Synthesis of Optically Active *N*-(1-Ethyl-3-methylhexahydro-1,3-diazin-5-yl)- and *N*-(1-Ethyl-5-methyloctahydro-1,5-diazocin-3-yl)pyridine-3-carboxamides

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As part of the structure-activity relationship of the dopamine D_2 and serotonin 5-HT_3 receptors antagonist **1**, which is a clinical candidate with a broad antiemetic activity, the synthesis and dopamine D_2 and serotonin 5-HT_3 receptors binding affinity of (*R*)-5-bromo-*N*-(1-ethyl-3-methylhexahydro-1,3-diazin-5-yl)- and (*R*)-5-bromo-*N*-(1-ethyl-5-methyloctahydro-1,5-diazocin-3-yl)-2-methoxy-6-methylaminopyridine-3-carboxamides (**2** and **3**) are described. Treatment of 1-ethyl-2-(*p*-toluenesulfonyl)amino-3-methylaminopropane dihydrochloride (**4a**) with paraformaldehyde and successive deprotection gave the 5-aminohexahydro-1,3-diazine **6** in excellent yield. 3-Amino-1-ethyl-5-methyloctahydro-1,5-diazocine (**15**) was prepared from 2-(benzyloxycarbonyl)amino-3-[[*N*-(*tert*-butoxycarbonyl)-*N*-methyl]amino]-1-ethylaminopropane (**9**) through the intramolecular amidation of (*R*)-3-[*N*-[(2-benzyloxycarbonylamino-3-methylamino)propyl]-*N*-ethyl]aminopropionic acid trifluoroacetate (**12**), followed by lithium aluminum hydride reduction of the resulting 6-oxo-1-ethyl-5-methyloctahydrodiazocine (**13**) in 41% yield. Reaction of the amines **6** and **15** with 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid furnished the desired **2** and **3**, which showed much less potent affinity for dopamine D_2 receptors than **1**.

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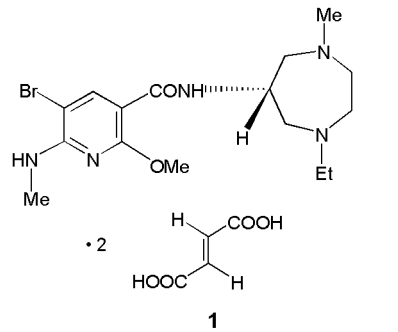
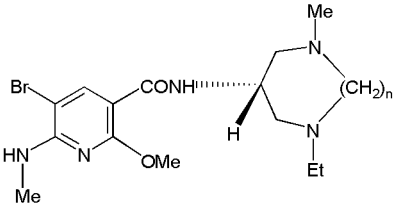
(*R*)-5-Bromo-*N*-(1-ethyl-4-methylhexahydro-1,4-diazepin-6-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide difumarate (**1**) is a potent dopamine D_2 and serotonin 5-HT_3 receptor dual antagonist and is considered as clinical candidate with a broad antiemetic activity [1]. In order to gain insight into the pharmacological properties of **1**, synthesis of the pyridine-3-carboxamides **2** and **3** having respectively six-membered and eight-membered heteroalicycles containing two nitrogen atoms (Figure 1) and their biological evaluation was essential. This modification of **1** may cause a change not only in the distance between the nitrogen atom in the amine moiety (amide group) and the pyridine ring but also in the preferred stable conformations of the molecule. The present paper deals with the synthesis, and serotonin 5-HT_3 and dopamine D_2 receptors binding affinity of 5-bromo-*N*-(1-ethyl-3-methylhexahydro-1,3-diazin-5-yl)- and 5-bromo-*N*-(1-ethyl-3-methyloctahydro-1,5-diazocin-3-yl)-2-methoxy-6-methylaminopyridine-3-carboxamides (**2** and **3**).



