

An improved formal total synthesis of (-)-anisomycin

Pei -Qiang Huang*, Xiao Zheng

Department of Chemistry, Xiamen University, Xiamen, Fujian 361005, CHINA

E-mail: pqhuang@xmu.edu.cn

Dedicate with best wishes to Professor Zhi-Tang Huang on the occasion of his 75th birthday

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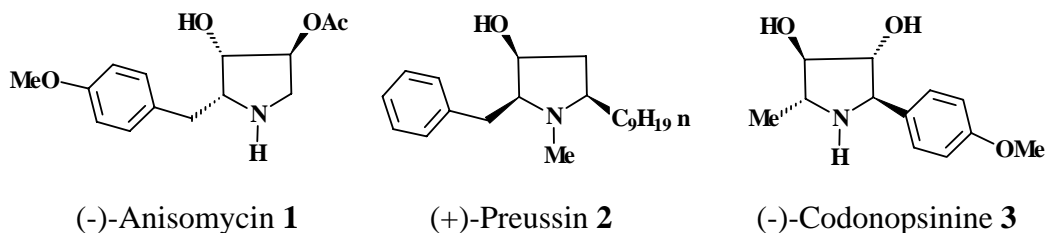
Abstract

(*R*)-1-Benzoyloxycarbonyl-2-(4-methoxyphenyl)methyl-3-pyrroline **14** was synthesized from (*S*)-*N*, *O*-dibenzyl malimide **5** via a highly regio and *trans* stereoselective reductive alkylation of **5**. This constitutes an improved formal asymmetric synthesis of natural (-)-anisomycin.

Keywords: Anisomycin, malic acid, reductive alkylation, asymmetric synthesis, malimide

Introduction

Polysubstituted pyrrolidines represent a class of bioactive natural products as exemplified by the antifungal antibiotics (-)-anisomycin **1**, (+)-preussin **2** and (-)-codonopsinine **3**.



Since its first isolation from *Streptomyces griseolus* and *S. roseochromogenes*¹ in the early fifties of last century, anisomycin has become an important tool in molecular biology.² It also has been used for the treatment of trichomonas vaginitis³ and amebic dysentery,⁴ and as an agricultural fungicide.⁵ More recently, it was reported that anisomycin showed high in vitro antitumor activity,⁶ and could be used in a synergistic fashion with a cyclin-dependent protein kinase inhibitor to kill carcinoma cells.⁷ Consequently, many approaches have been developed

