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Significant Substituent Effect on the Anomerization of Pyranosides: Mechanism of Anomerization and Synthesis of a 1,2-*cis* Glucosamine Oligomer from the 1,2-*trans* Anomer

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Abstract: Aminoglycosides containing a 2,3-*trans* carbamate group easily undergo anomerization from the 1,2-*trans* glycoside to the 1,2-*cis* isomer under mild acidic conditions. The N-substituent of the carbamate has a significant effect on the anomerization reaction; in particular, an *N*-acetyl group facilitated rapid and complete α-anomerization. The differences in reactivity due to the various N-substituents were supported by the results of DFT calculations; the orientation of the acetyl carbonyl group close to the anomeric position was found to contribute significantly to the directing of the anomerization reaction. By exploiting this reaction, oligoaminoglycosides with multiple 1,2-*cis* glycosidic bonds were generated from 1,2-*trans* glycosides in a one-step process.

Introduction

Oligosaccharides and glycoconjugates play important roles in many biological processes, including cell–cell communication, bacterial adhesion, masking of immunological epitopes, fertilization, and cell proliferation.[1–3] To carry out precise analyses of these roles, facile access to glycoconjugate-derived oligosaccharides is imperative. However, glycoconjugates are usually heterogeneous, consisting of various glycoforms, and the repertoire of homogeneous and structurally defined glycans obtainable from natural sources is limited. Hence, chemical synthesis of oligosaccharides would be an extremely useful complementary approach to produce homogeneous and well-defined substances. The chemical synthesis of glycosides has contributed greatly to glycobiology and glycotechnology;[4–10] in particular, the glycosylation reaction is recognized as one of the most essential reactions in oligosaccharide synthesis. This reaction, which involves the formation of a glycosidic linkage between a sugar donor and a glycosyl acceptor, has seen remarkable developments in recent times with respect to the wealth of synthetic methods available. Most 1,2-*trans* glycosides can be easily prepared by exploiting neighboring group participation of the 2-acyl protecting group. However, 1,2-*cis* glycosides are often difficult to synthesize, even with our current knowledge. 1,2-*cis* Aminoglycosides are particularly difficult to prepare in a completely stereoselective manner,[11–18] although they are found in many biologically active oligosaccharides such as heparin and antibiotics.[19–24] Since Lemieux and Paulsen reported a 2-azide-2-deoxy glycosyl donor for 1,2-*cis* aminoglycoside preparation, methods toward the synthesis of 1,2-*cis* aminoglycosides have not progressed.[25–27] Reasons for this gap in the literature are attributed to the low yields and selectivities for 2-azide pyranoside preparation and the moderate selectivity in glycosylation reactions.[27] Recently, 2,3-*trans* carbamates possessing pyranoside moieties have been developed for 1,2-*cis*-selective glycosylation.[28–33]

A typical glycosylation reaction involving glycosyl donors, such as thioglycosides, glycosylhalides, and imidates, proceeds by an exocyclic cleavage reaction through a cyclic cation (Scheme 1).[5–10] The endocyclic cleavage reaction, which gives an acyclic cation through a bond cleavage between the anomeric carbon and O5 oxygen, is extremely rare in pyranoside cleavage.[34,35] Although glycosyl donors with 2,3-*trans* carbamate or carbonate groups undergo cleavage through the typical exocyclic reaction mode, several research groups, in-

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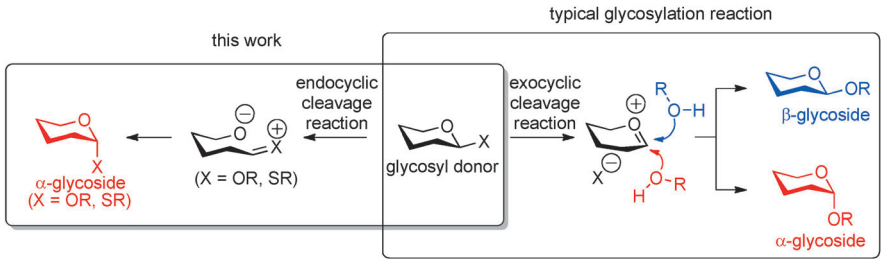


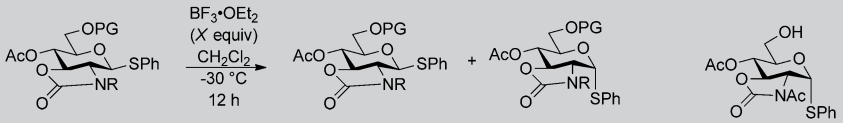
Scheme 1. Endocyclic cleavage reaction and exocyclic cleavage reaction.

cluding our own, reported that 2,3-*trans* carbamate- and carbonate-containing glycosides are easily cleaved in an endocyclic manner and can be anomerized from the 1,2-*trans* to 1,2-*cis* orientation under weak acidic conditions. Experimental evidence of the existence of an endocleavage pathway in pyranosides carrying 2,3-*trans* carbamate or carbonate moieties was demonstrated by the identification of adducts of the acyclic cations produced by the endocyclic cleavage reaction, captured by reduction, chlorination, and inter- or intramolecular Friedel–Crafts reactions;[36] however, the substrates failed to undergo complete conversion, resulting in isomeric mixtures.[31,35–38] Quantum-mechanical calculations revealed that inner strain caused by the fused rings (the pyranoside ring and the 2,3-*trans* carbamate group) is the predominant factor for the enhancement of the endocyclic cleavage reaction.[39] The excellent agreement between the transition-state energy and the experimentally observed reactivity indicates that this series of anomerization reactions is predominantly under kinetic control. Based on the experiments and the calculations, it was expected that the substituent on the nitrogen atom of the carbamate group would influence both the anomerization ratio and rate, and that complete anomerization to the 1,2-*cis* glycoside would be possible by selecting an appropriate substituent. Here, we report our experimental and computational investigations performed with the aim of identifying the optimal substituent group for the anomerization reaction, and how this endocyclic cleavage reaction can be used to synthesize new glycosides.

Results and Discussion

To investigate substituent effects at the 2,3-*trans* carbamate nitrogen site on the outcome of the anomerization reaction, several glycosides **1a**–**l** were prepared (see the Supporting Information); the anomerization reactions were carried out in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −30 °C for 12 h (Table 1). Benzyl-substituted carbamate **1a** (Table 1, entry 1) was smoothly anomerized to α-anomer **2a** in 63% yield. Pyranosides **1b** and **1c**, containing a carbamate substituted at nitrogen with a *p*-methoxybenzyl (electron-donating) group and an *o*-nitrobenzyl (electron-withdrawing) group, respectively, were also anomerized in favor of the α-anomers (entries 2 and 3). Carbamates substituted with nitrile (**1d**) and ester (**1e**) groups as intramolecular cation-stabilizing moieties, did not yield positive results (entries 4 and 5). Interestingly, however, compounds **1g**–**l** underwent anomerization to produce solely the α-anomers (entries 7–16). The isolated α-anomers **2g** and **2k** did not undergo the reverse reaction to the β-anomer under the same conditions, and **2g** and **2k** were recovered in 80 and 81% yield, respectively. These results suggest that the anomerization reaction is under kinetic control and that there is no equilibrium between the α- and β-anomers. In addition, these results clearly show that carbamates possessing *N*-acyl substitution significantly enhanced the anomerization reaction in the α-direction and that the anomerization reaction was irreversible under these conditions. Remarkably, on reducing the amount of $BF_3{\cdot}OEt_2$ from 2.0 to 0.5 equivalents, the yield of the α-product **2l** was increased (entries 12–14), which was attributed to the suppression of a deacetylation side reaction at the 6-position caused by the Lewis acidity of $BF_3{\cdot}OEt_2$. Compound **2m** was obtained in entries 12 and 13

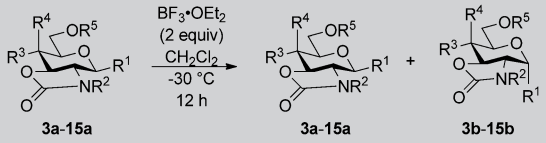
Table 1. Effect of carbamate N-substituents on the anomerization reaction.

