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# Palladium-Catalyzed Ullmann-Type Reductive Homocoupling of Iodoaryl Glycosides

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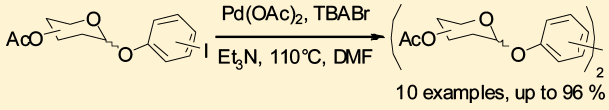
Supporting Information

**ABSTRACT:** A catalytic synthesis of novel biaryl-linked divalent glycosides was achieved using an electroreductive palladium-catalyzed iodoaryl−iodoaryl coupling reaction. This new method was optimized for the synthesis of divalent biaryl-linked mannopyranosides that was subsequently generalized toward several carbohydrate substrates with yields up to 96%.




Mammalian cells expose wide arrays of complex glycoconjugates on their surface.[1] These glycoconjugates are playing a key recognition role in many biological events ranging from cell adhesion or cell-growth to fertilization through cancer cell metastases. Pathogens often bind host cells via reinforced multivalent and highly selective glycoconjugate−protein interactions.[2] Antibody 2G12 against HIV-1 gp120,[3] DC-SIGN,[4] as well as bacterial lectins, like *Escherichia coli*'s FimH,[2] are examples of selective mannose binding proteins that play important roles in pathogen adhesion, providing an active site to infect the host cells or tissues.[2] Therefore, these specific interactions represent a therapeutic target to inhibit the adhesion of pathogens to host cells.[5,6]

Cross-linked lattices can form when multivalent protein receptors are mixed with synthetic divalent carbohydrates, as showed in previous studies.[7] Linker rigidity between two sugar arrays can modify the cross-linking ability depending on the targeted lectin.[7a,f,8] It is thus important to construct a variety of rigid linkers to study the interactions between lectins and divalent sugar ligands.

Organometallic reactions such as Sonogashira cross-coupling or Glaser homocoupling catalyze the fixation of many carbohydrates on multivalent platforms.[7f,9,10] All the previous coupling methods used in our group to produce divalent sugar-rods involved alkyne−alkyne or alkyne−iodoaryl reactions.[8b,11]

Syntheses of biaryl compounds as key building blocks for many agrochemicals, pharmaceuticals, and natural products, as well as asymmetric catalysts, have become important in several fields of chemistry.[12,13] Many synthetic approaches, involving transition metal catalysis (Ullmann, Heck, Suzuki, or Negishi) have been developed to achieve these goals.[13,14] Symmetrical biaryls are readily prepared from aryl halides using Ullmann conditions.[14,15] Since Ullmann synthesis required stoichiometric amounts of copper, modern Ullmann coupling involves palladium-catalyzed reductive coupling conditions.[16]

Alternatively, bisphenol glycosidation can produce divalent biaryl glycosides but only in low yields.[17] The only known divalent glycosides of analogous structures were prepared using Lewis-acid-promoted *bis*-glycosidation of phenyl 2,3,4,6-tetra-*O*-acetyl-1-seleno-α-D-mannopyranoside[17a] or per-*O*-acetylated glucose[17b] using 4,4′-bisphenol, which were obtained in generally low yields (Figure 1a). Considering the importance of such ligands in lectinology and the low yields obtained using the above methods, it appeared crucial to develop a new and versatile method to access this family of divalent glycosides in good yields.

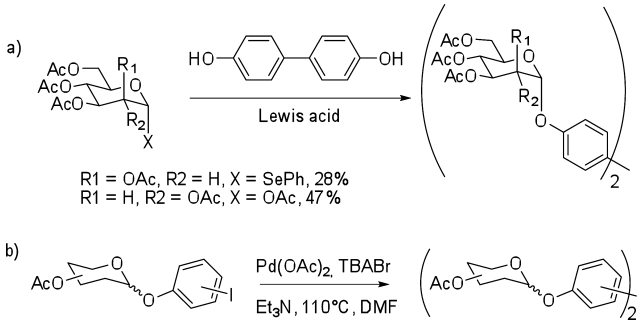



**Figure 1.** (a) Known method for the synthesis of divalent biaryl glycosides and (b) this work.

Finally, methods involving C−H functionalization could be interesting alternative strategies for the construction of these sugar-rods, but both low regioselective phenyl C−H activation or high catalyst loading represent important drawbacks.[18] Herein, we present a new efficient catalytic synthesis of divalent biaryl glycosides using iodo aryl−aryl homocoupling by electroreductive palladium catalysis (Figure 1b).

An initial reaction condition was developed toward the electroreductive palladium-catalyzed coupling reaction of peracetylated *p*-iodophenyl α-D-mannopyranoside (**1**) (Table 1). At first, $Pd(PPh_3)_4$, KOAc, and TBABr were attempted for the Ullmann coupling reaction, according to a published procedure.[16a,e] Moreover, the reaction was performed in DMF at 130 °C in standard glassware using a condenser (Table 1, entry 1). Consequently, compound **1** was converted into

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**Table 1. Optimisation of the Palladium Catalyzed Homocoupling of 1 to Provide Divalent Mannoside 2**


| entry | additive | reducing agent (or ligand) | catalyst | Δ (°C) | yield (%)[a,b] |
|---|---|---|---|---|---|
| 1 | TBABr | KOAc | **$Pd(PPh_3)_4$** | 130 | 30 |
| 2 | TBABr | KOAc | **$Pd(dba)_2$** | 130 | 40 |
| 3 | TBABr | KOAc | **$Pd(PPh_3)_2Cl_2$** | 130 | 57 |
| 4 | TBABr | KOAc | **$Pd(OAc)_2$** | 130 | 64 |
| 5 | TBABr | **$Cs_2CO_3$** | $Pd(OAc)_2$ | 130 | 0 |
| 6 | TBABr | **$Et_2NH$** | $Pd(OAc)_2$ | 130 | 0 |
| 7 | TBABr | **Pyridine** | $Pd(OAc)_2$ | 130 | 0 |
| 8 | TBABr | **4-DMAP** | $Pd(OAc)_2$ | 130 | 0 |
| 9 | TBABr | **DBU** | $Pd(OAc)_2$ | 130 | 0 |
| 10 | TBABr | **$PPh_3$** | $Pd(OAc)_2$ | 130 | 26 |
| 11 | TBABr | **KOAc/$PPh_3$**[c] | $Pd(OAc)_2$ | 130 | 60 |
| 12 | TBABr | **NaOAc** | $Pd(OAc)_2$ | 130 | 56 |
| 13 | TBABr | **$NaHCO_3$** | $Pd(OAc)_2$ | 130 | 68 |
| 14 | TBABr | **$Et_3N$** | $Pd(OAc)_2$ | 130 | 67 |
| 15 | TBABr | $Et_3N$ | $Pd(OAc)_2$ | **110** | 87 |
| 16 | TBABr | $Et_3N$ | $Pd(OAc)_2$ | **90** | 75 |
| 17 | **TBAI** | $Et_3N$ | $Pd(OAc)_2$ | 110 | 84 |
| 18 | **none** | $Et_3N$ | $Pd(OAc)_2$ | 110 | trace |
| 19 | TBABr | **$Et_3N$**[d] | $Pd(OAc)_2$ | 110 | 82 |
| 20 | TBABr | **$Et_3N$**[e] | $Pd(OAc)_2$ | 110 | 61 |
| 21 | TBABr | $Et_3N$ | **$Pd(OAc)_2$**[f] | 110 | **90** |

