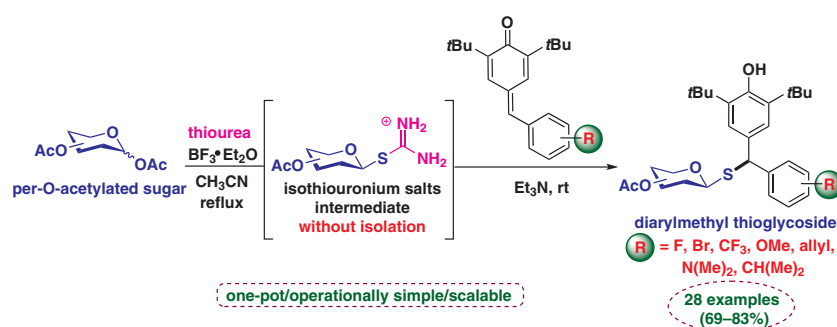


An Efficient One-Pot Protocol for Direct Access to Diarylmethyl Thioglycosides with *para*-Quinone Methides via *S*-Glycosyl Isothiuronium Salts

Atul Dubey^aPintu Kumar Mandal^{*a,b}

^a Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow, 226 031, India
pintuchem06@gmail.com
pk.mandal@cdri.res.in

^b Academy of Scientific and Innovative Research, New Delhi-11000, India



Received: 15.04.2020

Accepted after revision: 16.06.2020

Published online: 09.07.2020

DOI: 10.1055/s-0040-1707189; Art ID: st-2020-k0212-l

Abstract An efficient one-pot protocol has been developed for the direct preparation of diarylmethyl thioglycosides starting from per-O-acetylated sugars via glycosyl isothiuronium salts. The one-pot reaction conditions involve rapid conversion of the per-O-acetylated sugar with thiourea in the presence of boron trifluoride etherate as catalyst to give the corresponding glycosyl isothiuronium salt, which is subsequently treated with a *para*-quinone methide in the presence of a base to give the a diarylmethyl thioglycoside in excellent yield.

Keywords diaryl thioglycosides, one-pot reaction, thioureas, *para*-quinone methides

Sulfur-containing functionalized carbohydrates are a remarkably important class of compounds that find widespread use as pharmaceuticals.¹ Amongst them, thioglycosides are an important class of sugar derivatives that are considered as useful simulants of biologically relevant O-glycosides, because they are known to resist enzymatic hydrolysis² and can consequently be used as enzyme inhibitors in various biochemical studies.³

S-Glycosides are valuable glycomimetic derivatives that find a wide range of applications in pharmaceutical science.^{1a,c,4} Protected thioglycosides are often used in synthetic carbohydrate chemistry as versatile glycosyl donors⁵ because of their stability during various chemical transformations and the ease with which they can be converted into a variety of other functionalities.⁶ In addition, these derivatives serve as versatile intermediates in organic synthesis.⁷

Among the several glycosyl donors, thioglycosides are considered to be versatile intermediates because of their high degree of stability in many organic reactions. These derivatives are routinely used as glycosyl donor building blocks in producing a variety of glycosidic linkages;^{7a,8}

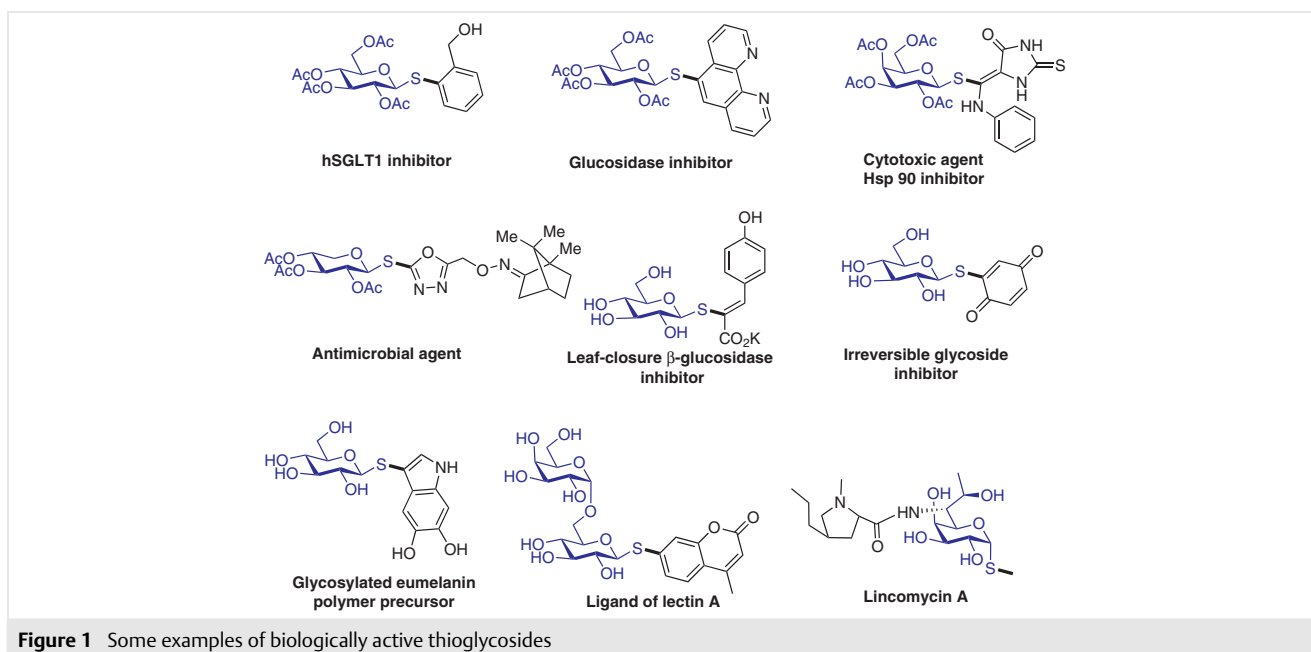
moreover, they are also found in various drugs, natural products, and medicinally active agents,⁹ including an hSGLT1 inhibitor, a ligand of lectin A, a cytotoxic Hsp90 inhibitor, inhibitors of galactosidase and glycosidase,¹⁰ and various antimicrobial agents (Figure 1). Interestingly, another representative natural product bearing a C–S glycosidic bond is the clinically used antibiotic lincomycin A¹¹ (Figure 1). These derivatives clearly hold great potential in medicinal chemistry as well as in carbohydrate chemistry. Therefore, the development of highly efficient synthetic methods to access functionalized sulfur-containing carbohydrates is particularly appealing.

