

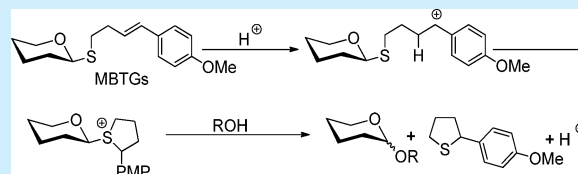
Acid-Catalyzed O-Glycosylation with Stable Thioglycoside Donors

Kristina D. Lacey, Rashanique D. Quarels, Shaofu Du, Ashley Fulton, Nicholas J. Reid, Austin Firesheets, and Justin R. Ragains*

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803, United States

Supporting Information

ABSTRACT: Two classes of thioglycoside, 4-(4-methoxyphenyl)-3-butenylthioglycosides (MBTGs) and 4-(4-methoxyphenyl)-4-pentenylthioglycosides (MPTGs), undergo acid-catalyzed O-glycosylations with a range of sugar and nonsugar alcohols at 25 °C. Electron density at the styrene alkene is critical for reactivity while sugar protecting group patterns have a minimal effect. In contrast with most methods for thioglycoside activation, acid-catalyzed activation of MBTGs is compatible with electroneutral alkenes.



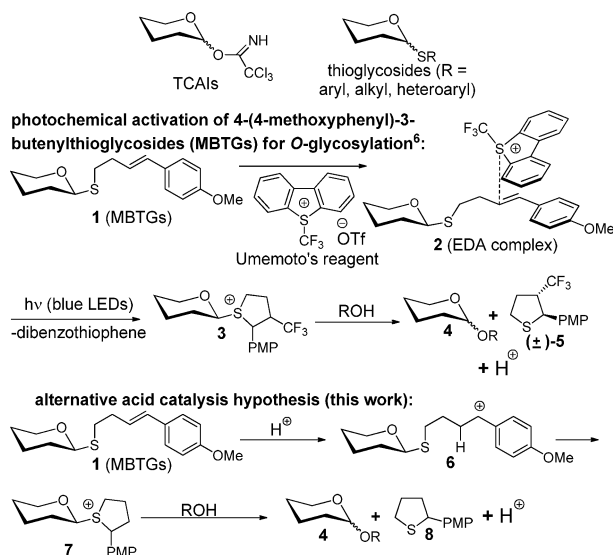
The microheterogeneity of oligosaccharides frequently prevents their isolation as pure substances from natural sources.¹ Accordingly, chemists often have to turn to enzymatic^{2,3} and chemical⁴ syntheses to generate serviceable quantities of pure material to discover function. Therefore, the most important step in the multistep synthesis of oligosaccharides is arguably O-glycosylation.

Two classes of glycosyl donor, glycosyl trichloroacetimidates (TCAIs)^{4a,b} and thioglycosides^{4c,e-g} (Scheme 1), have emerged as workhorses for O-glycosylation. TCAIs are marked by straightforward synthesis from lactols and are activated toward O-glycosylation under even mildly acidic conditions. Nevertheless, TCAIs cannot be carried easily through multistep synthesis. Due to TCAI instability in certain systems, it is wise to allow a minimal period of time between the

synthesis and application of these labile species. Even the related *N*-phenyltrifluoroacetimidates (PTFAIs, not pictured), which are often cited as a more stable alternative to TCAIs, have been bemoaned for their short shelf life.^{4d} Like TCAIs, thioglycosides are synthesized easily. In contrast to TCAIs, thioglycosides are prized for their stability toward a host of conditions (strongly acidic, basic, and nucleophilic) which make them ideal for multistep synthesis. Nevertheless, activation of thioglycosides toward O-glycosylation generally requires highly electrophilic thiophiles that necessitate low temperatures for activation and have poor compatibility toward alkenes.^{4c,e-g} While advances have been made recently in the development of mild and/or alkene-compatible reagents for thioglycoside activation,⁵ we wondered if the counterintuitive development of a glycosyl donor with the stability of a thioglycoside, but which could be activated using catalytic acids in the manner of TCAIs, could be enacted.

