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Novel synthesis of oligosaccharides linked with carbamate and urea bonds utilizing modified Curtius rearrangement

Daisuke Sawada, Shinya Sasayama, Hideyo Takahashi, Shiro Ikegami *

School of Pharmaceutical Sciences, Teikyo University, Sagamiko, Sagamihara, Kanagawa 229-0195, Japan

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ABSTRACT

We describe a novel synthesis of various carbamate- and urea-linked disaccharides stereospecifically using sugar carboxylic acids and sugar alcohols or sugar amines by the modified Curtius rearrangement. In this reaction, the reactivity of each hydroxyl group in glucose as an acceptor has been disclosed. Furthermore, we applied this method to the synthesis of carbamate-linked oligosaccharides including a dendritic molecule.

1. Introduction

Oligosaccharides are essential constituents in our body and play an important role in nature, often by conjugating the various peptides and lipids and as nucleic acids.[1] Many chemists have made much effort for the stereoselective synthesis of oligosaccharides, which has many problems even now. One of the reasons why oligosaccharide synthesis still involves various difficulties is due to the instability of the glycoside bond, which is acetal linkages. Recently, the novel glycosaccharides in which sugars were linked each other with carbamates or ureas other than acetals were reported,[2] and their bonds should be more stable than acetal bonds to provide the more stable oligosaccharide analogs. So the carbamate- or urea-linked glycosaccharides would make it possible to synthesize the complex oligosaccharide, which could be good mimics of oligosaccharide biomolecules. Furthermore, these novel oligosaccharides would be expected to show unique properties which could be good tools for the chemical biology and material sciences. In this time, we planed the synthesis of carbamate- and urea-linked oligosaccharides using Curtius rearrangement with sugar carboxylic acids and sugar alcohols or sugar amines in a stereospecific manner (Scheme 1).[3] Curtius rearrangement is known to proceed via an isocyanate intermediate with retaining the configuration of the chiral center adjacent to the reactive carboxylic acid, and we utilized this reaction for stereospecific synthesis of these oligosaccharides. Here, we described the novel stereospecific synthesis of various types of carbamate- and urea-linked oligosaccharides by the modified Curtius rearrangement.

2. Results and discussions

We started this synthetic method at obtaining the sugar α- and β-1-carboxylic acids stereospecifically, and the known lactones **1**–**3**,[4] derived from glucose, galactose, and mannose, respectively, were used for the synthesis of the carboxylic acids (Scheme 2). According to Ref. 5, gluconolactone **1** and galactonolactone **2** were transformed into both stereoisomers of alcohols **4**–**7**[5] and they were oxidized[6] to carboxylic acids **9**–**12**,[5,7] the substrates for the Curtius rearrangement. Mannolactone **3**, however, gave only β-alcohol **8**, which was oxidized to β-carboxylic acid **14**, because of the steric hindrance of the 2β-benzyloxy group in the hydroboration reaction. The inversion of the stereochemistry from the β-carboxylic acid **14** to the α-carboxylic acid **13** was successfully achieved in the efficient conversion yield as shown in Scheme 3. Thus, we could obtain both the stereoisomers of sugar 1-carboxylic acids **9**–**14** derived from glucose, galactose, and mannose.

Firstly, we investigated the synthesis of carbamate-linked disaccharides using the carboxylic acids **9**–**14** and alcohols **15**–**21**[8] (Table 1). The typical reaction conditions are as follows: a carboxylic acid and 2 equiv of an alcohol were refluxed in the presence of 2 equiv of diphenyl phosphorylazide (DPPA)[9] and base.[3] In some cases, the additional catalyst, Ag_2CO_3, increased the yield (entries

* Corresponding author. Tel./fax: +81 42 685 3714.
E-mail address: somc@pharm.teikyo-u.ac.jp (S. Ikegami).

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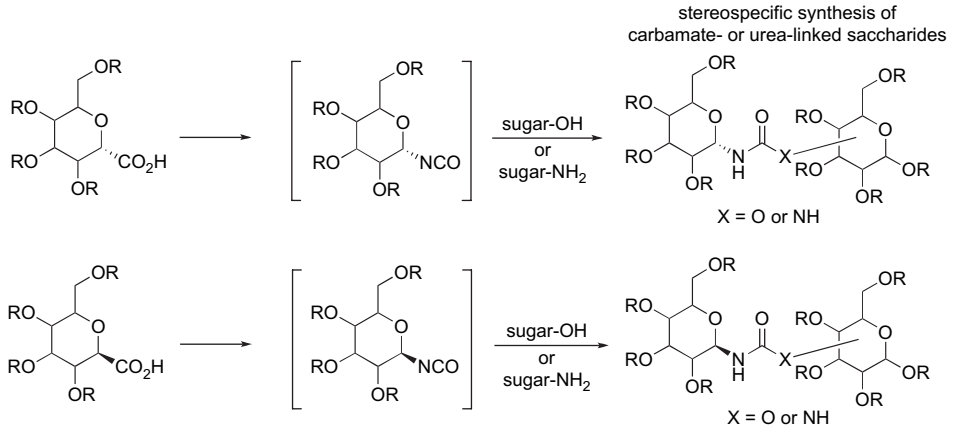
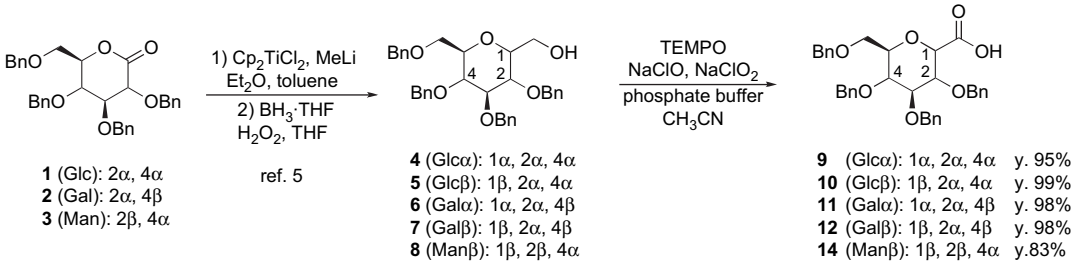
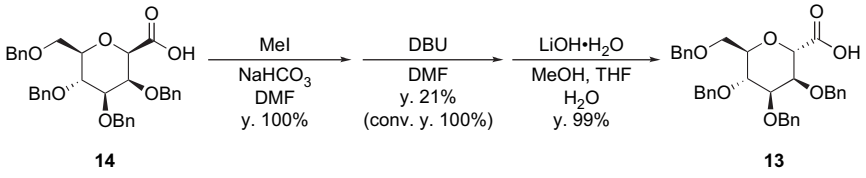


Scheme 1.



Scheme 2. Synthesis of sugar carboxylic acid.



Scheme 3. Synthesis of mannose derived β-carboxylic acid.

