An Organocatalytic Regioselective Acylation of Carbohydrates:
Toward the Development of Intelligent Catalysts

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Abstract: A catalytic one-step procedure for the chemo- and regioselective acylation of carbohydrates has been developed. With 1 mol% of an organocatalyst, acylation of octyl β-d-glucopyranoside took place preferentially on the secondary hydroxyl group at C(4) among four hydroxyl groups including the primary hydroxyl group at C(6) in 99% selectivity and in 98% yield. Competitive acylation between primary and secondary hydroxyl groups usually takes place chemoselectively at the primary one. On the other hand, with the present catalyst, chemoselective acylation in favor of a secondary hydroxyl group and regioselective acylation in favor of one out of three secondary hydroxyl groups can be performed with perfect selectivity.

1. Introduction

Chemo- and regioselective manipulation of one of the multiple hydroxyl groups of carbohydrates has been a fundamental challenge in organic synthesis. Carbohydrates are involved in a wide range of biological processes including infection, metastasis, and differentiation. In order to clarify the mechanism of these events and to develop new therapeutics, chemical synthesis of carbohydrates is indispensable. However, synthetic methods of carbohydrates have been relatively unexplored. Multistep protection/deprotection procedures are usually required for their synthesis because of the lack of reliable methods for the chemo- and regioselective manipulation of one of the multiple hydroxyl groups of carbohydrates.

For example, selective acylation of a primary hydroxyl group of octyl β-d-glucopyranoside has been achieved in 100% chemoselectivity by enzymatic processes, however, highly selective acylation of a certain secondary hydroxyl group of glucopyranosides had never been achieved even by enzymatic methods.

Here we describe the development of a catalytic one-step procedure for the chemo- and regioselective acylation of carbohydrates. The present method enables direct functionalization of one of the multiple hydroxyl groups of carbohydrates in up to >99% regioselectivity. With catalyst 5, acylation of octyl β-d-glucopyranoside took place preferentially on the secondary hydroxyl group at C(4) among four hydroxyl groups including the primary hydroxyl group at C(6) in >99% selectivity and in 98% yield (Figure 1b). This could be alternatively achieved by a conventional protection/deprotection procedure via five steps and in 46% overall yield (Figure 1a). Catalyst 5 promotes acylation exclusively at an intrinsically less reactive hydroxyl group via discrimination of four hydroxyl groups in different micro environments. Catalyst 5 enables to perform conventionally difficult molecular transformation via fine molecular recognition of the substrate structure. Accordingly, it may be an intelligent catalyst.

![Figure 1](image-url)
2. Current Aspects on Selective Acylation of Carbohydrates

Selective acylation of a primary hydroxyl group in the presence of three secondary hydroxyl groups of octyl β-D-glucopyranoside has been reported in ~100% chemoselectivity by an enzymatic process, however, concomitant diacylation was unavoidable (Scheme 1).²

Scheme 1

![Scheme 1](image)

Hu and Vesella reported that benzoylation of methyl 6-O-TBDPS-β-D-glucopyranoside with Oriyama's catalyst⁵ and benzoyl chloride gave the 4-O-benzoyl derivative in 84% yield (Scheme 2).⁶ Moitessier and coworkers have also reported highly selective 3-O-acetylation of 6-O-protected methyl α-D-glucopyranoside in up to 93% selectivity, albeit in relatively low yields (40-65%).⁷

Scheme 2

![Scheme 2](image)

We reported highly selective 3-O-acylation of 6-O-protected glucose derivatives. Treatment of octyl 6-O-TBS-β-D-glucopyranoside with isobutyric anhydride in the presence of 10 mol% of DMAP and 2,4,6-collidine in toluene at -20 °C for 7 days gave octyl 3-O-isobutyryl-6-O-TBS-β-D-glucopyranoside in a perfect regioselectivity (>99%) and in 89% yield for monoacylation (Scheme 3).³ We assume that high regioselectivity observed in the present study is the result from the intrinsically high reactivity of C(3)-OH due to intramolecular hydrogen-bonding networks of the 6-O-TBS octyl β-D-glucopyranosides. The success in achieving high regioselectivity may rely on the proper choice of substrates and an acid anhydride. Substrates with high solubility in non-polar solvents should enhance the intramolecular hydrogen-bonding networks of the carbohydrates. Isobutyric anhydride works effectively in the discrimination of hydroxyl groups on acylation because of its steric effects as well as its high kcat/kuncat ratio.⁹

