Synthesis of (−)-Epibatidine and Its Derivatives from Chiral Allene-1,3-dicarboxylate Esters

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(−)-Epibatidine, an excellent candidate of non-opioidal anesthesia, was formally synthesized in short steps from di-(*l*)-menthyl (*R*)-allene-1,3-dicarboxylate that was facilely prepared as a single isomer by means of crystallization-induced asymmetric transformation from a diastereomer mixture of (*R*)- and (*S*)-allene-1,3-dicarboxylates. Taking advantage of the chiral synthesis, derivatives of (−)-epibatidine were also prepared for targeting diagnostic agents that could bind nicotinic acetylcholine receptors (nAChRs) in the mammalian central nerve system.

Key words (−)-epibatidine; non-opioidal anesthesia; chiral allene-1,3-dicarboxylate; crystallization induced asymmetric transformation

(−)-Epibatidine (**1**) is an alkaloid isolated from the amphibian skin of the Equadorian poison frog, *Epipedobates tricolor*,[1] of which collection is forbidden by the international treaty for the protection of endangered species since it was enacted in 1984. Combined with the restrictions under the treaty, the scarce availability in nature and the exciting biological properties including anesthetic activity[2—4] required facile synthetic routes to **1** and its derivatives for further biological and pharmaceutical investigation. Although much progress has been attained in the last decade providing practical synthetic methods,[5—24] optically pure (−)-**1** still remains as an attractive synthetic target because it is focused on as an excellent candidate of non-opioidic analgesic agent for clinical use in accordance with the development of biological studies.

In the present paper, we would like to report the asymmetric synthesis of (−)-**1** and its derivatives by means of the crystallization-induced asymmetric transformation of allene-1,3-dicarboxylates, of which a practical method was established by our group.[25]

A mixture of (*S*)- and (*R*)-isomers of di-(*l*)-menthyl allene-1,3-dicarboxylate (diastereo ratio=5 : 4) prepared from di-(*l*)-menthyl 1,3-acetonedicarboxylate by reaction with 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and triethylamine was crystallized in the presence of triethylamine (0.01 eq) at low temperature to afford di-(*l*)-menthyl (*R*)-allene-1,3-dicarboxylate (**2**) as a single crystal. Repeating the same procedure three times gave **2** in total 90% yield. Encouraged by the results, we adopted the chiral allene-1,3-dicarboxylates **2** as a dienophile of Diels–Alder reaction with *N*-Boc-pyrrole **3**. Fortunately, the Diels–Alder reaction conducted in the presence of $AlCl_3$ at −78 °C in CH_2Cl_2 afforded *endo*-adduct **4** as the sole product in good yield while the same reaction of methyl allene-1,3-dicarboxylate and **3** gave an inseparable mixture of almost the same amounts of the *endo* and *exo* adducts both at low temperature (−78 °C) with the assistance of $AlCl_3$ in CH_2Cl_2 and at high temperature (90 °C) in the absence of the Lewis acid in toluene. The significant difference in *endo*/*exo* selectivity could be attributed to the steric repulsion between the Boc group of **3** and the (*l*)-menthyl group in the dienophile **2**.[26] After hydrogenation of the isolated double bond of the *endo* adduct (−)-**4**, the obtained diester **5** was ozonolyzed to *β*-ketoester **6**, which was derived to a known synthetic intermediate **7** of (−)-epibatidine by dealkoxycarbonylation and successive reprotection of the secondary amino group with the Boc_2O. All of the physical and spectral data of **7** were in complete agreement with those in the literature.[7] In order to avoid the generation of presumed by-products caused by excessive ozonolysis of the enol form derived from *β*-ketoester **6**, the synthetic route was revised to circumvent keto-enol tautomerization of the product in the ozonolysis. Namely, **5** was first reduced with lithium aluminum hydride to afford diol **8**, of which the double bond of the allylic alcohol moiety was next ozonolyzed to give *β*-keto alcohol **9**. Thus, it was oxidized by Jones oxidation and successively decarboxylated by heating in toluene to yield (−)-**7**. Although the overall yield from **5** to **7** was not substantially improved, the synthetic route afforded high reproducibility reflecting the fact that the tedious procedure of isolation in each step could be dispensed with (Chart 1).

