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Stereoselective Synthesis of a Broad Spectrum 1β-Methylcarbapenem, J-114,870

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Abstract—An ultra-broad spectrum carbapenem, J-114,870 (**1**), was synthesized from the corresponding C-2 side chain and 1β-methylcarbapenem enolphosphate. Synthesis of the C-2 side chain was accomplished by installation of the benzene part to (4*R*)-hydroxy-2-pyrrolidone **3**, affording 2-phenylpyrrolidine **8a**, and asymmetric Michael addition of chiral amine to α,β-unsaturated ester derived from **8a**.

Well-known 1β-methylcarbapenem antibiotics having a (3*S*,5*S*)-*cis*-disubstituted pyrrolidine ring as the C-2 side chain, such as meropenem,[1] S-4661,[2] and BO-2727,[3] have a broad antibacterial spectrum covering gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa*; however, these traditional carbapenems lack activity against methicillin-resistant *Staphylococcus aureus* (MRSA). In contrast, J-114,870 (**1**), a novel carbapenem identified by us, shows ultra-broad antibacterial activity against MRSA as well as *P. aeruginosa*, probably due to its unique (3*S*,5*R*)-*trans*-disubstituted pyrrolidine ring C-2 side chain (see Fig. 1).[4]

In SAR studies,[4] we constructed the (3*S*,5*R*)-*trans*-disubstituted pyrrolidine ring system of the C-2 side chain of J-114,870 (**1**) and related compounds in many synthetic steps with low overall yield, starting from the relatively unstable β-alkoxy butanal **2**[5] according to our previous paper.[6] In addition, we obtained the (*S*)-β-alanine amide part of the C-2 side chain of **1** by chromatographic separation of the diastereomeric intermediates. Unfortunately it was difficult to obtain a large amount of J-114,870 (**1**) by this disadvantageous synthetic procedure. After identifying **1** as a promising candidate for further evaluation, we needed effective procedures for the stereoselective construction of the (3*S*,5*R*)-*trans*-disubstituted pyrrolidine ring and the (*S*)-β-alanine amide systems of **1**. Here we report a new and practical way to synthesize J-114,870 (**1**).

As shown in Scheme 1, introduction of the aromatic portion onto the 2-position of appropriately protected (*R*)-4-hydroxy-2-pyrroridone **4** offered a more direct procedure for constructing the 2-arylpyrrolidine ring system (**a**), compared with the former method using β-alkoxy butanal **2** as a starting material.[7] After formation of α,β-unsaturated ester function (**b**), an optically active β-alanine amide moiety was constructed by means of asymmetric Michael addition of the chiral amine to afford the C-2 side chain thiol with high diastereomeric purity.

Results and Discussion

Synthesis of 2-phenylpyrrolidine (6)

Selective silylation of a hydroxyl group of pyrrolidone **3** and successive protection of amide nitrogen with a *t*-butoxycarbonyl (Boc) group provided a protected pyrrolidone **4** as a crystalline form in 92% yield. Grignard reagent **5** generated from 4-substituted bromobenzene was coupled with pyrrolidone **4** at 0°C, and formation of an adduct **6** was monitored by TLC. Product **6** could not be obtained in reasonable yield after usual aqueous work up and the following silica-gel chromatography, probably due to

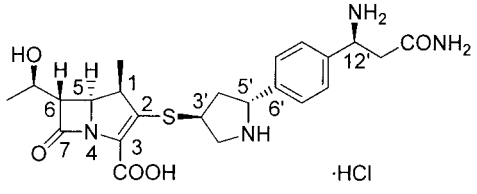

Figure 1. Structure of J-114,870 (**1**).

Keywords: asymmetric Michael addition; 1β-methylcarbapenem; J-114,870.

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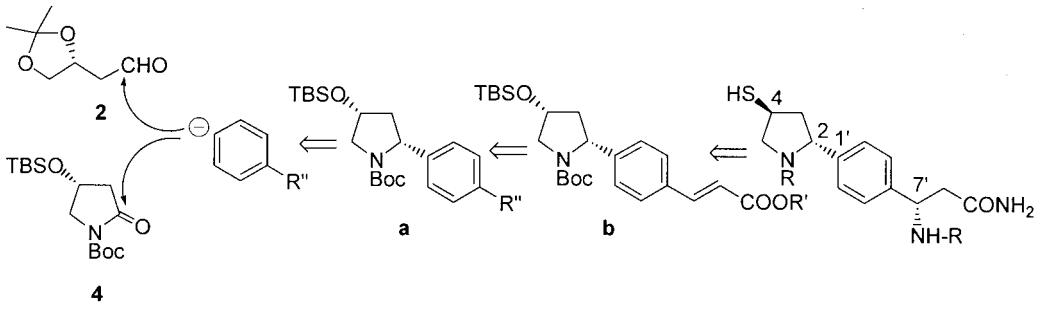


Scheme 1. Synthesis of the C-2 side chain of J-114,870 (**1**).

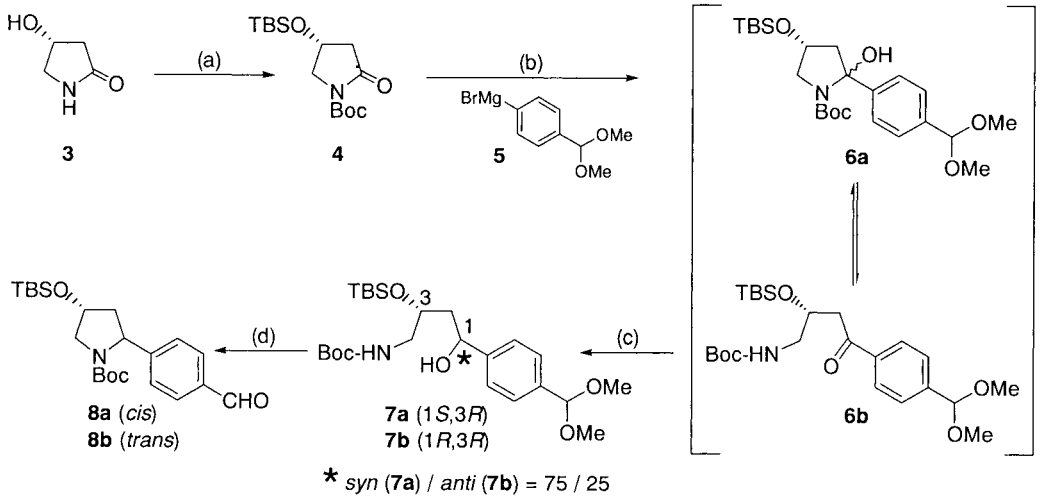
decomposition via β-elimination of the silyloxy group of **6b**, a linear form of the adduct **6**. Therefore, the adduct was isolated as a stable alcohol (**7**) by successive reduction of **6** in the same vessel. When $NaBH_4$ and MeOH was added at −10°C after the completion of Grignard reaction, reduction of the ketone **6b** proceeded smoothly to provide a stable 1,3-*syn*-alcohol **7a** (51%, >99% de) possessing the desired stereochemistry as the major isomer together with undesired 1,3-*anti*-alcohol **7b** (17, 96% de) by separation on silica-gel chromatography (Scheme 2). This reduction proceeded with significant diastereoselectivity (*syn*/*anti*=ca. 75/25), which was reasonably explained by a 1,3-metal-chelated transition state.

