ORGANIC LETTERS

2006
Vol. 8, No. 10
1975−1978

# Total Synthesis of Stephanotic Acid Methyl Ester

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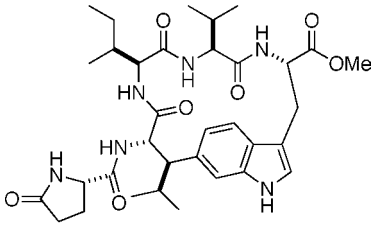
**Received January 19, 2006**

## 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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10.1021/ol060153c CCC: $33.50 
**Published on Web 04/21/2006**

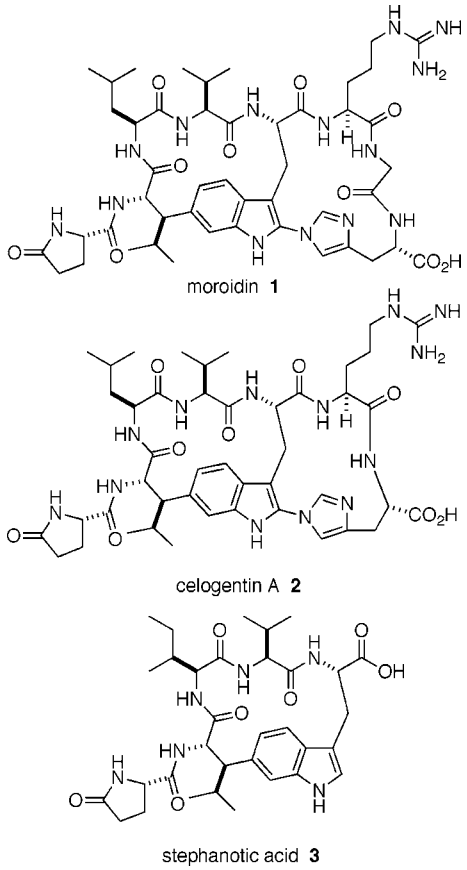


**Figure 1.** Moroidin family of macrocyclic peptides.

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

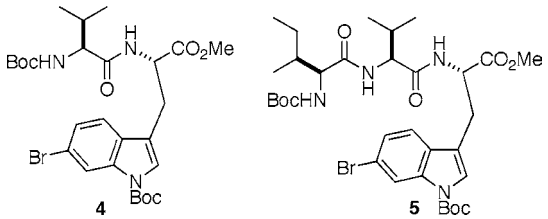


**Figure 2.** Previously synthesized tryptophan residues.

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

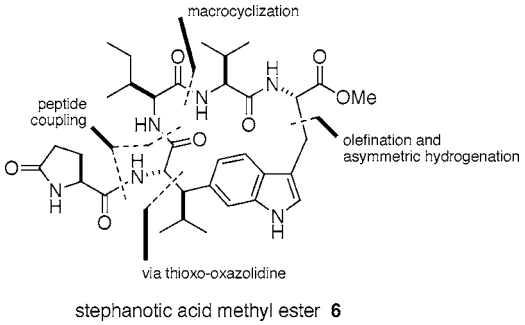


**Figure 3.** Retrosynthetic analysis.

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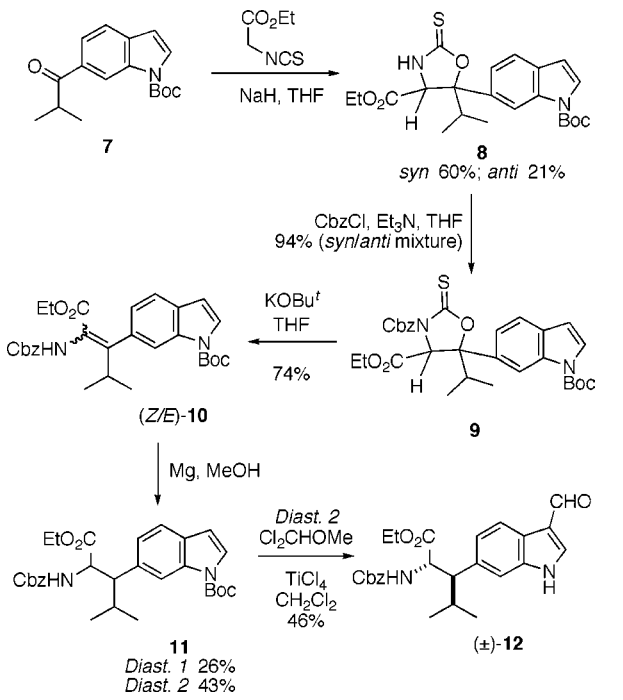
dehydroamino acid. Thus, ketone **7** was subjected to these conditions to give a mixture of diastereomeric thioxo-oxazolidines **8** that were converted into the separable alkenes (*E*)- and (*Z*)-**10** in a combined yield of 56% over the three steps (Scheme 1). Attempts at asymmetric hydrogenation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

