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A combined intramolecular–intermolecular one-pot glycosylation approach for the synthesis of a branched trisaccharide

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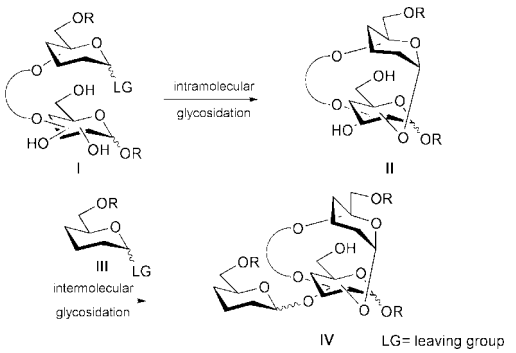
Intramolecular and intermolecular glycosidic couplings have been combined in a one-pot protocol for the synthesis of a branched trimannan.

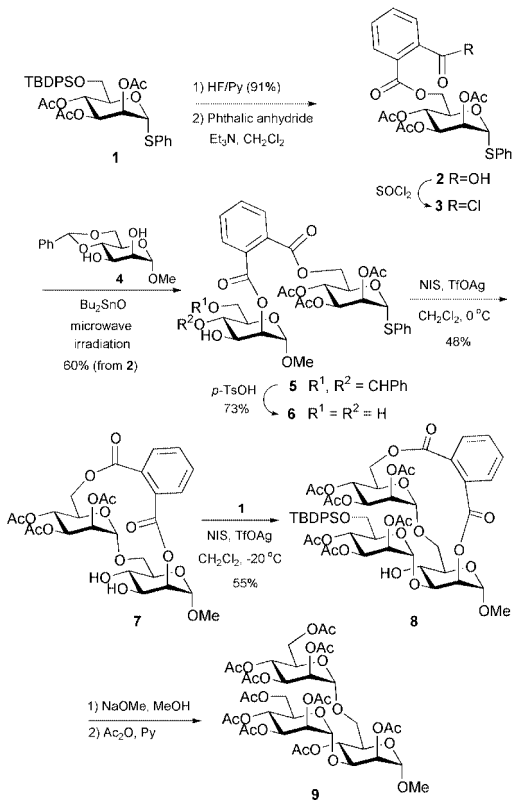
In the last few years strategies for stereocontrol in saccharide synthesis[1,2] based on intramolecular glycosidic couplings have been described,[3–15] and the rapid assembly of oligosaccharides has been addressed through a new chemoselective glycosylation strategy, the one-pot glycosylation,[16–20] which is based on reactivity differences between glycosyl donors.[21–23] Our group[8–10] has been interested in the development of an intramolecular approach for saccharide synthesis (*e.g.* **I→II**, Scheme 1), in which medium rings[8–15] rather than five-membered intermediates[3–7] are formed upon glycosidation. Here, we disclose some preliminary results of the extension of this approach for the synthesis of branched oligosaccharides by intermolecular glycosylation of an external glycosyl donor (*e.g.* **III**) onto the macrocyclic disaccharide (*e.g.* **II→IV**, Scheme 1). More interestingly, the sequence **I→IV** has also been carried out in one-pot operations, and applied to the preparation of the biologically important methyl 3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranose **9**[24] (Scheme 2).

Phenyl thioglycoside, **1**, was readily transformed into the phthaloyl derivative **2**, and its carboxylic acid function activated on treatment with $SOCl_2$ to furnish **3**. Dialkylstannilen mediated coupling[25,26] of acid chloride **3** with diol **4** gave mixed diester **5** which upon removal of the benzylidene ring led to triol **6**. Glycosylation of **6** (CH_2Cl_2, NIS, TfOAg, 0 °C) led to disaccharide **7**.† Intermolecular glycosylation of glycosyl donor **1** with **7** (CH_2Cl_2, NIS, TfOAg, −20 °C) proceeded regioselectively at *O*-3‡ to give branched trimannose derivative **8**§ (55% yield),¶ which upon deprotection and re-acetylation afforded methyl 3,6-di-*O*-(α-D-mannopyranosyl)-α-D-mannopyranose derivative, **9**.§ A one-pot sequential glycosylation strategy was next examined in which cycloglycosylation of **6** (CH_2Cl_2, TfOAg 0.3 equiv., 0.018 M, −13 °C, 20 min) was followed by addition of **1** (1.1 equiv, −27 °C, 10 min) resulting in the formation of **8** (39% yield) [Scheme 3(a)]. Reaction of premixed **1** and **6** at lower temperature (CH_2Cl_2, TfOAg 0.3 equiv., 0.014 M, −40 °C, 40 min, then −30 °C, 40 min) resulted in the isolation of pseudotrisaccharide **10** (19%) along with unreacted **6** (30%) [(Scheme 3(b)], thus showing that intermolecular glycosylation had taken place prior to the intramolecular coupling.‖ On the hypothesis that the latter result could be a consequence of the difference in reactivities between donors **6** and **1**, owing to the influence of the electron withdrawing ester at *O*-6 in compound **6** when compared with the OTBDPS substituent at *O*-6 in **1**, as recently reported by Ley and coworkers in mannose systems,[22] we decided to examine the one-pot glycosylation of **6** and **11**. Accordingly, treatment of compounds **6** and **11** with TfOAg (CH_2Cl_2, 0.03 M, TfOAg, −8 °C, 10 min) resulted in the formation of a mixture of saccharides from which the branched saccharide **12** (30% yield) was the major observed isomer [Scheme 3(b)].** The structure for trisaccharide **12** was assigned by correlation with compound **13**§ which had been prepared from trimannan **8** [Scheme 3(c)].

