Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

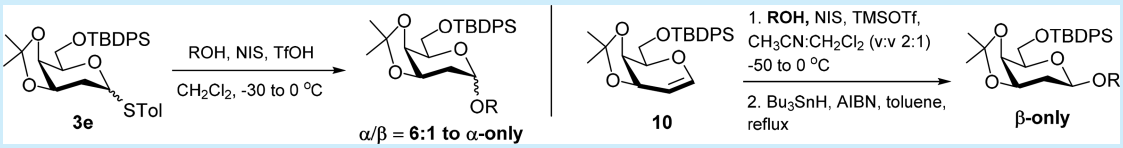
Stereocontrolled Synthesis of 2-Deoxy-galactopyranosides via Isopropylidene-Protected 6-*O*-Silylated Donors

Dan-Mei Yang,[†,§] Yue Chen,[†,§] Ryan P. Sweeney,[‡] Todd L. Lowary,[‡] and Xing-Yong Liang*[,†]

[†]School of Chemistry Engineering, Sichuan University of Science & Engineering, Zigong 643000, China

[‡]Alberta Glycomics Centre and Department of Chemistry, University of Alberta, Edmonton, AB T6G 2G2, Canada

Supporting Information

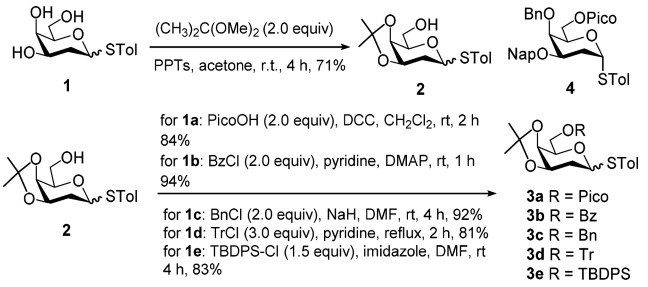


ABSTRACT: The stereocontrolled synthesis of 2-deoxy-D-*arabino*-hexopyranosides ("galactopyranosides") using 3,4-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-protected glycosyl donors is reported. 2-Deoxy-thioglycoside **3e** gives excellent α-selectivity, while galactal **9** leads to, in a two-step protocol, 2-deoxy-β-glycosides in high stereoselectivity. The selectivity of both reagents is believed to arise from the combination of the isopropylidene acetal spanning O-3 and O-4 together with the sterically demanding silyl group on O-6. The utility of the method was demonstrated through the synthesis of a trisaccharide that contains both 2-deoxy α- and β-D-galactopyranosyl residues.

2-Deoxy-glycosyl residues are present in many biologically active natural products and clinical agents, including anthracyclines, angucyclines, and aureolic acid antibiotics.[1] The lack of neighboring-group participation from substituents at the C-2 position and the enhanced conformational flexibility derived from the reduced number of substituents make it difficult to achieve glycosylation in a stereoselective manner.[2] Furthermore, the lack of an electron-withdrawing substituent at C-2 makes the resulting glycosides more acid labile.

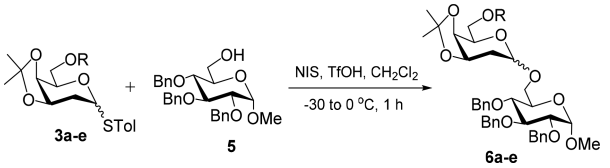
Strategies for the stereocontrolled synthesis of 2-deoxy-glycosides usually rely on indirect methods. Prominent among these are reductive cleavage of a halogen,[3] sulfur,[4] oxygen,[5] nitrogen,[6] or selenium[7] functionality at C-2 of the glycoside product. Direct synthesis of 2-deoxyglycosides using phosphate,[8] phosphoroamidite,[9] phosphite,[10] phosphorodithioate,[11] thioglycoside,[12] and (2-carboxyl)benzyl glycoside[13] donors is also known. Nevertheless, the synthesis of 2-deoxyglycosides with high stereoselectivity still remains a challenge. Here, we report two complementary methods for the synthesis, with high stereocontrol, of either 2-deoxy-α- or 2-deoxy-β-D-*arabino*-hexopyranosides ("galactopyranosides"), using 3,4-*O*-isopropylidene-6-*O*-TBDPS protected donors.

