **7**, mp 100–103 °C. An analytical sample was recrystallized from water: mp 101–103 °C; ^1H NMR (Me_2SO-d_6) δ 10.75 (broad singlet, 1, 5-NH), 8.12 (s, 1, H-6), 6.48 (s, 1, H-1′), 4.30 (q, 2, CH_2CH_3), 1.59 and 1.42 (two s, 3 and 3, isopropylidene methyls, Δδ = 0.17 ppm), 1.33 (t, 3, CH_2CH_3). Anal. Calcd for $C_{16}H_{20}N_5O_6Cl$: C, 44.50; H, 5.14; N, 16.22. Found: C, 44.74; H, 4.96; N, 16.16.

5-Amino-7-chloro-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine (9). A suspension of **5** (2.2 g, 5.6 mmol) in 0.1 N KOH (100 mL) was stirred and heated at reflux for 45 min. The cooled reaction solution was neutralized (pH 6.5, paper) with 1 N HCl, and the mixture was allowed to stand at 5 °C for 12 h. The gelatinous precipitate was collected by filtration, washed with water (50 mL), and redissolved in boiling water (100 mL). The solution was again kept at 5 °C for 12 h, and the precipitate was collected by filtration, washed with water (20 mL), and dried in vacuo at 80 °C over P_2O_5 for 12 h to give 1.6 g (89%) of **9**: mp 227–229 °C; UV λ_{max} (ε) (pH 1) 317 (13 900), 255 (5600) nm; UV λ_{max} (ε) (pH 11) 316 (13 600), 255 (5600) nm; ^1H NMR (Me_2SO-d_6) δ 7.13 (s, 2, NH_2), 6.77 (s, 1, H-6), 6.12 (d, 1, H-1′, $J_{1',2'}$ = 4.5 Hz). Anal. Calcd for $C_{10}H_{12}N_5O_4Cl$: C, 39.81; H, 4.01; N, 23.22. Found: C, 40.16; H, 4.38; N, 22.94.

5-Amino-7-ethoxy-3-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*b*]pyridine (10). A solution of **5** (1.0 g, 2.6 mmol) and powdered KOH (1.5 g, 26 mmol) in ethanol (100 mL) was stirred and heated at reflux for 5 h. The cooled solution was neutralized (pH 6, paper) with Amberlite IRC-50(H^+) resin (20 g), and the resin was removed by filtration. The filtrate was evaporated to dryness in vacuo, and the residual solid was recrystallized from water to afford 0.65 g (77%) of **10** (monohydrate): mp 141–143 °C; UV λ_{max} (ε) (pH 1) 294 (16 300), 252 (8700) nm; UV λ_{max} (ε) (pH 11) 295 (16 600), 268 sh (10 600) nm; ^1H NMR (Me_2SO-d_6) δ 6.58 (broad singlet, 2, NH_2), 6.07 (s, 1, H-6), 6.07 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 4.38 (q, 2, CH_2CH_3), 1.47 (t, 3, CH_2CH_3). Anal. Calcd for $C_{12}H_{17}N_5O_5 \cdot H_2O$: C, 43.76; H, 5.82; N, 21.27. Found: C, 43.75; H, 5.68; N, 21.46.

5-Amino-7-methylthio-3-(β-D-ribofuranosyl)-*v*-triazolo-[4,5-*b*]pyridine (11). A solution of sodium ethoxide in ethanol (1 N, 52 mL; prepared by reaction of sodium metal with ethanol) was added to a solution of **5** (2.0 g, 5.1 mmol) in ethanol (300 mL). The solution was cooled to 0 °C in an ice–salt water bath and then saturated with methyl mercaptan. The reaction mixture was stirred and heated at reflux for 6 h. The cooled solution was neutralized (pH 6, paper) with Amberlite IRC-50(H^+) resin (20 g), and the resin was removed by filtration. The filtrate was evaporated to dryness in vacuo, and the solid was recrystallized from ethanol/water (1:9) to afford 1.6 g (95%) of **11** (monohydrate): mp 149–151 °C; UV λ_{max} (ε) (pH 1) 324 sh (11 600), 310 sh (16 500), 297 (18 400), 235 sh (7400); UV λ_{max} (ε) (pH 11) 310 sh (14 900), 296 (16 600), 240 (10 000) nm; ^1H NMR (Me_2SO-d_6) δ 6.79 (s, 2, NH_2), 6.42 (s, 1, H-6), 6.08 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 3.45 (s, 2, H_2O), 2.60 (s, 3, CH_3). Anal. Calcd for $C_{11}H_{15}N_5O_4 \cdot H_2O$: C, 39.87; H, 5.17; N, 21.14. Found: C, 39.87; H, 5.27; N, 20.92.

