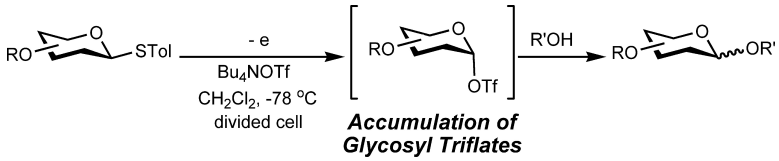
Article

Electrochemical Generation of Glycosyl Triflate Pools

Toshiki Nokami, Akito Shibuya, Hiroaki Tsuyama, Seiji Suga, Albert A. Bowers, David Crich, and Jun-ichi Yoshida

J. Am. Chem. Soc., **2007**, 129 (35), 10922-10928• DOI: 10.1021/ja072440x • Publication Date (Web): 14 August 2007



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 7 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 08/14/2007

Electrochemical Generation of Glycosyl Triflate Pools

Toshiki Nokami,[†] Akito Shibuya,[†] Hiroaki Tsuyama,[†] Seiji Suga,[†] Albert A. Bowers,[‡] David Crich,[‡] and Jun-ichi Yoshida*[,†]

Contribution from the Departments of Synthetic Chemistry, Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Kyoto 615-8510, Japan, and Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607-7061

Received April 7, 2007; E-mail: yoshida@sbchem.kyoto-u.ac.jp

Abstract: Glycosyl triflates, which serve as important intermediates in glycosylation reactions, were generated and accumulated by the low-temperature electrochemical oxidation of thioglycosides such as thioglucosides, thiogalactosides, and thiomannosides in the presence of tetrabutylammonium triflate (Bu_4NOTf) as a supporting electrolyte. Thus-obtained solutions of glycosyl triflates (glycosyl triflate pools) were characterized by low-temperature NMR measurements. The thermal stability of glycosyl triflates and their reactions with glycosyl acceptors were also examined.

Introduction

Among the many glycosyl cation equivalents, glycosyl triflates have been recognized as important intermediates in modern chemical glycosylation methodologies.[1] Kronzer and Schuerch developed the silver triflate-assisted methanolysis of glycosyl chloride and proposed the existence of glycosyl triflate intermediates.[2] Although related intermediates such as glycosyl toluenesulfonates were isolated and characterized in their subsequent studies,[3] glycosyl triflates have been successfully characterized only recently using low-temperature NMR mesurements.[1a,4] Since then, several methods for iterative glycosylation have been developed on the basis of the pregeneration of glycosyl triflates or related intermediates before the addition of glycosyl acceptors.[5] These glycosyl triflates usually have been generated from thioglycosides, which are the glycosyl donors of choice, because of their stability under atmospheric conditions and a variety of reaction conditions. However, this very stability on occasion leads to difficulties in the activation process. Indeed, strong thiophilic reagents are required for the generation of glycosyl triflates from thioglycosides resulting in the formation of activator-based byproducts, which can influence the stability and reactivity of glycosyl triflates. Therefore, a new straightforward method for the generation of glycosyl triflates is highly desired.

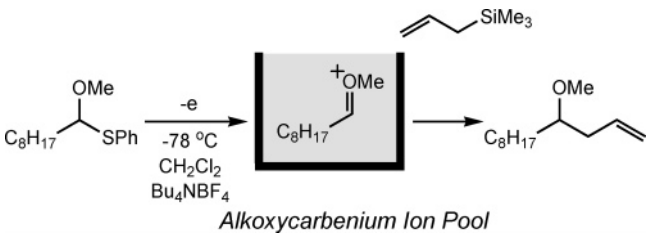
The electrochemical reactions serve as powerful methods for activation of organic compounds without using highly reactive chemical reagents.[6] We have developed the "cation pool" method that involves the irreversible electrochemical oxidative generation and accumulation of highly reactive carbocations in the absence of nucleophiles.[7] Successful generation and accumulation of alkoxy carbenium ions from α-silyl ethers encouraged us to generate and accumulate the glycosyl cations as "glycosyl cation pools" (Scheme 1). Unfortunately, the Bu_4NBF_4/CH_2Cl_2 system that is the standard supporting electrolyte/solvent system of the "cation pool" method gave fluoroglycosides from thioglycosides.[8,9] By using tetrabutylammonium perchlorate (Bu_4NClO_4) as a supporting electrolyte, however, we could accumulate glycosyl cation equivalents that gave

[†] Kyoto University.
[‡] University of Illinois at Chicago.

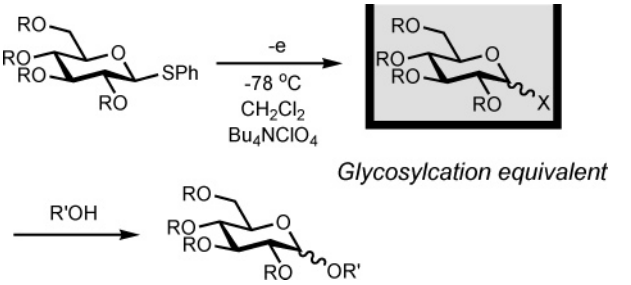
(1) (a) Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 667. (b) Codée, J. D. C.; Litjens, R. E. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769. (c) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503.
(2) (a) Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1973**, *27*, 379. (b) Lucas, T. J.; Schuerch, C. *Carbohydr. Res.* **1975**, *39*, 39. (c) Srivastava, V. K.; Schuerch, C. *Carbohydr. Res.* **1980**, *79*, C13. (d) Srivastava, V. K.; Schuerch, C. *J. Org. Chem.* **1981**, *46*, 1121. (e) Leroux, J.; Perlin, A. S. *Carbohydr. Res.* **1976**, *47*, C8.
(3) Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1973**, *27*, 379.
(4) (a) Crich, D.; Patel, M. *Carbohydr. Res.* **2006**, *341*, 1467. (b) Crich, D.; Banerjee, A. *J. Am. Chem. Soc.* **2006**, *128*, 8078. (c) Crich, D.; Bowers, A. A. *J. Org. Chem.* **2006**, *71*, 3452. (d) Crich, D.; Jayalath, P.; Hutton, T. K. *J. Org. Chem.* **2006**, *71*, 3064. (e) Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277. (f) Crich, D.; Banerjee, A. *Org. Lett.* **2005**, *7*, 1395. (g) Crich, D.; Vinod, A. U. *J. Org. Chem.* **2005**, *70*, 1291. (h) Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Asymmetry* **2005**, *16*, 105. (i) Crich, D.; Li, W.; Li, H. *J. Am. Chem. Soc.* **2004**, *126*, 15081. (j) Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930. (k) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386. (l) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 8232. (m) Crich, D.; Vinod, A. U.; Picione, J. *J. Org. Chem.* **2003**, *68*, 8453. (n) Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142. (o) Crich, D.; Yao, Q. *Org. Lett.* **2003**, *5*, 2189. (p) Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781. (q) Dudkin, V. Y.; Crich, D. *Tetrahedron Lett.* **2003**, *44*, 1787. (r) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867. (s) Crich, D.; Li, H. *J. Org. Chem.* **2002**, *67*, 4640. (t) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2002**, *124*, 2263. (u) Crich, D.; de la Mora, M.; Cruz, R. *Tetrahedron* **2002**, *58*, 35. (v) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015. (w) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819. (x) Crich, D.; Li, H.; Yao, Q.; Wink, D. J.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 5826.
(5) (a) Nguyen, H. M.; Poole, J. L.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 414. (b) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766. (c) Yamago, S.; Yamada, T.; Maruyama, T.; Yoshida, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2145. (d) Huang, X.; Huang, L.; Wang, H.; Ye, X. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221. (e) Yamada, T.; Kinjyo, S.; Yoshida, J.; Yamago, S. *Chem. Lett.* **2005**, *34*, 1556. (f) Yamada, T.; Takemura, K.; Yoshida, J.; Yamago, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7575.
(6) (a) *Rodd's Chemistry of Carbon Compounds;* Sainsbury, M., Ed.; Elsevier: Amsterdam, 2002; Vol. V. (b) *Organic Electrochemistry*, 4th ed.; Lund, H., Hammerich, O., Eds.; Marcel Dekker: New York, 2001. (c) *Novel Trends in Electroorganic Synthesis;* Torii, S., Ed.; Springer-Verlag: Tokyo, 1998.

