JOC Article

Efficient Synthesis of β-D-Mannosides and β-D-Talosides by Double Parallel or Double Serial Inversion

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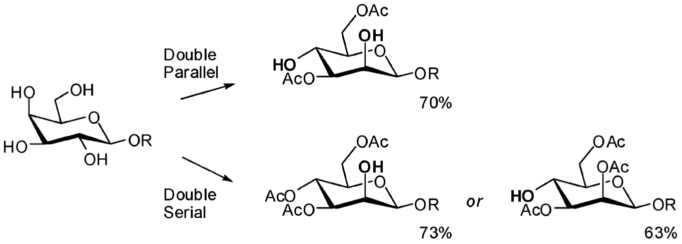

A neighboring equatorial ester group plays a highly important role in the Lattrell−Dax (nitrite-mediated) carbohydrate epimerization reaction, inducing the formation of inversion compounds in good yields. On the basis of this effect, efficient synthetic routes to β-D-mannosides and β-D-talosides, from the corresponding β-D-galactosides and β-D-glucosides, have been designed. The present routes are based on multiple regioselective acylation via the respective stannylene intermediates, followed by inversions to the corresponding manno- and talopyranoside structures by nitrite or acetate substitution. It was found that the ester group was able to induce the inversion of its two neighboring groups in high yields following either a double parallel or a double serial inversion process. By combination of direct inversion, and neighboring- as well as remote-group participation, several β-D-mannoside and β-D-taloside derivatives were very conveniently obtained in good yields.

Introduction

The β-mannopyranosidic linkage is a common structural element in a wide range of natural products.[1−4] This biologically important and widespread class of structures contains, as relevant component, β-D-Man*p* units, also for example present as a central component in the ubiquitous *N*-glycan core structure of glycoproteins,[1] and makes part of a range of fungi and bacteria (Figure 1, 2).[5,6] The chemical synthesis of this 1,2-*cis*-mannosidic linkage is, however, especially difficult. The α-mannosidic linkage is strongly favored because of the concomitant occurrence of both the α-directing anomeric effect and the repulsion between the axial C-2 substituent and the approaching nucleophile. Moreover, neighboring group participation of a 2-acyl substituent leads to α-mannosides only. The 1,2-*cis*-glycosidic linkage is present also in β-D-talopyranosides (Figure 2). However interesting, recently evaluated for their intriguing H-bonding motifs, these structures have been less investigated in part due to their cumbersome synthesis.[7−11]

As a consequence of these synthetic challenges, several different synthetic methods have been developed for β-mannoside synthesis. These include Koenigs−Knorr coupling methods using insoluble silver salt promoters blocking the α-face of mannosyl halides,[12−14] sequential oxidation/reduction

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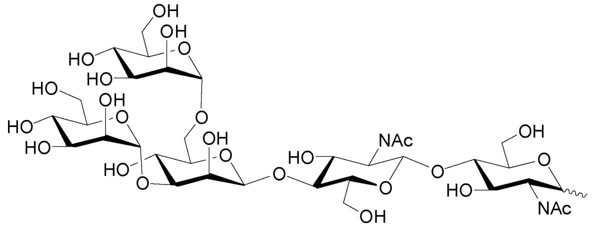
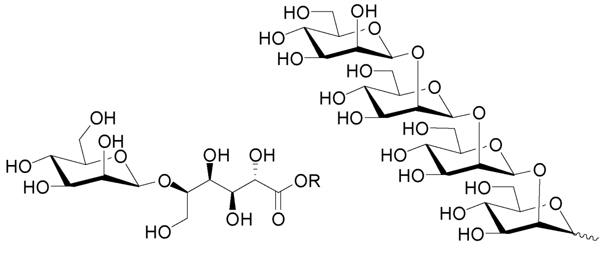


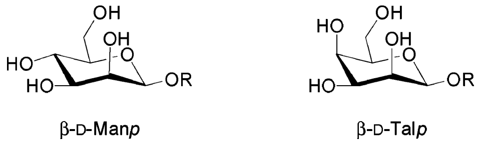
N-linked pentasaccharide core structure



Fungal metabolite
deacetyl-caloporoside

Partial structure of the cell wall
phosphomannan antigen

FIGURE 1. Natural entities containing β-mannopyranosidic linkages.



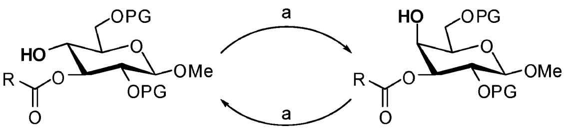
β-D-Man*p*

β-D-Tal*p*

FIGURE 2. β-D-Man*p* and β-D-Tal*p* structures.

routes,[15-17] use of 2-oxo- and 2-oximinoglycosyl halides,[18,19] use of intermolecular,[20-23] or intramolecular,[24-26] S_N2 reactions and intramolecular aglycon delivery method,[27-34] inversion of configuration of α-mannosyl triflate donors,[35-37] epimerization of β-glucopyranosides to β-mannopyranosides through S_N2 reactions,[38-42] as well as enzymatic methods,[43-45] all of which with their respective advantages and shortcomings. To date, expensive starting materials, complex processes, or rigid reaction conditions have resulted in that β-mannosides are relatively costly on the market.

SCHEME 1. Stereospecific Ester Activation in Nitrite-Mediated Carbohydrate Epimerization[a]



[a] Reagents and conditions. (a) i: Tf_2O, Py, CH_2Cl_2. ii: KNO_2 or $TBANO_2$, solvent.

An efficient carbohydrate epimerization reaction based on glycoside triflate displacement by nitrite ion (the Lattrell-Dax reaction),[46-49] under very mild conditions, was recently explored in our laboratory.[50] It was demonstrated that neighboring equatorial ester groups play highly important roles in this type of reaction, inducing the inversion reaction to proceed efficiently, and result in good yields (Scheme 1).

These studies suggested that new, efficient synthetic methods to complex glycosides would be feasible under the guidance of this principle, where the activating ester groups should be able to control the inversion of two neighboring positions simultaneously.

In this study, novel and efficient methods to synthesizing β-D-mannopyranoside and β-D-talopyranoside derivatives are reported on the basis of the ester-activated inversion reaction. Regioselective acylation of galacto- and glucopyranoside via the corresponding stannylene intermediates, followed by epimerization by nitrite- or acetate-treatment, produced the corresponding manno- and talopyranoside derivatives in high yields. Two different strategies were in addition proposed: (i) simultaneous inversion of both addressed hydroxyl groups, resulting in a double parallel inversion strategy, and (ii) stepwise inversion of the hydroxyl groups amounting to a double serial inversion protocol (Scheme 2). These two strategies allow the formation of highly complex structures in very few steps.

