# A Novel Method for Constructing β-D-Mannosidic, 2-Acetamido-2-deoxy-β-D-mannosidic, and 2-Deoxy-D-*arabino*-hexopyranosidic Units from the Bis(triflate) Derivative of β-D-Galactoside

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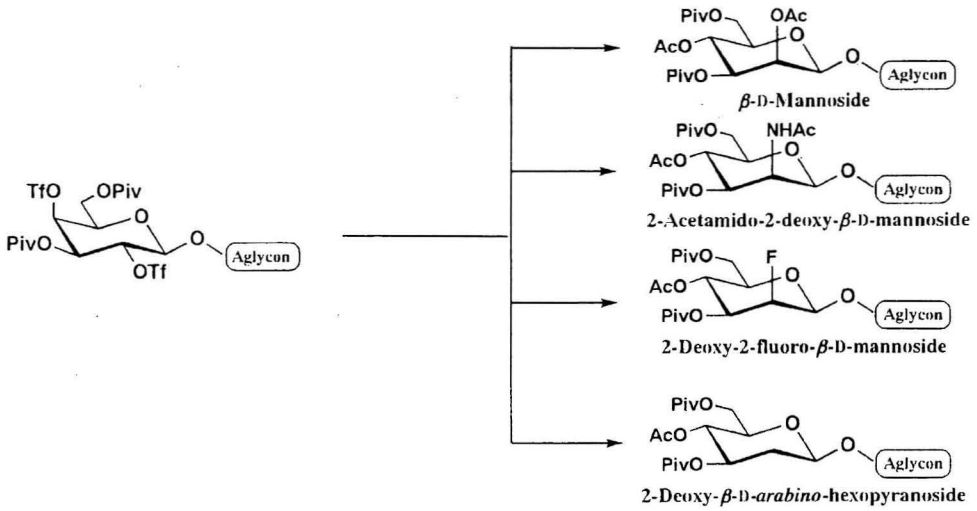
An efficient construction of the β-D-mannosidic, 2-Acetamido-2-deoxy-β-D-mannosidic, 2-deoxy-2-fluoro-β-D-mannosidic, and 2-deoxy-β-D-*arabino*-hexopyranosidic units from the same intermediate, 2-4-bis(*O*-trifluoromethylsulfonyl) derivative of β-D-galactoside, was achieved in good yields in a stepwise inversion at *C*-4 and *C*-2 by using cesium acetate, *n*-$Bu_4NN_3$, *n*-$Bu_4NF$, and *n*-$Bu_4NBH_4$. A convenient and practical protection of β-D-mannoside to the straightforward synthesis of antennary oligosaccharides was also achieved by using cesium trifluoroacetate.

Despite the recent explosive growth in the development of oligosaccharide synthetic methodology, the construction of β-D-mannosidic linkages remains a crucial step, which is still far from being adequately solved in preparative terms. The various β-D-mannosyl donors available are accessible either by only multistage synthesis, or they lack appreciable β-selectivity in glycosylations, or both.[1] Although recent strategies for intramolecular aglycon delivery[1,2] solve the β-selectivity problem, their practical utility for the synthesis of biologically relevant β-D-mannosides remains to be demonstrated. The application of the different methodologies developed for *C*-2-epimerization of β-D-glucosides[3] and for the β-D-mannosidase-promoted mannosyl transfer,[4] although promising, has not attained a practical stage. At present, the most relevant method for constructing β-D-mannosidic linkages appears to be an "indirect" one, involving β-D-glycosid-2-uloses as the key intermediates. These oxidized and reduced approaches have been extensively used,[5—13] despite the fact that the stereoselectivity of the reduction is rarely very high. More recently, 3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexopyranos-2-ulosyl bromide, a versatile glycosyl donor for efficient generation of β-D-mannosidic linkages, was reported[14] as an excellent method.

