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Amberlyst 15 as a mild and effective activator for the glycosylation with disarmed glycosyl trichloroacetimidate donors

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Abstract—Amberlyst 15 acidic resin has been shown to be a mild and effective activator for the glycosylation with commonly used disarmed glycosyl trichloroacetimidate donors. Glucosylation, galactosylation, rhamnosylation, and lactosylation of a panel of representative alcohol and thiol acceptors promoted by Amberlyst 15 allowed for the formation of structurally diverse O- or S-linked oligosaccharides and glycosylated amino acids in moderate to excellent yields.

1. Introduction

The rapid development of glycoscience promotes a great need for facile synthesis of pure and structurally well-defined oligosaccharides and glycosylated natural products.[1] Among the numerous oligosaccharide synthetic methodologies developed to date, glycosylations employing glycosyl imidate donors have been widely adopted in complex carbohydrate construction.[2] Traditionally, the glycosyl imidate-based glycosylations are activated by strong and moisture sensitive Lewis acids, including TMSOTf,[3] $BF_3 \cdot Et_2O$,[4] and TBSOTf[5] under strictly anhydrous, and in most cases, significant cooling conditions (up to −80 °C), which are practically inconvenient to handle. Although several moisture-stable solid promoters, such as I_2/Et_3SiH,[6] ytterbium triflate,[7] perchloric acid immobilized on silica gel ($HClO_4$/silica),[8] and 4 Å acids-washed molecular sieves (4 Å SW 300 MS)[9] have been also proved successful to activate glycosyl imidates, many of these methods suffer from disadvantages such as higher temperature, prolonged reaction time, large excess of reagents (4 Å SW 300 MS), low temperature (−10 °C for $HClO_4$/silica) or high cost (ytterbium triflate). Therefore, there has been a continuous pursuit of a more practical glycosylation protocol that employs ideally an inexpensive and mild catalyst than those currently in use. We hence sought to exploit the application of heterogeneous solid acid, namely, Amberlyst 15 resin to tackle this issue. Described herein is the use of Amberlyst 15 as an effective activator for the conventional glycosylation utilizing disarmed glycosyl trichloroacetimidate donors with carbohydrate, amino acid alcohol and thiol acceptors employing a mild and environmentally benign process.

2. Results and discussion

The effectiveness of Amberlyst 15 as a glycosylation activator was first tested by triggering the model experiment of disarmed donor 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate **1** (0.25 mmol) with phenylmethanol (0.2 mmol) in the presence of 20 wt % Amberlyst 15 (21 mg) at room temperature for ca. 5 h in diethyl ether (2.0 mL). As illustrated in Table 1, this resulted in only 50% isolated yield of desired 1,2-*trans* glycoside **13** (entry 1). We reasoned that the less satisfying yield might arise from partial hydrolysis of the donor, frequently observed in standard Lewis acid-mediated glycosylations,[10] since unreacted acceptor and hemiacetal of the donor were notably found at the end of the reaction period by TLC analysis. This prompted us to examine other methods devoid of such competitive side reaction by altering the Amberlyst loading. However, increased amount of Amberlyst (e.g., 40 wt %) led to a dramatic decomposition of the donor. Final survey revealed that premixing 100 wt % freshly activated 4 Å molecular sieves (4 Å MS), serving as a drying agent, with the coupling partners prior to the addition of Amberlyst minimized the unwanted hydrolysis effectively, and therefore, led to an improved and respectable 86% yield of **13** (entry 2).

Encouraged by the promising result, we further estimated the activating power of Amberlyst 15 in glycosylation.

