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# Transition-metal-free synthesis of aryl 1-thioglycosides with arynes at room temperature†

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A mild, convenient and transition-metal-free protocol for the synthesis of aryl 1-thioglycosides is presented *via* arynes generated *in situ* combined with glycosyl thiols in the presence of TBAF(*t*BuOH)<sub>4</sub>. The methodology provides a general and efficient way to prepare a series of functionalized thioglycosides in good to excellent yields with a perfect control of the anomeric configuration at room temperature. In addition, the reaction conditions tolerate a variety of the pentoses and hexoses, and the reaction also performs smoothly on protected monosaccharides and disaccharides.

## Introduction

Thioglycosides, as the analogue of the *O*-glycosides, are versatile intermediates in carbohydrate synthesis and have a wide range of potential applications,<sup>1</sup> and are regularly used as glycosyl donors<sup>2</sup> to construct various oligosaccharides and glycoconjugates. Additionally, they are more stable in both chemical and enzymatic degradations<sup>3</sup> and have also been employed extensively as inhibitors in a great number of biochemical studies.<sup>4</sup> Thioglycoside fragments are also widely used in various drugs, natural products and pharmaceutical active agents.<sup>5</sup> Some examples of the thioglycosides derivatives include the cytotoxic Hsp90 inhibitor,<sup>6</sup> MUS-CB,<sup>7</sup> hSGLT1 inhibitor,<sup>8</sup> lincomycin,<sup>9</sup> clindamycin,<sup>10</sup> as well as irreversible glycoside inhibitors<sup>11</sup> (Fig. 1). On account of the great significance of *S*-glycosides, some elegant synthetic protocols have been developed.

Originally, the approaches to prepare the 1-thioglycosides were that glycosyl donors reacted with sulfurs (or thiophenols) in the presence of the stoichiometric Lewis acids<sup>12</sup> or glycosyl halides reacted with thiolate anions under strong base conditions (Scheme 1a). However, the inferior stereo-selectivity or strong base of those traditional methods limited their application. With the efforts of Sticha, Xue, Messaoudi *et al.*, the synthesis of 1-thioglycosides achieved great advances in recent years. As shown in Scheme 1b, the functionalization of glycosyl thiols had been catalysed by the Ni,<sup>13</sup> Cu<sup>14</sup>, Pd<sup>15</sup> transition metal

*via* the Buchwald–Hartwig–Migita coupling reaction. These methods required an expensive catalyst or a high temperature (above 100 °C in some protocols of the Cu or Pd catalyst) and long reaction time, which limit the universality of the reaction to some extent. In 2019, Messaoudi and co-workers developed a protocol for the synthesis of aryl 1-thioglycosides *via* a Ni/photoredox dual catalyzed cross-coupling reaction<sup>16</sup> (Scheme 1c). Recently, Messaoudi's group described the first electrochemical method for coupling various anomeric glycosyl thiols with aryl bromides<sup>17</sup> (Scheme 1c). The reaction didn't need to perform in a strong base environment, and demonstrated superiority to synthesize highly complex thioglycosides under mild conditions. However, some functional groups are not compatible with this procedure.

Arynes are highly reactive transient intermediates and are also useful synthons in organic synthesis due to the unique triple bonds, and have been extensively used in the synthesis of natural products, drug molecules and functional materials.<sup>18</sup> Arynes have made remarkable achievements in nucleophilic reactions,<sup>19</sup> pericyclic reactions,<sup>20</sup> transition metal catalyzed reactions<sup>21</sup> and multicomponent reactions.<sup>22</sup> In recent years, *N*-arylation of carbohydrate amines<sup>23</sup> and *O*-arylation of carbohydrates<sup>24</sup> have been reported *via* the aryne insertion reactions with glycosyl

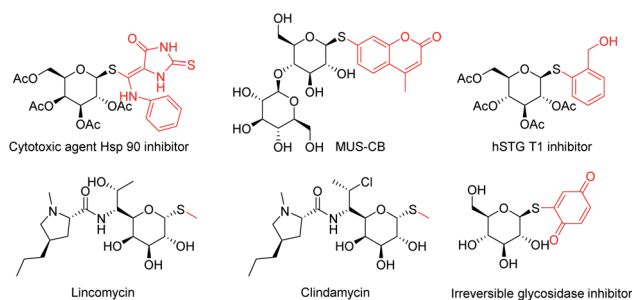


Fig. 1 Examples of biologically active thioglycosides.

