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Cooperative Brønsted Acid-Type Organocatalysis for the Stereoselective Synthesis of Deoxyglycosides

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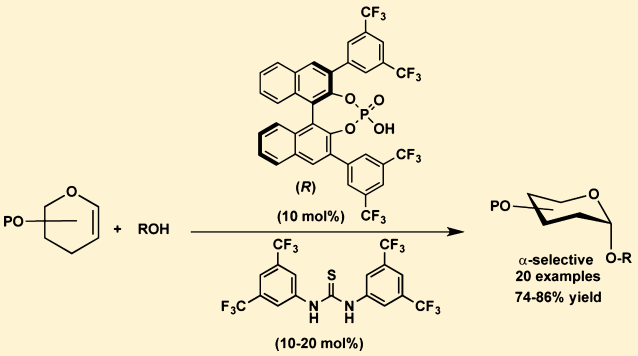
Supporting Information

ABSTRACT: A practical approach for the α-stereoselective synthesis of deoxyglycosides using cooperative Brønsted acid-type organocatalysis has been developed. The method is tolerant of a wide range of glycoside donors and acceptors, and its versatility is exemplified in the one-pot synthesis of a trisaccharide. Mechanistic studies suggest that thiourea-induced acid amplification of the chiral acid via H-bonding is key for the enhancement in reaction rate and yield, while stereocontrol is dependent on the chirality of the acid.

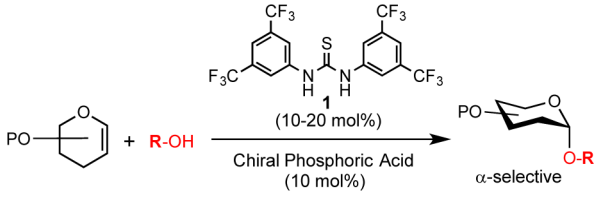


INTRODUCTION

Cooperative catalysis between thioureas and Brønsted acids, whereby the enhanced catalytic activity of the thiourea acts as an acid amplifier, has successfully been applied to asymmetric catalysis,[1] and more recently, reports have emerged from the Schmidt group applying this type of synergistic catalysis to glycosylation reactions involving *O*-glycosyl trichloroacetimidate donors to yield β-selective glycosides.[2]

Deoxy-hexoses are an important class of glycosides that occur widely in many natural products ranging from antibiotics to anticancer agents.[3] The stereoselective formation of glycosidic linkages employing 2-deoxyglycosides, where a substituent at C-2 that can direct the coupling reaction is lacking, is a very challenging endeavor and many efforts have been devoted to achieve their stereoselective synthesis.[4] Acid-catalyzed direct nucleophilic substitution on a glycal is one of the most widely used and efficient methods for their synthesis, however these reactions often give anomeric mixtures and side products (e.g., Ferrier rearrangement side-products).[4e,4r,5] As part of our ongoing interest in developing stereoselective glycosylation methods,[6] we decided to focus our attention on the synthesis of deoxyglycosides. Recently, our team reported a mild organocatalytic method for the preparation of 2-deoxygalactosides employing Schreiner's thiourea with excellent yields and α-selectivity.[4e,7] Although the method worked well with galactals, reactions needed to be refluxed over 24 h to reach completion, and in general, the thiourea catalyst was unable to activate glucal or rhamnal substrates. We postulated that synergistic acid/thiourea activation could provide a more efficient and practical glycosylation strategy for the preparation of deoxyglycosides than current methods that use hydrogen-bonding organocatalysts or acids as the sole promoters (Scheme 1).

Scheme 1. Proposed Cooperative Acid/Thiourea-Catalyzed Synthesis of Deoxyglycosides



To evaluate our hypothesis, thiourea **1** was chosen as the organocatalyst based on previous successful work from our group and others.[1a,b,2,7,8] Moreover, BINOL-derived phosphoric acids have been shown to be particularly effective in many asymmetric transformations,[9] including some success in glycosylations involving trichloroacetimidate glycoside donors.[10] More recently, chiral phosphoric acids have also been shown to catalyze the spiroketalization of cyclic enol ethers bearing a pendant alcohol nucleophile in a highly diastereoselective *syn*-selective concerted mechanism whereby the phosphoric acid acts as a bifunctional catalyst activating both the alkene and alcohol nucleophile.[11]

RESULTS AND DISCUSSION

Initial experiments began with the screening of a series of commercial BINOL-derived phosphoric acids for their ability to promote the stereoselective glycosylation of perbenzylated galactal **2a** with glucoside acceptor **3**[12] in the absence and presence of **1** in CH_2Cl_2 at room temperature. As summarized in Table 1, coupling reactions employing 10 mol % of chiral

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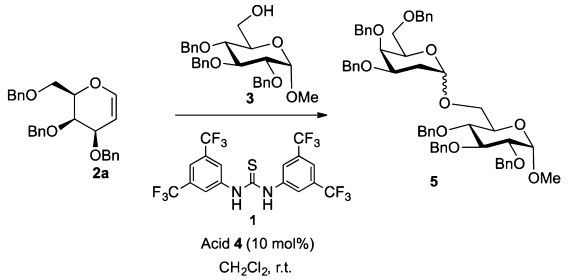
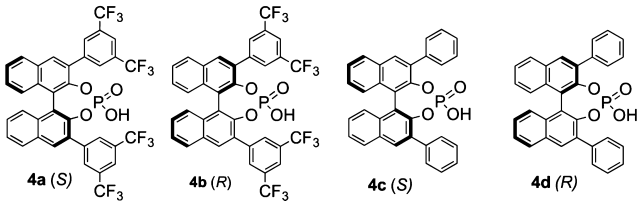
Table 1. Initial Catalyst Screen in the Glycosylation of Galactal 2a





entry	acid	time (h)	yield (%)[c]	α:β[c]
1	–	24	0	N/A
2	**4a**[a]	20	55	9:1
3	**4a**	3	82	7:1
4	**4b**[a]	20	70	>30:1
5	**4b**	3	89	>30:1
6	**4c**	20	82	8:1
7	**4d**	20	78	12:1
8	*p*TsOH[b] **4e**	16	76	20:1
9	$(O_2NC_6H_4O)_2P(O)OH$[b] 4f	6	65	9:1
10	**4b**[d]	3	89	>30:1
11	**4b**[e]	20	79	>30:1
12	**4b**[f]	20	74	3:1
13	**4b**[g]	20	75	>30:1

[a]Reactions in the absence of **1**. [b]5 mol %, as reactions at 10 mol % lead to rapid hydrolysis of **2a**. [c]From ^{1}H NMR; N/A = not applicable. [d]20 mol % of **1**. [e]Reaction at −40 °C-10 °C. [f]Reaction in MeCN. [g]Reaction in diethyl ether.

phosphoric acids (*S*)-**4a** and (*R*)-**4b** (pK_a = 2.63 in DMSO)[13] proceeded cleanly to give product **5**[7] in 55 and 70% yields, albeit after 20 h (entries 2 and 4) and with different degrees of α:β stereocontrol 9:1 and >30:1, respectively. When 10 mol % of **1** was added as the cocatalyst (entries 3 and 5), reactions were complete within 3 h, and glycoside **5** was obtained in improved yields of 82% and 89%, respectively, and with an α:β ratio of 7:1 for the (*S*)-acid and >30:1 for the (*R*)-acid catalyst. These results demonstrate the strong influence of thiourea **1**, as a cocatalyst, on reaction rate and yield, while the stereochemistry of the acid catalyst has the biggest effect on the α:β selectivity of the glycosylation reaction. This observation is not completely surprising, as Bennett and co-workers had already reported that the stereo-outcome of acid-catalyzed glycosylation reactions involving trichloroacetimidate donors was dependent on the chirality of the catalyst, the configuration of the leaving group in the glycoside donor, and the nature of the nucleophile acceptor.[14] It is important to note that glycosylation reactions with 10 mol % of thiourea **1** in CH_2Cl_2 (in the absence of acid) yielded only starting material (entry 1) as previously observed by our team,[7] likely due to catalyst inactivation via self-association at high catalyst loading,[1c] further demonstrating the importance of the synergy between both cocatalysts.