**Scheme 1**




the dehydroamino acid derivative (*Z*)-**10** using MeDuPHOS or MeBPE rhodium(I) catalysis, developed by Burk for $\beta,\beta$-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

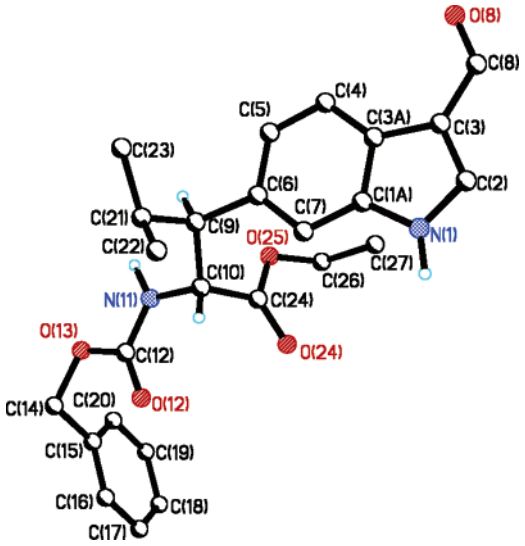
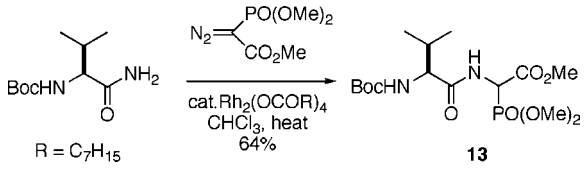



**Figure 4.** X-ray crystal structure of (±)-**12**.

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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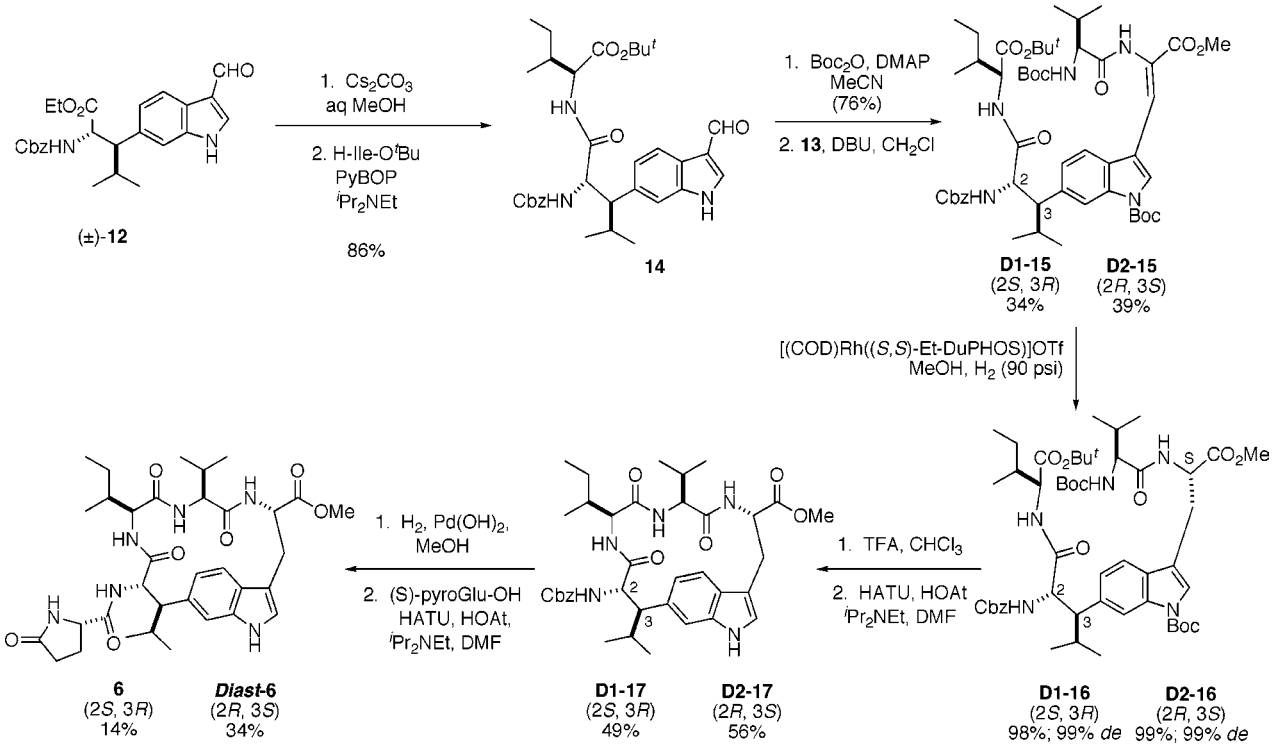
**Scheme 3**




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]

**Acknowledgment.** We thank the EPSRC for support (DTA Scheme), the EPSRC Mass Spectrometry Center at Swansea for mass spectra, Dane Toplis for preparative HPLC work, and Dr. Chris McErlean for helpful discussions.

**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.

OL060153C

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