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Preparation of a new chiral building block containing a benzylic quaternary stereogenic center and a formal total synthesis of (−)-physostigmine

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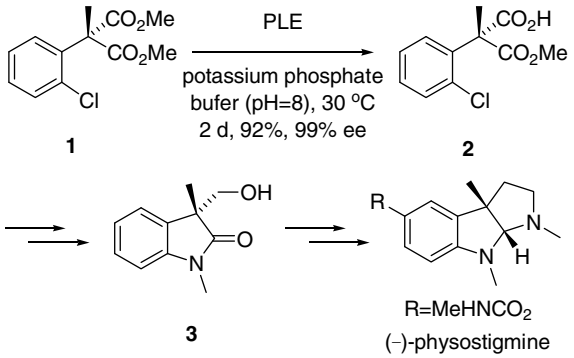
ABSTRACT

This paper describes the preparation of a new chiral building block containing a benzylic quaternary stereogenic center via the highly enantioselective PLE-mediated hydrolysis of dimethyl 2-(2-chloro-5-methoxyphenyl)-2-methylmalonate, as well as the absolute configuration of the new chiral building block, which has been elucidated through the formal total synthesis of (−)-physostigmine.

1. Introduction

(−)-Physostigmine (Scheme 1),[1] initially isolated from the seeds of *Physostigma venenosum* in 1864,[2,3] has been clinically used for the treatment of glaucoma, myasthenia gravis, atropine, and organophosphate intoxication, and for the relief of intoxication induced by overdoses of antidepressants, antihistamines, antipsychotics, and benzodiazepines.[1,4–6] (−)-Physostigmine is a potent inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), thereby showing wide biological activities. (−)-Physostigmine has been evaluated in clinical trials for the symptomatic treatment of Alzheimer's disease,[1,4–6] and various derivatives of (−)-physostigmine with improved pharmacological profile against Alzheimer's disease have been prepared.[1,7,8] Interestingly, the inhibition of AChE has been found to be enantioselective from the studies using acetylcholinesterase obtained from human tissues,[9] that is, (−)-physostigmine is some 1000 times more potent than its (+)-enantiomer,[9] thus implying the importance of the enantioselective total synthesis of (−)-physostigmine and its derivatives.



Scheme 1. Enantioselective PLE-mediated hydrolysis of dimethyl 2-(2-chlorophenyl)-2-methylmalonate **1** and a formal total synthesis of (−)-physostigmine.[10a]

Recently, we reported the highly enantioselective preparation of a new chiral building block **2** by the PLE (pig liver esterase)-mediated hydrolysis of dimethyl 2-(2-chlorophenyl)-2-methylmalonate **1**.[10a] The mono-ester **2** (99% ee) prepared in 92% yield was successfully converted into the synthetic intermediate **3**, which was reported by Kita et al. in the synthesis of (−)-physostigmine[7g] (Scheme 1).

However, the conversion of alcohol **3** into (−)-physostigmine requires the introduction of an oxygen atom at the benzene ring, and the overall yield of the two requisite steps is moderate.[8] These facts prompted us to investigate the preparation and enantioselective PLE-mediated hydrolysis of a new substrate incorporating a hydroxyl or equivalent group on the benzene ring of dialkyl 2-(2-chlorophenyl)-2-methylmalonate, since such a suitable chiral building block corresponding to mono-ester **2** not only would be useful for the enantioselective total synthesis of (−)-physostigmine, but also could be applied to the syntheses of (−)-aphanorphine, (−)-eptazocine, and their congeners (Fig. 1). Herein, we report the preparation of a new chiral building block by the highly enantioselective PLE-mediated hydrolysis of dimethyl 2-(2-chloro-5-methoxyphenyl)-2-methylmalonate **9** and the formal total synthesis of (−)-physostigmine.

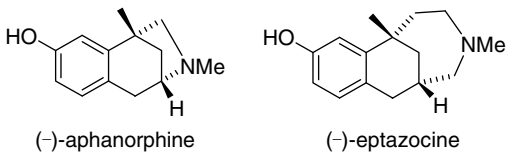


Figure 1. Respective structures of (−)-aphanorphine and (−)-eptazocine.

