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A FLEXIBLE APPROACH TO (*S*)-3-AMINO-2-PYRROLIDINONE DERIVATIVES

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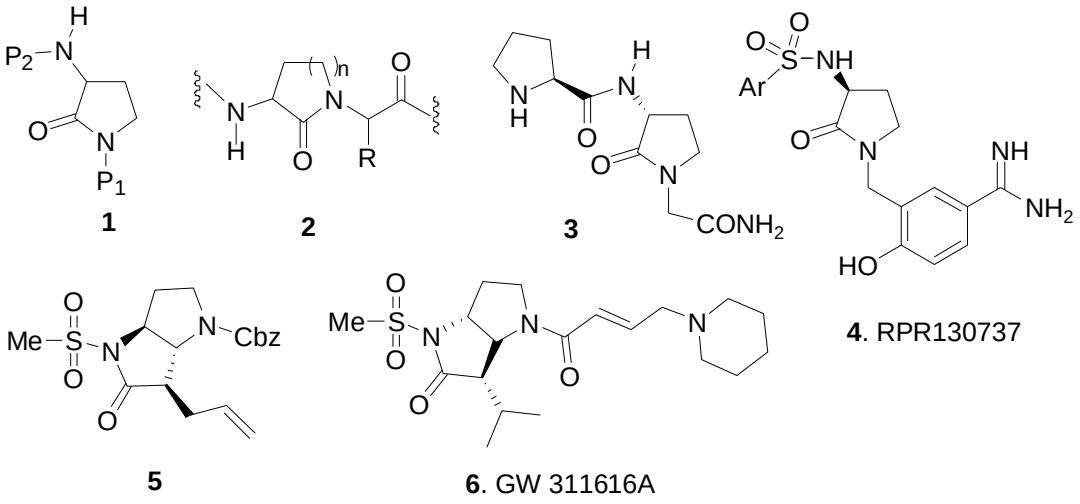
Abstract – Starting from (*S*)-aspartic acid, a flexible chemoselective approach to (*S*)-3-amino-2-pyrrolidinone derivatives was reported. The (*S*)-3-amino-2-pyrrolidinone derivatives thus synthesized are useful templates for designing medicinal interesting compounds.

INTRODUCTION

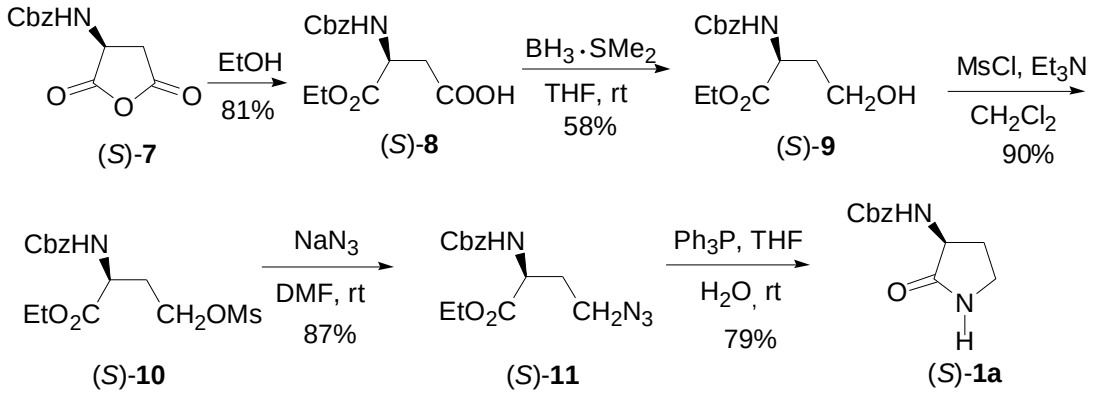
3-Amino-2-pyrrolidinones (**1**) are building block widely used in designing bioactive compounds.[1~5] For example, Freidinger's lactams[1] of type (**2**) have proven to be useful molecular scaffolds for designing pepetidomimetics in view of developing enzyme inhibitors and receptor modulators.[2] In this context, **3** was designed as a conformationally constrained analogue of Pro-Leu-Gly-NH_2 (PLG), and was shown to be 10 000 times more active than PLG in dopamine receptor modulation;[3a] RPR130737 (**4**) was shown to be a potent Factor Xa inhibitor with selectivity against structurally related serine proteases (>1000 times).[3b] In addition, 3-amino-2-pyrrolidinones (**1**) have been used in the synthesis of pyrrolidine-*trans*-lactams such as **5**, an inhibitor of serine protease elastin[5a] and GW 311616A (**6**), a potent inhibitor of human neutrophil elastase.[5b] Several methods have been reported for the synthesis of both (*R*)- and (*S*)-3-amino-2-pyrrolidinone derivatives (**1**).[1~6] In continuation of our interests in the synthesis of bioactive 2-pyrrolidinones,[7] we wish to report here a new approach to (*S*)-3-amino-2-pyrrolidinone derivatives (**1**) starting from (*S*)-aspartic acid.

