JOC Article
pubs.acs.org/joc

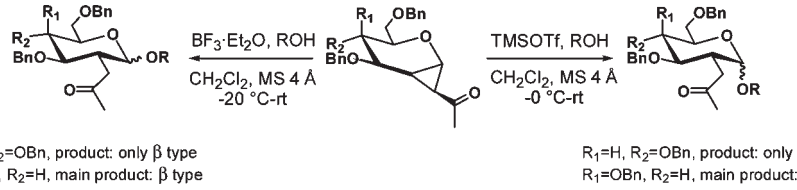
Stereoselective Synthesis of 2-*C*-Branched (Acetylmethyl) Oligosaccharides and Glycoconjugates: Lewis Acid-Catalyzed Glycosylation from 1,2-Cyclopropaneacetylated Sugars

Qiang Tian,[†] Liang Dong,[‡] Xiaofeng Ma,[†] Liyan Xu,[†] Changwei Hu,*[,‡] Wei Zou,[§] and Huawu Shao*[,†]

[†]*Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, China,* [‡]*Key Laboratory of Green Chemistry and Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China, and* [§]*Institute for Biological Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario K1A 0R6, Canada, and Graduate School of Chinese Academy of Sciences, China*

shaohw@cib.ac.cn; gchem@scu.edu.cn

Received September 25, 2010



1,2-Cyclopropaneacetylated sugars as glycosyl donors reacted with a series of glycosyl acceptors (monosaccharides, amino acids, and other alcohols) in the presence of Lewis acid to produce oligosaccharides and glycoconjugates containing 2-*C*-acetylmethylsugars. Galactosyl donor gave good to excellent α-selectivities with TMSOTf as a catalyst, whereas galactosyl donor offered moderate to good *β*-selectivities when $BF_3 \cdot Et_2O$ was used as a catalyst. However, glucosyl donors produced *β*-exclusive selectivity under both conditions. The stereoselectivities of glycosylation depend on the reactivity of donor sugars and Lewis acid catalyst, which effectively dictated the glycosylation pathways. The evidence suggests that galactosyl donors (e.g., **7**) can undergo S_N1 pathway with a strong Lewis acid (TMSOTf) and S_N2 pathway under $BF_3 \cdot Et_2O$, whereas the glucosyl donors (e.g., **8** and **10**) followed S_N2 pathway. The stereoselectivity was also consequential to the formation of a C2′-acetal intermediate formed via the 2-*C*-acetylmethyl group and the anomeric carbonium intermediate in glycosylation.

Introduction

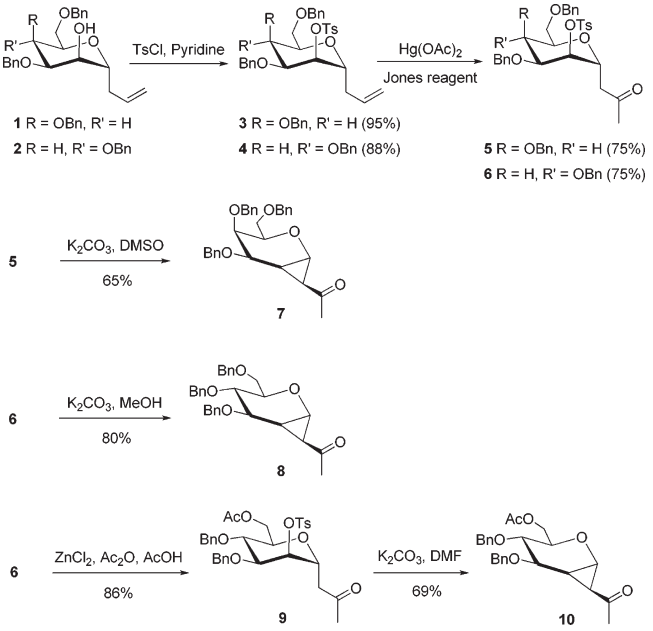
Promiscuous use of 2-*C*-acetylmethylsugars by eukaryotic enzymes as substrates leads to incorporation of 2-*C*-branched sugars into cell surface glycoconjugates as a replacement of 2-*N*-acetamidosugars,[1] consequently providing chemical targets for aminooxy and hydrazide compounds[2−4] and labeling of single-chain antibodies[5,6] for therapeutic and diagnostic purposes. For example, 2-*C*-acetylmethylsugar (2-keto-Gal) is used as a substrate for mutant GalT to detect *O*-GlcNAc-glycosylated proteins,[7−9] and LacNAc moiety of glycoproteins and glycolipids.[10]

(1) Hang, H. C.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2001**, *123*, 1242–1243.
(2) Lemieux, G. A.; Yarema, K. J.; Jacobs, C. L.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 4278–4279.
(3) Yarema, K. J.; Mahal, L. K.; Bruehl, R. E.; Rodriguez, E. C.; Bertozzi, C. R. *J. Biol. Chem.* **1998**, *273*, 31168–31179.
(4) Lee, J. H.; Baker, T. J.; Mahal, L. K.; Zabner, J.; Bertozzi, C. R.; Wiemer, D. F.; Welsh, M. J. *J. Biol. Chem.* **1999**, *274*, 21878–21884.
(5) Ramakrishnan, B.; Boeggeman, E.; Qasba, P. K. *Bioconjugate Chem.* **2007**, *18*, 1912–1918.
(6) Ramakrishnan, B.; Boeggeman, E.; Manzoni, M.; Zhu, Z. Y.; Loomis, K.; Puri, A.; Dimitrov, D. S.; Qasba, P. K. *Bioconjugate Chem.* **2009**, *20*, 1383–1389.
(7) (a) Khidekel, N.; Ficarro, S. B.; Clark, P. M.; Bryan, M. C.; Swaney, D. L.; Rexach, J. E.; Sun, Y. E.; Coon, J. J.; Peters, E. C.; Hsieh-Wilson, L. C. *Nat. Chem. Biol.* **2007**, *3*, 339–348. (b) Boeggeman, E.; Ramakrishnan, B.; Kilgore, C.; Khidekel, N.; Hsieh-Wilson, L. C.; Simpson, J. T.; Qasba, P. K. *Bioconjugate Chem.* **2007**, *18*, 806–814. (c) Khidekel, N.; Ficarro, S. B.; Peters, E. C.; Hsieh-Wilson, L. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 13132–13137.
(8) Tai, H. C.; Khidekel, N.; Ficarro, S. B.; Peters, E. C.; Hsieh-Wilson, L. C. *J. Am. Chem. Soc.* **2004**, *126*, 10500–10501.
(9) Khidekel, N.; Arndt, S.; Lamarre-Vincent, N.; Lippert, A.; Poulin-Kerstien, K. G.; Ramakrishnan, B.; Qasba, P. K.; Hsieh-Wilson, L. C. *J. Am. Chem. Soc.* **2003**, *125*, 16162–16163.
(10) Pasek, M.; Ramakrishnan, B.; Boeggeman, E.; Manzoni, M.; Waybright, T. J.; Qasba, P. K. *Bioconjugate Chem.* **2009**, *20*, 608–618.

DOI: 10.1021/jo1016579 Published on Web 01/19/2011
© 2011 American Chemical Society

To explore their potential applications in glycobiology and medicine, we decided to synthesize oligosaccharides and glycoconjugates containing 2-*C*-acetylmethyl-2-deoxysugar (2-ketosugar) with diverse structures. Currently, a few synthetic methods are available for simple 2-*C*-branched sugars and 2-*C*-acetylmethyl monosaccharides, typically, through selective ring-opening of 1,2-cyclopropanated sugar via solvolysis in the presence of a stoichiometric amount of mercury salt, strong acid, and halonium ions, or by a radical reaction from 2-iodosugars and glycals, and Baylis−Hillman reaction from α,β-unsaturated δ-lactones.[11] Although much progress has been made for 2-*C*-branched monosaccharide synthesis,[11,12] stereoselective integration of 2-*C*-branched sugars into oligosaccharides and glycoconjugates remains a significant challenge. Recently, Linker et al. demonstrated the direct syntheses of 2-*C*-malonyl disaccharides via CAN-mediated radical addition to D-glucal.[13] However, this protocol suffers from low yield and reactive complexity. Reissig et al.[14] and Pagenkopf et al.[15] respectively described NIS/TfOH-promoted glycosylations using thioglycoside donors for preparing 2-*C*-branched oligosaccharides. In addition, 1,2-cyclopropanated carbohydrate donors are employed in the preparation of 2-*C*-branched glycosides,[16] ring expanding septanosides,[17] and Lewis acid-assisted pyran ring expansion to oxepanes.[16b,18] But only Zeise's dimer ($[Pt(C_2H_4)Cl_2]_2$)[19] and NIS/TMSOTf[20] are effective in promoting the stereoselective glycosylation of 1,2-cyclopropanated sugar donors with sugar alcohols. Obviously, more effective synthetic methods to 2-*C*-branched oligosaccharides and glycoconjugaes are needed. Recently, we have developed a stereoselective glycosylation method using 1,2-cyclopropaneacetylated sugars as glycosyl donors and $BF_3\cdot OEt_2$ or TMSOTf as catalyst. The glyosylation with various glycosyl acceptors led to concurrent ring-opening and formation of 2-*C*-acetylmethylated oligosaccharides, glycosylamino acids, and glycosyl cholesterol.

