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ENANTIOSELECTIVE SYNTHESSES OF *ENT*-SEDRIDINE AND (+)-CONIINE VIA PROLINE-CATALYZED MANNICH REACTION

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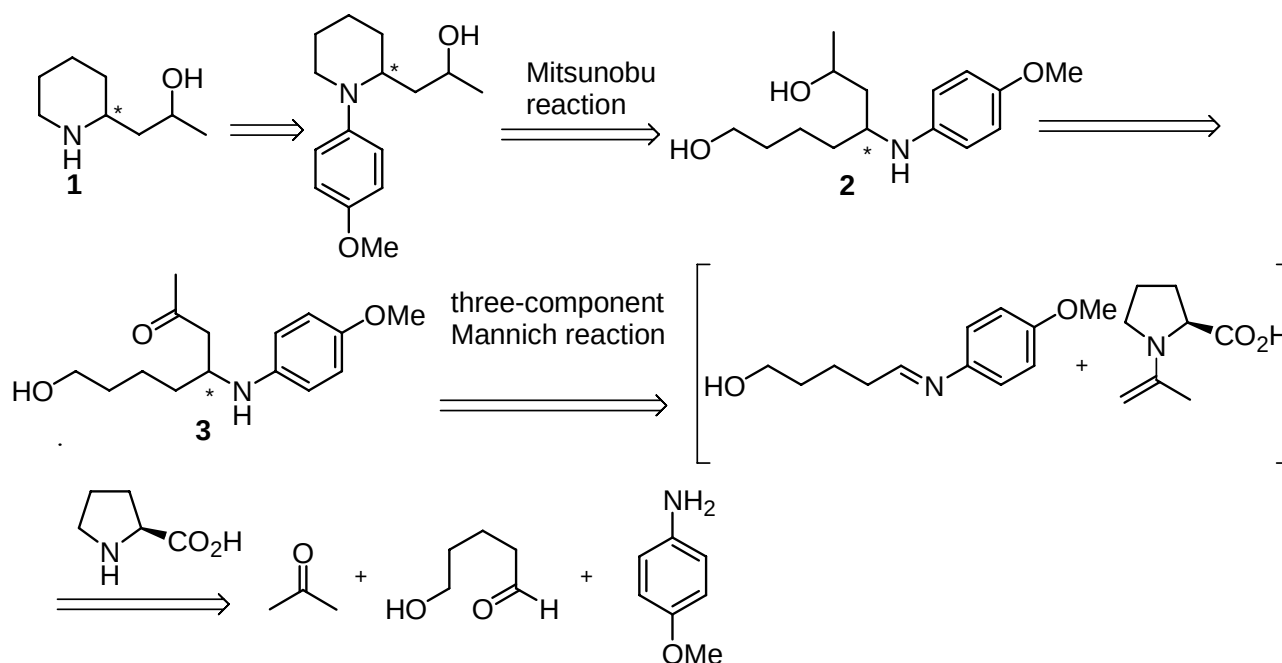
Abstract – Proline-catalyzed three component Mannich reaction using 5-hydroxypentanal as a substrate was achieved in high enantioselectivity to construct a chiral center at C-2 position of 2-substituted piperidine alkaloids. The method was applied to the total syntheses of *ent*-sedridine and (+)-coniine.

INTRODUCTION

2-Substituted piperidine alkaloids exist widely in nature and often show potent bioactivities.¹ The amount of these alkaloids in biological systems, however, is minute in most cases. Therefore, it is important to develop a general synthetic method of these alkaloids, and many approaches have been developed.² In the course of our study for the synthesis of indole alkaloids, we have found that proline-catalyzed Mannich reaction is effective for the construction of a chiral center at C-1-position of 3,4-dihydro- β -carboline.³ With these results in hand, we next applied the method to the synthesis of 2-substituted piperidine alkaloids. Although List *et al.* have reported that proline-catalyzed three-component Mannich reaction using aromatic aldehyde afforded β -aminoketones in a highly enantioselective manner,⁴ the application to aliphatic aldehydes was seldom examined and enantioselectivities of a few examples were only modest.^{4, 5} We have reinvestigated the three component Mannich reaction using aliphatic aldehyde to construct a chiral center at 2-position of 2-substituted piperidine alkaloids, and completed the syntheses of *ent*-sedridine and (+)-coniine using the method as a key step. In this paper we describe these results.⁶

RESULTS AND DISCUSSION

The synthetic strategy of sedridine (**1**) is shown in Scheme 1. Compound (**1**) was thought to be obtained from **2** by the Mitsunobu reaction. Compound (**3**), a precursor of **2**, could be synthesized by the three-component Mannich reaction catalyzed by proline.