RESULTS AND DISCUSSION

This paper is dedicatd to Dr. Pierre Potier on the occasion of his 70th birthday.



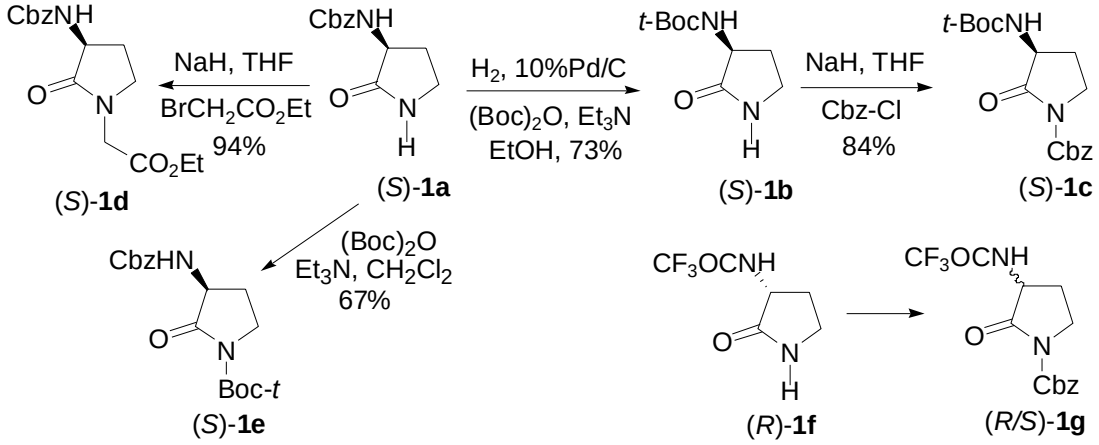
Our approach to (*S*)-**1a** is outlined in Scheme 1. The synthesis commenced with commercially available Cbz protected aspartic acid anhydride (*S*-**7**), which we obtained from L-aspartic acid.[8] Ethanolysis of (*S*)-**7** (EtOH, room temperature, 1.5 days) proceeded regioselectively, which gave pure regioisomer (*S*-**8**) after one recrystallization. Electronic inductive effect seems to be the origin of the high regioselectivity. Chemoselective reduction of carboxyl group in (*S*)-**8** was achieved by treatment of (*S*-**8**) with borane-dimethyl sulfide complex (2 days at 5 °C, then 12 h at room temperature), which afforded the desired (*S*)-**9** in 58% yield. Mesylation of (*S*)-**9** with mesyl chloride (NEt_3, CH_2Cl_2, 0 °C, 4 h, 90% yield), followed by treatment of the resulted mesylate (**10**) with sodium azide in dimethylformamide at room temperature for two days afforded the azidoester (*S*-**11**) in 87% yield. Treatment of a THF solution of (*S*)-**11** with triphenylphosphine at room temperature for 6 h, followed by addition of H_2O and stirring for an additional two days afforded, *via* an one-pot Staudinger reaction[9]-nucleophilic cyclization,[7c] the desired (*S*)-3-benzyloxycarbonylamino-2-pyrrolidinone (**1a**) in 79% yield.



