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# Functionalized DMAP catalysts for regioselective acetylation of carbohydrates

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**Abstract**—New functionalized DMAPs having carboxylic acid functionality are developed for regioselective acylation of carbohydrates. In these catalysts, DMAP (4-(*N*,*N*-dimethylamino)pyridine) is linked with −COOH (−COOMe or $-OSO_3H$ in reference catalysts) via methylene spacers of different length at the dimethylamino moiety. Utilizing one of these catalysts, 3-[*N*-decyl-*N*-(4-pyridyl)amino]propionic acid (**1**), regioselectivity for the primary 6-OH group in acetylation of 1-*O*-octyl β-D-glucopyranoside is increased from 16% to 89% with rather improved catalytic activity compared with the parent DMAP. Catalyst **1** regioselectively acetylates both anomers of 1-*O*-octyl glucopyranosides (89% and 88% regioselectivity for β- and α-anomer, respectively) and 1-*O*-octyl galactopyranosides (100% regioselectivity for both anomers) at position 6 in $CHCl_3$, but gives nearly 1:1 mixtures of 4- and 6-monoacetates in the case of 1-*O*-octyl mannopyranosides. Control experiments are done to investigate the mechanistic aspects of regiocontrol. 

## 1. Introduction

High efficiency and specificity of enzymes have been a challenge to chemists. Tremendous effort has been made toward the development of artificial enzymes to mimic and overwhelm Nature's counterparts.[1] Among enzyme reactions, we are particularly interested in regiospecific substitution of carbohydrates. We thus started to investigate acetylation of carbohydrates catalyzed by modified DMAP (4-(*N*,*N*-dimethylamino)pyridine).[2] Recently, several groups reported well-designed chiral acylation catalysts for kinetic resolution of secondary alcohols,[3] which has traditionally been achieved by using esterases. Lüning et al. recently reported selective acylation of diols including a carbohydrate derivative catalyzed by bimacrocyclic pyridines.[4]

We initiated our study by examining the acylation regiochemistry using unmodified DMAP.[5] DMAP-catalyzed acylation of unprotected carbohydrates was conducted, keeping the following points in mind.

1. A small acetyl group was introduced to glycosides to minimize steric influence.
2. Chloroform, a non-hydrogen-bonding solvent, was used, in which hydrogen bonding is effective. In chloroform, catalytic activity of DMAP is high and non-catalytic reaction pathway can be suppressed.
3. Reaction conditions were controlled to suppress introduction of more than one acetyl group.
4. Neutral, mild reaction conditions and a short reaction period were employed to avoid acetyl-group migration that gives thermodynamically stable regioisomers.

Unexpectedly, we found that secondary 3- and 4-OH groups of glucosides and mannosides were preferentially acetylated in the presence of the primary 6-OH group in the DMAP-catalyzed acetylation of glycosides. Detailed control experiments and mechanistic considerations revealed that intramolecular hydrogen-bonding network of carbohydrates facilitates preferential acetylation of secondary 3- and 4-OHs over the primary 6-OH group.

In order to investigate the effect of intermolecular hydrogen bonding interaction on acetylation of carbohydrates, we have introduced a −COOH group to DMAP. Carboxylic acid functionality of the Asp and Glu residue is often found in the active site of enzymes which catalyze glycosyl transfer or hydrolysis of glycosidic linkages,[6] although mechanistic details are not necessarily clear. Herein, we report that in the DMAP system, an interaction between the −COOH group and the carbohydrate can alter the

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**Table 1**. Acetylation of octyl β-D-glucopyranoside catalyzed by DMAP, **1**, **2**, **3**, **4**, and **5** under the reaction conditions shown in Eq. 1

| Catalyst | Product ratio (yield of one regioisomer/total yield) 2-*O*-Acetate | 3-*O*-Acetate | 4-*O*-Acetate | 6-*O*-Acetate | Yield (%)[a] |
|---|---|---|---|---|---|
| DMAP | 0.06 | 0.42 | 0.36 | 0.16 | 95 |
| **1** | 0.03 | 0.24 | 0.28 | 0.45 | 92 |
| **2** | 0.06 | 0.38 | 0.34 | 0.22 | 76 |
| **3** | 0.04 | 0.32 | 0.24 | 0.40 | quant. |
| **4** | 0.02 | 0.31 | 0.25 | 0.42 | quant. |
| **5** | [b] | 0.12 | 0.15 | 0.73 | 86 |

[a] NMR yield of monoacetates relative to $Ac_2O$.
[b] Not detected.

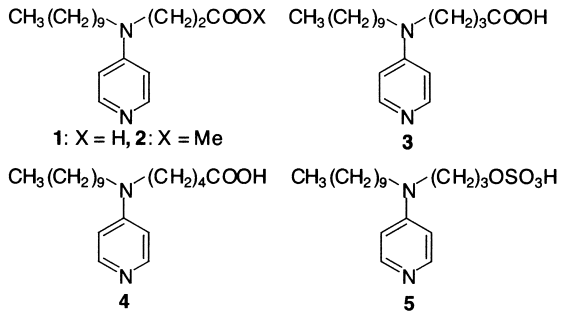
acetylation selectivity without retardation of the reaction, resulting in the regioselective 6-OH acetylation.

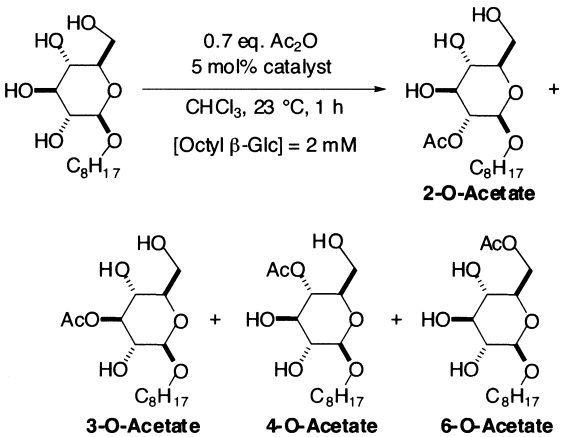
## 2. Results and discussion

### 2.1. Acetylation of octyl β-Glc catalyzed by new functionalized DMAPs

We prepared a series of functionalized DMAPs **1**, **3**, **4** having –COOH with different methylene spacers, and reference catalysts **2** and **5** to examine the effect of the polar functional groups attached to the catalysts on the regioselective acetylation of carbohydrates. Catalysts **1**-**4** were synthesized in an analogous way to the reported method.[7] Catalyst **5** was obtained by reaction of the precursory alcohol with chlorosulfonic acid.[8] All compounds were purified with gel-permeation chromatography and characterized with $^1$H NMR, $^{13}$C NMR and high-resolution mass spectroscopy.

