Total Synthesis of *ent*-Sedridine Using Proline-Catalyzed Asymmetric Addition as a Key Step

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Abstract: A total synthesis of *ent*-sedridine is described. The development of a new method for the construction of the C-2 chiral center of the piperidine ring was achieved using a proline-catalyzed Mannich reaction. Reaction of 4-hydroxybutanal and *p*-anisidine to form an imine and subsequent addition of acetone gave the key chiral aliphatic precursor with high enantioselectivity.

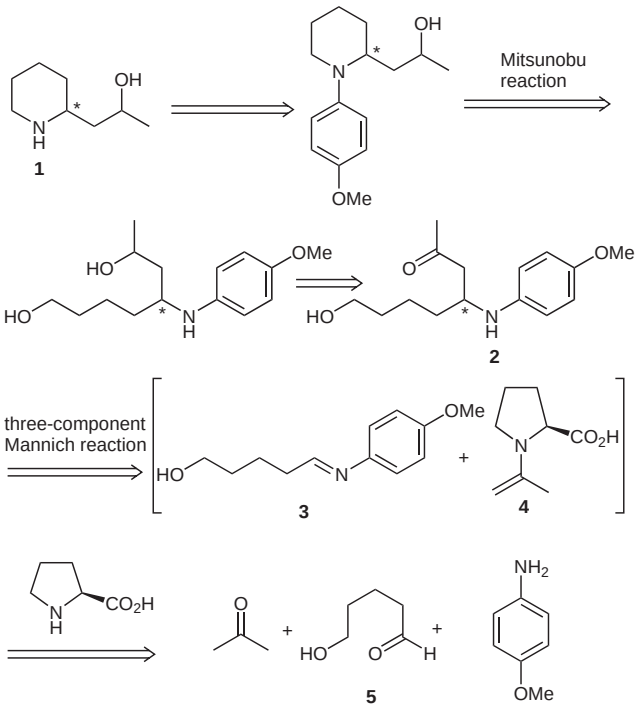
Key words: asymmetric catalysis, nucleophilic additions, total synthesis, alkaloids, piperidine

Piperidine alkaloids exist widely in nature and many of them have a chiral center at their C-2 position.[1] However, in most cases, the amount of these alkaloids in biological systems is minute and it is therefore important to develop general methods to obtain these compounds, which have possible bioactivity.[2]

In the course of our study into the synthesis of indole alkaloids,[3] we have found that a proline-catalyzed asymmetric Mannich reaction[4] serves as a highly effective tool for the construction of a chiral center which is crucial for asymmetric synthesis.[5] Based on previous work, we have tried to apply this catalytic system to the synthesis of piperidine alkaloids and have found that a total synthesis of *ent*-sedridine could be achieved using the proline-catalyzed Mannich reaction as a key step. This paper describes these results.

The piperidine alkaloid sedridine was isolated from *Sedum acre* in 1955,[6] several total syntheses were reported including those by Davis,[7] Murahashi,[8] Hootele,[9] Takahata,[10] and Litter.[11] The first four syntheses use chiral auxiliaries to obtain the chiral product. Litter and co-workers used the only synthesis involving a catalytic asymmetric transformation. In this paper, catalytic hydrogenation of a ketone was adopted as the asymmetric process, the ketoester intermediate was then reduced to the corresponding hydroxyester using Ru-BINAP as the catalyst under H_2 (200 psi). We thought that there were still drawbacks in the previous syntheses, namely the need for equimolar amounts of chiral sources or harsh reaction conditions.

We investigated a new method for the construction of the C-2 chiral center of the piperidine ring, using a proline-catalyzed Mannich reaction. List and co-workers reported



Scheme 1

a catalytic asymmetric Mannich reaction using imines, which were formed in situ by the reaction of an aromatic aldehyde and an amine, and enamines derived from (*S*)-proline and methyl ketones to give β-aminoketones in a highly enantioselective manner.[4] The application of the reaction to aldehydes was, however, seldom reported.[12]

Retrosynthesis for *ent*-sedridine is shown in Scheme 1. Sedridine (**1**) was to be obtained from an aliphatic precursor **2** by the Mitsunobu reaction. Compound **2** could be synthesized from the reaction of an imine **3** (formed by the reaction of 4-hydroxybutanal and *p*-anisidine) with an enamine **4** derived from (*S*)-proline and acetone.

Thus, we began our research by studying the optimization of the Mannich reaction conditions, the results are summarized in Table 1.

We first investigated the proline-catalyzed reactions using standard solvents, including DMSO, THF, and DMF (entries 1–3). In the presence of 3 mol% proline, the reaction gave low yields, but a high ee was obtained in the DMSO reaction (entry 3). Using DMSO as the solvent, we then studied increasing amounts of catalyst (entries 4 and 5).