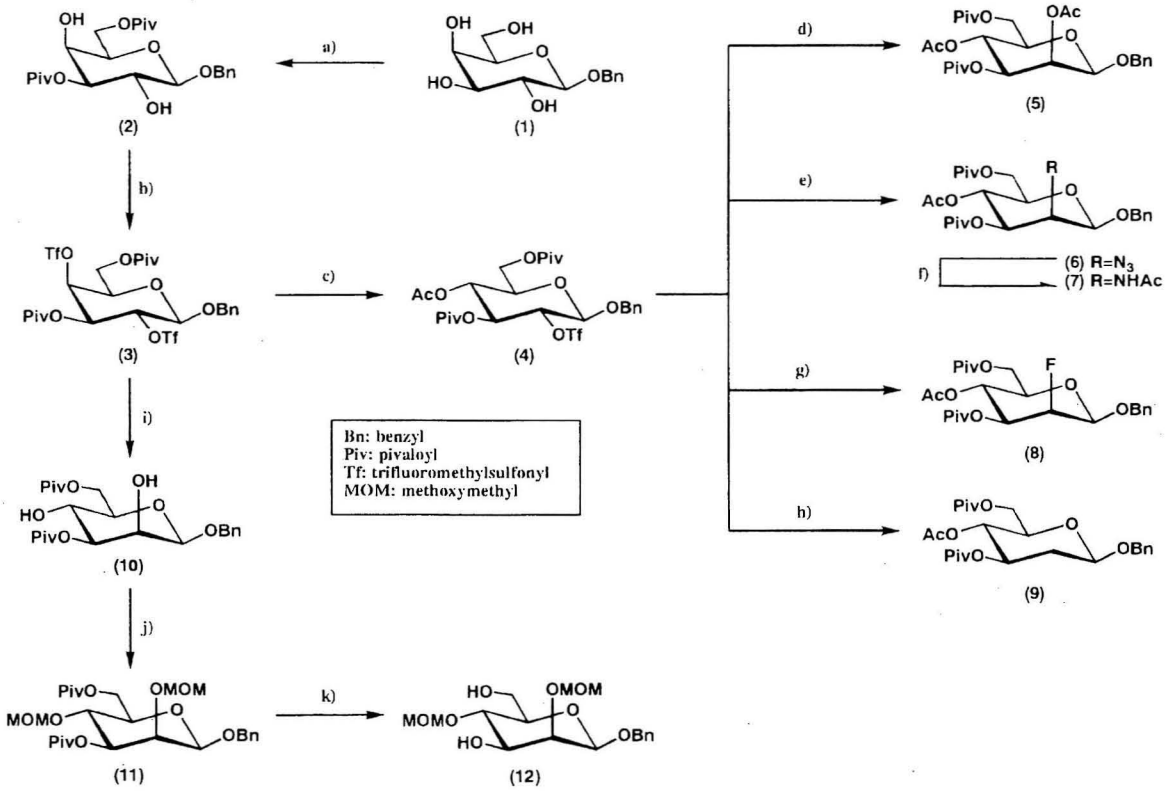
In this paper we describe the details of our previous communication[15] (construction of β-D-mannoside, 2-acetamido-2-deoxy-β-D-mannoside, and 2-deoxy-β-D-*arabino*-hexopyranoside units) as well as our new results concerning the construction of the 2-deoxy-2-fluoro-β-D-mannoside unit in short steps and high yields from 3,6-di-*O*-pivaloyl-2,4-bis(*O*-trifluoromethylsulfonyl)-β-D-galactoside, and the selective protection of the β-D-mannoside unit for synthesizing a high mannose sugar chain by double inversion with cesium trifluoroacetate. The stepwise inversion of the bis(triflate) at *C*-4 and *C*-2 was a key point in this work. As a result, the hitherto somewhat difficult construction of the β-linkage in D-*manno* and D-2-deoxy sugars was solved in a simple way (Scheme 1).

## Results and Discussion

The key starting material, benzyl 3,6-di-*O*-pivaloyl-β-D-galactopyranoside (**2**), was prepared in the following way. Glycosidation of 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose[16] with benzyl alcohol, in the presence of trimethylsilyl triflate as a promoter,[17] gave benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside in 80% yield. This compound was treated with NaOMe in methanol (pH 9) to give the corresponding de-*O*-acetylated derivative, benzyl β-D-galactopyranoside (**1**),[18] in quantitative yield. Compound **1** was treated with bis(tributyltin) oxide[19] (1.5 mol amt.) under reflux conditions, then with pivaloyl chloride (3.0 mol amt.) at room temperature in toluene, to give the selectively protected derivative **2** in 86% yield. Recently, it has been found that compound **2** was also synthesized easily by the treatment of **1** with pivaloyl chloride (3.0 mol amt.) in pyridine at room temperature to give **2** in 84% yield. Compound **2** was then treated with trifluoromethanesulfonic anhydride (3.0 mol amt.) and pyridine in $CH_2Cl_2$ at room temperature to give the corresponding 2,4-bis(triflate) **3** in 98% yield. Compound **3** is stable enough to purify on a column of silica gel. In this work, although compound **3** was prepared as a model compound, other aglycons, such as terpene, steroid, and sugar (especially blocked 2-acetamido-2-deoxy-β-D-glucoside), may also be used, instead of benzyl alcohol, in a similar manner. The reasons why the β-D-galactoside unit is important for synthesizing antennary oligosaccharides, are as follows: 1) it is easy to form the β-glycosidic linkage, 2) it is established to protect of 3,6-di-OH selectively[19] (it is easy to make 2,4-bis(triflate)), 3) a stepwise inversion of 2,4-bis(triflate) is possible, 4) it is possible to differentiate between 3,6-di-OH and 2,4-di-OH (4-OH) in twin inversion




