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Synthesis of 5- and 6-(6-Chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexanes. Epibatidine Analogs

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Abstract—Synthetic routes to *vicinal*-6-(6-Cl-3-pyridyl)- and *distal*-5-(6-Cl-3-pyridyl)-2-azabicyclo-[2.2.0]hexane analogs of the potent nicotinic receptor agonist epibatidine are described. Both *exo*-regioisomers are available from a readily available 2-azabicyclo[2.2.0]hex-5-ene by way of stereoselective reductive Heck addition of the 6-Cl-3-pyridyl moiety. Stereochemical inversion of the 6- and 5-aryl groups provides entry to the *endo* isomers.

Introduction

Daly and coworkers[1] isolated epibatidine (**1**) in 1992 from the skin of the Ecuadorian frog, *Epipedobates tricolor*. A highly potent agonist at nicotinic receptors (nAChRs), epibatidine (**1**) has been found to exhibit an antinociceptive response 200 times greater than L-nicotine[2] and 200–500 times that of morphine.[1] Nicotinic receptor agonists are of potential interest for treating neurological disorders such as Alzheimer's and Parkinson's diseases,[3] but there are undesirable toxicity effects associated with epibatidine (**1**) that preclude its use in humans.[4–6] Thus, there have been numerous attempts to synthesize analogs of the 7-azabicyclo[2.2.1]heptane structure of epibatidine in the hope of finding moieties with reduced toxicities, but high antinociceptive activity.[5–20] Among those analogs which retain the 6-chloro-3-pyridyl substitutent attached to an azabicyclic ring,[6–16] 2-azabicyclo[2.2.1]heptane **2** and **3** have been prepared by the groups of Malpass[6,7] and Maier.[8] We have described activities of the *syn*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octanes **4** and **5**, the higher homologues of structures **2** and **3** by virtue of an additional methylene unit in the one-carbon bridge,[9] and also the *vicinal* and *distal* homologues of epibatidine (**1**) in the nitrogen containing bridge. Structure **4** was found to display an ED_{50} within a factor of 4 relative to epibatidine in a mouse tail-flick assay. We anticipated that *endo*-aryl-2-azabicyclo-[2.2.0]hexane homologues **6** and **7**, which retain elements of structural rigidity without the methano- or ethano-bridges, would be useful for biological activity studies (Fig. 1).

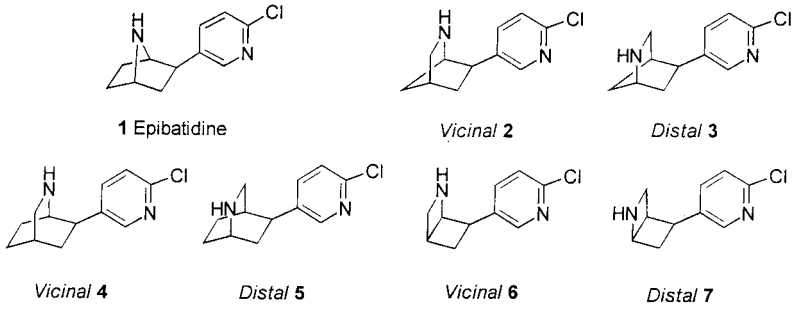

Fig. 1.

Keywords: Heck reaction; stereocontrol; bicyclic heterocyclic compounds; amines.
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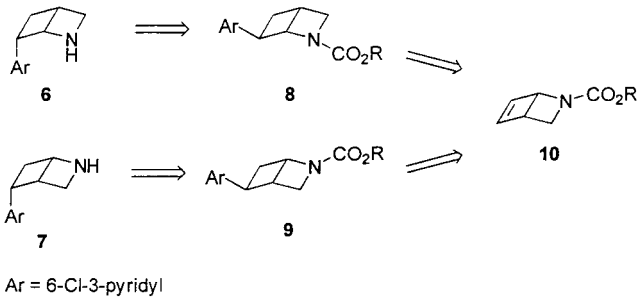
Results

Synthetic approaches to azabicyclo[2.2.0]hexane analogs 6 and 7

The retrosynthetic analysis shown in Scheme 1 envisioned that the desired 6-*endo*-aryl- and 5-*endo*-aryl-2-azabicyclo[2.2.0]hexane analogs **6** and **7** might be formed by isomerization of 5-*exo*-aryl- and 6-*exo*-aryl-2-azabicyclo[2.2.0]hexanes **8** and **9**. These might be synthesized via a reductive Heck protocol from readily available *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **10**.[21,22] Although the Heck reaction was unsuccessfully applied to the preparation of the 2-azabicyclo[2.2.2]octane homologues **4** and **5**,[9] it was used successfully in the preparation of the azabicyclo[2.1.1]heptane isomers **2** and **3**.[6–8]

