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TRIFLIC ACID ADSORBED ON SILICA GEL AS AN EFFICIENT CATALYST FOR *O*-ISOPROPYLIDENATION OF SUGAR DERIVATIVES

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Abstract – Triflic acid immobilized on silica gel has been identified as an excellent catalyst for the chemoselective *O*-isopropylideneation of free sugars and functionalized carbohydrates with acetone. This method is simple and economic for large-scale synthesis together with good to excellent yield, low catalyst loading and non-aqueous workup procedure.

Protection strategy is a very common tactic in multi-step synthesis of complex organic molecules such as modified oligosaccharides, glycopeptides and nucleosides. The efficient protection of hydroxyl group has become increasingly crucial especially in carbohydrate chemistry.¹ As far as hydroxyl group protection is concerned, the protection of 1,2- and 1,3-diols as *O*-isopropylidene derivatives (acetonides) has become inestimable to the carbohydrate chemist.² Acetonides of sugars are important not only because they are served as valuable building blocks in carbohydrate chemistry³ but also due to many of them have been used as key starting materials for nature product synthesis or important reaction intermediates for the synthesis of bioactive molecules.⁴ For example, the corresponding di-*O*-isopropylidene derivative of L-sorbose has been used for the large-scale preparation of 1-deoxynojirimycin.⁵ Similarly, 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal has been utilized for the total synthesis of a potent cytostatic agent (+)-phorboxazole A.⁶ And, 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol has been used in the total synthesis of (+)-7-*epi*-goniofufurone⁷ and other analogues. Notably, 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose exhibits antipyretic and anti-inflammatory activities with very low toxicity.⁸

Conventionally, the *O*-isopropylideneation of a carbohydrate molecule is performed by using anhydrous acetone or acetonide-forming agents in the presence of an acid catalyst. Over the past years, a diverse

array of catalyst have been explored for the *O*-isopropylidene of sugar derivatives.⁹ However, many of these mentioned reagents have one or more drawbacks such as the use of toxic chemical, an excessive amount of catalyst, low yielding, long reaction time, harsh reaction condition and cumbersome workup or purification. Hence, there is still a clear need to devise better alternatives by exploring new reagents for the synthesis of these valuable derivatives.

Over the past years, silica gel supported reagents have gained much attention as alternative catalysts in carbohydrate chemistry.¹⁰ The advantages of these heterogeneous catalysts over the homogeneous catalysts include stability, insensitivity toward air and moisture, ease of handling, lack of corrosion, and easy of recovery and regeneration. Triflic acid (TfOH) has been used as a catalyst in a vast array of organic reactions. However, TfOH is a fuming and highly corrosive liquid, so there are difficulties in storage, transportation, handling and waste disposal. Following the urgent demand of green chemistry, we herein wish to report the immobilization of TfOH on silica gel (TfOH-SiO₂).

In continuation of our interest in developing new method in organic synthesis,¹¹ especially our efforts toward solid supported acid as green catalyst.¹² Herein, we describe an efficient and suitable protocol for the chemoselective *O*-isopropylidene of free sugars and functionalized carbohydrates with acetone catalyzed by TfOH-SiO₂ (Figure 1).

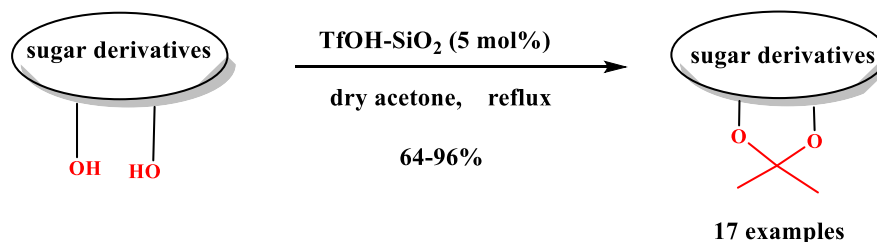


Figure 1. *O*-Isopropylidene of sugar derivatives

At the outset, L-rhamnose was selected as a model substrate (Table 1, entry 4) by using dry acetone in the presence of a catalytic amount of TfOH-SiO₂. When a mixture of commercially available L-rhamnose (2 mmol) in dry acetone (10 mL) was stirred at room temperature in the presence of 5 mol% TfOH-SiO₂ under N₂ atmosphere, no reaction took place even after several hours. Cheerfully, when warmed up the mixture to reflux, the starting material was completely converted to its corresponding *O*-isopropylidene product within 5 min in 96% yield. Encouraged by these results, D-mannose was kept for *O*-isopropylidene under the same reaction condition. The corresponding product 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose was obtained in 78% yield (Table 1, entry 2). This was consistent with the literature results that the isopropylidene of D-mannose usually provided the thermodynamically controlled furanoside derivatives preferably on reaction with acetone in the presence of an acid catalyst.¹³ Similarly, D-galactose afforded 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose in

