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Total Synthesis of Stephanotic Acid Methyl Ester

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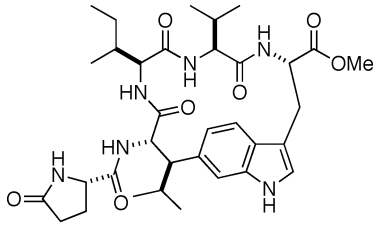
ABSTRACT



stephanotic acid methyl ester

The methyl ester of the naturally occurring macrocyclic pentapeptide stephanotic acid, containing an unusual β-substituted α-amino acid with a tryptophan C-6 to leucine β-carbon link, has been synthesized. The key steps include the formation of this amino acid through a thioxo-oxazolidine intermediate and a Horner–Wadsworth–Emmons reaction using a phosphonoglycine, derived by a dirhodium(II)-catalyzed N–H insertion reaction, to give a dehydroamino acid and subsequent rhodium(I)-catalyzed asymmetric hydrogenation to introduce the modified tryptophan residue.

Natural products of the moroidin family, many of which are potent inhibitors of tubulin polymerization, are characterized by the presence of a highly modified tryptophan within a macrocyclic peptide array. Thus, moroidin **1** itself (Figure 1), originally isolated from the leaves of the Australian rain forest bush *Laportea moroides*, and the structure determined by a combination of molecular modeling and detailed NMR experiments by the Williams group in Cambridge, contains the highly unusual direct linkages of the tryptophan C-2 and C-6 to the imidazole N-1 of histidine and the β-carbon of a leucine residue, respectively.[1] More recently, moroidin has been reisolated from the seeds of *Celosia argentia*, along with the closely related celogentins, for example, celogentin A **2**, which share a similar structural motif based on the same tryptophan core.[2] The simplest member of this family of cyclic peptides, stephanotic acid **3**, isolated from *Stephanotis floribunda*, lacks the right-hand histidine-containing ring of moroidin and has a leucine−isoleucine substitution.[3]

Despite their fascinating structures, these cyclic peptides have attracted little attention from synthetic chemists, although over a decade ago we developed a route to simple *N*-(2-indolyl)imidazoles[4] and subsequently used this methodology to prepare the right-hand cycle of moroidin.[5] Castle

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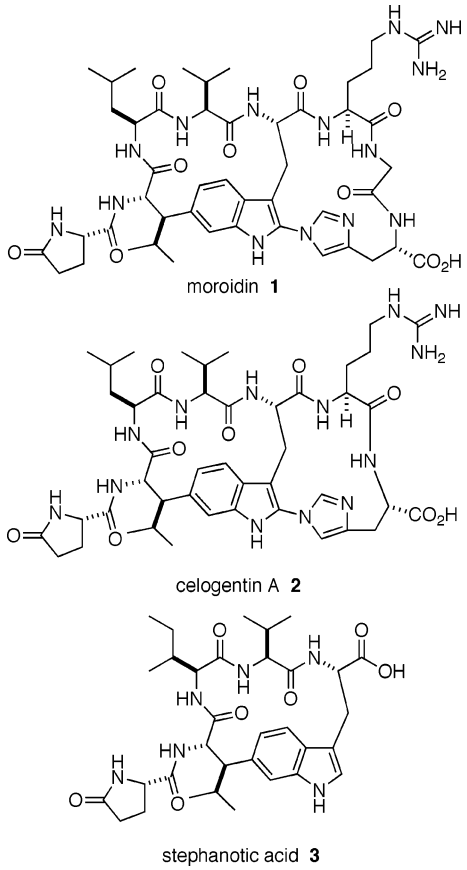

Figure 1. Moroidin family of macrocyclic peptides.

and Srikanth have reported an asymmetric synthesis of 6-(*tert*-butyldimethylsiloxy)methyl-2-triethylsilyltryptophan as a precursor for the central core of moroidin/celogentins,[6] using Cook's versatile tryptophan synthesis in which the indole is formed by the Larock methodology but replacing the original alkylation of a Schöllkopf auxiliary with a phase-transfer-catalyzed alkylation using the chiral catalyst developed by Park et al.

More recently, we reported an asymmetric synthesis of the central tryptophan residue of stephanotic acid, using dirhodium(II)-catalyzed carbene N−H insertion chemistry in conjunction with rhodium(I)-catalyzed asymmetric hydrogenation of dehydro di- and tripeptides to give the core tryptophan residues **4** and **5** (Figure 2).[7] We now report the

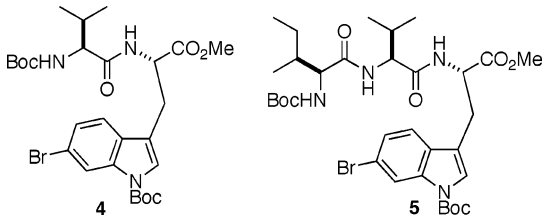

Figure 2. Previously synthesized tryptophan residues.

use of this methodology in the first total synthesis of stephanotic acid methyl ester **6**.

