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Both Enantiomers of *N*-Boc-indoline-2-carboxylic Esters

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An immobilized form of *Candida antarctica* lipase (Chirazyme L-2) catalyzed enantioselective hydrolysis ($E > 1000$) of *N*-Boc-indoline-2-carboxylic acid methyl ester. The reaction proceeded efficiently at 60 °C, a temperature over the melting point of substrate, in the conversion of 49.9% to provide the hydrolyzed product, (*S*)-carboxylic acid with >99.9% ee and the unreacted (*R*)-ester with 99.6% ee. A newly developed expeditious route to the racemic substrate (a total of six steps, 60% yield), starting from aniline and ethyl α-methylacetoacetate, established the scalable chemoenzymatic synthesis of the desired compounds in both enantiomerically pure forms.

Enantiomerically pure *N*-protected forms of indoline-2-carboxylic esters (**1**, Fig. 1) are the starting material of diamines, which are involved in catalytic asymmetric syntheses such as enantiofacially selective reductions.[1] They also play important roles in medicinal chemistry[2] and natural product synthesis.[3] So far, the traditional preferential crystallization of the diastereomeric amine salt[4] and an enzymatic hydrolysis of a non-*N*-protected form, pentyl 2-indolinecarboxylate,[5] have been reported for the enantiomeric resolution of racemates, along with the asymmetric syntheses.[6] Our recent success in the enzyme-catalyzed enantiomeric resolution of the *N*-protected form of proline esters[7] (**2**, Fig. 1) prompted us to establish a scalable way to **1**, involving expeditious synthesis of the racemic precursors.

For establishment of the conditions of kinetic enantiomeric resolution, the direct determination of the enantiomeric excess (ee) of the enzyme-catalyzed reaction product and/or the unreacted substrate is the most important process so that the enantiomeric ratio (*E* value)[8] and the conversion should be evaluated as quickly as possible. Between two candidates, Cbz derivative **3a** and Boc form **4a** (Fig. 1), the direct analysis of the ee of the former was successful (ChiralCel OB), but for the latter, the chromatographic determination of the ee was possible, only after derivatization to the corresponding alcohol **5**.

This situation prompted us to take (±)-**3a** as the initial objective for elaboration of the reaction conditions. Although *C. antarctica* lipase (Chirazyme L-2, immobilized form) showed an excellent enantioselectivity ($E > 200$) on (±)-**3a** (Scheme 1), as inferred from the structurally similar Cbz-proline ester **2**, there was a big difference from **2**, namely, the very low reaction rate. The reason for this was apparently the very low solubility

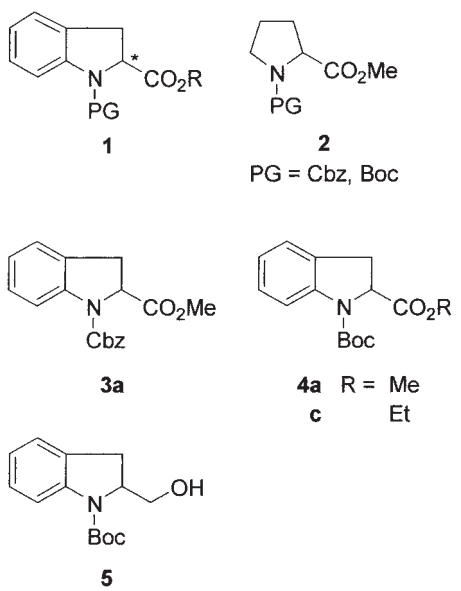
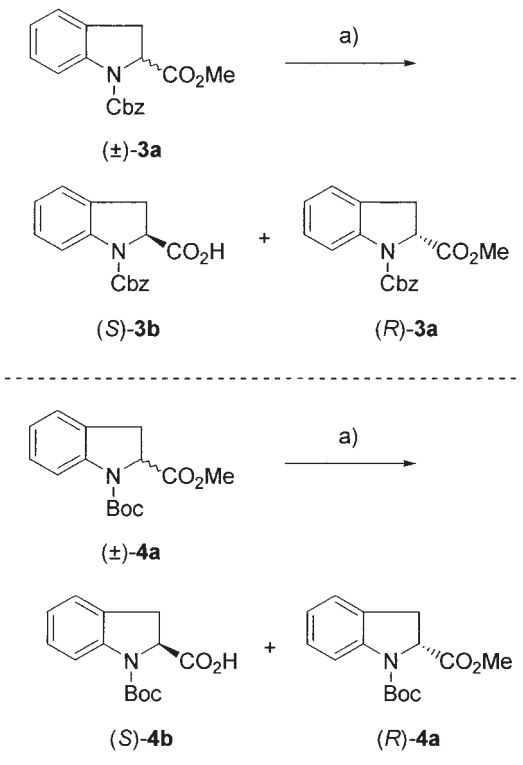


Fig. 1.



