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Efficient Enantioselective Total Synthesis of (−)-Horsfiline

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Abstract: A new efficient and concise enantioselective synthetic method for (−)-horsfiline is reported. (−)-Horsfiline could be obtained from diphenylmethyl *tert*-butyl malonate in 9 steps (32%, >99% *ee*) by using the enantioselective phase-transfer catalytic allylation (91% *ee*) as the key step. This approach can be applied as a practical route for the large-scale synthesis of spirooxindole natural products, which enables a systematic investigation of their biological activity to be performed.

Keywords: allylation · enantioselectivity · synthetic methods · total synthesis · horsfiline

Introduction

The spirooxindole structure has been frequently found in biologically active alkaloids such as coerulescine, horsfiline, elacomine, spirotryprostatin B, and strychnofoline (Figure 1).[1] Their unique spiro structures have challenged many synthetic chemists to develop an efficient synthetic method for the construction of the quaternary stereogenic center.[2] Among the various spirooxindole alkaloids, (−)-horsfiline was first isolated in 1991 from the leaves of the *Horsfieldia superba* plant by Bodo et al.[3] Up until now, many synthetic methods have been developed for the synthesis of horsfiline.[4] However, only four cases of enantiomerically enriched horsfiline were reported.[5]

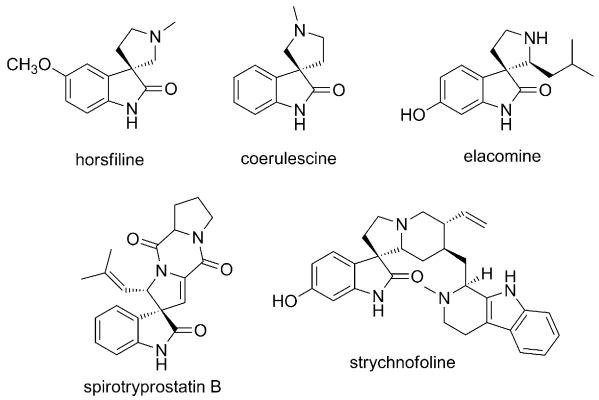

Figure 1. Biologically active spirooxindole alkaloids.

In 1994, Borschberg et al. confirmed the absolute configuration of horsfiline by the synthesis of both enantiomers through a diastereoselective oxidative rearrangement of chiral tetrahydro-β-carboline precursors, derived from an (L)-5-hydroxytryptophan.[5a] In 1999, Fuji et al. employed a chiral reagent for the α-nitroolefination of α-allyloxindole to introduce the quaternary chiral center.[5b] In 2001, Palmisano et al. set the pyrrolidine moiety by using the asymmetric cycloaddition of an azomethine ylide with chiral alcohol auxiliary substituted α,β-unsaturated ester, which subsequently formed the oxindole by intramolecular lactamization.[5c] In 2006, Trost et al. employed the first catalytic method of a palladium-catalyzed asymmetric allylation of 3-carboxyoxindoles to establish the spirostereogenic center of (−)-horsfiline (8 steps, 11%, key step 84% enantiomeric excess (*ee*)).[5d] In this paper, we report a new and efficient synthetic method for the preparation of (−)-horsfiline through the enantioselective phase-transfer catalytic α-allylation of malonate.[6]

Results and Discussion

Very recently, we reported a new synthetic method for chiral α,α-dialkylmalonates (**2**) by the enantioselective phase-transfer catalytic (PTC) α-alkylation of diphenylmethyl *tert*-butyl α-alkylmalonates (**1**) in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**3**) and successfully proved its usefulness by conversion to versatile chiral intermediates for the construction of the quaternary carbon center including the oxindole skeleton (Scheme 1).[7] Given this set of results, we attempted to apply our new method to the synthesis of a representative spirooxindole alkaloid,

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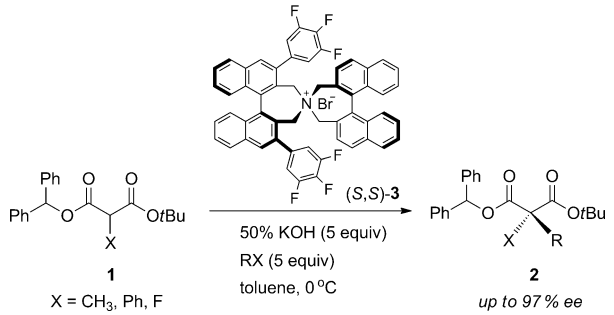
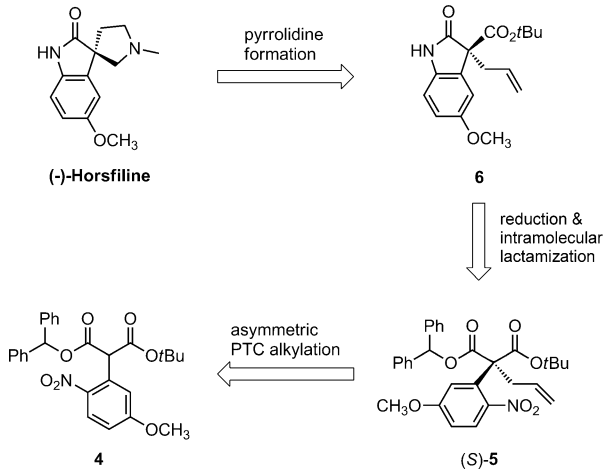


Scheme 1. Enantioselective PTC α-alkylation of malonates.

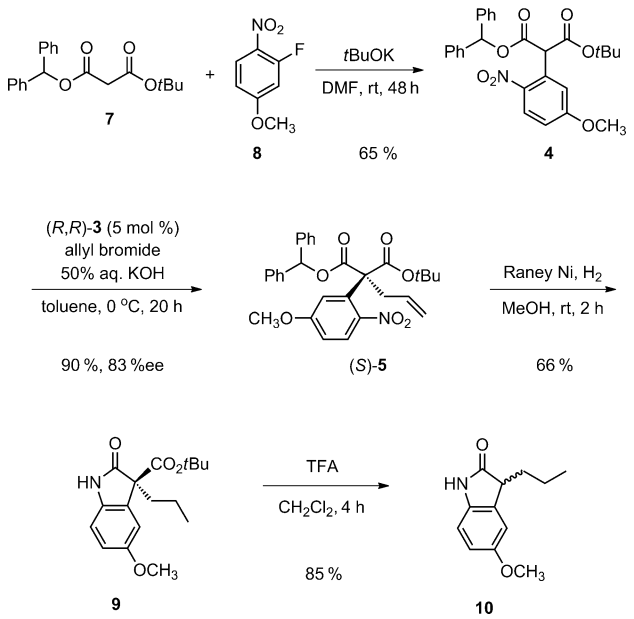
(−)-horsfiline, as the first application of our methodology for the total synthesis of a natural product.

