Synthesis of Ether-Linked Sugar by Nucleophilic Opening of Carbohydrate Oxiranes

Kazusa Nishiyama, Takahiro Nakayama, Hideaki Natsugari, Hideyo Takahashi*
School of Pharmaceutical Sciences, Teikyo University, Sagamiko, Sagamihara, Kanagawa 229-0195, Japan
Fax +81(426)853728; E-mail: hide-tak@pharm.teikyo-u.ac.jp
Received 9 July 2008; revised 25 August 2008

Abstract: A new synthesis of ether-linked sugar utilizing the nucleophilic ring-opening reaction of carbohydrate α- or β-oxirane was developed. The reaction of 2,3-anhydro-α-D-mannopyranosides resulted in the expected high regioselectivity. In contrast, 2,3-anhydro-α-D-allopyranosides showed an unusual regioselectivity shift. The differentiating properties of carbohydrate α- or β-oxirane were investigated by comparing various conditions of the reaction.

Key words: carbohydrates, epoxides, ethers, ring opening, regioselectivity

It was a promising discovery when coyolosa (Figure 1) was isolated from Acrocomia mexicana as a unique 6,6¢-ether-linked sugar. Since coyolosa has significant effects on fasting blood glucose levels, new light has been shed on the ether linkage of sugars with the expectation of a new candidate in the search for drugs to combat diabetes.

Figure 1

We have therefore investigated a novel synthesis of 6,6¢-ether-linked pyranoses through an acetalization–reduction procedure. While this approach was successfully applied to the synthesis of various new ether-linked sugars, we continued to examine an alternative method by which an ether linkage could be introduced at other positions of pyranoses. Herein, we describe a new synthesis of ether-linked sugar by regiospecific nucleophilic opening of carbohydrate oxiranes.

Carbohydrate oxiranes are useful in synthetic studies. Numerous studies have been carried out on 1,2-anhydro sugars as glycosyl donors in glycosylation. 1,6/2,3-Anhydro sugars were demonstrated to be appropriate intermediates in the preparation of various carbohydrate derivatives. We became interested in the oxirane ring opening of 2,3-anhydropyranosides and examined the regioselective nucleophilic attack by the hydroxy group of another pyranoside, by which ether-linked pyranosides could be provided efficiently.

The ring-opening reaction of carbohydrate oxirane with strong anionic nucleophiles (e.g., $\text{N}_3^-$) has been investigated with great interest. However, the use of weakly nucleophilic reagents has not been fully established. We therefore studied the nucleophilic opening of carbohydrate α- and β-oxiranes with alcohols or alkoxides under various conditions (Scheme 1).

Scheme 1

Regioselective nucleophilic opening of the oxirane on a six-membered ring

In general, the nucleophilic opening of an oxirane on a six-membered ring results in high regioselectivity; only an axial attack occurs (Fürst–Plattner rule). Thus, nucleophiles are presumed to attack the C-3 carbon of 2,3-β-oxirane, and the transition state requires the linearity of the entering nucleophile with a C–O bond to be broken to provide the 2,3-trans-diaxial conformation. Similarly, nucleophiles should attack the C-2 carbon of 2,3-α-oxirane to provide the 2,3-trans-diaxial conformation (Scheme 1). We therefore examined the regioselectivity of the reaction under various conditions. Particularly informative are comparisons of basic conditions using metal alkoxide as a nucleophile and acidic conditions using alcohol as a nucleophile in the presence of a Lewis acid as promoter.

First, we investigated the regioselectivity of the ring opening of the β-oxirane derivatives methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (1), and methyl
2,3-anhydro-4,6-di-O-benzyl-α-D-mannopyranoside (2)\textsuperscript{12} by the nucleophilic reaction of the alkoxides derived from the corresponding hydroxy derivatives methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (5a),\textsuperscript{13} methanol (5b), and benzyl alcohol (5c) (Table 1).