1

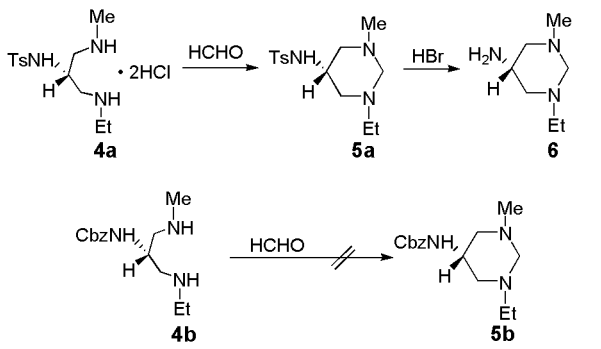


2; n = 1
3; n = 3

Figure 1

In this work, we first examined the synthesis of (*R*)-5-amino-1-ethyl-3-methylhexahydro-1,3-diazine (**6**). Reaction of **4a** [2] with paraformaldehyde gave 5-(*p*-toluenesulfonyl)amino-1-ethyl-3-methylhexahydro-1,3-diazine (**5a**) in 94% yield. The structure of **5a** was speculated from ^{1}H-nmr and ms spectra. On the other hand, treatment of the 5-(benzyloxycarbonyl)amino counterpart **4b** with para-

Scheme 1



4a **5a** **6**

4b **5b**

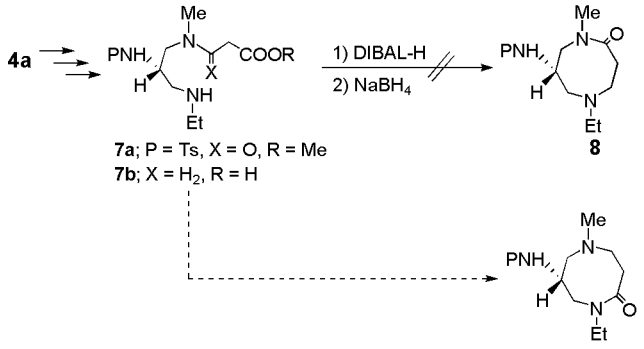
Cbz: benzyloxycarbonyl
Ts: *p*-toluenesulfonyl

formaldehyde smoothly proceeded, however, the desired product **5b** was not isolated. The reason for this result is unclear. The detosylation of **5a** was carried out in refluxing 47% aqueous hydrobromic acid solution to afford the desired amine **6** in quantitative yield (Scheme 1).

