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Combination of solid phase and solution phase synthesis of oligosaccharides using sonication

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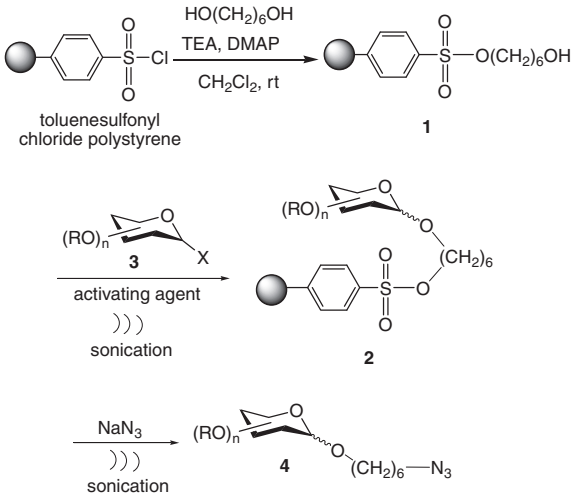
ABSTRACT

An approach that combines solid phase and solution phase synthesis of oligosaccharides via the assistance of sonication has been developed. By employing the traceless linker, the designed oligosaccharides can be obtained in pure form and, more importantly, ready for incorporation to aglycons of interest via 'Click' chemistry or amide linkage. The overall strategy will facilitate the studies of roles of carbohydrates in bioactive compounds.

The superb biocomplexity of carbohydrates makes oligosaccharides the most prevalent bio-molecules in nature. As a result, the synthesis of oligosaccharides has been the focus of carbohydrate synthesis pursued by researchers from different areas.[1–4] Solid phase synthesis of oligosaccharides is one of the most significant achievements in the methodology development for complex carbohydrate synthesis.[5,6] To achieve the complete transformation of solid phase reaction, the soluble reagents, such as glycosyl donors, are often used in excess. Since the syntheses of glycosyl donors could be labour intensive and resource consuming, increasing the efficiency of glycosylation may have a significant impact on the complex carbohydrate synthesis.

Sonication has been employed for enhancing the efficiency of glycosylation in solution phase synthesis.[7,8] When glycosylation is carried out under sonication, we have discovered that the reaction can be shortened and the yields can be improved. Therefore, we wish to explore the possible use of sonication in the solid phase synthesis of oligosaccharides. We selected toluenesulfonyl chloride polystyrene resin for our study (Scheme 1). Using 1,6-hexanediol as the spacer and following the glycosylation, the product can be traceless removed using NaN_3 leaving the carbohydrate with an azido terminal ready to be incorporated onto targets of interest via 'Click' chemistry or amide linkage.[9]

We began with the synthesis of monosaccharide using various glycosyl acetates as the donors and BF_3–OEt_2 as the activating agent. Glycosyl acetates can be easily prepared and serve as cost effective glycosyl donors. However, glycosyl acetates are also known for their relatively low reactivity towards glycosylation. Such a deficiency presents even a greater challenge in using these glycosyl donors for solid phase synthesis. The glycosylation was conducted with the assistance of sonication at ambient temperature. Following the washing of resin, the glycosylated adducted with monosaccharide can be cleaved from the resin using NaN_3 also with the assistance of sonication (Table 1). By employing this simple protocol, a panel of monosaccharides with 6-azidohexyl anomeric group can be prepared and ready for further applications via 'Click' chemistry. The stereoselectivity of glycosylation, in general, is governed by the neighbouring group assistance and the nature of the monosaccharides. Interestingly, the xylopyranose donor offered only the α glycoside rather than the expected β glycoside (entry 4). Due to the absence of C-6 group, xylopyranose is known to be more flexible in its conformation. Sonication is likely to provide additional energy that overcomes the conformation-related neighbouring group assistance and generates the α glycoside.



Scheme 1. Strategy for solid phase carbohydrates synthesis.

