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

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The useful constructions of β-D-mannosidic, 2-acetamido-2-deoxy-β-D-mannosidic, and 2-deoxy-β-D-*arabino*-hexopyranosidic units from the same intermediate, 2,4-bis(*O*-trifluoromethanesulfonyl) derivative of β-D-galactoside, were achieved in a stepwise inversion at *C*-4 and *C*-2 by using cesium acetate, Bu_4NBH_4 and Bu_4NN_3 in good yields. Convenient and practical protections of β-D-mannoside to the straightforward synthesis of antennary oligosaccharides also achieved by using cesium trifluoroacetate.

Despite of the recent explosive growth of oligosaccharide synthesis, the construction of β-D-mannosidic linkages remains a crucial step, far from being adequately solved in preparative terms. The various β-D-mannosyl donors available are accessible either by multistage synthesis only, or lack appreciable β-selectivity in glycosylations, or both.[1] Recent strategies for intramolecular aglycon delivery[1,2] solve the β-selectivity problem, yet their practical utility for the synthesis of biologically relevant β-D-mannosides remains to be demonstrated. The applications of the different methodologies developed for *C*-2-epimerization of β-D-glucosides[3] and for the β-D-mannosidase-promoted mannosyl transfer,[4] which, although promising, has not attain the practically stage. The present most relevant method for the construction of β-D-mannosidic linkages appears to be an "indirect" one, involving β-D-glycosid-2-uloses as the key intermediates. These oxidation and reduction approaches have extensively used[5-13] despite of 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 would like to describe the efficient method for construction of β-D-mannosidic, 2-acetamido-2-deoxy-β-D-mannosidic, and 2-deoxy-β-D-*arabino*-hexopyranosidic units, those of which have been somewhat difficult to construct, in short steps and high yields from 3,6-di-*O*-pivaloyl-2,4-bis(*O*-trifluoromethanesulfonyl)-β-D-galactoside. The stepwise inversions of the bis(triflate) at *C*-4 and *C*-2 were achieved by the conditions employed. (Scheme 1) The selective protections of β-D-mannosidic unit for synthesizing high mannose sugar chain were also achieved by double inversion with cesium trifluoroacetate.

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 with benzyl alcohol, in the presence of trimethylsilyl triflate as promoter,[15] gave benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactoside in 80% yield. This was de-*O*-acylated with NaOMe in methanol (pH 9) to give the corresponding benzyl β-D-galactoside (**1**) in quantitative yield. Compound **1** was treated with bis(tributyltin) oxide[16] (1.5 equiv.) under reflux in toluene, and then with pivaloyl chloride (3.0 equiv.) at r.t. in toluene to give the selectively protected derivative **2** in 85% yield. The pivaloyl group was used to distinguish it from acetyl groups. Compound **2** was treated with trifluoromethanesulfonic anhydride (3.0 equiv.) and pyridine in CH_2Cl_2 at 0 °C then at r.t. to give bis(triflate) **3** in 98% yield. In this work, **3** was prepared as a model compound, but naturally occurring compounds with other aglycons such as terpenes, steroids, and carbohydrates (especially blocked β-D-glucosaminide) may also be available as shown in Figure 1. Compound **3** was treated with CsOAc (1.5 equiv.) and 18-crown-6 in toluene at r.t. to give 4-*O*-monoacetyl derivative **4**, which is stable to purify on a column of silica gel, in 84% yield. Then, **4** was treated again with CsOAc at r.t. with ultrasonication (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 equiv. of CsOAc under the conditions with ultrasonication for 12 h in 93% yield. The above reaction carried out under reflux conditions (ca. 1 h) also gave **5** in 90% yield. In a similar way as mentioned above, **4** was treated with Bu_4NBH_4 or Bu_4NN_3 in benzene with ultrasonication to give the corresponding 2-deoxy derivative **6** in 82% yield or 2-azido-2-deoxy derivative **7** in 91% yield. Then, **7** was 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 **8** in 88% yield. As mentioned above, the otherwise difficult constructions of β-mannosidic linkage of 1,2-*cis* relationship and 2-deoxy-β-D-mannosidic linkage were achieved easily via our indirect method involving stepwise nucleophilic substitution.

