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Total Synthesis of a Frog Poison, (±)-Epibatidine, a Potent Non-opioid Analgesic

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A non-opioid analgesic, epibatidine (1), isolated from Ecuadoran poison frogs was synthesized in the racemic form starting from a readily available compound 2. A partial Curtius rearrangement product 5 of 2 was converted into 12c by way of the ketone 3 and its condensation product with the pyridine moiety 9c, and catalytic hydrogenation of 12c was specifically conducted in hydrochloric acid-containing 2-propanol for the preferential formation of an *exo*-product 15b. Conversion of the substituent from 15b to 15a in a single operation using the Vilsmeier reagent, followed by deprotection of the *p*-toluenesulfonyl group with hydrobromic acid completed an eight-step synthesis of (±)-1 from 2.

Keywords total synthesis; poison frog constituent; epibatidine; non-opioid analgesic

Epibatidine (**1**) is a novel alkaloid isolated in a trace amount by Daly *et al.* in 1992 from Ecuadoran poison frog, *Epipedobates tricolor*, of the family Dendrobatidae.[1] The chemical structure of **1** was determined by spectroscopic means without assignment of the absolute configuration. The preliminary biological tests showed **1** to be a non-opioid analgesic, 200—500 times as potent as morphine.[1] Recently however, high toxicity of **1** to mice was reported.[2a] Several groups have recently reported total syntheses of **1**.[2] We have also been engaged in a synthetic study, and here we disclose our synthesis of (±)-**1**, according to the plan shown in Chart 1. Compound **2**[3] having σ symmetry is readily prepared from the Diels–Alder adduct[4] between 1-(*p*-toluenesulfonyl)pyrrole and dimethyl acetylenedicarboxylate, and should be available as a starting material for the enantioselective synthesis of either enantiomer of **1** by conducting a regioselective functionalization of the carboxylate groups in **2** using a chemical or enzymatic procedure. A possible method for the partial functionalization is the conversion of one of the two methyl carboxylates into a heteroatom group to furnish finally the ketone derivative **3**.[5] The requisite 3-pyridyl function can be introduced into this ketone group to afford (±)-epibatidine (**1**).

For that purpose, the diester **2** was cleanly hydrolyzed to a monoester **4** with 1 molar eq of lithium hydroxide in a mixture of 1,2-dimethoxyethane (DME) and water (2 : 1) at room temperature in 70% yield (Chart 2). This acid **4** was treated with diphenylphosphoryl azide[6] (DPPA) and triethylamine in a solution of *tert*-butanol and *N*,*N*-dimethylformamide (DMF) (1 : 1) at 80—85 °C for 13.5 h, and the Curtius rearrangement product **5** was produced in 75% yield. To perform a stereoselective introduction of the necessary 2-chloro-5-pyridyl moiety into the 7-azabicyclo[2.2.1]heptane system with *exo* configuration, we initially planned the conjugate addition of a pyridyl anion to the α,β-unsaturated carboxylate **8**. Therefore, the carbamate **5** was catalytically hydrogenated over 10% palladium–carbon at a pressure of 3 atm at room temperature to afford **6** in 81% yield. A mild treatment of **6** with potassium carbonate in methanol at room temperature for 1 h gave an epimer **7** in a quantitative yield. However, attempted formation of the α,β-unsaturated ester **8** was unsuccessful under various conditions of base treatment for **6** and **7**.

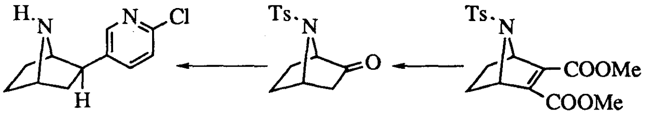


Chart 1

Preparation of the ketone **3** was next tried aiming at a steady introduction of the pyridyl part into the bicyclo system (Chart 3). Formation of **3** was readily achieved in a single step and in 68% yield by heating a solution of **5** in a mixture of 2% hydrogen chloride-containing 1,4-dioxane and water (3 : 2) at *ca.* 80 °C for 14.5 h under an Ar atmosphere. Pyridyllithium derived from 3-bromopyridine or 5-bromo-2-chloropyridine[7] using butyllithium in diethyl ether was allowed to react with this ketone **3** at *ca.* −80 °C for 20 min to afford the condensation product **9a** or **9b** in 76% or 88% yield, respectively, accompanied with the formation of an epimer **10a** in 2% yield in the former case. Dehydration of **9a** and **9b** was carried out with thionyl chloride in the presence of pyridine or 2,6-lutidine at −20 °C to give **12a** and **12b**

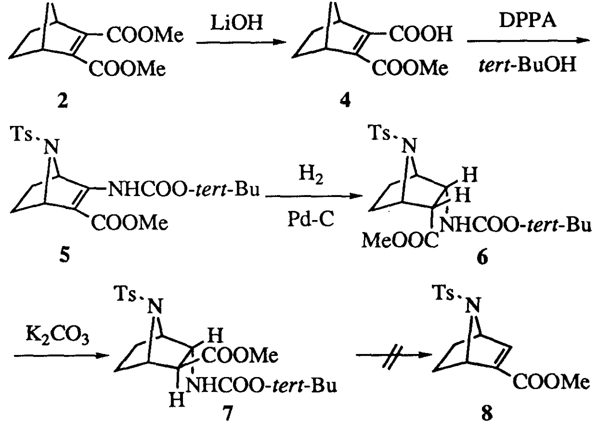
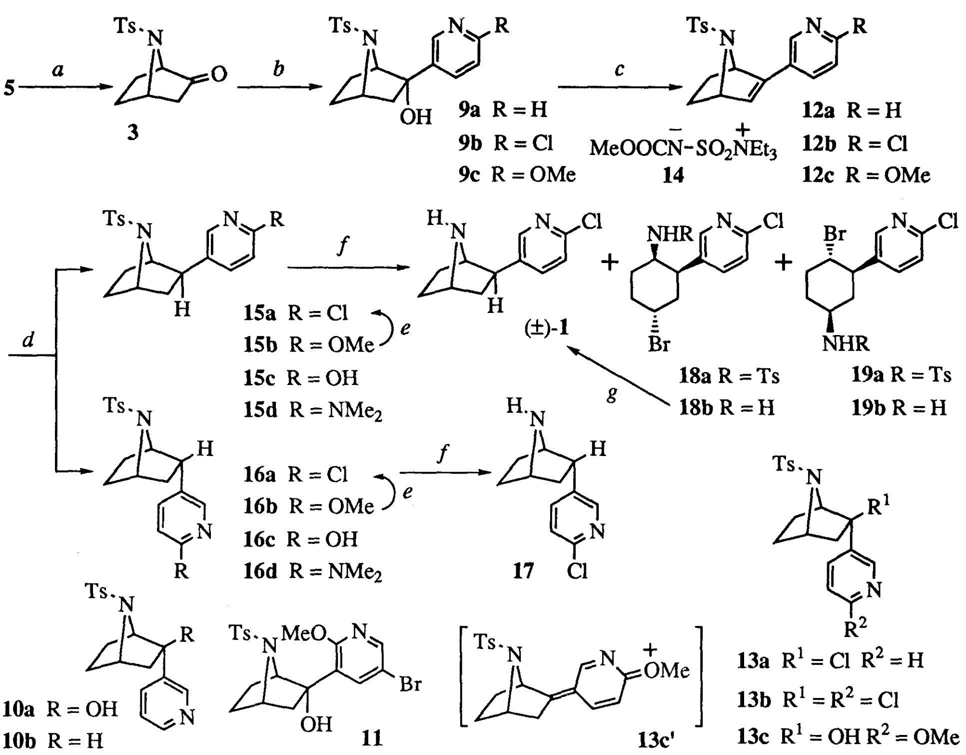