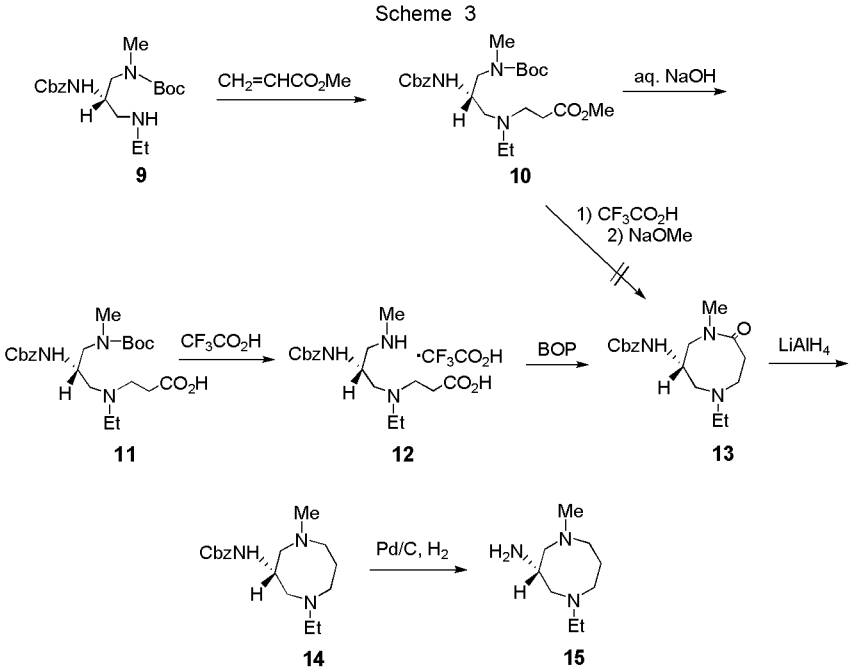
Next, the formation of 1-ethyl-5-methyloctahydro-1,5-diazocine ring was examined. Reaction of **4a** with malonyl dichloride did not afford the desired eight-membered compound. In addition, treatment of the 3-aminopropionic ester **7a**, derived from **4a**, with DIBAL-H at –70 °C, followed by sodium borohydride reduction [3] did not produce the 1-ethyl-5-methyloctahydro-1,5-diazocin-6-one **8** (Scheme 2). Previously, we reported that reaction of **4a** with glyoxal in the presence of boran-triethylamine complex directly produced the seven-membered product in good yield [4]. The method was applied; **4a** was treated with malondialdehyde [5] instead of glyoxal in the presence of boran-triethylamine, but the eight-membered products were not obtained at all. Finally, the method using intramolecular amidation of the 3-aminopropionic acid derivative **7b** was examined (Scheme 2). As shown in Scheme 3, reaction of **9** [2] with methyl acrylate gave the 3-aminopropionic ester **10** in 65% yield. After removal of the *tert*-butoxycarbonyl (Boc) group, intramolecular amidation of the resulting aminoester with sodium methoxide was unsuccessful. On the other hand, alkaline hydrolysis of **10**, followed by deprotection of Boc group of the resultant **11** by trifluoroacetic acid afforded the aminoacid **12** in excellent yield. Intramolecular amidation of **12** using benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophospate (BOP) proceeded smoothly to give the desired 1-ethyl-5-methyloctahydro-1,5-diazocin-6-one **13** in 89% overall yield from **10**. The structure of **13** was deduced from ^{1}H-nmr and ms spectra. Reduction of **13** with lithium aluminum hydride produced the 1-ethyl-5-methyloctahydro-1,5-diazocine **14** in 71% yield. Hydrogenolysis of **14** furnished 3-amino-1-ethyl-5-methyloctahydro-1,5-diazocine (**15**).

Condensation of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid [6] with the six-membered 5-amino-1,3-diazine **6** and the eight-membered 3-amino-1,5-diazocine **15** by *N*,*N'*-carbonyldiimidazole (CDI) gave the pyridine-3-carboxamides **2** and **3**, respectively (Scheme 4).

Scheme 2



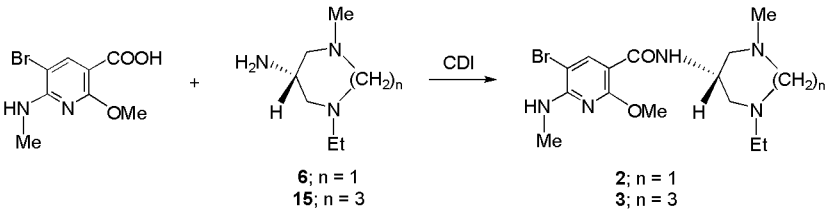
Scheme 3



Pharmacological Results.

The affinities of **2** and **3** for serotonin 5-HT$_3$ and dopamine D$_2$ receptors were determined using binding assays. The affinity for serotonin 5-HT$_3$ receptors was evaluated using competition for [^{3}H]GR65630 binding site

Scheme 4



6; n = 1
15; n = 3

2; n = 1
3; n = 3

in rat cortical membranes, [7] while the affinity for dopamine D_2 receptors was evaluated using [^{3}H]spiperone in the rat striatum [8] (Table 1). For comparison, data for **1** are included in Table 1.

