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A Protocol for Metal Triflate Catalyzed Direct Glycosylations with GalNAc 1-OPiv Donors

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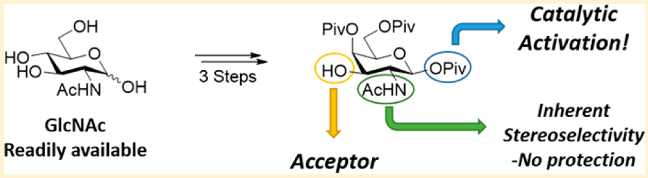
Supporting Information

ABSTRACT: Herein we report on the development of novel glycosylation methodology for the concise synthesis of naturally occurring glycoconjugate motifs containing *N*-acetylgalactosamine (GalNAc) from the cheaper and commercially available *N*-acetylglucosamine (GlcNAc). The stereoselective glycosylations proceed with catalytic amounts of a promoter and without the need for *N*-protection other than the biologically relevant *N*-acetyl group. Among the catalysts explored, both $Bi(OTf)_3$ and $Fe(OTf)_3$ were found to be highly active Lewis acids for this reaction. It was also found that other less reactive metal triflates such as those of Cu(II) and Yb(III) can be beneficial in glycosylation reactions on more demanding glycosyl acceptors. We have furthermore demonstrated that it is possible to control the anomeric stereoselectivity in the glycosylation via postglycosylation in situ anomerization to obtain good yields of α-galactosides. The present protocol was used to prepare important naturally occurring carbohydrate motifs, including a trisaccharide fragment of the naturally occurring marine sponge clarhamnoside.



INTRODUCTION

It is a well-known fact that both α- and β-linked *N*-acetylgalactosamine (GalNAc) are found abundantly in nature's "glycospace" forming part of complex carbohydrate structures.[1] Thus, many useful discoveries of biological interest must be expected from research concerning structures containing these motifs. However, pure glycoconjugates are not easily obtained from natural sources, and GalNAc and galactosamine ($GalNH_2$) are both very expensive starting materials. Therefore, powerful synthetic strategies for the preparation of naturally occurring oligosaccharides containing GalNAc are desired.

In synthetic carbohydrate chemistry, many approach the particular task of installing 2-acetamido-2-deoxysugar motifs by going through cumbersome protection/deprotection maneuvers in order to be able to employ classical glycosylation conditions with, e.g., thioglycoside donors.[2] Typically, the 2-amino function is protected as, e.g., phthalimide (PhthN), azide (N_3), or 2,2,2-trichloroethyl (TrocNH) and later converted to the biologically relevant acetamido function (NHAc) to avoid the formation of an oxazoline intermediate. Although this oxazoline species provides good β-selectivity upon opening, it often reacts sluggishly with challenging acceptor alcohols under typical glycosylation conditions. Another challenging feature of the acetamido function is its nucleophilic nature during both benzyl ether protection reactions[3] and glycosylation.[4,5] Another well-known practical drawback with *N*-acetylglycosamines is their challenging tendency to form gels or insoluble powders, which significantly complicates purification by chromatographic methods.

While glycosylations with, e.g., 2-phthalimido donors are often high-yielding and β-selective, these strategies result in an increased number of synthetic steps and thus diminished overall yields. It seems that when devising synthetic strategies with carbohydrates, researchers often mainly consider the yield of the glycosylation step in isolation without taking into account the synthesis of the donor and the need for postglycosylation deprotection steps.

In recent years, we[6] and others[7] have explored the possibility of performing direct β-selective glycosylation with *N*-acetylglucosamine (GlcNAc) using metal triflates as catalysts. In these reactions, the working hypothesis is that the Lewis acid catalyst facilitates both acetate departure and activation of the intermediate oxazoline.[6a,8]

Recently, a convenient procedure was published by Feng and Ling for the efficient conversion of inexpensive GlcNAc in only three steps to a derivative of the significantly higher priced GalNAc,[9] namely, β-*N*-acetyl-1,4,6-tri-*O*-pivaloylgalactosamine (**1**) (Scheme 1).[10] This reaction relied on the highly selective tripivaloylation of GlcNAc, leading only to small amounts of the tetrapivaloylation GlcNAc derivative **5**. To us, the somewhat conspicuous presence of a β-anomeric ester in this molecule prompted the question of whether this pivalate (1-OPiv) could act as a nucleofuge in a glycosylation reaction upon activation in a similar fashion to the acetyl group we had activated previously.[6a] Here, in this first literature example of catalytic activation of a glycopyranosyl-1-pivalate,[11,12] we report that it is indeed possible to employ ester **1** and derivatives thereof as a very useful combined donor and acceptor of GalNAc.

RESULTS AND DISCUSSION

Before attempting the activation of the anomeric pivalate, we initially converted **1** into the fully protected potential glycosyl

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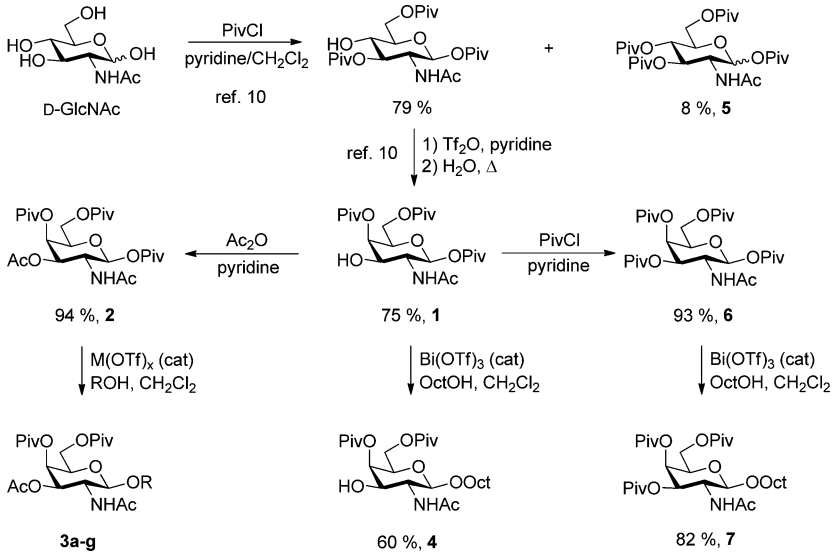
Scheme 1. General Scheme for Direct GalNAc-ylation



donor **2** in 94% yield by treatment with acetic anhydride in pyridine. We then sought to establish reaction conditions under which the anomeric pivaloyl ester **2** would be activated in a glycosylation reaction (Scheme 1, R = *n*-octyl). Different metal triflates were investigated as catalysts (Table 1), and we were very pleased to find that glycosyl donor **2** could be activated catalytically under conditions similar to those used in our previous research (15 mol % catalyst, refluxing CH_2Cl_2).[6a]

Table 1. Catalyst Screening for Activation of 1-OPiv Donors[a]

entry	donor	catalyst	time[b]	yield[c]
1	**2**	$Bi(OTf)_3$[d]	11 h	77%
2	**2**	$Bi(OTf)_3$	4 h	87%
3	**2**	$Fe(OTf)_3$	4 h	81%
4	**2**	$Sc(OTf)_3$	9 h	88%
5	**2**	$Cu(OTf)_2$	13 h	84%
6	**2**	$Fe(OTf)_3 \cdot 6.2DMSO$[14]	2 days	83%
7	**2**	$Yb(OTf)_3$	3 days	86%
8	**2**	AgOTf	5 days	79%
9	**2**	$FeCl_3 \cdot 6H_2O$	5 days	79%
10	**2**	TfOH	5 h	80%
11	**1**	$Bi(OTf)_3$[d]	11 h	60%
12	**1**	$Bi(OTf)_3$	4 h	44%
13	**6**	$Bi(OTf)_3$	5 h	82%

[a]Reactions were perfomed in CH_2Cl_2 at 40 °C with 3 equiv of 1-octanol as the acceptor and 15 mol % catalyst, unless otherwise noted. [b]Time required for full conversion of the donor as determined by TLC analysis. [c]Isolated yields after chromatography. All reaction products contained >95% *β*-anomer as determined by ^1H NMR spectroscopy. [d]5 mol % catalyst was used.

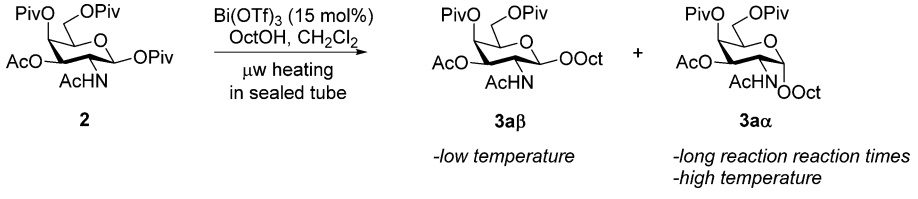
Prolonged reaction times were observed compared with the activation of tetraacetyl-*β*-GlcNAc from our previous study,[6a] as expected considering the increased steric bulk of the pivalate group compared with an acetate group (Table 1, entries 2−10). This was the case in spite of the well-established generally higher reactivity of galactosyl donors compared with glucosyl donors.[13]

Remarkably, the GalNAc glycosylation (GalNAc-ylation) yield with 1-octanol seemed largely unperturbed when the Lewis acid catalyst was changed, but the reaction time varied considerably from 4 h to 5 days. The two most active promoters studied were $Fe(OTf)_3$ and $Bi(OTf)_3$ (Table 1, entries 2 and 3). Interestingly, $Fe(OTf)_3$ was found to be much more catalytically active in this reaction than the $Fe(OTf)_3 \cdot$DMSO complex,[14] which again was more active than $FeCl_3 \cdot 6H_2O$. The least reactive catalysts tested were found to be AgOTf and $FeCl_3 \cdot 6H_2O$, but these catalysts also provided the glycoside product in acceptable yields (79% over 5 days; entries 8 and 9). The Brønsted acid TfOH (entry 10) was investigated as a catalyst and was found to be almost as active as the best-performing Lewis acids in terms of reaction time.

