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Disarming, non-participating 2-*O*-protecting groups in manno- and rhamnopyranosylation: scope and limitations of sulfonates, vinylogous esters, phosphates, cyanates, and nitrates

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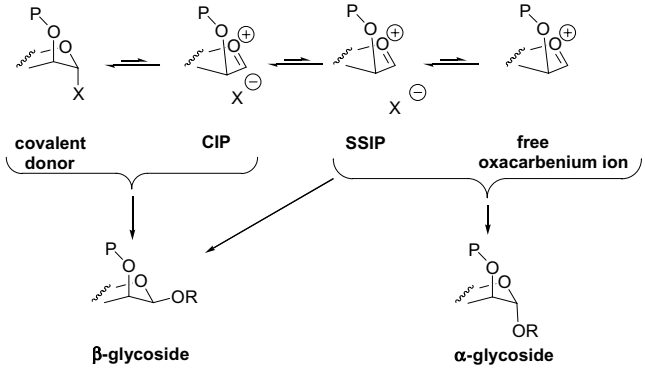
Abstract—A series of D-mannopyranosyl and L-rhamnopyranosyl thioglycosides protected with electron-withdrawing, non-participating protecting groups on O-2 have been prepared and investigated for their potential as β-glycosyl donors. Both α- and β-thioglycosides were investigated and the latter preferred on the grounds of enhanced stability at room temperature. A 2-*O*-nitro-L-rhamnosyl fluoride was also prepared and investigated. Moderate β-selectivities were observed with some of these donors. With the more powerfully electron-withdrawing groups reduced donor reactivity leads to a requirement for higher reaction temperatures and reduced selectivities. Decomposition temperatures of the intermediate glycosyl triflates were determined by variable temperature NMR spectroscopy and generally correlate with the disarming propensity of the protecting group system.

1. Introduction

Neighboring group participation by esters and related groups is one of the most fundamental and widely applied concepts of modern organic chemistry.[1] This is especially the case in carbohydrate chemistry[2] where the concept is very widely invoked, applied, and studied.[3] The high level of awareness arises from the central nature of neighboring group participation in the stereocontrolled synthesis of 1,2-*trans*-glycosidic bonds, which facilitates the preparation of the β-glucopyranosides and the α-mannopyranosides among others. In the absence of neighboring group participation, stereocontrolled glycosylation is inherently more difficult, being subject to the vagaries of the anomeric effect and the complex interplay between covalently bound donors and ion pairs, whether contact or solvent separated. Accordingly, the 1,2-*cis*-glycosidic bonds, as exemplified by the α-glucopyranosides and especially the β-mannopyranosides,[4] are considerably more difficult to prepare in a highly stereocontrolled manner than their 1,2-*trans*-counterparts. The problem is illustrated in Scheme 1 for the 1,2-*cis*-equatorial glycosidic bonds found in the β-manno- and β-rhamnopyranosides. The ideal situation involves the direct S_N2 attack of the acceptor alcohol on the covalently bound α-glycosyl donor, but the problem is compounded by the likelihood of the reaction actually taking place via the intermediacy of a transient contact ion pair, or even a solvent separated ion pair. Nucleophilic attack on a contact ion pair, in which the counterion is intimately associated with and blocks one face of the oxacarbenium ion, is functionally equivalent to the direct S_N2 attack. However, the dictates of the anomeric effect are such that any reaction proceeding through the solvent-separated ion pair is likely to lead at least in part to the axial glycoside, which is



Scheme 1. Abbreviated glycosylation mechanism.

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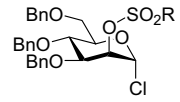
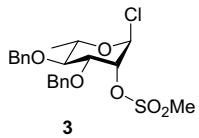
obviously the predominant product from any free oxacarbenium ions. In attempting any stereoselective 1,2-*cis*-glycosidic bond forming reaction it is imperative, therefore, to shift the complete series of equilibria in Scheme 1 as far to the left as possible such that the chemistry is dictated either by the covalently bound donor or the transient contact ion pair. At least in theory, this may be achieved by the use of non-polar solvents, weaker leaving groups, and the use of protecting groups likely to destabilize the oxacarbenium ion by their electron-withdrawing nature. Of course nothing is quite so simple: strongly covalently bound donors are inherently unreactive, and the use of electron-withdrawing protecting groups is widely recognized as being disarming,[5] that is leading to a further reduction in reactivity. Even more problematic in this regard is the fact that by far the most common and convenient disarming protecting groups are the carboxylate esters with their unavoidable predisposition for neighboring group participation.[6] Cyclic carbonates,[7] and related groups,[8] are strongly disarming and are stereoelectronically barred from participating, but only afford β-mannosides in heterogeneous, as opposed to homogeneous,[9] glycosylation reactions due to a conformational effect.

The potential of sulfonate esters as non-participating but powerfully electron-withdrawing protecting groups in carbohydrate chemistry was recognized by Schuerch et al., who reasoned that a powerfully electron-withdrawing, non-participating 2-*O*-sulfonate group on a mannosyl or rhamnosyl donor would lead to greater stability of the α- over the β-donor, by increasing the dipolar repulsion in the β-donor.[10,11] The Schuerch group further reasoned that the electron-withdrawing, non-participating 2-*O*-sulfonate group would increase the tightness of any transient ion pair arising from an α-donor, thereby leading to high β-selectivity in the difficult manno and rhamnopyranoside series. These expectations were borne out with a series of 2-*O*-sulfonyl protected mannosyl and rhamnosyl chlorides, **1**–**3**, which were transformed in to the corresponding anomeric sulfonates by metathesis with silver sulfonate salts prior to introduction of the glycosyl acceptor, and which took part in β-selective couplings with primary, and to a lesser extent secondary, alcohols.[10,12–14] Despite the promising nature of these glycosylations, this work lay dormant in the literature for many years, possibly because of the authors insistence on the high water sensitivity of the intermediate glycosyl sulfonates, the need for Schlenk line techniques, and the limited number of examples, until the description of a single β-selective mannosylation with each of the donors **4**–**6** by the Schmidt group in 2002[15] and our own work on β-selective 2-*O*-sulfonyl rhamnosyl thioglycosides in 2003.[16]

Herein we extend our earlier investigations on the use of 2-*O*-sulfonates in the formation of β-rhamnopyranosides[16] to the closely analogous β-mannosides. We address the previously neglected issue of the dependence of donor stability on the anomeric configuration, and the influence of the electron-withdrawing effect of these various groups on both reactivity and anomeric selectivity in coupling reactions. We also survey the potential of cyanate esters, vinylogous esters, phosphates, and nitrates[17,18] as non-participating, disarming protecting groups.



1: R = Me
2: R = Bn



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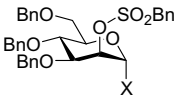
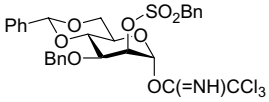


4: X = OC(=NH)CCl$_3$
5: X = S-2-pyr



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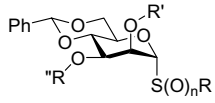
1.1. 2-*O*-sulfonyl protected thiomannosides

In recent years we have developed a powerful method for the stereocontrolled formation of β-mannopyranosides using 4,6-*O*-benzylidene blocked thiomannoside donors **7**, and/or their sulfoxides, protected by disarming ether groups on O-2 and O-3.[19–21] In this chemistry the thioglycoside and sulfoxide donors are transformed into glycosyl triflates **8**,[19c,22,23] the actual donor, by means of the combination of 1-benzenesulfinyl piperidine **BSP**[19c] and triflic anhydride or, for the sulfoxides, triflic anhydride alone.[24] The high β-selectivity in these glycosylations, which proceed via the intermediacy of transient contact ion pairs,[25] is attributed to the disarming nature[26–28] of the 4,6-*O*-benzylidene group, which serves to destabilize the oxacarbenium ion and shift the whole series of equilibria in Scheme 1 very strongly toward the left.



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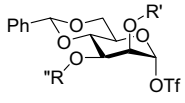

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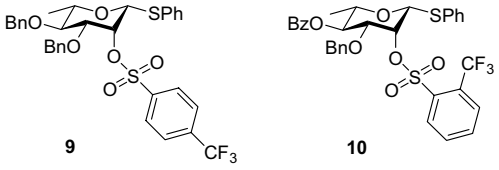
R = alkyl, aryl; R' = R" = allyl, benzyl; n = 0, 1

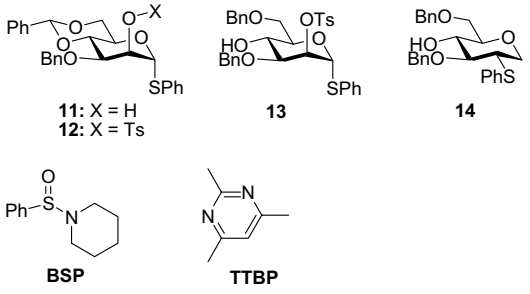
While the 4,6-*O*-benzylidene acetal, or its congenors, possess many advantages, they are not entirely devoid of limitations. Most pertinently, it is obviously not possible to employ this type of cyclic protecting group in the synthesis of the β-L-rhamnopyranosides, owing to the 6-deoxy functionality. Slightly less obvious, but equally pertinent to ongoing research, is the need for the selective cleavage of the 4,6-*O*-benzylidene acetal to the 6-*O*-benzyl ether-4-OH compound following glycosylation in the synthesis of the β-(1→4)-linked mannans and associated substances with alternating β-(1→3) and β-(1→4)-linkages. There are well-established methods to affect this cleavage selectively[29] but the conditions are harsh and, as we have found, rarely applicable to tri- and higher saccharides. In the synthesis of these β-(1→4)-linked mannans by the glycosyl triflate method a two step sequence involving hydrolytic cleavage of the benzylidene acetal and selective reprotection of the

6-OH, is therefore typically required.[20e,k,l] With these problems in mind, and cognizant of the work of Schuerch, we were attracted to the possibility that the use of a 2-*O*-sulfonyl protecting group might allow us to dispose with the need for the benzylidene acetal, thereby broadening our triflate-based approach to the 1,2-*cis*-equatorial glycosidic bonds.

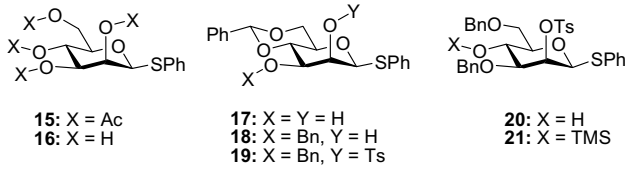
We first demonstrated that the 3,4-di-*O*-benzyl-2-*O*-sulfonyl-rhamnosyl donor **9** was an adequate donor for coupling to a simple model acceptor, 3β-cholestanol, by the BSP/Tf_2O method when a β:α ratio of 5.5:1 was obtained. However, further deactivation was required to obtain useful α:β ratios with more complex acceptors. Ultimately, the 4-*O*-benzoyl-3-*O*-benzyl-2-*O*-sulfonyl donor **10** was developed for this purpose and gave acceptable β:α ratios on coupling to a number of carbohydrate based acceptors.[16]



In attempting to transfer these results to the mannose series it was not clear to what extent the extra disarming effect of the C-6–O-6 bond would negate the need for the ester protecting group on O-4.[30] We therefore began with the preparation of set of simple 2-*O*-sulfonyl protected mannosyl thioglycosides, working first in the more readily available α-series. Thus, reaction of thioglycoside **11**[31] with tosyl chloride in the presence of silver nitrate and triethylamine afforded the sulfonate **12** in 81% yield. While it was possible to isolate and characterize this compound, and store it in the refrigerator, it was not indefinitely stable at room temperature and decomposed over a period of several days. Attempted conversion of **12** to the 6-*O*-benzyl-4-hydroxy analog **13**, such as may be useful for eventual use in the synthesis of a β-(1→4)-mannan, under the standard sodium cyanoborohydride/HCl conditions for this transformation, resulted only in the formation of the 1,2-dideoxy-2-phenylthioglucopyranose derivative **14**.