As shown in the retrosynthetic analysis (Scheme 2), the spirooxindole skeleton can, in principle, give rise to the formation of *N*-methylpyrrolidine through the chemical conversion of α,α-disubstituents of oxindole **6**, which can be obtained by intramolecular lactamization of (*S*)-**5** after reduction of the nitro group. Optically active (*S*)-**5** can be derived from the enantioselective phase-transfer catalytic allylation of **4** in the presence of (*R*,*R*)-**3**.



Scheme 2. First retrosynthetic analysis.

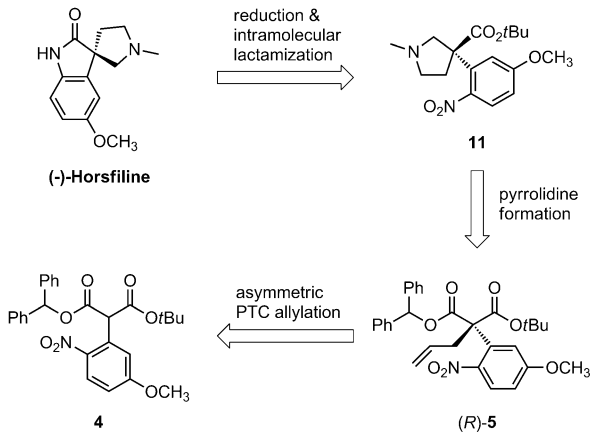
First, substrate (**4**) for PTC allylation was prepared from diphenylmethyl *tert*-butyl malonate (**7**)[7] (Scheme 3). Nucleophilic aromatic substitution of **7** with 2-fluoro-4-methoxy-1-nitro-benzene (**8**)[8] under *t*BuOK base conditions in dimethylformamide (DMF) at room temperature afforded α-arylmalonate **4** (65%). As a preliminary study, the enantioselective allylation of **4** was performed under the previously optimized phase-transfer catalysis condition.[7] The PTC allylation of **4** in the presence of (*R*,*R*)-**3**, along with allyl bromide (5.0 equiv) and 50% KOH (aq., 5.0 equiv) at 0 °C in toluene, gave the allylated compound (*S*)-**5** (90%, 83% *ee*). Before we investigated the optimization of PTC allylation to obtain higher enantioselectivity, we first studied the possibility of our retrosynthetic approach. Selective reduction of



Scheme 3. Enantioselective PTC α-allylation and oxindole formation.

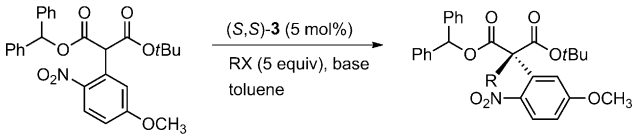
nitro group in **5** was attempted to obtain α-allyloxindole. However, several trials with various reduction conditions were not successful, and both the nitro and α-allyl group of **5** were reduced to afford **9**. In addition, the removal of the *tert*-butyl ester group of **9**, obtained through the reduction by using Raney Ni under atmospheric H_2, was accompanied with decarboxylation under the trifluoroacetic acid (TFA) conditions due to the β-keto functionality of oxindole **9**, resulting in α-propyloxindole **10**. Due to the non-selective reduction and the decarboxylation during conversion of *tert*-butyl ester group, we had to change our synthetic strategy.

The second retrosynthetic analysis is shown in Scheme 4. We changed the synthetic route from construction of oxindole moiety to introducing the *N*-methylpyrrolidine moiety from (*R*)-**5**. The PTC allylation of **4** was then optimized by variation of base and temperature conditions including allylating agents in the presence of (*S*,*S*)-**3** instead of (*R*,*R*)-**3**.



Scheme 4. Second retrosynthetic analysis.

Table 1. Optimization of PTC α-allylation of **4**.



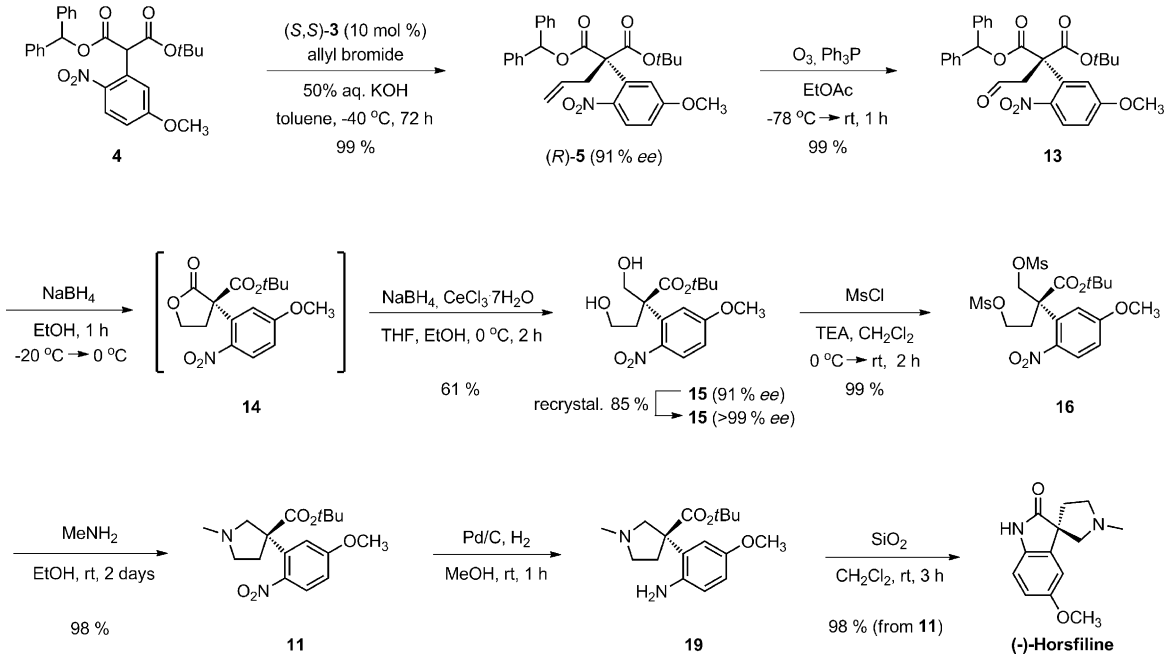
4 **12**

Entry	RX	Base	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1		50% KOH	0	12	83	82
2		50% KOH	−20	24	97	88
3		50% KOH	−40	72	90	90
4[c]		50% KOH	−40	72	99	91
5		KOH(s)	−40	48	80	81
6		50% KOH	−20	72	85	86
7		50% KOH	−20	5	93	87
8		50% KOH	−20	2	95	71

