View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by OIST Institutional Repository

C-Glycosidation of Unprotected Di- and Trisaccharide Aldopyranoses with Ketones Using Pyrrolidine-Boric Acid Catalysis

Author	Sherida Johnson, Avik Kumar Bagdi, Fujie Tanaka
journal or publication title	The Journal of Organic Chemistry
volume	83
number	8
page range	4581-4597
year	2018-03-29
Publisher	American Chemical Society
Rights	(C) 2018 American Chemical Society This document is the Accepted Manuscript version of a Published Work that appeared in final form in The Journal of Organic Chemistry, copyright (C) American Chemical Society after peer review and technical editing by the publisher. To access the final edited and published work see https://pubs.acs.org/articlesonrequest/AOR-jTxhZ9rJ4NVAtJBXyWYk, see http://pubs.acs.org/page/policy/articlesonrequest/index.html.
Author's flag	author
URL	http://id.nii.ac.jp/1394/00000723/

doi: info:doi/10.1021/acs.joc.8b00340

C-Glycosidation of Unprotected Di- and Trisaccharide Aldopyranoses with Ketones Using Pyrrolidine-Boric Acid Catalysis

Sherida Johnson, Avik Kumar Bagdi, and Fujie Tanaka*

Chemistry and Chemical Bioengineering Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan

Supporting Information

ABSTRACT: C-Glycoside derivatives are found in pharmaceuticals, glycoconjugates, probes, and other functional molecules. Thus, C-glycosidation of unprotected carbohydrates is of interest. Here the development of C-glycosidation reactions of unprotected di- and trisaccharide aldopyranoses with various ketones is reported. The reactions were performed using catalyst systems composed of pyrrolidine and boric acid under mild conditions. Carbohydrates used for the C-glycosidation included lactose, maltose, cellobiose, 3'-sialyllactose, 6'-sialyllactose, and maltotriose. Using ketones with functional groups, C-glycosides ketones bearing the functional groups were obtained. The pyrolidine-boric acid catalysis conditions did not alter the stereochemistry of non-C-C bond formation positions of the carbohydrates and led to the formation of the C-glycosidation products with high diastereoselectivity. For the C-glycosidation of the carbohydrates under the pyrrolidine-boric acid-catalysis, the hydroxy group at the 6-position of the reacting aldopyranose was necessary to afford the product. Our analyses suggest that the carbohydrates form iminium ions with pyrrolidine and that boric acid forms B-O covalent bonds with the carbohydrates during the catalysis to forward the C-C bond formation.

INTRODUCTION

Carbohydrates play important roles in biological systems and thus the synthesis of carbohydrate derivatives is of interest for the development of bioactives, probes, and other functional molecules.[1] C-Glycosidation, the C-C bond formation reaction at the anomeric carbon, of unprotected carbohydrates is an important reaction for the synthesis of carbohydrate-derived pharmaceuticals, glycoconjugates, and other functional carbohydrate derivatives.[1-9] However, the direct C-glycosidation reactions of unprotected carbohydrates are often difficult,[2-10] and the C-C bond formation reaction of unprotected carbohydrates has been considered as a task of enzymes.[11] One of difficulties in reactions of unprotected carbohydrates may be the presence of polyhydroxy groups in carbohydrates. In many reactions of carbohydrates, hydroxy groups must be protected first to avoid that acidic protons of the hydroxy groups react with reagents and/or that the hydroxy groups interrupt hydrogen bonding necessary for the catalysis and stereocontrol.[10] Another difficulty with direct C-glycosidation reactions of unprotected carbohydrates lies in the cyclic hemiacetal form of the aldoses.[9d] Although the aldehyde carbonyl group of the aldoses may be a good site to react with nucleophiles, the generation of the aldehyde group from the cyclic hemiacetal forms by opening the hemiacetal ring, especially from 6-membered hemiacetal forms of aldohexose derivatives, is not easy under mild reaction conditions that do not affect the functional groups of the carbohydrates and of the reactants used for the C-glycosidation reactions.[9d] Therefore, many non-enzymatic, chemical C-glycosidation reactions of carbohydrates have been performed on pre-activated forms of carbohydrates with protected hydroxy groups or on specific precursors bearing functional groups for the bond formation at the anomeric carbons.[10] Considering atom- and step-economy,

direct reactions on unprotected carbohydrates are more preferable than are reactions requiring protection and deprotection steps and/or strategies requiring the synthesis of pre-activated forms for the reactions at the anomeric carbons.[12]

Previously reported C-glycosidation reactions of unprotected carbohydrates include reactions with relatively highly reactive nucleophiles, such as β-diketones,[2] β-keto esters and related molecules,[3] nitromethane,[4] cyanide,[5] and Wittig and related reagents.[6] C-Glycosidation reactions of unprotected carbohydrates also include reactions with metal-activated reagents.[7] Whereas these reactions have afforded C-glycosidation products from certain unprotected carbohydrates, these reactions have limitations. For example, the reactions with β-diketones can be used only for the synthesis of acetone-attached and related C-glycosides because of the use of β-diketones as nucleophiles and because of the use of basic conditions under heating;[2b-h] functional groups that are not suited to the synthesis of the β-diketones and/or to the basic, heating C-glycosidation conditions cannot be introduced directly.

Recently C-glycosidation reactions of unprotected carbohydrates with simple ketones have been reported.[9] For example, the Mahrwald group has reported C-glycosidation of C_5-aldoses or aldopentoses (such as ribose) with simple ketones (such as acetones and 2-pentanone) catalyzed by proline-DBU.[9a] The Mahrwald group has also reported C-glycosidation of ketoses via the ketose-aldose rearrangement using amine-based catalysts.[9b] The Shimizu and Kanai group has reported C-glycosidation of aldoses using Cu catalysts.[9c] We have reported C-glycosidation of unprotected 2-*N*-acyl-aldopyranoses (such as 2-*N*-acetyl-D-mannosamine and 2-*N*-acetyl-D-glucosamine) with simple ketones using amine-based catalyst systems.[9d] These reactions have also limitations. For example, reaction conditions for the C-glycosidation of C_5-aldoses (aldopentoses) with ketones[9a] do not work well for the reactions of C_6-aldoses (aldohexoses) or C_6-aldopyranoses (aldohexopyranoses).[9d] Reactions of unprotected carbohydrates have often been performed using carbohydrates that do not have hydroxy group at the 2-position to the anomeric carbon.[7a,b,9c] In addition, the reported C-glycosidation reactions of unprotected carbohydrates have mostly been performed on unprotected monosaccharides with a few examples of reactions of disaccharides.[2e,g,h,6b,7h,9c]

There are approximately two or three times more hydroxy groups per molecule in di- and trisaccharides, respectively, as in monosaccharides. Because of this and/or because of other reasons, reaction catalysts and conditions that work for C-glycosidation of unprotected monosaccharides do not always work efficiently for disaccharides. For example, in the reported Cu-catalyzed reactions, the conditions established for the reactions of monosaccharides resulted in the formation of the product from a disaccharide in a low yield.[9c] Thus, to directly synthesize functionalized C-glycosides from unprotected di- and trisaccharides, advances were required. Here we report C-glycosidation reactions of di- and trisaccharide aldopyranoses with ketones using pyrrolidine-boric acid catalyst systems. We also report the reaction-based mechanistic investigation and the key factors of the catalysis.

RESULTS AND DISCUSSION

Design. C-Glycosides bearing ketone groups have been used for the synthesis of various C-glycoside derivatives.[1c,d] We designed C-glycosidation of unactivated, unprotected di- and trisaccharide aldoses with ketones. In our design, the following points were considered to develop the C-glycosidation reactions: (1) in situ-activation of aldopyranoses to enable the C-C bond formation at the anomeric center, (2) in situ-generation of enamines or enolates from ketones that react as nucleophiles with aldopyranoses, (3) catalyst systems that work in the presence of polyhydroxy-substituted compounds, and (4) reaction systems/catalyst systems that provide high stereoselectivity for the C-C bond formation without altering the carbohydrate stereochemistry. We sought amine-based catalysts[13] to address these points and to enable the generation of desired products under mild conditions. In our design, amine catalysts were expected to form enamines of ketones. At the same time, the catalyst systems would activate the carbohydrates to lead the C-C bond formation. Based on these considerations, we searched for catalysts of the C-glycosidation.

As described above, we recently reported C-glycosidation of unprotected 2-*N*-acyl-aldopyranoses.[9d] In these reactions, some catalyst systems were efficient for only certain carbohydrates; the efficiency of the catalyst systems depended on the carbohydrate structure/stereochemistry. For the C-glycosidation of di- and trisaccharide aldopyranoses with ketones, our focus was on the development of the catalyst systems that work for a series of carbohydrates, including functionalized carbohydrates, and for various ketones.

As described below, catalyst systems composed of pyrrolidine and boric acid accelerated the C-glycosidation reactions of unprotected di- and trisaccharides with ketones.

C-Glycosidation of Monosaccharide Aldopyranoses. We reasoned that catalyst systems that work for the C-glycosidation of di- and trisaccharide aldopyranoses with ketones should work for C-glycosidation of monosaccharide aldopyranoses to some degree. By analyzing the C-glycosidation products from monosacharaide aldopyranoses, features of the reactions, such as the possibility of isomerization at the 2-position of the carbohydrates, would be more easily recognized than by analyzing the products from di- and trisaccharides. Thus, first, results of the C-glycosidation reactions of monosaccharide aldopyranoses are described. When the reaction was performed using pyrrolidine and boric acid as catalyst,[9d] C-glycoside ketone **3aa** was obtained (Table 1).

For the reaction of D-glucose (**1a**) with acetone (**2a**), amine-based catalyst systems that have been commonly used in aldol and/or Mannich reactions of ketones with simple aldehydes (i.e., not carbohydrates), such as proline[13a,b] and amino acids,[13] did not give **3aa**. As 6-membered hemiacetals are usually stable as the cyclic forms,[14] aldopyranoses, such as D-glucose, are more difficult to react with nucleophiles at the anomeric carbon (or the aldehyde carbonyl group of the corresponding ring-opened form) than are aldopentoses such as ribose.[2b,3a-d,9d] Conditions used for catalyzing the C-glycosidation of ribose with simple ketones, such as proline-DBU,[9a] were also not optimal for the C-glycosidation of D-glucose with acetone.

In the presence of pyrrolidine and boric acid, the reaction of D-glucose (**1a**) with ethyl 5-oxohexanoate (**2b**) also afforded C-glycoside product **3ab** (Table 1). The ester group of ketone **2b** was not affected under the pyrrolidine-boric acid catalysis conditions. Reaction with acetophenone (**2c**) also afforded corresponding C-glycoside **3ac**. The reactions of C_6-aldoses bearing 2-hydroxy group with acetophenone were previously recognized as difficult reactions.[9c] Reaction of D-mannose

(**1b**) with ketone **2b** also afforded C-glycosidation product **3bb** when the pyrrolidine-boric acid combination was used as catalyst.

Table 1. C-Glycosidation of monosaccharide aldohexopyranoses.[a]

1 + 2 (pyrrolidine, H_3BO_3, DMSO) → 3

2a: R = CH_3
2b: R = $(CH_2)_3COOEt$
2c: R = Ph

1	product 3	yield
D-glucose (**1a**)	**3aa**	25%[b] 12%[c]
	3ab	37%
	3ac	17%
D-mannose (**1b**)	**3bb**	20%

[a] Conditions: Carbohydrate **1** (0.50 mmol), ketone **2** (2.0 mmol), pyrrolidine (0.25 mmol), H_3BO_3 (1.0 mmol) in DMSO (1.0 mL) at room temperature (25 °C) for 48 h. [b] Acetone (5.0 mmol). [c] Acetone (20 equiv to **1a**), boric acid (1.0 equiv to **1a**), 24 h; modified conditions; see Experimental Section.

Under the pyrrolidine-boric acid catalysis conditions, isomerization at the 2-position of the carbohydrates did not occur: The reaction of D-glucose affording **3ab** did not co-generate **3bb**, and the reaction of D-mannose affording **3bb** did not form **3ab**.

Isolated products **3** were stable at room temperature (25 °C) for at least one month. Acetal formation at the ketone group of these products and formation of ring-opened forms were negligible or were not detected.

Previously reported C-glycosidation reactions of C_6-aldoses with ketones (excluding 1,3-diketones and relatively nucleophilic ketones) were often performed with aldoses that did not have a hydroxy group at the 2-position of the aldoses.[7a,b,9c] The pyrrolidine-boric acid catalyst system allowed the synthesis of C-glycoside derivatives of C_6-aldopyranoses bearing a hydroxy group at the 2-position. Further, in the reactions catalyzed by the pyrrolidine-boric acid system, products were obtained as single diastereomers or with high diastereoselectivity with the β-isomer as the major diastereomer (dr (β-anomer/α-anomer) >10:1 to >20:1).

C-Glycoside products bearing ketone moieties were previously synthesized by the reactions of unprotected carbohydrates with β-diketones or with Horner-Wadsworth-Emmons (HWE) β-carbonyl phosphonate reagents.[2,6b] These reactions were performed at high temperature under basic conditions. The reactions of unprotected carbohydrates with ketones using pyrrolidine-boric acid catalyst afforded the products under mild conditions at room temperature. With the use of pyrrolidine-boric acid catalysis system, methyl ketone derivatives with the ester group and with the aryl group were able to be used as nucleophiles, and the synthesis of β-diketones[2] and of HWE reagents[6] was not required to obtain the C-glycoside products.

C-Glycosidation of Disaccharide Aldopyranoses. C-Glycosidation reactions of disaccharide aldopyranoses **4** are shown in Scheme 1. Under the pyrrolidine-boric acid catalysis conditions, reactions of D-lactose (**4a**) with ketones afforded the corresponding C-glycosidation products **5aa**-**5ah** (Scheme 1). These products were β-isomers (dr (β/α) >10:1) regardless of the reaction time lengths. Reactions with various ketones, such as acetone, unsymmetrical functionalized alkyl methyl ketones (including ketones bearing an ester group, an ethynyl group, or a cyclopropane ring), and aryl methyl ketones, afforded the desired C-glycosidation products.

When amine-based catalyst systems were screened to afford **5aa** in the reaction of D-lactose (**1a**) with acetone, commonly used amine-based catalysts such as proline[13a,b] did not catalyze the reaction. Proline with bases such as *N*,*N*-diisopropylethylamine[9d] also did not efficiently catalyze the reaction. Among catalyst systems tested, pyrrolidine-boric acid most efficiently catalyzed the reaction. Investigation of catalyst systems for the reaction of **4a** is further discussed in the later part (see below).

Under the pyrrolidine-boric acid catalysis conditions, reactions of D-maltose (**4b**) and of D-cellobiose (**4c**) also afforded the corresponding C-glycosides **5ba** and **5ca**, respectively (Scheme 1). Products **5ba** and **5ca** were also obtained as β-isomers (dr (β/α) >10:1).

The pyrrolidine-boric acid catalysis conditions did not affect the stereochemistry of the O-glycosylated carbon of the disaccharide (i.e., the 1'-position of the disaccharides) (Scheme 1). In the reaction of D-maltose (**4b**) affording **5ba**, formation of **5ca** was not observed, and in the reaction of D-cellobiose (**4c**) affording **5ca**, formation of **5ba** was not detected. For products **5** obtained from D-lactose, in the ^{1}H NMR spectra, the coupling constant *J* value of the proton at the 1'-position indicated that the stereochemistry of the 1'-position of the reactant was retained in the products.

Reactions of disaccharides **4a**, **4b**, and **4c** were faster than reactions of monosaccharides **1** under the same pyrrolidine-boric acid catalysis conditions when the reactions with the same ketones were compared. The yields of the disaccharide C-glycoside derivatives after 48 h were better than those of monosaccharide C-glycoside derivatives when the same ketones were used under the same reaction conditions (Scheme 1, **5ab** versus Table 1, **3ab** and **3bb**; Scheme 1, **5ac** versus Table 1, **3ac**). Yields of products **5** were improved with longer reaction time without increased formation of byproducts (Scheme 1, for **5aa**: 45% after 48 h, 61% after 96 h; for **5ab**: 45% after 48 h, 65% after 96 h; for **5ag**: 35% after 48 h, 55% after 96 h).

