

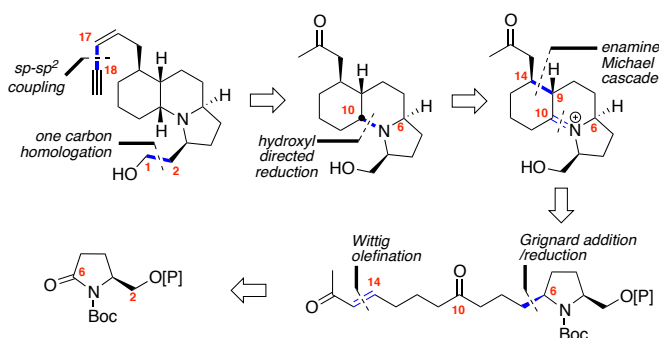
# A Cascade Strategy Enables a Total Synthesis of (-)-Gephyrotoxin\*\*

Shuyu Chu, Stephen Wallace and Martin D. Smith\*

**Abstract:** A concise and efficient synthesis of (-)-gephyrotoxin from (L)-pyroglutaminol has been realized. The key step in this approach is a diastereoselective intramolecular enamine-Michael cascade that forms two rings and two stereocenters and generates a stable tricyclic iminium cation. A hydroxyl-directed reduction of this intermediate plays a key role in establishing the required cis-decahydroquinoline ring system, enabling the total synthesis of (-)-gephyrotoxin in 9 steps and 14% overall yield. The absolute configuration of our synthetic material was confirmed by single crystal X-ray diffraction and is consistent with the structure originally proposed for naturally isolated material.

Gephyrotoxin is an alkaloid isolated from the skin extracts of the Columbian poison dart frog *Dendrobates histrionicus*, and possesses an interesting perhydropyrroloquinoline core and five stereocentres.<sup>[1]</sup> Unlike many other dendrobatid alkaloids, gephyrotoxin is relatively non-toxic<sup>[2]</sup> but does exhibit complex effects on transmission at the neuromuscular junction<sup>[3,4]</sup> and weak antimuscarinic actions, despite not interacting with the acetylcholine binding site.<sup>[5,6]</sup> The low natural abundance and unique neurological profile of gephyrotoxin has led to significant synthetic interest in these alkaloids, culminating in four elegant and inventive total syntheses from the laboratories of Kishi,<sup>[7]</sup> Hart,<sup>[8]</sup> Overman,<sup>[9]</sup> and Sato and Chida,<sup>[10]</sup> and numerous formal syntheses that intersect with an intermediate from Kishi's approach.<sup>[11]</sup> We rationalized that the tricyclic core of gephyrotoxin could be constructed from a *cis*-disubstituted pyrrolidine fragment bearing an alcohol side chain (scheme 1). Elaboration of this fragment to incorporate a ketone (at C-10) and an enone (at C-14) could, upon liberation of a nucleophilic pyrrolidine amine, permit a cascade cyclization that could generate the entire tricyclic framework in a single operation.<sup>[12]</sup> In this scenario, the C-2 alcohol plays a key stereodirecting role for reduction of a C-10 iminium cation to afford the *cis*-decahydroquinoline. Strategically, cascade reactions are

Strategy for the construction of the gephyrotoxin core



Scheme 1. Strategy for the synthesis of (-)-gephyrotoxin.

attractive as they offer the potential for the rapid generation of molecular complexity, which can shorten routes to natural product-like materials.<sup>[13]</sup> However, this must be balanced with the need for chemo- and stereoselectivity, and redox economy in order to not compromise overall efficiency.<sup>[14]</sup>

