(2) Determination of Positional Selectivity. 4-Cyanopyridine (10 mL of a 0.1 M solution) in anhydrous acetonitrile was combined with 5 mmol of alkene (the molar ratio of 4-cyanopyridine–alkene was 1:5) and 5 mL of anhydrous acetonitrile. The solution was irradiated for 1 h. At the end of the irradiation, it was concentrated or in the case of the methoxy, acetoxy and trimethylsilyl ether derivatives treated as mentioned before and analyzed by GC. No variation was found in the isomer ratio with respect to the preparative reactions whose values are reported in Table IV.

(3) Competitive Reactions. 4-Cyanopyridine (10 mL of a 0.1 M solution) in anhydrous acetonitrile was combined with an equimolar quantity of two different alkenes and 5 mL of anhydrous acetonitrile (the molar ratio of 4-cyanopyridine–alkene 1–alkene 2 was 1:2.5:2.5). The resulting solution was irradiated for 1 h and then treated as reported before. The relative reactivities are reported in Table I. Some experiments were run with different alkenes ratio, but no difference in the relative reactivities was found after correction for the different molar ratios. In any case, no difference was found in the isomer ratio.

Acknowledgment. We thank M.P.I. Roma for financial support.

Registry No. 1, 6975-71-9; 1-α, 89344-81-0; 1-β, 100190-68-9; 2, 771-98-2; 2-α, 100190-69-0; 2-β, 100190-70-3; 3, 61401-14-7; 3-α, 100190-71-4; 5, 20343-19-5; 7, 109-68-2; 7-α, 100190-72-5; 7-β, 100190-73-6; 7-β', 100190-74-7; 8, 89580-25-6; 8-α, 100190-75-8; $CH_3CH_2C(OSiMe_3)$=$CHCH_3$, 17510-47-3; CH_3CH=$C(OMe)$-CH_2CH_3, 41623-41-0; CH_3CH=$C(OAc)CH_2CH_3$, 13893-75-9; H_2, 1333-74-0; 1-acetylcyclohexene, 932-66-1; 4-cyanopyridine, 100-48-1; cyclohexene, 110-83-8; 1-methoxycyclohexene, 931-57-7; 1-chlorocyclohexene, 930-66-5; cycloheptene, 628-92-2; 1-[(trimethylsilyl)oxy]cyclohexene, 6651-36-1; 1-acetoxycyclohexene, 1424-22-2; 1-[(trimethylsilyl)oxy]cycloheptene, 22081-48-7; methyl 1-cyclohexenecarboxylate, 18448-47-0; 1-methoxycycloheptene, 50438-50-1; 1-phenylcycloheptene, 25308-75-2; 1-acetoxycycloheptene, 14477-74-8.

Total Synthesis of (4*R*)- and (4*S*)-5,6-Dihydro-1-β-D-ribofuranosyl-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol and (8*R*)- and (8*S*)-7,8-Dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol: Two Heterocyclic Analogues of the Nucleoside Antibiotic Coformycin

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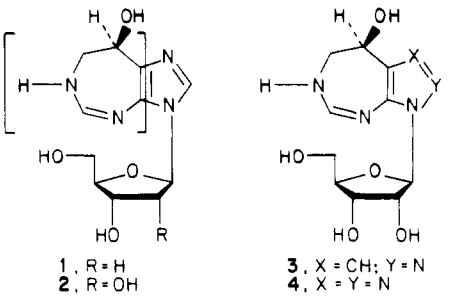
Received January 14, 1985

The reaction of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxaldehyde (**10**) with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) has provided 5-[((dimethylamino)methylene)amino]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxaldehyde (**11**). Subsequent reaction of the protected aldehyde **11** with trimethylsilyl cyanide (Me_3SiCN) afforded the protected trimethylsilyl cyanohydrins **12**. A reduction of the nitrile group of **12** in neutral media using cobalt boride catalyst yielded an aminomethyl intermediate which initiated an in situ annulation. Subsequent deprotection of the β-D-ribofuranosyl moiety of the product gave a mixture of the (4*R*)- and (4*S*)-5,6-dihydro-1-β-D-ribofuranosyl-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol (compounds **3** and **15**). A similar series of reactions, starting with 5-amino-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxaldehyde, has furnished a mixture of (8*R*)- and (8*S*)-7,8-dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol (**4** and **26**). The chromatographic separation of **4** and **26** followed by a spectroscopic characterization of each compound is described herein.

We have recently witnessed a burgeoning interest in the synthesis[1,2,6] of strong inhibitors of the ubiquitous enzyme adenosine deaminase[4] (these synthetic efforts have involved both chemical and fermentation methods). A recent chemical synthesis of the very potent adenosine deaminase inhibitor (8*R*)-3-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-*d*][1,3]diazepin-8-ol[2,3] (**1**, 2′-deoxycoformycin, pentostatin) has prompted us to report on our research efforts which have been directed toward the chemical synthesis of some heterocyclic analogs of coformycin (**2**), the 2′-hydroxy analogue of the nucleoside antibiotic pentostatin. Our efforts were prompted in part by the finding[5] that, as an antileukemic agent, pen-

Chart I



1, R = H
2, R = OH
3, X = CH; Y = N
4, X = Y = N

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(4) Agarwal, R. P.; Spector, T.; Parks, R. E., Jr. *Biochem. Pharmacol.* **1977**, *26*, 359.
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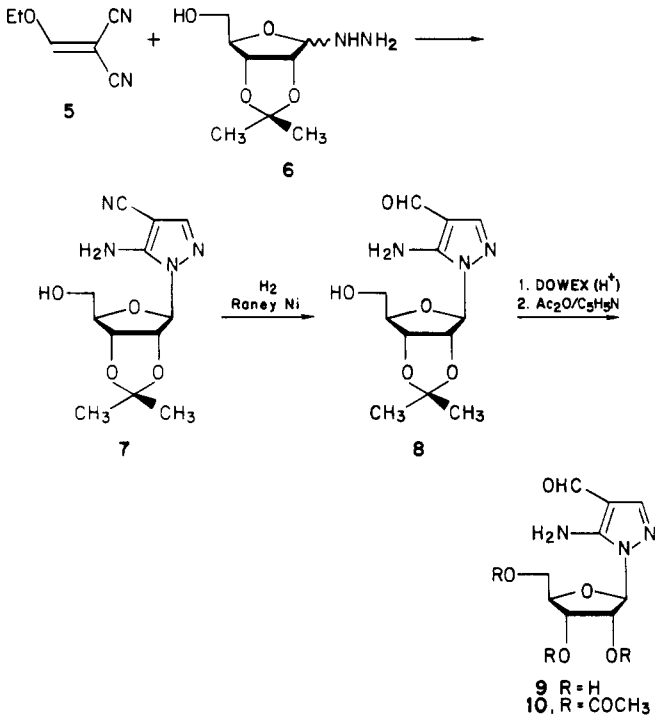
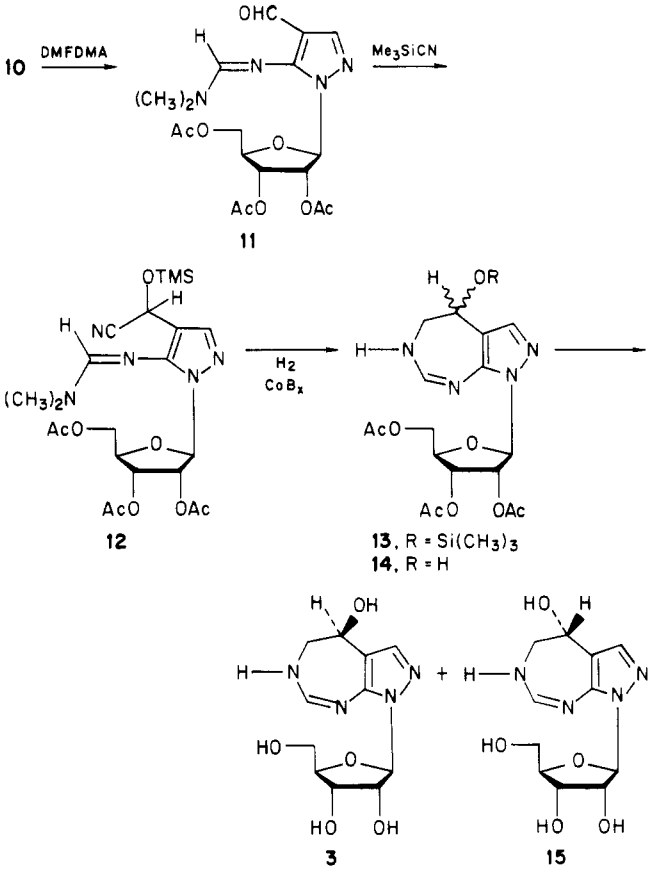
Scheme I



Scheme II



tostatin has exhibited some acute renal toxicity during clinical trials. Earlier reports[7,8] from our laboratory have described a methodology that we have developed for the formation of the 4,5-dihydro-3*H*-1,3-diazepin-5-ol ring (Chart I, in brackets) from an appropriately substituted pyrazole. We now wish to report on our synthesis of (4*R*)-5,6-dihydro-β-D-ribofuranosyl-4*H*-pyrazolo[3,4-*d*]-[1,3]diazepin-4-ol (**3**) and (8*R*)-7,8-dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol (**4**, 2-azacoformycin) using approaches previously developed in our laboratory.

