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Isolation, Structure Elucidation, and Biomimetic Total Synthesis of Versicolamide B and the Isolation of Antipodal (−)-Stephacidin A and (+)-Notoamide B from *Aspergillus versicolor NRRL 35600*

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Keywords

ent-stephacidin A; ent-notoamide B; Biosynthetic Diels-Alder; sclerotiamide

Prenylated indole alkaloids containing, the bicyclo[2.2.2]diazaoctane ring system as a structural core, now number more than thirty-eight family members. These natural substances, produced by various genera of fungi, in particular *Aspergillus* sp. and *Penicillium* spp., among others, exhibit a range of interesting structural and stereochemical features. Significantly, a myriad of biological activities are displayed by members of this family including insecticidal, anti-tumor, anthelmintic, calmodulin inhibitory, and anti-bacterial activities. Structurally, these substances arise from the oxidative condensation of one or two isoprene units, tryptophan and another cyclic amino acid residue, such as proline, β-methylproline or pipecolic acid. With respect to the relative stereochemistry within the core bicyclo[2.2.2]diazaoctane ring system, all of the known members of the paraherquamides (e.g., **1**, **2**)/stephacidins (e.g., **3**, **4**)/ asperparalines and notoamides (e.g., **5**, **6**) have been shown to possess the *syn*-stereochemistry, while only the brevianamides (**9**, **10**) have been shown to possess the *anti*-relative configuration (Schemes 1 and 2). The *syn*-/*anti*-relationship refers to the relative stereochemistry between the C-19 stereogenic center (sclerotiamide numbering) and the cyclic amino acid residue (proline, β-methylproline, or pipecolic acid; Scheme 2). This reveals that in the oxidative cyclization process(es) to construct this core ring system biosynthetically, both faces of the isoprene-derived dienophile participate in the ring-forming process. However, until now, this stereochemical divergence was cleanly separated between the brevianamides and all other members of this growing family of natural products. Herein, we describe the isolation, structure elucidation, and confirmatory biomimetic total synthesis of the first member of the paraherquamide-stephacidin family to possess the rare *anti*-relative stereochemistry within the

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Supporting Information Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

bicyclo[2.2.2]diazaoctane ring system. We propose the new name versicolamide B for this natural product (**8**), a minor metabolite of *Aspergillus versicolor* NRRL 35600, Based on CD spectra, we have assigned the absolute configuration to this compound, and have concluded that it possesses the *ent*-configuration with respect to the bicyclo[2.2.2]diazaoctane core. Surprisingly and as striking, we have also isolated (−)-stephacidin A and (+)-notoamide B from *Aspergillus versicolor* NRRL 35600 and conclude that these substances are produced as the corresponding antipodes to the structures that have been previously described for these natural products. The provocative biogenetic implications of these stereochemical findings are discussed herein.

Previous studies from our laboratory[1] as well as those of Birch[2] and Sammes[3] suggest that the bicyclo[2.2.2]diazaoctane core of these alkaloids likely arises in Nature *via* a biosynthetic intramolecular Diels-Alder construction. We have recently completed the total synthesis of several prenylated indole alkaloids containing the common bicyclo[2.2.2] diazaoctane ring system *via* biogenetically inspired intramolecular Diels-Alder cycloaddition reactions,[1a,4] including brevianamide B, stephacidin A, marcfortine C and the recently discovered fungal metabolite notoamide B (Scheme 1).[4,5] We demonstrate herein that this general strategy was easily amendable to the total synthesis of versicolamide B and provided unambiguous structural and relative stereochemical corroboration for this stereochemically unique natural product.

The isolate of *A. versicolor* was obtained from a basidioma of *Gandoderma australe* collected in a Hawaiian forest, and was selected for investigation as part of a project targeting mycoparasitic and fungicolous fungal isolates as sources of new bioactive natural products. [6] This isolate was cultured by solid-substrate fermentation on rice, and the crude extract of these cultures showed significant antiinsectan activity. Five “known” compounds (sterigmatocystin, brevianamide F, stephacidin A, norgeamide D, and notoamide B) were obtained from this extract. The structures of four of the known compounds were confirmed by comparison of their NMR and MS data with literature values,[7] while the structure of notoamide B was independently assigned because the report describing this metabolite[5] had not yet appeared in the literature. Sterigmatocystin was a major component, and appears to be responsible for most of the antiinsectan activity of the crude extract.

