HETEROCYCLES, Vol. 55, No. 5, 2001, pp. 861 -871, Received, 2nd October, 2000

SIMPLE SYNTHESIS OF (±) EPIBATIDINE

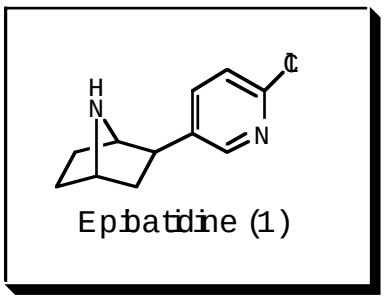
Balaram Roy, Hidenori Watanabe, and Takeshi Kitahara*

Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-8657, Japan. Fax: 81-3-5841-8019, e.mail: atkita@mail.ecc.u-tokyo.ac.jp

Abstract - Concise synthesis of racemic epibatidine (**1**) a non-opioid analgesic, alkaloid, was accomplished starting from 6-chloropyridyl-3-carbaldehyde (**6**) *via* Robinson annulation for the construction of the skeleton, by introduction of amino group through curtius rearrangement and finally by cyclization.

INTRODUCTION

Epibatidine (**1**), a new class of amphibian alkaloid, was isolated by Daily and co-workers [1] in 1992 in minute amount from the skin extract of the Ecudorian poison frog, *Epipedobates tricolo*r. This alkaloid possesses 7-azabicyclo[2.2.1]heptane skeleton and has been reported containing extremely higher potency as an analgesic than morphine.[2] Biological studies revealed that this remarkable activity of epibatidine is due to the action as an agonist of nicotinic acetylcholine receptor.[3-5] Because of its unique nitrogen-bridged ring system and powerful pharmacological activity, much attention have been paid to the synthesis of this molecule and derivatives to promote further biological studies as well as structure-activity relationship.



Epibatidine (1)

Figure 1

Thus A number of synthesis of epibatidine have already been reported both in racemic and enantiomeric forms.[6] The attractive nature of epibatidine (**1**) prompted us to synthesize and investigate the precise biological activities of **1** and related analogs. We describe Herein a simple and efficient stereocontrolled route for the synthesis of (±)-epibatidine

RESULTS AND DISCUSSION

Our retrosynthesis is shown in Figure **2**. The heterocyclic skeleton (**3**) of epibatidine (**1**) would be constructed by Robinson annulation between β-keto ester (**4**) and methyl vinyl ketone (**5**) in a single operation. Then Curtius or Hofmann type rearrangement should give amine (**2**) which would cyclize to give (**1**).

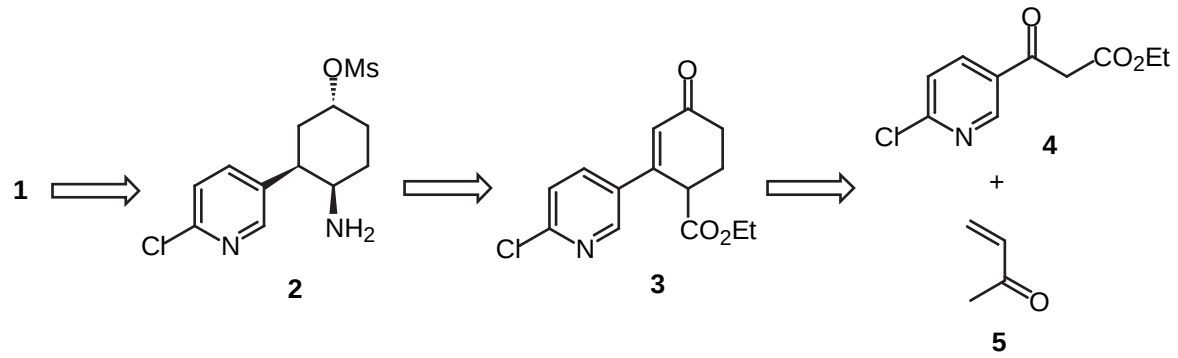
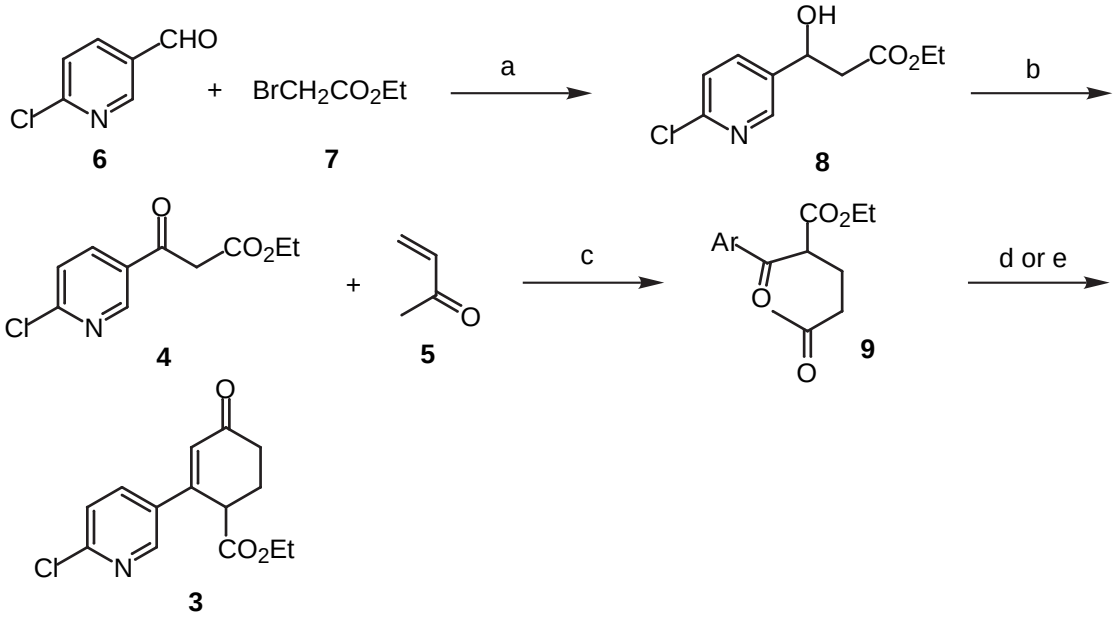


