Synthesis of "Sugar-Rods" with Phytohemagglutinin Cross-Linking Properties by Using the Palladium-Catalyzed Sonogashira Reaction

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Dedicated to Professor Pierre Sinaÿ on the occasion of his 62nd birthday

Abstract: A palladium-catalyzed Sonogashira reaction has been applied for the syntheses of divalent "sugar-rods" which exhibited excellent lectin cross-linking properties. The procedure, which involves a tetrakis(triphenylphosphine)-palladium-catalyzed cross-coupling reaction between an alkyne and a halogen-bearing sp^2-carbon in DMF at 60 °C, is very efficient and the dimeric or heterobifunctional "sugar-rods" (**8**–**13**, **15**–**17**) were isolated in 65–100% yields. Dimers **8a** and **15a** were both shown to form insoluble cross-linked lattices when mixed with the tetrameric plant lectin from *Canavalia ensiformis* (Concavalin A, **Con A**). Moreover, the relative inhibitory properties of the synthetic dimannosides were determined by means of the hemagglutination of rabbit erythrocytes, whereby dimer **15a** was shown to be 20-fold more potent than monomeric methyl α-D-mannopyranoside.

Keywords: alkenyls · carbohydrates · palladium · Sonogashira reaction · sugar-rods

Introduction

During the last few years, enormous efforts have been made in the area of transition metal mediated organic syntheses. In this respect, the Sonogashira reaction, which involves either a Pd^0- or a Pd^{II}-catalyzed cross-coupling reaction between an alkyne and a halogen-bearing sp^2-carbon, has attracted great interest.[1, 2] Usually, the palladium-catalyzed Sonogashira reaction is carried out in the presence of copper(I) iodide and an amine as the solvent. This reaction has proven to be extremely useful for the synthesis of key intermediates in a large variety of naturally occurring substances.[3] However, this useful reaction has scarcely been used in carbohydrate chemistry. The only other example of this type has recently been described by Vasella et al.[4] The application illustrates the synthesis of host molecules prepared by coupling 1,4-dialkynylated 1,6-anhydroglucitols with 6,6′-dibromo-2,2′-bipyridine as building blocks by the use of $[PdCl_2(PPh_3)_2]$, CuI, PPh_3, and Et_3N.

In view of the important role of multivalent carbohydrate derivatives in glycobiology,[5] we have initiated a program towards the synthesis of carbohydrate-containing clusters. Recently, we reported the use of Grubbs' catalyst for the efficient syntheses of carbohydrate homodimers [6] and heterodimers.[7] Such sugar dimers represent appealing tools to quickly evaluate distances between carbohydrate binding sites in polyvalent recognition and to act as potent reversible cross-linking reagents.[8] In our continuing efforts towards the design and synthesis of multivalent neoglycoconjugates,[9] we required a convenient route to prepare an exciting new class of carbohydrate dimers called "sugar-rods" in which two sugar moieties are connected by an aromatic ring and one or two acetylenic bonds to increase the hydrophobicity and rigidity of the molecules and thus diminish the entropic loss that is usually associated with flexible and hydrated carbohydrate ligands. An exhaustive review has recently summarized the preparation, properties, and applications of various molecular rods.[10] The Sonogashira acetylenic coupling seems to be an ideal tool to introduce such aromatic and alkynic substituents between carbohydrate residues. Herein, we report the application of the Sonogashira reaction, without the addition of a copper salt,[11] to the synthesis of biologically important "sugar-rods" with excellent yields (see Table 1). The procedure is appealing when compared to the bis-glycosylation strategy which usually provides mixtures of anomers.[12]

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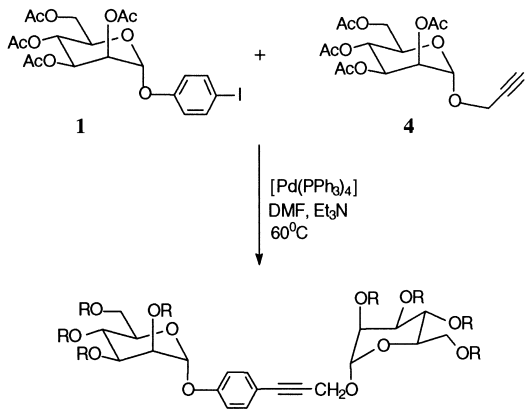
Results and Discussion

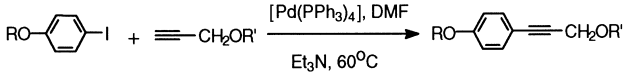
The requisite starting materials, 4-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (**1**) and 2-propynyl α-D-mannopyranoside (**4**), were synthesized from penta-*O*-acetyl-α,β-D-mannopyranose by BF_3-etherate-catalyzed glycosylation with 4-iodophenol or freshly distilled propargyl alcohol, in 54% and 74% yields, respectively.[13, 14] The Sonogashira reaction between **1** and **4** proceeded smoothly to yield the mannose-containing "dimer" **8** in 98% yield. In a typical reaction, $[Pd(PPh_3)_4]$ (0.1 mmol) and triethylamine (8 mL) were added to a degassed solution of **1** and **4** in anhydrous DMF (8 mL). The solution was heated at 60 °C under a nitrogen atmosphere for approximately 3 h. After the usual work-up, the residue was purified by silica gel column chromatography (ethyl acetate/hexane 1:1) to provide the desired dimer **8** (Scheme 1). The structure of **8** was fully confirmed by NMR and mass spectral data analyses.



Scheme 1. The Sonogashira reaction between **1** and **4**.

