Toward solution-phase automated iterative synthesis: fluorous-tag assisted solution-phase synthesis of linear and branched mannose oligomers†

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We report herein the first synthesis of linear and branched mannose oligosaccharides using fluorous-tag assistance with reagents and FSPE protocols that are amenable to automation. The particular fluorous linker proved to maintain solubility of the growing oligosaccharide chain such that identical reaction solvent conditions and purification protocols could be used between glycosylation and deprotection reactions, thereby rendering the procedures amenable to automation.

Introduction

Access to well-defined carbohydrates is vital for structure–function studies of the role of carbohydrates in immune responses and disease pathways and for the generation of carbohydrate-based drugs.[1] Unfortunately, isolation of these carbohydrates from natural sources is tedious because oligosaccharides generally are present as complex micro-heterogeneous mixtures. Solution-based chemical synthesis has provided a range of biologically important oligosaccharides, but these very time-consuming processes still cannot feed the demand for diverse carbohydrates. To circumvent this limitation, a robust automated process, as has been developed using solid-phase methods for the commercial synthesis of DNA[2] and peptide oligomers,[3] is needed for the rapid assembly of oligosaccharides from sugar building blocks. Decades of research on solid-phase chemistry automation platforms and on solid-phase oligosaccharide synthesis employing different solid supports, sugar donors and glycosylation agents[4] have resulted in the automated solid-phase synthesis of some oligosaccharides using a modified peptide synthesizer.[5] Unfortunately, all solid-phase approaches are inherently plagued by the need for large excesses of sugar donors for reasonable reaction rates at each coupling step and sugar building blocks require many more steps for their production compared to nucleic acid and peptide building blocks.

We reasoned that use of a kind of affinity tag that would be soluble in the usual organic solvents required for glycosylation and deprotection reactions but then adsorbed selectively onto a solid support for facile purification would provide the advantages of solution-phase reaction chemistry coupled with the benefits of solid-phase purification strategies. Large lipid tags[6] and fluorous-tags[7] have been used to these ends before. Based on their smaller size and the ease of characterization of carbohydrate-based intermediates by proton NMR with fluorous- *versus* lipid-tags, we decided to investigate the limitations of using a light fluorous (C_8F_{17}) tag for the synthesis of oligosaccharides larger than the previously reported mostly mono- to trisaccharides in conjunction with finding synthetic protocols amenable to automation. The fluorous-tag was also of interest as we recently demonstrated that sugars tagged with a single C_8F_{17} tag can be used directly for carbohydrate microarray formation and screening against carbohydrate-binding proteins.[8] However, the physical properties of such fluorous-tagged protected sugars beyond disaccharides are not clear. We questioned whether the solubility properties of the growing chain would be consistent enough for implementation of a routine, and eventually automated, fluorous solid-phase extraction (FSPE) protocol. As a result of these investigations, we report herein the first synthesis of linear and branched mannose oligosaccharides using fluorous-tag assistance with reagents and FSPE protocols that are amenable to automation.

As initial targets to test the limits of a fluorous-tag-assisted approach to oligosaccharide synthesis, several oligosaccharides of D-mannose, **1–6**, (Fig. 1) were chosen. D-Mannose oligomers are found in nature as essential substructures of many bioactive glycoconjugates, such as N-glycans, fungal cell wall mannans[9] and GPI anchors,[10] and as high affinity ligands for various mannose binding proteins, for example, concanavalin A (ConA)[11] and cyanovirin N.[12] As core structures, the 3,6-branched trimannosaccharide unit (Manα1-3[Manα1-6]Man) and pentamannoside unit [(Manα1-3[Manα1-6]Man) α1-6Man3-1αMan)] decorate a range of glycoproteins. They form part of all human asparagine-linked oligosaccharides (*N*-glycans) and they are a major ConA binding epitope.[13] Recently, these core trisaccharides and pentasaccharides were shown to be highly expressed on gp120 of HIV.[14] The mannose oligomers attach to DC-SIGN, thereby leading to HIV migration from mucous membranes to the lymph system.[15] Consequently, the syntheses of these core trisaccharides and pentasaccharides have become of interest.[16,17] Linear α-(1→2)-linked mannose oligosaccharides have also been synthesized by several groups using both solution[18] and solid-phase chemistry,[19,5a] including an automated solid-phase approach, for comparison.

