Stereoselective Synthesis of Conformationally Constrained Tropane Analogues: 6-Chloro-2,5-diazatetracyclo[8.5.0.0^{2,13}.0^{4,9}]pentadeca-4,6,8-triene-11-one and 6-Chloro-2,7-diazatetracyclo-[8.5.0.0^{2,13}.0^{4,9}]pentadeca-4,6,8-triene-11-one

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Two conformationally constrained tropane derivatives were prepared as rigid nicotinic acetylcholine receptor ligands. A palladium catalyzed intramolecular α-arylation reaction was employed to generate the tricyclic compounds in good yields from *N*-(bromo-chloropyridylmethyl)-8-azabicyclo[3.2.1]octan-3-ones.

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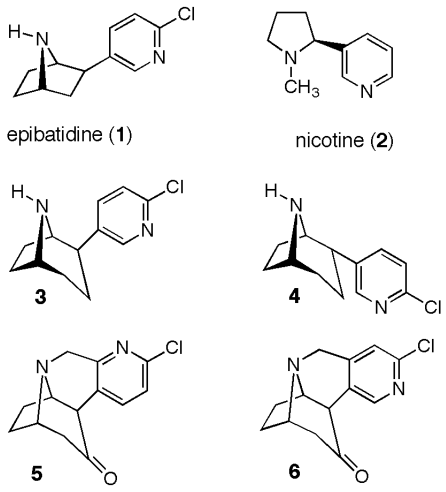
The alkaloid (-)-epibatidine (**1**), isolated from the skin of the Ecuadorian poison dart frog *Epipedobates tricolor* by Daly and co-workers[1], has been reported to be an exceptionally potent non-opioid analgesic and a nicotinic acetylcholine receptor agonist. Its uncommon 7-azabicyclo[2.2.1]heptane ring system and remarkable biological activity [2-4] has inspired numerous syntheses of epibatidine and related analogues [5-7]. Recent investigations have focused on the synthesis and biological screening of structurally similar analogues of **1** and nicotine (**2**) to discover compounds that possess low toxicity and greater selectivity at various nicotinic acetylcholine receptor subtypes [8-13]. Earlier studies in our laboratories reported a series of epibatidine homologues **3** and **4** as novel nicotinic acetylcholine receptor ligands [14,15]. The stimulant activity *in vivo* of **3** and **4** was found to be 30-100 fold less potent than **1**. The reduced potency of **3** and **4** relative to epibatidine was believed to be due to the increased conformational flexibility of the 8-azabicyclo[3.2.1]octane ring system. Therefore it was of interest to conformationally constrain the tropane analogues to determine if the potency could be improved. Herein we wish to report the synthesis of two conformationally constrained homologues of epibatidine, 6-chloro-2,5-diazatetracyclo[8.5.0.0^{2,13}.0^{4,9}]pentadeca-4,6,8-triene-11-one (**5**) and 6-chloro-2,7-diazatetracyclo[8.5.0.0^{2,13}.0^{4,9}]pentadeca-4,6,8-triene-11-one (**6**).



As illustrated in Scheme 1, the synthesis of the first of tricyclic homoepibatidines was envisaged to proceed from tropinone (**7**). Demethylation of **7** by treatment with methyl chloroformate in the presence of a catalytic amount of potassium carbonate afforded the methyl carbamate **8** [16] in 95% yield. The carbamate **8** was then heated at reflux with trimethylsilyliodide in chloroform. This furnished nortropinone (**9**) [17] in 86% yield. The required pyridine derivative **12** was synthesized by diazotization and chlorination of commercially available 2-amino-5-bromo-6-methylpyridine (**10**) to a provide the intermediate 2-chloro-5-bromo-6-methylpyridine (**11**) [18] in 60 % yield. Subsequent bromination of **11** with *N*-bromosuccinimide and benzoyl peroxide in carbon tetrachloride at reflux afforded **12** [19] in 73 % yield. The bromide **12** was then heated at reflux with nortropinone (**9**) in toluene and triethylamine to furnish the pyridyl-tethered tropinone derivative **13** in 60% yield. A palladium-catalyzed intramolecular α-arylation was then employed to affect the coupling of the two ring systems and generate the desired rigid tricyclic skeleton. Treatment of **13** with 10% *trans*-dichloro-bis(triphenylphosphine) palladium (II) and cesium carbonate in toluene at 100-110 °C catalyzed the intramolecular α-arylation reaction and furnished the desired diazatetracyclo[8.5.0.0^{2,13}.0^{4,9}]pentadeca-4,6,8-triene-11-one (**5**) in 82% isolated yield.

