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Selective radical synthesis of β-*C*-disaccharides

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Abstract—Several β-*C*-disaccharides have been selectively synthesized by radical cyclization of two temporarily tethered functionalized monosaccharides. In this process, intramolecular addition of a carbohydrate-derived radical onto an anomeric exomethylene group, followed by axial hydrogen addition, resulted in β stereochemistry. © 2001 Published by Elsevier Science Ltd.

C-Di and oligosaccharides are defined as close counterparts of natural di- or oligosaccharides in which the interglycosidic oxygen atom has been replaced by a methylene group or a substituted methylene group, such as hydroxymethylene. These non-natural mimetics, together with the easily available synthetic thiooligosaccharides,[1] should conserve the global geometry of the natural structure,[2] but contain a glycosidic linkage resistant to enzymatic cleavage. They are thus well qualified as stable potential surrogates of biologically active oligosaccharides or, more generally, as attractive new tools in glycobiology.

The first report on the chemical preparation of a *C*-disaccharide appeared in 1983,[3] and a great deal of attention has since then been devoted to their synthesis.[4] We have developed[5] over the years an entry to *C*-disaccharides based on a 8 or 9 *endo-trig* radical cyclization from two tethered monosaccharides. In this process, the critical carbon–carbon bond formation resulted from the initial attack of an anomeric radical onto a non-anomeric exomethylene double bond. An α-selectivity has generally been observed in this process,[6] which parallels the one observed in the intermolecular version.[7]

Hydrogen abstraction by anomeric radicals is known to selectively occur axially.[8] This suggests that addition of a carbohydrate-derived radical onto an anomeric exomethylene group ('exoglycal'), followed by preferred axial hydrogen abstraction by the generated anomeric radical, should lead to the desired β-stereochemistry, as shown in Fig. 1. Although intermolecular nucleophilic radical addition onto an enol ether is not favored, several examples of successful intramolecular trapping of this type have been reported.[9] We would like to report on the materialization of this so-called reversed strategy.

The previously reported 1-exomethylene *gluco* and *galacto* saccharides **5**[10] and **6**[11] were alternatively synthesized from the known benzylated orthoesters **1**[12] and **2**,[13] as shown in Scheme 1. Mild aqueous acetic acid selective opening of the orthoester function,[14] followed by PCC oxydation[15] of the resulting hemiacetal, gave the corresponding lactones **3** and **4**.[16] Chimioselective[17]

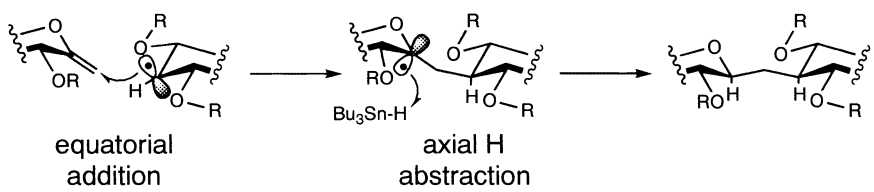

Figure 1.

Keywords: radicals; cyclization; carbohydrate mimetics; stereocontrol.

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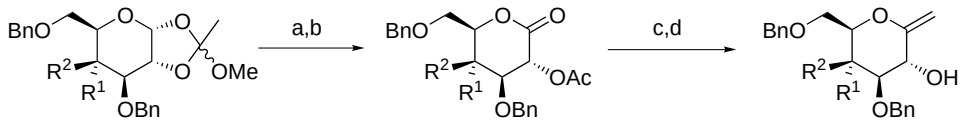


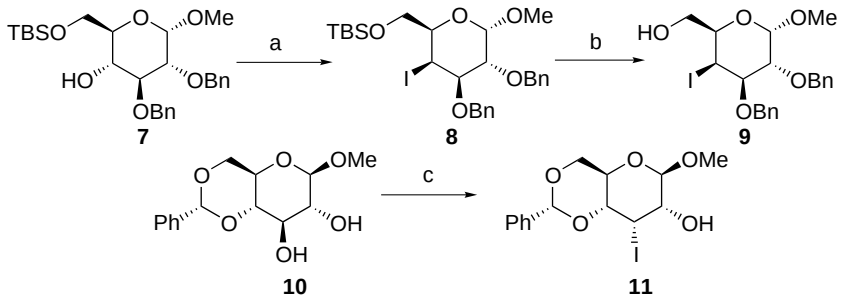
1 R^1=OBn, R^2=H
2 R^1=H, R^2=OBn
3 R^1=OBn, R^2=H
4 R^1=H, R^2=OBn
5 R^1=OBn, R^2=H
6 R^1=H, R^2=OBn