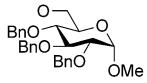
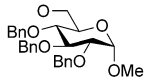
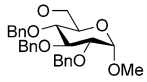
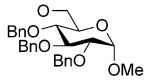
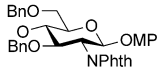


Entry	Substrate	R[c]	PG[c]	X	β-Product	Yield [%]	α-Product	Yield [%]
1	**1a**	Bn	Bn	2	**1a**	16	**2a**	63
2	**1b**	PMB	Bn	2	**1b**	15	**2b**	77
3	**1c**	*o*-nitrobenzyl	Bn	2	**1c**	26	**2c**	63
4	**1d**	CH_2CN	Bn	2	**1d**	15	**2d**	71
5[a]	**1e**	CH_2CO_2Me	Bn	2	**1e**	–	**2e**	–
6	**1f**	H	Bn	2	**1f**	69	**2f**	19
7	**1g**	CO_2Me	Bn	2	**1g**	0	**2g**	80
8	**1h**	CO_2All	Bn	2	**1h**	0	**2h**	88
9	**1i**	CO_2Bn	Bn	2	**1i**	0	**2i**	88
10	**1j**	$CO_2CH_2CCl_3$	Bn	2	**1j**	0	**2j**	88
11	**1k**	Ac	Bn	2	**1k**	0	**2k**	87
12	**1l**	Ac	Ac	2	**1l**	0	**2l**	70
13	**1l**	Ac	Ac	1	**1l**	0	**2l**	87
14	**1l**	Ac	Ac	0.5	**1l**	0	**2l**	90
15	**1l**	Ac	Ac	0.1	**1l**	65	**2l**	30
16[b]	**1l**	Ac	Ac	0.1	**1l**	2	**2l**	89

[a] Reaction with **1e** yielded a complex mixture. [b] Reaction period was 72 h. [c] PMB = *p*-methoxybenzyl ether. PG = protecting group.

Table 2. Scope and limitations of the anomerization reaction.[a]



Entry	Substrate	R^1	R^2	R^3	R^4	R^5	Products	Yield [%]
1	**3a**	SPh	H	H	OAc	Bn	**3a/3b**	22:66
2	**4a**	SPh	Ac	H	OAc	Bn	**4a/4b**	0:83
3	**5a**	SPh	Bn	H	OAc	Bn	**5a/5b**	0:90
4	**6a**	SMP	CO_2All	OAc	H	Bn	**6a/6b**	0:92
5	**7a**	OMe	Bn	OAc	H	Bn	**7a/7b**	29:64
6	**8a**	OMP	H	OAc	H	Bn	**8a/8b**	98:0
7	**9a**	OMP	Bn	OAc	H	Bn	**9a/9b**	94:0
8	**10a**	OMP	Ac	OAc	H	Bn	**10a/10b**	0:68
9	**11a**		H	OBn	H	TBDPS	**11a/11b**	86:0
10	**12a**		Bn	OAc	H	Bn	**12a/12b**	90:5
11	**13a**		CO_2Me	OBn	H	TBDPS	**13a/13b**	21:73
12	**14a**		Ac	OBn	H	TBDPS	**14a/14b**	0:88
13	**15a**		Ac	OBn	H	TBDPS	**15a/15b**	0:88
14	**16a**		Ac	OBn	H	TBDPS	**16a/16b**	0:62

[a] MP = *p*-methoxyphenyl; Phth = phthalimide; TBDPS = *tert*-butyldiphenylsilyl.

(Table 1). In the presence of only 0.1 equivalents of BF_3•OEt_2, anomerization did not proceed to completion over the 12 h reaction time, with the β-anomer **3** remaining in 65% yield (entry 15); however, after 72 h, the anomerization was nearly complete, with 89% of the α-product formed (entry 16).

Next, we focused on expanding the scope of substrates for the anomerization reaction (Table 2). We found that not only was there an effect of the *N*-acetyl substituent on the carbamate observed for glucosamine derivatives, but also that galactosamine with *N*-acetylcarbamate **4a** and *N*-benzylcarbamate **5a** showed complete anomerization to α-anomer **4b** and **5b** (Table 2, entries 2 and 3), whereas the β-anomer **3a** remained in 22% yield for the carbamate without a substituent (entry 1). The *p*-methoxy-substituted thioglycoside **6a** was also completely anomerized to α-anomer **6b** (entry 4). As with earlier work, which reported that *O*-aryl pyranosides do not easily anomerize,[40] our experiments also showed no anomerization for either the unsubstituted substrate **8a** or the benzyl-substituted compound **9a** (entries 6 and 7). However, the *p*-methoxyphenyl pyranoside with *N*-acetylcarbamate **10a** underwent anomerization, giving the α-product in 68% yield (entry 8). Disaccharides were also anomerized when a carbamate group was introduced. These trends in anomerization due to the different substituents were similar to those for the monosaccharides (entries 9–13); namely, when an acetyl group was present as the carbamate substituent, complete anomerization of **14a** and **15a** was observed (entries 12 and 13). However, the disaccharide with an unsubstituted carbamate **11a** was not anomerized (entry 9).

As we had previously reported,[41] a significant solvent effect was observed in the anomerization reaction. The anomerization reaction with compound **17a** was completed in CH_2Cl_2 within 30 min. In CH_3CN, the reaction was very quick and was completed within 1 min at −30 °C in the presence of 2 equivalents of BF_3•OEt_2. After 1 min in CH_3CN, the α-anomer was obtained in 91% yield and no β-anomer was obtained (Figure 1).

The experimental observation that the presence of the *N*-acetyl group on the carbamate significantly accelerated the anomerization reactions was further investigated theoretically for pyranosides **1f**, **1g**, and **1k** by DFT

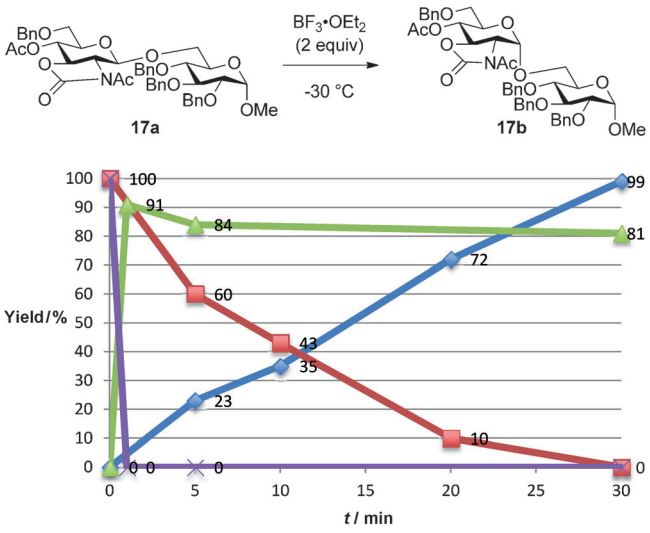


Figure 1. Time-course of anomerization reaction in CH_2Cl_2 and CH_3CN. Red line: yield of **17a** in CH_2Cl_2, blue line: yield of **17b** in CH_2Cl_2, purple line: yield of **17a** in CH_3CN, green line: yield of **17b** in CH_3CN. The numbers on the lines are yields of each compound.

analysis at the B3LYP/6-31G(d,p) level,[42,43] using the Gaussian 03 program.[44] In exploring the potential energy surface for **1 f** and **1 k** in the same manner as previously reported,[39,45] the transition states were found in the course of the C1–C2 bond rotation at ∠H1-C1-C2-H2 = −35.8 and −39.8°, respectively, after the bond breaking between C1 and O5 (Figure 2). The calculations were performed in the gas phase (solid lines in Figure 2), and the energies in CH_2Cl_2 solvent were estimated by using an integral-equation formalism-polarizable continuum model (IEF-PCM)[46] with the default parameters of Gaussian 03

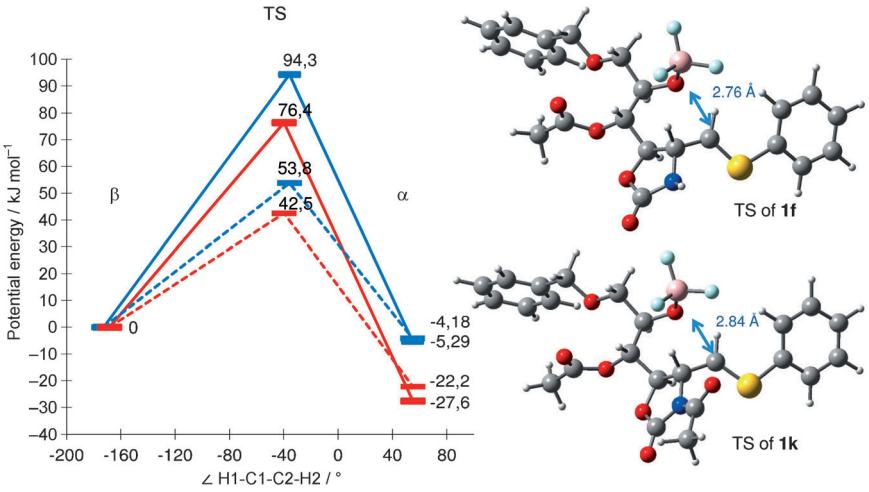


Figure 2. Results of the transition state analysis for **1 f** and **1 k** along the C1–C2 bond rotation. Potential energies of the reactant (β-anomer) and the product (α-anomer) as well as the transition-state energies are represented relative to the β-anomers. The calculations were performed in the gas phase (solid line). Energies in solution (CH_2Cl_2) were estimated using an IEF-PCM approach (dashed line). ——: **1 f**; ——: **1 k**; - - - -: **1 f** in CH_2Cl_2; - - - -: **1 k** in CH_2Cl_2.