Keywords: Amberlyst 15; Glycosylation; Trichloroacetimidate; Oligosaccharide.
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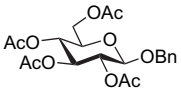
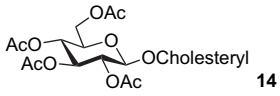
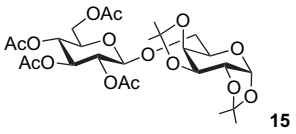
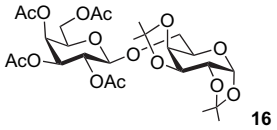
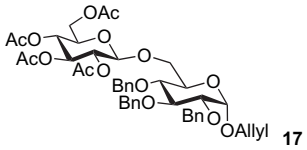
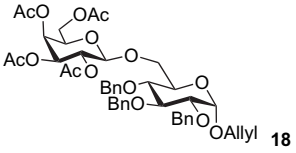
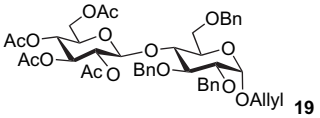
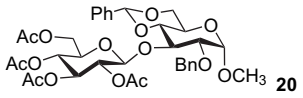
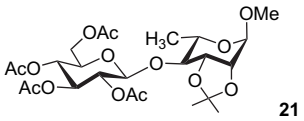
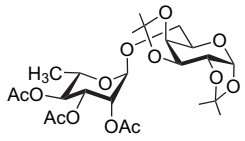
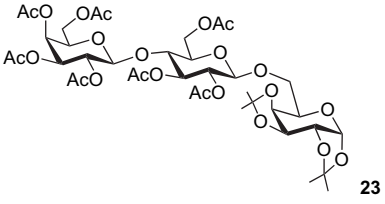
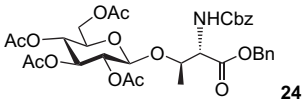
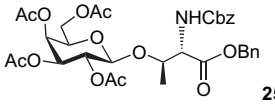
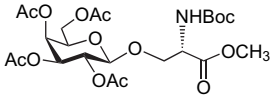
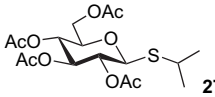
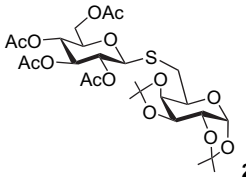
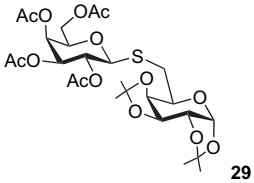
Table 1. 20 wt % Amberlyst 15-activated glycosylations of trichloroacetimidate donors (1.25–1.8 equiv) with alcohol and thiol acceptors (1.0 equiv)[a]

Entry	Donor	Acceptor	Product	Time (h)	Yield[b] (%)	Ref.
1[c]	**1**	Phenylmethanol	 **13**	5	50	11
2	**1**	Phenylmethanol		3	86	11
3	**1**	Cholesterol	 **14**	4	83	12
4	**1**	**5**	 **15**	3	84	11
5	**2**	**5**	 **16**	11	90	13
6	**1**	**7**	 **17**	4	79	—
7	**2**	**7**	 **18**	6	98	—
8	**1**	**8**	 **19**	4	72	—
9	**1**	**9**	 **20**	5	50	9a
10	**1**	**10**	 **21**	4	75	14
11	**3**	**5**	 **22**	5	95	15
12	**4**	**5**	 **23**	5	77	16

(*continued*)

Table 1. (*continued*)

Entry	Donor	Acceptor	Product	Time (h)	Yield[b] (%)	Ref.
13	**1**	**11**	 **24**	4	57	17
14	**2**	**11**	 **25**	4	95	17
15	**2**	**12**	 **26**	5	83	—
16	**1**	Isopropanethiol	 **27**	4	65	18
17	**1**	**6**	 **28**	6	76	—
18	**2**	**6**	 **29**	6	89	—

[a] Reactions were run with 100 wt % 4 Å MS at room temperature in diethyl ether.
[b] Isolated yield after column chromatography on silica gel.
[c] In the absence of 4 Å MS.

Thus, a series of peracetyl-protected glycosyl trichloroacetimidate donors **1**–**4** were synthesized and used for glycosylations with a panel of representative alcohols (Fig. 1). These included cholesterol, primary and secondary sugar acceptors, such as **5**, **7**, and **8**–**10**, for oligosaccharide synthesis, protected threonine and serine derivatives **11**, **12**, and thiol acceptors, isopropanethiol and **6**. To test the compatibility of the glycosylation conditions with a variety of potentially labile protecting groups, isopropylidene and benzylidene groups were also incorporated into these glycosyl acceptors.

Additionally, our selection of glycosyl trichloroacetimidates **1**–**4** as model systems was drawn to probe the effect of variation of sugar configurations (e.g., Glc (**1**) vs Gal (**2**)), as well as disaccharide system (**4**) on reaction outcome.