Scheme 1. Preparation of Compounds 3a−e



At the outset of this investigation, we envisioned applying the hydrogen-bond-mediated aglycone delivery (HAD[14]) strategy to synthesize 2-deoxy-β-D-galactopyranosides using a group at O-6 to direct the attack of the nucleophile. Thus, we prepared a donor modified at the primary position with a pyridine-2-carboxylic (Pico) ester (**3a**, Scheme 1). Its preparation started with thioglycoside **1**, which was obtained from D-galactose as

Table 1. Glycosylation of Alcohol 5 with Donors 3a−e[a]



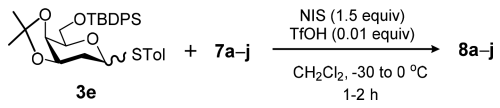
entry	donor	product	yield (%)[b]	α/β[c]
1	**3a**	**6a**	91	3/1
2	**3b**	**6b**	84	3/2
3	**3c**	**6c**	86	7/2
4	**3d**	**6d**	75	9/2
5	**3e**	**6e**	83	10/1
6[d]	**3e**	**6e**	81	α-only

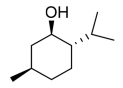
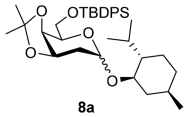
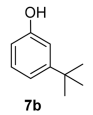
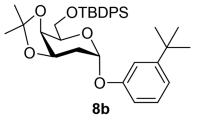
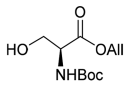
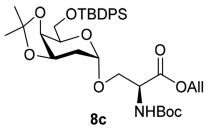
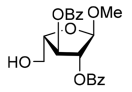
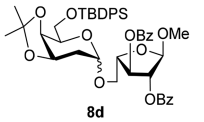
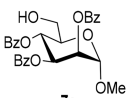
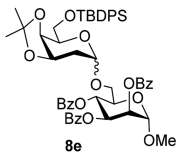
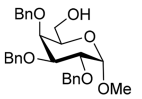
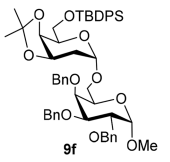
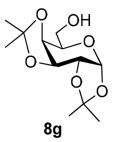
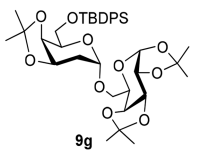
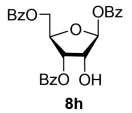
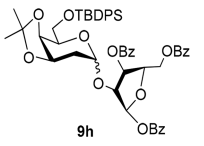
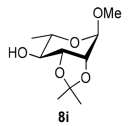
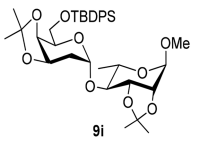
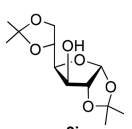
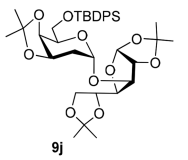
[a]All glycosylations were performed by treating the donor (1.2 equiv) and the acceptor (1.0 equiv) with NIS (1.5 equiv) and TfOH (0.1 equiv), in the presence of 4 Å molecular sieves in CH_2Cl_2, at −30 to 0 °C. [b]Combined total yield of both isomers. [c]Determined on the basis of the ^{1}H NMR of the corresponding mixture. [d]TfOH (0.01 equiv).

Received: February 21, 2018

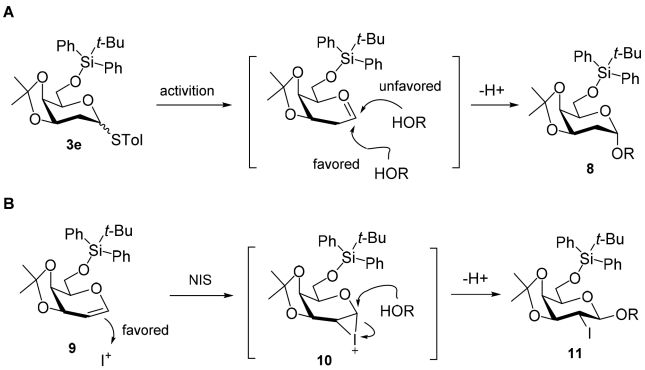
DOI: 10.1021/acs.orglett.8b00632
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Glycosylation of Alcohols 7a−7j with 3e



entry	acceptor	product	yield (%) (α/β)
1	 7a	 8a	87 (6:1)
2	 7b	 8b	89 (α-only)
3	 7c	 8c	81 (α-only)
4	 7d	 8d	91 (20:1)
5	 7e	 8e	93 (20:1)
6	 7f	 9f	85 (α-only)
7	 8g	 9g	77 (α-only)
8	 8h	 9h	80 (15:1)
9	 8i	 9i	86 (α-only)
10	 8j	 9j	74 (α-only)