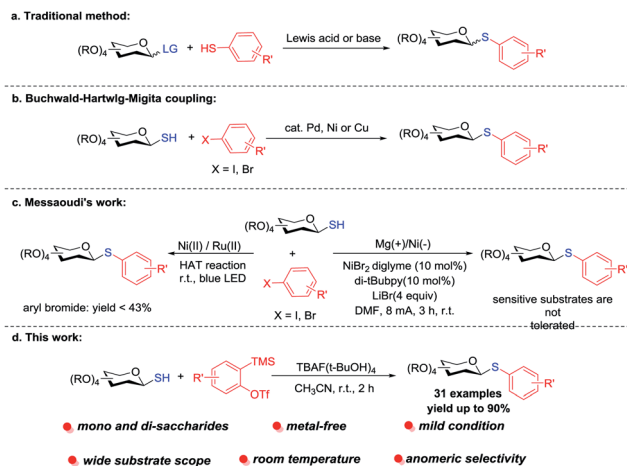
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Scheme 1 Methods for the synthesis of S-glycosides.

thiols. The methodology of using the aryne generated *in situ* to realize the functionalized thioglycosides was not developed yet. On the basis of our previous research in carbohydrates,<sup>25</sup> we report a novel protocol for the preparation of thioglycosides *via* a tandem intermolecular nucleophilic coupling of glycosyl thiols with arynes (Scheme 1c).

## Results and discussion

We started by optimizing the reaction conditions with tetra-*O*-acetylated 1-thio- $\beta$ -D-glucopyranose **1a** (1.0 equiv.), *o*-

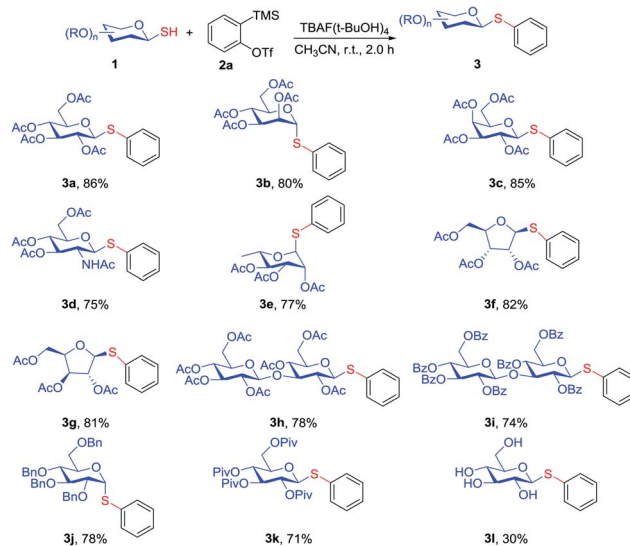
Table 1 Optimization conditions for the synthesis of S-glycosides<sup>a</sup>

