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The Amide Group in *N*-Acetylglucosamine Glycosyl Acceptors Affects Glycosylation Outcome

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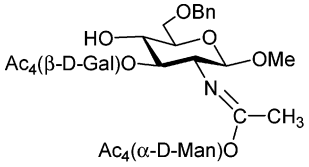
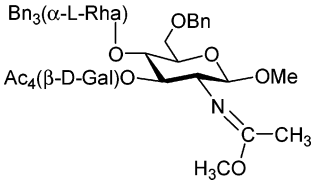


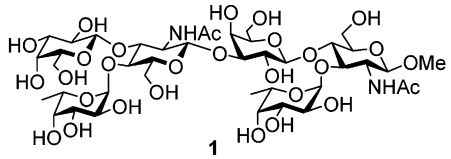


Glycosylation of a disaccharide containing *N*-acetylglucosamine with rhamnosyl and mannosyl trichloracetimidates under triethysilyl triflate catalysis led to the competitive formation of glycosyl imidates. While the rhamnosyl imidate could be rearranged to the thermodynamically favored trisaccharide, the mannosyl analogue was resistant to rearrangement. Glycosylation with perbenzylated thiorhamnosides activated with methyl triflate (MeOTf) gave the trisaccharide as well as the methyl imidate trisaccharide. The less reactive α-thioethyl donor led to a higher relative amount of methyl imidate trisaccharide to trisaccharide than the more reactive *β*-thioglycoside. When using a more reactive thioethyl fucoside only the trisaccharide was obtained. Interestingly, the acceptor treated with MeOTf gave the *N*-methyl imidate that could be easily rhamnosylated and subsequently converted to the *N*-acetamido trisaccharide. This strategy to glycosylate O-4 of *N*-acetylglucosamine is under further investigation. Alternatively, bis-*N*-acetylation of the glucosamine prevented the formation of imidates and allowed the efficient synthesis of two Lewis A trisaccharide analogues.

Introduction

The natural occurrence of numerous glycosides of *N*-acetylglucosamine in biologically important oligo- and polysaccharides such as bacterial polysaccharides and blood group antigens[1] often necessitates the efficient chemical synthesis of 2-amino-2-deoxyglycopyranosides. Among all hydroxyl groups of *N*-acetylglucosamine, the 4-OH group is well-known to be a poor glycosyl acceptor.[2] The lack of reactivity at this position often greatly impedes efficient chemical synthesis of oligosaccharides in which a 1 → 4 glycosidic bond to the *N*-acetylglucosamine is essential, for example, the tumor associated hexasaccharide Le^aLe^x **1** and Lewis blood group antigen trisaccharide Le^a **2**.

In fact, construction of such glycosidic bonds usually requires a highly reactive glycosyl donor[3] or sophisticated protection and deprotection schemes of the amino group.[4−6] The low reactivity of the 4-OH group of *N*-acetylglucosamine toward glycosylation has been believed to result



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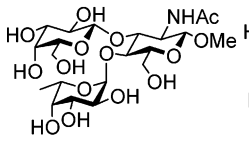

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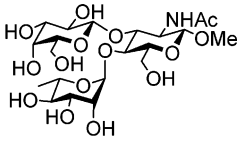

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from steric hindrance at this position.[2] Recently Crich et al. proposed an alternative explanation based on the formation of a hydrogen bond involving the glucosamine amide group that would lower the reactivity of such acceptors toward glycosylation.[4c] While engaged in the synthesis of analogue **3** via the coupling of acceptor **4** with trichloroacetimidate **5**, we have observed[7] the formation of a kinetically favored rhamnosyl imidate that could be rearranged to the desired trisaccharide, albeit in moderate yield. Thus, we argued that the competing formation of glycosyl imidates could provide a third explanation to the low reactivity of *N*-acetylglucosamine acceptors. We herein further investigate this explanation coupling

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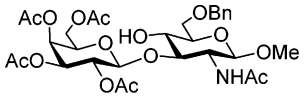

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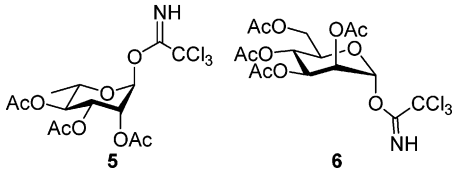
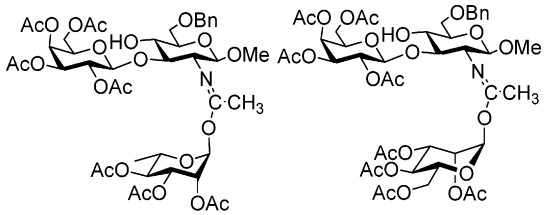


5 **6**

acceptor **4** with mannosyl trichloroacetimidate **6** using various concentrations of triethylsilyl trifluoromethanesulfonate (TESOTf) as an activator. As an alternative to the use of trichloroacetimidate glycosyl donors we also report our results when acceptor **4** was allowed to react with thioethyl glycosyl donors under methyl trifluoromethanesulfonate (MeOTf) activation. While no glycosyl imidates were formed in these conditions, we report here that trisaccharide methyl imidates may be isolated in amounts that will vary depending on the reactivity of the glycosyl donor. As communicated previously[7] we also expand on the use of a di-*N*-acetylated disaccharide acceptor to efficiently prepare the mannosylated trisaccharide using the trichloracetimidate donor.

Results and Discussion

As we have communicated,[7] coupling of **4** with the α-L-rhamnopyranosyl trichloroacetimidate[8] **5** at low temperature and with 0.1 equiv of TESOTf afforded the imidate derivative **7** in 42% yield. In contrast, no reaction was observed when trichloroacetimidate mannosyl donor **6**[9] and acceptor **4** were allowed to react in the same conditions. However, when the concentration of TESOTf was increased to 0.5 equiv the mannosyl imidate **8** was isolated in 86% yield, supporting the fact that the mannosyl donor **6** was less reactive than the rhamnosyl donor **5**. Even though donors such as **5** and **6** are prone[10] to give ortho esters during glycosylation, ^{1}H and ^{13}C NMR spectroscopy for **7** and **8** did not show any of the typical



7 **8**

signals expected[10] for such *O*-orthoacetates. In contrast, ^{1}H NMR spectroscopy showed the presence of exchangeable O*H* signals at C-4 of the glucosamine units and the absence of amide N*H* signals. The anomeric rhamnosyl and mannosyl H-1″ were found at unusually low fields (6.08 and 6.44 ppm, respectively) while the rhamnosyl and mannosyl anomeric carbons were found at higher fields (92 and 91 ppm, respectively) than usually observed for anomeric carbons. The $^1J_{C-1'',H-1''}$ coupling constants measured for the rhamnose and mannose anomeric carbons, 177 and 178 Hz, respectively, confirmed that these were α-linkages.[11] In our pervious communication,[7] a glycosyl imidate structure was assigned to **7** based on the observation that a methyl group signal was found at higher field (16 ppm) than expected for an acetyl methyl group (24 ppm) and that a quaternary signal assigned to the imidate C=N was found at 162 ppm. While similar signals were found for **8**, these characteristics do not unambiguously exclude the possibility that in both cases glycosylation might have occurred at the nitrogen atom, leading to *N*-rhamno- and *N*-mannoside, respectively. In fact, Dauben et al. have suggested[12] the formation of an *N*-glucosyl product when reacting benzyl 2-acetamido-3,6-di-*O*-acetyl-2-deoxy-α-D-glucopyranoside with tetra-*O*-benzoyl-α-D-glucopyranosyl bromide. And subsequently Clinch et al.[13] have reported that glycosylation of 4-nitrophenyl 2-acetamido-3-*O*-benzoyl-6-*O*-chloroacetyl-2-deoxy-*β*-D-glucopyranoside with tetra-*O*-benzoyl-α-D-galactopyranosyl bromide gave a product in which the galactose residue could be either *N*- or *O*-linked to the glucose *N*-acetyl group. In our case HMBC experiments acquired for **7** and **8** gave additional support to the glycosyl imidate structures. Indeed, while we found long-range correlations between Rha-H-1″ or Man-H-1″ and the quaternary carbons at 162 ppm (*C*=N), we did not find the correlations that would be expected for *N*-rhamno- or *N*-mannosylated structures, i.e., between Glu-C-2 and Rha- or Man-H-1″ as well as between Glu-H-2 and Rha- or Man- C-1″, in **7** or **8**, respectively. Thus we confirm that our products are indeed imidates **7** and **8** and are unlikely to be the *N*-rhamnosylated or *N*-mannosylated isomers. While Pougny and Sinaÿ[14] first reported the isolation of glycosyl imidates when treating a fully protected *N*-acetylglucosamine glycoside with glycosyl donors in Koenigs–Knorr conditions, their formation during the attempted glycosylation of an OH group has only been hypothesized by Hindsgaul et al.[15]

(3) For examples, see: (a) Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4063–4068. (b) Lemieux, R. U.; Bundle, D. R.; Baker, D. A. *J. Am. Chem. Soc.* **1975**, *97*, 4076–4083. (c) Jacquinet, J.-C.; Sinay, P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 319–322. (d) Manzoni, L.; Lay, L.; Schmidt, R. R. *J. Carbohydr. Res.* **1998**, *17*, 739–758.

