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Article

Utilizing Reusable Catalyst Phosphotungstic Acid for the Synthesis of Thioglycoside from Per-*O*-acetyl Saccharides with Microwave-Assisted and De-*O*-acetylation with Methanol

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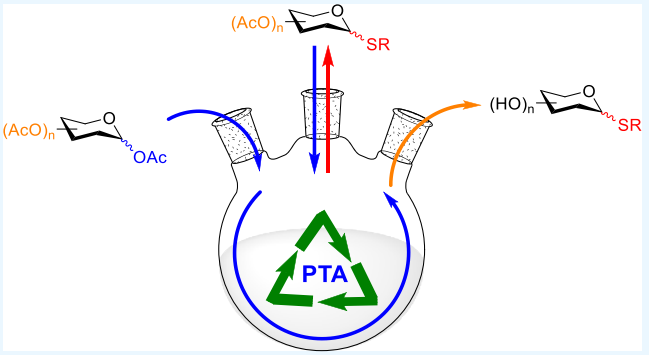
ABSTRACT: Traditional methods for synthesizing complex oligosaccharides currently developed are not efficient, requiring a new glycosylation methodology. Herein, using phosphotungstic acid (PTA) as a catalyst has demonstrated to be a simple possibility for carbohydrate synthesis. The methodology is engineered into a PTA-catalyzed thioglycoside preparation under microwave conditions and de-*O*-acetylation of carbohydrates. These easier operations and convenient protocols display a wide substrate scope. Moreover, both methods can be developed into a one-pot reaction for the efficient synthesis of carbohydrate analogues.

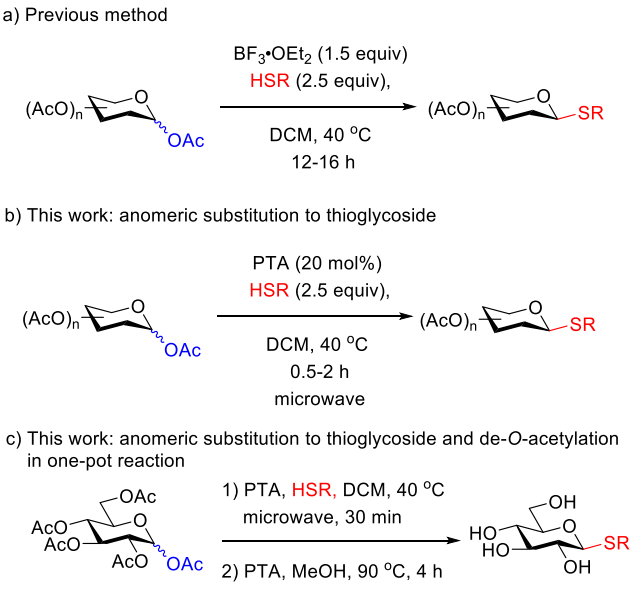


INTRODUCTION

The molecular diversity of oligosaccharides has attracted considerable attention in the field of glycobiology due to the essential roles it plays in important biological activities such as viral and bacterial infections, cell proliferation, and immune response.[1] However, only a few methods for the synthesis of complex oligosaccharides have been developed, most of which are time consuming and require multiple protection/deprotection steps.[2] Therefore, a new methodology with an efficient catalyst is still required.[3]

An effective glycosylation method depends on a simple glycosyl donor, which is activated by a catalytic amount of reagent.[4] Over the years, a variety of methods such as trichloroacetimidates, halides, as well as thioglycosides have been introduced to form the glycosyl donor, each method having its advantages and disadvantages.[5] Among them, thioglycosides are stable and versatile glycosyl donors in the synthesis of oligosaccharides[6] because the sulfide groups are easy to install and can be transformed into other types of glycosyl donors through oxidation, for instance, glycosyl sulfoxides[7] and sulfones.[8] Additionally, thioglycosides are also applied in the development of glycosyltransferase inhibitors, ligands for lectins, and carbohydrate-based vaccines when they are mimetic of *O*-glycoside.[9] Methods of synthetic thioglycoside are often reported with the use of per-*O*-acetylation of carbohydrates and a sulfhydryl in the presence of an acid catalyst (Scheme 1a).[10] However, the disadvantage of previously reported acidic catalysts was either highly corrosive or unstable. Hence, a replacement catalyst and high efficiency

Scheme 1. Synthesis of Thioglycoside



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are sought to carry out this reaction. Therefore, we report a novel catalyst for the synthesis of thioglycosides of these important glycosyl donors, from readily available per-*O*-acetyl saccharides through microwave-assisted substitution (Scheme 1b).

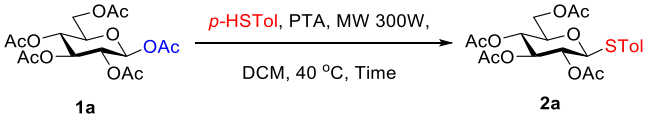
Although one-pot per-*O*-acetylated and anomeric substitution of thioglycoside have been employed widely in the synthesis of oligosaccharides,[11] anomeric substitutions and deacetylation one-pot reaction studies were less published in carbohydrate chemistry. The Zemplén procedure, using sodium methoxide or other basic reagents in methanol, is a well-known method for removing the acetyl groups.[12] Although the basic conditions allow the cleavage of ester bonds and base-labile groups,[13] acidic catalysts are unfavorable in carbohydrate chemistry due to the unstable glycosidic bonds in acidic circumstances.[14] Nevertheless, in the present work, we show that phosphotungstic acid (PTA) as a catalyst in de-*O*-acetylation may find wider application in saccharides. Apart from this, this research combines anomeric substitution to thioglycosides and de-*O*-acetylation in a one-pot reaction (Scheme 1c).

Recently, we have reported a multipurpose and recyclable catalyst, PTA, for the protection of saccharides and glycosylation.[15] PTA is the strongest heteropoly acid[16] and exhibits an eco-friendly characteristic along with good chemical and thermal stability,[17] non-toxicity, and efficient reuse/recyclability.[18] Despite the inadequate applications of PTA in carbohydrate chemistry, in this study, we have extended its use as a novel catalyst for anomeric substitution to thioglycoside, de-*O*-acetylation, and connecting two reactions in a one-pot reaction.

