Prearranged glycosides part 16. Non-symmetrically tethered glycosides via *o*-Hydroxycarbonyl-benzylidene-glycosides

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Abstract: An asymmetric *o*-methylbenzoyl tether for intramolecular glycosylations is prepared from *o*-methoxycarbonyl-benzylidene glucosamine by benzylation, saponification, condensation with phenyl 3,4,6-benzyl-1-thio-glucoside, and regioselective ring opening of the benzylidene moiety. Thus obtained prearranged glycoside affords the corresponding β(1,4)-linked disaccharide as the major product.

Keywords: glycosylation, intramolecular, prearranged glycosides

The strategy of intramolecular glycosylation by ring forming glycosylation reactions of tethered glycosyl donors and glycosyl acceptors (prearranged glycosides) has been shown by us[1-14] and others[15-25] to be a powerful tool for the diastereoselective formation of *O*-glycosidic bonds. Especially the construction of otherwise difficultly to establish β-D-mannosidic and β-L-rhamnosidic linkages[1,4,7,12] in oligosaccharide syntheses is superior to many classical glycosylation procedures. Recently, we developed non-symmetrical tethers for diastereoselective intramolecular glycosylations (i.e. benzyl carboxylates) which allow for regioselective ring opening after the glycosylation step and thus, extend the applicability of this strategy for the construction of higher oligosaccharides.[14] Previously, the asymmetrical tether was introduced into a suitable glycosyl donor or acceptor by reacting the latter with methyl bromomethyl benzoates under strongly alkaline conditions. This procedure, however, resulted in low yields in some cases where acyl protecting groups were present in the educts. In order to circumvent such preparative pitfalls and to shorten the tedious steps for preparation of suitably protected donors and acceptors we now applied an alternative strategy for the construction of tethered glycosides via o-methoxycarbonyl benzylidene glycosides. Such methoxycarboyl benzylidene glycosides can be obtained in good yield under mild acidic conditions and allow for efficient regioselective ring-opening of the benzylidene moiety at a later stage of the sequence and thus, resulting in higher overall yields for intramolecular glycosylation via prearranged glycosides. Alkoxycarbonyl benzylidene glyosides have also not been reported in the literature yet.

As the glycosyl acceptor we chose benzyl 2-deoxy-2-phthalimido-β-D-glucopyranoside **1**[26] which was trans-acetalized selectively at positions 4 and 6 with methyl 2-(dimethoxymethyl)benzoate **2** under acidic conditions to afford the corresponding benzyl 2-deoxy-4,6-*O*-(2-methoxycarbonyl)benzylidene-2-phthalimido-β-D-glucopyranoside **3** ($[\alpha]_D^{20}$ = +33.8°, c = 3.1, $CHCl_3$) in 70% yield.[#] Compound **2** is readily available from 2-formyl benzoic acid.[27] The 2-methoxycarbonylphenyl group adopts an equatorial position in **3** as was evident from its NMR spectra which showed characteristic shifts of 6,30 ppm for the acetal hydrogen atom and 98,6 ppm for the acetal carbon atom. Next, compound **3** was benzylated at position 3 with benzyl bromide and sodium hydride in DMF to give **4** ($[\alpha]_D^{20}$ = +18.5°, c = 2.8, $CHCl_3$) in 65% yield. This step is somewhat crucial because an excess of sodium hydride should be avoided in order to suppress saponification of the ester and phthalimido groups.[14] Thus, glycoside **3** was first completely deprotonated with an equimolar amount of sodium hydride in DMF at 0°C followed by addition of benzyl bromide and stirring at room temperature until TLC indicated that all starting was consumed. Selective saponification of the methyl ester group in **4** to give **5** ($[\alpha]_D^{20}$ = +15.8°, c = 1.9, $CHCl_3$) was achieved in 82% yield by refluxing the latter with an excess of lithium iodide in pyridine.[28]

