

PRACTICAL SYNTHESIS OF (*S*)-3-(*p*-NITROBENZYLOXY-CARBONYLAMINO)PYRROLIDINE AND ITS RELATED COMPOUNDS FROM L-ASPARTIC ACID

Hiroshi Tomori,^a Kuniko Shibutani,^b and Katsuyuki Ogura*

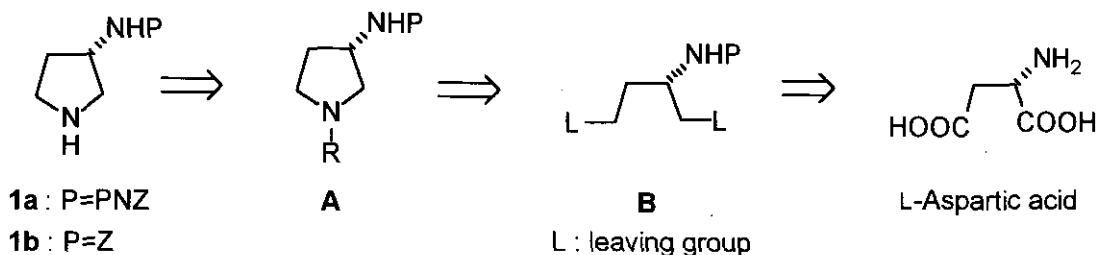
Department of Applied Chemistry, Faculty of Engineering and ^aGraduate School of Science and Technology, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263, Japan

^bProcess Development Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan

Abstract - An efficient method for the preparation of (*S*)-3-aminopyrrolidine derivatives was developed starting from L-aspartic acid, which involves an efficient formation of a pyrrolidine-ring from allylamine and a practical Pd/C-catalyzed cleavage of *N*-allyl protective group. This method affords the enantiomerically pure desired compounds (**1**) in high overall yields.

A widespread occurrence of (*S*)-3-amino-1-pyrrolidinyl moiety in biologically active compounds such as 1 β -methylcarbapenem antibiotics,¹ new quinolone antibacterials,^{2,3} and antitumor agents⁴ has stimulated the development of numerous methods for the synthesis of (*S*)-3-aminopyrrolidines.^{3,5,6} Among these, the methods that use L-aspartic acid as a starting material^{3a,6} are considered to be the most promising entry because of its commercial availability. Our attention was focused on the synthesis of (*S*)-3-(*p*-nitrobenzyloxycarbonylamino)pyrrolidine (**1a**) and (*S*)-3-(benzyloxycarbonylamino)pyrrolidine (**1b**), which are imperative in manufacturing the potent antibiotic agents with a wide range of antibacterial spectrum.¹ In this paper, we describe a practical method for preparing **1a** and **1b**. The retrosynthesis is as follows: A key intermediate (**B**) possessing two leaving groups at both termini, derived from natural L-aspartic acid, can react with a synthetic equivalent of ammonia to give a N1-protected **1** (**A**), and the selective N1-deprotection of **A** should give the target compound. A key to our success is to develop an efficient Pd/C-catalyzed deallylation procedure, which realizes the selective deprotection of **A** to provide a practical route

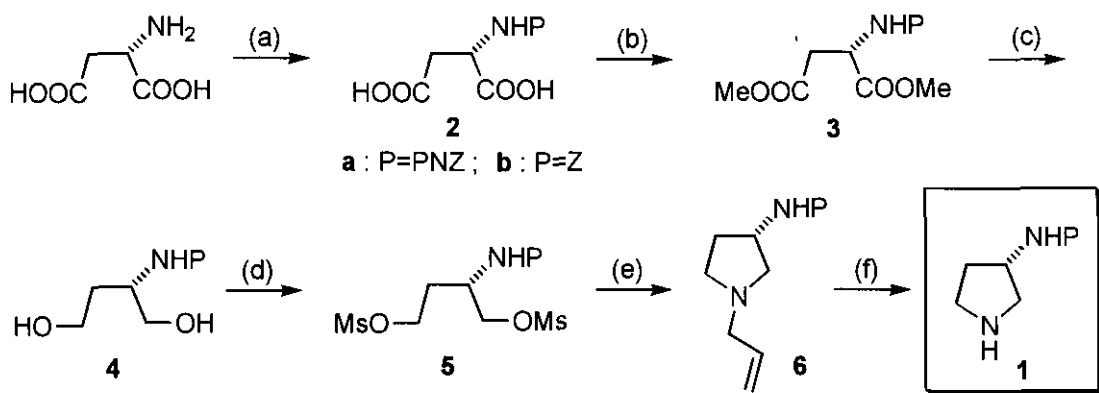
This paper is dedicated to Dr. Shigeru Oae, Professor Emeritus Tsukuba University, on the occasion of his 77th birthday.



to the target compounds. We also applied this methodology for the synthesis of (*S*)-3-(*t*-butoxycarbonyl-amino)pyrrolidine (**9**), an analog of **1**.

Our synthesis started from L-aspartic acid as depicted in Scheme 1. The amino group of L-aspartic acid was protected with *p*-nitrobenzyloxycarbonyl (PNZ) group under the modified Schotten-Baumann conditions⁷ to give **2a**, and the subsequent esterification afforded a diester (**3a**). Sodium borohydride reduction of two methoxycarbonyl groups of **3a** smoothly proceeded at 45–55 °C in THF-MeOH⁸ without racemization to give a diol (**4a**) with ~100% ee (determined by hplc). Reaction of **4a** with 2.2 equiv of methanesulfonyl chloride in the presence of pyridine furnished the key intermediate (**5a**) in 64% overall yield from L-aspartic acid. In a similar fashion, enantiomerically pure **5b** was prepared from commercially available *N*-benzyloxycarbonyl-L-aspartic acid (**2b**) in an excellent overall yield of 89%. Next we attempted the direct conversion of **5** into **1** by cyclization with NH₃ or NH₄OH, but the yield of the desired **1** was poor because of the lability of Z and PNZ groups under these reaction conditions.⁹ Hence, readily available synthetic equivalents for ammonia such as aminoacetone, allylamine, and trifluoroacetamide were examined.