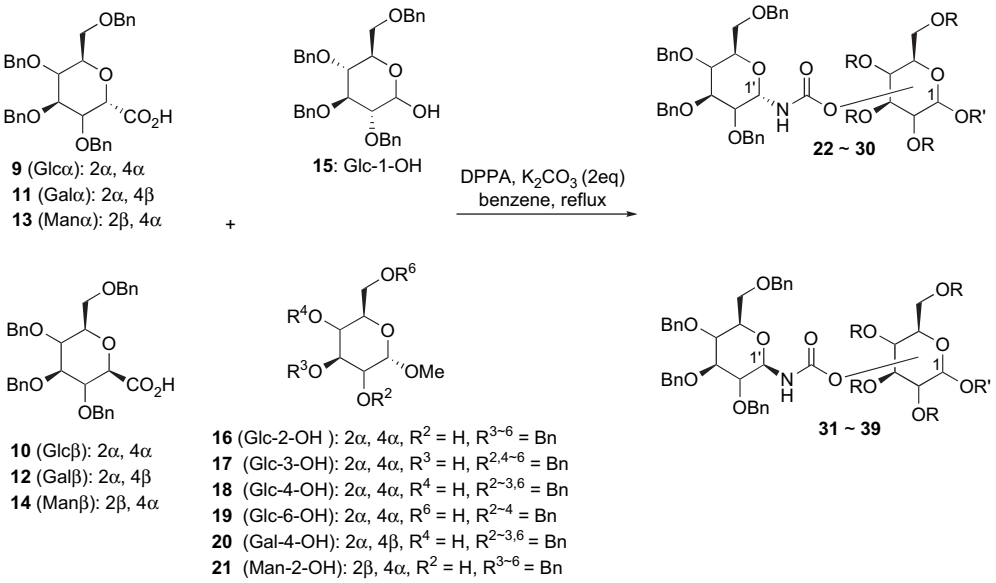
4–6, 8, 15, 17, 18). Although the carboxylic acids **9**–**14** gave similar results, the β-carboxylic acids **10**, **12**, and **14** showed better reactivity and afforded better yield than the corresponding α-carboxylic acids **9**, **11**, and **13**, respectively. Also, the α-carbamate linkages seemed to be rather unstable than the β-carbamate linkages under these reaction conditions, and, for example, in entries 3 and 6 in Table 1, the partial decomposition of the products took place, and that would cause the relatively lower yields (56% yield in entry 3 and 59% yield in entry 6). Among the acceptors **15**–**21**, the primary alcohol **19** (Glc-6-OH) showed the best reactivity and interestingly the hemiacetal (Glc-1-OH) **15** gave the good results.[10] It seemed that the rate-determining step of the reaction was the addition of the alcohol to the isocyanate intermediate, because the transformation of the carboxylic acid to the isocyanate was thought to be fast by the TLC analysis. Therefore, the reactivity should depend on the steric hindrance of both an acceptor and a donor dominantly, as shown in the evidence that alcohol **19** was the most reactive among the acceptors. As a base, K_2CO_3 should be used for the less reactive acceptors to accelerate their nucleophilicity.[11] And the additional catalyst, Ag_2CO_3, was also effective to promote the addition of the acceptor by coordinating the isocyanate. Thus, it was found that all of the α- and β-carbamate-linked disaccharides could be obtained stereospecifically by the modified Curtius rearrangement using α- and β-sugar carboxylic acids **9**–**14**.

To disclose the reactivity of each hydroxyl group in a sugar as an acceptor, we planned such reaction procedure that carboxylic acid **10** was reacted with the mixture of each 1 equiv of sugar alcohols **16**–**19**, for examining the reactivity of each hydroxyl group at the 2- to 6-position in the glucose derivatives, respectively (Scheme 4). The substrate **10** completely disappeared under the reaction conditions and the carbamate-linked disaccharides **32**–**35** were obtained in the ratio of 3.4:1.0:1.8:4.4 (**32**/**33**/**34**/**35**). This result shows that the order of the reactivity of the each hydroxyl groups is 6-, 2-, 4-, 3-position, and also indicates the unique reactivity of acceptors in this Curtius rearrangement.

Then, we tried the deprotection of the disaccharides **22**–**39** (Table 2). The representative method to remove a benzyl group worked very well, and the deprotected disaccharides **41**–**57** were obtained in excellent yield by Pd on carbon and H_2 without affecting both the carbamate bond and any stereochemistry, except giving some unidentified decomposed product from **22**.[12]

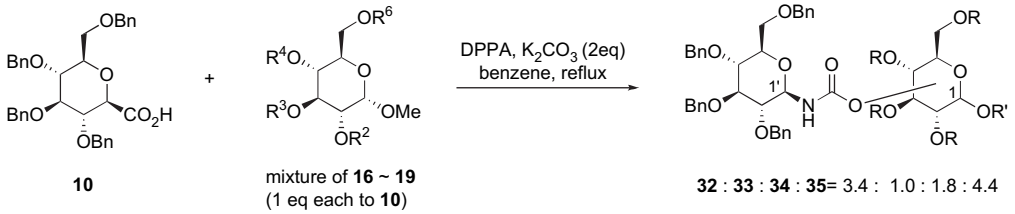
Next, we tried the synthesis of carbamate-linked oligosaccharides on the basis of the previous observation. Carboxylic acid **58**[3] and alcohol **59**[3] are thought to be useful for the synthesis of the linear oligosaccharide chain (Scheme 5). The same equivalent of **58** and **59** were reacted with 2 equiv of DPPA and triethylamine to give the desired disaccharides **60** in 84% yield. Using compound **60**, the elongation both at the 1-carboxylic acid and/or at the 6′-hydroxyl

Table 1
Synthesis of carbamate-linked disaccharides



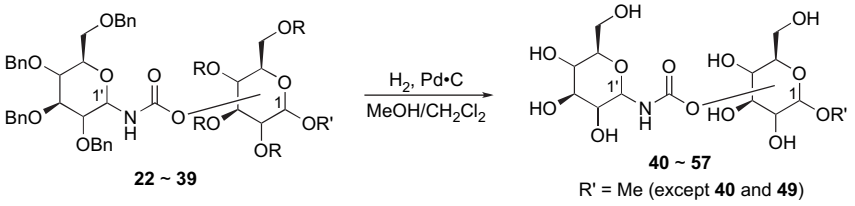
Entry	Carboxylic acid	Alcohol	Time (h)	Yield (%)	Entry	Carboxylic acid	Alcohol	Time (h)	Yield (%)
1	**9**	**15**	12	82 (**22**: Glc α1′-Glc 1)	10	**10**	**15**	8	94 (**31**: Glc β1′-Glc 1)
2	**9**	**16**	20	64 (**23**: Glc α1′-Glc 2)	11	**10**	**16**	10	73 (**32**: Glc β1′-Glc 2)
3	**9**	**17**	34	56 (**24**: Glc α1′-Glc 3)	12	**10**	**17**	29	87 (**33**: Glc β1′-Glc 3)
4[a]	**9**	**18**	29	78 (**25**: Glc α1′-Glc 4)	13	**10**	**18**	18	89 (**34**: Glc β1′-Glc 4)
5[a]	**9**	**19**	29	66 (**26**: Glc α1′-Glc 6)	14[b]	**10**	**19**	8	98 (**35**: Glc β1′-Glc 6)
6[a]	**9**	**20**	29	59 (**27**: Glc α1′-Gal 4)	15[a]	**10**	**20**	14	79 (**36**: Glc β1′-Gal 4)
7	**9**	**21**	29	65 (**28**: Glc α1′-Man 2)	16	**10**	**21**	15	71 (**37**: Glc β1′-Man 2)
8[a]	**11**	**19**	50	87 (**29**: Gal α1′-Glc 6)	17[a]	**12**	**19**	7	95 (**38**: Gal β1′-Glc 6)
9	**13**	**19**	15	85 (**30**: Man α1′-Glc 6)	18[a]	**14**	**19**	6	92 (**39**: Man β1′-Glc 6)

[a] Ag_2CO_3(0.1 equiv) was added.
[b] Triethylamine was used as a base.