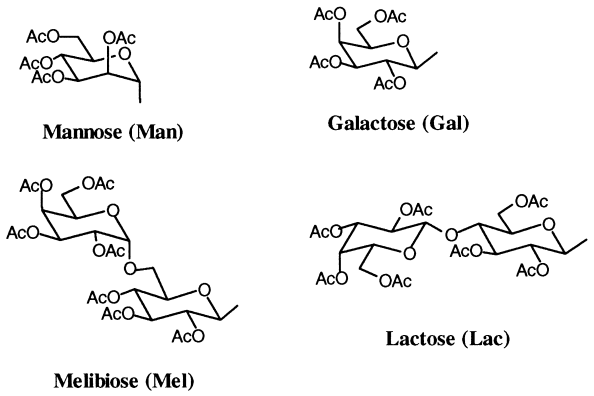
To extend the scope and generality of this reaction, various other carbohydrate precursors were synthesized. 4-Iodophenyl 2,3,4,6-*O*-tetra-*O*-acetyl-β-D-galactopyranoside (**2**) was prepared by a phase transfer catalyzed reaction[15] with tetrabutylammonium hydrogen sulfate, 4-iodophenol, and sodium hydrogen sulfate in 76% yield. Peracetylated 2-propynyl β-D-galactopyranoside (**5**) was synthesized in 80% yield by the same procedure as that described for **4**. The Sonogashira reaction between **2** and **5**, performed under the same reaction conditions, gave dimer **9** in 85% yield. Once the reaction conditions were optimized for monosaccharides, this simple but efficient method was extended to disaccharidic systems. For this purpose, peracetylated 2-propynyl β-D-melibioside (**3**) and peracetylated 4-iodophenyl β-D-melibioside (**6**) were synthesized under the conditions described for **2** and **4**. The reaction between **3** and **6** also proceeded smoothly and gave dimer **10** in 65% yield. Again, the success of the reaction prompted us to extend it to the cross-coupling of other sugar molecules. Thus, compound **2** was coupled with **4**, in the presence of $[Pd(Ph_3P)_4]$, DMF, and Et_3N, at 60 °C, to give "heterodimer" **11** (Gal–Man) in 80% yield. Similarly, compounds **1** and **6** gave **12** (Man–Mel), while compounds **2** and **7** gave **13** (Gal–Lac) in 80% and 92% yields, respectively. The results are summarized in Table 1.

Table 1. Palladium-catalyzed Sonogashira reactions of **1–3** with **4–7**.



1-3 **4-7** **8-13**

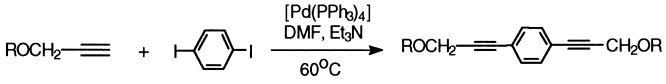
Entry	R	R^1	Product	Yield [%]
1	Man(1)	Man(4)	**8**	98
2	Gal(2)	Gal(5)	**9**	85
3	Mel(3)	Mel(6)	**10**	65
4	Gal(2)	Man(4)	**11**	80
5	Man(1)	Mel(6)	**12**	80
6	Gal(2)	Lac(7)	**13**	92



Encouraged by the successful synthesis of unsymmetrical dimers, we proceeded to expand the scope and generality of this reaction toward the synthesis of symmetrical carbohydrate dimers that have longer interglycosidic distances by the use of 1,4-diiodobenzene (**14**) and propargyl glycosides in a double Sonogashira reaction. In a typical reaction, peracetylated propargyl β-D-mannopyranoside (**4**) (2.2 mmol) and 1,4-diiodobenzene (1 mmol) were dissolved in anhydrous DMF (8 mL). Subsequently, $[Pd(PPh_3)_4]$ (0.1 mmol) and triethylamine (8 mL) were added. The usual work-up and purification by column chromatography gave homodimer (**15**) in quantitative yield. In a similar manner, compounds **5** and **7** reacted with **14**, and symmetrical dimers **16** and **17** were isolated in 72 and 71% yields respectively (Table 2).

The cross-linking properties of the "sugar-rods" that contain D-mannose, **8a** and **15a**, obtained by the deacetyla-

Table 2. Palladium-catalyzed Sonogashira reactions of **4**, **5**, and **7** with **14**.



4,5,7 **14** **15-17**

Entry	Substrate	R	Product	Yield [%]
1	**4**	Man(4)	**15**	100
2	**5**	Gal(5)	**16**	72
3	**7**	Lac(7)	**17**	71

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tion of **8** and **15**, respectively, under Zemplén conditions (NaOMe, MeOH), towards tetrameric plant lectin from *Canavalia ensiformis* (Concanavalin A, **Con A**) was initially demonstrated by microturbidimetric analyses.[9] To this end, microtitration plates were filled with a **Con A** solution (1 mg mL^{-1} in phosphate buffer solution (PBS), 90 μL), to which was added a solution of **8a** or **15a** (2.1 μmol mL^{-1} PBS, 10 μL). The capacity of the various dimers to form insoluble cross-linked lattices with the phytohemagglutinin is shown in Figure 1. Insoluble complexes were observed after only a few minutes. The results showed that the diyne-containing mannose "sugar-rod" (**15a**), which has a slightly longer spacer arm than the shorter mannose derivative (**8a**), exhibited slightly

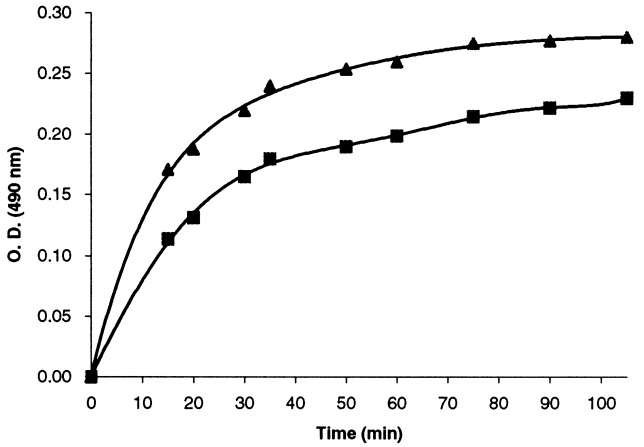
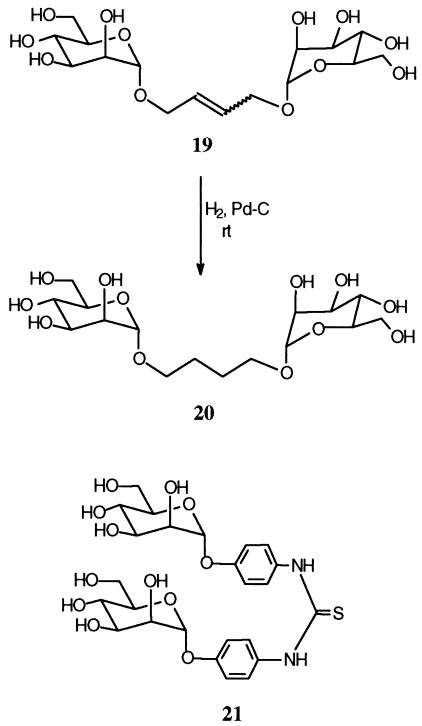


