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Stereoselective Synthesis of Brevianamide E

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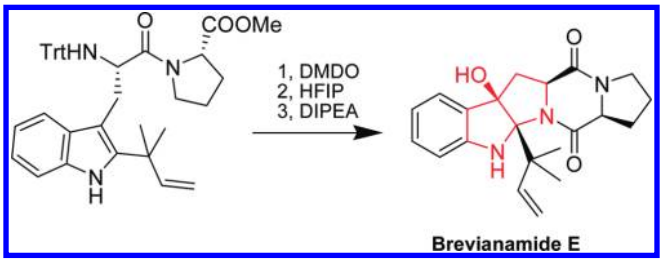
ABSTRACT



The hydroxypyrroloindolenine (Hpi) motif forms the fundamental core of the pentacyclic natural product, brevianamide E, the concise stereoselective synthesis of which, *via* oxidative cyclization, is described.

The brevianamides comprise a series of multicyclic natural products originally isolated from *Penicillium brevicompactum*.[1,2] These compounds represent challenging targets in terms of a concise organic synthesis. In particular, the pentacyclic natural product brevianamide E (**1**, Figure 1) represents an interesting challenge for the construction of five fused rings and four stereogenic centers, comprising a *syn-cis* configured hydroxypyrroloindolenine (Hpi) core (shown in red in abstract graphic and Figure 1). Moreover, the Hpi represents a "toxicophoric" motif in numerous other natural products of abiding and current general interest.[3−18] The interest in brevianamide E itself is underscored by the fact that it has been the subject of a number of syntheses over the past 30 years and still presents a challenge for creating a *syn-cis* Hpi.[1,19−23] Previous syntheses exploited a common strategy predicated on the formal construction of the reduced deoxybrevianamide E, as the penultimate product **2** (Figure 1), which is oxidatively cyclized to the title

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compound containing the Hpi-DKP (diketopiperazine) fused ring system. Several reports describing this transformation include photo-oxidation with the singlet oxygen sensitizer, Rose Bengal, in an O_2 atmosphere[20,21] and milder oxidation at low temperature with dimethyldioxirane (DMDO).[22] In addition, fluorinated analogues have been made using a fluoropyridinium salt.[24] Nevertheless, oxidative cyclization of deoxybrevianamide E always produced a mixture of diastereomers: *syn-cis* brevianamide E **1** and *anti-cis epi*-brevianamide E **iso-1** (Figure 1). Moreover, DMDO oxidation of **2** gave the *undesired anti-cis* diastereomer **iso-1** in 80% excess.[22]

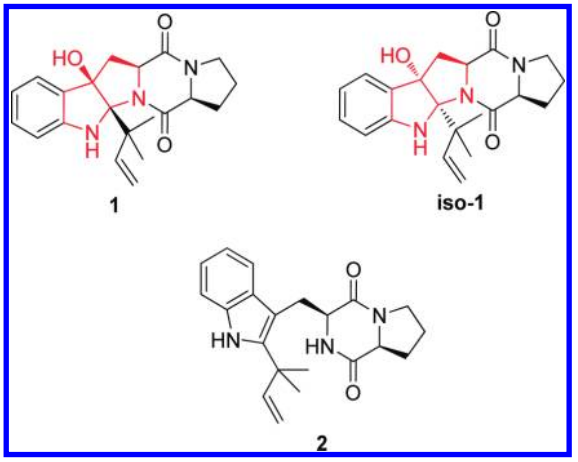
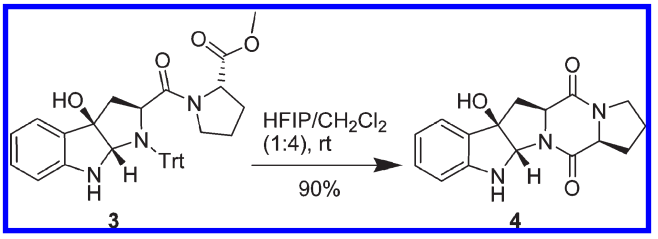


Figure 1. Brevianamide E (**1**), iso-brevianamide E (**iso-1**), and deoxybrevianamide E (**2**).

Herein, we exploit a stereoselective approach where a reverse prenylated N^{α}-Trt-Trp-Pro-OMe dipeptide is oxidized and deprotected to provide the title compound in a manner that provides, to the best of our knowledge, the first stereoselective synthesis of brevianamide E.

Previously, we reported the synthesis of various hydroxypyrroloindolenine dipeptides *via* DMDO oxidation of N^{α}-Trt-Xaa-OMe (where Xaa is one of 12 standard amino acids including valine).[25] Through these studies we noted that oxidative cyclization affords a high yielding mixture of diastereomers (*syn-cis* and *anti-cis*) with very modest diastereoselectivity at best. Notable exceptions to this trend were N^{α}-Trt-Trp-Pro-OMe and N^{α}-Trt-Trp-Src-OMe (Src = sarcosine, *i.e.* N^{α}-methyl glycine).[26] In these cases, we observed highly selective oxidative cyclization to the *syn-cis* diastereomer (dr > 10:1), in near-quantitative yield, suggesting utility in the construction of structurally related compounds. In addition, we discovered that treatment of the *syn-cis* N^{α}-Trt-Hpi-Pro-OMe **3** with HFIP simultaneously removed the trityl and induced diketopiperizination to give pentacycle **4**, which is closely related to brevianamide E (Scheme 1). This result motivated us to investigate a concise stereoselective synthesis of brevianamide E with identical *syn-cis* stereochemistry to the natural product.

