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Syntheses of (+)-Cytisine, (−)-Kuraramine, (−)-Isokuraramine, and (−)-Jussiaeiine A

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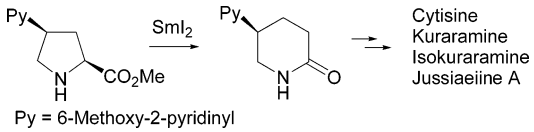

Total syntheses of (+)-cytisine, (−)-kuraramine, (−)-isokuraramine, and (−)-jussiaeiine A were achieved via a samarium diiodide-promoted reductive deamination reaction, followed by simultaneous recyclization of a proline derivative to give the corresponding δ-lactam derivative, as a key step.

Introduction

Naturally occurring lupine alkaloids, which have a wide range of structural and stereochemical features, continue to provide challenging synthetic targets.[1] Among them, (−)-cytisine (**1**)[2] has received special attention[3] and several synthetic methods have been developed,[4] since it has been shown to be an important probe in nicotinic acetylcholine receptor research[5] and shows high affinity at neuronal nicotinic receptors.[6]

(+)-Kuraramine (**2**) and (+)-jussiaeiine A (**3**), isolated from *Sophora flavescens*[7] and *Ulex jussiaei*,[8] respectively,

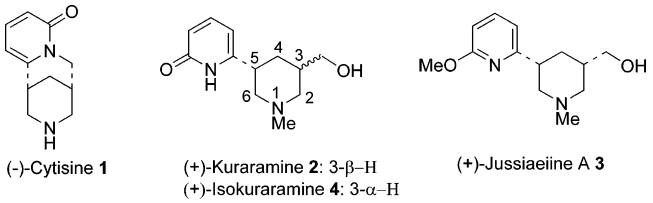

FIGURE 1. Structure of dipiperidine alkaloids.

are dipiperidine-type alkaloids with two chiral centers at the 3 and 5 positions of the piperidine ring, and are known to be oxidative metabolites of *N*-methylcytisine. Another dipiperidine-type alkaloid, (+)-isokuraramine (**4**)[9] was also isolated from the fresh flowers of *Sophora flavescens* as a minor constituent, and its structure was determined to be the diastereoisomer of (+)-kuraramine by spectroscopic methods.[9] However, little attention has been focused on the chiral synthesis of these alkaloids (Figure 1).

Thus, we planned to establish a novel synthetic route to these alkaloids, including cytisine, via a common synthetic intermediate. The key feature of our synthesis is based on a samarium diiodide-promoted reductive

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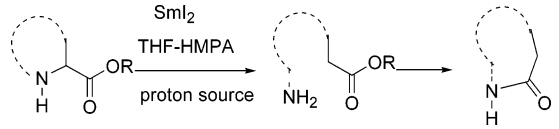

FIGURE 2. Reductive deamination of α-aminocarbonyl compounds.

deamination reaction of an α-amino ester, recently developed by us, as depicted in Figure 2.[10]

On the basis of a retrosynthetic analysis of these alkaloids as depicted in Scheme 1, we decided to exploit a readily available 4*R*-hydroxy-L-proline derivative as a starting material to synthesize the enantiomers of the aforementioned natural products, since the use of the antipodal starting material, D-hydroxyproline,[11] should lead to the synthesis of natural products if this synthetic strategy can be established.

Results and Discussion

Thus, 4-hydroxy-L-proline methyl ester **5** was converted to the corresponding triflate **8** in three steps. Treatment of **8** with 2-tributylstannyl-6-methoxypyridine **9** in the presence of a palladium catalyst[12] afforded the coupling product **10** in 88% yield. Hydrogenation of **10** over 10% palladium−charcoal in MeOH gave **11**, stereoselectively. After the Boc group was removed, samarium diiodide-promoted reductive deamination of the resulting **12**, followed by simultaneous cyclization of the resulting δ-amino ester, was carried out in THF−HMPA in the presence of methanol as a proton source to give the desired common intermediate, the δ-lactam **13**, in 78% yield.[10] (Scheme 2)

N-Methylation of **13** with iodomethane and sodium hydride in THF−HMPA furnished the corresponding *N*-methylpiperidone **14**, which was further converted into hydroxymethyl derivative as follows.

Treatment of the amide **14** with ethyl chlorocarbonate in the presence of LDA in THF gave an inseparable mixture of diastereomers (**15** and **16**), in a ratio of ca. 1:1. Reduction of the amide and ester functions of the mixture with $LiAlH_4$ in THF afforded the amino alcohols *ent*-**3** and **17** in respective yields of 50% and 46%. The spectroscopic data of *ent*-**3** obtained here were identical with those reported for (+)-jussiaeiine A (Scheme 3). Moreover, the sign of the optical rotation of the synthetic compound corresponded to that of the antipode {*ent*-**3**, $[\alpha]_D$ −5.2 (*c* 0.5, $CHCl_3$); lit.[8] $[\alpha]_D$ +3.3 (*c* 0.26, $CHCl_3$)}. Therefore, we were able to establish the first enantioselective synthesis of (−)-jussiaeiine A. Jussiaeiine A (*ent*-**3**) was converted into (−)-kuraramine (*ent*-**2**) by treatment with iodotrimethylsilane in refluxing acetonitrile.[13]

Again, the physicochemical properties of *ent*-**2** were identical with those reported in the literature, except for the sign of optical rotation[14] {*ent*-**2**: mp 78−80 °C, $[\alpha]_D$ −3.6 (*c* 2.1, EtOH); lit.[7] $[\alpha]_D$ +8.4 (*c* 0.52, EtOH)}.