[a]Reactions were monitored by TLC until the complete disappearance of the starting material (3−14 h) and were carried out in standard glassware using a condenser. [b]Yields refer to isolated pure product. [c]0.21 equiv of $PPh_3$ was added as a ligand. [d]1.5 equiv of $Et_3N$ was used. [e]1.1 equiv of $Et_3N$ was used. [f]5 mol % of catalyst was used.

divalent mannoside **2** in only 30% yield, and the major byproduct of this reaction came from hydro-dehalogenation[16c,d,19] of **1** into known phenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside.[20] In order to improve the reaction yield and limit the formation of byproducts, other sources of palladium (Table 1, entries 1−4) together with various reducing agents (Table 1, entries 5−14) were tried at different temperatures (Table 1, entries 15 and 16). $Pd(OAc_2)$, $Et_3N$, and 110 °C were the optimal reaction conditions with a yield of 87% (Table 1, entry 15), affording a much cleaner reaction along with less decomposition and hydro-dehalogenation. TBABr was crucial for the formation of divalent mannoside **2** (Table 1, entries 15, 17, and 18), and best results were obtained with 2.5 equiv of $Et_3N$ (Table 1, entries 19 and 20). Finally, the catalyst loading was decreased from 10 to 5 mol %, providing divalent mannoside **2** in a similar yield (90%) (Table 1, entry 21). The optimized reaction was also performed in a sealed tube with microwave irradiation in order to minimize reaction time. Time was decreased by almost half (from 3.5 to 2 h) but with a 20% yield drop in each case because of the formation of the hydro-dehalogenation byproduct.

The homocoupling reaction was performed on *para*-bromophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-manno-pyranoside using the previously optimized conditions, but the reaction was very slow, and only trace amounts of **2** were observed after a long period of reaction time (48 h).

The optimized homocoupling reaction condition was then applied onto substrates **3**−**9**, providing divalent glycosides **10**−**16** (Table 2).[8c,21] Divalent monosaccharides were obtained in slightly better yields than disaccharide dimers, and reactions conducted under microwave irradiation were two times faster but with a decrease of 20−30% yield. There were no significant reactivity differences between α and β iodophenyl glycosides, as similar yields were obtained from coupling of anomers **5** and **6** (Table 2, entries 5−8).

The optimized methodology was then applied on iodophenyl mannosides **17** and **18** (Table 3).[8a,c] These reactions provided 3,3′-*bis*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)-biphenyl **19** in 94% yield and 2,2′-*bis*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)biphenyl **20** in 33% yield, respectively (Table 3, entries 3 and 5).

Microwave irradiation decreased the reaction time for the synthesis of compound **19**, but it also decreased the yield significantly. Time needed for complete conversion of *o*-iodophenyl derivative **18** into **20** was much longer than for compounds **2** and **19**. The lower yield obtained for compound **20** was likely due to steric hindrance near the reactive site. To this end, microwave irradiation appeared to be a suitable alternative to heating in standard glassware using a condenser for the synthesis of **20**, hence reducing reaction time from 24 to 4 h with similar yields (Table 3, entries 5 and 6).

*ortho*-Substituted biaryl derivatives were subject to significant torsional angle restrictions around the aryl−aryl bond, thus introducing atropisomerism. This phenomenon has been studied in [1,1′-binaphthalene]-2,2′-diol (BINOL)-based chiral ligand synthesis,[22] and it has been previously described in bisphenol syntheses.[23] The homodimerization of **18** introduced atropisomerism de facto on the *ortho*-substituted biaryl linker,


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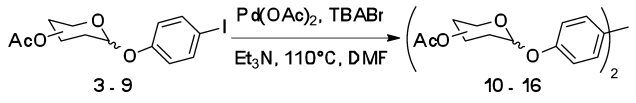
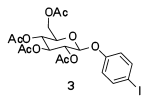
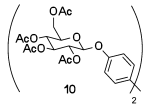
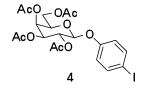
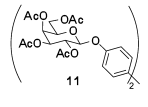
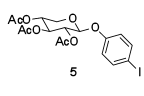
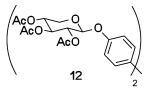
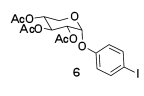
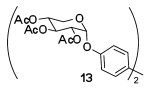
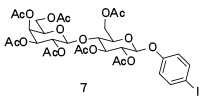
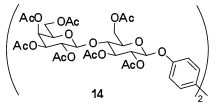
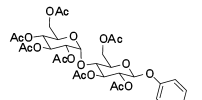
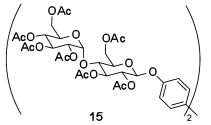
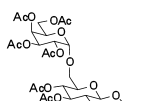
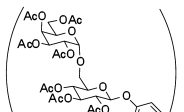
**Table 2. Divalent Glycoside 10−16 Synthesis through Electroreductive Palladium Coupling from Various *p*-Iodophenyl-*O*-glycosides 3−9**




| Entry | Substrate | Method[a] | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  | A 3.5 h |  | 81 |
| 2 | 3 | B 2 h | 10 | 60 |
| 3 |  | A 3.5 h |  | 96 |
| 4 | 4 | B 2 h | 11 | 70 |
| 5 |  | A 3 h |  | 94 |
| 6 | 5 | B 1.5 h | 12 | 72 |
| 7 |  | A 4 h |  | 91 |
| 8 | 6 | B 2 h | 13 | 69 |
| 9 |  | A 3 h |  | 84 |
| 10 | 7 | B 1.5 h | 14 | 54 |
| 11 |  | A 3 h |  | 80 |
| 12 | 8 | B 1.5 h | 15 | 57 |
| 13 |  | A 3 h |  | 87 |
| 14 | 9 | B 1.5 h | 16 | 60 |

[a]To a solution of the *O*-iodoaryl glycoside dissolved in DMF were added $Pd(OAc)_2$, $Et_3N$, and TBABr. The mixture was stirred for the indicated time (TLC monitoring) at 110 °C using a condenser in simple glassware (method A) or using microwaves (method B). [b]Yields refer to isolated pure product.

thus potentially producing compound **20** as two diastereoisomers. However, it seemed that only one diastereoisomer could be isolated as observed from the $^1H$ and $^{13}C$ NMR spectra. It is possible that chirality, steric hindrance, and electronic effects of the nearby saccharide could have induced chirality on the reactive site during the homocoupling reaction, thus favoring one diastereoisomer over the other. Atroposelective intermolecular biaryl couplings have been previously reported recently,[22,24] but the low yield obtained for **20** cannot be used to confirm atroposelective homocoupling of **18**. Further studies are needed to verify or disprove the possibility of atroposelective homocoupling to form **20**.

In order to evaluate the cross-linking potential of mannopyranoside dimers **2**, **19**, and **20** against multivalent lectins, acetylated hydroxyl groups were unprotected under Zemplén conditions (NaOMe, MeOH) to provide **21**−**23** in high yields (>90%) (Table 3). Dynamic light scattering and microturbidimetry studies were conducted on divalent ligands **21**−**23** toward the formation of insoluble cross-linked lattices with Con A. **21** and **22** form insoluble complexes and opalescent solutions within few minutes as shown in microturbidimetry studies. Those results are confirmed by dynamic light scattering studies in which complexes of larger hydrodynamic radius were observed for Con A in the presence of divalent ligands **21** and **22**. Divalent ligand **23** does not possess the ability to cross-link Con A because of the too close proximity between the sugar ligands. In those studies, **23** possesses the behavior of a monovalent ligand, and no opalescent solutions were obtained with Con A despite higher concentrations of ligand.[25]

In conclusion, an array of new symmetrical divalent glycosides was efficiently synthesized using an original electroreductive palladium-catalyzed coupling reaction. The homocoupling reactions of compounds **1** and **3** gave better yields to provide divalent glycosides **2** and **10** in comparison to more classical Lewis-acid-catalyzed glycosidations of per-*O*-acetylated glycosides with bisphenols. Best yields were obtained using $Pd(OAc)_2$, $Et_3N$, and TBABr in DMF at 110 °C. This new efficient procedure was applied toward various substrates to provide the corresponding divalent glycosides in high yields. De-*O*-acetylation of divalent mannosides **2**, **19**, and **20** using Zemplén conditions gave divalent mannopyranosides **21**−**23** in excellent yields. Divalent ligands **21** and **22** possess cross-linking abilities as shown in microturbidimetry and dynamic light scattering studies with Con A lectin.