We were pleased to find that under the suitable conditions (20 wt % Amberlyst 15, 100 wt % 4 Å MS, 1.25–1.8 equiv donor, 1.0 equiv acceptor, room temperature, diethyl ether), glucosylation, galactosylation, rhamnosylation, and lactosylation of the selected representative alcohol and thiol

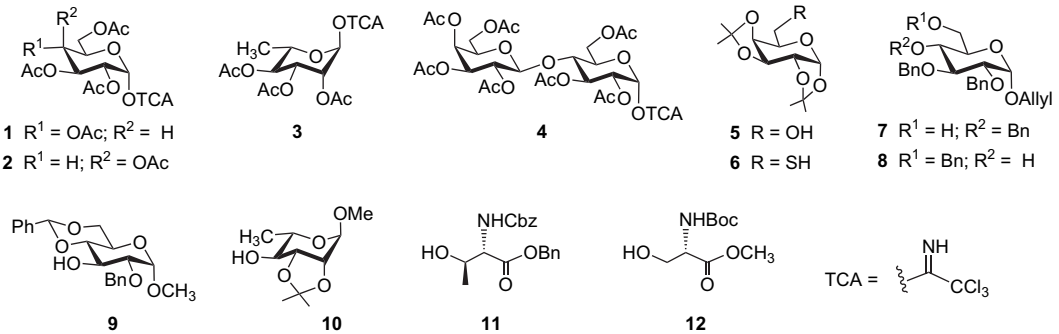


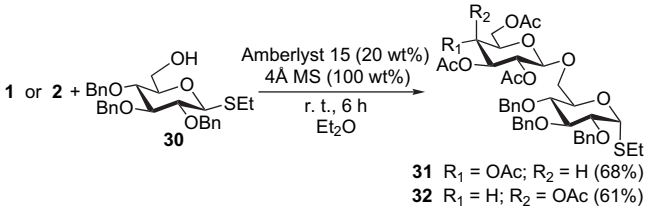
Figure 1. Disarmed glycosyl trichloroacetimidate donors (**1**–**4**) and acceptors (**5**–**12**).

acceptors afforded the expected O, S-glycosides and glycoamino acids in moderate to excellent yields (50–98%). Results of these experiments are summarized in Table 1.

In all cases, the observed formations of exclusive 1,2-*trans* glycosidic linkages of the glycosylation products are consistent with neighboring group participation of the C-2 acetate group. Reactions with primary acceptors **5** and **7** gave substantially better yields than reactions with more hindered secondary glycosyl acceptors **8**–**10** (entries 4–7 vs 8–10). Particularly, the feasible glycosylations of the disarmed donor **1** with the inert alcohols **8** and **9** in entries 8 and 9, respectively, demonstrated the sufficient ability of Amberlyst 15 to catalyze less reactive glycosylation substrates. Commonly used protecting groups, including isopropylidene, benzylidene acetals, and acetates were well tolerated. The good-to-excellent glycosylation yields of reactions using the peracetylated rhamnosyl trichloroacetimidate **3** and lactosyl trichloroacetimidate **4** indicated that this protocol was also effective for L-deoxy and disaccharide donor species (entries 11 and 12). The yields were generally higher for galactosyl imidate **2** than for glucosyl imidate **1** (entries 4–7), which evidenced a higher reactivity of the *galacto*-configured donor than its *gluco*-counterpart toward the corresponding acceptors under this condition.

The success of Amberlyst 15 as an activator for O-glycoside synthesis prompted extensive investigations toward glycoamino acid and S-glycoside synthesis. In the event, this mild activation system was also found to promote competently the couplings of the donors **1**, **2**, with both the amino acid alcohols **11**, **12**, and the thiols isopropanethiol, **6**, giving rise to the corresponding O-linked glycosylated amino acids **24**–**26** and thiosaccharides **27**–**29** with 1,2-*trans* stereoselectivity in equally good yields (entries 13–18). By comparison of both sets of the yields from entries 13 versus 14, and 17 versus 18, respectively, the same activity sequence was observed for the donors **1** and **2** in either glycoamino acid or S-glycoside synthesis as that of in O-glycoside synthesis. Overall, this is the first example for non-Lewis acid-mediated preparation of simple S-glycoside and (1→6)-linked-*S*-disaccharide with glycosyl imidate donors. It is apparently superior to the known approaches[19] due to its simplicity.

