The synthesis of 8-aza-3-deazaguanosine [6-amino-1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-*c*]pyridin-4-one] via a novel 1,3-dipolar cycloaddition reaction

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This paper is dedicated to Prof. Raymond U. Lemieux on the occasion of his 60th birthday

ROBERT A. EARL and LEROY B. TOWNSEND. Can. J. Chem. **58**, 2550 (1980).

8-Aza-3-deazaguanosine (**2**) has been prepared via a route which used a 1,3-dipolar cycloaddition reaction to provide a key intermediate. The reaction of 2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl azide (**13**) with methyl 4-hydroxy-2-butynoate (**11**) provided a good yield of crystalline methyl 5-hydroxymethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (**14**). A series of functional group transformations were then used to convert **14** into methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazolo-4-carboxylate (**19**). Treatment of **19** with liquid ammonia effected not only a smooth removal of the blocking groups, but also an aminolysis of the ester function which was then followed by a ring annulation to provide 8-aza-3-deazaguanosine (**2**). The structures of these nucleosides were established on the basis of proton nmr spectral data and nuclear Overhauser enhancement data. The nucleosides obtained in this study were also converted through a chemical degradation sequence into nucleosides which had been obtained during an earlier work from our laboratory. The present study also provides unequivocal proof of the structures of some triazole nucleosides obtained in the earlier study.

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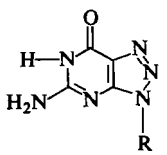
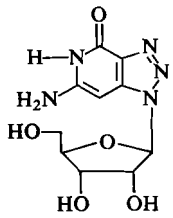
On a préparé l'aza-8 déaza-3 guanosine (**2**) en faisant appel à une réaction de cycloaddition dipolaire-1,3 pour obtenir l'intermédiaire clé. La réaction de l'azoture de tri-*O*-benzoyl-2′,3′,5′ β-D-ribofurannosyle (**13**) avec l'hydroxy-4 butyne-2 oate de méthyle (**11**) conduit avec un bon rendement à l'hydroxyméthyl-5 (tri-*O*-benzoyl-2,3,5 β-D-ribofurannosyle)-1 *v*-triazolecarboxylate-4 de méthyle (**14**). On a utilisé une série de réactions impliquant les groupements fonctionnels pour transformer le composé **14** en cyanométhyl-5 (tri-*O*-benzoyl-2,3,5 β-D-ribofurannosyle)-1 *v*-triazolecarboxylate-4 de méthyle (**19**). Lorsqu'on traite le composé **19** par l'ammoniac liquide, on obtient non seulement une déprotection douce, mais également une aminolyse de la fonction ester suivie d'une annélation du cycle qui conduit à l'aza-8 diaza-3 furannosine (**2**). On a établi la structure de ces nucléosides en se basant sur la rmn du proton et sur des données d'accroissement Overhauser nucléaire. On a également transformé ces nucléosides, par dégradation chimique, en des nucléosides obtenues antérieurement dans notre laboratoire. La présente étude apporte également une preuve univoque de structure de quelques nucléosides triazoles obtenus dans une étude antérieure.

[Traduit par le journal]

The isolation of (1) and characterization of the antibiotic pathocidin as 8-azaguanine (**1***a*) has created considerable interest in the synthesis of other aza, deaza, and aza/deaza guanine and guanosine analogs. Research activity in this area has resulted in the synthesis of 8-azaguanine (2) (**1***a*), 8-azaguanosine (3, 4) (**1***b*), and 2′-deoxy-8-azaguanosine (4); 3-deazaguanine (5) and 3-deazaguanosine (5); 1-deazaguanosine (6); 1-deaza-8-azaguanosine (7), and several (8, 9) guanosine analogs containing a bridgehead nitrogen.



1 *a*, R = H
b, R = β-D-ribofuranosyl



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Interesting biological and chemotherapeutic activities have been reported for some of the 8-azaguanosine (10) and 3-deazaguanosine (11) derivatives. However, little or no antitumor (*in vitro* or *in vivo*) activity was noted (12) for 1-deaza or 1-deaza-8-azaguanosine or their corresponding bases. Also, to date, only very weak antiviral activity has been reported (9) for one of the bridgehead-nitrogen guanosine analogs.

The interesting biological and chemotherapeutic activities observed in the 8-azaguanosine (10) and 3-deazaguanosine (11) series suggested that similar or enhanced activities might be expected for the guanosine analog 8-aza-3-deazaguanosine **2**. Also, a recent report (12) indicates that there may be a correlation between the biological activity and the pK_a's of certain guanosine analogs. On the basis of this study it was suggested (12) that 8-aza-3-deazaguanosine should possess a pK_a very similar

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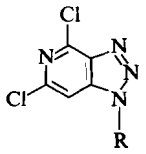
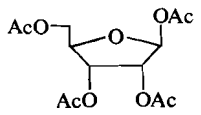
to that of the naturally occurring compounds (guanosine and 8-azaguanosine) and might be expected to exhibit definite biological and chemotherapeutic activities.

On the basis of the above, we initiated a program designed to synthesize 8-aza-3-deazaguanosine (**2**). In our initial approach, we synthesized (13) 4,6-dichloro-*v*-triazolo[4,5-*c*]pyrimidine (**3***a*) by a diazo ring-closure reaction involving 3,4-diamino-2,6-dichloropyridine (14) and carried out a fusion reaction of **3***a* with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**4**). However, this standard pro-



3 *a*, R = H
b, R = 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl



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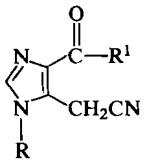
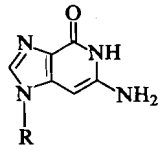
cedure for nucleoside synthesis was found (13) to yield a mixture of isomeric, acetylated ribonucleosides from which the 1-isomer (**3***b*) could be isolated in small amounts only after tedious chromatography. Based on these results, this standard approach seemed too cumbersome to be practical since numerous functional group transformations would be required in order to convert **3***b* into 8-aza-3-deazaguanosine (**2**).

Considerable success has been reported (5) in the synthesis of 3-deazaguanosine derivatives via the base-catalyzed ring-closure of imidazole precursors, e.g., **5***c* and **5***d* to **6***a* and **6***b*, respectively.



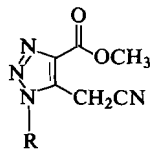
5*a*, R = H, R¹ = OCH_3
b, R = 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl
R¹ = OCH_3
c, R = H, R¹ = NH_2
d, R = β-D-ribofuranosyl
R¹ = NH_2



6*a*, R = H
b, R = β-D-ribofuranosyl

This report (5) suggested that this approach might be useful[2] for the synthesis of 8-aza-3-deazaguanosine provided that suitable triazole precursors were available.

Unfortunately, a survey of the literature revealed that the *v*-triazole precursor, *per se*, methyl 5(4)-cyanomethyl-*v*-triazole-4(5)-carboxylate (**7***a*) was unknown. To the best of our knowledge, other useful starting materials such as the *v*-triazole analogue of **5***c* were also unknown. Thus we were faced with the task of synthesizing a triazole derivative such as**7***a*. Based on the imidazole work (5), a condensation of **7***a* with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (**4**) would be expected to yield the triazole nucleoside derivative **7***b*. However, such a condensation using the imidazole derivative was found (5) to give both possible positional isomers. The ratio of these positional isomers could be changed depending on the amount of



7*a*, R = H
b, R = 2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl

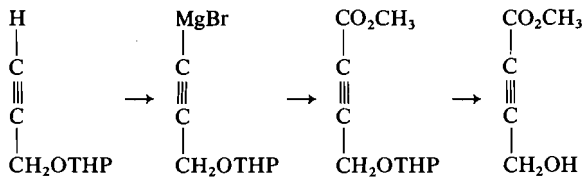
catalyst employed. In the case of the proposed triazole series, a third positional isomer is possible and would most likely be formed, based on our experience with 4,6-dichloro-*v*-triazolo[4,5-*c*]-pyridine (13) (**3***a*) and other related compounds (16). This suggested to us that we would again probably encounter serious problems with the separation of isomers possessing very similar chromatographic mobilities.

