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Rhamnosylation: Diastereoselectivity of Conformationally Armed Donors

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Supporting Information

ABSTRACT: The α/β-selectivity of super-armed rhamnosyl donors have been investigated in glycosylation reactions. The solvent was found to have a minor influence, whereas temperature was crucial for the diastereoselectivity. At very low temperature, a modest β-selectivity could be obtained, and increasing temperature gave excellent α-selectivity. The donors were highly reactive, and activation was observed at temperatures as low as −107 °C. Different promoter systems and leaving groups were investigated, and only activation with a heterogeneous catalyst increased the amount of the β-anomer significantly. By introducing an electron-withdrawing nonparticipating group, benzyl sulfonyl, on 2-O, an increase in β-product was observed.

INTRODUCTION

Rhamnose is a common component of many natural oligosaccharides and found in its free form in poison sumac and buckthorn. L-Rhamnose is the most common enantiomer and is found in many bacterial oligosaccharides especially in Gram negative bacteria.[1] Since rhamnosides are xenobiotic to humans and are found in connection with several diseases,[2] their chemistry is of general interest, and rhamnosides could become important in drug discovery. Whereas α-rhamnosides are easily synthesized, β-selective rhamnosylation is still a major challenge in glycosylation chemistry, and new methods as well as a fundamental understanding of the problem are important in order to access this class of compounds.

β-L-Rhamnosides are found in pathogen bacteria, such as the *Salmonella* serogroup,[3] *Shigella boydii* type 18,[4] and *Vibrio cholera*,[5] and consequently there is an increasing interest in their synthesis. This is however challenging because of the 1,2-cis relationship, which is disfavored by steric effects as well as the anomeric effect both favoring the α-anomer. The problem in the synthesis of the related β-mannosides has to a large extent been solved by the elegant procedure developed by Crich.[6]

This method is however not directly applicable to rhamnosides (6-deoxy mannosides), since the 4 and 6 positions cannot easily be tethered together. Approaches to use other tethering groups and glycosylation methods have been made, but a general method for a direct highly diastereoselective L-rhamnosylation is still not available.[7] We have earlier demonstrated the high stereoselectivity and reactivity of conformationally (super[8]) armed glycosyl donors and became interested in studying the effect of the rhamnosyl donor conformation on the diastereoselectivity. Early papers by Yamada and co-workers[9] on β-selective rhamnosylation using partly silyl-protected donors prompted our interest in this particular problem. Yamada observed that the β-selectivity could be increased by performing the reaction at low temperature and by using hindered (slow) promoters; the selectivity was however modest and limited to a single primary acceptor. Earlier we observed the same selectivity trend using a super-armed rhamnosyl donor when performing competition experiments on either a 6-OH or 4-OH thioglucoside acceptor (and donor).[10] The yields were excellent, and only activation of the super-armed donor was observed. A temperature dependence of the diastereoselectivity was also noticed; i.e., increasing α-selectivity when raising the temperature. The superior reactivity of a "super-armed" rhamnosyl donor was underlined by glycosylation of an *N*-acetylated glucosamine derivative in an excellent yield with complete α-selectivity.[11] From our own and Yamada's work in the area of "flipped"[12] rhamnosyl donors (Figure 1), a number of questions arose. To what extent does the anomeric effect favor the β-anomer when the ring is "flipped"?[12] What is the effect of solvents and different glycosylation methods on the selectivity? Would it be possible to increase the β-selectivity by decreasing the flipped[12] donor reactivity? In this work we will try to answer these questions by studying a range of different super-armed rhamnosyl donors with different substitution pattern under various glycosylation conditions, thereby illuminating the connection between conformation, reactivity, and diastereoselectivity.

The main conclusions from Yamada's work was that a modest β-selectivity could be obtained by performing the glycosylation at very low temperature in apolar solvents with bulky Lewis acid promoters all presumably leading to a S_N2 type mechanism. The glycosylation was performed with trichloroacetimidates, which were obtained as the thermody-

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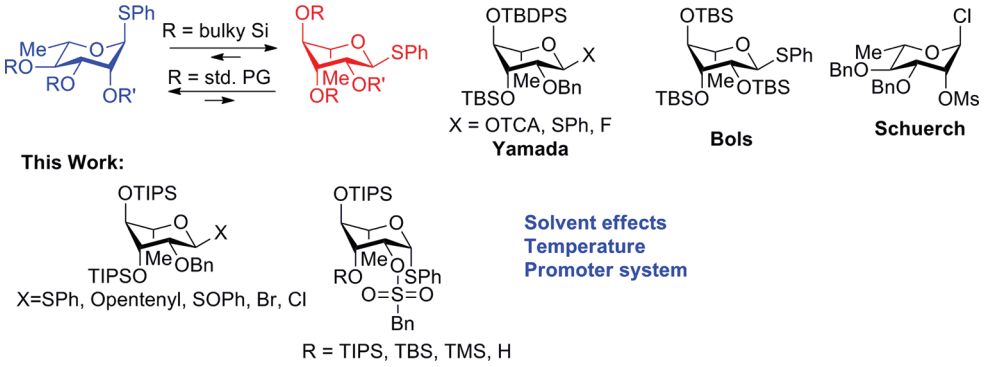
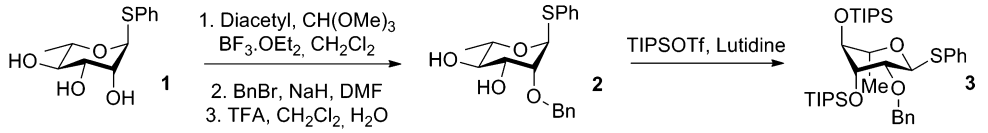


Figure 1. Conformationally flipped[12] rhamnosyl donors.

Scheme 1. Synthesis of the Super-Armed Donor 3



namic α-product.[13] This is in contrast with what we would expect from a flipped donor, where the β-anomer should be favored by the anomeric effect and hence be the thermodynamic product. An obvious place to start our investigation was to synthesize a derivative of Yamada's donor since it was clear from our own results that a bulky 2-O protective group made the β-face even less accessible.

RESULTS AND DISCUSSION

The donor **3** was synthesized from the triol **1** using Ley's protective group[14] followed by 2-*O*-benzylation, acidic deprotection to give **2**, and finally triisopropylsilylation (Scheme 1). The conformation of the donor **3** was confirmed to be "flipped"[12] from the ^{1}H NMR ^3J coupling constants showing a 1,2-trans-diaxial relationship ($^3J_{1-2}$ = 8.7 Hz) and small coupling constants between H2−H3 (2.2 Hz), H3−H4 (2.8 Hz), and H4−H5 (3.0 Hz). With the donor in hand, the influence of acceptor bulkiness was studied. Methoxyethanol, cyclohexanol, and 1-adamantanol were used using the standard activation of a super-armed glycosyl donor, i.e., NIS, TfOH at −78 °C followed by slow heating to room temperature. Good and similar yields were obtained, and the selectivity was between 2/1 and 3/1 in favor of α. Bulkiness did not appear to be important (entries 1−3, Table 1). When a competition experiment with the armed 4-OH thioglucoside **4** was performed, a good yield and excellent α-selectivity was obtained, demonstrating the superior reactivity of the super-armed donor **3**.

Solvents are known to influence reactivity and selectivity in glycosylations; therefore, a range of common, but in terms of polarity very different, solvents were investigated.

The simple achiral acceptor, cyclohexanol, was again chosen, and the glycosylations were carried out following a standard procedure starting at low temperature (−78 °C) except in the cases where the solvent has a higher melting point (MeCN and $MeNO_2$). Aprotic, nonparticipating solvents such as CH_2Cl_2, $MeNO_2$ were α-selective with $MeNO_2$ giving a ratio of 4.7:1 and CH_2Cl_2 1.8:1 (entries 13−17, Table 1). The higher α-selectivity can to a large extent be explained with the higher starting temperature due to the melting point of −29 °C for $MeNO_2$. This could be confirmed by performing the reaction in CH_2Cl_2 at different temperatures; at room temperature, only the α-product could be isolated in good yields, and at −78 and −107 °C, the β-anomer was observed as the minor product (in the ratios 1.8:1 and 4.3:1, respectively) (entries 16, 17, Table 1). It was noticed that the glycosylation took place at very low temperature but with a significant prolonged reaction time resulting in lower yields. In order to push the reaction toward a S_N2 type reaction, heptane was chosen as a nonpolar aprotic solvent. Activation of the glycosyl donor was very slow at low temperature. A change in reaction color, indicating formation of iodine, was not observed until the temperature reached 25 °C. The selectivity was again modest toward the α-product, indicating that a S_N2 type reaction (or "tight ion pair") was not favored with this kind of donor system. Similar result was obtained when activating the thiorhamnoside **3** by methylation using methyl triflate, where only the α-product was isolated (entry 4, Table 1). Other promoter systems, such as NIS, DMTST, or DPSO/Tf_2O resulted in lower selectivity, lower yields, and decomposition of the donor.

