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Novel Synthesis of Carbamate-Linked Oligosaccharides by a Modified Curtius Rearrangement

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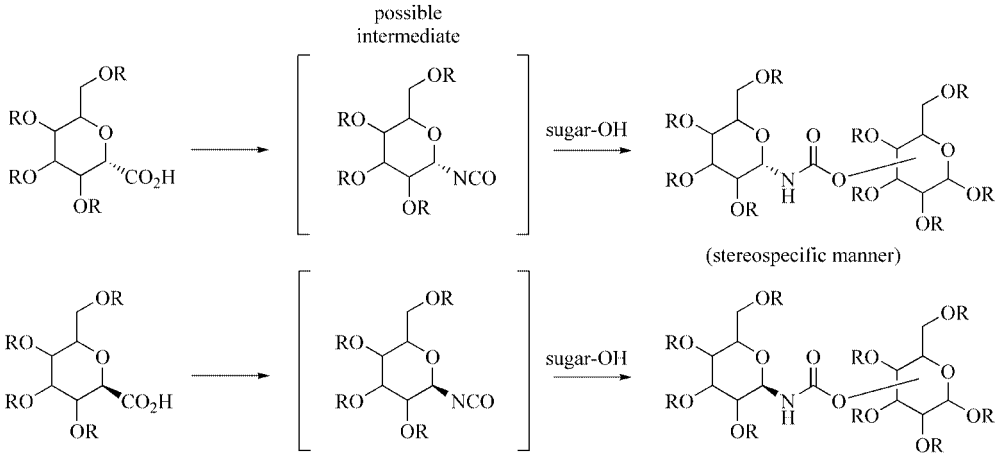
We describe a novel stereospecific synthesis of various carbamate-linked disaccharides using sugar carboxylic acids and sugar alcohols by a modified Curtius rearrangement. Furthermore, we applied this method to the synthesis of carbamate-linked oligosaccharides including a dendritic molecule.

Introduction

Sugars equipped with several hydroxy groups stereospecifically can produce a large number of oligosaccharides by variation of their bonding. It is well known that oligosaccharides that interact with glycopeptides, glycolipids etc. play an important role in a living body.[1] The glycoside bonds are, however, labile towards various chemical transformations, and their stereoselective formation is often troublesome. Inevitably, those problems restrict the synthesis of oligosaccharides. If it were possible to substitute a glycoside bond by a more stable linkage and to form this link stereoselectively, novel complex oligosaccharides would be synthesized, which would have unique structures, new functions, and interesting biological activity. Presently we have focused on a carbamate linkage as a substitution for a glycoside bond, and we have achieved the stereospecific synthesis of carbamate-linked disaccharides and provide its applications in oligosaccharide synthesis.[2,3]

The carbamate-linked disaccharide was first reported by Laupichler et al. in 1992,[2a] and recently, Ichikawa et al. and Prosperi et al. successively reported the stereospecific synthesis of disaccharides; however, there is no example of the synthesis of saccharides larger than disaccharides.[2c,2d] Their synthetic methods utilize a glycosyl isocyanate as an intermediate, whose precursor is a glycosyl isocyanide.[4] More recently, we reported the synthesis of carbamate- and urea-linked glycoconjugates by a modified Curtius rearrangement.[3] The advantages of our synthetic method are as follows: the reaction shows high reactivity and proceeds stereospecifically in a simple one-pot procedure by treating a glycosyl carboxylic acid and a sugar alcohol with diphenyl phosphoryl azide (DPPA).[5] Not only the elongation of the saccharide chains but also the synthesis of complex oligosaccharides are thought to be possible (Scheme 1).



Scheme 1. Stereospecific synthesis of the both anomeric isomers of carbamate-linked saccharides by using a glycosyl carboxylic acid and a sugar alcohol.