Chart 2



a: 2% HCl in 1,4-dioxane-H_2O. *b*: 3-bromopyridine, 5-bromo-2-chloropyridine, or 5-bromo-2-methoxypyridine, BuLi. *c*: $SOCl_2$, pyridine, or 2,6-lutidine; or $MeOOC\overset{-}{N}-SO_2\overset{+}{N}Et_3$ **14**. *d*: H_2, 10% Pd-C, HCl, iso-PrOH. *e*: DMF-$POCl_3$. *f*: 30% HBr-AcOH, PhOH. *g*: LiOH, DME-H_2O.

Chart 3

in 55% and 56% yields. The by-products **13a** and **13b** were generated in 9% and 34% yields, respectively. Usual catalytic hydrogenation of **12a** over Raney nickel (W-2) in ethanol at room temperature afforded, as anticipated, an *endo*-product **10b** in 40% yield, together with an inseparable mixture of an *exo*-product and the recovery of **12a**. When **12b** was hydrogenated catalytically with either 10% palladium on carbon or platinum oxide, reductive dechlorination on the pyridine ring proceeded predominantly with little formation of the desired compound **15a**.

To avoid this difficulty, we finally adopted a synthetic scheme by way of the 2-methoxy-5-pyridyl derivative **15b**. A lithium salt prepared from 5-bromo-2-methoxypyridine[8)] and butyllithium was condensed with the ketone **3** in tetrahydrofuran (THF) at *ca.* −75 °C for 20 min to provide **9c** in 89% yield. Along with the recovery of **3** in 5% yeild, **11** was formed in 1% yield as a by-product, indicative of the generation of 5-bromo-3-lithio-2-methoxypyridine in a trace amount at the carbanion formation step. This time, use of thionyl chloride for the dehydration of **9c** gave **12c** in only 44% yield. A major product was **13c** (47% yield), probably originating from the corresponding chloro derivative, which was readily hydrolyzed during work-up *via* the oxonium salt **13c'**. Therefore the Burgess reagent[9)] **14** was selected for the requisite dehydration reaction, and **12c** was obtained in 68% yield by refluxing a benzene solution of **9c** and **14** for 3 h under an Ar atmosphere. Since the usual hydrogenation of **12c** over 10% palladium–carbon in methanol afforded **15b** and **16b** in 19% and 76% yields, respectively, improvement of the hydrogenation conditions was tried by carrying out the reaction in an acidic medium. This idea was based on the assumption that the protonic cation associated with an alcohol molecule would interact with the electron-rich double bond of **12c** at the more reactive *exo* face of the bicyclo framework, assisted by participation of the slightly basic tosylamide nitrogen, so as to regulate approach of the palladium catalyst from the *endo* side of **12c**, favoring the production of **15b**. So the catalytic hydrogenation was carried out in a *ca.* 1% hydrochloric acid-containing solution of methanol and water (11 : 1) at room temperature for 4 h. The production ratio of **15b** and **16b** was dramatically changed to 69% and 26% yields, respectively. In the case of the protonated form of an alcohol, use of 2-propanol, which is bulkier than methanol, would further block the double bond at the *exo* side of **12c**, and the best result was obtained by performing the same palladium-catalyzed hydrogenation as above in a solution of 2-propanol and water (12 : 1) containing *ca.* 1% hydrochloric acid, affording **15b** and **16b** in 72% and 22% yields, respectively.

Two steps remained for completion of the synthesis, *i.e.*, conversion of the methoxy group to the chlorine atom and removal of the tosyl protecting group. For the former process, a pathway by way of the pyridone **15c** had been considered, but we employed a direct method using the Vilsmeier reagent[7)] for the transformation of **15b** into **15a**. When the methoxypyridines **15b** and **16b** were separately heated with the reagent in DMF at 95—99 °C for 3.5—4 h, the chloropyridines **15a** and **16a** were produced in 70.5% and 67% yields, respectively, together with the pyridones **15c** (6% yield) and **16c** (6% yield) as well as the dimethylaminopyridines **15d** (3% yield) and **16d** (6% yield). As for the final step of removal of the protecting group, the usual procedure involving a reductive *N*-tosyl bond cleavage was not applicable in this case due to the presence of a reduction-sensitive 2-chloropyridine moiety. So rather drastic conditions using a commercial solution of 30% hydrobromic acid in acetic acid[10)] were introduced for that purpose. Deprotection of **16a** was achieved cleanly by stirring an ethyl acetate solution of **16a**, 30 molar eq of 30% hydrobromic acid in acetic acid, and *ca.* 5 molar eq of phenol at room temperature for 18 h. The expected product **17** was obtained in 71% yeild, accompanied by the recovery of **16a** in 27% yield. The presence of phenol was essential for a clean reaction and good yield. By contrast, removal of the tosyl group from **15a** required forcing reaction conditions, *i.e.*, warming a chloroform solution of **15a** with the above amounts of 30% hydrobromic acid–acetic acid and phenol in a sealed tube at 55 °C for 18 h. The reaction products appeared complex on TLC, but after separation of **18a** (3% yield), **19a** (4% yield), and the recovery of **15a** (7% yield), a fraction containing (±)-**1** was found to be contaminated with **18b** and **19b**. Without further separation, this mixture was treated with lithium hydroxide in DME and water (2 : 1) at 55 °C for 15 h for recyclizing the bromoamines to the bicyclo system, and (±)-**1** was finally obtained in 76% yield. The ^{1}H- and ^{13}C-NMR spectra of this compound were in good accordance with those described in the literature.[2c)]