The DMAP-catalyzed acetylation reaction of unprotected glucopyranoside was conducted by mixing substrates, acetylating agents, and catalysts in chloroform as shown in Eq. 1. The yield of each regioisomer was readily determined with $^1$H NMR as already reported[5] and the results are listed in Table 1. It is noteworthy that the parent DMAP preferentially acetylated 3- and 4-OH groups of octyl β-D-glucopyranoside in the presence of the primary 6-OH group under these reaction conditions, and the regioselectivity for the 6-OH group was no more than 16%. Acetic anhydride was found to be a far superior acetylating reagent than acetyl chloride, because less than 1% of acetylated product was formed using acetyl chloride under otherwise the same reaction conditions. Utilizing acetic anhydride as an acetylating reagent and **1**, **3**, or **4** as a catalyst, the regioselectivity for the primary 6-OH group was improved from 16% to 40–45%. Importance of carboxylic acid functionality was obvious from the observation that catalyst **2**, the methyl ester of **1**, brought no increase in regioselectivity. The length of methylene spacers of catalyst **1**, **3**, and **4** did not affect regioselectivity significantly. On the other hand, catalyst **5** having a far more acidic $-OSO_3H$ group exhibited much higher regioselectivity (73%) under exactly the same reaction conditions.




(1)

**Table 2**. Acetylation of octyl β-D-glucopyranoside catalyzed by **1**, **2**, **3**, **4**, and **5** in the presence of NaOAc under otherwise the same reaction conditions shown in Eq. 1

| Catalyst | Product ratio (yield of one regioisomer/total yield) 2-*O*-Acetate | 3-*O*-Acetate | 4-*O*-Acetate | 6-*O*-Acetate | Yield (%)[a] |
|---|---|---|---|---|---|
| **1** | [b] | 0.09 | 0.16 | 0.75 | quant. |
| **2** | [b] | 0.49 | 0.30 | 0.21 | 52 |
| **3** | 0.03 | 0.19 | 0.16 | 0.62 | quant. |
| **4** | 0.02 | 0.16 | 0.16 | 0.66 | quant. |
| **5** | [b] | 0.11 | 0.15 | 0.74 | 86 |

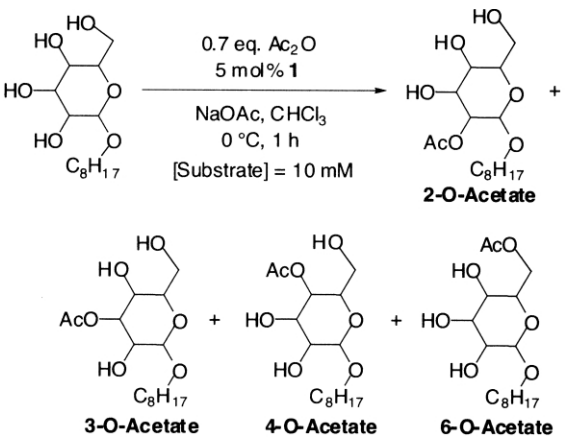
NaOAc (60 mg / 5 mL of chloroform) was added to the reaction mixture.
[a] NMR yield of monoacetates relative to $Ac_2O$.
[b] Not detected.

**Table 3**. Acetylation of monosaccharides catalyzed by **1** under the reaction conditions shown in Eq. 2

| Substrate | Product ratio (yield of one regioisomer/total yield) 2-*O*-Acetate | 3-*O*-Acetate | 4-*O*-Acetate | 6-*O*-Acetate | Yield (%)[a] |
|---|---|---|---|---|---|
| β-Glc | [b] | 0.02 | 0.09 | 0.89 | quant. |
| α-Glc | [b] | [b] | 0.12 | 0.88 | 95 |
| β-Man[c] | [b] | 0.05 | 0.42 | 0.53 | 88 |
| α-Man[c] | [b] | 0.05 | 0.43 | 0.52 | 83 |
| 2-*O*-α-Man | [b] | [b] | 0.50 | 0.50 | quant. |
| β-Gal[d] | [b] | [b] | [b] | 1.0 | 95 |
| α-Gal | [b] | [b] | [b] | 1.0 | quant. |

[a] NMR yield of monoacetates relative to $Ac_2O$.
[b] Not detected.
[c] Diacetylated β-Man and α-Man were formed in less than 10%.
[d] [β-Gal]=5 mM.

To achieve higher regioselection, several basic additives were explored. In the case of the DMAP-catalyzed acetylation, basic additives such as $K_2CO_3$ and 2,6-lutidine had no effect on regioselection.[5] Addition of soluble bases such as 2,6-lutidine and triethylamine had negligible effect on regioselection by **1**. In contrast, addition of solid bases, which are practically insoluble in chloroform, increased regioselectivity without loss of catalytic activity. Among the tested insoluble bases ($Na_2CO_3$, $K_2CO_3$, LiOAc, NaOAc, $Ca(OH)_2$, Amberlyst), NaOAc was found to be best, and increased the regioselectivity (75%) as shown in Table 2. Catalysts **3** and **4** exhibited similar but smaller regioselectivity-increase upon addition of NaOAc. On the other hand, regioselcctivity in **5**-catalyzed acetylation was not improved by addition of NaOAc, as well as in **2**-catalyzed acetylation. Further optimization of the reaction temperature and the substrate concentration revealed that by running the acetylation reaction in 10 mM at 0°C using catalyst **1** in the presence of NaOAc (Eq. 2), 6-*O*-acetyl-β-D-glucoside was produced in the highest regioselectivity (89%).