Scheme 1. Stereoselective Synthesis of the Pentacyclic Core of Brevianamide E



Hence, our efforts focused on oxidative cyclization of a reverse prenylated tryptophan-proline derivative with a view to providing a stereoselective route to brevianamide E. Initially, we opted for a route *via* N^{α}-Phth-Trp-Pro-OMe, as reported by Casimir et al.;[27] N^{α}-phthaloyl-tryptophan was first coupled to proline methyl ester in good yield using EDC/HOBt. Next, we attempted previously reported methods used to reverse-prenylate N^{α}-Phth-Trp-OMe.[22,28,29] Whereas reverse prenylation of N^{α}-Phth-Trp-Pro-OMe was successful, yields were suboptimal. More unfortunate was the lability of the phthalimide which, during workup, underwent DKP formation to yield deoxybrevianamide E **2**. Consequently, we could not selectively tritylate the α-nitrogen needed to prevent its oxidation while preserving sufficient nucleophilicity for cyclization, a feature that may be critical to stereoselective ring closure (*vide infra*). DKP formation notwithstanding, deoxybrevianamide E **2** is a known precursor to brevianamide E, which can be carried forward in a nondiastereoselective synthesis of **1** and **iso-1**, as in all previously reported cases.[20−22,24]

We therefore avoided this route in favor of a new strategy that started with reverse prenylated tryptophan (Scheme 2). To that end, N^{α}-phthaloyl-tryptophan methyl ester **5** was reverse prenylated in the presence of freshly prepared prenyl-9-BBN in excellent yield.[22] The phthaloyl and methyl groups were removed from compound **6** under basic conditions to give the lithium salt of 2-isoprenyl-tryptophan **7** *in situ* which, following flash chromatography ($MeOH/CH_2Cl_2$ 1% triethylamine), was converted to the triethylammonium hydrogen salt and then tritylated,[22] followed by reaction with proline methyl ester under standard EDC/HOBt coupling conditions to give dipeptide **8**. Dipeptide **8** was then subjected to DMDO oxidation at low temperature (−78 °C), whereupon Hpi formation ensued, resulting in a predominant product **9**, found to be in the *syn-cis* configuration (yield 82%, dr > 8:1,

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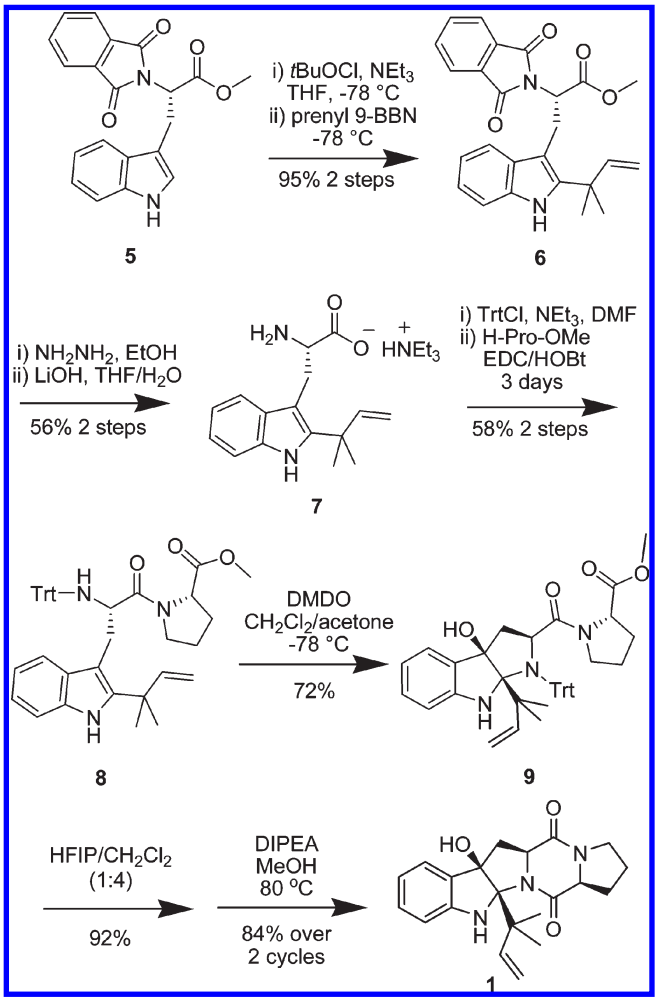
Scheme 2. Stereoselective Synthesis of Brevianamide E



the configurations of each diastereomer were determined by running 1D NOE experiments).[25] HFIP treatment removed the trityl to give Hpi-dipeptide which, in the presence of DIPEA, cleanly gave brevianamide E **1**. The *syn-cis* configuration of brevianamide E was confirmed by ^{1}H and ^{13}C NMR spectroscopy which provided spectra identical to those previously reported by Danishefsky et al.[22] Furthermore, the C4a carbon and proton chemical shifts identified by HSQC and HMBC experiments were consistent with previously reported values (see Supporting Information).[21]

