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Development of Ketoside-Type Analogues of Trehalose by Using α-Stereoselective O-Glycosidation of Ketose

Rie Namme,[a] Takashi Mitsugi,[a] Hideyo Takahashi,[a] and Shiro Ikegami*[a]

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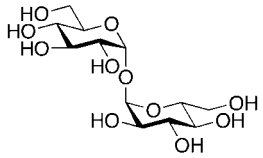
The stereoselective synthesis of ketoside-type analogues of trehalose is described. O-Glycosidation of hept-2-ulopyranose with trimethylsilyl α-pyranoside promoted by trimethylsilyl trifluoromethanesulfonate afforded α-ketopyranosyl α-aldopyranosides exclusively. α-Ketopyranosyl β-aldooyranosides and α-ketopyranosyl α-ketopyranosides were also synthesized in a similar manner. The benzyl protecting groups of the hydroxy moieties were removed by hydrogenolysis to afford fully deprotected trehalose analogues.

Introduction

Trehalose is a nonreducing disaccharide consisting of two D-glucose units connected by an α,α-1,1-linkage. Trehalose is distributed widely in nature such as in insects, algae, fungi, and invertebrates.[1] It is generally recognized that trehalose plays important roles in protecting proteins and cell membranes against natural stresses such as dryness or freezing.[2] Since industrial production was established in 1994,[3] trehalose has been used in the food and cosmetics industries. In the field of medical science, many biological functions of trehalose have been reported.[4]



Trehalose

It appears obvious that the 1,1-linkage of trehalose is stable under different chemical and enzymatic conditions.[5] Similarly, oligosaccharides with 1,1-linkages are expected to have high stability and could potentially be developed as bioactive compounds. Thus, designed oligosaccharides with the 1,1-linkage have been developed to mimic functional natural oligosaccharides. For example, heparin analogues with a trehalose moiety at the reducing end,[6] α-D-mannosyl β-D-galactoside to mimic Sialyl Lewis X,[7] and α-D-galactoyl α-D-glucoside to mimic Gb_2 disaccharides[8] have been developed. The synthesis and isolation of nitrogen-containing trehalose analogues such as trehalosamin[9] or N-glycoside analogues[10] have also been reported. The development of a method for producing new types of saccharides linked between anomeric centers is an attractive subject.

We have investigated the synthesis of ketoside-containing saccharides to mimic oligosaccharides. We found that the O-glycosidation of *exo*-glycals[11] or ketose[12] promoted by acid afforded α-ketopyranoside exclusively. It is noteworthy that the *gluco*-, *galacto*-, and *manno*-derivatives of benzylated 1-deoxy-2,6-anhydrohept-2-enitols and/or hept-2-uloses could be converted into α-hept-2-ulosides. We also investigated O-glycosidation with various glycosyl acceptors.[11d] Primary and secondary alcohols in the glycopyranosides and the glycono-1,5-lactones were efficiently glycosylated with *exo*-glycals to give α-ketopyranosides. We envisioned that glycosidation with the C-1 hemiacetal hydroxy group would proceed in the same manner to produce α-ketopyranosyl aldopyranoside, which is regarded as a ketoside-type analogue of trehalose.[13] When trehalose analogues such as ketosyl aldosides with various alkyl groups can be provided, their conformational flexibility would be affected by the bulkiness of the substituents and show interesting properties in their activity. Herein, we describe the synthesis of 1-deoxy-α-hept-2-ulosyl glycosides, which are one of the simplest ketoside-type analogues of trehalose.

Results and Discussions

For the stereoselective synthesis of trehalose-type disaccharides, it is necessary to control the stereochemistry of both anomeric centers of the two consisting saccharides.[14,15] As mentioned above, we thought that the anomeric center in ketoside could be controlled by our α-selective O-glycosidation of 1-deoxyhept-2-enitol or 1-deoxyhept-2-ulose. The basis of stereoselective glycosidation providing

[a] School of Pharmaceutical Sciences, Teikyo University, Sagamihara, Kanagawa, 229–0195 Japan
Fax: +81-42-685-3729
E-mail: somc@pharm.teikyo-u.ac.jp
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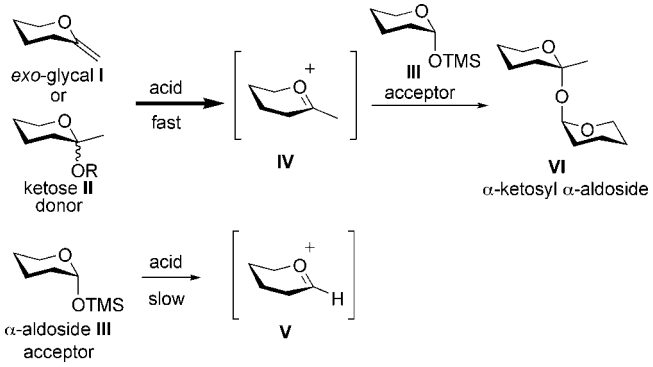
ketopyranosyl aldopyranoside is shown in Scheme 1. In our plan, *exo*-glycals **I** and/or ketoses **II** are used as glycosyl donors and anomerically pure trimethylsilyl α-aldopyranosides **III** are used as glycosyl acceptors. When the donor and acceptor are treated with acid, there is a possibility that both the ketosyl donor and the aldoside would behave as glycosyl donors. Silyl glycosides have often been employed as glycosyl donors.[15,16] However, we predicted that the formation of oxocarbenium ion **IV** from *exo*-glycal **I** or ketose **II** would proceed more rapidly than that of **V** from silyl aldoside **III** because generated oxocarbenium ion **IV** is stabilized by the alkyl substituent.[17] Then the nucleophile, 1-*O*-trimethylsilyl α-pyranoside **III**, would attack the α-face[18] of oxocarbenium ion **IV** to afford α-ketpyranosyl α-aldopyranoside **VI** without anomerization.[19] On the basis of this strategy, we attempted the synthesis of ketopyranosyl aldopyranoside as one trehalose analogue.

