A Large-Scale Preparation of (3*S*,4*S*)-3-(*tert*-Butoxycarbonyl)amino-4-methylpyrrolidine and Its Analogs from L-Aspartic Acid

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(3*S*,4*S*)-3-(*tert*-Butoxycarbonyl)amino-4-methylpyrrolidine (12a) was synthesized from L-aspartic acid (4) on a large scale. Methylation of dimethyl (2S)-*N*-benzyl-*N*-(9-phenylfluoren-9-yl)aspartate (5), easily derived from 4, with methyl iodide gave (3*R*)-3-methylaspartate (6a) in 91% yield with high diastereoselectivity. Reduction of 6a with lithium aluminum hydride, followed by hydrogenolysis, protection with di-*tert*-butyl dicarbonate, and mesylation gave 10a in 89% overall yield. Subsequently, reaction of 10a with benzylamine under a nitrogen atmosphere at room temperature, followed by hydrogenolysis, gave the target compound (12a) in 65% overall yield. In a similar manner to that described for the preparation of 12a from 5, compound 5 was converted into 4-ethyl and 4-propyl derivatives (12b, c) in 34% and 38% overall yields.

Key words (3*S*,4*S*)-3-(*tert*-butoxycarbonyl)amino-4-methylpyrrolidine; large-scale preparation; L-aspartic acid; (3*S*,4*S*)-3-(*tert*-butoxycarbonyl)amino-4-ethylpyrrolidine; (3*S*,4*S*)-3-(*tert*-butoxycarbonyl)amino-4-propylpyrrolidine

Quinolone antibacterial agents, such as ciprofloxacin (CPFX, **1**), are a major class of antiinfectives. The C-7 substituents of quinolones are classified in terms of their chemical structures into two major groups,[1] the piperazine derivatives (**2**), and the 3-aminopyrrolidine derivatives (**3**). The heterocyclic amine moieties are important for antibacterial activity. Recently, Di Cesare *et al.*[2] and others[3] reported that (3*S*,4*S*)-3-amino-4-methylpyrrolidine was an effective substituent at the C-7 position of quinolone. Several synthetic methods for (3*S*,4*S*)-3-amino-4-methylpyrrolidine (**12a**) have been reported; 1) optical resolution through fractional recrystallization of the racemate,[2,4] and 2) the stereoselective syntheses from L-aspartic acid or L-malic acid.[3,5]

Recently, Chamberlin *et al.*[6] reported that bulky *N*-(phenylfluorenyl)-protected D-aspartate[7] (enantiomer of **5**), easily derived from D-aspartic acid, could be methylated at the C-3 position with methyl iodide in the presence of lithium hexamethyldisilazane (LHMDS) to give a single product (enantiomer of **6**) in excellent yield. We used this methodology to synthesize optically pure *cis*-3-amino-4-methylpyrrolidine, and report herein a new

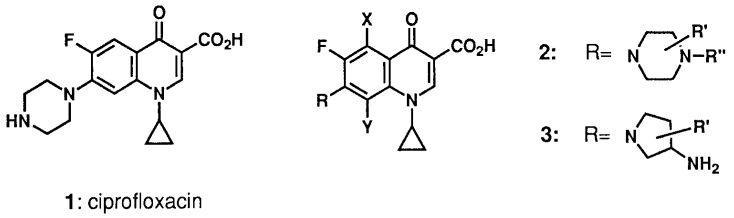
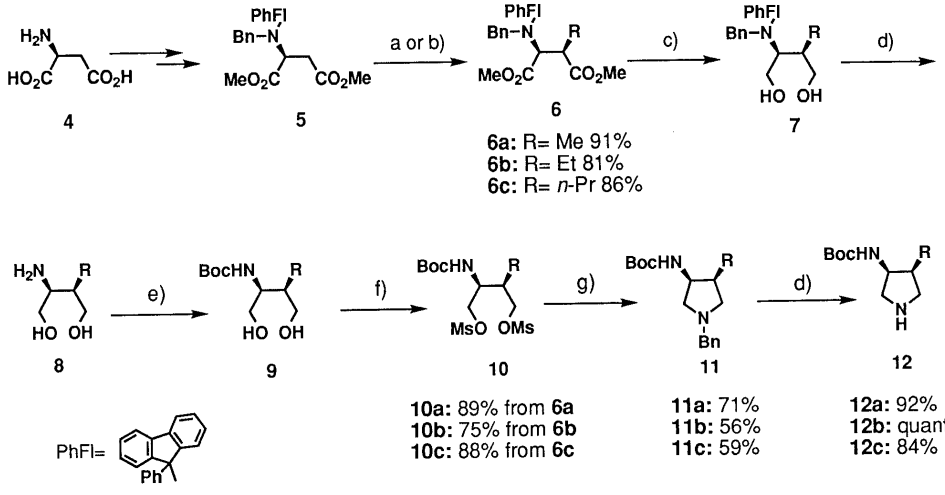