Scheme 1



(a) ClCO₂PNZ (1.2 equiv), BnNMe₃Cl (cat.)/aq. NaOH. (b) 1 *N* HCl/MeOH, room temperature. (c) NaBH₄ (2.0 equiv)/THF-MeOH, 45–55 °C. (d) MsCl (2.2 equiv), pyridine or Et₃N. (e) allylamine (excess), 40 °C. (f) 10% Pd/C (10 wt%), AcOH (2–3 equiv), reflux.

Among these reagents, allylamine reacted readily with **5** to afford a ring-closure product (**6**) exclusively. The byproduct possessing two allylamino groups at both termini was not detected by hplc and ^1H nmr. Of particular interest is that the cyclization reaction proceeds quantitatively at a high concentration even though an excess amount of allylamine is used instead of solvent. This intriguing result can be understood based on a difference between the two mesyl groups in electrophilic character. An analogous result was previously observed in a regioselective substitution of 2-dibenzylamino-1,4-butane-diol dimesylate.¹⁰ Having gained an efficient access to **6**, we turned to the selective deallylation of **6**.

For the deallylation of allylic amines, many methods have been exploited by the use of such transition metal catalysts as Rh(I),^{11,12} Rh(III),¹¹ Zr(II)¹³ and Pd(0).¹⁴ Most of these catalysts are structurally complicate, very expensive, and so unstable that special care is required for not poisoning these catalysts. We chose commercially available, rather stable Pd/C and Pd(II) complexes as a catalyst for the deallylation reaction. These results are summarized in Table 1 together with the results of some of Ru¹⁵ and Rh catalysts. Surprisingly, Pd/C showed a fascinating catalytic activity.¹⁶ In an aqueous solution, the Pd/C-catalyzed

Table 1. Transition Metal-Catalyzed Deallylation of **6**

Entry	Substrate	Catalyst /wt%	Additive /equiv	Solvent	Temp °C	Time /h	Yield ^a of 1 /%
1	6a	10% Pd/C ^b (10)	AcOH (2.7)	H ₂ O	100	1.5	96
2	6a	10% Pd/C ^b (10)	AcOH (5.3)	H ₂ O	100	3.5	89
3	6a	10% Pd/C ^b (10)	—	H ₂ O/ <i>n</i> -PrOH (1:1)	100	3	78
4	6a	RhCl(PPh ₃) ₃ (5)	—	H ₂ O/EtOH (1:1)	80	4.5	44 ^c
5	6a	RuCl ₂ (PPh ₃) ₃ (5)	—	H ₂ O/EtOH (1:1)	80	7	36 ^c
6	6b	10% Pd/C ^b (10)	AcOH (2.2)	H ₂ O	100	1.5	92
7	6b	PdCl ₂ (5)	AcOH (2.2)	H ₂ O	100	7	90
8	6b	Pd(acac) ₂ (5)	AcOH (2.2)	H ₂ O	100	7	82
9	6b	RuCl ₂ (PPh ₃) ₃ (3)	—	H ₂ O/EtOH (1:1)	80	5	91 ^c
10	6b	RhCl(PPh ₃) ₃ (3)	—	H ₂ O/EtOH (1:1)	80	2	83 ^c
11	6b	RhCl ₃ ·3H ₂ O (3)	—	H ₂ O/EtOH (1:1)	80	1	trace

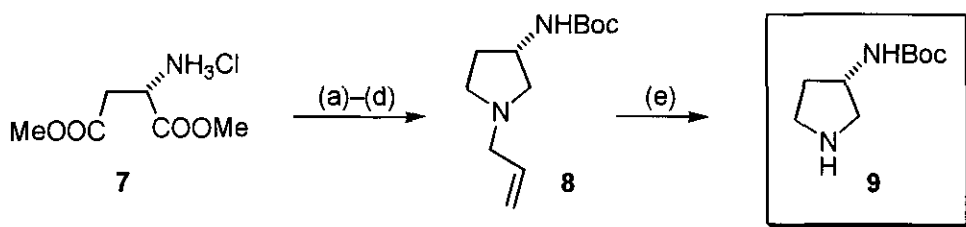
(a) Determined by hplc analysis using an external standard. (b) Wet Pd/C (water content: 50 wt%) was used. (c) Measured after treating crude product with AcOH-H₂O (1:2 v/v) to complete the hydrolysis.

deallylation of **6** proceeded smoothly at reflux temperature to generate **1** directly. The presence of AcOH depressed the formations of byproducts to increase the yield, though it retards the reaction (Entries 1–3). We recommended the use of 2–3 equiv of AcOH (based on **1**). Under these conditions, PdCl₂ and Pd(acac)₂ gave **1b** in 90% and 82% yields, respectively. RhCl(Ph₃P)₃ and RuCl₂(Ph₃P)₃ exhibited good catalytic activity toward **6b**, whereas they were deactivated during the reaction of **6a**.

