Pergamon

Tetrahedron 56 (2000) 9227–9232

TETRAHEDRON

Synthesis of 3- and 5-*endo*-(6-Chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hexane and 3-*endo*-(6-Chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hex-5-ene. ABT-594 Analogs

Grant R. Krow,[a,*] Jing Yuan,[a] Yuhong Fang,[a] Michael D. Meyer,[b] David J. Anderson,[b] Jeffrey E. Campbell[a] and Patrick J. Carroll[c]

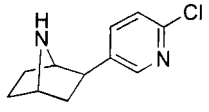
[a]*Department of Chemistry, Temple University, Philadelphia, PA 19122, USA*
[b]*Neuroscience Research, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064-3500, USA*
[c]*Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, USA*

Received 26 May 2000; accepted 25 September 2000

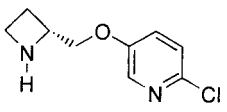
Abstract—Stereoselective photochemical ring closure of a 2-hydroxymethyl-1,2-dihydropyridine has been utilized for the syntheses of 3-*endo*-(6-Cl-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hex-5-ene and hexane analogs of the nicotinic acetylcholine receptor agonist ABT-594. The photochemical ring closure of a 4-hydroxymethyl-1,2-dihydropyridine has been utilized in the preparation of 5-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hexane.

Introduction

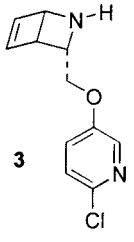
A unique alkaloid epibatidine (**1**) was originally isolated from the skin of the Ecuadoran poison frog, *Epipedobates tricolor*, by Daly and co-workers in 1992.[1,2] A highly potent agonist at nicotinic acetylcholine receptors (nAChRs), epibatidine (**1**) has been found to exhibit an antinociceptive response 200 times greater than L-nicotine[3] and 200–500 times that of morphine.[1] Nicotinic receptor agonists are of potential interest for treating neurological disorders such as Alzheimer's disease[4–7] and Parkinson's disease,[4,8] but there are undesirable toxicity effects (for example, hypertension, neuromuscular paralysis, and seizures) associated with epibatidine (**1**) that preclude its use in humans.[9–11] Through optimization of a series of compounds in a discovery program for nAChR modulators for Alzheimer's disease, Abbott Labs in 1998 discovered ABT-594 [(*R*)-5-(2-azetidinylmethoxy)-2-chloropyridine] (**2**), a nicotinic acetylcholine receptor (nAChR) modulator that exhibits potent antinociceptive activity in animal models of pain.[12–14] ABT-594 was reported to be 30–100 times more potent than morphine in animal models with a significantly improved therapeutic ratio and reduced side effect liabilities relative to epibatidine (**1**).[15] Structure–activity studies of analogs related to ABT-594 (**2**) and epibatidine (**1**) suggest that the *N*-unsubstituted azetidine moiety and the 2-chloro substituent on the pyridine ring are important contributors to potent analgesic activity.[13,14,16] We thus anticipated that the conformationally constrained *endo*-3-pyridyl ether compounds **3**, **4**, **5**, which retain both an azetidine moiety and a 2-chloro substituent on the pyridine ring, would be useful for biological activity studies.