(4) For examples, see: (a) Boons, G.-J.; Hale, K. *Organic Synthesis with Carbohydrates*; Sheffield Academic Press: Sheffield, England, 2000; Chapter 2, pp 51–53; Chapter 3, pp 76–84; Chapter 4, pp 122–124. (b) Lindhorst, T. K. *Essentials of Carbohydrate Chemistry and Biochemistry*, 2nd ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2003; Chapter 3, pp 72–74; Chapter 4, pp 97–100. (c) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825. (d) Crich, D.; Vinod, A. U. *Org. Lett.* **2003**, *5*, 1297–1300. For a review on synthesis of oligosaccharides of 2-amino-2-deoxy sugars, see: (e) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195. Herzner, H.; Reipen, T.; Schultz, M.; Kunz, H. *Chem. Rev.* **2000**, *100*, 4495–4537. For a review on *N*-protection for amino sugars, see: (f) Debenham, J.; Rodebaugh, R.; Fraser-Reid, B. *Liebigs Ann.* **1997**, 791–802.

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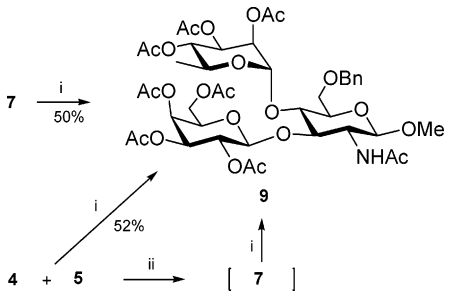
SCHEME 1[a]



[a] Reagents and conditions: (i) TESOTf (0.5 equiv), rt; (ii) TESOTf (0.1 equiv), −78 °C to rt.

In the latter work the suspected fucosyl imidate was seen to be highly sensitive to hydrolysis and degraded during chromatography. In our work while the rhamnosyl imidate **7** did partially degrade during purification, we observed that the mannosyl imidate **8** was fully stable to workup and purification leading to a much higher yield of **8** when compared to that of the rhamnosyl imidate **7**.

Since glycosyl imidates are known to be efficient glycosyl donors,[16] we investigated the ability of imidates **7** and **8** to behave as such and react via an inter- or intramolecular delivery of the rhamnosyl or mannosyl unit onto the free 4-OH group of the *N*-acetylglucosamine residue to give the corresponding trisaccharides. However, while we had observed[7] that imidate **7** could be rearranged to trisaccharide **9** in 50% yield upon stirring at room temperature in the presence of 0.5 equiv of TESOTf (Scheme 1), the mannosyl imidate **8** was found to be totally resistant to rearrangement even under harsh conditions (e.g. 1.2 equiv of TESOTf at 35 °C). With respect to the rhamnosyl imidate, we further report that it could be formed when coupling **5** and **4** at −78 °C (0.1 equiv of TESOTf) and subsequently rearranged in situ to trisaccharide **9** by adding more catalyst (up to 0.5 equiv) and raising the temperature (Scheme 1). Thus we conclude that imidates such as **7** may be formed kinetically when glycosylations of *N*-acetylglucosamine glycosyl acceptors are conducted at low temperature and in slightly basic,[12,15] neutral,[13] or mildly acidic reaction conditions. In these reactions, the formation of the desired glycosides at O-4 of the glucosamine residue appears to be under thermodynamic control and requires higher concentrations of Lewis acid and higher temperatures. However, in cases such as that of mannosyl imidate **8** the kinetically favored intermediates may not be able to rearrange to the glycosides and their competitive formation thus constitutes a third explanation for the poor results commonly observed when attempting to glycosylate the 4-OH group in *N*-acetylglucosamine derivatives.

As demonstrated above, the formation of glycosyl imidates and their rearrangement to the desired glycosides is highly dependent on the structure of the glycosyl donor and the reaction conditions. It is reasonable to expect that conditions employing an excess of Lewis acid could prevent the formation of glycosyl imidates through the neutralization of the *N*-acetamido group. We therefore investigated the reaction of thioglycosides **10**−**14** with acceptor **4** under activation with an excess (5 to 8 equiv) of MeOTf at room temperature (Table 1, entries 1−6).

Overall the activation of the known[17] peracetylated thioglycoside donors **10** and **11** with MeOTf proved to be very difficult and led in both cases to the formation of multiple compounds that were observed by TLC but could be neither purified nor identified. However, while no product could be isolated when using the α-thioglycoside **10** as a donor, coupling of the more reactive peracetylated *β*-thiorhamnoside gave trisaccharide **9** in 20% yield. As expected, the known[18,19] perbenzylated thiorhamnosides **12** and **13** were more easily activated (Table 1, entries 3 and 4). In the latter case, TLC showed that the starting materials had disappeared within 1 h of adding MeOTf giving two new products whose relative ratio assessed by TLC did not change overnight. In contrast, the reaction with use of the α-donor **12** proceeded more slowly but nevertheless gave the same two new products as **13**. These two new products were identified by NMR spectroscopy as being the methyl imidate trisaccharide **15** and the desired trisaccharide **16**. Signals corresponding to the anomeric H-1″ of the rhamnosyl unit were found at 5.00 and 4.90 ppm, for **15** and **16**, respectively, while signals at 98.7 and 97.7 ppm were assigned to the rhamnosyl C-1″ in **15** and **16**, respectively. In both products the α-configuration of the rhamnosidic bond was confirmed[11] by the value measured for the $^1J_{C-1'',H-1''}$ coupling constant of 169 and 168 Hz for **15** and **16**, respectively. However, while typical signals corresponding to the NH and acetamido groups were found at 5.74 (N*H*), 170 (*C*=O), and 20 ppm (*C*H_3) for trisaccharide **16**, it was not so for trisaccharide **15**. In fact, NMR spectroscopy of trisaccharide **15** showed analogous signals to the glycosyl imidates **7** and **8**, i.e., no N*H* but a quaternary *C*=N and a methyl carbon that were both shifted to 165 and 16.6 ppm, respectively. The HMBC showed a long-range correlation between the *C*=N signal and a new OC*H*$_3$ signal found at 3.66 ppm in the ^{1}H NMR spectrum supporting that this compound was methyl imidate **15**. Once again, *N*-methylation was excluded based on the absence of long-range correlations between the glucosamine C-2 signal at 65.8 ppm and the new C*H*$_3$ mentioned above as well as between the new carbon *C*H$_3$ found at 52.5 ppm and H-2 of the glucosamine residue at 3.69 ppm.

The syntheses of ethyl acetimidium fluoroborate salts[20] and alkyl acetimidates[21,22] by treating *N*-acetylglucosamine derivatives with triethyloxonium fluoroborate,[20] methyl perchlorate,[21] methyl iodide,[21a] or benzyl trichloroacetimidate[22] have been described. These are indeed useful intermediates to remove the acetamido group of *N*-acetylglucosamine with mild conditions.[20−22] In con-

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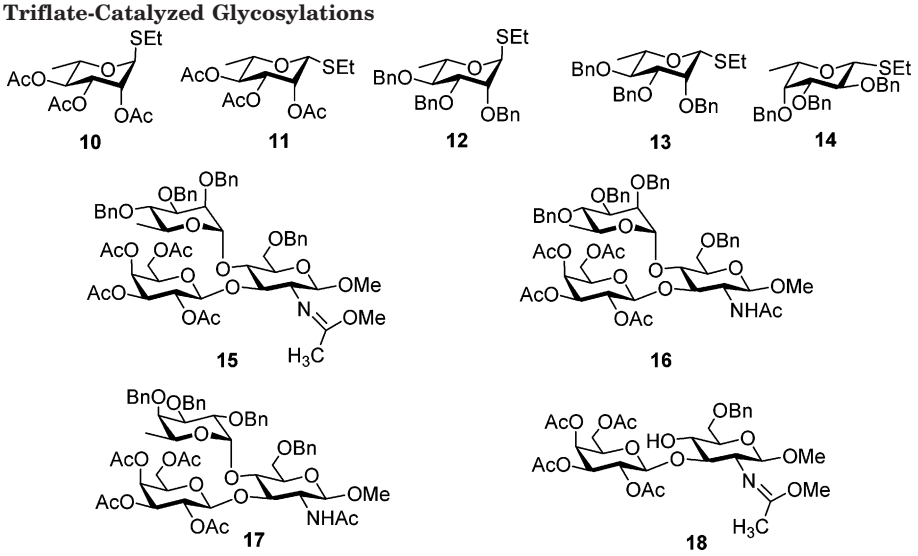
TABLE 1. Methyl Triflate-Catalyzed Glycosylations



entry	donor (M)	acceptor (M)	MeOTf (M)	time (h)	imidate (yield[a])	trisaccharide (yield[a])	recovered acceptor (yield[a])
1	**10** (0.05)	**4** (0.02)	0.15	48	*b*	*b*	*c*
2	**11** (0.05)	**4** (0.02)	0.10−0.15	42	*b*	**9** (20%)	*c*
3	**12** (0.05)	**4** (0.02)	0.10	18	**15** (58%)	**16** (24%)	*b*
4	**13** (0.05)	**4** (0.02)	0.10	18[d]	**15** (49%)	**16** (36%)	*b*
5	**14** (0.05)	**4** (0.02)	0.10	1	*b*	**17** (77%)	*b*
6	**14** (0.09)	**4** (0.03)	0.15	6−24	*b*	**17** (71%)	*b*
7	none	**4** (0.02)	0.10	18	**18** (47%)	*e*	48%
8	none	**4** (0.02)	0.50	18	**18** (76%)	*e*	*b*
9	**13** (0.05)	**18** (0.02)	0.10	1	**15** (85%)	*e*	*b*

[a] Isolated yields. [b] Note detected. [c] Not recovered. [d] After 1 h, no more acceptor **4** was detected by TLC. [e] Not applicable.

trast, the formation of such methyl imidates during a methyl triflate promoted *O*-glycosylation of *N*-acetylglucosamine acceptors has, to our knowledge, not been reported. In fact, only one similar methyl imidate derivative of sialic acid has been reported by Allen and Danishefsky[23] while attempting a difficult [3 + 3] coupling that involved a trisaccharide acceptor carrying an *N*-acetylated sialic acid residue.

