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Enantioselective Total Synthesis of (−)-(*S*)-Stepholidine

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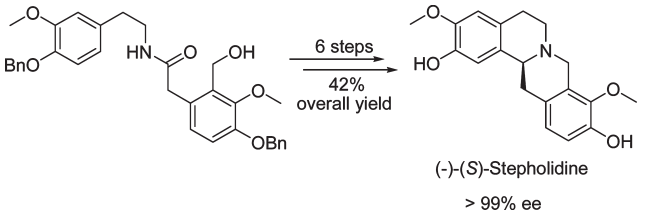

Enantioselective total synthesis of (−)-(*S*)-stepholidine, a drug candidate for the treatment of schizophrenia and/or drug abuse, is described. Asymmetric transfer hydrogenation of imines with use of Noyori's catalyst was used as the key step and (−)-(*S*)-stepholidine was synthesized in 6 steps, with 42% overall yield and >99% ee.

Tetrahydroprotoberberines(THPBs), a series of alkaloids isolated from the Chinese herb *Corydalis ambigua* and various species of *Stephania*,[1] was reported to possess a wide range of biological activities.[2] It was recently reported that they elicit profound effects on the dopaminergic pathway in the central nervous system. Among them, (−)-(*S*)-stepholidine (*l*-SPD, **1**, Figure 1), which is extracted from *Stephanie intermedi*, has attracted a great deal of attention since it was reported to display a unique pharmacological profile toward dopamine (DA) receptors. *l*-SPD acts as a D1 DA receptor agonist while it elicits antagonistic activity at the D2 DA receptor,[3] which accords perfectly with the acknowledged pathogenesis of schizophrenia, thus acting as a promising antipsychotic drug candidate with a novel mechanism. Besides, this compound was also described to possess a potential role in the treatment of drug abuse,[4] which would reduce drug abuse liability with diminished potential to induce extrapyramidal motor deficits. So far, clinical trial and animal studies have demonstrated that *l*-SPD is a potential candidate for the treatment of schizophrenia and/or drug abuse.[5]

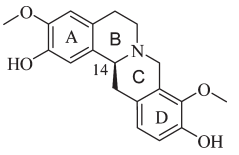

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FIGURE 1. Structure of (−)-(*S*)-stepholidine.

Chemically, *l*-SPD is a prototypical member of the tetrahydroprotoberberines, characterized by a tetracyclic ring skeleton, an isoquinoline core, and a chiral carbon at C(14). Although several asymmetric syntheses of tetrahydroprotoberberines have been reported,[6] the substitution pattern of stepholidine, which is characterized by 9,10-substitution at the D ring and the presence of two phenol groups, makes it a special target. Moreover, the extremely low content (∼0.1%) of this compound in natural sources and the need for large amounts of the compound for clinical research necessitate its total synthesis. Racemic synthesis of stepholidine has already been reported by Chiang and Brochmann-Hassen,[7,8] but the enantioselective preparation has not been reported yet. Herein, we present the first enantioselective synthesis of *l*-SPD via enantioselective reduction of imine.

Asymmetric transfer hydrogenation of imines with formic acid/triethylamine catalyzed by suitably designed chiral Ru(II) complexes has been developed by Noyori et al.,[9] and since then it has become the method of choice in enantioselective reduction of cyclic imines. Several asymmetric syntheses of tetrahydroisoquinolines have been reported with use of this protocol.[10] As outlined retrosynthetically in Scheme 1, our approach relies on the enantioselective reduction of cyclic imine **4**, using the method described by Noyori et al., in the hope of achieving high ee. This cyclic imine could be prepared from the corresponding amide **5** via Bischler−Napieralski cyclization.

