

Selective 3-O- and/or 6-O-Glycosidation of Unprotected *O*- and *S*-Glycosides Promoted by an Intramolecularly Coordinated Arylboronic Compound

Kenji Oshima,* Takeshi Yamauchi, Masato Shimomura, Shinnosuke Miyauchi, and Yasuhiro Aoyama*,†

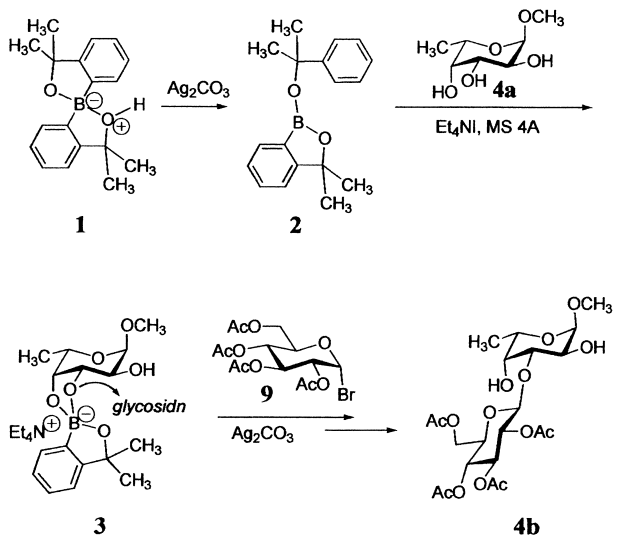
Department of BioEngineering, Nagaoka University of Technology, Kamitomioka, Nagaoka, Niigata 940-2188

†Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501

(Received November 2, 2001)

Arylboronic compound **1** that has intramolecular coordination promotes highly regioselective 3-O- and/or 6-O-glucosidation and -galactosidation of methyl fucopyanoside, methyl galactopyranoside, methyl mannopyranoside, *p*-methylphenyl 1-thiogalactopyranoside, and *p*-methylphenyl 1-thiomannopyranoside with peracetylated glucopyranosyl bromide or galactopyranosyl bromide as a glycosyl donor in the presence of Ag_2CO_3, Et_4NI, and molecular sieves 4A in THF. Glycosyl acceptors and promoter **1** form cyclic boronates at cis-vicinal diol (3,4-diol or 2,3-diol) and/or 4,6-diol moieties with concomitant activation of the less hindered 3-O (equatorial) and/or 6-O (primary) nucleophiles via intramolecular O → B coordination. This reaction provides a novel method of simultaneous one-pot 3,6-O-double glycosidation (glucosidation and galactosidation) to give trisaccharides. However, attempted mannosidation with peracetylated mannopyranosyl bromide only gives rise to orthoesters.

Selective functionallization, especially glycosidation, of unprotected sugars remains a challenge in synthetic glycochemistry. The protection/deprotection procedure in common use is essentially based on selective deactivation of all but one particular OH group. An alternative approach may rely on selective activation of a specific OH group, as demonstrated in the use of elegant Sn reagents.[1] In a preliminary study,[2] we have introduced a diarylborinic derivative **1** that undergoes Ag^+-assisted C–B bond cleavage to gives an arylboronic derivative **2** (Scheme 1). As such, it forms 5-membered and/or 6-membered boronates with cis-vicinal diol and/or 4,6-diol moieties, respectively, of a sugar.[3] Boronic acids are rather known as protective groups.[4] In the present case, however, the intramolecular O → B coordination of the ortho substituent gives an anionic tetracoordinated intermediate **3** (Scheme 1). This results in nucleophilic activation of coordinating sugar OH groups. In the presence of a glycosyl bromide as a glycosyl donor under appropriate conditions (Ag_2CO_3 + Et_4NI + molecular sieves (MS) 4A in THF), selective glycosidation takes place at the less hindered equatorial (vs axial) OH group or primary 6-OH (vs secondary 4-OH) group. Selective 3-O- and/or 6-O-glucosidation of alkyl fucoside, galactoside, and mannoside with peracetylated glucosyl bromide was reported in the preliminary communication, as shown in Scheme 1 for the glycosyl transfer from glucosyl bromide (**9**) to methyl fucoside (**4a**) to give disaccharide **4b**. The present work is intended to shed more light on the scope and limitation, in reference to glycosyl donors and acceptors, of this reaction. We report here that galactosidation does work but mannosidation does not.



Scheme 1. Selective 3-O-glycosidation of methyl fucoside (**4a**) via arylboronic intermediate.

Successful use of thioglycosides as glycosyl acceptors is also noted.

Results and Discussion

Glycosyl transfer from donor to acceptor occurs in THF in the presence of promoter **1**, Ag_2CO_3, Et_4NI, and MS 4A. Two types of glycosyl acceptors investigated are *O*-glycosides and *S*-glycosides otherwise having unprotected OH groups. The

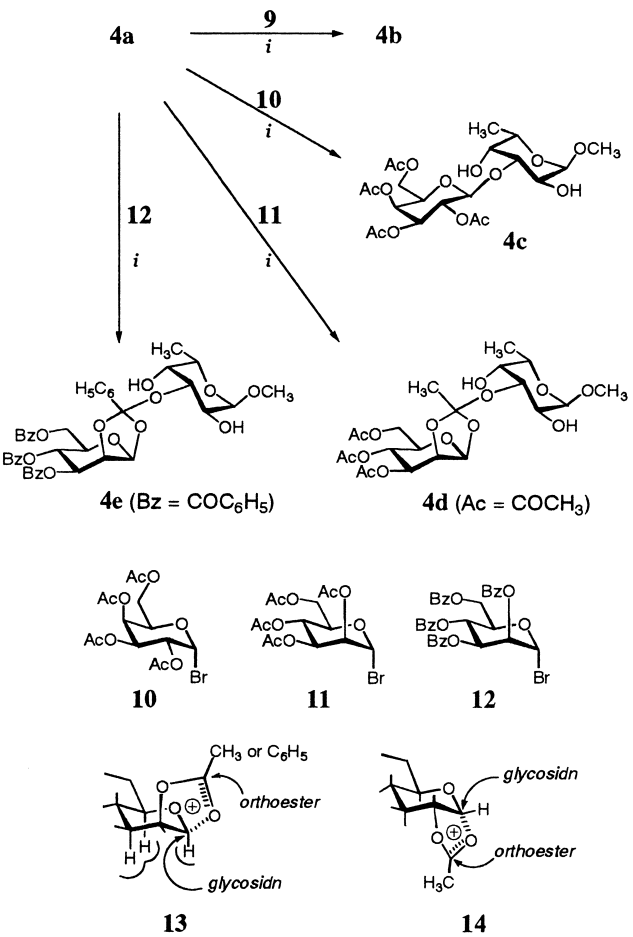
Table 1. Glycosidation of Various Acceptors (A) with Various Donors (D)[a)]

