Synthesis of bitriazolyl nucleosides and unexpectedly different reactivity of azidotriazole nucleoside isomers in the Huisgen reaction

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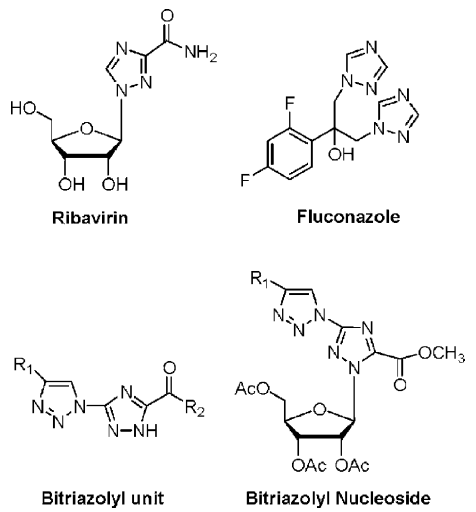
Novel bitriazolyl nucleosides were synthesized *via* the Huisgen reaction, starting with 3-azidotriazole nucleoside (**1**). Surprisingly, its isomer, 5-azidotriazole nucleoside (**1′**) did not yield the corresponding Huisgen reaction products efficiently because it was rapidly reduced to amine in the presence of Cu(II)–ascorbate. The significant differences between the reactivity of these two isomers in Cu(II)–ascorbate mediated reactions are mainly due to differences in their electronic properties and steric congestion as a result of different relative positions of the azido and the ribosyl moieties.

Introduction

Triazole units are heterocyclic structural motifs with considerable medicinal and agrochemical potential. Ribavirin (Scheme 1), a triazole nucleoside, which was the first synthetic nucleoside found to show antiviral activity,[1] is the only small-molecule drug currently available for treating patients infected with the hepatitis C virus.[2] Fluconazole (Scheme 1), which has two 1,2,4-triazole residues, is a powerful antifungal agent.[3] We recently discovered bitriazolyl compounds (Scheme 1) which showed promising activity against the tobacco mosaic virus (TMV).[4,5] In our ongoing research on novel triazole compounds with medicinal and agrochemical potentials,[4–6] we are interested in developing bitriazolyl ribonucleosides (Scheme 1) because nucleoside derivatives provide useful means of combating various viruses. Here we report on the synthesis and characterization of these novel bitriazolyl ribonucleosides using the Huisgen reaction with 3-azidotriazole nucleoside **1**, and describe the unexpected reduction of 5-azidotriazole nucleoside **1′** occurring in the mild Cu(II)–ascorbate system.

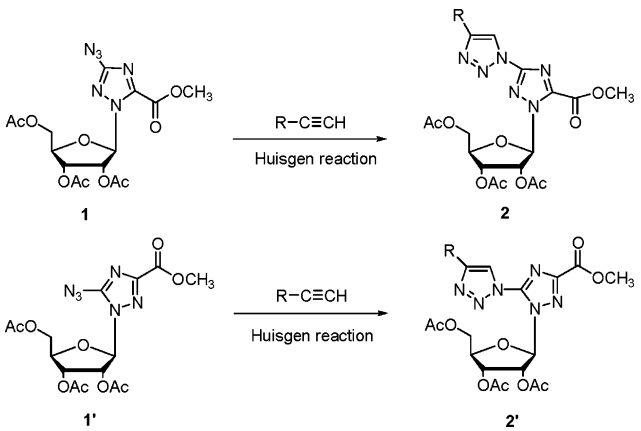


Scheme 1 Ribavirin, fluconazole, bitriazolyles and bitriazolyl nucleoside.

Results and discussion

1. Synthesis of bitriazolyl nucleosides

3-Azidotriazole nucleoside **1** and 5-azidotriazole nucleoside **1′**, the precursors of the photolabeling probes of ribavirin, which were previously developed at our laboratories,[7] were used as starting materials to synthesize the bitriazolyl nucleosides *via* the Huisgen reaction (Scheme 2).[8]



Scheme 2 Synthesis of the bitriazolyl nucleosides *via* Cu(I)-catalyzed Huisgen reaction.

In line with previous findings,[4,5] bitriazolyl nucleoside **2** was obtained in good to excellent yields from **1** under copper(I)-catalyzed Huisgen reaction conditions (Table 1), regardless of whether the substituents in the alkynes were aliphatic (entries 3–6 in Table 1), aromatic (entries 7–11 in Table 1), or electron-withdrawing groups (entries 1, 2 in Table 1). The reactions were conveniently carried out by simply stirring **1** and the corresponding terminal alkynes in the presence of $CuSO_4$ and sodium ascorbate

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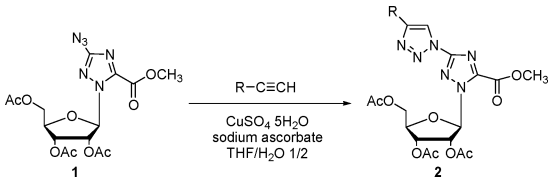
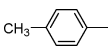
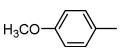
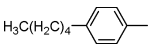
Table 1 Bitriazolyl nucleosides (**2**) synthesized *via* copper(I)-catalyzed Huisgen reaction using **1**



Entry	R	Product	Yield (%)[a]	Yield (%)[b]
1	$CH_3OC(=O)-$	**2a**	81.4	78.5
2	$CH_3CH_2OC(=O)-$	**2b**	77.6	72.7
3	$CH_3C(=O)OCH_2-$	**2c**	87.7	79.7
4		**2d**	81.1	74.0
5		**2e**	98.4	75.5
6		**2f**	70.1	85.0
7		**2g**	98.1	77.5
8		**2h**	85.9	83.9
9		**2i**	81.9	66.3
10		**2j**	73.2	70.2
11		**2k**	89.1	71.4