Scheme 1

To demonstrate the versatility of (*S*)-**1a** as a building block, its transformation into (*S*)-**1b** ~ (*S*)-**1e** was investigated (Scheme 2). Thus, in the presence of palladium catalyst and di-*tert*-butyl dicarbonate [10%

Pd / C, H_2, 1 atm, $(Boc)_2O$, EtOH, room temperature, 4 days], one-pot *N*-protective group switch occurred smoothly, affording protected **1b**[3b] in 73% yield (Scheme 1). Lactam (*S*-**1b**) has been used as a chiral building block in the synthesis of a series of Factor Xa inhibitors such as RPR130737 (**4**)[3b] Chemoselective *N*-deprotonation with sodium hydride followed by reaction with CbzCl led to (*S*)-**1c**, a member of pivotal building blocks for the synthesis of selective serine protease inhibitors such as pyrrolidine-*trans*-lactams (**5**).[5b,5c] Since the transformation of (*R*)-**1f** to (*R*)-**1g** under similar conditions was reported to result in partial racemization,[5b] the optical homogeneousity of (*S*)-**1c** was verified. Chiral HPLC analysis showed that the *ee* of (*S*)-**1c** was 99.9%, which indicated that during the transformation of (*S*)-**1b** to (*S*)-**1c**, no observable racemization occurred. Similar treatment of the anion derived from (*S*)-**1a** with ethyl bromoacetate afforded (*S*)-**1d** in 94% yield. 3-Amino-2-pyrrolidinones of type (*S*-**1d**)[3a,6a] are useful building blocks for constrained peptomimetics.[1~3] Finally, when (*S*)-**1** was treated with di-*tert*-butyl dicarbonate in dichloromethane and in the presence of triethylamine (room temperature, 1 day), chemoselective protection occurred, which afforded imide (*S*)-**1e** in 67% yield.



Scheme 2

CONCLUSION

In summary, starting from (*S*)-aspartic acid, we have achieved the chemoselective syntheses of five (3*S*)-3-amino-2-pyrrolidinone derivatives (**1a** ~ **1e**) in high enantiomeric purity (as verified on **1c**). The (*S*)-3-amino-2-pyrrolidinone derivatives thus synthesized are useful building blocks for designing pharmaceutically interesting compounds.

EXPERIMENTAL

Melting points were determined on a Yanaco MP-500 micro melting point apparatus. IR spectra were measured with a Nicolet Avatar 360 FT-IR spectrophotometer using film KBr pellet techniques. NMR spectra were recorded in $CDCl_3$ (^1H at 500 MHz and ^{13}C at 125 MHz) on a Varian unity +500

spectrophotometer with tetramethylsilane as an internal standard. MS spectra were recorded by a Bruker Dalton Esquire 3000 plus liquid chromatography-mass Spectrum (ESI direct injection). Optical rotations were measured with Perkin-Elmer 341 automatic polarimeter. THF was dried by distillation over metallic sodium and benzophenone; CH_2Cl_2 were distilled over P_2O_5. Silica gel (Zhifu, 300~400 mesh) was used for column chromatography, eluting with AcOEt / petroleum ether (PE) (bp 60-90 °C) mixtures.

1-Ethyl (S)-N-benzyloxycarbonylaspartate (8)