Chart 1



a) MeI b) $ROSO_2CF_3$ (**14**: R=Et, **15**: R= *n*-Pr) c) LAH d) H_2, 5 % Pd/C e) Boc_2O f) MsCl g) $PhCH_2NH_2$

Chart 2

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Table 1. Reaction Conditions for Ring Closure (**10a**→**11a**)

Entry	Amount of **10a** (g)	Bath temp. (°C)	Temp. of exothermic reaction (°C)	Time (h)	Isolated yield (%)
1	23	60	60—64	3	51
2	90	60	>96	3	49
3	100[a]	60	60—77	3	48
4	100	r.t.	20—30	48	52
5	329[b]	r.t.	21—35	72	71

a) Added in seven portions. *b*) The reaction was carried out under an N_2 atmosphere.

general synthetic method for large-scale preparation of **12a** and its analogues (**12b, c**) from L-aspartic acid (**4**), as shown in Chart 2.

Compound **5** was easily synthesized from **4** according to the literature.[6] The reaction of **5** with methyl iodide in the presence of LHMDS proceeded smoothly to afford the (3*R*)-3-methylaspartate (**6a**) in 91% yield with high diastereoselectivity. But, Chamberlin *et al.* reported that reaction of the antipode of **5** with ethyl iodide was tedious.[6] Use of a more reactive electrophile,[8] ethyl triflate (**14**) or propyl triflate (**15**), overcame this problem and gave the desired single product (**6b** or **c**) in good yield (81% or 86%) with high diastereoselectivity.

Reduction of **6** with lithium aliminum hydride (LAH) gave the diol **7**, and subsequent removal of the nitrogen-protecting groups of **7** by hydrogenolysis and reprotection with di-*tert*-butyl dicarbonate gave the diol **9** without epimerization. Reaction of **9** with mesyl chloride in the presence of triethylamine afforded the corresponding dimesylates (**10**) in an excellent yield.

Subsequently, according to the literature,[5] treatment of **10a** with benzylamine at 60 °C provided the key compound (**11a**) in 51% yield. The optical rotation of this compound agreed with the reported value[3] and its diastereoisomer was not detectable by HPLC. But this ring closure reaction was not suitable for large-scale preparation because the exothermic reaction took place suddenly and could not be controlled (entry 2). To overcome this problem, the reaction conditions were examined as shown in Table 1. The exothermic reaction could be controlled by addition of **10a** in portions at 60 °C, but the yield (49%) was not improved (entry 3). The reaction at room temperature proceeded smoothly to afford **11a**, but again the yield was not improved (entry 4). Finally, the optimal reaction condition was found to be under a nitrogen atmosphere at room temperature, and reaction under this condition gave **11a** in a satisfactory yield (71%). Under a similar condition, ring closures of the dimesylates **10b** and **10c** gave the desired compounds **11b** and **11c** in 56% and 59% yields, respectively.

Finally, hydrogenolysis of the benzyl group of **11** with 5% palladium on carbon in methanol gave the target compound (**12**) in a high yield.

