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The Horner–Wadsworth–Emmons reaction in the synthesis of macrocyclic peptides: the Trp-His-Gly-Arg derived macrocycle of moroidin

Justin R. Harrison and Christopher J. Moody*

School of Chemistry, University of Exeter, Stocker Road, Exeter EX4 4QD, UK

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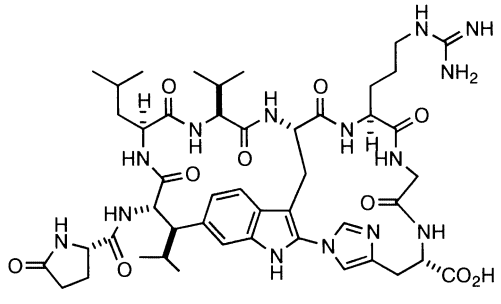
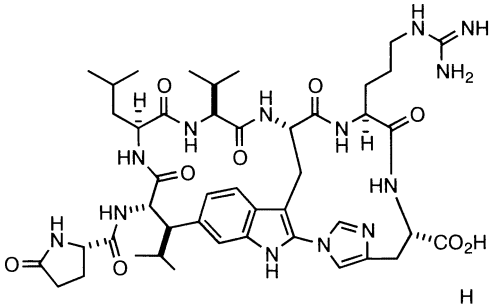
Abstract—The Trp-His-Gly-Arg derived macrocycle **4** of moroidin **1** containing the unusual tryptophan C-2 histidine N-1 link has been synthesised in protected form. The key steps are displacement of a 2-chloroindole with a histidine derived nucleophile, a Horner–Wadsworth–Emmons reaction followed by asymmetric hydrogenation to establish the tryptophan side chain, and incorporation of the Gly-Arg dipeptide by peptide coupling.

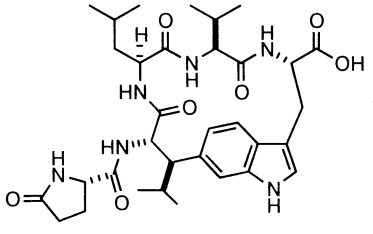
Moroidin **1** is a bicyclic peptide with potent biological activity. It was originally isolated from the leaves of the Australian rain forest bush *Laportea moroides*, and the structure determined by a combination of molecular modelling and detailed NMR experiments by the Williams group in Cambridge.[1] The bush from which moroidin is extracted is covered with stinging hairs, contact with which results in intense pain, and in extreme cases unconsciousness and death. Although not as bioactive as the crude plant extract, pure moroidin does elicit powerful acetylcholine like responses at the 5–10 microgram level. More recently moroidin has been re-isolated from the seeds of *Celosia argentea*, its structure confirmed, and shown to possess potent inhibitory activity on tubulin assembly.[2] The closely related celogentins, for example celogentin A **2**, have been isolated from the same seeds and also shown to have potent antimitotic effects,[3] whilst stephanotic acid **3**, isolated from *Stephanotis floribunda*,[4] is a related but slightly simpler cyclic peptide lacking the right-hand histidine-containing ring of moroidin.



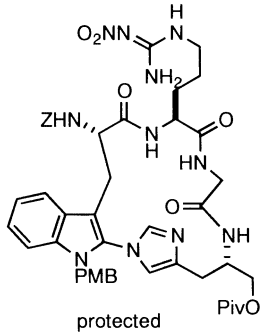
moroidin
1



celogentin A
2



stephanotic acid
3



protected TrpHisGlyArg macrocycle of moroidin
4

The structure of moroidin **1** is characterised by the presence of a highly modified tryptophan and several

* Corresponding author.

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amino acids in a double macrocyclic array, and is unique in the direct linkage of the indole C-2 to the imidazole N-1 of histidine, although *N*-linked histidine residues are known to occur in other macrocyclic peptides such as the theonellamides.[5] We now report the first synthesis of the (protected) Trp-His-Gly-Arg derived macrocycle **4** of moroidin, the fragment containing the unique indole-imidazole link.

