HETEROCYCLES, Vol. 63, No. 3, 2004, pp. 655 - 661
Received, 20th November, 2003, Accepted, 8th January, 2004, Published online, 16th January, 2004

SYNTHESES OF 1,2,3,4,6,7,12,12b-OCTAHYDROINDOLO[2,3-*a*]-QUINOLIZINE AND HARMICINE USING A CHIRAL 1-ALLYL-1,2,3,4-TETRAHYDRO-β-CARBOLINE AS THE STARTING MATERIAL

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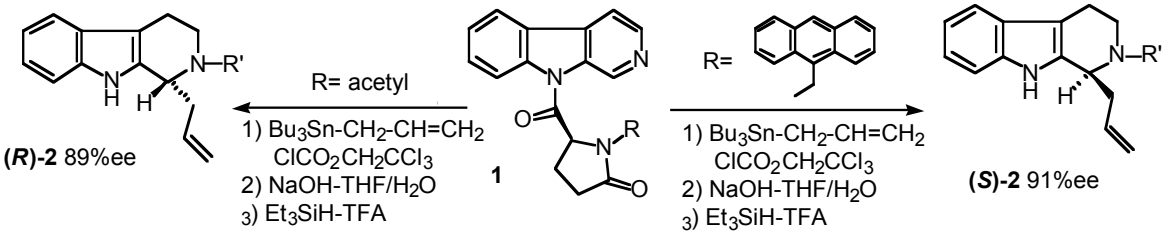
Abstract – Total syntheses of (*S*)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine and (*S*)-harmicine were carried out using chiral 1-allyl-1,2,3,4-tetrahydro-β-carboline as the starting material.

In recent years, we have developed a general method for the formation of a chiral center at the C-1 position of β-carboline nucleus using chiral auxiliaries derived from readily available amino acids and their derivatives.[1] Using the method, both enantiomers of the chiral 1-allyl derivatives (**2**) were obtained in a highly enantioselective manner by simply changing the *N*-protecting group of the chiral auxiliary derived from pyroglutamic acid (Scheme 1).



