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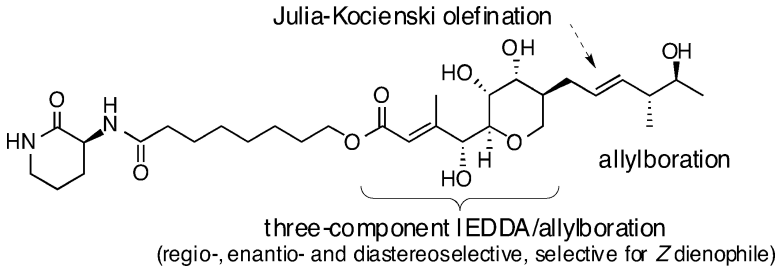

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Catalytic Asymmetric Synthesis of a Potent Thiomarinol Antibiotic

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The isolation and characterization of the pyran-containing pseudomonic acids have led to the commercial success of Bactroban, a topical antimicrobial medication for skin infections.[1] The active ingredient, pseudomonic acid A (mupirocin, **1**, Figure 1), displays poor oral absorptivity and low metabolic stability. Consequently, there has been significant interest in the development of improved, less toxic analogues that could also be suitable as bloodstream antibiotics. Thiomarinol A (**2**)[2] and derivative **3**[3] are rare marine natural products recently isolated from the bacterium *Alteromonas rava* sp. nov. SANK 73390.

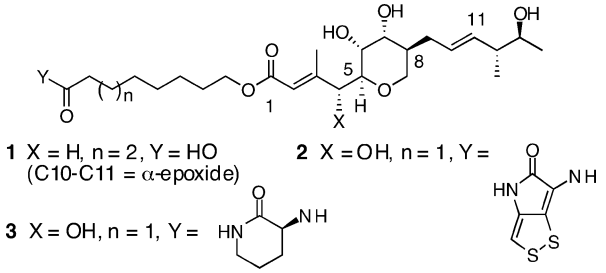


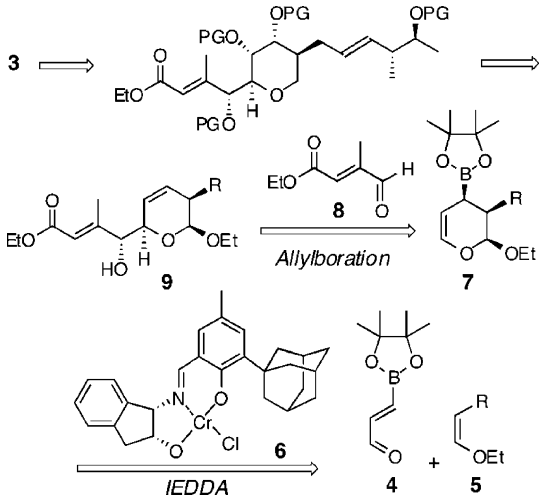
Figure 1. Pseudomonic acid A (**1**) and thiomarinol derivatives **2** and **3**.

The structures of **2** and **3** differ from **1** by the presence of a C4-hydroxyl, a shorter C1-alkoxy chain, and the replacement of the C10−C11 epoxide with an *E* alkene unit. Compounds **2** and **3** are distinguishable, respectively, by their holotin and anhydroornithine C1 amide end groups. These natural substances were found to be much more potent than pseudomonic acid A and possess a wider spectrum of activity (Gram-positive and Gram-negative bacteria). For example, the activity of derivative **3** against *S. aureus* was shown to be comparable to that of tetracycline and streptomycin.[3] These impressive properties justify the development of an efficient synthetic route to **2** and **3**, which is key to any future efforts at generating simplified analogues with higher potency and oral bioavailability. The five contiguous stereocenters of **2** and **3** (C4−C8), in particular the C4 hydroxyl, represent a significant challenge. Herein, we disclose the first total synthesis of a thiomarinol antibiotic.[4] Our concise route to **3** uses a stereoconvergent three-component strategy amenable to the design of analogues with attractive skeletal variations.