The enantiomeric excess of the thus obtained **1a** and **1b** was determined by hplc equipped with a chiral stationary phase column to be 100%, revealing that no racemization occurred in the whole process from L-aspartic acid to **1**. A distinct feature of the present route is that the intermediate is not isolated in each of the reactions and, at the final stage, **1** can be easily isolated in a pure form. This allows the present method to produce **1** in a large scale: For instance, a 400 mmol-scale synthesis of **1a** gave a 52% overall yield.

Since the present Pd/C-catalyzed deallylation is performed under slightly acidic conditions, *N*-*t*-butoxycarbonyl (Boc) group is expected to remain intact during the reaction. Hence, we applied the present methodology to the synthesis of (*S*)-3-(*t*-butoxycarbonylamino)pyrrolidine (**9**), which serves as an important building block in the syntheses of biologically active compounds.^{3d,4c} A requisite precursor (*S*)-1-allyl-3-(*t*-butoxycarbonylamino)pyrrolidine (**8**) was synthesized from dimethyl L-aspartate hydrogen chloride (**7**)¹⁷ in 35% overall yield by 4 steps: protection by Boc group, reduction of two methoxycarbonyl groups with NaBH₄, mesylation, and cyclization with allylamine.¹⁸ According to expectation, the Pd/C-catalyzed deallylation of **8** proceeded cleanly to provide **9** in a 94% yield.

In summary, we developed a practical and straightforward method for the production of enantiomerically pure **1a** and **1b** from natural L-aspartic acid. In the course of this study, we found an efficient Pd/C-catalyzed deprotection of allylic amines, which enables chemoselective removal of *N*-allyl group in the coexistence of urethane-type *N*-protective groups such as PNZ, Z, and Boc.



(a) Boc₂O (1.0 equiv), Et₃N (2.2 equiv). (b) NaBH₄ (2.0 equiv)/THF–MeOH. (c) MsCl (2.1 equiv), Et₃N (2.3 equiv). (d) allylamine (excess). (e) 10% Pd/C (10 wt%), AcOH (2.0 equiv), reflux, 3 h.

EXPERIMENTAL

Melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Optical rotations were measured with a Horiba SEPA-300 polarimeter. ^1H Nmr spectra were recorded on a JEOL JNM-GSX 400 (400 MHz) spectrometer, and chemical shifts were reported in ppm relative to tetramethylsilane as internal standard. Ir spectra were run on a JASCO FT/IR-8900 or JASCO IR-810 spectrophotometer. Column chromatography was carried out on a pre-packed glass column (Merck, LiChroprep Si 60, \varnothing 25 \times 310 mm). Preparative hplc was performed on a reversed-phase column (ODS-525-05-SR, \varnothing 50 \times 250 mm, YMC Co.). Analytical hplc was performed on a Shiseido Capcell Pak C18 SG120 column (\varnothing 4.6 \times 250 mm) [eluent, acetonitrile/0.02 M aq. AcONH_4 (2:3); flow rate, 1.0 ml min^{-1} ; column oven temperature, 40 $^\circ\text{C}$]. Pd/C was purchased from Kawaken Fine Chemicals Co., Ltd. and rhodium(III) chloride hydrate was obtained from Strem Chemicals, Inc. Other transition metal catalysts were the products of Aldrich Chemical Company, Inc. All other chemicals used herein were reagent grade.

***N*-(*p*-Nitrobenzyloxycarbonyl)-L-aspartic acid (2a)**. To a vigorously stirred mixture of L-aspartic acid (53.2 g, 0.400 mol), NaOH (32 g, 0.80 mol), and benzyltrimethylammonium chloride (2.66 g, 14.3 mmol) in water (47 ml) was added dropwise a 50.9 wt% toluene solution of *p*-nitrobenzyl chloroformate (186 g, 0.440 mol) at 25–31 $^\circ\text{C}$, and the pH was maintained at 11.1–11.5 by occasional addition of a 25% aqueous NaOH. The resulting mixture was stirred vigorously for 1 h at the same temperature. The organic layer was separated and the aqueous layer was washed with AcOEt (2 \times 160 ml). Then the aqueous solution was acidified with conc. HCl (73 ml) to be pH \sim 1 and extracted with AcOEt (1070 ml and 270 ml). The combined organic extracts were evaporated *in vacuo* to afford 139 g of crude **2a** as a viscous pale yellow oil, which contained a small amount of the solvent. An analytical sample of **2a** was obtained by crystallization from water: Colorless solid; mp 93–97 $^\circ\text{C}$ (H_2O); $[\alpha]^{20}_{\text{D}}$ -3.7° (*c* 1.02, EtOH); ir (KBr) 3500–2400, 1726, 1536, 1347 cm^{-1} ; ^1H nmr (CD_3OD) δ 2.80 (dd, $J=16.7$ and 7.2 Hz, 1H, CHHCO_2H), 2.88 (dd, $J=16.7$ and 5.0 Hz, 1H, CHHCO_2H), 4.55 (dd, $J=7.2$ and 5.0 Hz, 1H, CHNHPNZ), 5.21 (s, 2H, OCH_2Ar), 7.60 (d-like, $J=8.7$ Hz, 2H, ArH), 8.22 (d-like, $J=8.7$ Hz, 2H, ArH). Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_8$: C, 46.16; H, 3.87; N, 8.97. Found: C, 45.88; H, 3.83; N, 8.93.