Results and Discussion

Our primary aim was to develop a general route for the synthesis of azolo[1,3]diazepine nucleosides which would be structurally similar to coformycin (**2**) and pentostatin (**1**). Our initial goal involved the synthesis of (4*R*)-5,6-dihydro-1-(β-D-ribofuranosyl)-4*H*-pyrazolo[3,4-*d*][1,3]-diazepin-4-ol using an extension of the methodology which we have previously[7,8] described for the synthesis of the 1-methyl derivative. Using this method, there were two viable synthetic routes available for the preparation of the target compound: (1) introduction of the β-D-ribofuranosyl moiety as one of the final steps in the synthetic sequence or (2) use of a preformed nucleoside as a starting material or an early synthetic intermediate. The approach we selected involved the acetonation[9] of D-ribose to provide 2,3-*O*-isopropylidene-D-ribose, followed by a treatment of this intermediate with anhydrous hydrazine to yield 1-deoxy-1-hydrazinyl-2,3-*O*-isopropylidene-D-ribose (**6**). A subsequent condensation of **6** with ethoxymethylene malononitrile (**5**) in ethanol gave a single nucleoside product, which was characterized[10] as 5-amino-4-cyano-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole (**7**) on the basis of its ultraviolet and ^{1}H NMR spectrum as well as elemental analysis (C, H, N).

After numerous unsuccessful attempts, using a wide variety of reaction conditions and catalysis, we found that compound **7** could be catalytically reduced with Raney nickel[12] in a buffered solution consisting of pyridine–glacial acetic acid–water to afford a moderate yield of 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole-4-carboxaldehyde (**8**) (Scheme I). In anticipation of the projected instability[1b] of the target compound **3** to acid, the acid-labile isopropylidene protecting group of **8** was exchanged for base-labile acetyl protecting groups. To this end, the isopropylidene group was removed from compound **8** by treatment with DOWEX 50 × 4 (H^+) ion-exchange resin in methanol. Compound **9** was collected by filtration, dried, and immediately treated with acetic anhydride in pyridine. In this manner, crystalline 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxaldehyde (**10**) was obtained in 61% overall yield from compound **8**.

Compound **10** was then reacted with an excess of *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) in anhydrous methylene chloride to yield 5-[((dimethylamino)methylene)amino]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxaldehyde (**11**).[13] Compound **11** was allowed to react with trimethylsilyl cyanide

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(13) Reaction of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-pyrazole-4-carboxaldehyde (**10**) or 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)triazole-4-carboxaldehyde (**21**) with excess *N*,*N*-dimethylformamide dimethyl acetal gave excellent yields of the corresponding 5-[(dimethylamino)methylene]amino products. However, each product contained a small amount of the 5-(methoxymethylene)amino product as an impurity. In a previous report,[8] using a model compound, we have determined that this product undergoes trimethylsilyl cyanation and reduction–annulation in a manner analogous to the predominant product.

Table I. ^{13}C NMR Data for the Diastereomeric Mixture of (4*R*)- and (4*S*)-5,6-Dihydro-1-β-D-ribofuranosyl-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol (Nucleosides 3 and 15)[a]

C	major isomer[a]	minor isomer
C-3	137.41	137.41
C-4	63.46	63.49
C-5	49.84	49.84
C-7	147.66	147.61
C-3a	113.19	113.34
C-8a[b]	144.66	144.52
C-1′[c]	87.69	87.64
C-2′	73.70	73.70
C-3′	70.94	70.98
C-4′	84.49	84.49
C-5′	62.57	62.57

[a] Chemical shifts are expressed in ppm downfield from Me_4Si. Values were measured relative to an internal Me_2SO standard and converted to the Me_4Si scale using $(Me_4Si) = (Me_2SO) - 39.50$ ppm. Concentration, 15 mg/0.3 mL of Me_2SO-d_6. Temperature ca. 27 °C. W. M. Bruker (360 MHz) instrument. [b] Unambiguous assignment of the bridghead signals was made from a three-bond ^{13}C–^1H decoupling of the H-1′ proton with the C-8a carbon and a similar decoupling of the H-7 porton with the C-8a carbon. Details of this decoupling are given in ref 19. [c] The chemical shift sequence for the carbons of the β-D-ribofuranosyl moiety have been well established[20] for similar substituted nucleosides.

(Me$_3$SiCN, neat) to provide a mixture of the diastereomeric trimethylsilyl cyanohydrins **12**.

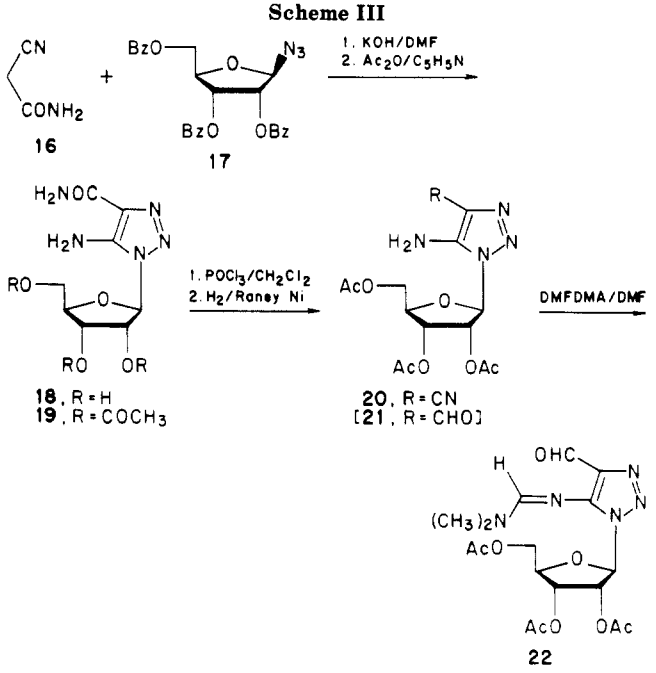
A reduction of the nitrile functionality of **12**, using a cobalt boride catalyst[14] and 30 atm of hydrogen, formed an intermediate aminomethyl group which was then involved in an in situ annulation. The product from this annulation was found to be a mixture of the 5,6-dihydro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol (**14**) and the corresponding 4-trimethylsilyl ether **13** (1:4, approximately: vide infra TLC analysis and inspection of the ^1H NMR spectrum of the mixture (Scheme II). However, pure **14** was obtained from an acidic hydrolysis of the trimethylsilyl group of **13** in the mixture. The ^1H NMR (360 MHz) spectrum of the *R* and *S* mixture at C-4 represented by structure **14** revealed the presence of two very similar compounds in an approximate ratio of 2:1. This proportionality was determined by an integration of the signals for the H-7, H-3, and H-1′ protons, with each signal being individually resolved for each diastereomer in the mixture (see Experimental Section).

Removal of the acetyl protecting groups from the β-D-ribofuranosyl moiety of **14** furnished a mixture of compounds **3** and **15**, which was assigned the structure (4*R*-) and (4*S*-)-5,6-dihydro-1-β-D-ribofuranosyl-4*H*-pyrazolo-[3,4-*d*][1,3]diazepin-4-ol, on the basis of its UV, ^1H NMR, and ^{13}C NMR spectra (see Table I) and elemental analysis. In particular, the ^1H NMR (360 MHz) spectrum of this mixture exhibited a single signal for each type of proton in the compounds, attesting to their great similarity.

We then initiated a synthesis of (8*R*)-7,8-dihydro-3-β-D-ribofuranosyl-6*H*-υ-triazolo[4,5-*d*][1,3]diazepin-8-ol (2-azacoformycin) using a υ-triazole nucleoside as the starting material. This synthesis of 2-azacoformycin would provide validity to our assumption that this synthetic route is a general method for the synthesis of the 4,5-dihydro-3*H*-1,3-diazepin-5-ol moiety using a variety of heterocycles as the parent rings.

A crucial intermediate for the synthesis of 2-azacoformycin was 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-υ-triazole-4-carboxamide (**19**). We were able to isolate a moderate yield of this nucleoside, on a preparative

Scheme III



scale, through a modification of an established literature procedure.[15] This modification gave us compound **18** from the 1,3-dipolar cycloaddition of cyanoacetamide and 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide[16] (**17**) under strongly basic conditions. A complete removal of the benzoyl protecting groups from the crude nucleoside product (partial removal of these groups had occurred during the course of the reaction) was effected and then followed by an in situ acetylation of 5-amino-1-β-D-ribofuranosyl-υ-triazole-4-carboxamide (**18**) as a crude product, to afford the desired compound **19** in 37% overall yield.

Dehydration of the carboxamide group of **19** using the literature procedure[17] provided 5-amino-4-cyano-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-υ-triazole (**20**) in fair yield (Scheme III). The actual yield of **20** was greatly diminished by our efforts to purify this compound. We found that the *p*-toluenesulfonic acid contaminant could not be easily removed. Our best yields (68%) of compound **20** were obtained from the rapid addition of excess phosphorus oxychloride at room temperature to a suspension of compound **19** in chloroform and triethylamine. A rapid aqueous workup of this reaction, followed by flash chromatography on silica gel provided **20** as a thick syrup.