As shown in Table 1, the ring-opening reaction of β-oxiranes 1 and 2 required an excess amount of metal alkoxide (10 equiv)\textsuperscript{14} and harsh conditions (refluxing DMF–THF, 1:1). The conformationally locked substrate 1 reacted with the sodium alkoxide of 5a to give the 3,6’-ether-linked sugar 6A\textsuperscript{15} in 84% yield, with no formation of 6B observed (Table 1, entry 1); as expected, the reaction was highly regioselective. This is the first example of the synthesis of the 3,6’-ether-linked sugar (the 3-position of D-altroside and the 6-position of D-glucoside are linked by ether bonding). Using lithium alkoxide lowered the yield of 6A, but complete regiospecificity was also observed (Table 1, entry 2). We then examined 2, which does not have a rigidly locked conformation. The reaction with the sodium alkoxide of 5a gave only the 2,3-trans-diaxial compound 7A\textsuperscript{16} in 34% yield (Table 1, entry 3). In this case, the lithium alkoxide of 5a proved to be a better nucleophile, affording 7A in 68% yield (Table 1, entry 4). Interestingly, a slight amount of 7B was obtained (7A/7B = 10:1) when toluene was used instead of N,N-dimethylformamide–tetrahydrofuran as the solvent (Table 1, entry 5). Sodium methoxide and sodium benzylxide were also examined as nucleophiles (Table 1, entries 6 and 7). While sodium methoxide attacked C-3 regioselectively to give α-D-altropyranoside 8A\textsuperscript{15} in 76% yield (entry 6), the bulkier sodium benzylxide, less potent as a nucleophile, gave mixture of products 9A and 9B (9A/9B\textsuperscript{17} = 4.5:1) in 55% yield (entry 7). As a whole, the stereochemical outcome in the reaction of β-oxiranes 1 and 2 is the result of the expected stereoelectronic preference for axial attack by the metal alkoxide. It is difficult to achieve the usual C-2 attack in this oxirane.

We next investigated the regioselectivity of the ring-opening reaction of α-oxiranes 3\textsuperscript{18} and 4 using the metal alkoxides of 5a (Table 2). Even the conformationally locked substrate 3 gave mixtures of the 2,3-trans-diaxial 10A\textsuperscript{15} and the 2,3-trans-diequatorial 10B\textsuperscript{15} in 64% yield (10A/10B = 8:1:1) (Table 2, entry 1). A marked selectivity shift was observed in the case of the more flexible oxirane 4 (11A/11B\textsuperscript{15} = 1.5:1) (Table 2, entry 3). A large solvent effect, which is a common feature of the reaction with lithium alkoxide, was also observed. While the best result with regard to the selectivity for C-2 attack was obtained with tetrahydrofuran (11A/11B = 4.3:1) (Table 2, entry 4), less polar solvents (benzene and toluene) increased the ratio of C-3 attack (entries 9 and 10). It is likely that the lithium ion, which has a strong ability to form a chelate structure with the oxygen atoms of the pyranoside substrate, and the solvent cooperatively functioned to provide

### Table 1: Nucleophilic Ring Opening of β-Oxiranes 1 and 2 with Alcohols 5

<table>
<thead>
<tr>
<th>Entry</th>
<th>β-Oxirane</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product Yield&lt;sup&gt;b&lt;/sup&gt; (%)</th>
<th>Ratio&lt;sup&gt;c&lt;/sup&gt; (A/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5a</td>
<td>CHPh</td>
<td></td>
<td>NaH (4)</td>
<td>DMF–THF (1:1)</td>
<td>2</td>
<td>6</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5a</td>
<td>CHPh</td>
<td></td>
<td>MeLi (10)</td>
<td>DMF–THF (1:1)</td>
<td>6</td>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5a</td>
<td>Bn</td>
<td>Bn</td>
<td>NaH (4)</td>
<td>DMF–THF (1:1)</td>
<td>12</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>5a</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>DMF–THF (1:1)</td>
<td>12</td>
<td>7</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>5a</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>toluene</td>
<td>6</td>
<td>7</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>5b&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (8)</td>
<td>–</td>
<td>16</td>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>5c&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Bn</td>
<td>Bn</td>
<td>NaH (8)</td>
<td>–</td>
<td>2</td>
<td>9</td>
<td>55</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reagents and conditions: 1 or 2 (1 equiv), 5 (10 equiv), base, solvent, reflux.

<sup>b</sup> The combined yield of the products.

<sup>c</sup> The ratio of the isolated products.

<sup>d</sup> Used as solvent.

the various conformations to 4, leading to such a change in the regioselectivity. In sharp contrast to lithium alkoxide, potassium alkoxide gave very low regioselectivity (Table 2, entries 11 and 12). We have so far not succeeded in obtaining excellent C-2 selectivity with metal alkoxides. However, it should be noted that C-3 attack, which is generally recognized as stereoelectronically unfavorable, was frequently observed in this case.

