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Asymmetric synthesis of the central tryptophan residue of stephanotic acid†

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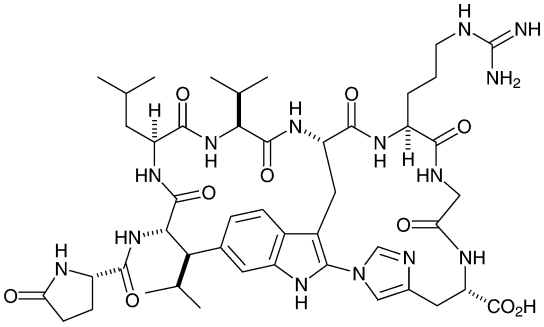
The C-6 substituted tryptophan di- and tri-peptides 5 and 6, representing the tryptophan core of stephanotic acid, have been synthesized, the key steps being the formation of the phosphono-di- and tri-peptides 8 and 10 by a highly chemoselective rhodium(II) catalyzed carbene N-H insertion reaction, their subsequent Horner–Wadsworth–Emmons reactions with *N*-Boc-6-bromoindole-3-carboxaldehyde, and the rhodium(I) catalyzed asymmetric hydrogenation of the resulting dehydro di- and tri-peptides.

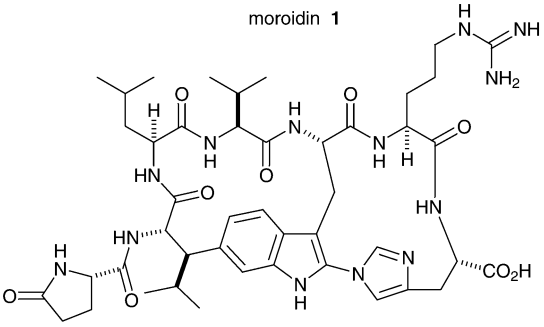
Natural products of the moroidin family, many of which are potent inhibitors of tubulin polymerization, are characterized by the presence of a highly modified tryptophan within a macrocyclic peptide array. Thus moroidin itself, **1**, originally isolated from the leaves of the Australian rain forest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

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 we have used this methodology to prepare the right-hand macrocycle of moroidin.[5] More recently Castle and Srikanth have reported an asymmetric synthesis of the central core **4** of moroidin/celogentins 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 Park *et al.*'s chiral catalyst.[6] We now report an alternative route to the tryptophan core **5/6** of stephanotic acid using rhodium(II) catalyzed carbene N-H insertion chemistry in conjunction with rhodium(I) catalyzed asymmetric hydrogenation of dehydro di- and tri-peptides.

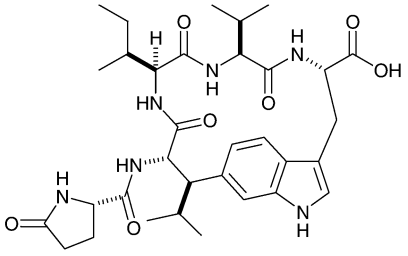
In order to generate the modified tryptophan stereocentre by asymmetric hydrogenation, an appropriate alkene (dehydroamino acid) was required. In general, simple dehydroamino acids are prepared by Horner–Wadsworth–Emmons reactions of a phosphonoglycine such as the commercially available *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester. However, we preferred to use a more complex phosphonoglycine that already incorporates one or more additional amino acids residues, thus making the synthesis more convergent, and we have recently shown that such phosphonoglycines can be readily accessed by dirhodium(II) catalyzed reactions of diazophosphonates.[7] Thus *N*-Boc-valinamide **7** was treated with trimethyl diazophosphonoacetate[8] in the presence of dirhodium tetraoctanoate in boiling chloroform; this resulted in chemoselective N-H insertion of the (presumed) intermediate rhodium carbene into the amide NH to give the phosphono-dipeptide **8** in 64% yield. Likewise the dipeptide amide, Boc-Ile-Val-NH_2 **9**, also reacted with the diazophosphonate to give the phosphono-tripeptide **10** albeit in 40% yield. Although the yield of the tripeptide **10** was modest, there was no evidence for products formed by reaction of the rhodium carbene at any other sites in the dipeptide amide **9**. The phosphono-tripeptide **10** could also be obtained from dipeptide **8** by TFA cleavage of the Boc-group followed by coupling to Boc-Ile-OH using bromotri(pyrrolidino)phosphonium hexafluorophosphate (PyBroP®) (Scheme 1). Phosphonopeptides **8** and **10** were obtained as mixtures of epimers at the new stereocentre and were used without further purification.



