Iterative, orthogonal strategy for oligosaccharide synthesis based on the regioselective glycosylation of polyol acceptors with partially unprotected *n*-pentenyl-orthoesters: further evidence for reciprocal donor acceptor selectivity (RDAS)

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An efficient iterative, orthogonal protocol based on the regioselective glycosyl coupling of D-mannose polyols with, partially unprotected, *n*-pentenyl orthoester donors permits the synthesis of linear and branched oligosaccharides with minimal protecting group tampering.

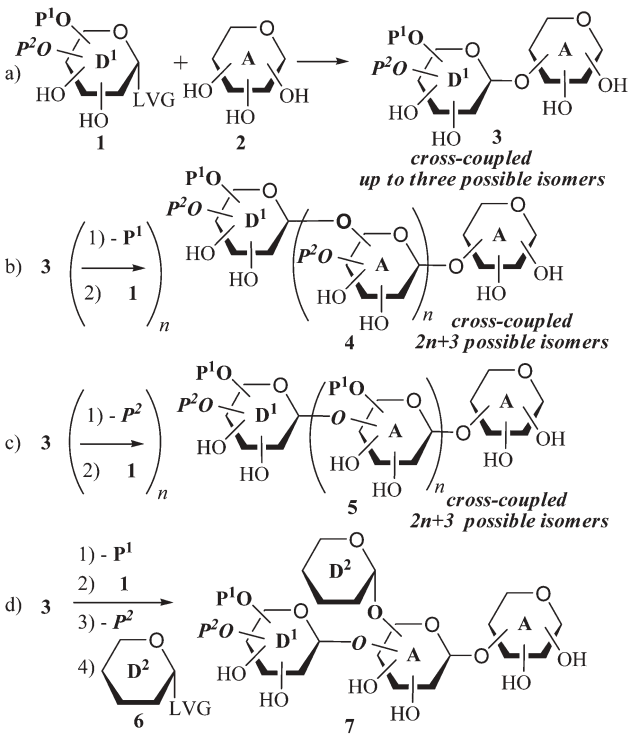
Oligosaccharide synthesis, commonly recognized as a difficult task,[1,2] is usually complicated by the cumbersome protection–deprotection steps required to expose only one hydroxyl group (in the glycosyl acceptor) to the glycosyl donor in the glycosidation event.[2] This issue, however, has recently been eased by refinements in the area of regioselective glycosyl couplings.[3,4] Thus, in some processes a diol acceptor can be exposed to a glycosyl donor to yield a single disaccharide, which could be further coupled with an additional glycosyl donor to produce a trisaccharide.[5] During the last few years our research groups have been interested in the development of regioselective glycosidation protocols which would obviate tedious protection–deprotection steps.[6,7]

There are, however, scarce examples of glycosylations in which the glycosyl donor has itself one or more free hydroxyl groups.[8,9] In this context, we have recently turned our attention to glycosylation strategies of glycosyl donors with free hydroxyl groups in regioselective glycosylations of polyol acceptors, which will result in a reduced number of protection–deprotection steps and would simplify the preparation of the monosaccharides required for glycosyl assembly. Such a process would demand an exquisite regioselectivity to avoid not only the formation of cross-glycosylated isomers but also that of saccharides resulting from self-coupling of the glycosyl donor.

Along these lines, we have been interested in the viability of the strategy outlined in Scheme 1. Glycosidation of triol acceptor (**2**) with a glycosyl diol donor (**1**) could lead, provided that some regiochemical control can be exerted, to a single disaccharide (**3**) (Scheme 1a). Subsequent unveiling of an additional hydroxyl group at the non-reducing end of compound **3**, and iteration of the process could eventually lead to oligosaccharides, *e.g.* **4** (Scheme 1b). The protocol could be extended to the preparation of isomeric linear saccharides (*e.g.* **5**) if a second (orthogonal) protecting group had been present in glycosyl donor **1** (Scheme 1c). And finally, the strategy could be also of use in the preparation of branched saccharides (*e.g.* **7**) by sequential manipulation of the orthogonal protecting groups in **3** followed by glycosylation with different donors *e.g.* **1** and **6**. In this communication we disclose the implementation of the strategies postulated in Scheme 1, which have resulted in the preparation of linear penta- and hexasaccharides as well as a branched trisaccharide.

For our studies we chose *n*-pentenyl orthoester (NPOE) **8** (to represent **1**), and disaccharide **10** (to represent **3**), the latter being readily obtained by glycosidating methyl glucoside **9** with NPOE **8** (Scheme 2a). Compound **10**, which already bears two orthogonal protecting groups, was transformed into triols **11** and **12** (Scheme 2b).

The synthesis of the first linear oligosaccharide involved iterative glycosylations of triol **11**, and polyol acceptors derived therefrom, with diol donor NPOE **8** (Scheme 3). Accordingly, glycosylation of **11**, with diol donor **8** (1 equiv.)[10] took place smoothly by treatment with NBS (1.5 equiv) and



Scheme 1 Synthesis of linear and branched saccharides.

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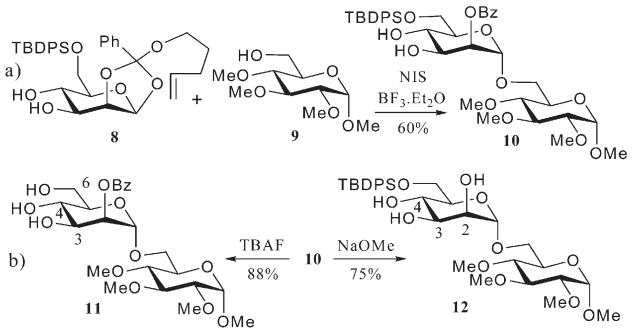
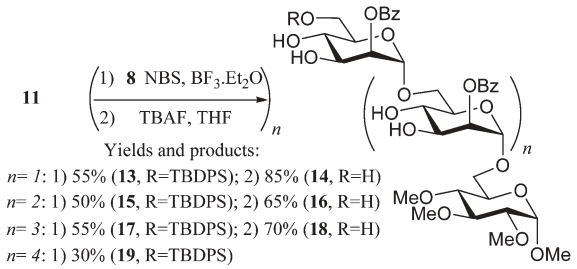


Scheme 2 Synthesis of building blocks for oligosaccharides.