SCHEME 1. Synthesis of 1,2-Cyclopropaneacetylated Sugars 7, 8, and 10



Results and Discussion

Synthesis of 1,2-Cyclopropaneacetylated Sugars (7, 8, and 10). Previously prepared allyl *C*-taloside **1**[21] and allyl *C*-mannoside **2**[22] were 2-*O*-tosylated (TsCl/Py) to give corresponding **3** and **4** (see Scheme 1), which was followed by olefin oxidation ($Hg(OAc)_2$/Jones reagent) to afford 1-*C*-talosyl acetone **5** and 1-*C*-mannosyl acetone **6**, respectively, with 1,2-*trans* configuration. However, treatment of **5** with K_2CO_3 in MeOH failed to produce ring-closing product **7**, instead resulting in complicated products, likely from competitive β-elimination and further elimination of 2′-*O*-Ts prior to nucleophilic ring-closing in protonic solvent,[23] whereas, under the same conditions, 1,2-cyclopropaneacetylated **8** was easily obtained from **6**.[24]

Fortunately, by replacing methanol with aprotic dimethyl sulfoxide as a solvent, the ring-closing reaction of **5** proceeded smoothly to provide desired **7** as the main product.[21] Furthermore, $ZnCl_2/Ac_2O$/AcOH-mediated selective debenzylation−acetolysis of **6** gave 6′-*O*-Ac-mannosyl acetone **9**, and subsequent intramolecular ring-closure under basic conditions (K_2CO_3/DMF) afforded cyclopropane **10**. Extensive NMR and other analytical methods confirmed that compounds **7**, **8**, and **10** were pure diastereoisomers, supported

(11) (a) Scott, R. W.; Heathcock, C. H. *Carbohydr. Res.* **1996**, *291*, 205–208. (b) Kim, C.; Hoang, R.; Theodorakis, E. A. *Org. Lett.* **1999**, *1*, 1295–1297. (c) Hoberg, J. O.; Claffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533–2536. (d) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694–7703. (e) Gammon, D. W.; Kinfe, H. H. *J. Carbohydr. Chem.* **2007**, *26*, 141–157. (f) Ramana, C. V.; Nagarajan, M. *Carbohydr. Lett.* **1998**, *3*, 117–120. (g) Sridhar, P. R.; Ashalu, K. C.; Chandrasekaran, S. *Org. Lett.* **2004**, *6*, 1777–1779. (h) Yin, J.; Spindler, J.; Linker, T. *Chem. Commun.* **2007**, 2712–2713. (i) Krishna, P. R.; Reddya, P. S.; Narsingama, M.; Sateeshb, B.; Sastry, G. N. *Synlett* **2006**, 595–599.

(12) Du, Y. G.; Chen, Q.; Liu, J. In *Glycoscience*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer-Verlag: Berlin, Germany, 2008; pp 305−342.

(13) Elamparuthi, E.; Kim, B. G.; Yin, J.; Maurer, M.; Linker, T. *Tetrahedron* **2008**, *64*, 11925–11937.

(14) Pfrengle, F.; Lentz, D.; Reissig, H. U. *Angew. Chem., Int. Ed.* **2009**, *48*, 3165–3169.

(15) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2003**, *59*, 2765–2771.

(16) For reviews, see: (a) Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165–174. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347.

(17) (a) Hewitt, R. J.; Harvey, J. E. *J. Org. Chem.* **2010**, *75*, 955–958. (b) Ganesh, N. V.; Raghothama, S.; Sonti, R.; Jayaraman, N. *J. Org. Chem.* **2010**, *75*, 215–218. (c) Ganesh, N. V.; Jayaraman, N. *J. Org. Chem.* **2009**, *74*, 739–746. (d) Batchelor, R.; Harvey, J. E.; Northcote, P. T.; Teesdale-Spittle, P.; Hoberg, J. O. *J. Org. Chem.* **2009**, *74*, 7627–7632. (e) Ganesh, N. V.; Jayaraman, N. *J. Org. Chem.* **2007**, *72*, 5500–5504.

(18) (a) Hoberg, J. O.; Bozell, J. J. *Tetrahedron Lett.* **1995**, *36*, 6831–6834. (b) Hoberg, J. O. *J. Org. Chem.* **1997**, *62*, 6615–6618. (c) Batchelor, R.; Hoberg, J. O. *Tetrahedron Lett.* **2003**, *44*, 9043–9045.

(19) (a) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137–12138. (b) Beyer, J.; Skaanderup, P. R.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 9575–9583.

(20) Sridhar, P. R.; Kumar, P. V.; Seshadri, K.; Satyavathi, R. *Chem.−Eur. J.* **2009**, *15*, 7526–7529.

(21) Tian, Q.; Xu, L. Y.; Ma, X. F.; Zou, W.; Shao, H. W. *Org. Lett.* **2010**, *12*, 540–543.

(22) Zou, W.; Wang, Z. R.; Lacroix, E.; Wu, S. H.; Jennings, H. J. *Carbohydr. Res.* **2001**, *334*, 223–231.

(23) (a) Shao, H. W.; Wang, Z. R.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zou, W. *J. Am. Chem. Soc.* **2002**, *124*, 2130–2131. (b) Wang, Z.; Shao, H. W.; Lacroix, E.; Wu, S. H.; Jennings, H. J.; Zou, W. *J. Org. Chem.* **2003**, *68*, 8097–8105.

(24) (a) Shao, H. W.; Ekthawatchai, S.; Wu, S. H.; Zou, W. *Org. Lett.* **2004**, *6*, 3497–3499. (b) Shao, H. W.; Ekthawatchai, S.; Chen, C. S.; Wu, S. H.; Zou, W. *J. Org. Chem.* **2005**, *70*, 4726–4734.

SCHEME 2. Hydrolysis of 1,2-Cyclopropaneacetylated Sugar 7

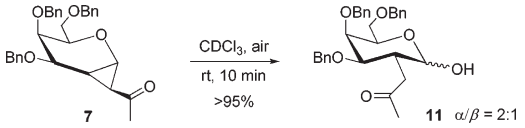
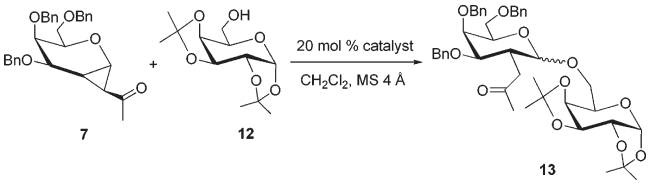


TABLE 1. Lewis Acid-Catalyzed Glycosylation of Glycosyl Donor 7 and Acceptor 12[a]



entry	catalyst	condition	yield[c] (%)	α/β[d]
1[b]	$BF_3 \cdot Et_2O$	−78−0 °C, 3 h	58	1:4
2	$BF_3 \cdot Et_2O$	−20 °C−rt, 2 h	84	1:5
3	$AlCl_3$	−20 °C−rt, 2 h	76	1:3
4	$BiCl_3$	−20 °C−rt, 2 h	80	1:4
5	$ZnCl_2$	−20 °C−rt, 2 h	73	1:2
6	$InCl_3$	−20 °C−rt, 16 h	trace	
7	$PdCl_2$	−20 °C−rt, 16 h	trace	
8	AgOTf	−20 °C−rt, 16 h	0	
9	TMSOTf	−20 °C−rt, 2 h	87	2:1
10	TMSOTf	0 °C−rt, 1.5 h	86	7:1

[a]Reactions were performed with 1.1 equiv of acceptor in CH_2Cl_2 (0.1 M). [b]10 mol % catalyst was employed. [c]Isolated yield. [d]Values were determined by ^1H NMR.

by the NOEs between H1′, H3, and H5, and the coupling constants ($J_{H1,H1'} \leq 2.1$ Hz).[23,25]

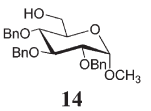
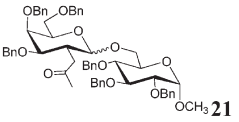
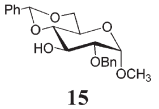
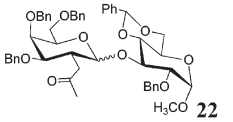
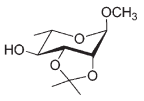
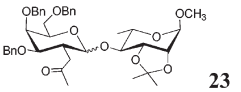
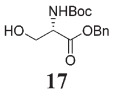
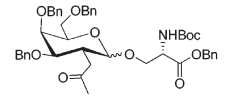
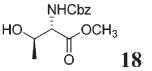
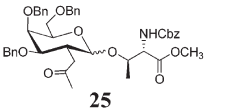
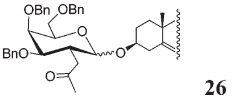
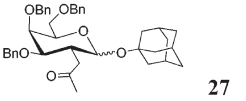
The stability of 1,2-cyclopropaneacetylated sugars appears to depend on the type of sugar. Galactose derivative **7** rapidly hydrolyzed in $CDCl_3$ to hemiacetal **11** as a 2:1 mixture of α- and β-isomers, whereas glucose derivatives **8** and **10** can be stored in $CDCl_3$ at −4 °C (Scheme 2).