## EXPERIMENTAL SECTION

**General Information.** Reactions were carried out in organic media under an argon atmosphere using freshly distilled solvents. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Microwave irradiation was conducted in a Biotage Initiator microwave. Optical rotations are reported in $10^{-1}$ deg $cm^2$ $g^{-1}$. Melting points are uncorrected. Roman numerals in ascending order are given to the residues from the reducing end. NMR spectra were recorded on 300 and 600 MHz spectrometers. Proton and carbon chemical shifts ($\delta$) are reported in ppm downfield from internal reference of residual solvents. Coupling constants ($J$) are reported in Hertz (Hz), and the following abbreviations are used: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), multiplet (m). Analysis and assignments were made using COSY experiments. The $\alpha$-stereochemistry of the *O*-glycosidic linkages was ascertained by comparison of experimental $^1J_{C-1,H-1}$ coupling constants, determined by a coupled HSQC experiment, with known data for $\alpha$-mannosides (ca. 170 Hz).

**Experimental Procedures for Syntheses of Starting Materials 5 and 6.** *4-Iodophenyl 2,3,4-tri-O-acetyl-β-D-xylopyranoside (5).* Tetra-*O*-acetyl-β-D-xylopyranose (2.19 g, 6.9 mmol) was transformed into the corresponding glycosyl bromide with 33% HBr/AcOH (8.75 mL) in 30 min. The reaction was diluted with $CH_2Cl_2$ (50 mL) and quenched with saturated $Na_2CO_3$ (150 mL), and the solution was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were washed with $H_2O$ (1 × 100 mL) and brine (1 × 100 mL) and then dried over anhydrous $MgSO_4$. After concentration under reduced pressure, this glycosyl bromide was used immediately without further purification. It was dissolved in EtOAc (50 mL, 0.1 M) and tetrabutylammonium hydrogen sulfate (TBAHS) (3.6 g, 10.3 mmol); 4-iodophenol (2.6 g, 11.7 mmol) in a sodium carbonate solution (1 M, 50 mL) was added. The reaction mixture was vigorously stirred at room temperature until


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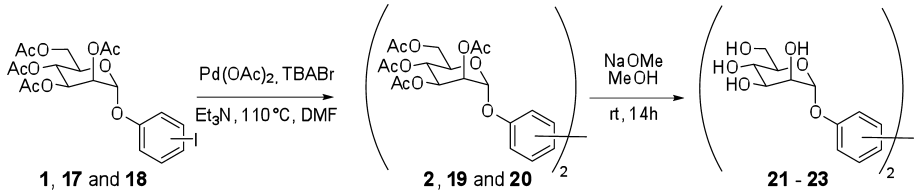
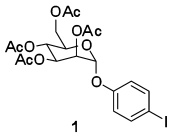
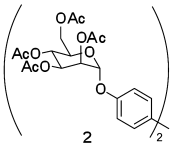
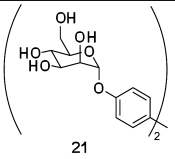
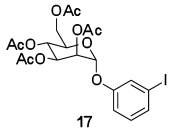
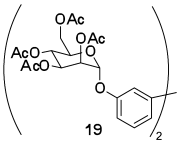
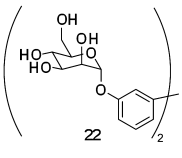
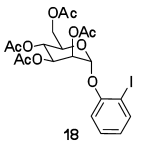
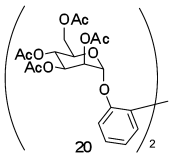
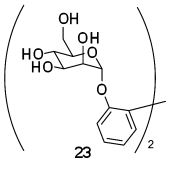
**Table 3. Divalent Mannoside 2, 19, and 20 Synthesis through Electroreductive Palladium Coupling from Iodophenyl 2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosides 1, 17, and 18, Followed by Unprotection of Alcohols Providing 21−23**




**1**, **17** and **18** — **2**, **19** and **20** — **21** - **23**

| Entry | Substrate | Method[a] | Coupling product | Yield (%)[b] | Deprotected compound | Yield (%)[b, c] |
|---|---|---|---|---|---|---|
| 1 |  | A 3.5 h |  | 90 |  | 93 |
| 2 | 1 | B 2 h | 2 | 70 | 21 | |
| 3 |  | A 3 h |  | 94 |  | 95 |
| 4 | 17 | B 1.5 h | 19 | 73 | 22 | |
| 5 |  | A 24 h |  | 33 |  | 90 |
| 6 | 18 | B 4 h | 20 | 23 | 23 | |

[a]To a solution of the corresponding *O*-iodoaryl mannopyranoside dissolved in DMF were added $Pd(OAc)_2$, $Et_3N$, and TBABr. The mixture was stirred for the indicated time (TLC monitoring) at 110 °C using a condenser in simple glassware (method A) or using microwave irradiation (method B). [b]Yields refer to isolated pure product. [c]To a solution of the corresponding acetylated divalent glycoside in MeOH was added a solution of 1 M NaOMe in MeOH until pH = 8−9. The mixture was stirred for 14 h, and fully deprotected divalent mannosides were recovered by neutralization with acidic Amberlyst resin.

complete conversion of starting material (14 h), as judged by TLC (hexane/EtOAc 7:3). The reaction mixture was diluted with EtOAc (50 mL), and the organic layer was separated. The organic solution was washed with a saturated aqueous $Na_2CO_3$ solution (2 × 30 mL), NaOH solution (0.5 N, 2 × 30 mL), water (30 mL), 5% HCl solution (2 × 30 mL), and water (2 × 30 mL). After drying over $MgSO_4$ and concentration under reduced pressure, the brown crude product was purified by column chromatography (hexane/EtOAc 86:14), and recrystallization in EtOH yielded the title compound **5** as white crystals in 70% yield (2.31 g): $R_f$ (hexane/EtOAc 1:1) 0.68; mp 130−131 °C (EtOH); $[\alpha]_D^{23}$ −34.4 (*c* 0.41, $CHCl_3$); IR (KBr, $cm^{-1}$) $\nu$ 3033, 1750 (C═O), 1228, 1089; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.59 (d, $^3J_{H,H}$ 8.4 Hz, 2H, $H_{Ar}$), 6.78 (d, $^3J_{H,H}$ 8.4 Hz, 2H, $H_{Ar}$), 5.30−5.16 (m, 2H, *H*−2 and *H*−3), 5.15 (d, $^3J_{1,2}$ 5.8 Hz, 1H, *H*−1), 5.00 (td, $^3J_{4,5a}$ 4.7 Hz, $^3J_{3,4}$ = $^3J_{4,5b}$ 7.4 Hz, 1H, *H*−4), 4.21 (dd, $^3J_{4,5a}$ 4.7 Hz, $^2J_{5a,5b}$ 12.4 Hz, 1H, *H*−5a), 3.53 (dd, $^3J_{4,5b}$ 7.4 Hz, $^2J_{5a,5b}$ 12.4 Hz, 1H, *H*−5b), 2.09 (s, 9H, 3 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.9, 169.8, 169.3 (C═O), 156.4, 138.5, 119.1 ($C_6H_4$), 98.3 (*C*−1), 85.8 ($C_6H_4$), 70.4, 69.9, 68.3, 61.8 (*C*−2 to *C*−5), 20.8, 20.7, 20.6 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{17}H_{19}IO_8$ $[M + Na]^+$ 501.0016, found 501.0007.

