Practical Synthesis of (*R*)-4-Mercaptopyrrolidine-2-thione from L-Aspartic Acid. Preparation of a Novel Orally Active 1-β-Methylcarbapenem, TA-949

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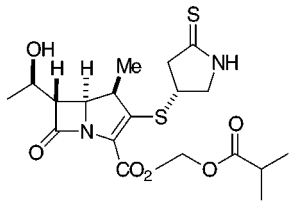
A facile and economical synthesis of a novel orally active 1-β-methylcarbapenem, TA-949 (**1**), is described. The key process involves an efficient synthesis of the C-2 side chain (*R*)-4-mercaptopyrrolidine-2-thione **2** from L-aspartic acid and the construction of the 1-β-methylcarbapenem skeleton. The mercapto group of **2** with an *R*-configuration was formed via deaminative bromination of the amino group of L-aspartic acid β-methyl ester hydrochloride **12** followed by a complete S_N2-type substitution with potassium benzenemethanethiolate. High-yield amination and cyclization of the chloride **15** to the pyrrolidin-2-one **16** was accomplished by a simple treatment with ammonia. Thiation of **16** and the Birch reduction of the resultant thiolactam **18** provided the C-2 side chain **2** in high yield with the asymmetric center retained as such. The side chain **2** was installed into the 1-β-methylcarbapenem skeleton either by coupling with the vinyl phosphate **5** or by the use of the counterattack strategy involving the Dieckmann-type cyclization of the thioester **8**. Removal of the protective groups of the coupling product **6** followed by esterification provided TA-949 (**1**) in high yield.

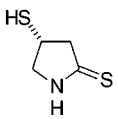
Introduction

The antibiotic 1-β-methylcarbapenems have been the subject of much investigation because of their chemical and metabolic stabilities as well as potent and broad antibacterial activities.[1] Although many candidates are currently under clinical trials and some have already been launched, orally active counterparts are of great rarity[2] and still in keen demand.

Our extensive efforts toward an orally active 1-β-methylcarbapenem resulted in the discovery of a promising candidate, TA-949 (**1**), which carries an (*R*)-pyrrolidine-2-thion-4-ylthio group at the C-2 position and an isobutyryloxymethyl ester.[3] For further investigation and development, an efficient and economical synthetic method of TA-949 (**1**) was required. In this paper, we detail a novel and practical synthesis of the C-2 side chain **2** and a preparation of TA-949 (**1**).



TA-949 (**1**)



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Results and Discussion

The retrosynthetic analysis shown in Scheme 1 indicates that TA-949 (**1**) is accessible by coupling the C-2 side chain **2** with a vinyl phosphate, **5**, followed by deprotection and esterification. The vinyl phosphate **5** is derived from the acetoxyazetidinone **3**[4] by the use of our procedure utilizing the benzoxazinone derivative **4**.[5] The counterattack method[6] involving the Dieckmann-type cyclization of the thioester **8** offers an attractive replacement for the preparation of the carbapenem intermediate **6**. The azetidinone propionic acid **7**, readily available from the acetoxyazetidinone **3** by coupling with the benzoxazinone derivative **4**,[5] serves as the precursor for the thioester **8**.

Synthesis of the C-2 Side Chain 2. Known procedures[2b] utilizing (*S*)-4-hydroxypyrrolidin-2-one **9**[7] were applied in our initial approach to the C-2 side chain **2** (Scheme 2). The yield of the Mitsunobu reaction of **9** with thioacetic acid was, however, moderate because of possible side reactions initiated by the E_2-type elimination of the hydroxyl group at the 4-position. A more economical two-step procedure involving the S_N2-type reaction of potassium thioacetate with the mesylate **11** also gave an unsatisfactory result.[2b] The synthesis of **2** from **9** is

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‡ Discovery Research Laboratory.

(1) For example see: (a) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29. (b) Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519. (c) Petersen,.P. J.; Jacobus, N. V.; Weise, W. J; Testa, R. T. *Antimicrob. Agents Chemother.* **1991**, *35*, 203.