Scheme 1

Thus, we first investigated proline-catalyzed Mannich reaction using 5-hydroxypentanal, *p*-anisidine, and acetone. Table 1 shows the solvent effects on the reaction yield and selectivity. When the reaction was carried out in the presence of 3 mol% (*S*)-proline in standard solvents used for the previously reported proline-catalyzed reaction (DMSO or DMF), the reaction yields were low accompanied by moderate to high enantioselectivity (Entries 1 and 2).

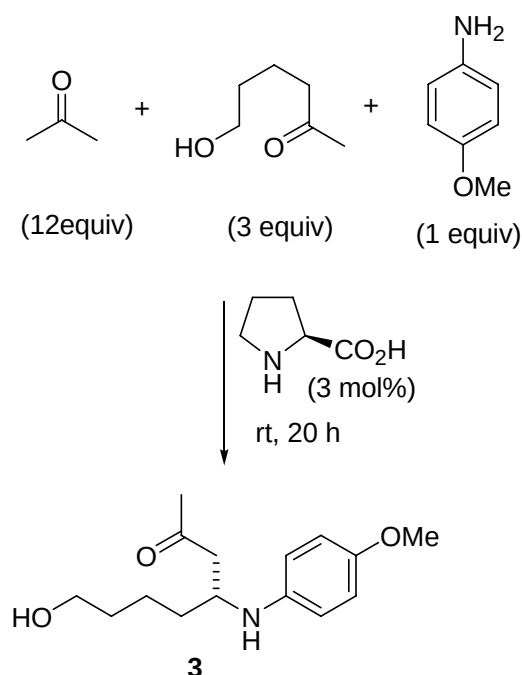


Table 1 Solvent effects on the reaction yield and selectivity

Entry	Solvent	Yield of 3 (%)	Ee of 3 (%)
1	DMSO	8	81
2	DMF	11	50
3	CH ₂ Cl ₂	3	7
4	THF	3	7
5	CH ₃ CN	<1	71
6	Toluene	<1	15
7	CHCl ₃	1	22
8	MeOH	7	23
9	EtOH	28	50
10	1-PrOH	62	63
11	2-PrOH	22	61
12	<i>i</i> -BuOH	40	76
13	1-BuOH	55	70

While aprotic solvents gave low yields (Entries 1-7), protic solvents were found to give better yields with moderate selectivity. Thus, we further examined the effect of the amount of the catalyst and the reaction temperature (Table 2). When 9 mol% of proline was used, the yield increased without dominant improvement of the stereoselectivity (Entries 1, 3, 5, 8, 10). In DMSO solvent, the sufficient result was not obtained even with a higher catalyst dose at possible lowest temperature. In alcoholic solvents, however, the ee was improved at lower temperature. The use of 2-propanol gave the best ee with an acceptable yield when the reaction was carried out with 30 mol% of catalyst at -10 °C (Entry 7), and this condition was used for the following total syntheses.