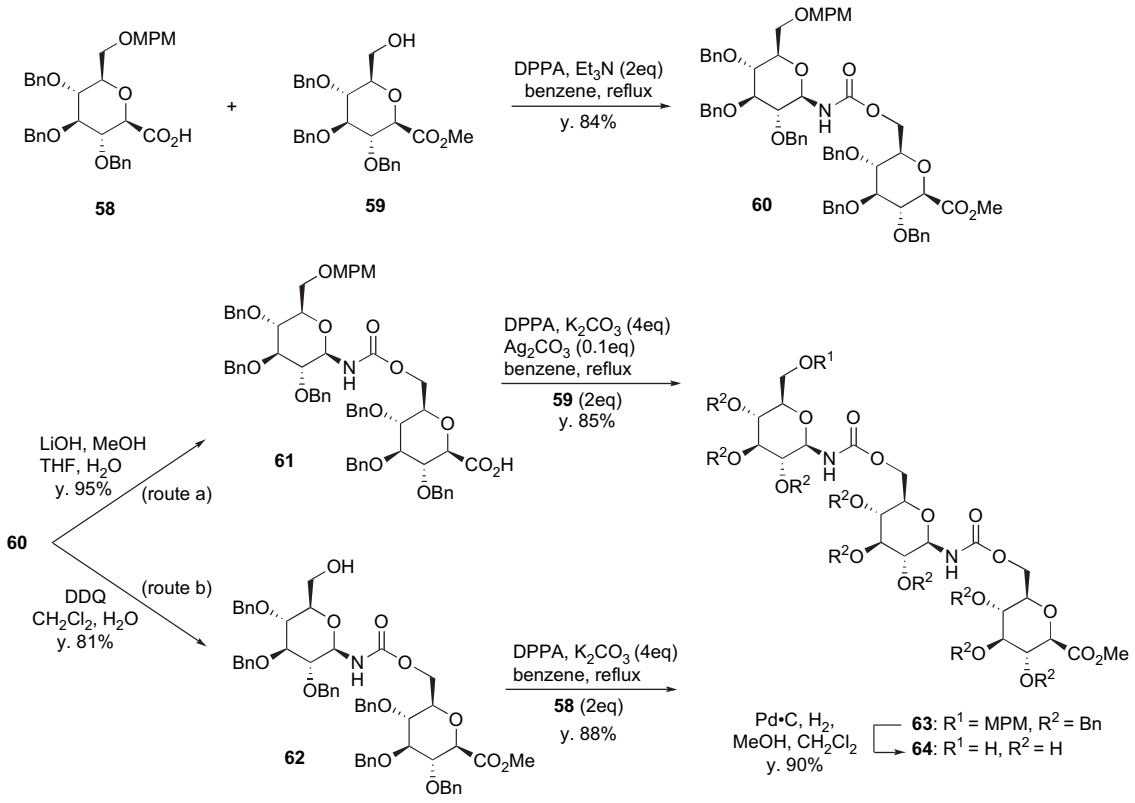


Scheme 4.

Table 2
Deprotection of carbamate-linked disaccharides



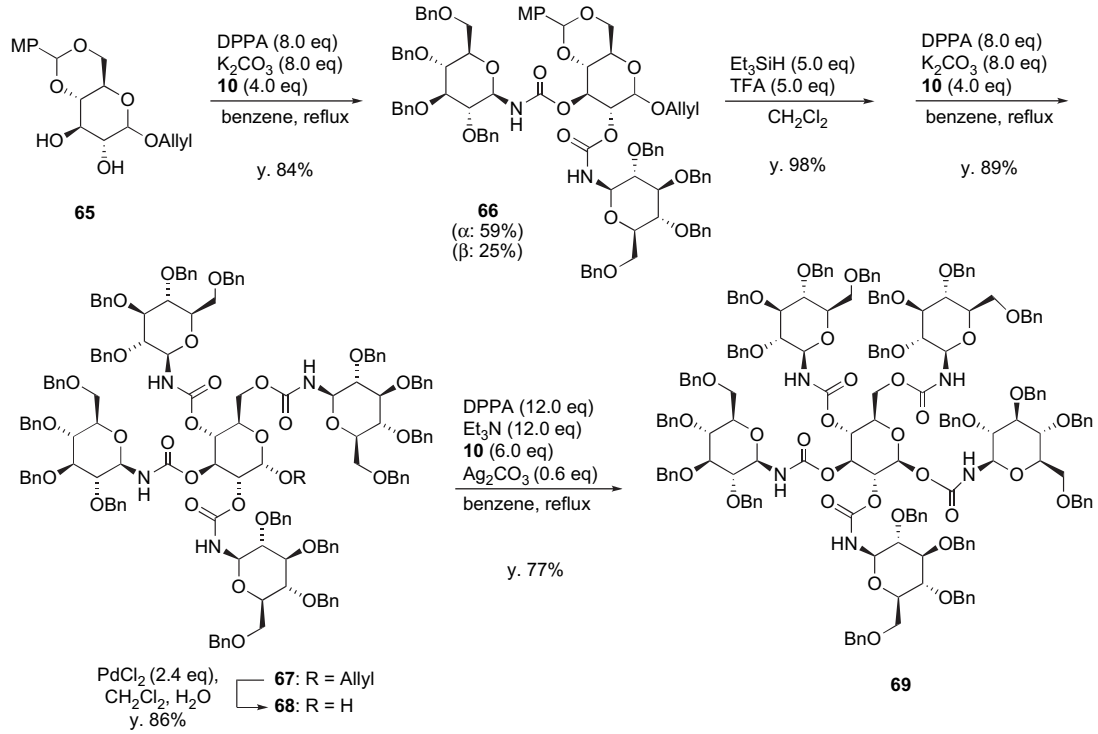
Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1	**22**	- (**40**)	10	**31**	99 (**49**)
2	**23**	99 (**41**)	11	**32**	97 (**50**)
3	**24**	99 (**42**)	12	**33**	99 (**51**)
4	**25**	97 (**43**)	13	**34**	95 (**52**)
5	**26**	95 (**44**)	14	**35**	99 (**53**)
6	**27**	92 (**45**)	15	**36**	95 (**54**)
7	**28**	95 (**46**)	16	**37**	95 (**55**)
8	**29**	71 (**47**)	17	**38**	98 (**56**)
9	**30**	100 (**48**)	18	**39**	91 (**57**)



Scheme 5. Synthesis of linear trisaccharide.

group would be possible, and disaccharide **60** was transformed into the carboxylic acid **61** by hydrolysis (95% yield, route a) or into the alcohol **62** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and H_2O (81% yield, route b). The modified Curtius rearrangement using the above carboxylic acids and alcohols, **59** and **61** (route a) or **58** and **62** (route b), afforded the same trisaccharide **63** in 85 and 88% yield, respectively. All the benzyl protections of **63** were removed by Pd on carbon and H_2 to give compound **64**, and thus the deprotected trisaccharide was obtained in the two independent ways.

Then, we embarked on the synthesis of a sugar dendritic molecule as an application of the present methodology (Scheme 6). The



Scheme 6. Synthesis of a dendritic molecule.

known monosaccharide **65**,[13] which is soluble in benzene was reacted with 4 equiv of **10** and 8 equiv of DPPA and K_2CO_3 to afford the trisaccharide **66** in 84% yield. Compound **66**, which had equipped two carbamate linkages in one step, was a mixture of anomeric isomers, which could be separated by column chromatography, and the major α-isomer was used for the further synthesis for precise structural evidence. The deprotection of the methoxybezylidene group of **66** was achieved by Et_3SiH and trifluoroacetic acid in 98% yield, and the resultant 4,6-diol was reacted with **10** as the above reaction to afford the pentasaccharide **67** in 89% yield. The removal of the allyl group in compound **67** resulted in the partial decomposition of the substrate under various conditions. Fortunately, it was found that the deprotection using $PdCl_2$ in CH_2Cl_2 and H_2O proceeded smoothly and the desired hemiacetal **68** was obtained in 86% yield. We investigated the final Curtius rearrangement to **68**, however, it was difficult due to the steric hindrance around the reactant hemiacetal group. After many attempts, the reaction with 6 equiv of compound **10**, 12 equiv of DPPA, triethylamine, and 0.6 equiv of Ag_2CO_3 successfully afforded the hexasaccharide **69**[14] in 77% yield. As above, we have finally developed the new way for the synthesis of unique dendritic molecule having a sugar core.

Now we established the synthetic methodology of carbamate-linked saccharides, then we shifted the next investigation to explore the synthesis of urea-linked saccharides using Curtius rearrangement with aminosugars **70**[15] and **71**[16] as acceptors (Scheme 7). To form a urea linkage from a carboxylic acid and an amine, a carboxylic acid must be converted to the intermediate isocyanate before reacting an amine, to avoid the transformation of the amide. So, we refluxed the carboxylic acid **9** or **10** with 2 equiv of DPPA and triethylamine for 1 h in advance, and then 1.5 equiv of amine **70** or **71** was added to the reaction mixture. The whole mixture was further refluxed until the intermediate isocyanate disappeared by the TLC analysis (1–5 h) and finally the urea-linked disaccharides **72**–**75** were obtained in excellent yield. With the aminosugar **70**, CH_3CN was used as a co-solvent, because of the insoluble property of **70** in benzene, in which 2-amino group selectively reacted with the isocyanate. The removal of all the benzyl groups and the benzylidene group of the disaccharides was successfully achieved by Pd on carbon and H_2 in MeOH and CH_2Cl_2 without affecting the urea linkage. As above, it was found that both the α- and β-urea-linked disaccharides could be obtained stereospecifically by Curtius rearrangement using α- and β-sugar carboxylic acids **9** and **10**.

