



## Synthesis of (–)-epibatidine†

Wen-Hua Chiou\* and Yu-Min Chiang

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An asymmetric synthesis to the *dendrobatid* alkaloid (–)-epibatidine has been described, featuring chiral resolution of both optically pure 7-azabicyclo[2.2.1]heptanecarboxylic acid, and subsequent transformations to (–)-epibatidine. The methodology provides a flexible access to various substituted chiral epibatidine analogues.

In 1992, Daly and coworkers reported a dendrobatid alkaloid, epibatidine (**1**), isolated in trace amounts from the skin of the Ecuadoran poison frog *Epipedobates tricolor*.<sup>1,2</sup> Epibatidine (**1**) has been found to be 200–400 times more potent than morphine as an analgesic, and appeared to act *via* a non-opioid mechanism since its effects are not blocked by the opiate receptor antagonist naloxone. In addition, epibatidine (**1**) is an extremely potent agonist of the nicotinic acetylcholine receptor.<sup>3</sup> Due to its pharmacological activity, epibatidine (**1**) has attracted much attention from synthetic chemists, resulting in abundant approaches. However, its high toxicity also prevents therapeutic applications, and has prompted a search for safer analogues such as epiboxidine (**2**) (Fig. 1).<sup>4</sup>

Various strategies have been developed for efficient syntheses of the molecule, which have been reviewed by Trudell<sup>5</sup> and Olivo.<sup>6</sup> One of these approaches to synthesize the unique 7-azabicyclo[2.2.1]heptane framework in epibatidine is the cycloaddition reaction. *N*-Protected pyrroles could undergo Diels–Alder reactions with substituted acetylene or ethylene derivatives. Transannular S<sub>N</sub>2 displacement also provides a practical route to synthesize epibatidine.<sup>7</sup> A well-established arrangement in a 1,4-disubstituted cyclohexyl ring system could trigger an S<sub>N</sub>2 reaction to give the 7-azabicyclo[2.2.1]heptane

structure. Direct coupling of the 7-azabicyclo[2.2.1]heptan-2-one or its derivatives with the aromatic ring is an effective strategy for syntheses of epibatidine and analogues. Due to the diversity of the approach, many elegant approaches to synthesize 7-azabicyclo[2.2.1]heptane derivatives have been reported,<sup>8</sup> including Aza-Prins-Pinacol rearrangement<sup>8c</sup> and Favorskii rearrangement of tropinone.<sup>9a,b</sup> As a part of the project devoted to asymmetric syntheses of alkaloids and derivatives for pharmaceutical purposes, here we describe a different approach to synthesize (–)-epibatidine (**1**). This strategy takes advantage of readily available carboxylic acid **3**, and features a practical preparation of enantiopure acid **3** and construction of the 2-chloropyridine moiety from the carboxylic acid end.

Our approach commences with the preparation of racemic 7-azabicyclo[2.2.1]heptanecarboxylic acid, using Fevig' conditions,<sup>9c</sup> a modification based on Bai's procedure.<sup>9a,b</sup> We envision both optically active 7-azabicyclo[2.2.1]heptane carboxylic acids **3** are available through covalent bond modification with a chiral compound to two separable diastereomers, followed by removal of the chiral auxiliary. Subsequent functionality transformations of the carboxylic acid end effect the formation of the 2-chloropyridine moiety in epibatidine. Such an approach does not only synthesize the 2-chloropyridine moiety, but also allow diversity by construction of various bioisosteric rings or other modification. For example, epiboxidine (**2**) can be achieved by an acetoxime addition–cyclization protocol.<sup>8g</sup> With racemic acid **3** in hand, transformation of (±)-**3** to separable diastereomers has been carried out by treating of acid **3** with SOCl<sub>2</sub> to the resulting acid chloride, followed by reaction with various chiral auxiliaries.

Department of Chemistry, National Chung Hsing University, Taichung, Taiwan, 402, Republic of China. E-mail: [wchiou@dragon.nchu.edu.tw](mailto:wchiou@dragon.nchu.edu.tw); Fax: +886-4-22862547; Tel: +886-4-22840411-420

† Electronic supplementary information (ESI) available: Experimental procedure, all <sup>1</sup>H, <sup>13</sup>C NMR spectra and assignment for all compounds, and HPLC chromatograms of **1**, **3**, **5**, **9**, **11**, **12** and **14**, and crystallographic data of **4a**. CCDC reference number 954104. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra00770k

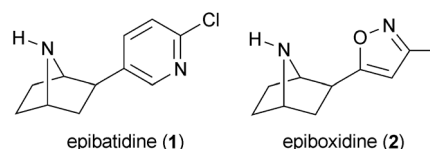


Fig. 1 (–)-Epibatidine (**1**) and epiboxidine (**2**).