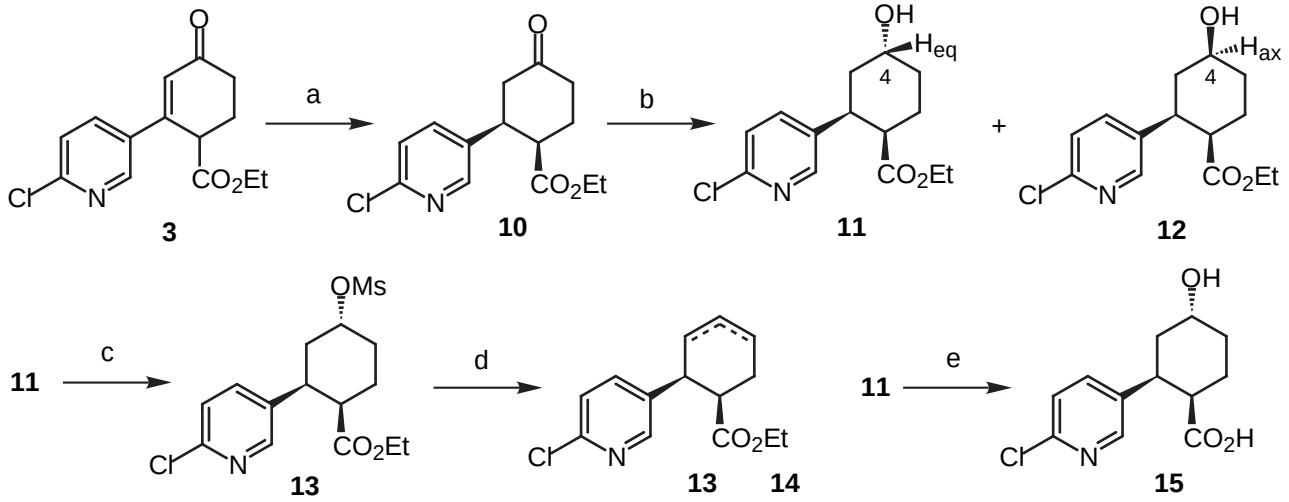
Figure 2

The synthesis of the intermediate (**3**) was achieved as depicted in Scheme **1**. The β-keto ester (**4**) was prepared from 6-chloropyridyl-3-carbaldehyde (**6**) in 2 steps. The aldehyde (**6**) was sub*J*ected to Reformatsky reaction with ethyl bromoacetate to give alcohol (**8**), which upon PCC oxidation at room temperature gave the desired β-keto ester (**4**). Michael addition of the β-keto ester (**4**) with methyl vinyl ketone in NaOEt/EtOH by the method of Watt *et al.*[7] gave diketone (**9**). Intramolecular aldol reaction proceeded smoothly by refluxing with pyrrolidine by the method of Heathcock *et al.*[8] to afford the desired enone (**3**) in good yield.



Scheme 1 a) Zn, benzene, reflux, 80%. b) PCC, CH_2Cl_2, MS-3A (powder), 52%. c) NaOEt, EtOH, rt, 2.5 h, 60%. d) conc. H_2SO_4, CH_3COOH, reflux, low yield. e) pyrrolidine, benzene, reflux, 6 h, 85%.

The next step was the reduction of the enone (**3**). Catalytic hydrogenation of **3** in the presence of excess amount of Rh/Al_2O_3 by the method of Barrett *et al.*[9] gave the desired ketone (**10**) with other undesired isomers. Selective hydrogenation of the double bond, however, was best achieved by using limited amount of the catalyst. Then, in order to obtain the desired *trans*-alcohol (**11**), the reduction of the ketone was attempted with several reducing reagents such as, L-Selectride/THF, $NaBH_4$/THF, $LiAlH(Ot\text{-}Bu)_3$/THF, DIBAL-H/CH_2Cl_2 and Super-Hydride/THF. In all cases, however, both *trans*- and *cis*-alcohol (**11** and **12**) were obtained and the yield and/or the ratio of the desired **11** was not satisfactory. While, K-Selectride reduction of the ketone (**10**) in THF gave the best result and the desired *trans*-alcohol (**11**, 80%) was obtained as a ma*J*or product along with **12** (20%). Stereochemistry of the product was easily determined from ^{1}H-NMR because H-4_{ax} in **12** showed large coupling constant (3.75 ppm, tt, J = 4.5, 11.0 Hz) compared with that of H-4_{eq} in **11** (4.31 ppm, br t, W1/2 = 8.5 Hz). The *trans*-alcohol (**11**) was treated with MsCl to give mesyloxy ester (**13**). When the mesyloxy ester (**13**) was sub*J*ected to acid hydrolysis by heating with 3M H_2SO_4 at 50-60˚C, concomitant elimination of mesyloxy group occurred to give a mixture of olefinic acid (**14**). So, the *trans*-hydroxy ester (**11**) was hydrolyzed under acidic condition to afford the desired *trans*-hydroxy acid (**15**).

