A Short and Efficient Total Synthesis of (±)-Epibatidine

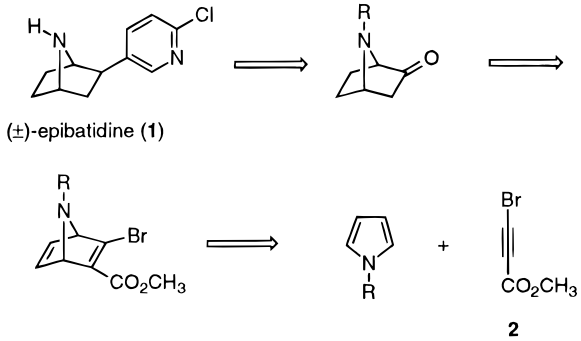
Chunming Zhang and Mark L. Trudell*

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

Received May 13, 1996

Epibatidine (**1**), which was isolated from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, by Daly and co-workers,[1] exhibits remarkable non-opioid analgesic properties.[1−4] Epibatidine (**1**) was found to be 200 to 500 times more potent an analgesic than morphine.[1] Due to this intriguing biological activity, the uncommon 7-azabicyclo[2.2.1]heptane ring system and its scarcity in nature (less than 0.5 mg was isolated from 750 frogs), the total synthesis of epibatidine (**1**) has attracted the attention of a number of synthetic laboratories around the world.[3−5] A variety of synthetic approaches to this novel alkaloid have been reported based primarily on four different methodologies for the construction of the novel azabicyclic system: (1) the [4 + 2] cycloaddition reaction of *N*-protected pyrroles with activated dienophiles;[6−9] (2) the intramolecular nucleophilic substitution ring closure of 1,4-aminocyclohexane derivatives;[10−17] (3) the [3 + 2] cycloaddition of nonstabilized azomethine ylide and substituted 6-chloro-3-vinylpyridine;[18] and (4) more recently, the ring contraction of the tropinone skeleton *via* a Favorskii rearrangement.[19]

Condensation of *N*-protected 7-azabicyclo[2.2.1]heptan-2-ones with 5-lithio-2-chloropyridine has been shown to be one of the most straightforward and versatile methods for the construction of the basic skeleton of epibatidine.[9,11,14,20] However, *N*-protected 7-azabicyclo[2.2.1]-heptan-2-ones are not readily available, and reported synthetic methods involve multiple step manipulations.[11,14,20] Recently, we discovered that methyl 3-bromopropiolate (**2**)[21] smoothly reacts with pyrrole derivatives to afford the [4 + 2] cycloaddition adducts in good yields.[22] Since **2** is considered an alkoxycarbonyl ketene equivalent,[23,24] we envisaged that the *N*-protected 7-azabicyclo[2.2.1]heptan-2-one could be synthesized from the cycloaddition adduct by simple transformations. Herein we wish to report a new short and efficient total synthesis of (±)-epibatidine (**1**). Distincly different from the previous approaches, the synthesis features the [4 + 2] cycloaddition reaction of methyl 3-bromopropiolate (**2**)[21] with *N-Boc*-pyrrole (**3**)[25] for the construction of the 7-azabicyclo-[2.2.1]heptane system. We have found this approach to be quite facile and efficient for the rapid preparation of (±)-epibatidine (**1**).