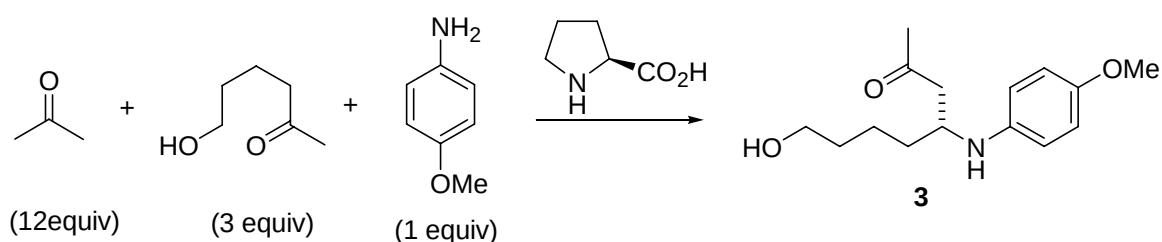
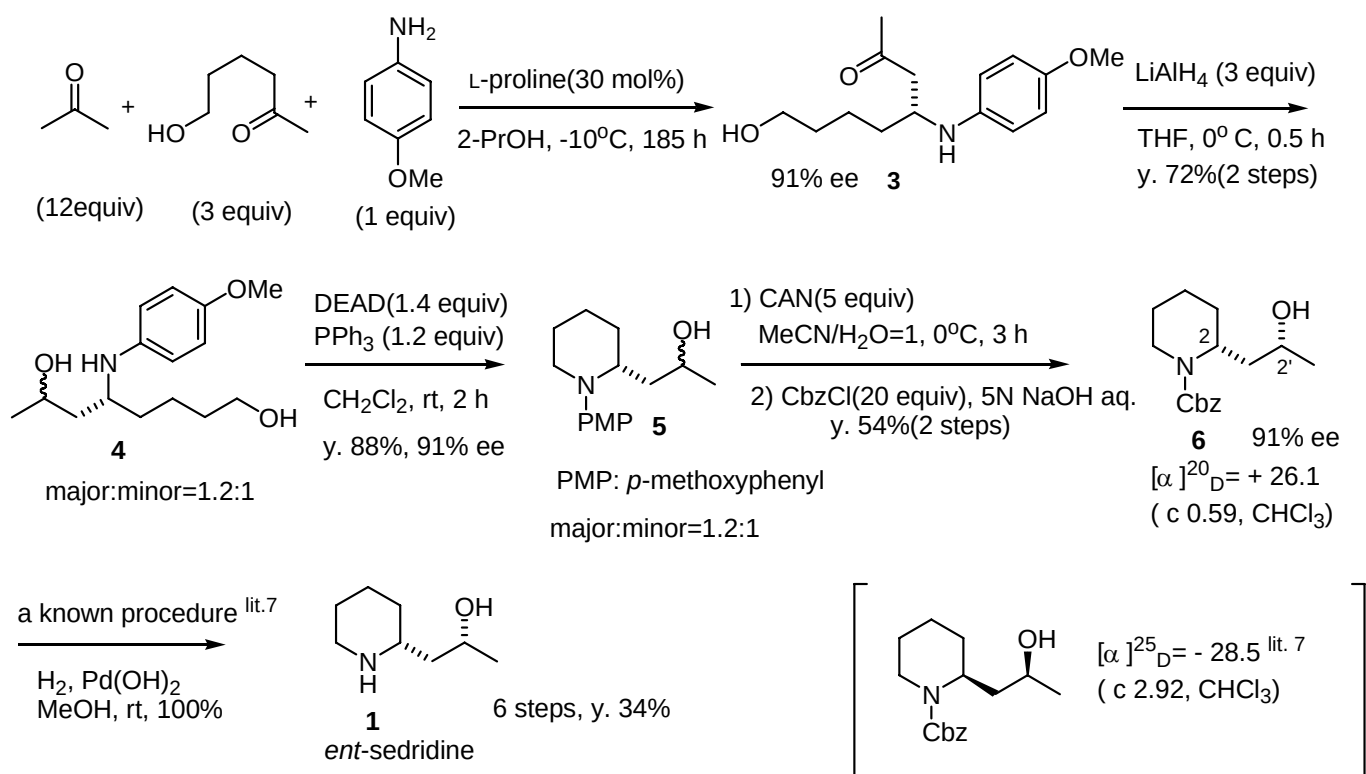


Table 2 Optimization of the reaction conditions

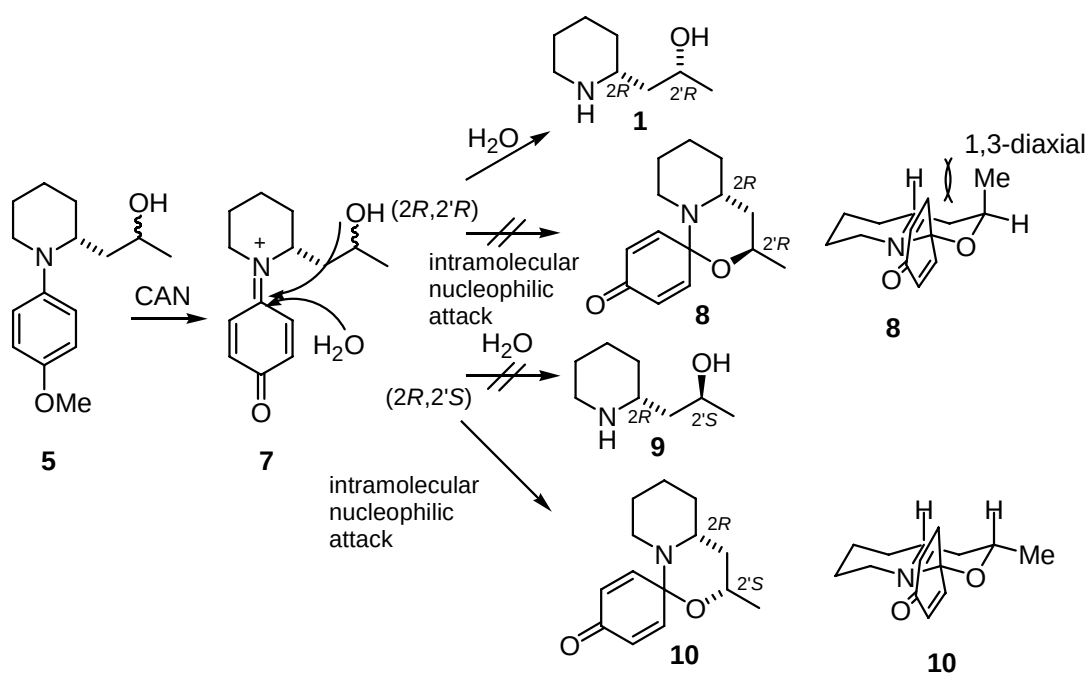
Entry	Catalyst (mol%)	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ee (%)
1	9	DMSO	rt	20	52	79
2	30	DMSO	5	132	31	83
3	9	1-PrOH	rt	20	86	66
4	30	1-PrOH	0	66	74	78
5	9	2-PrOH	rt	20	62	67
6	30	2-PrOH	0	87	80	86
7	30	2-PrOH	-10	185	76	91
8	9	<i>i</i> -BuOH	rt	20	70	75
9	30	<i>i</i> -BuOH	0	106	55	84
10	9	1-BuOH	rt	20	63	73
11	30	1-BuOH	0	107	55	83