[a] At 80 °C. [b] At 25 °C.

at 80 °C in a THF–H_2O solvent system for 1 h. Only the 1,4-disubstituted 1,2,3-triazoles were obtained, which is in agreement with the proposed reaction mechanism that the copper(I) acetylide intermediate formed may undergo stepwise addition with the azide, resulting in the regioselective product.[9] The structures of 1,4-disubstituted 1,2,3-triazoles were further confirmed by performing X-ray structural analysis on the two products **2a** and **2i** (Fig. 1). Although the X-ray crystallographic analysis only established the relative, not the absolute stereochemistry, it is worth noting that the bitriazolyl units in both **2a** and **2i** approach co-planarity, as previously observed in the case of bitriazolyl compounds.[5] The

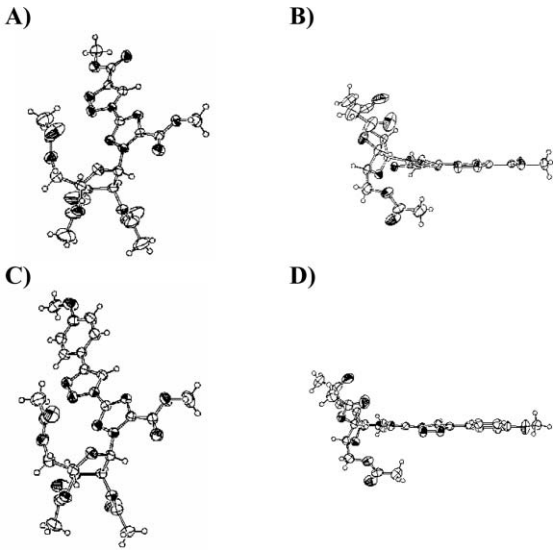
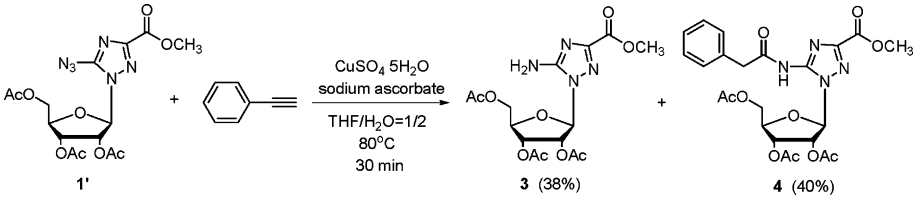


Fig. 1 X-Ray structures of **2a** (A and B) and **2i** (C and D) (ORTEP probability 50%).

bitriazolyl unit may therefore be an interesting motif for mimicking conjugated or enlarged nucleobases.

In addition, the Huisgen reaction between **1** and various alkynes occurred readily even at room temperature, although this gave slightly lower yields (Table 1). We know from our previous work that the azidotriazole without a ribosyl substituent was not able to undergo the Huisgen reaction at room temperature to give the corresponding bitriazolyl compounds.[4,5] Therefore, the introduction of the ribosyl group at N-1 of the triazole ring promotes the reactivity of **1** in the Huisgen reaction.

However, the Huisgen reaction was not straightforward in the case of 5-azidotriazole nucleoside (**1′**). The reaction led to numerous products, while **1′** was almost completely consumed. This isomer did not yield the corresponding Huisgen product efficiently either under conventional heating or by microwave irradiation in the presence or absence of catalysts such as Cu(II)–ascorbate, Cu(0)–Cu(II), CuI–NEt_3, CuBr and CuCl (data not shown). We first thought that this might be simply due to the steric congestion occurring between the azido group and the ribosyl moiety in **1′**. When phenylacetylene was used, two completely unexpected products were isolated: the amine **3** (38%) and the amide **4** (40%) (Scheme 3). To our great surprise, the 5-azidotriazole nucleoside **1′** was reduced to 5-aminotriazole nucleoside **3** under mild Cu(II)–ascorbate reaction conditions, although amide formation was reported to occur *via* a hydrative reaction between terminal alkynes, sulfonyl azides and water in the presence of a copper catalyst.[10] Although alkyne homocoupling might possibly be a side



Scheme 3 Cu(I)-catalyzed Huisgen reaction of 5-azidotriazole nucleoside **1′** with phenylacetylene.

reaction of the copper(I)-catalyzed Huisgen reaction,[8e,9b,11] we were not able to isolate or identify any alkyne homocoupling products.