[a] Yields of the isolated products. [b] Enantioselectivity was determined by HPLC analysis of α-allylated product (**12**) by using a chiral column (Chiralpak AD-H) with hexanes/2-propanol as eluents. [c] 10 mol% of catalyst **3** was used.

As shown in Table 1, lower reaction temperatures gave higher enantioselectivity with longer reaction time with 50% KOH as the base (entries 1–3). The increase of the amount of catalyst afforded higher chemical yield with comparable enantioselectivity (Table 1, entries 3 and 4). Solid–liquid PTC conditions using solid KOH base afforded both lower enantioselectivity and lower chemical yield than those of liquid–liquid PTC conditions using 50% KOH base (Table 1, entries 3 and 5). With regard to the allylating agent, allyl bromide showed the highest enantioselectivity among the used electrophiles at −20°C. We previously improved the enantioselectivity in the PTC allylation steps during the total synthesis of (−)-paroxetine and (+)-isonitramine by switching "allyl bromide" with "2-bromoallyl bromide" as an alternative allylating reagent.[9] However, increased enantioselectivity was not observed (Table 1, entry 6), and the other 2-substituted allylic bromides also showed lower enantioselectivity (Table 1, entries 7 and 8). We speculate that such no improvement of enantioselectivity is caused by the *ortho*-nitro group of **4**, which might inhibit a favorable binding conformation with PTC catalyst **3**. The best enantioselectivity was obtained in the case of allyl bromide with 50% KOH base conditions at −40°C (Table 1, entry 4, 99%, 91% *ee*).

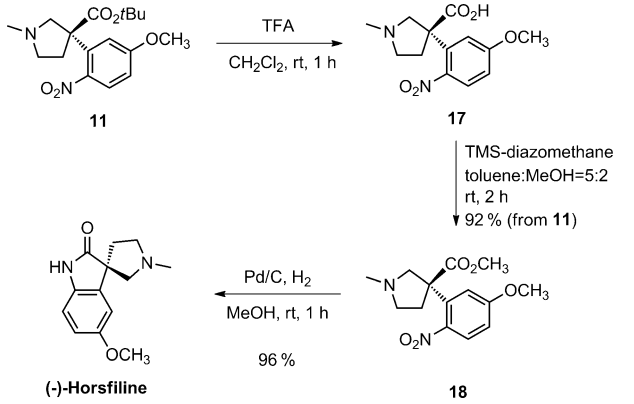
Ozonolysis of **5**, followed by reductive work up in the presence of triphenylphosphine afforded the corresponding aldehydes **13** (99%; Scheme 5). Aldehyde **13** was reduced by sodium borohydride in ethanol at −20°C to provide lactone **14**. Without purification, the lactone moiety of **14** could be selectively reduced again to the corresponding diols **15** in situ by additional treatment of sodium borohydride with cerium(III) trichloride heptahydrate and tetrahydrofuran (THF) as a co-solvent at 0°C (61% from **13**).[10] As a side reaction, removal of the α-hydroxymethyl group was partially observed by deformylation through the retroaldol reaction of **15**, caused by the α-nitrophenyl group. The major enantiomer of diol **15** could be easily purified as a single stereoisomer (>99% *ee*) with 85% yield by recrystallizing out the minor/major enantiomer pair (91% *ee*) using hexane and ethyl acetate (5:1). Dimesylation of **15** (99%), followed by double N-alkylation using excess meth-



Scheme 5. Completion of total synthesis of (−)-horsfiline.

ylamine successfully afforded *N*-methylpyrrolidines **11** (98%).

We then performed the final spiro-cyclization step. Spirooxindole natural products including (−)-horsfiline, are easily racemized through a retro-Mannich reaction in the presence of an acid.[11,5d] Therefore, the last spiro-cyclization step from oxindole or pyrrolidine intermediates under acidic conditions should be avoided. For the cyclization to form oxindole from **11** in neutral conditions, we first needed to convert the *tert*-butyl ester group to a smaller methyl ester group. The removal of *tert*-butyl ester of **11** in the TFA acidic conditions (**17**), followed by methyl ester formation using excess TMS-diazomethane afforded the corresponding methyl ester **18**, which was readily cyclized to the final oxindole product, (−)-horsfiline, under catalytic Pd/C hydrogenation (Scheme 6).



Scheme 6. Initial spirooxindole formation.

However, we also attempted to direct cyclization in the presence of the *tert*-butyl ester group to shorten the overall process. Reduction of the nitro group of **11** was performed by catalytic hydrogenation using Pd/C under atmospheric H_2. Unfortunately, the corresponding amine **19** was the only product obtained instead of further cyclized spirooxindole (Scheme 5). However, interestingly, during purification of the obtained amine **19** through column chromatography (SiO_2), the cyclized spirooxindole was partially obtained together with the corresponding amine **19**. We speculate that silica gel (SiO_2) may directly catalyze spiro cyclization in the presence of the *tert*-butyl ester group. Finally, (−)-horsfiline ($[\alpha]_D^{20} = -8.50$ ($c = 5$, MeOH); $[\alpha]_D^{20} = -7.20$ ($c = 1$, MeOH)[3]) was successfully obtained by stirring amine **19** with silica gel (SiO_2) in CH_2Cl_2 without racemization (98%, >99% *ee*). As far as we know, this is the first synthetic method to introduce the *N*-methylpyrrolidine part prior to the construction of the oxindole ring structure among the previously reported enantioselective synthetic methods.