Scheme 1.




a) PivCl / pyridine, r.t., y. 84%. b) $Tf_2O$, pyridine / $CH_2Cl_2$, y. 98%. c) CsOAc, 18-crown-6 / toluene, r.t., y. 84%. d) CsOAc, 18-crown-6 / toluene, ultrasonication, y. 94%. e) $Bu_4NN_3$ / benzene, ultrasonication, y. 91%. f) 5% Pd / C / benzene, then $Ac_2O$, y. 88%. g) $Bu_4NF$ / benzene, r.t., y. 53%. h) $Bu_4NBH_4$ / benzene, ultrasonication, y. 82%. i) $CsOCOCF_3$, 18-crown-6 / toluene - DMF, reflux, then aq. $NaHCO_3$ / MeOH, y. 76%. j) $CH_2(OMe)_2$, $P_2O_5$ / $(CH_2Cl)_2$, y. 93%. k) NaOMe/ MeOH, quant.

Scheme 2.

products, 5) it is possible to use for a large-scale synthesis. Compound **3** was treated with CsOAc (1.5 mol amt.) and 18-crown-6 (1.5 mol amt.) in toluene at room temperature to give 4-*O*-monoacetyl derivative **4**, which is stable to purification on a column of silica gel, in 84% yield. The structure of **4** was supported by $^1$H NMR (changes of the coupling constants at H-4, $J_{3,4}=2.6$ to 9.4 Hz and $J_{4,5}=0$ to 9.4 Hz). Compound **4** was then treated again with CsOAc under ultrasonication[20–22] ("Branson" Model 1210J, 47 KHz, 80 W, ca. 12 h) to give benzyl 2,4-di-*O*-acetyl-3,6-di-*O*-pivaloyl-β-D-mannopyranoside (**5**) in 94% yield, which was also obtained directly from **3** with 3 mol amt. of CsOAc under ultrasonication conditions for 12 h in 92% yield. The above reaction was also carried out under reflux conditions (ca. 1

Table 1. $^1$H NMR Spectral Data of Compounds **2**—**12**[a)]