2. Reduction of azide by the Cu (II)–ascorbate system

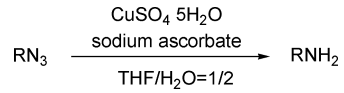
The copper(I)-catalyzed Huisgen reaction, which is a reliable and efficient method to generate triazole, has resulted in various elegant and important contributions in the field of organic synthesis and in the medicinal and material sciences. To our knowledge, however, the azide reduction found here to occur under mild Cu(II)–ascorbate Huisgen reaction conditions has never been reported so far. The reduction of **1′** occurring in the Cu(II)–ascorbate system prompted us to wonder whether these mild Huisgen reaction conditions might reduce other azides, which would seriously limit the general applicability of the Huisgen reaction. We therefore treated several azides with the Cu(II)–ascorbate system in the absence of any alkynes (Table 2). The 3-azidotriazole nucleoside **1** (entry 1 in Table 2) was found to be extremely stable in the Cu(II)–ascorbate system and could be recovered with a yield of more than 80% even after being refluxed for 25 h at 80 °C; whereas the 5-azidotriazole nucleoside **1′** (entry 2 in Table 2) underwent rapid reduction and gave an almost quantitative yield of the corresponding product, 5-aminotriazole nucleoside **3**, within 30 minutes. Reduction of azide **1′** to amine **3** occurred readily even at room temperature, although a much longer reaction time was required (entry 3 in Table 2). Without the Cu catalyst, the azide **1′** could also be reduced to the amine **3** by ascorbate, although at a much slower rate (entries 5 and 6 in Table 2). Yields of 50% and 80% were obtained when 0.5 eq and 1.0 eq sodium ascorbate was used, respectively. However, in the absence of sodium ascorbate (entry 4 in Table 2), azide **1′** could not be reduced to the corresponding amine in the presence of $CuSO_4$ or other Cu(I) catalysts such as CuI or CuBr.

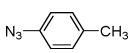
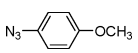
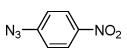
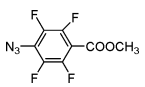
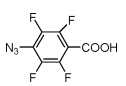
Our expanded studies on other azides revealed that electron-deficient aryl azides (entries 12–14 in Table 2) could be reduced to amine in the Cu(II)–ascorbate system, while aryl azides with electron-donating substituents and alkyl azides did not undergo reduction (entries 8 and 11 in Table 2). This finding suggests that the electronic properties of azides contribute significantly to their reduction to amines. Similar findings were previously reported by Knowles *et al.*[12] as regards the reduction of azides by propane-1,3-dithiol and recently by Wong *et al.* as regards the regioselective reduction of azides by the Staudinger reaction using trimethylphosphine.[13]

3. Different reactivity of azidotriazole nucleoside isomers

We were curious about the tremendous difference in reactivity observed between azidotriazole nucleoside isomers **1** and **1′**. In

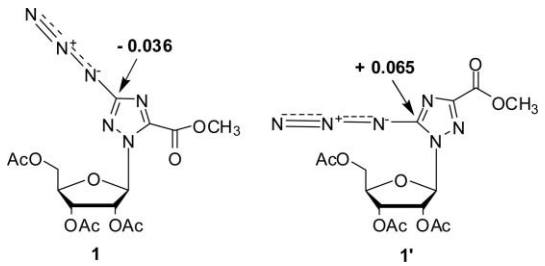
Table 2 Reduction of various azido compounds under Cu-catalyzed Huisgen conditions



Entry	Azide	$CuSO_4$	Sodium ascorbate	Temp./°C	Time/h	Yield[a](%)
1	**1**	0.16 eq	0.5 eq	80	25	—[b]
2	**1′**	0.16 eq	0.5 eq	80	0.5	97
3	**1′**	0.16 eq	0.5 eq	25	8.5	74 (21)
4	**1′**	0.16 eq[c]	No	80	23	—[b]
5	**1′**	No	0.5 eq	80	21.5	50 (41)
6	**1′**	No	1.0 eq	80	6.5	80
7	**1′**	No	No	80	8.0	—[b]
8		0.16 eq	0.5 eq	80	10.5	—[b]
9		0.16 eq	0.5 eq	80	10	—[b]
10		0.16 eq	0.5 eq	80	8	—[b]
11		0.16 eq	0.5 eq	80	10	—[b]
12		0.16 eq	0.5 eq	80	9	31 (48)
13		0.16 eq	0.5 eq	70[d]	16	25 (24)[e]
14		0.16 eq	0.5 eq	70[d]	22	68 (21)

[a] The yields stand for the isolated amine product. In some cases, the yield of starting material recovery is indicated in parentheses. [b] No reduction product could be detected and isolated. [c] $CuSO_4$, CuI and CuBr were tested respectively. [d] The reaction was carried out at 70 °C, not at 80 °C because the starting material was not stable and partially decomposed at 80 °C. [e] Part of the ester product was further hydrolyzed to the corresponding acid during the reaction.

order to explain this difference, theoretical calculations were carried out on these two isomers.[14] The results show that the azido-connecting carbon at the 3-position of **1** has a negative charge of −0.036, while the carbon at the 5-position of **1′** has a positive charge of +0.065 (Scheme 4), indicating that the carbon at the 3-position of **1** is electron-rich, while that at the 5-position of **1′** is electron-deficient. The azide group of **1** can be therefore taken to be attached to the electron-rich substituent, while that of **1′** is connected to the electron-deficient substituent. It was recently reported that the use of highly electron-deficient azides in the Huisgen reaction might be problematic.[15] Since electron-rich azides are favorable for the Huisgen reaction and electron-deficient azides are suitable for reduction, this readily explains the differences in reactivity observed for **1** and **1′** under Huisgen reaction conditions.



Scheme 4 Charge distribution on the triazole ring of **1** and **1′**.

