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Chemoenzymatic synthesis of (*S*)-2-cyanopiperidine, a key intermediate in the route to (*S*)-pipecolic acid and 2-substituted piperidine alkaloids

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Abstract

The preparation of (*S*)-2-cyanopiperidine **4** provides a new access to 2-substituted piperidines. This synthesis is based on an enantioselective (*R*)-oxynitrilase-catalyzed reaction for the preparation of (*R*)-(+)-6-bromo-2-hydroxyhexanenitrile **1** and the subsequent cyclization of this compound to yield the piperidine ring. The utilization of **4** as the starting material for the synthesis of (*S*)-2-aminomethylpiperidine **6**, (*R*)-(−)-coniine **10** and (*S*)-(−)-pipecolic acid **13** is also described. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Piperidine derivatives are present in a large number of natural products of biological importance.[1] The development of methods for the asymmetric synthesis of these compounds constitutes an area of considerable interest. Some significant examples such as enantiomerically pure 2-aminomethylpiperidine **6**, coniine **10** and pipecolic acid **13** are 2-substituted piperidines.

The structure of 2-aminomethylpiperidine **6** is a valuable synthon for the preparation of several pharmaceuticals[2] and is also a useful chiral ligand for asymmetric synthesis.[3] Froelich et al. recently described the asymmetric synthesis of this structure using the versatile 2-cyano-6-phenyloxazolopiperidine.[4] In this procedure, the obtention of the piperidine ring, using (−)-phenylglycinol as the source of chirality, is one exception to the general procedure in which the, not easily available, enantiopure pipecolic acid is used as starting material.[5] The interest in coniine and its analogues is demonstrated by the wealth of published material.[6] Finally, (*S*)-pipecolic acid **13**,[7] a nonproteinogenic amino acid, is a precursor to numerous bioactive compounds such as synthetic

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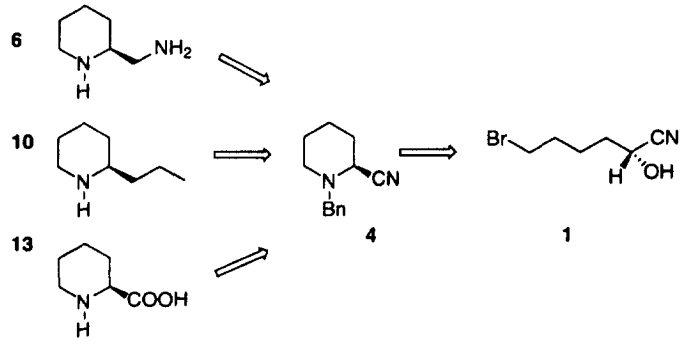
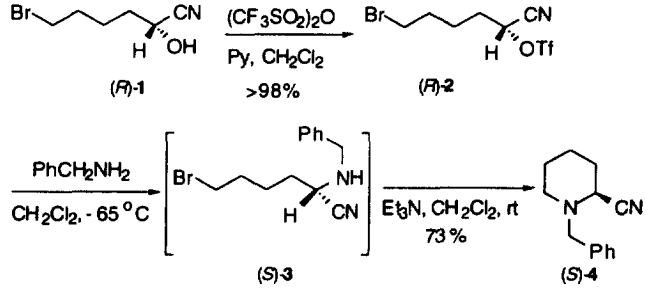
peptides,[8] local anesthetics[9] or potential enzyme inhibitors[10] and is a component of biologically-important natural products such as the immunomodulators rapamycin and demethoxyrapamycin,[11] the immunosuppressant FK506[12] or the antitumor antibiotic sandramycin.[13]



On the other hand, (*R*)-oxynitrilase from almonds [EC 4.1.2.10] catalyses the enantioselective preparation of cyanohydrins from aldehydes or ketones.[14] These cyanohydrins have been applied in the synthesis of some bioactive products of great pharmaceutical importance.[15] In a previous report,[16] we prepared (*R*)-(+)-6-bromo-2-hydroxyhexanenitrile **1** through an enzymatic transcyanation process catalyzed by (*R*)-oxynitrilase. We believe that the cyanohydrin **1**, obtained in high yield and enantiomeric excess, could be an adequate starting material for the preparation of the above mentioned piperidine heterocycles. In this paper, we propose a general approach to the synthesis of these heterocycles.