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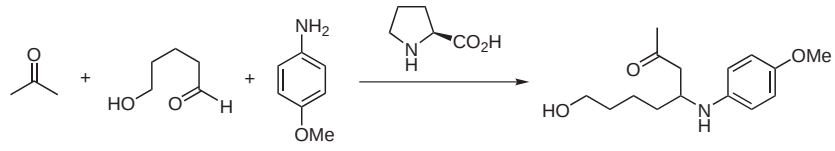
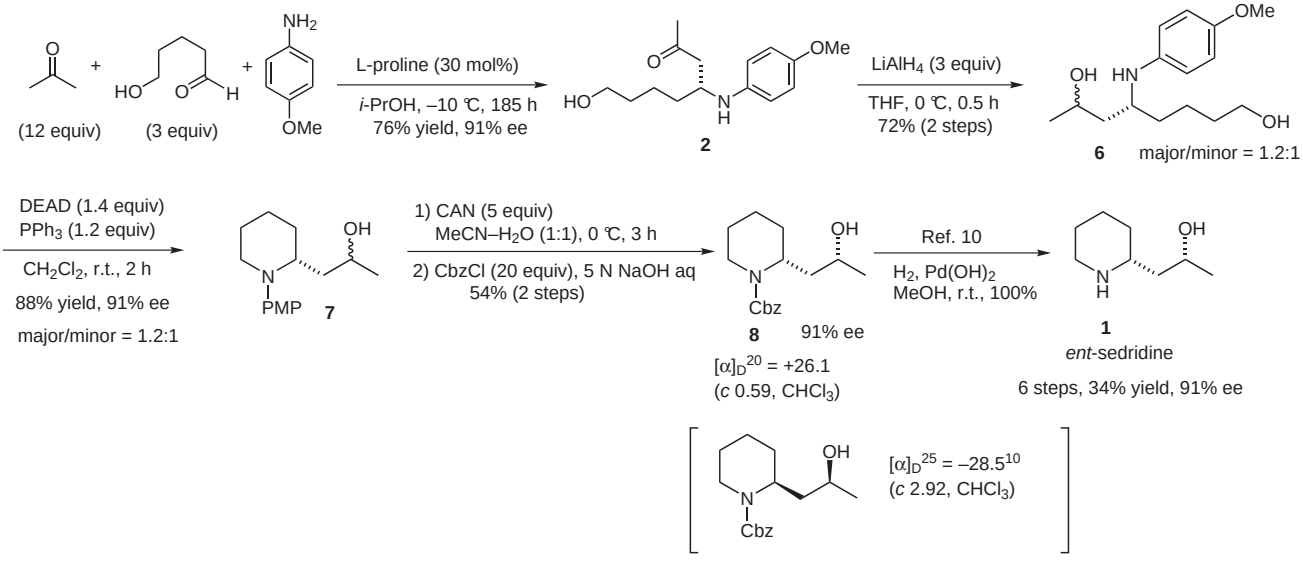
Table 1 The Three-Component Mannich Reaction



Entry	Solvent	Proline (mol%)	Temp	Time (h)	Yield (%)	ee (%)
1	DMF	3	r.t.	20	11	50
2	THF	3	r.t.	20	3	7
3	DMSO	3	r.t.	20	8	81
4	DMSO	9	r.t.	20	52	79
5	DMSO	30	5 °C	132	31	83
6	*n*-PrOH	3	r.t.	20	62	63
7	*n*-PrOH	9	r.t.	20	86	66
8	*n*-PrOH	30	0 °C	66	74	78
9	*i*-PrOH	3	r.t.	20	22	61
10	*i*-PrOH	9	r.t.	20	62	67
11	*i*-PrOH	30	0 °C	87	80	86
12	*i*-PrOH	30	–10 °C	185	76	91
13	*i*-BuOH	3	r.t.	20	40	76
14	*i*-BuOH	9	r.t.	20	70	75
15	*i*-BuOH	30	0 °C	106	55	84
16	*n*-BuOH	3	r.t.	20	55	70
17	*n*-BuOH	9	r.t.	20	63	73
18	*n*-BuOH	30	0 °C	107	55	83