The same treatment of the diastereoisomeric compound **17** gave isokuraramine *ent*-**4** as an amorphous solid, $[\alpha]_D$ −93.0 (*c* 2.1, EtOH).[9]

To achieve the total synthesis of (+)-cytisine from the common intermediate **13** through the formation of a carbon−nitrogen bond, as shown in Scheme 4, *N*-benzylation of **13** and subsequent ethoxycarbonylation of **18** with ethyl chlorocarbonate in the presence of LDA were carried out to provide a mixture of diastereoisomeric β-ketoesters (**19** and **20**) in a ratio of ca. 1:1.

Although the attempted isomerization of the mixture to the thermodynamically more stable 3,5-cis-compound under various reaction conditions, such as basic treatment of a mixture of **19** and **20** with lithium diisopropylamide in THF, sodium hydride in appropriate solvents, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene, did not improve the ratio, reduction of the mixture with $LiAlH_4$ gave the primary alcohols **21** and **22**, in respective yields of 48% and 43%. Finally, mesylation of **21** followed by thermal cyclization of the mesylate yielded the tricyclic compound **23**. Debenzylation of **23** under the hydrogenolysis conditions furnished *ent*-**1**, whose spectroscopic data were identical with those reported in the literature[15] except for the sign of optical rotation {*ent*-**1**: mp 152−153 °C, $[\alpha]_D$ +113.5 (*c* 0.3, EtOH); lit.[16] mp 152−153 °C, lit.[15] $[\alpha]_D$ −110 (*c* 0.5, EtOH), lit.[4e] $[\alpha]_D$ −114 (*c* 1, EtOH)}.

In summary, we have established novel and facile syntheses of dipiperidine-type lupine alkaloids, including cytisine. Although these syntheses give the antipodal forms of the natural products, we believe that the strategy developed here should be a useful tool for finding new drugs that are biologically related to cytisine.

Experimental Section

Methyl (2*S*)-*N*-*tert*-Butoxycarbonyl-4-[2′-(6′-methoxypyridyl)]-2,5-dihydropyrrole-2-carboxylate (10). To a stirred solution of vinyl triflate (**8**) (2.12 g, 5.65 mmol) and pyridyl(tributyl)stannane (**9**) (2.70 g, 6.78 mmol) in THF (30 mL) were successively added tetrakis(triphenylphosphine)-palladium(0) (327 mg, 0.283 mmol), lithium chloride (288 mg, 6.78 mmol), and copper(I) iodide (1.29 g, 6.78 mmol) at room temperature under argon. The mixture was heated at 65 °C for 4 h. After being cooled to room temperature, the mixture was diluted with Et_2O and the organic layer was washed with 5% NH_4OH. The aqueous layer was extracted with Et_2O. The combined ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to silica gel column chromatography. Elution with hexanes−Et_2O (3:2) afforded the coupling product (**10**) (1.66 g, 88%) as an inseparable mixture of rotational isomers. $[\alpha]^{25}_D$ −135 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 1755, 1709, 1470, 1433, 1400, 1368, 1346, 1329, 1273, 1257, 1202, 1176 and 1126; ^1H NMR δ 1.46 (5.85H, s), 1.53 (3.15H, s), 3.76 (1.95H, s), 3.77 (1.05H, s), 3.92 (1.95H, s), 3.94 (1.05H, s), 4.58−4.71 (2H, m), 5.15−

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(14) Although the value of the optical rotation of *ent*-**2** was slightly lower than that in the literature, we believe that our synthetic compound is optically pure, since the intermediate **10** was successfully transformed into cytisine with the correct optical rotation.

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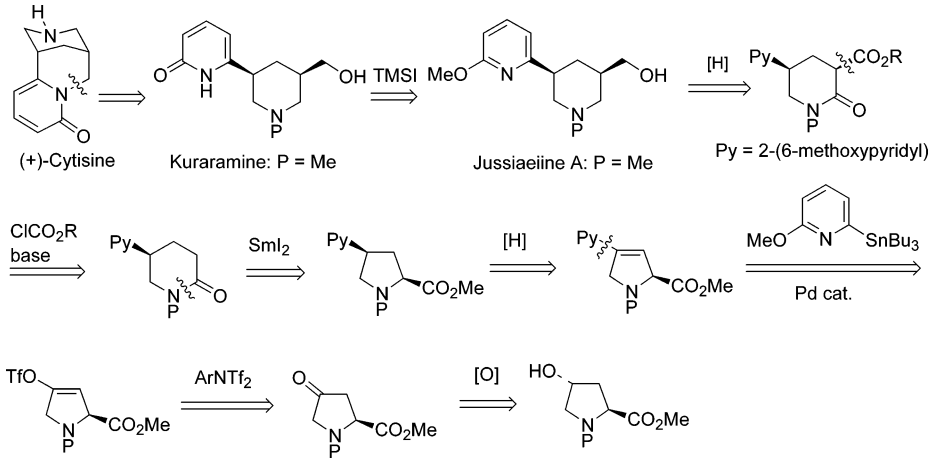
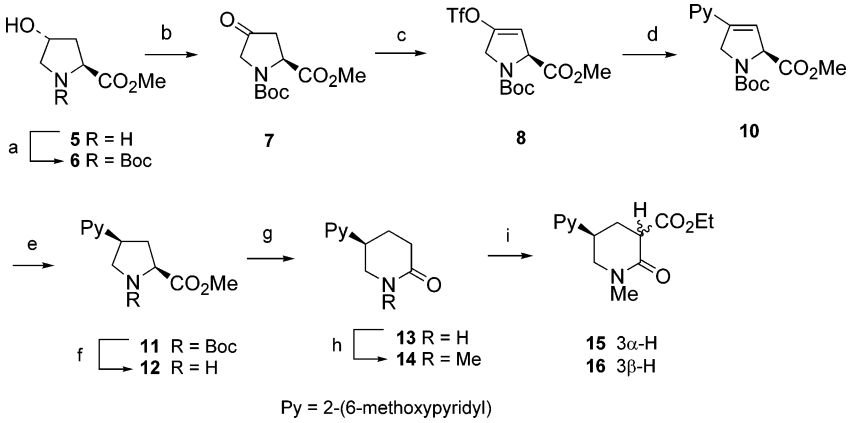
SCHEME 1. Retrosynthetic Route for Dipiperidine Alkaloids

