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Huisgen Cycloaddition Reaction of *C*-Alkynyl Ribosides under Micellar Catalysis: Synthesis of Ribavirin Analogues

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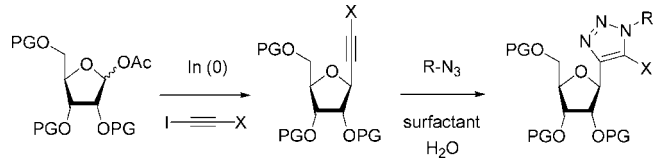

Carbonated analogues of ribavirin were synthesized from ethyl *C*-ribosylpropiolate obtained by an alkynylation reaction mediated by indium(0). The *C*-ribosides were then engaged in a Huisgen 1,3-dipolar cycloaddition reaction under a micellar catalysis. In these conditions, formation of 1,2,3-triazoles with control of the regioselectivity was observed. The regiochemistry of the adducts was determined by HMBC 2D-NMR analysis.

Introduction

Ribavirin is a ribosyl-1,2,4-triazole (Figure 1) that exhibits a broad-spectrum of antiviral activity against both DNA and RNA viruses.[1] It could act as an anti-metabolite against RNA viruses by mimicking natural purine ribonucleosides such as adenosine or guanosine, but very little is known about its mechanism against DNA viruses. The assumption is that ribavirin may act through a nonspecific or pleiotropic mechanism. As it enhances interferon properties, ribavirin has been used in combination therapy with interferon (Rebetrol). However, its use has been significantly limited by its safety profile and side effects, which include hemolytic anemia. Reducing the toxicity has then been an objective, and a large number of analogues of ribavirin have been synthesized, such as carba-1,2,3-triazoles,[2] 1,2,4-triazole analogues,[3] pyrazoles,[4] and tetrazoles.[5]

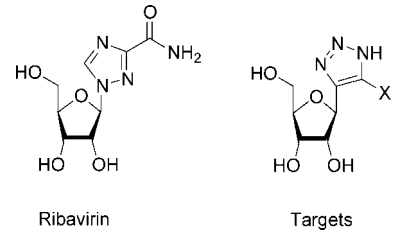

FIGURE 1. Ribavirin and target structures.

For some decades, 1,3-dipolar cycloaddition reactions (1,3-DCR) have been very popular, particularly the Huisgen cycloaddition involving an azide and an alkyne. However, this reaction requires heating and leads to a mixture of 1,4- and 1,5-disubstituted regioisomers. Recently, the lack of selectivity was resolved by the use of copper(I)[6] and Ru[7] salts. The copper catalysis directs the formation of only one regioisomer, namely, the 1,4-regioisomer, whereas Ru directs the 1,5-regioisomer. This very useful reaction has then become a reference in the click chemistry.[8] In addition, the Huisgen cycloaddition reaction has been described under various conditions such as using

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(1) (a) Gish, R. G. *J. Antimicrob. Chemother.* **2006**, *57*, 8–13. (b) Wu, J. Z.; Lin, C.-C.; Hong, Z. *J. Antimicrob. Chemother.* **2003**, *52*, 543–546.

(2) (a) Joubert, N.; Schinazi, R. F.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 11744–11750. (b) Perez-Castro, I.; Caamoño, O.; Fernandez, F.; Garcia, M. D.; Lopez, C.; De Clercq, E. *Org. Biomol. Chem.* **2007**, *5*, 3805–3813.

(3) (a) Chung, D.-H.; Kumarapperuma, S. C.; Sun, Y.; Li, Q.; Chu, Y.-K.; Arterburn, J. B.; Parker, W. B.; Smith, J.; Spik, K.; Ramanathan, H. N.; Schmaljohn, C. S.; Jonsson, C. B. *Antiviral Res.* **2008**, *79*, 19–27. (b) Chittepu, P.; Sirivolu, V. R.; Seela, F. *Bioorg. Med. Chem.* **2008**, *16*, 8427–8439.

(4) Nishimura, N.; Banno, M.; Maki, A.; Nishiyama, Y.; Maeba, I. *Carbohydr. Res.* **1998**, *307*, 211–215.

(5) Popsavin, M.; Torovic, L.; Spaic, S.; Stankov, S.; Kapor, A.; Tomic, Z.; Popsavin, V. *Tetrahedron* **2002**, *58*, 569–580.

(6) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

(7) (a) Zhang, L.; Chen, X. G.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999. (b) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680–8683. (c) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 8923–8930.

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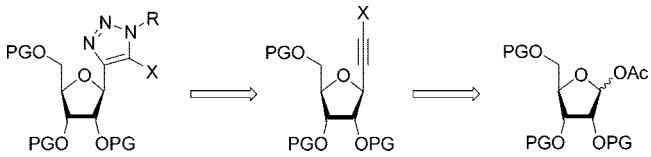
SCHEME 1



microwaves activation,[9] in aqueous medium with Cu(I) and Cu(II) salts or copper(0) or following a one-pot procedure.[10]

From a structural point of view, triazoles constitute an attractive feature in the context of medicinal chemistry, presenting a great stability under acidic, basic, and oxidative conditions. Triazoles being also aromatic heterocycles, this fact gives to heterocycles the ability of π-staking and hydrogen bonding interactions. Moreover, triazole is a structural pattern of interest in medicinal chemistry because of the isosteric character of the peptidic bond. Therefore we considered the synthesis of *C*-ribosyl-1,2,3-triazoles using a *C*-alkynylation reaction of ribose and a 1,3-DCR. This approach has been previously reported,[11] but neither the alkynylation nor the cycloaddition were completely controlled.

