ARYLBORONIC ACID-MEDIATED GLYCOSYLATION OF 1,2-DIHYDROXYGLUCOSES

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Abstract – We explored direct dehydrative coupling of tetrahydro-2H-pyran-2,3-diol or a 1,2-dihydroxy sugar with various alcohols using a range of arylboronic acids. Among the catalysts, 2-borono-4-trifluoromethylbenzoic acid efficiently promoted acetalization of tetrahydro-2H-pyran-2,3-diol. Ferroceniumboronic acid showed the best catalytic activity for glycosylation of the 1,2-dihydroxy sugar. The major products were 1,2-cis-α-D-glucopyranosides.

INTRODUCTION

Glycosylation is a key step for the synthesis of oligosaccharides and glycopeptides with a range of biological activities. Although there have been many reports on the glycosidic bond-forming reaction, new efficient synthetic methods remain to be explored from the perspectives of atom-economy, sustainability, yield, and selectivity. In the conventional glycosylation, glycosyl donors with acyloxy, alkylthio, halogen, 2,2,2-trichloro-1-iminoethoxy, and pent-4-enyloxy groups at the anomeric position are required for coupling with a free hydroxy group of a glycosyl acceptor in the presence of an appropriate Bronsted acid or Lewis acid (Scheme 1a). The activated glycosyl donors are generally not stable and need to be prepared and stored with care. Furthermore, glycosylation sometimes requires more than the stoichiometric amount of activator or additive and cooling or heating of the reaction mixture to attain a high yield and α/β-selectivity. To overcome these limitations, we planned to investigate catalytic dehydrative glycosylation of 1,2-dihydroxy sugars as inactivated glycosyl donors in the presence of arylboronic acids as catalysts (Scheme 1b).
To achieve this type of glycosylation (Scheme 2), we envisioned that the boronate ester \( D \), generated from electron-deficient arylboronic acid \( B_1 \) (\( X = \) electron withdrawing group) and 1,2-dihydroxy sugar \( A \), would form borate complex \( E \) via coordination of glycosyl acceptor \( C \). Successive intramolecular migration of the coordinated sugar \( C (\text{RO}–) \) to an oxocarbenium ion intermediate (\( E \rightarrow F \)) and ligand exchange of \( F \) with diol \( A \) would provide the desired glycoside \( G \) with 1,2-\( \text{cis-}\alpha \)-selectivity. Alternatively, using arylboronic acid \( B_2 \) bearing an acidic moiety (\( Y–H \)) at the ortho-position, the anomeric C–O bond of the obtained boronate ester \( H \) would cleave through activation by an intramolecular hydrogen-bonding interaction. Then, glycosyl acceptor \( C \) would attack the anomeric carbon of the resulting intermediate \( I \) from the bottom side with assistance from the conjugate base (\( Y– \)). After ligand exchange of \( J \) with diol \( A \), this would also give \( G \) as the predominant product.

To date, the catalytic system

Glycosylation of 1-hydroxy sugars usually requires a stoichiometric amount of dehydrating reagent,\(^4\) and only a few catalytic dehydrative reactions have been reported.\(^5,6\) To date, the catalytic system
Sn(OTf)$_2$/Me$_3$SiCl/LiClO$_4$ has been identified as the best combination of catalyst and additive for α-selective glycosylation. In this paper, we describe arylboronic acid-catalyzed dehydrative coupling of a 1,2-dihydroxyglycosyl donor with several alcohols for the synthesis of 1,2-cis-α-D-glucopyranosides.

RESULTS AND DISCUSSION

We first examined the reaction of phenylboronic acid and cyclic 1,2-diol (Scheme 3). A 1:1 mixture of phenylboronic acid and tetrahydro-2H-pyran-2,3-diol 1 (cis:trans = 0.8:1) was stirred in CDCl$_3$ at room temperature for 10 min. The corresponding phenylboronate ester 2 was obtained as the only product. The same treatment of 3,4,6-tri-O-benzyl-D-glucopyranose 3 (α:β = 1:1) with phenylboronic acid at 40 °C for 6 h provided the cis-bicyclic boronate ester 4 exclusively. The configurations of 2 and 4 were determined to be cis by NOESY of the crude products. We were unable to isolate these boronates because they were not stable on silica gel.

