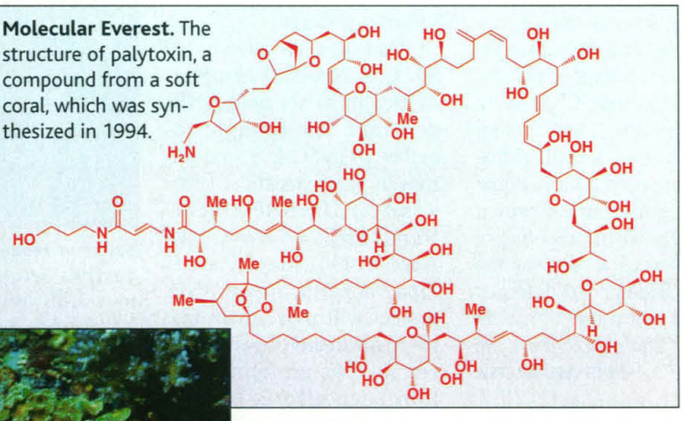
In a branch of chemistry called total synthesis, glory goes to the first team to reproduce a complex molecule from simple ingredients. But some wonder whether the competition is healthy

Race for Molecular Summits

When researchers at the Merck pharmaceutical firm discovered in 1995 that a compound newly isolated from a soil microbe had a novel anticancer activity, the finding touched off a race—not only among biologists to understand and test the new molecule, but also among synthetic chemists to craft it from scratch. Dubbed epothilone A, the compound thwarts cells' ability to divide, rather than killing them directly. That promising trait, along with epothilone's complex structure (37 atoms arrayed in a fishlike shape, with a contorted body and sideswept tail) made it an inviting target for synthetic chemists who specialize in reproducing the most complex naturally occurring molecules they can find. Epothilone stood out as a Himalayan summit in a field that prides itself on taking on every 8000-meter peak in view.

The race to plant a flag on this molecular mountain was a sprint, lasting only about a year, far shorter than the 10 years or more that are regularly spent on such endeavors. Still, some labs made an all-out assault on the structure, with half a dozen or more chemists trying a variety of synthetic strategies simultaneously in hopes that one would pan out. In the end, a group led by Samuel Danishefsky of the Memorial Sloan-Kettering Cancer Center and Columbia University in New York City crested the peak in December 1996, just a month ahead of another team led by K. C. Nicolaou at The Scripps Research Institute in La Jolla, California. The virtual tie was hailed in the pages of *Science* and other science press as a great achievement for organic chemistry.

Molecular Everest. The structure of palytoxin, a compound from a soft coral, which was synthesized in 1994.



But was it? Everyone agrees that the synthesis opened the door for medicinal chemists to tweak the molecule's structure in search of more potent analogs with fewer side effects. But the broader goal of this kind of work—long a prestigious subfield of chemistry that attracts the best and brightest—goes beyond the practical applications of understanding any particular molecule. Chemists want to learn the fundamental rules of how molecules react, to find new reactions and uncover surprising new ways to make and break bonds. In other words, the surprises encountered on the journey are supposed to be as important as the destination. And by that standard, some synthetic chemists say, the epothilone race brought little glory to the winners. "The early syntheses of the epothilones were not up to modern standards," says Steven Burke, a total synthesis researcher at the University of Wisconsin, Madison. "They wouldn't have been publishable if the molecule hadn't been such a high-profile target."

Nicolaou and Danishefsky acknowledge that the original epothilone syntheses didn't rewrite chemistry textbooks, although they say new reactions were discovered in the effort, and that it led to epothilone analogs that may improve on the original compounds. Nevertheless, Burke and a broad cross section of other total synthesis chemists say that these are trying times for the field. They argue that the chemical synthesis race is intensifying while the number of targets is shrinking, because of a slowdown in searches for promising new natural products (see sidebar, p. 186). As a result, more and more synthesis groups are racing after fewer inviting targets. To stay ahead, some researchers rely on safe, well-established reactions, and so make fewer fundamental discoveries along the way. At the same time, the rise of biological chemistry and materials science disciplines are siphoning off the talented students once attracted to the field.