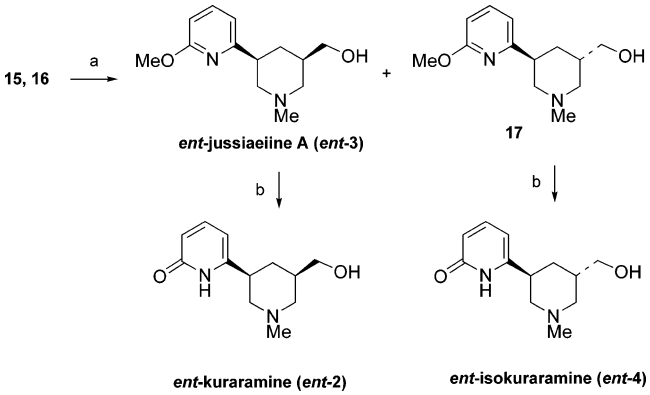


SCHEME 2. Preparation of the Key δ-Lactam[a]



[a] Reagents and conditions: (a) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt (quant.); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −40 °C to rt (91%); (c) LiHMDS, *N*-(5-chloro-2-pyridyl)triflimide, THF, −78 to −20 °C (89%); (d) $Pd(PPh_3)_4$, LiCl, CuI, 2-tributylstannyl-6-methoxypyridine (**9**), THF, 65 °C (88%); (e) H_2, Pd/C, MeOH, rt (quant.); (f) TFA, CH_2Cl_2, 0 °C (quant.); (g) SmI_2, THF-HMPA, MeOH, 0 °C to rt (78%); (h) NaH, MeI, THF-HMPA, 0 °C to rt (quant.); (i) LDA, $ClCO_2Et$, THF, −78 °C (quant.).

SCHEME 3. Synthesis of *ent*-Jussiaeiine A, *ent*-Kuraramine, and *ent*-Isokuraramine[a]

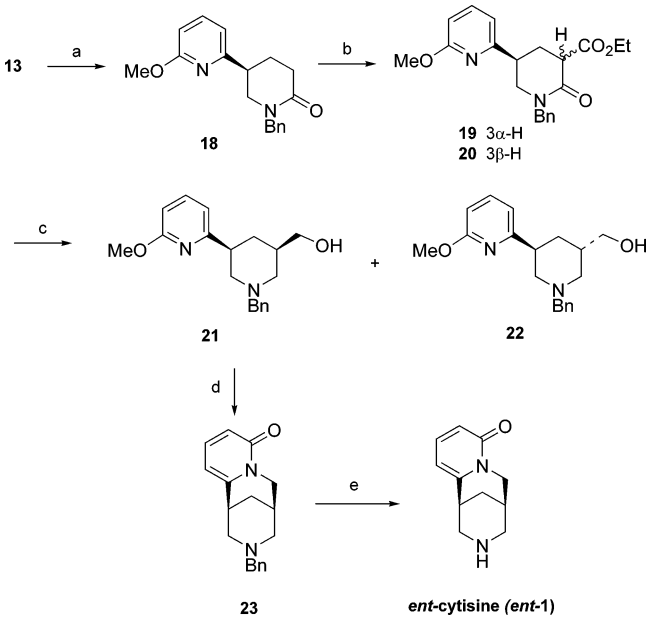


[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt (50% for *ent*-**3**; 46% for **17**); (b) TMSCl, NaI, MeCN, reflux (83% for *ent*-**2**; quant. for *ent*-**4**).

5.17 (0.65H, m), 5.21−5.25 (0.35H, m), 6.67 (1H, d, J = 8.2 Hz), 7.42 (1H, d, J = 7.4 Hz), 7.55 (1H, dd, J = 7.4 and 8.2 Hz); ^{13}C NMR δ up 52.6, 52.9, 80.2, 141.6 148.3, 148.4, 153.3, 153.8, 163.3, 170.4, 170.8, down 28.1, 28.3, 52.1, 52.2, 53.0, 66.9, 67.3, 110.6, 110.8, 113.3, 121.1, 121.5, 138.7; HRMS *m/z* (EI) calcd for $C_{17}H_{23}N_2O_5$ ($M^+ + 1$) 335.1607, found 335.1610. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.81; H, 6.62; N, 8.23.