Results and Discussion

Regioselective Protection of Methyl β-D-Galactoside and Methyl β-D-Glucoside. Methyl β-D-galactoside and methyl β-D-glucoside are two low-priced commercial starting materials, easily obtained in high amounts. It is well-known that organotin-

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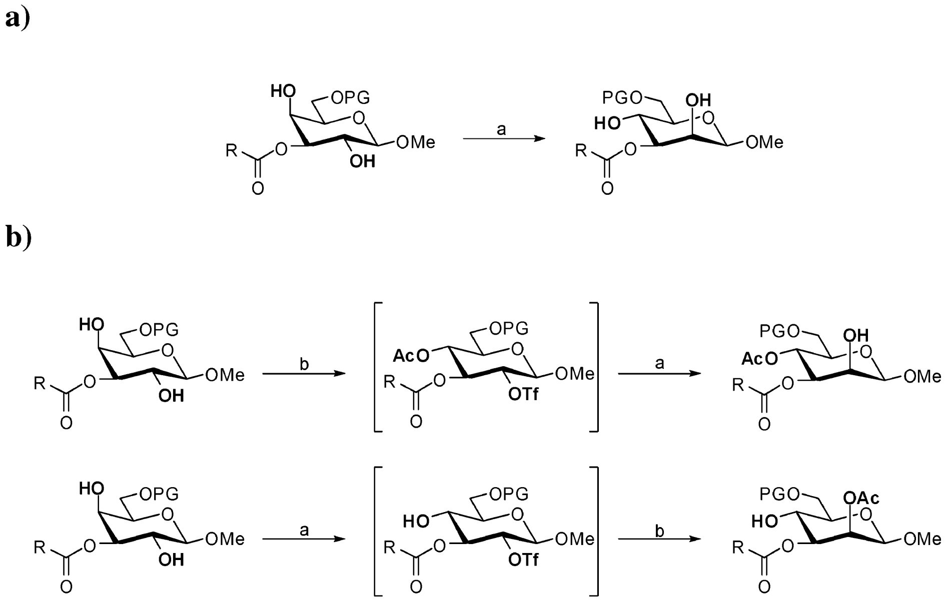
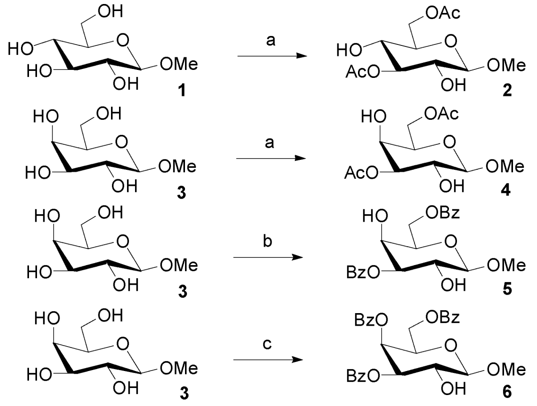
SCHEME 2. Double Parallel Inversion (a) and Double Serial Inversion (b)[a]



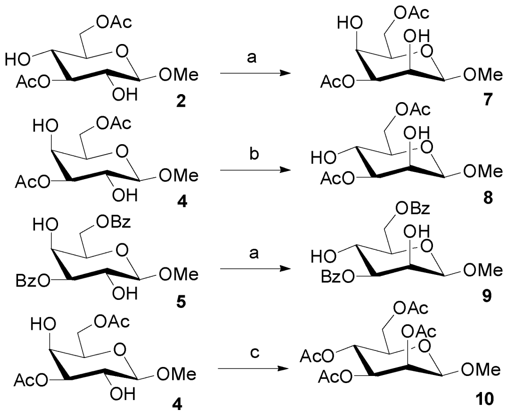
[a] Reagents and conditions. (a) i: Tf_2O, Py, CH_2Cl_2. ii: KNO_2 or $TBANO_2$, solvent. (b) i: Tf_2O, Py, CH_2Cl_2. ii: TBAOAc, solvent.

SCHEME 3. Regioselective Protection of Free Methyl *β*-D-Galactoside and Methyl *β*-D-Glucoside[a]



[a] Reagents and conditions. (a) i: Bu_2SnO, MeOH, 70 °C, 2h. ii: Ac_2O, DMF, 0 °C to 20 °C, 6 h (**2**, 70%; **4**, 90%). (b) i: Bu_2SnO, MeOH, 70 °C, 2 h. ii: BzCl, toluene, 20 °C, 6 h (**5**, 90%). (c) i: Bu_2SnO, MeOH, 70 °C, 2h. ii: BzCl, toluene, 90 °C, 2 h (**6**, 90%).

SCHEME 4. Double Parallel Inversion[a]



[a] Reagents and conditions. (a) i: Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. ii: $TBANO_2$, CH_3CN, 50 °C, 5 h (**7**, 85%; **9**, 70%). (b) i: Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. ii: $TBANO_2$, toluene, r.t., 5 h (**8**, 76%). (c) i: Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. ii: TBAOAc, CH_3CN, r.t., 5 h (**10**, 90%).

mediated esterification is an efficient method to enhance small reactivity differences, and to regioselectively protect chosen carbohydrate hydroxyl groups.[51−54] Commonly, a stoichiometric amount of tin reagent is employed, resulting in single hydroxyl esterification. Recently, however, an elegant method was described by Zhang and Wong in which a product with one or two free hydroxyl groups was produced by the use of excess organotin reagents.[55] This approach is potentially very convenient and efficient for multiple protection schemes, and was extensively studied in esterification reactions of methyl *β*-D-galactoside and methyl *β*-D-glucoside.[56] It was thus found that the product outcome could be controlled not only by the use of different solvents, but also using different acylation reagents, and an interesting pattern of dynamic migration was also shown. A summary of the experimental results from this study is displayed in Scheme 3.