Entry	A	D	D/A	Products (Yield/%)[b)]		Recovery of A%[c)]
1	**4a**	**9**	3.5	**4b** (93)		~0
2		**10**	3.5	**4c** (96)		~0
3		**11**	3.5	**4d** (60)		40
4		**12**	3.5	**4e** (32)		64
5	**5a**	**9**	1.1	**5b** (35)	**5c** (19)	41
6		**9**	7.1	**5b** (< 1)	**5c** (84)	~0
7		**10**	7.1	**5d** (18)[d)]	**5e** (44)	28
8	**6a**	**9**	1.1	**6b** (32)	**6c** (12)	47
9		**9**	7.1	**6b** (9)	**6c** (84)	~0
10		**10**	7.1	**6d** (4)	**6e** (90)	~0
11	**7a**	**9**	7.1	**7b** (80)		~0
12	**8a**	**9**	7.1	**8b** (84)		~0

a) A (0.42 mmol), Et_4NI (0.48 mmol), and MS 4A (1.5 g) in THF (20 cm^3) at 50 °C for 20–48 h with a molar ratio of A:D:1:Ag_2CO3 = 1:3.5:1.1:1.1 for entries 1–4; 1:1.1:1.1:1.1 for entries 5 and 8; or 1:7.1:2.1:2.1 for entries 6, 7, 9, 10, 11 and 12. b) Isolated yields. c) Analytical (HPLC) yields. d) 6-*O*-Monogalactosidated product was obtained in $\leqq$ 2% yield.

former includes methyl α-L-fucopyranoside (**4a**), methyl α-D-galactopyranoside (**5a**), and methyl α-D-mannopyranoside (**6a**) and the latter involves *p*-methylphenyl 1-thio-β-D-galactopyranoside (**7a**) and *p*-methylphenyl 1-thio-α-D-mannopyranoside (**8a**). Glycosyl donors, on the other hand, are peracylated glycosyl bromides, i.e., peracetylated α-D-glucopyranosyl bromide (**9**), peracetylated α-D-galactopyranosyl bromide (**10**), and peracetylated and perbenzoylated α-D-mannopyranosyl bromides (**11** and **12**, respectively). All the results of glycosidation are shown in Table 1 as well as in Schemes 2, 3, 4, and 5 for the reactions of focoside **4a**, galactoside **5a**, mannoside **6a**, and thioglycosides **7a** and **8a**, respectively.

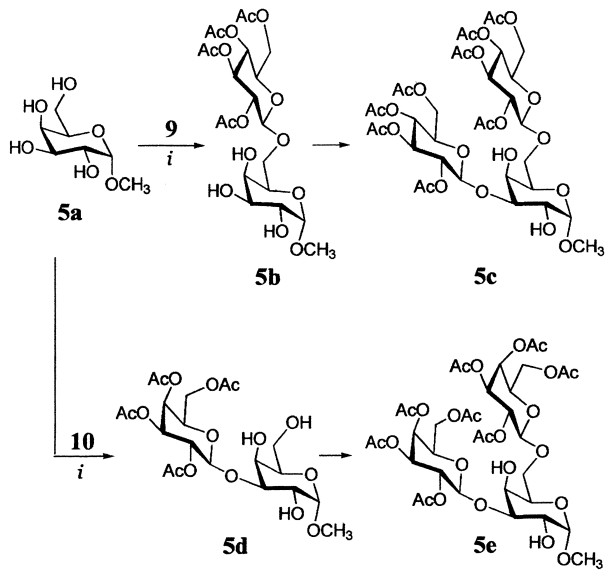
Methyl Fucoside. The reactions of fucoside **4a** are shown in Scheme 2. It has a cis-vicinal 3,4-diol moiety as the sole site of boronate formation.[5] It in fact forms a 3,4-*O*-boronate and, as reported, undergoes exclusive glucosidation with glucosyl bromide **9** at the equatorial 3-O nucleophile to give β-linked disaccharide **4b** (Scheme 1) in high yield at a donor/acceptor ratio of **9**/**4a** = 3.5 (entry 1). Galactosidation of focoside **4a** with galactosyl bromide **10** occurs in a similar manner and gives rise to 3-*O*-galactosidated disaccharide **4c** again in an excellent yield (entry 2). In marked contrast, however, attempted mannosidation with mannosyl bromide **11** or **12** only leads to the formation of orthoester **4d** or **4e** and no glycosidation product is obtained (entries 3 and 4).[6] Glycosidation is in competition with orthoester formation. The acyloxonium ion intermediate can be attacked by a glycosyl acceptor either on the anomeric carbon to lead to glycosidation or on the acyl carbon to give an orthoester. In the case of mannosyl intermediate **13**, acyl participation occurs from the equatorial direction. In order to be glycosidated, a glycosyl acceptor should attack the anomeric carbon from the endo direction which is highly crowded due to the presence of axial hydrogen atoms on 3-C and 5-C.[7] On the contrary, the glucosyl and galactosyl intermediates **14** have acyl participation in the axial position to allow glycosidation occurring from the less hindered exo direc-



Scheme 2. Reactions of methyl fucoside (**4a**). *i*) Et_4NI, Ag_2CO_3, MS 4A/THF.

tion.