The requisite amide **10** was prepared with Chiang's method.[8] Thus, phenylacetic acid **6** was subjected to a

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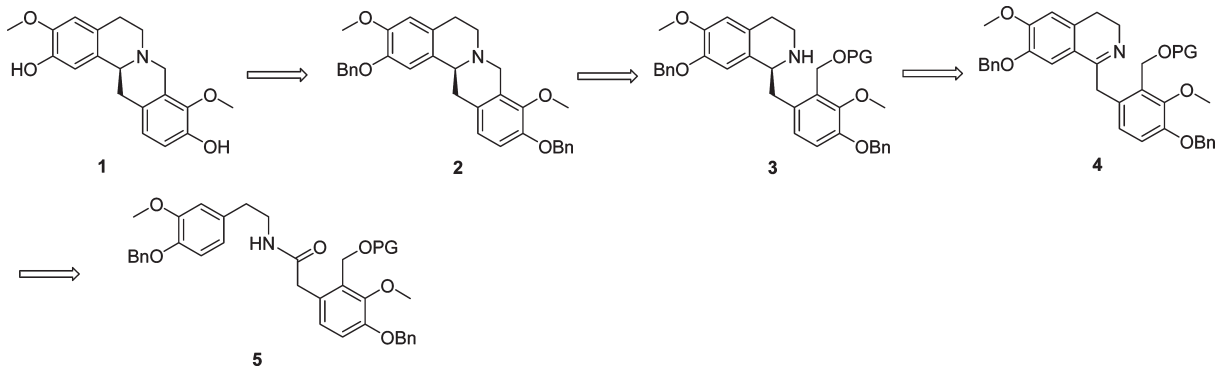
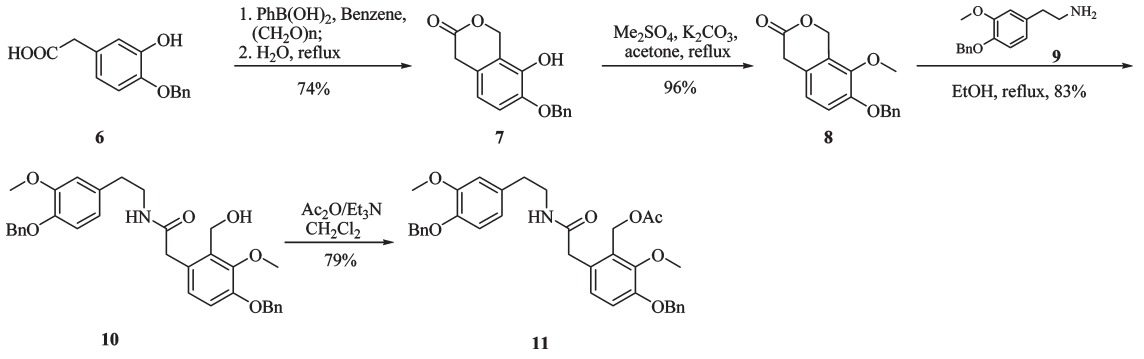
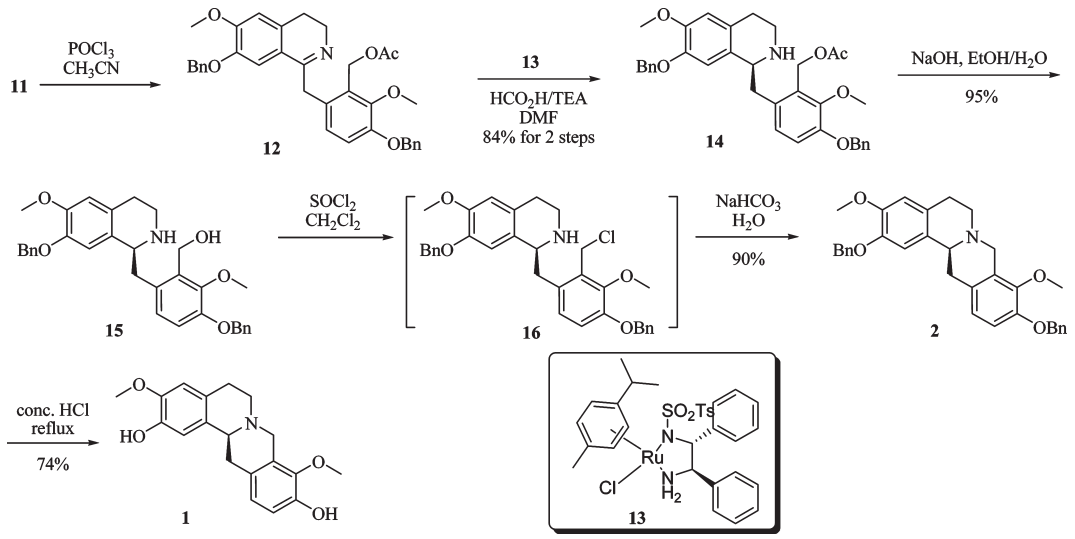
SCHEME 1. Retrosynthesis of (−)-(*S*)-Stepholidine



