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Combinatorial and Automated Synthesis of Phosphodiester Galactosyl Cluster on Solid Support by Click Chemistry Assisted by Microwaves

Gwladys Pourceau, Albert Meyer, Jean-Jacques Vasseur, and François Morvan*

Institut des Biomolécules Max Mousseron (IBMM), UMR 5247 CNRS - Université Montpellier 1 - Université Montpellier 2, Place Eugène Bataillon, CC1704, 34095 Montpellier Cedex 5, France

morvan@univ-montp2.fr

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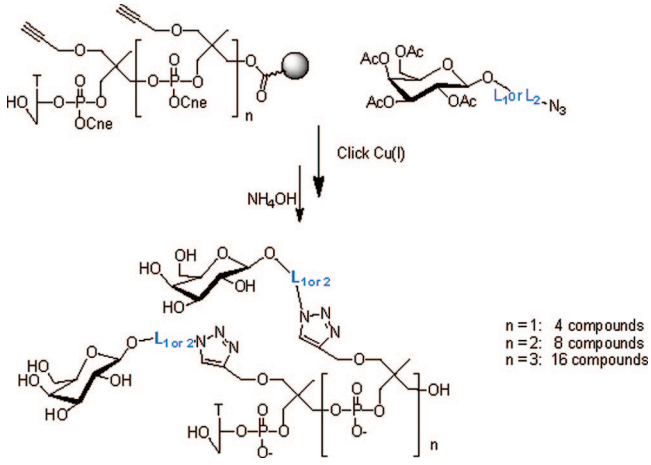
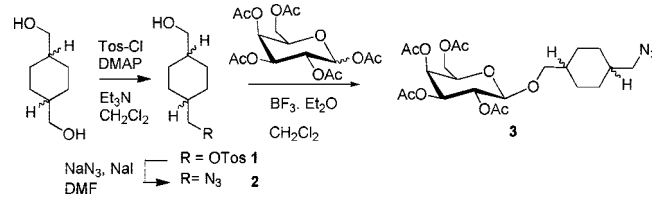


Small libraries of di-, tri-, and tetragalactosyl clusters were efficiently synthesized using combinatorial methodology, on solid support, by click chemistry assisted by microwaves, starting from different poly alkyne DNA-based scaffolds and two galactosyl azide derivatives. The scaffold was synthesized by standard DNA solid-supported phosphoramidite chemistry using a novel alkyne phosphoramidite and an alkyne solid support. The proportion of each glycocluster in a library was modulated using different molar ratios of both galactose azides.

Combinatorial methodology is useful to produce rapidly an exponential number of different molecules in few steps and is used in many areas of research.

Lectins are proteins that recognize carbohydrates and are involved in many biological functions including communication and intercellular adhesion, adhesion of viruses and bacteria, and activation of the innate immune system.[1] Interaction of lectin and carbohydrate is relatively weak, so multivalence is usually recommended to increase their binding.[2]

SCHEME 1. Synthesis of Tetraacetylgalactose Azide Derivative 3 with L2 Linker



Since synthesis of carbohydrates is difficult and time-consuming, an alternative is the synthesis of glycoclusters. Lots of glycoclusters have been designed and reported in literature.[2,3] However, they are mainly constituted of the same carbohydrate residue repeated several times. To synthesize glycoclusters with different carbohydrate residues, combinatorial methodology could be applied and will produce easily libraries of glycoclusters.[4,5]

We present herein a strategy to synthesize galactosyl clusters based on a DNA synthesis on solid support to prepare a polyalkyne scaffold and using copper-catalyzed alkyne−azide 1,3-dipolar cycloaddition (CuAAC) or click reaction[6–10] to form the glycocluster.

To demonstrate the feasibility of this approach, we synthesized galactosyl clusters exhibiting different linkers between the phosphodiester backbone and the galactosyl residue. We chose two galactosyl azide derivatives exhibiting a propyl or a 1,4-dimethylcyclohexane linker between the galactosyl part and azido function (i.e., 1-*O*-(3-azidopropyl)-2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranoside **4**[11] and 1-*O*-[[4-(azidomethyl)cyclohexyl]-methyl]-2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranoside **3**, Scheme 1). Thus, the different glycoclusters are expected to exhibit different retention times by RP HPLC and should displayed different masses allowing an easy monitoring of the click conjugation by mass spectrometry.

