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Fast and Low-Cost Purification Strategy for Oligosaccharide Synthesis Based on a Hop-On/Off Carrier

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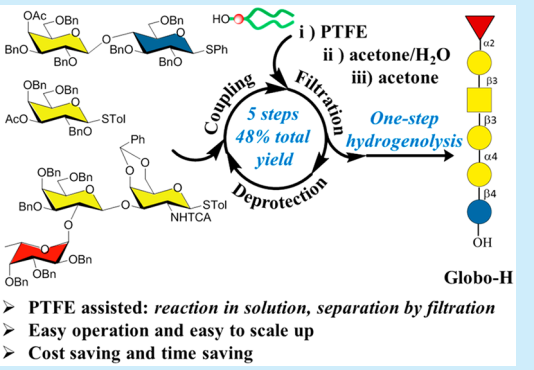
ABSTRACT: A feasible and convenient strategy for oligosaccharide synthesis, which realizes reaction in solution while product purification occurs only by solid–liquid filtration, has been developed. By using a hop-on/off carrier (polytetrafluoroethylene particle), rapid synthesis of tumor-associated antigen Globo-H hexasaccharide has been successfully achieved within 5 steps in 48% overall yield without any intermediate purification by column chromatography. Also, global deprotection, including the cleavage of the tag, proceeded simultaneously only by one-step hydrogenolysis.



The solid phase method revolutionized the chemical synthesis of peptides due to the simplicity of product purification. It has been estimated that solid phase peptide synthesis is ~50-fold less arduous than solution synthesis of the same target.[1] The solid phase method has allowed peptide synthesis to be widely accessible to laboratories throughout the world, which greatly promotes various related investigation, including peptide-based material science and drug/sensor development, etc.

The big dream of carbohydrate chemists is to push the synthesis of complex oligosaccharides to such a level. However, because of multiple hydroxyl groups in carbohydrates, stereoselectivity in glycosylation, and a tedious purification process, chemical synthesis of oligosaccharides is still very challenging. The great breakthrough came out when solid support, similar to that for peptide synthesis, was first proposed to construct complex oligosaccharides.[2] Later, various improvements[3] and a tailor-made synthesizer[4] were achieved. Besides the solid support protocol,[5] other strategies[6] have been developed to simplify the product purification process and thereby improve the efficiency of oligosaccharide syntheses, such as one-pot synthesis,[6a,b] HPLC-assisted oligosaccharide synthesis,[6c] ionic-tag-assisted oligosaccharide synthesis,[6d,e] electrochemical synthesis,[6f] hydrophobically assisted switching phase synthesis,[6g] fluorous-tag[6h] and sulfonate-tag[6i] assisted synthesis of oligosaccharides, and so on. However, due to the requirement of various glycosylation conditions, currently the oligosaccharide synthesizer could not easily reach the simplicity level of the peptide synthesizer, which hampers the accessibility of solid phase synthesis of oligosaccharides in common laboratories. Moreover, when solid support synthesis is applied to oligosaccharides, chemical control on the glycosylation steps becomes much more crucial and challenging than solution synthesis due to the difficulties in monitoring and controlling the heterogeneous reaction.[3b]

Thus, development of new synthetic techniques in order to achieve fast and accessible synthesis of oligosaccharides in laboratories is in great demand. Considering the advantages of both solid phase synthesis[4] and solution synthesis,[6a,b] we envision that the combination of those advantages of both methods[5c,c,6g,i] could be achieved if the oligosaccharide synthetic process is performed in solution phase while product purification is conducted with the aid of solid support. To this end, in this paper, we show a novel strategy to achieve fast oligosaccharide synthesis by employing a convenient solid carrier. The temporary attachment and detachment of the targeting oligosaccharide to the solid carrier can be easily controlled by just changing the solvent. Thus, with the aid of this "hop-on/off" carrier, the glycosylation reaction can be achieved in solution and separation of the oligosaccharide can be easily accessed by filtration, combining the advantages of both solid phase synthesis and solution synthesis of oligosaccharides. Moreover, with the optimized chemical method, the assembly of Globo-H hexasaccharide can be

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achieved within 5 steps in 48% overall yield without any intermediate purification by column chromatography.