Recently, we introduced 4-(4-methoxyphenyl)-3-butenylthioglycosides (MBTGs, **1**, Scheme 1) as glycosyl donors in a visible-light-promoted O-glycosylation.⁶ Blue LED irradiation of **1**, Umemoto's reagent, and an alcohol resulted in the formation of glycosidic linkages. We proposed a mechanism involving the intermediacy of an electron-donor–acceptor complex **2** and glycosylsulfonium ion **3**. Subsequently, we wondered if protonation of **1** to **6** using catalytic quantities of a strong acid could result in the formation of a **3**-like intermediate **7** (Scheme 1). Attack of an alcohol on **7** (or the corresponding oxocarbenium ion) would result in O-glycosides **4** with regeneration of the proton. Such an approach would be similar to the activation of pentenyl glycosides pioneered by Fraser-Reid.⁷ However, our approach would require a catalytic acid instead of a stoichiometric electrophile and the reactivity of glycosylsulfonium ion intermediates⁸ (instead of e.g. glycosyl bromides) would be exploited. We have demonstrated that **1** can be stored in a 4 °C refrigerator

Scheme 1. Glycosyl Trichloroacetimidates, Thioglycosides, and 4-(4-Methoxyphenyl)-3-butenylthioglycosides



Received: July 6, 2018

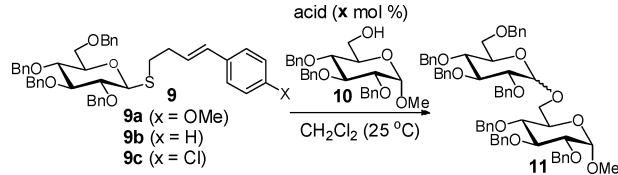
Published: August 27, 2018

for months and that the 4-aryl-3-butenylthioglycoside moiety is stable toward strongly basic and nucleophilic conditions, just as one could expect with other alkyl- and arylthioglycosides.⁶ However, the question of the stability of **1** toward various acids had not been answered with our initial studies.

Herein, we demonstrate that MBTGs are stable toward mildly acidic conditions, but have a reactivity profile similar to TCAIs wherein HOTf and TMSOTf can be utilized for their activation. High yields of *O*-glycosidic products can be obtained at 25 °C and in the presence of electroneutral alkenes. Further, we demonstrate that the remote activation⁹ features of this chemistry circumvent the deactivation problems encountered with tetra-acylated MBTG donors in our original photochemical approach.⁶ In addition, we demonstrate a potential latent-active strategy^{4g,9} utilizing cross-metathesis. Further, we demonstrate that **1** is orthogonal to TCAIs in an *O*-glycosylation reaction, provided that adequate temperature control is exercised. Finally, we introduce a new class of thioglycoside donor (4-(4-methoxyphenyl)-4-pentenylthioglycoside, MPTG) and demonstrate the utility in synthesizing hindered *O*-glycosides.

In our initial studies (Table 1), we employed tetrabenzyl-protected MBTG **9a**⁶ with acceptor **10** in dichloromethane.

Table 1. Initial Optimization^a



entry	acid	mol % (x)	acid	time (h)	yield (%) ^b	α/β
1 (9a)	TfOH	100		0.5	68	1.5:1
2 (9a)	TfOH	10		1	87	1.4:1
3 (9a)	TMSOTf	10		1	85	1.4:1
4 (9a)	CSA	10		24	0	n.a.
5 ^c (9a)	n.a.	n.a.		1	0	n.a.
6 ^c (9a)	TfOH	10		2	75	1.5:1
7 ^d (9a)	TfOH	10		1	50	1:1
8 ^e (9a)	TfOH	10		1	65	1.3:1
9 ^e (9a)	TfOH	10		4	89	1.6:1
10 ^f (9a)	TfOH	10		8	70	1:1.1
11 ^g (9a)	TfOH	10		24	27	2:1
12 ^h (9a)	TfOH	10		2	51	2:3
13 ⁱ (9a)	TfOH	10		1	88	3:1
14 (9b)	TfOH	10		24	0	n.a.
15 (9c)	TfOH	10		24	0	n.a.