5-Amino-7-benzyloxy-3-(β-D-ribofuranosyl)-*v*-triazolo-[4,5-*b*]pyridine (12). A solution of sodium benzylate in benzyl alcohol (1 N, 80 mL; prepared by reaction of sodium metal with benzyl alcohol) was added to a solution of **5** (3.0 g, 7.7 mmol) in freshly distilled benzyl alcohol (350 mL). The solution was stirred and heated in an 85 °C oil bath for 5 h in a nitrogen atmosphere. The solution was evaporated to a syrup in vacuo at 80 °C and the syrup dissolved in ethanol (200 mL). The insoluble salts were removed by filtration, and the solution was neutralized (pH 6, paper) with Amberlite IRC-50(H^+) resin (10 g). The resin was removed by filtration and the filtrate evaporated to dryness in vacuo. The residue was dissolved in a mixture of EtOAc and ethanol (50 mL, 1:1), and the sample solution was applied to an open-bed silica gel column (3 × 30 cm). The column was eluted with EtOAc/ethanol (9:1). The fractions containing the desired product [TLC, R_f 0.42 (EtOAc/ethanol, 9:1)] were concentrated in vacuo to 200 mL, hexane was added to the cloud point, and the mixture was allowed to stand at 5 °C for 12 h. The precipitate was collected by filtration, washed with EtOAc (20 mL), and dried to yield 2.1 g (72%) of **12**: mp 154–156 °C; UV λ_{max} (ε) (pH 1) 295 (16 300), 252 (11 200) nm; UV λ_{max} (ε) (pH 11) 296 (16 500), 263 (13 500) nm; ^1H NMR (Me_2SO-d_6) δ 7.48 (multiplet, 5, $CH_2C_6H_5$), 6.72 (s, 2, NH_2), 6.17 (s, 1, H-6), 6.08 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.42 (s, 2, $CH_2C_6H_5$). Anal. Calcd for $C_{17}H_{19}N_5O_5$: C, 54.68; H, 5.13; N, 18.76. Found: C,

54.46; H, 5.13; N, 18.76.

5-Amino-3-(β-D-ribofuranosyl)-v-triazolo[4,5-b]pyridin-7-one (14; 1-Deaza-8-azaguanosine). To a solution of **12** (2.0 g, 5.4 mmol) in ethanol (200 mL) was added 5% Pd/C (0.6 g). The mixture was shaken on a Paar apparatus at room temperature for 3 h under a hydrogen atmosphere (42 psi). The mixture was filtered through a Celite bed, and the bed was then washed with a hot mixture of ethanol/water (1:1). The filtrate was evaporated to dryness in vacuo, and the residual solid was recrystallized from water to afford 1.34 g (93%) of **14** (monohydrate): mp 148 °C (sinters); UV λ_{max} (ϵ) (pH 1) 296 (17:700), 250 (7900) nm; UV λ_{max} (ϵ) (pH 11) 284 (18 300) nm; ^{1}H NMR (Me_2SO-d_6) δ 11.27 (broad singlet, 1, 4-NH), 6.45 (s, 2, NH_2), 6.03 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.90 (s, 1, H-6). Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot H_2O$: C, 39.87; H, 5.02; N, 23.25. Found: C, 40.02; H, 5.08; N, 23.19.

