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Highly enantioselective synthesis of 5-phenyl-2-alkylprolines using phase-transfer catalytic alkylation†

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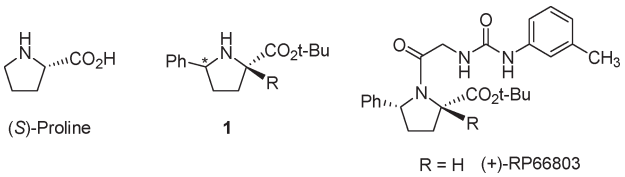
An efficient enantioselective synthetic method for the synthesis of (2*R*)-5-phenyl-2-alkylproline *tert*-butyl esters was reported. The phase-transfer catalytic alkylation of *tert*-butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate in the presence of chiral quaternary ammonium catalysts gave the corresponding alkylated products (up to 97% ee). The following diastereoselective reductions afforded chiral 5-phenyl-2-alkylprolines which can be applied to asymmetric synthesis as organocatalysts or synthesis of biologically active proline based compounds, such as chiral α-alkylated analogues of (+)-RP66803, as potential CCK antagonists.

Introduction

Since the first application of proline to enantioselective Robinson annulation, proline and proline analogues have been widely applied in asymmetric synthesis as efficient organocatalysts.[1] They were generally prepared from proline itself by chemical derivatization. According to the dramatic increase of newly developed organic reactions, new synthetic methods of diverse substituted prolines as efficient organocatalysts are in need *via* direct enantioselective construction of a pyrroline skeleton. Notably, the nonnatural substituted proline analogues can be considered as conformationally constrained amino acids and have actually been applied in biologically active peptidomimetics for structure–activity relationship studies.[2–5] Among the important proline analogues in medicinal chemistry, *cis*-5-phenylproline (**1**) has been applied as an element of nonpeptide cholecystokinin (CCK) antagonist (+)-RP66803.[6,7] In this article, we would like to report a new efficient catalytic synthesis of chiral 5-phenyl-2-alkylproline (**1**) as a new element of chiral proline derivatives which can be applied to asymmetric synthesis and medicinal chemistry *via* enantioselective phase-transfer catalysis.[8–12]



Results and discussion

A number of enantioselective synthetic methods for 5-phenyl-2-alkylprolines have been reported so far.[13–26] Most of these methods are based on the diastereoselective 1,3-dipolar cycloaddition, Pictet–Spengler reaction, and intramolecular iodocyclization. However, their total synthetic steps are relatively long or have low total chemical yields for large-scale production. Very recently, we reported a series of new synthetic methods for optically active α-alkylserines (**3**),[27] α-alkylcysteines (**5**)[28,29] and α-alkyl-α,β-diaminopropionic acids (**7**)[30] by the catalytic enantioselective α-alkylation of *tert*-butyl 2-phenyloxazoline-4-carboxylate (**2**), *tert*-butyl 2-phenylthiazoline-4-carboxylate (**4**), and *N*(1)-Boc-2-phenyl-2-imidazoline-4-carboxylic acid *tert*-butyl ester (**6**) under phase-transfer conditions, respectively (Scheme 1). These works demonstrated that the phase-transfer catalytic conditions are very efficient for the α-alkylation of the oxazoline-4-carboxylate, the thiazoline-4-carboxylate and the imidazoline-4-carboxylate systems. Based on our previous results, we attempted to apply the phase-transfer catalytic alkylation of *tert*-butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**8**) for the enantioselective synthesis of chiral 5-phenyl-2-alkylproline *tert*-butyl esters (**1**), as shown in the synthetic strategy (Scheme 2).

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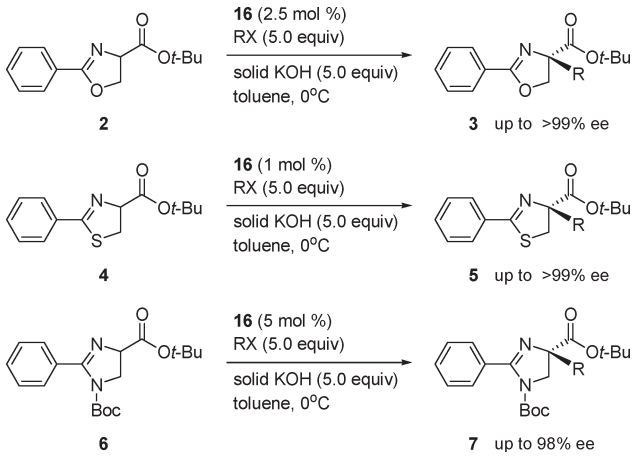
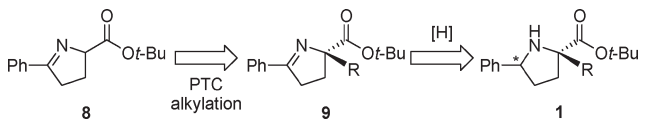
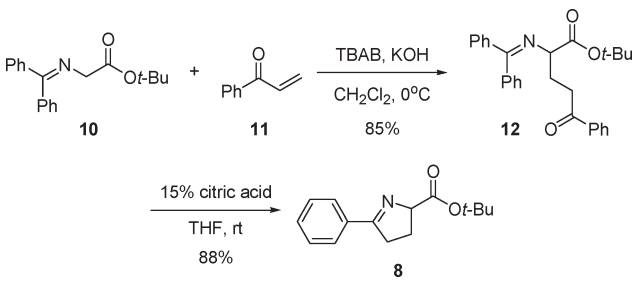


Scheme 1 Previous chiral phase-transfer catalysis of 5-membered heterocyclic carboxylates.