Conclusion

As the first application of the enantioselective phase-transfer catalytic α-alkylation of malonate system,[7] a new efficient synthetic approach for the synthesis of (−)-horsfiline was developed. (−)-Horsfiline was synthesized in 9 steps (including an in situ step) from diphenylmethyl *tert*-butyl malonate (**7**) by using enantioselective PTC allylation as the key step (32% overall yield, >99% *ee*). Both the high enantioselectivity and chemical yield make this approach a practical route for the large-scale synthesis of spirooxindole natural products, which allows a systematic investigation of their biological activity.[14] Further applications to the synthesis of spirooxindole compounds are now under investigation.

Experimental Section

General materials and methods: All reagents bought from commercial sources were unpurified. Organic solvents were concentrated under reduced pressure by using a Büchi rotary evaporator. As the commercially available KOH was a pellet type, solid KOH should be grinded to the powder form. 50% v/w aqueous KOH was used as a stock solution. Phase-transfer catalyst (*S*,*S*)-**3** and (*R*,*R*)-**3**[12] (Wako) was purchased from the commercial source. TLC analyses were performed using Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm). Flash column chromatography was carried out by using Merck Kieselgel 60 (230–400 mesh). Instrument (Hitachi, L-2130) and software (Hitachi, Version LaChrom 8908800–07) were used for HPLC analysis. The enantiomeric excess (*ee*) of the products were determined by HPLC using 4.6×250 mm DIACEL Chiralpak AD-H, Chiralcel OD-H, Chiralcel OJ-H columns. Infrared (IR) spectra were recorded on a JASCO FT/IR-300E and Perkin–Elmer 1710 FT spectrometer. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were measured on JEOL JNM-LA 300 (300 MHz (^{1}H)) spectrometer, JEOL JNM-GSX 400 [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer, using $[D_3]CHCl_3$ as solvent, and were reported in ppm relative to $CHCl_3$ ($\delta = 7.24$ ppm) for ^{1}H NMR spectroscopy and relative to the central $CDCl_3$ ($\delta = 77.23$ ppm) resonance for ^{13}C NMR spectroscopy. The unit of coupling constants (J) in the ^{1}H NMR spectra was Hz. Low-resolution mass spectra (MS) were recorded on a VG Trio-2 GC-MS spectrometer and high-resolution mass spectra (HRMS) were measured on a JEOL JMS 700, JEOL JMS 600-W (FAB), or Agilent 6530 Q-TOF (ESI) spectrometer. Melting points were measured on a Büchi B-540 melting point apparatus and were not corrected. Optical rotations were measured on a JASCO polarimeter P-2000 series.

Preparation of 2-fluoro-4-methoxy-1-nitrobenzene (8): Iodomethane (3.74 mL, 60 mmol) was added to a solution of 3-fluoro-4-nitrophenol (4.7 g, 30 mmol) and potassium carbonate (10.37 g, 75 mmol) in acetone (70 mL). The reaction mixture was enveloped in aluminium foil and stirred for 44 h at room temperature. The reaction mixture was evaporated and diluted with ethyl acetate (600 mL). The organic layer was washed with brine (2×150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 6:1) to afford **8** (5.03 g, 98% yield) as a pale-yellow solid. M.p. 62.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$–8.03 (m, 1H), 6.76–6.68 (m, 2H), 3.88 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.28$ (d, $J = 10.8$ Hz), 157.44 (d, $J = 263.5$ Hz), 127.85(d, $J = 0.9$ Hz), 110.33(d, $J = 3$ Hz), 103.13(d, $J = 24.2$ Hz), 56.30 ppm; IR (KBr): $\tilde{\nu} = 1607$, 1511, 1341, 849 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_7H_7FNO_3]^+$: 172.0410; found: 172.0420; The spectral data was identical with the reported data.[8]

1-Benzhydryl 3-*tert*-butyl 2-(5-methoxy-2-nitrophenyl) malonate (4): Potassium *tert*-butoxide (617 mg, 5.5 mmol) was added to a stirred solution

of benzhydryl *tert*-butyl malonate (**7**, 1.63 g, 5 mmol) in DMF (12 mL) at 0 °C. After stirring for 10 min, a solution of 2-fluoro-4-methoxy-1-nitrobenzene (**8**, 856 mg, 5 mmol) in DMF (3 mL) was slowly added to the reaction mixture and stirred for 48 h.[13] The reaction mixture was evaporated and diluted with ethyl acetate (150 mL), quenched with saturated aqueous solution of ammonium chloride (40 mL), washed with brine (40 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20:1–7:1) to afford **4** (1.55 g, 65 % yield) as a yellow solid. M.p. 68.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, J = 9.2 Hz, 1H), 7.37–7.22 (m, 10H), 6.98 (s, 1H), 6.89 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 6.77 (d, J = 2.7 Hz, 1H), 5.47 (s, 1H), 3.65 (s, 3H), 1.40 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.84, 165.94, 141.59, 139.21, 131.33, 128.50, 128.46, 128.13, 128.11, 127.88, 127.30, 127.26, 115.51, 114.18, 83.25, 78.50, 55.91, 55.71, 27.72 ppm; IR (KBr): $\tilde{\nu}$ = 2979, 1732, 1583, 1518, 1339, 1252, 1143, 752, 700 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{27}H_{28}NO_7]^+$: 478.1866; found: 478.1862.

(*S*)-1-Benzhydryl 3-*tert*-butyl 2-allyl-2-(5-methoxy-2-nitrophenyl)malonate (5): Allyl bromide (85 μL, 1 mmol) was added to a solution of **4** (95.5 mg, 0.2 mmol) and (*R*,*R*)-3,4,5-trifluorophenyl-NAS bromide ((*R*,*R*)-**3**, 9.1 mg, 0.01 mmol) in toluene (0.7 mL). At 0 °C, aqueous 50 % KOH (112 μL, 1 mmol) was added to the reaction mixture and stirred for 20 h.[7] EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixture was diluted with ethyl acetate (30 mL), washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 15:1) to afford (*S*)-**5** (93.2 mg, 90 % yield) as a yellow oil. The enantioselectivity was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane/2-propanol = 95:5), flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm, retention time, *R* (minor) 16.2 min, *S* (major) 21.5 min, 83 % *ee*]. $[\alpha]_D^{20}$ = −11.19 (83 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, J = 9.1 Hz, 1H), 7.30–7.17 (m, 10H), 6.91 (s, 1H), 6.82 (dd, J_1 = 9.1 Hz, J_2 = 2.7 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 5.73–5.59 (m, 1H), 4.95 (dd, J_1 = 17.1 Hz, J_2 = 1.8 Hz, 1H), 4.88 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 3.66 (s, 3H), 3.22 (d, J = 7.0 Hz, 2H), 1.25 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.43, 167.02, 162.48, 142.22, 139.44, 139.39, 135.45, 133.30, 128.36, 128.32, 127.95, 127.93, 127.36, 127.29, 118.82, 117.17, 111.89, 83.36, 78.37, 63.88, 55.63, 39.48, 27.52 ppm; IR (KBr): $\tilde{\nu}$ = 2979, 1732, 1580, 1520, 1346, 1252, 1152, 1018, 843, 756, 700 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{30}H_{32}NO_7]^+$: 518.2179; found: 518.2201.