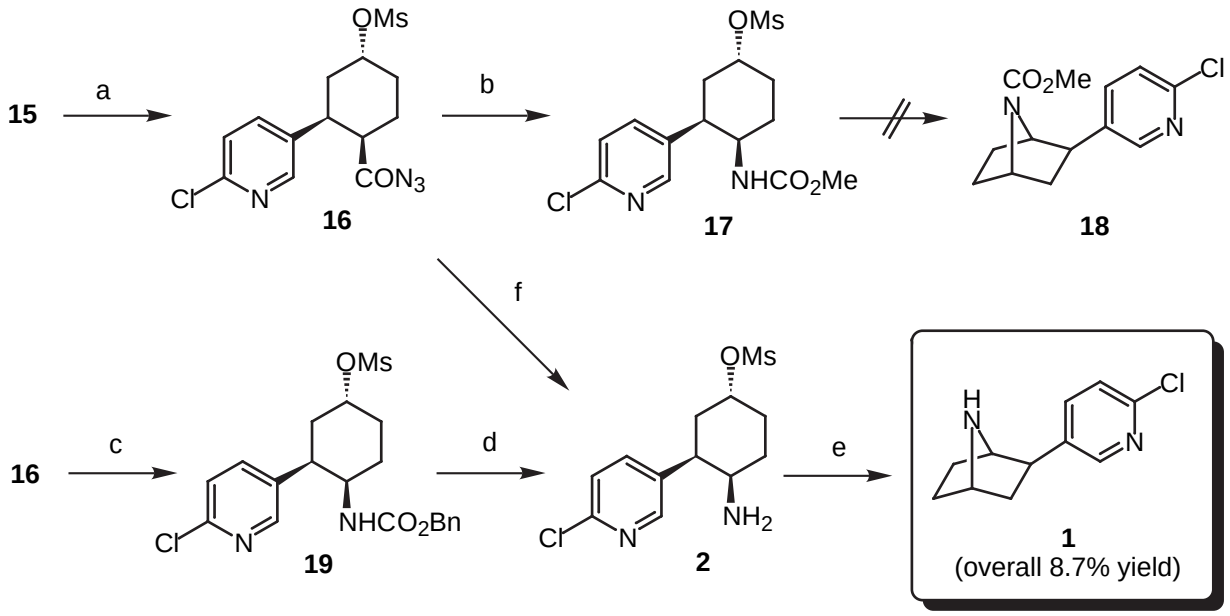


Scheme 2 a) H_2, Rh-Al_2O_3/EtOH, 30% w/w, 85%. b) K-Selectride/THF, -78˚C, quant. (**11**:**12** = 4:1). c) MsCl, pyridine, CH_2Cl_2, 82%. d) 3 M H_2SO_4, 50-60˚C. e) 3 M H_2SO_4, 60-65˚C, quant.

In order to complete the synthesis, the next step was the introduction of amino group *via* Curtius rearrangement. The hydroxy acid (**15**) was treated with MsCl/Et_3N in acetone at 0˚C and successively treated with NaN_3 by the method of Poulter *et al.*[10] to give crude acyl azide (**16**). Heating the azide (**16**) in benzene-MeOH (1:1) at 70˚C for 1 h gave methyl carbamate (**17**). Neither treatment of **17** with KO*t*-Bu

nor with KHMDS gave the desired bicyclic carbamate (**18**). To overcome this difficulty, benzyl carbamate (**19**) was first prepared from the azide (**16**) by heating in benzene in the presence of benzyl alcohol. Then, debenzylation and successive cyclization of the resulting amino mesylate (**2**) afforded the desired (±)-epibatidine (**1**), although the yield from the hydroxy acid (**15**) was extremely poor. On the other hand, heating the azide (**16**) with 2 eq. of conc. HCl in H_2O-THF (1:2) directly gave the amino mesylate (**2**), which on cyclization by refluxing with $CHCl_3$ gave rise to (±)-epibatidine (**1**) in much better yield. The spectral data (^{1}H-NMR, ^{13}C-NMR, MS) showed good accordance with those of the authentic sample.

In conclusion, (±)-epibatidine (**1**) was synthesized starting from readily available 6-chloropyridyl-3-carbaldehyde (**6**) in overall 8.7% yield through 10 steps, employing Robinson annulation and Curtius rearrangement as key steps. This route is rather short process and should be extended to enantioselective synthesis by employing a chiral base like amino acid for the annulation and the investigation under this protocol is in progress in this laboratory.



Scheme 3 a) MsCl, Et_3N, acetone, 0˚C., then NaN_3, H_2O. b) MeOH:C_6H_6 (1:1), 70˚C, 45% from **15**. c) BnOH, C_6H_6, 70˚C, 77% from **15**. d) H_2, 10%Pd/C, EtOH, HCl, 27%. e) $CHCl_3$, reflux, quant. f) THF-H_2O (2:1), conc. HCl (2 eq), reflux, 60% from **15**.