Interestingly, no such imidate was isolated or even detected by TLC when the β-thioethyl fucopyranoside[24] **14** was reacted with acceptor **4** (Table 1, entries 5 and 6) and after only 1 h of reaction (Table 1, entry 5) the trisaccharide **17** was isolated in 77% yield. Increasing the concentration of MeOTf and maintaining stirring at room temperature for either 6 or 24 h (Table 1, entry 6) did not lead to the formation of any detectable trisaccharide methyl imidate but only to the isolation of trisaccharide **17**. In contrast, disaccharide acceptor **4** treated with the same concentration of MeOTf in the absence of glycosyl donor (Table 1, entry 7) gave the disaccharide methyl imidate **18** in 47% yield while unreacted acceptor was also recovered in 48% yield. These observations prompted us to investigate if this reaction could be used as a temporary protection of the *N*-acetyl group in acceptor **4** and thus increase reactivity at O-4 of the glucosamine. Indeed, acceptor **4** was converted to the methyl imidate **18** in good yields by increasing the MeOTf concentration (Table 1, entry 8). In turn, coupling of methyl imidate **18** with donor **13** gave trisaccharide methyl imidate **15** in 85% isolated yield after only 1 h of reaction (Table 1, entry 9). Finally, we established simple yet efficient reaction conditions to convert the methyl imidate trisaccharide **15** to trisaccharide **16** in 91% yield using 23% AcOH in Ac_2O at 55 °C. Additional work on the applicability of this strategy with various combinations of donors, acceptors, and glycosylation methods is beyond the scope of this paper but ongoing in our laboratory.

Since the glycosylations with peracetylated glycosyl donors gave only mediocre results, we report here the results that we obtained when we investigated a synthetic strategy established for the glycosylation of the poorly reactive 8-OH group in sialic acid-containing glycosyl[25] acceptors and later applied to that of the 4-OH group of an *N*-acetylated glucosamine acceptor.[4c] In these syntheses the C-5 and C-2 amino groups in the sialic acid and glucosamine residues, respectively, were bis-acetylated prior to glycosylation. As communicated previously[7] the known[26] disaccharide **19** was easily converted in two steps to the desired glycosyl acceptor **21** (Scheme 2). Glycosylation of **21** with trichloroacetimidate donor **5** was conducted at low temperature with 0.15 equiv of TESOTf and gave trisaccharide **22** (91%). In contrast, coupling of the mannosyl donor **6** with disaccharide **21** did not

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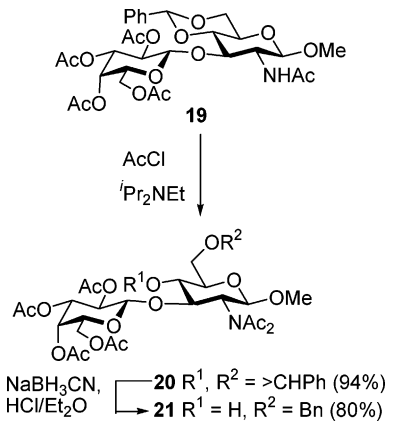
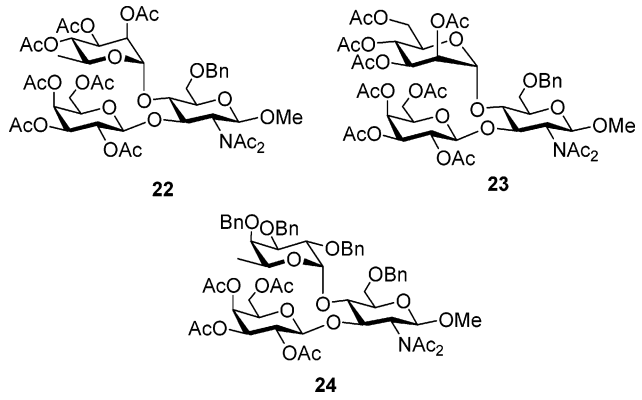
SCHEME 2

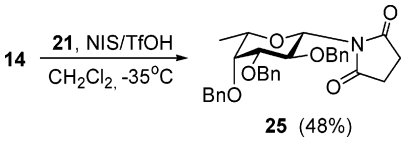


proceed when only 0.15 equiv of TESOTf was added, once again further supporting that mannosyl glycosyl donors are less reactive than the analogous rhamnosyl donors. However, increasing the concentration of TESOTf to 0.5 equiv led to the efficient coupling of donor **6** with acceptor **21** and gave mannosylated trisaccharide **23** in excellent yield (95%).



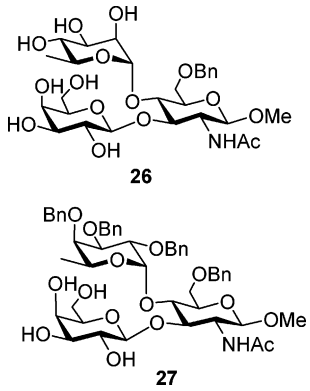
We first attempted to couple disaccharide **21** and fucosyl donor **14** using very mild activation conditions: *N*-iodosuccinimide and trifluoromethanesulfonic acid (TfOH) at low temperature. However, under these conditions donor **14** was promptly converted to the *N*-succinimide glycoside **25** and the unreacted acceptor **21** was recovered (Scheme 3). It is likely that formation of **25**

SCHEME 3



resulted from the greater nucleophilicity of the succinimide nitrogen over that of the 4-OH in glycosyl acceptor **21** and, in fact, **25** was formed readily at low temperature in the presence of aglycon **21** and before the addition of TfOH. Similar formations of *N*-succinimide glycosides[27] have been reported when using highly reactive glycosyl donors. Upon activation with MeOTf, coupling of the donor **14** with acceptor **21** gave trisaccharide **24** in 82% yield only modestly improving the yield over the fucosylation of *N*-acetylated acceptor **4** (Table 1, entries 5 and 6). However, when using the trichloroacetimidates **5** and **6**, these results show that bis-acetylation of the nitrogen in the glucosamine unit led to efficient glycosylations at OH-4 while preventing the formation of glycosyl imidates.

Since the D-mannosylated analogue **23** is not relevant to our overall research program it was not further deprotected. However, since our research program requires the synthesis of the Le^a trisaccharide **2** as well as that of the rhamnosylated analogue **3**, trisaccharides **9** or **22** and **24** were deprotected. Zemplèn deacetylation of **9** or **22** gave quantitatively in both cases the benzylated trisaccharide **26** which was easily converted to



rhamnosylated analogue **3**. Similarly, Zemplèn deacetylation of **24** gave quantitative yield of the benzylated trisaccharide **27**, which was converted to the trisaccharide Le^a (**2**) by hydrogenolysis (H_2-Pd/C). We therefore report here a new synthesis of the Le^a trisaccharide **2** that is overall simpler than that described previously by Yan and Kahne.[5]

Conclusions

Following our initial observation,[7] we have now clearly established that the formation of glycosyl imidates could be the predominant reaction during the glycosylation of *N*-acetylglucosamine glycosyl acceptors. Depending on their stability and the reaction conditions, these imidates formed kinetically may or may not rearrange to the desired thermodynamically favored glycosides. The formation of such imidates provides an explanation for the difficulties encountered when attempting to glycosylate poorly reactive hydroxyl groups in acceptors containing *N*-acetylglucosamine residues. Depending on the nature of the glycosyl donor we have shown that the glycosyation of such acceptors could be difficult or even impossible as was also observed but not explained recently by Lucas et al.[28] In contrast, coupling of such acceptor with thioglycosides activated by methyl triflate may lead to the formation of the *N*-methyl imidate trisaccharide. In fact, protection of the amido function through *N*-methyl imidate formation prior to glycosylation is currently under further investigation in our group since it led in

(27) (a) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (b) Oscarson, S.; Tedebark, U.; Turek, D. *Carbohydr. Res.* **1997**, *299*, 159−164. (c) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 1234−1238.