A solution of (*S*)-**7**[8] (2.18 g, 10.38 mmol) in ethanol (0.38 mL, 178 mmol) was stirred at rt for 1.5 days. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: AcOEt: PE = 1: 2) to afford (*S*)-**8** (2.09 g, 81%) as a colorless solid. mp 80.2-82.5 °C (AcOEt / PE). $[\alpha]_D^{20}$ +29.5° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3337, 3034, 2982, 2924, 1732, 1521, 1214 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.24 (t, *J* = 7.0 Hz, 3H, CH_3), 2.92 (dd, *J* = 4.4, 17.5 Hz, 1H, H-3), 3.09 (dd, *J* = 4.4, 17.5 Hz, 1H, H-3), 4.23 (q, *J* = 7.0 Hz, 2H, OCH_2), 4.62 (ddd, *J* = 4.2, 8.6, 8.6 Hz, 1H, H-2), 5.11 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 5.14 (d, *J* = 12.4 Hz, 1H, OCH_2Ph), 5.78 (br d, *J* = 7.8 Hz, 1H, NH), 6.28 (br s, 1H, COOH), 7.18-7.40 (m, 5H, Ph) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.9 (C-1), 170.5 (C-4), 156.0 ($\underline{C}O_2CH_2Ph$), 136.0, 128.5, 128.3, 128.1 (C-Ar), 67.2 ($CO_2\underline{C}H_2Ph$), 62.1 (C-2), 50.2 (C-3), 36.4 ($CO_2\underline{C}H_2CH_3$), 14.0 ($CO_2CH_2\,\underline{C}H_3$) ppm. MS (ESI, *m/z*): 296 ($M+H^+$, 100). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.72; H, 5.76; N, 4.58.

Ethyl (S)-2-(benzyloxycarbonylamino)-4-hydroxybutanoate (9)

To a stirring solution of (*S*)-**8** (1.52 g, 5.16 mmol) in anhydrous THF (2.44 mL) was added dropwise BH_3-SMe_2 (0.59 mL, 6.19 mmol) at –15 °C over a period of 30 min. The mixture was further stirred for 2 days at 5 °C, then allowed to warm up and stirred at rt for another 12 h. The mixture was quenched with H_2O (4 mL) in an ice / salt bath and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (eluent: AcOEt: PE = 1: 1) to afford (*S*)-**9** (0.68 g, 58%) as a colorless solid. mp 46.2-48.8 °C (AcOEt / PE). $[\alpha]_D^{20}$ +7.5° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3364, 2961, 2924, 1716, 1701, 1538, 1453, 1340, 1212, 1056 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, *J* = 7.3 Hz, 3H, CH_3), 1.66-1.74 (m, 1H, H-3), 2.04-2.12 (m, 1H, H-3), 2.90 (s, 1H, OH), 3.62-3.76 (m, 2H, H-4), 4.23 (q, *J* = 7.3 Hz, 2H, OCH_2), 4.62 (m, 1H, H-2), 5.11 (d, *J* = 12.1 Hz, 1H, OCH_2Ph), 5.14 (d, *J* = 12.1 Hz, OCH_2Ph), 5.76 (br, 1H, NH), 7.18-7.40 (m, 5H, Ph) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 172.6 (C-1), 156.8 ($\underline{C}O_2CH_2Ph$), 136.1, 128.6, 128.3, 128.1 (C-Ar), 67.3 ($CO_2\underline{C}H_2Ph$), 61.7 (C-2), 58.4 ($CO_2\underline{C}H_2CH_3$), 51.3 (C-4), 35.7 (C-3), 14.1 ($CO_2CH_2\underline{C}H_3$) ppm. MS (EI): 304 ($M+Na^+$, 100). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.31; H, 6.62; N 5.14.

Ethyl (S)-2-benzyloxycarbonylamino-4-methanesulfonyloxybutanoate (10)