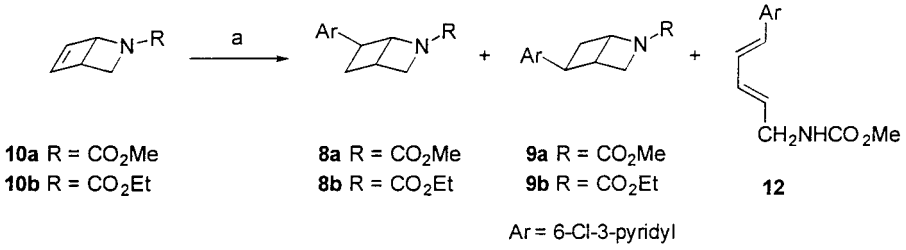
The palladium catalyzed reductive coupling protocol described by Clayton and Regan[23] was used to prepare *N*-alkoxycarbonyl adducts **8** and **9** (Scheme 2). When 2-chloro-5-iodopyridine (**11**) and *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-enes **10** were treated under reductive Heck conditions as shown in Table 1, variable mixtures of 6-*exo*-aryl- and 5-*exo*-aryl-2-azabicyclo[2.2.0]hexane isomers **8** and **9** were isolated by column chromatography in combined isolated yields of 28–58%. We were unable to obtain reproducible isomer ratios, even under apparently identical conditions. However, the highest overall yield was obtained with the *N*-methoxycarbonyl protecting group of alkene **10a** (Entry 5) at temperatures near 60–65°C. A third fluorescent compound formed in these reactions was the butadiene **12**, isolated in 12.4% yield from trial 1, but ignored in subsequent isolations. A proposed mechanism for formation of diene **12** is shown in Scheme 3. Attack of a nucleophilic species upon a palladium intermediate **13** might give a cyclobutene **14**, which could undergo disrotatory ring opening under the reaction conditions.[24]



Scheme 1.

The structural assignment of *N*-(ethoxycarbonyl)-6-*exo*-aryl isomer **8b** was verified by a high temperature (75°C) NMR experiment. The absence of coupling between H_{6n} at δ 3.84 and the neighboring bridgehead H_1 at δ 4.48 is as expected for a nearly 90° dihedral angle relationship between these two protons.[25] The H_{6n} proton appeared surprisingly as a triplet (J=8.1 Hz), suggesting that the cyclobutane ring is twisted so that the dihedral angle relationships between H_{6n} and both adjacent H_5 protons are almost identical. The bridgehead proton H_1 appeared as a doublet (J=4.8 Hz) coupled to H_4. The *N*-(methoxycarbonyl)-6-aryl analog **8a** was used in subsequent experiments.

The structural assignment of *N*-(ethoxycarbonyl)-5-*exo*-aryl isomer **9b** was verified by a high temperature (75°C) NMR

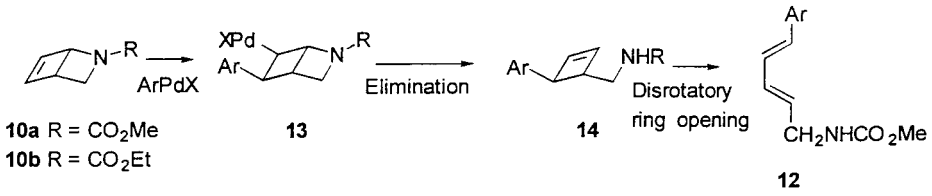


Scheme 2. (a) $Pd(OAc)_2$, Ph_3P, DMF, piperidine, HCOOH and 2-Cl-5-I-pyridine (**11**).

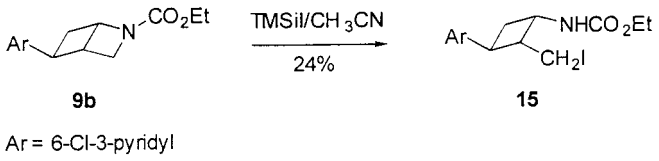
Table 1. Reductive Heck reactions of 2-chloro-5-iodopyridine (**11**) with 2-azabicyclo-[2.2.0]hexenes **10a** and **10b** (palladium acetate, triphenylphosphine, DMF, piperidine, HCOOH; time=24 h unless otherwise noted)

Entry	Starting material	R	Temperature (°C)	Product **8**	6-*exo*-Ar Yield (%)[a]	Product **9**	5-*exo*-Ar Yield (%)
1	**10a**	CO_2Me	70–74	**8a**	20	**9a**	18.5[b]
2	**10a**	CO_2Me	65–68	**8a**	20.5	**9a**	16
3	**10a**	CO_2Me	60–65	**8a**	20.5	**9a**	8
4	**10a**	CO_2Me	60–65	**8a**	22	**9a**	19.5
5	**10a**	CO_2Me	60–65	**8a**	14.5	**9a**	44
6	**10a**	CO_2Me	60	**8a**	10.5	**9a**	17.5
7	**10b**	CO_2Et	70–72	**8b**	4.5	**9b**	26
8	**10b**	CO_2Et	70	**8b**	7	**9b**	21.5
9	**10b**	CO_2Et	70[c]	**8b**	17	**9b**	23