Results and Discussion

As a first step, we focused our efforts on the Huisgen cycloaddition involving different glycosylalkynes for the synthesis of glycosyltriazoles. We were interested in exploring this reaction using micellar catalysis in order to avoid the use of a copper salts, although these conditions have been largely used in click chemistry. According to the retrosynthetic scheme (Scheme 1), the 1,3-DCR involved a disubstituted alkyne.

To the best of our knowledge, a limited number of publications deals with 1,3-DCR involving disubstituted alkynes.[12] We have considered that micellar catalysis[13] could accelerate and/or control the regioselectivity of this cycloaddition. Although no clear evidence showed that micelles could significantly accelerate organic reactions (Diels−Alder cycloaddition,[14] epoxidation[15]), use of micellar catalysis has been recently reported for a 1,3-dipolar reaction with nitrones.[16] Due to the polar dipolarophile character, interactions with the organized medium could be responsible for this acceleration. We chose to test the four surfactants SDS, DTAC, CTAB, and OGH (Figure 2) for their anionic, cationic, and neutral properties. The OGH surfactant (octoylglucosylhydrazide) was easily synthesized on a large scale by a simple condensation of octoylhydrazide with D-glucose.[17]

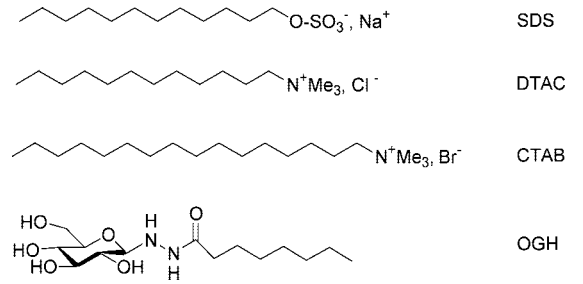
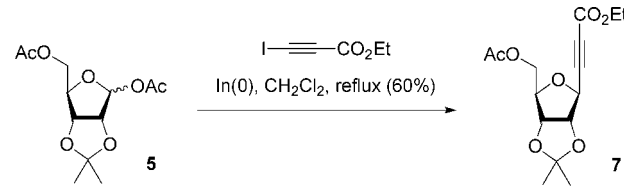


FIGURE 2. Surfactants.

SCHEME 2. Preparation of 1,5-Diacetyl-2,3-isopropylidene Riboside 7



First of all, the reaction was tried on two carbohydrate derivatives **1** and **2** in the presence of benzylazide under various conditions of catalysis and solvent. The adducts' stereochemistry was proved by comparison with the NMR spectrum of the adduct obtained under copper catalysis approach known to give the 1,4-regioisomer (Table 1, entries 1 and 8). The regiochemistry of the 1,5-adduct was correlated to the isolated compound obtained under thermal conditions[18] (Table 1, entries 2 and 9). Even if the reaction of **2** in water in the presence of SDS did not succeed (entry 10), with the more soluble compound **1** we observed a micellar catalysis (entries 3 and 4). The yield of the obtained triazole **4** was significantly improved with use of cationic or nonionic surfactants (entries 5−7).

After our demonstration that the micellar catalysis could promote a 1,3-DCR involving monosubstituted alkynes, we extended the study to the disubstituted ribosylalkyne **7**. As shown in Scheme 2, the carbohydrate derivative **7** can be obtained from 1,5-diacetyl-2,3-isopropylidene riboside **5** using an indium(0)-mediated alkynylation reaction with ethyl 3-iodopropiolate **6**, according to a procedure recently developed in our laboratory.[19]

The ribosylpropiolate **7** was then used for a 1,3-DCR leading to the 1,4,5-trisubstituted triazoles **8a** and **8b**. The reaction was initially conducted under thermal conditions to give the expected regioisomers (Scheme 3), separated by flash chromatography and identified by their 2D ^{1}H NMR spectra.

HMBC experiments have shown a correlation peak between H1 and C7 for compound **8a**, while compound **8b** displayed a correlation between C6 and the two H9. These experiments have allowed structure determinations without any ambiguity. Moreover, both compounds exhibit different anomeric coupling constants ($J_{1,2}$ = 3.3 Hz for **8a** and 5 Hz for **8b**).

(8) (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, *5*, 1–68. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.

(9) Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951–1954.

(10) (a) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331–2336. (b) Feldman, A. K.; Colasson, B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 3897–3899.

(11) (a) Lopez Herrera, F. J.; Pino Gonzalez, M. S.; Pabon, A. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, *12*, 2401–2406. (b) Buchanan, J. G.; Edgar, A. R.; Power, M. J.; Williams, G. C. *Carbohydr. Res.* **1977**, *55*, 225–238. (c) De Las Heras, F. G.; Tam, S.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1976**, *41*, 84–90.