Results and discussion

We have reported the use of a fluorous support for the synthesis of fluorous-tagged monosaccharides and disaccharides and their direct incorporation into carbohydrate microarrays.[8] The fluorous linker **8** was designed with an alkene that could easily be modified for complete removal of the tag or for incorporation of the synthetic oligosaccharides into multivalent or other structures. Also,

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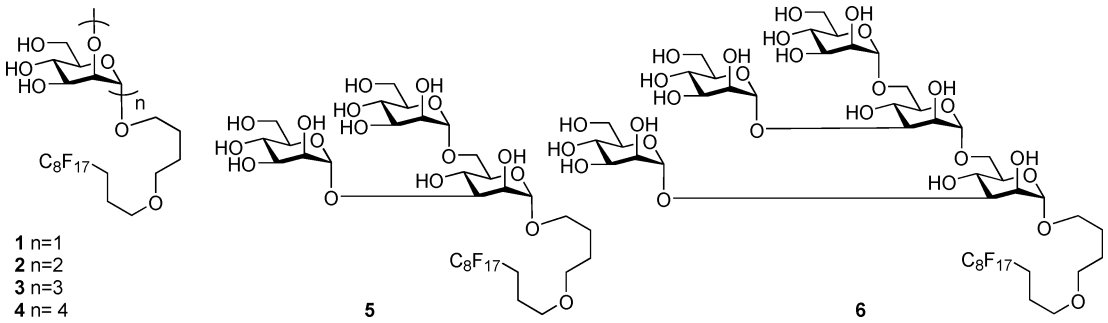
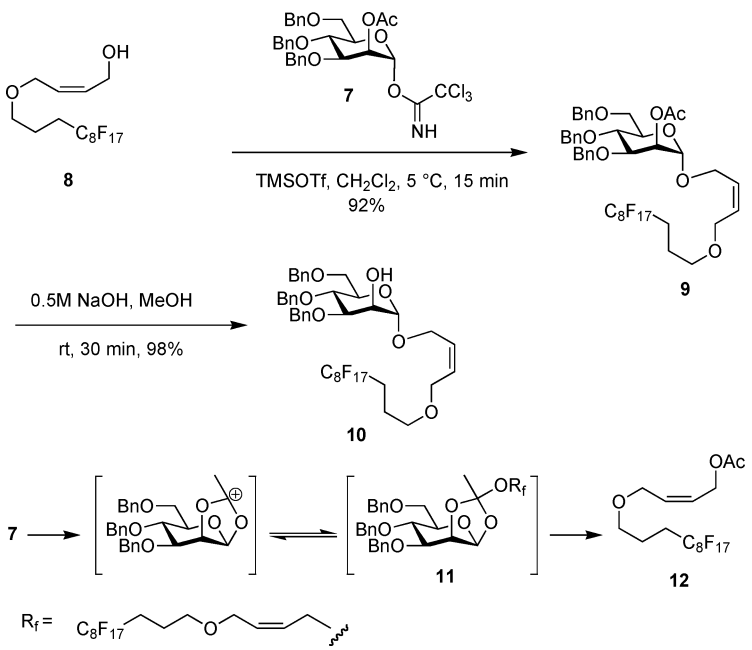


Fig. 1 Target mannose structures.

to mitigate the electron-withdrawing properties of the C_8F_{17} tag and to encourage solubility of the tagged compounds, the fluorous part of the tag is separated from the alkene by an oxygen heteroatom. In order to extend the scope of our particular fluorous-tagging method to polysaccharides and ultimately automate the approach, we decided to employ this strategy for the synthesis of linear α-(1→2)-linked mannose oligosaccharides and 3,6-modified branched mannose oligosaccharides. The linear α-(1→2)-linkages in mannose oligosaccharides are relatively simple to make and hence provide a good starting point to test the limitations of the fluorous-tag approach. Given adequate solubility properties, the fluorous-tagged compounds should be easily separated from the non-fluorous compounds by filtration of the crude product through a fluorous solid-phase extraction (FSPE) column. All glycosylations and protective group manipulations clearly then also need to be compatible with the fluorous linker as well as with standard automated reagent delivery platforms. To mimic the usual biosynthesis mode that often creates a range of capping structures on a central core, we chose to elongate the chain from the reducing end to the non-reducing end.