5-Amino-7-benzyloxy-v-triazolo[4,5-b]pyridine (16). A solution of 4-benzyloxy-2,3,6-triaminopyridine dihydrochloride[17] (**15**; 6.0 g, 19.8 mmol) in 1 N HCl (100 mL) was cooled to 5 °C in an ice–water bath. A solution of sodium nitrite (1.3 g, 19.8 mmol) in water (10 mL) was added dropwise to the stirred reaction solution over a 5-min period. The mixture was stirred at 5 °C for 1 h and then neutralized (pH 7, paper) with concentrated ammonium hydroxide. The precipitate was collected by filtration, washed with water (50 mL), and air-dried. The solid was dissolved in boiling ethanol (200 mL) and treated with Norit. The filtered solution was concentrated in vacuo to 50 mL, water (100 mL) was added, and the mixture was kept at 5 °C for 12 h. The precipitate was collected by filtration, washed with water (25 mL), and dried to afford 3.7 g (77%) of **16**: mp 194–195 °C; UV λ_{max} (ϵ) (pH 1) 296 (14 800), 257 (10 700) nm; UV λ_{max} (ϵ) (pH 11) 292 (10 400), 271 (8300) nm; ^{1}H NMR (Me_2SO-d_6) δ 7.52 (multiplet, 5, $CH_2C_6H_5$), 6.53 (s, 2, NH_2), 6.19 (s, 1, H-6), 5.43 (s, 2, $CH_2C_6H_5$). Anal. Calcd for $C_{12}H_{11}N_5O$: C, 59.74; H, 4.60; N, 29.03. Found: C, 59.47; H, 4.84; N, 29.12.

5-Amino-v-triazolo[4,5-b]pyridin-7-one (17; 1-Deaza-8-azaguanine).[25] To a solution of **16** (0.5 g, 2.1 mmol) in ethanol (100 mL) was added 5% Pd/C (0.5 g). The mixture was shaken on a Paar apparatus in a hydrogen atmosphere (42 psi) at room temperature for 6 h. The mixture was filtered through a Celite bed, and the bed was washed with a hot ethanol/water (50 mL, 1:1) mixture. The filtrate was concentrated in vacuo to 50 mL and kept at 5 °C for 12 h. The precipitate was collected by filtration, washed with water (20 mL), and dried in vacuo at 100 °C for 12 h to give 0.31 g (94%) of **17**: melting point darkens above 250 °C, and explodes at 296 °C; UV λ_{max} (ϵ) (pH 1) 297 (14 700), 264 (7100) nm; UV λ_{max} (ϵ) (pH 11) 284 (16 500) nm; ^{1}H NMR (Me_2SO-d_6) δ 11.50 (very broad singlet, 2,3,4-NH), 6.40 (s, 2, NH_2), 5.72 (s, 1, H-6). Anal. Calcd for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.98; H, 3.12; N, 46.06.

5-Amino-3-(β-D-ribofuranosyl)-v-triazolo[4,5-b]pyridine-7-thione (13; 1-Deaza-8-aza-6-thioguanosine). Anhydrous sodium hydrogen sulfide (2.9 g, 51 mmol) was added to a solution of ethyl 7-chloro-3-(β-D-ribofuranosyl)-v-triazolo[4,5-b]pyridine-5-carbamate (**5**; 2.0 g, 5.1 mmol) in dimethylformamide (200 mL). The blue solution was stirred at room temperature for 24 h. The solution was then evaporated to dryness in vacuo and the residue triturated with ethanol (200 mL) at reflux temperature. The insoluble salts were removed by filtration, and the filtrate was neutralized (pH 6, paper) with Amberlite IRC-50(H^+) resin (20 g). The resin was removed by filtration and the filtrate evaporated to dryness in vacuo. The residual solid was dissolved in 1 N KOH (50 mL), and the solution was then heated at reflux for 45 min. The cooled solution was extracted with EtOAc (3 × 20 mL), and these extracts were discarded. The aqueous solution was acidified to pH 2 (paper) with 1 N HCl, and the mixture was allowed to stand at 5 °C for 12 h. The precipitate was collected by filtration, washed with water (20 mL), dissolved in 1 N KOH (50 mL), and then reprecipitated with 1 N HCl to afford 1.1 g (65%) of **13** (monohydrate) after air drying: mp 113–116 °C; UV λ_{max} (ϵ) (pH 1) 329 (12 300), 320 (12 500), 310 (12 100), 287 (9900) nm; UV λ_{max} (ϵ) (pH 11) 310 (17 800), 248 (10 900) nm; ^{1}H NMR (Me_2SO-d_6) δ 6.59 (s, 1, H-6), 6.11 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.22 (very broad, 8, 4-NH, NH_2, H_2O, and sugar hydroxyls); TLC, R_f 0.37 (EtOAc/EtOH, 9:1), 0.22 (H_3CCN/concentrated NH_4OH, 9:1). Anal. Calcd for $C_{10}H_{13}N_5SO_4 \cdot H_2O$: C, 37.85; H, 4.76; N, 22.07; S, 10.11. Found: C, 37.87; H, 4.53; N, 22.28; S, 9.89.

