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An improved method for synthesizing antennary β-D-mannopyranosyl disaccharide units

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Abstract—The merits of an indirect protecting method for hydroxyl groups using allyl groups via allyloxycarbonyl groups in the synthesis of antennary β-D-mannopyranosyl disaccharides from β-D-galactopyranosyl disaccharides were studied. Regioselective allyloxycarbonylation and conversion reactions involving simultaneous double S_N2 nucleophilic substitution at C-2′ and C-4′ of benzyl *O*-[β-D-galactopyranosyl]-(1-4)-3,6-di-*O*-benzyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside were examined for comparison with the direct allylation method. The required β-D-mannopyranosyl disaccharide having proper protecting groups was obtained using this indirect method in 52% yield. In contrast, the reported direct allylation method using methyl *O*-(β-D-galactopyranosyl) disaccharide gave the corresponding β-D-mannopyranosyl disaccharide in only 7.5% yield.

The practical synthesis of antennary β-D-mannopyranosyl oligosaccharides is an important subject in bioactive oligosaccharide synthesis. The difficulties of the necessary 1,2-*cis* coupling are well known. To date, several papers[1] on the direct construction of the β-D-*manno* structure have been reported, but obtaining the proper protecting groups at the required positions of the intermediate compounds has proven to be a difficult problem. Several indirect methods involving S_N2 nucleophilic substitution aimed at synthesizing a suitably protected antennary β-D-mannopyranosyl unit have shown promise. David et al. has reported[2] a mode of building the very important β-mannopyranosyl residue by inversion of C-2, thereby bypassing the difficult step. Furthermore, Alais and David have also developed[3] a method for preparing disaccharides containing β-D-mannopyranosyl groups starting from *N*-phthaloyllactosamine derivatives by two simultaneous S_N2 substitutions. The authors were inspired by the work of David on constructing β-D-mannopyranosyl residues and have developed a practical method based on that work.[4]

In oligosaccharide syntheses, it is an important challenge to protect the individual hydroxyl group regioselectively. In this case, the regioselectivities and the yields are usually affected by the reaction conditions and the kind of protecting groups used. In the syntheses of antennary β-D-mannopyranosyl oligosaccharide units, the β-D-galactopyranosyl residue appears to be a better substrate than β-D-glucopyranosyl due to the ability to regioselectively protect the branching positions at 3 and 6 followed by S_N2 substitutions at the 4 and then the 2-positions (from *galacto* to *gluco* and then *manno* derivatives).[4] In previous work, Sato et al. have examined the effect of protecting groups at the 3- and 6-positions of β-D-galactosides on these double S_N2 substitution reactions using benzyl 3,6-di-*O*-acyl- or 3,6-di-*O*-allyl- and -*O*-benzyl-2,4-bis(*O*-trifluoromethansulfonyl)-β-D-galactopyranoside with CsOAc and found that 3,6-di-*O*-acyl derivatives give better yields than 3,6-di-*O*-allyl- or -benzyl derivatives.[5] In contrast, it has been reported that the regioselective protection of the 3- and 6-positions of the β-D-galactopyranosyl disaccharide, methyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-β-D-galactopyranosyl-2-phthalimido-β-D-glucopyranoside (**5**) with allyl groups using bis(tributyltin) oxide give the expected 3′,6′-di-*O*-allyl derivative (**6**) in only 16% yield despite otherwise typically good results for regioselective protection using the tin oxide method.[6] This decreased nucleophilicity has been reported[3] to be a property of disaccharides, especially toward organotin reagents. Considering the above results, we wanted to develop a new methodology that would overcome the