The structure of **5** was unequivocally established by X-ray crystallography and the ORTEP diagram is shown in

Scheme 1

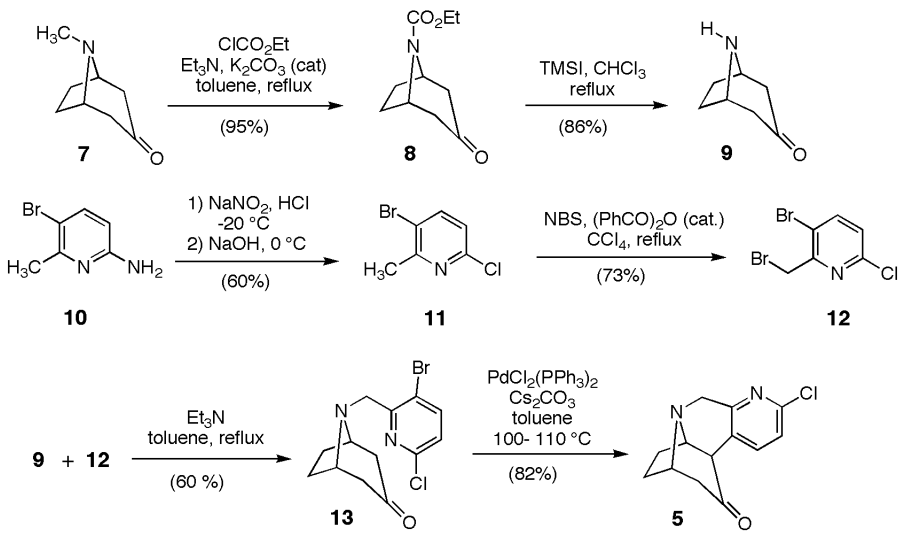
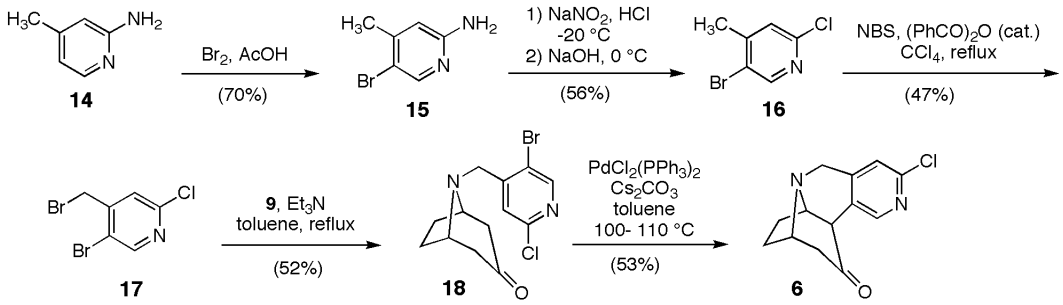


Figure 1 [20]. The regioselectivity of the α-arylation reaction of **13** is noteworthy, since it has been shown that the reaction of 2,5-dihalopyridines in cross-coupling reactions typically yield 2-substituted coupling products as the major regioisomer [21-23]. In addition, earlier studies in our laboratories demonstrated that the palladium catalyzed C-N cross-coupling reaction of 7-azabicyclo[2.2.1]heptane with 2-chloro-5-iodopyridine predominantly gave coupling products at the 2-position of the pyridine ring [24]. It is believed that the reversed regioselectivity observed for **13** in the intramolecular C-C coupling reaction is due to the thermodynamic preference of the system to form the 6-member ring of **5** over the less stable 7-member ring product that would result from coupling at the 2-chloro substitution.