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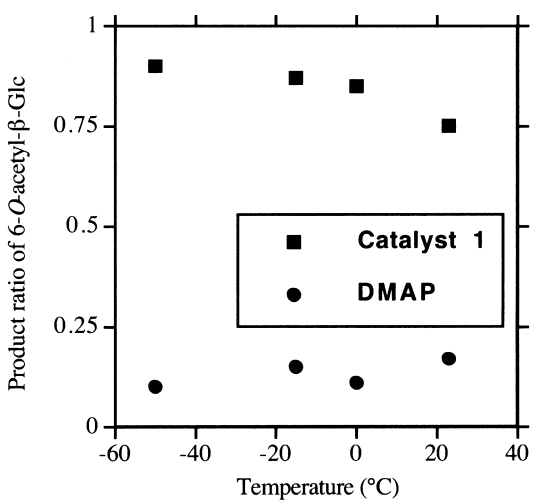



**Figure 1.** Plot of the product ratio of 6-*O*-acetyl-β-Glc against reaction temperatures. Acetylation was run in the presence of NaOAc using catalyst **1** or DMAP at the designated temperature under otherwise the same reaction conditions shown in Eq. (1). Product ratio was determined with $^1H$ NMR.

### 2.2. Regioselective acetylation of various monosaccharides catalyzed by 1. Effect of the substrate structure on regioselectivity

Representative monosaccharides were subjected to **1**-catalyzed acetylation reaction under the reaction conditions optimized for octyl β-Glc as shown in Eq. 2 and the results are listed in Table 3. As reported earlier,[5] the parent DMAP preferentially acetylated 3- and 4-OH of glucoside and mannoside, while it favored acetylation of 6-OH of galactoside. When catalyst **1** having a carboxylic acid functionality was utilized, both anomers of D-glucose and D-galactose were acetylated at position 6. In the case of galactosides, an excellent regioselection was achieved. On the other hand, the secondary 4-OH group in mannopyranosides exhibited reactivity comparable to the primary 6-OH group. Upon replacement of the axial 2-OH group of α-Man by a methoxy group, exactly the same tendency was observed. The catalyst **1** tolerates anomer stereochemistry of D-glucose and D-galactose and regioselectively acetylates both anomers, but is sensitive to the stereochemistry of the neighboring 2-position.

### 2.3. Effect of the reaction temperature on regioselectivity

Temperature effect was different between catalyst 1 and the parent DMAP as shown in Fig. 1. In the case of 1-catalyzed acetylation, lowering the reaction temperature raised the selectivity from 75% to 90%, although at −50°C, the

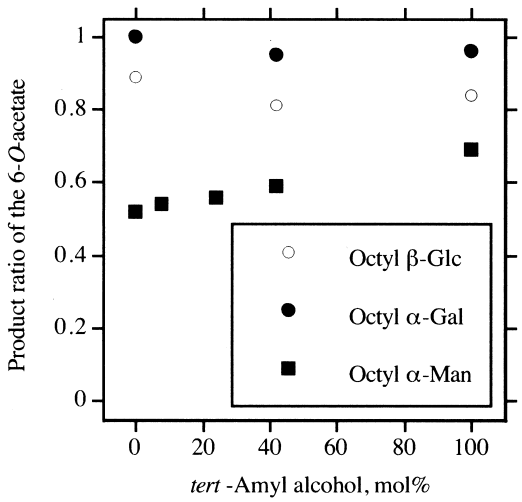



**Figure 2.** Plot of the product ratio of 6-*O*-acetates against alcohol concentration. Acetylation was run in chloroform–*tert*-amyl alcohol cosolvent of the designated mole fraction under otherwise the same reaction conditions shown in Eq. (2). Product ratio was determined with $^1$H NMR.

acetylation reaction was considerably suppressed (98% yield at −15°C, 7% yield at −50°C). On the other hand, lower reaction temperature did not increase the product ratio of 6-*O*-acetyl-β-D-glucopyranoside in the case of DMAP-catalyzed acetylation reaction.

### 2.4. Effect of solvent on regioselectivity

In order to probe the nature of the regioselection, effect of added *tert*-amyl alcohol on regioselectivity was investigated (Fig. 2). Acetylation of glycosides catalyzed by **1** proceeded in chloroform–*tert*-amyl alcohol medium, but the total yield of monoacetates was slightly decreased when acetylation was carried out in chloroform–*tert*-amyl alcohol compared with in pure chloroform. In the case of glucoside and galactoside, no change of regioselectivity was observed in a wide range of the alcohol concentration. Regioselection by **1** is not inhibited by added alcohol. Regioselectivity for the 6-OH group of mannoside, on the other hand, was gradually increased upon addition of *tert*-amyl alcohol.

Then, **1**- or **2**-catalyzed acetylation in several solvents was conducted and the results are listed in Table 4. In chloroform, effectiveness of catalyst **1**, DMAP having a –COOH group, was obvious, and catalyst **1** acetylated β-Glc with both higher regioselectivity and higher catalytic activity than catalyst **2** with a –COOMe group. This was true when polar solvents such as DMF, pyridine or *tert*-amyl alcohol were used as solvent. Notably, a –COOH group which is introduced to DMAP through the flexible methylene spacer discriminates the primary over secondary hydroxy groups, and also improves the catalytic activity of DMAP.

Relatively high regioselection was achieved (84%) when the acetylation reaction was run in *tert*-amyl alcohol, which is a better solvent for dissolving polar compounds like carbohydrates. As a practical-scale experiment, methyl α-D-glucopyranoside and methyl α-D-galactopyranoside (100 mg), which were practically insoluble in chloroform, were subjected to **1**-catalyzed acetylation reaction in *tert*-amyl alcohol. Methyl 6-*O*-acetyl-α-D-glucoside and methyl 6-*O*-acetyl-α-D-glactoside were obtained in 60% and 68% isolated yield, respectively, after chromatographic purification.