The strategy is outlined in Figure 1, and in addition to two straightforward peptide bond forming reactions, includes a Horner–Wadsworth–Emmons (HWE) reaction. The macrocycle **4** incorporates the histidine residue as a protected histidinol to prevent the facile racemisation which often occurs with histidinyl esters. The indolic nitrogen is also blocked, which not only protects the indole nitrogen but also modifies the reactivity of the indole-3-carboxaldehyde **6**. The aldehyde group is a key feature of the strategy for formation of a key carbon–carbon bond in an intra- or intermolecular HWE reaction, although only the intermolecular variant is described herein. Some years ago,[6] we developed a route to simple *N*-(2-indolyl)imidazoles based on the facile displacement of chloride from 2-chloroindole-3-carboxaldehydes, a reaction in which the formyl group plays a key role. Hence a similar displacement of chloride remained a key feature of our strategy for the synthesis of the macrocyclic fragment **4** of moroidin (Fig. 1).

The histidinol derivative **5** required for coupling to the indole 2-position was prepared as shown in Scheme 1. Thus reaction of histidinol dihydrochloride with an excess of di-*tert*-butyl dicarbonate gave the N^1,N^α-di-Boc-derivative, treatment of which with aqueous base cleaved the N^1-Boc group to give N^α-Boc-histidinol. Protection of the primary alcohol as its trimethylacetyl (Piv) ester then gave the required histidinol derivative **5**.

The indole **6** was readily prepared by protection of 2-chloroindole-3-carboxaldehyde, itself easily obtained on a large scale by reaction of oxindole with the Vilsmeier reagent.[7] Reaction of the 2-chloroindole **6** with the imidazolyl sodium salt, prepared by treating **5** with NaHMDS, in *N*,*N*-dimethylacetamide (DMA)

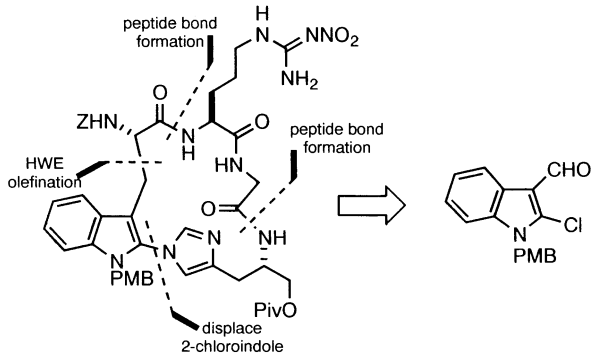
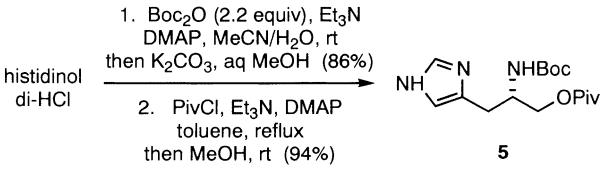


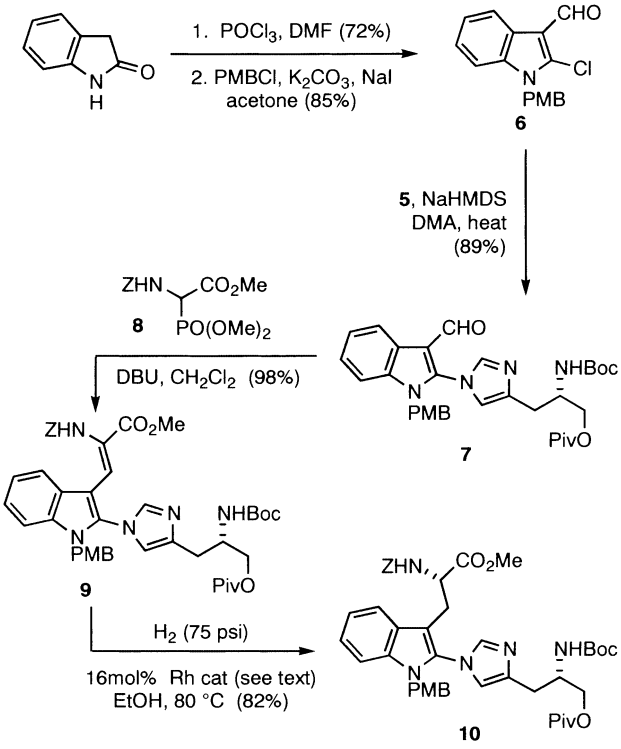
Figure 1.