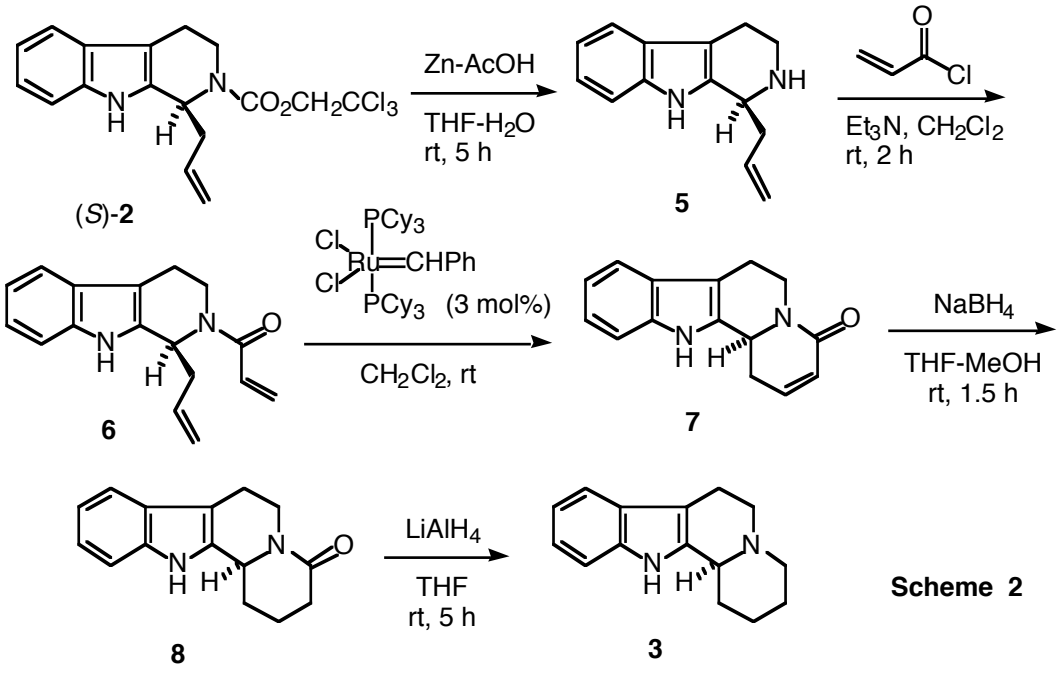
Scheme 1

Allyl group is a versatile tool for syntheses of other functional groups,[2] and there are several reports concerning the application of racemic allyl group at C-1 position of β-carboline to the synthesis of various indole alkaloids.[3] However, it has been well known that 1-substituted 1,2,3,4-tetrahydro-β-carboline derivatives are readily racemized under acidic conditions,[4] therefore, we decided to investigate the stability of the allyl adduct by transforming it to chiral natural products in rather straightforward ways. 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (**3**) was selected as the first target molecule because the synthesis of **3** was considered as a standard procedure to evaluate chiral synthetic

methods for various indole alkaloids.[5] Thereafter, the chiral precursor was applied to the synthesis of a natural product harmicine (**4**),[6] whose absolute configuration was not determined. This paper describes these results.[7]

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (**3**) is an alkaloid which was isolated from *Dragontomelum mangiferum*,[8] and has been a synthetic target as a model compound in connection with the preparation of structurally more complicated alkaloids. There have been several reports[5] concerning the asymmetric synthesis of the compound.

Our synthesis of **3** was commenced with the reaction of (*S*)-**2** with Zn-CH_3CO_2H in THF/H_2O to remove the trichloroethoxycarbonyl group (Scheme 2). The starting material ((*S*)-**2**) of 91% was obtained from the method reported earlier (overall yield 71% from β-carboline *via* 4 steps).[1d] The amine (**5**) thus obtained was allowed to react with acryloyl chloride in the presence of triethylamine to give the *N*-acryloyl derivative (**6**) in 88% yield. The compound (**6**) was treated with the Grubbs reagent to afford a ring-closing product (**7**). The C=C double bond in **7** was reduced with sodium borohydride to give a saturated amide (**8**) in an excellent yield. Single recrystallization of **8** raised the ee of the compound from 91% to 97%. Although the transformation of **8** to the target (**3**) was carried out according to the reported method,[5e] slight racemization occurred to give the product (**3**) in 85% yield and 90% ee.[9]

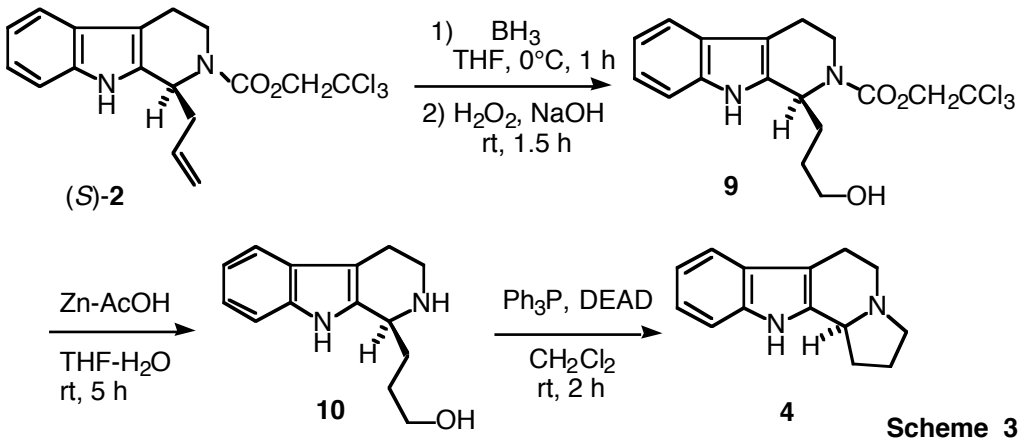


Scheme 2

Through the above transformation, it was found that the chiral allyl adduct (**2**) and its derivatives are stable under several reaction conditions. Thus, we next applied the compound (**2**) to the synthesis of an alkaloid whose stereochemistry was not determined.