In summary, a total synthesis of (±)-epibatidine (**1**) was accomplished in eight steps from a readily available compound **2** by way of **5**, **9c**, **12c**, **15b**, and **15a**. Enantioselective synthesis of the enantiomers of **1** is in progress.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are not corrected. MS and high-resolution MS (HRMS) were recorded on a Hitachi M-80B spectrometer at an ionizing voltage of 70 eV, and figures in parentheses indicate the relative intensities. IR spectra were measured on a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrometer in $CDCl_3$ with TMS as an internal reference. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were measured on a JEOL JNM-GX-400 spectrometer. Column chromatography was conducted on silica gel, Fuji Davison BW 200 and preparative TLC (PTLC) was carried out on glass plates (20 × 20 cm) coated with Merck Silica gel 60 PF_{254} (1 mm thick), unless otherwise specified. PTLC over alumina was carried out on glass plates (20 × 20 cm) coated with Merck Aluminum oxide 60 PF_{254} (type E) (1 mm thick). Usual work-up refers to washing of the organic layers with water or brine, drying over anhydrous Na_2SO_4, and evaporating off the solvents under reduced pressure.

3-Methoxycarbonyl-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]hept-2-ene-2-carboxylic Acid (4) A solution of **2** (304 mg, 0.833 mmol) and $LiOH \cdot H_2O$ (35 mg, 0.83 mmol) in DME (10 ml) and H_2O (5 ml) was stirred at 20 °C for 1 h. After evaporation of the solvents under reduced pressure at 20 °C, 1 N HCl–H_2O (2 ml) was added and the whole was extracted with 10% MeOH–CH_2Cl_2. Usual work-up gave a residue (310 mg), which was separated by column chromatography [hexane–THF (2 : 1)→10% MeOH–CH_2Cl_2] over silica gel to afford crude **2** (48 mg) and crude **4** (222 mg). The former was purified by PTLC (CH_2Cl_2) to give recovery of **2** (35.5 mg, 12%). The latter afforded pure **4** (205 mg, 70%) after recrystallization from THF–hexane as colorless prisms, mp 155—157 °C. *Anal.* Calcd for $C_{16}H_{17}NO_6S$: C, 54.69; H, 4.88; N, 3.99. Found: C, 54.68; H, 4.94; N, 4.01. MS *m*/*z*: 323 ($M^+ - H_2C{=}CH_2$, 28), 155 (35), 151 (58), 91 (100), 65 (27). IR (KBr) cm^{-1}: 1725. ^{1}H-NMR (90 MHz) δ: 1.16—1.43 (2H, m), 2.10—2.54 (2H, m), 2.43 (3H, s), 3.90 (3H, s), 4.94—5.19 (2H, m), 7.26 and 7.55 (A_2B_2, $J=8$ Hz).

Methyl 3-(*tert*-Butyloxycarbonyl)amino-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]hept-2-ene-2-carboxylate (5) DPPA (0.18 ml, 0.84 mmol) was added to a solution of **4** (84.5 mg, 0.24 mmol) and Et_3N (0.13 ml, 0.93 mmol) in *tert*-BuOH (5 ml) and DMF (5 ml), and the mixture was heated under an Ar atmosphere at 80—85 °C for 13.5 h, then cooled to 0 °C. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with Et_2O, and worked up as usual. Separation by PTLC [hexane–EtOAc (3 : 1)] gave crude **5** (84 mg), which was further purified by PTLC (CH_2Cl_2) to give **5** (76.5 mg, 75%) as a colorless syrup. MS *m*/*z*: 394 ($M^+ - H_2C{=}CH_2$, 13), 338 (11), 294 (51), 139 (70), 107 (20), 91 (48), 57 (100), 41 (40). IR ($CHCl_3$) cm^{-1}: 1745, 1733, 1680, 1625. ^{1}H-NMR (90 MHz) δ: 1.28—1.46 (2H, m), 1.50 (9H, s), 1.97—2.35 (2H, m), 2.40 (3H, s), 3.64 (3H, s), 4.79—4.92 (1H, m), 5.62—5.76 (1H, m), 7.17 and 7.58 (A_2B_2, $J=8.5$ Hz), 8.24 (1H, br s).

Methyl *endo*-3-(*tert*-Butyloxycarbonyl)amino-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane-*endo*-2-carboxylate (6) A suspension of **5** (22 mg, 0.052 mmol) and 10% Pd–C (12 mg) in MeOH (16 ml) was vigorously stirred under H_2 (3 atm) at 26 °C for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to afford a residue (22 mg). This was purified by PTLC [hexane–EtOAc (3 : 1)] to give **6** (18 mg, 81%) as a colorless syrup. MS *m*/*z*: 351 ($M^+ -$ *tert*-BuO, 2), 223 (21), 102 (25), 91 (24), 68 (100), 57 (55), 41 (23). IR ($CHCl_3$) cm^{-1}: 1732, 1712. ^{1}H-NMR (90 MHz) δ: 1.42 (9H, s), *ca.* 1.50—2.00 (4H, m), 2.44 (3H, s), 3.09—3.40 (1H, m), 3.70 (3H, s), 3.99—4.53 (3H, m), 6.48 (1H, br d, $J=6$ Hz), 7.25 and 7.80 (A_2B_2, $J=8.5$ Hz).

Methyl *endo*-3-(*tert*-Butyloxycarbonyl)amino-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane-*exo*-2-carboxylate (7) A mixture of **6** (9 mg, 0.02 mmol) and anhydrous K_2CO_3 (15 mg, 0.11 mmol) in MeOH (2 ml) was stirred at 25 °C for 1 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2, and worked up as usual. Purification by PTLC (CH_2Cl_2) gave **7** (9 mg, 100%) as a colorless syrup. MS *m*/*z*: 351 ($M^+ -$ *tert*-BuO, 1), 223 (12), 102 (31), 91 (23), 68 (100), 57 (43), 41 (20). IR ($CHCl_3$) cm^{-1}: 1740, 1714. ^{1}H-NMR (90 MHz) δ: 1.45 (9H, s), *ca.* 1.48—2.23 (5H, m), 2.42 (3H, s), 3.65 (3H, s), 4.12—4.58 (3H, m), 4.58—5.00 (1H, m), 7.26 and 7.78 (A_2B_2, $J=8.5$ Hz).