Scheme 2. Proposed Pathway for Glycosylations with 3e and 9



described by Ye and co-workers.[15] Acetalization of **1** with 2,2-dimethoxypropane and PPTS afforded **2** in a yield of 71%. Treatment with pyridine-2-carboxylic acid (PicoOH) and DCC furnished **3a** in 84% yield.

We anticipated that the product of the coupling between **3a** and acceptor **5** should be the *β*-isomer due to the HAD effect. However, we found that this reaction afforded product **6a** as a mixture (*α*:*β*,[16] 3:1, entry 1, Table 1). In previous work, donor **4** (Scheme 1) has been successfully used in the stereoselective synthesis of 2-deoxy-*β*-glycosides via HAD.[17] The major difference between **4** and **3a** is the presence of a cyclic protecting group on O-3 and O-4.

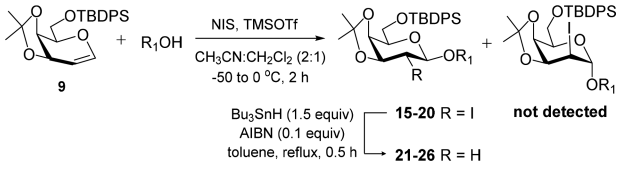
Based on these results, we hypothesized that the isopropylidene acetal in **3a** prevents the acceptor from attacking the *β*-face of the donor. We further postulated that additional tuning of the *α*-selectivity might be possible by the choice of protecting group at O-6. Thus, a series of other donors (**3b−e**) were synthesized from **2** (Scheme 1). Treatment with benzoyl bromide in pyridine afforded **3b** in 94% yield. Alkylation with benzyl bromide and sodium hydride gave **3c** in 92% yield. Introduction of a trityl ether by reaction with trityl chloride in pyridine led to **3d** in 81% yield. Finally, reaction with TBDPSCl provided **3e** in a yield of 83%. Compounds **3a−e** were obtained as a mixture of *α* and *β* anomers. Although some of these anomers could be separated, the mixtures were used in the glycosylations.

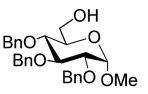
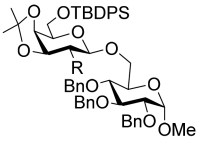
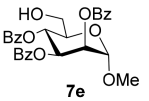
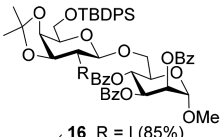
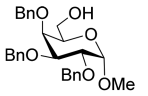
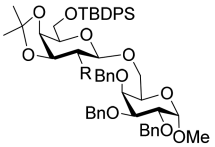
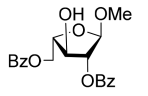
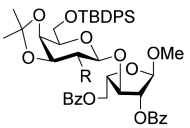
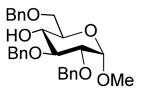
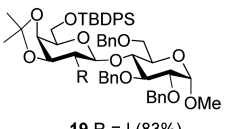
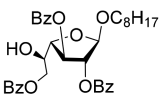
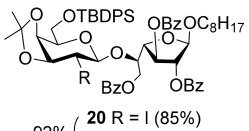
With these compounds in hand, their use in the glycosylation of **6** was investigated (Table 1). The 6-*O*-Bz, 6-*O*-Bn, or 6-*O*-Tr thioglycosides (**3b−d**) displayed modest *α*-selectivity, affording disaccharides **6b−d** in 75−84% yields as a mixture of anomers (3/2 to 9/2 *α*:*β* ratio, entries 2−4). These results are comparable to those obtained with **3a** (entry 1). However, to our delight, the 6-*O*-TBDPS-protected thioglycoside **3e** showed significantly improved selectivity (83% yield *α*:*β* > 10:1, entry 5). Interestingly, only the *α*-isomer was detected when the amount of TfOH decreased from 0.1 to 0.01 equiv (entry 6).