Another more novel approach to the synthesis of a *v*-triazole nucleoside such as **7***b* would be through the 1,3-dipolar cycloaddition of a ribofuranosyl azide derivative to a suitable acetylenic compound. This approach would enjoy the advantage of producing only two positional isomers. Several reports have appeared (17, 18) whereby glycosyl azides have been successfully added to acetylenic compounds to produce *v*-triazole nucleosides with a high degree of regioselectivity (the glycosyl and ester functions being located at the 1- and 4-positions of the triazole ring, respectively). In addition to a high degree of regioselectivity, these reactions (17, 18) also appeared to occur with com-

[2]It is interesting to note, however, that a similar approach has failed to yield 3,7-dideazaguanine from pyrrole precursors (15).

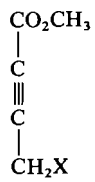
plete retention[3] of configuration at C-1 of the glycosyl moiety.

The 1,3-dipolar cycloaddition route looked very promising as a route for the synthesis of a functionalized triazole nucleoside such as **7***b*. A search of the literature revealed that the highly functionalized acetylenic derivative, methyl 4-hydroxy-2-butynoate (**11**), was a known (20) compound. The compound **11** had been prepared (20) previously, however, we were unable to reproduce the reported (20) yields and also encountered serious problems with emulsion formation during the workup of the carboxylation mixture using this procedure. Therefore, we modified (21) the original procedure, which eliminated the problem with emulsions and provided a 65% yield of **11** (based on **8**).[4]



8 **9** **10** **11**

It had been our intention to convert the hydroxymethyl group of **11** into a cyano methyl group to yield methyl 4-cyano-2-butynoate (**12***b*), since a reaction of **12***b* with a ribofuranosyl azide derivative should furnish a triazole nucleoside of the type represented by **7***b*. However, our attempts to bring about this modification were unsuccessful. Bromination of **11** using a published (20) procedure did not yield a pure product and gplc analysis indicated the presence of at least three new compounds in the reaction mixture. A pmr spectrum of the crude product indicated the presence of allenic compounds. Allenic compounds have been encountered by others (23) when attempting to iodinate certain acetylenic alcohols under very mild conditions. Other methods for bromination (24) and iodination (25) were also unsuccessful in converting **11** into a halo derivative. Similarly, methods (26) for the preparation of mesylates and tosylates from acetylenic alcohols did not give useful products from **11**. Although all of these methods showed evidence of giving some of the desired products, the highly reactive nature of these propargyl compounds ensure a difficult isolation. This isolation problem is due primarily to their tendency to undergo rearrangement (23) to allenic compounds or to react further (26) with bases present in the reaction mixture to give hydrolysis products or quaternary ammonium compounds.



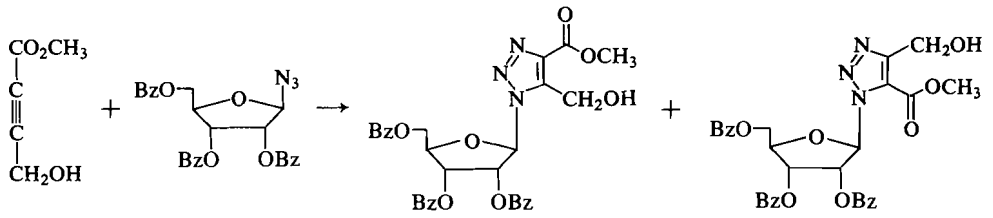
12*a*, X = Br
b, X = CN

In view of the problems we encountered while trying to modify methyl 4-hydroxy-2-butynoate (**11**), we decided to carry out a 1,3-dipolar cycloaddition reaction using **11** as the dipolarophile and to carry out further functional group transformations on the nucleoside rather than the acetylenic precursor. We chose 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide as a starting material since it has a known β configuration and is available (27) in pure, crystalline form. The reaction between crystalline 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (**13**) and methyl 4-hydroxy-2-propynoate (**11**) was found to proceed best when the temperature of the reaction was maintained in the range of 50–70°C with little or no solvent. Under these conditions, the reaction required 5 to 7 days for completion but the reaction was very clean resulting in the production of two close-running (tlc) nucleoside components in a ratio of ca. 4:1 (pmr).

When methanol was added to the hot reaction mixture, the predominant isomer, tentatively (17) assigned structure **14** (methyl 5-hydroxymethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate), crystallized from solution in a 60% yield. Chromatography of the product obtained from the supernatant yielded an additional 15% of the major isomer (**14**) as well as a 6% yield of the minor, slower running (tlc) nucleoside component. Elemental analysis and proton nmr spectral data indicated that the isolated products were isomeric since both products had the same empirical formula and displayed signals for a carbomethoxy and a hydroxymethyl group as well as the ribose moiety. Both compounds displayed anomeric signals (H-1′) with rather small coupling constants (1.8 Hz for **14** and 1.5 Hz for **15**) indicating (28) that they were both probably β-isomers. Furthermore, the anomeric signal for **15** (δ 7.07) was shifted downfield 0.21 ppm compared to the corresponding signal for **14** (δ 6.86) which sug-

[3]An apparent exception to this observation did not actually involve the cycloaddition of an azide to an acetylenic compound. Instead this reaction involved the reaction of a glycosyl azide with a carbanion followed by a ring closure reaction (see refs. 4 and 19).

[4]After this work was completed, a similar procedure for the removal of the tetrahydropyranyl protecting group was reported (22).