The other structural isomer **6** was synthesized in similar fashion from nortopinone (**9**) and the trihalogenated pyridine derivative **17**. As illustrated in Scheme 2, bromination of 2-amino-4-methylpyridine **14** at room temperature selectively gave 5-bromo-2-amino-4-methylpyridine (**15**) [25] in 70% yield. Diazotization and concomitant chlorination of **15** furnished the 5-bromo-2-chloro-4-methylpyridine **16** in 56% yield. Subsequent bromination of **16** with *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide in refluxing carbon tetrachloride furnished the desired 5-bromo-4-bromomethyl-2-chloropyridine **17** in 47% yield. The reaction of nortropinone (**9**) with **17** in refluxing toluene gave the pyridyl-tethered tropinone derivative **18** in 52% yield. Palladium catalyzed α-arylation of **18** furnished the 6-chloro-2,7-diazatetracyclo[8.5.0.0^{2,13}.0^{4,9}]pentadeca-4,6,8-triene-11-one (**6**) in 53% yield. The regioselectivity of the arylation reaction was confirmed by X-ray crystallographic analysis. As illustrated in Figure 2, the ORTEP diagram of **6** confirms the orientation of the pyridyl nitrogen atom relative to the trisubstituted nitrogen atom [20].

The binding affinities of the rigid epibatidine homologues **5** and **6** at nicotinic acetylcholine receptors were determined by the inhibition of [^{3}H]cytisine binding in homogenates of rat striatum. There are a variety of nACHRs subtypes that exist in the central nervous system; however, the α4β2-subtype is the predominant nicotinic acetylcholine receptor in rat striatum tissue. Therefore, the binding affinities most likely correspond to the neuronal

Scheme 2



α4β2-subtype receptors.[26] Upon comparison with the tropane analogue **3** (K_i = 1 nM) the conformationally constrained compounds **5** (37% inhibition @ 100 μM [^{3}H]cytisine) and **6** (14% inhibition @ 100 μM [^{3}H]cytisine) exhibited very little affinity for the nicotinic acetylcholine receptor. Similarly constrained analogues of epibatidine were also reported to be less potent than **1** at nicotinic acetylcholine receptors [27].

It was not surprising that the binding affinity of **5** was significantly less than epibatidine, nicotine or **3**, since the intramolecular nitrogen-nitrogen distance of **5** was considerably shorter than the optimum distances predicted by various pharmacophore models for high affinity receptor binding [28]. From the X-ray structure of **5** (Figure 1) the nitrogen-nitrogen distance was determined to be 3.74 Å as compared to 5.1 Å and 5.5 Å determined for the different rotational conformations of epibatidine [28,29]. Alternatively the nitrogen-nitrogen distance determined from the X-ray structure of **6** (Figure 2) was 5.12 Å and was comparable to nitrogen-nitrogen distances of epibatidine. From these results it is apparent that despite the similar structural features there appears to be a well-defined pharmacophore that is not met by the rigid homologues. Presumably the orientation of the pyridyl ring relative to the basic nitrogen of the saturated ring system contributes significantly to the binding affinity of compounds such as **1**, **2** and **3**. To this end, the constrained geometry of **5** and **6** appears to place the pyridyl ring in an unfavorable orientation relative to the basic nitrogen of the cyclic system for high affinity binding. As a result the constrained derivatives **5** and **6** exhibit very poor binding affinity for neuronal nicotinic acetylcholine receptors. It should also be noted that the poor binding affinities of **5** and **6** may be due to the conformational or substituent effects introduced by the carbonyl group. While the effects of carbonyl group incorporated into the 7-azabicyclo[2.2.1]heptane ring system epibatidine are not known, the poor affinities of **5** and **6** may be due to functional group intolerance at this position by the receptor. Further studies directed toward the elucidation of the nicotinic acetylcholine receptor pharmacophore are under investigation and will be reported elsewhere.

