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Solution and Solid-Phase Stereocontrolled Synthesis of 1,2-*cis*-Glycopyranosides with Minimally Protected Glycopyranosyl Donors Catalyzed by BF$_3$–*N*,*N*-Dimethylformamide Complex

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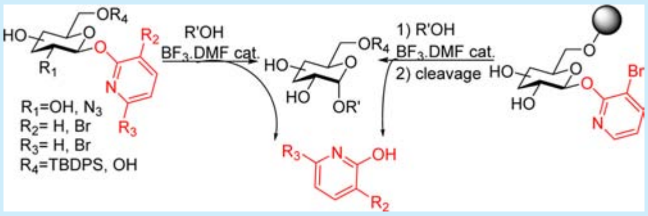
S *Supporting Information*

ABSTRACT: Methods are described for the stereoselective synthesis of 1,2-*cis* glycopyranosides in the D-galacto, D-gluco, and 2-azido-2-deoxy-D-glucopyranoside series utilizing minimally protected (3-bromo-2-pyridyloxy) β-D-glycopyranosyl donors in the presence of BF$_3$–*N*,*N*-dimethylformamide (DMF) as a catalyst and a variety of alcohol acceptors relying on the "remote activation concept". Precursors to antifreeze glycopeptide components are synthesized in excellent yields and high α/β ratios. The method is adaptable to one-pot sequential glycosidation as well as to solid-supported synthesis giving access to diverse sets of minimally protected α-D-glycopyranosides as major products.



In spite of major advances in the chemistry and biology of carbohydrates and their derivatives, the stereocontrolled synthesis of 1,2-*cis*-glycopyranosides remains as a major challenge.[1−3] The polyfunctional nature of sugar molecules acting as glycopyranosyl donors in natural product an oligosaccharide synthesis has necessitated the extensive use of O- and N-protecting groups and the exploitation of a variety of anomeric leaving groups in the quest for stereocontrolled glycoside formation.[4]Therefore, continued exploration of glycosidation methods that minimize hydroxyl or amino group protection are worthy of study.[5]

Herein we describe versatile methods for the *solution and solid-phase* stereocontrolled synthesis of 1,2-*cis*-hexopyranosides exemplified by a prototypical (3-bromo-2-pyridyloxy) β-D-galactopyranosyl donor containing a single 6-*O*-*tert*-butyldiphenylsilyl protecting group using a variety of alcohol acceptors. A novel feature of this glycosylation reaction is the anomeric heterocyclic leaving group with 5−20 mol % quantities of the BF$_3$–*N*,*N*-dimethylformamide (DMF) complex[6] which is utilized as a mild Lewis acid in glycoside synthesis for the first time. Upon addition of an alcohol to a dichloromethane solution containing the β-D-galactopyranosyl donor and the catalyst, a rapid reaction takes place at −20 to 0 °C with the formation of the 1,2-*cis*-D-galactopyranoside as the major product in the cases studied, accompanied by the liberation of the highly chromophoric 2-hydroxy-3-bromopyridine thereby allowing easy monitoring of the progression of the reaction.

The variety of alcohol acceptors listed in Table 1 attests to the versatility of the method which is based on our original "remote activation concept".[7] The impact of this type of remote anomeric activation was already demonstrated for the first time in the successful glycosylation of the aglycones of complex carbohydrate-containing natural products such as erythromycin A[8] and avermectin B1a[9] using 2-pyridylthio glycosyl donors.[7a]

The presently reported method of glycoside synthesis using (3-bromo-2-pyridyloxy) glycopyranosyl donors in conjunction with BF$_3$–DMF as a mild Lewis acid offers a number of practical and operational advantages.[10]

The crystalline catalyst is a convenient "solid form" of BF$_3$ which is released in the medium and catalytically recycled. It is stable to air, can be used in 5−20 mol % quantities, and is compatible with a variety of protective groups and other reactive functionalities. The comparable α/β ratios of product glycosides and the mildness of the reaction conditions, allowing the use of minimal equivalents of alcohols if needed, are important assets compared to the use of MeOTf.[11] We suggest that the BF$_3$ released from the BF$_3$–alcohol/BF$_3$–DMF complexes activates the β-3-bromo-2-pyridyloxy moiety of the donor.[12] The resulting oxycarbenium/BF$_3$-coordinated 3-bromo-2-pyridyloxy ion-pair intermediate is displaced with the alcohol in an S$_N$2-like reaction.[13] The departing 2-hydroxy-3-bromopyridine (or 2-pyridone tautomer) releases the bound BF$_3$ which resumes its catalytic cycle. In fact, the 2-hydroxy-3-bromopyridine BF$_3$ complex, prepared independently, acts as a competent catalyst. A plausible mechanism is shown in Scheme 1.