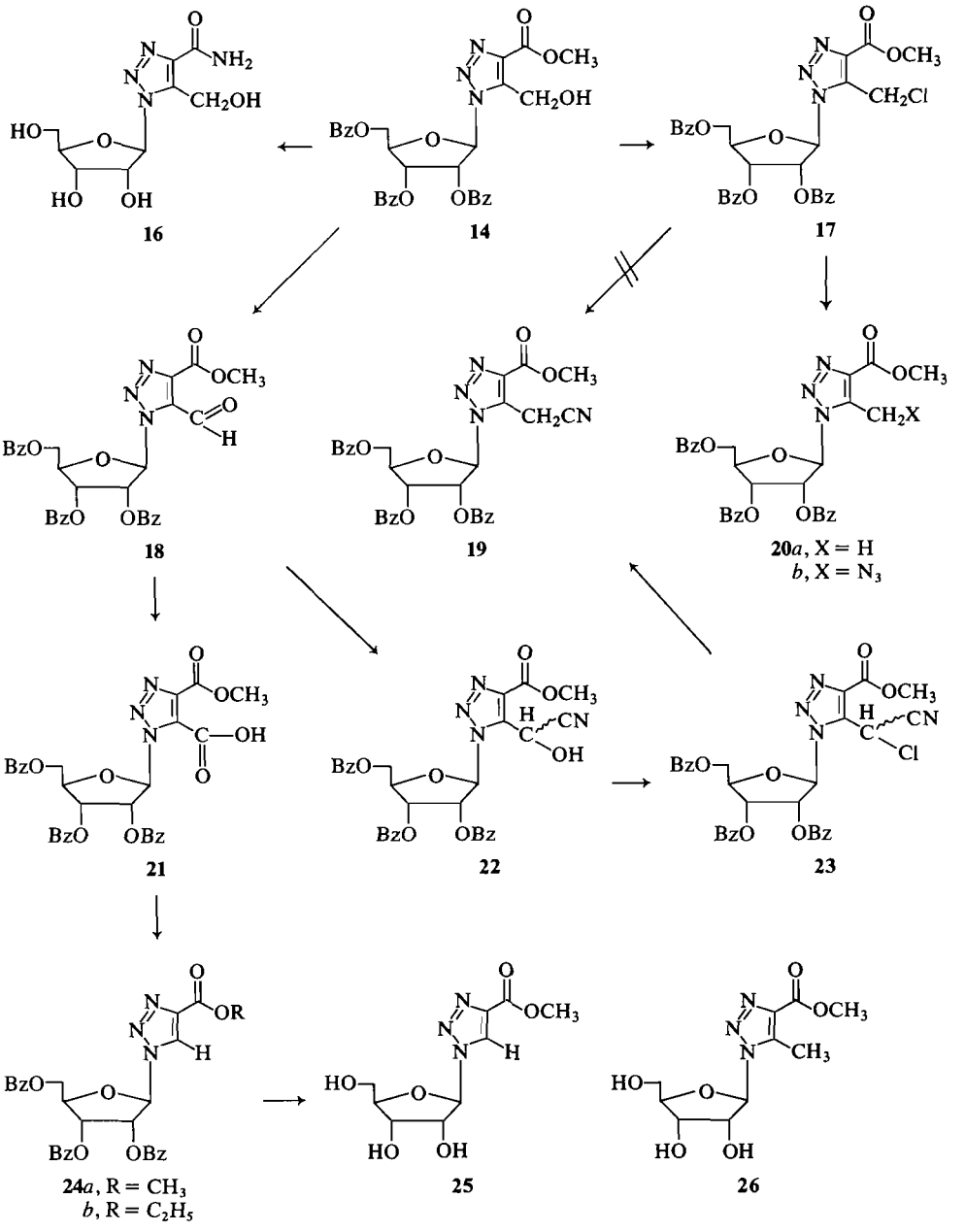


11 13 14 15

gested that our tentative (17) structural assignments were correct. It has been demonstrated previously in the case of benzimidazole (29*a*), imidazole (5), pyrimidine (29*b*), and 1,2,4-triazole nucleosides (29*c*, *d*) as well as in the case of certain nitrogen bridgehead nucleosides (29*e*) that when a ribosyl moiety is attached to a nitrogen atom α to a carbon atom bearing a carbonyl function (such as an ester group) then the anomeric signal is shifted downfield as compared to the situation where the ribosyl moiety is not adjacent to a carbonyl function. On the basis of this observation, the predominant isomer must have the structure indicated by **14** whereby H-1′ is located away from the carbomethoxy group.

Methanolic ammonia readily converted **14** into the crystalline carboxamide derivative **16**. Chlorination of **14** using thionyl chloride – DMF – methylene chloride provided a quantitative yield of the chloromethyl derivative **17**, isolated as a solid foam. This very reactive chloromethyl derivative (**17**) was readily reduced using catalytic hydrogenation (5% Pd/C) to provide the crystalline methyl derivative **20***a*. The structure of **20***a* was supported by its elemental analysis as well as by the appearance of a new 3-proton singlet in the pmr spectrum at δ 2.64 (methyl group). A reaction of the chloromethyl derivative (**17**) with sodium azide in acetonitrile furnished an 88% yield of the azidomethyl derivative **20***b*. Although the R_f (tlc) values of **17** and **20***b* were nearly identical, the compounds gave different colors when sprayed with 10% sulfuric acid and heated. The tlc indicated that 1 h of reaction at 70°C was probably sufficient for complete reaction. Potassium cyanide in DMSO (25°C) rapidly (3–5 min) converted the chloromethyl derivative **17** into a new product whose R_f was slower than that of the starting material. Although tlc suggested that the product was homogeneous, the pmr spectrum indicated that it was probably a mixture. The spectrum (pmr) was unexpectedly complex showing 5-"singlets" in the region δ 3.4–3.9 where the methoxy singlet should appear. At first, it appeared that the product was perhaps a dimer resulting from a bimolecular condensation of a cyanomethyl group with a carbomethoxy group. However, the mass spectrum was very complex showing peaks with masses much higher than that expected for a dimer. Furthermore, the mass spectrum did not show a molecular ion for the desired monomeric cyanomethyl derivative **19**. The reaction between chloromethyl derivative **17** and "naked" (30) cyanide ion (KCN–acetonitrile – 18-crown-6, 18 h, 45°C) also gave an unidentified product as above.

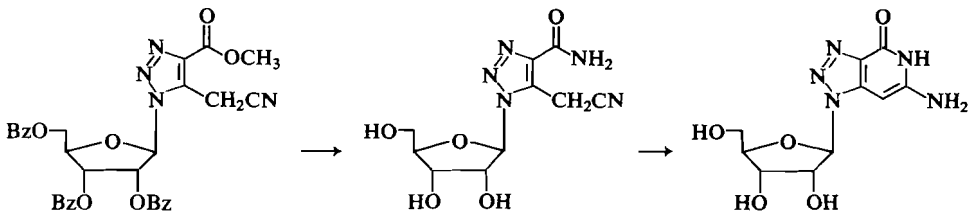
We, therefore, explored an alternate route for the synthesis of **19** which would not require a nucleophilic displacement with a strong base. During the course of this study, we found that the hydroxymethyl derivative **14** was readily converted (31) (85%) into the corresponding aldehyde **18** by treatment with activated (32) manganese dioxide in toluene at reflux. This compound was readily identified due to the presence of a sharp one-proton singlet in the pmr at δ 10.31 for the formyl proton. The aldehyde **18** could be converted into the cyanohydrin **22** (based on tlc data) using (33) a transcyanohydrination reaction between **18** and acetone cyanohydrin. However, the aldehyde **18** was so reactive that a simple treatment of **18** with 3 to 5 mol of hydrogen cyanide (34) in methylene chloride (25°C) converted it, quantitatively, into the cyanohydrin **22**. The cyanohydrin **22** was isolated as a crisp foam that was stable indefinitely, provided that it was kept dry. Thin layer chromatography resolved the diastereomeric mixture into two spots; however, attempts at column chromatography resulted in partial or complete reversion of **22** into the starting aldehyde **18**. The cyanohydrin was readily converted into the chlorocyanomethyl derivative **23** using thionylchloride–DMF–methylenechloride. Chromatography gave the diastereomeric mixture (**23**) as an analytically pure foam that showed a single spot (tlc) in two different chromatographic solvent systems. Hydrogenation of **23** (5% Pd/C) gave a nearly quantitative yield of the elusive cyanomethyl derivative **19** in the form of an analytically pure white foam. The tlc mobilities for **19** were different from those of the unidentified product(s) obtained from attempted displacement of the chloro group of **17** with cyanide ion. Later experiments demonstrated



that the hydroxymethyl derivative **16** could be converted into the cyanomethyl derivative **19** in an overall yield of 57% with only the chlorocyanomethyl derivative requiring purification by chromatography.

