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ARTICLE TYPE

Synthesis of (–)-Epibatidine

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An asymmetric synthesis to *dendrobatid* alkaloid (–)-epibatidine has been described, featuring chiral resolution of both optical 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 have reported a dendrobatid alkaloid, epibatidine (**1**), isolated in trace amount 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 have 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, and resulting in abundant approaches. However, its high toxicity also prevents therapeutic applications, and have prompted as search for safer analogues such as epiboxidine (**2**).[4]

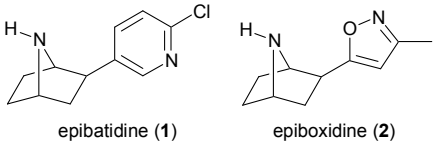


Figure 1. (–)-epibatidine **(1)** and epiboxidine **(2).**

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]hepatane 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, 9b] As a part of the project devoted to asymmetric syntheses of alkaloids and derivatives for pharmaceutical purpose, 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.

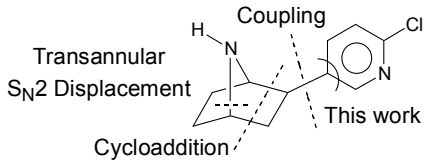
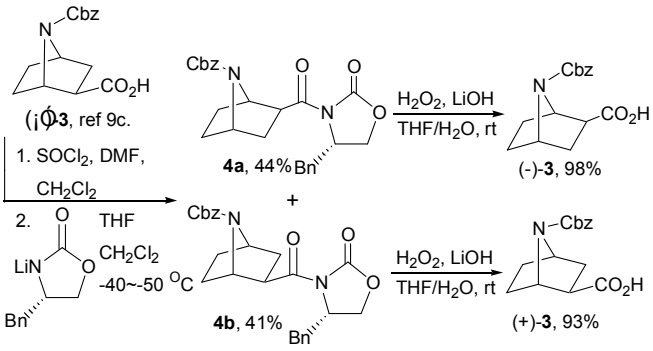


Figure 2. Approaches towards epibatidine.

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, 9b] 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.

We have utlized 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 (Figure 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 supporting information).



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

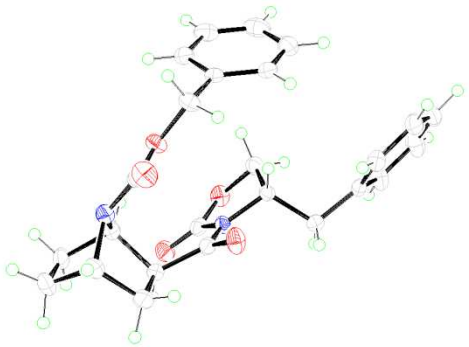
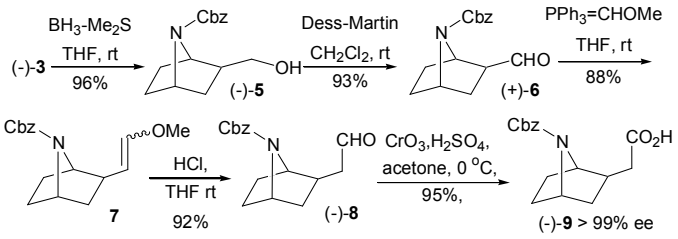


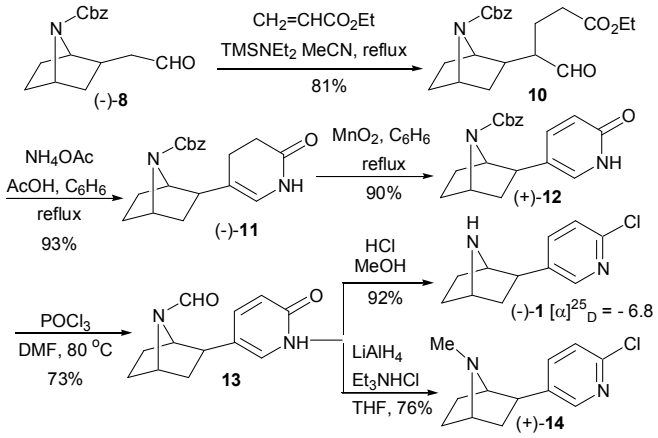
Figure 3. ORTEP drawing of oxazolidinone **4a**

The next efforts were involved with the construction of the 5-substituted-2-chloropyridine moiety (Scheme 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•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•Me_2S in THF, followed by Dess-Martin oxidation also afforded aldehyde (+)-**6** in 86% yield over two steps. Treatment aldehyde (+)-**6** with methoxymethylene yilde, 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).



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

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 (*c*: 1.00, $CHCl_3$).[13] Treatment of formamide **13** with alane complex, prepared by mixing $LiAlH_4$ and Et_3N•HCl,[14] produced *N*-methyl epibatidine analogue (+)-**14** in 76% yield with 99% ee (Scheme 3).



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

In conclusion, we have described an efficient preparation of both enantiomers of 7-azabicyclo[2.2.1] hepatane 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 a 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

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† Electronic Supplementary Information (ESI) available:**:**Experimental procedure, all ^{1}H, ^{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** in CIF format, See DOI: 10.1039/b000000x/

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