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SYNTHESIS OF CHIRAL 1,2-DIHYDROPYRIDINES AND 2,3,4-TRISUBSTITUTED PYRIDINES FROM α-AMINO ACIDS

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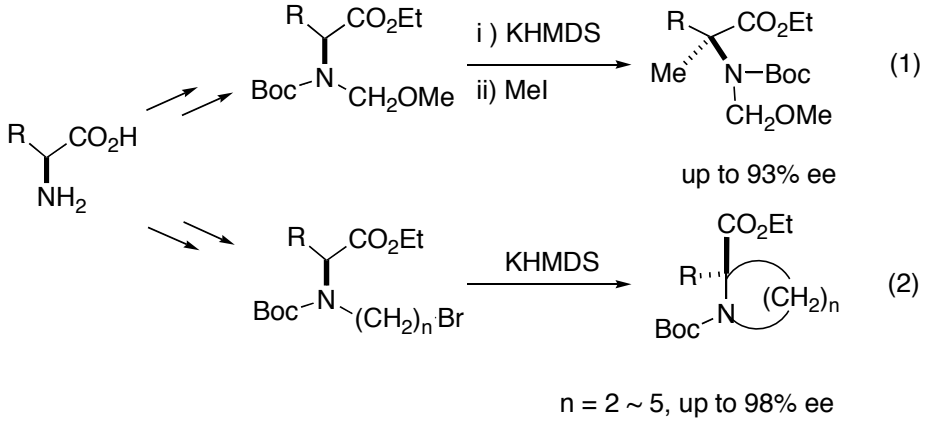
This paper is dedicated to the memory of late Professor Kiyoshi Tanaka.

Abstract – Chiral 1,2-dihydropyridines were prepared by Dieckmann condensation of α-amino acid derivatives. The dihydropyridines were converted to 2,3,4-trisubstituted pyridines.

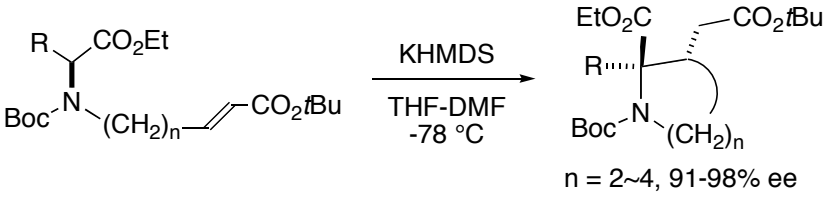
INTRODUCTION

The stereoselective construction of chiral quaternary stereocenters is one of the most challenging tasks in current synthetic organic chemistry.[1] We have developed a direct method for the enantioselective construction of α,α-disubstituted α-amino acids from α-amino acids via memory of chirality.[2,3] Under these conditions, α-methylation of *N*-*tert*-butoxycarbonyl(Boc)-*N*-methoxymethyl-α-amino acid derivatives takes place in up to 93% ee without the aid of external chiral sources such as chiral auxiliaries or chiral catalysts (Scheme 1, (1)).[4] We further developed a route for the straightforward synthesis of cyclic amino acids with a tetrasubstituted stereocenter from readily available α-amino acids via memory of chirality (Scheme 1, (2)).[5]



Scheme 1

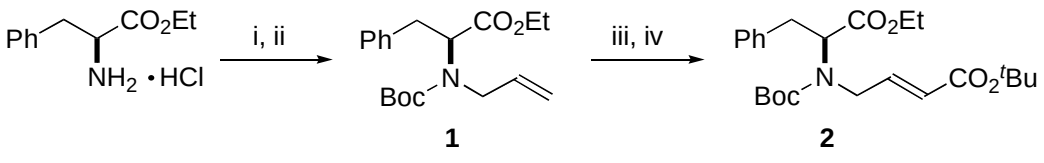
Recently, we developed a method for asymmetric construction of highly substituted nitrogen heterocycles via the intramolecular conjugate addition of enolates generated from α-amino acid derivatives (Scheme 2). Five-, six-, and seven-membered ring cyclization took place to give pyrrolidine-, piperidine-, azepane-, and tetrahydroisoquinoline derivatives, respectively with contiguous quaternary and tertiary stereocenters in high enantiomeric purity.[6] Attempted four-membered ring cyclization according to the strategy shown in Scheme 2 did not give the expected azetidine derivatives, but gave chiral dihydropyridine derivatives. Here we describe a method for the synthesis of chiral 1,2-dihydropyridines and 2,3,4-trisubstituted pyridines from α-amino acids.