Compound **20** was rapidly reduced to 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-υ-triazole-4-carboxaldehyde (**21**) with Raney nickel[12] and 1 atm of hydrogen, in a buffered solution of pyridine–glacial acetic acid–water. The yield of **21** from this reduction is directly dependent upon the speed with which the solvents used in the reduction are evaporated in vacuo and the product is purified by flash chromatography. Alternatively, after a thorough evaporation of the solvents, the crude product **21** could be immediately treated with *N*,*N*-dimethylformamide dimethyl acetal. The latter method was deemed superior since it reduced the handling time of the unstable[18] al-

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Table II. ^{13}C NMR Data for the Diastereomers (8*R*)- and (8*S*)-7,8-Dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol (Nucleosides 4 and 26)[a]

C	26	4
C-5	150.30	150.30
C-7	48.23	48.23
C-8	64.14	64.02
C-3a[b]	141.28	141.18
C-8a	136.88	136.88
C-1′[c]	87.90	87.78
C-2′	73.27	73.27
C-3′	70.85	70.85
C-4′	85.28	85.28
C-5′	62.29	62.29

[a] See ref *a*, Table I. [b] See ref *b*, Table I. [c] See ref *c*, Table I.

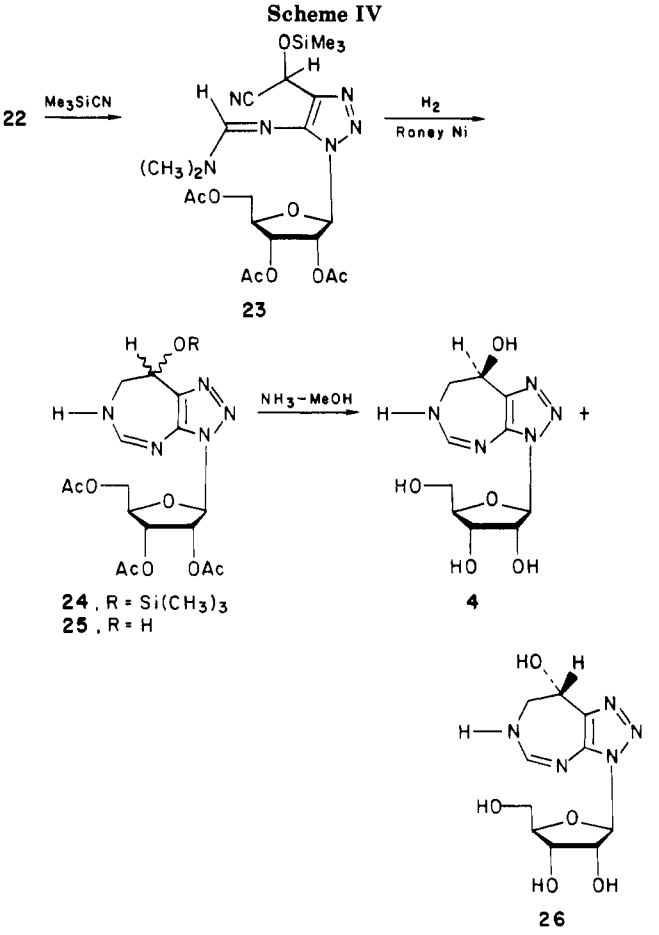
dehyde and provided a moderate (45%) yield of 5-[((dimethylamino)methylene)amino]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxaldehyde (**22**).[13] The chemical stability of the [(dimethylamino)methylene]-amino functionality allowed us to use normal chromatographic techniques for the isolation of analytically pure samples of compound **22**.

Trimethylsilyl cyanide added very smoothly to compound **22**; however, despite all precautions taken to maintain anhydrous conditions during the preparation and isolation of the diastereomeric 5-[((dimethylamino)-methylene)amino]-4-[cyano(trimethylsiloxy)methyl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*v*-triazole (**23**), low-pressure chromatography yielded these compounds in a disappointingly low 45% yield. With continued elution of the low-pressure column, we were able to isolate 20–25% yields of the starting aldehyde **22** from the almost unavoidable hydrolysis of the cyanohydrins. The diastereomeric cyanohydrins were characterized in part by a ^1H NMR spectrum which contained resonance peaks for the trimethylsilyl protons (δ 0.22), vinylic proton (δ 8.24), the dimethylamino protons (δ 3.18), and the ribosyl protons (δ 6.2–3.4).

The catalytic reduction of compound **23** was accomplished using special precautions to exclude all moisture from the catalyst and solvent (see the Experimental Section). Using an activated form of Raney nickel[12] under 30–35 atm of hydrogen, the trimethylsilyl cyanohydrins were cleanly reduced to afford the intermediate aminomethylene compounds. These compounds were not isolated but ring closed in situ to afford 7,8-dihydro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol as a mixture of the trimethylsilyl ether and the free alcohol (compounds **24** and **25**, respectively) (Scheme IV). This mixture was converted to **25** by a hydrolytic removal of the trimethylsilyl group from **24**.

Deprotection of the ribosyl moiety of **25**, yielded (8*R*)- and (8*S*)-7,8-dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo-[4,5-*d*][1,3]diazepin-8-ol (compounds **4** and **26**) as a mixture, in 64% yield. A programmed gradient elution of water–methanol through an ODS-3 reverse-phase column provided a clean separation of **4** and **26** (1:3, w/w). Compounds **4** and **26** are remarkably similar in their ^1H NMR,

Scheme IV



^{13}C NMR (see Table II), and UV spectra. Compound **4** has been tentatively assigned the *R* configuration at C-8 on the basis of the finding[24] that **4** is a tight-binding inhibitor of adenosine deaminase while **26** is a much weaker inhibitor. The *R* configuration at this carbon center is shared by similar tight-binding inhibitors of this particular enzyme.[1b,3]

Biological Evaluation

A mixture of the *R* and *S* diastereomers of 5,6-dihydro-1-β-D-ribofuranosyl-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol (compounds **3** and **15**) and the individual *R* and *S* diastereomers of 7,8-dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol (compounds **4** and **26**) were assayed as inhibitors of the enzyme adenosine deaminase. Of these, the compound **4** was found[25] to be a potent inhibitor of this enzyme based on a preliminary study. A full account of the pharmacokinetics and an evaluation of this series of compounds will appear subsequent to more extensive biological studies.

Summary

We have developed a short, facile synthetic sequence leading to a synthesis of the 4,5-dihydro-3*H*-1,3-diazepin-5-ol moiety using, as templates, several azolo amino aldehydes. The mild nature of the reaction conditions in each step of this scheme lends applicability of the method to most parent heterocycles and suitably protected nucleosides. The only major functional requirement is the assemblance of an aldehyde group in a position ortho to the amino group on the parent ring. Compounds with the

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necessary functional groups may be isolated with relative ease under carefully controlled acidic conditions.

A major finding which has emerged from these studies is that under specific conditions, the moisture-sensitive trimethylsilyl cyanohydrin nucleoside intermediates may be isolated and purified. These compounds may be chromatographed using anhydrous techniques that are described in the Experimental Section. Finally, we have developed a method for the catalytic reduction of the nitrile groups of these trimethylsilyl cyanohydrins under neutral conditions. Cobalt boride[14] or T-1 Raney nickel[12] catalysts under 20–35 atm of hydrogen effected a reduction of the nitrile groups with a subsequent in situ annulation.

We are currently applying this methodology to the synthesis of other closely related nucleosides.

Experimental Section

General Methods. Melting points are uncorrected. Column and flash chromatography was performed by using silica gel 60 (E. Merck, Darmstadt, West Germany; 70–230 mesh). Columns were packed with dry silica gel and then eluted with one void volume of the eluting solvent before a concentrated solution of the mixture in the eluting solvent was applied to the top of the column. Mixtures not readily soluble in the eluting solvent system were previously evaporated with a twofold (w/w) amount of silica gel 60, using an appropriate solvent. The mixture of compounds and silica gel was then applied as a dry powder to the top of the column. Thin-layer chromatography was performed by using prescored SilicAR 7GF Analtech (Newark, DE) silica gel (0.25-mm layer) plates. Nucleoside components were visualized with a short-wave (254 nm) UV lamp and further sprayed with a 10% aqueous solution of sulfuric acid to char these components upon heating on a hot plate. Low-pressure chromatography was performed using the silica gel 60 columns: Lobar (E. Merck), size B (25 × 310 mm), size C (37 × 440 mm); Michell-Miller (Ace Glass), size 22 × 300 mm, size 37 × 350 mm, size 22 × 130 mm precolumn. A fluid metering pump operating at 1.5–2.5 kg/cm^2 (20–35 lb/in.^{2}) was used to elute components. Flow rates of 5.0–10.0 mL/min were commonly used. An dual wavelength UV (254 and 280 nm) detector with a preparative flow cell was used to detect UV-absorbing components. Chromatography solvents include the following: A, ethyl acetate; B, ethyl acetate–methylene chloride (1:1); C, ethyl acetate–methylene chloride (3:2); D, ethyl acetate–benzene (9:1); E, ethyl acetate–water–1-propanol (4:2:1), upper layer; F, ethyl acetate–methanol (19:1); G, chloroform H, chloroform–methanol (40:1); I, acetonitrile–1 M aqueous ammonium chloride (4:1), upper layer.