Scheme 2 Synthetic strategy for optically active chiral 5-phenyl-2-alkylproline *tert*-butyl esters *via* enantioselective phase-transfer catalysis.



Scheme 3 Preparation of *tert*-butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**8**).

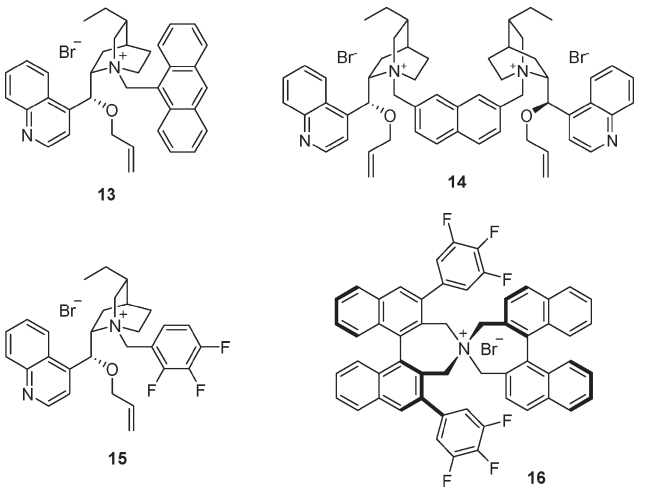
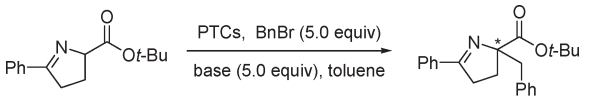


Fig. 1 Chiral phase-transfer catalysts (**13–16**).

Table 1 Optimization of PTC reaction conditions



Entry	Catalyst (mol%)	Base	T [°C]	t [h]	Yield[a] [%]	ee[b] [%]
1	**13** (5.0)	s-KOH	0	2.5	79	83
2	**14** (5.0)	s-KOH	0	2.0	92	43
3	**15** (5.0)	s-KOH	0	3.5	92	86
4	**16** (5.0)	s-KOH	0	20	78	93
5	**16** (5.0)	s-KOH	−20	25	92	97
6	**16** (2.5)	s-KOH	−20	25	94	97
7	**16** (2.5)	s-CsOH	−20	48	64	78
8	**16** (2.5)	50% KOH	−20	72	50	86
9	**16** (2.5)	50% CsOH	−20	72	51	89

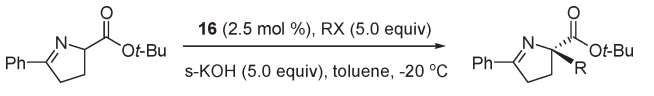
[a] Isolated yields. [b] The enantiomeric excess was determined by HPLC analysis of **9c** using a chiral column (Chiralcel OD-H) with hexanes–2-propanol as eluents.

First, we needed to prepare the substrate **8** for PTC alkylation. In 2010, the Lygo group reported the efficient diastereoselective reduction of (*S*)-**8** to synthesize *cis*-5-phenylproline, the precursor of (+)-RP66803.[31] We adopted their synthetic method for the preparation of (±)-**8**. *tert*-Butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**8**) was prepared from commercially available benzophenone imine of glycine *tert*-butyl ester (**10**) in 2 steps. Michael addition of **10** to phenylvinylketone (**11**), followed by intramolecular transimination using 15% citric acid afforded *tert*-butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**8**) (Scheme 3). For the phase-transfer catalytic alkylation, we used our previously reported reaction conditions.[27–30] The phase-transfer catalytic benzylation of **8** was performed using 5 mol% of the representative catalysts (**13**,[32] **14**,[33] **15**,[34] **16**[35]) along with benzyl bromide (5.0 equiv.) and solid KOH (5.0 equiv.) in toluene at 0 °C (Fig. 1).

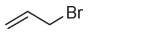
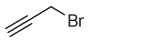
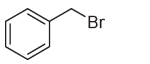
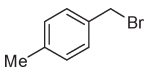
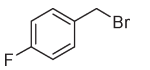
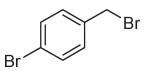
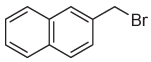
As shown in Table 1, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **16** (entry 4, 93% ee) gave the highest enantioselectivity, and all of the *cinchona* derived catalysts (**13–15**) afforded lower enantioselectivities compared to that of catalyst **16**, which was in accordance with previous results (entries 1–4).[27–30] Notably, aqueous 50% alkali bases showed longer reaction times with lower chemical yields than those of solid bases (entries 6–9). Lower temperature afforded higher enantioselectivity with higher chemical yields (entries 4–5). A decrease in the amount of catalyst **16** preserved the enantioselectivity and chemical yield until 2.5 mol% (entries 5 and 6). Best enantioselectivity was observed in the case of solid KOH base conditions at −20 °C (entry 6, 94%, 97% ee) in the presence of 2.5 mol% of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **16**.