73% yield (Table 1, entry 3). It was worthy to mention that when this reaction was started in a pre-heated oil-bath, only a pyranoside product was obtained, whereas slow elevation of the temperature resulted in a mixture of furanoside and pyranoside in 1:3 ratio. Within this protocol, L-arabinose led to the formation of the corresponding pyranoside derivative (Table 1, entry 7), whereas D-glucose, D-xylose, D-ribose and L-sorbose were converted to their furanoside derivatives. The results were summarized in Table 1.

Table 1. Synthesis of *O*-isopropylidene derivatives from free sugars using TfOH-SiO₂^a

| Entry | Substrate | Product ^b | Time (min) | Yield (%) ^c | Ref. |
|-------|-----------------|----------------------|------------|------------------------|------|
| 1 | D-glucose (1) | <p>9</p> | 30 | 71 | 9d |
| 2 | D-mannose (2) | <p>10</p> | 30 | 78 | 9d |
| 3 | D-galactose (3) | <p>11</p> | 30 | 73 | 9d |
| 4 | L-rhamnose (4) | <p>12</p> | 5 | 96 | 9g |
| 5 | D-xylose (5) | <p>13</p> | 25 | 85 | 9g |
| 6 | D-ribose (6) | <p>14</p> | 20 | 80 | 9d |
| 7 | L-arabinose (7) | <p>15</p> | 10 | 89 | 9d |
| 8 | L-sorbose (8) | <p>16</p> | 30 | 68 | 9d |

^a All reactions were started on a pre-heated oil bath.

^b Analytical datas were consistent with known products from the literature.

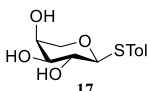
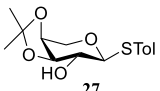
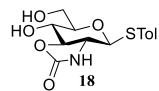
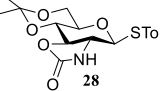
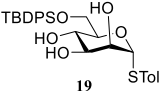
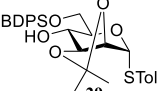
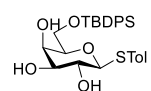
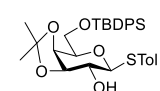
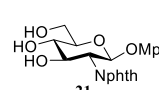
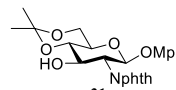
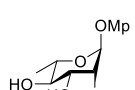
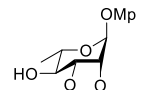
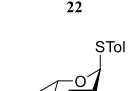
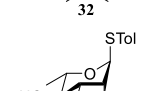
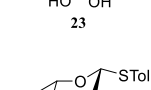
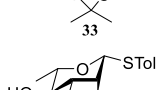
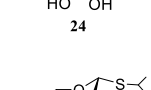
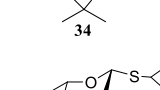
^c Isolated yield.

Notably, we have also found that the conversion of various free sugars to the respective *O*-isopropylidene derivatives could be achieved on a larger scale (100 mmol) without any difficulty by using only 2 mol% of the catalyst. For example, the reaction of L-rhamnose (18.2 g, 100 mmol) was investigated in dry acetone (400 mL) in the presence of TfOH-SiO₂ (2 mmol). The reaction was completed within 10 min,

and the desired product was obtained in 91% yield.

With the preliminary success in hands, the generality of this method was further examined with the optimal catalytic protocol. As shown in Table 2, a series of mono-saccharides with sulfur or oxygen containing substituents at the anomeric position gave their corresponding products in good to excellent yields. Notably, the starting substrate **20** gave its corresponding *O*-isopropylidene derivate **30** in 81% yield within only 20 min even at room temperature. It is worth noting that glucopyranoside **18** furnished the corresponding 4,6-*O*-isopropylidene derivative **28** due to slower rate of *trans* ring-fused acetonide formation.