The molecular formula of an additional minor component (versicolamide B; **8**) was established as $C_{26}H_{29}N_3O_4$ (14 unsaturations) on the basis of NMR and HRESIMS data. Analysis of ^{1}H, ^{13}C, and DEPT NMR data (Table 1) revealed that **8** is a member of the paraherquamide class of fungal metabolites. The presence of the 1,2,3,4-tetrasubstituted aromatic ring fused with an oxygen-containing six-membered ring was indicated by HMBC correlations of H-4 to C-6, C-7, and C-8; of H-5 to C-6, C-7, and C-9; of H-25 to C-6, C-7, C-8, C-27, C-28, and C-29; and of H-26 to C-7, C-27, C-28, and C-29. The remaining three oxygen atoms of the molecular formula were attributed to three carbonyl signals (δ_C 183.5, 173.5, 170.2), which must all correspond to amide carbons, leading to the assignment of two exchangeable proton signals at δ_H 9.49 and 7.72 as amide NH protons. HMBC correlations of the NH proton at δ_H 9.49 (H-1) to C-3, C-8 and C-9, and of H-4 to C-3, revealed the presence of an indolinone system. The shift of the C-2 carbonyl at δ_C 183.5 is consistent with its placement in the pyrrolidone ring as shown.[1a,8]

The bicyclo[2.2.2.]diazaoctane system and the C-13–C17 pyrrolidine ring were similarly assigned by analysis of 1D and 2D NMR data. The amide proton at δ_H 7.72 (H-21) showed correlations to C-10, and to quaternary sp^3 carbons C-11 and C-17, which were consistent with its assignment as the amide NH associated with carbonyl carbon C-20 at δ_C 173.5. The methine proton H-19 was coupled to H_2-18 to form an isolated $CHCH_2$ unit, which was incorporated as shown based on HMBC correlations. The linkage between the indolinone ring and the

bicyclo[2.2.2.]diazaoctane system via a five-membered ring was established by HMBC correlations of the isolated methylene protons (H_2-10) to C-2, C-3, C-11, and C-12; of H-19 to C-11, C12, C-18, C-23, and C-24; of amide proton H-21 to C-10, C-11, and C-17; and of H_2-18 to C-11, C-17, C-19, and C-20. Further HMBC correlations of H_2-10 to C-3, C-22, C-11, and the two amide carbonyl carbons C-2 and C-12 supported its location as shown. All shift assignments were made by detailed analysis of 2D NMR data, and are fully consistent with structure **8**.

The relative configuration of **8** was assigned on the basis of NOESY data. Key NOESY correlations between H-4, H-10β, H_3-24, H-18β, and H-21 indicated that N-21, H-10β, and H_3-24 are on the same face of the cyclopentane ring and are spatially close to aromatic proton H-4, leading to assignment of the relative configuration of spirocenter C-3 as shown. NOESY interactions between H-19, H-10α, H-18α, and H_3-23 placed the bridgehead proton H-19 on the opposite face of the cyclopentane ring, requiring an *anti*-relationship between H-19 and the C-20 amide bridge in the bicyclo[2.2.2.]diazaoctane ring system in **8**, which is unprecedented among the paraherquamides, but has been reported for the brevianamides.[1a] The structure of **8** differs from the known compound sclerotiamide, originally reported from *Aspergillus sclerotiorum*,[8a] by lacking the 10-OH group and possessing the opposite relative configuration at C-19.

CD spectroscopy has been utilized as a method to assign absolute configuration for *spiro*-oxindole alkaloids.[9] The Cotton effect at 250-350 nm is considered to be an indication of the configuration at *spiro*-stereogenic center C-3.[9a,b] The CD spectra of **8** and the (+)-notoamide B isolated from *A. versicolor* both show a positive Cotton effect at the *spiro*-oxindole absorbance region around 280 nm, suggesting the same 3*S*-configuration for each compound, in agreement with the configuration previously assigned for synthetic, *ent*-(+)-paraherquamide B (Scheme 3). Correspondingly, the absolute configuration of compound **8** is proposed as shown.

Of further interest, was the surprising observation that the (−)-stephacidin A and (+)-notoamide B samples isolated from *A. versicolor* possess *the opposite absolute configurations* to those previously reported.[5,7c] These assignments were based on examination of the CD spectra and optical rotation values of these substances (Scheme 3).