Although 2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]indole (**4**) has been used as a starting material for racemic total synthesis of many alkaloids such as tubifoline, condyfoline, fluorocurarine *etc*.,[10] the compound had been thought to be a non-natural product. It was recently isolated, however, from the leaf extract of *Kopsia griffithii*, and named as harmicine. The absolute configuration of the C-11b

chiral center was assigned as (*S*), but the definitive evidence was not shown.[6] Therefore, we applied the allyl adduct (**2**) to the synthesis of harmicine in order to determine the absolute configuration. The synthetic scheme is shown below (Scheme 3).



Scheme 3

Since the report[6] suggested the structure of **4** as the (*S*) isomer, we selected (*S*)-**2** as a starting material. A standard hydroboration-oxidation procedure afforded a 1-(3-hydroxypropyl)-β-carboline (**9**) without any noticeable racemization in 79% yield. At first, we tried the hydroboration-oxidation procedure by the use of the amine (**5**) as a substrate expecting the shortening of the synthetic procedures. In this case, however, the expected product (**10**) was not obtained. The reduction of trichloroethoxycarbonyl group by zinc/acetic acid readily eliminated the group to give 1-(3-hydroxypropyl)-1,2,3,4-tetrahydro-β-carboline (**10**) in 77% yield. The compound (**10**) was recrystallized from hexane-AcOEt to give an optically pure form. Then a Mitsunobu procedure[11] was applied to **10** and the ring-closed product (**4**) was obtained in good yield with high enantiopurity (84% yield, 98% ee). All the values of the ee were obtained from the chiral HPLC analysis. We started the synthesis using the (*S*) isomer, and the racemization did not occur in the reaction process. The value of the specific rotation was, however, showed $[\alpha]^{17}_{D}=-108.31°$ (c 0.10, $CHCl_3$), which has an opposite sign for the reported value of (+)-(*S*)-harmicine. Therefore, the present study suggested that the naturally occurring harmicine has an (*R*) configuration.

In this paper, we described the application of the chiral allyl adducts derived from β-carboline to the syntheses of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine and harmicine in short steps. The results showed that the chiral allyl adduct (**2**) was of use as a starting material for asymmetric synthesis of indole alkaloids, and that the reported configuration of (+)-harmicine was reversed.[12] Application of the allyl adducts to syntheses of other chiral alkaloids is now under investigation.

EXPERIMENTAL

General Remarks. Melting points are uncorrected. ^1H and ^{13}C NMR spectra of $CDCl_3$ and CD_3OD solutions were recorded at 500 and 125 MHz, respectively, with tetramethylsilane (TMS) as an internal standard. FAB-HRMS spectra were measured using *p*-nitrobenzyl alcohol as a matrix.

Synthesis of 1-allyl-1,2,3,4-tetrahydro-β-carboline (5). To the solution of (*S*)-**2** (40 mg, 0.1 mmol), acetic acid (30 μL) in THF (0.5 mL)/H_2O (0.5 mL) was added zinc powder (38 mg, 0.5 mmol), and the mixture was allowed to react for 1 h at rt. Then the excess zinc was removed by filtration, and the filtrate was diluted with H_2O. The solution was basified with K_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave the product (**5**).