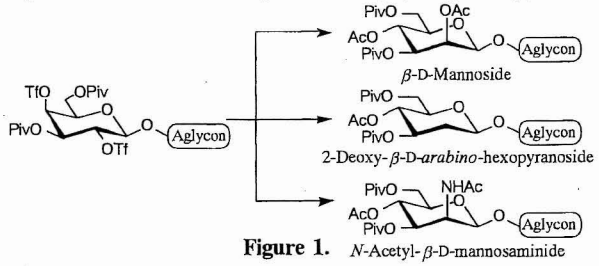
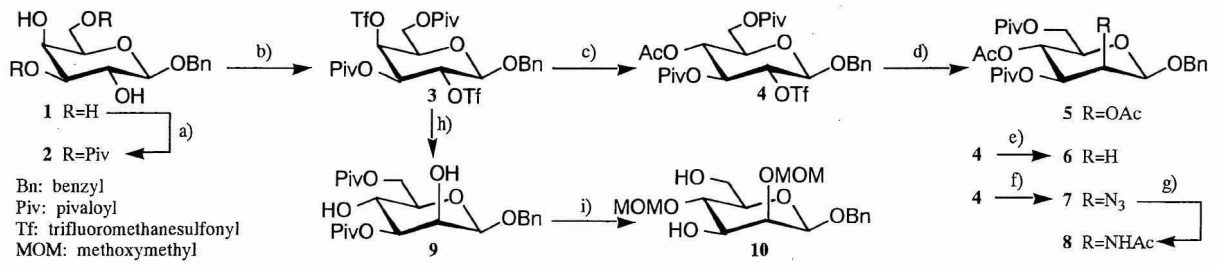


Figure 1. *N*-Acetyl-β-D-mannosaminide

For synthesizing asparagine-linked sugar chains, proper protection of β-D-mannoside is required. Concerning this request, we examined the selective protection of benzyl β-D-mannoside by employing SN2 inversion with cesium trifluoroacetate, because selective cleavage of acetyl and pivaloyl groups was difficult. The reaction of **3** with cesium trifluoroacetate and 18-crown-6 in toluene-DMF (3:1) at 80 °C gave a mixture of 2-*O*-, 4-*O*-, and 2,4-di-*O*-trifluoroacetyl derivatives. The mixed products were treated with aqueous sodium hydrogencarbonate in methanol gave benzyl 3,6-di-*O*-pivaloyl-β-D-mannoside **9** in 76% yield. Compound **9** 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 in 93% yield. Deacylation of the above product with NaOMe in methanol gave benzyl 2,4-bis(*O*-methoxymethyl)-β-D-mannopyranoside **10** in quantitative yield. This methodology to the straightforward synthesis of antennary oligosaccharides, branched at the center β-D-mannosidic unit, seems to be useful for synthesizing important sugar units.



a) $(Bu_3Sn)_2O$ / toluene, reflux, then PivCl (3.0 equiv.), r.t., y. 85%. b) Tf_2O (3.0 equiv.) and pyridine / CH_2Cl_2, 0 °C→r.t., y. 98%.
c) CsOAc (1.5 equiv.), 18-crown-6 / toluene, r.t., y. 84%. d) CsOAc (2.0 equiv.), 18-crown-6 / toluene, r.t., ultrasonication, y. 94%.
e) Bu_4NBH_4 / benzene, r.t., ultrasonication, y. 82%. f) Bu_4NN_3 (2.0 equiv.) / benzene, r.t., ultrasonication, y. 91%.
g) 5% Pd-C / benzene, H_2, then Ac_2O, r.t., y. 88%. h) $CsOCOCF_3$ (2.0 equiv.), 18-crown-6 / toluene-DMF, 80 °C, then aq. $NaHCO_3$ / MeOH, y. 76%.
i) $CH_2(OMe)_2$, P_2O_5 / $(CH_2Cl)_2$, 40 °C, y. 93%, then NaOMe / MeOH, r.t., ultrasonication, y. quant..

Scheme 1.