To extend the synthetic utility of the current protocol, we conducted selective activation reactions[20] with imidates **1**, **2**, and partially benzylated ethyl thioglycoside **30** in the presence of Amberlyst 15 (Scheme 1). As a result, **30**, as an acceptor, was readily glycosylated with **1** and **2** accompanied by anomerization of the 1-ethylthio group to form the 1,2-*trans*-linked disaccharide thioglycosides **31** and **32** in 68% and 61% yields, respectively. The preferential activation of trichloroacetimidate donor over thioglycoside donor was in full



Scheme 1.

accordance with the observations in Lewis[21a,b] or solid[21c] acids-promoted chemoselective activation procedures.

3. Conclusion

In summary, a heterogeneous solid acid Amberlyst 15-activated efficient glycosylation employing commonly used disarmed glycosyl trichloroacetimidate donors has been developed to generate structurally diverse O- or S-linked oligosaccharides, and glycosylated amino acids.[22] Compared with the existing techniques, this activation method is intentionally optimized to fulfill the requirements for a more practical glycosylation process, such as the mild activation conditions (typically room temperature), the utility of an inexpensive promoter, and comparable reaction yields.

4. Experimental

4.1. General

Amberlyst 15 (dry) ion-exchange resin and 4 Å molecular sieves were purchased from Acros Chemical. Solvents used in the reactions were distilled from appropriate drying agents prior to use. All reactions were performed under a nitrogen atmosphere and monitored by thin-layer chromatography (TLC) using silica gel GF_{254} plates with detection by charring with 10% (v/v) H_2SO_4 in EtOH or by UV detection. Silica gel (100–200 mesh) was used for column chromatography. Optical rotations were measured with a PE-314 automatic polarimeter at 20±1 °C for solutions in a 1.0 dm cell. HR ESI-MS spectra were acquired on BioTOF Q. ^{1}H and ^{13}C NMR spectra were recorded on Varian INOVA-400/54 spectrometer with tetramethylsilane (TMS) as internal reference. Chemical shifts (δ) are expressed in parts per million downfield from the internal TMS absorption.

4.2. General procedure for the Amberlyst 15-activated glycosylation with disarmed glycosyl trichloroacetimidates

To a stirred ca. 0.1 M solution of donor (1.25–1.8 equiv) and acceptor (1 equiv) in anhydrous diethyl ether was added freshly activated 4 Å molecular sieves (100 wt % with respect to the donor). The reaction mixture was stirred for 15 min at room temperature, and Amberlyst 15 (20 wt % with respect to the donor) was added. The mixture was allowed to stir for the desired time (indicated in Table 1) at room temperature until the reaction was complete as monitored by TLC analysis. The reaction mixture was filtered and concentrated under reduced pressure. The crude product was subjected to column chromatography on silica gel eluted with petroleum ether/EtOAc to afford the corresponding O, S-glycosides and glycoamino acid derivatives. Products **13**–**16**, **20**–**25**, and **27** are known compounds and their spectroscopic data matched the reported data. Spectral data of new compounds are listed below.

4.2.1. Allyl 2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (17). Colorless syrup; R_f 0.20 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ +7.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz):