3. Conclusion

We have developed a novel stereospecific synthesis of the α- and β-carbamate- and urea-linked disaccharides by the modified Curtius rearrangement. In these reactions, the reactivity of each hydroxyl group of glucose as an acceptor has been disclosed. Furthermore, we demonstrated the oligosaccharide syntheses by applying this method and the trisaccharide **64** could be easily synthesized in two different ways. Finally, the synthetic challenge to the dendritic molecule **69** involving one-step construction of two carbamate linkages has been accomplished. Hopefully, this methodology would make it possible to synthesize more complex and new glycoconjugates exhibiting interesting properties, and contribute to the chemical biology and material science.

4. Experimental

4.1. General procedures

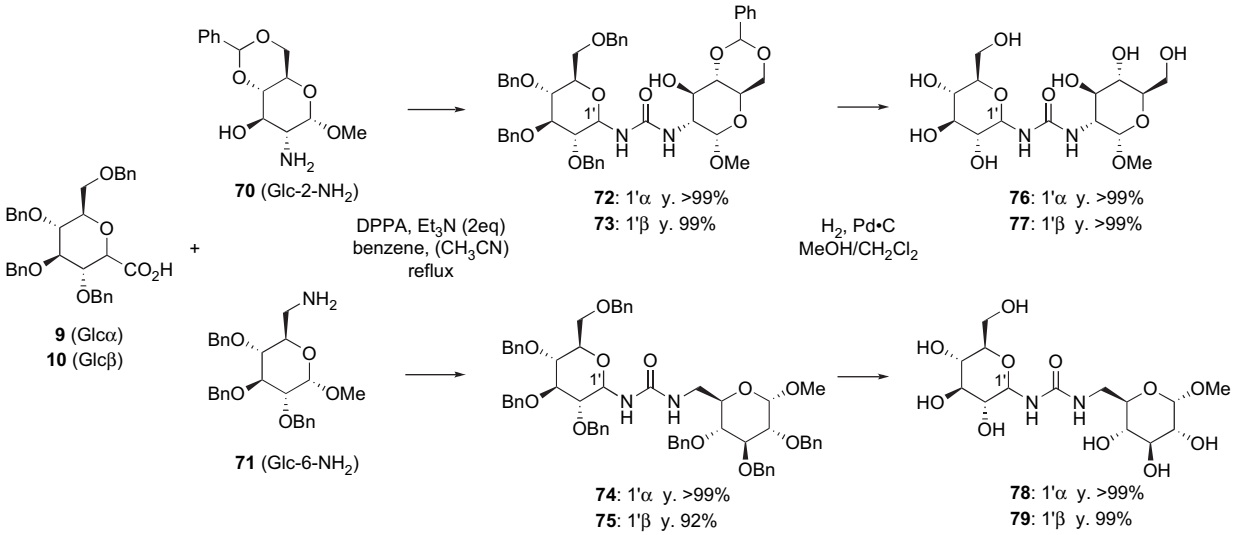
Infrared (IR) spectra were measured on a Jasco FT/IR-8000 Fourier transform infrared spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a JEOL JNM-GSX400, 600 (400, 600 MHz) pulse Fourier transform NMR spectrometer in $CDCl_3$ solution. Low-resolution mass spectra (MS) and high-resolution (HR) mass spectra were obtained with a JEOL JMS-SX102A mass spectrometer. Optical rotations were determined using a Jasco DIP-370 digital polarimeter. Thin-layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in ethanol/H_2O followed by heating. Except for special cases as mentioned, column chromatography was performed using SiO_2 (Wakogel C-300, Wako).

4.2. General procedure for the oxidation of sugar alcohols

The reaction of **4** is described as a representative example.

*4.2.1. 1-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)formic acid (**9**)*

To the solution of **4** (524 mg, 0.944 mmol) in CH_3CN (4.7 mL) were added TEMPO (21 mg, 0.13 mmol) and NaH_2PO_4 (0.67 M, 3.5 mL), and the mixture was warmed at 35 °C. A solution of NaClO (0.47 mL, 0.25%) and $NaClO_2$ (0.94 mL, 2 M) was added to the mixture over a period of 1 h. Then, saturated aqueous $Na_2S_2O_3$ was



Scheme 7. Synthesis of urea-linked disaccharides.

carefully added to the mixture at 0 °C and the whole mixture was stirred at room temperature. After 30 min, 2 N HCl was added to the mixture, which was acidified (pH 2). The aqueous layer was extracted with AcOEt (20 mL, three times) and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 1:1) to afford the desired product **9** (508 mg, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (m, 1H), 7.32–7.15 (m, 20H), 4.83 (d, J=11.2 Hz, 1H), 4.77 (d, J=11.0 Hz, 1H), 4.75–4.73 (m, 1H), 4.73 (d, J=11.7 Hz, 1H), 4.70 (d, J=11.7 Hz, 1H), 4.62–4.59 (m, 2H), 4.50–4.47 (m, 2H), 4.31–4.28 (m, 1H), 3.99–3.91 (m, 2H), 3.73–3.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.72, 137.95, 137.76, 137.47, 136.79, 128.17, 128.13, 128.10, 128.02, 127.92, 127.83, 127.74, 127.67, 127.56, 127.51, 127.49, 127.45, 80.89, 77.24, 76.74, 74.71, 74.23, 74.10, 73.70, 73.32, 73.22, 72.79, 68.45; MS (FAB—NBA+NaI): m/z 591 $(M+Na)^+$; HRMS (FAB—NBA+NaI): calcd for $C_{35}H_{36}NaO_7$ 591.2359, found 591.2348; $[\alpha]_D^{24}$ −9.70 (c 0.26, $CHCl_3$); IR (neat, cm^{-1}): 1734 (C=O).

4.2.2. 1-(2,3,4,6-Tetra-O-benzyl-α-D-mannopyranosyl)formic acid (**13**)

To the solution of **14** (305 mg, 0.536 mmol) in DMF (4 mL) were added $NaHCO_3$ (86 mg, 1.07 mmol) and methyl iodide (95 μL, 1.61 mmol), and the mixture was stirred at ambient temperature for 19 h. Then, water was added to the mixture, extracted with AcOEt (20 mL three times), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 5:1) to afford the ester (312 mg, 100%) as a colorless oil. The ester was successively used in the next step. To the solution of the ester (71 mg, 0.122 mmol) in DMF (1 mL) was added DBU (40 μL, 0.268 mmol) and the mixture was stirred at ambient temperature for 48 h. Then, saturated aqueous NH_4Cl was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 6:1–5:1) to afford the β-ester (15 mg, 21%) as a colorless oil with the recovered substrate, α-ester (56 mg, 79%). The β-ester was successively used in the next step. To the solution of the β-ester (60 mg, 0.103 mmol) in THF (1 mL), MeOH (1 mL), and water (0.3 mL) was added $LiOH\cdot H_2O$ (9 mg, 0.206 mmol) at 0 °C, and the mixture was stirred for 10 h at ambient temperature. Then, 1 N HCl was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 1:1) to afford the desired carboxylic acid **13** (58 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.26 (m, 18H), 7.18–7.14 (m, 2H), 4.86 (d, J=11.0 Hz, PhCH_2, 1H), 4.74 (d, J=12.2 Hz, 1H), 4.70–4.57 (m, 3H), 4.29 (m, 1H), 4.01–3.92 (m, 2H), 3.76 (m, 2H), 3.61 (dd, J=2.7, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.46, 137.95, 137.85, 137.83, 137.59, 128.43, 128.34, 128.28, 128.26, 128.25, 127.93, 127.89, 127.85, 127.72, 127.63, 127.55, 80.08, 77.32, 76.07, 75.06, 74.00, 73.91, 73.30, 72.17, 71.89, 69.28; MS (FAB—NBA+NaI) m/z 591 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{35}H_{36}O_7Na$ 591.2315, found 591.2337; $[\alpha]_D^{20}$ −1.41 (c 1.35, $CHCl_3$); IR (neat, cm^{-1}) 1730 (C=O).