 10.1021/ja072440x CCC: $37.00

Scheme 1



Scheme 2



glycosylation products after the addition of nucleophiles (Scheme 2).[8] Although the formation of glycosyl perchlorates was most likely, it proved difficult to determine the electrochemically generated species by NMR. We envisioned that the glycosyl triflates, which serve as important intermediates in glycosylation reactions, could be generated and accumulated by the electrochemical method using tetrabutylammonium triflate (Bu_4NOTf) as a supporting electrolyte. This idea has now been reduced to practice, and we report herein the successful generation and accumulation of glycosyl triflates and their characterization by the low-temperature NMR analysis. The thermal stability of glycosyl triflates and their reactions with glycosyl acceptors are also described.

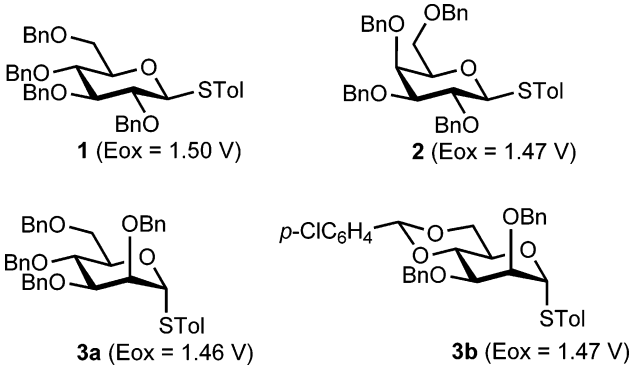


Figure 1. Oxidation potentials of thioglucosides.

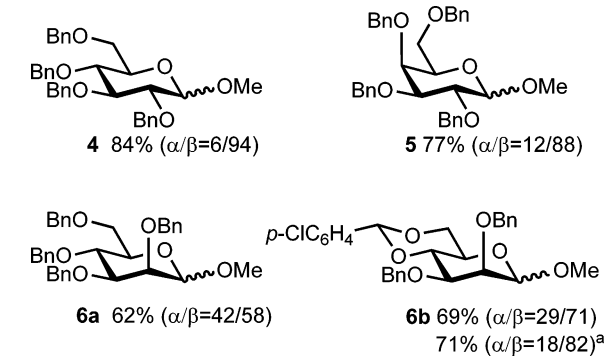


Figure 2. Electrochemical oxidation of thioglucosides followed by the reactions with methanol. [a] The reaction was carried out with 3.0 equiv of Bu_4NOTf.

Results and Discussion

Oxidation Potentials of Thioglycosides. We initiated our study by determining the oxidation potentials of thioglycosides by rotating disk electrode voltammetry using Bu_4NOTf as a supporting electrolyte in CH_2Cl_2 (Figure 1). All these thioglycosides **1**−**3** have sufficiently low oxidation potentials for preparative electrochemical oxidation in the Bu_4NOTf/CH_2Cl_2 system. It should be noted that the 4,6-*O*-benzylidene protecting group, which has been indispensable for the β-selective mannosylation, was oxidized and cleaved during the electrochemical oxidation. However, the use of the 4,6-*O*-*p*-chlorobenzylidene protecting group was effective for the selective oxidation of thiomannosides.

Coupling of Electrochemically Generated Glycosyl Triflates with Methanol. With data for oxidation potentials in hand, we examined the constant current electrochemical oxidation of thioglycosides **1**−**3** in the absence of an acceptor in CH_2Cl_2 at −78 °C, with Bu_4NOTf (6.0 equiv) intended to serve as both the supporting electrolyte and the source of a triflate anion. The use of a smaller amount of Bu_4NOTf resulted in higher cell voltage (>50 V). An H-type divided cell equipped with a carbon felt anode, a platinum plate cathode, and a glass filter separator was used, and the electrolysis was conducted under the conditions of constant current (4.0 mA, 1.5−2.0 F/mol of electricity). In the next step, the thus-generated intermediate was allowed to react with methanol (Figure 2). Under these conditions, thioglycoside **1** afforded the corresponding methyl