Scheme 3. Formation of boronate esters 2 and 4 from phenylboronic acid and 1,2-diols 1 and 3

Having confirmed the formation of boronate ester as a reaction intermediate, we next turned our attention to acetalization of model compound 1 with benzyl alcohol in the presence of a range of arylboronic acids containing electron-deficient functional groups (Scheme 4a). Commercially available boronic acids 6–8 were inefficient for the acetalization of 1, and did not give the desired products 5. After screening many catalysts, we found that ferroceniumboronic acids 9a and 9b, which were readily prepared from ferroceneboronic acid and silver salts (AgSbF$_6$ and AgOTf), showed moderate catalytic activity to produce benzyl acetals 5 in 29% (9a) and 34% (9b) yields as a mixture of C2-isomers (cis:trans = 34:66 for 9a and 37:63 for 9b).

Thus, we examined bifunctional arylboronic acids 10–13 to improve the yields of benzyl acetals 5 (Scheme 4b). In contrast to the result with phenol 11, ortho-carboxylic acid 10a gave a better yield of 5 in a cis:trans ratio of 42:58. Moreover, use of 10b, which has a CF$_3$ group at the para-position, in
nitromethane dramatically improved both the yield and stereoselectivity of 5 (87%, cis:trans = 58:42) compared with the reactions of 10a and 10b in acetonitrile. These results suggest that the ortho-carboxy group plays a crucial role in the synergistic activation of the anomeric C–O bond of the presumed boronate ester 2. This synergistic effect of boronic acid and carboxylic acid was further supported by the fact that neither dual catalysis with phenylboronic acid and benzoic acid nor use of meta- and para-substituted carboxylic acids 12 and 13 exhibited any catalytic activity.

![Scheme 4. Screening of arylboronic acids for the acetalization of 1 and BnOH](image)

To determine what type of active arylboronic acid, 9 or 10, was best for the acetalization, the reaction of 3,4,6-tri-O-benzyl-D-glucopyranose 3 with methanol in nitromethane was carried out in the presence of 9a, 9b, or 10b (Table 1). Unexpectedly, the pre-prepared ferroceniumboronic acid 9a showed the best catalytic performance, producing a 69:31 mixture of α-14a and β-14a in 78% yield (entries 1–3). By contrast, both 9b and 10b resulted in low yields of a mixture of α/β-14a. Next, we examined the reaction using ferroceniumboronic acids 9a and 9b prepared in situ from ferroceneboronic acid 8 and silver salts (entries 4 and 5). Catalysts 9a and 9b led to slight and significant decreases in the yield, respectively, probably because of formation of short-lived chemical species. However, the yield of 14a improved to 82% and the reaction time decreased to 24 h when 20 mol% of AgSbF6 was added to a solution of substrate 3, pre-catalyst 8, and methanol in nitromethane (entries 6 and 7). We evaluated the solvent
effect using 1,2-dichloroethane, ether, and THF, and found that only 1,2-dichloroethane could be used as an alternative solvent (entries 8–10).