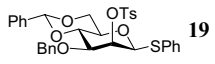
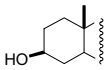
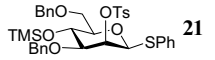
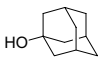
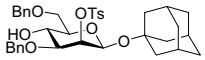
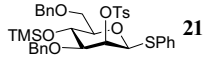
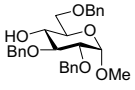
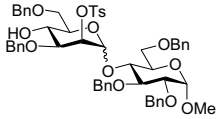
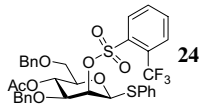
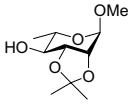
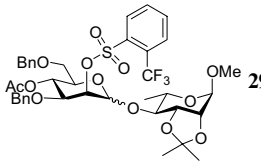
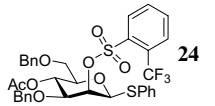
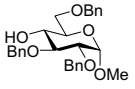
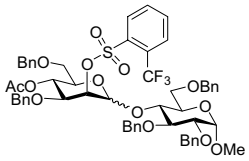
The basis of the instability of the 2-*O*-sulfonyl protected α-thiomannosides, which was also observed earlier with the analogous α-thiorhamnosides, arises from the *trans*-vicinal diaxial configuration of the nucleophilic thioether and the sulfonate esters, as is clear from the isolation of the rearrangement product **14**. Migrations related to the rearrangement of **12**–**14** are well known in the carbohydrate literature,[32] have found application in total synthesis,[33] and, beyond the bounds of carbohydrate chemistry, underpin many elegant syntheses of saturated heterocycles.[34] We therefore directed our attention at the synthesis of an analogous series of β-phenyl thioglycosides. Thus, acetobromomannose was exposed to thiophenol and sodium hydride in HMPA, followed by deacetylation, to first give the β-thioglycoside **15** and then the known thioglycoside **16**.[35] Introduction of the benzylidene group gave **17**, which was selectively converted to the 3-*O*-benzyl ether **18** in the usual manner by means of the dibutylstannylene acetal, benzyl bromide, and cesium fluoride. Sulfonylation with tosyl chloride, silver oxide, potassium iodide, and collidine then gave the stable donor **19** in 94% yield. Finally, exposure of **19** to excess sodium cyanoborohydride and HCl in ether afforded 74% of **20**, which was converted to the 4-*O*-trimethylsilyl derivative **21** in 95% yield with trimethylsilyl triflate.



The synthesis of **19** as an intermediate en route to **21** provided us with the opportunity to test the combined disarming effect of the 4,6-*O*-benzylidene group and of the 2-*O*-sulfonate. In the event, while activation was possible with the usual BSP/Tf_2O combination and under the DPSO/Tf_2O conditions, no coupling was ever observed, even to the relatively reactive acceptor, cholestanol (Table 1). This failure provided a first indication that it is possible for a donor to be too strongly disarmed.

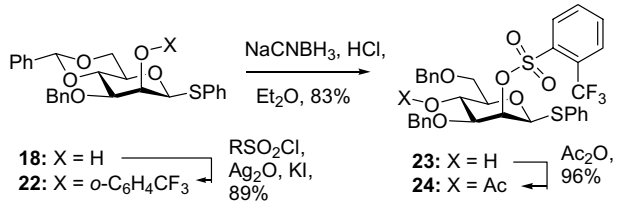
Coupling of donor **21** to 1-adamantanol by the diphenyl sulfoxide method gave the β-mannoside **25** in excellent yield, with no indication of formation of the corresponding α-anomer. However, as we have discussed previously,[36] 1-adamantanol routinely gives very high β-selectivity in our glycosyl triflate protocols[19b,19c] and is therefore an unreliable model. With the more demanding, but typical, glucose 4-OH acceptor **26** the selectivity fell to 2:1 in favor the unwanted α-anomer. We therefore fell back on the introduction of a second electron-withdrawing protecting group. Mindful of the need for maximum orthogonality of protection in any donor we elected to introduce a carboxylate ester, rather than a further sulfonate group, to fulfill this function. It was previously shown that 3-*O*-acyl groups are strongly α-directing in mannosylation by the glycosyl triflate method,[9,20f,37] presumably through neighboring group participation, therefore the only option was a 4-*O*-carboxylate ester or, possibly, a 6-*O*-carboxylate in the

Table 1. Coupling of 2-*O*-sulfonyl mannosyl donors to selected acceptors

Donor	Acceptor	Product (% yield; α:β ratio)	$^1J_{C1,H1}$ (Hz)
 **19**		—	—
 **21**		 **25** (82; β-only)[a,b]	β: 155.5
 **21**	 **26**	 **27** (77; 2:1)[a,c]	α: 176.1[d] β: 158.9[d]
 **24**	 **28**	 **29** (75; 1:10)[c]	α: 173.4[d] β: 159.1[d]
 **24**	 **26**	 **30** (76; 2:1)[c]	α: 172.0[d] β: 155.1[d]

[a] A treatment with Bu_4NF was included in the work-up.
[b] Conducted with the DPSO protocol.
[c] Directly analogous results were obtained by the DPSO method.
[d] Only the $^1J_{CH}$ coupling constants for the mannose residue are reported in this table.

mannose series. Thus, a 4-*O*-acetyl-2-*O*-(*o*-trifluoromethylbenzenesulfonyl) donor **24** was also prepared as illustrated in Scheme 2.

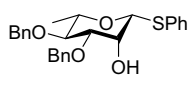


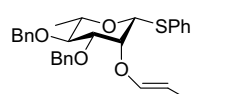
Scheme 2. Synthesis of a mannosyl donor.

With the relatively unhindered rhamnose derivative **28** as acceptor, donor **24** gave a satisfactory 75% yield of a 10:1 β:α mixture of glycosides **29**. Unfortunately, however, with the more demanding glucose 4-OH derivative **26**, the anomeric ratio was a disappointing 2:1 in favor of the α-anomer. Apparently, in the mannose series, the introduction of the extra electron-withdrawing group at O-4 has no significant effect on the outcome of the reaction with these already strongly disarmed donors.

1.2. Investigation of alternative non-participating, electron-withdrawing protecting groups at O-2

In addition to the 2-*O*-sulfonate esters, we have investigated several other protecting groups for their potential as non-participating, electron-withdrawing and, so, β-directing groups. A vinylogous ester **32** was obtained from **31**[16] in 64% yield by reaction with ethyl propiolate and *N*-methylmorpholine,[38] while bis(2,2,2-trichloroethyl)phosphate **33** was accessed from the corresponding phosphoryl chloride in 85% yield. A further donor, the 2-*O*-cyanate ester **34**, was obtained in 35% yield directly from **31** on treatment with potassium hexamethyldisilazide, then cyanogen bromide. Alternatively, **34** was obtained in 56% yield on dehydration of carbamate **35**, itself formed quantitatively from **31** with trichloroacetyl isocyanate, with triphenylphosphine and carbon tetrabromide.[39] Coupling of these donors to 3β-cholestanol was achieved by the standard **BSP** method leading to the results of Table 2. To our knowledge neither vinylogous esters, nor phosphates or cyanates have been employed in this manner previously in glycosylation reactions.


31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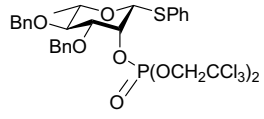

33

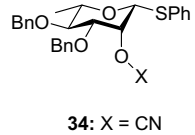
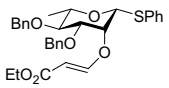
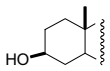
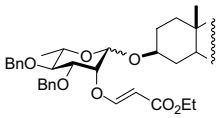
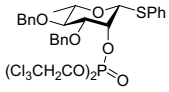
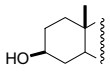
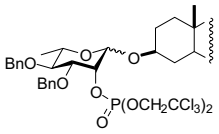
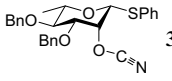
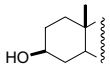
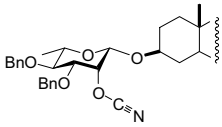
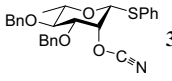
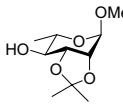
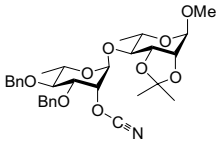
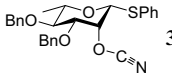
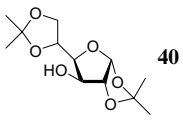
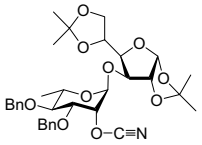
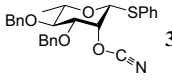
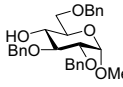

34: X = CN
35: X = $CONH_2$

Table 2. Coupling to alternate donors

Donor	Acceptor	Product (% yield; α:β ratio)	$^1J_{C1,H1}$ (Hz)
 **32**		 **36** (49; 1:1)[a]	α: 169.7 β: 153.8
 **33**		 **37** (73; 1:2.6)[a]	α: 170.3 β: 153.5
 **34**		 **38** (42; β-only)[a]	β: 154.2
 **34**	 **28**	 **39** (19; α-only)[a]	173.7[b]
 **34**	 **40**	 **41** (21; α-only)[a]	170.0[b]
 **34**	 **26**	—	—

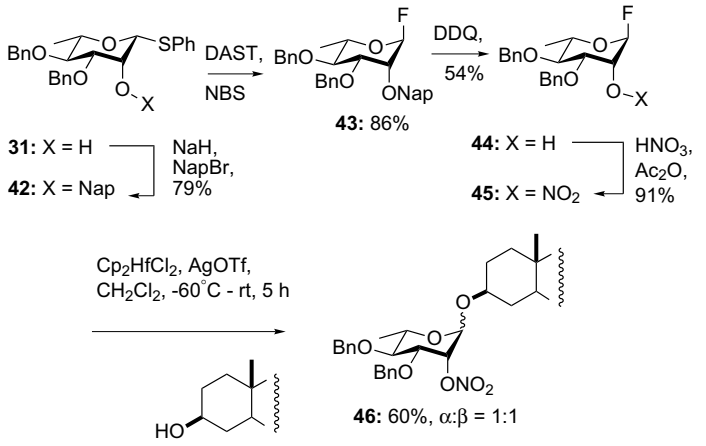
[a] Comparable results were obtained when these couplings were conducted by the DPSO method.
[b] Only the $^1J_{CH}$ coupling constants for the rhamnose residue are reported in this table.

Among the vinylogous esters, phosphates, and cyanates (Table 2) only the latter (**34**) was deemed sufficiently selective on coupling to cholestanol to warrant further investigation. Unfortunately our hopes for this moderately disarmed but sterically unencumbered rhamnosyl donor were short lived, as coupling reactions to the rhamnosyl acceptor **28** and to the glucofuranose acceptor **40** gave only the α-anomeric products in low yield (Table 2). With the less reactive glucosyl 4-OH acceptor **26** the situation was even worse with no coupling, and only decomposition of the donor being observed (Table 2). Obviously, the minimal steric bulk of the cyanate ester is insufficient to compensate for the only moderately disarming effect of this group (pK_a HOCN = 3.5). While the reason for the inefficient coupling with the cyanate donor is unclear at this point, it is possible that the cyanate itself is acting as a competing intermolecular nucleophile toward the intermediate glycosyl triflate in much the same way that acetonitrile participates in glycosylation reactions.[14] Alternatively, it may be that the cyanate group itself is undergoing nucleophilic attack by the acceptor alcohol in competition with the glycosylation reaction.

Finally, the powerfully disarming 2-*O*-nitrate ester was investigated. Methods for the introduction of nitrate esters are generally oxidizing and were considered incompatible with the presence of a thioglycoside. However, with the rapid conversion of glycosyl fluorides to glycosyl triflates by means of TMS triflate,[40] glycosyl fluorides[41] were considered as potentially suitable donors for use in conjunction with this novel protecting group. In the event, a 2-*O*-nitrate protected rhamnosyl fluoride **45** was prepared as outlined in Scheme 3.[42] Unfortunately, the nitrate ester (pK_a $HNO_3 = -1.3$) was found to be so disarming as to prevent activation by TMS triflate until the reaction temperature was raised to 0 °C, at which point decomposition was observed. Hafnocene dichloride in combination with silver triflate[43] was found, however, to activate the nitrate toward coupling, albeit slowly as the reaction mixture was allowed to warm to room temperature. The slow activation and high coupling temperature were then reflected in the poorly selective coupling to cholestanol when an unsatisfactory α:β ratio of 1:1 was observed (Scheme 3). On the basis of the slow activation and the inadequate selectivity, this direction of investigation was not pursued further.