moroidin **1**



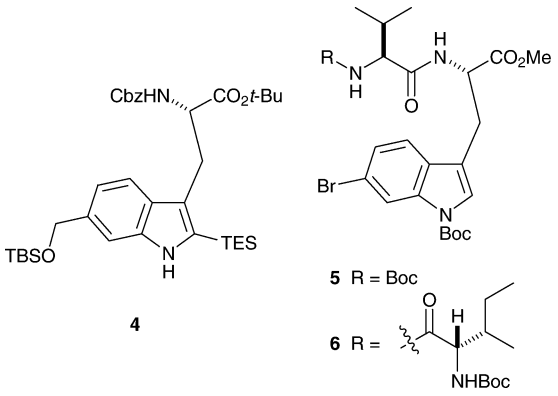
celogentin A **2**



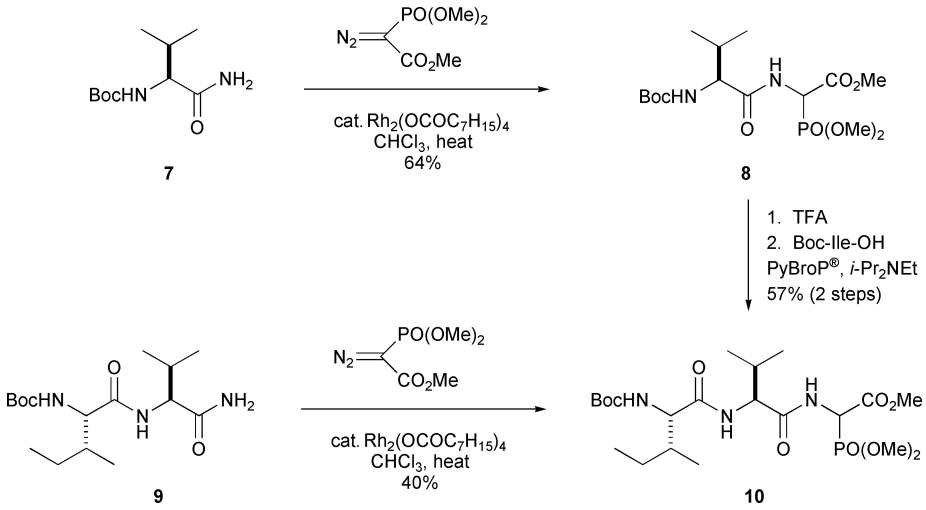
stephanotic acid **3**

† Electronic supplementary information (ESI) available. Experimental procedures for compounds **5–13**; HPLC data for compounds **5** and **6**. See http://www.rsc.org/suppdata/ob/b4/b414996c/