Dimethyl *N*-(*p*-nitrobenzyloxycarbonyl)-L-aspartate (3a). A mixture of the above crude **2a** (139 g) and 1*N* methanolic HCl (800 ml) was stirred at an ambient temperature. After 13 h, the resulting mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt (1250 ml) and washed with 5% aqueous

NaHCO₃ (250 ml) and then with water (250 ml). Concentration of the organic layer gave 127 g of crude **3a** as a pale yellow oil. An analytical sample of **3a** was obtained by preparative hplc (CH₃CN/H₂O, 2:3) as a colorless oil. Data for **3a**: [α]_D²⁰ -15.4° (*c* 1.00, EtOH); ir (neat) 3305, 1735, 1525, 1500, 1350, 1220 cm⁻¹; ¹H nmr (CDCl₃) δ 2.87 (dd, *J*=17.2 and 4.5 Hz, 1H, CHHCO₂Me), 3.06 (dd, *J*=17.2 and 4.6 Hz, 1H, CHHCO₂Me), 3.71(s, 3H, CH₃), 3.78 (s, 3H, CH₃), 4.64 (ddd, *J*=8.5, 4.6, and 4.5 Hz, 1H, CHNHPNZ), 5.22 (d, *J*=13.6 Hz, 1H, OCHHAr), 5.24 (d, *J*=13.6 Hz, 1H, OCHHAr), 5.91(d, *J*=8.5 Hz, 1H, NHPNZ), 7.52 (d-like, *J*=8.7 Hz, 2H, ArH), 8.22 (d-like, *J*=8.7 Hz, 2H, ArH). Anal. Calcd for C₁₄H₁₆N₂O₈ · 0.4 H₂O: C, 48.39; H, 4.87; N, 8.06. Found: C, 48.50; H, 4.70; N, 8.02.

(S)-3-(p-Nitrobenzyloxycarbonylamino)-1,4-butanediol (4a). This reaction was carried out in a slow stream of N₂. To a suspension of the crude **3a** (127 g) and NaBH₄ (28.2 g, 0.746 mol) in THF (630 ml) was added MeOH (26 ml) at 45 °C. The mixture was stirred at 45–55 °C for 25 min, and MeOH (52 ml) was added at such a rate to keep the temperature at 45–55 °C (*ca.* 20 min). After stirring for 1 h at the same temperature, the mixture was cooled to 20 °C. Then the remaining NaBH₄ was quenched by the addition of 2.5% aqueous NaHCO₃ (1300 ml). The resulting solution was extracted with 1-butanol (2×630 ml) and the combined organic extracts were washed with water (510 ml). Evaporation of the solvent afforded 99.6 g of crude **4a** with 100% ee as a yellow solid. The enantiomeric excess of the crude product was determined by hplc after its conversion to the corresponding diacetate (**10a**). Hplc analysis conditions: Column, Daicel Chiralcel OJ (ϕ 4.6×250 mm); eluent, hexane/IPA (2:1); flow rate, 1.0 ml min⁻¹; *t*_R of (*S*)-**10a**=16.7 min, *t*_R of (*R*)-**10a**=25.2 min. An analytical sample of **4a** was prepared by recrystallization from MeOH–AcOEt. Data for **4a**: Colorless crystals; mp 83–84 °C (MeOH–AcOEt); [α]_D²⁰ -26.4° (*c* 1.00, EtOH); ir (KBr) 3356, 3248, 1698, 1521, 1349, 1249 cm⁻¹; ¹H nmr (CDCl₃) δ 1.68–1.80 (m, 1H, CHHCH₂OH), 1.83–1.94 (m, 1H, CHHCH₂OH), 1.8 (br, 2H, 2×OH), 3.64–3.83 (m, 4H, 2×CH₂OH), 3.88–3.99 (m, 1H, CHNHPNZ), 5.22 (s, 2H, OCH₂Ar), 5.43(br d, *J*=7.2 Hz, 1H, NHPNZ), 7.52 (d-like, *J*=8.7 Hz, 2H, ArH), 8.23 (d-like, *J*=8.7 Hz, 2H, ArH). Anal. Calcd for C₁₂H₁₆N₂O₆: C, 50.70; H, 5.67; N, 9.85. Found: C, 50.67; H, 5.66; N, 9.88.

(S)-3-(p-Nitrobenzyloxycarbonylamino)-1,4-dimethanesulfonyloxybutane (5a). To a solution of the above crude **4a** (99.6 g) in pyridine (500 ml) was dropwise added methanesulfonyl chloride (88.3 g, 0.771 mol) over 30 min at -5 ~ -10 °C. The resulting reaction mixture was gradually warmed to 0 °C and stirred at the same temperature for 5.5 h. AcOEt (1000 ml) and H₂O–MeOH (9:1 v/v, 500 ml) were added and the organic layer was separated. The aqueous layer was extracted with AcOEt (300 ml) and the

extract was washed with H₂O–MeOH (9:1 v/v, 300 ml). The organic layer and the extract were combined and evaporated to ca. 180 g. An addition of warm MeOH (40 °C; 1200 ml) compelled crystals to deposit. The resulting suspension was gradually cooled to room temperature and then stirred for 40 min under ice-cooling. Filtration followed by being dried *in vacuo* afforded 113.0 g (64% overall yield from L-aspartic acid) of **5a** as a colorless solid: mp 65–66 °C; [α]²⁰_D -24.5° (*c* 1.00, acetone); ir (KBr) 3362, 1698, 1521, 1349, 1173 cm⁻¹; ¹H nmr (CDCl₃) δ 2.00–2.17 (m, 2H, CH₂CH₂OMs), 3.03 (s, 3H, CH₃), 3.06 (s, 3H, CH₃), 4.10–4.21 (m, 1H, CHNHPNZ), 4.26–4.44 (m, 4H, 2×CH₂OMs), 5.21 (s-like, 3H, OCH₂Ar+NHPNZ), 7.52 (d-like, *J*=8.6 Hz, 2H, ArH), 8.23 (d-like, *J*=8.6 Hz, 2H, ArH). Anal. Calcd for C₁₄H₂₀N₂O₁₀S₂: C, 38.18; H, 4.58; N, 6.36; S, 14.56. Found: C, 38.06; H, 4.39; N, 6.37; S, 14.74.

