A highly convergent synthesis of a branched *C*-trisaccharide employing a double SmI_2-promoted *C*-glycosylation

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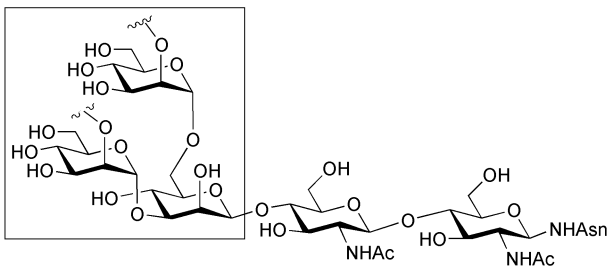
The branched *C*-trisaccharide analogue of α-D-Man-(1→3)-[α-D-Man-(1→6)]-D-Man has been synthesised by the SmI_2-mediated coupling of two mannosyl pyridyl sulfone units to a monosaccharide dialdehyde. This approach represents a highly convergent synthesis of a *C*-oligosaccharide.

C-Disaccharides, in which the interglycosidic linkage has been replaced by a methylene group, have proved to be valuable tools for studying conformational preferences of their parent *O*-glycosides both in solution and protein bound, as well as providing important insight into the mechanism of glycoside cleaving enzymes (glycosidases) owing to the inability of *C*-disaccharides to undergo hydrolysis.[1] Many synthetic approaches to these analogues have therefore been devised, but have mainly been restricted to disaccharides and not higher oligomers thereof owing to the synthetic challenge in preparing such compounds.[2,3] In previous reports, we have shown that reductive samariation of glycosyl pyridyl sulfones in the presence of a *C*-formyl branched sugar is a viable approach for the stereoselective construction of *C*-disaccharides.[4,5] The synthetic approach to these sugar mimics employs intact carbohydrate units as both *C*-glycosyl donors and acceptors, which are complementary to approaches exploited in standard *O*-glycoside synthesis. This suggested the possibility of applying this procedure for the construction of branched *C*-oligosaccharides as well, by a multiple *C*-glycosylation step of a carbohydrate unit containing more than one *C*-formyl chain. In this communication, we report on the success of this goal in the highly convergent construction of the *C*-glycoside analogue of the core region, α-D-Man-(1→3)-[α-D-Man-(1→6)]-D-Man, of the asparagine-linked oligosaccharides.

The synthetic approach to the branched *C*-trisaccharide **1** is illustrated in Fig. 1, comprising of the direct double coupling of dialdehyde **3** with two equivalents of the configurationally stable anomeric samarium species **2**, which in turn may easily be prepared *via* the *in situ* reduction of the anomeric pyridyl sulfone.[4,5] Subsequent radical-based deoxygenation of the two hydroxy groups formed would then complete this short synthesis of the protected *C*-trisaccharide.

We began the synthesis of the branched *C*-trisaccharide with the construction of the dideoxymannosyl unit **9** containing the C3 and C6 formyl groups *via* the stepwise introduction of two alkene groups at the denoted positions, as illustrated in Scheme 1.† Regioselective opening of the easily available epoxide **4** (5 steps from 1,6-anhydroglucose[6]) with excess vinylmagnesium bromide[7] and subsequent dibenzylation afforded the alkene **5** in 42% yield. In order to introduce the second alkene group at C-6, we took advantage of a recent report by Clark *et al.* in their synthetic approach to the marine polycyclic ethers of the brevetoxin and ciguatoxin family.[8] Hence, methanolysis of **5** led to the opening of the anhydro-ring affording only the methyl α-mannoside **6**, which could easily be transformed to the corresponding triflate by treatment with Tf_2O–2,6-lutidine. Alkynylation with the lithium anion of TMSacetylene in THF–HMPA then afforded the C6-alkyne branched sugar **7** (53%, 2