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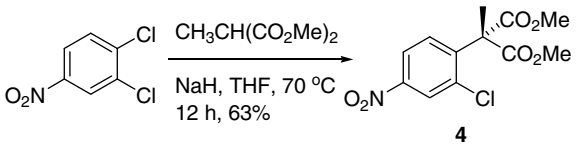
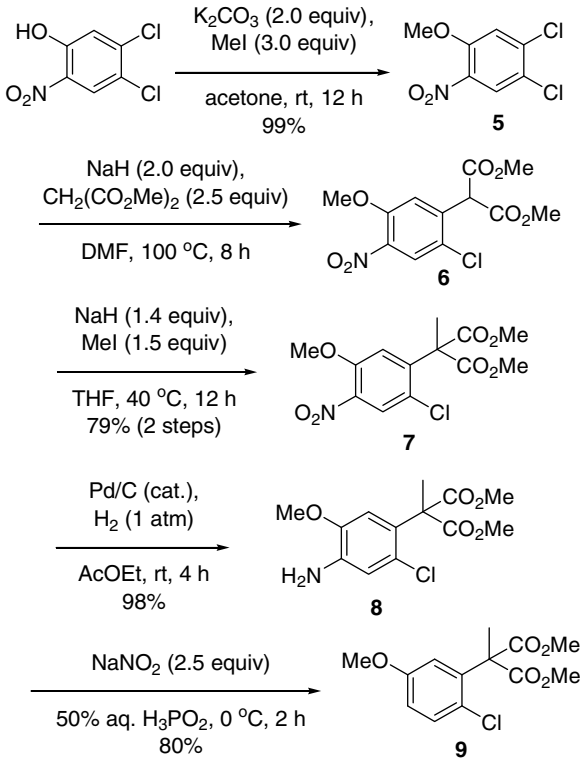
2. Results and discussion

We successfully induced the regioselective reaction of 1,2-dichloro-4-nitrobenzene with the anion of dimethyl 2-methylmalonate (Scheme 2) to afford compound **4** in 63% yield.[10a] Therefore, compound **7** (Scheme 3) was expected to be prepared by the same method. For this purpose, compound **5** was first prepared from a known compound, 4,5-dichloro-2-nitrophenol,[11] by methylation with iodomethane and potassium carbonate (99%). However, although we attempted to induce the reaction of compound **5** with the anion of dimethyl 2-methylmalonate, no products were formed. Comparing with 1,2-dichloro-4-nitrobenzene, compound **5** would be deactivated by the electron-donating methoxy group.



Scheme 2. Preparation of dimethyl 2-(2-chloro-4-nitrophenyl)-2-methylmalonate **4**.[10a]

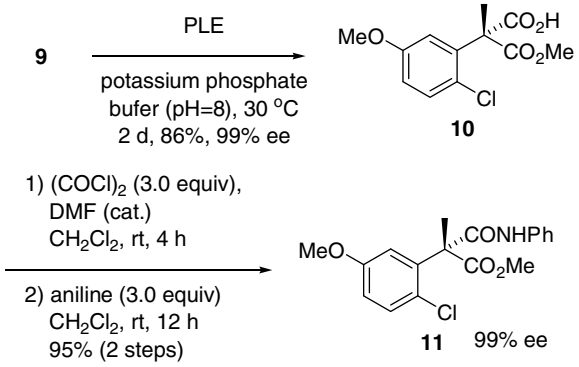
Next, the conversion of compound **5** into the dimethyl ester **7** was carried out in a stepwise manner (Scheme 3). The reaction of methyl ether **5** with the anion of dimethyl malonate in DMF at 100 °C proceeded successfully in a regioselective manner to afford the desired compound **6**, which was subsequently methylated with sodium hydride and iodomethane to provide dimethyl ester **7** (79% yield, two steps). Although the catalytic hydrogenation of the dimethyl ester **7** in methanol resulted in over-reduction, thus affording a product with no chlorine atom, the reaction in ethyl acetate successfully provided arylamine **8** chemoselectively (98% yield),



Scheme 3. Preparation of dimethyl 2-(2-chloro-5-methoxyphenyl)-2-methylmalonate **9**.

which was treated with sodium nitrite in aqueous hypophosphorous acid solution to afford the dimethyl ester **9** (80% yield).

The PLE-mediated hydrolysis of dimethyl ester **9** was performed under conventional conditions[10a] (Scheme 4). The PLE-mediated hydrolysis required two days to afford the corresponding mono-ester **10** in 86% yield. The mono-ester **10** was converted into the anilide **11** (95% yield, two steps), which was subsequently subjected to HPLC analysis using a chiral column to determine that the ee of the anilide **11** was 99%. This result also indicates that the ee of the mono-ester **10** prepared by the PLE-mediated hydrolysis of the dimethyl ester **9** is 99%.



Scheme 4. Enantioselective PLE-mediated hydrolysis of prochiral diester **9** and the preparation of the anilide **11**.