δ 1.95, 1.99, 2.01, 2.04 (4×s, each 3H), 3.45 (t, J=9.6 Hz, 1H), 3.52 (dd, J=3.6, 9.6 Hz, 1H), 3.62–3.66 (m, 1H), 3.69 (dd, J=4.4, 10.4 Hz, 1H), 3.81 (dd, J=2.8, 10.0 Hz, 1H), 3.98 (dd, J=6.4, 12.4 Hz, 1H), 4.00 (t, J=9.2 Hz, 1H), 4.04 (dd, J=1.2, 10.4 Hz, 1H), 4.10–4.16 (m, 2H), 4.23 (dd, J=4.8, 12.4 Hz, 1H), 4.50 (d, J=7.6 Hz, 1H), 4.52 (d, J=10.8 Hz, 1H), 4.64 (d, J=12.0 Hz, 1H), 4.75 (d, J=12.8 Hz, 1H), 4.78 (d, J=3.2 Hz, 1H), 4.80 (d, J=11.2 Hz, 1H), 4.86 (d, J=10.8 Hz, 1H), 5.00 (d, J=10.8 Hz, 1H), 5.05 (dd, J=8.0, 9.6 Hz, 1H), 5.08 (t, J=10.0 Hz, 1H), 5.17 (t, J=9.6 Hz, 1H), 5.21 (d, J=10.4 Hz, 1H), 5.32 (dd, J=1.2, 17.2 Hz, 1H), 5.86–5.96 (m, 1H), 7.25–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.7, 170.2, 169.3, 168.9, 138.8, 138.5, 138.1, 133.6, 128.4, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 118.2, 100.6, 95.4, 81.9, 79.8, 77.6, 75.6, 74.9, 73.1, 73.0, 71.8, 71.3, 69.8, 68.4, 68.1, 68.0, 61.9, 20.6, 20.6, 20.5, 20.5; HR ESI-MS: m/z calcd for $C_{44}H_{52}O_{15}$ $[M+Na]^+$: 843.3204; found: 843.3195.

4.2.2. Allyl 2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranoside (18). Colorless syrup; R_f 0.24 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ +1.0 (c 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.96, 1.96, 2.01, 2.11 (4×s, each 3H), 3.44 (t, J=9.6 Hz, 1H), 3.53 (dd, J=3.6, 9.6 Hz, 1H), 3.68 (dd, J=4.8, 10.8 Hz, 1H), 3.81–3.87 (m, 2H), 3.97 (dd, J=5.6, 13.2 Hz, 1H), 4.01 (t, J=9.2 Hz, 1H), 4.07–4.17 (m, 4H), 4.46 (d, J=8.0 Hz, 1H), 4.53 (d, J=10.8 Hz, 1H), 4.63 (d, J=12.0 Hz, 1H), 4.75 (d, J=12.0 Hz, 1H), 4.79 (d, J=3.2 Hz, 1H), 4.81 (d, J=10.8 Hz, 1H), 4.86 (d, J=11.2 Hz, 1H), 4.98 (dd, J=3.6, 10.4 Hz, 1H), 5.00 (d, J=10.8 Hz, 1H), 5.20 (d, J=10.4 Hz, 1H), 5.27 (d, J=18.4 Hz, 1H), 5.30 (dd, J=1.6, 17.2 Hz, 1H), 5.36 (d, J=4.0 Hz, 1H), 5.87–5.97 (m, 1H), 7.25–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 170.1, 170.0, 169.0, 138.7, 138.1, 138.0, 133.6, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.4, 118.1, 101.2, 95.3, 81.8, 79.8, 77.6, 75.5, 74.7, 73.0, 71.0, 70.6, 69.8, 68.7, 68.2, 67.9, 66.9, 61.0, 20.6, 20.5, 20.5, 20.4; HR ESI-MS: m/z calcd for $C_{44}H_{52}O_{15}$ $[M+Na]^+$: 843.3204; found: 843.3173.

4.2.3. Allyl 2,3,6-tri-*O*-benzyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucopyranoside (19). Colorless syrup; R_f 0.23 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ +6.3 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.93, 1.94, 1.97, 1.99 (4×s, each 3H), 3.25–3.29 (m, 1H), 3.49 (dd, J=4.0, 8.8 Hz, 1H), 3.58 (dd, J=1.6, 10.4 Hz, 1H), 3.68 (d, J=7.2 Hz, 1H), 3.77 (dd, J=3.2, 11.2 Hz, 1H), 3.84–3.89 (m, 3H), 4.00 (dd, J=6.8, 12.8 Hz, 1H), 4.10 (dd, J=6.4, 17.6 Hz, 1H), 4.09–4.17 (m, 1H), 4.40 (d, J=12.4 Hz, 1H), 4.50 (d, J=7.6 Hz, 1H), 4.58 (d, J=12.4 Hz, 1H), 4.72 (d, J=12.0 Hz, 1H), 4.75 (d, J=5.2 Hz, 1H), 4.77 (d, J=3.6 Hz, 1H), 4.78 (d, J=4.4 Hz, 1H), 4.89 (t, J=9.2 Hz, 1H), 4.95 (t, J=9.2 Hz, 1H), 4.98 (d, J=11.2 Hz, 1H), 5.02 (t, J=9.6 Hz, 1H), 5.22 (d, J=10.4 Hz, 1H), 5.32 (dd, J=1.6, 17.6 Hz, 1H), 5.88–5.93 (m, 1H), 7.08–7.40 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 170.0, 169.1, 168.8, 139.3, 138.2, 137.6, 133.6, 128.5, 128.2, 128.0, 127.9, 127.6, 127.2, 127.0, 117.9, 100.0, 95.8, 79.8, 79.0, 77.2, 75.0, 73.6, 73.2, 73.2, 71.9, 71.4, 69.9, 68.3, 68.1, 67.6, 61.5, 20.5, 20.5, 20.4, 20.4; HR ESI-MS: m/z calcd for $C_{44}H_{52}O_{15}$ $[M+Na]^+$: 843.3204; found: 843.3200.