2-Acetamido-2-deoxy-α-D-galactopyranosyl serine and threonine derivatives are important constituents of immunologically relevant glycoproteins (T$_N$ antigen).[14] They are also components of antifreeze glycopeptides[15] which inhibit the formation of ice; hence, they are essential for marine life at subzero temperatures. All reported methods for their synthesis require O-protecting groups and employ various anomeric activating groups. Yields and anomeric ratios in favor of the α-anomer have been generally acceptable.[16]

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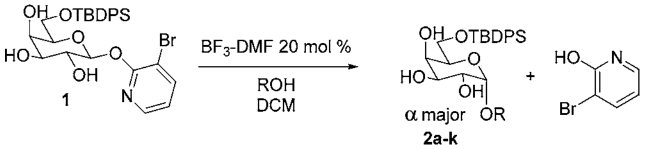
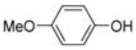
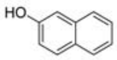
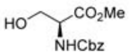
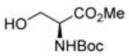
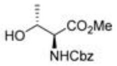
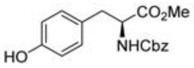
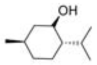
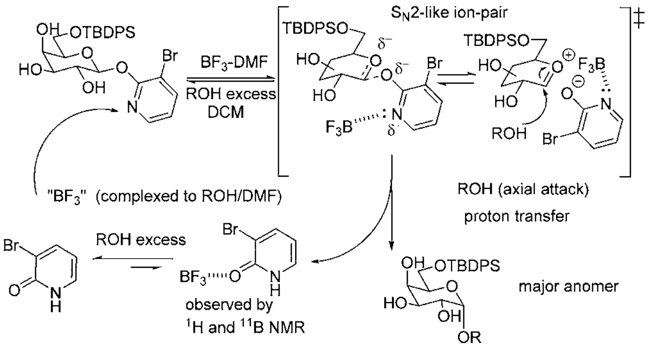
Table 1. BF_3–DMF Mediated Synthesis of Alkyl, Aryl, and Aminoacyl α-D-Galactopyranosides



entry	ROH[a]	temp (°C)/ t (h)	(%)[b]	α:β[c]
1	i-PrOH	0/ 0.15	100	2a 6.8:1
2	(as solvent)	-20/ 0.01	100	20:1[d]
3	t-BuOH (as solvent)	23/ 0.08	100	2b 8.3:1
4		-20/ 0.25	86	2c 10 :1
5		-20/ 0.5	81	2d 8.3:1
6		-20/ 0.5	88	2e 20:1
7		-20/ 0.5	87	2f 20:1
8		-20/ 0.5	86	2g 7:1
9		-20/ 0.5	88	2h 7.8:1
10		-20/0.5	88	2i 2.3 :1
11	Cholestanol	0/ 0.5	85	2j 2.3:1
12		0/ 0.5	95	2k 2.0 :1

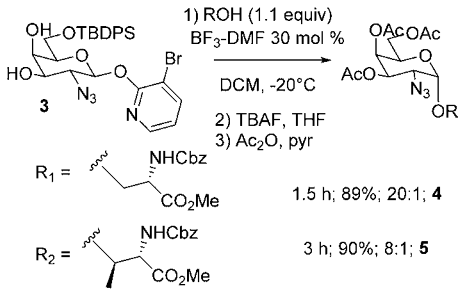
[a]10 equiv of ROH, except for entries 6, 7, 8, 9, and 12, where 5 equiv of ROH were used. [b]Yields α/β isolated from flash chromatography; α- and β-anomers are separable. [c]Ratio from ^{1}H NMR (400 MHz). [d]5 mol % BF_3–DMF, rt, 20 h, 59% conversion, 8.0:1 (α:β); see Supporting Information.

Scheme 1. Plausible Mechanism for the "Remote Activation Concept" Glycosylation of Alcohols Catalyzed by BF_3–DMF



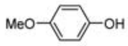
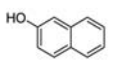
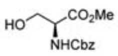
Herein we describe an expeditious method for the synthesis of 2-azido-2-deoxy-α-D-galactopyranosyl N-Cbz serine and N-Cbz threonine methyl esters in excellent yields and high α/β selectivities using only 1.1 equiv of the amino acid derivatives (Scheme 2). Treatment of the **3** with Cbz-Ser-OMe in the presence of BF_3–DMF led to **4** in 20:1 selectivity and 89% yield. The same reaction afforded **5** in 8.0:1 selectivity and 90% yield. Reaction times were a little longer in comparison with the same donor having a 2-hydroxy functionality. This might possibly be due to the participation of the 2-hydroxyl group in the activation step of the 3-bromo-2-pyridyloxy moiety.