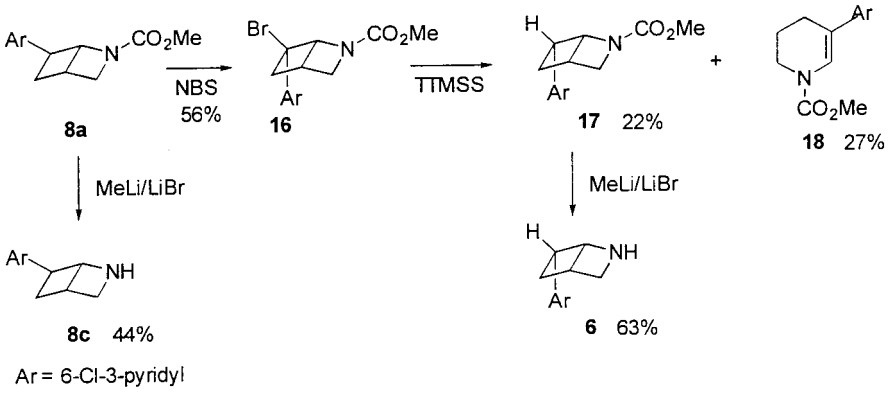
[a] Yields are of isolated material after chromatography.
[b] A 12.4% yield of diene **12** was also isolated.
[c] Time=12 h.



Scheme 3. A suggested mechanism for formation of diene **12**.



Scheme 4.



Scheme 5.

experiment. The H_{5n} proton at δ 3.79 (dt) shows a small coupling, J=3 Hz, with the neighboring bridgehead H_4 at δ 2.95.[25] The larger triplet coupling (J=7.8 Hz) suggests the cyclobutane ring of **9b** is twisted so that the dihedral angle relationships between H_{5n} and both adjacent H_6 protons are nearly identical. The 5-*exo*-aryl stereochemical assignment to **9b** was verified upon its reaction with trimethylsilyl iodide[16] in acetonitrile at 25°C to give the novel azetidine ring-opened cyclobutane **15** (Scheme 4), whose stereochemistry was confirmed by X-ray analysis.† The *N*-(methoxycarbonyl)-6-aryl isomer **9a** was used in subsequent experiments.

Conversion of the *exo-vicinal* isomer 8a to the *endo-vicinal* isomer 6

In order to invert the stereochemistry of the 6-*exo*-aryl substituent of **8a**, the adduct was brominated at the benzylic position using *N*-bromosuccinimide/AIBN in refluxing CCl_4 to give **16**, presumably with 6-*exo*-bromo stereochemistry for steric reasons (Scheme 5). Attempts to dehydrobrominate **16** to give alkene using DBU were unsuccessful,[25] so the bromide **16** was reduced directly using tris(trimethylsilyl)silane (TTMSS)/AIBN in toluene to give the 6-*endo*-aryl isomer **17**. The inversion of stereochemistry at carbon-6 was shown by comparison of the ^{1}H NMR spectra of 6-*exo*-aryl isomer **8a** with 6-*endo*-aryl isomer **17** (Table 2). Notably, proton H_1, which is *syn* to the aryl group in **8a**, appears at δ 4.47. This a more shielded position than observed for proton H_1 of **17** at δ 4.93.

Reduction product **17** was accompanied by the acyl enamine **18**, which showed a singlet at δ 7.21 for the vinyl proton H_2. The ring-opened product **18** might arise by rearrangement of initially formed radical **19** to radical **20**,[26] followed by hydrogen abstraction from TTMSS, as shown in Scheme 6.

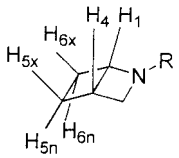
Finally, as shown in Scheme 5, the *N*-methoxycarbonyl group of **18** was cleaved by treatment with methyl lithium/lithium bromide ether solution in dry THF[22] to give the free amine **6**. Oxalic acid in ethanol was added to give an oxalate salt in 63% yield. Similarly, the *N*-methoxycarbonyl group of the 6-*exo*-aryl isomer **8a** was cleaved and converted to the oxalate salt of amine **8c** in 44% yield.

Conversion of the *exo*-distal isomer 9a to the *endo-distal* isomer 7

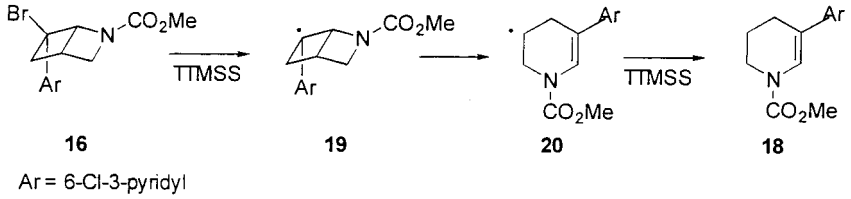
In order to invert the stereochemistry of the 5-*exo*-aryl substituent of **9a**, it was first brominated at the 5-benzylic position using *N*-bromosuccinimide/AIBN in refluxing CCl_4

† 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.