(*S*)-*tert*-Butyl 5-methoxy-2-oxo-3-propylindoline-3-carboxylate (9): Raney nickel (13 mg) was added to a stirred solution of (*S*)-**5** (52 mg, 0.1 mmol) in methanol (2 mL) under H_2 gas and stirred for 2 h.[7] The reaction mixture was filtered through the Celite 545 and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 3:1) to afford **9** (20.2 mg, 66 % yield) as a white solid. M.p. 160.6 °C; $[\alpha]_D^{20}$ = 44.31 (83 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.10 (s, 1H), 6.83–6.72 (m, 3H), 3.75 (s, 3H), 2.22–2.02 (m, 2H), 1.34 (s, 9H), 1.23–1.06 (m, 1H), 1.02–0.88 (m, 1H), 0.81 ppm (t, J = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.24, 168.23, 155.74, 134.96, 130.58, 113.09, 110.33, 82.26, 61.49, 55.72, 36.16, 27.70, 17.06, 14.02 ppm; IR (KBr): $\tilde{\nu}$ = 3251, 2962, 1738, 1492, 1251, 1203, 1158, 1033 cm^{-1}; HRMS (FAB) : *m/z* calcd for $[C_{17}H_{23}NO_4]^+$: 305.1627; found: 305.1635.

5-Methoxy-3-propylindolin-2-one (10): Trifluoroacetic acid (0.5 mL) was added to a solution of **9** (31 mg, 0.1 mmol) in dichloromethane (1.5 mL). At room temperature, the reaction mixture was stirred for 4 h. The reaction mixture was evaporated and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1:1) to afford **10** (17.5 mg, 85 % yield) as a white solid. M.p. 101.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.18 (s, 1H), 6.82–6.69 (m, 3H), 3.76 (s, 3H), 3.44 (t, J = 6.1 Hz, 1H), 2.02–1.82 (m, 2H), 1.51–1.21 (m, 2H), 0.90 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.84, 155.62, 135.22, 131.36, 112.00, 111.55, 109.92, 55.76, 46.51, 32.63, 19.01, 13.99 ppm; IR (KBr): $\tilde{\nu}$ = 3222, 2958, 1705, 1490, 1208, 1034 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{12}H_{15}NO_2]^+$: 205.1103; found: 205.1100.

General procedure for the asymmetric PTC allylation of 4: Substituted allyl bromide (2 mmol) was added to a solution of 1-benzhydryl 3-*tert*-butyl 2-(5-methoxy-2-nitrophenyl) malonate (**4**, 191 mg, 0.4 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide ((*S*,*S*)-**3**, 18.3 mg, 0.02 mmol) in toluene (1.4 mL). At the designated temperature, the base (2 mmol) was added to the reaction mixture and stirred for designated time. EYELA PSL-1400 was used for low temperature stirring and the stirring rate was 7. The reaction mixtures was diluted with ethyl acetate (50 mL), washed with brine (2 × 15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 15:1) to afford **5** or **12a–c**.

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-allyl-2-(5-methoxy-2-nitrophenyl)malonate (5): Following the general procedure, the reaction was started with allyl bromide (169 μL, 2 mmol), (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**3**, 36.6 mg, 0.04 mmol). At −40 °C, aq 50 % KOH (225 μL, 2 mmol) was added to the reaction mixture. After stirring for 72 h, (*R*)-**5** was obtained as a yellow oil (204.9 mg, 99 % yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane/2-propanol = 95:5), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *R* (major) 15.9 min, *S* (minor) 21.6 min, 91 % *ee*. $[\alpha]_D^{20}$ = 6.62 (91 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (d, J = 9.1 Hz, 1H), 7.30–7.17 (m, 10H), 6.91 (s, 1H), 6.82 (dd, J_1 = 9.1 Hz, J_2 = 2.7 Hz, 1H), 6.66 (d, J = 2.7 Hz, 1H), 5.73–5.59 (m, 1H), 4.95 (dd, J_1 = 17.1 Hz, J_2 = 1.8 Hz, 1H), 4.88 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 3.66 (s, 3H), 3.22 (d, J = 7.0 Hz, 2H), 1.25 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.43, 167.02, 162.48, 142.22, 139.44, 139.39, 135.45, 133.30, 128.36, 128.32, 127.95, 127.93, 127.36, 127.29, 118.82, 117.17, 111.89, 83.36, 78.37, 63.88, 55.63, 39.48, 27.52 ppm; IR (KBr): $\tilde{\nu}$ = 2979, 1732, 1580, 1520, 1346, 1252, 1152, 1018, 843, 756, 700 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{30}H_{32}O_7N]^+$: 518.2179; found: 518.2201.

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-(2-bromoallyl)-2-(5-methoxy-2-nitrophenyl) malonate (12a): Following the general procedure, the reaction was started with 2,3-dibromopropene (196 μL, 2 mmol). At −20 °C, aq 50 % KOH (225 μL, 2 mmol) was added to the reaction mixture. After stirring for 72 h, (*R*)-**12a** was obtained as a yellow oil (202.6 mg, 85 % yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane/2-propanol = 95:5), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *R* (major) 10.1 min, *S* (minor) 23.5 min, 86 % *ee*. $[\alpha]_D^{20}$ = 52.92 (86 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, J = 9.0 Hz, 1H), 7.31–7.22 (m, 10H), 7.0 (s, 1H), 6.82 (dd, J_1 = 9.0 Hz, J_2 = 2.7 Hz, 1H), 6.58 (d, J = 2.7 Hz, 1H), 5.70 (s, 1H), 5.38 (d, J = 1.7 Hz, 1H), 3.82 (dd, J_1 = 22.0 Hz, J_2 = 15.4 Hz, 2H), 3.59 (s, 3H), 1.22 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.83, 166.15, 162.06, 142.97, 139.11, 138.94, 133.20, 128.43, 128.38, 128.10, 128.06, 128.01, 127.83, 127.47, 127.36, 122.75, 118.41, 112.88, 84.02, 78.88, 64.84, 55.53, 44.83, 27.33 ppm; IR (KBr): $\tilde{\nu}$ = 2979, 1737, 1580, 1521, 1348, 1252, 1207, 1184, 1147, 757, 700 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{30}H_{31}BrNO_7]^+$: 596.1284; found: 596.1299.