Lewis Acid-Catalyzed Ring-Opening of 1,2-Cyclopropaneacetylated Sugars. The instability of 1,2-cyclopropaneacetylated sugar **7** in $CDCl_3$ demonstrated its high reactivity and suggested that this type of compound may be used as a novel glycosyl donor. Consequently, we attempted Lewis acid-catalyzed glycosylation of **7** with sugar alcohol **12**. Reaction of **7** with **12**, under 10 mol % of $BF_3 \cdot OEt_2$ in dichloromethane at −78 °C followed by gradual warming to 0 °C, gave the desired disaccharide **13** in 58% yield with α/β = 1:4 (Table 1, entry 1). Increasing the amount of $BF_3 \cdot OEt_2$ to 20 mol % and reaction at −20 °C to rt improved the yield to 84% with slightly higher β-selectivity (Table 1, entry 2). $AlCl_3$, $BiCl_3$, and $ZnCl_2$ were found to be less effective for *O*-glycosylation than $BF_3 \cdot OEt_2$ (Table 1, entries 3−5). $InCl_3$ and $PdCl_2$ only resulted in a trace amount of desired products, and the reaction did not occur in the presence of AgOTf (Table 1, entries 6−8).

Interestingly, a switch in diastereoselectivity was observed when TMSOTf was used under otherwise similar conditions,

(25) Proton−proton coupling constants in a cyclopropane system: J = 0−6 Hz for a trans stereochemistry and J=8−10 Hz for a cis stereochemistry. See: (a) Kawabata, N.; Nakagawa, T.; Nakao, T.; Yamashita, S. *J. Org. Chem.* **1977**, *42*, 3031–3035. (b) Wiberg, K. B.; Barth, D. E.; Schertler, P. H. *J. Org. Chem.* **1973**, *38*, 378–381. (c) Williamson, K. L.; Lanford, C. A.; Nicholso., C. R. *J. Am. Chem. Soc.* **1964**, *86*, 762–765.

TABLE 2. Glycosylation of 1,2-Cyclopropaneacetylated Sugar Donor 7

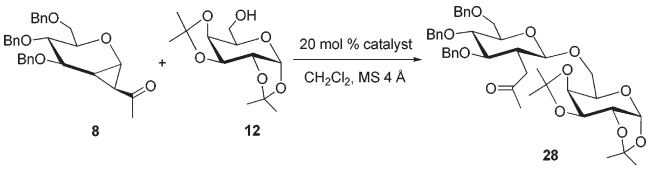
entry	acceptor	product	Yield[d] (%) (α:β)[e]
1[a]			82 (1:4)
2[b]			89 (10:1)
	14	**21**	
3[a]			71 (1:8)
4[b]			76 (20:1)
	15	**22**	
5[a]			85 (1:3)
6[b]			87 (6:1)
	16	**23**	
7[a]			71 (1:4)
8[b]			75 (4:1)
	17	**24**	
9[a]			77 (1:5)
10[b]			78 (8:1)
	18	**25**	
11[a]			87 (1:20)
12[c]			83 (15:1)
	19	**26**	
13[a]			74 (1:6)
14[c]			80 (12:1)
	20	**27**	

[a]Reactions were carried out with 20 mol % $BF_3 \cdot OEt_2$ at −20 °C to rt. [b]Reactions were carried out with 20 mol % TMSOTf at 0 °C to rt. [c]Reactions were carried out with 40 mol % TMSOTf at rt. [d]Isolated yield. [e]Values were determined by ^1H NMR.

which led to modest α-selectivity (Table 1, entry 9). The diastereoselectivity was improved to α/β = 7:1 with similar yield when the reaction was performed at 0 °C to rt (Table 1, entry 10). It is also noteworthy that no anomeric epimerization was observed in this Lewis acid-catalyzed glycosylation as monitored by TLC. These results suggest that the glycosylation likely proceeded in different pathways under the conditions of $BF_3 \cdot OEt_2$ and TMSOTf.

To investigate the scope of the reaction, a range of glycosyl acceptors were reacted with 1,2-cyclopropaneacetylated sugar **7**. As shown in Table 2, glycosylations of monosaccharides **14**−**16**, serine **17**, and threonine **18** as well as cholesterol and adamantanol gave disaccharides and glycoconjugates **21**−**27** in 71−89% yields. To our delight, in all cases TMSOTf-catalyzed couplings showed good α-anomeric selectivity. In contrast,

TABLE 3. Acid-Catalyzed Glycosylation of Glycosyl Donor 8 and Acceptor 12[a]



entry	catalyst[c]	condition	time (h)	yield[d] (%)
1	TMSOTf	−20 °C−rt	1	80
2	$BF_3\cdot Et_2O$	−20 °C−rt	1	89
3	AgOTf	−20 °C−rt	5	0
4	$Hg(OAc)_2$	−20 °C−rt	5	0
5	AcOH	−20 °C−rt	2	0
6	TFA	−20 °C−rt	2	0
7	*p*-TsOH	0 °C−rt	1.5	75
8[b]	Amberlyst 15	0 °C−rt	1.5	73
9	D-CSA	−20 °C−rt	1	69
10	TfOH	−20 °C−rt	1	61

[a]Reactions were performed with 1.25 equiv of donor and 1.0 equiv of acceptor in CH_2Cl_2. [b]20 wt % catalyst was employed. [c]20 mol % for donor. [d]Isolated yield.

$BF_3\cdot OEt_2$-catalyzed glycosylations led to anomeric selectivity and β-linked conjugates were isolated as major products. Furthermore, no ring expansion product was detected in this Lewis acid-promoted glycosylation that is often associated with unsubstituted and ester-substituted sugar cyclopropanes. We believe that both the 2′-acetyl substitution and Lewis acid catalysts are contributing factors to the chemoselectivity and diastereoselectivity of glycosylation.

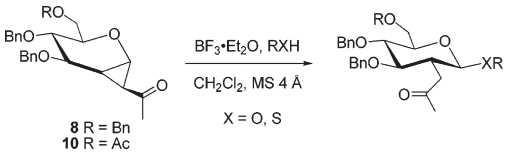
Next we examined the glycosylation using 1,2-cyclopropaneacetylated glucosyl donor **8**. Surprisingly, the reaction of **8** with **12** gave, exclusively, β-anomeric conjugate **28** under both $BF_3\cdot OEt_2$ and TMSOTf conditions in 89% and 80% yields, respectively (Table 3, entries 2 and 1). Other Lewis acids such as AgOTf and $Hg(OAc)_2$ did not catalyze the coupling reaction, neither did AcOH and trifluoroacetic acid as catalysts (Table 3, entries 3−6). Further study indicated that several sulfonic acids, for example *p*-TsOH, Amberlyst 15, D-CSA, and TfOH, could promote the ring-opening and glycosylation of cyclopropane **8**, to produce β-anomer **28** but with lower yields (Table 3, entries 7−10). The above results showed that glucosyl donor **8** favors β-anomeric glycosylation regardless of the acid catalysts used.