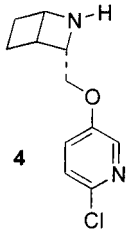
1 Epibatidine



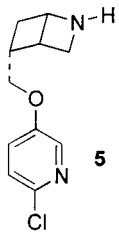
2 ABT-594



3



4



5

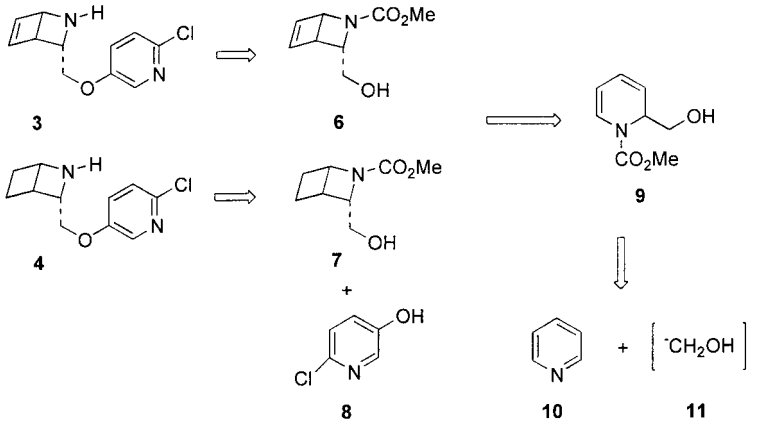
Results

Synthetic approaches to azabicyclo[2.2.0]hexane analogs 3 and 4

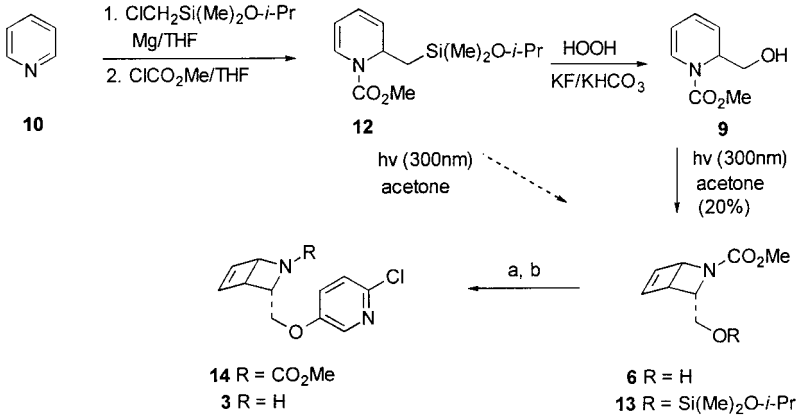
The retrosynthetic analysis of analogs **3** and **4** is shown in Scheme 1. The targets might be easily obtained from the Mitsunobu coupling reaction[17] between 2-chloro-5-hydroxypyridine **8** and 3-*endo*-hydroxymethyl-2-azabicyclo[2.2.0]-hex-5-ene **6** or its reduction product **7**. The key intermediate

Keywords: Mitsunobu reaction; Grignard reagent; stereocontrol; bicyclic heterocyclic compounds.
* Corresponding author. Tel.: +1-215-204-7154; fax: +1-215-204-1532; e-mail: grantkrow@aol.com

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00897-8



Scheme 1.



Scheme 2. (a) 2-chloro-5-hydroxypyridine (**8**), Ph_3P, DEAD (81%); (b) MeLi/LiBr, THF (61%).

compound **6** might be formed by electrocyclic ring closure of dihydropyridine **9**, which might be synthesized by adding the synthetic equivalent of anion **11** to pyridine **10**.

The synthesis of 1,2-dihydropyridine **9** was carried out as shown in Scheme 2. Addition of the Grignard reagent prepared from commercially available chlorodimethylisopropoxysilane to pyridine afforded adduct **12** in quantitative yield by ^{1}H NMR analysis according to the protocol for *N*-methoxycarbonyl 1,2-dihydropyridine synthesis described by Tsuchiya.[18,19] Direct photolysis of dihydropyridine **12** failed to give any desired azabicycle **13**; however dihydropyridine **12** could be oxidized by hydrogen peroxide in the presence of fluoride under basic conditions to give dihydropyridine alcohol **9**.[20] Irradiation of the alcohol **9** provided the key intermediate **6** in a torquoselective manner to give a single 3-*endo*-stereoisomer.[18,19]

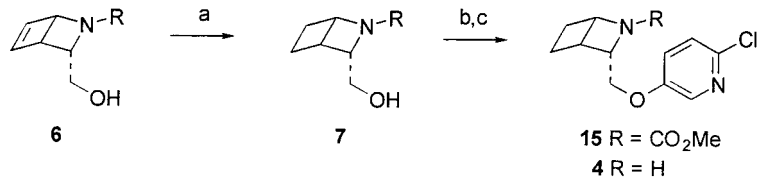
Alcohol **6** was coupled with 2-chloro-5-hydroxypyridine (**8**) according to the Mitsunobu procedure[17] to provide *N*-(methoxycarbonyl)-3-*endo*-pyridoxymethyl analog **14**. The 3-*endo* stereochemistry of **14**, and thus of alcohol **6**, was confirmed by X-ray analysis.[†] The *N*-methoxycarbonyl group of **14** was cleaved by treatment with methyl lithium/lithium bromide ether solution in dry THF[21,22] to give the free amine **3**, to which an equivalent amount of oxalic acid in ethanol was added to give an oxalate salt.

In a parallel set of reactions shown in Scheme 3 the alcohol **6** was reduced using Pd/C catalyzed hydrogenation in ethyl acetate to give alcohol **7**. This alcohol was also coupled with 6-chloro-3-hydroxypyridine (**8**) to provide *N*-(methoxycarbonyl)-3-pyridoxymethyl analog **15**, which was converted to the oxalic acid salt of amine **4**.

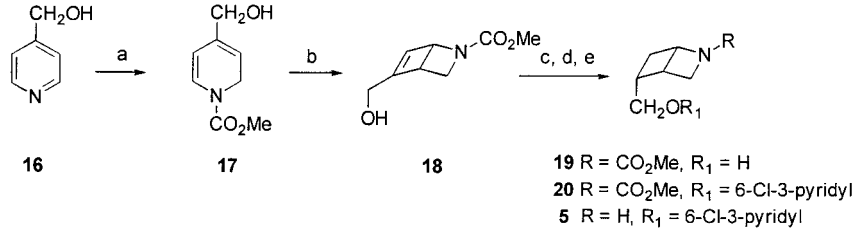
Synthesis of 5-pyridoxymethyl-2-azabicyclo[2.2.0]hexane analog 5

