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Synthesis of bridged analogs of epibatidine. 3-Chloro-5,7,8,9,9a,10-hexahydro-7,10-methanopyrrolo[1,2-*b*]-2,6-naphthyridine and 2-chloro-5,5a,6,7,8,10-hexahydro-5,8-methanopyrrolo[2,1-*b*]-1,7-naphthyridine

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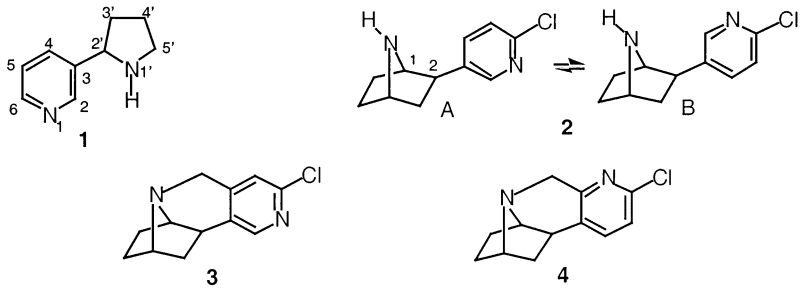
Abstract—The synthesis of conformationally locked analogs of epibatidine are described in which the key step is an intramolecular reductive palladium-catalyzed Heck-type coupling.

The alkaloid nicotine (**1**) interacts with nicotinic acetylcholine receptors (nAChRs) to produce a number of biological effects including antinociception.[1–3] Nicotine (**1**) is composed of a pyridine ring and a *N*-methyl pyrrolidine ring connected via the 3- and 2′-positions, respectively. In 1992, Daly and co-workers reported the isolation and structure determination of epibatidine (**2**, *exo*-2-(2′-chloro-5′-pyridinyl)-7-azabicyclo[2.2.1]heptane) from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*,[4] and along with other laboratories showed that **2** was a potent analgesic acting through the nAChRs.[5,6] There are a number of similarities between nicotine (**1**) and epibatidine (**2**); the most prominent being that both compounds possess a pyridine ring connected to a second ring containing a nitrogen group. Molecular modeling studies show that the nitrogen–nitrogen distance in nicotine (**1**) is 4.8 Å, whereas the nitrogen distance in the two local energy minimum conformations **2A** and **2B** for epibatidine is 4.5 and 5.5 Å.[7–9]

The unique structure of **2** combined with its novel pharmacological activity has attracted considerable interest in the synthesis of **2** and analogs. In previous reports from our laboratory, we have presented improved methods for the synthesis of epibatidine and its analogs.[10–12] Since the synthesis and evaluation of bridged analogs of nicotine have provided insight into the pharmacophore for the nAChR,[13,14] we envisioned that similar studies directed toward epibatidine analogs



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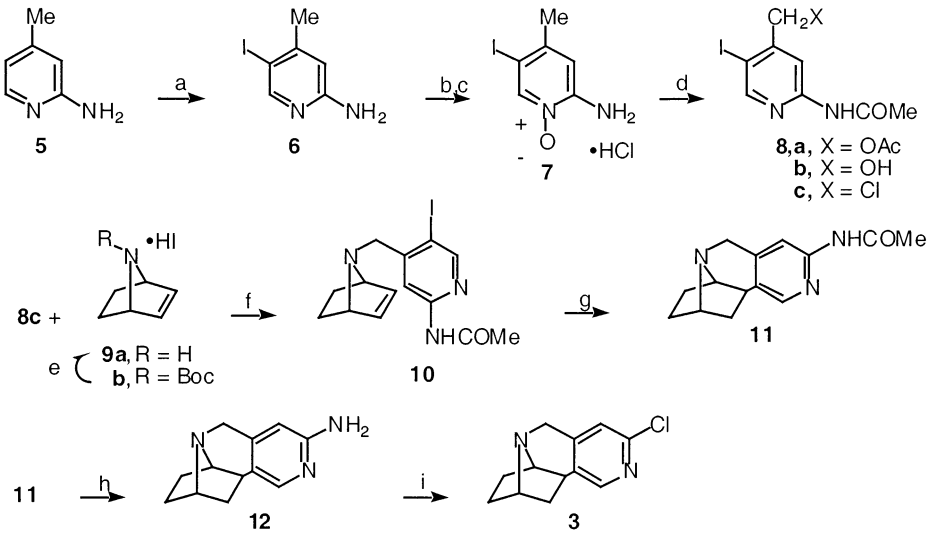
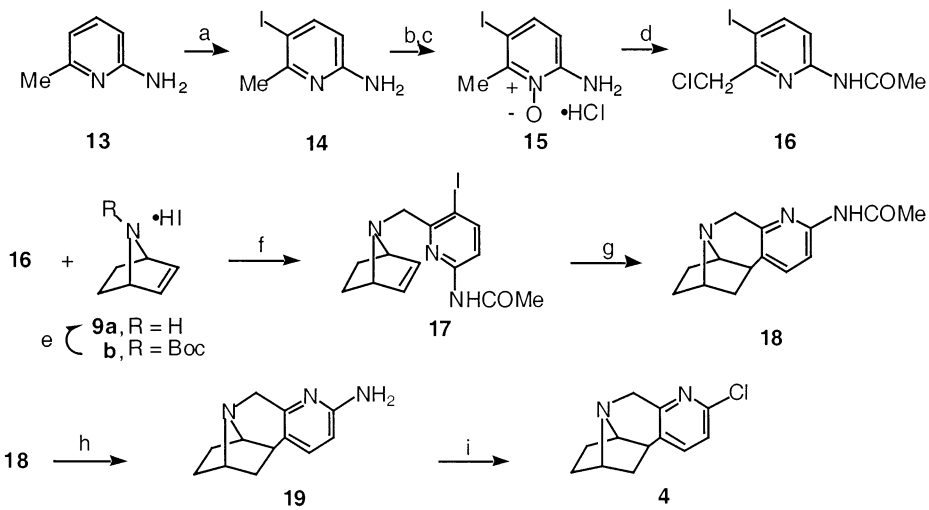
would also provide useful information. Thus, in this study, we report the synthesis of 3-chloro-5,7,8,9,9a,10-hexahydro-7,10-methanopyrrolo[1,2-*b*]-2,6-naphthyridine (**3**) and 2-chloro-5,5a,6,7,8,10-hexahydro-5,8-methanopyrrolo[2,1-*g*]-1,7-naphthyridine (**4**). Compounds **3** and **4** can be viewed as conformationally locked analogs of epibatidine (**2**) and are comparable to the two principle low energy conformations of the freely rotating pyridine ring in epibatidine.[7–9,15] In the 'syn' conformation of epibatidine the N-C1-C2-N dihedral angle is ~42° while in compound **4** the corresponding dihedral angle is ~43°.[16] In the 'anti' conformation of epibatidine the N-C1-C2-N dihedral angle is ~133° while in compound **3** the corresponding dihedral angle is ~138°. The nitrogen-to-nitrogen distances are somewhat shorter in the bridged analogs than in the corresponding epibatidine conformations (3.8 versus 4.6 Å for compound **4** 'syn' epibatidine pair and 5.1 versus 5.6 Å for compound **3** 'anti' epibatidine pair). However, the nitrogen-to-nitrogen distance for compound **3** in particular is within the 4.5 to 5.5 Å range that has been proposed by several authors for the nicotinic pharmacophore.[7–9,15]