Entry	F <sup>-</sup> sources	Solvent	Time/h	T/°C	Yield (%)
1	CsF	CH <sub>3</sub> CN	2.0	25	70(64 <sup>b</sup> )
2	AgF	CH <sub>3</sub> CN	2.0	25	51
3	KF	CH <sub>3</sub> CN	2.0	25	42
4	ZnF <sub>2</sub>	CH <sub>3</sub> CN	2.0	25	35
5	TBAF·3H <sub>2</sub> O	CH <sub>3</sub> CN	2.0	25	63
6	TBAF(THF)	CH <sub>3</sub> CN	2.0	25	67
7	<b>TBAF·(tBuOH)<sub>4</sub></b>	<b>CH<sub>3</sub>CN</b>	<b>2.0</b>	<b>25</b>	<b>86</b>
8	TBAF·(tBuOH) <sub>4</sub>	DCM	2.0	25	78
9	TBAF·(tBuOH) <sub>4</sub>	THF	2.0	25	40
10	TBAF·(tBuOH) <sub>4</sub>	Toluene	2.0	25	33
11	TBAF·(tBuOH) <sub>4</sub>	MeOH	2.0	25	37
12	TBAF·(tBuOH) <sub>4</sub>	DMSO	2.0	25	26
13	TBAF·(tBuOH) <sub>4</sub>	DMF	2.0	25	30
14	TBAF·(tBuOH) <sub>4</sub>	CH <sub>3</sub> CN	2.0	40	85
15	TBAF·(tBuOH) <sub>4</sub>	CH <sub>3</sub> CN	2.0	60	60
16	TBAF·(tBuOH) <sub>4</sub>	CH <sub>3</sub> CN	3.0	25	83 <sup>c</sup>
17	TBAF·(tBuOH) <sub>4</sub>	CH <sub>3</sub> CN	4.0	25	82

<sup>a</sup> Standard conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.11 mmol, 1.1 equiv.), TBAF·(tBuOH)<sub>4</sub> (0.2 mmol, 2.0 equiv.), CH<sub>3</sub>CN (1.5 mL) as solvent, r.t., 2 h. <sup>b</sup> **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.1 mmol, 1.0 equiv.), F<sup>-</sup> source (0.2 mmol, 2.0 equiv.), CH<sub>3</sub>CN (1.5 mL). <sup>c</sup> **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.11 mmol, 1.1 equiv.), TBAF·(tBuOH)<sub>4</sub> (0.3 mmol, 3.0 equiv.), CH<sub>3</sub>CN (1.5 mL) as solvent, r.t., 2 h.

(trimethylsilyl)aryl triflates **2a** (1.0 equiv.) as model substrate. Phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio- $\beta$ -D-glucopyranoside **3a** was isolated after 2 hours in 64% yield at room temperature (entry 1, Table 1). When the equivalent of aryne precursor increased to 1.1 equiv., the yield of desired product increased to 70% (entry 1, Table 1). Inspired by this result, other fluorides, such as AgF, ZnF<sub>2</sub>, KF, more widely used tetrabutyl ammonium fluoride (TBAF) and its analogs (entries 2–7, Table 1) were tested. To our delight, the yield of **3a** increased to 86% when TBAF·(tBuOH)<sub>4</sub> (ref. 26) was used as a fluorine source (entry 7, Table 1). Next, we also investigated the solvent effect by using various polar solvents and non-polar solvents (entries 8–13, Table 1). Nucleophilic solvents such as tetrahydrofuran, methanol, *N,N*-dimethylformamide and dimethyl sulfoxide exhibited low yields (26–40%), probably because the competitive reaction between nucleophilic solvents and the substrates. The yield of **3a** was decreased to 60% when the temperature increased to 60 °C (entry 15). We found that the yield of the target product was not influenced with extended reaction time.

With the optimized condition in hand, the scopes of the glycosyl thiols were further investigated and the results are presented in Scheme 2. Various acetyl-protected  $\beta$ -glycosyl thiols **1c**, **1d** reacted with arynes under the standard conditions and the corresponding  $\beta$ -configuration thioglycosides products (**3c**, **3d**) were obtained in good yields (85%, 75%). This conversion was also applicable for the  $\alpha$ -configuration glycosyl thiol substrate **1b** and **1e**, providing corresponding arylthioglycoside products **3b** and **3e** in 80% and 77% yield, respectively. Moreover, triacetyl protected-pentose glycosyl thiols **1f**, **1g** participated in this reaction smoothly and the yields of the corresponding thioglycoside products were 82% and 81%, respectively. The reaction was not limited to monosaccharides but also extended to disaccharides. Acetyl-protected cellobiose **1h** and benzoyl-protected cellobiose **1i** were reacted with arynes



