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Studies on the Selectivity between Glycosylation and Intermolecular Aglycone Transfer of Thioglucoside in Synthesis of Lactose Derivatives

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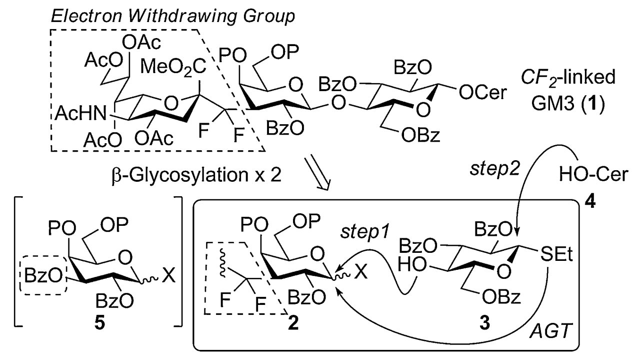
Glycosylation reaction of 2,3-di-*O*-benzoyl-protected galactosyl donors with ethyl thioglucoside acceptor to prepare lactose derivatives was investigated. The presence of benzyl ether moieties at the 4 and 6 positions of the donor drove the glycosylation reaction to completion and blocked the intermolecular aglycone transfer reaction with thioglucoside. On the other hand, the presence of benzoyl moieties at those positions promoted the intermolecular aglycone transfer reaction with thioglucoside.

Thioglycosides are convenient glycosyl donors for the synthesis of oligosaccharides and glycosylated natural products,[1,2] because the thiol group at the anomeric position is easy to install and several reliable activation methods have already been developed. Glycosyl sulfoxides, sulfones, and halides, which are readily available from thioglycoside, are also useful glycosyl donors,[1] so thioglycosides are recognized as important intermediates for synthesis of complex carbohydrate molecules. Moreover, since the relative reactivity of thioglycosides with various protecting groups has been systematically and comprehensively studied,[3] rapid synthesis of oligosaccharides should be possible even when different thioglycosides are used as glycosyl donors/acceptors.

On the other hand, aglycone transfer (AGT) reaction of thioglycoside is a serious side reaction, in which an oxacarbenium ion intermediate generated from the glycosyl donor reacts with sulfur of the glycosyl acceptor to give another thioglycoside.[4] In fact, we were faced with this problem. We have reported the design, synthesis, and biological activity of a sialidase-resistant ganglioside GM4 analog, in which the *O*-linked α(2,3)-sialylgalactose unit was replaced with a CF_2-linked unit.[5] To synthesize more complex ganglioside analogs such as CF_2-linked GM3 (**1**, Scheme 1), β-glycosylation of sialylgalactose donor **2** with a glucose unit is required. We planned to construct the analog **1** by sequential glycosylation with ceramide chain **4** after connection with glucose. For this purpose, glycosylation of a donor having electron-withdrawing groups at C3 (CF_2-group) and 2-O (neighboring participating group to obtain the β-glycoside) with the "disarmed" thioglucoside **3** acceptor, which is at risk for AGT reaction, seemed to be one of the most promising and straightforward combinations. Although until recently systematic studies of the AGT reaction have been limited, Gildersleeve reported two methods for preventing undesired AGT reaction, based on their mechanistic studies; one is the use of the bulky 2,6-dimethylphenylsulfanyl group as an anomeric substituent on glycosyl acceptors,[6] and the other is tuning of the combination of donors and acceptors based on the "armed–disarmed" concept, in which the increased

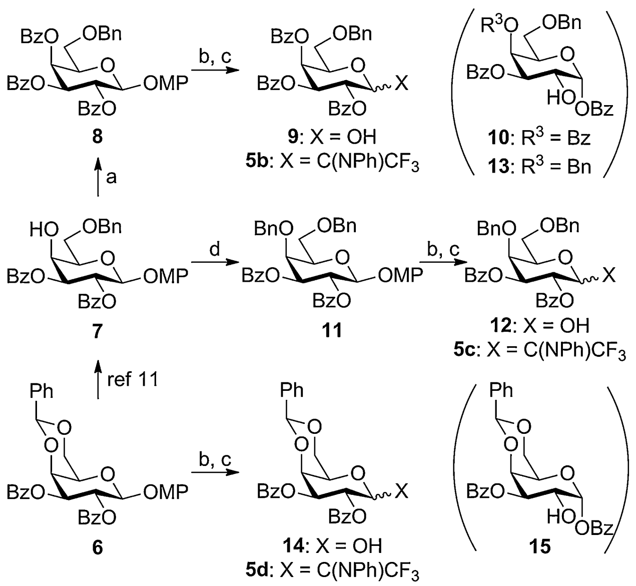


Scheme 1. Synthetic plan for CF_2-linked ganglioside analogs and structure of model glycosyl donor **5**.