(S)-1-Allyl-3-(p-nitrobenzyloxycarbonylamino)pyrrolidine (6a). A mixture of **5a** (110 g, 0.250 mmol) and allylamine (220 ml, 0.293 mol) was stirred for 3 h in a water-bath (40 °C), and then the remaining allylamine was removed by evaporation. After AcOEt (1100 ml) and 10% aqueous Na₂CO₃ (550 ml) were added to the residue, the organic layer was separated and the aqueous layer was extracted with AcOEt (550 ml). The organic layer and the extract were combined, washed with H₂O–MeOH (9:1 v/v, 550 ml), and concentrated to dryness to give 76.6g (quantitative) of **6a** (100% ee) as a pale yellow solid. The enantiomeric excess of this compound was determined by hplc analysis: Column, Daicel Chiralcel OD (ϕ 4.6×250 mm); eluent, hexane/IPA (20:1); flow rate, 1.0 ml min⁻¹; *t*_R of (*S*)-**6a**=29.7 min, *t*_R of (*R*)-**6a**=37.2 min. Data for **6a**: mp 64–66 °C; [α]²⁰_D -6.7° (*c* 0.57, EtOH); ir (KBr) 3301, 1687, 1553, 1539, 1352, 1265 cm⁻¹; ¹H nmr (CDCl₃) δ 1.60–1.78 (m, 1H, CHHCH₂N), 2.21–3.04 (m, 5H, CHHCH₂N+CH₂NCH₂), 3.13 (d, *J*=6.5 Hz, 2H, CH₂CH=), 4.15–4.33 (m, 1H, CHNHPNZ), 5.15 (d, *J*=10.6 Hz, 1H, CH=CHH), 5.18 (s, 2H, OCH₂Ar), 5.22 (d, *J*=16.6 Hz, 1H, CH=CHH), 5.40 (br d, *J*=6.7 Hz, 1H, NH), 5.89 (ddt, *J*=16.6, 10.6, and 6.5 Hz, CH₂CH=), 7.50 (d-like, *J*=8.6 Hz, 2H, ArH), 8.21 (d-like, *J*=8.6 Hz, 2H, ArH). Anal. Calcd for C₁₅H₁₉N₃O₄: C, 59.01; H, 6.27; N, 13.76. Found: C, 59.07; H, 6.14; N, 13.49.

Dimethyl N-benzyloxycarbonyl-L-aspartate (3b).¹⁹ *N*-Benzyloxycarbonyl-L-aspartic acid (30.0 g, 0.112 mol) was treated with 1*N* methanolic HCl (250 ml) overnight at an ambient temperature. A similar workup to that in the preparation of **3a** afforded 33.2 g of crude **3b** as a colorless oil. An analytical sample was prepared by column chromatography (hexane/AcOEt, 2:1). Data for **3b**: [α]²⁰_D -14.4° (*c* 1.00, EtOH); ir (*neat*) 3340, 1725, 1510, 1430, 1210 cm⁻¹; ¹H nmr (CDCl₃) δ 2.87 (dd, *J*=17.2 and 4.6 Hz,

1H, CHHCO_2Me), 3.05 (dd, $J=17.2$ and 4.5 Hz, 1H, CHHCO_2Me), 3.68 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.64 (ddd, $J=8.2$, 4.6 , and 4.5 Hz, 1H, CHNHZ), 5.13 (s, 2H, OCH_2Ar), 5.76 (br d, $J=8.2$ Hz, 1H, NHZ), 7.30–7.39 (m, 5H, ArH). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 56.77; H, 5.90; N, 4.99.

(S)-3-Benzoyloxycarbonylamino-1,4-butanediol (4b). The reduction of the crude **3b** (14.8 g) with NaBH_4 (3.78 g, 100 mmol) was carried out by a similar procedure to that in the reduction of **3a** to afford 11.9 g of crude **4b** with 100% ee. The enantiomeric excess was determined by hplc after its conversion to the corresponding diacetate (**10b**). Hplc analysis conditions: Column, Daicel Chiralcel OJ (\varnothing 4.6×250 mm); eluent, hexane/IPA (10:1); flow rate, 1.0 ml min^{-1} ; t_R of (*S*)-**10b**=19.2 min, t_R of (*R*)-**10a**=23.0 min. An analytical sample of **4b** was prepared by column chromatography (AcOEt/hexane, 3:2). Data for **4b**: Colorless solid; mp 45–48 °C; $[\alpha]_D^{20}$ -32.5° (c 0.41, EtOH); ir (KBr) 3314, 1693, 1550, 1278, 1052 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.59–1.72 (m, 1H, CHHCH_2OH), 1.77–1.90 (m, 1H, CHHCH_2OH), 2.66 (br s, 2H, $2\times\text{OH}$), 3.63–3.75 (m, 4H, $2\times\text{CH}_2\text{OH}$), 3.82–4.00 (m, 1H, CHNHZ), 5.10 (s, 2H, OCH_2Ar), 5.35 (br s, 1H, NHZ), 7.29–7.42 (m, 5H, ArH). Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.23; H, 7.15; N, 5.89.