Scheme 1. *Reagents and conditions*: (a) AcOH, H_2O, 20°C (**1**), or AcOH, H_2O, pyridine, 20°C (**2**); (b) PCC, 4 Å mol. sieves, CH_2Cl_2, 20°C; (c) Tebbe's reagent (1.05 equiv.), THF/pyridine 5/1, −40°C→20°C; (d) MeONa, MeOH, 20°C (**5**, 52% from **1**), or K_2CO_3, MeOH, 20°C (**6**, 33% from **2**).

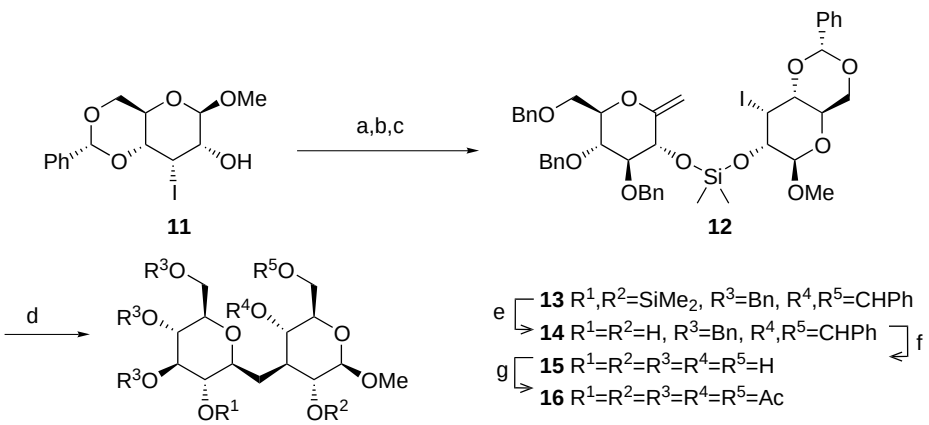
Tebbe methylenation[18] of the carbonyl function of the lactone, followed by deacetylation, afforded a new approach to the 'exoglycals' **5** and **6**. In these two compounds, the secondary hydroxyl group will be used for the anchoring to another saccharide and the cyclic enol ether as a radical acceptor.

Alkyl iodides are frequently used for radical carbon–carbon coupling reactions and, being easily and selectively prepared from saccharides,[19] we have selected them as progenitors of the radical donors. In our strategy, the iodosugars should also bear a free hydroxyl group for temporary attachment to the previously prepared exoglycals. The iodide **9**[20] was easily prepared from the known[21] secondary alcohol **7**, through the iodide **8**,[22] as shown in the self-explanatory Scheme 2. The other selected known iodide was **11**, selectively synthesized from the known diol **10**,[23] according to Samuelsson et al.[24]

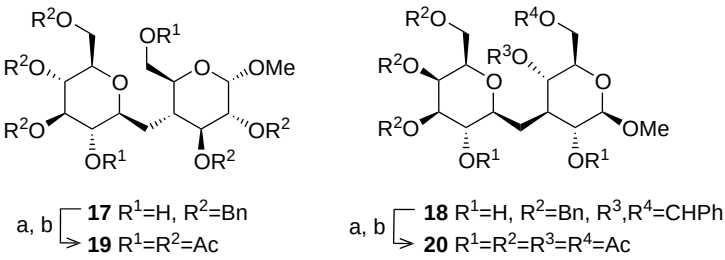
In a typical experiment (see Scheme 3), the radical donor **11** was connected to the radical acceptor **5** through a silaketal tether, following the procedure previously developed by us.[5] Tributyltinhydride mediated 8-*endo*-*trig* radical cyclization of compound **12** gave, after detethering of the non isolated intermediate **13**, the protected *C*-disaccharide **14** in 37% overall yield (from starting materials **5** and **11**). A clear-cut ^1H NMR analysis was achieved on the peracetate **16**,[25] obtained after hydrogenolysis to compound **15**, followed by peracetylation. Two asymmetric centers have been created in the condensation. The β stereochemistry is the one expected based on the previous premises. The stereochemistry of the other stereogenic center was not unexpected as it is known[26] that equatorial substituents adjacent to the radical center favor equatorial addition of cyclohexyl and non-anomeric hexopyranosyl radicals (Fig. 1). The *C*-laminaribioside **15** is of potential biological interest as it mimics the repeating disaccharide