Galactosyl azide **3** was synthesized from 1,4-dimethanolcyclohexane, which was first monotosylated **1** (72%) and then treated with sodium azide and sodium iodide affording azido derivative **2** (79%) which was finally reacted with pentaacetate-galactose in presence of $BF_3 \cdot Et_2O$ affording **3** (21%). Galactosyl azide **4** was synthesized according to literature.[11]

(1) Lis, H.; Sharon, N. *Chem. Rev.* **1998**, *98*, 637–674.
(2) Lundquist, J. J.; Toone, E. J. *Chem. Rev.* **2002**, *102*, 555–578.
(3) Morvan, F.; Meyer, A.; Jochum, A.; Sabin, C.; Chevolot, Y.; Imberty, A.; Praly, J. P.; Vasseur, J. J.; Souteyrand, E.; Vidal, S. *Bioconjugate Chem.* **2007**, *18*, 1637–1643, and references cited therein.
(4) Seeberger, P. H.; Haase, W. C. *Chem. Rev.* **2000**, *100*, 4349–4393.
(5) St Hilaire, P. M.; Meldal, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1162–1179.
(6) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
(7) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
(8) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, *2006*, 51–68.
(9) Lutz, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025.
(10) Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7–17.
(11) Joosten, J. A. F.; Loimaranta, V.; Appeldoorn, C. C. M.; Haataja, S.; ElMaate, F. A.; Liskamp, R. M. J.; Finne, J.; Pieters, R. J. *J. Med. Chem.* **2004**, *47*, 6499–6508.

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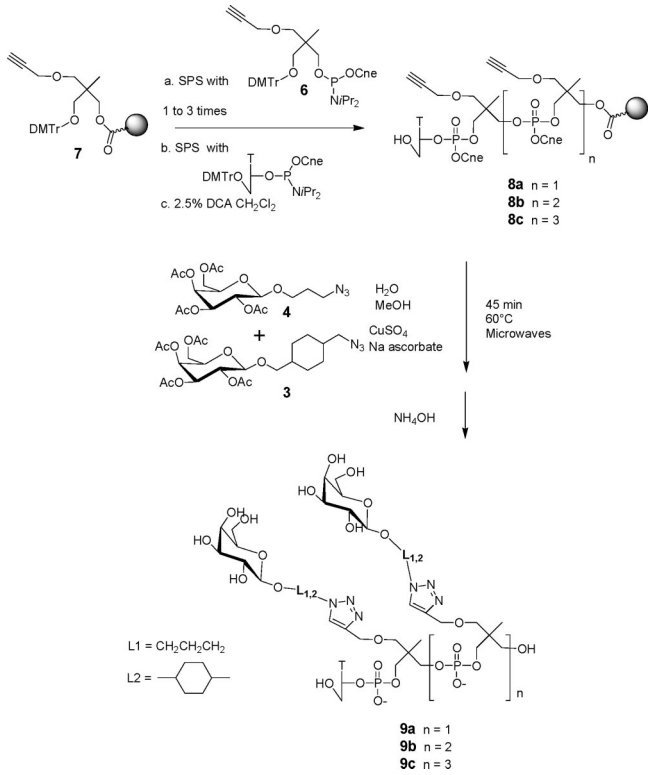
SCHEME 2. Solid-Supported Synthesis of Small Libraries of Di-, Tri-, and Tetragalactosyl Clusters[a]



[a] SPS: solid-phase synthesis. Conditions: (1) 2.5% dichloroacetic acid CH_2Cl_2; (2) phosphoramidite derivative + benzylthiotetrazole; (3) Ac_2O, *N*-Me imidazole, 2,6-lutidine; (4) 0.1 M I_2 THF/H_2O/pyridine.

