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Practical Total Syntheses of Epiquinamide Enantiomers

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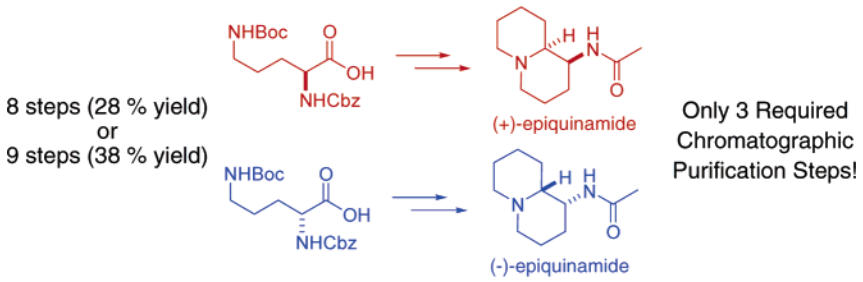
ABSTRACT



Short and practical syntheses of epiquinamide and its enantiomer were accomplished with high overall yields and high stereoselectivity from readily available starting materials.

Rainforest frogs have been a rich source of neurologically relevant alkaloids.[1−3] Epibatidine **1** was isolated from an Ecuadorian frog *Epipedobates tricolor* (Figure 1) in 1992

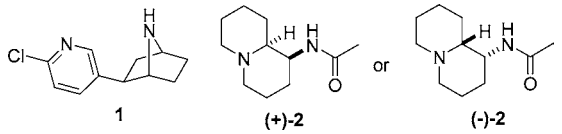


Figure 1. Neurologically relevant alkaloids from *Epipedobates.*

by Daly and co-workers and has become one of the cornerstone compounds in the field of nicotinic acetylcholine receptor (nAChR) studies.[3,4] Epiquinamide **2** was isolated along with **1** from the same frog species in 2003[1] and has attracted much attention due to its potent and selective agonistic activities against $\beta 2$ nicotinic receptors.[1,3] Its potential to be a lead compound in the development of pharmacological agents seems promising, following the history of epibatidine.[2,4] The varying abundance of nAChRs subtypes in different tissues should enable their selective therapeutic targeting.[5−7] However, the major limiting factor in testing this compound has been its low availability (240 μg from the skins of 183 frogs).[1] To date, two total syntheses of (+)-epiquinamide,[8,9] another synthesis of the antipode,[10] and a racemic synthesis[11] have been reported. However, these enantiospecific syntheses are relatively long (12,[8] 14,[9] and 13 steps,[10] respectively) and/or their starting materials are either highly expensive or not readily available. We therefore

(1) Fitch, R. W.; Garrafo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345−1350.
(2) Baker, D. D.; Alvi, K. A.*Curr. Opin. Biotechnol.* **2004**, *15*, 576−583.
(3) (a) Daly, J. W. *Cell. Mol. Neurobiol.* **2005**, *25*, 513−552. (b) Daly, J. W.; Spande, T. F.; Garrafo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556−1575.
(4) Spande, T. F.; Garrafo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478.
(5) Vincler, M. *Expert Opin. Invest. Drugs* **2005**, *14*, 1191−1198.
(6) Anthenelli, R. M. *Clin. Neurosci. Res.* **2005**, *5*, 175−183.
(7) Gotti, C.; Riganti, L.; Vailati, S.; Clementi, F. *Curr. Pharm. Design* **2006**, *12*, 407−428.
(8) Tong, S. K.; Barker, D. *Tetrahedron Lett.* **2006**, *47*, 5017−5020.
(9) Huang, P. Q.; Guo, Z. Q.; Ruan, Y. P. *Org. Lett.* **2006**, *8*, 1435−1438.
(10) Wijdeven, M. A.; Botman, P. N. M.; Wijtmans, R.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org. Lett.* **2005**, *7*, 4005−4007.
(11) Kanakubo, A.; Gray, D.; Innocent, N.; Wonnacott, S.; Gallagher, T. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4648−4651.

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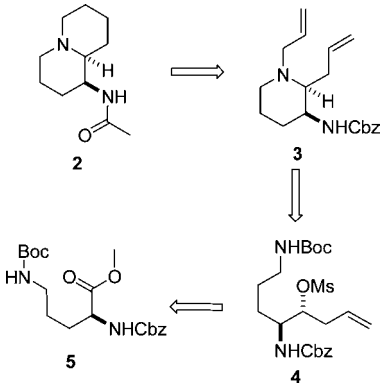
undertook the development of a practical and flexible synthesis that could provide substantial amounts of **2** (Scheme 1).