We found that this efficient method is applicable to synthesizing (3*S*,4*S*)-3-(*tert*-butoxycarbonyl)amino-4-alkylpyrrolidine from **4** on a large scale. In the reported reaction, lead(II) nitrate was required for conversion of dimethyl (2*S*)-*N*-benzylaspartate to **5**.[7] We found that treatment of this aspartate with phenyfluorenyl bromide in the absence of lead(II) nitrate proceeded to afford **5** in 82% yield, so that the use of lead was unnecessary.

Experimental

Commercial *n*-BuLi was used as a 1.66 M solution in *n*-hexane. Tetrahydrofuran (THF) and acetonitrile were dried with molecular sieves 4 Å. Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Elemental analyses were done with a Yanaco MT-5 elemental analysis apparatus. Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a JEOL JNM-A 500 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were taken on a JEOL DX-300 mass spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. HPLC analyses were performed with a JASCO BIP-I pumping system and a JASCO UNIDE D-100-V ultraviolet detector. Column chromatography was carried out with silica gel [Kieselgel 60 (Merck)]. TLC was conducted on 0.25 mm pre-coated silica gel plates ($60F_{254}$, Merck). The extracted solvents were dried over Na_2SO_4 and removed with a rotary evaporator under reduced pressure.

Dimethyl (2*S*,3*R*)-*N*-Benzyl-3-methyl-*N*-(9-phenylfluoren-9-yl)aspartate (6a) *n*-BuLi (1.96 l, 3.26 mol) was added dropwise to a solution of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (608 ml, 2.88 mol) in THF (3.20 l) at −10 °C under a nitrogen atmosphere and the resulting solution was stirred at the same temperature for 30 min. A solution of dimethyl (2*S*)-*N*-benzyl-*N*-(9-phenylfluoren-9-yl)aspartate (**5**; 942 g, 1.92 mol) in THF (3.20 l) was added dropwise to LHMDS solution at −25 °C and the mixture was stirred for 30 min at the same temperature. Methyl iodide (143 ml, 2.30 mol) was added dropwise to the above solution at −65 °C. The stirring was continued at −70 °C for 1.5 h and then at −20 °C for 1 h. Saturated aqueous ammonium chloride (3.80 l) was added to the reaction mixture to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic extracts were washed with brine, dried, and concentrated to leave crystalline residue, which was washed with methanol to afford **6a** (880 g, 91%). Recrystallization from methanol gave colorless plates, mp 153—155 °C (lit[6]; mp 154—155 °C (enantiomer of **6a**)). $[\alpha]_D^{20}$ −344.5° (*c*=1, $CHCl_3$). MS *m/z*: 505 (M^+), 241 (base peak). IR (KBr): 1730 (CO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 0.61 (3H, d, *J*=7.0 Hz, CH_3), 2.56 (1H, dq, *J*=11.5, 7.0 Hz, C_3-H), 2.91, 3.54 (each 3H, s, OCH_3), 3.78 (1H, d, *J*=11.5 Hz, C_2-H), 4.34, 4.68 (each 1H, d, *J*=14.5 Hz, $C\underline{H}_2$Ph), 7.14—7.99 (18H, m, Ar-H). *Anal.* Calcd for $C_{33}H_{31}NO_4$: C, 78.39; H, 6.18; N, 2.77. Found: C, 78.41; H, 6.15; N, 2.75.

In a similar manner to that described for the preparation of **6a** from **5**, compound **5** was converted into **6b** and **6c** by replacing methyl iodide with the triflates **14** and **15**.