The use of achiral *p*-toluenesulfonic acid (*p*TsOH, 5 mol %) **4e** or bis(4-nirophenyl)hydrogen phosphate **4f** or less acidic phosphoric catalysts **4c** and **4d** (pK_a = 3.86)[13] in combination with **1** proved to be detrimental to reaction rate, yield, and stereocontrol, with reactions needing 6−20 h for completion (entries 6−9). Next, we decided to explore the reaction conditions using **4b** and **1** as the cocatalyst. Increasing the acid loading to 20 mol % in the presence of 10 mol % of **1** had no effect on the outcome of the model reaction (entry 10), while lowering the reaction temperature significantly slowed product formation (entry 11). Changing the reaction solvent to either MeCN or diethyl ether (Table 1, entries 12 and 13) had a detrimental effect on the rate of the reaction. In the case of MeCN, which is known to participate during the glycosylation reaction involving oxocarbenium ions favoring β-glycoside products,[15] significant erosion of the α-selectivity was observed with **5** being isolated as a 3:1 α:β mixture (entry 11 vs entry 5).

Having established the optimum reaction conditions, our attention was then turned to exploring the scope of the cooperative catalytic system on coupling reactions between **2a** and a range of OH nucleophiles **6a**−**6j** (Table 2). In all cases, reactions proceeded smoothly within 2−6 h and in excellent yields and α-selectivity, as determined by the characteristic anomeric signals in the ^{1}H- and ^{13}C NMR spectra,[4i,6b,7] demonstrating that the catalytic system tolerates the presence of common alcohol and amine protecting groups such as acetals, ethers, esters, and carbamates. Glycosylations with primary alcohols **6a**−**6d** and Boc-protected serine **6h** afforded the corresponding glycoside products in 80−86% yield within 2−3 h and with a >30:1 α:β ratio (entries 1−4 and 8). Reactions with secondary alcohols such as phenols **6e**, glycosides **6f** and **6g**, Boc-protected threonine **6i**, or cholesterol **6j** prove to be more challenging and required higher reaction temperatures (45 °C) and the use of 20 mol % of **1** in combination with 10 mol % of **4b** in CH_2Cl_2, to drive reactions to completion within 5−6 h. Under these optimized conditions, the desired products were thus isolated with similar high α-selectivity (>30:1 α:β ratio) and yields of 74−85% (Table 2, entries 5−7, 9, and 10).

Our attention then turned to exploring the scope of the glycal donor. To that end, a series of differentially protected galactals **2b**−**2f**, glucals **8a**−**8c**, and L-rhamnal **9** bearing methyl, acetate, benzyl, allyl, silyl ether, and siloxane protecting groups were prepared and subjected to the reaction conditions with **3** or **6k**, which bears a secondary OH, as the acceptor (Table 3). Pleasingly, high yields and excellent selectivities for α-linked glycosides were obtained in most examples (entries 1, 3−5, and 7). Although substrate **2d**, which bears an acetate group at C-6, shows that ester groups can be tolerated (entry 3), in the case of acetyl-protected galactal **2c** (entry 2), an inseparable mixture of glycosides including Ferrier side-products[16] was observed after 20 h under the more forcing conditions (20 mol % of **4b** and reflux in CH_2Cl_2). This lack of reactivity has been previously noted for glycals bearing a deactivating group (e.g., ester) at C-3, which is in close proximity to the reacting double bond.[7,17] Encouragingly, the reaction was also amenable to glycosylations with glucal substrates, and both benzyl-derivative **8a** and 3,4-*O*-siloxane protected **8b**[6b] or **8c**[6b] afforded the corresponding glycosides with high α-stereocontrol within 2 h, albeit **11a** was isolated in a lower yield (40%) than **11b** (81% yield) or **11c** (82%). This is not completely unexpected, as **8b** has been shown to be a more

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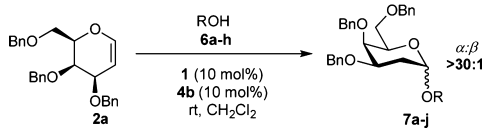
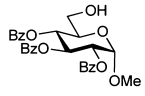
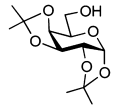
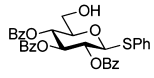
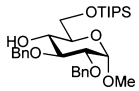
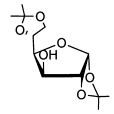
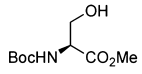
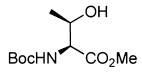
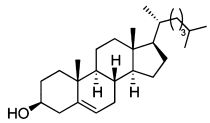
Table 2. Acceptor Scope in Glycosylation Reactions with Galactal 2a



Entry	ROH	Time	Yield (%)[a]
1	BnOH 6a	3	80
2	 6b	3	86
3	 6c	2	83
4	 6d	2	82
5	PhOH 6e	5[b]	84
6	 6f	6[b,c]	74
7	 6g	6[b]	78
8	 6h	3	83
9	 6i	5[b]	85
10	 6j	5[b]	74

[a]Yield of isolated product. [b]Reaction performed at 45 °C, 1.5 equiv of donor and thiourea **1** (20 mol %) (5−6 h). [c]Product was isolated as the desilylated disaccharide for purification purposes.

effective glycosylation donor than its benzylated counterpart (Table 3, entries 6−8).

2,6-Dideoxyglycosides are also an important class of compounds, and their stereoselective synthesis is further complicated by the lack of oxygen substituents at both C-2 and C-6.[18] Excitingly, activation of 3,4-*O*-siloxane protected L-rhamnal **9** afforded **12** in 74% yield within 3 h and with an 8:1 α:β ratio (entry 9). It is important to highlight that thiourea **1** alone was not able to activate any of the glucal and rhamnal substrates. These results further emphasize that the synergistic catalytic system works well across a range of reactivity profiles for both glycal donors and nucleophile acceptors.

Having found that thioglycosides are inert under the cooperative organocatalytic glycosylation conditions (Table 2, entry 4), we decided to evaluate the methodology in a three-component, one-pot synthesis of trisaccharide **13** (Scheme 2). Thus, galactal **2a** was reacted with thioglycoside **6d** under the optimized conditions. Following disaccharide formation, acceptor **6c** was added to the same pot along with NIS and catalytic TMSOTf and trisaccharide **13** was obtained in 58% yield with complete stereoselectivity.