4.3. General procedure for the synthesis of carbamate-linked disaccharides

The reaction of **9** and **18** is described as a representative example.

4.3.1. Methyl 2,3,6-tri-O-benzyl-4-O-[(N-2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)carbamoyl]-α-D-glucopyranoside (**25**)

To the mixture of carboxylic acid **9** (38 mg, 0.066 mmol) and alcohol **18** (63 mg, 0.132 mmol) in benzene (7 mL) were added K_2CO_3 (18 mg, 0.132 mmol), DPPA (0.029 mL, 0.132 mmol), and Ag_2CO_3 (1.8 mg, 0.0066 mmol) and the whole mixture was refluxed for 29 h. Then, saturated aqueous NH_4Cl was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 4:1) to afford the desired product **25** (53 mg, 78%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.01 (m, 35H), 5.53 (d, J=5.1 Hz, 1H), 5.48 (m, 1H), 4.96 (t, J=9.5 Hz, 1H), 4.85 (d, J=11.0 Hz, 1H), 4.79 (d, J=11.5 Hz, 1H), 4.77–4.68 (m, 4H), 4.67 (d, J=11.0 Hz, 1H), 4.58–4.56 (m, 2H), 4.55–4.28 (m, 6H), 3.90 (t, J=9.5 Hz, 1H), 3.81 (m, 1H), 3.70 (dd, J=5.1, 9.3 Hz, 1H), 3.63–3.53 (m, 7H), 3.45 (dd, J=5.9, 10.8 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.65 (C=O), 138.50, 138.20, 137.96, 137.89, 137.76, 137.74, 136.87, 128.38, 128.35, 128.34, 128.32, 128.28, 128.25, 128.19, 128.11, 128.07, 127.96, 127.91, 127.87, 127.83, 127.78, 127.73, 127.68, 127.64, 127.58, 127.48, 127.41, 127.36, 127.33, 98.07, 81.81, 79.19, 77.21, 77.04, 76.88, 75.52, 75.25, 74.94, 73.60, 73.53, 73.49, 73.42, 72.11, 70.71, 69.30, 68.89, 55.35; MS (FAB—NBA+NaI) m/z 1052 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{63}H_{67}NNaO_{12}$ 1052.4561, found 1052.4536; $[\alpha]_D^{24}$ +8.17 (c 0.55, $CHCl_3$); IR (neat, cm^{-1}) 1721 (C=O), 3285 (NH).

4.4. General procedure for the deprotection of carbamate-linked disaccharides

The reaction of **26** is described as a representative example.

4.4.1. Methyl 6-O-[(N-α-D-glucopyranosyl)carbamoyl]-α-D-glucopyranoside (**44**)

To the solution of carbamate **26** in dichloromethane (1 mL) and methanol (6 mL) was added Pd on carbon (3.3 mg), and the mixture was stirred under hydrogen for 26 h. Then, the mixture was evaporated and the residue was purified by silica gel flash chromatography (dichloromethane/methanol, 4:1) to afford the desired product **44** (12 mg, 95%) as a white powder: ^{1}H NMR (600 MHz, CD_3OD) δ 5.36 (d, J=5.2 Hz, 1H), 4.65 (d, J=3.6 Hz, 1H), 4.37–4.35 (m, 1H), 4.27 (dd, J=5.8, 11.8 Hz, 1H), 3.75 (dd, J=2.2, 11.8 Hz, 1H), 4.72–3.69 (m, 1H), 3.67–3.56 (m, 4H), 3.45–3.43 (m, 1H), 3.41–3.38 (m, 4H), 3.32–3.28 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 159.03, 101.27, 80.71, 74.98, 74.79, 74.06, 73.46, 71.79, 71.60, 71.32, 65.57, 62.73, 55.75; MS (FAB—NBA+NaI) m/z 422 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{14}H_{25}NNaO_{12}$ 422.1275, found 422.1274; $[\alpha]_D^{24}$ +13.1 (c 0.37, CH_3OH); IR (neat, cm^{-1}) 1711 (C=O), 3738–3030 (OH).

4.4.2. [2,3,4-Tri-O-benzyl-6-O-{(N-2,3,4-tris-O-benzyl-6-O-(4-methoxybenzyl)-β-D-glucopyranosyl)carbamoyl}-β-D-glucopyranosyl]formic acid methyl ester (**60**)

To the mixture of carboxylic acid **58** (38 mg, 0.066 mmol) and alcohol **59** (63 mg, 0.132 mmol) in benzene (7 mL) were added triethylamine (18 mg, 0.132 mmol) and DPPA (0.029 mL, 0.132 mmol), and the whole mixture was refluxed for 29 h. Then, saturated aqueous NH_4Cl was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 4:1) to

afford the desired product **60** (53 mg, 78%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 30H), 7.12 (m, 2H), 6.83 (m, 2H), 5.12 (d, J=9.0 Hz, 1H), 4.92–4.77 (m, 7H), 4.72 (d, J=9.2 Hz, 1H), 4.68 (d, J=8.8 Hz, 1H), 4.63–4.56 (m, 4H), 4.47 (d, J=10.7 Hz, 1H), 4.40 (d, J=11.0 Hz, 1H), 4.25 (m, 1H), 3.95–3.59 (m, 8H), 3.75 (s, 3H), 3.72 (s, 3H), 3.50 (m, 3H), 3.33 (t, J=8.54 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.04, 159.04, 155.16, 138.24, 138.05, 137.90, 137.52, 137.24, 129.71, 129.56, 128.86, 128.82, 128.37, 128.31, 128.26, 128.17, 128.13, 128.06, 128.02, 127.87, 127.79, 127.74, 127.64, 127.60, 127.54, 113.61, 86.07, 85.79, 81.64, 80.03, 79.73, 78.85, 78.10, 77.78, 77.54, 77.41, 76.09, 75.57, 75.19, 75.00, 74.79, 74.70, 73.02, 67.56, 63.93, 55.10, 52.36; MS (FAB—NBA+NaI) m/z 1110 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{65}H_{69}NNaO_{14}$ 1110.4616, found 1110.4628; $[\alpha]_D^{20}$ +4.3 (c 2.75, $CHCl_3$); IR (neat, cm^{-1}) 1705 (C=O), 3284 (NH).

4.4.3. *[2,3,4-Tri-O-benzyl-6-O-{(N-2,3,4-tris-O-benzyl-6-O-(4-methoxybenzyl)-β-D-glucopyranosyl)carbamoyl}-β-D-glucopyranosyl]formic acid (**61**)*

Compound **60** was dissolved in methanol, THF, and H_2O, and $LiOH\cdot H_2O$ was added to the solution. After stirring for 4 h at room temperature, saturated aqueous NH_4Cl was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 4:1) to afford the desired product **61** (53 mg, 78%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (m, 30H), 7.10 (m, 2H), 6.91 (m, 2H), 5.42 (br s, 1H), 4.92–4.73 (m, 13H), 4.57 (m, 2H), 4.45 (m, 2H), 4.37 (d, J=10.0 Hz, 1H), 4.27 (m, 1H), 3.98 (m, 1H), 3.82–3.29 (m, 10H), 3.72 (s, 3H), 3.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.07, 155.51, 138.26, 138.02, 137.88, 137.59, 137.31, 139.64, 129.55, 128.39, 128.33, 128.27, 128.20, 128.05, 128.90, 127.80, 127.69, 127.66, 127.58, 127.52, 113.66, 85.76, 85.51, 81.74, 80.18, 79.33, 77.50, 77.21, 76.00, 75.58, 75.45, 75.05, 74.81, 74.69, 72.92, 67.64, 63.60, 56.88, 55.12; MS (FAB—NBA+NaI) m/z 1097 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{64}H_{67}NNaO_{14}$ 1096.4459, found 1096.4442; $[\alpha]_D^{25}$ +15.3 (c 2.5, $CHCl_3$); IR (neat, cm^{-1}) 1710 (C=O), 3280 (NH).

