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Nitrogen Bridge Homoepibatidines. *syn*-6- and *syn*-5(6-Chloro-3-pyridyl)isoquinuclidines.

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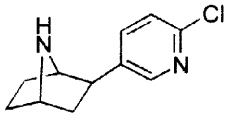
Abstract: The N-bridge *vicinal*-6(6-Cl-3-pyridyl) and *distal* 6-(6-Cl-3-pyridyl)-2-azabicyclo[2.2.2]octane homologs of the potent nicotinic receptor agonist epibatidine have been synthesized. Key steps involve stereoselective catalytic hydrogenations of both 6- and 5-(6-Cl-3-pyridyl)-2-azabicyclo[2.2.2]oct-5-enes **12** and **17** on the face *anti* to the nitrogen containing bridges. The *vicinal* homolog appears to be a potent nicotinic agonist.

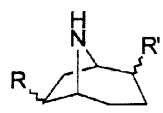
Keywords: Epibatidine homologs; stereocontrol; bicyclic heterocyclic compounds; amines

Introduction

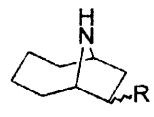
Epibatidine (**1**) [1-5], a highly potent nicotinic acetylcholine receptor agonist isolated by Daly and coworkers[1] from the Ecuadorian frog, *Epipedobates tricolor*, has been found to exhibit an antinociceptive response 200 times greater than L-nicotine [6] and 200-500 times that of morphine[1]. Nicotinic receptor agonists are of potential interest for treating neurological disorders (Alzheimer's and Parkinson's diseases)[7], and there is much recent interest in the synthesis and biological evaluation of epibatidine [1-5,8-40] and related structures [31,41-51]. Epibatidine homologs **2-4** in which an ethylene bridge has been expanded by one [31,41-43] or two [43] methylene groups have been synthesized. This paper describes syntheses of two new homologs of epibatidine (**1**) in which the smaller nitrogen bridge has been expanded by a methylene group; e. g., the nitrogen atom is either *vicinal* to the *syn*-(6-chloro-3-pyridyl) substituent as in **5** or *distal* as in **6**. In addition the potent nicotinic receptor binding properties and analgesic activities of these amines have been determined.



1 Epibatidine



2 R = 6-Cl-3-pyridyl, R' = H
3 R = H, R' = 6-Cl-3-pyridyl



4 R = 6-Cl-3-pyridyl

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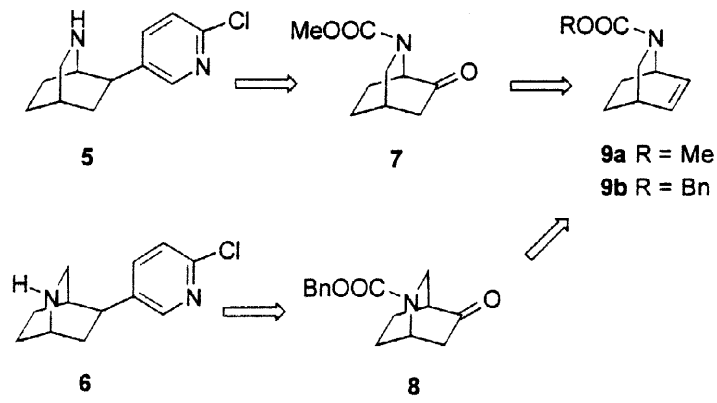
Results

A. Synthetic approaches to Epibatidine analogs 5 and 6.

A retrosynthetic analysis for *vicinal* and *distal* N-bridged epibatidine homologs **5** and **6** from ketones **7** and **8** is shown in Scheme 1. We have previously prepared both N-methoxycarbonyl-2-azabicyclo[2.2.2]octan-6-one (**7**) [52-53] and N-benzyloxycarbonyl-2-azabicyclo[2.2.2]octan-5-one (**8**) [54] regioselectively from the appropriate readily available N-alkoxycarbonyl-2-azabicyclo[2.2.2]oct-5-enes **9**.

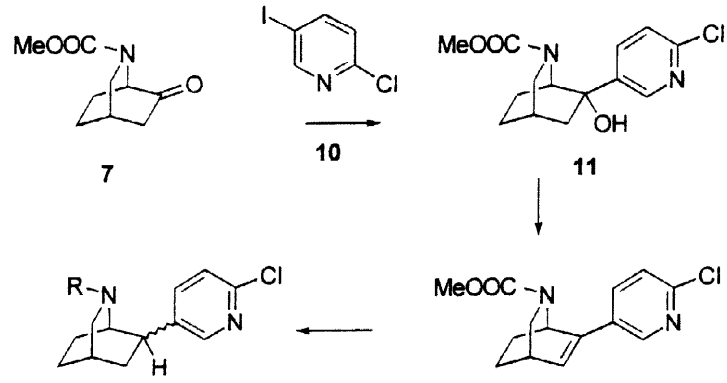
Scheme 1



1. *Vicinal* epibatidine homolog 5.