Participating solvents, such as nitriles and ether solvents, are known to affect the outcome of glycosylation by forming reactive intermediates favoring either the equatorial (β) or the axial product (α). The effect of these solvent systems have not earlier been observed when using "super-armed donors". Since our donor is predominantly in a flipped[12] conformation, one would expect the opposite selectivity as compared with the "normal" chair conformation, here the $^4C_1$ and $^1C_4$, respectively. Diethyl ether would therefore, according to the general proposed participation mechanism,[15] give the axial coupling, i.e., the β-product. To our surprise the exact opposite happened. Glycosylation in diethyl ether resulted in higher α-selectivity (17:1) and lower reactivity of the donor (activation at approximately −15 °C) (entry 8, Table 1). Nitrile solvents were expected to give the equatorial product (α) because of the nitrile effect,[16] but as with the ether effect we were surprised. There was hardly any effect of having nitrile solvents compared with CH_2Cl_2. Activation was observed promptly at −42 °C in MeCN (the melting point), when moving to EtCN and PrCN as solvents the temperature could be lowered to −78 and −107 °C, respectively, but the reaction was essentially unselective under these conditions (α:β ratio 1:1 and 1:1.4, respectively)

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Table 1. Rhamnosylation with the Super-Armed Rhamnosyl Donors 3, 5 and 6

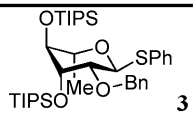
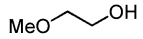
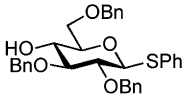
Entry	Donor	Acceptor	Promoter	Solvent	Temp.	Yield	α/β
1	 **3**		NIS/TfOH	CH_2Cl_2	-78 →25 °C	79 %	3.3/1
2	**3**	1-adamantanol	NIS/TfOH	CH_2Cl_2	-78 →25 °C	79 %	2.9/1
3	**3**	cyclohexanol	NIS/TfOH	CH_2Cl_2	-78 →25 °C	76 %	1.8/1
4	**3**	cyclohexanol	MeOTf	CH_2Cl_2	-78 →25 °C	58 %	1/0
5	**3**	cyclohexanol	DMTST	CH_2Cl_2	-78 →25 °C	0 %*	-
6	**3**	cyclohexanol	Ph_2SO,Tf_2O DTBMP	CH_2Cl_2	-78 →25 °C	0 %*	-
7	**3**	cyclohexanol	NIS	CH_2Cl_2	-78 →25 °C	58 %	2.4/1
8	**3**	cyclohexanol	NIS/TfOH	Et_2O	-78 →25 °C	89 %	17/1
9	**3**	cyclohexanol	NIS/TfOH	Heptane	-78 →25 °C	79 %	4/1
10	**3**	cyclohexanol	NIS/TfOH	MeCN	-42 →25 °C	62 %	3/1
11	**3**	cyclohexanol	NIS/TfOH	EtCN	-78 →25 °C	90 %	1/1
12	**3**	cyclohexanol	NIS/TfOH	PrCN	-107 °C	73 %	1.4/1
13	**3**	cyclohexanol	NIS/TfOH	CH_3NO_2	-29 →25 °C	89 %	4.7/1
14	**3**	cyclohexanol	NIS/TfOH	CH_2Cl_2, DMF	-78 →25 °C	79 %	2.3/1
15	**3**	cyclohexanol	NIS/TfOH	CH_2Cl_2	25 °C	78 %	1/0
16	**3**	cyclohexanol	NIS/TfOH	CH_2Cl_2	-78 °C	89 %	1.8/1
17	**3**	cyclohexanol	NIS/TfOH	CH_2Cl_2	-107 °C	75 %	4.3/1
18	**3**	cyclohexanol	1) ICl 2) TBAC, $EtNiPr_2$	CH_2Cl_2	-78 →25 °C	68 %	1/0
19	**3**	cyclohexanol	1) ICl 2) TBAC, $EtNiPr_2$	CH_2Cl_2	25 °C	88 %	25/1
20	**3**	cyclohexanol	1) Br_2 2) TEAB, $EtNiPr_2$	CH_2Cl_2	-78 →25 °C	72 %	1/0
21	**3**	cyclohexanol	1)ICl 2) Ag_2CO_3	CH_2Cl_2	-78 →25 °C	75 %	1/1.4
22	**3**	cyclohexanol	1) ICl 2) AgOTf, DTBMP	CH_2Cl_2	-78 →25 °C	75 %	28/1
23	**3**	5-Pentenol	1) ICl 2) AgOTf, DTBMP	CH_2Cl_2	-78 →25 °C	28 %	2.8/1
24	**3**	 **4**	NIS/TfOH	CH_2Cl_2	-78 °C	66 %	1/0

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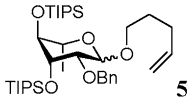
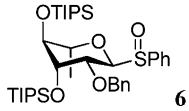
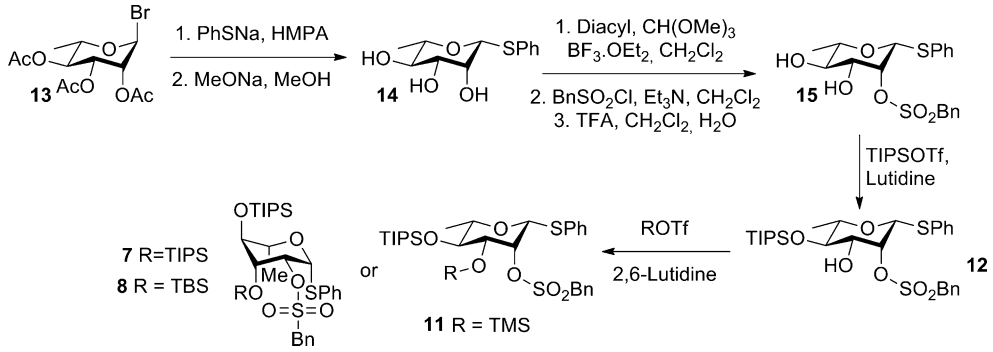
Table 1. continued

Entry	Donor	Acceptor	Promoter	Solvent	Temp.	Yield	α/β
25	 **5**	cyclohexanol	NIS, TESOTf	CH_2Cl_2	-78 →25 °C	36 %	1/0
26	 **6**	cyclohexanol	Tf_2O, TTBP	CH_2Cl_2	-78 →25 °C	27 %	1/0

*TIPS groups were lost.

Scheme 2. Synthesis of Conformational Armed Donors Having a Nonparticipating Strongly Electron-Withdrawing Group on 2-O



(entries 10−12, Table 1). A fast activation was observed around −60 °C in these nitrile solvents. It has recently been demonstrated that DMF addition to glycosylation gives imidate intermediates,[17] which upon addition of the acceptor reacts in a S_N2 fashion to give the axial product (normally the α). Applying the preactivation conditions with DMF on the super-armed rhamnosyl donor **3** at low temperature resulted in a 2.3:1 selectivity (entry 14, Table 1), virtually no change in selectivity, and hence no effect of the imidate intermediate.