Starting from methyl *β*-D-glucoside **1** and methyl *β*-D-galactoside **3**, using two equivalents of dibutyltin oxide followed by separate treatment with two equivalents of acetic anhydride at room temperature in DMF, the respective 3,6-di-*O*-acetyl derivatives were obtained in high yields. Similarly, starting from methyl *β*-D-galactoside **3**, using two equivalents of dibutyltin oxide followed by treatment with two equivalents of benzoyl chloride at room temperature in toluene, the methyl 3,6-di-*O*-

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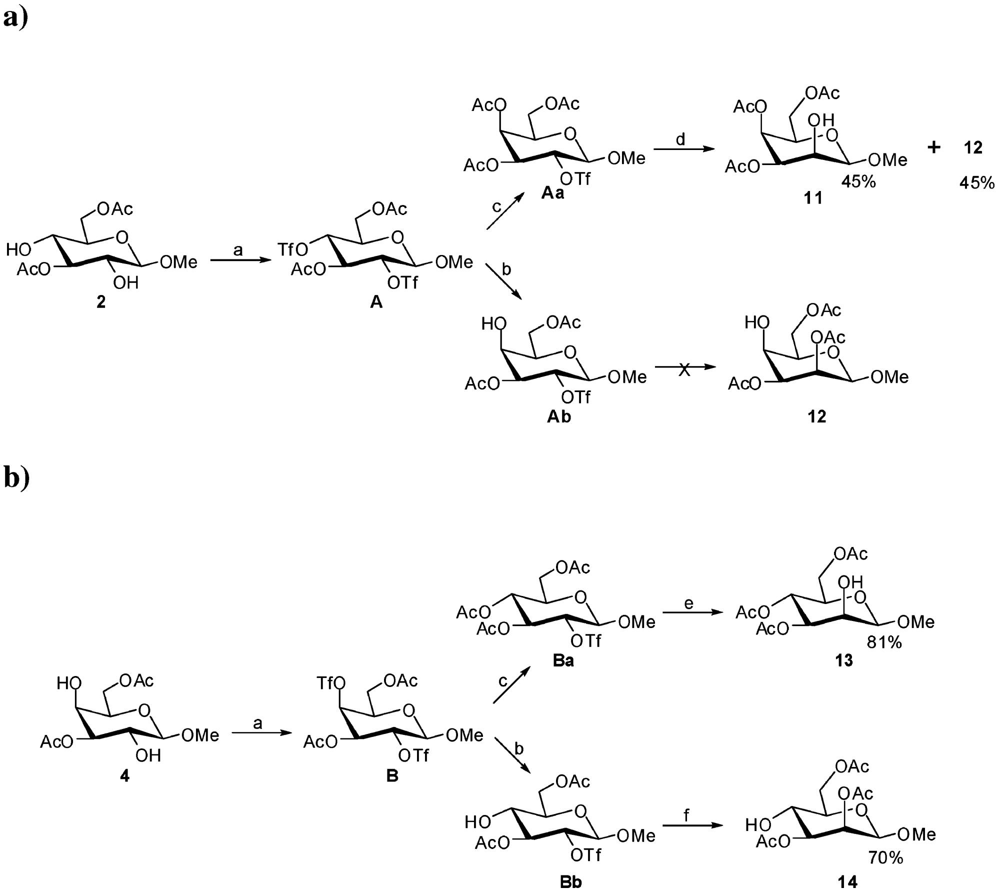
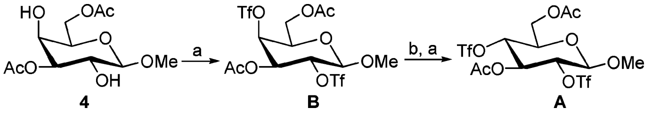
SCHEME 5. Double Serial Inversion[a]



[a] Reagents and conditions. (a) Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. (b) $TBANO_2$, CH_3CN, r.t., 1 h. (c) TBAOAc, toluene, r.t., 1 h. (d) $TBANO_2$, CH_3CN, 50 °C, 24 h. (e) $TBANO_2$, toluene, r.t., 6 h. (f) TBAOAc, CH_3CN, 50 °C, 6 h.

SCHEME 6. Alternative Double Serial Inversion Strategy to Intermediate A[a]



[a] Reagents and conditions. (a) Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. (b) $TBANO_2$, CH_3CN, r.t., 1 h.

benzoyl galactoside **5** was formed in 90% yield. When, however, three equivalents of dibutyltin oxide were instead used, followed by treatment with three equivalents of benzoyl chloride at 90 °C in toluene, the methyl 3,4,6-tri-*O*-benzoyl galactoside **6** was obtained in a very high yield as a consequence of dynamic migration.

Double Parallel Inversion. In order to evaluate whether an equatorial ester group in the 3-position would be able to activate the epimerization of the neighboring 2- and 4-positions at the same time, a series of inversion reactions was probed. Galacto- and gluco-type derivatives, where the 3- and 6-positions were protected with acetyl groups and the other two positions left unprotected, were subjected to conventional triflation by triflic anhydride followed by treatment with tetrabutylammonium nitrite in acetonitrile or toluene at 50 °C. The results are presented in Scheme 4. In acetonitrile, when methyl 3,6-di-*O*-acetyl glucopyranoside **2** was used as reactant, methyl 3,6-di-*O*-acetyl talopyranoside **7** was obtained in 85% yield. In contrast, the double inversion of methyl 3,6-di-*O*-acetyl galactopyranoside **4** was not successful under these conditions where a complex mixture was produced. This effect proved to be due to neighboring group participation from the 3-*O*-acetyl group, resulting in a mixture of 2-*O*-acetyl- and 3-*O*-acetyl derivatives. The free methyl β-D-mannopyranoside was then obtained in high yield when the mixture was deprotected under basic conditions.

It is, however, well-known that benzoyl groups are less reactive than acetyl counterparts to migration and neighboring group participation. In addition, neighboring group participation is disfavored in nonpolar solvent.[50,57] Thus, in order to avoid any neighboring group participation, both these approaches were tested (Scheme 4). On the one hand, reactions with methyl glucoside **2** and methyl galactoside **4** were performed in the nonpolar solvent toluene; on the other hand, the inversion of methyl 3,6-di-*O*-benzoyl galactopyranoside **5** was attempted in acetonitrile. For comparison, the triflate of methyl galactoside **4** reacting with tetrabutylammonium acetate was also tested in acetonitrile. When methyl glucoside **2** was inversed at 50 °C in toluene, the reaction time had to be prolonged to 12 h to obtain product **7** in 85% yield. This result indicates, as expected, that the reactivity was decreased in nonpolar solvent. In addition, both these approaches proved successful for the double inversion of the methyl galactosides, efficiently reducing the neighboring group participation.