Of the two catalysts found to be the most active, $Fe(OTf)_3$ and $Bi(OTf)_3$, we chose to carry on with the latter because of the hygroscopicity of $Fe(OTf)_3$. Given the efficiency of $Bi(OTf)_3$, we investigated the possibility of lowering the catalyst amount to 5 mol % and found a prolonged reaction time and a slightly eroded glycosylation yield (Table 1, entry 1). The important control experiment where a catalyst was left out gave no conversion of starting material over a period of 24 h (data not shown).

We also investigated the possibility of performing a glycosylation reaction with 1-octanol and donor **1** having a free 3-OH group under conditions otherwise identical to those described above ($Bi(OTf)_3$, 5 and 15 mol %). The expected

Scheme 2. Prolonged Heating at High Temperature Leads to the Formation of the *α*-Anomer



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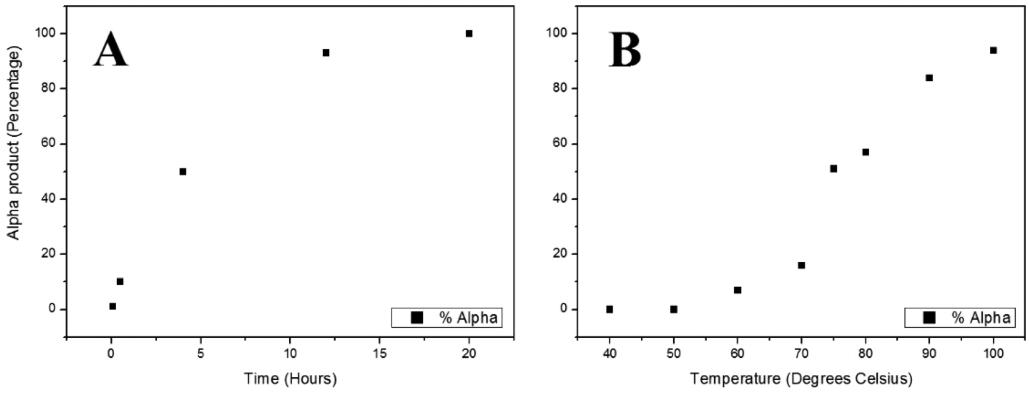
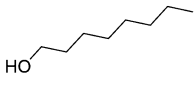
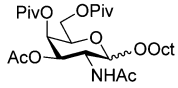
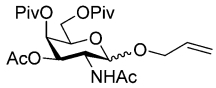
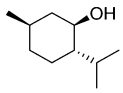
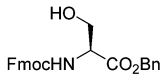
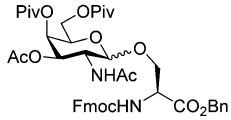


Figure 1. Percentage of α-product at the expense of β-product in glycosylation of **2** with 3 equiv of 1-octanol under microwave irradiation (A) as a function of reaction time at 80 °C and (B) as a function of temperature with heating for 5 h.

Table 2. Reactions with Donor 2 To Obtain α-Glycosides by Prolonged Heating at 80 °C[a]

Entry	Acceptor	Product	Time[b]	Selectivity[c]	Yield[d]
1	 **8**	 **3aα/β**	5 min	99 % β	89 %
2	**8**	**3aα/β**	20 h	100 % α	83 %
3	 **9**	 **3bα/β**	20 min	92 % β	78 %
4	**9**	**3bα/β**	20 h	90 % α	75 %
5	 **10**	**3cα/β**	10 min	92 % β	85 %
6	**10**	**3cα/β**	20 h	95 % α	78 %
7	 **11**	 **3dα/β**	20 h	60 % β	70 %
8[e]	**11**	**3dα/β**	20 h	70 % α	70 %
9[f]	**11**	**3dα/β**	20 h	71 % α	61 %

[a]Reactions were performed in CH_2Cl_2 using 3 equiv of acceptor and 15 mol % $Bi(OTf)_3$ as the catalyst. [b]Heating period. [c]Determined by NMR spectroscopy (^{13}C and ^{1}H data). [d]Isolated combined yields. [e]Performed at 90 °C. [f]Performed at 100 °C.

glycoside product **4** (Scheme 1) formed as found with donor **2**, albeit in somewhat diminished yields (Table 1, entries 11 and 12). No additional well-defined major products (e.g., disaccharide) were formed during this reaction, as judged by TLC analysis.

The 3-OH of key intermediate **1** was also protected as a 3-*O*-pivaloyl donor using pivaloyl chloride in pyridine to give **6** in 93% yield. This compound was activated with $Bi(OTf)_3$ (15 mol %) in the presence of 1-octanol to give β-glycoside **7** in a yield of 82% (Table 1, entry 13), similar to that obtained with the acetylated donor **2** (87%; entry 2).

In an attempt to increase the reaction rate even further by heating the reaction mixture under microwave irradiation in a sealed tube above the boiling point of CH_2Cl_2, it was noticed that the reaction time and temperature turned out to have profound impacts on the stereoselectivity in the glycosylation reaction (Scheme 2). Prolonged reaction times at high temperature yielded more of the α-product at the expense of the initially formed β-glycoside. This postglycosylation in situ anomerization reaction has previously been described by us[6a] and others with superstoichiometric ferric chloride[15] for GlcNAc-ylation. Under the present reaction conditions with donor **2** and 1-octanol, we established the degree of anomerization (Figure 1) as a function of (A) reaction time at 80 °C and (B) temperature with heating for 5 h.

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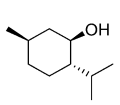
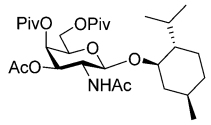
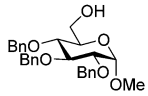
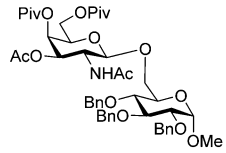
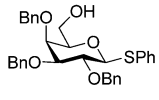
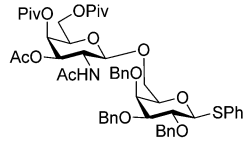
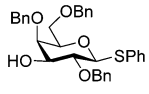
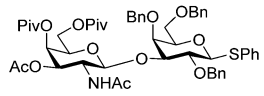
Table 3. Glycosylation with Donor 2 and $Bi(OTf)_3$ as the Catalyst[a]

Entry	Acceptor	D : A[b]	Product	Catalyst	Temp[c]	Time[d]	Yield[e]
1	 **10**	2 : 1	 **3cβ**	$Bi(OTf)_3$	40 °C	12 h	88 %
2	**10**	2 : 1	**3cβ**	$Bi(OTf)_3$	80 °C[g]	30 min	73 %
3	 **12**	2 : 1	 **3e**	$Bi(OTf)_3$	40 °C	21 h	92 %
4	**12**	2 : 1	**3e**	$Bi(OTf)_3$	80 °C[g]	7 h	52 % (44 %)
5	**12**	1.5 : 1	**3e**	$Bi(OTf)_3$	80 °C[g]	7 h	33 % (33 %)
6	**12**	1.5 : 1	**3e**	$Bi(OTf)_3$[f]	80 °C[g]	7 h	52 % (31 %)
7	**12**	1.5 : 1	**3e**	$Yb(OTf)_3$	80 °C[g]	2 h	87 %
8	 **13**	2 : 1	 **3f**	$Bi(OTf)_3$	40 °C	23 h	83 %
9	 **14**	2 : 1	 **3g**	$Bi(OTf)_3$	40 °C	72 h	15 % (73 %)
10	**14**	1.5:1	**3g**	$Yb(OTf)_3$[f]	80 °C[g]	2.5 h	59 %
11	**14**	1.5:1	**3g**	$Cu(OTf)_2$	70 °C[g]	5 h	70 %

[a]Reactions were conducted in CH_2Cl_2 with 5 mol % catalyst and provided only the β-glycoside products. [b]Donor:acceptor ratio. [c]All of the reactions were conducted in sealed vials. [d]No further conversion as determined by TLC analysis. [e]Isolated yields; values in parentheses are percentages of reisolated acceptor. [f]2.5 mol % catalyst was used. [g]The reaction was carried out under microwave irradiation.

Other acceptors were also explored as substrates for the catalytic formation of α-galactosides from donor **2** (Table 2). We were pleased to find that the conversion from the initially formed β-galactoside to the anomerized α-product under the reaction conditions was very applicable to all four acceptors investigated, even the biologically relevant acceptor **11**,[16] which upon anomerization would yield the important Tn antigen. Thus, for simple acceptors the selectivity can be controlled simply by choosing an appropriate run time and temperature.

The possibility of glycosylating another monosaccharide (**13**) using these conditions was also attempted but resulted in disintegration of the acceptor or reaction product, suggesting that the use of high temperature for prolonged periods of time is too harsh for the preparation of larger saccharides.