(2) (a) Rossi, T.; Biondi, S.; Contini, S.; Thomas, R. J.; Marchioro, C. *J. Am. Chem. Soc.* **1995**, *117*, 9604. (b) Miyauchi, M.; Endo, R.; Hisaoka, M.; Yasuda, H.; Kawamoto, I. *J. Antibiot.* **1997**, *50*, 429.

(3) (a) Iwasaki, T.; Kondo, K.; Horikawa, H.; Yamaguchi, T.; Matsushita, T. U.S. Patent 5153187, Oct 6, 1992. (b) Seki, M.; Kondo, K.; Iwasaki, T. 13th French-Japanese Symposium on Medicinal and Fine Chemistry, Hayama, Japan, May 25−28, 1998; Abstract P-12.

(4) (a) Seki, M.; Miyake, T.; Yamanaka, T.; Ohmizu, H. *Synlett* **1996**, 455. (b) Seki, M.; Yamanaka, T.; Miyake, T.; Ohmizu, H. *Tetrahedron Lett.* **1996**, *37*, 5565. (c) Seki, M.; Furutani, T.; Miyake, T.; Yamanaka, T.; Ohmizu, H. *Tetrahedron: Asymmetry* **1996**, *7*, 1241.

(5) (a) Kondo, K,; Seki, M.: Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1995**, *60*, 1096. (b) Kondo, K,; Seki, M.: Kuroda, T.; Yamanaka, T.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 2877.

(6) (a) Seki, M.; Kondo, K.; Iwasaki, T. *Synlett* **1995**, 315. (b) Seki, M.; Kondo, K.; Iwasaki, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2851.

(7) Seki, M.; Kondo, K. *Synthesis* **1999**, 745.

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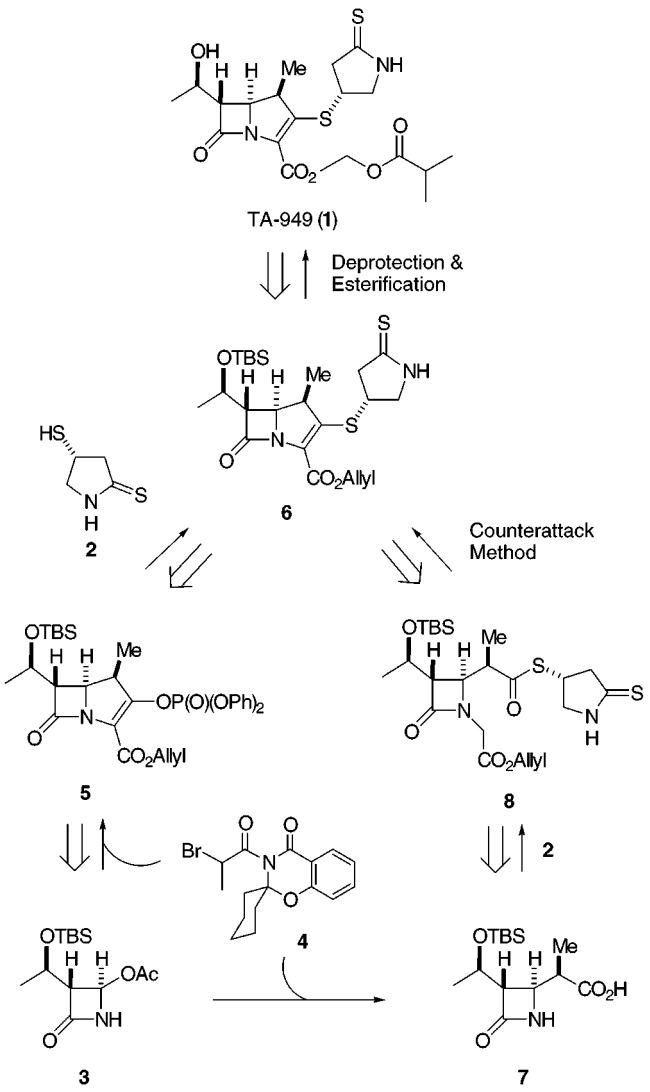
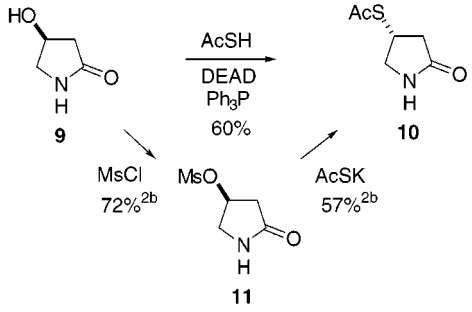
Scheme 1