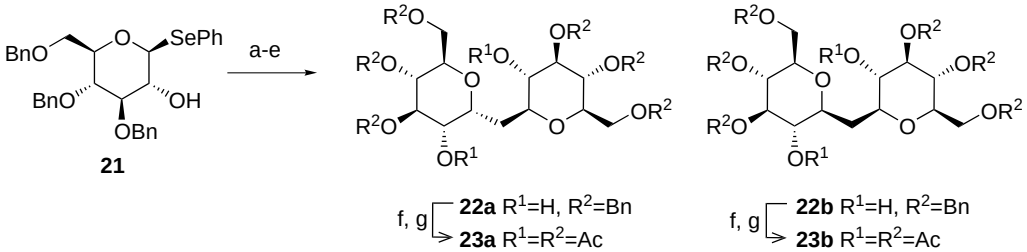
Scheme 2. *Reagents and conditions*: (a) PPh_3, I_2, imidazole, toluene, reflux, 82%; (b) CSA, MeOH, 20°C, 94%; (c) PPh_3, I_2, imidazole, toluene, 70°C, 68%.



Scheme 3. *Reagents and conditions*: (a) BuLi, THF; (b) Me_2SiCl_2; (c) **5**, DMAP, THF; (d) Bu_3SnH, AIBN, syringe-pump 17 h, toluene, reflux; (e) TBAF, THF, 37% from **11**; (f) H_2, Pd/C, MeOH; (g) Ac_2O, pyridine, 99% from **14**.



Scheme 4. *Reagents and conditions*: (a) H_2, Pd/C, MeOH; (b) Ac_2O, pyridine, 78% from **17** and 90% from **18**.



Scheme 5. *Reagents and conditions*: (a) BuLi, THF; (b) Me_2SiCl_2; (c) **5**, DMAP, THF; (d) Bu_3SnH, AIBN, syringe-pump 17 h, toluene, reflux; (e) TBAF, THF, 44% from **21** (**22a**/**22b** ~ 1); (f) H_2, Pd/C, MeOH; (g) Ac_2O, pyridine, 99% (from **22a** or **22b)**.

unit of fungal β-(1→3)-glucans, which have antitumoral and immunomodulating properties.

Following the same methodology, connection of compounds **5** and **9** afforded the *C*-cellobioside derivative **17** (17% overall yield), while the temporary tethering of saccharides **6** and **11** led to a protected *C*-mimic **18** of Gal-β-(1→3)-Glc (24% overall yield) (Scheme 4). The structure was again easily assigned after conversion into the peracetates **19**[27] and **20**,[28] respectively.

Finally, the exoglucal **5** was used to synthesize *C*-trehaloses. After tethering with the known[29,5a] phenyl *Se*-glycoside **21**, followed by cyclization and desilylation, an equimolar mixture of two *C*-disaccharides **22a** and **22b** was obtained, in 44% overall yield (Scheme 5). After separation, hydrogenolysis and acetylation, these two compounds have been identified as known[30] α,β-*C*-trehalose **23a** and β,β-*C*-trehalose[31] **23b**. We believe the loss of selectivity in this case is due to non-selective trapping of initial radical by the double bond, the H-abstraction by newly generated anomeric radical being probably as selective as in the former examples. This result is consistent with the absence of selectivity observed in another 8-*endo*-*trig* cyclization with the same radical precursor.[5a]

In conclusion, whereas our original procedure[5] often delivered α-*C*-disaccharides, this reversed version predictably provides β-*C*-disaccharides and enlarges the synthetic potential of the tether approach.

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