Scheme 1.

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due to the crystalline property of (±)-**3a** (80.0–80.6 °C). The addition of acetone, a water-miscible solvent,[9] in a two-phase reaction with toluene, was not effective, and only resulted in low (6–22%) consumption of the initial racemate. The addition of a detergent, Tween-80, could enhance its conversion to 49% with the retention of high enantioselectivity ($E > 200$), however, the purification of the product from this additive turned out to be a formidable task.

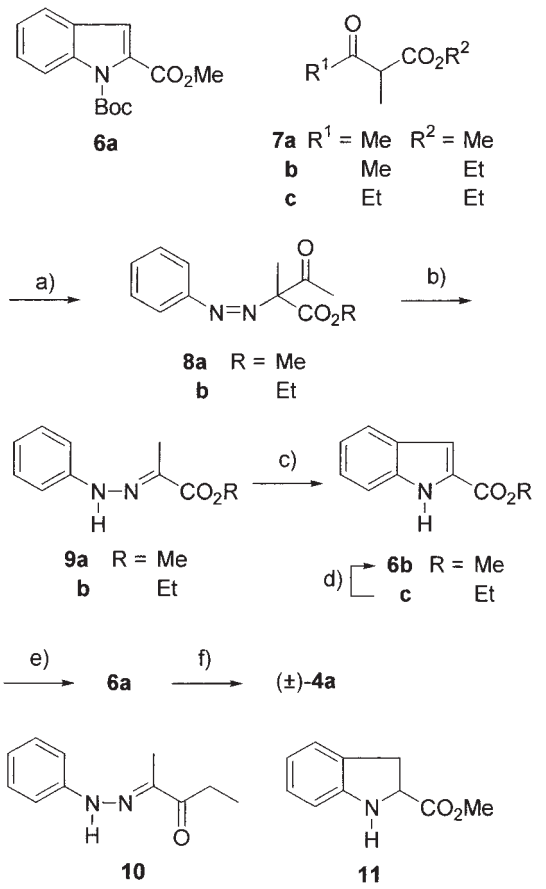
As this immobilized form of lipase (L-2) has substantial stability even at high temperature,[10] we next tried the hydrolysis reaction at a temperature of 85 °C, expecting that the enzyme-catalyzed hydrolysis would be facilitated on the molten substrate over the melting point. The reaction proceeded with the E value of 120, at the conversion of 30% to give the enzymatically hydrolyzed product (*S*)-**3b** (97.2% ee) and the unreacted substrate (*R*)-**3a** (41.4% ee).

An alternative candidate, Boc form (±)-**4a**, turned out to be an excellent substrate. As the melting point of the racemic form (54.1–54.5 °C) is lower than that of **3a** (see above), the reaction proceeded very smoothly at a lower reaction temperature (60 °C). The successful reaction gave the enzymatically hydrolyzed product (*S*)-**4b** (>99.9% ee) and the unreacted substrate (*R*)-**4a** (99.6% ee) with the E value over 1000, and the conversion reached 49.9% (Scheme 1). An ethyl ester (±)-**4c** (Fig. 1), which is an oil even at room temperature, was expected to be hydrolyzed at the conventional temperature, however, the reaction was very slow even at 50 °C, to result in conversion of as low as 28.9%, although the enantioselectivity was still high ($E > 1000$). The retardation is probably due to an increased steric hindrance of the ethyl ester.[11]

At this juncture, we turned our attention to attempts for an efficient preparation of the substrate (±)-**4a**, which is indispensable to establish a "chemo-enzymatic" synthesis. As the key intermediate, we selected the corresponding Boc derivative **6a**[12] (Scheme 2) of indole-2-carboxylic acid.[13] Methyl α-methylacetoacetate (**7a**) and aniline were chosen as the starting material through Japp–Klingemann azo ester synthesis.[14]

Toward this end, methyl acetoacetate was methylated,[15] and the resulting **7a** that contains 9% of α,α-dialkylated by-product[16] was submitted to the coupling reaction with benzenediazonium salt to give a mixture of an α-azo ester (**8a**) and α-hydrazone ester (**9a**).[17] The rather acid-labile **8a** was readily converged to **9a**, through a retro-Claisen condensation, by treatment with aqueous acetic acid (total 59% from **7a**). Fischer indole cyclization of **9a** in 30% HBr–acetic acid[4a] worked well to give the desired product **6b** in 80% yield.