EXPERIMENTAL

Tetrahydrofuran, benzene and toluene were distilled from Na/benzophenone ketyl. Methylene chloride was distilled over P_2O_5. All reactions involving oxygen or moisture sensitive compounds were performed under argon atmosphere. IR spectra were measured with a JASCO A-102, JASCO FT/IR-230

spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured with *J*EOL *J*NMEX–90 (90 MHz) or Bruker AC–300 (300 MHz) and *J*EOL *J*NM–A 500 (500 MHz) spectrometers. Silica gel column chromatography was performed on Merck Kieselgel 60, art No. 7734, while thin layer chromatography (TLC) was performed with silica gel 60 F_{254} (Merck).

Ethyl 3-[3-(6-chloropyridyl)]-3-hydroxypropanoate (8)

In 50 mL three necked round bottomed flask equipped with condenser was placed slurry of Zn powder (1.1 g, 16.9 mmol) in 5 mL of dry benzene under argon atmosphere and the suspension was heated until reflux starts. To this was added dropwise a solution of aldehyde (**6**, 1.5 g, 10.6 mmol) and ethyl bromoacetate (**7**, 1.96 g, 11.72 mmol) in 20 mL of dry benzene at such a rate of *ca*. 1 mL/min. After the addition was complete, the reflux was continued for another 2 h. The resulting pale yellow solution was poured into 80 mL of cold 20% sulfuric acid and the mixture was shaken until the colorless precipitate dissolved. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (150 mL x 3). The combined organic layer was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure *in vacuo* and the residue was chromatographed on silica gel (63 g). Elution with hexane-ethyl acetate (4:1) afforded **8** (1.93 g, 80%) as a colorless oil.**^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 8.36 (1H, d, *J* = 2.5 Hz); 7.71 (1H, dd, *J* = 2.5 Hz, 8.0 Hz); 7.32 (1H, d, *J* = 8.0 Hz); 5.15 (1H, m); 4.18 (2H, q, *J* = 7.2 Hz); 3.61 (1H, d, *J* = 3.5 Hz); 2.69 (2H, br d, *J* = 6.3 Hz); 1.25 (3H, t, *J* = 7.2 Hz). **IR** (neat) [cm^{-1}]: 3360; 1730 (s); 1590 (s); 1570 (s); 1460; 1380; 1280; 1160; 1100; 840; 740.

Ethyl 3-[3-(6-chloropyridyl)]-3-oxopropanoate (4)

To a solution of **8** (0.5 g, 2.18 mmol) in dry CH_2Cl_2 (15 mL) were added MS-3A powder (1 g) and pyridinium chlorochromate (1 g, 4.64 mmol) and the mixture was stirred at rt for 3 h. The reaction mixture was filtered through silica gel (20 g) and the silica gel was washed with ethyl acetate. The combined filtrate was evaporated to give a residue, which was chromatographed on silica gel (15 g). Elution with hexane-ethyl acetate (7:1) gave β-keto ester (**4**, 0.26 g, 52%) as a white solid. **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 8.85 (1H, d, *J* = 2.5 Hz); 8.13 (1H, dd, *J* = 2.5 Hz, 8.5 Hz), 7.41 (1H, d, *J* =8.5 Hz); 4.15 (2H, br q), 3.91 (2H, s); 1.19 (3H, t, *J* = 7.5 Hz). **IR** (KBr) [cm^{-1}]: 1740 (s); 1695(s); 1630; 1580; 1460; 1420; 1360; 1265; 1200; 1110; 1020; 800. Mp 49-52˚C; Anal. Calcd for $C_{10}H_{10}NO_3Cl$: C, 52.76; H, 4.42; N, 6.15. Found: C, 53.10; H, 4.53; N, 5.95.

Ethyl (±)-2-[3-(6-chloropyridyl)]-4-oxo-2-cyclohexene-1-carboxylate (3)

To a 2.5 mL of 2 M solution of sodium ethoxide (5.0 mmol) in ethanol at 0˚C under argon atmosphere was