Scheme 1. Retrosynthesis of (+)-Epiquinamide

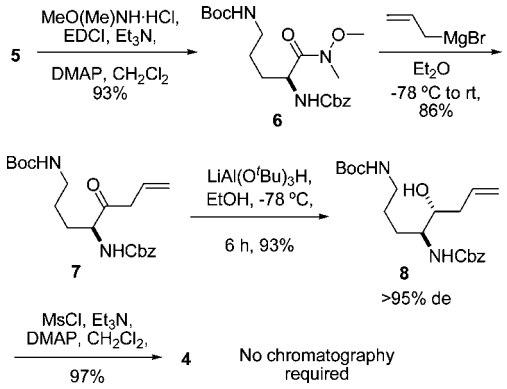


In the literature on epiquinamide, the optical rotation value of the natural product was never reported due to its low availability.[1] Access to both enantiomers is therefore of great importance. Herein described is the synthesis of epiquinamide and its enantiomer.

The quinolizidine ring could be derived from a piperidine with appropriate appendages that could be cyclized to give the second ring. Initially, we were interested in developing a reductive amination-type method for the construction of the first ring because there has been little effort to synthesize *cis*-2,3-disubstituted piperidines via such an approach.[12] This approach, however, was not fruitful in our hands; the reductive amination cyclization yielded *trans*-piperidine **10** in excellent de. The relative stereochemistry of this product was determined by X-ray crystallography after it was converted to the Cbz-protected quinolizidine (**11**).[13]

We then envisioned a dissection of the molecule in a manner similar to the first attempt but differing in the mode of the first cyclization. The intramolecular S_N2 cyclization would yield the 2,3-disubstituted piperidine **3** with the inverted stereochemistry. The substrate for the S_N2 reaction can be easily derived from a corresponding amino alcohol, such as **8**, which could be synthesized from ornithine. The synthesis of the intramolecular S_N2 substrate began with a commercially available ornithine derivative **5**, which was first converted smoothly to the Weinreb amide **6** using a common coupling condition (Scheme 2).[14] After simple washings, the

Scheme 2. Synthesis of Mesylate **4**



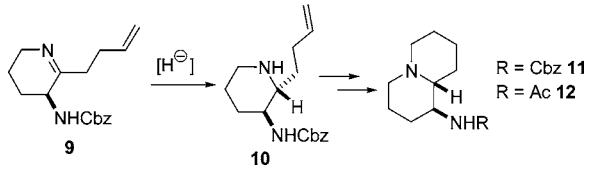
product was fairly pure and required no further purification. Upon treatment with an allyl Grignard reagent, we obtained the ketone **7** as white crystals. Chelation-controlled hydride reduction of **7** yielded a highly crystalline alcohol, **8**.[15] By ^1H and ^{13}C NMR, none of the other diastereomer was observed in the crystallized product, whose stereochemistry was ultimately proven by completion of the total synthesis and comparison to epi-epiquinamide (**12**).[16] Mesylation of the amino alcohol proceeded smoothly with an excellent yield, and again the product was crystalline. Therefore, the synthesis of the S_N2 substrate **4** was accomplished very conveniently and without chromatographic purification unless recovery of the residual amount of the product in the filtrate was desired.

Transformation of the mesylate **4** to the title compound was accomplished as shown in Scheme 3. Removal of the Boc group in TFA/CH_2Cl_2 followed by intramolecular S_N2 cyclization induced by K_2CO_3 and subsequent N-alkylation in acetonitrile yielded the diallyl piperidine **3** in good yield (**9** was not isolated or characterized).[17−19]

The synthesis of the epiquinamide skeleton was concluded by ring-closing metathesis (RCM) reaction on **3** using the Grubbs second-generation catalyst.[20] It is noteworthy that

(12) (a) Pal, K.; Behnke, M. L.; Tong, L. *Tetrahedron Lett.* **1993**, *34*, 6205−6208. (b) Singh, R.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 7711−7715. (c) Gómez-Monterrey, I.; González-Muñiz, R.; Herranz, R.; García-López, M. T. *Tetrahedron Lett.* **1993**, *34*, 3593−3594. (d) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911−2914.

(13) An initial attempt to asymmetrically synthesize the title compound was made.



(14) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815−3818. (b) Mentzel, M.; Hoffmann, H. M. R. *J. Prakt. Chem./ Chem.-Ztg.* **1997**, *339*, 517−524.

(15) (a) So, R. C.; Ndonye, R.; Izmirian, D. P.; Richardson, S. K.; Guerrera, R. L.; Howell, A. R. *J. Org. Chem.* **2004**, *69*, 3233−3235. (b) Haug, B. E.; Rich, D. H. *Org. Lett.* **2004**, *6*, 4783−4786.