thus unsuitable for the practical large-scale preparation. Chemoenzymatic synthesis of (*R*)-4-mercapto-2-pyrrolidin-2-one has recently been reported.[8] The key step involves pig-liver esterase catalyzed asymmetric hydrolysis of achiral 3-mercaptoglutaric acid derivative. However, the method is not completely satisfactory because the selectivity of the enzyme reaction is not complete and the starting material is expensive.

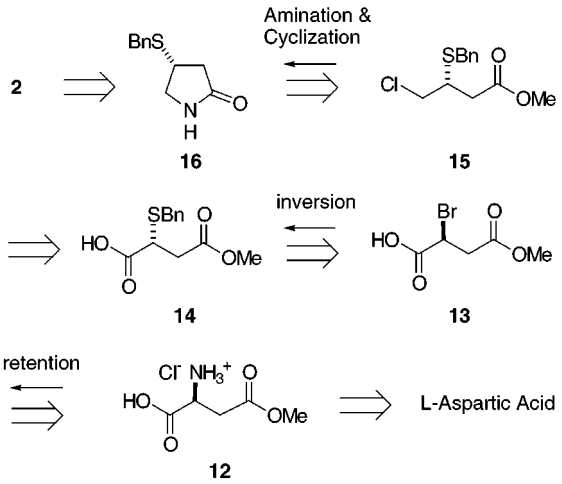
Scheme 2



We envisioned a possible use of L-aspartic acid for the synthesis of **2** (Scheme 3).[9] The required mercapto group

(8) Kobayashi, S.; Kobayashi, K.; Hirai, K. *Synlett* **1999**, 909.

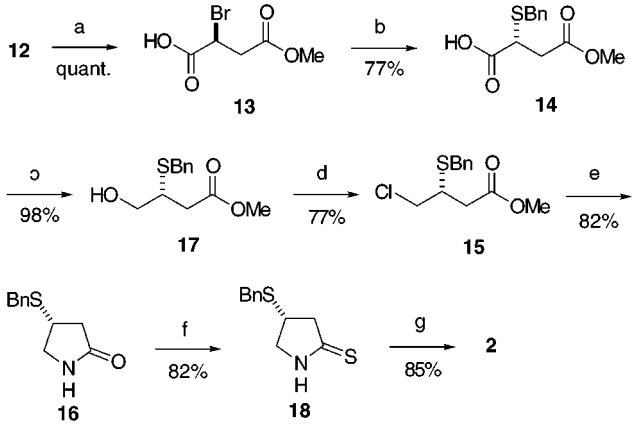
Scheme 3



with *R*-configuration was designed to form by deaminative bromination of the amino group of L-aspartic acid *β*-methyl ester hydrochloride **12** followed by the S_N2-type substitution with benzenemethanethiol. The pyrrolidin-2-one ring would be constructed by amination of the chloride **15** with ammonia followed by spontaneous cyclization. Thiation of the pyrrolidin-2-one **16** and cleavage of the benzyl protective group would afford **2**.