Methyl Galactoside and Methyl Mannoside. Scheme 3 shows the reactions of galactoside **5a**. It has two sites of boronate formation,[8] i.e., 3,4-diol and 4,6-diol moieties where 3-O (equatorial) and 6-O (primary) are the less hindered nucleophilic centers. Glucosidation at a low donor/accepter ratio (D/A = 1.1) affords 6-*O*-monoglucosidated disaccharide **5b** together with a smaller amount of 3,6-*O*-diglucosidated trisaccharide **5c** (entry 5). The latter (**5c**) in a good yield becomes practically the sole isolable product at a higher D/A ratio of 7.1 (entry 6). It is reasonable to assume that galactoside **5a** preferentially undergoes glucosidation at 6-O and then further at 3-O. Galactosidation is slower and, even at D/A = 7.1, leaves a significant amount of unreacted acceptor **5a** together with 3,6-*O*-digalactosidated trisaccharide **5e** and disaccharide **5d** which, in marked contrast to the glucosidation regioselectivity, is 3-*O*-galactosidated (entry 7). Thus, it seems that the primary site (3-O vs 6-O) of glycosidation of galactosided **5a** depends on the type of donors (glucosyl **9** vs galactosyl **10**), the reason for which is not clear at present.



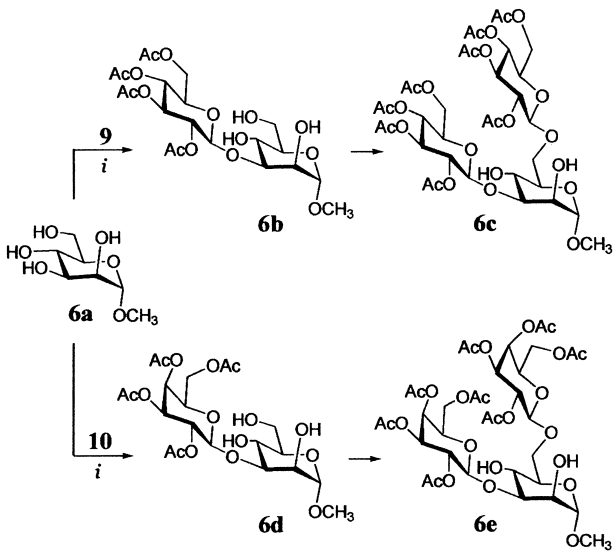
Scheme 3. Reactions of methyl galactoside (**5a**). *i*) Et_4NI, Ag_2CO_3, MS 4A/THF.

Mannoside **6a** has 2, 3-diol and 4, 6-diol moieties capable of forming boronates. Referring to Scheme 4, glucosidation at D/A = 1.1 gives 3-*O*-monoglucosidated disaccharide **6b** and 3,6-*O*-diglucosidated trisaccharide **6c** (entry 8). Preferential 6-O-glucosidation of galactoside **5a** and 3-O-glucosidation of mannoside **6a** makes an interesting contrast.[9] Trisaccharide product **6c** is obtained in a good yield at D/A = 7.1 (entry 9), as expected. This is also the case for galactosidation (entry 10).

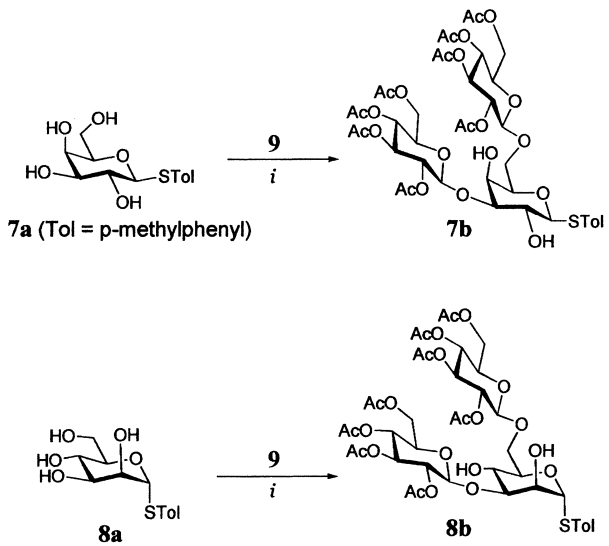
Thioglycosides. Thioglycosides are an interesting class of acceptors, since they can subsequently serve as glycosyl donors under particular conditions for further elongation of glycosidic chains.[10] *p*-Methylphenyl 1-thiogalactoside **7a** and 1-thiomannoside **8a** react smoothly with glucosyl donor **9** under the present conditions at D/A = 7.1 and afford 3,6-*O*-diglucosidated trisaccharides **7b** and **8b**, respectively (entries 11 and 12 and Scheme 5).

Conclusions

The present boronic-activation method allows highly regioselective 3-O- and/or 6-O-glucosidation and -galactosidation of unprotected sugars under classical glycosidation conditions with glycopyranosyl bromides as donors in the presence of a Ag^+ ion. As for the generality, the following points may be noted. (1) In addition to alkyl glycosides, thioglycosides can also be used as glycosyl acceptors. (2) The reactivities of various cyclic boronates, i.e., those derived from 3,4-diols in fucoside and galactoside, 2,3-diol in mannoside, and 4,6-diols in galactoside, mannoside, and glucoside are not uniform and even depend on the type of attacking glycosyl donors. (3) In marked contrast to glucosidation and galactosidation, mannosidation under otherwise identical conditions does not work



Scheme 4. Reactions of methyl mannoside (**6a**). *i*) Et_4NI, Ag_2CO_3, MS 4A/THF.



Scheme 5. Reactions of thioglycosides (**7a** and **8a**). *i*) Et_4NI, Ag_2CO_3, MS 4A/THF.

and only affords orthoesters. (4) Thus, the present method may find its most unique application in the one-pot preparation of 3,6-*O*-diglucosidated or -digalactosidated galactoside and mannoside with β-glycosidic linkages.

Experimental

Materials. 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide (**11**),[11] 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl bromide (**12**), *p*-methylphenyl 1-thio-β-D-galactopyranoside (**7a**), and *p*-methylphenyl 1-thio-α-D-mannopyranoside (**8a**)[12] were prepared by known methods. All other sugars used for glycosidation were commercial products: 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**9**) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**10**) from Fluka, methyl α-D-galactopyranoside monohydrate (**5a**) and methyl α-D-mannopyranoside (**6a**) from Nacarai tesque, and methyl α-L-fucopyranoside (**4a**) from TCI.