*4-Iodophenyl 2,3,4-tri-O-acetyl-α-D-xylopyranoside (**6**).* To a solution of tetra-*O*-acetyl-α-D-xylopyranose (255 mg, 0.801 mmol) and 4-iodophenol (300 mg, 1.362 mmol), in dry $CH_2Cl_2$ (4 mL, 0.2M) cooled down to 0 °C, was added trifluoromethanesulfonic acid (14 μL, 0.160 mmol) under argon. The reaction mixture was allowed to warm up to room temperature and was stirred for 14 h. The reaction mixture was quenched with $Et_3N$ (22 μL, 0.160 mmol). After concentration under reduced pressure, the brown crude product was purified by column chromatography (hexane/EtOAc 86:14), and recrystallization in EtOH yielded the title compound **6** as white crystals in 65% yield (248 mg): $R_f$ (hexane/EtOAc 1:1) 0.67; IR (KBr, $cm^{-1}$) $\nu$ 3024, 1757 (C═O), 1225, 1092; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.58 (d, $^3J_{H,H}$ 8.3 Hz, 2H, $H_{Ar}$), 6.85 (d, $^3J_{H,H}$ 8.3 Hz, 2H, $H_{Ar}$), 5.67 (t, $^3J_{2,3}$ = $^3J_{3,4}$ 10.1 Hz, 1H, *H*−3), 5.64 (d, $^3J_{1,2}$ 3.6 Hz, 1H, *H*−1), 5.05 (td, $^3J_{4,5a}$ 6.0 Hz, $^3J_{3,4}$ = $^3J_{4,5b}$ 10.1 Hz, 1H, *H*−4), 4.96 (dd, $^3J_{1,2}$ 3.6 Hz, $^3J_{2,3}$ 10.1 Hz, 1H, *H*−2), 3.85 (dd, $^3J_{4,5a}$ 6.0 Hz, $^2J_{5a,5b}$ 10.8 Hz, 1H, *H*−5a), 3.65 (t, $^3J_{4,5b}$ = $^2J_{5a,5b}$ 10.8 Hz, 1H, *H*−5b), 2.07, 2.05, 2.03 (3 × s, 3 × 3H, $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 170.1 170.0, 169.8 (C═O), 155.9, 138.4, 118.7 ($C_6H_4$), 94.2 (*C*−1), 85.5 ($C_6H_4$), 70.5, 69.3, 68.9, 59.0 (*C*−2 to *C*−5), 20.7, 20.6, 20.5 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{17}H_{19}IO_8$ $[M + Na]^+$ 501.0016, found 501.0012.

**General Procedure for Electroreductive Palladium-Catalyzed Coupling Reaction.** To a solution of 4-iodophenyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside **1** (50 mg, 0.09 mmol), tetrabutylammonium bromide (30 mg, 0.09 mmol), and $Et_3N$ (32 μL, 0.23 mmol), in dry DMF (1 mL, 0.1 M), was added palladium acetate (1 mg, 5 mol %). The reaction mixture was stirred at 110 °C for 3.5 h (2 h using microwaves irradiation; 25 W). The reaction mixture was allowed to cool down to room temperature and was then diluted with EtOAc (10 mL). The organic layer was washed with water (3 × 10 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. After concentration in vacuo, the brown crude product was purified by column chromatography (hexane/EtOAc 1:1) to afford 4,4′-bis-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)biphenyl[16e,17a] (**2**), as a yellowish solid, in 90% yield (35 mg) (70% yield using microwaves irradiation): $R_f$ (hexane/EtOAc 55:45) 0.19; mp 164−165 °C; $[\alpha]_D^{20}$ 108.7 (*c* 1, $CHCl_3$) (lit. 66.64 (*c* 1.44, $CHCl_3$));[17a] $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.48 (d, $^3J_{H,H}$ 8.8 Hz, 4H, 2 × $H_{Ar}$), 7.15 (d, $^3J_{H,H}$ 8.8 Hz, 4H, 2 × $H_{Ar}$), 5.57 (dd, $^3J_{2,3}$ 3.3 Hz, $^3J_{3,4}$ 10.2 Hz, 2H, 2 × *H*−3), 5.56 (d, $^3J_{1,2}$ 1.6 Hz, 2H, 2 × *H*−1), 5.48 (dd, $^3J_{1,2}$ 1.6 Hz, $^3J_{2,3}$ 3.3 Hz,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2H, 2 × *H*−2), 5.39 (t, $^3J_{3,4}$ = $^3J_{4,5}$ 10.2 Hz, 2H, 2 × *H*−4), 4.30 (dd, $^3J_{5,6a}$ 5.8 Hz, $^2J_{6a,6b}$ 12.6 Hz, 2H, 2 × *H*−6a), 4.15−4.07 (m, 4H, 2 × *H*−5 and *H*−6b), 2.22, 2.07, 2.05, 2.04 (4 × s, 4 × 6H, 8 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.0, 169.9, 169.7 (*C*═O) 154.9, 135.3, 127.9, 116.8 ($C_6H_4$), 95.8 (*C*−1), 69.3, 69.1, 68.8, 65.9, 62.1 (*C*−2 to *C*−6), 20.9, 20.7 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{40}H_{46}O_{20}$ [M + K]$^+$ 885.2214, found 885.2198.

*4,4′-Bis-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyloxy)biphenyl (10).*[17b] Yellowish solid: $R_f$ (hexane/EtOAc 1:1) 0.19; mp 198−200 °C (lit. 199−210 °C);[17b] $^1$H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, $^3J_{H,H}$ 8.8 Hz, 4H, 2 × $H_{Ar}$), 7.04 (d, $^3J_{H,H}$ 8.8 Hz, 4H, 2 × $H_{Ar}$), 5.35−5.25 (m, 4H, 2 × *H*−3 and *H*−2), 5.21−5.14 (m, 2H, 2 × *H*−4), 5.12 (d, $^3J_{1,2}$ 7.7 Hz, 2H, 2 × *H*−1), 4.30 (dd, $^3J_{5,6a}$ 5.2 Hz, $^2J_{6a,6b}$ 12.4 Hz, 2H, 2 × *H*−6a), 4.18 (dd, $^3J_{5,6b}$ 2.5 Hz, $^2J_{6a,6b}$ 12.4 Hz, 2H, 2 × *H*−6b), 3.91−3.85 (m, 2H, 2 × *H*−5), 2.07, 2.06, 2.05, 2.04 (4 × s, 4 × 6H, 8 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.2, 169.3, 169.2 (*C*═O), 156.1, 135.7, 127.9, 117.2 ($C_6H_4$), 99.0 (*C*−1), 72.6, 72.0, 71.1, 68.2, 61.9 (*C*−2 to *C*−6), 20.7, 20.6, 20.5, 20.4 ($COCH_3$).