Treatment of the cyanomethyl derivative **19** with methanolic ammonia (25°C, 18 h) gave a highly colored reaction mixture from which impure 5-cyanomethyl-1-(β-D-ribofuranosyl)-*v*-triazole-4-carboxamide (**27**) (ca. 25% yield) and 8-aza-3-deazaguanosine (**2**) could be isolated. When **19** was treated[5] with liquid ammonia (25°C) for 5 days, a light purple reaction mixture was obtained. Evaporation of the liquid ammonia followed by tritura-

[5]It should be noted that the ring closure of **19** to give **2** took place under much milder conditions than those required (5) for the corresponding reaction in the imidazole series. This is likely due to the greater electron withdrawing ability of a triazole ring as compared to an imidazole ring which renders the amide protons of **27** more acidic than those in **5***d*. This facilitates abstraction (5) of an amide proton of **27** which is followed by rapid ring closure.



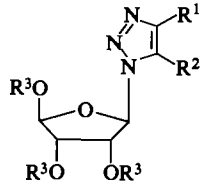
19 27 2

tion with ether and then acetone yielded a yellow-orange colored powder whose pmr spectrum indicated that it was nearly pure 8-aza-3-deazaguanosine (100% crude yield). The crude 8-aza-3-deazaguanosine (**2**) was converted into its sodium salt and absorbed on a Dowex 1 resin (formate form) column. Elution with 0.05 *N* formic acid gave pure 8-aza-3-deazaguanosine, mp 239–241°C in the form of a light, violet colored powder. The pmr spectrum of 8-aza-3-deazaguanosine (**2**) was very similar to that reported (5) for 3-deazaguanosine (**6***b*) showing an anomeric signal at δ 5.83 (δ 5.51 for **6***b*) which was split into a doublet with $J = 5$ Hz (6 Hz for **6***b*). The ring proton (H-7) appeared as a singlet at δ 5.50 (δ 5.52 for **6***a*). The uv spectrum of 8-aza-3-deazaguanosine was also very similar to that reported (5) for 3-deazaguanosine, however, these similarities are not sufficient to allow any conclusions regarding configuration or position of attachment of the ribose moiety in **2**. We had assumed a β-configuration for **2** and its triazole nucleoside precursors on the basis of the known (27) β-configuration of the starting azide **13**. A pmr spectrum (Table 1) of the aldehyde derivative **18** provided conclusive evidence (28) that the cycloaddition had proceeded with retention of configuration at C-1 of the ribose ring since the anomeric signal appeared as a sharp singlet at δ 7.01. The position of attachment of the ribosyl moiety in **2** and **14**, **16–23** remained to be established since we did not feel secure with assignments based on the relative positions of the anomeric signals of the original isomeric cycloadducts (**14** and **15**). We therefore carried out a chemical degradation of the major cycloadduct (**14**) in order to relate it to a nucleoside (**24***a*) of known structure. Oxidation of the hydroxymethyl group of **14** using Jones reagent (35) provided (88%) the carboxylic acid derivative **21**. The pmr spectrum of **21** showed considerable peak broadening suggesting the presence of paramagnetic species. Washing solutions of **21** with dilute mineral acid and even column chromatography did not improve the quality of the spectra. The crude product was triturated with dilute acetic acid, dried, and used without further purification for decarboxylation. Decarboxylation of **21** was carried out in toluene at reflux to give a crude product. This solid was crystallized[6] from methanol to give a 65% yield of methyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (**24***a*) whose physicochemical data (mp, pmr, and $[\alpha]_D$) were in excellent agreement with the published (17) data for **24***a*. Recrystallization of the crude decarboxylation product from ethanol gave the corresponding ethyl ester **24***b*. However, the published structure of **24***a* was not unequivocal since the assignment of a structure for **24***a* was based only on trends in pmr chemical shifts previously noted (36) for model *N*-methyl derivatives of triazoles. Therefore, compounds **24***a* and **20***a* were deblocked with methanolic sodium methoxide to provide **25** and **26**, respectively. The physicochemical properties of **25** were identical to those previously reported (37) for this compound. These nucleosides (**25** and **26**) were then examined for the presence of nuclear Overhauser enhancements (38, 39). When H-2′ of **25** was irradiated, an nOe of 18.5% was noted for H-5 (Table 2). Similarly, irradiation of H-1′ caused a 10% enhancement of H-5 in **25**. These results could only occur if the ribose moiety of **25** is attached to N-1 of the triazole ring since attachment at N-3 would place H-5 too far away from H-1′ and H-2′ to expect any significant nOe. Furthermore, when the methyl group at C-5 of **26** was irradiated, an enhancement of 16.5% was noted for H-1′ which provided additional evidence that the ribosyl group is in the position indicated. Thus, a combination of pmr and nOe spectral data provided unequivocal proof that **14**, **16–26** possessed the structures as tentatively assigned by us. These data have also provided proof that the cycloaddition reactions reported (17) by earlier workers proceeded with the regioselectivity that they had earlier indicated.

This work has demonstrated once again (40) the

[6]Recrystallization of the crude decarboxylation product from ethanol gave a 65% yield of the corresponding ethyl ester. This behavior is difficult to explain without invoking the presence of some impurity which is acting as a transesterification catalyst.

TABLE 1. Proton magnetic resonance spectral data for certain triazole nucleosides[a]



Compound number	R^1	R^2	R^3	H-1′($J_{1',2'}$ in Hz)	H-2′	H-3′	H-4′	H-5′, 5″	OCH_3	Other
14	CO_2CH_3	CO_2H	Bz	6.86 (1.8)	6.46 (dd)	6.26 (t)	5.00 (m)	4.65 (m)	3.86	5.03 (d, CH_2OH), 5.83 (t, CH_2OH)
15	CH_2OH	CO_2CH_3	Bz	7.07 (1.5)	6.57–6.08		5.10	4.60	3.90	4.68 (d, CH_2OH), 5.33 (t, CH_2OH)
17	CO_2CH_3	CH_2Cl	Bz	6.86 (2.0)	6.53 (dd)	6.16 (t)	5.09 (m)	4.67 (m)	3.91	5.26 (s, CH_2Cl)
20*a*	CO_2CH_3	CH_3	Bz	6.46 (5.0)[b]	5.87 (m)	5.87 (m)	5.00–4.32		3.90	2.64 (s, CH_3)
20*b*	CO_2CH_3	CH_2N_3	Bz	6.82 (4.0)	6.54 (dd)	6.22 (t)	4.50–5.20		3.89	5.00 (2, CH_2N_3)
18	CO_2CH_3	CHO	Bz	7.01 (0.0)	6.44 (d)	6.22 (t)	5.06 (m)	4.64 (m)	3.98	10.31 (s, CHO)
22	CO_2CH_3	CHCNOH	Bz	6.97 (1.0)	6.60 (dd)	6.22 (t)	5.11 (m)	4.67 (m)	3.94	6.60 (d, CHOHCN)
23	CO_2CH_3	CHCNCl	Bz	6.95 (1.5)	6.62 (d)	6.20 (t)	5.08 (m)	4.62 (m)	3.96	
19	CO_2CH_3	CH_2CN	Bz	6.93 (2.0)	6.60 (dd)	6.11 (t)	5.07 (m)	4.61 (m)	3.93	4.61 (s, CH_2CN)
21	CO_2CH_3	CO_2H	Bz	6.95 (2.0)	6.52 (dd)	6.25 (t)	5.07 (m)	4.67 (m)	3.92	
24*a*	CO_2CH_3	H	Bz	6.76 (3.2)[c]	6.31 (m)	6.12 (m)	4.99 (m)	4.66 (m)	3.87	9.04 (s, H5)
24*a*	CO_2CH_3	H	Bz	6.45 (3.4)[b,c]	6.23 (m)	6.07 (m)	4.83 (m)	4.83 (m)	3.88	8.37 (s, H5)
16	$CONH_2$	CH_2OH	H	6.06 (3.8)	4.69 (t)	4.25 (t)	3.98 (m)	3.51 (m)	—	4.91 (s, CH_2OH), 7.93 (s), 7.58 (s, $CONH_2$)
26	CO_2CH_3	CH_3	H	5.92 (4.0)	4.78 (t)	4.22 (t)	3.95 (m)	3.48 (m)	3.85	2.56 (s, CH_3)
24*b*	$CO_2C_2H_5$	H	H	6.55 (3.7)	6.20 (m)	6.20 (m)	4.83 (m)	4.83 (m)	—	8.37 (s, H5), 4.43 (q, 2, OCH_2CH_3), 1.37 (t, 3, OCH_2CH_3)
25	CO_2CH_3	H	H	6.03 (4.0)	4.40 (t)	4.32–3.77 (m)		3.62 (m)	3.83	9.03 (s, H5)

[a]Spectra run using DMSO-d_6 as solvent unless otherwise indicated.
[b]Spectrum run using $CDCl_3$ as solvent.
[c]Assigned using JEOL TPJ-PFT 100 instrument.