7-(*p*-Toluenesulfonyl)-7-azabicyclo[2.2.1]heptan-2-one (3) A solution of **5** (248 mg, 0.588 mmol) in freshly distilled 1,4-dioxane (10.5 ml) containing 5% HCl–H_2O (7 ml) was stirred under an Ar atmosphere at *ca.* 80 °C for 14.5 h, and allowed to cool. H_2O was added and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with saturated $NaHCO_3$–H_2O and worked up as usual to leave a residue (172 mg). Purification by PTLC [hexane–CH_2Cl_2 (1 : 3)], followed by recrystallization from CH_2Cl_2–MeOH gave **3** (105.5 mg, 68%) as colorless needles, mp 135—136 °C. *Anal.* Calcd for $C_{13}H_{15}NO_3S$: C, 58.55; H, 5.70; N, 5.28. Found: C, 58.82; H, 5.71; N, 5.23. MS *m*/*z*: 237 ($M^+ - H_2C{=}CH_2$, 28), 155 (20), 105 (49), 91 (100), 82 (46), 68 (36), 65 (34), 55 (60), 41 (42), 39 (31). IR (KBr) cm^{-1}: 1765. ^{1}H-NMR (400 MHz) δ: 1.56—1.68 (2H, m), 1.93 (1H, d, $J=17.5$ Hz), 2.05—2.19 (2H, m), 2.35—2.45 (1H, m), 2.44 (3H, s), 4.07—4.13 (1H, m), 4.56—4.62 (1H, m), 7.32 and 7.77 (A_2B_2, $J=8$ Hz).

***endo*-2-Hydroxy-*exo*-2-(3-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (9a) and *exo*-2-Hydroxy-*endo*-2-(3-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (10a)** BuLi in hexane (1.6 M, 0.75 ml, 1.20 mmol) was added to a pre-cooled (−80 °C) solution of 3-bromopyridine (0.12 ml, 1.23 mmol) in Et_2O (3.5 ml), and the solution was stirred under an Ar atmosphere at −80 °C for 10 min. A solution of **3** (106.5 mg, 0.402 mmol) in THF (2.5 ml) was added to the above solution, and the mixture was stirred under an Ar atmosphere at −80—−76 °C for 20 min. Saturated NH_4Cl–H_2O was added and the whole was extracted with 10% MeOH–CH_2Cl_2, then worked up as usual to give a residue (196 mg). Separation by PTLC [hexane–EtOAc (2 : 7)], followed by purification using PTLC (3% MeOH–CH_2Cl_2) gave **9a** (104.5 mg, 76%) and **10a** (3 mg, 2%). Purification using PTLC [hexane–CH_2Cl_2 (1 : 3) and then hexane–EtOAc (2 : 1)] afforded recovered **3** (5.5 mg, 5%). **9a**: Colorless syrup. MS *m*/*z*: 189 ($M^+ -$ Ts, 65), 122 (40), 106 (17), 91 (29), 78 (22), 68 (100). ^{1}H-NMR (90 MHz) δ: 1.39—1.95 (4H, m), 2.09—2.62 (2H, m), 2.41 (3H, s), 3.98—4.46 (2H + OH, m), 7.10 (1H, dd, $J=8$, 4.5 Hz), 7.22 and 7.66 (A_2B_2, $J=8$ Hz), 7.77—7.97 (1H, m), 8.07—8.29 (1H, m), 8.46—8.64 (1H, m). **10a**:

Colorless syrup. MS m/z: 189 ($M^+ - Ts$, 59), 122 (38), 106 (17), 91 (29), 78 (21), 68 (100). ^{1}H-NMR (90 MHz) δ: 2.45 (3H, s), 4.12—4.26 (1H, m), 4.33—4.50 (1H, m), 7.17—7.48 (1H, m), 7.30 and 7.84 (A_2B_2, $J=8.5$ Hz), 7.71—7.98 (1H,, m), 8.40—8.84 (2H, m).

***exo*-2-(2-Chloro-5-pyridyl)-*endo*-2-hydroxyl-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (9b)** A solution of **3** (55.5 mg, 0.21 mmol) in THF (2.5 ml) was added to a solution of 2-chloro-5-lithiopyridine, prepared as above from 5-bromo-2-chloropyridine (123 mg, 0.634 mmol) and 1.6 M BuLi in hexane (0.33 ml, 0.53 mmol) in Et_2O (2.5 ml), and the mixture was stirred under an Ar atmosphere at −76—−74 °C for 20 min. Work-up as above, followed by purification using PTLC [hexane–EtOAc (2 : 1) and 2.5% MeOH–CH_2Cl_2] afforded **9b** (69.5 mg, 88%) along with the recovery of **3** (5 mg, 9%). **9b**: Colorless syrup. MS m/z: 225 (12) and 223 (37) ($M^+ - Ts$), 158 (3) and 156 (9), 142 (4) and 140 (12), 114 (3) and 112 (8), 91 (30), 68 (100), 41 (17). ^{1}H-NMR (90 MHz) δ: 1.36—1.90 (4H, m), 2.11—2.59 (2H, m), 2.41 (3H, s), 3.86 (1H, br s, OH), 4.01—4.15 (1H, m), 4.15—4.34 (1H, m), 7.10 (1H, d, $J=9$ Hz), 7.23 and 7.64 (A_2B_2, $J=8$ Hz), 7.78 (1H, dd, $J=9$, 2.5 Hz), 8.37 (1H, d, $J=2.5$ Hz).

***endo*-2-Hydroxy-*exo*-2-(2-methoxy-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (9c) and *exo*-2-(5-Bromo-2-methoxy-3-pyridyl)-*endo*-2-hydroxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (11)** Similarly reaction of **3** (257 mg, 0.970 mmol) in THF (7 ml) with 5-lithio-2-methoxypyridine, prepared from 5-bromo-2-methoxypyridine (547 mg, 2.91 mmol) and 1.6 M BuLi in hexane (1.50 ml, 2.40 mmol) in THF (8 ml), gave **9c** (323.5 mg, 89%) and **11** (5 mg, 1%), along with recovery of **3** (12.5 mg, 5%). **9c**: Colorless syrup. MS m/z: 219 ($M^+ - Ts$, 52), 152 (64), 136 (14), 91 (27), 68 (100). ^{1}H-NMR (90 MHz) δ: 1.42—1.99 (4H, m), 2.17—2.66 (2H + OH, m), 2.42 (3H, s), 3.89 (3H, s), 4.06—4.33 (2H, m), 6.55 (1H, d, $J=9$ Hz), 7.22 and 7.64 (A_2B_2, $J=8$ Hz), 7.55—7.77 (1H, m), 8.20 (1H, d, $J=3$ Hz). **11**: Colorless syrup. MS m/z: 299 (18) and 297 (17) ($M^+ - Ts$), 234 (6) and 232 (5), 216 (4) and 214 (4), 91 (20), 68 (100). ^{1}H-NMR (90 MHz) δ: 1.46—2.12 (4H, m), 2.17—2.64 (2H, m), 2.42 (3H, s), 3.98 (3H, s), 4.06—4.36 (2H, m), 4.14 (1H, br s, OH), 7.21 and 7.61 (A_2B_2, $J=8.5$ Hz), 7.53 (1H, d, $J=2.5$ Hz), 8.04 (1H, d, $J=2.5$ Hz).