Instruments and Measurements. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded with a JEOL JNM EX-400 spectrometer at 400 MHz, 100 MHz, and 128 MHz, respectively. External $NaBF_4$ ($\delta_B = -20.4$ ppm) in D_2O was used as reference for δ_B. Yields of glycoside products were obtained by ^{1}H NMR with indole as a reference. Recovery of unreacted acceptors were determined by HPLC constructed with a Jasco 830-RI detector and a Shodex Asahipak NH2P-50-4E column with elution of acetonitrile–water (75/25). Methyl β-L-arabinopyranoside was used as internal standard.

Preparation of Compound 1. Butyllithium (1.6 M solution in hexane (1 M = 1 mol dm^{-3}); 135 cm^3) was added dropwise into a solution of *o*-bromo-1-methyl-1-phenylethanol (22.68 g, 105 mmol) in ether (80 cm^3) under nitrogen at −70 °C. The mixture was stirred for 4 h at −70 °C and for an additional 1 h at room temperature. Into the resulting mixture was added dropwise a solution of trimethyl borate (24.0 g, 231 mmol) in ether (50 cm^3) at −70 °C. The mixture was allowed to warm up gradually to room temperature under stirring over night. Aqueous 1 M H_2SO_4 was added to acidify the mixture and the crude product was extracted with ether. The boron compound was extracted from the ether phase three times with aqueous 1% KOH. The combined alkaline extract was acidified with 1 M H_2SO_4 and saturated with NaCl. Resulting precipitates were then extracted with ether. The extract was washed with brine, dried with Na_2SO_4, and evaporated to give colorless crystals of **1** (7.17 g, 49%): mp 182–184 °C; ^{1}H NMR ($CDCl_3$) δ 7.21–7.13 (6H, m, Ar), 6.99 (2H, d, Ar), 1.49 (12H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 151.1, 129.5, 127.0, 126.9, 119.5, 85.2, 31.0; ^{11}B NMR ($CDCl_3$) δ −5. Found: C, 76.98; H, 7.55%. Calcd for $C_{18}H_{21}BO_2$: C, 77.17; H, 7.55%.

Typical Glycosidation Procedure (entry 1). A mixture of promoter **1** (0.46 mmol), acceptor **4a** (0.42 mmol), donor **9** (1.48 mmol), and MS 4A (1.5 g) in dry THF (20 cm^3) was refluxed under nitrogen for 1 h. Et_4NI (0.48 mmol) was added at 0 °C with stirring. After 30 min, Ag_2CO_3 (0.87 mmol) was added to initiate the reaction. The mixture was stirred at room temperature for 48 h and at 50 °C for 20 h, diluted with dichloromethane, and filtered to remove insoluble salts. Dichloromethane was evaporated and the residue was chromatographed on silica gel with acetone–dichloromethane (3/7) as eluent. Elutions of donor **2** used in excess and of 1-methyl-1-phenylethanol derived from promoter **1** were followed by that of product disaccharide **4b** (0.39 mmol, 93%). In every case, more than 80% of excess amount of donor was recovered. Glycosidations using other substrates were carried out in essentially the same manner. The progress of the reactions was readily monitored by TLC.

Assignment of Structures of Disaccharide and Trisaccharide Products. The disaccharide and trisaccharide products were isolated by chromatography on silica gel and further converted to peracetyl derivatives when necessary for identification. The sites of glycosidation were assigned on the basis of ^{1}H–^{1}H and ^{1}H–^{13}C COSY spectra in reference to the glycosidation-induced shifts in δ_C[13] and the acetylation-induced shifts in δ_H.[14] The H1–H2 coupling constants ($J_{H1,H2} \cong 8$ Hz) indicate that all the newly formed glycosidic linkage have β-stereo chemistry. The detailed ^{1}H NMR assignments of the 3-*O*- and 6-*O*-glycoside moieties were based on NOE measurements.

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-α-L-fucopyranoside (4b): TLC R_f 0.43 (3/7 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.37 (OCH_3), 4.77 (H1^{I}, $J_{1,2}$ = 3.9 Hz), 3.94 (H2^{I}), 3.79 (H3^{I}), 3.67 (H4^{I}), 3.87 (H5^{I}), 1.25 (H6^{I}), 4.65 (H1^{II}, $J_{1,2}$ = 7.7 Hz), 4.99 (H2^{II}), 5.18 (H3^{II}), 5.03 (H4^{II}), 3.72 (H5^{II}), 4.19 and 4.13 (H6^{II}), where I and II refer to the fucoside and glucoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 55.20 (OCH_3), 99.33 (C1^{I}), 66.96 (C2^{I}), 82.23 (C3^{I}), 70.75 (C4^{I}), 65.13 (C5^{I}), 15.86 (C6^{I}), 100.54 (C1^{II}) 71.37 (C2^{II}), 72.26 (C3^{II}), 68.11 (C4^{II}), 71.99 (C5^{II}), 61.58 (C6^{II}). Found: C, 49.77; H, 6.42%. Calcd for $C_{21}H_{32}O_{14}$: C, 49.61; H, 6.34%. HRMS Found: *m/z* 531.1689. Calcd for $(M + Na)^+$: 531.1690.

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-α-L-fucopyranoside (4c): TLC R_f 0.50 (3/7 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.43 (OCH_3), 4.83 (H1^{I}, $J_{1,2}$ = 3.9 Hz), 4.00 (H2^{I}), 3.84 (H3^{I}), 3.72 (H4^{I}), 3.93 (H5^{I}), 1.31 (H6^{I}), 4.66 (H1^{II}, $J_{1,2}$ = 8.3 Hz) 5.24 (H2^{II}), 5.05 (H3^{II}), 5.40 (H4^{II}), 4.00 (H5^{II}), 4.16 (H6^{II}), where I and II refer to the fucoside and galactoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 55.13 (OCH_3), 99.27 (C1^{I}), 66.92 (C2^{I}), 82.29 (C3^{I}), 70.71 (C4^{I}), 65.11 (C5^{I}), 15.81 (C6^{I}), 101.07 (C1^{II}) 69.01 (C2^{II}), 70.38 (C3^{II}), 66.72 (C4^{II}), 71.04 (C5^{II}), 61.20 (C6^{II}). Found: C, 49.74; H, 6.31%. Calcd for $C_{21}H_{32}O_{14}$: C, 49.61; H, 6.34%. HRMS Found: *m/z* 531.1694. Calcd for $(M + Na)^+$: 531.1690.

