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Synthesis of Optically Pure Epibatidine Analogs: (*1R, 2R, 5S*)-2β-(2-Chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane and (*1R, 2S, 5S*)-2α-(2-Chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane From (-)-Cocaine

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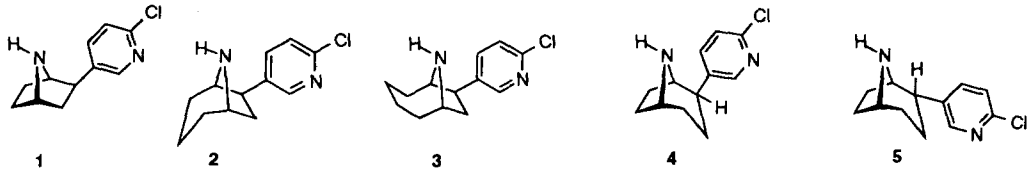
Abstract: Two optically pure epibatidine analogs, **4** and **5**, which contain the 8-azabicyclo[3.2.1]octane ring system were synthesized from (−)-cocaine. The nicotinic receptor binding affinity and the stimulant activity of **4** and **5** were measured to be significantly lower than racemic epibatidine (±-**1**).

Epibatidine (**1**), which was isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers,[1] has been reported to be a highly potent non-opioid analgesic and nicotinic acetylcholine receptor agonist.[2-4] Its low natural abundance (< 1 mg from 750 frogs) combined with its intriguing biological activity has resulted in numerous syntheses of **1** and related 7-azabicyclo[2.2.1]heptane analogs.[5-7] Remarkably, in spite of this intense activity, there exists few examples of epibatidine analogs with different ring systems.[8,9] More recently, the synthesis of (±)-homoepibatidine (**2**)[8,9] and (±)-*bis*-homoepibatidine (**3**)[9] have been reported. Interestingly, **2** was reported to show potent analgesic activity in hot-plate assays, comparable to that of (±)-epibatidine.[8] Herein, we wish to report the synthesis of two analogs of epibatidine, (*1R, 2R, 5S*)-2β-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane (**4**) and (*1R, 2S, 5S*)-2α-(2-chloro-5-pyridinyl)-8-azabicyclo[3.2.1]octane (**5**), derived from natural (−)-cocaine (**6**).

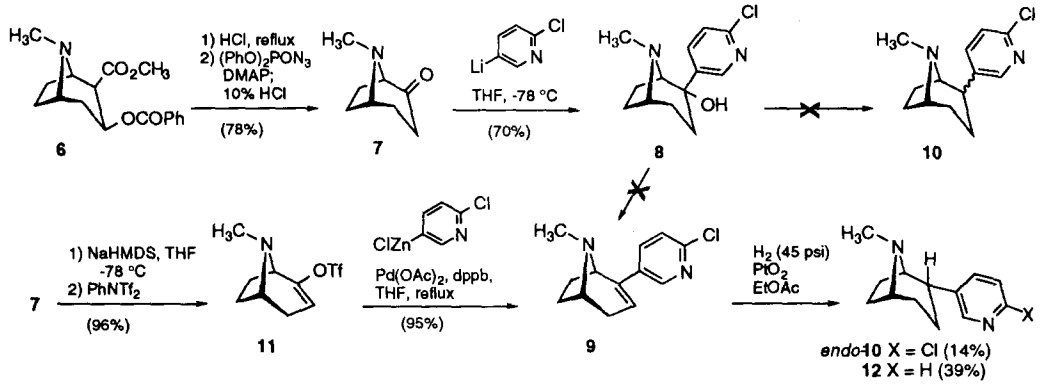


1 **2** **3** **4** **5**

As illustrated in Scheme 1, the enantiomeric syntheses of **4** and **5** were achieved using the enantiopure (*1R*)-2-tropinone (**7**) as the starting material, which was readily available on a large scale, in two steps from (−)-cocaine hydrochloride (**6**).[10] Treatment of ketone **7** with 5-lithio-2-chloropyridine, which was generated by lithiation of 2-chloro-5-iodopyridine[11] with butyllithium at −78 °C, afforded the tertiary alcohol **8** in 70% yield. Attempts to deoxygenate and/or dehydrate **8** were unsuccessful.