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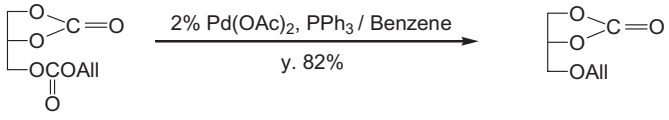
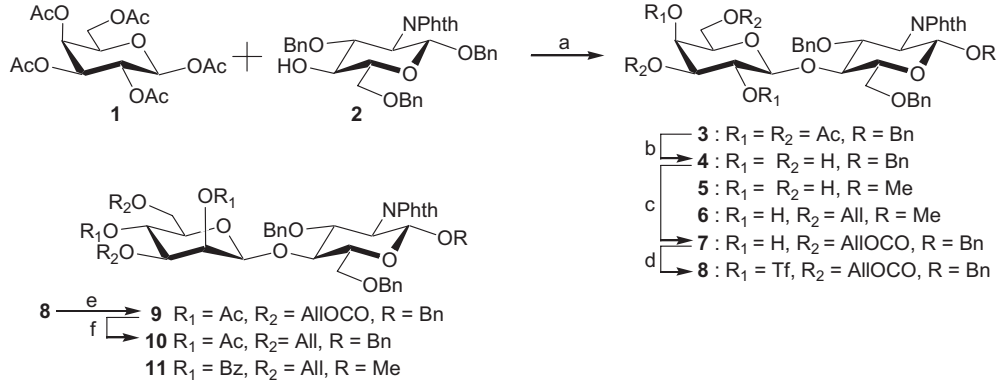
difficulties of synthesizing β-D-mannopyranosyl disaccharide units. We wanted to develop an indirect method involving as the key step, the transformation of allyloxycarbonyl protecting groups to allyl groups (Scheme 1).[7] In this paper, we describe the merits of this indirect method for synthesizing β-mannohexopyranosyl disaccharides, using the synthesis of benzyl *O*-[3,6-di-*O*-allyl-β-D-mannopyranosyl]-(1-4)-3,6-di-*O*-benzyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (**10**) via benzyl *O*-[3,6-di-*O*-allyloxycarbonyl-β-D-galactopyranosyl]-(1-4)-3,6-di-*O*-benzyl-2-deoxy-2-*N*-phthalimido-D-glucopyranoside (**7**) as an example.

The starting material, benzyl *O*-[2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl]-(1-4)-3,6-di-*O*-benzyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (**3**) was prepared by the method described by Alais and David.[3] Coupling of benzyl 3,6-di-*O*-benzyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranoside (**2**)[8] with 1,2,3,4,6-penta-*O*-acetyl-β-D-galactpyranose (**1**) in the presence of trimethylsilyl triflate as the promoter[9] gave the protected lactosamine derivative **3** [mp 194–202 °C; $[\alpha]_D^{25}$ +18 (*c* 1.0, $CHCl_3$)] in 72% yield. This was de-*O*-acetylated by alkaline methanolysis to give disaccharide **4** in quantitative yield, which has an unprotected β-D-galactopyranosyl group. The reaction of **4** and bis(tributyltin)oxide (1.5 equiv) in toluene under reflux conditions by using a Dean Stark apparatus with molecular sieves (MS 4A) for 3 h gave the corresponding (tributyltin)oxide derivative. This reaction mixture was treated with allyloxycarbonyl chloride (3.0 equiv) at room temperature until the disappearance of the starting material (for 24 h) gave the corresponding 3′,6′-di-*O*-allyloxycarbonyl derivative **7** [syrup; $[\alpha]_D^{25}$ +37 (*c* 0.9, $CHCl_3$)] in 84% yield. It was purified on a column of silica gel (hexane/ethyl acetate = 2:1). The structure of **7** was determined by ^{1}H NMR[10] (down field shift of H-3′, H-6′a, and H-6′b). Compound **7** was then treated with 3.0 equiv of Tf_2O in pyridine–CH_2Cl_2 (6:1) at −19 °C then room temperature under argon to give syrupy 2′,4′-bis(triflate) **8** quantitatively, the structure of which was determined by ^{1}H NMR[10] (down field shift of H-2′ and H-4′). The labile compound **8** was directly used for the following reaction without purification (Scheme 2).