The polyalkyne scaffolds were built following phosphoramidite oligonucleotide chemistry[12] using a monoalkyne phosphoramidite derivative **6** and its corresponding solid support **7**. Both compounds **6** and **7** were synthesized from 1,1,1-tris(hydroxymethyl)ethane which was successively monodimethoxytritylated, and alkylated with propargyl bromide in presence of NaH in THF providing 1-propargyl-2-[(4,4′-dimethoxytrityl)oxymethyl]-2-methylpropane-1,3-diol **5** (41% overall yield).[13] Compound **5** was then converted into its phosphoramidite derivative **6** using cyanoethyl tetraisopropylphosphorodiamidite activated with diisopropylammonium tetrazolide in dichloromethane (92%) or loaded on a succinyl LCAA CPG yielding **7** (32.2 μmol/g).[13]

Starting from solid support **7**, the monoalkyne phosphoramidite **6** was coupled one, two, or three times and eventually a commercial thymidine phosphoramidite, as a UV-tag, using a DNA synthesizer and standard phosphoramidite chemistry providing solid-supported di-, tri-, and tetraalkyne scaffolds with phosphotriester linkages (**8a**−**c**, Scheme 2).

Solid-supported compounds **8a**−**c** were split in three parts, and each part was added to a mixture of both galactosyl azide derivatives (**3** and **4**) using 3 molar equiv per alkyne, in the presence of $CuSO_4$ and sodium ascorbate, to catalyze the "click" 1,3-dipolar cycloaddition assisted by microwaves (MW)[13,14] Indeed, we have shown that the click reaction performed on solid support is much more efficient with microwave assistance.[14,15]Thus, the reactions were complete in a short amount of time without addition of copper(I) accelerating ligands like TBTA.[16] We studied the click reaction using different ratios of azido galactosyl derivatives **3**:**4** with molar ratios of 1:1, 1:2, and 2:1.

With a molar ratio of 1:1, if each azide derivative exhibits the same reactivity the click reaction done on **8a**−**c** would afford after ammonia treatment **9a**−**c** with 4, 8, and 16 compounds, respectively, in similar amounts. Among all these compounds, some of them are isomers displaying the same mass and the same retention time by HPLC. Hence, we should observe by HPLC for **9a** a 1:2:1 repartition, for **9b** a 1:3:3:1 repartition, and for **9c** a 1:4:6:4:1 repartition, and each family of isomers could be characterized by MALDI-TOF MS. For example, among the four digalactosyl clusters **9a**, one is constituted of two propyl linkages (**9aL1L1**), the two isomeric clusters have one propyl and one 1,4-dimethylcyclohexane linkage at different places (**9aL1L2** and **9aL2L1**), and the last one bears two 1,4-dimethylcyclohexane linkages (**9aL2L2**).

The click reactions were performed with **8a**−**c**, using different molar ratios of **4** and **3**, for 45 min at 60 °C under MW in presence of $CuSO_4$ and sodium ascorbate. After ammonia treatment (2 h at room temperature) followed by evaporation, the crude mixtures were analyzed by RP-HPLC and MALDI-TOF MS (Figure 1). HPLC profiles displayed the expected number of peaks (3, 4, and 5) which were isolated, and each one was characterized by MS. Each *m*/*z* signal was spaced from the others by 68.12 Da corresponding to C_5H_8, which is the difference in composition between L1 and L2.

As expected, the galactosyl clusters corresponding to the fastest eluted peaks were constituted of L1 linkers. Then the retention time of peaks increased with the number of L2 linkers. Hence, the peaks with the longest retention time were constituted of only L2 linkers.

For the 1:1 molar ratio of both galactosyl azides clicked with **8a**−**c**, a similar pattern was observed with a greater proportion of **9a**−**c** constituted of only L2 than those constituted with only L1 (between 3.5 and 7.3 times more, Table 1). This phenomenon was amplified when the click reaction was performed with a 2:1 molar ratio of **3**:**4** at such a point that **9c** with only L1 linker was not detected. In contrary, when click occurred with a 1:2 molar ratio of **3**:**4** more **9a**−**c** were constituted with L1 linkers (Table 1). This result suggests that azide **3** is more reactive than azide **4** (1.5−2 times). In each family, the isomeric galactosyl clusters are present in a same amount (e.g., amount of **9aL1L2** = amount of **9aL2L1**).