**Table 1. Optimization of the reaction conditions for glycosylation of 3**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Additive (x mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio (α:β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td></td>
<td>MeNO₂</td>
<td>48</td>
<td>78</td>
<td>69:31</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td></td>
<td>MeNO₂</td>
<td>48</td>
<td>12</td>
<td>59:41</td>
</tr>
<tr>
<td>3</td>
<td>10b</td>
<td></td>
<td>MeNO₂</td>
<td>48</td>
<td>9</td>
<td>53:47</td>
</tr>
<tr>
<td>4</td>
<td>8a</td>
<td>AgSbF₆ (10)</td>
<td>MeNO₂</td>
<td>48</td>
<td>70</td>
<td>53:47</td>
</tr>
<tr>
<td>5</td>
<td>8a</td>
<td>AgOTf (10)</td>
<td>MeNO₂</td>
<td>48</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8b</td>
<td>AgSbF₆ (10)</td>
<td>MeNO₂</td>
<td>48</td>
<td>15</td>
<td>31:69</td>
</tr>
<tr>
<td>7</td>
<td>8b</td>
<td>AgSbF₆ (20)</td>
<td>MeNO₂</td>
<td>24</td>
<td>82</td>
<td>62:38</td>
</tr>
<tr>
<td>8</td>
<td>8b</td>
<td>AgSbF₆ (20)</td>
<td>1,2-DCE</td>
<td>48</td>
<td>82</td>
<td>61:39</td>
</tr>
<tr>
<td>9</td>
<td>8b</td>
<td>AgSbF₆ (20)</td>
<td>Et₂O</td>
<td>48</td>
<td>37</td>
<td>51:49</td>
</tr>
<tr>
<td>10</td>
<td>8b</td>
<td>AgSbF₆ (20)</td>
<td>THF</td>
<td>48</td>
<td>27</td>
<td>48:52</td>
</tr>
</tbody>
</table>

* Catalyst 9a or 9b was prepared in situ by mixing 8 and the additive in MeNO₂, and then adding 3 and MeOH.

* Catalyst 9a was prepared in situ by mixing the additive with a solution of 8, 3, and MeOH.

Although further enhancement of α/β-selectivity is needed, we evaluated the scope of the nucleophile under the optimized conditions. The established reaction with 3 could be applied to several primary alcohols, such as ethanol, propargyl alcohol, and 4-chlorobenzyl alcohol, to give the corresponding glucosides 14b–d in 72%–88% yields with moderate α/β-selectivity (51:49 to 66:34) (Table 2). Secondary alcohols such as 2-propanol and cyclohexanol were also introduced into diol 3, and gave the desired products 14e and 14f with good selectivities (α:β = 74:26–81:19). Notably, dehydrative glycosylation of diol 3 with methyl-2,3,4-tri-O-benzyl-α-D-glucopyranoside 15 took place smoothly under the same optimized conditions to produce 1,6-disaccharide 14g in 52% yield as a 1:1 mixture of α- and β-isomers.
Although we obtained the corresponding glycosides \(14a-g\) in reasonable yields, the \(\alpha/\beta\)-selectivity was highly dependent on the alcohols used. To clarify the stereodetermining factor of the glycosylation, epimerization experiment of \(\alpha-14e\) and \(\beta-14e\) was carried out under the optimized conditions (Scheme 5). To our surprise, the same treatment of \(\alpha-14e\) or \(\beta-14e\) with ferroceneboronic acid \(8\) and AgSbF\(_6\) in the presence of 2 equiv of 2-propanol resulted in a mixture of \(\alpha-14e\) and \(\beta-14e\) in a similar ratio. These results suggest that the two products, \(\alpha-14\) and \(\beta-14\), are interconvertible under the conditions and that the \(\alpha:\beta\) ratio is controlled thermodynamically. We suspect that any acidic species might be generated in the reaction mixture by the reaction of ferroceneboronic acid \(8\) and the silver salt.

In conclusion, we developed a new catalytic method for dehydrative acetalization of tetrahydro-2H-pyran-2,3-diol using highly electron-deficient boronic acid \(9a\) and bifunctional arylboronic acid \(10b\). In addition, \textit{in situ} generation of ferroceniumboronic acid \(9a\) gave the best catalysis for dehydrative glycosylation. Catalytic dehydrative coupling of diol donor \(3\) and glucoside \(15\) was successfully applied to the synthesis of 1,6-linked disaccharide \(14g\), while both the yield and
α/β-selectivity need to be improved. Further synthetic and mechanistic studies are underway in our laboratory.

