

NEWS OF THE WEEK

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Automated Synthesis Of Oligosaccharides

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Automated solid-phase synthesis of oligosaccharides has been achieved by researchers at Massachusetts Institute of Technology--a feat that puts the ability to make oligosaccharides on demand, just like proteins and nucleic acids, one step closer.

The oligosaccharide synthesizer is the brainchild of [Peter H. Seeberger](#), an assistant professor of chemistry, working with graduate students Obadiah J. Plante, Emma R. Palmacci, and Daniel M. Ratner. At a symposium sponsored by the Division of Carbohydrate Chemistry, Seeberger showed examples of oligosaccharides that were assembled with the machine.

"Oligosaccharide synthesis is so cumbersome and requires such specialized expertise that only a few synthetic labs are capable of making large, biologically active structures," comments [Carolyn R. Bertozzi](#), an associate professor of chemistry at the University of California, Berkeley, whose research at the interface of chemistry and biology frequently requires assembly of complex oligosaccharides. "One hopes that Seeberger's automated synthesizer will make the synthesis of oligosaccharides no more complicated than ordering the essential building blocks and programming a computer with the desired sequence."

The machine is a modified version of a commercially available peptide synthesizer. It feeds monosaccharide building blocks (instead of amino acids) to a reaction vessel containing polystyrene beads with a linker. Following a programmed cycle, the machine adds specified amounts of protected sugar building blocks to the resin, delivers solvents and reagents, and controls the temperature of the reaction vessel.

The synthesizer brings together two chemistries developed recently in Seeberger's lab: differentially protected glycosyl phosphates as glycosyl donors and a novel olefin linker that's stable during synthesis but easily cleaved under mild conditions [*Org. Lett.*, **1**, 211 and 1811 (1999)]. Other types of donors can be used, Seeberger says, but "we have had the most success with glycosyl phosphates."

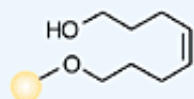
Using the machine, the MIT team has prepared a linear heptasaccharide in 19 hours with 94% average stepwise yield and 42% overall yield. Manual synthesis of the same heptasaccharide took 14 days and gave only 9% overall yield. To show that the machine can actually make something of biological interest, the team has embarked on automated synthesis of a branched dodecasaccharide that triggers a defense mechanism in plants. Half the molecule was assembled in 10 hours in 89% overall yield. As C&EN goes to press, the team is running analyses to confirm that the full molecule has been prepared.

A carbohydrate synthesizer should make any kind of oligosaccharide accessible, even highly branched

ones. The key to achieving this goal is the availability of properly protected building blocks. To help expand the scope of hydroxyl-protected sugars, Seeberger and MIT chemistry professor Stephen L. Buchwald recently developed halobenzyl ethers as protecting groups [*J. Am. Chem. Soc.*, **122**, 7148 (2000)].

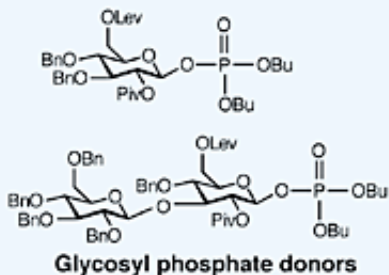
It's still a long way to an off-the-shelf piece of equipment. But, as Bertozzi points out: "Seeberger has made the important first step and identified the fundamental synthetic obstacles that must be overcome to achieve such automation. That his group has transferred the chemistry to a machine environment is a testament to ingenuity and commitment."

Automated synthesis with these reagents . . .



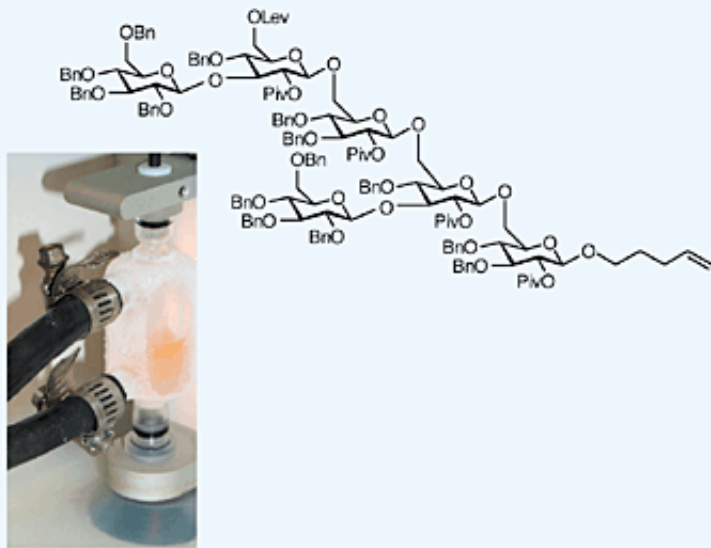
Solid-phase linker

Bn = benzyl
Bu = *n*-butyl
Lev = levunoyl
Piv = pivaloyl



Glycosyl phosphate donors

. . . produces this oligosaccharide



The product represents half of a naturally occurring molecule in fully protected form. To the reaction vessel (inset) containing solid-phase linker, the synthesizer adds the glycosyl donors according to a prescribed sequence and takes each donor through a coupling and deprotection cycle. When the requisite number of each donor type has been added, the linker-bound molecule is removed, and the oligosaccharide is cleaved from the linker.

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