2. Results and discussion

The (*R*)-(+)-6-bromo-2-hydroxyhexanenitrile **1** seems to be a good starting material for the synthesis of the cyanopiperidine cycle since only two simple steps are required (Scheme 1): the transformation of the hydroxyl into a good leaving group by the formation of the trifluoromethanesulfonyloxy derivative **2** and the treatment of this compound with an amine or ammonia. This second step is a double substitution process: the substitution of the trifluoromethanesulfonate group that should occur with inversion of the configuration and the following slower substitution of the bromine to yield the piperidine ring.



Scheme 1.

The reaction of **1** with trifluoromethanesulfonic anhydride/pyridine affords **2** quantitatively. Nevertheless, treatment of **2** with a solution of ammonia/H_2CCl_2 at room temperature to yield the corresponding 2-cyanopiperidine, occurs with partial racemization.

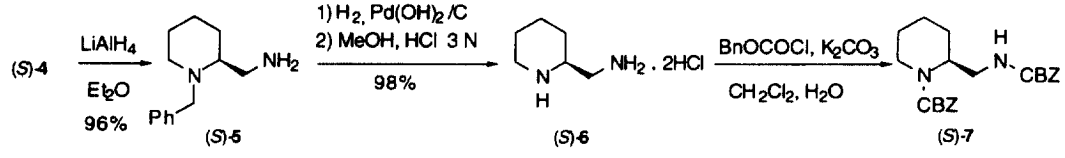
In order to obtain a complete inversion of configuration during the substitution of the triflate group, we studied the effect of temperature on this process. For this study the use of benzylamine as the nucleophile was more efficient, because the reaction with ammonia has several inconveniencies, especially the control

of the amount of the nucleophile and the low reaction rate when the process is carried out at temperatures below 0°C. The use of benzylamine has the additional advantage of the higher stability of the reaction product and the easy removal of the benzyl group.

The substitution of the trifluoromethanesulfonate group is carried out with two equivalents of benzylamine at −65°C. When this process is complete, triethylamine is added and the reaction is allowed to warm to room temperature for the substitution of the bromine. Under these conditions, we obtained (*S*)-(−)-*N*-benzyl-2-cyanopiperidine **4** without evidence of racemization.

These results are in accordance with those described by Effenberger et al. in the substitution process of 2-trifluoromethanesulfonyloxycarboxylic esters with amines, in which racemization or elimination side reactions can be avoided when the reactions take place at low temperatures.[17]

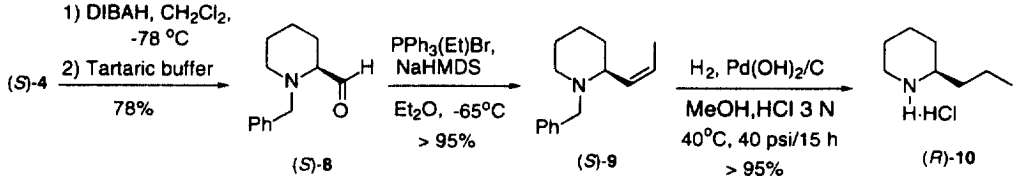
The preparation of the (*S*)-(−)-2-aminomethylpiperidine bishydrochloride **6** is carried out by the reduction of the cyanopiperidine **4** to the diamine **5** in a 96% yield (Scheme 2). The hydrogenolysis of the benzyl group yields the bishydrochloride salt (**6**) quantitatively.



Scheme 2.

In order to verify the enantiomeric excess of the diamine **6**, we prepared the racemate by hydrogenation of the commercially available 2-aminopyridine. Both diamines **6** are transformed into their benzyloxycarbonyl derivatives and compared by HPLC analysis. This analysis confirms that the enantiomeric excess of the starting cyanohydrin **1** remains after the synthetic process.