(S)-3-Benzoyloxycarbonylamino-1,4-dimethanesulfonyloxybutane (5b). To a solution of the above crude **4b** (11.5 g) and Et_3N (16.0 ml, 115 mmol) in AcOEt (160 ml) was dropwise added methanesulfonyl chloride (12.1 g, 106 mmol) at $-5 \sim -20$ °C over 30 min. Stirring was continued for 1 h at the same temperature. The resulting mixture was washed with water (2×46 ml) and concentrated *in vacuo*. The residual solid was slurried with MeOH (100 ml) and cooled with an ice-bath. After 1 h, the insoluble **5b** was isolated by filtration and dried *in vacuo*: 16.9 g (89% overall yield from **2b**); colorless crystals; mp 68–69 °C (AcOEt–hexane); $[\alpha]_D^{20}$ -27.2° (c 0.96, acetone); ir (KBr) 3371, 1694, 1523, 1348, 1174 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.92–2.15 (m, 2H, $\text{CH}_2\text{CH}_2\text{OMs}$), 2.98 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 4.08–4.2 (m, 1H, CHNHZ), 4.2–4.40 (m, 4H, $2\times\text{CH}_2\text{OMs}$), 5.05 (br d, $J=8.6$ Hz, 1H, NHZ), 5.11 (d, $J=12.4$ Hz, 1H, OCHHAr), 5.13 (d, $J=12.4$ Hz, 1H, OCHHAr), 7.27–7.43 (m, 5H, ArH). Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_8\text{S}_2$: C, 42.52; H, 5.35; N, 3.54; S, 16.22. Found: C, 42.52; H, 5.34; N, 3.58; S, 16.13.

(S)-1-Allyl-3-(benzyloxycarbonylamino)pyrrolidine (6b). A mixture of **5b** (3.95 g, 10.0 mmol) and allylamine (7.89 ml, 105 mmol) was stirred at 40 °C for 3 h. A similar workup to that in the preparation of **6a** afforded 2.60 g (quantitative) of **6b** with 100% ee as a colorless oil. The enantiomeric excess of this compound was determined by hplc analysis: Column, Daicel Chiralcel OD (\varnothing 4.6×250 mm);

eluent, hexane/IPA (50:1); flow rate, 1.0 ml min⁻¹; *t*_R of (*S*)-**6b**=23.5 min, *t*_R of (*R*)-**6b**=29.2 min. Data for **6b**: [α]_D²⁰ -9.6° (*c* 0.57, EtOH); ir (neat) 3319, 2966, 1701, 1535, 1260 cm⁻¹; ¹H nmr (CDCl₃) δ 1.56–1.73 (m, 1H, CHHCH₂N), 2.18–2.97 (m, 5H, CHHCH₂N+CH₂NCH₂), 3.10 (d, *J*=6.4 Hz, 2H, CH₂CH=), 4.11–4.33 (m, 1H, CHNHZ), 5.08 (s, 2H, OCH₂Ar), 5.13 (d, *J*=10.2 Hz, 1H, CH=CHH), 5.20 (d, *J*=17.4 Hz, 1H, CH=CHH), 5.25 (br, 1H, NH), 5.88 (ddt, *J*=17.4, 10.2, and 6.4 Hz, CH₂CH=), 7.28–7.43 (m, 5H, ArH). Anal. Calcd for C₁₅H₂₀N₂O₂: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.20; H, 7.60; N, 10.75.

Deallylation of 6b using 10% Pd/C. A suspension of **6b** (500 mg, 1.92 mmol), AcOH (0.25 ml, 4.4 mmol), and 10% Pd/C (50 mg) in water (2 ml) was refluxed for 1.5 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give the crude product which was assayed by hplc using an external standard method, showing a 92% yield of **1b**. Similarly, **6b** and **6a** were subjected to the deallylation using various transition metal catalysts. The reaction conditions and the results are listed in Table 1. When RhCl(PPh₃)₃ or RuCl₂(PPh)₃ was used as a catalyst, the solvent was degassed prior to use and the yield was measured after treatment of the crude product with AcOH–water (1:2, 15 ml) to complete the hydrolysis.

(*S*)-3-(*p*-Nitrobenzyloxycarbonylamino)pyrrolidine (1a). A suspension of **6a** (75.0 g, 246 mmol), 10% Pd/C (7.5 g), and AcOH (37.5 ml, 655 mmol) in water (300 ml) was heated under reflux for 2 h. After the mixture was cooled to room temperature, the catalyst was filtered and washed with EtOH (225 ml). The filtrate and the washing were combined and evaporated *in vacuo*. The residue was dissolved in EtOH (150 ml) and evaporated to remove water. To the residue were added EtOH (525 ml) and a 4*N* AcOEt solution of HCl (65 ml) at 40 °C. The resulting suspension was cooled gradually to 20 °C and then stirred for 50 min under ice-cooling. The precipitated **1a**·HCl was isolated by filtration, washed with cool EtOH (150 ml), and dried *in vacuo*: 60.5 g (82% yield); an orange solid. The enantiomeric excess (100% ee) of **1a** was determined by hplc after its conversion to the corresponding 1-trifluoroacetyl derivative (**11a**). Hplc analysis conditions: Column, Daicel Chiralpak AS (ø 4.6×250 mm); eluent, hexane/IPA (3:1); flow rate, 1.0 ml min⁻¹; *t*_R of (*S*)-**11a**=21.1 min, *t*_R of (*R*)-**11a**=27.4 min. An analytical sample of **1a**·HCl was obtained as colorless crystals by recrystallization from EtOH. Data for **1a**·HCl: mp 199–202 °C (EtOH); [α]_D²⁰ -15.7° (*c* 0.40, EtOH); ir (KBr) 3271, 3100–2200, 1705, 1523, 1356, 1249 cm⁻¹; ¹H nmr (DMSO-*d*₆) δ 1.80–1.92 (m, 1H, CHHCH₂N), 2.03–2.17 (m, 1H, CHHCH₂N), 3.04 (dd, *J*=11.9 and 4.8 Hz, 1H, NCHHCHN), 3.14–3.49 (m, 3H, CHHNCH₂), 4.09–4.26 (m, 1H, CHNHPNZ), 5.19