To probe the mechanism of our reaction, a 3:1 α/β-anomeric mixture of **5** was subjected to the reaction conditions and gave no change in the anomeric ratio, indicating that the high α-selectivity is not the result of anomerization. Moreover, reaction with deuterated galactal **14** yielded disaccharide **15** with the newly formed bonds *cis* to each other, as evidenced by the ^{1}H NMR shifts associated with H-1 (δ 4.62 ppm, d, 1H, J = 2.7 Hz) and H-2 (δ 2.03−1.99, m, 1H, H-2′) of the deuterated 2-deoxygalactoside[7] (Scheme 3), which suggest that both the C−H and the C−O bond formation steps are *syn*-diastereoselective. ^{1}H NMR spectroscopy studies in CD_2Cl_2 of mixtures of thiourea **1** and acid **4b** showed proton shifts associated with the aromatic signals from both acid and thiourea, indicating that an interaction between both catalysts occurs in solution. Furthermore, NMR mixtures of thiourea **1**, acid **4b**, and glycoside donor **2a** showed additional downfield H-shifts associated with the anomeric protons in **2a** (δ 6.33 ppm), while shifts for the OH signal from acceptor **3** (from δ 1.84 ppm to δ 2.54 ppm) were detected in mixtures of **1**, **4b**, and **3** (see Supporting Information for details). Thiourea **1** and chiral phosphoric acid **4b** have been shown to individually hydrogen bond with OH nucleophiles.[1b,11] Thus, as expected, mixtures of **3** and 10 mol % of thiourea **1** or **3** mixed with 10 mol % of acid **4b** also showed shifts associated with the OH protons of glycosyl acceptor **3**, although the magnitude of those shifts was different to that of mixtures of **3** and both cocatalysts (**1** and **4b**). These results further demonstrate that the combination of **1** and chiral acid (*R*)-**4b** leads to a cooperative catalytic system that can activate both enol ether and OH nucleophiles in a synergistic fashion, leading to an enhancement in reaction rate and α-stereocontrol of the glycosylation reaction. As proposed in Scheme 3, our findings suggest that a hydrogen-bond-mediated complex between thiourea **1** and acid **4b** leads to a urea-induced acid amplification, and proton addition from this complex to the less hindered face of the enol ether (**I**) forms a short-lived oxocarbenium intermediate (**II**) that is rapidly trapped by the OH nucleophile which is in turn activated by the phosphate intermediate that is generated *in situ*, to give **15**. This might help to explain the effect the chirality of the phosphoric acid has on the stereo outcome of the glycosylation reaction.

CONCLUSIONS

In summary, we have described a practical, highly stereoselective, and efficient direct glycosylation method for glycals using a cooperative Brønsted acid-organocatalytic promoter system. The reaction is widely applicable to a range of glycosyl donors and nucleophile acceptors, proceeds with excellent yields and high selectivity for the α-anomer, and is tolerant of most common protecting groups. We note that the stereoselectivity of the reaction is highly dependent on the chirality of the acid, with (*R*)-**4b** leading to the formation of α-glycosides preferentially, while both yield and rate of reaction are greatly enhanced by the synergistic interaction between thiourea and acid. Moreover, we exemplify the generality of the approach in the stereoselective synthesis of a series of disaccharides, glycosyl-amino acids, and other glycoconjugates and also in the one-pot chemo- and stereoselective synthesis of a trisaccharide. Further work from our lab is underway to exploit

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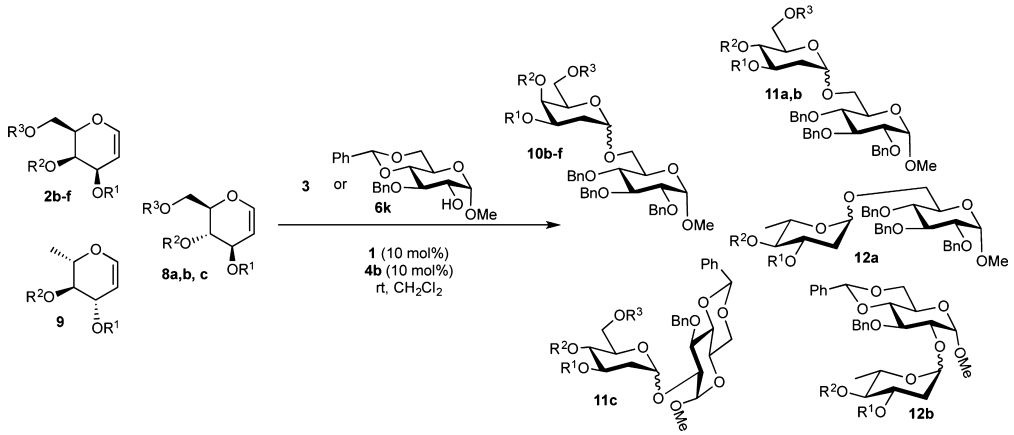
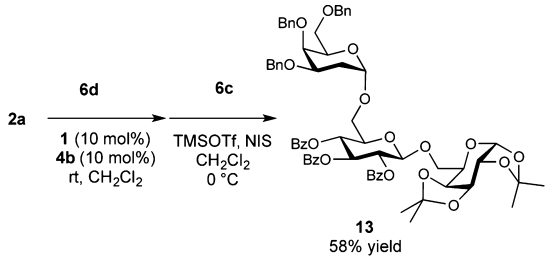
Table 3. Reaction of Glycals 2b–2f, 8a, 8b, and 9 with Model Acceptor 3 or 6k[a]



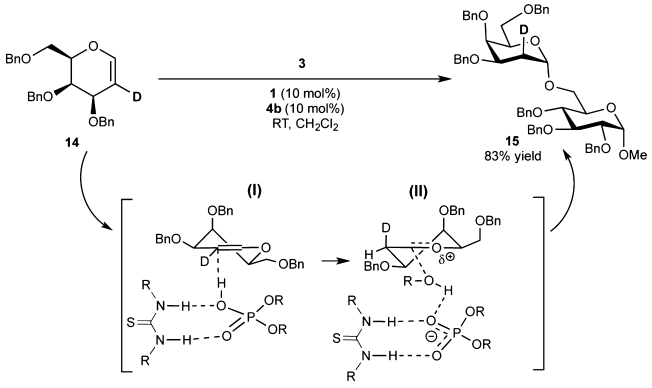
entry		R^1	R^2	R^3	time (h)	product	yield (%)[a]	α:β[b]
1	**2b**	Me	Me	Me	2	**10b**	80	>30:1
2	**2c**	Ac	Ac	Ac	20[c]	**10c**	N/A	N/A
3	**2d**	Bn	Bn	Ac	3	**10d**	86	>20:1
4	**2e**	allyl	allyl	allyl	3	**10e**	80	>30:1
5	**2f**	TBS	TBS	TBS	3	**10f**	79	>30:1
6	**8a**	Bn	Bn	Bn	2	**11a**	40[d]	>30:1
7	**8b**	$O[Si(i\text{-}Pr)_2]_2$		Bn	3	**11b**	81	>30:1
8	**8c**	$O[Si(i\text{-}Pr)_2]_2$		OTIPS	6[c]	**11c**	82	only α
9	**9**	$O[Si(i\text{-}Pr)_2]_2$		–	3	**12a**	74	8:1
10	**9**	$O[Si(i\text{-}Pr)_2]_2$		–	6[c]	**12b**	87	10:1

[a]Isolated yield. [b]Determined by ^{1}H NMR. [c]Reaction performed at 45 °C, 1.5 equiv of donor, and 0.2 equiv of thiourea. [d]Mixture of Ferrier product and disaccharide were produced. N/A: No reaction.

Scheme 2. One-Pot Trisaccharide Synthesis



Scheme 3. Proposed Mechanism



Scheme 3. Proposed mechanism.

the cooperative catalysis between organocatalysts and chiral acids for the stereoselective synthesis of other important glycosides and chiral acetals.