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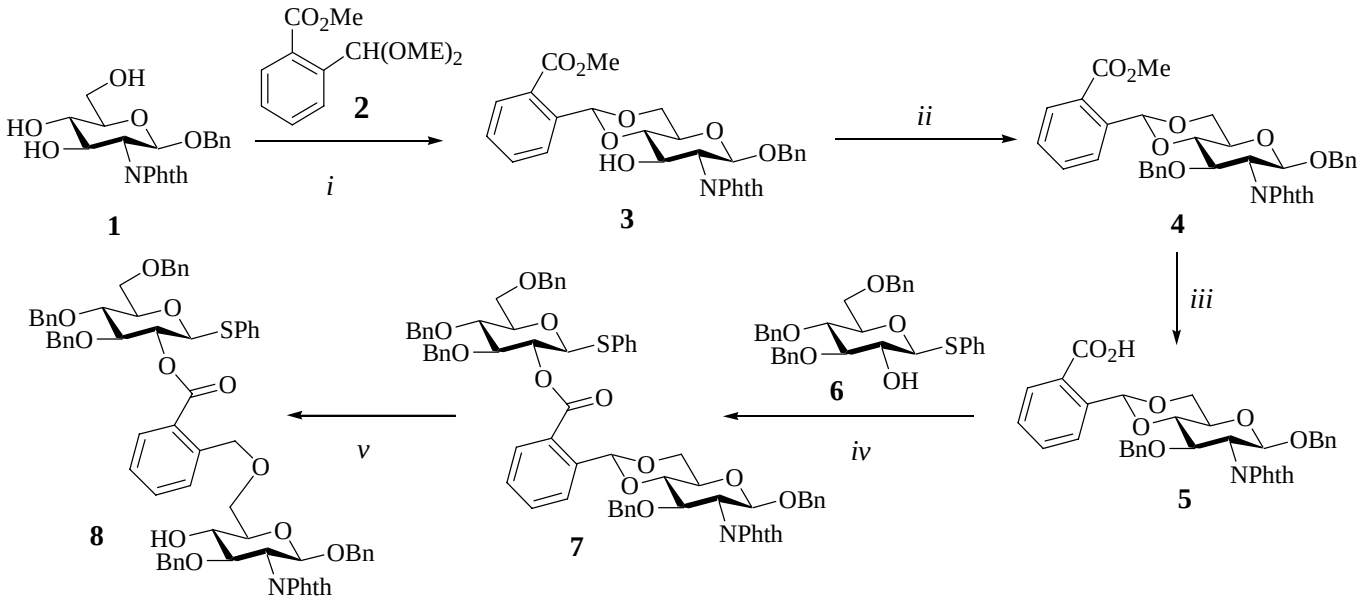
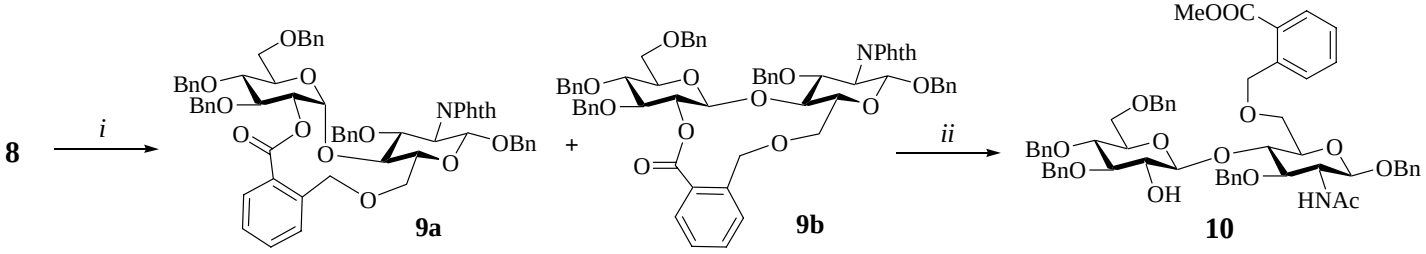
[#] All compounds were fully characterized by NMR and MS and gave satisfactory elemental analyses.