SCHEME 2. Preparation of Amide 11



SCHEME 3. Synthesis of (−)-(*S*)-Stepholidine from Amide 11



hydroxymethylation directed by phenylboronic acid in the presence of paraformaldehyde (Scheme 2).[11,12] The phenol group of **7** was methylated with Me_2SO_4 to yield the lactone **8**, and aminolysis of **8** with phenethylamine **9** afforded **10** in high yield. The benzyl alcohol group was converted to its acetate **11** under the condition of Ac_2O/Et_3N.

Bischler−Napieralski reaction[13,14] proceeded smoothly under the promotion of $POCl_3$ in CH_3CN (Scheme 3), to give the imine **12** in excellent yield. However, this compound was found to be unstable even at room temperature. For example, the purity of the freshly prepared sample dropped from 95% to about 70% after standing at 25 °C for 24 h. Therefore, freshly prepared **12** without further purification was used for the following reduction. Asymmetric transfer

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TABLE 1. Debenzylation of Substrate 2

method	conditions	ee (%)	yield
A	H_2, MeOH, Pd/C	70.4	95
B	37% HCl, reflux	99.6	74

hydrogenation was carried out under argon in DMF, in the presence of Noyori's catalyst (**13**) and formic acid/triethylamine (v/v = 5/2) as the hydrogen source. Tetrahydroisoquinoline **14** was obtained in 84% chemical yield from the amide **11**. Because the ee value of this compound was difficult to determine using chiral HPLC analysis, we convert **14** to the corresponding free hydroxyl derivative **15**, and the enantioselectivity of **15** was determined as 95.6% ee.

Closure of ring C was accomplished by chlorination of the benzyl alcohol group in **15** under the condition of $SOCl_2$/CH_2Cl_2 at 0 °C, giving the intermediate **16**, which transformed directly to **2** under the basifying of the CH_2Cl_2 solution with aqueous $NaHCO_3$.

Debenzylation of the benzyl ethers of **2** was first tried with Pd/C catalytic hydrogenation; however, the ee value of the product **1** was determined to be 70.4%, based on 99.8% ee of the substrate **2** (Method A, Table 1). It is presumed that a reversible process of dehydrogenation and hydrogenation in the presence of Pd/C and H_2 led to the oxidation of benzylic amine **2** to a doubly conjugated enamine (by dehydrogenation), which was hydrogenated to yield racemic product, thus leading to the partial racemization.[15] Therefore, the deprotection was carried out via refluxing **2** in 37% hydrochloric acid (Method B, Table 1), and (−)-(*S*)-stepholidine was isolated in 99.6% ee and 74% isolated yield. Spectral characteristics of the isolated sample in our laboratory are consistent with those reported in the literature.[16]

In conclusion, the first enantioselective total synthesis of (−)-(*S*)-stepholidine was accomplished with use of Noyori's protocol of enantioselective reduction of cyclic imine. The target alkaloid was prepared in 6 steps and 42% overall yield from the amide **10**, with an ee value over 99%.

