

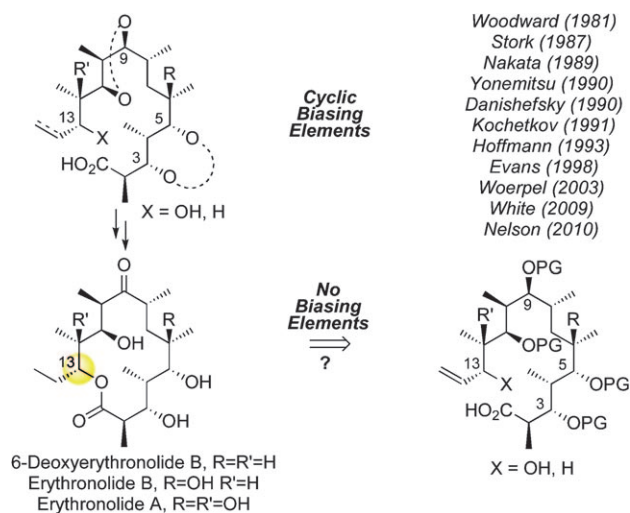
# On the Macrocyclization of the Erythromycin Core: Preorganization is Not Required\*\*

Erik M. Stang and M. Christina White\*

The erythromycins, discovered and isolated in the early 1950s, are the best-known members of the clinically important macrolide class of antibiotics.<sup>[1]</sup> The 14-membered macrolactone core imbedded in these natural products has inspired new synthetic methods for the construction of large ring lactones, beginning with the landmark synthesis of erythronolide B by the Corey group in 1978.<sup>[2]</sup> During these studies, a single acetonide protecting group was utilized at the C-3/C-5 position. Similarly, this protecting group was used by the Masamune group years later for the synthesis of 6-deoxyerythronolide B (6-dEB).<sup>[3]</sup> While no rationale was given for the use of this acetonide at the time, its function was revealed during the historic synthesis of erythromycin A in 1981 by Woodward et al. In three consecutive reports, the Woodward group extensively explored the conformational requirements for efficient acylation-based macrolactonization of erythromycin A seco acid derivatives. In particular, cyclic protecting groups were placed at various positions to serve as biasing elements, that is, artificial structural features intended to aid macrocyclic ring closure through substrate preorganization.<sup>[4]</sup> The results from this study led the Woodward group to conclude that “certain structural features such as ... cyclic protecting groups at C-3/C-5 and C-9/C-11 are required for efficient lactonization” and that “these structural requirements probably arise from conformational requirements for lactonization.” This conclusion—that preorganization is required for efficient cyclization—has become a well-accepted doctrine that has influenced the planning of all ensuing erythromycin syntheses (see below). We now report for the first time that conformational restraining elements are in fact not required for attaining efficient lactonization of the erythromycin core structure, 6-deoxyerythronolide B (6-dEB). Moreover, we demonstrate that the removal of biasing elements allows for more stereochemical flexibility in the cyclization of 6-dEB, thus enabling access to stereochemical

analogues that are not readily accessible with the biasing elements in place. Overall these findings require revision of the 30-year-old dogma that preorganization is mandatory for achieving macrocyclization of the erythromycins.

Inspired by the Woodward report, synthetic endeavors by the research groups of Stork, Nakata, Yonemitsu, Danishefsky, Kochetkov, Hoffmann, Evans, Woerpel, Nelson, and us have reduced the conformational space available to the seco acid backbones of the erythronolide series (that is, 6-dEB, erythronolide B, and erythronolide A) through the use of six-membered-ring protecting groups on C-3/C-5 and C-9/C-11 (Scheme 1).<sup>[5,6]</sup> In addition to scaffolds with cyclic protecting