(28) Lucas, R.; Hamza, D.; Lubineau, A.; Bonnaffé, D. *Eur. J. Org. Chem.* **2004**, 2107−2117.

the present study to a highly reactive glycosyl acceptor and excellent yields of the protected rhamnosylated trisaccharide **15** that was easily converted to trisaccharide **16**. Similarly to the formation of the methyl imidate, we have also prepared the corresponding bis-*N*-acetylated acceptor that was glycosylated with trichloroacetimidate glycosyl donors. This alternative strategy gave, as expected,[25,4c] the desired trisaccharides in excellent yields and we have efficiently prepared the Le^a trisaccharide **2** as well as analogue **3**. Thus these results shed some light on the particular behavior of *N*-acetylglucosamine and its derivatives in synthetic carbohydrate chemistry.

Experimental Section

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranosyl)-2-*N*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)acetimido-6-*O*-benzyl-2-deoxy-*β*-D-glucopyranoside (7). The disaccharide glycosyl acceptor **4** (50 mg, 76 μmol) and peracetylated α-L-rhamnopyranosyl trichloroacetimidate[8] **5** (66 mg, 150 μmol, 2 equiv) were dissolved in anhyd CH_2Cl_2 (3.3 mL). Powdered activated 4 Å molecular sieves (300 mg) were added and the mixture was stirred 5 h at room temperature and then cooled to −78 °C. A freshly prepared 0.37 M solution of TESOTf in anhyd CH_2Cl_2 (21 μL, 7.6 μmol, 0.1 equiv) was added and the temperature was allowed to reach room temperature over 2 h. The reaction was quenched with NEt_3 (10 μL) and the reaction mixture diluted with CH_2Cl_2 (50 mL) was filtered through Celite. The solids were washed with CH_2Cl_2 (3 × 10 mL) and the combined filtrate and washings was washed sequentially with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The aqueous phases were re-extracted with CH_2Cl_2 (30 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated. A quick column chromatography (98:2 CH_2Cl_2−MeOH) of the residue on silica gel (70−230 mesh) gave imidate **7** pure as a colorless glass (30 mg, 42%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.33 (m, 5H, Ar); 6.08 (d, 1H, J = 1.7 Hz, H-1″); 5.48 (dd, 1H, J = 3.3, 1.9 Hz, H-2″); 5.35 (bd, 1H, J = 3.4 Hz, H-4′); 5.26 (dd, J = 10.2, 3.5 Hz, H-3″); 5.19 (dd, 1H, J = 10.2, 8.4 Hz, H-2′); 5.14 (m, 1H, H-4″); 4.95 (dd, 1H, J = 10.4, 3.5 Hz, H-3′); 4.64, 4.60 (2d, 2H, J = 12.3 Hz, OCH_2Ph); 4.54 (d, 1H, J = 8.0 Hz, H-1′); 4.16 (d, 1H, J = 7.8 Hz, H-1); 4.11 (d, 2H, bd, J = 6.6 Hz, H-6a′, H-6b′); 4.02 (dd, 1H, J = 9.8, 6.2 Hz, H-5″); 3.98 (m, 1H, H-5′); 3.90 (s, 1H, OH); 3.89 (bs, 1H, H-6a); 3.69 (dd, 1H, J = 10.8, 6.0 Hz, H-6b); 3.56 (m, 2H, H-3, H-4); 3.47 (m, 4H, OCH_3, H-5); 3.25 (m, 1H, H-2); 2.20−1.77 (8 s, 8 × 3H, *N*-acetyl and *O*-acetyl); 1.23 (d, 3H, J = 6.0, H-6″). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 170.4, 170.1, 169.9, 169.3 (C=O); 161.6 (C=N); 138.5, 128.3, 127.6, 127.5 (Ar); 103.4 (C-1); 101.6 (C-1′); 92.1 (C-1″, $^1J_{C-H}$= 177 Hz); 88.1 (C-3); 75.6 (C-5); 73.6 (OCH_2Ph); 71.0, 70.9 (C-3′, C-5′); 70.7 (C-4″); 69.8 (C-6); 69.0, 68.8, 68.6 (C-3″, C-2′, C-5″); 68.2 (C-2″); 66.9 (C-4′); 63.8 (C-2); 61.6 (C-6′); 57.3 (OCH_3); 21.0, 20.9, 20.8, 20.7, 20.6, 20.5 (*O*-COCH_3); 17.7 (C-6″); 15.8 (*N*-acetimidate CH_3) HRCIMS calcd for $C_{42}H_{58}NO_{22}$ $[M + H]^+$ 928.3450, found 928.3427.

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-*β*-D-galactopyranosyl)-2-*N*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)acetimido-6-*O*-benzyl-2-deoxy-*β*-D-glucopyranoside (8). The disaccharide glycosyl acceptor **4** (25 mg, 30 μmol) and peracetylated α-D-mannopyranosyl trichloroacetimidate[9] **6** (74 mg, 150 μmol, 5 equiv) were dissolved in anhyd CH_2Cl_2 (1 mL). Powdered activated 4 Å molecular sieves (100 mg) were added and the mixture was stirred for 4 h at room temperature. A freshly prepared solution (0.37 M) of TESOTf in anhyd CH_2Cl_2 (41 μL, 15 μmol, 0.5 equiv) was added and the reaction was stirred for 18 h at room temperature. The reaction was then quenched with NEt_3 (10 μL) and workup was carried out as previously described for the synthesis of imidate **7**. The crude product was purified by flash chromatography (98:1 CH_2Cl_2−MeOH then 98:2 CH_2Cl_2−MeOH) to give imidate **8** (32.5 mg, 86%) pure as a colorless glass. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 5H, Ar); 6.44 (d, 1H, J = 1.7 Hz, H-1″); 5.39−5.36 (m, 3H, H-3′, H-4′, H-3″); 5.30 (bd, 1H, J = 1.0 Hz, H-2″); 5.21−5.11 (m, 2H, H-2′, H-5′); 4.76 (d, 1H, J = 7.8 Hz, H-1′); 4.63 (2d, 2H, J = 12.3 Hz, OCH_2Ph); 4.29 (dd, 1H, J = 12.9, 5.0 Hz, H-6a″); 4.19−4.08 (m, 6H, H-6b″, H-6a′, H-6b′, H-5″, H-4″, H-1); 3.9 (dd, 1H, J = 11.0, 1.6 Hz, H-6a); 3.67 (dd, 1H, J = 10.9, 5.9 Hz, H-6b); 3.57 (bs, 1H, OH); 3.54−3.46 (m, 3H, H-3, H-4, H-5); 3.44 (s, 3H, OCH_3); 3.26 (dd, 1H, J = 9.0, 7.7 Hz, H-2); 2.23−1.94 (9s, 9 × 3H, *N*-acetyl and *O*-acetyl). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2, 169.9, 169.9, 169.6, 169.5 (C=O); 161.4 (C=N); 138.4, 128.3, 127.5, 127.5 (Ar); 103.3 (C-1); 100.8 (C-1′); 90.9 (C-1″, $^1J_{C-H}$= 178 Hz); 86.8 (C-3); 75.9 (C-5); 73.6 (OCH_2Ph); 70.8, 70.6, 70.5, 69.0, 68.6, 68.0, 67.3, 65.9 (C-4, C-2′, C-3′, C-4′, C-5′, C-2″, C-3″, C-4″, C-5″); 69.8 (C-6); 64.0 (C-2); 62.2 (C-6″); 61.2 (C-6′); 57.1 (OCH_3); 21.1, 20.8, 20.8, 20.6, 20.5, 20.5 (*O*-COCH_3); 16.3 (*N*-acetimidate CH_3). HRESIMS calcd for $C_{44}H_{60}NO_{24}$ $[M + H]^+$ 986.3505, found 986.3553.

Methyl 2-Acetamido-6-*O*-benzyl-3-*O*-(*β*-D-tetra-*O*-acetyl-*β*-D-galactopyranosyl)-4-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-2-deoxy-*β*-D-glucopyranoside (9). **Method A.** Imidate **7** (20 mg, 22 μmol) was dissolved in anhyd CH_2Cl_2 (2 mL). Powdered activated 4 Å molecular sieves (200 mg) were added and the mixture was stirred for 3 h at room temperature. A freshly prepared TESOTf solution (0.37 M) in anhyd CH_2Cl_2 (29 μL, 11 μmol, 0.5 equiv) was added at room temperature and the mixture was stirred for 30 min. TLC (15:1 $CHCl_3$−MeOH) showed the disappearance of **7** and the formation of a new compound. The reaction was quenched with NEt_3 (10 μL) and worked up as described above for the synthesis of compound **7**. Column chromatography (98:2, CH_2Cl_2−MeOH) gave the pure trisaccharide **9** as a colorless glass (10 mg, 50%).