Further investigation on the scope and limitation in enantioselective PTC alkylation with various alkyl halides under the optimal reaction conditions (entry 6 in Table 1) was performed. As shown in Table 2, very high chemical yields (up to 98%) and enantioselectivities (up to 97% ee) were observed in

Table 2 Enantioselective phase-transfer alkylation of **8** with various alkyl halides



8 **9**

Entry	RX	t [h]	Yield[a] [%]	ee[b] [%] ($[\alpha]_D^{25}$)
a		24	61	92 (+)
b		36	82	96 (+)
c		25	95	97 (+)
d		23	98	96 (+)
e		30	68	95 (+)
f		48	96	91 [(+)-*R*][c]
g		30	95	90 (+)[d]

[a] Isolated yields. [b] The enantiomeric excess was determined by HPLC analysis of **9** using a chiral column (Chiralcel OD-H, Chiralpak AD-H, Chiralpak AS-H) with hexanes–2-propanol as eluents. [c] The absolute configuration was assigned by X-ray crystallographic structure of **9f** and the other absolute configurations were tentatively assigned as (*R*) based on the absolute configuration of **9f**. [d] The enantiomeric excess was determined by HPLC analysis of the methyl ester analogue of **9g** due to the low resolution of **9g** in chiral HPLC analysis.

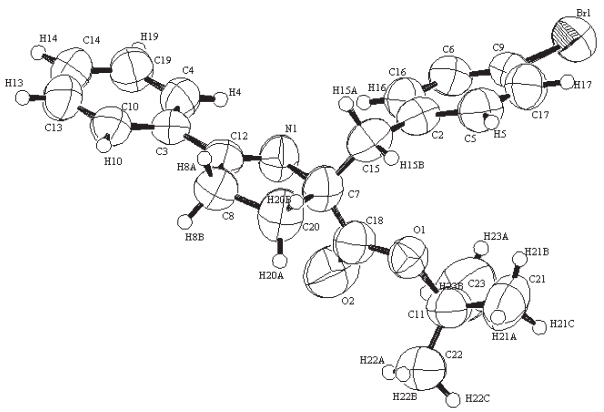
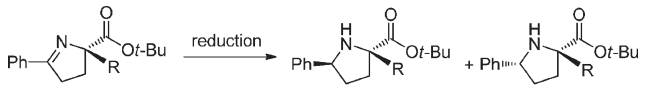


Fig. 2 X-ray crystallographic structure of **9f**.

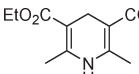
allylic, propargylic and benzylic halides, but unactivated alkyl halide such as methyl iodide provided poor chemical yield (CH_3I, 32%). The absolute configuration of **9f** was confirmed as (*R*) by X-ray crystallographic analysis (Fig. 2).[36]

Next, the diastereoselective reduction of an imine moiety of **9** was investigated. As shown in Table 3, the diastereoselectivities were quite variable depending upon the reducing agents. The reduction of **9c** with $NaCNBH_3$ in the presence of acetic acid provided a separable diastereomeric mixture of **17c** (2*R*,5*S*)[37] and **18c** (2*R*,5*R*)[37] (entry 1, **17c : 18c** = 50% : 22%).[38]

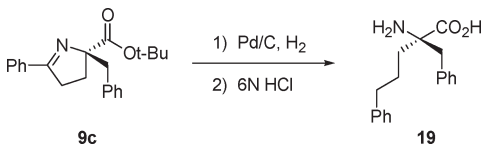
Table 3 Diastereoselective reductions of imine of **9a** and **9c** with various reducing agents



9 **17** **18**

Entry	R (**9**)	Reduction conditions	t [h]	Yield[a] [%] **17**	**18**
1	$PhCH_2$ (**9c**)	$NaCNBH_3$, AcOH,	1	50	22
2	$CH_2{=}CHCH_2$ (**9a**)	MeOH, RT	0.6	43	21
3	$PhCH_2$ (**9c**)	L-Selectride, THF, RT	24	0	52
4	$CH_2{=}CHCH_2$ (**9a**)		24	2	24
5[b]	$PhCH_2$ (**9c**)	$Na_2S_2O_4$, DMF, reflux	24	—	—
6	$PhCH_2$ (**9c**)	Pt/C, H_2, EtOH, RT	24	19	77
7	$PhCH_2$ (**9c**)	 DPP, CH_2Cl_2, 40 °C	48	0	20
8	$CH_2{=}CHCH_2$ (**9a**)		48	1	19

[a] Isolated yields. [b] No reaction was observed.



9c **19**

Scheme 4 Conversion of **9c** to amino acid **19**.

Interestingly, L-selectride and Hantzsch ester[39] in the presence of the catalytic amount of diphenyl phosphate (DPP) afforded only **18c** (entry 3, 52%; entry 7, 20%), which is opposite to that of $NaCNBH_3$. Hydrogenation of **9c** with Pt/C under atmospheric H_2 also provided **18c** as a major diastereoisomer (entry 6, **17c : 18c** = 19% : 77%). However, no reaction was observed in the case of $Na_2S_2O_4$ (entry 5). We speculate that the bulky reducing agents such as L-selectride and Hantzsch ester together with catalytic hydrogenation (Pt/C) can approach to the less sterically hindered β-face of **9c**, affording **18c** (entries 3, 6, 7) as a major diastereomer. In the case of $NaCNBH_3$, the chelation of $NaCNBH_3$ with oxygen of *tert*-butyl ester might let the hydride approach to the α-face of **9c**, affording **17c** as a major diastereomer. The allylated product **9a** also showed comparable results under the reduction conditions of $NaCNBH_3$ (entry 2, **17a : 18a** = 43% : 21%), L-selectride (entry 4, **17a : 18a** = 2% : 24%), and Hantzsch ester (entry 8, **17a : 18a** = 1% : 19%). Hydrogenolysis of **9c** (97% ee) using Pd/C under atmospheric H_2 followed by hydrolysis with 6 N HCl provided nonnatural amino acid **19** (Scheme 4).