*4,4′-Bis-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyloxy)-biphenyl (11).* Yellowish solid: $R_f$ (hexane/EtOAc 1:1) 0.13; mp 219−220 °C; $[\alpha]_D^{22}$ 11.9 (*c* 0.2, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3025, 1743 (C═O), 1239, 1037; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, $^3J_{H,H}$ 8.2 Hz, 4H, 2 × $H_{Ar}$), 7.06 (d, $^3J_{H,H}$ 8.2 Hz, 4H, 2 × $H_{Ar}$), 5.51 (dd, $^3J_{1,2}$ 8.0 Hz, $^3J_{2,3}$ 10.4 Hz, 2H, 2 × *H*−2), 5.48 (dd, $^3J_{4,5}$ 1.1 Hz, $^3J_{3,4}$ 3.3 Hz, 2H, 2 × *H*−4), 5.13 (dd, $^3J_{3,4}$ 3.3, $^3J_{2,3}$ 10.4 Hz, 2H, 2 × *H*−3), 5.08 (d, $^3J_{1,2}$ 8.0 Hz, 2H, 2 × *H*−1), 4.26 (dd, $^3J_{5,6a}$ 6.9 Hz, $^2J_{6a,6b}$ 11.2 Hz, 2H, 2 × *H*−6a), 4.16 (dd, $^3J_{5,6b}$ 6.0 Hz, $^2J_{6a,6b}$ 11.2 Hz, 2H, 2 × *H*−6b), 4.09 (ddd, $^3J_{4,5}$ 1.1 Hz, $^3J_{5,6b}$ 6.0 Hz, $^3J_{5,6a}$ 6.9 Hz, 2H, 2 × *H*−5), 2.20, 2.18, 2.09, 2.07 (4 × s, 4 × 6H, 8 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 169.4 (*C*═O) 156.3, 135.7, 128.0, 117.2 ($C_6H_4$), 99.7 (*C*−1), 71.0, 70.8, 68.6, 66.8, 61.3 (*C*−2 to *C*−6), 20.7. 20.6, 20.5 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{40}H_{46}O_{20}$ [M + Na]$^+$ 869.2475, found 869.2471.

*4,4′-Bis-(2,3,4-tri-O-acetyl-β-D-xylopyranosyloxy)biphenyl (12).* Yellowish solid: $R_f$ (hexane/EtOAc 1:1) 0.38; mp 174−176 °C; $[\alpha]_D^{24}$ −25.1 (*c* 0.24, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3035, 1741 (C═O), 1247, 1033; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, $^3J_{H,H}$ 8.6 Hz, 4H, 2 × $H_{Ar}$), 7.06 (d, $^3J_{H,H}$ 8.6 Hz, 4H, 2 × $H_{Ar}$), 5.30−5.16 (m, 6H, 2 × *H*−1 and *H*−2 and *H*−3), 5.03 (td, $^3J_{4,5a}$ 4.7 Hz, $^3J_{3,4}$ = $^3J_{4,5b}$ 7.7 Hz, 2H, 2 × *H*−4), 4.25 (dd, $^3J_{4,5a}$ 4.7 Hz, $^2J_{5a,5b}$ 12.1 Hz, 2H, 2 × *H*−5a), 3.55 (dd, $^3J_{4,5b}$ 7.7 Hz, $^2J_{5a,5b}$ 12.1 Hz, 2H, 2 × *H*−5b), 2.10, 2.09 (3 × s, 3 × 6H, 6 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.9, 169.8, 169.4 (C═O) 155.9, 135.5, 128.0, 117.1 ($C_6H_4$), 98.5 (*C*−1), 70.7, 70.1, 68.5, 61.9 (*C*−2 to *C*−5), 20.8, 20.7, 20.6 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{34}H_{38}O_{16}$ [M + Na]$^+$ 725.2052, found 725.2044.

*4,4′-Bis-(2,3,4-tri-O-acetyl-α-D-xylopyranosyloxy)biphenyl (13).* Yellowish solid: $R_f$ (hexane/EtOAc 1:1) 0.19; mp 84−86 °C; $[\alpha]_D^{24}$ 157.5 (*c* 0.21, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3028, 1748 (C═O), 1235, 1028; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, $^3J_{H,H}$ 8.5 Hz, 4H, 2 × $H_{Ar}$), 7.13 (d, $^3J_{H,H}$ 8.5 Hz, 4H, 2 × $H_{Ar}$), 5.74 (d, $^3J_{1,2}$ 3.1 Hz, 2H, 2 × *H*−1), 5.73 (t, $^3J_{2,3}$ = $^3J_{3,4}$ 10.6 Hz, 2H, 2 × *H*−3), 5.08 (td, $^3J_{4,5a}$ 6.1 Hz, $^3J_{3,4}$ = $^3J_{4,5b}$ 10.6 Hz, 2H, 2 × *H*−4), 5.00 (dd, $^3J_{1,2}$ 3.1 Hz, $^3J_{2,3}$ 10.6 Hz, 2H, 2 × *H*−2), 3.93 (dd, $^3J_{4,5a}$ 6.1 Hz, $^2J_{5a,5b}$ 10.6 Hz, 2H, 2 × *H*−5a), 3.74 (t, $^3J_{4,5b}$ = $^2J_{5a,5b}$ 11.0 Hz, 2H, 2 × *H*−5b), 2.09, 2.08, 2.06 (3× s, 3 × 6H, 6 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.3, 170.1, 170.0 (*C*═O), 155.4, 135.2, 128.0, 116.8 ($C_6H_4$), 94.2 (*C*−1), 70.6, 69.4, 69.1, 59.0 (*C*−2 to *C*−5), 20.8, 20.7 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{34}H_{38}O_{16}$ [M + Na]$^+$ 725.2052, found 725.2039.

*4,4′-Bis-(4-O-[2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl]-2,3,6-tri-O-acetyl-β-D-glucopyranosyloxy)biphenyl (14).* Yellowish solid: $R_f$ (hexane/EtOAc 4:6) 0.21; mp 130−132 °C; $[\alpha]_D^{25}$ −8.3 (*c* 0.33, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3030, 1743 (C═O), 1242, 1025; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, $^3J_{H,H}$ 8.8 Hz, 4H, 2 × $H_{Ar}$), 7.03 (d, $^3J_{H,H}$ 8.8 Hz, 4H, 2 × $H_{Ar}$), 5.36 (d, $^3J_{3',4'}$ 3.3 Hz, 2H, 2 × *H*−4′), 5.31 (t, $^3J_{2,3}$ = $^3J_{3,4}$ 8.8 Hz, 2H, 2 × *H*−3), 5.21 (dd, $^3J_{1,2}$ 7.8 Hz, $^3J_{2,3}$ 8.8 Hz, 2H, 2 × *H*−2), 5.12 (dd, $^3J_{1',2'}$ 8.0 Hz, $^3J_{2',3'}$ 10.4 Hz, 2H, 2 × *H*−2′), 5.09 (d, $^3J_{1,2}$ 7.5 Hz, 2H, 2 × *H*−1), 4.98 (dd, $^3J_{3',4'}$ 3.3 Hz, $^3J_{2',3'}$ 10.4 Hz, 2H, 2 × *H*−3′), 4.53−4.52 (m, 2H, 2 × *H*−6a), 4.52 (d, $^3J_{1',2'}$ 7.8 Hz, 2H, 2 × *H*−1′), 4.20−4.05 (m, 6H, 2 × *H*−6b, 2 × *H*−6a′ and 2 × *H*−6b′), 3.92 (m, 2H, 2 × *H*−5′), 3.89 (m, 2H, 2 × *H*−4), 3.83−3.78 (m, 2H, 2 × *H*−5), 2.17, 2.10, 2.09, 2.08, 2.07, 1.98 (7 × s, 7 × 6H, 14 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.3, 170.2, 170.1, 169.8, 169.6, 169.1 (C═O), 156.1, 135.7, 128.0, 117.2 ($C_6H_4$), 101.1, 98.7 (*C*−1 and *C*−1′), 76.2, 72.8, 72.7, 71.5, 70.9, 70.7, 69.1, 66.6, 62.0, 60.8 (*C*−2 to *C*−6 and *C*−2′ to *C*−6′), 20.8, 20.7, 20.6, 20.5 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{64}H_{78}O_{36}$ [M + Na]$^+$ 1445.4165, found 1445.4162.

