Biomimetic Diels−Alder Cyclizations for the Construction of the Brevianamide, Paraherquamide Sclerotamide, and VM55599 Ring Systems

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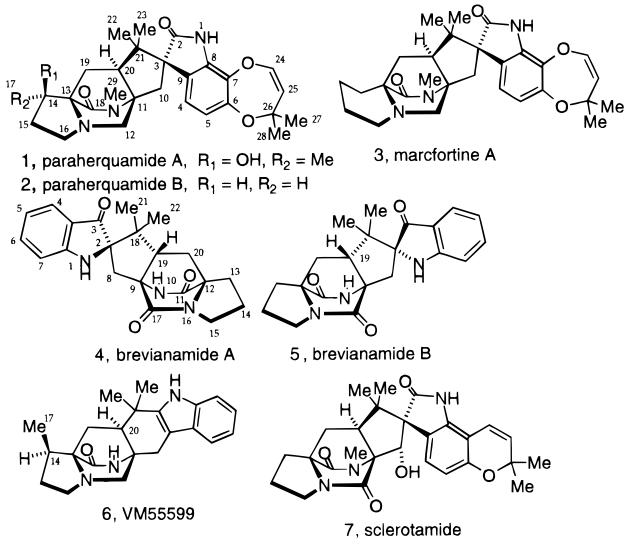
The paraherquamides,[1] brevianamides,[2] marcfortines,[3] VM55599,[4] and most recently, the sclerotamides[5] are indolic secondary metabolites isolated from various fungi. These substances have attracted considerable attention due to their molecular complexity and intriguing biogenesis,[6] and some members, most notably the paraherquamides, display potent anti-parasitic activity.[7] These alkaloids share the unusual bicyclo[2.2.2] ring system that has been proposed to arise via the [4+2] cycloaddition of the isoprene moiety across the α-carbons of the amino acid units.[8] A striking stereochemical difference between the brevianamides and all of the other members of this family is the relative stereochemical relationship at the tertiary carbon at C-19 (brevianamide numbering), which is *anti*[9] in the brevianamides and *syn* for all of the others. Previous work on the biosynthesis of these substances invoked a facial divergence in the Diels−Alder cyclization, which sets the relative stereochemical relationship at this stereogenic center.[10] In addition, recent theoretical work on an indoxyl-based Diels−Alder cyclization pathway supported the observed isomer production of the brevianamides in *Penicillium brevicompactum* which produces brevianamide A as the major metabolite and brevianamide B as the minor metabolite.[11] As part of a program directed primarily at elucidating the biosynthetic mechanism of formation of the unique bicyclo[2.2.2] ring system, particularly with respect to the question of possible enzymatic catalysis of this reaction, we report here a possibly biomimetic intramolecular Diels−Alder cyclization reaction that constructs the core framework of this class of alkaloids.



9-*epi*-Deoxybrevianamide E (**8**, Scheme 1) was synthesized according to the procedure of Kametani.[12] Conversion of this substance to the lactim ether (**9**) was accomplished with Me_3OBF_4 in CH_2Cl_2 in the presence of Na_2CO_3. Next, oxidation with DDQ gave the unsaturated substance **10**. Treatment of **10** with aqueous methanolic KOH at room temperature cleanly produced the labile azadiene **11**, which cyclized to give a mixture of **12** and **13** (2:1, 68% combined yield). The structures of the cyclization products were secured through analysis of their respective NMR spectra as well as by chemical correlation to known substances. Conversion of **12** to C-19-*epi*-brevianamide A (**16**), a nonnatural isomer of brevianamide A previously synthesized in this laboratory,[13] was accomplished by diastereoselective m-CPBA oxidation to the corresponding hydroxyindolenine (**14**, ca. quantitatively) and pinacol-type rearrangement (1 M NaOMe, MeOH, reflux) to the corresponding *spiro*-indoxyl; subsequent removal of the lactim ether with HCl afforded the corresponding ring-opened amino ester,[14] which was cyclized in hot toluene containing 2-hydroxypyridine furnishing *d*,*l*-**16** in 46% overall yield from **12**. This material was identical with the authentic material in every respect (except for being racemic). Conversion of **13** to *d*,*l*-brevianamide B was accomplished in like manner in 65% overall yield from **13** securing the relative

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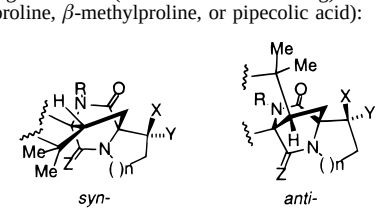
(9) The *syn*/*anti* relationship refers to the relative stereochemistry between the C-19 stereogenic center (brevianamide numbering) and the cyclic amino acid residue (proline, *β*-methylproline, or pipecolic acid):