(12) Diez-Gonzalez, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem.—Eur. J.* **2006**, *12*, 7558–7564.

(13) Lorello, G. R.; Legault, M.; Rakić, B.; Bisgaard, K.; Pezacki, J.-P. *Bioorg. Chem.* **2008**, *36*, 105–111.

(14) (a) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901–1904. (b) Van der Wel, G. K.; Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1996**, *61*, 9001–9006. (c) Wijnen, J. W.; Engberts, J. B. F. N. *J. Org. Chem.* **1997**, *62*, 2039–2044. (d) Wijnen, J. W.; Engberts, J. B. F. N. *Liebigs Ann. Recueil* **1997**, 1085–1088.

(15) Van den Broeke, L. J. P.; De Bruijn, V. G.; Heijnen, J. H. M.; Keurentjes, J. T. F. *Ind. Eng. Chem. Res.* **2001**, *40*, 5240–5245.

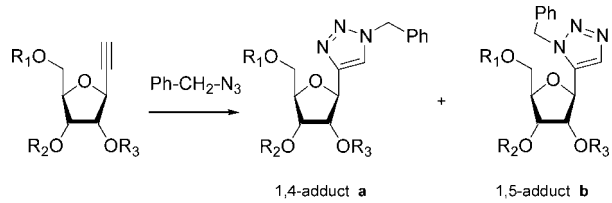
(16) Chatterjee, A.; Maiti, D. K.; Bhattacharya, P. K. *Org. Lett.* **2003**, *5*, 3967–3969.

(17) Augé, J.; Lubin-Germain, N. *J. Carbohydr. Chem.* **2000**, *19*, 379–392.

(18) Buchanan, J. G.; Edgar, A.; Power, M. *J. Chem. Soc., Perkin Trans. 1* **1974**, *16*, 1943–1949.

(19) Lubin-Germain, N.; Baltaze, J. P.; Coste, A.; Hallonet, A.; Lauréano, H.; Legrave, G.; Uziel, J.; Augé, J. *Org. Lett.* **2008**, *10*, 725–728. For a review on indium, see: Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764.

TABLE 1. 1,3-Dipolar Cycloaddition Reaction of Carbohydrate Derivatives 1 and 2



1 R_1 = H, R_2 = R_3 = isopropylidene
2 R_1 = R_2 = R_3 = Bn
3 R_1 = H, R_2 = R_3 = isopropylidene
4 R_1 = R_2 = R_3 = Bn

		conditions						
entry	ribosyl acetylene	solvent	catalyst	temp (°C)	time (h)	yield (%)	compound	ratio **a/b**
1	**1**	CH_3CN	CuI	rt	0.5	93	**3**	100/0
2	**1**	toluene		reflux	24	85	**3**	48/52
3	**1**	H_2O		70	30	tr	**3**	
4	**1**	H_2O	SDS 1.5 mM	70	24	56	**3**	58/42
5	**1**	H_2O	DTAC 1.5 mM	70	24	88	**3**	83/17
6	**1**	H_2O	CTAB 1.5 mM	70	24	73	**3**	59/41
7	**1**	H_2O	OGH 1.5 mM	70	24	82	**3**	87/13
8	**2**	CH_3CN	CuI	RT	20	79	**4**	100/0
9	**2**	toluene		85	30	79	**4**	50/50
10	**2**	H_2O	SDS 1 mM	70	48	0	**4**	

SCHEME 3. 1,3-DCR with Ribosylpropiolate 7 under Thermal Conditions

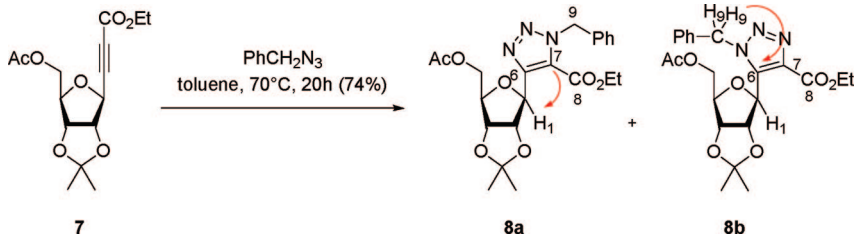


TABLE 2. 1,3-DCR with Disubstituted Ethyl Ribosylpropiolate 7

entry	solvent	additives	conditions[a]	yield (%)	ratio **8a/8b**
1	toluene		20 h	74	50/50
2	*t*-BuOH/H_2O 1:1		24 h	30	25/75
3	H_2O		3 days	0	
4	H_2O	SDS 1 mM	24 h	50	27/73
5	H_2O	SDS 2 mM	24 h	58	26/74
6	H_2O	SDS 4 mM	24 h	56	26/74
7	H_2O	SDS 8 mM	24 h	46	26/74
8	H_2O	SDS 20 mM	24 h	0	
9	H_2O	SDS 1.5 mM	3 days	79	27/73

[a] 70 °C.