With enantiomerically enriched compound (**3**) in hand, the asymmetric synthesis of sedridine was carried out (Scheme 2). Compound (**3**) was reduced with LiAlH_4 to give diol (**4**) as a mixture of epimers (major:minor = 1.2:1). Although the other reductants such as NaBH_4 , Red-Al, or $\text{LiAl}(\text{OtBu})_3\text{H}$ were tried, almost 1:1 mixtures of the epimers were obtained. When the reaction was performed using L-selectride, K-selectride, or LiEt_3BH , the opposite stereoselectivity was observed. Compound (**4**) was subjected to the Mitsunobu reaction to give cyclized compound (**5**) in 88% yield as a 1.2:1 mixture of epimers. Oxidative removal of *p*-methoxyphenyl group of **5**, which was a mixture of epimers, with CAN followed by the protection with a Cbz group afforded **6** as a single diastereomer. The stereochemi-



Scheme 2

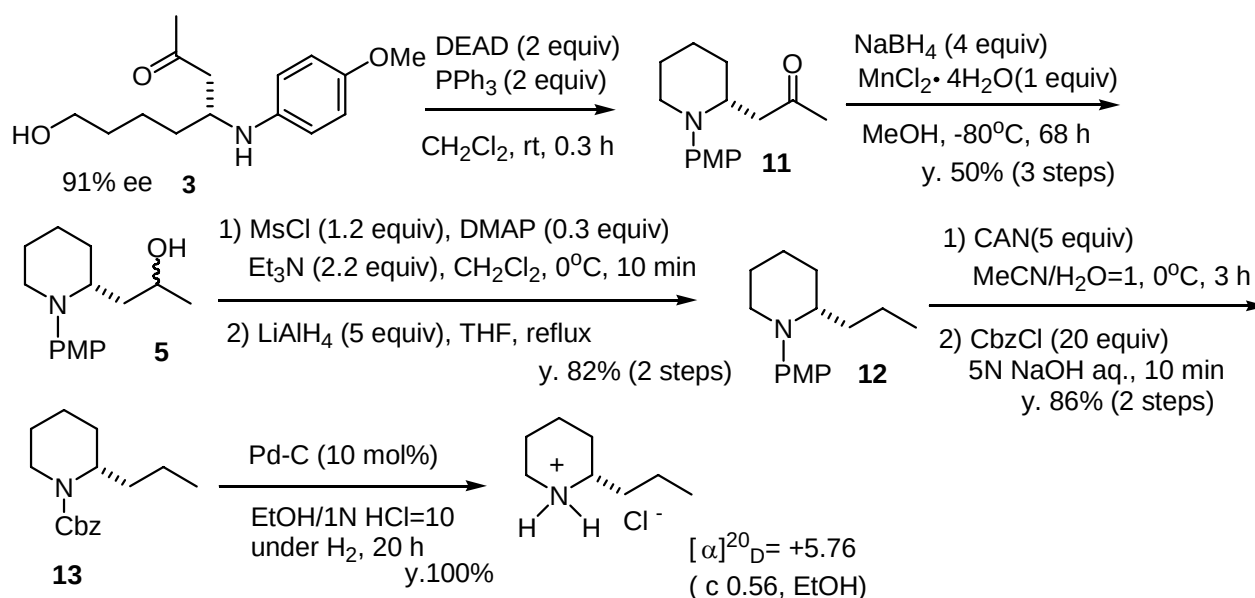
stry of **6** was determined to be (2*R*,2'*R*) by comparison of the $[\alpha]_{\text{D}}$ and NMR spectra with reported ones.⁷ Reductive cleavage of Cbz group of compound (**6**) using a reported method⁷ gave *ent*-sedridine in quantitative yield. The reason for the selective formation of (2*R*,2'*R*)-isomer (**6**) in the oxidation of diastereomeric mixture (**5**) was considered as follows (Scheme 3).