(dashed lines in Figure 2). The transition state energies for **1 k**, with an *N*-acetylcarbamate, were found to be 11–18 kJ mol^{-1} lower than those for **1 f**, with an unsubstituted carbamate. The C1–O5 bond lengths of the transition states for **1 f** and **1 k** were 2.76 and 2.84 Å, respectively. These results indicate that **1 k** should undergo the endocyclic cleavage–recyclization reaction more easily than **1 f**, through a kinetically predominant reaction mechanism. The results of the transition-state analysis are in good agreement with the experimental observations.

We hypothesize that the presence of a carbonyl group as the N-substituent is responsible for the acceleration of the anomerization reaction and that the interaction of the carbonyl oxygen with the anomeric site stabilizes the linear oxacarbenium ion produced by the endocyclic cleavage (Figure 3). As a result of this effect, the C1–O5 distance is increased, rendering the subsequent C1–C2 bond-rotation feasible. *N*-Acyloxazolidinones adopt two predominant conformers with the carbonyl dipoles aligned either *syn*- or *anti*-periplanar, with the latter being predominant.[37,47,48] The carbonyl group of an *anti*-conformer located near the anomeric position would assist endocyclic cleavage.

To confirm this hypothesis, we focused on the difference in reactivity of a pyranoside with 2,3-*trans*-*N*-methoxycarbonylcarbamate (e.g., compound **1 g**) and *N*-acetylcarbamate (e.g., compound **1 k**) substitution. A conformational search was performed upon the rotation of the N–C bond of the N-substituent for **1 g** and **1 k** in the gas phase. The geometries of **1 g** and **1 k** were optimized to the *anti* conformer at ∠C2-N-C-O = 5.5 and −3.2°, respectively (Figure 4a). The conformational search was initiated from the optimized geometries by progressively rotating the N–C bond from 0 to 330 (i.e., −30°) in steps of 30°. The minimum energy of the *syn* conformer of **1 k** was found to be 36.4 kJ mol^{-1} higher than that of the *anti* conformer, whereas the energy of *syn* conformer of **1 g** was only 6.9 kJ mol^{-1} higher than that of the *anti* conformer (Figure 4b). The lowest energy barrier between the *anti* and *syn* conformer of **1 k** was found to be 42.0 kJ mol^{-1}, or 16.7 kJ mol^{-1} higher than that of **1 g**. For both models, the dipole moment values of the *anti* conformers tended to be lower than those of the *syn* conformers, with a maximal difference of 3–4 Debye. These observations suggest that the pyranosides with *N*-acetylcarbamate substitution predominantly adopt the *anti* conformers, with the carbonyl oxygen oriented toward the anomeric site, resulting in a lower dipole moment. On the other hand, the *anti* and *syn* conformers of the glycosides with *N*-methoxycarbonylcarbamate are almost equally populated, with only a slight preference for the *anti* conformer. The theoretically estimated ordering of the populations of the *anti* conformers agrees with the experimentally observed ordering of the reactivity of anomerization. These computations support the hypothesis that the presence and orientation of the carbonyl group at the N-substituent position of the carbamate groups are important.

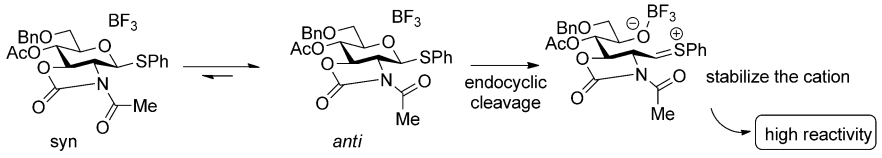


Figure 3. Mechanism of the reaction acceleration. The carbonyl group at the N-substituent position stabilizes the cation produced by endocyclic reaction. The *anti* conformer is assumed to be predominant.

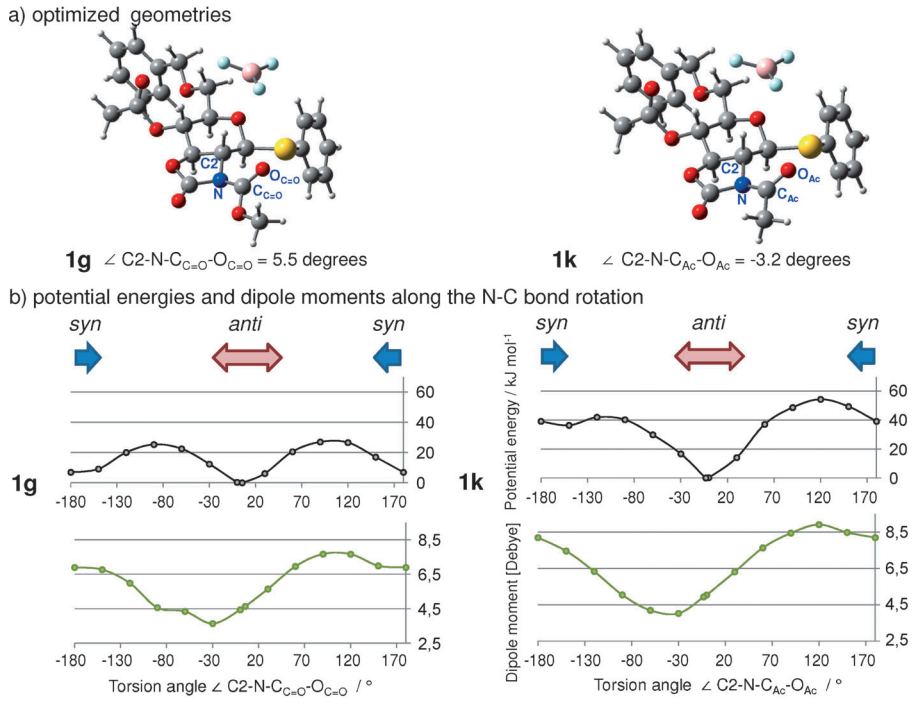


Figure 4. DFT analysis of geometries for **1 g** and **1 k** in the gas phase. a) Optimized geometries. Pyranosides **1 g** and **1 k** were optimized to the *anti*-conformer for the N–C bond; b) Potential energy and dipole moment plots along the N–C bond rotation. It is suggested that the pyranoside with *N*-acetylcarbamate (**1 k**) shows a higher-energy barrier between the *anti* and the *syn* conformers and a predominance of the *anti* conformer, whereas the pyranoside with *N*-methoxycarbonylcarbamate (**1 g**) shows a lower barrier between the *anti* and the *syn* conformers. The *anti* conformer exhibits lower dipole moment values for both **1 g** and **1 k**.

Finally, the utility of the endocyclic cleavage reaction was demonstrated by anomerization of multiple β-glycosyl linkages in a one-step operation. Chitin and chitosan are polymers consisting of *N*-acetyl glucosamine/glucosamine units linked by β-(1,4)-bonds and have many promising applications in water treatment, food science, cosmetics, and pharmaceutics. Cellulose and amylose are two similar polysaccharides comprised of 1,4-glucose units, but have distinct characteristics because of the higher-order structure difference imparted by the anomeric stereochemistry. The unique α-(1,4)-glucosamine polymer is generally not available because selective 1,2-*cis* aminoglycoside synthesis is difficult. Here, protected chitotetraose **23** was synthesized in a similar manner reported by Ogawa as shown in Scheme 2.[49] The glycosylation reaction between **18** and **19** proceeded in high yield. Disaccharide **20** was subsequently transformed to acceptor **21** and donor **22**. Glycosyl fluoride **22** was activated by hafnium(IV) triflate, $Hf(OTf)_4$, by a recently developed operationally simple method to give tetrasaccharide **23**.[50] Subsequent transformation to anomerization precursor **24** through introduction of the *N*-acetylcarbamate moieties was accomplished by treatment of aminoalcohol **23** with triphosgene in the presence of $NaHCO_3$ and subsequent acetylation in the presence of 4-dimethylaminopyridine (DMAP; Scheme 2). After $BF_3{\cdot}OEt_2$ treatment of **24** (coupling constants at anomeric position $J = 8.8$ Hz) in CH_3CN, the anomerized compound **25** (coupling constants at anomeric position $J = 2.4$, 2.8, and 3.2 Hz) was obtained in 83% yield.[51] The simultaneous anomerization of four 1,2-*trans* glycosidic bonds to 1,2-*cis* glycosides was thus accomplished in a single laboratory operation, in excellent yield.