EXPERIMENTAL SECTION

General. Dry DCM was obtained by distillation using standard procedures or by passage through a column of anhydrous alumina. Reactions requiring anhydrous conditions were performed under nitrogen. Glassware and needles were either flame-dried immediately prior to use or placed in an oven (150 °C) for at least 2 h and allowed to cool either in a desiccators or under reduced pressure. Liquid reagents, solutions, or solvents were added via syringe through rubber septa. Solid reagents were added via Schlenk-type adapters. Reactions were monitored by TLC on Kieselgel 60 F254 (Merck). Detection was by examination under UV light (254 nm) and by charring with 10% sulfuric acid in ethanol. Flash column chromatography was performed using silica gel [Merck, 230–400 mesh (40–63 μm)]. Extracts were concentrated *in vacuo* using both a Büchi rotary evaporator (bath temperatures up to 40 °C) at a pressure of either 15 mmHg (diaphragm pump) or 0.1 mmHg (oil pump), as appropriate, and a high-vacuum line at room temperature. ^{1}H NMR and ^{13}C NMR spectra were measured in the solvent stated at 400 or 500 MHz. Chemical shifts are quoted in parts per million from residual solvent peak ($CDCl_3$: ^{1}H, 7.26 ppm and ^{13}C, 77.16 ppm) and coupling constants (J) given in Hertz. Multiplicities are abbreviated as bs (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or combinations thereof. Positive ion matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were recorded using an HP-MALDI instrument using gentisic acid matrix. Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT mass spectrometer or a VG Quattro mass spectrometer.

General Glycosylation Procedure. Monosaccharide donor (1 equiv) and acceptor (0.83 equiv (~0.1 mmol)) were weighed into a microwave vial and placed under vacuum for 1 h, after which time the microwave vial was filled with N_2. A mixture of chiral acid (0.1 equiv) and thiourea (0.1 equiv for primary acceptors and 0.2 equiv for secondary acceptors) in anhydrous DCM (1 mL) was stirred for 30 min and then added to the microwave vial containing the donor and acceptor. The reaction mixture was stirred at RT (primary acceptors)

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or heated at reflux (secondary acceptors) until the reaction was determined to be complete by either TLC or NMR analysis of the crude material. The reaction mixture was purified by silica gel flash column chromatography.

*Methyl 2,3,4-Tri-O-benzyl-6-O-(2-deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**5**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **3** (46 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 6:1 to 3:1): **5** as a yellow oil (68 mg, 89%). ^{1}H NMR (400 MHz; CDCl3) δ 7.39−7.19 (30H, m, Ph), 5.02 (1H, app d, J = 2.4 Hz, H-1′), 4.98 (1H, d, J = 10.8 Hz, OCH HPh), 4.91 (1H, d, J = 11.6 Hz, OCH HPh), 4.84 (1H, d, J = 10.9 Hz, OCH HPh), 4.80 (1H, d, J = 10.8 Hz, OCHH Ph), 4.79 (1H, d, J = 12.2 Hz, OCH HPh), 4.68 (1H, d, J = 12.2 Hz, OCHH Ph), 4.60 (1H, d, J = 3.6 Hz, H-1), 4.60 (1H, d, J = 11.6 Hz, OCHH Ph), 4.57 (2H, s, OCH2 Ph), 4.52 (1H, d, J = 10.9 Hz, OCHH Ph), 4.41 (1H, d, J = 12.0 Hz, OCH HPh), 4.34 (1H, d, J = 12.0 Hz, OCHH Ph), 3.98 (1H, t, J = 9.2 Hz, H-3), 3.90−3.84 (3H, m, H-3′, H-4′, H-5′), 3.81 (1H, dd, J = 11.2, 4.6 Hz, H-6a), 3.72 (1H, ddd, J = 10.0, 4.5, 1.6 Hz, H-5), 3.61 (1H, dd, J = 11.4, 1.7 Hz, H-6b), 3.54 (1H, dd, J = 9.5, 7.3 Hz, H-6a′), 3.51 (1H, dd, J = 9.5, 3.5 Hz, H-2), 3.50 (1H, dd, J = 9.5, 5.9 Hz, H-6b′), 3.46 (1H, dd, J = 9.9, 9.0 Hz, H-4), 3.31(3H, s, OCH3), 2.20 (1H, td, J = 12.4, 3.7 Hz, H-2a′), 2.01 (1H, app dd, J = 12.7, 4.5 Hz, H-2b′); ^{13}C NMR (126 MHz; CDCl3) δ 139.0 (4 °C), 138.9 (4 °C), 138.5 (4 °C), 138.4 (4 °C), 138.30 (4 °C), 138.27 (4 °C), 128.6 (CH), 128.54 (CH), 128.45 (CH), 128.33 (CH), 128.32 (CH), 128.18 (CH), 128.16 (CH), 128.0 (CH), 127.82 (CH), 127.81 (CH),127.78 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 98.4 (C-1′), 98.0 (C-1), 82.3 (C-3), 80.1 (C-2), 78.1 (C-4), 76.0 (C H2 Ph), 75.1 (C H2 Ph), 74.41, 74.35 (C-3′, C H2 Ph), 73.5 (C H2 Ph), 73.4 (C H2 Ph), 73.1 (C-4′), 70.4, 70.2 (C-5′, CH2Ph), 70.0 (C-5), 69.5 (C-6′), 66.2 (C-6), 55.2 (OCH3), 31.2 (C-2′). Spectroscopic data in agreement with literature.[7]

*Benzyl 2-Deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranoside (**7a**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6a** (11 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 10:1 to 8:1): **7a** as a colorless oil (42 mg, 80%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.22 (20H, m, Ph), 5.08 (1H, d, J = 3.5 Hz, H-1), 4.93 (1H, d, J = 11.6 Hz, OC*H*HPh), 4.67 (1H, d, J = 11.9 Hz, OC*H*HPh), 4.62 (1H, d, J = 11.7 Hz, OCH*H*Ph), 4.59 (1H, m, OCH_2Ph), 4.50 (1H, d, J = 11.8 Hz, OC*H*HPh), 4.47 (2H, d, J = 11.9 Hz, OCH*H*Ph), 4.43 (1H, d, J = 11.8 Hz, OCH*H*Ph), 3.99 (1H, ddd, J = 12.0, 4.6, 2.5 Hz, H-3), 3.96 (1H, t, J = 6.7 Hz, H-5), 3.94 (1H, bs, H-4), 3.61 (1H, dd, J = 9.4, 6.8 Hz, H-6a), 3.56 (1H, dd, J = 9.4, 6.0 Hz, H-6b), 2.25 (1H, td, J = 12.4, 3.8 Hz, H-2a), 2.07−2.01 (1H, m, H-2b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1 (4 °C), 138.7 (4 °C), 138.3 (4 °C), 138.0 (4 °C), 128.54 (CH), 128.52 (CH), 128.51 (CH), 128.37 (CH), 128.35 (CH), 128.1 (CH), 127.9 (CH), 127.81 (CH), 127.77 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 97.3 (H-1), 75.0 (C-3), 74.4 (OCH_2Ph), 73.6 (OCH_2Ph), 73.2 (C-4), 70.7 (OCH_2Ph), 70.3 (C-5), 69.7 (C-6), 69.1 (OCH_2Ph), 31.3 (C-2). ESI-HRMS for $C_{34}H_{36}NaO_5^+$ (MNa^+) calcd: 547.2460; found: 547.2459. $[\alpha]_D$ = +24 (c = 1, $CHCl_3$).