| Compound | Chemical shifts (δ) and coupling constants (Hz) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | H-1 ($J_{1,2}$) | H-2 ($J_{2,3}$) | H-3 ($J_{3,4}$) | H-4 ($J_{4,5}$) | H-5 ($J_{5,6}$) | H-6 ($J_{6,6'}$) | H-6′ ($J_{5,6'}$) | $PhCH_2O$ ($J_{A,B}$)[b)] | Other signals |
| **2** | 4.40 d (7.6) | 3.89 ddd (10.1) $J_{2,OH}$=3.3 | 4.82 dd (3.4) | 3.96 dd (0) $J_{4,OH}$=5.5 | 3.74 dd (6.1) | 4.35 dd (11.6) | 4.32 dd (6.7) | 4.93, 4.63 (11.9) | 7.37—7.29 (Ph; m), 2.31 (2-OH; d), 2.18 (4-OH; d), 1.25, 1.22 (OPiv ×2; each s) |
| **3** | 4.69 d (7.6) | 4.99 dd (10.6) | 5.12 dd (2.6) | 5.29 d (0) | 4.01 dd (7.6) | 4.41 dd (14.2) | 4.01 dd (9.6) | 4.91, 4.70 (11.2) | 7.38—7.31 (Ph; m), 1.28, 1.22 (OPiv ×2; each s) |
| **4** | 4.64 d (7.8) | 4.75 dd (10.0) | 5.09 dd (9.4) | 5.37 dd (9.4) | 3.70 ddd (2.7) | 4.23 dd (12.5) | 4.12 dd (5.3) | 4.89, 4.69 (11.5) | 7.36—7.34 (Ph; m), 2.01 (OAc; s), 1.25, 1.18 (OPiv ×2; each s) |
| **5** | 4.62 d (0.9) | 5.49 dd (3.4) | 4.96 dd (10.0) | 5.30 dd (9.8) | 3.46 ddd (2.7) | 4.31 dd (12.2) | 4.18 dd (6.1) | 4.88, 4.65 (12.3) | 7.36—7.34 (Ph; m), 2.16, 2.01 (OAc ×2; each s), 1.26, 1.12 (OPiv ×2; each s) |
| **6** | 4.64 d (1.3) | 4.05 dd (3.9) | 4.89 dd (9.8) | 5.29 dd (9.9) | 3.60 ddd (2.4) | 4.27 dd (12.2) | 4.12 dd (5.9) | 4.95, 4.66 (12.2) | 7.37—7.35 (Ph; m), 2.01 (OAc; s), 1.26, 1.20 (OPiv ×2; each s) |
| **7** | 4.64 d (1.7) | 4.76 ddd (4.0) $J_{2,NH}$=8.9 | 4.89 dd (9.2) | 5.29 dd (9.2) | 3.60 dt (4.4) | 4.23 d | 4.23 d (4.4) | 4.84, 4.61 (12.0) | 7.34—7.31 (Ph; m), 5.70 (NH; d), 2.03, 2.02 (OAc; NHAc; each s), 1.27, 1.21 (OPiv ×2; each s) |
| **8** | 4.56 d (0) $J_{1,F}$=17.8 | 4.77 dd (2.3) $J_{2,F}$=51.1 | 4.87 ddd (9.9) $J_{3,F}$=27.1 | 5.38 dd (9.9) | 3.64 ddd (2.3) | 4.31 dd (11.8) | 4.17 dd (5.9) | 4.94, 4.68 (12.0) | 7.40—7.26 (Ph; m), 2.02 (OAc; s), 1.26, 1.18 (OPiv ×2; each s) |
| **9** | 4.64 dd $J_{1,2a}$=9.6 $J_{1,2e}$=2.0 | $2.32_{2e}$ ddd $1.74_{2a}$ ddd $J_{2a,2e}$=12.5 $J_{2a,3}$=11.5 $J_{2e,3}$=5.2 | 4.94 ddd (9.4) | 5.01 dd (9.5) | 3.62 ddd (5.8) | 4.25 dd (12.1) | 4.17 dd (2.7) | 4.87, 4.60 (11.9) | 7.37—7.30 (Ph; m), 2.01 (OAc; s), 1.24, 1.14 (OPiv ×2; each s) |
| **10** | 4.57 d (1.0) | 4.08 ddd (3.2) $J_{2,OH}$=2.4 | 4.71 dd (9.8) | 3.92 ddd (9.5) $J_{4,OH}$=4.9 | 3.48 ddd (2.7) | 4.48 dd (12.0) | 4.38 dd (5.6) | 4.90, 4.65 (12.0) | 7.36—7.30 (Ph; m), 2.60 (2-OH; d), 2.25 (4-OH; d), 1.25, 1.24 (OPiv ×2; each s) |
| **11** | 4.57 d (0.6) | 4.10 dd (2.9) | 4.83 dd (9.7) | 3.91 dd (9.5) | 3.56 ddd (2.3) | 4.61 dd (11.9) | 4.21 dd (7.3) | 4.90, 4.61 (12.1) | 7.36—7.28 (Ph; m), 4.79, 4.73 ($CH_2$OMe; ABq, $J_{AB}$=6.4), 4.77, 4.59 ($CH_2$OMe; ABq, $J_{AB}$=6.6), 3.39, 3.37 (OMe ×2; each s), 1.25, 1.23 (OPiv ×2; each s) |
| **12** | 4.56 d (1.0) | 4.02 dd (3.4) | 3.58 ddd (9.3) $J_{3,OH}$=5.8 | 3.68 dd (9.5) | 3.30 ddd (2.9) | 3.91 bd (12.0) | 3.80 bd (5.4) | 4.93, 4.65 (12.2) | 7.37—7.29 (Ph; m), 4.90, 4.83 ($CH_2$OMe; ABq, $J_{AB}$=6.7), 4.83, 4.72 ($CH_2$OMe; ABq, $J_{AB}$=6.7), 3.88 (3-OH; d), 3.46, 3.44 (OMe ×2; each s), 2.18 (6-OH, bs) |

a) Recorded in $CDCl_3$ with TMS as an internal standard. b) These protons showed a typical ABq pattern.

h) to give **5** in 94% yield. In general, the use of the ultrasonication conditions was more effective than heating in some of our experiments (depending on the substrates). The low reactivity at *C*-2 apparently is due to a dipole repulsion between the lone pair of the ring oxygen and the 1-*O*-benzyl and the nucleophile ($OAc^-$). In a similar way (as mentioned above), **4** was treated with *n*-$Bu_4NN_3$, *n*-$Bu_4NF$, or *n*-$Bu_4NBH_4$ in benzene under ultrasonication. The reaction of **4** with *n*-$Bu_4NN_3$ gave the corresponding 2-azido derivative **6** in 91% yield. The structure of **6** was supported by $^1$H NMR (changes of the coupling constants at H-2, $J_{1,2}$ = 7.8 to 1.3 Hz and $J_{2,3}$ = 10.0 to 3.9 Hz). Compound **6** was then reduced in the presence of 5% Pd/C and $H_2$ in benzene (bubbling-through system) with stirring, followed by acetylation to give benzyl 2-acetamido-4-*O*-acetyl-2-deoxy-3,6-di-*O*-pivaloyl-β-D-mannopyranoside (**7**) in 88% yield, the structure of which was supported by $^1$H NMR (δ = 5.67, d, $J_{NH,2}$ = 8.9 Hz, NHAc). In a similar way (as mentioned above), the reaction of **4** with *n*-$Bu_4NF$ in benzene at room temperature gave the corresponding 2-fluoro derivative **8** in 53% yield, the structure of which was supported by $^1$H NMR (coupling constants between H and F, $J_{1,F}$ = 17.8 Hz, $J_{2,F}$ = 51.1 Hz, and