Meanwhile, the structure of (−)-epibatidine [(−)-**1**] and its analogues, such as 3-(2(*S*)-azetidinylmethoxy)pyridine (**10**) (Fig. 1.),[27,28] must be labeled with radio isotopes, *e.g.*, ^{123}I, to develop further studies on binding to nicotinic acetylcholine receptors (nAChRs) in the mammalian central nerve system by using single photon emission computed tomography (SPECT), the most useful bioimaging method *in vivo*. Thus, (−)-epibatidine derivative **11** was designed as a novel diagnostic agent for pharmaceutical studies of (−)-**1**, and preparation from (−)-**7** using ^{126}I instead of ^{123}I as a model synthesis of radioactive **11** was attempted. Namely, (−)-**7** was treated with 2-bromo-5-iodopyridine[29,30] in the presence of *n*-butyl lithium to give *tert*-alcohol **12**,[7] of which the bromine group on the pyridine ring was replaced with iodine by the reaction with sodium iodide and hydrochloric acid in refluxed acetonitrile to afford **11**.[32] Having the secondary amino group, it was protected again with a *tert*-butyloxycarbonyl group to afford **13** for facile isolation (Chart 2).

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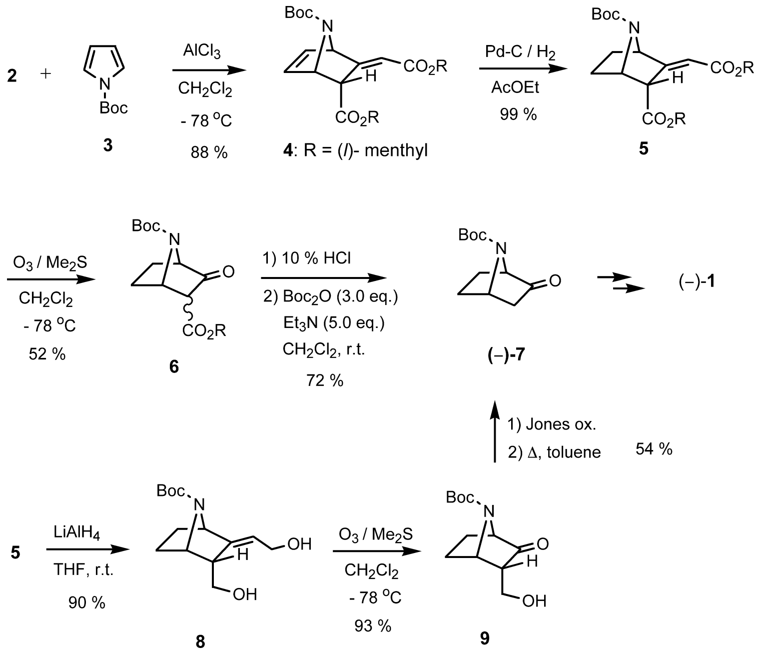

Chart 1

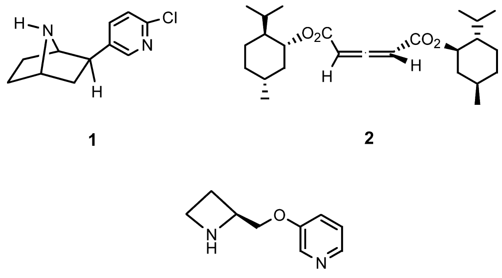

Fig. 1

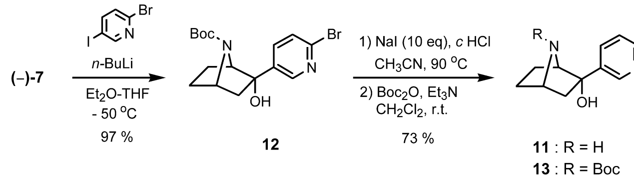

Chart 2

Experimental

General Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^{1}H-NMR spectra were obtained on a JEOL JNM-AL300, a Varian XL-300, or a JEOL JNM-LA 500 spectrometer with tetramethylsilane as an internal standard. ^{13}C-NMR spectra were obtained on a JEOL JNM-AL300 spectrometer with CDCl$_3$ as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Wakogel C-200 (silica gel) (100—200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed by using Silica Gel 60N (Kanto Chemical Co., Inc.) as a solid support of immobile phase. Kieselgel 60 F-254 plates (Merck) were used for thin-layer chromatography (TLC). Preparative TLC (PTLC) was conducted with Kieselgel 60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merck). Unless purification with silica gel gave a compound of sufficiently purity, the compounds were further treated with a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H). In the case it is possible, diastereomeric mixtures were also separated by a recycle HPLC (JAI LC-908) on silica gel column (Kusano Si-10) after the purification mentioned above.