Analytical HPLC determinations were performed on a Varian Micro Pak (MCH-10, 4 mm × 30 cm) ODS-1 reverse-phase column. Preparative separations were performed on a Whatman Partisil (M-20, 10 mm × 50 cm) ODS-3 reverse-phase column.

All solvents and reagents were reagent grade unless otherwise noted. Solvents were dried by distillation (tetrahydrofuran from $LiAlH_4$; pyridine from BaO; *p*-dioxane from Na°) or by storage over the appropriate activated Linde molecular sieves (*N*,*N*-dimethylformamide and acetonitrile, 4Å; acetone, dichloromethane, and benzene, 3Å). All evaporations were routinely conducted at 30–45 °C unless otherwise noted. Water aspirator vacuum (10–15 torr) was used to evaporate low boiling (bp < bp of ethanol) solvents and vacuum pump pressure (0.5–1.0 torr) was used to evaporate higher boiling solvents.

Hydrogenations at low hydrogen pressure (1–5 atm H_2) were carried out with a Parr hydrogenation apparatus and a 500-mL bottle at room temperature. Hydrogenations at high hydrogen pressure (8–35 atm H_2) were carried out with a stainless steel reaction vessel and glass sleeve. The contents of the sealed reaction vessel were heated by an oil bath and stirred with a magnetic stir bar and magnetic stirrer (with hot plate) combination.

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose and D-ribose were purchased from Pfanstiehl Laboratories of Waukegan, IL.

1-Deoxy-1-hydrazinyl-2,3-*O*-isopropylidene-D-ribose[10] (6). A solution of 2,3-*O*-isopropylidene-D-ribose[9] (29.2 g, 0.15 mol) in absolute methanol (200 mL) was treated with a solution of anhydrous hydrazine (40.3 g, 1.5 mol, 97% reagent grade) in absolute methanol (100 mL) dropwise over a period of 15 min and at room temperature. The nearly colorless solution was stirred at room temperature and under anhydrous conditions for 18 h. The solution was filtered, and the filtrate was evaporated in vacuo to afford a colorless syrup. The syrup was repeatedly coevaporated with absolute methanol (5 × 100 mL), and each portion was individually evaported in vacuo to remove the bulk of the excess hydrazine. The syrup was momentarily warmed (70 °C) under vacuum pump pressure (0.1 torr) and then kept at this pressure and room temperature for storage. The yield was 34.9 g (theoretical yield is 31.4 g), which includes some trapped hydrazine and water. This material was used without further purification for the next step: R_f 0.25, 0.10, solvent A; ^{1}H NMR (Me_2SO-d_6) δ 7.00 (d, 1, H-1, $J_{1,2'}$ = 3 Hz), 6.25 (br s, 3, $NHNH_2$, exchangeable), 1.30, 1.20 (2 s, 3, 3, isopropylidene) [identical with literature[10] values]. This spectrum also exhibited a large (water) signal at δ 4.9. This product deteriorates under continued storage and consequently *should be used within 48 h after preparation.*

5-Amino-4-cyano-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)pyrazole[10] (7). A solution of **6** (43.0 g, 0.21 mol) in absolute ethanol (300 mL) was purged with a steady stream of nitrogen for 30 min. A similarly purged solution of (ethoxymethylene)malononitrile (**5**, 27.8 g, 0.23 mol) in absolute ethanol (150 mL) was added dropwise to the rapidly stirred solution of **6** at room temperature during a 1-h period. The solution was stirred under nitrogen for an additional 30 min and then heated at reflux for 12 h. A single nucleoside product appeared on TLC as an UV-absorbing, charring (10% aqueous sulfuric acid spray) spot (R_f 0.55, solvent system D). The orange solution was cooled to room temperature, filtered, and evaporated in vacuo to yield a solid orange foam. This material was dissolved in ethyl acetate (100 mL) and then treated with silica gel (75 g). The mixture was evaporated to dryness in vacuo and the powder which resulted was applied to the top of a silica gel (500 g) column (6 × 30 cm, dry packed). The column was eluted with solvent system C (2.5 L), but the first fraction containing the nucleoside (fractions 33–44, 55 mL/fraction) were contaminated with an unidentified sugar fraction and were pooled separately. Fractions 45–70 containing the pure nucleoside product were pooled and then evaporated in vacuo to yield 12.0 g of a crisp white foam. Chromatography of the impure fractions on a similar column of silica gel (200 g), using solvent system C, yielded an additional 5.1 g of nucleoside **7**, for a total yield of 28.9%. The foams from both separations were triturated separately with cold anhydrous ether (10–20 mL) to yield amorphous solids, which were collected by filtration. These solids were combined and subsequently crystallized from boiling ether to afford 15.5 g of colorless plates: mp 116–117 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.72 (s, 1, H-3), 6.90 (m, 2, NH_2, exchangeable), 6.15 (s, 1, H-1′), 1.50, 1.30 (2 s, 3, 3, isopropylidene, Δδ = 12 Hz); UV λ_{max} [methanol] 288 nm ($\log_{10}\epsilon$ 2.75), 2.36 (4.02), 2.33 [pH 1] (4.03), 235 [pH 11] (4.05); IR ν_{max}^{KBr} 2220 cm^{-1} (CN). Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.43; H, 5.75; N, 19.99. Found: C, 51.20; H, 5.63; N, 19.98.

5-Amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-pyrazole-4-carboxaldehyde (8). Compound **7** (5.0 g, 17.7 mmol was dissolved in pyridine–acetic acid–water (50 mL, 1:1:1, v/v), and the solution was purged with a steady stream of nitrogen for 20 min. T-1 Raney nickel (1.5 g, weighed wet) was added to the solution and the mixture was shaken under hydrogen (45 psi) on a Parr hydrogenation appratus at room temperature for 10 h. The mixture was then filtered through packed Celite (15 g) on a 60-mL (4.5-cm internal diameter) sintered glass funnel, and the celite bed was promptly washed with water (100 mL) and ethanol (3 × 50 mL). The combined filtrates were evaporated in vacuo to afford a thick green syrup. This syrup was sequentially coevaporated with ethanol (3 × 50 mL) and toluene (4 × 50 mL), and the final suspension was evaporated to dryness in vacuo to yield a green residue. This residue was dissolved in ethanol (50 mL) and treated with silica gel (10 g) and the mixture evaporated in vacuo to afford a dark powder. The silica gel powder was applied to the top of a silica gel (30 g) column (3 × 4.5 cm) in a 60-mL sintered glass funnel. The aldehyde **8** was eluted from the column with solvent A (200 mL), and the eluates were evaporated to dryness in vacuo (water bath, 40 °C) to afford a light yellow syrup. This syrup was crystallized on trituration with dry diethyl ether

(10 mL) to yield 3.5 g (69.3%) of **8** as analytically pure yellow prisms: mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 9.65 (s, 1, CHO), 7.70 (s, 1, H-3), 6.10 (br m, 2, NH_2, exchangeable), 1.50, 1.30 (2 s, 3, 3, isopropylidene, $\Delta\delta$ = 12 Hz); UV λ_{max} [methanol] 284 nm ($\log_{10}$ ϵ 3.95), [pH 1] 284 (3.93), 236 (3.86) [pH 11] 284 (3.95), 237 (3.92), 222 (3.87). Anal. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.04; N, 14.83. Found: C, 51.04; H, 6.01; N, 14.67.

5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-pyrazole-4-carboxaldehyde (10). A solution of compound **8** (10.0 g, 35.5 mmol) in a mixture of methanol–water (150 mL, 2:1, v/v) was treated with DOWEX 50 × 4 (H^+) ion-exchange resin (8 mL, wet). Aqueous 1 N hydrochloric acid (20 mL) was added to this solution, and the mixture was stirred at room temperature for 48 h. During the course of the reaction, a yellow precipitate formed, corresponding to the deblocked aldehyde **20**. The solid material, consisting of the insoluble aldehyde and the spent resin, was collected by filtration and washed with cold absolute ethanol (30 mL). The material was then dried in a vacuum oven [35 °C (10 torr)] over P_2O_5 for 18 h. The resulting fluffy yellow material was suspended in anhydrous pyridine (100 mL), treated with acetic anhydride (15 mL), and then stirred under anhydrous conditions at room temperature for 12 h. The mixture was filtered through fluted filter paper onto crushed ice (100 mL), the resin bed was washed with chloroform (3 × 30 mL), and the combined filtrates were stirred at 0 °C for 20 min. The filtrates were extracted with chloroform (2 × 200 mL), and the combined chloroform extracts were successively washed with cold saturated aqueous sodium bicarbonate (3 × 50 mL), cold aqueous 1 N HCl (2 × 50 mL), and cold water (50 mL), dried over anhydrous magnesium sulfate (20 g), filtered, and then evaporated to dryness in vacuo to afford a thick yellow syrup. This syrup was repeatedly coevaporated with toluene (3 × 50 mL) in vacuo to afford a light yellow amorphous solid. This solid was triturated with warm ethanol (40 °C, 30 mL), the mixture was cooled in an ice bath, and the solid was collected by filtration. The filter cake was washed with cold ethanol (20 mL), and air-dried to afford 8.0 g (61.4%) of compound **10** as a light yellow solid: mp 134–135 °C; ^{1}H NMR ($CDCl_3$) δ 9.70 (s, 1, CHO), 7.70 (s, 1, H-3), 6.25 (m, 2, NH_2, exchangeable), 5.85 (s, 1, H-1′), 2.20, 2.10 (2 s, 6, 3, $COCH_3$); UV λ_{max} [methanol] 264 nm ($\log_{10}$ ϵ 2.45), 286 (3.94), [pH 1] 285 (3.94), 236 (3.87), [pH 11] 284 (3.89), 236 (3.87). Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 45.78; H, 5.18; N, 11.38. Found: C, 45.93; H, 5.25; N, 11.42.