Table 2. Protection of sugar acetonide using TfOH-SiO₂^a

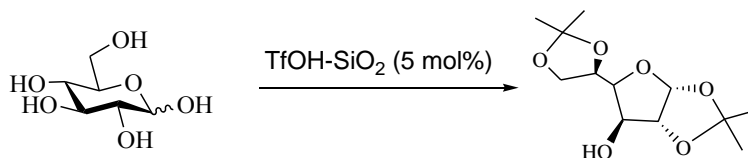
| Entry | Substrate | Product ^b | Time (min) | Yield (%) ^c | Ref. |
|-------|---|---|------------|------------------------|------|
| 1 |  |  | 30 | 75 | 14 |
| 2 |  |  | 30 | 64 | |
| 3 |  |  | 10 | 87 | |
| 4 |  |  | 30 | 81 | |
| 5 |  |  | 10 | 73 | 15 |
| 6 |  |  | 10 | 88 | 16 |
| 7 |  |  | 10 | 86 | 17 |
| 8 |  |  | 10 | 89 | |
| 9 |  |  | 10 | 81 | |

^a All reactions were started on a pre-heated oil bath.

^b Analytical datas were consistent with known products from the literature.

^c Isolated yield.

Finally, we investigated the recycling of TfOH-SiO₂ using D-glucose as model substrate. The solid catalyst was collected by filtration after the reaction was completed. Then the catalyst present in the filtrate was reused for the next cycle. As shown in Figure 2, the catalyst exhibited good catalytic activity even after three cycles.



| Entry | Catalyst use | Yield [%] |
|-------|--------------|-----------|
| 1 | fresh | 72 |
| 2 | 1st recycle | 70 |
| 3 | 2nd recycle | 68 |
| 4 | 3rd recycle | 65 |

In summary, an efficient protocol for the chemoselective *O*-isopropylidene of sugar derivatives had been demonstrated, which involves TfOH-SiO₂ as the catalyst. Due to its operational simplicity, generality, and efficacy, this method is expected to have much wider applicability for the preparation of *O*-isopropylidene sugar derivatives in a large scale in the future.

EXPERIMENTAL

All reagents were purchased from Adamas (China), and were used as received without further purification. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with silica gel plates (60F-254) using UV light. Yields refer to pure compounds. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer as indicated in the data list. Chemical shifts for proton nuclear magnetic resonance (¹H NMR) spectra are reported in parts per million relative to the signal residual (CDCl₃ at 7.26 ppm) or TMS. Chemical shifts for carbon nuclear magnetic resonance (¹³C NMR) spectra are reported in parts per million relative to the center line of the CDCl₃ triplet at 77.16 ppm. The abbreviations s, d, dd, t, q, br, and m stand for the resonance multiplicity singlet, doublet, doublet of doublets, triplet, quartet, broad and multiplet, respectively.

Preparation of TfOH-SiO₂

To a suspension of silica gel (5.0 g, mesh no.300-400) in anhydrous Et₂O (20 mL) was added TfOH (1.53 g, 10 mmol) dropwise and the mixture was stirred magnetically for 30 min at room temperature. Then the Et₂O was removed under reduced pressure (rotary evaporator) and the residue heated at 100 °C for 24 h under vacuum with the pressure values of -0.1 MPa to afford TfOH-SiO₂ (2 mmol/g) as a

free-flowing powder.

General procedure for the chemoselective *O*-isopropylidene of free sugars and functionalized carbohydrates:

To a slurry of the sugar derivative (2 mmol) in dry acetone (10 mL) was added TfOH-SiO₂ (80 mg) and the mixture was refluxed for the required time (Table 1 and Table 2). After completion the mixture was filtered and washed with CH₂Cl₂ (20 mL). The combined filtrate was concentrated under vacuum and the residue was purified by column chromatography to give the desired products.

1,2:5,6-Di-*O*-isopropylidene- α -D-glucofuranoside (9): $[\alpha]_{\text{D}}^{25}$ -18.5 (*c* 5.0, H₂O); ¹H NMR (400 MHz, CDCl₃) δ : 5.92 (d, *J* = 3.7 Hz, 1H), 4.51 (d, *J* = 3.7 Hz, 1H), 4.25–4.38 (m, 2H), 4.15 (dd, *J* = 8.7, 6.6 Hz, 1H), 4.04 (dd, *J* = 8.0, 2.9 Hz, 1H), 3.97 (dd, *J* = 8.7, 5.1 Hz, 1H), 1.48 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 112.0, 109.8, 105.4, 85.2, 81.3, 75.1, 73.4, 67.8, 27.0, 26.9, 26.3, 25.3.