Even chemists who are major forces in total synthesis acknowledge that the pressure to race for the finish line is limiting fundamental explorations. However, they also say that total synthesis remains a fundamentally healthy wellspring of chemical discovery and the ideal training ground for chemists in hot demand in the pharmaceutical industry. Complaints, they say, come largely from scientists without firsthand experience of work on chemistry's cutting edge. "To say this work isn't turning up anything only comes from someone who says surgery is surgery, so removing a corn on a toe is the same as an organ transplant," says Danishefsky.

It's a measure of how touchy the issue has become that many of those interviewed by *Science* agreed to talk on the condition that they not be identified. Yet the soul-searching runs deep, says George Whitesides, a synthetic chemist at Harvard University who is widely regarded as having a broad overview of the field. Total synthesis, it seems, is akin to a superpower in the post–Cold War world. "It's going from a dominant field to one thinking about what's next," says Whitesides. Just what is next depends on whom you talk to, but most in the field agree that biology will be a big part of the equation, as total synthesis retools to focus on the practical goal of creating novel medicines in a simple fashion.

Imitating nature

In the early days of the field—just after World War II—synthesis was performed not so much to uncover new reactions as to nail down the structure of particular molecules. By using a series of well-known reactions with predictable results, researchers could be sure of the three-dimensional shape of the molecule they created. But from the late 1940s through the 1970s, with the advent of other techniques to probe molecular structure—x-ray crystallography and nuclear magnetic resonance spectroscopy—natural products chemists lost their chief raison d'être.

They soon found others. Because synthetic chemists were no longer trying to infer structure from the reactions they used, they

SOURCE: NICOLAOU *ET AL., JOURNAL OF CHEMICAL EDUCATION, 75*, NO. 10 (1998); PHOTO: L. S. ROBERTS/VISUALS UNLIMITED

no longer had to limit themselves to familiar reactions. They were unleashed to explore the world of synthesis, to try to invent new reactions to make impossibly complex molecules from simple starting ingredients, such as amino acids. Natural products, with their wide variety of complex shapes, became ideal targets. "Early on, the issue was, can you make a complex natural product?" says Harvard chemist Eric Jacobsen, who searches for new "asymmetric" reactions that preferentially produce one of several mirror-image forms of some molecules. More recently, synthetic chemists have offered an additional rationale: finding ways to make and modify natural drug candidates that are either rare or hard to isolate in abundance.

But, for many chemists, the basic appeal of total synthesis was visceral, akin to the reason climbing pioneer George Mallory gave when he was asked why he wanted to climb Mount Everest: "Because it is there." The title "Total Synthesis of ..." began proliferating in the pages of the major chemistry journals.

Fortunately, the mountain-climbing approach proved fruitful for chemical discovery as well. By taking on daunting molecular targets such as vitamin B12, for example, Harvard University's R. B. Woodward—together with Albert Eschenmoser at the Federal Technical University in Zurich, Switzerland—laid the empirical foundation for what later became the Woodward-Hoffman rules spelling out how the electronic structures of molecules reorganize during reactions. "These helped make sense of a large body of chemical reactions and provided a way to rationalize why certain reactions take the course they do," says Erik Sorensen, a total synthesis chemist at Scripps. Other foundations of the discipline soon fell into place, and the advances earned a string of Nobel prizes. The names of the total synthesis pioneers—Woodward, Hoffman, Eschenmoser, and E. J. Corey—are as revered among chemists as the names Edmund Hillary and Tensing Norgay are among mountain climbers.

Like Hillary's Everest expedition, total synthesis "is often done in a kind of land war way," says Sorensen, with a heavy investment of personnel and time. The dozen or so large total synthesis labs around the world are each home to between 20 and 40 chemists, organized into teams pursuing separate projects. A few months ago in the Nicolaou lab, for example, one team was toiling on the synthesis of potential anticancer compounds called CP molecules, while another was doing follow-up work on a recently completed project to synthesize vancomycin, and others were following early ideas on compounds such as maitotoxin, a molecule from a marine sponge.

"[Total synthesis] is going from a dominant field to one thinking about what's next."