Treatment of commercially available 4-hydroxymethyl pyridine (**16**) with sodium borohydride and methyl chloroformate according to the procedure of Fowler[21,22] afforded *N*-(methoxycarbonyl)-1,2-dihydropyridine **17** as shown in Scheme 4. Irradiation of the crude 17 resulted in electrocyclic ring closure to give *N*-(methoxycarbonyl)-5-hydroxymethyl-2-azabicyclo[2.2.0]hex-5-ene (**18**). Hydrogenation of alcohol **18** would be expected to occur from the open *exo* face to afford 5-*endo*-hydroxymethyl-2-azabicyclo[2.2.0]hexane **19**. This stereochemical assignment was confirmed by a high temperature (70°C) ^{1}H NMR experiment (Table 1). Proton H_{6x} can be distinguished from proton H_{6n} by the absence of coupling between H_{6n}

[†] The atomic co-ordinates are available on request from the Director of the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW. Requests must include the full literature citation for this paper.

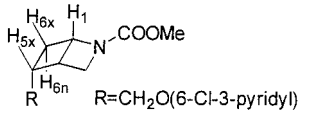


Scheme 3. (a) H_2, Pd-C, EtOAc (59%); (b) 2-chloro-5-hydroxy pyridine **8**, triphenylphosphine, DEAD (51%); (c) MeLi/LiBr, THF (59%).



Scheme 4. (a) NaH_4, $ClCO_2Me$, MeOH; (b) hv (300 nm), acetone (17% from **16**); (c) H_2, PtO_2, EtOAc (53%); (d) 2-Cl-5-OH-pyridine (**8**), Ph_3P, DEAD (44%); (e) MeLi/LiBr, THF (77%).

Table 1. Selected proton–proton couplings for 5-*endo*-pyridoxymethyl analog **19**



Entry	Proton	Shift (δ)	J (H_{6x}) Hz	J (H_{6n}) Hz	J (H_1)[a] Hz	J (H_{5x})[b] Hz
1	H_{6x}	2.57	–	13.5	5.4	10.8
2	H_{6n}	1.98	13.5	–	0	6.3

[a] Proton H_1 is at δ 4.55.
[b] Proton H_5 is at δ 3.02.

and H_1,[23] likely a consequence of the nearly 90° dihedral angle relationship for these protons. The larger 10.8 Hz coupling between H_{6x} and H_{5x} confirms the *cis* relationship of these hydrogens; the *trans* H_{6n} and H_{5x} hydrogens have a smaller 6.3 Hz coupling. Thus, the 5-substituent of **19** must be *endo* oriented.

Mitsunobu coupling of the hydroxyl of **12** with 2-chloro-5-hydroxypyridine (**8**) gave the 3-*endo*-pyridoxymethyl analog **20**. The *N*-methoxycarbonyl group of **20** was cleaved to give the free amine **5**,[21,22] which provided an oxalate salt in 77% yield.

Biological evaluation

The oxalate salts of racemic ABT-594 analogs **3**, **4**, and **5** were evaluated for binding to the high affinity nicotine binding site in rat brain (principally the $\alpha4\beta2$ nAChR subtype) by measuring the ability of these compounds to displace [^{3}H]cytisine.[24] The Ki values are shown in Table 2. The compounds were further evaluated for their ability to elicit ion flux in a human neuroblastoma clonal cell line (IMR-32) natively expressing a sympathetic ganglionic-like nicotinic receptor subtype.[25] A calcium imaging technique was used to measure ion flux, and agonist efficacy was indexed relative to the response of 100 μM nicotine.[26] As shown by the EC_{50} values, the unsaturated 3-*endo*-pyridoxymethyl analog **3** exhibited moderate potency but was only partially efficacious in this assay. The saturated 3-*endo*-pyridoxymethyl isomer **4** exhibited comparable potency, but with substantially greater efficacy. The 5-*endo*-aryl isomer **5** exhibited very weak partial agonist efficacy and was of comparable potency. The 3-*endo*-pyridoxymethyl isomers were evaluated in a mouse hot plate assay of analgesia. The saturated isomer **4** exhibited antinociceptive activity at 20 mg/kg, i.p., and was inactive at lower doses of 6.7 and 2.0 mg/kg. An analgesic response is produced by (−)-nicotine in this assay at 3 mg/kg, i.p. The data in Table 2 indicate that amines **3**–**5** are less effective as nicotine agonists than epibatidine (**1**) or ABT-594 (**2**).

Table 2. Comparative biological data for selected cholinergic channel ligands

Entry	Amine	K_i (nM)	EC_{50} (μM), max. rel. resp. (%)
1	**3**	14	2.8 (16%)
2	**4**	2.3	2.7 (34%)
3	**5**	12	1.0 (11%)
4	(±)-epibatidine (**1**)	0.043[a]	0.007[a]
5	ABT-594 (**2**)	0.04[a,b]	0.20[a,c]
6	(−)-nicotine	0.93	7.94

[a] See Ref. 13.
[b] (±) 0.03.
[c] (±) 0.08.