electron-withdrawing ability of the protecting groups on donors/acceptors decreases the reactivity of the hydroxy group of the acceptors and the leaving group of the donors.[7] In this letter, we report systematic investigations of the glycosylation with thioglycoside **3**[8] of model monosaccharide donors **5** possessing a participating 2-OBz substituent and a 3-OBz group which plays the role of the 3-CF_2 functionality in **2**, serving to block the AGT reaction by tuning the protecting group.

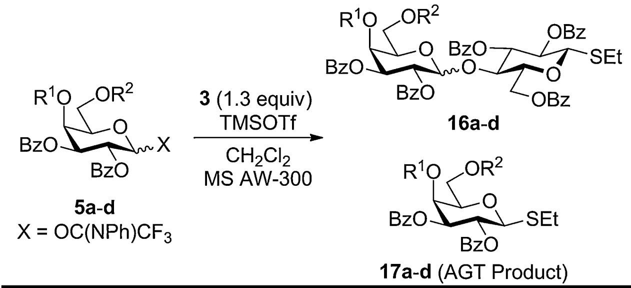
N-Phenyltrifluoroacetimidate was employed as a leaving group of donors for this glycosylation study.[9] First, four types of donors **5a**–**5d** having different protecting groups on 4-O and 6-O were prepared (Scheme 2). Donor **5a** was synthesized according to the literature,[10] and synthesis of **5b** was performed from known **7**[11] via a conventional three-step sequence. During the deprotection of the 4-methoxyphenyl group of **8** at the anomeric position with $Ce(NO_3)_6(NH_4)_2$ (CAN), a small amount of the migration product of the 2-OBz group to C1 was observed, affording **10**. Synthesis of **5c** was also performed from **7**, but formation of the benzyl ether at 4-O was quite difficult in the presence of the neighboring benzoyl group.[12] Although several other attempts failed, the use of 2-benzyloxy-1-methylpyridinium triflate[13] allowed the direct formation of **11** in 18% yield. Treatment of **11** with CAN gave **12** with concomitant formation of the migration product **13**. Finally, introduction of imidate functionality into the lactol derivative **12** afforded **5c**. Donor **5d** was prepared similarly from **6** (Scheme 2).[11]

Glycosylation of **5a**–**5c** with **3** was conducted under standard glycosylation conditions as described below. A solution of donor and acceptor in dichloromethane was treated with TMSOTf at −40 or −20 °C in the presence of molecular sieves AW-300. As we feared, in the case of donor **5a**, the AGT product **17a** was obtained as a major product at both −20 and −40 °C (Entries 1 and 2, Table 1). A small amount of lactose **16a** was obtained at



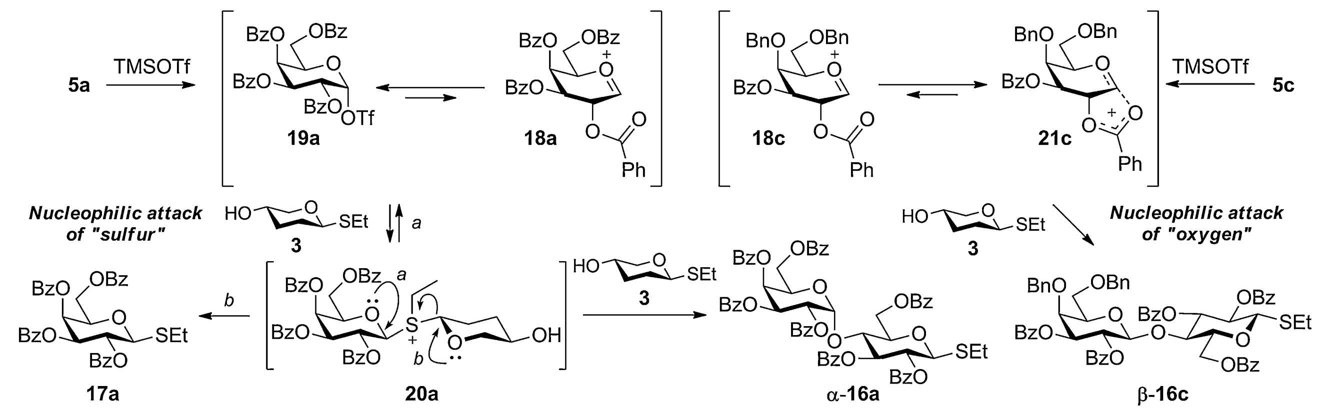
Scheme 2. a) BzCl, DMAP, CH_2Cl_2, 95%; b) $Ce(NO_3)_6$-$(NH_4)_2$, CH_3CN–H_2O–CCl_4 (8:1:1); for **8**, 0 °C to rt, **9**: 60% (α:β = 4:1), **10**: 8%; for **11**, 0 °C, **12**: 52% (α:β = 3:1), **13**: 14%; for **6**, 0 °C, **14**: 46% (α:β = 5:1), **15**: 15%; c) CF_3C-(NPh)Cl, K_2CO_3, acetone; for **9**: 99% (7:2 mixture); for **12**: 89% (5:3 mixture); for **14**: 64% (α only); d) 2-benzyloxy-1-methylpyridinium triflate, MgO, $ClCH_2CH_2Cl$, reflux, 18%.

