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Latest News

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Natural Products

Mystery Structure Solved

Total synthesis confirms structure of micrococcin P1

<u>Stu Borman</u>

AN EXTREMELY BIOACTIVE bacterial natural product isolated 61 years ago has been assigned its correct structure at long last. Using total synthesis, chemists at the University of British Columbia determined the structure of micrococcin P1.

Graduate student David Lefranc and synthetic organic chemist <u>Marco A. Ciufolini</u> carried out the total synthesis (*Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.200900621). The work could lead to micrococcin P1 analogs that might be useful as drugs because the natural product has powerful antibiotic, anticancer, and antimalarial actions. For example, it's active against microorganisms resistant even to the last-resort antibiotic vancomycin.

"The synthesis is certainly a landmark," says organic chemist <u>Christopher J. Moody</u> of the University of Nottingham, in England. It exemplifies "the power of organic synthesis in structure determination."

Micrococcin P1 was isolated in 1948 from a microorganism found in a sewer-water sample collected near Oxford, England. It does not form crystals, so its structure could not be determined by crystallography.

In 1977, a French group tried to pin down its structure but ended up misidentifying both its constitution (atomic connectivity) and configuration (stereochemistry). The next year, Barrie W. Bycroft and Maxim S. Gowland of the University of Nottingham corrected its constitution but not its configuration.

When Ciufolini and coworkers synthesized the Bycroft-Gowland structure in 1999, they found that it did not match the natural product. In 2002, they determined that the mismatch was in the configuration.

Beginning in 2004, Eleanor A. Merritt and organic chemist <u>Mark C. Bagley</u> at Cardiff University, in Wales, showed that the stereochemical misassignment was likely to be at a specific thiazole (bottom right in the structure shown). But the stereochemistry at that site was not determinable spectroscopically. That meant that total synthesis was the only means of verifying the configuration.

Micrococcin P1

Lefranc and Ciufolini now report the first total synthesis of micrococcin P1, based on an informed guess of the correct structure. They find the synthesized compound to be identical to the natural product, confirming the Bycroft-Gowland constitution and the configuration Merritt and Bagley predicted. Key to the synthesis, which took three years, was a modified Hantzsch reaction that made it possible to construct the central pyridine with the full complement of thiazoles around it.

Bacteria tend to develop resistance to thiopeptides like micrococcin P1. But modifying micrococcin P1 chemically might lead to better drugs, and the total synthesis should aid such efforts.

"It is a particular delight for us that the mystery regarding micrococcin P1's structure and stereochemistry has finally been resolved," Bagley says. "With this definitive synthesis, now at last we can consolidate the unique biological properties of the micrococcins based upon sound structural data."

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