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17 Physical data of each compound were as follows.
2: mp 138—139 °C; ^{1}H NMR δ=7.37—7.29 (5H, m, Ph), 4.93 and 4.63 (1H x2, each d, $J_{A,B}$=11.9Hz, -CH2-), 4.82 (1H, dd, $J_{3,2}$=10.1Hz, $J_{3,4}$=3.4 Hz, H-3), 4.40 (1H, d, $J_{1,2}$=7.6Hz, H-1), 4.35 (1H, dd, $J_{6,5}$=6.1Hz, $J_{6,6'}$= 11.6Hz, H-6), 4.32 (1H, dd, $J_{6',5}$=6.7Hz, H-6'), 3.96 (1H, m, H-4), 3.89 (1H, ddd, $J_{2,OH}$=3.2Hz, H-2), 3.74 (1H, m, H-5), 2.31 (1H, d, 2-OH), 2.18 (1H, d, $J_{OH,4}$=5.5Hz, 4-OH), 1.25 and 1.22 (9H x2, each s, OPiv x2), **3**: mp 69—73 °C; ^{1}H NMR δ=7.41—7.30 (5H, m, Ph), 5.29 (1H, dd, $J_{4,3}$=2.7Hz, H-4), 5.13 (1H, dd, $J_{3,2}$=10.5Hz, H-3), 4.99 (1H, dd, $J_{2,1}$=7.6Hz, H-2), 4.91 and 4.69 (1H x2, each d, $J_{A,B}$=11.5Hz, -CH2-), 4.69 (1H, d, H-1), 4.41 (1H, dd, $J_{6,5}$=9.5Hz, $J_{6,6'}$=14.2Hz, H-6), 4.35—3.96 (2H, m, H-5 and H-6'), 1.28 and 1.22 (9H x2, each s, OPiv x2), **4**: mp 121—123 °C; ^{1}H NMR δ=7.36—7.34 (5H, m, Ph), 5.37 (1H, dd, $J_{4,3}$=$J_{4,5}$=9.4Hz, H-4), 5.09 (1H, dd, $J_{3,2}$=9.8Hz, H-3), 4.89 and 4.69 (1H x2, each d, $J_{A,B}$=11.0 Hz, -CH2-), 4.75 (1H, dd, $J_{2,1}$=7.8Hz, H-2), 4.64 (1H, d, H-1), 4.23 (1H, dd, $J_{6,5}$=2.7Hz, $J_{6,6'}$=12.5Hz, H-6), 4.12 (1H, dd, $J_{6',5}$=5.3Hz, H-6'), 3.70 (1H, ddd, H-5), 2.01 (3H, s, OAc), 1.25 and 1.18 (9H x2, each s, OPiv x2), **5**: syrup; ^{1}H NMR δ=7.36—7.34 (5H, m, Ph), 5.49 (1H, dd, $J_{2,1}$=0.9 Hz, $J_{2,3}$=3.4Hz, H-2), 5.30 (1H, dd, $J_{4,3}$=$J_{4,5}$=10.0Hz, H-4), 4.96 (1H, dd, H-3), 4.88 and 4.65 (1H x2, each d, $J_{A,B}$=12.3Hz, -CH2-), 4.62 (1H, d, H-1), 4.31 (1H, dd, $J_{6,5}$=2.7Hz, $J_{6,6'}$=12.2Hz, H-6), 4.18 (1H, dd, $J_{6',5}$= 6.1Hz, H-6'), 3.46 (1H, ddd, H-5), 2.16 and 2.01 (3H x2, each s, OAc x2), 1.26 and 1.12 (9H x2, each s, OPiv x2), **6**: mp 57—59 °C (not recrystallized); ^{1}H NMR δ=7.37—7.30 (5H, m, Ph), 5.01 (1H, dd, $J_{4,3}$=$J_{4,5}$= 9.5Hz, H-4), 4.94 (1H, ddd, $J_{3,2e}$=5.2Hz, $J_{3,2a}$=11.5Hz, H-3), 4.87 and 4.60 (1H x2, each d, $J_{A,B}$=11.9Hz, -CH2-), 4.64 (1H, dd, $J_{1,2e}$=2.0Hz, $J_{1,2a}$=9.6Hz, H-1), 4.25 (1H, dd, $J_{6,5}$=2.7Hz, $J_{6,6'}$=12.1Hz, H-6), 