In their elegant total synthesis of stephacidin A, Baran and co-workers, have previously reported, optical rotation data and CD spectra of natural (+)-stephacidin A obtained from Professor Fenical's laboratory and corroborating data on synthetic (+)-stephacidin A.[10a] In addition, these workers recorded mirror-image CD spectra for natural (+)-stephacidin A and synthetic (−)-stephacidin A.[10c]

The optical rotation data for the natural samples derived from *Aspergillus versicolor* NRRL35600 utilized in this study are as follows: (+)-versicolamide B $[\alpha]_D$ = +26 (c 0.1, acetone); *ent*-stephacidin A $[\alpha]_D = -32$ (c = 0.05, CH_2Cl_2-MeOH; 1:1) lit. $[\alpha]_D = +61.5$ (c=0.26, 1:1 CH_2Cl_2/MeOH); [10] *ent*-notoamide B $[\alpha]_D$ = +102 (c = 0.05 MeOH) lit. $[\alpha]_D = -118$ (c= 0.064, MeOH).[5] We have further determined that the (−)-stephacidin A sample collected from *A. versicolor* is optically pure by chiral HPLC (see Supporting Information). These data, along with the CD spectra recorded, rigorously support the surprising fact that *A. versicolor* NRRL35600 produces the opposite enantiomers of stephacidin A and notoamide B to those obtained from the related fungi *Aspergillus ochraceus* WC76466 and the marine-derived *Aspergillus* sp. studied by Tsukamoto and co-workers.[5]

The structure and relative stereochemistry of versicolamide B were corroborated through a biomimetic, racemic total synthesis. Our synthesis of **8** commenced with a Mitsonobu-type elimination (PBu_3, DEAD) of the recently prepared alcohol **11**[4] to afford an intermediate

enamide which was then treated with Me_3OBF_4 and Cs_2CO_3 to cleanly provide the desired lactim ether **12** in good yield (Scheme 4).

With lactim ether **12** in hand, we were ready to try the key biomimetic cycloaddition reaction. As recently reported, treatment of lactim ether **12** with 20% aqueous KOH in MeOH (0 °C - rt, 6 h) effected tautomerization to the intermediate azadiene **13**, which spontaneously underwent intramolecular Diels-Alder cycloaddition to produce cycloadducts **14** and **15** as a 2.4 : 1 mixture of diastereomers favoring the *syn*-stereoisomer. Interestingly, the intermediate azadiene **13** is a metastable substance that could be observed by both thin-layer chromatography and ^{1}H NMR analysis. During the reaction, lactim ether **12** (R_f = 0.75, EtOAc) disappeared within 1.5 h by TLC analysis and azadiene **13** (R_f = 0.25, EtOAc) appeared. This TLC spot then slowly disappeared giving rise to cycloadducts **14** and **15** (R_f ~ 0.4, EtOAc). The azadiene intermediate **13** was also observable by ^{1}H NMR spectroscopy through treatment of lactim ether **12** with KOD in CD_3OD/D_2O in an NMR tube.

The tentative stereochemical assignments for cycloadducts **14** and **15** were confirmed upon their transformation to (±)-notoamide B (**6**) and (±)-versicolamide B (**8**), respectively. We recently reported that notoamide B (**6**) could be prepared *via* lactim ether cleavage of *syn*-cycloadduct **14** giving rise to stephacidin A, which was then subjected to a stereoselective oxidation and pinacol-type rearrangement to cleanly produce notoamide B (**6**).[4] This protocol, however, proved problematic for the completion of the synthesis of (±)-versicolamide B (**8**) from the corresponding *anti*-cycloadduct **15**. The intermediate indole derived from cleavage of the lactim ether of **15** was found to be unstable when exposed to the atmosphere and underwent a facile ring-opening/hydrolysis of the diketopiperazine to produce the corresponding amino acid.