We next turned to the β-selective glycosylation with more challenging acceptor alcohols. This generally returned excellent yields of the glycoside products with 5 mol % $Bi(OTf)_3$ as the catalyst (Table 3, entries 1, 3, and 8). Compared with the reaction of donor **2** with 1-octanol, the reaction time increased considerably with these sterically demanding and/or electron-deficient acceptors at 40 °C. Adjusting the reaction conditions by increasing the temperature (entries 2 and 4), using a smaller excess of glycosyl donor (entry 5), or employing a more demanding secondary acceptor (**14**; entry 9)[17] diminished the yield. Fortunately, changing the catalyst loading to 2.5 mol % (entry 6) and/or using the milder Lewis acid catalyst $Yb(OTf)_3$ (entries 7 and 10) provided significant improvements in the results.

Especially interesting is acceptor **14** (Table 3), which upon GalNAc-ylation would result in the naturally abundant β-GalNAc-(1→3)-Gal disaccharide motif (**3g**), which subsequently could be a valuable glycosyl donor for further reaction. The $Bi(OTf)_3$-promoted GalNAc-ylation conditions, which returned excellent yields in the reactions with primary alcohols **12**[18] and **13**,[19] afforded only a disappointing 15% yield of **3g** with a rather large proportion of unreacted acceptor remaining (entry 9). In view of the excellent yields of the reactions of donor **2** with primary alcohol acceptors and menthol, there seemed to be a good balance between the reactivities of the donor and acceptor under $Bi(OTf)_3$ catalysis at 40 °C. In an attempt to balance the

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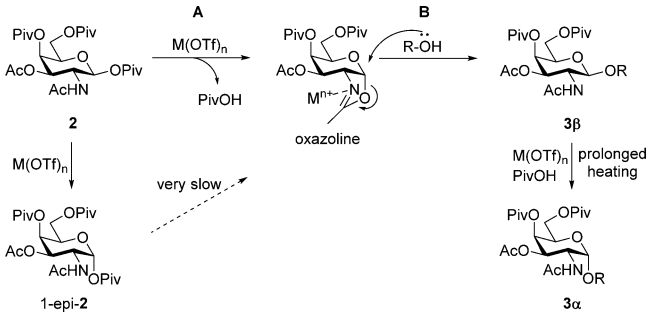
reactivity of donor **2** with that of acceptor **14** by the use of a milder Lewis acid on the basis of the results in entries 3−7 of Table 3, $Yb(OTf)_3$ was again applied and resulted in a considerably enhanced 59% yield of disaccharide **3g** (entry 10), although the product was contaminated with anomerized pivalate donor. Changing the catalyst to $Cu(OTf)_2$ with intermediate activity (Table 1) resulted in a 70% yield of **3g** (entry 11), which is highly satisfactory for direct catalytic GalNAc-ylation of a secondary alcohol.

This series of successful reaction optimization steps has demonstrated the importance of matching donor and acceptor reactivities. Since the activation occurs catalytically, it is possible to fine-tune the reaction by choosing different Lewis acid catalysts and catalyst loadings. Whereas the most reactive catalyst, $Bi(OTf)_3$, gives good yields and short reaction times with good acceptors such as primary alcohols and the non-electron-deficient secondary alcohol (−)-menthol, the yield drops significantly with more demanding acceptor substrates. We speculate that the reason for this might be that the intermediate oxazoline is activated too efficiently compared with the reactivity of a poorly reacting acceptor (Scheme 3). If a more slowly acting catalyst

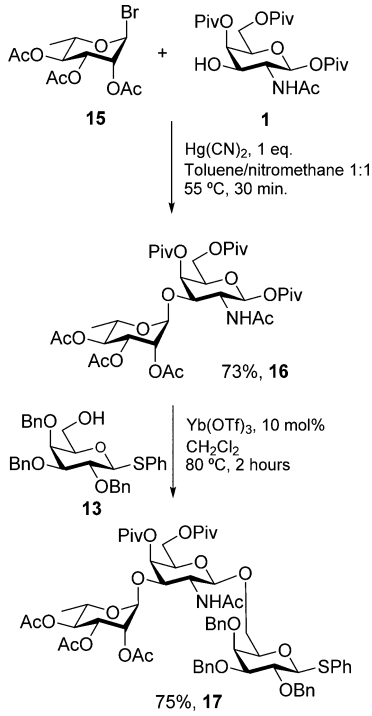
Scheme 3. Proposed Reaction Mechanism for Glycosylation



such as $Yb(OTf)_3$ or $Cu(OTf)_2$ is chosen and/or the catalyst loading is lowered, a better reactivity match can be achieved, which results in a better yield. Since anomerized donor (1-epi-**2**) was observed in the slowly running glycosylations, there probably is a lower limit with regard to catalyst loading and mildness to avoid formation of this poorly reactive donor. The reaction conditions must hence be chosen to ensure that oxazoline formation (Scheme 3A) is well-balanced with oxazoline breakdown (Scheme 3B) as well as with anomerization of both the donor (**2**) and product (**3*β***). This corresponds well with our previous findings for GlcNAc-ylation with SPh and *O*-pentenyl donors, which indicate that it is not desirable to obtain a high concentration of oxazoline in solution because of the adverse reactivity of this species.[6b]

Having thus successfully demonstrated the efficiency and versatility of the direct catalytic GalNAc-ylation procedure reported herein using the easily obtainable donor **2**, we went on to demonstrate the potential of exploiting the free 3-OH group of acceptor/donor **1**. The 3-OH of GalNAc building blocks is known to be a challenging acceptor for glycosylation.[20] A general literature search revealed that the method of choice in this situation is the Helferich conditions using a glycosyl bromide donor. To our delight, we found that activation of rhamnosyl bromide **15**[21] with $Hg(CN)_2$ in the presence of secondary acceptor **1** afforded disaccharide fragment **16** (Scheme 4) of the marine sponge clarhamnoside[22] in a satisfactory 73% yield. This demonstrates that the 1-OPiv functionality of the acceptor is not

Scheme 4. Synthesis of the Trisaccharide Part of the Marine Sponge Clarhamnoside



activated under Helferich conditions and that rhamnosylation of the amide functionality of **2** must be of small or no significance at all.[23] Disaccharide **16** still contained the anomeric pivalate, and it was decided to test whether a trisaccharide fragment of the above-mentioned clarhamnoside could be directly formed in a catalytic glycosylation using the newly established protocol. We were pleased to obtain trisaccharide **17** in 67% yield as the sole anomer using 5 mol % $Bi(OTf)_3$ at 40 °C. Exploitation of the developed optimized conditions for glycosylation at increased temperature afforded an optimized yield of 75% with 10 mol % $Yb(OTf)_3$ at 80 °C, as shown in Scheme 4. This demonstrates the key concept that our methodology efficiently makes use of both the directly obtained 3-OH and 1-OPiv functionalities in **1** as the acceptor and donor, respectively. As **17** contains a thioglycoside donor functionality, this could further be used directly in the total synthesis of the full structure of the naturally occurring marine sponge clarhamnoside.

■ CONCLUSION

Chemical glycosylation remains one of the most demanding tasks in organic chemistry because all acceptors are different to a first approximation and therefore require reaction optimization. Currently, no general approach for making the glycosidic bond exists, but many scientists in the field of carbohydrate chemistry agree on the fact that direct GalNAc-ylation in the presence of a 2-acetamido functionality in practice cannot be performed efficiently. In the present work, we have challenged this perception by demonstrating that a recently published protocol[10] for conversion of inexpensive and readily available GlcNAc affords a useful and otherwise expensive monosaccharide GalNAc 1-OPiv derivative that can be used directly in the stereoselective synthesis of β-GalNAc-containing oligosaccharides. Under more forceful conditions, we have furthermore demonstrated the possibility of anomerizing the reaction product to obtain full conversion to the α-galactoside. The results were obtained by

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using the current catalytic protocol and avoiding the use of compromising steps such as *N*-protecting group manipulations that lower the overall yield. Of the catalysts tested, $Bi(OTf)_3$ proved to be the most efficient in terms of easy handling in the laboratory in practice as well as yield and rate of reaction of reactive glycosyl acceptors such as menthol and primary alcohols. For more challenging secondary acceptor alcohols, improved and satisfactory yields could be obtained by changing the Lewis acid catalyst to the less active $Yb(OTf)_3$ or $Cu(OTf)_2$, demonstrating the importance of carefully matching the donor and acceptor reactivities. This is especially important in the present case of GalNAc-ylation since the formation and disappearance of the oxazoline intermediate must be balanced to achieve an acceptable yield. We have shown that the key GalNAc intermediate **1** can be converted to a useful donor but also can act as an acceptor in its own right and that the 1-OPiv functionality later can be chemoselectively activated. This was demonstrated in our synthesis of a marine sponge clarhamnoside trisaccharide fragment, and we expect that the present glycosylation protocol can be of high value in the synthesis of many other GalNAc-containing oligosaccharide targets.