Scheme 3

![Scheme 3](image)

Since the primary hydroxyl group at C-6 of glucose derivatives has the highest intrinsic reactivity, the selective introduction of an acyl group at C(6)-OH of carbohydrates is a reasonable consequence. On the other hand, chemoselective acylation of a secondary hydroxyl group in the presence of a free primary hydroxyl group is much more difficult. Yoshida and coworkers reported chemoselective acylation of a secondary hydroxyl group at C(4) of octyl α-D-glucopyranoside in 61% selectivity with an acetic anhydride-DMAP system, where diacylation was minimized by the use of less (0.70 equiv.) acetic anhydride.¹⁰ Recently, Griswold and Miller reported an excellent approach to the selective introduction of an acetyl group at a secondary hydroxyl group of octyl β-D-glucopyranoside by using peptide-based chiral catalysts (Scheme 4).¹¹ Moderately selective 4-O-acylation has been achieved in a ratio of 22:58:11:9 for 6-O-, 4-O-, 3-O-, and 2-O-acylate, respectively, without the formation of diacylates.

Scheme 4

![Scheme 4](image)

Kattnig and Albert reported reversal of regioselectivity of acylation depending on the acylating agent.¹² Treatment of octyl β-D-glucopyranoside with acetyl chloride in the presence of DMAP gave the 6-O-acetate in 85% selectivity in 73% yield, while that with acetic anhydride gave the 3-O-acetate in 57% selectivity in 60% yield (Scheme 5).

Scheme 5

![Scheme 5](image)

Selective acylation of a primary hydroxyl group of carbohydrates has been achieved in high chemoselectivity by various methods, however, highly selective methods for the direct introduction of an acyl group at a certain secondary hydroxyl group of carbohydrates has not yet been achieved.¹³ Recently, a multi-step, but one-pot method for regioselective protection of glucose derivatives has been developed.¹⁴
3. Design of Catalyst for Selective Acylation of a Secondary Hydroxyl Group in the Presence of a Free Primary Hydroxyl Group

Figure 2 shows a hypothetical picture of transition-state molecular assembly between the acylpyridinium ion generated from a functionalized 4-pyrrolidinopyridine (PPY) derivative and a carbohydrate substrate, which enables the selective acylation of a secondary hydroxyl group in the presence of a primary hydroxyl group. Since the primary hydroxyl group at C(6) of carbohydrates is the most reactive, it would preferentially form an H-bond with an amide carbonyl group of a catalyst. If additional interactions of the hydroxyl groups at C-2 and/or C-3 with a functionality (R) of the catalyst are operative, the combined effects of these attractive interactions would fix the conformation of the carbohydrate, where the hydroxyl group at C-4 is in close proximity to the reactive acyl group of the acyl pyridinium ion, so that it would selectively be acylated.

We chose tryptophan as a functional side chain (NHR in Figure 2) of the catalyst because its indole substructure is expected to be suitable for carbohydrate recognition through H-bonding and/or CH–π interaction. It has been also reported that pyrrole units, similar to indole units, were effectively used as recognition sites for carbohydrates. The notion that tryptophan can be used as a carbohydrate recognition site is also suggested by the facts that two tryptophan residues are highly preserved in the substrate-recognition site of a family of β-glucosidases. Based on these backgrounds, catalysts 1–4 and 5–6 were prepared from trans-4-hydroxy-L-proline and L-pyroglutamic acid, respectively. Catalysts 1–4 were designed with an expectation that the indole unit of catalysts in the C(4)-side chain would be located in proximity to the catalytically active pyridine nitrogen due to the turn structure caused by proline. Since the relative orientation of two indole units was supposed to be concerned with recognition of the substrate, all possible stereoisomers of dipeptides consisting of proline and tryptophan were introduced at C(4) of the pyrrolidine ring. C2-symmetric chiral PPYs 5 and 6 with two identical side chains consisting of L-, or D-tryptophan were also prepared. Octyl esters in 5 and 6 were employed under the expectation to enhance the solubility of catalysts in non-polar solvents where H-bonding works more effectively.