6-Amino-4-(α- and β-D-ribofuranosyl)amino-1,2,3-thiadiazolo[4,5-c]pyridine (19 and 20). A solution of **13** (50 mg) in dimethylformamide (0.5 mL) was heated on a hot plate (300 °C) for 30 s. The solvent was removed in vacuo at 80 °C and the residual solid triturated with ethyl ether (2 × 5 mL). The solid was dissolved in warm methanol (4 mL), water (4 mL) was added, and the solution was kept at 5 °C for 48 h. The yellow precipitate was collected by filtration, washed with water (5 mL), and dried in an Abderhalden apparatus in vacuo over toluene at reflux for 6 h to give 35 mg of a mixture (4:1) of **19** and **20**: mp 175–180 °C; UV λ_{max} (ϵ) (pH 1) 327 (15 500), 279 (8100) nm; UV λ_{max} (ϵ) (pH 11) 351 sh (5700), 315 (11 400), 244 (12 400), 233 (13 100) nm; UV λ_{max} (ϵ) (EtOH) 351 (5600), 319 (9200), 256 (9700), 236 (10 600) nm; ^{1}H NMR (Me_2SO-d_6) δ 8.29 (d, 1, 4-NH (β), $J_{1',4}$ = 10.0 Hz), 7.66 (d, 1, 4-NH (α), $J_{1',4}$ = 10.0 Hz), 6.52 (s, 2, NH_2), 6.33 (s, 1, H-7), 6.10 (q, 1, H-1′ (α), $J_{1',2'}$ = 4.5 Hz, $J_{1',4}$ = 10.0 Hz), 5.96 (q, 1, H-1′ (β), $J_{1',2'}$ = 4.5 Hz, $J_{1',4}$ = 10.0 Hz); TLC, R_f 0.49 (α) and 0.52 (β) (EtOAc/EtOH, 9:1), R_f 0.35 (α) and 0.39 (β) (H_3CCN/concentrated NH_4OH, 9:1).

Bis(5-amino-3-β-D-ribofuranosyl-v-triazolo[4,5-b]pyridin-7-yl) Disulfide (18). A solution of **13** (50 mg, 0.16 mmol) in dimethyl sulfoxide (0.5 mL) was allowed to stand at room temperature for 24 h. Ethyl acetate (5 mL) was added, and the mixture was allowed to stand at 5 °C for 12 h. The precipitate was collected by filtration, washed with ethyl acetate (5 mL), and air-dried. The solid was recrystallized from water and dried in an Abderhalden apparatus in vacuo over toluene at reflux temperature for 6 h to give the disulfide **18** (30 mg, 60%): melting point darkens above 214 °C, and decomposes at 224 °C; UV λ_{max} (ϵ) (pH 1) 319 (22 400), 282 (22 800) nm; UV λ_{max} (ϵ) (pH 11) 316 (24 900), 245 (18 000) nm; UV λ_{max} (ϵ) (EtOH) 321 (19 200), 277 (17 000), 240 (22 800) nm; ^{1}H NMR (Me_2SO-d_6) δ 7.03 (broad singlet, 2, NH_2), 6.76 (s, 1, H-6), 6.12 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz); TLC, R_f 0.15 (EtOAc/EtOH, 9:1), 0.11 (CH_3CN/concentrated NH_4OH, 9:1). Anal. Calcd for $C_{20}H_{24}N_{10}S_2O_8 \cdot 1.5H_2O$: C, 38.52; H, 4.36; N, 22.46; S, 10.28. Found: C, 38.13; H, 4.28; N, 22.41; S, 9.92.