Methyl 3-*O*-[1-(3,4,6-Tri-*O*-acetyl-β-D-mannopyranose-1,2-di-*O*-yl)ethyl]-α-L-fucopyranoside (4d): TLC R_f 0.30 (3/7 acetone–dichloromethane); ^{1}H NMR (DMSO-d_6) δ 3.24 (OCH_3), 4.49 (H1^{I}, $J_{1,2}$ = 3.4 Hz), 3.62 (H2^{I}), 3.67 (H3^{I}), 3.52 (H4^{I}), 3.70 (H5^{I}), 1.06 (H6^{I}), 5.56 (H1^{II}, $J_{1,2}$ = 2.5 Hz), 4.60 (H2^{II}), 5.28 (H3^{II}), 5.04 (H4^{II}), 3.89 (H5^{II}), 4.09 and 4.02 (H6^{II}), where I and II refer to the fucoside and mannose moieties, respectively; ^{13}C NMR (DMSO-d_6) δ 54.44 (OCH_3), 100.14 (C1^{I}), 65.60 (C2^{I}), 72.67 (C3^{I}), 70.86 (C4^{I}), 65.56 (C5^{I}), 16.37 (C6^{I}), 96.74 (C1^{II}) 75.62 (C2^{II}), 69.68 (C3^{II}), 65.45 (C4^{II}), 69.97 (C5^{II}), 61.92 (C6^{II}), 123.55 (CH_3CO_3). Found: C, 48.79; H, 6.19%. Calcd for $C_{21}H_{32}O_{14}\cdot 1/2\ H_2O$: C, 48.74; H, 6.42%.

Methyl 3-*O*-[α-(3,4,6-Tri-*O*-benzoyl-β-D-mannopyranose-1,2-di-*O*-yl)benzyl]-α-L-fucopyranoside (4e): TLC R_f 0.43 (2/8 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.21 (OCH_3), 4.63 (H1^{I}, $J_{1,2}$ = 3.9 Hz), 3.83 (H2^{I}), 3.73 (H3^{I}), 3.24 (H4^{I}), 3.60 (H5^{I}), 1.11 (H6^{I}), 5.85 (H1^{II}, $J_{1,2}$ = 2.9 Hz), 5.39 (H2^{II}), 5.67 (H3^{II}), 5.88 (H4^{II}), 4.10 (H5^{II}), 4.47 and 4.32 (H6^{II}), where I and II refer to the fucoside and mannose moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 55.16 (OCH_3), 99.62 (C1^{I}), 67.14 (C2^{I}), 74.31 (C3^{I}), 71.04 (C4^{I}), 65.22 (C5^{I}), 15.94 (C6^{I}), 97.87 (C1^{II}) 75.72 (C2^{II}), 71.13 (C3^{II}), 66.49 (C4^{II}), 71.97 (C5^{II}), 62.99 (C6^{II}), 122.43 ($C_6H_5CO_3$). Found: C, 65.30; H, 5.56%. Calcd for $C_{41}H_{40}O_{14}$: C, 65.07; H, 5.33%.

6-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (5b): TLC R_f 0.17 (1/1 acetone–dichloromethane). Found: C, 48.14; H, 6.21%. Calcd for $C_{21}H_{32}O_{15}$: C, 48.09; H, 6.15%. HRMS Found: 547. 1627. Calcd for $(M + Na)^+$: 547.1639. Preacetyl derivative (**5b-Ac**): TLC R_f 0.53 (1/9 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.34 (OCH_3), 4.91 (H1^I, $J_{1,2}$ = 3.4 Hz), 5.07 (H2^I), 5.27 (H3^I), 5.36 (H4^I), 4.12 (H5^I), 3.74 and 3.60 (H6^I), 4.50 (H1^{II}, $J_{1,2}$ = 7.8 Hz), 4.91 (H2^{II}), 5.13 (H3^{II}), 5.01 (H4^{II}), 3.66 (H5^{II}), 4.21 and 4.08 (H6^{II}), where I and II refer to the galactoside and glucoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 55.26 (O*C*H$_3$), 96.97 (C1^I), 68.11 (C2^I), 67.51 (C3^I), 68.61 (C4^I), 67.40 (C5^I), 67.98 (C6^I), 100.65 (C1^{II}) 71.02 (C2^{II}), 72.61 (C3^{II}), 68.20 (C4^{II}), 71.75 (C5^{II}), 61.73 (C6^{II}).

Methyl 3,6-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranoside (5c): TLC R_f 0.48 (3/7 acetone–dichloromethane). Found: C, 49.25; H, 5.93%. Calcd for $C_{35}H_{50}O_{24}$: C, 49.18; H, 5.90%. HRMS Found: 877.2595. Calcd for $(M + Na)^+$: 877.2590. Peracetyl derivative (**5c-Ac**): TLC R_f 0.28 (1/9 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.34 (OCH_3), 4.85 (H1^I, $J_{1,2}$ = 3.9 Hz), 5.10 (H2^I), 4.15 (H3^I), 5.34 (H4^I), 3.49 (H5^I), 4.06 and 3.87 (H6^I), 4.63 (H1^{II}, $J_{1,2}$ = 7.8 Hz), 4.87 (H2^{II}), 5.13 (H3^{II}), 5.02 (H4^{II}), 3.61 (H5^{II}), 4.15–4.11 (H6^{II}) 4.49 (H1^{III}, $J_{1,2}$ = 7.8 Hz), 4.96 (H2^{III}), 5.16 (H3^{III}), 5.04 (H4^{III}), 3.68 (H5^{III}), 4.26 and 4.08 (H6^{III}), where I, II, and III refer to the galactoside, 3-*O*-glucoside, and 6-*O*-glucoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 55.11 (O*C*H$_3$), 96.86 (C1^I), 70.21 (C2^I), 72.23 (C3^I), 70.29 (C4^I), 69.17 (C5^I), 68.44 (C6^I), 100.34 (C1^{II}) 71.15 (C2^{II}), 72.50 (C3^{II}), 68.15 (C4^{II}), 71.77 (C5^{II}), 61.38 (C6^{II}) 100.94 (C1^{III}) 71.09 (C2^{III}), 72.57 (C3^{III}), 68.20 (C4^{III}), 71.73 (C5^{III}), 61.63 (C6^{III}).