RESULTS AND DISCUSSION

In the beginning, we employed per-*O*-acetyl glucose **1a** and *p*-thiocresol for condition optimization, as shown in Table 1.

Table 1. Optimized Conditions for the Thioglycoside



1a **2a**

entry	acid (equiv)	HSTol (equiv)	time (h)	P. (yield)
1[a]	$BF_3{\cdot}OEt_2$ (1.5)	1.5	12	**2a** (85%)[b]
2[a]	PTA (0.2)	2.5	12	trace[b]
3	PTA (0.2)	2.5	12	trace[b]
4	PTA (0.2)	2.5	0.5	**2a** (80%)
5	PTA (0.15)	2.5	0.5	**2a** (44%)
6	PTA (0.25)	2.5	0.5	**2a** (54%)
7[c]	PTA (0.2)	2.5	0.5	**2a** (32%)
8[d]	PTA (0.2)	2.5	0.5	**2a** (77%)
9	PTA (0.2)	2.5	0.25	**2a** (49%)
10	PTA (0.2)	2.5	0.75	**2a** (60%)
11	PTA (0.2)	2.5	1	**2a** (69%)
12	PTA (0.2)	1.5	0.5	**2a** (53%)
13	PTA (0.2)	2.0	0.5	**2a** (79%)
14	PTA (0.2)	3.0	0.5	**2a** (69%)
15[e]	PTA (0.2)	2.5	0.5	**2a** (77%)

[a]The reaction was processed at room temperature. [b]The reaction was not under microwave. [c]The reaction was processed at 50 °C. [d]The reaction was under a microwave power of 400 W. [e]The reaction scale was 2.0 g.

Initially, the reaction used $BF_3{\cdot}Et_2O$ (1.5 equiv) and HSTol (1.5 equiv) at room temperature, which obtains the desired product **2a** in 85% yield (Table 1, entry 1). Next, we altered the catalyst to 20 mol % PTA and 2.5 equiv of *p*-thiocresol under the same conditions. Unfortunately, the reaction yielded a trace product when verified by thin-layer chromatography (TLC) plates (Table 1, entry 2). We also increased the reaction temperature to 40 °C, but the result was still not as expected (Table 1, entry 3). After utilizing the microwave as an energy source for the reaction, under the same equivalency of PTA, the reaction yield increased up to 80% (Table 1, entry 4). However, the yield of product **2a** decreased while the amount of PTA was changed (44 and 54%, Table 1, entries 5−6). Even though the reaction time was greatly reduced, after examination of multiple temperatures and power of the microwave, there was no significant change in the product yield (Table 1, entries 7−11). To sum up, entry 4 corresponded to a higher yield than the other entries; 20 mol % was chosen as the optimal PTA amount. Under the standard conditions, when the amount of HSTol was altered, the reaction had no significant changes; thus, it was kept at 2.5 as optimal equivalency (Table 1, entries 12−14). The gram-scale reaction of **1a** was carried out and amination product **2a** was obtained in 77% yield under standard conditions (Table 1, entry 15).

After screening the reaction conditions, the versatility of PTA-catalyzed anomeric substitution to synthesize thioglycoside derivatives was explored (Table 2). A variety of saccharides, including D-galactose, D-xylose, D-lyxose, and L-fucose, were well tolerated, giving **2b−2e** in good yields with 20 mol % of PTA as the catalyst. Since galactose yielded the best result, the reaction scope with different thiol and per-*O*-acetyl galactose **1b** was examined under the optimal condition. Among them, the substrates thiocresol with different substituted positions (**2f**, **2g**), short-chain thiols (**2h−2j**), as well as long-chain thiols (**2k**, **2l**) were all compatible in this protocol.

After completion of reactions, the recyclability of PTA in the synthesis of thioglycoside was examined (Table 3). The recycling procedure includes the washing of the catalyst by EtOAc to remove organic contaminants very thoroughly and acidification by ion exchange resin, in hydrogen form. The recycling PTA can be used for subsequent reactions.[15b] Utilizing the same method from Table 2, the reactions conducted gave optimal results in 84 to 88% yield for **2b** with the PTA recovery of over 80%. To our knowledge, it is the first time that catalytic formation of thioglycoside has been performed repeatedly with PTA.

According to our previous research,[15a] the cleavage of acetyl bonds when PTA is catalyzed under acetylation contains trace water. On the basis of the above-observed, we suppose that PTA could be the catalyst for de-acetylation.

To examine the possibility of de-acetylation, we used simple alcohol **1m** as our starting material in de-acetylation with PTA (Table 4). In the presence of PTA (10 mol %), the reaction conducted with **1m** in methanol at 60 °C for 4 h in a sealed tube could afford the desired product **3m** in good yield (85%, Table 4, entry 1). In an attempt to increase the yield of **3m**, the temperature of the reaction was changed, allowing an increase in the yield to 97% at 50 °C (Table 4, entries 2−3). When the amount of PTA was lowered to 5 mol %, the yield was the same as 10 mol % PTA (97%, Table 4, entry 4). However, continuously decreasing to 2.5 mol % resulted in the reduction