Method B. The glycosyl acceptor **4** (100 mg, 150 mmol) and peracetylated α-L-rhamnopyranosyl trichloroacetimidate[8] **5** (330 mg, 750 μmol, 5 equiv) were dissolved in anhyd CH_2Cl_2 (2.5 mL). Powdered activated 4 Å molecular sieves were added and the mixture was stirred for 5 h at room temperature. A freshly prepared solution (0.37 M) of TESOTf in anhyd CH_2Cl_2 (216 μL, 75 μmol, 0.5 equiv) was added and the mixture was stirred overnight at room temperature. The reaction was quenched with NEt_3 (20 μL) and worked up as described above for the synthesis of compound **7**. Chromatography as described above in method A gave the trisaccharide **9** pure as a colorless glass (74 mg, 52%).

Method C. The glycosyl acceptor **4** (60 mg, 90 μmol) and peracetylated α-L-rhamnopyranosyl trichloroacetimidate[8] **5** (79 mg, 180 μmol, 2 equiv) were dissolved in anhyd CH_2Cl_2 (4 mL). Powdered activated 4 Å molecular sieves (400 mg) were added, the mixture was stirred at room temperature for 3 h and then cooled to −78 °C. A freshly prepared solution (0.37 M) of TESOTf in anhyd CH_2Cl_2 (25.2 μL, 9 μmol, 0.1 equiv) was added and the temperature was allowed reach room temperature over 2 h. TLC (98:2 CH_2Cl_2−MeOH) showed the formation of imidate **7**. More TESOTf solution (0.37 M) in anhyd CH_2Cl_2 (125 μL, 45 μmol, 0.5 equiv) was added at room temperature and the mixture was stirred for 1 h until TLC showed complete conversion of imidate **7**. The reaction was quenched with NEt_3 (10 μL) and worked up as described above for the synthesis of compound **7**. Chromatography as described above in method A gave the trisaccharide **9** pure as a colorless glass (46 mg, 55%).

Method D. The glycosyl acceptor **4** (25 mg, 38 μmol) and ethyl 2,3,4-tri-*O*-acetyl-1-thio-*β*-L-rhamnopyranoside **11** (38 mg, 114 μmol, 3 equiv)[17] were dissolved in anhyd Et_2O (2 mL). Powdered activated 4 Å molecular sieves (200 mg) were added and the mixture was stirred at room temperature for 3 h. MeOTf was added (22 μL, 198 μmol, 5 equiv, 0.1 M) and the mixture was stirred at room temperature for 18 h. More MeOTf was added (13 μL, 114 mmol, 3 equiv, total 0.15 M) and the mixture was stirred at room temperature for another 24 h. The reaction was quenched with Et_3N (50 μL) and worked up as described above for the synthesis of compound **7**.

Chromatography as described above in method A gave the trisaccharide **9** pure as a colorless glass (7 mg, 20%).

Analytical Data for 9. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (m, 5H, Ar); 5.84 (d, 1H, J = 7.9 Hz, NH); 5.40 (d, 1H, J = 3.0 Hz, H-4′); 5.19−5.07 (m, 6H, H-1′, H-2′, H-3′, H-2″, H-3″, H-4″); 4.87 (bs, 1H, H-1″); 4.62 (d, 1H, J = 4.2 Hz, H-1); 4.57, 4.54 (2d, 2H, J = 12.3 Hz, OC*H*$_2$Ph); 4.30 (m, 1H, H-5″); 4.22 (dd, 1H, J = 10.9, 8.2 Hz, H-6a′); 4.17 (t, 1H, J = 6.5 Hz, H-5); 4.09 (dd, 10.9, 5.9 Hz, H-6b′); 3.99 (m, 2H, H-3, H-4); 3.81 (m, 1H, H-2); 3.71 (m, 3H, H-5′, H-6a, H-6b); 3.39 (s, 3H, OCH_3); 2.11−1.97 (8s, 8 × 3H, *N*-acetyl and *O*-acetyl); 1.28 (d, 3H, J = 6.1 Hz, H-6″). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2, 170.0, 170.0, 169.3 (C=O); 138.0, 128.3, 127.6 (Ar); 99.7 (C-1, $^1J_{C-H}$= 168 Hz); 99.0 (C-1′); 96.4 (C-1″, $^1J_{C-H}$= 172 Hz); 78.0 (C-3 or C-4); 73.4 (C-5′); 73.0 (O*C*H$_2$Ph); 72.8 (C-5); 70.8, 70.6, 70.0, 69.1, 68.3 (C-2′, C-2″, C-3″, C-4″, C-3′); 68.8 (C-6); 67.0 (C-4′); 66.7 (C-5″); 60.5 (C-6′); 55.6 (OCH_3); 54.5 (C-2); 23.3, 20.8, 20.7, 20.6, 20.5 (*O*- and *N*-CO*C*H$_3$); 17.2 (C-6″). HRCIMS calcd for $C_{42}H_{58}NO_{22}$ $[M + H]^+$ 928.3450, found 928.3513.

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-6-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-2-*N*-methylacetimido-2-deoxy-α-D-glucopyranoside (15) and Methyl 2-Acetamido-3-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-6-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl)-2-deoxy-α-D-glucopyranoside (16). **Method A.** The glycosyl acceptor **4** (25 mg, 38 μmol) and ethyl 2,3,4-tri-*O*-benzyl-1-thio-α-L-rhamnopyranoside **12** (55 mg, 114 μmol)[18] were dissolved in anhyd Et_2O (2 mL). Powdered activated 4 Å molecular sieves (200 mg) were added and the mixture was stirred for 3 h at room temperature. MeOTf was added (22 μL, 198 μmol, 5 equiv, 0.1 M) and the mixture was stirred for 18 h at room temperature. The reaction was quenched with Et_3N (40 μL) and worked up as described above for the synthesis of compound **7**. Chromatography (CH_2Cl_2−MeOH 100:1 then 98:2) of the dry residue first gave the methyl imidate trisaccharide **15** pure as a colorless glass (24 mg, 58%) and then the trisaccharide **16** pure as a colorless glass (10 mg, 24%).

Method B. The glycosyl acceptor **4** (22 mg, 34 μmol) and ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-rhamnopyranoside **13** (55 mg, 11 μmol, 3 equiv)[19] were dissolved in anhyd Et_2O (2 mL). Powdered activated 4 Å molecular sieves (200 mg) were added and the mixture was stirred for 3 h at room temperature. MeOTf was added (22 μL, 198 μmol, 5.8 equiv, 0.1 M) and the mixture was stirred at room temperature for 18 h. The reaction was then quenched with Et_3N (40 μL) and worked up as described above for the synthesis of compound **7**. Chromatography (CH_2Cl_2−MeOH 100:1 then 98:2) of the dry residue first gave the methyl imidate trisaccharide **15** pure as a colorless glass (18 mg, 49%) and then the trisaccharide **16** pure as a colorless glass (13 mg, 36%).

Glycosylation of Methyl Imidate Acceptor 18 To Give Trisaccharide 15. Methyl imidate **18** (32 mg, 47 μmol) and ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-rhamnopyranoside[19] **13** (53 mg, 110 μmol) were dissolved in anhyd Et_2O (2 mL). Powdered activated 4 Å molecular sieves (200 mg) were added and the mixture was stirred for 3 h at room temperature. MeOTf was added (22 μL, 198 μmol, 0.1 M) and the mixture was stirred for 1 h at room temperature. The reaction was quenched with Et_3N (40 μL) and worked up as described above for the synthesis of compound **7**. Chromatography (CH_2Cl_2−MeOH 100:1 then 98:2) of the dry residue gave the methyl imidate trisaccharide **15** pure as a colorless glass (44 mg, 85%).

Conversion of Methyl Imidate 15 to the *N*-Acetylated Trisaccharide 16. The imidate **15** (10 mg) was dissolved in a mixture of Ac_2O (720 μL) and AcOH (220 μL) and the solution was stirred at 55 °C for 3 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (3 × 50 mL) and water (50 mL). The aqueous washings were re-extracted with CH_2Cl_2 (30 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (CH_2Cl_2−MeOH 98:2) of the dry residue gave the trisaccharide **16** pure as a colorless glass (9 mg, 91%).

Analytical Data for Compound 15. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 23 H, Ar); 5.28 (d, 1H, J = 2.0 Hz, H-4′); 5.09 (dd, 1H, J = 10.1, 8.5 Hz, H-2′); 5.00 (m, 3H, H-1′, H-1″, OC*H*$_2$Ph); 4.79 (dd, 1H, J = 10.3, 6.9 Hz, H-3′); 4.69−4.56 (m, 7H, OC*H*$_2$Ph); 4.47 (m, 1H, H-5″); 4.33 (m, 1H, H-6a); 4.11 (m, 2H, H-6b, H-1); 3.90−3.73 (m, 5H, H-3, H-4, H-5, H-5′, H-2″); 3.67−3.59 (m, 2H, H-4″, H-6a′), 3.66 (s, 3H, N=C−OC*H*$_3$); 3.50 (m, H-6b′); 3.42 (s, 3H, OC*H*$_3$); 3.38 (m, 1H, H-3″); 3.29 (dd, 1H, J = 9.3, 8.5 Hz, H-2); 2.04, 1.99, 1.91, 1.91 1.55 (5s, 5 × 3H, *N*-acetyl and *O*-acetyl); 1.39 (d, 1H, J = 6.3 Hz, H-6″). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.2, 170.6, 170.4, 170.1, 168.9 (C=O); 165.1 (C=N); 139.2, 138.7, 138.6, 138.1 (Ar); 128.3, 128.3, 128.1, 127.7, 127.5, 127.3, 126.9, 126.1 (Ar); 103.9 (C-1, $^1J_{C-H}$ = 159 Hz); 100.3 (C-1′); 98.7 (C-1″, $^1J_{C-H}$ = 169 Hz); 80.7 (C-4″); 80.4, 80.1, 75.7, 74.1, 70.2 (C-3, C-4, C-5, C-5′, C-2″); 76.0 (C-3″); 75.2, 73.6, 72.4, 72.3 (O*C*H$_2$PH); 71.7 (C-3′); 68.8 (C-6′); 68.6 (C-2′); 68.2 (C-5″); 66.7 (C-4′); 65.8 (C-2); 61.0 (C-6); 57.1 (O*C*H$_3$); 52.5 (N=C−O*C*H$_3$); 20.7, 20.7, 20.5, 19.8 (O−CO*C*H$_3$); 17.8 (C-6″); 16.6 (N=C-*C*H$_3$). HRESIMS calcd for $C_{58}H_{71}NO_{19}Na$ $[M + Na]^+$ 1108.4518, found 1108.4473.