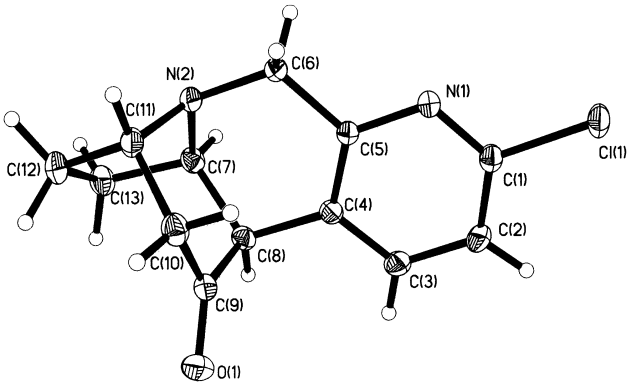


Figure 1. ORTEP Drawing of **5**.

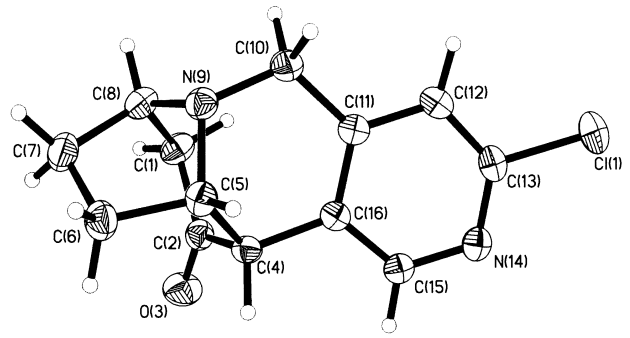


Figure 2. ORTEP Drawing of **6**.

EXPERIMENTAL

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Anhydrous tetrahydrofuran, dichloromethane and methanol was purchased from Baker Chemical Company and stored under argon. Chromatography refers to chromatography on silica gel (Silica Gel 60, 230-400 mesh, E. M. Science). Petroleum ether refers to pentanes with a boiling point range of 30-60°. Reported melting points are uncorrected. All spectra were recorded for the free base. All nmr specta were recorded on a Varian Gemini 400 MHz multiprobe spectrometer. Chemical shifts are reported as δ values from tetramethylsilane in deuteriochloroform. Mass spectra were recorded on a Micromass Autospec Mass Spectrometer fitted with a Fisson GC 8060. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA. Existence of fractional moles of water in some analytical samples persisted despite vigorous drying (110°, 24 h) under vacuum (0.01 mm Hg). All compounds were homogeneous by thin layer chromatography.

N-Ethoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one (**8**) [16].

A solution of 1.8 g (13 mmol) of tropinone (**7**) and a catalytic amount of potassium carbonate (100 mg) in 25 mL of toluene was heated at reflux under nitrogen. Methyl chloroformate (4 mL, 41.8 mmol) was added *via* syringe and the solution was heated at reflux overnight. The mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 50 mL of dichloromethane and washed with water. The organic layer was separated, and the aqueous layer was extracted with dichlormethane (2 x 50 mL). The organic layers were combined, dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by flash chromatography (silica gel-hexane:ethyl acetate, 9:1) to furnish a colorless liquid and yield 2.4 g (95%) of **8**; ir (neat): 1699, 1194, 1107 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 4.51 (brs, 2H), 4.16 (quartet, J = 7.2 Hz, 2H), 2.63 (brs, 2H), 2.31 (dd, J = 17.4, 1.6 Hz, 2H), 2.07-2.03 (m, 2H), 1.65 (d, J = 7.6 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 208.3, 154.1, 61.6, 53.2, 49.1, 29.5, 28.8, 14.9.

8-Azabicyclo[3.2.1]octan-3-one (**9**)[17].

To a solution of 2.7 g (14 mmol), of *N*-ethoxycarbonyl-8-azabicyclo[3.2.1]octan-3-one (**8**) in 50 mL of dry chloroform at reflux was added 5.9 mL (41 mmol) of trimethylsilyl iodide slowly over 10 minutes. The solution was heated at reflux for five hours then allowed cool to room temperature. Methanol (50 mL) was added slowly to destroy the excess any excess trimethylsilyl iodide. The solvent was removed under reduced pressure and the residue was dissolved in 50 mL of saturated sodium thiosulfate solution and extracted with dichloromethane (3 x 50 mL). The aqueous layer was made basic with 10% sodium hydroxide solution to pH 11 and extracted with chloroform (3 x 50 mL). The organic layers were combined, dried (sodium sulfate) and evaporated under reduced pressure to yield 1.45 g (84%) of the crude 8-azabicyclo[3.2.1]octan-3-one (**9**) that was of sufficient purity to be employed in subsequent reactions; ir (NaCl) 3350, 1775 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.74 (brs, 2H), 2.51 (dd, *J* = 16.4, 4.4 Hz, 2H), 2.20 (d, *J* = 16 Hz, 2H), 1.78-1.74 (m, 2H), 1.61-1.53 (m, 2H).