**EXPERIMENTAL**

Unless otherwise noted, all chemicals and solvents were obtained from commercial suppliers and used without further purification. Analytical thin-layer chromatography was performed with Merck Silica gel 60. Column chromatography was performed on Cica silica gel 60 (spherical/40–100 μm). Proton nuclear magnetic resonance (1H NMR) spectra were recorded with a JEOL JNM-AL 400 at 400 MHz, JEOL JNM-ECA 500 at 500 MHz, or Avance I 600 (Bruker Biospin AG, Switzerland) at 600 MHz. Chemical shifts are reported relative to TMS (δ 0.00) or CD3OD (δ 3.30). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); dd (doublet of doublets); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (13C NMR) spectra were recorded with a JEOL JNM-AL 400 at 100 MHz, JEOL JNM-ECA 500 at 125 MHz, or Avance I 600 (Bruker Biospin AG, Switzerland) at 150 MHz. Chemical shifts are reported relative to CDCl3 (δ 77.0) or CD3OD (δ 49.0). Infrared spectra were recorded on a JASCO FT/IR-4100. High resolution mass spectra were obtained on a Shimadzu LCMS-IT-TOF for ESI-MS. Optical rotations were recorded on a JASCO P-2200 polarimeter; concentrations are quoted in grams per 100 mL. Unless otherwise noted, all materials and solvents were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used without purification.

**Preparation of starting materials**

Compounds 1[10] and 3[10] are known compounds.

**Tetrahydro-2H-pyran-2,3-diol (1):** To a solution of mCPBA (15 mmol, 3.45 g) in Et2O (50 mL) were added 3,4-dihydro-2H-pyran (10 mmol, 0.905 mL) and H2O (5 mL) at 0 °C under argon atmosphere. The solution was stirred at 0 °C for 19 h before concentrated. Then, the mixture containing colorless precipitates was filtered through a glass filter using cold H2O. After the filtrate was coevaporated with toluene, the crude was purified by column chromatography (EtOAc) to provide 1 (861 mg, 73%, cis:trans = 0.8:1) as a colorless oil; 1H NMR (500 MHz, CDCl3, 40:60 mixture of anomers): δ 4.92 (s, 1.0H), 4.51 (d, J = 5.7 Hz, 0.6H), 4.42 (s, 0.4H), 3.97–3.90 (m, 1.0H), 3.69 (s, 0.6H), 3.55–3.40 (m, 2.2H), 2.89 (s, 0.4H), 2.10–2.07 (m, 0.6H), 1.90–1.46 (m, 3.2H); 13C NMR (125 MHz, CDCl3, 40:60 mixture of anomers): δ 98.5, 93.6, 70.3, 67.7, 65.1, 62.1, 29.1, 27.6, 24.0, 22.1.
Formation of boronic esters (2 and 4) (Scheme 3)
The compound 1 (11.8 mg, 0.10 mmol) and phenylboronic acid (12.2 mg, 0.10 mmol) were dissolved in CDCl₃ (0.50 mL), respectively, and both solutions were mixed at room temperature. The resulting solution was transferred to a NMR tube for taking the following spectral data; ¹H NMR (500 MHz, CDCl₃): δ 7.89 (d, J = 7.4 Hz, 2H), 7.52 (dd, J = 7.4, 7.4 Hz, 1H), 7.41 (dd, J = 7.7, 7.4 Hz, 2H), 5.81 (d, J = 5.7 Hz, 1H), 4.57 (dt, J = 5.7, 3.7 Hz, 1H), 3.82 (dt, J = 11.7, 6.9 Hz, 1H), 3.73 (dt, J = 11.7, 6.6 Hz, 1H), 2.10–2.04 (m, 1H), 1.94–1.86 (m, 1H), 1.78–1.72 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 135.6, 135.0, 131.8, 127.9, 98.5, 73.5, 58.0, 22.3, 16.5.
The compound 3 (22.5 mg, 0.050 mmol) and phenylboronic acid (6.1 mg, 0.050 mmol) were dissolved in CDCl₃ (0.50 mL), respectively. Both solutions were mixed, and stirred at 40 °C for 6 h. The resulting solution was transferred to a NMR tube for taking the following spectral data; ¹H NMR (500 MHz, CDCl₃): δ 7.77 (d, J = 6.9 Hz, 2H), 7.42 (t, J = 8.3 Hz, 1H), 7.33–7.17 (m, 15H), 7.08 (t, J = 3.7 Hz, 2H), 5.99 (d, J = 5.7 Hz, 1H), 4.74 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.52–4.50 (m, 2H), 4.43 (d, J = 12.6 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 3.84 (t, J = 4.3 Hz, 1H), 3.70 (d, J = 3.4 Hz, 2H), 3.61 (d, J = 2.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 137.9, 137.8, 135.6, 135.1, 132.0, 128.5, 128.3 (2C), 128.0, 127.9, 127.8 (2C), 127.6 (2C), 99.1, 80.3, 77.1, 74.5, 73.4, 73.0, 72.3, 70.4, 69.1.