### 2.5. Possibility of acetyl migration catalyzed by new functionalized DMAPs

Acyl groups introduced to carbohydrates could be readily migrated to the neighboring OH groups under certain reaction conditions. Even contact with weak bases or silica gel might cause acyl group migration to give thermodynamically stable isomers. Thus, it is important to ascertain whether new functionalized DMAPs do catalyze regioselective acetylation reaction, and not catalyze acetyl migration to the 6-OH group.

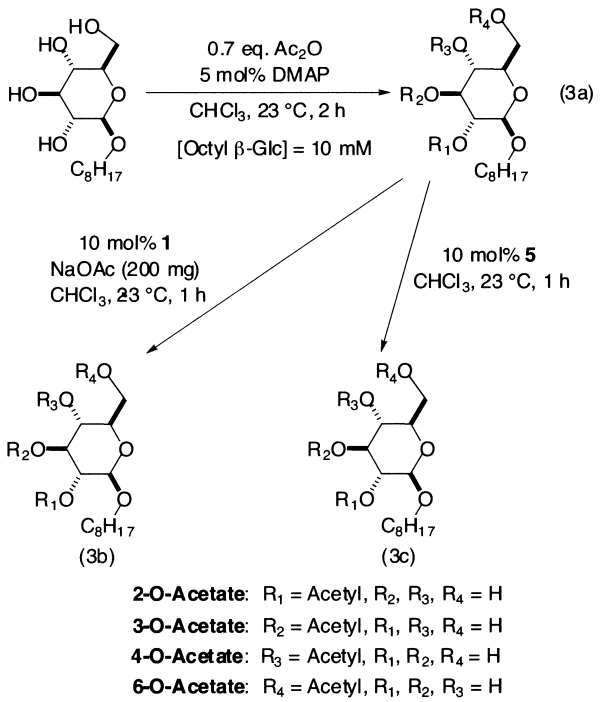
As shown in Eq. (3a), regioisomeric mixtures containing 3- and 4-*O*-acetyl-β-D-glucosides as major regioisomers were generated by DMAP-catalyzed acetylation of octyl β-D-glucopyranoside. Catalyst **1**/NaOAc or **5** was then added to the solution to evaluate the acetyl group migration upon contact with **1**/NaOAc or **5**. As shown in Table 5, the fraction of 6-*O*-acetate did not increase in either case. Therefore, selective acetylation of the primary 6-OH group

**Table 4**. Acetylation of octyl β-D-glucopyranoside catalyzed by **1** or **2**

| Catalyst | Solvent | Product ratio (yield of one regioisomer/total yield) 2-*O*-Acetate | 3-*O*-Acetate | 4-*O*-Acetate | 6-*O*-Acetate | Yield (%)[a] |
|---|---|---|---|---|---|---|
| **1** | $CHCl_3$ | [b] | 0.02 | 0.09 | 0.89 | quant. |
| **2** | $CHCl_3$ | [b] | 0.49 | 0.30 | 0.21 | 52 |
| **1** | DMF | [b] | 0.24 | 0.11 | 0.65 | 43 |
| **2** | DMF | [b] | 0.41 | 0.18 | 0.41 | 15 |
| **1** | Pyridine | [b] | 0.17 | 0.18 | 0.65 | 18 |
| **2** | Pyridine | [b] | 0.24 | 0.24 | 0.52 | 6 |
| **1** | *tert*-amyl alcohol | [b] | 0.11 | 0.05 | 0.84 | 56 |
| **2** | *tert*-amyl alcohol | [b] | 0.34 | 0.10 | 0.56 | 28 |

Acetylation was carried out in the designated solvent under otherwise the same reaction conditions shown in Eq. 2.
[a] NMR yield of monoacetates relative to $Ac_2O$.
[b] Not detected.

catalyzed by **1** or **5** was not due to acetyl migration.




(3)

## 2.6. Effect of the substrate and catalyst aggregation on regioselectivity

Alkyl glycosides tend to be self-aggregated in a non-polar solvent. $^1$H NMR dilution experiments showed that octyl β-D-glucopyranoside starts to form intermolecular hydrogen bonds with each other at 1 to 10 mmol/L in $CDCl_3$ at 22°C.[9] Self-aggregation of carbohydrates might influence the course of the acetylation reaction. We have already reported that DMAP-catalyzed acetylation of carbohydrates did not show concentration dependence.[5] Then, **1**-catalyzed acetylation was conducted at different concentrations of octyl β-D-glucopyranoside at 0°C (Table 6). Although regioselectivity was slightly reduced to 72% at a considerably low concentration (0.5 mM), octyl β-D-glucopyranoside was regioselectively acetylated when acetylation reaction was run at 2, 10, and 20 mM of octyl β-D-glucopyranoside. In addition, regioselectivity was not affected so much by addition of *tert*-amyl alcohol, which causes deaggregation of monosaccharides. These results indicate that self-aggregation of monosaccharides exerts practically no influence on regioselection.

Catalysts **1**, **3**, **4**, and **5**, having both acidic and basic functionality, are also supposed to be aggregated to a considerable extent in chloroform. Thus, effect of self-aggregation of catalysts was also evaluated by running the reaction at different concentrations of catalyst **1** (Table 7). Reliably high regioselectivity was obtained in a wide concentration range of catalyst **1** (from 10 to 500 μmol/L), and the acetylation rate was qualitatively proportional to the catalyst concentration. As already mentioned, regioselective acetylation was not inhibited by addition of *tert*-amyl alcohol, which could affect catalyst aggregation to some extent. Therefore, we can rule out any possibility of a decisive role of catalyst aggregates.