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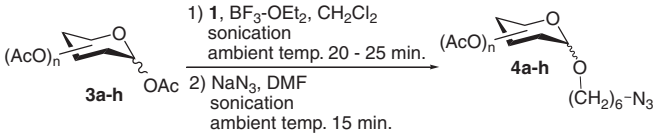
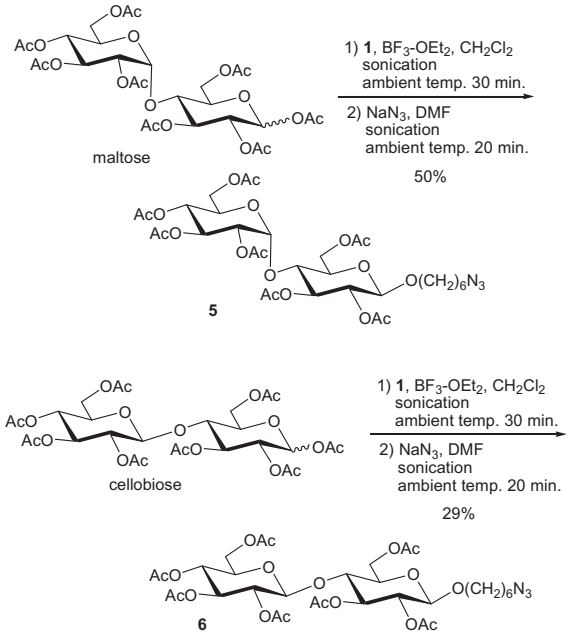
Table 1
Glycosylation using monosaccharide donors



Entry	Glycosyl donor	Product	Yield[18] (%)	αβ ratio[a]
1	Pentaacetyl D-glucopyranose (**3a**)	**4a**[8a]	14	β only
2	Pentaacetyl D-mannopyranose (**3b**)	**4b**[8a]	55	α only
3	Pentaacetyl D-galactopyranose (**3c**)	**4c**[8a]	70	1/1
4	Tetraacetyl D-xylopyranose (**3d**)	**4d**	58	α only
5	Tetraacetyl L-rhamnopyranose (**3e**)	**4e**[8a]	75	α only
6	Tetraacetyl D-fucopyranose (**3f**)	**4f**[8a]	65	β only
7	Acetyl 3-*O*-acetyl-2,4-di-*O*-benzyl-L-rhamnopyranose (**3g**)	**4g**	25	α only
8	Acetyl 2-*O*-acetyl-3,4-di-*O*-benzyl-L-rhamnopyranose (**3h**)	**4h**	32	α only
1	Pentaacetyl D-glucopyranose (**3a**)	**4a**[8a]	14	β only
2	Pentaacetyl D-mannopyranose (**3b**)	**4b**[8a]	55	α only
3	Pentaacetyl D-galactopyranose (**3c**)	**4c**[8a]	70	1/1
4	Tetraacetyl D-xylopyranose (**3d**)	**4d**	58	α only
5	Tetraacetyl L-rhamnopyranose (**3e**)	**4e**[8a]	75	α only
6	Tetraacetyl D-fucopyranose (**3f**)	**4f**[8a]	65	β only
7	Acetyl 3-*O*-acetyl-2,4-di-*O*-benzyl-L-rhamnopyranose (**3g**)	**4g**	25	α only
8	Acetyl 2-*O*-acetyl-3,4-di-*O*-benzyl-L-rhamnopyranose (**3h**)	**4h**	32	α only

[a] The αβ ratio is determined by ^{1}H NMR.



Scheme 2. Glycosylation using disaccharide donors.

Similar effect is noted for galactopyranose as well which results in the decrease of stereoselectivity (entry 3). Disaccharide donor can also be utilised in a similar fashion (Scheme 2).

Encouraged with this result, we further investigated the synthesis of more complex trisaccharides. We decided to focus on D-mannose- and L-rhamnose-based oligosaccharides due to their emerging significance in recent studies.[10,11] We employed mannopyranosyl acetate **7**[8a] as the donor (Scheme 3). Following the sonication-assisted glycosylation, the 2-*O*-acetyl group was removed with NaOMe, and then the second glycosylation was conducted in a similar fashion. Release of the disaccharide was accomplished using NaN_3 and the desired disaccharide was obtained. Since we have previously prepared the disaccharide donor, **11**[13], a similar approach leads to the synthesis of trimannosides with 1,2-linkages, **13**. A branched trimannoside **19** containing 1,6- and 1,2-glycosidic bonds can also be synthesised using donors **14**[8b] and **17**[8b] (Scheme 4).