Figure 1. Time course of the microtiter plate turbidimetric assay demonstrating the cross-linking properties of mannosylated dimers **8a** (■) and **15a** (▲) in the presence of the phytohemagglutinin Concanavalin A.

faster cross-linking properties. Finally, the reversibility and specificity of the carbohydrate–lectin interactions were demonstrated by the addition of a large excess of D-mannose (1 mg), which helped to resolubilize the lectin by inhibition while D-galactose failed to redissolve the complex.

We then turned our attention into an inhibition of hemagglutination assay[16] to evaluate the relative binding properties of the dimers **8a** and **15a** compared to the monomeric methyl α-D-mannopyranoside, *p*-nitrophenyl α-D-mannopyranoside, and two other dimer precursors, **20** and **21**, readily available from our previous work (Scheme 2).[17, 18] To this end, rabbit erythrocytes were allowed to hemagglutinate in the presence of either **Con A** or its analogous lectin from *Dioclea grandiflora* according to a published procedure.[16] In this assay, the minimum mannoside concentration necessary to inhibit the hemagglutination of the rabbit erythrocytes by the lectins was determined for each compound. All the compounds showed more or less the same trend with both lectins (Table 3). However, the inhibitory properties of all dimers were improved several fold compared to those of their monomeric counterparts. The more rigid derivative **15a** (125 μM) was the best inhibitor for both lectins. Interestingly, of the dimers, the more flexible dimanoside **20** appeared to be the least efficient inhibitor. These observations are in very good agreement with our notion that the more rigid molecules may have improved binding properties.



Scheme 2. Synthesis of **20** and structure of **21;** both compounds were used in the hemagglutination studies.

Table 3. Inhibitory properties of synthetic mannose derivatives for the hemagglutination[a] of rabbit erythrocytes mediated by Con A[b] or DGL.[c]

Sugar derivatives	Con A [μM][d]	DGL [μM][d]
Me α-D-Man	3100	3100
PNP α-D-Man[e]	1500	1500
8a	250	500
15a	125	375
20	450	475
21	289	NI (289)

[a] Buffer was 0.1M (Hepes), 0.15M NaCl, 5mM $MnCl_2$, 5mM $CaCl_2$. [b] Concanavalin A from Jack beans (*Canavalia ensiformis*). [c] *Dioclea grandiflora* lectin. [d] Minimum concentration required for complete inhibition of four hemagglutination units (NI, not inhibitory). [e] *p*-Nitrophenyl α-D-mannopyranoside.

It is still debatable, however, if the origin of the phenomenon for multivalent ligands is driven by kinetic or thermodynamic factors.

Conclusions

The palladium-catalyzed Sonogashira reaction has been successfully applied to the synthesis of rigid carbohydrate clusters that have great potential as protein or receptor cross-linkers. The procedure is general, high-yielding, and compatible with the readily removable protecting group on the acetate; the carbohydrate derivatives were isolated in excellent yields. In initial experiments, divalent mannose-containing "sugar-rods" **8a** and **15a** showed a strong and fast cross-linking ability towards the tetrameric plant lectin **Con A**. They also showed better inhibitory properties than their more flexible counterparts **20** and **21** in the inhibition of

the hemagglutination of rabbit erythrocytes by two plant lectins that have similar affinities towards α-D-mannopyranosides. Such ligands may also find useful applications as inhibitors in cell adhesion processes. Further work is in progress to reach this goal and to determine the relative binding energies between these "sugar-rods" and more flexible sugar dimers by means of isothermal microcalorimetry.[19]

Experimental Section

Materials: ^{1}H and ^{13}C NMR spectra were recorded at 500 or 200 MHz and 125 or 50 MHz, respectively, with tetramethylsilane ($\delta = 0.00$) as the internal reference. Thin-layer chromatography (TLC) was performed with silica gel 60 F_{254} aluminum sheets purchased from E. Merck. Reagents used for developing the plates include ceric sulfate (1% w/v) and ammonium sulfate (2.5% w/v) in 10% (v/v) aqueous sulfuric acid, iodine, dilute aqueous potassium permanganate, and UV light. TLC plates were heated to approximately 150 °C when necessary. Purifications were performed by gravity or flash chromatography on silica gel 60 (230–400 mesh, E. Merck No. 9385). Solvents were evaporated under reduced pressure on a Buchi rotary evaporator connected to a water aspirator. All chemicals used in experiments were of reagent grade. Solvents were purified by published procedures. The known homodimer **19** was prepared by the use of Grubbs' catalyst in our laboratory.[17] Compound **21** was obtained as previously described.[18]

