Total Synthesis Hot Paper

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

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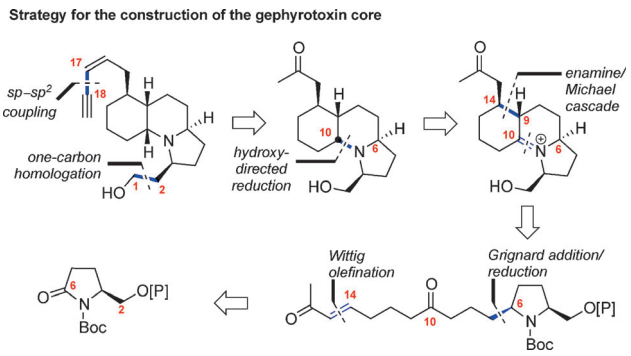
Abstract: *A concise and efficient synthesis of (−)-gephyrotoxin from* L*-pyroglutaminol has been realized. The key step in this approach is a diastereoselective intramolecular enamine/Michael cascade reaction that forms two rings and two stereocenters and generates a stable tricyclic iminium cation.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

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 stereocenters.[1] Unlike many other dendrobatid alkaloids, gephyroxin is relatively non-toxic,[2] but does exhibit complex effects on transmission at the neuromuscular junction[3,4] and weak antimuscarinic properties, despite not interacting with the acetylcholine binding site.[5,6] The low natural abundance and unique neurological profile of gephyrotoxin have led to significant synthetic interest in these alkaloids, culminating in four elegant and inventive total syntheses from the laboratories of Kishi,[7] Hart,[8] Overman,[9] and Sato and Chida[10] and numerous formal syntheses that intersect with an intermediate from Kishi's approach.[11] 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 C10) and an enone (at C14) could, upon liberation of a nucleophilic pyrrolidine amine, permit a cascade cyclization that could generate the entire tricyclic framework in a single operation.[12] In this scenario, the C2 alcohol plays a key stereodirecting role for reduction of the C10 iminium cation to afford the *cis*-decahydroquinoline. Strategically, cascade reactions are attractive as they offer the potential for the rapid generation of molecular complexity, which can shorten routes to natural-product-like materials.[13] However, this must be balanced with the need for chemo- and stereoselectivity and redox economy in order to not compromise overall efficiency.[14]



Scheme 1. Strategy for the synthesis of (−)-gephyrotoxin. Boc = *tert*-butyloxycarbonyl.

The route begins with protection of the nitrogen and oxygen of L-pyroglutaminol (**1**), which could be performed in a one-pot sequence in 84% overall yield to afford **2** (Scheme 2).[15] The integrity of the C3 stereocenter in **2** was established by HPLC analysis on a chiral stationary phase (>99:1 e.r.), and optical rotation confirmed the absolute configuration.[16] Treatment of **2** with a cyclopentene-containing Grignard reagent, conceived as a masked C10/C14 dicarbonyl unit, afforded an inconsequential mixture of C6 diastereoisomers, which was reduced in situ with L-selectride in the presence of $BF_3{\cdot}OEt_2$.[17] The 3,6-*cis*-pyrrolidine **3** was generated exclusively, presumably by hydride delivery to the least hindered face of the *N*-acyliminium cation generated in situ. The C10/C14 dicarbonyl unit was unmasked with ozone and the resultant terminal aldehyde **4** homologated in situ to *trans*-configured α,β-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 CH_2Cl_2 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 72 hours led to the formation of tricyclic iminium cation **7**, exclusively with the required C9 and C14 configuration. This transformation likely proceeds by intramolecular condensation of the pyrrolidine amine onto the C10 ketone to afford a bicyclic enamine **6**, which undergoes a diastereoselective intramolecular Michael addition onto the C14 enone.[18] The stereochemical outcome of this transformation can be rationalized by considering a chair-like transition state in which the Michael acceptor adopts a pseudoequatorial orientation to minimize