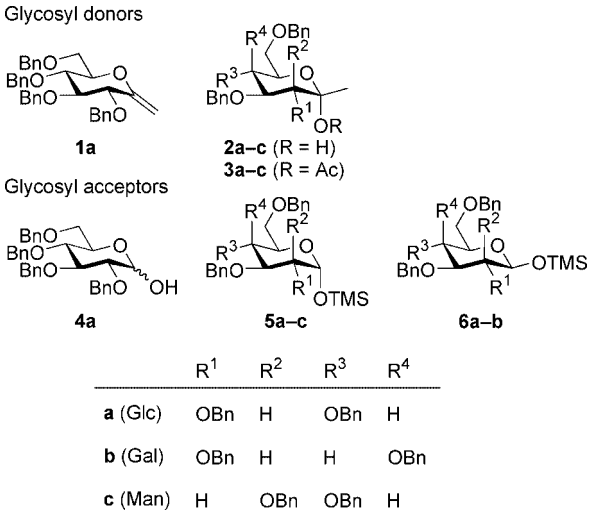


Scheme 1.

Glycosidation to Synthesize α-Hept-2-ulopyranosyl α-Pyranoside

We first optimized the glycosidation conditions for the stereoselective synthesis of 3,4,5,7-tetra-*O*-benzyl-1-deoxy-α-*gluco*-hept-2-ulopyranosyl 2,3,4,6-tetra-*O*-benzyl-α-glucopyranoside (**7aa**). *exo*-Glycal **1a**,[11a] ketoses **2a**,[12a] and **3a**[12b] derived from D-glucose were used as ketopyranosyl donors and glucopyranose **4a** and trimethylsilyl glucopyranoside **5a**[20] were used as glycosyl acceptors (Figure 1).

The glycosidation of *exo*-glycal **1a** with glucopyranose **4a** proceeded rapidly in the presence of 10 mol-% of trifluoromethanesulfonic acid (TfOH) to afford corresponding *gluco*-α-hept-2-ulopyranosyl glucopyranosides **7aa** and **8aa** in high yield (Table 1, Entry 1). Although a mixture of α,α- and α,β-linked disaccharides **7aa** and **8aa** was formed, β-ketosides as expected were not formed. To synthesize **7aa** selectively, trimethylsilyl α-glucoside **5a** was used as a glycosyl acceptor. However, the corresponding disaccharide was obtained in only 18% yield (Table 1, Entry 2). The use of a stoichiometric amount of Brønsted acid, such as TfOH, methanesulfonic acid and trifluoroacetic acid, or even the addition of a proton source, such as phenol, *tert*-butanol and trifluoroethanol, did not result in the improvement of the glycosidation of **1a** with silylated acceptor **5a**. Therefore, we shifted our focus to the use of ketoses as ketosyl donors.



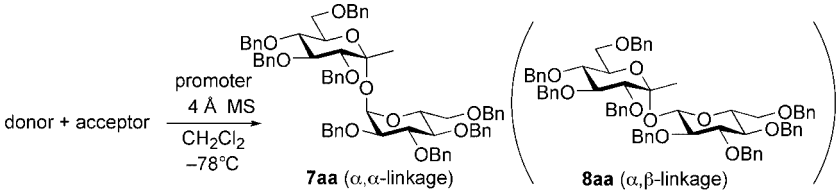
	R^1	R^2	R^3	R^4
a (Glc)	OBn	H	OBn	H
b (Gal)	OBn	H	H	OBn
c (Man)	H	OBn	OBn	H

Figure 1. Glycosyl donors and acceptors.

When the glycosidation of 1-deoxy-α-hept-2-ulose **2a** with trimethylsilyl α-glucoside **5a** catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf) was examined, desired α,α-isomer **7aa** was obtained in preference to anomerized α,β-isomer **8aa** (**7aa/8aa**, 6.7:1) (Table 1, Entry 3). Similarly, in the glycosidation of 2-*O*-acetyl-*gluco*-hept-2-ulose **3a** promoted by 10 mol-% of TMSOTf, **5a** was glycosylated to give **7aa** and **8aa** (7.7:1) (Table 1, Entry 4). The best result (yield 86%, **7aa/8aa**, 10.0:1) was obtained when the reaction of **3a** with **5a** was carried out using 20 mol-% of TMSOTf (Table 1, Entry 5). We investigated other promoters to improve the stereoselectivity, although, the promoters TfOH, $Sc(OTf)_3$, and $BF_3{\cdot}Et_2O$ were not effective for this glycosidation (Table 1, Entries 6–8).

For our goal to synthesize various types of ketopyranosyl aldopyranoside, we extended the reaction to galactoside and mannoside. Acetylated ketoses 1-deoxy-2-*O*-acetyl-*galacto*-hept-2-ulose **3b** and 1-deoxy-2-*O*-acetyl-*manno*-hept-2-ulose **3c** as ketosyl donors and silylated acceptors **5b** and **5c** were used for the glycosidation. This time, a slight excess of acceptor was used, and the reactions were performed in the presence of 20 mol-% of TMSOTf (Table 2). The glycosidation of *gluco*-hept-2-ulose **3a** with silyl α-galactoside **5b** and silyl α-mannoside **5c** proceeded α-selectively and the corresponding α-ketopyranosyl α-aldopyranosides were obtained, respectively (Table 2, Entries 2, 3). Different from the case of the glycosidation of **3a** with α-glucoside **5a** (Table 2, Entry 1), α,β-linked disaccharides were not obtained in these cases. *Galacto*-hept-2-ulose **3b** (Table 2, Entries 4–6) and *manno*-hept-2-ulose **3c** (Table 2, Entries 7–9) were found to be good ketosyl donors in the glycosidation. The corresponding α-ketopyranosyl α-aldopyranosides were formed in high yields with the desired α,α-configurations. In addition, the glycosidation of *galacto*- and *manno*-ketosyl donors **3b** and **3c** proceeded with an even shorter reaction time than in the case of *gluco*-ketosyl donor **3a**.