Thioglycoside derivatives are commonly prepared treating per-O-acetylated glycosyl precursors with a thiophenol in the presence of a Lewis acid,¹² by substituting the halogen atom of an acetohaloglycoside with a thiolate anion,¹³ or by a reaction of a 1-thioglycopyranose with an alkyl halide (Scheme 1a).¹⁴

An alternative route to access (het)arylthioglycosides involves the use of thioglycosides as nucleophiles under transition-metal catalysis (Scheme 1b).^{15,16} These derivatives have also been prepared from carbohydrate sulfenates¹⁷ or by free-radical addition of 1-thiosugars to alkenes.¹⁸

Despite these significant recent improvements, it is surprising to find that there have been no reports of the preparation of diarylmethyl thioglycosides from *para*-quinone methides (*p*-QMs) through the generation in situ of glycosyl isothiuronium salts from per-O-acetylated sugars (Scheme 1c).

In recent years, *p*-QMs have been explored extensively because of their unique ability to act as powerful Michael acceptors with a variety of nucleophiles to generate highly functionalized diarylmethane derivatives.^{19,20} Anand's group^{19d,21} and others²² have reported that a diversity of nucleophiles, including cyanides, malonates, glycine Schiff bases, dicyanoolefins, the Seyferth–Gilbert reagent, allenic

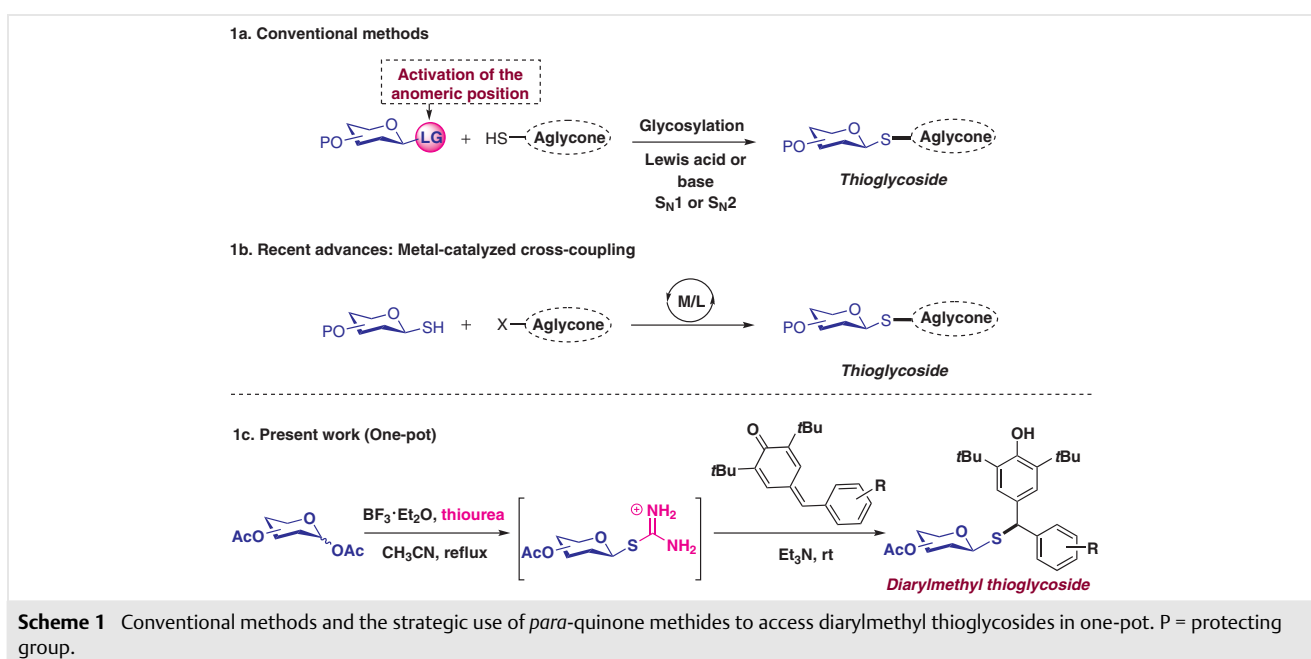


esters, styrenes, and β -naphthols, can be used in 1,6-conjugate additions to *p*-QMs.