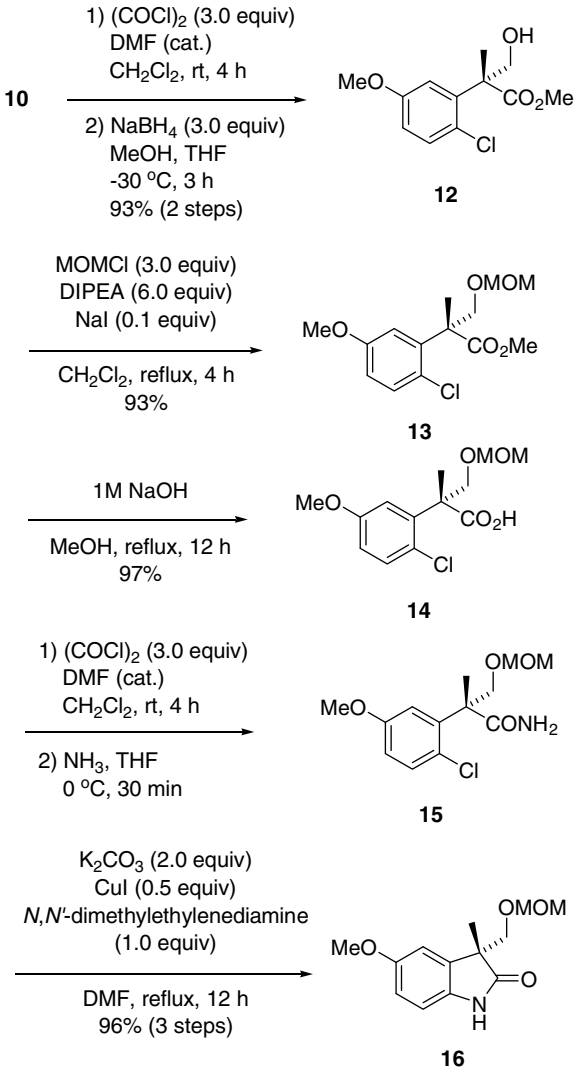
In order to determine the absolute configuration of the mono-ester **10**, we converted it into the known compound **20** (Scheme 6), which is a synthetic intermediate in Brossi's synthesis of (−)-physostigmine.[7v] Although we did not determine the absolute configuration of the mono-ester **10** at this point, we assumed its absolute structure as shown in Scheme 4 on the basis of analogy with the PLE-mediated hydrolysis of the similar dimethyl ester **1** (Scheme 1).

Mono-ester **10** was converted into the corresponding acid chloride (Scheme 5), which was reduced with sodium borohydride to provide alcohol **12** in 93% yield (two steps).[12] Alcohol **12** was subsequently converted into the MOM ether **13** (93% yield), which resisted conversion to amide **15** under any conditions. This can be attributed to the steric hindrance due to the quaternary carbon adjacent to the ester group. Therefore, the MOM ether **13** was subjected to hydrolysis, and the resulting carboxylic acid **14** was converted into the reactive acid chloride, followed by reaction with ammonia to provide amide **15**. Amide **15** was successfully converted into the lactam **16** under optimized conditions in excellent yield (96%).[10a,13]

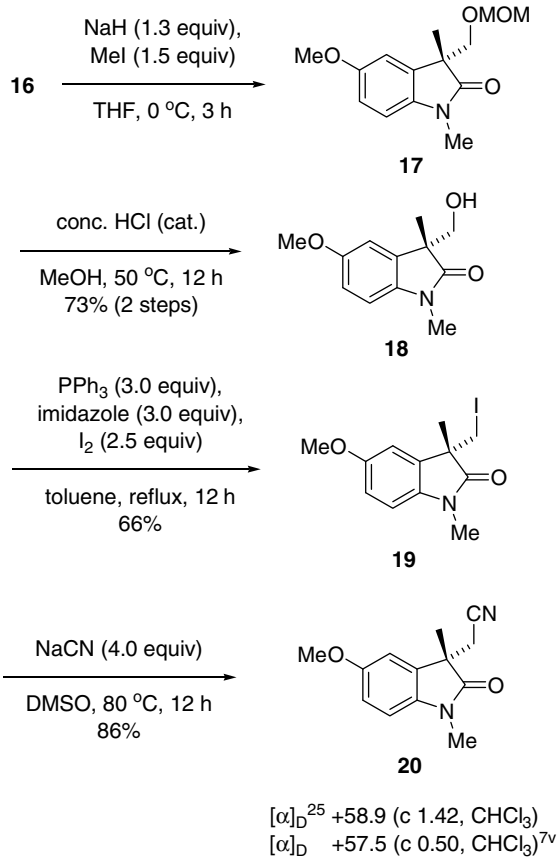
Lactam **16** was treated with sodium hydride and iodomethane to afford the N-methylated lactam **17** (Scheme 6), followed by the deprotection of the MOM group to provide the alcohol **18** (73% yield, two steps). The iodination of the alcohol **18** under conventional conditions afforded the iodide **19** (66% yield), which was subjected to a reaction with sodium cyanide, providing compound **20** (86% yield). The compound **20** synthesized was spectroscopically identical to the known compound in all respects, indicating that the absolute structure of the mono-ester **10** was determined as shown in Scheme 4, and thus marking the completion of the formal total synthesis of (−)-physostigmine.