added the keto ester (**4**, 1 g, 4.39 mmol) in 5 mL of ethanol over 5 min followed by the addition of methyl vinyl ketone (0.631 g, 9.00 mmol) in 5 mL of ethanol over 15 min. The resulting mixture was stirred at rt for 2.5 h and acidified to pH 2~3 by adding conc. HCl. Evaporation of the solvent left a residue, which was diluted with water and extracted with Et_2O (3 x 100 mL). The organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated *in vauco*. The residue was chromatographed on silica gel (60 g) eluting with hexane-ethyl acetate (5:1) to afford **9** (0.77g, 60%) as a colorless oil. **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 8.95 (1H, d, *J* = 2.5 Hz); 8.21 (1H, dd, *J* = 2.5 Hz, 8.5 Hz); 7.41 (1H, d, *J* = 8.5 Hz); 4.31 (1H, dd, *J* = 6.5 Hz, 8.0 Hz); 4.09 (2H, q, *J* = 7.0 Hz); 2.55 (2H, br q); 2.08 (3H, s); 1.12 (3H, t, *J* = 7.5 Hz). **IR** (neat) [cm^{-1}]: 3500 (br); 1720 (s); 1690 (s); 1580; 1460; 1360; 1245; 1190-1180; 1110; 1040; 920; 860. To a solution of the compound (**9**) (0.43 g, 1.44 mmol) in dry benzene (10 mL) was added pyrrolidine (0.11 g, 1.56 mmol). The mixture was allowed to reflux under argon atmosphere with continuous removal of water. After 5 h, solvent was concentrated *in vauco* and the residue was chromatographed on silica gel (20 g). Elution with hexane-ethyl acetate (5:1) gave **3** (0.343 g, 85%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 8.50 (1H, d, *J* = 2.5 Hz); 7.72 (1H, dd, *J* = 2.5 Hz, 8.5 Hz); 7.37 (1H, d, *J* = 8.5 Hz); 6.41 (1H, s); 4.11 (2H, q, *J* = 7.0 Hz); 3.86 (1H, t, *J* = 4.5 Hz); 2.63 (1H, m); 2.47-2.54 (2H, m); 2.39 (1H, m); 1.14 (3H, t, *J* = 7.0 Hz). **IR** (neat) [cm^{-1}]: 1730 (s); 1675 (s); 1610; 1580; 1555; 1460; 1375; 1330; 1250; 1180; 1155; 1110; 1040; 1025; 980; 900; 840. Anal. Calcd for $C_{14}H_{14}NO_3Cl$: C, 60.11; H, 5.05; N, 5.00. Found: C, 59.83; H, 5.51; N, 4.87.

Ethyl (1*R,2*S**)-2-[3-(6-chloropyridyl)]-4-oxocyclohexanecarboxylate (10)**

A solution of **3** (0.099 g, 0.354 mmol) in 5 mL of EtOH was stirred with 30% Rh/Al_2O_3 (0.03 g) under hydrogen atmosphere for 3 h. The reaction mixture was filtered through celite and the filter cake was washed with ethyl acetate and refiltered. The combined filtrate was evaporated and the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (5:1) to afford **10** (0.084 g, 85%) and **12** (0.009 g, 10%) as a colorless oil, respectively. **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 8.21 (1H, d, *J* = 2.5 Hz); 7.47 (1H, dd, *J* = 2.5 Hz, 8.5 Hz); 7.27 (1H, d, *J* = 8.5 Hz); 4.03 (1H, dq, *J* = 7.3 Hz, 11.0 Hz); 4.01 (1H, dq, *J* = 7.3 Hz, 11.0 Hz); 3.47 (1H, H-2, dt, *J* = 4.5 Hz, 11.0 Hz); 3.25 (1H, H-3_{ax}, ddd, *J* = 1 Hz, 11.0 Hz, 14.5 Hz); 3.08 (1H, H-1, br q, *J* = 4.8 Hz); 2.72 (1H, H-5_{ax}, ddd, *J* = 6 Hz, 11.0 Hz, 15 Hz); 2.58 (1H, H-3_{eq}, dd, *J* = 5.0 Hz, 14.5 Hz); 2.43 (1H, H-5_{eq}, ddt, *J* = 1.5 Hz, 5.3 Hz, 15 Hz); 2.26 (1H, H-6_{eq}, dq, *J* = 5.5 Hz, 14.5 Hz); 2.13 (1H, H-6_{ax}, ddt, *J* = 5.0 Hz, 11.0 Hz, 14.5 Hz); 1.11 (3H, t, *J* = 7.3 Hz). **IR** (neat) [cm^{-1}]: 1720 (s); 1460; 1380; 1235; 1180; 1100; 1020; 840; 740. Anal. Calcd for $C_{14}H_{16}NO_3Cl$: C, 59.68; H, 5.72; N, 4.96. Found: C, 60.12; H, 6.03; N, 5.49.

Ethyl (1*R,2*S**,4*R**)-2-[3-(6-chloropyridyl)]-4-hydroxycyclohexanecarboxylate (11)**

A solution of **10** (0.037 g, 0.131 mmol) in dry THF (2 mL) was cooled to –78˚C under argon atmosphere. To this was added K-Selectride (1 M, solution in THF, 0.242 g, 0.265 mmol) and the resulting mixture was stirred at the same temperature for 1 h. Water was added to the reaction mixture and the whole was warmed up to rt. The aqueous layer was extracted with Et_2O (4 x 25 mL). The combined extract was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the volatiles left a residue, which was chromatographed on silica gel (1.2 g). Elution with hexane-ethyl acetate (4:1) gave *trans*-isomer (**11**) (0.03 g, 80%) and *cis*-isomer (**12**) (0.007 g, 20%) as an oil, respectively.

11: ^{1}**H-NMR** ($CDCl_3$, 500 MHz): δ = 8.25 (1H, br. s); 7.54 (1H, dd, *J* = 3.0 Hz, 8.3 Hz); 7.23 (1H, d, *J* = 8.5 Hz); 4.31 (1H, H-4, br q, *J* = ~3.0 Hz); 3.93 (1H, dq, *J* = 7.2 Hz, 10.5 Hz); 3.89 (1H, dq, *J* = 7.2 Hz, 10.5 Hz); 3.44 (1H, H-2, dt, *J* = 4.3 Hz, 12.5 Hz); 2.89 (1H, H-1, q, *J* = 4.3 Hz); 2.58 (1H, H-3_{ax}, dt, *J* = 2.7 Hz, 12.9 Hz); 2.22 (1H, tt, *J* = 4.6 Hz, 13.3 Hz); 1.97~1.78 (3H, m); 1.66 (1H, m); 1.03 (3H, t, *J* = 7.3 Hz). **IR** (neat) [cm^{-1}]: 3380 (br); 1725 (s); 1580; 1560; 1460; 1380; 1235; 1180; 1105; 1060; 1020; 960; 740**.** Anal**.** Calcd for $C_{14}H_{18}NO_3Cl$: C, 59.26; H, 6.39; N, 4.93. Found: C, 59.15; H, 5.99; N, 4.59.