Scheme 3

In the process of CAN oxidation, a quinonoid (**7**) is a plausible intermediate, and the hydrolysis of **7** is supposed to give compounds (**1** and **9**). In the present case, however, an intramolecular attack of hydroxyl group would give alternative compounds (**8** and **10**). The formation of compound (**8**) might be more hindered than that of compound (**10**) due to an axial methyl substituent. Thus it was supposed that (2*R*,2'*R*)-epimer (**5**) was transformed to **1** without formation of sterically demanding **8**, whereas (2*R*,2'*S*)-epimer might be transformed to **10** without formation of the hydrolysis product (**9**). Unfortunately, supposed intermediate (**10**) was not isolated, but the participation of free hydroxyl group in the separation mechanism was suggested by the fact that both epimers of *O*-benzoate derivatives of **6** were obtained when benzoates of both epimers of **5** were oxidized with CAN and then protected with Cbz group.

Next, our reaction system was applied to the synthesis of coniine. The reaction was commenced with the same Mannich product (**3**), which was cyclized to **11** by the Mitsunobu reaction and then immediately reduced⁸ with NaBH₄ in the presence of MnCl₂·4H₂O⁹ to give **5** as a mixture of diastereomer (2*R*,2'*S*-isomer:2*R*,2'*R*-isomer=3.9:1) in 50% overall yield based on *p*-anisidine. In this case, the major compound was an epimer of the one obtained via LiAlH₄ reduction of **3**. Without separating the epimers, hydroxyl group of **5** was converted to mesylate and then reduced with LiAlH₄ to give **12** in 82% yield. When compound **5** was synthesized via LiAlH₄ reduction of **3** as shown in Scheme 2, the yield of **12** was 51%. The mesylate obtained from 2*R*,2'*R*-isomer of **5** was considered to be less reactive in the reaction with LiAlH₄ than that obtained from 2*R*,2'*S*-isomer of **5**. CAN oxidation of **12** followed by protection with Cbz-chloride gave compound (**13**). Finally, catalytic hydrogenation of **13** in the solvent of EtOH/1*N* HCl aq. =10 afforded (+)-coniine hydrochloride in quantitative yield ($[\alpha]_D^{20} = +5.76$ (c 0.56, EtOH), lit.,¹⁰ $[\alpha]_D^{20} = +5.2$ (c 1.0, EtOH)). The overall yield from *p*-anisidine is 35%.



In conclusion, we have accomplished the proline-catalyzed Mannich reaction using an aliphatic aldehyde in high enantioselectivity. In the reaction, alcoholic solvents were found to give better results than DMSO and DMF, which are standard solvents for proline-catalyzed reaction. Further, total syntheses of *ent*-sedridine and (+)-coniine were demonstrated with high enantiomeric purities using the present method in a key step. The application of the present reaction system to the synthesis of other piperidine alkaloids is now in progress.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz respectively, using tetramethylsilane as an internal standard. Melting points were measured on a Büchi 535 micro melting point apparatus and are uncorrected.

Proline-catalyzed Mannich reaction using 5-hydroxypentanal, *p*-anisidine, and acetone: the typical procedure; L-Proline (80 mg, 30 mol%) was added to a solution of 5-hydroxypentanal (750 μL , 6.95 mmol) and *p*-anisidine (286 mg, 2.32 mmol) in 2-propanol (10 mL) at $-10\text{ }^\circ\text{C}$ under an Ar atmosphere. After acetone (2.5 mL) was added, the reaction mixture was stirred at $-10\text{ }^\circ\text{C}$ for 185 h. Then AcOEt was added and the mixture was extracted with 1N HCl aqueous solution. The combined aqueous layer was neutralized with NaHCO_3 and extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and evaporated off to give crude **3**. Since compound (**3**) was unstable, it was used without further purification. The yield was determined by ^1H NMR using mesitylene as an internal standard. The enantiomeric excess was determined by the HPLC analysis using a chiral column (DAICEL Chiralcel OD, hexane/*i*-PrOH=3, 0.5 mL/min).

8-Hydroxy-4-(4-methoxyphenylamino)octan-2-one (**3**)

^1H NMR (CDCl_3) δ =1.39-1.63 (6H, m), 2.13 (3H, s), 2.60 (1H, dd, J =16.6, 6.4 Hz), 2.71 (1H, dd, J =16.6, 5.2 Hz), 2.85 (1H, br), 3.62 (2H, t, J =6.1 Hz), 3.74 (3H, s), 6.65 (2H, d, J =8.8 Hz), 6.77 (2H, d, J =8.8 Hz); ^{13}C NMR (CDCl_3) δ =22.4, 30.8, 32.4, 34.4, 47.4, 51.7, 55.7, 62.5, 115.0, 116.0, 139.9, 153.0, 208.1. HRMS (FAB^+) m/z Calcd for $\text{C}_{15}\text{H}_{24}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 266.1777, Found: 266.1749.