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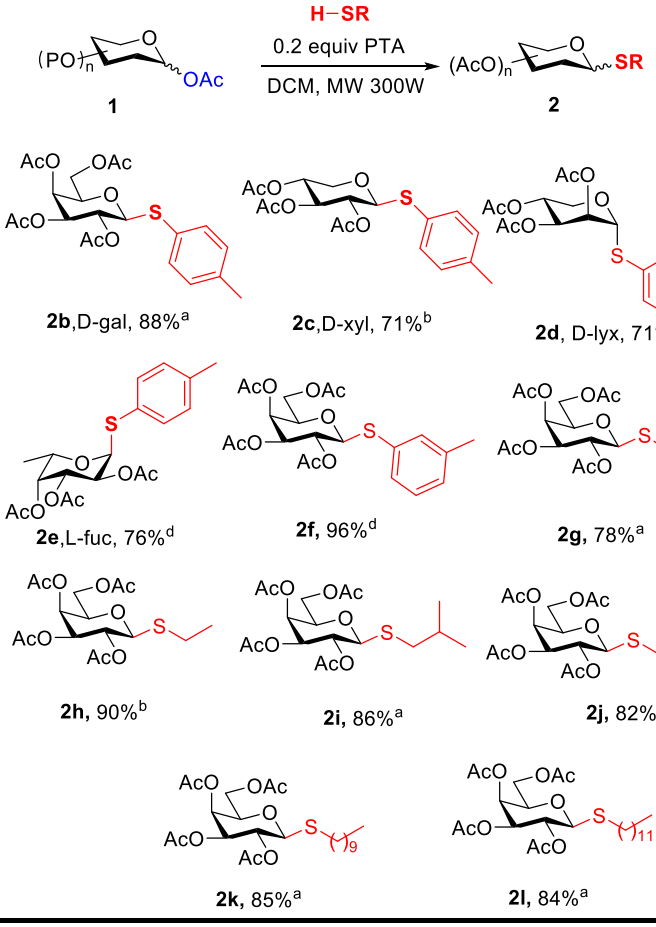
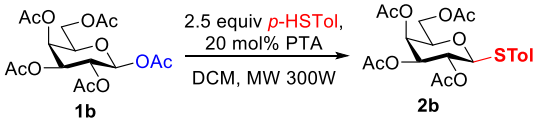
Table 2. Substrate Scope for the Synthesis of Thioglycoside



[a]Reaction time was 0.5 h. [b]Reaction time was 1.5 h. [c]Reaction time was 2 h. [d]Reaction time was 1 h.

Table 3. Reusing PTA for Substitution to Synthesize Thioglycoside



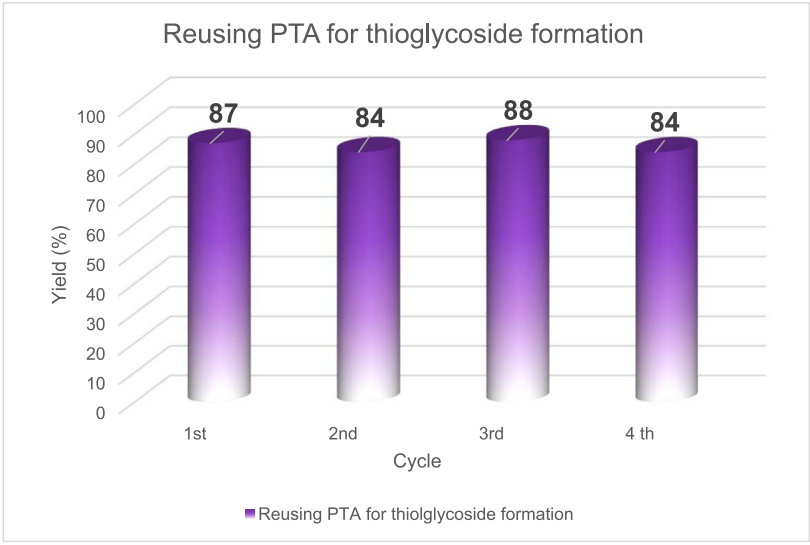


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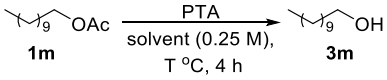
Table 4. Optimization of the Reaction Conditions for the De-acetylation in a Sealed Tube

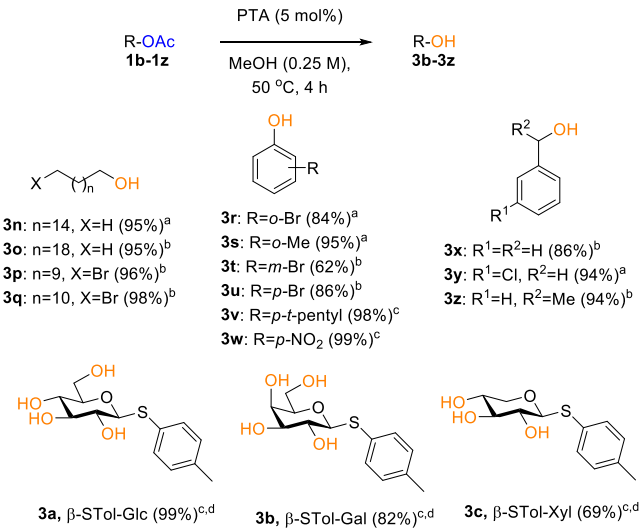


entry	PTA (equiv)	solvent	T (°C)	yield (%)
1	10 mol %	MeOH	60	85
2	10 mol %	MeOH	50	97
3	10 mol %	MeOH	25	67
4	5 mol %	MeOH	50	97
5	2.5 mol %	MeOH	50	85
6	5 mol %	EtOH	50	0
7	5 mol %	EtOH	80	90

of reactivity (85%, Table 4, entry 5). Additionally, changing the solvent to ethanol decreased immensely the reactivity of reaction under the previously optimized condition (0%, Table 4, entry 6). When the temperature requirement increased to 80 °C, a product yield of 90% was obtained (Table 4, entry 7). These results indicated that the temperature of the reaction was dependent on the difference in the reactivity of the solvent.

With the optimized conditions in hand, we inspected the scope of the substrate (Table 5). Various acetyl-protected-

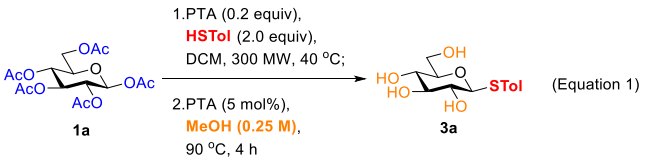
Table 5. PTA Catalyzed De-*O*-acetylation with Various Acetoxy Group Compounds in Sealed Tube



[a]Reaction time was 16 h. [b]Reaction time was 8 h. [c]Reaction time was 4 h. [d]Reaction temperature was 90 °C.

group substrates on long-chain **1n−1q**, aryl **1r−1w**, and benzylic **1x−1z** were smoothly converted into uncomplicated alcohol **3n−3z** in uniformly high to excellent yields. In addition, the method applied to carbohydrates in the reaction was efficient for the cleavage of acetyl groups **3a−3c**.