Despite these tremendous achievements, the development of new nucleophiles, such as various *S*-glycosides, for the 1,6-conjugate addition of *p*-QMs is still in great demand. The chemistry of *p*-QMs is well explored in organic synthesis and physical organic chemistry, but less so in carbohydrate chemistry. Keeping in mind the high reactivity of *p*-QMs toward nucleophiles, we surmised that these units

might serve as versatile diarylmethylating agent for the synthesis of diarylmethane *S*-glycosides.

The direct one-pot conversion of glycosyl isothiuronium salts derivatives into glycosyl thiol derivatives under phase-transfer conditions is a well-established process.²³ Therefore, glycosyl isothiuronium salts might be used for 1,6-conjugate addition of *p*-QMs in the presence of base to generate glycosyl thiols in situ. However, to the best of our knowledge, there are no reports that describe the synthesis



of diarylmethyl *S*-glycosides by nucleophilic addition of glycosyl thiols generate in situ with *p*-QMs. With this method diarylmethyl thioglycosides could be synthesized under mild conditions without the use of malodorous and toxic mercaptans such as alkyl or aryl thiols or expensive alkyl or aryl thiotrimethylsilanes.

Generally, the most-often-employed approaches involve cleavage of a glycosyl isothiuronium salt by treatment with potassium carbonate and sodium hydrogen sulfite or metabisulfite in water–acetone media, followed by reaction of the resulting acetylated 1-thioglycose with an alkyl or aryl halide.²⁴ In most cases, the presence of water in the reaction mixture does not permit the use of water-sensitive alkylation and acylation agents. Consequently, the 1-thio-sugar formed has to be isolated before alkylation, making the approach more laborious. The synthesis of alkyl- or arylthioglycosides and glycosyl thioesters via isothiuronium salts by using a base at room temperature has been recently described.²⁵

We attempted to develop a one-pot reaction protocol for the direct preparation of diarylmethyl thioglycoside from per-*O*-acetylated sugars via glycosyl isothiuronium derivatives through the strategic use of *p*-QMs in the presence of alkylamines in acetonitrile. Reports in the literature suggest that alkylamines are stronger bases but weaker nucleophiles than thiols; therefore, by converting the isothiuronium salts into more-nucleophilic thiolate anions, they should react readily with thioaldoses.

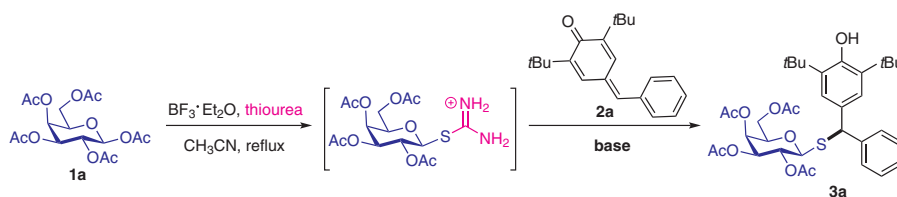
To standardize the reaction protocol, 2,3,4,6-tetra-*O*-acetyl- β -D-galactopyranose (**1**; 1.0 mmol) was treated with a mixture of thiourea (1.1 mmol) and boron trifluoride

etherate (1.1 mmol) in acetonitrile, and the mixture was heated to 80 °C for 30 minutes. TLC showed complete conversion of the sugar per-*O*-acetate into slower-moving *S*-glycosyl isothiuronium salts. The mixture was then cooled to room temperature, and the *p*-QM derivative **2a** (1.1 mmol) and excess alkylamine were added sequentially. The mixture was then stirred at room temperature for a further one hour. Various organic bases, such as mono-, di-, or trialkylamines, were found to be suitable for use in synthesis of the thioglycoside by the described procedure (Table 1). In the case of triethylamine, the reaction proceeded smoothly at room temperature to give the diarylmethyl *S*-glycoside **3a**²⁶ as a diastereomeric mixture (dr 1:1) in 83% yield (Table 1, entry 1); no improvement in the yield of **3a** was observed in the presence of diethylamine, DIPEA, DBU, or DABCO (Table 1, entries 2–6), even with longer reaction times. Less-basic amines, for example pyridine, were unable to cleave the glycosyl isothiuronium salt (entry 7).

After completion of the reaction, as monitored by TLC (hexane: EtOAc 1:1), the solvent was evaporated and the resulting syrup was diluted with CH₂Cl₂ and washed with water, which on evaporation gave the pure diaryl thioglycoside **3a** in 83% yield as a diastereomeric mixture in a one-pot process starting from the per-*O*-acetylated sugar.