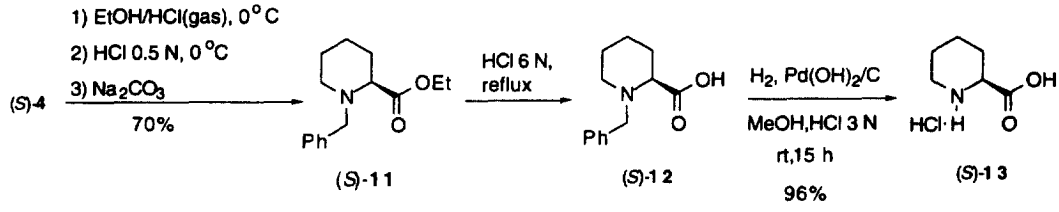
Treatment of **4** with DIBAL-H at −78°C, followed by a tartaric-buffer work up, yields the crude aldehyde **8** (Scheme 3), which is added, without further purification, to the already prepared ethyl Wittig ylide to afford the olefin **9** with a 74% overall yield. The hydrogenation of **9** and simultaneous removal of the benzyl group yields (*S*)-coniine hydrochloride **10** quantitatively. The spectral data and specific rotation of the coniine are in accordance with the literature values.[18]



Scheme 3.

Cyanopiperidine **4** could be a good starting material for the synthesis of pipecolic acid through simple hydrolysis of the nitrile function. Nevertheless, when this process is carried out by refluxing the cyanopiperidine **4** in concentrated HCl, racemic pipecolic acid is obtained. This result is in accordance with the report by Berrien et al.[7a]

In view of the easy racemization in these processes we carried out the transformation of the nitrile function into an imidate using ethanol saturated with anhydrous hydrochloric acid. The subsequent hydrolysis of the imidate with diluted HCl yields the ester **11** in a 70% yield (Scheme 4). A further hydrolysis of the ethyl ester with 6 N HCl at reflux and deprotection of the amino group by hydrogenation, gives (−)-pipecolic acid in 96% yield. Comparison of the specific rotation of this compound with the corresponding hydrochloride of the enantiopure commercial (−)-pipecolic acid, shows that no racemization had occurred during the process.



Scheme 4.

In conclusion, we have achieved an enantiospecific chemoenzymatic synthesis of 2-substituted piperidines. The method is based on the utilization of an (*R*)-cyanohydrin obtained through an oxynitrilase-catalyzed reaction. The versatility of this method is demonstrated by the preparation of three significant examples: (*S*)-2-aminomethylpiperidine, (*R*)-(−)-coniine and (*S*)-(−)-pipecolic acid. Further applications to the synthesis of other piperidine derivatives are currently in progress.

3. Experimental

Melting points were taken using a Gallenkamp apparatus and were uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin–Elmer 1720-X FT infrared spectrophotometer. ^{1}H and ^{13}C NMR were obtained with TMS (tetramethylsilane) as the internal standard; using a Bruker AC-300 (^{1}H 300 MHz and ^{13}C 75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett Packard 5987A and Finigan MAT/95 spectrometers. Microanalyses were performed on a Perkin–Elmer 240B elemental analyzer. All reagents were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). The ees were determined by chiral HPLC analysis using a CHIRALCEL-OD column (4.5×250 mm).

3.1. (R)-(+)-6-Bromo-2-hydroxyhexanenitrile (R)-1

The defatted ground almond meal was incubated with 5 ml of 0.02 M citrate buffer (pH 5.5) in a 250 ml reaction vessel. After 15 minutes 50 ml of diisopropyl ether, distilled substrate 5-bromopentanal (1.38 g, 8.4 mmol) and (±)-2-hydroxy-2-methylpentanenitrile (1.6 g, 12.6 mmol) were added to the suspension. The mixture was shaken at 30°C and 250 rpm in a rotatory shaker. After 24 h, the reaction mixture was filtered and washed with CH_2Cl_2. The combined filtrates were concentrated in vacuo, and the residue was purified by flash chromatography on silica gel with hexane:H_2CCl_2:AcOEt (7.5:1.5:1), to give the cyanohydrin (*R*)-**1** in 81% yield. $[\alpha]_D^{25}$ +10.7 (*c*=1.0, $CHCl_3$), ee 91%; ^{1}H NMR ($CDCl_3$) δ 1.63–2.14 (m, 6H), 3.15 (br s, 1H), 3.45 (t, 2H), 4.55 (t, 1H); ^{13}C NMR ($CDCl_3$) δ 23.1, 31.7, 33.0, 40, 60.8, 119.7; HMRS calcd for $C_6H_{10}BrNO$ 190.9946, found 190.9949.

