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Prearranged glycosides. Part 14: Intramolecular glycosylation of non-symmetrically tethered glycosides

Thomas Ziegler,* Gregor Lemanski and Jürgen Hürttlen

Institute of Organic Chemistry, University of Cologne, Greinstraße 4, D-50939 Cologne, Germany

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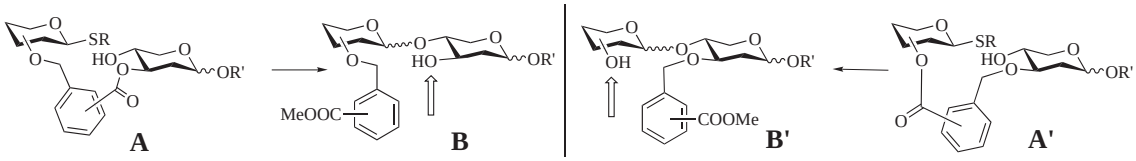
Abstract—Partially benzylated 1-thio-β-D-glucopyranosides were tethered via position 2 to position 3 of methyl α-D-glucopyranosyl and benzyl 2-phthalimido-2-deoxy-β-D-glucopyranosyl derivatives, respectively, by non-symmetrical *o*-, *m*-, and *p*-methylbenzoate linkers. Intramolecular glycosylation of these prearranged glycosides lead to the corresponding non-symmetrically tethered α-(1→4)-linked disaccharides as the exclusive or main products. The tethers were regioselectively opened by transesterification affording isomeric disaccharide acceptors which are susceptible for further elongation of the sugar chain at positions 3 and 2′, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

Intramolecular glycosylation by ring forming glycosylation reactions of tethered glycosyl donors and glycosyl acceptors (prearranged glycosides) has been shown by us[1] and others[2] to be a useful tool for the diastereoselective formation of *O*-glycosidic bonds. This strategy of intramolecular glycosylation of prearranged glycosides is especially powerful for the construction of otherwise difficult to establish β-D-mannosidic and β-L-rhamnosidic linkages[1a,e] and can be applied to oligosaccharide syntheses as well.[1h,2d] Since only symmetrical tethers have been used for this approach so far (i.e. aliphatic and aromatic dicarboxylates and xylylene groups) the deployment of non-symmetrical tethers appeared to be desirable because such tethers would allow for regioselective ring opening after the glycosylation step. Thus, it extends the applicability of this strategy to the construction of higher oligosaccharides. For example, isomeric prearranged glycosides of type **A** and **A′** tethered by benzyl carboxylates (Scheme 1) would result in saccharides **B** and **B′**, respectively, after subsequent intramolecular glycosylation and regioselective ring opening by transesterification. The latter saccharides **B** and **B′** could in turn be used directly as glycosyl acceptors for further elongation of the sugar chain. In this communication we would like to outline briefly the use of non-symmetrical tethers for some intramolecular α-glucosylation reactions as previously performed with symmetrical tethers in order to demonstrate the usefulness of this approach.

As glycosyl donors and acceptors the readily available partially benzylated 1-thio-β-D-glucosides **1**[3] and the glucoside derivatives **4**[4a] and **13**[4b] were used. First, **1a**[3a] was alkylated with *t*-butyl 2-bromomethyl benzoate[5] **2a**, followed by acidic hydrolysis of the ester group to give the corresponding glycosyl donor moiety **3a**. Similarly, 3-bromomethyl benzonitrile **2b**, and 4-bromomethyl benzonitrile **2c** were condensed with **1a** to afford 1-thio-glycosides **3b** and **3c**, respectively, after saponification of the intermediate nitriles. It should be noted that the condensation product of **1a** and 2-bromomethyl benzonitrile could not be completely sa-



Scheme 1. Intramolecular glycosylation of isomeric prearranged glycosides using non-symmetrical tethers.