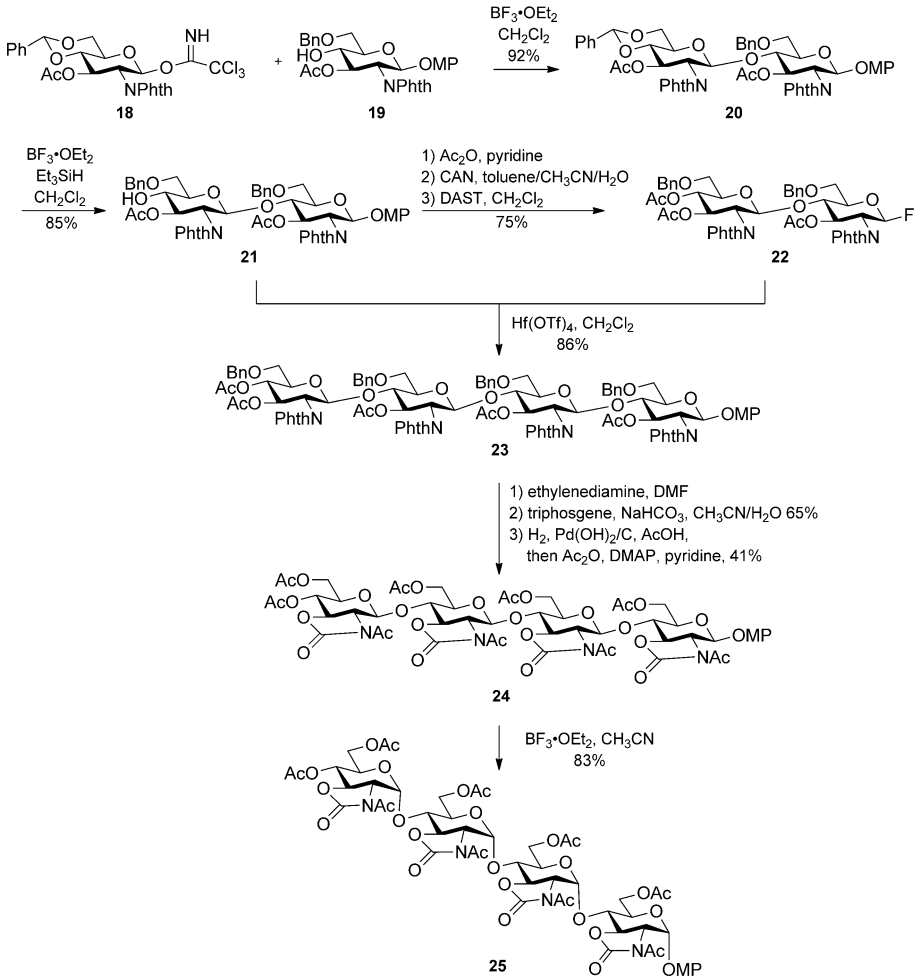
Conclusion

We have demonstrated that anomerization through an endocyclic cleavage–recyclization process is a powerful strategy to achieve complete 1,2-*cis* aminoglycoside preparation. We found that the presence of an acetyl group on the 2,3-*trans* carbamate has a significant positive effect on the anomerization reaction. Computational studies supported the feasibility of the endocyclic cleavage-induced anomerization reaction, and together with our previous calculations,[39,45] revealed that the inner strain caused by distorted carbamate group and the orientation of the carbonyl group toward the anomeric position are important factors in the reaction. In the anomerization reaction, the existing multiple 1,2-*trans* glycosyl bonds were converted into *cis* glycosyl bonds, which are difficult to obtain, in a single operation. Further investigations on extending this methodology for the synthesis of bioactive oligosaccharides and high-molecular-weight 1,2-*cis* chitosan derivatives, a new previously unknown class of polymers prepared from naturally occurring chitosan, will be reported in due course.

Experimental Section

General procedures

All commercial reagents were used without further purification. Analytical TLC was performed on silica gel 60 F254 plates (Merck) and visualized by UV fluorescence quenching and 12-molybdo(VI) phosphoric acid acid/phosphoric acid/sulfuric acid staining. Flash column chromatography was performed on a silica gel 60N (spherical, neutral, 40–100 μm Kanto Co.). Yields refer to chromatographically and spectroscopically pure compounds. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX 400 spectrometer (400 and 100 MHz, respectively) at ambient temperatures (23–24 °C) in $CDCl_3$. Chemical shifts (δ) are reported in ppm relative to internal TMS ($\delta = 0.00$ ppm) for ^{1}H and $CDCl_3$ ($\delta = 77.00$ ppm) for ^{13}C NMR spectra. HRMS were measured by quadrupole-TOF mass spectrometry. Optical rotations were measured at room temperature (JASCO DIP-310). Melting points are not corrected (YANACO micro melting point apparatus). Compounds **1 a**,[39] **2 a**,[39] **1 f**,[39] **2 f**,[39] **1 g**,[39] **2 g**,[39] **1 k**,[39] **2 k**,[39] **6 a**,[39] **1 l**,[52] **3 a**,[28] **5 a**,[31] **5 b**,[41] **7 a**,[41] **7 b**,[41] **8 a**,[40] **9 a**,[40] **18**,[53] **21**,[54] and **22**[50] were previously reported. Spectro-



Scheme 2. Synthesis of a new "1,2-*cis* chitosan" tetrasaccharide. DAST = diethylaminosulfur trifluoride; CAN = ceric ammonium nitrate.

scopic data of **1c**–**1e**, **1h**–**1j**, **2c**–**2d**, **2h**–**2j**, **3b**, **4a**, **4b**, **6b**, **10**–**16a**, **10**–**16b** are reported in the Supporting Information.

Synthesis

General procedure for anomerization: $BF_3{\cdot}OEt_2$ (2 equiv) was added to β-glycoside (1 equiv) in CH_2Cl_2 (substrate concentration: 0.077 M) at −30 °C. After 12 h, the mixture was quenched with sat. $NaHCO_3$ and the aqueous layer was extracted with $CHCl_3$ several times. The combined layers were washed with brine and dried over Na_2SO_4. After filtration, the mixture was concentrated in vacuo, and the residue was purified by preparative TLC.

Phenyl *N*-4-methoxybenzyl-2-amino-4-*O*-acetyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-β-D-glucopyranoside (1b): $[\alpha]_D^{24} = -29.0$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$ (d, $J =$ 6.8 Hz, 2H), 7.34–7.21 (m, 12H), 6.85 (d, $J = 8.4$ Hz, 2H), 5.23 (t, $J =$ 10.0 Hz, 1H), 4.81 (d, $J = 9.2$ Hz, 1H), 4.71 (d, $J = 15.2$ Hz, 1H), 4.60 (d, $J = 15.2$ Hz, 1H), 4.52 (d, $J = 11.6$ Hz, 1H), 4.47 (d, $J = 11.6$ Hz, 1H), 4.11 (t, $J = 10.8$ Hz, 1H), 3.79 (s, 3H), 3.60 (m, 1H), 3.53 (m, 2H), 3.50 ppm (t, $J = 11.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 158.7, 132.2, 129.9, 129.1, 128.3, 127.8, 127.7, 114.0, 86.9, 79.9, 88.0, 73.6, 68.8, 68.0, 59.9, 55.3, 20.8 ppm; HRMS: *m/z* calcd for $C_{30}H_{31}NO_7S + Na^+$: 572.1713 [M+Na^+]; found: 572.1710.

Phenyl *N*-4-methoxybenzyl-2-amino-4-*O*-acetyl-6-*O*-benzyl-2,3-*N*,*O*-carbonyl-2-deoxy-1-thio-α-D-glucopyranoside (2b): $[\alpha]_D^{24} =$ 122.1 ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J =$ 5.6 Hz, 2H), 7.38–7.21 (m, 8H), 7.11 (d, $J = 8.4$ Hz, 2H), 6.75 (d, $J =$ 8.4 Hz, 2H), 5.34 (d, $J = 4.4$ Hz, 1H), 5.25 (t, $J = 9.6$ Hz, 1H), 4.68 (d, $J =$ 14.4 Hz, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.37–4.43 (m, 2H), 4.24 (m, 1H), 4.07 (d, $J = 14.4$ Hz, 1H), 3.71 (s, 3H), 3.56 (dd, $J = 12.0$, 4.4 Hz, 1H) 3.51 (m, 2H), 1.95 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 169.0, 159.6, 157.9, 137.3, 132.6, 131.7, 130.2, 129.1, 128.3, 127.9, 127.8, 127.7, 126.0, 114.3, 84.9, 76.1, 73.5, 71.6, 68.3, 67.5, 59.7, 55.3, 47.4, 20.7 ppm; HRMS: *m/z* calcd for $C_{30}H_{31}NO_7S + Na^+$: 572.1713 [M+Na^+]; found: 572.1711.