5-[((Dimethylamino)methylene)amino]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole-4-carboxaldehyde (11). Compound **10** (7.61 g, 20.5 mmol) was dissolved in anhydrous methylene chloride (30 mL), and the solution was treated with *N,N*-dimethylformamide dimethyl acetal (Aldrich Chemical Co., DMFDMA, 6.8 mL, 51.3 mmol) under anhydrous conditions and at room temperature. The mixture was stirred for 2 h at room temperature and then evaporated to dryness in vacuo to yield a brilliant yellow oil. The oil was placed under vacuum pump pressure (0.1 torr) for 3 h and then dissolved in absolute ethanol (50 mL). The solution was allowed to stand at 5 °C for 36 h, and the crystalline material which had separated from solution was collected by filtration and washed with cold ethanol (20 mL) to afford 5.6 g (66.0%) of material, mp 110–112 °C. This material contains a large predominance of compound **11** (R_f 0.55, solvent A) over the [(methoxy)methylene]amino aldehyde[13] impurity (R_f 0.61, solvent A): ^{1}H NMR ($CDCl_3$) δ 9.68 (s, 1, CHO), 8.60 (s, 1, CH=N), 7.98 (s, 1, H-3), 6.20 (m, 1, H-1′), 3.15, 3.03 (2 s, 3, 3, *N,N*-dimethyl), 2.10, 2.00 (2 s, 6, 3, $COCH_3$); UV λ_{max} [methanol] 322 nm ($\log_{10}$ ϵ 4.03), 234 (4.57), [pH 1] 217 (4.45), [pH 11] 232 (4.79). Anal. Calcd for $C_{18}H_{23}N_4O_8$: C, 50.94; H, 5.69; N, 13.20. Found: C, 50.69; H, 5.69; N, 13.20. The ^{1}H NMR spectrum of the mixture also exhibited a signal which was just discernible for the methoxy protons of the minor product[13] at δ 4.0. This impurity did not significantly alter the elemental analysis as calculated for the major component, compound **11**. Routinely, these mixtures were not separated but used as such for the next synthetic step.

5-[((Dimethylamino)methylene)amino]-4-[cyano(trimethylsiloxy)methyl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrazole (12). A scrupulously dried 100-mL round-bottom flask containing the nucleoside **11**[13] (5.22 g, 12.3 mmol) was sealed with a septum and flushed for 20 min with nitrogen, using a dual set of needles. Trimethylsilyl cyanide[21] (Me_3SiCN, 7.8 mL, 51.5 mmol) was added via a syringe, keeping rigorous anhydrous conditions. The mixture was warmed slightly to effect dissolution and then cooled to 5 °C in an ice bath. A solution of BF_3·OEt_2 in ether (1 mL, 1:10, v/v) was added to the frozen mixture via a syringe, and the flask was then allowed to slowly thaw by a removal of the ice bath. Subsequently, the reaction was allowed to warm to room temperature and then stirred for 14 h under a positive pressure of nitrogen. The reaction was cooled to 5 °C, an additional 1 mL of dilute BF_3·OEt_2 was added, and the reaction was stirred at room temperature for an additional 6 h. The very dark solution was evaporated to dryness in vacuo, and the residue was kept under vacuum pump pressure (0.1 torr) for 3 h. The residue which solidified upon standing under vacuum was triturated with cold absolute ethanol (20 mL), the solid was collected by filtration, and the filter cake was washed with an additional portion of cold absolute ethanol (10 mL). The solid was then dried in vacuo at room temperature to yield 2.75 g of an off-white powder, mp 186–188 °C. The mother liquors were immediately evaporated to dryness in vacuo. The resulting syrup was dissolved in ethyl acetate (5 mL) and this solution chromatographed on a Michell-Miller column (300 mm length) and similar precolumn (100-mm length). Both columns had been previously treated with a solution of 2,2-dimethoxypropane in ethyl acetate (200 mL, 3%, v/v) to remove all traces of water. Low-pressure chromatography with solvent B (650 mL) as eluent and maintaining a flow rate of 5 mL/min [the progress of the separation was monitored with an Altex UV detector (254, 280 nm)] was performed using TLC for analysis of each fraction. A total of three 150-mL fractions were collected, the second of which contained all of the product with R_f 0.65, solvent A. This fraction was evaporated in vacuo to afford an additional 0.68 g of compound **12** as a thick syrup. The combined yield of products was 53%. ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1, CH=N), 7.35 (s, 1, H-3), 6.20 (d, s, H-1′, $J_{1',2'}$ = 2.9 Hz), 3.10 (s, 6, *N,N*-dimethyl), 2.10 (s, 9, $COCH_3$), 0.24 (s, 9, trimethylsilyl); UV λ_{max} [methanol] 273 nm ($\log_{10}$ ϵ 4.04). Anal. Calcd for $C_{22}H_{35}N_5O_8Si$: C, 50.46; H, 6.34; N, 13.38. Found: C, 50.53; H, 6.50; N, 13.47. The methoxy protons of the (methoxy)methylene)amino product were just discernible in the ^{1}H NMR spectrum at δ 4.0. This impurity did not significantly alter the elemental analysis as calculated for the major component, compound **12**.

(4*R*)- and (4*S*)-5,6-Dihydro-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol (14). A 500-mL Parr stainless steel reaction vessel fitted with a scrupulously dried glass sleeve and containing a solution of the trimethylsilyl cyanohydrins **12** (1.0 g, 1.90 mmol) in anhydrous *p*-dioxane (40 mL) was purged with a steady stream of nitrogen for 20 min. Raney nickel[12] (2.0 g, weighed wet) was washed with *p*-dioxane (4 × 10 mL) by decantation, and the final suspension was added to the solution of nucleoside **12**. The stainless steel vessel was sealed and then filled to 400 psi with hydrogen. The equilibrium pressure of 460 psi of hydrogen and 100 °C was maintained for 18 h. The reduction mixture was filtered through packed Celite (12 g) on a 60-mL (4.5-cm internal diameter) sintered glass funnel, and the catalyst and Celite bed were promptly washed with warm ethanol (60 mL). The combined filtrates were evaporated in vacuo to yield a colorless foam, which was dissolved in methanol (15 mL) and treated with aqueous 0.1 N acetic acid (2 mL). The mixture was then warmed to 50 °C in a water bath while being vigorously stirred for 30 min. The mixture was cooled, evaporated in vacuo and then successively coevaporated with ethanol (2 × 20 mL) and toluene (2 × 20 mL) in vacuo to yield a colorless residue. The residue was triturated with cold ethyl acetate (10 mL), and the precipitate was collected by filtration. The filter cake was washed with cold ethyl acetate (5 mL) and then dried in a vacuum oven [50 °C, (10 torr)] for 12 h to afford 380 mg (47%) of compound **14** as a amorphous white powder, mp 209–210 °C. This material is a mixture of *R* and *S* diastereomers at C-4, which is reflected in the duplicate ^{1}H NMR signals for the H-3, H-7, and $COCH_3$ protons: ^{1}H NMR (360 MHz, Me_2SO-d_6) δ 7.40, 7.41 (2 s, 1, H-3), 6.58, 6.42 (2 d, 1, H-7, $J_{7_A,N-H}$ = 4 Hz, $J_{7_B,N-H}$ = 4 Hz), 6.28 (br s, 1, H-1′), 3.43–3.26 (m, 2, H-5), 2.10–2.00 (6 s, 9, $COCH_3$); UV λ_{max} [methanol] 279 nm ($\log_{10}$ ϵ 3.99), [pH 1] 264 (3.87), 234 (3.74), [pH 11] 277 (4.07), 235 (3.83). Anal. Calcd for $C_{17}H_{22}N_4O_8$: C, 49.76; H, 5.40; N, 13.65. Found: C, 49.56; H, 5.52; N, 13.50.