We have utilized *L*-menthol and *L*-boreneol as the chiral auxiliary, but both have failed to give separable diastereomeric adducts. Fortunately, after racemic acid **3** has been coupled with (4*S*)-benzyl-2-oxazolidinone, readily available from *L*-phenylalanine, two diastereomeric adducts were easily separated by column chromatography, to yield the less polar product **4a** in 44% yield and the more polar product **4b** in 41% yield, respectively (Scheme 1). In addition, recrystallization of oxazolidinone **4a** within ethyl acetate and hexane provided a crystal for an X-ray analysis, which confirmed the absolute configuration as (1*R*,2*S*,4*S*)-7-azabicyclo[2.2.1]heptane moiety (Fig. 2).<sup>10</sup> The results also disclosed the absolute configuration of the other diastereomer, amide **4b**, as a (1*S*,2*R*,4*R*)-7-azabicyclo[2.2.1]heptane moiety. Subsequent basic hydrolysis conditions using H<sub>2</sub>O<sub>2</sub> in THF for the less polar oxazolidinone derivative **4a** proceeded successfully to yield optically pure (–)-acid **3** in 98% yield, while the more polar one **4b** gave optically pure (+)-acid **3** in 93% yield (Scheme 1). Chiral HPLC analyses display the optical purity of (–)-acid **3** is more than 99% ee, (*t*<sub>R</sub>: 18.4 min for (+)-**3**, 26.3 min for (–)-**3**, see ESI†) (Fig. 3).

The next efforts were involved with the construction of the 5-substituted-2-chloropyridine moiety (Schemes 2 and 3). With optically pure acid (–)-**3** in hand, we converted acid **3** to its homoaldehyde derivative by one-carbon homologation *via* an enol ether intermediate.<sup>11</sup> Thus, reduction of acid (–)-**3** with BH<sub>3</sub>·Me<sub>2</sub>S in THF produced alcohol (–)-**5** in 96% yield with 99% ee. Oxidation of alcohol (–)-**5** with Dess–Martin periodinane in CH<sub>2</sub>Cl<sub>2</sub> afforded aldehyde (+)-**6** in 93% yield. Direct treatment of oxazolidinone **4a** with BH<sub>3</sub>·Me<sub>2</sub>S in THF, followed by Dess–Martin oxidation also afforded aldehyde (+)-**6** in 86% yield over two steps. Treatment aldehyde (+)-**6** with methoxymethylene yield, prepared by mixing of methoxymethyltriphenylphosphonium chloride with NaHMDS, yielded methyl vinyl ether **7** in 88% yield. About 3 : 2

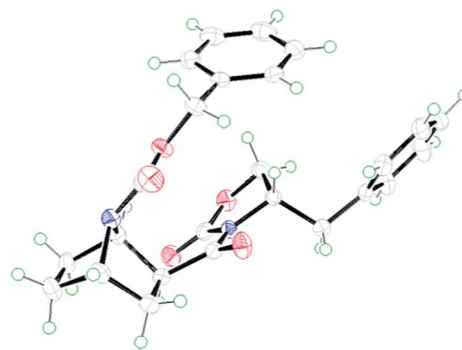
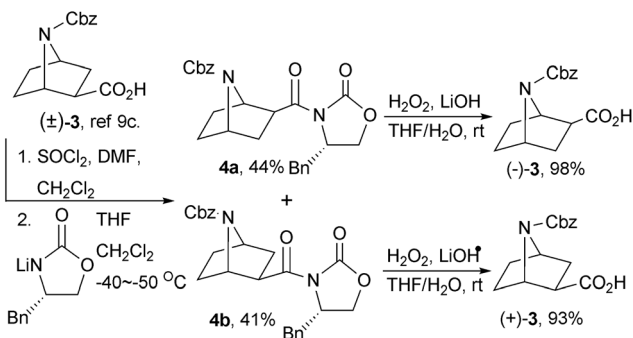


Fig. 3 ORTEP drawing of oxazolidinone **4a**.

ratio of the *trans* isomer to *cis* isomer was observed in <sup>1</sup>H-NMR spectra, *i.e.* a doublet at 6.27 ppm with coupling constant 12.8 Hz implied the *trans* isomer while a doublet at 5.70 ppm with coupling constant 6.0 Hz implied the *cis* isomer. Hydrolysis of vinyl ether **7** in 1 N HCl in THF furnished homoaldehyde (–)-**8** in 92% yield. To confirm the chiral integrity, homoaldehyde (–)-**8** was oxidized by Jones reagent to homoacid (–)-**9**. Chiral HPLC analysis of homoacid (–)-**9** confirmed the chiral integrity arrived intact during the processes mentioned above (>99% ee, Scheme 2).

