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Asymmetric Synthesis of (–)-1-Hydroxyquinolizidinone, a Common Intermediate for the Syntheses of (–)-Homopumiliotoxin 223G and (–)-Epiquinamide

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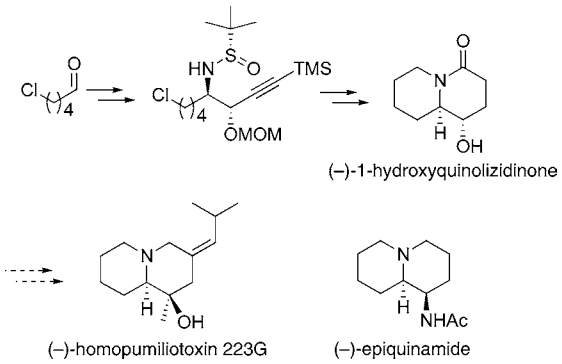
ABSTRACT



The short and efficient asymmetric synthesis of (–)-1-hydroxyquinolizidinone was achieved in seven steps and 25.2% overall yield from readily available 5-chloropentanal. It is a key intermediate in the formal syntheses of (–)-homopumilotoxin 223G and (–)-epiquinamide.

To date, more than 800 diverse alkaloids, representing over 20 structural classes, have been detected in amphibian skin.[1] Among them, pumiliotoxins **1a** and allopumiliotoxins **1b** (Figure 1), characterized by an indolizidine ring system, were discovered as some of the major active alkaloids from one population of a small neotropical Panamanian dendrobatid frog, the brightly colored (red or orange) *Dendrobates pumilio*.[1,2] Homopumiliotoxins **2**, in which the indolizidine moiety has been replaced with a quinolizidine ring, comprised other bicyclic alkaloids isolated, albeit in a much rarer occurrence, from *Dendrobates pumilio*,[1,3] but also from the Madagascan genus of mantelline frogs, *Mantella*,[4] and the New World genus of bufonid toads, *Melanophryniscus*.[5] It has been recently shown that pumiliotoxins, allo- and homopumiliotoxins are taken into the skin from the diet of frogs consisting mainly of small arthropods. The poison alkaloids are then stored in skin glands and presumably serve as a passive defense against predators and/or microorganisms by exhibiting myotonic and cardiotonic activity.[1,6]

(1) Daly, J. W.; Spande, T. S.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556−1575.
(2) Edwards, M. W.; Daly, J. W. *J. Nat. Prod.* **1988**, *51*, 1188−1197.
(3) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1987**, *43*, 643−652.
(4) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **1993**, *56*, 1016−1038.
(5) Garraffo, H. M.; Spande, T. F.; Daly, J. W. *J. Nat. Prod.* **1993**, *56*, 357−373.

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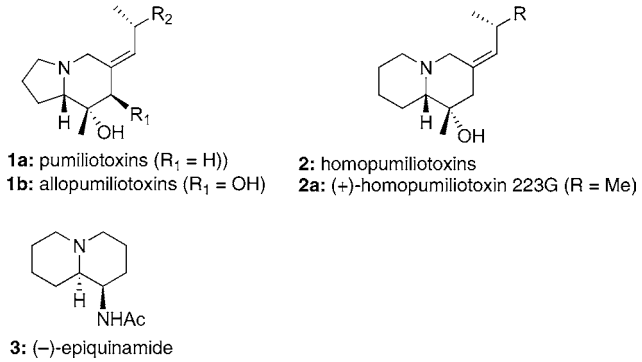


Figure 1. Structures of some frog poisonous alkaloids.

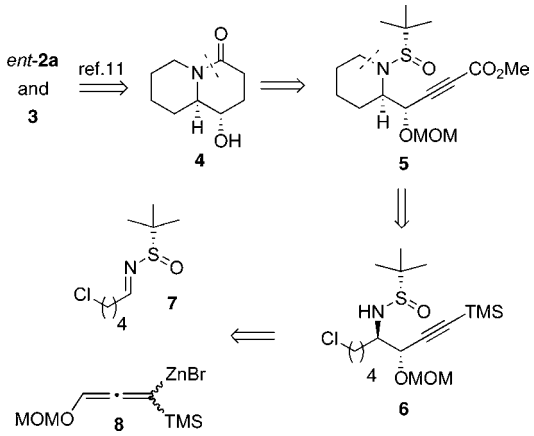
Epiquinamide **(3)** is another unprecedented quinolizidine alkaloid which was identified in 2003 from the methanolic skin extracts of an Ecuadoran frog, *Epipedobates tricolor*.[1,7] It was isolated in submilligram amounts from 187 frogs giving 6 mg of total alkaloids among which equinamide represents 240 μg, i.e., only 0.002% based on wet skin weight of frogs. Epiquinamide represents a new structural class of nicotinic agonist selective for nicotinic receptor containing the β2-subunit.[8] It might be regarded as a potential lead compound for the development of new therapeutics for neuronal receptors. However, due to its scarcity from natural sources, further investigations of the biological activity of epiquinamide are hampered. Moreover, the absolute stereochemistry of epiquinamide has not been assigned yet since neither the optical rotation nor the circular dichroism spectrum of the authentic natural product has been reported. For all these reasons, the synthesis of epiquinamide is still challenging.