Next, γ-aminobutanol **7a** thus obtained was cyclized to 2-aryl pyrrolidine **8a** via the corresponding mesylate. When alcohol **7a** was treated with methanesulfonyl chloride (MsCl) in the presence of triethylamine (Et_3N), intramolecular cyclization took place spontaneously under basic conditions without the formation of any mesylated intermediate, which could be monitored by TLC. The cyclized product was treated with *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) at atmospheric temperature to afford 2,4-*cis* pyrrolidine **8a** as a crystalline form. Similarly, **7b** afforded 2,4-*trans* pyrrolidine **8b** as an oil. Direct conversion of **6a** to the 2-aryl pyrrolidine ring system by reductive elimination of the benzylic hydroxyl group could not be achieved under various reaction conditions.[8]

Since the minor diastereomer **8b** did not form crystals, a more efficient and practical procedure was developed for the isolation of **8a** without column chromatographic separation. A mixture of **7a** and **7b** was applied directly to pyrrolidine formation reaction followed by acid cleavage of the acetal protection to form crystals **8a** from *n*-hexane solution. Absolute configuration of **8a** was determined by X-ray crystallographic analysis to be a (2*R*,4*R*) configuration (Fig. 2). Purification of the filtrate by column chromatography afforded (2*S*,4*R*)-*trans* isomer **8b** (87% de) as an oil. The key intermediate **8a** thus obtained showed excellent diastereomeric purity (>99% de).

Construction of the β-alanine amide structure

Of the many approaches for synthesizing chiral β-aminocarboxylic acid derivatives, we employed asymmetric Michael addition reported by Davies and Ichihara as a direct and practical method to obtain the C-2 side chain of



Reagents: (a) i: TBS-Cl, imidazole, DMF, 0 °C; ii: Boc_2O, TEA, DMAP, CH_3CN, 0 °C, (b) **5**, THF, 0 °C, (c) $NaBH_4$, MeOH, −10 °C, (d) i: MsCl, TEA, CH_2Cl_2, −60 °C; ii: *p*-TsOH, THF-H_2O, r.t., iii: crystallization.

Scheme 2. Synthesis of the key intermediate **8a**.

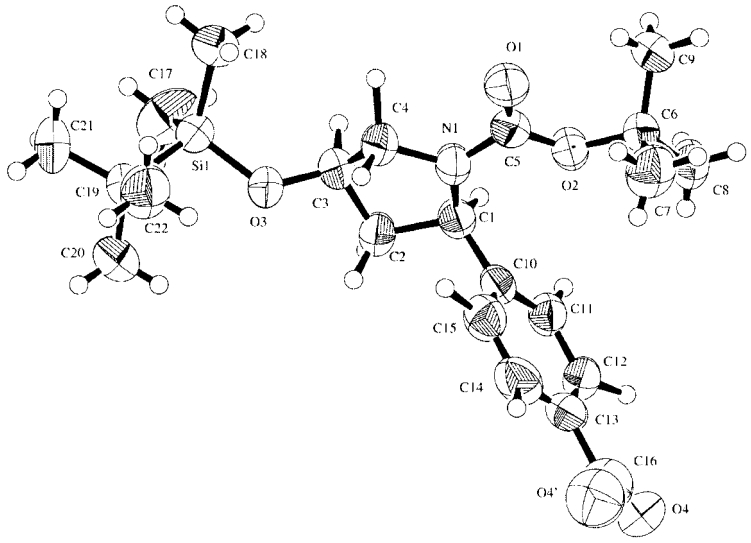
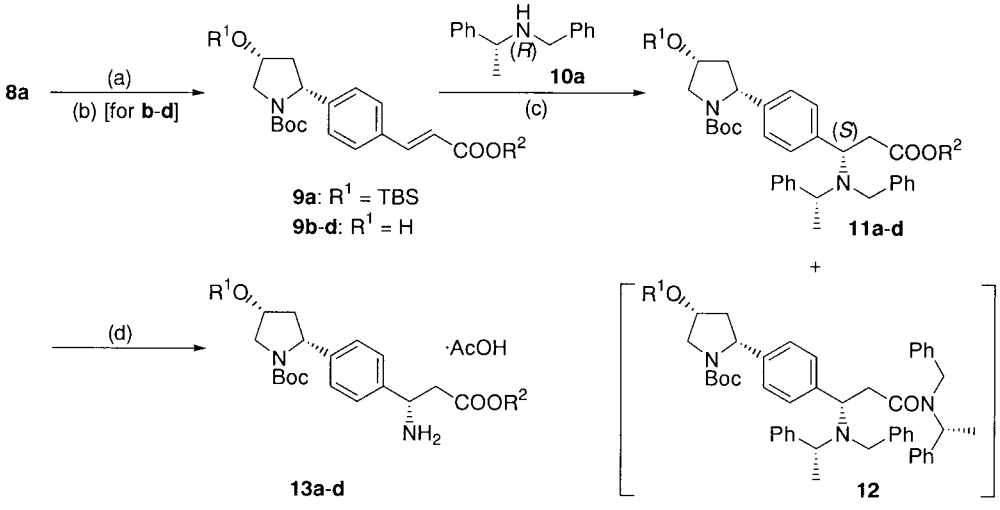


Figure 2. ORTEP drawing (50% ellipsoid) of **8a**.

J-114,870 (**1**).[9] Indeed, Michael addition of a chiral amine **10a** to an α,β-unsaturated ester **9** having appropriate protective groups provided the chiral center of the β-alanine amide structure with good diastereoselectivity (Scheme 3).

Aldehyde **8a** described above was converted to an α,β-unsaturated ester **9a** by conventional Horner–Emmons reaction in high yield (96%). Reaction of a lithium salt of (*R*)-*N*-(α-methylbenzyl)benzylamine **10a** with the conjugated ester **9a** yielded an adduct **11a** in moderate yield together with a significant amount of amide **12** as a by-product (total 66% conversion). Since the moderate yield might be due to a steric hindrance of the bulky TBS group of **9a**, silyl protection was removed by the action of tetrabutylammonium fluoride prior to the Michael reaction. A significant increase in yield was observed to afford the desired product **11b** when desilylated ester **9b** was used; however, amide **12** was also formed (total 94% conversion).



9	R^1	R^2	11+12 (yield)	11 : 12 (ratio)	13 (de)
a	TBS	Et	66%	68 : 32	93%
b	H	Et	94%	74 : 26	94%
c	H	*i*-Pr	97%	91 : 9	94%
d	H	*t*-Bu	99%	100 : 0	94%

Reagents: (a) $(EtO)_2P(O)CH_2COOR^2$, NaH, THF, r.t., (b) *n*-Bu_4NF, THF, r.t., (c) **10a**, *n*-BuLi, THF, −77 °C, (d) $Pd(OH)_2/C$, AcOH, MeOH, H_2, 3.5 atm, r.t.

