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synthesis enabled by interrupted Pummerer reaction mediated
glycosylation

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assembly strategy, which allows the flexible, rapid, and efficient
oligosaccharide assembly from reducing end to non-reducing end,
and also from non-reducing end to reducing end with the recovery
of fluororous-tag. The strategy relies on an updated IPRm glycosylation
method by designing a fluororous tagged OPTB anomeric leaving
group. It maintains the high coupling efficiency of solution-phase
synthesis and features the advantage of easy purification process
that is comparable to solid-phase synthesis.

The background picture was captured in Lulin town, Jingshan city in
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Recyclable fluororous-tag assisted two-directional oligosaccharide synthesis enabled by interrupted Pummerer reaction mediated glycosylation†

Lei Cai, Qi Chen, Jian Guo, Zhihua Liang, Dengxian Fu, Linghui Meng, Jing Zeng * and Qian Wan *

Herein, we report a novel fluororous-tag assisted two-directional oligosaccharide assembly strategy, which maintained the high coupling efficiency of solution-phase synthesis and featured the advantage of an easy purification process comparable to solid-phase synthesis. A well-designed fluororous tag was decorated on the latent anomeric leaving group in interrupted Pummerer reaction mediated (IPRm) glycosylation. The high efficiency of the in-solution phase glycosylation and the unique affinity of the fluororous tag towards polytetrafluoroethylene (PTFE) particles allowed flexible assembly from the reducing end to the non-reducing end and fast purification by PTFE-assisted filtration. Moreover, the fluororous-tagged latent anomeric leaving group could be activated by oxidation and cleaved by IPRm glycosylation, thus enabling the elongation of the carbohydrate chain from the non-reducing end to the reducing end as well as the recovery of the fluororous tag. The present two-directional synthetic strategy is used to assemble the repeating unit of *Streptococcus pneumoniae* type 14 capsular polysaccharide.

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Introduction

Saccharides are one of the most abundant biomolecules in nature.¹ However, the exploration of their various physiological functions is hampered by their extraordinarily complex chemical structures and poor availabilities. Consequently, the development of efficient oligosaccharide and polysaccharide assembly strategies is of great demand. Significant progress has been made in the past few decades² as exemplified by the access to many complex oligosaccharides and polysaccharides, especially the remarkable studies of Ye's 92-mer branched arabinogalactan,³ Yu's 128-mer liner glycan in solution-phase synthesis⁴ and Seeberger's 151-mer glycan in automated solid-phase synthesis.⁵ Despite these achievements, huge challenges are still encountered in carbohydrate synthesis, which largely encumbered the development of glycoscience. Among these challenges, one of the major obstacles is the tedious purification process.^{2g} Time-consuming and eco-unfriendly column chromatography is always required in conventional solution-phase synthesis (Fig. 1A(a)). Solid-phase synthesis is one of the most representative state of the art solutions to this problem,^{6–8} however, at the expense of consuming a large excess of carbohydrate building blocks due to the heterogeneous

reaction manner, while the carbohydrate building blocks are much more expensive compared to amino acids and nucleotides in solid-phase polypeptide and polynucleotide synthesis (Fig. 1A(b)).