The stereochemical outcome of this oxidation is consistent with reports by Danishefsky et al.; in their elegant reports on himastatin, they found that DMDO oxidatively cyclized N^{α}-Trt-Trp-O*t*Bu to the corresponding Hpi-ester with a nearly exclusive *syn-cis* configuration (dr 15:1) in a modest 55% yield.[5,8] In contrast, DMDO oxidation of compound **2** predominantly gave the undesired *anti-cis* stereochemistry, and hence Danishefsky et al. exploited electrophilic phenylselenium reagents, also described by Crich and Huang,[30] to selectively cyclize N^{1},N^{α}-Boc-Trp-OMe to the pyrroloindolenine phenylselenyl ether in the *syn-cis* configuration, which was then deliberately deselenated by *m*-CPBA with retention of configuration to give the desired Hpi.[31] Subsequently, this approach has been used extensively by others.[9,17,32−35] Danishefsky's explanation for stereoselective selenation invoked kinetic resolution of two rapidly equilibrating 2,3-phenylepiselenonium ions that form reversibly on either indole face. Minimization of steric compression between the C^{α}-methyl ester and the indole ring ultimately favors episelenonium ring opening to give the *syn-cis* configuration.

Unlike selenating agents, DMDO reacts with tryptophan in an irreversible manner to give a 2,3-epoxide, or the more stable, ring-open 3-hydroxyindolenyl-2,3-imine, either of which would be subsequently intercepted by the α-nitrogen to give the Hpi in either configuration. Therefore, kinetic resolution of two rapidly equilibrating diastereomeric 2,3-epoxides (or 3-hydroxyindolenyl-2,3-imines) is implausible, although not entirely impossible.

Due to the kinetic irreversibility of DMDO oxidation, our observed diastereoselectivity can only result if either (i) the indole face is facially blocked in a ground state conformation that is limited to secondary amides (or *tert*-butyl esters) and distinct from that of primary amides, or (ii) pyrrole ring closure occurs concomitantly with oxidation in a transition state that will favor the less sterically congested diastereomer. Previous examination of the crystal structures of N^{α}-Trt-Trp-Gly-OMe and N^{α}-Trt-Trp-Src-OMe revealed that, in each, the indole is positioned to favor C3 oxidation to give an Hpi-dipeptide in the *syn-cis* conformation. Yet two very similar conformations cannot explain why DMDO oxidation is facially selective only for the latter. In terms of the diastereoselectivity herein, molecular modeling did not provide any evidence of a preferential ground state conformation that would engender facially selective indole oxidation (data not shown).

Taken together, these findings argue against a ground state conformation that ensures facially selective oxidation. Instead, the diastereoselectivity likely arises from a transition state in which DMDO oxidation and pyrrole ring closure are synchronized to favor the *syn-cis* product; such synchronicity accounts for steric compression. Inasmuch as N^{α}-Trt-Trp-Src-OMe, N^{α}-Trt-Trp-Pro-OMe, and N^{α}-Trt-Trp-O*t*Bu are more sterically congested than normal peptide substrates, increased steric bulk greatly favors one diastereomeric transition state.

Based on these results, we suggest that a nucleophilic α-nitrogen, as in dipeptide **8**, may further promote facial indole reactivity in a transition state (Figure 2) that

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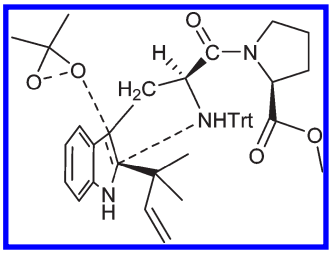

Figure 2. Concerted transition state of DMDO attack at the re-face mediates cyclization to the *syn-cis* product.

resembles the less sterically congested *syn-cis* product. In the absence of a nucleophilic nitrogen (e.g., in the case of **2**), DMDO may react with the indole with less selectivity prior to pyrrole ring closure. Such a transition state is consistent with the kinetic irreversibility of DMDO oxidation and steric considerations that favor the *syn-cis* configuration for more sterically hindered peptides such as **8**.

In summary, we report the first stereoselective synthesis of the natural product brevianamide E based on a highly selective DMDO oxidation. This result should be broadly applicable to those seeking diastereoselective indole oxidations en route to natural products containing a *syn-cis* configured Hpi and may obviate the need for selenation and subsequent oxidative deselenation. In addition, these results may have mechanistic implications for enzyme catalyzed biosyntheses of the same.

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Supporting Information Available. Experimental details and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.