4.4.4. *[2,3,4-Tri-O-benzyl-6-O-{(N-2,3,4-tris-O-benzyl-β-D-glucopyranosyl)carbamoyl}-β-D-glucopyranosyl]formic acid methyl ester (**62**)*

To the solution of carbamate **60** in dichloromethane (8 mL) and H_2O (3 mL) was added DDQ (10 mg), and the mixture was stirred for 26 h. Then, saturated aqueous NH_4Cl was added followed by the addition of dichloromethane (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with dichloromethane (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (dichloromethane/methanol, 60:1) to afford the desired product **62** (41 mg, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.22 (m, 30H), 5.48 (d, J=8.8 Hz, 1H), 4.95–4.74 (m, 12H), 4.62 (d, J=10.3 Hz, 1H), 4.61 (d, J=10.3 Hz, 1H), 4.44 (d, J=11.5 Hz, 1H), 4.35 (m, 1H), 3.96 (d, J=9.3 Hz, 1H), 3.91–3.58 (m, 9H), 3.66 (s, 3H), 3.47 (m, 1H), 3.36 (t, J=9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.25, 155.40, 138.16, 138.03, 137.81, 137.53, 137.49, 137.30, 128.41, 128.39, 128.36, 128.31, 128.28, 128.02, 127.91, 127.85, 127.78, 127.75, 127.73, 127.60, 127.55, 86.02, 85.59, 81.61, 80.44, 79.95, 78.01, 77.64, 77.37, 76.68, 75.67, 75.62, 75.25, 75.09, 74.93, 74.73, 63.72, 61.36, 52.37; MS (FAB—NBA+NaI) m/z 990 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{75}H_{61}NNaO_{13}$ 990.4041, found 990.4045; $[\alpha]_D^{25}$ +0.15 (c 2.9, $CHCl_3$); IR (neat, cm^{-1}) 1707 (C=O), 3288 (NH).

4.4.5. *[2,3,4-Tri-O-benzyl-6-O-{(N-2,3,4-tris-O-benzyl-6-O-(N-2,3,4-tris-O-benzyl-6-O-(4-methoxybenzyl)-β-D-glucopyranosyl)carbamoyl)-β-D-glucopyranosyl}carbamoyl]-β-D-glucopyranosyl]formic acid methyl ester (**63**)*

Route a. The general procedure for the synthesis of carbamate-linked disaccharides was followed by using **61** (29 mg, 0.027 mmol), 2 equiv of **59** (27 mg, 0.054 mmol), 2 equiv of K_2CO_3 and DPPA, and 0.1 equiv of Ag_2CO_3 to afford **63** (36 mg 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.21 (m, 45H), 7.11–7.09 (m, 2H), 6.82–6.80 (m, 2H), 5.17–5.10 (m, 2H), 4.92–4.68 (m, 17H), 4.55 (d, J=6.6 Hz, 1H), 4.53 (d, J=6.6 Hz, 1H), 4.60–4.52 (m, 2H), 4.47 (d, J=10.26 Hz, 1H), 4.38–4.32 (m, 4H), 4.27–4.22 (dd, J=3.7, 11.6 Hz, 2H), 3.87 (d, J=9.5 Hz, 1H), 3.68–3.61 (m, 6H), 3.74 (s, 3H), 3.68 (s, 3H), 3.57 (m, 1H), 3.52–3.42 (m, 4H), 3.34–3.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.24, 159.19, 155.35, 155.21, 138.41, 138.24, 138.19, 137.76, 137.66, 137.51, 137.35, 129.92, 129.66, 128.57, 128.51, 128.46, 128.44, 128.42, 128.40, 128.39, 128.31, 128.20, 128.17, 128.13, 128.02, 127.97, 127.91, 127.88, 127.79, 127.75, 127.67, 127.62, 113.72, 86.14, 86.11, 85.83, 85.68, 81.79, 81.58, 80.33, 80.16, 79.90, 79.79, 78.13, 78.02, 77.82, 77.57, 77.50, 77.40, 76.20, 75.73, 75.62, 75.24, 75.16, 75.09, 75.06, 74.86, 74.80, 73.07, 67.69, 64.02, 63.72, 61.81, 60.37, 55.15, 52.44, 52.41; MS (FAB—NBA+NaI) m/z 1586 $(M+Na)^+$, HRMS (FAB—NBA+NaI) calcd for $C_{93}H_{98}N_2NaO_{20}$ 1585.6613, found: 1585.6617; $[\alpha]_D^{26}$ −2.23 (c 0.7, $CHCl_3$); IR (neat, cm^{-1}) 1738 (C=O), 3328 (NH).

Route b. The general procedure for the synthesis of carbamate-linked disaccharides was followed by using **62** (14 mg, 0.0145 mmol), 2 equiv of **58** (17 mg, 0.029 mmol), and 4 equiv of K_2CO_3 and DPPA to afford **63** (20 mg, 88%) as colorless oil.

4.4.6. *[6-O-{(N-6-O-(N-β-D-Glucopyranosyl)carbamoyl)-β-D-glucopyranosyl}carbamoyl-β-D-glucopyranosyl]formic acid methyl ester (**64**)*

The general procedure for the deprotection of carbamate-linked disaccharides was followed by using **63** (19 mg 0.012 mmol) to afford **64** (6.9 mg 90%) as a colorless oil: ^{1}H NMR (400 MHz, D_2O) δ 4.83–4.80 (m, 3H), 4.50–4.45 (m, 2H), 4.28–4.24 (m, 2H), 4.05–4.02 (m, 1H), 3.91–3.83 (m, 2H), 3.74–3.74 (m, 4H), 3.56 (s, 3H), 3.58–3.35 (m, 7H); ^{13}C NMR (100 MHz, D_2O) δ 171.05, 170.45, 165.54, 152.08, 76.17, 74.07, 72.42, 71.88, 71.62, 71.41, 71.27, 70.85, 70.51, 62.23, 66.14, 65.92, 65.65, 65.55, 63.73, 63.52, 54.82; MS (FAB—NBA+NaI) m/z 655 $(M^+ + Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{22}H_{36}N_2NaO_{19}$ 655.1811, found: 655.1807; $[\alpha]_D^{23}$ −52.6 (c 0.92, H_2O); IR (neat, cm^{-1}) 1717 (C=O), 3326.

4.4.7. *Allyl 2,3-di-O-[(N-2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)carbamoyl]-4,6-O-(4-methoxybenzylidene)-α-D-glucopyranoside (**66α**) and allyl 2,3-di-O-[(N-2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)carbamoyl]-4,6-O-(4-methoxybenzylidene)-β-D-glucopyranoside (**66β**)*

To the mixture of carboxylic acid **10** (671 mg, 1.24 mmol) and alcohol **65** (104 mg, 0.31 mmol) in benzene (50 mL) were added K_2CO_3 (339 mg, 2.48 mmol) and DPPA (0.52 mL, 2.48 mmol), and the whole mixture was refluxed for 17 h. Then, saturated aqueous NH_4Cl was added to the mixture at 0 °C followed by the addition of AcOEt (100 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 3:1) to afford the desired product **66α** (264 mg, 59%) as a white powder and **66β** (116 mg, 25%) as white powder. Compound **66α**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.10 (m, 42H), 6.82–6.80 (m, 2H), 5.95–5.89 (m, 1H), 5.56 (t, J=9.6 Hz, 1H), 5.44 (s, 1H), 5.34 (dd, J=1.4, 17.3 Hz, 1H), 5.34 (dd, J=1.1, 10.5 Hz, 1H), 5.12–5.10 (m, 2H), 4.94–4.92 (m, 1H), 4.85–4.73 (m, 8H), 4.71 (d, J=11.3 Hz, 1H), 4.68–4.46 (m, 9H), 4.33–4.31 (m,