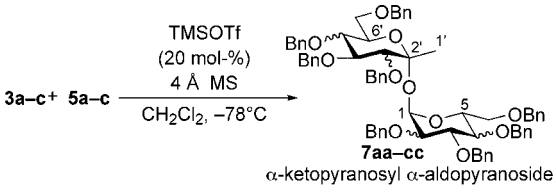
Table 1. The investigation of glycosidation to synthesize compound **7aa**.



Entry	Donor[a]	Acceptor[a]	Promoter (mol-%)	Time	Yield [%][b]	7aa/8aa
1	**1a**	**4** (α/β = 16.7:1)	TfOH (10)	15 min	96	8.7:1
2	**1a**	**5a**	TfOH (10)	2.5 h	18	-
3	**2a**	**5a**	TMSOTf (20)	6 h	86	6.7:1
4	**3a**	**5a**	TMSOTf (10)	19 h	84	7.7:1
5	**3a**	**5a**	TMSOTf (20)	9 h	86	10.0:1
6	**3a**	**5a**	TfOH (10)	17.5 h	trace	-
7	**3a**	**5a**	$Sc(OTf)_3$ (10)	43 h	trace	-
8	**3a**	**5a**	$BF_3•Et_2O$ (20)	10 h	N.R.	-

[a] Molar ratio donor/acceptor, 1.1:1. [b] Based on the amount of acceptors.

Table 2. O-Glycosidation of ketose with α-aldopyranoside.



Entry	Donor[a]	Acceptor[a]	Time [h]	Product	Yield [%][b]
1	**3a**	**5a**	9	**7aa,8aa**	93 (**7aa/8aa** = 10.0:1)
2	**3a**	**5b**	8	**7ab**	96
3	**3a**	**5c**	21	**7ac**	94
4	**3b**	**5a**	2.5	**7ba**	92
5	**3b**	**5b**	2	**7bb**	96
6	**3b**	**5c**	7	**7bc**	92
7	**3c**	**5s**	3	**7ca**	95
8	**3c**	**5b**	1.3	**7cb**	95
9	**3c**	**5c**	6	**7cc**	88

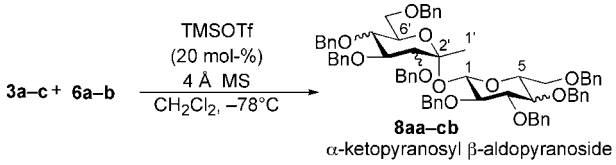
[a] Molar ratio donor/acceptor, 1:1.1. [b] Based on the amount of donors.

It is interesting that only the glycosidation of **3a** with **5a** gave the mixture of α,α- and α,β-ketosyl aldoside (Table 2, Entry 1).[21] In other cases, the formation of β-aldoside was not detected by the measurement of the ^{1}H NMR spectrum. It is speculated that the longer reaction time in the glycosidation of **3a** with α-glucoside **5a** causes the anomerization of aldoside to result in the formation of small amounts of α,β-linked disaccharide.

Glycosidation to Synthesize α-Hept-2-ulopyranosyl β-Pyranoside

To confirm the exclusive formation of the α,α-linked disaccharides, α,β-linked disaccharides were synthesized separately and the spectroscopic data were compared. When β-glucoside **6a** or β-galactoside **6b** was used as the glycosyl acceptor, the glycosidation of ketoses **3a**–**c** was examined under the same conditions (Table 3). The glycosidation of *galacto*- and *manno*-hept-2-ulose **3b** and **3c** proceeded more rapidly than that of *gulco*-hept-2-ulose **3a**, and, hence, α,β-linked disaccharides were selectively synthesized and the formation of α,α-isomers was not detected. The configuration of the C-1 anomeric center was assigned based on the ^{1}H NMR spectroscopic coupling constant (for α, J = 3.3–3.8 Hz; for β, J = 7.7–8.0 Hz). Thus, formation of α,α- and α,β-linked ketopyranosyl aldopyranoside was confirmed.

Table 3. O-Glycosidation of ketose with β-aldopyranoside.



Entry	Donor[a]	Acceptor[a]	Time [h]	Product	Yield [%][b]
1	**3a**	**6a**	9	**8aa**	98
2	**3a**	**6b**	10	**8ab**	92
3	**3b**	**6a**	0.5	**8ba**	93
4	**3b**	**6b**	1.5	**8bb**	95
5	**3c**	**6a**	2	**8ca**	94
6	**3c**	**6b**	1	**8cb**	94

[a] Molar ratio donor/acceptor, 1:1.1. [b] Based on the amount of donors.

