

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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(Received September 30, 1994)

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, Bu₄NBH₄ and Bu₄NN₃ in good yields. Convenient and practical protections of β -D-mannoside to the straightforward synthesis of antennary oligosaccharides also achieved by using cesium trifluoroacetate.

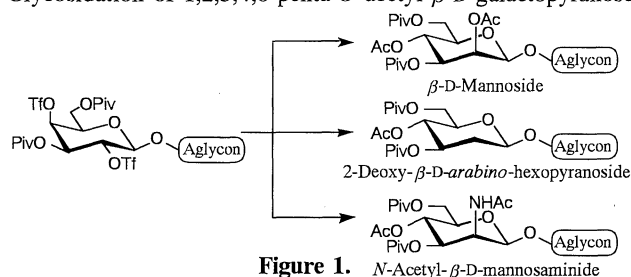
Despite of the recent explosive growth of oligosaccharide synthesis, the construction of β -D-mannosidic linkages remains a crucial step, far from being adequately solved in preparative terms. The various β -D-mannosyl donors available are accessible either by multistage synthesis only, or lack appreciable 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-glucosides³ 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 used⁵⁻¹³ 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 reported¹⁴ as an excellent method.

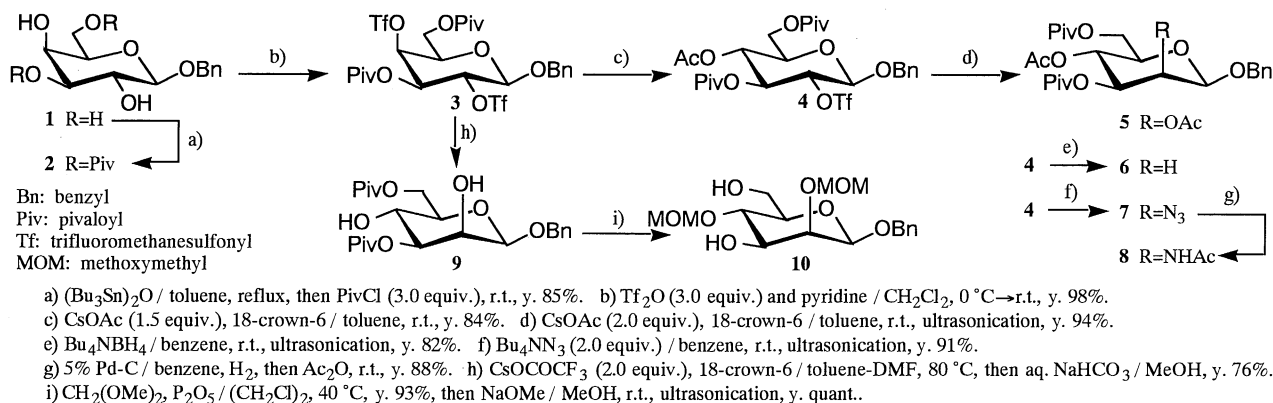
In this paper, we would like to describe the efficient method for construction of β -D-mannosidic, 2-acetamido-2-deoxy- β -D-mannosidic, and 2-deoxy- β -D-arabino-hexopyranosidic units, those of which have been somewhat difficult to construct, in short steps and high yields from 3,6-di-*O*-pivaloyl-2,4-bis(*O*-trifluoromethanesulfonyl)- 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) oxide¹⁶ (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 CH₂Cl₂ 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 Bu₄NBH₄ or Bu₄NN₃ 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 H₂ 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.

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 S_N2 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 CH₂(OMe)₂ and P₂O₅ in (CH₂Cl)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.





Scheme 1.

The authors greatly thank professor Frieder W. Lichtenthaler (Institut für Organische Chemie, Technische Hochschule Darmstadt, Germany) for kind discussion.