Next, we surveyed the glycosylation of a variety of alcohols with **3e**. All reactions were run using the alcohol (**7a−j**,[18] 1.0 equiv), thioglycoside **3e** (1.2 equiv), NIS (1.5 equiv), and TfOH (0.01 equiv), at −30 to 0 °C in CH_2Cl_2. As summarized in Table 2, we were pleased to find that all acceptors reacted very well with **3e**, resulting in the corresponding glycoside products **8a−j** in 74−93% yields with the *α*-anomer as the major product or sole product (*α*:*β* > 6:1). These included glycosylation of the noncarbohydrate alcohols menthol (**7a**, 6:1, *α*:*β* entry 1), 3-*tert*-butylphenol (**7b**, entry 2), and serine derivative **7c** (entry 3). In the cases of glycosyl acceptors, the

DOI: 10.1021/acs.orglett.8b00632
Org. Lett. XXXX, XXX, XXX−XXX

Table 3. Glycosylation of 5, 7f–g, and 12–14[a] with 9

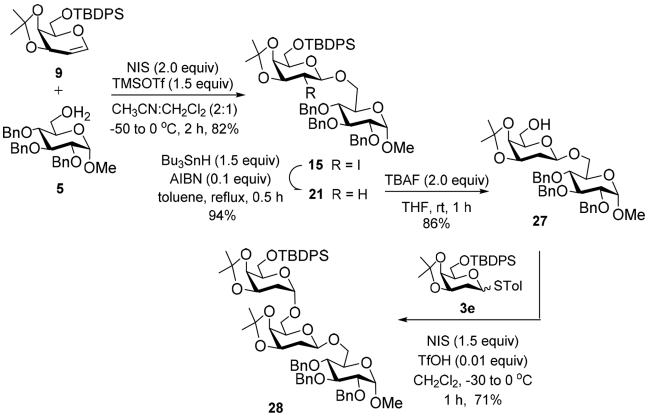


entry	acceptor	product (yield, %)[b]
1	 **5**	 94% **15** R = I (82%) **21** R = H
2	 **7e**	 92% **16** R = I (85%) **22** R = H
3	 **7f**	 87% **17** R = I (87%) **23** R = H
4	 **12**	 88% **18** R = I (86%) **24** R = H
5	 **13**	 91% **19** R = I (83%) **25** R = H
6	 **14**	 92% **20** R = I (85%) **26** R = H

[a]All glycosylations were performed by treating **9** (1.0 equiv) and the acceptor (1.5 equiv) with NIS (2.0 equiv), TMSOTf, (1.5 equiv), in the presence of 4 Å molecular sieves in CH_3CN/CH_2Cl_2 (v/v 2:1), at −50 to 0 °C. [b]The yield based on the donor.

reactions of **3e** with **7d–j** produced the expected α-linked glycosides **8d–j** with high diastereoselectivity (α:β > 15:1) and in good yields (>74%). Reactions with primary acceptors **7d–g** provided, in general, the same α-selectivities as reactions with more hindered secondary acceptors **7h–j** (entries 4–7 vs entries 8–10). Any sensitivity of the stereoselectivity to the structure of the acceptor is not obvious. Taken together, these results support our hypothesis that the combination of the isopropylidene acetal on O-3 and O-4 and the sterically

Scheme 3. Synthesis of the Trisaccharide 28



demanding TBDPS group on O-6 favors formation of the α-glycoside, via α-selective attack of the alcohol on an electrophilic intermediate formed upon activation of **3e** (Scheme 2A).

The ability to convert **3e** into α-glycosides with high selectivity prompted us to design another glycosylation based on the same general principles. We envisioned that galactal derivative **9**,[19] which has the same protecting groups as **3e**, could be used to prepare 2-deoxy-β-glycosides with high stereoselectivity via a two-step protocol. Treatment of **9** with NIS would be expected to afford the cyclic iodonium ion intermediate **10** (Scheme 2B). Nucleophiles would be expected to attack this species from the top face, thus affording the 2-deoxy-2-iodo-β-galactopyranoside **11**. Subsequent reduction of the C–I bond would give the 2-deoxy-glycoside.