$J_{3,F} = 27.1$ Hz) and elemental analysis. On the other hand, compound **4** was treated with $n$-$Bu_4NBH_4$ in benzene under ultrasonication to give the corresponding 2-deoxy derivative **9** in 82% yield, the structure of which was supported by $^1$H NMR ($J_{2a,2e} = 12.5$ Hz, $J_{1,2a} = 9.6$ Hz, $J_{1,2e} = 2.0$ Hz, $J_{2a,3} = 11.5$ Hz, and $J_{2e,3} = 5.2$ Hz). As mentioned above, the hitherto difficult construction of the units having a β-glycosidic linkage of the 1,2-*cis* relationship and a 2-deoxy-β-D-glycosidic linkage, was achieved easily in an indirect method involving stepwise nucleophilic substitution. For synthesizing asparagine-linked sugar chains, proper protection of β-D-mannoside is required. In this connection, we examined the selective protection of benzyl β-D-mannoside by employing $S_N2$ inversion with cesium trifluoroacetate, because selective deacylation between acetyl and pivaloyl is usually considered to be difficult. The reaction of **3** with cesium trifluoroacetate and 18-crown-6 in toluene under reflux conditions gave mixed products, 2-*O*-, 4-*O*-, and 2,4-di-*O*-trifluoroacetyl derivatives. The mixed products were treated with an aqueous sodium hydrogencarbonate solution in methanol to give benzyl 3,6-di-*O*-pivaloyl-β-D-mannopyranoside (**10**) in 76% yield. Compound **10** was then treated with $CH_2(OMe)_2$ and $P_2O_5$ in $(CH_2Cl)_2$ to give the corresponding 2,4-bis(*O*-methoxymethyl) derivative **11** in 93% yield. Subsequent deacylation of the above product with NaOMe in methanol gave benzyl 2,4-bis(*O*-methoxymethyl)-β-D-mannopyranoside (**12**) in quantitative yield (Scheme 2). In our unreported results,[23] removal of the methoxymethyl group by 70% acetic acid at 80 °C was possible without affecting the other protecting groups, such as the ether group and the ester group, or the glycosidic bond. This methodology to the straightforward synthesis of antennary oligosaccharides, those that are branched at the center β-D-mannosidic unit, seems to be useful for synthesizing important sugar units. These methods may also promise large-scale syntheses of the above-mentioned compounds.

## Experimental

All of the melting points were uncorrected. The solutions were evaporated under reduced pressure at a bath temperature not exceeding 40 °C. The optical rotations were measured in a 0.5 dm tube with a JASCO DIP-140 polarimeter in chloroform unless otherwise stated. $^1$H NMR spectra were recorded in chloroform-*d* with a JEOL FX-200 or JEOL EX-270 spectrometer. IR spectra were recorded with a Hitachi 270-30 spectrometer. Elemental analyses were performed on a Perkin–Elmer 2400 II elemental analyzer. The chemical shifts, coupling constants, and IR frequencies were recorded in δ, Hz, and $cm^{-1}$ units, respectively. Column chromatography was performed on silica gel (Silica gel 60, 70—230 mesh, Merck). Thin-layer chromatography (TLC) on silica gel (Silica gel 60 $F_{254}$, Merck) was used to monitor the reactions and to certify the reaction products.

**Benzyl 3, 6- Di- *O*- pivaloyl- β- D- galactopyranoside (2). Method A:** A solution of benzyl β-D-galactopyranoside (**1**) (2.14 g, 7.92 mmol) and bis(tributyltin) oxide (6.1 ml, 1.5 mol amt.) in toluene was refluxed for 3 h with a Dean–Stark apparatus; then, pivaloyl chloride (2.9 ml, 3.0 mol amt.) was added at 0 °C and stirred until the disappearance of **1** on TLC ($CHCl_3$/MeOH = 8/1) for 24 h at room temperature. The reaction mixture was diluted with ethyl acetate, treated with a saturated aqueous sodium hydrogencarbonate solution and potassium fluoride, filtered, and separated. The aqueous solution was extracted with ethyl acetate (2 times). The combined organic solution was washed with brine and water, dried over anhydrous magnesium sulfate, filtered, and evaporated to give crude **2**, which was purified on a column of silica gel (hexane/ethyl acetate = 2/1). The yield of **2** was 86% (2.99 g).