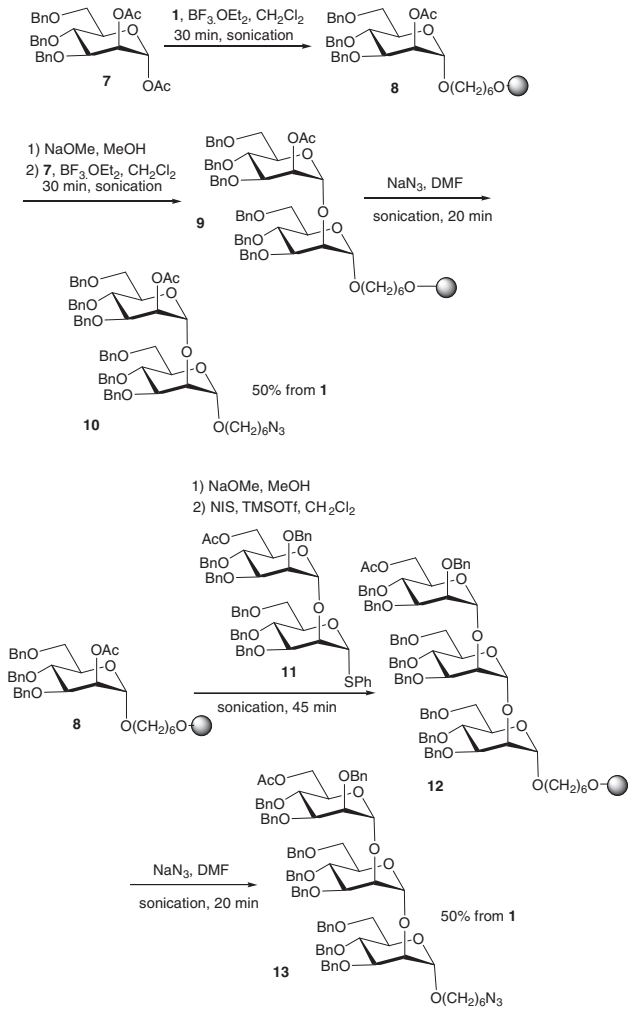
The synthesis of oligosaccharide consisting of L-rhamnose has also been attempted using the same strategy. We focused on the rhamnose donors with 2-*O*- and 3-*O*- acetyl groups due to their presence in the tetrasaccharide antigen found in anthrax (Fig. 1).[12] Using a convergent approach, various trirhamnosides can be assembled and used as the synthesis of analogues of anthrax antigen.

Rhamnose derivatives, **20**,[14] **21**,[11c] **22**,[15] **23**,[16] and **24**,[17] were synthesised from the modified procedures. Initial studies using sonication protocol for attaching rhamnose donor on resin followed by methoanolysis confirm the successful synthesis of the desired acceptors, **25** and **26** (Scheme 5). Unfortunately, the attempt to attach the second rhamnose was unsuccessful affording only compound **4g** after several trials. It is possible that the anomeric acetyl group on either **23** or **24** can undergo transesterification and acetylate the free OH on acceptor.