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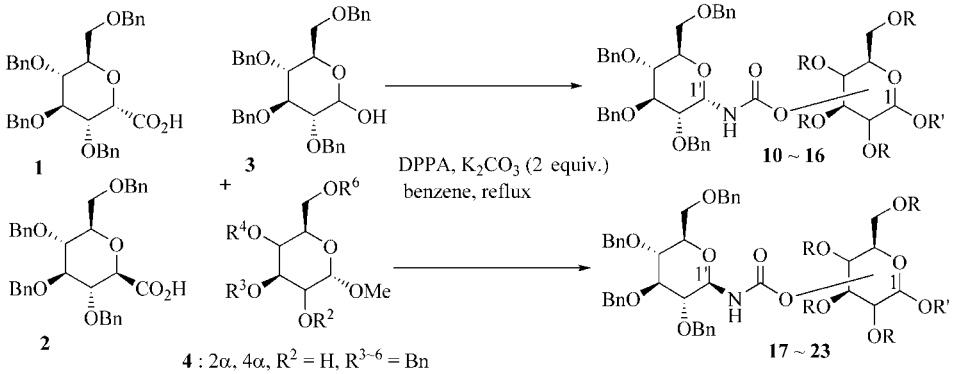
Results and Discussion

At first, we investigated the synthesis of a series of carbamate-linked disaccharides. As substrates, we utilized the stereoisomers of carboxylic acids **1** and **2**, which were derived from the corresponding alcohols[6] by a simple oxidation reaction,[7] as glycosyl donors and the hemiacetal **3** and alcohols **4** to **9**,[8] derived from D-glucose, galactose, and mannose, as glycosyl acceptors. A carboxylic acid and two equivalents of an alcohol were heated at reflux with two equivalents of DPPA and a base in benzene to afford the desired carbamate-linked disaccharides in moderate to good yields (Table 1). As reported previously K_2CO_3 was the most effective base[3] (however, in entry 12 it can be seen that the use of triethylamine also gave good results), and a catalytic amount of Ag_2CO_3 often improved the yield (entries 4, 5, 6, and 13). All the products were obtained with retention of the stereochemistry at the substrate glycosyl carboxylic acid. Thus, this procedure should stereospecifically provide both anomeric isomers of disaccharide with **1** and **2**.[3] α-Carboxylic acid **1** was found to be less reactive than β-carboxylic acid **2**, and primary alcohol **7** had the best reactivity among the acceptors **3** to **9**. Although hemiacetal **3** was an anomeric mixture, the stereochemistry at the 1-position of **10** and **17** tended predominantly towards a β-linkage.[9] The reason for this is that there is an equilibrium between the anomeric isomers of **3**, and the less-hindered β-isomer reacts much faster than the more-hindered α-alcohol. According to the overall results, the steric hindrance of the substrates reduces both the reactivity and the yield. The rate-determining step could be the addition step of a sugar alcohol to an isocyanate converted in situ from a glycosyl carboxylic acid.

We then tried the elongation of a saccharide by using carboxylic acid **24**[3] and alcohol **25**[10] (Scheme 2). Compounds **24** and **25** (the same number of equivalents) were treated with DPPA and triethylamine for 4 h, and disaccharide **26** was obtained in 84% yield. Carboxylic acid **27**, which was transformed from **26** by hydrolysis, was similarly