^aUnless otherwise stated, 0.15 mmol of **9a** and 0.075 mmol of **10** were used along with acid and 1 mL of CH₂Cl₂ and stirred at 25 °C for the indicated time. Products were purified with silica gel chromatography. ^bIsolated yields. ^cAdded 150 mg of AWMS. ^dUsed 0.0827 mmol of **9a**. ^eUsed 0.137 mmol of **10**. ^fStirred at –20 °C for 5 h and then at 0 °C for 3 h. ^g1:1 Et₂O/CH₂Cl₂ solvent. ^hCH₃CN solvent. ⁱToluene solvent.

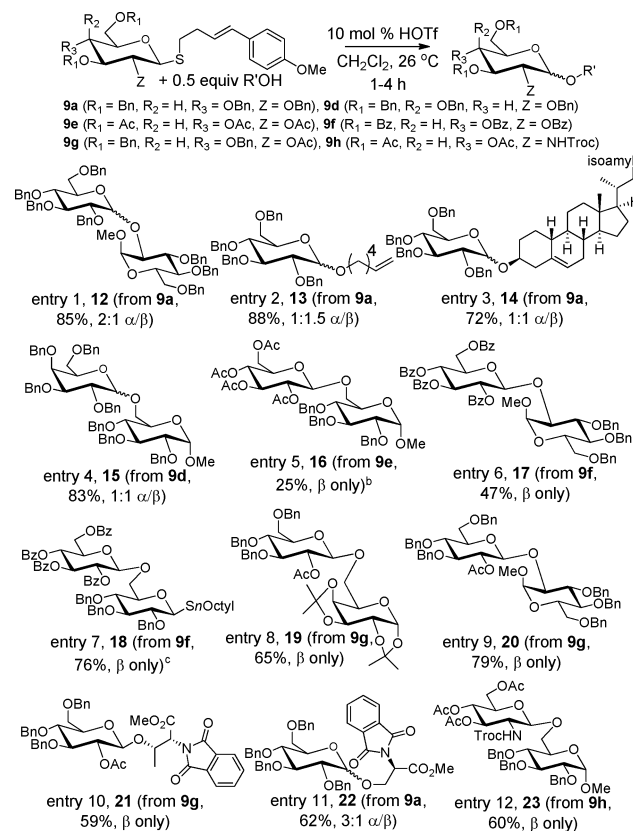
With 1 equiv of trifluoromethanesulfonic acid (HOTf, entry 1), we obtained a 68% yield of **11** after stirring for 30 min at 25 °C. In contrast, this same reaction required 24 h of irradiation with blue LEDs using our photochemical approach.⁶ Decreasing the HOTf loading to 10 mol % led to 87% of **11** with an increase in reaction time (entry 2). Next, we determined that TMSOTf is an adequate replacement for

HOTf (entry 3) while employment of camphorsulfonic acid (CSA, entry 4) resulted in no observed consumption of **9a** even after stirring for 24 h at 25 °C. Acid-washed molecular sieves (AWMS)¹⁰ were also inadequate for activation alone (entry 5) and provided no improvement in yield in conjunction with HOTf (entry 6). As such, MBTGs are stable to mildly acidic conditions that activate TCAIs.^{4a,b,10} Concentration studies (entries 2, 7–9) demonstrated that 0.15 mmol of **9a** and 0.075 mmol of **10** in 1 mL of dichloromethane produced the best results with regard to reaction rate. Nevertheless, 0.150 mmol of **9a** and 0.137 mmol **10** in 1 mL of dichloromethane provided an 89% yield of **11** with an extended reaction time of 4 h (entry 9). A 2 equiv amount of donor is not necessary for high yields.