Dimethyl (2*S*,3*R*)-*N*-Benzyl-3-ethyl-*N*-(9-phenylfluoren-9-yl)aspartate (6b) Yield 81%, colorless plates (MeOH), mp 162—164 °C (lit[6]; mp 161—163 °C (enantiomer of **6b**). $[\alpha]_D^{20}$ −331.8° (*c*=1, $CHCl_3$). IR (KBr): 1736, 1722 (CO_2) cm^{-1}. MS *m/z*: 519 (M^+), 241 (base peak). ^{1}H-NMR ($CDCl_3$) *δ*: 0.47 (3H, t, *J*=7.5 Hz, CH_3), 0.89—1.06 (2H, m, CH_2), 2.27—2.54 (1H, m, C_3-H), 2.92, 3.55 (each 3H, s, OCH_3), 3.83 (1H, d, *J*=11.5 Hz, C_2-H), 4.32, 4.62 (each 1H, d, *J*=14.0 Hz, $C\underline{H}_2$Ph), 7.12—7.92 (18H, m, Ar-H). *Anal.* Calcd for $C_{34}H_{33}NO_4$: C, 78.59; H, 6.40; N, 2.70. Found: C, 78.50; H, 6.48; N, 2.57.

Dimethyl (2*S*,3*R*)-*N*-Benzyl-*N*-(9-phenylfluoren-9-yl)-3-propylaspartate (6c) Yield 86%, colorless prisms (MeOH), mp 148—149 °C. $[\alpha]_D^{20}$ −309.9° (*c*=1, $CHCl_3$). IR (KBr): 1738, 1722 (CO_2) cm^{-1}. MS *m/z*: 533 (M^+), 241 (base peak). ^{1}H-NMR ($CDCl_3$) *δ*: 0.56 (3H, t, *J*=6.5 Hz, CH_3), 0.78—0.99 (4H, m, CH_2×2), 2.52—2.60 (1H, m, C_3-H), 2.92, 3.55 (each 3H, s, OCH_3), 3.80 (1H, d, *J*=11.0 Hz, C_2-H), 4.32, 4.61 (each 1H, d, *J*=14.0 Hz, $C\underline{H}_2$Ph), 7.13—7.88 (18H, m, Ar-H). *Anal.* Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61; N, 2.62. Found: C, 78.79; H, 6.59; N, 2.65.

(2*S*,3*R*)-2-[*N*-Benzyl-*N*-(9-phenylfluoren-9-yl)]amino-3-methylbutane-1,4-diol (7a) A solution of the ester **6a** (560 g, 1.11 mol) in THF (1.80 l) was added dropwise to a suspension of LAH (63.0 g, 1.66 mol) in THF (3.00 l) at 0 °C. The solution was stirred at room temperature for 30 min. Water (300 ml) and, after 5 min, 15% aqueous NaOH (110 ml) were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h, then filtered, and the filtrate was concentrated. The residue was

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dissolved in AcOEt and the solution was dried and concentrated to give crude **7a** (544 g). Purification by silica gel column chromatography with a mixture of AcOEt and *n*-hexane gave a colorless, viscous oil. $[\alpha]_D^{20}$ +106.7° ($c=1$, $CHCl_3$). MS *m/z*: 418 ($M^+ - CH_2OH$), 241 (base peak). IR (neat): 3324 (OH) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.54 (3H, d, $J=7.0$ Hz, CH_3), 1.50—1.60 (1H, m, C_3-H), 2.58—2.64 (1H, m, C_2-H), 2.84—2.93 (1H, m, C_4-H), 3.02—3.10 (1H, m, C_1-H), 3.12—3.19 (1H, m, C_4-H), 3.22—3.29 (1H, m, C_1-H), 4.18, 4.29 (each 1H, d, $J=15.5$ Hz, $C\underline{H}_2Ph$), 7.17—7.75 (18H, m, Ar-H).