The choice of the ethyl ester in the starting material brought about some advantages. The commercially available, pure ethyl ester **7b** was derived to a mixture of **8b** (63%) and **9b** (23%). Although the mixture of **8b** and **9b** was directly treated in aqueous HCl in ethanol, according to the previous paper,[14b] the reaction resulted in a very complex mixture. Then, the azo ester **8b** was converted to **9b**, and the combined yield of **9b** was remarkably enhanced to as high as 81%, compared with **9a**. In the Fischer indole cyclization with HBr–acetic acid, also an enhanced (85%) yield of **6c** was also recorded. The product was treated with a catalytic amount of DBU in methanol to give the corresponding methyl ester **6b** in good yield. The use of readily available homolog **7c** from ethyl propionate via a newly



a) aq. KOH, benzenediazonium chloride;
b) aq. AcOH; c) 30% HBr, AcOH; d) DBU, MeOH;
e) Boc_2O, DMAP; f) Mg, MeOH.

Scheme 2.

developed Claisen condensation[18] was also attempted. The enolate formation of this compound with an increased hydrophobicity was very slow and the hydrolysis of the ester predominated under the same conditions used for Japp–Klingemann azo ester synthesis. The major product under the treatment was a hydrazone **10**[19] by way of the decarboxylative hydrazone formation from the intermediate, azo carboxylic acid.

To route the optimum course from **6b** to (±)-**4a**, preliminary experiments provided an important suggestion: the *t*-butoxycarbonylation of indole-2-carboxylic ester **6b** was quite faster (at room temperature, 1 h, 99%) than that of the indoline-2-carboxylic ester **11** (at room temperature, 40 h, 69% of **4a**; 27% recovery of **11**). The difference is supposed to be due to the increased steric hindrance of the adjacent methoxycarbonyl group over the lone pair electron of the heterocyclic secondary amine. The indole derivative **6a** became available from **6c** in 96% yield in two steps. Accordingly, the remaining task was the selective hydrogenation on the C-2 and C-3 positions of indole to indoline. Inspired by the successful result on the reduction of **6b** with magnesium in methanol,[20] we submitted the Boc derivative **6a** to this reduction. The reaction worked well and the desired product (±)-**4a** was obtained in 92% yield. The Boc ester **6a** was highly susceptible to electron transfer re-

duction, and the use of alkali metal[21] only resulted in deprotection of the Boc group into CO and *t*-BuOH or resulted in over-reduction of the methoxycarbonyl group to a hydroxymethyl group. In the case of the use of magnesium in methanol, the undesired reaction via ketene formation could be suppressed due to the co-existing magnesium methoxide. Moreover, the seven-membered chelate structure[22] involving the magnesium ion stabilized the intermediate to prevent the release of methoxide. There is obviously an advantage that the feasibility of every steps in large quantity makes our route scalable, compared with the previous synthesis of (±)-**4a** which started from the metallation of Boc-indole at C-2 position with *t*-BuLi and the subsequent methoxycarbonylation.[12a]

In conclusion, an expeditious chemo-enzymatic route to both enantiomers of *N*-Boc-indoline-2-carboxylic esters, starting from ethyl α-methylacetoacetate (**7b**) and aniline, was established.

Experimental

General. No melting points were corrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 infrared spectrometer on KBr pellets or liquid film on NaCl. ^{1}H NMR spectra were recorded on a JEOL JNM EX-270 (270 MHz) or JEOL JNM GX-400 (400 MHz) spectrometer using $CDCl_3$ or DMSO-d_6 as a solvent and with tetramethylsilane as an internal standard. Analytical and preparative thin-layer chromatography (TLC) were developed on E. Merck Silica Gel 60 F_{256} plates (No. 5715; 0.25 mm and No. 5744; 0.50 mm), respectively. High-performance liquid chromatography (HPLC) analyses were performed with a SSC-5410 (Senshu Scientific Co., Ltd.) liquid chromatograph. Column chromatography was carried out with silica gel 60 (spherical, 100–210 μm, Kanto Chemical Co.37558-79). Optical rotations were recorded with a JASCO DIP-360 polarimeter. Melting points were measured by Yanaco MP-S3.