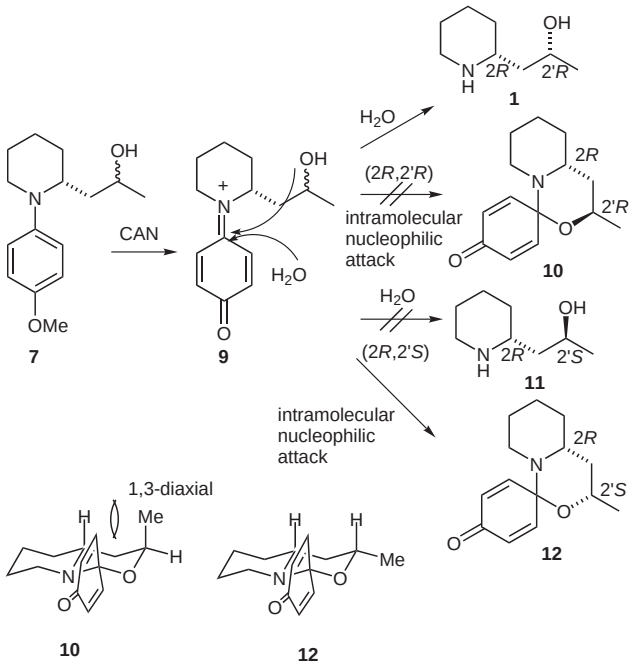
Scheme 2 The total synthesis of *ent*-sedridine

Using 9 mol% of proline, the yield increased but there was a loss of stereoselectivity. The reaction temperature was lowered to 5 °C (entry 5) in order to improve selectivity; however, only a slight improvement of ee was observed at the expense of the chemical yield and the catalyst loading. We then tried other solvents in the reaction and found that an alcoholic solvent afforded better results than those of conventional DMSO or DMF (entries 6–18). In conclusion, despite the long reaction time, the reaction conditions stated in entry 12 were used for the total synthesis.[13]

With chiral **2** in hand, the asymmetric synthesis of *ent*-sedridine was carried out according to Scheme 2.

Compound **2** was reduced using $LiAlH_4$ to give the diol **6** as a mixture of epimers (major/minor = 1.2:1).[14] Although various reducing agents were applied to the reaction, the selectivity was not improved. Compound **6** (as a mixture) was then treated with DEAD and PPh_3 to give a mixture of cyclized product **7** in 88% total yield[15] (major/minor = 1.2:1).[16] In order to determine the stereochemistry of the product, compound **7** was transformed to **8** by oxidative elimination of the PMP group followed by protection with a Cbz group.[17] To our surprise compound **8** was obtained as a single diastereomer, the stereochemistry of the compound was determined by comparison of $[\alpha]_D$ and NMR spectra with literature data.[10] Compound **8** was then readily transformed to *ent*-sedridine (**1**) by reductive cleavage of the Cbz group in quantitative yield. Thus, the total synthesis of **1** was accomplished in 34% overall yield from *p*-anisidine in six steps.

The explanation for the selective formation of the cyclic product **8** was considered to proceed as follows (Scheme 3). The oxidation of **7** with CAN putatively resulted in the formation of a quinonoid intermediate **9**, we supposed that hydrolysis by water would then give compound **1** and compound **11**. In this case, however, intramolecular attack by the hydroxyl group instead of hydrolysis was considered as the alternative reaction pathway to give cyclic products **10** and **12**.[18] As shown in Scheme 3, compound **10** is more sterically hindered than **12** because of the axial position of the methyl substituent. Thus, it was supposed that the (2*R*,2′*R*)-epimer **7** was transformed to **1** without the formation of the sterically demanding **10**, whereas, the (2*R*,2′*S*)-epimer might be cyclized to **12** without the formation of the hydrolysis product **11**.



Scheme 3

In this paper, we have described a novel catalytic asymmetric Mannich reaction using an aliphatic aldehyde as the substrate. The addition product obtained was transformed to an enantiomer of the piperidine alkaloid, sedridine. In the crucial asymmetric process, an alcohol solvent afforded better results than those of DMSO or DMF. This is the first example that uses an alcoholic solvent for the proline-catalyzed Mannich reaction. The application of the present reaction system to the synthesis of other piperidine alkaloids is now in progress.

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(13) **8-Hydroxy-4-[(4-methoxyphenyl)amino]octan-2-one (2).** 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 °C under an Ar atmosphere. After acetone (2.5 mL) was added, the reaction mixture was stirred at –10 °C for 185 h. Then EtOAc was added and the mixture was extracted with 1 N 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 **2**. ^1H NMR ($CDCl_3$): δ = 1.39–1.63 (m, 6 H), 2.13 (s, 3 H), 2.60 (dd, *J* = 16.6, 6.4 Hz, 1 H), 2.71 (dd, *J* = 16.6, 5.2 Hz, 1 H), 2.85 (br s, 1 H), 3.62 (t, *J* = 6.1 Hz, 2 H), 3.74 (s, 3 H), 6.65 (d, *J* = 8.8 Hz, 2 H), 6.77 (d, *J* = 8.8 Hz, 2 H); ^{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* $[M + H]^+$ calcd for $C_{15}H_{24}O_3N$: 266.1777; found: 266.1749. Enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD, hexane–*i*-PrOH = 3:1, 0.5 mL/min).