(2*S*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-3-methylbutane-1,4-diol (9a) A suspension of crude **7a** (524 g) and 5% palladium on carbon (52.4 g) in MeOH (3.30 l) was stirred at 40 °C under hydrogen (5 atm) for 2 h. The catalyst was removed by filtration and washed with methanol. The filtrate combined with the washing was concentrated and the residue was dissolved in iso-PrOH. Insoluble material was removed by filtration and the filtrate was concentrated to give crude **8a** (146 g). A mixture of the diol and di-*tert*-butyl dicarbonate (234 g, 107 mol) in iso-PrOH (640 ml) was stirred at room temperature for 30 min. The reaction mixture was concentrated to give crude **9a** (260 g). The residue was purified by silica gel column chromatography with a mixture of AcOEt and *n*-hexane to afford **9a**, a colorless, viscous oil. $[\alpha]_D^{20}$ −10.4° ($c=1$, $CHCl_3$). MS *m/z*: 188 ($N^+ - CH_2OH$), 57 (base peak). IR (neat): 3352 (OH), 1690 (CO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, $J=7.0$ Hz, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 1.75—1.90 (1H, m, C_3-H), 2.72, 3.17 (each 1H, br s, OH), 3.42—3.80 (5H, m, C_1-H_2, C_2-H, C_4-H_2), 5.23 (1H, br s, BocN$\underline{H}$).

(2*S*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-3-methyl-1,4-butanediyl Dimethanesulfonate (10a) Mesyl chloride (174 ml, 2.24 mol) was added dropwise to a solution of the diol (crude **9a**; 260 g) and NEt_3 (341 ml, 2.25 mol) in CH_2Cl_2 (1.60 l) at 0 °C. After 30 min at room temperature, the reaction mixture was poured into water and the solution was extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated to leave crystalline residue, which was washed with iso-PrOH to afford **10a** (344 g, 89% from **6a**), colorless crystals, mp 69—73 °C (dec.). $[\alpha]_D^{20}$ −26.0° ($c=1$, $CHCl_3$). MS *m/z*: 86 (base peak). IR (KBr): 3336 (NH), 1676 (CO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, $J=7.0$ Hz, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 2.10—2.22 (1H, m, C_3-H), 3.04, 3.06 (each 3H, s, OCH_3), 3.81—3.93 (1H, m, C_2-H), 4.15—4.40 (4H, m, C_1-H_2, C_4-H_2), 4.85 (1H, br s, BocN$\underline{H}$).

In a similar manner to that described for the preparation of **10a** from **6a**, compounds **6b** and **6c** were converted into **10b** and **10c**, respectively, without purification of the intermediates.

(2*S*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-3-ethyl-1,4-butanediyl Dimethanesulfonate (10b) Yield 75% from **6b**, pale brown solid, mp 75—77 °C (dec.). $[\alpha]_D^{20}$ −11.1° ($c=1$, $CHCl_3$). IR (KBr): 3380 (OH), 1692 (CO_2) cm^{-1}. MS *m/z*: 86 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, $J=7.5$ Hz, CH_3), 1.38—1.68 (2H, m, CH_2), 1.45 (9H, s, $C(CH_3)_3$), 1.90—2.00 (1H, m, C_3-H), 3.04, 3.05 (each 3H, s, CH_3), 4.00—4.09 (1H, m, C_2-H), 4.28—4.38 (4H, m, C_1-H_2, C_4-H_2), 4.80—4.91 (1H, m, BocN$\underline{H}$).

(2*S*,3*R*)-2-(*tert*-Butoxycarbonyl)amino-3-propyl-1,4-butanediyl Dimethanesulfonate (10c) Yield 88% from **6c**, pale brown solid, mp 77—79 °C (dec.). $[\alpha]_D^{20}$ −5.1° ($c=1$, $CHCl_3$). IR (KBr): 1676 (CO_2) cm^{-1}. MS *m/z*: 86 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, $J=6.5$ Hz, CH_3), 1.29—1.52 (4H, m, $CH_2 \times 2$), 1.45 (9H, s, $C(CH_3)_3$), 1.99—2.09 (1H, m, C_3-H), 3.04, 3.05 (each 3H, s, CH_3), 3.99—4.09 (1H, m, C_2-H), 4.22—4.35 (4H, m, C_1-H_2, C_4-H_2), 4.80—4.90 (1H, m, BocN$\underline{H}$).