Lipase-Catalyzed Enantioselective Hydrolysis of Methyl (±)-1-*t*-Butoxycarbonyl-indoline-2-carboxylate [(±)-4a]. To a suspension of (±)-**4a** (1.39 g, 5.01 mmol) in 0.1 M phosphate buffer solution (pH 7.0, 50 mL) was added *Candida antarctica* lipase (Chirazyme L-2, c-f, 2.50 g) at 60 °C. After having been vigorously stirred at 60 °C for 30 h, the mixture was cooled to room temperature and acidified by 4 M hydrochloric acid to pH 2.5. The mixture was diluted with EtOAc and filtered through a Celite pad. The filtrate was extracted with EtOAc three times and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (75 g). Elution with hexane–EtOAc (14:1) afforded (*R*)-**4a** (0.700 g, 50%) as colorless needles, and the further elution with hexane–EtOAc (1:2) gave (*S*)-**4b** (0.640 g, 49%) as a colorless solid.

(*S*)-**4b**: Mp 126.0–126.4 °C (lit.[1d] 124.1–124.8 °C); $[\alpha]_D^{20}$ −77.5 (*c* 1.03, $CHCl_3$) [lit.[1d] $[\alpha]_D^{20}$ −77.3 (*c* 1.00, $CHCl_3$)]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (9H, s), 3.01 (1H, d, J = 16.4 Hz), 3.51 (1H, dd, J = 12.0, 16.4 Hz), 4.75 (1H, dd, J = 4.2, 11.5 Hz), 6.92 (1H, dd, J = 7.1, 7.1 Hz), 7.16 (2H, m), 7.38 (0.3H, br), 7.73 (0.7H, br), 12.91 (1H, br); IR (KBr) 3500–2800 (br), 2978, 2650, 2567, 1711 (C=O), 1603, 1487, 1394, 1321, 1281, 1242, 1169, 1149, 1047 cm^{-1}. The spectral data were identical with those reported previously.[1d] Due to the limited rotation of *N*-Boc group, the signals on C-7 split unequally. Found: C, 63.87; H, 6.67; N, 5.25%. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32%. A small portion of (*S*)-**4b** was treated with $TMSCHN_2$ to afford (*S*)-**4a**. Then the methyl ester (*S*)-**4a** was reduced with $NaBH_4$ to afford an alcohol (*S*)-**5**,[6a] on which the ee was estimated to be 99.9% by the HPLC analysis. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.58 (9H, br), 2.80 (2H, br), 3.34 (1H, dd, J = 10.2, 16.3 Hz), 3.73 (2H, m), 4.60 (1H, br), 6.95 (1H, dd, J = 7.4, 7.4 Hz), 7.12–7.18 (2H, m), 7.55 (1H, br); IR (neat) 3427 (OH), 2976, 2931, 1697 (C=O), 1603, 1485, 1392, 1287, 1255, 1169, 1140, 1041, 1018 cm^{-1}. The HPLC conditions were as follows: column, ChiralCel OJ; eluent, hexane/*i*-PrOH = 29/1; flow rate, 0.5 mL/min; retention time, 26.8 (*S*) and 31.0 (*R*) min.

(*R*)-**4a**: Mp 51.3–52.0 °C (lit.[6a] 51.0–53.0 °C); $[\alpha]_D^{20}$ +72.3 (*c* 1.06, $CHCl_3$) [lit.[6a] $[\alpha]_D^{22}$ −73 (*c* 0.0088, $CHCl_3$) for (*S*)-**4a**]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (9H, br), 3.11 (1H, dd, J = 4.4, 16.6 Hz), 3.51 (1H, dd, J = 11.7, 16.1 Hz), 3.75 (3H, s), 4.87 (1H, br), 6.95 (1H, dd, J = 7.3, 7.3 Hz), 7.11 (1H, d, J = 7.3 Hz), 7.20 (1H, dd, J = 7.3, 7.3 Hz), 7.50 (0.3H, br), 7.89 (0.7H, br); IR (KBr) 2983, 1753 (C=O), 1703 (C=O), 1603, 1487, 1390, 1321, 1284, 1261, 1207, 1169, 1151, 1049 cm^{-1}. The spectral data were identical with those reported previously.[3a] Due to the limited rotation of *N*-Boc group, the proton NMR signal on C-7 split unequally. Found: C, 64.91; H, 6.82; N, 5.03%. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05%. The ee was estimated to be 99.6% by the HPLC analysis of (*R*)-**5** as above.