*4,4′-Bis-(4-O-[2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl]-2,3,6-tri-O-acetyl-β-D-glucopyranosyloxy)biphenyl (15).* Yellowish solid: $R_f$ (hexane/EtOAc 1:1) 0.18; mp 120−122 °C; $[\alpha]_D^{25}$ 58.0 (*c* 0.2, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3025, 1748 (C═O), 1234, 1027; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, $^3J_{H,H}$ 8.6 Hz, 4H, 2 × $H_{Ar}$), 7.04 (d, $^3J_{H,H}$ 8.6 Hz, 4H, 2 × $H_{Ar}$), 5.46 (d, $^3J_{1',2'}$ 4.1 Hz, 2H, 2 × *H*−1′), 5.38 (dd, $^3J_{3',4'}$ 9.6 Hz, $^3J_{2',3'}$ 10.4 Hz, 2H, 2 × *H*−3′), 5.35 (t, $^3J_{2,3}$ = $^3J_{3,4}$ 9.6 Hz, 2H, 2 × *H*−3), 5.19−5.10 (m, 4H, 2 × *H*−1 and 2 × *H*−2), 5.07 (t, $^3J_{3',4'}$ = $^3J_{4',5'}$ 9.6 Hz, 2H, 2 × *H*−4′), 4.88 (dd, $^3J_{1',2'}$ 4.1 Hz, $^3J_{2',3'}$ 10.4 Hz, 2H, 2 × *H*−2′), 4.51 (dd, $^3J_{5,6a}$ 2.7 Hz, $^2J_{6a,6b}$ 12.1 Hz, 2H, 2 × *H*−6a), 4.32−4.23 (m, 4H, 2 × *H*−6b and 2 × *H*−6a′), 4.13 (t, $^3J_{3,4}$ = $^3J_{4,5}$ 9.6 Hz, 2H, 2 × *H*−4), 4.07 (dd, $^3J_{5',6b'}$ 2.2 Hz, $^2J_{6a',6b'}$ 12.5 Hz, 2H, 2 × *H*−6b′), 4.05−3.96 (m, 2H, 2 × *H*−5), 3.92−3.88 (m, 2H, 2 × *H*−5′), 2.12, 2.11, 2.07, 2.06, 2.04, 2.02 (7 × s, 7 × 6H, 14 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.4, 170.2, 170.0, 169.6, 169.4 (C═O), 156.0, 135.7, 128.0, 117.2 ($C_6H_4$), 98.4, 95.6 (*C*−1 and *C*−1′), 75.3, 72.6, 72.3, 72.0, 70.0, 69.3, 68.6, 68.0, 62.8, 61.5 (*C*−2 to *C*−6 and *C*−2′ to *C*−6′), 20.9, 20.8, 20.7, 20.6, 20.5 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{64}H_{78}O_{36}$ [M + Na]$^+$ 1445.4165, found 1445.4173.

*4,4′-Bis-(6-O-[2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl]-2,3,6-tri-O-acetyl-β-D-glucopyranosyloxy)biphenyl (16).* Yellowish solid: $R_f$ (hexane/EtOAc 4:6) 0.21; mp 118−120 °C; $[\alpha]_D^{25}$ 85.6 (*c* 0.14, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3026, 1746 (C═O), 1236, 1025; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, $^3J_{H,H}$ 8.6 Hz, 4H, 2 × $H_{Ar}$), 7.03 (d, $^3J_{H,H}$ 8.6 Hz, 4H, 2 × $H_{Ar}$), 5.40 (dd, $^3J_{3',4'}$ 3.5 Hz, $^3J_{2',3'}$ 10.0 Hz, 2H, 2 × *H*−3′), 5.35−5.05 (m, 14H, 2 × *H*−1, *H*−2, *H*−3, *H*−4, *H*−1′, *H*−2′ and *H*−4′), 4.20 (t, $^3J_{5',6a'}$ = $^3J_{5',6b'}$ 6.5 Hz, 2H, 2 × *H*−5′), 3.97−3.76 (m, 8H, 2 × *H*−5, *H*−6a, *H*−6a′ and *H*−6b′), 3.60 (dd, $^3J_{5,6b}$ 1.4 Hz, $^2J_{6a,6b}$ 10.1 Hz, 2H, 2 × *H*−6b), 2.12, 2.10, 2.08, 2.07, 2.05, 2.01, 1.92 (7 × s, 7 × 6H, 14 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.3, 170.2, 170.0, 169.8, 169.4, 169.3 (*C*═O), 155.9, 135.7, 128.2, 116.7 ($C_6H_4$), 98.4, 96.2 (*C*−1 and *C*−1′), 72.9, 72.7, 71.1, 68.7, 68.1, 68.0, 67.3, 66.4, 66.3, 61.5 (*C*−2 to *C*−6 and *C*−2′ to *C*−6′), 20.8, 20.7, 20.6, 20.5, 20.4 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{64}H_{78}O_{36}$ [M + Na]$^+$ 1445.4165, found 1445.4160.

*3,3′-Bis-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyloxy)biphenyl (19).* Yellowish solid: $R_f$ (hexane/EtOAc 55:45) 0.24; decomposed over 160 °C; $[\alpha]_D^{23}$ 64.7 (*c* 0.2, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3027, 1751 (C═O), 1238, 1025; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, $^3J_{H,H}$ 7.9 Hz, 2H, 2 × $H_{Ar}$), 7.34−7.28 (m, 4H, 4 × $H_{Ar}$), 7.09 (dt, $^4J_{H,H}$ 1.3 Hz, $^3J_{H,H}$ 7.9 Hz, 2H, 2 × $H_{Ar}$), 5.62 (d, $^3J_{1,2}$ 2.2 Hz, 2H, 2 × *H*−1), 5.60 (dd, $^3J_{2,3}$ 3.3 Hz, $^3J_{3,4}$ 9.9 Hz, 2H, 2 × *H*−3), 5.48 (dd, $^3J_{1,2}$ 2.2 Hz, $^3J_{2,3}$ 3.3 Hz, 2H, 2 × *H*−2), 5.39 (t, $^3J_{3,4}$ = $^3J_{4,5}$ 9.9 Hz, 2H, 2 × *H*−4), 4.30 (dd, $^3J_{5,6a}$ 5.2 Hz, $^2J_{6a,6b}$ 12.0 Hz, 2H, 2 × *H*−6a), 4.17−4.10 (m, 2H, 2 × *H*−5), 4.07 (dd, $^3J_{5,6b}$ 1.9 Hz, $^2J_{6a,6b}$ 12.0 Hz, 2H, 2 × *H*−6b), 2.22, 2.07, 2.05, 1.97 (4 × s, 4 × 6H, 8 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.0, 169.9, 169.8 (*C*═O), 156.0, 142.2, 130.0, 121.8, 115.5, 115.3 ($C_6H_4$), 95.8 (*C*−1), 69.4, 69.2, 68.9, 65.9, 62.1 (*C*−2 to *C*−6), 20.9, 20.7, 20.5 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{40}H_{46}O_{20}$ [M + Na]$^+$ 869.2475, found 869.2466.