Table 1. Glycosylation of **5a**–**5d** with **3**



Entry	Donor	R[1]	R[2]	Temp/°C	**16** (α:β)[a]	**17**[a]
1	**5a**	Bz	Bz	−40	not obtained	50%
2				−20	10% (1:5)[b,c]	63%
3[d]				−20	11% (1:1)[b,e]	53%
4	**5b**	Bz	Bn	−40	20% (β only)	32%
5				−20	36% (β only)	56%
6	**5c**	Bn	Bn	−40	75% (β only)	not obtained
7				−20	69% (β only)	not obtained
8	**5d**	–CHPh–		−40	44% (1:2.4)[f]	not obtained
9				−20	43% (1:1.7)[f]	not obtained

[a]Yields of **16** and **17** were calculated on the basis of **5**. [b]The ratio of product **16a**–**16c** was determined by ^{1}H NMR. [c]Orthoester was obtained in 7% yield. [d]The reaction was conducted in CH_3CN. [e]Orthoester was obtained in 6% yield. [f]The ratio of product **16d** was calculated from the isolated yields.



Scheme 3. Representative plausible mechanism of the glycosylation of **5a** or **5c** with **3** for the formation of **α-16a**, **β-16c**, and **17a**.

−20 °C, but surprisingly it was a mixture of α- and β-isomers despite the presence of the participating 2-OBz group. Next, we examined the reaction using donors **5b** and **5c** with one or two benzyl group(s) on 4-O or 6-O. As shown in Table 1, the ratio of glycosylation product **16** and AGT product **17** was dramatically changed depending on the nature of the protecting groups on 4-O and 6-O of donors **5**. Replacement of the Bz group on 6-O with a Bn group resulted in the formation of lactose **16b** in moderate yield, but AGT product **17b** was still the major product (Entries 4 and 5). In contrast, the lactose **16c** was cleanly formed at both temperatures when donor **5c** with benzyl ether at both 4-O and 6-O was used (Entries 6 and 7). These results indicated that at least two electron-donating benzyl ethers are needed to allow this glycosylation to proceed to afford **16** without the formation of the undesired AGT product **17**.

In the present study, we focused on the effect of the number of electron-donating groups on the galactose donor in the reaction with thioglycoside acceptor. On the basis of plausible mechanisms of glycosylation[14] and AGT reaction,[5] our results can be explained as shown below. In this system, treatment of **5** with TMSOTf should first generate a cationic species and then provide an equilibrium mixture of oxacarbenium species **18**, dioxalenium species **21** arising from neighboring participation of the 2-OBz group, and neutral glycosyl triflate[15] **19** (Scheme 3). Next, in the presence of thioglycoside **3**, sulfonium intermediate **20** would be formed via nucleophilic attack of the sulfur atom, and/or glycosylation would occur via nucleophilic attack of the oxygen atom of **3**.