Time-course experiment of anomerization of 17a: To a solution of **17a** (70 mg-100 mg) in either CH_2Cl_2 or CH_3CN (substrate concentration 0.077 M), $BF_3{\cdot}OEt_2$ (2 equiv) was added at −30 °C under an Ar atmosphere. After appropriate reaction period, the reaction was quenched with sat. $NaHCO_3$ and the aqueous layer was extracted with EtOAc several times. The combined organic layers were washed with sat. $NaHCO_3$ and brine. After drying the extract over Na_2SO_4 and filtration, the mixture was concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc, 7:3).

Methyl (*N*-acetyl-2-amino-2,3-*N*,*O*-carbonyl-4-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranosyl)-(1→4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (17a): $[\alpha]_D^{24} = -3.7$ ($c = 0.88$ in $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.23 (m, 20H), 5.22 (dd, $J = 9.2$, 4.4 Hz, 1H), 4.99 (d, $J = 11.2$ Hz, 1H), 4.92–4.87 (m, 2H), 4.81 (d, $J = 11.2$ Hz, 1H), 4.75 (d, $J = 12.4$ Hz, 1H), 4.69 (d, $J = 11.2$ Hz, 1H), 4.60 (d, $J =$ 11.6 Hz, 1H), 4.54 (d, $J = 3.6$ Hz, 1H), 4.49 (d, $J = 12.0$ Hz, 1H), 4.45 (d, $J = 12.0$ Hz, 1H), 4.18 (t, $J = 9.2$ Hz, 1H), 4.11–4.06 (m, 2H), 3.99 (t, $J = 9.6$ Hz, 1H), 3.95 (m, 1H), 3.80–3.75 (m, 3H), 3.69–3.64 (m, 2H), 3.51 (dd, $J = 10.0$, 3.6 Hz, 1H), 2.35 (s, 3H), 2.07 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.1$, 169.6, 153.3, 138.8, 138.8, 138.2, 137.7, 129.0, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.7, 127.5, 100.7, 98.1, 82.2, 79.8, 78.4, 75.6, 75.5, 74.5, 73.4, 73.3, 70.7, 70.1, 69.8, 67.2, 60.1, 55.1, 24.5, 20.7 ppm; HRMS: *m/z* calcd for $C_{46}H_{51}NO_{13} + Na^+$: 848.3253 [$M$+$Na^+$]; found: 848.3254.

Methyl (*N*-acetyl-2-amino-2,3-*N*,*O*-carbonyl-4-*O*-acetyl-6-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→4)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (17b): $[\alpha]_D^{24} = 98.9$ ($c = 1.6$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37$–7.23 (m, 20H), 5.79 (d, $J = 2.4$ Hz, 1H), 5.36 (t, $J = 9.6$ Hz, 1H), 5.00 (d, $J = 10.4$ Hz, 1H), 4.86 (d, $J = 11.2$ Hz, 1H), 4.80 (d, $J = 10.8$ Hz, 1H), 4.77 (d, $J = 10.8$ Hz, 1H), 4.67 (d, $J =$

12.0 Hz, 1H), 4.58–4.55 (m, 2H), 4.40 (d, J=11.6 Hz, 1H), 4.43 (d, J=12.0 Hz, 1H), 3.98 (t, J=9.6 Hz, 1H), 3.84–3.79 (m, 4H), 3.69 (m, 1H), 3.53–3.46 (m, 3H), 3.35 (s, 3H), 3.35–3.30 (m, 1H), 2.94 (s, 3H), 1.98 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.9, 169.0, 152.9, 138.7, 138.1, 138.0, 137.5, 128.5, 128.4, 128.4, 128.1, 127.9, 127.9, 127.8, 127.6, 97.8, 95.6, 82.0, 70.8, 75.6, 74.7, 74.3, 73.5, 73.2, 71.2, 69.9, 68.4, 67.4, 66.8, 59.8, 55.1, 23.6, 20.6 ppm; HRMS: m/z calcd for $C_{46}H_{51}NO_{13}+Na^+$: 848.3253 [M+Na^+]; found: 848.3253.

***p*-Methoxyphenyl (4,6-*O*-benzylidene-2-deoxy-3-*O*-acetyl-2-phthalimido-β-D-glucopyranosyl)-(1→4)-2-deoxy-3-*O*-acetyl-6-*O*-benzyl-2-phthalimido-β-D-glucopyranoside**: BF_3·OEt_2 (21 μL, 0.174 mmol) was added to a solution of imidate **18** (0.74 g, 1.27 mmol) and acceptor **19** (0.63 g, 1.16 mmol) in CH_2Cl_2 (15 mL) at −60 °C. After 12 h, Et_3N was added to neutralize the mixture. The mixture was diluted with $CHCl_3$ and sat. $NaHCO_3$. After extraction of the aqueous layer with $CHCl_3$, the combined organic layers were washed with brine. The combined layers were dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel column chromatography (toluene/EtOAc 7:3–1:1) to give disaccharide **20** (1.03 g, 92%). $[\alpha]_D^{24}$=9.4 (c=0.89 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.82–7.79 (m, 4H), 7.71–7.58 (m, 4H), 7.42–7.10 (m, 8H), 6.76 (d, J=9.2 Hz, 2H), 6.63 (d, J=9.2 Hz, 2H), 5.82 (t, J=9.6 Hz, 1H), 5.76 (d, J=8.8 Hz, 1H), 5.71 (d, J=5.2 Hz, 1H), 5.58 (d, J=8.4 Hz, 1H), 5.47 (s, 1H), 4.39 (t, J=8.8 Hz, 1H), 4.28–4.16 (m, 4H), 4.10 (t, J=8.8 Hz, 1H), 3.71–3.69 (m, 3H), 3.67 (s, 3H), 3.58 (m, 2H), 1.95 (s, 3H), 1.85 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.2, 169.7, 167.9, 155.5, 150.5, 137.9, 136.7, 134.3, 131.4, 129.2, 129.0, 128.2, 128.2, 128.2, 127.5, 127.4, 126.2, 126.2, 125.3, 123.6, 119.0, 114.3, 101.7, 98.4, 97.4, 79.0, 75.5, 74.4, 72.7, 72.1, 69.6, 68.6, 67.3, 66.1, 55.7, 55.5, 54.9, 21.4, 20.8, 20.5 ppm; HRMS: m/z calcd for $C_{53}H_{48}N_2O_{16}+Na^+$: 991.2896 [$M$+$Na^+$]; found: 991.2908.

***p*-Methoxyphenyl (6-*O*-benzyl-2-deoxy-3-*O*-acetyl-2-phthalimido-β-D-glucopyranosyl)-(1→4)-2-deoxy-3-*O*-acetyl-6-*O*-benzyl-2-phthalimido-β-D-glucopyranoside (21)**: Et_3SiH (1.2 mL, 7.51 mmol) and BF_3·OEt_2 (0.19 mL, 1.33 mmol) was added to a solution of benzylidene compound **20** (0.64 g, 0.67 mmol) in CH_2Cl_2 (20 mL) at 4 °C. After 2 h, the mixture was diluted with sat. $NaHCO_3$ and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ and the organic layers were washed with brine. The extract was dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (toluene/EtOAc 7:3–1:1) to give alcohol **21** (0.55 g, 82%). $[\alpha]_D^{24}$=3.8 (c=0.88 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.81 (m, 4H), 7.69 (m, 4H), 7.33–7.16 (m, 10H), 6.76 (d, J=8.8 Hz, 2H), 6.63 (d, J=8.8 Hz, 2H), 5.72 (t, J=10.0 Hz, 1H), 5.69 (d, J=8.4 Hz, 1H), 5.57 (t, J=10.8 Hz, 1H), 5.46 (d, J=8.4 Hz, 1H), 4.55 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.0 Hz, 1H), 4.42–4.27 (m, 3H), 4.14–4.09 (m, 2H), 3.84–3.74 (m, 2H), 3.77–3.45 (m, 8H), 3.71 (s, 3H), 1.89 (s, 3H), 1.86 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.0, 170.0, 155.5, 150.6, 138.1, 137.4, 134.2, 131.5, 128.5, 128.2, 127.9, 127.7, 127.4, 123.5, 118.9, 114.3, 97.4, 97.2, 74.5, 74.4, 73.6, 73.5, 73.2, 72.7, 71.6, 70.0, 67.5, 55.5, 54.9, 20.6 ppm; HRMS: m/z calcd for $C_{53}H_{50}N_2O_{16}+Na^+$: 993.3053 [$M$+$Na^+$]; found: 993.3070.