1-Allyl-1,2,3,4-tetrahydro-β-carboline (5) Yield 85%; Colorless granules from hexane-AcOEt; mp 118-119°C; $[\alpha]^{20}_D$= -116.40° (c 0.64, $CHCl_3$); ee=91% (chiralcel OD, λ=254 nm, *i*PrOH/hexane=1/2); ^{1}H-NMR ($CDCl_3$) δ: 1.72-1.85 (1H, brs), 2.54-2.59 (2H, m), 2.68-2.81 (2H, m), 3.03 (1H, ddd, *J*=12.8, 8.6, 5.3 Hz), 3.37 (1H, ddd, *J*=12.8, 5.0, 3.7 Hz) 4.16 (1H, tt, *J*=6.3, 1.8 Hz), 5.20-5.29 (2H, m), 5.92 (1H, ddt, *J*=17.1, 10.2, 7.0 Hz), 7.09 (1H, td, *J*=7.0, 1.1 Hz), 7.15 (1H, td, *J*=7.0, 1.3 Hz), 7.29 (1H, d, *J*=7.0 Hz), 7.48 (1H, d, *J*=7.0 Hz), 7.96 (1H, brs); ^{13}C-NMR ($CDCl_3$) δ: 22.7, 39.5, 42.9, 51.6, 109.1, 110.6, 117.9, 118.4, 119.2, 121.4, 127.1, 134.6, 135.4, 135.6. Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.01; H, 7.71; N, 13.21.

Synthesis of 1-allyl-1,2,3,4-tetrahydro-2-propenoyl-β-carboline (6). To the CH_2Cl_2 solution (5 mL) of the compound (**5**) (492 mg, 2.3 mmol) and triethylamine (644 μL, 4.6 mmol) was added acryloyl chloride (196 μl, 2.4 mmol), and the mixture was allowed to react for 2 h at rt. Then the solution was washed with H_2O and brine, dried over $MgSO_4$, and evaporated off. The residue was chromatographed on silica gel (hexane/AcOEt = 4) to give the product (**6**).

1-Allyl-1,2,3,4-tetrahydro-2-propenoyl-β-carboline (6) Yield 88%; Pale yellow granules from CH_2Cl_2-*i*Pr_2O; mp 139-141°C; $[\alpha]^{18}_D$= +105.41° (c 0.56, $CHCl_3$); ee=91% (chiralcel OJ-R, λ=254 nm, H_2O:CH_3CN=4:3). The compound was obtained as a mixture of two conformational isomers, and the spectral data of the major one are shown below. ^{1}H-NMR ($CDCl_3$) δ: 2.60-2.71 (2H, m), 2.76-2.88 (2H, m), 3.49-3.55 (1H, m), 4.16-4.20 (1H, m), 5.07-5.12 (2H, m), 5.76 (1H, dd, *J*=10.7, 1.8 Hz), 5.84-5.96 (2H, m), 6.35 (1H, dd, *J*=7.1, 1.8 Hz), 6.70 (1H, dd, *J*=16.8, 10.7 Hz), 7.06-7.10 (1H, m), 7.12-7.17 (1H, m), 7.30 (1H, d, *J*=8.2 Hz), 7.44 (1H, d, *J*=7.6 Hz), 8.63 (1H, s); ^{13}C-NMR ($CDCl_3$) δ: 22.3, 38.8, 41.0, 49.4, 107.6, 111.1, 117.9, 118.3, 119.4, 121.7, 126.5, 128.0, 128.2, 133.7, 134.3, 136.1, 166.1. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.81; H, 7.18; N, 10.26.

Metathesis of 1-allyl-1,2,3,4-tetrahydro-2-propenoyl-β-carboline. To the CH_2Cl_2 solution (5 mL) of the compound (**6**) (266 mg, 1.0 mmol) was added the Grubbs catalyst (2.5 mg, 0.03 mmol), and the mixture was allowed to react for 1 h at rt. Then the solution was diluted with ether, and the precipitate thus formed was collected by filtration. The solid was washed with a small amount of CH_2Cl_2 to give the desired product (**7**) in a pure form (50 mg). The filtrate was evaporated off to leave a residue, which was chromatographed on silica gel (AcOEt) to give the product (**7**) (140 mg).