With this in mind, we glycosylated a panel of alcohols with **9** (Table 3). The glycosylation was promoted using the method developed by Mong and co-workers (NIS and TMSOTf).[20] As expected, acceptor **5** reacted very well with **9**, affording the desired 2-deoxy-2-iodo-β-D-galactopyranoside **15** (determined by the integration of NMR signals, $^3J_{H1,H2}$ = 9.6 Hz) in 92% yield. The 2-deoxy-2-iodo-α-D-talopyranoside derivative was not detected by TLC and NMR spectroscopy. Next, we carried out similar glycosylations of alcohols **7e–f** and **12–14**.[21] We were pleased to find that all acceptors also reacted very well with **9**, thus resulting in the products **16–20** in 83–87% yields. In all cases, none of the isomeric 2-deoxy-2-iodo-α-D-talopyranosides were detected. Subsequent reduction of the C–I bond with *n*-Bu_3SnH and AIBN led to the 2-deoxy-β-galactopyranoside derivatives in excellent yield.

To demonstrate the power of these methods, we targeted the preparation of a trisaccharide (**28**) that contained both 2-deoxy-α- and 2-deoxy-β-galactopyranoside linkages (Scheme 3). Thus, treatment of **5** and **9** with NIS and TMSOTf yielded disaccharide **15** in 82% yield. Then, the iodine was removed by means of free radical reduction (*n*-Bu_3SnH, AIBN) to give disaccharide **21**. Subsequent desilylation via TBAF in THF liberated the 6-OH of the β-2-deoxy-galactopyranosyl moiety, thus affording **27** in 86% yield. Finally, the coupling between **27** and thioglycoside **3e** produced **28** in 71% yield. The stereochemistry of the trisaccharide was confirmed by the combination of the $J_{1,2}$ values and the chemical shift of the anomeric carbon for these units.[16]

In conclusion, we report two novel approaches for the synthesis of 2-deoxy α- and β-D-galactopyranosides using the 3,4-*O*-isopropylidene-6-*O*-*tert*-butyldiphenylsilyl-protected do-

DOI: 10.1021/acs.orglett.8b00632
Org. Lett. XXXX, XXX, XXX–XXX

nors **3e** and **9**. The approach was successfully applied to the synthesis of a protected trisaccharide derivative **28**. Although the exact mechanism of these transformations is unclear at present, we believe the stereoselectivity results from the protecting groups directing the attack of either an alcohol (in the case of **3e**) or iodonium ion (in the case of **9**) to the α-face of the molecule. Efforts to better understand the mechanism of these processes and their application to the synthesis of other 2-deoxysugars 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.8b00632.

Experimental procedures, characterization data, and ^{1}H, ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: levesonk@163.com.

ORCID

Todd L. Lowary: 0000-0002-8331-8211

Xing-Yong Liang: 0000-0003-0328-6019

Author Contributions

§D.-M.Y. and Y.C. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (NSFC-21402131), Sichuan University of Science & Engineering (2014RC06, LYJ4204), and the China Scholarship Council and the Canadian Glycomics Network for financial support.

■ REFERENCES

(1) (a) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1. (b) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99. (c) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141.

(2) (a) Marzabadi, C. H.; Franck, R. W. *Tetrahedron* **2000**, *56*, 8385−8417. (b) Veyriéres, A. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, 2000; p 367. (c) Hou, D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1911. (d) Kharel, M. K.; Rohr, J. *Nat. Prod. Rep.* **2012**, *29*, 264. (e) Borovika, A.; Nagorny, P. *J. Carbohydr. Chem.* **2012**, *31*, 255.

(3) (a) Thiem, J.; Gerken, M.; Weigand, J. *Carbohydr. Res.* **1987**, *164*, 327. (b) Horton, D.; Priebe, W.; Sznaidman, M. *Carbohydr. Res.* **1989**, *187*, 149. (c) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *Tetrahedron Lett.* **2002**, *43*, 9047.

(4) (a) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723. (b) Roush, W. R.; Briner, K.; Gustin, D. J. *J. Org. Chem.* **1996**, *61*, 6098.