4-Iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (1): To a solution of penta-*O*-acetyl-α,β-D-manopyranoside (1 g) and 4-iodophenol (1 g) in dry CH_2Cl_2 (20 mL) was added BF_3-etherate (0.5 mL). The reaction mixture was kept at room temperature and the course of the reaction was monitored by TLC (AcOEt/hexane 1:1) until complete disappearance of the starting material (18 h). CH_2Cl_2 (75 mL) was added and the solution was washed with a saturated aqueous Na_2CO_3 solution (2 × 50 mL), NaOH solution (0.5 N, 2 × 50 mL), water (50 mL), 5% HCl solution (2 × 50 mL), and water (2 × 50 mL). After drying and evaporation of the solvent, the resulting crude product was crystallized from diethyl ether/hexane to give **1**. Yield: 0.955 g (54%); m.p. 127–129 °C; $[\alpha]_D^{22} = +65$ ($c = 1$ in $CHCl_3$); IR (film): $\tilde{\nu} = 1751, 1483, 1386, 1224\ cm^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.57, 6.85 (2 d, $J = 9.0$ Hz, 4H; C_6H_4), 5.50 (dd, $J = 10.1$ and 3.5 Hz, 1H; H3), 5.46 (d, $J = 1.9$ Hz, 1H; H1), 5.40 (dd, $J = 3.5$ and 1.9 Hz, 1H; H2), 5.33 (t, $J = 10.0$ Hz, 1H; H4), 4.24 (dd, $J = 12.4$, 5.5 Hz, 1H; H6), 4.06–3.99 (m, 2H; H5, H6′), 2.17, 2.03, 2.00 (3 s, 12H; 4 Ac); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.5, 170.0, 169.7$ (CO), 155.4, 138.5, 118.8, 85.8 (C_6H_4), 95.8 (C1), 69.4, 69.3, 68.8, 65.8 (C2, C3, C4, C5), 62.1 (C6), 20–9, 20.7 (CH_3CO); MS (FAB): m/z: 551.2269 [M++1].

4-Iodophenyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (2): Penta-*O*-acetyl-β-D-galactopyranoside (4 g) was transformed into the corresponding glycosyl bromide with HBr/AcOH following the standard procedure. After work-up, this glycosyl halide was used immediately without further purification. It was dissolved in CH_2Cl_2 (200 mL) and tetrabutylammonium hydrogen sulfate (4.76 g), 4-iodophenol (3.6 g), and sodium carbonate solution (1 M, 50 mL) were added. The reaction mixture was vigorously stirred at room temperature until the starting material was completely consumed (2 h) as judged by TLC (diethyl ether/hexane 2:1). The solution was then diluted with CH_2Cl_2 (200 mL) and the organic phase separated. The organic solution was washed with a saturated aqueous Na_2CO_3 solution (2 × 50 mL), NaOH solution (0.5 N, 2 × 50 mL), water (50 mL), 5% HCl solution (2 × 50 mL), and water (2 × 50 mL). After drying and evaporation of the solvent, the resulting crude product was purified by column chromatography (diethyl ether/hexane 2:1) to afford **2**. Yield: 5.68 g (76%); m.p. 55–56 °C; $[\alpha]_D^{22} = +10$ ($c = 1$ in $CHCl_3$); IR (film): $\tilde{\nu} = 1749$, 1482, 1368, 1227 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$, 6.75 (2 d, $J =$ 8.9 Hz, 4H; C_6H_4), 5.44 (dd, $J = 10.5$ and 7.9 Hz, 1H; H2), 5.43 (dd, $J = 3.5$ and 1.1 Hz, 1H; H4), 5.08 (dd, $J = 10.5$ and 3.5 Hz, 1H; H3), 4.98 (d, $J =$ 7.9 Hz, 1H; H1), 4.19 (dd, $J = 11.3$ and 7.2 Hz, 1H; H6), 4.03 (dd, $J = 11.3$ and 6.0 Hz, 1H; H6′), 4.03 (ddd, $J = 7.2$, 6.0 and 1.1 Hz, 1H; H5), 2.15 , 2.04, 2.04, 1.98 (4 s, 12H; 4 Ac); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4, 170.3,$ 170.1, 169.4 (CO), 156.3, 138.5, 119.2, 86.1 (C_6H_4), 99.5 (C1), 71.2, 70.8, 68.6, 66.8 (C2, C3, C4, C5), 61.4 (C6), 220.8, 20.7, 20.6 (CH_3CO); MS (FAB): m/z: 551.1329 [M++1].

General procedure for the synthesis of 2-propynyl D-glycopyranoside: A solution of 1,2,3,4,6-penta-*O*-acetyl-α,β-D-glycopyranose (5 g), freshly distilled propargyl alcohol (3 mL), and BF_3-etherate (3 mL) in CH_2Cl_2 (50 mL) was kept at room temperature for 2.5 d. CH_2Cl_2 (50 mL) was added and the resulting solution was washed with 20% aqueous Na_2CO_3 solution (150 mL) and water (100 mL). The organic phase was dried and the solvent evaporated to obtain a crude product that was then acetylated with Ac_2O/Py (10:10 mL). Conventional work-up gave a crude product which was purified to afford the corresponding 2-propynyl D-glycopyranoside.

2-Propynyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (4):[13] Compound was purified by column chromatography (silica gel, ethyl acetate/hexane 1:1) and isolated as a white solid. M.p. 100 °C; $[\alpha]_D^{22} = +56$ ($c = 2$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.31$ (dd, $J = 3.4$, 10.0 Hz, 1H; H3), 5.26 (t, $J = 10.0$ Hz, 1H; H4), 5.23 (dd, $J = 3.4$, 1.7 Hz, 1H; H2), 4.99 (d, $J = 1.7$ Hz, 1H; H1), 4.24 (dd, $J = 5.2$, 12.2 Hz, 1H; H6b), 4.24 (d, $J = 2.4$, 2H; H1′), 4.07 (dd, $J = 2.5$ Hz, 1H; H6a), 4.00 (ddd, 1H; H5), 2.44 (t, $J = 2.4$ Hz, 1H; H2′), 2.12, 2.07, 2.01, 1.96 (4 s, 12H; OAc); ^{13}C NMR (125 MHz, $CDCl_3$) $\delta =$ 170.5, 169.8, 169.7, 169.6 (CO), 96.2 (C1), 77.9 (C2′), 75.0 (C3′), 70.6, 69.3, 68.9, 67.9 (C2, C3, C4, C5), 62.3 (C6), 54.9 (C1′), 20.8, 20.7, 20.6, 20.6 (C-Me); MS (FAB): m/z: 387.1264 [M++1].