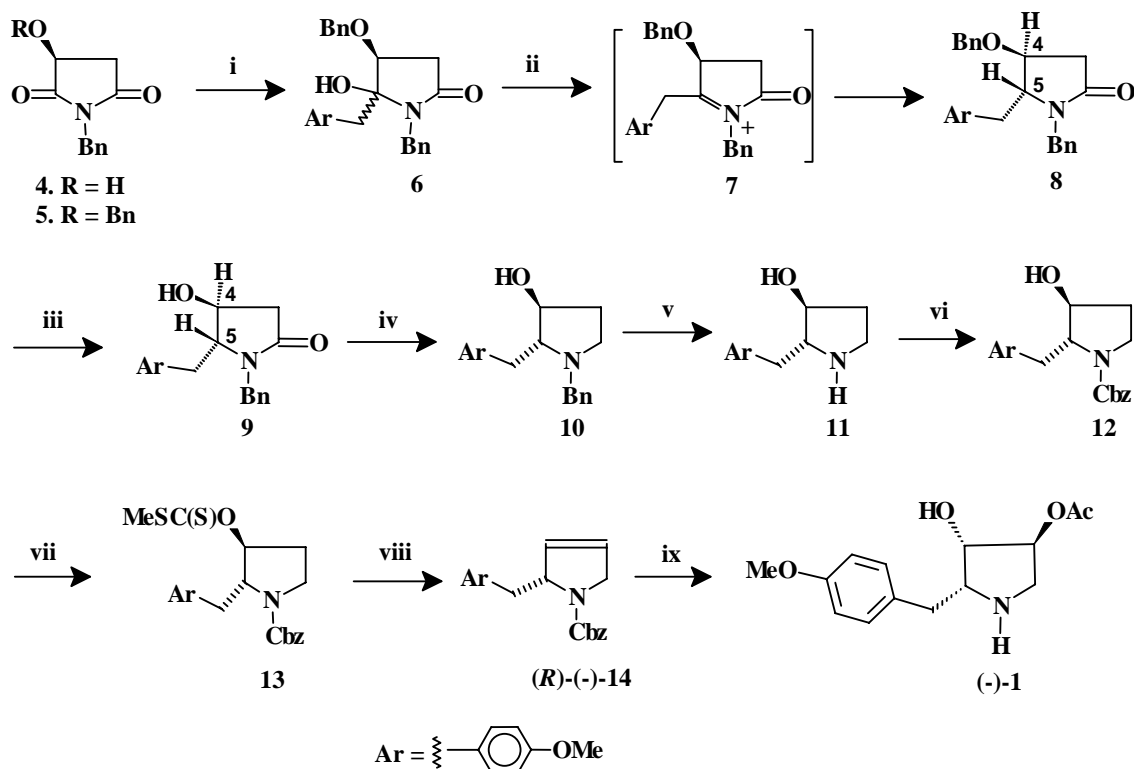
for the asymmetric synthesis of anisomycin.⁸ In continuation of our efforts on the development of malic acid-based methodology to bioactive N-containing compounds,⁹ we have communicated an asymmetric approach to (-)-anisomycin.¹⁰ In that approach, the key reductive alkylation of **4** led to **9** in modest regioselectivity. We would like to report herein an improved formal asymmetric synthesis to (-)-anisomycin, which featured the reductive alkylation of (*S*)-*N,O*-dibenzyl malimide **5** in high regio- and stereo-selectivity.

Results and Discussion

The synthesis began with the reductive alkylation of (*S*)-*N,O*-dibenzyl malimide **5** (**Scheme 1**), which was prepared starting from (*S*)-malic acid as described previously. Thus, the addition of *p*-methoxybenzylmagnesium chloride to **5** led smoothly to the desired α -hydroxylactam **6** as a diastereomeric mixture and in high regioselectivity, which was deduced in the followed step. The stereochemistry of the isomeric **6** was not assigned. This diastereomeric mixture, although separable by flash chromatography, was used in the next step as it was, since the followed Lewis acid mediated ionic hydrogenation¹¹ was considered to proceed by the intermediacy of the *N*-acyliminium **7**.^{9,12} Indeed, in the presence of 3.0 equivalents of boron trifluoride etherate, hydroxylactams **6** were reduced with excess of triethylsilane (CH₂Cl₂, -78°C~ r.t.) to yield predominantly *trans*-**8** in 94.8% yield. The coupling constant of ~0 Hz for H-4/H-5 in **8** indicates a *trans* orientation⁹ of these two protons, was later confirmed by converting **8** to known (*R*)-(-)-**14**^{8e,f,i}.

Catalytic hydrogenation (10% Pd/C, H₂, 1atm) of **8** afforded **9** in quantitative yield. 4-Hydroxypyrrolidinone **9** was reduced to pyrrolidine **10** (LiAlH₄, THF, reflux) in 90% yield. *N*-Debenzylation in the presence of Pearman's catalyst (H₂, Pd(OH)₂/C, EtOH, r.t.) followed by selective *N*-benzyloxycarbonylation (CbzCl, NEt₃, CH₂Cl₂, 0 °C → room temperature) gave *N*-protected pyrrolidine **12** in an overall yield of 77 %. Xanthation of alcohol **12** then provided **13** in 72% yield. Upon thermolysis of **13** at 190°C under reduced pressure, the desired (*R*)-3-pyrroline **14** {[α]_D²⁰ -214 (*c* 1.18, CHCl₃). lit. [[α]_D²⁰ +1.4 (e.e. = 90%) for (*S*)-**14**,^{8h} [α]_D -190.4 (*c* 1.0, CHCl₃);^{8l} [α]_D²⁵ -199 (*c* 1.17, CHCl₃);^{8m} [α]_D²⁰ -135.7 (*c* 0.76, CHCl₃),¹⁰ for (*R*)-**14**] } was obtained in 87.3% yield, of which the spectroscopic data fully matched those reported in the literature^{6m}.