Double Serial Inversion. During this epimerization process, it was found that the reactivity in the 4-position was, however,

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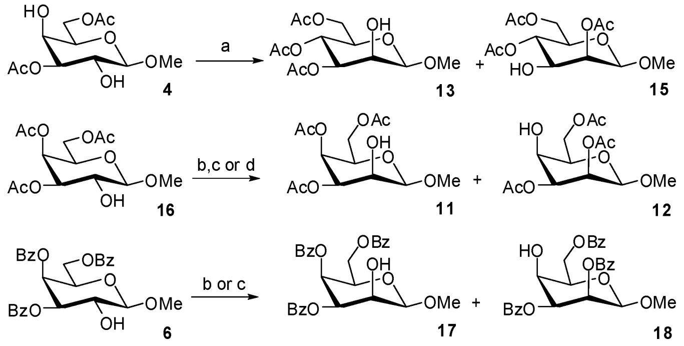
SCHEME 7. Epimerization by Neighboring and Remote Group Participation[a]



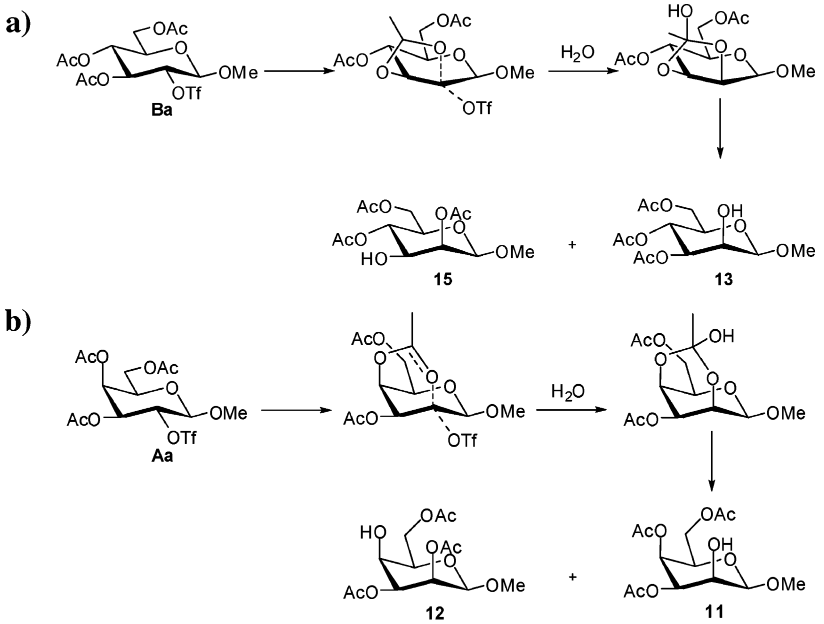
	13 (%)	15 (%)
	60	40

	11 (%)	12 (%)
b	50	50
c	45	55
d	52	48

	17 (%)	18 (%)
b	80	20
c	40	60

[a] Reagents and conditions. (a) i: Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. ii: TBAOAc, CH_3CN, r.t., 0.5h. iii: $TBANO_2$, CH_3CN, 50 °C, 6 h. (b) i: Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. ii: $TBANO_2$, CH_3CN, 50 °C, 30 h. (c) i: Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. ii: $TBANO_2$, DMF, 50 °C, 20 h. (d) i: Tf_2O, pyridine, CH_2Cl_2, −20 °C to 10 °C, 2 h. ii: TBAOAc, CH_3CN, 50 °C, 30 h. NMR ratios.

SCHEME 8. Neighboring Group Participation (a) and Remote Group Participation (b)



much higher than in the 2-position. At room temperature, the epimerization reaction in the 4-position occurred instantaneously, completed within 10−20 min, whereas in the 2-position the epimerization reaction proceeded very slowly under these conditions. This result incited us to make use of the reactivity difference between the different positions to develop a new method by which carbohydrate structures, where one position is a hydroxyl group and the other positions were protected with ester groups, could be obtained.

The resulting double serial inversion protocol is presented in Scheme 5. Using the same initial step for the double parallel inversion strategy, from methyl glycoside **2** and **4**, the 2,4-ditriflate intermediates **A** and **B** could be produced via a triflation process. The 4-triflates of these intermediates were subsequently inversed to the corresponding 4-*O*-acetyl intermediates **Aa** and **Ba** by substitution with tetrabutylammonium acetate, directly followed by inversion of the 2-position by tetrabutylammonium nitrite, to yield a mixture of methyl 3,4,6-tri-*O*-acetyl taloside **11** and methyl 2,3,6-tri-*O*-acetyl taloside **12**, as well as methyl 3,4,6-tri-*O*-acetyl mannoside **13** (pathways **a**−**c**−**d**/**a**−**c**−**e** in Scheme 5). Conversely, When the 4-triflates of intermediates **A** and **B** were first inversed to the corresponding 4-hydroxyl groups intermediates **Ab**, **Bb** via the use of tetrabutylammonium nitrite, directly followed by inversion of the 2-position by tetrabutylammonium acetate, methyl 2,3,6-tri-*O*-acetyl mannoside **14**, was efficiently produced (pathway **a**−**b**−**f**). In this case, however, product **12** could not be formed, likely due to the steric hindrance effect of the nucleophilic reagent.

In addition, due to the fact that methyl glucoside **2** was produced in a lower yield (70% in Scheme 3) than methyl galactoside 4 (90% in Scheme 3), following the double serial inversion strategy, an alternative, more high-yielding, synthetic route to methyl taloside could be devised starting from methyl galactoside 4 instead of methyl glucoside 2 (Scheme 6). Thus, methyl galactoside **4** could be inversed to the intermediate **A** via intermediate **Bb**. As a result, the use of methyl glucoside **2** can be avoided and the overall yield increased.

Neighboring and Remote Group Participation. When the inversion of intermediate **Ba** was performed in acetonitrile, a mixture of methyl mannosides **13** (60%) and **15** (40%) was obtained due to the neighboring group participation (Scheme 7). Thus, to avoid neighboring participation, a high yield of methyl mannoside **13** could only be obtained in nonpolar solvent (Scheme 5). It is, however, more difficult to explain how the mixture of methyl talosides **11** and **12** was generated. Changing the acetyl groups for benzoyl groups proved inefficient, and the inversion of the 2-position of methyl 3,4,6-tri-*O*-benzoyl galactoside **6** in acetonitrile resulted in a mixture of methyl talosides **17** and **18** (Scheme 7). In order to further analyze this reaction, methyl 3,4,6-tri-*O*-benzoyl galactoside **6** and methyl 3,4,6-tri-*O*-acetyl galactoside **16** were tested in the more polar solvent DMF. The experimental results indicate that the formation of methyl talosides **11** and **17**, where the hydroxyl group in the 2-position is unprotected, were more favored in nonpolar solvent (50%, 80%) and less favored in polar solvent (45%, 40%), whereas the formation of methyl talosides **12** and **18**, where the hydroxyl group in 4-position is free, were more favored in polar solvent (55%, 60%) and less favored in nonpolar solvent (50%, 20%). As a comparison, starting from the triflate of methyl glucoside **2** (intermediate **A** in Scheme 5), it was expected that the fully protected methyl taloside would be produced via the use of five equivalents of tetrabutylammonium acetate. However, the same mixture of methyl talosides **11** (52%) and **12** (48%) was produced.