2-Propynyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (5):[14] Compound **5** was isolated as a white solid by column chromatography (ethyl acetate/hexane 1:1) in 80% yield. M.p. 56 °C; $[\alpha]_D^{22} = -24$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.37$ (dd, $J = 1.0$, 3.4 Hz, 1H; H4), 5.19 (dd, $J = 5.2$, 8.0 Hz, 1H; H2), 5.02 (dd, $J = 3.4$, 8.0 Hz, 1H; H3), 4.71 (d, $J =$ 8.0 Hz, 1H; H1), 4.35 (d, $J = 2.4$ Hz, 1H; H1′), 4.16 (dd, $J = 6.6$, 11.3 Hz, 1H; H6b), 4.12 (dd, $J = 6.8$, 11.3 Hz, 1H; H6a), 3.89 (ddd, 1H; H4), 2.44 (t, $J = 2.4$ Hz, 1H; H1′), 2.12, 2.04, 2.02, 1.98 (4 s, 12H; OAc); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 170.3$, 170.2, 170.1, 169.5 (CO), 98.6 (C1), 78.2 (C3′), 75.3 (C2′), 70.8, 70.8, 68.5, 67.0 (C2, C3, C4, C5), 61.2 (C6), 55.9 (C1′), 20.8, 20.6, 20.6, 20.5 (Me); MS (FAB): m/z: 387.1359 [M++1].

2-Propynyl 6-*O*-[2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl]-2,3,4-tri-*O*-acetyl-β-D-glucopyranoside (6): To a solution of melibiose octaacetate (2.5 g) in dry CH_2Cl_2 (50 mL) was added freshly distilled propargyl alcohol (0.34 mL) and BF_3-etherate (0.7 mL). The reaction mixture was kept at room temperature for 14 h. CH_2Cl_2 (50 mL) was added and the resulting solution was washed with 20% aqueous Na_2CO_3 solution (150 mL) and water (100 mL). The organic phase was dried and the solvent evaporated. The crude product was acetylated with Ac_2O/Py (5:5 mL). Conventional work-up gave a crude product that was purified by column chromatography (AcOEt/hexane 1:19) to afford **6** as a foam solid (2.29 g, 92%). M.p. 79–81 °C; $[\alpha]_D^{22} = +88$ ($c = 1$ in MeOH); IR (KBr): $\tilde{\nu} = 3281, 1765, 1244,$ 1053 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 5.42$ (dd, $J = 3.2$ and 1.1 Hz, 1H; H4′), 5.30 (dd, $J = 10.7$ and 3.2 Hz, 1H; H3′), 5.21 (t, $J = 9.3$ Hz, 1H; H3), 5.12–4.88 (m, 4H; H2, H4, H1′, H2′), 4.73 (d, $J = 8.0$ Hz, 1H; H1), 4.33 (d, 2.4 Hz, 2H; $CH_2C{\equiv}CH$), 4.22, 4.08, 3.74–3.59 (3 m, 6H; H5, H6, H6, H5′, H6′, H6′), 2.51 (t, $J = 2.4$ Hz, 1H; C≡CH), 2.10, 2.09, 2.02, 2.01, 1.97, 1.95 (6 s, 21H; 7 Ac); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.2$, 171.0, 170.9, 170.8, 170.5, 170.0, 169.9 (CO), 98.5, 97.0 (C1,1′), 76.2, 73.5, 73.4, 71.5, 69.4, 68.6, 68.6, 68.0, 67.1, 66.9, 62.4 (C2, C3, C4, C5, C6, C2′, C3′, C4′, C5′, C6′, C≡C), 56.5 ($CH_2C{\equiv}CH$), 21.4, 21.2, 21.1, 21.0 (CH_3CO); MS (FAB): m/z: 713.4319 [M+K]$^+$.

General procedure for the cross coupling between 4-iodophenyl and propargyl glycosides

Syntheses of compounds 8–13: To a degassed solution of the 4-iodophenyl glycoside **1–3** (1 mmol) and the propargyl glycoside **4–7** (1.1 mmol) in DMF/Et_3N (8:8 mL) was added [$Pd(PPh_3)_4$] (0.1 mmol). The solution was then heated at 60 °C under a nitrogen atmosphere for 3–4 h. The Et_3N was removed by evaporation under vacuum. Diethyl ether/toluene (100:50 mL) was added to the residue and the solution was washed with 5% HCl (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and water (50 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated to yield a crude product that was purified by column chromatography.

Synthesis of 8 by the coupling reaction between 1 and 4: Column chromatography (AcOEt/hexane 1:1) gave **8** as a solid. M.p. 68–70 °C; $[\alpha]_D^{22} = +88$ ($c = 1$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 2351, 1772, 1741, 1604,$ 1509 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.37$, 7.02 (2 d, $J = 8.8$ Hz,

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4H; C_6H_4), 5.51 (dd, $J = 10.0$ and 3.5 Hz, 1H; H3a), 5.50 (d, $J = 1.7$ Hz, 1H; H1a), 5.40 (dd, $J = 3.5$ and 1.8 Hz, 1H; H2a), 5.35 (dd, $J = 9.9$ and 3.4 Hz, 1H; H3b), 5.32 (t, $J = 9.8$ Hz, 1H; H4a or H4b), 5.29 (t, $J = 9.9$ Hz, 1H; H4b or H4a), 5.28 (dd, $J = 3.4$, 1.7 Hz, 1H; H2b), 5.07 (d, $J = 1.6$ Hz, 1H; H1b), 4.45 (AB system, $J = 15.8$ Hz, $\Delta\delta$ 18.21 Hz, 2H; $CH_2C{\equiv}CH$), 4.27 (dd, $J = 12.3$, 5.0 Hz, 1H; H6), 4.24 (dd, $J = 12.3$ and 5.3 Hz, 1H; H6), 4.09 (dd, $J = 12.3$ and 3.4 Hz, 1H; H6′), 4.05–4.08 (m, 3H; H5a, H5b, H6′), 2.17, 2.13, 2.07, 2.02, 2.01, 2.00, 2.00, 1.97 (8s, 24H; 8Ac); ^{13}C NMR (175 MHz, $CDCl_3$): $\delta = 170.6$, 170.5, 169.9, 169.8, 169.7 (CO), 155.8, 133.4, 116.5 (C_6H_4), 96.1 (C1b), 95.6 (C1a), 86.5, 82.6 (C≡C), 69.5, 69.3, 69.2, 69.0, 68.9, 68.7 (C2a, C2b, C3a, C3b, C5a, C5b), 66.1, 65.9 (C4a, C4b) 62.3, 62.1 (C6a, C6b), 55.7 ($CH_2C{\equiv}C$), 20.8, 20.1, 20.7, 20.6 (CH_3CO); MS (FAB): m/z: 847 for $[M+K]^+$; $C_{37}H_{44}O_{20}$: calcd C 54.95, H 5.48; found C 54.97, H 5.46.