Since (+)-**14** has been converted into unnatural enantiomer (+)-anisomycin **1**^{8h,l,m}, the present work constitutes a new formal asymmetric synthesis of the natural enantiomer of this antibiotic.



Scheme 1. Reagents and conditions: i) p-MeOC₆H₄CH₂MgCl, THF, -15 °C ~ -10 °C, 94.5 %; ii) BF₃ • OEt₂, Et₃SiH, -78 °C, 94.8 %; iii) H₂, 1 atm, 10 % Pd/C, EtOH, 100 %; iv) LiAlH₄, THF, reflux, 90 %; v) H₂, 1atm, 20 % Pd(OH)₂/C, EtOH, r.t.; vi) CbzCl, Et₃N, CH₂Cl₂, r.t., 77 % over two steps; vii) NaH, THF, imidazole, 65 °C; CS₂, 60 °C; MeI, 60 °C, 72 %; viii) neat, 190 °C, < 10 mmHg, 87.3 %; ix) ref. 8h.

Experimental Section

General Procedures. Melting points were determined on a Yanaco MP-500 micro melting point apparatus. Infrared spectra were measured with a Shimadza IR-408 spectrometer or a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ¹H-NMR spectra were recorded in CDCl₃ on a Varian unity +500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by Finnigan Mat-LCQ (ESI direct injection). Optical rotations were measured with Perkin-Elmer 341 automatic polarimeter. THF and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane were distilled over P₂O₅. Silica gel (Zhifu, 300~400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60-90°C) mixtures.

(S)-1-Benzyl-4-benzyloxy-5-(4-methoxybenzyl)-2-pyrrolidinone (8). To a stirred cold solution of (*S*)-*O*-Benzyloxy malimide^{9a} (2.5 g, 8.47 mmol) in THF (15 mL) at -15 °C was added dropwise a 1.0 M solution of freshly prepared 4-methoxybenzylmagnesium chloride in THF (15 mL, 15 mmol) under an atmosphere of N₂. The mixture was stirred at -10 ~ -15 °C for 1 hour and then quenched by adding a saturated aqueous solution of NH₄Cl (15 mL) and water (10 mL) at -10 °C. After diluted by dichloromethane (100 mL) the mixture was poured into a separatory funnel. The organic layer were separated, and the aqueous phase was extracted with CH₂Cl₂ (3×25 mL). The combined organic phase was washed with brine, dried with anhydrous Na₂SO₄. After flash chromatographic purification (eluent: ethyl acetate: petroleum ether = 1:2), a white solid (3.34 g, 94.5%) were obtained which is a mixture of two diastereoisomers. This diastereomeric mixture (2.92 g, 7.0 mmol) was dissolved in dry dichloromethane (28 mL), and cooled to -78 °C. Et₃SiH (11.2 mL, 70 mmol) and BF₃•OEt₂ (2.6 mL, 21 mmol) were successively added. The resulting mixture was stirred at -78 °C for 6 hours, and then allowed to rise to room temperature. After stirred at room temperature for 6 hours the mixture was quenched by adding a saturated solution of NaHCO₃ (8 mL) at 0 °C. After diluted by dichloromethane (50 mL), the mixture was poured into a separatory funnel. The organic layer were separated. The aqueous phase was extracted with CH₂Cl₂ (3×10 mL). The combined organic phase was washed with brine, and dried with anhydrous Na₂SO₄. After flash chromatographic purification (eluent: ethyl acetate: petroleum ether = 1:1.5), pyrrolidinone **8** was obtained as a colorless oil (2.66 g, 94.8 %). [α]_D²⁰ 25.6 (*c* 0.6, CHCl₃). IR (film) ν_{max}: 3050, 2930, 2850, 1687, 1614, 1512, 1444, 1302, 1250, 1175, 1070, 1030, 820, 735, 695 cm⁻¹. ¹H-NMR (500 Mz, CDCl₃) δ: 2.45 (m, 2H, H-3), 2.51 (dd, J= 8.48, 13.94 Hz, 1H, H-6), 2.86 (dd, J= 4.52, 13.94 Hz, 1H, H-6), 3.68 (dd, J= 4.52, 8.48 Hz, 1H, H-5), 3.80 (s, 3H, OCH₃), 3.85 (dd, J= 2.07, 4.83 Hz, 1H, H-4), 3.96 (d, J= 15.20 Hz, 1H, NCH₂Ph), 4.11(d, J= 11.90 Hz, 1H, OCH₂Ph), 4.16 (d, J= 11.90 Hz, 1H, OCH₂Ph), 5.16 (d, J= 15.20 Hz, 1H, NCH₂Ph), 6.80-7.40 (4m, 14H, Ph-H) ppm; ¹³C-NMR (125 Mz, CDCl₃) δ: 36.08 (1C), 37.10 (1C), 44.27 (1C), 55.28 (1C), 64.11 (1C), 70.07 (1C), 74.80 (1C), 114.20 (2×Ar-CH), 127.56 (3×Ar-CH), 127.66 (1×Ar-CH), 127.93 (3×Ar-CH), 128.33 (2×Ar-CH), 128.73 (2×Ar-CH), 130.18 (2× Ar-CH), 136.17 (1× Ar-CH), 137.44 (1×Ar-CH), 158.60 (1×Ar-CH), 173.07 (C=O) ppm. MS (EI): 401 (M⁺, 2.5), 280 (29), 254 (11), 91 (100). HRMS calcd for [C₂₆H₂₇O₃N]⁺ 401.1991, found 401.1983.