In contrast, for D-melibiose (**4d**), in which the hydroxy group at the 6-position of the terminal aldopyranose is glycosylated, corresponding C-glycosidation products were not formed under the pyrrolidine-boric acid catalysis conditions.

Scheme 1. C-Glycosidation of disaccharides.[a]

D-lactose (**4a**), D-maltose (**4b**), or D-cellobiose (**4c**) → (pyrrolidine, H_3BO_3, DMSO) → **5**

5aa, from **4a**: 45%[b]; 61%[b,c]
5ab, from **4a**: 45%; 65%[c]
5ac, from **4a**: 36%
5ad, from **4a**: 45%
5ae, from **4a**: 35%
5af, from **4a**: 21%
5ag, from **4a**: 35%; 55%[c]
5ah, from **4a**: 25%
5ba, from **4b**: 46%[b,c]
5ca, from **4c**: 53%[b]

[a] Conditions: Carbohydrate **4** (0.5 mmol, 1.0 equiv), ketone **2** (2.0 mmol, 4.0 equiv), pyrrolidine (0.25 mmol, 0.5 equiv), H_3BO_3 (1.0 mmol, 2.0 equiv) in DMSO (1.0 mL) at room temperature (25 °C) for 48 h. [b] Modified conditions with **4** (1.0 equiv), acetone (20 equiv), pyrrolidine (0.5 equiv), and H_3BO_3 (1.0 equiv); see Experimental Section. [c] 96 h.

D-melibiose (**4d**)

C-Glycosidation of Trisaccharide Aldopyranoses. Reactions of trisaccharide aldopyranoses **6** were also performed using pyrrolidine-boric acid catalysis conditions. With the use of the pyrrolidine-boric acid catalyst system, reactions of 3'-sialyllactose (**6a**), 6'-sialyllactose (**6b**), and maltotriose (**6c**) with ketones afforded corresponding C-glycosides **7** (Scheme 2). Reactions with acetone, alkyl methyl ketones bearing various functional group or a cyclopropane ring, and aryl methyl ketones all gave the desired C-glycoside ketones **7**. Use of the pyrrolidine-boric acid catalyst system allowed the direct C-glycosidation reactions of highly functionalized carbohydrates such as *N*-acetylneuraminic acid-bearing carbohydrates.

Scheme 2. C-Glycosidation of trisaccharides.[a]

trisaccharide **6** + ketone → (pyrrolidine, H_3BO_3, DMSO) → trisaccharide C-glycoside ketone **7**

3'-sialyllactose (**6a**), 6'-sialyllactose (**6b**), or D-maltotriose (**6c**)

7aa, from **6a**: 74%
7ab, from **6a**: 40%
7ba, from **6b**: 80%
7ca, from **6c**: 35%
7cd, from **6c**: 30%
7cc: Ar = Ph, from **6c**: 22%
7cg: Ar = C_6H_4-*p*-Me, from **6c**: 25%
7ci: Ar = C_6H_4-*p*-CN, from **6c**: 22%

[a] For details, see Experimental Section.

Transformations of C-Glycoside Ketones. The methyl ketone moiety of monosaccharide C-glycoside ketones and of a few disaccharide C-glycosides has been used as reaction site for chemical transformations to derivatize the C-glycoside ketones.[1c,d,15-17] The C-glycoside ketones synthesized using the pyrrolidine-boric acid catalysis conditions were transformed to C-glycoside derivatives with more complex and/or elongated structures (Schemes 3, 4, and 5). The methyl ketone moiety was used as nucleophile[1d,15] (via the formation of enamines or enolates) to generate aldol condensation products **8** (Scheme 3). The methyl ketone moiety was also used as an electrophile[1c,d,16] to form hydrazone derivative **9** and oxime derivative **10** (Schemes 4 and 5).

Carbohydrate derivatives bearing a 6-methoxynaphthalen-2-yl-buten-2-one moiety are inhibitors of certain cancer-associated enzymes.[15b] Previously, monosaccharide C-glycoside ketones have been derivatized to afford aldol condensation products.[1d,15] In our study, di- and trisaccharide C-glycosides were transformed to the corresponding aldol condensation products **8a-e** using either proline-*N*,*N*-diisopropylethylamine or pyrrolidine-boric acid catalysis systems (Scheme 3). No protection of the polyhydroxy groups of the C-glycosides was necessary before the transformation. Through the formation of **8**, formation of **5** and **7** in the C-glycosidation reactions was further confirmed.

The C-glycosidation using the pyrrolidine-boric acid catalysis allowed the synthesis of C-glycoside ketones bearing functional groups (such as ethynyl, ester, and aryl ketone groups) as described above. These functional groups will also be useful for further derivatization.[1c,d]

Scheme 3. Transformations of C-glycoside ketones through aldol condensation.[a]

carbohydrate (**5** or **7**) + 6-methoxy-2-naphthaldehyde → (proline, *i*-Pr_2NEt or pyrrolidine, H_3BO_3; DMSO) → **8**

8a, from **5aa** 53%[b]

8b, from **5ba** 42%[c]

8c, from **5ca** 27%[b]

8d from **7aa** 40%[c]

8e from **7ba** 35%[c]

[a] For details, see Experimental Section. [b] Proline-*i*-Pr_2NEt catalysis. [c] Pyrrolidine-boric acid catalysis.

Scheme 4. Derivatization through hydrazone formation.

5aa + H_2NNHSO_2-tolyl → **9** 57%

Scheme 5. Derivatization through oxime formation followed by amide formation.

7aa → 1) H_2NOCH_2COOH; 2) $H_2N(CH_2)_5NH$-dansyl, DMTMM (Cl^-) → **10** 57% from **7aa**

Catalyst Systems in the C-Glycosidation. To understand the key factors that result in the generation of the C-glycosides from di- and trisaccharide aldopyranoses using pyrrolidine-boric acid catalysis system, related catalyst systems were also evaluated in the reaction of D-lactose (**4a**) with ketone **2b** to afford **5ab** and with ketone **2c** to afford **5ac** (Table 2).

Pyrrolidine alone or boric acid alone did not catalyze the reaction to form the C-glycosidation product; carbohydrate **4a** remained unreacted (entries 11 and 12). Substituting boric acid with bases, such as NaOH, Na_2CO_3, or DBU, in the catalyst system also did not afford **5ab** (entries 3-5). Substituting boric acid with NH_4Cl, phenol, or acetic acid also did not form the product (entries 6-8). On the other hand, the pyrrolidine-trimethyl borate catalyst system catalyzed the reaction to afford product **5ab** (entry 2). These results suggest that boric acid in the pyrrolidine-boric acid catalysis in the C-glycosidation acts not just as a Brønsted acid or base. It is likely that boric acid forms B-O covalent bonds with the carbohydrate.[18] This B-O covalent formation may be key to the formation of the C-glycosidation product (see below).

Further, the use of Et_3N or DBU instead of pyrrolidine in the pyrrolidine-boric acid catalysis system did not catalyze the reaction to give the C-glycosidation product (entries 9 and 10). Although DBU has been used to generate enolates from ketones,[19] the DBU-boric acid system was not effective for the C-glycosidation with ketones. However, substituting pyrrolidine with benzylamine in the pyrrolidine-boric acid catalysis system did afford C-glycosidation product **5ac** (entry 14). Benzylamine has been used as an amine component in enamine-forming catalyst systems.[20] These results indicated that both pyrrolidine (or amine, which can form an imine/iminium ion/enamine) and boric acid (or borate) have functions for catalyzing the C-glycosidation reaction. These

results suggest that the pyrrolidine-boric acid catalyst system involves both the formation of an iminium ion with the carbohydrate and the formation of an enamine of the ketones during the catalysis.

Table 2. Catalyst systems for the C-glycosidation of **4a**.[a]

2b, **5ab**: R = $(CH_2)_3COOEt$
2c, **5ac**: R = Ph

entry	catalyst system	product	yield (%)
1	pyrrolidine-H_3BO_3	**5ab**	45[b]
2	pyrrolidine-$B(OMe)_3$	**5ab**	39
3	pyrrolidine-NaOH	**5ab**	-[c]
4	pyrrolidine-Na_2CO_3	**5ab**	-[c]
5	pyrrolidine-DBU	**5ab**	<5
6	pyrrolidine-NH_4Cl	**5ab**	-[c]
7	pyrrolidine-phenol	**5ab**	<5
8	pyrrolidine-CH_3COOH	**5ab**	<5
9	Et_3N-H_3BO_3	**5ab**	-[c]
10	DBU-H_3BO_3	**5ab**	-[c]
11	pyrrolidine	**5ab**	-[c]
12	H_3BO_3	**5ab**	-[c]
13	pyrrolidine-H_3BO_3	**5ac**	36[b]
14	$PhCH_2NH_2$-H_3BO_3	**5ac**	30

[a] Conditions: For entry 2, carbohydrate **4a** (0.25 mmol), ketone **2b** or **2c** (2.0 mmol), pyrrolidine (0.13 mmol), $B(OMe)_3$ (0.5 mmol) in DMSO (0.5 mL) at room temperature (25 °C) for 48 h. For entries 3-12 and 14, H_3BO_3 and/or pyrrolidine were subtracted or replaced as indicated. [b] Data from Scheme 1. [c] Formation of **5ab** was not detected.

Detection of Intermediates of the C-Glycosidation. Detection of intermediates provides information necessary for understanding the mechanisms of catalyzed reactions. To detect intermediates (such as iminium ion and hemiaminal that would be generated from the carbohydrate and pyrrolidine), the reaction mixture was analyzed by mass spectrometry. When the reaction mixture containing D-lactose (**4a**), ketone **2b**, and the catalyst system (i.e., pyrrolidine and boric acid) was analyzed at 10 min after the preparation of the mixture, mass signals at m/z 396.1869 and m/z 554.2811, assigned to $C_{16}H_{30}NO_{10}$ (calcd 396.1864) and $C_{24}H_{44}NO_{13}$ (calcd 554.2807), were observed. These signals likely correspond to the protonated forms of **11** and **12**, respectively (i.e., $[M + H]^+$, in which M = **11** and **12**, respectively). Hemiaminal ether **11** is a cyclized form of the iminium ion derived from the ring-opened form of **4a** with pyrrolidine. Intermediate **11** may also be present as a ring-opened form (i.e., the iminium ion). The mass signal assigned as $C_{24}H_{44}NO_{13}$ may also be the $[M + H]^+$, in which M = **13**. Compound **11** was also isolated from the mixture of D-lactose (**4a**), pyrrolidine (1.0 equiv to **4a**), and boric acid (2.0 equiv to **4a**) in DMSO.

To analyze whether **11** is an intermediate, compound **11** was subjected to the reaction with ketone **2b** in the presence of pyrrolidine and boric acid under the conditions similar to those used for the reaction of **4a** to afford **5ab**. In this reaction, compound **11** was transformed to **5ab**, suggesting that compound **11** is an intermediate of the reaction of **4a**. These results support the involvement of the iminium ion formation from the carbohydrate with pyrrolidine during the C-glycosidation in the presence of pyrrolidine and boric acid.

To provide further information about the mechanism and the intermediates of the pyrrolidine-boric acid catalysis, ^{13}C NMR of D-lactose (**4a**) was analyzed in the presence of pyrrolidine alone, boric acid alone, and pyrrolidine-boric acid (Figure 1, see also Supporting Information). In the presence of boric acid (2.0 equiv to **4a**), some peaks of ^{13}C NMR spectra of D-lactose (**4a**) were shifted from those of **4a** in the absence of boric acid (Figure 1d versus Figure 1c). No aldehyde group was detected in these cases (Supporting Information Figure S1). In the presence of boric acid, the stereochemistry of the anomeric carbon of D-lactose (**4a**) was unaffected (Figure 1d). That is, lactose was present as the α-anomer[21] before the addition of boric acid, and this α-stereochemistry was retained after addition of boric acid.

When the ^{13}C NMR of D-lactose (**4a**) was analyzed in the presence of pyrrolidine (0.5 equiv to **4a**) in $(CD_3)_2SO$, ^{13}C peaks that were not present in the sample of **4a** alone in $(CD_3)_2SO$ appeared (Figure 1e versus Figure 1c). As described above, the lactose was present as the α-anomer[21] before the addition of pyrrolidine. The signals observed after the addition of pyrrolidine were in accord with the reported chemical shifts of the α- and β-anomers[21] of D-lactose. Based on the height of the signal corresponding to the ^{13}C at the 1-position (anomeric carbon; C1α and C1β, respectively) of **4a**, the ratio of α-anomer/β-anomer was estimated to be approximately 1.0:1.3 in the presence of pyrrolidine (0.5 equiv to **4a**) (Figure 1e). The α/β ratio was retained in the presence of an increased amount of pyrrolidine (1.0 equiv to **4a**; data not shown). The signals intensities and the α/β ratio of **4a** in the presence of pyrrolidine were not altered for at least 1 h. Neither an aldehyde group, an iminium ion, nor **11** was detected in the presence of pyrrolidine without boric acid. Signals that appeared by the addition of pyrrolidine to **4a** did not correspond to the signals of **11**.

When the ^{13}C NMR of D-lactose (**4a**) was analyzed in the presence of pyrrolidine (0.5 equiv to **4a**) and boric acid (2.0 equiv to **4a**) in $(CD_3)_2SO$, signals assigned as the ^{13}C at the 1-position of the α- and β-anomers of **4a** described above were observed only in trace amounts (Figure 1f). The signal corre-

sponding to the C1 was at a chemical shift similar to that of **11** (Figure 1f versus Figure 1h) and was different from those of the α- and β-anomers of **4a** in the presence of pyrrolidine without boric acid and from that in the presence of boric acid without pyrrolidine (Figure 1f versus Figure 1e and 1d). Other signals of the carbohydrate moiety in the presence of pyrrolidine and boric acid were also different from those of the signals in the presence of pyrrolidine alone and in the presence of boric acid alone. There were two main sets of signals for the carbohydrate moiety in the presence of pyrrolidine and boric acid (Figure 1f). One set was similar to that of the peaks of **11** (Figure 1f versus Figure 1h), although slightly shifted (these shifts may be attributed to the fact that boric acid was also present in the mixture). In addition, there were four ^{13}C signals (or two sets of ^{13}C signals) for the pyrrolidine moiety in Figure 1f, indicating that that there were two-types of pyrrolidine moieties. One set of peaks would correspond to free pyrrolidine (or a pyrrolidine-boric acid adduct) and another to **11**. That is, in the presence of pyrrolidine and boric acid, **11** and/or **11** covalently bound with boric acid were formed at a detectable level. In the NMR spectrum of **4a** in the presence of pyrrolidine and boric acid, no signals corresponding to the aldehyde and to the iminium ion (excluding cyclized form **11**) were observed.

In the presence of pyrrolidine, the carbohydrate hemiacetal ring may be opened, but the open-chain form may be rapidly closed, resulting in α/β-isomerization. This may be because the 6-membered cyclic forms are stable compared to the open-chain forms.[14] The hemiacetal ring opening in the presence of pyrrolidine may provide chances for pyrrolidine to react with carbohydrate to form an iminium ion. However, the iminium ion may be quickly hydrolyzed even if formed.

In the presence of pyrrolidine and boric acid, cyclization may be slowed by the formation of B-O bonds between boric acid and the carbohydrate 6- and 5- positions. In addition, the water molecule generated by the formation of the iminium ion from the carbohydrate and pyrrolidine may react with boric acid and/or boric acid-carbohydrate covalently attached derivatives instead of reacting to hydrolyze the iminium ion. As a result, the iminium ion may be able to exist and is used for the C-C bond-formation or for the formation of hemiaminal ether **11**.

^{13}C NMR spectra of the reaction mixture containing **4a**, 4'-methylacetophenone, pyrrolidine, and boric acid in $(CD_3)_2SO$ also showed signals correlated to the formation of **11** (Figure 1g).