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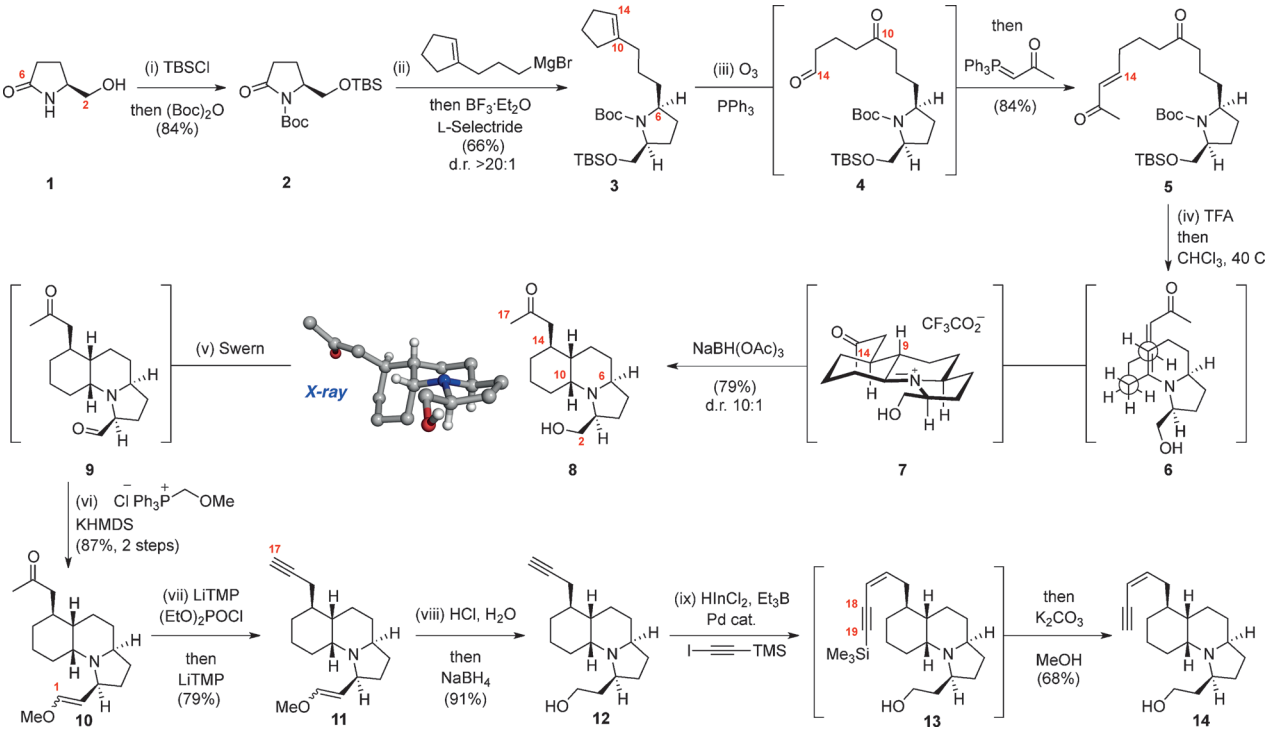

Scheme 2. Total synthesis of gephyrotoxin. (i) TBSCl (1.15 equiv), KHMDS (1.2 equiv), MeCN, RT; then Boc_2O (3.0 equiv), DMAP (0.05 equiv), RT. (ii) Grignard reagent (2.0 equiv), THF, −78 °C; $BF_3{\cdot}Et_2O$ (6.0 equiv), L-Selectride (2.0 equiv), −78 °C to RT. (iii) O_3, CH_2Cl_2, −78 °C; then PPh_3 (1.05 equiv), −78 °C to RT; then $Ph_3PCH_2COCH_3$ (1.1 equiv), RT. (iv) TFA/CH_2Cl_2 (1:3, v/v), 0 °C to RT; then $CHCl_3$, 40 °C, 72 h; then $NaBH(OAc)_3$ (1.5 equiv), CH_2Cl_2, RT. (v) oxalyl chloride (1.1 equiv), DMSO (2.5 equiv), Et_3N (5.0 equiv), CH_2Cl_2, −78 °C to RT. (vi) $Cl^-Ph_3P^+CH_2OMe$ (1.2 equiv), KHMDS (1.15 equiv), THF, −78 °C to RT. (vii) LiTMP (1.05 equiv), $(EtO)_2POCl$ (1.1 equiv), THF, −78 °C to RT; then LiTMP (2.25 equiv), THF, −78 °C to RT. (viii) HCl (20 equiv), THF/H_2O, 25 °C; then $NaBH_4$ (2.0 equiv), MeOH. (ix) $HInCl_2$ (1.5 equiv), Et_3B (1.0 equiv), AcOH (1.0 equiv), THF, −78 °C; then 1-iodo-2-(trimethylsilyl)acetylene (1.5 equiv), $[Pd_2(dba)_3{\cdot}CHCl_3]$ (0.005 equiv), tri(2-furyl)phosphine (0.045 equiv), DMF/THF, reflux; then K_2CO_3 (50 equiv), MeOH, RT. dba = dibenzylideneacetone, DMAP = 4-(dimethylamino)pyridine, KHMDS = potassium hexamethyldisilazane, TBS = *tert*-butyldimethylsilyl, TFA = trifluoroacetic acid, TMP = 2,2,6,6-tetramethylpiperidine.