—George Whitesides

"You eat, drink, and sleep your molecule," says Phil Baran, a Ph.D. student in Nicolaou's lab, who was part of the CP team. Creativity is prized for finding ways to knit desired bonds together. But most good ideas fail, says Baran. So it's typically those who work harder and try more reactions in the lab who come out ahead. "There's always a question of who will finish first," he says.

Embarrassment of riches

As molecular mountain after mountain has fallen under the onslaught, the field's very success has begun to change it. In 1994, Yoshito Kishi and his colleagues at Harvard pulled off the complete synthesis of palytoxin, a neurotoxin from a soft coral. Even today, the molecule is recognized as one of the most complex ever attempted. Palytoxin, Jacobsen explains, harbors more than 100 "stereocenters," where the molecule has mirror-image forms. Synthesizing it demanded not only forging the right bonds, but controlling the orientation of each stereocenter. "A lot of people saw that molecule as a defining moment in the field," says Jacobsen. "It put to rest the question of will it be possible to make any molecule that nature makes. The Mount Everest issue has been answered without exception," he adds. Given ample time, money, and skilled practitioners, any mountain would fall.

Not everyone agrees. Nicolaou, for example, points out that other molecular behemoths such as maitotoxin remain unclimbed, and others will undoubtedly be discovered. Still, as the summits become more attainable, the nuggets of discovery—the other key justification of the work—are becoming rarer as well. As one prominent California-based researcher puts it, organic chemists can work on discovering fundamental principles of organic chemistry, or they can make something, such as a natural product. "It used to be that the way to learn the principles was to engage in the second exercise," says the researcher. "That is less and less true. There's the rub."

"That much I'm ready to concede," says Danishefsky. The chemistry that is developed on the climb up the mountain "doesn't impact as many other projects" as the discoveries made in previous decades, he says. "I'm sure that's true," agrees Scripps total synthesis chemist Dale Boger. "At some point, [the chemistry] becomes so well developed that it becomes harder to justify chemistry for chemistry's sake." Ask synthetic chemists about recent first total syntheses, and for molecule after molecule they'll call the efforts "heroic," "impressive," and more. Privately, though, many wonder whether the chemistry developed is truly goundbreaking.

Some researchers blame competition for shrinking the yield of new science. "The quickest way to make a molecule is not to discover new reactions, but to use known reactions," says Jacobsen. "Rarely do you see a lot of new chemistry come out of that effort." As the California critic puts it, "You're taking known reactions and putting them in a new order."

And competition is on the rise. "I think it has increased over the years as the number of groups engaged in natural product synthesis has increased and the advances in synthetic methods have made it so that a large number of groups are able to tackle complex natural product targets," says Stuart Schreiber, a synthetic chemist at Harvard.

SOME RECENT TOTAL SYNTHESIS HIGHLIGHTS

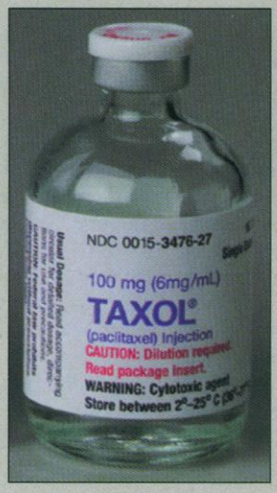
Compound	Activity	Lab	Year
CP molecules	Possible antitumor	K. C. Nicolaou, Scripps	1999
Preussomerins	Antifungal	Clayton Heathcock, UC Berkeley	1999
Olivomycin A	Antitumor/antibiotic	William Roush, U of Michigan	1999
Vancomycin	Antibiotic	David Evans, Harvard	1998
		K. C. Nicolaou, Scripps	1998
		Dale Boger, Scripps	1999
Himastatin	Antitumor/antibiotic	Samuel Danishefsky, Columbia/Mem. Sloan-Kettering	1998
Spongistatin 1	Antitumor	Yoshito Kishi, Harvard	1998
Manzamine A	Antitumor	Jeff Winkler, U of Penn.	1998
Spongistatin 2	Antitumor	David Evans, Harvard	1997
Resiniferatoxin	Possible analgesic	Paul Wender, Stanford	1997
Ecteinascidin 743	Antitumor	E. J. Corey, Harvard	1996

