HETEROCYCLES, Vol.104 , No. 5, 2022, pp. 969 - 978. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 5th January, 2022, Accepted, 2nd February, 2022, Published online, 7th February, 2022
DOI: 10.3987/COM-22-14621

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

Lisha Wu,[1] Shuying Li,[2] Wei Guo,[2] and Shiqiang Yan[1,2]*

[1]Weihai Ocean Vocational College, Weihai, 264300, China; [2]Shandong Dyne Marine Biopharmaceutical Limited Corporation, Weihai, 264300, China; E-mail: ysqiang@fudan.edu.cn.

Abstract – Triflic acid immobilized on silica gel has been identified as an excellent catalyst for the chemoselective *O*-isopropylidenation 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 chemistry[3] 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*-goniofufurone[7] 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*-isopropylidenation 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*-isopropylidenation 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-SiO_2).

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*-isopropylidenation of free sugars and functionalized carbohydrates with acetone catalyzed by TfOH-SiO_2 (Figure 1).

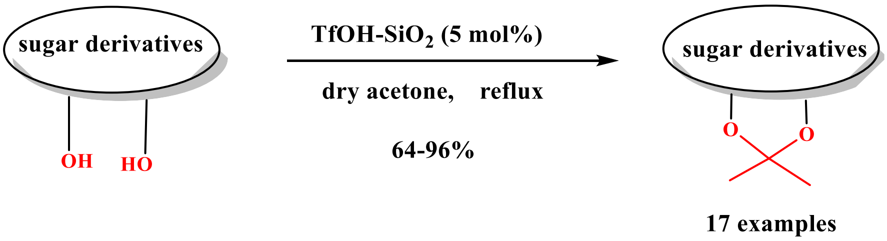
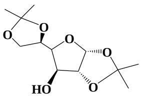
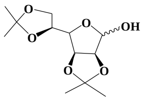
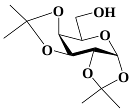
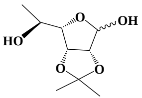
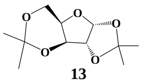
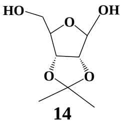
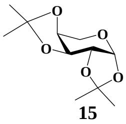
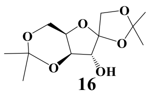


Figure 1. *O*-Isopropylidenation of sugar derivates

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-SiO_2. 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-SiO_2 under N_2 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*-isopropylidenation product within 5 min in 96% yield. Encouraged by these results, D-mannose was kept for *O*-isopropylidenation 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 isopropylidenation 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-SiO$_2$[a]

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

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

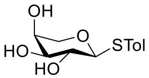
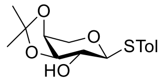
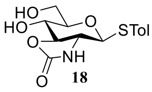
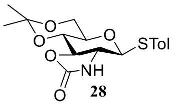
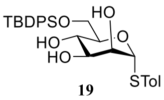
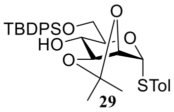
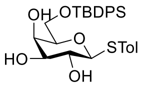
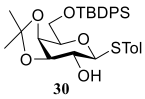
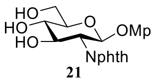
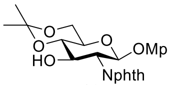
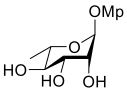
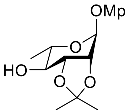
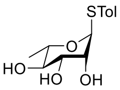
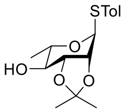
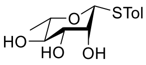
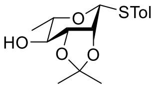
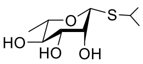
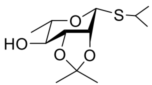
[b] Analytical datas were consistent with known products from the literature.