*Methyl 2,3,4-Tri-O-benzoyl-6-O-(3,4,6-tri-O-benzyl-2-deoxy-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**7b**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6b** (50 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 6:1 to 4:1): **7b** as a white solid (79 mg, 86%). Spectroscopic data in agreement with literature.[7]

*6-O-(3,4,6-Tri-O-benzyl-2-deoxy-α-D-lyxo-hexapyranosyl)-1,2,3,4-di-O-isopropylidene-α-D-galactopyranoside (**7c**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6x** (26 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 6:1 to 3:1) **7c** as a colorless oil (56 mg, 83%). Spectroscopic data in agreement with literature.[7]

*Phenyl 2,3,4-Tri-O-benzoyl-6-O-(2-deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranosyl)-α-D-thioglucopyranoside (**7d**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6d** (58 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 7:1 to 4:1): **7d** as a white solid (82 mg 82%). Spectroscopic data in agreement with literature.[7]

*Phenyl 2-Deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranosyl (**7e**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6e** (9 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc 20:1 to 12:1): **7e** as a colorless oil (43 mg 84%): ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.42−6.98 (20H, m, Ph), 5.59 (1H,d, J = 3.4 Hz, H-1), 4.85 (1H, d, J = 11.5 Hz, OC*H*HPh), 4.72 (2H, bs, OCH_2Ph), 4.67 (1H, d, J = 11.5 Hz, OCH*H*Ph), 4.28 (1H, d, J = 11.6 Hz, OCH*H*Ph), 4.24 (1H, d, J = 11.6 Hz, OCH*H*Ph), 4.02 (1H,ddd, H-3), 3.93 (1H, t, J = 7.3 Hz, H-5), 3.80 (1H, bs, H-4), 3.53 (1H, dd, J = 9.3, 7.3 Hz, H-6a), 3.40 (1H, dd, J = 9.3, 5.7 Hz, H-6b), 2.28 (1H, td, J = 12.4, 3.6 Hz, H-2a), 2.08 (1H, dd, J = 12.4, 4.4 Hz, H-2b); ^{13}C NMR (101 MHz; $CDCl_3$) δ 156.8 (4 °C), 138.8 (4 °C), 138.4 (4 °C), 138.0 (4 °C), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.1 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 121.9 (CH), 116.6 (CH), 96.5 (C-1), 74.5 (CH_2Ph), 74.4 (C-3), 73.3 (CH_2Ph), 72.8 (C-4), 70.6 (CH_2Ph), 70.5 (C-5), 69.1 (C-6), 31.2 (C-2). ESI-HRMS for $C_{33}H_{34}NaO_5^+$ (MNa^+) calcd: 533.2304; found: 533.2296. $[\alpha]_D$ = +36 (c = 1, $CHCl_3$).

*Methyl 2,3-Di-O-benzyl-4-O-(2-deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**7f**).* The general glycosylation procedure was followed using donor **2a** (50 mg, 0.12 mmol) and acceptor **6f** (53 mg, 0.10 mmol). The crude material was then dissolved in a 1 M THF solution of TBAF (0.5 mL, 0.5 mmol) and stirred for 2 h. The solution was then concentrated *in vacuo* and purified by column chromatography (Hexane:EtOAc, 6:1 to 4:1), affording **7f** as a colorless oil (58 mg, 74%). Spectroscopic data in agreement with literature.[7]

*3-O-(2-Deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranoside)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside (**7g**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6g** (26 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 6:1 to 3:1): **7g** as a white solid (53 mg 78%). Spectroscopic data in agreement with literature.[19]

*O-(2-Deoxy-3,4,6-tri-O-benzyl-D-lyxo-hexapyranosyl)-N-(tert-butoxycarbonyl)-L-serine Methyl Ester (**7h**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6h** (22 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 10:1 to 4:1): **7h** as a pale yellow oil (53 mg 83%). Spectroscopic data in agreement with literature.[20]

*O-(2-Deoxy-3,4,6-tri-O-benzyl-D-lyxo-hexapyranosyl)-N-(tert-butoxycarbonyl)-L-threonine Methyl Ester (**7i**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6i** (23 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 10:1 to 4:1): **7i** as a pale yellow oil (56 mg 85%). ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.37−7.23 (15H, m, Ph), 5.14 (1H, J = 9.8 Hz, NH), 4.94−4.89 (2H, m, H-1, OC*H*HPh), 4.62−4.53 (3H, m, OCH_2Ph, H-6a), 4.51 (1H, d, J = 11.8 Hz, OCH*H*Ph), 4.43 (1H, d, J = 11.8 Hz, OCH*H*Ph), 4.30−4.25 (2H, m, OCH*H*Ph, OC*H*(CH_3)CH(NH)), 3.94−3.89 (2H, m, H-6b, OCH(CH_3)C*H*(NH)), 3.84 (1H, m, H-3), 3.72 (3H, s, OCH_3), 3.60−3.51 (2H, m, 2H-4, H-5), 2.15 (1H, td, J = 12.3, 3.8 Hz, H-2a), 1.86 (1H, dd, J = 12.4, 4.4 Hz, H-2b), 1.48 (9H, s, 3 × CH_3), 1.25 (3H, d, J = 6.5 Hz, OCH(CH_3)CH(NH)); ^{13}C NMR (126 MHz; $CDCl_3$) δ 171.6 (CO), 156.0 (CO), 138.7 (4 °C), 138.3 (4 °C), 138.0 (4 °C), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 99.3 (C-1), 80.0 (4 °C), 75.3 (CH_2Ph), 74.2 (CH_2Ph), 74.2 (C-3), 73.5 (CH_2Ph), 72.9 (C-4), 70.3 [OCH(CH_3)CH(NH)], 70.3 (C-6), 58.2 [OCH(CH_3)CH(NH)], 52.2 (OCH_3), 31.2 (C-2), 28.3 (3 x OCH_3), 18.3 [OCH(CH_3)CH(NH)]. ESI-HRMS for $C_{37}H_{47}NO_9Na^+$ (MNa^+) calcd: 672.3149; found: 672.3144. $[\alpha]_D$ = +20 (c = 1, $CHCl_3$).

*Cholesteryl (2-Deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranosyl) (**7j**).* Following the general glycosylation procedure, donor **2a** (50 mg, 0.12 mmol) and acceptor **6j** (39 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 10:1 to 6:1): **7j** as a colorless oil (57 mg 74%). Spectroscopic data in agreement with literature.[21]

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*Methyl 2,3,6-Tri-O-benzyl-4-O-(2-deoxy-3,4,6-tri-O-methoxy-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**10b**).* Following the general glycosylation procedure, donor **2b** (23 mg, 0.12 mmol) and acceptor **3** (47 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 4:1 to 2:1): **5b** as a colorless oil (52 mg, 80%): ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41−7.22 (15H, m, Ph), 5.02−4.96 (2H, m, H-1′, OC*H*HPh), 4.92 (1H,d, J = 10.9 Hz, OC*H*HPh), 4.83−4.77 (2H, m, 2 OC*H*HPh), 4.68 (1H, d, J = 12.2 Hz, OC*H*HPh), 4.62 (1H, d, J = 4.6 Hz, OC*H*HPh), 4.60 (1H, d, J = 2.9 Hz, H-1), 4.01 (1H, t, J = 9.2 Hz, H-3), 3.88−3.79 (2H, m, H-4, 6a′), 3.74 (1H, ddd, J = 9.9, 4.4, 1.8 Hz, H-5), 3.63 (1H, dd, J = 11.4, 2.0 Hz, H-6b′), 3.61−3.56 (2H, m, 3′,5′), 3.56−3.51 (5H, m, H-4′, OCH_3, H-2), 3.51−3.40 (2H, m, H-6a, H-6b), 3.39, 3.37 (6H, 2s, 2 × OCH_3), 3.30 (3H, s, OCH_3), 2.04−1.90 (2H, m, H-2a′,H-2b′). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (4 °C), 138.2 (4 °C), 138.1 (4 °C), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.1 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 98.2 (C-1′), 97.9 (C-1), 82.1 (C-3), 80.0 (C-2), 77.8 (C-1), 75.9, 75.8, 74.9 (C-3′, C-4′, C-5′), 74.4 (CH_2Ph), 73.3 (CH_2Ph), 71.5 (CH_2Ph), 69.7 (C-6), 69.7 (C-5), 66.1 (C-4), 60.9 (OCH_3), 59.1 (OCH_3), 56.1 (OCH_3), 55.1 (OCH_3), 30.7 (C-2′) . ESI-HRMS for $C_{37}H_{48}NaO_{10}^+$ (MNa^+) calcd: 675.3145; found: 675.3144. $[\alpha]_D$ = +51 (c = 1, $CHCl_3$).

