Chemists synthesize a natural-born killer

It took 22 years and involved 64 chemical transformations, but chemists have finally succeeded in making a synthetic version of the natural insecticide azadirachtin. It is the longest-running project that Steven Ley's group, at the University of Cambridge, UK, has ever completed.

But it is unlikely that this 'total synthesis' will ever be repeated — even though Ley is confident that he could more than halve the number of steps — because it is much easier to extract azadirachtin from the seeds of the Indian neem tree (*Azadirachta indica*). For some chemists, these sorts of *tours de force* seem increasingly irrelevant.

Natural-product synthesis emerged in the 1820s when Friedrick Wöhler synthesized urea, showing for the first time that a chemical made by nature could be recreated in the lab. It has spawned some serendipitous discoveries: William Perkin made the first synthetic dye, mauveine, in 1856 while trying to synthesize the drug quinine at the Royal College of Chemistry, now part of Imperial College London.

"There is nothing more noble than what we're trying to achieve."

But for the past 20 years there's been a growing consensus among chemists that the routes to some target molecules are so complicated and low-yielding that making them in this way is pointless. Synthetic azadirachtin is unlikely ever to be used. "Sixty-four steps is not going to be possible for anyone to make on any scale," says Gemma Veitch, who helped derive the synthesis.

In fact, the trend now is to extract pesticides from their natural sources and to move away from either naturally based or purely synthetic compounds such as DDT (dichlorodiphenyltrichloroethane), says John Pickett, head of biochemistry research at Rothamsted Research in the United Kingdom.

But Ley insists that his quest was not in vain. "We won't quit now," he says. "We want to understand a lot more about the biology of the compound." He also expects to make simpler, more effective analogues of azadirachtin that lessen some of the sensitivity the compound shows towards light, acids and bases. Ley says he has also identified the protein in insects that binds to azadirachtin, and that without total synthesis, none of these things would have been possible. The full synthesis appears in the journal *Angewandte Chemie* (G. E. Veitch *et al. Angew.Chem.* doi:10.1002/anie.200703027; 2007).

Derek Lowe, a medicinal chemist and author of the blog 'In the pipeline', is a vocal critic of total synthesis. He says that the traditional justifications for the process, such as structure determination, have evaporated as characterization techniques including nuclear magnetic resonance spectroscopy and mass spectrometry have advanced. He also dismisses the need to make complicated molecules, calling it a trophy-grabbing exercise. "Making the molecule just for the sake of being able to do it is a waste of time," he says. "Some groups have lost track of the reason they're doing total synthesis."

"In the past we were peacocks, we liked to show off," Ley admits. But his attitude has changed. "Today it's all about the value of what you do." There is no point in going after "Everest" challenges, he says. "I don't have to be first; the elegance of the approach is what interests me."

Paul Wender, a synthetic chemist at Stanford University, suggests a different approach. Rather than attempting a very complex molecule, why not design simple but related target molecules, based on the structure and function of the complex natural product, he asks. "This addresses a major problem that many voice about complex molecule synthesis, namely that the targets, although exciting in function, are often too complex to be made in a practical fashion," Wender says.

Other total-synthesis chemists vehemently defend their craft. Phil Baran, from the Scripps Research Institute in La Jolla, California,

A genetic switch for gender bending

Female mice missing a gene involved in pheromone detection show the same sexual behaviour as males, researchers report this week (T. Kimchi *et al. Nature* doi:10.1038/nature06089; 2007).

The striking finding, by Catherine Dulac's group at Harvard University implies that female mice have a 'male behaviour' circuit in their brains, which can be activated by the flick of a single genetic switch.

Female mice genetically engineered to lack a gene called *Trpc2* engaged in exclusively male traits, such as pelvic thrusting, male calls and mounting other mice, both female and male. The TRPC2 protein is essential for the functioning of the vomeronasal organ — a part of the mouse nose that is involved in sensing pheromones.

The results prompt a rethink about how the brain regulates sexual behaviour according to gender, but some query whether they could simply be an effect of the lab environment, or of the types of mice used.