Experimental Section

6-((4-(Benzyloxy)-3-methoxyphenethylcarbamoyl)methyl)-3-(benzyloxy)-2-methoxybenzyl Acetate (11). To a solution of compound **10** (3.00 g, 5.54 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (3.8 mL, 27.7 mmol). The mixture was cooled to 0 °C, and acetic anhydride (1.6 mL, 16.6 mmol) was added dropwise. After being stirred overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by recrystallization from toluene to afford a white solid **11** (2.37 g, 79%). Mp 95 − 97 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.46−7.28 (m, 10 H), 6.90 (d, J = 8.3 Hz, 1 H), 6.84 (d, J = 8.3 Hz, 1 H), 6.73 (d, J = 8.2 Hz, 1 H), 6.64 (d, J = 1.9 Hz, 1 H), 6.46 (dd, J = 8.2, 1.9 Hz, 1 H), 5.46 (br, 1 H), 5.15 (s, 2 H), 5.12 (s, 2 H), 5.10 (s, 2 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.53 (s, 2 H), 3.42 (q, J = 7.0 Hz, 2 H), 2.65 (t, J = 7.0 Hz, 2 H), 2.00 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.7, 151.1, 150.1, 149.1, 146.7, 137.1, 136.6, 131.6, 129.0, 128.6 (×2), 128.5 (×2), 128.2, 128.0, 127.8, 127.7, 127.2 (×3), 126.2, 120.5, 114.6, 113.9, 112.1, 70.9, 70.6, 61.4, 58.4, 55.9, 40.7, 40.4, 35.0, 20.9. MS (EI) m/z (%): 583 (M^+, 9), 523 (5), 433 (7), 241 (15), 240 (79), 150 (8), 149 (34), 91 (100). HRMS (EI) calcd for $C_{35}H_{37}NO_7$ 583.2570, found 583.2542.

3-(Benzyloxy)-6-((7-(benzyloxy)-3,4-dihydro-6-methoxyisoquinolin-1-yl)methyl)-2-methoxybenzyl Acetate (12). To a solution of the amido ester **11** (5.02 g, 8.6 mmol) in dry acetonitrile (200 mL) was added $POCl_3$ (5 mL) then the mixture was refluxed for 2 h under nitrogen. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to yield a yellow solid (4.80 g), which was characterized as imine **12** but unstable at room temperature. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44−7.28 (m, 10 H), 6.96 (s, 1 H), 6.83 (d, J = 8.6 Hz, 1 H), 6.72 (d, J = 8.6 Hz, 1 H), 6.70 (s, 1 H), 5.24 (s, 2 H), 5.08 (s, 2 H), 5.00 (s, 2 H), 3.98 (s, 2 H), 3.92 (s, 3 H), 3.90 (s, 3 H), 3.69 (t, J = 7.5 Hz, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 2.03 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.7, 171.0, 156.9, 151.2, 149.5, 147.5, 136.4, 135.4, 133.9, 128.6 (×3), 128.2, 128.0, 127.6, 127.2 (×4), 126.8, 123.9, 117.3, 115.1, 114.9, 111.0, 71.2, 70.6, 61.5, 58.4, 56.5, 56.0, 41.1, 35.2, 25.4, 21.0. MS (ESI) m/z 566.2 $[M + H]^+$.