Drug Industry Looks to the Lab Instead of Rainforest and Reef

LA JOLLA, CALIFORNIA—Chemists who synthesize complex organic molecules from scratch take their lessons from nature. As a test of chemical artistry, they try to mimic the complex, pharmacologically active molecules made by obscure living things such as marine sponges, rainforest plants, and soil microbes. The field is at a turning point, with some chemists arguing that it isn't producing the fundamental insights of the past (see main text). And, to add to its troubles, natural products discovery—the effort to find candidate drugs in natural sources, which provides the chemists with their targets—has run into troubles of its own.

In February, Shaman Pharmaceuticals, a biotech start-up devoted to finding drugs in the rainforest, laid off the bulk of its staff after it had a hard time getting its top drug candidate past the U.S. Food and Drug Administration. In 1995, the large pharmaceutical company Abbott Laboratories put an end to its own natural products research, and pharma giants such as SmithKline Beecham have cut back their internal efforts considerably. Instead of looking for promising compounds in nature, they are turning to faster, cheaper techniques for generating and testing synthetic compounds by the thousands.

A decade ago, enthusiasm for stalking new drugs in rainforests and oceans ran high—and with good reason. Historically, natural products have been the main source of drugs, giving rise to everything from penicillin to salicin, the precursor to aspirin. A 1997 ranking showed that natural product drugs still make up 34% of the 25 best-selling drugs, according to Gordon Cragg, who heads natural products drug discovery at the National Cancer Institute in Bethesda, Maryland. But both business strategy and technology have taken the bloom from natural products discovery, Cragg and others said at a conference here recently.*



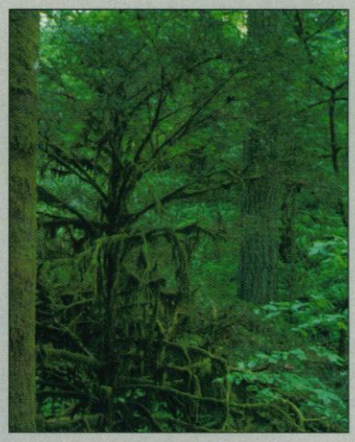
On the business side is industry's appetite for new products. Major pharmaceutical companies in recent years have grown at an impressive 12% a year over the last 5 years. To keep this up, they must come up with as many as six to eight new high-selling compounds a year, up from three to four a few years ago, says Sunil Kadam, a natural products drug discovery researcher at Eli Lilly in Indianapolis. And with natural products, the road to discovery is long.

First, finding novel plants and other organisms for testing requires extensive and painstaking fieldwork. Researchers must then create extracts that can be screened for a desired activity, such as inhibiting cell growth for a candidate cancer drug. Next, the active compound has to be isolated, purified, and tested again. Finally, if the compound passes all these hurdles, researchers must hope that it hasn't already been identified and patented by a previous screen. "All of this takes resources," says Pfizer's Jim Valentine. "There's only so much money to go around."

Over the last decade, much of this money has been channeled into a more industrial approach to drug discovery, combinatorial chemistry. Instead of extracting candidate compounds one by one, combinatorial chemistry synthesizes tens of thousands to millions of them at once. Robotic high-throughput techniques screen them en masse for drug leads (*Science*, 31 May 1996, p. 1266).

"If someone says I'm making 5 million compounds and another says I'll come up with 50,000 extracts, the former gets the money," says Kai Bindseil, executive director of AnalytiCon, a natural products discovery company in Potsdam, Germany. The combinatorial paradigm remains largely unproven: The first few drugs found this way are still working their way through clinical trials. But "the chemistry is improving rapidly," says Bindseil. "There will be further pressures on natural products."

Still, Bindseil and others believe that it's too early to count natural products out. For one, they argue that natural products have a key advantage: diversity. Evolution has done an extraordinary job of making compounds with a wide variety of three-dimensional structures, which is essential for turning up novel drug leads, says Cragg. Combinatorial chemistry, on the other hand, excels at making huge libraries of compounds all slightly different from one another. That can help optimize a drug lead, but it's not as useful in finding the lead in the first place.