After identifying the optimal one-pot conditions for this transformation (Table 1, entry 1), we examined the substrate scope of this transformation by using a wide range of *p*-QMs **2a–n**²⁷ bearing various substituents on the phenyl ring together with various easily accessible per-*O*-acetylated sugars (Table 2). Most of the *p*-QMs employed in the re-

Table 1 One-Pot Protocol for the Synthesis of Diarylmethyl Thioglycoside **3a**, and Screening of Various Amines^a



Entry	Base	Equiv	Time (h)	Yield ^b (%)
1	Et ₃ N	2	2	83
2	DIPEA	2	2	77
3	DBU	2	2	69
4	DABCO	2	2	68
5	MeNH ₂	2	2	68
6	Et ₂ NH	2	2	78
7	py	2	2	ND ^c
8	Et ₃ N	4	6	84

^a Reaction conditions: **1a** (1.0 mmol), thiourea (1.1 mmol), BF₃·Et₂O (1.1 mmol), MeCN (5 mL), 80 °C then **2a** (1.1 mmol), base (2 mmol), rt.

^b Isolated yield after silica gel chromatography.

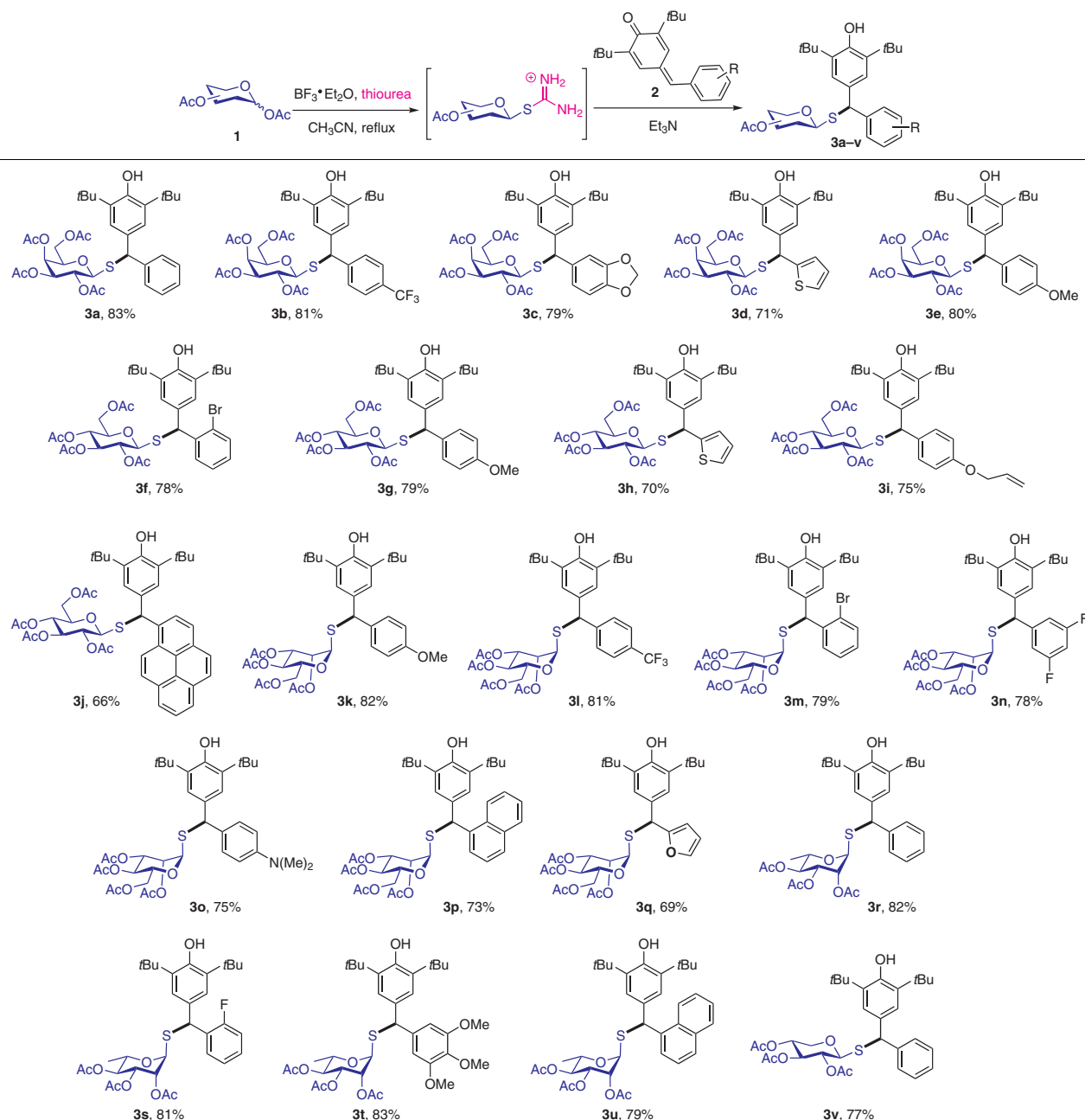
^c ND = not detected.

action with various per-*O*-acetylated sugars delivered the corresponding diarylmethyl thioglycoside **3a–v** in moderate to good yields (69–83%) in short reaction times.