The structural diversity and remarkable bioactivities of these alkaloids have meant that methods for their stereoselective preparation have been investigated. Thus, pumiliotoxins have been the subject of numerous publications. On the other hand, very few syntheses of homopumiliotoxins and more particularly of (+)- or (−)-homopumiliotoxin 223G **(2a)** are reported. Indeed, to the best of our knowledge, only two total asymmetric syntheses of (+)-homopumiliotoxin 223G **(2a)** have been disclosed.[9,10] Its antipode *ent*-**2a** has also been the subject of one formal asymmetric synthesis.[11]

Regarding epiquinamide, to date, three total syntheses of the (+)-isomer[12,13] and two other of the (−)-isomer[11,12] have been reported.

In a recent paper, Huang and co-workers[11] have shown that (−)-1-hydroxyquinolizidinone **(4)** could serve as a common intermediate for the syntheses of both (−)-homopumiliotoxin 223G **(***ent*-**2a)** and (−)-epiquinamide **(3)** (Scheme 1).

Scheme 1. Retrosynthetic Analysis



As for us, we have envisioned the preparation of (−)-1-hydroxyquinolizidinone (**4**) from piperidine **5** through the intramolecular condensation of the deprotected nitrogen onto the ester moiety followed by the deprotection of the methoxymethyl ether. Intermediate **5** could be readily available from 1,2-sulfinamidoalkyl ether **6** by the intramolecular displacement of the chlorine atom and the homologation of the C−C triple bond. Furthermore, we reasoned that **6** could be obtained using a methodology developed in our group over the past 10 years,[14] i.e. by the reaction of enantiopure (S_S)-sulfinimine **7** with racemic 3-(methoxymethoxy)allenylzinc **8**. This methodology has been previously successfully applied to the elaboration of acetylenic 1,2-aminoalcohol units[14a−c] and, recently, to the asymmetric synthesis of (−)-α-conhydrine {(*R*)-[(1*S*)-hydroxypropan-1-yl)]-2-piperidine}.[15]

With these considerations in mind, our synthesis started with the preparation of (S_S)-sulfinimine **7** in 73% yield from

(6) Saporito, R. A.; Garraffo, H. M.; Donnelly, M. A.; Edwards, A. L.; Longino, J. T.; Daly, J. W. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 8045−8050.

(7) Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345−1350.

(8) Daly, J. W. *Cell. Mol. Neurobiol*. **2005**, *25*, 513−552.

(9) (a) Kibayashi, C.; Aoyagi, S.; Wang, T.-C.; Saito, K.; Daly, J. W.; Spande, T. F. *J. Nat. Prod.* **2000**, *63*, 1157−1159. (b) Aoyagi, S.; Hirashima, S.; Kibayashi, C. *Tetrahedron Lett.* **1998**, *39*, 2149−2152.

(10) (a) For a total synthesis of racemic homopumiliotoxin 223G, see: Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6999−7001. (b) For a formal synthesis of racemic homopumiliotoxin 223G, see: Chen, B.-F.; Tasi, M.-R.; Yang, C.-Y.; Chang, J.-K.; Chang, N.-C. *Tetrahedron* **2004**, *60*, 10223−10231.

(11) Huang, P.-Q.; Guo, Z.-Q.; Ruan, Y.-P. *Org. Lett*. **2006**, *8*, 1435−1438.

(12) (a) Suyama, T. L.; Gerwick, W. H. *Org. Lett*. **2006**, *8*, 4541−4543. (b) Teng, S. T. A.; Barker, D. *Tetrahedron Lett.* **2006**, *47*, 5017−5020. (c) 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.