(1*S*,2*R*,3*E*,4*R*)-(−)-(*l*)-Menthyl 7-*tert*-Butoxycarbonyl-3-[2′-(*l*)-menthyloxy-2′-oxoethylidene]-7-azabicyclo[2.2.1]hept-5-ene-2-carboxylate [(−)-4] Aluminum chloride (1.78 g, 13.4 mmol) was added to a solution of (*R*)-(−)-bis-(*l*)-menthyl 2,3-pentadiendioate [(−)-**2**] (4.5 g, 11.1 mmol) in dichloromethane (50 ml) at −78 °C, and the mixture was stirred for 30 min. 1-*tert*-Butoxycarbonylpyrrole (18.6 g, 111.2 mmol) was added slowly, and the reaction mixture was stirred at −78 °C. The mixture was poured into ice-water after 2 d and extracted with chloroform. The organic layer was dried over sodium sulfate and condensed *in vacuo*. The residue was purified with silica gel column chromatography (hexane : ethyl acetate=10 : 1) to afford (−)-**4** (5.6 g, 88%) as colorless crystals.

mp 143—144 °C (methanol); ^{1}H-NMR (300 MHz, CDCl$_3$) δ: 0.70 (3H, d, *J*=6.6 Hz), 0.75 (3H, d, *J*=6.6 Hz), 0.86 (6H, d, *J*=6.6 Hz), 0.91 (6H, d, *J*=6.9 Hz), 0.85—1.09 (6H, m), 1.31—1.44 (3H, m), 1.41 (9H, s), 1.55 (1H, s), 1.64 (2H, s), 1.68 (2H, s), 1.84—2.04 (4H, m), 4.06 (1H, s), 4.55 (1H, dt, *J*=10.8, 4.3 Hz), 4.63 (1H, dt, *J*=11.0, 4.5 Hz), 4.90 (1H, s), 5.0 (1H, s), 6.04 (1H, d, *J*=1.7 Hz), 6.30 (1H, dd, *J*=2.0, 5.7 Hz), 6.40 (1H, d, *J*=3.5 Hz). ^{13}C-NMR (75 MHz, CDCl$_3$) δ: 16.1, 16.4, 20.6, 20.8, 21.92, 21.95, 23.1, 23.5, 25.6, 26.1, 28.1 (3), 31.3, 31.4, 34.19, 34.22, 40.5, 40.8, 46.8, 46.9, 49.8, 62.5, 67.1, 74.1, 74.8, 81.0, 115.6, 133.2, 135.2, 151.3, 154.1, 165.4, 168.3. IR (CHCl$_3$) cm^{-1}: 2958, 2930, 1705, 1369, 1175. FAB-MS *m*/*z*: 572.3955 (Calcd for $C_{34}H_{54}NO_6$: 572.3951). MS (FAB) *m*/*z*: 572 (M$^+$+H, 9). $[\alpha]_D^{17}$ −3.2° (*c*=0.68, CHCl$_3$). *Anal.* Calcd for $C_{34}H_{53}NO_6$: C, 71.42; H, 9.34; N, 2.45; O, 16.79. Found: C, 71.60; H, 9.17; N, 2.38; O, 16.64.

(1*S*,2*R*,3*E*,4*R*)-(−)-(*l*)-Menthyl 7-*tert*-Butoxycarbonyl-3-[2′-(*l*)-menthyloxy-2′-oxyethylidene]-7-azabicyclo[2.2.1]heptan-2-carboxylate [(−)-5] A catalytic amount of 10% Pd–C was added to a solution of (−)-**4** (1.00 g, 1.75 mmol) in ethyl acetate (24.0 ml), and the mixture was stirred under hydrogen atmosphere. After 1 h, the mixture was filtered to remove the catalyst and condensed *in vacuo*. The residue was purified with silica gel column chromatography (hexane : ethyl acetate=10 : 1) to afford (−)-**5** (1.00 g, 99%) as colorless crystals.