3-(Benzyloxy)-6-(((*S*)-7-(benzyloxy)-1,2,3,4-tetrahydro-6-methoxyisoquinolin-1-yl)methyl)-2-methoxybenzyl Acetate (14). A freshly prepared imine **12** (4.80 g, 8.5 mmol) was dissolved in anhydrous DMF (50 mL), and the solution was degassed for 5 min with argon. RuCl[(*R*,*R*)-TsDPEN(P-cymene)] (**13**, CAS: 192139-92-7) (54 mg, 1 mol %) was added followed by formic acid/triethylamine (v/v = 5/2, 5.0 mL), and the reaction mixture was stirred at room temperature for 8 h under argon. The reaction was quenched with sat. $NaHCO_3$ (100 mL) and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (CH_2Cl_2/CH_3OH/Et_3N = 100/1/1) to give **14** as light brown oil (4.06 g, 84%). $[\alpha]^{23}_D$ −51.9 (c 0.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48−7.28 (m, 10 H), 6.96 (d, J = 8.5 Hz, 1 H), 6.91 (d, J = 8.5 Hz, 1 H), 6.64 (s, 1 H), 6.61 (s, 1 H), 5.35 (d, J = 11.4 Hz, 2 H), 5.20 (d, J = 11.4 Hz, 2 H), 5.12 (s, 2 H), 5.08 (s, 2 H), 3.99−3.93 (m, 1 H), 3.92 (s, 3 H), 3.86 (s, 3 H), 3.24−3.16 (m, 1 H), 3.12−2.87 (m, 3 H), 2.82−2.70 (m, 2 H), 2.03 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 150.5, 149.3, 148.1, 145.9, 137.1, 136.7, 131.8, 128.8, 128.5 (×2), 128.4, 128.4, 127.9, 127.7, 127.3 (×2), 127.1 (×2), 126.8, 126.2, 114.6, 112.2, 111.9, 70.7, 70.6, 61.4, 58.2, 56.2, 55.8, 39.5, 38.6, 29.6, 28.6, 21.1. MS (EI) m/z (%): 507 (5), 492 (8), 476 (4), 417 (8), 416 (28), 414 (7), 269 (20), 268 (100), 177 (14), 149 (8), 148 (7), 91 (23). HRMS (EI) calcd for $C_{35}H_{37}NO_6$ 567.2621, found 567.2616.

(3-(Benzyloxy)-6-(((*S*)-7-(benzyloxy)-1,2,3,4-tetrahydro-6-methoxyisoquinolin-1-yl)-methyl)-2-methoxyphenyl)methanol (15). To a solution of **14** (2.00 g, 3.5 mmol) in ethanol (50 mL) was added 10% NaOH (50 mL) then the mixture was refluxed for 1 h. The mixture was cooled and ethanol was removed in vacuo. The residue was extracted with CH_2Cl_2 and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to yield **15** as light yellow solid (1.76 g, 95%, chiral HPLC: 95.6% ee). Mp 139−141 °C. $[\alpha]^{23}_D$ −16.7 (c 0.52, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48−7.27 (m, 10 H), 6.89 (d, J = 8.4 Hz, 1 H), 6.83(d, J = 8.4 Hz, 1 H), 6.78 (s, 1 H), 6.60 (s, 1 H), 5.17 (s, 2 H), 5.13 (s, 2 H), 4.83 (d, J = 11.6 Hz, 1 H), 4.45 (d, J = 11.6 Hz, 1 H), 4.02−3.95 (m, 1 H), 3.94 (s, 3 H), 3.88 (s, 3 H), 3.06−2.96 (m, 2 H), 2.92−2.81 (m, 2 H), 2.80−2.69 (m, 1 H), 2.62−2.54 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 148.3, 148.1, 146.3, 137.2, 137.2, 135.5, 131.8, 129.7, 128.5 (×4), 128.0, 127.9, 127.8, 127.3 (×2), 127.2 (×2), 125.2, 114.1, 112.9, 112.0, 71.5, 70.8, 61.8, 56.3, 55.9, 55.1, 40.6, 40.0, 29.1. MS (EI) m/z (%): 507 (6), 492 (13), 432 (9), 417 (7), 416 (25), 269

(15) For examples, see: (a) Parvulescu, A. N.; De Vos, D. E.; Jacobs, P. A. *Chem. Commun.* **2005**, *42*, 5307–5309. (b) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem.—Eur. J.* **2007**, *13*, 2034–2043. (c) Parvulescu, A. N.; Van der Eycken, E.; Jacobs, P. A.; De Vos, D. E. *J. Catal.* **2008**, *255*, 206–212.

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(18), 268 (100), 177 (13), 176 (5), 149 (9), 148 (6), 91 (26). HRMS calcd for $C_{33}H_{35}NO_5$ 525.2515, found 525.2500.