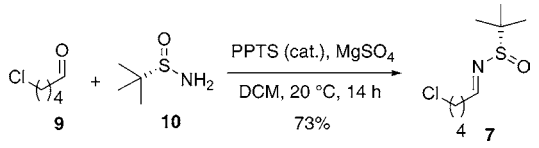
(13) For total syntheses of racemic epiquinamide, see: Kanakubo, A.; Gray, D.; Innocent, N.; Wonnacott, S.; Gallagher, T. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 4648−4651.

(14) (a) Botuha, C.; Chemla, F.; Ferreira, F.; Perez Luna, A.; Roy, B. *New J. Chem*. **2007**, *31*, 1552−1567. (b) Chemla, F.; Ferreira, F.; Gaucher, X.; Palais, L. *Synthesis* **2007**, 1235−1241. (c) Chemla, F.; Ferreira, F. *Synlett* **2006**, 2613−2616. (d) Palais, L.; Chemla, F.; Ferreira, F. *Synlett* **2006**, 1039−1042. (e) Ferreira, F.; Audouin, M.; Chemla, F. *Chem. Eur. J*. **2005**, *11*, 5269−5278. (f) Chemla, F.; Ferreira, F. *J. Org. Chem.* **2004**, *69*, 8244−8250. (g) Ferreira, F.; Denichoux, A.; Chemla, F.; Bejjani, J. *Synlett* **2004**, 2051−2065. (h) Chemla, F.; Ferreira, F. *Synlett* **2004**, 983−986.

(15) Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem*. **2007**, *72*, 5358−5361.

5-chloropentanal (**9**) and (S_S)-*N*-*tert*-butanesulfinamide (**10**) (Scheme 2). The latter is either commercially available, or

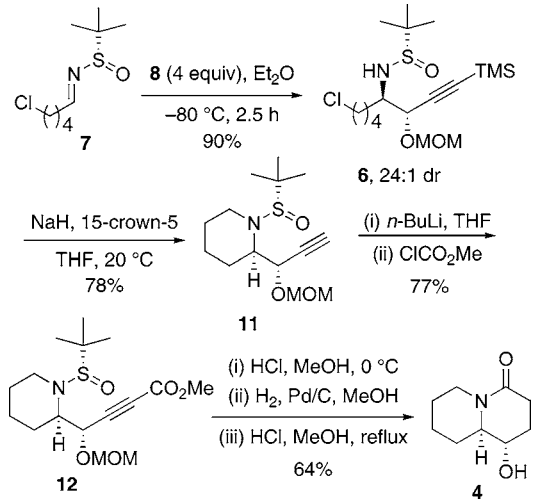
Scheme 2. Synthesis of (S_S)-Sulfinimine **7**



easily prepared by a two-step procedure in 58% yield from commercial and cheap di-*tert*-butyldisulfide.[16]

Reaction of enantiopure (S_S)-sulfinimine **7** at −80 °C with racemic allenylzinc **8**[17] (4 equiv), derived from (3-(methoxymethoxy)prop-1-ynyl)trimethylsilane,[18] gave after acidic workup the desired acetylenic 1,2-sulfinamidoalkyl ether **6** (Scheme 3). As seen by ^{1}H NMR analysis of the crude

Scheme 3. Access to (−)-1-Hydroxyquinolizidinone **(4)**



product, a high stereoselectivity was obtained since only two isomers were observed with a dr of 24:1. The relative and absolute stereochemistry of the major isomer was assigned according to our previous results. It was assumed to result from a highly efficient dynamic kinetic resolution of racemic **8** via a monocoordinated transition state (Figure 2).[14a−c] Silica gel chromatography afforded a mixture of the two inseparable major and minor isomers in 90% yield.

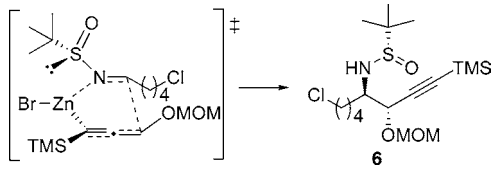


Figure 2. Origin of the stereochemistry of **6**.