The preparation of the chiral bromide **13** was accomplished in quantitative yield by diazotization of L-aspartic acid *β*-methyl ester hydrochloride **12** in the presence of potassium bromide (Scheme 4).[10] The reaction proceeds with complete retention of the configuration to give the (*S*)-bromide **13** stereoselectively.[10]

Scheme 4[a]



[a] Key: (a) $NaNO_2$, NaBr, H_2SO_4; (b) BnSK, EtOH; (c) $BH_3{\cdot}SMe_2$; (d) $SOCl_2$, pyridine; (e) NH_3, MeOH; (f) P_2S_5; (g) $Na-NH_3$.

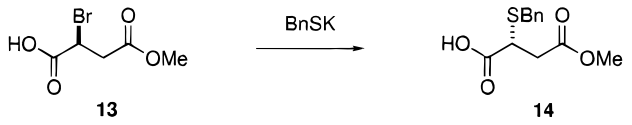
Introduction of a thiol group to the bromide **13** with inversion of the configuration was our next subject for investigation. Although the cesium salt of thiobenzoic acid has successfully been employed for the S_N2-type thiolation of α-bromocarboxylic acids,[11] potassium benzenemethanethiolate was chosen in the present study because of the intermediates' stability for the subsequent

(9) For reviews on the utilization of aspartic acid in drug synthesis see: (a) Matsumoto, K.; Seki, M. *J. Synth. Org. Chem. Jpn.* **1991**, *49*, 26. (b) Seki, M.; Matsumoto, K. *Bioindustry* **1995**, *12* (6), 5.

(10) Murakami, Y.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1978**, *26*, 307.

(11) Strijtveen, B.; Kellog, R. M. *Tetrahedron* **1987**, *43*, 5039.

Table 1



entry	solvent	temp (°C)	period (h)	ee (%)[a]	yield (%)[b]
1	THF	25	96	12	42
2	DMF	25	17	48	53
3	H_2O	25	17	72	53
4	EtOH	25	3	98	77

[a] Determined by HPLC. [b] Isolated yield.

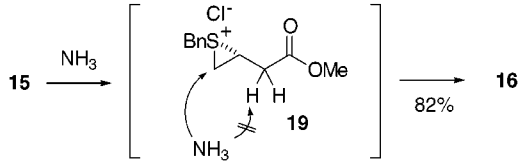
transformations. The reaction of potassium benzenemethanethiolate with the bromide **13** was investigated in various solvents (Table 1). Potassium benzenemethanethiolate was allowed to react with the bromide **13** in tetrahydrofuran (THF) at 25 °C for 96 h to afford the desired sulfide **14** in 42% yield with a poor selectivity (12% ee) (Table 1, entry 1). The yield and the selectivity were improved in a more polar *N*,*N*-dimethylformamide (DMF) to give **14** in 44% ee and 53% yield (Table 1, entry 2). Protic polar solvents such as water and ethanol were next examined for the reaction. It was found that in water compound **14** was obtained with much improved selectivity (72% ee, 53% yield) (Table 1, entry 3). A prolonged reaction period is undesirable due to racemization of the starting chiral halide by counterattack of the halide anion (in the present case, bromide anion) liberated by the reaction.[12] A shorter reaction period would thus improve the selectivity. Such accelaration of the reaction and improvement of the selectivity were realized in ethanol to give the desired sulfide **14** in 3 h with excellent selectivity (98% ee, 77% yield) (Table 1, entry 4).

The selective reduction of the carboxyl group of **14** in the presence of an ester group was accomplished by diborane−dimethyl sulfide complex to afford **17** in 98% yield. The chlorination of **17** was carried out by the use of thionyl chloride in the presence of pyridine to provide the desired chloride **15** in 77% yield. Addition of DMF or *N*,*N*-dimethylaniline instead of pyridine gave poorer yields (58% and 67%, respectively) due to the precedent lactonization of **17**.

