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STRAIGHTFORWARD ASYMMETRIC TOTAL SYNTHESIS OF (+)-EVODIAMINE, A MAJOR INDOLE ALKALOID IN HERBAL MEDICINE "Wu Zhu Yu"

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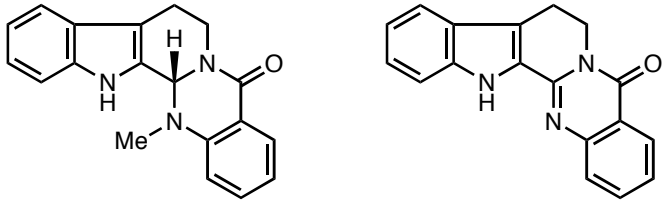
Abstract – The concise asymmetric total synthesis of evodiamine, an indole alkaloid in Evodia Fructus, was achieved by employing Noyori's ruthenium(II)-catalyzed asymmetric transfer hydrogenation.

INTRODUCTION

Evodia Fructus, which originates from a variety of Evodia species[1] (Rutaceae), is a Chinese herbal medicine (Chinese name "Wu Zhu Yu," Japanese name "Goshuyu") used as an analgesic to alleviate headache, thoracicoabdominal pain, and vomiting, or for the improvement of blood circulation. Recent pharmacological studies have shown the involvement of vanilloid receptors[2] induced by alkaloidal constituents in Evodia Fructus. The major alkaloids are evodiamine (**1**) and rutaecarpine (**2**) (Figure 1), which were first isolated by Asahina and Kashiwaki more than 90 years ago.[3] The asymmetric total synthesis of evodiamine (**1**), which has a simple indoloquinazoline structure, was accomplished by Danieli et al.[4] In their synthesis, however, induction of chirality of the asymmetric center at C3 was



(+)-evodiamine (**1**) rutaecarpine (**2**)

Figure 1

attained by utilizing the chirality of the α-carbon of tryptophan, followed by decarboxylation of the amino acid residue. As far as we know, there is no report on the direct asymmetric synthesis of this biologically important alkaloid. Here, we describe the concise (four steps from tryptamine) asymmetric total synthesis of evodiamine (**1**) by utilizing Noyori's ruthenium(II)-catalyzed asymmetric transfer hydrogenation.[5]

RESULTS AND DISCUSSION

It is known that rhetsinine (**6**), one of the constituents of Evodia Fructus, exists in the cyclic iminium form (**5**) in acidic medium.[6] Thus, we initially examined its tendency toward reducing agents (Table 1). When rhetsinine (**6**), which was prepared by condensation of lactam **3** and methyl *N*-methylanthranilate (**4**), was reduced with $NaBH_3CN$ in AcOH, racemic evodiamine (**1**) was obtained in 32% yield (Entry 1). Treatment of **6** with BH_3, which is known to have Lewis acid property, in THF improved the yield of **1** to 80% (Entry 2). Under catalytic hydrogenation conditions (H_2-PtO_2 in AcOH), compound **6** was converted into **1** in 51% yield (Entry 3). By changing the solvent from AcOH to HCO_2H/Et_3N (5:2), evodiamine (**1**) was obtained in high yield (Entry 4).

Table 1

Entry	Reductant	Solvent	Yield of racemic (**1**) (%)
1	$NaBH_3CN$	AcOH	32
2	BH_3	THF	80
3	H_2-Pt_2O	AcOH	51
4	H_2-Pt_2O	HCO_2H/Et_3N (5:2)	93

On the basis of these data, we next attempted the asymmetric reduction of **6**. Employing Corey's oxazaborolidine reagent,[7] evodiamine (**1**) was obtained in 56% chemical yield with low enantiomeric excess (3% *ee*), as determined by chiral HPLC analysis. Next, we chose ruthenium(II)-catalyzed asymmetric transfer hydrogenation developed by Noyori for the asymmetric reduction of ketones.[5] Based on the mechanistic considerations[8] depicted in Figure 2, the formation of natural enantiomer (C3 *S* configuration) was anticipated when 1*S*, 2*S*-diamine catalyst was used. Actually, the reaction of rhetsinine (**6**) in a 5:2 HCO_2H/Et_3N mixture containing 3 mol% (*S,S*)-**7** at rt gave (+)-evodiamine (**1**) in 90% yield with 99% *ee*, as determined by chiral HPLC analysis. Synthetic evodiamine {$[\alpha]_D$ +338° (*c* 0.36, Me_2CO);