Table 1
Affinity of (*R*)-5-Bromo-*N*-(1-ethyl-3-methylhexahydro-1,3-diazin-5-yl)- and (*R*)-5-Bromo-*N*-(1-ethyl-5-methyloctahydro-1,5-diazocin-3-yl)-2-methoxy-6- methylaminopyridine-3-carboxamides (**2** and **3**) for Serotonin 5-HT_3 and Dopamine D_2 Receptors

	Receptor Binding Affinity: IC_{50} (nM)	
Compound	Dopamine D_2 [a]	Serotonin 5-HT_3 [b]
2	698	47.5
3	595	1.6
1	2.5	1.1

[a] Determined in rat brain synaptic membranes using [^{3}H]spiperone; [b] in rat cortical membranes using [^{3}H]GR65630.

The affinity of **2** and **3** for dopamine D_2 receptors was much less potent than that of **1**. On the other hand, the pyridine-3-carboxamide **3** with its eight-membered ring showed strong affinity for serotonin 5-HT_3 receptors with an IC_{50} of 1.6 nM. This affinity for serotonin 5-HT_3 receptors was approximately equal to that of **1** (1.6 nM vs. 1.1 nM). The binding affinity for serotonin 5-HT_3 receptors of the pyridine-3-carboxamide **2** with its six-membered ring was less potent than that of the pyridine-3-carboxamide **1** with its seven-membered ring. From these results, it is clear that **3** exhibits potent affinity for serotonin 5-HT_3 receptors but not for dopamine D_2 receptors whereas **2** shows weak affinity for both receptors. It can, therefore, be speculated that the dopamine D_2 receptor site has a narrow permissible area and that the serotonin 5-HT_3 receptor site has a relatively broad permissible area. The conformational analysis for dopamine D_2 and serotonin 5-HT_3 receptors binding sites are now in progress.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus without correction. The ir spectra were recorded on a Shimadzu FTIR-8200PC spectrometer with potassium bromide disks. Atmospheric pressure chemical ionization and secondary ion mass spectra were obtained on a Hitachi M-1000 spectrometer. The ^{1}H-nmr spectra were recorded on a Varian Gemini-200 (200 MHz) or a JEOL JNM-LA300 (300 MHz) spectrometer using dilute solution in deuteriochloroform unless otherwise stated. Chemical shifts are expressed as δ (ppm) values from tetramethylsilane as an internal standard. Optical rotations were measured at 589 nm with a Jasco P-1020 digital polarimeter. Organic extracts were dried over anhydrous magnesium sulfate. The solvents were evaporated under reduced pressure.

(*R*)-1-Ethyl-3-methyl-5-(*p*-toluenesulfonylamino)hexahydro-1,3-diazine (**5a**).

A mixture of **4a** (5.0 g, 14 mmol), paraformaldehyde (0.5 g, 17 mmol), triethylamine (2.8 g, 28 mmol), and methyl alcohol (50 ml) was heated to reflux for 5 hours and cooled to room temperature. The solvent was then evaporated to leave a residue, which was diluted with aqueous potassium carbonate solution and extracted with chloroform. The extract was concentrated to give a solid, which was chromatographed on silica gel with chloroform/methyl alcohol = 50/1 to afford 3.9 g (94%) of **5a**. The authentic sample was obtained by recrystallization from ethyl acetate/hexane, mp 96—97 °C. ^{1}H-nmr: δ 0.94 (t, *J* = 7.5 Hz, 3H, CH_2*Me*), 2.11 (s, 3H, C_6H_4*Me*), 2.42 (s, 3H, NMe), 1.9—2.6 (m, 7H), 3.42 (m, 1H), 3.54 (m, 1H, 5-CH), 5.52 (m, 1H, NH), 7.28 (d, *J* = 8.4 Hz, 2H, arom. H), 7.77 (d, *J* = 8.4 Hz, 2H, arom. H); ms: m/z 298 (MH^+); ir: 2795, 1475, 1464, 1335, 1165, 1094. $[\alpha]_D^{29}$ = + 0.95° (*c* = 1.0, MeOH).