1.3. Variable temperature NMR studies and glycosyl triflate decomposition

Variable-temperature NMR-derived decomposition temperatures for several of the intermediate glycosyl triflates employed in this study were determined with a view to checking the central premise of this paper: non-participating, electron-withdrawing protecting groups should stabilize covalent glycosyl triflates. As is



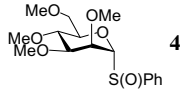
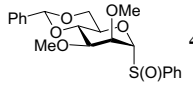
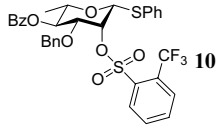
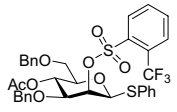
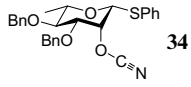
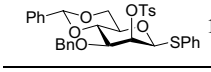
Scheme 3. Synthesis and coupling of a nitrate protected rhamnosyl donor.

apparent from the results presented in Table 3, this overarching principle generally holds with the more disarmed triflates decomposing at higher temperatures. The triflate derived from thioglycoside **19** is of particular interest as it illustrates the combined effect of the torsionally disarming 4,6-*O*-benzylidene protecting group and that of the more classically inductively disarming 2-*O*-sulfonyl group. The combination is obviously powerful as it results both in a substantial deactivation of the thioglycoside itself toward activation and an increased decomposition temperature of approximately 20 °C.

2. Conclusion

2-*O*-Sulfonyl protected mannosyl thioglycosides are readily prepared, stable glycosyl donors, provided β-thioglycosides are employed. These donors are moderately selective for the formation of the β-glycosides with simple alcohols, and less hindered carbohydrate acceptors. However, with the more demanding glucose 4-OH acceptor the selectivity is considerably reduced. A number of other non-participating, electron-withdrawing protecting groups were investigated but none

Table 3. Thioglycoside activation times and glycosyl triflate decomposition temperatures

Thioglycoside	Act. time, temp (°C)	δ_{H1} for glycosyl triflate	Decomp. temp (°C)
 **47**[a,b]	<3 min, −78	6.17, br s	−30
 **48**[a,b]	<3 min, −78	6.20, br s	−10
 **10**	<1 min, −60	6.26, d (J = 1.8 Hz)	10
 **24**	<1 min, −60	6.28, s	−10
 **34**	<1 min, −60	6.24, s	−30
 **19**	1 h, −60	6.24, d (J = 1.8 Hz)	20

[a] Taken from Ref. 22 for comparison purposes.
[b] Activation with Tf_2O.

compared favorably with the 2-*O*-sulfonates. An important lesson, gleaned from the relative lack of reactivity of the 4,6-*O*-benzylidene-2-*O*-sulfonyl protected system **19**, and the 2-*O*-nitrate **45**, is that it is possible for a system to be disarmed to a point at which it is insufficiently reactive. This leads to a need for increased reaction temperatures and, ultimately, to reduced selectivities.

3. Experimental

3.1. General

Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution. Optical rotations were recorded in $CHCl_3$ solution, unless otherwise stated. All solvents were dried and distilled by standard protocols. All reactions were conducted under a blanket of dry nitrogen or argon. All organic extracts were dried over sodium sulfate, and concentrated under aspirator vacuum at room temperature. Chromatographic purifications were carried out over silica gel. Room temperature is referred to as rt.

3.2. General procedure for coupling to thioglycosides

To a solution of substrate in CH_2Cl_2 (0.03 M in substrate), containing activated molecular sieves BSP (1.1 equiv), and TTBP (2 equiv) were added and the reaction mixture cooled to −60 °C, after which Tf_2O (1.2 equiv) was added slowly. After stirring for the prescribed activation time at −60 °C, the acceptor (2 equiv) in CH_2Cl_2 (2 M in substrate) was added slowly over a period of 1 min. The cloudy reaction mixture was stirred for further 30 min at −60 °C, then was removed from the cooling bath and left to stir for a further 15 min. The clear orange solution was then quenched by adding saturated aqueous $NaHCO_3$. Brine was then added and the contents were extracted with CH_2Cl_2. The combined organic layer was dried and the solvent removed. Chromatographic purification (eluting with mixtures of hexane and ethyl acetate) afforded the coupled products. The DPSO protocol is identical save for the replacement of BSP by DPSO.

3.3. *S*-Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(*p*-toluenesulfonyl)-α-D-thiomannopyranoside 12

To a solution of **11** (1.31 g, 2.9 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (1.2 mL, 8.7 mmol) and tosyl chloride (1.48 g, 5.8 mmol) followed by $AgNO_3$ (0.99 g, 5.8 mmol). The reaction mixture was stirred at rt for 12 h after which it was filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was separated, dried, and concentrated. Chromatographic purification (10% ethyl acetate in hexane) afforded **12** (1.42 g, 81%). $[\alpha]_D^{25} = +31.9$ (*c* 1.6, $CHCl_3$); ^{1}H NMR δ: 7.79–7.78 (d, J = 7.0 Hz, 2H), 7.49–7.48 (dd, J = 2.0, 8.0 Hz, 2H), 7.42–7.26 (m, 11H), 7.21–7.16 (m, 4H), 5.63 (d, J = 1.5 Hz, 1H), 5.62 (s, 1H), 5.02–5.01 (m, 1H), 4.57–4.55 (d, J = 12.0 Hz, 1H), 4.47–4.45 (d, J = 12.0 Hz, 1H), 4.27–4.21 (m, 2H), 4.13 (t, J = 9.5 Hz, 1H), 3.96–3.93 (dd, J = 3.5, 9.5 Hz, 1H), 3.87 (t, J = 9.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR δ: 144.9, 137.5, 137.3, 133.1, 132.5, 132.3, 129.7, 129.3, 128.9, 128.3, 128.27, 128.26, 128.2, 127.7, 126.0, 101.6, 87.4, 78.9, 78.3, 73.4, 72.5, 68.3, 65.4, 21.7; ESIHRMS Calcd for $C_{33}H_{33}O_7S_2Na$ $[M+H]^+$: 605.1668. Found: 605.1684.

3.4. 3,6-Di-*O*-benzyl-1,2-dideoxy-2-phenylthioglucopyranose 14

To a stirred solution of **12** (1.35 g, 2.2 mmol) in THF (25 mL) was added $NaBH_3CN$ (2.09 g, 33.3 mmol) and a pinch of methyl orange at 0 °C. After 15 min a 2.0 M solution of HCl in Et_2O (20 mL) was added slowly until the color of the solution became permanently pink. The reaction mixture was stirred at rt for 12 h and diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution, water, and brine. The organic layer was separated, dried, and concentrated. Chromatographic purification (12% ethyl acetate in hexane) afforded **14** (0.82 g, 85%). $[\alpha]_D^{26} = -10.8$ (*c* 0.3, $CHCl_3$); ^{1}H NMR δ: 7.48–7.46 (m, 2H), 7.43–7.41 (m, 2H), 7.38–7.24 (m, 11H), 5.03–5.01 (d, J = 11.0 Hz, 1H), 4.83–4.80 (d, J = 11.0 Hz, 1H), 4.60–4.57 (d, J = 11.5 Hz, 1H), 4.55–4.52 (d, J = 12.5 Hz, 1H), 4.02–3.99 (m, 1H), 3.68–3.64 (m, 3H), 3.39–3.35 (m, 4H); ^{13}C NMR δ: 138.4, 137.9, 133.7, 132.1, 129.2, 128.8, 128.6, 128.4, 128.2, 127.9, 127.5, 84.2, 79.1, 77.6, 77.2, 76.8, 75.6, 73.8, 72.9, 70.6, 70.2, 49.6; ESIHRMS Calcd for $C_{26}H_{28}O_4SNa$ $[M+Na]^+$: 459.1572. Found 459.1571.

3.5. *S*-Phenyl 4,6-*O*-benzylidene-β-D-thiomannopyranoside 17

To a solution of *S*-phenyl β-D-thiomannopyranoside **16** (3.4 g, 12.5 mmol)[35] and catalytic camphorsulfonic acid in THF (150 mL) was added benzaldehyde dimethyl acetal (2.0 mL, 2.1 g). The reaction mixture was heated to reflux for 1 h then concentrated. Chromatographic purification (EtOAc/hexane, 1/1) gave **17** (3.2 g, 71%) as white solid. $[\alpha]_D^{20} = -46.4$ (*c*, 1.1); mp 195 °C; ^{1}H NMR δ: 7.20 (m, 10H), 5.43 (s, 1H), 4.81 (d, J = 1.2 Hz, 1H), 4.21 (dd, J = 5.1, 10.5 Hz, 1H), 4.10 (d, J = 2.7 Hz, 1H), 4.04 (br s, 2H), 3.79 (t, J = 9.6 Hz, 1H), 3.72 (t, J = 10.5 Hz, 1H), 3.63 (dd, J = 3.6, 9.6 Hz, 1H), 3.29 (dt, J = 5.1, 9.9 Hz, 1H); ^{13}C NMR δ:130.9, 129.0, 128.2, 127.4, 126.2, 120.1, 88.4, 78.3, 72.7, 71.5, 71.0, 68.4. Anal. Calcd for $C_{19}H_{20}O_5S{\cdot}0.33H_2O$: C, 62.29; H, 5.68. Found: C, 62.33; H, 5.62.

3.6. *S*-Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-thiomannopyranoside 18

Diol **17** (70 mg, 0.19 mmol) and Bu_2SnO (72 mg, 0.29 mmol) were heated to reflux with stirring in a mixture of benzene (5 mL) and MeOH (0.5 mL) for 3 h. After cooling to rt and concentration, the residue was taken up in toluene (10 mL), benzyl bromide (24 μL 43.0 mg, 0.2 mmol) and Bu_4NI (80 mg, 0.4 mmol) were added, and the reaction mixture heated to 100 °C for 8 h. After concentration, chromatographic purification of the residue (EtOAc/hexane, 1/3) gave **18** (43 mg,

50%). $[\alpha]_D^{20} = -18.5$ (*c* 0.4, $CHCl_3$); ^1H NMR δ: 7.39 (m, 15H), 5.62 (s, 1H), 4.89 (s, 1H), 4.86 and 4.75 (2d, $J = 12.0$ Hz, 2H), 4.33 (dd, $J = 5.1$, 10.8 Hz, 1H), 4.31 (s, 1H), 4.18 (t, $J = 9.3$ Hz, 1H), 3.93 (t, $J = 10.5$ Hz, 1H), 3.69 (dd, $J = 3.4$, 9.6 Hz, 1H), 3.43 (dt, $J = 5.1$, 9.9 Hz, 1H); ^{13}C NMR δ: 138.8, 136.2, 131.4, 129.2, 128.7, 128.4, 128.2, 128.1, 127.7, 126.2, 101.7, 87.8, 78.4, 77.9, 73.0, 71.6, 71.2, 68.7. Anal. Calcd for $C_{26}H_{26}O_5S$: C, 69.31; H, 5.82. Found: C, 69.50; H, 6.08.