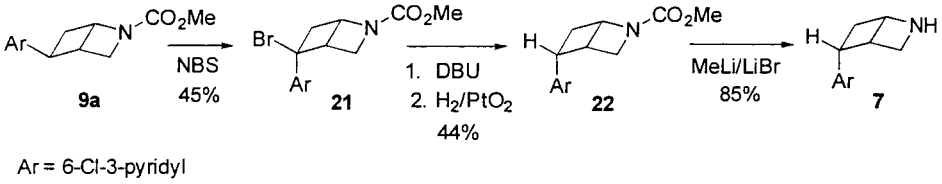
Table 2. Selected ^{1}H NMR chemical shift data for 5- and 6-(6-chloro-3-pyridyl)-2-aza-bicyclo[2.2.0]hexanes



Entry	Structure	R	Aryl position	H_1 (δ)	H_4 (δ)	H_{6n} (δ)	H_{6x} (δ)	H_{5n} (δ)	H_{5x} (δ)
1	**8a**	CO_2Me	6-*exo*	4.47	3.00	3.79	–	2.73	2.56
2	**8b**	CO_2Et	6-*exo*	4.48	3.01	3.84	–	2.73	2.63
3	**9a**	CO_2Me	5-*exo*	4.69	2.93	2.93	2.51	3.77	–
4	**9b**	CO_2Et	5-*exo*	4.72	2.95	2.95	2.54	3.79	–
5	**17**	CO_2Me	6-*endo*	4.93	2.90	–	3.99	2.90	2.50
6	**22**	CO_2Me	5-*endo*	4.66	3.34	2.63	2.99	–	4.00



Scheme 6. A suggested mechanism for formation of enamide **18**.



Scheme 7.

to give **21**, presumably with 5-*exo*-bromo stereochemistry for steric reasons (Scheme 5). Dehydrobromination of **21** using neat DBU at 70°C 25 followed by immediate reduction from the *exo* face using H_2/PtO_2 afforded the 5-*endo*-aryl isomer **22**.

Comparison of the ^{1}H NMR spectra of the 5-*exo*-aryl isomer **9a** and the reduced product clearly indicates a stereochemical inversion has occurred for the aryl group at C_5 of **22** (Table 2). Notably, the chemical shift for H_4 at δ 3.34 in the 5-*endo*-aryl isomer **22** is downfield of the resonance for the more shielded proton H_4 at δ 2.93 in the 5-*exo*-aryl isomer **9a**. The *N*-methoxycarbonyl group of **22** was cleaved by reaction with methyl lithium/lithium bromide ether solution[22] in dry THF to give the free amine **7**, to which an equivalent amount of oxalic acid in ethanol was added to give an oxalate salt (Scheme 7).

Biological evaluation

The oxalate salts of racemic epibatidine analogs **6**, **7**, and **8c** 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.[27] The results are shown in Table 3. 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.[28] A calcium imaging technique was used to measure ion flux, and agonist efficacy was indexed relative to the response of 100 μM nicotine.[29] The 6-*exo*-aryl isomer **8c** exhibited moderate potency but was only partially efficacious in this assay. The 5-*endo*-aryl isomer **7** exhibited comparable potency, but with substantially greater efficacy. The 6-*endo*-aryl isomer **6** exhibited only partial agonist efficacy and was significantly less potent. The most potent compound, the 5-*endo*-aryl isomer **7** was evaluated in a mouse hot plate assay of analgesia, and was found to be inactive at doses of 1.8, 5.9 and 18 mg/kg, ip. An analgesic response is produced by (−)-nicotine in this assay at 3 mg/kg, ip. The results of the present study are in agreement with the finding of Bai and coworkers that a bridged ring is crucial for analgesic activity of epibatidine analogs.[10]

Table 3. Comparative biological data for nicotine, epibatidine (**1**) and selected 5- and 6-(6-chloro-3-pyridyl)2-azabicyclo[2.2.0]hexanes

Entry	Amine	K_i (nM)	EC_{50} (μM), max. rel. resp. (%)
1	**6**	3.9	12 (26%)
2	**7**	5.0	2.57 (69%)
3	**8c**	39.0	1.55 (27%)
4	(±)-epibatidine (**1**)	0.043	0.007[a]
5	(−)-nicotine	0.93	7.94

[a] See Ref. [30].

Experimental

General methods

Thin layer chromatography was performed on precoated plates of silica gel GF 250 microns (Analtec, Inc.). Preparative thin layer chromatography was performed on precoated plates of silica gel GF 1000 or 2000 microns (Analtec, Inc.) Anhydrous $MgSO_4$ was used as drying agent. Solvents were removed under reduced pressure. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz routinely in $CDCl_3$ solvent or in D_2O, as noted; the NMR spectra were complicated by the presence of carbamate rotamers and pairs of ^{13}C NMR lines due to a single carbon, identified with the aid of proton-carbon correlation experiments, have been presented in parentheses. High resolution mass spectra (FAB^+) were performed at Drexel University or Merck Research Laboratories, West Point, PA. Methyllithium/Lithium bromide (1.5 M ether solution) was purchased from Aldrich Chemical Company.