4. Regioselective Acylation of Octyl β-D-Glucopyranoside with Catalysts 1–6

Isobutyric anhydride was employed as an acylating agent because it has been known to show high selectivity in acylative kinetic resolution of racemic alcohols due to the high kcat/kuncat ratio. Effects of catalysts on regioselectivity of acylation of octyl β-D-glucopyranoside were investigated (Table 1). 0.08 M Solution of octyl β-D-glucopyranoside in toluene was treated with 1.1 mol equiv. of isobutyric anhydride in the presence of 10 mol% of a catalyst and 1.5 equiv. of collidine at 20 °C for 12 h (Table 1). Analysis of the products was unambiguously performed by the comparison with authentic samples of 6-O-, 4-O-, 3-O-, and 2-O-isobutyryl octyl β-D-glucopyranosides, which were independently prepared via conventional protection-deprotection sequences. With DMAP as a catalyst, four monoacylates, 6-O-, 4-O-, 3-O-, and 2-O-isobutyryl octyl β-D-glucopyranosides, were obtained in a ratio of 36:26:26:12 in a combined yield of 47% together with 22% of the diacylates and 31% recovery (entry 1). Thus, totally random acylation took place by DMAP-catalysis. With catalysts 2–4 acylation took place in the regioselectivity similar to that with DMAP, giving the 6-O-acylate as the major product (entries 3–5). On the other hand, in the acylation with catalyst 1 the secondary hydroxyl group at C(4) was predominantly acylated (60%) even in the presence of a free primary hydroxyl group at C(6) (entry 2). These observations indicate that the relative orientation of two indole units of catalysts is critically involved in the selective acylation of one out of four hydroxyl groups of octyl β-D-glucopyranosides. We further investigated acylation of octyl β-D-glucopyranoside with C2-symmetric catalysts 5 and 6. Selectivity for monoacylation as well as 4-O-acylation were significantly increased in to 84% and 86%, respectively, when catalyst 5 with L-tryptophan side chain was employed (entry 6).

Solvent effects on the regioselectivity of acylation of octyl β-D-glucopyranoside with 5 were investigated (Table 2). In addition to toluene used in Table 1, CHCl3, THF, and DMF were examined. The polarity of the solvents roughly correlated with the chemo- and regioselectivity of acylation. The highest selectivities for monoacylation (90%) and 4-O-acylation (91%) were observed in CHCl3 (entry 2), whereas the primary hydroxyl group was predominantly acylated (63%) in...
the reaction in DMF (entry 4). The observed solvent effects suggest that H-bonding rather than CH–π interaction between a substrate and a catalyst may be responsible for the selective 4-O-acylation. Another interesting phenomenon is that a higher ratio of 4-O-acylation is associated with a higher yield for monoacylation (entries 1–4), which suggests that acylation of the secondary hydroxyl group at C-4 would proceed in an accelerative manner.

Temperature effects of acylation of octyl β-D-glucopyranoside with 5 were investigated (Table 3). A decrease in the reaction temperature to 0 °C increased the regioselectivity for 4-O-acylation to 98% (entry 2). The reaction was carried out with a substrate concentration of 0.08 M. The reaction was carried out with a substrate concentration of 0.1 M.

Table 1. Effects of catalysts on regioselectivity of acylation of octyl β-D-glucopyranoside.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>monoacylate (%)</th>
<th>regioselectivitya</th>
<th>diacylate (%)</th>
<th>recovery (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>DMAP</td>
<td>47</td>
<td>36 : 26 : 26 : 12</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>66</td>
<td>30 : 60 : 10 : 0</td>
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<tr>
<td>4</td>
<td>3</td>
<td>67</td>
<td>55 : 33 : 10 : 1</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>62</td>
<td>49 : 39 : 11 : 1</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>84</td>
<td>11 : 86 : 3 : 0</td>
<td>12</td>
<td>2</td>
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<tr>
<td>7</td>
<td>6</td>
<td>71</td>
<td>20 : 73 : 7 : 0</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

a % Regioselectivity among four monoacylates.