Scheme 2

RESULTS AND DISCUSSION

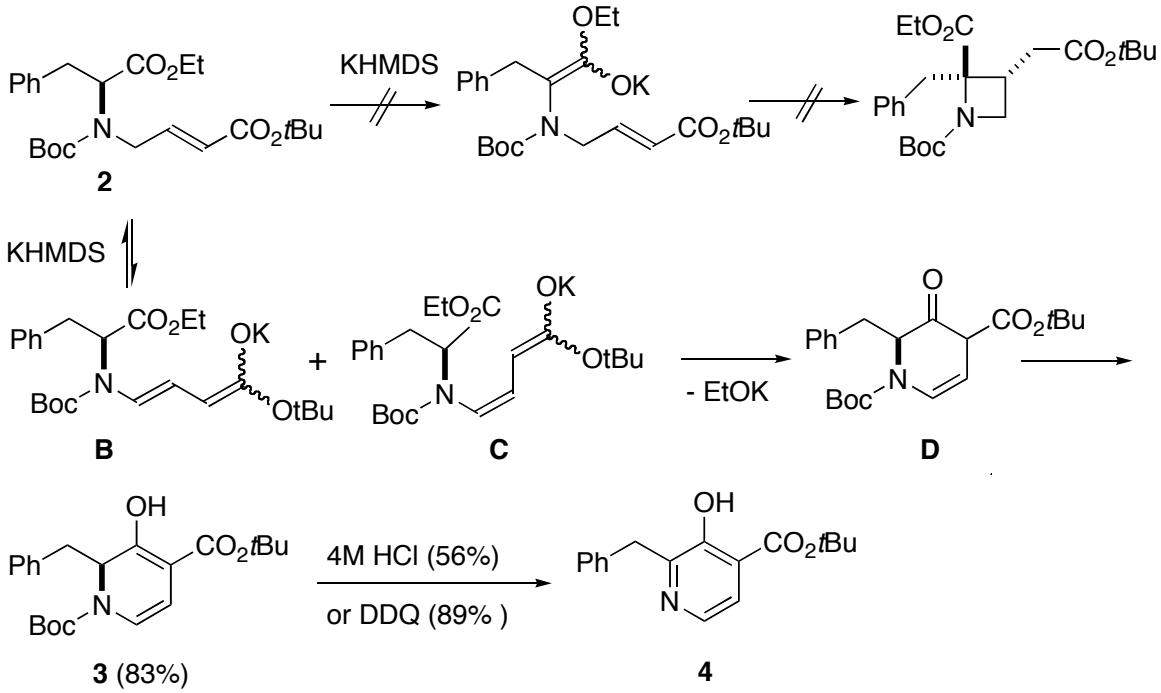
Four-membered ring cyclization via intramolecular conjugate addition of enolates was attempted (Scheme 4). Precursor (**2**) for the cyclization reaction was prepared from phenylalanine ethyl ester through *N*-allylation, introduction of a Boc group to the nitrogen, ozonolysis of the double bond, followed by Wittig reaction (Scheme 3). Treatment of **2** with 1.1 equiv. of KHMDS did not give the expected azetidine, while 1,2-dihydropyridine (**3**) was obtained in 48% yield. Use of 2.2 equiv. of KHMDS gave **3** in 83% yield (Scheme 4). Enamino enolates **B** and **C** would be generated by γ–proton abstraction of α,β-unsaturated ester (**2**). *Z*-geometry of the enamino enolate is indispensable for the Dieckmann cyclization to take place to give **D**. Since selective formation of *Z*-enolate **C** is unlikely, equilibrium between (**B**+**C**) and **2** through a protonation-deprotonation step might be responsible for the formation of **C**. Determination of the enantiomeric excess of **3** was not possible due to its lability. Removal of the Boc group of **3** with 4M HCl in EtOAc followed by treatment with $NaHCO_3$ gave trisubstituted pyridine