EXPERIMENTAL SECTION

General Remarks. Air- and moisture-sensitive reactions were conducted in flame-dried glassware under an atmosphere of Ar or N_2. Anhydrous solvents were dried over aluminum oxide and dispensed from a solvent purification system. DMF and dioxane were purchased as anhydrous. Solvents were removed under reduced pressure at 40 °C. Flash column chromatography was performed using silica gel (230−400 mesh), unless otherwise noted. TLC analysis was conducted on silica gel-coated aluminum foil (Kieselgel 60 F_{254}) and observed under UV light or visualized by staining in 10% H_2SO_4 with orcinol followed by vigorous heating. Chemical shifts (δ) are reported in parts per million relative to the residual solvent signals ($CDCl_3$ 7.26 ppm, CD_3OD 4.87 ppm, or DMSO-d_6 2.50 ppm for ^{1}H NMR; $CDCl_3$ 77.2 ppm, CD_3OD 49.0 ppm, or DMSO-d_6 39.5 ppm for ^{13}C NMR). ^{1}H and ^{13}C NMR spectra were interpreted on the basis of *g*COSY, *g*HMQC, and DEPT-135 techniques and, where necessary, 1D-selective ^{1}H TOCSY, proton-coupled ^{13}C, or HMBC spectra. Optical rotations are reported in units of deg·cm^2·g^{-1}. Concentrations are reported in g/100 mL. Reaction times listed for microwave experiments refer to "hold time" at the specified temperature. Reaction mixture temperatures during microwave experiments were measured with an external IR sensor.

2-Acetamido-3-*O*-acetyl-2-deoxy-1,4,6-tri-*O*-pivaloyl-β-D-galactopyranose (2). Tri-*O*-pivaloyl-β-GalNAc **1**[10] (5.0 g, 11 mmol) and acetic anhydride (1.5 mL, 16 mmol) were stirred in anhydrous pyridine (40 mL) at 80 °C under an atmosphere of N_2. After 1.5 h, the reaction mixture was quenched by addition of MeOH. The mixture was concentrated under reduced pressure, and the residue was coevaporated with toluene and then CH_2Cl_2. The resulting residue was crystallized from heptane/CH_2Cl_2 to afford donor **2** (5.1 g, 94%) as colorless crystalline needles. R_f (EtOAc/pentane 1:1) 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.63 (d, 1H, $J_{1,2}$ = 8.9 Hz, H1), 5.39−5.37 (m, 2H, N*H*, H4), 5.06 (dd, 1H, $J_{2,3}$ = 11.3 Hz, $J_{3,4}$ = 3.4 Hz, H3), 4.47 (dt, 1H, $J_{NH,2}$ = 9.4 Hz, H2), 4.18−4.05 (m, 3H, H5, H6a, H6b), 1.98 (s, 3H, $COCH_3$), 1.90 (s, 3H, $NHCOCH_3$), 1.28 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$), 1.16 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.6, 177.4 (*C*O), 170.7, 169.9 ($NHCOCH_3$, *C*O), 93.1 (C1), 71.9 (C5), 70.8 (C3), 65.9 (C4), 60.9 (C6), 49.8 (C2), 39.4, 39.0, 38.9 ($C(CH_3)_3$), 27.3, 27.2, 27.0 ($C(CH_3)_3$), 23.4 ($NHCOCH_3$), 20.7 ($OCOCH_3$). $[\alpha]_D^{299\ K}$ 1.2 (*c* 1, $CHCl_3$). Mp (uncorr.) 209−211 °C (heptane/CH_2Cl_2). HRMS (ES+): calcd for $C_{25}H_{41}NO_{10}Na$ 538.2628, found 538.2629.

2-Acetamido-2-deoxy-1,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranose (6). Tri-*O*-pivaloyl-β-GalNAc **1** (1.0 g, 2.1 mmol) and pivaloyl chloride (780 μL, 6.3 mmol) were stirred in anhydrous pyridine (10 mL) under an atmosphere of N_2. A catalytic amount of DMAP was added, and the reaction mixture was heated to 80 °C and left overnight. The mixture was concentrated under reduced pressure, and the residue was coevaporated twice with toluene. Flash column chromatography (EtOAc/pentane 1:6 → 1:2) afforded tetrapivaloyl-β-GalNAc **6** as a white foam (1.1 g, 93%). R_f (EtOAc/pentane 1:2) 0.59. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.62 (d, 1H, $J_{1,2}$ = 8.8 Hz, H1), 5.39 (d, 1H, $J_{3,4}$ = 3.2 Hz, H4), 5.31 (d, 1H, $J_{NH,2}$ = 9.8 Hz, N*H*), 5.09 (dd, 1H, $J_{2,3}$ = 11.3 Hz, H3), 4.52 (dd, 1H, H2), 4.18−4.15 (m, 1H, H6a), 4.09−4.01 (m, 2H, H5, H6b), 1.86 (s, 3H, $NHCOCH_3$), 1.29 (s, 9H, $C(CH_3)_3$), 1.20 (s, 9H, $C(CH_3)_3$), 1.17 (s, 9H, $C(CH_3)_3$), 1.13 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 178.5, 178.0, 177.5, 177.1 (*C*O), 169.5 ($NHCOCH_3$), 93.2 (C1), 72.2 (C5), 70.6 (C3), 66.0 (C4), 60.9 (C6), 50.0 (C2), 39.3, 39.1, 39.0, 38.9 ($C(CH_3)_3$), 27.4, 27.2, 27.1, 27.0 ($C(CH_3)_3$), 23.3 ($NHCOCH_3$). $[\alpha]_D^{299\ K}$ −4.8 (*c* 1, $CHCl_3$). Mp (uncorr.) 97−102 °C (heptane/CH_2Cl_2). HRMS (ES+): calcd for $C_{28}H_{47}NO_{10}Na$ 580.3098, found 580.3094.

General Procedure A for Table 1. Donor (100−200 mg, 1 equiv), 1-octanol (3 equiv), and catalyst (in accordance with Table 1) were placed in a vial equipped with a sealed cap. Sufficient anhydrous CH_2Cl_2 to give a donor concentration of 0.15 M was added, and the vial was flushed with Ar. The reaction mixture was stirred and heated to 40 °C. Upon reaction completion as judged by TLC analysis, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water. The aqueous layer was extracted thrice with CH_2Cl_2 (50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using an appropriate eluent.

***n*-Octyl 2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-β-D-galactopyranoside (3aβ).** General procedure A was followed using donor **2** (100 mg, 0.20 mmol), 1-octanol (92 μL, 0.58 mmol), and $Bi(OTf)_3$ (15 mol %). Flash column chromatography (acetone/pentane 1:19 → 1:4) afforded **3aβ** (92 mg, 87%) as a sticky oil. R_f (acetone/pentane 1:4) 0.44. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.90 (d, 1H, $J_{NH,2}$ = 8.6 Hz, N*H*), 5.31−5.25 (m, 2H, H3, H4), 4.67 (d, 1H, $J_{1,2}$ = 8.4 Hz, H1), 4.11 (dd, 1H, J_{gem} = 10.9 Hz, $J_{5,6a}$ = 6.8 Hz, H6a), 4.04−3.99 (m, 1H, H6b), 3.93 (t, 1H, H5), 3.90−3.77 (m, 2H, H2, OC*H*HCH$_2$), 3.41 (dt, 1H, J_{gem} = 9.5 Hz, *J* = 6.9 Hz, OCH*H*CH$_2$), 1.91 (s, 3H, OC(O)CH_3), 1.89 (s, 3H, NHC(O)CH_3), 1.57−1.48 (m, 2H, OCH$_2$CH_2), 1.23−1.18 (m, 10H, octyl CH_2), 1.20 (s, 9H, $C(CH_3)_3$), 1.12 (s, 9H, $C(CH_3)_3$), 0.82 (t, 3H, *J* = 6.8 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.6 (*C*O), 170.5, 170.3 (NHC(O)CH_3, OC(O)CH_3), 100.8 (C1), 70.7 (C5), 70.2 (C3), 69.8 (OCH$_2$CH$_2$), 66.4 (C4), 61.4 (C6), 51.8 (C2), 39.2, 38.7 ($C(CH_3)_3$), 31.8, 29.5, 29.3, 29.3 (octyl CH_2), 27.2, 27.1 ($C(CH_3)_3$), 25.9 (OCH$_2$CH$_2$CH$_2$), 23.4 (NHC(O)CH_3), 22.6 (OCH$_2$CH$_2$), 20.7 (OC(O)CH_3), 14.1 (CH_2CH_3). $[\alpha]_D^{299\ K}$ −5.0 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{28}H_{49}NO_9H$ 544.3486, found 544.3471.

***n*-Octyl 2-Acetamido-2-deoxy-4,6-di-*O*-pivaloyl-β-D-galactopyranoside (4).** General procedure A was followed using donor **1** (100 mg, 0.21 mmol), 1-octanol (100 μL, 0.63 mmol), and Bi(OTf) (5 mol %). Flash column chromatography (20% acetone in toluene) afforded the desired glycoside **4** (64.5 mg, 60%) as a sticky oil. R_f (40% acetone in toluene) 0.53. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.88 (d, 1H, $J_{NH,2}$ = 5.2 Hz, N*H*), 5.27 (d, 1H, $J_{3,4}$ = 3.0 Hz, H4), 4.54 (s, 1H, O*H*), 4.52 (d, 1H, $J_{1,2}$ = 8.3 Hz, H1), 4.13 (dd, 1H, J_{gem} = 11.2 Hz, $J_{5,6a}$ = 7.3 Hz, H6a), 4.06 (dd, 1H, $J_{5,6b}$ = 6.2 Hz, H6b), 3.95−4.02 (m, 1H, H3), 3.80−3.90 (m, 2H, H5, OC*H*HCH$_2$), 3.63 (ddd, 1H, $J_{2,3}$ = 10.3 Hz, H2), 3.44 (dt, 1H, J_{vic} = 7.0 Hz, J_{gem} = 9.3 Hz, OCH*H*CH$_2$), 2.01 (s, 3H, NHC(O)CH_3), 1.67−1.50 (m, 2H, OCH$_2$CH_2), 1.37−1.13 (m, octyl CH_2), 1.24, 1.17 (s, 18H, $C(CH_3)_3$), 0.86 (t, 3H, *J* = 6.7 Hz, CH_2CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 178.1, 178.0 (*C*O), 173.0 (NHC(O)CH_3), 100.4 (C1), 71.9 (C3), 71.4 (C5), 69.8 (OCH$_2$CH$_2$), 68.5 (C4), 62.0 (C6), 55.9 (C2), 39.3, 38.8 ($C(CH_3)_3$), 31.9 (OCH$_2$CH$_2$), 29.5, 29.39, 29.36, 26.1, 22.7 (octyl CH_2), 27.3, 27.2 ($C(CH_3)_3$), 23.5 (NHC(O)CH_3), 14.2 (CH_2CH_3). $[\alpha]_D^{299\ K}$ −27.0 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{26}H_{47}NO_8H$ 502.3374, found 502.3397.