Preparation of arylboronic acids (9 and 10)
Catalysts 6, 7, 8, and 10a are commercially available. The known catalysts 9a and 10b were prepared according to the reported procedure.

Ferroceniumboronic acid trifluoromethanesulfonate salt (9b): The title compound (107 mg, 65%) was prepared as dark green solids by a similar method as described in the literature, starting from ferroceneboronic acid (100 mg, 0.435 mmol) and AgOTf (112 mg, 0.435 mmol). The ¹H and ¹³C NMR spectra were not able to obtain in high quality due to the paramagnetism of iron (III). ¹⁹F NMR (376 MHz, acetone-d₆): δ –72.3 (br s, 3F); IR (ATR): 3399, 3112, 1656, 1418, 1225, 1164, 1025 cm⁻¹; HRMS (ESI) calcd for C₁₁H₁₃O₂BFe [M–OTf–H₂O+CH₃OH]⁺: 244.0355; Found: 244.0362; calcd for C₁₂H₁₅O₂BFe [M–OTf–2H₂O+2CH₃OH]⁺: 258.0512; Found: 258.0517; calcd for CO₃F₃S [M–C₁₀H₁₁O₂BFe]⁻: 148.9526; Found: 148.9530.

2-Borono-4-methoxybenzoic acid (10c): The title compound (139 mg, 31%) was obtained as an ivory solid according to the literature, starting from tert-butyl 4-methoxybenzoate (469 mg, 2.2 mmol); ¹H NMR (500 MHz, CD₂OD): δ 7.89 (d, J = 8.6 Hz, 1H), 6.95 (dd, J = 8.6, 2.3 Hz, 1H), 6.91 (d, J = 2.3 Hz, 1H), 3.85 (s, 3H); ¹³C NMR (125 MHz, CD₂OD): δ 172.1, 164.8, 132.1, 131.2, 127.0, 116.2, 114.8, 55.9;
IR (ATR): 3201, 1596, 1463, 1286, 1242, 1148, 1086, 869 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{10}H_{12}O_5B\) [M–2H\(_2\)O+2CH\(_3\)OH–H]\(^-\): 223.0785; Found: 223.0783.

**General procedure for the synthesis of benzyl acetals (5) with arylboronic acids (6–13) (Scheme 4)**

Both cis-5\(^{11}\) and trans-5\(^{12}\) are known compounds, but their \(^{13}\)C NMR spectral data have not been reported.

2-(Benzyloxy)tetrahydro-2\(^H\)-pyran-3-ol (cis-5 and trans-5): To a mixture of 1 (0.10 mmol, 11.8 mg) and catalyst (0.010 mmol) in MeCN (1.0 mL) was added BnOH (0.30 mmol, 31 \(\mu\)L). The reaction mixture was stirred at 40 °C for 48 h, before concentrated. The crude was purified by column chromatography (hexane/EtOAc = 3:1) to provide a mixture of cis-5 and trans-5 as a colorless oil.

**cis-5:** \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.37–7.30 (m, 5H), 4.82 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 2.9 Hz, 1H), 4.53 (d, J = 11.0 Hz, 1H), 3.73 (td, J = 10.4, 3.9 Hz, 1H), 3.55–3.52 (m, 1H), 2.02 (br s, 1H), 1.87–1.67 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 137.6, 128.4, 127.9, 127.8, 97.7, 69.2, 68.0, 59.9, 27.7, 24.1.