(s, 2H, OCH_2Ar), 7.62 (d-like, $J=8.5$ Hz, 2H, ArH), 7.84 (d, $J=6.1$ Hz, 1H, NHCO), 8.25 (d-like, $J=8.5$ Hz, 2H, ArH). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_3\text{O}_4\text{Cl}$: C, 47.77; H, 5.35; N, 13.93; Cl, 11.75. Found: C, 47.62; H, 5.37; N, 13.82; Cl, 11.79. Treatment of **1a**-HCl with 10 % aqueous NaOH gave free **1a** as a pale yellow solid. Data for **1a**: mp 103–106 °C; $[\alpha]_{\text{D}}^{20}$ -12.8° (c 0.40, EtOH); ir (KBr) 3300, 3201, 1713, 1514, 1344, 1267 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.65–1.83 (m, 1H, CHHCH_2N), 2.08–2.23 (m, 1H, CHHCH_2N), 2.70–3.60 (m, 5H, $\text{CH}_2\text{NCH}_2+\text{NH}$), 4.11–4.30 (m, 1H, CHNHPNZ), 5.19 (s, 2H, OCH_2Ar), 5.39 (br d, 1H, NHCO), 7.50 (d-like, $J=8.6$ Hz, 2H, ArH), 8.21 (d-like, $J=8.5$ Hz, 2H, ArH). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.20; H, 5.51; N, 15.66.

(S)-3-(Benzyloxycarbonylamino)pyrrolidine (1b). A mixture of **6b** (1.63 g, 6.26 mmol), 10% Pd/C (0.16 g), and AcOH (0.82 ml, 14 mmol) in water (6.5 ml) was heated for 2 h under reflux. After the mixture was cooled to room temperature, the catalyst was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml), washed with 10% aqueous Na_2CO_3 , and evaporated *in vacuo* to afford 1.27 g (92%) of **6b** with 100% ee as a pale yellow oil. The enantiomeric excess of **1b** was measured as the corresponding 1-trifluoroacetyl derivative (**11b**). Hplc analysis conditions: Column, Daicel Chiralpak AS (ϕ 4.6×250 mm); eluent, hexane/IPA (15:1); flow rate, 1.0 ml min^{-1} ; t_{R} of (*S*)-**11b**=35.4 min, t_{R} of (*R*)-**11b**=44.5 min. Data for **1b**: $[\alpha]_{\text{D}}^{20}$ -14.1° (c 0.40, EtOH); ir (neat) 3319, 1701, 1535, 1260 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.63–1.80 (m, 1H, CHHCH_2N), 2.04–2.20 (m, 1H, CHHCH_2N), 2.80–3.65 (m, 5H, $\text{CH}_2\text{NCH}_2+\text{NH}$), 4.22 (br m, 1H, CHNHZ), 5.09 (s, 2H, OCH_2Ar), 5.32 (br s, 1H, CONH), 7.29–7.40 (m, 5H, ArH). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2 \cdot 0.2\text{H}_2\text{O}$: C, 64.38; H, 7.38; N, 12.51. Found: C, 64.46; H, 7.30; N, 12.44.

Dimethyl *N*-(*t*-butoxycarbonyl)-L-aspartate.²⁰ To a mixture of dimethyl L-aspartate hydrogen chloride (**7**)¹⁷ (9.30 g, 47.1 mmol) and Et_3N (14.4 ml, 103 mmol) in CH_2Cl_2 (56 ml) was dropwise added a solution of di-*t*-butyl dicarbonate (10.3 g, 47.1 mmol) in CH_2Cl_2 (18 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 3 h and diluted with CH_2Cl_2 (65 ml). The resulting solution was washed with water (50 ml) and with 5% aqueous NaHCO_3 , dried (Na_2SO_4), and concentrated *in vacuo* to afford 10.3 g of crude dimethyl *N*-(*t*-butoxycarbonyl)-L-aspartate as a colorless solid. An analytical sample of this compound was obtained by recrystallization from ether–hexane as colorless crystals: mp 65–67 °C (ether–hexane); $[\alpha]_{\text{D}}^{20}$ -18.0° (c 1.00, EtOH); ir (KBr) 3408, 1741, 1706, 1349, 1161 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.45 (s, 9H, $3 \times \text{CH}_3$), 2.83 (dd, $J=17.0$ and 4.8 Hz, 1H, CHHCO_2Me),

3.01 (dd, $J=17.0$, and 4.5 Hz, 1H, CHHCO_2Me), 3.70 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.58 (ddd, $J=8.1$, 4.8, and 4.5 Hz, 1H, CHNHBoc), 5.48 (d, $J=8.1$ Hz, 1H, NHCO). Anal. Calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_6$: C, 50.57; H, 7.33; N, 5.36. Found: C, 50.87; H, 7.00; N, 5.36.