5-Amino-v-triazolo[4,5-b]pyridine-7-thione (21; 1-Deaza-8-aza-6-thioguanine). A solution of ethyl 7-chloro-v-triazolo[4,5-b]pyridine-5-carbamate (**1**; 0.5 g, 2.1 mmol) and anhydrous sodium hydrosulfide (1.2 g, 21 mmol) in dimethylformamide (125 mL) was heated in an oil bath (95 °C) for 12 h. The solution was then evaporated to dryness in vacuo at 80 °C. The solid residue was triturated with boiling ethanol (100 mL), the mixture was allowed to cool to room temperature, and the insoluble salts were removed by filtration. The ethanol solution was neutralized (pH 6, paper) with Amberlite IRC-50(H^+) resin (10 g), the resin was removed by filtration, and the filtrate was evaporated to dryness in vacuo. The residue was dissolved in 0.1 N KOH (100 mL) and the solution heated at reflux for 5 h. The cooled solution was extracted with ethyl acetate (3 × 20 mL, discarded). The aqueous solution was acidified to pH 2 (paper) with 6 N HCl and allowed to stand at 5 °C for 48 h. The dark yellow precipitate was collected by filtration, washed with water (10 mL), and dried to give 0.15 g (40%) of **21** (hemihydrate): melting point darkens above 190 °C, and decomposes at 232 °C (lit.[23] 236–237 °C); UV λ_{max} (ϵ) (pH 1) 330 (11 700), 316 (14 000), 308 (14 000), 299 sh (13 200) nm; UV λ_{max} (ϵ) (pH 11) 310 nm (17 900) [lit.[23] (0.1 NaOH) 217 (19 100), 308 (19 700) nm]; ^{1}H NMR (Me_2SO-d_6) δ ~12 (very broad peak, 2, 3,4-NH), 6.89 (broad singlet, 3, NH_2, $0.5H_2O$), 6.59 (s, 1, H-6). Anal. Calcd for $C_5H_5N_5S \cdot 0.5H_2O$: C, 34.08; H, 3.43; N, 39.75; S, 18.20. Found: C, 34.24; H, 3.25; N, 39.65; S, 17.98.

Ethyl 3-(β-D-Ribofuranosyl)-v-triazolo[4,5-b]pyridine-5-carbamate (8). To a solution of ethyl 7-chloro-3-(β-D-ribofuranosyl)-v-triazolo[4,5-b]pyridine-5-carbamate (**5**; 1.0 g, 2.5 mmol) in ethanol (150 mL) was added 5% Pd/C (0.3 g) and 1 N KOH (2.5 mL). The mixture was shaken on a Paar apparatus in a hydrogen atmosphere (42 psi) at room temperature for 3 h. The mixture was filtered through a Celite bed, and the bed was washed with ethanol (50 mL). The filtrate was concentrated in vacuo to 25 mL and water (50 mL) was added. The mixture was allowed to stand at 5 °C for 12 h. The precipitate was collected by filtration, washed with water (20 mL), and air-dried. Recrystallization from water/ethanol (4:1) afforded 0.81 g (93%) of **8**: mp 183–185 °C; UV λ_{max} (ϵ) (pH 1) 311 sh (15 000), 302 (18 200), 256 (6300) nm; UV λ_{max} (ϵ) (pH 11) 311 sh (15 200), 302 (18 100), 254 (6900) nm; ^{1}H NMR (Me_2SO-d_6) δ 10.56 (s, 1, 5-NH), 8.53 (d, 1, H-7, $J_{6,7}$ = 9.6 Hz), 8.00 (d, 1, H-6, $J_{6,7}$ = 9.6 Hz), 6.27 (d, 1, H-1′, $J_{1',2'}$ = 4.0 Hz), 4.25 (q, 2, CH_2CH_3), 1.35 (t, 3, CH_2CH_3). Anal. Calcd for $C_{13}H_{17}N_5O_6$: C, 46.01; H, 5.05; N, 20.64. Found: C, 45.81; H, 4.97; N, 20.77.

Ethyl v-Triazolo[4,5-b]pyridine-5-carbamate (22). To a solution of ethyl 7-chloro-v-triazolo[4,5-b]pyridine-5-carbamate (**1**; 0.5 g, 2.1 mmol) in ethanol (50 mL) was added 5% Pd/C (1.0 g). The mixture was shaken on a Paar apparatus in a hydrogen atmosphere (42 psi) at room temperature for 72 h. The mixture was filtered through a Celite bed, and the bed was washed with hot ethanol (30 mL). The filtrate was concentrated in vacuo to 20 mL and water (25 mL) was added. The solution was brought to pH 6 (paper) with concentrated ammonium hydroxide and allowed to stand at 5 °C for 12 h. The precipitate was collected by filtration, washed with water (30 mL), and dried to give 0.32 g (75%) of **22**, mp 182–184 °C. An analytical sample was recrystallized from water: mp 182–184 °C; UV λ_{max} (ϵ) (pH 1) 308 sh (14 200), 302 (15 600), 251 (4600), 240 (6500) nm; UV

λ_{max} (ϵ) (pH 11) 303 nm (15 100); ^{1}H NMR (Me_2SO-d_6) δ 15.84 (broad singlet, 1, 3-NH), 10.54 (s, 1, 5-NH), 8.44 (d, 1, H-7, $J_{6,7}$ = 9.6 Hz), 8.00 (d, 1, H-6, $J_{6,7}$ = 9.6 Hz), 4.22 (q, 2, CH_2CH_3), 1.31 (t, 3, CH_2CH_3). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.22; H, 4.42; N, 33.67.