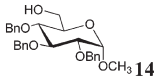
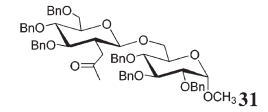
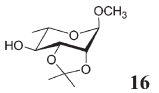
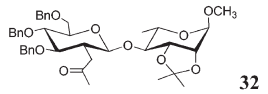
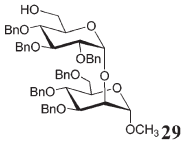
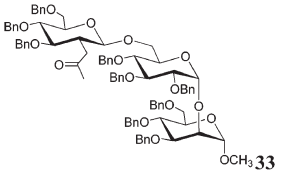
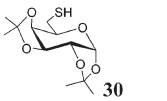
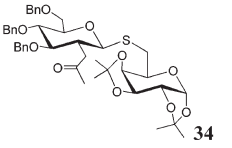
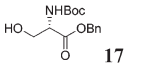
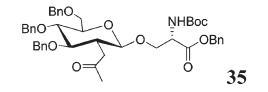
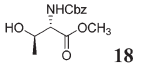
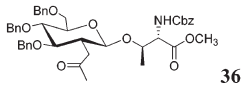
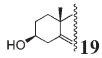
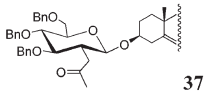
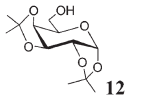
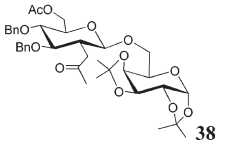
The $BF_3\cdot OEt_2$-catalyzed glycosylation with donor **8** was further applied to an array of sugar alcohols including primary and secondary alcohols as well as a thiol to obtain corresponding β-anomeric products in 72−93% yields (Table 4, entries 1−4). As the first step toward *O*-glycoprotein with 2-*C*-acetylmethyl glucose as a replacement of 2-*N*-acetamidoglucosamine, we performed the reaction of **8** with serine and threonine derivatives **17** and **18**. As expected, glycoamino acids, **35** and **36**, were obtained in 79% and 76% yields, respectively (Table 4, entries 5 and 6). Similarly, reaction of **8** with cholesterol produced **37** steroselectively (Table 4, entry 7). In addition, the coupling of 6-*O*-Ac cyclopropane **10** with acceptor **12** also proceeded smoothly under those conditions, producing disaccharide **38** in 81% yield (Table 4, entry 8). Overall, the glycosylation method provided highly stereoselective β-anomeric products in good to excellent yields.

Mechanistic Studies and Neighboring Group Participation. The relative energy difference between glucosyl **8** and galactosyl **7** was 22.2 kJ/mol calculated under optimal B3LYP/6-31G**, which suggests that the cyclopropane ring of **8** is more stable than that of **7**. The isolation of a significant amount of ketal **39** (42% yield) and serine conjugates **24** (27% yield, α/β =1:3.5) from the reaction of **7** and L-serine derivative **17** in the $BF_3\cdot OEt_2$-catalyzed glycosylation (Scheme 3) suggests that the reaction may proceed through an enol ether intermediate **42**.

On the basis of the above results, we propose three possible reaction pathways as illustrated in Scheme 4. $BF_3\cdot OEt_2$-catalyzed β-selective glycosylation of **7** (pathway a) was consistent with an S_N1 mechanism involving an anomeric

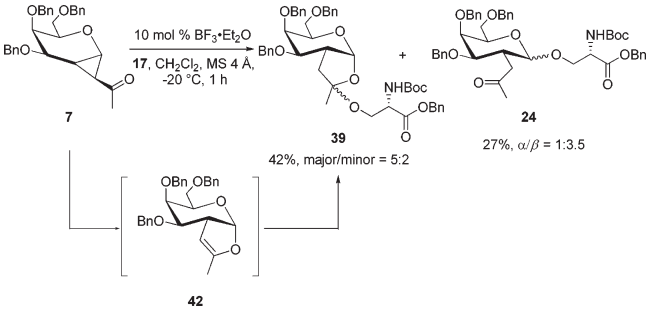
TABLE 4. Glycosylation of 1,2-Cyclopropaneacetylated Sugar Donor 8 and 10[a]



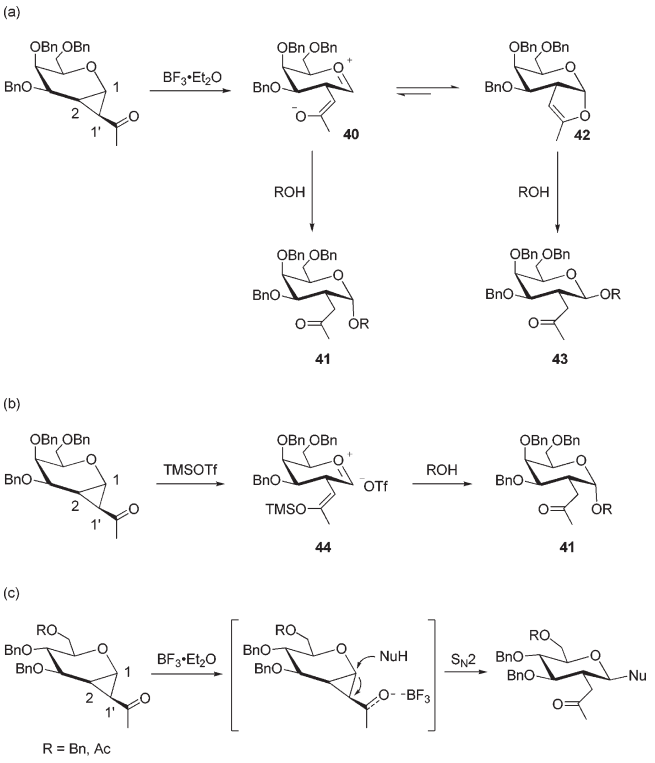
entry	acceptor	product	Yield[c] (%)
1	 **14**	 **31**	86
2	 **16**	 **32**	72
3	 **29**	 **33**	73
4	 **30**	 **34**	93
5	 **17**	 **35**	79
6	 **18**	 **36**	76
7	 **19**	 **37**	88
8[b]	 **12**	 **38**	81

[a]Reactions were carried out with 20 mol % $BF_3\cdot OEt_2$ at −20 °C to rt. [b]Glycosyl donor **10** was used. [c]Isolated yield.

SCHEME 3. The Coupling of 1,2-Cyclopropaneacetylated Sugar 7 and L-Serine Derivative 17

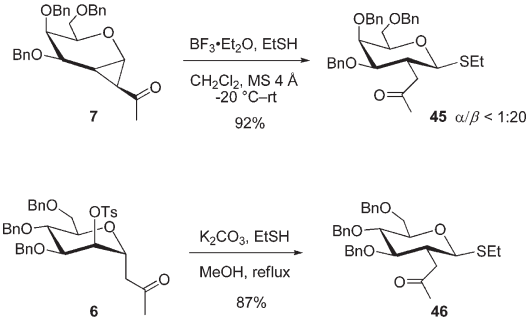


SCHEME 4. Proposed Potential Mechanism for the $BF_3 \cdot OEt_2$- or TMSOTf-Catalyzed Ring-Opening of 1,2-Cyclopropaneacetylated Sugars 7, 8, and 10

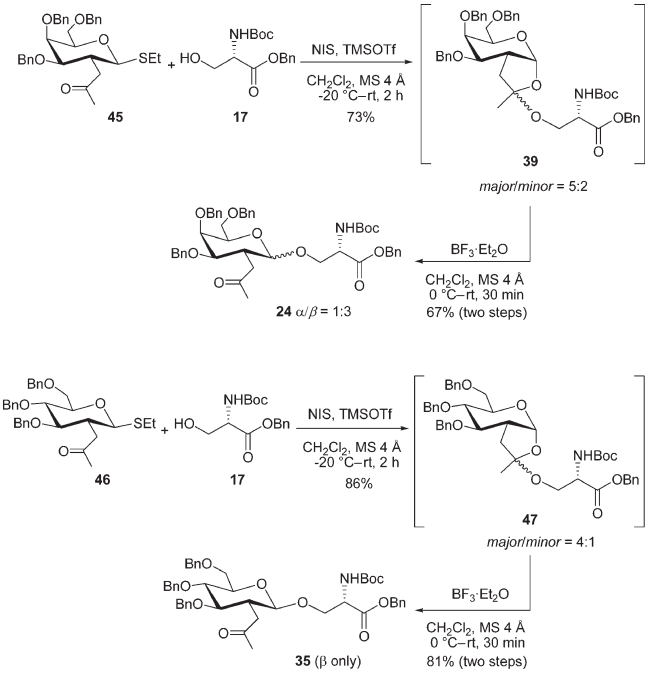


carbonium or oxocarbenium intermediate and a neighboring group participation, and Lewis acid-induced nucleophilic addition from β face to cyclopropane and enol intermediate **42**. For the TMSOTf-catalyzed α-selective glycosylation of **7** (pathway b), a tight coordination of the carbonyl oxygen atom with TMSOTf followed by C1−C1′ bond breakage may produce an oxocarbenium triflate and the formation of 2-*C*-trimethylsilyl enol ether **44**[26] that eliminated neighboring