**Method B:** To a solution of **1** (1.50 g, 5.55 mmol) in dry pyridine (10 ml), pivaloyl chloride (2.1 ml, 3.0 mol amt.) was added dropwise at room temperature with stirring. After the disappearance of **1** on TLC ($CHCl_3$/MeOH = 8/1), a small amount of methanol was added to the reaction mixture at 0 °C. The reaction mixture was evaporated to dryness, extracted with ethyl acetate, washed with 1% hydrochloric acid, with brine and water, then dried over anhydrous magnesium sulfate. The organic layer was evaporated to give crude **2**, which was purified on a column of silica gel (hexane/ethyl acetate = 2/1). The yield of **2** was 84% (2.05 g). **2**: Mp 138—139 °C (EtOH–hexane); $[\alpha]_D^{25}$ +22 ° (*c* 1.0, $CHCl_3$); IR 3452 $cm^{-1}$ (OH) and 1716 $cm^{-1}$ (C=O); $^1$H NMR (EX-270) data are shown in Table 1. Found: C, 63.24; H, 8.30%. Calcd for $C_{23}H_{34}O_8$: C, 62.99; H, 7.82%.

**Benzyl 3,6-Di-*O*-pivaloyl-2,4-bis(*O*-trifluoromethylsulfonyl)-β-D-galactopyranoside (3).** To a solution of **2** (2.21 g, 5.04 mmol) in pyridine and dichloromethane (6 : 1, 17.0 ml), trifluoromethanesulfonic anhydride (2.5 ml, 3.0 mol amt.) was added under argon at −19 °C. The reaction mixture was stirred at room temperature until the disappearance of **2** on TLC (hexane/ethyl acetate = 2/1), then poured into a saturated aqueous sodium hydrogencarbonate solution, and separated. The aqueous layer was extracted with dichloromethane (3 times). The combined organic layer was washed with brine and water, dried over anhydrous magnesium sulfate, and evaporated to give crude **3**, which was purified on a short column of silica gel (hexane/ethyl acetate = 3/1). The yield of **3** was 98% (3.47 g). **3**: Mp 142—144 °C (EtOH–hexane); $[\alpha]_D^{25}$ −43.5 ° (*c* 1.3, $CHCl_3$); IR 1743 $cm^{-1}$ (C=O); $^1$H NMR (EX-270) data are shown in Table 1. Found: C, 43.20; H, 4.52%. Calcd for $C_{25}H_{32}F_6O_{12}S_2$: C, 42.74; H, 4.59%.

**Benzyl 4-*O*-Acetyl-3,6-di-*O*-pivaloyl-2-*O*-(trifluoromethylsulfonyl)-β-D-glucopyranoside (4).** The reaction mixture of **3** (2.09 g, 2.97 mmol), cesium acetate (0.86 g, 1.5 mol amt.), and 18-crown-6 (1.18 g, 1.5 mol amt.) in dry toluene (50 ml) was stirred for 6 h at room temperature until the disappearance of **3** on TLC (hexane/ethyl acetate = 3/1); it was then poured into a saturated aqueous sodium hydrogencarbonate solution and separated into two phases. The aqueous layer was extracted with ethyl acetate (3 times). The combined organic layer was washed with brine and water, dried over anhydrous magnesium sulfate, and evaporated to give crude **4**, which was purified on a column of silica gel (hexane/ethyl acetate = 4/1). The yield of **4** was 84% (1.53 g). **4**: Mp 121—123 °C (EtOH–hexane); $[\alpha]_D^{25}$ −21 ° (*c* 1.0, $CHCl_3$); IR 1758 and 1740 $cm^{-1}$ (C=O); $^1$H NMR (FX-200) data are shown in Table 1. Found: C, 50.74; H, 5.93%. Calcd for $C_{26}H_{35}F_3O_{11}S$: C, 50.98; H, 5.76%.