Notice that it is possible to modulate the repartition of each family by mixing the different crudes obtained with the different molar ratios of **4** and **3**.

Each library was obtained with an excellent purity allowing direct use for biological evaluations. In addition, each family could be isolated by HPLC before evaluation.

Alternatively, each compound could be separately synthesized starting from **8a**−**c** and **3** or **4** affording **9a**−**c** bearing only galactosyl clusters with L2 or L1 linkers following the same protocol. In contrast, the synthesis of mixed galactosyl clusters with L2 and L1 linkers would require extra steps (e.g., for

(12) Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859–1862.

(13) Lietard, J.; Meyer, A.; Vasseur, J. J.; Morvan, F. *J. Org. Chem.* **2008**, *73*, 191–200.

(14) Bouillon, C.; Meyer, A.; Vidal, S.; Jochum, A.; Chevolot, Y.; Cloarec, J. P.; Praly, J. P.; Vasseur, J. J.; Morvan, F. *J. Org. Chem.* **2006**, *71*, 4700–4702.

(15) Chevolot, Y.; Bouillon, C.; Vidal, S.; Morvan, F.; Meyer, A.; Cloarec, J. P.; Jochum, A.; Praly, J. P.; Vasseur, J. J.; Souteyrand, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 2398–2402.

(16) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853–2855.

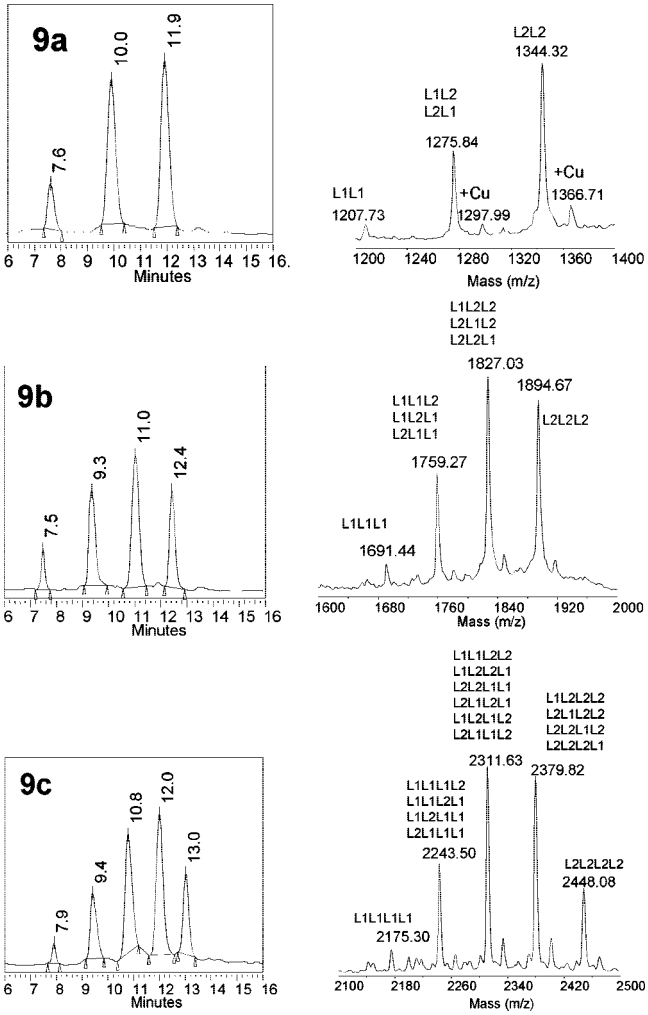


FIGURE 1. C18 RP-HPLC profiles and MALDI-TOF MS of crude **9a**−**c** formed from **8a**−**c** and **3**:**4** with a 1:1 molar ratio.