Another more classic way to synthesize axial glycosidic linkages was developed by Lemieux and co-workers.[18] The halide-ion-catalyzed glycosylation takes advantage of the higher reactivity of equatorial halides over axial and the in situ anomerisation when having excess of halide ions present in the reaction mixture. With the flipped[12] super-armed donor, we expected to observe a faster reaction of the α-bromide (equatorial) giving the β-anomer as the major product. The rhamnosyl chloride was made in situ by reaction of **3** with iodine monochloride. From ^{1}H NMR a clean conversion of the thio-glycoside into the L-rhamnosyl chloride was observed. An attempt to isolate this chloride failed, presumably because of the inherent high reactivity of such a super-armed glycosyl halide. To the rhamnosyl chloride in CH_2Cl_2 was added 1 equiv of tetrabutylammonium chloride (TBAC) as the ion source, and the reaction was cooled to −78 °C, where the acceptor was added after approximately 30 min. The reaction was allowed to warm up slowly to room temperature. At low temperature, no reaction took place; however, at room temperature slow conversion could be observed by TLC. Surprisingly, only the α-anomer was isolated in a decent yield of 68%. Performing the entire reaction at 25 °C improved the yield to 88%, but the α-selectivity was still high (entries 18, 19, Table 1). Changing to the more reactive bromide, which was obtained from the reaction of Br_2 with the thioglycoside **3** and tetraethylammonium bromide as the ion-source, gave essentially the same result; starting from −78 °C with slow heating to rt gave the α-product in 72% yield (entry 20, Table 1).

The use of solid promoters is known to lead to increased formation of equatorial products. Indeed, this method is classic in carbohydrate chemistry.[19] This would give the equatorial α-anomer, but since the donor seemed unpredictable, the reaction was tried out using silver carbonate as the solid catalyst and the glycosyl chloride donor at −78 °C to rt. Surprisingly, it turned out to be slightly β-selective (1:1.4) (entry 21, Table 1).

Glycosyl triflates have had an amazing impact on glycosylation chemistry during the past decades, where α-triflates have made β-mannosides easily accessible.[6] However, rhamnosyl triflates have so far found little use as donors for accessing β-L-rhamnosides.[7] From the work, especially on mannosides, it is clear that the reactivity of the triflate is crucial for the outcome of the glycosylation.[20] Nevertheless, super-armed rhamnosyl triflates were investigated. The triflate was obtained from the chloride by treating it with silver triflate at low temperature or by Kahne's sulfoxide method.[21] In both cases the α-anomer was obtained in excellent selectivity, with the silver triflate giving the best result in terms of yield. Performing the reaction on a primary alcohol, 4-penten-1-ol, resulted in a dramatic decrease in α-selectivity to 2.8:1 with a modest yield of 28% (entry 23, Table 1).

Finally, another widely used glycosylation method in form of the *n*-pentenyl donor[22] **5** was tested. However, only the α-product was formed in a modest yield (entry 25, Table 1).

From the above study, it appeared that the superior reactivity of the super-armed rhamnosyl donor favored the α-product and that the bulky group at 3-O, together with methyl group, to some extent hampered the β-attack because of 1,3-diaxial interactions;[23] these steric and stereoelectronic effects seem to overrule the "flipped" anomeric effect, which we expected to

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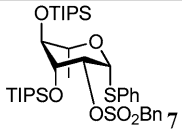
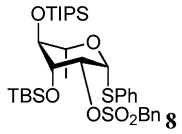
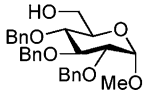
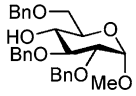
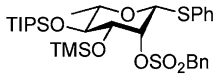
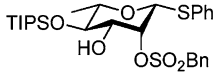
Table 2. Rhamnosylation with 2-*O*-Sulfonylated Donors 7−8, 11−12

Entry	Donor	Acceptor	Promoter	Solvent	Temp.	Yield	α/β
1	 **7**	Cyclohexanol	NIS/TfOH	CH_2Cl_2	-78 →25 °C	62 %	1/1
2	 **8**	Cyclohexanol	NIS/TfOH	CH_2Cl_2	-78 →25 °C	83 %	1/1.5
3	**8**	Cyclohexanol	ICl TBAC DIPEA	CH_2Cl_2	-78 →25 °C	[a]	
4	**8**	Cyclohexanol	Br_2 TBAB DIPEA	CH_2Cl_2	78 →25 °C	[a]	
5	**8**	 **9**	NIS/TfOH	CH_2Cl_2	-78 →25 °C	88 %	1/1
6	**8**	 **10**	NIS/TfOH	CH_2Cl_2	-78 →25 °C	55 %	1/0
7	 **11**	Cyclohexanol	NIS/TfOH	CH_2Cl_2	-78 →25 °C	62 %	1/2
8	 **12**	Cyclohexanol	NIS/TfOH	CH_2Cl_2	-78 →25 °C	43 %	1/1.5

[a]Donor decomposed under the activation conditions.

increase the amount of the axial β-anomer. Too high reactivity of a glycosyl donor has earlier been argued to give low selectivity and especially, in the cases with manno-stereochemistry, α-selectivity.[24] One way to deal with this is to lower the reactivity by installing an electron-withdrawing group on the donor. This approach was originally developed by Schuerch[25] and later taken up by Schmidt[26] and Crich,[27] who all focused on the 2-position and showed an effect of this deactivation. Kim and co-workers have recently expanded this concept to cover all positions on the donor ring and thereby obtaining excellent results in terms of β-selectivity in mannosylations.[28] We speculated how a super-armed donor would respond to a strongly electron-withdrawing group close to the anomeric center and decided to introduce a benzylsulfonyl group on 2-O.[29]

The donor was synthesized inspired by the synthesis performed by Crich and co-workers.[27] Crich prepared the β-thiorhamnoside **14** as a way to avoid decomposition of the donor by a 1,2 migration of the thiophenyl group. This migration can only take place with 1,2-trans diaxial groups (the group on C2 must be a good leaving group) and is precluded in **14**. The β-thioglycoside was synthesized from the peracetylated rhamnosyl bromide **13**, followed by treatment with thiophenolate, deacetylation, and BDA protection of 3-O and 4-O (Scheme 2). The unprotected 2-O was then benzylsulfonylated using the sulfonyl chloride. Acid-mediated removal of the BDA liberated the 3OH and 4OH to give **15**, ready for triisopropylsilylation, which surprisingly caused problems. The 3-OH **12** was very unreactive under the standard conditions, and only small amounts of the desired disilylated donor **7** could be obtained. This could to some extent be solved by using the less bulky TBS-group to protect the 3-OH giving **8** under forced conditions. Using the even smaller TMS group proceeded smoothly to give the rhamnosyl donor **11** having the standard $^1C_4$ conformation, whereas the 3-*O*-TIPS and 3-*O*-TBS both were in axial rich conformations.[30]

Glycosylation with the new set of donors was again performed with cyclohexanol as the acceptor. The reaction mixture was cooled to −78 °C before activating the donor, and the activation temperature was estimated from the change in

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color from transparent to purple. All the donors activated at ca. −40 °C, i.e., comparable reactivity to an armed donor (perbenzylated). The relative high reactivity, despite the strongly electron-withdrawing (disarming) sulfonyl group, can be explained by the easier ring flip and thereby lower TS together with the 6-deoxy functionality, which is not electron-withdrawing and thereby arming. The donors are both stereoelectronically armed, because of the conformation, and disarmed by the sulfonyl group on O2. In glycosylation the lower reactivity has a positive influence on the amount of β-product formed, where **7** and **8** gives an α:β ratio of 1:1 and 1:1.5, respectively (entry 1−2, Table 2). When using the smaller TMS group on 3-O (**11**), an even better ratio is observed illustrating the steric effect from the protective group on the glycosylation outcome, which also suggests a common activated conformation for the 3 donors. Because of the extremely low reactivity of the 3-OH in **12**, it could easily be used as the donor in a glycosylation without any self-coupling observed; again, the glycosylation was slightly β-selective (1:1.5) (entry 3, Table 2).

After establishing that the 2-*O*-sulfonylated donor, despite its relative high reactivity, was β-selective when using a simple secondary achiral acceptor, more demanding glycosylations were investigated. Cross coupling to a 6-OH acceptor **9** gave virtually no selectivity, and a more "difficult" acceptor, **10**, gave exclusively the α-anomer (55%) (entry 5, Table 1). Attempts to use Lemieux's in situ anomerization glycosylation failed, and only donor decomposition was observed.