***N*-(Methoxycarbonyl)-6-*exo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (8a), *N*-(methoxycarbonyl)-5-*exo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (9a), *N*-(methoxycarbonyl)-1-(6-chloro-3-pyridyl)-5-amino-1,3-pentadiene (12).** To palladium acetate (180 mg, 0.8 mmol) and triphenyl phosphine (446 mg, 1.7 mmol) there was added anhydrous DMF (30 mL), the resulting solution was stirred for 5 min at room temperature, and a yellow precipitate formed. There was then added *N*-(methoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (**10a**) (1.39 g, 10 mmol), 2-chloro-5-iodopyridine (5.98 g, 25 mmol), piperidine (2.56 g, 2.97 mL, 30 mmol), and formic acid (0.92 g, 0.77 mL, 20 mmol). The mixture was stirred under argon at 70–74°C for 24 h, water (20 mL) was added and the solution was extracted with ether (5×25 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to give a brown residue, which was purified by silica gel flash column chromatography (ether:hexane=1:3→2:1) to afford the 6-*exo*-aryl adduct **8a** (376.0 mg, 14%) at R_f=0.29 (hexane:ethyl acetate 1:1); ^1H NMR δ 8.26 (1H, br), 7.53 (1H, m), 7.28 (1H, d, J=8.4 Hz), 4.47 (1H, br), 4.37 (1H, dd, J=9.0, 6.0 Hz), 4.13 (1H, dd, J=9.0, 2.4 Hz), 3.79 (1H, m), 3.69 (3H, s), 3.00 (1H, m), 2.76–2.69 (1H, br), 2.56 (1H, m); ^{13}C NMR δ 156.6, 149.4, 148.0, 147.8, (137.3 and 137.1), 136.8, 124.1, (68.9 and 68.4), (57.8 and 56.9), 52.3, (44.3 and 43.7), 32.6, 28.6; HRMS Calcd for $C_{12}H_{14}N_2O_2^{35}Cl$ (M+1): 253.0744, found 253.0737; $C_{12}H_{14}N_2O_2^{37}Cl$ (M+1): 255.0714, found 255.0714. There was also obtained the 5-*exo*-aryl adduct **9a** as a yellow oil (1.14 g, 44%) at R_f=0.25 (hexane:ethyl acetate 1:1); ^1H NMR δ 8.22 (1H, d, J=2.4 Hz), 7.51 (1H, dd, J=8.4, 2.4 Hz), 7.28 (1H, d, J=8.4 Hz), 4.69 (1H, br), 4.38 (1H, dd, J=8.7, 6.6 Hz), 4.12 (1H, dd, J=8.7, 3.0 Hz), 3.77 (1H, ddd, J=7.5, 7.5, 3.0 Hz), 3.69 (3H, s), 3.00–2.87 (2H, br), 2.51 (1H, m); ^{13}C NMR δ 156.3, 149.4, 148.0, 139.0, 136.8, 124.1, (60.9 and 60.5), (57.7 and 56.8), 52.2, 41.9, 38.3, (37.8 and 37.5); HRMS Calcd for $C_{12}H_{14}N_2O_2^{35}Cl$ (M+1): 253.0744, found 253.0735; $C_{12}H_{14}N_2O_2^{37}Cl$ (M+1): 255.0714, found 255.0717. There was also obtained the diene **12** (312.4 mg, 12.4%) at R_f=0.33 (hexane:ethyl acetate 1:1); ^1H NMR δ 8.33 (1H, d, J=2.4 Hz), 7.65 (1H, dd, J=8.4, 2.4 Hz), 7.25 (1H, d, J=8.4 Hz), 6.76 (1H, dd, J=15.9, 10.5 Hz), 6.44 (1H, d, J=15.9 Hz), 6.32 (1H, dd, J=15.0, 10.5 Hz), 5.86 (1H, dt, J=15.0, 6.0 Hz), 4.86 (1H, br, NH), 3.90 (2H, m), 3.69 (3H, s); ^{13}C NMR δ 156.9, 149.8, 147.9, 135.1, 132.3, 131.8, 130.9, 130.7, 127.0, 124.1, 52.2, 42.6; HRMS Calcd for $C_{12}H_{13}N_2O_2Na^{35}Cl$ (M+22): 275.0563, found 275.0559; $C_{12}H_{13}N_2O_2Na^{37}Cl$ (M+22): 277.0534, found 277.0556.

***N*-(Ethoxycarbonyl)-6-*exo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (8b) and *N*-(ethoxycarbonyl)-5-*exo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (9b).** According to the previous procedure, *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (**10b**) (100 mg, 0.65 mmol) was reacted with palladium acetate (12 mg, 8% mol), triphenyl phosphine (0.29 mg), 2-chloro-5-iodopyridine (389 mg, 1.62 mmol), piperidine (166 mg, 1.95 mmol), and formic acid (60 mg, 1.30 mmol) in DMF (2 mL) at 70°C for 12 h to provide after column chromatography (cyclohexane:ethyl acetate 1:2) 28 mg (17%) of 6-*exo*-aryl adduct **8b** (R_f=0.52, hexane:ethyl acetate 1:1); ^1H NMR (75°C) δ 8.31 (1H, d, J=2.4 Hz), 7.56 (1H, dd, J=8.4, 2.4 Hz), 7.31 (1H, d, J=8.4 Hz), 4.48 (1H, d, J=4.8 Hz), 4.38 (1H, dd, J=9.0, 6.0 Hz), 4.17 (3H, m), 3.84 (1H, t, J=8.1 Hz), 3.01 (1H, m), 2.73 (1H, ddd, J=13.5, 8.1, 3.0 Hz), 2.63 (1H, ddd, J=13.5, 8.1, 6.6 Hz), 1.27 (3H, t, J=6.9 Hz); ^{13}C NMR δ 155,7, 149.4, 147.1, 140.4, 137.1, 124.0, 68.9, 61.0, (57.7 and 56.7), 44.2, 32.3, 28.5, 14.3; HRMS Calcd for $C_{13}H_{16}N_2O_2^{35}Cl$ (M+1): 267.0900, found 267.0908. There was also obtained 38 mg (23%) of the 5-*exo*-aryl adduct **9b** (R_f=0.21, CH_2Cl_2:ethyl acetate 10:1); ^1H NMR (75°C) δ 8.25 (1H, d, J=2.4 Hz), 7.48 (1H, dd, J=8.4, 2.7 Hz), 7.26 (1H, d, J=8.4 Hz), 4.72 (1H, dd, J=5.4, 4.8 Hz), 4.39 (1H, dd, J=8.7, 6.6 Hz), 4.15 (3H, m), 3.79 (1H, td, J=7.8, 3.0 Hz), 2.95 (2H, br), 2.54 (1H, ddd, J=13.5, 7.8, 5.4 Hz), 1.27 (3H, t, J=7.2 Hz); ^{13}C NMR δ 155.9, 149.3, 147.9, 139.0, 136.7, 124.0, 60.8, 60.3, 56.7, 41.9, 38.2, 37.7, 14.7; HRMS Calcd for $C_{13}H_{16}N_2O_2^{35}Cl$ (M+1): 267.0900, found 267.0905.