## 2.7. Mechanistic aspects of regiocontrol by functionalized DMAP

A –COOH or $-OSO_3H$ attached to DMAP obviously play a crucial role in regioselective acetylation of glycosides. As shown in Table 1, catalyst **1** having –COOH instead of –COOMe improves the regioselectivity for the 6-OH group from 22% to 45%. Other catalysts having a carboxylic acid group via methylene spacers of different lengths (catalysts **3** and **4**) acetylate the 6-OH group in a similar regioselectivity (40% and 42%, respectively), indicating the importance of carboxylic acid functionality. In addition, catalyst **5** having a far more acidic sulfate group acetylates the 6-OH group of

**Table 5**. Change in the product distribution upon contact with catalyst **1** /NaOAc or catalyst **5**

| | | Product ratio (yield of one regioisomer/total yield) | | | | |
|---|---|---|---|---|---|---|
| | Catalyst | 2-*O*-Acetate | 3-*O*-Acetate | 4-*O*-Acetate | 6-*O*-Acetate | Yield (%)[a] |
| 3a | DMAP | 0.10 | 0.37 | 0.32 | 0.21 | 91 |
| 3b | **1**/NaOAc | [b] | 0.46 | 0.41 | 0.13 | quant. |
| 3c | **5** | [b] | 0.43 | 0.36 | 0.21 | quant |

[a] NMR yield of monoacetates relative to $Ac_2O$.
[b] Not detected.

**Table 6**. Dependence of the product distribution on the concentration of octyl β-D-glucopyranoside in the **1**-catalyzed acetylation of octyl β-D-glucopyranoside

| | Product ratio (yield of one regioisomer/total yield) | | | | |
|---|---|---|---|---|---|
| [β-Glc] (mmol/L) | 2-*O*-Acetate | 3-*O*-Acetate | 4-*O*-Acetate | 6-*O*-Acetate | Yield (%)[a] |
| 0.5 | [b] | 0.14 | 0.14 | 0.72 | quant |
| 2 | [b] | 0.04 | 0.11 | 0.85 | quant |
| 10 | [b] | 0.02 | 0.10 | 0.88 | quant |
| 20 | [b] | 0.02 | 0.09 | 0.89 | quant |

Acetylation was carried out at the designated concentration of β-Glc under otherwise the same reaction conditions shown in Eq. 2.
[a] NMR yield of monoacetates relative to $Ac_2O$.
[b] Not detected.

**Table 7**. Dependence of the product distribution on the concentration of catalyst **1** in the **1**-catalyzed acetylation of octyl β-D-glucopyranoside

| [**1**] (μmol/L) | Product ratio (yield of one regioisomer/total yield) 2-*O*-Acetate | 3-*O*-Acetate | 4-*O*-Acetate | 6-*O*-Acetate | Yield (%)[a] |
|---|---|---|---|---|---|
| 10 | [b] | 0.01 | 0.09 | 0.90 | 27 |
| 51 | [b] | 0.01 | 0.10 | 0.89 | 47 |
| 102 | [b] | 0.01 | 0.09 | 0.90 | 73 |
| 526 | [b] | 0.02 | 0.09 | 0.89 | quant. |

Acetylation was carried out using the designated amount of catalyst **1** under otherwise the same reaction conditions shown in Eq. 2.
[a] NMR yield of monoacetates relative to $Ac_2O$.
[b] Not detected.

β-Glc in much higher regioselectivity (73%) under exactly the same reaction conditions. The above-mentioned results suggest that regioselective acetylation is achieved by bifunctional catalysis of DMAP, and acidic −COOH or $-OSO_3H$. It should be noted that functionalized DMAPs described in this paper do not have any bulky substituent in the vicinity of a nucleophilic site at all. However, the regioselectivity for the primary 6-OH group is substantially increased, and additionally catalytic activity is rather improved compared with the control catalyst **2**. One possible explanation is formation of the zwitterionic acetyl pyridinium intermediate as shown in Fig. 3. Upon activation of acetic anhydride, −COOH or $-OSO_3H$ functionality donates proton to acetic anhydride. The resulting zwitterionic intermediate preferentially acetylates the primary 6-OH group through interaction between $COO^-$ or $-OSO_3^-$ covalently attached to the acetyl pyridinium ion, and sugar hydroxy as depicted in Fig. 3.

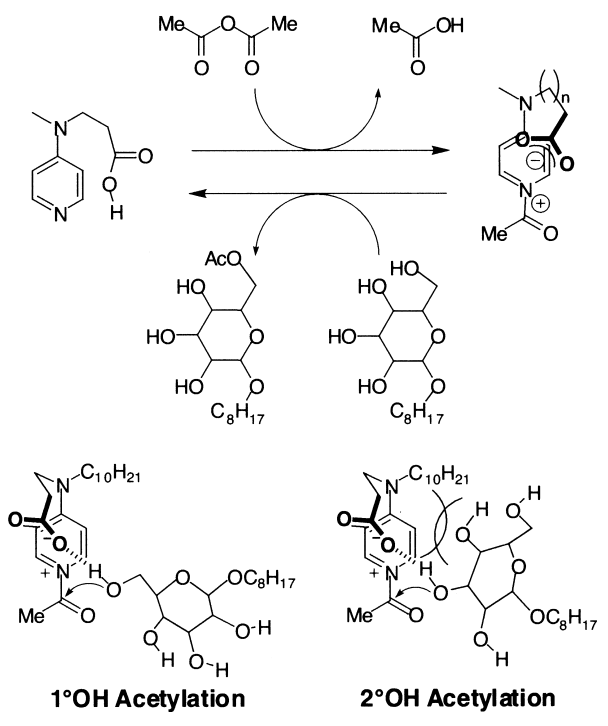



**Figure 3.** Proposed mechanism for regioselective acylation of carbohydrates catalysed by **1**.

## 3. Conclusion

New functionalized DMAPs having carboxylic acid functionality have been developed for regioselective acylation of unprotected carbohydrates. These catalysts do not have any rigid molecular architecture around a nucleophilic site at all. However, regioselectivity for the primary 6-OH group was substantially increased. Althogh regioselection by these simple catalysts remained to be improved from a practical veiwpoint, the present study will provide some clue to the catalyst design for the regioselective substitution of carbohydrates.

