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Spotlights on Recent *JACS* Publications

FULL COURT PRESS TOWARD LEUPYRRINS

Dirk Menche and co-workers describe the full stereostructural assignment of leupyrrin A_1 and B_1—members of a class of natural products with potent antiproliferative, anti-HIV, and antifungal activity—and the first total synthesis of leupyrrin A_1 (DOI: 10.1021/jacs.5b01894).

For the configurational assignment, the researchers rely on high-field NMR studies in combination with molecular modeling and derivatization. They first confirm the conclusions of an earlier partial structural characterization, and then proceed to establish correlations between proton NMR signals around the 18-membered non-symmetric macrocycle. Mosher ester analysis enables determination of the molecule's absolute configuration.

A key step in the convergent and scalable total synthesis of leupyrrin A_1 is the zirconium-mediated oxidative cyclization of a highly functionalized substrate to assemble the unique dihydrofuran with two exocyclic alkylidenes.

Leupyrrins efficiently inhibit DNA, RNA, and protein syntheses without disrupting other cellular systems. This selective mechanism of action suggests that an as yet undefined molecular target may be involved, the authors say. Enhanced understanding of the structurally intriguing, biologically relevant leupyrrin natural products may be facilitated through this multidisciplinary endeavor blending isolation, NMR studies, molecular modeling, and total synthesis.

Sonja Krane, Ph.D.

DRUG SCAFFOLDS—STRAIGHTFORWARD THROUGH STRAIN

Neil Garg, K. N. Houk, and co-workers report the first synthesis of 3,4-piperidyne, an intermediate that is useful in the construction of annulated piperidines (DOI: 10.1021/jacs.5b01589). Piperidines are among the most common *N*-heterocycles found in therapeutic small molecules; in fact, over 70 drugs approved by the U.S. Federal Drug Administration, including a number of blockbuster drugs, incorporate piperidines.

Piperidynes are highly strained six-membered rings containing both a nitrogen atom and a triple bond. The researchers generate this molecule in situ by treating a silyl triflate with the base cesium fluoride. They validate formation of the piperidyne through Diels–Alder trapping with a variety of dienes. Further experiments using unsymmetrical cycloaddition partners such as nitrone-, diazo-, and azide-containing molecules afford bicyclic piperidine products with some regioselectivity. A number of the products generated are analogues of known medicinally important scaffolds, and some represent new, unique frameworks.

"Our findings not only provide a new platform to access medicinally privileged piperidine scaffolds, but also lay the foundation for further studies geared toward strategically harnessing strained heterocyclic alkynes as useful synthetic building blocks," the authors conclude.

Sonja Krane, Ph.D.

DIRECTING MOLECULAR TRAFFIC WITH CHEMICAL GRADIENTS IN HYDROGELS

Nanoscale sensors that rely on analyte diffusion suffer from sensitivity limitations and long response times due to the low probability that a molecule will enter the sensor's vicinity to be detected. A new technique developed by Paul Braun and colleagues, which concentrates molecules by transporting them up or down a chemical gradient, could help solve this problem (DOI: 10.1021/jacs.5b00240).

The researchers report a gradient-directed molecular transport strategy that enables analytes to migrate up to several millimeters. In their proof-of-principle demonstration, the team observes a 40-fold greater concentration of anions at the center of radially symmetric cationic gradients—the result of analytes moving to the location within the cation gradient where binding frequency is maximized. The gradients are embedded within a hydrogel film composed of polyacrylamide, an inert material that can be chemically modified to yield gradients for separating molecules on the basis of different functionalities. The hydrogel film also enables the researchers to deposit chemical species out of the air and eliminates the need to immerse the substrate in a liquid.

The authors envision that the chemical gradients may be used to increase the concentration of molecules near nanosensors, resulting in enhanced sensitivity due to a higher probability of analyte–nanosensor interactions.

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