6-*O*-Benzyl-2-deoxy-di-3,4-*O*-acetyl-2-phthalimido-β-D-glucopyranosyl-(1→4)-2-deoxy-3-*O*-acetyl-6-*O*-benzyl-2-phthalimido-β-D-glucopyranosyl fluoride (22): Alcohol **21** (0.30 g, 0.309 mmol) was dissolved in pyridine (3 mL) and Ac_2O (1 mL) was added. After stirring at room temperature overnight, the mixture was concentrated. The residue was purified by silica gel column chromatography (toluene/EtOAc 4:1) to give the corresponding acetate (0.31 g, quant.). $[\alpha]_D^{24}$=26.0 (c=1.78 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.81 (m, 4H), 7.70–7.69 (m, 4H), 7.35–7.17 (m, 10H), 6.76 (d, J=9.2 Hz, 2H), 6.63 (d, J=9.2 Hz, 2H), 5.73 (t, J=8.8 Hz, 1H), 5.70 (d, J=8.8 Hz, 1H), 5.57 (t, J=9.2 Hz, 1H), 5.47 (d, J=8.0 Hz, 1H), 4.55 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.0 Hz, 1H), 4.42–4.27 (m, 3H), 4.14–4.09 (m, 2H), 3.81 (t, J=9.2 Hz, 1H), 3.76 (dd, J=10.0, 4.4 Hz, 1H), 3.69–3.66 (m, 1H), 3.68 (s, 3H), 3.58 (m, 1H), 3.51–3.42 (m, 3H), 1.88 (s, 3H), 1.85 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.0, 170.0, 155.5, 150.6, 138.1, 137.3, 134.2, 131.4, 128.5, 128.2, 127.9, 127.7, 127.4, 123.5, 118.9, 114.3, 97.3, 97.2, 74.5, 74.4, 73.6, 73.5, 73.2, 72.7, 71.6, 71.4, 70.0, 67.5, 55.5, 54.9, 54.9, 21.6, 20.6 ppm; HRMS: m/z calcd for $C_{55}H_{52}N_2O_{17}+Na^+$: 1035.3158 [$M$+$Na^+$]; found: 1035.3168.

Cerium ammonium nitrate (3.2 mL, 3.66 mmol) was added to a solution of *p*-methoxyphenyl glycoside (1.19 g, 1.18 mmol) in toluene (14 mL), CH_3CN (18 mL) and H_2O (14 mL) at 4 °C. After 2 h, the mixture was diluted with H_2O and $CHCl_3$. After separation, the aqueous layer was extracted with $CHCl_3$ and washed with brine. The combined layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (toluene/EtOAc) to give hemiacetal. The hemiacetal was dissolved in CH_2Cl_2 (20 mL) and *N*,*N*-diethylaminosulfur trifloride (0.31 mL, 2.36 mmol) was added. After 30 min, the reaction was quenched with sat. $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ and the combined layers were washed with brine. After concentration, the residue was purified by silica gel column chromatography (toluene/EtOAc, 7:3) to give fluoride **22** (804 mg, 75%).

***p*-Methoxyphenyl (6-*O*-benzyl-2-deoxy-di-3,4-*O*-acetyl-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(2-deoxy-3-*O*-acetyl-6-*O*-benzyl-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(2-deoxy-3-*O*-acetyl-6-*O*-benzyl-2-phthalimido-β-D-glucopyranosyl)-(1→4)-(2-deoxy-3-*O*-acetyl-6-*O*-benzyl-2-phthalimido-β-D-glucopyranoside (23)**: $Hf(OTf)_4$ was added to a solution of fluoride **22** (1.22 g, 1.34 mmol) and acceptor **21** (0.97 mg, 1.00 mmol) in CH_2Cl_2 (20 mL) at −40 °C (1.16 g, 1.50 mmol). The mixture was stirred at −40 °C for 1 h, then at −20 °C for 1 h, and finally at 0 °C for 3 h. The reaction was quenched with sat $NaHCO_3$ and the mixture was diluted with EtOAc. The mixture was filtered through Celite. The aqueous layer was extracted with EtOAc and the combined layers were washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography (toluene/EtOAc, 7:3–1:1) to give tetrasaccharide 23 (1.54 g, 83%). $[\alpha]_D^{24}$=−3.2 (c=1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.88–7.85 (m, 4H), 7.78–7.72 (m, 8H), 7.67–7.65 (m, 4H), 7.33–7.18 (m, 17H), 7.15–7.12 (m, 2H), 7.12–7.10 (m, 2H), 6.90 (m, 1H), 6.74–6.64 (m, 2H), 6.61–6.60 (m, 2H), 5.66–5.61 (m, 3H), 5.46–5.43 (m, 2H), 5.33 (d, J=8.4 Hz, 1H), 5.23–5.13 (m, 3H), 4.50–4.32 (m, 10H), 4.14–3.98 (m, 7H), 3.65 (s, 3H), 3.56–3.46 (m, 4H), 3.40–3.32 (m, 4H), 3.26 (dd, J=10.4, 8.4, Hz, 1H), 3.18 (dd, J=10.4, 8.4 Hz, 1H), 3.00 (d, J=10.0 Hz, 1H), 2.74 (d, J=10.0 Hz, 1H), 1.83 (s, 3H), 1.79 (s, 3H), 1.78 (s, 3H), 1.77 (s, 3H), 1.63 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=170.3, 170.2, 169.4, 168.1, 167.2, 155.4, 150.6, 138.2, 138.1, 137.9, 137.6, 134.3, 131.4, 129.0, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 127.1, 126.9, 125.3, 123.6, 123.5, 118.8, 114.3, 97.4, 96.5, 96.4, 95.9, 74.4, 73.9, 73.6, 73.4, 73.3, 72.8, 72.6, 72.5, 72.2, 72.2, 72.1, 70.9, 70.9, 70.7, 69.4, 55.5, 55.3, 55.2, 55.0, 54.8, 21.4, 20.6, 20.5, 20.4 ppm; HRMS: m/z calcd for $C_{101}H_{94}N_4O_{31}+Na^+$: 1181.5794 [$M$+$Na^+$]; found: 1881.5810.

***p*-Methoxyphenyl (2-deoxy-di-4,6-*O*-acetyl-2,3-*N*,*O*-carbonyl-β-D-glucopyranosyl)-(1→4)-(6-acetyl-2-deoxy-2,3-*N*,*O*-carbonyl-β-D-glucopyranosyl)-(1→4)-(6-acetyl-2-deoxy-2,3-*N*,*O*-carbonyl-β-D-glucopyranosyl)-(1→4)-(6-acetyl-2-deoxy-2,3-*N*,*O*-carbonyl-β-D-glucopyranoside (24)**: Phthaloyl-protected tetrasaccharide **23** (2.00 g. 1.08 mmol) was dissolved in DMF (10 mL) and ethylenediamine (5 mL) and stirred at 80 °C under N_2 for 2 d. After concentration, the crude was purified by Sephadex LH-20 chromatography ($CHCl_3$/MeOH 1:1) to give tetraamine (1.28 g, quant.). Due to its