Experimental

General methods

Thin layer chromatography was performed on precoated plates of silica gel GF 250 microns (Analtec, Inc.). Anhydrous $MgSO_4$ and Na_2CO_3 were used as drying agents. Chemical Grade solvents were used without further treatment except as explained. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR were recorded at 75 MHz in $CDCl_3$, unless otherwise noted, or D_2O solvent. The NMR spectra were complicated by the presence of carbamate rotamers and pairs of ^{13}C NMR lines due to a single carbon, identified using proton–carbon correlation experiments, have been presented in parentheses. High resolution (FAB^+) mass spectra were performed at Drexel University or Merck Research Laboratories, West Point, PA.

***N*-(Methoxycarbonyl)-3-*endo*-hydroxymethyl-2-azabicyclo-[2.2.0]hex-5-ene (6).** A 100 mL, three necked flask was equipped with a pressure-equalizing dropping funnel, a magnetic stirrer, a reflux condenser connected with a nitrogen bubbler. The flask was charged with magnesium turnings (3.16 g, 130 mmol) that were dried under a rapid stream of argon with a heat gun. After the flask was cooled to room temperature, the rate of argon flow was reduced. Several milliliters of a solution of (isopropoxydimethylsilyl)methyl chloride (22.34 g, 130 mmol) in dry THF (65 mL) and about 1 crystal of I_2 were added. The mixture was heated until an exothermic reaction started. The remaining solution was added dropwise at room temperature over ca. 20 min at such a rate as to maintain a gently exothermic reaction. After the addition was complete, the tan-gray mixture was heated at reflux for 0.5 h and then was cooled to 0°C to −5°C with an ice-salt bath. A solution of freshly distilled pyridine (7.91 g, 100 mmol) in dry THF (20 mL) was added dropwise with stirring over 20 min. The resultant mixture was stirred for another 20 min, and then a solution of methyl chloroformate (9.74 g, 100 mmol) in THF (100 mL) was added dropwise at such a rate as to maintain the temperature below −5°C. The solution was stirred at −5°C for another two hours, at room temperature for 1 h, and then was hydrolyzed by addition of H_2O (20 mL). The organic layer was separated. The aqueous layer was extracted with diethyl ether (4×10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated to give a yellow oil **12**; ^1H NMR δ 6.56 (d, J=7.5 Hz, 1H), 5.82 (m, 1H), 5.64 (m, 1H), 5.23 (m, 1H), 4.95–4.84 (br, 1H), 3.98 (m, 1H), 3.76 (s, 3H), 1.14 and 1.12 (two d, J=3.9 Hz, 6H), 0.94–0.79 (br, 2H), 0.13 (s, 6H); ^{13}C NMR δ 157.6, 124.8, (124.2 and 123.9), (120.6 and 120.1), (105.9 and 105.7), 64.9, 52.9, 49.5, 25.7, (23.7 and 22.8), (−0.25 and −0.55). To the yellow oil **12**, in a 500 mL round-bottomed flask equipped with a magnetic stirrer and a thermometer, there was added THF (100 mL), methanol (100 mL), potassium bicarbonate (10 g, 100 mmol), and potassium fluoride (11.7 g, 200 mmol). To this stirred mixture there was added 50% hydrogen peroxide (7 mL, 120 mmol) in one portion at room temperature. A somewhat cloudy organic layer and a milky-white, heavy inorganic layer resulted. The mixture was stirred at room temperature for 5 h until no starting material remained. The remaining H_2O_2 was decomposed by careful dropwise addition of an aqueous 50% solution of sodium thiosulfate with stirring over 10 min until a negative starch-iodide test was observed. A white precipitate formed and diethyl ether (100 mL) was added to ensure further precipitation. The mixture was filtered with suction, and the filter cake was washed with diethyl ether (3×20 mL). The combined filtrate and washes were concentrated until much of the water has been removed. The remaining oil was diluted with diethyl ether (100 mL), transferred to a separatory funnel, and washed with brine to remove the remaining water. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give hydroxymethyl-1,2-dihydropyridine **9** as a yellow oil (22.9 g), which was directly photolyzed in acetone (435 g, 19 g/g of **9**) at 300 nm for 3–4 days to give a crude product, which upon purification by silica gel column chromatography (diethyl ether–hexane=2:1) afforded bicyclic alkene **6** as a yellow oil (2.31 g, 19.0% from pyridine), R_f=0.20 (diethyl ether–hexane=2:1); ^1H NMR δ 6.39 and 6.30 (two s, 2H), 4.69 (br, 1H), 4.41 (br, 1H), 4.30 (m, 1H), 3.78–3.67 (br, 2H), 3.61 (s, 3H), 3.48 (m, 1H); ^{13}C NMR δ 157.6, 141.7, 140.5, 63.9, 63.3, 62.3, 52.3, 40.8; HRMS Calcd for $C_8H_{12}NO_3$ (M+1): 170.0817, found 170.0818.