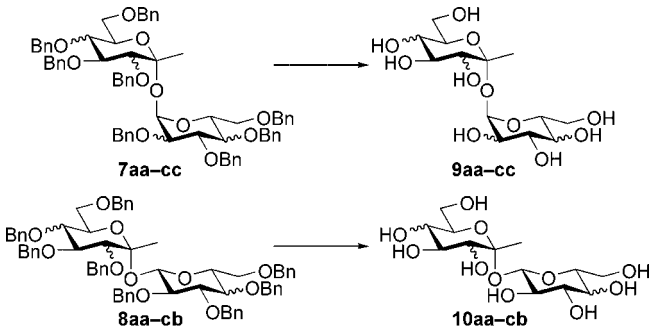
In the comparison of ketosyl donors **3a**–**c**, the glycosidation of *galacto*-heptulose **3b** and *manno*-heptulose **3c** proceeded more rapidly than that of *gluco*-heptulose **3a**. Because the reaction is assumed to involve the distortion of the chair conformation into a flattened half-chair conformation in the oxocarbenium ion, the differences in the reac-

tion rate would be rationalized due to the ease of formation of the oxocarbenium ion. Thus, since *galacto*- and *manno*-hept-2-ulopyranoside **3b** and **3c** have the axial hydroxy group, the ring distortion would easily occur and would make the concomitant reaction faster. A similar finding is seen in the hydrolysis of pyranosides having axial hydroxy groups.[22]

Deprotection of Disaccharides

Deprotection of benzylated ketopyranosyl aldopyranoside was achieved by hydrogenolysis under slightly basic conditions. We previously investigated the removal of benzyl groups in ketosides and found that Pd-catalyzed hydrogenolysis in the presence of basic alumina was effective.[11d] Since ketosides are easily hydrolyzed even under neutral hydrogenolysis, basic alumina was added to suppress the cleavage of the ketoside bond. In this reaction, the deprotection was carried out under our optimized procedure. Ketopyranosyl aldopyranosides **7aa**–**cc** and **8aa**–**cb** were treated with a catalytic amount of $Pd(OH)_2/C$ and basic alumina under a hydrogen atmosphere, and fully deprotected disaccharides **9aa**–**cc** and **10aa**–**cb** were obtained, respectively (Table 4). These deprotected compounds are stable in storage and compound **7aa** was found to be unchanged after a month in MeOH solution at room temperature.

Table 4. Deprotection of ketopyranosyl aldopyranoside.[a]

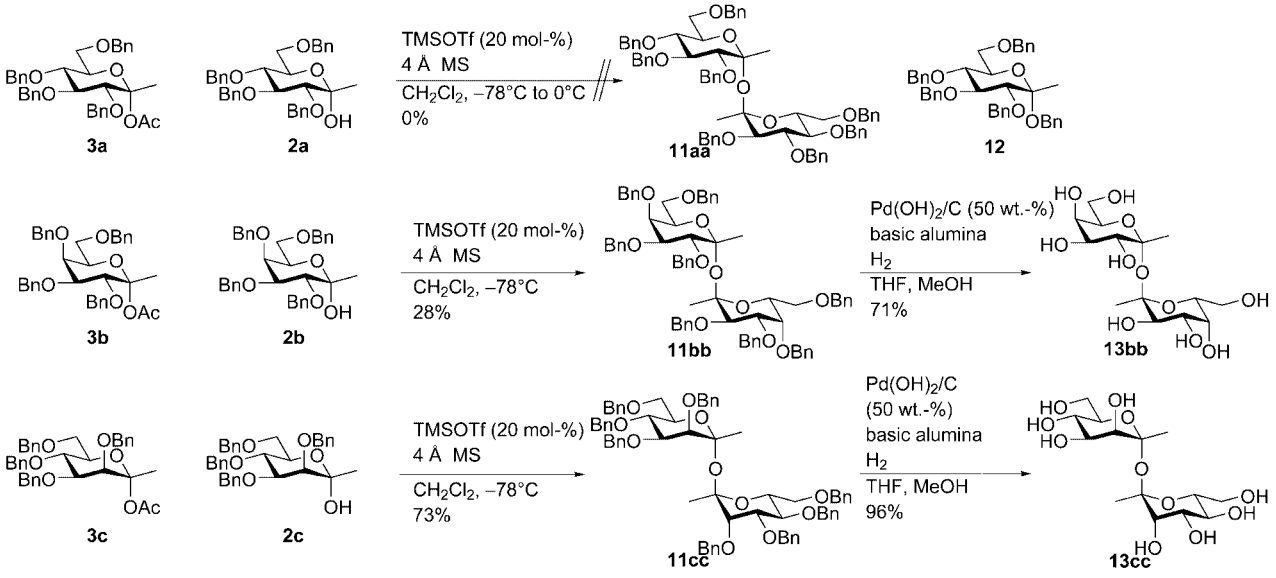


Entry	Substrate	Product	Yield [%]
1	**7aa**	**9aa**	100
2	**7ab**	**9ab**	97
3	**7ac**	**9ac**	100
4	**7ba**	**9ba**	99
5	**7bb**	**9bb**	95
6	**7bc**	**9bc**	90
7	**7ca**	**9ca**	98
8	**7cb**	**9cb**	98
9	**7cc**	**9cc**	87
10	**8aa**	**10aa**	97
11	**8ab**	**10ab**	97
12	**8ba**	**10ba**	95
13	**8bb**	**10bb**	94
14	**8ca**	**10ca**	98
15	**8cb**	**10cb**	85

[a] Reaction conditions: $Pd(OH)_2/C$ (50 wt.-%), basic alumina (25 wt.-%), H_2 (balloon), THF, MeOH.

Synthesis of α-Hept-2-ulopyranosyl α-Hept-2-ulopyranoside

As we had great interest in the symmetrical structure of the dimethyl analogue of trehalose, we next attempted the synthesis of α-hept-2-ulopyranosyl α-hept-2-ulopyranoside, that is, 1,1′-di-*C*-methyltrehalose. It was anticipated that the nucleophilic substitution at the highly hindered quaternary anomeric center with ketose, a bulky nucleophile, might be less likely. Disappointingly, the glycosidation of *gluco*-hept-2-ulose **3a** with **2a** did not afford disaccharide **11aa**, and **12** was obtained instead. The use of heptenitol



Scheme 2. Synthesis of α-ketopyranosyl α-ketopyranoside.