low solubility, the aminoalcohol was used without further purification. Triphosgene (362.0 mg, 1.22 mmol) was added to a solution of tetrasaccharide amino alcohol (430.0 mg, 0.381 mmol) and $NaHCO_3$ (640 mg, 7.62 mmol) in CH_3CN (12 mL) and H_2O (3 mL). After 12 h, additional triphosgene (180.0 mg, 0.61 mmol) and $NaHCO_3$ (320.0 mg, 3.81 mmol) were added. The mixture was diluted with $CHCl_3$ and brine, and the extracted with $CHCl_3$. The combined layers were washed with brine and the dried over Na_2SO_4. After concentration, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH 9:1) to give the carbamate intermediate **24** (303 mg, 64%). $[\alpha]_D^{24} = -24.5$ ($c = 0.60$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$–7.24 (m, 20H), 6.97 (d, $J =$ 8.8 Hz, 2H), 6.80 (d, $J = 8.8$ Hz, 2H), 6.21 (s, 1H), 6.10 (s, 1H), 5.91 (s, 1H), 5.82 (s, 1H), 5.00 (d, $J = 7.6$ Hz, 1H), 4.69–4.43 (m, 11H), 4.21 (m, 2H), 4.20 (m, 2H), 3.98–3.96 (m, 4H), 3.78–3.60 (m, 12H), 3.76 (s, 3H), 3.53–3.45 (m, 4H), 3.31–3.30 (m, 3H), 3.14 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.2$, 159.1, 154.9, 150.0, 138.8, 138.5, 138.4, 128.2, 128.2, 127.5, 118.1, 114.5, 100.2, 100.2, 98.9, 79.2, 78.8, 78.6, 77.1, 76.5, 74.4, 72.6, 72.2, 68.1, 66.7, 58.7, 58.5, 55.4, 55.4 ppm; HRMS: *m/z* calcd for $C_{63}H_{68}N_4O_{22} + Na^+$: 1255.4217 [$M$+$Na^+$]; found: 1255.4215. A suspension of benzyl ether (200 mg, 0.162 mmol) and 20% [$Pd(OH)_2$]/C in EtOH (8 mL) and AcOH (8 mL) was stirred under H_2 atmosphere for 2 h. The catalyst was filtered through filter paper and then washed with AcOH. After evaporation, pentaol was obtained (71.0 mg, 52%). The pentaol-carbamate (35.3 mg, 0.0404 mmol) and DMAP (1 mg, 0.008 mmol) were dissolved in pyridine (0.5 mL), and then Ac_2O (0.5 mL) was added. The mixture was stirred at room temperature overnight. After evaporation, the crude was purified by silica gel column chromatography to obtain *N*-acetylcarbamate tetrasaccharide **23** (39.7 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J =$ 8.8 Hz, 2H), 5.64 (d, $J = 6.4$ Hz, 1H), 5.31–5.28 (m, 3H), 5.14 (dd, $J =$ 9.6, 3.2 Hz, 1H), 4.61–4.08 (m, 25H), 3.97 (dd, $J = 12.8$, 6.4 Hz, 1H), 3.90–3.83 (m, 2H), 3.77 (s, 3H), 2.52 (s, 12H), 2.14 (s, 3H), 2.12 ppm (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 170.4, 169.6, 155.4, 153.0, 152.7, 152.7, 152.6, 150.7, 118.2, 114.5, 98.9, 98.7, 98.2, 98.1, 78.3, 76.2, 76.1, 76.0, 75.9, 75.6, 74.6, 70.1, 64.5, 64.4, 64.3, 60.5, 55.7, 24.3, 21.0, 20.8 ppm; HRMS: *m/z* calcd for $C_{53}H_{62}N_4O_{31} + Na^+$: 1273.3290 [$M$+$Na^+$]; found: 1273.3292.

***p*-Methoxyphenyl (2-deoxy-di-4,6-*O*-acetyl-2,3-*N,O*-carbonyl-α-D-glucopyranosyl)-(1→4)-(6-acetyl-2-deoxy-2,3-*N,O*-carbonyl-α-D-glucopyranosyl)-(1→4)-(6-acetyl-2-deoxy-2,3-*N,O*-carbonyl-α-D-glucopyranosyl)-(1→4)-(6-acetyl-2-deoxy-2,3-*N,O*-carbonyl-α-D-glucopyranoside (25)**: $BF_3{\cdot}OEt_2$ (9 μL, 0.0624 mmol) was added to a solution of 1,2-*trans* tetrasaccharide **24** (39.0 mg, 0.0312 mmol) in CH_3CN (0.3 mL) at 0 °C. After the mixture was stirred at 0 °C for 3 h, the reaction was quenched with sat. $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ and the combined layers were washed with brine. The organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography to give 1,2-*cis* tetrasaccharide **25** (32.2 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.96$ (d, $J = 8.8$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.17 (d, $J = 2.4$ Hz, 1H), 6.00 (d, $J = 2.8$ Hz, 1H), 5.98 (d, $J =$ 2.4 Hz, 1H), 5.97 (d, $J = 2.8$ Hz, 1H), 5.32 (t, $J = 9.6$ Hz, 1H), 4.79 (t, $J = 9.2$ Hz, 1H), 4.76–4.40 (m, 6H), 4.28–4.08 (m, 9H), 4.02–3.98 (m, 2H), 3.91–3.37 (m, 4H), 3.87–3.74 (m, 3H), 3.80 (s, 3H), 2.56 (s, 3H), 2.55 (s, 3H), 2.54 (s, 3H), 2.52 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.09 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.9$, 171.8, 171.8, 171.1, 170.5, 170.4, 170.3, 169.1, 156.0, 152.4, 152.3, 152.1, 149.7, 118.7, 114.7, 96.7, 96.6, 96.3, 95.4, 76.3, 75.9, 75.5, 75.0, 74.5, 74.4, 73.7, 71.9, 71.9, 71.3, 71.1, 67.7, 62.0, 61.8, 61.8, 61.4, 59.8, 59.8, 59.8, 59.7, 55.7, 23.7, 20.8, 20.7 ppm; HRMS: *m/z* calcd for $C_{53}H_{62}N_4O_{31} + Na^+$: 1273.3290 [$M$+$Na^+$]; found: 1273.3291.

The number of imaginary frequencies of the transition states

The transition state structures for pyranosides **1 f** and **1 k** were located by using the Synchronous Transit-Guided Quasi-Newton (STQN) method by using the QST3 option and vibrational analysis of the Gaussian 03 program. The number of imaginary frequencies of the transition states are **1 f** (−91.7033) and **1 k** (−73.7274).

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[1] Y. van Kooyk, G. A. Rabinovich, *Nat. Immunol.* **2008**, *9*, 593–601.
[2] B. Ernst, J. L. Magnani, *Nat. Rev. Drug Discovery* **2009**, *8*, 661–677.
[3] P. H. Seeberger, *Nat. Chem. Biol.* **2009**, *5*, 368–372.
[4] D. P. Galonić, D. Y. Gin, *Nature* **2007**, *446*, 1000–1007.
[5] T. J. Boltje, T. Buskas, G.-J. Boons, *Nat. Chem.* **2009**, *1*, 611–622.
[6] M. T. C. Walvoort, J. Dinkelaar, L. J. van den Bos, G. Lodder, H. S. Overkleeft, J. D. C. Codée, G. A. van der Marel, *Carbohydr. Res.* **2010**, *345*, 1252–1263.
[7] L. K. Mydock, A. V. Demchenko, *Org. Biomol. Chem.* **2010**, *8*, 497–510.
[8] D. Crich, *J. Org. Chem.* **2011**, *76*, 9193–9209.
[9] I. Cumpstey, *Org. Biomol. Chem.* **2012**, *10*, 2503–2508.
[10] S. C. Ranade, A. V. Demchenko, *J. Carbohydr. Chem.* **2013**, *32*, 1–43.
[11] J. E. Yule, T. C. Wong, S. S. Gandhi, D. Qiu, M. A. Riopel, R. R. Koganty, *Tetrahedron Lett.* **1995**, *36*, 6839–6842.
[12] J. Banoub, P. Boullanger, D. Lafont, *Chem. Rev.* **1992**, *92*, 1167–1195.
[13] A. Imamura, H. Ando, S. Korogi, G. Tanabe, O. Muraoka, H. Ishida, M. Kiso, *Tetrahedron Lett.* **2003**, *44*, 6725–6728.
[14] J. Park, S. Kawatkar, J.-H. Kim, G.-J. Boons, *Org. Lett.* **2007**, *9*, 1959–1962.
[15] E. A. Mensah, H. M. Nguyen, *J. Am. Chem. Soc.* **2009**, *131*, 8778–8780.
[16] E. A. Mensah, F. Yu, H. M. Nguyen, *J. Am. Chem. Soc.* **2010**, *132*, 14288–14302.
[17] F. Yu, H. M. Nguyen, *J. Org. Chem.* **2012**, *77*, 7330–7343.
[18] R. Enugala, L. C. R. Carvalho, M. J. Dias Pires, M. B. Marques, *Chem. Asian J.* **2012**, *7*, 2482–2501.
[19] I. Capila, R. J. Linhardt, *Angew. Chem.* **2002**, *114*, 426–450; *Angew. Chem. Int. Ed.* **2002**, *41*, 390–412.
[20] J.-C. Lee, X.-A. Lu, S. S. Kulkani, Y.-S. Wen, S.-C. Hung, *J. Am. Chem. Soc.* **2004**, *126*, 476–477.