**Scheme 1.** Cyclic biasing elements in erythromycin's synthetic history. PG = protecting group.

groups, other types of biasing elements (for example, heterocycles, olefins) have been employed in similar positions to rigidify the hydroxy acid backbone.<sup>[7,8]</sup> In a particularly notable example, Paterson and Rawson validated this approach by using two olefinic rigidifying elements in place of cyclic protecting groups.<sup>[9]</sup> Furthermore, Martin and co-workers demonstrated that steric bulk at C-5 (a desosamine sugar appendage) coupled to a C-9/C-11 cyclic acetal could enable cyclization.<sup>[10]</sup> The steadfast application of one<sup>[3]</sup> or more structural biasing elements in erythromycin's synthetic history demonstrates the resonating impact of Woodward's cyclization studies.

We recently reported a late-stage C–H oxidation strategy for the total synthesis of 6-deoxyerythronolide B (6-dEB), by using a palladium(II)/bis(sulfoxide) (**1**) catalyzed C–H oxidative macrolactonization reaction.<sup>[6,11]</sup> As a part of our

[\*] E. M. Stang, Prof. M. C. White  
Department of Chemistry, Roger Adams Laboratory  
University of Illinois  
Urbana, IL 61801 (USA)  
Fax: (+1) 217-244-8024  
E-mail: white@scs.illinois.edu  
Homepage: <http://www.scs.illinois.edu/white>

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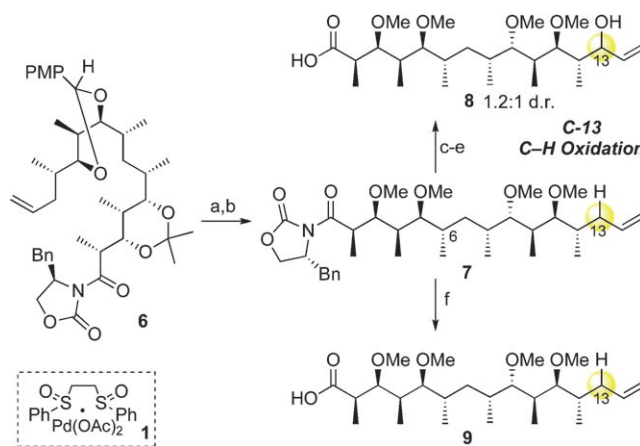
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synthetic planning, we also chose to employ traditional cyclic protecting groups at C-9/C-11 and C-3/C-5 (**2**) to facilitate macrocyclic ring closure (see Scheme 3). In the presence of these biasing elements, the 14-membered macrolide product was formed in 34% yield (45% recovered starting material (rSM)); 56% yield after recycling twice) and with >40:1 d.r. in favor of the natural C-13 diastereomer **3** (Scheme 3). Based on the Hammond postulate, we attributed the inability to form the unnatural C-13 diastereomer under the chelate-controlled C–H oxidative macrolactonization conditions to the large difference in the ground-state product energies between the C-13 diastereomers (the natural C-13 diastereomer was calculated to be 3 kcal mol<sup>-1</sup> more stable than the C-13 epimer). Similarly, while an acylation-based Yamaguchi cyclization of **5** provided the natural macrolide **3** in high yield, the unnatural C-13 diastereomer (**4**) could not be formed.

Upon revisiting the studies of Woodward et al., in which the positioning of cyclic protecting groups had been optimized for the natural erythromycin structure, we questioned whether the biasing elements were in fact hampering the cyclization of stereochemical analogues. In this vein, we recognized the absence of a key control experiment: the attempted cyclization of a substrate completely devoid of biasing elements. Surprisingly, this experiment has remained unreported in the literature, despite over 30 years of erythromycin syntheses. We therefore set out to test the well-accepted idea that preorganization is necessary for cyclization of the erythromycin structure.