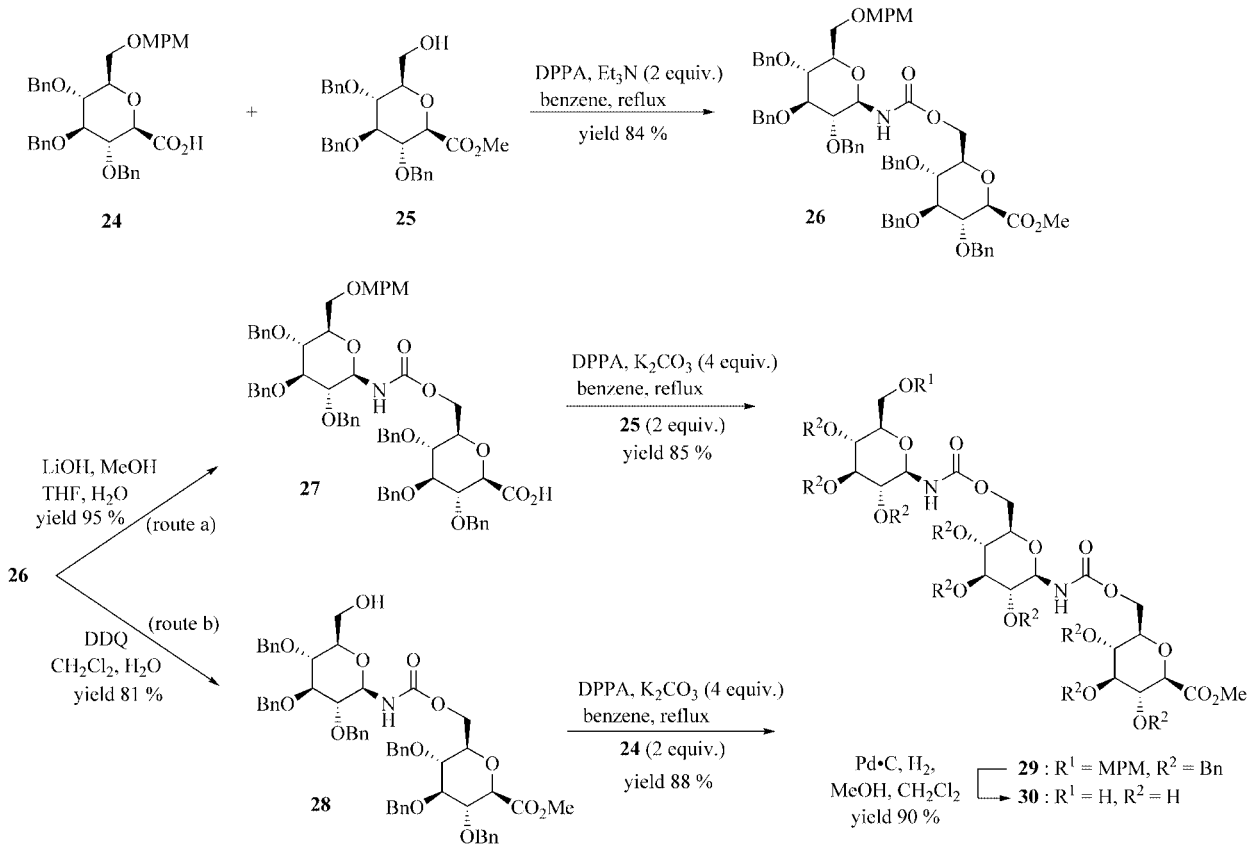
Table 1. Synthesis of carbamate-linked disaccharides.