NMR spectra of D-maltose (**4b**) and of D-cellobiose (**4c**) were also analyzed in the presence of pyrrolidine alone, boric acid alone, and pyrrolidine-boric acid, respectively (Supporting Information Figures S4 and S5, respectively). Although **4b** and **4c** were presented as β-anomers initially, observations in the NMR analyses of **4b** and of **4c** were similar to those observed in the lactose case. That is, in the presence of pyrrolidine, both α- and β-anomers were generated. In the presence of pyrrolidine and boric acid, new signals were observed for the carbohydrate moiety including the signal corresponding to the carbon originally at the 1-position of the carbohydrates. Further, there were four ^{13}C signals for the pyrrolidine moiety, indicating that there were two-types of pyrrolidine moieties.

^{11}B NMR of D-lactose (**4a**) in the presence of pyrrolidine and boric acid was also analyzed (Supporting Information Figure S3). The boron NMR of boric acid in $(CD_3)_2SO$ showed a broad peak.[22] The ^{11}B NMR of a mixture of pyrrolidine and boric acid in the same solvent showed the broad peak and a sharp peak. On the other hand, the ^{11}B NMR of a mixture of D-lactose (**4a**), pyrrolidine, and boric acid in $(CD_3)_2SO$ showed multiple signals. These boron NMR analyses results support that boric acid forms covalent B-O bonds with the carbohydrate.[7f,18,22]

Catalysis Systems for the Ketone Activation. To assess the efficiency of the pyrrolidine-boric acid catalysis for the ketone activation (or for the formation of enamines/enolates from the ketones that act as nucleophiles in the C-C bond formation of the C-glycosidation), the pyrrolidine-boric acid catalyst system and related catalyst systems were evaluated in the reaction of acetone with 4-nitrobenzaldehyde.[13a,b] Because of the electron-withdrawing nitro group, this aldehyde would readily react with the enamines/enolates generated in situ. When the reaction of acetone with 4-nitrobenzaldehyde was performed in the presence of pyrrolidine (0.2 equiv to the aldehyde) and acetic acid (0.2 equiv),[19a] the conversion of the aldehyde was 60% (i.e., 40% of the aldehyde remained unreacted) after 1 h. When the reaction of the same substrates was performed in the presence of pyrrolidine (0.2 equiv) and in the presence of pyrrolidine (0.2 equiv) and boric acid (0.2 equiv), the conversion was more than 90% and 95%, respectively, after 1 h, and the main product was the aldol product in both cases. With the use of pyrrolidine (0.5 equiv) and boric acid (2.0 equiv), the reaction afforded the aldol product, aldol condensation products 4-(4-nitrophenyl)but-3-en-2-one, and more complex products.[23] On the other hand, boric acid alone did not catalyze the reaction. In the reactions catalyzed by the pyrrolidine-boric acid catalysis system, enamines of ketones with pyrrolidine may be formed to act as nucleophiles.[13,19] The efficiency in the enamine/enolate formation using pyrrolidine-boric acid was superior to that using pyrrolidine-acetic acid based on the conversion yields. Increased loading of pyrrolidine and boric acid led the formation of aldol condensation product; this may be attributed to the involvement of the Mannich reaction route that uses the iminium ions generated from the aldehyde and pyrrolidine.[9d,24]

Pyrrolidine alone also catalyzed the aldol reaction of acetone and 4-nitrobenzaldehyde, indicating that acetone enamine/enolate was formed in the presence of pyrrolidine. However, pyrrolidine alone did not catalyze the C-glycosidation of carbohydrates with ketones (including acetone). Thus, the ketone activation alone does not lead the C-glycosidation with the ketone. For the C-glycosidation of carbohydrates with ketones, activation of both the carbohydrates and the ketones is necessary.

In the reactions of carbohydrates with ketones, including ketones for which formation of enamines/enolates is relatively difficult (such as 4'-methylacetophenone), the use of the pyrrolidine-boric acid catalyst system afforded the C-glycosidation products. As the pyrrolidine-boric acid catalyst system efficiently formed nucleophiles from ketones, this catalyst system was also useful for the transformation of the C-glycoside ketones as shown in Scheme 3.

Plausible Mechanisms. A plausible mechanism of the C-glycosidation reaction of di- and trisaccharide aldopyranoses in the presence of pyrrolidine and boric acid is shown in Schemes 6 and 7. In the presence of pyrrolidine and boric acid, the carbohydrate forms B-O bonds with boric acid and also forms an iminium ion with pyrrolidine (Scheme 6, **A**). Imini-

um ion **A** reacts with the enamine generated from the ketone with pyrrolidine via a Mannich reaction route to generate intermediate **B**. Elimination of pyrrolidine from **B**, through the protonation of the nitrogen, results in the formation of **C**. Cyclization of **C** leads the formation of **D**. Intermediate **B** may also be cyclized directly to lead the formation of **D**. After hydrolysis, product **E** is generated. As no isomerization at the 2-position was observed, formation of enamine **F** does not occur. Formation of cyclized form **G** from **A** may suppress the formation of **F**. Alternatively, formation of enamine **F** may be significantly slow because of the hydroxy group-substituent at the 2-position (compared to the formation of the enamine of the corresponding non-hydroxy group-substituted compound).[19a] **G** is a resting state intermediate for providing active intermediate **A**. Compound **11** that was isolated (see above) is a boric acid-dissociated form of **G**. Cyclized, hemiaminal ether form **G** may also be present as nitrogen-protonated form **H**. **H** may also react with the enamine of the ketone to give **D** via an S_N2 reaction route or via an oxonium ion. Based on the previously reported Mannich reaction route,[24] the route via **B** may be more favored than the route via **H**. In the presence of pyrrolidine-boric acid, the cyclic forms may be in the equilibrium with the open-chain forms. The equilibrium between **C** and **D** may be a reason for resulting in the formation of the stable β-isomer as the major product. The β-isomer may also be formed kinetically at the oxa-Michael addition step (**C** to **D**) through chair form transition state **G**.

The aldehyde group generated from the cyclic hemiacetal of the carbohydrates may directly react with the enamine generated from the ketone with pyrrolidine. But, as described above, the DBU-boric acid did not catalyze the C-glycosidation of lactose with a ketone, indicating that the formation of an iminium ion of the carbohydrate is required for the generation of the C-glycosidation product. Thus, the reaction with the iminium ion of the carbohydrates (i.e., the Mannich reaction route) is more likely used than the reaction with the aldehyde group (i.e., aldol reaction route).

When the 6-position of the hydroxy group was glycosylated, (such as in melibiose (**4d**)), the C-glycosidation of the carbohydrate with ketones in the presence of pyrrolidine-boric acid did not occur. Thus, the B-O bond formation with the hydroxy group at the 6-position is necessary for the formation of the B-O bond at the hydroxy group at the 5-position in the presence of pyrrolidine. That is, the B-O bond formation with both 6- and 5-hydroxy groups of the carbohydrates in the presence of pyrrolidine is key to forwarding the C-glycosidation via the generation of an aldehyde group from the hemiacetal and the formation of an iminium ion of the aldehyde with pyrrolidine (Scheme 7). Hydroxy groups at positions other than the 6- and 5-positions of the carbohydrates may also form B-O bonds with boric acid, but these do not result the generation of the aldehyde group, and thus do not result in the formation of the C-glycosidation product. B-O bonds are easily exchanged (the boron atom of a B-O bond is easily liberated from the oxygen atom and the boron atom easily reacts with hydroxy groups and other oxygen species to form a new B-O bond);[25] because of this, the use of only 1 or 2 equivalents of boric acid relative to the carbohydrate in the presence of pyrrolidine functioned to catalyze the reaction to afford the C-glycosidation product.

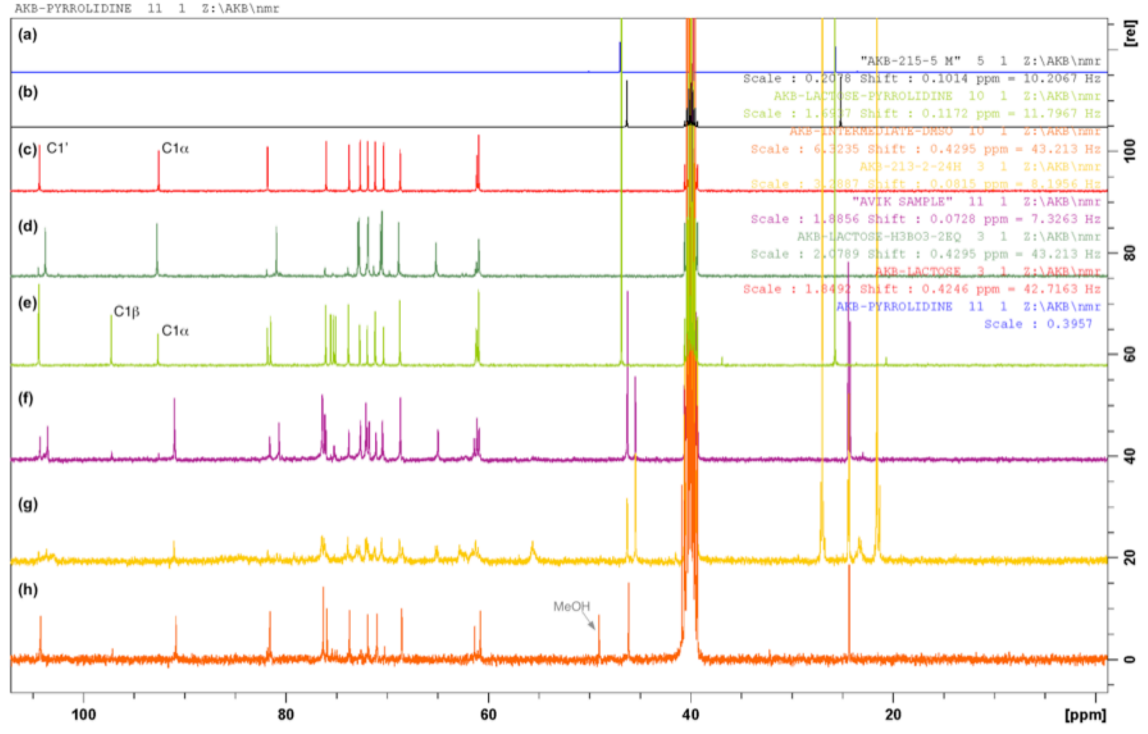

Figure 1. ^{13}C NMR spectra of (a) pyrrolidine, (b) pyrrolidine and boric acid, (c) D-lactose, (d) D-lactose and boric acid, (e) D-lactose and pyrrolidine, (f) D-lactose, pyrrolidine, and boric acid, (g) D-lactose, 4'-methylacetophenone, pyrrolidine, and boric acid (i.e., the C-glycosidation reaction of D-lactose with 4'-methylacetophenone using the pyrrolidine-boric acid catalysis), after 24 h, (h) compound **11**, in $(CD_3)_2SO$. For (a)-(f), the NMR was analyzed at 5 min after the preparation of the solution.

Scheme 6. Plausible mechanism of the C-glycosidation reaction.

Scheme 7. Plausible mechanism of the formation of intermediate **A**.

The pyrrolidine-boric acid catalysis system did not alter the stereochemistry of the 1'-position of disaccharide aldopyranoses **4** (see Scheme 1). This result indicates that the catalyst system does not open the carbohydrate acetal ring (or does not open the carbohydrate hemiacetal ring when the hydroxy group at the anomeric carbon is glycosylated). That is, the B-O bond formation with the hydroxy group at the 6'-position alone does not forward the B-O formation with the hydroxy group at the 5'-position in the presence of pyrrolidine. The result indicates that the B-O bond formation with both the hydroxy groups at the 6- and 5-positions occurs in the presence of pyrrolidine only when the anomeric carbon (1-position) has a hydroxy group (i.e., when the hydroxy group at the anomeric carbon is not glycosylated) (Scheme 7). The result also suggests that the deprotonation of the hydroxy group at the anomeric carbon is the trigger for the formation of intermediate **A** (Scheme 7).

The reaction of lactose was faster than that of glucose when the same ketone was used as the nucleophile. In lactose, the hydroxy group at the 4-position is glycosylated. Thus, in the presence of pyrrolidine, when boric acid forms a covalent B-O bond with the oxygen of the hydroxy group at the 6-position of lactose, the boron may also form a covalent B-O bond with the oxygen of the hydroxy group at the 5-position. For glucose, however, when boric acid forms a covalent B-O bond with the oxygen of the hydroxy group at the 6-position, the boron may also form a bond with the hydroxy group at the 4-position. The covalent B-O bond formation with the 4-position-hydroxy group may slow the B-O bond formation with the 5-position-hydroxy group and may result in the slow C-glycosidation of glucose.

CONCLUSION

We have developed C-glycosidation reactions of unprotected di- and trisaccharide aldopyranoses with ketones catalyzed by pyrrolidine and boric acid. The reactions afforded C-glycoside ketones under mild conditions. With the developed reaction methods, polyhydroxylated di- and trisaccharide carbohydrates, including functionalized carbohydrates (such as 3'-sialyllactose and 6'-sialyllactose), were directly transformed to the corresponding C-glycoside ketones. With using ketones bearing functional groups in the reactions, C-glycoside ketones bearing functional groups were obtained. The C-glycosidation reactions catalyzed by the pyrrolidine-boric acid catalyst system did not alter the stereochemistries at the 2-position and at the O-glycosylated anomeric carbons of the carbohydrates.

We have also uncovered the key factors of the C-glycosidation and proposed the mechanisms for the C-glycosidation under the pyrrolidine-boric acid catalysis. For the C-glycosidation reactions catalyzed by pyrrolidine-boric acid, both pyrrolidine and boric acid were required to forward

the reactions. The hydroxy group at the 6-position of the reacting aldopyranoses was required for carbohydrates to be transformed to the C-glycoside ketones under the pyrrolidine-boric acid catalysis. The analyses performed suggest that the hydroxy group at the 6-position forms a B-O bond with boric acid to allow the B-O bond formation with the hydroxy group at the 5-position and also to allow the generation of an iminium ion intermediate with pyrrolidine, which is used for the C-C bond formation to lead the formation of the C-glycosidation products. The analyses also suggest that the deprotonation of the hydroxy group at the anomeric carbon is required to form the iminium ion intermediate. Pyrrolidine was involved in the activation of both the carbohydrates and ketones in the presence of boric acid. Pyrrolidine and boric acid worked cooperatively to form the iminium ion intermediate and to afford the C-glycosidation products.

Our developed C-glycosidation reaction methods that use the pyrrolidine-boric acid catalyst system allow access to di- and trisaccharide-derived C-glycosides derivatives including those that are previously difficult to synthesize. Insights obtained from our investigation on the mechanisms of the pyrrolidine-boric acid catalysis for the C-glycosidation will be useful for the development of related catalyzed reactions.

EXPERIMENTAL SECTION

General. For thin layer chromatography (TLC), Merck silica gel 60 F254 aluminum sheets were used. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh) or Yamazen flash column (60 Å, 40 µm). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 400. ^{11}B NMR was recorded on a Jeol ECZ600R. Proton chemical shifts are reported in ppm downfield from tetramethylsilane or from the residual solvent as internal standard in $CDCl_3$ (δ 7.26 ppm), in CD_3OD (δ 3.31 ppm), and in $(CD_3)_2SO$ (δ 2.50 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 77.0 ppm), in CD_3OD (δ 49.0 ppm), and in $(CD_3)_2SO$ (δ 39.5 ppm). High-resolution mass spectra were recorded on a Thermo Scientific LTQ Orbitrap ESI ion trap mass spectrometer.