Methyl (2*S*,4*S*)-2-*N*-*tert*-Butoxycarbonyl-4-[2′-(6′-methoxypyridyl)]pyrrolidine-2-carboxylate (11). A solution of compound **10** (100 mg, 0.315 mmol) in MeOH (1.6 mL) containing 10% palladium−carbon (10 mg) was stirred at room temperature under an atmospheric pressure of hydrogen for 2 h. After the insoluble material was removed by filtration through a pad of Celite, the filtrate was concentrated to give a residue, which was subjected to silica gel column chromatography. Elution with hexanes−EtOAc (4:1) afforded the reduction product (**11**) (101 mg, 100%) as an inseparable mixture of rotational isomers. $[\alpha]^{24}_D$ −20.7 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 1753, 1703, 1603, 1590, 1579, 1468, 1439, 1402, 1366, 1290, 1260, 1200, 1179, 1160, 1119, and 1136; ^1H NMR δ 1.43 (6.03H, s), 1.47 (2.97H, s), 2.34 (1H, ddd, J = 9.6, 11.0, and 12.4 Hz), 2.62 (1H, ddd, J = 6.9, 7.4, and 12.4 Hz), 3.41 (1H, dddd, J = 6.9, 7.4, 10.4, and 11.0 Hz), 3.64 (0.33H, dd, J = 10.4 and 10.9 Hz), 3.67 (0.67H, dd, J = 10.4 and 10.9 Hz), 3.74 (2.01H, s), 3.76 (0.99H, s), 3.90 (2.01H, s), 3.91 (0.99H, s), 4.03 (1H, dd, J = 7.4 and 10.9 Hz), 4.34 (0.67H, dd, J = 7.4 and 9.6 Hz), 4.41 (0.33H, dd, J = 7.4 and 9.6 Hz), 6.60 (1H, dd, J = 0.5 and 8.2 Hz), 6.73 (0.67H, br d, J = 7.3 Hz), 6.76 (0.33H, br d, J = 7.3 Hz), 7.49 (1H, dd, J = 7.3 and 8.2 Hz); ^{13}C NMR δ up 35.8, 36.6, 51.3, 80.1, down 28.3, 28.4, 44.5, 45.3, 51.9, 52.1, 53.2, 59.1, 59.3, 109.0, 114.6, 138.8; HRMS *m/z* (EI) calcd for $C_{17}H_{24}N_2O_5$ (M^+) 336.1685, found 336.1683.

SCHEME 4. Synthesis of *ent*-Cytisine[a]



[a] Reagents and conditions: (a) NaH, BnBr, THF-HMPA, THF, 0 °C to rt (quant.); (b) LDA, $ClCO_2Et$, THF, −78 °C (quant.); (c) $LiAlH_4$, THF, 0 °C to rt (48% for **19**; 43% for **20** from **13**); (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, then toluene, reflux (89% from **21**); (e) H_2, $Pd(OH)_2$, ammonium formate, MeOH, reflux (81%).

Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.21. Found: C, 60.47; H, 7.27; N, 8.21.

Methyl (2*S*,4*S*)-4-[2′-(6′-Methoxypyridyl)]pyrrolidine-2-carboxylate (12). To a stirred solution of **11** (50.0 mg, 0.149 mmol) in CH_2Cl_2 (0.7 mL) was added trifluoroacetic acid (0.23 mL, 2.98 mmol) at 0 °C under argon, and the resulting solution was stirred for 2 h at room temperature. After the mixture was concentrated, the residue was treated with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to silica gel column chromatography. Elution with $CHCl_3$−MeOH (20:1) afforded the amine **12** (35.0 mg, 100%) as a colorless oil. $[\alpha]^{23}_D$ −40.4 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 1740, 1600, 1579, 1469, 1438, 1418, 1280, 1260, 1210, 1135 and 805; ^1H NMR δ 2.19 (1H, ddd, J = 7.7, 7.9 and 12.9 Hz), 2.32 (1H, br s), 2.58 (1H, td, J = 8.2 and 12.9 Hz), 3.24−3.27 (2H, m), 3.31−3.47 (1H, m), 3.75 (3H, s), 3.90 (3H, s), 3.90−3.95 (1H, m), 6.56 (1H, dd, J = 0.7 and 8.2 Hz), 6.70 (1H, br d, J = 7.2 Hz), 7.45 (1H, dd, J = 7.2 and 8.2 Hz); ^{13}C NMR δ up 35.1, 50.5, 155.6, 164.2, 169.4, down 43.9, 53.4, 58.6, 100.5, 110.1, 115.1, 139.5; HRMS *m/z* (EI) calcd for $C_{12}H_{16}N_2O_3$ (M^+) 236.1161, found 236.1147.

5(*S*)-[2′-(6′-Methoxypyridyl)]-2-piperidone (13). A 0.2 M THF solution of samarium diiodide was prepared as follows. To a stirred solution of Sm metal (1.15 g, 7.63 mmol) in THF (16 mL) was slowly added a solution of diiodoethane (1.79 g, 6.37 mmol) in THF (16 mL) at ambient temperature under argon, and the resulting dark blue solution was stirred for 30 min at the same temperature. The solution was cooled to 0 °C. HMPA (3 mL) was added and the whole was stirred for an additional 15 min at the same temperature. To this solution were added dry MeOH (0.129 mL, 3.18 mmol) and a solution of **12** (300 mg, 1.27 mmol) in THF (3 mL) at the same temperature, and the resulting mixture was stirred for 40 min at ambient temperature. The mixture was treated with saturated $NaHCO_3$ solution (2 mL), Celite (10 g), and $CHCl_3$−MeOH (50 mL, 10/1, v/v). Insoluble materials were filtered off, and the filtrate was treated with NaCl (5 g) and 20% NH_4OH solution (20 mL). The organic layer was separated, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel with EtOAc−MeOH (10:1) as an eluent to afford the δ-lactam (**13**) (204 mg, 78%) as crystals. $[\alpha]^{27}_D$ −42.5 (*c* 1.0, $CHCl_3$); mp 130−131 °C (colorless prisms from hexane−CH_2Cl_2); IR (cm^{-1}) 1668, 1600, 1580, 1496, 1468, 1439, 1414, 1316, 1285, 1036, 808, and 775; ^1H NMR δ 2.11−2.25 (2H, m), 2.42−2.60 (2H, m), 3.55−3.68 (2H, m), 3.91 (3H, s), 5.90 (1H, br s), 6.62 (1H, d, J = 8.2 Hz), 6.78 (1H, d, J = 7.3 Hz), 7.52 (1H, dd, J = 7.3 and 8.2 Hz); ^{13}C NMR δ up 26.6, 30.8, 46.7, 158.6, 163.6, 172.1, down 40.6, 53.1, 108.8, 114.1, 139.0; HRMS *m/z* (EI) calcd for $C_{11}H_{14}N_2O_2$ (M^+) 206.1055, found 206.1078. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.81; H, 6.83; N, 13.42.