Scheme 2. Stereocontrolled Synthesis of Antifreeze Glycoprotein Subunits and T_N Antigen as 2-Azido Precursors



Stereocontrolled alkyl α-D-galactopyranoside synthesis can be also efficiently accomplished on solid phase with yields comparable to reactions in solution. The (3-bromo-2-pyridyloxy) β-D-galactopyranosyl donors were immobilized via silyl ether tethers on polystyrene beads[17] and then treated with the appropriate alcohol in the presence of BF_3–DMF complex to give the corresponding α-D-galactopyranosides as major isomers in good to excellent yields (Table 2).

Table 2. BF_3–DMF Mediated Glycoside Synthesis on Solid Support

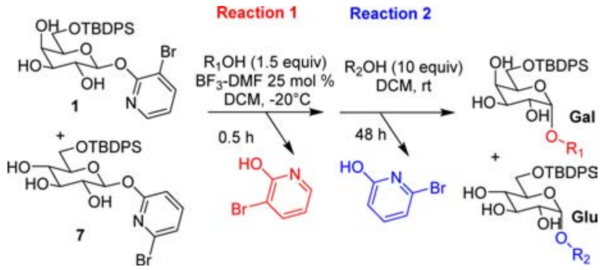
entry	ROH	temp (°C)/ t (h)	(%)[a]	α:β[b]
1	i-PrOH (10 equiv)	0/ 0.75	100	6a[c] 7:1
4		0/ 1.5	100	6b 10 :1
5		0/ 2	88	6c 8.5:1
6		0/ 1.5	92	2e[d] 20:1
10	(-)-Menthol	0/ 1.5	88	2i 2.3 :1
11	Cholestanol	0/0.5	85	6d 2.3:1

[a]Yields α/β of acetylated compounds; after flash chromatography; α- and β-anomers are separable. [b]Ratio from ^{1}H NMR (400 MHz) of the crude. [c]See Supporting Information. [d]**2e** as in Table 1; TBDPSCl, imidazole, DMF after step 3; see Supporting Information.

The differential reactivity of 3- and (6-bromo-2-pyridyloxy) β-glycopyranosyl donors in the D-gluco and D-galacto series led us to explore one-pot sequential glycosidations with two different alcohols. Previous one-pot glycoside syntheses have required O- and N-protecting groups and different anomeric activation protocols such as thioglycosides vs trichloroacetimidate glycopyranosyl donors or glycopyranosyl fluorides.[18]

In the presently described method, sequential glycosylation reactions occur with minimal protection using a bromo-2-pyridyloxy leaving group from two different β-D-glycopyranosyl donors in one reaction vessel (Scheme 3). The reactivity of the pyridyl moiety is modulated by the position of the bromo substituent, which affects the electronic character of the nitrogen atom.[19]

Scheme 3. Sequential One-Pot Glycosidation



These prototypical one-pot sequential glycosidations are exemplified by the use of D-galacto and D-gluco donors and different alcohol acceptors (Scheme 3, Table 3). Thus, the more reactive **1** is consumed within 30 min *in the presence of only 1.5 equiv of 2-naphthol* with the release of 2-hydroxy-3-bromopyridine and the formation of the **2d** as the major product (α:β = 6.5:1). Adding (−)-menthol as a second alcohol, now in excess, to the solution containing the still unreacted 7, leads to the corresponding α-D-**8** as the major product, albeit requiring a longer reaction time for a hindered secondary alcohol. The sequential glycosidation of 4-methoxyphenol followed by Cbz-Ser-OMe furnishes the corresponding α-D-galactopyranoside (α:β = 6.8:1) and α-D-glucopyranoside (α:β = 7.8:1) respectively. The progress of the second glycosylation reaction can be monitored directly by LC-MS and TLC with the appearance of the 2-hydroxy-6-bromopyridine. This protocol allows for the one-pot synthesis of *diverse sets of glycosides* with appropriate alcohols as acceptors, simply by choosing the more reactive donor and the less accessible alcohol in the first pass. Applications to solid-supported syntheses are possible.