In this "hop-on/off" carrier design, the linkage between the solid support and the oligosaccharide could not be the previous covalent linkages that were used for peptide synthesis and solid support oligosaccharide synthesis. The linkage provided by the "hop-on/off" carrier should be fully reversible. Considering the ease of procedure in laboratories and, more importantly, the reversibility of the linkage, we utilized the fluorous−fluorous interaction, which can be easily tuned by changing solvent. The crucial aspect to achieve this design of "hop-on/off" carrier, is the employment of the inert and commercial available polytetrafluoroethylene particle (PTFE particle, 100 μm), which is well-known in material science. It is worth mentioning that, since the fluorous technique[7] was first introduced by Horváth and Rábai,[7a] the fluorous tagging strategy (including fluorous liquid−liquid extractions (F-LLE) and fluorous solid-phase extraction (F-SPE)) has been widely used in the synthesis of small molecules and separation of peptides[7b] and oligosaccharides.[6h,8] However, PTFE has not been employed in any fluorous tagging strategy to our knowledge and it is much cheaper and easier to access than the perfluorinated solvent used in F-LLE and fluorous-modified silica gel used in F-SPE.

Thus, the design of this "hop-on/off" carrier based on the PTFE bead can be explained in Figure 1. To interact with the

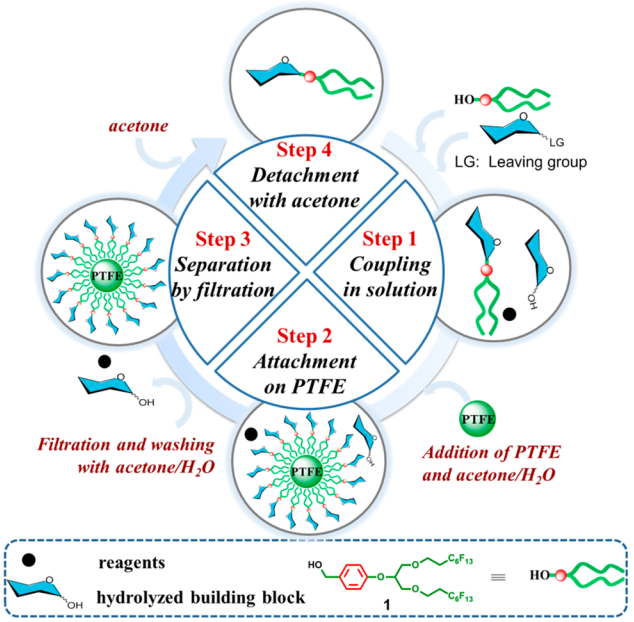

Figure 1. General procedure for PTFE-assisted synthesis of oligosaccharides.

PTFE bead, a recyclable benzyl-type fluorous tag **1**[9] was employed. As shown in Figure 1, after each coupling or deprotection reaction proceeded in a traditional solution-phase manner, inert and commercial available polytetrafluoroethylene particles (PTFE particles, 100 μm) were added into reaction mixtures. The fluorous−fluorous interaction in the presence of polar solvent (e.g., acetone/H_2O) leads to attachment of fluorous-tagged oligosaccharides on the PTFE particle surface. Therefore, the nonfluorous components that remain in the solution phase could be readily separated from fluorous-tagged oligosaccharides only by simple filtration. Afterward, the fluorous-tagged product can be detached by elution with conventional organic solvent to continue the next coupling or deprotection steps. In short, this strategy has both advantages of solution-phase reaction and solid-phase synthesis of oligosaccharides: (a) The homogeneous reaction can be monitored by traditional methods such as TLC, NMR, and MS; (b) The purification process is very simple and rapid, avoiding the use of fluorous solvent and tedious transfer process; (c) PTFE particles are cheap and stable under general conditions in carbohydrate synthesis, which makes the particles easily recyclable to save cost.

To screen the appropriate solvent and the ratio of water for the separation of fluorous oligosaccharides from nonfluorous compounds, the behavior of fluorous-tagged lactose **3** (Figure 2) in mixture solvent was first investigated and acetone was