## 4. Experimental

### 4.1. Instrumentation

$^1H$ and $^{13}C$ NMR spectra were recorded using a JEOL A-500 spectrometer. $^1H$ and $^{13}C$ NMR chemical shifts in $CDCl_3$ or $CD_3OD$ were referenced to $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77.0 ppm), respectively or $CHD_2OD$ (3.30 ppm) and $CD_3OD$ (49 ppm), respectively. NMR data were collected at 30°C. Gel permeation chromatography (GPC) was performed on Recycling Preparative HPLC (LC-908 or LC-918) equipped with a JAIGEL-2H column (Japan Analytical Industry) and a refractive index detector; flow rate, 3.8 mL $min^{-1}$; mobile, phase, chloroform containing 1% of triethylamine. Water content in chloroform was measured with a Karl-Fischer equipment (HIRANUMA, AQUACOUNTER AQ-7).

### 4.2. Materials

Octyl β-D-glucopyranoside and octyl α-D-glucopyranoside were purchased from Wako Pure Chemical Industries and SIGMA, respectively, and used as received. Preparations of other octyl glycopyranosides were already reported.[10] Chloroform stabilized with 2-methyl-2-butene was purchased from Tokyo Chemical Industry and dried over molecular sieves, 3 Å. Acetic anhydride was purified by distillation after azeotropic removal of acetic acid with toluene. DMF and pyridine were distilled over $P_2O_5$ and $CaH_2$, respectively. *tert*-Amyl alcohol was dried by refluxing with and distilling from sodium. 4-Dimethylaminopyridine (DMAP) was recrystallized from benzene and dried in vacuo. $Na_2CO_3$, $K_2CO_3$, LiOAc, NaOAc and KOAc were dried in vacuo over $P_2O_5$. Column chromatography was carried out with Silica Gel 60 N (spherical, neutral, 40–100 μm) from Kanto Chemicals. $CDCl_3$ was

completely deacidified by passing through activated alumina just before use.

### 4.3. General procedure for the DMAP-catalyzed acetylation

In every experiment, it was confirmed that water content of chloroform was less than 5 ppm. Stock solutions of catalyst **1** and acetic anhydride were prepared beforehand by dissolving **1** (5.2 mg, 17 μmol) in chloroform (1 mL) and acetic anhydride (62.2 mg, 609 μmol) in chloroform (2.7 mL), respectively.

Octyl β-D-glucopyranoside (3.0 mg, 10 μmol) was dissolved in chloroform (1 mL) under Ar. NaOAc (200 mg) was added to the solution. Then the catalyst stock solution (31 μL, 0.53 μmol) was added to the solution via microsyringe. The solution was stirred well with a magnetic stirrer. The temperature was kept at 0°C during the acetylation reaction. Finally, the acetic anhydride stock solution (32 μL, 7.2 μmol) was added to initiate the acetylation reaction. After being stirred for 1 h, the reaction was quenched with methanol (0.2 mL). After 5 min at 0°C, the reaction mixture was passed through a silica gel short column (1 g) to remove the catalyst. Monoacetylated sugars, together with the remaining unreacted sugar, were eluted by ethyl acetate–methanol solvent (4:1; 15 mL). The solvent was evaporated off and the product was dried in vacuo. The product was taken up in chloroform (2 mL) and passed through a polypropylene filter to remove traces of silica gel. The chloroform was then evaporated off. The sample was completely dried in vacuo at room temperature for 4 h and subjected to NMR analysis.

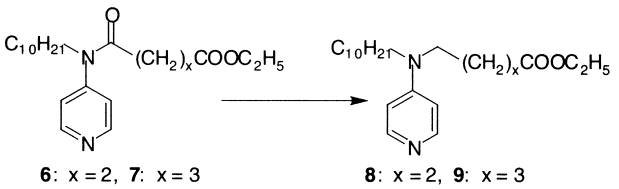
### 4.4. Preparation of 1-5

**4.4.1. 3-[*N*-Decyl-*N*-(4-pyridinyl)amino]propionic acid (1) and methyl 3-[*N*-decyl-N-(4-pyridinyl)amino]propionate (2).** **1** and **2** were synthesized according to the literature.[7] **1** and **2** were purified by GPC using chloroform containing 1% of triethylamine as an eluent. Compounds were passed through the column several times. Purified DMAP derivatives were dissolved in ethyl acetate and washed with distilled water three times and then saturated NaCl solution to remove all traces of triethylammonium hydrochloride. The organic layer was dried over $Na_2SO_4$. The solvent was evaporated off and products were dried in vacuo at 60°C for 12 h.

**1**: GPC $t_R$=44 min; $^1$H NMR ($CD_3OD$, 500 MHz) δ 8.038 (d, *J*=7.5 Hz, 2H), 6.980 (d, *J*=7.5 Hz, 2H), 3.806 (t, *J*=7.3 Hz, 2H), 3.565 (t, *J*=8 Hz, 2H), 2.479 (t, *J*=7.3 Hz, 2H), 1.700-1.600 (m, 2H), 1.400-1.240 (m, 14H), 0.887 (t, *J*=7 Hz, 3H), $^{13}$C NMR ($CD_3OD$, 125.65 MHz) δ 178.39, 157.70, 140.82, 108.50 (signals in the methylene region are omitted.); HRMS calcd for $C_{18}H_{30}N_2O_2$ *m/z* 306.2307, found 306.2303 (EI).

**2**: GPC $t_R$=48 min; $^1$H NMR ($CDCl_3$, 500 MHz) δ 8.179 (d, *J*=6.5 Hz, 2H), 6.432 (d, *J*=7 Hz, 2H), 3.672 (s, 3H), 3.621 (t, *J*=7.3 Hz, 2H), 3.267 (t, *J*=7.8 Hz, 2H), 2.572 (t, *J*=7.5 Hz, 2H), 1.600-1.500 (m, 2H), 1.300−1.190 (m, 14H), 0.858 (t, *J*=6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125.65 MHz) δ 172.03, 151.99, 150.11, 106.51 (signals in the methylene region are omitted.); HRMS calcd for $C_{19}H_{32}N_2O_2$ *m/z* 320.2464, found 320.2462 (EI).