1. C-Glycosidation of Monosaccharide Aldopyranoses (Table 1)

General procedure for the synthesis of C-glycosides 3. A mixture of carbohydrate (0.50 mmol, 1.0 equiv) and ketone (2.0 mmol, 4.0 equiv) in DMSO (1.0 mL) was stirred at room temperature (25 °C) for 5 min to solubilize the carbohydrate. To the solution, pyrrolidine (0.25 mmol, 0.5 equiv) and boric acid (1.0 mmol, 2.0 equiv) were added and the mixture was stirred at the same temperature for 48 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH or $CHCl_3$/MeOH) to give corresponding C-glycoside **3**.

Additional information. In our observation, after 48 h reaction time, starting material carbohydrate **1** remained significantly, and thus the moderate yields of **3** were obtained. The corresponding hemiketal forms[2b] were possibly generated as a portion during the reactions depending on reaction conditions and also depending on carbohydrates and ketones used in the reactions, although they were not isolated or confirmed.

Compound 3aa. Synthesized by the general procedure from D-glucose (90 mg, 0.50 mmol) but using 10 equiv of acetone (368 µL, 5.0 mmol), purified by flash column chromatography ($CHCl_3$/MeOH = 88:12 to 85:15), colorless gum, 27 mg, 25%. Compound **3aa** is a known compound.[2b,6b,17]

R_f = 0.37 (CH_2Cl_2/MeOH = 5:1). ^{1}H NMR (400 MHz, CD_3OD): δ 3.78 (dd, *J* = 12.0 Hz, 1.7 Hz, 1H), 3.66 (td, *J* = 9.2 Hz, 2.9 Hz, 1H), 3.61 (dd, *J* = 12.0 Hz, 5.0 Hz, 1H), 3.36-3.29 (m, 1H), 3.28-3.20 (m, 2H), 3.06 (t, *J* = 9.2 Hz, 1H), 2.88 (dd, *J* = 16.0 Hz, 2.9 Hz, 1H), 2.59 (dd, *J* = 16.0 Hz, 9.2 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 210.2, 81.6, 79.6, 77.2, 75.1, 71.7, 62.8, 47.1, 30.6. HRMS (ESI): calcd for $C_9H_{17}O_6$ ($[M + H]^+$) 221.1020, found 221.1023.

Procedure using pyrolidine (0.5 equiv) and boric acid (1.0 equiv). To a mixture of pyrrolidine (28.0 µL, 0.34 mmol) in DMSO (1.0 mL), acetone (1.0 mL, 13.6 mmol) and boric acid (42.0 mg, 0.68 mmol) were added at room temperature (25 °C), and the mixture was stirred for 5 min. To this mixture, glucose (150 mg, 0.68 mmol) was added and the resulting mixture was stirred at the same temperature for 24 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 86:14 to 78:22) to give **3aa** (19.1 mg, 12%) with the 5-membered ring isomers[2b,6b] and the further cyclized forms[2b] through hemiketal formation.

Procedure using L-proline and triethylamine. To a mixture of L-proline (192 mg, 1.67 mmol) in PEG (5.0 mL), acetone (4.90 mL, 66.6 mmol) and triethylamine (116 µL, 0.833 mmol) were added at room temperature (25 °C), and the mixture was stirred for 5 min. To this mixture, glucose (600 mg, 3.33 mmol) was added and the resulting mixture was stirred at the same temperature for 24 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 86:14 to 78:22) to give a mixture of product including **3aa** with the 5-membered ring isomers[2b,6b] and further cyclized forms[2] through hemiketal formation (93.0 mg, 88%). Based on further purification by silica gel flash column chromatography (CH_2Cl_2/MeOH = 86:14 to 78:22) and ^{1}H NMR analyses of fractions containing **3aa**, the yield of **3aa** was estimated to be 18%.

Compound 3ab. Synthesized by the general procedure, from D-glucose (90 mg, 0.50 mmol) and ethyl 5-oxohexanoate (320 µL, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 88:12 to 80:20), pale yellow gum, 59 mg, 37%.

R_f = 0.25 (CH_2Cl_2/MeOH = 5:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.08 (q, *J* = 7.2 Hz, 2H), 3.75 (dd, *J* = 11.9 Hz, 2.2 Hz, 1H), 3.63 (td, *J* = 9.2 Hz, 2.8 Hz, 1H), 3.59 (dd, *J* = 11.9 Hz, 5.8 Hz, 1H), 3.33-3.28 (m, 1H), 3.25 (dd, *J* = 9.2 Hz, 9.0 Hz, 1H), 3.21-3.16 (m, 1H), 3.04 (t, *J* = 9.2 Hz, 1H), 2.81 (dd, *J* = 15.6 Hz, 2.8 Hz, 1H), 2.60-2.52 (m, 3H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.81 (quint, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 211.1, 175.1, 81.6, 79.6, 77.3, 75.1, 71.6, 62.7, 61.4, 46.4, 43.0, 34.0, 19.7, 14.5. HRMS (ESI): calcd for $C_{14}H_{25}O_8$ ($[M + H]^+$) 321.1544, found 321.1543.

Compound 3ac. Synthesized by the general procedure, from D-glucose (90 mg, 0.50 mmol) and acetophenone (233 µL, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 86:14 to 80:20), pale yellow gum, 24 mg, 17%. Compound **3ac** is a known compound.[2e]

R_f = 0.29 (CH_2Cl_2/MeOH = 5:1). ^{1}H NMR (400 MHz, CD_3OD): δ 8.01-7.99 (m, 2H), 7.60 (tt, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.52-7.47 (m, 2H), 3.86 (td, *J* = 9.0 Hz, 2.5 Hz, 1H), 3.74 (dd, *J* = 11.9 Hz, 2.4 Hz, 1H), 3.61 (dd, *J* = 11.9 Hz, 5.0 Hz, 1H), 3.42 (dd, *J* = 16.4 Hz, 2.5Hz, 1H), 3.41-3.30 (m, 2H),

3.25-3.17 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 200.6, 138.5, 134.3, 129.7, 129.3, 81.5, 79.7, 77.3, 75.1, 71.6, 62.7, 42.4. HRMS (ESI): calcd for $C_{14}H_{19}O_6$ ($[M + H]^+$) 283.1176, found 283.1176.

Compound 3bb. Synthesized by the general procedure, from D-mannose (90 mg, 0.50 mmol) and ethyl 5-oxohexanoate (320 µL, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 88:12 to 80:20), pale yellow gum, 32 mg, 20%.

R_f = 0.27 (CH_2Cl_2/MeOH = 5:1). ^{1}H NMR (400MHz, CD_3OD): δ 4.11 (q, *J* = 7.2 Hz, 2H), 3.92 (ddd, *J* = 7.6 Hz, 5.3 Hz, 0.9 Hz, 1H), 3.80 (dd, *J* = 11.8 Hz, 2.4 Hz, 1H), 3.72 (dd, *J* = 3.2 Hz, 0.8 Hz, 1H), 3.65 (dd, *J* = 11.8 Hz, 5.6 Hz, 1H), 3.54 (t, *J* = 9.4 Hz, 1H), 3.48 (dd, *J* = 9.4 Hz, 3.2 Hz, 1H), 3.18 (ddd, *J* = 9.4 Hz, 5.6 Hz, 2.4 Hz, 1H), 2.87 (dd, *J* = 16.6 Hz, 7.6 Hz, 1H), 2.65 (dd, *J* = 16.6 Hz, 5.3 Hz, 1H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.33 (t, *J* = 7.2 Hz, 2H), 1.84 (quint, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 210.5, 175.1, 82.0, 76.3, 75.7, 72.4, 68.5, 62.9, 61.4, 44.9, 42.9, 34.1, 19.8, 14.5. HRMS (ESI): calcd for $C_{14}H_{24}O_8Na$ ($[M + Na]^+$) 343.1363, found 343.1364.

3aa 3ab 3ac 3bb

2. C-Glycosidation of Di- and Trisaccharide Aldopyranoses (Schemes 1 and 2)

Procedures for the synthesis of C-glycosides 5 and 7

Procedure A. To a solution of pyrrolidine (0.15 mmol, 0.5 equiv) in DMSO (1.0 mL), acetone (5.8 mmol, 20 equiv) and boric acid (0.29 mmol, 1.0 equiv) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, carbohydrate (0.28~0.29 mmol, 1.0 equiv) was added and the mixture was stirred at the same temperature for 24 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH) to give corresponding C-glycoside **5** or **7**.

Procedure B. To a solution of pyrrolidine (0.15 mmol, 0.5 equiv) in DMSO (0.35 mL), acetone (5.8 mmol, 20 equiv) and boric acid (0.29 mmol, 1.0 equiv) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, carbohydrate (0.28~0.29 mmol, 1.0 equiv) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH) to give corresponding C-glycoside **5** or **7**.

Procedure C. A mixture of carbohydrate (0.50 mmol, 1.0 equiv) and ketone (2.0 mmol, 4.0 equiv) in DMSO (1.0 mL) was stirred at room temperature (25 °C) for 5 min to solubilize the carbohydrate. To the solution, pyrrolidine (0.25 mmol, 0.5 equiv) and boric acid (1.0 mmol, 2.0 equiv) were added and the mixture was stirred at the same temperature for 48 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH) to give corresponding C-glycoside **5** or **7**.

Compound 5aa. Synthesized by procedure A, from D-lactose and acetone. To a solution of pyrrolidine (12.0 µL, 0.146 mmol) in DMSO (1.0 mL), acetone (429 µL, 5.84 mmol) and boric acid (18.0 mg, 0.292 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, D-lactose monohydrate (100 mg, 0.278 mmol) was added and the mixture was stirred at the same temperature for 24 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 71:29 to 63:37) to give **5aa** (48.1 mg, 45%, dr >10:1) as a colorless solid. Compound **5aa** is a known compound.[6b]

Synthesized by procedure B. To a solution of pyrrolidine (12.0 µL, 0.146 mmol) in DMSO (350 µL), acetone (429 µL, 5.84 mmol) and boric acid (18.0 mg, 0.292 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, D-lactose monohydrate (100 mg, 0.278 mmol) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 71:29 to 63:37) to give **5aa** (64.5 mg, 61%, dr >10:1) as a colorless solid.

Synthesized by procedure C but using 10 equiv of acetone (368 µL, 5.0 mmol), from D-lactose monohydrate (180 mg, 0.50 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 70:30 to 65:35), colorless solid, 57 mg, 30%.

R_f = 0.28 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.36 (d, *J* = 7.6 Hz, 1H), 3.85-3.75 (m, 3H), 3.75-3.63 (m, 2H), 3.62-3.46 (m, 6H), 3.39-3.34 (m, 1H), 3.15 (t, *J* = 8.8 Hz, 1H), 2.90 (dd, *J* = 16.4 Hz, 2.2 Hz, 1H), 2.61 (dd, *J* = 16.4 Hz, 9.2 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 210.0, 105.1, 80.8, 80.2, 77.9, 77.1, 74.81, 74.78, 72.6, 70.3, 62.5, 62.0, 47.0, 30.6. HRMS (ESI): calcd for $C_{15}H_{27}O_{11}$ ($[M + H]^+$) 383.1548, found 383.1530.

5aa 5ab 5ac 5ad 5ae 5af 5ag 5ah 5ba 5ca

Compound 5ab. Synthesized by procedure C, from D-lactose and ethyl 5-oxohexanoate. A mixture of D-lactose monohydrate (180 mg, 0.50 mmol) and ethyl 5-oxohexanoate (320 µL, 2.0 mmol) in DMSO (1.0 mL) was stirred at room temperature (25 °C) for 5 min to solubilize the carbohydrate. To the solution, pyrrolidine (21 µL, 0.25 mmol) and H_3BO_3 (61 mg, 1.0 mmol) were added and the mixture was stirred at the same temperature for 48 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 70:30 to 64:36) to give **5ab** (109 mg, 45%, dr >20:1) as a colorless solid.

Synthesized by modified procedure C, from D-lactose and ethyl 5-oxohexanoate, with reaction time for 96 h. A mixture of D-lactose monohydrate (180 mg, 0.50 mmol) and ethyl 5-oxohexanoate (320 µL, 2.0 mmol) in DMSO (1.0 mL) was stirred at room temperature (25 °C) for 5 min to solubilize the carbohydrate. To the solution, pyrrolidine (21 µL, 0.25 mmol) and H_3BO_3 (61 mg, 1.0 mmol) were added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 65:35 to 60:40) to give **5ab** (156 mg, 65%, dr >10:1) as a colorless solid.

R_f = 0.27 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.35 (d, *J* = 7.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.82-3.75 (m, 4H), 3.72-3.65 (m, 2H), 3.60-3.46 (m, 5H), 3.36-3.32 (m, 1H), 3.14 (dd, *J* = 9.4 Hz, 8.8 Hz, 1H), 2.85 (dd, *J* = 15.7 Hz, 2.9 Hz, 1H), 2.62-2.56 (m, 3H), 2.32 (t, *J* = 7.2 Hz, 2H), 1.84 (quint, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 211.0, 175.1, 105.0, 80.8, 80.1, 77.9, 77.2, 77.0, 74.8, 72.5, 70.2, 62.4, 61.9, 61.4, 46.3, 43.1, 34.0, 19.8, 14.5. HRMS (ESI): calcd for $C_{20}H_{35}O_{13}$ ([M + H]$^+$) 483.2072, found 483.2062.

Compound 5ac. Synthesized by procedure C, from D-lactose monohydrate (180 mg, 0.50 mmol) and acetophenone (233 µL, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 74:26 to 65:35), colorless solid, 80 mg, 36%, dr >10:1.

R_f = 0.27 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.96 (d, *J* = 7.0 Hz, 2H), 7.63-7.61 (m, 1H), 7.54-7.50 (m, 2H), 5.25 (d, *J* = 5.7 Hz, 1H), 5.09 (d, *J* = 4.1 Hz, 1H), 4.77 (d, *J* = 4.8 Hz, 1H), 4.70 (d, *J* = 0.9 Hz, 1H), 4.64 (t, *J* = 5.2 Hz, 1H), 4.51 (d, *J* = 4.5 Hz, 1H), 4.37 (t, *J* = 6.0 Hz, 1H), 4.21 (d, *J* = 7.2 Hz, 1H), 3.73 (td, *J* = 9.3 Hz, 2.4 Hz, 1H), 3.64-3.59 (m, 2H), 3.57-3.44 (m, 4H), 3.37-3.27 (m, 5H), 3.23-3.18 (m, 1H), 3.16-3.05 (m, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 198.0, 136.9, 133.0, 128.6, 128.0, 103.8, 80.9, 78.6, 76.2, 75.57, 75.52, 73.25, 73.22, 70.5, 68.1, 60.5, 60.3, 41.0. HRMS (ESI): calcd for $C_{20}H_{29}O_{11}$ ([M + H]$^+$) 445.1704, found 445.1700.

Compound 5ad. Synthesized by procedure C, from D-lactose monohydrate (180 mg, 0.50 mmol) and cyclopropyl methyl ketone (198 µL, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 7:3 to 6:4), colorless solid, 92 mg, 45%.

R_f = 0.27 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.36 (d, *J* = 7.5 Hz, 1H), 3.86-3.63 (m, 5H), 3.60-3.46 (m, 6H), 3.38-3.32 (m, 1H), 3.17 (dd, *J* = 9.2 Hz, 8.8 Hz, 1H), 3.02 (dd, *J* = 16.0 Hz, 2.6 Hz, 1H), 2.72 (dd, *J* = 16.4 Hz, 9.2 Hz, 1H), 2.15-2.09 (m, 1H), 1.00-0.89 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD): δ 212.0, 105.0, 80.7, 80.1, 77.9, 77.0, 76.8, 74.7, 74.6, 72.5, 70.2, 62.4, 61.9, 46.6, 21.7, 11.5, 11.2. HRMS (ESI): calcd for $C_{17}H_{29}O_{11}$ ([M + H]$^+$) 409.1704, found 409.1698.

Compound 5ae. Synthesized by procedure C, from D-lactose monohydrate (180 mg, 0.50 mmol) and benzyl 5-oxohexanoate (440 mg, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 70:30 to 64:36), colorless gum, 95 mg, 35%.