2,3:5,6-Di-*O*-isopropylidene- α -D-mannofuranoside (10): $[\alpha]_{\text{D}}^{25}$ +16.5 (*c* 2.5, EtOH); ¹H NMR (400 MHz, CDCl₃) δ : 5.39 (s, 1H), 4.81 (dd, *J* = 7.2, 6.2 Hz, 1H), 4.63 (d, *J* = 6.2 Hz, 1H), 4.38–4.44 (m, 1H), 4.20 (dd, *J* = 7.2, 3.7 Hz, 1H), 4.08 (dd, *J* = 10.2, 6.8 Hz, 1H), 4.03 (dd, *J* = 10.2, 6.1 Hz, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 112.8, 109.3, 101.4, 85.7, 80.3, 79.8, 73.5, 66.7, 26.9, 26.0, 25.3, 24.6.

1,2:3,4-Di-*O*-isopropylidene- α -D-galactopyranoside (11): $[\alpha]_{\text{D}}^{25}$ -59.5 (*c* 1.5, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ : 5.56 (d, *J* = 5.0 Hz, 1H), 4.61 (dd, *J* = 7.9, 1.7 Hz, 1H), 4.36–4.30 (m, 1H), 4.27 (d, *J* = 7.9 Hz, 1H), 3.91–3.81 (m, 2H), 3.73 (t, *J* = 8.2 Hz, 1H), 2.26 (d, *J* = 7.9 Hz, 1H), 1.53 (s, 3H), 1.45 (s, 3H), 1.33 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ : 109.6, 108.8, 96.4, 71.5, 70.8, 70.6, 68.4, 62.1, 26.1, 26.0, 25.0, 24.4.

2,3-*O*-Isopropylidene-*L*-rhamnofuranoside (12): $[\alpha]_{\text{D}}^{25}$ +17.6 (*c* 2.8, H₂O); ¹H NMR (400 MHz, CDCl₃) δ : 5.37 (s, 1H), 4.88–4.77 (m, 1H), 4.58 (dd, *J* = 5.9, 1.0 Hz, 1H), 4.08 – 3.96 (m, 1H), 3.91 (dd, *J* = 6.7, 3.8 Hz, 1H), 3.58 (d, *J* = 1.2 Hz, 1H), 2.79 (d, *J* = 5.7 Hz, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 112.9, 101.1, 85.6, 83.6, 80.3, 66.8, 26.1, 24.7, 20.6.

1,2:3,5-Di-*O*-isopropylidene- α -D-xylofuranoside (13): $[\alpha]_{\text{D}}^{25}$ +12.2 (*c* 1.5, H₂O); ¹H NMR (400 MHz, CDCl₃) δ : 6.01 (d, *J* = 4.0 Hz, 1H), 4.53 (d, *J* = 4.0 Hz, 1H), 4.30 (d, *J* = 2.4 Hz, 1H), 4.08–4.10 (m, 2H), 4.03–4.04 (m, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 111.8, 105.3, 97.6, 84.8, 73.3, 71.7, 60.3, 29.0, 26.9, 26.3, 18.8.

2,3-*O*-Isopropylidene-*D*-ribofuranoside (14): $[\alpha]_{\text{D}}^{25}$ -24.7 (*c* 1.1, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ : 5.42 (s, 1H), 4.85 (d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 4.40 (brs, 1H), 3.55–3.83 (m, 2H), 1.48 (s, 3H), 1.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 112.8, 103.0, 87.9, 86.9, 81.8, 63.7, 26.5,

24.8.

1,2:3,4-Di-*O*-isopropylidene- α -L-arabinopyranoside (15): $[\alpha]_{\text{D}}^{25} +6.2$ (*c* 1.5, H₂O); ¹H NMR (400 MHz, CDCl₃) δ : 5.49 (d, *J* = 5.0 Hz, 1H), 4.55 (dd, *J* = 7.9, 1.9 Hz, 1H), 4.31–4.26 (m, 1H), 4.21 (d, *J* = 7.9 Hz, 1H), 3.82 (dd, *J* = 12.9, 1.7 Hz, 1H), 3.65 (d, *J* = 12.9 Hz, 1H), 1.52 (s, 3H), 1.47 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 115.6, 115.1, 102.6, 84.1, 83.8, 83.5, 66.8, 32.7, 31.6, 30.9.

