to glucose-sensing by glucokinase, whose K_m is much higher compared to hexokinase[12].

Although Lau *et al.* have provided convincing evidence for this switching effect in cells, its effect within whole organisms is not yet known. The switching hypothesis may open a new avenue for the understanding of growth factor receptor signaling by metabolic flux by way of the hexosamine pathway. The lattice model provided by Lau *et al.*[1] is also intriguing in that extracellular interactions can control the rate of endocytosis of cell surface receptors. Although endocytosis of receptors has been studied only with regard to cytoplasmic events such as interactions between cytoplasmic tails of receptors and adaptor proteins, this work clearly shows an extra level of control executed by the extracellular environment. Direct visualization of the lattice under several different conditions should yield fruitful indications for understanding the switch between cellular growth and arrest.

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COMPETING INTERESTS STATEMENT

The author declares no competing financial interests.

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Sugars synthesized in a snap

Peng George Wang

The chemical synthesis of natural oligosaccharides by sequentially stitching monosaccharides together remains a major challenge because of the complexity of carbohydrate structures. A recent paper reports a versatile technology for creating selectively protected synthetic intermediates, thus providing easy access to complex oligosaccharides.

Understanding the biological roles of polysaccharides has been a significant challenge because of several factors, including the heterogeneity of sugar substituents, the molecular redundancy of many sugars, and their structural diversity. Accordingly, one important part of saccharide research has been the chemical synthesis of carbohydrates to confirm presumed structures or to better understand the molecular interactions driving a biological process. Because of these complex structures, however, synthetic methods for obtaining complex carbohydrates are often just as unwieldy as deciphering the original biological system. This is particularly apparent in the cumbersome and laborious preparation necessary to create selectively functionalized raw materials on a large scale. This difficulty in preparing synthetic carbohydrates is reflected in our minimal understanding of the major biological roles played by these very important biomolecules. Recent work by Wang *et al.* offers new hope for advances in carbohydrate synthesis, as they report a versatile combinatorial and regioselective one-pot methodology for the synthesis of orthogonally protected monosaccharide units[1].

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Selectively protected building blocks are necessary in the chemical synthesis of biopolymers. However, unlike proteins and nucleotides, which are linear biopolymers, the branching in carbohydrates makes their preparation more tedious because (i) more functional groups must be protected and (ii) the diversity of desired structures requires that the protecting groups not only be orthogonal (like the protecting groups on amino acid side chains and nucleotide bases) but also be amenable to further reactions. Problems are further encountered in achieving high-yielding and stereoselective couplings for multifunctional carbohydrate donors and acceptors, but these can also be traced back to the protection groups on saccharide units. To circumvent this problem, a number of different methods for selective protection and deprotection of hydroxyls on monosaccharides have been developed. For example, Wong *et al.* developed an efficient orthogonal protection-deprotection strategy to achieve combinational carbohydrate synthesis[2]. Even with this and similar advances, the arduous reactions and workup procedures that are required continue to make carbohydrate research a difficult field.

In the recent report by Wang *et al.*[1], the authors cleverly designed a new method for distinguishing the reactivity of all non-anomeric hydroxyls on glucose by preforming a *per*-trimethylsilylated glucoside (**Fig. 1**). The resultant intermediate serves as the basis for the remainder of the synthetic strategy, as it is a precursor to a panel of useful and well-characterized carbohydrate derivatives. The beauty of this one-pot method is that the orthogonal protection and selective deprotection to furnish any of the required donors can be accomplished by the sequential addition of reagents in one reaction flask without isolating any intermediates, thereby sidestepping many of the shortcomings of previous synthetic methods.

To obtain the orthogonally protected monosaccharide, trimethylsilyl trifluoromethanesulfonate (TMSOTf) was used as an ideal reagent to catalyze protecting group exchange in the one-pot strategy. Substituted and unsubstituted benzyl ethers were selected as optimal protecting groups because they can be deprotected under distinctive reaction conditions, and can thus be installed in a tandem process. In particular, the authors made judicious use of known chemistry in the initial reaction of C6-*O*-TMS acetal with an aryl aldehyde followed by the TMSOTf-catalyzed cyclization with O4 to a thermodynamically more stable six-membered cyclic arylidine. TMSOTf similarly catalyzed the formation of a second TMS acetal at the C3 position of the sugar with another aryl aldehyde. The last step of the initial sequence highlights the innovative design of this one-pot orthogonal protection strategy: the increased stability of the C2-*O*-TMS relative to the rest of the TMS ethers on the monosaccharide allowed a final conversion to an ester using catalytic TMSOTf and acid anhydride.