Treatment of **6** with NaH (4 equiv) in THF in the presence of 15-crown-5 (3 equiv) at 20 °C gave rise to cyclization by the intramolecular displacement of the chlorine atom.[19] Under these conditions, the desilylation of the acetylenic position also occurred, furnishing piperidine **11** as a single isomer with 78% yield after purification, the minor isomer being separated. Further functionnalization of the acetylenic carbon by lithiation and treatment with methyl chloroformate (3 equiv) led to intermediate **12** in 77% isolated yield. Treatment of **12** with methanolic HCl at 0 °C resulted in the removal of the *tert*-butanesulfinyl auxiliary on the nitrogen. Hydrogenation (1 atm) in the presence of Pd/C (10% weight) and subsequent cyclization led to a bicyclic compound which was then treated with refluxed methanolic HCl to give (−)-1-hydroxyquinolizidinone **(4)** with 64% overall yield from intermediate **12**.

One asymmetric synthesis of **4**[11] and two of one of its diastereomers[20] have been disclosed in the literature. **4** obtained following our methodology exhibited IR, ^{1}H, and ^{13}C NMR data identical to those reported.[11] Moreover, the optical rotation obtained for **4** {$[\alpha]^{28}_D = -8.1$ (*c* 0.72, $CHCl_3$)} was in agreement with that given in the literature {$[\alpha]^{20}_D = -8.5$ (*c* 0.7, $CHCl_3$)}.[11] This was the ultimate confirmation of the relative and absolute (1*S*,9a*R*)-configuration of the product.

In summary, we have disclosed a short and efficient asymmetric synthesis of (−)-1-hydroxyquinolizidinone **(4)** in seven steps and 25.2% overall yield from 5-chloropentanal **(9)**. This synthesis is competitive with that of Huang and co-workers for which compound **4** was prepared in 12 steps with 13% yield from (*S*)-glutamic acid.[11,12] **4** can be converted into (−)-homopumiliotoxin 223G **(*ent*-2a)** (seven steps/29.6% yield)[11] and (−)-epiquinamide **(3)** (four steps/41.3% yield).[12] Thus, our synthesis of **4** matched with that of Huang and co-workers constitutes a straightforward formal preparation of (−)-homopumiliotoxin 223G **(*ent*-2a)** and (−)-epiquinamide **(3)** in 13 steps (7.4%) and 11 steps (10.4% yield), respectively. Moreover our formal syntheses represent a good alternative to syntheses earlier published which all use more or less easily available amino acid derivatives as starting materials: (*S*)-*N*-Boc-2-acetylpiperidine,[9a]

(16) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1317−1320 and references cited therein.

(17) Allenylzinc **8** was generated in situ at −80 °C in Et_2O by the lithiation of (3-(methoxymethoxy)prop-1-ynyl)trimethylsilane with *s*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and subsequent transmetallation with anhydrous zinc bromide (see ref 14c).

(18) (3-(Methoxymethoxy)prop-1-ynyl)trimethylsilane was prepared in a two-step procedure from propargyl alcohol by (i) silylation of the acetylenic position; see Jones, T. K.; Denmark, S. E. *Org. Synth.* **1985**, *64*, 182−185; followed by (ii) treatment of the resulting product with an excess of dimethoxymethane in $CHCl_3$ in the presence of an excess of P_2O_5.

(19) For other examples of cyclizations of this type, see: (a) Ruano, J. L.; Alemán, J.; Cid, M. B. *Synthesis* **2006**, 687−691. (b) Davis, F. A.; Prasad, K. R.; Nolt, M. B.; Wu, Y. *Org. Lett*. **2003**, *5*, 925−927.

(20) (a) Katoh, M.; Mizutani, H.; Honda, T. *Heterocycles* **2006**, *69*, 193−216. (b) D'Oca, M. G. M., Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709−9712.

(21) (a) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem*. **2004**, *69*, 6001−6009. (b) Huang, P.-Q.; Liu, L.-X.; Wei, B.-G.; Ruan, Y.-P. *Org. Lett*. **2003**, *5*, 1927−1929. (c) Gringore, O. H.; Rouessac, F. P. In *Organic Syntheses*; Freeman. J. P., Ed.; John Wiley & Sons: New York, 1990; Collect. Vol. VII, p 99.

N-Cbz-pipecolic acid,[9b] and (*S*)-glutamic acid[11] for (+)- or (−)- homopumiliotoxin 223G; (*S*)-glutamic acid,[11] *N*-γ-Boc-*N*-α-Cbz-ornithine,[12a] (−)-pipecolinic acid,[12b] and L-allysine ethylene acetal[12c] for (+)- or (−)-epiquinamide.

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Supporting Information Available: General methods, detailed experimental procedures, physical and spectroscopical data, ^{1}H and ^{13}C spectra for compounds **4**, **6**, **7**, **11** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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