CYCLOADDITION OF ACETYLENES WITH 5-AZIDO-5-DEOXY- D-ALDOPENTOSE DERIVATIVES: SYNTHESIS OF TRIAZOLE REVERSED NUCLEOSIDE ANALOGS[¶]

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Abstract - 1,3-Dipolar cycloadditions of 5-azido-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**1**) or methyl 5-azido-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (**4**) with various acetylenes lead in most cases to mixtures of isomeric triazoles, the C-4 substituted product predominating in each case. The D-xylose derivative (**10**) and D-ribose derivative (**12**) were used as precursors to reversed nucleoside analogs (**16**) and (**17**).

Nucleoside analogs having modifications in both the sugar and heterocycle moeities have important medicinal potential. Such nucleoside mimics as ribavirin,[1] a synthetic purine analog containing a modified heterocycle (a 3-carbamoyl-1,2,4-triazole group at C-1 of β-D-ribofuranose), demonstrate significant antiviral activity, and analogs such as acyclovir,[2] which contains an acyclic non-sugar side-chain attached to the heterocyclic function, constitute clinically effective antivirals. Such modified nucleosides such as 3'-azido-3'-deoxythymidine (AZT)[3] and 5,5,5-trifluorothymidine[4] represent further examples of important antivirals, the former being effective against human immunodeficiency virus (HIV),[5] the latter against herpes simplex virus (HSV).[6]

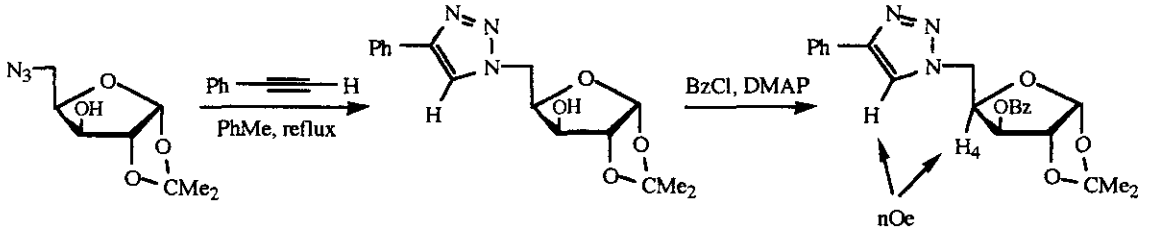
The synthesis of nucleoside analogs in which the heterocyclic group is placed at positions other than the anomeric position of the sugar moeity has received attention. When the heterocycle is placed at C-5 of an

aldopentose, such compounds have been termed "reversed nucleosides".[7]

Our laboratory has had a sustained interest in synthetic routes to nucleoside mimics bearing variously substituted heterocyclic functionalities and modifications in the sugar moeities.[8] We now report the synthesis of several 1,2,3-triazole purine analogs of the "reversed nucleoside" class in which the key step is cycloaddition of an acetylene to a 5-azido-5-deoxy-D-xylose or -D-ribose derivative.

1,3-Dipolar Cycloadditions

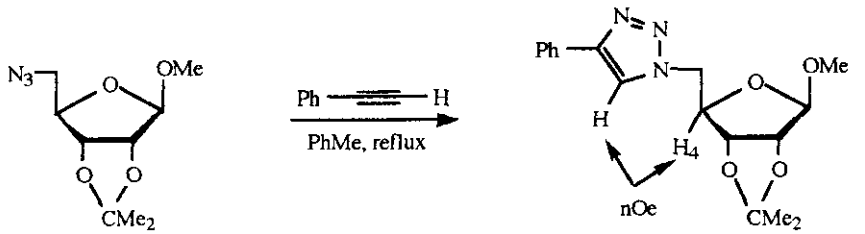
1,3-Dipolar cycloaddition of 5-azido-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**1**)[9] with phenylacetylene in refluxing toluene gave a single crystalline product in 82% yield, identified as 5-deoxy-1,2-O-isopropylidene-5-C-(4-phenyl-1,2,3-triazol-1-yl)-α-D-xylofuranose (**2**). Assignment of compound (**2**) as the 4-substituted triazole, and not the 5-phenyl regioisomer, is based on steric considerations and NOESY data. Crowding in the transition state for formation of the 4-phenyl isomer should be less than in the alternative situation leading to the corresponding 5-phenyl triazole. Numerous studies, including many with azidodeoxy sugars, have shown that the 4-substituted derivative is generally favored in cycloadditions of this type,[10] and it is often the exclusive product if the acetylene substituent is of sufficient size. Treatment of **2** with benzoyl chloride in pyridine afforded the crystalline 3-benzoate (**3**), the ^{1}H-nmr spectrum of which proved to be better resolved than that of **2** and allowed for unequivocal assignment of the sugar ring protons. The NOESY spectrum of **3** showed interaction between H-5 of the triazole ring and H-4 of the sugar. This would not be expected if **3** were the 5-substituted triazole.