*2,2′-Bis-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyloxy)biphenyl (20).* Yellowish solid: $R_f$ (hexane/EtOAc 1:1) 0.26; decomposed over 160 °C; $[\alpha]_D^{23}$ 20.7 (*c* 0.2, $CHCl_3$); IR (KBr, cm$^{-1}$) ν 3027, 1745 (C═O), 1243, 1028;$^1$H NMR (300 MHz, $CDCl_3$) δ 7.39 (td, $^4J_{H,H}$ 1.7 Hz, $^3J_{H,H}$ 7.1 Hz, 2H, 2 × $H_{Ar}$), 7.36−7.28 (m, 4H, 2 × $H_{Ar}$), 7.18 (td, $^4J_{H,H}$ 1.1 Hz, $^3J_{H,H}$ 7.1 Hz, 2H, 2 × $H_{Ar}$), 5.68 (d, $^3J_{1,2}$ 1.9 Hz, 2H, 2 × *H*−1), 5.32 (dd, $^3J_{1,2}$ 1.9 Hz, $^3J_{2,3}$ 3.3 Hz, 2H, 2 × *H*−2), 5.19 (t, $^3J_{3,4}$ = $^3J_{4,5}$ 10.2 Hz, 2H, 2 × *H*−4), 4.90 (dd, $^3J_{2,3}$ 3.3 Hz, $^3J_{3,4}$ 10.2 Hz, 2H, 2 × *H*−3), 4.11 (dd, $^3J_{5,6a}$ 5.2 Hz, $^2J_{6a,6b}$ 12.2 Hz, 2H, 2 × *H*−6a), 3.92 (dd, $^3J_{5,6b}$ 1.9 Hz, $^2J_{6a,6b}$ 12.2 Hz, 2H, 2 × *H*−6b), 3.61−3.57 (m, 2H, 2 × *H*−5), 2.14, 2.01, 1.96, 1.92 (4 × s, 4 × 6H, 8 × $COCH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.6, 169.9, 169.6 (*C*═O), 153.1,


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130.8, 129.2, 129.1, 123.3, 116.1 ($C_6H_4$), 96.9 (*C*−1), 69.1, 68.9, 68.8, 65.5, 62.0 (*C*−2 *to* C−6), 20.8, 20.7, 20.6 ($COCH_3$); HRMS (ESI) *m*/*z* calcd. for $C_{40}H_{46}O_{20}$ $[M + Na]^+$ 869.2475, found 869.2466.

**General Procedure for De-*O*-acetylation of Compounds 2, 19, and 20 Using Zemplén Conditions.** Compound **2** (35 mg, 0.04 mmol) was dissolved in methanol (0.5 mL, 0.1 M) to which was added a solution of 1 M NaOMe in MeOH until pH = 8−9. The reaction was stirred at room temperature for 14 h and then neutralized by addition of acidic Amberlyst resin (IR−120). The solution was filtered, concentrated under reduced pressure, and lyophilized to afford 3,3′-bis-(α-D-mannopyranosyloxy)biphenyl **21** as a yellowish solid in quantitative yield (21 mg): decomposed over 220−225 °C; $[\alpha]_D^{20}$ 129.6 (*c* 1, DMSO-$d_6$); IR (KBr, $cm^{-1}$) $\nu$ 3027, 2835 (O−H br), 1031; $^1H$ NMR (300 MHz, DMSO-$d_6$ and $D_2O$ exchange) $\delta$ 7.50 (d, $^3J_{H,H}$ 6.9 Hz, 4H, 2 × $H_{Ar}$), 7.10 (d, $^3J_{H,H}$ 6.9 Hz, 4H, 2 × $H_{Ar}$), 5.38 (s, 2H, 2 × *H*−1), 3.86−3.40 (m, 12H, 2 × *H*−2, *H*−3, *H*−4, *H*−5, *H*−6a and *H*−6b); $^{13}C$ NMR (75 MHz, DMSO) $\delta$ 155.7, 133.5, 127.4, 117.2 ($C_6H_4$), 99.0 (*C*−1), 75.1, 70.7, 70.1, 66.7, 61.1 (*C*−2 to *C*−6); HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{30}O_{12}$ $[M + Na]^+$ 533.1629, found 533.1625.

*3,3′-Bis-(α-D-mannopyranosyloxy)biphenyl (**22**).* Yellowish solid: decomposed over 140 °C; $[\alpha]_D^{22}$ 97.3 (*c* 0.23, $H_2O$); IR (KBr, $cm^{-1}$) $\nu$ 3029, 2837 (O−H br), 1024; $^1H$ NMR (300 MHz, DMSO-$d_6$ and $D_2O$ exchange) $\delta$ 7.35 (t, $^3J_{H,H}$ 7.7 Hz, 2H, 2 × $H_{Ar}$), 7.28−7.24 (m, 4H, 4 × $H_{Ar}$), 7.05 (dt, $^4J_{H,H}$ 1.2 Hz, $^3J_{H,H}$ 7.7 Hz, 2H, 2 × $H_{Ar}$), 5.43 (d, $^3J_{1,2}$ 1.6 Hz, 2H, 2 × *H*−1), 3.85 (dd, $^3J_{1,2}$ 1.6 Hz, $^3J_{2,3}$ 3.3 Hz, 2H, 2 × *H*−2), 3.70 (dd, $^3J_{2,3}$ 3.3 Hz, $^3J_{3,4}$ 8.9 Hz, 2H, 2 × *H*−3), 3.57−3.40 (m, 8H, 2 × *H*−4, *H*−5, *H*−6a and *H*−6b); $^{13}C$ NMR (75 MHz, DMSO-$d_6$) $\delta$ 157.4, 142.1, 130.9, 121.4, 116.9, 115.8 ($C_6H_4$), 99.4 (*C*−1), 75.2, 71.0, 70.6, 67.1, 61.4 (*C*−2 to *C*−6); HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{30}O_{12}$ $[M + Na]^+$ 533.1629, found 533.1624.

*2,2′-Bis-(α-D-mannopyranosyloxy)biphenyl (**23**).* Yellowish solid: decomposed over 150 °C; $[\alpha]_D^{23}$ 18.3 (*c* 0.27, $H_2O$); IR (KBr, $cm^{-1}$) $\nu$ 3036, 2829 (O−H br), 1025; $^1H$ NMR (600 MHz, DMSO-$d_6$ and $D_2O$ exchange) $\delta$ 7.33 (td, $^4J_{H,H}$ 1.7 Hz, $^3J_{H,H}$ 7.4 Hz, 2H, 2 × $H_{Ar}$), 7.29 (dd, $^4J_{H,H}$ 1.2 Hz, $^3J_{H,H}$ 7.4 Hz, 2H, 2 × $H_{Ar}$), 7.19 (dd, $^4J_{H,H}$ 1.7 Hz, $^3J_{H,H}$ 7.4 Hz, 2H, 2 × $H_{Ar}$), 7.09 (td, $^4J_{H,H}$ 1.2 Hz, $^3J_{H,H}$ 7.4 Hz, 2H, 2 × $H_{Ar}$), 5.27 (d, $^3J_{1,2}$ 1.7 Hz, 2H, 2 × *H*−1), 3.58 (dd, $^3J_{1,2}$ 1.7 Hz, $^3J_{2,3}$ 3.2 Hz, 2H, 2 × *H*−2), 3.52 (dd, $^3J_{5,6a}$ 2.1 Hz, $^2J_{6a,6b}$ 12.0 Hz, 2H, 2 × *H*−6a), 3.46 (dd, $^3J_{5,6b}$ 5.3 Hz, $^2J_{6a,6b}$ 12.0 Hz, 2H, 2 × *H*−6b), 3.45 (t, $^3J_{3,4}$ = $^3J_{4,5}$ 9.5 Hz, 2H, 2 × *H*−4), 3.27 (dd, $^3J_{2,3}$ 3.2 Hz, $^3J_{3,4}$ 9.5 Hz, 2H, 2 × *H*−3), 3.25−3.20 (m, 2H, 2 × *H*−5); $^{13}C$ NMR (150 MHz, DMSO-$d_6$) $\delta$ 154.4, 131.7, 129.6, 129.2, 122.8, 117.0 ($C_6H_4$), 100.1 (*C*−1), 74.9, 70.9, 70.5, 66.8, 61.2 (*C*−2 to *C*−6); HRMS (ESI) *m*/*z* calcd. for $C_{24}H_{30}O_{12}$ $[M + Na]^+$ 533.1629, found 533.1616.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