1H), 4.28 (dd, J=5.0, 10.5 Hz, 1H), 4.21 (dd, J=5.2, 12.9 Hz, 1H), 4.04–3.99 (m, 2H), 3.78–3.76 (m, 1H), 3.76 (s, 3H), 3.69–3.55 (m, 8H), 3.39–3.38 (m, 1H), 3.35–3.33 (m, 1H), 3.29 (t, J=8.0 Hz, 1H), 3.20 (t, J=8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.76, 154.74, 154.53, 138.28, 138.03, 137.98, 137.71, 137.67, 137.60, 133.25, 129.43, 128.85, 128.77, 128.73, 128.58, 128.29, 128.25, 128.21, 128.11, 127.88, 127.83, 127.63, 127.59, 127.53, 127.48, 117.74, 113.33, 101.33, 96.24, 85.95, 85.89, 81.60, 81.56, 79.57, 78.46, 78.38, 78.35, 77.49, 77.42, 77.21, 76.13, 76.02, 75.55, 74.79, 74.74, 74.19, 73.97, 73.49, 73.39, 72.00, 70.33, 68.75, 68.72, 68.20, 68.10, 68.09, 62.49, 55.20; MS (FAB—NBA+NaI): m/z 1491 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{87}H_{92}N_2NaO_{19}$ 1491.6192, found 1491.6199; $[\alpha]_D^{24}$ +8.48 (c 1.27, $CHCl_3$); IR (neat, cm^{-1}): 1746 (C=O), 3339 (NH). Compound **66β**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.10 (m, 42H), 6.83–6.81 (m, 2H), 5.89–5.85 (m, 1H), 5.46 (s, 1H), 5.32–5.29 (m, 2H), 5.18–5.16 (m, 1H), 5.05 (t, J=8.3 Hz, 1H), 4.94–4.84 (m, 6H), 4.81–4.67 (m, 7H), 4.63–4.61 (m, 2H), 4.54–4.46 (m, 4H), 4.39–4.31 (m, 4H), 4.10 (dd, J=5.3, 12.9 Hz, 1H), 3.82 (t, J=10.1 Hz, 1H), 3.76 (s, 3H), 3.72–3.65 (m, 6H), 3.62–3.56 (m, 3H), 3.34–3.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.76, 154.57, 154.27, 138.23, 138.22, 138.05, 137.66, 137.63, 137.52, 133.20, 129.24, 129.13, 128.62, 128.24, 128.19, 128.16, 128.14, 127.89, 127.79, 127.55, 127.46, 117.46, 113.33, 101.22, 100.40, 86.11, 86.04, 81.60, 81.51, 78.54, 77.70, 77.43, 77.41, 77.38, 75.90, 75.87, 75.87, 75.85, 75.57, 74.64, 74.62, 73.92, 73.84, 73.49, 73.37, 73.10, 72.74, 70.20, 68.45, 67.99, 66.14, 55.15; MS (FAB—NBA+NaI): m/z 1491 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{87}H_{92}N_2NaO_{19}$ 1491.6192, found 1491.6196; $[\alpha]_D^{24}$ −169.2 (c 2.52, $CHCl_3$), IR (neat, cm^{-1}): 1748 (C=O), 3385 (NH).

4.4.8. Allyl 2,3,4,6-tetra-O-[(N-2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)carbamoyl]-α-D-glucopyranoside (**67**)

To the solution of **66α** (14 mg, 0.01 mmol) in dichloromethane (2 mL) were added triethylsilane (0.008 mL, 0.05 mmol) and trifluoroacetic acid (0.004 mL, 0.05 mmol) at 0 °C, and the mixture was stirred for 1.5 h at room temperature. Then, saturated aqueous $NaHCO_3$ was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 1:1) to afford the diol (13 mg, 98%) as a colorless oil. The product was successively used in the next step. To the mixture of carboxylic acid **10** (206 mg, 0.362 mmol) and diol **66** (123 mg, 0.091 mmol) in benzene (30 mL) were added K_2CO_3 (100 mg, 0.725 mmol) and DPPA (0.156 mL, 0.725 mmol), and the whole mixture was refluxed for 24 h. Then, saturated aqueous NH_4Cl was added to the mixture at 0 °C followed by the addition of AcOEt (100 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 5:1) to afford the desired product **67** (201 mg, 89%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.10 (m, 80H), 5.91 (m, 1H), 5.76 (m, 1H), 5.32–5.29 (m, 2H), 5.52 (t, J=9.3 Hz, 1H), 5.35 (m, 1H), 5.07 (m, 1H), 4.94–4.39 (m, 42H), 4.18 (m, 1H), 4.11–4.07 (m, 3H), 3.72–3.48 (m, 20H), 3.28 (m, 3H), 3.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.98, 154.64, 154.45, 154.35, 138.30, 138.20, 137.97, 137.81, 137.76, 137.68, 137.63, 133.14, 129.56, 128.68, 128.51, 128.33, 128.22, 128.17, 128.13, 128.13, 127.88, 127.79, 127.73, 127.68, 127.55, 127.46, 117.69, 95.11, 85.84, 85.70, 81.96, 81.43, 80.02, 77.20, 76.18, 75.86, 75.47, 74.76, 74.66, 74.51, 74.20, 73.95, 73.39, 73.23, 73.12, 68.56, 68.05, 67.36; MS (FAB—NBA+NaI) m/z 2504 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{149}H_{156}N_4O_{30}Na$ 2504.0697, found 2504.0694; $[\alpha]_D^{24}$ +6.04 (c 0.53, $CHCl_3$); IR (neat, cm^{-1}): 1746 (C=O), 3325 (NH).

4.4.9. 1,2,3,4,6-Penta-O-[(N-2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)carbamoyl]-D-glucopyranoside (**69**)

To the solution of **67** (43 mg, 0.017 mmol) in dichloromethane (2 mL) and H_2O (0.135 mL) was added $PdCl_2$ (7.4 mg, 0.04 mmol), and the mixture was stirred at ambient temperature for 32 h. Then, H_2O was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 1:1) to afford the desired product **68** (37 mg, 86%) as a white powder, and this compound was immediately used in the next step. To the mixture of carboxylic acid **10** (14 mg, 0.024 mmol) and hemiacetal **68** (10 mg, 0.004 mmol) in benzene (4 mL) were added triethylamine (0.007 mL, 0.048 mmol), DPPA (0.011 mL, 0.048 mmol), and Ag_2CO_3 (0.7 mg, 0.0024 mmol), and the whole mixture was refluxed for 5 h. Then, saturated aqueous NH_4Cl was added to the mixture at 0 °C followed by the addition of AcOEt (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (hexane/AcOEt, 2:1) to afford the desired product **69** (9.6 mg, 77%) as a white powder: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41–7.04 (m, 100H), 5.88 (m, 1H), 5.71 (m, 1H), 5.54 (m, 1H), 5.39 (m, 1H), 5.31–5.29 (m, 1H), 5.19 (m, 1H), 5.11–5.02 (m, 3H), 4.90–4.39 (m, 47H), 4.16 (m, 1H), 3.93 (m, 1H), 3.79 (m, 1H), 3.47–3.68 (m, 23H), 3.33 (m, 1H), 3.26–3.23 (m, 1H), 3.10–3.19 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.04, 154.39, 153.28, 138.56, 138.44, 138.33, 138.22, 138.12, 138.08, 138.02, 137.95, 137.77, 137.43, 129.07, 128.97, 128.72, 128.62, 128.59, 128.49, 128.35, 128.29, 128.24, 128.15, 128.03, 127.85, 127.79, 127.71, 127.63, 127.53, 127.49, 92.90, 86.00, 85.90, 85.71, 82.15, 81.69, 80.56, 80.33, 77.89, 77.47, 76.41, 75.80, 75.67, 75.47, 74.96, 74.86, 74.81, 74.76, 74.48, 74.18, 73.46, 73.24, 68.51, 68.15. Anal. Calcd for $C_{181}H_{187}N_5O_{36}$: C, 72.26; H, 6.27; N, 2.33. Found: C, 72.12; H, 6.46; N, 2.20; $[\alpha]_D^{24}$ +4.19 (c 0.42, H_2O); IR (neat, cm^{-1}) 1746 (C=O), 3317.