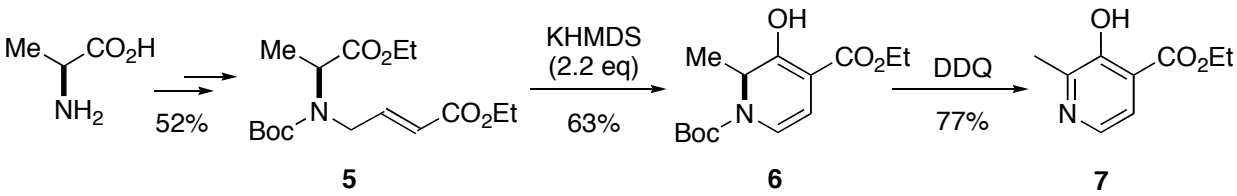
Reagents: i, allyl bromide, DMF, K_2CO_3, rt; ii, Boc_2O, DIPEA, DCM, rt (77% for two steps); iii, O_3, MeOH-DCM, -60 °C then Me_2S; iii, $Ph_3P{=}CHCO_2tBu$, DCM rt (72% for two steps)

Scheme 3

4 in 56% yield. Alternatively, **4** was obtained in 89% yield by the treatment of **3** with DDQ. Similarly, alanine derivative (**5**) was treated with 2.2 equiv. of KHMDS to give dihydropyridine (**6**) in 63% yield, which was then converted into trisubstituted pyridine (**7**)[7] in 77% yield by treatment with DDQ (Scheme 5).