Analytical Data for Compound 16. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 25H, Ar); 5.74 (d, 1H, J = 8.5 Hz, NH); 5.36 (d, 1H, J = 3.0 Hz, H-4′); 5.15 (dd, 1H, J = 10.5, 8.0 Hz, H-2′); 4.99 (dd, 1H, J = 10.5, 3.5 Hz, H-3′); 4.95 (d, 1H, J = 11.0 Hz, OC*H*$_2$Ph); 4.90 (d, 1H, J = 1.5 Hz, H-1″); 4.79 (d, 1H, J = 8.0 Hz, H-1′); 4.69−4.56 (m, 7 H, OC*H*$_2$Ph); 4.52 (d, 1H, J = 4.3 Hz, H-1); 4.14 (m, 2H, H-6a, H-6b); 3.96−3.88 (m, 4 H, H-4, H-5, H-5′, H-5″); 3.79 (m, 1H, H-2); 3.76−3.58 (m, 6H, H-3, H-6a′, H-6b′, H-2″, H-3″, H-4″); 3.39 (s, 3H, OCH_3); 2.05−1.85 (5s, 5 × 3H, *N*-acetyl and *O*-acetyl); 1.33 (d, 1H, J = 6.2 Hz, H-6″). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.3, 169.6 (C=O); 128.4, 128.3, 127.9, 127.9, 127.7, 127.6, 127.5 (Ar); 100.3 (C-1, $^1J_{C-H}$ = 166 Hz); 99.4 (C-1′); 97.7 (C-1″, $^1J_{C-H}$ = 168 Hz); 79.9 (C-4″); 79.1 (C-3); 75.5, 72.7, 70.7, 68.8 (C-4, C-5, C-5′, C-5″); 75.3, 73.4, 72.7, 71.9 (O*C*H$_2$Ph); 74.7, 74.7 (C-2″, C-3″); 70.9 (C-3′); 69.7 (C-6′); 68.4 (C-2′); 66.9 (C-4′); 60.9 (C-6); 56.0 (O*C*H$_3$); 51.6 (C-2); 23.4, 20.8, 20.6, 20.6, 20.4 (*N*-CO*C*H$_3$ and *O*-CO*C*H$_3$); 17.9 (C-6″). HRESIMS calcd for $C_{57}H_{73}N_2O_{19}$ $[M + NH_4]^+$ 1089.4808, found 1089.4833.

Methyl 2-Acetamido-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-β-D-glucopyranoside (17). A solution of glycosyl acceptor **4** (25 mg, 38 μmol) and glycosyl donor ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside[24] **14** (55 mg, 114 μmol, 3 equiv) in anhyd Et_2O (2 mL) containing powdered activated 4 Å molecular sieves (200 mg) was stirred for 3 h at room temperature. MeOTf was added (22 μL, 198 μmol, 5 equiv, 0.1 M) and the reaction mixture was stirred for 1 h at room temperature. The reaction was quenched with Et_3N (40 μL) and worked up as described above for the synthesis of compound **7**. The dry residue was submitted to chromatography with $CHCl_3$−MeOH (30:1 then 25:1) and gave trisaccharide **17** pure as a colorless glass (31 mg, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40−7.25 (m, 20 H, Ar); 6.67 (d, 1H, J = 9.3 Hz, *N*H); 5.39 (d, 1H, J = 3.4 Hz, H-4′); 5.25 (d, 1H, J = 3.9 Hz, H-1″); 5.15 (dd, 1H, J = 10.5, 8.0 Hz, H-2′); 5.02−4.66 (m, 8H, H-1′, H-3′, OC*H*$_2$Ph); 4.55 (d, 1H, J = 2.7 Hz, H-1); 4.59−4.49 (2d, 2H, J = 11.9 Hz, OC*H*$_2$Ph); 4.14 (m, 3H, H-4, H-5, H-2″); 4.08 (m, 2H, H-6a′, H-6b′); 4.01 (m, 2H, H-5″, H-2); 3.97 (m, 1H, H-6a); 3.89 (m, 2H, H-3, H-5′); 3.83 (dd, 1H, J = 10.0, 2.7 Hz, H-3″); 3.71 (d, 1H, J = 2.0 Hz, H-4″); 3.67 (dd, 1H, J = 10.3, 4.7 Hz, H-6b); 3.41 (s, 3H, OCH_3); 2.07, 2.01, 1.99, 1.97 (4s, 4 × 3H, *O*-acetyl); 1.60 (s, 3H, *N*-acetyl); 1.18 (d, 3H, J = 6.5 Hz, H-6″). ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 169.7, 169.4 (C=O); 138.6, 138.4, 137.9,129.3−127.2 (Ar); 100.8 (C-1, $^1J_{C-H}$= 167 Hz); 99.5 (C-1′); 93.1 (C-1″); 79.9 (C-3″); 77.1 (C-4″); 70.6, 70.8 (C-3′, C-5′); 76.2, 70.8 (C-2″, C-5); 75.0 (C-3); 69.4, 66.9, 49.8 (C-2, C-4, C-5″); 68.3 (C-2′); 66.9 (C-4′); 74.8, 73.8, 73.1, 72.9 (O*C*H$_2$Ph); 69.8 (C-6); 60.6 (C-6′); 55.8 (OCH_3); 22.8, 20.8,

20.6, 20.6 (*O*- and *N*-CO*C*H$_3$); 16.7 (C-6″). HRESIMS calcd for $C_{57}H_{70}NO_{19}$ [M + H]$^+$ 1072.4542, found 1072.4546.

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl)-6-*O*-benzyl-2-*N*-methylacetimido-2-deoxy-β-D-glucopyranoside (18). A solution of disaccharide glycosyl acceptor **4** (75 mg, 120 μmol) in anhyd Et$_2$O (6 mL) containing 4 Å powdered activated molecular sieves (300 mg) was stirred for 3 h at room temperature. MeOTf (330 μL, 3 mmol, 0.5 M) was added and the mixture was stirred for 18 h at room temperature. The reaction was quenched with Et$_3$N (420 μL) and worked up as described above for the synthesis of compound **7**. Chromatography (CH$_2$Cl$_2$−MeOH 98:2) of the dry residue gave compound **18** pure as a colorless glass (57 mg, 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (m, 6H, Ar); 5.36 (d, 1H, *J* = 2.74, H-4′); 5.19 (dd, 1H, *J* = 10.2, 8.2 Hz, H-2′); 4.96 (dd, 1H, *J* = 10.4, 3.2 Hz, H-3′); 4.64 (2d, 2H, *J* = 12.3 Hz, OC*H*$_2$Ph); 4.58 (d, 1H, *J* = 8.2 Hz, H-1′); 4.20 (d, 1H, *J* = 7.7 Hz, H-1); 4.12 (m, 2H, H-6a′, H-6b′); 3.99 (m, 1H, H-5′); 3.93 (br s, 1H, O*H*); 3.91 (br s, 1H, H-6a); 3.69 (m, 1H, H-6b); 3.61 (s, 3H, N=C−C*H*$_3$); 3.55 (m, 2H, H-3, H-4); 3.46 (s, 3H, OC*H*$_3$); 3.45 (m, 1H, H-5); 3.25 (t, 1H, *J* = 7.8 Hz, H-2); 2.15, 2.02, 2.00, 1.99, 1.87 (*N*-acetyl and *O*-acetyl). ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 185.7, 175.7, 174.1, 171.4 (C=O); 164.9 (C=N); 152.1, 141.8, 138.5, 137.8 (Ar); 128.3, 127.6, 127.5 (Ar); 104.0 (C-1); 102.1 (C-1′); 89.0, 75.7, 68.8 (C-3, C-4, C-5); 73.6 (O*C*H$_2$Ph); 71.1 (C-3′); 70.9 (C-5′); 70.0 (C-6); 68.6 (C-2′); 66.8 (C-4′); 63.7 (C-2); 61.5 (C-6′); 57.2 (O*C*H$_3$); 52.4 (N=C−O*C*H$_3$); 20.6, 20.5, 20.5, 20.2 (O−CO*C*H$_3$); 16.1 (N=C−*C*H$_3$). HRESIMS calcd for $C_{31}H_{44}NO_{15}$ [M + H]$^+$ 670.2711, found 670.2731.