3. Conclusion

In conclusion, we have prepared a new chiral building block with a benzylic quaternary stereogenic center, a chlorine atom at C2, and an oxygen atom at C5 of the benzene ring by the highly



Scheme 5. Conversion of the mono-ester **10** into compound **16**.



Scheme 6. Conversion of the lactam **16** into compound **20**, a known intermediate in Brossi's synthesis[7v] of (−)-physostigmine.

enantioselective PLE-mediated hydrolysis of dimethyl 2-(2-chloro-5-methoxyphenyl)-2-methylmalonate. The newly synthesized chiral building block might be useful for the total synthesis of natural products incorporating a benzylic quaternary stereogenic center in a fused ring system, such as (−)-aphanorphine, (−)-eptazocine, and their congeners.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-400 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Melting points (mp) are uncorrected, recorded on a Yanaco melting point apparatus equipped with a digital thermometer. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP-1000. Chiral HPLC analysis was performed on a JASCO PU-980 and UV-970. Mass spectrometric analyses and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254). THF was distilled from sodium/benzophenone ketyl and methylene chloride (CH_2Cl_2), and benzene from calcium hydride. Toluene was distilled from sodium. DMF and DMSO were distilled from CaH_2 under reduced pressure. All reagents were purchased from Aldrich, TCI, Merck, or Kanto Chemical Co. Ltd.

4.2. 1,2-Dichloro-4-methoxy-5-nitrobenzene 5

To a stirred solution of 4,5-dichloro-2-nitrophenol (3.17 g, 15.2 mmol) in acetone (80 mL) were added K_2CO_3 (4.21 g, 30.4 mmol) and MeI (2.85 mL, 45.6 mmol) successively at room temperature. After 12 h, saturated aqueous NH_4Cl solution (80 mL) was added to the reaction mixture. The resultant solution was concentrated under reduced pressure, and the residue was extracted with Et_2O (80 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 30:1) to afford **5** (3.32 g, 99%) as a yellow solid: R_f = 0.44 (hexane/ethyl acetate = 4:1); mp 66–71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, s), 7.20 (1H, s), 3.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 138.6, 137.9, 127.0, 123.9, 115.6, 57.1; IR (KBr) ν_{max} 1515, 1343, 1269, 933 cm^{-1}.

4.3. Dimethyl 2-(2-chloro-5-methoxy-4-nitrophenyl)-malonate 6

To a suspension of NaH (1.03 g, 25.8 mmol) in DMF (100 mL) was added dimethyl malonate (3.69 mL, 32.3 mmol) dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. Then, to the reaction mixture was added a solution of **5** (2.84 g, 12.9 mmol) in DMF (10 mL) via a cannula at 0 °C, and the reaction mixture was warmed to 100 °C. After 8 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (100 mL), and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude di-ester **6** was used for the next step without further purification: R_f = 0.32 (hexane/ethyl acetate = 2:1); mp 93–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, s), 7.37 (1H, s), 5.28 (1H, s), 3.98 (3H, s), 3.82 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 151.5, 139.1, 136.6, 126.1, 125.2, 115.8, 56.9, 53.5, 53.4; IR (KBr) ν_{max} 1770, 1739, 1573, 1526, 1271, 1221, 1144 cm^{-1}; HRMS (FAB) [M+H]$^+$ Calcd for $C_{12}H_{13}ClNO_7$: 318.0381, found: 318.0374.

4.4. Dimethyl 2-(2-chloro-5-methoxy-4-nitrophenyl)-2-methylmalonate 7

To a suspension of NaH (723 mg, 18.1 mmol) in THF (100 mL) was added a solution of **6** in THF (10 mL) dropwise at 0 °C, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added MeI (1.21 mL, 19.4 mmol) at 0 °C, and stirring was continued at 40 °C for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (100 mL × 2), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 8:1) to afford **7** (3.38 g, 79% (2 steps)) as a yellow solid: R_f = 0.28 (hexane/ethyl acetate = 2:1); mp 101–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.01 (1H, s), 3.95 (3H, s), 3.82 (6H, s), 1.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 151.4, 143.7, 138.1, 127.8, 124.8, 114.0, 59.7, 56.6, 53.4, 21.9; IR (KBr) ν_{max} 1752, 1728, 1570, 1509, 1266, 1222, 1113 cm^{-1}; HRMS (FAB) [M+H]$^+$ Calcd for $C_{13}H_{15}ClNO_7$: 332.0537, found: 332.0551.