All of these results support a 4-position participation mechanism, where a six-membered ring is generated first, and then opened by trace water to produce either a free 4-hydroxyl group or a free 2-hydroxyl group in a reaction that is favored by polar solvents (Scheme 8). The direct nitrite competition reaction resulted in that the 2-hydroxyl group products (**11**, **17**) were favored in less polar solvents. In combination with the steric effects of the nucleophilic reagent, this also explains why a mixture of methyl talosides **11** and **12** were primarily obtained when tetrabutylammonium acetate was employed as a nucleophilic reagent.

To further support this mechanism, the triflate of methyl taloside **16** was directly tested in wet acetonitrile at 50 °C for 20 h. As a result, a complex mixture was obtained, not only including methyl talosides **11** and **12**. However, these experimental results also showed that the nucleophilic reagent tetrabutylammonium nitrite/acetate play an important role for the remote group participation. The test for neighboring group participation of intermediate **Ba** also supported this result. When the intermediate **Ba** was directly subjected to reaction in wet acetonitrile at 50 °C for 20 h, a very low conversion was recorded, whereas with 2 equiv of tetrabutylammonium nitrite, talosides **13** and **15** were obtained in 60% and 40% yield during the same reaction time. The experimental results indicate that not only the neighboring ester group can activate the nitrite-mediated epimerization but also suggest that the nitrite ion can activate the neighboring or remote group participation.

Conclusion

In conclusion, novel and convenient double parallel and double serial inversion methods have been developed, by which methyl β-D-mannosides and methyl β-D-talosides have been efficiently synthesized in very high yields at very mild conditions in few steps. By use of the reactivity difference of the hydroxyl groups or the neighboring/remote group participation between the 2- and 3-position/2- and 4-positions, a range of methyl β-D-mannoside and methyl β-D-taloside derivatives could be easily synthesized. It was found that not only the neighboring ester group can activate the nitrite-mediate epimerization but also that the nitrite ion can activate the neighboring or remote group participation. The results also indicate that an ester group can, either in parallel or serially, activate its two neighboring groups in the epimerization reaction.

Experimental Section

General Acylation Procedure. Methyl β-D-glycoside (194 mg, 1 mmol) and dibutyltin oxide (550 mg, 2.2 mmol) were dissolved in methanol (30 mL), and refluxed for 2 h. After evaporation of the solvent, the residue was dried under vacuum, and then dissolved in solvent (10 mL toluene, DMF, chloroform). After cooling the solution to 0−5 °C, a solution of acylation reagent (2.2 mmol or 3.3 mmol) in anhydrous solvent (1 mL) was added dropwise, and then allowed to react at room temperature for 2−12 h. The resulting mixture was directly purified by flash column chromatography (2:1 to 1:1 hexane−ethyl acetate), yielding the acylated products.

General Synthesis of Triflate Derivatives. To a solution of the suitably *O*-protected methyl β-D-glycoside, carrying unprotected OH groups at C-2 and C-4 (140 mg, 0.5 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 3 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification.

General Double Parallel Inversion. $TBANO_2$ (5 eq.) was added to a solution of the protected triflate residue (50 mg) in dry acetonitrile/toluene (2.0 mL). After stirring at room temperature or 50 °C for 1−6 h, the solvent was removed, the residue redissolved in CH_2Cl_2, and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography (2:1 to 1:1 hexane−ethyl acetate) afforded the inversion products.

General Double Serial Inversion. $TBANO_2$/TBAOAc (1.2 eq.) was added to a solution of the protected triflate residue (50 mg) in dry acetonitrile/toluene (2.0 mL). After stirring at room temperature for 0.5 h, followed by heating to 50 °C for 0.5 h, TBAOAc/$TBANO_2$ (3.0 eq.) was added to the mixture and kept at room temperature or 50 °C for 6−24 h. The solvents were removed, and the product redissolved in CH_2Cl_2, and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography (3:1 to 2:1 hexane−ethyl acetate) afforded the inversion products.

Methyl 3,4,6-Tri-*O*-benzoyl-β-D-galactopyranoside (6). Methyl β-D-galactoside **3** (194 mg, 1 mmol) and dibutyltin oxide (550 mg, 2.2 mmol) were dissolved in methanol (30 mL), and refluxed for 2 h. After evaporation of the solvent, the residue was dried under vacuum, and then dissolved in toluene (10 mL). A solution of benzoyl chloride (3.3 mmol) in anhydrous toluene (1 mL) was added dropwise, and then allowed to react at 90 °C for 2 h. The resulting mixture was directly purified by flash column chromatography (5:2 hexane−ethyl acetate), yielding **6** as a colorless syrup (455 mg, 90%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.2−8.1 (m, 15 H, 3 × OBz), 5.91 (d, 1 H, $J_{3,\,4}$ 3.45 Hz, H_4), 5.39 (dd, 1 H, $J_{3,\,2}$ 10.1 Hz, $J_{4,\,3}$ 3.45 Hz, H_3), 4.65 (dd, 1 H, $J_{6a,\,6b}$ 11.3 Hz, $J_{6a,\,5}$ 6.55 Hz H_{6a}), 4.47 (d, 1 H, $J_{1,\,2}$ 7.6 Hz, H_1), 4.37 (dd, 1 H, $J_{6a,\,6b}$ 11.3 Hz, $J_{6b,\,5}$ 6.55 Hz H_{6b}), 4.24 (d, 1 H, $J_{5,\,6}$ 6.55 Hz, H_5), 4.10 (dd, 1 H, $J_{2,\,3}$ 10.1 Hz, $J_{2,\,1}$ 7.6 Hz, H_2), 3.64 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$ 125 MHz): δ 166.2, 166.1, 165.6, 133.7, 133.4, 133.3, 130.1, 130.0, 129.9, 129.6, 129.4, 129.3, 128.7, 128.6, 128.4, 104.5, 73.5, 71.4, 70.1, 68.3, 62.2, 57.7; $[\alpha]^{20}_D = -3$ ($c = 0.26$, $CHCl_3$). Anal. Calcd for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found: C, 66.17; H, 5.08.