Methyl 2-(*N*-Acetylacetamido)-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-4,6-*O*-benzylidene-2-deoxy-β-D-glucopyranoside (20). *N*,*N*-Diisopropylethylamine (134 μL, 77 μmol, 10 equiv) and acetyl chloride (279 μL, 3.85 mmol, 50 equiv) were added at room temperature to a solution of methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranoside[26] **19** (50 mg, 77 μmol) in anhyd CH$_2$Cl$_2$ (5 mL). The reaction mixture was stirred overnight at room temperature, diluted with CH$_2$Cl$_2$ (50 mL), and washed sequentially with saturated NaHCO$_3$ (30 mL) and brine (30 mL). The aqueous phases were re-extracted with CH$_2$Cl$_2$ (30 mL) and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated. Chromatography (EtOAc−hexane 40:60) gave compound **20** as a colorless glass (50 mg, 94%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48−7.37 (m, 5H, Ar); 5.53 (s, 1H, >C*H*Ph); 5.25 (d, 1H, *J* = 3.4 Hz, H-4′); 5.12 (dd, 1H, *J* = 10.4, 8.2 Hz, H-2′); 5.11 (d, 1H, *J* = 7.8 Hz, H-1); 4.88 (dd, 1H, *J* = 10.3, 3.5 Hz, H-3′); 4.76 (dd, 1H, *J* = 9.5, 8.4 Hz, H-3); 4.54 (d, 1H, *J* = 8.1 Hz, H-1′); 4.35 (dd, 1H, *J* = 10.5, 4.9 Hz, H-6a′); 4.01 (dd, 1H, *J* = 10.9, 8.6 Hz, H-6a); 3.87 (dd, 1H, *J* = 10.9, 8.7 Hz, H-6b′); 3.81−3.70 (m, 3H, H-2, H-4, H-6b); 3.59 (m, 1H, H-5′); 3.52 (m, 1H, H-5); 3.46 (s, 3H, OCH$_3$); 2.48−1.91 (6s, 6 × 3H, *N*-acetyl and *O*-acetyl). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 174.9, 174.7, 170.2, 170.1, 169.2 (C=O); 136.9, 129.3, 128.4, 126.0 (Ar); 101.6 (>*C*HPh); 100.8 (C-1′); 100.4 (C-1″); 81.4 (C-4); 77.4 (C-3); 71.1 (C-3′); 70.4 (C-5); 69.2 (C-2′); 68.8 (C-6′); 66.6 (C-4′); 65.4 (C-5′); 63.3 (C-2); 60.5 (C-6); 57.5 (OCH$_3$); 28.3, 25.3, 20.7, 20.6, 20.5 (*O*- and *N*-CO*C*H$_3$). HRCIMS calcd for $C_{32}H_{42}NO_{16}$ [M + H]$^+$ 696.2504, found 696.2517.

Methyl 2-(*N*-Acetylacetamido)-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (21). Sodium cyanoborohydride (37 mg, 590 μmol, 8 equiv) was added to a solution of disaccharide **20** (50 mg, 72 μmol) in anhyd THF (2 mL) containing powdered activated 4 Å molecular sieves (50 mg) and the mixture was cooled to 0 °C. A 2 M solution of HCl in Et$_2$O (650 μL) was added at 0 °C over ∼30 min and stirring was maintained at 0 °C for an additional 30 min. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL) and washed sequentially with 0.5 M HCl (30 mL), saturated aqueous NaHCO$_3$ (30 mL), and brine (30 mL). The aqueous phases were re-extracted with CH$_2$Cl$_2$ (30 mL) and the combined organic layers were dried (Na$_2$SO$_4$) and concentrated. Chromatography (EtOAc−hexane 4:6) gave acceptor **21** as a colorless glass (40 mg, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35−7.26 (m, 5H, Ar); 5.36 (d, 1H, *J* = 3.3 Hz, H-4′); 5.24 (dd, 1H, *J* = 10.4, 8.1 Hz, H-2′); 5.01 (d, 1H, *J* = 7.7 Hz, H-1); 4.94 (dd, 1H, *J* = 10.4, 3.4 Hz, H-3′); 4.63 (bs, 2H, OC*H*$_2$-Ph); 4.45 (m, 1H, H-3); 4.41 (d, 1H, *J* = 8.0 Hz, H-1′); 4.16−4.10 (m, 3H, OH, H-6a′, H-6b′); 4.00 (m, 1H, H-5′); 3.85 (dd, 1H, *J* = 10.9, 1.7 Hz, H-6a); 3.70 (dd, 1H, *J* = 10.9, 5.3 Hz, H-6b); 3.60 (m, 2H, H-2, H-4); 3.55 (m, 1H, H-5); 3.46 (s, 3H, OCH$_3$); 2.49−1.97 (6s, 6 × 3H, *N*-acetyl and *O*-acetyl).^{13}C NMR (100.6 MHz, CDCl$_3$) δ 175.2, 174.7, 170.4, 170.0, 169.9, 169.6 (C=O); 138.3, 128.3, 127.5 (Ar); 101.4 (C-1′); 99.6 (C-1); 83.9 (C-3); 75.0 (C-5); 73.5 (O*C*H$_2$Ph); 71.2, 71.0 (C-3′, C-5′); 70.3 (C-4); 69.3 (C-6); 68.7 (C-2′); 66.8 (C-4′); 62.8 (C-2); 61.7 (C-6′); 57.1 (OCH$_3$); 28.5, 25.4, 20.7, 20.6, 20.4, 20.4 (*O*- and *N*-CO*C*H$_3$). HRCIMS calcd for $C_{32}H_{47}N_2O_{16}$ [M + NH$_4$]$^+$ 715.2926, found 715.2998.

Methyl 2-(*N*-Acetylacetamido)-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-4-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (22). Acceptor **21** (300 mg, 430 μmol) and peracetylated α-L-rhamnopyranosyl trichloroacetimidate[8] **5** (930 mg, 2.14 mmol, 5 equiv) were dissolved in anhyd CH$_2$Cl$_2$ (7.5 mL) containing powdered activated 4 Å molecular sieves (600 mg) and the mixture was stirred for 5 h at room temperature. The reaction mixture was cooled to −78 °C and a freshly prepared solution (0.37 M) of TESOTf in anhyd CH$_2$Cl$_2$ (177 μL, 64.5 μmol, 0.15 equiv) was added. The reaction was then allowed to reach room temperature slowly (over 2 h) and was quenched with NEt$_3$ (20 μL). Workup was carried out as previously described for the synthesis of imidate **7** and chromatography (EtOAc−hexane 1:1) gave trisaccharide **22** as a colorless glass (378 mg, 91%). ^{1}H NMR (400 MHz, CDCl$_3$, 308 K) δ 7.32−7.25 (m, 5H, Ar); 5.35 (d, 1H, *J* = 3.2 Hz, H-4′); 5.24 (m, 2H, H-2″, H-3″); 5.16 (m, 2H, H-2′, H-4″); 5.02 (bs, 1H, H-1″); 4.90 (d, 1H, *J* = 7.7 Hz, H-1); 4.85 (dd, 1H, *J* = 10.4, 3.7 Hz, H-3′); 4.80 (t, 1H, *J* = 9.3 Hz, H-3); 4.62−4.53 (m, 3H, OC*H*$_2$Ph, H-5″); 4.42 (d, 1H, *J* = 8.1 Hz, H-1′); 4.37 (dd, 1H, *J* = 11.2, 7.1 Hz, H-6a′); 4.17 (dd, 1H, *J* = 11.2, 6.5 Hz, H-6b′); 3.90−3.70 (m, 4H, H-4, H-5′, H-6a, H-6b); 3.64 (dd, 1H, *J* = 9.8, 8.0 Hz, H-2); 3.50 (m, 1H, H-5); 3.42 (s, 3H, OCH$_3$); 2.40−1.92 (9s, 9 × 3H, *N*-acetyl and *O*-acetyl); 1.30 (d, 3H, *J* = 6.2 Hz, H-6″). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 170.1, 169.8 (C=O); 138.1, 128.3, 127.5 (Ar); 99.9 (C-1′); 99.8 (C-1, $^1J_{C-H}$ = 164 Hz); 97.4 (C-1″, $^1J_{C-H}$ = 172 Hz); 75.4 (C-3); 74.7 (C-5); 73.2 (O*C*H$_2$Ph); 71.6, 71.5 (C-4″, C-3′, C-5′); 70.4 (C-2″ or C-3″); 69.4 (C-2″ or C-3″); 69.0 (C-2′); 68.5 (C-6); 67.3 (C-4′); 66.6 (C-5″); 64.6 (C-2); 60.8 (C-6′); 57.1 (OCH$_3$); 20.8, 20.6, 20.6, 20.3 (*O*- and *N*- CO*C*H$_3$); 17.5 (C-6″). HRCIMS calcd for $C_{44}H_{63}NO_{23}$ [M + NH$_4$]$^+$ 987.3822, found 987.3848.

