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ENANTIOSELECTIVE SYNTHESIS OF (–)-*N*-BOC-7-AZABICYCLO-[2.2.1]HEPTAN-2-ONE AND (+)-*N*-BOC-4-AMINO-2-CYCLOHEXEN-1-ONE: FORMAL TOTAL SYNTHESIS OF BOTH ENANTIOMERS OF EPIBATIDINE

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Abstract- we succeeded in the stereoselective synthesis of (–)-*N*-Boc-7-azabicyclo[2.2.1]heptan-2-one ((–)-**2**) and (+)-*N*-Boc-4-amino-2-cyclohexen-1-one ((+)-**3**), key intermediates to (–) and (+)-epibatidine from a common chiral building block ethyl (1*R*,2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate (**4**) . This constitutes the formal total synthesis of both enantiomers of epibatidine, a potent analgesic.

(–)-Epibatidine (**1**) is a new class of amphibian alkaloid, isolated in a trace amount (*ca.*1 mg from 750 frogs) from the skin of the Ecuadorian poison frog *Epipedobates tricolor* by Daly and co-workers in 1992.[1] This alkaloid possesses a 7-azabicyclo[2.2.1]heptane skeleton and has been reported to contain extremely higher potency as an analgesic than morphine.[2] Biological studies revealed that this remarkable activity of epibatidine is due to the action as an agonist of nicotinic acetylcholine receptor.[3-5] Interestingly, it has been shown in analgesic tests that both enantiomers of epibatidine are nearly equipotent.

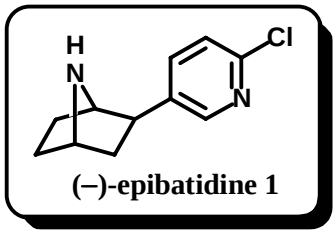
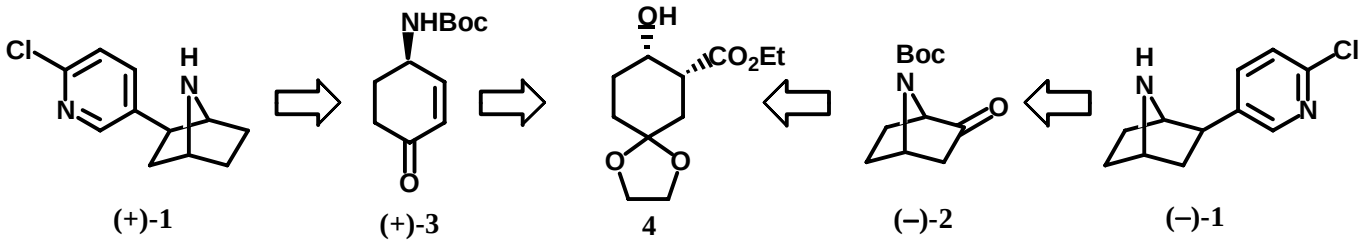


Figure-1

Because of its unique nitrogen-bridged ring system and powerful pharmacological activity, much attention has been paid to the synthesis of this molecule and derivatives to promote

further biological studies as well as the structure-activity relationship. Thus, a number of methods for synthesis of epibatidine have already been reported in both racemic and enantiomeric forms.[6-8] Recently, we succeeded in a simple and efficient stereocontrolled route for the synthesis of racemic epibatidine.[9]

We noted that both **2** and **3** are key intermediates of epibatidine and we show here a novel enantioselective approach to (–)-**2** and (+)-**3** using our chiral building block, ethyl (1*R*, 2*S*)-5,5-ethylenedioxy-2-hydroxycyclohexanecarboxylate (**4**), which is available in large quantity by simple operation *via* baker's yeast reduction.[10a,b] We have already succeeded in total synthesis of natural products, sporogen-AO1,[10b] other phytotoxins,[10c] dendriphiellin C[10d] and pironetin[10e] using this building block. (Scheme-1)