5(*S*)-[2′-(6-Methoxypyridyl)]-*N*-methyl-2-piperidone (14). To a mixture of lactam **13** (406 mg, 1.97 mmol) and sodium hydride (60% in oil) (118 mg, 2.96 mmol) in dry THF (10 mL) containing hexamethylphosphoric triamide (0.514 mL, 2.96 mmol) was added iodomethane (0.514 mL, 2.37 mmol) at 0 °C, and the resulting mixture was stirred for 90 min at room temperature. The mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$−MeOH (25:1, v/v) gave the *N*-methyl compound **14** (433 mg, 99%) as a colorless solid: $[\alpha]^{26}_D$ −37.3 (*c* 1.0, $CHCl_3$); mp 48−50 °C (colorless prisms from Et_2O−hexane); IR (cm^{-1}) 1640, 1600, 1578, 1466, 1286, and 1130; ^1H NMR δ 2.09−2.18 (2H, m), 2.47−2.55 (2H, m), 3.00 (3H, s), 3.17 (1H, m), 3.46−3.67 (2H, m), 3.91 (3H, s), 6.62 (1H, d, J = 8.2 Hz), 6.76 (1H, d, J = 7.2 Hz), 7.52 (1H, dd, J = 7.2 and 8.2 Hz); ^{13}C NMR δ up 27.1, 31.4, 54.2, 158.6, 163.7, 169.6, down 34.7, 41.2, 53.2, 108.8, 114.1, 139.0; HRMS *m/z* (EI) calcd for $C_{12}H_{16}N_2O_2$ (M^+) 220.1212, found 220.1215. Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.49; H, 7.33; N, 12.68.

3-Ethoxycarbonyl-5(*S*)-[2′-(6′-methoxypyridyl)]-*N*-methyl-2-piperidones 15 and 16. To a solution of the *N*-methyl compound **14** (200 mg, 0.909 mmol) in dry THF (4.5 mL) in the presence of lithium diisopropylamide [prepared from diisopropylamine (0.64 mL, 4.55 mmol) and *n*-butyllithium (1.58 M hexane solution) (3.00 mL, 4.55 mmol)] was added ethyl chloroformate (0.130 mL, 1.36 mmol) at −78 °C under argon, and the solution was stirred for 1 h at the same temperature. The mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexanes−EtOAc (1:3, v/v) gave an inseparable mixture of the esters **15** and **16** (433 mg, 99%) as a colorless oil: IR (cm^{-1}) 1739, 1650, 1600, 1578, 1468, 1292, 1266, 1186, 1156, and 1032; ^1H NMR δ 1.30 (1.5H, t, J = 7.1 Hz), 1.31 (1.5H, t, J = 7.1 Hz), 2.28−2.60 (2H, m), 3.00 (1.5H, s), 3.03 (1.5H, s), 3.14−3.26 (0.5H, m), 3.40−3.76 (3.5H, m), 3.90 (1.5H, s), 3.92 (1.5H, s), 4.15−4.33 (2H, m), 6.62 (0.5H, d, J = 8.2 Hz), 6.63 (0.5H, d, J = 8.2 Hz), 6.76 (0.5H, d, J = 7.3 Hz), 6.77 (0.5H, d, J = 7.3 Hz), 7.52 (0.5H, dd, J = 7.1 and 8.2 Hz), 7.53 (0.5H, dd, J = 7.3 and 8.2 Hz); ^{13}C NMR δ up 30.3, 30.9, 54.0, 54.4, 61.3, 61.4, 157.5, 157.8, 163.8, 165.7, 170.9, 171.3, down 14.1, 35.0, 35.1, 37.7, 40.6, 47.4, 49.6, 53.2, 53.3, 109.0, 109.3, 114.1, 114.4, 139.1; HRMS *m/z* (EI) calcd.for $C_{15}H_{20}N_2O_4$ (M^+) 292.1423, found 292.1421.