**trans-5:** \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.37–7.30 (m, 5H), 4.86 (d, J = 11.6 Hz, 1H), 4.55 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 5.8 Hz, 1H), 3.97–3.92 (m, 1H), 3.56–3.47 (m, 2H), 2.35 (br s, 1H), 2.11–2.03 (m, 1H), 1.79–1.49 (m, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 137.5, 128.4, 128.0, 127.8, 102.3, 69.9, 68.5, 63.7, 28.0, 22.9.

**General procedure for the synthesis of methyl 3,4,6-tri-O-benzyl-D-glucopyranoside (14a) (Table 1)**

Both \(\alpha\)-14a\(^{13}\) and \(\beta\)-14a\(^{14}\) are known and their spectral data were identical to the reported data of the authentic samples.

**Method A in entries 1–3** The reaction was performed in MeNO\(_2\) according to the procedure for the synthesis of 5, giving a mixture of \(\alpha\)-14a and \(\beta\)-14a.

**Method B in entries 4–5** A mixture of 8 (0.010 mmol) and AgSbF\(_6\) or AgOTf (0.010 mmol) in MeNO\(_2\) (0.10 mL) was stirred at room temperature for 30 min under argon atmosphere. Then, MeOH (0.30 mmol) and a solution of 3 (0.10 mmol) in MeNO\(_2\) (1.9 mL) were successively added, and the resulting mixture was stirred at 40 °C for 48 h. Then, the mixture was concentrated at 30–35 °C. The crude was purified by column chromatography (hexane/EtOAc = 2:1 \(\rightarrow\) 1:1) to afford a mixture of \(\alpha\)-14a and \(\beta\)-14a.

**Method C in entries 6–10** To a solution of 3 (0.10 mmol), 8 (0.010 mmol), and MeOH (0.30 mmol) in MeNO\(_2\) (2.0 mL) was added AgSbF\(_6\) (0.010 or 0.020 mmol) in a glove box, and the reaction mixture was stirred at 40 °C for 24 h. Then, the reaction mixture was concentrated at 30–35 °C. The crude was purified by column chromatography (hexane/EtOAc = 2:1 \(\rightarrow\) 1:1) to afford a mixture of \(\alpha\)-14a and \(\beta\)-14a.

**Ethyl 3,4,6-tri-O-benzyl-D-glucopyranoside (14b) (Entry 1 in Table 2):** The reaction was performed according to method C for the synthesis of 14a, providing a mixture of \(\alpha\)-14b and \(\beta\)-14b (34.5 mg, 72%,
α:β = 51:49), starting from substrate 3 (45.1 mg, 0.10 mmol) and EtOH (17.5 μL, 0.30 mmol). The spectral data of β-14b were identical to the reported data of the authentic sample.¹⁵

α-14b: A colorless solid; [α]D²⁵ +81.7 (c 1.0, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ 7.39–7.27 (m, 13H), 7.14 (dd, J = 7.7, 2.2 Hz, 2H), 4.94 (d, J = 11.0 Hz, 1H), 4.91 (d, J = 3.8 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 4.63 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.49 (d, J = 10.4 Hz, 1H), 3.80–3.74 (m, 4H), 3.71 (dd, J = 9.3, 3.8 Hz, 1H), 3.67 (dd, J = 10.7, 1.9 Hz, 1H), 3.64 (t, J = 9.3 Hz, 1H), 3.54 (dq, J = 9.3, 7.1 Hz, 1H), 2.12 (br s, 1H), 1.23 (t, J = 7.1 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃): δ 138.7, 138.2, 137.9, 128.4 (2C), 127.9 (3C), 127.7 (2C), 127.6, 98.1, 83.5, 77.4, 75.3, 75.0, 73.5, 73.0, 70.5, 68.5, 63.5, 15.0; IR (ATR): 3455, 3030, 2911, 1453, 1361, 1273, 1043, 1027 cm⁻¹; HRMS (ESI) calcd for C₂₉H₃₄O₆Na [M+Na⁺]: 501.2248; Found: 501.2237.