(S)-1-Benzyl-4-hydroxy-5-(4-methoxybenzyl)-2-pyrrolidinone (9). To a mixture of **8** (800 mg, 2 mmol) and 10 % Pd-C (170 mg) was added ethanol (10 mL). The mixture was stirred at room temperature and under an atmosphere of H₂ for 7 days. The mixture was filtered over celite. Flash chromatographic purification on silica gel (eluent: ethyl acetate: petroleum ether = 2 : 1) provided pyrrolidinone **9** as a colorless oil (620 mg, 100%). [α]_D²⁰ + 4.80 (*c* 1.0, CHCl₃). IR (film) ν_{max}: 3350, 2820, 1660, 1510, 1450, 1250, 1175, 1025, 690 cm⁻¹. ¹H-NMR (500 Mz, CDCl₃) δ: 2.27 (dd, J= 1.07, 17.50 Hz, 1H, H-3), 2.45 (dd, J= 6.14, 17.50 Hz, 1H, H-3), 2.55 (dd, J= 7.98, 14.05 Hz, 1H, H-6), 2.86 (dd, J= 4.76, 14.05 Hz, 1H, H-6), 3.50 (dd, J= 4.76, 7.98 Hz, 1H, H-5), 3.78 (s, 3H, OCH₃), 3.93 (d, J= 15.20 Hz, 1H, NCH₂Ph), 4.16 (s, 1H, H-4), 5.12 (d, J= 15.20 Hz, 1H, NCH₂Ph), 6.80- 7.40 (m, 9H, Ph-H) ppm; ¹³C-NMR (125 Mz, CDCl₃) δ: 36.05

(1C), 39.59 (1C), 44.30 (1C), 55.28 (1C), 67.06 (1C), 68.96 (1C), 114.30 (2×Ar-CH), 127.65 (1×Ar-CH), 128.03 (2×Ar-CH), 128.17 (1×Ar-CH), 128.78 (2×Ar-CH), 130.11 (2× Ar-CH), 136.16 (1×Ar-CH), 158.65 (1×Ar-CH), 172.88 (C=O) ppm. MS (EI): 311 (M^+ , 3.2), 293 (M-18, 43.5), 190 (83.1), 91(100), 57 (99); HRMS calcd for $[C_{19}H_{19}NO_2 (M^+-H_2O)]$ 293.1416, found 293.1413.