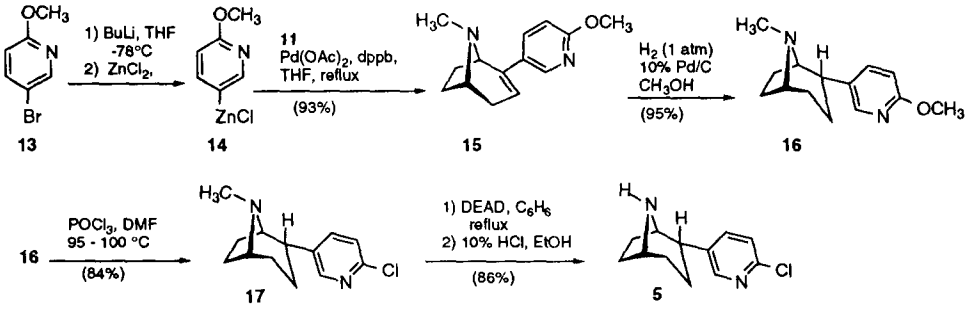
Alternatively, the ketone **7** was converted into the enol triflate **11** by deprotonation with NaHMDS and trapping with *N*-phenyltriflimide (96% yield).[12] The pyridinyl group was then introduced into the 8-azabicyclo[3.2.1]octane ring system by a palladium catalyzed coupling reaction. Treatment of **11** with 2-chloro-5-pyridinyl zinc chloride (prepared *in situ* by transmetalation of the corresponding lithium derivative with zinc chloride) in the presence of $Pd(OAc)_2$ (5 mol %) and 1,4-bis(diphenylphosphine)butane (dppb; 5 mol %) in THF at reflux under argon, afforded **9** in high yield (95%). Subsequent catalytic hydrogenation of **9** with either 10% palladium on carbon or Adam's catalyst resulted in the dechlorination of the pyridine ring (**12**) and formation of *endo*-**10** (Scheme 1).

Scheme 1



To avoid the problem of dechlorination of the pyridine ring, the 2-methoxy-5-pyridinyl derivative was prepared (Scheme 2). Palladium catalyzed coupling reaction of **11** with 2-methoxy-5-pyridinyl zinc chloride (**14**), which was generated *in situ* from the corresponding lithium salt prepared from 5-bromo-2-methoxypyridine (**13**)[13] and butyllithium at – 78 °C, afforded **15** in 93% yield. Subsequent hydrogenation of **15** over 10% palladium on carbon in methanol under ambient conditions furnished the *endo*-product **16** stereoselectively. Conversion of the methoxy group of **16** into the chloro substituent was achieved in straightforward fashion using Vilsmeier conditions. Treatment of **16** with $POCl_3$ in DMF at 95 – 100 °C under argon afforded **17** in 84% yield.[14] Demethylation of **17** with DEAD (diethyl azodicarboxylate) in refluxing benzene, followed by hydrolysis with hydrochloric acid in aqueous ethanol produced the desired compound **5** in 86% isolated yield.[15,16] An attempt to epimerize the *endo*-isomer **17** into the *exo*- isomer by

Scheme 2



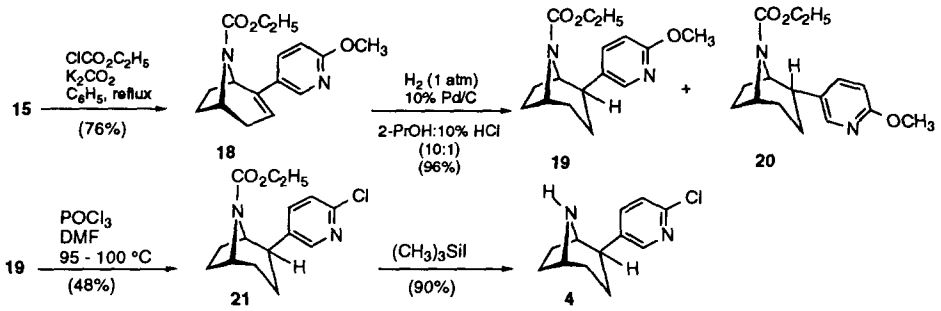
treatment of **17** with *t*-BuOK in refluxing *t*-BuOH was unsuccessful in contrast to the 7-azabicyclo-[2.2.1]heptane ring system.[17]

Considering that the stereoselective formation of the *endo*-product **16** might be the result of coordination of the nitrogen atom of **15** with palladium leading to the observed selectivity for the delivery of hydrogen to the *exo*-face of the carbon-carbon double bond, it was envisaged that protection of the nitrogen atom may lead to the desired *exo*-product. As shown in Scheme 3, demethylation of **15** by treatment with ethyl chloroformate in the presence of a catalytic amount of K_2CO_3 afforded the carbamate **18** in 76% yield. Hydrogenation of **18** over 10% palladium on carbon was carried out in 2-propanol–10% HCl (10:1), to furnish **19** and **20** in 96% yield (Scheme 3, **19**:**20**; 4:1). This result was consistent with previously

described observations reported for the hydrogenation of a 7-tosyl-7-azabicyclo[2.2.1]heptene derivative employed in a recent synthesis of (±)-epibatidine.[18]