Anal. Calcd. for $C_{14}H_{23}N_3O_2S$: C, 56.54; H, 7.79; N, 14.13; S, 10.78. Found: C, 56.56; H, 8.06; N, 14.29; S, 10.51.

(*R*)-5-Amino-1-ethyl-3-methylhexahydro-1,3-diazine (**6**).

A solution of **5a** (1.5 g, 5.1 mmol) in hydrobromic acid (15 ml of 48% aqueous solution) was heated to reflux for 1 hour and cooled to room temperature. The reaction mixture was washed with chloroform, basified with 48% aqueous sodium hydroxide solution, and extracted with chloroform. The extract was evaporated to leave 0.7 g (quantitative yield) of **6** as a yellow oil, which was used in the next amidation step without further purification; ^{1}H-nmr: δ 1.11 (t, *J* = 7.5 Hz, 3H, CH_2*Me*), 1.62 (br. s, 2H), 2.44 (s, 3H, NMe), 2.1—2.8 (m, 7H), 2.99 (m, 1H), 3.50 (m, 1H, 5-CH); ms: m/z 144 (MH^+).

Methyl (*R*)-3-[*N*-[[2-Benzyloxycarbonylamino-3-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino]propyl]-*N*-ethyl]aminopropionate (**10**).

A mixture of **9** (9.6 g, 26 mmol), methyl acrylate (2.8 g, 33 mmol), and methyl alcohol (50 ml) was stirred at room temperature for 16 hours and concentrated to dryness. The residue was chromatographed on silica gel with chloroform/methyl alcohol = 100/1 to give 7.7 g (65%) of **10** as a pale yellow oil; ^{1}H-nmr: δ 0.97 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 1.43 (s, 9H, ^{t}Bu), 2.15—2.62

(m, 6H), 2.65—2.96 (m, 2H), 2.88 (s, 3H, NMe), 3.1—3.7 (m, 2H), 3.64 (s, 3H, OMe), 3.81 (m, 1H), 5.08 (s, 2H, CH_2Ph), 5.65 (br., 1H), 7.33 (m, 5H, arom. H); hrms: Calcd. for $C_{23}H_{37}N_3O_6$: 451.2681. Found: 451.2690.

(*R*)-3-[*N*-[[2-Benzyloxycarbonylamino-3-(*N*-*tert*-butoxycarbonyl-*N*-methyl)amino]propyl]-*N*-ethyl]aminopropionic Acid (**11**).

A mixture of **10** (7.7 g, 17 mmol), 2 *N* aqueous sodium hydroxide solution (12.7 ml, 25 mmol), and ethyl alcohol (10 ml) was heated to reflux for 2 hours and cooled to room temperature. After evaporation of ethyl alcohol, the resulting aqueous solution was washed with diethyl ether and then acidified (pH 3—4) with aqueous citric acid solution and extracted with chloroform. The extract was washed with brine and evaporated to give 6.7 g (90%) of **11** as a colorless oil; ^{1}H-nmr: δ 1.14 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 1.43 (s, 9H, ^{t}Bu), 1.8—2.3 (m, 3H), 2.5—2.75 (m, 3H), 2.88 (s, 3H, NMe), 2.75—3.1 (m, 4H), 4.03 (m, 1H, 2-CH), 5.06 (d, *J* = 6.4 Hz, 1H, PhCH_2), 5.12 (d, *J* = 6.4 Hz, 1H, PhCH_2), 6.08 (m, 1H, NH), 7.1—7.4 (m, 5H, arom. H); hrms: Calcd. for $C_{22}H_{35}N_3O_6$: 437.2525. Found: 437.2545.

(*R*)-3-Benzyloxycarbonylamino-1-ethyl-5-methyl-6-oxo-1,5-octahydrodiazocine (**13**).