1 **2** **3**

Reaction of methyl 5-azido-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (**4**)[11] with phenylacetylene in refluxing toluene also afforded a single product, formulated as methyl 5-deoxy-2,3-O-isopropylidene-5-C-(4-phenyl-1,2,3-triazol-1-yl)-β-D-ribofuranoside (**5**), in 81% yield. As in the case for the D-xylo analog (**2**), the product was formulated as the 4-substituted triazole (**5**) on the basis of steric considerations and

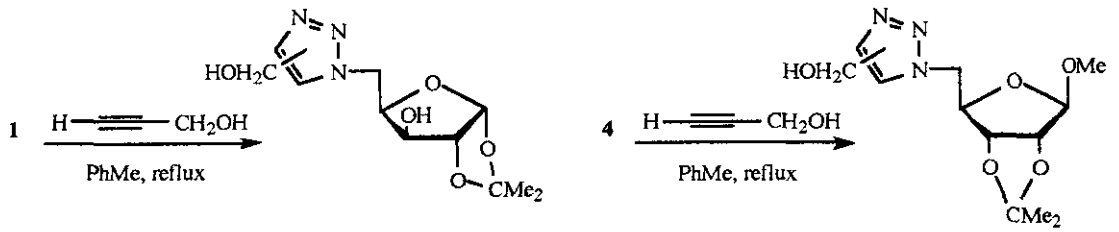
consideration of its NOESY spectrum. The ^1H nmr spectrum of this product showed a singlet for H-5 of the triazole ring at 7.87 ppm, close to the corresponding signal for D-xylo analogs (**2**) and (**3**) (vide infra).



4 **5**

Whereas azides (**1**) and (**4**) reacted with phenylacetylene to form a single product in each case, both compounds were found to yield mixtures of isomeric triazoles when heated with propargyl alcohol or ethyl propiolate.

Treatment of D-xylo azide (**1**) with an excess of propargyl alcohol in refluxing toluene gave a syrupy mixture of two compounds considered, on the basis of mass-spectral and ^1H nmr data, to be the isomeric triazoles (**6**) and (**7**). Formed in approximately equal amounts (based on integration of the signals for the triazole ring protons in the ^1H nmr spectrum of the syrup), the two compounds could not be cleanly separated on silica gel and specific assignment of triazole ring substitution could not be made.

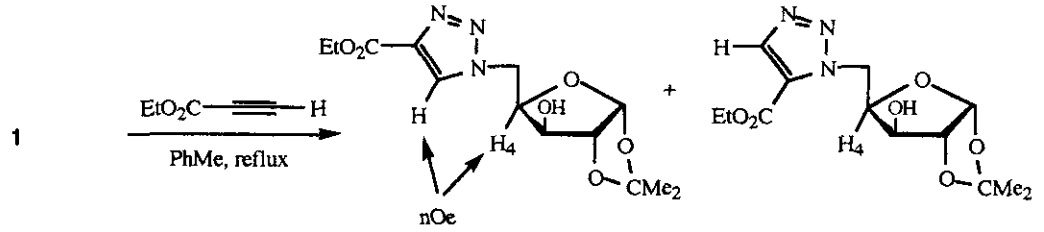


6, 7 **8, 9**

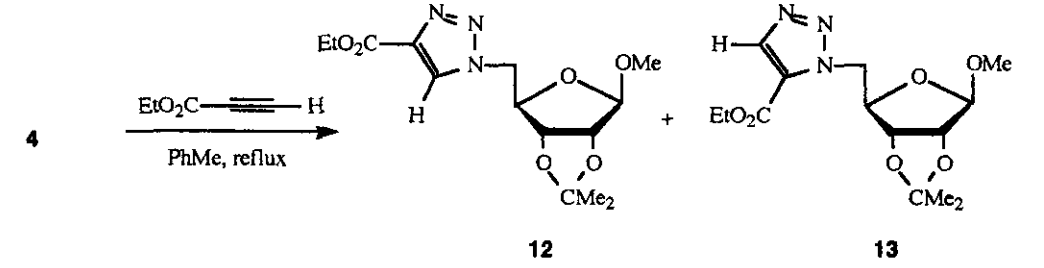
Likewise, D-ribo azide (**4**) afforded a syrupy mixture of isomeric triazoles upon reaction with propargyl alcohol, in this case in ~2.3:1 ratio. The major isomer in this mixture was considered to be the 4-substituted triazole (**8**) and the minor isomer the 5-substituted analog (**9**). As in the D-xylo example above, resolution of the mixture on silica gel could not be effected.