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranoside (5d): TLC R_f 0.14 (1/1 acetone–dichloromethane). Found: C, 48.01; H, 6.14%. Calcd for $C_{21}H_{32}O_{15}$: C, 48.09; H, 6.15%. HRMS Found: 525.1833. Calcd for $(M + H)^+$: 525.1819. Peracetyl derivative (**5d-Ac**): TLC R_f = 0.91 (1/1 acetone–dichloromethane) ^{1}H NMR ($CDCl_3$) δ 3.40 (OCH_3), 4.92 (H1^I, $J_{1,2}$ = 3.4 Hz), 5.16 (H2^I), 4.22 (H3^I), 5.45 (H4^I), 4.18–4.10 (H5^I), 4.18–4.02 (H6^I), 4.65 (H1^{II}, $J_{1,2}$ = 7.8 Hz), 5.09 (H2^{II}), 4.94 (H3^{II}), 5.35 (H4^{II}), 3.87 (H5^{II}), 4.18–4.10 (H6^{II}), where I and II refer to the methyl galactoside and 3-*O*-galactoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 55.24 (O*C*H$_3$), 97.03 (C1^I), 70.36 (C2^I), 71.70 (C3^I), 69.52 (C4^I), 66.85 (C5^I), 62.37 (C6^I), 100.65 (C1^{II}) 68.77 (C2^{II}), 70.56 (C3^{II}), 66.70 (C4^{II}), 70.69 (C5^{II}), 60.94 (C6^{II}).

Methyl 3,6-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-galactopyranoside (5e): TLC R_f 0.42 (3/7 acetone–dichloromethane). Found: C, 48.67; H, 5.85%. Calcd for $C_{35}H_{50}O_{24}$: C, 49.18; H, 5.90%. HRMS Found: 877.2590. Calcd for $(M + Na)^+$: 877.2590. Peracetyl derivative (**5e-Ac**): TLC R_f 0.20 (1/9 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.38 (OCH_3), 4.88 (H1^I, $J_{1,2}$ = 3.9 Hz), 5.14 (H2^I), 4.20 (H3^I), 5.38 (H4^I), 4.12 (H5^I), 3.93 and 3.50 (H6^I), 4.64 (H1^{II}, $J_{1,2}$ = 7.8 Hz), 5.08 (H2^{II}), 4.94 (H3^{II}), 5.34 (H4^{II}), 3.87 (H5^{II}), 4.11 (H6^{II}) 4.49 (H1^{III}, $J_{1,2}$ = 7.8 Hz), 5.20 (H2^{III}), 5.00 (H3^{III}), 5.38 (H4^{III}), 3.92 (H5^{III}), 4.15 (H6^{III}), where I, II, and III refer to the methyl galactoside, 3-*O*-galactoside, and 6-*O*-galactoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 55.07 (O*C*H$_3$), 96.81 (C1^I), 70.42 (C2^I), 71.93 (C3^I), 70.25 (C4^I), 68.37 (C5^I), 69.06 (C6^I), 100.68 (C1^{II}) 68.73 (C2^{II}), 70.53 (C3^{II}), 66.72 (C4^{II}), 70.65 (C5^{II}), 60.96 (C6^{II}) 101.32 (C1^{III}) 68.61 (C2^{III}), 70.62 (C3^{III}), 66.83 (C4^{III}), 70.56 (C5^{III}), 60.96 (C6^{III}).

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-mannopyranoside (6b): TLC R_f 0.40 (1/1 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.32 (OCH_3), 4.69 (H1^I, $J_{1,2}$ = 1.5 Hz), 3.80 (H2^I), 3.70 (H3^I), 3.89 (H4^I), 3.49 (H5^I), 3.81 (H6^I), 4.60 (H1^{II}, $J_{1',2'}$ = 7.8 Hz), 4.98 (H2^{II}), 5.18 (H3^{II}), 5.00 (H4^{II}), 3.76 (H5^{II}), 4.14 (H6^{II}), where I and II refer to the mannoside and glucoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 54.76 (O*C*H$_3$), 100.41 (C1^I), 69.58 (C2^I), 83.58 (C3^I), 65.41 (C4^I), 71.68 (C5^I), 61.80 (C6^I), 101.07 (C1^{II}), 71.33 (C2^{II}), 72.28 (C3^{II}), 68.37 (C4^{II}), 71.95 (C5^{II}), 61.93 (C6^{II}). Found: C, 47.90; H, 6.31%. Calcd for $C_{21}H_{32}O_{15}$: C, 48.09; H, 6.15%. HRMS Found: *m/z* 547.1613. Calcd for $(M + Na)^+$: 547.1639.

Methyl 3,6-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-mannopyranoside (6c): TLC R_f 0.66 (3/7 acetone–dichloromethane). Found: C, 49.20; H, 6.05%. Calcd for $C_{35}H_{50}O_{24}$: C, 49.18; H, 5.90%. HRMS Found: 877.2592. Calcd for $(M + Na)^+$: 877.2590. Peracetyl derivative (**6c-Ac**): TLC R_f 0.34 (1/9 acetone–dichloromethane): ^{1}H NMR (C_6D_6) δ 3.11 (OCH_3), 4.65 (H1^I, $J_{1,2}$ = 1.5 Hz), 5.40 (H2^I), 4.17 (H3^I), 5.47 (H4^I), 3.93 (H5^I), 4.08 and 3.59 (H6^I), 4.16 (H1^{II}, $J_{1,2}$ = 7.8 Hz), 5.08 (H2^{II}), 5.28 (H3^{II}), 5.15 (H4^{II}), 3.07 (H5^{II}), 4.28 and 3.84 (H6^{II}), 4.34 (H1^{III}, $J_{1,2}$ = 7.3 Hz), 5.35 (H2^{III}), 5.41 (H3^{III}), 5.24 (H4^{III}), 3.22 (H5^{III}), 4.24 and 3.98 (H6^{III}), where I, II, and III refer to the mannoside, 3-*O*-glucoside, and 6-*O*-glucoside moieties, respectively; ^{13}C NMR (C_6D_6) δ 54.70 (O*C*H$_3$), 98.58 (C1^I), 73.25 (C2^I), 75.88 (C3^I), 67.01 (C4^I), 70.30 (C5^I), 68.73 (C6^I), 100.18 (C1^{II}) 71.88 (C2^{II}), 73.39 (C3^{II}), 68.16 (C4^{II}), 71.94 (C5^{II}), 61.47 (C6^{II}) 101.37 (C1^{III}) 71.69 (C2^{III}), 69.59 (C3^{III}), 68.73 (C4^{III}), 72.13 (C5^{III}), 61.63 (C6^{III}).