Conclusion

We developed a very efficient enantioselective synthetic methodology for the synthesis of (2*S*)-5-phenyl-2-alkylproline

tert-butyl ester by the phase-transfer catalytic alkylation of *tert*-butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**8**), followed by diastereoselective reduction. The easy preparation of the substrate, the high enantioselectivity, and the very mild reaction conditions could make this method very practical for large scale processes of the versatile synthetic intermediate, chiral 5-phenyl-2-alkylprolines, which can be applied to asymmetric synthesis as organocatalysts or synthesis of biologically active proline based compounds.

Experimental section

General methods

All reagents bought from commercial sources were used as sold. As the commercially available KOH was a pellet type, KOH should be ground to the powder form for successful phase-transfer catalytic reaction and high enantiopurity. The phase-transfer catalyst **16**, (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide, was purchased from the commercial source (Wako). Flash column chromatography was carried out using silica gel (230–400 mesh). Nuclear magnetic resonance spectra were measured on a 300 MHz or 400 MHz instrument. All ^{1}H-NMR spectra were reported in ppm relative to $CHCl_3$ (δ 7.24). All ^{13}C-NMR spectra were reported in ppm relative to the central $CDCl_3$ (δ 77.23) or CD_3OD (δ 49.15). All HPLC analyses were performed using a 4.6 mm × 250 mm chiral column as the stationary phase.

Preparation of the phase-transfer catalysis substrate

***tert*-Butyl-2-(diphenylmethylene-amino)-5-oxo-5-phenylpentanoate (12).**[31] *tert*-Butyl 2-(diphenylmethylene-amino)-acetate **10** (413 mg, 1.40 mmol), solid KOH (157 mg, 2.8 mmol) and tetrabutylammonium bromide (45 mg, 0.14 mmol) were added to a 25 mL round bottom flask. Dichloromethane (4 mL) was added, then 1-phenyl-propenone **11** (277 mg, 2.1 mmol) in dichloromethane (4 mL) was added slowly to the reaction mixture over 2 h. After stirring for 0.5 h, the reaction mixture was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 25 : 1) to afford *tert*-butyl-2-(diphenylmethylene-amino)-5-oxo-5-phenylpentanoate (**12**) (506 mg, 85% yield) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94–7.10 (m, 15H), 4.05 (t, J = 6.1 Hz, 1H), 3.17–2.94 (m, 2H), 2.34–2.26 (m, 2H), 1.43 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.7, 171.1, 170.6, 132.9, 132.4, 130.3, 130.0, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.7, 81.1, 64.8, 34.7, 28.2, 28.0 ppm; IR (KBr) 2972, 1733, 1686, 1622, 1598, 1578, 1447, 1367, 1278, 1217, 1150, 1075, 1001, 848, 745, 686 cm^{-1}; HRMS (FAB$^+$): Calcd for $[M + H]^+$ $[C_{28}H_{30}NO_3]^+$ 428.2226; Found 428.2237.

5-*tert*-Butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (8).[31] To the mixture of *tert*-butyl-2-(diphenylmethylene-amino)-5-oxo-5-phenylpentanoate (**12**) (481 mg, 1.1 mmol) in THF (9.6 mL) was added 15% citric acid (4.8 mL). The reaction mixture was stirred for 2 h, then the reaction mixture was concentrated *in vacuo*. The residue was diluted with dichloromethane, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 10 : 1) to afford 5-*tert*-butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**8**) (244 mg, 88% yield) as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87–7.35 (m, 5H), 4.82–4.76 (m, 1H), 3.16–2.88 (m, 2H), 2.36–2.02 (m, 2H), 1.47 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.8, 172.3, 134.0, 130.8, 128.3, 128.0, 81.1, 75.3, 35.3, 28.0, 26.7 ppm; IR (KBr) 2978, 1733, 1614, 1576, 1449, 1392, 1367, 1256, 1213, 1153, 1030, 846, 764, 693 cm^{-1}; HRMS (FAB$^+$): Calcd for $[M + H]^+$ $[C_{15}H_{20}NO_2]^+$ 246.1494; Found 246.1512.

General procedure for asymmetric phase-transfer catalytic alkylation

Alkyl halide (0.41 mmol) was added to a solution of 5-*tert*-butyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**8**, 20 mg, 0.082 mmol) and (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **16** (phase-transfer catalyst, 1.9 mg, 0.0021 mmol) in toluene (0.3 mL) at −20 °C. After weighing of the powdered KOH (23 mg, 0.41 mmol), it was quickly added to the reaction mixture. The reaction mixture was stirred for specified time, then diluted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, filtered, concentrated *in vacuo*, and purified by column chromatography (hexane–EtOAc = 25 : 1).