(−)-Jussiaeiine A (*ent*-3) and (3*S*,5*S*)-3-Hydroxymethyl-5-[2′-(6′-methoxypyridyl)]-*N*-methylpiperidine (17). To a stirred suspension of lithium aluminum hydride (494 mg, 13.0 mmol) in THF (7 mL) was added a solution of the esters **15** and **16** (634 mg, 2.17 mmol) in THF (4 mL) at 0 °C, and the resulting mixture was stirred for 12 h at room temperature. A 10% NaOH solution was carefully added to this mixture and the insoluble material was filtered off by filtration through a pad of Celite. The filtrate was concentrated to leave a residue, which was purified by column chromatography on

silica gel with $CHCl_3$−MeOH (50:1) as an eluent to afford jussiaeiine A (*ent*-**3**) (257 mg, 50%) as a colorless oil. $[\alpha]^{27}_D$ −5.2 (*c* 0.5, $CHCl_3$); IR (cm^{-1}) 3360, 1600, 1590, 1578, 1466, 1440, 1416, 1317, 1292, 1270, 1070, 1037, and 1028; ^1H NMR δ 1.25−1.39 (1H, m), 1.66−1.75 (2H, m), 1.97−2.13 (2H, m), 2.35 (3H, s), 2.92−3.09 (3H, m), 3.54 (1H, dd, J = 6.8 and 10.7 Hz), 3.61 (1H, dd, J = 5.6 and 10.7 Hz), 3.91 (3H, s), 6.56 (1H, d, J = 8.2 Hz), 6.73 (1H, d, J = 7.3 Hz), 7.48 (1H, dd, J = 7.3 and 8.2 Hz); ^{13}C NMR δ up 32.6, 58.9, 61.1, 66.0, 160.7, 163.5, down 39.2, 43.7, 46.4, 53.1, 107.8, 114.1, 138.8; HRMS *m/z* (EI) calcd for $C_{13}H_{20}N_2O_2$ (M^+) 236.1525, found 236.1509.

Further elution with the same solvent system afforded trans-alcohol **17** (238 mg, 46%) as a colorless oil. $[\alpha]^{27}_D$ +6.4 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 3370, 1600, 1578, 1466, 1440, 1414, 1275, and 1039; ^1H NMR δ 1.88−2.03 (3H, m), 2.27 (3H, s), 2.32−2.38 (2H, m), 2.89−2.99 (2H, m), 3.35−3.46 (1H, m), 3.85 (1H, dd, J = 1.8 and 10.4 Hz), 3.92 (3H, s), 4.00 (1H, dd, J = 4.4 and 10.4 Hz), 6.56 (1H, d, J = 8.2 Hz), 7.25 (1H, d, J = 7.3 Hz), 7.48 (1H, dd, J = 7.3 and 8.2 Hz); ^{13}C NMR δ up 32.7, 58.8, 60.9, 68.2, 161.0, 163.5, down 34.6, 40.9, 46.5, 53.1, 107.8, 114.4, 138.7; HRMS *m/z* (EI) calcd for $C_{13}H_{20}N_2O_2$ (M^+) 236.1525, found 236.1530.

(−)-Isokuraramine (*ent*-4). A mixture of trans-alcohol **14** (75.0 mg, 0.318 mmol), chlorotrimethylsilane (0.403 mL, 3.18 mmol), sodium iodide (119 mg, 0.795 mmol), and dry acetonitrile (3.2 mL) was heated at reflux for 2 h. After being cooled to room temperature, the mixture was treated with 20% NH_4OH solution and concentrated to leave an aqueous layer. The aqueous layer was extracted with CH_3Cl−MeOH (10:1, v/v). The extract was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to silica gel column chromatography. Elution with $CHCl_3$−MeOH−NH_4OH (6:1:0.1) afforded isokuraramine (***ent*-4**) (70.1 mg, 100%) as an amorphous solid. $[\alpha]^{29}_D$ −93.0 (*c* 2.1, EtOH); IR (cm^{-1}) 3355, 1650, 1550, 1464, 1455, and 1050; ^1H NMR δ 1.50−2.29 (5H, m), 2.30 (3H, s), 2.63 (2H, br s), 3.03 (1H, br s), 3.53 (1H, dd, J = 5.1 and 11.4 Hz), 3.80 (1H, br s), 6.02 (1H, d, J = 6.9 Hz), 6.42 (1H, d, J = 9.2 Hz), 7.37 (1H, dd, J = 6.9 and 9.2 Hz), 12.8 (1H, br s); ^{13}C NMR δ up 32.0, 57.8, 57.9, 63.6, 152.3, 165.0, down 34.8, 35.6, 46.4, 103.7, 116.9, 141.9; HRMS *m/z* (EI) calcd for $C_{12}H_{18}N_2O_2$ (M^+) 222.1368, found 222.1343.

(−)-Kuraramine (*ent*-2). Kuraramine (*ent*-**2**) was obtained from *ent*-**3** (130 mg, 0.551 mmol), chlorotrimethylsilane (0.699 mL, 5.51 mmol), and sodium iodide (206 mg, 1.38 mmol) in acetonitrile (5.5 mL) by the same procedure as for the preparation of isokuraramine to give kuraramine *ent*-**2** (101 mg, 83%) as crystals. $[\alpha]^{28}_D$ −3.6 (*c* 2.1, EtOH); mp 78−80 °C (colorless needles from acetone−hexane); IR (cm^{-1}) 3280, 1651, 1615, 1550, and 1457; ^1H NMR δ 1.20−1.34 (1H, m), 1.8 (1H, br t, J = 11.0 Hz), 1.95−2.09 (3H, m), 2.34 (3H, s), 2.52 (1H, br s), 2.84−2.95 (1H, m), 3.06 (2H, br d, J = 11.0 Hz), 3.51−3.60 (2H, m), 6.07 (1H, br d, J = 6.9 Hz), 6.44 (1H, dd, J = 0.8 and 9.1 Hz), 7.37 (1H, dd, J = 6.9 and 9.1 Hz); ^{13}C NMR δ up 31.6, 58.3, 60.1, 65.2, 150.9, 165.3, down 38.7, 39.7, 46.0, 103.7, 117.6, 141.8; HRMS *m/z* (EI) calcd for $C_{12}H_{18}N_2O_2$ (M^+) 222.1368, found 222.1392.