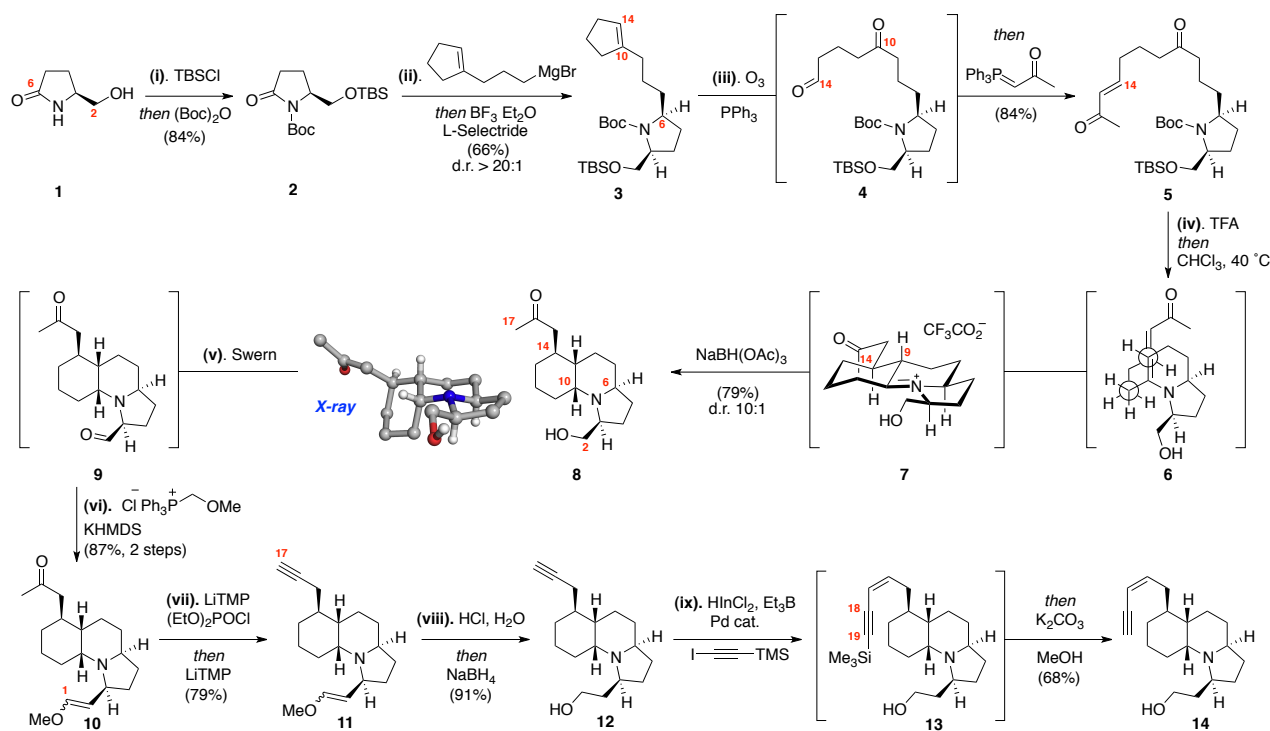
The route begins with *N*- and *O*-protection of L-pyroglutaminol **1**, which could be performed in a one-pot sequence in 84% overall yield to afford **2** (scheme 2).<sup>[15]</sup> The integrity of the C-3 stereocentre in **2** was established by chiral stationary phase HPLC (>99:1 e.r.), and optical rotation confirmed absolute configuration.<sup>[16]</sup> Treatment of **2** with a cyclopentene-containing Grignard reagent, conceived as a masked C-10/C-14 dicarbonyl unit, afforded an inconsequential mixture of C-6 diastereoisomers, which was reduced *in situ* with L-selectride in the presence of BF<sub>3</sub>·OEt<sub>2</sub>.<sup>[17]</sup> The 3,6-*cis*-pyrrolidine **3** was generated exclusively, presumably *via* hydride delivery to the least hindered face of the *in situ* generated *N*-acyliminium cation. The C-10/C-14 dicarbonyl unit was unmasked with ozone, and the resultant terminal aldehyde **4** homologated *in situ* to a *trans*-configured  $\alpha,\beta$ -unsaturated ketone **5** using 1-(triphenylphosphoranylidene)-2-propanone. This afforded the key cascade precursor for the generation of the gephyrotoxin core. Removal of the *tert*-butoxycarbonyl group was cleanly achieved with TFA in DCM at room temperature; this also led to hydrolysis of the primary *tert*-butyldimethylsilyl ether. The excess TFA was removed and subsequent warming of a chloroform solution to 40°C for 72h led to the formation of a tricyclic iminium cation **7**, exclusively with the required C-9 and C-14 configuration. This transformation likely proceeds *via* intramolecular condensation of the pyrrolidine amine onto the C-10 ketone to afford a bicyclic enamine **6** that undergoes a diastereoselective intramolecular Michael addition onto the C-14 enone.<sup>[18]</sup> The stereochemistry of this transformation can be rationalized through a chair-like transition state in which the Michael acceptor adopts a pseudoequatorial orientation to minimize diaxial interactions, with facial discrimination of the bicyclic enamine a consequence of the hydroxymethyl substituent and its effect on the conformation of the

[\*] Shuyu Chu, Dr Stephen Wallace,  
Prof. Dr Martin D. Smith  
Chemistry Research Laboratory  
University of Oxford  
12 Mansfield Road, Oxford, OX1 3TA (UK)  
E-mail: martin.smith@chem.ox.ac.uk  
Homepage: <http://msmith.chem.ox.ac.uk>

[\*\*] The European Research Council has provided financial support (FP7/2007-2013) / ERC grant agreement no. 259056. We gratefully acknowledge the Diamond Light Source for an award of instrument time on I19 (MT9981) and thank John Jolliffe for help with X-ray crystallography. We are extremely grateful to Professor Yoshito Kishi (Harvard University) for helpful discussions and exchange of information.