5-(4-Methoxyphenylamino)octane-1,7-diol (**4**)

Compound (**3**) obtained from the above reaction was dissolved in THF (25 mL), and LiAlH_4 (264 mg, 6.96 mmol) was added at $0\text{ }^\circ\text{C}$. The reaction mixture was stirred for 3.5 h under Ar atmosphere and quenched with H_2O . The resulting mixture was extracted with CH_2Cl_2 and the organic layer was dried over MgSO_4 and evaporated off. The residue was purified by silica gel column chromatography (AcOEt/hexane=7/3) to give the compound (**4**) (445 mg, 72% from *p*-anisidine) as a mixture of diastereomers (major: minor=1.2:1). The ^1H and ^{13}C NMR spectra of minor one are shown in

parentheses; ^1H NMR(CDCl_3) δ =1.19 (3H, d, J =6.1 Hz) (1.21 (3H, d, J =6.6 Hz)), 1.29-1.76 (8H, m), 2.85 (3H, br), 3.44 (1H, m), 3.55-3.61 (2H, m), 3.75 (3H, s) (3.74 (3H, s)), 4.06 (1H, m), 6.77 (2H, d, J =4.9 Hz) (6.64 (2H, d, J =9.0 Hz)), 6.79 (2H, d, J =5.1 Hz) (6.69 (2H, d, J =8.8 Hz)); ^{13}C NMR (CDCl_3) δ =21.9(22.2), 23.9(24.0), 32.58(32.61), 35.1(34.9), 42.7, 55.7(55.8), 56.6(52.3), 62.5(62.6), 68.6(65.3), 114.9(115.0), 117.4, 140.4(141.5), 153.4(152.6). HRMS (FAB^+) m/z Calcd for $\text{C}_{15}\text{H}_{26}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 268.1969, Found 268.1892.

1-[1-(4-Methoxyphenyl)piperidin-2-yl]propan-2-ol (5).

To a solution of compound (4) (400 mg, 1.50 mmol) in CH_2Cl_2 (25 mL) were added PPh_3 (472 mg, 1.80 mmol) and DEAD (950 μL , 2.10 mmol). The mixture was stirred for 2 h at rt under Ar atmosphere. Then AcOEt was added and extracted with 1N HCl aqueous solution. The combined aqueous layer was neutralized with NaHCO_3 and extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and evaporated off. The residue thus obtained was purified by silica gel column chromatography (AcOEt/hexane=1/4) to give the compound (5) (328 mg, 88%) as a mixture of epimers (major: minor=1.2:1): The ^1H and ^{13}C NMR spectra of minor one are shown in parentheses; ^1H NMR(CDCl_3) δ =1.17 (3H, d, J =6.1 Hz) (1.04 (3H, d, J =6.1 Hz)), 1.45-1.90 (8H, m), 3.07 (1H, m) (2.85 (1H, m)), 3.23 (1H, br s), 3.52 (1H, m), 3.77 (3H, s) (3.78 (3H, s)), 3.95 (1H, m), 6.82-6.85 (4H, m) (6.98-7.06 (4H, m)); ^{13}C NMR (CDCl_3) δ =20.3(22.1), 24.0(23.7), 24.1(25.8), 28.1(29.5), 37.6(38.2), 51.9(46.0), 55.53(55.46), 57.2(56.4), 67.6(65.6), 114.4, 122.4(120.2), 145.3(144.9), 154.8(153.7). HRMS (FAB^+) m/z Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{N}$ ($\text{M}+\text{H}$) $^+$: 250.1852, Found: 250.1792. The enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL Chiralcel AD-H, hexane/*i*-PrOH=30, 0.5 mL/min).

(2R, 2'R)-Benzyl 2-(2-hydroxypropyl)piperidine-1-carboxylate (6).

To a cold solution (0 $^\circ\text{C}$) of compound (5) (60 mg, 0.24 mmol) in MeCN (8.4 mL), CAN 658 mg (1.2 mmol) in H_2O (8.4 mL) was added dropwise and the mixture was stirred for 5 h. After the solution was made basic with 5N NaOH aqueous solution, Cbz-Cl (690 μL , 4.80 mmol) was added. The reaction mixture was stirred for 10 min and neutralized with 1N HCl aqueous solution. The mixture was filtered through a celite pad and the filtrate was extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and evaporated off. The residue thus obtained was purified by silica gel column chromatography (AcOEt/hexane=1/9) to give the compound (6) (36 mg, 54%): ^1H NMR (CDCl_3) δ =1.18 (3H, d, J =6.1 Hz), 1.20-1.76 (7H, m), 1.99 (1H, td, J =13.2, 2.2 Hz), 2.76 (1H, td, J =12.9, 2.4 Hz), 3.26 (1H, br s), 3.53 (1H, br s), 4.05 (1H, br d, J =12.2 Hz), 4.50 (1H, br s), 5.13 (1H, d, J =13.4 Hz), 5.15 (1H, 12.4 Hz), 7.29-7.39 (5H, m); ^{13}C NMR (CDCl_3) δ =19.1, 22.5, 25.5, 29.3, 39.3, 39.4, 47.5, 63.3, 67.5, 127.9, 128.1, 128.4, 136.5, 157.0. HRMS (FAB^+) m/z Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$: 278.1703, Found: 278.1777. $[\alpha]_{\text{D}}^{20}$ =+26.1 (c 0.59, CHCl_3).