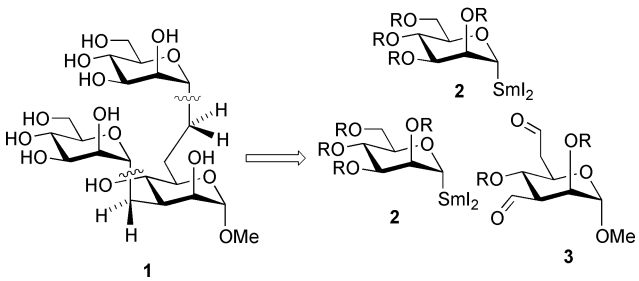
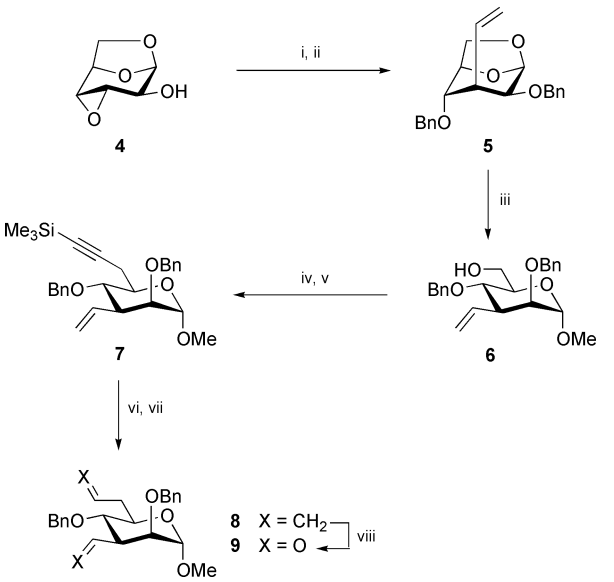


Fig. 1



Scheme 1 *Reagents and conditions:* i, 3 equiv. of $CH_2CHMgBr$, THF, 60 °C; ii, NaH, BnBr, DMF, 42% (2 steps); iii, conc. HCl in MeOH, reflux, 56%; iv, Tf_2O, 2,6-lutidine, CH_2Cl_2, −40 °C; v, $Me_3SiCCLi$, THF–HMPA, −78 °C to 20 °C, 53% (2 steps); vi, Bu_4NF, THF, 20 °C; vii, H_2, Lindlar's catalyst, quinoline, EtOAc, 20 °C, 77% (2 steps); viii, O_3, CH_2Cl_2–MeOH, −78 °C, then Ph_3P, 77%.

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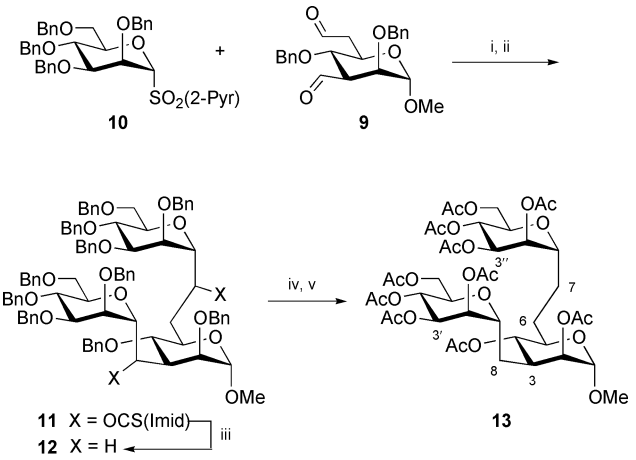

Scheme 2 *Reagents and conditions:* i, 4.7 equiv. of **10**, 10 equiv. of SmI_2, THF, 20 °C; ii, 25 equiv. of $(Imid)_2CS$, CH_3CN, reflux, 67% (2 steps); iii, 4 equiv. of F_5C_6OH, 5.2 equiv. of Ph_3SnH, AIBN (cat.), toluene, 90 °C, 53%; iv, Pd/C, H_2, MeOH–AcOH; v, Ac_2O, DMAP (cat.), pyridine.

steps), which was first desilylated and then hydrogenated with Lindlar's catalyst providing the dialkene **8** in 77% yield (2 steps). Finally, ozonolysis led to the required dialdehyde **9**.