diaxial interactions, with the facial discrimination of the bicyclic enamine being a consequence of the hydroxymethyl substituent and its effect on the conformation of the pyrrolidine ring. This tricyclic iminium species was sufficiently stable to be isolable (as its trifluoroacetate salt, d.r. > 20:1), but in practice, it 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*-configured ring junction by virtue of the stereoelectronically preferred axial delivery mode.[19] Consequently, we explored intramolecular delivery of hydride by the tethered hydroxymethyl group at the C2 position using sodium triacetoxyborohydride;[20] a related approach has been elegantly applied by Ciufolini et al. in the synthesis of cylindricine C.[21] 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 reaction was probed by single-crystal X-ray diffraction, which confirmed that all five stereocenters of the natural product had been installed correctly.[22] Conversion of this intermediate into the natural product required installation of the enyne side chain at the C16 ketone and a one-carbon homologation of the C2 alcohol. This was achieved by oxidation of the C2 alcohol to an aldehyde under Swern conditions to afford **9**;[23] in our hands, this method was superior to the use of Dess–Martin periodinane[24] or tetrapropylammonium perruthenate (TPAP).[25] 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 tetramethylpiperidine 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 and co-workers.[26] Hydrolysis of the methyl enol ether was achieved by stirring in aqueous HCl, affording a C1 aldehyde, which, after removal of aqueous THF and addition of methanol, was reduced with sodium borohydride to afford C1 alcohol **12**. The final carbon–carbon bond in the synthesis was formed through a hydrometalation/cross-coupling strategy. An in situ generated dichloroindium hydride species was used for the *trans*-hydrometalation of **12** in the presence of triethylborane to generate a vinyl indium species; this

intermediate was cross-coupled with trimethylsilyl-protected iodoacetylene in the presence of pre-mixed [$Pd_2(dba)_3$] and tri(2-furyl)phosphine to afford **13**.[27] Work-up with potassium carbonate and methanol effected terminal desilylation to afford (−)-gephyrotoxin in 68% yield from **12**. The ^1H and ^{13}C NMR spectra of synthetic gephyrotoxin **14** are identical to those published for authentic material obtained from the natural source.[28] Based on the enantiopure L-pyroglutaminol starting material, we were confident that the absolute configuration of our synthetic gephyrotoxin was as depicted by structure **14**.[29,30] To further investigate this, we crystallized the hydrochloride salt of our synthetic material **14**, which confirmed its relative and absolute configuration (Figure 1).

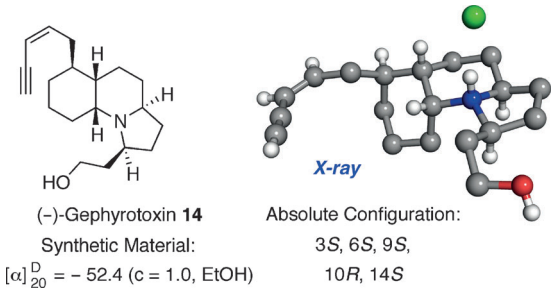

Figure 1. Confirmation of the absolute configuration: X-ray structure of the hydrochloride salt of synthetic material **14**; some hydrogen atoms are omitted for clarity.

Measurement of the optical rotation of synthetic **14** gave $[\alpha]_{20}^{D} = -52.3$ ($c = 1.0$, EtOH).[31] This value is consistent with that reported for material isolated from natural sources ($[\alpha]_{20}^{D} = -51.5$ ($c = 1.0$, EtOH)) in which the 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 and co-workers for synthetic material of the same proposed absolute configuration ($[\alpha]_{20}^{D} = +50.0$ ($c = 1.0$, EtOH)).[32] On this basis, it was suggested that the absolute configuration of the natural product should be revised.[7b,33,34] Unfortunately, a sample of natural gephyrotoxin was not available for direct comparison with our synthetic material, and hence we could not unequivocally confirm the absolute configuration of the natural product.

A synthesis of (−)-gephyrotoxin **14** has been achieved in nine steps and 14% overall yield from L-pyroglutaminol (**1**). Key features of the synthesis are the diastereoselective intramolecular enamine/Michael cascade reaction, which generates two rings and two stereocenters in a single operation, and the hydroxy-directed reduction to obtain the correct configuration at the C10 position. 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 of the current methods.[35,36] However, this requirement does permit the 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.

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[29] We have derivatized our synthetic (−)-gephyrotoxin **14** by C1 *O*-acylation with both enantiomers of methoxy(trifluoromethyl)-phenylacetic acid. In both cases, a single diastereoisomer of the product was observed by ^{1}H and ^{19}F NMR spectroscopy. These diastereoisomeric esters are non-coincident by ^{1}H and ^{19}F NMR spectroscopy (see the Supporting Information for full details). This result is consistent with our synthetic (−)-gephyrotoxin **14** sample being produced as a single enantiomer.
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