Formation of the oxalate salt of 6-*exo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (8c). To a CH_3Li/LiBr (1.980 mL of 1.5 M ether solution, 2.99 mmol) solution in dried THF (3.5 mL) there was added the 6-*exo*-aryl adduct **8a** (215 mg, 0.85 mmol) in THF (2.5 mL) at −10 to −5°C. The resultant mixture was stirred at this temperature until no starting material remained (ca. 20 min). Water (5 mL) and brine (5 mL) were 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 in vacuo to give 181 mg of the crude free amine; ethanol (2 mL) and then oxalic acid (78.6 mg, 0.84 mmol) was added. The resultant solution was cooled over night, and ether was added to afford a precipitate. Solvent was removed and the residue was washed with diethyl ether and dried to give 106.6 mg (44%) of the oxalate salt of **8c** for testing purposes; ^1H NMR (300 MHz, D_2O) δ 8.21 (1H, s), 7.75 (1H, d, J=8.4 Hz), 7.44 (1H, d, J=8.4 Hz), 4.67 (1H, br), 4.52 (1H, dbr, J=10.5 Hz), 4.37 (1H, dbr, J=10.5 Hz), 4.33 (1H, m), 3.27 (1H, m), 2.85 (1H, m), 2.62 (1H, m); ^{13}C NMR (D_2O) δ 165.0, 148.8, 147.3, 138.5, 136.5, 124.8, 66.6, 53.3, 40.5, 32.7, 31.1; HRMS of

8c Calcd for $C_{10}H_{12}N_2^{35}Cl$ (M+1): 195.0684, found 195.0681; $C_{10}H_{12}N_2^{37}Cl$ (M+1): 197.0655, found 197.0652.

Ring cleavage of 5-*exo*-aryl adduct 9b. Preparation of *N*-(ethoxycarbonyl)-*cis*-1-amino-2-iodomethyl-3-*trans*-(6-chloro-3-pyridyl)cyclobutane (15). To a solution of 6-*exo*-aryl adduct **9b** (44.0 mg, 0.16 mmol) in anhydrous CH_3CN (1 mL) there was added TMSI (70 μL, 99.0 mg, 0.48 mmol).16 The resulting solution was stirred at room temperature for 1.5 h, quenched with methanol (5 mL) and the solvent was removed in vacuo to give a yellow oil. The oil was dissolved in 30% AcOH (5 mL), extracted again with ether (4×5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a brown oil, which was purified by silica gel flash column chromatography (3:1 hexane:ethyl acetate) to give 15.9 mg (24.4%) of cyclobutane **15** as a yellow solid, R_f=0.57 (1:1 hexane:ethyl acetate); ^{1}H NMR δ 8.51 (1H, d, *J*=2.4 Hz), 7.67 (1H, dd, *J*=8.3, 2.4 Hz), 7.34 (1H, d, *J*=8.3 Hz), 5.04 (1H, br), 4.44 (1H, br), 4.19 (2H, q, *J*=7.2 Hz), 3.45–3.25 (3H, br), 3.07–2.95 (1H, br), 2.60–2.50 (1H, br), 2.47–2.36 (1H, br), 1.31 (3H, t, *J*=7.2 Hz); ^{13}C NMR δ 156.1, 149.6, 148.6, 137.2, 137.1, 124.1, 61.3, 49.5, 46.8, 40.8, 32.4, 14.6, 4.8; HRMS Calcd for $C_{13}H_{17}N_2O_2ICl$ (M+1): 395.0023, found 395.0011. The structure was confirmed by X-ray analysis.