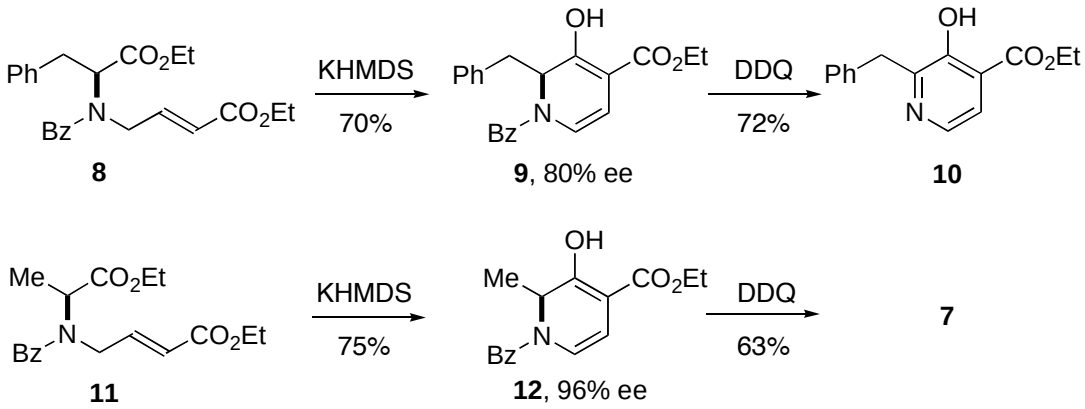
Scheme 4



Scheme 5

In order to determine the enantiomeric excess of the 1,2-dihydropyridine derivatives, the reaction of *N*-benzoyl derivative (**8**) was investigated. Treatment of **8** with 1.9 equiv. of KHMDS gave **9** in 70% yield. While dihydropyridine (**9**) was not stable under atmospheric conditions, purification of **9** by usual SiO_2 preparative TLC was possible and the ee was determined to be 80% by HPLC analysis with a chiral stationary phase. Similar treatment of alanine derivative (**11**) gave chiral dihydropyridine (**12**) in 75% yield in 96% ee.[8] Dihydropyridines (**9** and **12**) were stable and no conversion to pyridines (**10** and **7**) was observed when kept in freezer (-18 °C) at least for two months, whereas **9** and **12** were slowly converted to a 39:61 mixture of **9** and **10** and a 85:15 mixture of **12** and **7**, respectably, after a week under atmospheric conditions ($CHCl_3$ solution at room temperature). On treatment of **9** and **12** with DDQ,

2,3,4-trisubstituted pyridines (**10** and **7**) were obtained in 72% and 63% yield, respectively.



Scheme 6

In conclusion, we have developed a unique method for the synthesis of chiral 1,2-dihydropyridines with 2, 3,4-substituents from α–amino acids.[9] Since 1,2-dihydropyridines are utilized as dienes for Diels-Alder reactions,[10] multisubstituted chiral 1,2-dihydropyridines might be useful intermediates for the synthesis of complex nitrogen heterocyles.

EXPERIMENTAL

NMR spectra were obtained with a Varian Gemini 200 (200 MHz) spectrometer or a JEOL JMN 400 spectrometer, chemical shifts being given in ppm units (tetramethylsilane or chloroform as internal standards, indicating 0 or 7.24, respectively). IR spectra were recorded with a JACSO FT/IR–300 spectrometer. Specific rotation was measured with a Horiba SEPA–200 automatic digital polarimeter. MS spectra were recorded with a JEOL JMS–DX300 mass spectrometer. TLC analysis and preparative TLC were performed on commercial glass plates bearing a 0.25 mm layer and 0.5 mm layer of Merck Kiesel–gel 60 F_{254}, respectively. Silica gel chromatography was carried out Wakogel C–200, Fuji Silysia BW–1277H, or Nacalai Tesque Silica gel 60 (150–325 mesh). Dry solvents (THF, ether, hexane, dichloromethane, and toluene; <50 ppm water contents) were purchased from Kanto Chemical CO., Inc. and used without further treatment.

(*S*)-*N*-*tert*-Butoxycarbonyl-*N*-{2-(*E*)-3-(*tert*-butoxycarbonyl)allyl}phenylalanine ethyl ester (2). A mixture of phenyl alanine ethyl ester hydrochloride (1.20 g, 5.22 mmol), K_2CO_3 (1.59g, 11.5 mmol), allyl bromide (0.68 mL, 7.83 mmol) in DMF (5mL) was stirred at rt for 2 h. The reaction mixture was poured onto ice-water and and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The syrupy liquid thus obtained was used

for Boc protection under the standard protocol with Boc_2O (1.37 g, 6.26 mmol) and DIPEA (1.00 mL, 5.74 mmol) in CH_2Cl_2. After 21 h, usual work up and column chromatography with short pad silica gel afforded **1** as a syrup (1.34 g, 77%). Ozone was passed through the solution of **1** in MeOH- CH_2Cl_2 (1:1) at –60ºC until blue color persistently appears. Me_2S (3.0 mL) was then added and the resulting mixture was warmed up to rt. After evaporation of solvent, CH_2Cl_2 (10 mL) and Wittig ylide ($Ph_3PCHCO_2{}^tBu$, 2.03 g, 5.39 mmol) was added to the residue and the resulting mixture was stirred at rt overnight. The crude product was purified by SiO_2 column chromatography (12% EtOAc-hexane) to give the **2** as colorless crystals in 72% yield.