6-Deoxyerythronolide B, the aglycone precursor to the erythromycins, serves as the archetypical core of the polyketide macrolide antibiotics. In nature, a seco acid bearing unadorned hydroxy groups at C-3, C-5, and C-11 and a ketone functionality at C-9 is cyclized to form 6-dEB, which is then hydroxylated at the C-6- and C-12-positions through enzymatic C–H functionalization to form erythronolides B and A, respectively. In addition to practical considerations of eliminating the formation of unwanted ring sizes,<sup>[12]</sup> the introduction of protecting groups was deemed necessary to prevent preorganization through 1,3-hydrogen bonding.<sup>[13]</sup> Polypropionate molecules typically adopt conformations that minimize *syn*-pentane interactions, and thus will have inherent preorganization that may aid cyclization.<sup>[14]</sup> However, in attempts to minimize artificial bias (bias not present in the native polypropionate structure), we selected methyl ether protecting groups for this study because of their inability to induce electrostatic preorganization while maintaining similar steric properties as the free hydroxy groups of the natural substrate. We reasoned that the use of any other protecting group, albeit potentially more synthetically useful, might inadvertently enable cyclization through either steric or electronic preorganization of the substrate.<sup>[15]</sup> Accordingly, we synthesized a tetramethyl ether protected hydroxy acid **8** and alkenoic acid **9** as the unbiased cyclization precursors (Scheme 2).

The syntheses of both unbiased cyclization precursors **8** and **9** proceeded conveniently via a common intermediate, terminal olefin **7**. Global deprotection of a previously synthesized bisacetal intermediate (**6**),<sup>[6]</sup> followed by permethylation with Me<sub>3</sub>OBF<sub>4</sub> furnished tetramethylated terminal olefin **7** (Scheme 2). Straightforward removal of the chiral