As shown in Scheme 2, the protocol described by Fletcher and coworkers [9,14], was used to add the 5-lithio-2-chloropyridyl anion, prepared from 2-chloro-5-iodopyridine (**10**) and *n*-butyl lithium [14], to N-methoxycarbonyl 2-azabicycylo[2.2.2]octan-6-one (**7**) [52-53]. The result, as shown by x-ray structure determination, was a single stereoisomeric alcohol **11** in which the 6-(6-chloro-3-pyridyl) group is *syn* to the nitrogen containing bridge.[1] The

Scheme 2.



13 *syn*-6-Cl-3-pyridyl, R = COOMe
5 *syn*-6-Cl-3-pyridyl, R = H
14 *anti*-6-Cl-3-pyridyl, R = COOMe

[1] 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.

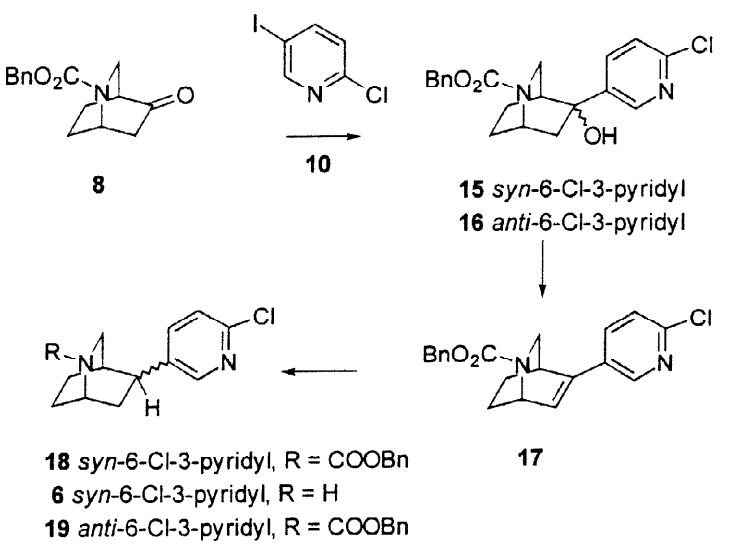
stereoselective addition of phenylmagnesium bromide to the 6-carbonyl group from the face *syn* to an ethoxycarbonyl group has been noted previously [55]. Pyrolysis of the xanthate derived from alcohol **11** gave alkene **12** [9,14], which upon reduction over Pt in ethyl acetate gave a 9:1 mixture of 6-*syn*:6-*anti* stereoisomers **13**:**14**, as determined by ^{1}H NMR NOE experiments. Irradiation of the COOMe of **13** at δ3.51 gave 17% enhancement of $H_{6'}$ adjacent to the pyridyl nitrogen, 8% enhancement of $H_{3'}$, and -2% enhancement of $H_{4'}$. The minor *anti*-6-(6-chloro-3-pyridyl) isomer **14** was prepared independently to confirm the structural assignment. The carbamate protecting group of **13** was removed by hydrolysis using HBr/HOAc to afford *vicinal* homoepibatidine **5** [56].

2. *Distal* epibatidine homolog 6.

Addition of the 5-lithio anion derived from 2-chloro-5-iodopyridine (**10**) [14] to N-benzyloxycarbonyl-2-azabicyclo[2.2.2]-octan-5-one [54] (**8**) gave a 2:1 mixture of 5-*syn*:5-*anti* stereoisomers **15**:**16** (Scheme 3). This result contrasts with the addition of PhMgBr solely from the face *syn* to the carbonyl group in the N-ethoxycarbonyl analog of ketone **8** [55]. The stereochemistry of alcohol **15** was confirmed by x-ray structure analysis.[1] Pyrolysis of the corresponding xanthates of the mixture of alcohols **15**/**16** afforded the alkene **17**, which upon reduction over Pt gave a 3:1 mixture of 5-*syn*:5-*anti* stereoisomers **18** and **19** [14], which could be enriched in the desired **18** by TLC. The 5-*syn*-(6-chloro-3-pyridyl) isomer **18** can be characterized by the upfield shift for proton H_{3n} at δ3.26 relative to proton H_{3n} at δ3.52 in the 5-*anti* isomer **19**. Assignment of stereochemistry to the isomers was facilitated by hydrolytic removal of the carbamate protecting group using HBr/HOAc [56] and conversion of the free bases to oxalate salts. A single crystalline oxalate salt of the major *syn*-chloropyridyl isomer **6** (68%) was isolated. ^{1}H NMR NOE experiments on this oxalate salt of **6** are consistent with the 5-*syn*-(6-chloro-3-pyridyl) stereochemistry; irradiation of H_3 at δ3.14 gave NOE enhancements to the pyridyl hydrogens of 29% ($H_{3'}$), 19% ($H_{4'}$), and 35% ($H_{6'}$).