Our original plan was to use the bromine functionality incorporated in the model tryptophans **4** and **5** to introduce a carbon side chain at C-6, for example, by a Pd-catalyzed coupling reaction. However, this proved unsatisfactory and therefore an alternative strategy was developed as outlined in Figure 3. This requires a macrocyclization between the

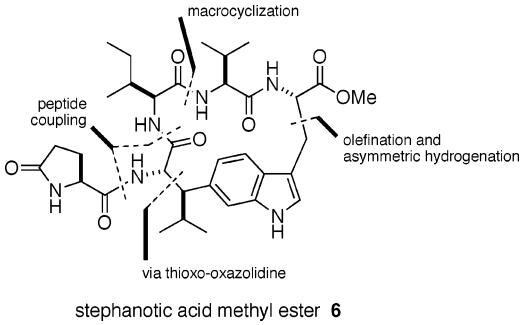

Figure 3. Retrosynthetic analysis.

isoleucine and valine residues along with other peptide coupling reactions, the formation of the tryptophan stereocenter by olefination and asymmetric hydrogenation, and the use of a thioxo-oxazolidine ring to form the unusual β-substituted leucine residue. The formation of this sterically hindered β-substituted α-amino acid is a key step in the overall synthesis.[8]

The starting point for our synthesis was *N*-*tert*-butoxycarbonyl-6-isobutyrylindole **7**, readily prepared from 6-cyanoindole by reaction with excess isopropylmagnesium chloride followed by N-protection. Attempts to prepare a dehydroamino acid derivative by Horner−Wadsworth−Emmons reaction of ketone **7** with N-protected trimethyl phosphonoglycine derivatives were unfortunately unsuccessful.[9] Further, although in model studies on isobutyrophenone we had demonstrated the successful application of the Schöllkopf protocol using ethyl isocyanoacetate to give an *N*-formyl-protected dehydroamino acid ester,[10] this was unsuccessful when applied to the isopropyl ketone **7**, and therefore, a less direct route was adopted using the methodology for the formation of hindered dehydroamino acids developed by Hoppe some years ago.[11] The method uses the reactive reagent ethyl isothiocyanatoacetate to give a thioxo-oxazolidine that, after N-acylation, fragments with loss of COS upon treatment with base to give the protected

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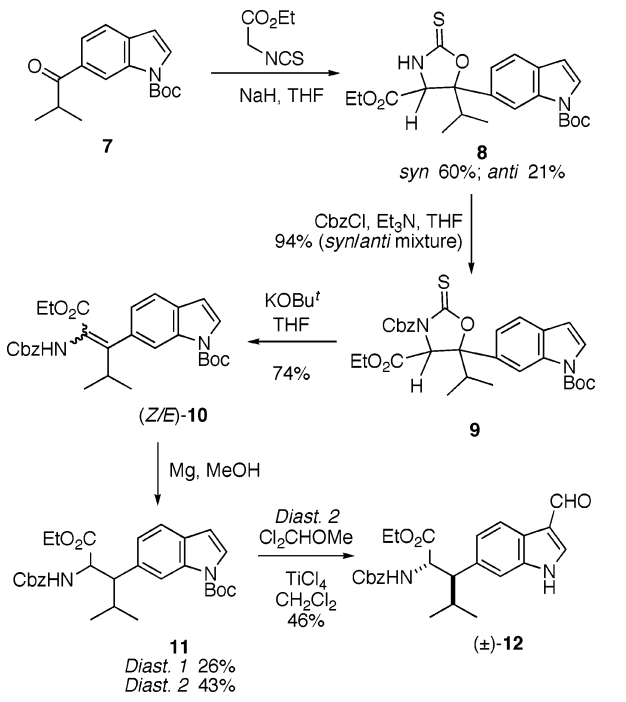
dehydroamino acid. Thus, ketone **7** was subjected to these conditions to give a mixture of diastereomeric thioxo-oxazolidines **8** that were converted into the separable alkenes (*E*)- and (*Z*)-**10** in a combined yield of 56% over the three steps (Scheme 1). Attempts at asymmetric hydrogenation of