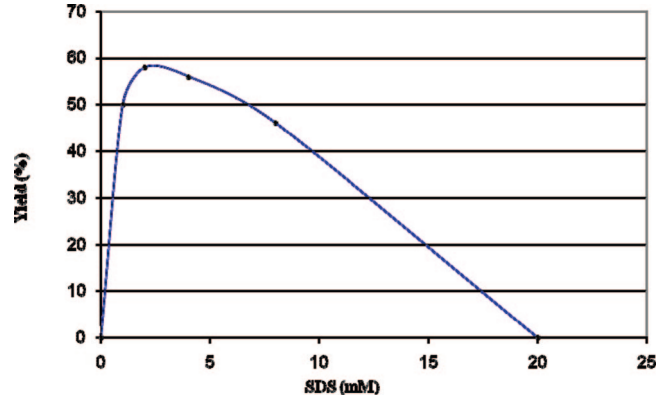


FIGURE 3. Determination of the optimal SDS concentration.

Ethyl ribosylpropiolate **7** was then used in the 1,3-DCR under various conditions at 70 °C, in order to improve the regioselectivity (Table 2). It was recently reported that this cycloaddition involving alkynes, activated or not, could be improved in aqueous media.[20] However, at 70 °C no adduct was observed; in a water/*tert*-butanol mixture only 30% triazole was formed. In parallel, we have obtained the adducts under micellar catalysis with SDS, as it was observed for monosubstituted ribosylacetylene **1**. We have optimized the SDS concentration (Table 2, entries 4−8) and determined that the better concentration was 1.5 mM (below the CMC = 8.3 mM), as shown in Figure 3.

Ultimately, the best yield was observed when the reaction time was extended up to 3 days (Table 2, entry 9). The regioselectivity was similar to what we observed using water/*tert*-butanol mixture. Moreover, because SDS concentration was significantly lower than CMC, the organization of the medium in the presence of *tert*-butanol or SDS should be similar, explaining the comparable results.

As previously tested for the monosubstituted ribosylacetylene **1**, we have investigated the effect of cationic and neutral surfactants and discovered that DTAC and CTAB were ineffective to promote the reaction (Table 3, entries 3 and 4). Our explanation for this unexpected result is that these surfactants do not establish any stabilizing interaction with the carbohydrate **7** (contrary to the case of carbohydrate **1**). Under these conditions, OGH led to high yield, like for the ribosylacetylene compound **1** (Table 3, entry 2).

(20) (a) Li, P.; Wang, L. *Lett. Org. Chem.* **2007**, *4*, 23–26. (b) Li, Z.; Seo, T. S.; Ju, J. *Tetrahedron Lett.* **2004**, *45*, 3143–3146.