(7) (a) Yoshida, J.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**, *121*, 9546. (b) Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 10244. (c) Suga, S.; Okajima, M.; Yoshida, J. *Tetrahedron Lett.* **2001**, *42*, 2173. (d) Suga, S.; Okajima, M.; Fujiwara, K.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 7941. (e) Suga, S.; Suzuki, S.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 30. (f) Yoshida, J.; Suga, S. *Chem.−Eur. J.* **2002**, *8*, 2650. (g) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (h) Suga, S.; Nagaki, A.; Yoshida, J. *Chem. Commun.* **2003**, 354. (i) Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J. *Org. Lett.* **2003**, *5*, 945. (j) Suga, S.; Kageyama, Y.; Babu, G.; Itami, K.; Yoshida, J. *Org. Lett.* **2004**, *6*, 2709. (k) Suga, S.; Suzuki, S.; Maruyama, T.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1545. (l) Suga, S.; Nishida, T.; Yamada, D.; Nagaki, A.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14338. (m) Nagaki, A.; Kawamura, K.; Suga, S.; Ando, T.; Sawamoto, M.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 14702. (n) Okajima, M.; Suga, S.; Itami, K.; Yoshida, J. *J. Am. Chem. Soc.* 2005, *127*, 6930. (o) Maruyama, T.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 7324. (p) Nagaki, A.; Togai, M.; Suga, S.; Aoki, N.; Mae, K.; Yoshida, J. *J. Am. Chem. Soc.* **2005**, *127*, 11666. (q) Suga S.; Matsumoto, K.; Ueoka, K.; Yoshida, J. *J. Am. Chem. Soc.* **2006**, *128*, 7710. (r) Maruyama, T.; Suga, S.; Yoshida, J. *Tetrahedron* **2006**, *62*, 6519. (s) Maruyama, T.; Mizuno, Y.; Shimizu, I.; Suga, S.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 1902.

(8) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3755.

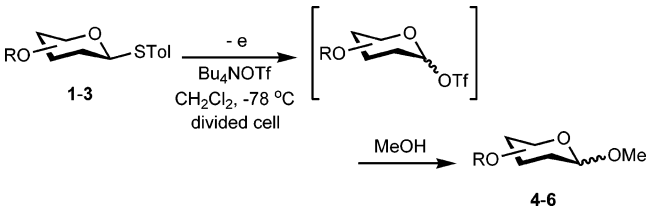
(9) Electrochemical glycosylation: (a) Noyori, R.; Kurimoto, I. *J. Org. Chem.* **1986**, *51*, 4322. (b) Amatore, C.; Jutand, A.; Mallet, J.-M.; Meyer, G.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1990**, 718. (c) Balavoine, G.; Gref, A.; Fischer, J.-c.; Lubineau, A. *Tetrahedron Lett.* **1990**, *31*, 5761. (d) Mallet, J.-M.; Meyer, G.; Yvelin, F.; Jutand, A.; Amatore, C.; Sinay, P. *Carbohydr. Res.* **1993**, *244*, 237. (e) Amatore, C.; Jutand, A.; Meyer, G.; Bourhis, P.; Machetto, F.; Sinay, P.; Tabeur, C.; Zhang, Y.-M. *J. Appl. Electrochem.* **1994**, *24*, 725. (f) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-c.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1217. (g) Balavoine, G.; Berteina, S.; Gref, A.; Fischer, J.-c.; Lubineau, A. *J. Carbohydr. Chem.* **1995**, *14*, 1237. (h) Yamago, S.; Kokubo, K.; Yoshida, J. *Chem. Lett.* **1997**, 111. (i) Nokami, J.; Osafune, M.; Ito, Y.; Miyake, F.; Sumida, S.; Torii, S. *Chem. Lett.* **1999**, 1053. (j) Yamago, S.; Kokubo, K.; Hara, O.; Masuda, S.; Yoshida, J. *J. Org. Chem.* **2002**, *67*, 8584. (k) France, R. R.; Rees, N. V.; Wadhawan, J. D.; Fairbanks, A. J.; Compton, R. G. *Org. Biomol. Chem.* **2004**, *2*, 2188. (l) France, R. R.; Compton, R. G.; Davis, B. G.; Fairbanks, A. J.; Rees, N. V.; Wadhawan, J. D. *Org. Biomol. Chem.* **2004**, *2*, 2188. (m) Mitsudo, K.; Kawaguchi, T.; Miyahara, S.; Matsuda, W.; Kuroboshi, M.; Tanaka, H. *Org. Lett.* **2005**, *7*, 4649.

glucoside **4** in 84% yield (α/β = 6/94). Di(*p*-tolyl)disulfide was obtained as a byproduct (55%), which is inactive to thioglycosides.

Chemical generation of the glycosyl triflate from **1** was also examined. Treatment of **1** with trifluoromethanesulfonic acid in the presence of diphenylsulfoxide (DPSO) and tri-*t*-butylpyrimidine (TTBP) in CH_2Cl_2 at −78 °C for 15 min followed by the reaction of thus-generated species with methanol at the same temperature for 1 h gave **4** in 87% yield (α/β = 36/64).[10] It is important to note that α/β selectivity of the chemical method is lower than that of the electrochemical method, although the yield is comparable. Another advantage of the electrochemical method is no use of TTBP, which is rather difficult to remove by simple operation, whereas the supporting electrolyte (Bu_4NOTf) can be easily removed by filtration through a short silica gel column. Separation of di(*p*-tolyl)disulfide formed by the electrochemical method is also easy. Therefore, higher α/β selectivity and purification ease are benefits of the present electrochemical protocol from a synthetic point of view.

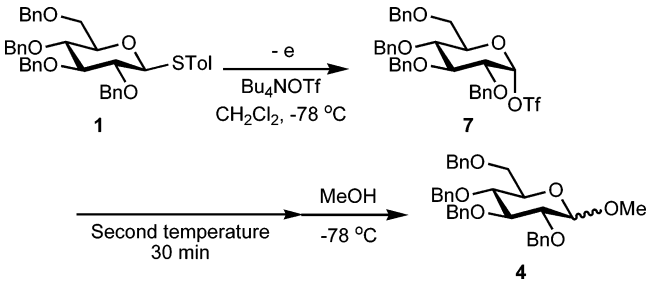
Thiogalactoside **2** also gave the corresponding β-methyl galactoside **5** with moderate selectively. On the other hand, the reaction of thiomannoside **3a** afforded a ca. 1:1 mixture of the α- and β-methyl mannoside **6a**. It is interesting to note that both yield and β-selectivity of the mannosylation reaction were improved by the introduction of *p*-chloro-4,6-*O*-benzylidene protecting group. Moreover, the use of a smaller amount of Bu_4NOTf (3.0 equiv) led to better β-selectivity in the case of the mannosides. These selectivities fit the pattern previously established for glycosylation reactions conducted with chemically generated glycosyl triflates.[4] If the α-glycosyl triflate is viewed as a reservoir for a transient β-selective contact ion pair and an associated α-selective solvent-separated ion pair, the decrease in β-selectivity seen with the benzylidene-protected mannosyl donor with increased concentration of Bu_4NOTf must be due to the corresponding increase in solvent polarity which supports a greater concentration of the solvent separated ion pair.[4k] Alternatively, the possibility that increased triflate concentration promotes in situ anomerization and the intermediacy of a low concentration of a more reactive α-selective β-glycosyl triflate and associated contact ion pair cannot be excluded.[11] The generally increased β-selectivity seen with the benzylidene-protected mannosyl triflate derived from **3b** over that seen with the corresponding perbenzyl system **3a** is due to the locking of the C5−C6 bond in its most electron-withdrawing trans-gauche conformation, which limits the concentration of the solvent-separated ion pair.[12]