Scheme 3. Asymmetric Michael addition.

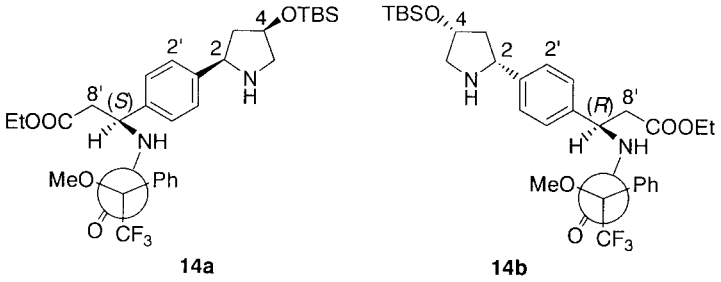


Figure 3. MTPA amides for the advanced Mosher method.

To avoid the undesired formation of amide **12**, more bulky esters, iso-propyl ester **9c** and *tert*-butyl ester **9d**, were prepared from aldehyde **8a** by the same method as the ethyl ester **9b**. As expected, formation of the amide **12** was completely suppressed and the adduct **11d** was produced in an almost quantitative yield (99%) when the most bulky ester **9d** was used. This diastereoselective Michael addition reaction has proceeded according to the reaction mechanism which was suggested by Davies et al.,[9c] in case of (*S*)-*N*-(α-methylbenzyl)benzylamine provided C7′-(*R*)-isomer with 96% de in high yield. Catalytic hydrogenolysis using $Pd(OH)_2$ on carbon (Degussa type) removed benzyl and phenethyl residues on the nitrogen of **11d** to yield **13d** in excellent yield (98%) without affecting the other benzylic carbon–nitrogen bonds of **11d**. The diastereoselectivity of the present conjugated addition reaction was measured by HPLC analysis of **13** using a CHIRALCEL OD-RH (150×4.6 mm) column.

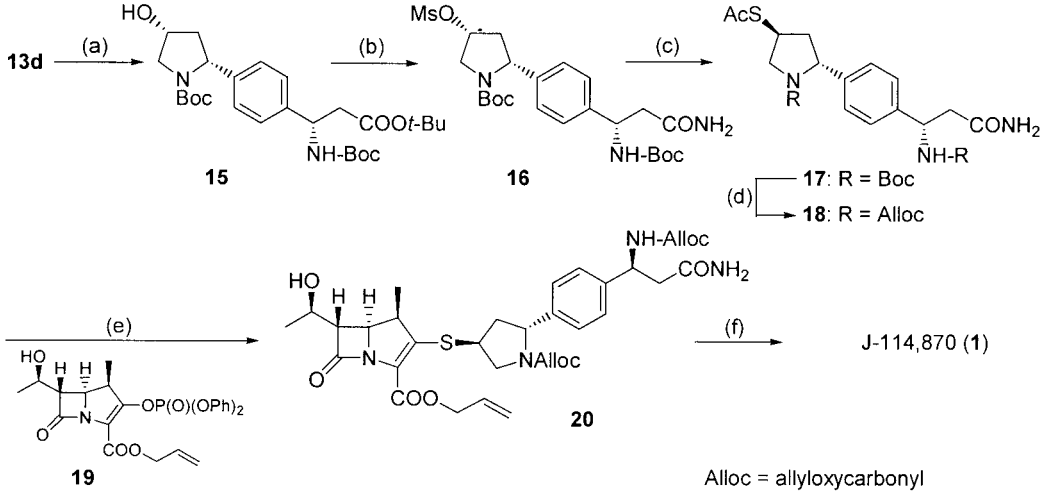
Stereochemistry of β-aminoester

Absolute configuration of the newly formed chiral center of **11a** was determined by the advanced Mosher method.[10] Amides **14a** and the corresponding diastereomer **14b** (Fig. 3)[10] were prepared from **11a** and its diastereomer, respectively, by the following reactions: (1) removal of the benzyl and phenethyl groups by hydrogenolysis, (2) acylation with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA)

Table 1. ^{1}H NMR of MTPA amides, **14a** and **14b**

Proton	2	3	4	5	2′	3′	7′	8′	10′	11′
14a	4.077	1.720 2.400	4.452	2.918 3.034	7.356	7.142	5.442	2.850 2.921	4.084	1.187
14b	4.087	– 2.403	4.454	2.921 3.039	7.411	7.259	5.440	2.807 2.900	4.023	1.137
$\Delta\delta\times10^{-3}$ ppm	−10	–[a] −3	−2	−3 −5	−55	−117	−2	+43 +21	+61	+50

[a] Overlapped with water signal.



Reagents: (a) Boc_2O, dioxane-H_2O, r.t., (b) i: NaOH, EtOH, 100 °C; ii: MsCl, TEA, THF, –20 °C; iii: NH_3, (c) AcSK, DMF, 55 °C, (d) i: HCl/EtOAc, r.t.; ii: Alloc-Cl, TEA, CH_2Cl_2, 0 °C, (e) i: NaOH, MeOH, 0 °C; ii: **19**, *i*-Pr_2NEt, CH_3CN, 0 °C, (f) *n*-Bu_3SnH, $(PPh_3)_2PdCl_2$, H_2O, CH_2Cl_2, 0 °C.

Scheme 4. Synthesis of J-114,870 (**1**).

chloride, and (3) removal of Boc protection using TFA. ^{1}H NMR (Table 1)[11] of the thus prepared MTPA amides indicated that **11a** had (*S*) configuration at the C-7′ position.

Synthesis of J-114,870 (1)

The primary amino group of **13d** was protected with a Boc group to afford **15** as crystals (98% de), which was converted to amide **16** through three steps: (1) alkaline hydrolysis of the ester, (2) simultaneous mesylation of the resulting carboxylic acid and *sec*-hydroxyl group by MsCl-triethylamine and (3) chemo-selective ammonolysis of the mixed anhydride generated in situ. The mesyloxy group of **16** was displaced with AcSK in DMF to afford a thioaceate **17** (62% yield from **15**, >99% de). Removal of the Boc protecting group of **17** by HCl/EtOAc and the subsequent treatment with allyloxycarbonyl (Alloc) chloride afforded **18** in a good yield (92%).

Hydrolysis of thioaceate **18** by sodium hydroxide in methanol formed a thiol compound that was coupled with 1β-methylcarbapenem diphenylphosphate **19**[11] in the presence of diisopropylethylamine to provide the adduct **20** in 82% yield. Deprotection of **20** by the method of Guibe et al.[12] and purification of the resulting residue on reversed phase column chromatography yielded J-114,870 (**1**) in 75% yield (>99% de) (see Scheme 4).

In summary, J-114,870 (**1**) was synthesized in 18 steps with 9% overall yield using (4*R*)-hydroxy-2-pyrrolidone **3** as a starting material. The aromatic portion of the C-2 side chain was installed directly on the pyrrolidone **4** by simple operations including the addition of the Grignard reagent and cyclization to afford optically active 2-phenylpyrrolidine **8a**. Stereoselective construction of the β-alanine amide structure was successfully achieved by means of asymmetric Michael reaction of the chiral amine with conjugated ester **9d** derived from **8a**.