In contrast to the reaction with propargyl alcohol, the products from reaction of D-xylo azide (**1**) with ethyl propiolate were readily separated by column chromatography to afford 5-deoxy-5-C-(4-ethoxycarbonyl-1,2,3-triazol-1-yl)-1,2-O-isopropylidene-α-D-xylofuranose (**10**) as a colorless crystalline solid (51%) and

5-deoxy-5-C-(5-ethoxycarbonyl-1,2,3-triazol-1-yl)-1,2-O-isopropylidene-α-D-xylofuranose (**11**) also as a colorless solid (26%). Initial formulation of compounds (**10**) and (**11**) as being 4- and 5-substituted triazoles respectively was made from steric considerations during the cycloaddition step, and unambiguous confirmation was provided by a single-crystal X-ray analysis of compound (**11**).[12] Correlations in the NOESY spectrum of compound (**10**) (between H-4 of the xylofuranose ring and the triazole proton) helped confirm the regiochemical assignments of **10** and **11**, since such interaction was not observed for compound (**11**).



The D-ribo azide (**4**) showed similar reactivity with ethyl propiolate and afforded a pair of isomeric triazoles, methyl 5-deoxy-5-C-(4-ethoxycarbonyl-1,2,3-triazol-1-yl)-2,3-O-isopropylidene-β-D-ribofuranoside (**12**) as a colorless crystalline solid (65%) and methyl 5-deoxy-5-C-(5-ethoxycarbonyl-1,2,3-triazol-1-yl)-2,3-O-isopropylidene-β-D-ribofuranoside (**13**) as a colorless syrup (23%).



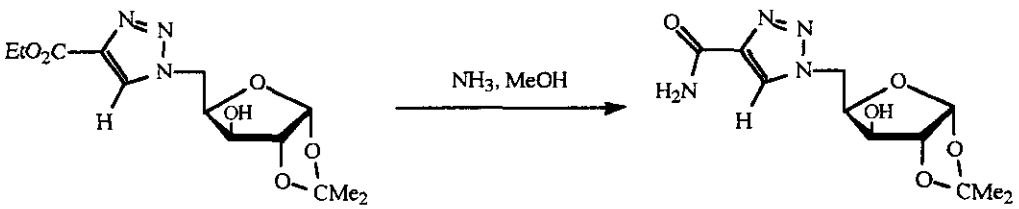
It has been suggested previously[13] that the chemical shifts of the triazole ring protons can be used to differentiate between 4- and 5-substituted isomers. However, in the case of compounds (**12**) and (**13**), this rationale was not reliable, since the heterocyclic ring protons resonated at almost identical chemical shifts (8.22 ppm for **12** and 8.17 ppm for **13**). The overall ^{1}H nmr spectra of these compounds were quite similar, and the major isomer was assigned as the 4-substituted triazole (**12**) by analogy with the reaction of

D-xylo azide (**1**) with ethyl propiolate, the regiochemical outcome of which had been proven unequivocally by the X-ray analysis of compound (**11**).

Additional supporting evidence for the regiochemical assignments of isomers (**12**) and (**13**) may be garnered from consideration of the ^{13}C nmr shifts for C-5 and C-4 of the triazole rings as compared with those found in D-xylose-derived analogs (**10**) and (**11**). In each case, the 4-substituted triazoles (**10**) and (**12**), and likewise the 5-substituted triazoles (**11**) and (**13**), differ only in their substitution at N-1 of the triazole ring. This difference in substitution would not be expected to cause a significant change in ^{13}C chemical shifts for the isomeric triazoles when moving from the D-xylo series to the D-ribo series. Thus, taking the chemical shift (137.8 ppm) for C-4 in compound (**11**) as a reference (the structure of **11** having been solved by X-ray crystallography), the corresponding shift for C-4 in D-ribo analog (**13**) is found to be 138.0 ppm. Likewise, since compound (**10**) must be the C-4 substituted product, the chemical shift for C-5 (140.2 ppm) should, and indeed does, correlate with that found in the D-ribo analog (**12**) (140.5 ppm).