Registry No.—**1**, 38359-73-8; **2**, 22860-91-9; **3**, 62805-39-4; **4**, 67505-63-9; **5**, 62805-40-7; **6**, 67505-64-0; **7**, 67505-65-1; **8**, 67505-66-2; **9**, 67505-67-3; **10**, 67505-68-4; **11**, 67505-69-5; **12**, 62805-41-8; **13**, 67505-70-8; **14**, 62805-42-9; **15** 2 HCl, 53995-24-7; **16**, 62805-37-2; **17**, 60282-60-2; **18**, 67505-71-9; **19**, 67505-72-0; **20**, 67505-73-1; **21**, 60282-66-8; **22**, 67505-74-2.

References and Notes

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Synthesis and Carbon-13 Nuclear Magnetic Resonance Spectra of *all-trans*-Geranylgeraniol and Its Nor Analogues

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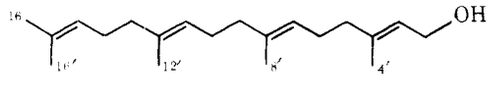
Syntheses of the five possible nor analogues of *all-trans*-geranylgeraniol are described. The 4′-nor isomer (**10**) is prepared from *trans,trans*-farnesol by means of two-carbon chain extension and phosphonate olefination reactions (Scheme I). The 16′- and 16-nor analogues (**26** and **27**) are obtained through Biellmann isoprenoid coupling reactions of 3-methyl-2,6(*E,Z*)-octadien-1-yl phenyl sulfide (8′-norgeranyl phenyl sulfide, **22**) and its 6,7(*E*) isomer (**23**) with benzyl 8-chloro-3,7-dimethyl-2,6(*E,E*)-octadien-1-yl ether (**15**, Scheme II). The Wittig–Schlosser reaction for stereoselective trans olefination is the key reaction in the synthetic routes (Scheme IV) to 8′-nor- and 12′-norgeranylgeraniol (**34** and **43**). Proton-decoupled carbon-13 NMR spectral data are reported for *all-trans*-geranylgeraniol and the series of nor analogues and the distinctive shifts associated with the disubstituted double bonds and nearby carbons are noted.

Structural analogues of *trans,trans*-farnesyl pyrophosphate and 2,3-dihydrosqualene 2,3-oxide lacking one or more of the methyl groups have proven useful in investigations on the mechanism and substrate specificity of squalene synthetase[2] and various triterpene cyclases.[3] Since *all-trans*-geranylgeranyl pyrophosphate (1-OPP) serves similarly as the



1-OH

biosynthetic precursor of the diterpene and carotene families of natural products, it would clearly be desirable to have synthetic access to its nor analogues. In this paper we report syntheses of the five possible nor analogues of *all-trans*-geranylgeraniol as well as carbon-13 NMR spectral data for the parent diterpene alcohol and the series of nor analogues.

all-trans-Geranylgeraniol (1-OH) was synthesized by two different methods previously described in the literature, one originating from *trans,trans*-farnesol[4] and the other from geraniol.[5] In the former approach (Scheme I) *trans,trans*-farnesylacetone (**3**) was prepared by alkylation of ethyl sodioacetoacetate with farnesyl bromide (**2**-Br) followed by hydrolysis and decarboxylation of the resulting β-keto ester.[4b,c] Condensation of farnesylacetone with the sodium salt of trimethyl phosphonoacetate[4d] afforded methyl *all-trans*-geranylgeranate (**4**) which, after purification by column chromatography to remove a small amount of the 2,3-cis isomer, was reduced to geranylgeraniol (1-OH) with lithium aluminum monoethoxyhydride.[6]

The preceding reaction sequence was modified in order to synthesize 4′-norgeranylgeraniol (**10**). The reaction of farnesyl

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