R_f = 0.27 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 7.36-7.30 (m, 5H), 5.10 (s, 2H), 4.36 (d, *J* = 7.6 Hz, 1H), 3.83 (dd, *J* = 3.1 Hz, 0.7 Hz, 1H), 3.81-3.65 (m, 5H), 3.62-3.48 (m, 5H), 3.36-3.32 (m, 1H), 3.16 (dd, *J* = 9.2 Hz, 8.8 Hz, 1H), 2.84 (dd, *J* = 15.8 Hz, 2.9 Hz, 1H), 2.61-2.54 (m, 3H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.85 (quint, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ 211.0, 174.7, 137.5, 129.5, 129.1, 105.0, 80.8, 80.0, 77.7, 77.1, 76.9, 74.76, 74.70, 72.4, 70.2, 67.1, 62.4, 61.9, 46.2, 43.0, 34.0, 19.7. HRMS (ESI): calcd for $C_{25}H_{37}O_{13}$ ([M + H]$^+$) 545.2229, found 545.2210.

Compound 5af. Synthesized by procedure C, from D-lactose monohydrate (180 mg, 0.50 mmol) and 5-hexyn-2-one (192 mg, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 75:25 to 70:30), colorless solid, 44 mg, 21%.

R_f = 0.27 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.35 (d, *J* = 7.6 Hz, 1H), 3.84-3.80 (m, 3H), 3.80-3.75 (m, 1H), 3.72-3.64 (m, 2H), 3.60-3.46 (m, 6H), 3.36-3.32 (m, 1H), 3.15 (dd, *J* = 9.6 Hz, 8.8 Hz, 1H), 2.87 (dd, *J* = 16.0 Hz, 2.8 Hz, 1H), 2.82-2.74 (m, 2H), 2.62 (dd, *J* = 16.0 Hz, 9.1 Hz, 1H), 2.39 (td, *J* = 7.1 Hz, 2.6 Hz, 2H), 2.20 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 209.2, 105.0, 84.0, 80.7, 80.1, 77.9, 77.1, 77.0, 74.8, 72.5, 70.3, 69.6, 62.5, 61.9, 46.2, 43.1, 13.3. HRMS (ESI): calcd for $C_{18}H_{29}O_{11}$ ([M + H]$^+$) 421.1704, found 421.1698.

Compound 5ag. Synthesized by procedure C, from D-lactose monohydrate (180 mg, 0.50 mmol) and 4'-methylacetophenone (267 µL, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 74:26 to 65:35), colorless solid, 80 mg, 35%.

Synthesized by procedure C, but for 96 h, from D-lactose monohydrate (180 mg, 0.50 mmol) and 4'-methylacetophenone (267 µL, 2.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 74:26 to 65:35), colorless solid, 126 mg, 55%.

R_f = 0.27 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.36 (d, *J* = 7.5 Hz, 1H), 3.86-3.73 (m, 6H), 3.71 (dd, *J* = 11.6 Hz, 4.8 Hz, 1H), 3.62-3.51 (m, 5H), 3.49 (dd, *J* = 10.0 Hz, 3,6 Hz, 1H), 3.37-3.33 (m, 1H), 3.28-3.20 (m, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 200.2, 145.5, 136.0, 130.2, 129.5, 105.0, 80.7, 80.1, 78.0, 77.2, 77.0, 74.79, 74.76, 72.5, 70.3, 62.5, 61.8, 42.1, 21.6. HRMS (ESI): calcd for $C_{21}H_{31}O_{11}$ ([M + H]$^+$) 459.1861, found 459.1852.

Compound 5ah. Synthesized by procedure C, from D-lactose monohydrate (180 mg, 0.50 mmol) and 4'-nitroacetophenone (330 mg, 2.0 mmol), purified by column chromatography (CH_2Cl_2/MeOH = 68:32 to 60:40), colorless solid, 61 mg, 25%.

R_f = 0.27 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.32 (d, *J* = 8.9 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H), 5.32 (d, *J* = 5.6 Hz, 1H), 5.11 (d, *J* = 3.7 Hz, 1H), 4.81 (s, 1H), 4.73 (s, 1H), 4.68-4.67 (m, 1H), 4.55 (d, *J* = 4.5 Hz, 1H), 4.42 (t, *J* = 5.9 Hz, 1H), 4.21 (d, *J* = 7.3 Hz, 1H), 3.70 (td, *J* = 9.1 Hz, 2.7 Hz, 1H), 3.65-3.58 (m, 2H), 3.57-3.44 (m, 4H), 3.41-

3.28 (m, 5H), 3.23-3.15 (m, 2H), 3.13-3.06 (m, 1H). ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 197.6, 149.8, 141.7, 129.5, 123.8, 103.8, 80.8, 78.7, 76.1, 75.6, 75.5, 73.3, 73.2, 70.6, 68.1, 60.5, 60.3, 41.8. HRMS (ESI): calcd for $C_{20}H_{28}NO_{13}$ ($[M + H]^+$) 490.1555, found 490.1557.

Compound 5ba. Synthesized by modified procedure A, from D-maltose monohydrate and acetone. To a solution of pyrrolidine (11.0 μL. 0.134 mmol) in DMSO (1.0 mL), acetone (408 μL, 5.55 mmol) and boric acid (17.0 mg, 0.277 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, D-maltose monohydrate (100 mg, 0.277 mmol) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 70:30 to 63:37) to give **5ba** (49.1 mg, 46%, dr >10:1) as a pale yellow gum. Compound **5ba** is a known compound.[2g]

R_f = 0.38 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400M Hz, CD_3OD): δ 5.16 (d, J = 3.6 Hz, 1H), 3.86-3.74 (m, 3H), 3.72-3.58 (m, 5H), 3.52 (t, J = 9.2 Hz, 1H), 3.45 (dd, J = 9.8 Hz, 3.8 Hz, 1H), 3.35-3.24 (m, 2H), 3.13 (t, J = 9.2 Hz, 1H), 2.88 (dd, J = 16.0 Hz, 2.8 Hz, 1H), 2.61 (dd, J = 16.0 Hz, 9.0 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 210.2, 102.8, 81.4, 80.3, 79.4, 77.2, 75.0, 74.69, 74.66, 74.2, 71.5, 62.7, 62.2, 47.0, 30.6. HRMS (ESI): calcd for $C_{15}H_{27}O_{11}$ ($[M + H]^+$) 383.1548, found 383.1538.

Compound 5ca. Synthesized by procedure A, from D-cellobiose and acetone. To a solution of pyrrolidine (12.0 μL. 0.146 mmol) in DMSO (1.0 mL), acetone (429 μL, 5.84 mmol) and boric acid (18.0 mg, 0.292 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, D-cellobiose (100 mg, 0.292 mmol) was added and the mixture was stirred at the same temperature for 48 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 76:24 to 66:34) to give **5ca** (58.7 mg, 53%, dr >10:1) as a pale yellow solid. Compound **5ca** is a known compound.[2g,17]

R_f = 0.43 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.10 (d, 1H, J = 8.0 Hz), 3.88 (dd, J = 11.6 Hz, 2.0 Hz, 1H), 3.85-3.78 (m, 2H), 3.72-3.63 (m, 2H), 3.54 (t, J = 9.0 Hz, 2H), 3.49 (t, J = 8.6 Hz, 1H), 3.41-3.28 (m, 4H), 3.24 (dd, J = 8.8 Hz, 8.0 Hz, 1H), 3.15 (dd, J = 9.2 Hz, 8.8 Hz, 1H), 2.89 (dd, J = 16.4 Hz, 2.8 Hz, 1H), 2.61 (dd, J = 16.4 Hz, 9.2 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 210.4, 104.5, 80.8, 80.1, 78.0, 77.8, 77.7, 76.9, 74.9, 74.8, 71.3, 62.4, 61.9, 47.0, 30.7. HRMS (ESI): calcd for $C_{15}H_{27}O_{11}$ ($[M + H]^+$) 383.1548, found 383.1548.

Compound 7aa. Synthesized by modified procedure C, from 3'-sialyllactose sodium salt and acetone. To a solution of pyrrolidine (13.0 μL, 0.158 mmol) in DMSO (370 μL), acetone (448 μL g, 6.09 mmol) and boric acid (38.0 mg, 0.614 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, 3'-sialyllactose sodium salt (200 mg, 0.305 mmol) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 61:39 to 45:55) to give **7aa** (151.4 mg, 74%, dr >10:1) as a pale yellow gum.

R_f = 0.53 (CH_2Cl_2/MeOH = 1:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.43 (d, J = 7.6 Hz, 1H), 4.05 (dd, J = 9.6 Hz, 3.2 Hz, 1H), 3.95-3.91 (m, 1H), 3.89-3.47 (m, 16H), 3.39-3.34 (m, 1H), 3.14 (t, J = 9.0 Hz, 1H), 2.89 (dd, J = 16.0 Hz, 2.8 Hz, 1H), 2.86 (d, J = 12.4 Hz, 4.0 Hz, 1H), 2.61 (dd, J = 16.0 Hz, 9.2 Hz, 1H), 2.20 (s, 3H), 2.01 (s, 3H), 1.79-1.68 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 210.2, 175.5, 174.9, 105.1, 101.1, 81.3, 80.2, 77.8, 77.6, 77.2, 77.0, 74.9, 74.8, 73.0, 70.8, 70.1, 69.4, 69.0, 64.6, 62.7, 62.2, 54.0, 47.1, 42.1, 30.6, 22.6. HRMS (ESI): calcd for $C_{26}H_{44}NO_{19}$ ($[M + H]^+$) 674.2502, found 674.2493.

7aa

7ab

7ba

7ca

7cc

7cd

7cg

7ci

Compound 7ab. Synthesized by procedure C in a 0.25 mmol-scale for 42 h, from 3'-sialyllactose sodium salt (164 mg, 0.25 mmol) and ethyl 5-oxohexanoate (160 μL, 1.0 mmol), purified by column chromatography ($CHCl_3$/MeOH = 45:55 to 30:70), colorless gum, 80 mg, 40%.

R_f = 0.27 (CH_2Cl_2/MeOH = 1:1). ^{1}H NMR (400 MHz, CD_3OD): δ 4.42 (d, J = 7.9 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 4.04 (dd, J = 9.7 Hz, 3.1 Hz, 1H), 3.92 (brd, J = 2.8 Hz, 1H), 3.87-3.55 (m, 14H), 3.53-3.47 (m, 2H), 3.37-3.33 (m, 1H), 3.14 (t, J = 9.1 Hz, 1H), 2.87-2.80 (m, 2H), 2.67-2.53 (m, 3H), 2.32 (t, J = 7.1 Hz, 2H), 2.01 (s, 3H), 1.84 (quint, J = 7.1 Hz, 2H), 1.77-1.69 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR

(100 MHz, CD_3OD): δ 211.1, 175.4, 175.1, 174.9, 105.0, 101.0, 81.0, 80.1, 77.7, 77.5, 77.2, 76.9, 74.9, 74.8, 72.9, 70.7, 70.0, 69.2, 68.9, 64.4, 62.6, 62.0, 61.4, 53.9, 46.3, 43.1, 42.0, 34.0, 22.6, 19.7, 14.5. HRMS (ESI): calcd for $C_{31}H_{52}O_{21}N$ ($[M + H]^+$) 774.3026, found 774.3020.

Compound 7ba. Synthesized by modified procedure C, from 6'-sialyllactose sodium salt and acetone. To a solution of pyrrolidine (13.0 μL, 0.158 mmol) in DMSO (370 μL), acetone (448 μL g, 6.09 mmol) and boric acid (38.0 mg, 0.614 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, 6'-sialyllactose sodium salt (200 mg, 0.305 mmol) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 54:46 to 33:67) to give **7ba** (164.4 mg, 80%, dr >10:1) as a pale yellow gum.

R_f = 0.23 (CH_2Cl_2/MeOH = 1:1). ^1H NMR (400 MHz, CD_3OD): δ 4.33 (d, J = 7.2 Hz, 1H), 4.06 (dd, J = 9.8 Hz, 7.8 Hz, 1H), 3.94-3.46 (m, 17H), 3.42-3.36 (m, 1H), 3.24-3.17 (m, 1H), 2.93 (dd, J = 16.0, 2.8 Hz, 1H), 2.80 (dd, J = 12.0 Hz, 4.4 Hz, 1H), 2.63 (dd, J = 16.0 Hz, 8.8 Hz, 1H), 2.21 (s, 3H), 2.01 (s, 3H), 1.66 (t, J = 12.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 210.3, 175.0, 174.6, 105.2, 101.5, 81.8, 80.1, 77.8, 76.8, 75.7, 75.0, 74.7, 74.2, 73.2, 72.4, 70.6, 70.3, 69.7, 64.63, 64.55, 62.2, 53.9, 47.0, 42.3, 30.7, 22.9. HRMS (ESI): calcd for $C_{26}H_{44}NO_{19}$ ($[M + H]^+$) 674.2502, found 674.2491.

Compound 7ca. Synthesized by modified procedure A, from D-maltotriose and acetone. To a solution of pyrrolidine (8.0 μL, 0.097 mmol) in DMSO (1.0 mL), acetone (292 μL g, 3.97 mmol) and boric acid (12.0 mg, 0.194 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, D-maltotriose (100 mg, 0.198 mmol) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 70:30 to 63:37) to give **7ca** (37.9 mg, 35%, dr >10:1) as a pale yellow gum.

R_f = 0.20 (CH_2Cl_2/MeOH = 2:1). ^1H NMR (400 MHz, CD_3OD): δ 5.165 (d, J = 3.6 Hz, 1H), 5.159 (d, J = 3.6 Hz, 1H), 3.90-3.59 (m, 12H), 3.54-3.43 (m, 4H), 3.35-3.24 (m, 2H), 3.13 (t, J = 9.4 Hz, 1H), 2.88 (dd, J = 16.2 Hz, 2.8 Hz, 1H), 2.61 (dd, J = 16.2 Hz, 9.2 Hz, 1H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 210.2, 102.8, 102.6, 81.4, 81.2, 80.2, 79.3, 77.2, 75.0, 74.9, 74.71, 74.65, 74.2, 73.8, 73.3, 71.4, 62.7, 62.3, 62.1, 47.0, 30.7. HRMS (ESI): calcd for $C_{21}H_{37}O_{16}$ ($[M + H]^+$) 545.2076, found 545.2067.

Compound 7cc. Synthesized by procedure C in a 0.25 mmol-scale, from D-maltotriose (126 mg, 0.25 mmol) and acetophenone (117 μL, 1.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 60:40 to 50:50), colorless gum, 33 mg, 22%.

R_f = 0.27 (CH_2Cl_2/MeOH = 1:1). ^1H NMR (400 MHz, CD_3OD): δ 8.01 (d, J = 7.2 Hz, 2H), 7.60 (tt, J = 7.4Hz, 1.2 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 5.18 (d, J = 4.0 Hz, 1H), 5.16 (d, J = 3.7 Hz, 1H), 3.91-3.80 (m, 5H), 3.79-3.73 (m, 3H), 3.72-3.43 (m, 9H), 3.41-3.19 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD): δ 200.5, 138.5, 134.3, 129.7, 129.3, 102.8, 102.6, 81.4, 81.2, 80.1, 79.4, 77.2, 75.0, 74.9, 74.7, 74.6, 74.2, 73.8, 73.2, 71.4, 62.7, 62.1, 42.2. HRMS (ESI): calcd for $C_{26}H_{39}O_{16}$ ($[M + H]^+$) 607.2233, found 607.2216.

Compound 7cd. Synthesized by procedure C in a 0.25 mmol-scale, from D-maltotriose (126 mg, 0.25 mmol) and cyclopropyl methyl ketone (100 μL, 1.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 65:35 to 50:50), colorless gum, 42 mg, 30%.