From the experiments performed in this work, some new pieces for the β-rhamnosyl donor puzzle have been added. It has been shown that it is possible to get some β-selectivity when having a very reactive donor. The protective groups do have an influence on the stereochemical outcome, and a smaller group is giving more β-product. However, if the group gets too small a ring flip cost more energy and reactivity might be lost, and the conformation of the reactive intermediate changed. It is therefore not necessary to lock the ring in order to get selectivity. Despite the resemblance between the flipped[12] β-rhamnoside and α-glucoside, both having preference for *cis*-1,2-vicinal groups (according to the anomeric effect), no connection could be found. The β-product was not significantly favored when having a $^4C_1$ L-rhamnoside donor. The anomeric effect was however observable with halides, which anomerized into the thermodynamic β-product. Hence, when a thiorhamnoside was treated with iodine chloride or bromine, only the β-anomeric (axial) halide was observed. Anomerization of the glycosylation products (α−β mixtures) into β-rhamnosides in a related fashion did however not occur, which means that the products were stable under the various glycosylation conditions. When anomerisation was attempted with Lewis acids such as $TiCl_4$, $SnCl_4$, $BF_3{\cdot}OEt_2$, or $AlCl_3$, only decomposition was observed. $AuCl_3$ and TMSOTf resulted in a slow desilylation but no change in anomeric ratio.

The use of rhamnosyl halides as the donors afforded products with high α-selectivity. This could be due to the reaction taking place through an oxocarbenium intermediate (red in Figure 2) or direct attack on the β-halide, which was thermodynamically preferred because of the anomeric effect (see Figure 2). If the latter is the case, the difference in reactivity between the α- and β-halide is minimal since in situ anomerization following Lemieux's procedure essentially gave the same selectivities. It is expected that the equilibration between anomers is fast, since the rhamnosyl donor is highly

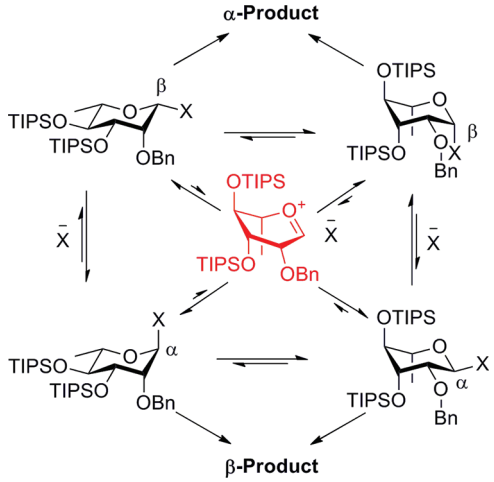

Figure 2. Proposed scenario of rhamnosyl halides. The α−β equilibrium is catalyzed by excess of halide ions (Lemieux conditions). The equatorial halides are more reactive than their axial counter parts, and an axial rich conformation is more reactive.

reactive and halide ions are in excess. If the equatorial halide (α) was much more reactive, the axial product (β) would be the major (due to the Curtin−Hammett principle); this suggests that the oxocarbenium ion is the common reactive species. Only when using a solid promoter, silver carbonate, a difference in selectivity toward the β-anomer was observed. Since the β-halide predominates in the starting material, one would expect the α-product to form preferentially. However, the result can be explained by an easier activation of the equatorial and less hindered α-halide giving rise to a modest β-selectivity. Attempts to push the reaction toward a S_N2 type mechanism by using apolar nonprotic solvents such as heptanes had no influence on the product ratio. This is in line with the donor being "super-armed" by stabilizing the oxocarbenium intermediate, which has been underlined by these results, where different solvents had very little effect. Participating solvents, diethyl ether and nitriles, performed as would be expected in glycosylation with a donor in the low energy chair conformation ($^1C_4$ for a L-rhamnosyl donor) and not as expected for donors with a flipped conformation. This also points at a common intermediate as the reactive species, regardless of the starting conformation.

■ CONCLUSION

In conclusion, we have showed that super-armed rhamnosyl donors have excellent reactivity and high α-selectivity. Reactions can be performed at very low temperature in many solvents. β-Selectivity can be obtained at low temperatures using the in situ generated halide and a solid promoter or, even better, a conformational armed 2-*O*-sulfonylated donor, which in reactivity is comparable to an armed glycosyl donor. The scope, in terms of β-selectivity, of the current donor is however limited to relative simple acceptors, and more research into the optimal reactive β-selective rhamnosyl donor is needed.

■ EXPERIMENTAL SECTION

General Methods. NMR assignments were based on COSY NMR experiments throughout. The mass spectra were performed on an electrospray mass spectrometer analyzing time-of-flight.

Phenyl 2-*O*-Benzyl-3,4-di-*O*-TIPS-1-thio-α-L-rhamnopyranoside (3). Phenyl 2-*O*-benzyl-1-thio-α-L-rhamnopyranoside (100 mg, 0.289 mmol) was dissolved in 3 mL of dry 2,6-lutidine. Then TIPSOTf (0.24 mL, 0.865 mmol) was added, and the mixture was

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stirred at 80 °C overnight. The mixture was cooled, ethyl acetate was added, and then it was extracted 2 times with 1 M HCl and one time with brine. The organic layer was dried with Na_2SO_4 and evaporated to dryness. The crude compound was purified by flash column chromatography (petroleum ether, CH_2Cl_2, 5:1) giving the product as colorless syrup. Yield: 0.174 g, 92%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.54 (m, 2H, Ar.), 7.42−7.15 (m, 8H, Ar.), 5.47 (d, J = 8.7 Hz, 1H, H1), 4.69 (d, J = 11.2 Hz, 1 H, benzyl), 4.58 (d, J = 11.2 Hz, 1H, benzyl), 4.24 (t, J = 2.8 Hz, 1H, H3), 4.05 (qd, J = 6.9, 3.0 Hz, 1H, H5), 3.90 (t, J = 3.0 Hz, 1H, H4), 3.83 (dd, J = 8.7, 2.2 Hz, 1H, H2), 1.44 (d, J = 7.0 Hz, 3H, H6), 1.16−0.96 (m, 42H, TIPSO); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.15(Ar, ipso), 135.4(Ar, ipso), 131.2(Ar.), 128.9(Ar.), 128.4(Ar.), 128.2(Ar.), 127.6(Ar.), 126.7(Ar.), 82.1(C1), 75.7(C2,C4), 75.1(C5), 74.2(C3), 73.1(CH_2-benzyl), 18.4−18.3(C6, CH_3-TIPS), 12.8(CH-TIPS), 12.6(CH-TIPS); $[\alpha]^{RT}_D$ −62.8° (c 1.0, CH_2Cl_2); HRMS calculated $C_{37}H_{62}O_4SSi_2Na$ = 681.3805, found 681.3817

Phenyl 2-*O*-Benzyl-3,4-di-*O*-TIPS-1-thio-α-L-rhamnopyranoside Sulfoxide (6). Phenyl 2-*O*-benzyl-3,4-di-*O*-TIPS-1-thio-α-L-rhamnopyranoside (114 mg, 0.173 mmol) was dissolved in 5 mL CH_2Cl_2. The solution was cooled to −78 °C, and *m*-CPBA was added (0.04 g, 0.173 mmol). The solution was slowly warmed up to room temperature and then washed with saturated bicarbonate solution and brine. The organic layer was dried with Na_2SO_4 and evaporated to dryness. The crude compound was purified by flash column chromatography (petroleum ether, CH_2Cl_2, 5:1) giving the product as colorless syrup. Yield: 0.091 g, 78%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.17 (m, 7 H), 5.02 (d, J = 8.7 Hz, 1H), 4.82 (d, J = 11.0 Hz, 0.4 H, benzyl), 4.73 (d, J = 11.0 Hz, 0.4H), 4.60 (d, J = 11.5 Hz, 1 H), 4.50 (d, J = 9.3 Hz, 0.4H), 4.50 (d, J = 11.6 Hz, 1H), 4.41 (dd, J = 9.5, 2.2 Hz, 0.4H), 4.35 (t, J = 2.4 Hz, 0.4H), 4.28 (t, J = 2.6 Hz, 1H), 4.13−4.07 (m, 0.4H), 3.95 (dd, J = 8.7, 2.3 Hz, 1H), 3.83−3.79 (m, 1H), 3.79−3.76 (m, 0.4H), 3.62 (qd, J = 6.7, 4.0 Hz, 3H), 1.33 (d, J = 6.8 Hz, 1.2H), 1.12 (d, J = 6.9 Hz, 1H), 1.09−0.92 (m, 54H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 140.7, 137.4, 137.3, 130.6, 130.2, 129.5, 129.1, 128.5, 128.2, 128.1, 128.0, 127.7, 127.7, 127.4, 125.3, 124.9, 92.6, 89.6, 76.7, 76.6, 76.0, 75.6, 73.9, 73.1, 72.8, 72.5, 72.3, 71.0, 18.7, 18.1, 18.0, 18.0, 18.0, 18.0, 17.9, 12.5, 12.5, 12.4, 12.3; HRMS calculated $C_{37}H_{62}O_5SSi_2Na$ = 697.3754, found 697.3795