3.7. *S*-Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(*p*-toluenesulfonyl)-β-D-thiomannopyranoside 19

To a stirred solution of **18** (280 mg, 0.62 mmol) in CH_2Cl_2 (4 mL) were added *sym*-collidine (1 mL), KI (206 mg, 1.22 mmol), Ag_2O (288 mg, 1.24 mmol) and tosyl chloride (178 mg, 0.93 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and for 16 h at rt before it was diluted with CH_2Cl_2 and filtered. The filtrate was washed with aqueous $CuSO_4$ then satd. $NaHCO_3$. The organic layer was separated, dried, and concentrated. Chromatographic purification (hexane/ethyl acetate, 5:1) then gave **19** (344 mg, 94%) as white solid. $[\alpha]_D^{26} = -52.3$ (*c* 1.0, $CHCl_3$); mp 140 °C; ^1H NMR: 7.94–7.92 (d, $J = 8.0$ Hz, 2H), 7.86–7.84 (d, $J = 8.5$ Hz, 1H), 7.47–7.25 (m, 16H), 5.58 (s, 1H), 5.49–5.48 (d, $J = 3.0$ Hz, 1H), 4.88 (s, 1H), 4.85–4.83 (d, $J = 12.0$ Hz, 1H), 4.71–4.69 (d, $J = 12.5$ Hz, 1H), 4.29–4.25 (dd, $J = 5.0$, 10.0 Hz, 1H), 4.04–4.01 (t, $J = 9.5$ Hz, 1H), 3.89–3.85 (t, $J = 10.0$ Hz, 1H), 3.75–3.72 (dd, $J = 3.0$, 10.0 Hz, 1H), 3.43–3.38 (m, 1H), 2.42 (s, 3H); ^{13}C NMR δ: 144.5, 137.5, 137.2, 134.4, 133.5, 131.8, 131.5, 130.4, 129.4, 129.1, 128.9, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 126.0, 101.5, 86.8, 79.9, 77.6, 77.0, 75.9, 72.4, 71.9, 68.2, 22.0, 21.7; ESIHRMS Calcd for $C_{33}H_{32}O_7S_2Na$ $[M+Na]^+$: 627.1487. Found 627.1500. Anal. Calcd for $C_{33}H_{32}O_7S_2$: C, 65.54; H, 5.33: Found: C, 65.31; H, 5.48.

3.8. *S*-Phenyl 3,6-di-*O*-benzyl-2-*O*-(*p*-toluenesulfonyl)-β-D-thiomannopyranoside 20

Compound **19** was converted to **20** (74%) by the protocol used for the formation of **14** from **12**. $[\alpha]_D^{26} = -57.3$ (*c* 1.2, $CHCl_3$); ^1H NMR δ: 7.93–7.91 (d, $J = 8.5$ Hz, 2H), 7.52–7.50 (m, 2H), 7.43–7.23 (m, 15H), 5.48 (d, $J = 2.5$ Hz, 1H), 4.98–4.95 (d, $J = 12.0$ Hz, 1H), 4.85 (s, 1H), 4.55 (d, $J = 1.5$ Hz, 2H), 4.53–4.51 (d, $J = 11.5$ Hz, 1H), 3.86–3.83 (m, 2H), 3.76–3.73 (dd, $J = 6.5$, 11.0 Hz, 1H), 3.54–3.51 (m, 1H), 3.50–3.48 (dd, $J = 2.5$, 9.0 Hz, 1H), 2.72 (br s, 1H), 2.41 (s, 3H); ^{13}C NMR δ: 144.5, 138.2, 137.2, 134.4, 134.2, 131.2, 129.4, 129.1, 128.6, 128.4, 128.3, 128.2, 128.1, 127.7, 127.64, 127.62, 85.3, 80.3, 79.5, 78.1, 73.6, 72.1, 70.4, 67.2, 21.7; ESIHRMS Calcd for $C_{33}H_{34}O_7S_2Na$ $[M+Na]^+$: 629.1644. Found 629.1619.

3.9. *S*-Phenyl 3,6-di-*O*-benzyl-2-*O*-(*p*-toluenesulfonyl)-4-*O*-(trimethylsilyl)-β-D-thiomannopyranoside 21

To a solution of **20** (0.116 g, 0.19 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (67 μL, 0.48 mmol). After 15 min, TMSOTf (42 μL, 0.23 mmol) was added at −20 °C. The reaction mixture was stirred for 1 h at −20 °C then was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was separated, dried, and concentrated. Chromatographic purification (8% ethyl acetate in hexane) afforded **21** (0.123 g, 95%). $[\alpha]_D^{24} = -55.8$ (*c* 1.1, $CHCl_3$); ^1H NMR δ: 7.88–7.87 (d, $J = 7.0$ Hz, 2H), 7.52–7.50 (m, 2H), 7.41–7.39 (m, 2H), 7.35–7.26 (m, 8H), 7.22–7.20 (m, 5H), 5.46 (d, $J = 2.5$ Hz, 1H), 4.89–4.87 (d, $J = 11.5$ Hz, 1H), 4.84 (s, 1H), 4.57 (d, $J = 2.5$ Hz, 2H), 4.48–4.46 (d, $J = 11.5$ Hz, 1H), 3.84–3.80 (t, $J = 8.5$ Hz, 1H), 3.78–3.75 (dd, $J = 2.0$, 11.0 Hz, 1H), 3.68–3.65 (dd, $J = 6.5$, 11.0 Hz, 1H), 3.48–3.47 (m, 1H), 3.44–3.42 (dd, $J = 3.0$, 9.0 Hz, 1H), 2.40 (s, 3H), 0.01 (s, 9H); ^{13}C NMR δ: 144.2, 138.5, 137.1, 134.9, 134.5, 131.1, 129.3, 128.9, 128.3, 128.2, 128.0, 127.7, 127.6, 127.5, 127.4, 85.3, 81.1, 78.9, 73.4, 72.3, 69.6, 67.5, 21.6, 0.4; ESIHRMS Calcd for $C_{36}H_{42}O_7S_2SiNa$ $[M+Na]^+$: 701.2039. Found 701.2007.

3.10. *S*-Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-(2-trifluoromethylbenzenesulfonyl)-β-D-thiomannopyranoside 22

Following the procedure applied for the preparation of **19**, **22** was obtained from **18** and *o*-trifluoromethylbenzenesulfonyl chloride (89%). $[\alpha]_D^{24} = -37.2$ (*c* 1.8, $CHCl_3$); ^1H NMR δ: 8.26–8.24 (d, $J = 7.5$ Hz, 1H), 7.84–7.83 (d, $J = 7.5$ Hz, 1H), 7.63–7.60 (t, $J = 7.5$ Hz, 1H), 7.58–7.54 (t, $J = 7.5$ Hz, 1H), 7.46–7.25 (m, 15H), 5.60 (s, 1H), 5.45–5.44 (d, $J = 3.5$ Hz, 1H), 4.87 (d, $J = 0.5$ Hz, 1H), 4.68–4.65 (d, $J = 12.5$ Hz, 1H), 4.56–4.53 (d, $J = 12.5$ Hz, 1H), 4.33–4.29 (dd, $J = 4.5$, 10.5 Hz, 1H), 4.07–4.03 (t, $J = 10.0$ Hz, 1H), 3.91–3.87 (t, $J = 10.5$ Hz, 1H), 3.71–3.69 (dd, $J = 3.0$, 9.5 Hz, 1H), 3.43–3.38 (m, 1H); ^{13}C NMR δ: 137.3, 131.6, 131.4, 129.2, 128.9, 128.3, 128.2, 128.0, 127.8, 127.7, 126.0, 101.5, 86.6, 82.1, 77.9, 75.6, 72.5, 71.7, 68.4; ESIHRMS Calcd for $C_{33}H_{30}F_3O_7S_2$ $[M+H]^+$: 659.1385. Found 659.1378.

3.11. *S*-Phenyl 3,6-di-*O*-benzyl-2-*O*-(2-trifluoromethylbenzenesulfonyl)-β-D-thiomannopyranoside 23

Compound **22** was converted to **23** in 83% yield analogously to the preparation of **14** from **12**. $[\alpha]_D^{26} = -61.5$ (*c* 2.4, $CHCl_3$); ^1H NMR δ: 8.27–8.25 (d, $J = 7.5$ Hz, 1H), 7.86–7.85 (d, $J = 8.0$ Hz, 1H), 7.67–7.64 (t, $J = 7.5$ Hz, 1H), 7.60–7.57 (t, $J = 7.5$ Hz, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.44–7.43 (d, $J = 4.0$ Hz, 1H), 7.34–7.21 (m, 13H), 5.46–5.45 (d, $J = 2.5$ Hz, 1H), 4.83–4.80 (d, $J = 11.5$ Hz, 1H), 4.82 (s, 1H), 4.61–4.59 (d, $J = 11.5$ Hz, 1H), 4.58–4.56 (d, $J = 12.0$ Hz, 1H), 4.46–4.43 (d, $J = 11.5$ Hz, 1H), 3.93–3.89 (t, $J = 9.5$ Hz, 1H), 3.86–3.83 (dd, $J = 3.5$, 10.5 Hz, 1H), 3.79–3.76 (dd, $J = 6.0$, 11.0 Hz, 1H), 3.51–3.49 (m, 1H), 3.47–3.44 (dd, $J = 3.0$, 9.5 Hz, 1H), 2.62 (br s, 1H); ^{13}C NMR δ: 138.0, 137.0, 136.0, 133.9, 133.3, 131.8, 131.4, 131.2, 129.0, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 85.1, 80.1, 79.9, 79.3, 73.6, 72.1, 70.4, 67.7; ESIHRMS

Calcd for $C_{33}H_{31}F_3O_7S_2Na$ $[M+Na]^+$: 683.1361. Found 683.1354.

3.12. *S*-Phenyl 4-*O*-acetyl-3,6-di-*O*-benzyl-2-*O*-(2-trifluoromethylbenzenesulfonyl)-β-D-thiomannopyranoside 24

To a stirred solution of **23** (0.422 g, 0.64 mmol) and DMAP (0.008 g, 0.06 mmol) in pyridine (10 mL) was added Ac_2O (97 μL, 0.96 mmol). After 6 h, the reaction mixture was concentrated, dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ solution and brine. The organic layer was separated, dried, and concentrated. Chromatographic purification (20% ethyl acetate in hexane) afforded **24** (0.432 g, 96%). $[\alpha]_D^{26} = -83.1$ (*c* 0.8, $CHCl_3$); ^{1}H NMR δ: 8.21–8.19 (d, $J = 7.5$ Hz, 1H), 7.76–7.75 (d, $J = 8.0$ Hz, 1H), 7.53–7.48 (m, 4H), 7.34–7.20 (m, 11H), 7.08–7.06 (m, 2H), 5.50–5.49 (d, $J = 3.5$ Hz, 1H), 5.21–5.17 (t, $J = 10.0$ Hz, 1H), 4.88 (s, 1H), 4.56–4.53 (d, $J = 11.0$ Hz, 1H), 4.52–4.49 (d, $J = 12.0$ Hz, 1H), 4.51 (s, 1H), 4.33–4.31 (d, $J = 12.0$ Hz, 1H), 3.69–3.67 (m, 1H), 3.62–3.58 (m, 3H), 1.86 (s, 3H); ^{13}C NMR δ: 169.5, 138.1, 136.9, 136.0, 133.9, 133.1, 131.8, 131.2, 129.1, 128.3, 128.1, 128.08, 128.03, 127.8, 127.7, 127.68, 127.6, 127.5, 85.1, 80.3, 78.5, 77.9, 73.6, 72.1, 69.9, 67.9, 20.8; ESIHRMS Calcd for $C_{35}H_{33}F_3O_8S_2Na$ $[M+Na]^+$: 725.1467. Found 725.1451.

3.13. (1-Adamantanyl) 3,6-di-*O*-benzyl-2-*O*-(*p*-toluenesulfonyl)-β-D-mannopyranoside 25

Coupling of **21** with 1-adamantanol, with a 20 min activation period, gave **25β** in 82% yield. $[\alpha]_D^{24} = -28.2$ (*c* 0.3, $CHCl_3$); ^{1}H NMR δ: 7.86–7.84 (d, $J = 9.0$ Hz, 2H), 7.45–7.43 (d, $J = 8.5$ Hz, 2H), 7.34–7.21 (m, 10H), 5.02–5.01 (d, $J = 2.5$ Hz, 1H), 4.91–4.89 (d, $J = 11.0$ Hz, 1H), 4.86 (d, $J = 1.5$ Hz, 1H), 4.56–4.54 (d, $J = 12.0$ Hz, 1H), 4.52–4.50 (d, $J = 11.5$ Hz, 1H), 4.48–4.45 (d, $J = 11.0$ Hz, 1H), 3.93–3.90 (dd, $J = 4.0$, 10.0 Hz, 1H), 3.89–3.87 (t, $J = 8.0$ Hz, 1H), 3.65–3.62 (dd, $J = 7.0$, 10.5 Hz, 1H), 3.47–3.44 (m, 1H), 3.38–3.36 (dd, $J = 3.0$, 8.5 Hz, 1H), 2.40 (s, 3H), 2.09 (br s, 2H), 1.99 (br s, 2H), 1.74–1.72 (d, $J = 12.0$ Hz, 2H), 1.69–1.66 (d, $J = 11.5$ Hz, 2H), 1.62–1.51 (m, 6H), 1.44–1.42 (d, $J = 11.5$ Hz, 2H); ^{13}C NMR δ: 143.7, 138.7, 137.8, 135.4, 129.2, 128.2, 128.1, 128.0, 127.5, 127.3, 91.0 ($^1J_{CH} = 155.5$ Hz), 79.4, 78.5, 76.5, 75.0, 74.7, 73.1, 72.3, 70.3, 65.9, 42.6, 42.2, 36.2, 36.1, 30.8, 30.6, 29.6, 21.5; FABHRMS Calcd for $C_{37}H_{43}O_8S$ $[M-H]^+$: 647.2678. Found 647.2672.