R_f = 0.27 (CH_2Cl_2/MeOH = 1:1). ^1H NMR (400 MHz, CD_3OD): δ 5.19-5.15 (m, 2H), 3.89-3.81 (m, 4H), 3.81-3.60 (m, 8H), 3.58-3.44 (m, 4H), 3.35-3.25 (m, 2H), 3.16 (td, J = 9.0 Hz, 2.4 Hz, 1H), 3.02 (d, J = 16.2 Hz, 1H), 2.76-2.69 (m, 1H), 2.15-2.09 (m, 1H), 0.98-0.93 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD): δ 212.1, 102.7, 102.6, 81.3, 81.2, 80.1, 79.3, 76.9, 75.0, 74.9, 74.7, 74.5, 74.1, 73.7, 73.2, 71.4, 62.6, 62.1, 62.0, 46.6, 21.7, 11.6, 11.3. HRMS (ESI): calcd for $C_{23}H_{39}O_{16}$ ($[M + H]^+$) 571.2233, found 571.2231.

Compound 7cg. Synthesized by procedure C in a 0.25 mmol-scale, from D-maltotriose (126 mg, 0.25 mmol) and 4'-methylacetophenone (134 μL, 1.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 60:40 to 50:50), colorless gum, 39 mg, 25%.

R_f = 0.27 (CH_2Cl_2/MeOH = 1:1). ^1H NMR (400 MHz, CD_3OD): δ 7.90 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 5.17 (d, J = 3.8 Hz, 1H), 5.15 (d, J = 3.8 Hz, 1H), 3.91-3.80 (m, 5H), 3.78-3.72 (m, 3H), 3.70-3.67 (m, 2H), 3.66-3.63 (m, 1H), 3.63-3.56 (m, 2H), 3.54-3.52 (m, 1H), 3.51-3.48 (m, 1H), 3.45 (dd, J = 9.7 Hz, 3.7 Hz, 1H), 3.39 (dd, J =16.4 Hz, 2.3 Hz, 1H), 3.34-3.31 (m, 1H), 3.30-3.23 (m, 2H), 3.19 (dd, J = 16.4 Hz, 8.9 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 200.2, 145.5, 135.9, 130.3, 129.5, 102.8, 102.6, 81.4, 81.3, 80.1, 79.4, 77.2, 75.0, 74.9, 74.7, 74.6, 74.2, 73.8, 73.2, 71.5, 62.6, 62.13, 62.10, 42.1, 21.6. HRMS (ESI): calcd for $C_{27}H_{41}O_{16}$ ($[M + H]^+$) 621.2389, found 621.2374.

Compound 7ci. Synthesized by procedure C in a 0.25 mmol-scale, from D-maltotriose (126 mg, 0.25 mmol) and 4'-cyanoacetophenone (145 mg, 1.0 mmol), purified by flash column chromatography (CH_2Cl_2/MeOH = 60:40 to 49:51), colorless gum, 35 mg, 22%.

R_f = 0.27 (CH_2Cl_2/MeOH = 1:1). ^1H NMR (400 MHz, CD_3OD): δ 8.08 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 5.14-5.11 (m, 2H), 3.85-3.76 (m, 5H), 3.73-3.66 (m, 3H), 3.64-3.54 (m, 5H), 3.52-3.35 (m, 5H), 3.26-3.21 (m, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 199.2, 141.6, 133.6, 129.9, 118.9, 117.1, 102.7, 102.5, 81.2, 81.1, 80.1, 79.3, 77.0, 74.9, 74.8, 74.6, 74.5, 74.0, 73.7, 73.1, 71.3, 62.5, 62.08, 62.04, 42.2. HRMS (ESI): calcd for $C_{27}H_{38}NO_{16}$ ($[M + H]^+$) 632.2185, found 632.2174.

3. Transformations of the C-Glycoside Ketones (Schemes 3, 4, and 5)

Compound 8a. To a mixture of L-proline (8.0 mg, 0.069 mmol) in DMSO (0.5 mL), 6-methoxy-2-napthaldehyde (24.4 mg, 0.131 mmol) and *N*,*N*-diisopropylethylamine (11.0 μL, 0.063 mmol) were added at room temperature (25 °C), and the mixture was stirred for 5 min. To this mixture, compound **5aa** (50.0 mg, 0.131 mmol) was added and the resulting mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 86:14 to 79:21) to give **8a** (38.0 mg, 53%) as a pale yellow solid.

To a solution of pyrrolidine (5.0 μL, 0.061 mmol) in DMSO (1.0 mL), 6-methoxy-2-napthaldehyde (24.4 mg, 0.131 mmol) and boric acid (4.0 mg, 0.065 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, compound **5aa** (50.0 mg, 0.131 mmol) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chroma-

tography ((CH_2Cl_2/MeOH = 86:14 to 79:21) to give **8a** (27.3 mg, 38%) as a pale yellow solid.

R_f = 0.32 (CH_2Cl_2/MeOH = 4:1). ^{1}H NMR (400 M Hz, CD_3OD): δ 7.98 (s, 1H), 7.82-7.71 (m, 4H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.15 (dd, *J* = 9.0 Hz, 2.6 Hz, 1H), 6.96 (d, *J* = 16.4 Hz, 1H), 4.39 (d, *J* = 7.2 Hz, 1H), 3.91 (s, 3H), 3.91-3.45 (m, 11H), 3.43-3.37 (m, 1H), 3.31-3.25 (m, 1H), 3.17 (dd, *J* = 16.0 Hz, 2.4 Hz, 1H), 2.96 (dd, *J* = 16.0 Hz, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 201.1, 160.5, 145.5, 137.5, 131.7, 131.23, 131.16, 130.1, 128.7, 126.5, 125.2, 120.5, 107.1, 105.1, 80.8, 80.1, 77.9, 77.3, 77.0, 74.8, 74.7, 72.5, 70.3, 62.5, 61.9, 55.9, 44.1. HRMS (ESI): calcd for $C_{27}H_{35}O_{12}$ ([M + H]$^+$) 551.21230, found 551.21002.

Compound 8b. To a solution of pyrrolidine (5.0 µL, 0.061 mmol) in DMSO (1.0 mL), 6-methoxy-2-napthaldehyde (24.4 mg, 0.131 mmol) and boric acid (4.0 mg, 0.065 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, compound **5ba** (50.0 mg, 0.131 mmol) was added and the mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 90:10 to 82:18) to give **8b** (30.1 mg, 42%) as a pale yellow gum.

R_f = 0.47 (CH_2Cl_2/MeOH = 4:1). ^{1}H NMR (400 MHz, CD_3OD): δ 8.00 (s, 1H), 7.82-7.77 (m, 2H), 7.80 (d, *J* = 16.4 Hz, 1H), 7.74 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.16 (dd, *J* = 8.8 Hz, 2.6 Hz, 1H), 6.97 (d, *J* = 16.4 Hz, 1H), 5.18 (d, *J* = 4.0 Hz, 1H), 3.92 (s, 3H), 3.86-3.75 (m, 4H), 3.75-3.53 (m, 5H), 3.46 (dd, *J* = 9.2 Hz, 4.0 Hz, 1H), 3.37-3.31 (m, 1H), 3.30-3.22 (m, 2H), 3.16 (dd, *J* = 15.6 Hz, 2.6 Hz, 1H), 2.95 (dd, *J* = 15.6 Hz, 9.2 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 201.1, 160.6, 145.5, 137.6, 131.6, 131.3, 130.2, 128.7, 126.5, 125.3, 120.5, 107.2, 102.9, 81.5, 80.3, 79.5, 77.6, 75.1, 74.81, 74.75, 74.3, 71.1, 62.8, 62.2, 55.9, 44.3. HRMS (ESI): calcd for $C_{27}H_{35}O_{12}$ ([M + H]$^+$) 551.21230, found 551.21008.

Compound 8c. To a mixture of L-proline (8.0 mg, 0.069 mmol) in DMSO (1.0 mL), 6-methoxy-2-napthaldehyde (24.0 mg, 0.129 mmol) and *N*,*N*-diisopropylethylamine (11.0 µL, 0.063 mmol) were added at room temperature (25 °C), and the mixture was stirred for 5 min. To this mixture, compound **5ca** (50.0 mg, 0.131 mmol) was added and the resulting mixture was stirred at the same temperature for 96 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 86:14 to 79:21) to give **8c** (19.0 mg, 27%) as a pale yellow solid.

R_f = 0.66 (CH_2Cl_2/MeOH = 4:1). ^{1}H NMR (400 MHz, CD_3OD): δ 7.99 (s, 1H), 7.81-7.77 (m, 2H), 7.80 (d, *J* = 16.2 Hz, 1H), 7.74 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.97 (d, *J* = 16.2 Hz, 1H), 4.43 (d, *J* = 8.0 Hz, 1H), 3.92 (s, 3H), 3.92-3.77 (m, 4H), 3.68 (dd, *J* = 12.0 Hz, 5.6 Hz, 1H), 3.60 (t, *J* = 8.8 Hz, 1H), 3.54 (t, *J* = 8.8 Hz, 1H), 3.41-3.31 (m, 4H), 3.30-3.21 (m, 2H), 3.15 (dd, *J* = 15.8 Hz, 2.6 Hz, 1H), 2.96 (dd, *J* = 15.8 Hz, 9.0 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 201.1, 160.6, 145.5, 137.6, 131.7, 131.3, 131.2, 130.2, 128.7, 126.5, 125.3, 120.5, 107.1, 104.6, 80.8, 80.2, 78.1, 78.0, 77.8, 77.4, 74.9, 71.4, 62.4, 61.9, 55.9, 44.2. HRMS (ESI): calcd for $C_{27}H_{35}O_{12}$ ([M + H]$^+$) 551.21230, found 551.21227.

Compound 8d. To a solution of pyrrolidine (3.0 µL, 0.037 mmol) in DMSO (1.0 mL), 6-methoxy-2-napthaldehyde (14.0 mg, 0.075 mmol) and boric acid (5.0 mg, 0.081 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, compound **7aa** (50.0 mg, 0.074 mmol) was added and the mixture was stirred at the same temperature for 48 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 69:31 to 51:49) to give **8d** (24.6 mg, 40%) as a pale yellow solid.

R_f = 0.16 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 7.99 (s, 1H), 7.82-7.76 (m, 2H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.74 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 7.25 (d, 1H, *J* = 2.4 Hz), 7.16 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.96 (d, *J* = 16.0 Hz, 1H), 4.45 (d, *J* = 8.0 Hz, 1H), 4.06 (dd, *J* = 9.6 Hz, 3.2 Hz, 1H), 3.94-3.46 (m, 17H), 3.92 (s, 3H), 3.42-3.37 (m, 1H), 3.26 (dd, *J* = 9.6 Hz, 8.8 Hz, 1H), 3.15 (dd, *J* = 15.6 Hz, 2.4 Hz, 1H), 2.95 (dd, *J* =15.6 Hz, 9.0 Hz, 1H), 2.89-2.83 (m, 1H), 2.01 (s, 3H), 1.79-1.68 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 201.1, 175.5, 174.9, 160.6, 145.4, 137.5, 131.6, 131.2, 130.2, 128.7, 126.5, 125.3, 120.5, 107.1, 105.0, 101.1, 81.1, 80.2, 77.9, 77.6, 77.5, 77.0, 74.9, 74.8, 73.0, 70.8, 70.1, 69.3, 69.0, 64.5, 62.7, 62.0, 55.9, 53.9, 44.2, 42.1, 22.6. HRMS (ESI): calcd for $C_{38}H_{52}NO_{20}$ ([M + H]$^+$) 842.3077, found 842.3051.

Compound 8e. To a solution of pyrrolidine (3.0 µL, 0.037 mmol) in DMSO (1.0 mL), 6-methoxy-2-napthaldehyde (14.0 mg, 0.075 mmol) and boric acid (5.0 mg, 0.081 mmol) were added at room temperature (25 °C) and the mixture was stirred for 5 min. To this mixture, compound **7ba** (50.0 mg, 0.074 mmol) was added and the mixture was stirred at the same temperature for 48 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 69:31 to 51:49) to give **8e** (21.5 mg, 35%) as a pale yellow solid.

R_f = 0.16 (CH_2Cl_2/MeOH = 2:1). ^{1}H NMR (400 MHz, CD_3OD): δ 7.99 (s, 1H), 7.82-7.72 (m, 3H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.97 (d, *J* = 16.0 Hz, 1H), 4.33 (d, *J* = 7.6 Hz, 1H), 4.07 (dd, *J* = 10.0 Hz, 8.0 Hz, 1H), 3.92 (s, 3H), 3.92-3.45 (m, 17H), 3.43-3.37 (m, 1H), 3.36-3.30 (m, 1H), 3.19 (dd, *J* = 16.0 Hz, 2.4 Hz, 1H), 2.96 (dd, *J* = 16.0 Hz, 8.8 Hz, 1H), 2.82 (dd, *J* = 12.0 Hz, 4.8 Hz, 1H), 2.00 (s, 3H), 1.68 (t, *J* = 12.0 Hz,

1H). ^{13}C NMR (100 MHz, CD_3OD) δ 201.2, 174.9, 174.5, 160.6, 145.5, 137.6, 131.7, 131.3, 131.2, 130.2, 128.7, 126.5, 125.3, 120.5, 107.1, 105.2, 101.5, 81.7, 80.0, 77.9, 77.2, 75.8, 75.0, 74.6, 74.2, 73.2, 72.5, 70.6, 70.3, 69.8, 64.64, 64.61, 62.1, 55.9, 53.8, 44.2, 42.5, 22.8. HRMS (ESI): calcd for $C_{38}H_{52}NO_{20}$ ($[M + H]^+$) 842.3077, found 842.3055.

Compound 9. A mixture of **4a** (50 mg, 0.13 mmol) and *p*-toluenesulfonyl hydrazide (32 mg, 0.17 mmol) in EtOH (1.0 mL) was stirred at room temperature (25 °C) for 18 h. The mixture was purified silica gel flash column chromatography (CH_2Cl_2/MeOH = 87:13 to 80:20) to give **9** (41 mg, 57%) as a light brown solid.

R_f = 0.26 (CH_2Cl_2/MeOH (5:1). ^1H NMR (400MHz, CD_3OD) δ 7.82 (d, *J* = 8.0 Hz, 2H x 2/5), 7.80 (d, *J* = 8.0 Hz, 2H x 3/5), 7.39-7.34 (m, 2H), 4.35 (d, *J* = 7.6 Hz, 1H), 3.85-3.37 (m, 11H), 3.34-3.26 (m, 1H x 2/5), 3.21-3.16 (m, 1H x 3/5), 3.09 (t, *J* = 8.8 Hz, 1H x 3/5), 3.07 (t, *J* = 8.8 Hz, 1H x 2/5), 2.73 (dd, *J* = 14.8 Hz, 2.8 Hz, 1H x 3/5), 2.65-2.55 (m, 2H x 2/5), 2.42 (s, 3H), 2.27 (dd, *J* = 14.8 Hz, 9.2 Hz, 1H x 3/5), 1.94 (s, 3H x 2/5), 1.86 (s, 3H x 3/5). ^{13}C NMR (100 MHz, CD_3OD) δ 159.3, 159.1, 145.2, 145.1, 137.6, 137.3, 130.5, 130.4, 129.1, 129.0, 105.0, 80.8, 80.4, 80.2, 80.0, 78.5, 77.9, 77.6, 77.1, 77.0, 74.84, 74.79, 74.76, 74.6, 72.52, 72.48, 70.3, 62.49, 62.46, 62.0, 61.6, 41.6, 34.7, 23.9, 21.5, 17.2. HRMS (ESI): calcd for $C_{22}H_{35}O_{12}N_2S$ ($[M + H]^+$) 551.1905, found 551.1871.

Compound 10. A mixture of **7aa** (100 mg, 0.148 mmol) and (aminooxy)acetic acid hemihydrochloride (H_2N-O-CH_2COOH • 1/2 HCl) (24.0 mg, 0.220 mmol) in DMSO (1.0 mL) was stirred at room temperature (25 °C) for 18 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 54:46 to 26:74) to give the corresponding oxime ether derivative (110 mg, 99%). A mixture of the oxime ether (100 mg, 0.134 mmol), dansylcadaverine (49.0 mg, 0.146 mmol), and 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (56.0 mg, 0.200 mmol) in MeOH (1.0 mL) was stirred at room temperature (25 °C) for 18 h. The mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 82:18 to 50:50) to give **10** (81.8 mg, 57%) as a pale yellow solid.