Through the one-pot reaction, the reaction time efficiency increased in saccharides synthesis; we then turned our attention to the evaluation that connected the two methods (eq 1). Notably, the reaction yield by the one-pot reaction was similar to the result achieved by two-step reactions, which was demonstrated by observing a good strategy in synthesis. Utilizing per-*O*-acetyl glucose **1a** as the starting material, the process proceeded smoothly and afforded the desired product **3a**.



CONCLUSIONS

In conclusion, we have developed a new protocol for the thioglycoside formation of per-*O*-acetyl saccharides and deprotection of acetoxy compounds using PTA as a catalyst, resulting in greater yields and broader substrate scope. These features make it evident that PTA is a convenient catalyst with potential use in carbohydrate synthesis. Furthermore, the key component of the process is the uncovering of PTA as a catalyst, capable of a distinct methodology connecting in the one-pot processes from different reactions. Further studies along this direction are currently underway in our laboratories and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All reactions were conducted in flame-dried glassware, under nitrogen atmosphere, unless mentioned. Dichloromethane, tetrahydrofuran, toluene, and acetonitrile were purified and dried from a safe purification system containing activated Al_2O_3. All reagents obtained from commercial sources were used without purification. Column chromatography was carried out on silica gel 60 (23−60 mesh, E. Merck). TLC was performed on pre-coated glass plates of Silica Gel 60 F254 (0.25 mm, E. Merck); detection was executed by spraying with a solution of $Ce(NH_4)_2(NO_3)_6$ (0.5 g), $(NH_4)_6Mo_7O_{24}$ (24.0 g), and H_2SO_4 (28.0 mL) in water (500 mL) and subsequent heating on a hot plate. Melting points were determined on Mel Temp II (Laboratory Devices) with a capillary apparatus and were uncorrected. Optical rotations were measured on Rudolph Autopol V using a 100 mm cell at 589 nm (Na). ^{1}H and ^{13}C NMR were measured by using Varian Mercury-400 MHz, JEOL JNM-ECZR NMR 400 Hz spectrometers. Chemical shift was reported as δ values in ppm and calibrated by using a residual undeuterated solvent [$CDCl_3$ (7.26 ppm)] as the internal reference for ^{1}H NMR and the deuterated solvent [$CDCl_3$ (77.0 ppm)] as the internal standard for ^{13}C NMR. Coupling constants were reported in Hz, and multiplicities were indicated as follows: s (singlet), d (doublet), t (triplet), and m (mltiplet). Infrared (IR) spectra were taken with a Fourier-transform infrared spectrometer using NaCl plates and attenuated total reflectance method. Mass spectra were analyzed on a Finnigan LTQ-OrbitrapxL instrument with an ESI source.

*General Procedure for the Synthesis of Thioglycoside (**2**).* To a solution of saccharides **1** (300 mg for **1a**; 200 mg for **1b−c**, **1e**, and **1f−l**; 100 mg for **1d**) in dichloromethane (5−10 mL), thiol (2.5 equiv) and phosphotungstic acid (20 mol %) were added at room temperature. Then, the reaction mixture was stirred in microwave 300 W at 40 °C for 30−120 min. After completion of the reaction, it was neutralized by the treatment of triethylamine, and the mixture was extracted with dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. It was purified by column chromatography on silica gel to obtain the desired products **2a−2l**.

*p-Methylphenyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-gluco-pyranoside (**2a**).* Prepared according to the general procedure

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discussed above: as a white solid (296 mg, 85%); R_f: 0.53 (EtOAc/Hex = 1/1); IR (NaCl) ν: 3460, 3023, 2953, 1754, 1560, 1494, 1372, 1226, 1040, 981; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 7.3 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 5.21 (t, J = 9.5 Hz, 1H), 5.02 (t, J = 9.8 Hz, 1H), 4.93 (t, J = 9.7 Hz, 1H), 4.63 (d, J = 10.2 Hz, 1H), 4.20 (d, J = 5.5 Hz, 2H), 3.70 (d, J = 10.2 Hz, 1H), 2.35 (s, 3H), 2.09 (s, 6H), 2.01 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.2, 169.4, 169.2, 138.8, 133.8, 129.7, 127.5, 85.7, 75.7, 74.0, 69.8, 68.1, 62.1, 21.2, 20.8, 20.6; HRMS: (ESI, M + Na^+) calcd for $C_{21}H_{26}NaO_9S$, 477.11952; found, 477.11997.

*p-Methylphenyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2b**).* Prepared according to the general procedure discussed above: as a white solid (320 mg, 92%); R_f: 0.67 (EtOAc/Hex = 1/1); IR (NaCl) ν: 3302, 2970, 2940, 2870, 1751, 1494, 1434, 1370, 1223, 1083, 1055, 900; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 5.40 (t, J = 9.4 Hz, 1H), 5.21 (t, J = 10.0 Hz, 1H), 5.03 (t, J = 9.7 Hz, 1H), 4.64 (d, J = 10.0 Hz, 1H), 4.14 (dd, J = 5.6, 3.8 Hz, 2H), 3.91 (ddd, J = 10.0, 4.8, 2.8 Hz, 1H), 2.34 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 170.2, 170.1, 169.4, 133.1, 129.6, 87.0, 74.3, 72.0, 67.23, 67.16, 61.6, 21.2, 20.9, 20.7, 20.6; HRMS: (ESI, M + Na^+) calcd for $C_{21}H_{26}NaO_9S$, 477.11952; found, 477.11942.