To a cooled (–20 °C) solution of (*S*)-**9** (0.40 g, 1.42 mmol) in anhydrous CH_2Cl_2 (4.3 mL) were added dropwise Et_3N (0.30 mL, 2.13 mmol) and MsCl (0.13 mL, 1.70 mmol). After the addition, the temperature was allowed to arise to 0 °C over a period of 4 h. The reaction was quenched with 1N aqueous HCl (4 mL) and H_2O (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The extracts were washed successively with H_2O (1 mL), saturated aqueous $NaHCO_3$ (2 mL) and brine (2 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: AcOEt: PE = 1: 2) to afford (*S*)-**10** (0.46 g, 90%) as a colorless solid. mp 77.6-78.8 °C (AcOEt / PE). $[\alpha]_D^{20}$ +23.3° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3367, 3064, 3032, 2981, 2939, 1782, 1722, 1528, 1455, 1353, 1261, 1025 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, *J* = 7.0 Hz, 3H, CH_3), 2.10-2.20 (m, 1H, H-3), 2.30-2.40 (m, 1H, H-3), 3.02 (s, 3H, SO_2CH_3), 4.22 (q, *J* = 7.0 Hz, 2H, OCH_2), 4.34 (m, 2H, H-4), 5.11(d, *J* = 12.1 Hz, 1H, OCH_2Ph), 5.14 (d, *J* = 12.1 Hz, OCH_2Ph), 5.54 (br d, *J* = 7.0 Hz, 1H, NH), 7.30-7.45 (m, 5H, Ph) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 171.4 (C-1), 155.9 ($\underline{C}O_2CH_2Ph$), 136.1, 128.6, 128.3, 128.2 (C-Ar), 67.2 ($CO_2\underline{C}H_2Ph$), 65.8 (C-2), 62.1 (C-4), 50.9 ($CO_2\underline{C}H_2CH_3$), 37.2 ($SO_2\underline{C}H_3$), 32.0 (C-3), 14.1 ($CO_2CH_2\underline{C}H_3$) ppm. MS (ESI, *m/z*): 360 ($M+H^+$, 100). Anal. Calcd for $C_{15}H_{21}NO_7S$: C, 50.13; H, 5.89; N, 3.90. Found: C, 50.06; H, 5.94; N, 4.09.

Ethyl (S)-4-azido-2-benzyloxycarbonylaminobutanoate (11)

To a solution of (*S*)-**10** (1.79 g, 4.98 mmol) in DMF (15 mL) was added NaN_3 (1.9 g, 29.9 mmol). After stirring at rt for 2 days, the mixture was quenched with H_2O (45 mL) and extracted with ether (5×20 mL). The combined organic phases were washed successively with H_2O (15 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: AcOEt: PE = 1: 4) to afford (*S*)-**11** (1.33 g, 87%) as a colorless oil. $[\alpha]_D^{20}$ +26.1° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3349, 2931, 2100, 1733, 1540, 1455, 1339, 1260, 1060 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.29 (t, *J* = 7.0 Hz, 3H, CH_3), 1.90-2.00 (m, 1H, H-3), 2.10-2.18 (m, 1H, H-3), 3.35-3.44 (m, 2H, H-4), 4.27 (q, *J* = 6.7 Hz, 2H, OCH_2), 4.42-4.50 (m, 1H, H-2), 5.10 (m, 2H, OCH_2Ph), 5.50 (br d, *J* = 6.7 Hz, 1H, NH), 7.30-7.40 (m, 5H, Ph) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 171.6 (1C), 155.9 (1C), 136.1, 128.6, 128.3, 128.2 (6C), 67.2 (1C), 61.9 (1C), 51.8 (1C), 47.6 (1C), 31.8 (1C), 14.1 (1C) ppm. MS (ESI, *m/z*): 324 (M^++H_2O, 100), 329 ($M+Na^+$, 80). HRMS Calcd for $[C_{14}H_{18}N_4O_4+Na]^+$: 329.1226; found: 329.1220. Anal. Calcd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.61; H, 5.92; N, 18.50.

(S)-3-Benzyloxycarbonylamino-2-pyrrolidinone (1a)