Next, we investigated acidic conditions. For this, a strong Lewis acid is needed to activate the oxirane. A survey of a number of Lewis acids was carried out, and trimethylsilyl triflate was found to be the most promising promotor. First, the conformationally locked substrate 1 was treated with 5a in the presence of trimethylsilyl triflate (1 equiv) (Scheme 2). It was found, however, that 4,6-benzylidene protection was unstable under such strongly acidic conditions, and a major byproduct was detected, which was determined to be the partially deprotected ether-linked version of product 12. To avoid a cumbersome separation process, we adopted the ring-opening reaction followed by acidic deprotection of the benzylidene group (AcOH, THF) to obtain triol 12 as the product (Scheme 2). Although the addition of a small amount of tetramethylurea (TMU)\(^{19}\) to this system increased the yields, further improvement was not likely.\(^{20}\)

We therefore turned to oxirane 2, of which the conformation is not rigidly locked. The reaction proceeded highly regioselectively to provide the 2,3-trans-diaxial 7A (Table 3, entry 1). When a large excess of nucleophile 5a (10 equiv) was used in the presence of trimethylsilyl triflate (1 equiv), 7A was obtained as the sole product in 82% yield (Table 3, entry 1). It is interesting that invariable regioselectivity was again observed in this case.

### Table 2  Nucleophilic Ring Opening of α-Oxiranes 3 and 4 with Alkoxides\(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Oxirane</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Equiv of 5a</th>
<th>Base (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio(^{c}) (A/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>CHPh</td>
<td>4</td>
<td>NaH (4)</td>
<td>DMF–THF (1:1)</td>
<td>1.5</td>
<td>10</td>
<td>64</td>
<td>8.1:1(^{d})</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>CHPh</td>
<td>20</td>
<td>NaH (4)</td>
<td>DMF–THF (1:1)</td>
<td>2.5</td>
<td>10</td>
<td>88</td>
<td>7.8:1(^{d})</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>NaH (4)</td>
<td>DMF–THF (1:1)</td>
<td>2</td>
<td>11</td>
<td>84</td>
<td>1.5:1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>THF</td>
<td>13.5</td>
<td>11</td>
<td>71</td>
<td>4.3:1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>DMF–THF (1:1)</td>
<td>5.5</td>
<td>11</td>
<td>77</td>
<td>4:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>DMSO(^{e})</td>
<td>4</td>
<td>11</td>
<td>95</td>
<td>2.9:1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>MeCN</td>
<td>13</td>
<td>11</td>
<td>84</td>
<td>2.8:1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>dioxane</td>
<td>11</td>
<td>11</td>
<td>89</td>
<td>2.5:1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>benzene</td>
<td>33</td>
<td>11</td>
<td>59</td>
<td>1.1:1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>MeLi (10)</td>
<td>toluene</td>
<td>12</td>
<td>11</td>
<td>83</td>
<td>1.1:1</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>t-BuOK (4)</td>
<td>DMF–THF (1:1)</td>
<td>18</td>
<td>11</td>
<td>61</td>
<td>1.1:1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>t-BuOK (4)</td>
<td>toluene</td>
<td>2</td>
<td>11</td>
<td>85</td>
<td>1:1</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Reagents and conditions: 3 or 4 (1 equiv), 5a, base, solvent, reflux.

\(^{b}\) The combined yield of the products.

\(^{c}\) The ratio was determined by NMR.

\(^{d}\) The ratio of the isolated products.

\(^{e}\) At 125 °C.
Fortunately, no reaction occurred with the secondary hydroxyl group of carbohydrate \( \text{5d} \) (Table 3, entry 2). It is likely that the poor nucleophilicity and the bulkiness of the secondary alcohol prevent the reaction from occurring. Yet the strongly nucleophilic thiol \( \text{5e} \) reacted with \( \beta \)-oxirane \( \text{2} \) to give the corresponding \( \text{13A} \) stereoselectively in 66% yield (Table 3, entry 3). It should be stressed that the ring-opening reaction of \( \beta \)-oxirane \( \text{2} \) occurred stereospecifically at the C-3 position in all cases.

Finally, ring opening of \( \alpha \)-oxiranes \( \text{3} \) and \( \text{4} \) was examined under acidic conditions. This gave messy reactions, although the addition of boron trifluoride–diethyl ether complex \( \text{23} \) to the system partially improved the results. It is strange that the 4,6-benzylidene-protected \( \text{3} \) provided stereoelectronically unfavored \( \text{10A} \) (structure shown in Table 2) solely, but in very low yield (7%). The reaction of the more flexible \( \alpha \)-oxirane \( \text{4} \) gave mixtures of 2,3-trans-diaxial \( \text{11A} \) and 2,3-trans-diequatorial \( \text{11B} \) (\( \text{11A}/\text{11B} = 1:2.4 \)) (Scheme 3). Although limited, the data suggest a tendency of \( \alpha \)-oxirane to give the 2,3-trans-diequatorial product under acidic conditions.