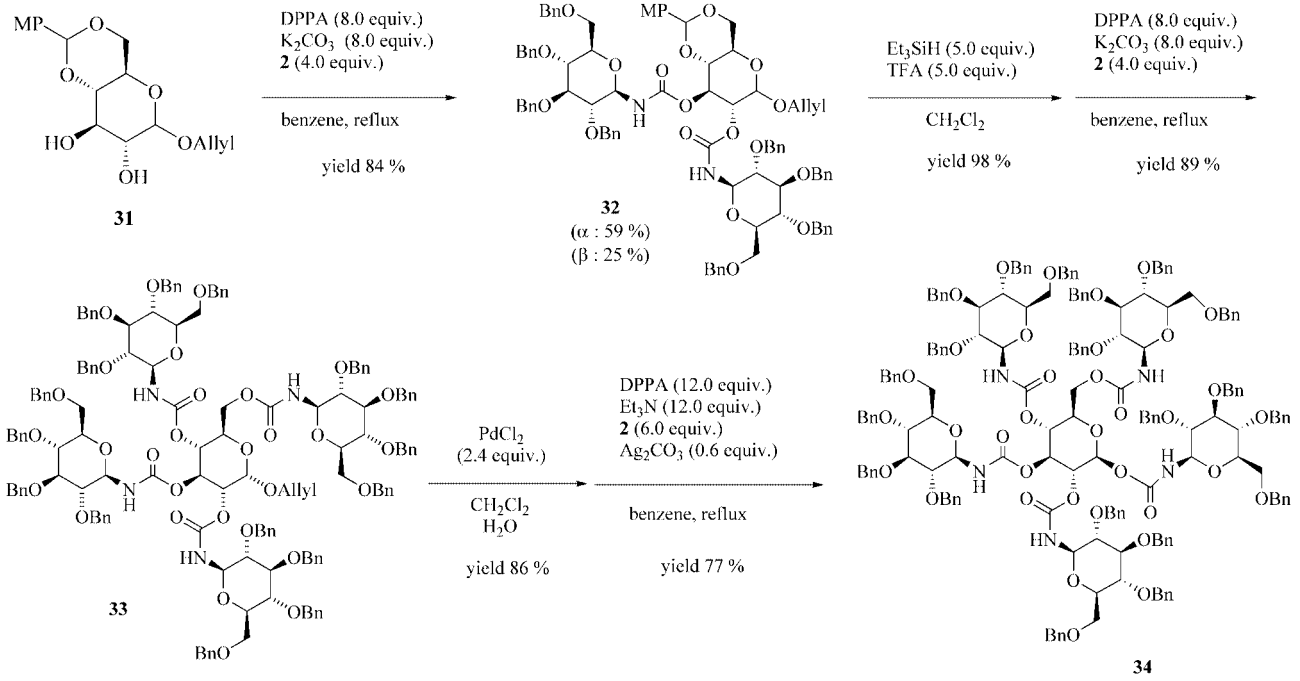
4 : 2α, 4α, R^2 = H, R^{3-6} = Bn
5 : 2α, 4α, R^3 = H, $R^{2, 4-6}$ = Bn
6 : 2α, 4α, R^4 = H, $R^{2-3,6}$ = Bn
7 : 2α, 4α, R^6 = H, R^{2-4} = Bn
8 : 2α, 4β, R^4 = H, $R^{2-3,6}$ = Bn
9 : 2β, 4α, R^2 = H, R^{3-6} = Bn

Entry	Carboxylic acid	Alcohol	Time [h]	Yield [%]
1	**1**	Glc-1-OH (**3**)	12	82 (Glc α1'-Glc 1, **10**)
2	**1**	Glc-2-OH (**4**)	20	64 (Glc α1'-Glc 2, **11**)
3	**1**	Glc-3-OH (**5**)	34	56 (Glc α1'-Glc 3, **12**)
4[a]	**1**	Glc-4-OH (**6**)	29	78 (Glc α1'-Glc 4, **13**)
5[a]	**1**	Glc-6-OH (**7**)	29	66 (Glc α1'-Glc 6, **14**)
6[a]	**1**	Gal-4-OH (**8**)	29	59 (Glc α1'-Gal 4, **15**)
7	**1**	Man-2-OH (**9**)	29	65 (Glc α1'-Man 2, **16**)
8	**2**	Glc-1-OH (**3**)	8	94 (Glc β1'-Glc 1, **17**)
9	**2**	Glc-2-OH (**4**)	10	73 (Glc β1'-Glc 2, **18**)
10	**2**	Glc-3-OH (**5**)	29	87 (Glc β1'-Glc 3, **19**)
11	**2**	Glc-4-OH (**6**)	18	89 (Glc β1'-Glc 4, **20**)
12[b]	**2**	Glc-6-OH (**7**)	8	98 (Glc β1'-Glc 6, **21**)
13[a]	**2**	Gal-4-OH (**8**)	14	79 (Glc β1'-Gal 4, **22**)
14	**2**	Man-2-OH (**9**)	15	71 (Glc β1'-Man 2, **23**)

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



Scheme 2. Elongation of a saccharide chain both at the carboxylic acid end and alcohol end.