**Benzyl 2,4-Di-*O*-acetyl-3,6-di-*O*-pivaloyl-β-D-mannopyranoside (5).** The reaction mixture of **4** (300 mg, 0.49 mmol), cesium acetate (282 mg, 3.0 mol amt.), and 18-crown-6 (388 mg, 3.0 mol amt.) in dry toluene (10 ml) was kept in a water bath under ultrasonication for 12 h until the disappearance of **4** on TLC (hexane/ethyl acetate = 3/1). The reaction mixture was poured into a saturated aqueous sodium hydrogencarbonate solution, separated, extracted with ethyl acetate (3 times), washed with brine and water,

dried over anhydrous magnesium sulfate, and evaporated to give **5**, which was purified on a column of silica gel (hexane/ethyl acetate = 3/1). The yield of **5** was 94% (235 mg). Compound **5** was also derived by a treatment of **4** under reflux conditions for 1 h in a similar way as that mentioned above in 94% yield. It is possible to reduce the reaction time by using the reflux conditions instead of ultrasonication. **5**: 138—139 °C (EtOH–hexane); $[\alpha]_D^{26}$ −40.4 ° (*c* 1.0, $CHCl_3$); IR 1752 $cm^{-1}$ (C=O); $^1H$ NMR (FX-200) data are shown in Table 1. Found: C, 61.82; H, 7.23%. Calcd for $C_{27}H_{38}O_{10}$: C, 62.05; H, 7.33%.

**Benzyl 4-*O*-Acetyl-2-azido-2-deoxy-3,6-di-*O*-pivaloyl-β-D-mannopyranoside (6). Method A:** The reaction mixture of **4** (101 mg, 0.16 mmol) and tetrabutylammonium azide (94 mg, 2.0 mol amt.) in dry benzene (3.0 ml) was kept for 12 h in a water bath under ultrasonication until the disappearance of **4** on TLC (hexane/ethyl acetate = 4/1). The reaction mixture was diluted with ethyl acetate, washed with brine and water, dried over anhydrous magnesium sulfate, and evaporated to give crude **6**, which was purified on a column of silica gel (hexane/ethyl acetate = 4/1). The yield of **6** was 91% (76 mg).

**Method B:** The reaction mixture of **4** (2.02 g, 3.30 mmol), sodium azide (0.64 g, 3.0 mol amt.), and tetrabutylammonium chloride (2.75 g, 3.0 mol amt.) in benzene (20 ml)[24] was treated in a similar manner as mentioned above. The yield of **6** was 90% (1.5 g). **6**: Syrup; $[\alpha]_D^{27}$ −71 ° (*c* 0.9, $CHCl_3$); IR 2110 $cm^{-1}$ ($N_3$) and 1737 $cm^{-1}$ (C=O); $^1H$ NMR (EX-270) data are shown in Table 1. Found: C, 59.31; H, 6.93; N, 8.20%. Calcd for $C_{25}H_{35}N_3O_8$: C, 59.39; H, 6.98; N, 8.31%.

**Benzyl 2-Acetamido-4-*O*-acetyl-2-deoxy-3,6-di-*O*-pivaloyl-β-D-mannopyranoside (7).** Compound **6** (50 mg, 0.10 mmol) was hydrogenated in dry benzene (3.0 ml) in the presence of a catalytic amount of 5% Pd/C under hydrogen. After the disappearance of **6** on TLC (hexane/ethyl acetate = 2/1), the catalyst was filtered off, and acetic anhydride was added to the solution. The reaction mixture was stirred at room temperature until the disappearance of the amino compound, quenched with methanol, and evaporated to give crude **7**, which was purified on a column of silica gel (hexane/ethyl acetate = 2/1). The yield of **7** was 88% (45 mg). **7**: Mp 194—195 °C (EtOH–hexane); $[\alpha]_D^{26}$ −36.4 ° (*c* 0.8, $CHCl_3$); IR 1722 $cm^{-1}$ (C=O) and 1677 $cm^{-1}$ (CONH); $^1H$ NMR (EX-270) data are shown in Table 1. Found: C, 62.05; H, 7.39; N, 2.25%. Calcd for $C_{27}H_{39}NO_9$: C, 62.17; H, 7.54; N, 2.69%.

**Benzyl 4-*O*-Acetyl-2-deoxy-2-fluoro-3,6-di-*O*-pivaloyl-β-D-mannopyranoside (8).** To a solution of **4** (900 mg, 1.47 mmol) in dry benzene (50 ml), 1 M (1 M = 1 mol $dm^{-3}$) tetrabutylammonium fluoride/oxolane (7.25 ml) was added dropwise at 0 °C under argon. The reaction mixture was stirred for 24 h at room temperature until the disappearance of **4** on TLC (hexane/ethyl acetate = 3/1), then poured into a saturated aqueous sodium hydrogencarbonate solution, extracted with ethyl acetate, washed with brine and water, dried over anhydrous magnesium sulfate, filtered, and evaporated to give crude **8**, which was purified on a column of silica gel (hexane/ethyl acetate = 4/1). The yield of **8** was 53% (376 mg). **8**: Mp 51—53 °C (ether–hexane); $[\alpha]_D^{25}$ −78.3 ° (*c* 0.9, $CHCl_3$); IR 1734 $cm^{-1}$ (C=O); $^1H$ NMR (EX-270) data are shown in Table 1. Found: C, 62.48; H, 7.49%. Calcd for $C_{25}H_{35}FO_8$: C, 62.23; H, 7.31%.