TABLE 1. Proportion of Each Family Compound Formed during the Click Reaction Using 1:1, 2:1, and 1:2 Molar Ratios of 3 and 4 with 8a−**c To Form 9a**−**c**[a]

9a: **3**:**4**	L_{11} (**1**)	L_{12} (2)	L_{22} (1)		
1:1	1.0	4.0	4.5		
2:1	1.0	4.3	6.2		
1:2	2.4	3.0	1.0		
9b: **3**:**4**	L_{111} (1)	L_{112} (3)	L_{122} (3)	L_{222} (1)	
1:1	1.0	4.0	6.4	3.5	
2:1	1.0	5.3	3.8	9.2	
1:2	1.5	3.4	3.3	1.0	
9c: **3**:**4**	L_{1111} (1)	L_{1112} (4)	L_{1122} (6)	L_{1222} (4)	L_{2222} (1)
1:1	1.0	6.0	15.0	15.0	7.3
2:1	0.0	1.0	5.6	20.3	21.7
1:2	2.7	7.0	6.7	3.8	1.0

[a] L_{12} represents digalactosyl clusters formed with one L1 and one L2 linkers, whatever their position. The number in parentheses corresponds to the number of isomers of each family.

synthesis of **9aL1L2**, solid support **7** should be first clicked with **3** and then transferred into the column to further introduce **7** and thymidine amidites, clicked with **4** and treated with ammonia corresponding to one additional step). The number of extra steps will increase with the number of carbohydrates to introduce (e.g., synthesis of **9cL1L2L1L2** would require five extra steps).

The synthesis of the solid supported alkyne scaffold was efficient, and the number of alkyne functions could also be increased easily.

The CuAAC click reaction was powerfully applied for the synthesis of small libraries of di-, tri-, and tetragalactosyl clusters bearing a phosphodiester linkage containing 4, 8, and 16 compounds, respectively. They were obtained on solid support, assisted by microwaves, that allows rapid synthesis with an easy workup affording after cleavage from the solid support by ammonia and evaporation the almost pure library in a flask. The interaction of these galactosyl-clusters with the RCA_{120} lectin which recognizes galactose will be presented elsewhere.

This strategy could be applied for other carbohydrate azide derivatives. The number of carbohydrates to click, here only two, and the number of alkyne functions, here up to four, could be easily increased to provide rapidly more complex libraries.

Experimental Section

[4-(*p*-Toluenesulfonyloxymethyl)cyclohexyl]methanol (1). To a solution of 1,4-cyclohexanedimethanol (mixture of *cis* and *trans*) (1.42 g, 10 mmol) and DMAP (61 mg, 0.5 mmol), dried by azeotropic distillation with anhydrous pyridine, in anhydrous dichloromethane (15 mL), were added *p*-toluenesulfonyl chloride (954 mg, 5 mmol) and anhydrous triethylamine (1.05 mL, 7.5 mmol). After 3 h of stirring at rt, the reaction was quenched by adding 50 mL of saturated bicarbonate solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the organic layers were combined, dried over Na_2SO_4, and evaporated to dryness. The crude product was then purified by silica gel column chromatography (0−5% MeOH in CH_2Cl_2) to afford **1** (1.08 g, 72%) as a pink oil. R_f = 0.55 (CH_2Cl_2/MeOH, 95:5, v/v). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85−1.95 (m, 11H), 2.47 (s, 3H), 3.44−3.95 (m, 2H), 3.83−3.95 (m, 2H), 7.36 (d, 2H, J = 8.1 Hz), 7.80 (d, 2H, J = 8.3 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 22.0, 25.2, 25.3, 28.8, 35.0, 37.7, 38.1, 40.5, 66.3, 68.7, 73.5, 75.6, 128.3, 130.2, 133.4, 145.0. ESIMS$^+$: m/z 299.2 (M + H)$^+$, 127.1 (M + H − OTs)$^+$, 109.1 (M + H − OTs − H_2O)$^+$. HRMS ESI$^+$: m/z calcd for $C_{15}H_{23}O_4S_1$ (M + H)$^+$ 299.1317, found 299.1305.