***N*-(Methoxycarbonyl)-3-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hex-5-ene (14).** A 50 mL, three-necked flask was equipped with a pressure-equalizing dropping funnel, magnetic stirrer, and low temperature thermometer. The flask was charged with **6** (114.8 mg, 0.68 mmol), 2-chloro-5-hydroxypyridine **8** (58.6 mg, 0.45 mmol), Ph_3P (180 mg. 0.68 mmol), and THF (3 mL). A solution of DEAD (118.2 mg, 0.68 mmol) in THF (2 mL) was added dropwise to the mixture at 5°C, and then the mixture was stirred at room temperature until no starting material remained. The solvent was removed and the residue was purified by silica gel column chromatography (ether–hexane=1:1) to give the product **14** as a colorless liquid (50.8 mg, 81.4%), R_f=0.36 (ether–hexane=2:1); ^1H NMR δ 8.02 (br, 1H), 7.20 and 7.15 (m, 2H), 6.54 and 6.37 (two s, 2H), 4.84 (br, 1H), 4.45 (m, 1H), 4.31–4.03 (br, 2H), 3.66 (s, 3H), 3.77–3.66 (br, 1H); ^{13}C NMR δ 156.4, 154.0 and 152.9, 142.7, 140.6, 141.2, (137.4 and 136.9), (126.2 and 124.7), 124.5, 66.4, 63.6, 56.9, 52.4, 41.6; HRMS Calcd for $C_{13}H_{14}N_2O_3^{35}Cl$ (M+1): 281.0693, found 281.0691, $C_{13}H_{14}N_2O_3^{37}Cl$ (M+1): 283.0663, found 283.0668.

Preparation of the oxalate salt of 3-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo [2.2.0]hex-5-ene (3). To a CH_3Li/LiBr (579.4 μL of 1.5 M ether solution, 0.87 mmol) solution in dried THF (1.3 mL) was added **14** (69.7 mg, 0.25 mmol) in THF (0.5 mL) at 0°C. The resultant mixture was stirred at 0°C until no starting material remained (ca. 60 min). Water was added, and two layers were separated. The aqueous layer was extracted with diethyl ether (5×5 mL). The combined organic layers were washed with brine, dried over Na_2CO_3, filtered, and concentrated to give the crude free amine **3** (33.9 mg, 61.4%).

To the crude amine solution in ethanol (0.5 mL) there was added oxalic acid (13.7 mg, 0.15 mmol). The resultant solution was cooled, and ether was added to give a precipitate.

After removal of solvent in vacuo, the residue was extracted with ether to leave the salt of amine **3** (41.4 mg, 53.4%); ^{1}H NMR (500 MHz, D_2O) δ 8.01 (d, J=3.0 Hz, 1H), 7.42 (dd, J=9.0, 3.0 Hz, 1H), 7.38 (d, J=9.0 Hz, 1H), 6.70 (br, 1H), 6.46 (br, 1H), 5.05 (br, 1H), 4.83 (br, 1H), 4.43 (dd, J=11.0, 4.5 Hz, 1H), 4.27 (m, 1H), 3.88 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 164.4, 153.6, 145.2, 137.7, 142.4, 136.4, 126.5, 125.2, 66.6, 61.9, 56.2, 42.7; HRMS of 3 Calcd for $C_{11}H_{12}N_2O^{35}Cl$ (M+1): 223.0633, found 223.0604; $C_{11}H_{12}N_2O^{37}Cl$ (M+1): 225.0604, found 225.0574.

***N*-(Methoxycarbonyl)-3-*endo*-hydroxymethyl-2-azabicyclo-[2.2.0]hexane (7).** To a solution of **6** (364.7 mg, 2.16 mmol) in EtOAc (40 mL) there was added Pd-C (180 mg), the resulting solution was stirred at room temperature under a H_2 balloon for 4 h, at which time no starting material remained. The solution was filtered, and solvent was removed in vacuo to give a colorless oil (327.9 mg), which was purified by silica column chromatography (ether–hexane=2:1) to give the product **7** as a colorless oil (218.8 mg, 59.3%), R_f=0.38 (ether–hexane=3:1); ^{1}H NMR δ 4.64 (m, 1H), 4.51 (m, 1H), 4.45 (br, 1H), 4.25 (m, 1H), 3.72 (m, 1H), 3.67 (s, 3H), 2.99 (br, 1H), 2.48 (br, 1H), 2.25 (br, 3H); ^{13}C NMR δ 157.6, 67.1, 64.0, 61.8, 52.4, 33.7, 29.4, 19.2; HRMS Calcd for $C_8H_{14}NO_3$ (M+1): 172.0974, found 172.0979.