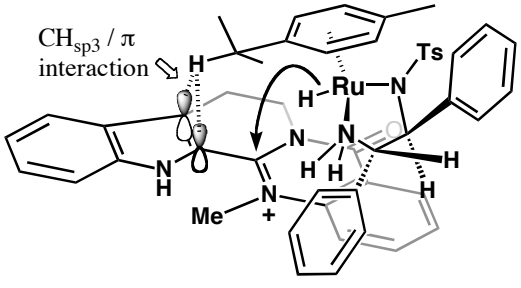
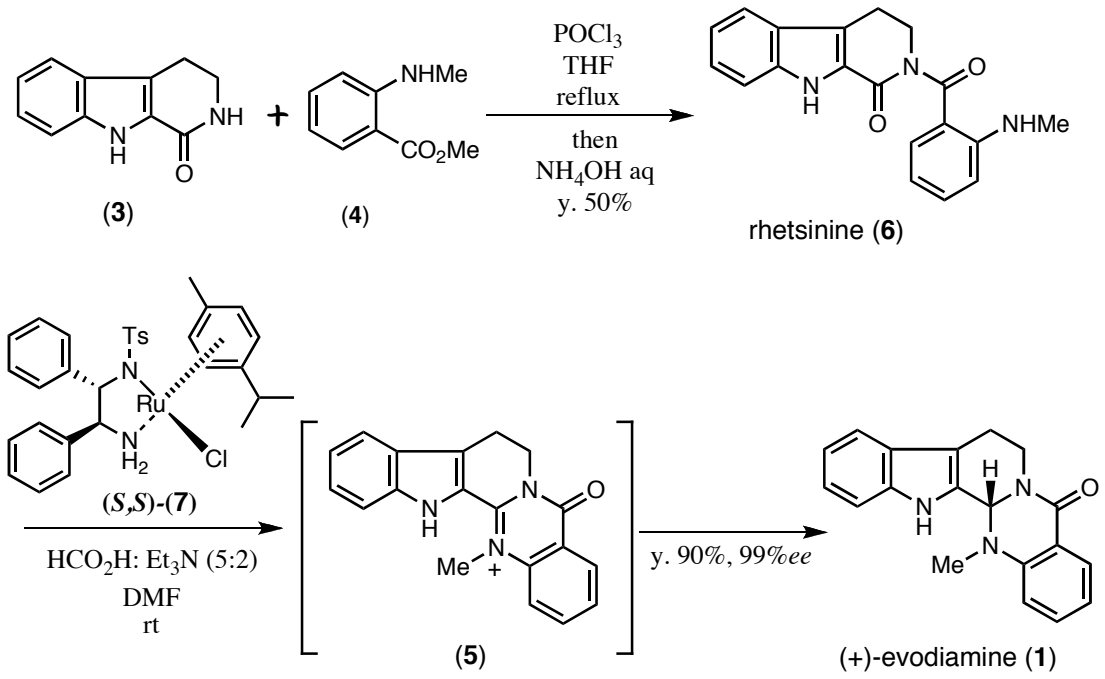


Figure 2

natural, $[\alpha]_D$ +352° (Me_2CO)} was completely identical with the natural product in all respects.



Scheme 1

In summary, we have developed a concise and straightforward asymmetric total synthesis of a biologically important *Evodia* alkaloid, evodiamine (**1**), by employing Noyori's ruthenium(II)-catalyzed asymmetric transfer hydrogenation.

EXPERIMENTAL

UV: recorded in MeOH on a JASCO V-560 instrument. IR: recorded on a JASCO FT/IR-230 spectrophotometer. ^1H and ^{13}C NMR spectra: recorded on a JEOL JNM A-400 or JNM ECP-400 spectrometer, *J* values are given in Hz. EI-MS: direct probe insertion at 70 eV recorded on a JEOL JMS GC-mate spectrometer. FAB-MS: recorded on a JEOL JMS-AX500 or JMS-HX110 mass spectrometer. Optical rotation: measured with a JASCO P-1020 polarimeter. Melting Point: Yanagimoto Micro Melting Point Apparatus 1631A. TLC: precoated Kieselgel 60 F_{254} plates (Merck, 0.25 mm thick). Column chromatography: Kieselgel 60 [Merck, 70-230 mesh (for open chromatography)], Chromatorex NH [Fuji Silysia Chemical, 100-200 mesh (for amino-silica gel column chromatography)]. Chiral HPLC analysis: chiral cell OD (Daicel), *n*-hexane/isopropanol = 90:10, flow rate 0.5 mL/min, 25°C.