Scheme 1



the dehydroamino acid derivative (*Z*)-**10** using MeDuPHOS or MeBPE rhodium(I) catalysis, developed by Burk for β,β-disubstituted dehydroamino acids,[12] gave only poor enantioselectivities (up to 28% ee) and yields. Therefore, a less elegant achiral reduction, followed by a subsequent separation/resolution, was resorted to. Although the (*E*/*Z*)-alkenes **10** could be separated, it was more convenient to reduce the mixture using magnesium in methanol[13] to give a mixture of racemic diastereomers **11** in good overall yield in a ca. 3:2 ratio. Formylation of the major isomer, with concomitant *N*-Boc deprotection, was achieved using titanium(IV) chloride and dichloromethyl methyl ether[14] to give the (±)-amino acid derivative **12** in modest yield. X-ray crystallography established the relative stereochemistry as (2-*S*/*R*, 3-*R*/*S*) as required for the natural product (Figure 4).

To generate the tryptophan stereocenter by asymmetric hydrogenation, an appropriate dehydrotryptophan was required. Simple dehydroamino acids can be prepared by Horner−Wadsworth−Emmons reactions of a phosphonoglycine such as the commercially available *N*-benzyloxycarbonyl

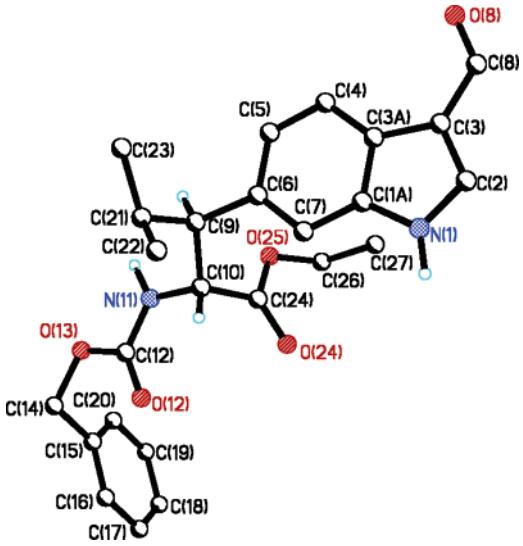
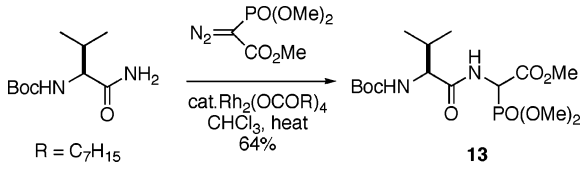


Figure 4. X-ray crystal structure of (±)-**12**.

trimethyl phosphonoglycine. However, we recently reported a route to dehydrodi- and -tripeptides using a more complex phosphonoglycine that already incorporated one or more additional amino acid residues.[7,15] Hence, phosphonoglycine **13** was made by dirhodium(II)-catalyzed N−H insertion of the (presumed) carbene intermediate of trimethyl diazophosphonoacetate into the amide NH of *N*-Boc-valinamide (Scheme 2).

Scheme 2



A Horner−Wadsworth−Emmons reaction using phosphonoglycine **13** directly onto the indole-3-carboxaldehyde **12** would have led to protecting group selectivity problems between the methyl and ethyl esters. The racemic compound **12** was therefore subjected to hydrolysis, and the free acid was coupled to isoleucine *tert*-butyl ester to give a mixture of inseparable diastereomers **14** in good yield (Scheme 3). The indole **14** was N-protected as its Boc derivative to activate the aldehyde for the subsequent Horner−Wadsworth−Emmons reaction with phosphonoglycine **13**. This was carried out using Schmidt's (*Z*)-selective DBU protocol[16] and gave the dehydroamino acid **15**. At this stage, the ~1:1 mixture of diastereomers **15** was readily separable by