[4-(Azidomethyl)cyclohexyl]methanol (2). To a solution of **1** (mixture of *cis* and *trans*) (1.02 g, 3.4 mmol) in DMF (25 mL) were added sodium iodide (2.06 g, 13.7 mmol) and sodium azide (890 mg, 13.7 mmol), and the mixture was stirred 3 h at 75 °C. The solvent was removed under reduced pressure and the resulting residue dissolved in 100 mL of CH_2Cl_2. The organic layer was washed with saturated bicarbonate solution (2 × 50 mL) and brine (2 × 50 mL), dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by silica gel column chromatography (7−60% AcOEt in cyclohexane) to afford **2** (456 mg, 79%) as a colorless oil: R_f = 0.29 (cyclohexane/AcOEt, 7:3, v/v). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.85−1.95 (m, 11H), 3.15−3.26 (m, 2H), 3.47−3.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 25.1, 26.3, 28.8, 30.0, 35.5, 37.9, 38.3, 40.4, 55.4, 58.0, 66.0, 68.5. ESIMS$^+$: m/z 170.2 (M + H)$^+$; 142.1 (M + H − N_2)$^+$; 124.1 (M + H − N_2 − H_2O)$^+$; 113.2 (M + H − CH_3N_3)$^+$; 107.1 (M + H − N_2 − H_2O − NH_3)$^+$; 95.1 (M + H − CH_3N_3 − H_2O)$^+$. FTIR: 3343, 2922, 2856, 2524, 2096, 1451, 1378, 1345, 1262, 1132, 1097, 1036, 992, 955, 941, 885, 825, 655, 588, 556. HRMS ESI$^+$: m/z calcd for $C_8H_{16}N_3O_1$ (M + H)$^+$ 170.1293, found 170.1315.

1-*O*-[[4-(Azidomethyl)cyclohexyl]methyl]-2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranoside (3). To a solution of peracetylated D-galactose (414 mg, 1.05 mmol), dried by azeotropic distillation with anhydrous acetonitrile, in anhydrous CH_2Cl_2 (20 mL), was added compound **2** (170 mg, 1 mmol). The reaction mixture was cooled

to 0 °C before addition of boron trifluoride etherate (630 μL, 5 mmol). After 4 h of stirring at rt, the reaction was quenched by adding 50 mL of saturated bicarbonate solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), and the organic layers were combined, dried over Na_2SO_4, and evaporated to dryness. The crude product was then purified by silica gel column chromatography (0−30% AcOEt in cyclohexane) to afford **3** (104 mg, 21%) as a colorless oil. R_f = 0.29 (AcOEt/cyclo, 1:1, v/v). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.85−2.08 (m, 22H), 3.05−3.35 (m, 3H), 3.65−3.86 (m, 2H), 4.00−4.17 (m, 2H), 4.34−4.39 (m, 1H), 4.94 (dd, 1H, J = 3.2 Hz, J = 10.5 Hz), 5.14 (dd, 1H, J = 7.8 Hz, J = 10.5 Hz), 5.32 (d, 1H, J = 3.2 Hz). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 19.9, 20.0, 20.3, 24.3, 24.4, 25.3, 25.5, 28.0, 28.2, 29.1, 29.2, 34.2, 34.8, 37.0, 37.4, 54.7, 57.1, 60.5, 66.3, 68.2, 69.9, 70.2, 72.3, 74.8, 100.9, 168.7, 169.5, 169.6,169.7. ESIMS$^+$: m/z 500.3 $(M + H)^+$, 331.1 $(M + H - (HO\text{-}DMCH\text{-}N_3))^+$, 271.1 $(M + H - (HO\text{-}DMCH\text{-}N_3) - CH_3CO_2H)^+$, 211.1 $(M + H - (HO\text{-}DMCH\text{-}N_3) - 2CH_3CO_2H)^+$, 169.1 $(M + H - C_{14}H_{19}O_9)^+$. HRMS ESI$^+$: m/z calcd for $C_{22}H_{34}N_3O_{10}$ $(M + H)^+$ 500.2244, found 500.2244.

1-*O*-(3-Azidopropyl)-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (4). Synthesized according ref 11.