**4.4.2. 4-[*N*-Decyl-*N*-(4-pyridinyl)amino]butyric acid (3) and 5-[*N*-decyl-*N*-(4-pyridinyl)amino]pentanoic acid (4).** Compounds **3** and **4** were synthesized following the reported procedure for the homologs of **3** and **4**,[7] except for the reduction of amide bonds (Eq. 4). Both amide and ester functionality were reduced with the literature method. To prevent reduction of ester functionality, the following method was employed.




**6**: x = 2, **7**: x = 3 **8**: x = 2, **9**: x = 3 (4)

**4.4.3. 4-[*N*-Decyl-*N*-(4-pyridinyl)amino]butyric acid (3).** **6** (528.9 mg, 1.46 mmol) was dissolved in THF (14.6 mL). Borane–THF complex (1 M in THF, 14.6 mL, 14.6 mmol) was added at room temperature and the reaction mixture was heated at 60°C for 5 min. Excess borane was then decomposed by the careful slow addition of 8% HCl in ethanol (40 mL) at 0°C. The mixture was stirred at room temperature for 3 h. After evaporation of the solvent, the residue was dissolved in water (10 mL). The solution was made basic with 1 M NaOH (50 mL) and then extracted with ethyl acetate (50 mL×3). The combined organic phases were washed with saturated aqueous NaCl (20 mL×2) and dried over $Na_2SO_4$. The solvent was evaporated off and the residue was purified by flash column chromatography (chloroform:hexane:triethylamine=5:20:1) to yield **8** contaminated with **6**. Without further purification, the mixture was subjected to the hydrolysis step to yield crude **3**. Purification was performed in exactly the same way as catalyst **1** to give **3** (37.8 mg, 0.118 mmol) in 8% yield.

**3**: GPC $t_R$=42 min; $^1$H NMR ($CD_3OD$: $CDCl_3$=1: 1, 500 MHz) δ 7.961 (d, *J*=6 Hz, 2H), 6.948 (d, *J*=6.5 Hz, 2H), 3.496 (t, *J*=8 Hz, 2H), 3.451 (t, *J*=7.8 Hz, 2H), 2.249 (t, *J*=6.5 Hz, 2H), 1.91-1.82 (m, 2H), 1.68-1.57 (m, 2H), 1.40-1.20 (m, 14H), 0.845 (t, *J*=7 Hz, 3H); $^{13}$C NMR ($CD_3OD$: $CDCl_3$=1: 1, 125.65 MHz) δ 180.00, 156.52, 141.42, 107.81 (signals in the methylene region are omitted.); HRMS calcd for $C_{19}H_{32}N_2O_2$ *m/z* 320.2464, found 320.2457 (EI).

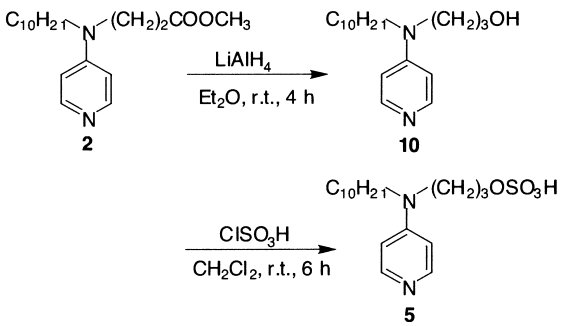
**4.4.4. 5-[*N*-Decyl-*N*-(4-pyridinyl)amino]pentanoic acid (4).** **7** (313.1 mg, 0.83 mmol) was dissolved in THF (29 mL). Borane–THF complex (1 M in THF, 5 mL, 5 mmol) was added at room temperature and the reaction mixture was heated at 60°C for 30 min. Excess borane was then decomposed by the careful slow addition of 8% HCl in ethanol (18 mL) at 0°C. The mixture was stirred at room temperature for 3 h. After the evaporation of the solvent, the residue was dissolved in water (10 mL). The solution was made basic with 1 M NaOH (50 mL) and then extracted

with ethyl acetate (50 mL×3). The combined organic phases were washed with saturated aqueous NaCl (20 mL×2) and dried over $Na_2SO_4$. The solvent was evaporated and the residue was purified by flash column chromatography (chloroform:hexane:triethylamine=5:20:1) to yield **9** contaminated with **7**. Without further purification, the mixture was subjected to the hydrolysis step to yield crude **4**. Purification was performed in exactly the same way as catalyst **1** to give **4** (58.5 mg, 0.175 mmol) in 21% yield.

**4**: GPC $t_R$=45 min; $^1$H NMR ($CD_3OD$: $CDCl_3$=10: 1,500 MHz) $\delta$ 8.024 (d, $J$=7 Hz, 2H), 6.881 (d, $J$=7.5 Hz, 2H), 3.55-3.45 (m, 4H), 2.246 (t, $J$=6.8 Hz, 2H), 1.70-1.60 (m, 6H), 1.40-1.20 (m, 14H), 0.880 (t, $J$=7 Hz, 3H); $^{13}$C NMR ($CD_3OD$: $CDCl_3$=10: 1, 125.65 MHz) $\delta$ 181.50, 157.14, 141.79, 108.22 (signals in the methylene region are omitted); HRMS calcd for $C_{20}H_{34}N_2O_2$ *m/z* 334.2620, found 334.2611 (EI).

**4.4.5. 3-[*N*-Decyl-*N*-(4-pyridinyl)amino]propyl hydrogen sulfate (5).** **5** was synthesized according to Eq. 5 as follows. To a suspension of $LiAlH_4$ (18 mg, 0.47 mmol) in ether (0.5 mL) was added a solution of **2** (101.4 mg, 0.316 mmol) in ether (1.5 mL). The reaction mixture was stirred at room temperature for 4 h and then excess $LiAlH_4$ was decomposed by addition of ethyl acetate and then water. The aqueous solution was extracted with ethyl acetate (10 mL×3) and the combined organic phase was dried over $Na_2SO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (chloroform: hexane:triethylamine=5:2:1) to yield **10** (69.1 mg, 0.236 mmol) in 75% yield.