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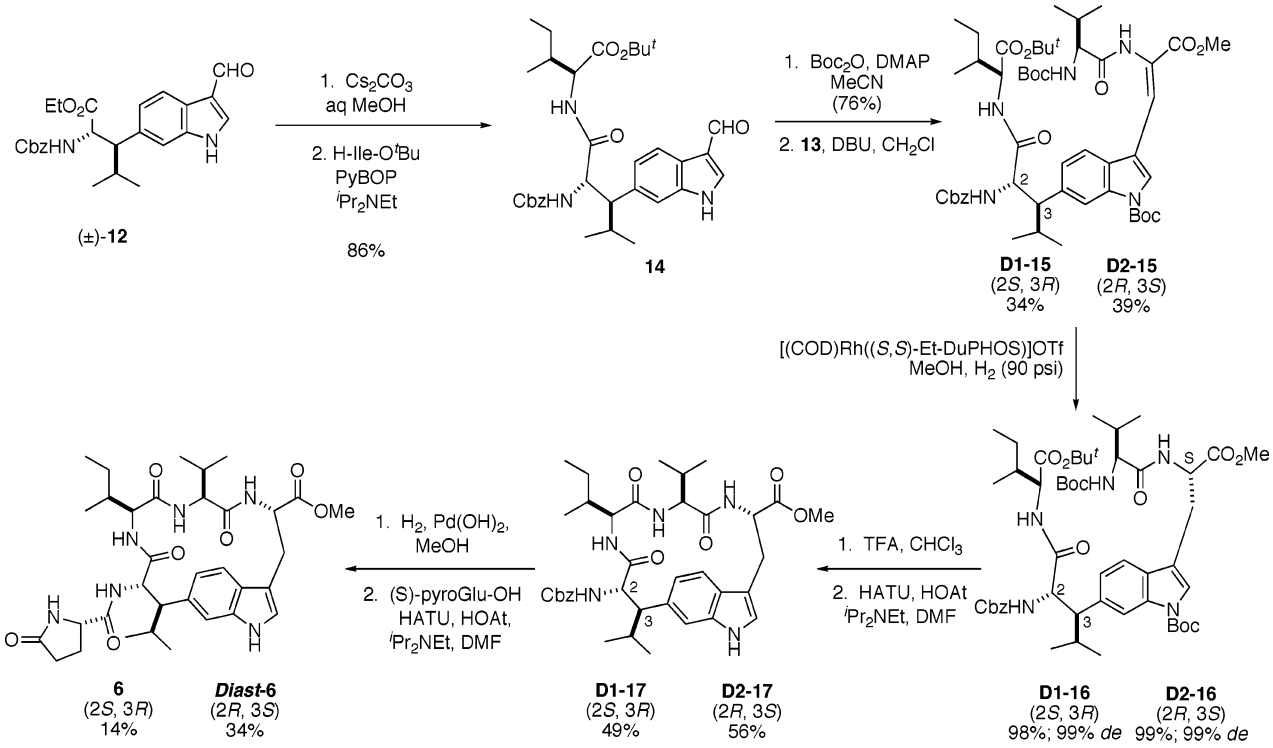
Scheme 3



standard chromatography thereby completing the necessary resolution step in the synthesis.

Because we did not know which diastereomer of **15**, **D1**, or **D2** was which at this stage, each was subjected to asymmetric hydrogenation in methanol using Burk's (*S*,*S*)-EtDuPHOS Rh(I) catalytic system [(+)-(1,2-bis(2*S*,5*S*)-2,5-diethyl phospholano)benzene(1,5-cyclooctadiene)rhodium^{I}-trifluoromethanesulfonate] under 90 psi of hydrogen,[17] which gave each product **16** in excellent yield and as a single diastereomer as evidenced by ^{1}H NMR spectroscopy. The stereoselectivity was confirmed by hydrogenation of each diastereomer of **15** (**D1-15** and **D2-15**) using an *achiral* rhodium(I) catalyst [1,1′-bis(diisopropylphosphino)ferrocene-(1,5-cyclooctadiene)rhodium^{I}tetrafluoroborate]. Comparison of the achiral reaction products with **D1-16** and **D2-16** by HPLC on a chiral stationary phase confirmed that the asymmetric hydrogenation had proceeded with 99% diastereomeric excess in each case. The stereochemistry of the new chiral centers was assigned as (*S*) on the basis of previous literature.[7,15]

Macrocyclization of each diastereomer of **16** was initiated by simultaneous deprotection of the valine *N*-Boc group and the isoleucine *tert*-butyl ester by treatment with trifluoroacetic acid, with concomitant loss of the tryptophan *N*-Boc. The resulting amino acids were cyclized under high dilution conditions using HATU/HOAt as coupling agents[18] to give the macrocycles **D1-17** and **D2-17**. It was apparent by ^{1}H NMR spectroscopy that, although **D2-17** was formed cleanly, some epimerization had occurred during the formation of **D1-17**. Each of the macrocycles **D1-17** and **D2-17** was then individually subjected to deprotection by hydrogenolysis over Pearlman's catalyst to give the free amine that was directly coupled to pyroglutamic acid using HATU/HOAt. The pyroglutamic acid coupling arising from **D2-17** gave a single compound **Diast-6**. As expected, the pyroglutamic acid coupling arising from **D1-17** gave the diastereomeric product **6**, contaminated by a further diastereomer as a result of the epimerization referred to above. Purification by preparative HPLC provided pure stephanotic acid methyl ester **6** whose ^{1}H and ^{13}C NMR spectra were identical to those provided in the literature.[3]

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Supporting Information Available: Full experimental details for compounds **6**−**12** and **14**−**17**, copies of NMR spectra, and HPLC analysis of **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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