It is notable that the organolithium reagent prepared from **10** adds predominantly *syn* to the

Scheme 3.

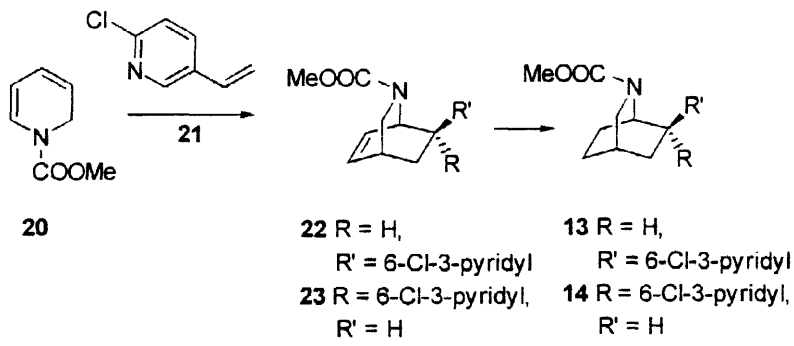


nitrogen-containing bridge of ketones **7** and **8**, while the Pt catalyzed addition of hydrogen to the alkenes **12** and **17** occurs predominantly from the face *anti* to the nitrogen containing bridge. It can be speculated that lithium coordination to the carbamate substituent is *syn*-face directing [16]. In the absence of coordination the Pt catalyst prefers the *anti*-face of the alkenes opposite the bulky carbamate substituents.

3. A Diels-Alder route to homoepibatidine 5.

The Diels-Alder reaction between N-methoxycarbonyl-1,2-dihydropyridine [57] (**20**) and 2-chloro-5-vinylpyridine [13,15] (**21**) (Scheme 4) afforded a 21:79 mixture of cycloadducts **22** and **23**. Hydrogenation of the mixture afforded the major 6-*anti*-(6-chloro-3-pyridyl) adduct **14** and the desired minor 6-*syn*-(6-chloro-3-pyridyl) adduct **13**, identical to the product described in Scheme 1. Attempted enrichment of a mixture of the reduced cycloadducts **13/14** by heating with potassium *t*-butoxide in refluxing *t*-butanol [9,14,31] was unsuccessful, since only trace amounts of the desired N-methoxycarbonyl homoepibatidine **13** could be isolated.

Scheme 4.



20

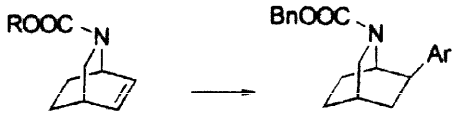
22 R = H, R' = 6-Cl-3-pyridyl
23 R = 6-Cl-3-pyridyl, R' = H

13 R = H, R' = 6-Cl-3-pyridyl
14 R = 6-Cl-3-pyridyl, R' = H

4. Attempted vinyl-aryl coupling routes to homoepibatidines 5 and 6.

A palladium-catalyzed reductive coupling of 2-chloro-5-iodopyridine **10** to a vinyl group was used successfully in the Clayton and Regan [11] synthesis of epibatidine (**1**). Our pilot studies (Scheme 5, Eq. 1) indicated that when olefin **9a** and iodobenzene were heated to 85 °C in DMF containing piperidine, formic acid, and 8 mol % of $(Ph_3P)_2Pd(OAc)_2$ for 13 h, a single reductive addition product **24** was obtained in a low yield (10%). The *syn-vicinal* stereochemistry of this adduct **24** is surprising in light of the stereochemical outcome observed during Heck arylations of azabicyclo[2.2.1]alkene **27** to afford either *distal* epibatidine analog **28** [44] or a mixture of analogs **28** and **29** (Scheme 5, Eq. 2) [51]. Unfortunately, our attempts to prepare the *vicinal* homoepibatidine (**5**) precursor **25** by palladium catalyzed reductive coupling between 2-chloro-5-iodo-pyridine **10** and olefins **9b** or **9b** in DMF containing piperidine, formic acid and either $Pd(OAc)_2$ with added Ph_3P (method one), $Pd(OAc)_2(PPh_3)_2$ or $Pd(Ph_3P)_4$ were unsuccessful. Additionally, attempted coupling of olefin **9b** with 2-amino-5-iodo-pyridine to afford adduct **26** using Carroll's conditions was unsuccessful [39].