6,7,12,12b-Tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (7). Yield 71%; A colorless powder from CH_2Cl_2-*i*Pr_2O; mp 229-231°C; $[\alpha]^{18}_D$= -425.61° (c 0.60, THF); ee=91% (chiralcel OJ-R, λ=254 nm, H_2O:CH_3CN=7:3). ^{1}H-NMR (DMSO-d_6) : δ 2.22-2.30 (1H, m), 2.64-2.71 (1H, m), 2.79-2.84 (2H, m), 3.03 (1H, dt, *J*=17.7, 5.8 Hz), 4.77-4.80 (1H, m), 4.87 (1H, dd, *J*=13.4, 4.6 Hz), 5.92 (1H, dd, *J*=9.8, 2.7 Hz), 6.80 (1H, ddd, *J*=9.2, 6.1, 1.8 Hz), 6.99 (1H, t, *J*=7.6 Hz), 7.07 (1H, t, *J*=7.6 Hz), 7.33 (1H, d, *J*=7.6 Hz), 7.44 (1H, d, *J*=7.6 Hz), 10.96 (1H, s); ^{13}C-NMR (DMSO-d_6): δ 20.5, 30.3, 38.2, 51.2, 107.0,

111.1, 117.8, 118.6, 121.1, 124.7, 126.1, 133.6, 136.3, 139.4, 164.1. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.22; H, 5.92; N, 11.68.

Synthesis of 6,7,12,12b-tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (8). To the THF/MeOH(10:1) solution (1 mL) of the starting material (**7**) (24 mg, 0.1 mmol) was added sodium borohydride (4 mg, 0.1 mmol), and the mixture was allowed to react for 2.5 h at rt. Then H_2O was added to the mixture, which was extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated off to leave a residue, which was chromatographed on silica gel (AcOEt) to give the product.

6,7,12,12b-Tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (8). Yield 93%; A colorless powder from EtOH-H_2O ; mp 250-255°C; $[\alpha]^{17}_D$= -234.1° (c 0.20, $CHCl_3$); ee=97% (chiralcel OJ-H, λ=254 nm, hexane:*i*PrOH=1:1). ^{1}H-NMR ($CDCl_3$) : δ 1.73-2.00 (3H, m), 2.36-2.49 (2H, m), 2.56-2.61 (1H, m), 2.74-2.92 (3H, m), 4.76-4.79 (1H, m), 5.14-5.22 (1H, m), 7.12 (1H, td, *J*=7.4, 1.1 Hz), 7.18 (1H, td, *J*=7.2, 1.2 Hz) 7.34 (1H, d, *J*=7.9 Hz), 7.51 (1H, d, *J*=7.7 Hz), 8.04 (1H, br s); ^{13}C-NMR ($CDCl_3$): δ 19.4, 21.0, 29.1, 32.4, 40.1, 54.4, 109.6, 110.9, 118.4, 119.8, 122.1, 126.9, 133.3, 136.2, 169.2.

Synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (3). To the THF solution (2 mL) of the starting material (**8**) (48 mg, 0.2 mmol) was added $LiAlH_4$ (30 mg, 0.8 mmol) under Ar atmosphere, and the mixture was allowed to react for 5 h at rt. The mixture was cooled to –0°C, and H_2O was added to quench the excess $LiAlH_4$. Then aqueous 1 M NaOH solution (4.7 mL) and CH_2Cl_2 (24 mL) were added to the mixture, and the precipitate thus formed was filtered off using Celite. The filtrate was extracted with CH_2Cl_2, which was dried over $MgSO_4$, and evaporated off. The residue was chromatographed on alumina (CH_2Cl_2) to give the product (**3**) (41 mg).

