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A Potential Glucuronate Glycosyl Donor with 2-O-acyl-6,3-lactone Structure: Efficient Synthesis of Glycosaminoglycan Disaccharides

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ABSTRACT

Development of β-selective glucuronosylation reaction using phenyl 2,4-di-O-acyl-1-thio-β-D-glucopyranosidurono-6,3-lactone was described. Glycosylations of this glycosyl donor with hexosamine derivatives proceeded with excellent yield and β-stereoselectivity to afford glycosaminoglycan-type disaccharides.

Hence, we designed glucuronate derivative 1 as a key synthon for synthesis of GAGs fragments (Fig. 1), since GAGs contain the β-GlcA moiety in repeating disaccharide units. The conformation of 1 is fixed by a 6,3-lactone bridge in C1a, with all substituents in an axial orientation. In more axial rich conformation, the reactivity increase is expected due to the different mode of σ-σ* or dipole interactions. Also, to enhance 1,2-trans stereoselectivity, to suppress side reactions in coupling steps, and to enhance the activation of the thioglycoside, we selected a well-used 2-O-acyl protection to employ neighboring group participation. In addition, the rigid 3,6-lactone structure might also activate the orthoester-type intermediate formed by the participation of the 2-O-acyl group on donor 1.

Donors

Acceptors

Figure 1. donors and acceptors employed in this study. MP: p-methoxy phenyl.
Table 1. Glycosylations with GalN₃ derivative 5 under NIS/TIOH system

<table>
<thead>
<tr>
<th>#</th>
<th>donor</th>
<th>Conditions⁴</th>
<th>product α:β ratio⁵</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>quant.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>10 (β only)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>trace⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁴(A) donor (1.5 eq.), acceptor (1.0 eq.), NIS (1.5 eq.), TIOH (0.2 eq.), DCM (0.07 M), -40 °C, 1 h; (B) donor (1.2 eq.), acceptor (1.0 eq.), NIS (1.2 eq.), TIOH (0.2 eq.), DCM (0.1 M), -40 °C, 2 h.

⁵Isolated ratio.

⁶Detected only by MALDI-TOF MS.

In summary, we designed a novel glucuronate donor with 6,3-lactone and 2-O-acetyl substituents, we carried out reactions of glucosamine derivative 6 as an acceptor substrate to afford HA type disaccharide. (Table 2, # 1-4) The coupling of donor 1 and acceptor 6 under an optimized condition afforded β-linked disaccharide 15 quantitatively. (# 1) Meanwhile, when C₄ donor 3 was employed, disaccharide 16 was obtained only in 22% yield. (# 2) The glycoside 17 which was obtained from the donor 4 was also unstable at -10 °C. (# 3) By keeping the reaction at -40 °C, however, disaccharide 17 was isolated quantitatively with a slight increase of β-selectivity. (# 4) Thus, the remarkable high yield, β-selectivity, and stability under acidic conditions of glycoside 15 clarified the advantage of donor 1.

In the last place, synthesis of HS type disaccharide was evaluated by using a 2,3-carmamate protected glucosamine derivative 7 as an acceptor which can apply to a donor for α-selective glycosylation⁶ at further glycosylation steps. (# 5-8) Glycosylation reaction to 4-OH of N-acetylglucosamine derivatives is a well-known challenge because of the poor nucleophilicity.⁷ Indeed, the coupling of donor 1 and acceptor 7 at -10 °C gave HS-type disaccharide 18 only in 22% yield. (# 5) Analysis of this reaction revealed the existence of orthoester at -10 °C. This fact suggested that the conversion to the glycoside was incomplete. Tracing the reaction at 0 °C identified that the orthoester disappeared in 3 hours and the β-glycoside 18 was isolated in 63% yield. (# 6) The yield was still moderate but enough for the fragment synthesis as in previous excellent studies.⁸ As expected, a donor 3 with acetyl group at O-2 afforded β-linked disaccharide 19 only in 18% yield. (# 7) Interestingly, disaccharide 20 was stable even at 0 °C and the yield was 93% yield as a α-rich mixture. (# 8)

In summary, we designed a novel glucuronate donor with 6,3-lactone and 2-O-acetyl protection for the construction of glucuronic acid-containing entities. The 6,3-lactone donor 1 demonstrated an excellent versatility via a series of GAGs disaccharide syntheses. In particular, ideal β-selectivities, high yields, and stable glycosides are noteworthy features. Therefore, we believe that donor 1 provides a practical approach to prepare various glycosides and glycoconjugates containing unonate moieties. Currently, further application of this glucuronate donor for longer GAG oligosaccharide synthesis is in progress.

Acknowledgments
We thank S. Oka at the Center for Instrumental Analysis, Hokkaido University, for ESI-MS measurement. This work was supported partly by a grant for a "Promotion for Young Research Talent and Network" from Northern Advancement Center for Science & Technology (NOASTEC) and “Innovation COE Program for Future Drug Discovery and Medical Care” from the Ministry of Education, Culture, Science, Sports and Technology of Japan.

Table 2. Glycosylation with glucosamine derivatives 6 and 7 under NIS/TfOH system

<table>
<thead>
<tr>
<th>#</th>
<th>donor</th>
<th>acceptor</th>
<th>Conditions</th>
<th>product α:β ratio</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6</td>
<td>A</td>
<td>quant.</td>
<td>15 (β only)</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>6</td>
<td>A</td>
<td>22</td>
<td>16 (α only)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>6</td>
<td>A</td>
<td>50</td>
<td>17 (α:β = 5:2)4</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>6</td>
<td>B</td>
<td>quant.</td>
<td>17 (α:β = 5:3)</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>7</td>
<td>A</td>
<td>22</td>
<td>18 (β only)</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>7</td>
<td>C</td>
<td>63</td>
<td>19 (β only)</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>7</td>
<td>C</td>
<td>18</td>
<td>20 (α:β = 7:3)</td>
</tr>
</tbody>
</table>

1(A) donor (1.5 eq.), acceptor (1.0 eq.), NIS (1.5 eq.), TfOH (0.2 eq.), DCM (0.07 M), -40 °C, 1 h, then -10 °C, 1 h; (B) donor (1.2 eq.), acceptor (1.0 eq.), NIS (1.2 eq.), TfOH (0.2 eq.), DCM (0.1 M), -40 °C, 2 h; (C) donor (1.5 eq.), acceptor (1.0 eq.), NIS (1.5 eq.), TfOH (0.2 eq.), DCM (0.07 M), -40 °C, 2 h, then 0 °C, 3 h.

2Isolated ratio.

3Isolated yields based on the acceptor.

4Determined by 1H-NMR analysis.

References and notes


17. See supporting information, Scheme 2.