***tert*-Butyl 2-allyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9a).** The general procedure was employed. After stirring for 24 h, **9a** was obtained by column chromatography as a yellow oil (14 mg, 64% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane–2-propanol = 99 : 1), flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: 5.1 min (minor), 6.3 min (major), 92% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86–7.35 (m, 5H), 5.83–5.69 (m, 1H), 5.15–5.04 (m, 2H), 3.11–2.96 (m, 2H), 2.68 (d, J = 3.4 Hz, 2H), 2.68–2.29 (m, 1H), 2.02–1.92 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.5, 130.8, 129.0, 128.4, 128.1, 124.6, 118.5, 83.3, 81.2, 42.6, 35.8, 30.8, 28.4, 28.0 ppm; IR (KBr) 3074, 2978, 2931, 1726, 1640, 1615, 1576, 1496, 1450, 1392, 1368, 1343, 1254, 1151, 1062, 1029, 996, 919, 848, 763, 693 cm^{-1}; HRMS (FAB$^+$): Calcd for $[M + H]^+$ $[C_{18}H_{24}NO_2]^+$ 286.1807; Found: 286.1799; $[\alpha]_D^{20}$ = +68.94 (c 1.0, $CHCl_3$).

***tert*-Butyl 5-phenyl-2-(prop-2-yn-1-yl)-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9b).** The general procedure was employed. After stirring for 36 h, **9b** was obtained by column chromatography as a pale yellow solid (19 mg, 82% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane–2-propanol = 99 : 1), flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: 9.6 min (minor), 11.6 min (major), 96% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.87–7.35 (m, 5H), 3.15–3.08 (m, 2H), 2.86 (ddd, J = 18.3 Hz, J = 16.7 Hz, J = 1.2 Hz, 2H), 2.51–2.40 (m, 1H), 2.22–2.12 (m, 1H), 1.90–1.88 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.5, 171.7, 130.9, 129.0, 128.4, 128.2, 82.7, 81.7, 80.4, 70.1, 36.5, 30.9, 28.1, 27.9 ppm; IR (KBr) 3295, 2978, 2930, 1727, 1614, 1576, 1496, 1451, 1426, 1392, 1368, 1344, 1273, 1254, 1223, 1157, 1071, 942, 846, 763, 693 cm^{-1}; HRMS (FAB$^+$): Calcd for

$[M + H]^+$ $[C_{18}H_{22}NO_2]^+$ 284.1651; Found 284.1645; m.p. = 96.4–96.7 °C; $[\alpha]_D^{25}$ = +39.76 (*c* 0.5, $CHCl_3$).

***tert*-Butyl-2-benzyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9c).** The general procedure was employed. After stirring for 25 h, **9c** was obtained by column chromatography as a pale yellow solid (26 mg, 95% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane–2-propanol = 99 : 1), flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: 6.1 min (major), 7.3 min (minor), 97% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88–7.23 (m, 10H), 3.29 (dd, *J* = 41.2 Hz, *J* = 6.8 Hz, 2H), 2.98–2.86 (m, 1H), 2.43–2.29 (m, 2H), 2.17–2.07 (m, 1H), 1.54 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.6, 173.3, 136.9, 134.2, 130.8, 130.6, 128.3, 127.9, 127.8, 126.3, 84.0, 81.2, 43.4, 35.6, 30.8, 28.0 ppm; IR (KBr) 3029, 2928, 1725, 1615, 1576, 1496, 1453, 1391, 1367, 1343, 1254, 1154, 1083, 1057, 846, 762, 695 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{22}H_{26}NO_2]^+$ 336.1964; Found 336.1971; m.p. = 98.4–100.6 °C; $[\alpha]_D^{25}$ = +11.06 (*c* 1.0, $CHCl_3$).

***tert*-Butyl 2-(4-methylbenzyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9d).** The general procedure was employed. After stirring for 23 h, **9d** was obtained by column chromatography as a pale yellow solid (28 mg, 98% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane–2-propanol = 99 : 1), flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: 10.4 min (minor), 11.7 min (major), 96% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81–6.96 (m, 9H), 3.23 (dd, *J* = 17.3 Hz, *J* = 6.8 Hz, 2H), 2.89–2.77 (m, 1H), 2.38–2.27 (m, 2H), 2.27 (s, 3H), 2.06–1.96 (m, 1H), 1.45 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.5, 171.7, 130.9, 129.0, 128.4, 128.2, 82.7, 81.7, 80.4, 70.1, 36.5, 30.9, 28.1, 27.9 ppm; IR (KBr) 2976, 2926, 2857, 1725, 1615, 1576, 1514, 1454, 1392, 1368, 1343, 1274, 1254, 1154, 1059, 847, 762, 693 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{23}H_{28}NO_2]^+$ 350.2120; Found 350.2119; m.p. = 80.9–81.2 °C; $[\alpha]_D^{25}$ = +65.17 (*c* 1.0, $CHCl_3$).

***tert*-Butyl 2-(4-fluorobenzyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9e).** The general procedure was employed. After stirring for 30 h, **9e** was obtained by column chromatography as a yellow oil (20 mg, 68% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralcel OD-H, hexane–2-propanol = 99 : 1), flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: 7.1 min (major), 8.0 min (minor), 95% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80–6.83 (m, 9H), 3.23 (dd, *J* = 25.7 Hz, *J* = 6.9 Hz, 2H), 2.91–2.79 (m, 1H), 2.41–2.22 (m, 2H), 2.02–1.93 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.9, 160.5, 132.6, 132.2, 132.1, 128.6, 128.4, 128.0, 114.7, 114.5, 42.6, 35.6, 30.9, 29.7, 28.0, 27.8 ppm; IR (KBr) 2927, 2854, 1726, 1606, 1576, 1509, 1451, 1368, 1345, 1255, 1223, 1155, 1100, 1059, 846, 761, 693 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{22}H_{25}FNO_2]^+$ 354.1869; Found 354.1856; $[\alpha]_D^{25}$ = +81.31 (*c* 1.0, $CHCl_3$).