SCHEME 4. Preparation of Compounds 9, 11, 12, 13, and 14

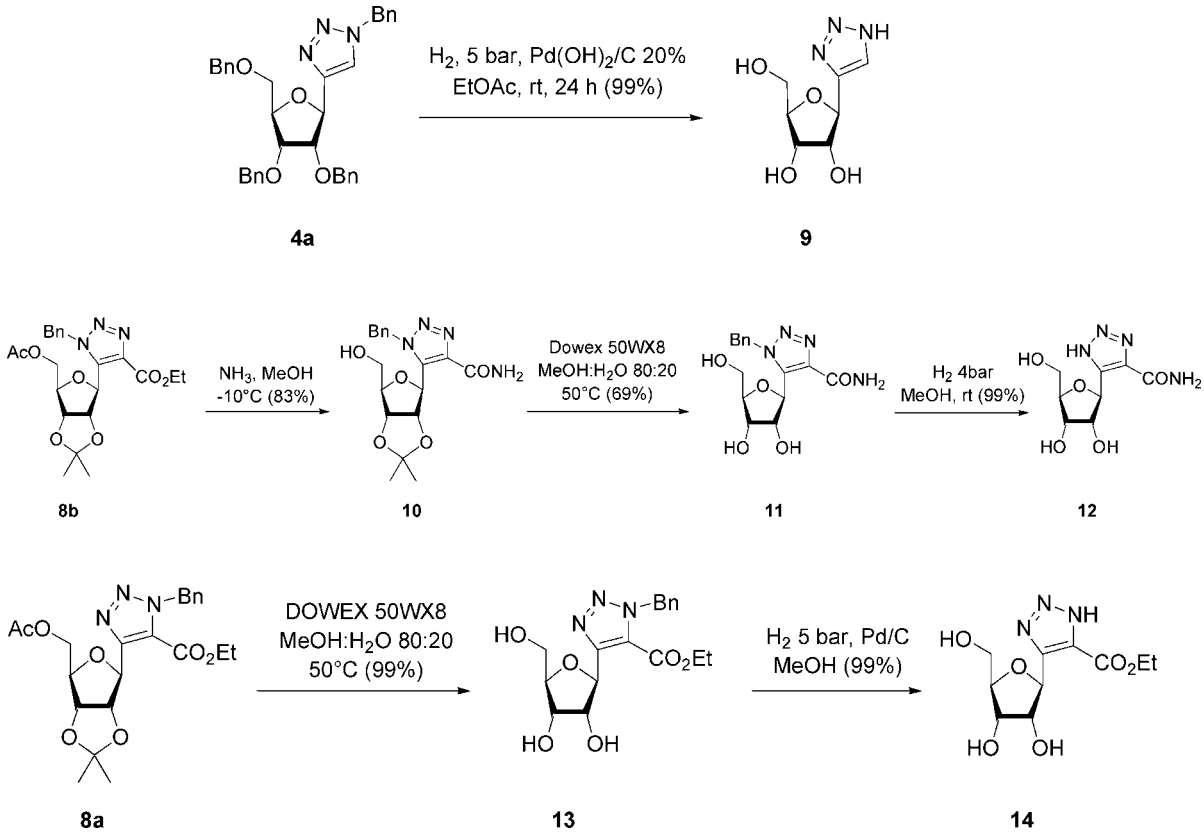


TABLE 3. 1,3-DCR with Disubstituted Ethyl Ribosylpropiolate 7

entry	solvent	additives	conditions	yield (%)	ratio **8a/8b**
1	H_2O	SDS 2 mM	24 h	58	26/74
2	H_2O	OGH 1.5 mM	24 h	67	27/73
3	H_2O	DTAB 1.5 mM	24 h	tr	26/74
4	H_2O	CTAB 1.5 mM	24 h	tr	26/74

The second part of this work is related to the functionalization of the adducts to obtain carbonated analogues of ribavirin (Scheme 4). We thus prepared the compounds **9**, **11**, **12**,[21] **13**, and **14** from ribosyl-1,2,3-triazoles **4a**, **8a**, and **8b**, using conventional deprotection procedures (Scheme 4). The amide functional group was obtained by aminolysis of the ester in the presence of ammonia in methanol.

Conclusion

The compounds **9**, **11**, **12**, **13**, and **14** were synthesized via a C-alkynylation reaction mediated by indium(0) followed by a 1,3-DCR with benzyl azide. This latter reaction was partially regiocontrolled under micellar catalysis, and these original conditions gave the expected adducts even with disubstituted alkynes. The crucial choice of the surfactant nature is dependent on the degree of substitution of the ribosylalkynes; however, in any case, the neutral OGH proved to be efficient. The compounds **9**, **11**, **12**, **13**, and **14** are currently under investigation for possible biological properties (antiviral tests).

Experimental Section

1-Benzyl-4-(2,3-isopropylidene-β-D-ribosyl)-1,2,3-triazole (3a). To a solution of isopropylideneribosylacetylene **1** (196 mg, 1.0 mmol) in acetonitrile (10 mL) was added benzylazide (160 mg, 1.2 mmol) followed by DIPEA (388 mg, 3.0 mmol) and CuI (381 mg, 2.0 mmol). The reaction mixture was stirred at room temperature for 30 min. A saturated NH_4Cl solution (10 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate 95:5) to give **3a** (309 mg, 93%) as a yellow solid; mp = 69−71 °C; $[\alpha]^{28}_D = -28.3$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 3497, 3076, 2990, 2919; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.49 (s, 3H), 3.60 (dd, J = 12.6, 3.4 Hz, 1H), 3.82 (dd, J = 12.6, 2.3 Hz, 1H), 4.04 (s, 1H), 4.27 (s, 1H), 4.86 (d, J = 1.8 Hz, 2H), 4.98 (s, 1H), 5.42 (s, 2H), 7.24 (m, 2H), 7.30 (m, 3H), 7.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 27.3, 54.3, 63.7, 79.8, 82.8, 85.9, 86.2, 113.5, 121.7, 128.2, 128.9, 129.1, 134.0, 147.5. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{17}H_{21}N_3O_4$, 331.1532; found 331.1519.

1-Benzyl-5-(2,3-isopropylidene-β-D-ribosyl)-1,2,3-triazole (3b). Obtained as a mixture with **3a**. ^1H (400 MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.52 (s, 3H), 3.62 (dd, J = 11.9, 3.2 Hz, 1H), 3.64 (m, 1H), 3.72 (dd, J = 11.92, 3.2 Hz, 1H), 4.12 (dd, J = 6.9, 3.2 Hz, 1H), 4.62 (t, J = 6.0 Hz, 1H), 4.71 (d, J = 5.5 Hz, 1H), 4.74 (dd, J = 6.4, 3.2 Hz, 1H), 5.60 (s, 2H), 7.17 (m, 2H), 7.32 (m, 3H), 7.56 (s, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 25.1, 27.1, 52.2, 61.8, 76.9, 82.1, 84.1, 85.5, 114.7, 127.3, 128.0, 128.6, 134.0, 134.5, 146.9.