The epibatidine analog **3** was synthesized as shown in Scheme 1 starting with 2-amino-4-methylpyridine (**5**). Iodination of **5** using iodine in a periodic, sulfuric, acetic acid mixture afforded a 71% yield of 2-amino-5-iodo-4-methylpyridine (**6**). The structure of **6** was established by analysis of the ^{1}HNMR spectrum, which showed singlets at δ 2.23, 6.46, and 8.27 ppm for the C4-methyl, H-3, and H-6 protons, respectively. Reaction of **6** with meta-chloroperbenzoic acid in acetone gave the *N*-oxide **7**, which was isolated as the hydrochloride salt in 85% yield. We treated the hydrochloride salt of **7** with acetic anhydride in dioxane expecting to obtain the 4-acetoxymethyl or 4-hydroxymethyl compounds **8a** and **8b**, respectively. Surprisingly, 2-acetamido-4-chloromethyl-5-iodopyridine (**8c**) was isolated in 56% yield. Apparently, chloride ion displaced the ace-



Scheme 1. *Conditions*: (a) H_5IO_6, I_2, H_2SO_4, HOAc, H_2O, 80°C; (b) MCPBA; (c) ethereal HCl; (d) Ac_2O, dioxane; (e) $(CH_3)_3$ SiI, $CHCl_3$; (f) NaOMe, MeOH; (g) KO_2CH, $Pd(OAc)_2$, Bu_4NCl, DMF, 90°C; (h) 3N HCl, reflux; (i) $NaNO_2$, conc. HCl



Scheme 2. *Conditions*: (a) H_5IO_6, I_2, H_2SO_4, HOAc, H_2O, 80°C; (b) MCPBA; (c) ethereal HCl; (d) Ac_2O, dioxane; (e) $(CH_3)_3$ SiI, $CHCl_3$; (f) NaOMe, MeOH; (g) KO_2CH, $Pd(OAc)_2$, Bu_4NCl, DMF, 90°C; (h) 3N HCl, reflux; (i) $NaNO_2$, conc. HCl

toxy or hydroxy group from the expected 4-acetoxymethyl or 4-hydroxymethyl intermediate to give **8c**. Alkylation of 7-azabicyclo[2.2.1]hept-2-ene (**9a**),[17] generated from *tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene (**9b**) using trimethylsilyl iodide in chloroform, with **8c** provided the *N*-alkylated product **10** in 43% yield. Two possible approaches for the conversion of **10** to **11** were Heck cyclization[18–20] and radical initiated cyclization.[21,22] We found that intramolecular cyclization of **10** using reductive Heck conditions similar to that used for intermolecular coupling[12] (palladium diacetate, potassium formate, and tetrabutyl ammonium chloride in DMF at 90°C) provided the hexahydro-7,10-methanopyrrolo-2-[1,2-*b*]-2,6-naphthyridine **11** in 45% yield. Hydrolysis of **11** using refluxing 3N hydrochloric acid effected aminolysis of the 3-acetylamino group to give 90% of the 3-amino analog **12**. Diazotization of **12** using sodium nitrite in concentrated hydrochloric acid yielded the desired epibatidine analog **3** in 28% yield.

Epibatidine analog **4** was synthesized from 2-amino-6-methylpyridine (**13**) by a set of reactions exactly analogous to those used to prepare analog **3** (see Scheme 2). The yield in each step was similar to the analogous step in the synthesis of **3**.

Even though the analogs **3** and/or **4** possess several of the structural features in proposed pharmacophores for the $\alpha_4\beta_2$ nAChR, they did not show high affinity for this receptor site. This information provides important insight into the design of new $\alpha_4\beta_2$ nAChR ligands.

In summary, we have developed synthetic methods to prepare the conformationally locked analogs of epibatidine **3** and **4**. The synthetic strategy provides intermediates **12** and **19** that can be manipulated to provide access to additional epibatidine analogs.

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