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Intramolecular Glycosylation of Prearranged Glycosides Part 5. α-(1→4)-Selective Glucosylation of Glucosides and Glucosamines

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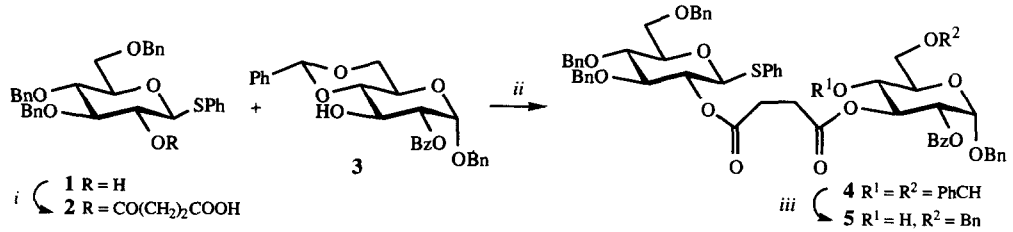
Abstract: The intramolecular (1 →4) glucosylation of partially protected alkyl glucosides and glucosamines with phenyl 1-thioglucoside that is preconnected *via* its position 2 by a succinyl spacer to positions 3 of the glucosyl acceptor affords the α-linked disaccharides. The anomeric selectivity depends on the stereochemistry of the donor-acceptor-interaction and is not governed by neighboring group participation. In contrast, connecting the glucosyl donor by the succinyl bridge to position 6 of the glucosamine acceptor results in an α/β-mixture of the corresponding disaccharides upon intramolecular glycosylation. © 1997 Elsevier Science Ltd.

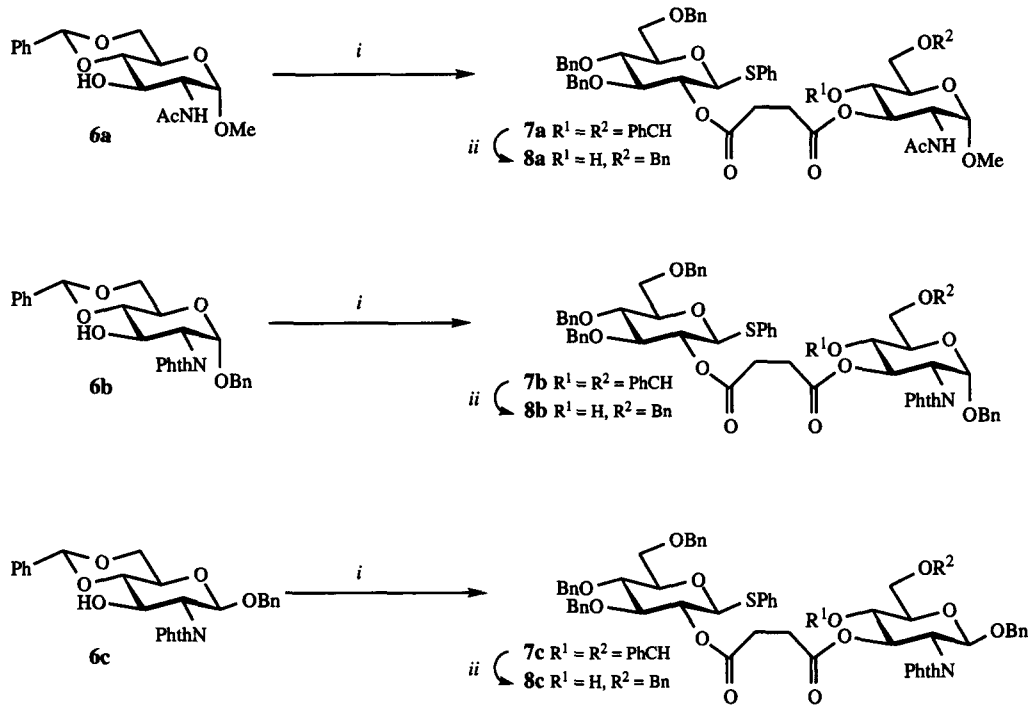
Previously, it was shown for rhamnosylations of alkyl glycopyranosides that the anomeric selectivity of the glycosylation reaction is strongly influenced by a bridging spacer group attached to various positions of the rhamnosyl donor and the glycoside acceptor, respectively *prior* to the formation of the *O*-glycosidic bond (*i.e.*, intramolecularization of the glycosylation reaction *via* prearranged glycosides).[1,2] With this novel glycosylation strategy,[1] otherwise difficultly to establish β-(1→4)-selective L-rhamnosylations could be realized in up to 60% yield when the succinyl bridge was attached to position 2 of the donor and to position 3 of the acceptor.[1,3] It was previously speculated that a double diastereoselection may occur during ring closure of the respective prearranged glycosides which compensates the neighboring group participation of the acyl group at position 2 of the L-rhamnosyl donor and thus, leads to high yields of the corresponding β-L-rhamnosides. Therefore, the relative configuration of the succinyl-bridged donor and acceptor should strongly influence the anomeric outcome of the glycosylation reaction. This was recently supported by D-mannosylation reactions *via* prearranged glycosides where the anomeric selectivity of the condensation depended on the relative configuration of the donor-acceptor pair.[4] Here, the principle of ruling the diastereoselectivity of glycosylation reactions by the strategy of prearranged glycosides is further extended to D-glucosylations of simple alkyl D-glucopyranosides and D-glucosamines.