Preparation of 4-Carbamoyl-1,2,3-triazole "Reversed Nucleoside" Analogs

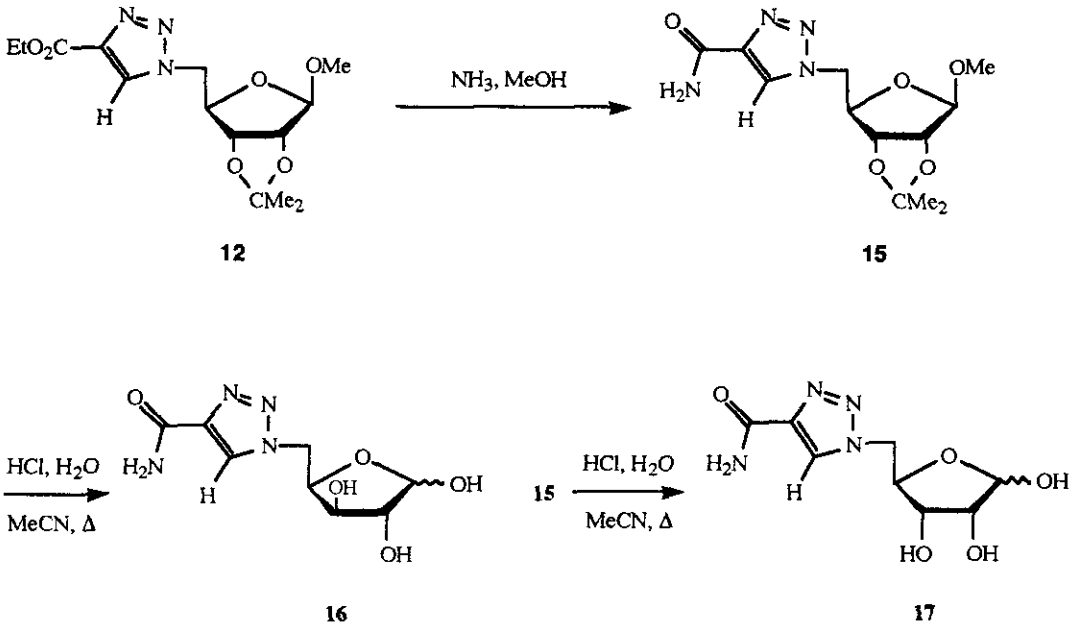
The 4-ethoxycarbonyl-substituted 1,2,3-triazoles (**10**) and (**12**) were chosen for conversion into 1,2,3-triazoles bearing 4-carbamoyl groups, since the structures of these compounds had been firmly established from X-ray and ^{13}C data. Thus, treatment of D-xylo derivative (**10**) with methanolic ammonia afforded a crystalline solid identified as **14**, a heterocycle-truncated "reversed purine nucleoside" analog.



10 **14**

Likewise, treatment of D-ribo derivative (**12**) with methanolic ammonia yielded a crystalline solid identified as protected 4-carbamoyl-1,2,3-triazolyl reversed nucleoside (**15**). The structures of compounds (**14**) and (**15**) followed from their ^{1}H and ^{13}C nmr spectra as well as their elemental analyses. In both cases, deprotection of the sugar portions of **14** and **15** proved straightforward using aqueous hydrochloric acid to

afford the free sugar analogs (**16**) and (**17**) in good yields.



In conclusion, the cycloaddition reactions of 5-azido-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**1**) and methyl 5-azido-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (**4**) with several acetylenes have been studied as a route to reversed nucleoside analogs. In most cases the C-4 substituted triazole predominates when a mixture of regioisomeric products are formed. Ethoxycarbonyl-substituted derivatives (**10**) and (**12**) served as convenient precursors to reversed purine nucleoside analogs (**16**) and (**17**).

EXPERIMENTAL

General Methods– Solutions were evaporated at 40 °C under diminished pressure. Melting points were determined with a Thomas–Hoover Unimelt apparatus and are uncorrected. Optical rotations were measured in a 1-dm polarimeter tube with a Perkin–Elmer model 141 polarimeter at 25 °C. Infrared spectra were obtained with a Bio-Rad SPC 3200 FT-IR instrument. ^{1}H nmr and ^{13}C nmr spectra were recorded on a Varian Gemini 300 instrument (300 MHz for ^{1}H, 75 MHz for ^{13}C) for solutions in $CDCl_3$, Me_2SO-d_6, and D_2O. Chemical shifts (ppm) are relative to Me_4Si (δ = 0.00) as the internal standard in $CDCl_3$ and Me_2SO-d_6 solutions. Mass spectra were recorded on a Finnegan 4600 instrument at the Laboratory of

Table 1. ^{1}H Nmr chemical shifts and coupling constants for D-xylo triazole derivatives