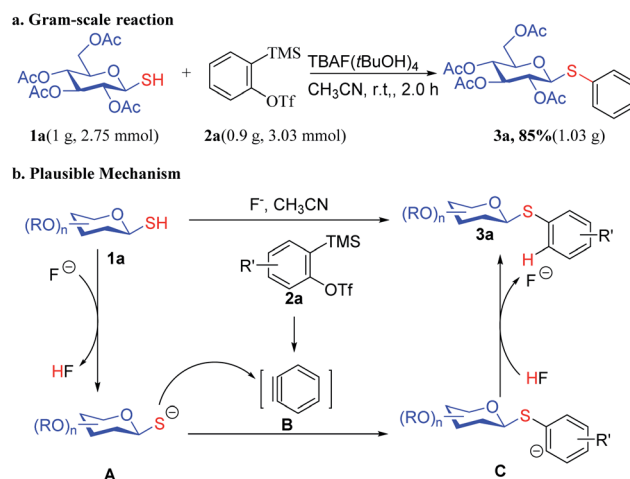
Scheme 2 Scopes of glycosyl thiols **1** reacted with aryne **2a**. Standard conditions: **1** (0.1 mmol, 1.0 equiv.), **2a** (0.11 mmol, 1.1 equiv.), TBAF·(tBuOH)<sub>4</sub> (0.2 mmol, 2.0 equiv.), dry CH<sub>3</sub>CN (1.5 mL).



successfully and obtained the  $\beta$ -disaccharide in good yields, indicated the electronic-effect of the protecting groups did not have significant influence for the reaction efficiency. Meanwhile, we also found the  $\alpha$ -glycosyl thiols with OBn protected group can react with **2a** when the temperature improved to 45 °C and the yield of corresponding product **3j** was 78%. The sugar **1k** with OPiv group provided **3k** in 71% yield under optical condition. However, the reactivity of unprotected glycosyl thiol was decreased and the yield of product was only 30%.

Subsequently, we also investigated the electronic effects and regioselectivity of this reaction *via* different aryne precursors and glycosyl thiols **1**. Regardless of the electron-donating or -withdrawing properties of the symmetrical aryne precursors **2**, the corresponding products were obtained in good yields. The difluoro substituted aryne **2b** reacted with **1** gave the thio-glycosides derivatives **4a–4h** in 71–82% yields. Aryne precursor **2c** reacted with a series of glycosyl thiols under standard reaction condition to afford the corresponding products **4i–4l** in good yields (72–84%). Also, the dimethyl substituted aryne precursors reacted with **1a** under standard condition to give corresponding aryl 1-thioglycoside **4m** with 78% yield.

Meanwhile, 3-methoxy non-symmetric aryne precursor **2d** exhibited excellent regioselectivity due to the steric effect and electronic effects, and single target thio-glycosides **4n**, **4o** were obtained in good yields (80%, 78%). However, we found that 4-methylbenzynes precursor **2e** reacted with **1a** and **1f** gave a near equimolar mixture of two inseparable regioisomers, providing



Scheme 4 Gram-scale reaction and plausible mechanism.

corresponding products in 82% and 90% yield, respectively. 1,2-Naphthynes precursor **2f** under the same conditions also provided a near equimolar mixture of two inseparable regioisomers (Scheme 3).

To demonstrate the synthetic utility of this transformation, we next performed a scale-up reaction of **3a**. As shown in Scheme 4a, a gram scale reaction of 1-thio- $\beta$ -D-glucopyranose **1a** with aryne precursor **2a** proceeded to give **3a** in 85% yield. A plausible mechanism was proposed in Scheme 4b, based on the basis of the experimental results and the related report by Jin and co-workers.<sup>27</sup>