*p-Methylphenyl 2,3,4-Tri-O-acetyl-1-thio-β-D-xylopyranoside (**2c**).* Prepared according to the general procedure discussed above: as a colorless oil (213 mg, 71%); R_f: 0.56 (EtOAc/Hex = 1/1); IR (NaCl) ν: 2952, 2925, 1754, 1493, 1370, 1244, 1066, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.15 (t, J = 8.4 Hz, 1H), 4.89 (m, 2H), 4.69 (d, J = 8.4 Hz, 1H), 4.24 (dd, J = 11.8, 4.8 Hz, 1H), 3.37 (dd, J = 11.8, 8.8 Hz, 1H), 2.33 (s, 3H), 2.08 (s, 3H), 2.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 169.8, 169.3, 138.6, 133.4, 129.4, 128.0, 86.3, 72.2, 69.8, 68.4, 65.3, 21.2, 20.8, 20.7; HRMS: (ESI, M + Na^+) calcd for $C_{18}H_{22}NaO_7S$, 405.09839; found, 405.09836.

*p-Methylphenyl 2,3,4-Tri-O-acetyl-1-thio-α-D-lyxopyranoside (**2d**).* Prepared according to the general procedure discussed above: as a colorless oil (85 mg, 71%); R_f: 0.57 (EtOAc/Hex = 1/1); IR (NaCl) ν: 2925, 1750, 1494, 1372, 1224, 1068, 777; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.17 (t, J = 8.4 Hz, 1H), 4.91 (dd, J = 8.4, 3.2 Hz, 2H), 4.71 (d, J = 8.8 Hz, 1H), 4.25 (dd, J = 11.8, 5.2 Hz, 1H), 3.39 (dd, J = 11.8, 8.8 Hz, 1H), 2.34 (s, 3H), 2.10 (d, J = 6.0 Hz, 3H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 169.8, 169.3, 138.6, 133.5, 129.8, 128.0, 86.3, 72.2, 69.8, 68.4, 65.3, 21.2, 20.8, 20.7; HRMS: (ESI, M + Na^+) calcd for $C_{18}H_{22}NaO_7S$, 405.09840; found, 405.09870.

*p-Methylphenyl 2,3,4-Tri-O-acetyl-1-thio-β-L-fucopyranoside (**2e**).* Prepared according to the general procedure discussed above: as a colorless oil (177 mg, 76%). R_f: 0.57 (EtOAc/Hex = 1/3); IR (NaCl) ν: 2985, 2939, 1761, 1370, 1245, 1223, 1084, 1056, 810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 5.25−5.27 (m, 2H), 5.03 (dd, J = 10.0, 3.6 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 3.80 (d, J = 6.8 Hz, 1H), 2.34 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 1.97 (s, 3H), 1.23 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 170.2, 169.5, 138.2, 132.9, 129.7, 129.6, 129.0, 86.8, 73.1, 72.4, 70.3, 67.3, 21.1, 20.9, 20.7, 16.4; HRMS: (ESI, M + Na^+) calcd for $C_{19}H_{24}NaO_7S$, 419.11404; found, 419.11268.

*m-Methylphenyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2f**).* Prepared according to the general procedure discussed above: as a colorless oil (222 mg, 96%); R_f: 0.45 (EtOAc/Hex = 1/2); IR (NaCl) ν: 3480, 3054, 2968, 2869, 1752, 1650, 1370, 1152, 1083, 1055, 899, 781 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, J = 6.6 Hz, 2H), 7.20 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 5.42 (d, J = 7.6 Hz, 1H), 5.24 (t, J = 10.0 Hz, 1H), 5.06 (dd, J = 10.0, 3.1 Hz, 1H), 4.72 (d, J = 10.0 Hz, 1H), 4.24−4.10 (m, 2H), 3.94 (t, J = 6.6 Hz, 1H), 2.34 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.1, 170.0, 162.5, 138.7, 132.9, 132.3, 129.3, 128.9, 128.7, 86.9, 74.4, 72.0, 67.3, 61.6, 21.3, 20.8, 20.6. HRMS: (ESI, M + Na^+) calcd for $C_{21}H_{26}O_9S_1Na$, 477.1195; found, 477.1194.

*o-Methylphenyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2g**).* Prepared according to the general procedure discussed above: as a colorless oil (174 mg, 75%); R_f: 0.69 (EtOAc/Hex = 1/1); IR (NaCl) ν: 3480, 3059, 2966, 2860, 1751, 1370, 1223, 1084, 1055, 900, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.6 Hz, 1H), 7.25−7.18 (m, 2H), 7.18−7.13 (m, 1H), 5.42 (dd, J = 3.6, 0.8 Hz, 1H), 5.30 (t, J = 10.0 Hz, 1H), 5.04 (dd, J = 10.0, 3.6 Hz, 1H), 4.66 (d, J = 10.0 Hz, 1H), 4.20−4.08 (m, 2H), 3.91 (t, J = 10.0, 3.8 Hz, 1H), 2.40 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.2, 170.0, 169.4, 140.0, 132.7, 132.5, 130.3, 128.2, 126.5, 87.1, 74.4, 72.0, 67.4, 67.2, 61.6, 20.9, 20.8, 20.64, 20.60, 20.55. HRMS: (ESI, M + Na^+) calcd for $C_{21}H_{26}O_9S_1Na$, 477.1195; found, 477.1176.

*Ethyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2h**).* Prepared according to the general procedure discussed above: as a colorless oil (181 mg, 90%); R_f: 0.31 (EtOAc/Hex = 1/1); IR (NaCl) ν: 2970, 2873, 1749, 1433, 1370, 1223, 1153, 108, 1054, 900 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (d, J = 3.2 Hz, 1H), 5.24 (t, J = 10.0 Hz, 1H), 5.05 (dd, J = 10.0, 3.4 Hz, 1H), 4.49 (d, J = 10.0 Hz, 1H), 4.19−4.09 (m, 2H), 3.93 (t, J = 6.8 Hz, 1H), 2.79−2.68 (m, 2H), 2.16 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H), 1.29 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.2, 170.0, 169.5, 84.0, 74.4, 71.9, 67.3, 67.2, 61.5, 24.3, 20.8, 20.63, 20.55, 14.8; HRMS: (ESI, M + Na^+) calcd for $C_{16}H_{24}O_9S_1Na$, 415.1039; found, 415.1035.

*Isobutyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2i**).* Prepared according to the general procedure discussed above: as a colorless oil (235 mg, 86%); R_f: 0.53 (EtOAc/Hex = 1/2); IR (NaCl) ν: 3481, 2961, 2871, 1752, 1465, 1434, 1370, 1224, 1084, 1055, 900 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (d, J = 3.2 Hz, 1H), 5.23 (t, J = 10.0 Hz,, 1H), 5.04 (dd, J = 10.0, 3.4 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H), 4.22−4.06 (m, 2H), 3.92 (t, J = 6.8 Hz, 1H), 2.58 (dd, J = 13.6, 7.2 Hz, 2H), 2.16 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.87−1.79 (m, 1H), 1.00 (d, J = 3.3 Hz, 1H), 0.98 (d, J = 3.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 170.2, 170.1, 169.5, 84.5, 74.3, 71.9, 67.4, 67.2, 61.4, 39.2, 28.7, 22.0, 21.8, 20.8, 20.62, 20.56. HRMS: (ESI, M + Na^+) calcd for $C_{18}H_{28}O_9S_1Na$, 443.1352; found, 443.1358.

*2-Methylbutyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2j**).* Prepared according to the general procedure discussed above: as a colorless oil (149 mg, 82%); R_f: 0.53 (EtOAc/Hex = 1/2); IR (NaCl) ν: 3481, 2963, 2876, 1752, 1459, 1434, 1370, 1223, 1084, 1055, 900 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (d, J = 3.2 Hz, 1H), 5.23 (t, J = 10.0 Hz, 1H), 5.04 (dd, J = 10.0, 3.6 Hz, 1H), 4.46 (d, J = 10.0 Hz, 1H),

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4.21−4.09 (m, 2H), 3.92 (t, J = 6.8 Hz, 1H), 2.69 (dd, J = 12.4, 6.0 Hz, 1H), 2.56 (dd, J = 12.4, 7.0 Hz, 1H), 2.16 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.63 (d, J = 6.8 Hz, 1H), 1.51−1.43 (m, 1H), 1.23 (dd, J = 14.0, 7.0 Hz, 1H), 0.97 (d, J = 6.8 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 170.2, 170.1, 169.5, 84.6, 74.3, 71.9, 67.4, 67.3, 61.4, 37.2, 35.0, 28.4, 20.8, 20.63, 20.56, 18.9, 11.2. HRMS: (ESI, M + Na^+) calcd for $C_{19}H_{30}O_9S_1Na$, 457.1508; found, 457.1507.

*Decyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2k**).* Prepared according to the general procedure discussed above: as a colorless oil. (218 mg, 85%); R_f: 0.72 (EtOAc/Hex = 1/1); IR (NaCl) ν: 3482, 2926, 2855, 1753, 1459, 1436, 1370, 1223, 1084, 1055, 900 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (d, J = 3.2 Hz, 1H), 5.23 (t, J = 10.0 Hz, 1H), 5.04 (dd, J = 10.0, 3.2 Hz, 1H), 4.47 (d, J = 10.0 Hz, 1H), 4.18−4.08 (m, 2H), 3.92 (t, J = 6.8 Hz, 1H), 2.74−2.63 (m, 2H), 2.15 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H), 1.64−1.60 (m, 1H), 1.26 (s, 15H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.2, 170.0, 169.5, 84.2, 74.3, 71.9, 67.3, 61.4, 31.8, 30.2, 29.7, 29.5, 29.3, 29.1, 28.8, 22.6, 20.8, 20.6, 20.5, 14.1; HRMS: (ESI, M + Na^+) calcd for $C_{24}H_{40}O_9S_1Na$, 527.2291; found, 527.2268.

*Dodecyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**2l**).* Prepared according to the general procedure discussed above: as a colorless oil (193 mg, 84%); R_f: 0.56 (EtOAc/Hex = 1/2); IR (NaCl) ν: 3483, 2925, 2854, 1753, 1461, 1436, 1369, 1222, 1084, 1055, 900 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.43 (d, J = 3.4 Hz, 1H), 5.23 (t, J = 10.0 Hz, 1H), 5.05 (dd, J = 10.0, 3.4 Hz, 1H), 4.47 (d, J = 10.0 Hz, 1H), 4.19−4.10 (m, 2H), 3.93 (t, J = 6.8 Hz, 1H), 2.74−2.63 (m, 2H), 2.16 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.99 (s, 3H), 1.61 (s, 1H), 1.32 (s, 19H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.2, 170.1, 169.5, 84.2, 79.9, 74.3, 71.8, 67.2, 61.4, 31.8, 30.2, 29.6, 29.6, 29.5, 29.3, 29.1, 28.8, 22.6, 20.8, 20.6, 20.6, 14.1; HRMS: (ESI, M + Na^+) calcd for $C_{26}H_{44}O_9S_1Na$, 555.2604; found, 555.2604.

General Procedure for Deacetylation. To a solution of acetyl compound (**1**) (100 mg for **3m−3z**, **3b−c**; 200 mg for **3a**, 1.0 equiv) in methanol (0.25 M) was added PTA (0.05 equiv) at room temperature in a sealed tube. After the mixture was stirred at the reaction temperature (50 °C for **3m−3z**; 90 °C for **3a−3c**) for 4−16 h, the mixture was diluted with water and extracted with ethyl acetate (100 mL × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by chromatography to afford the desired product **3a−3c** and **3m−3z**.

*1-Undecanol (**3m**).* Prepared according to the general procedure discussed above: as a colorless liquid (84 mg, 97%); R_f: 0.30 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3728, 3627, 3344, 2925, 2825, 1464, 1378, 1056, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60 (t, J = 6.7 Hz, 2H), 1.57−1.49 (m, 2H), 1.35−1.20 (m, 16H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.1, 32.8, 31.9, 29.6, 29.4, 29.3, 25.7, 22.7, 14.1; HRMS: (ESI, M + Na^+) calcd for $C_{11}H_{24}Na_1O_1$, 195.17248; found, 195.17271.