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.2011xxxxxx>.

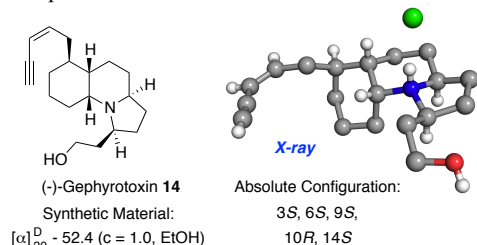


**Scheme 2.** Total synthesis of gephyrotoxin: (i). TBSCl, (1.15 eq.), KHMDS (1.2 eq.), MeCN, RT; then  $\text{Boc}_2\text{O}$  (3.0 eq.), DMAP (0.05 eq.), RT. (ii). Grignard (2.0 eq.), THF,  $-78^\circ\text{C}$ ;  $\text{BF}_3\cdot\text{Et}_2\text{O}$  (6.0 eq.), L-Selectride (2.0 eq.),  $-78^\circ\text{C}$  to RT. (iii).  $\text{O}_3$ , DCM,  $-78^\circ\text{C}$ ; then  $\text{PPh}_3$  (1.05 eq.),  $-78^\circ\text{C}$  to RT; then  $\text{Ph}_3\text{PCH}_2\text{COCH}_3$  (1.1 eq.), RT. (iv). TFA/DCM (1:3, v/v),  $0^\circ\text{C}$  to RT; then  $\text{CHCl}_3$ ,  $40^\circ\text{C}$ , 72h; then  $\text{NaBH}(\text{OAc})_3$  (1.5 eq.), DCM, RT. (v). oxalyl chloride (1.1 eq.), DMSO (2.5 eq.),  $\text{Et}_3\text{N}$  (5.0 eq.), DCM,  $-78^\circ\text{C}$  to RT. (vi).  $\text{Cl}^-\text{Ph}_3\text{P}^+\text{CH}_2\text{OMe}$  (1.2 eq.), KHMDS (1.15 eq.), THF,  $-78^\circ\text{C}$  to RT. (vii). LiTMP (1.05 eq.),  $(\text{EtO})_2\text{POCHl}$  (1.1 eq.), THF,  $-78^\circ\text{C}$  to RT; then LiTMP (2.25 eq.), THF,  $-78^\circ\text{C}$  to RT. (viii). HCl (20 eq.), THF/ $\text{H}_2\text{O}$ ,  $25^\circ\text{C}$ ; then  $\text{NaBH}_4$  (2.0 eq.), MeOH. (ix).  $\text{HInCl}_2$  (1.5 eq.),  $\text{Et}_3\text{B}$  (1.0 eq.), AcOH (1.0 eq.), THF,  $-78^\circ\text{C}$ ; then TMS-iodoacetylene (1.5 eq.),  $\text{Pd}(\text{dba})_3\cdot\text{CHCl}_3$  (0.005 eq.), tri(2-furyl)phosphine (0.045 eq.), DMF/THF, reflux; then  $\text{K}_2\text{CO}_3$  (50 eq.), MeOH, RT.

pyrrolidine ring. This tricyclic iminium species was sufficiently stable to be isolable (as its trifluoroacetate salt, d.r. >20:1) but in practice was reduced *in situ*. Reduction with non-chelating hydride sources such as sodium cyanoborohydride was efficient and diastereoselective but unfortunately produced the 9,10-*trans*- ring junction by virtue of the stereoelectronically preferred axial delivery mode.<sup>[19]</sup> Consequently, we explored intramolecular delivery of hydride via the tethered hydroxymethyl group at C-2 using sodium triacetoxyborohydride;<sup>[20]</sup> a related approach has been elegantly applied by Ciufolini in the synthesis of Cylindricine C.<sup>[21]</sup> This afforded the tricyclic gephyrotoxin core **8** with the requisite 9,10-*cis*- stereochemistry with good diastereoselectivity (10:1, *cis:trans*, separable by chromatography) and in 79% overall yield from **5**. The stereochemical outcome of this cascade was probed by single crystal X-ray diffraction, which confirmed that all five stereocentres for the natural product had been installed correctly.<sup>[22]</sup> Conversion of this intermediate to the natural product required installation of the enyne sidechain from the C-16 ketone and a one-carbon homologation of the C-2 alcohol. This was achieved by oxidation of the C-2 alcohol to an aldehyde under Swern conditions to afford **9**;<sup>[23]</sup> in our hands this method was superior to Dess-Martin periodinane<sup>[24]</sup> and TPAP.<sup>[25]</sup> The aldehyde could be purified, but in practice was used crude in subsequent transformations after work-up. Treatment of aldehyde **9** with (methoxymethyl)triphenylphosphonium chloride and KHMDS in THF afforded vinyl ether **10** as an inconsequential 1:1 mixture of geometrical isomers. The ketone functional group in **10** was transformed into an intermediate enol phosphate through kinetic deprotonation with lithium tetramethyl piperidine in THF and trapping with diethylphosphoryl chloride; subsequent addition