1a as a donor also resulted in the formation of **12**. Interestingly, the glycosidation of *galacto*- and *manno*- derivatives promoted by TMSOTf was able to proceed, and α-*galacto*-hept-2-ulopyranosyl α-*galacto*-hept-2-ulopyranoside **11bb** and α-*manno*-hept-2-ulopyranosyl α-*manno*-hept-2-ulopyranoside **11cc** were obtained in 28 and 73% yield, respectively. Their structures were determined by ^{1}H and ^{13}C NMR spectroscopy and FAB-MS. The ^{1}H and ^{13}C NMR spectra indicated that ketopyranosyl ketopyranosides **11bb** and **11cc** have C_2 symmetry. These were deprotected to afford dimethyl analogues of trehalose **13bb** and **13cc** (Scheme 2).

The results show that *gluco*-hept-2-uloside **3a** is less reactive than the *galacto*- and *manno*- derivatives, **3b** and **3c**. This is comparable to the results of glycosidation between ketopyranose and aldopyranose discussed in the previous section. We speculate that the glycosidation of *gluco*-hept-2-ulose **3a** with a hindered nucleophile such as ketose involves a high energy barrier, and thus the formation of by-product **12** took precedence.

Conclusions

We developed a method for the synthesis of ketopyranoside analogues of trehalose utilizing our α-selective O-glycosidation of ketoses. The glycosidation of *gluco*-, *galacto*- and *manno*-hept-2-uloses **3a**–**c** with trimethylsilyl aldopyranosides **5a**–**c** and **6a**–**b** promoted by TMSOTf afforded α-ketopyranosides exclusively. In addition, silyl aldopyranosides were glycosylated in a mostly anomerization-free manner so that stereocontrolled syntheses of α-ketopyranosyl α-aldopyranosides and α-ketopyranosyl β-aldopyranosides were achieved. Furthermore, the glycosidation between two ketoses was also demonstrated and symmetrical disaccharides, α-ketopyranosyl α-ketopyranosides **11bb** and **11cc**, were synthesized.

Experimental Section

General Information: IR spectra were recorded with a Jasco FTIR-8000 Fourier-transform infrared spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a JEOL ECP 600 (600 MHz) NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded with a JEOL JMS-SX102A mass spectrometer with FAB using 3-nitrobenzyl alcohol (NBA) as the matrix. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. TLC was performed on precoated plates (Merck TLC Aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in EtOH/H_2O, followed by heating. Column chromatography was performed using SiO_2 (Silica Gel 60 N, spherical, neutral, Kanto).

General Procedure 1: Glycosidation of 1-*O*-Acetyl-1-deoxy-hept-2-ulose with Trimethylsilyl Glycoside.[23] **3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulopyranosyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (7aa):** To a stirred mixture of *gluco*-hept-2-ulose **3a** (51 mg, 0.086 mmol), trimethylsilyl glucopyranoside **5a** (58 mg, 0.095 mmol), and 4 Å MS (86 mg) in CH_2Cl_2 (1.7 mL) was added TMSOTf (3.1 μL, 0.017 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 9 h and then quenched with triethylamine. After removal of the solvent, the residue was purified by column chromatography (silica gel, neutral, hexane/ethyl acetate, 10:1) to give a mixture of disaccharides **7aa** and **8aa** (86 mg, 93%, **7aa**/**8aa**, 10.0:1). Compounds **7aa** and **8aa** were partially separated by further separation by column chromatography (hexane/ethyl acetate, 15:1), and **7aa** was obtained in pure form. For **7aa**: $[\alpha]_D^{20}$ = +75.0° (c = 0.97, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.13 (m, 40 H, Ar*H*), 5.34 (d, J = 3.6 Hz, 1 H, 1-H), 4.94 (d, J = 10.7 Hz, 1 H, PhCH_2-), 4.92 (d, J = 11.3 Hz, 1 H, PhCH_2-), 4.87 (m, 2 H, 2 × PhCH_2-), 4.84 (d, J = 10.7 Hz, 1 H, PhCH_2-), 4.80 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.80 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.69 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.64 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.59 (d, J = 11.3 Hz, 1 H, PhCH_2-), 4.57 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.51 (d, J = 12.4 Hz, 1 H, PhCH_2-), 4.48 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.47 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.37 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.36 (d, J = 12.4 Hz, 1 H, PhCH_2-), 4.27 (ddd, J = 1.9, 3.6, 10.2 Hz, 1 H, 6′-H), 4.18 (m, 1 H, 5-H), 4.06–4.01 (m, 2 H, 3-H, 4′-H), 3.67 (dd, J = 9.4, 10.2 Hz, 1 H, 4-H), 3.63 (dd, J = 9.4, 10.2 Hz, 1 H, 5′-H), 3.58–3.55 (m, 2 H, 2-H, 6-H), 3.38 (dd, J = 2.2, 10.5 Hz, 1 H, 6-H), 3.37 (dd, J = 3.6, 10.7 Hz, 1 H, 7′-H), 3.33 (dd, J = 1.9, 10.7 Hz, 1 H, 7′-H), 3.28 (d, J = 9.6 Hz, 1 H, 3′-H), 1.49 (s, 3 H, 1′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.8, 138.7, 138.6, 138.2, 138.0, 128.3, 128.3, 128.3, 128.3, 128.2, 128.2, 127.9, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 127.5, 127.5, 127.5, 127.4, 127.3, 127.3, 127.2, 101.0 (C-2′), 90.2 (C-1), 85.1 (C-3′), 82.7 (C-4′), 81.9 (C-3), 80.2 (C-2), 78.5 (C-5′), 78.0 (C-4), 75.4 (Ph*C*H$_2$-), 75.3 (Ph*C*H$_2$-), 74.7 (Ph*C*H$_2$-), 74.6 (Ph*C*H$_2$-), 73.4 (Ph*C*H$_2$-), 73.4 (Ph*C*H$_2$-), 73.1 (Ph*C*H$_2$-), 71.1 (C-6′), 70.0 (C-5), 68.5 (C-7′), 68.3 (C-6), 22.7 (C-1′) ppm. IR (neat): $\tilde{\nu}$ = 3030.54, 2928.30, 2866.57, 1496.94, 1454.50, 1361.91, 1084.13, 1028.18, 734.97, 698.32 cm^{-1}. HRMS (FAB): calcd. for $C_{69}H_{72}O_{11}Na$ 1099.4972, found 1099.4965. $C_{69}H_{72}O_{11}$ (1076.8): calcd. C 76.93, H 6.74; found C 77.10, H 6.65.