2-(3-Pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (12a) and *exo*-2-Chloro-*endo*-2-(3-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo-[2.2.1]heptane (13a) $SOCl_2$ (0.50 ml, 6.85 mmol) was added at −20 °C to a solution of **9a** (102.5 mg, 0.298 mmol) in pyridine (4 ml), and the mixture was stirred under an Ar atmosphere at the same temperature for 30 min. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with 10% MeOH–CH_2Cl_2, and worked up as usual. Separation by PTLC [hexane–EtOAc (2 : 3)] gave **12a** (54 mg) and **13a** (9.5 mg, 9%). The former was purified by recrystallization from THF–hexane to afford **12a** (53 mg, 55%) as colorless needles, mp 155—156.5 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.17; H, 5.64; N, 8.53. HRMS Calcd for $C_{18}H_{18}N_2O_2S$: 326.1088. Found: 326.1098. MS m/z: 326 (M^+, 1), 298 (84), 171 (13), 155 (40), 143 (21), 91 (100), 65 (25). ^{1}H-NMR (90 MHz) δ: 1.00—1.52 (2H, m), 2.03—2.45 (2H, m), 2.29 (3H, s), 4.71—4.87 (1H, m), 4.93—5.08 (1H, m), 6.02 (1H, d, $J=2$ Hz), 7.04 and 7.52 (A_2B_2, $J=8$ Hz), 7.04—7.41 (2H, m), 8.19—8.36 (1H, m), 8.36—8.56 (1H, m). **13a**: Colorless syrup. HRMS Calcd for $C_{18}H_{19}{}^{37}ClN_2O_2S$ and $C_{18}H_{19}{}^{35}ClN_2O_2S$: 364.0825 and 362.0855. Found: 364.0853 and 362.0871. MS m/z: 364 (4) and 362 (8) (M^+), 298 (7), 223 (31), 209 (6) and 207 (17), 142 (12) and 140 (34), 91 (53), 68 (100), 65 (21), 41 (30). ^{1}H-NMR (90 MHz) δ: 1.54—2.30 (4H, m), 2.41 (3H, s), 2.50—3.09 (2H, m), 4.22—4.41 (1H, m), 4.50—4.64 (1H, m), 7.05—7.32 (1H, m), 7.19 and 7.57 (A_2B_2, $J=8.5$ Hz), 7.59—7.86 (1H, m), 8.37—8.59 (1H, m), 8.65—8.88 (1H, m).

2-(2-Chloro-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]hept-2-ene (12b) and *exo*-2-Chloro-*endo*-2-(2-chloro-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (13b) In the same manner as described above, **9b** (8.5 mg, 0.02 mmol) was treated with $SOCl_2$ (33 μl, 0.45 mmol) in the presence of 2,6-lutidine (0.10 ml, 0.86 mmol) in CH_2Cl_2 (2 ml) to afford **12b** (4.5 mg, 56%) and **13b** (3 mg, 34%). **12b**: Colorless syrup. MS m/z: 362 (0.7) and 360 (1.4) (M^+), 334 (21) and 332 (54), 207 (3) and 205 (9), 179 (5) and 177 (13), 155 (40), 91 (100), 68 (15), 65 (29), 41 (22). ^{1}H-NMR (90 MHz) δ: 1.06—1.44 (2H, m), 2.04—2.48 (2H, m), 2.34 (3H, s), 4.70—4.80 (1H, m), 4.80—5.04 (1H, m), 6.03 (1H, d, $J=2.5$ Hz), 7.07 (1H, br d, $J=8$ Hz), 7.17—7.38 (1H, m), 7.17 and 7.52 (A_2B_2, $J=8.5$ Hz), 7.99—8.11 (1H, m). **13b**: Colorless syrup. HRMS Calcd for $C_{18}H_{18}{}^{37}Cl_2N_2O_2S$, $C_{18}H_{18}{}^{37}Cl^{35}ClN_2O_2S$ and $C_{18}H_{18}{}^{35}Cl_2N_2O_2S$: 400.0406, 398.0435 and 396.0465. Found: 400.0396, 398.0425 and 396.0448. MS m/z: 400 (1), 398 (4) and 396 (6) (M^+); 334 (2) and 332 (4); 245 (1), 243 (7) and 241 (10); 223 (25); 180 (2) and 178 (6); 178 (6), 176 (9) and 174 (12); 155 (11); 91 (51); 68 (100); 65 (18); 41 (32). ^{1}H-NMR (90 MHz) δ: 2.41 (3H, s), 2.51—3.01 (2H, m), 4.23—4.49 (2H, m), 7.13 (1H, d, $J=2.5$ Hz), 7.19 and 7.55 (A_2B_2, $J=8.5$ Hz), 7.67 (1H, dd, $J=8.5$, 2.5 Hz), 8.42 (1H, d, $J=2.5$ Hz).

2-(2-Methoxy-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]-hept-2-ene (12c) (i) With Burgess Reagent: Commercial 97% Burgess reagent (203 mg, 0.826 mmol) was added to a solution of **9c** (154.5 mg, 0.413 mmol) in benzene (15 ml) and the mixture was heated under an Ar atmosphere at 87—90 °C for 3 h, then allowed to cool. H_2O was added and the whole was extracted with Et_2O, and worked up as usual. Purification by column chromatography over silica gel [hexane–EtOAc (5 : 2)], followed by recrystallization from THF–hexane afforded **12c** (100 mg, 68%) as colorless prisms, mp 145—147 °C or needles, mp 126—128 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O_3S$: C, 64.03; H, 5.66; N, 7.86. Found: C, 64.03; H, 5.68; N, 7.80. HRMS Calcd for $C_{19}H_{20}N_2O_3S$: 356.1193. Found: 356.1189. MS m/z: 356 (M^+, 2), 328 (89), 201 (16), 173 (100), 91 (49), 65 (23). ^{1}H-NMR (90 MHz) δ: 1.04—1.40 (2H, m), 1.97—2.39 (2H, m), 2.29 (3H, s), 3.90 (3H, s), 4.65—4.85 (1H, m), 4.85—5.02 (1H, m), 5.79 (1H, d, $J=2.5$ Hz), 6.58 (1H, d, $J=8.5$ Hz), 7.04 and 7.51 (A_2B_2, $J=8$ Hz), 7.15 (1H, dd, $J=8.5$, 2.5 Hz), 7.87 (1H, d, $J=2.5$ Hz).