(S)-1-Benzyl-3-hydroxy-2-(4-methoxybenzyl)-pyrrolidine (10). To a ice-cooled suspension of LAH (230 mg, 4.5 mmol) in anhydrous THF (3.0 mL), was added, under an atmosphere of N_2 , a solution of **9** (430 mg, 1.38 mmol) in THF (4 mL). After stirred at room temperature for 2 hours, then at 50 °C for 4 hours, the mixture was cooled with a ice-bath, then wet diethyl ether (6 mL), 10% solution of sodium hydroxide (107 mL) and water (0.3 mL) were added successively. The mixture was allowed to reach room temperature, stirred for 30 min, and filtered through celite. After concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: ethyl acetate: petroleum ether : NH_3 aq. = 2 : 1 : 0.01). The pyrrolidine **10** (382 mg, yield, 93%) was obtained as a colorless oil. $[\alpha]_D^{20}$ -54.3 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} : 3450, 2850, 1610, 1510, 1450, 1245, 1175, 1025, 690 cm^{-1} . 1H -NMR (500 Mz, $CDCl_3$) δ : 1.61 (m, 1H, H-4), 1.99 (m, 1H, H-4), 2.48-2.58 (m, 2H, H-5, H-6), 2.65 (m, 1H, H-5), 2.87 (m, 1H, H-2), 2.95 (dd, *J* = 4.45, 13.51 Hz, 1H, H-6), 3.46 (d, *J* = 13.00 Hz, 1H, NCH_2Ph), 3.78 (s, 3H, OCH_3), 4.02 (d, *J* = 13.00 Hz, 1H, NCH_2Ph), 4.08 (m, 1H, H-3), 6.80-7.40 (m, 9H, Ph-H) ppm; ^{13}C -NMR (125 Mz, $CDCl_3$) δ : 32.34 (1C), 37.75 (1C), 51.49 (1C), 55.24 (1C), 58.86 (1C), 74.05 (1C), 76.03 (1C), 114.01 (2×Ar-CH), 127.07 (1× Ar-CH), 128.30 (2×Ar-CH), 129.01 (2×Ar-CH), 130.25 (2×Ar-CH), 130.85 (1×Ar-CH), 138.99 (1× Ar-CH), 158.11 (1×Ar-CH) ppm. MS (EI): 297 (M^+ , 9), 279 (M^+-H_2O , 69), 277 (3.19), 176(100), 91(92.24); HRMS calcd for $[C_{11}H_{14}NO (M^+-p-CH_3OC_6H_4CH_2)]$ 176.1075, found 176.1072.

(S)-1-Benzoyloxycarbonyl-3-hydroxy-2-(4-methoxybenzyl)-pyrrolidine (12). To a mixture of **10** (460 mg, 1.55 mmol) and 10% Pd-C (187 mg) was added ethanol (8 mL). The mixture was stirred at room temperature and under an atmosphere of H_2 for 15 hours. The mixture was filtered over celite, washed with ethyl acetate (1% NH_3 aq.). After concentrated under reduced pressure, the crude pyrrolidine **11** was obtained as a yellow oil (300 mg, yield, 93.7%), which was used in the next step as it was.