Table 2. Solvent effects on regioselectivity of acylation of octyl β-D-glucopyranoside with 5.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>monoacylate (%)</th>
<th>regioselectivitya</th>
<th>diacylate (%)</th>
<th>recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>84</td>
<td>11 : 86 : 3 : 0</td>
<td>12</td>
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<td>2</td>
<td>CHCl3</td>
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<td>4 : 91 : 5 : 0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>51</td>
<td>27 : 51 : 22 : 0</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>63</td>
<td>12 : 24 : 1</td>
<td>26</td>
<td>21</td>
</tr>
</tbody>
</table>

a % Regioselectivity among four monoacylates. b The reaction was carried out with a substrate concentration of 0.08 M. c The reaction was carried out with a substrate concentration of 0.1 M.

Table 3. Effects of temperature on regioselectivity of acylation of octyl β-D-glucopyranoside with 5 in CHCl3.

<table>
<thead>
<tr>
<th>entry</th>
<th>mol% of 1</th>
<th>temperature (°C)</th>
<th>time (h)</th>
<th>monoacylate (%)</th>
<th>regioselectivitya</th>
<th>diacylate (%)</th>
<th>recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>90</td>
<td>4 : 91 : 5 : 0</td>
<td>4</td>
<td>3</td>
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<tr>
<td>2</td>
<td>10</td>
<td>0</td>
<td>12</td>
<td>97</td>
<td>0 : 98 : 2 : 0</td>
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<td>97</td>
<td>2 : 96 : 2 : 0</td>
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<td>10</td>
<td>-20</td>
<td>12</td>
<td>98</td>
<td>0 : 99 : 1 : 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>-20</td>
<td>24</td>
<td>98</td>
<td>0 : 99 : 1 : 0</td>
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<tr>
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<td>10</td>
<td>-50</td>
<td>38</td>
<td>98</td>
<td>0 : 99 : 1 : 0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

a % Regioselectivity among four monoacylates.
5. Mechanistic Investigation for Regioselective Acylation Catalyzed by 5

Highly regioselective acylation of the secondary hydroxyl group at C(4) of octyl β-D-glucopyranoside was achieved by 5. The selective acylation at C(4)-OH, however, might be the result from migration of the 6-O-aclyate into the 4-O-aclyate. In order to examine this possibility, the 6-O-isobutyrate of octyl β-D-glucopyranoside was independently prepared and was treated under the reaction conditions similar to those in entry 2 in Table 3, except that isobutyric anhydride was absent. The 6-O-isobutyrate was recovered in 99% yield and migration into the 4-O-isobutyrate did not observed at all. This clearly indicates that acylation of secondary alcohol at C(4)-OH took place directly under the influence of catalyst 5.

Scheme 7

In order to estimate the hypothesis that H-bonding between primary hydroxyl group at C(6) of a carbohydrate substrate and a catalyst is critical for the regioselectivity, the 6-OMe derivative of octyl β-D-glucopyranoside was prepared and treated under the reaction conditions similar to those in entry 4 in Table 3 (Scheme 8a). The 4-O-, 3-O-, and 2-O-isobutyrates were obtained in a ratio of 31:67:2 in a combined yield of 95%. Non-selective acylation of octyl β-D-glucopyranoside took place to give the 6-O-, 4-O-, 3-O-, and 2-isobutyrate in a ratio of 38:23:38:1 in a combined yield of 69% when DMAP was employed as a catalyst (Scheme 8b). Accordingly, catalyst 5 behaves like the non-selective catalyst, DMAP, when the primary hydroxyl group at C(6) is protected. These results indicate that H-bonding between primary hydroxyl group at C(6) of the carbohydrate substrate and the catalyst is critically involved in regioselective acylation caused by 5.