12: ^{1}**H-NMR** ($CDCl_3$, 500 MHz): δ = 8.24 (1H, d, *J* = 2.5 Hz); 7.56 (1H, dd, *J* = 2.5 Hz, 8.3 Hz); 7.23 (1H, d, *J* = 8.3 Hz); 3.93 (1H, dq, *J* = 7.2 Hz, 11 Hz); 3.89 (1H, dq, *J* = 7.2 Hz, 11 Hz); 3.75 (1H, H-4_{ax}, tt, *J* = 4.5 Hz, 11 Hz); 2.90 (1H, H-2_{ax}, dt, *J* = 4.0 Hz, 13.0 Hz); 2.83 (1H, H-1_{eq}, br m); 2.36 (1H, H-3_{ax}, ddd, *J* = 11 Hz, 12Hz, 13 Hz); 2.16 (1H, dq, *J* = 3.0 Hz, 14.0 Hz); 2.04 (1H, dm, *J* = 14 Hz); 1.92 (1H, dm, *J* = 12.5 Hz); 1.77 (1H, ddt, *J* = 3.7 Hz, 5.2 Hz, 14.0 Hz); 1.64 (1H, m); 1.03 (3H, t, *J* = 7.2 Hz).

(1*R,2*S**,4*R**)-2-[3-(6-Chloropyridyl)]-4-hydroxycyclohexanecarboxylic acid (15)**

A solution of **11** (0.036 g, 0.127 mmol) in 3M H_2SO_4 (1 mL) was heated at 60-65˚C for 4 h. The resulting mixture was cooled to rt and pH was adJusted to ~7.0 by portionwise addition of solid sodium bicarbonate. It was then poured into saturated ammonium sulfate solution. The aqueous layer was extracted with Et_2O (5 x 50 mL). The combined extract was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (1.7 g). Elution with ethyl acetate afforded **15** (0.032 g, quantitative yield) as a colorless oil**.** ^{1}**H-NMR** ($CDCl_3$, 500 MHz): δ = 8.3 (1H, d, *J* = 2.5 Hz); 7.55 (1H, dd, *J* = 2.5 Hz, 8.5 Hz); 7.23 (1H, d, *J* = 8.5 Hz); 4.30 (1H, H-4_{eq}, br s); 3.44 (1H, H-2_{ax}, dt, *J* = 4.1 Hz, 12.3 Hz); 2.94 (1H, H-1_{eq}, br q, *J* = 4 Hz); 2.59 (1H, dt, *J* = 2.5 Hz, 13.5 Hz); 2.25 (1H, tt, *J* = 4.6 Hz, 15.0 Hz); 1.96-1.90 (2H, m); 1.81 (1H, dm, *J* = 14 Hz); 1.68 (1H, dm, *J* = 13 Hz).

Anal. Calcd for $C_{12}H_{14}NO_3Cl$: C, 56.37; H, 5.52; N, 5.48. Found; C, 56.09; H, 5.34; N, 5.14.

(1*R,2*S**,4*R**)-1-*N*-Benzyloxycarbonyl-2-[3-(6-chloropyridyl)]-4-methanesulfonyloxy-cyclohexylamine (19)**

To a solution of the hydroxy acid (**15**, 0.025 g, 0.10 mmol) in 1 mL of freshly distilled acetone was added triethylamine (0.124 g, 1.22 mmol) under argon atmosphere. To this at 0˚C was added methanesulfonyl chloride (0.074 g, 0.646 mmol) and the mixture was stirred for 30 min at the same temperature. To this was added sodium azide (0.042 g, 0.646 mmol) in 0.3 mL of water and the stirring was continued for another 15 min. The mixture was quenched by the addition of water and diluted with Et_2O. The ethereal layer was separated and the aqueous layer was extracted with Et_2O (25 mL x 3). The combined organic layer was dried over anhydrous $MgSO_4$. Evaporation of the volatiles left crude acyl azide (**16**, 0.035 g), which was used for the next step without further purification. To a solution of **16** (0.0175g) in benzene (1.5 mL) was added benzyl alcohol (0.0114 g, 0.106 mmol). The mixture was heated at 70˚C under argon atmosphere for overnight. Solvent was evaporated and the residue was chromatographed on silica gel (2.4 g). Elution with hexane-ethyl acetate (6:1) afforded compound (**19**) (0.016 g, 77% from **15**) as an oil. **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 8.19 (1H, d, *J* = 2.5 Hz); 7.42 (1H, br. m); 7.30-7.27 (3H, br. m); 7.23-7.15 (3H, br. m); 5.14 (1H, H-4, br s); 4.94-4.75 (3H, br. m, -CH_2Ar, and –NH); 4.19 (1H, H-1_{eq}, br. m); 3.35 (1H, H-2, br. m); 3.03 (3H, s); 2.22-1.85 (5H, m); 1.71 (1H, br t, *J* = 14). **IR** (neat) [cm^{-1}]: 3380 (br); 1700 (st); 1530; 1460; 1340; 1240; 1175; 1105; 1000; 910; 840; 740; 700.