4.2.4. Methyl *N*-[(*tert*-butoxy)carbonyl]-L-serine 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (26). Colorless syrup; R_f 0.13 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ +7.7 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.45 (s, 9H), 1.97, 2.04, 2.10, 2.14 (4×s, each 3H), 3.75 (s, 3H), 3.84 (dd, J=3.2, 10.4 Hz, 1H), 3.88 (t, J=6.4 Hz, 1H), 4.08–4.15 (m, 2H), 4.25 (dd, J=2.4, 10.0 Hz, 1H), 4.39–4.41 (m, 1H), 4.47 (d, J=8.0 Hz, 1H), 5.00 (dd, J=3.2, 10.4 Hz, 1H), 5.16 (dd, J=8.0, 10.4 Hz, 1H), 5.30 (d, J=7.2 Hz, 1H), 5.37 (d, J=2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 170.0, 169.8, 169.5, 101.7, 70.8, 70.7, 69.6, 68.5, 66.8, 61.0, 53.8, 52.5, 50.2, 28.2, 20.6, 20.6, 20.5, 20.5; HR ESI-MS: m/z calcd for $C_{23}H_{35}NO_{14}$ $[M+Na]^+$: 572.1955; found: 572.1971.

4.2.5. 1,2:3,4-Di-*O*-isopropylidene-6-thio-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (28). Colorless syrup; R_f 0.22 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ −39.2 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33, 1.34, 1.45, 1.53 (4×s, each 3H), 2.00, 2.02, 2.05, 2.08 (4×s, each 3H), 2.80 (dd, J=6.0, 14.0 Hz, 1H), 2.98 (dd, J=7.2, 14.0 Hz, 1H), 3.67–3.72 (m, 1H), 3.90 (t, J=7.6 Hz, 1H), 4.07–4.14 (m, 2H), 4.24 (dd, J=5.2, 12.4 Hz, 1H), 4.29–4.31 (m, 1H), 4.61 (dd, J=2.4, 8.0 Hz, 1H), 4.70 (d, J=10.0 Hz, 1H), 5.00 (t, J=9.2 Hz, 1H), 5.07 (t, J=9.6 Hz, 1H), 5.22 (t, J=9.2 Hz, 1H), 5.51 (d, J=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 170.1, 169.3, 169.3, 109.3, 108.6, 96.4, 83.8, 75.8, 73.9, 71.7, 70.8, 70.3, 70.1, 68.9, 68.4, 62.1, 26.0, 25.9, 24.8, 24.5, 20.6, 20.6, 20.5, 20.5; HR ESI-MS: m/z calcd for $C_{26}H_{38}O_{14}S$ $[M+Na]^+$: 629.1880; found: 629.1867.

4.2.6. 1,2:3,4-Di-*O*-isopropylidene-6-thio-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranoside (29). Colorless syrup; R_f 0.22 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ −38.4 (c 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.33, 1.34, 1.45, 1.53 (4×s, each 3H), 1.98, 2.04, 2.06, 2.15 (4×s, each 3H), 2.80 (dd, J=6.0, 13.6 Hz, 1H), 2.98 (dd, J=7.2, 14.0 Hz, 1H), 3.90–3.94 (m, 2H), 4.11–4.14 (m, 2H), 4.28–4.31 (m, 2H), 4.61 (dd, J=2.4, 8.0 Hz, 1H), 4.70 (d, J=10.0 Hz, 1H), 5.05 (dd, J=3.2, 10.0 Hz, 1H), 5.21 (t, J=10.0 Hz, 1H), 5.42 (d, J=2.4 Hz, 1H), 5.51 (d, J=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.1, 170.0, 169.9, 169.4, 109.3, 108.6, 96.4, 84.2, 74.3, 71.8, 71.7, 70.8, 70.3, 69.0, 67.4, 67.2, 61.4, 26.0, 25.9, 24.8, 24.4, 20.6, 20.6, 20.5, 20.5; HR ESI-MS: m/z calcd for $C_{26}H_{38}O_{14}S$ $[M+Na]^+$: 629.1880; found: 629.1873.