1-[1-(4-Methoxyphenyl)piperidin-2-yl]propan-2-one (11)

To the CH₂Cl₂ (25 mL) solution of compound (**3**), which was obtained by the procedure described above, was added PPh₃ (1.2 g, 4.64 mmol) and DEAD (2.1 mL, 4.64 mmol). The mixture was stirred for 20 min at rt under Ar atmosphere. Then AcOEt was added and extracted with 1N HCl aqueous solution. The combined aqueous layer was neutralized with NaHCO₃ and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and evaporated off to give crude **11**. Since compound (**11**) was racemized during the process of column chromatography, the mixture was used for the next reaction without further purification. To a solution of **11** in MeOH (25 ml) was added MnCl₂·4H₂O (460 mg, 2.32 mmol). After the solution was cooled to -80 °C, NaBH₄ (176 mg, 4.64 mmol) was added. The reaction mixture was stirred for 68 h under an Ar atmosphere. Then AcOEt was added and the mixture was extracted with 1N HCl aqueous solution. The combined aqueous layer was neutralized with NaHCO₃ and extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and evaporated off. The residue thus obtained was purified by silica gel column chromatography (AcOEt/hexane=1/4) to give the compound (**5**) (290 mg, 50% from *p*-anisidine) as a mixture of epimers (major: minor=3.9:1).

Compound 11: ¹H NMR(CDCl₃) δ=1.54-1.73 (6H, m), 1.99 (3H, s), 2.44 (1H, dd, *J*=3.44, 16.3 Hz), 2.57 (1H, dd, *J*=9.04, 16.1 Hz), 2.91 (1H, br s), 3.02 (1H, m), 3.76 (3H, s), 3.89 (1H, m), 6.82 (2H, d, *J*=9.24 Hz), 6.94 (2H, br s); ¹³C NMR(CDCl₃) δ= 20.6, 25.9, 30.1, 30.7, 43.0, 48.6, 54.4, 55.7, 114.5, 121.1, 144.8, 154.4, 208.1. HRMS (FAB⁺) *m/z* Calcd for C₁₅H₂₂NO₂ (M+H)⁺: 248.1697, Found :248.1635.

1-(4-Methoxyphenyl)-2-propylpiperidine (12)

To a solution of **5** (77 mg, 0.309 mmol) in CH₂Cl₂ (4 mL) were added Et₃N (95 μL, 0.68 mmol) and DMAP (11.4 mg, 0.093 mmol), then MsCl (29 μL, 0.37 mmol) was added slowly at 0 °C. The reaction mixture was stirred for 30 min under an Ar atmosphere. After CH₂Cl₂ was evaporated off, THF (8 mL) was added. The solution was cooled to 0 °C and LiAlH₄ (59 mg, 1.55 mmol) was added. Then the reaction mixture was refluxed for 1h. After water was added, the mixture was filtered through a celite pad and the filtrate was extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and evaporated off. The residue thus obtained was purified by silica gel column chromatography (AcOEt/hexane=1/49) to give the compound (**12**) (59 mg, 82%): ¹H NMR(CDCl₃) δ=0.81 (3H, t, *J*=6.84 Hz), 1.10-1.82 (10H, m), 2.99-3.03 (2H, m), 3.36-3.39 (1H, m), 3.76 (3H, s), 6.81 (2H, d, *J*=9.28 Hz), 6.9 (2H, d, *J*=8.8 Hz); ¹³C NMR(CDCl₃) δ=14.2, 19.8, 20.7, 26.0, 28.9, 30.7, 48.1, 55.5, 57.9, 114.2, 120.5, 145.8, 153.7. HRMS (FAB⁺) *m/z* Calcd for C₁₅H₂₄NO (M+H)⁺: 234.1895, Found: 234.1847.