Methyl 3-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-mannopyranoside (6d): TLC R_f 0.45 (1/1 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 3.39 (OCH_3), 4.76 (H1^I, $J_{1,2}$ = 1.0 Hz), 3.84 (H2^I), 3.74 (H3^I), 3.94 (H4^I), 3.57 (H5^I), 3.87 (H6^I), 4.61 (H1^{II}, $J_{1,2}$ = 8.2 Hz), 5.22 (H2^{II}), 5.06 (H3^{II}), 5.41 (H4^{II}), 4.03 (H5^{II}), 4.19–4.10 (H6^{II}), where I and II refer to the mannoside and galactoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 54.73 (O*C*H$_3$), 100.30 (C1^I), 69.69 (C2^I), 83.68 (C3^I), 65.68 (C4^I), 71.57 (C5^I), 61.99 (C6^I), 101.62 (C1^{II}) 69.05 (C2^{II}), 70.40 (C3^{II}), 66.83 (C4^{II}), 71.13 (C5^{II}), 61.49 (C6^{II}). Found: C, 48.30; H, 6.11%. Calcd for $C_{21}H_{32}O_{15}$: C, 48.09; H, 6.15%. HRMS Found: *m/z* 525.1794. Calcd for $(M + H)^+$: 525.1819.

Methyl 3,6-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-mannopyranoside (6e): TLC R_f 0.63 (3/7 acetone–dichloromethane). Found: C, 48.99; H, 5.88%. Calcd for $C_{35}H_{50}O_{24}$: C, 49.18; H, 5.90%. HRMS Found: *m/z* 877.2590. Calcd for $(M + Na)^+$: 877.2590. Peracetyl derivative (**6e-Ac**): TLC R_f 0.21 (1/9 acetone–dichloromethane); ^{1}H NMR (C_6D_6) δ 3.13 (OCH_3), 4.69 (H1^I, $J_{1,2}$ = 1.5 Hz), 5.39 (H2^I), 4.23 (H3^I), 5.52 (H4^I), 3.94 (H5^I), 4.15 and 3.56 (H6^I), 4.15 (H1^{II}, $J_{1,2}$ = 7.8 Hz), 5.41 (H2^{II}), 5.06 (H3^{II}), 5.44 (H4^{II}), 3.34 (H5^{II}), 4.04 (H6^{II}) 4.31 (H1^{III}, $J_{1,2}$ =7.8 Hz), 5.67 (H2^{III}), 5.17 (H3^{III}), 5.49 (H4^{III}), 3.39 (H5^{III}), 4.09 (H6^{III}), where I, II and III refer to the mannoside, 3-*O*-galactoside, and 6-*O*-galactoside moieties, respectively; ^{13}C NMR (C_6D_6) δ 54.72 (O*C*H$_3$), 98.54 (C1^I), 69.79 (C2^I), 75.84 (C3^I), 67.23 (C4^I), 70.25 (C5^I), 68.51 (C6^I), 100.70 (C1^{II}) 69.30 (C2^{II}), 71.47 (C3^{II}), 67.08 (C4^{II}), 70.78 (C5^{II}), 61.10 (C6^{II}) 101.74 (C1^{III}) 69.13 (C2^{III}), 71.31 (C3^{III}), 67.40 (C4^{III}), 70.96 (C5^{III}), 61.32 (C6^{III}).

***p*-Methylphenyl 3,6-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-β-D-galactopyranoside (7b):** TLC R_f 0.57 (2/8 acetone–dichloromethane). Found: C, 51.43; H, 5.78%.

Calcd for $C_{41}H_{54}O_{23}S\cdot 1/2H_2O$: C, 51.51; H, 5.80%. Peracetyl derivative (**7b-Ac**): TLC R_f 0.69 (2/8 acetone–dichloromethane); ^{1}H NMR (C_6D_6) δ 2.14 ($SC_6H_4CH_3$), 4.56 ($H1^I$, $J_{1,2}$ = 10.3 Hz), 5.60 ($H2^I$), 3.69 ($H3^I$), 5.41 ($H4^I$), 3.57 ($H5^I$), 3.87 and 3.74 ($H6^I$), 4.53 ($H1^{II}$, $J_{1,2}$ = 7.8 Hz), 5.12 ($H2^{II}$), 5.36 ($H3^{II}$), 5.18 ($H4^{II}$), 3.36 ($H5^{II}$), 4.30 and 4.16 ($H6^{II}$), 4.33 ($H1^{III}$, $J_{1,2}$ = 7.8 Hz), 5.33 ($H2^{III}$), 5.34 ($H3^{III}$), 5.27 ($H4^{III}$), 3.21 ($H5^{III}$), 4.21 and 4.06 ($H6^{III}$), where I, II, and III refer to the galactoside, 3-*O*-glucoside, and 6-*O*-glucoside moieties, respectively; ^{13}C NMR (C_6D_6) δ 18.96 ($SC_6H_4CH_3$), 85.22 ($C1^I$), 67.66 ($C2^I$), 75.98 ($C3^I$), 68.34 ($C4^I$), 75.56 ($C5^I$), 67.21 ($C6^I$), 99.14 ($C1^{II}$) 69.80 ($C2^{II}$), 71.03 ($C3^{II}$), 66.82 ($C4^{II}$), 70.46 ($C5^{II}$), 59.51 ($C6^{II}$ or $C6^{III}$), 99.06 ($C1^{III}$) 69.93 ($C2^{III}$), 71.54 ($C3^{III}$), 66.73 ($C4^{III}$), 70.26 ($C5^{III}$), 59.58 ($C6^{III}$ or $C6^{II}$).