A simultaneous double S_N2 substitution of 2′,4′-bis(triflate) **8** with CsOAc (3.0 equiv) and 18-crown-6 (3.0 equiv) in toluene with ultrasonication[4] in a water bath was carried out until the disappearance of **8** (for 12 h) gave the corresponding syrupy 2′,4′-di-*O*-acetyl-β-D-mannopyranosyl derivative **9** [$[\alpha]_D^{27}$ −11 (*c* 0.4, $CHCl_3$)] in 86% yield, which was purified on a column of silica gel (hexane/ethyl acetate = 2/1). The structure of **9** was determined by ^{1}H NMR[10] (**8**: $J_{1',2'}$ = 7.9 Hz, $J_{2',3'}$ = 10.4 Hz, $J_{3',4'}$ = 3.7 Hz, $J_{4',5'}$ = 0 Hz; **9**: $J_{1',2'}$ = 0 Hz, $J_{2',3'}$ = 3.7 Hz, $J_{3',4'}$ = 9.7 Hz, $J_{4',5'}$ = 9.7 Hz). In a similar reaction, 2′,4′-bis(trifrate) of methyl 3,6-di-*O*-benzyl-2-deoxy-4-*O*-(3,6-di-*O*-allyl-β-D-galactopyranosyl)-2-phthalimido-β-D-glucopyranoside with tetrabutylammonium benzoate has been reported[3] to give the corresponding 2′,4′-di-*O*-benzoyl mannopyranosyl disaccharide **11** in 47% yield. From the results, the double S_N2 substitution of these 2′,4′-bis(triflate) compounds with cesium acylate appears to provide better yields than that with the use of tetrabutylammonium acylate. It is also possible to obtain a mono-substituted β-D-glucopyranosyl product if we want, because this reactions proceeded firstly at C-4′. These results may promise the wide applications in the syntheses of β-D-mannopyranosyl as well as β-D-glucopyranosyl



Scheme 1. A reported conversion method of allyloxycarbonyl groups into allyl ether groups.[7]



Scheme 2. Reagents and conditions: (a) TMSOTf/CH_2Cl_2, −25 °C to rt (72%); (b) NaOMe/MeOH, 0 °C (quant.); (c) (i) $(Bu_3Sn)_2O$/toluene, reflux; (ii) AllOCOCl/toluene, rt (84%); (d) Tf_2O/Py.–CH_2Cl_2, −19 °C to rt (quant.); (e) CsOAc, 18-crown-6/toluene, ultrasonication (86%); (f) $(Ph_3P)_4Pd$/benzene, −19 °C to rt (72%).

disaccharides having a variety of functional groups at C-2′.[4] Allyloxycarbonyl derivative **9** was then transformed with $(Ph_3P)_4Pd$[7] into the corresponding allyl ether derivative **10** in 72% yield. The structure of **10** was supported by ^{1}H NMR[10] (high field shift of H-3′, H-6′a, and H-6′b). Compound **10** may be useful for synthesizing antennary mannopyranosyl oligosaccharides, because it is possible to remove each protecting group individually.

In summary, the combination of indirect allylation and a double S_N2 substitution of the 2′,4′-bis(triflate) derivative of β-D-galactopyranosyl disaccharide using CsOAc was shown to work well for the synthesis of β-D-mannopyranosyl disaccharides, which form the core of antennary β-D-mannopyranosyl oligosaccharides. The ease of reaction and the dramatically improved yields, should make this a very useful method for performing this and similar kinds of oligosaccharide syntheses.