***n*-Octyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-pivaloyl-β-D-galactopyranoside (7).** General procedure A was followed using donor **6** (200 mg, 0.36 mmol), 1-octanol (170 μL, 1.08 mmol), and $Bi(OTf)_3$ (15 mol %). Flash column chromatography (EtOAc/pentane 1:9 → 3:7) afforded the desired glycoside **7** (187 mg, 82%) as a clear sticky oil. R_f

(acetone/pentane 1:9) 0.26. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.44 (d, 1H, $J_{NH,2}$ = 8.8 Hz, N*H*), 5.36 (d, 1H, $J_{3,4}$ = 2.6 Hz, H4), 5.25 (dd, 1H, $J_{2,3}$ = 11.2 Hz, H3), 4.62 (d, 1H, $J_{1,2}$ = 8.4 Hz, H1), 4.16 (dd, 1H, J_{gem} = 10.7 Hz, $J_{5,6a}$ = 6.5 Hz, H6a), 4.10−4.00 (m, 2H, H2, H6b), 3.96 (t, 1H, $J_{5,6}$ = 6.8 Hz, H5), 3.85 (dt, 1H, J_{gem} = 9.2 Hz, J_{vic} = 6.4 Hz, OC*H*HCH$_2$), 3.46 (dt, 1H, J_{vic} = 6.9 Hz, OCH*H*CH$_2$), 1.90 (s, 3H, NHCOC*H*$_3$), 1.61−1.52 (m, 2H, OCH$_2$C*H*$_2$), 1.30−1.24 (m, 10H, octyl CH$_2$), 1.25 (s, 9H, C(C*H*$_3$)$_3$), 1.17 (s, 9H, C(C*H*$_3$)$_3$), 1.12 (s, 9H, C(C*H*$_3$)$_3$), 0.87 (t, 3H, J = 6.5 Hz, CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 178.1, 178.0, 177.1, 169.9 (*C*O), 101.3 (C1), 71.1 (C5), 70.3 (C3), 69.9 (O*C*H$_2$CH$_2$), 66.6 (C4), 61.5 (C6), 51.8 (C2), 39.2, 39.0, 38.8 (*C*(CH$_3$)$_3$), 31.9, 29.6, 29.4, 29.4 (octyl CH$_2$), 27.3, 27.2, 27.1 (C(*C*H$_3$)$_3$), 26.0 (CH$_2$*C*H$_2$CH$_3$), 23.4 (NHCO*C*H$_3$), 22.8 (*C*H$_2$CH$_3$), 14.2 (CH$_2$*C*H$_3$). $[\alpha]_D^{299\ K}$ −13.0 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{31}H_{55}NO_9H$ 586.3955, found 586.3942.

General Procedure B for Figure 1A: Determination of Anomeric Selectivity in the Synthesis of 3a*α*/*β* with Bi(OTf)$_3$ under Microwave Conditions as a Function of Reaction Time at 80 °C. Donor **2** (200 mg, 0.39 mmol), 1-octanol (184 μL, 1.2 mmol), and Bi(OTf)$_3$ (15 mol %) were placed in a vial equipped with a sealed cap. Sufficient anhydrous CH_2Cl_2 was added to give a donor concentration of 0.15 M, and the vial was flushed with Ar. The reaction mixture was stirred and heated to 80 °C under microwave irradiation for various times as shown in Figure 1A. After reaction completion, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed thrice with water (50 mL). The aqueous layer was extracted thrice with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (acetone/pentane 1:19 → 1:4) to afford a mixture of **3a*α*** and **3a*β*** as a sticky oil, which was analyzed by NMR spectroscopy.

n*-Octyl 2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-*α*-D-galactopyranoside (3a*α*).** General procedure B was followed. Flash column chromatography (acetone/pentane 1:19 → 1:4) afforded **3a*α (176 mg, 83%) as a clear sticky oil. R_f (acetone/pentane 2:8) 0.55. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.58 (d, 1H, $J_{NH,2}$ = 9.7 Hz, N*H*), 5.35 (d, 1H, $J_{3,4}$ = 2.7 Hz, H4), 5.14 (dd, 1H, $J_{2,3}$ = 11.2 Hz, H3), 4.85 (d, 1H, $J_{1,2}$ = 3.6 Hz, H1), 4.55 (ddd, 1H, H2), 4.17 (t, 1H, J = 6.7 Hz, H5), 4.09−3.99 (m, 2H, H6a, H6b), 3.66 (dt, 1H, J_{gem} = 9.6 Hz, J_{vic} = 6.8 Hz, OC*H*HCH$_2$), 3.39 (dt, 1H, J_{vic} = 6.6 Hz, OCH*H*CH$_2$), 1.94 (s, 6H, NHCOC*H*$_3$, OCOC*H*$_3$), 1.62−1.53 (m, 2H, OCH$_2$C*H*$_2$), 1.31−1.23 (m, octyl CH$_2$), 1.24 (s, 9H, C(C*H*$_3$)$_3$), 1.16 (s, 9H, C(C*H*$_3$)$_3$), 0.86 (t, 3H, J = 6.8 Hz, CH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 178.0, 177.7 (*C*O), 170.9, 170.0 (NHCOCH$_3$, OCOCH$_3$), 97.6 (C1), 68.9 (C3), 68.4 (O*C*H$_2$CH$_2$), 67.0 (C5), 67.0 (C4), 62.0 (C6), 48.0 (C2), 39.3, 38.8 (*C*(CH$_3$)$_3$), 31.9, 29.4, 29.4, 29.3 (octyl CH$_2$), 27.2, 27.2 (C(*C*H$_3$)$_3$), 26.3 (*C*H$_2$CH$_2$CH$_3$), 23.4 (NHCO*C*H$_3$), 22.7 (*C*H$_2$CH$_3$), 20.8 (OCO*C*H$_3$), 14.2 (CH$_2$*C*H$_3$). $[\alpha]_D^{299\ K}$ 60.6 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{28}H_{49}NO_9H$ 544.3486, found 544.3466.

General Procedure C for Figure 1B: Determination of Anomeric Selectivity in the Synthesis of 3a*α*/*β* with Bi(OTf)$_3$ under Microwave Conditions at Various Temperatures. Donor **2** (50 mg, 0.097 mmol), 1-octanol (46 μL, 0.29 mmol), and Bi(OTf)$_3$ (15 mol %) were placed in a vial equipped with a sealed cap. Sufficient anhydrous CH_2Cl_2 was added to give a donor concentration of 0.15 M, and the vial was flushed with Ar. The reaction mixture was heated at the desired temperature for 5 h and then concentrated under reduced pressure. A ^{13}C NMR spectrum of the resulting crude material was obtained and analyzed to determine the ratio of the signals corresponding to C1 of the *α*- and *β*-products (97.6 and 100.6 ppm, respectively) listed in Figure 1B.

General Procedure D for Table 2. Donor **2** (200 mg, 0.39 mmol), acceptor (1.2 mmol), and Bi(OTf)$_3$ (15 mol %) were placed in a vial equipped with a sealed cap. Sufficient anhydrous CH_2Cl_2 was added to give a donor concentration of 0.15 M, and the vial was flushed with Ar. The reaction mixture was stirred and heated to 80 °C under microwave irradiation. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water. The aqueous layer was extracted thrice with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The anomeric ratio was determined on the crude mixture before purification by flash column chromatography using an appropriate eluent.