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*gluco*-hept-2-ulopyranosyl 2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranoside (8aa): To a stirred mixture of *gluco*-hept-2-ulose **3a** (44 mg, 0.074 mmol), trimethylsilyl glucopyranoside **6a** (50 mg, 0.081 mmol), and 4 Å MS (74 mg) in CH_2Cl_2 (1.7 mL) was added TMSOTf (2.7 μL, 0.015 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 9 h and then quenched with triethylamine. After removal of the solvent, the residue was purified by column chromatography (silica gel, neutral, hexane/ethyl acetate, 10:1) to afford **8aa** (78 mg, 98%). $[\alpha]_D^{27}$ = +48.2° (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.29–7.12 (m, 40 H, Ar*H*), 5.04 (d, J = 11.6 Hz, 1 H, PhCH_2-), 4.93 (d, J = 11.3 Hz, 1 H, PhCH_2-), 4.91 (m, 2 H, 2 × PhCH_2-), 4.90 (d, J = 10.7 Hz, 1 H, PhCH_2-), 4.85 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.80 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.77 (d, J = 8.0 Hz, 1 H, 1-H), 4.75 (d, J = 10.7 Hz, 1 H, PhCH_2-), 4.67 (d, J = 11.6 Hz, 1 H, PhCH_2-), 4.67 (d, J = 11.3 Hz, 1 H, PhCH_2-), 4.54 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.53 (d, J = 11.0 Hz, 1 H, PhCH_2-), 4.50 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.46 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.44 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.36 (m, 1 H, 6′-H), 4.31 (d, J = 12.1 Hz, 1 H, PhCH_2-), 4.17 (dd, J = 9.3, 9.6 Hz, 1 H, 4′-H), 3.77 (dd, J = 9.3, 10.2 Hz, 1 H, 5′-H), 3.62 (dd, J = 9.4, 9.9 Hz, 1 H, 3-H), 3.62 (m, 1 H, 7′-H), 3.59–3.51 (m, 4 H, 4-H, 6-H, 6-H, 7′-H), 3.45 (dd, J = 8.0, 9.4 Hz, 1 H, 2-H), 3.41 (ddd, J = 2.2, 4.7, 9.9 Hz, 1 H, 5-H), 3.38 (d, J = 9.6 Hz, 1 H, 3′-H), 1.49 (s, 3 H, 1′-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.7, 138.6, 138.6, 138.3, 138.2, 128.1, 128.1, 128.3, 128.3, 128.3, 128.2, 128.2, 128.2, 128.2, 128.1, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.4, 127.1, 102.4 (C-2′),

97.2 (C-1), 84.8 (C-3), 84.3 (C-3′), 83.0 (C-4′), 81.7 (C-2), 78.4 (C-5′), 77.7 (C-4), 75.8 (Ph*C*H$_2$-), 75.6 (Ph*C*H$_2$-), 75.4 (Ph*C*H$_2$-), 74.9, 74.9, 74.7 (Ph*C*H$_2$-), 74.4 (Ph*C*H$_2$-), 73.3 (Ph*C*H$_2$-), 73.3 (Ph*C*H$_2$-), 72.2 (C-6′), 69.0 (C-6), 68.4 (C-7′), 22.2 (C-1′) ppm. IR (neat): $\tilde{\nu}$ = 3032.47, 2912.87, 2858.85, 1495.01, 1454.50, 1361.91, 1068.69, 734.97, 698.32 cm^{-1}. HRMS (FAB): calcd. for $C_{69}H_{72}O_{11}Na$ 1099.4972; found 1099.4988.

General Procedure 2: Deprotection of Disaccharide.[23] **1-Deoxy-α-D-*gluco*-hept-2-ulopyranosyl α-D-Glucopyranoside (9aa):** To a solution of **7aa** (51 mg, 0.047 mmol) in THF (1.6 mL) was added basic alumina (13 mg), and 20% Pd(OH)$_2$/C (23 mg) was added under an argon atmosphere, and then the mixture was stirred under a hydrogen atmosphere (balloon) at room temperature. After 90 min, MeOH (1.6 mL) was added to the mixture and stirred for 30 min. The reaction mixture was filtered through filter paper, and the filtrate was evaporate and dried to give **9aa** (17 mg, quant.). $[\alpha]_D^{27}$ = +140.0° (*c* = 0.85, CH_3OH). ^{1}H NMR (600 MHz, CD_3OD): δ = 5.13 (d, *J* = 3.6 Hz, 1 H, 1-H), 3.98 (ddd, *J* = 10.2, 2.5, 5.2 Hz, 1 H, 6′-H), 3.72 (m, 1 H, 5-H), 3.72 (dd, *J* = 9.6, 9.9 Hz, 1 H, 3-H), 3.68 (dd, *J* = 9.6, 9.3 Hz, 1 H, 4′-H), 3.68 (dd, *J* = 2.5, 11.8 Hz, 1 H, 7′-H), 3.66 (dd, *J* = 2.5, 12.1 Hz, 1 H, 6-H), 3.59 (dd, *J* = 5.0, 12.1 Hz, 1 H, 6-H), 3.56 (dd, *J* = 5.2, 11.8 Hz, 1 H, 7′-H), 3.35 (dd, *J* = 3.6, 9.9 Hz, 1 H, 2-H), 3.24 (dd, *J* = 9.6, 9.9 Hz, 1 H, 4-H), 3.20 (dd, *J* = 9.3, 10.2 Hz, 1 H, 5′-H), 3.04 (d, *J* = 9.6 Hz, 1 H, 3′-H), 1.42 (s, 3 H, 1′-H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 102.1 (C-2′), 93.2 (C-1), 78.6 (C-3′), 74.9 (C-4′), 74.6 (C-3), 73.9 (C-6′), 73.6 (C-2), 73.5 (C-5), 72.1 (C-5′), 72.1 (C-4), 62.8 (C-7′), 62.6 (C-6), 23.7 (C-1′) ppm.