Synthesis of 9 by the coupling reaction between 2 and 5: Column chromatography (ether/hexane 1:1 → 1:0) gave **9** as a solid. M.p. 76–78 °C; $[\alpha]_D^{22} = -16$ ($c = 1$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1761$, 1605, 1509, 1241, 1061 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.34$ (d, 1H; $J = 8.8$ Hz, H-aromatic), 6.92 (d, $J = 8.8$ Hz, 1H; H-aromatic), 5.46 (dd, $J = 7.9$, 10.5 Hz, 1H; H2a), 5.43 (dd, $J = 1.0$, 3.5 Hz, 1H; H4a), 5.37 (dd, $J = 1.0$, 3.4 Hz, 1H; H4b), 5.21 (dd, $J = 10.4$, 8.0 Hz, 1H; H2b), 5.09 (dd, $J = 3.4$, 10.4 Hz, 1H; H3a), 5.04 (dd, $J = 3.6$, 10.4 Hz, 1H; H3b), 5.03 (d, $J = 8.0$ Hz, 1H; H1a), 4.76 (d, $J = 8.0$ Hz, 1H; H1b), 4.56 (d, $J = 0.8$ Hz, 2H; H1′), 4.20–3.92 (m, 6H; H6ab, H6aa, H6ba, H6bb, H5a, H5b), 2.15, 2.13, 2.03, 2.03, 2.01, 2.01, 1.98, 1.96 (8s, 24H; OAc); MS (FAB): m/z: 847 for $[M+K]^+$; HRMS calcd for $[M+K]$ $C_{37}H_{44}O_{20}$: 847.2063; found 847.2296.

Synthesis of 11 by the coupling reaction between 2 and 4: Column chromatography (AcOEt/hexane 1:1) gave **11** as a solid. M.p. 59–60 °C; $[\alpha]_D^{22} = +42$ ($c = 1$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1754$, 1605, 1509, 1240, 1063 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.33$, 6.89 (2d, $J = 8.6$ Hz, 4H; C_6H_4), 5.44–5.40 (m, 2H), 5.33–5.24 (m, 3H), 5.07 (m, 1H), 5.05 (brs, 1H; H1b), 5.01 (d, $J = 8.0$ Hz, 1H; H1a), 4.43 (m, 2H; AB system, $J = 15.8$ Hz, $\Delta\delta$ 18.21 Hz, 2H; $CH_2C{\equiv}CH$), 4.24 (dd, $J = 12.2$, 4.9 Hz, 1H; H6), 4.18–4.00 (m, 5H; H5a, H5b, H6, H6′, H6′), 2.13, 2.11, 2.01, 2.01, 1.99, 1.95, 1.94 (8s, 24H; 8Ac); ^{13}C NMR (175 MHz, $CDCl_3$): $\delta = 170.5$, 170.2, 170.1, 169.9, 169.8 169.6, 169.2 (CO), 156.9, 133.3, 116.9, 116.7 (C_6H_4), 99.1 (C1a), 96.1 (C1b), 86.5, 82.6 (C≡C), 71.1, 70.7, 69.4, 68.9, 68.9, 68.5, 66.8, 66.0 (C2a, C2b, C3a, C3b, C4a, C4b, C5a, C5b), 62.3, 61.3 (C6a, C6b), 55.6 ($CH_2C{\equiv}C$), 20.8, 20.6, 20.6, 20.5, 20.4 (CH_3CO); MS (FAB): m/z: 847 for $[M+K]^+$; HRMS calcd for $[M+K]$ $C_{37}H_{44}O_{20}$ 847.2063; found 847.2464.

Synthesis of 10 by the coupling reaction between 3 and 6: Column chromatography (ether/hexane 3:1 → 2:1) gave **10** as a solid. M.p. 100–101 °C; $[\alpha]_D^{22} = +61$ ($c = 1$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1757$, 1605, 1510, 1238, 1055 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.42–6.90$ (2d, $J = 8.8$ Hz, 4H; C_6H_4), 5.43 (dd, $J = 3.3$ and 1.2 Hz, 1H; H4′), 5.33–5.05 (m, 12H), 5.11 (d, $J = 7.7$ Hz, 1H; H1a), 4.94 (dd, $J = 9.6$ and 8.0 Hz, 1H; H2), 4.82 (d, $J = 7.9$ Hz, 1H; H1b), 4.52 (AB system, $J = 16.1$ Hz, $\Delta\delta = 18.6$ Hz, 2H; $CH_2C{\equiv}CH$), 4.19 (m, 1H), 4.08–4.03 (m, 3H), 3.90 (dd, $J = 6.4$ and 3.2 Hz, 2H; H6), 3.83 (m, 1H), 3.80–3.70 (m, 1H), 3.63 (m, 1H), 3.55 (dd, $J = 11.2$ and 2.2 Hz, 1H; H6), 2.11, 2.10, 2.09, 2.07, 2.04, 2.03, 2.02, 2.02, 2.00, 2.00, 1.98, 1.96, 1.95 (13s, 42H; 14Ac); ^{13}C NMR (175 MHz, $CDCl_3$): $\delta =$ 170.6, 170.4, 170.3, 170.2, 170.1, 169.8, 169.7, 169.5, 169.3, 169.2 (CO), 156.7, 133.4, 117.2, 116.5 (C_6H_4), 98.1, 97.9, 96.2 (C1a, C1′a, C1b, C1′b),86.3, 83.0 (C≡C), 73.1, 72.9, 72.7, 72.5, 71.1, 68.9, 68.6, 68.0. 67.9, 67.4, 67.3, 66.5, 66.4 (C2a, C2′a, C3a, C3′a, C4a, C4′a, C5a, C5′a, C2b, C2′b, C3b, C3′b, C4b, C4′b, C5b, C5′b), 66.3, 66.2, 61.7, 61.5 (C6a, C6′a, C6b, C6′b), 56.5 ($CH_2C{\equiv}C$), 20.75–20.54 (7 peaks, CH_3CO); MS (FAB): m/z: 1384 for $[M+K]^+$; $C_{61}H_{76}O_{36}$: calcd C 52.89, H 5.53; found C 52.70, H 5.48.