**Benzyl 4-*O*-Acetyl-2-deoxy-3,6-di-*O*-pivaloyl-β-D-*arabino*-hexopyranoside (9).** The reaction mixture of **4** (120 mg, 0.20 mmol) and tetrabutylammonium tetrahydroborate (151 mg, 0.59 mmol, 3.0 mol amt.) in dry benzene (2.0 ml) was kept in a water bath under ultrasonication until the disappearance of **4** on TLC (hexane/ethyl acetate = 3/1). The reaction mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and evaporated to give crude **9**, which was purified on a column of silica gel (hexane/ethyl acetate = 4/1). The yield of **9** was 82% (75 mg). **9**: Mp 57—59 °C (EtOH–hexane); $[\alpha]_D^{25}$ −15.9 ° (*c* 0.9, $CHCl_3$); IR 1734 $cm^{-1}$ (C=O); $^1H$ NMR (EX-270) data are shown in Table 1. Found: C, 64.82; H, 7.59%. Calcd for $C_{25}H_{36}O_8$: C, 64.63; H, 7.81%.

**Benzyl 3,6-Di-*O*-pivaloyl-β-D-mannopyranoside (10).** The reaction mixture of **3** (218 mg, 0.31 mmol), cesium trifluoroacetate (229 mg, 0.93 mmol, 3.0 mol amt.), and 18-crown-6 (246 mg, 3.0 mol amt.) in a mixed solvent of toluene–*N*,*N*-dimethylformamide (3/1, 20 ml) was heated at 80 °C in an oil bath under argon until the disappearance of **3** on TLC (hexane/ethyl acetate = 3/1), then neutralized (pH 7) with pyridine at room temperature, and evaporated to give a residue. To a methanolic solution of the residue, a saturated aqueous sodium hydrogencarbonate solution was added and stirred at room temperature for 1 h. The reaction mixture was filtered to remove the precipitates, neutralized with 70% acetic acid, and evaporated. The remaining residue was purified on a column of silica gel to give **10** in 76% yield (103 mg). **10**: Mp 45—46 °C (EtOH–hexane); $[\alpha]_D^{27}$ −85.0 ° (*c* 0.3, $CHCl_3$); IR 3520 and 3464 $cm^{-1}$ (OH), 1717 $cm^{-1}$ (C=O); $^1H$ NMR data (FX-200) are shown in Table 1. Found: C, 62.82; H, 8.07%. Calcd for $C_{23}H_{34}O_8$: C, 62.99; H, 7.82%.

**Benzyl 2,4-Bis(*O*-methoxymethyl)-3,6-di-*O*-pivaloyl-β-D-mannopyranoside (11).** The reaction mixture of **10** (99 mg, 0.23 mmol), an excess amount of dimethoxymethane (2.0 ml) and a catalytic amount of phosphorus(V) oxide in 1,2-dichloroethane (2.0 ml), was kept in a water bath under ultrasonication until the disappearance of **10** on TLC (hexane/ethyl acetate = 2/1) for 2 h. The reaction mixture was poured into a saturated aqueous sodium hydrogencarbonate solution, extracted with chloroform (3 times), washed with water, dried over anhydrous magnesium sulfate, and evaporated to give **11**, which was purified on a column of silica gel (hexane/ethyl acetate = 3/1). The yield of **11** was 93% (111 mg). **11**: Mp 65—67 °C (EtOH–hexane); $[\alpha]_D^{27}$ −27.0 ° (*c* 1.1, $CHCl_3$); IR 1731 $cm^{-1}$ (C=O); $^1H$ NMR data (FX-200) are shown in Table 1. Found: C, 61.65; H, 7.88%. Calcd for $C_{27}H_{42}O_{10}$: C, 61.58; H, 8.04%.

**Benzyl 2,4-Bis(*O*-methoxymethyl)-β-D-mannopyranoside (12).** To a solution of **11** (111 mg, 0.21 mmol) in methanol (5.0 ml), 1 M sodium methoxide in methanol was added and kept at pH 10 with stirring until the disappearance of **11** on TLC (hexane/ethyl acetate = 2/1). The reaction mixture was carefully neutralized by using a just amount of Dowex 50W $H^+$ ion-exchange resin; the resin was then filtered off, and evaporated to give pure **12**, in quantitative yield (76 mg). **12**: Mp 119—120 °C (EtOH–hexane); $[\alpha]_D^{25}$ −103.5 ° (*c* 1.0, $CHCl_3$); IR 3452 $cm^{-1}$ (OH); $^1H$ NMR (EX-270) data are shown in Table 1. Found: C, 57.19; H, 7.31%. Calcd for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31%.

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