1,3:5,7-Di-*O*-isopropylidene-L-sorbofuranoside (16): $[\alpha]_{\text{D}}^{25} -146.5$ (*c* 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ : 4.57 (dd, *J* = 7.7, 2.9 Hz, 1H), 4.32 (dd, *J* = 2.9 Hz, 1H), 4.21 (ddd, *J* = 7.7, 2.0, 0.8 Hz, 1H), 3.88 (dd, *J* = 13.0, 2.0 Hz, 1H), 3.79 (dd, *J* = 13.0, 0.8 Hz, 1H), 3.66 (d, *J* = 10.7 Hz, 1H), 3.62 (d, *J* = 10.7 Hz, 1H), 2.28 (brs, 1H), 1.38 (s, 3H), 1.35 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 113.0, 110.6, 96.2, 85.6, 72.0, 70.9, 62.2, 59.0, 27.6, 26.1, 25.2, 17.3.

***p*-Tolyl 3,4-*O*-isopropylidene-1-thio- α -L-arabinopyranoside (27):** $[\alpha]_{\text{D}}^{25} +23.1$ (*c* 1.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, *J* = 8.1 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.43 (d, *J* = 9.4 Hz, 1H), 4.27–4.16 (m, 2H), 4.07 (t, *J* = 6.1 Hz, 1H), 3.75 (dd, *J* = 13.1, 2.8 Hz, 1H), 3.59 (ddd, *J* = 9.4, 7.0, 2.5 Hz, 1H), 2.66 (d, *J* = 2.5 Hz, 1H), 2.30 (s, 3H), 1.43 (s, 3H), 1.33 (s, 3H); ¹³C-NMR (150 MHz, CDCl₃): 138.5, 133.2, 129.7, 128.1, 110.0, 88.6, 77.9, 72.9, 71.3, 65.8, 27.8, 26.1, 21.0.

***p*-Tolyl 2-amino-4,6-*O*-isopropylidene-2-*N*,3-*O*-carbonyl-2-deoxy-1-thio- β -D-glucopyranoside (28):** $[\alpha]_{\text{D}}^{25} -55.1$ (*c* 1.60, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.37 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 5.33 (s, 1H), 4.71 (d, *J* = 9.8 Hz, 1H), 4.19 (t, *J* = 10.4 Hz, 1H), 3.96 (dd, *J* = 15.0, 7.2 Hz, 2H), 3.86 (t, *J* = 10.5 Hz, 1H), 3.48–3.28 (m, 2H), 2.34 (s, 3H), 1.49 (s, 3H), 1.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 158.7, 139.7, 134.2, 130.4, 126.2, 100.3, 85.7, 81.4, 74.5, 71.9, 62.2, 59.8, 29.0, 21.4, 19.4.

***p*-Tolyl 2,3-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-1-thio- α -D-mannopyranoside (29):** $[\alpha]_{\text{D}}^{25} -16.5$ (*c* 1.0, CHCl₃); ¹H NMR: (400 MHz, CDCl₃): δ 7.64–7.69 (t, 4H), 7.34–7.45 (m, 6H), 7.27–7.29 (d, *J* = 8.3 Hz, 2H), 6.99–7.01 (d, *J* = 7.9 Hz, 2H), 5.67 (s, 1H, H-1), 4.34 (d, *J* = 5.6 Hz, 1H), 4.19 (t, 1H), 4.09 (dd, *J* = 4.7, 9.9 Hz, 1H), 3.96 (t, 1H), 3.82–3.89 (m, 2H), 2.92 (d, *J* = 2.4 Hz, 1H), 2.29 (s, 3H), 1.54 (s, 3H), 1.38 (s, 3H), 1.05 (s, 9H); ¹³C NMR: (100 MHz, CDCl₃): δ 137.7, 135.6, 135.5, 132.8, 132.5, 129.8, 129.7, 129.2, 127.8, 127.7, 84.2, 77.9, 75.9, 71.6, 69.7, 64.5, 28.0, 26.7, 26.3, 21.1, 19.1; HRMS (ESI): *m/z* calcd for C₃₂H₄₀O₅SSiNa: [M + Na]⁺ 587.2263, Found 587.2271.