NMR spectra of all compounds and qualitative cross-linking assays. This material is available free of charge via the Internet at http://pubs.acs.org/.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) Varki, A. *Glycobiology* **1993**, *3*, 97−130.
(2) (a) Chabre, Y. M.; Roy, R. *Curr. Top. Med. Chem.* **2008**, *14*, 1237−1285. (b) Chabre, Y. M.; Roy, R. *Adv. Carbohydr. Chem. Biochem.* **2010**, *63*, 165−393. (c) Röckendorf, N. L. *Top. Curr. Chem.* **2001**, *217*, 201−238. (d) Touaibia, M.; Roy, R. Application of multivalent mannosylated dendrimers in glycobiology. In *Comprehensive Glycoscience*; Kamerling, J. P., Ed.; Elsevier Ltd.: Oxford, U.K., 2007; Vol. *3*, Chapter 3.36: Carbohydrate−Protein and Carbohydrate−Carbohydrate Interactions, pp 821−870.
(3) Saphire, E. O.; et al. *Science* **2001**, *293*, 1155−1159.
(4) (a) Geijtenbeek, T. B. *Cell* **2000**, *100*, 587−597. (b) Alvarez, C. P. *J. Virol.* **2002**, *76*, 6841−6844. (c) Navarro-Sanchez, E. *EMBO Rep.* **2003**, *4*, 723−728.
(5) Karlsson, K.-A. *Curr. Opin. Struct. Biol.* **1995**, *5*, 622−635.
(6) Touaibia, M.; Roy, R. *Mini-Rev. Med. Chem.* **2007**, *7*, 1270−1283.
(7) (a) Dam, T. K.; Oscarson, S.; Roy, R.; Das, S. K.; Pagé, D.; Macaluso, F.; Brewer, C. F. *J. Biol. Chem.* **2005**, *280*, 8640−8646. (b) Brewer, C. F. *Biochim. Biophys. Acta* **2002**, *1572*, 255−262. (c) Olsen, L. R.; Dessen, A.; Gupta, D.; Sabesan, S.; Sacchettini, J. C.; Brewer, C. F. *Biochemistry* **1997**, *36*, 15073−15080. (d) Pagé, D.; Roy, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1765−1770. (e) Roy, R.; Pagé, D.; Figueroa, S.; Perez, V.; Bencomo, V. *Glycoconjugate J.* **1998**, *15*, 251−263. (f) Lameignere, E.; Shiao, T. C.; Roy, R.; Wimmerova, M.; Dubreuil, F.; Varrot, A.; Imberty, A. *Glycobiology* **2010**, *20*, 87−98.
(8) (a) Roy, R.; Trono, M. C.; Giguère, D. Effects of linker rigidity and orientation of mannoside clusters for multivalent interactions with proteins. In *Glycomimetics: Modern Synthetic Methodologies*; Roy, R., Ed.; American Chemical Society: Washington, D.C., 2005; Vol. *896*, pp 137−150. (b) Das, S. K.; Trono, M. C.; Roy, R. *Methods Enzymol.* **2003**, *362*, 3−18. (c) Roy, R.; Das, S. K.; Santoyo-Gonzalez, F.; Hernandez-Mateo, F.; Dam, T. K.; Brewer, C. F. *Chem.—Eur. J.* **2000**, *6*, 1757−1762.
(9) Chinchilla, R.; Nàjera, C. *Chem. Rev.* **2007**, *107*, 874−922.
(10) Touaibia, M.; Roy, R. *J. Org. Chem.* **2008**, *73*, 9292−9302.
(11) R. Roy, R.; Das, S. K.; Dominique, R.; Trono, M. C.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Pure Appl. Chem.* **1999**, *71*, 565−571.
(12) (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470. (b) Bringmann, R. W.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977−991. (c) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327−3359.
(13) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9047−9050.
(14) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382−2384.
(15) Fanta, P. E. *Synthesis* **1974**, *1*, 9−21.
(16) (a) Yu, M.; Tang, R.-Y.; Li, J.-H. *Tetrahedron* **2009**, *65*, 3409−3416. (b) Pachon, L. D.; Elsevier, C. J.; Rothenberg, G. *Adv. Synth. Catal.* **2006**, *348*, 1705−1710. (c) Qafisheh, N.; Mukhopadhyay, S.; Sasson, Y. *Adv. Synth. Catal.* **2002**, *344*, 1079−1083. (d) Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559−2560. (e) Bergeron-Brlek, M.; Trono, M. C.; Roy, R. *Carbohydr. Res.* **2011**, *346*, 1479−1489.
(17) (a) Hayes, W.; Osborn, H. M. I.; Osborne, S. D.; Rastall, R. A.; Romagnoli, B. *Tetrahedron* **2003**, *59*, 7983−7996. (b) Smits, E.; Engberts, J. B. F. N.; Kellogg, R. M.; van Doren, H. A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2873−2877.
(18) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094−5115.
(19) (a) Satyanarayana, G.; Maier, M. E. *Eur. J. Org. Chem.* **2008**, 5543−5552. (b) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Wiener, H.; Sasson, Y. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2481−2484. (c) Mukhopadhyay, S.; Ratner, S.; Spernat, A.; Qafisheh, N.; Sasson, Y. *Org. Process Res. Dev.* **2002**, *6*, 297−300.
(20) Yamanoi, T.; Yamazaki, I. *Tetrahedron Lett.* **2001**, *42*, 4009−4011.
(21) (a) Learmonth, D. A. *Synth. Commun.* **2004**, *34*, 1565−1575. (b) Orlandi, S.; Annunziata, R.; Benaglia, M.; Cozzi, F.; Manzoni, L. *Tetrahedron* **2005**, *61*, 10048−10060. (c) Kleine, H. P.; Weinberg, D.

V.; Kaufman, R. J.; Sidhu, R. S. *Carbohydr. Res.* **1985**, *142*, 333−337. (d) Dea, I. C. M. *Carbohydr. Res.* **1970**, *12*, 297−299.
(22) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384−5427.
(23) (a) Tsubaki, K.; Hai, D. T. T.; Reddy, V. K.; Ohnishi, H.; Fuji, K.; Kawabata, T. *Tetrahedron: Asymmetry* **2007**, *18*, 1017−1021. (b) Ottaviani, P.; Maris, A.; Caminati, W. *J. Mol. Struct.* **2004**, *695*−*696*, 353−356.
(24) Huang, S.; Petersen, T. B.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 14021−14023.
(25) See the Supporting Information for cross-linking assays of compound **21**−**23**.


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