R_f = 0.38 (CH_2Cl_2/MeOH (3:1). ^1H NMR (400 MHz, CD_3OD): δ 8.55 (d, *J* = 8.8 Hz, 1H), 8.36 (d, *J* = 8.4 Hz, 1H), 8.19 (dd, *J* = 7.2 Hz, 0.8 Hz, 1H), 7.62-7.55 (m, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 4.44 (d, *J* = 8.0 Hz, 1H x 1/3), 4.43 (d, *J* = 8.0 Hz, 1H x 2/3), 4.39 (s, 2H × 2/3), 4.38 (s, 2H x 1/3), 4.08-4.03 (m, 1H), 3.95-3.92 (m, 1H), 3.90-3.46 (m, 16H + 1H x 1/3), 3.46-3.39 (m, 1H x 2/3), 3.34 – 3.30 (m, 1H), 3.18-3.11 (m, 1H), 3.09-3.00 (m, 2H), 2.95 (dd, *J* = 14.4 Hz, 3.2 Hz, 1H x 1/3), 2.88 (s, 6H), 2.88-2.80 (m, 3H), 2.71 (dd, *J* = 14.4 Hz, 2.8 Hz, 1H x 2/3), 2.58 (dd, *J* = 14.4 Hz, 8.8 Hz, 1H x 1/3), 2.28 (dd, *J* = 14.4 Hz, 9.2 Hz, 1H x 2/3), 2.01 (s, 3H), 1.96 (s, 3H × 2/3), 1.90 (s, 3H x 1/3), 1.78-1.70 (m, 1H), 1.38-1.25 (m, 4H), 1.20-1.10 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 175.5, 174.9, 172.5, 172.4, 160.3, 160.2, 153.2, 137.2, 131.2, 131.1, 131.0, 130.1, 129.1, 124.3, 120.6, 116.4, 105.1, 101.1, 81.4, 80.22, 80.17, 78.5, 78.2, 77.9, 77.6, 77.0, 75.5, 75.1, 74.9, 73.1, 73.0, 72.9, 70.8, 70.1, 69.3, 69.0, 64.6, 62.7, 62.3, 54.0, 45.8, 43.7, 42.1, 39.8, 39.7, 30.1, 29.8, 24.7, 22.6, 20.7, 15.1. HRMS (ESI): calcd for $C_{45}H_{70}N_5O_{22}S$ ($[M + H]^+$) 1064.4228, found 1064.4231.

4. Evaluation of Catalyst Systems

Procedure for the evaluation of the catalyst systems for the C-glycosidation (Table 2)

Entries 2-8. A mixture of D-lactose monohydrate (90 mg, 0.25 mmol, 1.0 equiv) and ethyl 5-oxohexanoate (160 μL, 1.0 mmol, 4.0 equiv) in DMSO (0.5 mL) was stirred at room temperature (25 °C) for 5 min to solubilize the carbohydrate. To the solution, pyrrolidine (10.5 μL, 0.13 mmol, 0.5 equiv) and the other component listed in the entry (0.50 mmol, 2.0 equiv) were added and the mixture was stirred at the same temperature for 48 h. Formation of product **5ab** was monitored by TLC analyses (CH_2Cl_2/MeOH = 5:1). When formation of **5ab** was observed on the TLC, the mixture was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 70:30 to 64:36) to give **5ab** to determine the yield.

Entries 9 and 10. The reaction was performed by the same procedure as that of entries 2-8 described above except using Et_3N or DBU (0.13 mmol, 0.5 equiv) as indicated instead of pyrrolidine.

Entries 11 and 12. The reaction was performed by the same procedure as that of entries 2-8 described above except using pyrrolidine (0.13 mmol, 0.5 equiv) or boric acid (0.5 mmol, 2.0 equiv) alone as catalyst, as indicated.

Entry 14. The reaction was performed by the same procedure as that of entries 2-8 described above except using acetophenone (1.0 mmol, 4.0 equiv) and benzylamine (0.13 mmol, 0.5 equiv) instead of ethyl 5-oxohexanoate and pyrrolidine.

Procedure for the evaluation of the catalyst systems for the ketone activation

To a solution of acetone (0.4 mL) and 4-nitrobenzaldehyde (30 mg, 0.2 mmol, 1.0 equiv) in DMSO (1.6 mL), the catalyst was added at room temperature (25 °C) and the mixture was stirred for 1 h. The mixture was diluted with EtOAc, added to aqueous 1 N HCl solution, and extracted with EtOAc. Organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, concentrated, and analyzed by ^1H NMR to determine the conversion and the products distributions. Catalyst systems tested in this reaction were pyrrolidine (3.3 μL, 0.04 mmol, 0.2 equiv), pyrrolidine (3.3 μL, 0.04 mmol, 0.2 equiv)-boric acid (2.5 mg, 0.04 mmol, 0.2 equiv), pyrrolidine (8.2 μL, 0.10 mmol, 0.5 equiv)-boric acid (31 mg, 0.40 mmol, 2.0 equiv), pyrrolidine (3.3 μL, 0.04 mmol, 0.2 equiv)-acetic acid (2.3 μL, 0.04 mmol, 0.2 equiv), and boric acid (2.5 mg, 0.04 mmol, 0.2 equiv).

5. Synthesis of Intermediate 11 and the Reaction of 11

Compound 11. A mixture of D-lactose monohydrate (180 mg, 0.50 mmol), pyrrolidine (42 μL, 0.50 mmol), and H_3BO_3 (61 mg, 1.0 mmol) in DMSO (1.0 mL) was stirred at room temperature (25 °C) for 24 h. The mixture was purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 2:3) to give **11** (β-anomer, 29 mg, 15%) as a pale yellow gum. Based on the NMR, the obtained **11** was β-isomer. By TLC analyses, the conversion was estimated >90% after 24 h and the main spot on the TLC had the same R_f value as that of isolated **11**. It seems that compound **11** was decomposed (hydrolyzed) in the presence of silica gel or was not fully eluted from the silica gel column.

R_f = 0.21 (CH_2Cl_2/MeOH = 5:2). ^1H NMR (400MHz, CD_3OD): δ 4.36 (d, *J* = 7.5 Hz, 1H), 4.07 (d, *J* = 8.9 Hz, 1H), 3.91-3.86 (m, 1H), 3.85-3.80 (m, 2H), 3.78-3.76 (m, 1H), 3.72-3.68 (m, 1H), 3.61-3.57 (m, 2H), 3.57-3.47 (m, 4H), 3.45-3.37 (m, 1H), 3.03-2.94 (m, 2H), 2.92-2.85 (m, 2H),

1.82-1.74 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD) δ 105.1, 92.1, 81.2, 77.7, 77.6, 77.0, 74.8, 72.8, 72.5, 70.3, 62.4, 62.3, 47.4, 25.3. HRMS (ESI): calcd for $C_{16}H_{30}NO_{10}$ ($[M + H]^+$) 396.1864, found 396.1860.

Reaction of compound 11 with ketone 2b under the pyrrolidine-boric acid catalysis system

A mixture of compound **11** (β-isomer, 15.0 mg, 0.038 mmol), ketone **2b** (24.3 μL, 0.15 mmol), pyrrolidine (1.6 μL, 0.019 mmol), and H_3BO_3 (61 mg, 1.0 mmol) in $(CD_3)_2SO$ (0.3 mL) was stirred at room temperature (25 °C). Formation of **5ab** was observed (>50% at 48 h).

6. NMR Analyses of the Reaction Mixtures and Related Mixtures

Procedure of the preparation of the mixture used for the NMR analyses (Figure 1)

A mixture of D-lactose monohydrate (180 mg, 0.50 mmol) in $(CD_3)_2SO$ (1.0 mL) was stirred at room temperature (25 °C) for 5 min to solubilize the carbohydrate. To the solution, pyrrolidine (21 μL, 0.25 mmol) and/or H_3BO_3 (61 mg, 1.0 mmol) were added as indicated and the mixture was stirred at the same temperature. After 5 min, a portion was taken from the mixture and was analyzed by NMR. For the analysis of pyrrolidine and boric acid alone in $(CD_3)_2SO$, the mixture was prepared without the carbohydrate. For the analysis of the reaction mixture containing 4'-methylacetophenone, the reaction mixture was prepared according to procedure C but using $(CD_3)_2SO$ and was analyzed by NMR. The spectra were of ^{13}C NMR (100 MHz). ^{13}C NMR signal assignments of D-lactose shown in Figure 1 are based on the previously reported data.[21]

^{13}C NMR spectra (range 220 ppm to –20 ppm) of the solutions shown in Figure 1(a)-(f) are shown in Figure S1; the analyzed time is indicated. ^{13}C NMR spectra at 5 min, 24 h, and 48 h of the reaction mixture shown in Figure 1(g) are shown in Figure S2. ^{11}B NMR spectra of the same mixture as that of Figure 1(b) and of Figure 1(f) are shown in Figure S3.

NMR analyses similar to Figure 1 using D-maltose and D-cellobiose instead of D-lactose are shown in Figures S4 and S5, respectively. ^{13}C NMR signal assignments of D-maltose and D-cellobiose shown in Figures S4 and S5 are based on the previously reported data.[26]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Figures S1-S5 and NMR spectra (compounds). (PDF)

AUTHOR INFORMATION

Corresponding Author

* ftanaka@oist.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank Dr. Michael Chandro Roy, Research Support Division, Okinawa Institute of Science and Technology Graduate University for mass analyses. This study was supported by the Okinawa Institute of Science and Technology Graduate University and in part by the MEXT/JSPS (Japan) Grant-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" (No. 26105757).

REFERENCES

(1) (a) Schmaltz, R. M.; Hanson, S. R. Wong, C.-H. Enzymes in the Synthesis of Glycoconjugates. *Chem. Rev.* **2011**, *111*, 4259-4303. (b) Bokor, E.; Kun, S.; Goyard, D.; Toth, M.; praly, J.-P.; Vidal, S.; Somsak, L. C-Glycopyranosyl Arenes and Hetarenes: Synthetic Methods and Bioactivity Focused on Antidiabetic Potential. *Chem. Rev.* **2017**, *117*, 1687-1764. (c) Palaniappan, K. K.; Bertozzi, C. R. Chemical Glycoproteomics. *Chem. Rev.* **2016**, *116*, 14277-14306. (d) Lalitha, K.; Muthusamy, K.; Prasad, Y. S.; Vemula, P. K. Nagarajan, S. ChemInform Abstract: Recent Developments in β-C-Glycosides: Synthesis and Applications. *Carbohydr. Res.* **2015**, *402*, 158-171.

(2) (a) Richter, C.; Krumrey, M.; Bahri, M.; Trunschke, S.; Mahrwald, R. Amine-Catalyzed Cascade Reactions of Unprotected Aldoses—An Operationally Simple Access to Defined Configured Stereotetrads or Stereopentads. *ACS Catal.* **2016**, *6*, 5549-5552. (b) Wang, J.; Li, Q.; Ge, Z.; Li, R. A Versatile and Convenient Route to Ketone C-Pyranosides and Ketone C-Furanosides From Unprotected Sugars. *Tetrahedron* **2012**, *68*, 1315-1320. (c) Bragnier, N.; Scherrmann, M.-C. One-Step Synthesis of β-C-Glycosidic Ketones in Aqueous Media: The Case of 2-Acetamido Sugars. *Synthesis* **2005**, 814-818. (d) Riemann, I.; Papadopoulos, M. A.; Knorst, M.; Fessner, W.-D. C-Glycosides by Aqueous Condensation of β-Dicarbonyl Compounds with Unprotected Sugars. *Aust. J. Chem.* **2002**, *55*, 147-154. (e) Feng, W.; Fang, Z.; Yang, J.; Zheng, B.; Jiang, Y. Microwave-Assisted Efficient Synthesis of Aryl Ketone β-C-Glycosides from Unprotected Aldoses. *Carbohydr. Res.* **2011**, *346*, 352-356. (f) Liu, L.; Motaal, B. A.; Schmidt-Supprian, M.; Pohl, N. L. B. Multigram Synthesis of Isobutyl-β-C-galactoside as a Substitute of Isopropylthiogalactoside for Exogenous Gene Induction in Mammalian Cells. *J. Org. Chem.* **2012**, *77*, 1539-1546. (g) Hersant, Y.; Abou-Jneid, R.; Canac, Y.; Lubineau, A.; Philipp, M.; Semeria, D.; Radisson, X.; Scherrmann, M.-C. One-Step Synthesis of β-C-Glycolipid Derivatives from Unprotected Sugars. *Carbohydr. Res.* **2004**, *339*, 741-745. (h) Rodrigues, F.; Canac, Y.; Lubineau, A. A Convenient, One-Step, Synthesis of β-C-Glycosidic Ketones in Aqueous Media. *Chem. Commun.* **2000**, 2049-2050. (i) Scherrmann, M.-C. Knoevenagel Reaction of Unprotected Sugars. *Top. Curr. Chem.* **2010**, *295*, 1-18.

(3) (a) Voigy, B.; Mahrwald, R. Organocatalyzed Cascade Reactions of Carbohydrates – A Direct Access to C-Glycosides. *Chem. Commun.* **2014**, *50*, 817-819. (b) Voigt, B.; Matviitsuk, A.; Mahrwald, R. Organocatalyzed Knoevenagel-Addition—Simple Access to Carbon Chain-Elongated Branched Carbohydrates. *Tetrahedron* **2013**, *69*, 4302-4310. (c) Voigt, B.; Scheffler, U.; Mahrwald, R. Stereoselective Amine-Catalyzed Carbohydrate Chain Elongation. *Chem. Commun.* **2012**, *48*, 5304-5306. (d) Mahrwald, R. The Long Underestimated Carbonyl Function of Carbohydrates – An Organocatalyzed Shot into Carbohydrate Chemistry. *Chem. Commun.* **2015**, *51*, 13868-13877. (e) Winzar, R.; J. Philips, J.; Kiefel, M. J. A Simple Synthesis of C-8 Modified 2-Keto-3-deoxy-d-manno-octulosonic Acid (KDO) Derivatives. *Synlett* **2010**, 583-587.

(4) Sowden, J.; Fischer, H. O. L. The Condensation of Nitromethane with D- and L-Arabinose: Preparation of L-Glucose and L-Mannose. *J. Am. Chem. Soc.* **1947**, *69*, 1963-1965.

(5) Wood, H. B.; Fletcher, H. G. 2-Deoxy-D-ribose. VI. The Preparation of Derivatives of 3-Deoxy-D-ribo-hexonic Acid and 3-Deoxy-D-arabino-hexonic Acid Therefrom. Some Observations on the Kiliani Synthesis. *J. Org. Chem.* **1961**, *26*, 1969-1973.

(6) (a) van Kalkeren, H. A.; van Rootselaar, S.; Haasjes, F. S.; Rutjes, F. P. J. T.; van Delft, F. L. Protective Group-Free Synthesis of 3,4-Dihydroxytetrahydrofurans from Carbohydrates: Formal Total Synthesis of Sphydrofuran. *Carbohydr. Res.* **2012**, *362*, 30-37. (b) Ranoux, A.; Lemiegre, L.; Benoit, M.; Guegan, J.-P.; Benvegnu, T. Horner-Wadsworth-Emmons Reaction of Unprotected Sugars in Water or in the Absence of Any Solvent: One-Step Access to C-Glycoside Amphiphiles. *Eur. J. Org. Chem.* **2010**, 1314-1323.