Phenyl 3,4-Di-*O*-(2,3-dimethoxybutane-2,3-diyl)-2-*O*-sulfonylbenzyl-1-thio-β-L-rhamnopyranoside. Phenyl 3,4-di-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-L-rhamnopyranoside (0.511 g. 1.40 mmol) was dissolved in 5 mL of dry pyridine. Then benzylsulfonylchloride (0.790 g, 4.14 mmol) was added to the mixture, and it was stirred for 1 h. To the mixture was then added ethyl acetate, and it was extracted 3 times with 1 M HCl, one time with saturated sodium bicarbonate, and one time with brine. The organic layer was dried with Na_2SO_4 and evaporated to dryness. The crude compound was purified by flash column chromatography (petroleum ether, EtOAc, 3:1) giving the product as a white foam. Yield: 0.700 g, 97%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60−7.51 (m, 4H, Ar.), 7.44−7.37 (m, 4H, Ar.), 7.34−7.27 (m, 4H, Ar.), 5.28 (dd, J = 3.1, 1.0 Hz, 1H, H2), 4.92 (d, J = 1.0 Hz, 1H, H1), 4.67 (q, J = 13.9 Hz, 2H, CH_2-benzyl), 3.90 (dd, J = 10.3, 3.1 Hz, 1H, H3), 3.81−3.74 (m, 1H, H4), 3.55 (dq, J = 9.4, 6.1 Hz, 1H, H5), 3.32 (d, J = 1.1 Hz, 6H), 1.39 (s, 3H, Me), 1.37 (d, J = 6.1 Hz, 3H, H6), 1.32 (s, 3H, Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.0(Ar.), 132.0(Ar.), 131.2(Ar.), 129.2(Ar.), 128.94(Ar.), 128.90(Ar.), 128.6(Ar.), 127.9(Ar.), 86.0(C1), 80.5(C2), 75.1(C5), 70.2 (C3), 68.3(C4), 57.9(CH_2-benzyl), 48.6(CH_3O), 48.1(CH_3O), 17.9(CH_3), 17.9(CH_3), 17.0(C6); $[\alpha]^{RT}_D$ −32.8° (c 1.0, $CHCl_3$); HRMS calculated $C_{25}H_{32}O_8S_2Na$ = 547.1436, found 547.1458

Phenyl 2-*O*-Sulfonylbenzyl-1-thio-β-L-rhamnopyranoside (15). Phenyl 3,4-di-*O*-(2,3-dimethoxybutane-2,3-diyl)-2-*O*-sulfonylbenzyl-1-thio-β-L-rhamnopyranoside (0.700 g, 1.33 mmol) was dissolved in 10 mL of CH_2Cl_2, and then 2 mL of TFA and 0.2 mL of water were added. The mixture was stirred for 1 h and quenched with saturated sodium bicarbonate solution, and ethyl acetate was added. The organic layer was separated, washed with brine, dried with Na_2SO_4, and evaporated to dryness. The crude compound was purified by flash column chromatography (petroleum ether, EtOAc, 1:1) giving the product as white foam. Yield: 0.484 g (88%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.50 (m, 4H, Ar.), 7.44−7.40 (m, 3H, Ar.), 7.36−7.30 (m, 3H, Ar.), 5.29 (dd, J = 3.1, 1.0 Hz, 1H, H2), 4.91 (d, J = 1.0 Hz, 1H, H1), 4.69 (d, J = 13.9 Hz, 1H, benzyl), 4.59 (d, J = 13.9, 1 H, benzyl), 3.65 (dd, J = 9.0, 3.1 Hz, 1H, H3), 3.43−3.35 (m, 2H, H4, H5), 1.40 (d, J = 5.7 Hz, 3H, H6); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.5(Ar.), 131.9(Ar.), 131.2(Ar.), 129.4(Ar.), 129.4(Ar.), 129.1(Ar.), 128.2(Ar.), 127.4(Ar.), 85.3(C1), 81.4(C2), 76.8(C5), 73.7(C3), 72.8(C4), 57.7(CH_2-benzyl), 18.0(C6); $[\alpha]^{RT}_D$ 32.2° (c 1.0, $CHCl_3$); HRMS calculated $C_{19}H_{22}O_6S_2Na$ = 433.0755, found 433.0778

Phenyl 2-*O*-Sulfonylbenzyl-4-*O*-TIPS-1-thio-β-L-rhamnopyranoside (12). Phenyl 2-*O*-sulfonylbenzyl-1-thio-β-L-rhamnopyranoside (2.87 g, 7.0 mmol) was dissolved in 20 mL of 2,6-lutidine, and then TIPSOTf (10.5 mmol, 2.8 mL) was added. The mixture was heated in an oil bath at 80 °C for 4 h. The mixture was cooled, and ethyl acetate was added. Extraction was performed 3 times with 1 M HCl, once with saturated bicarbonate solution and once with brine. The organic layer was dried with $MgSO_4$ and evaporated. The crude residue was purified by flash column chromatography with CH_2Cl_2 as eluent giving the product **8** as white foam. Yield: 2.2 g, 55%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.48 (m, 4H, Ar.), 7.42−7.38 (m, 3H, Ar.), 7.36−7.28 (m, 3H, Ar.), 5.29 (dd, J = 3.2, 0.8 Hz, 1H, H2), 4.91 (d, J = 0.8 Hz, 1H, H1), 4.69 (d, J = 13.9 Hz, 1H, CH_2-benzyl), 4.56 (d, J = 13.9 Hz, 1H CH_2-benzyl), 3.64 (ddd, J = 9.0, 7.7, 3.2 Hz, 1H, H3), 3.56 (t, J = 8.9 Hz, 1H, H4), 3.36 (dq, J = 8.7, 6.2 Hz, 1H, H5), 2.57 (d, J = 7.6 Hz, 1H,OH3), 1.41 (d, J = 6.1 Hz, 3H, H6), 1.18−1.09 (m, 3H TIPS), 1.06−0.99 (m, 18H, TIPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 133.8(Ar.), 131.6(Ar.), 131.2(Ar.), 129.3(Ar.), 129.0(Ar.), 128.0(Ar.), 127.6(Ar.), 85.1(C1), 82.2(C2), 78.0(C5), 74.8(C4), 74.3(C3), 57.7(CH_2-benzyl), 18.5(C6), 18.41−18.40(TIPS), 13.2-(TIPS); $[\alpha]^{RT}_D$ 25.8° (c 1.0, CH_2Cl_2); HRMS calculated $C_{28}H_{42}O_6S_2SiNa$ = 589.2090, found 589.2083

Phenyl 2-*O*-Sulfonylbenzyl-3,4-di-*O*-TIPS-1-thio-β-L-rhamnopyranoside (7). Phenyl 2-*O*-sulfonylbenzyl-1-thio-β-L-rhamnopyranoside (2.60 g, 6.32 mmol) was dissolved in 20 mL of 2,6-lutidine, and then TIPSOTf (15.8 mmol, 4.3 mL) was added. The mixture was heated in an oil bath at 80 °C for 24 h. The mixture was cooled, ethyl acetate was added, and it was extracted 3 times with 1 M HCl, once with saturated bicarbonate solution and finally on time with brine. The organic layer was dried with $MgSO_4$ and evaporated. The crude compound was purified by flash column chromatography with CH_2Cl_2 as eluent giving the product as clear syrup. Yield: 0.193 g, 4%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53−7.48 (m, 2H, Ar.), 7.39 (d, J = 7.2 Hz, 2H,Ar.), 7.35−7.20 (m, 6H, Ar.), 5.44 (d, J = 5.6 Hz, 1H, H1), 5.38 (dd, J = 5.7, 2.7 Hz, 1H, H2), 4.41 (d, J = 1.9 Hz, 2H, CH_2-benzyl), 4.35−4.31 (m, 1H, H3), 4.08 (d, J = 4.3 Hz, 1H, H4), 4.02 (q, J = 7.6 Hz, 1H, H5), 1.75 (d, J = 7.5 Hz, 3H, H6), 1.19−1.03 (m, 42H, TIPS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3(Ar.), 130.9(Ar.), 129.1(Ar), 129.02(Ar.), 128.96(Ar.), 127.5(Ar.), 126.8(Ar.), 84.3(C1), 76.5(C5), 75.2(C2), 74.8(C4), 73.1(C3), 57.9(CH_2-benzyl), 20.5(C6), 18.44(TIPS), 18.43(TIPS), 18.23(TIPS), 18.17(TIPS), 17.9(TIPS), 12.8(TIPS), 12.6(TIPS), 12.4(TIPS); $[\alpha]^{RT}_D$ 49.7° (c 1.0, $CHCl_3$); HRMS calculated $C_{37}H_{62}O_6S_2Si_2Na$ = 745.3424, found 745.3409