4.2.7. Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-α-D-glucopyranoside (31). Colorless syrup; R_f 0.24 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ +54.0 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (t, J=7.6 Hz, 3H), 1.95, 1.99, 2.01, 2.04 (4×s, each 3H), 2.49–2.57 (m, 2H), 3.45 (t, J=8.8 Hz, 1H), 3.60–3.65 (m, 1H), 3.72 (dd, J=4.4, 10.8 Hz, 1H), 3.78 (dd, J=5.2, 9.2 Hz, 1H), 3.83 (dd, J=9.6, 18.0 Hz, 1H), 4.05 (dd, J=1.6, 10.8 Hz, 1H), 4.11 (dd, J=2.4, 12.0 Hz, 1H), 4.18–4.25 (m, 2H), 4.44 (d, J=8.0 Hz, 1H), 4.52 (d, J=11.2 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 4.73 (t, J=11.6 Hz, 2H), 4.85 (d, J=11.2 Hz, 1H), 4.95 (d, J=10.8 Hz, 1H), 5.04 (dd, J=8.0, 9.6 Hz, 1H), 5.08 (t, J=9.6 Hz, 1H), 5.16 (t, J=9.2 Hz, 1H), 5.36 (d, J=5.2 Hz, 1H), 7.24–7.38 (m,

15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 170.2, 169.2, 168.9, 138.6, 138.2, 137.7, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 100.6, 82.7, 82.3, 79.4, 77.3, 75.5, 74.7, 72.3, 71.7, 71.2, 71.0, 69.9, 68.3, 68.2, 61.9, 23.6, 20.6, 20.6, 20.5, 20.5, 14.6; HR ESI-MS: *m/z* calcd for $C_{43}H_{52}O_{14}S$ $[M+Na]^+$: 847.2975; found: 847.2966.

4.2.8. Ethyl 2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-thio-α-D-glucopyranoside (32). Colorless syrup; R_f 0.24 (petroleum ether/EtOAc, 3:1); $[\alpha]_D^{21}$ +36.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, *J*=7.2 Hz, 3H), 1.98, 1.98, 2.02, 2.12 (4×s, each 3H), 2.48–2.59 (m, 2H), 3.45 (t, *J*=8.8 Hz, 1H), 3.72 (dd, *J*=4.4, 10.8 Hz, 1H), 3.80 (dd, *J*=5.6, 9.6 Hz, 1H), 3.84–3.89 (m, 2H), 4.07–4.18 (m, 3H), 4.23 (dd, *J*=2.8, 10.0 Hz, 1H), 4.44 (d, *J*=8.0 Hz, 1H), 4.55 (d, *J*=11.2 Hz, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 4.74 (t, *J*=11.6 Hz, 2H), 4.87 (d, *J*=10.8 Hz, 1H), 4.96 (d, *J*=10.8 Hz, 1H), 5.00 (dd, *J*=3.6, 10.4 Hz, 1H), 5.27 (dd, *J*=8.0, 10.4 Hz, 1H), 5.36 (d, *J*=4.8 Hz, 1H), 5.39 (d, *J*=5.2 Hz, 1H), 7.24–7.38 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.3, 170.1, 170.0, 169.0, 138.6, 138.2, 137.8, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 101.2, 82.7, 82.3, 79.5, 77.4, 75.5, 74.7, 72.3, 71.1, 70.6, 69.9, 68.7, 68.3, 66.9, 61.1, 23.5, 20.7, 20.5, 20.5, 20.4, 14.6; HR ESI-MS: *m/z* calcd for $C_{43}H_{52}O_{14}S$ $[M+Na]^+$: 847.2975; found: 847.2970.

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