Compd.	Triazole H	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5'}$	H-5 $J_{4,5}$	H-5' $J_{5,5'}$	CMe_2	other
2[a]	7.90	6.02d 3.5	4.62d 0.0	3.25d 4.6	4.50m	4.81dd 6.6	4.60m 13.9	1.33, 1.47	7.36-7.82 (Ar)
3[a]	7.93	6.08d 3.7	4.73d 0.0	5.58d 2.0	4.77m 8.2	4.85dd 3.3	4.55dd 14.0	1.33, 1.51	7.33-8.04 (Ar)
6, **7**[a]	7.65, 7.69	5.98d 3.2	——	——	4.21-4.80m	——	——	1.31, 1.46	
10[a]	8.27	6.01d 3.3	4.61d 0.0	4.31br s	4.50m 7.1	4.85dd 5.5	4.65dd 14.2	1.32, 1.39	1.40t, 4.39q 7.3 7.3
11[a]	8.16	5.98d 3.5	4.60d 0.0	4.15br s	4.51m 8.7	5.23dd 5.2	4.86dd 13.5	1.32, 1.47	1.40t, 4.39q 7.3 7.3
14[b]	8.52	5.88d 3.4	4.48d 3.5	5.66 4.6	4.43m 7.4	4.65dd 3.5	4.52dd 13.7	1.24, 1.36	7.86,7.48 br s (NH)

Table 2. ^{13}C Nmr chemical shifts for D-xylo triazole derivatives

Compd.	C-4, C-5 (tr)	C-1	C-2	C-3	C-4	C-5	CMe_2	CMe_2	other
2[a]	147.9, 130.1	105.2	74.6[c]	79.4[c]	85.5[c]	49.1	112.1	26.9, 26.2	128.9, 128.4, 125.8, 121.4 (Ar)
3[a]	148.1, 130.5	105.0	76.6[c]	76.9[c]	83.5[c]	49.3	112.7	26.6, 26.1	129.8, 128.8c, 128.1, 125.7, 120.6 (Ar), 165.1 (CO)
6, **7**[a]	147.4, 123.6	105.0	74.2[c]	79.1[c]	85.3[c]	52.4	112.1	26.7, 26.1	55.7 (CH_2OH)
10[a]	140.2, 128.8	105.1	74.6[c]	78.9[c]	85.4[c]	49.4	112.2	26.8, 26.2	160.6 (CO), 61.5 (OCH_2CH_3), 14.4 (OCH_2CH_3)
11[a]	137.8, 128.7	105.0	74.2[c]	77.4[c]	85.0[c]	47.3	112.0	26.7, 26.1	158.6 (CO), 62.2 (OCH_2CH_3), 14.0 (OCH_2CH_3)
14[b]	143.0, 127.1	104.6	73.6[c]	79.0[c]	85.1[c]	49.2	110.9	26.6, 26.1	161.6 (CO)

a spectrum taken in $CDCl_3$

b spectrum taken in Me_2SO-d6

c interchangeable

Table 3. ^{1}H Nmr chemical shifts and coupling constants for D-ribo triazole derivatives

Compd.	triazole H	H-1 $J_{1,2}$	H-2 $J_{2,3}$	H-3 $J_{3,4}$	H-4 $J_{4,5'}$	H-5 $J_{4,5}$	H-5' $J_{5,5'}$	CMe_2 OMe	other
5[a]	7.87	5.05s 0.0	4.81d 6.0	4.70d 0.0	4.63m 10.0	4.81dd 10.0	4.60m 16.0	1.32, 1.47 3.42	7.34-7.83 (Ar)
8, 9[a]	7.62, 7.65	5.02s, 5.06s 0.0	———	———	4.51-4.93m	———	———	1.30, 1.46 3.40	
12[a]	8.22	5.05s 0.0	4.76d 5.8	4.68d 0.0	———	4.53-4.60m	———	1.33, 1.48 3.41	1.41t, 4.42q 7.5 7.5
					7.1	5.5	14.2		
13[a]	8.17	5.04s 0.0	4.84d 5.8	4.72d 0.0	4.64t 7.1	———	4.89m ———	1.31, 1.46	1.40t, 4.39q 7.4 7.4
15[a]	8.64	4.99s 0.0	4.82d 4.82	4.68d 6.0	———	4.49-4.62m	———	1.28, 1.39 3.34	7.88,7.51br s (NH)

Table 4. ^{13}C Nmr chemical shifts for D-ribo triazole derivatives

Compd.	C-4, C-5 (tr)	C-1	C-2	C-3	C-4	C-5	$\underline{C}Me_2$	CMe_2	OMe	other
5[a]	148.0, 130.5	110.1	81.8[c]	85.0[c]	85.2[c]	53.2	112.9	26.3, 24.9	55.6	128.8, 128.2, 125.8, 119.8 (Ar)
8, 9[a]	137.1, 133.6	110.6	82.2[c]	85.3[c]	85.4[c]	53.3	113.3	26.9, 25.4	56.1	51.4 (CH_2OH)
12[a]	140.5, 127.9	110.2	81.6[c]	84.9[c]	85.0[c]	53.4	113.1	26.3, 24.8	55.7	160.7 (CO), 61.3 ($OC\underline{H}_2CH_3$), 14.2 ($OCH_2C\underline{H}_3$)
13[a]	138.1, 128.1	110.1	81.6[c]	84.8[c]	85.2[c]	52.6	112.7	26.3, 24.8	55.4	158.5 (CO), 62.0 ($OC\underline{H}_2CH_3$), 14.1 ($OCH_2C\underline{H}_3$)
15[b]	143.2, 126.8	109.1	81.1[c]	81.4[c]	84.5[c]	52.6	111.8	26.2, 24.6	54.7	161.4 (CO)