* Corresponding author. Fax: +49 (0)221 470 5057; e-mail: thomas.ziegler@uni-koeln.de

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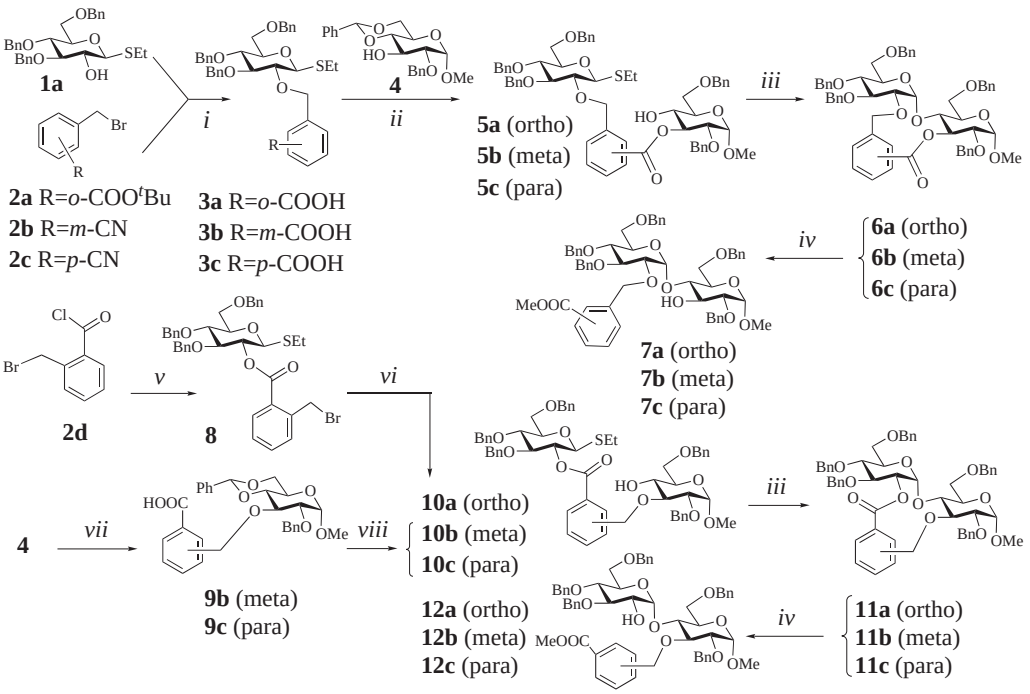
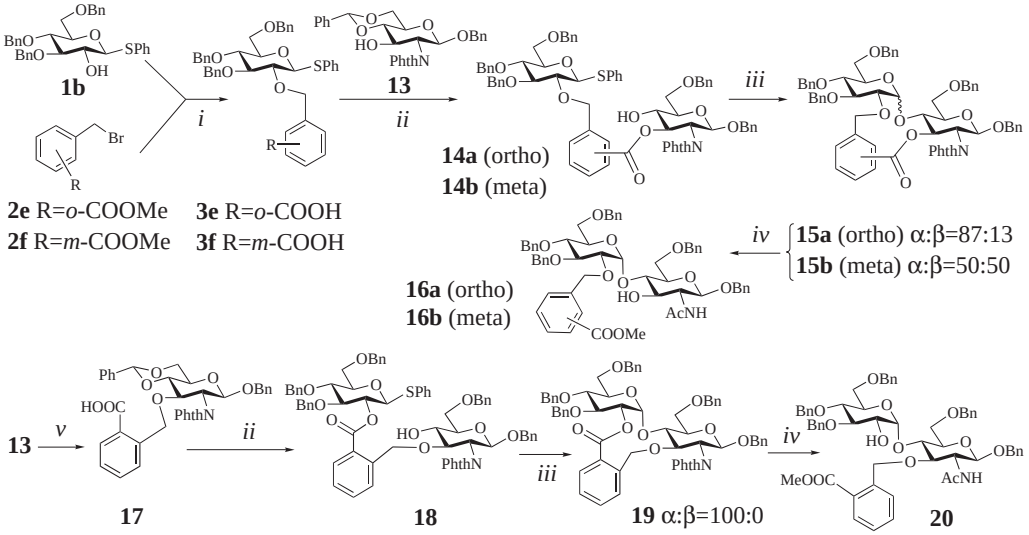
ponified and resulted in an *o*-benzamide derivative corresponding to compounds **3** (details are not shown here). Glycosides **3a**–**c** were condensed with position 3 of methyl α-D-glucopyranoside derivative **4** and the benzylidene groups of the intermediates were regioselectively opened[6] to afford the prearranged glycosides **5**[7] (Scheme 2). As was expected from previous intramolecular glucosylations of similarly tethered glycosides[1] solely α-(1→4)-linked disaccharides **6** were obtained by ring closing glycosylation of compounds **5**. Finally, regioselective opening of the non-symmetrical tether of saccharides **6** was performed by NaOMe-catalyzed transesterification in methanol to give disaccharides **7** in 80–85% yield.[7]