Experimental

General methods

Melting points were measured on a METTLER FP62 melting point apparatus and were not corrected. The ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer, Varian Gemini-300 and JEOL JNM-A500 spectrometer with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-A500 and JEOL JNM-EX270. IR absorption spectra were recorded with a Horiba FT-200 spectrometer. Specific rotations were measured with a Jasco DIP-370 polarimeter. Mass spectra (MS) were measured on a JEOL JMS-SX102A spectrometer. TLC was performed with Merck Kieselgel F_{254} precoated plates. The silica gel used for column chromatography was WAKO gel C-300. Reversed phase column chromatography was carried out on YMC-gel ODS-AQ 120-S50. All reactions involving air-sensitive reagents were performed under nitrogen using syringe-septum cap techniques.

(*R*)-1-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsiloxy-2-pyrrolidone 4. To a solution of (*R*)-4-hydroxy-2-pyrrolidone **3** (500 g, 4.95 mol) in DMF (2500 ml) were added *tert*-butyldimethylchlorosilane (784 g, 5.21 mol) and imidazole (506 g, 7.43 mol) under a nitrogen atmosphere at 0°C and the mixture was stirred for 30 min at room temperature. The mixture was poured into H_2O and the resulting precipitate was collected by filtration and dried to give (*R*)-4-*tert*-butyldimethylsiloxy-2-prrolidone (1054 g, 99%) as white crystals. Mp 73–74°C; $[\alpha]_D^{20}$=9.8 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 1704, 1660 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.89 (9H, s), 2.25 (1H, dd, *J*=17.0, 6.8 Hz), 2.27 (1H, dd, *J*=17.0, 4.3 Hz), 3.23 (1H, dd, *J*=9.9, 3.5 Hz), 3.58 (1H, dd, *J*=9.9, 6.1 Hz); 4.56 (1H, dddd, *J*=6.8, 6.1, 4.3, 3.5 Hz), 5.66 (1H, br s); ^{13}C NMR (67.5 MHz, $CDCl_3$), δ −4.9, −4.8, 17.9, 25.6, 40.4, 51.6, 67.8, 176.6; FAB-HRMS Calcd for $C_{10}H_{22}NO_2Si$ $(M+H)^+$: 216.1420, Found 216.1416; Anal. Calcd for $C_{10}H_{21}NO_2Si$: C, 55.77; H, 9.83; N, 6.50, Found: C, 55.57; H, 9.87; N, 6.54.

To a solution of (*R*)-4-*tert*-butyldimethylsiloxy-2-pyrrolidone (1054 g, 4.90 mol) in CH_3CN (1000 ml) were added consecutively 4-dimethylaminopyridine (340 g, 2.78 mol), triethylamine (298 g, 2.94 mol) and Boc_2O (1123 g, 5.14 mol) under a nitrogen atmosphere at 0°C. The reaction mixture was stirred for overnight at room temperature and then poured into H_2O. The whole was extracted with EtOAc and the organic layer was washed successively with 1 M aqueous HCl, 1 M aqueous NaOH and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting precipitate was washed with hexane and dried to give **4** (1423 g, 92.1%) as white crystals. Mp 108–109°C; $[\alpha]_D^{20}$=−6.8 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 1766 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.88 (9H, s), 1.53 (9H, s), 2.45 (1H, dd, *J*=17.3, 3.4 Hz), 2.72 (1H, dd, *J*=17.3, 6.3 Hz), 3.62 (1H, dd, *J*=11.2, 3.0 Hz), 3.86 (1H, dd, *J*=11.2, 5.3 Hz), 4.56 (1H, dddd, *J*=6.3, 5.3, 3.4, 3.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$), δ −4.6, −4.5, 18.2, 25.9, 28.3, 43.4, 55.7, 64.1, 83.1, 150.2, 172.4; FAB-HRMS Calcd for $C_{15}H_{30}NO_4Si$ $(M+H)^+$: 316.1944, Found 316.1927; Anal. Calcd for $C_{15}H_{29}NO_4Si$: C, 57.11; H, 9.27; N, 4.44, Found: C, 56.99; H, 9.36; N, 4.54.

(1*S*,3*R*)-4-*tert*-Butoxycarbonylamino-3-*tert*-butyldimethylsiloxy-1-(4-dimethoxymethylphenyl)butanol 7a and (1*R*,3*R*)-4-*tert*-butoxycarbonylamino-3-*tert*-butyldimethylsiloxy-1-(4-dimethoxymethylphenyl)butanol 7b. To a suspension of Mg (1.7 g, 69.8 mmol) in THF (30 ml) was added 4-bromobenzaldehyde dimethylacetal (8.1 g, 34.9 mmol) dropwise under a nitrogen atmosphere at room temperature, and the mixture was stirred for 1 h at reflux temperature. The reaction mixture was allowed to cool at room temperature. To this mixture was added a solution of **4** (5.5 g, 17.4 mmol) in THF (40 ml) over 1.5 h under a nitrogen atmosphere at 0°C. Then MeOH (35 ml) and $NaBH_4$ (991 mg, 26.1 mmol) were immediately added to the reaction mixture at −10°C. The mixture was poured into 10% aqueous NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography (*n*-hexane/EtOAc=5:1–4:1) gave **7a** (4.21 g, 51.5%) and