We also conducted studies at low temperature (entry 10). Stirring for 5 h at –20 °C resulted in no observed consumption of **9a**. However, warming the same reaction mixture to 0 °C and stirring for 3 h resulted in a 70% yield of **11** (entry 10). We were intrigued by the low reactivity at –20 °C, and this observation suggested strategies for orthogonal syntheses employing temperature control (*vide infra*). The alternative solvent mixture of 1:1 Et₂O/CH₂Cl₂ (entry 11) and acetonitrile (entry 12) provided decreases in yield while toluene (entry 13) provided a comparable yield to dichloromethane. Further, we demonstrated that donors **9b** and **9c** were unreactive under the entry 2 conditions, likely due to the lack of an electron-donating group on benzene (entries 14, 15). Due to short reaction times and high yields, we elected to employ the entry 2 conditions (Table 1) for further study. Finally, reaction of 1 mmol of **9a** with 1 mmol of alcohol **10** resulted in a 73% yield of **11** after stirring for 3 h at 25 °C, demonstrating the scalability of this reaction (see Supporting Information (SI) for details).

Substrate scope studies (Scheme 2) commenced with donor **9a**. We demonstrated that glycosylation could proceed in high yield with a 2° carbohydrate alcohol (entry 1). Further, moderate to high yields of *O*-glycosylation products containing electroneutral alkenes could be obtained with 5-hexen-1-ol (entry 2) and cholesterol (entry 3). We observed no conversion of acceptor-linked alkene. In contrast, our photochemical approach resulted in low yields of the desired products in entries 2/3 along with consumption of the acceptor-linked alkene.⁶ These results are particularly significant, as alkene-compatible thioglycoside activation is elusive.^{5a,b} Then, we demonstrated the efficacy of galactosyl donor **9d** (entry 4).

Next, we examined tetraacetyl donor **9e**⁶ for glycosylation of **10** (entry 5). Replacement of four benzyl groups with four acetyl groups results in an ~1000-fold decrease in reactivity toward conventional thioglycoside activation due to electron-withdrawing effects.¹¹ In our previous photochemical studies, we had determined that **9e** was unreactive toward *O*-glycosylation, suggesting that the electron density at sulfur played a role in the reaction. In contrast, **9e** was consumed after 4 h in the presence of 10 mol % HOTf. As expected, this suggested a styrene protonation event (that is independent of the electronics of the sugar moiety) followed by fast cyclization to generate sulfonium ions such as **7** (Scheme 1). Despite this encouraging result, the reaction generated a disappointing 25% yield of *O*-glycoside **16** along with 37% of the product of acetylation of the alcohol. Results such as this are common with acetyl protecting groups and are a consequence of the attack of alcohol onto dioxolenium ions resulting from

Scheme 2. Substrate Scope^a

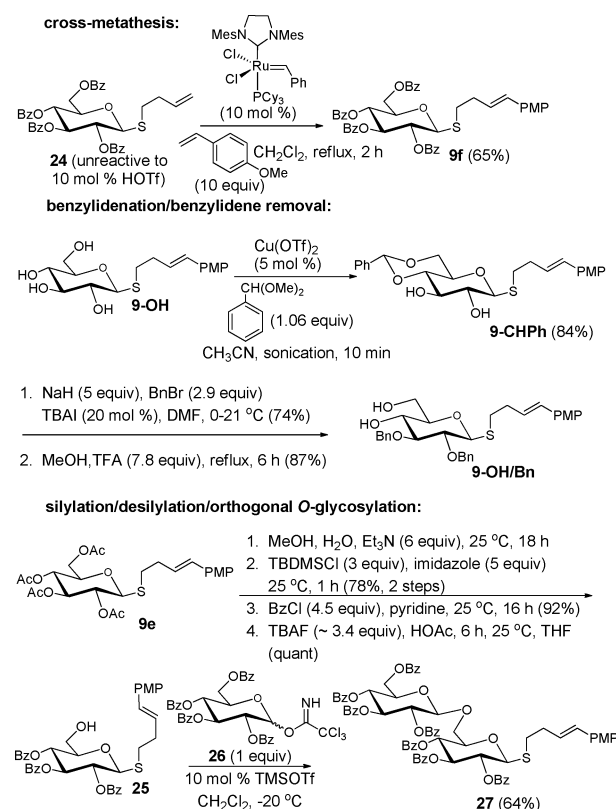
^aUnless otherwise stated, 0.15 mmol of MBTG donor and 0.075 mmol of alcohol were used along with 10 mol % HOTf and 1 mL of CH₂Cl₂ and stirred at 25 °C until the alcohol had been consumed (TLC). 20 mol % of Et₃N was then added. After evaporation, products were purified with silica gel chromatography and yields of isolated products were determined. ^b37% of the product of alcohol acetylation was also isolated. ^cUsed 0.15 mmol of alcohol.