Scheme 3. Synthesis of dendritic molecules.

treated with 2 equiv. alcohol **25** to give trisaccharide **29** in 85% yield (route a). On the other hand, alcohol **28**, converted from **26** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), was treated with 2 equiv. carboxylic acid **24** to afford **29** in 88% yield (route b). The deprotection of compound **29** was successfully achieved by Pd•C, H_2 in MeOH, and CH_2Cl_2 to give **30** in 90% yield. As above, it has been indicated that this synthetic method makes it pos-

sible to elongate the saccharide chain both at the carboxylic acid end and the alcohol end by simple transformations. In addition, this method has a powerful application in carbamate-linked oligosaccharide synthesis.

On the basis of the above experiments, we set out to synthesize dendritic compound **34** having a sugar as the core structure, and started from the known monosaccharide **31**,[11] which was soluble in benzene (Scheme 3). At first, compound **31** was heated at reflux with 4 equiv. carboxylic acid **2** and 8 equiv. DPPA and K_2CO_3, and after 17 h, gratifyingly, we obtained trisaccharide **32** in 84% yield in one step with the carbamate-linked saccharide chains at the 2- and 3-positions of the core glucose. The anomeric isomers of **32** were then separated, and the major α isomer was used in further transformations in order to attain a clear analysis of the reactions. After the removal of the methoxybenzylidene acetal group of **32** (α isomer), the given 4,6-diol was similarly treated with **2**, DPPA, and K_2CO_3 to give pentasaccharide **33** in 89% yield. The allyl group of compound **33** was removed by $PdCl_2$, and the resultant acetal should then be the substrate for the introduction of the last carbamate-linked saccharide. Unfortunately, it was found that the substrate acetal was not stable and decomposed under the reaction conditions when K_2CO_3 was used. After several attempts with triethylamine, Ag_2CO_3, and 6 equiv. **2**, we finally succeeded in obtaining hexasaccharide **34** in 77% yield.[12] Dendritic hexasaccharide **34** was afforded in only 5 steps in 34% overall yield by using α-**32** obtained from the simple monosaccharide **31**.

Conclusions

We have accomplished the stereospecific synthesis of carbamate-linked oligosaccharides by using a modified Curtius rearrangement. This synthetic method has made it possible to synthesize unique oligosaccharides, which are chemically stable, and would be applicable in the synthesis of functional molecules. The synthesis of various complex molecules is now in progress in our laboratory.

Experimental Section

Typical procedure for the synthesis of a carbamate-linked saccharide by the modified Curtius rearrangement (Table 1, entry 4): Diphenyl phosphoryl azide (29 uL, 0.132 mmol) was added to the solution of **1** (38 mg, 0.066 mmol), **6** (63 mg, 0.132 mmol), K_2CO_3 (18 mg, 0.132 mmol), and Ag_2CO_3 (1.8 mg, 0.0066 mmol) in benzene (7 mL), and the whole mixture was heated at reflux for 29 h. Saturated aqueous NH_4Cl solution (30 mL) was then added at 0 °C, and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layer was washed with brine (30 mL), dried with Na_2SO_4, then filtered and evaporated to give the crude product, which was purified by silica gel chromatography (hexane/EtOAc, 4:1) to afford **13** (53 mg, 78%): $[a]_D^{24}$ = +8.17° (*c* = 0.55, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1721 (C=O), 3285 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.01 (m, 35 H), 5.53 (d, *J* = 5.13 Hz, 1 H), 5.48 (m, 1 H); 4.96 (t, *J* = 9.52 Hz, 1 H), 4.85 (d, *J* = 10.98 Hz, 1 H), 4.79 (d, *J* = 11.48 Hz, 1 H), 4.77–4.68 (m, 4 H), 4.67 (d, *J* = 10.98 Hz, 1 H), 4.58–4.56 (m, 2 H), 4.55–4.28 (m, 6 H), 3.90 (t, *J* = 9.52 Hz, 1 H), 3.81 (m, 1 H), 3.70 (dd, *J* = 5.13, 9.27 Hz, 1 H), 3.63–3.53 (m, 7 H), 3.45 (dd, *J* = 5.86, 10.75 Hz, 1 H), 3.36 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.65, 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 ppm. 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.