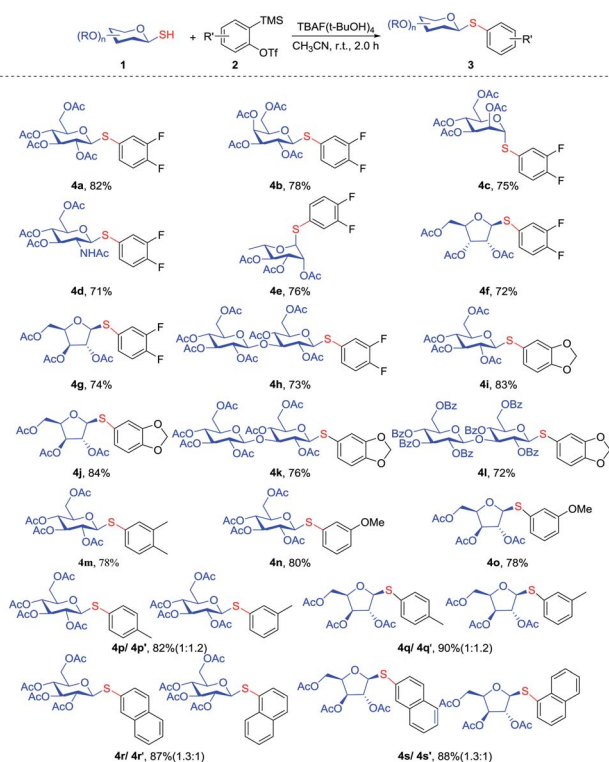
## Conclusions

In conclusion, we have developed a convenient method for the preparation of aryl-thioglycosides under mild and metal-catalyst-free conditions *via* a tandem intermolecular nucleophilic coupling of glycosyl thiols with arynes. Meanwhile, the method is applicable for various monosaccharide and disaccharide substrates, which has wide practical value between biochemistry and medicinal chemistry. In addition, 1,2-*trans*-thioglycosides were stereoselectively formed by the reaction of the *in situ* generated arynes with glycosyl thiols in good to excellent yields. Importantly, we provided a new protocol for the synthesis of functionalized thioglycosides and the possibility for further derivatization of glycosyl donors.

## Experimental

### General information

All reactions were carried out in dried glassware. The solvent in the reaction were dried use activated 4 Å molecular sieve, commercial reagents were used without further purification unless otherwise stated. Purification of reaction products were carried out by flash chromatography on silica gel (200–300 mesh). NMR spectra were measured in CDCl<sub>3</sub> (with TMS as internal standard) on a Bruker AV400 (<sup>1</sup>H at 400 MHz, <sup>13</sup>C at 100 MHz, <sup>19</sup>F at 376 MHz) magnetic resonance spectrometer.



Scheme 3 Scope of aryne precursors **2** reacted with glycosyl thiol. Standard condition: **1** (0.1 mmol, 1.0 equiv.), **2** (0.11 mmol, 1.1 equiv.), TBAF·(t-BuOH)<sub>4</sub> (0.2 mmol, 2.0 equiv.), dry CH<sub>3</sub>CN (1.5 mL).



### The general procedure for the reaction of glycosyl thiols **1** with arylene precursors **2**

The glycosyl thiol **1** (50 mg, 0.14 mmol, 1.0 equiv.), arylene precursor **2** (45 mg, 0.150 mmol, 1.1 equiv.) and TBAF·(*t*BuOH)<sub>4</sub> (0.274 mmol, 2.0 equiv.) were sequentially added in a clean and dry Schlenk tube, and the tube was then evacuated and back-filled with nitrogen (this sequence was repeated three times). Under nitrogen atmosphere, MeCN (1.5 mL) was added to the mixture system, then the mixture was stirred at room temperature for 2.0 hours. Saturated NaCl solution was added to dilute the system and extracted with EtOAc (3 × 2 mL). The combined organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated *in vacuo*. Finally, the crude product was purified *via* flash column chromatography on silica gel to give the desired product.

#### Phenyl-2,3,5-tri-*O*-acetyl-1-thio-β-D-xylofuranoside (**3g**)

Purified by flash column chromatography  $R_f = 0.39$  (petroleum ether/AcOEt = 3 : 1), white solid (29.8 mg, 81% yield);  $[\alpha]_D^{25} = -55.4$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.55–7.46 (m, 2H, ArH), 7.40–7.28 (m, 3H, ArH), 5.18 (t,  $J = 8.2$  Hz, 1H), 5.06–4.87 (m, 2H), 4.80 (d,  $J = 8.4$  Hz, 1H), 4.28 (dd,  $J = 11.8, 4.9$  Hz, 1H), 3.42 (dd,  $J = 11.8, 8.7$  Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.9, 169.8, 169.3, 132.7, 132.2, 129.1, 128.3, 86.2, 71.9, 69.8, 68.4, 65.2, 20.8, 20.8, 20.7; HRMS (ESI)  $m/z$  calcd for C<sub>17</sub>H<sub>20</sub>O<sub>7</sub>SN<sup>+</sup> (M + Na)<sup>+</sup> 391.0822, found 391.0822.