Trifluoroacetic acid (40 ml) was added to a solution of **11** (6.2 g, 14 mmol) in dichloromethane (80 ml) at room temperature. The mixture was stirred at the same temperature for 3 hours and concentrated to dryness. The residue was dissolved in chloroform, and then the volatiles were completely evaporated to give 8.0 g of (*R*)-3-[*N*-[(2-benzyloxycarbonylamino-3-methylamino)propyl]-*N*-ethyl]aminopropionic acid trifluoroacetate (**12**) as an oil, which was used in the next step without further purification; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 1.20 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 2.60 (s, 3H, NMe), 2.74 (m, 2H), 2.4—2.8 (m, 8H), 4.22 (m, 1H, 2-CH), 5.07 (s, 2H, CH_2Ph), 7.3—7.5 (m, 5H, arom. H), 7.58 (d, 1H, *J* = 9.0 Hz), 8.69 (br. s, 2H); ms: m/z 338 (MH^+).

To a mixture of **12** (8.0 g), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophospate (6.3 g, 14 mmol), and dichloromethane (300 ml) was added dropwise triethylamine (5.7 g, 56 mmol) at room temperature. The whole was stirred at the same temperature for 16 hours and washed successively with water, 2 *N* aqueous sodium hydroxide solution, and brine. The solvent was evaporated to leave a residue, which was chromatographed on silica gel with chloroform/methyl alcohol = 50/1 to give 4.5 g (99% from **11**) of **13** as a white solid. The authentic sample was obtained by recrystallization from ethyl acetate, mp 102—104 °C; ^{1}H-nmr: δ 1.01 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 2.4—2.8 (m, 8H), 2.94 (s, 3H, NMe), 2.94 (m, 1H), 3.62 (m, 1H), 3.86 (m, 1H), 5.09 (d, *J* = 12.2 Hz, 1H, PhCH_2), 5.12 (d, *J* = 12.2 Hz, 1H, PhCH_2), 5.18 (br., 1H, NH), 7.35 (s, 5H, arom. H); ms: m/z 320 (MH^+); ir: 3271, 1707, 1618, 1533, 1248, 1036. $[\alpha]_D^{29}$ = –15.5° (*c* = 1.0, MeOH).

Anal. Calcd. for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 63.82; H, 7.83; N, 13.29.

(*R*)-3-Benzyloxycarbonylamino-1-ethyl-5-methyl-1,5-octahydrodiazocine (**14**).

To a solution of **13** (1.4 g, 4.4 mmol) in anhydrous tetrahydrofuran (15 ml) was added lithium aluminum hydride (0.39 g, 10.0 mmol) at 5 °C. The mixture was stirred at the same temperature for 3 hours and excess lithium aluminum hydride was decomposed by addition of saturated aqueous potassium sodium tartarate tetrahydrate solution. The organic layer was separated by decantation, and the insoluble materials were washed with chloroform. The combined organic solution was dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel with chloroform/methyl alcohol = 4/1 to give 0.95 g (71%) of **14** as a colorless oil; ^{1}H-nmr: δ 1.00 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 1.6—1.9 (m, 2H), 2.35 (s, 3H, NMe), 2.4—2.85 (m, 10H), 3.64 (m, 1H, 3-CH), 5.09 (s, 2H, CH_2Ph), 5.52 (br., 1H, NH), 7.28—7.4 (s, 5H, arom. H); hrms: Calcd. for $C_{17}H_{27}N_3O_2$: 305.2102 Found. 305.2101

(*R*)-3-Amino-1-ethyl-5-methyl-1,5-octahydrodiazocine (**15**).

A solution of **14** (0.8 g, 2.6 mmol) in ethyl alcohol (20 ml) was hydrogenated over 10% palladium on carbon (0.2 g) under atmospheric pressure at room temperature for 2 hours. The catalyst was filtered off, and the filtrate was concentrated to dryness to give 0.45 g (quantitative yield) of **15** as a colorless oil, which was used in the next amidation step without further purification; ^{1}H-nmr: δ 1.12 (t, *J* = 7.1 Hz, 3H, CH_2*Me*), 1.7—2.05 (m, 2H), 2.54 (s, 3H, NMe), 2.55—3.00 (m, 12H), 3.28 (br., 1H, 3-CH); ms: m/z 172 (MH^+).