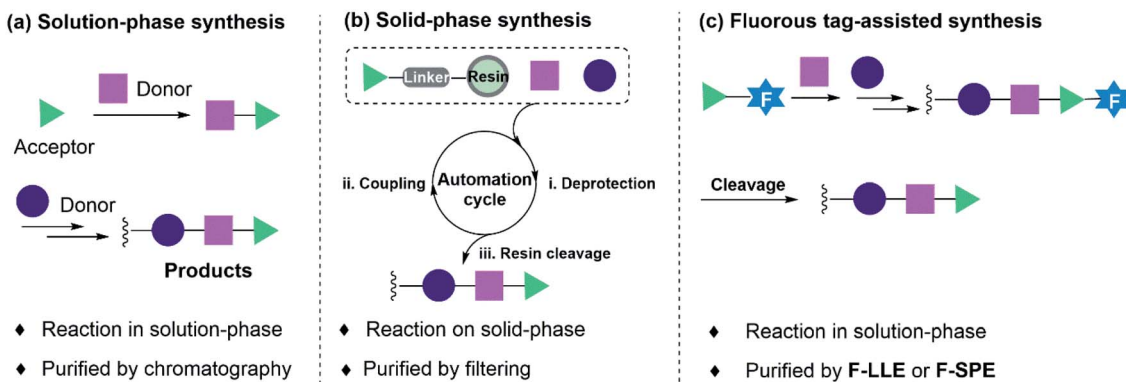
As a complementary type of solution-phase synthesis and solid-phase synthesis, fluororous synthesis pioneered by Zhu,⁹ Horváth¹⁰ and Curran¹¹ *et al.* began to flourish in organic synthesis from the middle 1990s.^{12,13} Fluororous techniques retain the advantages of solution-phase synthesis and solid-phase purification. In this strategy (Fig. 1A(c)), a fluororous tag was installed on substrates, which allowed the reaction to be performed in a homogenous system. Upon completion of the reaction, fluororous solid-phase extraction (F-SPE)¹⁴ or fluororous liquid–liquid extraction (F-LLE)^{11b,15} was implemented for the purification by virtue of the unique interactions between fluororous-tag labeled substrates and fluororous silica gel or fluororous solvent, thus significantly simplifying the purification processes.¹⁶ This superiority has also enriched the carbohydrate synthesis. Since Curran firstly introduced a benzyl type fluororous protecting group as a tag for disaccharide synthesis,¹⁷ Seeberger,¹⁸ Pohl,¹⁹ Mizuno²⁰ and others²¹ have developed diversified fluororous tags for carbohydrate chemical synthesis in the past few decades. To address the problem of the requirement of expensive fluororous solvent and fluororous silica gel in purification steps, Chai and co-workers introduced cheap and reusable polytetrafluoroethylene (PTFE) particles for F-SPE, which allowed purification by simple filtration, namely PTFE assisted filtration. This process significantly simplified the purification step and made the isolation efficiency comparable to that of

Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, Hubei 430030, China. E-mail: wanqian@hust.edu.cn

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A) Oligosaccharide synthesis enabled by conventional solution-phase, solid-phase, and fluoruous technologies



B) Solution-phase synthesis based on interrupted Pummerer reaction mediated (IPRm) glycosylation

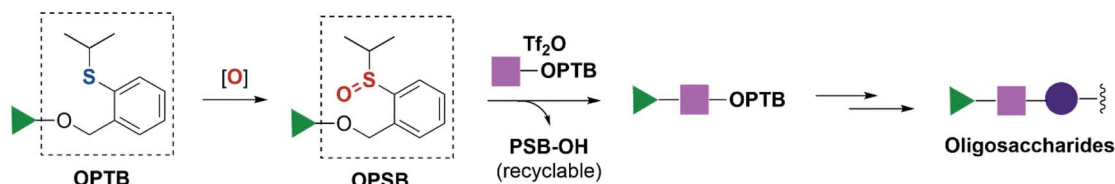
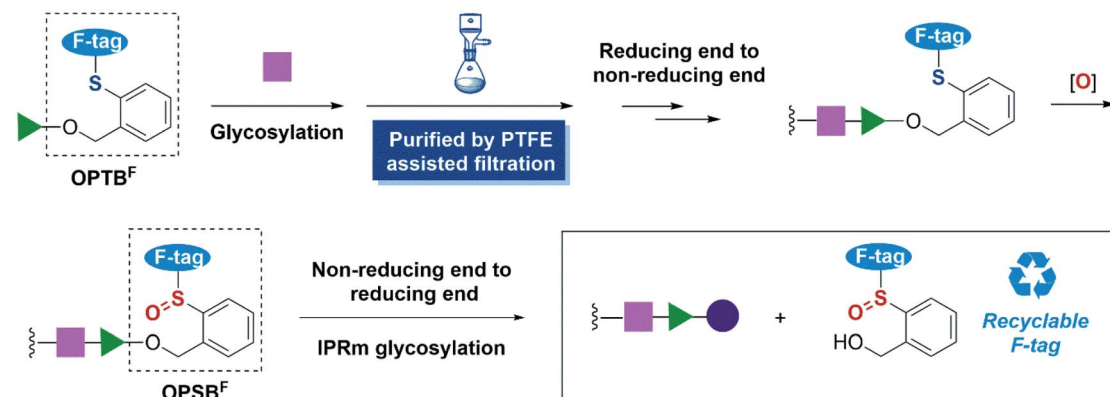
C) Recyclable fluoruous-tag assisted two directional oligosaccharide synthesis (*This work*)