To elaborate the substrate scope further, this one-pot method was extended to 1,6-conjugate addition of several per-*O*-acetylated disaccharide moieties with wide range of

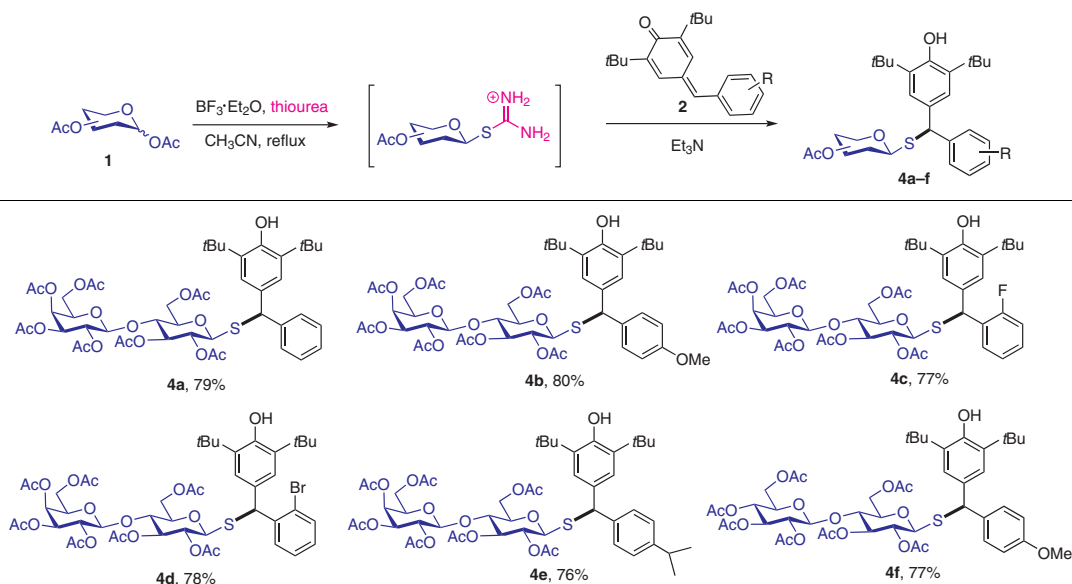
p-QMs **2** to give corresponding desired diarylmethyl thioglycosides **4a–f**²⁸ (Table 3). The reaction conditions were successfully applied to the preparation of diarylthioglycosides from *D*- or *L*-sugars as well as from disaccharides. The reaction proceeded smoothly at room temperature affording the products in high yields. A series of thioglycosides of

Table 2 Substrate Scope of a Diverse Range of *p*-QMs **2a–n** and Various Per-*O*-acetylated Sugars^a



^a Reaction conditions: **1** (1.0 mmol), thiourea (1.1 mmol), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.1 mmol), MeCN (5 mL), 80 °C; then **2** (1.1 mmol), Et_3N (2 mmol), rt.

^b Isolated yield after silica gel chromatography (dr ≈ 1:1).

Table 3 Substrate Scope of a Diverse Range of *p*-QMs with Various Per-*O*-acetylated Disaccharides^a

^a Reaction conditions: **1** (1.0 mmol), thiourea (1.1 mmol), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.1 mmol), MeCN (5 mL), 80 °C; then **2** (1.1 mmol), Et_3N (2 mmol), rt.

^b Isolated yield after silica gel chromatography (dr ≈ 1:1).

mono- and disaccharides were prepared by using this one-pot procedure in short reaction times not exceeding two hours.

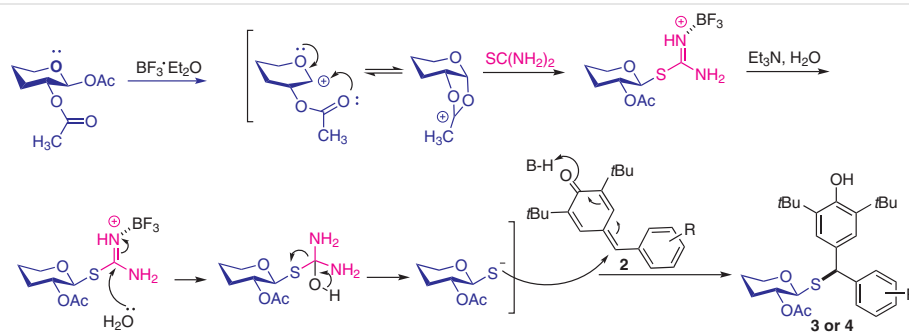
Based on the above results and previously reports,²⁹ a plausible mechanism for the formation of **3** and **4** is proposed (Scheme 2). The reaction is probably initiated by BF_3 -induced formation of the 1,2-acyloxonium ion as an intermediate that reacts with nucleophiles in only one possible way, leading exclusively to 1,2-*trans*-substitution products. The isothiurea intermediates obtained in 30 minutes without isolation can be directly converted into thioglycosides by 1,6-conjugate addition under basic conditions.

In conclusion, we have demonstrated the first strategic use of *p*-QMs to access diarylmethyl *S*-glycosides from the per-*O*-acetyl sugars through sequential thioglycosidation

via *S*-glycosyl isothiuronium salts. The reaction conditions are operationally simple, mild, reproducible, high-yielding, and can be scaled up for large-scale preparation. We therefore believe that this method will open a route to novel diarylmethyl thioglycosides as a novel and largely unexplored structural class of glycomimetic compounds.

Funding Information

A. D. thanks UGC, New Delhi for providing Research Fellowship. The author gratefully acknowledges financial support from DST-SERB, New Delhi (Scheme No. EMR/2017/001791) and SAIF Division of CSIR-CDRI for providing the spectroscopic and analytical data. CDRI communication no. 10081.