Our results showed that the orientation of the oxirane on the pyranose ring affects the reactivity and regioselectivity toward nucleophilic ring-opening reactions. 2,3-Anhydro-\( \alpha \)-D-mannopyranosides (\( \beta \)-oxiranes) afforded the 3,6-ether-linked sugar selectively in good yields. In contrast, the reaction of 2,3-anhydro-\( \alpha \)-D-allopyranosides (\( \alpha \)-oxiranes) resulted in an unusual selectivity shift. Although we have only limited information on the properties of \( \alpha \)- and \( \beta \)-oxiranes, a closer examination of these compounds might contribute to further progress in the ring-opening reactions of carbohydrate oxiranes in the future.

In conclusion, a new synthesis of ether-linked sugar utilizing nucleophilic ring opening was developed. We also found that the differentiating property of 2,3-\( \alpha \)-D-oxirane affects the results of the nucleophilic ring-opening reaction.

All reactions sensitive to air or moisture were conducted under an argon atmosphere. Materials were obtained from commercial suppliers. All anhydrous solvents were purified according to standard methods. NMR spectra were recorded on a JEOL AL-400 spectrometer at 400 MHz for \( ^1 \)H NMR and 100 MHz for \( ^1 \)C NMR. Chemical shifts are given relative to TMS as an internal standard.

---

### Table 3  Nucleophilic Ring Opening of \( \beta \)-Oxirane 2 with Alcohol Promoted by Trimethylsilyl Triflate

<table>
<thead>
<tr>
<th>Entry</th>
<th>( \text{5} )</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ratio (A/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{5a} )</td>
<td>10</td>
<td>7</td>
<td>82</td>
<td>1:0</td>
</tr>
<tr>
<td>2</td>
<td>( \text{5d} )</td>
<td>4</td>
<td>–</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>( \text{5e} )</td>
<td>10</td>
<td>13</td>
<td>66</td>
<td>1:0</td>
</tr>
</tbody>
</table>

*Reagents and conditions: 2 (1 equiv), 5, TMSOTf (1 equiv), CH\(_2\)Cl\(_2\), –10 °C.*

*a* The combined yield of the products.

The ratio of the isolated products.

---

Scheme 3  Nucleophilic ring opening of \( \text{4} \) with \( \text{5a} \) promoted by trimethylsilyl triflate. *Reagents and conditions:* (a) TMSOTf, BF\(_3\)-OEt\(_2\), CH\(_2\)Cl\(_2\).*
El and ESI mass spectra were measured on JEOL JMS-SX102A and JEOL LCMS-ITTOF spectrometers, respectively. FAB mass spectra were obtained with m-nitrobenzyl alcohol (NBA) as a matrix. Melting points were determined on a Yanaco micro melting point apparatus. Analytical TLC was carried out on Merck silica gel 60 F254. Column chromatography was performed on silica gel (Whatkogel C-300, 45–60 μm).

Oxiranes 2 and 4

Pd(OH)2/C (30 mg) was added to 1 or 3 (290.5 mg, 1.10 mmol) in EtOH (110 mL). The reaction mixture was stirred at rt for 12 h under an atmosphere of H2. After filtration, the filtrate was evaporated to dry the crude diol, which was directly dissolved in DMF–THF (5:1, 12 mL). The mixture was treated with 60% NaH in oil (114 mg), and BnCl (0.4 mL, 3.4 mmol) at 0 °C and gradually warmed to r.t. After the mixture had stirred for 6.5 h, ice water (100 mmol) was added and the mixture was extracted with EtOAc (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 1:4); this gave 2 (from 1) or 4 (from 3).

Methyl 2,3-Anhydro-4,6-di-O-benzyl-α-L-mannopyranoside (2)

Yield: 337 mg (86%); Rf = 0.50 (EtOAc–hexane, 1:2); [α]D23 +169.4 (c 1.00, CHCl3).