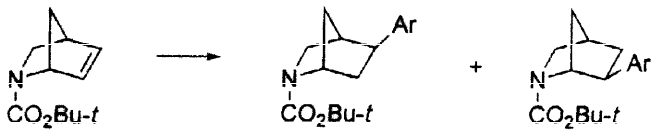
Scheme 5.



Eq. 1

9a R = Me
9b R = Bn

24 Ar = phenyl
25 Ar = 6-Cl-3-pyridyl
26 Ar = 6-NH_2-3-pyridyl



Eq. 2

27

28 Ar = 6-Cl-3-pyridyl **29** Ar = 6-Cl-3-pyridyl

B. Biological evaluation.

The oxalate salts of racemic homoepibatidines **5** and **6** were tested for their ability to compete for [^{3}H]cytisine binding to nicotinic receptors obtained from rat brain cortices [58]. The K_i values for the *vicinal* amine **5**, the *distal* amine **6** and *l*-epibatidine (free base) were 470, 340 and 90 pM, respectively. These three compounds were also tested in a mouse tail-flick assay. Approximate ED_{50} values at 30 min. for tail-flick activities were 0.04 and 1.4 mg/kg, s.c.; respectively for the *vicinal* amine **5** and *distal* amine **6**.[2] Epibatidine (**1**) displays an ED_{50} of about 0.01 mg/kg, s.c. [59]. The tail-flick activity and some of the side effects of the *vicinal* amine **5** (0.05 mg/kg, s.c.) were partially antagonized by pretreatment with the nicotinic receptor antagonist mecamylamine (1 mg/kg, s.c.).[2] The muscarinic and opioid antagonists, atropine (3 mg/kg, s.c.) and naloxone (5 mg/kg, i.p.), respectively, did not antagonize either tail-flick or side effects. These results suggest that homoepibatidines **5** and **6** may be potential probes for nicotinic receptors, although they possess significant side effects at tail-flick analgetic doses. Functionally modified homoepibatidines are under active investigation.

Experimental Section

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.). HPLC was performed using a Semipreparative Rainin C_{18} reverse phase Dynamax column (40% to 100% CH_3CN/ water). Melting points are uncorrected. Anhydrous $MgSO_4$ was used as drying agent. Solvents were removed under reduced pressure. ^{1}H NMR spectra were recorded at 300 or 500 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ solvent. High resolution mass spectra were performed at Davey Laboratory, Pennsylvania State University, PA.

[2]For both amines **5** and **6**, marked sedation/lethargy, tremors and labored breathing were concomitant with the apparent tail-flick activity; thus apparent analgetic activity may be influenced by these side effects. Also, for the *vicinal* amine **5**, convulsions occurred at the apparent ED_{50} dose in 1/5 mice; lethality occurred in 1/5 mice at about twice the apparent ED_{50} dose. In contrast, at the ED_{50} dose for tail-flick activity, epibatidine displays fewer additional effects, such as sedation, occasional labored breathing and Straub tail. At 3-10 times the effective tail-flick dose of epibatidine, tremors, vocalizations and convulsions progressively develop.

N-Methoxycarbonyl-*syn*-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octan-6-ol (11). At -78 °C, *n*-butyllithium in pentane (2.0 M) (0.64 mL, 1.27 mmol) was added dropwise to a solution of 2-chloro-5-iodopyridine (**10**) (0.311 g, 1.27 mmol) in dry THF (15 mL). The reaction was stirred for 30 min at -78 °C, whereupon the ketone **7** (0.233 g, 1.27 mmol) in THF (10 mL) was added slowly. The reaction was stirred at -78° C for 0.5 h followed by 1 h at 25° C. After the reaction was quenched with sat. aq. ammonium chloride (10 mL), it was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water, dried, and evaporated *in vacuo* to give a brown oil (0.321 g). The residue was chromatographed on silica gel, eluting with EtOAc/petroleum ether (4:1 to 1:1), to give unreacted starting ketone **7** (77 mg, 67% conversion) and the alcohol **11** (0.156 g, 66%) as a solid, mp 150-151 °C (EtOAc): ^{1}H NMR (300 MHz) δ 8.38 (1 H, d, J = 2.1 Hz), 7.81 (1 H, dd, J = 2.4, 8.4 Hz) 7.24, (1 H, d, J = 8.7 Hz), 4.12 (1 H, t, J = 2.4 Hz), 3.59 (3 H, s), 3.28 (2 H, m), 2.34-1.64 (6 H, m); ^{13}C NMR ($CDCl_3$) δ 158.1, 150.1, 147.5, 141.5, 136.5, 123.6, 73.1, 52.6, 51.5, 47.7, 42.6, 26.9, 22.7, 21.7. Anal. Calcd for $C_{14}H_{17}N_2O_3Cl$: C: 56.66, H: 5.77, N: 9.44. Found: C: 56.54, H: 5.83, N: 9.34.