Nature's gift. The anticancer drug taxol and its source, the yew tree.

To speed their work, natural products researchers are also turning to technology. In recent years, devices for purifying and analyzing compounds in complex mixtures have improved dramatically, says Kadam. Separations and analysis that used to take months can now be done in days. "This will really speed up natural products discovery," says Bindseil. His company is betting on it. Last December, AnalytiCon embarked on an ambitious program to create a library of some 50,000 natural product extracts by 2002. The company will then license the extracts to pharmaceutical companies for screening.

Meanwhile, researchers at Diversa, a San Diego–based biotech firm, are banking on a new approach to isolating natural products from microorganisms. Microbes—by far the most numerous and varied organisms on Earth—have been prolific sources of breakthrough compounds, particularly antibiotics. And their sheer diversity suggests that a rich panoply of compounds remains to be discovered. But researchers have traditionally been able to sample compounds only from organisms they could grow in culture, perhaps less than 1% of the species thought to exist. "There's a tremendous amount of chemical information that has not been tapped yet," says Cragg.

Diversa gets around the culturing problem by isolating DNA from new microbes and cloning random fragments—containing genes or families of genes—into the common lab microbe, *Escherichia coli*. The *E. coli* produce the novel proteins, which sometimes work as biosynthesis machines, producing novel compounds found in the original, unculturable organisms. Finally, the researchers isolate both the new proteins and their handiwork and scan them for druglike activity.

It's still too early to know if these or other approaches to high-speed natural products discovery will be adopted throughout the industry. But in the end, says Kadam, "this is a 'show me' science." If natural products researchers show that they can turn out novel compounds at a relatively low cost, their discipline may again thrive. **–R.F.S.**

* "Natural Products Discovery: At the Crossroads of New Technology and Genomics," La Jolla, California, 13–14 May 1999.

CREDITS: (LEFT TO RIGHT) BRISTOL MEYERS-SQUIBB; P. K. ZIMINSKI/VISUALS UNLIMITED

Others blame the science media—including news articles in *Science*—for celebrating the races and lavishing recognition on teams that are the first, perhaps by only a few weeks or months, to complete a molecule, instead of mentioning subtler accomplishments, such as developing a more elegant and concise way to make a medically important compound. "If someone comes up with a truly superior synthesis, it would probably not be given as much credit as it should because the summit had already been achieved," says Burke. Adds Nicolaou, "You don't get much credit for rediscovering the wheel."

"I believe these races are minimizing our opportunity to make fundamental discoveries," says Schreiber. "I feel it's not a healthy development in our field." It may also be jeopardizing the field's future, some chemists say. Because of the competition, the handful of big groups that can put the most grad students and postdocs on a project tend to dominate the field. "If you're a young organic chemist, you can't compete with these teams," says one researcher. As a result, promising students may be looking elsewhere. "I think that the best people aren't going into this area," says one synthetic chemist from the Midwest who is not involved with total synthesis. Instead, other areas where synthesis is used as a tool to make materials or drugs, rather than as an end in itself, are siphoning off much of the talent. "Straight synthesis has a lot of competition it didn't use to have," adds the chemist.

But even if total synthesis is facing a period of soul-searching, it will continue to be valued as a way to test cutting-edge chemical techniques and as a robust training ground for the pharmaceutical industry. Companies gobble up graduates from total synthesis labs as fast as they can be minted, putting them to work on crafting potential drug molecules. The targeted, goal-oriented, problem-solving training that students get in total synthesis labs "is very important for what we do," says Paul Anderson, vice president for chemical and physical sciences at the DuPont Pharmaceutical Co. in Wilmington, Delaware.

Synthesis experts also argue that by no means does every total synthesis wind up in a race. And they say they are far from exhausting the veins of new science to be mined. "As long as you are facing new structural types, you will learn new chemistry" in order to make them, says Nicolaou. Harvard synthesis pioneer E. J. Corey adds that the total synthesis field is still assimilating the recent discovery of novel asymmetric catalytic reactions, which have had an enormous impact on how complex molecules are made. "The way people do syntheses now is totally different than [it was] 15 years ago," he says.