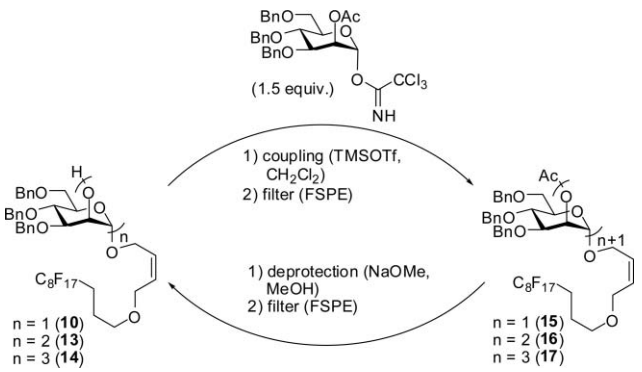
Synthesis of linear mannose oligomers

The known mannose trichloroacetimidate **7**[20] was chosen as the donor building block because it can be prepared on a multigram scale, is activated at low temperature, and bears a C2-ester functionality to control the anomeric configuration of the glycosylation reactions. Initial experiments on coupling of the fluorous linker **8**[8b] with mannose donor **7** at 0 °C resulted in the formation of fluorous-tagged mannose **9**[8b] and 30% transacetylation product **12** (Scheme 1). Transacetylation is known to be a very common side reaction in glycosylation reactions.[21] The transacetylated product is likely formed *via* an orthoester intermediate (**11**). Prior solutions to avoid formation of the transacetylation product include: (1) use of a bulky pivaloyl group instead of an acetyl,[22] (2) an increase of concentration of the glycosylation reaction,[23] and (3) an increase of temperature of the reaction to above 0 °C. When the mannose coupling was run at 5 °C, the desired glycosylated product was obtained with no transacetylated product. Deprotection of the temporary acetyl group with NaOMe–MeOH produced compound **10**[8b] in 98% yield after passing through a FSPE



Scheme 1 Synthesis of fluorous-tagged mannose.

column. In a typical glycosylation reaction, the fluorous alcohol was dissolved in dichloromethane and cooled to 5 °C. Mannose trichloroacetimidate was added as a solution in the same solvent to mimic a robotic reagent addition followed by a catalytic amount of TMSOTf in solution. The reaction was stirred for 15 min and quenched with triethylamine. The reaction mixture was concentrated and the crude product was dissolved in a minimal amount of methanol and loaded on a fluorous solid phase extraction (FSPE) column. The non-fluorous compounds were eluted by washing the column three times with 80% MeOH–water and the desired fluorous-tagged mannose product was obtained in high purity by washing the column with 100% methanol. The methanolic eluent was directly treated with 0.5 M NaOH (2 equiv.) in methanol to limit the number of time-consuming concentration steps. After 30 min at ambient temperature, the deacetylated mannose was obtained. The resulting deacylated product was purified by FSPE as before and then coevaporated with toluene. Glycosylation and deprotection steps were repeated to obtain the linear di-, tri- and tetrasaccharides respectively (Scheme 2). The linear α-(1→2)-linked mannose tetrasaccharide **17** was synthesized in 79% overall yield from the monosaccharide building block using 6 equivalents total of **7** and all intermediates could be purified using only a FSPE column. For comparison, a solid-phase automated synthesis produced a linear mannose trisaccharide in 74% yield using 60 equivalents total of glycosyl donor **7**.[5a] No problems were encountered in solubilizing or eluting the smaller or larger fluorous-tagged protected sugars in the FSPE procedures using the same solvent as the chain grew larger. In addition, all the reagents and building blocks could be added to the reactions in liquid forms in a process amenable to future automation. Interestingly, after this work was complete, a fluorous-tagged synthesis of a glucose tetramer was reported in which solubility problems were mentioned that required reaction solvent switching from methylene chloride to trifluorotoluene for the initial glycosylation.[7n] Apparently our incorporation of an oxygen spacer in the fluorous-tag rather than using only a hydrocarbon spacer is key to maintaining solubility of the tag.