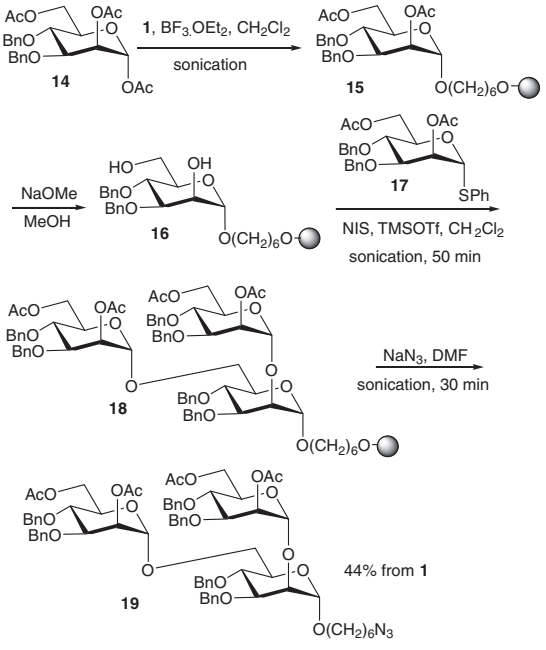
An alternative approach combining solid phase and solution phase synthesis was adopted (Scheme 6). In this approach, compound **24** was employed as the glycosyl donor and the monorhamnoside was prepared using sonication-assisted solid phase strategy. After cleaving from the resin, the second and the third glycosylation using compound **27** as the glycosyl donor was accomplished leading to the synthesis of the trirhamnoside, compound **29**, which can serve as an important precursor for the synthesis of anthrax tetrasaccharide reported in the literature.[11a–d]

In conclusion, we have demonstrated that sonication can also be applied to the solid phase synthesis of oligosaccharides. By employing the traceless linker, the designed oligosaccharides can be obtained in pure form and, more importantly, ready for incorporation to aglycons of interest via 'Click' chemistry or amide linkage. In the event where solid phase synthesis cannot yield satisfactory results, a combination of solid phase and solution phase approach may serve as a valuable alternative. The overall strategy will facilitate the studies of roles of carbohydrates in bioactive compounds.

A typical experimental procedure is as followed: the resin is allowed to swell in anhydrous methylene chloride for 1 h after which the glycosyl donor (3–6 equiv) is added followed by Lewis acid and the reaction mixture is sonicated for 20–25 min at ambi-



Scheme 3. Solid phase synthesis of di- and trimannosides.



Scheme 4. Solid phase synthesis of branched trimannosides.