To a solution of (*S*)-**11** (1.33 g, 4.35 mmol) in THF (17.4 mL) was added PPh_3 (1.14 g, 4.35 mmol). The mixture was stirred at rt for 6 h, and then H_2O (1.6 mL, 87 mmol) was added dropwise. After stirring at rt for another 2 days, the mixture was extracted with H_2O (10 mL) and the aqueous phase was washed with AcOEt (3×10 mL) and CH_2Cl_2 (3×10 mL). After concentrated under reduced pressure, the residue was crystallized from ethanol-ether to afford **1a** (0.81 g, 79%) as colorless crystals. mp 171.0-173.3 °C. $[\alpha]_D^{20}$ –13.2° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3300, 2920, 1692, 1548, 1393, 1293, 1075, 1024 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.96 (m, 1H, H-4), 2.58 (m, 1H, H-4), 3.35 (m, 2H, H-5), 4.26 (m, 1H, H-3), 5.12 (s, 2H, OCH_2Ph), 5.56 (s, 1H, $NHCO_2$), 6.64 (s, 1H, NH) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 29.9 (1C), 39.0 (1C), 51.9 (1C), 67.0 (1C), 128.1, 128.5, 136.3 (6C), 156.5 (1C), 175.4 (1C) ppm. MS (ESI, *m/z*): 357 ($M+Na^+$, 100). Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.39; H, 6.12; N, 11.91.

(S)-3-tert-Butyloxycarbonylamino-2-pyrrolidinone (1b)

To a mixture of **1a** (310 mg, 1.32 mmol) and 10% Pd / C (40 mg) were added methanol (5.3 mL) and triethylamine (0.37 mL, 2.64 mmol), followed by $(Boc)_2O$. The mixture was stirred at rt and under an atmosphere of H_2 for 4 days. The mixture was filtered over celite. Flash chromatographic purification on silica gel (eluent: AcOEt: PE = 4: 1) afforded known **1b**[3b] (193 mg, 73%) as a colorless solid. mp 168.0-170.3 °C (AcOEt / PE). $[\alpha]_D^{20}$ –11.2° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3300, 2977, 1691, 1532, 1390, 1294, 1171, 1069 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.50 (s, 9H, *t*-Bu), 2.00 (m, 1H, H-4), 2.74 (m, 1H, H-4), 3.35 (m, 2H, H-5), 4.26 (m, 1H, H-3), 5.20 (br s, 1H, $NHCO_2$), 6.84 (m, 1H, NH) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 28.3 (3C), 30.2 (1C), 39.0 (1C), 51.6 (1C), 79.9 (1C), 155.9 (1C), 175.8 (1C) ppm. MS (ESI, *m/z*): 223 ($M+Na^+$, 100), 201 ($M+H^+$, 70).

Benzyl (S)-(3-tert-butyloxycarbonylamino-2-oxopyrrolidin-1-yl)carboxylate (1c)

To a suspension of NaH (38 mg, 60% in mineral oil, 1.59 mmol) in anhydrous THF (7.2 mL), was added, under an atmosphere of N_2, a solution of **1b** (289 mg, 1.44 mmol) in THF (7.2 mL) and Cbz-Cl (0.25 mL, 1.73 mmol). The mixture was stirred at –78 °C for 4 h, quenched with saturated aqueous solution of NH_4Cl (4 mL). After concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: AcOEt: PE = 1: 2) to afford **1c** (280 mg, 84% based on the recovered starting material **1b**, 121 mg) as a colorless solid. The enantiomeric purity of **1c** was determined by chiral HPLC and found to be 99.9% *ee*. mp 139.7-142.3 °C. (lit.,[5b] mp 139-141 °C for *R*-**1c**). $[\alpha]_D^{20}$ –10.5° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3365, 2977, 2928, 1794, 1716, 1521, 1456, 1384, 1299, 1165, 1036 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.56 (s, 9H, $C(CH_3)_3$), 1.82-1.94 (m, 1H, H-4), 2.60-2.68 (m, 1H, H-4), 3.50-3.60 (m, 1H, H-5), 3.78-3.88 (m, 1H, H-5), 4.28-4.36 (m, 1H, H-3), 5.16 (br s, 1H,

NH), 5.24 (s, 2H, OCH_2Ph), 7.14-7.40 (m, 5H, Ar-H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 26.8 (1C), 28.0 (3C), 42.8 (1C), 53.9 (1C), 67.2 (1C), 83.6 (1C), 128.2, 128.3, 128.6, 136.0 (6C), 149.8 (1C), 156.2 (1C), 171.5 (1C) ppm. MS (ESI, *m/z*): 357 ($M+Na^+$, 100).