Propargyl 3,4,6-tri-O-benzyl-D-glucopyranoside (14c) (Entry 2 in Table 2): The reaction was performed according to method C for the synthesis of 14a, providing a mixture of α-14c and β-14c (38.4 mg, 79%, α:β = 66:34), starting from substrate 3 (45.1 mg, 0.10 mmol) and HC≡CCH₂OH (17.7 μL, 0.30 mmol). The spectral data of β-14c were identical to the reported data of the authentic sample.¹₆

α-14c: A colorless oil; [α]D²⁵ +92.8 (c 0.50, CHCl₃); ¹H NMR (500 MHz, CDCl₃): δ 7.38–7.27 (m, 13H), 7.15 (dd, J = 7.2, 2.0 Hz, 2H), 5.10 (d, J = 2.9 Hz, 1H), 4.92 (d, J = 11.5 Hz, 1H), 4.85 (d, J = 11.5 Hz, 1H), 4.82 (d, J = 10.9 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.50 (d, J = 10.9 Hz, 1H), 4.28 (d, J = 2.3 Hz, 2H), 3.82–3.74 (m, 4H), 3.68–3.64 (m, 2H), 2.44 (t, J = 2.3 Hz, 1H), 2.12 (d, J = 8.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 138.6, 138.1, 137.8, 128.4 (2C), 127.9 (2C), 127.7 (2C), 127.6, 98.1, 83.5, 77.4, 75.3, 75.0, 73.5, 73.0, 70.5, 68.5, 63.5, 15.0; IR (ATR): 3546, 3286, 3030, 2922, 2863, 1496, 1454, 1360, 1039 cm⁻¹; HRMS (ESI) calcd for C₃₀H₃₂O₆Na [M+Na⁺]: 511.2091; Found: 511.2084.

4-Chlorobenzyl 3,4,6-tri-O-benzyl-D-glucopyranoside (14d) (Entry 3 in Table 2): The reaction was performed according to method C for the synthesis of 14a, providing a mixture of α-14d and β-14d (50.6 mg, 88%, α:β = 61:39), starting from substrate 3 (45.1 mg, 0.10 mmol) and 4-ClC₆H₄CH₂OH (42.8 mg, 0.30 mmol).

α-14d: A colorless oil; [α]D²⁵ +64.0 (c 0.86, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ 7.37–7.27 (m, 17H), 7.14 (dd, J = 7.4, 1.9 Hz, 2H), 5.00 (d, J = 3.8 Hz, 1H), 4.91 (d, J = 11.0 Hz, 1H), 4.84 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 11.0 Hz, 1H), 4.70 (d, J = 12.1 Hz, 1H), 4.62 (d, J = 12.1 Hz, 1H), 4.52 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.49 (d, J = 12.1 Hz, 1H), 3.80–3.71 (m, 4H), 3.64 (dd, J = 9.9, 8.8 Hz, 1H), 3.61 (dd, J = 10.7, 1.9 Hz, 1H), 2.09 (d, J = 8.8 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃): δ 138.6, 138.0, 137.9, 135.5, 133.8, 129.5, 128.7, 128.4 (2C), 128.2, 127.9 (3C), 127.8, 127.7 (2C), 97.9, 83.3,
IR (ATR): 3446, 3031, 2922, 1492, 1453, 1027, 1013 cm\(^{-1}\);