We further studied the frontier orbitals of **1** and **1′** (Fig. 2) in order to better understand their different chemical reactivity. It is well known that the energy and the population of frontier orbitals are important factors to chemical reactivity. During the reaction, the electrons are transferred from the highest occupied molecular orbital (HOMO) of the donor to the lowest unoccupied molecular orbital (LUMO) of the acceptor. The interaction of HOMO–LUMO is stronger if the energy difference between the HOMO and LUMO is smaller or if the spatial overlap between the orbitals involved is more efficient. Therefore, the reaction proceeds faster when the HOMO energy is raised or the LUMO energy decreased or the spatial overlap of orbitals is more favorable. Based on the proposed mechanism for the copper(I) mediated Huisgen reaction, the azide will undergo nucleophilic addition to the copper(I) acetylide intermediate, indicating that the HOMO orbital of azide

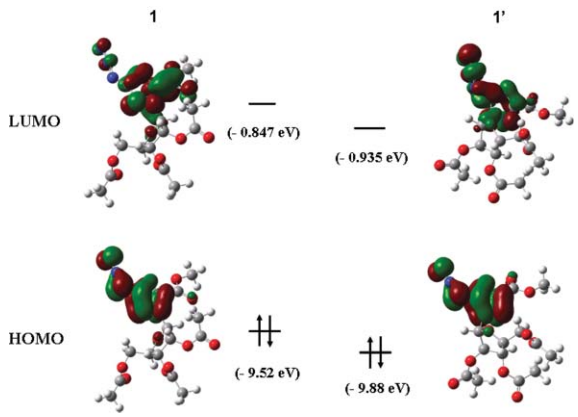


Fig. 2 The energy and the shape of the HOMO and LUMO orbitals of **1** and **1′**, respectively.

will be engaged in the Huisgen reaction. In the reduction reaction, azide is going to receive the electrons in order to be reduced to the corresponding amine. Therefore, the unoccupied LUMO of azide will be engaged. Calculations showed that **1**, on one hand, has the HOMO orbital with higher energy than **1′** (Fig. 2), suggesting that **1** is more favorable to undergo Huisgen reaction than **1′**. The steric crowding around the azido group in **1′** may also be an additional factor to the problematic Huisgen cycloaddition. On the other hand, the higher energy LUMO orbital as well as the practically null LUMO orbital coefficient at the nitrogen atom to be reduced makes it difficult for the reduction of **1** to the corresponding amine. Contrary to **1**, the lower energy LUMO orbital and higher orbital coefficient at the nitrogen concerned make the reduction of **1′** favorable. Taken together, results from both calculation and experiments are in good agreement and demonstrate the significant difference in the reaction activity between **1** and **1′**.

4. Biological evaluation

The synthesized bitriazolyl nucleosides **2a–k** were evaluated for their antiviral activity against the tobacco mosaic virus (TMV), a basic model in the search for antiviral agents capable of combating the agricultural plant virus. The antiviral activity of **2** was assessed with the fresh leaves of tobacco plants using the conventional half-leaf juice rubbing method[16] as we have employed for the non-nucleosidic bitriazolyl compounds.[5] The results are listed in Table 3, together with that of ribavirin, the control reference. Compounds **2g** and **2h** showed similar level of antiviral activity to that of ribavirin (Table 3). These results together with our previous results[5] have demonstrated the potential of bitriazolyl compounds as antiviral candidates.

Conclusions

In conclusion, we have accomplished the convenient synthesis of a series of novel bitriazolyl nucleosides *via* the Huisgen reaction. During the synthesis, we have discovered the surprisingly different reactivity of 3-azidotriazole nucleoside (**1**) and 5-azidotriazole nucleoside (**1′**) in a Cu(II)–ascorbate mediated reaction: **1** underwent efficient Cu(I)-catalyzed Huisgen reaction, whereas **1′** was rapidly reduced to the corresponding amine. A calculation has been used to interpret this different reactivity, which is mainly due to their different electronic properties: **1** is an electron-rich azide which is favorable for the Huisgen reaction, while **1′** is

Table 3 Antiviral activity of the synthesized triazole nucleosides against tobacco mosaic virus

Compound	Antiviral activity (%)
Ribavirin	49 ± 8
2a	11 ± 9
2b	12 ± 8
2c	21 ± 7
2d	17 ± 3
2e	25 ± 5
2f	8 ± 5
2g	40 ± 3
2h	42 ± 8
2i	8 ± 5
2j	18 ± 10
2k	28 ± 6

electron-deficient azide which is favorable for reduction. Additionally, the steric crowding of **1′** may also be responsible for the problematic Huisgen reaction. The different reactivity between **1** and **1′** may be further exploited for synthesizing structurally different triazole compounds with various biological activities. Studies in this direction are currently under way in our laboratories.

Experimental

General method

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 150 MHz, respectively, on Varian Mercury-VX300 and Varian Inova-600 spectrometers. The chemical shifts were recorded in parts per million (ppm) with TMS as the internal reference. FAB and ESI MS were determined using ZAB-HF-3F or Finnigan LCQ Advantage mass spectrometer. High resolution mass spectra were obtained by Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) using an IonSpec 4.7 Tesla fourier transform mass spectrometer. All compounds were purified by performing flash chromatography on silica gel (200–300 mesh).

General procedure for the synthesis of the bitriazolyl derivatives 2 through a copper(I)-catalyzed Huisgen reaction. The azide **1**[7] (100 mg, 0.23 mmol) and alkynes (0.28 mmol) were dissolved in a mixed solvent system (THF–H_2O, 1 : 2, 9 mL). A freshly prepared aqueous solution of sodium ascorbate (0.12 mmol, 0.2 mL) was added, followed by a freshly prepared aqueous solution of $CuSO_4 \cdot 5H_2O$ (0.04 mmol, 0.2 mL). The yellowish reaction mixture was stirred at 80 °C or at 25 °C, until complete consumption of **1**. The solvent was evaporated under reduced pressure and the crude material was purified by column chromatography (petroleum ether–EtOAc, 1 : 1). The residue was dried *in vacuo* to afford **2**.