**Scheme 2** Plausible mechanism of the reaction.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0040-1707189>.

References and Notes

- (1) (a) Witczak, Z. J. *Curr. Med. Chem.* **1999**, *6*, 165. (b) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160. (c) Samuni-Blank, M.; Izhaki, I.; Dearing, M. D.; Gerchman, Y.; Trabelcy, B.; Karasov, A. L. W. H.; Arad, Z. *Curr. Biol.* **2012**, *22*, 1218.
- (2) (a) Rye, C. S.; Withers, S. G. *Carbohydr. Res.* **2004**, *339*, 699. (b) Metaferia, B. B.; Fetterolf, B. J.; Shazad-ul-Hussan, S.; Moravec, M.; Smith, J. A.; Ray, S.; Gutierrez-Lugo, M.-T.; Bewley, C. A. *J. Med. Chem.* **2007**, *50*, 6326.
- (3) (a) Brajeswar, P.; Walter, K. *Carbohydr. Res.* **1984**, *126*, 27. (b) Kuhn, C. S.; Lehmann, J.; Steck, J. *Tetrahedron* **1990**, *46*, 3129. (c) Appar, C.; Driguez, H.; Williamson, G.; Svensson, B. *Carbohydr. Res.* **1995**, *277*, 313.
- (4) (a) Driguez, H. *Top. Curr. Chem.* **1997**, *187*, 85. (b) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160.
- (5) (a) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734. (b) Lian, G.; Zhan, X.; Yu, B. *Carbohydr. Res.* **2015**, *403*, 13. (c) Basu, N.; Maity, S. K.; Ghosh, R. *RSC Adv* **2012**, *2*, 12661. (d) Xiong, D.-C.; Zhang, L.-H.; Ye, X.-S. *Adv. Synth. Catal.* **2008**, *350*, 1696.
- (6) (a) Eisele, T.; Toepfer, A.; Kretzschmar, G.; Schmidt, R. R. *Tetrahedron Lett.* **1996**, *37*, 1389. (b) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503. (c) Fukase, K.; Hasuoka, A.; Kinoshita, I.; Aoki, Y.; Kusumoto, S. A. *Tetrahedron* **1995**, *51*, 4923.
- (7) (a) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleef, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769. (b) Johannes, M.; Reindl, M.; Gerlitzki, B.; Schmitt, E.; Hoffmann-Röder, A. *Beilstein J. Org. Chem.* **2015**, *11*, 155. (c) Zeng, Y.; Wang, Z.; Whitfield, D.; Huang, X. *J. Org. Chem.* **2008**, *73*, 7952. (d) Fridman, M.; Belakhov, V.; Lee, L. V.; Liang, F.-S.; Wong, C.-H.; Baasov, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 447.
- (8) (a) Fügedi, P.; Garegg, P. J.; Lönn, H.; Norberg, T. *Glycoconjugate J.* **1987**, *4*, 97. (b) Kaeothip, S.; Demchenko, A. V. *Carbohydr. Res.* **2011**, *346*, 1371.
- (9) (a) Castaneda, F.; Burse, A.; Boland, W.; Kinne, R. K.-H. *Int. J. Med. Sci.* **2007**, *4*, 131. (b) Rodrigue, J.; Ganne, G.; Blanchard, B.; Saucier, C.; Giguère, D.; Shiao, T. C.; Varrot, A.; Imbert, A.; Roy, R. *Org. Biomol. Chem.* **2013**, *11*, 6906. (c) Elgemeie, G. H.; Farag, A. B.; Amin, K. M.; El-Badry, O. M.; Hassan, G. S. *Med. Chem.* **2014**, *4*, 814; DOI: 10.4172/2161-0444.1000234.
- (10) (a) Kato, E.; Nagano, H.; Yamamura, S.; Ueda, M. *Tetrahedron* **2003**, *59*, 5909. (b) Schnabelrauch, M.; Vasella, A.; Withers, S. G. *Helv. Chim. Acta* **1994**, *77*, 778.
- (11) Herr, R. R.; Bergy, M. E. *Antimicrob. Agents Chemother.* **1962**, *560*.
- (12) (a) Furneaux, R.; Ferrier, R. *Methods Carbohydr. Chem.* **1980**, *8*, 251. (b) Nicolaou, K. C.; Randall, J. L.; Furst, G. T. *J. Am. Chem. Soc.* **1985**, *107*, 5556. (c) Tai, C.-A.; Kulkarni, S. S.; Hung, S.-C. *J. Org. Chem.* **2003**, *68*, 8719. (d) Agnihotri, G.; Tiwari, P.; Misra, A. K. *Carbohydr. Res.* **2005**, *340*, 1393.
- (13) (a) Fischer, E.; Delbrück, K. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 1476. (b) Blanc-Muesser, M.; Defaye, J.; Driguez, H. *Carbohydr. Res.* **1978**, *67*, 305. (c) Appar, M.; Blanc-Muesser, M.; Defaye, J.; Driguez, H. *Can. J. Chem.* **1981**, *59*, 314.
- (14) (a) Durette, P. L.; Shen, T. Y. *Carbohydr. Res.* **1980**, *81*, 261. (b) Lee, R. T.; Lee, Y. C. *Carbohydr. Res.* **1982**, *101*, 49. (c) Hasegawa, A.; Morita, M.; Kojima, Y.; Ishida, H.; Kiso, M. *Carbohydr. Res.* **1991**, *214*, 43. (d) Defaye, J.; Guillot, J. M. *Carbohydr. Res.* **1994**, *253*, 185.
- (15) (a) Ibrahim, N.; Alami, M.; Messaoudi, S. *Asian J. Org. Chem.* **2018**, *7*, 2026. (b) Brachet, E.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Adv. Synth. Catal.* **2013**, *355*, 477.