(14) **5-[(4-Methoxyphenyl)amino]octane-1,7-diol (6).** Compound **2** was dissolved in THF (25 mL) and cooled to 0 °C, $LiAlH_4$ (264 mg, 6.96 mmol) was added. The reaction mixture was stirred for 3.5 h under an Ar atmosphere and was then 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 product was purified using column chromatography (EtOAc–hexane, 7:3) to give compound **6** (445 mg, 72% from *p*-anisidine). The NMR spectra of the main diastereomer are given; ^1H NMR ($CDCl_3$): δ = 1.19 (d, *J* = 6.1 Hz, 3 H), 1.29–1.76 (m, 8 H), 2.85 (br s, 3 H), 3.44 (m, 1 H), 3.55–3.61 (m, 2 H), 3.75 (s, 3 H), 4.06 (m, 1 H), 6.77 (d, *J* = 4.9 Hz, 2 H), 6.79 (d, *J* = 5.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ = 21.9, 23.9, 32.6, 35.1, 42.7, 55.7, 56.6, 62.5, 68.6, 114.9, 117.4, 140.4, 153.4. HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{26}O_3N$: 268.1969; found 268.1892.

(15) **1-[1-(4-Methoxyphenyl)piperidin-2-yl]propan-2-ol (7).** To solution of compound **6** (400 mg, 1.50 mmol) in CH_2Cl_2 (25 mL) was added PPh_3 (472 mg, 1.80 mmol) and DEAD (950 μL, 2.10 mmol). The mixture was stirred for 2 h at r.t. under an Ar atmosphere. Then EtOAc was added and the mixture was extracted with 1 N HCl aqueous solution. The combined aqueous layers were neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated off. The product was purified by column chromatography (EtOAc–hexane, 1:4) to give compound **7** (328 mg, 88%). The NMR spectra of the main diastereomer are given; ^1H NMR ($CDCl_3$): δ = 1.17 (d, *J* = 6.1 Hz, 3 H), 1.45–1.90 (m, 8 H), 3.20–3.26 (m, 2 H), 3.52 (m, 1 H), 3.77 (s, 3 H), 3.95 (m, 1 H), 6.82–6.85 (m, 4 H); ^{13}C NMR ($CDCl_3$): δ = 20.3, 24.0, 24.1, 28.1, 37.6, 51.9, 55.5, 56.4, 65.6, 114.4, 122.4, 145.3, 154.8. HRMS–FAB: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{24}O_2N$: 250.1852; found: 250.1792.

(16) Although the mixture of diastereomers **7** could not be separated, the configuration of the major isomer was shown to be (2*R*,2′*R*), since (2*R*,2′*R*)-epimer **8** was obtained in 54% yield from the reaction of **7**.

(17) **(2*R*,2′*R*)-Benzyl 2-(2-Hydroxypropyl)piperidine-1-carboxylate (8).** To a cold solution (0 °C) of compound **7** (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. The solution was then made basic using 5 N NaOH aqueous solution, CbzCl (690 μL, 4.80 mmol) was added. The reaction mixture was stirred for 10 min and neutralized with 1 N 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 product was purified by column chromatography (EtOAc–hexane, 1:9) to give compound **8** (36 mg, 54%). ^1H NMR ($CDCl_3$): δ = 1.18 (d, *J* = 6.1 Hz, 3 H), 1.20–1.76 (m, 7 H), 1.99 (td, *J* = 13.2, 2.2 Hz, 1 H), 2.76 (td, *J* = 12.9, 2.4 Hz, 1 H), 3.26 (br s, 1 H), 3.53 (br s, 1 H), 4.05 (br d, *J* = 12.2 Hz, 1 H), 4.50 (br s, 1 H), 5.13 (d, *J* = 13.4 Hz, 1 H), 5.15 (12.4 Hz, 1 H), 7.29–7.39 (m, 5 H); ^{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* $[M + H]^+$ calcd for $C_{16}H_{24}O_3N$: 278.1703; found: 278.1777. $[\alpha]_D^{20}$ +26.1 (c 0.59, $CHCl_3$).

(18) When benzoates of both isomers of **7** were oxidized with CAN and then protected with Cbz, both epimers of the benzoate derivatives of **8** were obtained. The result suggested that the free hydroxyl group participates in the mechanism of separation of **7**.