*1-Hexadecanol (**3n**).* Prepared according to the general procedure discussed above: as a white solid (87 mg, 95%); R_f: 0.30 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3729, 3626, 3606, 3231, 2955, 2919, 2850, 1462, 1063, 1040, 729, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (t, J = 6.4 Hz, 2H), 1.57−1.51 (m, 2H), 1.31−1.25 (m, 26H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.1, 32.8, 31.9, 29.7, 29.4, 29.4, 25.7, 22.7, 14.1; HRMS: (ESI, M + Na^+) calcd for $C_{16}H_{34}Na_1O_1$, 265.25073; found, 265.25083.

*1-Icosanol (**3o**).* Prepared according to the general procedure discussed above: as a white solid (85.2 mg, 97%); R_f: 0.35 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3708, 2954, 2918, 2849, 1462, 1063, 729, 719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.66−3.62 (m, 2H), 1.31−1.25 (m, 34H), 0.88 (t, J = 14.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.1, 32.8, 31.9, 29.7, 29.6, 29.4, 29.4, 25.7, 22.7, 14.1; HRMS: (ESI, M + Na^+) calcd for $C_{16}H_{34}Na_1O_1$, 321.31333; found, 321.31444.

*11-Bromo-1-undecanol (**3p**).* Prepared according to the general procedure discussed above: as a white solid (82 mg, 96%); R_f: 0.19 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3424, 3380, 2966, 2921, 2851, 1466, 1346, 1002, 736, 724, 644; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (t, J = 6.6 Hz, 2H), 3.41 (t, J = 6.9 Hz, 2H), 1.92−1.75 (m, 2H), 1.55 (dd, J = 14.3, 6.8 Hz, 2H), 1.41 (dd, J = 14.6, 7.1 Hz, 2H), 1.35−1.23 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.1, 34.1, 32.8, 32.7, 29.5, 29.4, 29.4, 28.7, 28.1, 25.7; HRMS: (ESI, M + Na^+) calcd for $C_{11}H_{23}Br_1Na_1O_1$, 273.08230; found, 273.08229.

*12-Bromo-1-undecanol (**3q**).* Prepared according to the general procedure discussed above: as a white solid (89 mg, 98%); R_f: 0.20 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3746, 3674, 2927, 2855, 1741, 1463, 1366, 1240, 1039, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (t, J = 6.6 Hz, 2H), 3.41 (t, J = 6.9 Hz, 2H), 1.89−1.80 (m, 2H), 1.55 (dd, J = 14.1, 7.2 Hz, 2H), 1.44−1.37 (m, 2H), 1.36−1.27 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 63.2, 34.2, 32.9, 32.8, 29.7, 29.6, 29.5, 28.9, 28.3, 25.8; HRMS: (ESI, M + Na^+) calcd for $C_{12}H_{25}Br_1Na_1O_1$, 287.09865; found, 287.09867.

*2-Bromophenol (**3r**).* Prepared according to the general procedure discussed above: as a yellow liquid (65 mg, 80%); R_f: 0.33 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3705, 3601, 2924, 2852, 1476, 1195, 827, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, J = 8.1, 1.7 Hz, 1H), 7.29−7.17 (m, 1H), 7.02 (dd, J = 8.2, 1.7 Hz, 1H), 6.81 (ddd, J = 8.1, 7.4, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2, 132.0, 129.2, 121.8, 116.1, 110.2; HRMS: (ESI, M + Na^+) calcd for $C_6H_4Br_1O_1$, 170.9455; found, 170.9448.

*2-Methylphenol (**3s**).* Prepared according to the general procedure discussed above: as a brown liquid (71 mg, 95%); R_f: 0.30 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3728, 1706, 3032, 2351, 1552, 1041, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−7.07 (m, 2H), 6.87 (t, J = 7.4 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 131.0, 127.1, 123.7, 120.7, 114.8, 15.7; HRMS: (ESI, M + Na^+) calcd for $C_7H_7O_1$, 107.04969; found, 107.05000.

*3-Bromophenol (**3t**).* Prepared according to the general procedure discussed above: as a yellow liquid (49 mg, 62%); R_f: 0.30 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3366, 2929, 2680, 1924, 1584, 1473, 1245, 996, 862, 770, 678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−6.98 (m, 3H), 6.77 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4, 130.7, 123.8, 122.7, 118.8, 114.2; HRMS: (ESI, M + Na^+) calcd for $C_6H_4Br_1O_1$, 170.94450; found, 170.94500.

*4-Bromophenol (**3u**).* Prepared according to the general procedure discussed above: as a white solid (69 mg, 86%); R_f: 0.25 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3631, 3357, 3067, 2795, 2066, 1873, 1587, 1489, 1431, 1354, 1169, 822, 607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (d, J = 8.9 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$):

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δ 154.6, 132.4, 117.1, 112.8; HRMS: (ESI, M + Na^+) calcd for $C_6H_4Br_1O_1$, 170.94455; found, 170.94442.

*4-tert-Amylphenol (**3v**).* Prepared according to the general procedure discussed above: as a white solid (85 mg, 98%); R_f: 0.30 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3745, 3252, 2965, 2924, 2876, 1919, 1598, 1513, 1450, 1375, 1294, 1243, 1183, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21−7.17 (m, 2H), 6.80−6.74 (m, 2H), 4.67 (s, 1H), 1.63−1.57 (m, 3H), 1.25 (s, 6H), 0.67 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 141.7, 127.1, 114.6, 37.3, 36.9, 28.6, 9.10; HRMS: (ESI, M + Na^+) calcd for $C_{11}H_{15}O_1$, 163.11229; found, 163.11287.

*4-Nitrophenol (**3w**).* Prepared according to the general procedure discussed above: as a yellow solid (76 mg, 99%); R_f: 0.50 (ethyl acetate/hexane = 1/2); IR (NaCl) ν: 3633, 3079, 1611, 1593, 1496, 1434, 1388, 1341, 1294, 1203, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21−8.09 (m, 2H), 6.95−6.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 141.5, 126.3, 115.7; HRMS: (ESI, M + Na^+) calcd for $C_6H_4N_1O_3$, 138.01912; found, 138.01899.