SCHEME 5. The Synthesis of Thioglycosyl Donors 45 and 46



SCHEME 6. The Glycosylations of Thiogalactosyl Donor 45 or 46 with 17



group participation[27] thus to afford α-glycoside **41**, as favored by anomeric effect. On the other hand, the glycosylation reactions of cyclopropane **8** and **10** are believed to proceed through an S_N2-type pathway (pathway c) involving electrophilic cyclopropane acetyl activation by $BF_3 \cdot OEt_2$ followed by C1−C1′ bond cleavage and nucleophilic attack from the β face to the anomeric center, similar to the glycosylation of 1,2-anhydrosugars.[28] Notably, this method does not cause Lewis acid-promoted removal of the 3-OR group, as occurred in ring enlargement by C1−C2 cleavage of unsubstituted and ester-substituted sugar cyclopropanes.[18]

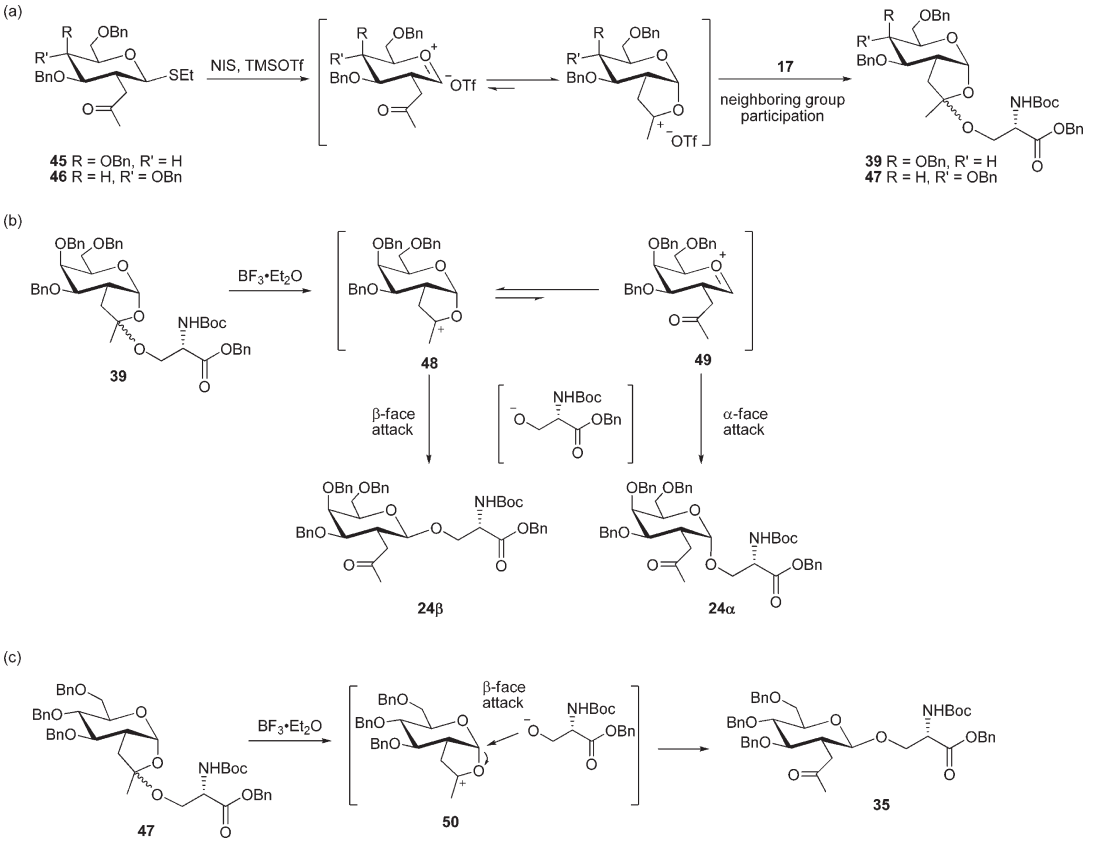
The neighboring participation by the 2-*C*-acetylmethyl group could be verified by using 2-acetylmethylthioglycosides (**45** and **46**) as glycosyl donors, which were prepared from $BF_3 \cdot OEt_2$-catalyzed nucleophilic ring-opening of **7** with ethyl thiol and from **6** and ethyl thiol by a tandem S_N2-S_N2 reaction, respectively (Scheme 5). Interestingly,

(26) Glycosyl triflates or the corresponding oxocarbenium triflates were used as glycosyl donors. See: (a) Leroux, J.; Perlin, A. S. *Carbohydr. Res.* **1978**, *67*, 163–178. (b) Lacombe, J. M.; Pavia, A. A. *J. Org. Chem.* **1983**, *48*, 2557–2563. (c) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321–8348.

(27) We hypothesized that trimethylsilyl enol ether **42** could form temporarily due to the fast coordination between the oxygen atom of acetyl and the trimethylsilyl cation, and decompose after nucleophilic attack because of the free proton. During this process, the trimethylsilyl enol ether **42** can hardly contribute to the stabilization of the oxocarbenium triflate.

(28) (a) Li, Y; Tang, P. P.; Chen, Y. X.; Yu, B. *J. Org. Chem.* **2008**, *73*, 4323–4325. (b) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380–1419. (c) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661–6666.

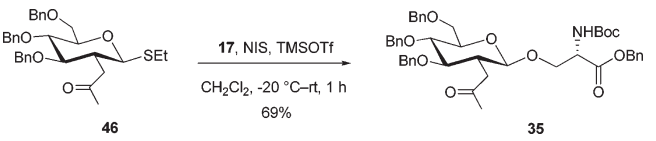
SCHEME 7. The Neighboring Group Participation from C2 Acetylmethyl Group with $BF_3 \cdot OEt_2$ or TMSOTf As Catalyst



glycosylations of thioglycosyl donors **45** and **46** with **17** using 1.5 equiv of NIS and 0.2 equiv of TMSOTf as the catalyst system in dichloromethane at −20 °C followed by gradual warming to room temperature produced ketal products **39** in 73% yield with major/minor = 5:2, and **47** in 86% yield with major/minor = 4:1, respectively (Scheme 6). When a catalytic amount of $BF_3 \cdot OEt_2$ was added to the reaction system at 0 °C the intermediates **39** and **47** were transformed into corresponding glycosides, **24** and **35**, in good yield (Scheme 6). Obviously, the ketal conjugates indicated that the neighboring group participation from C2 acetylmethyl indeed occured and the subsequent $BF_3 \cdot OEt_2$-promoted intramolecular rearrangement gave rise to 1,2-*trans* products (Scheme 7). However, the rearrangement of **39** to **24** was not as highly β-selective as that of **47** to **35**, where the 4-*O*-benzyl group of Gal may induce α-addition to some degree. Thus, the neighboring participation by the 2-*C*-acetyl group and the steric effect by the 4-*O*-benzyl group of Gal are opposing factors to anomeric stereoselectivity. Three possible pathways, as shown in Scheme 7, all involve neighboring participation by the 2-*C*-acetylmethyl group.

Because the proposed mechanism involves an acid-catalyzed intramolecular rearrangement to form glycosides, removal of acid such as TfOH produced in the NIS- and TMSOTf-catalyzed coupling reactions by addition of 4 Å molecular sieve should effectively stall the glycosylation reaction. To test this hypothesis, 2-acetylmethyl-thioglycosyl donor **46** was reacted with **17** under otherwise similar conditions (NIS/TMSOTf) without MS 4 Å. The reaction proceeded smoothly, as expected, to give the desired conjugate

SCHEME 8. The Glycosylation of 2-Acetylmethyl-Thioglycosyl Donor 46 with 17 Catalyzed by NIS/TMSOTf



35 in 69% yield together with a small amount of hydrolyzed product (Scheme 8).

Conclusions

We have developed a TMSOTf- and $BF_3 \cdot OEt_2$-catalyzed glycosylation reaction using 1,2-cyclopropaneacetylated sugars as a new type of glycosyl donor. The glycosylation is efficient and provides a method for stereoselective synthesis of 2-*C*-acetylmethyl-2-deoxy-glycosides, oligosaccharides, glycosylamino acids, and other 2-*C*-acetylmethylglycosides. The glycosylation of glucosyl donors **8** and **10** is totally stereoselective in favor of β-anomer products and in good to excellent yield, whereas the stereoselectivity in couplings of galactosyl donor **7** with acceptors depends on the catalysts ($BF_3 \cdot OEt_2$ and TMSOTf). In addition, 2-*C*-acetylmethyl-2-deoxy-thioglycosides are also effective glycosyl donors and provide neighboring group participation in glycosylation.