(3*S*,4*S*)-1-Benzyl-3-(*tert*-butoxycarbonyl)amino-4-methylpyrrolidine (11a) Method 1) A mixture of the dimesylate (**10a**; 23.0 g, 0.06 mol) and benzylamine (67.0 ml, 0.60 mol) was heated at 60 °C for 2.5 h (internal temperature was 60 to 64 °C), then poured into ice-water, and the mixture was stirred for 30 min. The precipitate was collected by filtration and washed with water to give **11a** (8.96 g, 51%). Recrystallization from iso-PrOH gave colorless needles, mp 100—102 °C. $[\alpha]_D^{20}$ +30.3° ($c=0.5$, $CHCl_3$). (lit[3]; mp 98—100 °C. $[\alpha]_D^{20}$ +31.0° ($c=1.0$, $CHCl_3$). MS *m/z*: 290 (M^+), 173 (base peak). IR (KBr): 3380 (NH), 1686 (CO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, $J=6.5$ Hz, CH_3), 1.44 (9H, s, $C(CH_3)_3$), 2.15—2.30 (1H, m, C_5-H), 2.30—2.47 (2H, m, C_2-H, C_4-H), 2.62—2.75 (1H, m, C_5-H), 2.80—2.90 (1H, m, C_2-H), 3.56, 3.60 (each 1H, d, $J=13.5$ Hz, $C\underline{H}_2Ph$), 4.00—4.25 (1H, br s, C_3-H), 4.72 (1H, br s, BocN$\underline{H}$), 7.20—7.37 (5H, m, Ar-H). *Anal.* Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.42; H, 9.28; H, 9.43. Optical purity: >99% ee; HPLC using a Chiralcel AD column [Daicel Chemical Co., Ltd., 4.6 × 250 mm, solvent; *n*-hexane : iso-PrOH (100 : 1 and 50 : 1), flow rate 0.5 ml/min] and a Chiralcel AS column [Daicel Chemical Co., Ltd., 4.6 × 250 mm, solvent; *n*-hexane : iso-PrOH (100 : 1), flow rate 0.5 ml/min] with UV (220 nm) detection.

Method 2) The dimesylate (**10a**; 329 g, 0.87 mol) was added in small portions to benzylamine (960 ml, 8.79 mol) with stirring over 72 h at 21 to 35 °C (at room temperature) under a nitrogen atmosphere. The reaction mixture was poured into ice-water (3.00 l), and the whole was stirred for 30 min. The precipitate was collected by filtration and washed with water to give **11a** (181 g, 71%) which was identical with **11a** synthesized by method 1).

In a similar manner to that described for the preparation of **11a** from **10a**, compounds **10b** and **10c** were converted into the **11b** and **11c**, respectively.

(3*S*,4*S*)-1-Benzyl-3-(*tert*-butoxycarbonyl)amino-4-ethylpyrrolidine (11b) Yield 56%, colorless needles (*n*-hexane), mp 97—99 °C. $[\alpha]_D^{20}$ +31.9° ($c=1$, $CHCl_3$). IR (KBr): 1688 (CO_2) cm^{-1}. MS *m/z*: 304 (M^+), 158 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, $J=7.5$ Hz, CH_3), 1.14—1.30 (1H, m, CH_2), 1.39—1.52 (1H, m, CH_2), 1.44 (9H, s, $C(CH_3)_3$), 2.10—2.21 (1H, m, C_4-H), 2.26—2.34 (1H, m, C_5-H), 2.41—2.48 (1H, m, C_2-H), 2.60—2.71 (1H, m, C_5-H), 2.78—2.82 (1H, m, C_2-H), 3.56, 3.66 (each 1H, d, $J=13.0$ Hz, $C\underline{H}_2Ph$), 4.18—4.29 (1H, m, C_3-H), 4.74—4.83 (1H, m, BocN$\underline{H}$), 7.20—7.35 (5H, m, Ar-H). *Anal.* Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02: H, 9.27; H, 9.20. Found: C, 71.02; H, 9.55; N, 8.93.