(16) The bridgehead proton of **2** has a chemical shift of δ 3.91 ppm, and that of **12** has a shift of δ 3.95 ppm in MeOH-d_4. Otherwise, the two compounds have exactly the same carbon framework and molecular weight by NMR and LRMS.

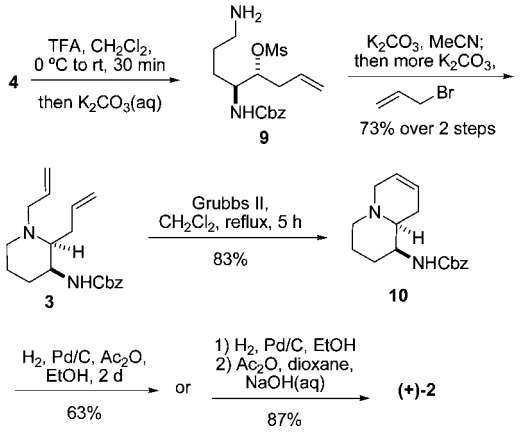
(17) (a) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473−1480. (b) Wang, Q.; Sasaki, N. A. *J. Org. Chem.* **2004**, *69*, 4767−4773.

(18) Cyclization was extremely slow in the absence of base.

(19) (a) Sundberg, R. J.; Amat, M.; Fernando, A. M. *J. Org. Chem.* **1987**, *52*, 3151−3159. (b) Kinderman, S. S.; Wekking, M. M. T.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 5519−5527.

(20) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527.

Scheme 3. Synthesis of (+)-Epiquinamide



this is one of the first examples of a basic *N*-allyl group undergoing ruthenium-catalyzed RCM.[21] The scope of functional group tolerance by the Grubbs second-generation catalyst may be even greater than the current concensus.[20b,22] However, the purification of this rather polar RCM product presented difficulties.[23] The problem was overcome when Cho and Kim's method was employed with a small modification.[24] Deprotection, alkene reduction, and acetylation were accomplished in one pot by hydrogenation of **10** in ethanol with acetic anhydride.[25] A better yield was observed when this process was separated into two steps as shown in Scheme 3.[10] By ^{1}H and ^{13}C NMR, a single isomer was observed. The reproducible overall yields of **2** beginning from **5** were 38% and 28% for the longer and shorter sequences, respectively (**(+)-2** $[\alpha]^{22}_D = +24°$ (*c* 0.10, $CHCl_3$)).[26] Only three chromatographic purification steps were required throughout the synthesis.

The synthesis of the other enantiomer was performed in the same manner starting with commercially available δ*N*-Boc-α*N*-Cbz-D-ornithine. This latter synthesis was accomplished in two weeks, demonstrating the practicality of this synthetic route (**(−)-2** $[\alpha]^{22}_D = -22°$ (*c* 0.13, $CHCl_3$)).[27]

Because neither the optical rotation value nor the circular dichroism spectrum of the authentic natural product was reported, the absolute stereochemistry of the natural product could not be determined despite our access to both enantiomers. We then sought to learn the biological properties of the two isomers. However, contrary to our expectation, neither of the enantiomers showed activity in our routine Na^+ channel blocking/activation assays, H460 cancer cytotoxicity assay, or brine shrimp toxicity assay. Our results are consistent with a recent report for synthetic (±)-epiquinamide which was inactive in competitive binding assays using [^{3}H]epibatidine and thus makes further uncertain the identity of the pharmacologically active material from the frogs.[11]

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all intermediates leading to (+)-epiquinamide. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) To our knowledge, one such example was accomplished recently with a water-soluble ruthenium catalyst. See: Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508−3509.

(22) Vernall, A. J.; Abell, A. D. *Aldrichimica Acta* **2003**, *36*, 93−105.

(23) Published methods for the removal of the ruthenium catalyst are better suited for nonpolar compounds. For examples, see: (a) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137−4140. (b) Haack, K. L.; Ahn, Y. M.; Georg, G. I. *Mol. Diversity* **2005**, *9*, 301−303.

(24) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531−533.

(25) Shinada, T.; Hayashi, K.; Yoshida, Y.; Ohfune, Y. *Synlett* **2000**, *10*, 1506−1508.

(26) The literature value of **(+)-2** was $[\alpha]^{20}_D = +28°$ (*c* 0.23, $CHCl_3$) (see ref 10) and $[\alpha]^{22}_D = +26.2°$ (*c* 0.23, $CHCl_3$) (see ref 8).

(27) The literature value of **(−)-2** was $[\alpha]^{20}_D = -25°$ (*c* 0.26, $CHCl_3$) (see ref 9).