But leaders of big and small groups alike say it's time for the field to move on to new goals, such as developing techniques to make exotic compounds with just a few steps, so that the synthesis is commercially practical, or making natural products and their kin in large quantities so biologists can study their effects. Whether the field embraces these aims or continues to be gripped by the lure of racing for unclimbed summits could determine how it fares in its period of greatest uncertainty.

–ROBERT F. SERVICE

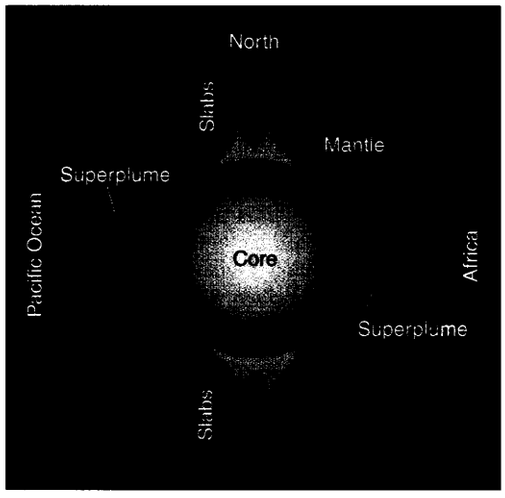
GEOPHYSICS

The Great African Plume Emerges as a Tectonic Player

A massive upwelling of hot rock beneath southern Africa may be shaping the continent as it cools Earth's core, in the flip side of plate tectonics

Plate tectonics gets all the glory. We humans ride the plates across the planet at their stately (and now measurable) pace and marvel at the natural wonders they produce—the soaring Himalayas, the deep-sea trenches, the earthquakes, the volcanoes. All this geologic hubbub happens because, through plate tectonics, Earth's mantle is cooling itself. Hot new ocean crust forms at midocean ridges, cools, and sinks back into the mantle, shedding heat and driving the plates. But geophysicists have long suspected that Earth might have another, less obvious way of chilling out. Almost 3000 kilometers down at the bottom of the mantle, they figured, heat from the molten iron core may churn up towering plumes of hot rock that slowly rise to the surface to spew volcanic outpourings. A narrow plume has recently been spied beneath Iceland (*Science*, 14 May, p. 1095), and another may fuel Hawaii's volcanoes—small potatoes in Earth's cooling system. But geophysicists are now accumulating increasing evidence of two huge "superplumes" cooling the core.

Deep beneath southern Africa, the "Great African Plume" is shaping up as the clearest example of a superplume. At the spring meeting of the American Geophysical Union (AGU) in Boston and in recent publications, geophysicists report signs that a blob of hot rock several thousand kilometers wide at its base, long known to lurk beneath southern Africa, extends toward the surface, spanning the mantle from the core to the volcanic hotspot of northeastern Africa. Its ascent could be pushing up much of southern Africa, and it could be feeding a dozen or more volcanic hotspots across the continent.



Blowing hot and cold. Superplumes loft heat from Earth's core, while cold slabs sink inward.

SOURCE: A. FORTE/U. WESTERN ONTARIO; ILLUSTRATION: L. CARROLL

Another likely superplume seethes beneath the southwest Pacific. Together, the plumes are a major force in the 80% of the planet that is the mantle, says geophysicist Alessandro Forte of the University of Western Ontario in London, who sees them forming half of "the dominant large-scale structure of the deep mantle." They might even shape climate.

Earth scientists have only just convinced themselves and most of their colleagues that narrower structures span the mantle from top to bottom. By using earthquake waves crisscrossing the mantle as a global version of the x-ray CT scans in medicine, seismologists have seen slabs of cold, dense ocean plate sinking below a depth of 670 kilometers into the lower mantle—in places, apparently, all the way to the bottom (*Science*, 31 January 1997, p. 613). A curtain of slabs descends around the Pacific Rim of Fire, while others plunge under the Mediterranean Sea and India.

The slabs show up on seismic images because colder rock speeds up seismic waves. Hot, seismically slow features are tougher to pin down. Two great blobs of seismically slow mantle, one beneath the southern tip of Africa and the other beneath French Poly-