TABLE 2. Nuclear Overhauser effects observed for **25** and **26**

Compound	Proton irradiated	Proton observed	Percent enhancement
25	H-1′	H-5	10.0
	H-2′	H-5	18.5
26	CH_3(at C5)	H-1′	16.5

usefulness of the 1,3-dipolar cycloaddition reaction for a quick entry into 5-membered heterocycles with varied functionality. It has also demonstrated that highly functionalized acetylenic derivatives such as methyl 4-hydroxy-2-butynoate (**11**) may be used successfully as dipolarphiles while still obtaining a high degree of regioselectivity in the cycloaddition reactions.

The synthesis of **2** and some closely related derivatives via an alternate route has recently been reported (41).

Experimental

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on Varian EM-360 and EM-390 spectrophotometers using DMSO-d_6 and $CDCl_3$ as solvents with tetramethylsilane as internal standard. Rotations were obtained with a Perkin–Elmer Model 141 digital readout polarimeter and were determined on samples dissolved in DMSO and having a concentration of 1 g/100 mL, unless otherwise stated. Thin layer chromatography (tlc) was carried out using glass plates precoated with a layer (0.25 mm) of Silicar 7GF silica gel as supplied by Analtech, Inc. ("Uniplate"). Compounds were detected using an ultraviolet lamp (Mineralight, 254 mm) or by spraying the tlc plates with 10% sulfuric acid in water (v/v) followed by heating at 120°C. Column chromatography was carried out using Silica Gel 60 F_{254} (70–230 mesh) as obtained from E. Merck, Darmstadt, West Germany. Columns were packed with dry silica gel and then eluted with one void volume of the eluting solvent before a concentrated solution of impure compound was applied to the top of the column. Elution was carried out using Solvent System A: (SSA) (chloroform–acetone, 19:1 (v/v)) unless otherwise noted. All concentrations of solutions were carried out, *in vacuo*, at 25–35°C unless otherwise noted. Solutions were dried over anhydrous sodium sulfate unless stated otherwise.

Nuclear Overhauser experiments were carried out using a JEOL TPJ-PFT 100 instrument and using an EC-100 data system. Compounds were dissolved in and then freeze dried from deuterium oxide (3 cycles) in order to replace exchangeable protons with deuterium. The deuterated compounds were then dissolved in DMSO-d_6 and deoxygenated by freezing under vacuum and thawing under a nitrogen atmosphere (3 cycles). The solutions (concentration, 5 mg in 0.5 mL DMSO) were then sealed in the nmr tubes while under vacuum.

Methyl 4-Hydroxy-2-butynoate (11)

Caution! Methyl 4-hydroxy-2-butynoate (**11**) is a potent vesicant which causes painful burns on contact with skin. All operations should be carried out in an efficient fume hood and gloves should be worn at all times.

Propargyl alcohol was converted into 1-(tetrahydropyran-2-yloxyprop-2-yne (**8**) in 78% yield using a published (42) general procedure. The THP-propargyl alcohol had a bp of 75–77°C (15–20 Torr), $n_D^{22°} = 1.4594$ (lit. (20) bp 78°C (25 Torr, $n_D^{20°} = 1.4570$); pmr (90 MHz, neat) δ: 4.63 (s, 1H, H-1′), 4.03 (d, 2H, C≡C—H, J = 1 Hz), 1.18–1.93 (br m, 6H, H-2′, H-4′).

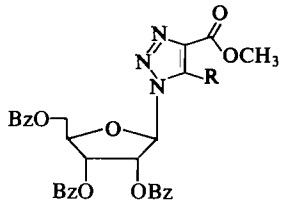
A solution of 280.4 g (2 *M*) of the THP-propargyl alcohol **8** in 2 L of dry tetrahydrofuran was added, dropwise, during 0.75 h to a stirred solution of ethylmagnesium bromide (2 *M*, purchased from Aldrich Chemical Company as a 3 *M* solution in diethyl ether) in diethyl ether (ca. 660 mL). Vigorous boiling and gas (C_2H_4) evolution took place during the addition. The solution was then stirred an additional 1.5 h at 25°C. The acetylenic Grignard reagent, **9**, was then added dropwise under a nitrogen atmosphere, to a vigorously stirred, cold (−10 to −15°C) solution of methyl chloroformate (275.2 g, 2.9 *M*) in 0.5 L of dry tetrahydrofuran during 2 h. The temperature was maintained at −10 to −15°C with continued mechanical stirring for another 0.5 h, and then was stirred at 0°C for an additional 1.5 h. The mixture was stored at +5°C for 18 h and then the supernatant was removed from the magnesium salts by filtration. The salts were washed with cold (0°C) toluene (3 × 300 mL), the filtrates were combined and concentrated, *in vacuo*, to ca. 1-L volume, and the dark-brown solution washed with saturated brine (5 × 200 mL). The solution was dried and concentrated *in vacuo* to remove the toluene. The residue was dissolved in anhydrous methanol (1.25 L), Dowex 50 (50 mL of H^+ form, prewashed with anhydrous methanol) was added, and the mixture stirred for 1.5 h at 25°C. The ion exchange resin was removed by filtration and the resin was then washed with anhydrous methanol (2 × 100 mL). The solvent and by-product (2-methoxytetrahydropyran) were removed by first using a water aspirator and then an oil pump at 0.5 Torr pressure. This residue was then treated a second time with anhydrous methanol (1 L) and Dowex 50 (50 mL) followed by concentration as described above. The dark, oily residue was distilled *in vacuo* through a Claison head to give **11** (147.8 g, 64.8%), bp 66–69°C/0.2 Torr, (lit. (20) bp 70°C/0.5 Torr), $n_D^{22°} = 1.4720$; ir (neat): 3410 (strong, br, OH), 2240 (strong, C≡C), 1715 (strong, ester) cm^{-1}; pmr (DMSO-d_6) δ: 5.57 (t, 1H, OH), 4.31 (d, 2H, CH_2OH, J = 6 Hz), 3.79 (s, 3H, OCH_3). *Anal.* calcd. for $C_5H_6O_3$: C 52.63, H 5.30; found: C 52.67, H 5.46.