\(\beta\)-14d: A colorless solid; \([\alpha]\)\(_D\)\(^{25}\) \(-16.4\) (c 1.1, CHCl\(_3\)); \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.37–7.27 (m, 17H), 7.18 (d, \(J = 7.7\) Hz, 2H), 4.90 (d, \(J = 11.5\) Hz, 1H), 4.89 (d, \(J = 11.5\) Hz, 2H), 4.62 (d, \(J = 12.1\) Hz, 1H), 4.60 (d, \(J = 11.5\) Hz, 2H), 4.54 (d, \(J = 12.1\) Hz, 2H), 4.34 (d, \(J = 7.1\) Hz, 1H), 3.75 (d, \(J = 11.0\) Hz, 1H), 3.70 (dd, \(J = 11.0, 4.4\) Hz, 1H), 3.64–3.56 (m, 3H), 3.48 (dd, \(J = 9.9, 4.4\) Hz, 1H), 2.32 (br s, 1H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 138.5, 138.1, 138.0, 135.7, 133.7, 129.4, 128.6, 128.5, 128.4 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 101.7, 84.5, 77.5, 75.2 (2C), 75.0, 74.6, 73.5, 70.2, 68.8; IR (ATR): 3288, 3030, 2923, 1494, 1451, 1361, 1059, 1043 cm\(^{-1}\); HRMS (ESI) calcd for C\(_{34}\)H\(_{35}\)O\(_6\)ClNa [M+Na\(^+\)]: 597.2014; Found: 597.2010.

**Isopropyl 3,4,6-tri-O-benzyl-D-glucopyranoside (14e) (Entry 4 in Table 2):** The reaction was performed according to method C for the synthesis of 14a, providing a mixture of \(\alpha\)-14e and \(\beta\)-14e (36.5 mg, 74%, \(\alpha:\beta = 81:19\)), starting from substrate 3 (45.1 mg, 0.10 mmol) and i-PrOH (23.0 \(\mu\)L, 0.30 mmol). The spectral data of the obtained products \(\alpha\)-14e and \(\beta\)-14e were identical to the reported data of the authentic samples \(\alpha\)-14e\(^{17}\) and \(\beta\)-14e\(^{14,17}\).

**Cyclohexyl 3,4,6-tri-O-benzyl-D-glucopyranoside (14f) (Entry 5 in Table 2):** The reaction was performed according to method C for the synthesis of 14a, providing a mixture of \(\alpha\)-14f and \(\beta\)-14f (30.8 mg, 58%, \(\alpha:\beta = 74:26\)), starting from substrate 3 (45.1 mg, 0.10 mmol) and C\(_6\)H\(_{11}\)OH (31.7 \(\mu\)L, 0.30 mmol). The spectral data of the obtained products \(\alpha\)-14f and \(\beta\)-14f were identical to the reported data of the authentic samples \(\alpha\)-14f\(^{15}\) and \(\beta\)-14f\(^{14}\).

**Methyl 3,4,6-tri-O-benzyl-D-glucopyranosyl-(1→6)-2,3,4-tri-O-benzyl-a-D-glucopyranoside (14g) (Entry 6 in Table 2):** The reaction was performed according to method C for the synthesis of 14a, providing a mixture of \(\alpha\)-14g and \(\beta\)-14g (46.6 mg, 52%, \(\alpha:\beta = 50:50\)), starting from substrate 3 (45.1 mg, 0.10 mmol) and 15 (139 mg, 0.30 mmol). The spectral data of the obtained products \(\alpha\)-14g and \(\beta\)-14g were identical to the reported data of the authentic samples \(\alpha\)-14g and \(\beta\)-14g\(^{18}\).

**The epimerization experiment of \(\alpha\)-14e and \(\beta\)-14e (Scheme 5):** To a solution of \(\alpha\)-14e (24.6 mg, 50 \(\mu\)mol), 8 (1.1 mg, 5.0 \(\mu\)mol), and i-PrOH (7.7 \(\mu\)L, 0.10 mmol) in MeNO\(_2\) (1.0 mL) was added AgSbF\(_6\) (3.4 mg, 10 \(\mu\)mol) in a glove box, and the reaction mixture was stirred at 40 °C for 48 h. Then, the reaction mixture was concentrated at 30–35 °C. The crude was purified by column chromatography (hexane/EtOAc = 3:1) to give a mixture of \(\alpha\)-14e and \(\beta\)-14e (21.5 mg, 87%, \(\alpha:\beta = 73:27\)).

The reaction of \(\beta\)-14e (23.2 mg, 47 \(\mu\)mol) was performed in the same way, providing a mixture of \(\alpha\)-14e and \(\beta\)-14e (20.7 mg, 89%, \(\alpha:\beta = 70:30\)).
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