a spectrum taken in $CDCl_3$

b spectrum taken in Me_2SO–$\underline{d}_6$

c interchangeable

Analytical Chemistry of the National Institutes of Health, Bethesda, MD. Tlc was performed on precoated aluminum plates of silica gel 60F-254 (E. Merck) and spots were detected by spraying with 10% H_2SO_4 in ethanol and subsequent heating. Column chromatography was performed with silica gel 60 (E. Merck, Darmstadt, Germany). Microanalyes were performed by Atlantic Microlab, Inc., Norcross, GA.

5-Deoxy-1,2-O-isopropylidene-5-C-(4-phenyl-1,2,3-triazol-1-yl)-α-D-xylofuranose (2) and its 3-benzoate (3). 5-Azido-5-deoxy-1,2-O-isopropylidene-α-D-xylofuranose[9] (**1**, 108 mg, 0.505 mmol) and phenylacetylene (0.25 ml, 2.5 mmol) were dissolved in dry toluene (2 ml) and the mixture was heated under reflux for 20 h. Tlc analysis (1:1 ethyl acetate–hexane) showed complete consumption of the starting material and formation of a major product, R_f 0.32. Evaporation of solvent gave a syrupy residue which was triturated with a mixture of hexane and EtOAc (~6:1) to afford a colorless solid (130 mg, 82%). Recrystallization from the same solvents gave **2** as colorless crystals; mp 163-165 °C; $[\alpha]_D$ -39.6° (c 1.2, $CHCl_3$); m/z 318 (M^+ + 1); ir ($CHCl_3$) 3325, 1412, 1170, 1090 cm^{-1}.

Benzoyl chloride (240 mg, 2.0 mmol) was added dropwise to a solution of triazole (**2**) (317 mg, 1.0 mmol) in dry pyridine (5 ml) which had been cooled to 0 °C. After warming the solution to room temperature and stirring for 24 h, tlc (3:1 hexane–EtOAc) showed consumption of starting material and formation of a major, uv-active product, R_f 0.60. The mixture was poured into ice (10 g), extracted with chloroform (3 x 10 ml), and the combined organic extracts washed successively with water (10 ml), 5% H_2SO_4 (10 ml), saturated sodium hydrogencarbonate (10 ml), and again with water (10 ml). After drying (Na_2SO_4), the solvent was evaporated to leave a syrup from which toluene (2 x 10 ml) was evaporated. Crystallization with hexane–EtOAc afforded **3** as colorless crystals (302 mg, 72%): mp 178-179 °C ; $[\alpha]_D$ -5° (c 1.2, $CHCl_3$); ms m/z 422 (M^+ + 1); ir ($CHCl_3$) 3050, 1725, 1450, 1190, 1170 cm^{-1}. Anal. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.56; H, 5.46; N, 9.98 Found : C, 65.34; H, 5.54; N, 9.95.

Methyl 5-deoxy-1,2-O-isopropylidene-5-C-(4-phenyl-1,2,3-triazol-1-yl)-β-D-ribofuranoside (5). A mixture of methyl 5-azido-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside (**4**)[11] (187 mg, 0.82 mmol) and phenylacetylene (0.4 mL, 4.1 mmol) in toluene (2 ml) was heated under reflux for 5 h, after which time tlc (6:1 hexane–EtOAc) showed a single product, R_f = 0.19. After removal of solvent, the syrupy residue was passed through a column of silica gel, using 3:1 hexane–EtOAc as eluent, to afford

triazole (**5**) as a colorless solid. Recrystallization from hexane–EtOAc gave colorless crystals (213 mg, 81%): mp 135–136 °C; $[\alpha]_D$ +19.7° (c 0.1, $CHCl_3$); m/z 332 (M + 1); ir ($CHCl_3$) 3050, 1460, 1170, 1120 cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_3O_4$: C, 61.63; H, 6.34; N, 12.69. Found : C, 61.47; H, 6.28 ; N, 12.74.