Homoaldehyde (–)-**8** was treated with pyrrolidine in the presence of K<sub>2</sub>CO<sub>3</sub> to the corresponding enamine, followed by reaction with ethyl acrylate, and then hydrolysis in an acidic media to furnish glutarate semialdehyde **10** in 55% yield. The yield was improved to 81% yield by Hagiwara's protocol,<sup>12</sup> using TMSNET<sub>2</sub> and ethyl acrylate in refluxing acetonitrile. Glutarate semialdehyde **10** underwent a double condensation process with NH<sub>4</sub>OAc in refluxing benzene to yield dihydropyridone (–)-**11** in 93% yield with 99% ee. Oxidation with 9 equivalents of MnO<sub>2</sub> in refluxing benzene produced 5-substituted 2-pyridone (+)-**12** in 90% yield. Slow addition of MnO<sub>2</sub> during a long period was crucial for the yield in that addition at once brought about a yield decrease in this reaction. Treatment of 2-pyridone (+)-**12** with POCl<sub>3</sub> and in DMF did not only convert the 2-pyridone group to the 2-chloropyridine group, but also replaced the Cbz group by a formyl group as formamide **13** in 73% isolated yield. Since two sets of peaks with almost equal intensity have been observed in <sup>13</sup>C-NMR, the product appeared to be a mixture of *E/Z* isomers with equal amount due to the restrict rotation of the formamide bonding. Exposure of formamide **13** in 5% HCl in MeOH afforded final product epibatidine (–)-**1** in 92% yield with >99% ee. The specific rotation value of (–)-**1**, [α]<sub>D</sub><sup>25</sup> – 6.8 (c: 1.04 CHCl<sub>3</sub>) was consistent with the reported value, [α]<sub>D</sub><sup>25</sup> – 6.5



Scheme 1 Separation of racemic acid **3** using (4*S*)-benzyl-2-oxazolidinone.

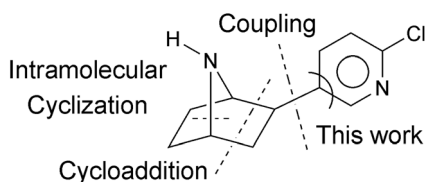
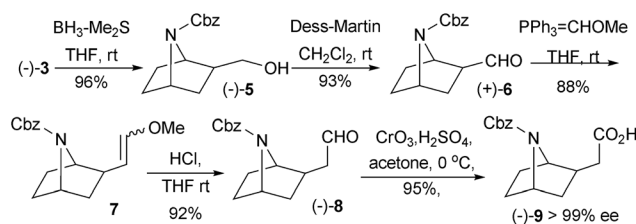
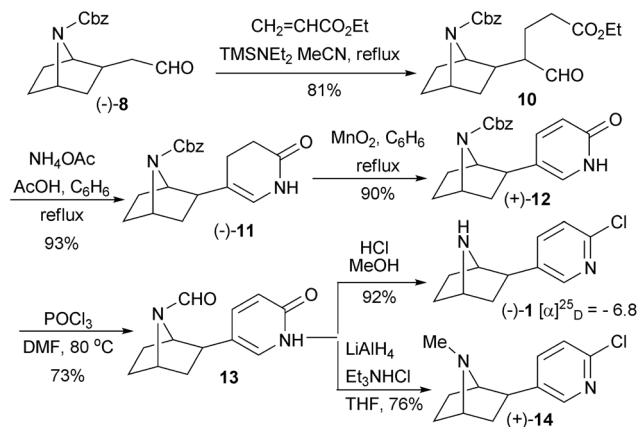


Fig. 2 Approaches towards epibatidine.



Scheme 2 Synthesis of chiral aldehyde (–)-**8**.



Scheme 3 Syntheses of (–)-epibatidine and (+)-methylepibatidine.

(c: 1.00,  $\text{CHCl}_3$ ).<sup>13</sup> Treatment of formamide **13** with alane complex, prepared by mixing  $\text{LiAlH}_4$  and  $\text{Et}_3\text{N} \cdot \text{HCl}$ ,<sup>14</sup> produced *N*-methyl epibatidine analogue (+)-**14** in 76% yield with 99% ee (Scheme 3).

In conclusion, we have described an efficient preparation of both enantiomers of 7-azabicyclo[2.2.1]heptane carboxylic acid **3**, and a feasible strategy to synthesize a 5-substituted 2-chloropyridine structure from a cycloalkanecarboxylic acid, demonstrated as the synthesis of (–)-epibatidine **1**. The methodology provides flexible access to various substituted alkaloids bearing a 7-azabicyclo[2.2.1]heptane moiety, which may benefit the development of more potent and safer analgesics. Subsequent extension of this methodology towards other natural products of interest is currently underway.