Synthesis of 13 by the coupling reaction between 2 and 7: Column chromatography (AcOEt/hexane 1:1 → 5:1) gave **13** as a solid. M.p. 109–110 °C; $[\alpha]_D^{22} = -12$ ($c = 0.5$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1753$, 1605, 1509, 1237, 1062 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$, 6.92 (2d, $J = 8.8$ Hz, 4H; C_6H_4), 5.45 (dd, $J = 10.5$ and 7.9 Hz, 1H; H2a), 5.43 (dd, $J = 3.2$ and 0.8 Hz, 1H; H4a), 5.31 (dd, $J = 3.4$ and 0.9 Hz, 1H; H4′b), 5.20 (t, $J = 9.3$, 1H; H3b), 5.08 (dd, $J = 10.5$ and 3.4 Hz, 1H; H3a), 5.07 (dd, $J = 10.4$ and 8.0 Hz, 1H; H2′b), 5.04 (d, $J = 7.9$ Hz, 1H; H1a), 4.92 (dd, $J = 10.5$ and 3.3 Hz, 1H; H3′b), 4.90 (dd, $J = 9.4$ and 7.8 Hz, 1H; H2b) 4.76 (d, $J = 7.9$ Hz, 1H; H1b), 4.50 (brs, 2H; $CH_2C{\equiv}CH$), 4.46 (m, 1H; H6b), 4.45 (d, $J = 7.8$ Hz, 1H; H1′b), 4.20–4.03 (m, 6H; H5a, H6a, H6a, H6b, H6′b, H6′b), 3.85 (brt, $J =$ 7.0 Hz, 1H; H5′b), 3.80 (t, $J = 9.8$ Hz, 1H; H4b), 3.64 (ddd, $J = 9.9$, 4.7 and 1.9 Hz, 1H; H5), 2.15, 2.12, 2.07, 2.03, 2.03, 2.02, 2.01, 2.01, 2.00, 1.98, 1.93 (11s, 33H; 11Ac); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4$, 170.4, 170.2, 170.2, 170.1, 170.1, 169.8, 169.7, 169.4, 169.1 (CO), 157.0, 133.3, 117.0, 116.8 (C_6H_4), 101.1 (C1′b), 99.2,(C1a), 98.1 (C1b), 86.5, 82.9 (C≡C), 76.1 (C4b), 72.8, 72.7 (C3a, C5a), 71.4, 71.1, 70.9, 70.8, 70.7, 69.1 (C3a, C5a, C2b, C2′b, C3′b, C5′b), 68.5 (C2a) 66.8 (C4a), 66.6 (C4′b), 61.9 (C6b), 61.3, 60.8 (C6a, C6′b),56.9 ($CH_2C{\equiv}C$), 20.9, 20.8, 20.7, 20.6, 20.5 (CH_3CO); MS (FAB): m/z: 1135 for $[M+K]^+$; $C_{49}H_{60}O_{28}$: calcd C 53.65, H 5.51; found C 53.75, H 5.45.

General procedure for the synthesis of dimers 15–17: To a degassed solution of the 1,4-diiodobenzene (1 mmol) and the propargyl glycosides **4**, **5**, or **7** (2.2 mmol) in DMF/Et_3N (8:8 mL) was added $[Pd(PPh_3)_4]$ (0.1 mmol). The solution was then heated at 60 °C under a nitrogen atmosphere for 3.5 h. The Et_3N was removed by evaporation under vacuum. Diethyl ether/toluene (100:50 mL) was added to the residue and the solution was washed with 5% HCl (50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and water (50 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated to yield a crude product which was purified by column chromatography.

Synthesis of 15 by the coupling reaction between 4 and 1,4-diiodobenzene (14): Column chromatography (diethyl ether/hexane 10:1) gave **15** as a solid. M.p. 69–71 °C; $[\alpha]_D^{22} = +80$ ($c = 1$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1756$, 1506, 1240, 1137, 1060 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.37$ (s, 4H; C_6H_4), 5.32–5.23 (m, 6H; H2, H3, H4), 5.07 (d, $J = 1.1$ Hz, 2H; H1), 4.47 (brs, 4H; $CH_2C{\equiv}C$), 4.27 (dd, $J = 12.3$ and 5.2 Hz, 2H; H6), 4.07 (dd, $J =$ 12.3 and 2.4 Hz, 2H; H6′), 4.03 (m, 2H; H5), 2.13, 2.06, 2.01, 1.97 (4s, 24H; 8Ac); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 171.2$, 170.6, 170.5, 170.3 (CO), 132.4, 123.1 (C_6H_4), 96.8 (C1), 87.2, 85.7 (C≡C), 70.0, 69.6, 69.6, 66.3 (C2, C3, C4, C5), 62.9 (C6), 56.2 ($CH_2C{\equiv}C$), 21.6, 21.5, 21.3 (CH_3CO); $C_{40}H_{46}O_{20}$: calcd C 56.73, H 5.48; found C 56.33, H 5.74.