Scheme 8

(a) 

(b) 

Effects of the catalyst functionality on the regioselectivity of acylation were then investigated (Table 4). With catalyst 7 and 8 in which the indole substructure of 5 was replaced by an N-Me surrogate or by 2-naphthalene, respectively, acylation at the secondary hydroxyl group at C(4) took place predominantly, but with decreased regioselectivity (60-65%, entries 2 and 3). The observation suggests two important factors for the regioselectivity; (1) H-bonding between primary hydroxyl group at C(6) of the carbohydrate substrate and the catalyst, and (2) H-bonding between indole NH of catalyst 5 with another hydroxyl group of the carbohydrate substrate.

Table 4. Effects of catalysts on regioselectivity of acylation of octyl β-D-glucopyranoside.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>monoacylate (%)</th>
<th>regioselectivity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>diacylate (%)</th>
<th>recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>97</td>
<td>6-0 : 4-0 : 3-0 : 2-0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>69</td>
<td>14 : 60 : 26</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>74</td>
<td>7 : 65 : 28</td>
<td>0</td>
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<td>13 : 66 : 20</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>DMAP</td>
<td>61</td>
<td>33 : 24 : 43</td>
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</tr>
<tr>
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</tbody>
</table>
<sup>a</sup> % Regioselectivity among four monoaclaytes.

The notion of accelerative acylation is experimentally supported by the competitive acylation between octyl...
β-D-glucopyranoside and a primary alcohol or a secondary alcohol (Scheme 9). When a 1:1 mixture of octyl β-D-glucopyranoside and 2-phenylethanol was treated under the conditions similar to those in entry 4 of Table 3, octyl 4-O-isobutyryl β-D-glucopyranoside was obtained in 99% regioselectivity and in 98% yield for monoacylation (Scheme 9a). Similarly, competitive acylation between octyl β-D-glucopyranoside and 1-phenylethanol (racemic) gave the 4-O-isobutyrate in >99% regioselectivity and in 99% yield for monoacylation (Scheme 9b). The existence of the primary or secondary alcohol did not affect the selective acylation of the carbohydrate at all, indicating that acylation of the secondary hydroxyl group at C(4) of the carbohydrate with 5 proceeds in an accelerative manner.

Scheme 9

(a) octyl β-D-glucopyranoside
(b) octyl β-D-thioglucopyranoside
(c) octyl α-D-glucopyranoside
(d) octyl β-D-mannopyranoside
(e) octyl β-D-galactopyranoside

The C2-symmetric structure of 5 seems to be important. An approach of the carbohydrate substrate from the face of the C(2')-side chain of the acylpyridinium ion generated from 5 would lead to the transition state structure shown in Figure 4, which is supposed to be identical with that caused by the substrate approach from the face of the C(5')-side chain. This notion was supported by the results of the corresponding reaction with non-C2-symmetric catalyst 9 (Table 4, entry 4). Acylation of octyl β-D-glucopyranoside with 9 gave the 4-O-acylate as the major product, but in the decreased regioselectivity of 66% (entries 1 vs. 4). A substrate approaching from the β-face (the face of the C(2')-side chain) of the acylpyridinium ion generated from 9 would undergo selective acylation at C(4)-OH, while a substrate approaching from the less-hindered α-face (C(5')-side chain is absent in 9) would undergo non-selective acylation. As the result, 4-O-acylation proceeded preferentially, but in the diminished regioselectivity in the acylation with 9.