The key coupling step of the dialdehyde with the mannosyl pyridyl sulfone **10** was achieved by quickly adding a 0.1 M solution of SmI_2 (10 equiv.) to a mixture of **9** with excess **10** (4.7 equiv.) at 20 °C leading to the immediate consumption of both reagents (Scheme 2).[4,5] Subsequent work-up led to a complex mixture of diastereomers, which was immediately subjected to a surplus of thiocarbonyldiimidazole (25 equiv.) in refluxing acetonitrile. A quick reaction was observed as monitored by TLC analysis leading to the introduction of a single thiocarbonylimidazole unit, which was most likely to occur at the sterically less encumbered carbon adjacent to C6. However, the slow evaporation of the solvent under heating finally led to the formation of a second more polar product at the expense of the first, which was identified as compound **11** as a mixture of diastereomers containing two functionalised alcohol groups (67% yield, 2 steps). The slow removal of the solvent is necessary for the successful introduction of the second thicarbonylimidazole moiety as previously observed in similar cases for the functionalisation of sterically hindered secondary alcohols.[4]

Finally, radical-based deoxygenation employing our established procedure with the F_5C_6OH–Ph_3SnH–AIBN combination in hot toluene[4] completed this short synthesis of the desired branched *C*-trisaccharide **12**, obtained as a single stereoisomer in 53% yield. Further characterisation of **12** was made by its conversion to the decaacetate **13** easily prepared by a two-step protocol involving catalytic hydrogenation and peracetylation.‡,§

In conclusion, we have successfully applied the SmI_2 promoted *C*-glycosylation procedure to the expedient and convergent synthesis of a branched *C*-trisaccharide related to the core structure of the asparagine-linked oligosaccharides. Work can now commence in studying its conformational behaviour in comparison to its parent *O*-glycoside, the investigation of which will be reported in due course.

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Notes and references

† We initially attempted several routes to introduce simultaneously the two alkene units into the easily available methyl 2,4-di-*O*-benzyl-α-D-mannopyranoside, although this synthetic pathway was unrewarding.

‡ *Selected data for* **13**: (400 MHz, C_6D_6) δ_H 5.53 (dd, 1H, *J* 6.0, 3.0 Hz, H3′), 5.48 (dd, 1H, *J* 8.8, 3.6 Hz, H3″), 5.45 (dd, 1H, *J* 8.8, 7.6 Hz, H4″), 5.38 (dd, 1H, *J* 3.6, 3.2 Hz, H2″), 5.28 (dd, 1H, *J* 6.4, 3.0 Hz, H2′), 5.25 (dd, 1H, *J* 2.4, 1.6 Hz, H2), 5.23 (dd, 1H, *J* 10.4, 9.2 Hz, H4), 5.17 (dd, 1H, *J* 6.0, 4.8 Hz, H4′), 4.72 (dd, 1H, *J* 11.6, 7.2 Hz, H6a′), 4.64 (d, 1H, *J* 1.6 Hz, H1), 4.48 (dd, 1H, *J* 12.0, 7.2 Hz, H6a″), 4.16 (ddd, 1H, *J* 7.6, 6.4, 4.8 Hz, H1′), 4.04 (dd, 1H, *J* 12.0, 2.8 Hz, H6b″), 4.00 (m, 2H, H5′, H6b′), 3.95 (ddd, 1H, *J* 10.4, 3.6, 3.2 Hz, H1″), 3.89 (ddd, 1H, *J* 7.6, 7.2, 2.8 Hz, H5″), 3.69 (ddd, 1H, *J* 9.2, 9.2, 2.8 Hz, H5), 2.96 (s, 3H, OMe), 2.54 (m, 1H, H3); HR-MS (ES) calcd for $C_{41}H_{58}O_{24}$ (*M* + Na): 957.3215, found 957.3216.

§ The stereochemistry at C1 for both of the non-reducing sugars in **13** was assigned to the α-configuration, based on the similar coupling patterns observed for the H1′ and H1″ protons compared to those observed in the *C*-disaccharides of α-D-Man-(1→3)-D-Man and α-D-Man-(1→6)-D-Man. In addition, all previous reactions performed with the mannosyl pyridyl sulfone **10** have led only to the formation of α-*C*-mannosides.

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