Spectral Data for 29: $[a]_D^{26}$ = –2.23° (*c* = 0.7, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1738 (C=O), 3328 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.32 (m, 45 H), 7.09–7.11 (m, 2 H), 6.80–6.82 (m, 2 H), 5.10–5.17 (m, 2 H), 4.68–4.92 (m, 17 H), 4.55 (d, *J* = 6.59 Hz, 1 H), 4.53 (d, *J* = 6.59 Hz, 1 H), 4.52–4.60 (m, 2 H), 4.47 (d, *J* = 10.26 Hz, 1 H), 4.32–4.38 (m, 4 H), 4.24–4.27 (dd, *J* = 3.72, 11.58 Hz, 2 H), 3.87 (d, *J* = 9.53 Hz, 1 H), 3.61–3.68 (m, 6 H), 3.74 (s, 3 H), 3.68 (s, 3 H), 3.57 (m, 1 H), 3.42–3.52 (m, 4 H), 3.28–3.34 (m, 2 H) ppm. ^{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 ppm. 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.

Spectral Data for 30: $[a]_D^{23}$ = –52.6° (*c* = 0.92, H_2O). IR (neat): $\tilde{\nu}$ = 1717 (C=O), 3326 cm^{-1}. ^1H NMR (400 MHz, D_2O): δ = 4.80–4.83 (m, 3 H), 4.45–4.50 (m, 2 H), 4.24–4.28 (m, 2 H), 4.02–4.05 (m, 1 H), 3.83–3.91 (m, 2 H), 3.67–3.74 (m, 4 H), 3.56 (s, 3 H), 3.35–3.58 (m, 7 H) ppm. ^{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 ppm. 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.

Spectral Data for 34: $[a]_D^{24}$ = +4.19° (*c* = 0.42, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1746 (C=O), 3317 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.41–7.04 (m, 100 H), 5.88 (m, 1 H), 5.71 (m, 1 H), 5.54 (m, 1 H), 5.39 (m, 1 H), 5.31–5.29 (m, 1 H), 5.19 (m, 1 H), 5.11–5.02 (m, 3 H), 4.90–4.39 (m, 47 H), 4.16 (m, 1 H), 3.93 (m, 1 H), 3.79 (m, 1 H), 3.47–3.68 (m, 23 H), 5.19 (m, 1 H), 3.33 (m, 1 H), 3.26–3.23 (m, 1 H), 3.10–3.19 (m, 3 H) ppm. ^{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 ppm. $C_{181}H_{187}N_5O_{36}$ (3008.48): calcd. C 72.26, H 6.27, N 2.33; found C 72.12, H 6.46, N 2.20.

Acknowledgments

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[9] By using **3**, which is a mixture of the stereoisomers at the 1-position in a 3:1 ratio (α/β), **10** was exclusively obtained with a 1-β-linkage and **17** was obtained as a mixture of stereoisomers at the 1-position in a 1:10 ratio (α/β).
[10] Compound **25** was prepared from **24** in two steps – conversion to the methyl ester with MeI and $NaHCO_3$ (100% yield) and then deprotection of the MPM group with DDQ (96% yield).
[11] T. Oka, K. Fujiwara, A. Murai, *Tetrahedron* **1998**, *54*, 21–44. It is difficult to separate the anomeric isomers of compound **31**.
[12] On the basis of the results in Table 1, the stereochemistry at the 1-position of the core sugar in **34** should be a β-linkage, and a trace amount of the stereoisomer could be isolated in this reaction, whose structure was not determined.

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