7b (1.37 g, 16.8%). [HPLC analysis: column, YMC-pack Pro C18 AS-303 (250×4.6 mm); detection 220 nm; eluent, 10 mM $(NH_4)_2HPO_4/CH_3CN$=30:70; flow rate, 1.2 ml/min; t_R of **7a**, 17.3 min; t_R of **7b**, 16.0 min]. **7a**: >99% de; $[\alpha]_D^{20}$ −11.6 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 1712, 1693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.91 (9H, s), 1.44 (9H, s), 1.84 (2H, m), 3.21 (1H, m), 3.31 (6H, s), 4.08 (1H, m), 4.80 (1H, m), 4.91 (1H, m), 5.37 (1H, s), 7.35 (2H, d, *J*=8.4 Hz), 7.42 (2H, d, *J*=8.4 Hz); FAB-HRMS Calcd for $C_{24}H_{43}NO_6SiNa$ $(M+Na)^+$: 492.2757, Found 492.2745. **7b**: 96% de; $[\alpha]_D^{20}$=+14.8 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 1714, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.92 (9H, s), 1.44 (9H, s), 1.85 (2H, m), 3.17 (1H, m), 3.32 (6H, s), 4.06 (1H, m), 4.76 (1H, m), 4.90 (1H, m), 5.34 (1H, s), 7.35 (2H, d, *J*=8.3 Hz), 7.42 (2H, d, *J*=8.3 Hz); FAB-HRMS Calcd for $C_{24}H_{43}NO_6SiNa$ $(M+Na)^+$: 492.2757, Found 492.2740.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsiloxy-2-(4-formylphenyl)pyrrolidine 8a and (2*S*,4*R*)-1-*tert*-butoxycarbonyl-4-*tert*-butyldimethylsiloxy-2-(4-formylphenyl)pyrrolidine 8b. To a mixture of **7a** and **7b** (13.1 g, 28.0 mmol; **7a/7b**=75/25) in CH_2Cl_2 (260 ml) were added triethylamine (8.5 g, 84.0 mmol) and methanesulfonyl chloride (3.53 g, 30.8 mmol) under a nitrogen atmosphere at −60°C. After being stirred for 30 min, the reaction mixture was poured into H_2O and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in THF (50 ml) and H_2O (8 ml), and was treated with *p*-TsOH·H_2O (500 mg, 2.82 mmol) for 1 h at room temperature. The mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was crystallized from *n*-hexane, collected by filtration and dried to give **8a** (6.4 g, 56.3%) as colorless plate crystals. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=10:1–6:1) to give **8b** (1.9 g, 16.7%) as a colorless oil. [HPLC analysis: column, YMC ODS-AQ AQ-303 (250×4.6 mm); detection 254 nm; eluent, CH_3CN/10 mM aqueous $(NH_4)_2PO_4$=80: 20; flow rate, 1.0 ml/min; t_R of **8a**, 14.2 min; t_R of **8b**, 14.8 min]. **8a**: >99% de; mp 102–103°C; $[\alpha]_D^{20}$=+49.0 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 1708, 1673, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.72 (9H, s), 1.18 (6H, s), 1.43 (3H, s), 1.88 (1H, m), 2.48 (1H, m), 3.43 (1H, m), 3.80 (1H, m), 4.40 (1H, m), 4.79 (0.34H, m), 4.81 (0.66H, m), 7.40 (2H, d, *J*=7.0 Hz), 7.78 (2H, d, *J*=7.0 Hz), 9.96 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$, major signals) δ −5.2, −5.1, 17.7, 25.4, 28.0, 44.1, 55.1, 60.2, 70.1, 79.7, 126.6, 129.5, 134.9, 152.1, 154.2, 191.9; FAB-HRMS Calcd for $C_{22}H_{36}NO_4Si$ $(M+H)^+$: 406.2414, Found 406.2390; Anal. Calcd for $C_{22}H_{36}NO_4Si$: C, 65.15; H, 8.70; N, 3.45, Found: C, 65.11; H, 8.84; N, 3.52. **8b**: 87% de; $[\alpha]_D^{20}$=−45.0 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 1714, 1685, 1603 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.08 (6H, s), 0.86(9H, s), 1.12 (6H, s), 1.41 (3H, s), 1.84 (1H, m), 2.28 (1H, m), 3.60 (2H, m), 4.38 (1H, m), 4.89 (0.7H, m), 5.01 (0.3H, m), 7.34 (2H, d, *J*=8.3 Hz), 7.81 (2H, d, *J*=8.3 Hz), 9.96 (1H, s); FAB-HRMS Calcd for $C_{22}H_{36}NO_4SiNa$ $(M+Na)^+$: 428.2233, Found 428.2242.

X-ray crystallographic data of 8a. A colorless plate crystal having approximate dimensions of 0.25×0.18×0.35 mm^3 was mounted on a glass fiber. All data were collected on a Rigaku AFC7R single crystal diffractometer, using Cu K_α radiation (λ=1.5418 Å), ω–2θ scans, to a maximum 2θ value of 120.1°. $C_{22}H_{35}NO_4Si$, *M*=405.61, orthorhombic, *a*=14.745(2) Å, *b*=25.978(1) Å, *c*=6.272(1) Å, *V*=2402.6(5) $Å^3$, space group $P2_12_12_1$ (#19), *Z*=4, *D*calc=1.12 g/cm^3, μ=10.6 cm^{-1}. A total of 2109 reflections were collected. All data were corrected for Lorentz and polar factors. All calculations were performed using the teXsan [Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992)]. The structure was solved by a direct method. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement was based on 2082 observed reflections [$I>0.00\sigma(I)$] and 248 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of: R=0.056 R_W =0.052. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.49 and −0.25 $e^-/Å^3$, respectively.

Details of the crystal structure determination at 123 K for both form I and form II can be obtained from the Director, Cambridge Cryatallographic Data Centre (CCDC), 12 Union Road, Cambridge, Cambridgeshire CB2 1EZ, England. Any request for this supplementary data should quote the full literature citation and the reference number 135/319.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-2-[4-[(*E*)-2-(*tert*-butoxycarbonyl)vinyl]phenyl]-4-hydroxypyrrolidine 9d. To a solution of *tert*-butyl diethyl phosphonoacetate (37.3 g, 148 mmol) in THF (300 ml) was added 60% NaH (5.92 g, 148 mmol) dropwise at 0°C, and the mixture was stirred for 30 min at the same temperature. A solution of **8a** (50 g, 123 mmol) in THF (100 ml) was added dropwise at 0°C, and the mixture was stirred for 1 h at the same temperature. The mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. To a solution of the residue in THF (200 ml) was added tetra-*n*-butylammonium fluoride (1 M in THF, 123 ml, 123 mmol) at room temperature. The mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with phosphate buffer (pH 6.0) and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The mixture was poured into *n*-hexane and the resulting precipitate was collected by filtration and dried to give **9d** (44.3 g, 92.2%) as white crystals. Mp 196–197°C; $[\alpha]_D^{20}$=+71.8 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 3401, 1693, 1645, 1434, 1324, 987 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (6H, br s), 1.44 (12H, s), 1.96 (1H, m), 2.61 (1H, m), 3.58 (1H, d, *J*=10.3, 2.5 Hz), 3.87 (1H, m), 4.48 (1H, m), 4.89 (1H, m), 6.33 (1H, d, *J*=16.3 Hz), 7.29 (2H, d, *J*=8.2 Hz), 7.45 (2H, d, *J*=8.2 Hz), 7.57 (1H, d, *J*=16.3 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$, major signals) δ 28.6, 44.3, 55.2, 60.5, 70.1, 80.3, 80.8, 120.0, 126.6, 128.4, 133.5, 143.7, 154.8, 166.9; FAB-HRMS Calcd for $C_{22}H_{32}NO_5$ $(M+H)^+$: 390.2280, Found 390.2277; Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60, Found: C, 67.83; H, 8.21; N, 3.53.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-4-hydroxy-2-[4-[(*S*)-1-[(*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amino]-2-*tert*-butoxycarbonylethyl]phenyl]pyrrolidine 11d. To a solution of (*R*)-*N*-(α-methylbenzyl)-*N*-benzylamine **10a** (13.6 g, 64.3 mmol) in THF (150 ml) was added *n*-BuLi (1.58 M in *n*-hexane, 40.7 ml, 64.3 mmol) dropwise under a nitrogen atmosphere at 0°C, and the mixture was stirred for 30 min at the same temperature. A solution of **9d** (5 g, 12.9 mmol) in THF (70 ml) was added dropwise at −77°C, and the mixture was stirred for 1 h at the same temperature. The mixture was poured into saturated aqueous NH_4Cl and the whole was extracted with EtOAc. The organic layer was washed with 1 M aqueous HCl, 1 M aqueous NaOH, and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc=1:1–1:2) to give **11d** (7.65 g, 99.2%) as a colorless oil. $[\alpha]_D^{20}=+33.6$ (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 3398, 1693, 1652, 1417, 1257, 723 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (6H, br s), 1.22 (15H, s), 1.94 (1H, m), 2.53 (3H, m), 3.54 (1H, d, *J*=12.0, 3.8 Hz), 3.65 (2H, s), 3.88 (1H, m), 3.94 (1H, q, *J*=6.9 Hz), 4.37 (1H, dd, *J*=9.2, 5.5 Hz), 4.42 (1H, m), 4.79 (1H, br s), 7.22 (14H, m); FAB-HRMS Calcd for $C_{37}H_{49}N_2O_5$ $(M+H)^+$: 601.3641, Found 601.3618.