(4*R*)- and (4*S*)-5,6-Dihydro-1-β-D-ribofuranosyl-4*H*-pyrazolo[3,4-*d*][1,3]diazepin-4-ol (3 and 15). A mixture of the *R* and *S* diastereomers of **14** (0.15 g, 0.36 mmol) in methanolic sodium methoxide (5.75 mL, 0.13 N) was stirred at room temperature for 1 h. The pH of the solution was adjusted to 7 with DOWEX 50 × 4 (H^+) ion-exchange resin, and the mixture was stirred at room temperature for an additional 10 min. The solution was filtered, the resin bed was washed with additional methanol (10 mL), andd the combined filtrates were evaporated to dryness in vacuo to yield a colorless gum. The gum was crystallized from warm (50 °C) ethanol (2 mL), and the solid was collected by filtration. This material was dried in a vacuum oven [50 °C (10 torr)] for 12 h to afford a mixture (90 mg, 86%) of compounds **3** and **15** as a white amorphous powder: mp 185–187 °C; ^{1}H NMR (360 MHz, Me_2SO-d_6) δ 7.82 (br s, 1 NH, exchangeable), 7.28 (s, 1, H-3) 6.97 (d, 1, H-7, $J_{7,6}$ = 2.8 Hz), 6.03 (d, 1, H-1′, $J_{1,2'}$ = 3.9 Hz), 4.66 (m, 1, H-4), 3.30–3.10 (m, 2, H-5); UV λ_{max} [methanol] 278 nm ($\log_{10}\epsilon$ 3.95), 241 (3.60), [pH 1] 263 (3.82), 235 (3.77), [pH 11] 277 (3.97), 238 (3.66). Anal. Calcd for $C_{11}H_{16}N_4O_5$: C, 46.48; H, 5.67; N, 19.71. Found: C, 46.24; H, 5.78; N, 19.47. For data on ^{13}C NMR see Table I. HPLC chromatography of this mixture on an ODS-3 packed column, using several programmed gradient elutions of methanol–water, did not resolve the *R* and *S* mixture contained in this product. A full description of these techniques is given in the Experimental Section for compounds **4** and **26**.

5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxamide (19). *N*,*N*-Dimethylformamide (300 mL) was added to a cold (0 °C) solution of potassium hydroxide (6.40 g, 0.11 mol) in water (50 mL) and the solution stirred at this temperature for 10 min. Cyanoacetamide (9.53 g, 0.11 mol) was added to this solution, and the mixture was then stirred at 0 °C until all of the solid material had dissolved. To this solution was added 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide[16] (**17**, 36.8 g, 76 mmol) in one portion, and the reaction was stirred at −5 °C for 14 h. The amber solution was evaporated in vacuo (water bath 80 °C) to afford an orange semisolid, which was successively coevaporated with absolute ethanol (2 × 50 mL) and toluene (3 × 50 mL) in vacuo to afford a thick orange gum. The gum was dissolved in anhydrous methanol (150 mL), methanolic sodium methoxide was added (1 N, 25 mL), and the solution was stirred at room temperature under anhydrous conditions for 6 h. The amber solution was treated with DOWEX 50 × 4 (H^+) ion-exchange resin (ca. 35 mL wet resin) to adjust the pH to 6. The solution was filtered, the resin bed was washed with an additional 50 mL of methanol, and the combined filtrates were evaporated to dryness in vacuo (water bath 80 °C) to yield an orange gum. The gum was repeatedly triturated with ethyl acetate (6 × 50 mL), and each portion was in turn decanted until the gum solidified to a tan amorphous solid. The solid was suspended in anhydrous pyridine (120 mL) and acetic anhydride (50 mL), stirred under anhydrous conditions at room temperature for 18 h, and then filtered through a shallow bed of packed Celite (15 g) in a 250-mL (6.5-cm internal diameter) sintered glass funnel. The Celite bed was washed with fresh pyridine (50 mL), and the combined filtrates were evaporated to dryness in vacuo to yield a brown gum. The gum was treated with a solution of ethyl acetate–methanol (50 mL; 1:1, v/v) and stirred at room temperature for a few minutes. The mixture was further cooled in an ice bath, and the material which had crystallized after 30 min at this temperature was collected by filtration. The crystalline material was washed with cold methanol (2 × 50 mL) and air-dried. The off-white crude product (15.5 g, 53% yield, mp 168–170 °C) was chromatographically pure (R_f 0.42, solvent A). Analytically pure material was obtained by recrystallization of this product from absolute ethanol (400 mL) to yield white needles, 11.8 g (40.8%), mp 175–176 °C. A second recrystallization did not alter the melting point of this product: ^{1}H NMR (Me_2SO-d_6) δ 7.55 (m, 2, $CONH_2$, exchangeable), 6.70 (br s, 2, NH_2, exchangeable), 6.25 (d, 1, H-1′, $J_{1',2'}$ = 3 Hz), 2.10, 1.97 (2 s, 6, 3, $COCH_3$); UV λ_{max} [methanol] 259 nm), ($\log_{10}\epsilon$ 3.96), 236 (4.02), [pH 1] 261 (4.02), 233 (4.11), [pH 11] 252 (3.93), 236 (3.89). Anal. Calcd for $C_{14}H_{19}N_5O_8$: C, 43.64; H, 4.96; N, 18.17. Found: C, 43.58; H, 4.73; N, 18.35. A small sample of this material was dissolved in excess methanolic ammonia (saturated at 0 °C) and the solution stirred at room temperature for 8 h. The solvent was removed in vacuo and the resulting residue was crystallized from methanol to obtain a product which was identical (mp, UV, ^{1}H NMR) with the nucleoside described in ref 15 as 5-amino-1-β-D-ribofuranosyl-*v*-triazole-4-carboxamide, (**18**).

5-Amino-4-cyano-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl-*v*-triazole (20). A suspension of the nucleoside **19** (10 g, 26 mmol) in anhydrous chloroform (200 mL) and triethylamine (40 mL) was treated dropwise with a solution of phosphorus oxychloride (5.4 mL, 52 mmol) in 50 mL of anhydrous chloroform over a period of 10 min. The heat generated from this addition caused all solid material to dissolve (final temperature, 45 °C), and the resulting dark solution was stirred at 40 °C for 12 h. The solution was poured onto crushed ice (150 mL) and stirred (cold) for 20 min. The organic layer was separated and washed successively with cold water (50 mL), cold aqueous 0.1 N HCl (2 × 50 mL), and cold water (50 mL). The chloroform was dried over anhydrous magnesium sulfate (15 g) and filtered and the filtrate evaporated in vacuo to afford a brown foam. This form was dissolved in ethyl acetate (50 mL), and the solution was applied to the top of a shallow bed (6.5 × 2 cm) of silica gel (40 g) in a 250-mL sintered glass funnel. The compound **20** was eluted with solvent A (350 mL). The eluates were evaporated to dryness in vacuo to yield an orange foam, 6.5 g (68%): R_f 0.78, solvent A; ^{1}H NMR (Me_2SO-d_6) δ 7.48 (m, 2, NH_2, exchangeable), 6.28 (d, 1, H-1′, $J_{1',2'}$ = 3 Hz), 2.10, 1.95 (2 s, 6, 3, $COCH_3$); IR (thin film) δ_{max} 2220 cm^{-1} (CN); UV λ_{max} [methanol] 255 nm ($\log_{10}\epsilon$ 3.75), 2.30 (3.94), [Ph 1] 255 (3.70), 228 (3.90), [pH 11] 254 (3.80), 233 (3.89). Anal. Calcd for $C_{14}H_{17}N_5O_7{\cdot}0.5\ H_2O$: C, 44.58; H, 5.05; N, 18.27. Found: C, 44.58; H, 4.82; N, 18.61.

5-[((Dimethylamino)methylene)amino]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxaldehyde[13] (22). The nucleoside **20** (3.60 g, 9.57 mmol) was dissolved in a mixture of pyridine–acetic acid–water (100 mL; 2:1:1, v/v) in a Parr hydrogenation bottle (500 mL). The solution was purged with a steady stream of nitrogen for 20 min and then treated with Raney nickel[12] (3.0 g, weighed wet). The mixture was shaken under hydrogen (45 psi) on a Parr hydrogenator for a total of 3 h. The reaction mixture was filtered through packed Celite (18 g) on a 60-mL (4.5-cm internal diameter) sintered glass funnel, and the catalyst bed was promptly washed with absolute ethanol (50 mL). The combined filtrates were evaporated to dryness in vacuo (water bath ~50 °C) to yield a dark brown syrup. This syrup was successively coevaporated with toluene (3 × 50 mL) and absolute ethanol (3 × 50 mL) in vacuo to yield a dark brown gum. [Alternatively, the dark brown syrup obtained by evaporation of the pyridine–acetic acid–water was dissolved in cold ethyl acetate (250 mL) and filtered. The filtrate was then washed successively with cold water (50 mL), cold saturated aqueous sodium bicarbonate solution (2 × 50 mL), cold aqueous 1 N HCl (2 × 50 mL), and cold water (50 mL). The organic layer was dried over anhydrouns magnesium sulfate (25 g), filtered, and evaporated in vacuo to afford a thick brown gum.] The gum obtained from either method, which contained the crude aldehyde intermediate **21**, was immediately dissolved in anhydrous *N*,*N*-dimethylformamide (30 mL) and treated with *N*,*N*-dimethylformamide dimethyl acetal (2.5 mL, 19 mmol). The reaction mixture was stirred at room temperature for 3 h under anhydrous conditions and then evaporated under vacuum pump pressure (water bath 70 °C) to yield a dark brown gum. The gum was dissolved in ethyl acetate (50 mL) and treated with silica gel (6 g) and the mixture evaporated to dryness in vacuo. The granular material was applied to the top of a shallow bed of silica gel (18 g) (2 × 4.5 cm) in a 60-mL sintered glass funnel. Elution of this column with solvent A (250 mL) and evaporation of the eluates in vacuo afforded 2,4 g (56%) of the 5-[((dimethylamino)methylene)amino]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxaldehyde[13] (**22**) as a yellow foam: R_f 0.57, solvent A; ^{1}H NMR ($CDCl_3$) δ 10.02 (s, 1, CHO), 9.24 (br s, 1, CH=N), 6.24 (d, 1, H-1′, $J_{1',2'}$ = 2.5 Hz), 3.14, 3.08 (2 s, 3, 3, *N*,*N*-dimethyl), 2.08 (m, 9, $COCH_3$) [and a trace of ethyl acetate at δ 2.0, 1.6, and 4.0]; UV λ_{max} [methanol] 315 nm ($\log_{10}\epsilon$ 3.86), 261 (3.92), 224 (4.21), [pH 1] 312 (3.79), 263 (3.93), [pH 11] 311 (3.81), 264 (3.94), 229 (4.21). This foam contained a small amount of ethyl acetate as a trapped contaminant and this was reflected in the elemental analysis. Anal. Calcd for $C_{17}H_{23}N_5O_8{\cdot}0.25\ CH_3CO_2C_2H_5$: C, 48.58; H, 5.40; N, 15.58. Found: C, 48.32; H, 5.65; N, 15.65. Evidence for the presence of the (methoxymethylene)amino minor product[13] in the mixture

was seen as a small singlet for the methoxy protons in the ^1H NMR spectrum at δ 4.20.