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- Physical data of each compound were as follows.
2: mp $138\text{--}139^\circ\text{C}$; $^1\text{H NMR}$ $\delta=7.37\text{--}7.29$ (5H, m, Ph), 4.93 and 4.63 (1H x2, each d, $J_{A,B}=11.9\text{Hz}$, $-\text{CH}_2-$), 4.82 (1H, dd, $J_{3,2}=10.1\text{Hz}$, $J_{3,4}=3.4\text{Hz}$, H-3), 4.40 (1H, d, $J_{1,2}=7.6\text{Hz}$, H-1), 4.35 (1H, dd, $J_{6,5}=6.1\text{Hz}$, $J_{6,6}=11.6\text{Hz}$, H-6), 4.32 (1H, dd, $J_{6,5}=6.7\text{Hz}$, H-6'), 3.96 (1H, m, H-4), 3.89 (1H, ddd, $J_{2,\text{OH}}=3.2\text{Hz}$, H-2), 3.74 (1H, m, H-5), 2.31 (1H, d, 2-OH), 2.18 (1H, d, $J_{\text{OH},4}=5.5\text{Hz}$, 4-OH), 1.25 and 1.22 (9H x2, each s, OPiv x2), **3**: mp $69\text{--}73^\circ\text{C}$; $^1\text{H NMR}$ $\delta=7.41\text{--}7.30$ (5H, m, Ph), 5.29 (1H, dd, $J_{4,3}=2.7\text{Hz}$, H-4), 5.13 (1H, dd, $J_{3,2}=10.5\text{Hz}$, H-3), 4.99 (1H, dd, $J_{2,1}=7.6\text{Hz}$, H-2), 4.91 and 4.69 (1H x2, each d, $J_{A,B}=11.5\text{Hz}$, $-\text{CH}_2-$), 4.69 (1H, d, H-1), 4.41 (1H, dd, $J_{6,5}=9.5\text{Hz}$, $J_{6,6}=14.2\text{Hz}$, 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 $121\text{--}123^\circ\text{C}$; $^1\text{H NMR}$ $\delta=7.36\text{--}7.34$ (5H, m, Ph), 5.37 (1H, dd, $J_{4,3}=J_{4,5}=9.4\text{Hz}$, H-4), 5.09 (1H, dd, $J_{3,2}=9.8\text{Hz}$, H-3), 4.89 and 4.69 (1H x2, each d, $J_{A,B}=11.0\text{Hz}$, $-\text{CH}_2-$), 4.75 (1H, dd, $J_{2,1}=7.8\text{Hz}$, H-2), 4.64 (1H, d, H-1), 4.23 (1H, dd, $J_{6,5}=2.7\text{Hz}$, $J_{6,6}=12.5\text{Hz}$, H-6), 4.12 (1H, dd, $J_{6,5}=5.3\text{Hz}$, 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; $^1\text{H NMR}$ $\delta=7.36\text{--}7.34$ (5H, m, Ph), 5.49 (1H, dd, $J_{2,1}=0.9\text{Hz}$, $J_{2,3}=3.4\text{Hz}$, H-2), 5.30 (1H, dd, $J_{4,3}=J_{4,5}=10.0\text{Hz}$, H-4), 4.96 (1H, dd, H-3), 4.88 and 4.65 (1H x2, each d, $J_{A,B}=12.3\text{Hz}$, $-\text{CH}_2-$), 4.62 (1H, d, H-1), 4.31 (1H, dd, $J_{6,5}=2.7\text{Hz}$, $J_{6,6}=12.2\text{Hz}$, H-6), 4.18 (1H, dd, $J_{6,5}=6.1\text{Hz}$, 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 $57\text{--}59^\circ\text{C}$ (not recrystallized); $^1\text{H NMR}$ $\delta=7.37\text{--}7.30$ (5H, m, Ph), 5.01 (1H, dd, $J_{4,3}=J_{4,5}=9.5\text{Hz}$, H-4), 4.94 (1H, ddd, $J_{3,2}=5.2\text{Hz}$, $J_{3,2a}=11.5\text{Hz}$, H-3), 4.87 and 4.60 (1H x2, each d, $J_{A,B}=11.9\text{Hz}$, $-\text{CH}_2-$), 4.64 (1H, dd, $J_{1,2a}=2.0\text{Hz}$, $J_{1,2a}=9.6\text{Hz}$, H-1), 