*Methyl 2,3,4-Tri-O-benzyl-4-O-6-O-(6-O-acetyl-2-deoxy-3,4-di-O-benzyl-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**10d**).* Following the general glycosylation procedure, donor **2d** (50 mg, 0.12 mmol) and acceptor **3** (47 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc 6:1 to 3:1): **10d** as a colorless oil (73 mg, 86%): ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41−7.19 (25H, m, Ph), 5.03 (1H, d, J = 3.3 Hz, H-1′), 4.99 (1H, d, J = 10.7 Hz, OC*H*HPh), 4.94 (1H, d, J = 11.7 Hz, OC*H*HPh), 4.87 (1H, d, J = 11.0 Hz, OC*H*HPh), 4.83−4.77 (2H, m, OC*H*HPh), 4.72−4.63 (2H, m, OC*H*HPh), 4.63−4.55 (3H, m, H-1, OC*H*HPh), 4.48 (1H, d, J = 11.1 Hz, OC*H*HPh), 4.11−3.95 (3H, m, H-3, H-6a′,H-6b′), 3.84 (1H, ddd, J = 11.9, 4.5, 2.3 Hz, H-3′), 3.74 (4H, m, H-4′, H-6a, H-2, H-5), 3.60 (1H, d, J = 10.5 Hz, H-6b), 3.51 (1H, dd, J = 9.6, 3.6 Hz, H-2), 3.43 (1H, t, J = 9.3 Hz, H-4), 3.31 (3H, s, OCH_3), 2.20 (1H, td, J = 12.3, 3.6 Hz, H-2a′), 2.03 (1H, dd, J = 12.5, 4.4 Hz, H-2b′), 1.85 (3H, s, CH_3CO). ^{13}C NMR (101 MHz,$CDCl_3$) δ 170.5 (CH_3CO) 138.6 (4 °C), 138.4 (4 °C), 138.2 (4 °C), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.7 (CH), 127.5 (CH), 127.4 (CH), 98.0 (C-1′), 97.8 (C-1), 82.1 (C-3), 79.9 (C-2), 77.9 (C-4), 75.8 (CH_2Ph), 74.9 (CH_2Ph), 74.2 (C-3′), 74.0 (CH_2Ph), 73.2 (CH_2Ph), 72.5 (C-5′), 70.3 (CH_2Ph), 69.7 (H-4′), 69.1(H-5), 65.9 (C-6), 64.0 (C-6′), 55.0 (OCH_3), 30.7 (C-2′), 20.8 ($COCH_3$). ESI-HRMS for $C_{50}H_{56}NaO_{11}^+$ (MNa^+) calcd: 855.3720; found: 855.3711. $[\alpha]_D$ = +8 (c = 1, $CHCl_3$).

*Methyl 2,3,6-Tri-O-benzyl-4-O-(2-deoxy-3,4,6-tri-O-allyl-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**10e**).* Following the general glycosylation procedure, donor **2e** (32 mg, 0.12 mmol) and acceptor **3** (46 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 5:1 to 4:1): **10e** as a pale yellow oil (58 mg, 80%): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.41−7.22 (15H, m, Ph), 6.00−5.79 (3H, m, CH═CH_2), 5.30 (1H, dt, J = 3.4, 1.6 Hz, CH═CH_2), 5.26 (1H, q, J = 1.8 Hz, CH═CH_2), 5.23 (1H, tt, J = 2.3, 1.1 Hz, CH═CH_2), 5.17 (1H, dt, J = 3.4, 1.6 Hz, CH═CH_2), 5.15−5.12 (2H, m, CH═CH_2), 5.01 (1H, d, J = 2.6 Hz, H-1′), 4.99 (1H, d, J = 10.8 Hz, OC*H*HPh), 4.91 (1H, d, J = 10.8 Hz, OC*H*HPh), 4.82 (1H, d, J = 5.3 Hz, OC*H*HPh), 4.80 (1H, d, J = 6.6 Hz, OC*H*HPh), 4.69 (1H, d, J = 12.2 Hz, OC*H*HPh), 4.62 (1H, d, J = 2.5 Hz, H-1), 4.61 (1H, d, J = 4.8 Hz, OC*H*HPh), 4.35 (1H, ddt, J = 12.7, 5.6, 1.4 Hz, OC*H*HCH═CH_2), 4.13−4.06 (1H, m, OC*H*HCH═CH_2), 4.05−4.02 (2H, m, OC*H*HCH═CH_2, H-3), 4.01−3.97 (1H, m, OC*H*HCH═CH_2), 3.94−3.91 (2H, OC*H*HCH═CH_2), 3.88−3.81 (2H, m, H-4, H-6a′), 3.78−3.73 (3H, m, H-4′, H-3′, H-5), 3.64 (1H, dd, J = 11.4, 2.0 Hz, H-6b′), 3.58 (1H, dd, J = 9.3, 7.3 Hz, H-5′), 3.56−3.52 (1H, m, H-2), 3.51−3.46 (2H, m, H-6a, H-6b), 3.37 (3H, s, OCH_3), 2.14−2.07 (1H, m, H-2a′), 1.95−1.90 (1H, m, H-2b′).^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7 (4 °C), 138.2 (4 °C), 138.1 (4 °C), 135.6 (CH═CH_2), 134.8 (CH═CH_2), 134.6 (CH═CH_2), 128.5 (CH), 128.4 (CH), 128.04 (CH), 127.9 (CH), 127.7 (CH), 127.7 (CH), 116.9 (CH═CH_2), 116.8 (CH═CH_2), 116.6 (CH═CH_2), 98.2 (C-1′), 97.9 (C-1), 82.1 (C-3), 80.0 (C-5′), 77.9 (C-2), 75.8 (CH_2Ph), 74.9 (CH_2Ph), 73.9 (C-4′), 73.5 (OCH_2CH), 73.3 (CH_2Ph), 72.4 (H-5), 72.2 (OCH_2CH), 69.8 (2C, C-4, C-3′), 69.2 (OCH_2CH), 69.1 (C-6), 66.0 (C-6′), 55.0 (OCH_3), 31.1 (C-2′). ESI-HRMS for $C_{43}H_{54}NaO_{10}^+$ (MNa^+) calcd: 753.3615; found: 753.3610. $[\alpha]_D$ = +20 (c = 1, $CHCl_3$).