Phenyl 2-*O*-Sulfonylbenzyl-3-*O*-TBS-4-*O*-TIPS-1-thio-β-L-rhamnopyranoside (8). Phenyl 2-*O*-sulfonylbenzyl-4-*O*-TIPS-1-thio-β-L-rhamnopyranoside (0.5 g, 0.882 mmol) was dissolved in 5 mL of 2,6-lutidine, and then TBSOTf (1.76 mmol, 0.41 mL) was added. The mixture was heated in an oil bath at 80 °C for 24 h. The mixture was cooled, ethyl acetate was added, and the mixture was extracted 3 times with 1 M HCl, once with saturated bicarbonate solution and finally once with brine. The organic layer was dried with $MgSO_4$ and evaporated. The crude compound was purified by flash column chromatography with petroleum ether as eluent with a gradient of CH_2Cl_2 giving the product **8** as clear syrup. Yield: 0.5 g, 78%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54−7.49 (m, 2H), 7.40 (m, J = 7.4 Hz, 2H), 7.31 (q, J = 7.6 Hz, 3H), 7.28−7.22 (m, 3H), 5.27 (dd, J = 4.9, 2.6 Hz, 1H, H2), 5.24 (d, J = 4.9 Hz, 1H, H1), 4.48−4.40 (m,

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2H, CH_2-benzyl), 4.12−4.07 (m, 1H, H3), 3.96−3.88 (m, 2H, H4, H5), 1.68 (d, J = 7.3 Hz, 3H, H6), 1.06 (d, 18H, TIPS), 0.98 (s, 9H, CH_3-TBS), 0.21 (s, 3H, Me-TBS), 0.12 (s, 3H, Me-TBS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8(Ar.), 130.90(Ar.), 130.87(Ar.), 129.1(Ar.), 129.03(Ar.), 128.97(Ar.), 127.72(Ar.), 126.96(Ar.), 84.3(C1), 77.0, 76.4(C2), 74.6, 73.3(C3), 57.9(CH_2-benzyl), 26.1(CH_3-TBS), 20.2(C6), 18.33(TBS), 18.27(TIPS), 18.2(TIPS), 12.7, −4.3(CH_3-TBS), −4.7(CH_3-TBS); $[\alpha]^{RT}_D$ 67.2° (c 1.0, $CHCl_3$); HRMS calculated $C_{34}H_{56}O_6S_2Si_2Na$ = 703.2955, found 703.2949

Phenyl 2-*O*-Sulfonylbenzyl-4-*O*-TIPS-3-*O*-TMS-1-thio-*β*-L-rhamnopyranoside (11). Phenyl 2-*O*-sulfonylbenzyl-4-*O*-TIPS-1-thio-*β*-L-rhamnopyranoside (0.200 g, 0.353 mmol) was dissolved in 3 mL of 2,6-lutidine, and then TMSOTf (0.706 mmol, 0.13 mL) was added. The mixture was stirred for 2 h, then ethyl acetate was added, and extraction was performed 3 times with 1 M HCl, once with saturated bicarbonate solution and once with brine. The organic layer was dried with $MgSO_4$ and evaporated. The crude compound was purified by flash column chromatography with petroleum ether and CH_2Cl_2 (2:1) as eluent giving the product as white foam. Yield: 0.162 g, 73%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.47 (m, 4H, Ar.) 7.39−7.35 (m, 3H)., 7.30 (dddd, J = 13.7, 7.0, 4.6, 2.1 Hz, 3H), 5.19 (dd, J = 2.6, 1.3 Hz, 1H, H2), 4.95 (d, J = 1.2 Hz, 1H, H1), 4.65 (d, J = 13.7 Hz, 1H, CH_2-benzyl), 4.52 (d, J = 13.7 Hz, 1H, CH_2-benzyl)), 3.84 (t, J = 8.2 Hz, 1H, H4), 3.70 (dd, J = 8.4, 2.7 Hz, 1H, H3), 3.47−3.40 (m, 1H, H5), 1.45 (d, J = 6.4 Hz, 3H, H6), 1.16−1.04 (m, 21H, TIPS), 0.21 (s, 9H, TMS); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.6(Ar.), 131.4(Ar.), 131.1(Ar.), 129.2(Ar.), 129.0(Ar.), 128.9(Ar.), 128.2(Ar.), 127.7(Ar.), 85.1(C1), 82.5(C2), 78.1(C5), 75.1(C3), 74.2(C4), 58.1(CH_2-benzyl), 18.8(C6), 18.6(TIPS), 18.3(TIPS), 13.9(TIPS), 0.5(TMS); $[\alpha]^{RT}_D$ 39.8° (c 1.0, CH_2Cl_2); HRMS calculated $C_{31}H_{50}O_6S_2Si_2Na$ = 661.2485, found 661.2481

General Procedure for Glycosylations. Equivalent amounts of donor and acceptor[31] were dried under a vacuum. Then solvent (1 mL per 1 mmol donor) and 4 Å molecular sieves were added, and the solution was stirred for an hour. The solution was cooled to the desired temperature, and the promoter[32] was added. The reaction mixture was slowly warmed up to room temperature and quenched with Et_3N. The solution was washed with 1 M HCl, saturated bicarbonate solution, NaS_2O_5 solution, and brine. The organic layer was dried with Na_2SO_4 and evaporated to dryness. NMR measurements of the crude product were done to check the α/β selectivity, and the crude compound was purified by flash column chromatography.

General Procedure for Desilylation. The compound was dissolved in a small amount of THF, and 4 equiv of 1 M TBAF(THF) was added.

The mixture was stirred until the deprotection was finished. To the mixture was added ethyl acetate, and the organic layer was extracted with 1 M HCl, saturated bicarbonate solution, and brine. The organic layer was dried with $MgSO_4$ and evaporated to dryness. NMR measurements of the crude product were done to check the α/β selectivity, and the crude compound was purified by flash column chromatography.

Cyclohexyl 2-*O*-Benzyl-3,4-di-*O*-TIPS-*α*,*β*-L-rhamnopyranoside. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.22 (m, 10H), 5.12 (d, J = 6.7 Hz, 1H), 5.01 (d, J = 3.3 Hz, 1H), 4.86 (d, J = 11.6 Hz, 1H), 4.83 (d, J = 11.9 Hz, 1H), 4.67 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.9 Hz, 1H), 4.16 (s, 1H), 4.10 (dd, J = 4.9, 3.2 Hz, 1H), 4.01 (dd, J = 5.1, 3.1 Hz, 1H), 3.90 (s, 1H), 3.81 (t, J = 3.3 Hz, 1H), 3.79 (s, 1H), 3.76−3.72 (m, 1H), 3.72−3.65 (m, 2H), 3.63 (dd, J = 6.7, 2.3 Hz, 1H), 1.97 (s, 4H), 1.78 (d, J = 8.2 Hz, 4H), 1.55 (d, J = 7.2 Hz, 3H), 1.40 (d, J = 6.9 Hz, 3H), 1.36−1.20 (m, 8H), 1.18−0.98 (m, 84H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.1, 139.0, 128.2, 128.12, 128.10, 127.8, 127.34, 127.27, 96.7, 95.5, 76.6, 76.1, 75.6, 75.0, 74.7, 74.3, 73.2, 73.0, 71.6, 34.0, 33.6, 32.2, 31.5, 29.9, 26.0, 25.9, 24.6, 24.4, 24.3, 24.2, 20.5, 19.0, 18.5, 18.41, 18.39, 18.36, 18.34, 18.30, 13.1, 13.0; HRMS calculated $C_{37}H_{68}O_5Si_2Na$ = 671.4503, found 671.4488