Lipase-Catalyzed Enantioselective Hydrolysis of Methyl (±)-1-Benzyloxycarbonyl-indoline-2-carboxylate [(±)-3a]. To an emulsion of (±)-**3a**[23] (101 mg, 0.324 mmol) and Tween-80 (18.4 mg) in 0.1 M phosphate buffer (pH 7.0, 4.0 mL) and toluene (1.1 mL) was added *Candida antarctica* lipase (Chirazyme L-2, c-f, 202 mg) at 50 °C. This mixture was vigorously stirred at 50 °C for 36 h. A similar workup to that given above afforded (*R*)-**3a** (51 mg, 51%) and (*S*)-**3b** (46 mg, 47%). A small portion of (*S*)-**3b** was treated with $TMSCHN_2$ to afford (*S*)-**3a** for the HPLC analysis.

(*S*)-**3a**: Mp 81.0–81.5 °C; $[\alpha]_D^{21}$ −71.4 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (1H, dd, J = 4.0, 16.7 Hz), 3.57 (3H, br s), 3.41–3.75 (1H, m), 4.90 (1H, m), 5.07–5.35 (2H, m), 6.83–7.94 (9H, m); IR (KBr) 2949, 1751 (C=O), 1703 (C=O), 1601, 1487, 1408, 1369, 1317, 1269, 1207, 1182, 1167, 1049 cm^{-1}. The absolute configuration was confirmed by comparing its sign of rotation with that of the authentic (*S*)-**3a** [$[\alpha]_D^{21}$ −76.6 (*c* 0.99, $CHCl_3$)], prepared from the commercially available (*S*)-indoline-2-carboxylic acid (Aldrich. 34,680-2). The spectral data were identical with those reported previously.[1a] Due to the limited rotation of *N*-Cbz group, the NMR signals broadened. Found: C, 69.31; H, 5.66; N, 4.44%. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50%. The ee of (*S*)-**3a** was determined to be 96.9% by the HPLC analysis, and the conditions were as follows: column, ChiralCel OB; eluent, hexane/*i*-PrOH = 5/1; flow rate, 0.5 mL/min; retention time, 36.0 (*R*) and 58.4 (*S*) min.

(*R*)-**3a**: Mp 78.1–78.8 °C; $[\alpha]_D^{20}$ +69.6 (*c* 1.10, $CHCl_3$). The ee was estimated to be 92.5% by the HPLC analysis as above. Found: C, 69.06; H, 5.68; N, 4.31%. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50%.

Ethyl 2-Methyl-2-phenylazoacetoacetate (8b) and Ethyl 2-(Phenylhydrazono)propionate (9b). According to the reported procedure,[14b] to a mixture of aniline (3.73 g, 40.1 mmol), conc. HCl (10.1 mL), and water (19.0 mL) was added dropwise a solution of $NaNO_2$ (2.88 g, 41.7 mmol) in water (5.4 mL) with external cooling in an ice–salt bath (−5 °C). After the addition, the mixture was stirred at 0 °C for 15 min and then brought to pH 3.5 by the addition of NaOAc (3.15 g, 38.4 mmol). In another flask separately, to a solution of ethyl α-methylacetoacetate (**7b**, 5.01 g, 34.8

mmol) in ethanol (27 mL) was added a solution of KOH (1.95 g, 34.7 mmol) in water (2.71 mL) at 0 °C, followed by the addition of ice (54.2 g). After stirring at 0–4 °C for 1 h, the benzenediazonium salt prepared above was added in one portion to the enolate solution. The mixture was then adjusted to pH 6.0; this was stirred at 0 °C for 3 h, and was further stirred at 4 °C for 12 h. The mixture was extracted with EtOAc three times and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford a dark viscous residue (8.2 g). A small portion of the residue (72.0 mg) was purified by preparative TLC [20 × 20 cm, two plates, developed with hexane–EtOAc (4:1)] to afford **8b** (47.8 mg) as red oil and **9b** (15.0 mg) as yellow oil. The yields of **8b** and **9b** were estimated to be 63% and 23%, respectively.