Deoxy-α-D-*gluco*-hept-2-ulopyranosyl β-D-Glucopyranoside (10aa): To a solution of **8aa** (19.5 mg, 0.018 mmol) in THF (0.6 mL) was added basic alumina (5 mg), and 20% Pd(OH)$_2$/C (10 mg) was added under an argon atmosphere, and then the mixture was stirred under a hydrogen atmosphere (balloon) at room temperature. After 60 min, MeOH (0.6 mL) was added to the mixture and stirred for 30 min. The reaction mixture was filtered through filter paper, and the filtrate was evaporate and dried to give **10aa** (6.2 mg, 97%). $[\alpha]_D^{27}$ = +71.4° (*c* = 0.68, CH_3OH). ^{1}H NMR (600 MHz, CD_3OD): δ = 4.56 (d, *J* = 7.7 Hz, 1 H, 1-H), 4.13 (ddd, *J* = 2.2, 7.2, 10.2 Hz, 1 H, 6′-H), 3.76 (dd, *J* = 2.2, 11.8 Hz, 1 H, 6-H), 3.75 (dd, *J* = 2.2, 11.8 Hz, 1 H, 7′-H), 3.58 (dd, *J* = 9.1, 9.4 Hz, 1 H, 4′-H), 3.49 (dd, *J* = 7.2, 11.8 Hz, 1 H, 7′-H), 3.44 (dd, *J* = 7.2, 11.8 Hz, 1 H, 6-H), 3.29 (dd, *J* = 9.1, 9.3 Hz, 1 H, 3-H), 3.20 (m, 1 H, 5-H), 3.13 (dd, *J* = 7.7, 9.3 Hz, 1 H, 2-H), 3.11–3.07 (m, 3 H, 4-H, 3′-H, 5′-H), 1.40 (s, 3 H, 1′-H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 103.3 (C-2′), 98.2 (C-1), 78.3 (C-5), 78.3 (C-3′), 77.6 (C-3), 75.0 (C-6′), 75.0 (C-2), 74.9 (C-4′), 72.5 (C-4), 71.9 (C-5′), 63.5 (C-7′), 63.2 (C-6), 22.6 (C-1′) ppm.

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulopyranosyl 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*galacto*-hept-2-ulopyranoside (11bb): To a stirred mixture of **3b** (56 mg, 0.093 mmol), **2b** (57 mg, 0.102 mmol), and 4 Å MS (110 mg) in CH_2Cl_2(1.9 mL) was added TMSOTf (3.4 μL, 0.019 mmol) at –78 °C. After being stirred for 17 h at the same temperature, the reaction mixture was quenched with triethylamine and filtered through a pad of celite. The solvent was evaporated, and the residue was purified by column chromatography (silica gel, neutral, hexane/ethyl acetate, 10:1) to give **11bb** (28 mg, 28%). $[\alpha]_D^{22}$ = +61.7° (*c* = 1.41 $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31–7.14 (m, 40 H, Ar*H*), 4.93 (d, *J* = 11.5 Hz, 2 H, PhC*H*$_2$-), 4.92 (d, *J* = 11.6 Hz, 2 H, PhC*H*$_2$-), 4.64 (d, *J* = 11.5 Hz, 2 H, PhC*H*$_2$-), 4.63 (d, *J* = 12.1 Hz, 2 H, PhC*H*$_2$-), 4.60 (d, *J* = 12.1 Hz, 2 H, PhC*H*$_2$-), 4.57 (d, *J* = 11.7 Hz, 2 H, PhC*H*$_2$-), 4.39 (d, *J* = 12.0 Hz, 2 H, PhC*H*$_2$-), 4.39 (m, 2 H, 6-H), 4.31 (d, *J* = 12.0 Hz, 2 H, PhC*H*$_2$-), 4.01 (dd, *J* = 2.8, 9.5 Hz, 2 H, 4-H), 3.85 (m, 2 H, 5-H), 3.65 (d, *J* = 9.5 Hz, 2 H, 3-H), 3.45 (dd, *J* = 6.3, 9.4 Hz, 2 H, 7-H), 3.40 (dd, *J* = 6.9, 9.4 Hz, 2 H, 7-H), 1.55 (s, 6 H, -C*H*$_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.1, 139.1, 138.8, 138.4, 128.2, 128.2, 128.1, 128.1, 128.0, 127.7, 127.5, 127.5, 127.4, 127.3, 127.1, 101.2 (C-2), 82.7 (C-3), 80.6 (C-4), 75.3 (Ph*C*H$_2$- or C-5), 75.2 (Ph*C*H$_2$- or C-5), 74.4 (Ph*C*H$_2$-), 73.2 (Ph*C*H$_2$-), 72.6 (Ph*C*H$_2$-), 69.7 (C-6), 69.3 (C-7), 22.5 (C-1) ppm. IR (neat): $\tilde{\nu}$ = 3030.54, 2922.51, 2864.64, 1469.94, 1454.50, 1097.63, 1060.98 cm^{-1}. HRMS (FAB): calcd. for $C_{70}H_{74}O_{11}Na$ 1113.5129; found 1113.5132. $C_{70}H_{74}O_{11}$ (1090.77): calcd. C 77.04, H 6.83; found C 77.02, H 6.80.