Methoxyethyl 2-*O*-Benzyl-3,4-di-*O*-TIPS-*α*,*β*-L-rhamnopyranoside. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42−7.20 (m, 7.5H), 5.00 (d, J = 6.7 Hz, 1H), 4.89 (d, J = 3.4 Hz, 0.3H), 4.84 (d, J = 11.7 Hz, 1H), 4.77 (d, J = 12.0 Hz, 0.3H), 4.66 (d, J = 11.7 Hz, 1H), 4.58 (d, J = 12.0 Hz, 0.3H), 4.16 (d, J = 2.6 Hz, 1H), 4.14−4.10 (m, 0.3H), 4.03−3.94 (m, 1.6H), 3.92−3.86 (m, 1H), 3.83 (t, J = 3.3 Hz, 0.3H), 3.82−3.77 (m, 1.3H), 3.76−3.70 (m, 1H), 3.67 (dd, J = 6.7, 2.4 Hz, 1H), 3.63 (t, J = 5.0 Hz, 2H), 3.61−3.55 (m, 1H), 3.42 (s, 3H), 3.39 (s, 1H), 1.55 (d, J = 7.2 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.17−0.98 (m, 56H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.99, 138.96, 128.3, 128.1, 127.9, 127.4, 99.6, 98.67, 98.65, 76.6, 75.3, 74.8, 74.4, 74.0, 73.5, 72.9, 72.1, 72.0, 71.5, 67.9, 59.1, 20.0, 19.0, 18.5, 18.4, 18.32, 18.28, 13.0, 12.9, 12.8, 12.7; HRMS calculated $C_{34}H_{64}O_6Si_2Na$ = 647.4139, found 647.4199

Adamantyl 2-*O*-Benzyl-3,4-di-*O*-TIPS-*α*,*β*-L-rhamnopyranoside. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.22 (m, 7.5), 5.40 (d, J = 7.1 Hz, 1H), 5.09 (d, J = 2.6 Hz, 0.3H), 4.98 (d, J = 12.1 Hz, 0.3H), 4.89 (d, J = 11.5 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 4.55 (d, J = 12.1 Hz, 0.3H), 4.18 (s, 1H), 4.07−3.91 (m, 1.6 H), 3.78 (s, 1H), 3.75 (t, J = 2.6 Hz, 0.3 H), 3.60 (dd, J = 7.2, 2.5 Hz, 1.6 H), 2.18 (s, 5H), 2.02−1.77 (m, 10H), 1.73−1.60 (m, 10H), 1.52 (d, J = 6.9 Hz, 1.3H), 1.43 (d, J = 6.3 Hz, 3.7H), 1.23−0.95 (m, 78H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 139.0, 128.3, 128.0, 127.9, 127.4, 127.2, 126.9, 91.7, 90.0, 75.9, 74.9, 74.4, 74.3, 74.11, 74.08, 73.3, 72.3, 42.9, 42.5, 36.5, 30.7, 30.7, 20.3, 18.43, 18.39, 18.33, 18.28, 18.25, 18.22, 18.17, 13.3, 12.6, 12.5; HRMS calculated $C_{41}H_{72}O_5Si_2Na$ = 723.4816, found 723.4816

1-Pentenyl 2-*O*-Benzyl-3,4-di-*O*-TIPS-*α*,*β*-L-rhamnopyranoside (5). Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45−7.22 (m, 7.7H), 6.00−5.65 (m, 1.3H), 5.07 (dd, J = 3.5, 1.6 Hz, 1H), 5.06 (dd, J = 3.6, 1.7 Hz, 0.3H), 5.04 (dd, J = 3.5, 1.6 Hz, 1H), 5.03 (dd, J = 3.6, 1.7 Hz, 0.3H), 5.00 (dt, J = 2.2, 1.2 Hz, 1H), 5.00−4.99 (m, 0.3H), 4.98 (dt, J = 2.2, 1.2 Hz, 1H), 4.98−4.97 (m, 0.3H), 4.96 (d, J = 6.7 Hz, 1H), 4.83 (d, J = 1.8 Hz, 0.3H), 4.81 (d, J = 6.1 Hz, 1H), 4.73 (d, J = 12.0 Hz, 0.3H), 4.67 (d, J = 11.7 Hz, 1H), 4.58 (d, J = 12.0 Hz, 0.3H), 4.16 (t, J = 2.7 Hz, 1H), 4.15−4.12 (m, 0.3H), 4.00 (dd, J = 4.6, 2.5 Hz, 0.3H), 3.96−3.75 (m, 4.3H), 3.64 (dd, J = 6.7, 2.3 Hz, 1H), 3.53 (dt, J = 9.7, 6.6 Hz, 1H), 3.32 (dt, J = 9.4, 6.7 Hz, 0.3H), 2.29−2.14 (m, 2.8H), 1.83−1.67 (m, 2.8H), 1.55 (d, J = 7.3 Hz, 1.2H), 1.40 (d, J = 6.9 Hz, 3H), 1.19−0.98 (m, 66H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.95, 138.90, 138.8, 138.5, 128.2, 127.9, 127.4, 114.9, 114.6, 98.8, 98.5, 76.4, 75.3, 74.9, 74.4, 74.1, 73.7, 73.0, 72.8, 71.6, 68.5, 68.1, 30.7, 30.5, 29.2, 29.1, 20.0, 19.0, 18.5, 18.4, 18.34, 18.32, 18.29, 18.25, 13.0, 12.84, 12.79, 12.7; HRMS calculated $C_{36}H_{66}O_5Si_2Na$ = 657.4346, found 657.4327

Phenyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2-*O*-benzyl-3,4-di-*O*-TIPS-*α*-L-rhamnopyranosyl)-1-thio-*β*-D-glucopyranoside. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64−7.59 (m, 2H), 7.44−7.18 (m, 23H), 5.17 (d, J = 10.8 Hz, 1H), 5.13 (d, J = 7.6 Hz, 1H), 4.83−4.65 (m, 6H), 4.56 (q, J = 11.8 Hz, 2H), 4.20 (t, J = 2.5 Hz, 1H), 4.01 (m, 2H), 3.95 (t, J = 9.5 Hz, 1H), 3.86 (dd, J = 10.8, 5.8 Hz, 1H), 3.81 (s, broad, 1H), 3.71−3.64 (m, 2H), 3.58−3.48 (m, 2H), 1.28 (d, J = 7.1 Hz, 3H), 1.05 (dd, J = 32.6, 3.6 Hz, 42H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.9, 138.5, 138.4, 133.9, 132.1, 129.0, 128.6, 128.44, 128.39, 128.34, 128.27, 128.2, 127.8, 127.7, 127.5, 127.43, 127.36, 97.6, 87.3, 85.1, 80.4, 80.1, 76.3, 75.8, 75.6, 75.0, 74.9, 73.7, 73.3, 69.1, 18.37, 18.35, 18.2, 18.0, 12.7, 12.5; $[\alpha]^{RT}_D$ −26.1° (c 1.0, CH_2Cl_2); HRMS calculated $C_{64}H_{90}O_9SSi_2Na$ = 1113.5742, found 1113.5828

Cyclohexyl 2-*O*-Sulfonylbenzyl-3,4-di-*O*-TIPS-*α*,*β*-L-rhamnopyranoside. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.09 (m, Ar.), 5.37 (d, J = 5.6 Hz, 1H,), 5.31 (dd, J = 5.7, 2.7 Hz, 1H), 5.16 (d, J = 6.9 Hz, 1H), 4.94 (dt, J = 6.7, 3.5 Hz), 4.73 (dd, J = 7.4, 2.6 Hz), 4.54 (d, J = 13.7 Hz), 4.42−4.22 (m), 4.19−4.12 (m), 4.03−3.91 (m), 3.89 (dd, J = 4.9, 2.9 Hz), 3.81 (s), 3.70 (qd, J = 7.1, 2.9 Hz), 3.60 (s), 3.54 (tt, J = 9.0, 3.7 Hz), 1.98−1.78 (m), 1.67 (t, J = 10.3 Hz), 1.47 (d, J = 7.2 Hz), 1.43−1.32 (m), 1.32−0.92 (m,); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2, 130.92, 130.90, 130.87, 129.1, 129.0, 128.94, 128.89, 128.1, 128.0, 127.5, 126.8, 94.9, 92.1, 84.3, 80.3, 76.7, 76.6, 76.54, 76.47, 75.8, 75.16, 75.12, 74.8, 74.2, 73.1, 72.8, 57.9, 57.3, 34.0, 33.6, 32.2, 31.6, 31.4, 30.4, 30.3, 29.8, 25.8, 25.7, 24.6, 24.5, 24.3, 20.5, 20.4, 18.42, 18.41, 18.36, 18.3, 18.21, 18.15, 13.0, 12.9, 12.8, 12.6; HRMS calculated $C_{37}H_{68}O_7SSi_2Na$ = 735.4122, found 735.4175