Results and Discussion

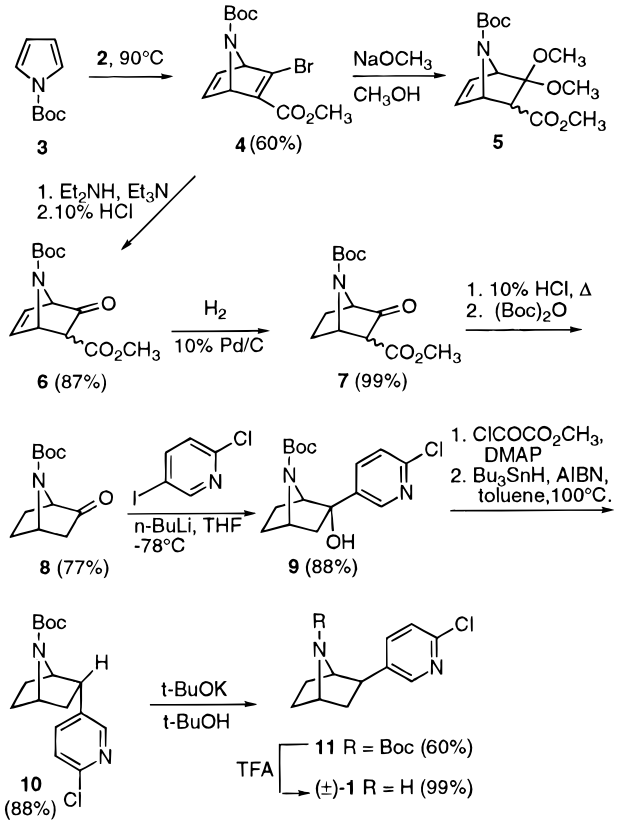
As illustrated in Scheme 1, heating **2** with 5 equiv of **3** at 90−95 °C for 30 h gave the expected cycloaddition adduct **4** in 60% yield. With **4** in hand, conversion of the vinyl bromide into the 7-azabicyclo[2.2.1]heptan-2-one ketone was first attempted using reported methods.[23,24] Treatment of **4** with sodium methoxide in methanol afforded the corresponding dimethyl ketal **5**. However, **5** was found to be resistant to hydrolysis. Alternatively, treatment of adduct **4** with 1.1 equiv of diethylamine in the presence of 5 equiv of triethylamine in acetonitrile at room temperature (2 h), followed by hydrolysis with 10% HCl at room temperature, afforded the desired β-keto ester **6** in 87% yield as a mixture of isomers (*endo*/*exo*, 7:1) (Scheme 1).[26] Attempts to decarboxylate **6** to the corresponding ketone with 10% HCl (100 °C) were unsuccessful due to susceptibility of a retro [4 + 2] cycloaddition reaction. This problem was overcome by hydrogenation of the carbon-carbon double bond of **6** over 10% Pd/C (H_2, 1 atm) to afford **7** as a mixture of isomers (*endo*/*exo*, 3:2) in quantitative yield. The β-keto ester **7** was then decarboxylated using a reported procedure[20] to provide the desired ketone **8** in 77% yield (Scheme 1).

Treatment of ketone **8** with 5-lithio-2-chloropyridine, which was generated by lithiation of 2-chloro-5-iodopyridine[27] with *n*-BuLi at −78 °C under argon, afforded the tertiary alcohol **9** in 88% yield. Successful removal of the hydroxyl function was then achieved by using the procedure developed by Dolan and MacMillan.[28] Treat-

(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.
(2) Bradley, D. *Science* **1993**, *261*, 1117.
(3) For a recent review see: Szántay, C.; Kardos-Balogh, Z.; Szántay, C., Jr. *The Alkaloids*; Academic Press: New York, 1995; Vol. 46, p 95.
(4) For a review on the synthesis of the 7-azabicyclo[2.2.1]heptane system see: Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179.
(5) Broka, C. A. *Med. Chem. Res.* **1994**, *4*, 449.
(6) Huang, D. F.; Shen, T. Y. *Tetrahedron Lett.* **1993**, *34*, 4477.
(7) Kotian, P. L.; Carroll, F. I. *Synth. Commun.* **1995**, *25*, 63.
(8) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493.
(9) Okabe, K.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 1432.
(10) Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251.
(11) (a) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Hobbs, S. C.; Mitchell, P. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1216. (b) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, G. R. *J. Org. Chem.* **1994**, *59*, 1771.
(12) Corey, E. J.; Loh, T.-P.; AchyuthaRao, S.; Daley, D. C.; Sarshar, S. *J. Org. Chem.* **1993**, *58*, 5600.
(13) Szántay, C.; Kardos-Balogh, Z.; Moldvai, I.; Szántay, C., Jr.; Temesvári-Major , E.; Blaskó, G. *Tetrahedron Lett.* **1994**, *35*, 3171.
(14) Senokuchi, K.; Nakai, H.; Kawamura, M.; Katsube, N.; Nonaka, S.; Sawaragi, H.; Hamanaka, N. *Synlett* **1994**, 343.
(15) Sestanj, K.; Melenski, E.; Jirkovsky, I. *Tetrahedron Lett.* **1994**, *35*, 5417.
(16) Ko, S. Y.; Lerpiniere, J.; Linney, I. D.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1775.
(17) Albertini, E.; Barco, A.; Benetti, S.; Risi, C. D.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9297.
(18) Pandey, G.; Bagul, T. D.; Lakshmaiah, G. *Tetrahedron Lett.* **1994**, *35*, 7439.
(19) Xu, R.; Chu, G.; Bai, D. *Tetrahedron Lett.* **1996**, *37*, 1463.
(20) Hernández, A.; Marcos, M.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 2683.
(21) Leroy, J. *Synth. Commun.* **1992**, *22*, 567.
(22) Zhang, C.; Trudell, M. L. Unpublished results.
(23) Chamberlain, P.; Rooney, A. E. *Tetrahedron Lett.* **1979**, 383.
(24) Leroy, J. *Tetrahedron Lett.* **1992**, *33*, 2969.
(25) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296.
(26) Ji, J.; Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1160.
(27) Hama, Y.; Nobuhara, Y.; Aso, Y.; Otsubo, T.; Ogura, F. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1683.
(28) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1588.