3-[4-(Methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2a). White crystal (97.5 mg, 81.4%). R_f 0.25 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (s, 1H, *H-triazole*), 7.02 (d, $J = 2.4$ Hz, 1H, *H-1′*), 5.88 (dd, $J = 2.7$, 5.1 Hz, 1H, *H-2′*), 5.66–5.69 (m, 1H, *H-3′*), 4.45–4.50 (m, 2H, *H-4′* + *H-5′*), 4.24 (dd, $J = 5.1$, 12.3 Hz, 1H, *H-5′*), 4.09 (s, 3H, –OCH_3), 4.01 (s, 3H, –OCH_3), 2.16 (s, 6H, –C(O)CH_3), 2.09 (s, 3H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.1, 165.0, 164.9, 155.8, 152.4, 149.4, 141.3, 135.8, 122.2, 85.5, 76.6, 69.7, 66.2, 58.1, 49.5, 48.1, 16.2, 16.0; ESI-MS: *m/z* 510.9 [M + H]$^+$, 532.9 [M + Na]$^+$, 1042.6 [2M + Na]$^+$, calcd for $C_{19}H_{22}N_6O_{11}$ *510*. Crystallographic data of **2a**: $C_{19}H_{22}N_6O_{11}$ (Mr 510.43), monoclinic space group c 2, $Z = 4$, $a = 11.8185$ (4), $b = 11.0156$ (4), $c = 18.8659$ (8) Å, $\alpha = 90.00$, $\beta = 95.528$ (3), $\gamma = 90.00$, $V = 2444.69$ (16) Å^3, MoK_α radiation, $\lambda = 0.71073$ Å, $3.86° < \theta < 26.00°$, 2366 reflections, $T = 293$ K on a Brucker-Nonius Kappa CCD. The structure was solved using direct methods (SHELXS 97) and refined with SHELXL97 to final $R(F^2 > 2\sigma F^2) = 0.0425$ and $wR = 0.119$ [$w = 1/[\sigma^2(Fo^2) + (0.0889P)^2 + 0.6416P]$, where $P = (Fo^2 + 2Fc^2)/3$]. The X-ray structure data has been deposited in the Cambridge Crystallographic Data Center with deposition no. CCDC 639564. Copy of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (email: deposit@ccdc.cam.ac.uk).†

3-[4-(Ethoxycarbonyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2b). Colorless oil (95.5 mg, 77.6%). R_f 0.28 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.82 (s, 1H, *H-triazole*), 7.00 (d, $J = 3.0$ Hz, 1H, *H-1′*), 5.87 (dd, $J = 3.0$, 5.1 Hz, 1H, *H-2′*), 5.64–5.68 (m, 1H, *H-3′*), 4.42–4.49 (m, 4H, *H-4′* + *H-5′* + –CH_2–), 4.22 (dd, $J = 4.8$, 12.0 Hz, 1H, *H-5′*), 4.07 (s, 3H, –OCH_3), 2.14 (s, 6H, –C(O)CH_3), 2.08 (s, 3H, –C(O)CH_3), 1.43 (t, 3H, $J = 7.1$ Hz, –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.6, 169.5, 169.4, 159.9, 156.9, 153.9, 145.8, 140.6, 126.7, 90.0, 81.2, 74.3, 70.7, 62.6, 61.7, 54.0, 20.7, 20.51, 20.48, 14.3; ESI-MS: *m/z* 524.8 [M + H]$^+$, 546.9 [M + Na]$^+$, 1070.5 [2M + Na]$^+$, calcd for $C_{20}H_{24}N_6O_{11}$ *524*; HRMS: calcd. for $C_{20}H_{24}N_6O_{11}Na^+$ 547.1401. Found 547.1393.

3-[4-(Acetoxymethyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2c). Colorless oil (107.9 mg, 87.7%). R_f 0.30 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 (s, 1H, *H-triazole*), 7.01 (d, $J = 3.0$ Hz, 1H, *H-1′*), 5.88 (dd, $J = 3.0$, 5.1 Hz, 1H, *H-2′*), 5.67–5.70 (m, 1H, *H-3′*), 5.30 (s, 2H, –CH_2–O–C(O)–CH_3), 4.44–4.49 (m, 2H, *H-4′* + *H-5′*), 4.23 (dd, $J = 5.7$, 12.3 Hz, 1H, *H-5′*), 4.06 (s, 3H, –OCH_3), 2.13 (s, 6H, –C(O)CH_3), 2.10 (s, 3H, –C(O)CH_3), 2.06 (s, 3H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 170.8, 169.7, 169.6, 157.2, 154.5, 145.8, 143.7, 123.1, 90.1, 81.3, 74.4, 71.0, 63.0, 57.4, 54.1, 21.0, 20.9, 20.7; ESI-MS: *m/z* 525.0 [M + H]$^+$, 1048.8 [2M]$^+$, calcd for $C_{20}H_{24}N_6O_{11}$ *524*; HRMS: calcd. for $C_{20}H_{24}N_6O_{11}Na^+$ 547.1401. Found 547.1378.

3-[4-(1-Hydroxycyclopentyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2d). Colorless oil (102.1 mg, 81.1%). R_f 0.28 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (s, 1H, *H-triazole*), 7.01 (d, $J = 3.0$ Hz, 1H, *H-1′*), 5.89 (dd, $J = 2.7$, 5.1 Hz, 1H, *H-2′*), 5.67–5.71 (m, 1H, *H-3′*), 4.45–4.50 (m, 2H, *H-4′* + *H-5′*), 4.23 (dd, $J = 5.7$, 13.2 Hz, 1H, *H-5′*), 4.07 (s, 3H, –OCH_3), 2.27 (br s, 1H, –O*H*), 2.15–2.22 (m, 8H, –C(O)CH_3 + –CH_2–), 2.09 (s, 3H, –C(O)CH_3), 1.86–2.05 (m, 6H, –CH_2–). ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 169.8, 169.6, 157.3, 155.1, 154.7, 145.7, 119.4, 90.0, 81.2, 79.0, 74.5, 71.0, 63.1, 54.1, 41.4, 23.8, 20.9, 20.7; ESI-MS: *m/z* 558.8 [M + Na]$^+$, 1096.5 [2M + Na]$^+$, calcd for $C_{22}H_{28}N_6O_{10}$ *536*; HRMS: calcd. for $C_{22}H_{28}N_6O_{10}Na^+$ 559.1765. Found 559.1749.