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10. ^{1}H NMR (500 MHz, in $CDCl_3$) data of compound **7**–**10**. Compound **7**:δ 7.63 (4H, m, Phth), 7.52–6.70 (5H × 3, m, Ph × 3), 5.93, 5.86 (1H × 2, each m, –CH_2–C*H*=CH_2 × 2), 5.37, 5.27 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.29, 5.23 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.13 (1H, d, H-1, $J_{1,2}$ = 8.5 Hz), 4.79, 4.40 (1H × 2, each d, $J_{A,B}$ = 12.8 Hz, –C*H*$_2$Ph), 4.78, 4.60 (1H × 2, each d, $J_{A,B}$ = 12.8 Hz, –C*H*$_2$Ph), 4.78, 4.45 (1H × 2, each d, $J_{A,B}$ = 12.8 Hz, –C*H*$_2$Ph), 4.64 (1H, d, H-1′, $J_{1',2'}$ = 7.3 Hz), 4.66, 4.45 (2H × 2, each m, –C*H*$_2$–CH=CH_2 × 2), 4.60 (1H, dd, H-3′, $J_{2',3'}$ = 11.0 Hz, $J_{3',4'}$ = 2.3 Hz), 4.36 (1H, dd, H-3, $J_{2,3}$ = 10.4 Hz, $J_{3,4}$ = 8.6 Hz), 4.25 (1H, dd, H-6′a, $J_{5',6'a}$ = 5.2 Hz, $J_{6'a,6'b}$ = 11.3 Hz), 4.22 (1H, dd, H-6′b, $J_{5',6'b}$ = 7.9 Hz), 4.20 (1H, dd, H-2), 4.14 (1H, dd, H-4, $J_{4,5}$ = 9.8 Hz), 4.06 (1H, dd, H-4′, $J_{4',5'}$ = 0 Hz, $J_{4',OH}$ = 4.9 Hz), 4.03 (1H, dd, H-6a, $J_{5,6a}$ = 3.1 Hz, $J_{6a,6b}$ = 11.6 Hz), 3.93 (1H, ddd, H-2′, $J_{2',OH}$ = 3.7 Hz), 3.80 (1H, dd, H-6b, $J_{5,6b}$ = 1.8 Hz), 3.72 (1H, d, H-2′OH), 3.67 (1H, ddd, H-5), 3.55 (1H, ddd, H-5′), 2.49 (1H, d, 4′-OH).
Compound **8**:δ 7.78–6.83 (5H × 3 and 4H, m, Ph × 3 and Phth), 5.98, 5.93 (1H × 2, each m, –CH_2–C*H*=CH_2 × 2), 5.42, 5.33 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.41, 5.33 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.19 (1H, d, H-4′,$J_{4',3'}$ = 3.1 Hz), 5.13 (1H, d, H-1, $J_{1,2}$ = 8.2 Hz), 4.90, 4.34 (1H × 2, each d, $J_{A,B}$ = 11.9 Hz, –C*H*$_2$Ph), 4.81, 4.48 (1H × 2, each d, $J_{A,B}$ = 12.5 Hz, –C*H*$_2$Ph), 4.73–4.67 (2H × 2, each m, –C*H*$_2$–CH=CH_2 × 2), 4.65 (1H, dd, H-2′), 4.64, 4.32 (1H × 2, each d, $J_{A,B}$ = 11.9 Hz, –C*H*$_2$Ph), 4.58 (1H, dd, H-3′, $J_{3',2'}$ = 10.4 Hz, $J_{3',4'}$ = 3.1 Hz), 4.49 (1H, d, H-1′, $J_{1',2'}$ = 7.6 Hz), 4.23 (1H, dd, H-3, $J_{2,3}$ = 6.7 Hz), 4.22 (1H, dd, H-2), 4.20 (1H, dd, H-6′a), 4.17 (1H, dd, H-4, $J_{4,3}$ = 9.8 Hz), 3.92 (1H, dd, H-6a, $J_{6a,6b}$ = 11.3 Hz, $J_{6a,5}$ = 2.8 Hz), 3.82 (1H, dd, H-6′b, $J_{6'b,6'a}$ = 11.3 Hz, $J_{6'b,5'}$ = 8.2 Hz), 3.79 (1H, dd, H-6b, $J_{6b,5}$ = 1.2 Hz), 3.59 (1H, dd, H-5, $J_{5,4}$ = 9.8 Hz), 3.46 (1H, dd, H-5′, $J_{5',6'a}$ = 6.4 Hz).