Methyl 5-Hydromethxyl-1-(2,3,5-tri-O-benzoyl- β-D-ribofuranosyl)-v-triazole-4-carboxylate (14) and Methyl 5-Carbomethoxy-4-hydroxymethyl-1- (2,3,5-tri-O-benzoyl-β-D-ribofuranosyl-v-triazole-4-carboxylate (15)

Crystalline 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (**27**) (**13**, 58.5 g, 0.12 *M*), methyl 4-hydroxy-2-butynoate (**11**, 13.7 g, 0.12 *M*), and 5 mL of toluene were heated and gently stirred at 50–55°C for 5 days. At the end of days 1, 2, and 3, additional amounts of **11** (1 mL each addition) were added. The temperature was raised to 70°C and heating was continued for an additional 2 days. After seven days, the azide could not be detected in the tlc. Methanol (134 mL) was added, the mixture was heated to boiling, cooled to 25°C, and the product allowed to stand for 3 days. The crystalline product was collected by filtration to give 46.6 g of product (mp 75–79°C). This solid was recrystallized once from ethanol to give the pure product **14** (needles), 43.1 g (59.8%), $[\alpha]_D^{22°}$ 30.2°, mp 87–89.5°C (bubbly, viscous melt). *Anal.* calcd. for $C_{31}H_{27}N_3O_{10}$: C 61.89, H 4.52, N 6.99; found: C 61.73, H 4.43, N 6.79. See Table 1 for pmr spectral data. The supernatants were combined and concentrated to give 38 g of a syrup which was chromatographed over silica gel (270 g) (column, 7 × 35 cm). Elution was carried out with SSA. The first liter of eluent was discarded and then 20-mL fractions were collected. Fractions 30–50 contained additional amounts of pure **14**, 11.05 g (15.3%, total yield 75.1%). Fractions 51–80 (17 g) contained the slower moving isomer **15** and were saved for rechromatography.

A portion (6.18 g) of the concentrates containing the slower moving isomer was rechromatographed over silica gel (270 g of

TABLE 3. Values[a] of R_f for certain 2′,3′,5′-tri-*O*-benzoylated *v*-triazole nucleosides



Compound number	R	SSA[b]		SSB[b]	
		R_f	R_f/R_f Std.	R_f	R_f/R_f Std.
14	CH_2OH	0.26	0.38	0.19	0.31
17	CH_2Cl	0.56	0.84	0.46	0.75
18	CHO	0.50	0.75	0.46	0.75
19	CH_2CN	0.42	0.63	0.30	0.49
20*a*	CH_3	0.49	0.73	0.36	0.59
20*b*	CH_2N_3	0.56	0.84	0.45	0.73
22	CHCNOH	0.25, 0.31	0.37, 0.46	0.22, 0.27	0.36, 0.44
23	CHCNCl	0.59	0.88	0.49	0.80
Standard[c]		0.67	—	0.61	—

[a]Chromatography was carried out using 20 cm × 5 cm glass plates coated with a 250 μm layer of silica gel 7GF as supplied by Analabs. Each spot contained 0.1 mg of compound applied as a solution in chloroform.
[b]SSA = Solvent system composed of chloroform–acetone, 19:1 (v/v). SSB was a mixture of benzene – ethyl acetate, 17:3 (v/v).
[c]1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose was used as the standard.

silica gel, column 7 cm × 35 cm). Elution was carried out using SSA and 17 mL fractions were collected. Fractions 35–45 contained the slower moving isomer **15**, 1.55 g, $[\alpha]_D^{25°}$ 20.1°. *Anal.* calcd. for $C_{31}H_{27}N_3O_{10}$: C 61.89, H 4.52, N 6.99; found: C 62.07, H 4.78, N 6.88.

5-Hydroxymethyl-1-(β-D-ribofuranosyl)-v-triazole-4-carboxamide (16)

A solution of **14** (3 g, 5.0 mmol) in 50 mL of methanolic ammonia (saturated at 0°C) was sealed in a pressure bottle at 25°C for 2 days. A single spot (R_f 0.3, $CHCl_3$–CH_3OH, 7:3, v/v) was observed with some difficulty by tlc since it absorbed uv light only very slightly, but the spot charred when it was sprayed with 10% H_2SO_4 and then heated. The solvent was removed *in vacuo* and the residue triturated repeatedly with anhydrous ether (5 × 40 mL) to give a white crystalline solid, 1.15 g (89.3%), mp 136–138°C. The solid was dissolved in 20 mL of boiling ethanol containing a few drops of water and the solution concentrated to 9 mL by boiling. The product (**16**) crystallized out of solution as white spears on cooling to room temperature, 1.08 g, mp 138.5–141°C; $[\alpha]_D^{25°}$ −82.6°. *Anal.* calcd. for $C_9H_{14}N_4O_6$: C 39.42, H 5.15, N 20.43; found: C 39.72, H 5.21, N 20.40.

Methyl 5-Formyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-v-triazole-4-carboxylate (18)

Activated (32) manganese dioxide (89 g) was suspended in 750 mL of boiling toluene and water was then removed using a Dean–Stark trap. Compound **14** (29.75 g, 49.5 mmol) was added and the mixture stirred and heated at reflux temperature for 3 h while removing water by azeotropic distillation. Another 30 g of manganese dioxide was added, and the mixture stirred and heated an additional 5 h with continued removal of water. The mixture was then filtered, while still hot, through a dry-packed bed of Celite (5 cm × 10 cm), and the filter-cake washed with hot acetone (5 × 100 mL). The filtrates were combined and concentrated *in vacuo* to yield a light yellow colored foam (**18**, 26.1 g, 87%) (one spot, tlc, SSA). A small sample (0.5 g) was chromatographed over silica gel (50 g) using SSA to yield 430 mg of a white foam; $[\alpha]_D^{25°}$ −31.0°. The aldehyde eventually crystallized on standing; white crystals, mp 185–186°C (ethyl acetate – ligroin, 1:5, v/v). *Anal.* calcd. for $C_{31}H_{25}N_3O_{10}$: C 62.10, H 4.20, N 7.01; found: C 61.94, H 4.13, N 6.86.

Methyl 5-(α-Cyano-α-hydroxymethyl)-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-v-triazole-4-carboxylate (22)

Unchromatographed methyl 5-formyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (**18**, 8.15 g, 13.5 mmol) was dissolved in 18 mL of methylene chloride, the solution was cooled to −50°C, and the flask and contents weighed. Liquid (34) hydrogen cyanide was added (ca. 1 mL) and weighing by differences indicated that 1.05 g (38.9 mmol) of HCN was present. The flask was tightly stoppered and allowed to stand at ambient temperature for 6.3 h when tlc indicated that only a trace of aldehyde was present. The cyanohydrin showed two spots (R_f 0.25 and 0.31, SSA) on tlc (diastereoisomeric mixture). The cyanohydrin was unstable on silica gel and if the tlc plates were allowed to stand for more than a few minutes before development, the amount of aldehyde in the mixture increased. Concentration *in vacuo* **(in the hood)** yielded a syrup which readily formed a white foam under oil pump vacuum, 8.47 g (99.4%). A sample was dissolved in chloroform and treated with a small amount of Norite. Filtration through dry-packed Celite and then concentration *in vacuo* yielded a white foam; $[\alpha]_D^{25°}$ 22.7°. *Anal.* calcd. for $C_{32}H_{26}N_4O_{10}$: C 61.34, H 4.18, N 8.94; found: C 61.24, H 4.19, N 8.67.