4.5. Dimethyl 2-(4-amino-2-chloro-5-methoxyphenyl)-2-methylmalonate 8

A mixture of **7** (3.35 g, 10.1 mmol), 10% Pd/C, and AcOEt (100 mL) was stirred under H_2 atmosphere (1 atm) at room temperature for 4 h. After the reaction was completed, the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 8:1) to afford **8** (2.99 g, 98%) as a white solid: R_f = 0.21 (hexane/ethyl acetate = 2:1); mp 106–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.55 (1H, s), 3.80 (3H, s), 3.79 (6H, s), 1.89 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 145.4, 136.6, 126.1, 125.3, 116.5, 110.1, 59.2, 55.5, 53.0, 22.4; IR (KBr) ν_{max} 3441, 3358, 2958, 1730, 1578, 1514, 1259, 1229, 1114, 1035 cm^{-1}; HRMS (FAB) [M]$^+$ Calcd for $C_{13}H_{16}ClNO_5$: 301.0717, found: 301.0720.

4.6. Dimethyl 2-(2-chloro-5-methoxyphenyl)-2-methylmalonate 9

To a stirred solution of **8** (2.99 g, 9.91 mmol) in aqueous 50% H_3PO_2 (80 mL) was added $NaNO_2$ (1.71 g, 25.7 mmol) at 0 °C. After 2 h, K_2CO_3 was added to the reaction mixture. The aqueous layer was extracted with Et_2O (60 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 8:1) to afford **9** (2.27 g, 80%) as a white solid: R_f = 0.21 (hexane/ethyl acetate = 4:1); mp 71–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, d, J = 8.8 Hz), 6.77 (1H, dd, J = 8.8, 2.9 Hz), 6.71 (1H, d, J = 2.9 Hz), 3.80 (6H, s), 3.78 (3H, s), 1.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 158.0, 138.1, 131.4, 124.6, 115.1, 112.8, 59.6, 55.1, 52.8, 21.6; IR (KBr) ν_{max} 2958, 1751, 1723, 1602, 1576, 1295, 1253, 1113, 1045 cm^{-1}; HRMS (FAB) [M+H]$^+$ Calcd for $C_{13}H_{16}ClO_5$: 287.0686, found: 287.0699.

4.7. (*R*)-2-Methoxycarbonyl-2-(2-chloro-5-methoxyphenyl)propanoic acid 10

To a suspension of **9** (2.27 g, 7.92 mmol) in pH 8 phosphate buffer (190 mL) was added PLE (1900 units, esterase solution, from porcine liver suspension in 3.2 M $(NH_4)_2SO_4$ solution, pH 8, purchased from Sigma–Aldrich), and the reaction mixture was stirred at 30 °C for 2 days. After the reaction was completed, to the reaction mixture was added 2 M HCl to make the pH of the solution to pH 3. The aqueous layer was extracted with EtOAc (50 mL × 2), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford **10** (1.86 g, 86%) as a colorless oil: R_f = 0.18 (CH_2Cl_2/MeOH = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (1H, br), 7.29 (1H, d, J = 8.8 Hz), 7.02 (1H, d, J = 2.9 Hz), 6.84 (1H, dd, J = 8.8, 2.9 Hz), 3.83 (3H, s), 3.79 (3H, s), 1.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 171.8, 158.4, 137.2, 130.5, 124.9, 115.6, 113.5, 56.5, 55.5, 54.2, 23.2; IR (neat) ν_{max} 2956, 1744, 1604, 1578, 1414, 1296, 1250, 1114, 1044 cm^{-1}; HRMS (FAB) [M+H]$^+$ Calcd for $C_{12}H_{14}ClO_5$: 273.0530, found: 273.0540; $[\alpha]_D^{21} = +27.1$ (c 1.44, $CHCl_3$).

4.8. (*R*)-Methyl 2-phenylcarbamoyl-2-(2-chloro-5-methoxyphenyl)propanoate 11

To a stirred solution of **10** (72.2 mg, 0.265 mmol) in CH_2Cl_2 (2 mL) were added $(COCl)_2$ (0.070 mL, 0.802 mmol) and one drop of DMF with a Pasteur pipet at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. All volatile materials were removed under reduced pressure to afford the crude carboxylic acid chloride, which was used for the next step without further purification. To a solution of the carboxylic acid chloride in CH_2Cl_2 (2 mL) was added aniline (0.075 mL, 0.814 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. After the reaction was completed, to the reaction mixture was added H_2O (1 mL), and the aqueous layer was extracted with ether (1 mL × 3). The combined organic layer was washed with 2 M HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by PTLC (hexane/ethyl acetate = 2:1) to afford **11** (87.3 mg, 95% (2 steps)) as a pale yellow solid: R_f = 0.43 (hexane/ethyl acetate = 2:1); mp 105–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (1H, s), 7.60 (2H, dd, J = 8.3, 1.2 Hz), 7.32 (2H, dd, J = 8.3, 7.3 Hz), 7.26 (1H, d, J = 8.5 Hz), 7.10 (1H, tt, J = 7.3, 1.2 Hz), 7.02 (1H, d, J = 2.9 Hz), 6.80 (1H, dd, J = 8.5, 2.9 Hz), 3.80 (3H, s), 3.74 (3H, s), 1.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 168.1, 158.4, 139.1, 137.9, 130.4, 128.9, 125.2, 124.3, 120.0, 115.8, 113.1, 57.8, 55.4, 53.5, 24.0; IR (KBr) ν_{max} 2951, 1720, 1678, 1599, 1549, 1298, 1270, 1126, 1038 cm^{-1}; HRMS (FAB) [M+H]$^+$ Calcd for $C_{18}H_{19}NClO_4$: 348.1003, found: 348.1001; $[\alpha]_D^{21} = -16.5$ (c 1.49, $CHCl_3$); 99% ee; ee was determined by HPLC using racemic **11** as the standard; DICEL CHIRALCEL OD-H 0.46 cm ϕ × 25 cm; hexane/2-propanol = 9:1; flow rate = 0.5 mL/min; retention time: 16.6 min for (*S*)-methyl 2-phenylcarbamoyl-2-(2-chloro-5-methoxyphenyl)propanoate, 19.3 min for (*R*)-methyl 2-phenylcarbamoyl-2-(2-chloro-5-methoxyphenyl)propanoate.