(5) Sato, K.; Yoshitomo, A.; Takai, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 885.

(6) Capozzi, G.; Dios, A.; Franck, R. W.; Tamarez, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 777.

(7) (a) Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75. (b) Nicolaou, K. C.; Mitchell, H. J.; Suzuki, H.; Rodriguez, R. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1089.

(8) Koch, A.; Lamberth, C.; Wetterich, F.; Giese, B. *J. Org. Chem.* **1993**, *58*, 1083.

(9) Hao, L.; Meijin, C.; Kang, Z. *Tetrahedron Lett.* **1997**, *38*, 6143.

(10) Hashimoto, S.-I.; Sano, A.; Sakamoto, H.; Ikegami, S. *Synlett* **1995**, *1995*, 1271.

(11) Laupichler, L.; Sajus, H.; Thiem, J. *Synthesis* **1992**, *1992*, 1133.

(12) (a) Sun, L.; Li, P.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 7147−7150. (b) Lear, M. J.; Yoshimura, F.; Hirama, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 946−949. (c) Jaunzems, J.; Kirschning, A. *Tetrahedron Lett.* **2003**, *44*, 637−639.

(13) Kim, K. S.; Park, J.; Lee, Y. J.; Seo, Y. S. *Angew. Chem., Int. Ed.* **2003**, *42*, 459.

(14) (a) Yasomanee, J. P.; Demchenko, A. V. *J. Am. Chem. Soc.* **2012**, *134*, 20097−20102. (b) Yasomanee, J. P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 10453. (c) Liu, Q. W.; Bin, H. C.; Yang, J. S. *Org. Lett.* **2013**, *15*, 3974.

(15) Lu, Y. S.; Ye, X. S. *Synlett* **2010**, *2010*, 1519.

(16) Paul, S.; Jayaraman, N. *Carbohydr. Res.* **2007**, *342*, 1305. The stereochemistry was determined by ^{1}H NMR spectroscopy. In the α-glycosides, the anomeric hydrogen appeared as a doublet with a $J_{1,2}$ of 3.0−4.0 Hz; the H-2 protons resonated between 2.30 and 1.85 ppm, H_{2ax} appeared as a doublet of triplets, and H_{2eq} appeared as a doublet of doublets. The chemical shift of the anomeric carbon in the α-anomer resonated at 96−98 ppm. In comparison, in all β-isomers the H-1 resonance appeared as a double of doublets, with $J_{1,2ax}$ = 8.0−10.0 Hz and $J_{1,2b}$ = 2.0−3.0 Hz. The H-2 resonances appeared between 2.20 and 1.60 ppm. The resonances for H_{2ax} appeared as a doublet of doublet of doublets, and H_{2eq} appeared as a multiplet. The chemical shift of the anomeric carbon in the β-anomer resonated at 98−101 ppm.

(17) Ruei, J. H.; Venukumar, P.; Mong, K.-K. T. *Chem. Commun.* **2015**, *51*, 5394.

(18) Alcohols **7a**, **7b**, and **7h** are commercially available. All others were prepared by reported methods. **7c**: Arnaud, O.; Koubeissi, A.; Ettouati, L.; Falson, P. *J. Med. Chem.* **2010**, *53*, 6720. **7d**: Reference 15c. **5**, **7e**−**f**: Lipták, A.; Imre, J.; Neszmélyi, A. *Tetrahedron* **1982**, *38*, 3721. **7g**, **7j**: Wouters, A. *Synthesis* **2013**, *45*, 2222. **7i**: Capozzi, G. *J. Org. Chem.* **2001**, *66*, 8787.

(19) Marcaurelle, L. A.; Bertozzi, C. R. *Org. Lett.* **2001**, *3*, 3691.

(20) Pradhan, T. K.; Mong, K.-K. T. *Org. Lett.* **2014**, *16*, 1474.

(21) **12** and **13**: Ishikawa, T.; Shimizu, Y. *Org. Lett.* **2003**, *5*, 3879. **14**: Completo, G. C.; Lowary, T. L. *J. Org. Chem.* **2008**, *73*, 4513.

DOI: 10.1021/acs.orglett.8b00632
Org. Lett. XXXX, XXX, XXX−XXX