(2*R*,4*R*)-2-[4-[(*S*)-1-Amino-2-*tert*-butoxycarbonylethyl]-phenyl]-1-*tert*-butoxycarbonyl-4-hydroxypyrrolidine acetic acid 13d. To a solution of **11d** (6.75 g, 11.2 mmol) in MeOH (160 ml) were added acetic acid (771 μl, 13.4 mmol) and palladium hydroxide on carbon (Degussa type, 1.6 g) and the resultant suspension was stirred with 3.5 atm of hydrogen at room temperature for 20 h. After filtration and evaporation, the resulting precipitate was washed with *n*-hexane and dried to afford **13d** (5.14 g, 98.0%) as white crystals. [HPLC analysis: column, DAICEL CHIRALPACK OD-RH (150×4.6 mm); detection 230 nm; eluent, CH_3CN/0.5 M aqueous $NaClO_4$ +0.5 M aqueous $HClO_4$ (pH 2.0)=30:70; flow rate, 0.2 ml/min; t_R of corresponding 7′-(*R*)-isomer, 30.3 min; t_R of **13d**, 33.6 min], 94% de; mp 131–133°C; $[\alpha]_D^{20}=+57.8$ (*c* 1.0, MeOH); IR (Nujol) ν_{max} 3392, 1720, 1627, 1556, 1178, 659 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.14 (6H, br s), 1.39 (12H, s), 1.82 (1H, m), 1.91 (3H, s), 2.59 (1H, m), 2.78 (1H, dd, *J*=15.7, 7.4 Hz), 2.86 (1H, dd, *J*=15.7, 7.2 Hz), 3.42 (1H, m), 3.83 (1H, dd, *J*=12.5, 6.5 Hz), 4.38 (1H, m), 4.49 (1H, m), 7.36 (4H, br s); ^{13}C NMR (67.5 MHz, CD_3OD, major signals) δ 24.3, 29.0, 29.3, 42.2, 45.7, 53.7, 56.4, 62.4, 70.7, 81.8, 83.6, 128.5, 128.9, 138.0, 148.1, 157.0, 171.5, 180.1; FAB-HRMS Calcd for $C_{22}H_{35}N_2O_5$ $(M+H)^+$: 407.2586, Found 407.2569; Anal. Calcd for $C_{22}H_{34}N_2O_5{\cdot}CH_3COOH$: C, 61.78; H, 8.21; N, 6.00, Found: C, 61.90; H, 8.40; N, 5.91.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-2-[4-[(*S*)-1-*tert*-butoxycarbonylamino-2-*tert*-butoxycarbonylethyl]phenyl]-4-hydroxypyrrolidine 15. To a solution of **13d** (46.8 g, 100 mmol) in 1,4-dioxane (350 ml) and H_2O (150 ml) was added $(Boc)_2O$ (24 g, 110 mmol) maintained at pH 10 using 5 M aqueous NaOH at room temperature. The reaction mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was crystallized from *n*-hexane/EtOAc to give **15** (41.6 g, 82.0%) as white crystals. [HPLC analysis: column, DAICEL CHIRALPACK OD-H (250×4.6 mm); detection 230 nm; eluent, *n*-hexane/*iso*-PrOH=95: 5; flow rate, 1.0 ml/min; t_R of **15**, 19.6 min; t_R of corresponding 7′-(*R*)-isomer, 22.9 min], 98% de; mp 171–172°C; $[\alpha]_D^{20}=+18.2$ (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 3428, 3369, 1716, 1677, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (6H, br s), 1.34 (9H, s), 1.41 (12H, s), 1.95 (1H, m), 2.57 (1H, m), 2.72 (2H, m), 3.54 (1H, dd, *J*=11.9, 4.0 Hz), 3.86 (1H, br s), 4.43 (1H, m), 4.82 (1H, br s), 5.03 (1H, br s), 5.43 (1H, br s), 7.22 (4H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$, major signals) δ 27.8, 28.1, 28.2, 42.0, 43.9, 51.0, 54.6, 59.8, 69.6, 79.5, 81.0, 125.7, 126.1, 139.7, 143.7, 154.4, 154.9, 170.1; FAB-HRMS Calcd for $C_{27}H_{42}N_2O_7Na$ $(M+Na)^+$: 529.2890, Found 529.2898; Anal. Calcd for $C_{27}H_{42}N_2O_7$: C, 64.01; H, 8.36; N, 5.53, Found: C, 64.06; H, 8.58; N, 5.51.

(2*R*,4*R*)-1-*tert*-Butoxycarbonyl-2-[4-[(*S*)-1-*tert*-butoxycarbonylamino-2-carbamoylethyl]phenyl]-4-mesyloxypyrrolidine 16. To a solution of **15** (34.2 g, 67.6 mmol) in EtOH (210 ml) and H_2O (80 ml) was added 5 M aqueous NaOH (68 ml, 338 mmol) at 0°C, and the mixture was stirred for 1 h at 100°C. After neutralization and evaporation, the reaction mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was used for the next reaction without further purification. The spectrum data of the purified (2*R*,4*R*)-1-*tert*-butoxycarbonyl-2-[4-[(*S*)-1-*tert*-butoxycarbonylamino-2-carboxyethyl]phenyl]-4-hydroxypyrrolidine is shown below. [HPLC analysis: column, DAICEL CHIRALPACK OD-RH (150×4.6 mm); detection 230 nm; eluent, CH_3CN/0.5 M aqueous $NaClO_4$ +0.5 M aqueous $HClO_4$ (pH 2.0)=275:725; flow rate, 0.2 ml/min; t_R of title compound, 40.3 min; t_R of corresponding 7′-(*R*)-isomer, 44.8 min], 98% de; $[\alpha]_D^{20}=+12.6$ (*c* 1.0, MeOH); IR (Nujol) ν_{max} 1727, 1695, 1687, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (6H, br s), 1.42 (12H, br s), 1.96 (1H, m), 2.53 (1H, m), 2.84 (2H, m), 3.54 (1H,m), 3.80 (1H, m), 4.40 (1H, m), 4.74 (1H, br s), 5.03 (1H, m), 5.53 (1H, br s), 7.22 (4H, s); FAB-HRMS Calcd for $C_{23}H_{34}N_2O_7Na$ $(M+Na)^+$: 473.2264, Found 473.2273.