Allyl 2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (3b*β*). General procedure D was followed using allyl alcohol (79 μL, 1.2 mmol). TLC analysis showed full conversion of the donor after 20 min. Flash column chromatography (acetone/pentane 1:4 → 3:7) afforded allyl *β*-galactoside **3b*β*** (132 mg, 72%) as a clear oil. R_f (acetone/pentane 3:7) 0.50. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.6, 170.5, 170.4 (*C*O), 133.8 (CH$_2$*C*H═CH$_2$), 117.8 (CH$_2$CH═*C*H$_2$), 99.9 (C1), 70.8 (C5), 70.2 (C3), 69.9 (*C*H$_2$CH═CH$_2$), 66.4 (C4), 61.4 (C6), 51.8 (C2), 39.3, 38.8 (*C*(CH$_3$)$_3$), 27.2, 27.1 (C(*C*H$_3$)$_3$), 23.5 (NHC(O)*C*H$_3$), 20.7 (OC(O)*C*H$_3$). $[\alpha]_D^{299\ K}$ 4.8 (*c* 1, $CHCl_3$); lit. −13.3 (*c* 1, $CHCl_3$).[24] HRMS (ES+): calcd for $C_{23}H_{37}NO_9H$ 472.2547, found 472.2545. The ^{1}H NMR spectral values were in accordance with those previously published.[24]

Allyl 2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-*α*-D-galactopyranoside (3b*α*). General procedure D was followed using allyl alcohol (79 μL, 1.2 mmol). The reaction mixture was heated for 20 h. Flash column chromatography (acetone/pentane 1:9 → 3:7) afforded allyl *α*-galactoside **3b*α*** (124 mg, 68%) as a clear oil. R_f (acetone/pentane 3:7) 0.52. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.6, 170.9, 170.1 (*C*O), 133.3 (CH$_2$*C*H═CH$_2$), 118.4 (CH$_2$CH═*C*H$_2$), 96.9 (C1), 68.8 (C3), 68.7 (*C*H$_2$CH═CH$_2$), 67.1, 67.0 (C4, C5), 62.0 (C6), 47.9 (C2), 39.3, 38.8 (*C*(CH$_3$)$_3$), 27.2, 27.2 (C(*C*H$_3$)$_3$), 23.4 (NHC(O)*C*H$_3$), 20.7 (OC(O)*C*H$_3$). $[\alpha]_D^{299\ K}$ 65.2 (*c* 1, $CHCl_3$); lit. 72 (*c* 0.8, $CHCl_3$).[25] HRMS (ES+): calcd for $C_{23}H_{37}NO_9H$ 472.2547, found 472.2546. The ^{1}H NMR spectral values were in accordance with those previously published.[25]

(−)-Menthyl 2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-*β*-D-galactopyranoside (3c*β*). General procedure D was followed using (−)-menthol (182 mg, 1.2 mmol). TLC analysis showed full conversion of the donor after 10 min. Flash column chromatography (EtOAc/pentane 3:7 → 1:1) afforded menthyl *β*-galactoside **3c*β*** (173 mg, 78%) as a white crystalline solid. R_f (EtOAc/pentane 1:1) 0.30. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.46 (dd, 1H, $J_{2,3}$ = 11.3, $J_{3,4}$ = 3.4 Hz, H3), 5.39 (d, 1H, $J_{NH,2}$ = 8.1 Hz, N*H*), 5.35 (d, 1H, H4), 4.87 (d, 1H, $J_{1,2}$ = 8.3 Hz, H1), 4.11−4.01 (m, 2H, H6a, H6b), 3.93 (t, 1H, $J_{5,6}$ = 6.9 Hz, H5), 3.67 (td, 1H, H2), 3.41 (td, 1H, J = 10.4 Hz, J = 4.3 Hz, C*H*OGalNAc), 2.30−2.21 (m, 1H), 2.01−1.89 (m, 1H), 1.96 (s, 3H, NHC(O)C*H*$_3$), 1.94 (s, 3H, OC(O)C*H*$_3$), 1.64−1.61 (m, 2H), 1.34−1.14 (m, 2H), 1.25 (s, 9H, C(C*H*$_3$)$_3$), 1.16 (s, 9H, C(C*H*$_3$)$_3$), 1.03−0.76 (m, 3H), 0.90 (d, 3H, J = 6.9 Hz, C*H*$_3$CHCH$_3$), 0.88 (d, 3H, J = 7.3 Hz, CH$_3$CHC*H*$_3$), 0.74 (d, 3H, J = 6.8 Hz, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 178.0, 177.5, 170.4, 170.2 (*C*O), 98.1 (C1), 78.3 (*C*HOGalNAc), 70.5 (C5), 70.1 (C3), 66.6 (C4), 61.7 (C6), 52.6 (C2), 47.7, 40.8 (menthyl), 39.2, 38.7 (*C*(CH$_3$)$_3$), 34.4, 31.5 (menthyl), 27.2, 27.1 (C(*C*H$_3$)$_3$), 25.2 (menthyl), 23.5 (NHC(O)*C*H$_3$), 23.2, 22.3, 20.9 (menthyl), 20.7 (OC(O)*C*H$_3$), 15.8 (*C*H$_3$). $[\alpha]_D^{299\ K}$ −43.8 (*c* 1, $CHCl_3$). Mp (uncorr.) 220−223 °C ($CHCl_3$). HRMS (ES+): calcd for $C_{30}H_{51}NO_9Na$ 592.3462, found 592.3456.

(−)-Menthyl 2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-*α*-D-galactopyranoside (3c*α*). General procedure D was followed using (−)-menthol (182 mg, 1.2 mmol). The reaction mixture was heated for 20 h. Flash column chromatography (EtOAc/pentane 3:7 → 1:1) afforded menthyl *α*-galactoside **3c*α*** (164 mg, 74%) as a white crystalline solid. R_f (EtOAc/pentane 1:1) 0.56. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 5.60 (d, 1H, $J_{NH,2}$ = 9.5 Hz, N*H*), 5.33 (d, 1H, $J_{3,4}$ = 2.4 Hz, H4), 5.13 (dd, 1H, $J_{2,3}$ = 11.4 Hz, H3), 4.96 (d, 1H, $J_{1,2}$ = 3.6 Hz, H1), 4.48 (ddd, 1H, H2), 4.30 (t, 1H, H5), 4.02 (dd, J_{gem} = 11.2 Hz, $J_{5,6a}$ = 6.9 Hz, H6a), 3.95 (dd, $J_{5,6b}$ = 7.0 Hz, H6b), 3.30 (td, 1H, J = 10.6 Hz, J = 4.3 Hz, C*H*OGalNAc), 2.12−2.03 (m, 2H), 1.91 (s, 3H, NHC(O)C*H*$_3$), 1.88 (s, 3H, OC(O)C*H*$_3$), 1.65−1.53 (m, 2H), 1.39−1.23 (m, 2H), 1.21 (s, 9H, C(C*H*$_3$)$_3$), 1.14 (s, 9H, C(C*H*$_3$)$_3$), 1.06−0.92 (m, 2H), 0.89 (d, 3H, J = 7.6 Hz, C*H*$_3$CHCH$_3$), 0.87 (d, 3H, J = 7.1 Hz, CH$_3$CHC*H*$_3$), 0.84−0.76 (m, 1H), 0.72 (d, 3H, J = 7.0 Hz, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.6, 170.9, 169.8 (*C*O), 99.2 (C1), 81.2 (*C*HOGalNAc), 68.6 (C3), 66.9, 66.9 (C4, C5), 61.9 (C6), 48.9 (menthyl), 48.6 (C2), 42.6 (menthyl), 39.3, 38.7 (*C*(CH$_3$)$_3$), 34.2, 31.7 (menthyl), 27.2, 27.2 (C(*C*H$_3$)$_3$), 25.6 (menthyl), 23.2 (NHC(O)*C*H$_3$), 22.7, 22.3, 21.3 (menthyl), 20.7 (OC(O)*C*H$_3$), 15.7 (menthyl C*H*$_3$).

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$[\alpha]_D^{299\ K}$ 49.4 (*c* 1, $CHCl_3$). Mp (uncorr.) 215−218 °C ($CHCl_3$). HRMS (ES+): calcd for $C_{30}H_{51}NO_9H$ 570.3642, found 570.3644.

***N*-(Fluoren-9-ylmethoxycarbonyl)-*O*-(2-acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-α/β-D-galactopyranosyl)-L-serine Benzyl Ester (3dα/β).** Donor **2** (50 mg, 0.10 mmol), *N*-(fluoren-9-ylmethoxycarbonyl)-L-serine benzyl ester[16] (121 mg, 0.29 mmol), and $Bi(OTf)_3$ (15 mol %) were placed in a vial equipped with a sealed cap. Sufficient anhydrous CH_2Cl_2 was added to give a donor concentration of 0.15 M, and the vial was flushed with Ar. The reaction mixture was stirred and heated to 80 °C under microwave irradiation for 20 h and concentrated under reduced pressure. The resulting residue was a mixture of anomers and was purified by flash column chromatography (silica gel 60, 30% → 35% EtOAc in toluene), which afforded the α-anomer **3dα** (22.5 mg, 28%) as a clear oil and the β-anomer **3dβ** (34.2 mg, 42%) as a clear oil.

Data for **3dα**: R_f (40% EtOAc in toluene) 0.50. The NMR signals were significantly broadened because of the presence of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80−7.12 (m), 5.77 (br d, *J* = 8.2 Hz), 5.65 (br d, *J* = 9.1 Hz), 5.40−5.00 (m), 4.79 (br s), 4.65−4.32 (m), 4.28−3.82 (m), 1.98 (s), 1.90 (s), 1.27 (s), 1.16 (s). HRMS (ES+): calcd for $C_{45}H_{54}N_2O_{13}H$ 831.3704, found 831.3712. To ascertain the nature of the anomeric configuration, the sample was subjected to deprotection with DBU (7 μL) in the NMR tube, upon which a signal was observed at 99.0 ppm in the ^{13}C NMR spectrum, indicating α-stereochemistry. The deprotected compound was further identified by mass spectrometry. HRMS (ES+): calcd for $C_{30}H_{44}N_2O_{11}H$ 609.3023, found 609.3026.