2: mp 55-57 °C. $[\alpha]_D^{20}$-93 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2979, 2935, 1697 1455, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.13 (m, 5H), 6.58–6.51 (m, 1H), 5.80, 5.73 (two d, *J* = 15.8, 15.8 Hz, ratio = 4:3, 1H), 4.37-3.83 (m, 4H), 3.32 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.21–3.03 (m, 2H), 1.46, 1.41 (two s, ratio = 4:1, 18H), 1.31, 1.25 (two t, *J* = 7.2, 7.5 Hz, ratio = 4:3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.50, 170.28, 164.97, 164.83, 154.41, 154.05, 142.58, 141.96, 137.43, 137.32, 128.90, 128.31, 128.11, 126.43, 126.31, 124.03, 123.46, 80.96, 80.51, 80.03, 61.93, 61.22, 61.07, 48.94, 36.17, 35.45, 28.20, 28.10, 14.09; EI (*m/z*) 433, 377, 333, 321, 260, 242, 186 (100%), 176, 91. HRMS calcd for $C_{24}H_{35}NO_6$: 433.2464; Found: 433.2474.

(*S*)-Di-*tert*-butyl 2-benzyl-3-hydroxypyridine-1,4(2*H*)-dicarboxylate (3) and *tert*-butyl 2-benzyl-3-hydroxypyridine-4-carboxylate (4): General procedure for the preparation of dihydropyridines and pyridines from amino acid derivatives. A solution of KHMDS (0.48M, 0.53 mL, 0.25 mmol) in THF was slowly added to the solution of **2** (50 mg, 0.12 mmol) in THF (2 mL) at –78 ºC. The reaction mixture was stirred at the same temperature for 20 h, then quenched with sat. aq. NH_4Cl solution and extracted with Et_2O. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give a residue. The crude product was purified by column chromatography (12:1 hexane-EtOAc) to give **3** (37 mg, 83 %) as a viscous liquid. This compound was dissolved in THF (1 mL) and cooled to 0 °C. A solution of DDQ (35 mg, 0.15 mmol) in THF (1 mL) was added to the solution of **3** and the resulting mixture was stirred for 2 h. Extractive work up and followed by purification with PTLC (25% EtOAc-hexane) afforded **4** as a viscous oil in 89% yield (74% overall yield from **2**).

3: IR ($CHCl_3$) 3440, 2980, 1740, 1700, 1480, 1370, 1160 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 12.25, 12.16 (two s, ratio = 3:2, 1H), 7.28-7.11 (m, 5H), 6.52, 6.29 (two dd, *J* = 8.2, 1.4 Hz, 7.6, 1.2 Hz, ratio = 3:2, 1H), 5.71, 5.50 (two d, *J* = 7.6, 7.6 Hz, ratio = 3:2, 1H), 5.12–5.05 (m, 0.4H), 4.92–4.84 (m, 0.6H), 2.95–2.80 (m, 2H), 1.53, 1,52 (two s, ratio = 3:2, 9H), 1.32, 1.12 (two s, ratio = 2:3, 9H); EI (*m/z*) 387, 314, 296, 254, 240, 230, 184, 140 (100%), 122, 91, 57; HRMS calcd for $C_{22}H_{29}NO_5$: 387.2045; Found: 387.2062.

4: viscous oil. IR ($CHCl_3$) 3142 (br), 2979, 1673, 1604, 1372, 1338, 1146 cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$) δ 10.87 (s, 1H), 8.11 (d, *J* = 5.2 Hz, 1H), 7.42 (d, *J* = 5.2 Hz, 1H), 7.38-7.12 (m, 5H), 4.24 (s, 2H), 1.60 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.68, 153.98, 152.00, 139.04, 138.98, 129.06, 128.24, 126.10, 120.35, 118.99, 84.17, 38.72, 28.09; EI (*m/z*) 286, 285 (M^+), 228 (100%), 211, 210, 183, 154, 127, 103, 91, 57; HRMS calcd for $C_{17}H_{19}NO_3$: 285.1365; Found: 285.1363.