To a solution of the above in THF (600 ml) were added triethylamine (47 ml, 338 mmol) and methanesulfonyl chloride (15.7 ml, 203 mmol) under a nitrogen atomsphere at −20°C. The mixture was stirred for 20 min at the same temperature and 28% aqueous NH_3 was added dropwise. After evaporation, the reaction mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with 3 M aqueous NaOH and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in EtOH/H_2O and the resulting precipitate was collected by filtration to afford **16** (26.7 g, 75.0%) as a crystalline solid. [HPLC analysis: column, DAICEL CHIRALPACK OD-RH (150×4.6 mm); detection 230 nm; eluent, CH_3CN/0.5 M aqueous $NaClO_4$ +0.5 M aqueous $HClO_4$ (pH 2.0)=65:35; flow rate, 0.2 ml/min; t_R of **16**, 26.0 min; t_R of corresponding 7′-(*R*)-isomer, 29.0 min], >99% de; mp 97–99°C; $[\alpha]_D^{20}=+12.8$ (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 3218, 1708, 1699, 1687, 1652, 912 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (6H, br s),

1.38 (12H, s), 2.34 (1H, m), 2.67 (3H, m), 2.69 (3H, br s), 3.83 (1H,m), 3.92 (1H, br s), 4.96 (1H, m), 5.23 (1H, br s), 5.29 (1H, br s), 5.98 (1H, br s), 7.19 (2H, d, J=8.4 Hz), 7.24 (2H, d, J=8.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$, major signals) δ 28.7, 38.8, 40.9, 42.1, 51.8, 53.3, 59.6, 69.3, 80.0, 80.7, 126.1, 126.5, 138.6, 140.8, 154.5, 155.8, 167.0, 173.4; FAB-HRMS Calcd for $C_{24}H_{37}N_3O_8SNa$ $(M+Na)^+$: 550.2199, Found 550.2195; Anal. Calcd for $C_{24}H_{37}N_3O_8S\cdot 1/2H_2O$: C, 53.72; H, 7.14; N, 7.83; S, 5.98, Found: C, 53.53; H, 7.12; N, 7.53; S, 6.27.

(2*R*,4*S*)-4-Acetylthio-1-*tert*-butoxycarbonyl-2-[4-[(*S*)-1-*tert*-butoxycarbonylamino-2-carbamoylethyl]phenyl] pyrrolidine 17. To a solution of **16** (26.7 g, 50.6 mmol) in DMF (900 ml) was added potassium thioacetate (17.3 g, 152 mmol) under a nitrogen atmosphere at room temperature, and the mixture was stirred for 10 h at 55°C. The resulting mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in acetone/H_2O and the resulting precipitate was collected by filtration to afford **17** (21.2 g, 82.6%) as a crystalline solid. [HPLC analysis: column, DAICEL CHIRALPACK OD (250×4.6 mm^2); detection 230 nm; eluent, *n*-hexane/*iso*-PrOH=80:20; flow rate, 0.5 ml/min; t_R of corresponding 7′-(*R*)-isomer, 18.8 min; t_R of **17**, 20.9 min], >99% de; mp 187–189°C; $[\alpha]_D^{20}$=+13.6 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 3222, 1702, 1699, 1687, 1650 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (6H, br s), 1.43 (12H, s), 2.22 (1H, m), 2.33 (3H, s), 2.36 (1H, m), 2.74 (2H, br s), 3.51 (1H,m), 4.01 (2H, m), 4.99 (1H, m), 5.28 (1H, br s), 5.69 (1H, br s), 5.87 (1H, br s), 7.14 (2H, d, J=8.2 Hz), 7.26 (2H, d, J=8.2 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$, major signals) δ 28.7, 30.9, 36.8, 39.8, 42.1, 51.8, 53.1, 60.6, 79.9, 80.1, 125.9, 126.0, 126.5, 126.8, 143.1, 154.5, 155.8, 162.9, 173.5, 195.5; FAB-HRMS Calcd for $C_{25}H_{37}N_3O_6SNa$ $(M+Na)^+$: 530.2301, Found 530.2293; Anal. Calcd for $C_{25}H_{37}N_3O_6S\cdot 1/2H_2O$: C, 58.12; H, 7.41; N, 8.13; S, 6.21, Found: C, 58.35; H, 7.55; N, 8.33; S, 6.02.

(2*R*,4*S*)-4-Acetylthio-1-allyloxycarbonyl-2-[4-[(*S*)-1-allyloxycarbonylamino-2-carbamoylethyl]phenyl] pyrrolidine 18. To a solution of **17** (1.0 g, 1.97 mmol) in EtOAc (10 ml) was added 4 M HCl/EtOAc (20 ml), and the mixture was stirred for 6 h at room temperature. After evaporation, to the suspension of the residue in CH_2Cl_2 (40 ml) were added triethylamine (2.75 ml, 19.7 mmol) and allyl chloroformate (627 μl, 5.91 mmol) at −10°C. The reaction mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/acetone=8:1) to give **18** (863 mg, 92.1%) as a foam. $[\alpha]_D^{25}$=+9.6 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 1687, 1648, 1263 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (1H, m), 2.33 (3H, s), 2.72 (2H, br s), 3.59 (1H,m), 4.03 (2H, m), 4.46 (1H, m), 4.54 (2H, s), 5.03 (3H, m), 5.26 (4H, m), 5.68 (1H, br s), 5.90 (1H, m), 6.28 (1H, br s), 7.16 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz); FAB-HRMS Calcd for $C_{23}H_{30}N_3O_6S$ $(M+H)^+$: 476.1855, Found 476.1876.

Allyl (1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-1-allyloxycarbonyl-5-[4-[(*S*)-1-allyloxycarbonylamino-2-carbamoylethyl]phenyl]-pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate 20. To an ice-cooled solution of **18** (3.6 g, 7.58 mmol) in MeOH (50 ml) was added 1 M aqueous NaOH (8.4 ml, 8.4 mmol) under a nitrogen atmosphere. After being stirred for 30 min at the same temperature, the reaction mixture was adjusted to pH 7.0 with 1 M aqueous HCl and concentrated under reduced pressure. The mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. To a stirred solution of the residue in CH_3CN (20 ml), allyl (1*R*,5*S*,6*S*)-2-diphenylphosphoryloxy-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylate **19** (3.79 g, 7.58 mmol) and diisopropylethylamine (1.58 ml, 9.1 mmol) in CH_3CN (80 ml) were added dropwise at 0°C. After being stirred overnight at 4°C under a nitrogen atmosphere, the mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (acetone) to give **20** as a foam (4.23 g, 82.0%). [HPLC analysis: column, DAICEL CHIRALPACK AD (250×4.6 mm^2); detection 290 nm; eluent, *n*-hexane/EtOH=60:40; flow rate, 1.0 ml/min; t_R of **20**, 14.2 min; t_R of corresponding 12′-(*R*)-isomer, 11.0 min], >99% de; $[\alpha]_D^{20}$=+69.4 (*c* 1.0, $CHCl_3$); IR (Nujol) ν_{max} 3340, 1780, 1668, 1645, 1147, 971, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (3H, d, J=7.0 Hz), 1.33 (3H, d, J=6.3 Hz), 1 79 (1H, m), 2.24 (1H, m), 2.46 (1H, m), 2.68 (2H, m), 3.22 (1H, dd, J=7.2, 2.4 Hz), 3.30 (1H, m), 3.72 (2H, m), 4.03 (1H, m), 4.22 (2H, m), 4.42 (1H, m), 4.53 (2H, m), 4.67 (1H, dd, J=12.1, 4.2 Hz), 4.83 (1H, dd, J=13.5, 5.4 Hz), 5.18 (5H, m), 5.43 (2H, m), 5.90 (3H, m), 6.43 (1H, m), 7.21 (1H, d, J=7.6 Hz), 7.25 (1H, d, J=7.6 Hz); FAB-HRMS Calcd for $C_{34}H_{42}N_4O_9SNa$ $(M+Na)^+$: 705.2570, Found 705.2569.