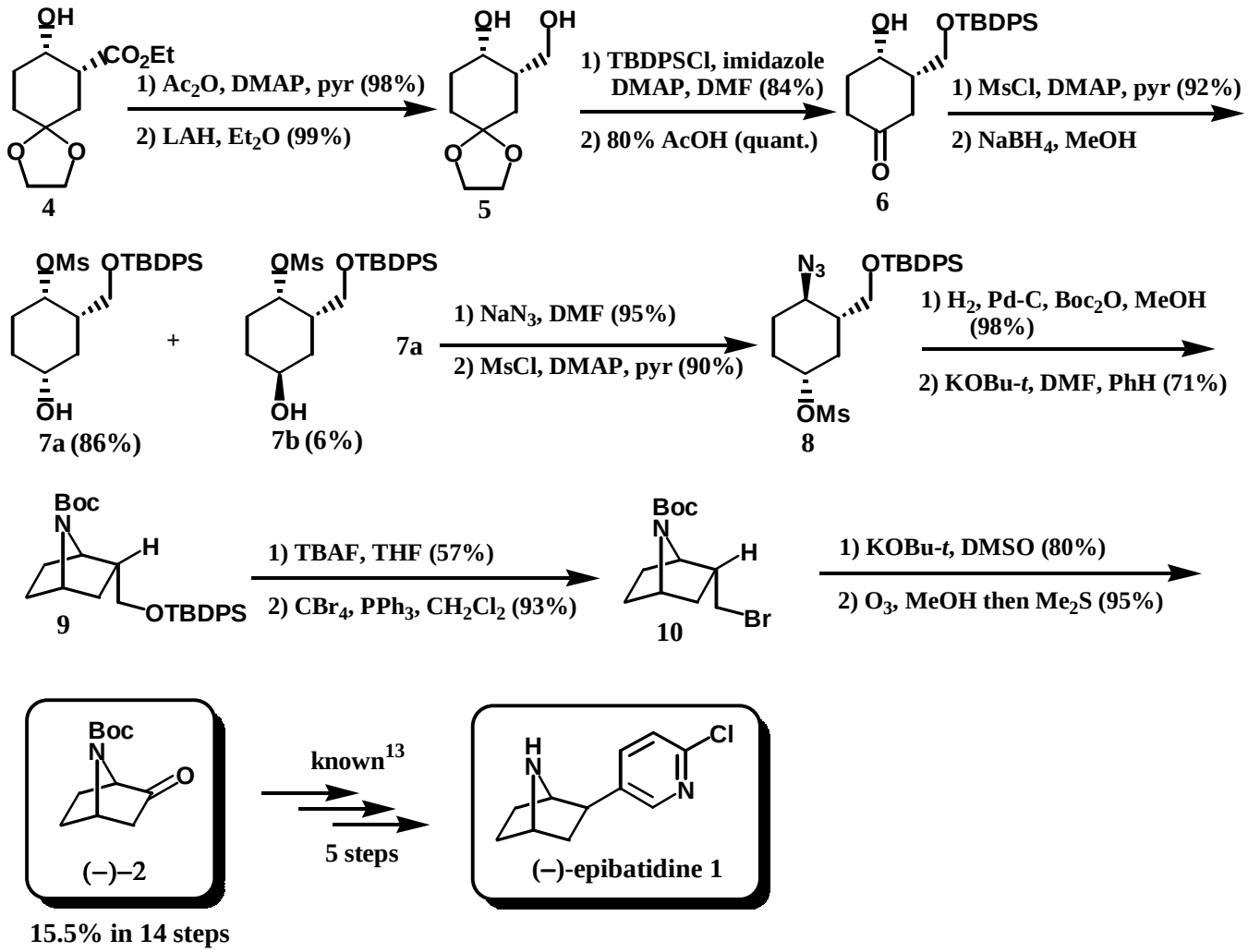


Scheme-1: Synthetic plan

Synthesis of (–)-2 is shown in Scheme-2.