Data for **3dβ**: R_f (40% EtOAc in toluene) 0.39. The NMR signals were significantly broadened because of the presence of rotamers. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.80−7.15 (m), 5.85 (br d, *J* = 7.4 Hz), 5.37−5.13 (m), 4.75 (br d, *J* = 7.6 Hz), 4.60−3.74 (m), 1.98 (s), 1.83 (s), 1.25 (s), 1.17 (s). HRMS (ES+): calcd for $C_{45}H_{54}N_2O_{13}H$ 831.3704, found 831.3712. To ascertain the nature of the anomeric configuration, the sample was subjected to deprotection with DBU (7 μL) in the NMR tube, upon which a signal was observed at 101.8 ppm in the ^{13}C NMR spectrum, indicating β-stereochemistry. The deprotected compound was further identified by mass spectrometry. HRMS (ES+): calcd for $C_{30}H_{44}N_2O_{11}H$ 609.3023, found 609.3029.

General Procedure E for Table 3. Donor **2** (50−200 mg), acceptor, and catalyst (in accordance with Table 3) were placed in a vial equipped with a sealed cap. Sufficient anhydrous CH_2Cl_2 was added to give a donor concentration of 0.15 M, and the vial was flushed with N_2. The reaction mixture was stirred and heated by conventional heating or under microwave irradiation. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with water. The aqueous layer was extracted thrice with CH_2Cl_2 (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using an appropriate eluent.

Methyl *O*-(2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3e). General procedure E was followed using donor **2** (200 mg, 0.39 mmol), primary acceptor **12** (90 mg, 0.19 mmol), and $Bi(OTf)_3$ (5 mol %). TLC analysis showed full conversion of donor after 21 h. Flash column chromatography (EtOAc/pentane 2:3 → 1:1) afforded the desired disaccharide **3e** (156 mg, 92%) as an amorphous solid. R_f (EtOAc/pentane 3:2) 0.23. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.33−7.26 (m, 15H, Ar*H*), 5.52 (d, 1H, $J_{NH,2}$ = 8.6 Hz, N*H*), 5.33 (d, 1H, $J_{3',4'}$ = 3.0 Hz, H4′), 5.26 (dd, 1H, $J_{2',3'}$ = 11.1 Hz, H3′), 4.98 (d, 1H, J_{gem} = 11.0 Hz, C*H*HPh), 4.84 (d, 1H, J_{gem} = 11.0 Hz, C*H*HPh), 4.79 (d, 1H, CH*H*Ph), 4.77 (d, 1H, J_{gem} = 10.5 Hz, C*H*HPh), 4.67 (d, 1H, $J_{1',2'}$ = 8.3 Hz, H1′), 4.65 (d, 1H, CH*H*Ph), 4.61 (d, 1H, $J_{1,2}$ = 3.9 Hz, H1), 4.59 (d, 1H, CH*H*Ph), 4.10−3.93 (m, 6H, H2′, H5′, H6′, H3, H6a), 3.79−3.76 (m, 1H, H5), 3.70 (dd, 1H, J_{gem} = 10.8, $J_{5,6b}$ = 4.5 Hz, H6b), 3.52 (dd, 1H, $J_{2,3}$ = 9.6 Hz, H2), 3.45 (t, 1H, $J_{3,4}$ = 9.4 Hz, H4), 3.36 (s, 3H, OCH_3), 1.93 (s, 3H, OC(O)CH_3), 1.82 (s, 3H, NHC(O)CH_3), 1.22 (s, 9H, C(CH_3)$_3$), 1.14 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.5 (*C*O), 170.3, 170.1 (NHC(O)CH$_3$, OC(O)CH$_3$), 138.8, 138.4, 138.2, 128.6, 128.5, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7 (Ar), 101.1 (C1′), 98.1 (C1), 82.1 (C3), 79.9 (C2), 77.6 (C4), 75.8, 74.6, 73.4 (CH$_2$Ph), 70.9 (C5′), 70.1 (C3′), 69.7 (C5), 67.7 (C6), 66.3 (C4′), 61.2 (C6′), 55.2 (OCH$_3$), 51.6 (C2′), 39.2, 38.8 (*C*(CH$_3$)$_3$), 27.2, 27.1 (C(*C*H$_3$)$_3$), 23.5 (NHC(O)*C*H$_3$), 20.7 (OC(O)*C*H$_3$). $[\alpha]_D^{299\ K}$ 36.0 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{48}H_{63}NO_{14}H$ 878.4327, found 878.4328.

Phenyl *O*-(2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (3f). General procedure E was followed using donor **2** (133 mg, 0.26 mmol), primary acceptor **13** (70 mg, 0.13 mmol), and $Bi(OTf)_3$ (5 mol %). TLC analysis showed full conversion of donor after 23 h. Flash column chromatography (Et_2O/CH_2Cl_2 1:19 → 1:4) afforded the desired disaccharide **3f** (102 mg, 83%) as an amorphous solid. R_f (Et_2O/CH_2Cl_2 1:9) 0.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.54−7.50 (m, 2H, SPh), 7.32−7.17 (m, 18H, Ar*H*), 5.24 (d, 1H, $J_{3',4'}$ = 3.0 Hz, H4′), 5.03 (d, 1H, $J_{NH,2}$ = 9.2 Hz, N*H*), 4.93 (dd, 1H, $J_{2',3'}$ = 11.2 Hz, H3′), 4.88 (d, 1H, J_{gem} = 11.4 Hz, C*H*HPh), 4.73−4.66 (m, 4H, 2CH_2Ph), 4.56 (d, 1H, J_{gem} = 11.5 Hz, CH*H*Ph), 4.55 (d, 1H, $J_{1,2}$ = 9.6 Hz, H1), 4.47 (d, 1H, $J_{1',2'}$ = 8.5 Hz, H1′), 4.02−3.96 (m, 3H, H2′, H6′a, H6′b), 3.86 (t, 1H, $J_{2,3}$ = 9.4 Hz, H2), 3.79 (t, 1H, $J_{5',6'}$ = 7.1 Hz, H5′), 3.74−3.73 (m, 3H, H4, H6a, H6b), 3.52−3.46 (m, 2H, H3, H5), 1.88 (s, 3H, OC(O)CH_3), 1.66 (s, 3H, NHC(O)CH_3), 1.16 (s, 9H, C(CH_3)$_3$), 1.09 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 178.0, 177.6, 170.5, 170.4 (*C*O), 138.4, 138.2, 138.2, 134.1, 132.2, 129.3, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.8, 127.7 (Ar), 101.8 (C1′), 88.1 (C1), 84.1 (C3), 78.8 (C5), 77.4 (C2), 75.9, 74.4 (CH$_2$Ph), 73.9 (C4), 73.1 (CH$_2$Ph), 70.7 (C3′, C5′), 69.3 (C6), 66.0 (C4′), 61.1 (C6′), 51.1 (C2′), 39.3, 38.8 (*C*(CH$_3$)$_3$), 27.3, 27.2 (C(*C*H$_3$)$_3$), 23.4 (NHC(O)*C*H$_3$), 20.7 (OC(O)*C*H$_3$). $[\alpha]_D^{299\ K}$ −8.6 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{53}H_{65}NO_{13}SH$ 956.4255, found 956.4261.

Phenyl *O*-(2-Acetamido-3-*O*-acetyl-2-deoxy-4,6-di-*O*-pivaloyl-β-D-galactopyranosyl)-(1→3)-2,4,6-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (3g). General procedure E was followed using donor **2** (71 mg, 0.14 mmol), secondary acceptor **14** (50 mg, 0.09 mmol), and $Cu(OTf)_2$ (5 mol %). The reaction mixture was heated to 70 °C under microwave irradiation for 5 h. Flash column chromatography (silica gel 60, 7% Et_2O in CH_2Cl_2) afforded the desired disaccharide **3g** (69 mg, 70% NMR-corrected yield) contaminated with anomerized donor as a sticky oil. R_f (Et_2O/CH_2Cl_2 1:9) 0.48. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.47−7.43 (m, 2H, SPh), 7.34−7.17 (m, 15H, Ar*H*), 7.13−7.09 (m, 3H, SPh), 5.26 (d, 1H, $J_{3',4'}$ = 2.8 Hz, H4′), 4.98−4.88 (m, 3H, H3′, CH_2Ph), 4.82 (d, 1H, $J_{1',2'}$ = 8.2 Hz, H1′), 4.81 (d, 1H, $J_{NH,2}$ = 9.1 Hz, N*H*), 4.56−4.49 (m, 3H, H1, CH_2Ph), 4.39 (d, 1H, J_{gem} = 11.8 Hz, C*H*HPh), 4.31 (d, 1H, CH*H*Ph), 4.17−4.03 (m, 3H, H2′, H6′a, H6′b), 3.93 (d, 1H, $J_{3,4}$ = 2.0 Hz, H4), 3.88 (t, 1H, $J_{5',6'}$ = 6.7 Hz, H5′), 3.82 (t, 1H, $J_{2,3}$ = 9.4 Hz, H2), 3.72 (dd, 1H, H3), 3.60−3.49 (m, 2H, H5, H6a), 3.40 (dd, 1H, J_{gem} = 8.6 Hz, $J_{5,6b}$ = 5.0 Hz, H6b), 1.85 (s, 3H, OC(O)CH_3), 1.44 (s, 3H, NHC(O)CH_3), 1.15 (s, 9H, C(CH_3)$_3$), 1.08 (s, 9H, C(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 178.0, 177.5, 170.5, 170.0 (*C*O), 138.9, 138.9, 138.1, 134.3, 131.4, 129.0, 128.8, 128.5, 128.5, 128.3, 128.0 127.9, 127.8, 127.6, 127.2, 126.8 (Ar), 102.5 (C1′), 87.9 (C1), 83.9 (C3), 77.7 (C5), 77.6 (C2), 76.1 (C4), 74.9, 74.6, 73.6 (CH$_2$Ph), 71.0 (C5′), 70.6 (C3′), 69.3 (C6), 66.3 (C4′), 61.5 (C6′), 51.6 (C2′), 39.3, 38.8 (*C*(CH$_3$)$_3$), 27.2, 27.2 (C(*C*H$_3$)$_3$), 23.1 (NHC(O)*C*H$_3$), 20.7 (OC(O)*C*H$_3$). $[\alpha]_D^{299\ K}$ −9.0 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{53}H_{65}NO_{13}SNH_4$ 973.4520, found 973.4524.