***N*-(Methoxycarbonyl)-3-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hexane (15).** A 50 mL, three necked flask was equipped with a pressure-equalizing dropping funnel, magnetic stirrer, and low temperature thermometer. The flask was charged with **7** (194.1 mg, 1.13 mmol, crude product including 115.1 mg pure **7**), 2-chloro-5-hydroxy-pyridine (**8**) (176.2 mg, 1.35 mmol), triphenyl phosphine (360.5 mg. 1.35 mmol), and THF (5 mL). A solution of DEAD (236.9 mg, 1.35 mmol) in THF (3 mL) was added dropwise to the mixture at 0°C, and the mixture was stirred at room temperature until no starting material remained. The solvent was removed and the residue was purified by silica gel column chromatography (ether–hexane=2:1) to give the product **15** as a colorless oil (97.5 mg, 51.3%), R_f=0.36 (ether–hexane=2:1); ^{1}H NMR δ 8.06 (d, J=1.5, 1H), 7.26 –7.25 (br, 2H), 4.81 (dd, J=13.4, 6.9 Hz, 1H)), 4.59 (br, 1H), 4.55–4.42 (br, 2H), 3.14 (m, 1H), 2.61–2.50 (br, 1H), 2.37–2.28 (br, 2H), 2.26–2.21 (br, 1H); ^{13}C NMR δ 156.7, (154.0 and 152.7), (142.8 and 141.3), (137.2 and 136.7), (126.3 and 124.9), 124.5, 65.7, 62.1, 61.9, 52.3, 34.3, 29.5, 18.9; HRMS Calcd for $C_{13}H_{16}N_2O_3^{35}Cl$ (M+1): 283.0849, found 283.0851, $C_{13}H_{16}N_2O_3^{37}Cl$ (M+1): 285.0820, found 285.0836.

Preparation of the oxalate salt of 3-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo [2.2.0]hexane (4). Using the same method described for amine **3**, the oxalate salt of **4** (60.4 mg, 58.5%) was obtained from **15** (92.8 mg, 0.33 mmol); ^{1}H NMR (300 MHz, D_2O) δ 8.06 (d, J=1.2 Hz, 1H), 7.49 (dd, J=1.2, 8.7 Hz, 1H), 7.39 (d, J=8.7 Hz, 1H), 5.10 (m, 1H), 4.74–4.66 (br, 2H), 4.50–4.45 (br, 1H), 3.36–3.30 (br, 1H), 2.86–2.73 (br, 1H), 2.64–2.45 (br, 3H); ^{13}C NMR (75 MHz, D_2O) δ 163.9, 153.7, 142.3, 136.3, 126.7, 125.3, 65.8, 60.8 (2C), 35.8, 26.0, 19.1; HRMS of **4** Calcd for $C_{11}H_{14}N_2O^{35}Cl$ (M+1): 225.0789, found 225.0775; $C_{11}H_{14}N_2O^{37}Cl$ (M+1): 227.0760, found 227.0746.

***N*-(Methoxycarbonyl)-5-hydroxymethyl-2-azabicyclo-[2.2.0]hex-5-ene (18).** To the solution of 4-pyridylcarbinol **16** (5.46 g, 50 mmol) in methanol (40 mL) at −30°C there was added sodium borohydride (2.4 g, 63 mmol). After the resulting solution was cooled to −72°C, a solution of methyl chloroformate (4.7 g, 50 mmol) in diethyl ether (13 mL) was added dropwise under argon balloon so that the temperature never exceed −69°C. The resulting mixture was stirred an additional 2 h. After the temperature was raised to −40°C, ice water was poured into it. The mixture was extracted with ether (5×50 mL). The combined extracts were washed with water (4×40 mL), brine, and dried over sodium carbonate. The solvent was removed in vacuo to give the crude *N*-(methoxycarbonyl)-5-hydroxymethyl-1,2-dihydropyridine **17** (4.87 g, 57.6%). Without further purification, a 3% acetone (91 g) solution of crude **17** (4.87 g) was irradiated for 68 h at 300 nm. Solvent was removed in vacuo to give the crude product, which upon silica gel flash column chromatography (diethyl ether–hexane 2:1) gave product **18** (1.47 g, 17%) as a yellow oil (R_f=0.33, diethyl ether); ^{1}H NMR δ 6.33 and 6.27 (br, 1H), 4.65 (br, 1H), 4.15 (s, 2H), 3.87 (m, 1H), 3.60 (s, 3H), 3.44 (m, 1H), 3.33 (m, 1H); ^{13}C NMR δ 157.7, 156.0, 131.8, (62.1 and 61.4), 59.3, 52.2, (49.4 and 48.7), 36.8; HRMS Calcd for $C_8H_{11}NO_3Na$ (M+22): 192.0637, found 192.0637.