3.2. (R)-6-Bromo-2-trifluoromethanesulfonyloxyhexanenitrile (R)-2

To a vigorously stirred solution of cyanohydrin (*R*)-**1** (887 mg, 4.5 mmol) in pyridine (0.8 ml, 9 mmol) and 60 ml of dry CH_2Cl_2 under N_2 atmosphere at 0°C, was added dropwise trifluoromethanesulfonic anhydride (1.2 ml, 6.8 mmol). The resulting mixture was stirred for 15 minutes, then filtered and the solvent evaporated. The crude residue was purified by flash chromatography on silica gel (hexane:AcOEt, 8:1) to afford the compound (*R*)-**2** as a colorless oil in 98% yield; $[\alpha]_D^{25}$ +28.9 (*c*=1.1, $CHCl_3$), ee 91%; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 2H), 1.97 (m, 2H), 2.13 (m, 2H), 3.44 (t, *J*=6.41 Hz, 2H), 5.38 (t, *J*=6.41

Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 31.1, 32.0, 32.7, 71.5, 113.5, 121.3; MS (EI) exact mass calcd for ($C_7H_9BrF_3NO_3S$–CF_3SO_2) 189.9868, found 189.9867.

3.3. (S)-1-Benzyl-2-cyanopiperidine (S)-4

To a stirred solution of (*R*)-**2** (1 g, 3.09 mmol) in 10 ml of CH_2Cl_2 at −65°C, was added dropwise (for 30 minutes) a solution of benzylamine (674 μl, 6.17 mmol) in 1 ml of H_2CCl_2. The resulting mixture was stirred for 24 h at the same temperature, then 5 ml of Et_3N was added and the reaction mixture was allowed to warm to rt and stirred for 24 h. The resulting mixture was filtered over Celite and the solvent evaporated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane:H_2CCl_2:AcOEt, 7.5:1.5:1) to yield the compound (*S*)-**4** as a colorless oil (450 mg, 73%); $[\alpha]_D^{25}$ −86.5 (*c*=1.4, $CHCl_3$), ee 91%; ^1H NMR ($CDCl_3$) δ 1.50–1.88 (m, 6H), 2.42 (dt, *J*=10.68, 3.06 Hz, 1H), 2.77 (br d, *J*=11.51 Hz, 1H), 3.52 (d, *J*=13.1 Hz, 1H), 3.69 (d, *J*=13.10 Hz, 1H), 3.73 (br s, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.7, 25.2, 28.9, 50, 52.3, 61.0, 117, 127.8, 128.7, 129.3, 137.2; HRMS calcd for $C_{13}H_{16}N_2$ 200.1313, found 200.1319.

3.4. (S)-2-Aminomethyl-1-benzylpiperidine (S)-5

To a suspension of $LiAlH_4$ (198 mg, 5.22 mmol) in 12 ml of anhydrous Et_2O was added a solution of (*S*)-**4** (232 mg, 1.16 mmol) in 6 ml of anhydrous Et_2O at −10°C and the reaction mixture was stirred for 2 h at rt. To the resulting mixture was added a solution of NaOH (15%, 2.5 ml). The resulting white precipitate was filtered and washed several times with Et_2O. After removal of the solvent under reduced pressure, the crude residue was purified by flash chromatography on silica gel ($CHCl_3$:MeOH, 2:3) to yield the compound (*S*)-**5** as colorless oil (228 mg, 96% yield); $[\alpha]_D^{25}$ −57.2 (*c*=3.0, EtOH), ee 91%; lit.,[5] $[\alpha]_D^{25}$ −61.2 (*c*=3.0, EtOH); ^1H NMR ($CDCl_3$) δ 1.26–1.74 (m, 8H), 2.04 (br t, *J*=9.89 Hz, 1H), 2.26 (m, 1H), 2.78 (m, 2H), 3.01 (dd, *J*=13.32, 5.16 Hz, 1H), 3.23 (d, *J*=13.33 Hz, 1H), 4.02 (d, *J*=13.33 Hz, 1H), 7.30–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.7, 24.7, 28.2, 43.2, 51.9, 57.5, 62.3, 126.6, 128.1, 128.7, 139.4; MS (EI) m/z 204 (M^+<1), 174 (100), 91(100); FABS m/z 205 (M+1, 25), 174 (100), 147 (40).