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Cyclohexyl 2-*O*-Sulfonylbenzyl-α,β-L-rhamnopyranoside. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51−7.47 (m), 7.45−7.40 (m), 7.39−7.33 (m), 4.97 (d, *J* = 3.0 Hz), 4.78 (d, *J* = 1.5 Hz), 4.76−4.69 (m), 4.67 (s), 4.52−4.40 (m), 3.91 (dd, *J* = 9.6, 3.1 Hz), 3.76 (tt, *J* = 9.2, 3.7 Hz), 3.67 (ddd, *J* = 12.0, 9.2, 4.7 Hz), 3.49 (dt, *J* = 8.6, 4.8 Hz), 3.36 (t, *J* = 9.5 Hz,), 3.33−3.22 (m), 2.00−1.85 (m), 1.83−1.63 (m), 1.58−1.46 (m), 1.43 (s), 1.34−1.16 (m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.1, 131.0, 129.2, 129.0, 128.9, 128.8, 128.4, 127.8, 95.9, 95.7, 82.2, 80.1, 77.3, 76.0, 73.2, 72.8, 72.4, 72.1, 69.8, 68.3, 57.5, 57.4, 33.5, 33.3, 31.7, 31.5, 25.6, 24.14, 24.09, 24.0, 23.8, 17.8, 17.6; HRMS calculated $C_{19}H_{28}O_7SNa$ = 423.1453, found 423.1463

Methyl 2,3,4-Tri-*O*-benzyl-6- *O*-(2-*O*-sulfonylbenzyl-α,β-L-rhamnopyranosyl)-α-D-glucopyranoside. Data: ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.48−7.20 (m), 5.04 (d, *J* = 2.9 Hz), 4.99 (d, *J* = 10.8 Hz), 4.94 (d, *J* = 11.0 Hz), 4.92−4.87 (m), 4.84−4.76 (m), 4.73 (d, *J* = 10.9 Hz), 4.70 (d, *J* = 1.5 Hz), 4.69−4.63 (m), 4.61 (d, *J* = 3.4 Hz), 4.57 (d, *J* = 3.2 Hz), 4.55 (d, *J* = 4.3 Hz), 4.53 (d, *J* = 2.5 Hz), 4.51 (d, *J* = 3.0 Hz), 4.46−4.40 (m), 4.18 (dd, *J* = 11.0, 3.7 Hz), 3.97 (dt, *J* = 15.6, 9.3 Hz), 3.86 (dd, *J* = 9.6, 3.2 Hz), 3.80 (d, *J* = 11.0 Hz), 3.74 (ddd, *J* = 16.1, 11.3, 3.7 Hz), 3.68−3.56 (m), 3.53−3.46 (m), 3.41−3.27 (m), 1.31 (d, *J* = 5.4 Hz), 1.26 (d, *J* = 6.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 138.7, 138.5, 138.18, 138.16, 131.1, 130.9, 129.3, 129.1, 129.0, 128.9, 128.61, 128.58, 128.54, 128.50, 128.46, 128.2, 128.13, 128.07, 127.98, 127.96, 127.94, 127.85, 127.8, 127.67, 127.65, 98.4, 98.2, 97.93, 97.85, 82.1, 81.8, 80.5, 80.1, 78.8, 77.9, 77.6, 75.9, 75.7, 75.1, 73.51, 73.46, 73.2, 72.9, 72.5, 72.3, 70.1, 69.8, 68.3, 68.0, 66.7, 57.6, 57.5, 55.5, 55.4, 17.6, 17.5; HRMS calculated $C_{41}H_{48}O_{12}SNa$ = 787.2764, found 787.2415

Methyl 2,3,6-Tri-*O*-benzyl-4- *O*-(2-*O*-sulfonylbenzyl-α,β-L-rhamnopyranosyl)-α-D-glucopyranoside. Data: ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.41−7.20 (m, 20H), 5.12−5.04 (m, 2H, H1R, benzyl), 4.80 (dd, *J* = 3.1, 1.7 Hz, 1H, H2R), 4.74 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 10.9 Hz, 1H), 4.65−4.56 (m, 3H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.32 (s, 2H), 3.91−3.76 (m, 4H), 3.72−3.56 (m, 4H), 3.36 (s, 3H), 3.23 (td, *J* = 9.6, 4.0 Hz, 1H, H4R), 2.63 (d, *J* = 6.3 Hz, 1H, OH3), 2.05 (d, *J* = 4.0 Hz, 1H, OH4), 0.96 (d, *J* = 6.2 Hz, 3H, H6R); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 138.0, 130.9, 129.2, 129.0, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.61, 127.57, 98.0 (C1G), 97.4 (C1R), 80.5, 80.0, 79.0 (C2R), 75.6, 74.7, 73.4, 73.3, 73.2(C4R), 69.9, 69.8, 68.8, 68.5, 57.5, 55.4, 55.4, 17.2 (C6R); $[\alpha]^{RT}_D$ 27.8° (*c* 1.0, CH_2Cl_2); HRMS calculated $C_{41}H_{48}O_{12}SNa$ = 787.2764, found 787.2809

Cyclohexyl 2-*O*-Sulfonylbenzyl-4-*O*-TIPS-α,β-L-rhamnopyranoside. Data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 5.3, 2.1 Hz), 7.58−7.34 (m), 5.01−4.95 (m), 4.83 (d, *J* = 1.8 Hz), 4.77 (dd, *J* = 3.1, 1.9 Hz), 4.76−4.72 (m,), 4.66 (d, *J* = 13.9 Hz), 4.54−4.47 (m), 4.43 (d, *J* = 14.1 Hz), 3.89 (dd, *J* = 9.0, 3.2 Hz), 3.77 (td, *J* = 9.2, 4.6 Hz), 3.71−3.60 (m), 3.58−3.47 (m), 3.40−3.29 (m), 2.00−1.62 (m), 1.60−1.47 (m), 1.42−1.18 (m), 1.18−0.99 (m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.0, 131.1, 130.9, 129.2, 129.1, 129.00, 128.97, 128.9, 128.3, 127.9, 125.2, 95.9, 95.7, 81.4, 80.6, 77.0, 76.2, 75.4, 75.3, 73.6, 73.0, 70.7, 69.3, 57.6, 57.5, 33.83, 33.76, 33.5, 33.4, 31.6, 25.7, 25.3, 24.2, 24.1, 24.0, 23.9, 18.5, 18.44, 18.40, 18.1, 13.2, 13.1; HRMS calculated $C_{28}H_{48}O_7SSiNa$ = 579.2788, found 579.2787

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{13}C and ^{1}H NMR spectra of all prepared compounds. 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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(30) The conformation is analyzed from ^{1}H NMR data. See the Supporting Information.
(31) When cyclohexanol was used as donor, it was added at same time as the molecular sieves.
(32) The promoters used were NIS (1.2 equiv), TfOH (10 mol%); MeOTf (1.2 equiv); DMTST (1.2 equiv); Ph_2SO (2.8 equiv); Tf_2O (1.4 equiv); DTBMP (2 equiv); (1) ICl (1 equiv) (2) TBAC (1 equiv), Hünigs base (1 equiv); (1) Br_2 (1 equiv) (2) TEAB (1 equiv), Hünigs base (1 equiv); (1) ICl (1 equiv) (2) Ag_2CO_3 (3 equiv); (1) ICl (1 equiv) (2) AgOTf (3 equiv), DTBMP (3 equiv); NIS (1.3 equiv), TESOTf (0.25 equiv) or Tf_2O (1.2 equiv), TTBP (2 equiv).