1-Benzyl-4-(2,3,5-tri-*O*-benzyl-β-D-ribosyl)-1,2,3-triazole (4a). A mixture of 2,3,5-tri-*O*-benzyl-ribosylacetylene **2** (0.40 g, 0.93 mmol), benzyl azide (0.15 g, 1.12 mmol), CuI (0.35 g, 1.86 mmol), and DIPEA (0.36 g, 2.79 mmol) in CH_3CN (20 mL) was stirred at room temperature for 20 h. The mixture was evaporated, and the residue was partitioned between ethyl acetate and H_2O (20 mL). The organic layer was washed with NH_4Cl (2 × 10 mL) and brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (cyclohexane/

(21) De Las Heras, F. G.; Tam, S. Y. K.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1976**, *41*, 84–90.

ethyl acetate 8:2) to give **4a** (0.41 g, 79%) as a yellow solid; mp = 122−124 °C; $[\alpha]^{28}_D = -3.40$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 3061, 2888, 1479, 1454, 1349, 1048, 910, 751, 671; ^1H NMR (400 MHz, $CDCl_3$) δ 3.59 (dd, J = 10.5, 3.7 Hz, 1H), 3.75 (dd, J = 10.5, 2.8 Hz, 1H), 4.05 (dd, J = 6.9, 5.0 Hz, 1H), 4.25 (t, J = 4.1 Hz, 1H), 4.31 (m, 1H), 4.42 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 11.9 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.68 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 11.9 Hz, 1H), 5.19 (d, J = 15.1 Hz, 1H), 5.29 (d, J = 3.1 Hz, 1H), 5.36 (d, J = 15.1 Hz, 1H), 7−7.3 (m, 20H), 7.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.0, 69.4, 72.0, 72.1, 73.3, 76.7, 80.6, 80.8, 122.5, 127.7−128.7, 129.0, 134.7, 137.8, 137.9, 138.2, 148.2. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{35}H_{35}N_3O_4$, 561.2628; found 561.2634.

1-Benzyl-5-(2,3,5-tri-*O*-benzyl-*β*-D-ribosyl)-1,2,3-triazole (4b). Obtained as a mixture with **4a**. Yellow oil, ^1H NMR (400 MHz, $CDCl_3$) 3.39 (dd, J = 3.7, 10.6 Hz, 1H), 3.44 (dd, J = 3.7, 10.6 Hz, 1H), 3.85 (dd, J = 10.9, 5 Hz, 1H), 3.95 (dd, J = 4.6, 6.9 Hz, 1H), 4.16 (m, 1H), 4.2 (m, 1H), 4.35 (m, 2H), 4.4 (m, 1H), 4.48 (m, 2H), 4.9 (d, J = 7.3 Hz, 1H), 5.46 (d, J = 15 Hz, 1H), 5.5 (d, J = 15 Hz, 1H), 7−7.3 (m, 20H), 7,42 (s, 1H). HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{35}H_{35}N_3O_4$, 561.2628; found 561.2639.

Ethyl 3-(2,3-Isopropylidene-5-acetyl-*β*-D-ribosyl)propiolate (7). Indium (0,272 g, 2.19 mmol) was stirred during 30 min under vacuum/argon in a sealed tube. Then a solution of ethyl iodopropiolate **6** (0.408 g, 1.82 mmol) and 1,5-diacetyl-2,3-isopropylidene riboside **5** (0.25 g, 0.91 mmol) in anhydrous CH_2Cl_2 (9 mL) was introduced in the medium, which was refluxed for 3 days. The mixture was evaporated, and the residue was directly purified by flash column chromatography (cyclohexane/ethyl acetate 8:2) to give **7** (0.17 g, 60%) as a yellow oil; $[\alpha]^{28}_D = -0.68$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 2985, 1743,1710, 1220, 1066, 860, 749. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 6.9 Hz, 3H), 1.27 (s, 3H), 1.45 (s, 3H), 2.05 (s, 3H), 4.11 (dd, J = 5.5, 11.9 Hz, 1H) 4.16 (q, J = 6.9 Hz, 2H), 4.19 (dd, J = 4.6, 11.5 Hz, 1H), 4.80 (dt, J = 2.3, 5.0 Hz, 1H), 4.67 (dd, J = 2.3, 6.0 Hz, 1H), 4.74 (d, J = 2.3 Hz, 1H); 4,83 (dd, J = 2.3, 6.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.9, 20.8, 25.1, 26.8, 62.26, 63.8, 74.7, 78.4, 82.8, 83.4, 83.8, 85.8, 114.1, 152.8, 170.5. HRMS-EI: *m/z* $[M]^+$ calcd for $C_{15}H_{20}O_7$, 312.1209; found 312.1210.

Ethyl 1-Benzyl-4-(2,3-isopropylidene-5-acetyl-*β*-D-ribosyl)-1,2,3-triazole-5-carboxylate (8a). To a solution of ethyl ribosylpropiolate **7** (0.100 g, 0.320 mmol) in water (10 mL) were added benzyl azide (0.043 g, 0.320 mmol) and SDS (0.02 mmol). The mixture was stirred at 70 °C for 24 h. After evaporation of the solvent, the crude product was purified by flash column chromatography (cyclohexane/ethyl acetate 9:1) to give compounds **8a** (0.022 g, 15%) and **8b** (0.061 g, 43%). Compound **8a**: yellow oil; $[\alpha]^{28}_D = -36.78$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 2984, 1725, 1497, 1370, 1211, 1097, 859; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.30 (s, 3H), 1.51 (s, 3H), 1.97 (s, 3H), 4.05 (d, J = 5.2 Hz, 2H), 4.21 (m, 1H), 4.29 (q, J = 7.2 Hz, 2H), 4,77 (dd, J = 6.4, 3.2 Hz, 1H), 5.22 (dd, J = 6.4, 3.2 Hz, 1H), 5.46 (d, J = 3.3 Hz, 1H), 5.78 (d, J = 14.2 Hz, 1H), 5.82 (d, J = 14.2 Hz, 1H), 7.23 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.8, 25.4, 27.2, 53.9, 62.1, 64.2, 76.4, 78.1, 82.6, 83.4, 83.9, 114.2, 125.7, 128.0, 128.5, 128.8, 134.7, 148.4, 158.2, 170.6. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{22}H_{27}N_3O_7$, 445.1849; found 455.1828.

