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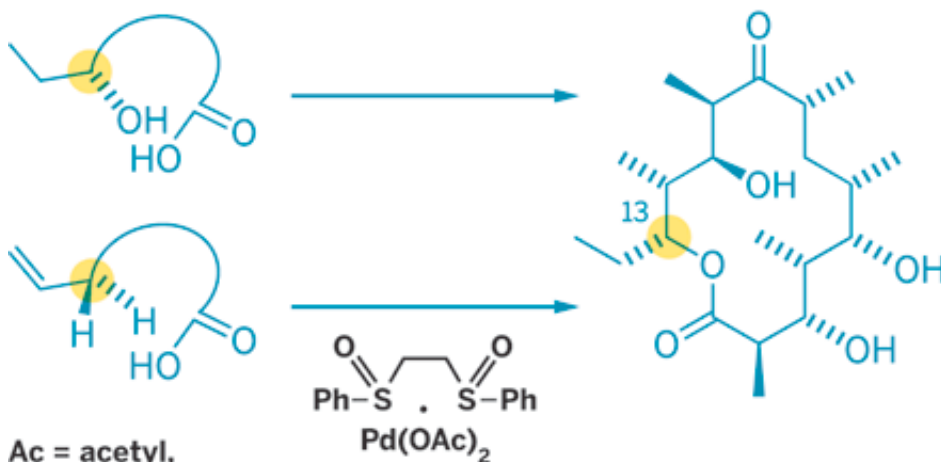
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[Organic Chemistry](#)

New Approach To A Classic Structure

Oxidative ring-closing reaction boosts yield of key erythromycin precursor

[Stu Borman](#)

New Twist The classical approach (top reaction) to 6-dEB (right) was an acylation-based ring-closing at a stereochemically defined alcohol (top left), whereas the new strategy (bottom) involves oxidation of a stereochemically versatile C-H bond. The ring-closing site (C13) is yellow.



Courtesy of M. Christina White [View Enlarged Image](#)

REVISIONISTS Stang (left) and White updated three previous 6-dEB syntheses (behind them) by devising an oxidative (yellow) instead of ester-forming (red) ring-closing reaction.

The natural product erythromycin has long been a challenging target for synthetic organic chemists. An efficient and versatile strategy just developed for forming its large ring shows that the antibiotic remains a test bed for innovative approaches that could aid the syntheses of other natural products and analogs.

The first synthesis of erythronolide B, an erythromycin precursor, was accomplished in 1978 by Harvard University chemistry professor E. J. Corey. Many other groups have synthesized the erythronolides and erythromycin since then. In all these syntheses, creating the large central ring has always been carried out by acylation-based macrolactonization—a ring-closing esterification between an acyclic precursor's hydroxyl and carboxyl groups.

Now, associate professor of chemistry [M. Christina White](#) and graduate student Erik M. Stang of the University of Illinois, Urbana-Champaign, report a radically different approach (*Nat. Chem.*, DOI: 10.1038/nchem.351). Their work marks the first use of a highly selective C–H oxidative macrolactonization to create the core structure, in a new total synthesis of 6-deoxyerythronolide B (6-dEB).

White's group developed the reaction earlier (*J. Am. Chem. Soc.* **2006**, *128*, 9032) but had not previously demonstrated its use on a natural product or a molecule as complex as 6-dEB.

They carried out the reaction at a late stage (step 19 of 22) in the 6-dEB synthesis. They marked the carbon atom to be oxygenated (designated C13) with an adjacent double bond that then served as a target for the Pd/bis-sulfoxide catalyst they used. The group developed a catalytic chelate-control model to predict that oxidative macrolactonization would occur stereoselectively at that particular carbon.

Late-stage ring-closing eliminates the need to put a reactive oxygen at C13 through a large part of the synthetic sequence, which can cause side reactions. Instead, only a C–H group needs to be propagated through the synthesis at the position to be eventually oxygenated. The strategy contributed to the synthesis' 8% yield, as compared with a next-best 5% among the three earlier 6-dEB syntheses.

The approach also improves synthetic flexibility because diastereomers and analogs can be created by modifying a late synthetic step instead of an early one; modifying an early step often makes it necessary to redesign an entire subsequent synthesis.

White and Stang showed that modifying the late oxidative macrolactonization step leads to a stereochemically distinct product. "This unconventional endgame should enable structural diversification, potentially leading to novel erythromycin antibiotics after glycosylation," comments chemistry professor [Ian Paterson](#) of the University of Cambridge.

This research "draws on prior work by White's group but takes that to a new level, as studies on simple model systems often do not extend to multi- and densely functionalized synthetic targets" such as 6-dEB, says chemistry professor [Paul A. Wender](#) of Stanford University. "The numerical outcome is noteworthy in step count and overall yield. More significantly, this study has many ramifications in synthesis. It provides new ways to think about bond construction and thereby new and more step-economical ways of achieving practical supply-impacting syntheses."

"It's a beautiful showcase of how C–H functionalization can be used in complex natural product synthesis," adds C–H insertion specialist [Huw Davies](#) of Emory University.

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