Preparation of lactam 3

To a stirred suspension of tryptamine (2.00 g, 12.5 mmol) in a mixture of CH_2Cl_2 (60 mL) and 5% aqueous $NaHCO_3$ (40 mL) was added phenyl chloroformate (1.88 mL, 15.0 mmol) dropwise at 0° C and

the mixture was stirred vigorously for 2 h at the same temperature. The reaction mixture was extracted with $CHCl_3$ and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by SiO_2 open column chromatography (EtOAc/*n*-hexane = 4:1) to give N_b-carbamate (3.43 g, 98%) as a brown oil, a portion of which was used in the next reaction. To a stirred solution of carbamate (50.2 mg, 0.180 mmol) in benzene (3.0 mL) was added BF_3-Et_2O (27.3 μL, 0.216 mmol) at 0° C, and the reaction mixture was stirred under reflux for 23 h under Ar atmosphere. The reaction mixture was quenched with chilled water and then with saturated aqueous $NaHCO_3$ and the whole mixture was extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by SiO_2 open column chromatography (EtOAc) to give **3** (34.3 mg, quant) as pale white crystals. mp 184 °C ($CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.31 (1H, br s), 7.60 (1H, d, J = 8.1 Hz), 7.47 (1H, d, J = 8.5 Hz), 7.33 (1H, ddd, J = 1.0, 7.1, 8.2 Hz), 7.16 (1H, ddd, J = 0.7, 7.8, 8.0 Hz), 5.78 (1H, br s), 3.73 (2H, ddd, J = 2.7, 7.3, 7.3 Hz), 3.08 (2H, dd, J = 7.1, 7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.6, 137.6, 126.4, 125.4, 125.2, 120.3, 120.3, 120.0, 112.8, 42.3, 20.9. *Anal*. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.85; H, 5.40; N, 15.17.

Preparation of rhetsinine (6)

To a stirred solution of **3** (56.0 mg, 0.301 mmol) in THF (20 mL) was added $POCl_3$ (33.0 μL, 0.361 mmol) at 60 °C, and the mixture was stirred at the same temperature under Ar atmosphere. After 25 min, methyl *N*-methylanthranilate (61.4 μL, 0.481 mmol) was added and the reaction mixture was stirred vigorously under reflux for 3 days. The reaction mixture was cooled to rt and the reaction was quenched with aqueous ammonia. After stirring for 30 min, the whole mixture was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by amino-silica gel open column chromatography ($CHCl_3$/*n*-hexane = 4:1) to give rhetsinine (**6**) (48.2 mg, 50%) as orange crystals. mp 207 °C (EtOH/$CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (1H, d, J = 7.8 Hz), 7.45 (1H, dd, J = 1.5, 8.0 Hz), 7.36 (1H, dd, J = 7.2, 7.2 Hz), 7.28 (1H, dd, J = 7.2, 7.2 Hz), 7.19 (1H, d, J = 6.0 Hz), 7.15 (1H, d, J = 7.2 Hz), 7.07 (1H, d, J = 8.3 Hz), 6.78 (1H, d, J = 8.3 Hz), 6.52 (1H, dd, J = 8.1, 8.1), 4.20 (2H, dd, J = 6.5, 6.5 Hz), 3.21 (2H, dd, J = 6.5, 6.5 Hz), 2.96 (3H, d, J = 5.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.8, 162.1, 151.0, 138.6, 134.5, 132.4, 126.1, 124.7, 122.8, 120.7, 120.5, 115.9, 114.6, 113.2, 111.0, 47.5, 29.7, 21.2. *Anal.* Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.44; H, 5.36; N, 13.18.

Preparation of (+)-evodiamine (1) using Noyori's procedure

To a stirred solution of rhetsinine (**6**, 20.0 mg, 0.063 mmol) and a ruthenium catalyst (RuCl[(*S, S*)-Tsdpen](*p*-cymene)) (1.2 mg, 3.0 mmol%) in DMF (0.1 mL) was added a 5:2 HCO_2H-triethylamine mixture (40 μL) at rt under Ar atmosphere. After stirring for 24 h at rt, the reaction mixture was diluted with Et_2O and the combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated.

The residue was purified by amino-silica gel open column chromatography (acetone) and then recrystallized from $CHCl_3$/EtOH solution to give (+)-evodiamine (**1**, 17.1 mg, 90%, 99% *ee*) as colorless prisms. mp 278 °C. $[\alpha]_D$ +338° (*c* 0.36, Me_2CO). UV (MeOH) λ_{max}: 292, 283, and 268 nm. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (1H, dd, *J* = 1.5, 7.8 Hz), 7.59 (1H, d, *J* = 7.1 Hz), 7.48 (1H, m), 7.42 (1H, ddd, *J* = 1.0, 1.0, 8.0 Hz), 7.20 (4H, m), 5.91 (1H, dd, *J* = 1.7, 1.7 Hz), 4.87 (1H, ddd, *J* = 2.4, 4.9, 12.9 Hz), 3.29 (1H, ddd, *J* = 5.3, 10.1, 12.9 Hz), 2.96 (2H, m), 2.50 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1, 148.8, 136.5, 133.4, 130.6, 128.0, 126.0, 121.8, 120.3, 119.2, 118.9, 118.2, 117.4, 111.6, 111.5, 69.7, 40.9, 36.4, 19.5. EIMS *m/z*: 303 $[M]^+$. HREIMS *m/z* 303.1369 (Calcd for $C_{19}H_{17}N_3O$, 303.1371). *Anal.* Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.12; H, 5.68; N, 13.84.

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