1H NMR (400 MHz, CDCl3): δ = 7.32–7.25 (m, 10 H), 4.91 (s, 1 H, H1), 4.71 (d, J = 11.6 Hz, 1 H), 4.59 (d, J = 12.0 Hz, 1 H), 4.48 (d, J = 12.0 Hz, 1 H), 4.47 (d, J = 11.6 Hz, 1 H), 3.72 (d, J = 9.2, 4.8, 1.6 Hz, 1 H, H5), 3.64 (d, J = 9.2 Hz, 1 H, H4), 3.62 (dd, J = 9.2, 1.6 Hz, 1 H, H6), 3.56 (dd, J = 9.2, 4.8 Hz, 1 H, H6), 3.45 (t, J = 3.6 Hz, 1 H, H3), 3.29 (d, J = 3.6 Hz, 1 H, H3), 3.08 (s, J = 3.6 Hz, 1 H, H2).

13C NMR (100 MHz, CDCl3): δ = 138.0, 137.3, 128.3, 128.3, 128.2, 128.0, 127.9, 127.9, 127.8, 127.6, 127.4, 95.9, 73.1, 72.0, 68.9, 68.9, 67.1, 55.4, 53.3, 49.6.

HRMS (EI): m/z = 356 [M+].

HRMS (EI): m/z calcd for C21H24O5: 356.1623; found: 356.1622.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.

HRMS (EI): m/z calcd for C21H24O5Na: 358.1632; found: 358.1630.
Methyl 4,6-Di-O-benzyl-3-O-methyl-D-altropyranosido (8A)
A 60% suspension of NaH in oil (84.0 mg, 2.10 mmol) was added to a solution of 2 (93.6 mg, 0.263 mmol) in MeOH (1.05 mL) at 0 °C and the mixture was refluxed for 16 h. H₂O (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 1:1); this gave 8A.

Yield: 77.2 mg (76%); Rₛ = 0.18 (EtOAc–hexane, 1:1); [α]D²⁰ +77.3 (c 0.27, CHCl₃).

¹H NMR (600 MHz, CDCl₃): δ = 7.34–7.25 (m, 10 H), 4.63 (d, J = 11.8 Hz, 1 H), 4.61 (d, J = 3.0 Hz, 1 H), 4.59 (d, J = 11.0 Hz, 1 H), 4.54 (d, J = 12.1 Hz, 1 H), 4.52 (d, J = 12.1 Hz, 1 H), 4.17 (dd, J = 7.4, 4.4, 3.3 Hz, 1 H), 3.95 (dd, J = 5.6, 3.0 Hz, 1 H), 3.90 (dd, J = 7.4, 3.6 Hz, 1 H), 3.70 (dd, J = 10.7, 4.4 Hz, 1 H), 3.66 (dd, J = 10.7, 3.3 Hz, 1 H), 3.56 (dd, J = 5.6, 3.6 Hz, 1 H), 3.45 (s, 3 H), 3.42 (s, 3 H).

¹³C NMR (150 MHz, CDCl₃): δ = 138.1, 138.0, 130.8, 129.3, 127.9, 127.7, 126.7, 102.2, 78.7, 73.5, 71.8, 71.9, 69.5, 69.3, 58.8, 55.8.

MS (EI, 70 eV): m/z = 588 [M⁺].

HRMS (EI): m/z calc for C₃₂H₃₉O₉: 588.1886; found: 588.1886.

Methyl 3,4,6-Tri-O-benzyl-a-D-glucopyranosido (9A) and Methyl 2,4,6-Tris-O-benzyl-a-D-glucopyranosido (9B)
A 60% suspension of NaH in oil (82.2 mg, 2.05 mmol) was added to a solution of 1 (91.5 mg, 0.257 mmol) in EtOH (1.28 mL) at 0 °C and the mixture was refluxed for 2 h. H₂O (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 3:7); this gave 9A [yield: 53.3 mg (45%)] and 9B [yield: 12.4 mg (10%)].

Compounds 10A and 10B
A 60% suspension of NaH in oil (30.2 mg, 0.76 mmol) was added to a solution of 5a (1.76 g, 3.78 mmol) in DME–THF (1:1, 3.8 mL) at 0 °C and the mixture was stirred at r.t. After 30 min, 3 (50 mg, 0.19 mmol) was added to the mixture, which was then stirred at reflux for 2.5 h. H₂O (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 3:7); this gave 10A (78%) and 10B (10%).

Compound 10A
Yield: 106.5 mg (78%); Rₛ = 0.4 (EtOAc–hexane, 1:1); [α]D²⁰ +47.2 (c 1.00, CHCl₃).