4.9. (*R*)-Methyl 2-(2-chloro-5-methoxyphenyl)-3-hydroxy-2-methylpropanoate 12

To a stirred solution of **10** (1.20 g, 4.40 mmol) in CH_2Cl_2 (40 mL) were added $(COCl)_2$ (1.15 mL, 13.2 mmol) and one drop of DMF with a Pasteur pipet, and the reaction mixture was stirred at room temperature for 4 h. All volatile materials were removed under reduced pressure to afford the crude carboxylic acid chloride, which was used for the next step without further purification. To a solution of the carboxylic acid chloride in THF (40 mL) was added $NaBH_4$ (499 mg, 13.2 mmol) portionwise at −30 °C, and then MeOH was added (4.4 mL) at the same temperature. After 3 h, 2 N HCl was slowly added to the reaction mixture to adjust pH of the solution to pH 2, and the aqueous layer was extracted with Et_2O (30 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford **12** (1.06 g, 93% (2 steps)) as a colorless oil: R_f = 0.22 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 8.8 Hz), 6.98 (1H, d, J = 2.9 Hz), 6.77 (1H, dd, J = 8.8, 2.9 Hz), 4.32 (1H, d, J = 11.5 Hz), 3.81 (3H, s), 3.72 (3H, s), 3.55 (1H, d, J = 11.5 Hz), 2.76 (1H, br), 1.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 158.5, 139.1, 131.3, 125.0, 115.2, 113.0, 67.2, 55.5, 52.5, 51.6, 21.2; IR (neat) ν_{max} 3444, 2952, 1732, 1602, 1576, 1414, 1296, 1246, 1114, 1048 cm^{-1}; HRMS (FAB) [M+H]$^+$ Calcd for $C_{12}H_{16}ClO_4$: 259.0737, found: 259.0734; $[\alpha]_D^{22} = +52.3$ (c 1.61, $CHCl_3$).

4.10. (*R*)-Methyl 2-(2-chloro-5-methoxyphenyl)-3-methoxymethoxy-2-methylpropanoate 13

To a stirred solution of **12** (1.00 g, 3.87 mmol) in CH_2Cl_2 (40 mL) were added NaI (57.9 mg, 0.387 mmol), DIPEA (4.04 mL, 23.2 mmol), and MOMCl (0.881 mL, 11.6 mmol) successively at room temperature, and the mixture was refluxed for 4 h. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (40 mL) was slowly added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10:1) to afford **13** (1.09 g, 93%) as a colorless oil: R_f = 0.44 (hexane/ethyl acetate = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, J = 8.5 Hz), 6.94 (1H, d, J = 2.9 Hz), 6.75 (1H, dd, J = 8.5, 2.9 Hz), 4.58 (1H, d, J = 6.6 Hz), 4.52 (1H, d, J = 6.6 Hz), 4.12 (1H, d, J = 9.5 Hz), 4.01 (1H, d, J = 9.5 Hz), 3.80 (3H, s), 3.70 (3H, s), 3.23 (3H, s), 1.67 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 158.2, 140.2, 131.1, 124.9, 115.6, 112.5, 96.5, 71.2, 55.4, 55.2, 52.4, 50.9, 21.7; IR (neat) ν_{max} 2948, 1736, 1602, 1576, 1470, 1296, 1250, 1110, 1046 cm^{-1}; HRMS (FAB) [M]$^+$ Calcd for $C_{14}H_{19}ClO_5$: 302.0921, found: 302.0912; $[\alpha]_D^{22} = +10.5$ (c 0.84, $CHCl_3$).

