# Building Chemicals the New-Fashioned Way

When organic chemists aim to build a specific chemical structure, they often spend most of their time and money trying to isolate it from a brew of by-products that form during the synthesis. That's why molecule makers admire the chemical mastery of organisms, which make and use complex enzymes to coax reactions into yielding a single product.

Scientists at Harvard University now have devised a versatile strategy of achieving such specificity in the laboratory. They say their efforts will pay off in easier, more efficient and cheaper synthesis of drugs, vitamins and other chemicals. The researchers have made a variety of small, relatively simple molecules —which they call "chemzymes"—that can pull off enzyme-like feats. Like huge and complex biological enzymes, "chemzymes bring together different reactants and force them to react at an accelerated rate," says chemist Elias J. Corey, head of the research effort.

At this week's National Organic Symposium held at Cornell University in Ithaca, N.Y., Corey reported designing, making and using chemzymes that fine-tune even today's most widely used molecule-building reactions to churn out only the desired products. Since virtually no by-products form in the first place, many difficult chemical separation and purification steps become unnecessary. "This reaction specificity is the direction toward the future," remarks MIT chemist K. Barry Sharpless, who also is developing reaction-tuning tactics.

Corey's group has designed a chemzyme that catalyzes the first of a series of reactions for making prostaglandins, a family of naturally occurring chemicals that regulate blood flow, blood pressure and other vital signs. Physicians use prostaglandins to induce labor and treat ulcers, among other things.

In the first step of the synthesis, a molecule containing two pairs of double-bonded carbon atoms — a diene — reacts with another molecule, a dienophile, which readily combines with the diene to form a ring of carbon atoms. When Corey first reported a laboratory synthesis of prostaglandins 21 years ago, chemists had no way of controlling the orientation at which these two reactants would approach each other during this step, known as a Diels-Alder reaction. The result was a brew of nearly identical products called isomers, from which chemists had to painstakingly isolate the desired prostaglandin precursor.

With the new approach, says Corey, "the chemzyme brings together the diene and dienophile in a very specific three-dimensional arrangement that gives only one of the 16 possible products. This makes the whole synthesis easier and more cost effective." The importance of controlling reactions in this way mushrooms when the target chemical can have isomers based on many of its carbon atoms. For molecules of medium complexity like prostaglandins, which have about eight such carbon atoms, there can be as many as 256 isomers.

In another example, Corey and graduate student Gregory Reichard designed a chemzyme for a more elegant synthesis of fluoxetine, an antidepressant drug. The drug comes as a mixture of two mirror-image isomers, called enantiomers, only one of which is thought to be therapeutic. Using a chemzyme, the Harvard chemists have designed a reaction sequence that yields either one or the other enantiomer. By eliminating unwanted isomers, drug makers hope to reduce side effects.

At the meeting, Corey described other chemzymes his team has made. "Our approach has been to develop chemzymes for the most powerful synthetic construction reactions [such as the Diels-Alder reaction] because that's where they are needed and will have the greatest impact," he says. Another bonus: Their simplicity should open a new window on basic reaction mechanisms.

Also at the meeting, chemist Philip D. Magnus of the University of Texas at Austin described a different strategy for making new drugs. Many biologically active compounds such as insulin are based on peptide bonds, which connect amino acids into proteins, including enzymes and some hormones. Doctors must inject peptide drugs rather than give them orally, because digestive enzymes snip peptide bonds. Magnus described efforts to make metabolically stable "synthetic proteins" by linking pentagonal pyrrole molecules adorned with the same side groups found on amino acids. So far, he has shown that short pyrrole strings twist into shapes akin to protein helices. *— I. Amato*

## Human origins recede in southern Asia

Scientists have identified southern Asia's earliest known remains of anatomically modern humans, dating to approximately 28,000 years ago, according to a report in the June CURRENT ANTHROPOLOGY.

"We now know the southernmost part of Asia was inhabited by modern humans at a time relatively contemporary with anatomically modern *Homo sapiens* fossils recovered from sites in Europe, Africa and Australia," says anthropologist Kenneth A.R. Kennedy of Cornell University in Ithaca, N.Y.

Researchers excavated the Asian fossils — as well as 17 miniature stone blades, the remains of several animal species, a number of bone tools, bits of charcoal and fragments of quartz and chert—in 1982 in a cave on Sri Lanka, an island off the southeastern coast of India. Sri Lankan archaeologist Siran U. Deraniyagala conducted the excavation, then analyzed the remains in collaboration with Kennedy.

Human skeletal remains include a lower jaw bone, skull fragments and several hand bones. The bones show signs of exposure to fire, Kennedy says. This is more likely due to their proximity to hearths than to intentional cremation, he asserts.

The stone blades, or microliths, are also the earliest such artifacts found in southern Asia. Each triangular or crescent-shaped microlith is about the size of a fingernail. The cave dwellers apparently set 10 to 20 microliths into the groove of a shaft at the end of a harpoon or spear, Kennedy says. Modern *H. sapiens* began using these weapons around 30,000 years ago as barbs that killed animals more effectively than single spear points.

Animal remains in the cave include unidentified cats about the size of a lynx, as well as beavers, fish and birds. Kennedy says inhabitants may have butchered these relatively easily hunted creatures outside the cave, bringing in choice pieces for cooking.

The researchers detected no ruins of a hearth in the cave. Nevertheless, in Kennedy's view, the charcoal in the prehistoric sediment most likely resulted from human-produced fire, since natural fires would have had difficulty spreading into the recesses of the cave. Three independent laboratories have confirmed the charcoal's radiocarbon dates, he adds.

Deraniyagala's team also found stone tools and charcoal in six sediment levels above the layer containing the 28,000-year-old humans. More complete human skeletons recovered in 1981 from one of those levels date to about 16,000 years ago. No other site in southern Asia has yielded a fossil record of anatomically modern humans as large and as old as those in the Sri Lankan cave, Kennedy says. *— B. Bower*