(7) (a) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. Use of an Organometallic Reagent in Water: $Sc(OTf)_3$-Catalyzed Allylation Reactions of Aldehydes in Micellar Systems. *Chem. Lett.* **1997**, 831-832. (b) Toshima, K.; Matsuo, G.; Ishizuka, T.; Ushiki, Y.; Nakata, M.; Matsumura, S. Aryl and Allyl C-Glycosidation Methods Using Unprotected Sugars. *J. Org. Chem.* **1998**, *63*, 2307-2313. (c) Schmid, W.; Whitesides, G. M. Carbon-Carbon Bond Formation in Aqueous Ethanol: Diastereoselective Transformation of Unprotected Carbohydrates to Higher Carbon Sugars using Allyl Bromide and Tin Metal. *J. Am. Chem. Soc.* **1991**, *113*, 6674-6675. (d) Palmelund, A.; Madsen, R. Chain Elongation of Aldoses by Indium-Mediated Coupling with 3-Bromopropenyl Esters. *J. Org. Chem.* **2005**, *70*, 8248-8251. (e) J.-B. Behr, J.-B.; Hottin, A.; Ndoye, A. Highly Selective Indium Mediated Allylation of Unprotected Pentosylamines. *Org. Lett.* **2012**, *14*, 1536-1539. (f) Kimura, Y.; Ito, S.; Shimizu, Y.; Kanai, M. Catalytic Anomeric Aminoalkynylation of Unprotected Aldoses. *Org. Lett.* **2013**, *15*, 4130-4133. (g) Wei, X-F.; Shimizu, Y.; Kanai, M. An Expeditious Synthesis of Sialic Acid Derivatives by Copper(I)-Catalyzed Stereodivergent Propargylation of Unprotected Aldoses. *ACS Cent. Sci.* **2016**, *2*, 21-26. (h) Santos, R. G.; Xavier, N. M.; Bordado, J. C.; Rauter, A. P. Efficient and First Regio- and Stereoselective DirectC-Glycosylation of a Flavanone Catalysed by $Pr(OTf)_3$ Under Conventional Heating or Ultrasound Irradiation. *Eur. J. Org. Chem.* **2013**, 1441-1447.

(8) Hong, Z.; Liu, L.; Hsu, C.-C.; Wong, C.-H. Three-Step Synthesis of Sialic Acids and Derivatives. *Angew. Chem., Int. Ed.* **2006**, *45*, 7417-7421.

(9) (a) Witte, S. N. R.; Voigt, B.; Mahrwald, R. Amine-Catalyzed Cascade Reactions of Unprotected and Unactivated- Carbohydrates: Direct Access to C-Glycosides. *Synthesis* **2015**, *47*, 2249-2255. (b) Richter, C.; Krumrey, M.; Klaue, K.; Mahrwald, R. Cascade Reactions of Unprotected Ketoses with Ketones - A Stereoselective Access to C-Glycosides. *Eur. J. Org. Chem.* **2016**, 5309-5320. (c) Wei, X.; Shi, S.; Xie, X.; Shimizu, Y.; Kanai, M. Copper(I)-Catalyzed Dehydrative C-Glycosidation of Unprotected Pyranoses with Ketones. *ACS Catal.* **2016**, *6*, 6718-6722. (d) Johnson, S.; Tanaka, F.; Direct Synthesis of C-Glycosides from Unprotected 2-*N*-Acyl-Aldohexoses via Aldol Condensation–Oxa-Michael Reactions with Unactivated Ketones. *Org. Biomol. Chem.* **2016**, *14*, 259-264.

(10) (a) Adak, L.; Kawamura, S.; Toma, G.; Takenaka, T.; Isozaki, K.; Takaya, H.; Orita, A.; Li, H. C.; Shing, T. K. M.; Nakamura, M. Synthesis of Aryl C-Glycosides via Iron-Catalyzed Cross Coupling of Halosugars: Stereoselective Anomeric Arylation of Glycosyl Radicals. *J. Am. Chem. Soc.* **2017**, *139*, 10693-10701. (b) Zhu, F.; Rourke, M. J.; Yang, T.; Rodriguez, J.; Walczak, M. A. Highly Stereospecific Cross-Coupling Reactions of Anomeric Stannanes for the Synthesis of C-Aryl Glycosides. *J. Am. Chem. Soc.* **2016**, *138*, 12049-12052. (c) Zhao, C.; Jia, X.; Wang, X.; Gong, H. Ni-Catalyzed Reductive Coupling of Alkyl Acids with Unactivated Tertiary Alkyl and Glycosyl Halides. *J. Am. Chem. Soc.* **2014**, *136*, 17645-17651. (d) Kramer, J. R.; Deming, T. J. Glycopolypeptides via Living Polymerization of Glycosylated-L-lysine N-Carboxyanhydrides. *J. Am. Chem. Soc.* **2010**, *132*, 15068-15071. (e) McGarvery, G. J.; LeClair, C. A.; Schmidtmann, B. A. Studies on the Stereoselective Synthesis ofC-Allyl Glycosides. *Org. Lett.* **2008**, *10*, 4727-4730. (f) Gong, H.; Gagne, M. R. Diastereoselective Ni-Catalyzed Negishi Cross-Coupling Approach to Saturated, Fully Oxygenated C-Alkyl and C-Aryl Glycosides. *J. Am. Chem. Soc.* **2008**, *130*, 12177-12183. (g) Enders, D.; Gasperi, T. Proline Organocatalysis as a New Tool for the Asymmetric Synthesis of Ulosonic Acid Precursors. *Chem. Commun.* **2007**, 88-90. (h) Gillingham, D. G.; Stallforth, P.; Adibekian, A.; Seeberger, P. H.; Hilvert, D. Chemoenzymatic Synthesis of Differentially Protected 3-Deoxysugars. *Nat. Chem.* **2010**, *2*, 102-105. (i) Hsu, C.-H.; Schelwies, M.; Enck, S.; Huang, L.-Y.; Huang, S.-H.; Chang, Y.-F.; Cheng, T.-J. R.; Cheng,W.-C.; Wong, C.-H. Iminosugar C-Glycoside Analogues of α-D-GlcNAc-1-Phosphate: Synthesis and Bacterial Transglycosylase Inhibition. *J. Org. Chem.* **2014**, *79*, 8629-8637.

(11) (a) Kim, M. J.; Hennen, W. J.; Sweers, M.; Wong, C.-H. Enzymes in Carbohydrate Synthesis: N-Acetylneuraminic Acid Aldolase Catalyzed Reactions and Preparation of N-Acetyl-2-Deoxy-D-Neuraminic Acid Derivatives. *J. Am. Chem. Soc.* **1988**, *110*, 6481-6486. (b) Simon, E.; Bednarski, M. D.; Whitesides, G. Synthesis of CMP-NeuAc from N-Acetylglucosamine: Generation of CTP from CMP using Adenylate Kinase *J. Am. Chem. Soc.* **1988**, *110*, 7159-7163. (c) Yu, H.; Huang, S.; Chokhawala, H.; Sun, M.; Zhang, H.; Chen, X. Highly Efficient Chemoenzymatic Synthesis of Naturally Occurring and Non-Natural α-2,6-Linked Sialosides: AP. damsela α-2,6-Sialyltransferase with Extremely Flexible Donor-Substrate Specificity. *Angew. Chem., Int. Ed.* **2006**, *45*, 3938-3944. (d) Chokhawala, H. C.; Cao, H.; Yu, H.; Chen, X. Enzymatic Synthesis of Fluorinated Mechanistic Probes for Sialidases and Sialyltransferases. *J. Am. Chem. Soc.* **2007**, *129*, 10630-10631. (e) Bednarski, M. D.; Chenault, H. K.; Simon, E. S.; Whitesides, G. M. Membrane-Enclosed Enzymic Catalysis (MEEC): a Useful, Practical New Method for the Manipulation of Enzymes in Organic Synthesis. *J. Am. Chem. Soc.* **1987**, *109*, 1283-1285. (f) Tsai, C.-S.; Yen, H.-Y.; Lin, M.-I.; Tsai, T.-I.; Wang, S.-Y.; Huang, W.-I.; Hsu, T.-L.; Cheng, Y.-S. E.; Fang, J.-M.; Wong, C.-H. Cell-Permeable Probe for Identification and Imaging of Sialidases. *Proc. Natl. Acad. Sci.* **2013**, *110*, 2466-2471. (g) Sasaki, E.; Lin, C.; Lin, K.-Y.; Liu, H. Construction of the Octose 8-Phosphate Intermediate in Lincomycin A Biosynthesis: Characterization of the Reactions Catalyzed by LmbR and LmbN. *J. Am. Chem. Soc.* **2012**, *134*, 17432-17435. (h) Brovetto, M.; Gamenara, D.; Mendez, P. S.; Seoane, G. C−C Bond-Forming Lyases in Organic Synthesis. *Chem. Rev.* **2011**, *111*, 4346-4403.

(12) (a) Young, I. S.; Baran, P. S. Protecting-Group-Free Synthesis as an Opportunity for Invention. *Nat. Chem.* **2009**, *1*, 193-205. (b) Trost, B. M. The Atom Economy--A Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471-1477.

(13) (a) List. B.; Lerner, R. A.; Barbas III, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon−Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267. (c) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. Direct Catalytic Asymmetric Synthesis of anti-1,2-Amino Alcohols and Syn-1,2-Diols through Organocatalyticanti-Mannich and syn-Aldol Reactions. *J. Am. Chem. Soc.* **2007**, *129*, 288-289. (d) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Tanaka, F.; Barbas, C. F., III. Mimicking Fructose and Rhamnulose Aldolases: Organocatalytic syn-Aldol Reactions with Unprotected Dihydroxyacetone. *Angew. Chem., Int. Ed.* **2007**, *46*, 5572-5575. (e) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. Catalysis of 3-Pyrrolidinecarboxylic Acid and Related Pyrrolidine Derivatives in Enantioselective anti-Mannich-Type Reactions: Importance of the 3-Acid Group on Pyrrolidine for Stereocontrol. *J. Am. Chem. Soc.* **2008**, *130*, 875-886. (f) Cui, H.-L.; Tanaka, F. Catalytic Enantioselective Formal Hetero-Diels-Alder Reactions of Enones with Isatins to Give Spirooxindole Tetrahydropyranones. *Chem.-Eur. J.* **2013**, *19*, 6213-6216.

(14) (a) Machajewski, T. D.; Wong, C.-H. The Catalytic Asymmetric Aldol Reaction. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352-1374. (b) Garrabou, X.; Castillo, J. A.; Guerard-Helaine, C.; Parella, T.; Joglar, J.; Lemaiire, M.; Clapes, P. Asymmetric Self- and Cross-Aldol Reactions of Glycolaldehyde Catalyzed by D-Fructose-6-phosphate Aldolase. *Angew. Chem., Int. Ed.* **2009**, *48*, 5521-5525. (c) Northrup, A. B.; MacMillan, D. W. C. Two-Step Synthesis of Carbohydrates by Selective Aldol Reactions. *Science* **2004**, *305*, 1752-1755. (d) Chouthaiwale, P. V.; Tanaka, F. Reactions of Pyruvates: Organocatalytic Synthesis of Functionalized Dihydropyrans in One Pot and further Transformations to Functionalized Carbocycles and Heterocycles. *Chem. Commun.* **2014**, *50*, 14881-14884.

(15) (a) Ajay, A.; Sharma, S.; Gupt, M. P.; Bajpai, V.; Hamidullah, Kumar, B.; Kaushik, M. P.; Knowar, R.; Ampapathi, R. S.; Tripathi, R. P. Diversity Oriented Synthesis of Pyran Based Polyfunctional Stereogenic Macrocyles and Their Conformational Studies. *Org. Lett.* **2012**, *14*, 4306-4309. (b) Riafecha, L. E.; Rodriguez, O. M.; Vullo, D.; Supuran, C. T.; Colinas, P. A. Attachment of Carbohydrates to Methoxyaryl Moieties Leads to Highly Selective Inhibitors of the

Cancer Associated Carbonic Anhydrase Isoforms IX and XII. *Bioorg. Med. Chem.* **2014**, *22*, 5308-5314.

(16) Price, N. P.; Bowman, M. J.; Gail, S. L.; Berhow, M. A.; Kendra, D. F.; Lerouge, P. Functionalized C-Glycoside Ketohydrazones: Carbohydrate Derivatives that Retain the Ring Integrity of the Terminal Reducing Sugar. *Anal. Chem.* **2010**, *82*, 2893-2899.

(17) Howard, S.; Withers, S. G. Bromoketone C-Glycosides, a New Class of β-Glucanase Inactivators. *J. Am. Chem. Soc.* **1998**, *120*, 10326-10331.

(18) Teichert, J. F.; Mazunin, D.; Bode, J. W. Chemical Sensing of Polyols with Shapeshifting Boronic Acids As a Self-Contained Sensor Array. *J. Am. Chem. Soc.* **2013**, *135*, 11314-11321.

(19) (a) Zhang, D.; Tanaka, F. Determination of Relative Frequency of Carbanion Formation at α-Positions of Ketones under Aldol Reaction Catalysis Conditions. *Org. Lett.* **2017**, *19*, 3803-3806. (b) Zhang, D.; Tanaka, F. Aldol Reactions of Ketone Donors with Aryl Trifluoromethyl Ketone Acceptors Catalyzed by 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) for Concise Access to Aryl- and Trifluoromethyl-Substituted Tertiary Alcohols. *Adv. Synth. Catal.* **2015**, *357*, 3458-3462. (c) Markert, M.; Mulzer, M.; Schetter, B.; Mahrwald, R. Amine-Catalyzed Direct Aldol Addition. *J. Am. Chem. Soc.* **2007**, *129*, 7258-7259.

(20) Cui, H.-L.; Chouthaiwale, P. V.; Yin, F.; Tanaka, F. Reaction-Based Mechanistic Investigations of Asymmetric Hetero-Diels-Alder Reactions of Enones with Isatins Catalyzed by Amine-Based Three-Component Catalyst Systems. *Asian J. Org. Chem.* **2016**, *5*, 153-161.

(21) Bailey, K.; Butterfield, A. G. Structure of Condensation Products between Isonicotinylhydrazine and Reducing Sugars by ^{13}C NMR Spectroscopy. *Can. J. Chem.* **1981**, *59*, 641-646.

(22) (a) van den Berg, R.; Peters, J. A.; van Bekkum, H. The Structure and (Local) Stability Constants of Borate Esters of Mono- and Di-Saccharides as Studied by ^{11}B and ^{13}C NMR Spectroscopy. *Carbohydr. Res.* **1994**, *253*, 1-12. (b) Shimomura, M.; Ono, B.; Oshima, K.; Miyauchi, S. Complexation of Sugars with Dihydroxyborylphenyl Groups Attached to Magnetite Particles via Graft Polymerization of Acrylic Acid. *Polymer* **2006**, *47*, 5785-5790.

(23) (a) Aelvoet, K.; Batsanov, A. S.; Blatch, A. J.; Grosjean, C.; Patrick, L. G. F.; Smethurst, C. A.; Whiting, A. A Catalytic Aldol Reaction and Condensation through In Situ Boron "Ate" Complex Enolate Generation in Water. *Angew., Chem., Int. Ed.* **2008**, *47*, 768-770. (b) Batsanov, A. S.; Georgiou, I.; Girling, P. R.; Pommier, L.; Shen, H. C.; Whiting, A. Asymmetric Synthesis and Application of Homologous Pyrroline-2-alkylboronic Acids: Identification of the B-N Distance for Eliciting Bifunctional Catalysis of an Asymmetric Aldol Reaction. *Asian J. Org. Chem.* **2014**, *3*, 470-479.

(24) Opalka, S. M.; Steinbacher, J. L.; Lambiris, B. A.; McQuade, D. T. Thiourea/Proline Derivative-Catalyzed Synthesis of Tetrahydrofuran Derivatives: A Mechanistic View. *J. Org. Chem.* **2011**, *76*, 6503-6517.

(25) Taylor, M. S. Catalysis Based on Reversible Covalent Interactions of Organoboron Compounds. *Acc. Chem. Res.* **2015**, *48*, 295-305.

(26) Heyraud, A.; Rinaudo, M.; Vignon, M. ^{13}C-NMR Spectroscopic Investigation of α- and β-1,4-D-Glucose Homooligomers. *Biopolymers* **1979**, *18*, 167-185.