(ii) With $SOCl_2$: In the same manner as described for the preparation of **12a**, **9c** (9.5 mg, 0.025 mmol) was treated with $SOCl_2$ (40 μl, 0.55 mmol) in the presence of 2,6-lutidine (0.13 ml, 1.12 mmol) in CH_2Cl_2 (2 ml) to afford **12c** (4 mg, 44%) and *exo*-2-hydroxy-*endo*-2-(2-methoxy-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (**13c**) (4.5 mg, 47%) as a colorless syrup. **13c**: MS m/z: 219 ($M^+ - Ts$, 46), 152 (61), 136 (14), 91 (27), 68 (100), 41 (14). ^{1}H-NMR (90 MHz) δ: 1.04—1.95 (4H, m), 2.08—2.28 (2H, m), 2.44 (3H, s), 3.14 (1H, br s, OH), 3.91 (3H, s), 4.09—4.25 (1H, m), 4.28—4.50 (1H, m), 6.71 (1H, d, $J=8.5$ Hz), 7.30 and 7.84 (A_2B_2, $J=8.5$ Hz), 7.63 (1H, dd, $J=8.5$, 2.5 Hz), 8.15 (1H, d, $J=2.5$ Hz).

***exo*-2-(2-Methoxy-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo-[2.2.1]heptane (15b) and *endo*-2-(2-Methoxy-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (16b)** A solution of **12c** (62.5 mg, 0.18 mmol) in 2-propanol (17.5 ml) and 10% HCl (1.5 ml) was hydrogenated with 10% Pd–C (28.5 mg) at 19 °C for 4 h. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2, and worked up as usual. Separation and purification by PTLC [hexane–DME (4 : 1) and hexane–EtOAc (4 : 1)] afforded **15b** (45 mg) and **16b** (14 mg, 22%). The former was recrystallized from CH_2Cl_2–MeOH to give **15b** (45 mg, 72%) as colorless needles, mp 127—128 °C. *Anal.* Calcd for $C_{19}H_{22}N_2O_3S$: C, 63.67; H, 6.18; N, 7.82. Found: C, 63.56; H, 6.22; N, 7.71. HRMS Calcd for $C_{19}H_{22}N_2O_3S$: 358.1350. Found: 358.1339. MS m/z: 358 (M^+, 11), 223 (8), 203 (100), 136 (86), 122 (33), 91 (46), 68 (97), 41 (52). ^{1}H-NMR (400 MHz) δ: 1.43—1.61 (2H, m), 1.76—1.89 (3H, m), 1.95 (1H, dd, $J=12.5$, 9 Hz), 2.43 (3H, s), 2.77 (1H, dd, $J=9$, 5 Hz), 3.90 (3H, s), 4.06 (1H, d, $J=3.5$ Hz), 4.34 (1H, dd, $J=4$, 4 Hz), 6.60 (1H, d, $J=9$ Hz), 7.29 and 7.79 (A_2B_2, $J=8$ Hz), 7.54 (1H, dd, $J=9$, 2.5 Hz), 7.91 (1H, d, $J=2.5$ Hz). **16b**: Colorless syrup. HRMS Calcd for $C_{19}H_{22}N_2O_3S$: 358.1350. Found: 358.1363. MS m/z: 358 (M^+, 12), 223 (10), 203 (100), 136 (85), 122 (37), 91 (45), 68 (100), 41 (47). ^{1}H-NMR (400 MHz) δ: 1.37—1.52 (2H, m), 1.52—1.62 (1H, m), 1.57 (1H, dd, $J=12$, 5.5 Hz), 1.76—1.87 (1H, m), 2.32 (1H, dddd, $J=12$, 12, 5, 3 Hz), 2.43 (3H, s), 3.49—3.57 (1H, m), 3.91 (3H, s), 4.27 (1H, dd, $J=5$, 5 Hz), 4.30 (1H, dd, $J=5$, 5 Hz), 6.71 (1H, d, $J=8.5$ Hz), 7.31 and 7.85 (A_2B_2, $J=8$ Hz), 7.36 (1H, dd, $J=8.5$, 2 Hz), 7.98 (1H, d, $J=2$ Hz).

***exo*-2-(2-Chloro-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]-heptane (15a)** A solution of **15b** (49 mg, 0.14 mmol) in DMF (4 ml) was cooled at 0 °C and $POCl_3$ (0.38 ml, 4.08 mmol) was added. The mixture was stirred under an Ar atmosphere at 0 °C for 1 h, and heated at 95—99 °C for 3.5 h, then allowed to cool. Saturated $NaHCO_3$–H_2O was carefully added and the whole was extracted with Et_2O, and worked up as usual. Separation of the residue (66 mg) by PTLC [hexane–CH_2Cl_2 (1 : 4)] afforded crude **15a** (36 mg), crude **15c** (3.5 mg) and crude **15d** (13.5 mg). Crude **15a** was recrystallized from benzene–hexane to give **15a** (35 mg, 70.5%) as colorless prisms, mp 134—135 °C. *Anal.* Calcd for $C_{18}H_{19}ClN_2O_2S$: C, 59.58; H, 5.27; N, 7.72. Found: C, 59.72; H, 5.31; N, 7.69. HRMS Calcd for $C_{18}H_{19}{}^{37}ClN_2O_2S$ and $C_{18}H_{19}{}^{35}ClN_2O_2S$: 364.0825 and 362.0855. Found: 364.0837 and 362.0836. MS m/z: 364 (6) and 362 (14) (M^+), 223 (21), 209 (8) and 207 (21), 142 (9) and 140 (25), 91 (45), 68 (100), 65 (19), 41 (39). ^{1}H-NMR (400 MHz) δ: 1.45—1.62 (2H, m), 1.76—1.92 (3H, m), 1.99 (1H, dd, *J*=12, 9 Hz), 2.44 (3H, s), 2.83 (1H, dd, *J*=9, 5 Hz), 4.10 (1H, br d, *J*=3.5 Hz), 4.36 (1H, dd, *J*=4, 4 Hz), 7.18 (1H, d, *J*=8.5 Hz), 7.30 and 7.78 (A_2B_2, *J*=8 Hz), 7.63 (1H, dd, *J*=8.5, 3 Hz), 8.16 (1H, d, *J*=3 Hz). Crude **15c** was purified by PTLC (3% MeOH–CH_2Cl_2) to afford *exo*-2-(2-hydroxy-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (**15c**) (3 mg, 6%) as a colorless amorphous powder. HRMS Calcd for $C_{18}H_{20}N_2O_3S$: 344.1193. Found: 344.1208. MS *m*/*z*: 344 (M^+, 14), 223 (9), 189 (89), 122 (67), 108 (16), 91 (44), 68 (100), 65 (21), 41 (38). IR (KBr) cm^{-1}: 1667, 1620. ^{1}H-NMR (400 MHz) δ: 1.42—1.57 (2H, m), 1.69—1.78 (1H, m), 1.78—1.91 (2H, m), 1.90 (1H, dd, *J*=12.5, 9 Hz), 2.42 (3H, s), 2.59 (1H, dd, *J*=9, 5 Hz), 3.97—4.02 (1H, m), 4.32—4.37 (1H, m), 6.45 (1H, d, *J*=10 Hz), 7.11 (1H, d, *J*=2.5 Hz), 7.31 and 7.78 (A_2B_2, *J*=8 Hz), 7.44 (1H, dd, *J*=10, 2.5 Hz). Crude **15d** was purified by PTLC [hexane–EtOAc (3 : 2)] to afford *exo*-2-(2-dimethylamino-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (**15d**) (1.5 mg, 3%) as a colorless syrup. HRMS Calcd for $C_{20}H_{25}N_3O_2S$: 371.1666. Found: 371.1667. MS *m*/*z*: 371 (M^+, 10), 216 (100), 149 (37), 135 (21), 133 (12), 119 (22), 91 (36), 68 (19), 65 (15), 41 (17). ^{1}H-NMR (90 MHz) δ: 1.32—2.13 (6H, m), 2.43 (3H, s), 2.69 (1H, dd, *J*=8, 5 Hz), 3.06 (6H, s), 3.99—4.13 (1H, m), 4.21—4.39 (1H, m), 6.39 (1H, d, *J*=9 Hz), 7.26 and 7.79 (A_2B_2, *J*=8.5 Hz), 7.45 (1H, dd, *J*=9, 2.5 Hz), 7.92 (1H, d, *J*=2.5 Hz).