(3*S*,4*S*)-1-Benzyl-3-(*tert*-butoxycarbonyl)amino-4-propylpyrrolidine (11c) Yield 59%, colorless needles (*n*-hexane), mp 75—76 °C. $[\alpha]_D^{20}$ +32.5° ($c=1$, $CHCl_3$). IR (KBr): 1686 (CO_2) cm^{-1}. MS *m/z*: 318 (M^+), 158 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, $J=7.5$ Hz, CH_3), 1.13—1.49 (4H, m, $CH_2 \times 2$), 1.44 (9H, s, $C(CH_3)_3$), 2.20—2.35 (2H, m, C_4-H, C_5-H), 2.41—2.48 (1H, m, C_2-H), 2.60—2.69 (1H, m, C_5-H), 2.78—2.82 (1H, m, C_2-H), 3.56, 3.64 (each 1H, d, $J=13.5$ Hz, $C\underline{H}_2Ph$), 4.18—4.27 (1H, m, C_3-H), 4.76—4.83 (1H, m, BocN$\underline{H}$), 7.20—7.31 (5H, m, Ar-H). High-resolution MS *m/z*: Calcd for $C_{19}H_{30}N_2O_2$: 318.2307. Found: 318.2310.

(3*S*,4*S*)-3-(*tert*-Butoxycarbonyl)amino-4-methylpyrrolidine (12a) A suspension of 1-benzylpyrrolidine (**11a**; 60.0 g, 0.207 mol) and 5% palladium on carbon (6.00 g) in MeOH (500 ml) was stirred at 40 °C under hydrogen (5 atm) for 3 h. The catalyst was removed by filtration and washed with MeOH. The filtrate was concentrated to give **12a** (38 g, 92%). Recrystallization from *n*-hexane gave colorless needles; mp 83—85 °C. $[\alpha]D_D^{20}$ +19.6° ($c=1$, $CHCl_3$). (lit[3]; mp 84—85 °C. $[\alpha]_D^{20}$ +18.9° ($c=1.5$, $CHCl_3$)). IR (KBr): 1694 (CO_2) cm^{-1}. MS *m/z*: 201 ($M^+ + H$), 83 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, $J=7.0$ Hz, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 2.20—2.30 (1H, m, C_4-H), 2.44—2.53 (1H, m, C_5-H), 2.70 (1H, dd, $J=11.5$, 4.5 Hz, C_2-H), 3.15 (1H, m, dd, $J=11.5$, 7.5 Hz, C_5-H), 3.20—3.30 (1H, m, C_2-H), 4.05—4.20 (1H, m, C_3-H), 4.62 (1H, br s, BocN$\underline{H}$). High-resolution MS *m/z*: Calcd for $C_{10}H_{20}N_2O_2 + H$: 201.1603. Found: 201.1601.

In a similar manner to that described for the preparation of **12a** from **11a**, compounds **11b** and **11c** were converted into **12b** and **12c**, respectively.

(3*S*,4*S*)-3-(*tert*-Butoxycarbonyl)amino-4-ethylpyrrolidine (12b) Yield quant., pale yellow needles (*n*-hexane), mp 63—66 °C. $[\alpha]_D^{20}$ +2.3° ($c=1$, $CHCl_3$). IR (KBr): 1712 (CO_2) cm^{-1}. MS *m/z*: 215 ($M^+ + H$), 57 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, $J=7.5$ Hz, CH_3), 1.20—1.33 (1H, m, CH_2), 1.39—1.51 (1H, m, CH_2), 1.44 (9H, s, $C(CH_3)_3$), 1.98—2.08 (1H, m, C_4-H), 2.49—2.57 (1H, m, C_5-H), 2.75—2.81 (1H, m, C_2-H), 3.10—3.24 (2H, m, C_2-H, C_5-H), 4.09—4.20 (1H, m, C_3-H), 4.68—4.79 (1H, m, BocN$\underline{H}$). High-resolution MS *m/z*: Calcd for $C_{11}H_{22}N_2O_2 + H$: 215.1760. Found: 215.1764.