5-Bromo-2-chloro-6-methylpyridine (**11**)[18].

Sodium nitrite (1.4 g, 20 mmol) was added slowly to a solution of 6-amino-3-bromo-2-methylpyridine (**10**) (1.9 g, 10 mmol) in 25 mL of concentrated hydrochloric acid at –20°. After 1 hour, the reaction was allowed to warm to room temperature and then stirred for 2 h. Ice-cold 10 *N* sodium hydroxide solution was then added to the reaction mixture until pH 11 was reached while keeping the temperature below 5°. The aqueous solution was extracted with ether (3 × 50 mL). The organic layers were combined, washed with brine, dried (sodium sulfate), and evaporated to give a white solid to yield 1 g (48%) of 5-bromo-2-chloro-6-methylpyridine (**11**), mp 46-47° (lit. [18] mp 43 – 45°); ir (NaCl): 1566, 1420, 819 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 2.60 (s, 3H). ^{13}C nmr (deuteriochloroform): δ 158.1, 149.1, 142.1, 122.9, 119.7, 24.7.

3-Bromo-2-bromomethyl-6-chloropyridine (**12**)[19].

A solution of 3.2 (16 mmol) of 5-bromo-2-chloro-6-methylpyridine (**11**), 3.4 g (19 mmol) of *N*-bromosuccinimide and 10 mol% benzoyl peroxide (380 mg, 1.6 mmol) in 35 mL of dried carbon tetrachloride were heated at reflux for over 28 hours. The succinimide was removed by filtration, and then the solution was washed successively with water, brine, and dried (sodium sulfate). The solution was evaporated under reduced pressure and the residue was distilled under reduced pressure (3 mmHg, 95°-100°) to give 2.3 g (50%), of **12** as a colorless oil; ir (neat): 1558, 1419, 829 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 4.62 (s, 2H); ^{13}C nmr (deuteriochloroform): δ 155.6, 149.9, 143.6, 125.6, 119.6, 32.3.

N-(3-Bromo-6-chloro-2-pyridylmethyl)-8-azabicyclo[3.2.1]-octan-3-one (**13**).

A solution of 2.3 g (7.8 mmol) of 3-bromo-2-bromomethyl-6-chloropyridine (**12**), 0.66 g (5.3 mmol) of 8-azabicyclo[3.2.1]-octan-3-one (**9**) and 1.1 mL (7.8 mmol) of triethylamine in 20 mL of dried toluene (20 mL) was heated at reflux for 4 hours. After the solution was allowed to cool to room temperature, saturated sodium carbonate solution (20 mL) and ether (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with ether (2 x 20 mL). The organic layers were combined, dried (sodium sulfate) and evaporated to give a crude solid, which was purified by flash chromatography (silica gel-hexane: ethyl acetate, 10:1, v/v) to yield 1.0 g (60%) of a yellow solid **13**, mp 100-102°. This compound was converted into the oxalate salt affording a white powder, mp 162° (decomp.); ir (NaCl): 1713, 1423, 1152,1044 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 7.77 (d, *J* = 8 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 2.58 (brs, 2H). 2.68 (dd, *J* = 16, 4.4 Hz, 2H), 2.16 (d, *J* = 15.6 Hz, 2H), 2.14-2.07 (m, 2H), 1.62-1.56 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 210.1, 158.0, 149.4, 143.1, 124.3, 120.3, 59.5, 55.9, 48.3, 28.0. MS (CI) *m/z* 330 (MH^+, 100), 249 (85).

Anal. Calcd. for $C_{13}H_{14}N_2BrClO•C_2H_2O_4$: C, 42.93; H, 3.84; N, 6.68. Found: C, 43.08; H, 3.97; N, 6.59.