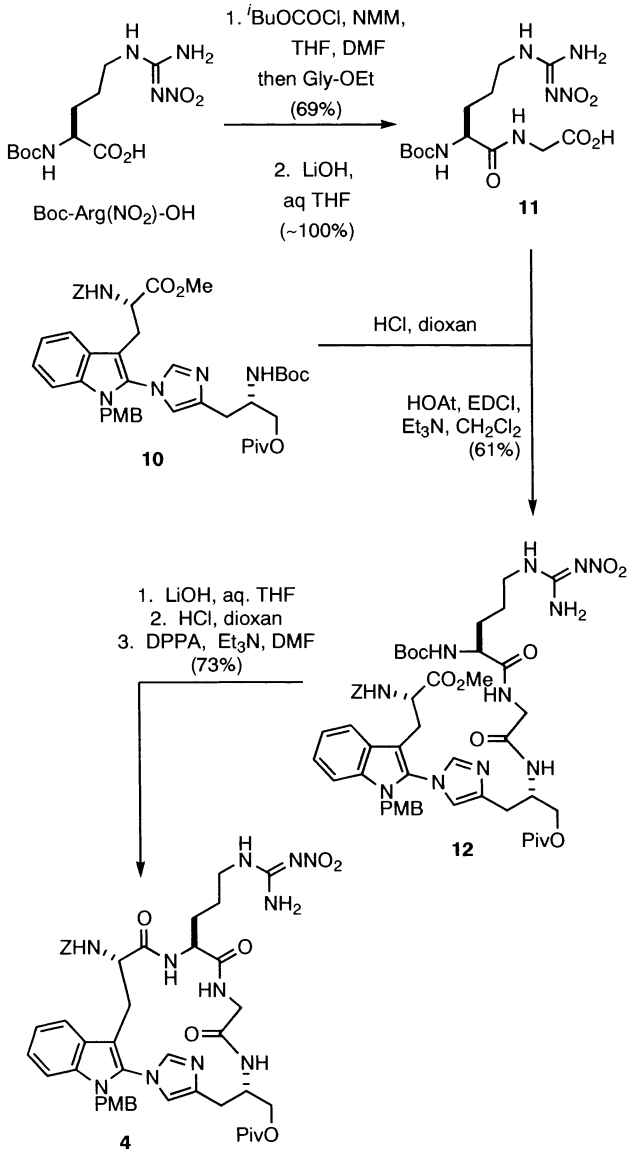
Scheme 1.

gave the desired coupled product **7** in an optimised yield of 89%. Subsequent HWE reaction of the aldehyde **7** with the protected aminophosphonate **8** in the presence of DBU[8] gave the dehydrotryptophan derivative **9** in excellent yield. The stereochemistry of the alkene is assigned on the basis of literature precedent, Schmidt's DBU protocol being highly *Z*-selective.[8,9] The stage was now set for the asymmetric hydrogenation of the dehydro amino acid **9**, and on the basis of literature precedent,[9,10] the DuPHOS and DIPAMP ligands were selected, with the (*R*,*R*)-DIPAMP rhodium(I) catalyst giving better results. This gave the desired protected amino acid derivative **10** in excellent yield (Scheme 2). Although this compound was apparently a single diastereomer as evidenced by NMR, this was not conclusive, HPLC evidence suggesting that the reduction had proceeded with ca. 70% ee.

The remaining Arg-Gly fragment was then incorporated into the macrocycle by peptide bond forming reactions. The Boc-Arg(NO_2)-Gly-OH dipeptide **11** was prepared by conventional methodology from commercially available Boc-Arg(NO_2)-OH, and coupled to the amine derived by cleavage of the *N*-Boc-protected indole-imidazole 'dipeptide' **10**. This gave the protected



Scheme 2.



Scheme 3.

'tetrapeptide' **12**, the substrate for macrocyclisation (Scheme 3). The terminal carboxyl and amino groups were deprotected sequentially by treatment with aqueous lithium hydroxide and then HCl in dioxan. The resulting amino acid was cyclised under high dilution using the diphenylphosphoryl azide (DPPA) protocol[11] to give the macrocycle **4**, comprising the complete right-hand Trp-His-Gly-Arg fragment of moroidin in fully protected form.

In summary, we have described the first synthesis of the unusual macrocyclic peptide fragment of moroidin containing the unique direct link between the tryptophan indole C-2 and histidine imidazole N-1 residues. Further studies are underway.

Acknowledgements

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