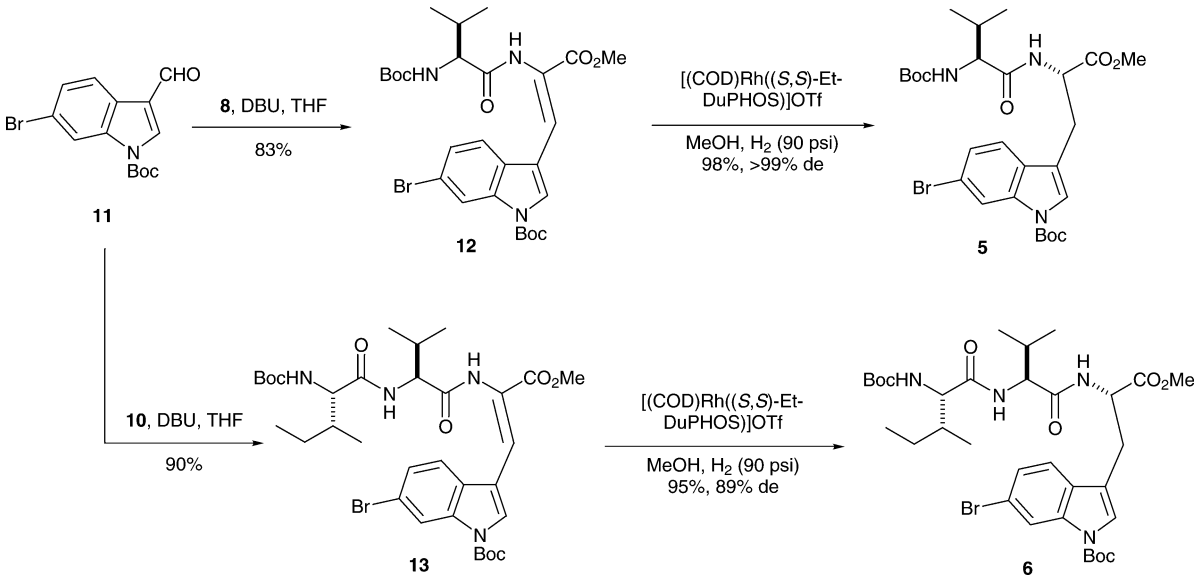
DOI: 10.1039/b414996c



In order to allow for the subsequent elaboration of the β-substituted leucine residue at tryptophan C-6, a bromine substituent was incorporated. 6-Bromoindole was formylated at C-3 under Vilsmeier–Haack conditions, and the resulting aldehyde treated with di-*tert*-butyl dicarbonate to give the known *N*-Boc-6-bromoindole-3-carboxaldehyde[9] **11** in good yield. The Horner–Wadsworth–Emmons reaction of this indole aldehyde with both phosphonoglycines **8** and **10** in the presence of DBU proceeded in excellent yield to give the (*Z*)-dehydrotryptophan peptides **12** and **13** (Scheme 2). The stereochemistry of the alkene is assigned on the basis of literature precedent, Schmidt's DBU protocol being highly *Z*-selective.[10] The stage was now set for the asymmetric hydrogenation of the dehydro peptides, and on the basis of literature precedent for simple dehydro amino acid derivatives,[11] Burk's DuPHOS ligands were selected. Hydrogenation of **12** in methanol using the (*S*,*S*)-EtDuPHOS system [(+)-1,2-bis-(2*S*,5*S*)-2,5-diethylphospholano)benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate] under 90 psi of hydrogen gave the dipeptide **5** in excellent yield as a single diastereomer as evidenced by ^{1}H NMR spectroscopy. In order to confirm the stereoselectivity of the reaction, the hydrogenation of **12** was repeated using an achiral rhodium(I) catalyst [1,1′-bis(di-isopropylphosphino)ferrocene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate]. Comparison of the product with **5** by HPLC on a chiral stationary phase confirmed that the asymmetric hydrogenation had proceeded with >99% diastereomeric excess, a pleasing result for a relatively complex substrate. The stereochemistry of the new chiral centre was assigned as (*S*) on the basis of previous literature reports using the (*S*,*S*)-EtDuPHOS ligand,[11] but was confirmed by debromination of **5** by hydrogenolysis over palladium-on-charcoal, and comparison



Scheme 1



Scheme 2

of the product with an authentic sample obtained from the known dipeptide,[12] Boc-(*S*)-valine-(*S*)-trytophan-OMe. In a similar manner, asymmetric hydrogenation of the dehydro tripeptide **13** gave the (*S*,*S*,*S*)-tripeptide **6** in excellent yield, but with somewhat lower stereoselectivity (89% de determined by HPLC comparison with the product obtained by hydrogenation over the achiral rhodium(I) catalyst).

Studies on the total synthesis of stephanotic acid **3** using this methodology are in progress.

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References

1 (*a*) T.-W. C. Leung, D. H. Williams, J. C. J. Barna, S. Foti and P. B. Oelrichs, *Tetrahedron*, 1986, **42**, 3333; (*b*) S. D. Kahn, P. M. Booth, J. P. Waltho and D. H. Williams, *J. Org. Chem.*, 1989, **54**, 1901; (*c*) S. D. Kahn, P. M. Booth, J. P. Waltho and D. H. Williams, *J. Org. Chem.*, 2000, **65**, 8406.
2 (*a*) H. Morita, K. Shimbo, H. Shigemori and J. Kobayashi, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 469; (*b*) J. Kobayashi, H. Suzuki, K. Shimbo, K. Takeya and H. Morita, *J. Org. Chem.*, 2001, **66**, 6626; (*c*) H. Suzuki, H. Morita, S. Iwasaki and J. Kobayashi, *Tetrahedron*, 2003, **59**, 5307; (*d*) H. Suzuki, H. Morita, M. Shiro and J. Kobayashi, *Tetrahedron*, 2004, **60**, 2489.
3 K. Yoshikawa, S. Tao and A. Arihara, *J. Nat. Prod.*, 2000, **63**, 540.
4 M. F. Comber and C. J. Moody, *Synthesis*, 1992, 731.
5 J. R. Harrison and C. J. Moody, *Tetrahedron Lett.*, 2003, **44**, 5189.
6 S. L. Castle and G. S. C. Srikanth, *Org. Lett.*, 2003, **5**, 3611.
7 R. T. Buck, P. A. Clarke, D. M. Coe, M. J. Drysdale, L. Ferris, D. Haigh, C. J. Moody, N. D. Pearson and E. Swann, *Chem. Eur. J.*, 2000, **6**, 2160.
8 S. Hanessian, V. Mascitti and O. Rogel, *J. Org. Chem.*, 2002, **67**, 3346.
9 U. Schmidt and J. Wild, *Liebigs Ann. Chem.*, 1985, 1882.
10 U. Schmidt, H. Griesser, V. Leitenberger, A. Lieberknecht, R. Mangold, R. Meyer and B. Riedl, *Synthesis*, 1992, 487.
11 (*a*) M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125; (*b*) M. J. Burk, M. F. Gross, T. G. P. Harper, C. S. Kalberg, J. R. Lee and J. P. Martinez, *Pure Appl. Chem.*, 1996, **68**, 37.
12 E. Caballero, C. Avendano and J. C. Menéndez, *Tetrahedron: Asymmetry*, 1998, **9**, 3025.