Experimental Section

General Procedure for $BF_3 \cdot OEt_2$-Catalyzed β-Selective Glycosylation Reactions of 1,2-Cyclopropaneacetylated Sugar 7. Procedure A (for compounds 13, 21−27). A suspension of

glycosyl donor **7** (47.3 mg, 0.10 mmol) and acceptor alcohol (0.11 mmol, 1.1 equiv) containing activated 4 Å molecular sieves (75 mg) in dry CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min under argon. After cooling to −20 °C, the solution of $BF_3 \cdot OEt_2$ (2.5 μL, 0.02 mmol) in dry CH_2Cl_2 (0.25 mL) was added dropwise. The reaction mixture was then warmed slowly to room temperature, stirred for 1−2 h, and then quenched by the addition of Et_3N. The suspension was diluted with CH_2Cl_2 (5.0 mL) and filtered through Celite. The filtrate was concentrated in vacuo and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate) to give the corresponding coupled products.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-*C*-acetylmethyl-2′-deoxy-*β*-D-galactopyranosyl)-α-D-galactopyranoside (13*β*). Following procedure A, **13*β*** was obtained as a colorless syrup; yield 84%, α/β = 1:5. $[\alpha]^{20}_D$ −28.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.22 (m, 15H), 5.48 (d, *J* = 5.0 Hz, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.55 (dd, *J* = 7.4, 2.2 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 8.2 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.26 (dd, *J* = 4.7, 2.1 Hz, 1H), 4.14 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.99 (dd, *J* = 11.3, 3.1 Hz, 1H), 3.94−3.90 (m, 2H), 3.67 (dd, *J* = 8.6, 8.0 Hz, 1H), 3.61−3.54 (m, 3H), 3.46 (dd, *J* = 10.8, 1.6 Hz, 1H), 2.65−2.60 (m, 2H), 2.54 (dd, *J* = 17.6, 7.8 Hz, 1H), 2.09 (s, 3H), 1.50 (s, 3H), 1.41 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.6, 138.7, 138.0, 137.7, 128.4, 128.1, 127.9, 127.9, 127.8, 127.8, 127.5, 109.3, 108.6, 103.7, 96.3, 81.0, 74.3, 73.5, 73.5, 71.6, 71.4, 70.8, 70.7, 70.4, 69.2, 68.9, 67.9, 41.7, 40.1, 29.7, 26.0, 25.9, 25.0, 24.3; ESI-HRMS *m*/*z* calcd for $C_{42}H_{52}O_{11}Na$ $[M + Na]^+$ 755.3402, found 755.3379.

General Procedure for TMSOTf-Catalyzed α-Selective Glycosylation Reactions of 1,2-Cyclopropaneacetylated Sugar 7. Procedure B (for compounds 13, 21−25). A suspension of glycosyl donor **7** (47.3 mg, 0.10 mmol) and acceptor alcohol (0.11 mmol, 1.1 equiv) containing activated 4 Å molecular sieves (75 mg) in dry CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min under argon. After cooling to 0 °C, TMSOTf (3.6 μL, 0.02 mmol) was added. The reaction mixture was then warmed to room temperature, stirred for 1−2 h, and then quenched by the addition of Et_3N. The suspension was diluted with CH_2Cl_2 (5.0 mL) and filtered through Celite. The filtrate was concentrated in vacuo and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate) to give the corresponding coupled products.

Procedure C (for compounds 26 and 27). A suspension of glycosyl donor **7** (47.3 mg, 0.10 mmol) and acceptor alcohol (0.11 mmol, 1.1 equiv) containing activated 4 Å molecular sieves (75 mg) in dry CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min under argon. Then TMSOTf (7.2 μL, 0.04 mmol) was added to the above mixture at room temperature, and the stirring was continued for 1−2 h. The reaction was quenched by the addition of Et_3N. The suspension was diluted with CH_2Cl_2 (5.0 mL) and filtered through Celite. The filtrate was concentrated in vacuo and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate) to give the corresponding coupled products.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-*C*-acetylmethyl-2′-deoxy-α-D-galactopyranosyl)-α-D-galactopyranoside (13α). Following procedure B, **13α** was obtained as a colorless syrup; yield 86%, α/β = 7:1. $[\alpha]^{20}_D$ +33.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.20 (m, 15H), 5.51 (d, *J* = 5.1 Hz, 1H), 4.93 (d, *J* = 3.5 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.58 (dd, *J* = 7.9, 2.3 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.30 (dd, *J* = 5.2, 2.4 Hz, 1H), 4.16 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.97 (br s, 1H), 3.95 (dd, *J* = 7.1, 6.3 Hz, 1H), 3.91 (dd, *J* = 7.1, 5.9 Hz, 1H), 3.73 (dd, *J* = 10.7, 7.1 Hz, 1H), 3.65 (dd, *J* = 8.7, 8.3 Hz, 1H), 3.62 (dd, *J* = 10.4, 2.2 Hz, 1H), 3.59 (dd, *J* = 10.6, 5.9 Hz, 1H), 3.55 (dd, *J* = 9.1, 5.5 Hz, 1H), 2.98−2.94 (m, 1H), 2.72 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.48 (dd, *J* = 17.2, 8.3 Hz, 1H), 2.08 (s, 3H), 1.51 (s, 3H), 1.41 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 138.8, 138.1, 138.0, 128.4, 128.2, 128.0, 127.9, 127.7, 127.7, 127.6, 127.5, 109.3, 108.5, 98.7, 96.4, 78.2, 74.4, 73.5, 71.7, 71.4, 71.3, 71.1, 70.7, 70.5, 69.6, 69.0, 65.6, 65.6, 41.6, 36.6, 30.1, 26.1, 26.0, 24.9, 24.5; ESI-HRMS *m*/*z* calcd for $C_{42}H_{52}O_{11}Na$ $[M + Na]^+$ 755.3402, found 755.3382.

Cholesteryl 3,4,6-Tri-*O*-benzyl-2-*C*-acetylmethyl-2-deoxy-α-D-galactopyranoside (26α). Following procedure C, **26α** was obtained as a colorless syrup; yield 83%, α/β = 15:1. $[\alpha]^{20}_D$ +41.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.23 (m, 15H), 5.25 (d, *J* = 4.6 Hz, 1H), 5.05 (d, *J* = 3.3 Hz, 1H), 4.86 (d, *J* = 11.6 Hz, 1H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 4.01 (dd, *J* = 6.6, 6.6 Hz, 1H), 3.96 (br s, 1H), 3.64 (dd, *J* = 8.9, 7.6 Hz, 1H), 3.60−3.55 (m, 2H), 3.40−3.34 (m, 1H), 2.92−2.86 (m, 1H), 2.75 (dd, *J* = 17.1, 5.2 Hz, 1H), 2.41 (dd, *J* = 17.0, 8.9 Hz, 1H), 2.30−2.21 (m, 2H), 2.08 (s, 3H), 2.01−0.89 (m, 32H), 0.87 (d, *J* = 2.5 Hz, 3H), 0.86 (d, *J* = 2.5 Hz, 3H), 0.67 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.0, 140.8, 138.8, 138.1, 138.0, 128.4, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 121.7, 97.3, 78.6, 74.4, 73.5, 72.0, 71.4, 69.6, 69.5, 56.8, 56.2, 50.1, 42.3, 42.1, 40.1, 39.8, 39.5, 37.0, 36.9, 36.7, 36.2, 35.8, 31.9, 30.0, 28.2, 28.0, 27.9, 24.3, 23.8, 22.8, 22.6, 21.0, 19.4, 18.7, 11.9; ESI-HRMS *m*/*z* calcd for $C_{57}H_{78}O_6K$ $[M + K]^+$ 897.5430, found 897.5413.