S0022-3263(96)00868-7 CCC: $12.00

Scheme 1



ment of **9** with methyl oxalyl chloride in the presence of 2 equiv of 4-(dimethylamino)pyridine (DMAP) in dry acetonitrile for 10 min afforded the corresponding methyl oxalyl ester **9**, which without purification was subjected to radical deoxygenation with Bu_3SnH in the presence of AIBN in toluene at 100 °C (1 h). This afforded the deoxygenated product stereoselectively as the *endo*-isomer **10** in 87% yield. This represented a significant improvement over previous methods used for the deoxygenation of the alcohol.[9,11,14]

Epimerization of **10** using potassium *tert*-butoxide in refluxing *tert*-butyl alcohol[11] afforded the desired *exo*-isomer **11** in 60% yield. Deprotection of the *N*-Boc-protected *exo*-isomer **11** using trifluoroacetic acid in CH_2Cl_2 at room temperature furnished (±)-epibatidine (**1**) as a white solid in almost quantitative yield (99%) (Scheme 1).

In summary, a short and practical process has been developed for the synthesis of (±)-epibatidine (**1**) from readily available materials using mild and easily controlled reactions. It is noteworthy that the 7-azabicyclo-[2.2.1]heptan-2-one **8** was conveniently synthesized by the [4 + 2] cycloaddition reaction of methyl 3-bromopropiolate (**2**) and *N*-Boc-pyrrole (**3**). In addition, the tertiary alcohol **9** was successfully deoxygenated by a radical reaction *via* its methyl oxalyl ester with Bu_3SnH in the presence of AIBN. This has resulted in a facile and practical route to (±)-epibatidine and its analogs.

Experimental Section

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Ether (E. M. Science) and THF were dried by distillation from Na/benzophenone. Acetonitrile was dried by distillation over P_2O_5. Chromatography refers to flash chromatography on silica gel (silica gel 60, 230−400 mesh, E. M. Science), and petroleum ether refers to pentanes with a boiling point range of 30−60 °C. Reported melting points are uncorrected. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

Methyl 2-Bromo-7-(*tert*-butoxycarbonyl)-7-azabicyclo-[2.2.1]hepta-2,5-diene-2-carboxylate (4). A mixture of methyl 3-bromopropiolate (**2**)[21] (2.12 g, 13.0 mmol) and *N*-Boc-pyrrole (**3**)[25] (10.85 g, 65.0 mmol) was stirred at 90−95 °C under argon for 30 h. The resulting mixture was cooled to room temperature and subjected to column chromatography (EtOAc/petroleum ether, 1:15). The first fraction contained unreacted **3** (8.8 g), followed by the adduct **4** (2.58 g, 60%) as a slightly yellow oil: IR (NaCl) 1709, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (br s, 2H), 5.47 (s, 1H), 5.13 (s, 1H), 3.79 (s, 3H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 162.5, 153.8, 147.6, 143.6, 141.6, 140.7, 81.5, 75.5, 68.8, 51.9, 20.2; MS (CI, CH_4) m/z 332 (M + 1, 100), 330 (M + 1, 98). Anal. Calcd for $C_{13}H_{16}BrNO_4$: C, 47.29; H, 4.88; N, 4.24. Found: C, 47.26; H, 4.92; N, 4.27.