In our opinion, several aspects of the synthetic scheme deserve further comment: (i) tethered cyclo-glycosylation of triol **6** takes place with complete regio- and stereo-control at *O*-6 to afford disaccharide **7**; (ii) intermolecular glycosylation of donor **1** and diol **7** occurs regioselectively at *O*-3 to yield trisaccharide **8**. The regio- and stereo-selectivies in the glycosyl couplings observed in this work (i, ii) are similar to those reported by Kaur and Hindsgaul in their relevant synthesis of a related trimannan by classical non-tethered methods with minimal hydroxy group protection.[24]



Scheme 1



Scheme 2

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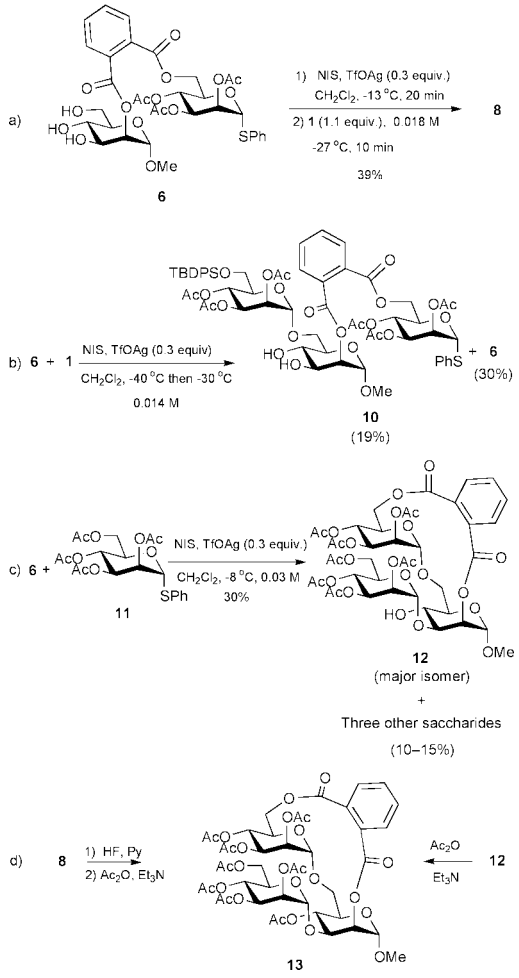

Scheme 3

Another interesting aspect of our results, with implications in the success of the synthetic scheme, is the striking difference in behavior between glycosyl donors **1** and **11**, which is illustrated by the contrast between the results in Scheme 3(b) and 3(c). Thus, while one-pot glycosylation of **6** and **1** [Scheme 3(b)] resulted in the formation of pseudotrisaccharide **10** (with the intermolecular glycosylation taking place prior to the tethered cyclo-glycosylation), the one-pot glycosylation of **6** and **11** [Scheme 3(c)] yielded trisaccharide **12**, as the major isomer formed,** where the cyclo-glycosylation had preceded the intermolecular glycosyl coupling. The tuning of donor reactivity, by changes in the protecting group at *O*-6, in mannopyranosyl donors, **1** and **11**, is thus responsible for this behavior,[22] and, in our opinion, when coupled to further tuning between intra- and inter-molecular glycosidic coupling could open a new avenue for the preparation of branched saccharides and small saccharide libraries.

The procedures outlined here, although not yet optimized, serve to illustrate a novel concept for one-pot glycosylation which relies in the kinetic acceleration of an intramolecular *versus* an intermolecular glycosidic coupling rather than in large disparities between the reactivities of different glycosyl donors. The optimization of this protocol by changes in the concentration and/or nature of the glycosyl donors is currently under study.

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Notes and references

† A minor amount of the corresponding α-1,3 derivative was also isolated 3–5%.

‡ When the reaction was carried out at 0 °C in the presence of 1.7 equiv. of glycosyl donor **1**, a tetrasaccharide resulting from the glycosylation of **1** at positions *O*-3 and *O*-4 in **8** was the only isolated compound (68%).

§ *Selected data*: for **8**: $[\alpha]_D$ −5.7 (*c* 0.5, $CHCl_3$); for **9**: $[\alpha]_D$ +17.6 (*c* 1, $CHCl_3$), API-ES positive (M^+Na^+): *m*/*z* 961.2; for **13**: $[\alpha]_D$ −35.5 (*c* 0.9, $CHCl_3$), API-ES positive (M^+Na^+): *m*/*z* 1007.5.

¶ Hydrolysis of the anomeric thiophenyl group was also observed.

‖ Other attempts to carry out the one-pot glycosylation with premixed **1** and **6** (*e.g.* CH_2Cl_2, TfOAg 0.3 equiv., 0.03 M, −13 °C, 20 min) gave complex reaction mixtures.

** Three other saccharides (10–15%) were also present in the reaction mixture, possibly resulting from the glycosidic coupling of **11** with hydrolyzed **6**.

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