In the case of **5a**, cationic oxacarbenium species **18a** would be destabilized due to the electron-withdrawing effect of the protecting group. NMR experiments reported by Huang et al. indicated that the α-glycosyl triflate **19a** was the only observable intermediate generated from 2,3,4,6-tetra-*O*-benzoylgalactose donor having a TolS– group as a leaving group stimulated by AgOTf and p-TolSCl, and the oxacarbenium species **18a** was not detected. They have also shown that treatment of α-glycosyl triflate **19a** with per-benzoylated acceptor did not produce any glycosylated products.[16] In accordance with Huang's observations, reaction of **5a** with the oxygen atom of **3** was only a minor process in this case, since neutral α-glycosyl triflate **19a** has low reactivity. Instead, nucleophilic attack of the sulfur atom on **18a** (or **19a**) would be favored, giving sulfonium ion **20a**, which would be the predominant intermediate in this reaction. Reversal to oxacarbenium species **18a** (Scheme 3, path a) appears to be unfavorable, so AGT reaction from **18a** (Scheme 3, path b) would proceed preferentially to afford **17a**. A small amount of α-**16a** was observed even in the presence of a participating functionality on 2-O. Displacement of sulfonium ion **20a** by alcohol of acceptor **3**[1,17] or unusual nucleophilic attack of **3** toward the α-face[18] of minor intermediate **18a** would provide α-**16a**. Although we examined the reaction in CH_3CN in order to increase the amount of **18a** (by solvation), the yield of **16a** was not improved, and the selectivity was decreased (Table 1, Entry 3).

A benzyl group at the 6-O position (**5b**) enhanced the reverse reaction from the corresponding sulfonium ion to the cationic oxalenium intermediate (Scheme 3, path a), in which the slight electron-donating effect from 6-O might contribute to increase the electron density of 5-O and stabilize the cationic species. As a result, the yield of β-**16b** was increased, and no α-isomer α-**16b** was observed, although AGT product **17b** was still the major product. It appeared that the two benzyl groups of **5c** bias the equilibrium toward cationic intermediates such as **18c** and **21c** and away from the corresponding neutral intermediate and/or sulfonium ion, thereby promoting the glycosylation pathway, in which no AGT product and no α-isomer α-**16c** are formed. Since Huang et al. observed formation of the dioxalenium species in NMR experiments with 3,4,6-tri-*O*-benzyl-2-*O*-benzoylgalactose derivatives,[16] the intermediate from **5c** might also be dioxalenium **21c**, even though one benzyl group was replaced with a benzoyl group. According to Li and Gildersleeve, only in the case of the use of "armed" perbenzylated 2-azide GalNAc donor with "disarmed" perbenzoylated thioglycoside acceptor did the glycosylation successfully proceed to give a GalNAcα1-3Gal disaccharide without formation of the AGT product.[7] On the other hand, our results suggest that tuning the number of electron-donating groups on donor molecules is effective to control the reaction pathway for the glycosylation with "disarmed" thioglycoside acceptor.[18]

To verify the effect of the electron-donating group, glycosylation of the 4,6-benzylidene-protected donor **5d** was also examined. As we expected, lactose derivative **16d** was obtained in moderate yield without formation of AGT product **17d**. In this case, the α-isomer of α-**16d** was obtained in a significant amount, even in the presence of the participating 2-OBz group, as reported previously (Entries 8 and 9, Table 1).[19–21] Stabilization of cationic oxacarbenium species (similar to **18c**) and destabilization of the dioxalenium species (similar to **21c**) due to the ring strain of the 4,6-benzylidene group might account this reactivity and low stereoselectivity.

In conclusion, we confirmed the ability of electron-donating groups on the galactose donor in the reaction with thioglycoside acceptor to prevent AGT reaction in lactose synthesis.[22] We hope to apply this finding to galactose donors having CF_2-functionality at C3, aiming at the synthesis of complex sialidase-resistant CF_2-linked ganglioside analogs.