3-[4-(1-Hydroxycyclohexyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2e). Colorless oil (127.1 mg, 98.4%). R_f 0.28 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H, *H-triazole*), 7.01 (d, $J = 2.7$ Hz, 1H, *H-1′*), 5.89 (dd, $J = 3.2$, 5.3 Hz, 1H, *H-2′*), 5.67–5.71 (m, 1H, *H-3′*), 4.44–4.51 (m, 2H, *H-4′* + *H-5′*), 4.22 (dd, $J = 5.7$, 13.2 Hz, 1H, *H-5′*), 4.07 (s, 3H, –OCH_3), 2.37 (br s, 1H, –O*H*), 2.13 (s, 6H, –C(O)CH_3), 2.07 (s, 3H, –C(O)CH_3), 1.30–2.04 (m, 10H, –CH_2–); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 169.8, 169.6, 157.3, 156.3, 154.8, 145.7, 119.3, 90.0, 81.3, 74.5, 71.1, 69.8, 63.0, 54.2, 38.1, 25.5, 22.1, 21.0, 20.74,

† CCDC reference numbers 639564 and 639565. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b703420b

20.70; ESI-MS: *m/z* 573.0 [M + Na]$^+$, calcd for $C_{23}H_{30}N_6O_{10}$ *550*; HRMS: calcd. for $C_{23}H_{30}N_6O_{10}Na^+$ 573.1921. Found 573.1896.

3-(4-Cyclohexenyl-1*H*-1,2,3-triazol-1-yl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2f). Colorless oil (87.5 mg, 70.1%). R_f 0.45 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13 (s, 1H, *H-triazole*), 7.02 (d, J = 1.8 Hz, 1H, *H-1′*), 6.73 (br, 1H, –C*H*=C–), 5.91 (br, 1H, *H-2′*), 5.71–5.73 (m, 1H, *H-3′*), 4.48–4.50 (m, 2H, *H-4′* + *H-5′*), 4.23 (dd, J = 4.8, 12.0 Hz, 1H, *H-5′*), 4.08 (s, 3H, –OCH_3), 2.41 (br, 2H, –CH_2–), 2.24 (m, 2H, –CH_2–), 2.15 (s, 6H, –C(O)CH_3), 2.07 (s, 3H, –C(O)CH_3), 1.79–1.80 (m, 2H, –CH_2–), 1.69–1.71 (m, 2H, –CH_2–); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8, 169.7, 169.6, 157.3, 154.8, 150.0, 145.6, 127.1, 126.4, 117.2, 90.0, 81.3, 74.5, 71.0, 62.9, 54.1, 26.5, 25.5, 22.5, 22.3, 20.9, 20.7, 20.6; ESI-MS: *m/z* 533.2 [M + H]$^+$, 1065.6 [2M + H]$^+$, calcd for $C_{23}H_{28}N_6O_9$ *532*; HRMS: calcd. for $C_{23}H_{28}N_6O_9Na^+$ 555.1815. Found 555.1825.

3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2g). White solid (121.6 mg, 98.1%). R_f 0.55 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (s, 1H, *H-triazole*), 7.93 (d, J = 7.5 Hz, 2H, Ar*H*), 7.39–7.50 (m, 3H, Ar*H*), 7.04 (d, J = 3.0 Hz, 1H, *H-1′*), 5.93 (dd, J = 3.0, 5.7 Hz, 1H, *H-2′*), 5.72–5.76 (m, 1H, *H-3′*), 4.47–4.53 (m, 2H, *H-4′* + *H-5′*), 4.26 (dd, J = 6.0, 13.2 Hz, 1H, *H-5′*), 4.09 (s, 3H, –OCH_3), 2.15 (s, 6H, –C(O)CH_3), 2.09 (s, 3H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 169.8, 169.6, 157.3, 154.7, 148.4, 145.8, 129.6, 129.2, 129.0, 126.3, 118.7, 90.1, 81.3, 74.5, 71.0, 63.0, 54.2, 21.0, 20.73, 20.71; ESI-MS: *m/z* 528.9 [M + H]$^+$, 551.1 [M + Na]$^+$, 1056.8 [2M]$^+$, calcd for $C_{23}H_{24}N_6O_9$ *528*; HRMS: calcd. for $C_{23}H_{24}N_6O_9Na^+$ 551.1502. Found 551.1478.