***N*-(Methoxycarbonyl)-6-bromo-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (16).** To a CCl_4 (6 mL) solution of 6-*exo*-aryl adduct **8a** (244.2 mg, 0.97 mmol) there was added *N*-bromosuccinimide (258.0 mg, 1.46 mmol) and AIBN (20 mg). The resulting solution was refluxed under argon for 4 h, cooled to room temperature, filtered, concentrated in vacuo, and the residue was purified by flash column chromatography (1:1 ether:hexane) to give 148.0 mg (56.1% yield based on recovery of 63.7 mg of unreacted **8a**) of bromide **16** as a yellow oil (R_f=0.42, hexane:EtOAc=1:1); ^{1}H NMR δ 8.45 (1H, d, *J*=2.4 Hz), 7.77 (1H, two br), 7.30 (1H, d, *J*=8.1 Hz), 5.26 (1H, br), 4.26 (1H, dd, *J*=8.4, 6.9 Hz), 3.68 (1H, d, *J*=8.4 Hz), 3.60 (3H, s), 3.34–3.26 (3H, br); ^{13}C NMR δ 155.8, 150.8, 148.5, 148.1, 137.7, 136.5, 123.8, 73.9, 73.8, 62.0, (56.8 and 56.3), 52.4, 44.9, 44.5, 27.5; HRMS Calcd for $C_{12}H_{13}N_2O_2^{79}Br^{35}Cl$ (M+1): 330.9849, found 330.9847, $C_{12}H_{13}N_2O_2^{81}Br^{37}Cl$ (M+1): 334.9799, found 334.9808.

***N*-(Methoxycarbonyl)-6-*endo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (17).** To a toluene (10 mL) solution of bromide **16** (148.0 mg, 0.45 mmol) there was added tris-(trimethylsilyl)silane (TTMSS) (0.57 g, 2.25 mmol), and AIBN (10 mg). The resulting solution was refluxed under argon for 6 h until no starting material remained. The solvent was removed and the residue was purified by silica gel flash column chromatography (ether:hexane=1:1→2:1) to give 25.3 mg (22.4%) of reduced **17** as a colorless oil, R_f=0.22 (hexane:ethyl acetate 1:1); ^{1}H NMR δ 8.24 (1H, br), 7.64 (1H, br), 7.24 (1H, br), 4.99 and 4.88 (1H, br), 4.32 (1H, m), 3.99 (1H, m), 3.89 (1H, m), 3.56 and 3.30 (3H, two s), 2.94–2.86 (2H, br), 2.53–2.46 (1H, br); ^{13}C NMR δ 157.0, 156.5, 150.3, 149.2, 148.6, 138.2, 137.7, 134.8, 134.1, 123.4, 67.4, 66.9, 58.8, 57.8, 52.2, 51.9, 41.5, 32.1, 31.2, 27.8; HRMS Calcd for $C_{12}H_{14}N_2O_2^{35}Cl$ (M+1) 253.0744, found 253.0742, $C_{12}H_{14}N_2O_2^{37}Cl$ (M+1) 255.0714, found 255.0713. There also was obtained 31.0 mg (27.5%) of a cleavage product **20** at R_f=0.51 (hexane:ethyl acetate 1:1); ^{1}H NMR δ 8.34 (1H, d, *J*=1.8 Hz), 7.60 (1H, dd, *J*=1.8, 8.4 Hz), 7.25 (1H, d, *J*=8.4 Hz), 7.21 (1H, s), 3.79 (3H, s), 3.65 (2H, br), 2.40 (2H, t, *J*=6.0 Hz), 1.97 (2H, m); ^{13}C NMR δ 155.6, 148.5, 145.4, 134.2, 134.3, 124.5, 124.0, 123.7, 113.0, 112.8, 53.3, 41.7, 41.9, 23.6, 23.3, 21.3; HRMS Calcd for $C_{12}H_{14}N_2O_2^{35}Cl$ (M+1): 253.0744, found 253.0732, $C_{12}H_{14}N_2O_2^{37}Cl$ (M+1): 255.0714, found 255.0712.

Preparation of the oxalate salt of 6-*endo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (6). Using the method described for cleavage of the carbamate of 6-*exo*-aryl adduct **8a**, a solution of MeLi/LiBr (450 μL of 1.5 M ether solution, 0.67 mmol) cleaved 6-*endo*-aryl adduct **18** (48.8 mg, 0.19 mmol) to provide 38.3 mg of amine **6**, which upon reaction with oxalic acid (17.4 mg, 18.9 mmol) in ethanol (0.5 mL) gave for testing purposes the oxalate salt of **6** (34.7 mg, 63.2%); ^{1}H NMR (D_2O) δ 8.21 (1H, s), 7.69 (1H, d, *J*=8.4 Hz), 7.48 (1H, d, *J*=8.4 Hz), 5.18 (1H, br), 4.74–4.68 (1H, br), 4.56–4.42 (2H, br), 3.28–3.19 (1H, br), 3.14–3.04 (1H, br), 2.84–2.75 (1H, br); ^{13}C NMR (D_2O) δ 164.2, 149.3, 147.7, 139.2, 132.4, 124.9, 66.5, 54.6, 37.0, 30.7, 29.5; HRMS Calcd for $C_{10}H_{12}N_2^{35}Cl$ (M+1): 195.0684, found 195.0672; $C_{10}H_{12}N_2^{37}Cl$ (M+1): 197.0655, found 197.0643.