8b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, t, $J = 7.1$ Hz), 1.68 (3H, s), 2.35 (3H, s), 4.30 (2H, q, $J = 7.1$ Hz), 7.50 (3H, m), 7.77 (2H, m). **9b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.38 (3H, t, $J = 7.1$ Hz), 2.07 (3H, s), 4.33 (2H, q, $J = 7.1$ Hz), 6.92 (1H, t, $J = 7.3$ Hz), 7.15–7.33 (4H, m), 7.70 (1H, br). Its NMR spectrum was identical with that reported previously.[24]

Ethyl 2-(Phenylhydrazono)propionate (9b). A mixture of **8b** and **9b** (1.03 g) in AcOH (7.5 mL) and water (1.5 mL) was stirred at room temperature for 15 h, and the reaction mixture was poured into ice-cooled sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc three times, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (40 g). Elution with hexane–EtOAc (7:1) afforded **9b** (732 mg, 81%) as yellow crystals. Mp 116.0–116.5 °C (lit.[24] 116.0–117.0 °C). Its NMR spectrum was identical with the sample above.

Methyl 2-(Phenylhydrazono)propionate (9a). In a similar manner, methyl α-methylacetoacetate [**7a**, containing 9% of α,α-dimethylated by-product:[16] δ ($CDCl_3$) 1.36 (6H, s), 2.12 (3H, s)] was converted to **9a**. Mp 101.0–101.5 °C (lit.[17] 93.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (3H, s), 3.85 (3H, s), 6.95 (1H, t, $J = 7.3$ Hz), 7.15–7.33 (4H, m), 7.72 (1H, br). Its NMR spectrum was identical with that reported previously.[17]

Ethyl Indole-2-carboxylate (6c). A suspension of **9b** (1.00 g, 4.85 mmol) in 30% HBr solution of acetic acid (5.0 mL, 25.1 mmol) was stirred at room temperature for 2 h. After the reaction mixture was poured into an ice-cooled 0.1 M phosphate buffer solution (pH 8.0), the mixture was extracted with EtOAc three times. The combined organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (46 g). Elution with hexane–EtOAc (9:1) afforded **6c** (0.780 g, 85%) as colorless needles. Mp 121.4–122.1 °C (lit.[25] 121.0–124.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.42 (3H, t, $J = 7.1$ Hz), 4.42 (2H, q, $J = 7.1$ Hz), 7.12–7.44 (4H, m), 7.69 (1H, d, $J = 8.1$ Hz), 9.07 (1H, br). Its NMR spectrum was identical with that reported previously.[25]

In the same manner, **6b** was prepared from **9a** in 80% yield. Mp 150.0–151.3 °C (lit.[26] 147.0–150.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.95 (3H, s), 7.12–7.44 (4H, m), 7.69 (1H, d, $J = 8.1$ Hz), 9.00 (1H, br). Its NMR spectrum was identical with that reported previously.[12b]

Methyl 1-*t*-Butoxycarbonylindole-2-carboxylate (6a). To a solution of **6c** (571 mg, 3.02 mmol) in MeOH (15 mL) was added DBU (105 mg, 0.690 mmol), and the mixture was stirred under reflux for 3 h. After cooling, the mixture was concentrated in vacuo. To the solution of crude **6b** in THF (12 mL) was added Boc_2O (780 mg, 3.57 mmol) and DMAP (4-dimethylaminopyridine, 44.0 mg, 0.360 mmol). After stirring for 1 h at room temperature, the reaction mixture was diluted with water. The mixture was extracted with EtOAc three times, and the combined organic layer was washed with sat. aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (45 g). Elution with hexane–EtOAc (24:1) afforded **6a** (795 mg, 96%) as a colorless solid. Mp 65.0–65.5 °C (lit.[12b] 63.0–65.0 °C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.60 (9H, s), 3.92 (3H, s), 7.10 (1H, s), 7.25 (1H, dd, $J = 7.4$, 7.4 Hz), 7.41 (1H, dd, $J = 7.4$, 7.4 Hz), 7.60 (1H, d, $J = 7.4$ Hz), 8.09 (1H, d, $J = 7.4$ Hz). Its NMR spectrum was identical with that reported previously.[12] Found: C, 65.60; H, 6.28; N, 4.99%. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09%.

Methyl (±)-1-*t*-Butoxycarbonylindoline-2-carboxylate [(±)-4a]. To a solution of **6a** (338 mg, 1.23 mmol) in MeOH (8 mL) was added Mg (92.0 mg, 3.78 mmol) at 0 °C. The mixture was stirred at 0 °C for 4 h, and then sat. aq. NH_4Cl solution was added. The mixture was extracted with EtOAc three times, and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (20 g). Elution with hexane–EtOAc (16:1) afforded **4a** (316 mg, 92%) as colorless needles. Mp 54.1–54.4 °C. The ^{1}H NMR and IR data were identical with those of (*R*)-**4a** given before. Found: C, 64.94; H, 6.69; N, 5.03%. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05%.

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