***O*-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-1,4,6-tri-*O*-pivaloyl-β-D-galactopyranose (16).** Rhamnosyl bromide **15**[21] (112 mg, 0.32 mmol) and tri-*O*-pivaloyl-β-GalNAc **1** (75 mg, 0.16 mmol) were dissolved in a 1:1 mixture of anhydrous nitromethane and toluene (1 mL). Oven-dried $CaSO_4$ (200 mg) was added, and the mixture was heated to 55 °C (oil bath temperature) for 15 min before $Hg(CN)_2$ (80 mg, 0.32 mmol) was added. The reaction was followed by TLC analysis (40% EtOAc in toluene). After 30 min, the reaction mixture was concentrated under reduced pressure. To facilitate purification, the crude material was redissolved in Ac_2O (2.5 mL) and pyridine (2.5 mL), and the solution was stirred at room temperature overnight. The mixture was quenched with MeOH, diluted with EtOAc (100 mL), and washed with 1 M aqueous HCl (2 × 100 mL), H_2O (5 × 100 mL), saturated aqueous $NaHCO_3$ (100 mL), and H_2O (100 mL). After the organic phase was dried ($MgSO_4$) and concentrated under reduced pressure, flash column

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chromatography (silica gel 60, 35 → 50% EtOAc in toluene) afforded the desired disaccharide **16** (86.7 mg, 73%) as a sticky oil. R_f (40% EtOAc in toluene) 0.33. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.01 (d, 1H, $J_{NH,2}$ = 9.2 Hz, N*H*), 5.99 (d, 1H, $J_{1,2}$ = 9.2 Hz, H1), 5.35 (d, 1H, $J_{3,4}$ = 3.0 Hz, H4), 5.08 (dd, 1H, $J_{2',3'}$ = 3.3 Hz, $J_{3',4'}$ = 10.1 Hz, H3′), 5.05−5.01 (m, 2H, H2′), 5.00 (t, 1H, $J_{4',5'}$ = 10.0 Hz, H4′), 4.82 (d, 1H, $J_{1',2'}$ = 1.1 Hz, H1′), 4.40 (dd, 1H, $J_{2,3}$ = 10.8 Hz, H3), 4.11 (dd, 1H, $J_{5,6a}$ = 7.4 Hz, $J_{5,6b}$ = 14.3 Hz, H5), 4.08−3.96 (m, 3H, H5′, H6a, H6b), 3.82 (q, 1H, H2), 2.08 (s, 3H, OC(O)CH_3), 2.02 (s, 3H, OC(O)CH_3), 1.95 (s, 3H, OC(O)CH_3), 1.91 (s, 3H, NHC(O)CH_3), 1.28 (s, 9H, C(CH_3)$_3$), 1.19 (s, 9H, C(CH_3)$_3$), 1.15 (s, 9H, C(CH_3)$_3$), 1.14 (d, 3H, $J_{5',6'}$ = 7.0 Hz, H6′). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.5, 176.8 (OC(O)C(CH$_3$)$_3$), 171.2 (NHC(O)CH$_3$), 170.3, 170.2, 169.9 (OC(O)CH$_3$), 98.7 (C1′, $J_{C1',H1'}$ = 171 Hz as determined using non-decoupled ^{13}C NMR), 91.6 (C1), 75.1 (C3), 72.0 (C5), 70.8, 70.1, 68.7 (C2′, C3′, C4′), 67.8 (C4), 67.1 (C5′), 61.1 (C6), 53.5 (C2), 39.3, 38.9, 38.8 (*C*(CH$_3$)$_3$), 27.3, 27.1, 27.0 (C(*C*H$_3$)$_3$), 23.2 (NHC(O)*C*H$_3$), 20.93, 20.89, 20.8 (OC(O)*C*H$_3$), 17.3 (C6′). $[\alpha]_D^{299\ K}$ 9.0 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{35}H_{55}NO_{16}H$ 746.3594, found 746.3591.

Phenyl *O*-(*O*′-(2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl)-(1→3)-2-acetamido-2-deoxy-4,6-di-*O*-pivaloyl-β-D-galactopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-galactopyranoside (17). Disaccharide donor **16** (50 mg, 0.07 mmol), acceptor **13** (73 mg, 0.13 mmol), and Yb(OTf)$_3$ (10 mol %) were placed in a vial equipped with a sealed cap. Anhydrous CH_2Cl_2 (0.5 mL) was added, and the vial was flushed with Ar. The reaction mixture was heated to 80 °C under microwave irradiation. After 2 h, the reaction mixture was concentrated under reduced pressure. Flash column chromatography (silica gel 60, 35% EtOAc in toluene) afforded the desired trisaccharide **17** (59.3 mg, 75%) as a sticky oil. R_f (40% EtOAc in toluene) 0.46. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.55−7.20 (m, 20H, Ar), 5.49 (d, 1H, $J_{NH,2'}$ = 7.2 Hz, N*H*), 5.29 (d, 1H, $J_{3',4'}$ = 3.3 Hz, H4′), 5.10 (dd, 1H, $J_{2'',3''}$ = 3.3 Hz, $J_{3'',4''}$ = 9.8 Hz, H3″), 5.09−5.04 (m, 1H, H2″), 5.03 (t, 1H, $J_{4'',5''}$ = 9.6 Hz, H4″), 4.97 (d, 1H, $J_{1',2'}$ = 8.3 Hz, H1′), 4.94 (d, 1H, J_{gem} = 11.4 Hz, C*H*HPh), 4.79 (d, 1H, J_{gem} = 10.3 Hz, C*H*HPh), 4.76 (d, 1H, $J_{1'',2''}$ = 1.4 Hz, H1″), 4.75−4.69 (m, 3H, CH_2Ph), 4.72 (d, $J_{1,2}$ = 9.6 Hz as determined using 1D-selective TOCSY ^{1}H NMR, 1H, H1), 4.64 (d, 1H, CH*H*Ph), 4.57 (dd, 1H, $J_{3',4'}$ = 3.4 Hz, $J_{2',3'}$ = 10.8 Hz, H3′), 4.05−3.97 (m, 3H, H5″, H6′a, H6′b), 3.94 (t, 1H, $J_{1,2}$ = 9.4 Hz, H2), 3.90 (dd, 1H, $J_{5,6a}$ = 5.2 Hz, J_{gem} = 10.4 Hz, H6a), 3.86−3.80 (m, 2H, H4, H5′), 3.74 (dd, 1H, $J_{5,6b}$ = 7.0 Hz, H6b), 3.63−3.56 (m, 2H, H3, H5), 3.23 (dt, 1H, H2′), 2.12 (s, 3H, OC(O)CH_3), 2.04 (s, 3H, OC(O)CH_3), 1.99 (s, 3H, OC(O)CH_3), 1.83 (s, 3H, NHC(O)CH_3), 1.28 (s, 9H, C(CH_3)$_3$), 1.18 (s, 9H, C(CH_3)$_3$), 1.18 (d, 3H, $J_{5'',6''}$ = 5.0 Hz, H6″). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 177.9, 177.5 (OC(O)C(CH$_3$)$_3$), 171.9 (NHC(O)CH$_3$), 170.3, 170.2, 170.1 (OC(O)CH$_3$), 138.5, 138.3 (2C), 134.3, 131.0, 129.0, 128.6, 128.48, 128.45, 128.4, 128.1, 127.92, 127.89, 127.8, 127.7, 127.2 (Ar), 99.4 (C1′), 98.7 (C1″, $J_{C1'',H1''}$ = 173 Hz as determined using non-decoupled ^{13}C NMR), 87.0 (C1), 84.2 (C3), 77.5, 77.4 (C2, C5), 75.8, 74.4, 73.1 (CH$_2$Ph), 74.2 (C3′), 73.8 (C5′), 71.2 (C4), 70.9, 70.1, 68.8 (C2″, C3″, C4″), 68.9 (C6), 68.3 (C4′), 67.0 (C5), 61.5 (C6′), 56.0 (C2′), 39.3, 38.8 (*C*(CH$_3$)$_3$), 27.3, 27.2 (C(*C*H$_3$)$_3$), 23.5 (NHC(O)*C*H$_3$), 21.0, 20.9, 20.8 (OC(O)*C*H$_3$), 17.3 (C6″). $[\alpha]_D^{299\ K}$ −14.2 (*c* 1, $CHCl_3$). HRMS (ES+): calcd for $C_{63}H_{79}NO_{19}SH$ 1186.5040, found 1186.5049.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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