1-*O*-(4,4′-Dimethoxytrityl)-2-propargyloxymethyl-2-methyl-3-{*O*-[(2-cyanoethyl)-*N*,*N*-diisopropylphosphoramidite]-1,3-propanediol (6). 1-Propargyl-2-[(4,4′-dimethoxytrityl)oxymethyl]-2-methylpropane-1,3-diol **5**[13] (325 mg, 0.7 mmol) and diisopropylammonium tetrazolide (60 mg, 0.35 mmol) were dried three times by coevaporation with anhydrous acetonitrile and then dissolved in anhydrous CH_2Cl_2 (5 mL) before addition of 2-cyanoethyl tetraisopropyl phosphorodiamidite (258 μL, 0.84 mmol) at rt. The resulting mixture was stirred at room temperature for 3 h and then diluted with EtOAc (25 mL). The organic layer was washed with brine (2 × 50 mL), dried (Na_2SO_4), filtered, and evaporated. The residue was purified by chromatography on silica gel (Cyclohexane/CH_2Cl_2 100/0 to 80/20 with 4% Et_3N) affording the phosphoramidite **6** (422 mg 92%) as an oil. R_f (cyclohexane/CH_2Cl_2/Et_3N 7:2:1 v/v/v) = 0.5. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.00−1.21 (m, 15H), 2.42 (bs, 1H), 2.53−259 (t, 2H, J = 6.5 Hz), 3.03 (s, 2H), 3.43−3.79 (m, 8H), 3.82 (s, 6H), 4.11−4.18 (bs, 2H), 6.83−7.49 (m, 13H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 17.8, 20.3, 24.5, 24.6, 41.2, 41.3, 43.2, 43.3, 53.3, 55.2, 58.3, 58.5, 58.6, 58.7, 65.2, 66,5, 66.6, 66.7, 72.8, 72.9, 73.9, 80.2, 85.7, 113.0, 117.4, 126.5, 127.6, 128.4, 130.2, 136.5, 145.3, 158.5. ^{31}P NMR ($CDCN_3$, 80 MHz): δ 148.6, 148.7. HRFABMS (positive mode, nitrobenzylic alcohol): m/z calcd for $C_{38}H_{50}N_2O_6P_1$ $[M + H]^+$ 661.3407, found 661.3383.

Synthesis of Solid-Supported Phosphotriester Alkyne Scaffolds. The solid-supported phosphotriester alkyne scaffolds were synthesized on a DNA synthesizer (ABI 394) using standard phosphoramidite chemistry on the monoalkyne solid support **7** using alkyne phosphoramidite **6** (0.09 M in anhydrous CH_3CN) or commercially available thymidine phosphoramidite (0.075 M in anhydrous CH_3CN) and benzylmercaptotetrazole (0.3 M in anhydrous CH_3CN) as activator.

General Procedure for Cu(I)-Catalyzed 1,3-Dipolar Cycloaddition. To a solid-supported oligoalkyne phosphotriester **8a**−**c** (0.3 μmol) was added a mixture of 1-*O*-(3-azidopropyl)-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **4** (1.5 equiv by alkyne, 0.1 M solution in MeOH) and 1-*O*-[[4-(azidomethyl)cyclohexyl]methyl]-2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside **3** (1.5 equiv by alkyne, 0.1 M solution in MeOH), and $CuSO_4$ (0.4 equiv, 0.12 μmol, 3 μL of a 40 mM solution in H_2O), freshly prepared sodium ascorbate (2 equiv, 0.6 μmol, 12 μL of a 50 mM solution in H_2O), water, and MeOH were added to obtain a total volume of 200 μL (1:1, v/v). The other compounds with different ratios of carbohydrates (1:2, 2:1) were prepared similarly. The resulting preparation was treated in a sealed tube with microwave synthesizer Initiator from Biotage set at 100 W with a 30 s premixing time. The temperature was monitored with an internal infrared probe to 60 °C during 45 min. The solution was removed, and the CPG beads were washed with H_2O (2 mL) and MeOH (2 mL) and then dried.

General Procedure for Deprotection. Beads were treated with concentrated aqueous ammonia (500 μL) for 2 h at room temperature, and the supernatant was withdrawn and evaporated to dryness. The residue was dissolved in water for subsequent analyses.

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Supporting Information Available: ^{1}H and ^{13}C and ^{31}P NMR spectra of new compounds. HPLC and MALDI-TOF spectra of **9a**−**c** with click performed in the presence of 1:2 and 2:1 molar ratio of **4**:**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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