Acetylation of **4**, followed by reduction with lithium aluminum hydride gave diol (**5**).[10b] Selective *tert*-butyldiphenylsilyl (TBDPS) protection of the primary hydroxyl group, and then hydrolysis with 80% acetic acid gave hydroxy ketone (**6**). Mesylation of the hydroxyl group of **6**, followed by reduction of carbonyl group with sodium borohydride afforded a diastereo mixture of **7** in a ratio of *ca*. **7a**:**7b**=14:1. These diasteomers could be separated by silica gel column chromatography easily. The desired major isomer (**7a**) was treated with sodium azide and successive mesylation of the secondary hydroxy group gave azide (**8**). Reduction of azide and protection of the generated amino group were performed simultaneously in the presence of palladium on carbon and di-*tert*-butyl dicarbonate under hydrogen atmosphere. Cyclization with potassium *tert*-butoxide resulted in formation of azabicyclo[2.2.1]heptane skeleton (**9**).[11] Deprotection of the TBDPS group with tetrabutylammonium fluoride, followed by bromination with carbon tetrabromide and triphenylphosphine afforded bromide (**10**). Dehydrobromination was carried out with potassium *tert*-butoxide as a base in dimethyl sulfoxide. Finally, ozonolysis of *exo*-methylene group gave (–)-**2**.[12] (overall 14 steps, 15.5% yield from **4**)

The conversion from (–)-**2** to (–)-epibatidine was reported by Fletcher and co-workers in 1994.[13]