3.14. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[3,6-di-*O*-benzyl-2-*O*-(*p*-toluenesulfonyl)-α-D-mannopyranosyl]-α-D-glucopyranoside 27α and the β-manno-isomer 27β

Coupling of **21** with to alcohol **26**, with a 20 min activation period, gave **27α** and **27β** in 51% and 26% yield, respectively. **27α**: $[\alpha]_D^{25} = -7.0$ (*c* 1.5, $CHCl_3$); ^{1}H NMR δ: 7.60–7.58 (d, $J = 6.5$ Hz, 2H), 7.44–7.43 (d, $J = 7.0$ Hz, 2H), 7.39–7.36 (t, $J = 7.5$ Hz, 2H), 7.32–7.26 (m, 19H), 7.16–7.14 (d, $J = 7.5$ Hz, 2H), 7.01–6.99 (d, $J = 8.0$ Hz, 2H), 5.37 (d, $J = 2.0$ Hz, 1H), 5.04–5.02 (d, $J = 11.5$ Hz, 1H), 4.93–4.92 (t, $J = 2.5$ Hz, 1H), 4.80–4.78 (d, $J = 12.0$ Hz, 1H), 4.67–4.65 (d, $J = 12.0$ Hz, 1H), 4.59–4.58 (d, $J = 4.0$ Hz, 1H), 4.55–4.52 (d, $J = 11.5$ Hz, 1H), 4.54–4.51 (d, $J = 12.0$ Hz, 1H), 4.52 (s, 1H), 4.46–4.41 (t, $J = 12.5$ Hz, 2H), 4.32–4.30 (d, $J = 11.0$ Hz, 1H), 4.20–4.18 (d, $J = 11.0$ Hz, 1H), 3.88–3.78 (m, 5H), 3.72–3.69 (m, 2H), 3.66 (d, $J = 2.5$ Hz, 1H), 3.65 (s, 1H), 3.64–3.63 (d, $J = 2.5$ Hz, 1H), 3.56–3.53 (dd, $J = 3.5$, 9.0 Hz, 1H), 3.38 (s, 3H), 2.61 (br s, 1H), 2.29 (s, 3H); ^{13}C NMR δ: 144.4, 138.8, 138.1, 137.9, 137.8, 137.5, 133.8, 129.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.78, 127.76, 127.68, 127.6, 127.5, 127.3, 127.0, 99.7 ($^1J_{CH} = 176.1$ Hz), 97.8 ($^1J_{CH} = 166.9$ Hz), 80.8, 80.1, 77.4, 76.4, 74.9, 74.8, 73.6, 73.3, 73.2, 72.1, 71.4, 70.4, 69.7, 68.9, 67.6, 55.3, 21.6; ESI-HRMS Calcd for $C_{55}H_{60}O_{13}SNa$ $[M+Na]^+$: 983.3653. Found 983.3630. **27β**: $[\alpha]_D^{25} = -39.0$ (*c* 0.6, $CHCl_3$); ^{1}H NMR δ: 7.76–7.74 (d, $J = 6.5$ Hz, 2H), 7.41–7.15 (m, 27H), 4.96–4.95 (d, $J = 3.0$ Hz, 1H), 4.81–4.79 (d, $J = 12.0$ Hz, 1H), 4.76–4.74 (d, $J = 11.5$ Hz, 1H), 4.71–4.68 (d, $J = 12.0$ Hz, 1H), 4.63–4.61 (d, $J = 11.5$ Hz, 1H), 4.60–4.57 (d, $J = 12.5$ Hz, 1H), 4.56 (s, 1H), 4.44–4.42 (d, $J = 12.0$ Hz, 1H), 4.41 (s, 2H), 4.39–4.38 (d, $J = 3.5$ Hz, 1H), 4.37–4.35 (d, $J = 12.0$ Hz, 1H), 4.26–4.23 (d, $J = 12.0$ Hz, 1H), 3.82–3.79 (t, $J = 9.5$ Hz, 1H), 3.73–3.70 (m, 2H), 3.63–3.59 (m, 2H), 3.55–3.51 (t, $J = 9.5$ Hz, 1H), 3.49–3.45 (dd, $J = 5.0$, 10.5 Hz, 1H), 3.40 (s, 3H), 3.39–3.34 (m, 2H), 3.17–3.15 (m, 1H), 3.12–3.10 (dd, $J = 3.0$, 9.5 Hz, 1H), 2.77 (br s, 1H), 2.36 (s, 3H); ^{13}C NMR δ: 144.3, 139.7, 138.3, 137.9, 137.7, 137.5, 134.9, 129.3, 128.6, 128.5, 128.4, 128.1, 128.07, 128.04, 127.99, 127.95, 127.9, 127.7, 127.6, 127.4, 126.9, 98.5 ($^1J_{CH} = 169.2$ Hz), 97.9 ($^1J_{CH} = 158.9$ Hz), 79.9, 78.9, 78.8, 77.7, 76.6, 74.9, 74.4, 73.7, 73.6, 73.5, 71.8, 70.8, 69.3, 68.7, 68.5, 55.4, 21.6; ESIHRMS Calcd for $C_{55}H_{60}O_{13}SNa$ $[M+Na]^+$: 983.3653. Found 983.3621.

3.15. Methyl 4-*O*-[4-*O*-acetyl-3,6-di-*O*-benzyl-2-*O*-(2-trifluoromethylbenzenesulfonyl)-α-D-mannopyranosyl]-2,3-*O*-isopropylidene-α-L-rhamnopyranoside 29α and the β-mannosyl anomer 29β

Coupling of **24**–**28**, with a 1 h activation period, gave **29α** and **29β** in 7% and 68% yield, respectively. **29α**: $[\alpha]_D^{24} = +2.4$ (*c* 0.1, $CHCl_3$); ^{1}H NMR δ: 8.21–8.19 (d, $J = 8.0$ Hz, 1H), 7.70–7.69 (d, $J = 7.5$ Hz, 1H), 7.54–7.50 (t, $J = 7.0$ Hz, 1H), 7.44–7.41 (t, $J = 8.0$ Hz, 1H), 7.34–7.26 (m, 8H), 7.08–7.06 (m, 2H), 5.42–5.38 (t, $J = 10.0$ Hz, 1H), 5.24 (d, $J = 1.5$ Hz, 1H), 4.97–4.96 (dd, $J = 2.0$, 3.0 Hz, 1H), 4.84 (s, 1H), 4.58–4.56 (d, $J = 11.5$ Hz, 1H), 4.46–4.43 (d, $J = 12.0$ Hz, 1H), 4.36–4.34 (d, $J = 12.5$ Hz, 1H), 4.31–4.28 (d, $J = 12.5$ Hz, 1H), 4.12–4.04 (m, 3H), 3.84–3.81 (dd, $J = 2.5$, 10.0 Hz, 1H), 3.66–3.62 (dd, $J = 6.5$, 10.5 Hz, 1H), 3.58–3.56 (m, 2H), 3.44–3.40 (dd, $J = 7.0$, 10.0 Hz, 1H), 3.38 (s, 3H), 1.84 (s, 3H), 1.49 (s, 3H), 1.32–1.31 (s, $J = 7.0$ Hz, 3H), 1.27 (s, 3H); ^{13}C NMR δ: 169.5, 138.0, 137.3, 133.4, 131.9, 131.7, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.3, 109.4, 98.1 ($^1J_{CH} = 173.4$ Hz), 97.9 ($^1J_{CH} = 169.6$ Hz), 80.8, 76.7, 76.6, 75.9, 74.3, 73.6, 71.9, 69.9, 69.3, 68.3, 64.6, 54.9, 27.9, 26.3, 20.8, 17.4; ESI-HRMS Calcd for

$C_{39}H_{45}F_3O_{13}SNa$ [M+Na]$^+$: 833.2431. Found 833.2430. **29β**: $[\alpha]_D^{24} = -61.5$ (*c* 1.2, $CHCl_3$); ^{1}H NMR δ: 8.18–8.17 (d, J = 7.5 Hz, 1H), 7.77–7.75 (d, J = 6.5 Hz, 1H), 7.56–7.48 (m, 2H), 7.34–7.24 (m, 8H), 7.19–7.13 (m, 2H), 5.27 (d, J = 3.0 Hz, 1H), 5.16–5.12 (t, J = 9.5 Hz, 1H), 5.02 (s, 1H), 4.82 (s, 1H), 4.57–4.55 (d, J = 12.0 Hz, 1H), 4.54–4.52 (d, J = 12.0 Hz, 1H), 4.51–4.49 (d, J = 11.5 Hz, 1H), 4.35–4.33 (d, J = 12.0 Hz, 1H), 4.06–4.05 (dd, J = 2.5, 5.5 Hz, 2H), 3.63–3.55 (m, 4H), 3.51–3.48 (m, 1H), 3.35 (s, 3H), 3.27–3.24 (dd, J = 6.0, 10.0 Hz, 1H), 1.87 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.14–1.13 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ: 169.5, 137.9, 137.1, 132.8, 131.7, 131.2, 128.33, 128.29, 128.25, 128.22, 127.9, 127.9, 127.7, 127.5, 109.5, 97.6 ($^1J_{CH}$ = 169.4 Hz), 96.1 ($^1J_{CH}$ = 159.1 Hz), 78.2, 78.0, 77.9, 76.5, 76.0, 74.1, 73.6, 71.4, 69.9, 68.6, 63.8, 54.7, 27.9, 26.4, 20.8, 17.2; ESI-HRMS Calcd for $C_{39}H_{45}F_3O_{13}SNa$ [M+Na]$^+$: 833.2431. Found 833.2433.