#### 3,4-Difluorophenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**4a**)

Purified by flash column chromatography  $R_f = 0.30$  (petroleum ether/AcOEt = 3 : 1), white solid (39.1 mg, 82% yield);  $[\alpha]_D^{25} = -20.7$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42 (ddd,  $J = 10.2, 7.5, 2.2$  Hz, 1H), 7.24–7.19 (m, 1H), 7.10 (dt,  $J = 10.0, 8.3$  Hz, 1H), 5.21 (t,  $J = 9.4$  Hz, 1H), 5.00 (t,  $J = 9.8$  Hz, 1H), 4.90 (t,  $J = 9.6$  Hz, 1H), 4.63 (d,  $J = 10.0$  Hz, 1H), 4.19 (d,  $J = 3.8$  Hz, 2H), 3.73 (dt,  $J = 10.1, 3.8$  Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H); <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>) δ -135.81 (dt,  $J = 19.7, 9.3$  Hz), -136.61 (m); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -135.81 (d,  $J = 20.9$  Hz), -136.61 (d,  $J = 21.0$  Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.6, 170.1, 169.3, 169.2, 150.9 (dd,  $J = 251.0, 12.3$  Hz), 149.9 (dd,  $J = 251.1, 12.5$  Hz), 130.3 (dd,  $J = 6.4, 3.6$  Hz), 127.1 (dd,  $J = 6.2, 4.2$  Hz), 122.9 (d,  $J = 18.2$  Hz), 117.5 (d,  $J = 17.6$  Hz), 85.1, 75.9, 73.8, 69.6, 68.0, 62.0, 20.7, 20.6, 20.5; HRMS (ESI)  $m/z$  calcd for C<sub>20</sub>H<sub>22</sub>F<sub>2</sub>O<sub>9</sub>SN<sup>+</sup> (M + Na)<sup>+</sup> 499.0845, found 499.0843.

#### 3,4-Difluorophenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranoside (**4b**)

Purified by flash column chromatography  $R_f = 0.28$  (petroleum ether/AcOEt = 3 : 1), colorless oil (37.1 mg, 78% yield);  $[\alpha]_D^{25} = 6.8$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47 (ddd,  $J = 10.2, 7.5, 2.2$  Hz, 1H), 7.24–7.19 (m, 1H), 7.11 (dt,  $J = 10.0, 8.4$  Hz, 1H), 5.41 (dd,  $J = 3.3, 1.1$  Hz, 1H), 5.18 (dd,  $J = 9.9$  Hz, 1H), 5.03 (dd,  $J = 9.9, 3.3$  Hz, 1H), 4.64 (d,  $J = 9.9$  Hz,

1H), 4.20–4.09 (m, 2H), 3.95 (td,  $J = 5.8, 2.9$  Hz, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 1.96 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 169.4, 169.1, 168.9, 168.3, 149.6 (dd,  $J = 250.8, 12.5$  Hz), 148.9 (dd,  $J = 250.9, 13.0$  Hz), 128.5 (dd,  $J = 6.2, 3.7$  Hz), 127.1 (dd,  $J = 6.1, 4.2$  Hz), 121.1 (d,  $J = 18.3$  Hz), 116.4 (d,  $J = 17.7$  Hz), 84.9, 73.6, 70.8, 66.2, 65.9, 60.8, 19.8, 19.6, 19.5, 19.5; <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>) δ -135.92 (dt,  $J = 19.8, 9.3$  Hz), -137.16 (m); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -135.92 (d,  $J = 21.0$  Hz), -137.17 (d,  $J = 20.9$  Hz). HRMS (ESI)  $m/z$  calcd for C<sub>20</sub>H<sub>22</sub>F<sub>2</sub>O<sub>9</sub>SN<sup>+</sup> (M + Na)<sup>+</sup> 499.0845, found 499.0841.