For the preparation of disaccharides bearing the same tethers at reversed positions of the donor and acceptor part two approaches were tested. Esterification of **1a** with 2-bromomethyl benzoyl chloride[8] afforded first intermediate **8** which was subsequently condensed with **4** followed by regioselective ring opening of the benzylidene moiety to give prearranged glycoside **10a**.[7] As outlined above for the preparation of **5**, glycosyl acceptor **4** was alkylated with **2b** and **2c**, respectively, and the benzylidene groups of intermediates **9** were once again opened to afford tethered glycosides **10b** and **10c**.[7] Both variants afforded the prearranged glycosides **10** in 21–23% overall yield in three and four steps, respectively. Final intramolecular glycosylation of the latter gave once again the corresponding α-(1→4)-linked disaccharides **11** which were transesterified to give saccharides **12** in 79–84% yield.[7] The anomeric configuration of all tethered disaccharides **6** and **11**, respectively, were unambiguously assigned by NMR spectroscopy which showed significant ^1J-coupling constants[9] of 169.6 Hz (**6a**), 167.4 Hz (**6b**), 168.3 Hz (**6c**), 168.3 Hz (**11a**), 169.1 Hz (**11b**), and 170.0 Hz (**11c**). Compared to related intermolecular 1,4-selective glycosylations with similarly protected non-tethered 1-thio-glycosides[10] diastereoselectivities of intramolecular glycosylations of **5** and **10** were significantly increased or even inverted.

In a very similar sequence, phenyl 1-thio-glucoside **1b** was alkylated with methyl 2-bromomethyl benzoate **2e** and methyl 3-bromomethyl benzoate **2f** to give directly intermediates **3e** and **3f**. Condensation of the latter with glucosamine derivative **13** followed by benzylidene ring opening of the intermediates as outlined above gave the prearranged glycosides **14**.[7] Intramolecular glycosylation of **14a** and **14b** having an *o*- and *m*-methylbenzoate tether, respectively, resulted in a anomeric mixtures of disaccharides **15** (Scheme 3).[7] Both anomers, however, could be separated by CC and the anomeric configuration was unambiguously assigned by the $^3J_{1',2'}$-coupling constants that showed 3.2 and 2.9 Hz for the α-anomers and 8.4 Hz for the β-anomers of **15a** and **15b**.[7] Compared to the related ring closing glycosylation of compound **6a** (Scheme 2) the more bulky phthalimido group must be responsible for the lower anomeric selectivity in this case. Similar observations