3.16. Methyl 2,3,6-tri-*O*-benzyl-4-*O*-[4-*O*-acetyl-3,6-di-*O*-benzyl-2-*O*-(2-trifluoromethylbenzenesulfonyl)-α-D-mannopyranosyl]-α-D-glucopyranoside 30α and the β-mannosyl anomer 30β

Coupling of **24**–**26**, with a 1 h activation period, gave **30α** and **30β** in 25% and 51% yield, respectively. **30α**: $[\alpha]_D^{24} = -2.9$ (*c* 1.9, $CHCl_3$); ^{1}H NMR δ: 7.63–7.61 (d, J = 8.0 Hz, 1H), 7.43–7.35 (m, 6H), 7.32–7.19 (m, 20H), 6.92–6.90 (m, 2H), 5.46 (d, J = 2.5 Hz, 1H), 5.18–5.14 (t, J = 10.0 Hz, 1H), 5.06–5.04 (d, J = 11.5 Hz, 1H), 5.01–5.00 (t, J = 3.0 Hz, 1H), 4.79–4.77 (d, J = 11.5 Hz, 1H), 4.67–4.65 (d, J = 12.0 Hz, 1H), 4.58–4.57 (d, J = 3.5 Hz, 1H), 4.55–4.52 (d, J = 12.5 Hz, 1H), 4.54–4.52 (d, J = 12.0 Hz, 1H), 4.47–4.45 (d, J = 11.5 Hz, 1H), 4.44–4.41 (d, J = 12.0 Hz, 1H), 4.43–4.40 (d, J = 11.5 Hz, 1H), 4.08–4.05 (d, J = 11.5 Hz, 1H), 4.04–4.01 (d, J = 11.5 Hz, 1H), 3.94–3.92 (m, 1H), 3.87–3.85 (dd, J = 2.5, 7.0 Hz, 2H), 3.83–3.80 (dd, J = 4.5, 11.0 Hz, 1H), 3.79–3.77 (dd, J = 3.0, 9.5 Hz, 1H), 3.70–3.69 (m, 1H), 3.66–3.64 (dd, J = 2.0, 11.0 Hz, 1H), 3.56–3.53 (m, 1H), 3.52–3.49 (dd, J = 5.5, 10.5 Hz, 1H), 3.46–3.43 (dd, J = 3.5, 11.0 Hz, 1H), 3.38 (s, 3H), 1.84 (s, 3H); ^{13}C NMR δ: 169.5, 138.7, 138.0, 137.9, 137.8, 137.2, 133.1, 131.7, 131.3, 129.0, 128.8, 128.5, 128.4, 128.3, 128.26, 128.22, 128.19, 128.15, 128.1, 127.97, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 126.9, 99.6 ($^1J_{CH}$ = 172.0 Hz), 97.9 ($^1J_{CH}$ = 167.0 Hz), 80.6, 79.9, 78.1, 74.9, 74.4, 73.5, 73.3, 71.5, 71.2, 69.9, 69.8, 68.9, 68.2, 68.1, 55.3, 20.8; ESI-HRMS ESI-HRMS Calcd for $C_{57}H_{59}F_3O_{14}SNa$ [M+Na]$^+$: 1079.3476. Found 1079.3464. **30β**: $[\alpha]_D^{24} = -15.8$ (*c* 0.3, $CHCl_3$); ^{1}H NMR δ: 8.12–8.11 (d, J = 8.0 Hz, 1H), 7.75–7.73 (d, J = 8.0 Hz, 1H), 7.55–7.52 (t, J = 7.5 Hz, 1H), 7.44–7.41 (t, J = 8.0 Hz, 1H), 7.34–7.19 (m, 23H), 7.11–7.10 (d, J = 8.0 Hz, 2H), 5.09–5.06 (t, J = 9.5 Hz, 1H), 4.99–4.98 (d, J = 3.0 Hz, 1H), 4.77–4.75 (d, J = 13.0 Hz, 1H), 4.76–4.74 (d, J = 10.5 Hz, 1H), 4.71–4.69 (d, J = 12.0 Hz, 1H), 4.60–4.58 (d, J = 12.5 Hz, 1H), 4.54–4.53 (d, J = 3.5 Hz, 1H), 4.50–4.49 (d, J = 4.5 Hz, 1H), 4.47–4.46 (d, J = 3.0 Hz, 1H), 4.45 (s, 1H), 4.41–4.39 (d, J = 12.0 Hz, 1H), 4.32–4.29 (d, J = 12.0 Hz, 1H), 4.25–4.23 (d, J = 12.5 Hz, 1H), 4.14–4.12 (d, J = 11.0 Hz, 1H), 3.83–3.80 (t, J = 9.5 Hz, 1H), 3.73–3.71 (dd, J = 2.5, 11.0 Hz, 1H), 3.62–3.57 (m, 2H), 3.53–3.49 (t, J = 9.5 Hz, 1H), 3.41–3.36 (br s, 5H), 3.26–3.23 (m, 2H), 3.20–3.18 (dd, J = 3.0, 9.5 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR δ: 169.5, 139.5, 138.3, 138.2, 137.8, 137.3, 136.7, 132.9, 131.8, 131.2, 128.6, 128.4, 128.3, 128.2, 128.1, 128.08, 128.03, 128.0, 127.94, 127.9, 127.8, 127.7, 127.6, 127.4, 127.2, 127.1, 98.5 ($^1J_{CH}$ = 163.4 Hz), 97.8 ($^1J_{CH}$ = 155.1 Hz), 79.9, 78.7, 78.3, 78.1, 77.3, 75.1, 73.9, 73.64, 73.61, 73.5, 71.5, 70.2, 69.2, 68.7, 68.5, 55.3, 20.8; ESI-HRMS Calcd for $C_{57}H_{59}F_3O_{14}SNa$ [M+Na]$^+$: 1079.3476. Found 1079.3439.

3.17. *S*-Phenyl 3,4-di-*O*-benzyl-2-*O*-(3-ethoxycarbonyl-1-*E*-vinyl)-thio-β-L-rhamnopyranoside 32

To alcohol **31** (0.36 g, 0.82 mmol) in CH_2Cl_2 (7 mL) *N*-methyl morpholine (0.14 mL, 1.2 mmol) was added followed by ethyl propiolate (0.13 mL, 1.2 mmol), after which the reaction mixture was stirred for 4 h. Concentration followed by column chromatography afforded **32** (0.28 g, 64%). $[\alpha]_D^{25} = +36.2$ (*c* 0.9, $CHCl_3$); ^{1}H NMR δ: 7.57–7.54 (d, J = 11.2 Hz, 1H), 7.48–7.29 (m, 15H), 5.55–5.52 (d, J = 12.4 Hz, 1H) 4.87 (d, J = 10.0 Hz, 1H), 4.77 (s, 1H), 4.72 (s, 2H), 4.64 (d, J = 10.8 Hz, 1H), 4.35 (d, J = 2.4 Hz, 1H), 4.24–4.16 (m, 2H), 3.63 (dd, J = 3.2, 9.6 Hz, 1H), 3.54 (t, J = 9.2 Hz, 1H), 3.44–3.37 (m, 1H), 1.40 (d, J = 5.6 Hz, 3H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR δ: 167.8, 163.4, 137.9, 137.3, 134.1, 131.3, 129.1, 128.9, 128.6, 128.4, 128.3, 128.2, 128.18, 128.1, 127.97, 127.91, 127.7, 124.8, 98.6, 85.7, 82.7, 81.8, 79.5, 76.3, 75.7, 73.1, 59.8, 18.1, 14.5; ESIHRMS Calcd for $C_{31}H_{34}O_6NaS$ [M+Na]$^+$: 557.1974. Found: 557.1987.

3.18. *S*-Phenyl 3,4-di-*O*-benzyl-2-*O*-[bis(2,2,2-trichloroethyl)phosphoryl]-thio-β-L-rhamnopyranoside 33

To a stirred solution of **31** (0.22 g, 0.50 mmol) in CH_2Cl_2 (6 mL) at 0 °C Et_3N (0.22 mL, 1.5 mmol) was added followed by bis(2,2,2-trichloroethyl) phosphorochloridate (0.38 g, 1.0 mmol). The reaction mixture was stirred for 3 h at 0 °C, then was quenched by addition of saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried, and the solvent removed. Column chromatography (hexanes/ethyl acetate, 8:1) afforded **33** (0.33 g, 85%) $[\alpha]_D^{25} = +47.2$ (*c* 0.6, $CHCl_3$); ^{1}H NMR δ: 7.53–7.29 (m, 15H), 5.31–5.29 (dd, J = 9.0, 3.0 Hz, 1H), 4.96–4.94 (d, J = 10.5 Hz, 1H), 4.93–4.91 (d, J = 11.0 Hz, 1H), 4.87–4.83 (dd, J = 6.5, 11.0 Hz, 1H), 4.80 (d, J = 2.5 Hz, 1H), 4.77–4.74 (dd, J = 6.0, 11.0 Hz, 1H), 4.68–4.65 (d, J = 11.0 Hz, 1H), 4.63–4.60 (d, J = 10.5 Hz, 1H), 4.55–4.52 (dd, J = 6.0, 11.5 Hz, 1H), 4.42–4.38 (dd, J = 5.5, 11.0 Hz, 1H), 3.65–3.63 (ddd, J = 1.0, 3.0 and 9.5 Hz, 1H), 3.52–3.48 (t, J = 9.5 Hz, 1H), 3.44–3.41 (m, 1H), 1.39 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ: 138.2, 137.2, 134.0, 132.1, 129.6, 129.2, 129.0, 128.9, 128.7, 128.5, 128.3, 95.14 (d, J = 17.0 Hz), 86.2 (d, J = 6.25 Hz), 82.0, 79.1, 78.7 (d, J = 5.0 Hz), 77.7, 76.8, 76.1, 73.3, 30.1, 18.6.

Anal. Calcd for $C_{30}H_{31}Cl_6O_7$ PS: C, 46.24 H, 4.01. Found: C, 46.51 H, 4.15.

3.19. *S*-Phenyl 3,4-di-*O*-benzyl-2-*O*-cyano-thio-β-L-rhamnopyranoside 34

To a solution of **31** (0.30 g, 0.69 mmol) in toluene (7 mL) was added KHMDS (0.5 M solution in toluene, 2.4 mL) at −78 °C. Cyanogen bromide (0.11 g, 1.03 mmol in 2.8 mL of toluene) was then added over 1 h via syringe pump. The reaction mixture was then allowed to slowly warm to rt and was then stirred for 36 h before it was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layer was dried, concentrated, and purified by column chromatography (hexanes/ethyl acetate, 9:1) to give **35** as a white solid (112 mg, 0.24 mmol, 35%). Alternatively, **34** was obtained by dehydration of **35**: To a stirred solution at −20 °C of **35** (430 mg, 0.90 mmol), PPh_3 (590 mg, 2.25 mmol), and Et_3N (250 μL, 1.80 mmol) in CH_2Cl_2 (15 mL) was added dropwise a solution of CBr_4 (895 mg, 2.70 mmol) in CH_2Cl_2 (5 mL). The resultant solution was stirred −20 °C for 3 h then concentrated. The crude product was triturated by addition of hexanes/CH_2Cl_2 (10:1, 22 mL) then filtered. Concentration of the filtrate and chromatographic purification (eluting with 25% EtOAc in hexanes) afforded **34** (233 mg, 0.51 mmol, 56%). $[\alpha]_D^{25} = +38.4$ (*c* 0.6, $CHCl_3$); mp 112 °C; ^{1}H NMR δ: 7.50–7.28 (m, 15H), 4.95 (d, J = 3.0 Hz, 1H), 4.90 (d, J = 11.0 Hz, 1H), 4.87 (d, J = 11.5 Hz, 1H), 4.73 (s, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.0 Hz, 1H), 3.70 (dd, J = 3.0, 9.0 Hz, 1H), 3.51 (t, J = 9.5 Hz, 1H), 3.40–3.34 (m, 1H), 1.37 (d, J = 6.5 Hz, 3H); ^{13}C NMR δ: 138.0, 137.1, 133.2, 132.4, 129.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 113.4, 88.9, 84.5, 80.9, 79.0, 76.8, 76.3, 73.3, 18.4. IR (thin film) ν (cm^{-1}) 2235; ESIHRMS Calcd for $C_{27}H_{27}NO_4NaS$ $[M+Na]^+$: 484.1559. Found: 484.1563.

3.20. *S*-Phenyl 3,4-di-*O*-benzyl-2-*O*-carbamoyl-thio-β-L-rhamnopyranoside 35

To a stirred solution at 0 °C of **31** (500 mg, 1.15 mmol) in CH_2Cl_2 (10 mL) was added $Cl_3CC(O)NCO$ (275 μL, 2.30 mmol). The resulting solution was stirred for 30 min then concentrated. The residue was dissolved in MeOH (20 mL) and H_2O (2 mL) and cooled to 0 °C before addition of K_2CO_3 (477 mg, 3.45 mmol), followed by stirring for 1 h at 0 °C, then 1 h at rt. The reaction mixture was then concentrated, diluted with water (10 mL), and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried, and concentrated. Purification by flash column chromatography (40% EtOAc in Hexanes) then yielded pure **35** (550 mg, >99%). $[\alpha]_D^{25} = +62.6$ (*c* 1.0, $CHCl_3$); mp 140–142 °C; ν_{max} (KBr)/cm^{-1} 1731; ^{1}H NMR δ: 7.53–7.49 (m, 2H), 7.35–7.26 (m, 13H), 5.69 (dd, J = 1.0, 3.5 Hz, 1H), 4.94 (br s, 2H), 4.92 (d, J = 10.5 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.84 (d, J = 5.1 Hz, 1H), 4.63 (d, J = 10.5 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 3.65 (dd, J = 3.5, 9.0 Hz, 1H), 3.50 (t, J = 9.5, 1H), 3.42 (dq, J = 6.0, 9.5 Hz, 1H), 1.41 (d, J = 6.0 Hz, 3H); ^{13}C NMR: 156.0, 138.3, 138.6, 134.1, 131.5, 129.1, 128.5, 128.4, 128.1, 127.9, 127.8, 127.7, 85.6, 81.3, 71.4, 76.2, 75.6, 71.8, 71.2, 18.3; ESIHRMS Calcd for $C_{27}H_{29}NO_5NaS$ $[M+Na]^+$ 502.1664. Found 502.1650.