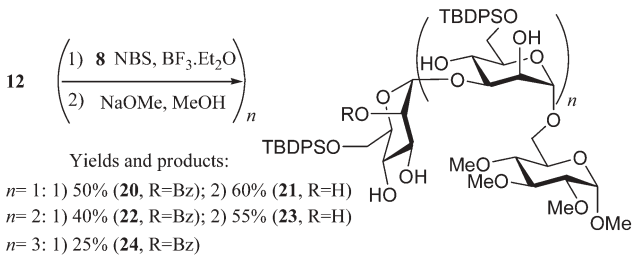


Scheme 3 Synthesis of linear saccharide **19**.

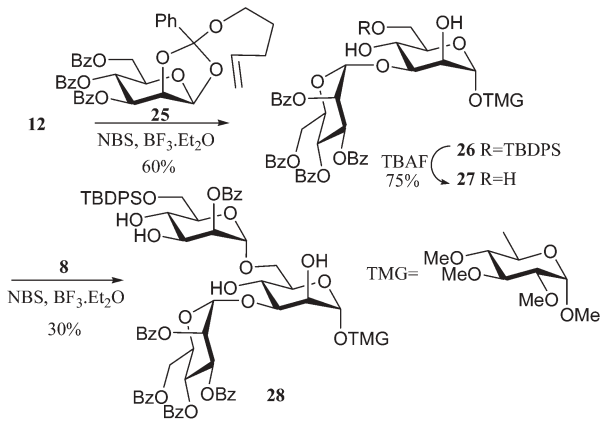
$BF_3{\cdot}Et_2O$ (0.3 equiv.) in dichloromethane in the presence of molecular sieves (4 Å) at −30 °C, and yielded trisaccharide **13** (55%) as the only observed coupling product. Deprotection of the *tert*-butyl diphenylsilyl group (TBDPS) yielded pentaol **14** in 85% yield. In the second iteration, glycosylation of **14** with **8** under our standard conditions, furnished tetrasaccharide **15** in 50% yield, and again as the only coupled product observed, and desilylation afforded tetrasaccharide **16**, bearing seven free hydroxyl groups. A third iteration (55% and 70%, respectively), resulted in the formation of pentasaccharide **18** bearing nine free hydroxyl groups. Glycosidation with diol donor **8** then gave hexasaccharide **19** in 30% yield.

The synthesis of the second linear saccharide followed a similar plan starting with 2,3,4-mannose triol **12**. Glycosylation with **8** *occurred with complete regioselectivity at O3* to give trisaccharide **20** in 50% yield (Scheme 4), debenzoylation of which yielded pentaol **21** in 60% yield. A second iteration of coupling (40%) and debenzoylation (55%) allowed the formation of tetrasaccharide **23** bearing seven free hydroxyl groups. Glycosylation with donor **8** then gave the single pentasaccharide **24** (25% yield).

Next, the value of the strategy for the formation of branched saccharides was tested. Glycosylation of **12** with NPOE **25** was



Scheme 4 Synthesis of saccharide **24**.



Scheme 5 Synthesis of branched trimannan **28**.

completely regioselective to give trisaccharide **26** (60% yield) (Scheme 5). Removal of the silyl protecting group from **26** exposed the 2,4,6-triol **27** in 75% yield, which underwent iterative glycosylation with NPOE **8**, completely regioselective, to furnish trimannan **28** in 30% yield.[11–13]

Several features of these strategies deserve further comment. We have chosen acyl and silyl substituents as orthogonal protecting groups because of their mild removal conditions. The success of the strategy is entirely based on the use of NPOEs as glycosyl donors: first because of their exquisite regioselectivity towards D-mannose 2,3,4- and 3,4,6-triols, and second because of their potential as masked 2-*O*-benzoyl acceptors. This regioselectivity was not met with armed glycosyl donors. *Thus, an armed thiophenyl glycosyl donor reacted with* **12** *to give a complex reaction mixture consisting of at least 4 different tri- and tetrasaccharides.* The NPOE results therefore prove the value of the reciprocal donor acceptor selectivity (RDAS) concept.[5]

The glycosylations described herein take place with unprecedented regioselectivity, as exemplified in Scheme 3 where NPOE **8** has to choose between *nine* free hydroxyl groups in the glycosyl acceptor **18** (cross-coupling) plus *two* of its own (self-coupling). *No other regioisomers*[10] *were observed in the glycosylation processes.* The reaction sequences were stopped with compounds **19** and **24** since product yields were below 10% due undoubtedly to poor solubility of the polyol substrates.

The strategy disclosed in this communication permits access to biologically important D-mannose derivatives with a *O*-3, or *O*-6 substitution pattern, and to trimannan derivative **28**.[14] Although some of the glycosyl couplings described in this paper proceed only with moderate yields, this protocol illustrates that "less-reactive" hydroxyl groups can remain unprotected throughout synthetic sequences for oligosaccharides, thus avoiding the need for fully protected monomers and the final deprotection step.

In summary we have reported an iterative orthogonal strategy for oligosaccharide synthesis which permits an efficient entry into linear or branched oligomannan-derivatives by coupling of partially unprotected *n*-pentenyl orthoesters with mannose-derived triols.

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