Scheme 2. (i) (a) **1a**+**2a**, NaH, DMF, 25°C, 1 h, (b) CF_3COOH, CH_2Cl_2, 25°C, 3 h, 82% **3a**; (a) **1a**+**2b**,**c** NaH, DMF, 25°C, 1.5 h, (b) NaOH, EtOH, Δ, 8 h, 51% **3b**, 47% **3c**. (ii) (a) **3a**–**c**+**4**, DCC, cat. DMAP, CH_2Cl_2, 25°C, 18 h; (b) $NaCNBH_3$, HCl in Et_2O, THF, 0°C, 5 min, 49% **5a**, 55% **5b**, 48% **5c**. (iii) NIS, cat. TMSOTf, CH_2Cl_2, −30°C, 15 min, 50% **6a**, 78% **6b**, 70% **6c**, 53% **11a**, 82% **11b**, 71% **11c**. (iv) NaOMe, MeOH, Δ, 4.5 h, 85% **7a**, 80% **7b**, 82% **7c**, 84% **12a**, 79% **12b**, 82% **12c**. (v) **1a**+**2d**, pyridine, 25°C, 16 h, 60% **8**. (vi) **4**+**8**, NaH, DMF, 25°C, 1 h, (b) $NaCNBH_3$, HCl in Et_2O, THF, 0°C, 5 min, 37% **10a**. (vii) (a) **4**+**2b**,**c** NaH, DMF, 25°C, 1 h, 78% **9b**, 80% **9c**. (viii) (a) **1a**+**9b**,**c**, DCC, cat. DMAP, CH_2Cl_2, 25°C, 20 h; (b) $NaCNBH_3$, HCl in Et_2O, THF, 0°C, 5 min, 53% **10b**, 44% **10c**.



Scheme 3. (i) (a) **1b**+**2e**,**f**, NaH, DMF, 25°C, 1.5 h then H_2O, 55% **3e**, 61% **3f**. (ii) (a) **3e**,**f**+**13**, **1b**+**17**, DCC, cat. DMAP, CH_2Cl_2, 25°C, 15 h; (b) $NaCNBH_3$, HCl in Et_2O, THF, 0°C, 5 min, 42% **14a**, 36% **14b**, 39% **18**. (iii) NIS, cat. TMSOTf, CH_2Cl_2, 0°C, 20 min, 76% **15a** (α-anomer), 11% **15a** (β-anomer), 19% **15b** (α-anomer), 19% **15b** (β-anomer), 67% **19**. (iv) (a) N_2H_4, EtOH, Δ, 5 h; (b) Ac_2O, pyridine, 25°C, 15 h; (c) NaOMe, MeOH/toluene, Δ, 6 h, 38% **16a**, 40% **16b**, 37% **20**. (v) (a) **13**+**2e**, NaH, DMF, 25°C, 3 h then H_2O; (b) LiI, pyridine, Δ, 4 d, 42% **17**.

have been previously made as well for symmetrically tethered glucosamine acceptors.[1d] As encountered in other cases[1,2] this example also shows the strong dependence of the anomeric diastereoselectivity of intramolecular glycosylations from the ring size. Regioselective ring opening of the tethers of saccharides **15** (only the α-anomers were used here) was achieved under carefully optimized conditions by subsequent hydrazinolysis of the phthaloyl group followed by reacetylation of the formed amine and transesterification of the benzoate as performed above. The resulting disaccharide acceptors **16** were susceptible for further elongation of the sugar chain at positions 3. The inverted regioselectivity for the partial cleavage of the tether was realized in an approach similar to that of compounds **9b** and **9c**. Alkylation of **13** with **2d**, condensation of intermediate **17** with **1b** and benzylidene ring opening gave prearranged glycoside **18**.[7] When the latter was intramolecularly glycosylated solely α-(1→4)-linked disaccharide **19** was obtained.[7] This is in contrast to the cyclizations of isomeric **14** which afforded anomeric mixtures. The dependence of the anomeric selectivity on the nature and position of the tether is evident from this observation. Final opening of the *o*-methyl benzoate tether gave disaccharide **20** which can be used for chain elongation at position 2′.[7]

The examples outlined here show that the use of nonsymmetrical tethers for intramolecular glycosylations is straightforward and allows for the efficient diastereoselective preparation of oligosaccharide acceptors. Further examples and applications of this strategy for the preparation of more complex saccharide structures are now under investigation.

Acknowledgements

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