***p*-Tolyl 3,4-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-1-thio- β -D-galactopyranoside (30):** $[\alpha]_{\text{D}}^{25} -14.1$ (*c* 1.0, CHCl₃); ¹H NMR: (400 MHz, CDCl₃): δ 7.71–7.73 (m, 4H), 7.36–7.45 (m, 8H), 7.07–7.09 (d, *J* = 7.9 Hz, 2H), 4.40 (d, *J* = 10.3 Hz, 1H), 4.28 (dd, *J* = 1.5, 5.1 Hz, 1H), 4.08 (t, 1H), 3.97 (m, 2H), 3.91 (t, 1H), 3.52–3.57 (m, 1H), 2.55 (d, *J* = 2.0 Hz, 1H), 2.32 (s, 3H), 1.43 (s, 3H), 1.35 (s, 3H), 1.07 (s, 9H); ¹³C NMR: (100 MHz, CDCl₃): δ 138.1, 135.6, 133.2, 132.8, 129.7, 129.6, 128.3, 127.7, 127.6, 78.9,

73.2, 71.5, 62.8, 28.1, 26.7, 26.2, 21.1, 19.1; HRMS (ESI): m/z calcd for $C_{32}H_{40}O_5SSiNa$: $[M + Na]^+$ 587.2263, Found 587.2275.

***p*-Methoxyphenyl 4,6-*O*-isopropylidene-2-deoxy-2-phthalimido- β -D-glucopyranoside (31):** $[\alpha]_D^{25}$ +3.1 (*c* 1.0, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ : 7.82 (s, 2H), 7.69 (d, $J = 3.3$ Hz, 2H), 6.80 (d, $J = 8.0$ Hz, 2H), 6.70 (d, $J = 8.3$ Hz, 2H), 5.72 (d, $J = 8.2$ Hz, 1H), 4.49 (t, $J = 9.3$ Hz, 1H), 4.41 (t, $J = 9.3$ Hz, 1H), 3.96 (dd, $J = 10.4, 4.9$ Hz, 1H), 3.84 (t, $J = 10.4$ Hz, 1H), 3.73–3.65 (m, 1H), 3.68 (s, 3H), 3.51 (dd, $J = 14.6, 9.4$ Hz, 1H), 2.76 (s, 1H), 1.51 (s, 3H), 1.39 (s, 3H).

***p*-Methoxyphenyl 2,3-*O*-isopropylidene- α -L-rhamnopyranoside (32):** $[\alpha]_D^{25}$ -49.7 (*c* 1.1, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ : 6.97–7.02 (m, 2H), 6.81–6.86 (m, 2H), 5.60 (s, 1H), 4.35 (d, $J = 5.8$ Hz, 1H), 4.22 (dd, $J = 5.8, 7.2$ Hz, 1H), 3.82 (m, 1H), 3.78 (s, 3H), 3.46 (dd, $J = 7.4$ Hz, 1H), 2.79 (bs, 1H), 1.56 (s, 6H), 1.40 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.0, 150.4, 117.4, 114.2, 99.3, 72.5, 70.8, 70.7, 69.0, 54.6, 16.6.

***p*-Tolyl 2,3-*O*-isopropylidene-1-thio- α -L-rhamnopyranoside (33):** $[\alpha]_D^{25}$ +81.1 (*c* 1.1, $CHCl_3$); 1H NMR (400 MHz, $CDCl_3$) δ : 7.42 (d, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 7.9$ Hz, 2H), 4.94 (d, $J = 1.9$ Hz, 1H), 4.39 (dd, $J = 5.4, 1.9$ Hz, 1H), 4.02–3.88 (m, 1H), 3.47 (t, $J = 8.3$ Hz, 1H), 3.22 (dd, $J = 9.6, 6.1$ Hz, 1H), 2.87 (br, 1H), 2.31 (s, 3H), 1.56 (s, 3H), 1.39 (s, 3H), 1.33 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 137.8, 132.5, 129.8, 129.7, 129.4, 109.6, 83.9, 78.3, 76.4, 75.1, 66.7, 28.1, 26.3, 21.1, 17.0.

***p*-Tolyl 2,3-*O*-isopropylidene-1-thio- β -L-rhamnopyranoside (34):** $[\alpha]_D^{25}$ +16.5 (*c* 1.0, $CHCl_3$); 1H NMR: (400 MHz, $CDCl_3$): δ 7.43–7.45 (d, $J = 7.8$ Hz, 2H), 7.11–7.13 (d, $J = 7.8$ Hz, 2H), 4.95 (d, $J = 1.6$ Hz, 1H), 4.41 (dd, $J = 2.0, 5.5$ Hz, 1H), 3.99 (t, 1H), 3.48 (t, 1H), 3.22–3.26 (m, 1H), 2.89 (br, 1H), 1.58 (s, 3H), 1.40 (s, 3H), 1.35 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 137.7, 131.6, 131.1, 110.6, 84.2, 80.2, 76.3, 74.6, 28.1, 26.3, 21.1, 17.6; HRMS (ESI): m/z calcd for $C_{16}H_{22}O_4SNa$: $[M + Na]^+$ 333.1136, Found 333.1125.