With the required chiral chloride **15** in hand, amination of **15** was investigated using ammonia. It was found that treatment of the chloride **15** with ammonia in methanol at ambient temperature for 17 h allowed the concomitant amination and cyclization to provide **16** in 82% yield (Scheme 4). In this reaction, any byproducts due to the E_2-type elimination of the benzylthio group of **15** were not detected. We assumed that the formation of a thiilanium salt, **19**, suppressed the E_2-type elimination because the orientation of the C-3 carbon−sulfur bond toward the methylene carbon−hydrogen bond is not suitable for the antiperiplanar E_2-type elimination (Scheme 5).[13]

The formation of the thiolactam **18** from the pyrrolidin-2-one **16** was readily conducted by the use of phosphorus pentasulfide to give **18** in 82% yield (Scheme 4). Cleavage of the benzyl protective group of **18** by the Birch reduction

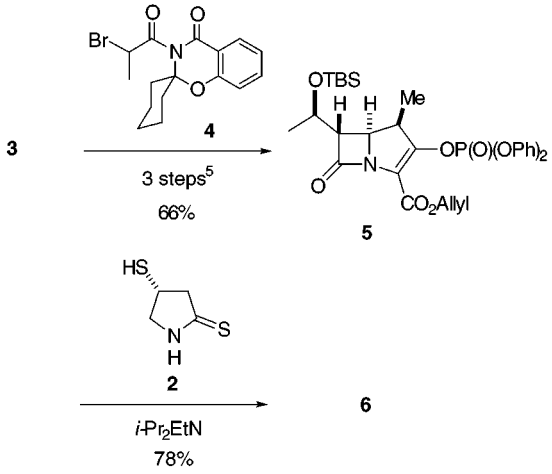
Scheme 5



gave the desired chiral thiol **2** in 85% yield. The optical purity of the product **2** was confirmed to be >99.9% ee by chiral HPLC.

Construction of the Carbapenem Skeleton. The C-2 side chain **2** was installed into the carbapenem skeleton in two ways. The vinyl phosphate **5** prepared in 66% yield in three steps from acetoxyazetidinone **3** by the use of the benzoxazinone derivative **4**[5] was allowed to react with **2** to provide the coupling product **6** in good yield (78%) (Scheme 6). The compound **6** was readily isolated by crystallization.

Scheme 6



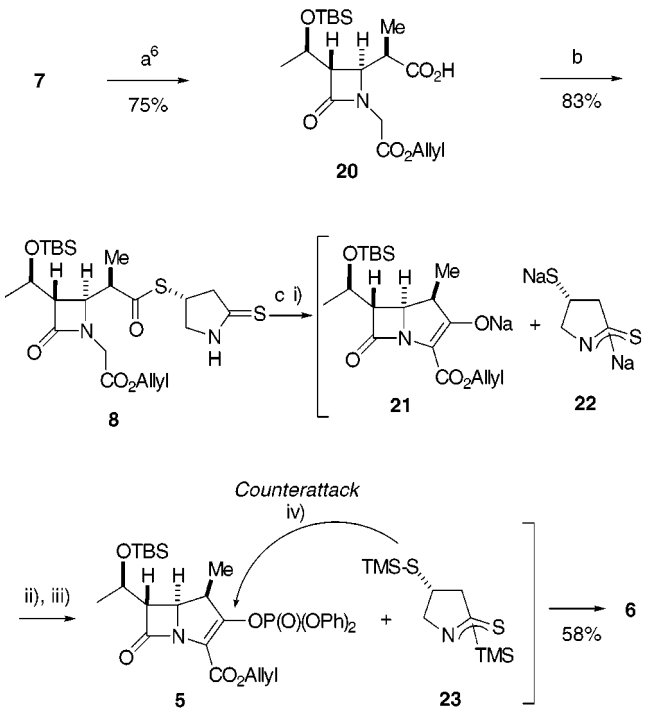
A conceptually attractive counterattack strategy was applied to the coupling reaction. The side chain **2** was first installed into the azetidinone derivative **20**[6] using dicyclohexylcarbodiimide (DCC) and *N*,*N*-(dimethylamino)pyridine (DMAP) to give the thioester **8** in 83% yield (Scheme 7). Treatment of **8** with 3.3 equiv of sodium bis(trimethylsilylamide) [$NaN(TMS)_2$] resulted in the clean cyclization to afford an enolate anion, **21**, and a dianion, **22**. Treatment of the reaction mixture with 2.3 equiv of chlorotrimethylsilane ensured the protection of the side chain. Subsequent addition of diphenyl phosphorochloridate and elevation of the reaction temperature provided the vinyl phosphate **5** which was detected by thin-layer chromatography. The "*counterattack*" of the thiolate anion to the in situ generated vinyl phosphate **5** was realized by addition of tetra-*n*-butylammonium fluoride (TBAF) to give the desired coupling product **6** in 58% yield from **8** and in crystals.