(3*S*,4*S*)-3-(*tert*-Butoxycarbonyl)amino-4-propylpyrrolidine (12c) Yield 84%, colorless needles (*n*-octane), mp 70—71 °C. $[\alpha]_D^{20}$ +9.90° ($c=1$, $CHCl_3$). IR (KBr): 1690 (CO_2) cm^{-1}. MS *m/z*: 229 ($M^+ + H$), 111 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, $J=7.5$ Hz, CH_3), 1.18—1.51 (4H, m, $CH_2 \times 2$), 1.49 (9H, s, $C(CH_3)_3$), 1.99—2.15 (1H, m, C_4-H), 2.45—2.55 (1H, m, C_5-H), 2.47—2.81 (1H, m, C_2-H), 3.10—3.23 (2H, m, C_2-H, C_5-H), 4.08—4.20 (1H, m, C_3-H), 4.67—4.80 (1H, m, BocN$\underline{H}$). High-resolution MS *m/z*: Calcd for $C_{12}H_{24}N_2O_2 + H$: 229.1916. Found: 229.1916.

Ethyl Triflate (14) A solution of EtOH (6.00 g, 0.130 mol) and pyridine (10.3 g, 0.130 mol) in CH_2Cl_2 (12.0 ml) was added dropwise to a solution of trifluoromethanesulfonic anhydride (36.7 g, 0.150 mol) in CH_2Cl_2 (120 ml) at −5 to 3 °C. After 30 min at the same temperature, the reaction mixture was poured into water and the solution was extracted with CH_2Cl_2. The extract was dried and concentrated and the

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residue was distilled to give **14** (12.2 g, 55%), a colorless oil, bp 90—101 °C (640 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.52 (3H, t, J=7.0 Hz, CH_3), 4.62 (2H, q, J=7.0 Hz, CH_2).

Propyl Triflate (15) In a similar manner to that described for the preparation of **14** from MeOH, propanol was converted to **15** (59%), a colorless oil, bp 27—29 °C (8 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7.0 Hz, CH_3), 1.87 (2H, sex, J=7.0 Hz, CH_2), 4.51 (2H, t, J=7.0 Hz, CH_2).

Dimethyl (2*S*)-*N*-Benzyl-*N*-(9-phenylfluoren-9-yl)aspartate (5) 9-Bromo-9-phenyfluorene (1.36 kg, 4.24 mol) was added to a suspension of dimethyl (2*S*)-*N*-benzylaspartate (887 g, 3.53 mol) and anhydrous K_3PO_4 (900 g, 4.24 mol) in acetonitrile (7.10 l) under cooling with water. Stirring was continued for 24 h at room temperature, then MeOH (1.80 l) was added to the reaction mixture and the whole was stirred for 20 min. The precipitate was removed by filtration through Celite and the filtrate was concentrated. The residue was neutralized with 2% aqueous citric acid (2.60 l) and the solution was extracted with AcOEt (4.40 l). The extract was washed with brine, dried and concentrated to leave crystalline residue, which was recrystallized from a mixture of acetone and MeOH to give pure **5** (1.43 kg, 82%), colorless powder, mp 147—149 °C. $[\alpha]_D^{20}$ +66.9° (c=1, $CHCl_3$). (lit[6]; mp 144—146 °C. $[\alpha]_D^{20}$ −54° (c=1.2, $CHCl_3$) (enantiomer of **5**)). IR (KBr): 1732 (CO_2) cm^{-1}. MS m/z: 491 (M^+), 241 (base peak). ^{1}H-NMR ($CDCl_3$) δ: 1.84 (1H, dd, J=16.0, 3.0 Hz, CH_2), 2.52 (1H, dd, J=16.0, 10.5 Hz, CH_2), 3.20, 3.38 (each 3H, s, OMe), 3.92 (1H, dd, J=10.5, 3.0 Hz, NCH), 3.95, 4.26 (each 1H, d, J=14.0 Hz, C<u>H</u>$_2$Ph), 7.19—7.83 (18H, m, Ar-H). *Anal.* Calcd for $C_{32}H_{29}NO_4$: C, 78.19; H, 5.95; H, 2.85. Found: C, 78.29; H, 5.84; N, 2.75.

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