6. Scope of Regioselective Acylation of Various Monosaccharides

Regioselective acylation of various monosaccharides with 5 was examined. The results are summarized in Figure 5. Acetylation of octyl β-D-glucopyranoside with 1 mol% of 5 at −20 °C for 24 h gave the 4-O-acetyl derivative in 96% regioselectivity and in 96% yield for monoacylation (Figure 5a). Acylation of octyl β-D-thioglucopyranoside with isobutyric anhydride or acetic anhydride at −60 °C gave the 4-O-isobutyrate in 97% regioselectivity (92% yield for monoacylation) or the 4-O-acetyl derivative in 95% regioselectivity (99% yield for monoacylation), respectively (Figure 5b). The acylated thioglycosides are expected to be used directly for glycosylation because thioglycosides can be used as glycosyl donors. Acylation of octyl α-D-glucopyranoside with isobutyric anhydride at 20 °C gave the 4-O-isobutyrate surrogate as a major product but with a largely diminished selectivity (54% regioselectivity and 75% yield for monoacylation, Figure 5c). Acylation of octyl β-D-mannopyranoside with isobutyric anhydride at −50 °C gave the 4-isobutyrate derivative in 85% regioselectivity and in 61% yield for monoacylation (Figure 5d). Acylation proceeded preferentially on the secondary hydroxyl group at C-4 in glucopyranosides and in a mannopyranoside in which C(4)-OH is equatorially oriented (Figure 5a-d). On the other hand, acylation of octyl β-D-galactopyranoside, whose C(4)-OH is axially oriented, took place predominantly at the primary hydroxyl group at C(6) (Figure 5e). This indicates that equatorial orientation is crucial for the selective acylation of C(4)-OH.

The transition state molecular assembly shown in Figure 4 may reasonably explain the difference in the regioselectivity profiles of acylation of monosaccharides with 5. A difference between octyl β-D-glucopyranoside (Figure 5a) and octyl β-D-mannopyranoside (Figure 5d) is the orientation of the hydroxyl group in which C(4)-OH is equatorially oriented, took place predominantly at the primary hydroxyl group at C(6) (Figure 5e). This indicates that equatorial orientation is crucial for the selective acylation of C(4)-OH.
tion state assembly shown in Figure 4, selective 4-O-acylation is also expected for the mannose derivative (85% regioselective acylation). On the other hand, a transition state assembly shown in Figure 4 is not possible with carbohydrates that have an axial hydroxyl group at C(4). Accordingly, acylation of the galactose derivative proceeded in a totally different manner, and gave the 6-O-acylate as a major product (Figure 5e), because the intrinsically most reactive primary hydroxyl group should be acylated preferentially in the absence of effective control by the catalyst. In the case of octyl \( \alpha \)-D-glucopyranoside (Figure 5c), a transition state assembly shown in Figure 4 may be possible, however, it is somewhat disfavored by the unfavorable interaction between an \( \alpha \)-octyloxy substituent at C(1) of the carbohydrate with the acylpyridinium ion. Accordingly, acylation of C(4)-OH of octyl \( \alpha \)-D-glucopyranoside took place predominantly, but in the diminished regioselectivity (54%).

7. Conclusions

We have developed highly chemo- and regioselective acylation of carbohydrates by organocatalysis. With catalyst 5, acylation of the secondary hydroxyl group at C(4) of octyl \( \beta \)-D-glucopyranoside proceeds exclusively even in the presence of a free primary hydroxyl group. The present method enables direct functionalization of one of the multiple hydroxyl groups of carbohydrates. We expect that the protocol for the regioselective protection may be applicable to regioselective activation of one of multiple hydroxyl groups of carbohydrates. Ultimate goal of this research is its application to total synthesis of polyol natural products in extremely short steps through direct activation and protection of one of the multiple hydroxyl groups under the control by intelligent catalysts.

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References

13) Recently, site-selective acylation of erythromycin has been developed, see: Lewis, C. A.; Miller, S. J. Angew. Chem. Int. Ed. 2006, 45, 5616.
Takeo Kawabata is Professor of Kyoto University. He was born in Osaka in 1955. He received his Ph.D. degree in 1983 from Kyoto University under the guidance of Professor Eiichi Fujita. After working as a postdoctoral fellow (1983–1985) at Indiana University with Professor Paul A. Grieco, he joined Sagami Chemical Research Center as a researcher (1985–1989). He was appointed Assistant Professor of Institute for Chemical Research, Kyoto University in 1989, promoted to Associate Professor in 1998, and to Professor in 2004. He received the Pharmaceutical Society of Japan Award for Young Scientists in 1995. His research interests include organocatalysis for fine organic synthesis, enolate chemistry with dynamic chirality, and asymmetric synthesis.