Efficient synthesis of ginkgo compound could lead to new drugs, 'green' insecticides

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Credit: Scripps

Chemists at Scripps Research have invented an efficient method for making a synthetic version of the plant compound bilobalide, which is naturally produced by gingko trees. It's a significant feat because bilobalide—and closely related compounds—hold potential commercial value as medicines and "green" insecticides.

Ginkgo trees produce the compound to repel insect pests, but it is effectively non-toxic to humans. The method, published in *Nature*, allows chemists to make and study bilobalide and related compounds relatively easily and much more affordably than previously possible.

"This process demonstrates how inventing the right new chemical reactions allows quick access to complex natural compounds," says Ryan Shenvi, Ph.D., professor in the Department of Chemistry at Scripps Research. "Now we can access bilobalide and the chemical space around it, much of which might have even better properties."

The ginkgo tree (*Ginkgo biloba*) is considered a living fossil. Closely related species lived on Earth 270 million years ago, before dinosaurs, and managed to survive subsequent global cataclysms that extinguished the dinosaurs as well as most other kinds of plant and animal.

Unsurprisingly, given that legacy, individual ginkgo trees today are unusually hardy and long-lived; some specimens are said to be thousands of years old. Traditional Chinese medicine includes the use of ginkgo extracts for a variety of ailments, and even the leaves are said to have been used in ancient times as bookmarks to protect against paper-eating insects like silverfish.

A likely factor in *G. biloba*'s longevity is the set of insecticidal compounds found in its leaves and nuts. These include ginkgolide compounds, which can cause dangerous bleeding in humans who ingest them at high enough doses, but also the less well known bilobalide, which has powerful effects on insects but appears to be essentially non-toxic to people. Bilobalide also breaks down quickly in the environment, adding to its attributes for a "green" insecticide.

However, bilobalide has a complex carbon-skeleton structure with eight oxygen atoms that makes it inherently tricky to synthesize. Previously

published methods were lengthy, in part because of the difficulty of getting all those oxygen atoms into the proper positions.

"We tried a different approach," Shenvi says. "Rather than chiseling away at the structure by putting oxygen atoms in one-by-one, we started with large, oxygen-containing fragments, and then pieced them together, like assembling Ikea furniture."

The new synthesis method, developed principally by graduate students Meghan Baker and Robert Demoret, as well as postdoc Masaki Ohtawa, culminated with a procedure in which the bowl-like molecular architecture was opened and a final oxygen atom was placed at a precise location inside it.

"Figuring out how to do the last part was a monumental effort," Shenvi says.

The synthesis, on the whole, involves far less time and effort compared to prior methods, and its development means that chemists now have a practical organic-synthesis method for making not only bilobalide but also derivative compounds, in order to investigate their properties as insecticides or even as potential pharmaceuticals. Researchers have reported in previous studies that bilobalide reverses cognitive deficits in an animal model of Down syndrome, and that it protects dopamine neurons in a model of Parkinson's disease.

"We were first interested in bilobalide because of its potential relevance for human neuroscience," Shenvi says. "However, since word has spread about the new synthesis, we've had the strongest expression of interest from the agrochemical industry, because of bilobalide's good characteristics as an insecticide and its safety profile."

Shenvi and his colleagues plan to use their new method to make

bilobalide analogs and explore their properties.

More information: Meghan A. Baker et al, Concise asymmetric synthesis of (−)-bilobalide, *Nature* (2019). DOI: 10.1038/s41586-019-1690-5 Meghan A. Baker et al. Concise asymmetric synthesis of (−)-bilobalide, *Nature* (2019). DOI: 10.1038/s41586-019-1690-5

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