We therefore decided to perform the oxidation/pinacol rearrangement to the *spiro*-oxindole prior to cleavage of the methyl lactim ether. Indeed, we were pleased to find that treatment of cycloadducts **14** and **15** with excess oxaziridine **16**[11] in CH_2Cl_2 cleanly provided the desired *spiro*-oxindoles **19** and **20**, respectively. The stereochemical result of these oxidative rearrangements can be rationalized by considering that epoxidation of the 2,3-disubstituted indoles **14** and **15** occurs from the less-hindered α-face, followed by ring-opening of the incipient epoxides to their respective 2-alkoxyindole intermediates **17** and **18**. A subsequent α-face ring contraction by a [1,5] sigmatropic shift successfully furnished **19** and **20**, each as a single diastereomer. Finally, the lactim ethers of both **19** and **20** were uneventfully cleaved by treatment with 0.1 M HCl (3 equiv) in THF (0 °C, 5 min) to successfully provide (±)-notoamide B (**6**) and (±)-versicolamide B (**8**), respectively. The biomimetic synthesis of (±)-versicolamide B was thus completed in eighteen steps and 1.8% overall yield and (±)-notoamide B was completed in eighteen steps and 4.2% overall yield, both from commercially available 6-hydroxyindole. All ^{1}H and ^{13}C NMR spectral properties were identical to those of natural notoamide B (**6**) and versicolamide B (**8**) corroborating the relative stereochemical assignment based on NMR as discussed above.

The discovery of (+)-versicolamide B and the co-occurring metabolites (−)-stephacidin A and (+)-notoamide B, adds another intriguing twist to the emerging picture on the biogenesis of these alkaloids. Some possible biosynthetic relationships are depicted in Scheme 5. In this view, notoamide E (**21**) is envisioned to be the key biosynthetic progenitor.[12] Oxidation and tautomerization of **21** would yield the key, *achiral* azadiene species **22** that can, in principle, undergo cycloaddition to produce four stereoisomers: stephacidin A (as the (+)- and (−)-enantiomers) and C-6-*epi*stephacidin A (**23**) (also as the (+)- and (−)-enantiomers; only one is shown). Oxidation of the 2,3-indolic moiety of (−)-stephacidin A to the corresponding *spiro*-oxindole produces (+)-notoamide B. Similar face-selective oxidation of C-6-*epi*-stephacidin A (**23**) would produce (+)-versicolamide B. This reasonable biogenetic relationship also

implies that C-6-*epi*-stephacidin A (**23**) may be an as yet undetected natural product produced in *A. versicolor* with the absolute configuration shown in Scheme 5. What is most curious, is the enantio-facial divergence of this presumed cycloaddition in the different species of *Aspergillus* that have been demonstrated to produce stephacidin A. Thus far, (+)-stephacidin A, is the enantiomer produced in *Aspergillus ochraceus* WC76466[7c] and the marine-derived *Aspergillus* sp. described by Tsukamoto and co-workers.[5] The occurrence of (−)-stephacidin A and it's presumed oxidation metabolite (+)-notoamide B in the same stereochemical series, but distinct from that reported from these other *Aspergillus* isolates is striking. If the proposed IMDA-based biogenesis is correct, this would mandate that each fungal species evolved a means to select for the production of one enantiomeric cycloadduct (i.e., (+)- or (−)-stephacidin A), either through manipulation of the pre-cyclization conformers of putative azadiene **22**, or perhaps through selective catabolism of one enantiomer from an initially produced racemate. The latter seems less plausible as we have confirmed the optical purity of the (−)-stephacidin A here and Baran has previously confirmed the optical purity of natural (+)-stephacidin A.[10] The occurrence of (+)-versicolamide B as a co-metabolite with (−)-stephacidin A and (+)-notoamide B, is even more perplexing, since the bicyclo[2.2.2]diazaoctane core of this metabolite is *pseudo*-enantiomeric to that of these co-metabolites (but corresponds to that of (+)-stephacidin A). Does this occur through the selection of two of the four possible transition state stereochemistries accessible to **22**?

Alternatively, notoamide E (**21**) could be oxidized to give a diastereomer (**23**) of the natural oxindole species notoamide C[5] by an *S*-selective indole oxidase. Further oxidation and enolization of **23** could provide azadiene **24** that could undergo intramolecular Diels-Alder cycloaddition to directly furnish (+)-versicolamide (**8**). *Ab initio* calculations suggest,[13] and experimental model studies support[14] that the intrinsic facial bias of azadiene species similar to **24** have a strong proclivity to form the C-19-*anti*-stereochemistry present in versicolamide B. We are currently preparing isotopically labeled substrates, including **21** and **23** to further penetrate this fascinating and apparent stereochemical paradox.