N-Methoxycarbonyl-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (12). To a mixture of KH (0.15g, 0.758 mmol, 20% in mineral oil) in THF (10 mL), the alcohol **11** (0.15 g, 0.505 mmol) in THF (10 mL) was added slowly at 0 °C. The reaction was stirred for 30 min at rt followed by addition of CS_2 (0.12 g, 1.58 mmol) and, after 20 min, MeI (0.11 g, 0.775 mmol) at 0 °C. After 1 hr of stirring at rt, the reaction was quenched with water, extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried, and evaporated to give a light brown oil. Toluene was added and the crude xanthate was heated at reflux for 12 h. Chromatography of the resulting oil on silica gel, eluting with petroleum ether/ether (1:1), gave olefin **12** (134 mg, 95%) at R_f = 0.38: ^{1}H-NMR δ 8.41 (1 H, d, J = 2.1 Hz), 7.80 (1 H, dd, J = 2.4, 8.4 Hz), 7.24 (1 H, d, J = 8.4 Hz), 6.63 (1 H, t, J = 6.9 Hz), 5.15 (1 H, br), 3.62 (3 H, s), 3.30 (1 H, dd, J = 10.2, 1.8 Hz), 3.01 (1 H, dt, J = 10.2, 1.8 Hz), 2.90 (1 H, m), 2.09-1.37 (4 H, br); ^{13}C-NMR δ 159.9, 150.0, 146.2, 135.4, 134.9, 130.3, 129.7, 124.0, 52.3, 48.0, 47.8, 31.2, 26.4, 22.0; HRMS calcd for $C_{14}H_{15}{}^{35}ClN_2O_2$ m/z 278.0824, found 278.0812.

N-Methoxycarbonyl-*syn*-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (13) and N-Methoxycarbonyl-*anti*-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (14). Olefin **12** (0.11 g, 0.395 mmol) was hydrogenated over PtO_2 (170 mg) in EtOAc (15 mL) for 1.5 h at rt.[14] The reaction mixture was filtered and evaporated to give a 9:1 mixture of stereoisomers (R_f = 0.46, hexanes) consisting mainly of product *syn*-isomer **13** (780 mg, 70%): ^{1}H NMR δ: 8.18 (1 H, d, J = 2.4 Hz), 7.85 (1 H, dd, J = 2.4, 8.4 Hz), 7.20 (1 H, d, J = 8.4 Hz), 4.10 and 3.85 (1 H, m), 3.60 and 3.40 (3 H, s), 3.39 (2 H, m), 3.00 (1 H, m), 2.25-1.60 (7 H, m); NOE (deoxygenated acetone-d_6) irradiation at δ3.51 gave enhancement at δ7.20 (8%), δ7.85 (-2%), 8.18 (17%); ^{13}C-NMR δ 156.3, 149.1, 139.3, 138.3, 137.3, 123.9, 52.4, 49.4, 49.1, 40.4, 32.5, 27.6, 25.9, 23.0; HRMS calcd for $C_{14}H_{17}{}^{35}ClN_2O_2$ m/z 280.0980, found 280.0958. The *anti*-isomer **14** was prepared independently by the Diels-Alder route (See below).

***syn*-6-(6-Chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (5).** A mixture (100 mg, 0.34 mmol) of 6-*syn*- and 6-*anti*-(6-chloro-3-pyridyl) isomers **13** and **14** and 30% w/w HBr/HOAc (1.5 mL)

was stirred at 25 °C for 20 h. The reaction was quenched with ether, solvent was removed *in vacuo*, the residue was diluted with methanol and purified with silica gel (CH_2Cl_2:MeOH: NH_4OH, 90:10:1 eluent) to give a light yellow oil (36 mg). This oil was dissolved in EtOH (abs.), and oxalic acid (20 mg) was added with a few drops of EtOAc to give an oxalate salt of amine **5**; ^{1}H-NMR (oxalate salt, CD_3OD) δ 8.42 (1H, d, J = 1.5 Hz), 7.90 (1H, dd, J = 1.5, 8.0 Hz), 7.46 (1H, d, J = 8.0 Hz), 3.72 (1H, br), 3.42 (1H, dd, J = 11.5, 2 Hz), 3.28 (2H, br), 2.34 (2H, br), 2.14-2.03 (3H, m), 1.85 (1H, m); ^{13}C NMR δ 162.1, 148.8, 138.8, 135.8, 124.1, 49.5, 44.8, 35.7, 27.7, 23.1, 22.9, 22.4; HRMS of amine **5** Calcd for $C_{12}H_{15}{}^{35}ClN_2$ m/z 222.0925, found 222.0917.