4.17 (1H, dd, $J_{6',5}$=5.8Hz, H-6'), 3.62 (1H, ddd, H-5), 2.32 (1H, ddd, $J_{2e,2a}$=12.5Hz, H-2e), 2.01 (3H, s, OAc), 1.75 (1H, ddd, H-2a), 1.25 and 1.14 (9H x2, each s, OPiv x2), **7**: syrup; ^{1}H NMR δ=7.37—7.35 (5H, m, Ph), 5.29 (1H, dd, $J_{4,3}$=$J_{4,5}$=9.8Hz, H-4), 4.95 and 4.66 (1H x2, each d, $J_{A,B}$=12.2Hz, -CH2-), 4.89 (1H, dd, $J_{3,2}$=3.9Hz, H-3), 4.64 (1H, d, $J_{1,2}$=1.0Hz, H-1), 4.27 (1H, dd, $J_{6,5}$=2.4Hz, $J_{6,6'}$=12.2Hz, H-6), 4.12 (1H, dd, $J_{6',5}$=5.9Hz, H-6'), 4.05 (1H, dd, H-2), 3.60 (1H, ddd, H-5), 2.01 (3H, s, OAc), 1.26 and 1.20 (9H x2, each s, OPiv x2), **8**: mp 194—195 °C; ^{1}H NMR δ=7.34—7.31 (5H, m, Ph), 5.67 (1H, d, $J_{NH,2}$=8.8Hz, NH), 5.29 (1H, dd, $J_{4,3}$=$J_{4,5}$=9.8Hz, H-4), 4.89 (1H, dd, $J_{3,2}$=3.9Hz, H-3), 4.84 and 4.61 (1H x2, each d, $J_{A,B}$=12.3Hz, -CH2-), 4.76 (1H, ddd, $J_{2,1}$=1.0Hz, H-2), 4.64 (1H, d, H-1), 4.23 (1H x2, each d, $J_{6,5}$=$J_{6',5}$=4.4Hz, H-6 and H-6'), 3.60 (1H, ddd, H-5), 2.03 and 2.02 (3H x2, each s, OAc and NAc), 1.27 and 1.21 (9H x2, each s, OPivx2), **9**: mp 45—46 °C (not recrystallized); ^{1}H NMR δ=7.36—7.30 (5H, m, Ph), 4.90 and 4.65 (1H x2, each d, $J_{A,B}$=12.0 Hz, -CH2-), 4.73 (1H, dd, $J_{3,2}$=3.2Hz, $J_{3,4}$=9.8Hz, H-3), 4.58 (1H, d, $J_{1,2}$=0.9Hz, H-1), 4.49 (1H, dd, $J_{6,5}$=2.7Hz, $J_{6,6'}$=12.0Hz, H-6), 4.36 (1H, dd, $J_{6',5}$=6.1Hz, H-6'), 4.08 (1H, ddd, $J_{2,OH}$=2.4Hz, H-2), 3.92 (1H, ddd, $J_{4,5}$=9.5Hz, $J_{4,OH}$=4.9Hz, H-4), 3.94 (1H, ddd, H-5), 2.52 and 2.36 (1H x2, each d, OH x2), 1.25 and 1.24 (9H x2, each s, OPiv x2), **10**: mp 119—120 °C; ^{1}H NMR δ=7.37—7.29 (5H, m, Ph), 4.93 and 4.65 (1H x2, each d, $J_{A,B}$=12.2Hz, -CH2-), 4.90 and 4.83 (1H x2, each d, $J_{A,B}$=6.7 Hz, -CH2-), 4.83 and 4.71 (1H x2, each d, $J_{A,B}$=6.7Hz, -CH2-), 4.56 (1H, d, $J_{1,2}$=1.0Hz, H-1), 4.02 (1H, dd, $J_{2,3}$=3.4Hz, H-2), 3.91 (1H, m, H-6), 3.88 (1H, d, $J_{OH,3}$=5.8Hz, 3-OH), 3.82 (1H, m, H-6'), 3.68 (1H, dd, $J_{4,3}$= $J_{4,5}$=9.5Hz, H-4), 3.58 (1H, ddd, H-3), 3.46 and 3.44 (3H x2, each s, OMe x2), 3.30 (1H, ddd, $J_{5,6}$=2.8Hz, $J_{5,6'}$=5.4Hz, H-5), 2.18 (1H, m, 6-OH).