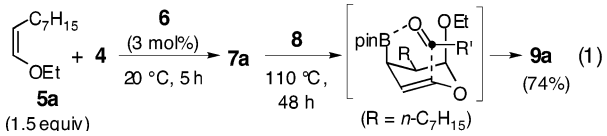
We envisioned that the pyran core and the C4-hydroxyl of **3** could be constructed stereoselectively with an endo-selective three-component hetero[4 + 2] cycloaddition/allylboration approach[5−7] from 3-boronoacrolein pinacolate **4**, a suitably functionalized (*Z*)-2-substituted enol ether **5**, and aldehyde **8** (Scheme 1). From intermediate **9**, alkene dihydroxylation and acetal reduction would provide the correct functionalization of the pyran ring, and completion of the C8 chain would involve a trans olefination. The requisite C12−C13 propionate fragment could be accessed via either Brown crotylboration[8] or our own catalytic system.[9]

We have previously demonstrated that Jacobsen's chiral Cr(III) complex **6**[10] efficiently catalyzes the cycloaddition between **4** and

Scheme 1



ethyl vinyl ether.[6] It is known, however, that 2-substituted enol ethers are difficult substrates in inverse electron demand Diels−Alder (IEDDA) cycloadditions because of the added steric effect of the 2-substituent.[11] Our work with **4** highlighted its exceptional reactivity as a heterodiene,[6] which we hoped could overcome the low reactivity of a 2-substituted enol ether as a dienophilic partner. Thus, model studies examined the behavior of model *Z*-enol ether **5a**[12] in the IEDDA/allylboration process (eq 1). The IEDDA



reaction was indeed more difficult with a 2-substituted enol ether. Whereas ethyl vinyl ether reacted with **4** in less than 2 h with 1 mol % of catalyst **6**,[6] **5a** required more than 5 h with 3 mol % of **6** (neat, 20 °C). Nonetheless, the all-cis endo adduct **7a** was cleanly formed as a single stereoisomer. To our surprise, it was the allylboration step that proved problematic. Whereas the adduct of ethyl vinyl ether (**7** with R = H) reacted with various aldehydes at a temperature of 45 °C,[6] an astonishing 110 °C was needed to produce **9a** from **7a** and **8**. As a result, the tandem process could not be performed in "one-pot", and we found it necessary to remove catalyst **6** with a quick silica filtration to afford a clean allylboration product. In the putative allylboration transition state leading to **9a** (eq 1), the ring assumes an unfavorable chairlike conformation with both pseudoaxial boronate and ethoxy substituents.[13] It is possible that gauche interactions from the C8 chain (R) further increase the barrier for conformational change. The C4−C5 stereochemistry can be explained as before.[6]