*Methyl 2,3,6-Tri-O-benzyl-4-O-(2-deoxy-3,4,6-tri-O-tert-butyldimethylsilyl-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**10f**).* Following the general glycosylation procedure, donor **2f** (50 mg, 0.10 mmol) and acceptor **3** (39 mg, 0.09 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 5:1 to 4:1): **10f** as a colorless oil (64 mg, 79%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38−7.24 (15H, m, Ph), 4.99−4.95 (2H, m, H-1′, OC*H*HPh), 4.87 (1H, d, J = 10.8 Hz, OC*H*HPh), 4.83 (1H, d, J = 10.7 Hz, OCH*H*Ph), 4.80 (1H, d, J = 12.2 Hz, OC*H*HPh), 4.67 (1H, d, J = 12.2 Hz, OCH*H*Ph), 4.61 (1H, d, J = 10.8 Hz, OCH*H*Ph), 4.57 (1H, d, J = 3.6 Hz, H-1), 4.05 (1H, m, H-3′), 3.99 (1H, t, J = 9.2 Hz, H-2), 3.80 (1H, bs, H-4′), 3.77−3.73 (2H, m, H-3, H-6′a), 3.70−3.62 (4H, m, H-5′, H-6a, H-6b, H-6′b), 3.49 (1H, dd, J = 9.6, 3.6 Hz, H-4), 3.42 (1H, t, J = 9.6 H-5), 3.36 (3H, s, OCH_3), 2.08 (1H, td, J = 12.1, 3.5, H-2a′), 1.65 (1H, dd, J = 12.7, 4.5 H-2b′), 0.94−0.86 (27H, m, 3 × $SiC(CH_3)_3$), 0.12−0.00 (18H, m, 6 x $SiCH_3$); ^{13}C NMR (126 MHz; $CDCl_3$) 138.7 (4 °C), 138.2 (4 °C), 138.1 (4 °C), 128.4−127.7 (Ph), 97.9 (C-1′), 97.6 (C-1), 82.1 (C-2), 79.9 (C-4), 78.5 (C-5), 75.8 (OCH_2Ph), 75.1 (OCH_2Ph), 73.3 (OCH_2Ph), 72.7 (C-5′), 70.3 (C-4′), 68.3 (C-3′), 65.2 (C-6′), 62.6 (C-6), 54.7 (OCH_3), 33.5 (C-2′), 26.2 ($SiC(CH_3)_3$), 26.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 18.6 ($SiC(CH_3)_3$), 18.5 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), −3.9 ($SiCH_3$), −4.4 ($SiCH_3$), −4.8 ($SiCH_3$), −5.0 ($SiCH_3$), −5.3 ($SiCH_3$), −5.4 ($SiCH_3$). ESI-HRMS for $C_{52}H_{84}NaSi_3O_{10}^+$ (MNa^+) calcd: 975.5270; found: 975.5277. $[\alpha]_D$ = +16 (c = 1, $CHCl_3$).

*Methyl 2,3,4-Tri-O-benzyl-6-O-(2-deoxy-3,4,6-tri-O-benzyl-α/β-D-erythrohexapyranosyl)-α-D-glucopyranoside (**11a**).* Following the general glycosylation procedure, donor **8a** (50 mg, 0.10 mmol) and acceptor **3** (50 mg, 0.08 mmol) afforded the following purification by column chromatography (Hexane:EtOAc 5:1 to 4:1): **11a** as colorless oil (28 mg, 40%). Spectroscopic data in agreement with literature.[6b]

*Methyl 2,3,6-Tri-O-benzyl-4-O-(2-deoxy-3,4-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6-O-triisopropylsilyl-α-D-erythro-hexapyranosyl)-α-D-glucopyranoside (**11b**).* Following the general glycosylation procedure, donor **8b** (50 mg, 0.10 mmol) and acceptor **3** (40 mg, 0.08 mmol) afforded the following purification by column chromatography (Hexane:EtOAc 5:1 to 4:1): **11b** as colorless oil (66 mg, 81%). Spectroscopic data in agreement with literature.[6b]

*Methyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(2-deoxy-3,4-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-6-O-triisopropylsilyl-α-D-erythro-hexapyranosyl)-α-D-glucopyranoside (**11c**).* Following the general procedure, donor **8c** (50 mg, 0.10 mmol) and acceptor **6k** (30 mg, 0.08 mmol) afforded the following purification by column chromatography (Hexane:EtOAc 5:1 to 4:1): **11c** as colorless oil (60 mg, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50−7.44 (2H, m, Ph), 7.41−7.31 (5H, m, Ph), 7.25−7.20 (3H, m, Ph), 5.53 (1H, s, PhC*H*O_2), 5.09 (1H, d, J = 3.3 Hz, H-1′), 4.99 (1H, d, J = 3.3 Hz, H-1), 4.88 (1H, d, J = 11.7 Hz, OC*H*HPh), 4.78 (1H, d, J = 11.7 Hz, OCH*H*Ph), 4.29 (1H, dd, J = 9.9, 4.5 Hz, C*H*H), 4.13 (1H, ddd, J = 11.3, 8.3, 5.3 Hz, H-3′), 4.07−4.01 (1H, m, C*H*H), 3.94 (1H, dd, J = 9.4, 3.4 Hz, H-2), 3.92 (1H, dd, J = 9.4, 8.9 Hz, H-3), 3.87−3.75 (3H, m, H-5, H-5′, CH*H*), 3.71 (1H, t, J = 10.1 Hz, CH*H*), 3.61 (1H, t, J = 9.1 Hz, H-4), 3.51 (1H, dd, J = 9.2, 8.4 Hz, H-4′), 3.43 (3H, s, OCH_3), 2.25 (1H, app dd, J = 13.2, 5.1 Hz, H-2a′), 1.73 (1H, ddd, J = 13.5, 11.4, 3.7 Hz, H-2b′), 1.17−0.86 (49H, m, 7 x $SiCH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.0 (4 °C), 137.6 (4 °C), 129.0 (CH), 128.28 (CH), 128.25 (CH), 127.7 (CH), 127.4 (CH), 126.2 (CH), 101.5 (PhC*H*O_2), 97.4 (C-1), 92.9 (C-1′), 81.5 (H-4), 77.3 (C-3), 75.2 (PhCH_2O), 74.7 (C-4′), 73.7 (CH), 73.5 (C-2), 71.9 (C-3′), 69.2, 63.5 (C-6, C-6′), 62.6 (CH), 55.3 (OCH_3), 38.0 (C-2′), 18.24 ($Si(CH(CH_3)_2)$), 18.20 ($Si(CH(CH_3)_2)$), 18.15 ($Si(CH(CH_3)_2)$), 17.7 ($Si(CH(CH_3)_2)$), 17.6 ($Si(CH(CH_3)_2)$)0, 17.59 ($Si(CH-(CH_3)_2)$), 17.53 ($Si(CH(CH_3)_2)$), 17.48 ($Si(CH(CH_3)_2)$), 17.45

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($Si(CH(CH_3)_2)$), 17.4 ($Si(CH(CH_3)_2)$), 13.1 ($Si(CH(CH_3)_2)$), 12.5 ($Si(CH(CH_3)_2)$), 12.4 ($Si(CH(CH_3)_2)$), 12.2 ($Si(CH(CH_3)_2)$), 12.2 ($Si(CH(CH_3)_2)$). MALDI-HRMS for $C_{48}H_{80}NaO_{11}Si_3^+$ (MNa^+) calcd: 939.4869; found: 939.4896. $[\alpha]_D^{22}$ = +51 (c = 0.0030, $CHCl_3$).