3.5. (S)-2-Aminomethylpiperidine bishydrochloride (S)-6

To a suspension of (*S*)-**5** (162 mg, 0.79 mmol) and palladium hydroxide (20% on charcoal, 13 mg) in MeOH (2 ml) was added a solution of MeOH/3 N HCl (3 ml). The mixture was hydrogenated at 40 psi for 15 h. The resulting mixture was filtered over Celite and concentrated under reduced pressure to afford a bishydrochloride salt as a white solid quantitatively; $[\alpha]_D^{25}$ −4.7 (*c*=2.8, MeOH), ee 91%, lit.,[4] $[\alpha]_D^{25}$ −5.7 (*c*=0.42, MeOH); ^1H NMR (D_2O) δ 1.52, 1.83, 2.0 (m, 6H), 2.98 (td, 1H), 3.23 (dd, *J*=13.6, 7.0 Hz, 2H), 3.20 (dd, *J*=13.3, 5.8 Hz, 2H), 3.4 (m, 2H); ^{13}C NMR (D_2O) δ 21.5, 22.0, 26.5, 41.7, 45.7, 54.4; MS (EI) m/z 115 (M+1) (100), 84 (10). Anal. calcd for $C_6H_{16}N_2Cl_2$: C, 38.51; H, 8.61; N, 14.97. Found: C, 38.25; H, 8.77; N, 14.59.

3.6. (S)-1-Benzyloxycarbonyl-2-[N-(benzyloxycarbonyl)aminomethylpiperidine] (S)-7

To a mixture of H_2O (5 ml) and CH_2Cl_2 (2 ml) was added Na_2CO_3 (627 mg, 4.53 mmol) and bishydrochloride (*S*)-**6** (106 mg, 0.567 mmol). The mixture was cooled at 0°C and benzyloxycarbonyl chloride (0.64 ml, 4.53 mmol) was added dropwise. After stirring for 16 h at rt the mixture was extracted

with CH_2Cl_2 following a general work up procedure. The obtained crude product was purified by flash chromatography on silica gel (hexane:CH_2Cl_2:AcOEt, 7.5:1.5:1) to give the compound (*S*)-**7** as a white solid (119 mg, 55%); $[\alpha]_D^{25}$ −27.8 (*c*=2.1, $CHCl_3$), ee 91%; ^{1}H NMR ($CDCl_3$) δ 1.35–1.82 (6H), 2.91 (br t, 1H), 3.25 (m, 1H), 3.61 (br s, 1H), 4.10 (br s, 1H), 4.42 (br s, 1H), 5.07 (s, 2H), 5.10 (s, 2H), 7.25–7.42 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.0, 25.1, 26.2, 39.4, 40.6, 50.3, 66.5, 67.0, 126.9, 127.9, 128.4, 136.5; MS (EI) 382 M^+ (<1), 218 (17), 174 (33), 91 (100). Anal. calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.77; H, 6.85; N, 7.25.

3.7. (±)-1-Benzyloxycarbonyl-2-[N-(benzyloxycarbonyl)aminomethylpiperidine] (±)-7

To a solution of 2-aminomethylpyridine (2 g, 18.5 mmol) in methanol (10 ml), was added a solution of 3 N HCl (9 ml) and palladium hydroxide (20% on charcoal, 160 mg). The mixture was hydrogenated at 300 psi for 15 h at rt. After filtration on Celite, the solvent was concentrated under reduced pressure to give a white solid residue. ^{1}H NMR shows a mixture of bischloride salt (±)-**7** and a pyridinium salt of the starting material (1:1). The pyridinium salt (±)-**7** was precipitated from the mixture of MeOH–Et_2O. After filtration and removal of the solvent under reduced pressure, a pure piperidinium salt (±)-**6** was obtained as a white solid. The synthesis of the protected compound (±)-**7** was carried out using the general procedure for the preparation of the carbamate (*S*)-**7**, in 53% yield.