3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulopyranosyl 3,4,5,7-Tetra-*O*-benzyl-1-deoxy-α-D-*manno*-hept-2-ulopyranoside (11cc): To a stirred mixture of **3c** (56 mg, 0.094 mmol), **2c** (58 mg, 0.104 mmol), and 4 Å MS (110 mg) in CH_2Cl_2 (1.9 mL) was added TMSOTf (3.4 μL, 0.019 mmol) at –78 °C. After being stirred for 6.5 h at the same temperature, the reaction mixture was quenched with triethylamine and filtered through a pad of celite. The solvent was evaporated, and the residue was purified by column chromatography (silica gel, neutral, hexane/ethyl acetate, 10:1) to give **11cc** (75 mg, 73%). $[\alpha]_D^{22}$ = +37.5° (*c* = 0.86, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 40 H, ArH), 4.92–4.88 (m, 4 H, PhC*H*$_2$-), 4.65 (d, *J* = 11.8 Hz, 2 H, PhC*H*$_2$-), 4.64 (d, *J* = 12.1 Hz, 2 H, PhC*H*$_2$-), 4.62 (d, *J* = 11.8 Hz, 2 H, PhC*H*$_2$-), 4.56 (d, *J* = 10.5 Hz, 2 H, PhC*H*$_2$-), 4.55 (d, *J* = 11.3 Hz, 2 H, PhC*H*$_2$-), 4.52 (d, *J* = 12.1 Hz, 2 H, PhC*H*$_2$-), 3.98–3.93 (m, 4 H, 4-H, 5-H), 3.76–3.68 (m, 6 H, 6-H, 7-H, 7-H), 3.60 (d, *J* = 2.2 Hz, 2 H, 3-H), 1.66 (s, 6 H, -C*H*$_3$) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 138.6, 138.6, 138.5, 138.4, 128.5, 128.4, 128.3, 128.2, 128.2, 127.7, 127.7, 127.6, 127.6, 127.4, 127.3, 127.3, 102.4 (C-2), 81.6 (C-4), 79.7 (C-3), 75.3 (Ph*C*H$_2$-), 75.2 (Ph*C*H$_2$-), 75.0 (C-5), 73.4 (Ph*C*H$_2$-), 73.2 (C-6), 72.4 (Ph*C*H$_2$-), 69.4 (C-7), 21.8 (C-1) ppm. IR (neat): $\tilde{\nu}$ = 3030.54, 2914.80, 2860.78, 1469.94, 1454.50, 1367.70, 1207.59, 1107.27, 1070.62 cm^{-1}. HRMS (FAB): calcd. for $C_{70}H_{74}O_{11}Na$ 1113.5129; found 1113.5135. $C_{70}H_{74}O_{11}$ (1090.77): C 77.04, H 6.83; found C 76.89, H 6.96.

1-Deoxy-α-D-*galacto*-hept-2-ulopyranosyl 1-Deoxy-α-D-*galacto*-hept-2-ulopyranoside (13bb): To a solution of **11bb** (27.0 mg, 0.025 mmol) in THF (0.8 mL) was added basic alumina (6.8 mg) and 20% Pd(OH)$_2$/C (13.5 mg) under an argon atmosphere. The mixture was then stirred under a hydrogen atmosphere (balloon) at room temperature. After 2 h, MeOH (0.8 mL) was added to the mixture and stirred for 1 h. The reaction mixture was filtered through filter paper, and the filtrate was evaporate and dried to give **13bb** (6.6 mg, 71%). $[\alpha]_D^{21}$ = +152.8° (*c* = 0.60, CH_3OH). ^{1}H NMR (600 MHz, CD_3OD): δ = 4.10 (m, 2 H, 6-H), 3.85–3.83 (m, 4 H, 4-H, 5-H), 3.59 (dd, *J* = 6.3, 11.3 Hz, 2 H, 7-H), 3.56 (dd, *J* = 6.6, 11.3 Hz, 2 H, 7-H), 3.34 (d, *J* = 9.4 Hz, 2 H, 3-H), 1.56 (s, 6 H, 1-H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 102.7 (C-2), 76.5 (C-3), 72.4 (C-6), 72.3 (C-4), 71.5 (C-5), 71.2 (C-7), 23.1 (C-1) ppm.

1-Deoxy-α-D-*manno*-hept-2-ulopyranosyl 1-Deoxy-α-D-*manno*-hept-2-ulopyranoside (13cc): To a solution of **11cc** (15.2 mg, 0.014 mmol) in THF (0.5 mL) was added basic alumina (3.8 mg) and 20% Pd(OH)$_2$/C (7.6 mg) under an argon atmosphere. The mixture was then stirred under a hydrogen atmosphere (balloon) at room temperature. After 3.5 h, MeOH (0.5 mL) was added to the mixture and stirred for 30 min. The reaction mixture was filtered through filter paper, and the filtrate was evaporate and dried to give **13cc** (5.0 mg, 96%). $[\alpha]_D^{22}$ = +74.7° (*c* = 0.59, H_2O). ^{1}H NMR (600 MHz, CD_3OD): δ = 3.82–3.78 (m, 4 H, 4-H, 7-H), 3.70 (dd, *J* = 4.9,

11.8 Hz, 2 H, 7-H), 3.59 (d, J = 3.0 Hz, 2 H, 3-H), 3.56–3.52 (m, 4 H, 5-H, 6-H), 1.66 (s, 6 H, 1-H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 103.5 (C-2), 75.5 (C-6), 75.3 (C-3), 73.0 (C-4), 68.3 (C-5), 63.0 (C-7), 22.0 (C-1) ppm.

Supporting Information (see footnote on the first page of this article): Spectroscopic data for all other synthesized disaccharides.

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