Electrochemical Generation of a Glucosyl Triflate Pool. To confirm the generation of glycosyl triflates, the anodic



solution was characterized by low-temperature NMR spectroscopy. For example, the anodic solution obtained by the low-temperature electrochemical oxidation of thioglucoside **1** in CD_2Cl_2 at −78 °C exhibited a single set of signals in its ^1H NMR spectrum (Figure 3). Together with the absence of the signals from the starting thioglucoside **1**, this indicates complete conversion and the formation of a single new species. A signal at δ 6.10 (doublet, ^3J H^1H^2 = 2.9 Hz) was assigned to the anomeric proton. No signal around 9.5 ppm due to the proton adjacent to the cationic carbon was observed.[7b] Therefore, the observed species is covalent rather than ionic. The coupling constant points to the glucosyl triflate **7** being the α-anomer.[13] A single set of signals was also observed by ^{13}C NMR spectroscopy, with the resonance at δ 106.9 assigned to the anomeric carbon, as confirmed by the presence of a cross-peak with the ^1H signal at δ 6.10 in the $^1H-^{13}C$ HMQC spectrum. On the basis of these observations, it is reasonable to consider that an α-glucosyl triflate **7** was generated and accumulated under the conditions of the low-temperature electrochemical oxidation.

The thermal stability of glucosyl triflate **7** was investigated by the method we reported previously (Figure 4).[7b] A solution of glucosyl triflate **7**, which was produced by the electrochemical oxidation of thioglycoside **1** at −78 °C, was allowed to warm to the second temperature. After equilibration for 30 min, the resulting solution was recooled to −78 °C and then allowed to react with methanol for 30 min. Figure 4 shows that yields of methyl glucoside **4** changed around 10% at temperatures between −78 and −50 °C. Thus, we assume that glucosyl triflate **7** is stable at temperatures lower than −50 °C.



Electrochemical Generation of a Galactosyl Triflate Pool. Successful characterization of glucosyl triflate **7** encouraged us to confirm the generation of other glycosyl triflates by low-temperature NMR spectroscopy. The anodic solution obtained by the low-temperature electrochemical oxidation of thiogalactoside **2** in CD_2Cl_2 at −78 °C exhibited a single set of signals in its ^1H NMR spectrum (Figure 5). Together with the absence of the signals from the starting thiogalactoside **2**, this indicates complete conversion and the formation of a single new species. A signal at δ 6.14 (doublet, ^3J H^1H^2 = 3.4 Hz) was assigned to

(10) (a) Codée, J. D. C.; Litjens, R. E. J. N.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519. (b) van den Bos, L. J.; Codée, J. D. C.; van Boom, J. H.; Overkleeft, H. S.; van der Marel, G. A. *Org. Biomol. Chem.* **2003**, *1*, 4160. (c) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1947. (d) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *Tetrahedron* **2004**, *40*, 1057. (e) van den Bos, L. J.; Codée, J. D. C.; van der Toorn, J. C.; Boltje, T. J.; van Boom, J. H.; Overkleeft, H. S.; van der Marel, G. A. *Org. Lett.* **2004**, *6*, 2165. (f) Litjens, R. E. J. N.; van den Bos, L. J.; Codée, J. D. C.; van den Berg, R. J. B. H. N.; Overkleeft, H. S.; van der Marel, G. A. *Eur. J. Org. Chem.* **2005**, 918.

(11) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.

(12) (a) Jensen, H. H.; Nordstrom, M.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205. (b) Litjens, R. E. J. N.; van den Bos, L. J.; Codée, J. D. C.; Overkleeft, H. S.; van der Marel, G. A. *Carbohydr. Res.* **2007**, *342*, 419.

(13) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

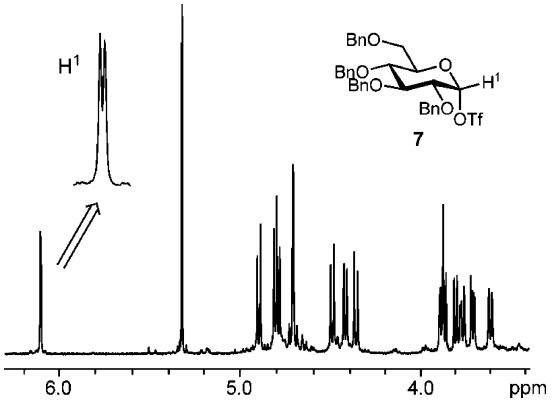


Figure 3. ^{1}H NMR spectrum of glucosyl triflates **7**.

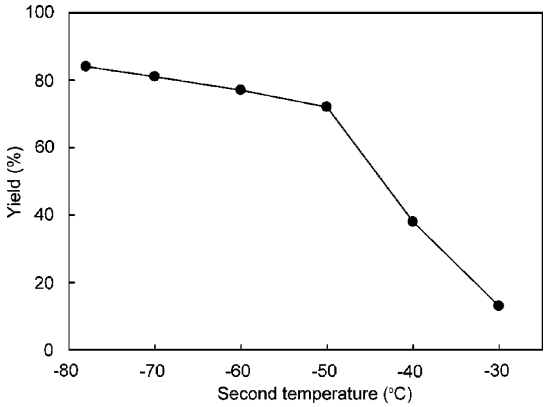


Figure 4. Thermal stability of glucosyl triflates **7**.