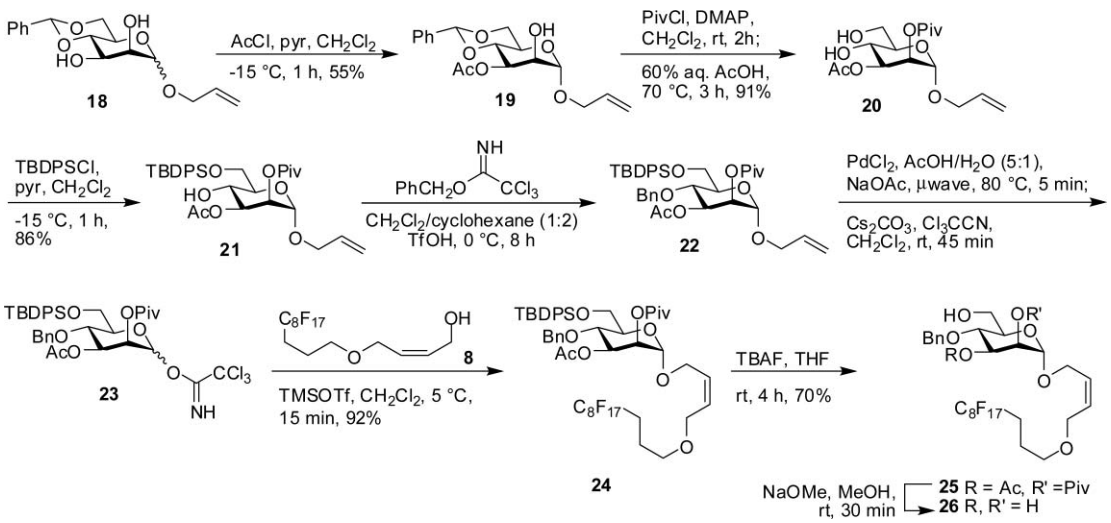


Scheme 2 Iterative synthesis of linear mannosides.

Synthesis of branched mannose oligosaccharides

After successfully achieving the synthesis of the linear mannose oligomers, we put our attention towards synthesizing branched mannose oligosaccharides to assess any differences in their behavior in the FSPE procedure. To extend the horizon of fluorous-tagged oligosaccharides, we selected mannose trisaccharide **5** and mannose pentasaccharide **6** (Fig. 1) for synthesis on fluorous support.

Trisaccharide **5** and pentasaccharide **6** require the same building block to elongate the chain at the 3- and 6-positions respectively. Two orthogonal protecting groups are required at the 3- and 6-position. Various combinations of protecting groups were explored in designing a useful building block for the branch point of the 3,6-modified mannose oligosaccharides. Acetyl groups have been reported to be removed selectively in the presence of a pivaloyl on a neighboring sugar using sodium methoxide.[24] However, it was unclear whether this reaction would be general enough to rely on such a selective deprotection scheme in an automation protocol. To test this idea, we designed a building block with an acetyl group at the 3-position, a TBDPS at the 6-position, and a pivaloyl at the 2-position for neighboring group participation to construct the desired α-linkages (Scheme 3). In



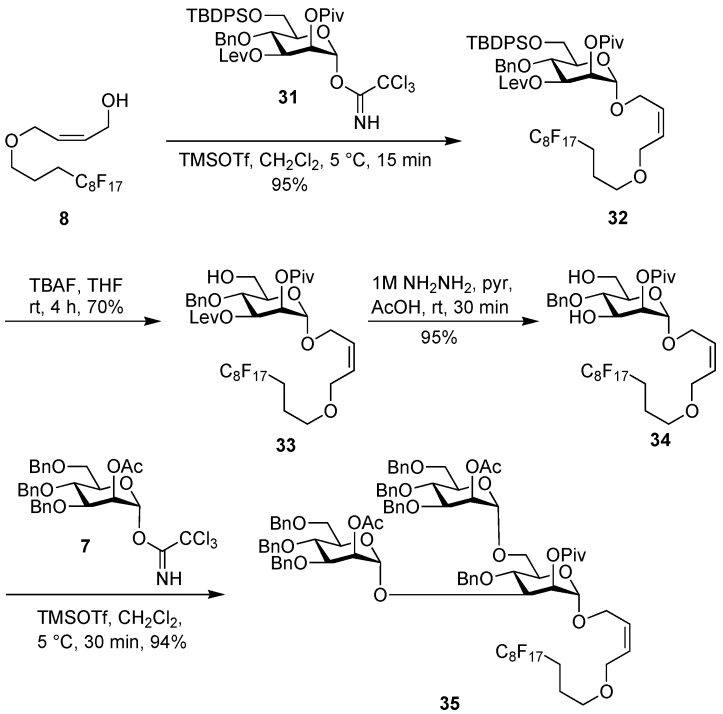
Scheme 3 Initial synthesis of the fluorous-tagged branch point building block.