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (3) Yield 85%; Pale yellow granules from EtOH-H_2O; mp 149-152°C; $[\alpha]^{16}_D$= -73.97° (c 1.99, MeOH); ee=90% (chiralcel OD, λ=254 nm, hexane:*i*PrOH=2:1). ^{1}H-NMR and ^{13}C-NMR ($CDCl_3$) spectra were consistent with the reported ones. ^{1}H-NMR ($CDCl_3$): δ 1.37-1.53 (2H, m), 1.64-1.75 (2H, m), 1.81 (1H, d, *J*=12.5 Hz), 1.97 (1H, dd, *J*=12.5, 2.7 Hz), 2.31 (1H, td, *J*=11.1, 3.9 Hz), 2.52-2.67 (2H, m), 2.90-3.02 (3H, m), 3.16 (1H, d, *J*=11.0 Hz), 7.00 (1H, td, *J*=7.3, 1.2 Hz), 7.05 (1H, td, *J*=7.5, 1.5 Hz), 7.21 (1H, d, *J*=7.3 Hz), 7.39 (1H, d, *J*=7.5 Hz), 7.69 (1H, bs).; ^{13}C-NMR ($CDCl_3$): δ 21.5, 24.3, 25.7, 29.9, 53.5, 55.7, 60.2, 108.0, 110.7, 118.1, 119.3, 121.2, 127.4, 135.0, 135.9.

Synthesis of 1,2,3,4-tetrahydro-1-(3-hydroxypropyl)-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (9). To the THF solution (10 mL) of (*S*)-**2** (1.95 g, 5 mmol) was added 1M BH_3-THF solution (7.5 mL, 7.5 mmol) at 0°C, and the mixture was allowed to react for 1 h at 0°C. Then H_2O (10 mL) was added to quench excess BH_3, and 3M aqueous NaOH solution (2 mL) and 30% aqueous H_2O_2 solution (2 mL) were successively added to the mixture, which was allowed to react another 30 min at rt. Thereafter, saturated aqueous NaCl solution was added, and the mixture was extracted with CH_2Cl_2. The organic layer thus obtained was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel (AcOEt: CH_2Cl_2=1:1) to give the alcohol (**9**) (1.596 g).

1,2,3,4-Tetrahydro-1-(3-hydroxypropyl)-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (9) Yield 79%; Colorless oil; $[\alpha]^{14}_D$= +77.36° (c 0.97, $CHCl_3$); ee=91% (chiralcel OD, λ=254 nm, hexane:*i*PrOH=1:3). The compound was obtained as a mixture of two conformational isomers, and the

spectral data of the major one are shown below. ^{1}H-NMR ($CDCl_3$): δ 1.74-1.80 (2H, m), 1.83-2.00 (1H, m), 2.02-2.13 (1H, m), 2.25 (1H, brs), 2.76 (1H, dd, *J*=15.4, 2.9 Hz), 2.90 (1H, td, *J*=15.5, 5.5 Hz), 3.23-3.36 (1H, m), 3.73-3.89 (2H, m), 4.49 (1H, dd, *J*=13.6, 4.5 Hz), 4.79 (1H, d, *J*=12.0 Hz), 4.83 (1H, d, *J*=12.0 Hz), 5.42-5.48 (1H, m), 7.07-7.17 (2H, m), 7.28 (1H, d, *J*=7.7 Hz), 7.47 (1H, d, *J*=7.3 Hz), 8.75 (1H, s); ^{13}C-NMR ($CDCl_3$): 21.6, 28.2, 31.4, 38.8, 51.7, 62.5, 75.1, 95.6, 107.7, 111.0, 118.0, 119.4, 121.8, 126.6, 133.7, 135.9, 154.4. Anal. Calcd for $C_{17}H_{19}N_2O_3$ Cl_3: C, 50.33; H, 4.72; N, 6.90. Found: C, 50.47; H, 4.71; N, 6.55.