(2*R*,5*S*)-*tert*-Butyl 2-(4-bromobenzyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9f). The general procedure was employed. After stirring for 48 h, **9f** was obtained by column chromatography as a white solid (33 mg, 96% yield). The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AS-H, hexane–2-propanol = 99 : 1), flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: 4.8 min (minor), 5.7 min (major), 91% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80–7.77 (m, 2H), 7.45–7.27 (m, 5H), 7.12–7.10 (m, 2H), 3.23 (dd, *J* = 25.7 Hz, *J* = 6.9 Hz, 2H), 2.93–2.82 (m, 1H), 2.48–2.22 (m, 2H), 2.00–1.90 (m, 1H), 1.44 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.6, 172.9, 136.1, 134.0, 132.4, 130.8, 130.7, 128.3, 127.8, 120.4, 83.7, 81.3, 42.8, 35.6, 31.0, 27.9 ppm; IR (KBr) 3429, 3060, 3030, 2977, 2930, 1901, 1725, 1615, 1576, 1488, 1450, 1403, 1392, 1367, 1344, 1270, 1253, 1153, 1108, 1071, 1059, 1033, 1012, 922, 846, 803, 761, 719, 693, 637 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{22}H_{25}BrNO_2]^+$ 414.0990; Found 414.1066; m.p. = 91.2–92.8 °C; $[\alpha]_D^{25}$ = +20.07 (*c* 1.0, $CHCl_3$).

***tert*-Butyl-2-(naphthalene-2-ylmethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9g).** The general procedure was employed. After stirring for 30 h, **9g** was obtained by column chromatography as a yellow oil (30 mg, 95% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79–7.36 (m, 12H), 3.23 (dd, *J* = 20.4 Hz, *J* = 6.8 Hz, 2H), 2.90–2.77 (m, 1H), 2.35–2.26 (m, 2H), 2.12–2.03 (m, 2H), 1.46 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.7, 173.2, 134.7, 134.2, 133.2, 132.1, 130.6, 129.3, 129.2, 128.3, 127.9, 127.6, 127.5, 127.1, 125.7, 125.3 ppm; IR (KBr) 3057, 2974, 2928, 1724, 1614, 1576, 1508, 1451, 1391, 1367, 1343, 1252, 1153, 1064, 848, 822, 758, 693 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{26}H_{28}NO_2]^+$ 386.2120; Found 386.2132; $[\alpha]_D^{25}$ = +132.65 (*c* 1.0, $CHCl_3$).

Methyl-2-(naphthalene-1-ylmethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (9ga, methyl ester analogue of 9g). To the mixture of *tert*-butyl 2-(naphthalene-2-ylmethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9g**) (20 mg, 0.052 mmol) in dichloromethane (0.5 mL) was added trifluoroacetic acid (0.5 mL) and triethylsilane (0.02 mL, 0.13 mmol). The reaction mixture was stirred for 1 h, then the reaction mixture was concentrated *in vacuo*. To the mixture of residue in toluene (0.25 mL) and methanol (0.1 mL) was added TMS-diazomethane in 2 M diethyl ether (0.1 mL, 0.17 mmol). The reaction mixture was stirred for 0.5 h, then the reaction mixture was diluted with EtOAc, washed with water, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 25 : 1) to afford methyl 2-(naphthalene-1-ylmethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9ga**) (16 mg, 90% yield) as a yellow oil. The enantioselectivity was determined by chiral HPLC analysis (DIACEL Chiralpak AD-H, hexane–2-propanol = 99 : 1), flow rate = 1.0 mL min^{-1}, λ = 254 nm, retention time: 22.4 min (minor), 32.3 min (major), 90% ee. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.79–7.30 (m, 12H), 3.76 (s, 3H), 3.46 (dd, *J* = 23.8 Hz, *J* = 6.8 Hz, 2H), 2.91–2.81 (m, 1H), 2.44–2.10 (m, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.7, 134.0, 133.2, 132.2, 131.0, 129.4, 129.0, 128.4, 128.1, 127.6, 127.5, 127.3, 125.8, 125.5 ppm; IR (KBr) 3057, 2924, 2853, 1733, 1614, 1576, 1508, 1449, 1367, 1344, 1250, 1157, 1062, 899, 859, 823, 758, 693 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{23}H_{22}NO_2]^+$ 344.1651; Found 344.1653; $[\alpha]_D^{25}$ = +133.87 (*c* 0.5, $CHCl_3$).