Preparation of TA-949. Removal of the hydroxyl and carboxyl protective groups from the carbapenem derivative **6** was accomplished by our previously developed procedures.[14] The *tert*-butyldimethylsilyl group of **6** was successfully cleaved by treatment with ammonium bifluoride to give the alcohol **24** in 90% yield. The reaction conditions were mild enough to keep the sensitive car-

(12) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375.
(13) A similar type of suppression of the E_2-type elimination was observed in the zinc reagent derived from L-serine: Jackson, R. F. W.; Moore, R. J.; Dexter, C. S. *J. Org. Chem.* **1998**, *63*, 7875.

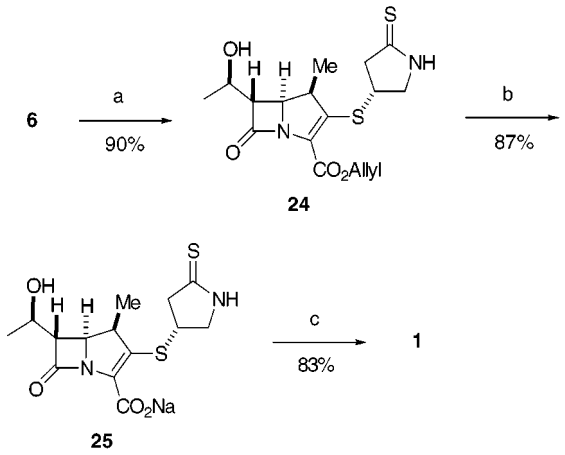
(14) Seki, M.; Kondo, K.; Kuroda, T.; Yamanaka, T.; Iwasaki, T. *Synlett* **1995**, 609.

Scheme 7[a]



[a] Key: (a) (i) TBS-Cl, NaH, (ii) $BrCH_2CO_2Allyl$, NaH, (iii) citric acid; (b) **2**, DCC, DMAP; (c) (i) $NaN(TMS)_2$, (ii) TMS-Cl, (iii) $ClP(O)(OPh)_2$, (iv) TBAF.

Scheme 8[a]



[a] Key: (a) $NH_4F{\cdot}HF$; (b) $Pd(OAc)_2$, $P(OEt)_3$, $NaHCO_3$, H_2O, (c) ICH_2OCO-*i*-Pr, *i*-Pr_2EtN.

bapenem skeleton and the C-2 side chain intact during the reaction. Removal of the allyl protective group of **24** was best conducted using inexpensive palladium acetate in aqueous THF.[14] The product rapidly crystallized out during the reaction to give the sodium salt **25** in 87% yield. Finally, esterification of **25** with isobutyryloxymethyl iodide gave TA-949 (**1**) in 83% yield. The absolute structure of TA-949 (**1**) prepared by the present method was unequivocally confirmed by X-ray crystallographic analysis.[15]

Conclusion

An orally active 1-β-methylcarbapenem, TA-949 (**1**), was synthesized in 33% overall yield in eight steps from acetoxyazetidinone **3** through the route described in Schemes 6 and 8. The C-2 side chain **2** was efficiently synthesized from L-aspartic acid β-methyl ester hydrochloride **12** in 33% overall yield in seven steps. The 1-β-methylcarbapenem skeleton was constructed in a highly efficient manner by the use of the benzoxazinone derivative and/or the counterattack method. The simple procedure and economical operation would provide a practical appraoch to the synthesis of the orally active 1-β-methylcarbapenem TA-949 (**1**).