5-[((Dimethylamino)methylene)amino]-4-[cyano(trimethylsiloxy)methyl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-*v*-triazole[13] (23). A scrupulously dried 100-mL round-bottom flask containing the nucleoside **22** (4.73 g, 6.57 mmol) was sealed with a septum and flushed with nitrogen for 20 min by using dual set of needles. Trimethylsilyl cyanide[21] (Me_3SiCN, 4.3 mL, 34 mmol) was added via a syringe, keeping rigorous anhydrous conditions. The mixture was warmed slightly to effect dissolution and then cooled to 5 °C in an ice bath. A solution of $BF_3{\cdot}OEt_2$ in ether (1 mL; 1:10, v/v) was added to the frozen mixture via a syringe, and then the mixture was allowed to thaw by a removal of the ice bath. Subsequently, the reaction mixture was allowed to warm to room temperature and then stirred under nitrogen for 14 h. The reaction mixture was cooled to 5 °C, and an additional 1 mL of dilute $BF_3{\cdot}OEt_2$ was added. The very dark solution was stirred at room temperature for an additional 6 h and then evaporated to dryness in vacuo to afford a dark brown residue. The residue was dissolved in solvent system B (8 mL), and this solution was chromatographed on a Michell-Miller column (300-mm length) and precolumn (100-mm length). Both columns had been previously treated with a solution of 2,2-dimethoxypropane in ethyl acetate (200 mL, 3%, v/v) to remove all traces of water. A low-pressure chromatography apparatus was used with solvent system B (650 mL) as eluent and maintaining a flow rate of 5 mL/min. The progress of the separation was monitored with an Altex UV detector (254 and 280 nm) and TLC analysis of each fraction. Three fractions were collected (200 mL/fraction); the second fraction contained the product with R_f 0.78 (solvent system B). This fraction was evaporated in vacuo to afford 2.83 g (48%) of compound **23** as a light yellow syrup: ^1H NMR ($CDCl_3$) δ 8.24 (br s, 1, CH=N), 6.30 (m, 1, H-1′), 3.18 (br s, 6, *N,N*-dimethyl), 2.3–2.1 (m, 9, $COCH_3$); UV λ_{max} [methanol] 265 nm ($\log_{10}\epsilon$ 3.82). Anal. Calcd for $C_{21}H_{36}N_6O_8Si$: C, 48.08; H, 6.14; N, 16.02. Found: C, 48.11; H, 6.03; N, 15.98. The methoxy protons of the minor component of this mixture[13] were just discernible in the ^1H NMR spectrum at δ 4.02. This impurity did not significantly alter the elemental analysis as calculated for the major component, compound **23**.

(8*R*)- and (8*S*)-7,8-Dihydro-3-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol (25). A 500-mL Parr stainless steel reaction vessel fitted with a scrupulously dried glass sleeve and containing a solution of the nucleoside **23**[13] (0.22 g, 0.42 mmol) in ahydrous *p*-dioxane (40 mL) was purged with a steady stream of dry nitrogen for 20 min. Raney nickel[12] (0.30 g weighed wet) was washed with anhydrous *p*-dioxane (4 × 10 mL) by decantation. The final suspension was added to the purged solution of the nucleoside **23**, and the vessel was sealed. The Parr stainless steel vessel was charged with 450 psi of hydrogen and then heated to 110 °C in an oil bath. The equilibrium hydrogen pressure of 510 psi was maintained for 12 h. After this time, the reduction mixture was filtered through packed Celite (6 g) on a 60-mL (4.5-cm internal diameter) sintered glass funnel, and the catalyst and Celite bed were promptly washed with absolute ethanol (50 mL). The combined filtrates were evaporated in vacuo to afford a clear, colorless syrup. This syrup exhibited two major products on TLC corresponding to the trimethylsilyl ether **24** (R_f 0.50, solvent system B), and two minor products corresponding to the *R* and *S* isomers of **25** (R_f 0.10–0.15, solvent system B). The syrup was dissolved in methanol (10 mL), cooled to 0 °C, and treated with cold aqueous acetic acid (2 mL, 20%, v/v). The mixture was stirred at 0 °C for 3 h, and then the solvents were evaporated in vacuo (water bath, 40 °C) to yield a thick syrup. The syrup was successively coevaporated with absolute ethanol (2 × 20 mL) and toluene (2 × 20 mL) in vacuo. The resulting residue was triturated with cold ethyl acetate (5 mL) to yield a white precipitate, which was collected by filtration. Trituration of this product with a second portion of ethyl acetate (5 mL) yielded 68 mg (39.4%) of **25** as a white powder: mp 162–165 °C; ^1H NMR (360 MHz, Me_2SO-d_6) δ 8.28 (m, 1, NH, exchangeable), 7.18 (d, 1, H-5, $J_{5,6}$ = 4 Hz), 6.20 (d, 1, H-1′, $J_{1',2'}$ = 3.5 Hz), 5.56 (m, 1, OH, exchangeable), 4.06 (m, 1, H-8), 3.21–3.31 (2 m, 2, H-7_A, H-7_B), 2.06–1.96 (m, 9, $COCH_3$); UV λ_{max} [methanol] 279 nm ($\log_{10}\epsilon$ 4.02), [pH 1] 261 (391), [pH 11] 277 (4.09). Anal. Calcd for $C_{16}H_{21}N_5O_8$: C, 46.72; H, 5.14; N, 17.03. Found C, 46.45; H, 5.19; N, 16.77.

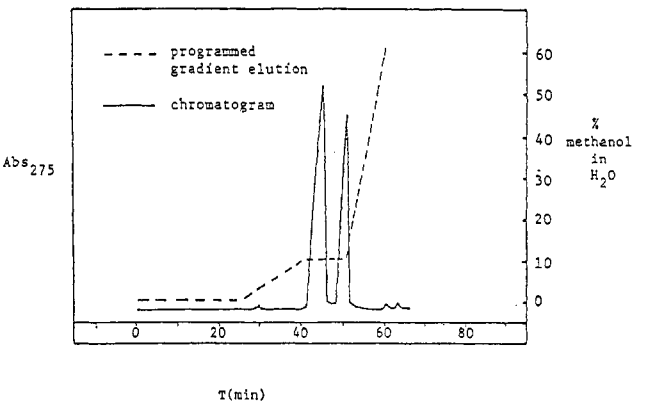

Figure 1. HPLC chromatogram of compounds 4 and 26.

Table III. ^1H NMR (Me_2SO-d_6, 360 MHz) for Compounds 4 and 26.

H	chemical shifts[a] 4	26
H-5	7.13 (d, $J_{5,NH}$ = 3.0 Hz)[b]	7.13 (d, $J_{5,NH}$ = 3.1 Hz)[b]
H-7_A,7_B	3.19 (d), 3.30 (dd, $J_{7_a,7_b}$ = 12.6 Hz, $J_{7_a,8}$ = 4.4 Hz, $J_{7_b,8}$ < 1 Hz)	3.19 (d), 3.31 (dd, $J_{7_a,7_b}$ = 12.8 Hz, $J_{7_a,8}$ = 4.4 Hz, $J_{7_b,8}$ < 1 Hz)
H-8	3.89 (m, J_{width} ~ 4.5 Hz)	3.89 (m, J_{width} ~ 4.6 Hz)
H-1′	5.93 (d, $J_{1',2'}$ = 4.4 Hz)	5.94 (m, $J_{1',2'}$ = 4.5 Hz)
H-2′	5.40 (m, $J_{2',3'}$ < 1 Hz)	5.05 (m, $J_{2',3'}$ < 1 Hz)
H-3′	4.54 (q, $J_{3',4'}$ = 4.6 Hz)	4.54 (t, $J_{3',4'}$ = 4.7 Hz)
H-4′	4.19 (q, $J_{4',5'}$ = 5.1 Hz)	4.18 (5, $J_{4',5'}$ = 4.8 Hz)
H-5′	3.55 (m), 3.42 (m, $J_{5a',5b'}$ = 11.9 Hz)	3.55 (m), 3.40 (m, $J_{5a',5b'}$ = 10.8)
NH	8.2 (m)[c]	8.1 (m)[c]

[a] Chemical Shifts are expressed in ppm downfield from Me_4Si. Multiplicities: d, doublet, dd, doublet of doublets; m, multiplet; q, quartet. Concentrations, 3 mg/0.3 mL. Temperature, ca. 25 °C. [b] Signal collapses to a singlet upon exchange of NH with D_2O. [c] Exchanges with D_2O.