5-Deoxy-5-C-(4-hydroxymethyl-1,2,3-triazol-1-yl)-1,2-O-isopropylidene-α-D-xylofuranose and 5-deoxy-(5-hydroxymethyl-1,2,3-triazol-1-yl)-1,2-O-isopropylidene-5-C-α-D-xylofuranose (6 and 7). A mixture of azide (**1**) (0.11 g, 0.51 mmol) and propargyl alcohol (0.15 ml, 2.55 mmol) in dry toluene (2 ml) was refluxed for 4 h, the solvent evaporated, and the residue chromatographed on silica gel using 5:1 toluene–MeOH as eluent. The product (R_f = 0.20–0.23) was collected as a colorless syrup (0.123 g, 94%). For the mixture: m/z 272 (M^+ + 1); ir (neat) 3300, 1650, 1480, 1425 cm^{-1}. Anal. Calcd for $C_{11}H_{17}N_3O_5$: C, 48.71; H, 6.27. Found : C, 49.00; H, 6.79.

Methyl 5-deoxy-5-C-(4-hydroxymethyl-1,2,3-triazol-1-yl)-2,3-O-isopropylidene-β-D-ribofuranoside and methyl 5-deoxy-5-C-(5-hydroxymethyl-1,2,3-triazol-1-yl)-2,3-O-isopropylidene-β-D-ribofuranoside (8 and 9). Azide (**4**) (0.11 g, 0.48 mmol) and propargyl alcohol (0.14 ml, 2.4 mmol) in dry toluene (2 ml) was refluxed for 18 h. Tlc (5:1 toluene–MeOH) showed two closely migrating products, R_f = 0.32 and 0.38. Evaporation of solvent and purification of the remaining syrup on silica gel using 5:1 toluene–MeOH as eluent afforded the isomeric products as a colorless syrup (0.118 g, 86%). For the mixture: m/z 286 (M^+ + 1); ir (neat) 1650, 1480, 1425 cm^{-1}. Anal. Calcd for $C_{12}H_{19}N_3O_5$: C, 50.53; H, 6.67; N, 14.74. Found : C, 50.74; H, 6.71; N, 14.71.

5-Deoxy-5-C-(4-ethoxycarbonyl-1,2,3-triazol-1-yl)-1,2-O-isopropylidene-α-D-xylofuranose (10) and 5-deoxy-5-C-(5-ethoxycarbonyl-1,2,3-triazol-1-yl)-1,2-O-isopropylidene-α-D-xylofuranose (11). A mixture of azide (**1**)[9] (0.94 g, 4.37 mmol) and ethyl propiolate (1 ml, 9.6 mmol) in dry toluene (15 ml) was refluxed for 4 h and then evaporated to a syrup. Tlc analysis revealed two products, R_f 0.33 and 0.17 (1:1 hexane–EtOAc), which were separated on a column of silica gel using 1:1 hexane–EtOAc as eluent. The less-polar component of the mixture was isolated as a colorless solid and identified as the 5-substituted triazole (**11**) (0.35 g, 26%): mp 116-118 °C (recrystallized from hexane–EtOAc); $[\alpha]_D$ -21.2° (c 4.2, $CHCl_3$); m/z 314 (M^+ + 1); ir ($CHCl_3$) 3350, 1725, 1210, 1080 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_3O_6$: C, 49.84; H, 6.07; N, 13.42. Found: C, 49.91; H, 6.05; N, 13.32.

The more-polar product was collected as a colorless solid and identified as 4-substituted triazole (**10**) (0.70 g, 51%): mp 130-131 °C; $[\alpha]_D$ -20° (c 5.0, $CHCl_3$); m/z 314 (M^+ + 1); ir ($CHCl_3$) 3325, 1725, 1215, 1085 cm^{-1}. Anal. Calcd for $C_{13}H_{19}N_3O_6$: C, 49.84; H, 6.07; N, 13.42. Found : C, 49.96; H, 6.10; N, 13.49.

Methyl 5-deoxy-5-C-(4-ethoxycarbonyl-1,2,3-triazol-1-yl)-2,3-O-isopropylidene-β-D-ribo-furanoside (12) and methyl 5-deoxy-5-C-(5-ethoxycarbonyl-1,2,3-triazol-1-yl)-2,3-O-isopropylidene-β-D-ribofuranoside (13). A solution of azide (**4**)[11] (1.1 g, 4.8 mmol) and ethyl propiolate (1 ml, 9.6 mmol) in toluene (15 ml) was refluxed for 3 h and then evaporated to a syrup. Separation of the syrupy mixture by flash chromatography (silica gel), using 3:1 hexane–EtOAc as eluent, afforded two products. First, the 5-substituted triazole (**13**) was isolated as a colorless syrup (0.395 g, 25%): R_f 0.33 (3:1 hexane–EtOAc); $[\alpha]_D$ -33.3° (c 4.3, $CHCl_3$); m/z 328 (M^+ + 1); ir (neat) 2950, 1728, 1545, 1450 cm^{-1}. Anal. Calcd for $C_{14}H_{21}N_3O_6$: C, 51.38; H, 6.42; N, 12.84. Found : C, 51.27; H, 6.45; N, 12.76.