mp 152—153 °C (methanol); ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 0.72 (3H, d, *J*=6.9 Hz), 0.77 (3H, d, *J*=6.9 Hz), 0.87—1.41 (18H, m), 1.43 (9H, s), 1.49—2.15 (16H, m), 4.00 (1H, s), 4.50—4.54 (2H, m), 4.63 (2H, tt, *J*=10.6, 4.2 Hz), 5.88 (1H, d, *J*=2.6 Hz). ^{13}C-NMR (75 MHz, CDCl$_3$) δ: 16.0, 16.4, 20.6, 20.9, 21.95, 21.98, 23.0, 23.5, 25.0, 25.6, 26.1, 27.4, 28.2 (3), 31.3, 31.4, 34.2, 34.2, 40.7, 40.9, 46.8, 46.9, 53.1, 58.9, 63.6, 73.8, 74.8, 80.6, 112.6, 154.9, 157.0, 165.5, 168.6. IR (CHCl$_3$) cm^{-1}: 2959, 2872, 1701, 1369, 1161. FAB-MS *m*/*z*: 574.4113 (Calcd for $C_{34}H_{56}NO_6$: 574.4113). MS (FAB) *m*/*z*: 574 (M$^+$+H, 10). $[\alpha]_D^{17}$ −75.1° (*c*=1.2, CHCl$_3$). *Anal.* Calcd for $C_{34}H_{55}NO_6$: C, 71.17; H, 9.66; N, 2.44; O, 16.73. Found: C, 71.12; H, 9.50;

N, 2.40; O, 16.45.

(1*S*,4*R*)-(*l*)-Menthyl 7-*tert*-Butoxycarbonyl-3-oxo-7-azabicyclo[2.2.1]-heptan-2-carboxylate (6) Ozone gas was passed through a solution of (−)-**5** (100 mg, 0.17 mmol) in dichloromethane (20 ml) at −78 °C until the blue color remained in the solution, and then nitrogen gas was bubbled. Dimethyl sulfide (54 mg, 0.87 mmol) was added, and the mixture was stirred at room temperature for 1 d. The organic solvent was evaporated off, and the residue was purified with silica gel column chromatography (hexane : ethyl acetate=7 : 1) to afford **6** (23 mg, 52%) as colorless oil, and the spectral data showed it to be a mixture of *exo*- and *endo*-isomers (1 : 1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.75 (3H, d, J=6.8 Hz), 0.88—1.26 (7H, m), 1.46 (9H, s), 1.43—1.52 (1.5H, m), 1.63—1.73 (5H, m), 1.88—2.05 (6H, m), 2.97 (0.5H, s), 3.43 (0.5H, d, J=5.2 Hz), 4.31 (0.5H, d, J=5.6 Hz), 4.37 (0.5H, m), 4.68—4.77 (2×0.5H, m), 4.84 (0.5H, m). IR ($CHCl_3$) cm^{-1}: 2959, 1778, 1717, 1701, 1369, 1221, 1161. FAB-MS *m/z*: 394.2607 (Calcd for $C_{22}H_{36}O_5N$: 394.2594). MS (FAB) *m/z*: 394 (M^++H, 7).

(1*R*,4*S*)-(−)-7-*tert*-Butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-one [(−)-7] 10% Hydrochloric acid (1.5 ml) was added to **6** (59 mg, 0.15 mmol) and the mixture was refluxed. Ethanol was added to the mixture after 12 h, and the solvent was evaporated off. The residue was dried and dissolved in dichloromethane (4.0 ml), to which triethylamine (46 mg, 0.45 mmol) and di-*tert*-butyl dicarbonate (65 mg, 0.30 mmol) were added. After stirring the mixture for 1 d at room temperature, the reaction mixture was poured into saturated aqueous solution of sodium chloride and extracted with chloroform. The organic layer was dried over sodium sulfate and condensed *in vacuo*. The residue was purified with silica gel column chromatography (hexane : ethyl acetate=7 : 1) to afford (−)-**7** (23 mg, 72%) as colorless oil.[7)]

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.45 (9H, s), 1.57—1.67 (2H, m), 1.94—2.06 (3H, m), 2.47 (1H, dd, J=17.4, 5.2 Hz), 4.24 (1H, d, J=4.9 Hz), 4.55 (1H, t, J=4.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 24.3, 27.4, 28.0 (3), 45.0, 55.9, 63.8, 80.6, 154.9, 209.3. IR ($CHCl_3$) cm^{-1}: 1760, 1690. FAB-MS *m/z*: 212.1297 (Calcd for $C_{11}H_{18}NO_3$: 212.1287). MS (FAB) *m/z*: 212 (M^++H, 25). $[\alpha]_D^{17}$ −74.5° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63; O, 22.72. Found: C, 62.47; H, 7.92; N, 6.61; O, 22.45.