Isopropyl 2,3-*O*-isopropylidene-1-thio- β -L-rhamnopyranoside (35): $[\alpha]_D^{25}$ +116.0 (*c* 1.0, $CHCl_3$); 1H NMR: (400 MHz, $CDCl_3$): δ 4.87 (d, $J = 1.6$ Hz, 1H), 4.27 (dd, $J = 2.0, 3.5$ Hz, 1H), 3.98 (t, 1H), 3.44–3.49 (m, 1H), 3.18–3.28 (m, 2H), 2.29 (d, $J = 2.7$ Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.31 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 110.5, 80.2, 79.8, 74.9, 74.6, 35.4, 28.1, 26.3, 23.5, 23.4, 17.6; HRMS (ESI): m/z calcd for $C_{12}H_{22}O_4SNa$: $[M + Na]^+$ 285.1136, Found 285.1147.

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REFERENCES

1. T. W. Green and P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 4th ed.; Wiley & Sons: New York, 2007, 306.
2. D. M. Clode, [Chem. Rev., 1979, 79, 491](#).
3. (a) T. Yamanoi, Y. Oda, S. Matsuda, I. Yamazaki, K. Matsumura, K. Katsuraya, M. Watanabe, and T. Inazu, [Tetrahedron, 2006, 62, 10383](#); (b) N. M. Xavier and A. P. Rauter, [Carbohydr. Res., 2008, 343, 1523](#).
4. M. A. Alam and Y. D. Vankar, [Tetrahedron Lett., 2008, 49, 5534](#).
5. J. Behling, P. Farid, J. R. Medich, M. G. Scaros, and M. Prunier, [Synth. Commun., 1991, 21, 1383](#).
6. G. Pattenden, M. A. González, P. B. Little, D. S. Millan, A. T. Plowright, J. A. Tornos, and T. Ye, [Org. Biomol. Chem., 2003, 1, 4173](#).
7. V. K. Yadav and D. Agrawal, [Chem. Commun., 2007, 48, 5232](#).
8. A. Goi, T. Bruzzese, A. F. Notarianni, M. Riva, and A. Ronchini, *Arzneim.-Forsch./ Drug Res.*, 1979, **29**, 986.
9. (a) P. P. Singh, M. M. Gharia, F. Dasgupta, and H. C. Srivastava, [Tetrahedron Lett., 1977, 18, 439](#); (b) K. P. R. Kartha, [Tetrahedron Lett., 1986, 27, 3415](#); (c) A. P. Rauter, F. Ramôa-Ribeiro, A. C. Fernandes, and J. A. Figueiredo, [Tetrahedron, 1995, 51, 6529](#); (d) S. Pedatella, A. Guaragna, D. D'Alonzo, M. DeNisco, and G. Palumbo, *Synthesis*, 2006, 305; (e) V. K. Rajput and B. Mukhopadhyay, [Tetrahedron Lett., 2006, 47, 5939](#); (f) C. C. Lin, M. D. Jan, S. S. Weng, C. C. Lin, and C. T. Chen, [Carbohydr. Res., 2006, 341, 1948](#); (g) A. T. Khan and M. M. Khan, [Carbohydr. Res., 2010, 345, 154](#); (h) A. T. Khan, M. M. Khan, and A. Adhikary, [Carbohydr. Res., 2011, 346, 673](#); (i) B. Lal, R. M. Gidwani, and R. H. Rupp, *Synthesis*, 1989, 711; (j) E. Manzo, G. Barone, and M. Parrilli, *Synlett*, 2000, 887; (k) C. R. Schmid, J. D. Bryant, M. Dowlatzedah, J. L. Phillips, D. E. Prather, R. D. Schautz, N. L. Sear, and C. S. Vianco, *J. Org. Chem.*, 1991, **56**, 4056; (l) J. G. Shim, H. Nakamura, and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 8470; (m) K. W. Hering, K. Karaveg, K. W. Moremen, and W. H. Pearson, [J. Org. Chem., 2005, 70, 9892](#).
10. (a) Y. Du, G. Wei, S. Cheng, Y. Hua, and R. J. Linhardt, [Tetrahedron Lett., 2006, 47, 307](#); (b) B. Mukhopadhyay, S. V. Maurer, N. Rudolph, R. van Well, D. A. Russell, and R. A. Field, [J. Org. Chem., 2005, 70, 9059](#); (c) B. Mukhopadhyay, D. A. Russell, and R. A. Field, [Carbohydr. Res., 2005, 340, 1075](#); (d) B. Mukhopadhyay, B. Collet, and R. A. Field, [Tetrahedron Lett., 2005, 46, 5923](#); (e) S. Dasgupta, K. Pramanik, and B. Mukhopadhyay, [Tetrahedron, 2007, 63, 12310](#); (f) S. Dasgupta and B. Mukhopadhyay, [Eur. J. Org. Chem., 2008, 5770](#); (g) P. R. Verma and B. Mukhopadhyay, [Carbohydr. Res., 2010, 345, 432](#); (h) P. Verma, R. Raj, B. Roy, and B. Mukhopadhyay, [Tetrahedron:Asymmetry, 2010, 21, 2413](#); (i) A. Agarwal, S. Rani, and Y. D. Vankar,