3.8. Determination of enantiomeric excess of (S)-7

A sample (20 μl) of a solution of (*S*)-**7** or (±)-**7** (3 mg) in a mixture of hexane:isopropanol, 80:20 (6 ml), was analyzed by HPLC with a flow rate of 0.8 cm^3 min^{-1}. Two peaks (t_R 10.113 and 13.060) for (±)-**7** and (t_R 10.949 and 14.978) for (*S*)-**7** were resolved.

3.9. (S)-1-Benzyl-2-formylpiperidine (S)-8

To a stirred solution of nitrile (*S*)-**4** (626 mg, 3.13 mmol) in 4 ml of CH_2Cl_2 at −78°C under N_2 atmosphere was added dropwise a 1 M solution of DIBAH in CH_2Cl_2 (4.17 ml). The resulting mixture was stirred at −78°C for 2 h, then poured into a 0°C solution of tartaric buffer (30 ml, pH 4). After being stirred for 2 h at 0°C, the solution was adjusted to pH 9 by addition of 1 N NaOH. The aqueous phase was extracted with ether (3×10 ml) and the combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and evaporated under vacuum to yield the aldehyde (*S*)-**8** (496 mg). The aldehyde is relatively stable after its purification but this process implies a considerable lost of yield; then, the crude aldehyde was immediately used without further purification in the next step of the synthesis. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.25–1.81 (m, 6H), 2.05 (m, 1H), 2.88 (m, 2H), 3.34 (d, *J*=13.4 Hz, 1H), 3.78 (d, *J*=13.4 Hz, 1H), 7.32 (m, 5H), 9.59 (d, *J*=3.96 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 24.7, 26.0, 51.0, 61.3, 70.5, 127.2, 128.2, 129.0, 137.5, 204.3.

3.10. (S)-cis-1-Benzyl-2-[1-propenyl]piperidine] (S)-9

A suspension of $Ph_3P(Et)(Br)$ (664 mg, 1.19 mmol) in Et_2O (16.37 ml) was vigorously stirred for 15 minutes under N_2 at rt and cooled to −65°C, then a solution of 1 M NaHMDS in THF (1.79 ml) was added. The resulting mixture was stirred for 20 min before the slow addition of a solution of the crude aldehyde (242 mg) in 2 ml of Et_2O. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, then filtered over silica gel and the solvent evaporated. The crude residue was purified

by flash chromatography on silica gel to afford the propenylpiperidine (*S*)-**9** as a colorless oil (243 mg, 95%); $[\alpha]_D^{25}$ (cis) −58.64 (*c*=1.03, $CHCl_3$), ee 91%; IR (KBr) υ (cis) 3026, 3024, 2933, 2854, 2933, 2854, 2791, 1658, 1604, 1450, 736, 717, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–1.75 (m, 7H), 1.70 (d, *J*=5.28 Hz, 3H), 1.92 (dt, *J*=11.4, 3.52 Hz, 1H), 2.80–3.0 (m, 1H), 3.08 (d, *J*=13.2 Hz, 1H), 4.07 (d, *J*=13.2 Hz, 1H), 5.50–5.68 (m, 2H, olefin), 7.15–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.4, 24.1, 25.8, 32.6, 52.4, 59.2, 59.6, 124.7, 126.5, 127.9, 129.2, 134.5, 139; MS (EI) m/z 215 M^+ (40), 174 (49), 91 (100)

*3.11. (R)-2-Propylpiperidine hydrochloride, (−)-coniine (R)-**10***

A suspension of (*S*)-**9** (170 mg, 0.79 mmol) and palladium hydroxide (20% on charcoal, 29 mg) in MeOH (3 ml) and 3 N HCl (1 ml) was hydrogenated at 40 psi and 40°C for 15 h. The resulting mixture was filtered over Celite and concentrated under reduced pressure to afford the coniine hydrochloride as a white solid (124 mg, 96%); $[\alpha]_D^{25}$ −5.2 (*c*=0.7, EtOH), ee 91%, lit.[18] $[\alpha]_D^{25}$ −5.8 (*c*=1, EtOH); ^1H NMR ($CDCl_3$) d 0.90 (t, *J*=7.1 Hz, 3H), 1.28–2.09 (m, 10H), 2.51–3.0 (m, 2H), 3.40 (br d, 1H), 9.25 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 13.61, 18.44, 22.05, 22.29, 28.00, 35.20, 44.64, 57.02. Anal. calcd for $C_8H_{18}NCl$: C, 58.70; H, 11.08; N, 8.56. Found: C, 58.75; H, 11.24; N, 8.64.