3.21. (3β-Cholestanyl) 3,4-di-*O*-benzyl-2-*O*-(3-ethoxycarbonyl-1-*E*-vinyl)-α-L-rhamnopyranoside 36α and the β-anomer 36β

Coupling of **32** to 3β-cholestanol, with a 20 min activation, gave **36α** and **36β**, both in 24% yield. **36α**: $[\alpha]_D^{25} = -15.1$ (*c* 0.7, $CHCl_3$); ^{1}H NMR δ: 7.51–7.30 (m, 11H), 5.37–5.34 (d, J = 12.4 Hz, 1H), 4.94 (s, 1H), 4.88–4.86 (d, J = 11.2 Hz, 1H), 4.69 (s, 2H), 4.62–4.59 (d, J = 11.2 Hz, 1H), 4.22–4.14 (m, 2H), 3.98–3.95 (dd, J = 2.8, 9.6 Hz, 1H), 3.84–3.77 (m, 1H), 3.56–3.44 (m, 2H), 1.98–0.59 (m, 53H); ^{13}C NMR δ: 166.1, 160.2, 138.0, 137.1, 133.2, 132.4, 129.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 99.9, 88.9, 84.5, 80.9, 79.0, 76.8, 76.3, 73.3, 56.9, 56.7, 54.8, 45.3, 43.0, 40.5, 39.9, 37.3, 36.6, 35.8, 35.6, 35.5, 33.9, 32.0, 29.1, 28.8, 28.3, 28.0, 24.2, 23.8, 22.8, 22.6, 21.3, 18.7, 17.7, 12.4, 12.1. **36β**: $[\alpha]_D^{25} = +32.4$ (*c* 0.6, $CHCl_3$); ^{1}H NMR δ: 7.52–7.29 (m, 11H), 5.36 (d, J = 12.3 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.78 (s, 1H), 4.69 (s, 2H), 4.62 (d, J = 11.2 Hz, 1H), 4.22–4.18 (m, 2H), 3.98 (dd, J = 3.0, 10.0 Hz, 1H), 3.86–3.80 (m, 1H), 3.56–3.44 (m, 2H), 1.98–0.58 (m, 53H); ^{13}C NMR δ: 166.1, 160.1, 138.0, 137.1, 133.2, 132.4, 129.7, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 99.9, 91.4, 84.5, 80.9, 79.0, 76.7, 76.3, 73.3, 56.7, 56.7, 54.8, 45.3, 43.0, 40.5, 39.9, 37.3, 36.6, 35.8, 35.6, 35.5, 33.9, 32.0, 29.1, 28.8, 28.3, 28.0, 24.2, 23.8, 22.8, 22.6, 21.3, 18.7, 17.7, 12.4, 12.1.

3.22. (3β-Cholestanyl) 3,4-di-*O*-benzyl-2-*O*-[bis(2,2,2-trichloroethyl)phosphoryl]-α-L-rhamnopyranoside 37α and the β-anomer 37β

Coupling of **33** to 3β-cholestanol, with a 20 min activation, gave **37α** and **37β** in 20% and 53% yield, respectively. **37α**: $[\alpha]_D^{25} = -14.8$ (*c* 0.8, $CHCl_3$); ^{1}H NMR δ: 7.57–7.31 (m, 10H), 5.10 (d, J = 1.5 Hz, 1H), 4.93–4.92 (d, J = 6.5 Hz, 1H), 4.91–4.89 (m, 1H), 4.87–4.85 (d, J = 11.5 Hz, 1H), 4.66 (dd, J = 5.0, 10.0 Hz, 1H), 4.61 (d, J = 6.5 Hz, 2H), 4.56–4.52 (dd, J = 6.5, 11.0 Hz, 1H), 4.45–4.42 (dd, J = 5.5, 11.0 Hz, 1H), 3.99–3.96 (m, 1H), 3.87–3.81 (m, 1H), 3.58–3.53 (m, 1H), 3.48–3.44 (t, J = 9.5 Hz, 1H), 1.98–0.58 (m, 50H); ^{13}C NMR δ: 143.3, 138.5, 137.9, 137.0, 135.8, 134.0, 131.9, 131.8, 129.8, 129.7, 129.3, 129.2, 128.9, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 124.7, 95.9 (d, J = 5.1 Hz), (J_{CH} = 170.3 Hz), 95.1 (q, J = 8.1 Hz, J = 4.0 Hz), 80.2, 78.8–78.7 (d, J = 3.0 Hz), 77.6–77.6 (d, J = 3.5 Hz), 77.5, 77.0, 76.5–76.5 (d, J = 5.4 Hz), 76.0, 73.0, 56.8, 56.6, 54.7, 45.0, 43.0, 40.4, 39.9, 37.4, 36.6, 36.2, 35.9, 35.9, 34.5, 32.4, 29.5, 29.2, 28.6, 28.4, 24.6, 24.2, 23.2, 23.0, 21.6, 19.1, 18.2, 12.7, 12.5; ESIHRMS Calcd for $C_{51}H_{73}Cl_6O_8NaP$ $[M+Na]^+$: 1077.3072 Found: 1077.3069. **37β**: $[\alpha]_D^{25} = +29.7$ (*c* 0.8, $CHCl_3$), ^{1}H NMR δ: 7.46–7.29 (m, 10H), 5.04 (dd, J = 3.0, 9.5 Hz, 1H), 4.94 (d, J = 11.0 Hz, 2H), 4.81–4.77 (dd, J = 6.0, 11.0 Hz, 1H), 4.75–4.71 (dd, J = 6.0,

10.5 Hz, 1H), 4.67–4.65 (d, J = 11.0 Hz, 1H), 4.62–4.60 (m, 2H), 4.59–4.58 (d, J = 11.5 Hz, 1H), 4.42–4.39 (dd, J = 5.5, 11.0 Hz, 1H), 3.68–3.60 (m, 2H), 3.43–3.33 (t, J = 9.0 Hz, 1H), 3.37–3.34 (m, 1H), 1.99–0.59 (m, 50H); ^{13}C NMR δ: 138.3, 137.5, 128.9, 128.9, 128.8, 128.6, 128.5, 128.4, 96.8–96.8 (d, J = 3.5 Hz), (J_{CH} = 153.5 Hz), 95.4 (d, J = 13.6 Hz), 81.0, 79.4, 78.9, 77.4–77.3 (d, J = 4.8 Hz), 76.8–76.8 (d, J = 6.4 Hz), 75.9, 72.6, 72.0, 56.9, 56.7, 54.7, 45.3, 43.0, 40.4, 39.9, 37.2, 36.5, 36.2, 35.9, 35.9, 32.4, 29.0, 28.6, 28.4, 28.3, 24.6, 24.2, 23.2, 23.0, 21.6, 19.1, 18.4, 12.7, 12.5. Anal. Calcd for $C_{51}H_{73}Cl_6O_8P$: C, 57.91 H, 6.96. Found: C, 58.20 H, 6.97.

3.23. (3β-Cholestanyl) 3,4-di-*O*-benzyl-2-*O*-cyano-β-L-rhamnopyranoside 38

Coupling of **34** to 3β-cholestanol, with a 20 min activation, gave **38** in 42% yield. $[\alpha]_D^{25} = +28.7$ (c 0.5, $CHCl_3$); ^{1}H NMR δ: 7.43–7.26 (m, 10H), 4.90 (d, J = 11.0 Hz, 1H), 4.83 (d, J = 11.5 Hz, 1H), 4.70–4.66 (m, 2H), 4.63 (d, J = 11.0 Hz, 1H), 4.60 (s, 1H), 3.66–3.56 (m, 1H), 3.64 (dd, J = 2.7, 9.0, 1H), 3.43–3.38 (t, J = 9.2 Hz, 1H), 3.34–3.27 (m, 1H), 1.97–0.56 (m, 50H); ^{13}C NMR δ: 138.7, 138.4, 128.3, 128.1, 127.5, 127.4, 113.1, 97.6 (J_{CH} = 154.2 Hz), 80.7, 80.3, 75.7, 75.5, 75.4, 72.8, 72.1, 67.9, 45.3, 43.0, 40.5, 39.9, 37.3, 36.6, 35.8, 35.6, 35.5, 33.9, 32.0, 29.1, 28.8, 28.3, 28.0, 24.2, 23.8, 22.8, 22.6, 21.2, 18.7, 18.0, 12.2, 12.1; ESIHRMS Calcd for $C_{48}H_{69}NO_5Na$ $[M+Na]^+$: 762.5073. Found: 762.5077.

3.24. Methyl 4-*O*-[3,4-di-*O*-benzyl-2-*O*-cyano-α-L-rhamnopyranosyl]-2,3-*O*-isopropylidene-α-L-rhamnopyranoside 39

Coupling of **34** to rhamnoside **28**, with 20 min activation, gave **39** in 19% yield. $[\alpha]_D^{25} = -40.9$ (c 0.8, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2235, 1092; ^{1}H NMR δ: 7.46–7.41 (m, 2H), 7.39–7.26 (m, 8H), 5.49 (d, J = 2.0 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.85 (s, 1H), 4.82 (d, J = 11.5 Hz, 1H), 4.76 (t, J = 2.2 Hz, 1H), 4.69 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.0 Hz, 1H), 4.10 (d, J = 5.5 Hz, 1H), 4.04 (dd, J = 1.5, 5.5 Hz, 1H), 3.90 (dd, J = 3.0, 9.0 Hz, 1H), 3.76–3.73 (m, 1H), 3.61–3.57 (m, 1H), 3.45 (t, J = 9.5 Hz, 1H), 3.43 (t, J = 9.5 Hz, 1H), 3.37 (s, 3H), 1.64 (s, 3H), 1.35 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ: 137.8, 137.1, 128.6, 128.5, 128.2, 128.0, 112.6, 109.6, 97.9, 95.5 (J_{CH} = 173.7), 85.8, 79.3, 79.0, 78.1, 77.5, 76.1, 75.8, 72.8, 68.6, 63.6, 55.0, 27.9, 26.3, 17.8, 17.6; FABHRMS Calcd for $C_{31}H_{39}NO_9Na$ $[M+Na]^+$ 592.2522. Found 592.2465.

3.25. 3-*O*-(3,4-Di-*O*-benzyl-2-*O*-cyano-α-L-rhamnopyranosyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose 41

Coupling of **35** to acceptor **40**, with 20 min activation, gave the α-glycoside **41** in 21% yield. $[\alpha]_D^{25} = -52.4$ (c 1.8, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 2236, 1075; ^{1}H NMR δ: 7.32–7.25 (m, 10H), 5.86 (d, J = 3.5 Hz, 1H), 5.14 (d, J = 1.5 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.77 (d, J = 11.5 Hz, 1H), 4.69 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 3.0 Hz, 1H), 4.50 (d, J = 3.5 Hz, 1H), 4.34 (d, J = 2.5 Hz, 1H), 4.12–4.08 (m, 4H), 3.94–3.91 (m, 1H), 3.42 (dd, J = 3.0, 9.5 Hz, 1H), 3.41 (t, J = 9.5 Hz, 1H), 1.50 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.24 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ: 138.2, 137.0, 128.6, 128.4, 128.3, 127.7, 127.6, 112.5, 112.3, 109.4, 105.2, 93.4 (J_{CH} = 170.0 Hz), 85.7, 81.5, 80.8, 78.9, 77.4, 77.2, 75.3, 73.0, 71.8, 68.6, 68.0, 26.8, 26.7, 26.2, 25.2, 17.3; ESIHRMS Calcd for $C_{33}H_{41}NO_{10}Na$ $[M+Na]^+$ 634.2628, found 634.2629.