neighboring group participation of 2-position acetyl.¹² As an alternative, we turned to tetrabenzoyl donor 9f and obtained modest yields of product 17 (entry 6) and respectable yields of 18, also demonstrating orthogonality to alkylthioglycosides (entry 7). The modest yields in entry 6 are a consequence of the difficult purification of product 17 due to coeluting impurities. Similarly difficult purifications were incurred with the reaction of 9f with acceptor 10 leading to modest yields of the glycosidic product (46%, data not shown). A potential solution to these problems is presented with MPTG donor 28 (*vide infra*).

Continuing studies demonstrated the efficacy of donor 9g⁶ (entries 8–10) while entries 10 and 11 demonstrate efficacy with amino acid derived alcohols. Entry 8 suggests utility in the preparation of acid-sensitive products such as 19. Finally, entry 12 demonstrates the utility of the 2-amino-2-deoxy donor 9h.

To further demonstrate the utility of MBTGs as intermediates for synthesis, we performed a series of transformations and a synthesis capitalizing on the orthogonality of MBTGs to conditions that can activate TCAIs and PTFAs (Scheme 3). First, we synthesized 3-butenylthioglycoside 24 and determined that it is inert toward activation with 10 mol % HOTf in CH₂Cl₂. However, heating 24 in the presence of 10 mol % of the second generation Grubbs catalyst and 4-methoxystyrene in CH₂Cl₂ at reflux resulted in 9f (65%)

Scheme 3. Additional Transformations with MBTGs (PMP = 4-Methoxyphenyl)

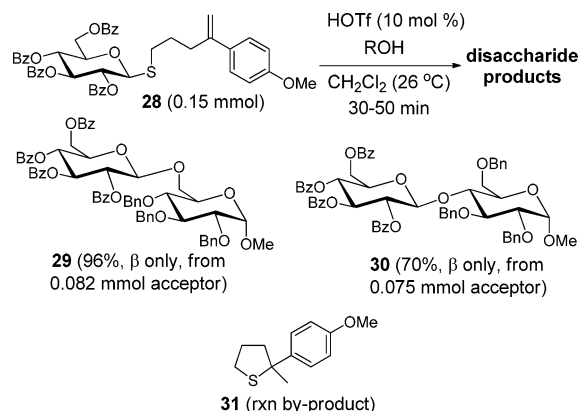


which is an effective donor, as shown in Scheme 2. Glycosylation of 3-butenylthioglycoside alcohol acceptors with MBTG donors followed by cross metathesis of the butenyl side chain to generate a new MBTG side chain will be the subject of future iterative approaches to oligosaccharide synthesis.