N-Benzyloxycarbonyl-*syn/anti*-5-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octan-5-ols (15) and (16). At -78 °C, *n*-butyllithium in pentane (2.5 M) (3.4 mL, 8.5 mmol) was added dropwise to a solution of 2-chloro-5-iodopyridine (**10**) (2.05 g, 8.48 mmol) in dry THF (25 mL). The reaction was stirred for 30 min at -78 °C, whereupon the ketone **8** (2.0 g, 7.7 mmol) in THF (10 mL) was added slowly. The reaction was stirred at -78° C for 3 h followed by 3 h at 25° C. After the reaction was quenched with sat. aq. ammonium chloride (10 mL), it was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water, dried, and evaporated *in vacuo* to give a brown oil (1.875 g). The residue was chromatographed on silica gel, eluting with EtOAc/petroleum ether (4:1 to 1:1), to give unreacted starting ketone **8** (245 mg, 12% conversion) and a light yellow foam consisting of a 2:1 mixture of *syn/anti*-alcohols **15** and **16** (1.70 g, 67%); these could be separated by chromatography (CH_2Cl_2/acetone 8:1) or, if the mixture was allowed to stand for a week, the *syn*-(6-chloro-3-pyridyl) isomer **15** solidified: mp 144-146 °C; ^{1}H-NMR δ 8.52 (1 H, br), 7.68 (1 H, dd, J = 8.4, 2.4 Hz), 7.34 (5 H, s), 7.21 (1 H, d, J = 8.4 Hz), 5.14 (2 H, br), 4.34 (1 H, br), 3.30 (1 H, dd, J = 12.3, 2.4 Hz), 3.08 (1 H, m), 2.70 (1 H, m), 2.42 (1 H, m), 2.05 (1 H, br), 1.90 (3 H, m), 1.65 (1 H, m); ^{13}C-NMR δ 150.4, 147.8, 140.9, 136.7, 128.5, 128.0, 127.8, 123.6, 72.5, 66.9, 45.4, 45.0, 42.8, 38.6, 25.6, 19.1; the *anti*-(2-chloro-5-pyridyl) isomer **16:** ^{1}H-NMR δ 8.53 (1 H, br), 7.84 (1 H, d, J = 8.4 Hz), 7.37 (1 H, br, 6H), 5.16 (2 H, s), 4.37 (1 H, br), 4.14 (1 H, m), 3.34 (1 H, m), 2.46 (1 H, b, J = 14.7 Hz), 2.21-1.90 (4 H), 1.68-1.54 (2 H, m), 1.39-1.27 (1 H, m); ^{13}C-NMR δ 150.4, 147.4, 140.5, 137.0, 128.4, 127.8, 127.6, 123.9, 72.1, 66.8, 44.5, 44.0, 42.4, 38.1, 25.1, 20.0; HRMS of the mixture Calcd for $C_{20}H_{21}{}^{35}ClN_2O_3$ m/z 372. 1214, found 372.1214.

N-Benzyloxycarbonyl-5-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (17). To a stirred suspension of NaH (80% w/w suspension in mineral oil) (49 mg, 0.758 mmol) in THF (10 mL), the alcohols **15**and **16** (202 mg, 543 mmol) in THF (10 mL) were added slowly at 0 °C. The reaction was stirred for 1 h at rt followed by addition at 0 °C of CS_2 (97 mg, 1.27 mmol) and, after 10 min, MeI (0.11 g, 0.775 mmol). After 1 hr of stirring at 25 °C, the reaction was quenched with water, extracted with CH_2Cl_2, and the combined organic layers were washed with water, dried, and evaporated to give a yellow oil (165 mg, 65%, R_f = 0.48 pet ether/ether): ^{1}H-NMR δ 8.44 (1 H, J = 2.4 Hz), 5.13 (2 H, q, J = 12.3 Hz), 4.38 and 4.29 (1 H, br), 3.31 (1 H, ddd, J = 2.4, 2.4, 9.6 Hz), 2.97 (2 H, m), 2.22 (3 H, s), 2.54-2.18 (3 H, m), 1.94-1.75 (4H, m). Toluene was added and the crude xanthate was heated at reflux for 12 h. Chromatography of the resulting oil on silica, eluting with petroleum ether/ether (1:1), gave

olefin **17** (294 mg, 77%) as a colorless oil, $R_f = 0.46$: ^{1}H-NMR δ 8.44 (1 H, d, J = 2.4 Hz), 7.64 (1 H, dd, J = 2.4, 8.1 Hz), 7.34 (6 H, m), 6.81 (1 H, dd, J = 1.8, 6.3 Hz), 5.15 (2 H, m), 4.98 and 4.87 (1 H, br), 3.49 (1 H, m), 3.24 (2 H, m), 1.65 (1 H, br), 1.35 (1 H, m), 1.05 (2 H, m); ^{13}C-NMR δ 155.1, 150.3, 146.2, 141.2, 140.8, 136.8 and 132.0, 135.1, 129.2, 128.5 and 127.9, 127.0, 124.1, 66.83, 47.8, 46.2, 33.1, 26.8, 22.3; HRMS calcd for $C_{20}H_{19}{}^{35}ClN_2O_2$ m/z 354.1163, found 3354.1134.