(*S*)-*N*-*tert*-Butoxycarbonyl-*N*-{2-(*E*)-3-(ethoxycarbonyl)allyl}alanine ethyl ester (5): viscous oil. Prepared from L-alanine according to the procedure for **2** in 52% overall yield**:** IR ($CHCl_3$) 2980, 1701, 1446, 1393, 1367, 1277, 1164, 1038, 863, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95–6.85 (m, 1H), 6.01, 5.93 (two d, *J* = 15.4, 15.8 Hz, ratio = 1:1, 1H), 4.67–4.64 (m, 0.5H), 4.26–4.15 (m, 5.5H), 3.94–3.72 (m, 1H), 1.53–1.26 (m, 9H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 171.96, 166.28, 166.21, 166.19, 155.19, 154.80, 145.26, 144.57, 122.21, 121.70, 81.05, 80.85, 61.22, 60.44, 55.55, 47.32, 46.28, 28.27, 15.80, 15.47, 14.24, 14.11; EI (*m/z*) 329, 273, 256, 228, 200, 184, 156 (100%), 110, 83, 57; HRMS calcd for $C_{16}H_{27}NO_6$: 329.1838; Found: 329.1827.

(*S*)-Ethyl *N*-*tert*-butoxycarbonyl-2-methyl-3-hydroxypyridine-4(2*H*)-carboxylate (6): viscous oil. IR ($CHCl_3$) 2979, 1711, 1660, 1420, 1348, 1293, 1230, 1173, 1120, 1035, 857, 727 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.01, 11.97 (two s, ratio = 4:5, 1H), 6.45, 6.30 (two d, *J* = 7.9, 7.9 Hz, ratio = 4:5, 1H), 5.61, 5.54 (two d, *J* = 7.9, 7.9 Hz, ratio = 4:5, 1H), 4.93, 4.78 (two d, *J* = 6.9, 6.9 Hz, ratio = 5:4, 1H), 4.28 (q, *J* = 6.8 Hz, 2H), 1.51, 1.50 (two s, ratio = 4:5, 9H), 1.33 (t, *J* = 6.8 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H); EI (*m/z*) 283, 268, 236, 227, 212, 181 (100%), 168, 154, 137, 122, 94, 84, 57.

Ethyl 2-methyl-3-hydroxypyridine-4-carboxylate (7): colorless crystals, mp 45-47 °C. IR ($CHCl_3$) 1685, 1610, 1400, 1315, 1195 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.08 (d, *J* = 5.2 Hz, 1H), 7.48 (d, *J* = 5.2 Hz, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.43, 154.16, 150.45, 138.91, 119.52, 116.96, 62.24, 19.05, 14.09; EI (*m/z*) 181, 135 (100%), 107, 84, 79; HRMS calcd for $C_9H_{11}NO_3$: 181.1719; Found: 181.0736.

(*S*)-*N*-Benzoyl-*N*-{2-(*E*)-3-(ethoxycarbonyl)allyl}phenylalanine ethyl ester (8). A mixture of phenylalanine ethyl ester hydrochloride (500 mg, 2.18 mmol), K_2CO_3 (720 mg, 5.21 mmol), ethyl 4-bromocrotonate (670 mg, 3.47 mmol) and DMF (5 mL) was stirred at rt for 4 h. The reaction mixture was then poured onto ice-water and extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The syrupy liquid thus obtained was dissolved in CH_2Cl_2 (5 mL). To the solution, were added DIPEA (1.10 mL, 6.31 mmol) and benzoyl chloride (0.66 mL, 5.56 mmol) at rt. After stirring for 30 min at the same temperature, the solution was poured into ice-water and extracted with Et_2O. Usual work up and purification by SiO_2 column chromatography gave **8** (670 mg, 75%) as a colorless oil.

8: viscoul oil. $[\alpha]_D^{20}$ –130 (*c* 1.6, $CHCl_3$); IR ($CHCl_3$) 2981, 1721, 1644, 1277, 1182 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.15 (m, 8H), 7.02-6.85 (m, 2H), 6.54–6.40 (m, 1H), 6.05–5.85 (m, 1H), 4.68–4.00

(m, 6H), 3.95–2.92 (m, 3H), 1. 29 (t, *J* = 7.2 Hz,, 6H); EI (*m/z*) 409, 364, 336, 304, 246, 233, 196, 176, 128, 105 (100%), 77 ; HRMS calcd for $C_{24}H_{27}NO_5$: 409.1889; Found: 409.1892.