*Benzyl Alcohol (**3x**).* Prepared according to the general procedure discussed above: as a colorless liquid (88 mg, 86%); R_f: 0.20 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3731, 3343, 3031, 2931, 2874, 1454, 1207, 1020, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.27 (m, 5H), 4.70 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 128.3, 127.3, 126.8, 64.6; HRMS: (ESI, M + Na^+) calcd for $C_7H_8Na_1O_1$, 131.04728; found, 131.04658.

*3-Chlorobenzyl Alcohol (**3y**).* Prepared according to the general procedure discussed above: as a colorless liquid (73 mg, 94%); R_f: 0.20 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3726, 3334, 3066, 2928, 2876, 1600, 1577, 1475, 1432, 1205, 1019, 780; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41−7.00 (m, 4H), 4.56 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 131.0, 127.1, 123.7, 120.7, 114.5, 15.7; HRMS: (ESI, M + Na^+) calcd for $C_7H_7Cl_1Na_1O_1$, 165.00831; found, 165.05695.

*1-Phenylethanol (**3z**).* Prepared according to the general procedure discussed above: as a colorless liquid (60 mg, 80%); R_f: 0.30 (ethyl acetate/hexane = 1/9); IR (NaCl) ν: 3358, 2974, 1493, 1452, 1204, 1077, 899, 760; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49−7.14 (m, 5H), 4.86 (q, *J* = 6.5 Hz, 1H), 1.47 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 128.4, 127.4, 125.3, 70.3, 25.1; HRMS: (ESI, M + Na^+) calcd for $C_8H_{10}O_1$, 122.06293; found, 122.06300.

*p-Methylphenyl 1-Thio-β-D-glucopyranoside (**3a**).* Prepared according to the general procedure discussed above: as a white solid (124 mg, 99%); R_f: 0.56 (EtOAc/MeOH = 9/1); IR (ATR-in H_2O) ν: 3352, 1741, 1490, 1386, 1211, 1083, 1042, 1019 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.33 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 4.56 (d, *J* = 9.9 Hz, 1H), 3.72 (dd, *J* = 12.4, 2.0 Hz, 1H), 3.55 (dd, *J* = 12.5, 5.6 Hz, 1H), 3.39−3.12 (m, 4H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, D_2O): δ 139.1, 132.5, 130.0, 128.0, 87.6, 79.9, 77.3, 71.7, 69.4, 60.8, 20.2; HRMS: (ESI, $[M]^-$) calcd for $C_{13}H_{18}O_5S$, 285.07967; found, 285.07957.

*p-Methylphenyl 1-Thio-β-D-galactopyranoside (**3b**).* Prepared according to the general procedure discussed above: as a white solid (52 mg, 82%); R_f: 0.53 (EtOAc/MeOH = 9/1); IR (ATR-in H_2O) ν: 3347, 1492, 1351, 1242, 1074, 1048, 927 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.44 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 4.65 (d, *J* = 9.7 Hz, 1H), 3.93 (d, *J* = 3.3 Hz, 1H), 3.75−3.60 (m, 4H), 3.55 (t, *J* = 9.6 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, D_2O): δ 138.8, 132.0, 130.0, 128.8, 88.5, 79.0, 74.0, 69.2, 68.8, 61.0, 20.2; HRMS: (ESI, $[M]^-$) calcd for $C_{13}H_{18}O_5S$, 285.07967; found, 285.07970.

*p-Methylphenyl 1-Thio-β-D-xylopyranoside (**3c**).* Prepared according to the general procedure discussed above: as a white solid (74.2 mg, 69%); R_f: 0.42 (ethyl acetate/MeOH = 9/1); IR (ATR-in H_2O) ν: 3386, 2923, 1492, 1400, 1334, 1207, 1041, 810 cm^{-1}; ^1H NMR (400 MHz, D_2O): δ 7.42 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.13 (d, *J* = 5.7 Hz, 1H), 3.94 (ddd, *J* = 7.6, 7.0, 3.3 Hz, 3H), 3.50 (ddd, *J* = 17.6, 12.3, 4.5 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, D_2O): δ 139.5, 133.7, 130.0, 127.3, 89.3, 84.7, 73.9, 70.9, 61.9, 20.2; HRMS: (ESI, $[M]^-$) calcd for $C_{13}H_{18}O_5S$, 255.06907; found, 255.06910.

Procedure for the One-Pot Reaction. To a solution of **1a** (200 mg, 0.51 mmol) in dichloromethane (7 mL), *p*-HSTol (128 mg, 1.03 mmol) and PTA (297 mg, 0.2 mmol) were added at room temperature. The reaction mixture was stirred in microwave 300 W at 40 °C for 30 min. After completion of the reaction, it was concentrated. To the mixture, MeOH (2 mL) and phosphotungstic acid (293.6 mg, 0.1 mmol) were added at room temperature. Then, the reaction mixture was stirred at 90 °C for 12 h. After completion of the reaction, it was neutralized by triethylamine, and the mixture was filtered and concentrated. It was purified by column chromatography on silica gel to give the product **3a** (111 mg, 76%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c00362.

NMR spectrum of important compounds (PDF)

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Author Contributions

J.-S.C. and T.-C.L. contributed equally. J.-S.C. and S.-Y.L. developed the concept and designed the experiments. J.-S.C., T.-C.L., and Y.-C.H. optimized the conditions for the reaction

of Table 1. Y.-C.H., T.-C.L., H.-Y.L., and M.-W.H., prepared compounds in Table 2. J.-S.C. and T.-C.L. optimized the conditions for the reaction of Table 3. T.-C.L. optimized the conditions for the reaction of Table 4. T.-C.L., M.L., and C.-H.C. prepared compounds in Table 5. J.-S.C. and C.-H.C. optimized the conditions for the reaction of eq 1. H.R.W. analyzed the mass data. J.-S.C., M.L., and S.-Y.L. wrote the manuscript with the help of S.-Y.L.

Notes

The authors declare no competing financial interest.

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