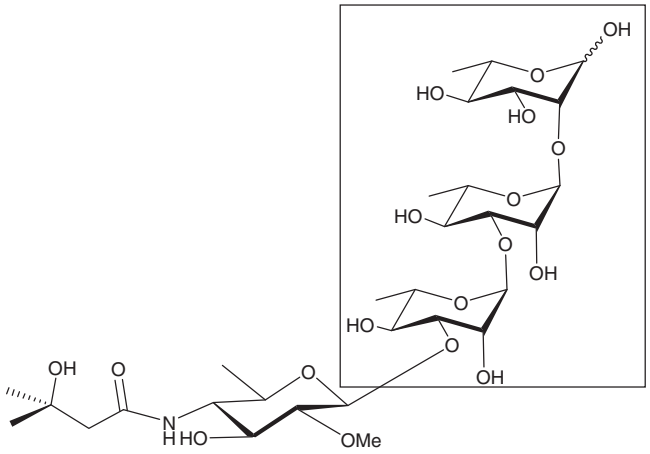
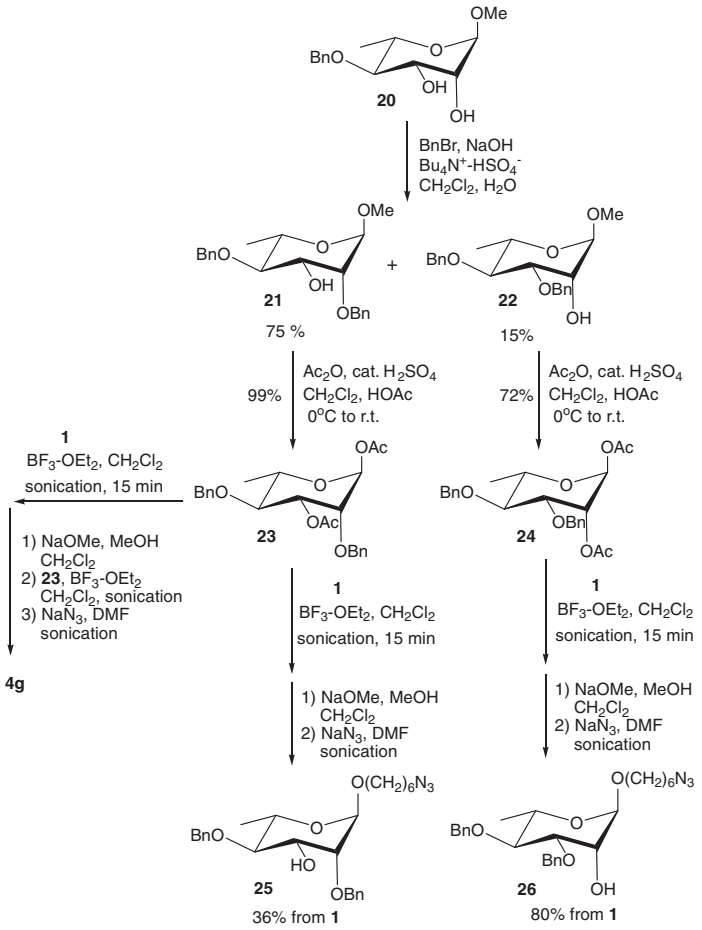
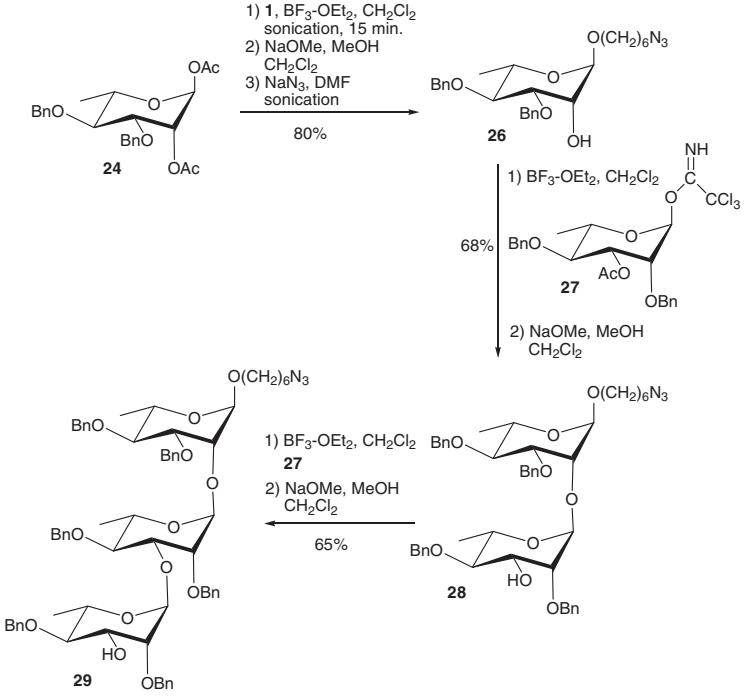


Figure 1. Anthrax tetrasaccharide.

ent temperature. After that the resin is washed with methylene chloride followed by methanol and methylene chloride again (three times). Then the resin is dried under vacuum. The dried resin is swelled in DMF, followed by addition of NaN_3 (2 equiv) and the mixture is sonicated for 30 min and filtered through Celite (twice) to remove the solids. The solvent was evaporated and the desired product can be obtained. If the crude product is not pure



Scheme 5.



Scheme 6.

enough, it can be further purified by a flash column (gradient Hex/EtOAc from 100:0 to 70:30). For the reaction carried out with phenylthioglycosides as the donors, longer reaction time was needed to enable the reaction to proceed. Since the overall yield can be affected by the loading efficiency of 1,6-hexanediol linker, repeating the loading step for the preparation of **1** is recommended.

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Supplementary data

Supplementary data (spectroscopic information for the synthesised compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.027.

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18. The low yield of some examples is likely due to the loading efficiency of 1,6-hexanediol linker on sulfonyl resin and incomplete glycosylation as 6-azidohexanol was obtained as the by-product in several syntheses. Therefore, repeating the loading step for the preparation of **1** is recommended.