As glucosyl donor part, phenyl 1-thio-β-D-glucopyranoside **2** was chosen which was prepared as previously described in the L-rhamno and D-manno series[1,2,4] from phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside[5] **1** in 89% yield. Next, **2** was condensed with benzyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside[1a] **3** and transferred into the prearranged glycoside **5**[6] by reductive ring opening of the benzylidene acetal[7] of intermediate **4**.



Scheme 1. *i*: 8 eq. succinic anhydride, cat. DMAP, pyridine, rt, 20h then reflux, 48h. *ii*. 1 eq. **2**, 1.1 eq. **3**, cat. DMAP, 1.5 eq. DCC, CH_2Cl_2, 0°C→rt, 1h, 88% **4**. *iii*. 10 eq. $NaCNBH_3$, HCl in Et_2O, THF, rt, 15 min., 95% **5**.

The condensation of the donor moiety **2** with alkyl glucosamine derivatives **6a**,[8] **6b**[9] and **6c**[9] was performed similarly to the preparation of compound **4**. However, due to the predominant formation of acyl urea from DCC and **2** under DMAP catalysis[10] a combination with acid catalysis[11] was applied. Thus, the succinyl linked disaccharides **7** were obtained in good yield. Final reductive ring opening as described for compound **5** afforded the prearranged glucosamine derivatives **8**.[6]