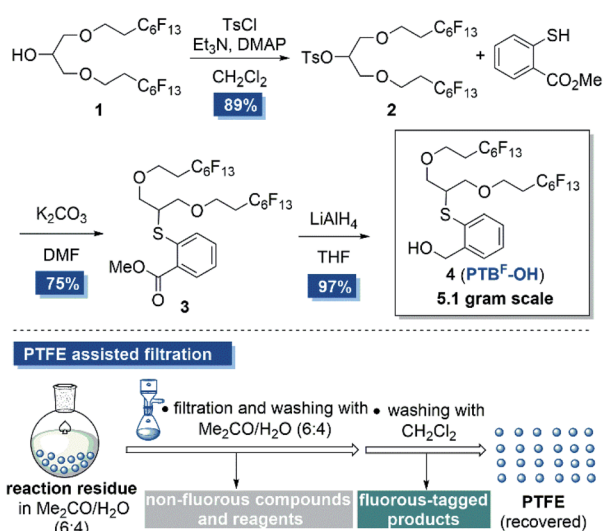
Fig. 1 Prior arts in oligosaccharide assembly and this work.

solid-phase synthesis.²² Among the various fluoruous-tag assisted carbohydrate synthesis methods, the installation of a fluoruous tag at the reducing end displayed exceptional advantages due to the stability and the flexibility. It also facilitated the synthesis of carbohydrate microarrays^{19a} and automated solution-phase iterative synthesis^{19c} advanced by Pohl and co-workers. The final cleavage of the fluoruous tags in this strategy was generally relied on alcoholysis,^{21f} olefin metathesis,^{18b,19e} oxidative cleavage,^{20a,b} reductive hydrogenation^{22a,b} and so on, and consequently only allowed single directional assembly from the reducing end to the non-reducing end and very few of the cleaved fluoruous tags were reported to be recovered and recycled.^{20a,21f,22a}

We have recently developed a solution-phase oligosaccharide synthesis strategy based on interrupted Pummerer reaction mediated (IPRm) glycosylation.²³ In this strategy, we

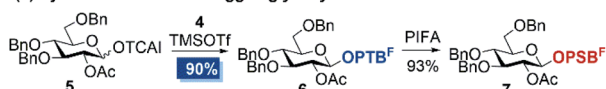
comprehensively applied latent *O*-2-(2-propylthiol)-benzyl (OPTB) glycosides and its active counterpart *O*-2-[(propan-2-yl) sulfinyl]benzyl (OPSB) glycosides as glycosyl donors in glycosylation. It enables efficient and rapid assembly of complex oligosaccharides and also allows the recovery and regeneration of the anomeric leaving group (Fig. 1B).^{24–27} In view of these advantages, we envisioned that the installation of fluoruous side chains on anomeric OPTB and OPSB functionalities (OPTB^F and OPSB^F respectively) would further facilitate the reducing end to non-reducing end assembly sequence by virtue of the PTFE assisted filtration technology. Most importantly, the fluoruous tagged anomeric leaving group would be amenable to be cleaved and recovered by IPRm glycosylation and thus allow the non-reducing end to reducing end assembly and overall, provide a two-directional oligosaccharide synthesis (Fig. 1C).



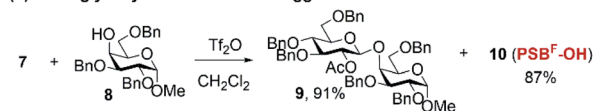


Scheme 1 Synthesis of fluorous-tagged PTB^F-OH via PTFE assisted filtration.

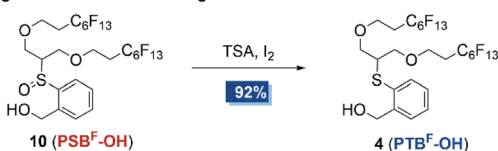
(a) Synthesis of fluorous-tagged glycosyl donor



(b) IPRm glycosylation of fluorous-tagged donor



(c) Regeneration of fluorous-tag



Scheme 2 Proof of concept.