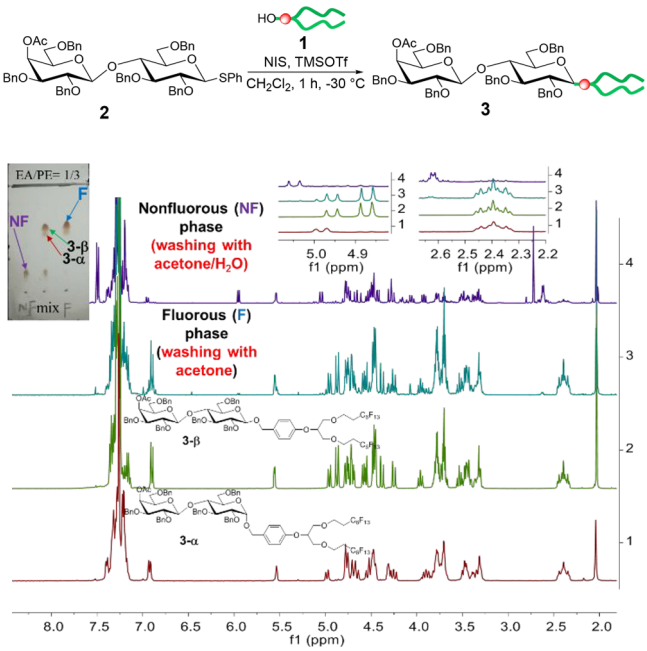

Figure 2. Compared spectra of nonfluorous and fluorous components separated by PTFE.

preferentially used in the evaluation. It was found that obvious turbidity appeared when the ratio of water was increased to 28%, indicating strong fluorous−fluorous interaction drove the molecules together. Thus, under this condition, once the PTFE particles are added, their large surface area leads to the anchoring of the fluorous-tagged oligosaccharide to their surface, which supports separation of the latter from nonfluorous compounds.

To prove this separation efficiency assisted by PTFE, the purification of reaction mixtures between fluorous tag **1** and lactose building block **2** was tested. Just as in the process in Figure 1, after 1.5 h, TLC analysis showed the complete consumption of fluorous tag **1**; PTFE powder (100 μm, roughly 5−10 times the mass of starting materials[7c]) was added to the reaction mixtures, and the solvent was completely removed under reduced pressure. Then, a mixed solvent of acetone and water (v/v = 7/3) was added, followed by stirring at room temperature for 10−20 min. The resulting mixtures were filtrated through a sand core funnel and washed with additional acetone/H_2O to thoroughly remove nonfluorous components that remain in solution. Finally, the crude product

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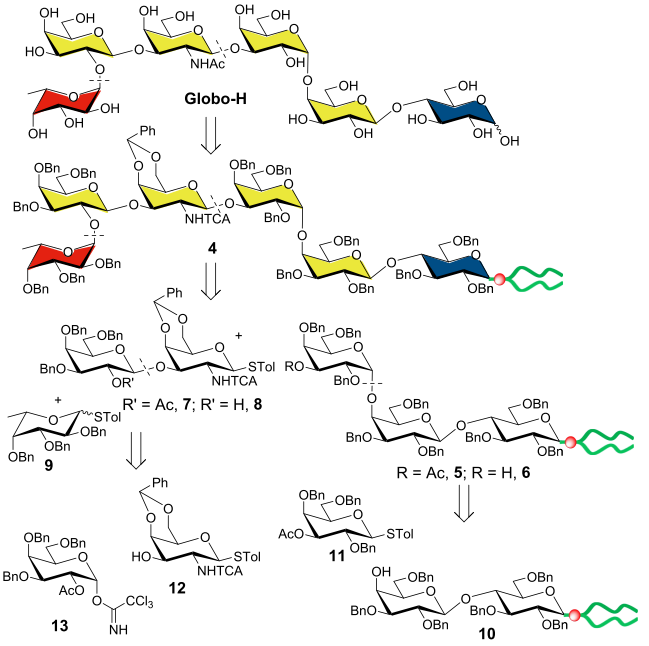
of **3** was collected by washing with acetone. TLC plate and ^{1}H NMR spectra (Figure 2) showed that byproduct and reagents (nonfluorous part, line 4, dark blue spectrum) produced in the coupling reaction were almost removed from the reaction mixtures, and crude product (line 3, soft blue spectrum) with high purity was obtained by comparison with β configuration (line 2, green spectrum) and α configuration (line 1, red spectrum) of compound **3**. The ratio of β to α (**3-β**/**3-α** = 2/1) configuration can be readily confirmed by the ^{1}H NMR spectra. It should be noted that additional postprocessing, i.e. washing with $Na_2S_2O_3$ aqueous, was avoided after glycosylation in the presence of NIS (*N*-iodosuccinimide), since the excess of NIS and the nonfluorous byproducts can be simultaneously removed by washing with acetone/H_2O. Therefore, the workup and purification for oligosaccharide syntheses were simplified and time consumption on the postprocessing procedure (including purification) can be largely shortened to only 0.5−1 h. Feasible and convenient glycosylation by combining the advantages of traditional liquid-phase reaction and solid-phase reaction was well demonstrated by this strategy.