General Procedure for $BF_3 \cdot OEt_2$-Catalyzed *β*-Selective Glycosylation Reactions of 1,2-Cyclopropaneacetylated Sugar 8 and 10 (for compounds 28, 31−38). The mixture of donor **8** (59.0 mg, 0.125 mmol) or **10** (53.0 mg, 0.125 mmol), acceptor (0.1 mmol), and freshly dried powdered MS 4 Å (75 mg) in CH_2Cl_2 (1.0 mL) was stirred under Ar atmosphere at room temperature for 30 min and then cooled to −20 °C. $BF_3 \cdot OEt_2$ (3.1 μL, 0.025 mmol) was added. The reaction mixture was warmed slowly to room temperature, stirred for 1−2 h, and then quenched by the addition of Et_3N. The suspension was diluted with CH_2Cl_2 (5.0 mL) and filtered through Celite. The filtrate was concentrated in vacuo and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate) to give the corresponding coupled products.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3′,4′,6′-tri-*O*-benzyl-2′-*C*-acetylmethyl-2′-deoxy-*β*-D-gluco- pyranosyl)-α-D-galactopyranoside (28). 28 was obtained as white solid; yield 89%. Mp 110−111 °C; $[\alpha]^{20}_D$ −30.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.25 (m, 15H), 5.48 (d, *J* = 4.9 Hz, 1H, H-1), 4.86 (d, *J* = 11.0 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.58−4.54 (m, 4H), 4.40 (d, *J* = 8.6 Hz, 1H, H-1′), 4.27 (dd, *J* = 4.9, 2.5 Hz, 1H), 4.16 (dd, *J* = 8.0, 1.7 Hz, 1H), 4.03 (dd, *J* = 11.0, 3.1 Hz, 1H), 3.94−3.91 (m, 1H), 3.76−3.72 (m, 2H), 3.65 (dd, *J* = 9.3, 9.1 Hz, 1H), 3.60 (dd, *J* = 11.2, 7.8 Hz, 1H), 3.53 (dd, *J* = 10.8, 9.0 Hz, 1H), 3.48−3.44 (m, 1H), 2.59 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.49 (dd, *J* = 16.4, 5.5 Hz, 1H), 2.25−2.20 (m, 1H), 2.06 (s, 3H, $COCH_3$), 1.50 (s, 3H), 1.42 (s, 3H), 1.30 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 207.6, 138.3, 138.2, 138.1, 128.4, 128.3, 127.8, 127.7, 127.7, 127.6, 127.5, 109.3, 108.5, 103.4, 96.3, 82.5, 79.8, 75.1, 74.6, 74.6, 73.5, 71.4, 70.5, 70.4, 69.4, 68.9, 67.8, 44.5, 41.4, 29.8, 26.0, 25.9, 25.0, 24.3; ESI-HRMS *m*/*z* calcd for $C_{42}H_{52}O_{11}Na$ $[M + Na]^+$ 755.3402, found 755.3368.

Ethyl 3,4,6-Tri-*O*-benzyl-2-*C*-acetylmethyl-2-deoxy-1-thio-*β*-D-galactopyranoside (45). Following procedure A, **45** was obtained as colorless syrup; yield 92%. $[\alpha]^{20}_D$ +6.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.22 (m, 15H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.59 (d, *J* = 10.4 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.44

(d, J = 11.8 Hz, 1H), 4.35 (d, J = 11.3 Hz, 1H), 3.95 (d, J = 2.3 Hz, 1H), 3.67−3.60 (m, 4H), 2.79 (dd, J = 17.0, 4.1 Hz, 1H), 2.72−2.58 (m, 3H), 2.55 (dd, J = 17.1, 5.9 Hz, 1H), 2.04 (s, 3H), 1.23 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.7, 138.9, 138.0, 137.7, 128.4, 128.4, 128.1, 127.9, 127.9, 127.8, 127.8, 127.8, 127.4, 84.7, 81.5, 74.2, 73.5, 71.3, 71.0, 69.1, 42.2, 38.8, 30.4, 24.3, 14.9; ESI-HRMS m/z calcd for $C_{32}H_{38}O_5SNa$ [M + Na]$^+$ 557.2332, found 557.2315.

Ethyl 3,4,6-Tri-*O*-benzyl-2-*C*-acetylmethyl-2-deoxy-1-thio-β-D-glucopyranoside (46). To a solution of **6** (129 mg, 0.2 mmol) and ethyl thiol (45 μL, 0.6 mmol) in MeOH (10 mL) was added K_2CO_3 (276 mg, 2.0 mmol). The suspension was stirred at 70 °C for 2 h. The mixture was filtrated, and the filtrate was concentrated in vacuo and purified by silica gel flash column chromatography (petroleum ether/ethyl acetate, 10:1, v/v) to afford the title compound **46** (107 mg, 87%) as a syrup. **46**: $[\alpha]^{20}_D$ +4.0 (c 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.16 (m, 15H), 4.90 (d, J = 11.5 Hz, 1H), 4.77 (d, J = 10.9 Hz, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.55 (d, J = 10.6 Hz, 2H), 3.77−3.71 (m, 2H), 3.67 (dd, J = 10.1, 9.0 Hz, 1H), 3.62 (dd, J = 9.6, 8.8 Hz, 1H), 3.53−3.49 (m, 1H), 2.73−2.66 (m, 2H), 2.63 (dd, J = 12.6, 7.4 Hz, 1H), 2.52 (dd, J = 17.3, 5.2 Hz, 1H), 2.26−2.20 (m, 1H), 2.01 (s, 3H), 1.25 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.0, 138.3, 138.3, 138.1, 128.4, 128.4, 128.3, 127.8, 127.8, 127.7, 127.7, 127.5, 84.3, 83.3, 80.0, 79.4, 74.7, 74.7, 73.4, 69.2, 43.6, 42.2, 30.3, 24.4, 15.0; ESI-HRMS m/z calcd for $C_{32}H_{38}O_5SNa$ [M + Na]$^+$ 557.2332, found 557.2317.

NIS/TMSOTf-Catalyzed Glycosylations of Thioglycosyl Donor 45 or 46 with L-Serine 17. Protocol A (for compounds 39 and 47). A mixture of the glycosyl donor (64.2 mg, 0.12 mmol), the acceptor (29.5 mg, 0.10 mmol), and powdered 4 Å molecular sieves (75 mg) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min under argon and then cooled to −20 °C. NIS (33.7 mg, 0.15 mmol) and TMSOTf (3.6 μL, 0.02 mmol) were successively added. The reaction mixture was warmed slowly to room temperature, stirred for 1 h, and then quenched by the addition of Et_3N. The suspension was diluted with CH_2Cl_2 (5 mL) and filtered through a pad of Celite, and the filtrate was washed successively with 10% $Na_2S_2O_3$ (2 mL) and brine (10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by flash column chromatography (petroleum ether/ethyl acetate, 6:1, v/v).

39 was obtained as a syrup (56.1 mg, 73%, major/minor = 5:2). ^{1}H NMR (600 MHz, acetone-d_6) major, δ 7.44−7.24 (m, 20H), 5.93 (d, J = 8.9 Hz, 1H), 5.22 (d, J = 4.1 Hz, 1H), 5.12 (ABq, J = 12.9 Hz, 2H), 4.91 (d, J = 11.5 Hz, 1H), 4.82 (d, J = 11.9 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 4.37−4.34 (m, 1H), 4.14−4.12 (m, 1H), 4.01−3.97 (m, 1H), 3.69 (dd, J = 9.3, 7.3 Hz, 1H), 3.64 (dd, J = 9.5, 3.5 Hz, 1H), 3.56 (dd, J = 9.3, 5.8 Hz, 1H), 3.44 (dd, J = 10.3, 2.3 Hz, 1H), 2.38−2.33 (m, 1H), 2.08−2.03 (m, 1H), 1.89 (dd, J = 13.8, 1.6 Hz, 1H), 1.40 (s, 9H), 1.21 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 170.5, 155.3, 139.3, 138.7, 138.5, 136.1, 128.4, 128.3, 128.2, 128.2, 128.1, 127.7, 127.4, 127.3, 104.1, 101.1, 78.6, 73.9, 72.9, 72.0, 70.7, 70.3, 69.1, 66.5, 61.7, 54.3, 40.6, 38.9, 27.6, 23.3; ESI-HRMS m/z calcd for $C_{45}H_{53}NO_{10}Na$ [M + Na]$^+$ 790.3562, found 790.3542. ^{1}H NMR (600 MHz, acetone-d_6) minor, δ 7.44−7.24 (m, 20H), 6.16 (d, J = 8.2 Hz, 1H), 5.46 (d, J = 4.9 Hz, 1H), 5.27 (d, J = 12.6 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 4.88 (d, J = 11.5 Hz, 1H), 4.77 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 11.5 Hz, 1H), 4.57−4.49 (m, 3H), 4.43−4.39 (m, 1H), 4.17−4.12 (m, 2H), 4.04 (d, J = 10.1, 2.3 Hz, 1H), 3.91 (d, J = 3.7 Hz, 2H), 3.74 (dd, J = 9.1, 7.7 Hz, 1H), 3.64−3.60 (m, 1H), 2.50−2.46 (m, 1H), 2.17 (dd, J = 13.4, 1.9 Hz, 1H), 2.11 (dd, J = 13.6, 8.0 Hz, 1H), 1.40 (s, 9H), 1.37 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 170.5, 155.3, 139.0, 138.5, 136.3, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 106.3, 102.6, 79.8, 78.8, 73.9, 72.2, 71.5, 71.3, 68.7, 66.2, 62.1, 54.4, 40.4, 39.6, 27.7, 23.0; ESI-HRMS m/z calcd for $C_{45}H_{53}NO_{10}Na$ [M + Na]$^+$ 790.3562, found 790.3542.