The second product, identified as the 4-substituted triazole (**12**), was isolated as a colorless solid (0.788 g, 50%): mp 100-102 °C (recrystallized from hexane–EtOAc); R_f 0.14 (3:1 hexane–EtOAc); $[\alpha]_D$ -11.0° (c 4.0, $CHCl_3$); m/z 328 (M + 1); ir ($CHCl_3$) 2980, 1745, 1560, 1455 cm^{-1}. Anal. Calcd for $C_{14}H_{21}N_3O_6$: C, 51.38; H, 6.42; N, 12.84. Found : C, 51.31; H, 6.39; N, 12.89.

5-Deoxy-5-C-(4-carbamoyl-1,2,3-triazol-1-yl)-1,2-O-isopropylidene-α-D-xylofuranose (14). To a saturated solution of ammonia in methanol (15 ml) held at 0 °C was added triazole (**10**) (145 mg, 0.46 mmol). The mixture was stirred for 16 h at room temperature and the solvent removed to afford amide (**14**) as a colorless solid (120 mg, 92%). Recrystallization from absolute ethanol gave **14** as a colorless powder: mp 220-221 °C; R_f 0.42 (3:1 toluene–MeOH); $[\alpha]_D$ -11° (c 1.1, Me_2SO); m/z 285 (M^+ + 1). Anal. Calcd for $C_{14}H_{21}N_3O_6$: C, 46.48; H, 5.63; N, 19.72. Found: C, 46.57; H, 5.67; N, 19.75.

Methyl 5-Deoxy-5-C-(4-carbamoyl-1,2,3-triazol-1-yl)-2,3-O-isopropylidene-β-D-ribofuranoside (15). Triazole (**12**) (250 mg, 0.76 mmol) was treated with ammonia-saturated methanol exactly as in the last experiment. Evaporation of solvent after 16 h at room temperature afforded amide (**15**) as a colorless solid which was recrystallized from boiling EtOAc (200 mg, 88%); mp 227-228 °C; R_f 0.47

(toluene–MeOH, 3:1); $[\alpha]_D$ -13° (c 0.5, Me_2SO); ms ($M^+ + 1$) m/z 299. Anal. Calcd for $C_{12}H_{18}N_4O_5$: C, 48.32; H, 6.04; N, 18.79. Found: C, 48.12; H, 6.00; N, 18.70.

5-C-(4-Carbamoyl-1,2,3-triazol-1-yl)-5-deoxy-α,β-D-xylofuranose (16). To a solution of triazole (**14**) (300 mg, 1.05 mmol) in acetonitrile (15 ml) was added water (3 ml) and concentrated hydrochloric acid (2 drops). The solution was heated at reflux for 8 h and then cooled and neutralized with solid $NaHCO_3$. The solvents were evaporated off and the residue was extracted with hot methanol (5 x 5 ml). Decolorization of the extracts with charcoal, filtration, and evaporation afforded reversed nucleoside (**16**) as a colorless syrup (185 mg, 72%); ^1H nmr (Me_2SO-d_6) δ 8.26 (s, 1 H, H-5 triazole), 7.85 (br s, 1 H, NH), 7.47 (br s, 1 H, NH), 3.24-4.68 (m, 9 H, sugar ring protons, OH); m/z 262, 210, 167, 150, 130 (base).

5-C-(4-Carbamoyl-1,2,3-triazol-1-yl)-5-Deoxy-α,β-D-ribofuranose (17). In a manner similar to the preceding experiment, triazole (**15**) (100 mg, 0.31 mmol) was refluxed in a mixture of water (1 ml), concentrated hydrochloric acid (1 drop), and acetonitrile (5 ml) for 8 h. Isolation as in the previous experiment gave compound (**17**) as a colorless syrup (56 mg, 77%); ^1H nmr (Me_2SO-d_6) δ 8.23 (s, 1 H, H-5 triazole), 7.86 (br s, 1 H, NH), 7.48 (br s, 1 H, NH), 3.40-4.83 (m, 9 H, sugar ring protons, OH); m/z 262, 210, 180, 150, 130 (base).

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REFERENCES AND NOTES

¶ Dedicated to Professor Harold Shechter on the occasion of his 75th birthday.

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12. Details of the solution of the crystal structure of compound (**11**) will be reported separately.

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