7-(*tert*-Butoxycarbonyl)-3-(methoxycarbonyl)-7-azabicyclo[2.2.1]hept-5-ne-2-one (6). To a solution of **4** (2.00 g, 6.06 mmol) and triethylamine (4.20 mL, 30.3 mmol) in acetonitrile (15 mL) was added dropwise a solution of diethylamine (0.69 mL, 6.67 mmol) in acetonitrile (10 mL) under an argon atmosphere. The mixture was stirred at room temperature for 1.5 h. A 10% HCl (20 mL) solution was then added dropwise. The reaction mixture was stirred for an additional 4 h. Water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The CH_2Cl_2 solution was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed (EtOAc/petroleum ether, 1:6) to afford the β-keto ester **6** (1.40 g, 86.5%) as an oil (*endo*/*exo*, 7:1): IR (NaCl) 1776, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.95 (d, J = 3.7 Hz, 0.88H), 6.75 (s, 0.12H), 6.50 (s, 0.12H), 6.35 (d, J = 3.7 Hz, 0.88H), 5.42 (s, 0.12H), 5.09 (s, 0.88H), 4.69 (s, 1H), 3.75 (s, 2.64H), 3.72 (s, 0.36H), 3.40 (d, J = 3.5 Hz, 0.88H), 2.93 (s, 0.12H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 195.7, 167.2, 166.7, 154.1, 142.3, 128.6, 81.6, 81.6, 68.3, 61.2, 52.7, 51.6, 20.2; MS (CI, CH_4) m/z 268 (M + 1, 43.5), 212 (100). Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.39; H, 6.39; N, 5.28.

7-(*tert*-Butoxycarbonyl)-3-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-one (7). A suspension of **6** (800 mg, 3.0 mmol) and 10% Pd/C (100 mg) in methanol (10 mL) was vigorously stirred under a hydrogen atmosphere (1 atm) at room temperature for 10 h. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure and flash chromatographed on silica gel (EtOAc/petroleum ether, 1:6) to afford **7**[20] (804 mg, 99%) as a colorless oil (*endo*/*exo*, 3:2): ^1H NMR ($CDCl_3$) δ 4.83 (d, J = 3.7 Hz, 0.4H), 4.72 (t, J = 4.4 Hz, 0.6H), 4.35 (d, J = 3.7 Hz, 0.4H), 4.32 (d, J = 4.4 Hz, 0.6H), 3.74 (s, 1.2H), 3.72 (s, 1.8H), 3.44 (d, J = 5.0 Hz, 0.6H), 2.99 (s, 0.4H), 2.00−2.09 (m, 2H), 1.64−1.90 (m, 2H), 1.45 (br s, 9H); ^{13}C NMR ($CDCl_3$) δ 202.2, 202.1, 167.2, 166.3, 154.5, 154.1, 81.5, 81.0, 64.4, 63.0, 59.8, 58.9, 58.6, 57.8, 52.7, 52.5, 28.1, 27.4, 24.9, 24.7, 23.9.

7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-one (8). A solution of the β-keto ester **7** (930 mg, 3.457 mmol) in 10% HCl (75 mL) was heated at 100−110 °C for 3 h under an argon atmosphere. The solution was allowed to cool to room temperature and evaporated under reduced pressure. The trace of remaining water was removed by azeotropic distillation with EtOH and dried. The residue was dissolved in CH_2Cl_2 (50 mL), and Et_3N (1.9 mL, 14 mmol) and $(Boc)_2O$ (1.50 g, 6.9 mmol) were added. The solution was stirred for 24 h at room temperature and then washed with saturated Na_2CO_3. The organic layer was dried (Na_2SO_4), filtered, and concentrated to provide a yellow oily residue which was chromatographed (EtOAc/petroleum ether, 1:5) to afford the ketone **8**[20] (0.56 g, 77%) as a white solid. mp 60−62 °C; ^1H NMR ($CDCl_3$) δ 4.57 (t, J = 4.6 Hz, 1H), 4.26 (d, J = 4.6 Hz, 1H), 2.47 (dd, J = 17.6, 5.3 Hz, 1H), 1.99−2.05 (m, 3H), 1.57−1.68 (m, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 209.2, 154.8, 80.7, 63.9, 56.0, 15.2, 28.2, 27.6, 24.5.

***exo*-2-(2-Chloro-5-pyridinyl)-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-ol (9).** To a solution of 2-chloro-5-iodopyridine (264 mg, 1.1 mmol) in ether (5 mL) and THF (2.5 mL) at −78 °C was added *n*-BuLi (0.675 mL, 1.56 M solution in hexane, 1.05 mmol) dropwise. The mixture was stirred at −78 °C for 30 min before a solution of ketone **8** (211 mg, 1.0 mmol) in ether (3 mL) was added dropwise. The mixture was stirred at −78 °C for 3 h and then warmed to −50 °C and stirred for an