4.11. (*R*)-2-(2-Chloro-5-methoxyphenyl)-3-methoxymethoxy-2-methylpropanoic acid 14

To a stirred solution of **13** (1.08 g, 3.57 mmol) in MeOH (15 mL) was added 1 M NaOH (15 mL) at room temperature, and the mixture was refluxed for 12 h. After the reaction was completed, the mixture was concentrated under reduced pressure. 2 M HCl was slowly added to the aqueous layer to adjust pH of the solution to pH 3, and the aqueous layer was extracted with Et_2O (30 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford **14** (1.00 g, 97%) as a colorless oil: R_f = 0.50 (CH_2Cl_2/MeOH = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, J = 8.8 Hz), 6.94 (1H, d, J = 2.9 Hz), 6.76 (1H, dd, J = 8.8, 2.9 Hz), 4.60 (1H, d, J = 6.6 Hz), 4.54 (1H, d, J = 6.6 Hz), 4.12 (1H, d, J = 9.5 Hz), 4.03 (1H, d, J = 9.5 Hz), 3.80 (3H, s), 3.24 (3H, s), 1.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 158.2, 139.4, 131.2, 125.0, 115.6, 112.8, 96.5, 70.9, 55.5, 55.3, 50.9, 21.6; IR (neat) ν_{max} 3084, 2944, 1710, 1602, 1576, 1472, 1294, 1244, 1152, 1046 cm^{-1}; HRMS (FAB) [M]$^+$ Calcd for $C_{13}H_{17}ClO_5$: 288.0765, found: 288.0755; $[\alpha]_D^{24} = +10.9$ (c 1.92, $CHCl_3$).

4.12. (*R*)-2-(2-Chloro-5-methoxyphenyl)-3-methoxymethoxy-2-methylpropanamide 15

To a stirred solution of **14** (0.745 g, 2.58 mmol) in CH_2Cl_2 (25 mL) were added $(COCl)_2$ (0.675 mL, 7.74 mmol) and one drop of DMF with Pasteur pipet, and the reaction mixture was stirred at room temperature for 4 h. All volatile materials were removed under reduced pressure affording the crude carboxylic acid chloride, which was used for the next step without further purification. Into a stirred solution of the carboxylic acid chloride in THF (25 mL) was bubbled NH_3 gas at 0 °C for 30 min. After the reaction was completed, the mixture was concentrated under reduced pressure. The crude amide **15** was used for the next step without further purification.

4.13. (*R*)-5-Methoxy-3-methoxymethoxymethyl-3-methylindolin-2-one 16

To a stirred solution of **15** in DMF (60 mL) were added K_2CO_3 (0.713 g, 5.16 mmol), CuI (0.246 g, 1.29 mmol), and *N*,*N*′-dimethylethylenediamine (0.283 mL, 2.58 mmol) successively at room temperature, and the mixture was refluxed for 12 h. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford **16** (0.622 g, 96% (3 steps)) as a white solid: R_f = 0.20 (hexane/ethyl acetate = 1:1); mp 77–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, s), 6.87 (1H, d, J = 2.4 Hz), 6.86 (1H, d, J = 8.3 Hz), 6.74 (1H, dd, J = 8.3, 2.4 Hz), 4.52 (1H, d, J = 6.6 Hz), 4.48 (1H, d, J = 6.6 Hz), 3.83 (1H, d, J = 9.3 Hz), 3.79 (3H, s), 3.78 (1H, d, J = 9.3 Hz), 3.24 (3H, s), 1.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 155.7, 134.5, 134.3, 112.3, 110.4, 110.2, 96.2, 71.6, 55.7, 55.1, 50.0, 19.7; IR (KBr) ν_{max} 3283, 1721, 1682, 1493, 1200, 1116, 1049, 1030 cm^{-1}; HRMS (FAB) [M]$^+$ Calcd for $C_{13}H_{17}NO_4$: 251.1158, found: 251.1161; $[\alpha]_D^{21} = -36.6$ (c 1.34, $CHCl_3$).

4.14. (*R*)-5-Methoxy-3-methoxymethoxymethyl-1,3-dimethylindolin-2-one 17

To a suspension of NaH (0.123 g, 3.07 mmol) in THF (20 mL) was added a solution of **16** (0.594 g, 2.36 mmol) in THF (2 mL) dropwise at 0 °C, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added MeI (0.221 mL, 3.55 mmol) at 0 °C, and stirring was continued at 0 °C for 3 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The crude **17** was sufficiently pure, and was used for the next step without further purification: R_f = 0.30 (hexane/ethyl acetate = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, d, J = 2.4 Hz), 6.80 (1H, dd, J = 8.3, 2.4 Hz), 6.76 (1H, d, J = 2.4 Hz), 4.50 (1H, d, J = 6.6 Hz), 4.45 (1H, d, J = 6.6 Hz), 3.80 (3H, s), 3.78 (1H, d, J = 9.3 Hz), 3.77 (1H, d, J = 9.3 Hz), 3.21 (3H, s), 3.17 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 155.9, 137.1, 134.1, 111.9, 110.6, 108.1, 96.3, 71.7, 55.8, 55.1, 49.3, 26.3, 19.8; IR (neat) ν_{max} 2944, 1712, 1500, 1148, 1112, 1042 cm^{-1}; HRMS (FAB) [M]$^+$ Calcd for $C_{14}H_{19}NO_4$: 265.1314, found: 265.1311; $[\alpha]_D^{26} = -47.3$ (c 1.32, $CHCl_3$).