3.26. *S*-Phenyl 3,4-di-*O*-benzyl-2-*O*-(2-naphthylmethyl)-β-L-thiorhamnopyranoside 42

To a stirred solution of **31** (2.00 g, 4.58 mmol) in THF (30 mL) at 0 °C was added NaH (60% in mineral oil, 367 mg, 9.2 mmol). After 10 min stirring, $NapCH_2Br$ (1.52 g, 6.9 mmol) was added, and the solution was heated to reflux and stirred for 14 h. Addition of NH_4Cl (satd. aq.) was followed by extraction with EtOAc, and the combined organic extracts were then washed with brine, dried, then concentrated. Purification by flash column chromatography (20% EtOAc in hexanes) afforded pure **42** (2.08 g, 79%). $[\alpha]_D^{25} = +18.9$ (c 1.0, $CHCl_3$); mp 98–100 °C; ^{1}H NMR δ: 7.89–7.80 (m, 4H), 7.69–7.65 (m, 1H), 7.50–7.45 (m, 4H), 7.38–7.21 (m, 13H), 5.19 (d, J = 11.5 Hz, 1H), 5.06 (d, J = 11.5 Hz, 1H), 4.96 (d, J = 10.5 Hz, 1H), 4.76–4.69 (m, 4H), 4.20 (d, J = 2.0 Hz, 1H), 3.76 (t, J = 9.0 Hz, 1H), 3.61 (dd, J = 3.0, 9.5 Hz, 1H), 3.42–3.39 (m, 1H), 1.41 (d, J = 6.0 Hz, 3H); ^{13}C NMR δ: 135.8, 135.6, 133.2, 133.1, 130.8, 128.9, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.1, 127.0, 126.7, 125.9, 125.8, 87.6, 84.2, 79.9, 77.6, 76.3, 75.6, 75.1, 72.7, 18.3. Anal. Calcd for $C_{37}H_{36}O_4S$: C, 77.05; H, 6.29. Found: C, 77.18; H, 6.29.

3.27. 3,4-Di-*O*-benzyl-2-*O*-(2-naphthylmethyl)-α-L-rhamnopyranosyl fluoride 43

To a stirred solution of **42** (1.5 g, 2.60 mmol) in CH_2Cl_2 (10 mL) at rt was added dropwise DAST (515 μL, 3.90 mmol), and the solution cooled to −78 °C and stirred for 10 min before the addition of NBS (602 mg, 3.38 mmol). The solution was stirred and allowed to warm to rt over 6 h. The reaction mixture was then diluted with CH_2Cl_2 (20 mL), poured into $NaHCO_3$ (satd. aq.) and the organic layer washed with $NaHCO_3$ (satd. aq.) then NaCl (satd. aq.). The organic extracts were dried then concentrated. Purification by flash column chromatography (10% EtOAc in hexanes) afforded **43** (1.08 g, 86%). $[\alpha]_D^{25} = -18.0$ (c 0.4, $CHCl_3$); ^{1}H NMR δ: 7.88–7.78 (m, 4H), 7.55–7.50 (m, 3H), 7.37–7.34 (m, 10H), 5.54 (dd, J = 1.8, 50.7 Hz, 1H), 4.99 (d, J = 10.5 Hz, 1H), 4.98 (d, J = 12.3 Hz, 1H), 4.87 (d, J = 12.3 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.69 (d, J = 10.5 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 3.93–3.85 (m, 3H), 3.73 (t, J = 9.5 Hz, 1H), 1.40 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ: 138.4, 138.3, 135.3, 133.3, 133.2, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.1, 126.4, 126.3, 126.1, 106.0 (d, J = 221.6 Hz, J_{CH} = 183.2 Hz), 79.7, 79.2, 77.3, 75.5, 73.7, 73.4, 72.8, 70.6, 18.1; ^{19}F NMR δ: −64.71 (d,

$J = 50.7$ Hz); ESIHRMS Calcd for $C_{31}H_{31}FO_4Na$ $[M+Na]^+$ 509.2104. Found 509.2122.

3.28. 3,4-Di-*O*-benzyl-α-L-rhamnopyranosyl fluoride 44

To a stirred solution of **43** (50 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) and H_2O (0.2 mL) at rt was added DDQ (35 mg, 0.16 mmol), and the resultant solution was stirred for 5 h. Addition of $NaHCO_3$ (satd. aq.) was followed by extraction with CH_2Cl_2, and the combined organic extracts were dried, then concentrated to yield the crude product. Purification by flash column chromatography (20% EtOAc in hexanes) afforded pure **44** (23 mg, 64%). $[\alpha]_D^{25} = -10.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ: 7.36–7.26, (m, 10H), 5.58 (dd, $J = 1.5$, 49.0 Hz, 1H), 4.90 (d, $J = 10.5$ Hz, 1H), 4.74 (d, $J = 11.5$ Hz, 1H), 4.69 (d, $J = 11.5$ Hz, 1H), 4.66 (d, $J = 10.5$ Hz, 1H), 4.11–4.10 (m, 1H), 3.93–3.85 (m, 1H), 3.84 (dd, $J = 1.0$, 3.5 Hz, 1H), 3.5 (t, $J = 9.5$ Hz, 1H), 2.62 (br s, 1H), 1.35 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR δ: 138.1, 137.6, 128.7, 128.5, 128.2, 128.1, 128.0, 127.9, 107.0 (d, $J = 216.5$ Hz, $J_{CH} = 181.3$ Hz), 79.05, 78.9, 75.5, 72.5, 69.9, 67.6, 67.2, 17.8; ^{19}F NMR δ: −67.40 (d, $J = 49.0$ Hz); ESIHRMS Calcd for $C_{20}H_{23}FO_4Na$ $[M+Na]^+$ 369.1478. Found 369.1465.

3.29. 3,4-Di-*O*-benzyl-2-*O*-nitro-α-L-rhamnopyranosyl fluoride 45

To a stirred solution of **44** (285 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added 20 drops of a solution of Ac_2O (2 mL) and HNO_3 (0.1 mL), and the resulting solution was stirred for 3 h. Addition of $NaHCO_3$ (satd. aq.) was followed by extraction with CH_2Cl_2, and the combined organic extracts were dried, then concentrated to yield **45** (293 mg, 91%), which was used without further purification. $[\alpha]_D^{25} = +6.5$ (*c* 1.0, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 1651, 1279, 854, 746, 698; ^{1}H NMR δ: 7.32–7.26 (m, 10H), 5.63 (dd, $J = 1.5$, 49.0 Hz, 1H), 5.45 (dd, $J = 1.5$, 1.5 Hz, 1H), 4.90 (d, $J = 10.5$ Hz, 1H), 4.70 (d, $J = 11.5$ Hz, 1H), 4.68 (d, $J = 11.5$ Hz, 1H), 4.64 (d, $J = 10.5$ Hz, 1H), 4.01 (ddd, $J = 1.0$, 2.5, 9.5 Hz, 1H), 3.93–3.90 (m, 1H), 3.47 (t, $J = 9.5$ Hz, 1H), 1.34 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR δ: 137.9, 137.2, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 104.1 (d, $J = 220.3$ Hz, $J_{CH} = 184.5$ Hz), 78.9, 76.8, 75.9, 75.7, 75.6, 73.1, 70.1, 17.7; ^{19}F NMR δ: −64.07 (d, $J = 49.0$ Hz); ESIHRMS Calcd for $C_{20}H_{22}FNO_6Na$ $[M+Na]^+$ 414.1329. Found 414.1347.

3.30. (3β-Cholestanyl) 3,4-di-*O*-benzyl-2-*O*-nitro-α-L-rhamnopyranoside 46α and the β-anomer 46β

To a stirred solution of Cp_2HfCl_2 (243 mg, 0.64 mmol) and 3 Å MS (50 mg) in CH_2Cl_2 (1 mL) at rt was added AgOTf (164 mg, 0.64 mmol) and the resultant solution was stirred for 30 min. 3β-Cholestanol (100 mg, 0.26 mmol) was then added and the solution cooled to −60 °C prior to addition of **45** (50 mg, 0.13 mmol) in CH_2Cl_2 (1 mL). The resulting solution was stirred and allowed to slowly warm to rt over 3 h. Filtration of the reaction mixture through Celite was followed by dilution with CH_2Cl_2 and addition of H_2O. Extraction with CH_2Cl_2 and washing of the combined organic extracts with brine, followed by drying and concentration gave the crude product mixture. Purification by flash column chromatography (10% EtOAc in hexanes) yielded **46α** (28 mg, 29%) and **46β** (30 mg, 31%). **46α**: $[\alpha]_D^{25} = -8.4$ (*c* 0.5, $CHCl_3$); mp 124–126 °C; ν_{max} (KBr)/cm^{-1} 1633, 1279, 861, 737, 694; ^{1}H NMR δ: 7.35–7.26 (m, 10H), 5.34 (dd, $J = 1.5$, 1.5 Hz, 1H), 5.02 (d, $J = 1.5$ Hz, 1H), 4.88 (d, $J = 10.5$ Hz, 1H), 4.70 (d, $J = 11.5$ Hz, 1H), 4.63 (d, $J = 10.5$ Hz, 1H), 4.60 (d, $J = 10.5$ Hz, 1H), 4.05 (dd, $J = 3.0$, 9.5 Hz, 1H), 3.84–3.74 (m, 1H), 3.58–3.50 (m, 1H), 3.41 (t, $J = 9.5$ Hz, 1H), 1.95–0.55 (m, 50H); ^{13}C NMR δ: 138.2, 137.7, 128.5, 128.1, 127.9, 127.8, 94.0 ($^1J_{CH} = 170.0$ Hz), 80.1, 78.4, 77.9, 77.25, 76.6, 75.7, 72.6, 67.8, 56.5, 56.3, 54.3, 44.6, 42.6, 40.0, 39.5, 37.0, 36.2, 35.8, 35.6, 35.5, 34.0, 32.1, 31.6, 29.1, 28.8, 28.3, 28.1, 24.2, 23.9, 22.9, 22.7, 22.6, 21.2, 18.7, 17.8, 12.3, 12.1; FABHRMS Calcd for $C_{47}H_{69}NO_7Na$ $[M+Na]^+$ 782.4972. Found 782.4916. **46β**: $[\alpha]_D^{25} = +31.1$ (*c* 0.4, $CHCl_3$); mp 130–132 °C; ν_{max} (KBr)/cm^{-1} 1634, 1282, 876, 751, 696; ^{1}H NMR δ: 7.35–7.26 (m, 10H), 5.57 (d, $J = 2.5$ Hz, 1H), 4.89 (d, $J = 10.5$ Hz, 1H), 4.73 (d, $J = 11.5$ Hz, 1H), 4.65 (d, $J = 1.0$ Hz, 1H), 4.62 (d, $J = 10.5$ Hz, 1H), 4.60 (d, $J = 11.5$ Hz, 1H), 3.69 (dd, $J = 3.5$, 9.5 Hz, 1H), 3.65–3.57 (m, 1H), 3.40 (t, $J = 9.5$ Hz, 1H), 3.36–3.29 (m, 1H), 2.00–0.52 (m, 50H); ^{13}C NMR δ: 138.1, 137.2, 128.8, 128.6, 128.5, 128.2, 128.1, 127.9, 95.9 ($^1J_{CH} = 156.0$ Hz), 79.8, 79.7, 78.1, 77.9, 75.6, 72.2, 71.6, 56.5, 56.3, 54.4, 44.9, 40.1, 39.5, 36.8, 36.2, 35.8, 35.6, 35.5, 32.1, 28.7, 28.1, 28.3, 28.1, 27.6, 24.2, 23.9, 22.9, 22.6, 21.3, 18.7, 17.9, 12.3, 12.1; ESIHRMS Calcd for $C_{47}H_{69}NO_7Na$ $[M+Na]^+$ 782.4972, found 782.4942.

Acknowledgements

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