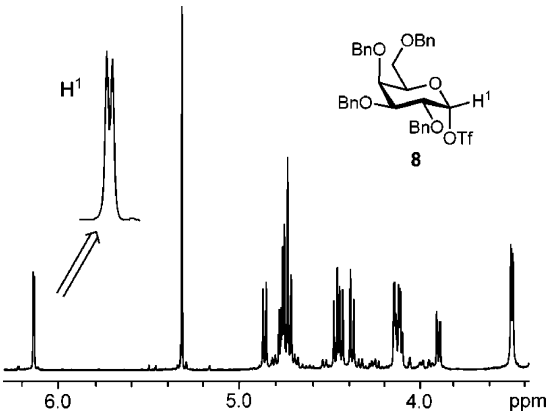


Figure 5. ^{1}H NMR spectrum of galactosyl triflates **8**.

the anomeric proton. The chemical shift indicated that the observed species is covalent rather than ionic. The coupling constant points to the galactosyl triflate **8** being the α-anomer. A single set of signals was also observed by ^{13}C NMR spectroscopy, with the resonance at δ 108.2 assigned to the anomeric carbon, as confirmed by the presence of a cross-peak with the ^{1}H signal at δ 6.14 in the ^{1}H−^{13}C HMQC spectrum. On the basis of these observations, it is reasonable to consider that an α-galactosyl triflate **8** was also generated and accumulated under the conditions of the low-temperature electrochemical oxidation.

The thermal stability of galactosyl triflate **8** was also investigated by the same method used to study glucosyl triflate **7** (Figure 6). A solution of galactosyl triflate **8**, which was produced by the electrochemical oxidation of thiogalactoside **2** at −78 °C, was allowed to warm to a second temperature. After

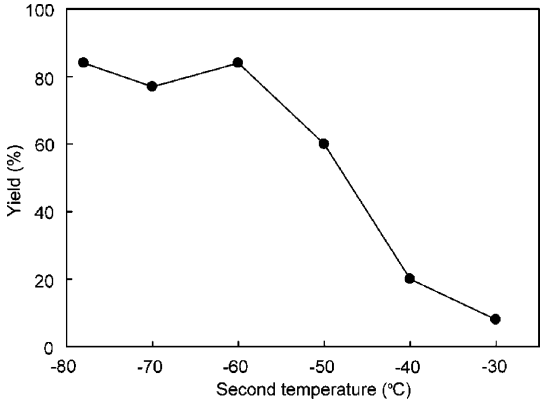


Figure 6. Thermal stability of galactosyl triflates **8**.

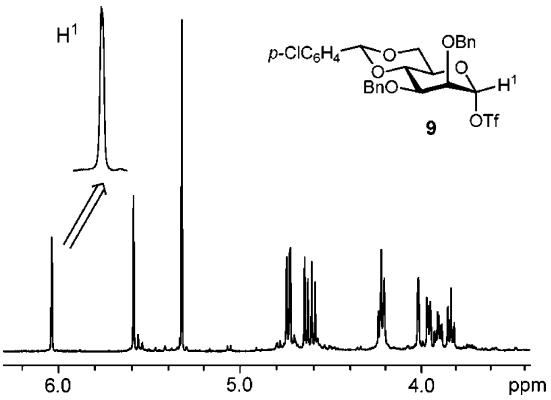
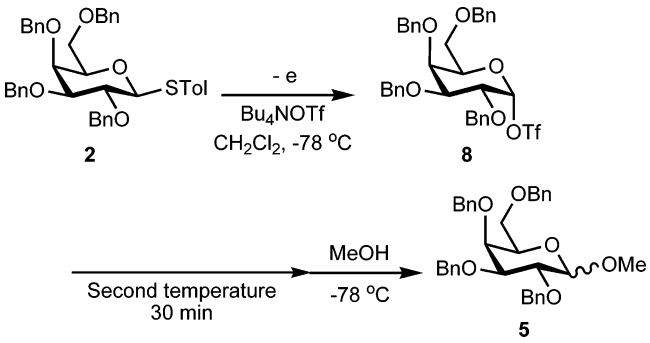


Figure 7. ^{1}H NMR spectrum of mannosyl triflate **9**.

equilibration for 30 min, the resulting solution was recooled to −78 °C and then allowed to react with methanol for 30 min. It is evident that galactosyl triflate **8** is stable at temperatures lower than −60 °C. This result indicates that the thermal stability of galactosyl triflate **8** is almost the same as that of glucosyl triflate **7**.



Electrochemical Generation of a Mannosyl Triflate Pool. Mannosyl triflate **9**, generated from the corresponding thiomannoside **3b**, was also characterized by NMR spectroscopy (Figure 7). A signal at δ 6.04 (singlet) was assigned to the anomeric proton. Again, the chemical shift indicated that the observed species is covalent rather than ionic. A single set of signals was also observed by ^{13}C NMR spectroscopy, with the resonance at δ 105.3 assigned to the anomeric carbon, as confirmed by the presence of a cross-peak with the ^{1}H signal at δ 6.04 in the ^{1}H−^{13}C HMQC spectrum. Additionally, the ^{1}H NMR spectrum of triflate **9** generated by the electrochemical method matched that obtained from thioglycoside **3b** by the

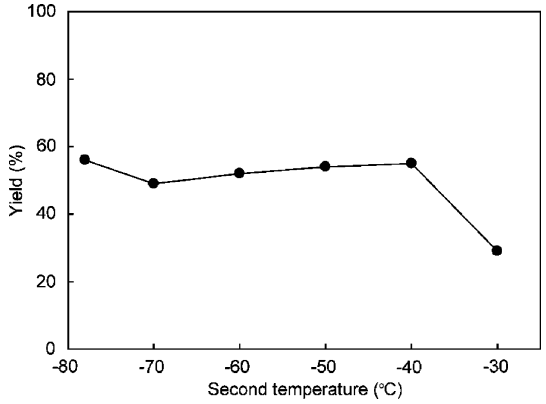
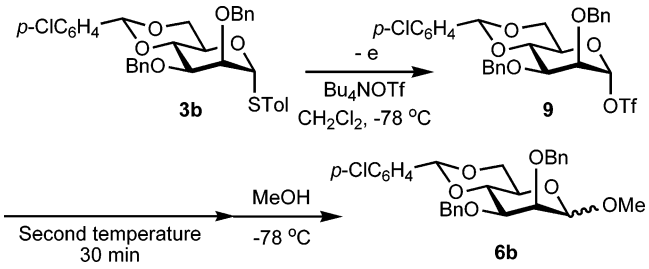


Figure 8. Thermal stability of mannosyl triflates **9**.

more conventional activation with DPSO and trifluoromethanesulfonic anhydride (Supporting Information).[10] In the glucose and galactose series, we assume that the β-selective glycosylations with methanol stem from the α-configuration of the intermediate glycosyl triflates. The reason for the lower β-selectivity observed in the reaction of mannosyl triflate **9**, which also has the α-configuration, remains to be clarified.