***p*-Methylphenyl 3,6-Di-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1-thio-α-D-mannopyranoside (8b):** TLC R_f 0.53 (2/8 acetone–dichloromethane); ^{1}H NMR ($CDCl_3$) δ 2.35 ($SC_6H_4CH_3$), 5.46 ($H1^I$, $J_{1,2}$ = 1.5 Hz), 4.08 ($H2^I$), 3.72 ($H3^I$), 3.80 ($H4^I$), 4.23 ($H5^I$), 4.11 and 3.90 ($H6^I$), 4.66 ($H1^{II}$, $J_{1,2}$ = 7.8 Hz), 5.02 ($H2^{II}$), 5.27 ($H3^{II}$), 5.07 ($H4^{II}$), 3.83 ($H5^{II}$), 4.29–4.15 ($H6^{II}$), 4.64 ($H1^{III}$, $J_{1,2}$ = 7.8 Hz), 4.98 ($H2^{III}$), 5.17 ($H3^{III}$), 5.07 ($H4^{III}$), 3.63 ($H5^{III}$), 4.29–4.15 ($H6^{III}$), where I, II, and III refer to the mannoside, 3-*O*-glucoside, and 6-*O*-glucoside moieties, respectively; ^{13}C NMR ($CDCl_3$) δ 21.00 ($SC_6H_4CH_3$), 87.95 ($C1^I$), 71.15 ($C2^I$), 83.49 ($C3^I$), 65.66 ($C4^I$), 72.87 ($C5^I$), 68.45 ($C6^I$), 100.98 ($C1^{II}$) 71.31 ($C2^{II}$), 72.12 ($C3^{II}$), 68.30 ($C4^{II}$ or $C4^{III}$), 72.17 ($C5^{II}$), 61.75 ($C6^{II}$ or $C6^{III}$), 100.98 ($C1^{III}$) 71.42 ($C2^{III}$), 72.79 ($C3^{III}$), 68.41 ($C4^{III}$ or $C4^{II}$), 71.64 ($C5^{III}$), 61.82 ($C6^{III}$ or $C6^{II}$). Found: C, 51.72; H, 5.75%. Calcd for $C_{41}H_{54}O_{23}S$: C, 52.00; H, 5.75%. HRMS Found: *m/z* 969.2676. Calcd for $(M + Na)^+$: 969.2674.

References

1 For acylation: a) M. A. Nashed and L. Anderson, *Tetrahedron Lett*., **1976**, 3503. b) T. Ogawa and M. Matsui, *Tetrahedronn*, **37**, 2363 (1981). c) Y. Tsuda, M. D. Haque, and K. Yoshimoto, *Chem. Pharm. Bull*., **31**, 1612 (1983). For alkylation: d) T. Ogawa and M. Matsui, *Carbohydr. Res*., **62**, C1 (1978). e) S. David, A. Thieffry, and A. Veyrières, *J. Chem . Soc., Perkin Trans. 1*, **1981**, 1796. For sulfation: f) A. Lubineau and R. Lemoine, *Tetrahedron Lett*., **35**, 8795 (1994). For orthoester formation: g) T. Ogawa, K. Katano, and M. Matsui, *Carbohydr. Res*., **64**, C3 (1978). An excellent review for acylation, alkylation, and other functionalization: h) Y. Tsuda, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.*), **55**, 907 (1997).

2 Preliminary results of this work appeared in K. Oshima and Y. Aoyama, *J. Am. Chem. Soc*., **121**, 2315 (1999).

3 a) R. J. Ferrier, *J. Chem. Soc*., **1961**, 2325. b) E. Huttunen, *Ann. Acad. Sci. Fenn. Ser. A2*, **201**, 1 (1984). c) J. F. Verchere and M. Hlaibi, *Polyhedron*, **6**, 1415 (1987). d) K. Kondo, T. Shiomi, M. Saisho, T. Harada, and S. Shinkai, *Tetrahedron*, **48**, 8239 (1992). e) K. Oshima, H. Toi, and Y. Aoyama, *Carbohydr. Lett*., **1**, 223 (1995).

4 R. J. Ferrier, D. Prasad, A. Rudowski, and I. Sangster, *J. Chem. Soc*., **1964**, 3330.

5 K. Oshima, E. Kitazono, and Y. Aoyama, *Tetrahedron Lett*., **38**, 5001 (1997).

6 Regioselective orthoester formation and its advantage to obtain an intermediate for α-mannoside has been described, see: Ref. 1g and W. Wang and F. Kong, *Angew. Chem., Int. Ed*., **38**, 1247 (1999).

7 Although 2-*O*-etherified mannosyl bromide as a donor, which should not form orthoester, was expected to be a possible alternative, the mannosidation with 2,3,4,6-tetra-*O*-benzyl-α-mannosyl bromide afforded few amount of glycosides with no regioselectivity.

8 G. Wullf and H.-G. Poll, *Makromol. Chem*., **188**, 741 (1987).

9 Such greater reactivity of 3-O than 6-O in mannopyranoside was also observed in the complexation-promoted allylation using a stannylene reagent: Ref. 1d.

10 Z. Zhang, I. R. Ollmann, X.-S. Ye, R. Wischnat, T. Baasov, and C.-H. Wong, *J. Am. Chem. Soc*., **121**, 734 (1999), and references therein.

11 F. M. Winnik, J-.R. Brisson, J. P. Carver, and J. J. Krepinsky, *Carbohydr. Res*., **103**, 15 (1982).

12 O. Arjona, A. de Dios, C. Montero, and J. Plumet, *Tetrahedron Lett*., **51**, 9191 (1995).

13 T. Usui, K. Matsuda, K. Tuzimura, H. Sugiyama, and S. Seto, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2425.

14 a) R. U. Lemieux and J. D. Stevens, *Can. J. Chem*., **43**, 2059 (1965). b) B. Casu, M. Reggiani, G. G. Gallo, and A. Vigevani, *Carbohydr. Res*., **12**, 157 (1970).