(8*R*)- and (8*S*)-7,8-Dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol (4 and 26). The mixture of *R* and *S* isomers **25** (0.10 g, 0.24 mmol) was dissolved in a saturated solution of ammonia in anhydrous methanol (20 mL, saturated at 0 °C) in a 100-mL glass pressure bottle. The reaction mixture was stirred at room temperature for 18 h, and then the solvent was then evaporated to dryness in vacuo to yield a thick residue. The residue was triturated with chloroform (2 × 15 mL), and the gum which resulted was placed under vacuum pump pressure for 1 h. The residue was dissolved in warm ethanol (50 °C, 3 mL) and then stored at 5 °C for 18 h. The crystalline material was collected by filtration, washed with cold ethanol (1 mL), and dried in a vacuum oven [50 °C (0.1 torr)] for 3 h to afford 45 mg (64%) of a mixture of **4** and **26** as a white powder: R_f 0.29, solvent system E; mp 185–190 °C (sinters 180 °C); ^1H NMR (360 MHz, Me_2SO-d_6) δ 8.18 (br s, 1, NH, exchangeable 7.13 (d, 1, H-5, $J_{5,6}$ = 5.0 Hz), 5.94 (d, 1, H-1′, $J_{1',2'}$ = 5.0 Hz), 4.93 (t, 0.75, c-8OH, exchangeable, isomer A), 4.87 (t, 0.25, C(8)-OH, exchangeable, isomer B), 3.89 (m, 1, H-8), 3.35–3.15 (m, 2, H-7_A, H-7_B); UV λ_{max} [methanol] 277 nm ($\log_{10}\epsilon$ 4.00), [pH 1] 260 (3.92), [pH 11] 275 (4.08). Anal. Calcd for $C_{10}H_{15}N_5O_5$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.23; H, 5.47; N, 24.72. For ^{13}C NMR data, refer to Table II.

HPLC Separation of the Mixture of *R* and *S* Diastereomers of 7,8-Dihydro-3-β-D-ribofuranosyl-6*H*-*v*-triazolo[4,5-*d*][1,3]diazepin-8-ol (4 and 26). The mixture of compounds **4** and **26** (0.15 g, 0.53 mmol) was dissolved in water (0.5 mL, purified through a four-bowl Millipore Milli-Q system, catalog No. ZD2011574). This solution was chromatographed (two injections) on a Whatman Partisil M-20 (10 mm × 50 cm) ODS-3 reverse-phase silica gel column while maintaining a flow rate of 10 mL/min. A gradient elution of water–methanol (Burdick and Jackson, spectrograde quality) programmed by a Varian Vista 54 Series liquid chromatograph and Varian CDS 401 data station coupled to a Varian UV 50 variable wavelength detector (at 275

nm) provided a separation of compounds 4 and 26 (see Figure 1).

Two fractions were collected, centered at times t_A = 45.5 min and t_B = 51.8 min, corresponding to isomers A and B, respectively. These fractions were lyophilized to obtain diastereomer A (100 mg) as an amorphous glass and diasteromer B (33 mg) as a white powder. Isomer A has been tentatively assigned the *S* configuration (26) at C-8 and isomer B and the *R* configuration (4). These assignments have been made on the relative inhibitory activities[22] against adenosine deaminase of A and B. Isomer A (amorphous glass): k' (HPLC)^{23} = 3.14; $[\alpha]^{23}_D$ −29.4° (*c* 2.18, H_2O); UV λ_{max} [methanol] 277 nm ($\log_{10} \epsilon$ 3.90), [pH 1] 260 (3.78), [pH 11] 276 (3.96). Isomer B: mp 210 °C, dec; k' (HPLC)^{23} = 3.71; $[\alpha]^{23}_D$ −79.70 (*c* 1.33, H_2O); UV λ_{max} [methanol] 278 nm ($\log_{10} \epsilon$ 3.88), [pH 1] 260 (3.88), [pH 11] 277 (4.05). For ^{1}H NMR data, see Table III. For ^{13}C NMR data see Table II.

Acknowledgment. This investigation was supported by Grant CA-28381, by the National Cancer Institute, DHEW, and in part by the Filariasis Working Group of the World Bak/UNDP/WHO Special Program for Research and Training in Tropical Diseases (I.D. 800134 and 840398).

Registry No. 3, 88970-13-2; 4, 98720-84-4; 5, 123-06-8; 6, 55781-00-5; 7, 55726-09-5; 8, 99249-11-3; 9, 99249-12-4; 10, 99249-13-5; 11, 99249-14-6; 12 (isomer 1), 99249-15-7; 12 (isomer 2), 99249-16-8; 14 (isomer 1), 99249-18-0; 14 (isomer 2), 99249-17-9; 15, 88970-12-1; 17, 7408-41-5; 18, 38874-49-6; 19, 99249-19-1; 20, 99249-20-4; 21, 99249-22-6; 22, 99249-21-5; 23 (isomer 1), 99267-48-8; 23 (isomer 2), 99267-49-9; 24 (isomer 1), 99249-23-7; 24 (isomer 2), 99249-24-8; 25 (isomer 1), 99249-25-9; 25 (isomer 2), 99249-26-0; 26, 99249-27-1; 2,3-*O*-isopropylidene-D-ribose, 13199-25-2; *N*,*N*-dimethylformamide, 4637-24-5; trimethylsilyl cyanide, 7677-24-9; cyanoacetamide, 107-91-5.

A Novel Three-Step Synthesis of a Pyrrolo[3,2-*d*]pyrimidine C-Nucleoside[1]

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Received February 15, 1985

The phosphorus ylide, [(2,4-dimethoxy-5-nitropyrimidin-6-yl)methyl]triphenylphosphorane (10) was synthesized in two steps from 6-(bromomethyl)-2,4-dimethoxy-5-nitropyrimidine (8). Compound 10 was condensed with 2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-D-ribofuranose (1) to form the anomeric pair of protected homo-C-nucleosides, 2,4-dimethoxy-5-nitro-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl)-methyl]pyrimidine (11) and 2,4-dimethoxy-5-nitro-6-*C*-[(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)methyl]pyrimidine (12). Compound 10 also reacted with 2,3-*O*-isopropylidene-D-ribofuranose (6) to form the nontritylated compounds 2,4-dimethoxy-6-*C*-[(2,3-*O*-isopropylidene-β- and -α-D-ribofuranosyl)-methyl]-5-nitropyrimidines (14 and 15). Acid treatment of 11 or 12 afforded the deblocked homo-C-nucleoside 6-*C*-[(β-D-ribofuranosyl)methyl]-5-nitropyrimidine-2,4-dione (16), while reduction of 11 produced the 5-amino-pyrimidine homo-C-nucleoside 17 in quantitative yield. 6-(Cyanomethyl)-2,4-dimethoxy-5-nitropyrimidine (18) reacted with 2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-D-ribofuranosyl chloride (19) to form the *R* and *S* diastereomers of 2-(2,4-dimethoxy-5-nitropyrimidin-6-yl)-2-(2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-α-D-ribofuranosyl)acetonitrile (20a and 20b). The major component (20a) was reduced catalytically to the pyrrolo[3,2-*d*]pyrimidine 21. Under mild acid treatment 21 was deblocked to form 2,4-dimethoxy-7-*C*-(α-D-ribofuranosyl)pyrrolo[3,2-*d*]pyrimidine (22). Strong, aqueous acid treatment of 21 afforded a 1/1 mixture of 22 and the β anomer 23.

Homo-C-nucleosides are a growing class of nucleosides[2-6] which are composed structurally of a sugar portion and an aglycon linked via a methylene bridge between the anomeric carbon atom in the sugar and a carbon atom in the aglycon. Viewed as synthons, it was thought that these homo-C-nucleosides should provide an attractive alternative synthetic route to the preparation of bicyclic C-nucleosides with potential biological activity. The present study explores the applicability of this synthetic strategy, and we now report two new procedures for the formation of 6-*C*-[(1-D-ribofuranosyl)methyl]pyrimidine homo-C-nucleosides, one of which leads to the three-step synthesis of a novel pyrrolo[3,2-*d*]pyrimidine C-nucleoside which is an analogue of the 9-deazapurine C-nucleoside, 9-deazaxanthosine.[7]

Results and Discussion

The condensation of stabilized ylides such as (carboethoxymethylene)triphenylphosphorane (2) or (cyanomethylene)triphenylphosphorane (3) with the sugar 1 has afforded[8] the versatile C-nucleoside precursors ethyl 2-[2,3-*O*-isopropylidene-5-*O*-(triphenylmethyl)-β-D-ribofuranosyl]acetate (4) and 2-[2,3-*O*-isopropylidene-5-*O*-

(1) This study was supported in part by funds from the National Institutes of Health (Training Grant 5-T32-GM 07767) and the American Cancer Society (Grant CH-133).

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