The thermal stability of mannosyl triflate **9** was also investigated (Figure 8). A solution of mannosyl triflate **9**, which was produced by the electrochemical oxidation of thiomannoside **3b** at −78 °C, was allowed to warm to a second temperature. After equilibration for 30 min, the resulting solution was recooled to −78 °C and then allowed to react with methanol for 30 min. Although it is difficult to explain why yields were the same at −40 to −78 °C, mannosyl triflate **9** gave the methyl mannoside in moderate yield even at −40 °C.[14] This result indicates the higher thermal stability of mannosyl triflate **9**. The diminished donation of electrons into the σ^* orbital of the C−OTf bond by a carbon−oxygen bond relative to a carbon−hydrogen bond seems to be responsible for the enhanced stability of the mannosyl triflate.



Reactions of Glycosyl Triflates with Carbohydrate Acceptors. To examine reactivity of electrochemically generated glycosyl triflate pools, couplings to carbohydrate acceptors were performed (Figure 9). Reactions of triflates **7**, **8**, and **9** with methyl 2,3,4-tri-*O*-benzyl-α-D-glucoside gave the disaccharides **11**, **12**, and **13a**, respectively, in moderate yields and moderate-to-high β-selectivity. It is interesting to note that the reaction of **9** with methyl 2,3-*O*-isopropylidene-α-L-rhamnopyranoside as a glycosyl acceptor gave only the β-isomer of the disaccharide **13b**. The bulkiness of the acceptor may be responsible for the excellent stereoselectivity. In this method, it is advantageous that thioglycosides having a free hydroxyl group can be used as acceptors. For example, the electrochemical oxidation of thioglycosides **1** and **2** followed by reaction with a thioglycoside acceptor afforded disaccharides **14** and **15**, respectively, which can be used as donors in further glycosylation reactions. The ability to work with thioglycoside-bearing acceptors in this manner is significant. First, it indicates that, unlike the chemical systems where an additional thiophile such as a trialkyl phosphite must be added in such instances,[13a] the byproduct of the electrochemical activation process (i.e., diaryldisulfide) is not itself an oxidant for thioglycosides. Second, it opens up the possibility of sequential glycosylation sequences without the need for intermediate functional group manipulations.[1b]

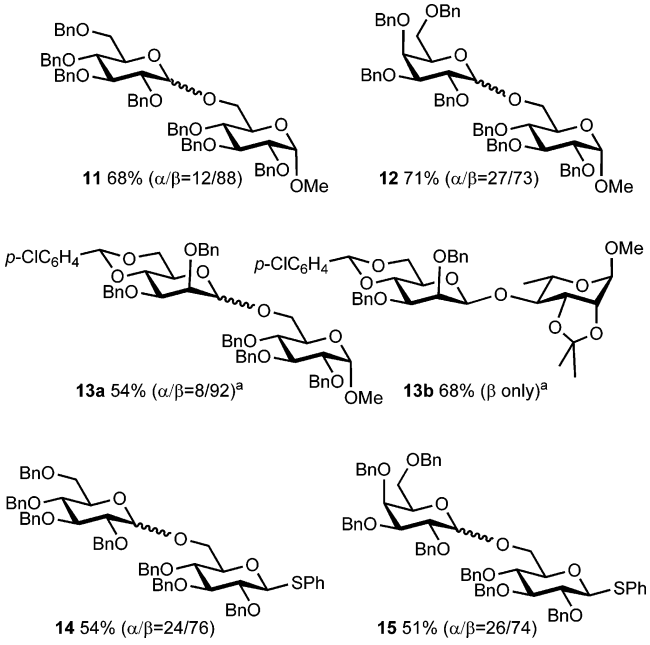


Figure 9. Preparation of disaccharides. [a] Reactions were carried out with 1.5 equiv of Bu_4NOTf.

Conclusions

In conclusion, we have developed a new and simple method for access to glycosyl triflate intermediates using electrochemical oxidation. Solutions of triflates generated by this method are free from byproducts derived due to activator, which are inevitably present when chemical methods are employed. This feature should be advantageous not only from the viewpoint of mechanistic studies but also in the synthesis of polysaccharides. Further mechanistic studies and applications to iterative glycosylation are in progress.

Experimental Section

General Procedures. ^1H and ^{13}C NMR spectra were recorded on a Varian MercuryPlus-400 spectrometer (^1H 400 MHz, ^{13}C 100 MHz). Low-temperature ^1H, ^{13}C NMR, and $^1H-^{13}C$ HMQC spectra were recorded on a JEOL ECA-600P spectrometer (^1H 600 MHz, ^{13}C 150 MHz). EI and CI mass spectra were recorded on a JEOL JMS-SX102A spectrometer, and FAB mass spectra were recorded on a JEOL JMS-HX110A spectrometer. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4 A. Rotating-disk electrode voltammetry was carried out using a BAS 600BS analyzer and BAS RDE-2 rotating disk electrode. Measurements were carried out in 0.1 M Bu_4NOTf/

(14) Although we elongated the reaction time of mannosyl triflate **9** with methanol, yields were not improved.

CH_2Cl_2 using a glassy carbon disk working electrode, a platinum wire counter electrode, and an SCE reference electrode with sweep rate of 10 mV/s at 3000 rpm.

Low-Temperature NMR Analysis of Electrochemically Generated Glycosyl Triflates. The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 250 °C/1 mmHg for 2.5 h before use) and a platinum plate cathode (10 mm × 10 mm). In the anodic chamber were placed **1** (64.6 mg, 0.10 mmol) and 0.1 M Bu_4NOTf in CD_2Cl_2 (5.0 mL). In the cathodic chamber were placed trifluoromethanesulfonic acid (22 μL, 0.25 mmol) and 0.1 M Bu_4NOTf in CD_2Cl_2 (5.0 mL). The constant current electrolysis (4.0 mA) was carried out at −78 °C with magnetic stirring. After 1.25 F/mol of electricity was consumed, an aliquot of the anodic solution was transferred to a 5 mm ϕ NMR tube with a septum cap under Ar atmosphere at −78 °C. The NMR measurement was carried out at −80 °C. Chemical shifts were reported using signals of CH_2Cl_2 at 5.32 ppm (^{1}H NMR) and CD_2Cl_2 at 53.8 ppm (^{13}C NMR) as standards.

Triflyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranoside (7). Selected data for **7** (6.5−3.5 ppm for ^{1}H NMR and 110−60 ppm for ^{13}C NMR). ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 6.10 (d, J = 2.8 Hz, 1 H, anomeric H), 4.90 (d, J = 10.3 Hz, 1 H), 4.80 (d, J = 9.6 Hz, 1 H), 4.79 (d, J = 9.7 Hz, 1 H), 4.72 (d, J = 11.6 Hz, 1 H), 4.69 (d, J = 12.4 Hz, 1 H), 4.49 (d, J = 11.0 Hz, 1 H), 4.42 (d, J = 10.3 Hz, 1 H), 4.36 (d, J = 11.0 Hz, 1 H), 3.90−3.86 (m, 2 H), 3.81 (d, J = 9.6 Hz, 1 H), 3.77 (dm, J = 8.9 Hz, 1 H), 3.71 (dd, J = 9.6, 2.8 Hz, 1 H), 3.62 (d, J = 9.6 Hz, 1 H). ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 106.9 (C1), 79.7, 76.4, 75.5, 75.0, 74.4, 73.8, 73.0, 72.5, 66.1.

Triflyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranoside (8). The anodic oxidation of **2** (64.6 mg, 0.10 mmol) afforded **8**. Selected data for **8**. (6.5−3.4 ppm for ^{1}H NMR and 110−60 ppm for ^{13}C NMR). ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 6.14 (d, J = 3.4 Hz, 1 H, anomeric H), 4.86 (d, J = 10.3 Hz, 1 H), 4.78−4.72 (m, 4 H), 4.47 (d, J = 11.7 Hz, 1 H), 4.44 (d, J = 10.3 Hz, 1 H), 4.38 (d, J = 11.7 Hz, 1 H), 4.15−4.11 (m, 3 H), 3.90 (dd, J = 10.3, 2.0 Hz, 1 H), 3.49 (d, J = 6.8 Hz, 2 H). ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 108.2 (C1), 77.1, 74.8, 73.4, 72.94, 72.89, 72.7, 72.1, 71.8, 66.6.

Triflyl 2,3-Di-*O*-benzyl-4,6-*O*-*p*-chlorobenzylidene-α-D-mannopyranoside (9). The anodic oxidation of **3b** (125 mg, 0.21 mmol) afforded **9**. Selected data for **9** (6.5−3.4 ppm for ^{1}H NMR and 110−60 ppm for ^{13}C NMR). ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 6.04 (s, 1 H, anomeric H), 5.59 (s, 1 H), 4.74 (d, J = 11.7 Hz, 1 H), 4.73 (d, J = 11.0 Hz, 1 H), 4.64 (d, J = 11.0 Hz, 1 H), 4.60 (d, J = 11.7 Hz, 1 H), 4.25−4.21 (m, 2 H), 4.00−3.96 (m, 2 H), 3.92 (td, J = 10.3, 4.8 Hz, 1 H), 3.82 (sm, 4 H). ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 105.3 (C1), 100.2, 76.2, 74.14, 74.11, 73.9, 72.6, 66.9, 66.7.

Reaction of Electrochemically Generated Glycosyl Triflates. Typical Procedure. The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 160 mg, dried at 250 °C/1 mmHg for 2.5 h before use) and a platinum plate cathode (10 mm × 20 mm). In the anodic chamber was placed a solution of tolyl thioglucoside **1** (64.2 mg, 0.10 mmol) in 0.1 M Bu_4NOTf/CH_2Cl_2 (5 mL). In the cathodic chamber was placed a solution of TfOH (22 μL, 0.25 mmol) in 0.1 M Bu_4NOTf/CH_2Cl_2 (5 mL). The constant current electrolysis (4 mA) was carried out at −78 °C with magnetic stirring until 1.5 F/mol of electricity was consumed. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (93 mg, 0.2 mmol, 0.2 M CH_2Cl_2 solution) was added to the solution in the anodic chamber. After additional stirring (−78 °C, 1 h), Et_3N (70 μL, 0.5 mmol) was added and the mixture was warmed to room temperature. After filtering through a short column (2 × 3 cm) of silica gel to remove Bu_4NOTf and evaporation of the solvent under reduced pressure, the crude product was purified with preparative gel permeation chromatography (eluent: $CHCl_3$) to afford a mixture of methyl glucosides **11**α and **11**β in 68% yield (66.3 mg, 0.067 mmol, **11**α/**11**β = 12/88).