Methyl 3,6-Di-*O*-acetyl-β-D-talopyranoside (7). To a solution of methyl β-D-glucoside **2** (140 mg, 0.5 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. $TBANO_2$ (720 mg, 2.5 mmol) was added to a solution of the protected triflate residue in dry acetonitrile (5 mL), and then allowed to react at 50 °C for 5 h. The resulting mixture was directly purified by flash column chromatography (2:1 to 1:1 hexane−ethyl acetate), yielding **7** as a colorless syrup (117 mg, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.75 (t, 1 H, $J_{3,2}$ 2.7 Hz, $J_{3,4}$ 2.7 Hz, H_3), 4.31−4.42 (m, 3 H, H_1, H_{6a}, H_{6b}), 4.09 (d, 1 H, $J_{2,3}$ 2.7 Hz, H_2), 3.91 (dd, 1 H, $J_{4,3}$ 2.7 Hz, $J_{4,OH}$ 10.1 Hz H_4), 3.65 (t, 1 H, $J_{5,6}$ 6.3 Hz, H_5), 3.60 (s, 3 H, OMe), 3.52 (d, 1 H, $J_{OH,4}$ 10.1 Hz, 4-OH), 2.78 (s, 1 H, 2-OH), 2.20 (s, 3H, OAc), 2.07 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$ 125 MHz): δ 171.0, 170.5, 100.6, 73.5, 70.9, 70.1, 67.3, 62.8, 57.1, 21.2, 21.0; $[\alpha]^{20}_D = -16$ ($c = 0.1$, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_8$: C, 47.48; H, 6.52. Found: C, 47.37; H, 6.37.

Methyl 3,6-Di-*O*-acetyl-β-D-mannopyranoside (8). To a solution of methyl β-D-galactoside **4** (140 mg, 0.5 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. $TBANO_2$ (720 g, 2.5 mmol.) was added to a solution of the protected triflate residue in dry toluene (5.0 mL), and then allowed to react at room temperature for 5 h. The resulting mixture was directly purified by flash column chromatography (2:1 to 1:1 hexane−ethyl acetate), yielding **8** as a colorless syrup (105 mg, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.81 (dd, 1 H, $J_{3,2}$ 3.0 Hz, $J_{3,4}$ 9.8 Hz, H_3), 4.56 (dd, 1 H, $J_{6a,6b}$ 12.3 Hz, $J_{6a,5}$ 4.4 Hz, H_{6a}), 4.47 (d, 1 H, $J_{1,2}$ 0.6 Hz, H_1), 4.30 (dd, 1 H, $J_{6a,6b}$ 12.3 Hz, $J_{6b,5}$ 2.2 Hz, H_{6b}), 4.12 (d, 1 H, $J_{2,3}$ 3.0 Hz, H_2), 3.91 (t, 1H, $J_{4,3}$ 9.8 Hz, $J_{4,5}$ 9.8 Hz, H_4), 3.55 (s, 3 H, OMe), 3.45 (m, 1 H, H_5), 2.17 (s, 3H, OAc), 2.12 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$ 125 MHz): δ 172.1, 171.3, 100.6, 75.5, 74.6, 69.3, 65.2, 63.3, 57.2, 21.3, 21.1; $[\alpha]^{20}_D = -118$ ($c = 0.1$, $CHCl_3$). Anal. Calcd for $C_{11}H_{18}O_8$: C, 47.48; H, 6.52. Found: C, 47.19; H, 6.36.

Methyl 3,6-Di-*O*-benzoyl-β-D-mannopyranoside (9). To a solution of methyl β-D-galactoside **5** (201 mg, 0.5 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol) in CH_2Cl_2 (1 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. $TBANO_2$ (720 mg, 2.5 mmol) was added to a solution of the protected triflate residue in dry acetonitrile (5 mL), and then allowed to react at 50 °C for 5 h. The resulting mixture was directly purified by flash column chromatography (2:1 hexane−ethyl acetate), yielding **9** as a colorless syrup (140 mg, 70%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.4−8.2 (m, 10 H, 2 × OBz), 5.09 (dd, 1 H, $J_{3,2}$ 2.8 Hz, $J_{3,4}$ 9.7 Hz, H_4), 4.77 (dd, 1 H, $J_{6a,6b}$ 12.1 Hz, $J_{6a,5}$ 4.9 Hz, H_{6a}), 4.64 (dd, 1 H, $J_{6b,6a}$ 12.1 Hz, $J_{6b,5}$ 2.4 Hz H_{6b}), 4.58 (d, 1 H, $J_{1,2}$ 0.63 Hz, H_1), 4.26 (d, 1 H, $J_{2,3}$ 2.8 Hz, H_2), 4.19 (t, 1 H, $J_{4,3}$ 9.7 Hz, $J_{4,5}$ 9.7 Hz, H_4), 3.66 (m, 1 H, H_5), 3.58 (s, 3 H, OMe); ^{13}C NMR ($CDCl_3$ 125 MHz): δ 167.3, 166.8, 133.7, 133.5, 130.2, 130.1, 128.7, 128.6, 100.8, 76.3, 74.8, 69.4, 65.7, 63.9, 57.2; $[\alpha]^{20}_D = -40$ ($c = 0.7$, $CHCl_3$). Anal. Calcd for $C_{21}H_{22}O_8{\cdot}1/2H_2O$: C, 61.31; H, 5.64. Found: C, 60.92; H, 5.55.