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## Notes and references

- 1 T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. C. Yeh, L. Pannell and J. W. Daly, *J. Am. Chem. Soc.*, 1992, **114**, 3475.
- 2 J. W. Daly, H. M. Garraffo, T. F. Spande, M. W. Decker, J. P. Sullivan and M. Williams, *Nat. Prod. Rep.*, 2000, **17**, 131.
- 3 B. Badio and J. W. Daly, *Mol. Pharmacol.*, 1994, **45**, 563.
- 4 B. Badio, H. M. Garraffo, C. V. Plummer, W. L. Padgett and J. W. Daly, *Eur. J. Pharmacol.*, 1997, **321**, 189.
- 5 Z. Chen and M. L. Trudell, *Chem. Rev.*, 1996, **96**, 1179.
- 6 H. F. Olivo and M. S. Hemenway, *Org. Prep. Proced. Int.*, 2002, **34**, 1.
- 7 For the synthesis published before 2002, please see ref. 5 and 6. Published after 2002, please see: (a) Y. Hoashi, T. Yabuta and Y. Takemoto, *Tetrahedron Lett.*, 2004, **45**, 9185; (b) V. K. Aggarwal and B. Olofsson, *Angew. Chem., Int. Ed.*, 2005, **44**, 5516–5519; (c) C.-L. K. Lee and T.-P. Loh, *Org. Lett.*, 2005, **7**, 2965; (d) Y. Hoashi, T. Yabuta, P. Yuan, H. Miyabe and Y. Takemoto, *Tetrahedron*, 2006, **62**, 365; (e) D. R. Boyd, N. D. Sharma, M. Kaik, P. B. A. McIntyre, P. J. Stevenson and C. C. R. Allen, *Org. Biomol. Chem.*, 2012, **10**, 2774; (f) X. Huang, H. Shi, J. Ren, G. Liu, Y. Tang and B. Zeng, *Chin. J. Chem.*, 2012, **30**, 1305; (g) K. L. Jensen, C. F. Weise, G. Dickmeiss, F. Morana, R. L. Davis and K. A. Jorgensen, *Chem.–Eur. J.*, 2012, **18**, 11913.
- 8 For the reports published before 2002, please see ref. 5 and 6. Published after 2002, please see: (a) T. Tachihara, H. Watanabe and T. Kitahara, *Heterocycles*, 2002, **57**, 781; (b) C. Che, G. Petit, F. Kotzyba-Hibert, S. Bertrand, D. Bertrand, T. Grutter and M. Goeldner, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1001; (c) A. J. Moreno-Vargas and P. Vogel, *Tetrahedron: Asymmetry*, 2003, **14**, 3173; (d) M.-Y. Chang and H.-P. Chen, *Heterocycles*, 2005, **65**, 1705; (e) A. Armstrong and S. E. Shanahan, *Org. Lett.*, 2005, **7**, 1335; (f) H. Kimura, T. Fujiwara, T. Katoh, K. Nishide, T. Kajimoto and M. Node, *Chem. Pharm. Bull.*, 2006, **54**, 399; (g) A. Armstrong, Y. Bhonoah and S. E. Shanahan, *J. Org. Chem.*, 2007, **72**, 8019; (h) E. Gomez-Sanchez, E. Soriano and J. Marco-Contelles, *J. Org. Chem.*, 2007, **72**, 8656; (i) E. Gomez-Sanchez, E. Soriano and J. Marco-Contelles, *J. Org. Chem.*, 2008, **73**, 6784; (j) A. Armstrong, Y. Bhonoah and A. J. P. White, *J. Org. Chem.*, 2009, **74**, 5041; (k) J. Bexrud and M. Lautens, *Org. Lett.*, 2010, **12**, 3160.
- 9 (a) D. Bai, R. Xu, G. Chu and X. Zhu, *J. Org. Chem.*, 1996, **61**, 4600; (b) R. Xu, G. Chu and D. Bai, *Tetrahedron Lett.*, 1996, **37**, 1463; (c) T. E. Fevig, T. E. Anjeh, J. P. Lawson, D. P. Walker and D. G. Wishka, U. S. Patent 0173063 A1, Pfizer Inc., 2006.
- 10 ESI.†
- 11 Although there are many reported valuable homologation methods, the present route has been taken for the reliable and safety reason.
- 12 H. Hagiwara, N. Komatsubara, H. Ono, T. Okabe, T. Hoshi, T. Suzuki, M. Ando and M. Kato, *J. Chem. Soc., Perkin Trans. 1*, 2001, 316.
- 13 S. R. Fletcher, R. Baker, M. S. Chambers, R. H. Herbert, S. C. Hobbs, S. R. Thomas, H. M. Verrier, A. P. Watt and R. G. Ball, *J. Org. Chem.*, 1994, **59**, 1771.
- 14 W. Chiou, G.-H. Lin, C.-C. Hsu, S. J. Chaterpaul and I. Ojima, *Org. Lett.*, 2009, **11**, 2659.