Scheme 1. (i) 1 eq. **1**, 3 eq. **2**, 0,1 eq. *p*-TosOH, DMF, 25°C, 24 h, 70% **3**. (ii) a) 1 eq. **3**, 1,1 eq. BnBr, 1,1 eq. NaH, DMF, 25°C, 3 h, 65% **4**. (iii) 1 eq. **4**, 4 eq. LiI, pyridine, reflux, 3 d, 82% **5**. (iv) 1 eq. **5**, 1 eq. **6**, 1 eq. DCC, cat. DMAP, CH_2Cl_2, 25°C, 15 h**,** 70% **7**. (v) 1 eq. **7**, 12 eq. $NaCNBH_3$, HCl in Et_2O, THF, 25°C, 5 h, 89% **8**.

As the glycosyl donor we chose phenyl 1-thio-3,4,6-tri-O-benzyl-β-D-glucopyranoside **6**.[29] Condensation of the latter with **5** applying dicyclohexyl carbodiimide (DCC) according to the procedure of Hassner[30] yielded the linked glycoside **7** ($[\alpha]_D^{20}$ = +74.5°, c = 1.0, $CHCl_3$) in 70%. Next, the benzylidene acetal of **7** was regioselectively opened with $NaCN(BH_3)$ under acidic conditions[31] to afford **8** ($[\alpha]_D^{20}$ = +16.7°, c = 1.8, $CHCl_3$) in 89% yield. It is noteworthy that the regioselective reductive ring opening proceeds more smoothly here than was previously observed for unsubstituted benzylidene acetals.[1-14] This might be attributed to an anchimeric assistance of the ortho-carboylate during opening of the cyclic acetal as was observed in similar hydroxycarbonyl-benzylidene acetals of cyclohexan-1,2-diols.[32] Further studies on the application of alkoxycarbonyl-benzylidene groups for regioselective protecting strategies of glycosides are currently in progress and will be published elsewhere.

Intramolecular glycosylation of prearranged glycoside **8** was achieved by activation of the phenylthio group of the glucose moiety with N-iodosuccinimide (NIS) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) as previously described.[5,13,14] In sharp contrast to the corresponding intramolecuar glycosylation of an identical prearranged glucosyl donor glucosamine acceptor pair linked by a succinate tether compound **8** afforded the α(1,4)-linked disaccharide **9a** ($[\alpha]_D^{20}$ = +68.2°, c = 1.7, $CHCl_3$) in 12% and the β(1,4)-linked disaccharide **9b** ($[\alpha]_D^{20}$ = +31.1°, c = 1.7, $CHCl_3$) in 59% yield, respectively. Previously, the succinate tethered counterpart afforded solely the α(1,4)-linked disaccaride.[5]



Scheme 2. (i) 1 eq. **8**, 5 eq. NIS, 0,5 eq. TMSOTf, CH_2Cl_2, 0°C, 15 min., 12% **9a**, 59% **9b**. (ii) a) 1 eq. **9b**, 16eq. $N_2H_4 \cdot H_2O$, EtOH (95%), reflux, 6 h; b) 45 eq. Ac_2O, pyridine, 25°C, 20 h; c) cat. NaOMe, MeOH/toluene 1/1, 25°C, 12 h, 40% **10**.

Both anomers **9a** and **9b** were unambiguously assigned by NMR spectroscopy.[33-35] While **9a** showed coupling constants for the anomeric center of the glucose moiety of $J_{H1',H2'}$ = 3,2 Hz and $J_{C1',H1'}$ = 174,2 Hz, the β-anomer **9b** showed $J_{H1',H2'}$ = 8,0 Hz and $J_{C1',H1'}$ = 158,7 Hz, respectively. The found anomeric ratio for intramolecular glycosylation of **8** (α/β = 1/5) compared to the selectivity of the corresponding succinate tethered counterpart (α/β = 1/0)[5] can be attributed to the increased conformational stiffness of the *o*-methylbenzoate tether here. Similar observations have been previously made for other intramolecular glycosylations.[5,14]

Finally, disaccharide **9b** was subsequently *N*-deprotected and regioselectively ring opened at the ester moiety of the tether by hydrazinolysis followed by *N*-acetylation with acetic anhydride (Ac_2O) in pyridine and methanolysis under alkaline conditions to afford **10** ($[\alpha]_D^{20}$ = +35.5°, c = 2.0, $CHCl_3$) in 70% overall yield. Disaccharide **10** can be further glycosylated at position 2' for convenient preparation of higher oligosaccharides.

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