- J. Org. Chem.*, 2004, **69**, 6137; (j) A. K. Misra, P. Tiwari, and G. Agnihotri, *Synthesis*, 2005, **260**;
- (k) N. Iranpoor, H. Firouzabadi, A. Jamalian, and F. Kazemi, *Tetrahedron*, 2005, **61**, 5699; (l) N. Iranpoor, H. Firouzabadi, and A. Jamalian, *Synlett*, 2005, **1447**; (m) K. S. Kim, Y. H. Song, B. H. Lee, and C. S. Hahn, *J. Org. Chem.*, 1986, **51**, 404; (n) Z. Cohen, E. Keinan, Y. Mazur, and A. Ulman, *J. Org. Chem.*, 1976, **41**, 2651; (o) T. Tatsumi, M. Nakamura, and H. Tominaga, *Chem. Lett.*, 1989, **18**, 419.
11. (a) S. Q. Yan, M. X. Xie, Y. J. Wang, Q. Xiao, N. Ding, and Y. X. Li, *Tetrahedron*, 2020, **76**, 130950; (b) S. Q. Yan, N. Ding, W. Zhang, P. Wang, Y. X. Li, and M. Li, *J. Carbohydr. Chem.*, 2012, **31**, 571; (c) S. Q. Yan, W. Guo, W. S. Wang, and W. Zhang, *Chin. J. Org. Chem.*, 2019, **39**, 1469; (d) S. Q. Yan, S. W. He, S. Y. Li, Z. Q. Hu, and W. Zhang, *Heterocycles*, 2020, **100**, 547; (e) S. Q. Yan, D. Q. Dong, C. W. Xie, W. S. Wang, and Z. L. Wang, *Chin. J. Org. Chem.*, 2019, **39**, 2560; (f) L. S. Wu, S. Q. Yan, W. S. Wang, and Y. T. Li, *Res. Chem. Intermed.*, 2020, **46**, 4311.
12. (a) S. Q. Yan, N. Ding, W. Zhang, P. Wang, Y. X. Li, and M. Li, *Carbohydr. Res.*, 2012, **354**, 6; (b) Y. X. Chun, S. Q. Yan, X. P. Li, N. Ding, W. Zhang, P. Wang, M. Li, and Y. X. Li, *Tetrahedron Lett.*, 2011, **52**, 6196; (c) S. Q. Yan, N. Ding, W. Zhang, and Y. X. Li, *Chin. J. Org. Chem.*, 2012, **32**, 2081; (d) J. L. Xiong, S. Q. Yan, N. Ding, W. Zhang, and Y. X. Li, *J. Carbohydr. Chem.*, 2013, **32**, 184.
13. R. V. Stick, *Carbohydrates: The Sweet Molecules of Life*, Academic Press: New York, 2001, 55.
14. D. Zheng, L. Zhou, Y. Guan, X. Chen, W. Zhou, X. Chen, and P. Lei, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5439.
15. T. M. Slaghek, Y. Nakahara, T. Ogawa, J. P. Kamerling, and J. F. G. Vliegthart, *Carbohydr. Res.*, 1994, **255**, 61.
16. X. Cai, G. Zong, Y. Xu, J. Zhang, X. Liang, and D. Wang, *Carbohydr. Res.*, 2010, **345**, 1230.
17. S. Q. Yan, X. M. Liang, P. Y. Diao, Y. Yang, J. J. Zhang, D. Q. Wang, and F. Z. Kong, *Carbohydr. Res.*, 2008, **343**, 3107.