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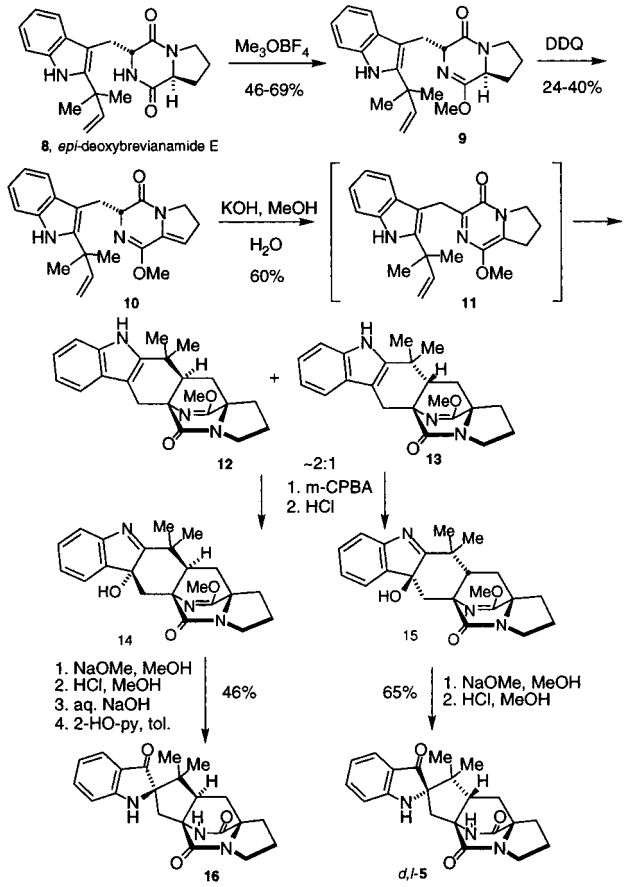
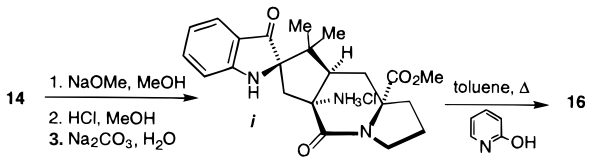
Scheme 1



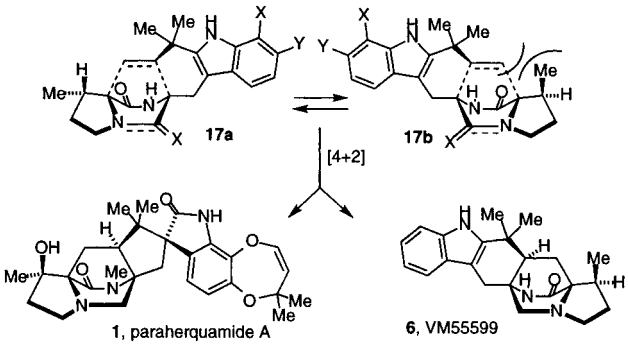
stereochemistry of each respective isomer **12** and **13**. However, in this case the cleavage of the lactim ether with HCl in aqueous methanol led directly to brevianamide B without any intermediate ring-opened amino ester detectable.

A significant implication of these observations concerns the biogenesis and stereochemistry of the related metabolite VM 55599 (**6**) isolated from the paraherquamide-producing mold *Penicillium* sp. IMI332995. Since paraherquamide A and VM 55599 both possess the bicyclo[2.2.2] monoketopiperazine ring system, it seems plausible that these substances arise via a related or common [4+2] cycloaddition. The relative stereochemistry of VM55599 was assigned by extensive ^{1}H NMR nOe studies where the methyl group in the β-methylproline moiety was assigned as being *syn* to the bridging isoprene unit.[4] Thus, if a similar Diels−Alder cyclization, whether it be un-catalyzed or enzyme-catalyzed, is operating in the biosynthetic construction of these metabolites, the isoprene unit must approach the azadiene

(14) Cleavage of the lactim ether derived from **14** with HCl produced the ring-opened amino-ester ***i*** that can be isolated by PTLC. Cyclization of this substance with 2-hydroxypyridine in hot toluene provided **16**.



Scheme 2



from the *same* face as the methyl group in the proline ring (**17b**, Scheme 2), whereas in paraherquamide A, which has been shown by this laboratory[15] to be derived from L-isoleucine, Diels−Alder cyclization must occur from the face *opposite* to the methyl group (**17a**, Scheme 2). The absolute stereochemical implications of the *relationship* of VM55599 to the biosynthesis of the paraherquamides have been previously discussed[15] and are an issue that is currently under study. Efforts are underway to determine the intrinsic facial bias of related Diels−Alder cyclizations on β-methylproline-containing substrates to address these issues.

This study demonstrates that the core bicyclo[2.2.2] ring system common to this family very likely arises by an intramolecular Diels−Alder cyclization from a preformed dioxopiperazine[16] that subsequently undergoes oxidation to an azadiene species. It is significant that the diastereofacial bias of the Diels−Alder cyclization of **11** is not strongly affected by solvent. The same ratio of **12:13** (~2:1) was obtained in THF as in aqueous methanol. We have also shown that C-19-*epi*- metabolites (corresponding to **14** and **16**) are not produced by *Penicillium brevicompactum* and there have been no reports on the isolation of similarly epimeric metabolites from paraherquamide- or sclerotamide-producing organisms. Thus, in each biosynthetic system, there appears to be complete facial exclusivity in the construction of the bicyclo[2.2.2] ring nucleus; such is not the case for the laboratory cycloaddition reported here. Uncertainties as to the oxidation state of the indole moiety as being either oxindole (for the paraherquamides, marcfortine and sclerotamide) or indoxyl (for the brevianamides) as opposed to the non-oxidized indole (for VM55599) at the [4+2] cyclization phase as well as the question of possible protein organization of the transition state structures still exists and are the subject of intense investigation in these laboratories.

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Supporting Information Available: Spectral data for all new compounds employed in this study (11 pages). See any current masthead page for ordering and Internet access instructions.

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