Methyl 3,4,6-Tri-*O*-acetyl-β-D-talopyranoside (11). To a solution of methyl β-D-glucoside **2** (140 mg, 0.5 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. TBAOAc (180 mg, 0.6 mmol) was added to a solution of the protected triflate residue in dry acetonitrile (5 mL), and then allowed to react at room temperature for 0.5 h followed heating to 50 °C for 0.5 h. $TBANO_2$ (430 mg, 1.5 mmol) was added to the mixture and heating was continued at 50 °C for 24 h. The resulting mixture was directly purified by flash column chromatography (2:1 hexane−ethyl acetate), yielding **11** as a colorless syrup (73 mg, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.33 (d, 1 H, $J_{4,3}$ 3.5 Hz, $J_{4,5}$ 1.3 Hz, H_4), 4.91 (t, 1 H, $J_{3,4}$ 3.4 Hz, $J_{3,2}$ 3.4 Hz, H_3), 4.41 (s, 1 H, H_1), 4.24 (dd, 1 H, $J_{6a,6b}$ 11.2 Hz, $J_{6a,5}$ 6.6 Hz, H_{6a}), 4.18 (dd, 1 H, $J_{6b,6a}$ 11.2 Hz, $J_{6b,5}$ 6.6 Hz, H_{6b}), 3.96 (b, 1 H, H_2), 3.87 (dt, 1H, $J_{5,4}$ 1.3 Hz, $J_{5,6}$ 6.6 Hz, H_5), 3.59 (s, 3 H, OMe), 2.47 (b, 1 H, 2-OH), 2.13 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$ 125 MHz): δ 170.6, 170.3, 169.9, 101.9, 71.5, 69.6, 68.9, 66.7, 61.5, 57.4, 21.0, 20.9, 20.8; $[\alpha]^{20}_D = -27$ ($c = 0.6$, $CHCl_3$). MS (M+Na):343.1005. Observed: 343.1000. Anal. Calcd for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29. Found: C, 48.45; H, 6.20.

Methyl 2,3,6-Tri-*O*-acetyl-β-D-talopyranoside (12). Prepared by the same route as methyl taloside **11**, yielding **12** as a colorless syrup (72 mg, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (d, 1 H, $J_{2,3}$ 3.5 Hz, H_2), 4.89 (t, 1 H, $J_{3,2}$ 3.5 Hz, $J_{3,4}$ 3.5 Hz, H_3), 4.47 (d, 1 H, $J_{1,2}$ 1.0 Hz, H_1), 4.40 (dd, 1 H, $J_{6a,6b}$ 11.4 Hz, $J_{6a,5}$ 6.8 Hz, H_{6a}), 4.32 (dd, 1 H, $J_{6b,6a}$ 11.4 Hz, $J_{6b,5}$ 5.9 Hz, H_{6b}), 3.88 (b, 1 H, H_4), 3.69 (m, 1H, H_5), 3.54 (s, 3 H, OMe), 2.61 (b, 1 H, 4-OH), 2.17 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.07 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$ 125 MHz): δ 170.8, 170.1, 169.6, 100.2, 73.8, 69.5, 69.1, 66.8, 62.7, 57.4, 21.0, 21.0, 20.9; $[\alpha]^{20}_D = -34$ ($c = 0.6$, $CHCl_3$). Anal. Calcd for $C_{13}H_{20}O_9{\cdot}$ $1/2H_2O$: C, 47.42; H, 6.43. Found: C, 47.15; H, 6.13.

Methyl 3,4,6-Tri-*O*-acetyl-β-D-mannopyranoside (13). To a solution of methyl β-D-galactoside **4** (140 mg, 0.5 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. TBAOAc (180 mg, 0.6 mmol) was added to a solution of the protected triflate residue in dry toluene (5 mL), and then allowed to react at room temperature for 0.5 h followed by heating to 50 °C for 0.5 h. $TBANO_2$ (430 mg, 1.5 mmol) was added to the mixture and kept at room temperature for 6 h. The resulting mixture was directly purified by flash column chromatography (2:1 hexane−ethyl acetate), yielding **13** as a colorless syrup (130 mg, 81%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.37 (dd, 1 H, $J_{4,3}$ 9.8 Hz, $J_{4,5}$ 9.8 Hz H_4), 4.97 (dd, 1 H, $J_{3,4}$ 9.8 Hz, $J_{3,2}$ 3.0 Hz, H_3), 4.49 (s, 1 H, H_1), 4.30 (dd, 1 H, $J_{6a,6b}$ 13.0 Hz, $J_{6a,5}$ 4.9 Hz, H_{6a}), 4.1−4.2 (m, 2 H, H_{6b}, H_2), 3.62 (m, 1H, H_5), 3.56 (s, 3 H, OMe), 2.33 (b, 1 H, 2-OH), 2.10 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.03 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$ 125 MHz): δ 171.0, 170.6, 169.7, 100.6, 73.1, 72.4, 69.2, 66.1, 62.6, 57.3, 21.0, 20.9, 20.8; $[\alpha]^{20}_D = -59$ ($c = 0.3$, $CHCl_3$). MS (M+Na): 343.1005. Observed: 343.1001. Anal. Calcd for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29. Found: C, 48.60; H, 6.25.

Methyl 2,3,6-Tri-*O*-acetyl-β-D-mannopyranoside (14). To a solution of methyl β-D-galactoside **4** (140 mg, 0.5 mmol), in CH_2Cl_2 (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH_2Cl_2 and washed with 1 M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. $TBANO_2$ (170 mg, 0.6 mmol) was added to a solution of the protected triflate residue in dry acetonitrile (5 mL), and then allowed to react at room temperature for 0.5 h followed by heating to 50 °C for 0.5 h. TBAOAc (450 mg, 1.5 mmol.) was added to the mixture and kept at room temperature for 6 h. The resulting mixture was directly purified by flash column chromatography (2:1 hexane−ethyl acetate), yielding **14** as a colorless syrup (112 mg, 70%). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 5.45 (dd, 1 H, $J_{2,3}$ 3.1 Hz, $J_{2,1}$ 0.9 Hz, H_2), 5.05 (dd, 1 H, $J_{3,4}$ 10.6 Hz, $J_{3,2}$ 3.3 Hz, H_3), 4.57 (d, 1 H, $J_{1,2}$ 0.9 Hz, H_1), 4.49 (dd, 1 H, $J_{6a, 6b}$ 12.2 Hz, $J_{6a, 5}$ 2.0 Hz, H_{6a}), 4.39 (dd, 1 H, $J_{6a, 6b}$ 12.2 Hz, $J_{6b, 5}$ 5.0 Hz, H_{6b}), 4.06 (t, 1 H, $J_{4,3}$ 10.4 Hz, $J_{4,5}$ 10.4 Hz, H_4), 3.73 (m, 1H, H_5), 3.51 (s, 3 H, OMe), 2.16 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.06 (s, 3H, OAc); ^{13}C NMR (CDCl$_3$ 100 MHz): δ 171.3, 170.8, 170.3, 100.5, 75.3, 73.7, 69.5, 63.9, 58.2, 53.6, 21.5, 21.4, 21.2; $[\alpha]^{20}_D = -80$ ($c = 0.35$, CHCl$_3$). Anal. Calcd for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29. Found: C, 48.70; H, 6.22.