Ethyl 1-Benzyl-5-(2,3-isopropylidene-5-acetyl-*β*-D-ribosyl)-1,2,3-triazole-4-carboxylate (8b). Yellow solid; mp = 75−77 °C; $[\alpha]^{28}_D = -1.63$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 2989, 1739, 1728, 1439, 1379, 1237, 1188, 1096, 858; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.46 (s, 3H), 1.99 (s, 3H), 4,05 (d, J = 5.0 Hz, 1H), 4.24 (m, 2H), 4.35 (m, 2H), 4.37 (m, 1H), 4.43 (dd, J = 6.9, 5.0 Hz, 1H), 5.50 (d, J = 5.0 Hz, 1H), 5.63 (d, J = 16 Hz, 1H), 5.71 (d, J = 16 Hz, 1H), 7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 16.5, 20.9, 22.9, 26.6, 48.8, 57.2, 59.2, 76.7, 81.3, 82.7, 84.3, 111.8, 127.0, 128.0, 128.7, 129.1, 130.5, 133.3, 133.4, 156.7, 166.2. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{22}H_{27}N_3O_7$, 445.1849; found 455.1864.

4-*β*-D-Ribosyl-1,2,3-triazole (9). The compound **4a** (0.070 g, 0.12 mmol) was dissolved in methanol (5 mL), and $Pd(OH)_2/C$ (20%) was added. The reaction mixture was hydrogenated at room temperature for 24 h under 5 bar. The catalyst was removed after filtration on Celite and washed with MeOH. The solvents were then evaporated to give **9** (0.070 g, 99%) as a white solid; mp = 118−120 °C; $[\alpha]^{28}_D = +11.3$ (*c* 1.0, CH_3OH); IR (ATR, cm^{-1}) 3335, 2965, 2374, 1675, 995, 897. ^1H NMR (400 MHz, CD_3OD) δ 3.63 (dd, J = 11.9, 5.0 Hz, 1H), 3.77 (dd, J = 11.9, 3.2 Hz, 1H), 3.95 (dd, J = 7.8, 4.6 Hz, 1H), 4.12 (dd, J = 10.1, 5.5 Hz, 1H), 4.14 (t, J = 5.5 Hz, 1H), 4.95 (s, 1H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 62.2, 71.3, 76.2, 77.6, 84.8, 128.0, 143.9. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_7H_{11}N_3O_4$, 201.0750; found 201.0746.

1-Benzyl-5-(2,3-isopropylidene-*β*-D-ribosyl)-1,2,3-triazole-4-carboxamide (10). A solution of compound **8b** (0.100 g, 0.224 mmol) in MeOH (5 mL) was cooled to −10 °C and treated with gaseous NH_3. The solution was maintained at −10 °C for 8 h and then warmed to room temperature overnight. The reaction mixture was evaporated, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 1:1) to give **10** (0.080 g, 83%) as a white powder; mp = 178−180 °C; $[\alpha]^{28}_D = -22.39$ (*c* 1.0, $CHCl_3$); IR (ATR, cm^{-1}) 3409, 3278, 2921, 1730, 1663, 1602, 1466, 1245, 1054, 870; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.40 (s, 3H), 3.72 (dd, J = 12.4, 11.2 Hz, 1H), 3.86 (d, J = 12.4 Hz, 1H), 4.18 (s, 1H), 4.24 (d, J = 11.2 Hz, 1H), 4.97 (m, 3H), 5.60 (d, J = 15.5 Hz, 1H), 5.62 (d, J = 15.5 Hz, 1H), 7.12−7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 23.0, 48.3, 57.9, 71.9, 72.1, 77.0, 79.9, 81.0, 110.4, 122.4, 124.2, 124.7, 124.8, 129.6, 132.4, 134.6, 158.12. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}N_4O_5$, 374.1590; found 374.1585.