*3.12. (S)-1-Benzyl-2-piperidinecarboxylic acid ethyl ester (S)-**11***

To a solution of nitrile (*S*)-**4** (163 mg, 0.815 mmol) in dry EtOH (2 ml) at 0°C, was poured a saturated anhydrous solution of HCl gas in EtOH (3 ml). The resulting solution was stirred for 24 h at the same temperature. After removal of a part of the solvent under reduced pressure, a 0.5 N aqueous HCl solution (5 ml) was added and the solution stirred for 48 h at 0°C. Solid Na_2CO_3 was added slowly and the pH adjusted to between 8 and 9. The aqueous phase was extracted with ethyl acetate (3×5 ml) and the combined organic fractions were dried, filtered and evaporated under reduced pressure to afford a crude oil. The crude residue was purified by flash chromatography on silica gel (hexane:CH_2Cl_2:AcOEt, 7.5:1.5:1) to afford (*S*)-**11** as a colorless oil (140 mg, 70%); $[\alpha]_D^{25}$ −39.4 (*c*=0.6, $CHCl_3$), ee 91%; ^1H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.0 Hz, 3H), 1.57 (m, 2H), 1.84 (m, 2H), 2.13 (m, 2H), 2.94 (m, 2H), 3.12 (m, 1H), 3.40 (d, *J*=13.1 Hz, 1H), 3.81 (d, *J*=13.1 Hz, 1H), 4.23 (q, *J*=7.0 Hz, 2H) 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2, 22.5, 25.1, 29.5, 50.1, 60.2, 60.5, 64.6, 126.9, 128.0, 129.2, 138.0, 173.9; MS (EI) m/z 247 M^+ (<1), 174 (100), 91 (46).

*3.13. (S)-2-Piperidine-2-carboxylic acid hydrochloride (S)-**13***

A solution of the ester (*S*)-**11** (136.1 mg, 0.55 mmol) in 6 N HCl (5 ml) was refluxed for 10 h. The solution was concentrated under reduced pressure. Methanol (3×5 ml) was added and the solvent concentrated to yield a crude product as a solid material of *N*-benzylpipecolic acid (*S*)-**12**. ^1H NMR (MeOD) δ 1.85–2.15 (m, 6H), 1.50–62 (m, 1H), 3.33 (m, 1H), 3.63 (m, 1H), 4.20–4.45 (m, 1H), 4.87 (m, 1H), 7.73 (m, 5H); ^{13}C NMR (MeOD) δ 22.2, 23.2, 29.0, 52.5, 60.7, 65.6, 130.1, 131.1, 132.6, 171.5.

The *N*-benzylpipecolic acid (*S*)-**12** (171 mg) was dissolved in a (2:1) mixture MeOH:3 N HCl (3 ml) and palladium hydroxide (20% on charcoal, 29 mg) was added. The resulting mixture was hydrogenated for 15 h at room temperature and filtered over Celite. The solvent was concentrated under reduced pressure to afford (*S*)-**13** as a white solid (pure by ^1H and ^{13}C NMR), (124 mg, 96%); mp 261–264°C $[\alpha]_D^{25}$ −10.3 (*c*=0.2, H_2O), ee 91%, [lit.[19] mp 254–257°C, $[\alpha]_D^{25}$ −11.5 (*c*=1.07, H_2O)]; ^1H NMR

(D_2O) δ 1.45–1.70 (m, 3 H), 1.75–1.90 (m, 2H), 2.15–2.28 (m, 1H), 2.90–3.05 (m, 1H), 3.30–3.45 (m, 1H), 3.75–3.85 (m, 1H); ^{13}C NMR (D_2O) δ 24.2, 24.3, 28.7, 46.6, 60.1, 175.2.