*Methyl 2,3,4-Tri-O-benzyl-6-O-(2,6-deoxy-3,4-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α/β-L-erythro-hexapyranosyl)-α-D-glucopyranoside (**12a**).* Following the general glycosylation procedure, donor **9** (50 mg, 0.13 mmol) and acceptor **3** (52 mg, 0.11 mmol) afforded the following purification by column chromatography (Hexane:EtOAc, 8:1 to 4:1) **12** as a colorless oil (78 mg, 74%, α:β = 9:1). Spectroscopic data in agreement with literature.[7]

*Methyl 3-O-Benzyl-4,6-O-benzylidene-2-O-(2,6-deoxy-3,4-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-α/β-L-erythro-hexapyranosyl)-α-D-glucopyranoside (**12b**).* Following the general procedure, donor **9** (50 mg, 1.3 mmol) and acceptor **6k** (42 mg, 1.1 mmol) afforded the following purification by column chromatography (Hexane:EtOAc 20:1 to 10:1): **12b** as colorless oil (72 mg, 87%, α:β = 10:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52−7.48 (2H, m, Ph), 7.40−7.25 (8H, m, Ph), 5.58 (1H, s, PhC*H*O_2 α-anomer), 5.56 (1H, s, PhC*H*O_2 β-anomer), 5.07 (1H, d, J = 3.9 Hz, H-1′), 4.88−4.84 (2H, m, H-1, OC*H*HPh), 4.78 (1H, d, J = 11.4 Hz, OCH*H*Ph), 4.30 (1H, dd, J = 9.9, 4.5 Hz, H-6a), 4.07 (1H, ddd, J = 11.3, 8.3, 5.3 Hz, H-3′), 3.97 (1H, t, J = 9.3, H-5′), 3.89−3.72 (3H, m, H-4, H-5, H-6b), 3.69−3.60 (2H, m, *H*-2, H-3), 3.45 (1H, s, OCH_3 β-anomer), 3.45 (1H, s, OCH_3 α-anomer), 3.27 (1H, J = 8.7 Hz, H-4′) (2.24 (1H, app dd, J = 13.2, 5.1 Hz, H-2a′), 1.74 (1H, ddd, J = 13.5, 11.4, 3.7 Hz, H-2b′), 1.29 (3H, d, J = 6.3 Hz, CH_3) 1.14−1.02 (28H, m, 4 × $SiCH(CH_3)_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.66 (4 °C), 137.42 (4 °C), 128.89 (CH), 128.28 (CH), 128.19 (CH), 127.7 (CH), 127.57 (CH), 126.0 (CH), 101.25 (PhC*H*O_2), 100.6 (C-1′), 100.25 (C-1), 82.0 (C-2), 80.37 (C-3), 79.99 (C-4′), 77.94 (C-5), 75.25 (PhCH_2O), 71.22 (C-3′), 69.07 (C-6), 68.3(C-5′), 62.23 (C-4), 55.2 (OCH_3), 38.67 (C-2′), 29.7 (CH3), 18.14−12.27 (4 × $Si(CH(CH_3)_2)$). ESI-HRMS for $C_{39}H_{60}NaO_{10}^+$ (MNa^+) calcd: 767.3623; found: 767.4002. $[\alpha]_D$ = +25 (c = 1, $CHCl_3$). $[\alpha]_D^{22}$ = +32 (c = 1, $CHCl_3$).

*One-Pot Trisaccharide Synthesis: 6-O-(2,3,4-Tri-O-benzoyl-6-O-(2-deoxy-3,4,6-tri-O-benzyl-α-D-lyxo-hexapyranosyl)-α-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (**13**).* Following general procedure, donor **2a** (50 mg, 0.12 mmol), acceptor **6d** (58 mg, 0.0998 mmol), and a solution mixture, prepared containing chiral acid (∼0.012 mmol) and thiourea (∼0.012 mmol) in anhydrous DCM (1 mL), were mixed together. After 2 h, the disaccharide formation was determined to be complete by TLC. The reaction mixture was then cooled to 0 °C, and molecular sieves 4 Å were added. Once cooled, a solution of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranoside **6c** (26 mg, 0.0998 mmol) in anhydrous DCM (0.5 mL) was added followed by addition of NIS (45 mg, 0.2 mmol) and finally the dropwise addition of a solution of TMSOTf (95 μL, 40 μL in 20 mL anhydrous DCM, 0.001 mmol). After 1 h, the reaction was determined to be complete and was quenched with Et_3N (0.1 mL), diluted with DCM (25 mL), washed with $Na_2S_2O_3$ (sat. aq.) (25 mL), brine (25 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (Hexane:EtOAc, 10:1 to 3:1) afforded product **13** as a white solid (59 mg, 51%). Spectroscopic data in agreement with literature.[7]

*Methyl 2,3,4-Tri-O-benzyl-6-O-(2-deoxy-3,4,6-tri-O-benzyl-2-^{2}H-α-D-lyxo-hexapyranosyl)-α-D-glucopyranoside (**15**).* Following the general glycosylation procedure, donor **14** (50 mg, 0.12 mmol) and acceptor **3** (46 mg, 0.10 mmol) afforded the following purification by column chromatography (Hexane:EtOAc 20:1 to 12:1): **15** as a yellow oil (72 mg 83%): ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.40−7.21 (m, 30H, Ar−H), 5.04 (1H, d, J = 1.3 Hz, H-1′), 5.00 (1H, d, J = 10.8 Hz, OC*H*HPh), 4.93 (1H, d, J = 11.6 Hz, OC*H*HPh), 4.86 (1H, d, J = 10.9 Hz, OC*H*HPh), 4.83−4.78 (2H, m, OC*H*HPh), 4.69 (1H, d,J = 12.2 Hz, OC*H*HPh), 4.62 (1H, d, J = 2.7 Hz, H-1), 4.61 (1H, d, J = 5.4 Hz, OC*H*HPh), 4.58 (2H, s, OC*H*HPh), 4.54 (1H, d, J = 10.8 Hz, OC*H*HPh), 4.42 (1H, d, J = 11.8 Hz, OC*H*HPh), 4.35 (1H, d, J = 11.8 Hz, OC*H*HPh), 4.04−3.96 (1H, t, J = 9.3 Hz, H-3), 3.89 (3H, t, J = 3.1 Hz, H-3′, H-4′, H-5′), 3.83 (1H, dd, J = 11.4, 4.7 Hz, H-6a), 3.74 (1H, ddd, J = 10.0, 4.6, 1.8 Hz, H-5), 3.63 (1H, dd, J = 11.4, 1.9 Hz, H-6b), 3.58−3.54 (2H, m, H-6a, H-2), 3.54−3.51 (1H, m, H-6b), 3.48 (1H, dd, J = 10.1, 8.9 Hz, H-4), 3.33 (3H, s, OCH_3), 2.03−1.99 (1H, m, H-2′). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9 (4 °C), 138.7 (4 °C), 138.4 (4 °C), 138.3 (4 °C), 138.16 (4 °C), 138.1 (4 °C), 128.41 (CH), 128.2 (CH), 127.7 (CH), 98.3 (C-1′), 97.9 (C-1), 82.1 (C-3), 80.0 (C-2), 77.9 (C-4), 75.8 (CH_2Ph), 74.9 (CH_2Ph), 74.3 (CH_2Ph), 74.16 (C-3′), 73.3 (CH_2Ph), 73.3 (CH_2Ph), 72.9 (C-4′), 70.2 (CH_2Ph), 70.1 (CH_2Ph), (C-5′), 69.8 (C-5), 69.4 (C-6′), 66.0 (C-6), 55.0 (OCH_3), 29.7 (C-2′). ESI-HRMS for $C_{55}H_{59}DNaO_{10}^+$ (MNa^+) calcd: 904.4147; found: 904.4142. $[\alpha]_D$ = +25 (c = 1, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02498.

Detail NMR experiments and full characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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