#### 3,4-Difluorophenyl-2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (**4d**)

Purified by flash column chromatography  $R_f = 0.28$  (petroleum ether/AcOEt = 1 : 2), white solid (33.6 mg, 71% yield);  $[\alpha]_D^{25} = -24.5$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.43 (ddd,  $J = 10.0, 7.4, 2.1$  Hz, 1H), 7.25–7.19 (m, 1H), 7.09 (dt,  $J = 10.1, 8.4$  Hz, 1H), 5.76 (d,  $J = 9.1$  Hz, 1H), 5.19 (t,  $J = 9.8$  Hz, 1H), 5.02 (t,  $J = 9.7$  Hz, 1H), 4.77 (d,  $J = 10.4$  Hz, 1H), 4.21–4.13 (m, 2H), 4.00 (q,  $J = 9.8$  Hz, 1H), 3.77–3.67 (m, 1H), 2.08 (s, 3H), 2.02 (s, 6H), 1.98 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 171.0, 170.6, 170.1, 169.3, 150.6 (dd,  $J = 251.0, 12.6$  Hz), 149.9 (dd,  $J = 250.9, 12.8$  Hz), 129.6 (dd,  $J = 6.3, 3.6$  Hz), 128.2 (dd,  $J = 6.3, 4.2$  Hz), 122.1 (d,  $J = 18.2$  Hz), 117.5 (d,  $J = 17.5$  Hz), 86.4, 75.9, 73.5, 68.2, 62.3, 53.2, 23.3, 20.6, 20.6, 20.5; <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>) δ -135.93 (dt,  $J = 19.9, 9.3$  Hz), -137.28 (m); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -135.93 (d,  $J = 21.4$  Hz), -137.29 (d,  $J = 21.0$  Hz). HRMS (ESI)  $m/z$  calcd for C<sub>20</sub>H<sub>23</sub>F<sub>2</sub>NO<sub>8</sub>SN<sup>+</sup> (M + Na)<sup>+</sup> 498.1005, found 498.1006.

#### 3,4-Difluorophenyl-2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamno-pyranoside (**4e**)

Purified by flash column chromatography  $R_f = 0.47$  (petroleum ether/AcOEt = 3 : 1), white solid (31.8 mg, 76% yield);  $[\alpha]_D^{25} = -116.0$  ( $c = 1.0$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.31 (ddd,  $J = 10.0, 7.3, 2.2$  Hz, 1H), 7.21–7.17 (m, 1H), 7.11 (dt,  $J = 10.0, 8.3$  Hz, 1H), 5.45 (dd,  $J = 3.3, 1.7$  Hz, 1H), 5.35 (d,  $J = 1.6$  Hz, 1H), 5.21 (dd,  $J = 10.1, 3.2$  Hz, 1H), 5.14 (t,  $J = 9.8$  Hz, 1H), 4.34–4.26 (m, 1H), 2.14 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.25 (d,  $J = 6.2$  Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 170.1, 170.0, 170.4, 150.5 (dd,  $J = 250.5, 12.6$  Hz), 150.3 (dd,  $J = 251.8, 13.1$  Hz), 129.4 (dd,  $J = 6.1, 4.1$  Hz), 128.6 (dd,  $J = 6.3, 3.7$  Hz), 121.2 (d,  $J = 18.2$  Hz), 118.0 (d,  $J = 17.7$  Hz), 86.0, 71.1, 71.0, 69.4, 68.1, 21.0, 20.9, 20.8, 17.4; <sup>19</sup>F {<sup>1</sup>H} NMR (376 MHz, CDCl<sub>3</sub>) δ -135.57 (dt,  $J = 20.9, 9.2$  Hz), -137.48 (m); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -135.57 (d,  $J = 20.9$  Hz), -137.50 (d,  $J = 21.0$  Hz). HRMS (ESI)  $m/z$  calcd for C<sub>18</sub>H<sub>20</sub>F<sub>2</sub>O<sub>7</sub>SN<sup>+</sup> (M + Na)<sup>+</sup> 441.0790, found 441.0795.

