



Latest News

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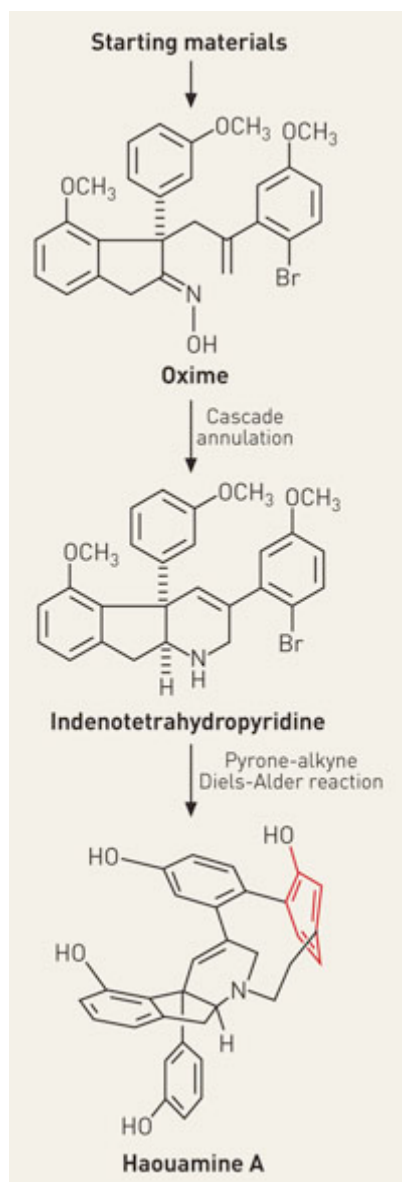
ORGANIC SYNTHESIS

Anticancer Natural Product Synthesized

Researchers blaze synthetic trail to the complex bent-ring alkaloid haouamine A

[Stu Borman](#)

Since the alkaloid natural product haouamine A was discovered about four years ago and found to exhibit promising anticancer activity, at least nine research groups have been trying to synthesize it from simple starting materials. Now, [Phil S. Baran](#) and Noah Z. Burns of Scripps Research Institute have succeeded, putting the compound together in a surprising manner and inventing some novel chemistry along the way ([J. Am. Chem. Soc. 2006, 128, 3908](#)).



Synthetic Approach

Baran and Burns designed an oxime to resemble a proposed biosynthetic precursor, invented an annulation reaction to convert it to an indenotetrahydropyridine, and then devised a pyrone-alkyne Diels-Alder reaction to create haouamine A, which contains a highly

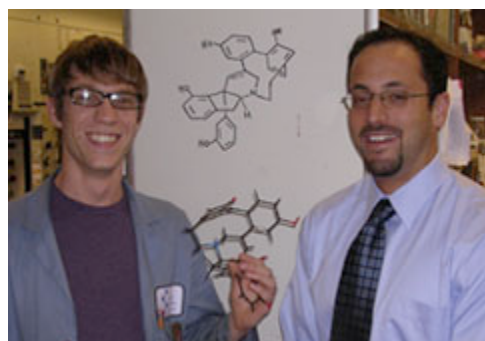
unusual bent phenolic ring (red).

[Eva Zubía](#) and coworkers at the University of Cádiz, Spain, discovered haouamine A in a tunicate (a marine chordate animal) off the coast of Spain, determined its structure, and found it to exhibit selective cytotoxic activity against a human colon cancer cell line. The compound has a complex heptacyclic framework, including an unusual highly strained azaparacyclophane with a bent phenolic ring.

The bent-ring structure presented an interesting synthetic challenge, sparking interest among synthetic chemists. Baran and Burns approached the problem by first proposing a logical biosynthetic pathway for the natural product. They designed an oxime that closely resembled a key proposed biosynthetic precursor and invented a cascade annulation reaction to convert the oxime into an indenotetrahydropyridine. And they devised a scheme in which a pyrone is added to the indenotetrahydropyridine. Then, in a pyrone-alkyne Diels-Alder reaction, the pyrone changes into a nonaromatic ring before rearranging to form haouamine A's bent phenolic ring.

Baran and Burns “have certainly done a beautiful job of developing new chemistry and using it to put together a structurally unprecedented molecule with a very complex skeleton,” comments [Barry B. Snider](#) of Brandeis University. “There are two highlights of the study,” he says. First is “the halogen-induced cyclization of the unsaturated oxime, which goes through several rearrangements to give the desired tetrahydropyridine ring system.” Next is the “intramolecular Diels-Alder reaction followed by loss of CO₂ to put together a very strained biphenyl that would probably be hard to form by other methods. Other people have worked on the synthesis of haouamine A and haven't gotten nearly as far.”

“The really unique feature of the haouamines is the strained azaparacyclophane system,” says [Steven M. Weinreb](#) of Pennsylvania State University. His group and others have been working on haouamine A, he says, “and I think all of us would at least at first try to construct the paracyclophane by standard biaryl coupling methodology. From Baran and Burns's paper, it seems this does not work. Thus there is a serious challenge as to how to build this thing.”



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PHOTO

Synthesizers Burns (left) and Baran with haouamine A model and drawing.

Use of the intramolecular Diels-Alder reaction to solve the problem was clever, Weinreb says, but “is definitely not the final word,” because the percent conversion is relatively low. “There is room for further innovation here,” he says.

[Dirk Trauner](#), professor of chemistry at the University of California, Berkeley, whose group has also been pursuing haouamine A, says the Baran-Burns study “features some highly creative and unusual steps. It shows what can be achieved in synthesis if one thinks outside the box.”

Baran and coworkers are currently working to further tweak the synthesis, adapt it to the sister structure haouamine B, and probe haouamine A’s medicinal properties.

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