3-(4-*p*-Tolyl-1*H*-1,2,3-triazol-1-yl)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2h). White solid (109.3 mg, 85.9%). R_f 0.50 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.50 (s, 1H, *H-triazole*), 7.81 (d, J = 8.1 Hz, 2H, Ar*H*), 7.27 (d, J = 7.2 Hz, 2H, Ar*H*), 7.03 (d, J = 2.7 Hz, 1H, *H-1′*), 5.93 (dd, J = 3.0, 5.1 Hz, 1H, *H-2′*), 5.71–5.75 (m, 1H, *H-3′*), 4.46–4.51 (m, 2H, *H-4′* + *H-5′*), 4.25 (dd, J = 5.7, 12.3 Hz, 1H, *H-5′*), 4.08 (s, 3H, –OCH_3), 2.40 (s, 3H, –CH_3), 2.14 (s, 6H, –C(O)CH_3), 2.08 (s, 3H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 169.8, 169.6, 157.3, 154.8, 148.5, 145.7, 139.0, 129.9, 126.8, 126.2, 118.3, 90.1, 81.3, 74.5, 71.0, 63.0, 54.2, 21.6, 21.0, 20.73, 20.70; ESI-MS: *m/z* 542.8 [M + H]$^+$, 565.0 [M + Na]$^+$, 1084.6 [2M]$^+$, 1106.6 [2M + Na]$^+$, calcd. for $C_{24}H_{26}N_6O_9$ *542*; HRMS: calcd. for $C_{24}H_{26}N_6O_9Na^+$ 565.1659. Found 565.1663.

3-[4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2i). White crystal (107.3 mg, 81.9%). R_f 0.50 (petroleum ether–EtOAc, 1 : 1); mp: 163.4–163.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (s, 1H, *H-triazole*), 7.85 (d, J = 8.7 Hz, 2H, Ar*H*), 7.03 (d, J = 2.7 Hz, 1H, *H-1′*), 7.00 (d, J = 8.7 Hz, 2H, Ar*H*), 5.93 (dd, J = 3.0, 5.1 Hz, 1H, *H-2′*), 5.71–5.75 (m, 1H, *H-3′*), 4.46–4.51 (m, 2H, *H-4′* + *H-5′*), 4.25 (dd, J = 5.7, 12.9 Hz, 1H, *H-5′*), 4.08 (s, 3H, –OCH_3), 3.86 (s, 3H, –OCH_3), 2.15 (s, 6H, –C(O)CH_3), 2.08 (s, 3H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.9, 169.8, 169.6, 160.3, 157.3, 154.8, 148.3, 145.7, 127.6, 122.3, 117.8, 114.6, 90.1, 81.3, 74.5, 71.1, 63.0, 55.6, 54.2, 21.0, 20.74, 20.71; FAB-MS: *m/z* 559.0 [M + H]$^+$, calcd for $C_{24}H_{26}N_6O_{10}$ *558*. Crystallographic data of **2i**: $C_{24}H_{26}N_6O_{10}$ (Mr 558.51), monoclinic space group p 21 21 21, Z = 4, a = 7.5396 (10), b = 7.9351 (2), c = 43.1982 (6) Å, α = 90.00, β = 90.00 (3), γ = 90.00, V = 2584.44 (8) Å^3, MoK_α radiation, λ = 0.71073 Å, 0.47° < θ < 28.24°, 2946 reflections, T = 293 K on a Brucker-Nonius Kappa CCD. The structure was solved using direct methods (SHELXS 97) and refined with SHELXL97 to final $R(F^2 > 2sF^2) = 0.0613$ and $wR = 0.1449$ [$w = 1/[\sigma^2(Fo^2) + (0.1151P)^2 + 0.0000P]$, where $P = (Fo^2 + 2Fc^2)/3$]. The X-ray structure data has been deposited in the Cambridge Crystallographic Data Center with deposition no. CCDC 639565. Copy of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK (email: deposit@ccdc.cam.ac.uk).†

3-[4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2j). White solid (93.8 mg, 73.2%). R_f 0.48 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 (s, 1H, *H-triazole*), 7.90 (dd, $^4J_{HF}$ = 5.4 Hz, $^3J_{HH}$ = 9.0 Hz, 2H, Ar*H*), 7.17 (dd, $^3J_{HF}$ = 8.4 Hz, $^3J_{HH}$ = 9.0 Hz, 2H, Ar*H*), 7.04 (d, J = 3.0 Hz, 1H, *H-1′*), 5.92 (dd, J = 3.0, 5.4 Hz, 1H, *H-2′*), 5.71–5.75 (m, 1H, *H-3′*), 4.47–4.53 (m, 2H, *H-4′* + *H-5′*), 4.26 (dd, J = 6.0, 13.2 Hz, 1H, *H-5′*), 4.09 (s, 3H, –OCH_3), 2.15 (s, 6H, –C(O)CH_3), 2.09 (s, 3H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8, 169.8, 169.6, 163.2 (d, 1C, $^1J_{CF}$ = 248.3 Hz), 157.3, 154.7, 147.6, 145.8, 128.1 (d, 2C, $^3J_{CF}$ = 6.3 Hz), 125.9, 118.5, 116.2 (d, 2C, $^2J_{CF}$ = 21.3 Hz), 90.2, 81.3, 74.6, 71.1, 63.0, 54.1, 20.9, 20.7; FAB-MS: *m/z* 547.0 [M + H]$^+$, 569.0 [M + Na]$^+$, calcd for $C_{23}H_{23}FN_6O_9$ *546*; HRMS: calcd. for $C_{23}H_{23}FN_6O_9Na^+$ 569.1408. Found 569.1420.