(*R*,*E*)-1-Benzhydryl 3-*tert*-butyl 2-(but-2-en-1-yl)-2-(5-methoxy-2-nitrophenyl) malonate (12b): Following the general procedure, the reaction was started with crotyl bromide (206 μL, 2 mmol). At −20 °C, aq 50 % KOH (225 μL, 2 mmol) was added to the reaction mixture. After stirring for 5 h, (*R*)-**12b** was obtained as a yellow oil (197.5 mg, 93 % yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane/2-propanol = 95:5), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *R* (major) 18.9 min, *S* (minor) 21.5 min, 87 % *ee*. $[\alpha]_D^{20}$ = −12.45 (87 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, J = 9.0 Hz, 1H), 7.27–7.24 (m, 10H), 6.92 (s, 1H), 6.86 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1H), 6.81 (d, J = 2.5 Hz, 1H), 5.47–5.26 (m, 2H), 3.73 (s, 3H), 3.16 (d, J = 6.2 Hz, 2H), 1.47 (d, J = 5.9 Hz, 3H), 1.29 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.38, 166.99, 162.54, 142.25, 139.56, 135.90, 129.81, 128.28, 128.14, 127.86, 127.78, 127.29, 127.22, 125.29, 117.00, 111.72, 83.01, 78.18, 63.83, 55.61, 38.55, 27.52, 17.78 ppm; IR (KBr): $\tilde{\nu}$ = 2979, 1732, 1580, 1520, 1346, 1258, 1202, 1184, 1152, 757, 701 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{31}H_{34}NO_7]^+$: 532.2335; found: 532.2317.

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-(5-methoxy-2-nitrophenyl)-2-(3-methylbut-2-en-1-yl) malonate (12c): Following the general procedure, the reac-

tion was started with 3,3-dimethylallyl bromide (231 μL, 2 mmol). At the −20 °C, aq 50 % KOH (225 μL, 2 mmol) was added to the reaction mixture. After stirring for 2 h, (*R*)-**12c** was obtained as a yellow oil (207.4 mg, 95 % yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane/2-propanol = 95:5), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *R* (major) 18.2 min, *S* (minor) 20.3 min, 71 % *ee*. $[\alpha]_D^{20} = -11.42$ (71 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 9.1 Hz, 1H), 7.30–7.17 (m, 10H), 6.89 (s, 1H), 6.83 (dd, J_1 = 9.1 Hz, J_2 = 2.7 Hz, 1H), 6.73 (d, *J* = 2.7 Hz, 1H), 5.01 (t, *J* = 6.4 Hz, 1H), 3.70 (s, 3H), 3.22–3.06 (m, 2H), 1.51 (s, 3H), 1.44 (s, 3H), 1.27 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.53, 167.09, 162.54, 142.33, 139.62, 136.00, 135.27, 128.28, 128.03, 127.86, 127.77, 127.30, 127.21, 118.62, 117.07, 111.78, 82.96, 78.20, 63.74, 55.59, 34.23, 27.50, 25.68, 17.79 ppm; IR (KBr): $\tilde{\nu}$ = 2978, 2931, 1732, 1580, 1520, 1345, 1316, 1250, 1183, 1150, 845, 757, 700 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{32}H_{36}NO_7]^+$: 546.2492; found: 546.2476.

(*R*)-1-Benzhydryl 3-*tert*-butyl 2-(5-methoxy-2-nitrophenyl)-2-(2-oxoethyl) malonate (13): A solution of (*R*)-**5** (440 mg, 0.85 mmol) in EtOAc (10 mL) was purged with O_3 at −78 °C until no more starting material was observed by TLC analysis (20 min). The excess O_3 in the solution was removed by purging of argon at −78 °C for 20 min. To the mixture, four equivalents of triphenyl phosphine (892 mg, 3.4 mmol) were added at −78 °C, and then stirred at −78 °C to room temperature for 20 min. After all solvent was removed on a rotary evaporator, the residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1) to afford **13** (437 mg, 99 % yield) as a pale-yellow viscous oil. $[\alpha]_D^{20} = 65.18$ (91 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.68 (s, 1H), 8.13 (d, *J* = 9.1 Hz, 1H), 7.31–7.24 (m, 10H), 7.02 (s, 1H), 6.88 (dd, J_1 = 9.1 Hz, J_2 = 2.5 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 3.60 (s, 3H), 3.45 (ddd, J_1 = 59.0 Hz, J_2 = 17.2 Hz, J_3 = 1.79 Hz, 2H), 1.25 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.61, 167.98, 166.29, 162.84, 141.61, 138.71, 138.56, 134.25, 128.93, 128.49, 128.43, 128.38, 128.26, 128.18, 127.45, 127.21, 116.39, 112.91, 84.74, 79.37, 62.43, 55.61, 48.21, 27.29 ppm; IR (KBr): $\tilde{\nu}$ = 2979, 1726, 1580, 1521, 1346, 1261, 1150, 756, 700 cm^{-1}; HRMS (ESI): *m/z* calcd for $[C_{29}H_{29}NO_8Na]^+$: 542.1785; found: 542.1810.