- (16) (a) Brachet, E.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Adv. Synth. Catal.* **2013**, *355*, 2627. (b) Bruneau, A.; Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. Eur. J.* **2015**, *21*, 8375.
- (17) Fokt, I.; Szeja, W. *Carbohydr. Res.* **1992**, *232*, 169.
- (18) Lacombe, J. M.; Rakotomanomana, N.; Pavia, A. A. *Tetrahedron Lett.* **1988**, *29*, 4293.
- (19) (a) Jarava-Barrera, C.; Parra, A.; López, A.; Cruz-Acosta, F.; Collado-Sanz, D.; Cárdenas, D. J.; Tortosa, M. *ACS Catal.* **2016**, *6*, 442. (b) Lou, Y.; Cao, P.; Jia, T.; Zhang, Y.; Wang, M.; Liao, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 12134. (c) López, A.; Parra, A.; Jarava-Barrera, C.; Tortosa, M. *Chem. Commun.* **2015**, *51*, 17684. (d) Reddy, V.; Anand, R. V. *Org. Lett.* **2015**, *17*, 3390. (e) Chu, W.-D.; Zhang, L.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Zhang, G.-B.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9229.
- (20) (a) Li, W.; Xu, X.; Liu, Y.; Gao, H.; Cheng, Y.; Li, P. *Org. Lett.* **2018**, *20*, 1142. (b) Zhang, X.-Z.; Gan, K.-J.; Liu, X.-X.; Deng, Y.-H.; Wang, F.-X.; Yu, K.-Y.; Zhang, J.; Fan, C.-A. *Org. Lett.* **2017**, *19*, 3207. (c) Ge, L.; Lu, X.; Cheng, C.; Chen, J.; Cao, W.; Wu, X.; Zhao, G. *J. Org. Chem.* **2016**, *81*, 9315. (d) Zhao, K.; Zhi, Y.; Wang, A.; Enders, D. *ACS Catal.* **2016**, *6*, 657.
- (21) (a) Goswami, P.; Singh, G.; Anand, R. V. *Org. Lett.* **2017**, *19*, 1982. (b) Jadhav, A. S.; Anand, R. V. *Eur. J. Org. Chem.* **2017**, *3716*. (c) Jadhav, A. S.; Anand, R. V. *Org. Biomol. Chem.* **2017**, *15*, 56. (d) Arde, P.; Anand, R. V. *Org. Biomol. Chem.* **2016**, *14*, 5550. (e) Arde, P.; Anand, R. V. *RSC Adv.* **2016**, *6*, 77111. (f) Zhang, X.-Z.; Deng, Y.-H.; Yan, X.; Yu, K.-Y.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. *J. Org. Chem.* **2016**, *81*, 5655. (g) Jadhav, A. S.; Pankhade, Y. A.; Hazra, R.; Anand, R. V. *J. Org. Chem.* **2018**, *83*, 10107. (h) Zhou, T.; Li, S.; Huang, S.; Li, C.; Zhao, Y.; Chen, J.; Chen, A.; Xiao, Y.; Liu, L.; Zhang, J. *Org. Biomol. Chem.* **2017**, *15*, 4941.
- (22) (a) Santra, S.; Porey, A.; Guin, J. *Asian J. Org. Chem.* **2018**, *7*, 477. (b) Molleti, N.; Kang, J. Y. *Org. Lett.* **2017**, *19*, 958. (c) Yang, C.; Gao, S.; Yao, H.; Lin, A. *J. Org. Chem.* **2016**, *81*, 11956. (d) Pan, R.; Hu, L.; Han, C.; Lin, A.; Yao, H. *Org. Lett.* **2018**, *20*, 1974. (e) Yuan, Z.; Liu, L.; Pan, R.; Yao, H.; Lin, A. *J. Org. Chem.* **2017**, *82*, 8743.
- (23) Fujihira, T.; Takido, T.; Seno, M. *J. Mol. Catal. A: Chem.* **1999**, *137*, 65.
- (24) (a) Ěrný, M.; Pacák, J. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2566. (b) Ěrný, M.; Pacák, J. *Collect. Czech. Chem. Commun.* **1961**, *6*, 2084. (c) Claeysens, M.; De Bruyne, C. K. *Carbohydr. Res.* **1972**, *22*, 460.
- (25) (a) Ibatullin, F. M.; Selivanov, S. I.; Shavva, A. G. *Synthesis* **2001**, *419*. (b) Belz, T.; Williams, S. J. *Carbohydr. Res.* **2016**, *429*, 38. (c) Lipták, A.; Sajtos, F.; Jánossy, L.; Gehle, D.; Szilágyi, L. *Org. Lett.* **2003**, *5*, 3671.
- (26) **(3,5-Di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl 2,3,4,6-Tetra-O-acetyl-1-thiohexopyranoside (3a); Typical Procedure**
Thiourea (84 mg, 1.1 mmol) and BF₃·Et₂O (136 μL, 1.1 mmol) were added to a solution of 2,3,4,6-tetra-O-acetyl-β-D-galactopyranose (**1a**; 390 mg, 1.0 mmol) in MeCN (5 mL), and the mixture was refluxed at 80 °C until the starting material was fully consumed (TLC; 30 min). The mixture was then cooled to rt, and Et₃N (279 μL, 2.0 mmol) and p-QM **2a** (353 mg, 1.2

mmol) were added with stirring. The mixture was kept at rt for 2 h then diluted with CH₂Cl₂ and washed with H₂O. The resulting organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel; hexane–EtOAc (5:1)] to give a colorless oil; yield: 546 mg (83%; dr 1:1).