Table 3. Sequential One-Pot Glycosidation in Solution

	Reaction 1[a]			Reaction 2[a]		
	R_1OH	(%)[b]	α:β[c]	R_2OH	(%)[b]	α:β[c]
1	2-Naphthol	64	6.5:1 **2d**	(−)-Menthol	68	2.3:1 **8**
2	4-OMe-Phenol	67	6.8:1 **2c**	Cbz-Ser-OMe	65	7.8:1 **9**

[a] Reaction 1 time: 0.5 h. Reaction 2 time: 48 h. [b] Yields (%) α/β obtained from flash chromatography; α- and β-anomers are separable with a careful chromatography. [c] Ratio of α- and β-anomers from ^1H NMR (400 MHz).

In conclusion, we have reported practical and expeditious methods for the stereocontrolled synthesis of otherwise arduously accessible α-D-galacto-, α-D-gluco-, and 2-azido-2-deoxy-α-D-glycopyranosides with minimal O-protection using the hitherto seldom used BF_3−DMF as a mild Lewis acid, in solution and on solid phase. The method allows facile monitoring of the reactions with the release of the chromophoric 3-bromo-2-hydroxypyridine which is an asset when adapted to solid phase glycosidations.

The sequential formation of diverse 1,2-*cis*-glycosides as major products offers the opportunity to exploit the remote activation concept toward the synthesis of sets of anomerically functionalized carbohydrates including esters as prodrugs,[20] as substrates for enzyme inhibition,[21] and in carbohydrate mediated drug delivery.[22]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01263.

Experimental procedures for synthesis of glycopyranosyl donors, general glycosidation procedure, characterization data, and NMR spectra of all new obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For relevant reviews, see: (a) Alphert, E.; van der Marel, G. A.; Codée, J. D. C. In *Modern Synthetic Methods in Carbohydrate Chemistry*; Werz, D. B., Vidal, S., Eds.; Wiley-VCH: Weinheim, 2014; pp 97−124. (b) Komanova, B. S.; Ustyuzhanina, N. E.; Tsvetkov, Y. E.; Nifantev, N. E. In *Modern Synthetic Methods in Carbohydrate Chemistry*; Werz, D. B., Vidal, S., Eds.; Wiley-VCH: Weinheim, 2014; pp 125−159. (c) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193−9209. (d) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687−2704.

(2) (a) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4063. (b) Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244−1251.

(3) (a) Christensen, H. M.; Oscarson, S.; Jensen, H. H. *Carbohydr. Res.* **2015**, *408*, 51−95. (b) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900−1934. (c) Jung, K.-H.; Muller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423−44424.

(4) (a) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576−1624. (b) Gamblin, D. P.; Scanlan, E. M.; Davis, B. G. *Chem. Rev.* **2009**, *109*, 131−163. (c) Yang, Y.; Zhang, X.; Yu, B. *Nat. Prod. Rep.* **2015**, *32*, 1331−1355.

(5) For example, see: (a) Davis, B. G.; Wood, S. D.; Maughan, A. T. *Can. J. Chem.* **2002**, *80*, 555−558. (c) Gudmundsdottir, A. V.; Nitz, M. *Org. Lett.* **2008**, *10*, 3461−3463. (d) Mamidyala, K. S.; Finn, G. M. *J. Org. Chem.* **2009**, *74*, 8417−8420. (e) Tanaka, T.; Matsumoto, T.; Noguchi, M.; Kobayashi, A.; Shoda, S.-I. *Chem. Lett.* **2009**, *38*, 458−459. (f) Park, T.-J.; Weïwer, M.; Yuan, X.; Baytas, S. N.; Munoz, E. M.; Murugesan, S.; Linhardt, R. J. *Carbohydr. Res.* **2007**, *342*, 614−620.

(g) Meng, B.; Zhu, Z.; Baker, C. D. *Org. Biomol. Chem.* **2014**, *12*, 5182−5191. (h) Williams, R. J.; Paul, C. E.; Nitz, M. *Carbohydr. Res.* **2014**, *386*, 73−77. (i) Armada, D. H.; Santos, J. T.; Richards, M. R.; Cairo, C. W. *Carbohydr. Res.* **2015**, *417*, 109−116. See also: (j) Hanessian, S.; Lou, B. *Chem. Rev.* **2000**, *100*, 4443−4464.

(6) Muetterties, E. J.; Rochow, E. G. *J. Am. Chem. Soc.* **1953**, *75*, 490−491.

(7) (a) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17. (b) Hanessian, S. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997, 381−388. See also: (c) Koide, K.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1991**, *32*, 7065−7068.

(8) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3215−3217. For an alternative approach, see: Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717−3727.