compound **18**, the equatorial hydroxyl group is more acidic than the axial,[25] the 3-position hydroxyl group was selectively acetylated to give compound **19** in 55% yield. The acetylated mannose **19** was subjected to pivaloyl chloride and DMAP to provide **20**. At this stage the 6-position hydroxyl group was selectively silylated with TBDPSCl to give compound **21** in 86% yield. Acid-catalyzed benzylation, microwave-assisted cleavage of the allyl group[8a] followed by reaction with trichloroacetonitrile gave the desired trichloroacetimidate donor **23**. A large excess of benzyl trichloroacetimidate was used for the benzylation step and trace amounts of this reagent remained in **23**, but the compound could be used in the glycosylation reaction as is for our initial trials since the glycosyl acceptor is the limiting reagent.

Glycosylation of the resulting donor **23** with fluorous alcohol **8** was performed as for the glycosylation reactions in the linear mannose oligomer synthesis in dichloromethane with a catalytic amount of TMSOTf (Scheme 3). The coupling reaction worked well resulting in a 92% yield of the glycosylated product **24** based on the alcohol. The product was purified by passing through a FSPE column. Deprotection of the TBDPS group with 1 M TBAF gave compound **25** in 70% yield. Unfortunately, subjection of the sugar to methanolic sodium methoxide resulted in the cleavage of both the acetyl and pivaloyl groups to provide **26**. Other reaction conditions reported for selective acetyl group removal using $Mg(OMe)_2$[26] and guanidine[27] also were unsuccessful.

Clearly, selective removal of an acetyl group in the presence of a neighboring pivaloyl is not a general enough process to rely upon in an automation strategy. Therefore, a levulinoyl protecting group was installed at the 3-position (Scheme 4) as it could be removed under milder conditions. Selective protection of the 3-position hydroxyl group using levulinic acid and DCC followed by pivaloylation of the 2-position hydroxyl group produced fully protected mannose **27** in 53% yield over two steps. Cleavage of the benzylidene acetal followed by selective silylation of the 6-position hydroxyl group gave compound **29**. Benzylation of the 4-position and deprotection of the allyl group followed by reaction with trichloroacetonitrile produced the required activated building block **31**.

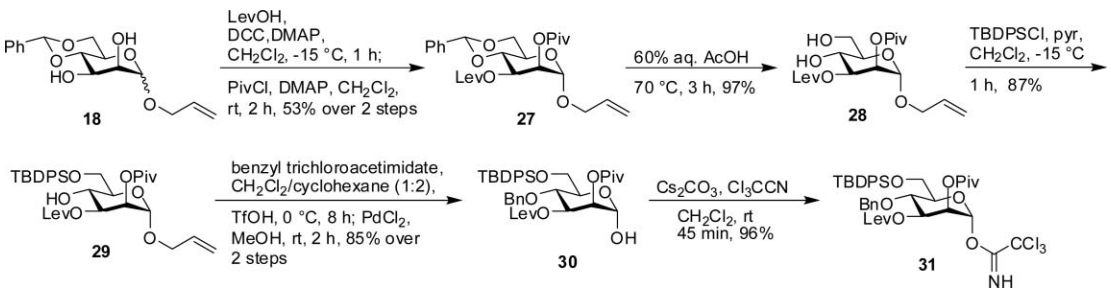
Glycosylation of mannose donor **31** with fluorous alcohol **8** was performed using catalytic TMSOTf as described earlier (Scheme 5). The resulting fluorous-tagged mannose **32** was desilylated with 1 M TBAF to produce compound **33** in 70% yield. Treatment of compound **33** with buffered hydrazine (1 M in pyridine–acetic acid, 3 : 2) for 30 min gave the desired