References and Notes

1 a) G.-J. Boons, in *Glycoscience: Chemistry and Chemical Biology*, ed. by B. Fraser-Reid, K. Tatsuta, J. Thiem, Springer-Verlag Berlin Heidelberg, **2001**, Vol. 1, Chap. 3.3.2, pp. 551–581. b) W. Zhong, G.-J. Boons, D. Crich, A. A. Bowers, W. Szeja, G. Grynkiewicz, in *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*, ed. by A. V. Demchenko, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2008**, Chap. 4, pp. 261–361.
2 K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503.
3 Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 734.
4 Selected examples of AGT reactions: a) J. Kihlberg, E. Eichler, D. R. Bundle, *Carbohydr. Res.* **1991**, *211*, 59. b) S. Knapp, S. R. Nandan, *J. Org. Chem.* **1994**, *59*, 281. c) D. A. Leigh, J. P. Smart, A. M. Truscello, *Carbohydr. Res.* **1995**, *276*, 417. d) Y. Du, J. Lin, R. Linhardt, *J. Carbohydr. Chem.* **1997**, *16*, 1327. e) H. Yu, B. Yu, X. Wu, Y. Hui, X. Han, *J. Chem. Soc., Perkin Trans. 1* **2000**, 1445. f) T. Zhu, G.-J. Boons, *Carbohydr. Res.* **2000**, *329*, 709. g) A. A. Sherman, O. N. Yudina, Y. V. Mironov, E. V. Sukhova, A. S. Shashkov, V. M. Menshov, N. E. Nifantiev, *Carbohydr. Res.* **2001**, *336*, 13. h) R. Geurtsen, G.-J. Boons, *Tetrahedron Lett.* **2002**, *43*, 9429. i) H. Tanaka, M. Adachi, T. Takahashi, *Tetrahedron Lett.* **2004**, *45*, 1433. j) J. Xue, S. D. Khaja, R. D. Locke, K. L. Matta, *Synlett* **2004**, 861. k) J. D. C. Codée, B. Stubba, M. Schiattarella, H. S. Overkleeft, C. A. A. van Boeckel, J. H. van Boom, G. A. van der Marel, *J. Am. Chem. Soc.* **2005**, *127*, 3767.
5 a) G. Hirai, T. Watanabe, K. Yamaguchi, T. Miyagi, M. Sodeoka, *J. Am. Chem. Soc.* **2007**, *129*, 15420. b) T. Watanabe, G. Hirai, M. Kato, D. Hashizume, T. Miyagi, M. Sodeoka, *Org. Lett.* **2008**, *10*, 4167. c) M. Sodeoka, G. Hirai, T. Watanabe, T. Miyagi, *Pure Appl. Chem.* **2009**, *81*, 205.
6 Z. Li, J. C. Gildersleeve, *J. Am. Chem. Soc.* **2006**, *128*, 11612.
7 Z. Li, J. C. Gildersleeve, *Tetrahedron Lett.* **2007**, *48*, 559.
8 T. Mukaiyama, K. Takeuchi, H. Jona, H. Maeshima, T. Saitoh, *Helv. Chim. Acta* **2000**, *83*, 1901.
9 a) B. Yu, H. Tao, *Tetrahedron Lett.* **2001**, *42*, 2405. b) B. Yu, H. Tao, *J. Org. Chem.* **2002**, *67*, 9099.
10 W. Peng, X. Han, B. Yu, *Synthesis* **2004**, 1641.
11 Z. Zhang, G. Magnusson, *J. Org. Chem.* **1996**, *61*, 2383.
12 M. A. Nashed, M. S. Chowdhary, L. Anderson, *Carbohydr. Res.* **1982**, *102*, 99.
13 a) K. W. C. Poon, S. E. House, G. B. Dudley, *Synlett* **2005**, 3142. b) K. W. C. Poon, G. B. Dudley, *J. Org. Chem.* **2006**, *71*, 3923.
14 As a recent review: L. K. Mydock, A. V. Demchenko, *Org. Biomol. Chem.* **2010**, *8*, 497.
15 Recent example: T. Nokami, Y. Nozaki, Y. Saigusa, A. Shibuya, S. Manabe, Y. Ito, J. Yoshida, *Org. Lett.* **2011**, *13*, 1544.
16 Y. Zeng, Z. Wang, D. Whitfield, X. Huang, *J. Org. Chem.* **2008**, *73*, 7952.
17 J.-H. Kim, H. Yang, J. Park, G.-J. Boons, *J. Am. Chem. Soc.* **2005**, *127*, 12090.
18 H. D. Prematilake, L. K. Mydock, A. V. Demchenko, *J. Org. Chem.* **2010**, *75*, 1095.
19 L. Chen, F. Kong, *Tetrahedron Lett.* **2003**, *44*, 3691.
20 J.-C. Jacquinet, *Carbohydr. Res.* **2004**, *339*, 349.
21 Using the same donor as in ref. 17, β-selective glycosylation was realized: S. Janssen, R. R. Schmidt, *J. Carbohydr. Chem.* **2005**, *24*, 611.
22 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.