(*S*)-Ethyl 1-benzoyl-2-benzyl-3-hydroxypyridine-4(2*H*)-carboxylate (9): viscous oil. $[\alpha]_D^{20}$ 342 (*c* 1.2, $CHCl_3$); HPLC condition: OJ column, flow: 1.5 ml/min, 2% EtOH-hexane, retention time: 12.41 min (minor), 19.71 min (major); ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.07 (s, 1H), 7.41-7.20 (m, 10H), 5.96 (d, *J* = 7.6 Hz, 1H), 5.58 (t, *J* = 6.4 Hz, 1H), 5.53 (d, *J* = 7.6 Hz, 1H), 4.30 (q, *J* = 6.8Hz, 2H), 3.13 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.98 (dd, *J* = 13.2, 6.4 Hz, 1H), 1.34 (t, *J* = 6.8 Hz, 3H); EI (*m/z*) 363, 362, 306, 286, 272, 257, 211, 210, 154, 139, 105 (100%), 77; HRMS calcd for $C_{22}H_{21}NO_4$: 363.1471; Found: 363.1459.

Ethyl 2-benzyl-3-hydroxypyridine-4-carboxylate (10): viscous oil. IR ($CHCl_3$) 3150 (br), 1682, 1374, 1316, 1176 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.14 (d, *J* = 5.2 Hz, 1H), 7.50 (d, *J* = 5.2 Hz, 1H), 7.38–7.17 (m, 5H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.25 (s, 2H), 1.41 (t, *J* = 7.2Hz, 3H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 169.28, 153.89, 152.22, 139.30, 138.91, 129.10, 128.33, 126.22, 120.11, 117.81, 62.27, 38.73, 14.08; EI (*m/z*) 259, 257 (100%), 256, 228, 211, 210,183, 154, 127, 105, 84; HRMS calcd for $C_{15}H_{15}NO_3$: 257.1052; Found: 257.1064.

(*S*)-*N*-Benzoyl-*N*-{2-(*E*)-3-(ethoxycarbonyl)allyl}alanine ethyl ester (11): Prepared in Yield 67% from L-alanine according to the procedure for the preparation of **8**.

11: viscous oil. $[\alpha]_D^{20}$ –56 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 2983, 1740, 1720, 1700, 1644, 1447, 1183 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 5H), 7.05–6.90 (m, 1H), 6.20–5.90 (m, 1H), 4.65–3.90 (m, 3H), 4.21 (q, *J* = 7.2 Hz, 4H), 1.64–1.38 (m, 3H), 1.30 (t, J = 7.2 Hz, 6H); EI (*m/z*) 333, 312, 2888, 260, 228, 200, 154, 105 (100%); HRMS calcd for $C_{18}H_{23}NO_5$: 333.1576; Found: 333.1574.

(*S*)-Ethyl 1-benzoyl-2-benzyl-3-hydroxypyridine-4(2*H*)-carboxylate (12): viscous oil. HPLC condition: OJ column, flow: 1.5 mL/min, 1% IP-hexane, retention time: 14.5 min (minor), 18.2 min (major); IR ($CHCl_3$) 3360, 2990, 2965, 1730, 1660, 1600, 1410, 1355 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.12 (s, 1H), 7.51–7.28 (m, 5H), 6.03 (d, *J* = 7.6 Hz, 1H), 5.65 (d, *J* = 7.6 Hz, 1H), 5.31 (q, *J* = 7.2 Hz, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 1.37, (d, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H); EI (*m/z*) 287, 272, 241, 230, 212, 182, 136, 105 (100%), 77; HRMS calcd for $C_{16}H_{17}NO_4$: 287.1157; Found: 287.1158.

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