4.5. General procedure for the synthesis of urea-linked disaccharides

The reaction of **9** and **70** is described as a representative example.

4.5.1. Methyl 4,6-O-benzylidene-2-deoxy-2-[(N′-2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)ureido]-α-D-glucopyranoside (**72**)

To the solution of carboxylic acid **9** (28 mg, 0.048 mmol) and in benzene (3.5 mL) were added triethylamine (0.013 mL, 0.092 mmol), and DPPA (0.021 mL, 0.092 mmol), and the mixture was refluxed for 1 h. Next, amine **70** (20 mg, 0.072 mmol) in CH_3CN (1.5 mL) was added at room temperature and the whole mixture was further refluxed for 5 h. Then the mixture was cooled to 0 °C and saturated aqueous NH_4Cl was added followed by the addition of dichloromethane (20 mL). The organic layer was separated and the aqueous layer was further extracted twice with dichloromethane (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was purified by silica gel flash chromatography (dichloromethane/methanol, 60:1) to afford the desired product **72** (41 mg, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H), 7.38–7.28 (m, 21H), 7.17–7.15 (m, 2H), 5.84 (br s, 1H), 5.56 (s, 1H), 5.53 (br s, 1H), 5.24 (br s, 1H), 4.86 (t, J=11.0 Hz, 1H), 4.79 (d, J=11.0 Hz, 1H), 4.73 (d, J=11.0 Hz, 1H), 4.64–4.42 (m, 6H), 4.26 (dd, J=10.7, 15.9 Hz, 1H), 4.04 (m, 1H), 3.83–3.65 (m, 8H), 3.54–3.49 (m, 2H), 3.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.77, 138.21, 138.03, 137.41, 137.02, 129.09, 128.49, 128.35, 128.30, 128.27, 128.18, 128.11, 128.07,

127.85, 127.79, 127.62, 126.25, 101.86, 98.84, 81.92, 81.76, 78.02, 77.91, 76.78, 75.72, 74.99, 73.61, 72.94, 70.53, 70.06, 68.86, 67.93, 62.22, 55.01; MS (FAB—NBA+NaI) *m/z* 869 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{49}H_{54}N_2O_{11}Na$ 869.3625, found 869.3640; $[\alpha]_D^{23}$ +83.4 (*c* 1.9, $CHCl_3$); IR (neat, cm^{-1}) 1562, 1651 (C=O), 3275 (NH).

4.6. General procedure for the deprotection of urea-linked disaccharides

The reaction of **72** is described as a representative example.

*4.6.1. Methyl 2-deoxy-2-[(N′-α-D-glucopyranosyl)ureido]-α-D-glucopyranoside (**76**)*

To the solution of carbamate **72** in dichloromethane (8 mL) and methanol (3 mL) was added Pd on carbon (10 mg), and the mixture was stirred under hydrogen for 26 h. Then, the mixture was evaporated and the residue was purified by silica gel flash chromatography (dichloromethane/methanol, 4:1) to afford the desired product **76** (12 mg, 100%) as a white powder: ^1H NMR (600 MHz, CD_3OD) δ 5.32 (d, *J*=5.2 Hz, 1H), 4.73 (d, *J*=9.1 Hz, 1H), 4.63 (m, 2H), 4.55 (br s, 1H), 3.78 (m, 2H), 3.72 (m, 2H), 3.66–3.57 (m, 4H), 3.50–3.44 (m, 5H), 3.30 (m, 2H), 3.27 (s, 3H), 3.12 (m, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 160.76, 100.26, 82.45, 79.10, 75.11, 74.33, 73.92, 73.81, 73.51, 73.41, 72.02, 71.44, 62.68, 55.56; MS (FAB—NBA+NaI) *m/z* 421 $(M+Na)^+$; HRMS (FAB—NBA+NaI) calcd for $C_{14}H_{26}N_2O_{11}Na$ 421.1433, found 421.1447; $[\alpha]_D^{26}$ +101.7 (*c* 0.75, CH_3OH); IR (neat, cm^{-1}) 1559, 1649 (C=O), 3580–3060 (OH).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.089.

References and notes

1. Dwek, A. R. *Chem. Rev.* **1996**, *96*, 683–720.
2. (a) Laupichler, L.; Thiem, J. *Synlett* **1992**, 159; (b) García Fernández, J. M.; Mellet, C. O.; Díaz Pérez, V. M.; Fuentes, J.; Kovács, J.; Pintér, I. *Tetrahedron Lett.* **1997**, *38*, 4161–4164; (c) Prosperi, D.; Ronchi, S.; Panza, L.; Rencurosi, A.; Russo, G. *Synlett* **2004**, 1529–1532; (d) Ichikawa, Y.; Matsukawa, Y.; Nishiyama, T.; Isobe, M. *Eur. J. Org. Chem.* **2004**, 586–591; (e) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *Synlett* **2000**, 1253–1256; (f) Ichikawa, Y.; Nishiyama, T.; Isobe, M. *J. Org. Chem.* **2001**, *66*, 4200–4205; (g) Nishiyama, T.; Ichikawa, Y.; Isobe, M. *Synlett* **2003**, 47–50; (h) Prosperi, D.; Ronchi, S.; Lay, L.; Rencurosi, A.; Russo, G. *Eur. J. Org. Chem.* **2004**, 395–405; (i) Ichikawa, Y.; Matsukawa, Y.; Isobe, M. *J. Am. Chem. Soc.* **2006**, *128*, 3934–3938.
3. (a) Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Tetrahedron Lett.* **2006**, *47*, 7219–7223; (b) Sawada, D.; Sasayama, S.; Takahashi, H.; Ikegami, S. *Eur. J. Org. Chem.* **2007**, 1064–1068.
4. (a) Kuzuhara, H.; Fletcher, H. G., Jr. *J. Org. Chem.* **1967**, *32*, 2531–2534; (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4977.
5. (a) Csuk, R.; Glänzer, B. I. *Tetrahedron* **1991**, *47*, 1655–1664; (b) RajanBabu, T. V.; Reddy, G. S. *J. Org. Chem.* **1986**, *51*, 5458–5461; (c) Griffin, F. K.; Paterson, D. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **1999**, *38*, 2939.
6. Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.
7. Lockhoff, O. *Angew. Chem., Int. Ed.* **1998**, *37*, 3436–3439.
8. Alcohol **15**: Pravdic, N.; Danilov, B. *Carbohydr. Res.* **1974**, *36*, 167–180; Alcohol **16**: Lecourt, T.; Herault, A.; Pearce, J. A.; Sollogoub, M.; Sinaÿ, P. *Chem.—Eur. J.* **2004**, *10*, 2960–2971; Alcohols **17**, **18**: Koto, S.; Takeda, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 291–293; Alcohol **19**: Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963–966; Alcohol **20**: Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97–101; Alcohol **21**: Franks, N. E.; Montgomery, R. *Carbohydr. Res.* **1968**, *6*, 286–298.
9. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6204.
10. Using **15**, which is a mixture of the stereoisomers at the 1-position in the ratio of 3:1 (α/β), **22** was exclusively obtained with 1-β-linkage, and **31** was obtained as a mixture of the stereoisomers at the 1-position in the ratio of 1:10 (α/β). The stereochemistry of **22** and **31** were determined by the analysis of the coupling constants in the ^1H NMR.
11. In entry 14 in Table 1, both **10** and **19** are so reactive that the yield of this reaction by Et_3N is slightly better than that using K_2CO_3 as a base.
12. Using **22**, the reaction should afford the desired product, however, some unknown decomposed products were included, which were difficult to be separated.
13. Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1998**, *54*, 21–44.
14. The stereochemistry at the 1-position of the core sugar in **69** should be β-linkage on the basis of the results in Table 1, and a trace amount of the stereoisomer might be isolated, whose structure was not determined.
15. Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Tetrahedron: Asymmetry* **2005**, *16*, 213–221.
16. Reitz, A. B.; Tuman, R. W.; Marchione, C. S.; Jordan, A. D.; Bowden, C. R.; Maryanoff, B. E. *J. Med. Chem.* **1989**, *32*, 2110–2116.