***N*-Benzyl-5(*S*)-[2′-(6′-methoxypyridyl)]-2-piperidone (18).** To a mixture of the lactam **13** (215 mg, 1.04 mmol) and sodium hydride (60% in oil) (50.1 mg, 1.25 mmol) in dry THF (5 mL) containing hexamethylphosphoric triamide (0.272 mL, 1.57 mmol) was added benzyl bromide (0.186 mL, 1.57 mmol) at 0 °C, and the resulting mixture was stirred for 90 min at room temperature. The mixture was treated with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$−MeOH (25:1, v/v) gave the *N*-benzyl compound **18** (309 mg, 99%) as a colorless oil: $[\alpha]^{26}_D$ +5.6 (*c* 1.0, $CHCl_3$); IR (cm^{-1}) 1643, 1578, 1468, 1289, and 1031; ^1H NMR δ 2.09 (1H, dddd, J = 4.2, 5.0, 10.2, and 19.3 Hz), 2.18 (1H, dddd, J = 6.0, 6.8, 9.9, and 19.3 Hz), 2.56 (1H, ddd, J = 6.8, 10.2, and 17.6 Hz), 2.67 (1H, ddd, J = 4.2, 6.0, and 17.6 Hz), 3.11 (1H, dddd, J = 5.0, 5.1, 9.9, and 10.1 Hz), 3.43 (1H, ddd, J = 1.2, 5.1, and 12.0 Hz), 3.54 (1H, dd, J = 10.1 and 12.0 Hz), 3.85 (3H, s), 4.51 (1H, d, J = 14.6 Hz), 4.79 (1H, d, J = 14.6 Hz), 6.58 (1H, d, J = 8.2 Hz), 6.67 (1H, d, J = 7.3 Hz), 7.72−7.35 (5H, m), 7.46 (1H, dd, J = 7.3 and 8.2 Hz); ^{13}C NMR δ up 26.9, 31.6, 50.3, 51.6, 137.1, 158.5, 163.6, 169.5, down 41.3, 53.1, 108.7, 114.1, 127.3, 128.2, 128.5, 139.0; HRMS *m/z* (EI) calcd for $C_{18}H_{20}N_2O_2$ (M^+) 296.1525, found 296.1526.

***N*-Benzyl-3-ethoxycarbonyl-5(*S*)-[2′-(6′-methoxypyridyl)]-2-piperidone 19 and 20.** Ethoxycarbonylation of **18** (70 mg, 0.237 mmol) was carried out by using the same procedure as for the preparation of the mixture of **15** and **16** and gave an inseparable mixture of **19** and **20** (368 mg, 99%) as a colorless oil: IR (cm^{-1}) 1736, 1648, 1600, 1578, and 1468; ^1H NMR δ 1.33 (3H, t, J = 7.1 Hz), 2.35−2.61 (2H, m), 3.06−3.18 (0.5H, m), 3.34−3.68 (3.5H, m), 3.84 (1.5H, s), 3.87 (1.5H, s), 4.21−4.32 (2H, m), 4.37 (0.5H, d, J = 14.7 Hz), 4.48 (0.5H, d, J = 14.7 Hz), 4.82 (0.5H, d, J = 14.7 Hz), 4.98 (0.5H, d, J = 14.7 Hz), 6.58 (0.5H, d, J = 8.3 Hz), 6.59 (0.5H, d, J = 8.3 Hz), 6.66 (0.5H, d, J = 7.2 Hz), 6.69 (0.5H, d, J = 7.2 Hz), 7.28−7.36 (5H, m), 7.46 (1H, dd, J = 7.2 and 8.3 Hz); ^{13}C NMR δ up 30.2, 30.8, 50.3, 50.5, 51.2, 51.8, 61.3, 61.4, 136.6, 136.7, 157.4, 157.7, 163.6, 163.7, 165.5, 165.7, 170.8, 171.3, down 14.1, 37.8, 40.5, 47.7, 49.7, 53.1, 53.2, 108.9, 109.1, 114.1, 114.4, 127.3, 127.4, 128.0, 128.1, 128.5, 128.6, 138.9, 139.0; HRMS *m/z* (EI) calcd for $C_{21}H_{24}N_2O_4$ (M^+) 368.1736, found 368.1716.

(3*R*,5*S*)-*N*-Benzyl-3-hydroxymethyl-5-[2′-(6′-methoxypyridyl)]piperidine (21) and (3*S*,5*S*)-*N*-Benzyl-3-hydroxymethyl-5-[2′-(6′-methoxypyridyl)]piperidine (22). Reduction of the esters **19** and **20** (50 mg, 0.136 mmol) with lithium aluminum hydride (30.9 mg, 0.815 mmol) was carried out by using the same procedure as for the preparation of *ent*-**3** and **17** and gave the cis-alcohol **21** (20.4 mg, 48%) and trans-alcohol **22** (18.3 mg, 43%), respectively.