Lab conditions, says Dulac, might cause mice to be more limited in their behaviour than they otherwise would be. So, her group tested the same mutant mice under more natural conditions, leaving them in a larger enclosure for a month. The *Trpc2*-knockout mice still behaved sexually as if they were males.

The genetic make-up of lab mice

M. GUELDRY/SPL

Better times? The jury is out on whether natural-product synthesis has a place in modern chemistry.

admits that total synthesis is not a fashionable pursuit but he insists that it will endure. "Anybody who downplays the Ley achievement as anything other than a landmark is simply jealous." Baran is driven by what he describes as "the creation of beauty" and says: "If you focus on generating complexity in new ways, you have the opportunity to open up new realms of chemical space." He cites examples of important reactions discovered in the course of solving a seemingly intractable synthesis, including a reaction called the Nozaki–Hiyama–Kishi coupling to form carbon–carbon bonds.

Lowe dismisses this idea. "You're more likely to find new chemistry if you're looking for it," he says. But he admits that Ley's work is different, because Ley invented new reagents and general synthetic routes to reach his goal.

Ley himself is well aware of the debates surrounding total synthesis, which he attributes to a squeeze on funding, and says that those who criticize are those who are unwilling to do the tough chemistry themselves. "There is nothing more noble than what we're trying to achieve," he says. ■

Katharine Sanderson

might also affect the results. There are three types of mouse, says geneticist Fernando Pardo-Manuel de Villena, of the University of North Carolina in Chapel Hill. There are the classical lab mice, descended from one original pool of pets, bred to be less aggressive than average; wild-derived lab strains, which are not bred on the basis of behaviour; and wild mice. Wild and lab mice are effectively chalk and cheese, with "strikingly different behaviour", says Pardo-Manuel de Villena.

Dulac's group bred two of the most common classical lab mouse strains — the C57BL and the 129/Sv types — together, and used the offspring in their experiments. But wild mice may behave very differently, points out mouse geneticist Elissa Chesler, of Oak Ridge National Laboratory in Tennessee. "Would there be any compensation for this gene if this mutant was crossed to wild mice?"

Dulac's group is aware of this problem and is now breeding wild mice with the *Trpc2*-mutant mice, to experiment with a 'wilder' version. ■

Kerri Smith

See News & Views, doi:10.1038/nature05892

LEE JIN-MAN/AP

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US genetics bill blocked again

US Senator Tom Coburn is single-handedly blocking the passage of a bill through the Senate that aims to protect people from genetic discrimination.

Coburn (Republican, Oklahoma) is using a legislative tactic called a hold to block a Senate vote on the Genetic Information Nondiscrimination Act (GINA), which was passed in April by the House of Representatives on a vote of 420 to 3 (see *Nature* 447, 14–15; 2007). The bill would make it illegal for employers or insurers to use genetic information in hiring, firing, promotion or insurance-coverage decisions. President George W. Bush has promised to sign the bill into law should it reach his desk.

"I believe the bill, as drafted, contains unintended consequences," Coburn wrote in a 1 August letter to his constituents, who have since deluged his office with complaining letters, e-mails and phone calls. "Congress has both the moral and legal responsibility to pay attention to details and get them right. I want to assure you that my hold on GINA is not because I oppose the bill's purpose, but because I am concerned about its lack of precision."

"The goalposts keep moving."

Coburn, who has holds on 87 bills, voted for essentially the same bill when the Senate passed it unanimously in 2005. At that time, both the House and Senate were controlled by Republicans, but the House refused to bring the bill to a vote. With Democrats now in charge of both, the bill is just one senator away from becoming law.

Coburn wants changes in the bill that would make it harder for victims to sue employers in some cases. He also says that the bill's definition of genetic tests isn't identical in the sections dealing with employers and insurers.

But its advocates dismiss these concerns as manufactured excuses. "The goalposts keep moving," says Kathy Hudson, director of the Genetics and Public Policy Center at Johns Hopkins University in Baltimore, Maryland. "He raises a concern and that concern gets addressed or negated and all of a sudden there is a new concern." ■

Meredith Wadman