(15) The X-ray data of TA-949 (**1**) have been deposited at the Cambridge Crystallographic Data Centre.

Experimental Section

General Procedures. Melting points are uncorrected. Infrared spectra are reported as λ_{max} (cm^{-1}). ^1H and ^{13}C NMR are reported in δ values. Mass spectra were taken at an ionizing potential of 70 eV. Thin-layer chromatography was performed on E. Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development was accomplished using either 20% phosphomolybdic acid in ethanol−heat or visualized by UV light where feasible. Flash chromatography was accomplished using Kieselgel 60 (230−400 mesh, E. Merck). Tetrahydrofuran was distilled from calcium hydride and stored over 4 Å molecular sieves.

(*S*)-2-Bromo-3-methoxycarbonylpropionic Acid (13). To a solution of L-aspartic acid β-methyl ester hydrochloride **12** (155 g, 0.843 mol) in water (1900 mL) were added sulfuric acid (433 g, 4.31 mol) and potassium bromide (402 g, 3.38 mol) at 20 °C. Sodium nitrite (69.8 g, 1.01 mol) in water (150 mL) was then added at 10−12 °C over 45 min. After the addition, the mixture was stirred at 10−15 °C for 2 h and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give **13** (181.5 g, quantitative) as a colorless oil: IR (Nujol) 1746 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.84 (br s, 1H), 4.63 (dd, J = 6.6, 4.6 Hz, 1H), 3.74 (s, 3H), 3.31 (dd, J = 6.6, 18 Hz, 1H), 3.01 (dd, J = 6, 18 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 203.3 (s), 34.6 (d), 53.7 (2t); SIMS m/z 212 ($M^+ + 1$); $[\alpha]^{25}_D$ −52.60° (*c*, 1.02, MeOH).

Potassium Benzenemethanethiolate. *CAUTION: This compound has an extremely bad smell and should be prepared and handled in a well-ventilated hood.* Benzenemethanethiol (100 g, 0.805 mol) was added to a solution of potassium hydroxide (85%, 38.4 g, 0.684 mol) in methanol (1 L) at 5−10 °C, and the mixture was stirred at 5−10 °C for 10 min and at 20 °C for 15 min. The mixture was evaporated in vacuo and coevaporated with toluene (2 × 300 mL). The residue was triturated in ether (300 mL), and the crystals formed were collected and dried under reduced pressure to afford potassium benzenemethanethiolate (100.1 g, 90%) in colorless crystals.

(*R*)-2-Benzylthio-3-methoxycarbonylpropionic Acid (14). Potassium benzenemethanethiolate (122 g, 0.752 mol) was added to a mixture of **13** (79.4 g, 0.376 mol) in ethanol (500 mL) at 5 °C, and the mixture was stirred at 25 °C for 3 h. After the mixture was acidified to pH 3−4 by 2 N hydrochloric acid, ethanol was removed by evaporation. The mixture was extracted with chloroform, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The crystals formed were collected by adding *n*-hexane to afford **14** (73.9 g, 77%) as colorless crystals: mp 91−92 °C; IR (Nujol) 1730, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.09 (br s, 1H), 7.21−7.41 (m, 5H), 4.00 (d, J = 13 Hz, 1H), 3.86 (d, J = 13 Hz, 1H), 3.66 (s, 3H), 3.58 (dd, J = 5, 10 Hz, 1H), 2.94 (dd, J = 10, 14 Hz, 1H), 2.58 (dd, J = 5, 14 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 177.8, 170.4, 137.0 (3s), 129.2, 126.6, 127.5 (3d), 52.1 (q), 40.7 (d), 36.4, 35.7 (2t); MS m/z 254 (M^+); $[\alpha]^{25}_D$ +200.78° (*c*, 1.03, MeOH); optical purity 98.0% ee (HPLC: CHIRAL PAC AD (Daicel), *n*-hexane:ethanol:trifluoroacetic acid = 90:10:0.1, 1 mL/min, 30 °C, 254 nm). Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.67; H, 5.55. Found: C, 56.87; H, 5.63.