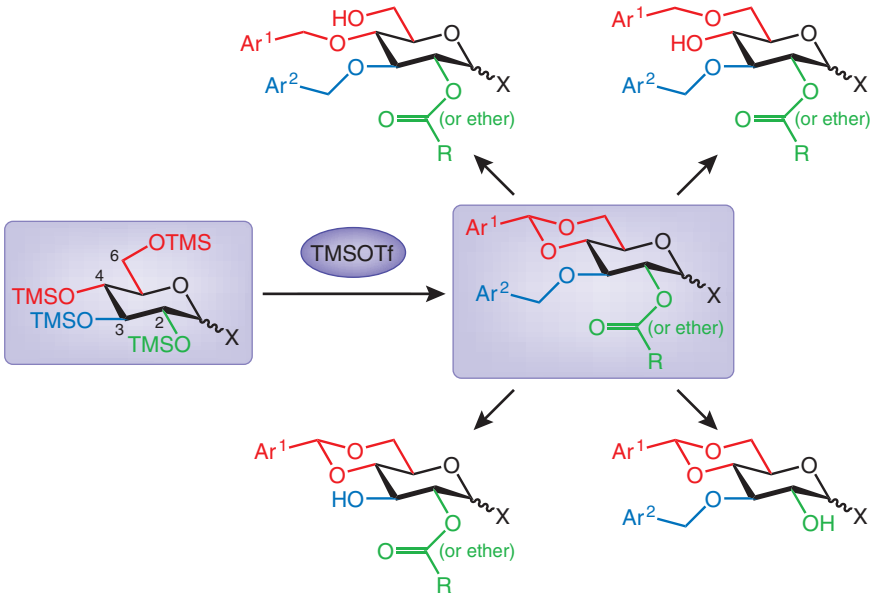

Figure 1 Strategies for selective protection of glucose hydroxyls with different protecting groups. The O4 and O6 formed a six-member arylidene ring when catalyzed by TMSOTf. The arylmethyl ether was introduced on the O3 by reaction with arylaldehyde followed by reduction with triethyl silane. The O2 was protected as an ester by treating with acid anhydride in the presence of TMSOTf or an ether in the presence of a base and electrophile. The C6 hydroxyl was freed via reduction with borane, whereas the C4 hydroxyl was freed with sodium cyanoborane as reagent. The protection group on O3 was oxidatively removed, and the silyl group on O2 was deprotected by treatment with fluoride reagent. Colors signify the site of functional group modification; Ar^1 and Ar^2 are different aryl groups; R = alkyl or aryl; X = α–methoxy or β-thiotoluenyl.

This second intermediate then serves as a key branch point for further structural manipulation (**Fig. 1**). The regioselective reduction of the cyclized arylidine protecting group, which is controlled by using different reducing agents, allows introduction of ether functionalities onto either the C4 or C6 hydroxyl. For example, the regioselective deprotection of 4,6-*O*-arylidene with borane under catalytic TMSOTf released a C6-hydroxy sugar (**Fig. 1**, top left). On the other hand, when sodium cyanoborane was used as a reductive reagent in acidic conditions, the C4 hydroxyl was released (**Fig. 1**, top right). The O3 protecting group, on the other hand, could be converted to an ether group by reduction with trimethyl silane or freed to the unmodified hydroxyl using oxidation-sensitive protective groups, such as *para*-methoxybenzyl or 2-naphthyl ether (**Fig. 1**, bottom left). The TMS group on O2 could be deprotected when it was treated with *t*-butyl ammonium fluoride to yield the 2-hydroxy saccharide (**Fig. 1**, bottom right).

By combining these potential reaction pathways, the authors successfully applied this one-pot methodology in the synthesis of a combinatorial library of fully protected donors and acceptors. With these building blocks in hand, the authors investigated the utility of the one-pot glycosylation method for assembling di-, tri-, tetra- and pentasaccharides with β(1-6) linkages. A trisaccharide unit on the human cell receptor for H5N1 avian influenza, SA-α(2-6)-Gal-β(1-4)-GlcNHAc, was also prepared; this was the first one-pot synthesis of this trisaccharide unit.

This combinatorial one-pot synthesis of monosaccharides is certainly very useful to the carbohydrate community. A good protecting group strategy has to face the challenge that certain protection groups may influence the reactivity of glycosyl donors and acceptors. The iterative one-pot glycosylation is independent of the differential glycosyl donor reactivity[3]. The outcome, however, varies case by case. The one-pot protocol developed by Wong *et al.* uses the relative reactivity values of thioglycosides (resulting from different protection groups) to construct oligosaccharides[4]. Moreover, this one-pot protection methodology limits the choice of glycosylation methods; for example, the widely used Schmidt's trichloroacetimide would not be amenable to these conditions[5]. Additional orthogonal protecting groups will need to be added into the combinatorial one-pot protocol. Although this research provides one important new approach, finding a universal method for the chemical synthesis of complex oligosaccharides in good quantities is still a challenge to the carbohydrate community.

COMPETING INTERESTS STATEMENT
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