***N*-(Methoxycarbonyl)-5-*endo*-hydroxylmethyl-2-azabicyclo-[2.2.0]hexane (19).** To the solution of alcohol **18** (0.3 g, 1.8 mmol) in ethyl acetate (3 mL) there was added platinum oxide (45 mg). The mixture was stirred at room temperature under a hydrogen balloon for 3 h until no starting material remained. The mixture was filtered, and the solvent was removed in vacuo to give the crude product, which was purified by silica gel chromatography (diethyl ether–hexane 4:1) to give reduced alcohol **19** (160 mg, 52.7%), R_f=0.24 (diethyl ether); ^{1}H NMR (70°C) δ 4.55 (br, 1H), 4.25 (dd, J=2.1, 9.6 Hz, 1H), 4.20 (m, 1H), 3.94 (dd, J=9.3, 10.8 Hz, 1H), 3.80 (dd, J=6.6, 10.8 Hz, 1H), 3.65 (s, 3H), 3.02 (m, 1H), 2.85 (m, 1H), 2.57 (ddd, J=5.4, 10.8, 13.5 Hz, 1H), 1.98 (dd, J=6.3, 13.5 Hz, 1H), 1.67 (s, 1H); ^{13}C NMR δ 155.8, 62.4, (60.6 and 60.2), 52.1, (51.2 and 50.2), 35.0, 32.1, (31.6 and 31.2); HRMS Calcd for $C_8H_{14}NO_3$ (M+1): 172.0974, found 172.0972.

***N*-(Methoxycarbonyl)-5-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo[2.2.0]hexane (20).** To the mixture of 2-chloro-5-hydroxypyridine (**8**) (139.8 mg, 1.08 mmol), alcohol **12** (154 mg, 0.90 mmol), and Ph_3P (283.2 mg, 1.08 mmol) in THF (3 mL) at −3°C there was added dropwise DEAD (188.0 mg, 1.08 mmol) in THF (2 mL). The resulting mixture was stirred for 16 h at 25°C. The solvent was removed, and crude product was purified by silica gel column chromatography (diethyl ether–hexane 2:3) to provide pure 20 (0.11 g, 43.5%) at R_f=0.52 (diethyl ether); ^{1}H NMR δ 8.05 (s,1H), 7.20 (br, 2H), 4.60 (br, 1H), 4.31–4.16 (br, 4H), 3.66 (s, 3H), 3.17 (br, 2H), 2.70 (m, 1H), 2.12 (m, 1H); ^{13}C NMR δ 156.0, 154.0, 142.7, 136.6, 124.8, 124.4, 68.4, (60.9 and 60.5), 52.2, (51.3 and 50.4), 32.4, (31.7 and 31.3), 29.7; HRMS Calcd for

$C_{13}H_{15}N_2O_3Na^{35}Cl$: (M+22): 305.0669, found 305.0659; $C_{13}H_{15}N_2O_3Na^{37}Cl$ (M+22): 307.0639, found 307.0642.

Preparation of the oxalate salt of 5-*endo*-(6-chloro-3-pyridoxy)-methyl-2-azabicyclo [2.2.0]hexane (5) To the solution of MeLi/LiBr (1.5 M in ether, 760 μL, 1.15 mmol) in dry THF (1 mL) at −5 to −10°C there was added slowly the *N*-methoxycarbonyl adduct **20** (93 mg, 0.33 mmol) in THF (1 mL). The reaction mixture was stirred for 20 min in a cold bath, and H_2O (1 mL) was added followed by brine (1 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3×5 mL). The combined organic extracts were dried over anhydrous sodium carbonate, filtered, and the solvent was removed in vacuo to give free amine **5**, which was dissolved in ethanol (0.5 mL). Anhydrous oxalic acid (29.72 mg, 0.33 mmol) was added to generate salt, and any organic residue was removed by washing the salt with diethyl ether (2 mL) and $CHCl_3$ (2 mL) to give (80 mg, 77.3%) of the oxalate salt of amine **5**. ^{1}H NMR (Methanol-*d*) δ 8.13 (d, 1H), 7.52 (m, 1H), 7.42 (d, 1H), 5.04 (br, 5H), 3.43 (br, 1H), 3.33 (m, 1H), 2.98 (m, 1H), 2.83 (m, 1H); ^{13}C NMR δ 163.6, 154.5, 142.2, 136.4, 125.2, 124.5, 68.4, 58.6, 47.3, 35.9, 32.6, 28.0; HRMS of 5 Calcd for $C_{11}H_{14}N_2O^{35}Cl$ (M+1): 225.0789, found 225.0802; $C_{11}H_{14}N_2O^{37}Cl$ (M+1): 227.0760, found 227.0776.

Acknowledgements

The authors are indebted to Zilun Hu and George Kemmerer of Temple University and James P. Guare and Charles W. Ross III of Merck Research Laboratories for helpful suggestions and assistance. A Temple University Grant-in-aid supported this work.