***N*-(Methoxycarbonyl)-5-bromo-5-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (21).** To a CCl_4 (20 mL) solution of *N*-(methoxycarbonyl)-5-*exo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane **9a** (712.7 mg, 2.82 mmol) there was added *N*-Bromosuccinimide (853.4 mg, 4.79 mmol) and AIBN (50 mg). The resulting solution was refluxed under argon for 5 h, cooled to room temperature, filtered, concentrated in vacuo and the resulting oil was purified by silica flash column chromatography (1:1 ether:hexane) to give 377.8 mg (44% corrected for 68.7 mg recovery of **9a**) of bromide **21** as a yellow liquid (R_f=0.56, 1:1 hexane:EtOAc); ^{1}H NMR δ 8.31 (1H, d, *J*=2.4 Hz), 7.54 (1H, dd, *J*=8.4, 2.4 Hz), 7.34 (1H, d, *J*=8.4 Hz), 4.87 (1H, br), 4.17 (1H, dd, *J*=9.6, 8.1 Hz), 3.92 (1H, m), 3.70 (1H, m), 3.59 (3H, s), 3.60–3.55 (1H, br), 3.43–3.33 (1H, br); ^{13}C NMR δ 155.8, 150.9, 147.5, 137.2, 136.6, 124.3, 58.4, 57.7, (52.8 and 52.6), 52.3, 47.9, 46.6; HRMS Calcd for $C_{12}H_{13}N_2O_2^{79}Br^{35}Cl$ (M+1): 330.9849, found 330.9839, $C_{12}H_{13}N_2O_2^{81}Br^{35}Cl$ (M+1): 332.9828, found 332.9820.

***N*-Methoxycarbonyl-5-*endo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (22).** To bromide **21** (468.6 mg, 1.41 mmol) there was added DBU (10 mL). The resulting solution was stirred under argon at 70°C for 2.5 h, was cooled to room temperature, water (10 mL) was added, and the reaction mixture was extracted with ether (5×20 mL). The combined extracts were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo to give 433.5 mg of crude 5-aryl-2-azabicyclo[2.2.0]hex-5-ene, R_f=0.48 (ether), which was dissolved in ethyl acetate (45 mL). PtO_2 (120 mg) was added and the mixture was stirred at room temperature under a H_2 balloon for 3.5 h until no starting material remained. The solvent was filtered and removed in vacuo to give a crude oil (363.8 mg), which was purified by silica gel flash column chromatography

(ether:hexane=2:1) to afford after two steps 156.8 mg (44.0%) of 5-*endo*-aryl adduct **22** as an oil (R_f=0.30, ether); ^{1}H NMR δ 8.18 (1H, d, J=2.4 Hz), 7.50 (1H, dd, J=8.1, 2.4 Hz), 7.31 (1H, d, J=8.1 Hz), 4.66 (1H, br), 4.09 (1H, dd, J=9.6, 7.2 Hz), 4.02–4.00 (1H, br), 3.77 (1H, dd, J=9.6, 1.2 Hz), 3.65 (3H, s), 3.38–3.31 (1H, br), 3.04–2.94 (1H, br), 2.70–2.56 (1H, br); ^{13}C NMR δ 155.9, 149.5, 148.9, 137.7, 134.9, 123.9, (60.0 and 59.6), 52.2, (51.4 and 50.5), (35.7 and 35.5), 35.0, (33.7 and 33.0); HRMS Calcd for $C_{12}H_{14}N_2O_2^{35}Cl$ (M+1): 253.0744, found 253.0736; $C_{12}H_{14}N_2O_2^{37}Cl$ (M+1): 255.0714, found 255.0709.

Preparation of the oxalate salt of 5-*endo*-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.0]hexane (7). According to the procedure described for cleavage of 6-*exo*-aryl adduct **8a**, a CH_3Li/LiBr (432 μL of 1.5 M ether solution, 0.65 mmol) solution in dried THF (1.0 mL) was reacted with 5-*endo*-aryl adduct 22 (46.8 mg, 0.185 mmol) in THF (0.5 mL) at 0°C to afford 33.8 mg (93.9%) of amine **7**, which upon addition to an ethanolic solution of oxalic acid (16.6 mg, 0.18 mmol) afforded for testing purposes 47.1 mg (89.4%) of oxalate salt of **7**; ^{1}H NMR (D_2O) δ 8.16 (1H, d, J=1.5 Hz), 7.66 (1H, dd, J=1.5, 8.1 Hz), 7.48 (1H, d, J=8.1 Hz), 4.68 (1H, br), 4.26 (1H, dd, J=12.2, 7.5 Hz), 4.16 (1H, m), 4.00 (1H, dd, J=12.2, 4.2 Hz), 3.69 (1H, m), 3.30–3.20 (1H, br), 3.09–3.00 (1H, br); ^{13}C NMR (D_2O) δ 164.5, 148.4, 147.5, 139.3, 135.0, 124.7, 57.8, 47.4, 37.5, 34.7, 29.6; HRMS Calcd for $C_{10}H_{12}N_2^{35}Cl$ (M+1): 195.0684, found 195.0693; $C_{10}H_{12}N_2^{37}Cl$ (M+1): 197.0655, found 197.0662.

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