of excess lithium tetramethylpiperidine led to elimination to afford terminal alkyne **11**, consistent with the method described by Negishi.<sup>[26]</sup> Hydrolysis of the methyl enol ether was achieved by stirring in aqueous HCl, affording a C-1 aldehyde which, after removal of aqueous THF and addition of methanol, was reduced with sodium borohydride to afford C-1 alcohol **12**. The final carbon-carbon bond in the synthesis was formed through a hydrometalation/cross-coupling strategy. *Trans*-hydrometalation of **12** by *in situ* generated dichloroindium hydride in the presence of triethylborane generated a vinyl indium species; this was cross-coupled with trimethylsilyl-protected iodoacetylene in the presence of pre-mixed tris(dibenzylideneacetone)dipalladium(0) and tri(2-furyl)phosphine to afford **13**.<sup>[27]</sup> Work-up with potassium carbonate and methanol effected terminal desilylation to afford (-)-gephyrotoxin in 68% yield from **12**. Synthetic gephyrotoxin **14** exhibited identical  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopic data to that published for authentic naturally obtained material.<sup>[28]</sup> Based on the enantiopure L-pyrroglutaminol starting material, we were confident that the absolute configuration of our synthetic gephyrotoxin was as depicted by structure **14**.<sup>[29,30]</sup> To further investigate this, we crystallized the hydrochloride salt of our synthetic **14**, which confirmed its relative and absolute configuration (Figure 1). Measurement of the optical rotation of synthetic **14** gave  $[\alpha]_{20}^D = -52.3$  ( $c = 1.0$ , EtOH).<sup>[31]</sup> This is consistent with the value reported for material isolated from natural sources ( $[\alpha]_{20}^D = -51.5$  ( $c = 1.0$ , EtOH)) in which absolute configuration was assigned through X-ray analysis of a single crystal of gephyrotoxin hydrobromide. However, this value is opposite in sign to that reported by Kishi for synthetic material of the same proposed absolute configuration

( $[\alpha]_{20}^D = +50.0$  ( $c = 1.0$ , EtOH)).<sup>[32]</sup> On this basis, it was suggested that the absolute configuration of the natural product should be revised.<sup>[7b,33,34]</sup> Unfortunately, a sample of natural gephyrotoxin is not available for direct comparison with our synthetic material and hence we cannot unequivocally confirm the absolute configuration of the natural product.



**Figure 1.** Confirmation of absolute configuration: X-ray structure of HCl salt of synthetic material **14** (some hydrogen atoms omitted for clarity).

A synthesis of (-)-gephyrotoxin **14** has been achieved in 9 steps and 14% overall yield from L-pyroglutaminol **1**. Key features of the synthesis are the diastereoselective intramolecular enamine-Michael cascade (which generates two rings and two stereocentres in a single operation) and the hydroxyl-directed reduction to install the correct configuration at C-10. From a strategic perspective, the requirement for a one-carbon homologation of the primary alcohol (from **8**) is both redox and step inefficient, and represents a limitation in current methods.<sup>[35,36]</sup> However, this requirement does permit reagent directed *cis*- or *trans*-selective reduction of iminium species **7** to allow the synthesis of analogues. Consequently, this approach compares well with other syntheses of gephyrotoxin, offers rapid and stereoselective access to this class of natural products and may provide a more general approach to decahydroquinoline-containing alkaloids.

Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

**Keywords:** gephyrotoxin • cascade • total synthesis • asymmetric • alkaloid

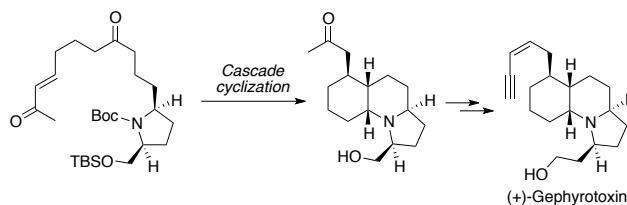
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## Total Synthesis

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