**10**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 8.060 (d, $J$=6 Hz, 2H), 6.444 (d, $J$=6.6 Hz, 2H), 4.200 (br s, 1H), 3.664 (t, $J$=5.7 Hz, 2H), 3.419 (t, $J$=7.2 Hz, 2H), 3.245 (t, $J$=7.7 Hz, 2H), 1.84-1.74 (m, 2H), 1.59-1.45 (m, 2H), 1.35-1.10 (m, 14H), 0.840 (t, $J$=6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 152.85, 149.23, 106.50 (signals in the methylene region were omitted.); HRMS calcd for $C_{18}H_{32}N_2O$ *m/z* 292.2515, found 292.2520 (EI).




(5)

**10** was converted to **5** according to the method reported for the preparation of 10-[*N*-butyl-*N*-(4-pyridinyl)amino]decyl sulfate.[8] To a solution of **10** (150.7 mg, 0.52 mmol) in $CH_2Cl_2$ (0.5 mL) was added chlorosulfonic acid (133 mg, 1.14 mmol) in $CH_2Cl_2$ (0.92 mL). The reaction mixture was stirred at room temperature for 17 h. The reaction was quenched by the addition of $CH_3OH$ (5 mL) and triethylamine (1 mL), and then the solvent was evaporated. The crude product was passed through a short silica column (chloroform:methanol=1:1) and was then subjected to GPC purification (1% triethylamine–chloroform as eluent). The obtained solid material was suspended in 1 M NaOH (0.5 mL) in saturated NaCl (50 mL), and the aqueous phase was extracted with ethyl acetate (30 mL×3). The combined organic phase was washed with saturated NaCl solution (10 mL×3) and was then dried over $Na_2SO_4$. The solvent was evaporated off and the product was dried in vacuo at 60°C for 12 h. **5** (72.4 mg, 0.19 mmol) was obtained in 37% yield as a viscous oil.

**5**: GPC $t_R$=37 min; $^1$H NMR ($CD_3OD$: $CDCl_3$=1: 1, 500 MHz) $\delta$ 7.992 (d, $J$=4.5 Hz, 2H), 6.575 (d, $J$=6 Hz, 2H), 4.068 (t, $J$=5.8 Hz, 2H), 3.493 (t, $J$=7.3 Hz, 2H), 3.334 (t, $J$=7.8 Hz, 2H), 2.010-1.900 (m, 2H), 1.620-1.500 (m, 2H), 1.430-1.190 (m, 14H), 0.840 (t, $J$=7 Hz, 3H); $^{13}$C NMR ($CD_3OD$: $CDCl_3$=1: 1, 125.65 MHz) $\delta$ 154.16, 147.80, 107.41 (signals in the methylene region are omitted); HRMS calcd for $C_{18}H_{32}N_2O_4S{\cdot}H^+$ *m/z* 373.2161, found 373.2162 (FAB).

### 4.5. 1-Catalyzed acetylation in *tert*-amyl alcohol

**4.5.1. Methyl 6-*O*-acetyl-α-D-glucopyranoside.** Methyl α-D-glucopyranoside (100.6 mg, 0.518 mmol) was completely dissolved in *tert*-amyl alcohol (104 mL) by stirring for several hours. Catalyst **1** (7.9 mg, $2.58\times10^{-2}$ mmol) was then added to the solution. After dissolving the sugar and the catalyst, NaOAc (20 g) was added to the solution. The solution was stirred under Ar at 0°C for half an hour and then acetic anhydride (84 mg, 0.82 mmol) was added to the solution. After being stirred for 2 h, the reaction was quenched with methanol (1 mL). After 10 min at 0°C, NaOAc was removed by filtration and the solvent was evaporated. The crude product was dissolved in a small amount of chloroform–methanol (20:1) and subjected to flash column chromatography (toluene:acetone=1:1) to give methyl 6-*O*-acetyl-α-D-glucopyranoside (73.4 mg, 0.31 mmol) in 60% yield.

$^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 4.643 (d, $J$=3.5 Hz, 1H) 4.346 (dd, $J$=12, 2.5 Hz, 1H), 4.185 (dd, $J$=12, 6 Hz, 1H), 3.695 (ddd, $J$=8.5, 6, 2.5 Hz, 1H), 3.599 (dd, $J$=9, 9 Hz, 1H), 3.388 (s, 3H), 3.387 (dd, $J$=9.5, 4 Hz, 1H), 3.269 (dd, $J$=10, 9 Hz, 1H), 2.050 (s, 3H); $^{13}$C NMR ($CD_3OD$, 125.65MHz) $\delta$ 172.83, 101.27, 75.01, 73.44, 71.83, 70.96, 64.93, 55.57, 20.69; HRMS calcd for $C_9H_{16}O_7{\cdot}H^+$ *m/z* 237.0974, found 237.0964 (FAB).

**4.5.2. Methyl 6-*O*-acetyl-α-D-galactopyranoside.** Methyl α-D-galactopyranoside monohydrate (101.6 mg, 0.479 mmol) was selectively acetylated in exactly the same way to give methyl 6-*O*-acetyl-α-D-galactopyranoside (77.4 mg, 0.328 mmol) in 68% yield.

$^1$H NMR ($CD_3OD$, 500 MHz) $\delta$ 4.693 (d, $J$=3.5 Hz, 1H), 4.242 *(dd, J*=11.5, 7.5 Hz, 1H), 4.191 (dd, $J$=11.5, 4.5 Hz, 1H), 3.939 (ddd, $J$=7.5, 4.5, 1 Hz, 1H), 3.848 (dd, $J$=3.5, 1 Hz, 1H), 3.758 (dd, $J$=10, 3.5 Hz, 1H), 3.706 (dd, $J$=10, 3.5 Hz, 1H), 3.380 (s, 3H), 2.044 (s, 3H); $^{13}$C NMR ($CD_3OD$, 125.65 MHz) $\delta$ 172.66, 101.49, 71.23, 70.88, 70.06, 69.62, 65.13, 55.58, 20.69; HRMS calcd for $C_9H_{16}O_7{\cdot}H^+$ *m/z* 237.0974, found 237.0977 (FAB).

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