References

1. Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475–3478.
2. Badio, B.; Daly, J. W. *Mol. Pharmacol.* **1994**, *45*, 563–569.
3. Damaj, M. I.; Creasy, K. R.; Grove, A. D.; Rosecrans, J. A.; Martin, B. R. *Brain Res.* **1994**, *664*, 34–40.
4. Baron, J. A. *Br. Med. Bull.* **1996**, *52*, 58–73.
5. Lee, N. *Neuroepidemiology* **1994**, *13*, 131–144.
6. van Duijin, C. M.; Hofman, A. *Br. Med. J.* **1991**, *302*, 1491–1494.
7. For related references, see Decker, M. W.; Brioni, J. D. Neuronal Nicotinic Receptors: Potential Treatment of Alzheimer's Disease with Novel Cholinergic Channel Modulators. In *Pharmacological Treatment of Alzheimer's Disease: Molecular and Neurobiological Foundations*; Brioni, J. D., Decker, M. W. Eds.; Wiley-Liss: New York, 1997; p 433.
8. Smith, C. J.; Giacobini, E. *Rev. Neurosci.* **1992**, *3*, 25–43.
9. Sullivan, J. P.; Decker, M. W.; Brioni, J. D.; Donnelly-Roberts, D.; Anderson, D. J.; Bannon, A. W.; Kang, C.-H.; Adams, P.; Piattoni-Kaplan, M.; Buckley, M.; Gopalakrishnan, M.; Williams, M.; Arneric, S. P. *J. Pharmacol. Exp. Ther.* **1994**, *271*, 624–631.
10. Bonhaus, D. W.; Bley, K. R.; Broka, C. A.; Fontana, D. J.; Leung, E.; Lewis, R.; Shieh, A.; Wong, E. H. F. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 1199–1203.
11. Rao, T. S.; Correa, L. D.; Reid, R. T.; Lloyd, G. K. *Neuropharmacology* **1996**, *35*, 393–405.
12. Bannon, A. W.; Decker, M. W.; Holladay, M. W.; Curzon, P.; Donnelly-Roberts, D.; Puttfarcken, P. S.; Bitner, R. S.; Diaz, A.; Dickenson, A. H.; Porsolt, R. D.; Williams, M.; Arneric, S. P. *Science* **1998**, *279*, 77–81.
13. Holladay, M. W.; Wasicak, J. T.; Lin, N.; He, Y.; Ryther, K. B.; Bannon, A. W.; Buckley, M. J.; Kim, D. J. B.; Decker, M. W.; Anderson, D. J.; Campbell, J. E.; Kuntzweiler, T. A.; Donnelly-Roberts, D. L.; Piattoni-Kaplan, M.; Briggs, C. A.; Williams, M.; Arneric, S. P. *J. Med. Chem.* **1998**, *41*, 407–412.
14. Holladay, M. W.; Decker, M. W. *Adv. Med. Chem.* **2000**, *5*, 85–113.
15. Lynch, J. K.; Holladay, M. W.; Ryther, K. B.; Bai, H.; Hsiao, C.; Morton, H. E.; Dickman, D. A.; Arnold, W.; King, S. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2791–2794.
16. Holladay, M. W.; Bai, H.; Li, Y.; Lin, N.; Daanen, J. F.; Ryther, K. B.; Wasicak, J. T.; Kincaid, J. F.; He, Y.; Hettinger, A.; Huang, P.; Anderson, D. J.; Bannon, A. W.; Buckley, M.; Campbell, J. E.; Donnelly-Roberts, D. L.; Gunther, K. L.; Kim, D. J. B.; Kuntzweiler, T. A.; Sullivan, J. P.; Decker, M. W.; Arneric, S. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2797–2802.
17. Mitsunobu, O. *Synthesis* **1981**, *1*, 1–28.
18. Kurita, J.; Iwata, K.; Sakai, H.; Tsuchiya, T. *Chem. Pharm. Bull.* **1985**, *33*, 4572–4580.
19. Kurita, J.; Iwata, K.; Tsuchiya, T. *Chem. Pharm. Bull.* **1987**, *35*, 3166–3174.
20. Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth. Coll.* **1983**, *8*, 315–321.
21. Beeken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, I. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677–6682.
22. Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321–1323.
23. Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558–8560.
24. Linn, N. H.; Gunn, D. E.; Ryther, K. B.; Garvey, D. S.; Donnelly-Roberts, D. L.; Decker, M. W.; Brioni, J. D.; Buckley, M. J.; Rodrigues, A. D.; Marsh, K. G.; Anderson, D. J.; Buccafusco, J. J.; Pendergast, M. A.; Sullivan, J. P.; Williams, M.; Arneric, S. P.; Holladay, M. W. *J. Med. Chem.* **1997**, *40*, 385–390.
25. Lukas, R. J. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 294–302.
26. Kuntzweiler, T. A.; Arneric, S. P.; Donnelly-Roberts, D. L. *Drug Dev. Res.* **1998**, *44*, 14–20.