6-Chloro-2,5-diazatetracyclo[8.5.0.$0^{2,13}$.$0^{4,9}$]pentadeca-4,6,8-triene-11-one (**5**).

A Schlenk tube, flame-dried *in vacuo*, was placed under an argon atmosphere on a vacuum line. The tube was charged with 70 mg (10 mol%, 0.1 mmol) of *trans*-dichloro-bis(triphenylphosphine) palladium, 980 mg (3 mmol) cesium carbonate, 330 mg (1 mmol) *N*-(3-bromo-6-chloro-2-pyridylmethyl)-8-azabicyclo[3.2.1]octan-3-one (**13**) and 5 mL of dry toluene. The Schlenk tube was sealed and heated in a oil bath (100-110°) for10 hours. The mixture was allowed to cool to room temperature and diluted with 10 mL of water. The mixture was then extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine, and dried (magnesium sulfate). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel-hexane:ethyl acetate, 1:1, v/v). This afforded 180 mg (71%) of a white solid to give **5**, mp 166-

Table 1

Crystal Data and Structure Refinement for **5**

Empirical formula	$C_{13}H_{13}ClN_2O$	
Formula weight	248.70	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 6.6270(2) Å	α = 74.4830(10)°
	b = 8.6521(3) Å	β= 81.9170(10)°
	c = 10.2975(4) Å	γ = 85.9910(10)°
Volume	562.94(3) $Å^3$	
Z	2	
Density (calculated)	1.467 Mg/m^3	
Absorption coefficient	0.322 mm^{-1}	
F(000)	260	
Crystal size	0.4 x 0.7 x 0.7 mm^3	
Theta range for data collection	2.07 to 34.44°.	
Index ranges	$-10 \le h \le 10, -13 \le k \le 13, -16 \le l \le 16$	
Reflections collected	11505	
Independent reflections	4516 [R(int) = 0.0185]	
Completeness to theta = 34.44°	94.8 %	
Absorption correction	Empirical	
Max. and min. transmission	1.000000 and 0.713709	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4516 / 0 / 206	
Goodness-of-fit on F^2	1.067	
Final R indices [I>2sigma(I)]	R1 = 0.0316, wR2 = 0.0935	
R indices (all data)	R1 = 0.0385, wR2 = 0.0961	
Largest diff. peak and hole	0.444 and -0.336 $e.Å^{-3}$	

168°. This compound was converted into the oxalate salt affording a white powder, mp 196 °(decomp.); ir (NaCl): 1717, 1542, 1458, 1135 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.33 (d, *J* = 8 Hz, 1H), 7.10 (d, *J* = 8 Hz, 1H), 4.59 (d, *J* = 20 Hz, 1H), 4.28 (d, *J* = 20 Hz, 1H), 3.82 (t, *J* = 5.4 Hz, 1H), 3.56 (d, *J* = 6.4 Hz, 1H), 3.50 (s, 1H), 2.39 (ddd, *J* = 15, 5.0, 2.2 Hz, 1H), 2.19-2.04 (m, 3H), 1.78-1.71 (m, 1H), 1.62-1.56 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 206.8, 156.8, 150.5, 139.1, 127.4, 122.5, 62.5, 58.1, 57.6, 51.0, 42.9, 28.5, 27.0. MS (CI) *m/z* 249 (MH^+, 100), 215 (14), 79 (15).

Anal. Calcd. for $C_{13}H_{13}N_2ClO•C_2H_2O_4$: C, 53.18; H, 4.46; N, 8.27. Found: C, 53.25; H, 4.68; N, 8.06.

2-Amino-5-bromo-4-methylpyridine (**15**) [25].