Methyl 2,4,6-Tri-*O*-acetyl-β-D-mannopyranoside (15). To a solution of methyl β-D-galactoside **4** (140 mg, 0.5 mmol), in CH$_2$Cl$_2$ (5 mL) was added pyridine (0.53 mL) at −20 °C. Trifluoromethanesulfonic anhydride (420 mg, 1.5 mmol) in CH$_2$Cl$_2$ (2 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH$_2$Cl$_2$ and washed with 1 M HCl, aqueous NaHCO$_3$, water, and brine. The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. TBAOAc (180 mg, 0.6 mmol) was added to a solution of the protected triflate residue in dry acetonitrile (5.0 mL), and then allowed to react at room temperature for 0.5 h followed heating to 50 °C for 0.5 h. TBANO$_2$ (430 mg, 1.5 mmol) was added to the mixture and kept at 50 °C for 6 h. The resulting mixture was directly purified by flash column chromatography (2:1 hexane−ethyl acetate), yielding **15** as a colorless syrup (50 mg, 31%). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.40 (dd, 1 H, $J_{2,3}$ 3.6 Hz, $J_{2,1}$ 1.1 Hz, H_2), 5.04 (t, 1 H, $J_{4,3}$ 9.3 Hz, $J_{4,5}$ 9.3 Hz, H_4), 4.51 (d, 1 H, $J_{1,2}$ 1.1 Hz, H_1), 4.34 (dd, 1 H, $J_{6a, 6b}$ 12.1 Hz, $J_{6a, 5}$ 5.5 Hz, H_{6a}), 4.19 (dd, 1 H, $J_{6a, 6b}$ 12.1 Hz, $J_{6b, 5}$ 2.7 Hz, H_{6b}), 3.85 (dd, 1 H, $J_{3,4}$ 9.3 Hz, $J_{3,2}$ 3.6 Hz, H_3), 3.64 (m, 1H, H_5), 3.51 (s, 3 H, OMe), 2.19 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.09 (s, 3H, OAc); ^{13}C NMR (CDCl$_3$ 125 MHz): δ 171.3, 170.9, 100.2, 72.3, 71.4, 70.9, 69.7, 62.9, 57.5, 21.1, 21.1, 21.0; $[\alpha]^{20}_D = -92$ ($c = 0.1$, CHCl$_3$). MS (M+Na): 343.1005. Observed: 343.0995. Anal. Calcd for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29. Found: C, 48.57; H, 6.22.

Methyl 3,4,6-Tri-*O*-benzoyl-β-D-talopyranoside (17). To a solution of methyl β-D-galactoside **6** (253 mg, 0.5 mmol), in CH$_2$Cl$_2$ (5 mL) was added pyridine (0.35 mL) at −20 °C. Trifluoromethanesulfonic anhydride (280 mg, 1 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise, and the mixture was stirred while allowing to warm from −20 °C to 10 °C over 2 h. The resulting mixture was subsequently diluted with CH$_2$Cl$_2$ and washed with 1 M HCl, aqueous NaHCO$_3$, water, and brine. The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo at low temperature. The residue was used directly in the next step without further purification. TBANO$_2$ (720 mg, 2.5 mmol) was added to a solution of the protected triflate residue in dry acetonitrile (5 mL), and then allowed to react at 50 °C for 30 h. The resulting mixture was directly purified by flash column chromatography (5:2 hexane−ethyl acetate), yielding **17** as a colorless syrup (177 mg, 70%). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.2−8.1 (m, 15 H, 3 × OBz), 5.85 (d, 1 H, $J_{4, 3}$ 3.2 Hz, H_4), 5.33 (t, 1 H, $J_{3, 2}$ 3.5 Hz, $J_{3,4}$ 3.5 Hz, H_3), 4.74 (dd, 1 H, $J_{6a, 6b}$ 11.3 Hz, $J_{6a, 5}$ 6.9 Hz H_{6a}), 4.61 (d, 1 H, $J_{1, 2}$ 0.3 Hz, H_1), 4.45 (dd, 1 H, $J_{6a, 6b}$ 11.3 Hz, $J_{6b, 5}$ 6.6 Hz H_{6b}), 4.2−4.4 (m, 2 H, H_2, H_5), 3.66 (s, 3 H, OMe), 2.61 (d, 1H, 2-OH); ^{13}C NMR (CDCl$_3$ 125 MHz): δ 166.2, 165.7, 165.6, 133.8, 133.6, 133.5, 130.1, 130.1, 129.9, 128.9, 128.6, 128.5, 101.9, 71.9, 70.5, 68.8, 67.4, 62.4, 57.5; $[\alpha]^{20}_D = -32$ ($c = 1.7$, CHCl$_3$). Anal. Calcd for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found: C, 66.09; H, 5.11.

Methyl 2,3,6-Tri-*O*-benzoyl-β-D-talopyranoside (18). Triflation of methyl β-D-galactoside **6** was performed according to the route for compound **17**. TBANO$_2$ (720 mg, 2.5 mmol) was subsequently added to a solution of the protected triflate residue in dry DMF (5 mL), and then allowed to react at 50 °C for 20 h. The resulting mixture was directly purified by flash column chromatography (5:2 hexane−ethyl acetate), yielding **18** as a colorless syrup (130 mg, 51%). ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.2−8.1 (m, 15 H, 3 × OBz), 5.86 (d, 1 H, $J_{2,3}$ 3.5 Hz, H_2), 5.28 (t, 1 H, $J_{3, 2}$ 3.5 Hz, $J_{3,4}$ 3.5 Hz, H_3), 4.73 (t, 2 H, $J_{6,5}$ 6.1 Hz, H_{6a}, H_{6b}), 4.72 (d, 1 H, $J_{1, 2}$ 0.9 Hz, H_1), 4.24 (dd, 1 H, $J_{4,3}$ 3.5 Hz, $J_{4,OH}$ 10.7 Hz H_4), 4.05 (t, 1 H, $J_{5, 6}$ 6.1 Hz, H_5), 3.58 (s, 3 H, OMe), 2.88 (d, $J_{OH,4}$ 10.7 Hz, 4-OH); ^{13}C NMR (CDCl$_3$ 125 MHz): δ 166.5, 165.7, 165.6, 133.7, 133.7, 133.4, 130.1 130.0, 129.9, 128.9, 128.7, 128.6, 100.6, 74.0, 70.3, 69.8, 67.0, 63.3, 57.5; $[\alpha]^{20}_D = -60$ ($c = 0.26$, CHCl$_3$). Anal. Calcd for $C_{28}H_{26}O_9$: C, 66.40; H, 5.17. Found: C, 66.56; H, 5.08.

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