47 was obtained as a syrup (66.0 mg, 86%, major/minor = 4:1). **47** (major) as a syrup: $[\alpha]^{20}_D$ +17.5 (c 0.4, acetone); ^{1}H NMR (600 MHz, acetone-d_6) δ 7.41−7.24 (m, 20H), 5.98 (d, J = 8.5 Hz, 1H), 5.34 (d, J = 5.7 Hz, 1H), 5.18 (d, J = 12.1 Hz, 1H), 5.15 (d, J = 12.6 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.70 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 12.2 Hz, 1H), 4.41−4.37 (m, 1H), 3.98 (dd, J = 9.7, 3.8 Hz, 1H), 3.78−3.73 (m, 1H), 3.70−3.62 (m, 5H), 2.63−2.59 (m, 1H), 2.06−2.02 (m, 1H), 1.97 (dd, J = 13.2, 7.9 Hz, 1H), 1.40 (s, 9H), 1.39 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 170.6, 155.4, 138.9, 138.8, 138.5, 136.1, 128.4, 128.2, 128.2, 128.0, 127.9, 127.6, 127.5, 127.5, 127.3, 78.6, 77.9, 76.7, 72.8, 72.4, 71.8, 71.3, 70.0, 66.4, 61.5, 54.3, 41.1, 39.9, 27.7, 21.8; ESI-HRMS m/z calcd for $C_{45}H_{53}NO_{10}Na$ [M + Na]$^+$ 790.3562, found 790.3542. **47** (minor) as a syrup: $[\alpha]^{20}_D$ +41.0 (c 0.2, acetone); ^{1}H NMR (600 MHz, acetone-d_6) δ 7.37−7.24 (m, 20H), 6.37 (d, J = 7.8 Hz, 1H), 5.56 (d, J = 5.6 Hz, 1H), 5.32 (d, J = 12.8 Hz, 1H), 5.08 (d, J = 12.6 Hz, 1H), 4.79 (d, J = 11.6 Hz, 2H), 4.67 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.8 Hz, 1H), 4.58 (d, J = 12.6 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 4.43−4.38 (m, 1H), 4.12−4.06 (m, 2H), 3.97 (dd, J = 9.4, 3.4 Hz, 1H), 3.85 (dd, J = 7.2, 1.0 Hz, 1H), 3.76 (dd, J = 10.6, 3.6 Hz, 1H), 3.72−3.66 (m, 2H), 2.36−2.30 (m, 1H), 2.15 (dd, J = 13.2, 1.6 Hz, 1H), 2.09−2.05 (m, 1H), 1.36 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, acetone-d_6) δ 170.3, 155.4, 139.4, 139.0, 138.7, 136.4, 128.3, 128.2, 128.1, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 81.5, 78.6, 78.0, 73.9, 73.5, 73.4, 73.0, 69.9, 66.1, 62.5, 54.3, 44.2, 41.1, 27.7, 22.4; ESI-HRMS m/z calcd for $C_{45}H_{53}NO_{10}Na$ [M + Na]$^+$ 790.3562, found 790.3542.

Protocol B (for compounds 24 and 35). A mixture of the glycosyl donor (64.2 mg, 0.12 mmol), the acceptor (29.5 mg, 0.10 mmol), and powdered 4 Å molecular sieves (75 mg) in CH_2Cl_2 (1.0 mL) was stirred at room temperature for 30 min under argon and then cooled to −20 °C. NIS (33.7 mg, 0.15 mmol) and TMSOTf (3.6 μL, 0.02 mmol) were successively added. The reaction mixture was warmed slowly to room temperature, stirred for 1 h, and then cooled to 0 °C. $BF_3\cdot OEt_2$ (2.5 μL, 0.02 mmol) was added. The mixture was stirred for 30 min and then quenched by the addition of Et_3N. Usual workup and flash column chromatography (petroleum ether/ethyl acetate, 5:1, v/v) afforded **24** (51.5 mg, 67%, α/β = 1:3). **24β**, colorless syrup: $[\alpha]^{20}_D$ −0.6 (c 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.15 (m, 20H), 5.56 (d, J = 8.6 Hz, 1H), 5.21 (d, J = 13.0 Hz, 1H), 5.10 (d, J = 12.7 Hz, 1H), 4.87 (d, J = 11.3 Hz, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.47−4.42 (m, 1H), 4.45 (d, J = 11.9 Hz, 1H), 4.36 (d, J = 11.6 Hz, 1H), 4.29−4.24 (m, 2H), 3.93 (br s, 1H), 3.68 (dd, J = 8.7, 7.9 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 3.58 (dd, J = 9.1, 5.4 Hz, 1H), 3.53 (dd, J = 6.2, 5.9 Hz, 1H), 3.35 (d, J = 10.8 Hz, 1H), 2.62 (dd, J = 15.2, 4.1 Hz, 1H), 2.59−2.53 (m, 1H), 2.31 (dd, J = 15.2, 7.1 Hz, 1H), 1.99 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.9, 170.0, 155.7, 138.6, 137.9, 137.5, 135.6, 128.5, 128.5, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 103.5, 80.3, 79.8, 74.7, 73.7, 73.6, 71.6, 70.9, 69.5, 68.7, 67.0, 54.0, 42.2, 40.3, 29.2, 28.3; ESI-HRMS m/z calcd for $C_{45}H_{53}NO_{10}Na$ [M + Na]$^+$ 790.3562, found 790.3547. **24α**, colorless syrup: $[\alpha]^{20}_D$ +55.0 (c 0.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.21 (m, 20H), 5.47 (d, J = 8.6 Hz, 1H), 5.13 (ABq, J = 12.9 Hz, 2H), 4.89 (d, J = 2.0 Hz, 1H), 4.82 (d, J = 11.3 Hz, 1H), 4.66 (d, J = 11.3 Hz, 1H), 4.52 (d, J = 11.3 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H), 4.49−4.45 (m, 1H), 4.43 (d, J = 11.7 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 3.93 (br s, 1H), 3.85−3.80 (m, 3H), 3.61 (dd, J = 8.5, 7.9 Hz, 1H), 3.55 (dd, J = 9.1, 5.8 Hz, 1H), 3.46 (d, J = 10.8 Hz, 1H), 2.88−2.82

(m, 1H), 2.67 (dd, J = 17.5, 4.6 Hz, 1H), 2.19 (dd, J = 17.5, 9.3 Hz, 1H), 2.03 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 170.5, 155.5, 138.6, 138.0, 137.8, 135.3, 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 100.1, 80.1, 78.1, 74.4, 73.6, 71.4, 69.9, 69.0, 67.2, 54.2, 41.5, 36.5, 30.0, 28.3; ESI-HRMS m/z calcd for $C_{45}H_{53}NO_{10}Na$ [M + Na]$^+$ 790.3562, found 790.3560.

35 (62.2 mg, 81%, β only), colorless syrup: $[\alpha]^{20}_D$ +10.1 (c 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32−7.18 (m, 15H), 5.53 (d, J = 8.4 Hz, 1H), 5.20 (d, J = 12.4 Hz, 1H), 5.13 (d, J = 12.3 Hz, 1H), 4.87 (d, J = 11.2 Hz, 1H), 4.77 (d, J = 10.9 Hz, 1H), 4.61 (d, J = 10.8 Hz, 1H), 4.59 (d, J = 12.3 Hz, 1H), 4.53 (d, J = 11.2 Hz, 1H), 4.51 (d, J = 11.9 Hz, 1H), 4.47−4.46 (m, 1H), 4.32−4.30 (m, 2H), 3.75−3.65 (m, 4H), 3.45−3.38 (m, 2H), 2.53 (dd, J = 15.7, 4.5 Hz, 1H), 2.30 (dd, J = 15.4, 7.2 Hz, 1H), 2.13−2.05 (m, 1H), 1.96 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.8, 170.0, 155.7, 138.1, 138.0, 135.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 102.9, 81.9, 79.8, 79.6, 75.2, 74.9, 74.7, 73.5, 69.4, 68.7, 67.0, 54.1, 44.9, 42.1, 29.2, 28.3; ESI-HRMS m/z calcd for $C_{45}H_{53}NO_{10}Na$ [M + Na]$^+$ 790.3562, found 790.3543.

Protocol C (for compound 35). To a solution of the glycosyl donor **46** (64.2 mg, 0.12 mmol) and the acceptor **17** (29.5 mg, 0.10 mmol) in dry CH_2Cl_2 (1.0 mL) was added NIS (33.7 mg, 0.15 mmol) and TMSOTf (3.6 μL, 0.02 mmol) successively at −20 °C. The reaction mixture was warmed slowly to room temperature, stirred for 1 h, and then quenched by the addition of Et_3N. Usual workup and flash column chromatography (petroleum ether/ethyl acetate, 5:1, v/v) afforded **35** (53.0 mg, 69%, β only).

Acknowledgment. We are grateful for the financial support from the Chinese Academy of Sciences (Hundreds of Talents Program) and the National Science Foundation of China (20972151).

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