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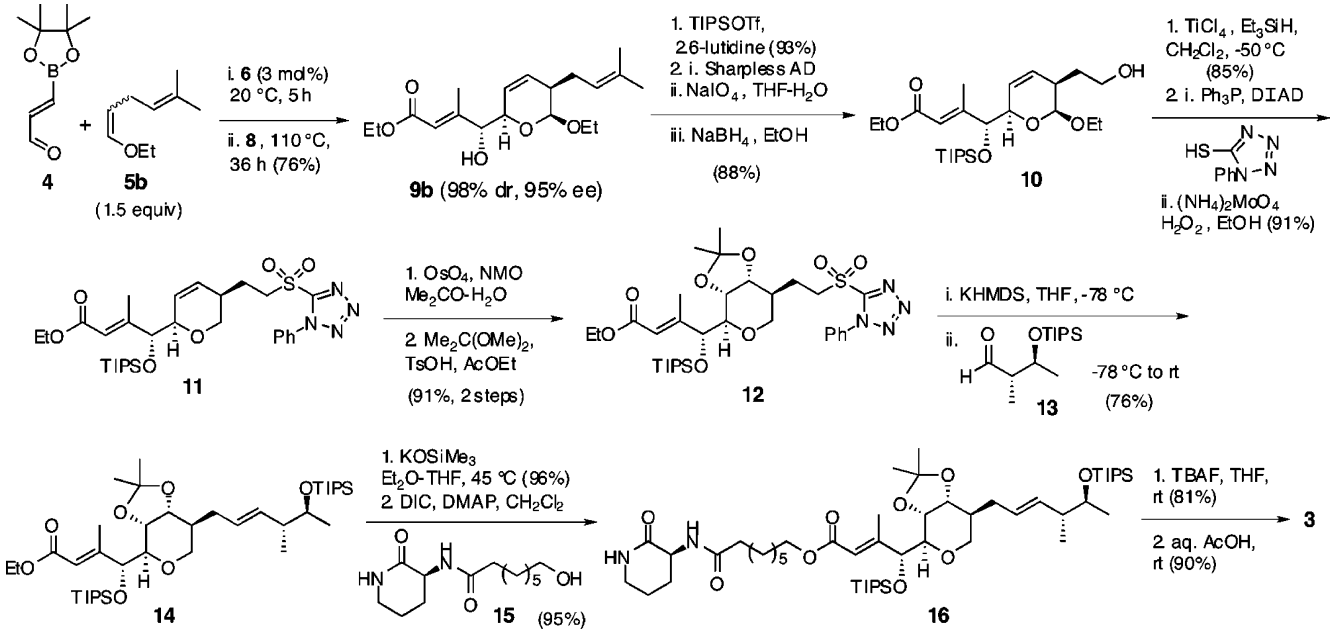
Scheme 2



The synthesis of **3** was initiated with the sequential three-component coupling between **4**,[6] enol ether **5b**,[12] and commercial aldehyde **8** (Scheme 2). Interestingly, it was difficult to obtain isomerically pure enol ether *Z*-**5b** but luckily, the *Z*-isomer was found to be more reactive than the *E*-isomer. Reactions with a mixture of isomers only afforded product consistent with a kinetically selective cycloaddition of the *Z*-isomer. It appears that *Z*-**5b** may be more reactive simply as a result of steric control by the huge catalyst **6**.[14] In any event, the desired pyran **9b** was isolated in 76% yield as a single diastereomer in >95% enantiomeric excess. Remarkably, all three key stereocenters of thiomarinols: C4, C5, and C8 are set in this process. After protection of the secondary hydroxyl of **9b**, a high-yield sequence for selective oxidative cleavage of the exocyclic alkene furnished alcohol **10**. Reduction of the cyclic acetal with $Et_3SiH/TiCl_4$ was best planned at this stage. The primary hydroxyl was then transformed into the tetrazolyl sulfone **11** required for the olefination.[15] Ring dihydroxylation was carried out first, occurring selectively from the face opposite to the C5/C8 substituents. The protected diol **12** was then subjected to the Julia−Kocienski coupling[15] with aldehyde **13**[12] to give advanced intermediate **14** in good yield. More than 3 g of this intermediate was obtained, which is testimony to the efficiency of the chosen sequence. Hydrolysis of the C1 ester, re-esterification with side chain alcohol **15**[12] to afford **16**, and final removal of the protecting groups afforded **3**.[16]

In summary, we have achieved the first total synthesis of a member of the thiomarinol class of marine antibiotics. Compound **3** was reached in a remarkable global yield of 22% (from **4**). The highlight of this synthesis is the efficient catalytic enantio-, regio-, *E*/*Z*-, and diastereoselective three-component IEDDA/allylboration sequence. This key operation provides a rare example of an enantioselective HDA reaction involving acyclic 2-substituted enol ethers. Moreover, this reaction featured an unusual but fortuitous kinetic selection that favored the requisite *Z*-dienophile from a mixture of isomers. It is also noteworthy that two key allylboration reactions have been employed to set four of the eight stereogenic centers of **3**. The convergent synthetic strategy should facilitate our future efforts at generating improved thiomarinol analogues.

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Supporting Information Available: Experimental details and spectral reproductions for all experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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