4.15. (*R*)-3-Hydroxymethyl-5-methoxy-1,3-dimethylindolin-2-one 18

To a stirred solution of crude **17** in MeOH (20 mL) was added a few drops of concd HCl with Pasteur pipet, and the reaction mixture was stirred at 50 °C for 12 h. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with AcOEt (20 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford **18** (0.382 g, 73% (2 steps)) as a white solid: R_f = 0.11 (hexane/ethyl acetate = 1:1); mp 134–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, d, J = 2.4 Hz), 6.82 (1H, dd, J = 8.3, 2.4 Hz), 6.78 (1H, d, J = 8.3 Hz), 3.83 (1H, d, J = 10.7 Hz), 3.80 (3H, s), 3.73 (1H, d, J = 10.7 Hz), 3.20 (3H, s), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 156.2, 137.0, 133.1, 112.2, 110.5, 108.5, 67.6, 55.8, 50.3, 26.3, 19.0; IR (KBr) ν_{max} 3385, 2927, 1686, 1493, 1294, 1042 cm^{-1}; HRMS (FAB) $[M]^+$ Calcd for $C_{12}H_{15}NO_3$: 221.1052, found: 221.1048; $[\alpha]_D^{26} = -15.7$ (c 0.84, $CHCl_3$).

4.16. (*S*)-3-Iodomethyl-5-methoxy-1,3-dimethylindolin-2-one 19

To a stirred solution of **18** (0.127 g, 0.574 mmol) in toluene (5 mL) were added imidazole (0.117 g, 1.72 mmol), PPh_3 (0.452 g, 1.72 mmol), and I_2 (0.364 g, 1.44 mmol) successively at room temperature, and the mixture was refluxed for 12 h. After the reaction was completed, a mixture of saturated aqueous $NaHCO_3$ solution (3 mL) and saturated aqueous $Na_2S_2O_3$ solution (3 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4:1) to afford **19** (0.125 g, 66%) as a colorless solid: R_f = 0.52 (hexane/ethyl acetate = 1:1); mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, d, J = 2.4 Hz), 6.86 (1H, dd, J = 8.5, 2.4 Hz), 6.79 (1H, d, J = 8.5 Hz), 3.82 (3H, s), 3.51 (1H, d, J = 9.8 Hz), 3.41 (1H, d, J = 9.8 Hz), 3.23 (3H, s), 1.51 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 156.0, 136.6, 133.9, 112.5, 110.3, 108.5, 55.8, 48.9, 26.4, 23.0, 10.8; IR (KBr) ν_{max} 1705, 1693, 1498, 1224 cm^{-1}; HRMS (FAB) $[M]^+$ Calcd for $C_{12}H_{14}INO_2$: 331.0069, found: 331.0070; $[\alpha]_D^{28} = -17.3$ (c 1.35, $CHCl_3$).

4.17. (*S*)-(5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetonitrile 20

To a stirred solution of **19** (75.3 mg, 0.227 mmol) in DMSO (3 mL) was added a NaCN (44.6 mg, 0.910 mmol), and the reaction mixture was stirred at 80 °C. After the starting material disappeared, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate = 2:1) to afford **20** (45.0 mg, 86%) as a colorless oil: R_f = 0.35 (hexane/ethyl acetate = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, d, J = 2.4 Hz), 6.87 (1H, dd, J = 8.5, 2.4 Hz), 6.82 (1H, d, J = 8.5 Hz), 3.82 (3H, s), 3.23 (3H, s), 2.85 (1H, d, J = 16.6 Hz), 2.57 (1H, d, J = 16.6 Hz), 1.52 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 156.4, 136.0, 132.2, 116.5, 113.4, 110.4, 109.1, 55.8, 45.2, 26.5, 26.3, 22.1; IR (neat) ν_{max} 1712, 1602, 1506, 1454, 1292, 1042 cm^{-1}; HRMS (FAB) $[M]^+$ Calcd for $C_{13}H_{14}N_2O_2$: 230.1055, found: 230.1055; $[\alpha]_D^{25} = +58.9$ (c 1.42, $CHCl_3$), lit. $[\alpha]_D = +57.5$ (c 0.50, $CHCl_3$).[7v]

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