Conversion of **19** into **4** was then achieved by treatment of **19** with $POCl_3$ in DMF at 95–100 °C. This furnished the chloropyridine analog **21** in 48% yield. Subsequent deprotection of **21** with iodotrimethylsilane furnished **4** in 90% yield.[16]

Scheme 3



The nicotinic receptor binding and stimulant effects of **4** and **5** were determined and are compared to the activity of (±)-**1**.[7d] As shown in Table 1, the ability of **4** to displace bound [^{3}H]-**1** was significantly lower than that of (±)-**1**, while **5** was 2500-fold less potent than (±)-**1**.[19] In addition, the stimulant activity (arterial pressure response) *in vivo* of **4** and **5** was found to be 30-100-fold less potent than (±)-**1**.[20] These preliminary results suggest that the attachment of the 2β-(6-chloropyridinyl) group to rigid the two carbon bridge of 7-azabicyclo[2.2.1]heptane ring systems and related homologs (i.e.**1** and **2**) is an important structural feature for molecular recognition of epibatidine-related compounds at nicotinic receptors.

Table 1. Inhibition of [^{3}H]Epibatidine Binding at Nicotinic Receptors (IC_{50}) and In Vivo Nicotinic Stimulant Effect on Arterial Pressure (ED_{30}).

Agent	IC_{50} (μg/mL) [range]	Number of Assays[a]	ED_{30} (μg/kg)[b] [range]	Number of Assays[c]
(±)-**1**	0.06 [0.02 - 0.1]	3	0.8 [0.4 - 2.5]	7
4	1.6 [1.4 - 1.8]	2	25 [20 - 30]	5
5	150 [140 - 160]	2	90 [70 - 110]	3

[a]Ligand binding displacement experiments with [^{3}H](±)-epibatidine, using eight concentrations of each test compound were performed using electric organ membranes of the *Torpedo californica* as previously described for [^{3}H]nicotine displacement (ref. 19).

[b]Dose producing a 30% increase of mean arterial pressure.

[c]Spinal rat preparation: Adult Harlane, male albino rats were anesthetized with ethylurea (1.2 g/kg i.p.). The trachea was cannulated for artificial ventilation with an O_2/air mixture. Arterial blood pressure was recorded from a cannulated carotid artery. Injections of the agents were given into a cannulated external jugular vein in volumes of 0.2 mL. After complete transection of the spinal cord at high cervical level the blood pressure was allowed to stabilize for 15 -20 min. "Six-point" assays were made using 3 doses of the test agent and 3 doses of (±)-epibatidine on each animal. Relative potencies were calculated based on 30% increases of the main blood pressure using "Instat" (GraphPad Co., San Diego) statistical program. Note: This test is not specific for peripheral nicotinic receptor stimulation since epibatidine has been shown to produce pressor response, in addition to sympathetic ganglion stimulation, via releasing vasopressin (ref. 20). However, it is useful in the initial characterization of compounds with significantly lower potency than that of epibatidine.

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16. Satisfactory spectral and analytical data were obtained for all new compounds. Selected spectral data of **4**: $[\alpha]_D^{20}$ = (–)-45.5 (c = 0.43 in $CHCl_3$), IR (NaCl) 3433, 1571, 1455 cm^{-1}. ^1H NMR (300 MHz/$CDCl_3$) δ 8.38 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 2.4, 8.1 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 3.53 (m, 2H), 2.74 (d, J = 6.3 Hz, 1H), 1.7–2.1 (m, 8H), 1.45 (m, 1H); MS (e/z) 223 (M^+ + 1, 100), 187 (M^+ – Cl, 15). Selected spectral data of **5**: $[\alpha]_D^{20}$ = (+)-11.8 (c = 0.44 in $CHCl_3$), IR (NaCl) 3413, 1566, 1465, 693 cm^{-1}. ^1H NMR (300 MHz/$CDCl_3$) δ 8.25 (d, J = 1.9 Hz, 1H), 7.52 (dd, J = 1.9, 8.3 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 3.75 (m, 2H), 3.25 (m, 1H), 2.80 (br s, 1H), 1.81–1.99 (m, 4H), 1.65–1.76 (m, 4H); MS (e/z) 223 (M^+ + 1, 100), 187 (M^+ – Cl, 10).
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