N-Benzyloxycarbonyl-*syn*-5-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (18) and N-Benzyloxycarbonyl-*anti*-5-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (19). A suspension of the alkene **17** (145 mg, 0.41 mmol) and platinum dioxide (267 mg) in ethyl acetate (20 mL) was stirred under H_2 (1 atm) at 26° C for 3 h.[14] The catalyst was removed by filtration, the filtrate was concentrated *in vacuo*, and the resulting oil was purified by chromatography (2:1 ether:petroleum ether) to give 90.5 mg of an oil ($R_f = 0.55$). HPLC of this oil (retention time 20 min) gave 85 mg (58%) of an inseparable mixture of colorless oils **18** (76 ± 3%) and **19**. Further TLC (64.5 mg) of the mixture with separation of the top portion of the band afforded 16 mg of an 85:15 mixture enriched in the major *syn*-isomer **18**: ^{1}H-NMR (500 MHz) δ 8.26 (1 H, br), 7.44 (1 H, m), 7.37 (5 H, br), 7.20 (1 H, d, J = 8.5 Hz), 5.16 (2H, m), 4.32 and 4.24 (1 H, br), 3.35 (1 H, overlapping d, J = 12.5 Hz), 3.26 (1 H, two d, J = 12.5 Hz), 3.13 (1 H, m), 2.13 (2 H, m), 1.94 (1 H, m), 1.86-1.59 (4H, m); ^{13}C-NMR δ 155.0, 149.5, 138.5, 137.6, 136.8, 128.4, 127.9, 123.9, 66.7, 44.3, 43.7, 37.4, 33.1, 32.5, 25.7, 25.5. The minor product was the *anti*-isomer **19**: ^{1}H-NMR (500 MHz) δ 8.30 (1 H, br), 7.54 (1 H, m), 7.37 (6 H, br), 5.16 (2H, m), 4.29 and 4.21 (1 H, br), 3.67 (1 H, overlapping d, J = 11 Hz), 3.52 (1 H, two d, J = 11 Hz), 3.13 (1 H, m), 2.14-1.52 (6H, br); HRMS of the mixture calcd for $C_{20}H_{21}{}^{35}ClN_2O_2$ m/z 356.1322, found 356.1283.

***syn*-6-(6-Chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (6).** A mixture (300 mg, 0.84 mmol) of 5-*syn*- and 5-*anti*-(6-chloro-3-pyridyl) isomers **18** and **19** and 30% w/w HBr/HOAc (1.5 mL) was stirred at 25 °C for 1.5 h. The reaction was quenched with ether, solvent was removed *in vacuo*, the residue was diluted with methanol and purified with silica gel (CH_2Cl_2:MeOH: NH_4OH, 90:10:1 eluent) to give a light yellow oil. This oil was dissolved in EtOH (abs.), and oxalic acid (76 mg) was added with a few drops of EtOAc to give an oxalate salt of amine **5**, basification and extraction with ether gave 127 mg of the amine **6** (68%), ^{1}H-NMR (oxalate salt) (500MHz, D_2O) δ 8.38 (1H, d, J = 2 Hz, 7.97 (1H, dd, J = 8.5, 2 Hz), 7.59 (1H, d, J = 8.5 Hz); 3.66 (1H, d, J = 3 Hz); 3.33 (1H, dd, J = 5, 1 Hz); 3.14 (2H, br), 2.37 (1H, J = ddd, 3, 11, 14.5 Hz), 2.16-2.02 (4H, m), 1.91-1.80 (2H, m); ^{13}C NMR (75 MHz, D_2O) δ (CO lost in noise), 146.7, 141.2, 138.5, 126.0, 45.2, 40.3, 34.8, 28.1, 27.6, 23.0, 20.8; HRMS of amine **6** Calcd for $C_{12}H_{15}{}^{35}ClN_2$ m/z 222.0925, found 222.0938.