Results and discussion

Our study commenced on the design of a fluorous tagged anomeric leaving group by installing appropriate fluorous chains on the anomeric PTB group at appropriate positions. Inspired by Chai's work,^{22b} we intended to directly fix two perfluoroalkane chains on the terminal position of PTB-OH by ether linkages aimed at simplifying the synthesis and minimizing the impact of the fluorous chains on the glycosylation efficiency (Scheme 1). In addition, the two perfluoroalkane chains would maintain the high affinity of the extended sugar chains to the PTFE particles. To this purpose, known alcohol **1** bearing two perfluoroalkyl ether chains was selected as the starting material.^{22a} The tosylation of alcohol **1** followed by a S_N2 displacement with methyl thiosalicylate under basic conditions furnished **3** in good yield. The subsequent reduction of the ester group of **3** produced PTB^F-OH **4** in 97% yield. It's worth noting that all the purification steps in this synthetic procedure were

Table 1 Orthogonal glycosylations of fluorous-tagged glycosyl acceptors

Entry	Donor	Conditions	13
1	5	TMSOTf, -20 °C	13a (93%)
2	11a	Tf ₂ O, 0 °C	13a (91%)
3	11b	Tf ₂ O, 0 °C	13b (98%)
4	11c	Rh ₂ (Oct) ₄ , TfOH, 0 °C	13c (94%)
5	11d	NIS, TMSOTf, 0 °C	13d (91%)
6	11e	PPh ₃ AuOTf, rt	13e (92%)

performed by PTFE assisted filtration, that is the adsorption of the reaction residues on PTFE powder (200 μm particle size) in a solvent mixture of acetone/H₂O (6 : 4, v/v), followed by filtration with a sand core funnel and successive washing with acetone/H₂O and dichloromethane (Scheme 1). Each purification could be finished within half an hour and the synthesis was easy to scale up to 5 grams in one batch. This newly designed fluorous-tagged PTB^F-OH has great stability and is amenable to be stored on shelf at least for 10 months without detectable decomposition.

With fluorous-tagged PTB^F-OH in hand, we embarked on proving the concept (Scheme 2). The attachment of the fluorous tag on carbohydrate was achieved by coupling of **4** with glucosyl trichloroacetimidate donor **5** in the presence of a catalytic amount of TMSOTf at -20 °C. The standard PTFE assisted filtration procedure delivered OPTB^F glycoside **6** in 90% yield. Further oxidation of **6** by [bis(trifluoroacetoxy)iodo]benzene (PIFA) provided the OPSB^F glycosyl donor **7** in 93% yield. Subsequently, the possibility of the cleavage of the fluorous-tagged anomeric leaving group by the IPRm glycosylation reaction was examined. Subjecting OPSB^F donor **7** and acceptor **8** to a standard IPRm glycosylation procedure²³ afforded the



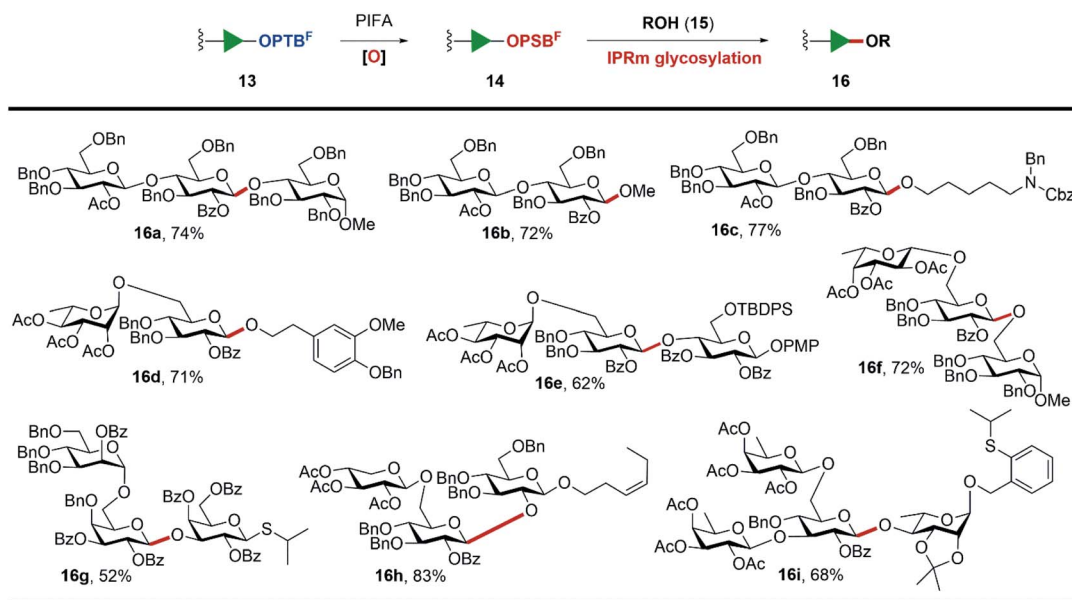
desired disaccharide **9** in 91% yield. In the meantime, the fluoros-tag derivative **10** (PSB^F-OH) was isolated in 87% yield. Moreover, PSB^F-OH was found to be easily reduced to PTB^F-OH (**4**) in the presence of thiosalicic acid (TSA) and a catalytic amount of iodine. This regenerated PTB^F-OH was able to be installed as the latent leaving group again and thus was almost completely recycled. The results indicated that the attached fluoros tag is highly conducive to the IPRm glycosylation reaction and our design of the recyclable fluoros tag assisted two-directional oligosaccharide synthesis is conceptually realized.