(1*R,2*S**,4*R**)-2-[3-(6-Chloropyridyl)]-4-methanesulfonyloxy-1-cyclohexylamine (2)**

Method A: To a solution of **19** (0.025 g, 0.059 mmol) in EtOH (2.5 mL) containing a trace amount of conc. HCl was added 0.005 g of 10% Pd/C. The resulting mixture was stirred under H_2 atmosphere at rt for 7 h. The reaction mixture was then filtered through celite in the presence of solid sodium bicarbonate . Evaporation of the volatiles left a residue, which was chromatographed on silica gel (1.5 g). Elution with chloroform-methanol-28% ammonia aq. (10:1:0.1) afforded **2** (0.0047 g, 27%) as an oil, which was used for cyclization without further purification.

Method B: The hydroxy acid (**15**, 0.016g, 0.062 mmol) was treated in the same manner as described above to give a crude azide (**16**). A solution of **17** in THF-H_2O (2:1, ~3 mL) containing conc. HCl (0.016 mL) was heated at 70˚C for 2 h. The reaction mixture was then cooled to rt and poured into aq. saturated sodium bicarbonate. The aqueous layer was extracted with chloroform and the extract was evaporated to dryness. The residue was chromatographed on silica gel (1 g). Elution with chloroform-methanol-28% aq. ammonia (10:1:0.1) afforded **2** (0.0113 g, 60% from **15**) as an oil, which was used for cyclization without

further purification.

(±)-Epibatidine (1)

A solution of **2** (0.0113 g, 0.037 mmol) in chloroform (4 mL) was refluxed under argon atmosphere for 20 h. The reaction mixture was diluted with chloroform and washed with 5% aq. sodium bicarbonate. The aqueous layer was extracted with chloroform. The combined organic layer was dried over anhydrous K_2CO_3 and concentrated *in vacuo*. The residue was chromatographed on silica gel (1 g). Elution with chloroform-methanol-28% aq.ammonia (10:1:0.1) afforded (±)–epibatidine (**1**) (0.008 g, quantitative yield) as a colorless oil. **^{1}H-NMR** ($CDCl_3$, 500 MHz): δ = 8.26 (1H, d, *J* = 2.5 Hz); 7.80 (1H, dd, *J* = 2.5 Hz, 8.5 Hz); 7.23 (1H, d, *J* = 8.5 Hz); 3.82 (1H, H-4, br t, *J* = 3.0 Hz); 3.58 (1H, H-1, br d, *J* = 3.5 Hz); 2.77 (1H, H-2, dd, *J* = 5.3 Hz, 8.8 Hz); 2.20 (1H, br., NH 1.92 (1H, H-3a, dd, *J* = 9.3 Hz, 12.3 Hz); 1.67-1.50 (5H, H-3b, H-5(2H) and H-6(2H), m). **^{13}C-NMR** ($CDCl_3$, 125 MHz): δ = 149.0 (C); 148.8 (CH); 140.6 (C); 137.6 (CH); 123.9 (CH); 62.7 (CH); 56.5 (CH); 44.4 (CH); 40.1 (CH_2); 31.2 (CH_2); 29.9 (CH_2). **IR** (neat) [cm^{-1}]: 3265; 2960; 2870; 1580; 1562; 1457; 1100; 1055; 750. **HR-MS**: Calcd for $C_{11}H_{14}N_2Cl$, 209.085. Found, 209.091(MH^+).

ACKNOWLEDGMENT

We thank Professor Chihiro Kibayashi, Tokyo University of Pharmacy and Life Science, for the generous gift of the spectral data of the authentic epibatidine. We are also grateful to Mrs. Hiroko Naito, Department of Applied Biological Chemistry, The University of Tokyo, for elemental analysis. B.R. acknowledges to Japanese Ministry of Education, Science, Culture and Sports (JMESCS) for providing the fellowship for the foreign graduate students. Thanks are due to Mitsubishi Chemical Co. for the generous gift of the starting material, 6-chloropyridyl-3-carbaldehyde. This work was supported by a Grant in Aid for the scientific research from JMESCS.

REFERENCES

1. T. F. Spande, H. M. Garraffo, M. W. Edwards, H *J.* C. Yeh, L Pannell and *J.* W. Daly, *J. Am. Chem. Soc.*, 1992, **114**, 3475.
2. C. Li. Qian, T. Y. Shen, G. L. Libertine and *J.* B. Eckman, *Eur. J. Pharmacol.*, 1993, **250**, R13.
3. B. Badio and *J.* W. Daly, *Mol. Pharmacol.*, 1994, **45**, 563.
4. M. Fisher, D. F. Haung, T. Y. Shen and P. G. Guyenet, *J. Pharmacol. Exp. Ther.*, 1994, **270**, 702.