Reduction of 9c

(2*R*,5*S*)-*tert*-Butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (17c) *via* $NaCNBH_3$. To the mixture of *tert*-butyl-2-benzyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9c**) (168 mg, 0.50 mmol) in methanol (5 mL) was added sodium cyanoborohydride (375 mg, 6.0 mmol) and acetic acid (342 μL, 6.0 mmol). The reaction mixture was stirred for 1 h, the reaction mixture was diluted with EtOAc, washed with water, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 20 : 1) to afford (2*R*,5*S*)-*tert*-butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (**17c**) (82 mg, 50% yield) as a colorless oil and (2*R*,5*R*)-*tert*-butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (**18c**) (37 mg, 22% yield) as a colorless oil. Compound **17c**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48–7.17 (m, 10H), 4.25 (t, 1H), 3.08 (dd, J = 67.3 Hz, J = 13.0 Hz, 2H), 2.64 (s, 1H), 2.30–2.19 (m, 1H), 2.13–1.94 (m, 2H), 1.65–1.52 (m, 1H), 1.42 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.1, 145.6, 137.7, 130.3, 128.1, 127.8, 126.64, 126.60, 126.4, 81.0, 70.3, 61.4, 46.1, 35.4, 34.3, 28.0 ppm; IR (KBr) 3352, 3084, 3061, 3029, 3003, 2975, 2931, 2871, 1947, 1878, 1807, 1721, 1603, 1584, 1494, 1475, 1454, 1412, 1392, 1367, 1324, 1299, 1255, 1213, 1152, 1080, 1058, 1030, 983, 939, 911, 896, 847, 744, 700, 664, 636 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{22}H_{28}NO_2]^+$ 338.2120; Found 338.2124; $[\alpha]_D^{25}$ = −99.33 (*c* 1.0, $CHCl_3$).

(2*R*,5*R*)-*tert*-Butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (18c) *via* hydrogenation. To the mixture of *tert*-butyl-2-benzyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9c**) (144 mg, 0.43 mmol) and Pt/C (14 mg) in methanol (3 mL), H_2 gas was added. The reaction mixture was stirred for 24 h, the reaction mixture was filtered by Celite 545, washed with methanol, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 20 : 1) to afford (2*R*,5*R*)-*tert*-butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (**18c**) (111 mg, 77% yield) as a colorless oil and (2*R*,5*S*)-*tert*-butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (**17c**) (28 mg, 19% yield) as a colorless oil. Compound **18c**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.41–7.17 (m, 10H), 4.19–4.14 (m, 1H), 3.29 (dd, J = 17.3 Hz, J = 6.6 Hz, 2H), 2.42–2.35 (m, 1H), 2.12–2.03 (m, 1H), 1.99–1.89 (m, 1H), 1.68–1.52 (m, 3H), 1.37 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.4, 143.7, 137.8, 130.2, 128.4, 127.9, 127.1, 126.8, 126.4, 81.3, 71.0, 63.2, 45.3, 37.4, 34.9, 27.9 ppm; IR (KBr) 3356, 3086, 3062, 3030, 2975, 2929, 2857, 1720, 1604, 1494, 1454, 1392, 1367, 1323, 1257, 1218, 1153, 1089, 1031, 982, 913, 848, 760, 744, 700 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{22}H_{28}NO_2]^+$ 338.2120; Found 338.2113; $[\alpha]_D^{25}$ = −9.95 (*c* 1.0, $CHCl_3$).

(2*R*,5*R*)-*tert*-Butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (18c) *via* L-selectride. To the *tert*-butyl-2-benzyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9c**) (67 mg, 0.20 mmol) was added L-selectride solution, 1.0 M in THF (2.4 mL, 2.4 mmol). The reaction mixture was stirred for 24 h. The reaction mixture was quenched with water and 1 M HCl, then the water layer was saturated with NaCl. The mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 20 : 1) to afford (2*R*,5*R*)-*tert*-butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (**18c**) (35 mg, 52% yield) as a colorless oil.

(2*R*,5*R*)-*tert*-Butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (18c) *via* Hantzsch ester. To the *tert*-butyl-2-benzyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9c**) (84 mg, 0.25 mmol) in a screw-capped vial was added a dichloromethane solution (2 mL) of Hantzsch ester (95 mg, 0.38 mmol) and diphenyl phosphate (3 mg, 0.13 mmol). The vial was flushed with argon gas and the reaction mixture was stirred for 48 h at 40 °C. The reaction solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane–EtOAc = 20 : 1) to afford (2*R*,5*R*)-*tert*-butyl-2-benzyl-5-phenylpyrrolidine-2-carboxylate (**18c**) (16 mg, 20% yield) as a colorless oil.

Reduction of 9a

(2*R*,5*S*)-*tert*-Butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (17a) *via* $NaCNBH_3$. To the mixture of *tert*-butyl-2-allyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9a**) (83 mg, 0.29 mmol) in methanol (3 mL) was added sodium cyanoborohydride (219 mg, 3.49 mmol) and acetic acid (200 μL, 3.49 mmol). The reaction mixture was stirred for 40 min, the reaction mixture was diluted with EtOAc, washed with water, washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 30 : 1 > 10 : 1) to afford (2*R*,5*S*)-*tert*-butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (**17a**) (36 mg, 43% yield) as a colorless oil and (2*R*,5*R*)-*tert*-butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (**18a**) (17.5 mg, 21% yield) as a colorless oil. Compound **17a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42–7.18 (m, 5H), 5.94–5.84 (m, 1H), 5.14–5.06 (m, 2H), 4.26 (t, J = 7.44 Hz, 1H), 2.74 (s, 1H), 2.61–2.56 (m, 1H), 2.46–2.41 (m, 1H), 2.22–2.05 (m, 2H), 1.91–1.85 (m, 1H), 1.71–1.62 (m, 1H), 1.47 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 176.2, 145.3, 134.3, 128.1, 126.7, 126.5, 117.6, 80.9, 69.2, 61.5, 45.0, 34.6, 34.3, 28.1 ppm; IR (KBr) 3353, 3077, 3027, 2977, 2932, 2871, 1723, 1641, 1604, 1493, 1475, 1455, 1393, 1368, 1323, 1295, 1254, 1227, 1145, 1081, 1059, 1029, 1000, 915, 849, 755, 700, 666 cm^{-1}; HRMS (FAB^+): Calcd for $[M + H]^+$ $[C_{18}H_{26}NO_2]^+$ 288.1964; Found 288.1964; $[\alpha]_D^{20}$ = −70.16 (*c* 1.0, $CHCl_3$).