(1*R*,5*S*,6*S*)-2-[(3*S*,5*R*)-5-[4-[(*S*)-1-Amino-2-carbamoylethyl]phenyl]pyrrolidin-3-ylthio]-6-[(*R*)-1-hydroxyethyl]-1-methyl-1-carbapen-2-em-3-carboxylic acid hydrochloride 1 (J-114,870). To an ice-cooled solution of **20** (35 g, 51.1 mmol) in CH_2Cl_2 (1400 ml) were successively added H_2O (11.2 ml), bis(triphenylphosphine)palladium(II) dichloride (2.17 g, 3.08 mmol) and tributyltin hydride (67.0 g, 230 mmol) under a nitrogen atmosphere. After being stirred for 15 min at the same temperature, the reaction mixture was poured into H_2O. The separated aqueous layer was washed with CH_2Cl_2 and concentrated under reduced pressure to ca. 1700 ml. After removal of the insoluble matter by filtration, the concentrated aqueous layer was subjected to reversed phase column chromatography. The eluent was monitored by HPLC and the fraction eluted with 5–10% CH_3CN/H_2O were combined and adjusted to pH 5.8 with 1 M aqueous HCl. The combined fractions were concentrated under reduced pressure and lyophilized to give **1** (19.6 g, 74.5%). [HPLC analysis: column, YMC ProC18 AS-303 (250×4.6 mm^2); detection 220 nm; eluent, 20 mM NaH_2PO_4/MeOH=99:1–90:10 (5 min, gradient mode)–90:10 (10 min, isocratic mode)–50:50 (30 min, gradient mode); flow rate, 1.0 ml/min; t_R of **1**, 15.5 min; t_R of corresponding 12′-(*R*)-isomer, 16.8 min]; >99% de; $[\alpha]_D^{20}$=+1.2 (*c* 1.0, H_2O); IR (KBr)

ν_{max} 1751, 1672, 1585, 1388, 1259, 1147, 773, 665 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 1.04 (3H, d, J=7.0 Hz), 1.08 (3H, d, J=6.4 Hz), 2.36 (1H, dd, J=14.0, 7.0 Hz), 2.61 (1H, m), 2.81 (1H, dd, J=15.6, 7.3 Hz), 2.88 (1H, dd, J=15.6, 7.3), 3.18 (1H, dq, J=8.8, 7.0 Hz), 3.28 (1H, dd, J=5.8, 2.8 Hz), 3.31 (1H, br d, J=12.8 Hz), 3.72 (1H, dd, J=12.8, 5.8 Hz), 4.05 (3H, m), 4.59 (1H, t, J=7.3 Hz), 4.92 (1H, dd, J=11.0, 7.0 Hz), 7.36 (4H, m); ^{13}C NMR (125 MHz, D_2O) δ 15.3, 19.7, 35.7, 37.8, 40.7, 42.0, 51.2, 51.8, 55.6, 58.5, 61.2, 64.7, 127.6, 128.2, 134.3, 134.7, 136.3, 136.5, 167.3, 173.3, 176.3; FAB-HRMS Calcd for $C_{23}H_{31}N_4O_5S$ $(M+H)^+$: 475.2015, Found 475.2011; Anal. Calcd for $C_{22}H_{30}N_4O_5S{\cdot}HCl{\cdot}2H_2O$: C, 50.50; H, 6.45; N, 10.24; S, 5.86, Found: C, 50.61; H, 6.55; N, 10.32; S, 5.60.

(2*R*,4*R*)-4-*tert*-Butyldimethylsiloxy-2-[4-[(*S*)-1-[(*R*)-(α-methoxy-α-trifluoromethyl)benzyl-carbonylamino]-2-ethoxycarbonylethyl]phenyl]pyrrolidine 14a and (2*R*,4*R*)-4-*tert*-butyldimethyl-siloxy-2-[4-[(*S*)-1-[(*S*)-(α-methoxy-α-trifluoromethyl)benzylcarbonylamino]-2-ethoxycarbonylethyl]phenyl]pyrrolidine 14b. To a solution of **11a** (431 mg, 0.63 mmol) in EtOH (10 ml) was added $Pd(OH)_2$ (Degussa type, 200 mg), and the mixture was stirred for 36 h under a hydrogen atmosphere. The catalyst was filtered off and washed with EtOH. The filtrate and washings were combined and concentrated under reduced pressure. To a solution of the residue in THF (15 ml) were added triethylamine (127 mg, 1.26 mmol) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (192 mg, 0.76 mmol) at 0°C, and the mixture was stirred for overnight at room temperature. The mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. To a solution of the residue in CH_2Cl_2 (6 ml) was added TFA (0.5 ml) at 0°C, and the mixture was further stirred for 1 h at the same temperature. The mixture was poured into H_2O and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=20:1–10:1) to give **14a** (176 mg, 46.0%) as a colorless oil. Similarly, the corresponding 7′-(*R*) isomer (178 mg, 0.26 mmol) obtained by using (*S*)-*N*-(α-methylbenzyl)-*N*-benzylamine afforded **14b** (74.4 mg, 47.0%) as a colorless oil. **14a**: $[\alpha]_D^{20}=-19.2$ (*c* 1.0, $CHCl_3$); IR (Neat) ν_{max} 3413, 3340, 1731, 1693, 1506, 1095, 1020, 837, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) data are shown in Table 1; FAB-HRMS Calcd for $C_{31}H_{44}N_2O_5F_3Si$ $(M+H)^+$: 609.2972, Found 609.2943; **14b**: $[\alpha]_D^{20}=+28.0$ (*c* 1.0, $CHCl_3$); IR (Neat) ν_{max} 3412, 3333, 1736, 1695, 1498, 1096, 1020, 837, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) data was showed in Table 1; FAB-HRMS Calcd for $C_{31}H_{44}N_2O_5F_3Si$ $(M+H)^+$: 609.2972, Found 609.2980.

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