additional 30 min. Saturated aqueous NH_4Cl (2 mL) was added, and the mixture was allowed to warm to room temperature. Water (5 mL) was added, and the organic layer was separated. The aqueous phase was extracted with EtOAc (10 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed (EtOAc/petroleum ether, 1:3) to give the tertiary alcohol **9**[11b] (286 mg, 88%) as a colorless solid. mp 147−150 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 2.6 Hz, 1H), 7.86 (dd, J = 8.4, 2.5 Hz, 1H), 7.25 (d, J = 8.4 Hz, 1H), 4.29 (br s, 1H), 4.20 (br s, 1H), 2.9−3.3 (m, 1H), 2.29−2.41 (m, 2H), 1.64−1.90 (m, 4H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 154.7, 149.4, 146.95, 142.8, 136.4, 123.4, 80.2, 65.5, 60.5, 57.2, 48.0, 28.3, 23.0.

***endo*-2-(Chloro-5-pyridinyl)-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane (10).** To a solution of the tertiary alcohol **9** (130 mg, 0.4 mmol) and 4-(dimethylamino)pyridine (DMAP, 73.3 mg, 0.6 mmol) in dry CH_3CN (5 mL) was added methyl oxalyl chloride (0.055 mL, 0.6 mmol). The mixture was stirred for 10 min at room temperature under an argon atmosphere and then diluted with EtOAc (20 mL). The mixture was then washed successively with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL). The organic portion was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was coevaporated twice with toluene to afford the methyl oxalyl ester. Without further purification, the crude ester was added to a mixture of Bu_3SnH (0.180 mL, 0.63 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN, 10 mg) in dry toluene (5 mL) under an argon atmosphere. The mixture was heated at 100 °C for 1 h, and the solvent was removed under reduced pressure. The residue was purified by chromatography (EtOAc/hexane, 1:9) to afford the *endo*-isomer **10**[11b] (105 mg, 85%) as a white solid and a trace of the *exo*-isomer **11** (less than 5 mg). **10**: mp 80−82 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 2.3 Hz, 1H), 7.46 (dd, J = 8.2, 2.3 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 4.3 (m, 2H), 3.44 (m, 1H), 2.29 (m, 1H), 1.84 (m, 1H), 1.40−1.60 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 155.5, 149.5, 138.6, 134.8, 124.0, 80.2, 66.1, 60.5, 57.5, 43.8, 34.6, 30.5, 28.6, 23.6.

***exo*-2-(2-Chloro-5-pyridinyl)-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]heptane (11). Epimerization of 10.** A mixture of **10** (103 mg, 0.334 mmol) and *t*-BuOK (187 mg, 1.669 mmol) in *tert*-butyl alcohol (5 mL) was refluxed for 45 h under an argon atmosphere. The solvent was evaporated, and the residue was chromatographed (EtOAc/hexane, 1:9) to afford the *endo*-isomer **10** (35.1 mg) and the *exo*-isomer **11**[11b] (40.5 mg, 60% based on recovered **10**) as a colorless solid: mp 67−69 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 4.35 (br s, 1H), 4.13 (br s, 1H), 2.85 (dd, J = 8.9, 4.9 Hz, 1H), 1.95 (d, J = 8.8 Hz, 1H), 1.80 (m, 3H), 1.55 (m, 2H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 155.0, 149.1, 148.5, 139.9, 137.1, 124.0, 79.9, 61.9, 56.1, 44. 9, 40.4, 29.8, 28.9, 28.8.

(±)-*exo*-2-(2-Chloro-5-pyridinyl)-7-azabicyclo[2.2.1]-heptane ((±)-epibatidine) (1). To a solution of **11** (40.5 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added dropwise with stirring under argon trifluoroacetic acid (0.15 mL, 1.95 mmol). The mixture was stirred for 3 h at room temperature and rendered basic with saturated Na_2CO_3 (3 mL). The organic layer was separated, and the water phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (CH_2Cl_2/MeOH/Et_3N, 90:10:1) to give **1** (27 mg, 99%) as a white solid: mp 50−51 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (d, J = 2.5 Hz, 1H), 7.75 (dd, J = 8.3, 2.5 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 3.80 (br s, 1H), 3.57 (br s, 1H), 2.77 (dd, J = 8.8, 4.9 Hz, 1H), 1.91 (dd, J = 12.2, 9.0 Hz, 1H), 1.50−1.63 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 148.8, 148.6, 140.7, 137.5, 123.8, 62.8, 56.5 44.5, 40.3 31.3 , 30.2.

Acknowledgment. We are grateful to the National Institute on Drug Abuse (NIDA First Award, DA08055) for the financial support of this research.

JO9608681