#### 3,4-Difluorophenyl-2,3,5-tri-*O*-acetyl-1-thio-β-D-xylo-furanoside (**4g**)

Purified by flash column chromatography  $R_f = 0.38$  (petroleum ether/AcOEt = 3 : 1), white solid (29.9 mg, 74% yield);  $[\alpha]_D^{25} = -56.9$  ( $c = 0.5$ , CHCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.35 (ddd,  $J = 10.0, 7.4, 2.2$  Hz, 1H), 7.24–7.19 (m, 1H), 7.11 (dt,  $J = 10.1, 8.3$  Hz, 1H), 5.17 (t,  $J = 8.1$  Hz, 1H), 4.94–4.85 (m, 2H), 4.73 (d,  $J = 8.2$  Hz, 1H), 4.27 (dd,  $J = 11.8, 4.9$  Hz, 1H), 3.43 (dd,  $J = 11.8, 8.6$  Hz, 1H), 2.10 (s, 3H), 2.04 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)



$\delta$  170.0, 169.9, 169.5, 150.9 (dd,  $J = 250.9, 12.5$  Hz), 150.1 (dd,  $J = 251.7, 12.9$  Hz), 130.1 (dd,  $J = 5.9, 3.8$  Hz), 128.0–127.7 (m), 122.6 (d,  $J = 18.0$  Hz), 117.8 (d,  $J = 17.6$  Hz), 85.9, 71.8, 69.7, 68.3, 65.3, 20.9, 20.9, 20.8;  $^{19}\text{F}$   $\{^1\text{H}\}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -135.81 (dt,  $J = 21.3, 9.2$  Hz), -136.89 (m);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta$  -135.81 (d,  $J = 21.5$  Hz), -136.90 (d,  $J = 21.4$  Hz). HRMS (ESI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{18}\text{F}_2\text{O}_7\text{SNa}^+$  ( $M + \text{Na}$ ) $^+$  427.0634, found 427.0633.

### 6-Benzo[*d*][1,3]dioxolyl-2,3,6,2',3',4',6'-hepta-*O*-acetyl-1-thio- $\beta$ -cellobioside (4k)

Purified by flash column chromatography  $R_f = 0.41$  (petroleum ether/AcOEt = 1 : 1), white solid (58.6 mg, 76% yield);  $[\alpha]_D^{25} = -24.5$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.01 (d,  $J = 1.8$  Hz, 1H), 6.95 (dd,  $J = 8.0, 1.8$  Hz, 1H), 6.73 (d,  $J = 8.0$  Hz, 1H), 5.97 (s, 2H), 5.14 (dt,  $J = 14.9, 9.3$  Hz, 2H), 5.05 (t,  $J = 9.6$  Hz, 1H), 4.90 (dd,  $J = 9.2, 7.9$  Hz, 1H), 4.82 (t,  $J = 9.7$  Hz, 1H), 4.58 (dd,  $J = 11.9, 2.0$  Hz, 1H), 4.50 (dd,  $J = 13.5, 9.0$  Hz, 2H), 4.37 (dd,  $J = 12.5, 4.2$  Hz, 1H), 4.07 (dd,  $J = 11.9, 5.3$  Hz, 1H), 4.01 (dd,  $J = 12.5, 2.3$  Hz, 1H), 3.69 (t,  $J = 9.5$  Hz, 1H), 3.65–3.56 (m, 2H), 2.12 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.6, 170.4, 170.4, 169.9, 169.6, 169.4, 169.1, 148.6, 147.9, 128.8, 122.8, 114.8, 108.6, 101.6, 100.9, 85.8, 76.4, 73.8, 73.0, 72.1, 71.7, 70.0, 67.8, 61.9, 61.6, 20.9, 20.8, 20.7, 20.6.

## Conflicts of interest

There are no conflicts to declare.

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