We previously demonstrated the compatibility of the MBTG side chain to methanolysis (NaOMe, MeOH), Williamson etherification (NaH, BnBr), and 10 mol % CSA in CH₂Cl₂. However, we were interested in probing the lability of the MBTG side chain in other common transformations. Thus, we demonstrated that installation of the benzylidene acetal (9-OH → 9-CHPh, Scheme 3) proceeded in high yield with catalytic Cu(OTf)₂ and sonication in CH₃CN.¹³ Benzoylation of 9-CHPh followed by the removal of benzylidene (TFA, MeOH) afforded 9-OH/Bn, which further demonstrated the stability of MBTGs toward mild acid. Further, 9e underwent smooth deacetylation, silylation, benzoylation, and silyl deprotection in the presence of a TBAF buffer with HOAc to generate MBTG alcohol 25. Silyl deprotection using MeOH/pTsOH was also successful (see S1). TCAIs would show poor stability toward any of the aforementioned conditions. Most importantly, we demonstrated that activation of TCAIs in the presence of MBTGs could be effected through control of temperature. Glycosylation of MBTG acceptor 25 with TCAI 26¹⁴ using 10 mol % TMSOTf (64%) occurred without any detected activation of the MBTG side chain at -20 °C. Our continuing efforts will exploit this orthogonality with the further elaboration of intermediates such as 27 and synthesis of oligosaccharides utilizing the aforementioned latent-active strategy.

Toward the completion of this study, we synthesized 4-(4-methoxyphenyl)-4-pentenylthioglycoside (MPTG) **28** (Scheme 4). Using conditions similar to the optimized

Scheme 4. O-Glycosylation with MPTG Donor 28



conditions from Table 1, we demonstrate the high-yielding synthesis of disaccharides **29** (96%) and **30** (70%). Synthesis of **29** using MBTG donor **9f** under the standard conditions had proceeded in 46% yield (data not shown) due to purification issues that also plagued the synthesis of **17** (Entry 6, Scheme 2). In addition, synthesis of **30** using MBTG **9f** had afforded a 20% yield of O-glycoside (data not shown) using the standard conditions. It is encouraging that a product such as **30** resulting from glycosylation of a very hindered acceptor can be generated in high yield at 25 °C. Finally, in support of the protonation/sulfur cyclization/O-glycosylation hypothesis from Scheme 1, we were able to isolate known tetrahydrothiophene **8**¹⁵ (Scheme 1) from reactions using donors **9a** and **9d–h** (Table 1; Scheme 2) and tetrahydrothiophene **31** (Scheme 4) from reactions using donor **28**.

In conclusion, we have demonstrated that MBTGs and an MPTG are stable and effective donors for O-glycosylation that combine the stability of thioglycosides with convenient activation at 25 °C using catalytic protic acid. O-Glycosylations occur with a range of MBTG/MPTG donors and alcohols under conditions that have low reactivity toward electroneutral alkenes, a rare occurrence with thioglycosides. Further, we have demonstrated the potential utility of MBTG donors in various applications including a latent-active strategy involving alkene cross metathesis. In addition, we have demonstrated the orthogonality of MBTGs to TCAs at –20 °C. Finally, we have confirmed the utility of an MPTG donor in the high-yielding synthesis of a hindered 1 → 4 linkage. Further studies involving MBTGs/MPTGs and related donors are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02125.

Experimental procedures, characterization data, ¹H and ¹³C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jragains@lsu.edu.

ORCID

Justin R. Ragains: 0000-0002-2521-5396

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the National Science Foundation (CHE-1665208) and Louisiana State University (LSU) for generous support of this research. We thank Ms. Connie David (LSU) for assistance with high resolution mass spectrometry.