1-Benzyl-5-*β*-D-ribosyl-1,2,3-triazole-4-carboxamide (11). To a solution of compound **10** (0.067 g, 0.179 mmol) in methanol/water (4:1) (5 mL) was added Dowex 50WX8 (0.5 g). The reaction mixture was stirred at 50 °C for 6 h, then filtered and washed with MeOH. After solvent evaporation, the crude powder **11** (0.041 g, 69%) was directly used directly for the next step without any further purification; mp = 208−210 °C; $[\alpha]^{28}_D = +3.95$ (*c* 1.0, CH_3OH); IR (ATR, cm^{-1}) 3389, 2937, 1652, 1497, 1286, 1111, 872; ^1H NMR (400 MHz, CD_3OD) δ 3.60 (dd, J = 12.4, 2.7 Hz, 1H), 3.64 (dd, J = 12.4, 3.2 Hz, 1H), 3.83 (d, J = 2.7 Hz, 1H), 3.93 (dd, J = 6.0, 3.2 Hz, 1H), 4.03 (dd, J = 7.8, 6.4 Hz, 1H), 5.36 (d, J = 7.8 Hz, 1H), 5.75 (d, J = 15.6 Hz, 1H), 5.8 (d, J = 15.6 Hz, 1H), 7.2 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 61.8, 70.9, 74.7, 75.2, 86.9, 126.9, 127.8, 128.5. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{18}N_4O_5$, 334.1277; found 334.1256.

5-*β*-D-Ribosyl-1,2,3-triazole-4-carboxamide (12). Compound **11** (0.100 g, 0.267 mmol) was dissolved in methanol (5 mL), and Pd/C (10%) was added. The reaction mixture was hydrogenated at room temperature for 24 h under 5 bar. The catalyst was removed after filtration on Celite and washed with MeOH. The solvents were then evaporated to give **12** (0.07 g, 99%) as a yellow solid; mp = 204−206 °C; $[\alpha]^{28}_D = +13.82$ (*c* 1.0, CH_3OH); IR (ATR, cm^{-1}) 3327, 2927, 2365, 1670, 1540, 1459, 1225, 1110, 995, 897; ^1H NMR (400 MHz, CD_3OD) δ 3.72 (dd, J = 12.4, 3.7 Hz, 1H), 3.85 (dd, J = 12.4, 2.8 Hz, 1H), 4.01 (dd, J = 3.7, 2.8 Hz, 1H), 4.14 (s, 2H), 5.38 (d, J = 3.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 61.2, 70.1, 75.8, 76.1, 84.7. HRMS-CI: *m/z* $[M + H]^+$ calcd for $C_8H_{12}N_4O_5$, 244.0808; found 244.0811.

Ethyl 1-Benzyl-4-*β*-D-ribosyl-1,2,3-triazole-5-carboxylate (13). To a solution of compound **8a** (0.115 g, 0.258 mmol) in methanol/water (4:1) (10 mL) was added Dowex 50WX8 (1.30 g). The mixture was stirred at 50 °C for 6 h, then filtered and washed with MeOH. After solvent evaporation, the crude **13** (0.100 g, 99%) obtained as a yellow oil was used directly for the next step without any further purification. $[\alpha]^{28}_D = +5.22$ (*c* 1.0, CH_3OH); IR (ATR, cm^{-1}) 3269, 2928, 2499, 1722, 1455, 1256, 1102, 1029, 852, 730; H NMR (400 MHz, CD_3OD) δ 1.26 (t, J = 7.1 Hz, 3H), 3.67 (dd, J = 11.9, 4.1 Hz, 1H), 3.82 (dd, J = 11.9, 2.8 Hz, 1H), 3.99 (ddd, J = 5.1, 4.1, 2.8 Hz, 1H), 4.24 (dd, J = 5.5, 5.1 Hz, 1H), 4.32−4.37

(m, 3H), 5.34 (d, $J = 5.0$ Hz, 1H), 5.85 (s, 2H), 7.2 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.2, 54.9, 63.3, 63.4, 72.4, 77.0, 78.2, 86.1, 127.1, 128.6, 129.2, 129.7, 136.6, 150.2, 159.5. HRMS-CI: m/z $[M + H]^+$ calcd for $C_{17}H_{21}N_3O_6$, 363.1430; found 363.1425.

Ethyl 4-β-D-Ribosyl-1,2,3-triazole-5-carboxylate (14). Compound **13** (0.100 g, 0.275 mmol) was dissolved in methanol (5 mL), and Pd/C (10%) was added. The reaction mixture was hydrogenated at room temperature for 24 h under 5 bar pressure. The catalyst was removed after filtration on Celite and washed with MeOH. The solvents were then evaporated to give **14** (0.072 g, 99%) as a yellow oil. $[\alpha]^{28}_D = +18.46$ (c 1.0, CH_3OH); IR (ATR, cm^{-1}) 3325, 2856, 1719, 1446, 1227, 1113, 1017, 789; ^{1}H NMR (400 MHz, CD_3OD) δ 1.37 (t, $J = 7.3$ Hz, 3H), 3.73 (dd, $J = 12.3$, 3.6 Hz, 1H), 3.90 (dd, $J = 12.3$, 3.2 Hz, 1H), 4.00 (m, 1H), 4.15−4.18 (m, 2H), 4.36 (q, $J = 7.3$ Hz, 2H), 5 (s, 4H), 5.43 (d, $J = 4.1$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 13.1, 60.8, 61.4, 70.4, 76.3, 77.2, 84.1, 134.1, 145.2, 161.8. HRMS-CI: m/z $[M + H]^+$ calcd for $C_{10}H_{15}N_3O_6$, 273.0961; found 273.0971.

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Supporting Information Available: General experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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