To an anhydrous CH_2Cl_2 (7 mL) solution of the crude pyrrolidine **11** and a catalytic amount of DMAP, was successively added Et_3N (0.4 mL, 2.9 mmol) and $CbzCl$ (0.6 mL, 1.25 mmol) dropwise at 0 °C and under an atmosphere of N_2 . The mixture was stirred at room temperature for 4 hours. After concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1 : 1) affording **12** (409 mg, yield, 82.8%) as a colorless oil. $[\alpha]_D^{20}$ + 17.7 (*c* 1.1, $CHCl_3$). IR (film) ν_{max} : 3320, 2950, 1675, 1510, 1410, 1360, 1248, 1105, 1030, 980, 690 cm^{-1} . 1H -NMR (500 Mz, $CDCl_3$) (show the peaks of two rotamers) δ : 1.75-1.95 (2m, 2H, H-4), 2.45 (m, 1H, H-2), 2.95, 3.12 (2dd, *J* = 3.30, 13.66; 2.80, 13.66, 1H, H-6), 3.47, 3.61 (2m, 2H, H-5), 3.76, 3.78 (2s, 3H, OMe), 3.92, 3.93 (2dd, *J* = 2.61, 13.66; 2.12, 13.66 Hz, 1H, H-6), 4.16 (s br, 1H, H-3), 5.10-5.22 (m, 2H, NCH_2Ph), 6.70-7.40 (m, 9H, Ph-H) ppm; ^{13}C -NMR (125 Mz, $CDCl_3$) (show the peaks of two rotamers) δ :

30.94, 31.49 (1C), 37.38, 38.43 (1C), 44.41, 44.65 (1C), 55.24 (C-3), 66.70, 67.10 (1C), 67.81, 68.36 (1C), 73.46, 74.36 (1C), 113.99(2×Ar-CH), 127.83, 127.95 (1×Ar-CH), 128.06 (2×Ar-CH), 128.50 (2×Ar-CH), 129.97 (2×Ar-CH), 130.14 (1×Ar-CH), 130.34 (2×Ar-CH), 136.68, 136.93 (1×Ar-CH), 155.09 (1×Ar-CH), 158.28 (C=O) ppm. MS (EI): 341(M⁺, 6.09), 220 (18.88), 176 (25.25), 121 (19.29), 91 (100); HRMS calcd for [C₂₀H₂₃NO₄] 341.1627, found 341.1628.

(2R, 3S) – 1 - (Benzyloxycarbonyl) – 2 - (4-methoxybenzyl) pyrrolidin – 3 - yl S-Methyl Xanthate (13). To a suspension of NaH (170 mg, 50% in petrolatum, 3.53 mmol) and imidazole (75 mg) in anhydrous THF (2.0 mL), was added, under an atmosphere of N₂, a solution of **12** (370 mg, 1.08 mmol) in THF (5 mL). After stirred at 60 °C for 2 hours, carbon disulfide (0.3 mL, 6 mmol) was added dropwise. The mixture was stirred at 60 °C for 4 hours. Then, methyl iodide (0.3 mL, 4.8 mmol) was added, and the mixture was refluxed for additional 4 hours. The mixture was cooled with an ice-bath, then quenched by water (4 mL). The reaction mixture was extracted with ethyl acetate (3×10 mL). The combined organic phase was washed with brine, dried with anhydrous Na₂SO₄. After concentrated at reduced pressure, the residue was purified by flash chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1 : 5) to yield **13** (286 mg, yield, 72%) as a yellow oil. $[\alpha]_D^{20} - 3.3$ (c 1.5, CHCl₃). IR (film) ν_{\max} : 2950, 1700, 1510, 1410, 1345, 1250, 1210, 1100, 1040, 690 cm⁻¹. ¹H-NMR (500 Mz, CDCl₃) (show the peaks of two rotamers) δ : 1.70 (m, 1H, H-4), 2.04 (m, 1H, H-4), 2.50 (s, 3H, S-CH₃), 2.78, 2.90 (2dd, J= 7.52, 13.82; 7.67, 13.82, 1H, H-6), 2.95, 3.07 (2dd, J= 3.68, 13.82; 3.15, 13.82 Hz, 1H, H-6), 3.40- 3.62 (m, 2H, H-5), 3.77, 3.79 (2s, 3H, OMe), 4.22, 4.31 (2dd, J= 3.15, 3.68, 7.52, 7.67 Hz, 1H, H-2), 5.16, 5.24 (2dd, J= 12.10, 12.59; 12.10, 12.59 Hz, 2H, NCH₂Ph), 5.75 (m, 1H, H-3), 6.70-7.40 (m, 9H, Ph-H) ppm; ¹³C-NMR (125 Mz, CDCl₃) (show the peaks of two rotamers) δ : 19.06 (S-C), 28.41, 29.24 (1C), 36.35, 37.59 (1C), 44.85, 45.19 (1C), 55.23 (C-3), 64.54, 64.96 (1C), 66.83, 67.23 (1C), 85.67, 86.42 (1C), 113.96, 113.99(2×Ar-CH), 127.85 (1×Ar-CH), 128.06, 128.13 (2×Ar-CH), 128.54 (2×Ar-CH), 128.97, 129.16 (1×Ar-CH), 130.42, 130.58 (2×Ar-CH), 136.55, 136.86 (1×Ar-CH), 154.71, 154.82 (1×Ar-CH), 158.28 (C=O), 214.75 (C=S) ppm. MS (EI): 431 (M⁺, 8.9), 323 (19.5), 310 (33.9), 159 (19.29), 91 (100).