Methyl 5-(α-Chloro-α-cyanomethyl)-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-v-triazole-4-carboxylate (23)

The cyanohydrin **22** (8.26 g, 13.2 mmol) was dissolved in 42 mL of dry methylene chloride and then 1.43 mL of dry dimethylformamide and 1.42 mL of thionyl chloride were added in succession. The reaction mixture was allowed to stand in a sealed flask (25°C) for 4 h. Methanol (0.75 mL) was then added and the mixture allowed to stand for another hour at 25°C. The

solution was evaporated *in vacuo* and then co-evaporated twice with toluene (2 × 50 mL) followed by drying overnight, *in vacuo*. This syrup was then dissolved in ethyl acetate (200 mL) and washed in succession with water (50 mL), saturated aqueous sodium bicarbonate solution (2 × 20 mL), water (50 mL), and then saturated brine. The solution was dried and then concentrated *in vacuo* to yield a tan colored foam (8.14 g, 96%). The foam was dissolved in chloroform (12 mL) and applied to the top of a silica gel column (5 cm × 50 cm, 270 g of silica gel). The column was eluted with chloroform–acetone (24:1, v/v) and 18 mL fractions were collected. Fractions 70–85 contained the product (4.79 g, 56%). Concentration of fraction 75 yielded an analytical sample (540 mg) as a colorless foam; $[\alpha]_D^{25°}$ −23.1°. *Anal.* calcd. for $C_{32}H_{25}ClN_4O_9$: C 59.58, H 3.91, N 8.69, Cl 5.50; found: C 59.35, H 3.74, N 8.45, Cl 5.75.

*Methyl 5-Cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-*D*-ribofuranosyl)-*v*-triazole-4-carboxylate (19)*

Method 1

The α-chloro-α-cyano derivative **23** (4.23 g, 6.56 mmol), 1.5 g of 5% Pd/C, ethyl acetate (75 mL), and triethylamine (1.0 mL, 7.16 mmol) were added in that order, while purging with nitrogen, to a hydrogenation flask. The mixture was stirred for 4.5 h, under a hydrogen atmosphere at ambient temperature and pressure. The solids were removed by filtration through dry-packed Celite (bed, 1.5 cm × 5 cm) and the filter-cake washed with ethyl acetate (3 × 10 mL). The filtrates were combined and washed in succession with 1% (v/v) aqueous hydrochloric acid (2 × 20 mL), water (15 mL), and then saturated brine (15 mL). After drying, the solvent was removed *in vacuo* to yield a light tan colored syrup, 3.82 g (95.5%). A small sample (500 mg) was chromatographed in the usual manner (SSA, silica gel) to yield a white foam (450 mg). *Anal.* calcd. for $C_{32}H_{26}N_4O_9$: C 63.02, H 4.29, N 9.18; found: C 63.01, H 4.41, N 8.86.

Method 2

Pure methyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-hydroxymethyl-*v*-triazole-4-carboxylate (**14**, 29.75 g, 49.5 mmol), 119 g of activated manganese dioxide, and 750 mL of toluene were heated at reflux temperature and with azeotropic removal of water as previously described. Workup as before yielded the aldehyde **18** as a light yellow foam (26.1 g, 87%). The crude aldehyde was treated, as previously described, with liquid hydrogen cyanide (3.6 g, 133 mmol) in methylene chloride for 3 h at 25°C. Concentration, *in vacuo*, gave the cyanohydrin **22** in the form of a pale yellow foam, 26.1 g. The crude cyanohydrin was then treated with 14.9 g (125 mmol) of thionyl chloride and 9 mL of DMF in 250 mL of methylene chloride to yield, after the usual washing and drying operations, 26.6 g of a brown foam. Chromatography over 469 g of silica gel (dry-packed and eluted using SSA) gave the pure α-chloro-α-cyanomethyl derivative (**23**, 18.4 g). This was then subjected to catalytic hydrogenation over 5% Pd/C (6 g) to yield 17.3 g of essentially pure (pmr, tlc) methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (**19**) in an overall yield of 57.6% based on the starting methyl 5-hydroxymethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (**14**).

*6-Amino-1-(β-D-ribofuranosyl)-*v*-triazolo[4,5-c]pyridin-4-one(8-aza-3-deazaguanosine) (2)*

Methyl 5-cyanomethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (**19**, 16.8 g, 27.5 mmol) was dissolved in liquid ammonia (100 mL). The solution was sealed in a steel reaction vessel and allowed to stand at room temperature for 4 days. The ammonia was then allowed to evaporate and the residue was triturated with anhydrous ether (6 × 200 mL) to give a yellow-orange powder (8.7 g). This powder was triturated with acetone (8 × 50 mL) to give 7.8 g (100%) of crude product. A sample (1 g) of the product was dissolved in 1.03 *N* sodium hydroxide solution (3.90 mL) and the dark, purple solution was applied to the top of a glass column (2 cm × 35 cm) prepacked with Dowex 1 resin (formate form). The column was washed with 200 mL of water. The copumn was then eluted with dilute formic acid (0.05 *N*) with 23 mL fractions being collected. The progress of the chromatography was monitored by uv at 286.5 nm. Fractions 17–40 (550 mL) contained the product and were combined and concentrated, *in vacuo*, to ca. 6 mL of a clear, light violet solution. Ethanol (34 mL) was added to the solution which was then concentrated to ca. 20 mL by boiling. Ethanol (20 mL) was added again and the solution concentrated to 20 mL once more by boiling. The solution was slowly cooled to 25°C and the product separated out as a pale, purple colored powder that was washed with ethanol (4 × 5 mL) and then ethyl ether (2 × 5 mL). The dried solid weighed 283 mg (29.3% recovery), mp 239–241°C (vig. bubbling). Ultraviolet λ_{max} (pH 1): 286.5 nm (ε, 14 700); λ_{min} (pH 1): 245 nm (ε, 1 700); λ_{max} (MeOH): 287.5 nm (ε, 16 700); λ_{min} (MeOH): 245 nm (ε, 900); λ_{max} (pH 11): 230 nm (ε, 19 500), 286 (7 200), 314.5 (7 100); λ_{min} (pH 11): 256.5 nm (ε, 1 900), 298.5 (6 200). Proton magnetic resonance (DMSO-d_6) δ: 10.64 (br s, 1H, N—H), 6.10 (s, 2H, NH_2), 5.83 (d, 1H, H-1′, $J_{H-1',H-2'}$ = 5 Hz), 5.50 (s, 1H, H-7), 4.64 (t, 1H, H-2′), 4.20 (t, 1H, H-3′), 3.97 (q, 1H, H-4′), 3.48 (m, 2H, H-5′, 5″); $[\alpha]_D^{25°}$ −123.2°. *Anal.* calcd. for $C_{10}H_{13}N_5O_5$: C 42.40, H 4.63, N 24.73; found: C 42.64, H 4.54, N 24.76.

*Methyl 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-chloromethyl-*v*-triazole-4-carboxylate (17)*

Dry DMF (4.0 mL) and thionyl chloride (4.0 mL) were added, in one portion, to a stirred solution of methyl 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5-hydroxymethyl-*v*-triazole-4-carboxylate (**14**, 4.0 g, 6.65 mmol) in dry methylene chloride (200 mL). After 20 min, no starting material (R_f 0.2; SSA) was present as determined by tlc, instead a single new faster moving spot (R_f 0.6) had appeared. Methanol (4 mL) was added, dropwise, to the stirred solution (5 min) and the solution allowed to stir another 10 min. The solution was then washed in succession with ice-water (3 × 25 mL), saturated, aqueous sodium carbonate solution (20 mL), water (20 mL), and finally saturated brine (20 mL). The solution was dried (Na_2SO_4) and then concentrated *in vacuo* to afford a syrup (4.12 g, 100%) which did not crystallize even after a sample was purified by chromatography over silica gel (SSA). The compound (chromatographic sample) gave a strongly positive Beilstein test; $[\alpha]_D^{25°}$ −26.6°. *Anal.* calcd. for $C_{31}H_{26}ClN_3O_9$: C 60.05, H 4.23, N 6.78, Cl 5.72; found: C 59.97, H 4.22, N 6.56, Cl 5.91.