Encouraged by these results, we synthesized a series of OPTB^F acceptors **12** (for details, see the ESI†) and examined their orthogonality to various classical glycosylation methods (Table 1). To our delight, the fluoros-tagged acceptors glycosylated efficiently with various types of glycosyl donors under the corresponding activation conditions, and all the reactions are highly conducive to the practical PTFE assisted filtration purification procedure. The fluoros tag was proved to be stable under acidic (**13a–13d**) and transition metal-catalyzed (**13e**) conditions, which are frequently used to activate the trichloroacetimidate glycosyl donor (**5**),²⁸ OPSB/SPSB glycoside donors (**11a/11b**),^{23,29–31} *n*-pentenyl glycosyl donor (**11d**),^{32,33} thioglycoside donor (**11c**)³⁴ and *o*-alkynylbenzoate (Abz) glycosyl donor (**11e**).^{35,36} The high glycosylation efficiency of these reactions implied the limited restrictions of the method in the assembly of complex oligosaccharides from the reducing end to the non-reducing end, because many nice glycosylation methods are amenable to be selected to address particular coupling problems that may be encountered in the assembly sequence. In addition, the OPTB^F moiety at the reducing end was able to be transformed to the active leaving group for

further elongation *via* IPRm glycosylation. These flexibilities as well as the ease of purification processes highlighted its great potential in the oligosaccharide synthesis.

Subsequently, the scope and limitations on the cleavage of the fluoros tag by IPRm glycosylation and meanwhile the elongation of the sugar chains at the reducing end were examined (Scheme 3). Firstly, various glycosides **13** possessing terminal OPTB^F groups were oxidized to active OPSB^F glycosides **14** by PIFA in aqueous CH₃CN. These oxidation reactions proceeded smoothly and most importantly their purification by simple aqueous workup followed by extraction delivered the OPSB^F glycosides in good quality, which were pure enough for next IPRm glycosylations in most cases (for details, see the ESI†).

A variety of acceptors including simple alcohols such as MeOH, *N*-benzyl-*N*-benzyloxycarbonyl-5-aminopentanol, 3-methoxy-4-*O*-benzyl phenylethanol and diversified carbohydrate acceptors were found to be effective nucleophiles in this fluoros assisted IPRm glycosylation. The standard IPRm glycosylation reaction conditions delivered glycosidic products **16a–16i** in good to excellent overall yields. Among these examples, it is worth noting that: (1) *p*-methoxyphenyl group (**16e**), *cis*-alkene (**16h**), and other acid-sensitive groups such as *tert*-butyldiphenylsilyl group (**16e**) and acetonide (**16i**) were tolerated well under current conditions. (2) The thioglycoside acceptor (**16g**) and OPTB acceptor (**16i**) remained stable in glycosylation reactions and would be beneficial to further orthogonal glycosylations. (3) Disaccharide **16d** and trisaccharide **16h** were the protected forms of dictamphenosides *E* and (*Z*) 3-hexenol glycosides, which were recently isolated from *Cortex Dictamni*³⁷ and *Physalis alkekengi* var. *franchetii*,³⁸ respectively. Their good glycosylation output laid the basis for



Scheme 3 Synthesis of OPSB^F glycosyl donors and their IPRm glycosylations. General conditions for oxidation: OPTB^F glycosides **13** (1.0 equiv.), PIFA (1.2 equiv.), MeCN/H₂O (9 : 1, v/v), and rt. General conditions for IPRm glycosylation: OPSB^F glycosides **14** (1.0 equiv.), Tf₂O (1.0 equiv.), acceptor **15** (1.2 equiv.), CH₂Cl₂, and –40 °C. Yield means isolated yield for two steps.

