

TAGGING NATURAL PRODUCTS

CHEMICAL BIOLOGY: New approach yields target information

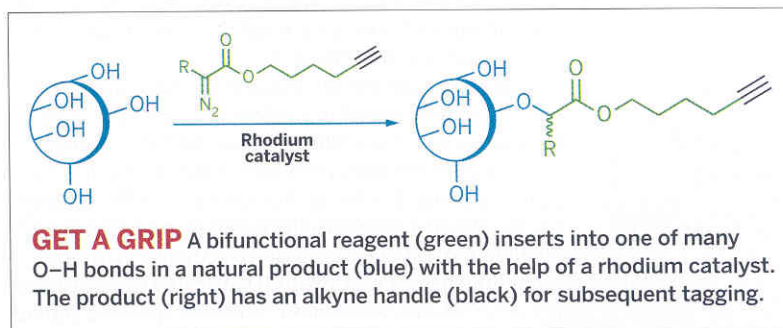
A NEW STRATEGY could make natural products more user-friendly for studies spanning drug discovery and chemical biology (*J. Am. Chem. Soc.*, DOI: 10.1021/ja0733686). Harnessing a transition-metal-catalyzed reaction, a team led by Daniel Romo at Texas A&M University and Jun O. Liu at Johns Hopkins University School of Medicine have simultaneously readied natural products for biological assays and gleaned structure-activity information without multi-step synthesis or large amounts of material.

Although natural products are mainstays as drug leads, identifying their biological targets often takes years. “Solving the ‘target ID problem’ is one of the most important challenges facing chemical biologists,” says Stuart L. Schreiber of the Broad Institute at Harvard University and MIT. Natural-product-based assays, whether for target identification or other applications, require that a reporter tag be installed on the natural product. Tagging the molecule in a way that is both chemically selective and biologically unobtrusive is difficult.

The team’s two-step tagging approach exploits a natural product’s alcohol groups to rapidly discern which chunks of the molecule are important for bioactivity and which are suitable for tagging. In the first step, a rhodium catalyst activates a bifunctional reagent in the presence of a natural product with alcohol groups. A rhodium carbenoid intermediate forms and inserts into an alcohol’s O–H bond. The reaction discriminates among two or more alcohols in several natural products.

“These types of carbenoids offer great advantages in synthesis because they exhibit very high selectivity,” comments organic chemist Huw M. L. Davies of the State University of New York, Buffalo. The reaction product bears an alkyne, to which biotin or other tags can be attached by conventional methods in the second step.

The reaction conditions are mild compared with traditional alcohol-tagging strategies such as acylation, Romo says, a plus for sensitive natural products. In addition, the linkages generated in the reaction are stable in vitro. The team successfully used a conjugate of the natural product FK506 in an affinity chromatography experiment with cell lysates.



The team also can change the insertion reaction’s selectivity, directing the tag to a different alcohol by tuning the catalyst. Evaluating sites on intact compounds from natural sources in this way is less time-consuming than generating tag attachment points by multistep natural product synthesis, they say.

“This is a fine contribution,” says William H. Fenical, a chemistry professor at the University of California, San Diego, and Scripps Institution of Oceanography. “There is no doubt that this exciting new technology will facilitate studies of the biochemical targets of a wider variety of bioactive natural products.”—CARMEN DRAHL