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Synthesis of (−)-epibatidine†

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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.*[1,2] 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.[3] 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).[4]

Various strategies have been developed for efficient syntheses of the molecule, which have been reviewed by Trudell[5] and Olivo.[6] 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_N2 displacement also provides a practical route to synthesize epibatidine.[7] A well-established arrangement in a 1,4-disubstituted cyclohexyl ring system could trigger an S_N2 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,[8] including Aza-Prins-Pinacol rearrangement[8e] and Favorskii rearrangement of tropinone.[9a,b] 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,[9c] a modification based on Bai's procedure.[9a,b] 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.[8g] With racemic acid **3** in hand, transformation of (±)-**3** to separable diastereomers has been carried out by treating of acid **3** with $SOCl_2$ to the resulting acid chloride, followed by reaction with various chiral auxiliaries.

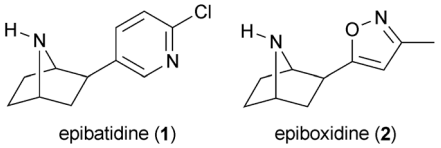

Fig. 1 (−)-Epibatidine (**1**) and epiboxidine (**2**).

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† Electronic supplementary information (ESI) available: Experimental procedure, all ^1H, ^{13}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

We have utilized L-menthol and L-borenol 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).[10] 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_2O_2 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_R: 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.[11] Thus, reduction of acid (−)-**3** with $BH_3 \cdot Me_2S$ in THF produced alcohol (−)-**5** in 96% yield with 99% ee. Oxidation of alcohol (−)-**5** with Dess–Martin periodinane in CH_2Cl_2 afforded aldehyde (+)-**6** in 93% yield. Direct treatment of oxazolidinone **4a** with $BH_3 \cdot Me_2S$ 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 ratio of the *trans* isomer to *cis* isomer was observed in ^{1}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).

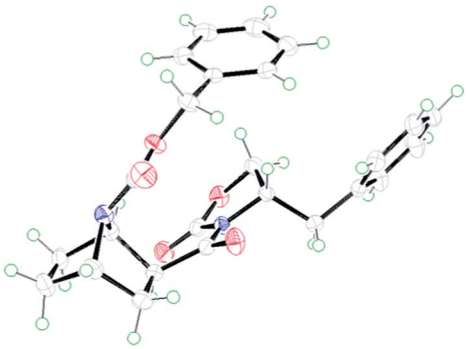
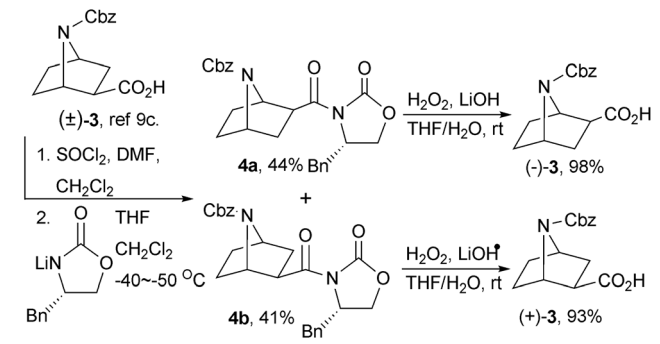


Fig. 3 ORTEP drawing of oxazolidinone **4a**.

Homoaldehyde (−)-**8** was treated with pyrrolidine in the presence of K_2CO_3 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,[12] using $TMSNEt_2$ and ethyl acrylate in refluxing acetonitrile. Glutarate semialdehyde **10** underwent a double condensation process with NH_4OAc in refluxing benzene to yield dihydropyridone (−)-**11** in 93% yield with 99% ee. Oxidation with 9 equivalents of MnO_2 in refluxing benzene produced 5-substituted 2-pyridone (+)-**12** in 90% yield. Slow addition of MnO_2 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 $POCl_3$ 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 ^{13}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**, $[\alpha]_D^{25}$ − 6.8 (*c*: 1.04 $CHCl_3$) was consistent with the reported value, $[\alpha]_D^{25}$ − 6.5



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

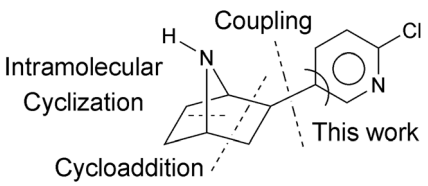
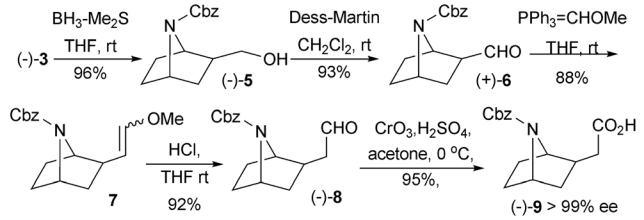
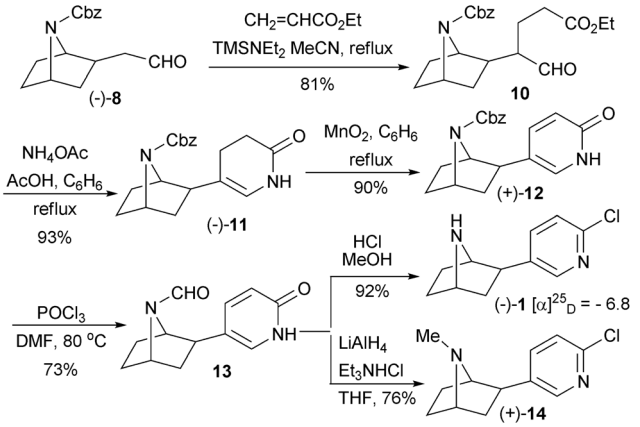


Fig. 2 Approaches towards epibatidine.



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



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

(*c*: 1.00, $CHCl_3$).[13] Treatment of formamide **13** with alane complex, prepared by mixing $LiAlH_4$ and $Et_3N{\cdot}HCl$,[14] 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.

Acknowledgements

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