14-(*S*)-3,9-Dimethoxyl-2,10-dibenzyloxytetrahydroprotoberberine (2). A solution of **15** (1.50 g, 2.8 mmol) in CH_2Cl_2 (100 mL) was cooled to 0 °C, and thionyl chloride (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h before it was cooled to 0 °C and sat. $NaHCO_3$ (100 mL) was added slowly. After being stirred for another 1 h, the reaction was stopped and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to yield a thick yellow oil, which was recrystallized from ethyl acetate−petroleum ether to give yellow solid **2** (1.28 g, 90%, 99.8% ee). Mp 104−106 °C. $[\alpha]^{23}_D$ −198.4 (*c* 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48−7.27 (m, 10 H), 6.83 (d, J = 8.5 Hz, 2 H), 6.79 (d, J = 8.5 Hz, 2 H), 6.74 (s, 1 H), 6.65 (s, 1 H), 5.14 (s, 2 H), 5.11 (s, 2 H), 4.24 (d, J = 15.8 Hz, 1 H), 3.90 (s, 3 H), 3.88 (s, 3 H), 3.56−3.46 (m, 2 H), 3.23−3.05 (m, 3 H), 2.77−2.60 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.2, 148.2, 146.4, 145.6, 137.2 (×2), 129.6, 128.7 (×4), 128.5, 128.2, 127.8 (×2), 127.5, 127.4 (×2), 127.2 (×2), 123.7, 113.0, 112.0, 111.8, 71.5, 70.9, 60.2, 59.1, 55.9, 53.9, 51.4, 36.2, 29.0. MS (EI) m/z (%): 507 (M^+, 14), 416 (100), 149 (78), 91 (71). HRMS (EI) calcd for $C_{33}H_{33}NO_4$ 507.2410, found 507.2409.

(−)-(*S*)-Stepholidine (1). Method A. A mixture of compound **2** (0.60 g, 1.2 mmol) and 10% Pd−C (60 mg) in CH_3OH (30 mL) was stirred under hydrogen atmosphere for 2 h. After the Pd−C catalyst was filtered off, the solvent was removed under reduced pressure and the residue was purified by column chromatography (CH_2Cl_2/CH_3OH = 50/1) to yield the title compound **1** (0.36 g, 95%, 70.4% ee).

Method B. Compound **2** (0.60 g, 1.2 mmol) was refluxed in a mixture of concentrated hydrochloric acid (30 mL) and EtOH (10 mL) for 2 h. The reaction mixture was cooled to 0 °C and basified with concentrated ammonia solution (50 mL). The mixture was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the crude product, which was purified as described in Method A to give **1** (0.29 g, 74%, 99.6% ee). Mp 128−129 °C [lit.[16] mp 125−126 °C]. $[\alpha]^{23}_D$ −281.7 (*c* 1.0, CH_3OH). ^{1}H NMR (CD_3OD, 300 MHz): δ 6.78−6.66 (m, 3 H), 6.63 (s, 1 H), 4.15 (d, J = 15.7 Hz, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.50−3.38 (m, 2 H), 3.32−2.98 (m, 3 H), 2.74−2.52 (m, 3 H). ^{13}C NMR (CD_3OD, 100 MHz): δ 149.3, 148.3, 146.5, 145.5, 131.2, 129.2, 127.7, 126.7, 125.9, 116.9, 113.6, 113.0, 61.1, 60.9, 56.8, 55.3, 53.3, 37.0, 29.7. MS (EI) m/z (%): 327 (M^+, 84), 325 (62), 296 (16), 178 (100), 176 (21), 150 (18), 135 (20). Anal. Calcd for $C_{19}H_{23}NO_5$ (**1** + H_2O): C, 66.07; H, 6.71; N, 4.06. Found: C, 65.85; H, 6.64; N, 3.97.

Acknowledgment. We thank Shanghai institute of organic chemistry, Chinese academy of sciences, for the ee determination of the chiral compounds in this paper.

Supporting Information Available: Synthetic procedures and characterizing data for compounds **6**−**10**, ^{1}H, ^{13}C spectra for all new compounds, and details of ee determination of compounds **15**, **2**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.