To a solution of 2-amino-4-methylpyridine **14** (1.1 g, 10 mmol) in 3 mL of acetic acid, was added a solution of 1.6 g (10 mmol) of bromine in 1 mL of acetic acid with vigorous stirring over 30 minutes. The mixture was heated at 50° for 3 hours then allowed to cool to room temperature. The mixture was diluted with 5 mL of water, and basified to pH 11 by slow addition of 5 *N* sodium hydroxide solution. The white precipitate was collected by vacuum filtration and washed with water. The solid was suspended in 5 mL of hexane and heated at reflux for 10 minutes and then collected by vacuum filtration. The filtrate was washed with hot hexane three times to yield 1.3 g (70%) a pale-yellow powder, mp 134-135°(Lit. mp 134 °[25]). ir (KBr): 3436, 1541, 1476, 1440, 854 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.09 (s, 1H), 6.41 (s, 1H), 4.36 (brs, 2H), 2.29 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 157.7, 148.9, 148.4, 112.0, 110.7, 22.5. MS (ESI) *m/z* 187 (MH^+).

5-Bromo-2-chloro-4-methylpyridine (**16**).

Sodium nitrite (1.4 g, 20 mmol) was added slowly to a solution of 1.9 g (10 mmol) of 2-amino-5-bromo-4-methylpyridine (**15**) in 20 mL concentrated hydrochloric acid at –20°. After 1 hour, the reaction mixture was allowed to warm to room temperature and stirred for 2 hours. A cold 10 *N* sodium hydroxide solution was added slowly to adjust the reaction mixture to pH 11 while keeping the temperature below 5°. The aqueous mixture was extracted with dichloromethane (3 x 50 mL) and the combined organic phases were washed with brine, dried (sodium sulfate) and evaporated to give 1.0 g (48%) of a yellow liquid, **16**; ir (NaCl): 1577, 1451, 1030, 886 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.32 (s, 1H), 7.12 (s, 1H), 2.30 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 151.0, 150.3, 150.1, 126.1, 122.1, 22.4. An analytically pure sample was obtained for the hydrochloride salt.

Anal. Calcd. for $C_6H_5NBrCl•HCl$: C, 29.67; H, 2.49; N, 5.77. Found: C, 29.62; H, 2.33; N, 5.80.

5-Bromo-4-bromomethyl-2-chloropyridine (**17**).

A solution of 2.1 g (10 mmol) of 5-bromo-2-chloro-4-methylpyridine (**16**), 2.0 g (11 mmol) of *N*-bromosuccinimide and 242 mg of benzoyl peroxide (10 mol%,) in 60 mL of dry carbon tetrachloride was heated at reflux overnight. The succinimide was removed by filtration and the solution was washed successively with water and brine, and dried (sodium sulfate). The solution was evaporated under reduced pressure and the residue was purified by vacuum distillation to yield 0.80 g (47% based on recovered starting material) of a colorless oil **17**, bp 125-130° at 0.3 mmHg; ir (NaCl): 1571, 1447, 1111 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.44 (s, 2H), 8.50 (s, 1H), 7.45 (s, 1H).

Anal. Calcd. for $C_6H_4NBr_2Cl$: C, 25.25; H, 1.41; N, 4.91. Found: C, 25.00; H, 1.51; N, 5.00.

N-(5-Bromo-2-chloro-4-pyridylmethyl)-8-azabicyclo[3.2.1]-octan-3-one (**18**).

A solution of 3.8 g (13 mmol) of 5-bromo-4-bromomethyl-2-chloropyridine (**17**), 1.1 g (8.8 mmol) of 8-azabicyclo[3.2.1]-octan-3-one (**9**) and 2.5 mL (18 mmol) of triethylamine in 40 mL of dry toluene were heated at reflux for 18 hours. The reaction mixture was allowed to cool to room temperature and 40 mL of saturated sodium carbonate solution and 40 mL of ether were added. The organic layer was separated and the aqueous layer was extracted by ether (2 x 40 mL). The organic layers were combined, dried (sodium sulfate) and evaporated to give a crude solid, which was purified by flash chromatography (silica gel-hexane: ethyl acetate, 10:1, v/v) to yield 1.5 g (52%) of a yellow solid. This compound was converted into the oxalate salt affording a white powder, mp 159 °(decomp.); ir (KBr): 2955, 1713, 1570, 1331, 1090, 893 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.38 (s, 1H), 7.64 (s, 1H), 3.72 (s, 2H), 3.45 (s, 2H), 2.68 (dd, *J* = 16.4, 4.4 Hz, 2H), 2.24 (d, *J* = 16 Hz, 2H), 2.14-2.10 (m, 2H), 1.70-1.64 (m, 2H); ^{13}C nmr (deuteriochloroform): δ 209.1, 151.7, 151.3, 128.8, 125.0, 120.5, 60.0, 54.7, 48.8, 28.1. MS (EI) *m/z* 329 (M^+, 70), 273 (100), 191 (61).