N-Methoxycarbonyl-*syn*-7-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (22) and N-Methoxycarbonyl-*anti*-7-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]oct-5-ene (23). Diels-Alder. A solution of 6-chloro-3-vinylpyridine (**21**) and N-methoxycarbonyl-1,2-dihydropyridine [57] (**20**) in decalin (10mL) was refluxed for 12 h under argon. The solvent was removed by flash column washing with hexanes and the mixture was purified using hexanes:ethyl acetate (1:1) as eluent to give 0.948 g (44%) of a 21:79 mixture of *syn*- and *anti*-

6-(6-chloro-3-pyridyl) cycloadducts **22** and **23** (comparative NMR integration of δ 4.90 vs 4.68; R_f = 0.45 (hexanes:ethyl acetate 1:1); ^{1}H NMR (75 °C) of **23**: δ 8.17 (1H, d, J = 2.1 Hz), 7.41 (1H, dd, J = 8.1, 2.4 Hz), 7.17 (1H, d, J = 8.1 Hz), 6.58 (1H, t, J = 7.5 Hz), 6.27 (1H, m), 4.68 (1H, b), 3.42 (3H, s), 3.40 (1H, m), 3.33 (1H, dd, J = 10.5, 2.1 Hz), 3.04 (1H, d, J = 10.5 Hz), 2.90 (1H, b), 2.18 (1H, ddd, J = 12.6, 10.5, 2.5 Hz), 1.61 (1H, m); ^{13}C NMR δ 155.7, 149.4, 138.3, 137.6, 135.6, 130.0, 123.6, 52.4, 50.0, 46.5, 41.4, 31.2, 31.0; LRMS Calcd for $C_{14}H_{15}{}^{35}ClN_2O_2$ 278.0822, found No M^+ peak by CI method because of the ease of the reverse Diels Alder reaction. The sample was characterized via its reduction products **13** and **14**.

N-Methoxycarbonyl-*syn*-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (13) and N-Methoxycarbonyl-*anti*-6-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.2]octane (14). The mixture of cycloaducts **22** and **23** (0.194 g, 0.7 mmol) was hydrogenated in EtOAc (5 mL) with 10% Pd on C (20 mg) by bubbling hydrogen into the stirred mixture via a balloon for 12 h. The catalyst was filtered through silica gel and solvent was removed to give 176 mg (90%) of a 26:74 mixture, R_f = 0.46 (hexanes:EtOAc 1:1), of *syn*- and *anti*-6-(6-chloro-3-pyridyl) cycloadducts **13** and **14** (comparative ^{1}H NMR integration of δ3.00 vs 3.31); ^{1}H-NMR of 6-*anti*-product **14** δ: 8.30 (1H, d, J = 2Hz), 7.56 (1H, dd , J = 2.5, 8 Hz), 7.03 (1H, d, J = 8.0 Hz), 4.01 and 3.93 (1H, br), 3.72 (3H, s), 3.45 (1H, m), 3.31 (1H, m), 2.15 (2H, m), 1.87 (1H, m), 1.65 (4H, m); ^{13}C NMR δ 156.3, 149.8, 138.7, 137.9, 124.4, 52.9, 49.7, 48.9, 40.8, 30.2, 26.5, 24.8, 21.3; HRMS Calcd for $C_{14}H_{18}{}^{35}ClN_2O_2$ (M + H) 281.1056, found 281.1059.

N-Benzyloxycarbonyl-*syn*-6-phenyl-2-azabicyclo[2.2.2]octane (24). A mixture of N-benzyloxycarbonyl-2-azabicyclo-2.2.2-oct-5-ene (**9b**) (155 mg, 0.63 mmol), $Pd(OAc)_2$ (25.6 mg, 0.11 mmol), Ph_3P (60.5 mg, 0.23 mmol), phenyl iodide (329.4 mg, 1.58 mmol), piperidine (0.19 mL, 1.9 mmol), formic acid (0.05 mL, 1.27 mmol) and DMF (2 mL) was heated at 85 °C for 15 h. The reaction was diluted with water (5 mL) and extracted several times with ether. The combined organic layers were dried and solvent was removed *in vacuo* to give a dark oil, which was chromatographed over silica gel (4:1 hexane:EtOAc) to give 21 mg (10%) of adduct **25** as a solid, mp 92-94 °C; R_f = 0.58 (2:1 hexane:EtOAc); ^{1}H NMR δ7.42-6.85 (10H, m), 4.90 (2H, dd, J = 12.6, 9.6 Hz), 4.01 (1H, m), 3.67-3.61 (2H, m), 3.54-3.48 (1H, m), 3.10 (1H, m), 2.18-1.78 (6H, m); ^{13}C NMR δ 144.9, 136.6, 128.4, 127.4, 126.2, 66.3, 49.9, 49.5, 44.1, 32.3, 27.9, 26.0, 23.4; Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.86; H, 7.43; N, 4.24.

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