3-[4-(4-Pentylphenyl)-1*H*-1,2,3-triazol-1-yl]-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-5-carboxylic acid methyl ester (2k). Colorless oil (125.1 mg, 89.1%). R_f 0.45 (petroleum ether–EtOAc, 1 : 1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.52 (s, 1H, *H-triazole*), 7.83 (d, J = 7.8 Hz, 2H, Ar*H*), 7.28 (d, J = 7.8 Hz, 2H, Ar*H*), 7.04 (d, J = 3.0 Hz, 1H, *H-1′*), 5.93 (dd, J = 3.0, 5.4 Hz, 1H, *H-2′*), 5.73–5.75 (m, 1H, *H-3′*), 4.49–4.52 (m, 2H, *H-4′* + *H-5′*), 4.24–4.27 (m, 1H, *H-5′*), 4.09 (s, 3H, –OCH_3), 2.65 (t, J = 7.5 Hz, 2H, –CH_2–), 2.16 (s, 6H, –C(O)CH_3), 2.09 (s, 3H, –C(O)CH_3), 1.64–1.68 (m, 2H, –CH_2–), 1.33–1.37 (m, 4H, –CH_2–), 0.90 (t, J = 6.9 Hz, 3H, –CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.8, 169.7, 169.6, 157.3, 154.7, 148.5, 145.7, 144.0, 129.2, 127.0, 126.2, 118.3, 90.1, 81.3, 74.5, 71.0, 63.0, 54.1, 35.9, 31.6, 31.2, 22.7, 20.9, 20.68, 20.66, 14.2; ESI-MS: *m/z* 599.1 [M + H]$^+$, 1196.9 [2M]$^+$, 1198.1 [2M + H]$^+$, calcd. for $C_{28}H_{34}N_6O_9$ *598*; HRMS: calcd. for $C_{28}H_{34}N_6O_9Na^+$ 621.2285. Found 621.2295.

Procedure for Cu(I)-catalyzed Huisgen reaction of 5-azidotriazole nucleoside 1′ with phenylacetylene. The azide **1′**[7] (30 mg, 0.07 mmol) and phenylacetylene (9.3 μL, 0.08 mmol) were dissolved in a mixed solvent system (THF–H_2O, 1 : 2, 3.0 mL). A freshly prepared aqueous solution of sodium (6.9 mg, 0.035 mmol, 0.2 mL) was added, followed by a freshly prepared aqueous solution of $CuSO_4 \cdot 5H_2O$ (2.5 mg, 0.01 mmol, 0.2 mL). The yellowish reaction mixture was stirred at 80 °C, until complete consumption of the azide. The solvent was evaporated under reduced pressure and the crude material was purified by column

chromatography. The residue was dried *in vacuo* to afford the title compound **3** (10.9 mg, 38.7%) and **4** (14.7 mg, 40.4%).

5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (3). White solid. R_f 0.35 (CH_2Cl_2–CH_3OH, 20 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (d, J = 4.5 Hz, 1H, *H-1′*), 5.75–5.78 (m, 1H, *H-2′*), 5.68 (br s, 2H, –NH_2), 5.48–5.51 (m, 1H, *H-3′*), 4.31–4.39 (m, 3H, *H-4′* + *H-5′*), 3.90 (s, 3H, –OCH_3), 2.09 (s, 9H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.7, 169.7, 160.5, 156.3, 151.6, 88.6, 81.0, 73.0, 70.6, 63.0, 52.7, 20.8, 20.7, 20.6; FAB-MS: *m/z* 401.0 [M + H]$^+$, 423.0 [M + Na]$^+$, calcd for $C_{15}H_{20}N_4O_9$ *400*; HRMS: calcd. for $C_{15}H_{20}N_4O_9Na^+$ 423.1128. Found 423.1117.

5-(2-Phenylacetamido)-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-1,2,4-triazole-3-carboxylic acid methyl ester (4). Yellowish solid. R_f 0.4 (CH_2Cl_2–CH_3OH, 20 : 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.12 (brs, 1H, –N*H*), 7.22–7.26 (m, 5H, Ar*H*), 6.06 (brs, 1H, *H-1′*), 5.89–5.90 (m, 1H, *H-2′*), 5.70 (dd, J = 5.9, 11.7 Hz, 1H, *H-3′*), 4.39–4.47 (m, 2H, *H-4′* + *H-5′*), 4.19 (dd, J = 5.1, 11.7 Hz, 1H, *H-5′*), 3.94 (s, 3H, –OCH_3), 3.83 (s, 2H, –CH_2), 2.12 (s, 3H, –C(O)CH_3), 2.09 (s, 3H, –C(O)CH_3), 2.05 (s, 3H, –C(O)CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): 170.8, 170.6, 169.4, 169.1, 159.5, 152.3, 148.4, 133.2, 129.4, 129.0, 127.7, 89.9, 80.6, 74.4, 70.5, 63.1, 52.7, 43.1, 20.6, 20.5; ESI-MS: *m/z* 519.0 [M + H]$^+$, 541.1 [M + Na]$^+$, 1036.7 [2M]$^+$, 1058.9 [2M + Na]$^+$, calcd. for $C_{23}H_{26}N_4O_{10}$ *518*; HRMS: calcd. for $C_{23}H_{26}N_4O_{10}Na^+$ 541.1547. Found 541.1544.

General procedure for the reduction of various azides under copper(I)-catalyzed Huisgen conditions. The azide was dissolved in a mixed solvent system (THF–H_2O, 1 : 2). A freshly prepared aqueous solution of sodium ascorbate was added, followed by a freshly prepared aqueous solution of $CuSO_4 \cdot 5H_2O$. The yellowish reaction mixture was stirred at 80 °C, until complete consumption of the azide. The solvent was evaporated under reduced pressure and the crude material was purified by column chromatography. The residue was dried *in vacuo* to afford the corresponding amine.

Procedure for calculation. Calculations were performed using the AMPAC version 8.50.9 computational modeling program with the semi-empirical method AM1.[14]

Antiviral evaluation against tobacco mosaic virus. Antiviral activity of the synthesized bitriazolyl nucleosides against TMV was performed by the conventional half-leaf method.[16]

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