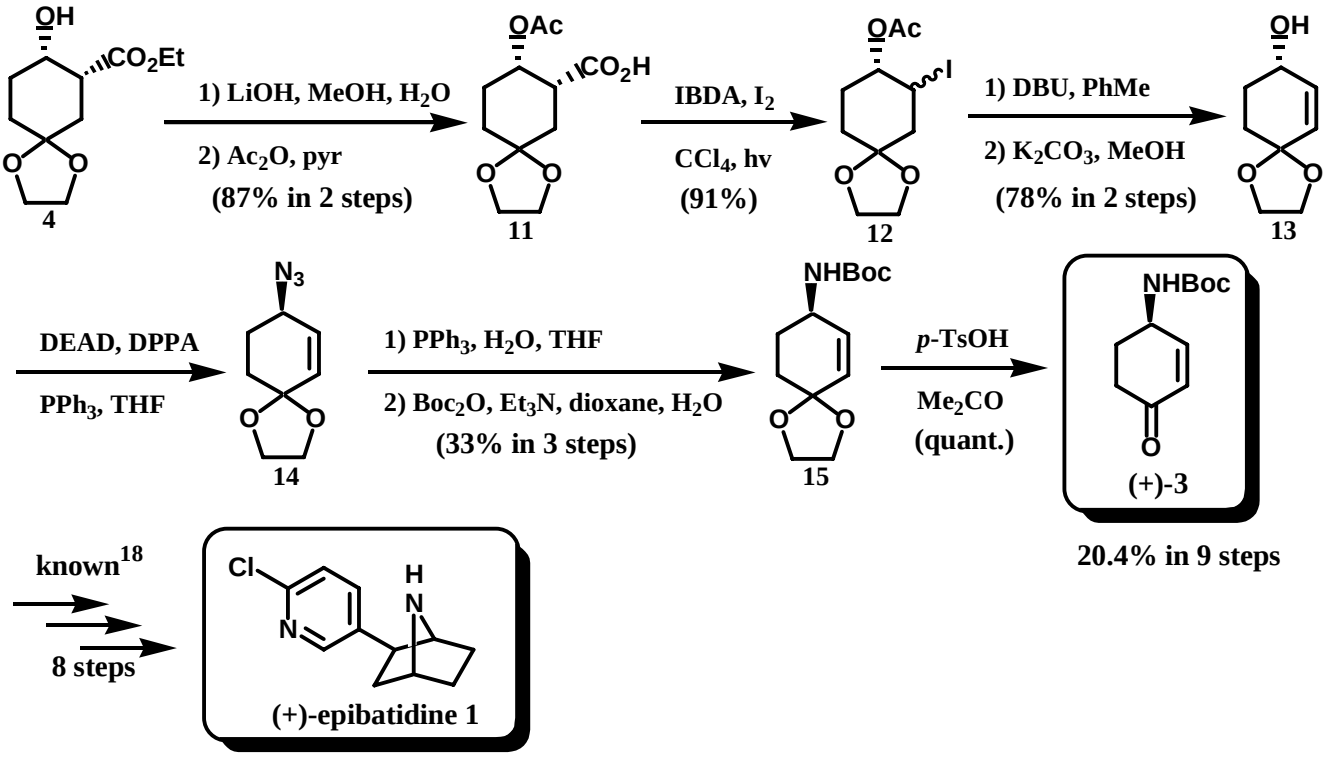


Scheme-2: Synthesis of (–)-2 and formal total synthesis of (–)-epibatidine

Synthesis of (+)-**3** is shown in Scheme-3.

Hydrolysis of the ester group of **4**, followed by acetylation of the hydroxyl group gave carboxylic acid (**11**). Oxidative decarboxylation of **11** with iodobenzene diacetate (IBDA) and iodine in carbon tetrachloride afforded iodide (**12**)[14] as an inseparable diastereo mixture. (*ca.* 1:1) Dehydroiodination with DBU, and then methanolysis of the acetyl group gave allylic alcohol (**13**). Azidation of alcohol (**13**) under Mitsunobu conditions gave azide (**14**).[15] Reduction of the azide group with palladium on carbon under hydrogen atmosphere proceeded with concomitant reduction of olefin, but treatment of triphenylphosphine and water in tetrahydrofuran afforded the desired allylic amine.[16] Boc protection of the amino group gave *N*-Boc-amine (**15**). Finally, acetal exchange with a catalytic amount of *p*-toluenesulfonic acid in acetone gave (+)-*N*-Boc-4-amino-2-cyclohexen-1-one (**3**).[17] (overall 9 steps, 20.4% yield from **4**)

The conversion from (–)-**3** to (–)-epibatidine was reported by Trost and co-workers in 1996.[18] It was reported that (+)-epibatidine was prepared in the same manner from (+)-**3**. Both (–)-**2** and (+)-**3** were identical with those reported. (^{1}H NMR, IR and $[\alpha]_D$)



Scheme-3: Synthesis of (+)-3 and formal total synthesis of (+)-epibatidine

In conclusion, we have succeeded in a stereoselective synthesis of (–)-**2** and (+)-**3**, key intermediates to (–) and (+)-epibatidine, from a common chiral building block. In this way we were able to show the formal total synthesis of both enantiomers of epibatidine.

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12. Compound (–)-**2**: ^{1}H NMR(300 MHz, $CDCl_3$): δ 4.55(t, 1H, J=5.0 Hz), 4.25(d, 1H, J=4.8 Hz), 2.47(dd, 1H, J=17.4, 5.1 Hz), 2.00(d, 1H, J=17.4 Hz), 1.91-2.17(m, 2H), 1.50-1.68(m, 2H), 1.45(s, 9H); IR(film) 2979, 1767, 1706, 1368, 1143cm^{-1}; $[\alpha]_D^{20}$ –79.0° (*c* 1.05, $CHCl_3$); lit.,[8e] $[\alpha]_D$ –72.8° (*c* 1.6, $CHCl_3$); HRMS (M-CO) calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1219
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17. Compound (+)-**3**: mp 112-113℃; ^{1}H NMR(300 MHz, $CDCl_3$): δ 6.83(dt, 1H, J=10.2, 1.8 Hz), 6.00(dd, 1H, J=10.2, 2.1 Hz), 4.68(br s, 1H), 4.52(br s, 1H), 2.29-2.58(m, 3H), 1.86-1.91 (m, 1H), 1.46(s, 9H); IR(nujor) 3344, 1683, 1519, 1311, 1164cm^{-1}; $[\alpha]_D^{23}$ +125° (*c* 0.58, CH_2Cl_2); lit.,[18] $[\alpha]_D^{23}$ –124° (*c* 1.14, CH_2Cl_2) (for (–)-**3**); HRMS (M-C_4H_8) calcd for $C_7H_9NO_3$ 155.0582, found 155.0541
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