

THE *Current*

August 12, 2025

[Harrison Tasoff](#)

New method to synthesize carbohydrates could pave the way to biomedical advances

Carbohydrate is a familiar term. It's the bagel you had for breakfast, the bread in your sandwich, the slice of cake you're thinking about sneaking later today. But carbs aren't only in baked goods, and they're not just found in foods. Small yet structurally complex carbohydrates serve as elements of cell walls and are important in intercellular interactions.

Scientists can quickly and reliably make many biomolecules, from DNA to proteins, using automated instruments. So it may come as a surprise that for decades, scientists have had major difficulty with small carbohydrates.

Researchers at UC Santa Barbara and the Max Planck Institute of Colloids and Interfaces (MPIKG) have discovered a way to selectively create the links that connect single sugars into short-chain carbohydrates, called oligosaccharides. The new technique enables precise control over the stereochemistry, or handedness, of the connecting bonds between sugar molecules. The team successfully used this method to construct sugar chains on an automated instrument.

Their [results](#), published in Nature Synthesis, will provide biologists and biochemists access to oligosaccharides that were previously difficult to construct. This, in turn, could open up new avenues of biomedical research into these versatile molecules.

“The holy grail in carbohydrate chemistry is a one-size-fits-all synthetic method. And that’s what we’re approaching,” said senior author [Liming Zhang](#), a chemistry professor at UCSB.

Deceptively simple molecules

Oligosaccharides are carbohydrates that consist of three to 10 sugar molecules (monosaccharides) linked together. They aren’t structural carbohydrates, like cellulose or chitin. Nor do they store energy, like starch. They are often found on the surface of cells where they play critical roles in intercellular communication and signaling, viral and bacterial infection, immune system modulation and developmental processes.

Despite their relatively small size, oligosaccharide structures are anything but simple, with variations between their components, connecting locations and the handedness of the connecting bonds. Scientists estimate that there can be more than 100 million kinds of five-unit oligosaccharides. And this is what makes synthesizing them so challenging: gaining precise control over the spatial orientation of these bonds despite the structure complexity.

A chemical reaction is just as likely to produce a lefthanded bond as a righthanded bond. “So, when you make those sugar-sugar linkages you often get a mixture of configurations/handedness,” Zhang explained.

In contrast, the various building blocks that comprise proteins and nucleic acids only bond in one way, without distinct handedness. And they’re never branched, explained co-author Peter Seeberger, a scientist at MPIKG. Because each sugar-sugar bond can take one of two spatial orientations, an oligosaccharide’s permutations grow exponentially with its size. There are over 2,000 possibilities for the same 10-sugar molecule. “It renders non-stereoselective chemistry useless,” Zhang said.

How to get what you want

Unfortunately, it isn’t feasible to isolate many oligosaccharides from nature either. When scientists break them down, they get a complex mixture of similar molecules

that's practically impossible to isolate, Zhang explained. So if scientists want one, they have to synthesize it. Enzymes are quite efficient for producing specific molecules, but they are generally limited to specific reactants. Enzymes also take time and money to evolve, so aren't ideal for the early phases of research.

A major challenge in chemical synthesis is simply separating the product from all the side products and byproducts. This can require lots of solvent and filter material, contributing to the labor involved, waste produced and production cost, Zhang said. That's why the authors opted to develop chemistry suitable for solid-phase synthesis, where the process is conducted with one end anchored to a polymer support. In this way they can build the oligosaccharide piece by piece, knowing that only their desired product will stick to the support structure when they wash the apparatus between steps.

The development of solid-phase synthesis for peptides earned its inventor the 1984 Nobel Prize in Chemistry, and it has since become routine in oligonucleotide synthesis, as well. Seeberger pioneered the process for carbohydrate synthesis in 2001 and has improved on it over the past 25 years.

The comings and goings of chemical groups

A molecule's behavior depends not just on composition, but also shape. So the same molecular formula could have many different arrangements, or isomers. Scientists can reliably construct a particular orientation when one simple sugar bonds to another. But controlling the orientations across a broad range of bonding scenarios with one unifying approach remains highly challenging and, so far, out of reach.

To meet the challenge, Zhang's lab used a reaction called bimolecular nucleophilic substitution (S_N2). This is a one-step process where the new sugar arrives at the growing oligosaccharide at the same time as the departing component breaks off. As a result, the new sugar can only approach in one orientation: with the leaving component facing away. This S_N2 process allows chemists to reliably control bonding orientation in a broadly applicable manner.

But getting the coming and going to happen simultaneously is very tricky in the context of oligosaccharide structural complexity. That's why the team added a directing molecule to the leaving group. This provides the reaction with a helping

hand by promoting attack by the incoming sugar before the leaving group departs too early.

This directed S_N2 approach works for many types of sugar-sugar connections the Zhang lab has examined so far, and reactions in solution as well as solid-phase chemistry. It can be conducted under conditions that are neither particularly acidic nor basic. What's more, the automated solid-phase synthesis doesn't require a technician to possess a great deal of specialized training.

Bringing oligosaccharides to the masses

This achievement is a long time coming. "Developing stereoselective glycosylation has been worked on since the early 20th century," Seeberger said. Zhang's team first began their work on the task in 2018.

Automated oligosaccharide synthesis will most benefit non-chemists. Right now, if a biologist wants a particular oligosaccharide, they'd have to hire a contractor to manually synthesize the compound, which could take months and be costly. "The idea is you can do this iterative process, using a machine, and that machine can automatically synthesize it," Zhang said. Seeberger has founded a company that offers both the service and the machine that runs it, providing a direct path for application.

Given the cost of the technique, the authors anticipate it'll find most use in biomedical research. "Among those applications are diagnostic tests for autoimmune diseases and vaccines to prevent hospital-acquired bacterial and fungal infections," Seeberger said.

The methodology is ideal for early experiments, where scientists may need only small quantities of a substance to explore its potential. Once researchers find a promising oligosaccharide, they can invest in enzymatic or chemoenzymatic approaches to synthesize it more efficiently.

Going the extra mile

Zhang's glycosylation technique already works with a wide range of sugars and can produce a broad array of different structures. Yet he plans to test it on more

uncommon sugars. The sugars made by eukaryotes are just a small fraction of those produced by bacteria, he explained, and many of these are important in biological and medical research.

There is also one particular bond, the so-called “beta mannosidic” linkage, that still remains unsolved. “Our teams will try to crack that nut,” Seeberger said.

Solving challenges like automated oligosaccharide synthesis is crucial to making more applied breakthroughs. Exciting developments like new cancer drugs, broad-spectrum vaccines and more potent antibiotics aren’t possible without advances in basic methodologies.

“By developing this chemistry, we open up many more possibilities,” Zhang said.

Media Contact

Harrison Tasoff

Science Writer

(805) 893-7220

harrisontasoff@ucsb.edu

About UC Santa Barbara

The University of California, Santa Barbara is a leading research institution that also provides a comprehensive liberal arts learning experience. Our academic community of faculty, students, and staff is characterized by a culture of interdisciplinary collaboration that is responsive to the needs of our multicultural and global society. All of this takes place within a living and learning environment like no other, as we draw inspiration from the beauty and resources of our extraordinary location at the edge of the Pacific Ocean.