[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-SiO$_2$ (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*-isopropylidenation 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-SiO_2[a]

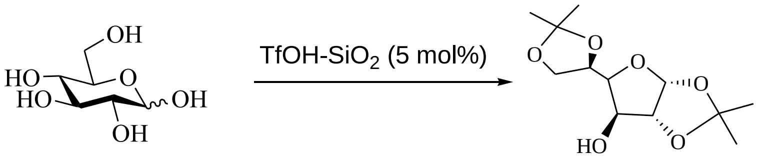
Entry	Substrate	Product[b]	Time (min)	Yield (%)[c]	Ref.
1	 **17**	 **27**	30	75	14
2	 **18**	 **28**	30	64	
3	 **19**	 **29**	10	87	
4	 **20**	 **30**	30	81	
5	 **21**	 **31**	10	73	15
6	 **22**	 **32**	10	88	16
7	 **23**	 **33**	10	86	17
8	 **24**	 **34**	10	89	
9	 **25**	 **35**	10	81	

[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-SiO_2 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*-isopropylidenation of sugar derivatives had been demonstrated, which involves TfOH-SiO_2 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 (^{1}H NMR) spectra are reported in parts per million relative to the signal residual ($CDCl_3$ at 7.26 ppm) or TMS. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million relative to the center line of the $CDCl_3$ 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-SiO_2

To a suspension of silica gel (5.0 g, mesh no.300-400) in anhydrous Et_2O (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 Et_2O 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-SiO_2 (2 mmol/g) as a free-flowing powder.

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

To a slurry of the sugar derivative (2 mmol) in dry acetone (10 mL) was added TfOH-SiO_2 (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 CH_2Cl_2 (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): $[\alpha]_D^{25}$ -18.5 (*c* 5.0, H_2O); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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): $[\alpha]_D^{25}$ +16.5 (*c* 2.5, EtOH); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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): $[\alpha]_D^{25}$ -59.5 (*c* 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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): $[\alpha]_D^{25}$ +17.6 (*c* 2.8, H_2O); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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): $[\alpha]_D^{25}$ +12.2 (*c* 1.5, H_2O); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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): $[\alpha]_D^{25}$ -24.7 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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): $[\alpha]_D^{25}$ +6.2 (*c* 1.5, H_2O); ^{1}H NMR (400 MHz, $CDCl_3$) *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); ^{13}C NMR (100 MHz, $CDCl_3$) *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): $[\alpha]_D^{25}$ -146.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *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) ; ^{13}C NMR (100 MHz, $CDCl_3$) *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):** $[\alpha]_D^{25}$ +23.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *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); ^{13}C-NMR (150 MHz, $CDCl_3$): 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):** $[\alpha]_D^{25}$ -55.1 (*c* 1.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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*-butyldiphenylsiyl-1-thio-α-D-mannopyranoside (29):** $[\alpha]_D^{25}$ -16.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$): *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); ^{13}C NMR: (100 MHz, $CDCl_3$): *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 $C_{32}H_{40}O_5SSiNa$: $[M + Na]^+$ 587.2263, Found 587.2271.

***p*-Tolyl 3,4-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsiyl-1-thio-*β*-D-galactopyranoside (30):** $[\alpha]_D^{25}$ -14.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR: (400 MHz, $CDCl_3$): *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); ^{13}C NMR: (100 MHz, $CDCl_3$): *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); ^{1}H 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, $CHCl_3$); ^{1}H 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* = 5.8Hz, 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, $CHCl_3$); ^{1}H 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, $CHCl_3$); ^{1}H 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, $CHCl_3$); ^{1}H 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.

ACKNOWLEDGEMENTS

We gratefully acknowledge the financial support from Natural Science Foundation of Shandong Province (Grant No. ZR2020KH002) and the National Major Scientific and Technological Special Project for “Significant New Drugs Development” (2018ZX09721003-008-026).

REFERENCES

1. T. W. Green and P. G. M. Wuts, *Protecting Groups in Organic Synthesi*s, 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. Vliegenthart, *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.