IR (neat): 3644, 3021, 2967, 1752, 1522, 1348, 1225, 1157, 1052, 760, 668 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.49–7.46 (m, 1 H), 7.39–7.34 (m, 2 H), 7.31–7.19 (m, 3 H), 7.15–7.13 (m, 1 H), 5.43 (s, 0.6 H), 5.38 (s, 0.4 H), 5.35–5.33 (m, 1 H), 5.29–5.22 (m, 1.5 H), 5.15 (s, 0.5 H), 4.91–4.85 (m, 1 H), 4.14–4.03 (m, 3 H), 3.60–3.55 (m, 1 H), 2.14 (s, 3 H), 2.07 (s, 3 H), 2.05 (s, 3 H), 1.95 (s, 3 H), 1.3 (s, 18 H). ¹³C NMR (100 MHz, CDCl₃): δ = 170.3, 170.2, 170.1, 170.0, 169.5, 169.4, 153.2, 153.1, 140.9, 140.5, 136.1, 135.8, 130.3, 130.2, 128.6, 128.5, 128.4, 128.3, 127.5, 127.2, 125.1, 125.0, 83.7, 83.4, 74.3, 74.2, 72.0, 71.9, 67.4, 67.3, 67.2, 61.5, 61.4, 53.3, 52.7, 34.4, 34.3, 30.3, 30.1, 20.9, 20.8, 20.7, 20.6, 20.5. HRMS (ESI-TOF): *m/z* [M + NH₄]⁺ calcd for C₃₅H₅₀NO₁₀S: 676.3150; found: 676.3152.

(27) (a) Richter, D.; Hampel, N.; Singer, T.; Ofial, A. R.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 3203. (b) Yuan, Z.; Pan, R.; Zhang, H.; Liu, L.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2017**, 359, 4244.

(28) **Compound 4a (Table 3); Typical Procedure**

Thiourea (84 mg, 1.1 mmol) and BF₃·Et₂O (136 μL, 1.1 mmol) were added to a solution of peracetyl-β-D-lactose (678 mg, 1.0 mmol) in MeCN (10 mL), and the mixture was refluxed at 80 °C until the starting material was completely consumed (TLC, 30

min). The mixture was then cooled to rt and Et₃N (279 μL, 2.0 mmol) and *p*-QM **2a** (353 mg, 1.2 mmol) were added with stirring. The mixture was kept at rt for 2 h then diluted with CH₂Cl₂ and washed with H₂O. The resulting organic phase was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, hexane–EtOAc (1:1)] to give a colorless oil; yield: 748 mg (79%; dr 1:1).

IR (neat): 3617, 2958, 2568, 1753, 1623, 1374, 1225, 1165, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.46–7.41 (m, 1 H), 7.37–7.33 (m, 2 H), 7.31–7.26 (m, 2 H), 7.22–7.18 (m, 1 H), 7.12–7.11 (m, 1 H), 5.39 (br s, 1 H), 5.33–5.32 (m, 1 H), 5.22–5.14 (m, 1 H), 5.08–5.03 (m, 2 H), 5.00–4.89 (m, 2 H), 4.50–4.34 (m, 2 H), 4.12–4.02 (m, 4 H), 3.86–3.82 (m, 1 H), 3.77–3.2 (m, 1 H), 3.28–3.23 (m, 1 H), 2.17 (s, 3 H), 2.13 (s, 2 H), 2.04 (s, 12 H), 1.95 (s, 3 H), 1.38 (s, 18 H). ¹³C NMR (100 MHz, CDCl₃): δ = 170.3, 170.1, 170.0, 169.7, 169.6, 169.5, 169.1, 169.0, 153.2, 153.1, 140.9, 140.4, 136.1, 135.8, 130.3, 130.2, 128.6, 128.5, 128.4, 128.2, 128.1, 127.6, 127.2, 125.1, 124.9, 124.8, 101.2, 101.1, 82.8, 82.4, 77.2, 76.4, 76.3, 74.1, 73.9, 71.1, 70.6, 70.5, 70.4, 69.1, 66.5, 62.3, 62.2, 60.7, 53.3, 52.5, 34.4, 34.3, 30.4, 30.2, 20.9, 20.8, 20.7, 20.6, 20.5, 20.4. HRMS (ESI-TOF): *m/z* [M + NH₄]⁺ Calcd for C₄₇H₆₆NO₁₈S: 964.3995; found: 964.3968.

(29) (a) Luzzio, F. A. *Synth. Commun.* **1984**, 14, 209. (b) Ibatullin, F. M.; Shabalin, K. A.; Jänis, J. V.; Shavva, A. G. *Tetrahedron Lett.* **2003**, 44, 7961.