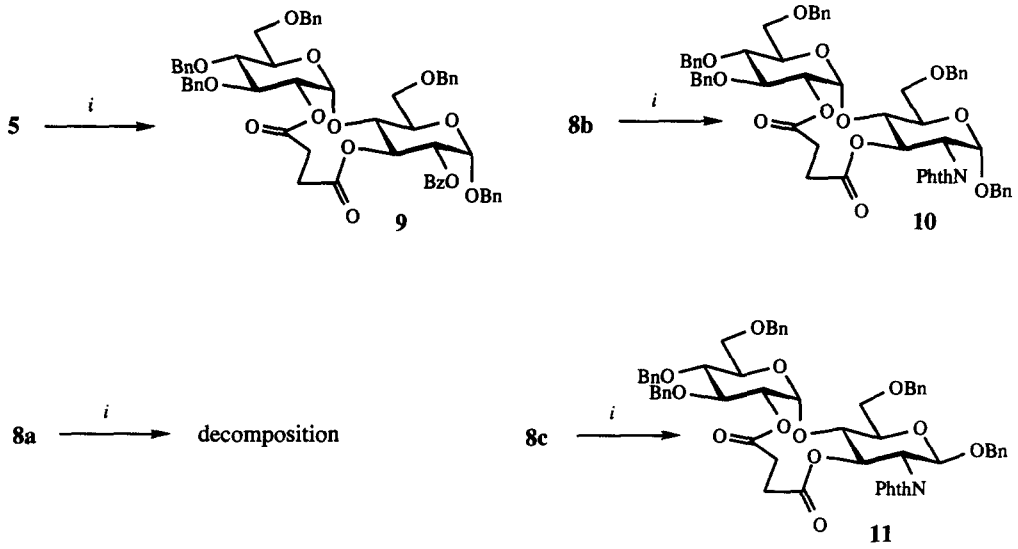


Scheme 2. *i*. 1 eq. **2**, 1.1 eq. **6**, 0.1 eq. DMAP, 0.1 eq. TosOH, 1.5 eq. DCC, pyridine, 10°C→rt, 12-24h, 72% **7a**, 69% **7b**. *ii*. 10 eq. $NaCNBH_3$, HCl in Et_2O, THF, rt, 10 min., 70% **8a**, 65% **8b**.

Rather unexpectedly, when compounds **5** and **8** were treated with *N*-iodosuccinimide and a catalytic amount of TMSOTf as previously described[1] the intramolecular ring closure afforded solely the corresponding α-(1→4)-linked disaccharides **9**[6] (80%), **10**[6] (75%) and **11**[6] (40%). No reaction occurred with compound **8a**, probably due to the presence of the acetamido group in the acceptor moiety and the known reduced nucleophilicity of position 4 in 2-acetamido-3-*O*-acetyl-2-deoxy-glucopyranosides (see below). The α-linkage in products **9** and **10** was evident from their NMR spectra which showed characteristic α-couplings at the anomeric center of the newly formed *O*-glycosidic bond ($J_{H\text{-}1',H\text{-}2'}$ = 3,7 Hz for **9**, 3.5 Hz for **10** and 3.6 Hz for **11**; $J_{H\text{-}1,C}$ = 170.3 Hz for **9** and **10** and 170.2 for **11** respectively).

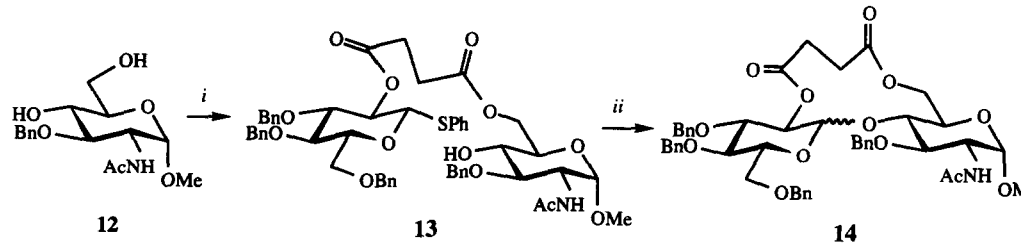
The finding that prearranged glycosides **5**, **8b** and **8c** exclusively gave the α-linked disaccharides is in contrast to previous findings of similar intramolecular glycosylations. For example, the corresponding prearranged glycoside having a mannosyl donor moiety instead of a glucosyl donor moiety, as in **5** and **8** afforded the α-linked product as well upon intramolecular (1→4)-selective glycosylation.[4] Since the anomeric outcome of all previously performed cyclizations[1,3,4] of prearranged glycosides strongly depended on the relative configuration of the linked monosaccharides it was thus expected for compounds **5** and **8** (*i.e.*, D-

glucosyl donor instead of a D-mannosyl donor) to afford a higher content of the corresponding β-(1→4)-linked disaccharide. Therefore, further examples were needed in order to show if a double diastereoselection is operative during intramolecular glycosylation of prearranged glycosides and to predict unambiguously the anomeric outcome of this novel glycosylation strategy.



Scheme 3. *i*: 5 eq. NIS, cat. TMSOTf, MeCN, -30°C→0°C, 30 min, 80% **9**, 75% **10**, 40% **11**.