Preparation of the 5-Bromo-2-methoxy-6-methylaminopyridine-3-carboxamides **2** and **3**.

A solution of 5-bromo-2-methoxy-6-methylaminopyridine-3-carboxylic acid (0.78 g, 3.0 mmol) and *N*,*N*′-darbonyldiimidazole (CDI) (0.5 g, 3.1 mmol) in *N*,*N*-dimethylformamide (10 ml) was stirred at room temperature for 4 hours. After addition of the amines **6** and **15** (3.1 mmol), the mixture was stirred at the same temperature for 16 hours. The solvent was evaporated to leave a residue, which was dissolved in ethyl acetate. The solution was washed successively with water, 2 *N* aqueous sodium hydroxide solution, water, and brine. The solvent was evaporated, and the residue was chromatographed on silica gel with chloroform to chloroform + methyl alcohol to give the corresponding pyridine-3-carboxamides **2** and **3**. The oily compound **3** was converted to the fumarate, which was recrystallized from ethyl alcohol.

(*R*)-5-Bromo-*N*-(1-ethyl-3-methylhexahydro-1,3-diazin-5-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide (**2**).

Compound **2** has mp 131—132 °C (ethyl acetate/hexane); ^{1}H-nmr: δ 1.10 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 2.25 (s, 3H, NMe), 2.3—2.8 (m, 7H), 3.06 (d, *J* = 5.0 Hz, 3H, NH*Me*), 3.41 (d, *J* = 10 Hz, 1H), 4.03 (s, 3H, OMe), 4.28 (m, 1H, 5-CH), 5.26 (d, *J* = 5.0 Hz, 1H, N*H*Me), 8.12 (br., 1H, CONH), 8.37 (s, 1H); ms: m/z 386, 388 (MH^+); ir: 3425, 3296, 2974, 2943, 2783, 1636, 1601, 1454, 1381, 1277, 1221; $[\alpha]_D^{29}$ = -7.3° (C=1.0, MeOH).

Anal. Calcd. for $C_{15}H_{24}BrN_5O_2$: C, 46.64; H, 6.26; Br, 20.68; N, 18.13. Found: C, 46.73; H, 6.24; Br, 20.48; N, 18.02.

(*R*)-5-Bromo-*N*-(1-ethyl-5-methylhexahydro-1,5-octahydrodiazocin-3-yl)-2-methoxy-6-methylaminopyridine-3-carboxamide 3/2Fumarate (**3**).

Compound **3** has mp 188—189 °C; ^{1}H-nmr (dimethylsulfoxide-d_6): δ 1.02 (t, *J* = 7.0 Hz, 3H, CH_2*Me*), 1.90 (br., 2H), 2.49 (s, 3H, NMe), 2.71 (q, *J* = 7.0 Hz, 2H, CH_2Me), 2.93 (d, *J* = 4.6 Hz, 3H, NH*Me*), 2.75—3.1 (m, 8H), 4.00 (s, 3H, OMe), 4.08 (m, 1H, 3-CH), 6.54 (s, 3H, fumaric acid), 7.03 (d, *J* = 4.6 Hz, 1H, N*H*Me), 7.92 (d, *J* = 7.9 Hz, 1H, CONH), 8.08 (s, 1H); ms: m/z 414, 416 (MH^+); ir: 3383, 2953, 1682, 1599, 1516, 1464, 1383, 1279; $[\alpha]_D^{29}$ = +7.9° (C=1.0, MeOH).

Anal. Calcd. for $C_{17}H_{28}BrN_5O_2 \cdot 3/2C_4H_4O_4$: C, 46.94; H, 5.82; Br, 13.58; N, 11.90. Found: C, 46.94; H, 5.90; Br, 13.39; N, 11.83.

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