Methyl 2-(*N*-Acetylacetamido)-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (23). Acceptor **21** (20 mg, 29 μmol) and trichloroacetimidate[9] **6** (71 mg, 140 μmol, 5 equiv) were dissolved in anhyd CH$_2$Cl$_2$ (2 mL) containing powdered activated 4 Å molecular sieves (200 mg) and the mixture was stirred for 5 h at room temperature. The reaction mixture was cooled to −78 °C and a freshly prepared solution (0.37 M) of TESOTf in anhyd CH$_2$Cl$_2$ (44 μL, 16 μmol, 0.55 equiv) was added. The reaction was allowed to reach room temperature slowly over 2 h and was quenched with NEt$_3$ (10 μL). Workup was carried out as previously described for the synthesis of imidate **7** and chromatography (EtOAc−hexane 1:1) of the dry residue gave trisaccharide **23** pure as a colorless glass (28 mg, 95%). ^{1}H NMR (400 MHz, CDCl$_3$, 313 K) δ 7.34−7.26 (m, 5H, Ar); 5.43 (bs, 1H, H-2″); 5.29 (m, 4H, H-1″, H-3″, H-4″, H-4′); 5.19 (dd, 1H, *J* = 10.1, 8.2 Hz, H-2′); 4.95 (d, 1H, *J* = 7.7 Hz, H-1); 4.85 (m, 2H, H-3, H-3′); 4.67, 4.57 (2d, 2H, *J* = 12.2 Hz, OC*H*$_2$Ph); 4.37 (d, 1H, *J* = 8.0 Hz, H-1′); 4.26 (dd, 1H, *J* = 11.3, 7.2 Hz, H-6a or H-6a′); 4.18−3.95 (m, 4H, H-6a or H-6a′, H-6b, H-6b′, H-5″); 3.88−3.65 (m, 5H, H-4, H-5, H-5′, H-6a″, H-6b″); 3.60 (dd, 1H, *J* = 10.1, 8.0 Hz, H-2); 3.44 (s, 3H, OCH$_3$); 2.39 (bs, 6H, *N*-acetyl); 2.14−1.93 (8s, 8 × 3H,

O-acetyl). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 170.2, 169.9, 169.8 (C=O); 138.1, 128.4, 127.7, 127.5 (Ar); 100.2 (C-1, $^1J_{C-H}$= 165 Hz); 99.5 (C-1′); 99.3 (C-1″, $^1J_{C-H}$ = 176 Hz); 77.0, 74.3, 71.7 (C-4, C-5, C-5′); 76.2 (C-3); 71.6 (C-3′); 69.8 (C-2″); 69.3, 69.1 (C-2′, C-5″); 69.2, 66.8, 66.8 (C-4′, C-3″, C-4″); 64.1 (C-2); 73.5 (O*C*H_2Ph); 69.8 (C-6″); 62.5 (C-6′); 60.6 (C-6); 57.1 (OCH_3); 20.9, 20.6, 20.4, 20.3 (*N*- and *O*-CO*C*H_3). HRESIMS calcd for $C_{46}H_{61}NO_{25}Na$ $[M + Na]^+$ 1050.3430, found 1050.3575.

Methyl 2-(*N*-Acetylacetamido)-3-*O*-(2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)- 6-*O*-benzyl-4-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-*β*-D-glucopyranoside (24). Glycosyl acceptor **21** (100 mg, 140 μmol) and ethyl 2,3,4-tri-*O*-benzyl-1-thio-*β*-L-fucopyranoside[24] **14** (215 mg, 450 μmol, 3 equiv) were dissolved in anhyd Et_2O (5 mL) containing powdered activated 4 Å molecular sieves (500 mg). The mixture was stirred at room temperature for 3 h, MeOTf (85 μL, 0.7 mmol, 5 equiv) was added, and the reaction was allowed to proceed at room temperature for 18 h. It was then quenched with NEt_3 (200 μL) and worked up as previously described for the synthesis of imidate **7**. Chromatography (EtOAc−hexane 3:7) gave trisaccharide **24** as a colorless glass (130 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 20 H, Ar); 5.32 (bd, 1H, J = 3.5 Hz, H-4′); 5.14 (d, 1H, J = 3.8 Hz, H-1″); 5.08 (dd, 1H, J = 10.4, 8.2 Hz, H-2′); 5.00 (d, 1H, OC*H*Ph); 4.91−4.74 (m, 7 H, H-1, H-3, H-3′, 4 OC*H*Ph); 4.69 (m, 1H, H-5″); 4.66 (d, 1H, OC*H*Ph); 4.41 (bs, 2H, OCH_2Ph); 4.34 (d, 1H, J = 8.2 Hz, H-1′); 4.25 (dd, 1H, J = 10.5, 9.1 Hz, H-6a′), 4.17 (dd, 1H, J = 8.5, 3.8 Hz, H-2″); 4.05−3.85 (m, 4H, H-4, H-6a, H-6b′, H-3″); 3.77 (m, 2H, H-5′, H-4″); 3.60 (m, 2H, H-2, H-6b); 3.50 (m, 1H, H-5); 3.41 (s, 3H, OCH_3); 2.46, 2.32 (2 bs, 2 × 3H, *N*-acetyl); 2.02, 2.01, 1.93, 1.77 (4s, 4 × 3H, *O*-acetyl); 1.31 (d, 1H, J = 6.5 Hz, H-6″). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.9, 169.8, 169.1 (C=O); 138.7, 138.6, 138.3, 138.0, 128.6−127.0 (Ar); 100.0 (C-1′); 99.4 (C-1); 97.6 (C-1″); 80.7, 76.4, 75.6, 74.9, 73.7, 71.5, 70.4, 68.6 (C-3, C-4, C-5, C-3′, C-5′, C-2″, C-3″, C-4″); 74.9, 74.0, 73.1, 72.2 (O*C*H_2Ph); 67.3 (C-2′); 66.5 (C-6); 66.3, 66.3 (C-4′, C-5″); 64.4 (C-2); 57.0 (OCH_3); 20.6, 20.5, 20.4 (*O*- and *N*-CO*C*H_3); 17.0 (C-6″). HRESIMS calcd for $C_{59}H_{71}N_2O_{20}$-Na $[M + Na]^+$ 1136.4467, found 1136.4556.

Succinimidate 2,3,4-Tri-*O*-benzyl-1-*N*-*β*-L-fucopyranoside (25). A solution of acceptor **21** (20 mg, 30 μmol) and donor[24] **14** (68 mg, 140 μmol, 5 equiv) in CH_2Cl_2 (2 mL) containing powdered activated 4 Å molecular sieves (200 mg) was stirred at room temperature for 3 h. The temperature was then brought down to −40 °C and *N*-iodosuccinimide (37 mg, 165 μmol, 5.5 equiv) was added followed by a 0.15 M solution of TfOH in anhyd CH_2Cl_2 (30 μL, 4.5 μmol, 0.15 equiv). After the solution was stirred at −40 °C for 30 min, the reaction was quenched with NEt_3 (10 μL) and workup was carried out as previously described for the synthesis of imidate **7**. Chromatography (EtOAc−hexane 1:1) of the dry residue gave compound **25** (35 mg, 48%) and unreacted gycosyl acceptor **21** (20 mg, quant).

Analytical Data for 25. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 15 H, Ar); 6.13 (d, 1H, J = 7.5 Hz, H-1); 5.00−4.74 (m, 5H, OCH_2Ph); 4.67 (dd, 1H, J = 7.8, 3.0 Hz, H-3); 4.48 (d, 1H, J = 11.5, OCH_2Ph); 4.28 (m, 1H, H-5); 3.72 (d, 1H, J = 2.4 Hz, H-4); 2.59 (m, 4H, 2 × OCCH_2); 1.09 (d, 3H, J = 6.4 Hz, H-6). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.9 (C=O), 138.9, 138.5, 138.0, 128.4−127.5 (Ar); 80.5 (C-1); 77.0 (C-3); 76.7 (C-2); 74.8 (C-4); 72.7 (C-5); 75.0, 73.6, 73.2 (O*C*H_2Ph); 28.2 (OC*C*H_2); 17.4 (C-6). HRESIMS calcd for $C_{31}H_{34}NO_{16}$ $[M + H]^+$ 516.2386, found 516.2419.

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Supporting Information Available: Experimental procedures and analytical data for the deprotection of **9** or **22** and **24** leading to **26** and **27**, respectively, as well as those to obtain **2** and **3** from **27** and **26**; ^{1}H, Jmod, COSY, and HSQC spectra for **2** and **3** in D_2O; ^{1}H, Jmod, COSY, HSQC, and HMBC for **7**, **8**, **15**, and **18** in $CDCl_3$; ^{1}H, Jmod, COSY, and HSQC for **9**, **16**, **17**, and **22**−**25** in $CDCl_3$, and **26** and **27** in CD_3OD; and ^{1}H and Jmod for **20** and **21** in $CDCl_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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