(*R*)-*tert*-Butyl 4-hydroxy-2-(hydroxymethyl)-2-(5-methoxy-2-nitrophenyl) butanoate (15): Sodium borohydride (45.4 mg, 1.2 mmol) was added to a solution of **13** (519.5 mg, 1 mmol) in ethanol (6 mL) at −20 °C. The reaction mixture was stirred for 1 h and allowed to warm to 0 °C until the entire substrate was converted into intermediate **14** by TLC analysis. Tetrahydrofuran (1.5 mL) and cerium(III) trichloride heptahydrate (745.2 mg, 2 mmol) were then added at 0 °C. After stirring the reaction mixture for 10 min at 0 °C, sodium borohydride (189 mg, 5 mmol) was added and stirred for 10 min then a second charge of sodium borohydride (189 mg, 5 mmol) was added.[10] The reaction mixture was stirred for 2 h until no more intermediate **14** was observed by TLC analysis, then AcOH (0.5 mL) was added dropwise for quenching the extra sodium borohydride. After all of solvent was removed in vacuo, the reaction mixture was diluted with of ethyl acetate (20 mL) and of water (20 mL). The organic layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1:1 to only EtOAc) to afford **15** (208.1 mg, 61 % yield) as a white solid. The enantioselectivity was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane/2-propanol = 90:10), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *S* (minor) 18.5 min, *R* (major) 21.0 min, 91 % *ee*]. The obtained **15** was recrystallized three times with hexane-ethyl acetate (5:1) to afford the *R*-enantiomer **15** (131.2 mg, 63 %) as a single stereoisomer. The residual liquid was evaporated in vacuo to give an enantiomeric mixture of **15** as a solid. The residual solid was recrystallized six times again as the same procedure above to afford the *R* enantiomer **15** (45.6 mg, 22 %). The enantioselectivity of the combined *R* enantiomer **15** (total 176.8 mg, 85 %) was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane/2-propanol = 90:10), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *R* (only major peak) 21.8 min, > 99 % *ee*]. m.p. 122.8 °C; $[\alpha]_D^{20} = -87.79$ (> 99 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 9.0 Hz, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 6.84 (dd, J_1 = 9.0 Hz, J_2 = 2.6 Hz, 1H), 4.13 (dd, J_1 = 126.0 Hz, J_2 = 11.6 Hz, 2H), 3.88 (s, 3H), 3.88–3.79 (m, 1H), 3.67–3.59 (m, 1H), 3.33 (s, 1H), 2.57–2.34 (m, 2H), 2.28 (s, 1H), 1.39 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.08, 162.88, 142.74, 137.57, 128.40, 116.57, 111.31, 83.23, 67.79, 59.09, 55.85, 55.14, 37.79, 27.74 ppm; IR (KBr): $\tilde{\nu}$ = 3403, 2925, 1721, 1578, 1519, 1348, 1256, 1158, 1036, 842, 756 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{16}H_{24}NO_7]^+$: 342.1553; found: 342.1544.

(*R*)-*tert*-Butyl 3-(5-methoxy-2-nitrophenyl)-2-oxotetrahydrofuran-3-carboxylate (14): Lactone **14** could be obtained by the selective reduction of **13**. Sodium borohydride (45.4 mg, 1.2 mmol) was added to a solution of **13** (519.5 mg, 1 mmol) in ethanol (6 mL) at −20 °C. The reaction mixture was stirred for 1 h until entire substrate was converted into lactone **14** by TLC analysis. 1 N NaOH (3–4 drops) was added dropwise to the reaction mixture for quenching the extra sodium borohydride. After all solvent was removed on a rotary evaporator, the mixture was diluted with ethyl acetate (20 mL) and brine (20 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5:1–3:1) to afford **14** (313.5 mg, 93 % yield) as a white solid. M.p. 109.5 °C; $[\alpha]_D^{20} = 8.00$ (91 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 9.1 Hz, 1H), 6.91 (dd, J_1 = 9.1 Hz, J_2 = 2.7 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 4.55 (td, J_1 = 8.5 Hz, J_2 = 4.2 Hz, 1H), 4.21 (q, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 3.62 (dt, J_1 = 13.7 Hz, J_2 = 8.2 Hz, 1H), 2.50 (dq, J_1 = 13.8 Hz, J_2 = 4.2 Hz, 1H), 1.38 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.82, 165.94, 163.59, 140.86, 135.33, 129.02, 115.99, 112.57, 84.09, 66.42, 61.72, 56.02, 36.02, 27.46 ppm; IR (KBr): $\tilde{\nu}$ = 2979, 1773, 1731, 1581, 1519, 1344, 1260, 1155, 1032, 841, 756 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{16}H_{20}NO_7]^+$: 338.1240; found: 338.1252.

(*R*)-*tert*-Butyl 2-(5-methoxy-2-nitrophenyl)-2-(methanesulfonyloxymethyl)-4-methanesulfonyloxybutanoate (16): Methanesulfonyl chloride (116 μL, 1.5 mmol) was added to a solution of **15** (170.7 mg, 0.5 mmol) and triethylamine (209 μL, 1.5 mmol) in dichloromethane (8 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 h. Saturated aqueous solution of $NaHCO_3$ (15 mL) was added dropwise to the reaction mixture for quenching and the mixture was diluted with dichloromethane (20 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 1:1) to afford **16** (246 mg, 99 % yield) as a colorless oil. $[\alpha]_D^{20} = -116.20$ (> 99 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 2.6 Hz, 1H), 6.91 (dd, J_1 = 9.0 Hz, J_2 = 2.6 Hz, 1H), 4.85 (dd, J_1 = 45.6 Hz, J_2 = 10.2 Hz, 2H), 4.18 (t, *J* = 7.3 Hz, 2H), 3.90 (s, 3H), 2.96 (s, 3H), 2.88 (s, 3H), 2.78–2.59 (m, 2H), 1.41 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.32, 162.90, 142.45, 13380, 128.72, 116.67, 112.41, 84.46, 71.88, 65.55, 56.01, 52.99, 37.39, 37.26, 33.54, 27.62 ppm; IR (KBr): $\tilde{\nu}$ = 1726, 1580, 1522, 1355, 1261, 1175, 960, 840, 755 cm^{-1}; HRMS (FAB) : *m/z* calcd for $[C_{18}H_{27}NO_{11}S_2]^+$: 497.1026; found: 497.1034.