In summary, the first member of the larger paraherquamide family of prenylated indole alkaloids that contains the C-19-*anti*-relative configuration in the bicyclo[2.2.2]diazaoctane ring system has been isolated and the structure of this substance, named versicolamide B, has been rigorously elucidated through spectroscopic means and total synthesis.

The production of this metabolite by *A. versicolor* suggests that the putative biosynthetic IMDA construction that leads to the major metabolites within the producing organism may suffer some stereochemical “leakage” with respect to the facial selectivity of addition to the reverse isoprene moiety anchored at the indole 2-position. Assuming that the biosynthesis of the distinct antipodes of (+)- and (−)-stephacidin A, and the presumed further oxidation products (−)- and (+)-notoamide B, respectively, proceed through stereochemically parallel pathways in the respective *Aspergillus* species, it is additionally fascinating that each organism must contain specific *R*- and *S*-selective indole oxidases paired to their respective stephacidin A enantiomer. Based on our observations, it is reasonable to anticipate that stereochemically related members of this family may be produced by other fungi, albeit in trace amounts. The surprising stereochemical paradox posed by the existence of (+)-versicolamide B[15] along with the opposite enantiomers of stephacidin A and notoamide B demand explanation on biogenetic grounds and constitute a major thrust of our ongoing work. Studies to further establish the relationship of these and simpler precursor metabolites in the biosynthesis of this family of agents, as well as efforts to carefully study the metabolite profile of *A. versicolor* are under investigation in these laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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12. Notoamide E has recently been verified to be a natural metabolite of the marine-derived *Aspergillus* spp. by comparison to an authentic, synthetic sample provided by this laboratory (ref. 4b) (S. Tsukamoto, private communication); to be reported elsewhere.
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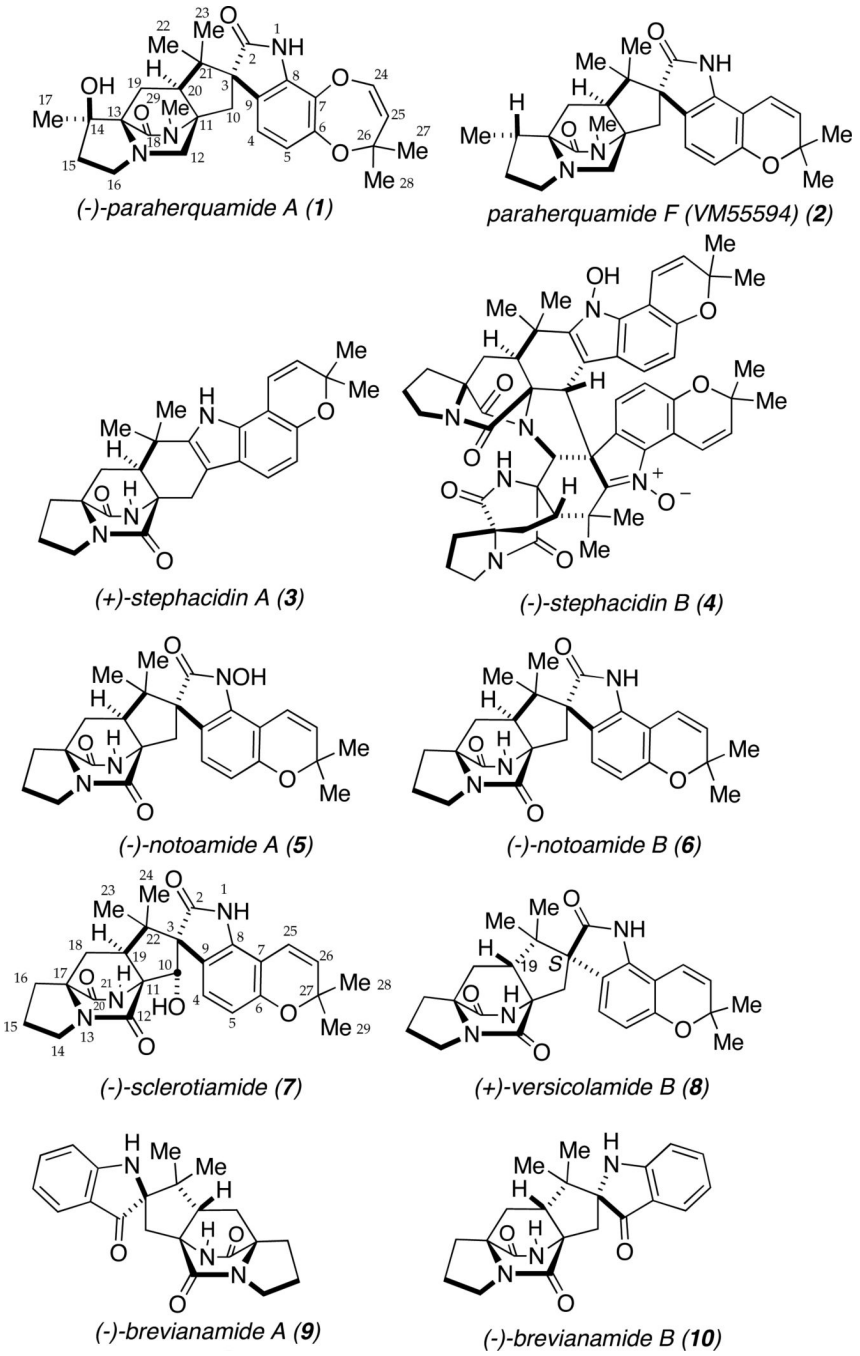
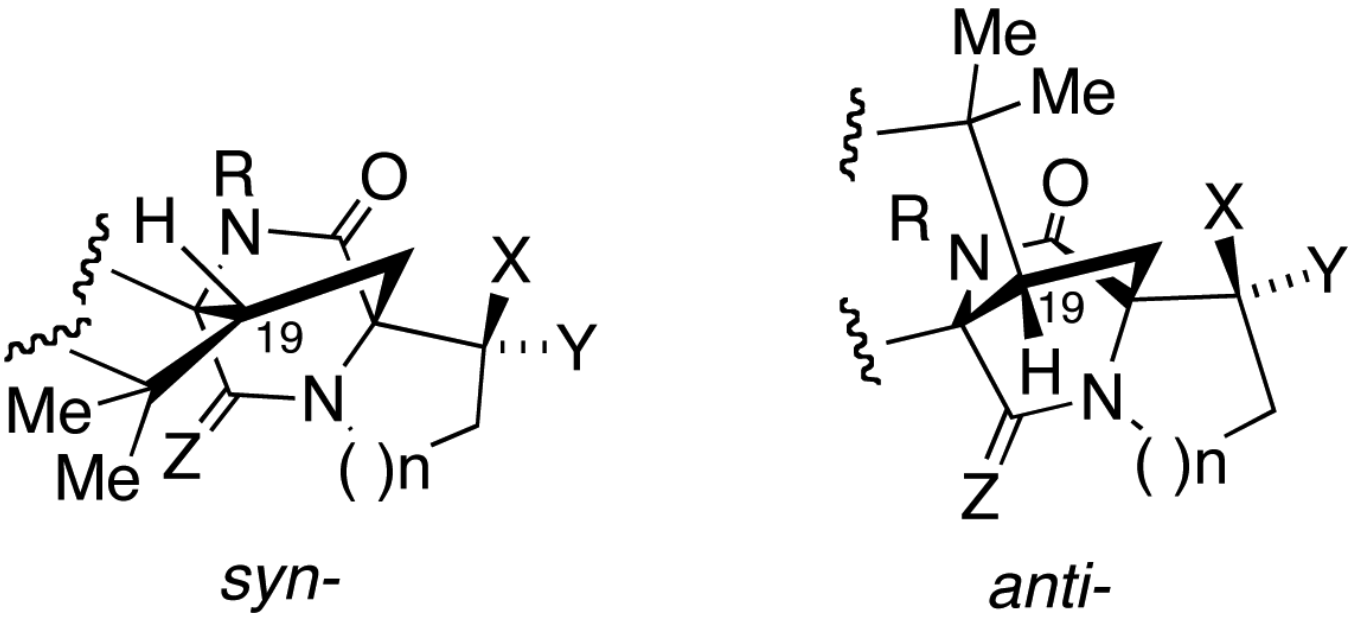
15. We chose the descriptor versicolamide “B” with the anticipation that the as yet undiscovered “A” series would be constituted from β-methylproline in paraherquamide-producing fungi. Efforts to detect such potential metabolites are under investigation.