To evaluate the applicability of the above protocol, tumor-associated carbohydrate antigen Globo-H with a complex structure which is overexpressed on tumor cells (such as breast, colon, lung, ovary, prostate tumors) was selected as a synthetic target. Although state-of-the-art technologies have been applied in literature[10] to synthesize Globo-H, a new route suitable for our purification strategy was designed with consideration of easy access of building blocks and least number of deprotection steps. Retrosynthetic analysis (Scheme 1) shows that the protected hexasaccharide **4** can be prepared

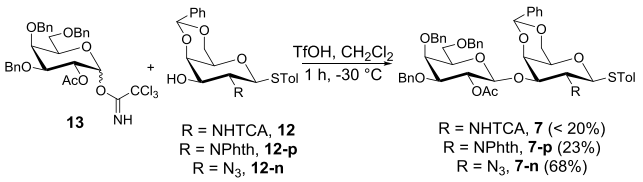
Scheme 1. Retrosynthetic Analysis of Globo-H



by successive coupling of **6** with **7** and **9**. The construction of 1,2-*cis*-glycosidic linkages of **10** and **11** will be ensured by remote anchimeric assistance[9,11] of acyl groups at *O*-3 in the thioglycosides **11**. To stereoselectively construct 1,2-*trans*-glycoside of **6** and **7** as well as **12** and **13**, the 2-*N*-position of **12** and 2-*O*-position of **13** were protected with the participating group TCA (trichloroacetyl)[10h] and acetyl, respectively. To guarantee the 1,2-cis-glycoylation, the 2-*O*-position of **9** was protected with nonparticipating Bn (benzyl) group. After successful assembly of hexasaccharide **4**, all of the protecting groups including the fluorous tag, benzyl, benzylidene, and chlorine will be globally removed only by one-step hydrogenolysis.

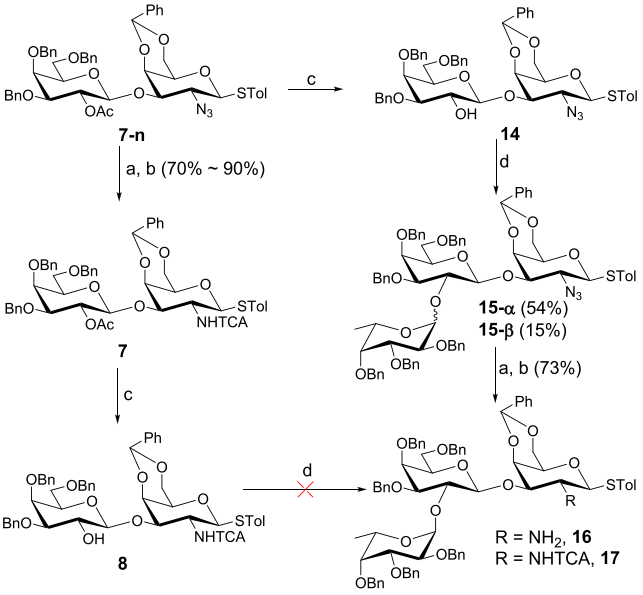
Initially, trichloroacetyl (TCA) and phthalimide (Phth) protected acceptor **12** and **12-p** were respectively attempted in the glycosylation with **13**, and only minor product was afforded (Scheme 2). However, when azido-containing acceptor **12-n**[10g] was used, glycosylation of **12-n** with **13** was smoothly promoted by trifilic acid using the inverse procedure,[12] and the disaccharide **7-n** was achieved in 68% yield.

Scheme 2. Preparation of Disaccharide 7



With **7-n** in hand, the azide group was reduced with PPh_3 and then protected with TCA[13] followed by deacetylation to give compound **8** (Scheme 3). However, pretest studies on glycosylation between **8** and **9** showed that there was almost no reaction and disaccharide **8** was recovered in CH_2Cl_2 while the glycosylation was complete but complex mixtures were afforded in toluene.[14] The problem regarding the synthesis of trisaccharide **17** was solved by switching the reaction sequence (See Scheme 3). Thus, deacetylation of **7-n** led to **14**, which was coupled with fucose building block **9** smoothly in toluene in the presence of TfOH to provide the desired trisaccharide **15** with α configuration as the main product (54% yield). Finally, the azide was reduced by Staudinger reduction followed by protection with TCA to provide compound **17** in 73% yield in two steps (Scheme 3).