(*R*)-*tert*-Butyl 3-(5-methoxy-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate (11): Compound **16** (199 mg, 0.4 mmol) was dissolved in methylamine solution (33 wt % in absolute ethanol (10 mL).[4k] At room temperature, the reaction mixture was stirred for 48 h. After all of solvent was removed in vacuo, the residue was purified by column chromatography (silica gel, hexane/EtOAc/acetone/methanol = 10:16:4:1) to afford **11** (313.5 mg, 93 % yield) as a yellow solid. The enantioselectivity was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane/2-propanol = 99:1), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *R* (only major peak) 11.9 min, > 99 % *ee*]. M.p. 89.7 °C; $[\alpha]_D^{20} = 86.23$ (> 99 % *ee*, *c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 2.8 Hz, 1H), 6.76 (dd, J_1 = 9.0 Hz, J_2 = 2.8 Hz, 1H), 3.85 (s, 3H), 3.26 (d, *J* = 10.3 Hz, 1H), 3.01–2.84 (m, 2H), 2.75 (d, *J* = 10.3 Hz, 1H), 2.46 (q, *J* = 8.6 Hz, 1H), 2.35 (s, 3H), 2.15–2.05 (m, 1H), 1.33 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.59, 163.10, 142.75, 141.27, 127.66, 115.53, 110.44, 81.55, 66.92, 57.55, 56.28, 55.66, 41.80, 38.24, 27.57 ppm; IR (KBr): $\tilde{\nu}$ = 2975, 2940,

2788, 1731, 1612, 1577, 1518, 1347, 1273, 1258, 1155, 1074, 1035, 842, 756 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{17}H_{25}N_2O_5]^+$: 337.1763; found: 337.1762.

(*R*)-Methyl 3-(5-methoxy-2-nitrophenyl)-1-methylpyrrolidine-3-carboxylate (18): Trifluoroacetic acid (1.2 mL) was added to a stirred solution of **11** (80 mg, 0.24 mmol) in dichloromethane (2 mL). After stirring for 1 h, both dichloromethane and trifluoroacetic acid were removed in vacuo. The crude product (**17**) was concentrated in vacuo for 3 h and dissolved in a mixture of toluene/MeOH = 5:2 (3 mL). TMS-diazomethane (0.48 mL, 0.95 mmol) was added to a stirred solution. After stirring for 2 h, the reaction mixture was evaporated in vacuo and diluted with EtOAc (50 mL), washed with brine (2×20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, dichloromethane/methanol = 20:1) to afford **18** (64.4 mg, 92% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 9.0 Hz, 1H), 7.25 (s, 1H), 6.80 (dd, J_1 = 9.0 Hz, J_2 = 2.8 Hz, 1H), 3.87 (s, 3H), 3.61 (s, 3H), 3.04 (dd, J_1 = 115.9 Hz, J_2 = 10.1 Hz, 2H), 2.97–2.90 (m, 2H), 2.54 (q, J = 7.3 Hz, 1H), 2.36 (s, 3H), 2.16–2.06 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.24, 163.27, 142.11, 141.14, 127.95, 115.64, 110.77, 66.69, 56.81, 56.05, 55.74, 52.30, 41.76, 38.02 ppm; IR (KBr): $\tilde{\nu}$ = 2950, 2841, 2789, 1739, 1577, 1516, 1346, 1257, 1034 cm^{-1}; HRMS (FAB) : *m/z* calcd for $[C_{14}H_{19}N_2O_5]^+$: 295.1294; found: 295.1306.

(*R*)-*tert*-Butyl 3-(2-amino-5-methoxyphenyl)-1-methylpyrrolidine-3-carboxylate (19): Amine **19** could be isolated by the reduction (Pd/C, H_2) of **11** without further intramolecular lactonization using silica gel in the following procedure. $[\alpha]_D^{20} = -25.53$ (>99% *ee*, c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.65–6.53 (m, 3H), 3.97 (s, 2H), 3.71 (s, 3H), 3.09 (dd, J_1 = 70.7 Hz, J_2 = 9.7 Hz, 2H), 2.94–2.85 (m, 1H), 2.68–2.50 (m, 2H), 2.34 (s, 3H), 2.15–2.06 (m, 1H), 1.36 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.30, 152.05, 138.93, 128.20, 117.77, 113.86, 112.74, 81.07, 64.41, 57.91, 55.76, 55.69, 42.09, 33.81, 27.77 ppm; IR (KBr): $\tilde{\nu}$ = 3438, 3370, 3188, 2974, 2937, 2833, 2783, 1718, 1503, 1455, 1368, 1275, 1252, 1224, 1156, 1045, 847, 812 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{17}H_{26}N_2O_3]^+$: 306.1943; found: 306.1947.

(−)-Horsfiline: Pd/C (17 mg) was added to a stirred solution of **11** (67.3 mg, 0.2 mmol) in methanol (4 mL) under H_2 gas and stirred for 1 h. The reaction mixture was filtered through the Celite 545 and concentrated in vacuo to afford quantitative **19** as a yellow oil. Silica gel (673 mg) was added to a stirred solution of **19** (67.3 mg, 0.2 mmol) in dichloromethane (2 mL) and stirred for 3 h. The absorbed residue was purified by column chromatography (silica gel, dichloromethane/methanol = 20:1–8:1) to afford (−)-horsfiline (45.5 mg, 98% yield) as a white solid. The enantioselectivity was determined by chiral HPLC analysis [chiral HPLC analysis (DIACEL Chiralcel OJ-H, hexanes/2-propanol = 98:2), flow rate = 1.0 mL min^{-1}, 20 °C, λ = 254 nm, retention time, *R* (only major peak) 31.1 min, >99% *ee*]. M.p. 163.8 °C; $[\alpha]_D^{20} = -8.5$ (>99% *ee*, c = 5, MeOH) (Reported value for natural (−)-horsfiline[3] : $[\alpha]_D^{20} = -7.2$ (c = 1, MeOH)); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.49 (s, 1H), 6.97 (d, J = 2.1 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.67 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1H), 3.74 (s, 3H), 2.96 (q, J = 8.1 Hz, 1H), 2.83 (q, J = 9.4 Hz, 2H), 2.76 (q, J = 7.9 Hz, 1H), 2.42 (s, 3H), 2.42–2.35 (m, 1H), 2.09–2.01 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.37, 156.00, 137.53, 133.73, 112.30, 110.11, 110.02, 66.22, 56.65, 55.75, 54.18, 41.72, 37.93 ppm; IR (KBr): $\tilde{\nu}$ = 3222, 2925, 2851, 1709, 1490, 1305, 1205, 1033, 811, 755, 683, 624 cm^{-1}; HRMS (FAB): *m/z* calcd for $[C_{13}H_{17}N_2O_2]^+$: 233.1290; found: 233.1292.

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