5. T. L. Qian, *J.* Eckman, D. F. Haung and T. Y. Shen, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 2759.

6. C. A. Broka, *Tetrahedron Lett.*, 1993, **34**, 3251. E. *J.* Corey, T. P. Loh, S. A. Rao, D. C. Daly and S. Sarshar, *J. Org. Chem.*, 1993, **58**, 5600. D. F. Haung and T. Y. Shen, *Tetrahedron Lett.*, 1993, **34**, 4477. S. C. Clayton and A. C. Regan, *Tetrahedron Lett.*, 1993, **34**, 7493. S. R. Fletcher, R. Baker, M. S. Chambers, H. Herbert, S. C. Hobbs, S. R. Thomas, H. M. Verrier, A. P. Watt and R. G. Ball, *J. Org. Chem.*, 1994, **59**, 1771. K. Senokuchi, H. Nakai, M. Kawamura, N. Katsube, S. Nonaka, H. Sawaragi and N. Hamanaka, *Synlett*, 1994, 343. K. Okabe and M. Natsume, *Chem. Pharm. Bull.*, 1994, **42**, 1432. K. Sestan*J*, E. Melenski and I. *J*irokovsky, *Tetrahedron Lett.*, 1994, **35**, 5417. E. Albertini, A. Barco, S. Benetti, C. D. Risi, G. P. Pollini, R. Romagnoli and V. Zanirato, *Tetrahedron Lett.*, 1994, **35**, 9297. S. Y. Ko, *J.* Lerpiniere, I. D. Linney and R. Wrigglesworth, *J. Chem. Soc., Chem. Commun.*, 1994, 1775. G. Pandey, T. D. Bagul and G. Lakshmaiah, *Tetrahedron Lett.*, 1994, **35**, 7439. P. C. Kotian and F. I. Caroll, *Synth. Commun.*, 1995, 63. A. Hernandez, M. Marcos and H. Rapport, *J. Org. Chem.*, 1995, **60**, 2683. D. Bai, R. Xu, G. Chu and X. Zhu, *J. Org. Chem.*, 1996, **61**, 4600. B. M. Trost and G. R. Cook, *Tetrahedron Lett.*, 1996, **37**, 7485. C. Zhang and M. L. Trudell, *J. Org. Chem.*, 1996, **61**, 7189. C. Szántay, Z. Kardos-Balogh, I. Moldvai, C. Szántay. *J*r, E. Temesvári-Major and G. Blasko, *Tetrahedron*, 1996, **52**, 11053. E. Albertini, A. Barco, S. Benetti, C. D. Risi, G. P. Pollini and V. Zanirato, *Tetrahedron Lett.*, 1997, **38**, 681. N. S. Sirisoma and C. R. *J*ohnson, *Tetrahedron Lett.*, 1998, **39**, 2059. S. Aoyagi, R. Tanaka, M. Naruse and C. Kibayashi, *Tetrahedron Lett.*, 1998, **39**, 4513. D. L. J. Clive and V. S. C. Yeh, *Tetrahedron Lett.*, 1998, **39**, 4789. D. M. Hodgson, C. R. Maxwell, I. R. Matthews, *Synlett*, 1998, 1349. M. P. Giblin, C. D. *J*ones and N. S. Simpkins, *J. Chem. Soc.*, , *Perkin Trans.* 1, 1998, 3689. A. G. Horti, U. Scheffel, A. S. Kimes, J. L. Musachio, H. T. Ravert, W. B. Mathews, Y. Zhan, P. A. Finley and R. F. Dannals, *J. Med. Chem.*, 1998, **41**, 4199. A. Avenoza, J. H. Busto, C. Cativiela and J. M. Peregrina, *Synthesis*, 1998, 1335. L. E. Brieaddy, F. Liang, P. Abraham, J. R. Lee and F. I. Carroll, *Tetrahedron Lett.*, 1998, **39**, 5321. M. T. Barros, C. D. Maycock and M. R. Ventura, *Tetrahedron Lett.*, 1999, **40**, 557. A. Palmgren, L. E. Larsson, J. E. Baeckvall and P. Helquist, *J. Org. Chem.*, 1999, **64**, 836. J. C. Namyslo and D. E. Kaufmann, *Synlett*, 1999, 804. J. R. Malpass and C. D. Cox, *TetrahedronLett.*, 1999, **40**, 1419. S. Singh, K. S. Avor, B. Pouw, T. W. Seale and G. P. Basmadjian, *Chem. Pharm. Bull.*, 1999, **47**, 1501. F. J. Karstens, M. J. Moollenaar and P. J. Floris, *Tetrahedron Lett.*, 1999, **40**, 8629. H. F. Olivo and M. S. Hemenway, *J. Org. Chem.*, 1999, **64**, 8968. S. Radl, P. Hezky,

W. Hafner, M. Budesinsky, L. Hejnova, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 55. A. Hall, P. D. Bailey, D. C. Rees, G. M. Rosair and R. H. Wightman, *J. Chem. Soc. Perkin 1*, 2000, 329. D. I. Cabanal, J. F. Berrien, L. Ghosez, H. P. Husson and J. Royer, *Tetrahedron*, 2000, **56**, 3763. D. I. Cabanal, J. F. Berrien and J. Royer, *Tetrahedron: Asymmetry*, 2000, **11**, 2525.

7. D. L. Snitman, R. J. Himmelsbach and D. S. Watt, *J. Org. Chem.*, 1978, **43**, 4758.
8. J. S. Dutcher, J. G. Macmillan and C. H. Heathcock, *J. Org. Chem.*, 1976, **41**, 2663.
9. A. G. M. Barrett and T. M. Raynham, *Tetrahedron Lett.*, 1987, **28**, 5615.
10. T. L. Capson and C. D. Poulter, *Tetrahedron Lett.*, 1984, **25**, 3515.