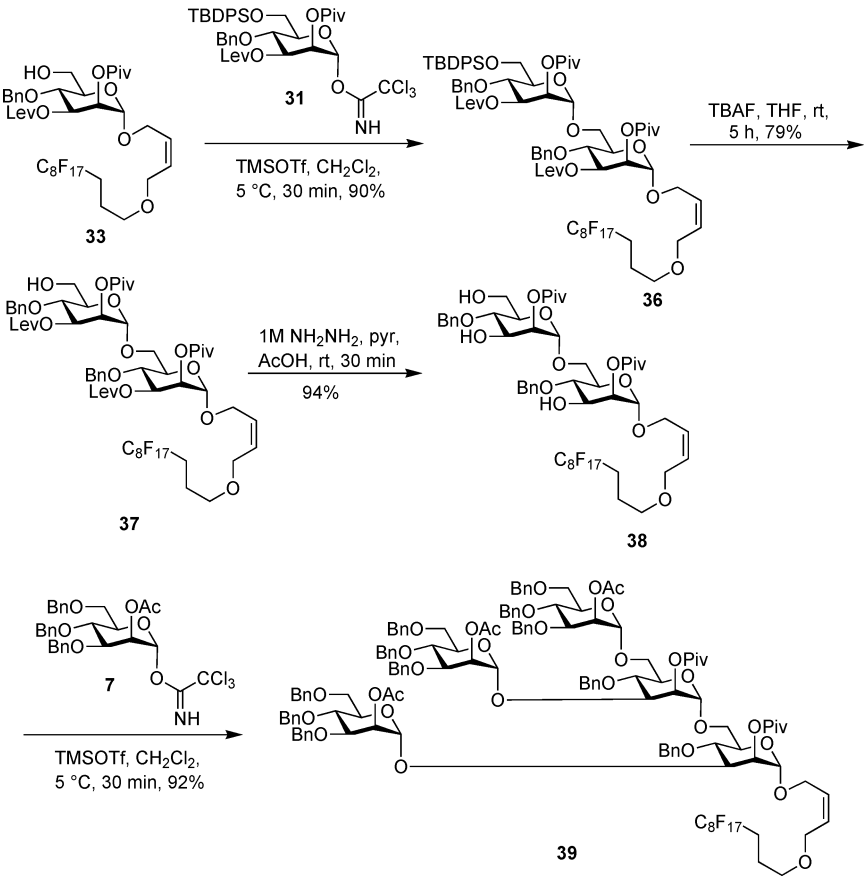
Scheme 5 Synthesis of the branched mannose trisaccharides.

product **34** in 95% yield. Coupling of the fluorous-tagged mannose **34** with mannose trichloroacetimidate **7** gave trimannoside **35** in 94% yield. For comparison, the solid phase approach required 9 equivalents of all of the building blocks for a 38% overall yield;[16a] the fluorous-tag assisted approach required 4.5 equivalents of all of the building blocks for a 58% overall yield.

The branched pentamannoside **39** was synthesized by first coupling fluorous-tagged mannose **33** with mannose trichloroacetimidate **31** to make mannose α-(1→6)-disaccharide **36** (Scheme 6). Removal of the 6-position silicon protecting group followed by deprotection of the two levulinyl groups gave the requisite mannose acceptor **38**. Triple glycosylation of disaccharide **38** with mannose trichloroacetimidate **7** resulted in the formation of mannose pentasaccharide **39** in 92% yield. Interestingly, both the branched and linear mannose structures were readily soluble in the aqueous–organic mixtures required for loading of FSPE columns.



Scheme 4 Synthesis of revised branch point building block.



Scheme 6 Synthesis of the branched mannose pentasaccharide.

Conclusions

In summary, several protected mannose oligosaccharides were synthesized using fluorous-tag assistance. The fluorous tag was shown to be stable to all the reaction conditions required for the requisite glycosylation and deprotection conditions delivered in a manner amenable to automation. Except in the case of desilylation with TBAF, all purification steps to build the oligosaccharides were performed using only fluorous solid phase extraction (FSPE) with identical conditions regardless of the oligosaccharide length. Most importantly, this particular fluorous linker, in contrast with an earlier report, allow both small and large oligosaccharides and the fluorous tag itself to maintain their solubility in the organic solvents used in glycosylations and in the aqueous–organic mixtures used for purification by FSPE. Clearly, the linker design is crucial for the design of a reliable solution-phase automation strategy. These results prove promising for an automated fluorous-phase approach to oligosaccharide synthesis.

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