■ REFERENCES

- (1) (a) *Essentials of Glycobiology*, 2nd ed.; Varki, A., Cummings, R. D., Esko, J. D., Freeze, H. H., Stanley, P., Bertozzi, C. R., Hart, G. W., Etzler, M. E., Eds.; Cold Spring Harbor Laboratory Press: Cold Spring Harbor: New York, 2009. (b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357. (c) Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046. (d) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nat. Chem.* **2009**, *1*, 611.
- (2) (a) Chokhawala, H. A.; Chen, X. Enzymatic Approaches to O-Glycoside Introduction: Glycosyltransferases. In *Comprehensive Glycoscience*; Kamerling, J. P., Ed.; Elsevier Ltd.: Oxford, 2007; Vol. 1, pp 415–451. (b) Yu, H.; Chen, X. *Org. Biomol. Chem.* **2016**, *14*, 2809.
- (3) Li, H.; Zhang, H.; Yi, W.; Shao, J.; Wang, P. G. *ACS Symp. Ser.* **2005**, *900*, 192.
- (4) (a) Knerr, L.; Schmidt, R. R. The Use of O-Glycosyl Trichloroacetimidates for the Polymer-Supported Synthesis of Oligosaccharides. In *Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries*; Seeberger, P. H., Ed.; John Wiley & Sons, Inc.: New York, 2001; pp 67–98. (b) Schmidt, R. R.; Jung, K. H. Trichloroacetimidates. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaý, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 5–59. (c) Seeberger, P. H. *Acc. Chem. Res.* **2015**, *48*, 1450. (d) Yu, B.; Sun, J. *Chem. Commun.* **2010**, *46*, 4668. (e) Wittmann, V. Synthesis of Oligosaccharides on Solid Support Using Thioglycosides and Pentenyl Glycosides. In *Solid Support Oligosaccharide Synthesis and Combinatorial Carbohydrate Libraries*; Seeberger, P. H., Ed.; John Wiley & Sons, Inc.: New York, 2001; pp 99–116. (f) 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. (g) Shiao, T. C.; Roy, R. *Top. Curr. Chem.* **2010**, *301*, 69.
- (5) (a) Goswami, M.; Ellern, A.; Pohl, N. L. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 8441. (b) Kabotso, D. E. K.; Pohl, N. L. B. *Org. Lett.* **2017**, *19*, 4516. (c) Adhikari, S.; Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. *ACS Catal.* **2013**, *3*, 57. (d) Wever, W. J.; Cinelli, M. A.; Bowers, A. A. *Org. Lett.* **2013**, *15*, 30. (e) Chu, A.-H. A.; Minciunescu, A.; Bennett, C. S. *Org. Lett.* **2015**, *17*, 6262. (f) Chu, A.-H. A.; Minciunescu, A.; Montanari, V.; Kumar, K.; Bennett, C. S. *Org. Lett.* **2014**, *16*, 1780.
- (6) Spell, M. L.; Deveaux, K.; Bresnahan, C. G.; Bernard, B. L.; Sheffield, W.; Kumar, R.; Ragains, J. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 6515.
- (7) (a) Fraser-Reid, B.; Anilkumar, G.; Gilbert, M. R.; Joshi, S.; Kraehmer, R. Glycosylation Methods: Use of *n*-Pentenyl Glycosides. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaý, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 135–154. (b) Fraser-Reid, B.; Merritt, J. R.; Handlon, A. L.; Andrews, C. W. *Pure Appl. Chem.* **1993**, *65*, 779. (c) Mootoo, D. R.; Date, V.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 2662. (d) Mootoo, D. R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.
- (8) (a) Nokami, T. *Trends Glycosci. Glycotechnol.* **2012**, *24*, 203. (b) Singh, G. P.; Watson, A. J. A.; Fairbanks, A. J. *Org. Lett.* **2015**, *17*, 4376. (c) Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J. *Org. Lett.* **2007**, *9*, 1959. (d) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090.

- (9) (a) Spell, M. L.; Deveau, K.; Bresnahan, C. G.; Ragains, J. R. *Synlett* **2017**, 28, 751. (b) Ranade, S. C.; Demchenko, A. V. *J. Carbohydr. Chem.* **2013**, 32, 1.
- (10) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Org. Lett.* **2003**, 5, 987.
- (11) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, 121, 734.
- (12) Kondo, H.; Aoki, S.; Ichikawa, Y.; Halcomb, R. L.; Ritzen, H.; Wong, C.-H. *J. Org. Chem.* **1994**, 59, 864.
- (13) Tran, A.-H.; Jones, R. A.; Pastor, J.; Boisson, J.; Smith, N.; Galan, M. C. *Adv. Synth. Catal.* **2011**, 353, 2593.
- (14) Elsaidi, H. R. H.; Paszkiewicz, E.; Bundle, D. R. *Carbohydr. Res.* **2015**, 408, 96.
- (15) Robertson, F. J.; Wu, J. *J. Am. Chem. Soc.* **2012**, 134, 2775.