(R)-1-Benzyloxycarbonyl-2-(4-methoxybenzyl)-3-pyrroline (14). Neat **13** was heated to 190 ~ 200 °C under reduced pressure (<10 mmHg) for 2 hours. The resulting residue was purified by flash chromatography on silica gel (eluent: ethyl acetate: petroleum ether = 1 : 8) affording pyrroline **14** (131 mg, yield, 87.3%) as a yellow solid. $[\alpha]_D^{20} - 214$ (c 1.18, CHCl₃). lit. $[\alpha]_D^{20} + 1.4$ (e.e. = 90%) for (S)-**14**; ^{8h} $[\alpha]_D - 190.4$ (c 1.0, CHCl₃); ^{8l} $[\alpha]_D^{25} - 199$ (c 1.17, CHCl₃); ^{8m} $[\alpha]_D^{20} - 135.7$ (c 0.76, CHCl₃), ¹⁰ for (R)-**14**. IR (film) ν_{\max} : 2900, 1700, 1610, 1510, 1410, 1360, 1320, 1245, 1100, 1025, 690 cm⁻¹. ¹H-NMR (500 Mz, CDCl₃) (show the peaks of two rotamers) δ : 2.78, 2.90 (2dd, J= 7.98, 13.21; 8.06, 13.20, 1H, H-6), 3.02, 3.13 (2dd, J= 3.10, 13.20; 3.07, 13.21 Hz, 1H, H-6), 3.76, 3.78 (2s, 3H, OMe), 3.80, 3.83 (2m, 1H, H-5), 4.14, 4.20 (2dm, 1H, H-5), 4.75, 4.80 (2m, 1H, H-2), 5.20, 5.25 (2dd, J= 12.08, 12.51; 12.08, 12.51 Hz, 2H, NCH₂Ph), 5.60-5.72 (m, 1H, H-3), 6.70-7.50 (m, 9H, Ph-H) ppm; ¹³C-NMR (125 Mz, CDCl₃) (show the peaks of two rotamers) δ : 38.31, 39.73 (1C), 53.56, 53.99 (1C), 55.18 (C-3), 65.36, 65.87 (1C), 66.55,

67.06 (1C), 113.44, 113.54 (2×Ar-CH), 125.29, 125.53 (=CH), 127.86, 127.94 (1×Ar-CH), 128.10, 128.16 (2×Ar-CH), 128.48, 128.57 (2×Ar-CH), 129.40, 129.49 (=CH)129.57, 129.63 (1×Ar-CH), 130.59, 130.79 (2×Ar-CH), 136.78, 137.08 (1×Ar-CH), 154.41, 154.65 (1×Ar-CH), 158.04, 158.11 (C=O) ppm. MS (EI): 323 (M⁺, 16.1), 219 (7.3), 202 (29.0), 158 (35.5), 91(92.24); HRMS calcd for [C₁₂H₁₂NO₂ (M-CH₃OC₆H₄CH₂)] 202.0907, found 202.0868.

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