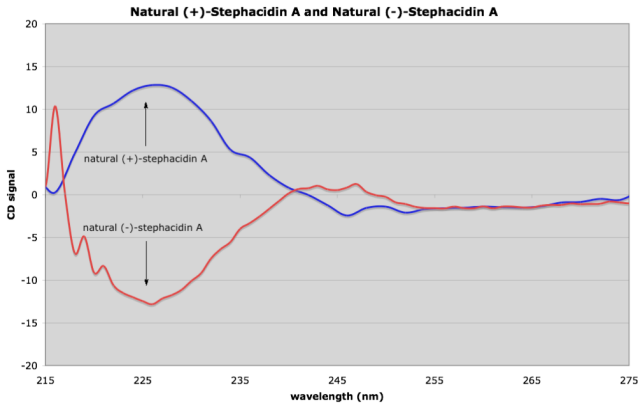


Scheme 1.
Structures of several members of the paraherquamide/stephacidin/brevianamide family of prenylated indole alkaloids.

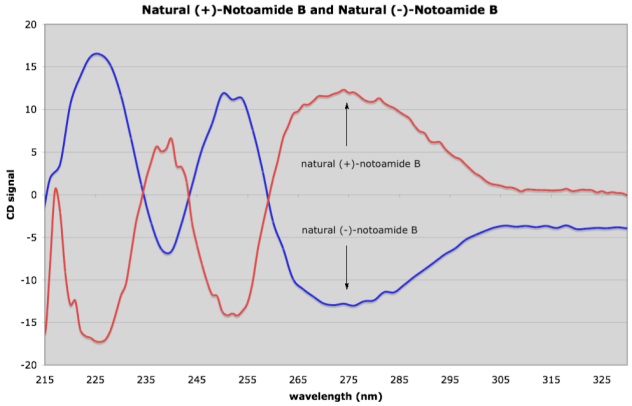


Scheme 2.
Syn- and *anti*-relative configurations at C-19 of the bicyclo[2.2.2]diazaoctane ring system (sclerotiamide numbering).

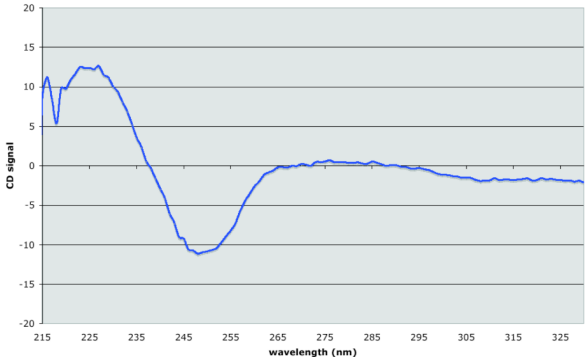
(a)



(b)