(1*R*,3*S*,4*S*)-(+)-7-*tert*-Butoxycarbonyl-2-(2′-hydroxyethylidene)-3-hydroxymethyl-7-azabicyclo[2.2.1]heptane [(+)-8] To a suspension of lithium aluminum hydride (595 mg, 15.7 mmol) in tetrahydrofuran (10 ml), a solution of (−)-**5** (4.50 g, 7.84 mmol) in tetrahydrofuran (5 ml) was added dropwise, and the mixture was stirred at room temperature. After 24 h, saturated aqueous solution of sodium sulfate was added to the reaction mixture which was dried over sodium sulfate, filtrated, and evaporated. The residue was purified by silica gel column chromatography (chloroform : methanol=20 : 1) to afford (+)-**8** (2.11 g, 90%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.44 (9H, s), 1.45—2.05 (6H, m), 2.97—3.02 (1H, m), 3.68—3.79 (2H, m), 4.02—4.13 (2H, m), 4.29—4.41 (2H, m), 5.96 (1H, dt, J=4.7, 2.8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 23.5, 28.2 (3), 28.7, 46.7, 58.7, 59.7, 61.6, 64.2, 80.1, 118.8, 145.4, 155.5. IR ($CHCl_3$) cm^{-1}: 3030, 3012, 2885, 1683, 1367, 1165. FAB-MS *m/z*: 270.1713 (Calcd for $C_{14}H_{24}NO_4$: 270.1705). MS (FAB) *m/z*: 270 (M^++H, 20). $[\alpha]_D^{25}$ +47.1° (c=1.0, $CHCl_3$).

(1*R*,3*S*,4*S*)-(−)-7-*tert*-Butoxycarbonyl-3-hydroxymethyl-7-azabicyclo[2.2.1]heptan-2-one [(−)-9] Ozone gas was passed through a solution of **8** (760 mg, 2.82 mmol) in dichloromethane (30 ml) at −78°C until the blue color was remained in the solution, and then nitrogen gas was bubbled. Dimethyl sulfide (876 mg, 14.1 mmol) was added, and the mixture was stirred at room temperature for 1 d. The organic solvent was evaporated off, and the residue was purified with silica gel column chromatography (chloroform : methanol=15 : 1) to afford (−)-**9** (630 mg, 93%) as colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.46 (9 H, s), 1.53—1.59 (1H, m), 1.79—1.94 (2H, m), 2.01—2.13 (1H, m), 2.77—2.83 (1H, m), 2.94 (1H, br s), 3.64 (1H, dd, J=8.4, 11.4 Hz), 3.87 (1H, dd, J=5.3, 11.4 Hz), 4.27 (1H, d, J=5.7 Hz), 4.60 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.6, 25.4, 28.0 (3), 56.1, 58.4, 59.1, 64.6, 80.9, 154.8, 210.7. IR ($CHCl_3$) cm^{-1}: 3032, 2984, 2361, 1751, 1699, 1369, 1209. FAB-MS *m/z*: 242.1399 (Calcd for $C_{12}H_{20}NO_4$: 242.1393). MS (FAB) *m/z*: 242 (M^++H, 22). $[\alpha]_D^{25}$ −70.8° (c=1.5, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81; O, 26.52. Found: C, 59.73; H, 7.87; N, 5.70; O, 26.67.

Chemical Conversion from (−)-9 to (−)-7 Jones reagent (5 ml) was added to a solution of (−)-**9** (332 mg, 1.38 mmol) in acetone (30 ml) at 0 °C and the mixture was stirred for 1.5 h at room temperature. After the reaction, 2-propanol (0.2 ml) was added to the reaction mixture, which was dried over sodium sulfate and evaporated. The residue was dissolved in toluene (30 ml) and the solution was refluxed for 24 h. The organic solvent was evaporated and the residue was purified by silica gel column chromatography (chloroform : methanol=15 : 1) to afford (−)-**7** (156 mg, 54%).