*Methyl 5-Methyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (20a)*

The chloromethyl derivative **17** (182 mg, 0.29 mmol) and triethylamine (100 μL) were added to a suspension of 5% Pd/C (182 mg) in ethyl acetate (5 mL). The mixture was stirred under an atmosphere of hydrogen for 20 h and then filtered through a dry-packed bed of Celite. The filter-cake was washed with small portions of ethyl acetate (3 × 4 mL), the filtrates were then combined and concentrated to give a mass of white needles. These needles were recrystallized from ethanol (4 mL) to give 91 mg (53.6%) of **20***a* as white needles, mp 106–108°C, $[\alpha]_D^{25°}$ −25.4°. *Anal.* calcd. for $C_{31}H_{27}N_3O_9$: C 63.36, H 4.65, N 7.17; found: C 63.16, H 4.43, N 6.99.

*Methyl 5-Methyl-1-(β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (26)*

The tri-*O*-benzoyl derivative **20***a* (900 mg, 1.54 mmol) was suspended in dry methanol (30 mL). A solution of sodium methoxide (2 mL of a 1.0 *N* solution) was added to this suspension and the mixture heated at reflux temperature for 5 min. The

solution was cooled to room temperature and Dowex 50 (H^+ form, prewashed with methanol) was then added, portionwise (about 1 mL required), until the "pH" was ca. 5. The resin was removed by filtration and washed with methanol (4 mL). The supernatant was concentrated *in vacuo* and the residue triturated with diethyl ether (3 × 20 mL) to remove methyl benzoate. The remaining residue was recrystallized from ethyl acetate (8 mL) to yield pure **26**, 185 mg (44%), mp 125–127°C. *Anal.* calcd. for $C_{10}H_{25}N_3O_6$: C 43.96, H 5.53, N 15.38; found: C 43.77, H 5.56, N 15.45.

*Methyl 5-Azidomethyl-1-(2,3,5-tri-*O*-benzoyl-* β-D-*ribofuranosyl)-*v*-triazole-4-carboxylate (**20**b)*

Powdered sodium azide (1.0 g, dried 18 h/25°C/0.1 Torr) was added to a stirred solution of the chloromethyl derivative **17** (3.2 g, 5.16 mmol) in dry DMF (20 mL) and stirring was continued for an additional 4 h at 25°C. Thin layer chromatography (SSA) indicated that the reaction was probably complete at this time since the grey-black spot of starting material had been replaced by a yellow-orange spot with the same R_f (detection: 10% sulfuric acid, 110°C). The mixture was stirred an additional 1.5 h at 70°C, allowed to stand at room temperature without stirring for 18 h, and then evaporated to dryness. The residue was dissolved in ethyl acetate (50 mL) and washed with saturated brine, dried, and evaporated to dryness to yield 2.82 g (88%) of a yellow syrup. The syrup was chromatographed using SSA (silica gel column, 5 cm × 35 cm) with 23 mL fractions being collected. Fraction 17 contained a single spot (630 mg) and was used to obtain an analytical sample as a pale yellow foam. Fractions 16, 18–23 were combined (to yield 1.14 g) and were nearly as pure as fraction 17. However, these combined fractions did contain a trace of a slower moving spot. *Anal.* calcd. for $C_{31}H_{26}N_6O_9$: C 59.42, H 4.18, N 13.41; found: C 59.60, H 4.27, N 13.17.

*Methyl 1-(2,3,5-Tri-*O*-benzoyl-*β-D-*ribofuranosyl)-5-carboxy-*v*-triazole-4-carboxylate (**21**)*

Methyl 5-hydroxymethyl-1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*v*-triazole-4-carboxylate (**14**, 1.5 g, 2.5 mmol) was dissolved in acetone (120 mL). This solution was stirred and cooled at 10–15°C while 2.5 mL of Jones reagent (35) was added over a period of 2 h. A small amount of the aldehyde intermediate (**18**) could still be detected so the solution was cooled to 0°C and an additional 0.2 mL of Jones reagent was added and the mixture stirred for another hour at 0°C. Isopropanol (0.5 mL) was then added and stirring was continued until the yellow color of dichromate ion was discharged (about 1 min). Water (150 mL) was added and then the solution was concentrated (25°C) to ca. 150 mL. The product was isolated by extraction with ether (3 × 100 mL). The extracts were combined and washed in succession with 0.1 *N* aqueous hydrochloric acid (2 × 40 mL), water (2 × 40 mL), and then saturated brine (2 × 40 mL). This solution was dried and then evaporated to give a green colored gum. This gum was triturated with 49:1 water – acetic acid (400 mL, v/v) to give a powdery solid. Repetition of this procedure using 97:3 water – acetic acid (400 mL, v/v) furnished 1.34 g (87%) of a white powder. The pmr spectra (see Table 1) of crude and chromatographed samples showed considerable line broadening suggesting the presence of some inorganic (Mn^{2+}) ion. The ir spectrum ($CHCl_3$ smear) displayed a moderate absorption at 2638 cm^{-1} indicating the presence of a carboxylic acid group (OH bonded). This product was not characterized but used without further purification for decarboxylation.

*Ethyl 1-(2,3,5-Tri-*O*-benzoyl-*β-D-*ribofuranosyl)-*v*-triazole-4-carboxylate (**24**b) and Methyl 1-(2,3,5-Tri-*O*-benzoyl-*β-D-*ribofuranosyl)-*v*-triazole-4-carboxylate (**24**a)*

The crude carboxylic acid (**21**, 1.0 g, 1.63 mmol) was dissolved in toluene (50 mL) and heated at reflux temperature for 26 h. The solution was filtered and the filtrate was evaporated to afford a solid residue. This solid was triturated with ethanol (7 mL) and then collected by filtration to afford 602 mg (64.8%) of **24***b*; mp 171–174°C. One recrystallization from ethanol (30 mL) gave pure **24***b* (518 mg); mp 175–176.5°C. *Anal.* calcd. for $C_{31}H_{27}N_3O_9$: C 63.58, H 4.65, N 7.18; found: C 63.30, H 4.60, N 7.22.

Decarboxylation was carried out on a 1.0 g (1.63 mmol) sample of crude **21**. However, the product from this reaction was recrystallized from methanol (50 mL) to give 602 mg (64.8%) of **24***a* as white crystals; mp 191–193.5°C (lit. (17) mp 195°C). Further recrystallization from methanol did not raise the mp; $[\alpha]_D^{25°}$ −74.3° (*c* 1.0, $CHCl_3$) (lit. (17) $[\alpha]_D$ −73.7° (*c* 0.55, $CHCl_3$)); $[\alpha]_D^{25°}$ −58.7° (*c* 1.0, DMSO). The pmr spectral data (Table 1) was nearly identical to that previously reported (17) for **24***a*. *Anal.* calcd. for $C_{30}H_{25}N_3O_9$: C 63.04, H 4.41, N 7.35; found: C 63.06, H 4.54, N 7.25.

*Methyl 1-(*β-D-*Ribofuranosyl)-*v*-triazole-4-carboxylate (**25**)*

The tri-*O*-benzoyl derivative **24***a* (493.8 mg, 0.864 mmol) was deblocked with sodium methoxide and methanol using the same procedure as used for the preparation of **26**. The crude product weighed 200 mg (89%) and had a mp of 147–150°C. Recrystallization from ethyl acetate (10 mL) containing a few drops of methanol gave a pure product in the form of white needles, 164 mg (73%); mp 150–151.5°C (lit (37) mp 151–153°C); $[\alpha]_D^{25°}$ −80.5°. *Anal.* calcd. for $C_9H_{13}N_3O_6$: C 41.79, H 5.07, N 16.22; found: C 41.89, H 5.13, N 16.39.

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