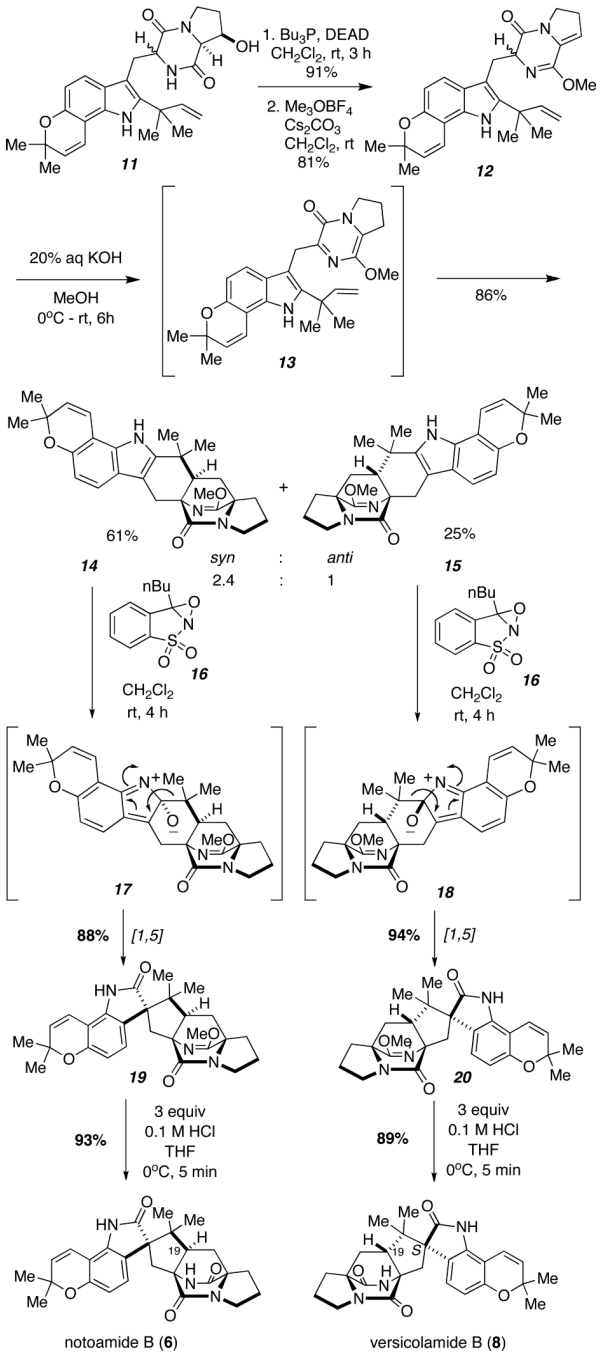


(c)



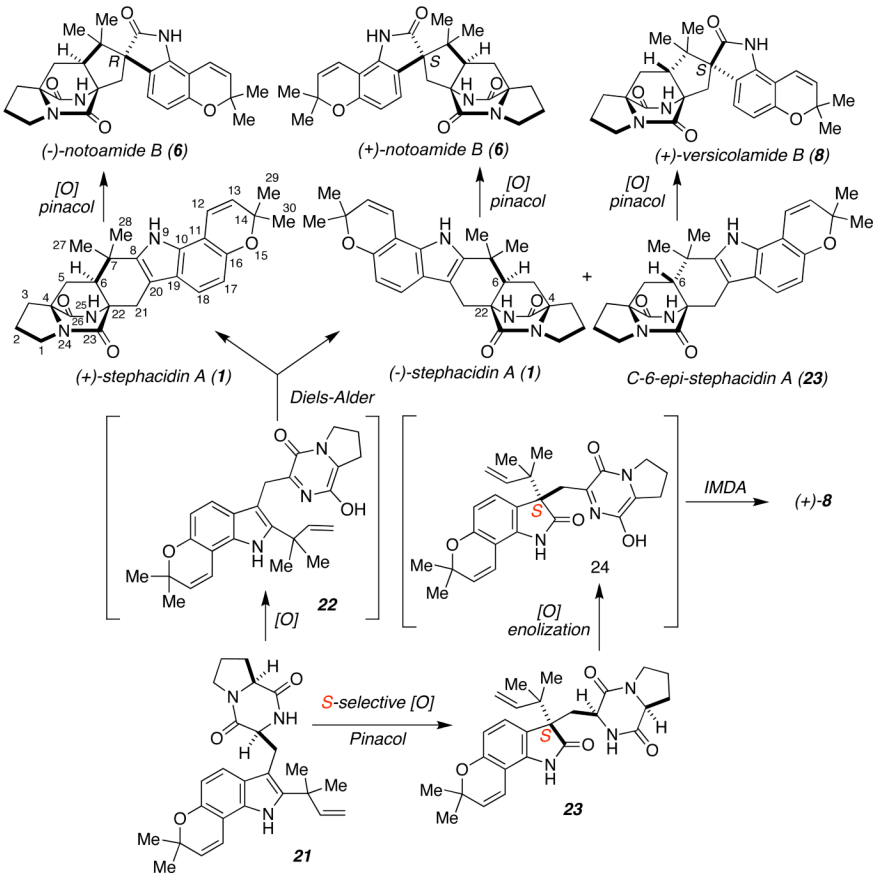
Scheme 3.

CD spectra of *Aspergillus versicolor* NRRL 35600 metabolites: (a) *ent*-(−)-stephacidin A; (b) *ent*-(+)-notoamide B; (c) versicolamide B. All CD spectra were recorded in 1:1 CH_2Cl_2:MeOH.



Scheme 4.

Synthesis of *d*,*l*-**6** and *d*,*l*-**8**. Structures are depicted with the correct relative and absolute configuration for the natural materials isolated from *Aspergillus versicolor* NRRL 35600; all substances after **11** were produced in racemic form.



Scheme 5.
Some possible biosynthetic relationships.