***endo*-2-(2-Chloro-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (16a)** In the same manner as described above, treatment of **16b** (40.5 mg, 0.11 mmol) with $POCl_3$ (0.32 ml, 3.43 mmol) in DMF (3.5 ml) gave **16a** (27.5 mg, 67%), **16c** (2.5 mg, 6%) and **16d** (2.5 mg, 6%). **16a**: Colorless syrup. HRMS Calcd for $C_{18}H_{19}{}^{37}ClN_2O_2S$ and $C_{18}H_{19}{}^{35}ClN_2O_2S$: 364.0825 and 362.0855. Found: 364.0847 and 362.0875. MS *m*/*z*: 364 (5) and 362 (9) (M^+), 223 (17), 209 (7) and 207 (16), 142 (7) and 140 (21), 91 (31), 68 (100), 65 (13), 41 (36). ^{1}H-NMR (400 MHz) δ: 1.36—1.47 (2H, m), 1.54—1.68 (1H, m), 1.61 (1H, dd, *J*=12.5, 5.5 Hz), 1.77—1.90 (1H, m), 2.40 (1H, dddd, *J*=12.5, 12, 5, 3 Hz), 2.44 (3H, s), 3.57—3.66 (1H, m), 4.30 (1H, dd, *J*=5, 5 Hz), 4.35 (1H, dd, *J*=5, 5 Hz), 7.29 (1H, d, *J*=8 Hz), 7.32 and 7.84 (A_2B_2, *J*=8 Hz), 7.45 (1H, dd, *J*=8, 3 Hz), 8.22 (1H, d, *J*=3 Hz). *endo*-2-(2-Hydroxy-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (**16c**): Colorless prisms, mp 228—229 °C (CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.77; H, 5.85; N, 8.13. Found: C, 62.61; H, 5.88; N, 8.13. HRMS Calcd for $C_{18}H_{20}N_2O_3S$: 344.1193. Found: 344.1204. MS *m*/*z*: 344 (M^+, 10), 223 (8), 189 (68), 122 (57), 108 (14), 91 (43), 68 (100), 65 (23), 41 (39). IR (KBr) cm^{-1}: 1654, 1620. ^{1}H-NMR (400 MHz) δ: 1.30—1.40 (1H, m), 1.36 (1H, dd, *J*=12.5, 5.5 Hz), 1.41—1.51 (1H, m), 1.53—1.64 (1H, m), 1.74—1.87 (1H, m), 2.27 (1H, dddd, *J*=12.5, 11.5, 4.5, 3.5 Hz), 2.44 (3H, s), 3.32—3.40 (1H, m), 4.24 (1H, dd, *J*=4.5, 4.5 Hz), 4.25 (1H, dd, *J*=4.5, 4.5 Hz), 6.56 (1H, d, *J*=9.5 Hz), 7.18 (1H, d, *J*=2.5 Hz), 7.30 and 7.82 (A_2B_2, *J*=8.5 Hz), 7.31 (1H, dd, *J*=9.5, 2.5 Hz). *endo*-2-(2-Dimethylamino-5-pyridyl)-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (**16d**): Colorless syrup. HRMS Calcd for $C_{20}H_{25}N_3O_2S$: 371.1666. Found: 371.1663. MS *m*/*z*: 371 (M^+, 10), 216 (100), 149 (33), 135 (20), 133 (12), 119 (19), 91 (29), 68 (20), 65 (11), 41 (14). ^{1}H-NMR (90 MHz) δ: 1.17—2.06 (5H, m), 2.06—2.52 (1H, m), 2.43 (3H, s), 3.06 (6H, s), 3.26—3.66 (1H, m), 4.16—4.36 (2H, m), 6.50 (1H, d, *J*=9 Hz), 7.26 (1H, dd, *J*=9, 2.5 Hz), 7.32 and 7.81 (A_2B_2, *J*=8.5 Hz), 8.02 (1H, d, *J*=2.5 Hz).