21: $[\alpha]^{26}_D$ +22.7 (*c* 0.75, $CHCl_3$); IR (cm^{-1}) 3360, 1599, 1590, 1578, 1466 and 1440, 1412, 1036; ^1H NMR δ 1.26−1.42 (1H, m), 1.57 (1H, br s), 1.72−1.80 (1H, m), 1.95−2.08 (2H, m), 2.12−2.20 (1H, m), 2.92−3.14 (3H, m), 3.48−3.60 (4H, m), 3.90 (3H, m), 6.54 (1H, d, J = 8.1 Hz), 7.70 (1H, d, J = 7.3 Hz), 7.22−7.35 (5H, m), 7.45 (1H, dd, J = 7.3 and 8.1 Hz); ^{13}C NMR δ up 33.2, 56.6, 59.1, 63.3, 66.3, 138.0, 161.0, 163.4, down 39.0, 43.7, 53.1, 107.7, 114.1, 126.9, 128.1, 129.2, 138.7; HRMS *m/z* (EI) calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1838, found 312.1849.

22: $[\alpha]^{27}_D$ +43.7 (*c* 0.5, $CHCl_3$); IR (cm^{-1}) 3360, 1597, 1579, 1466, and 1037; ^1H NMR δ 1.57 (1H, br s), 1.93−2.06 (3H, m), 2.31−2.47 (2H, m), 2.96−3.05 (2H, m), 3.38−3.49 (1H, m), 3.52 (2H, s), 3.85 (1H, dd, J = 1.8 and 10.5 Hz), 3.90 (3H, s), 3.98 (1H, dd, J = 4.0 and 10.5 Hz), 6.54 (1H, d, J = 8.2 Hz), 6.75 (1H, d, J = 7.3 Hz), 7.28−7.35 (5H, m), 7.46 (1H, dd, J = 7.3 and 8.2 Hz); ^{13}C NMR δ up 33.7, 57.1, 58.7, 63.4, 68.9, 137.8, 161.1, 163.4, down 34.5, 41.1, 53.1, 107.7, 114.6, 127.2, 128.3, 128.9, 138.7; HRMS *m/z* (EI) calcd for $C_{19}H_{24}N_2O_2$ (M^+) 312.1838, found 312.1832.

(+)-*N*-Benzylcytisine (23). To a stirred solution of **21** (63.0 mg, 0.202 mmol) in CH_2Cl_2 (3.4 mL) in the presence of triethylamine (56.3 μL, 0.404 mmol) was added methanesulfonyl chloride (23.5 μL, 0.303 mmol) at 0 °C, and the resulting mixture was stirred for 30 min at the same temperature. The mixture was diluted with CH_2Cl_2 and washed with brine. Evaporation of the solvent gave a residue, which was dissolved in toluene (1.6 mL). The solution was heated at reflux for 3 h and concentrated to leave a residue, which was purified by column chromatography on silica gel with $CHCl_3$−MeOH (10:1) as an eluent to afford **23** (50.0 mg, 89%) as colorless crystals. $[\alpha]^{26}_D$ +216 (*c* 0.42, $CHCl_3$); mp 143−145 °C (colorless prisms from CH_2Cl_2−hexane); IR (cm^{-1}) 1654, 1570, 1546, and 1138; ^1H NMR δ 1.76−1.84 (1H, m), 1.88−1.96 (1H, m), 2.29−2.47 (3H, m), 2.81−2.98 (3H, m), 3.38 (1H, d, J = 13.7 Hz), 3.47 (1H, d, J = 13.7 Hz), 3.89 (1H, dd, J = 6.6 and 15.3 Hz), 4.11 (1H, d, J = 15.3 Hz), 5.91 (1H, dd, J = 1.5 and 6.9 Hz), 6.50 (1H, dd, J = 1.5 and 9.1 Hz), 6.97−7.01 (2H, m), 7.16−7.31

(4H, m); ^{13}C NMR δ up 25.9, 50.0, 59.9, 60.0, 62.0, 138.0, 151.4, 163.6, down 28.1, 35.5, 104.6, 116.5, 126.9, 128.1, 138.5; HRMS *m/z* (EI) calcd for $C_{18}H_{20}N_2O$ (M^+) 280.1576, found 280.1549.

(+)-Cytisine (*ent*-1). To a stirred solution of *N*-benzylcytisine (**23**) (20.0 mg, 7.14×10^{-2} mmol) in MeOH (1.8 mL) were added ammonium formate (90.1 mg, 1.43 mmol) and 20% $Pd(OH)_2$ on carbon (10.0 mg). The mixture was heated at reflux under an atmospheric pressure of hydrogen for 1 h and then cooled to room temperature. After filtration of the insoluble material, the filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel with $CHCl_3$−MeOH−NH_4OH (7:1:0.1, v/v) as an eluent to afford *ent*-**1** (11 mg, 81%) as colorless crystals. $[\alpha]_D^{29}$ +113.5 (*c* 0.3, EtOH); mp 152−153 °C (colorless prisms from acetone); IR (cm^{-1}) 3420, 1645, 1545 and 1156; ^{1}H NMR δ 1.53 (1H, br s), 1.95−1.97 (2H, m), 2.32 (1H, br s), 2.82−2.90 (1H, m), 2.97−3.13 (4H, m), 3.90 (1H, dd, J = 6.6 and 15.8 Hz), 4.13 (1H, d, J = 15.8 Hz), 6.00 (1H, dd, J = 1.0 and 6.9 Hz), 6.46 (1H, dd, J = 1.0 and 9.1 Hz), 7.30 (1H, dd, J = 6.9 and 9.1 Hz); ^{13}C NMR δ up 26.3, 49.7, 53.0, 53.9, 151.0, 163.6, down 27.7, 35.6, 104.9, 116.7, 138.7; HRMS *m/z* (EI) calcd for $C_{11}H_{14}N_2O$ (M^+) 190.1106, found 190.1085.

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Supporting Information Available: Experimental procedures and product characterization for new compounds and selected ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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