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References

1. (a) Strunz, G. M.; Findlay, J. A. Pyridine and Piperidine Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp. 89. (b) Fodor, G. B.; Colasati, B. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 3, p. 1. (c) Numata, A.; Ibuka, I. Alkaloids from Ants and Other Insects. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, pp. 193. (d) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 17. (e) *Ibid.* 491–504. (f) Wuonola, M. A. *Org. Prep. Proced. Int.* **1992**, 583. (g) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581. (h) Harrison, T. *Cont. Org. Synth.* **1995**, *2*, 209. *Ibid.* **1996**, *3*, 259.
2. (a) Norton, T. R.; Benson, A. A.; Seibert, R. A.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1946**, *68*, 1330. (b) Banitt, E. H.; Conard G. J. *J. Labelled Compd. and Radiopharm.* **1981**, *28*, 713. (c) Becchietti, V.; Signorini, M.; Giordani, A. Eur. Pat. appl. EP 260, 041, 1988, (*Chem. Abstr.* **1988**, *109*, 92801g). (d) Terada, A.; Iizuka, Y.; Wachi. K.; Fujibayashi, K. Eur. Pat. Appl. EP 356, 247, 1990. (*Chem. Abstr.* **1990**, *113*, 78419g).
3. (a) Froelich, O.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron: Asymmetry* **1993**, *4*, 2335. (b) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.* **1994**, *60*, 297. (c) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098. (c) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.* **1994**, *60*, 297.
4. Froelich, O.; Desos P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 6700.
5. Perumattam, J.; Shearer, B. G.; Confer, W. L.; Mathew, R. M. *Tetrahedron Lett.* **1991**, *32*, 7183.
6. For recent synthesis of coniine, see: (a) Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047. (b) Moody, C. J.; Lighfot, A. P.; Gallagher, P. T. *J. Org. Chem.* **1997**, *62*, 746 and references cited therein. (c) Weymann, H.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151.
7. For asymmetric synthesis of pipecolic acid, see: (a) Berrien, J.-F.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1994**, *59*, 3769. (b) Fernández-García, C.; McKervey, A. *Tetrahedron: Asymmetry*, **1995**, *6*, 2905. For resolution of pipecolic acid, see: (c) Hardtman, G. E.; Houlihan, W. J.; Giger, A. US Patent, 4,760,065, Jul. 26, 1988. (*Chem. Abstr.* **1987**, *107*, 236730s). (d) Ng-Youn Chem. M. C.; Serreqi, A. N.; Huang, Q.; Kazlauskas, R. J. *J. Org. Chem.* **1994**, *59*, 2075.
8. Copeland, T. D.; Wondrak, E. M.; Tozser, J.; Roberts M. M.; Oroszlan, S. *Biochem. Biophys. Res. Commun.* **1990**, *169*, 310.
9. Af Ekenstam, B. T.; Bovin C. US Patent 4695576, 1987. (*Chem. Abstr.* **1988**, *108*, 57228n).
10. (a) Kikumoto, R.; Tamao, Y.; Tezuka, T.; Tonomura, S.; Hara, H.; Ninomiya, K.; Hijikata, A.; Okamoto, S.; *Biochemistry*, **1984**, *23*, 85. (b) Flynn, G. A.; Giruox, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914.
11. Smith III, A. B.; Condon, S. M.; McCauley, J. A.; Leazer Jr., J. L.; Leahy, J. W.; Maleczka Jr., R. E. *J. Am. Chem. Soc.* **1997**, *119*, 962.
12. Ireland, R. E. Gleason; J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem.* **1996**, *61*, 5856.
13. Boger, D. L.; Chen, J.-H.; Saionz, K. W. *J. Am. Chem. Soc.* **1996**, *118*, 1629.
14. (a) Effenberger, F. *Angew. Chem. Int. Ed. Eng.* **1994**, *33*, 1555. (b) North, M. *Synlett.* **1993**, 807. (c) Kanerva, L. T. *Acta Chem. Scand.* **1996**, *50*, 234.
15. (a) Effenberger, F.; Jäger J. **1997**, *62*, 3867 and references cited therein. (b) Effenberger, F.; Jäger, J.; *Chem. Eur. J.* **1997**, *3*, 1370.
16. Menéndez, E.; Brieva, R.; Rebolledo, F.; Gotor, V. *J. Chem. Soc., Chem. Commun.* **1995**, 989.
17. Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem.* **1986**, 314.
18. Gerrier, L.; Royer, J.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.
19. Hockless, D. C. R.; Mayadunne, R. C.; Wild, S. B.; *Tetrahedron: Asymmetry* **1995**, *6*, 3031.