(1*R*,2*S*,4*S*)-(+)-2-(2′-Bromopyridin-5′-yl)-7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-ol [(+)-12] *n*-Buthyl lithium (1.6 M solution in hexane, 1.48 ml, 2.37 mmol) was added to a solution of 2-bromo-5-iodopyridine (673 mg, 2.37 mmol) in diethyl ether (5.0 ml) and tetrahydrofuran (5.0 ml) at −78 °C, and the mixture was stirred for 20 min. A solution of (−)-**7** (250 mg, 1.18 mmol) in tetrahydrofuran (2.0 ml) was added to the solution, and the mixture was stirred at −50 °C for 30 min. After the reaction, the reaction mixture was poured into saturated aqueous solution of ammonium chloride and extracted with chloroform. The organic layer was dried over sodium sulfatesodium sulfate and condensed *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=15 : 1) to afford (+)-**12** (423 mg, 97%) as colorless crystals.

mp 152—153 °C (methanol); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.39 (9H, s), 1.65—1.67 (3H, m), 1.82 (1H, br s), 2.27—2.30 (1H, m), 2.39—2.43 (1H, m), 3.62 (1H, br s), 4.18 (1H, s), 4.27 (1H, s), 7.40 (1H, d, J=8.4 Hz), 7.74 (1H, dd, J=8.4, 1.7 Hz), 8.47 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.6, 28.2 (3), 28.8, 48.0, 57.2, 65.6, 78.0, 80.3, 127.4, 136.2, 140.3, 143.2, 147.7, 154.9. IR ($CHCl_3$) cm^{-1}: 2985, 2930, 1705, 1369, 1175. FAB-MS *m/z*: 369.0817 (Calcd for $C_{16}H_{22}N_2O_3Br$: 369.0814). MS (FAB) *m/z*: 369 (M^++H, 100). $[\alpha]_D^{22}$ +17.6° (c=1.0, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}N_2O_3Br$: C, 52.04; H, 5.73; N, 7.59; O, 13.00; Br, 21.64. Found: C, 51.74; H, 5.66; N, 7.37; O, 13.27; Br, 21.52.

(1*R*,2*S*,4*S*)-(+)-2-(2′-Iodopyridin-5′-yl)-7-*tert*-butoxycarbonyl-7-azabicyclo[2.2.1]heptan-2-ol [(+)-13] Sodium iodide (2.436 g, 16.2 mmol) and 35% hydrochloric acid (2 portion) were added to a solution of (−)-**12** (600 mg, 1.62 mmol) in acetonitrile (20 ml), and the mixture was refluxed for 1 d. After the reaction, the reaction mixture was poured into saturated aqueous solution of sodium bicarbonate and extracted with chloroform. The organic layer was washed with saturated aqueous solution of sodium thiosulfate, dried over sodium sulfatesodium sulfate, and condensed *in vacuo* to give a crude of (1*R*,2*S*,4*S*)-2-(2′-iodopyridin-5′-yl)-7-azabicyclo[2.2.1]heptan-2-ol (**11**). To a solution of this crude product in dichloromethane (14 ml) were added triethylamine (246 mg, 2.43 mmol) and di-*tert*-butyl dicarbonate (530 mg, 2.43 mmol), and the mixture was stirred at room temperature. After 10 h, the reaction mixture was poured into saturated aqueous solution of sodium chloride and extracted with chloroform. The organic layer was dried over sodium sulfate, and condensed *in vacuo*. The residue was purified by silica gel column chromatography (chloroform : methanol=20 : 1) to afford (+)-**13** (492 mg, 73%) as colorless crystals.

mp 194 °C (methanol); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.41 (9H, s), 1.61—1.69 (4H, m), 2.20 (1H, s), 2.36—2.41 (2H, m), 4.22 (1H, s), 4.32 (1H, s), 7.54 (1H, dd, J=8.2, 2.4 Hz), 7.66 (1H, d, J=8.2 Hz), 8.56 (1H, d, J=2.4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.7, 28.2 (3), 28.8, 48.1, 57.3, 65.4, 78.2, 80.3, 116.2, 134.2, 135.3, 143.4, 148.6, 154.9. IR ($CHCl_3$) cm^{-1}: 3584, 3391, 2982, 1693, 1450, 1369, 1161, 1080, 760. FAB-MS *m/z*: 417.0681 (Calcd for $C_{16}H_{22}N_2O_3I$: 417.0675). MS (FAB) *m/z*: 417 (M^++H, 100). $[\alpha]_D^{22}$ +11.7° (c=1.1, $CHCl_3$).

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