Scheme 3. Preparation of Trisaccharide 17



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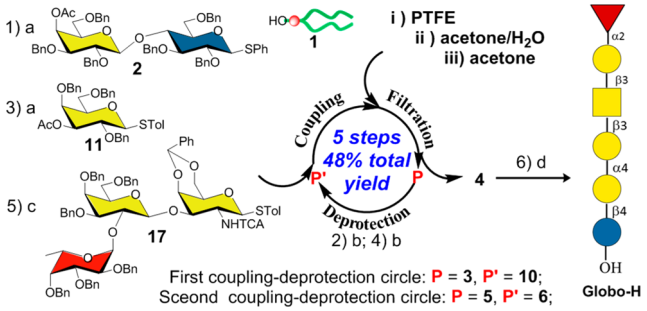
After successful preparation of compound **17**, PTFE particle-assisted synthesis of Globo-H was carried out according to the procedure in Scheme 4. First, the coupling

Scheme 4. Preparation of Globo-H Assisted by PTFE



between compound **1** and **2** proceeded and the product was purified by the previously established procedure (Figure 1). Although there was a high ratio of **3-*α*** in the crude product, aiming at free Globo-H with the reducing end, the crude product **3** separated from PTFE beads with acetone was collected and used immediately in the next step without further purification. After removal of acetyl in **3** (neutralized with Dowex 50WX8 ion-exchange resin or purified by PTFE), glycosylation with **11** was carried out. It is demonstrated that remote anchimeric assistance[9,11] of acyl groups at *O*-3 in the thioglycosides **11** leads to high efficiency and stereoselectivity of the glycosylation. Afterward, the same operation with PTFE was used to purify the product. As apparent from ^{1}H NMR spectrum (Figure S17), the nonfluorous components that eluted with actone/H_2O (7/3, v/v) were almost completely removed, and the purity of the fluorous phase compound detached with acetone was quite high compared with the pure ^{1}H NMR spectrum of compound **5**. After treatment with MeONa/MeOH to remove acetyl again, the final glycosylation of **6** with trisaccharide **17** was carried out. The pretest study demonstrated that when TMSOTf was used to catalyze the reaction, only minor product was afforded. To our delight, the desired *β*-anomer of compound **4** was provided in 91% yield with TfOH instead of TMSOTf. To confirm the configuration of **4**, the heteronuclear J-resolved spectroscopy (JRES) of compound **6** was measured (Figure S15). The two 170 Hz values of the $^1J_{C1-H1}$ coupling constant imply the existence of the two *α* configurations in compound **6**. Under the optimal conditions, the synthesis of Globo-H assisted by PTFE was conducted. As expected, both MALDI-TOF mass spectrometry (Figure S19) and ^{1}H NMR (Figure S18) demonstrated that the protected Globo-H **4** with high purity was provided only by separation with PTFE assistance. According to these results, the hydrolyzed product of compound **17** was almost completely removed in the process of washing with acetone/H_2O. The crude product was purified by silica gel column chromatography, and the protected Globo-H was obtained in 48% overall yield in 5 steps. The efficiency is higher than the solid-phase synthesis (30% total yield)[10h] and comparable with multicomponent one-pot synthesis (47% total yield)[10g] of Globo-H. Finally, global deprotection under a hydrogen atmosphere[15] gave Globo-H as a target compound.

In summary, we have developed a polytetrafluoroethylene particle (PTFE)-assisted strategy for oligosaccharides synthesis. This new strategy employs the advantages of solution phase synthesis and solid phase separation, which means that TLC monitor and regular purification are available for oligosaccharide synthesis. These advantages have been supported by fast and high-yield synthesis of complex oligosaccharide Globo-H. Considering the routine synthesis procedure and separation steps during this process, and the low cost of PTFE beads, this strategy makes the oligosaccharide synthesis accessible by general laboratories in chemistry and material science with routine equipment. With the aid of solution synthesis and TLC monitoring, the regioselectivity, stereoselectivity, and efficiency of coupling reactions can be optimized, which are critical to the rapid syntheses of oligosaccharides. Moreover, by combination of our strategy with enzymatic glycosylation, it is possible to expand the library of oligosaccharides. And finally we expect the general access to oligosaccharides could greatly promote the development of related research in drug discovery and material science.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00477.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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