Synthesis of 16 by the coupling reaction between 5 and 14: Column chromatography (diethyl ether/hexane 8:1) gave **16** as a solid. M.p. 110–112 °C; $[\alpha]_D^{22} = -42$ ($c = 1$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 2365$, 1753, 1235, 1058 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.37$ (s, 4H; C_6H_4), 5.38 (dd, $J = 3.4$ and 1.1 Hz, 2H; H4), 5.23 (dd, $J = 10.5$ and 7.8 Hz, 2H; H2), 5.05 (dd, $J = 10.5$ and 3.4 Hz, 2H; H3), 4.76 (d, $J = 7.8$ Hz, 2H; H1), 4.58 (s, 4H; $CH_2C{\equiv}C$), 4.19 (dd, $J = 11.2$ and 6.8 Hz, 2H; H6), 4.08 (dd, $J = 11.2$ and 6.2 Hz, 2H; H6′), 3.91 (dt, $J = 6.8$, 6.2, 1.1 Hz, 2H; H5), 2.14, 2.03, 2.02, 1.97 (4s, 24H; 8Ac); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ (CO), 132.6, 123.2 (C_6H_4), 99.6 (C1), 86.9, 86.2 (C≡C), 71.4, 69.2, 67.5 (C2, C3, C4, C5), 61.8 (C6), 57.4 ($CH_2C{\equiv}C$), 21.4, 21.3, 21.2, 21.0 (CH_3CO); HRMS calcd for $[M+K]$: $C_{40}H_{46}O_{20}$: 885.2220; found 885.2189.

Synthesis of 17 by the coupling reaction between 7 and 14: Column chromatography (AcOEt/diethyl ether 1:5) gave **17** as a solid. M.p. 134–135 °C; $[\alpha]_D^{22} = -30$ ($c = 1$ in $CHCl_3$); IR (KBr): $\tilde{\nu} = 1762$, 1505, 1242, 1057 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.37$ (s, 4H; C_6H_4), 5.30 (brd, $J = 2.7$ Hz, 2H; H4′), 5.21 (t, $J = 9.2$ Hz, 2H; H3), 5.08 (dd, $J = 10.5$ and 7.9 Hz, 2H; H2′), 4.95–4.87 (m, 4H; H2, H3′), 4.76 (d, $J = 7.8$ Hz, 2H; H1), 4.53 (brs , 4H; $CH_2C{\equiv}C$), 4.45 (d, $J = 7.7$ Hz, 2H; H1′), 4.46 (m, 2H; H6), 4.13–4.02 (m, 6H; H6, H6, H6′), 3.86 (m, 2H; H5′), 3.80 (t, $J = 9.0$ Hz, 2H; H4), 3.64 (m, H5), 2.12, 2.08, 2.02, 2.01, 2.00, 1.93 (7s, 42H; 14Ac); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.9$, 170.8, 170.7, 170.6, 170.4, 170.3, 169.6 (CO), 132.6, 123.1 (C_6H_4), 101.6 (C1′), 98.7 (C1), 87.0, 86.0 (C≡C), 76.8, 73.3, 72.0, 71.5, 71.2, 69.8, 69.6, 67.1 (C2, C2′, C3, C3′, C4, C4′, C5, C5′), 62.4, 61.4 (C6, C6′), 57.3 ($CH_2C{\equiv}C$), 21.4, 21.2, 21.1 (CH_3CO); $C_{64}H_{78}O_{36}$: calcd C 54.01, H 5.52; found C 54.22, H 5.53.

Deacetylation of compound 8 to give 8a: A solution of **8** (50 mg, 0.06 mmol) in MeONa/MeOH (0.2 M, 10 mL) was stirred at ambient temperature for 6 h. The resulting solution was neutralized [Dowex-50W (H^+)], and the resin was filtered and washed (MeOH). Volatiles were evaporated from the combined filtrates and the residue was dissolved in water (2 mL) and lyophilized to obtain the pure compound **8a** (29 mg, 100%) as a foam; $[\alpha]_D^{22} = -2$ ($c = 1$ in water); ^{1}H NMR (500 MHz, D_2O): $\delta = 7.54$, 7.20 (2d, $J = 8.9$ Hz, 4H; C_6H_4), 5.70 (d, $J = 1.6$ Hz, 1H; H1a), 5.16 (d, $J = 1.6$ Hz, 1H; H1b), 4.60 (AB q, $J = 16.0$ Hz, 2H; $CH_2C{\equiv}CH$), 4.23 (dd, $J = 3.5$, 1.6 Hz, 1H; H2a), 4.10 (dd, $J = 3.5$, 9.6 Hz, 1H; H3a), 4.03 (dd, $J = 1.6$, 3.4 Hz, 1H; H2b), 3.90 – 3.7 (m, 9H; H4a, H5a, H6, H3b, H4b, H5b, H6′); MS (FAB): m/z: 511.6312 for $[M+K]^+$.

Deacetylation of compound 15 to give 15a: Compound **15a** was prepared from **15**, as described for **8a**, as a foam in 100% yield. $[\alpha]_D^{22} = -3$ ($c = 0.6$ in water); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.55$ (s, 4H; C_6H_4), 5.16 (d, $J =$ 1.7 Hz, 2H; H1), 4.6 (AB q, $J = 16.2$ Hz, 2H; $CH_2C{\equiv}C$), 4.04 (dd, $J = 1.7$,

3.4 Hz, 2H; H2), 3.99–3.77 (m, 10H; H3, H4, H5, H6); FB (MS): *m/z*: 549.1345 $[M+K]^+$.

1,4-Bis(α-D-mannopyranosyloxy)butane (20): To a solution of compound **19** (50 mg, 0.12 mmol) in methanol (2 mL) was added 10% palladium/carbon (10 mg) and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 3 h. The catalyst was filtered off and the filtrate concentrated to afford compound **20** (50 mg, 100%) as a thick syrup. $[\alpha]_D^{22} = +76$ ($c = 1$, in water); ^{1}H NMR (200 MHz, D_2O): $\delta = 4.82$ (s, 2H; H1), 3.88–3.47 (m, 16H; H1′, H2, H3, H4, H5, H6), 1.65 (br s, 4H; H2′); ^{13}C NMR (50 MHz, D_2O): $\delta = 101.1$ (C1), 74.2, 72.1, 71.7, 68.9, 68.2 (C1′, C2, C3, C4, C5), 62.4 (C6), 26.9 (C2′); HRMS calcd for $[M+1]$ $C_{16}H_{30}O_{12}$: 415.1816; found 415.1800.

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