(*S*)-3-(*t*-Butoxycarbonylamino)-1,4-butanediol.^{3a} NaBH_4 reduction of the above crude dimethyl ester (10.0 g) was performed in a similar manner to that described in the reduction of **3a**, affording 5.51 g of crude (*S*)-3-(*t*-butoxycarbonylamino)-1,4-butanediol. An analytical sample of this compound was obtained by recrystallization from ether-hexane as colorless crystals: mp $38\text{--}41$ °C (ether-hexane); $[\alpha]^{20}_{\text{D}} -30.0^\circ$ (c 0.49, EtOH); ir (KBr) 3377, 1691, 1518, 1246, 1049 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.45 (s, 9H, $3\times\text{CH}_3$), 1.57–1.70 (m, 1H, CHHCH_2OH), 1.76–1.89 (m, 1H, CHHCH_2OH), 2.71 (br s, 2H, $2\times\text{OH}$), 3.60–3.80 (m, 4H, $2\times\text{CH}_2\text{OH}$), 3.85 (quintet-like, $J=4.4$ Hz, 1H, CHNHBoc), 4.9 (br s, 1H, NHCO). Anal. Calcd for $\text{C}_9\text{H}_{19}\text{NO}_4$: C, 52.67; H, 9.33; N, 6.82. Found: C, 52.41; H, 9.19; N, 6.81.

(*S*)-3-(*t*-Butoxycarbonylamino)-1,4-dimethanesulfonyloxybutane.^{3a} The above obtained crude diol (5.0 g) was subjected to mesylation in a similar manner to that described in **4b** to give 5.30 g (35% overall yield from **7**) of (*S*)-3-(*t*-butoxycarbonylamino)-1,4-dimethanesulfonyloxybutane as a colorless solid: mp $70\text{--}74$ °C; $[\alpha]^{20}_{\text{D}} -26.3^\circ$ (c 1.00, acetone); ir (KBr) 3387, 1687, 1514, 1347, 1171 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.50 (s, 9H, $3\times\text{CH}_3$), 1.88–2.18 (m, 2H, $\text{CH}_2\text{CH}_2\text{OMs}$), 3.05 (s, 3H, SO_2CH_3), 3.06 (s, 3H, SO_2CH_3), 3.98–4.2 (m, 1H, CHNHBoc), 4.2–4.44 (m, 4H, $2\times\text{CH}_2\text{OMs}$), 4.81 (br d, $J=8.5$ Hz, 1H, NHCO). Anal. Calcd for $\text{C}_{11}\text{H}_{23}\text{NO}_8\text{S}_2$: C, 36.55; H, 6.41; N, 3.88; S, 17.74. Found: C, 36.40; H, 6.33; N, 3.86; S, 17.51.

(*S*)-1-Allyl-3-(*t*-butoxycarbonylamino)pyrrolidine (8**).** A mixture of the above dimesylate (1.15 g, 3.18 mmol) and allylamine (3.3 ml, 44 mmol) was stirred at 45 °C for 2.5 h. A similar workup to that described in **6a** afforded 0.67 g (94% yield) of **8** as a colorless solid: mp $43\text{--}44$ °C; $[\alpha]^{20}_{\text{D}} -17.5^\circ$ (c 0.10, EtOH); ir (KBr) 3207, 2971, 1702, 1548, 1294, 1175 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.43 (s, 9H, $3\times\text{CH}_3$), 1.63–1.82 (m, 1H, CHHCH_2N), 2.17–3.1 (m, 5H, $\text{CHHCH}_2\text{N}+\text{CH}_2\text{NCH}_2$), 3.19 (br d, $J=7$ Hz, 2H, $\text{CH}_2\text{CH}=\text{}$), 4.16–4.37 (m, 1H, CHNHBoc), 5.12 (br s, 1H, NHCO), 5.20 (d, $J=10.2$ Hz, 1H, $\text{CH}=\text{CHH}$), 5.26 (d, $J=17.1$ Hz, 1H, $\text{CH}=\text{CHH}$), 5.93 (ddt, $J=17.1$, 10.2, and 7 Hz, $\text{CH}_2\text{CH}=\text{}$). Anal. Calcd for $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_2$: C, 63.69; H, 9.80; N, 12.38. Found: C, 63.58; H, 9.96; N, 12.28.

(*S*)-3-(*t*-Butoxycarbonylamino)pyrrolidine (9**).** A mixture of **8** (256 mg, 1.13 mmol), 10% Pd/C (26 mg), and AcOH (128 μl , 2.24 mmol) in water (6.5 ml) was heated for 2 h under reflux. A similar workup to that described in **1b** afforded 199 mg (95% yield) of **9** as a colorless solid: mp $68\text{--}78$ °C;

$[\alpha]^{20}_{\text{D}} -20.7^\circ$ (c 0.46, EtOH) [lit.,^{4a} mp 70–74 °C; $[\alpha]^{26}_{\text{D}} -20.9^\circ$ (c 1.0, EtOH)]; ir (KBr) 3327, 3194, 2971, 1694, 1567, 1179 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.43 (s, 9H, $3\times\text{CH}_3$), 1.62–1.75 (m, 1H, CHHCH_2N), 2.02–2.20 (m, 1H, CHHCH_2N), 2.70–3.63 (m, 5H, $\text{CH}_2\text{NCH}_2+\text{NH}$), 4.16 (br m, 1H, CHNHBOc), 4.92 (br d, $J=4$ Hz, 1H, CONH). These spectral data are identical with those of a commercial sample.

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