¹H NMR (600 MHz, CDCl₃): δ = 7.39–7.29 (m, 20 H), 5.43 (s, 1 H), 4.92 (d, J = 10.7 Hz, 1 H), 4.88 (d, J = 11.0 Hz, 1 H), 4.74 (d, J = 10.7 Hz, 1 H), 4.73 (d, J = 12.1 Hz, 1 H), 4.63 (d, J = 11.0 Hz, 1 H), 4.61 (d, J = 12.1 Hz, 1 H), 4.54 (d, J = 11.0 Hz, 1 H), 4.53 (dd, J = 3.6, 1.1 Hz, 1 H), 4.23 (dd, J = 10.0, 5.2 Hz, 1 H), 4.07 (dd, J = 10.0, 5.2 Hz, 1 H), 3.94 (m, J = 9.3 Hz, 1 H), 3.83 (s, 3 H), 3.75 (s, 3 H).

¹³C NMR (150 MHz, CDCl₃): δ = 129.3, 128.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 126.4, 102.4, 99.3, 98.2, 82.3, 80.1, 78.7, 77.8, 76.8, 76.1, 75.2, 73.6, 70.5, 70.0, 69.4, 67.2, 58.4, 55.8, 55.5.

MS (FAB) (MeCN–NBA + Na⁺): m/z = 752 [M + Na⁺].

HRMS (FAB) (MeCN–NBA + Na⁺): m/z calc for C₃₄H₄₃O₁₁Na: 843.3720; found: 843.3719.

Compounds 11A and 11B
A 1.6 M solution of MeLi in Et₂O (0.88 mL, 1.4 mmol) was added to a solution of 5a (650 mg, 1.4 mmol) in DMSO (1.40 mL) at 0 °C and the mixture was stirred at r.t. After 0.5 h, 4 (50 mg, 0.14 mmol) was added and the mixture was refluxed for 4 h. H₂O (100 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 100 mL). The crude product was purified by chromatography (silica gel, EtOAc–hexane, 1:3); this gave the mixture of 11A and 11B.

Yield: 108.2 mg (95%); 11A/11B = 2.9:1.

Compound 11A
Rₛ = 0.45 (EtOAc–hexane–acetone, 1:1); [α]D²⁰ +41.0 (c 0.50, CHCl₃).

¹H NMR (600 MHz, CDCl₃): δ = 7.35–7.07 (m, 20 H), 5.43 (s, 1 H), 4.87 (d, J = 11.0 Hz, 1 H), 4.74 (d, J = 11.0 Hz, 1 H), 4.73 (d, J = 2.5 Hz, 1 H), 4.70 (d, J = 12.0 Hz, 1 H), 4.66 (d, J = 10.7 Hz, 1 H), 4.58 (d, J = 12.0 Hz, 1 H), 4.58 (d, J = 3.9 Hz, 1 H), 4.54 (d, J = 10.7 Hz, 1 H), 4.21 (dd, J = 10.2, 4.7 Hz, 1 H), 4.15 (dd, J = 11.7, 2.2 Hz, 1 H), 3.87 (t, J = 9.6 Hz, 1 H), 3.84 (dd, J = 11.7, 2.2 Hz, 1 H), 3.74 (dd, J = 10.2, 5.0 Hz, 1 H), 3.67–3.64 (m, 4 H), 3.59 (dd, J = 9.9, 2.2, 2.2 Hz, 1 H), 3.46 (m, 1 H), 3.45 (dd, J = 9.6, 3.9 Hz, 1 H), 3.38 (s, 3 H), 3.27 (s, 3 H).

¹³C NMR (150 MHz, CDCl₃): δ = 128.9, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.9, 127.5, 127.5, 126.0, 101.4, 99.8, 98.2, 81.9, 81.2, 80.9, 80.0, 72.2, 75.7, 75.1, 73.4, 73.2, 70.3, 69.0, 62.7, 55.4, 55.3.

MS (FAB) (MeCN–NBA + Na⁺): m/z = 752 [M + Na⁺].

HRMS (FAB) (MeCN–NBA + Na⁺): m/z calc for C₃₄H₄₃O₁₁Na: 875.3095; found: 875.3070.
Acknowledgment

We wish to thank Ms. J. Shimode, Ms. A. Tonoki, and Ms. A. Kawaji for spectroscopic measurements. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, Culture and Technology, Japan. Support from the Takeda Research Foundation, Uehara Memorial Foundation, and Research Foundation for Pharmaceutical Sciences to H.T. are gratefully acknowledged.

References


(14) In every reaction, the theoretical amount of alcohol was recovered almost completely.
(15) The product was derivatized as its acetate to confirm the structure.

(20) TMSOTf might be deactivated by partially deprotected oxirane and product, which would lower the yield of 12.