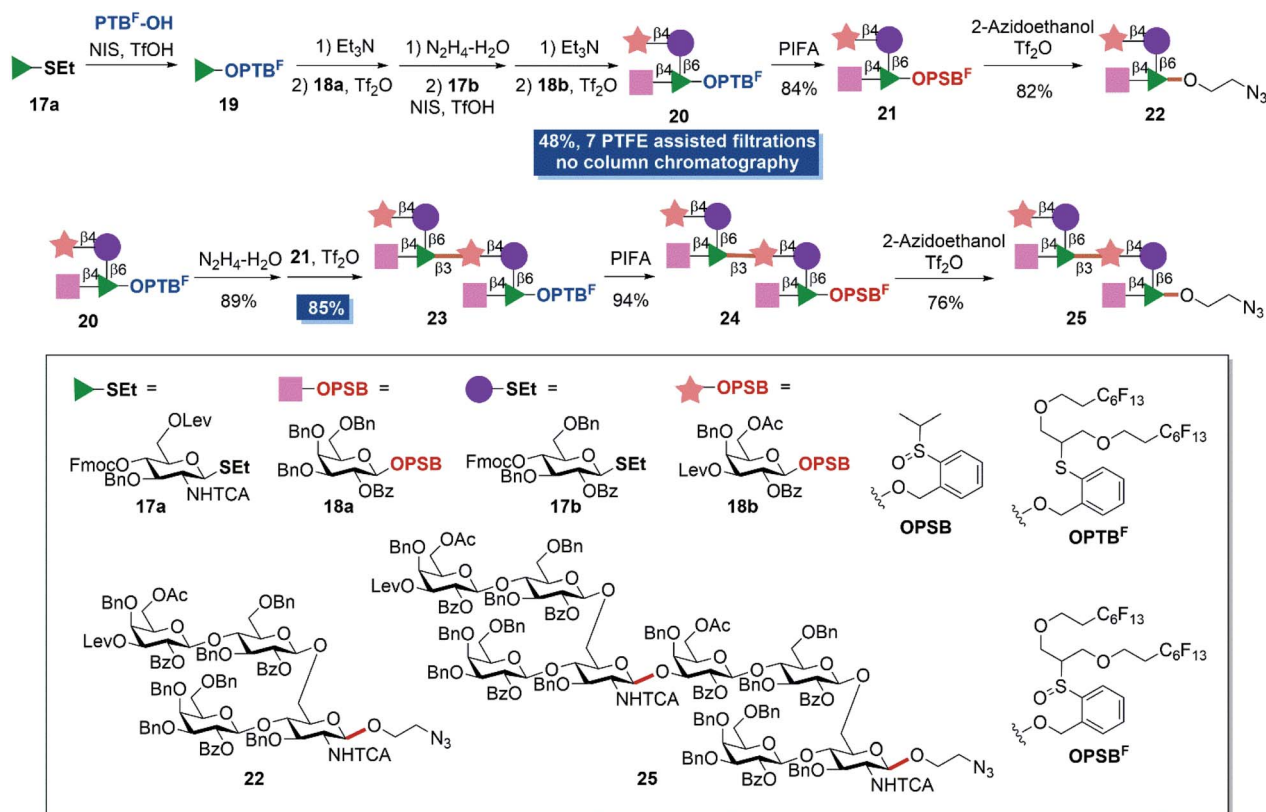


more complicated oligosaccharide assembly through the established PTFE assisted two-directional synthetic protocol.