Selected data of major product. Methyl 2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl-(1 → 6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (11*β*).[15] ^{1}H NMR (400 MHz) δ 7.34−7.14 (m, 35 H), 4.96 (d, J = 11.2 Hz, 1 H), 4.95 (d, J = 10.4 Hz, 1 H), 4.89 (d, J = 10.8 Hz, 1 H), 4.79 (d, J = 9.6 Hz, 1 H), 4.77 (d, J = 11.2 Hz, 2 H), 4.73 (d, J = 11.2 Hz, 1 H), 4.70 (d, J = 10.8 Hz, 1 H), 4.64 (d, J = 12.0 Hz, 1 H), 4.59 (d, J = 3.6 Hz, 1 H), 4.55 (d, J = 11.6 Hz, 2 H), 4.52 (d, J = 10.0 Hz, 1 H), 4.50 (d, J = 10.0 Hz, 1 H), 4.33 (d, J = 7.6 Hz, 1 H), 4.17 (dd, J = 10.8, 2.0 Hz, 1 H), 3.98 (t, J = 8.8 Hz, 1 H), 3.84−3.80 (m, 1 H), 3.71 (dd, J = 10.8, 2.0 Hz, 1 H), 3.66 (d, J = 10.8 Hz, 1 H), 3.65 (d, J = 10.8 Hz, 1 H), 3.61 (d, J = 8.8 Hz, 1 H), 3.57 (d, J = 9.2 Hz, 1 H), 3.53−3.49 (m, 3 H), 3.46 (d, J = 8.8 Hz, 1 H), 3.42 (ddd, J = 9.6, 4.4, 2.0 Hz, 1 H), 3.32 (s, 3 H). ^{13}C NMR (100 MHz) δ 138.7, 138.4, 138.2, 138.2, 138.1, 138.0, 137.9, 128.3, 128.2, 128.2, 128.2, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.4, 127.4, 103.7, 98.0, 84.8, 82.1, 82.0, 79.8, 78.0, 77.9, 75.7, 75.7, 75.0, 75.0, 74.9, 73.4, 73.3, 69.9, 69.0, 68.6, 55.2.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-*p*-chlorobenzyliden-α-D-mannopyranosyl-(1 → 6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (13aα). Glycosylation of **3b** (176 mg, 0.30 mmol) with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (284 mg, 0.61 mmol) afforded **13a**α (138 mg, 0.15 mmol) and **13a**β (12 mg, 0.013 mmol) in 54% yield (**13a**α/**13b**β = 8/92). TLC (hexane/ethyl acetate 5:2): R_f 0.30 (**13a**α), 0.25 (**13a**β). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.18 (m, 29 H), 5.57 (s, 1 H), 4.99 (d, J = 10.8 Hz, 1 H), 4.88−4.85 (m, 2 H), 4.82−4.77 (m, 3 H), 4.74−4.61 (m, 4 H), 4.55 (d, J = 3.6 Hz, 1 H), 4.49 (d, J = 10.8 Hz, 1 H), 4.21 (t, J = 9.6 Hz, 1 H), 4.14 (dd, J = 9.6, 3.6 Hz, 1 H), 3.97 (t, J = 9.2 Hz, 1 H), 3.88 (dd, J = 9.6, 2.8 Hz, 1 H), 3.84−3.75 (m, 4 H), 3.69−3.66 (m, 1 H), 3.60 (d, J = 11.2 Hz, 1 H), 3.45 (dd, J = 9.6, 3.6 Hz, 1 H), 3.38−3.32 (m, 1 H), 3.29 (s, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 138.5, 138.2, 138.0, 137.9, 136.1, 134.5, 128.4, 128.3, 128.21, 128.18, 127.88, 127.85, 127.81, 127.78, 127.66, 127.56, 127.4, 100.7, 99.6, 97.8, 82.0, 80.0, 79.1, 77.6, 76.3, 75.8, 75.7, 75.0, 73.5, 73.3, 72.9, 69.8, 68.8, 66.2, 64.3, 55.1. HRMS (FAB) m/z calcd for $C_{55}H_{57}ClO_{11}$ $[M - H]^+$, 927.3511; found, 927.3527.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-*p*-chlorobenzyliden-*β*-D-mannopyranosyl-(1 → 6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (13a*β*). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.13 (m, 29 H), 5.53 (s, 1 H), 5.15 (d, J = 10.8 Hz, 1 H), 4.90 (d, J = 12.0 Hz, 1 H), 4.84−4.75 (m, 5 H), 4.66 (d, J = 11.6 Hz, 2 H), 4.57 (d, J = 11.6 Hz, 2 H), 4.49 (d, J = 11.6 Hz, 1 H), 4.23 (dd, J = 10.4, 4.8 Hz, 1 H), 4.15 (t, J = 9.6 Hz, 1 H), 4.07−4.05 (m, 1 H), 4.01 (t, J = 9.6 Hz, 1 H), 3.88 (t, J = 10.0 Hz, 1 H), 3.84−3.68 (m, 2 H), 3.51−3.41 (m, 4 H), 3.32 (s, 3 H), 3.19 (td, J = 9.6, 4.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 138.2, 138.1, 137.9, 136.0, 134.6, 128.6, 128.4, 128.33, 128.26, 128.22, 128.1, 128.02, 127.97, 127.92, 127.83, 127.79, 127.54, 127.48, 127.45, 127.39, 101.9, 100.6, 97.8, 82.2, 79.8, 78.6, 77.8, 75.7, 75.6, 74.7, 74.6, 73.3, 72.4, 69.6, 68.5, 68.3, 67.5, 55.1. HRMS (FAB) m/z calcd for $C_{55}H_{57}ClO_{11}$ $[M - H]^+$, 927.3511; found, 927.3527.

Methyl 2,3-Di-*O*-benzyl-4,6-*O*-*p*-chlorobenzylidene-*β*-D-mannopyranosyl-(1 → 4)-2,3-*O*-isopropylidene-α-L-rhamnopyranoside (13b). Glycosylation of **3b** (217 mg, 0.37 mmol) with methyl 2,3-*O*-isopropylidene-α-L-rhaminoside (165 mg, 0.76 mmol) afforded **13b** (173 mg, 0.25 mmol) as a sole product in 68% yield TLC (hexane/ethyl acetate 5:1): R_f 0.30. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46−7.41 (m, 4 H), 7.36−7.26 (m, 10 H), 5.58 (s, 1 H), 5.00 (s, 1 H), 4.92 (d, J = 12.0 Hz, 1 H), 4.87 (s, 1 H), 4.81 (d J = 12.4 Hz, 1 H), 4.63 (d, J = 12.8 Hz, 1 H), 4.59 (d, J = 12.4 Hz, 1 H), 4.26 (dd, J = 10.4, 4.8 Hz, 1 H), 4.19 (t, J = 9.6 Hz, 1 H), 4.14−4.09 (m, 2 H), 3.98−3.92 (m, 2 H), 3.71−3.61 (m, 3 H), 3.41 (s, 3 H), 3.37−3.27 (m, 1 H), 1.51 (s, 3 H), 1.34 (s, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 138.1, 136.0, 134.5, 128.2, 128.0, 127.4, 127.4, 127.4, 127.3, 109.2, 100.6,

(15) Jona, H.; Mandai, H.; Chavasiri, W.; Takeuchi, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291.

100.1, 97.8, 78.6, 78.4, 78.0, 77.8, 76.4, 76.1, 74.9, 72.1, 68.6, 67.6, 64.2, 54.9, 27.9, 26.5, 17.8. HRMS (FAB) *m*/*z* calcd for $C_{37}H_{43}ClO_{10}$ $[M - H]^+$, 681.2467; found, 681.2470.

Acknowledgment. J.Y. and T.N. dedicate this article to the late Professor Yoshihiko Ito in honor of his outstanding contribution to synthetic chemistry. This work was financially supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science. A.A.B. thanks JSPS and NSF for financial support for a study visit to Japan, and the NIH (GM62160) for the support of his work in Chicago. We thank Dr. Takeshi Yamada of Kyoto University for fruitful discussions.

Supporting Information Available: Experimental procedures and spectroscopic data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA072440X