That the relative configuration of the succinyl linked donor and acceptor still plays an essential role for the diastereoselectivity of the glycosylation was demonstrated for compound **13**. Here, the donor moiety **2** was linked to position 6 of methyl 2-acetamido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside[12] **12**, the intermediate prearranged glycoside **13** exhibited an inverted relative configuration compared to compound **8** and should afford an higher β-content. Furthermore, position 3 of the acceptor part is now benzylated and thus, the reactivity of position 4 is enhanced and should enable the glycosylation of this position. Indeed, cyclization of **13** gave a 40:60 mixture of the α/β-linked disaccharides **14**.[6] The somewhat lower yield of **14** (49%) was due to the formation of a less favoured[1b] 12-membered ring compared to compounds **9**-**11** which gave 11-membered rings. The anomeric configuration of **13** was unambiguously assigned by NMR spectroscopy ($J_{H-1',H-2'}$ = 3,5 Hz for **14**α and 7.5 Hz for **14**β; $J_{H-1,C}$ = 171.5 Hz for **14**α and 157.8 Hz for **14**β, respectively).



Scheme 4. *i*. 1 eq. **2**, 1.1 eq. **12**, 0.1 eq. DMAP, 0.1 eq. TosOH, 1.5 eq. DCC, pyridine, 100°C, 12h, 65% **13**. *ii*: 5 eq. NIS, cat. TMSOTf, MeCN, -40°C, 30 min, 20% **14**α, 29% **14**β.

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6. All new compound gave satisfactory elemental analyses. Selected physical data. **5**: $[\alpha]_D^{20}$ = +22.5 (*c* = 1.0, $CHCl_3$); **8a**: mp (EtOH) 185 °C; $[\alpha]_D^{20}$ = +22.0 (*c* = 1.0, $CHCl_3$); **8b**: $[\alpha]_D^{20}$ = +84.5 (*c* = 1.0, $CHCl_3$); **8c**: $[\alpha]_D^{20}$ = -10.4 (*c* = 1.0, $CHCl_3$); **9**: $[\alpha]_D^{20}$ = +53.5 (*c* = 1.0, $CHCl_3$); ^1H NMR: δ = 5.86 (d, 1H, J = 3.7 Hz, H-1'), 5.84 (d, 1H, J = 3.5 Hz, H-1); ^{13}C NMR: δ = 100.1 (C-1'), 95.0 (C-1); **10**: $[\alpha]_D^{20}$ = +118.0 (*c* = 1.0, $CHCl_3$); ^1H NMR: δ = 5.24 (d, 1H, J = 3.5 Hz, H-1'), 4.93 (d, 1H, J = 3.9 Hz, H-1); ^{13}C NMR: δ = 100.0 (C-1'), 96.4 (C-1); **11**: $[\alpha]_D^{20}$ = +15.8 (*c* = 1.0, $CHCl_3$); ^1H NMR: δ = 5.39 (d, 1H, J = 8.4 Hz, H-1), 5.18 (d, 1H, J = 3.6 Hz, H-1'); ^{13}C NMR: δ = 100.1 (C-1'), 97.2 (C-1); **13**: mp (ethyl acetate/hexane) 189 °C; $[\alpha]_D^{20}$ = +25.7 (*c* = 1.0, $CHCl_3$); **14α**: $[\alpha]_D^{20}$ = +43.4 (*c* = 1.0, $CHCl_3$); ^1H NMR: δ = 4.68 (d, 1H, J = 2.9 Hz, H-1), 4.51 (d, 1H, J = 3.5 Hz, H-1'); ^{13}C NMR: δ = 95.1 (C-1), 93.3 (C-1'); **14β**: $[\alpha]_D^{20}$ = +27.5 (*c* = 1.0, $CHCl_3$); ^1H NMR: δ = 4.71 (d, 1H, J = 2.8 Hz, H-1), 4.41 (d, 1H, J = 7.5 Hz, H-1'); ^{13}C NMR: δ = 102.2 (C-1'), 100.5 (C-1).
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