As a final endeavor to demonstrate the utilization potential of the protocol, structurally more complex *S. pneumoniae* type 14 (ST14) tetrasaccharide and octasaccharide were chosen as synthetic targets (Scheme 4).^{39,40} The tetrasaccharide repeating unit is the smallest structure to induce ST14-specific antibody effects^{41,42} and represents an important component for the development of synthetic or semi-synthetic pneumococcal vaccines.⁴³ Savage⁴⁴ and Seeberger^{42,45} have developed glycoconjugate vaccine candidates, which are advantageous to clinically used vaccines on the basis of solution-phase synthesized tetrasaccharide fragments. Besides, Salwiczak also has synthesized ST14 tetrasaccharide and octasaccharide antigens by a solid-phase method.⁴¹ We believe that the present two-directional assembly strategy has great potential to provide fast access to ST14 oligosaccharides and would be beneficial to vaccine development. With PTB^F-OH, thioglycosides **17a** and **17b**, and OPSB glycosides **18a** and **18b** in hand, fluoros-tag assisted two-directional assembly was conducted. PTB^F-OH was firstly glycosylated to building block **17a** and provided OPTB^F monosaccharide **19**. Further removal of the 4-*O*-Fmoc protecting group, installation of galactoside **18a** *via* IPRM glycosylation and removal of the 6-*O*-levulinyl group provided the disaccharide OPTB^F acceptor. The subsequent introduction of glucosyl building block **17b**, removal of the 4-*O*-Fmoc protecting group and installation of galactosyl building block **18b**

gave OPTB^F tetrasaccharide **20** in 48% overall yield in seven steps. It's worth mentioning that tetrasaccharide **20** was obtained without column chromatography with the aid of PTFE assisted filtration. The existence of a levulinyl group at the non-reducing end allows the further elongation of the repeating polysaccharide chain. Additionally, the OPTB^F moiety at the reducing end permits the elongation at the reducing end by IPRM glycosylation.

Simple oxidization of OPTB^F tetrasaccharide **20** and coupling with 2-azidoethanol successfully provided the minimum repeating unit tetrasaccharide **22** in 82% yield with the introduction of a biological compatible tail for further elaboration in biological studies. Meanwhile the anomeric fluoros tag was cleaved. The treatment of tetrasaccharide **20** with hydrazinium hydroxide solution to remove the levulinyl group furnished the tetrasaccharide OPTB^F acceptor. Next, the dimerization reaction between tetrasaccharide donor **21** (2.0 equiv.) and tetrasaccharide acceptor under standard IPRM glycosylation conditions performed very well and provided octasaccharide **23** in 85% yield with PTFE assisted filtration. Finally, the oxidation and elaboration of 2-azidoethanol accomplished the synthesis of octasaccharide dimer **25** in overall eleven steps and 26% yield from mono-saccharide building blocks. Eight PTFE assisted filtrations were adopted in the whole synthesis that largely minimized the column chromatography separation steps and simplified the purification processes.



Scheme 4 Fluoros-tag assisted two-directional syntheses of ST14 repeating units.



Conclusions

In conclusion, we developed a fluoros-tag assisted two-directional oligosaccharide assembly strategy. The strategy relied on our recently developed IPRm glycosylation by designing a fluoros tagged OPTB anomeric leaving group. The upgraded IPRm glycosylation allowed flexible, rapid and efficient oligosaccharide assembly from the reducing end to the non-reducing end with the aid of PTFE assisted filtration purification technology. Upon the completion of the reducing end to non-reducing end assembly, the terminal OPTB^F was able to be oxidized to the OPSB^F group, which could be cleaved and recycled by another IPRm glycosylation and at the same time elongated the oligosaccharide chain at the reducing end. The efficacy was exemplified by fast access to the ST14 tetrasaccharide and octasaccharide fragments. Additionally, encouraged by recent remarkable achievements in automated fluoros-assisted solution-phase oligosaccharide synthesis⁴⁶ and HPLC-based automated synthesis of glycans in solution,⁴⁷ we expect to employ the developed fluoros-tag assisted synthetic strategy in an automated platform and we are currently studying on this issue.

Data availability

Experimental data including experimental procedures, characterization data, and NMR spectra for the new compounds have been uploaded as ESI material.†

Author contributions

Lei Cai and Qi Chen carried out most of the experiments, brought the project to completion and prepared the draft. Jian Guo and Zhihua Liang synthesized PTB^F-OH and some fluoros-tagged glycosyl acceptors. Dengxian Fu participated in the revision of the draft. Lingkuai Meng contributed to the discussion of the project and revision of the draft. Qian Wan conceived the idea. Jing Zeng and Qian Wan oversaw the project, discussed the results, and edited and reorganized the manuscript.

Conflicts of interest

There are no conflicts to declare.

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