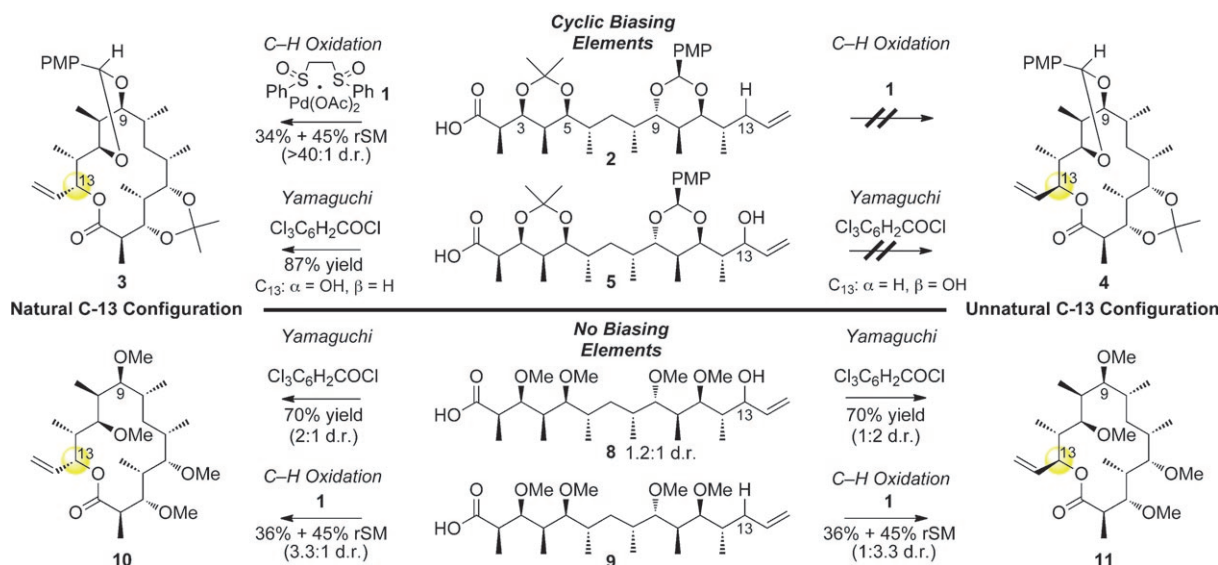


**Scheme 2.** Synthesis of hydroxy acid **8** and alkenoic acid **9**. Conditions: a) 1 M HCl (aq), 70% yield; b) Me<sub>3</sub>OBF<sub>4</sub>, proton sponge, 62% yield; c) **1** (10 mol%), benzoquinone (2.0 equiv), *p*-NO<sub>2</sub>BzOH (1.5 equiv), 45 °C, 72 h, 1.2:1 d.r., 59% yield; d) LiOOH (aq); e) K<sub>2</sub>CO<sub>3</sub>, MeOH, 89% (2 steps); f) LiOOH (aq), 99% yield. Bn = benzyl, Bz = benzoyl, PMP = *p*-methoxyphenyl.

auxiliary with LiOOH provided the C–H oxidative cyclization substrate **9** in 99% yield. Intermolecular palladium(II)/bis(sulfoxide) (**1**) catalyzed C–H oxidation provided the C-13 oxidized products as diastereomeric allylic *p*-nitrobenzoates in 59% yield (1.2:1 d.r.). Hydrolysis of the chiral auxiliary with LiOOH and methanolysis of the *p*-nitrobenzoates furnished the unbiased seco acid **8** in 89% yield (over 2 steps, 1.2:1 d.r.). Notably, C–H oxidation greatly aided these studies by circumventing *de novo* syntheses of both epimeric Yamaguchi precursors **8**.<sup>[6,16,17]</sup>

To evaluate if preorganization is needed for efficient macrolactonization of erythromycin precursors we attempted a traditional acylation-based macrolactonization with unbiased hydroxy acids **8** (1.2:1 d.r., Scheme 3).<sup>[18,19]</sup> Strikingly, both the natural and unnatural C-13 diastereomeric hydroxy acids cyclized efficiently under standard Yamaguchi macrolactonization conditions, to afford the 14-membered macrolide products **10** and **11** in 70% yield (2:1 d.r.)! The ease with which these hydroxy acids cyclized in the absence of biasing elements is remarkable; matching the best yield obtained from the original preorganization studies by Woodward et al.<sup>[4]</sup> Despite decades of erythromycin syntheses, this is the first reported case where precursors to any member of the erythromycins have been cyclized successfully without the use of biasing elements to aid in the formation of the 14-membered macrolide.

The C–H oxidative macrolactonization of unbiased alkenoic acid (**9**→**10/11**) also proceeded in the absence of biasing elements, with comparable yields (36% yield, 45% recovered SM) to the analogue containing biasing elements (**2**→**3**, Scheme 3). More importantly, in contrast to previous results with cyclic protecting groups at C-9/C-11 and C-3/C-5, the unnatural C-13 diastereomer **11** could be now be accessed from this unbiased precursor (1:3.3 d.r. from **9** versus 1: >40 d.r. from **2**). On the basis of these results we may conclude that Pd/bis(sulfoxide)-catalyzed C–H oxidative macrolactonization of erythromycin precursors also does not



**Scheme 3.** Macrocyclization studies on biased and unbiased 6-dEB precursors.

require biasing elements, although such elements can significantly improve the diastereomeric outcome of the cyclization.

These results definitively demonstrate that artificial preorganization is not a requirement for the efficient cyclization of erythromycin's polypropionate core (6-dEB). In other words, the inherent conformation of the linear polypropionate structure is sufficient for facile macrolactonization.<sup>[20]</sup> Significantly, we have shown that designed preorganization has a dramatic impact on the cyclization outcome of stereochemical analogues of the erythromycins. Removal of artificial biasing elements allows for increased stereochemical flexibility in the macrocyclization process. We anticipate that empowered with the knowledge that preorganization is not a requirement for cyclization, a broader evaluation of protecting groups<sup>[15]</sup> will lead to the syntheses of stereochemically modified and/or functional group deficient analogues of erythromycin that may have been difficult or impossible to generate under the former perceived constraints.

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