Anal. Calcd for $C_{13}H_{14}N_2BrClO•C_2H_2O_4•0.5H_2O$: C, 42.03; H, 4.00; N, 6.53. Found: C, 41.76; H, 3.84; N, 6.26.

6-Chloro-2,7-diazatetracyclo[8.5.0.$0^{2,13}$.$0^{4,9}$]pentadeca-4,6,8-triene-11-one (**6**).

A Schlenk tube, flame-dried *in vacuo*, was placed under an Ar atmosphere on a vacuum line. The tube was charged with 70 mg (10 mol%, 0.1 mmol) of *trans*-dichloro-bis(triphenylphosphine) palladium, 980 mg (3 mmol) cesium carbonate, 330 mg (1 mmol) *N*-(5-bromo-2-chloro-4-pyridylmethyl)-8-azabicyclo[3.2.1]-

Table 2

Crystal Data and Structure Refinement for **6**

Empirical formula	$C_{13}H_{13}ClN_2O$	
Formula weight	248.70	
Temperature	150(2)K	
Wavelength	0.71073 Å	
Crystal system, space group	Orthorhombic, Pbca	
Unit cell dimensions	a = 6.9021(4)Å	α = 90°
	b = 14.6333(9)Å	β = 90°
	c = 22.7108(14)Å	γ = 90°
Volume	2293.8(2) $Å^3$	
Z, Calculated density	8, 1.440 Mg/m^3	
Absorption coefficient	0.316 mm^{-1}	
F(000)	1040	
Crystal size	0.15 x 0.30 x 0.45 mm	
Theta range for data collection	2.78 to 28.89 deg.	
Limiting indices	-9<=h<=9, -19<=k<=19, -30<=l<=29	
Reflections collected / unique	19131 / 2911 [R(int) = 0.0629]	
Completeness to theta = 28.89	96.4 %	
Absorption correction	Empirical	
Max. and min. transmission	1.000000 and 0.576179	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2911 / 165 / 206	
Goodness-of-fit on F^2	0.998	
Final R indices [I>2sigma(I)]	R1 = 0.0410, wR2 = 0.1049	
R indices (all data)	R1 = 0.0576, wR2 = 0.1120	
Largest diff. peak and hole	0.400 and -0.260 e. $Å^{-3}$	

octan-3-one (**18**) and 5 mL of dry toluene. The Schlenk tube was sealed and heated in an oil bath (100-110 °C) for10 hours. The mixture was allowed to cool to room temperature and diluted with 10 mL of water. The mixture was then extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine, and dried (magnesium sulfate). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel-hexane:ethyl acetate, 1:1, v/v). This afforded 130 mg (53%) of a white solid to give **6**, mp 142-144°. This compound was converted into the oxalate salt affording a white powder, mp 188 °(decomp.). ^{1}H nmr (deuteriochloroform): δ 8.10 (s, 1H), 7.16 (s, 1H), 4.55 (d, J = 20 Hz, 1H), 4.26 (d, J = 19.6 Hz, 1H), 3.77 (t, J = 5.2 Hz, 1H), 3.54 (s, 1H), 3.48 (d, J = 7.2 Hz, 1H), 2.32 (ddd, J = 14.8, 4.8, 2 Hz, 1H), 2.19-2.01 (m, 3H), 1.81-1.74 (m, 1H), 1.63-1.57 (m, 1H); ^{13}C nmr deuteriochloroform): δ 206.2, 150, 149.2, 147.7, 128.5, 121.1, 62.2, 58.1, 54.6, 48.0, 42.8, 28.3, 27.0. MS (ESI) *m/z* 249 (MH^+).

Anal. Calcd for $C_{13}H_{13}N_2ClO•C_2H_2O_4•H_2O$: C, 50.5; H, 4.80; N, 7.85. Found: C, 50.82; H, 4.54; N, 7.44.

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