Compound **9**: δ 7.65 (4H, m, Phth), 7.43–6.76 (5H × 3, m, Ph × 3), 5.92, 5.87 (1H × 2, each m, –CH_2–C*H*=CH_2 × 2), 5.48 (1H, dd, H-2′, $J_{1',2'}$ = 0.9 Hz, $J_{2',3'}$ = 3.4 Hz), 5.35, 5.28 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.31, 5.22 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.17 (1H, dd, H-4′, $J_{3',4'}J_{4',5'}$ = 10.1 Hz), 5.05 (1H, d, H-1, $J_{1,2}$=8.2 Hz), 4.81, 4.37 (1H × 2, each d, $J_{A,B}$ = 12.5 Hz, –C*H*$_2$Ph), 4.79, 4.54 (1H × 2, each d, $J_{A,B}$ = 12.3 Hz, –C*H*$_2$Ph), 4.77, 4.46 (1H × 2, each d, $J_{A,B}$ = 12.2 Hz, –C*H*$_2$Ph), 4.77 (1H, d, H-1′, $J_{1',2'}$ = 0.6 Hz), 4.69 (1H, dd, H-3′), 4.63, 4.56 (2H × 2, each m, –C*H*$_2$–CH=CH_2 × 2), 4.22 (1H, dd, H-6′a, $J_{5',6'a}$ = 5.2 Hz, $J_{6'a,6'b}$ = 11.9 Hz), 4.21 (1H, dd, H-3, $J_{2,3}$ = 10.7 Hz, $J_{3,4}$ = 8.2 Hz), 4.17 (1H, dd, H-2, $J_{2,1}$ = 8.2 Hz), 4.12 (1H, dd, H-4, $J_{4,5}$ = 9.8 Hz), 4.06 (1H, dd, H-6′b, $J_{5',6'b}$ = 3.3 Hz), 3.80 (1H, dd, H-6a, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 11.6 Hz), 3.76 (1H, dd, H-6b, $J_{5,6b}$ = 1.8 Hz), 3.51 (1H, ddd, H-5), 3.39 (1H, ddd, H-5′), 2.14, 2.04 (3H × 2, each s, OAc × 2).
Compound **10**: δ 7.68 (4H, m, Phth), 7.65–6.86 (5H × 3, m, Ph × 3), 5.79, 5.76 (1H × 2, each m, –CH_2–C*H*=CH_2 × 2), 5.34 (1H, dd, H-2′, $J_{1',2'}$ = 0 Hz, $J_{2',3'}$ = 3.4 Hz), 5.23, 5.17 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.20, 5.15 (1H × 2, each m, –CH_2–CH=C*H*$_2$), 5.10 (1H, d, H-1, $J_{1,2}$ = 8.3 Hz), 4.92 (1H, dd, H-4′, $J_{3',4'}J_{4',5'}$ = 9.8 Hz), 4.84, 4.40 (1H × 2, each d, $J_{A,B}$ = 11.9 Hz, –C*H*$_2$Ph), 4.80, 4.52 (1H × 2, each d, $J_{A,B}$ = 12.2 Hz, –C*H*$_2$Ph), 4.79, 4.48 (1H × 2, each d, $J_{A,B}$ = 12.5 Hz, –C*H*$_2$Ph), 4.65 (1H, s, H-1′), 4.24 (1H, dd, H-3, $J_{2,3}$ = 10.7 Hz, $J_{3,4}$ = 8.0 Hz), 4.20 (1H, dd, H-2), 4.09 (1H, dd, H-4, $J_{4,5}$ = 10.1 Hz), 4.06, 4.02 (1H × 2, each m, –C*H*$_2$–CH=CH_2), 4.03, 4.01 (1H × 2, each m, –C*H*$_2$–CH=CH_2), 3.82 (1H, dd, H-6a, $J_{5,6a}$ = 3.4 Hz, $J_{6a,6b}$ = 11.0 Hz), 3.77 (1H, dd, H-6b, $J_{5,6b}$ = 2.1 Hz), 3.57 (1H, ddd, H-5), 3.50 (1H, dd, H-6′a, $J_{5',6'a}$ = 1.9 Hz), 3.35 (1H, dd, H-6′b,$J_{6'b,6'a}$ = 12.6 Hz, $J_{6'b,5'}$ = 6.8 Hz), 3.28 (1H, dd, H-3′), 3.23 (1H, ddd, H-5′), 2.12, 2.06 (3H × 2, each s, OAc × 2).