(2*R*,5*S*)-*tert*-Butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (18a) *via* L-selectride. To the *tert*-butyl-2-allyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9a**) (70 mg, 0.25 mmol) was added L-selectride solution, 1.0 M in THF (2.9 mL, 2.9 mmol). The reaction mixture was stirred for 24 h. The reaction mixture was quenched with water and 1 M HCl, then the water layer was saturated with NaCl. The mixture was extracted with EtOAc, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane–EtOAc = 30 : 1 > 10 : 1) to afford (2*R*,5*S*)-*tert*-butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (**17a**) (1.5 mg, 2% yield) as a colorless oil and (2*R*,5*R*)-*tert*-butyl-2-allyl-5-

phenylpyrrolidine-2-carboxylate (**18a**) (17 mg, 24% yield) as a colorless oil. Compound **18a**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40–7.19 (m, 5H), 5.87–5.77 (m, 1H), 5.08 (t, J = 15.08 Hz, 2H), 4.26 (dd, J_1 = 9.78 Hz, J_2 = 5.8 Hz, 1H), 2.58–2.53 (m, 2H), 2.42–2.31 (m, 2H), 2.15–2.07 (m, 1H), 1.88–1.81 (m, 1H), 1.70–1.60 (m, 1H), 1.46 (s, 9H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.6, 143.8, 134.3, 128.4, 127.1, 126.8, 117.8, 81.1, 69.7, 63.3, 44.6, 36.8, 35.3, 28.0 ppm; IR (KBr) 3356, 3073, 3029, 3004, 2977, 2932, 2871, 1950, 1875, 1828, 1720, 1640, 1604, 1526, 1495, 1476, 1454, 1436, 1412, 1392, 1368, 1320, 1254, 1229, 1151, 1030, 1000, 988, 915, 849, 759, 700 cm^{-1}; HRMS (FAB$^+$): Calcd for $[M + H]^+$ $[C_{18}H_{26}NO_2]^+$ 288.1964; Found 288.1961; $[\alpha]_D^{20}$ = −14.58 (c 1.0, $CHCl_3$).

(2*R*,5*R*)-*tert*-Butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (18a) *via* Hantzsch ester. To the *tert*-butyl-2-allyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9a**) (68 mg, 0.24 mmol) in a screw-capped vial was added a dichloromethane solution (2 mL) of Hantzsch ester (85 mg, 0.33 mmol) and diphenyl phosphate (3 mg, 0.01 mmol). The vial was flushed with argon gas and the reaction mixture was stirred for 48 h at 40 °C. The reaction solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane–EtOAc = 30 : 1 > 10 : 1) to afford (2*R*,5*S*)-*tert*-butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (**17a**) (0.8 mg, 1% yield) as a colorless oil and (2*R*,5*R*)-*tert*-butyl-2-allyl-5-phenylpyrrolidine-2-carboxylate (**18a**) (13 mg, 19% yield) as a colorless oil.

2-Amino-2-benzyl-5-phenylpentanoate (19). To the mixture of *tert*-butyl-2-benzyl-5-phenyl-3,4-dihydro-2*H*-pyrrole-2-carboxylate (**9c**) (147 mg, 0.44 mmol) and Pd/C (74 mg) in methanol (3 mL), H_2 gas was added. The reaction mixture was stirred for 24 h, the reaction mixture was filtered by Celite 545, washed with methanol, and concentrated *in vacuo*. To the mixture of residue in methanol (2 mL) was added 6 M aqueous HCl (2 mL). The reaction mixture was refluxed for 1 h, then the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue was purified by ion-exchange column chromatography with a DOWEX® 50WX8-100 ion-exchange resin to afford 2-amino-2-benzyl-5-phenylpentanoate (**19**) (68 mg, 54% yield) as a white solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27–7.08 (m, 10H), 2.98 (dd, J = 47.3 Hz, J = 7.2 Hz), 2.58–2.53 (m, 2H), 1.89–1.81 (m, 1H), 1.66–1.50 (m, 3H) ppm; ^{13}C-NMR (100 MHz, CD_3OD) δ 1752, 142.0, 134.1, 130.1, 129.0, 128.7, 127.9, 126.2, 65.7, 48.9, 41.8, 35.4, 34.7, 24.9 ppm; IR (KBr) 3436, 3061, 3028, 2925, 2854, 1603, 1496, 1454, 1392, 1330, 1172, 1097, 1032, 781, 745, 700 cm^{-1}; HRMS (FAB$^+$): Calcd for $[M + H]^+$ $[C_{18}H_{22}NO_2]^+$ 284.1651; Found 284.1648; m.p. = 252.2–254.2 °C; $[\alpha]_D^{25}$ = +7.05 (c 0.5, MeOH).

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