4.25 (1H, dd, $J_{6,5}=2.7\text{Hz}$, $J_{6,6}=12.1\text{Hz}$, H-6), 4.17 (1H, dd, $J_{6,5}=5.8\text{Hz}$, H-6'), 3.62 (1H, ddd, H-5), 2.32 (1H, ddd, $J_{2e,2a}=12.5\text{Hz}$, 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; $^1\text{H NMR}$ $\delta=7.37\text{--}7.35$ (5H, m, Ph), 5.29 (1H, dd, $J_{4,3}=J_{4,5}=9.8\text{Hz}$, H-4), 4.95 and 4.66 (1H x2, each d, $J_{A,B}=12.2\text{Hz}$, $-\text{CH}_2-$), 4.89 (1H, dd, $J_{3,2}=3.9\text{Hz}$, H-3), 4.64 (1H, d, $J_{1,2}=1.0\text{Hz}$, H-1), 4.27 (1H, dd, $J_{6,5}=2.4\text{Hz}$, $J_{6,6}=12.2\text{Hz}$, H-6), 4.12 (1H, dd, $J_{6,5}=5.9\text{Hz}$, 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 $194\text{--}195^\circ\text{C}$; $^1\text{H NMR}$ $\delta=7.34\text{--}7.31$ (5H, m, Ph), 5.67 (1H, d, $J_{\text{NH},2}=8.8\text{Hz}$, NH), 5.29 (1H, dd, $J_{4,3}=J_{4,5}=9.8\text{Hz}$, H-4), 4.89 (1H, dd, $J_{3,2}=3.9\text{Hz}$, H-3), 4.84 and 4.61 (1H x2, each d, $J_{A,B}=12.3\text{Hz}$, $-\text{CH}_2-$), 4.76 (1H, ddd, $J_{2,1}=1.0\text{Hz}$, H-2), 4.64 (1H, d, H-1), 4.23 (1H x2, each d, $J_{6,5}=J_{6,6}=4.4\text{Hz}$, 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, OPiv x2), **9**: mp $45\text{--}46^\circ\text{C}$ (not recrystallized); $^1\text{H NMR}$ $\delta=7.36\text{--}7.30$ (5H, m, Ph), 4.90 and 4.65 (1H x2, each d, $J_{A,B}=12.0\text{Hz}$, $-\text{CH}_2-$), 4.73 (1H, dd, $J_{3,2}=3.2\text{Hz}$, $J_{3,4}=9.8\text{Hz}$, H-3), 4.58 (1H, d, $J_{1,2}=0.9\text{Hz}$, H-1), 4.49 (1H, dd, $J_{6,5}=2.7\text{Hz}$, $J_{6,6}=12.0\text{Hz}$, H-6), 4.36 (1H, dd, $J_{6,5}=6.1\text{Hz}$, H-6'), 4.08 (1H, ddd, $J_{2,\text{OH}}=2.4\text{Hz}$, H-2), 3.92 (1H, ddd, $J_{4,5}=9.5\text{Hz}$, $J_{4,\text{OH}}=4.9\text{Hz}$, 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 $119\text{--}120^\circ\text{C}$; $^1\text{H NMR}$ $\delta=7.37\text{--}7.29$ (5H, m, Ph), 4.93 and 4.65 (1H x2, each d, $J_{A,B}=12.2\text{Hz}$, $-\text{CH}_2-$), 4.90 and 4.83 (1H x2, each d, $J_{A,B}=6.7\text{Hz}$, $-\text{CH}_2-$), 4.83 and 4.71 (1H x2, each d, $J_{A,B}=6.7\text{Hz}$, $-\text{CH}_2-$), 4.56 (1H, d, $J_{1,2}=1.0\text{Hz}$, H-1), 4.02 (1H, dd, $J_{2,3}=3.4\text{Hz}$, H-2), 3.91 (1H, m, H-6), 3.88 (1H, d, $J_{\text{OH},3}=5.8\text{Hz}$, 3-OH), 3.82 (1H, m, H-6'), 3.68 (1H, dd, $J_{4,3}=J_{4,5}=9.5\text{Hz}$, H-4), 3.58 (1H, ddd, H-3), 3.46 and 3.44 (3H x2, each s, OMe x2), 3.30 (1H, ddd, $J_{5,6}=2.8\text{Hz}$, $J_{5,6}=5.4\text{Hz}$, H-5), 2.18 (1H, m, 6-OH).