Benzyl 2-propylpiperidine-1-carboxylate (13)

To a cold solution (0 °C) of compound (**12**) (61 mg, 0.26 mmol) in MeCN (9.2 mL), CAN (718 mg, 1.2 mmol) in H₂O (9.2 mL) was added dropwise and the mixture was stirred for 5 h. After the solution was

made basic with 5N NaOH aqueous solution, Cbz-Cl (750 μ L, 5.24 mmol) was added. The reaction mixture was stirred for 10 min and neutralized with 1N HCl aqueous solution. The mixture was filtered through a celite pad and the filtrate was extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and evaporated off. The residue thus obtained was purified by silica gel column chromatography (AcOEt/hexane=1/19) to give the compound (**13**)(59 mg, 86%): ^1H NMR(CDCl_3) δ =0.90 (3H, t, J =7.08 Hz), 1.26-1.72 (10H, m), 2.83 (1H, t, J =13.6 Hz), 4.04 (1H, d, J =11.6 Hz), 4.30 (1H, s), 5.10 (1H, d, J =12.7 Hz), 5.13 (1H, d, J =12.5 Hz), 7.27-7.37 (5H, m); ^{13}C -NMR(CDCl_3) δ =14.0, 19.0, 19.5, 25.7, 28.4, 31.9, 39.1, 50.6, 66.8, 127.76, 127.80, 128.4, 137.2, 155.6. HRMS (FAB $^+$) m/z Calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_2$ (M+H) $^+$: 262.1820, Found: 262.1803.

(+)-Coniine hydrochloride

To a solution of the compound **13** (59 mg, 0.23 mmol) in EtOH (2 mL) was added 1N aq. HCl (0.2 mL) and 10% Pd-C (24 mg, 0.23 mmol). The mixture was stirred for 18 h under H_2 atmosphere and filtered through a celite pad. The filtrate was evaporated to dryness to give (+)-coniine hydrochloride (37 mg, 100%); mp 215-217 $^\circ\text{C}$ (lit., 11 mp 218-221 $^\circ\text{C}$); ^1H NMR(CDCl_3) δ = 0.965 (3H, br s), 1.48-1.94 (10H, m), 2.88 (1H, br s), 3.00 (1H, br s), 3.47(1H, br s), 9.08 (1H, br s), 9.30 (1H, br s); ^{13}C -NMR(CDCl_3) δ =13.8, 18.7, 22.3, 22.4, 28.2, 35.5, 45.3, 57.2. HRMS (FAB $^+$) m/z Calcd for $\text{C}_8\text{H}_{19}\text{NCl}$ (M+H) $^+$:164.1215, Found: 164.1230. $[\alpha]^{20}_{\text{D}} = +5.76$ (c 0.56, EtOH)(lit., 10 $[\alpha]^{20}_{\text{D}} = +5.2$ (c 1.0, EtOH)).

CAN oxidation of 1-[1-(4-methoxyphenyl)piperidin-2-yl]propan-2-yl benzoate and protection with Cbz-Cl

To a cold solution (0 $^\circ\text{C}$) of 1-[1-(4-methoxyphenyl)piperidin-2-yl]propan-2-yl benzoate ((2*R*, 2'*S*)-isomer: (2*R*, 2'*R*)-isomer=3.1:1) (69 mg, 0.20 mmol) in MeCN (6.8 mL), CAN (535 mg, 0.98 mmol) in H_2O (6.8 mL) was added dropwise and the mixture was stirred for 3 h. After the solution was made basic with 5N NaOH aqueous solution, Cbz-Cl (560 μ L, 3.90 mmol) was added. The reaction mixture was stirred for 10 min and neutralized with 1N HCl aqueous solution. The mixture was filtered through a celite pad and the filtrate was extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 and evaporated off. The residue thus obtained was purified by silica gel column chromatography (AcOEt/hexane=1/19) to give Benzyl 2-(2-benzoyloxypropyl)piperidine-1-carboxylate (59 mg, 79%) as a mixture of epimers ((2*R*, 2'*S*)-isomer: (2*R*, 2'*R*)-isomer=2.2:1).

Benzyl 2-(2-benzoyloxypropyl)piperidine-1-carboxylate

The ^1H and ^{13}C NMR spectra of minor one are shown in parentheses. ^1H NMR (CDCl_3) δ =1.22-1.70 (10H, m), 2.27 (1H, br s) (2.00-2.10(1H, m)), 3.00 (1H, t, J =11.5 Hz) (2.84 (1H, t, J =12.3 Hz)), 4.09 (1H, br s), 4.52 (1H, br s), 5.06 (1H, br s), 5.10-5.12 (2H, m), 7.25-7.55 (8H, m), 8.01 (2H, br s);

^{13}C -NMR(CDCl_3) δ =18.9, 19.0, 20.1, 25.5, 28.5, 39.3(35.7), 48.0(53.4), 66.9(69.3), 67.0(69.7), 127.8, 127.9, 128.31(128.26), 128.42, 129.53(129.48), 130.6(130.8), 132.8(132.7), 136.9, 155.3, 166.1. HRMS (FAB^+) m/z Calcd for $\text{C}_{23}\text{H}_{28}\text{NO}_4(\text{M}+\text{H})^+$:382.2038, Found: 382.2006.

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