(9) (a) Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; Andre, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776−2778. (b) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dubé, D.; Andre, C. *Pure Appl. Chem.* **1987**, *59*, 299−316.

(10) The 3-bromo-2-pyridyloxy donors are shelf stable crystalline solids that can be prepared in quantity and used as needed. See Supporting Information.

(11) Different BF_3-coordinated species can be observed by ^{11}B and ^{19}F NMR. See Supporting Information.

(12) Lou, B.; Reddy, G. V.; Wang, H.; Hanessian, S. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; pp 389−412.

(13) (a) Woerpel, K. A.; Yang, M. T. *J. Org. Chem.* **2009**, *74*, 545−553. (b) Woerpel, K. A.; Beaver, M. G. *J. Org. Chem.* **2010**, *75*, 1107−1118. (c) Hosoya, T.; Takano, T.; Kosma, P.; Rosenau, T. *J. Org. Chem.* **2014**, *79*, 7889−7894.

(14) Ju, T.; Otto, V. I.; Cummings, R. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1770−1791.

(15) (a) Harding, M. M.; Anderberg, P. I.; Haymet, A. D. J. *Eur. J. Biochem.* **2003**, *270*, 1381−1392. (b) Gamblin, D.-P.; Scanlan, E. M.; Davis, B. G. *Chem. Rev.* **2009**, *109*, 131−163. (c) Bang, J. K.; Lee, J. H.; Murugan, R. N.; Lee, S. G.; Do, H.; Koh, H. Y.; Shim, H.-E.; Kin, H.-C.; Kim, H. *Mar. Drugs* **2013**, *11*, 2013−2041.

(16) For selected examples, see: (a) Polt, R.; Szabo, L.; Treiberg, J.; Yushun, L.; Hruby, J. I. *J. Am. Chem. Soc.* **1992**, *114*, 10249−10258. (c) Yule, J. E.; Wong, T. C.; Gandhi, S. S.; Qiu, D.; Riopel, M. A.; Koganty, R. R. *Tetrahedron Lett.* **1995**, *36*, 6839−6842. (d) Elofsson, M.; Salvador, L. A.; Kihlberg, J. *Tetrahedron* **1997**, *53*, 369−390. (e) Rodriguez, E. C.; Winans, K. A.; King, D. S.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 9905−9906. (f) Monasson, O.; Sizun-Thomé, G.; Lubin-Germain, N.; Uziel, J.; Augé, J. *Carbohydr. Res.* **2012**, *352*, 202−205. (h) Nagel, L.; Budke, C.; Erdmann, R. S.; Dreyer, A.; Wennemers, H.; Koop, T.; Sewald, N. *Chem. - Eur. J.* **2012**, *18*, 12783−12793.

(17) Savin, K. A.; Woo, J. C. G.; Danishefsky, S. J. *J. Org. Chem.* **1999**, *64*, 4183−4186.

(18) For one-pot glycoside synthesis, see: (a) Tanaka, H.; Adachi, M.; Takahashi, T. *Chem. - Eur. J.* **2005**, *11*, 849−862. (b) Wu, C.-Y.; Wong, C.-H. *Top. Curr. Chem.* **2010**, *301*, 223−252 and refrences cited therein.

(19) Gordon, A.; Katritzky, A. R.; Roy, S. K. *J. Chem. Soc. B* **1968**, *0*, 556−561.

(20) (a) Hanessian, S.; Mascitti, V.; Lu, P.-P.; Ishida, H. *Synthesis* **2002**, *2002*, 1959−1968. (b) Hanessian, S.; Lu, P.-P.; Ishida, H. *J. Am. Chem. Soc.* **1998**, *120*, 13296.

(21) (a) Park, S.; Hyun, S.; Yu, J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2441−2444. (b) Viana, P. A.; de Rezende, S. T.; de A. Alves, A.; Manfrini, R. M.; Alves, R. J.; Bemquerer, A. P.; Santoro, M. M.; Guimaraes, V. M. *Carbohydr. Res.* **2011**, *346*, 602−605.

(22) (a) Ahmad, M. U.; Ali, S. M.; Ahmad, A.; Sheikh, S.; Chen, P.; Ahmad, I. *Chem. Phys. Lipids* **2015**, *186*, 30−38. (b) Prakash, T. P.; Wan, W. B.; Low, A.; Yu, J.; Chappell, A. E.; Gaus, H.; Kinberger, G. A.; Østergaard, M. E.; Migawa, M. T.; Swayze, E. E.; Seth, P. P. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4127−4130.