Synthesis of 1,2,3,4-tetrahydro-1-(3-hydroxypropyl)-β-carboline (10). To the THF/H_2O (1:1) solution (1 mL) of the alcohol (**9**) (40 mg, 0.1 mmol) and AcOH (30 μL) was added zinc powder (38 mg, 0.5 mmol), and the mixture was allowed to react for 1 h at rt. Then, excess Zn was removed by filtration, and the filtrate was diluted with H_2O. The solution was basified with saturated aqueous K_2CO_3 solution, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue (18 mg, 77%), which was an almost pure product. The ee of the compound was confirmed as 96% using HPLC (Chiralcel OD-R, MeOH). A crystallization with AcOEt-hexane raised the ee to 99.6%.

1,2,3,4-Tetrahydro-1-(3-hydroxypropyl)-β-carboline (10) Yield 77%; Colorless powder from AcOEt-hexane; mp 133.2-133.8°C ; $[\alpha]^{17}_D$= -74.72° (c 0.81, CH_3OH); ee=99.6% (chiralcel OD-R, λ=254 nm, MeOH). ^{1}H-NMR (CD_3OD): δ 1.60-1.78 (3H, m), 1.99-2.06 (1H, m), 2.64 (1H, dtd, *J*=15.9, 4.4, 1.6Hz), 2.69-2.75 (1H, m), 2.89 (1H, ddd, *J*=12.5, 8.8, 4.8 Hz), 3.22 (1H, dt, *J*=12.5, 5.6 Hz) 3.59 (2H, td, *J*=6.2, 1.0 Hz) 3.97-3.99 (1H, m) 6.96 (1H, ddd, *J*= 7.9, 7.0, 1.0 Hz) 7.03 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz), 7.27 (1H, dt, *J*=8.0, 1.0 Hz), 7.37 (1H, dt, *J*=7.9, 1.0 Hz); ^{13}C-NMR (CD_3OD): δ 22.8, 29.4, 32.4, 43.2, 53.7, 63.0, 108.8, 111.8, 118.5, 119.6, 121.9, 128.6, 136.6, 137.7. Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.90; H, 8.04; N, 12.02.

Synthesis of harmicine (4). To the CH_2Cl_2 solution (10 mL) of the compound (**10**) (198 mg, 0.86 mmol) was added triphenyl phosphine (270 mg, 1.03 mmol) and diethyl azodicarboxylate (179 mg, 1.03 mmol), and the mixture was allowed to react for 3 h at rt. Then CH_2Cl_2 was added to the mixture, which was extracted with 1M aqueous HCl (12 mL x 4). The aqueous layer was basified with K_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on NH silica gel (AcOEt) to give the product. The spectral data were consistent with those of the reported one except the value of the specific rotation.

(*ent*)-Harmicine (**4**) Yield 84%; Colorless powder from CH_2Cl_2-hexane; mp 161.5-164.5°C ; $[\alpha]^{17}_D$= -108.31° (c 0.10, $CHCl_3$); ee=98% (chiralcel OD, λ=254 nm, hexane:*i*PrOH=1:3). ^{1}H-NMR ($CDCl_3$): δ 1.80-1.96 (3H, m), 2.21-2.32 (1H, m), 2.65 (1H, ddt, *J*=15.4, 4.7, 2.0 Hz), 2.83-2.99 (3H, m), 3.08 (1H, ddd, *J*=12.8, 10.6, 4.6 Hz), 3.32 (1H, ddd, *J*=12.8, 5.1, 2.0 Hz), 4.21-4.24 (1H, m), 7.09 (1H, td, *J*=7.1, 1.3 Hz), 7.13 (1H, td, *J*=7.1, 1.3 Hz), 7.29 (1H, d, *J*=7.1 Hz), 7.49 (1H, d, *J*=7.1 Hz), 7.92 (1H, br s); ^{13}C-NMR ($CDCl_3$): δ 17.9, 23.5, 29.5, 46.0, 49.4, 57.0, 107.7, 110.6, 118.0, 119.3, 121.3, 127.2, 135.1, 135.8.

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