***endo*-1-(2-Chloro-5-pyridyl)-7-azabicyclo[2.2.1]heptane (17)** Commercially available 30% HBr–AcOH (0.25 ml) was added to a solution of **16a** (11 mg, 0.030 mmol) and phenol (15 mg, 0.16 mmol) in EtOAc (2 ml). The flask was firmly stoppered and the mixture was stirred at 24 °C for 18 h. NaOH (3 N, 4.5 ml) was added and the whole was extracted with CH_2Cl_2, and worked up as usual. Separation by PTLC (10% MeOH–CH_2Cl_2) gave crude **17** (6 mg) and crude **16a**; the latter was purified by PTLC [hexane–EtOAc (7 : 2)] to give the recovery of **16a** (3 mg, 27%). The former, probably in the form of a silica acid salt in part, was made free by addition of 3 N NaOH (1 ml), and shaken thoroughly with H_2O (4 ml) and CH_2Cl_2. Usual work-up and purification by Al_2O_3 PTLC (0.5% MeOH–CH_2Cl_2) gave **17** (4.5 mg, 71%) as a colorless syrup. HRMS Calcd for $C_{11}H_{13}{}^{37}ClN_2$ and $C_{11}H_{13}{}^{35}ClN_2$: 210.0737 and 208.0767. Found: 210.0746 and 208.0759. MS *m*/*z*: 210 (2) and 208 (5) (M^+), 142 (3) and 140 (8), 104 (3), 69 (100), 68 (46). ^{1}H-NMR (400 MHz) δ: 1.32—1.48 (3H, m), 1.52 (1H, dd, *J*=12.5, 5.5 Hz), 1.59—1.73 (1H, m), 2.14 (1H, dddd, *J*=12.5, 12, 5, 3 Hz), 3.28—3.37 (1H, m), 3.79 (1H, dd, *J*=5, 5 Hz), 3.80 (1H, dd, *J*=5, 5 Hz), 7.28 (1H, d, *J*=8 Hz), 7.48 (1H, dd, *J*=8, 2.5 Hz), 8.25 (1H, d, *J*=2.5 Hz). ^{13}C-NMR (100 MHz) δ: 24.0, 30.9, 34.8, 44.7, 57.5, 61.1, 123.8, 135.7, 138.4, 149.1, 149.5.

(±)-Epibatidine (1) A solution of **15a** (28.5 mg, 0.079 mmol), phenol (41 mg, 0.44 mmol) and 30% HBr–AcOH (0.64 ml) in $CHCl_3$ (5.5 ml) was heated in a sealed tube at *ca.* 55 °C for 18 h, and allowed to cool. NaOH (3 N, 15 ml) was added and the whole was extracted with CH_2Cl_2, and worked up as usual. Separation by PTLC (5% MeOH–CH_2Cl_2) gave a mixture (16 mg) of **1**, **18b** and **19b**, accompanied by a mixture (14.5 mg) of **15a**, **18a** and **19a**. The former mixture was dissolved in a solution of DME (3 ml) and H_2O (1.5 ml) containing $LiOH \cdot H_2O$ (35 mg), and the solution was stirred at *ca.* 55 °C for 15 h. After evaporation of the solvents under reduced pressure at 20 °C, H_2O (3 ml) was added and the whole was extracted with CH_2Cl_2, then worked up as usual. Purification by Al_2O_3 PTLC [hexane–CH_2Cl_2 (1 : 3)] gave (±)-**1** (12.5 mg, 76%) as a colorless syrup. HRMS Calcd for $C_{11}H_{13}{}^{37}ClN_2$ and $C_{11}H_{13}{}^{35}ClN_2$: 210.0737 and 208.0767. Found: 210.0728 and 208.0768. MS *m*/*z*: 210 (2) and 208 (6) (M^+), 181 (1) and 179 (3), 142 (3) and 140 (7), 69 (100), 68 (44). ^{1}H-NMR (400 MHz) δ: 1.45—1.67 (5H, m), 1.92 (1H, dd, *J*=12, 9 Hz), 2.77 (1H, dd, *J*=9, 5 Hz), 3.54—3.59 (1H, m), 3.78—3.83 (1H, m), 7.24 (1H, d, *J*=8 Hz), 7.78 (1H, dd, *J*=8, 2.5 Hz), 8.28 (1H, d, *J*=2.5 Hz). ^{13}C-NMR (100 MHz) δ: 30.1, 31.3, 40.3, 44.5, 56.4, 62.8, 123.9, 137.7, 141.0, 148.8, 148.9. The mixture of **15a**, **18a** and **19a** was further separated by PTLC [hexane–EtOAc (2 : 1)] to give **19a** (1.5 mg, 4%) and a mixture of **15a** and **18a**. This mixture was separated by PTLC [hexane–CH_2Cl_2 (1 : 3)] to afford recovered **15a** (2 mg, 7%) and **18a** (1 mg, 3%). **18a**: Colorless syrup. MS *m*/*z*: 446 (4), 444 (12) and 442 (9) (M^+); 365 (4) and 363 (10); 291 (3), 289 (10) and 287 (7); 237 (2), 235 (6) and 233 (5); 209 (4) and 207 (11); 155 (19); 142 (18) and 140 (54); 129 (11) and 127 (35); 91 (100); 65 (32); 41 (17); 39 (17). ^{1}H-NMR (400 MHz) δ: 1.98—2.14 (4H, m), 2.14—2.32 (2H, m), 2.46 (3H, s), 3.45 (1H, ddd, *J*=13, 3.5, 3.5 Hz), 3.49—3.55 (1H, m), 4.61 (1H, d, *J*=7 Hz, NH), 4.79—4.84 (1H, m), 6.94 (1H, d, *J*=8.5 Hz), 7.14 (1H, dd, *J*=8.5, 3 Hz), 7.14 and 7.31 (A_2B_2, *J*=8 Hz), 7.93 (1H, d, *J*=3 Hz). **19a**: Colorless syrup. MS *m*/*z*: 446 (7), 444 (22) and 442 (16) (M^+); 365 (4) and 363 (9); 323 (3) and 321 (8); 291 (1), 289 (4) and 287 (3); 209 (2) and 207 (5); 194 (4) and 192 (11); 155 (30); 91 (100); 65 (24); 41 (11); 39 (13). ^{1}H-NMR (400 MHz) δ: 1.38 (1H, dddd, *J*=13, 12, 12, 4 Hz), 1.47 (1H, ddd, *J*=13, 12, 12 Hz), 1.88—2.02 (2H, m), 2.11 (1H, dddd, *J*=13, 4, 3, 3 Hz), 2.43 (3H, s), 2.47 (1H, dddd, *J*=13.5, 4, 4, 3 Hz), 2.87 (1H, ddd, *J*=12, 12, 3 Hz), 3.32 (1H, ddddd, *J*=12, 12, 8, 4, 4 Hz), 3.88 (1H, ddd, *J*=12, 12, 4 Hz), 4.65 (1H, d, *J*=8 Hz, NH), 7.28 (1H, d, *J*=8 Hz), 7.31 and 7.75 (A_2B_2, *J*=8 Hz), 7.41 (1H, dd, *J*=8, 2.5 Hz), 8.18 (1H, d, *J*=2.5 Hz).

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