Ethyl (S)-(3-benzyloxycarbonylamio-2-oxopyrrolidin-1-yl)acetate (1d)

To a solution of **1a** (50 mg, 0.21 mmol) in THF (8.9 mL) were added, at 0 °C, NaH (60% in mineral oil, 13 mg, 0.32 mmol). After stirring at 0 °C for 1 h, ethyl bromoacetate (0.03 mL, 0.26 mmol) was added and the mixture was stirred overnight at 0 °C. The reaction was diluted with AcOEt (5 mL) and quenched by brine. The layers were separated and the aqueous layer was extracted for three times with AcOEt. The combined organic layers were dried over (Na_2SO_4) and concentrated under reduced pressure. The residue product was purified by column chromatography (eluent: AcOEt: PE = 1: 1) to yield **1d** (62 mg, 94%) as colorless oil, which crystallized upon standing up. mp 86.8-88.0 °C. IR (film) ν_{max}: 3318, 3061, 3032, 2982, 2931, 1744, 1699, 1532, 1456, 1407, 1205, 1026 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) (rotamer) δ: 1.23 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.84-2.04 (m, 1H, H-4), 2.54-2.72 (m, 1H, H-4), 3.24-3.34 (m, 1H, H-5), 3.36-3.46 (m, 1H, H-5), 3.80-3.96 (m, 1H, NCH_2), 4.07 (m, 1H, NCH_2), 4.10 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 4.20-4.36 (m, 1H, H-3), 5.04 (m, 2H, CH_2Ph), 5.40 (br s, 1H, NH), 7.34-7.40 (m, 5H, Ar-H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) (rotamer) δ: 14.1 (1C), 27.9 (1C), 37.8 (1C), 43.5, 44.5, 45.1 (1C), 52.3, 54.2 (1C), 61.4 (1C), 66.8, 66.9 (1C), 128.1, 128.5, 129.0, 132.7, 133.5, 134.2, 136.1 (Ar-C), 156.3 (1C), 168.1, 168.5 (1C), 172.5 (1C) ppm. MS (ESI, *m/z*): 321 ($M+H^+$, 100), 343 ($M+Na^+$, 70).

tert-Butyl (S)-(3-benzyloxycarbonylamino-2-oxopyrrolidin-1-yl)carboxylate (1e)

To a cooled (0 °C) solution of **1b** (0.81 g, 3.47 mmol) in anhydrous CH_2Cl_2 (13.4 mL) were added Et_3N (1.20 mL, 8.66 mmol) and $(Boc)_2O$ (1.60 mL, 6.93 mmol). The mixture was stirred at rt for 1 day, then quenched with H_2O (5 mL). The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic phases were washed with brine (5 mL), dried over anhydrous Na_2SO_4. After concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: AcOEt: PE = 1: 2) to afford **1e** (0.77 g, 67%) as a colorless oil. $[\alpha]_D^{20}$ –11.7° (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3345, 2978, 2929, 1789, 1719, 1532, 1456, 1370, 1317, 1258, 1153, 1059 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.56 (s, 9H, $C(CH_3)_3$), 1.82-1.94 (m, 1H, H-4), 2.60-2.68 (m, 1H, H-4), 3.50-3.60 (m, 1H, H-5), 3.78-3.88 (m, 1H, H-5), 4.28-4.36 (m, 1H, H-3), 5.14 (s, 2H, OCH_2Ph), 5.40 (br s, 1H, NH), 7.14-7.40 (m, 5H, Ar-H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 26.8 (1C), 28.0 (3C), 42.8 (1C), 53.9 (1C), 67.2 (1C), 83.6 (1C), 128.2, 128.3, 128.6, 136.0 (6C), 149.8 (1C), 156.2 (1C), 171.5 (1C) ppm. MS (ESI, *m/z*): 357 ($M+Na^+$, 100). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.06; H, 6.63; N, 8.38. Found: C, 61.32; H, 6.71; N, 8.37.

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