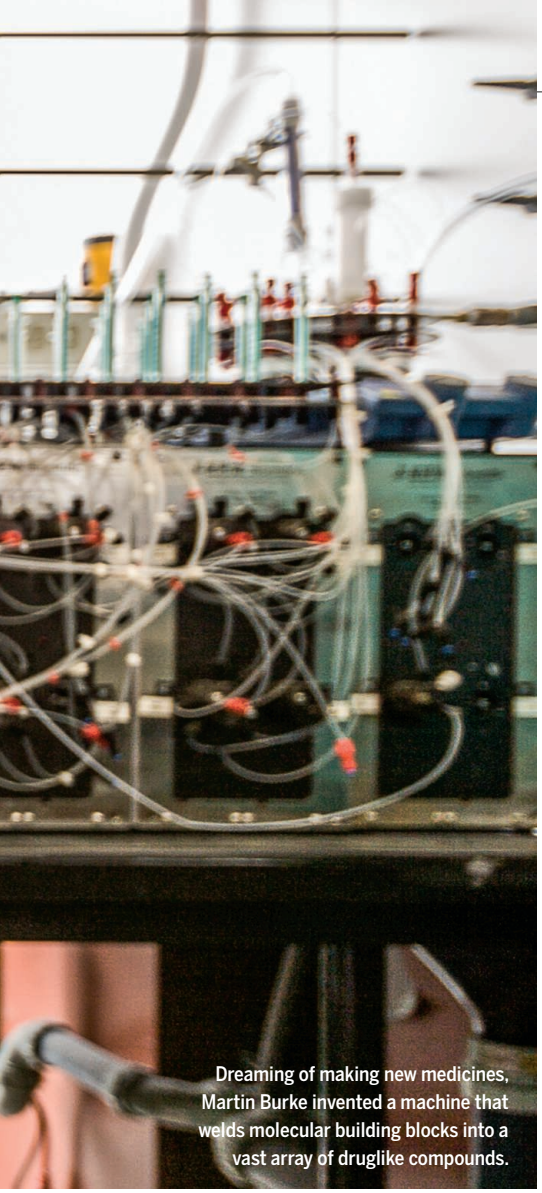

Dreaming of making new medicines, Martin Burke invented a machine that welds molecular building blocks into a vast array of druglike compounds.

Organic chemistry is an ordeal—just ask most science majors. There are the bewildering names of molecules, the elements, bonds, reactions, and reagents. There are the recipes, lab work, and late nights hovering over flasks. There are the separations, purifications, and analysis. Even for experts, making molecules is slow, painstaking work.

"We think we can change that," says Martin Burke, a chemist at the University of Illinois, Urbana-Champaign. And to drive the point home, he offers to transform a chemistry neophyte—me—into a synthetic chemist.

Burke steers me into Room 456 of the Roger Adams Laboratory building and toward a black lab bench holding a contraption about the size of one of those industrial espresso machines you see at Starbucks. Atop it sits two aluminum blocks, drilled through with 2.4-centimeter-wide holes, for holding nine vials. A tangle of thin tubes connects all the different pieces. But its basic principle is simple: It's a chemistry version of a highway cloverleaf, intended to steer ingredients from one place to another. Burke and his students call it simply "The Machine."

Michael Schmidt, a second-year graduate student in Burke's lab, gives me a recipe for crocacin C, an antifungal compound first synthesized in 2000 by three Australian chemists. Plastic vial number 1, which contains a pinch of a white crystalline powder, goes in slot number 1. Vial number 2, with a different white crystalline powder, goes in slot number 2, and so on. Schmidt has me connect a few spaghetti-width tubes to feed in water, organic solvent, air, and nitrogen gas. Then I press "run" on the Dell laptop below the lab bench, and my work is done.

But The Machine is just getting started. With a soft whir, it proceeds through dozens of steps: preparing, reacting, purifying, washing, preparing, reacting, purifying, washing, and on and on. Two days later, Burke sends word by e-mail that my first total synthesis is complete. The result: 8.6 milligrams of an off-white, powdery crocacin C.

Crocacin C is just one of a host of organic molecules that Burke's machine can make. On page 1221 of this issue, Burke and his colleagues report that they've used their automated synthesizer to produce a wide variety of molecules—stringlike linear compounds, rings, and bowls—all with bonds twisting this way and that. Like an automated DNA synthesizer, the new machine works by snapping together premade building blocks. And because thousands of such building blocks are already sold commercially, the machine could speed the production of potentially billions of different organic compounds that can be tested as new drugs, agricultural compounds, and materials.

"This is an amazing technology," says Cathleen Crudden, an organic chemist at Queen's University in Kingston, Canada. "It's a huge advance in small-molecule synthesis." Peter Seeberger of the Max Planck Institute of Colloids and Interfaces in Potsdam, Germany, agrees. "It's an important milestone, and there will be more to come," says Seeberger, who pioneered his own automated synthesizer for a different kind of molecule, the oligosaccharide sugar chains that cap many proteins and lipids. Improved automation, he and others say, will give biologists and many other researchers unprecedented access to compounds they need, while freeing organic chemists to pursue projects more challenging than churning out molecules they already know how to make. "The better we make this tool and the more we make it available, the more it will enhance science," Seeberger says.

ORGANIC CHEMISTRY has largely resisted automation since the first organic molecules were synthesized in the 1820s. The primary exception has been biopolymers, molecules made with a small number of building blocks that are all linked with the same type of chemical bond. That single bond acts like a train hitch capable of linking boxcars together in any desired order. Today, dedicated synthesizers churn out three such biopolymers: DNA fragments called oligonucleotides, protein fragments called peptides, and oligosaccharides.

This automation has produced powerful results. According to the business research firm MarketsandMarkets, by 2019 the oligonucleotide synthesis business will be worth $1.7 billion. Synthetic peptide-based drugs, meanwhile, already account for more than $14 billion in sales annually. "If you could do similar things with small molecules, it would have a huge impact," says Richard Whitby, an organic chemist at the University of Southampton in the United Kingdom. That's because these molecules not only represent the backbone of the pharmaceutical industry, but are also used in countless other products such as dyes, agricultural chemicals, light emitters, and biological probes.

That hasn't been possible, because small molecules assume a near-infinite variety of shapes. One recent report, for example, calculated that small molecules containing just carbon, oxygen, and nitrogen could be assembled in 10^{60} different ways, more than the number of atoms in the universe. "You need a lot of reactions to put together complex molecules," Crudden says.

Making organic molecules has always been less like linking boxcars than like building furniture. Woodworkers can use many kinds of wood, linked with a variety of joints: mortise and tenon, dovetail, lap joints, and so on. And like craftsmen joining pieces of wood, organic chemists must ensure that each bond is oriented in the proper direction. Attach a carbon atom facing away from the core of the molecule instead of inward, and the biological result could be as useless as a chair with one leg jutting skyward. As a result, except for automating several common industrial reactions, organic chemists tend to rely on complex recipes to forge bonds one at a time, slowly building their molecules in dozens or hundreds of steps. Most synthetic chemists consider that methodical approach the only way to ensure they make exactly what they want. "That has been the dogma for 180 years," Burke says.