[21] C. Noti, J. L. de Paz, L. Polito, P. H. Seeberger, *Chem. Eur. J.* **2006**, *12*, 8664 – 8686.
[22] S. Arungundram, K. Al-Mafraji, J. Asong, F. E. Leach III., I. J. Amster, A. Venot, J. E. Turnbull, G.-J. Boons, *J. Am. Chem. Soc.* **2009**, *131*, 17394 – 17405.
[23] K. Ajayi, V. V. Thakur, R. C. Lapo, S. Knapp, *Org. Lett.* **2010**, *12*, 2630 – 2633.
[24] M. M. L. Zulueta, S.-Y. Lin, Y.-T. Lin, C.-J. Huang, C.-C. Wang, C.-C. Ku, Z. Shi, C.-L. Chyan, D. Irene, L.-H. Lim, T.-I. Tsai, Y.-P. Hu, S. D. Arco, C.-H. Wong, S.-C. Hung, *J. Am. Chem. Soc.* **2012**, *134*, 8988 – 8995.
[25] H. Paulsen, Č. Kolář, W. Stenzel, *Chem. Ber.* **1978**, *111*, 2358 – 2369.
[26] R. U. Lemieux, R. M. Ratcliffe, *Can. J. Chem.* **1979**, *57*, 1244 – 1251.
[27] G. Ngoje, Z. Li, *Org. Biomol. Chem.* **2013**, *11*, 1879 – 1886, and references therein.
[28] K. Benakli, C. Zha, R. J. Kerns, *J. Am. Chem. Soc.* **2001**, *123*, 9461 – 9462.
[29] P. Wei, R. J. Kerns, *J. Org. Chem.* **2005**, *70*, 4195 – 4198.
[30] M. Boysen, E. Gemma, M. Lahmann, S. Oscarson, *Chem. Commun.* **2005**, 3044 – 3046.
[31] S. Manabe, K. Ishii, Y. Ito, *J. Am. Chem. Soc.* **2006**, *128*, 10666 – 10667.
[32] Y. Geng, L.-H. Zhang, X.-S. Ye, *Chem. Commun.* **2008**, 597 – 599.
[33] S. Manabe, K. Ishii, Y. Ito, *Eur. J. Org. Chem.* **2011**, 497 – 516.
[34] Discussion of the endocyclic cleavage reaction: a) W. N. Haworth, L. N. Owen, F. Smith, *J. Chem. Soc.* **1941**, 88 – 102; b) B. Lindberg, *Acta Chem. Scand.* **1949**, *3*, 1153 – 1169; c) C. A. Bunton, T. A. Lewis, D. R. Llewellyn, C. A. Vernon, *J. Chem. Soc.* **1955**, 4419 – 4423; d) A. J. Kirby, *Acc. Chem. Res.* **1984**, *17*, 305 – 311; e) R. D. Gandour, J. Tirado-Rives, F. R. Fronczek, *J. Org. Chem.* **1986**, *51*, 1987 – 1991; f) S. Ueno, T. Oshima, T. Nagai, *J. Org. Chem.* **1986**, *51*, 2131 – 2134; g) P. G. Jones, A. J. Kirby, *J. Chem. Soc. Chem. Commun.* **1986**, 444 – 445; h) C. B. Post, M. Karplus, *J. Am. Chem. Soc.* **1986**, *108*, 1317 – 1319; i) A. J. Bennet, M. L. Sinnott, *J. Am. Chem. Soc.* **1986**, *108*, 7287 – 7294; j) R. B. Gupta, R. W. Franck, *J. Am. Chem. Soc.* **1987**, *109*, 6554 – 6556; k) T. H. Fife, T. J. Przystas, *J. Chem. Soc. Perkin Trans. 2* **1987**, 143 – 150; l) D. R. McPhail, J. R. Lee, B. Fraser-Reid, *J. Am. Chem. Soc.* **1992**, *114*, 1905 – 1906; m) J. L. Liras, E. V. Anslyn, *J. Am. Chem. Soc.* **1994**, *116*, 2645 – 2646; n) C. McDonnell, O. López, P. Murphy, J. G. Fernández Bolaños, R. Hazell, M. Bols, *J. Am. Chem. Soc.* **2004**, *126*, 12374 – 12385; o) P. Deslongchamps, S. Li, Y. L. Dory, *Org. Lett.* **2004**, *6*, 505 – 508.
[35] Examples of anomerization of pyranosides: a) R. U. Lemieux, W. P. Shyluk, *Can. J. Chem.* **1955**, *33*, 120 – 127; b) Y. Guindon, P. C. Anderson, *Tetrahedron Lett.* **1987**, *28*, 2485 – 2488; c) J. F. Normant, A. Alexakis, A. Ghribi, P. Mangeney, *Tetrahedron* **1989**, *45*, 507 – 516; d) N. Ikemoto, O. K. Kim, L.-C. Lo, V. Satyanarayana, M. Chang, K. Nakanishi, *Tetrahedron Lett.* **1992**, *33*, 4295 – 4298; e) R. Olsson, P. Rundström, B. Persson, T. Frejd, *Carbohydr. Res.* **1998**, *307*, 13 – 18; f) R. Olsson, U. Berg, T. Frejd, *Tetrahedron* **1998**, *54*, 3935 – 3954; g) C. O'Brien, M. Poláková, N. Pitt, M. Tosin, P. V. Murphy, *Chem. Eur. J.* **2007**, *13*, 902 – 909; h) Y. Wang, H.-S. Cheon, Y. Kishi, *Chem. Asian J.* **2008**, *3*, 319 – 326; i) W. Pilgrim, P. V. Murphy, *J. Org. Chem.* **2010**, *75*, 6747 – 6755; j) S. R. Vidadala, T. M. Pimpalpalle, T. Linker, S. Hotha, *Eur. J. Org. Chem.* **2011**, 2426 – 2430.
[36] S. Manabe, K. Ishii, D. Hashizume, H. Koshino, Y. Ito, *Chem. Eur. J.* **2009**, *15*, 6894 – 6901.
[37] D. Crich, A. U. Vinod, *J. Org. Chem.* **2005**, *70*, 1291 – 1296.
[38] J. D. M. Olsson, L. Eriksson, M. Lahmann, S. Oscarson, *J. Org. Chem.* **2008**, *73*, 7181 – 7188.
[39] H. Satoh, S. Manabe, Y. Ito, H. P. Lüthi, T. Laino, J. Hutter, *J. Am. Chem. Soc.* **2011**, *133*, 5610 – 5619.
[40] S. Manabe, K. Ishii, H. Satoh, Y. Ito, *Tetrahedron* **2011**, *67*, 9966 – 9974.
[41] S. Manabe, Y. Ito, *Tetrahedron Lett.* **2009**, *50*, 4827 – 4829.
[42] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648 – 5652.
[43] P. J. Stephens, F. J. Devlin, C. F. Chabalowski, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623 – 11627.
[44] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
[45] H. Satoh, J. Hutter, P. H. Lüthi, S. Manabe, K. Ishii, Y. Ito, *Eur. J. Org. Chem.* **2009**, 1127 – 1131.
[46] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999 – 3094.
[47] E. A. Noe, M. Raban, *J. Am. Chem. Soc.* **1975**, *97*, 5811 – 5820, and references therein.
[48] R. H. Taaning, K. B. Lindsay, B. Schiøtt, K. Daasbjerg, T. Skrydstrup, *J. Am. Chem. Soc.* **2009**, *131*, 10253 – 10262.
[49] H. Kuyama, Y. Nakahara, T. Nukada, Y. Ito, Y. Nakahara, T. Ogawa, *Carbohydr. Res.* **1993**, *243*, C1 – C7.
[50] S. Manabe, Y. Ito, *J. Org. Chem.* **2013**, *78*, 4568 – 4572.
[51] The 2,3-*trans* carbamate-containing glucosamine has a near $^4C_1$ conformation. Determination of proton coupling constants (^{1}H NMR spectroscopy) is indicative of the stereochemistry at the anomeric position and a commonly accepted procedure. For X-ray analyses of pyranoside with 2,3-*trans* carbamate, see: S. Manabe, K. Ishii, D. Hashizume, Y. Ito, *Acta Crystallogr. Sect. E* **2008**, *64*, o1868.
[52] S. Manabe, Y. Aihara, Y. Ito, *Chem. Commun.* **2011**, *47*, 9720 – 9722.
[53] M. Morando, Y. Yao, S. Martín-Santamaría, Z. Zhu, T. Xu, F. J. Cañada, Y. Zhang, J. Jiménez-Barbero, *Chem. Eur. J.* **2010**, *16*, 4239 – 4249.
[54] Y. Yang, Y. Li, B. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 12076 – 12077.

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