Methyl (*R*)-3-Benzylthio-4-hydroxybutanoate (17). To a solution of the compound **14** (4.78 g, 0.0188 mol) was added $BH_3{\cdot}SMe_2$ (10 M, 2.04 mL, 0.0204 mol) at −20 °C, and the

mixture was gradually warmed to 25 °C for 1 h. After the mixture was refluxed for 1 h, the mixture was carefully treated with methanol at 20 °C and evaporated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 4:1) to afford **17** (4.44 g, 98%) as a colorless oil: IR (Nujol) 3458, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5H), 3.79 (s, 2H), 3.68 (s, 3H), 3.59 (dd, J = 1.2, 5.7 Hz, 1H), 3.17 (dd, J = 5.6, 7.1 Hz, 1H), 2.61 (dd, J = 6.9, 10.5 Hz, 2H); MS m/z 240 (M^+); $[\alpha]^{25}_D$ +8.30° (*c*, 0.976, MeOH); optical purity 99.0% ee (HPLC: CHIRAL PAC AD (Daicel), *n*-hexane:ethanol:trifluoroacetic acid = 90:10:0.1, 1 mL/min, 30 °C, 254 nm).

Methyl (*R*)-3-Benzylthio-4-chlorobutanoate (15). To a mixture of **17** (6 g, 0.025 mol) in chloroform (50 mL) were added pyridine (2.02 mL, 0.025 mol) and thionyl chloride (1.91 mL, 0.026 mol) at 5−10 °C, and the mixture was stirred at 5−10 °C for 1 h. The mixture was evaporated in vacuo and dissolved in ethyl acetate (100 mL). The mixture was washed successively with 2 N hydrochloric acid and water, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane:AcOEt = 10:1) to afford **15** (4.94 g, 77%) as a colorless oil: IR (Nujol) 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20−7.40 (m, 5H), 3.90 (s, 2H), 3.67 (s, 3H), 3.44−3.70 (m, 2H), 3.15−3.31 (m, 1H), 2.90 (dd, J = 7, 16 Hz, 1H), 2.50 (dd, J = 8.5, 16 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.2, 137.7 (2s), 130.0, 129.7, 127.4 (3d), 51.8 (q), 47.2 (t), 42.8 (d), 37.2, 36.6 (2t); MS m/z 258 (M^+); $[\alpha]^{25}_D$ −19.7° (*c*, 0.965, MeOH); optical purity 100% ee (HPLC: CHIRAL PAC AD (Daicel), *n*-hexane:ethanol:trifluoroacetic acid = 90:10:0.1, 1 mL/min, 30 °C, 254 nm).

(*R*)-4-Benzylthiopyrrolidin-2-one (16). Compound **15** (2 g, 7.8 mmol) was dissolved in ammonia in methanol (21.5% w/w, 12 mL), and the mixture was stirred at 25 °C for 72 h. The mixture was evaporated in vacuo, and water (50 mL) was added. The mixture was extracted with chloroform, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$:EtOH = 30:1) to afford **16** (1.32 g, 82%) as colorless crystals: mp 75−76 °C; IR (Nujol) 3224, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15−7.40 (m, 5H), 6.73 (br s, 1H), 3.76 (s, 2H), 3.50−3.62 (m, 1H), 3.28−3.46 (m, 1H), 3.15−3.25 (m, 1H), 2.59 (dd, J = 8, 17 Hz, 1H), 2.25 (dd, J = 6, 17 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 176.5, 137.8 (2s), 128.7, 127.6 (2d), 48.1, 37.8 (2t), 37.5 (d), 36.1 (t); MS m/z 207 (M^+); $[\alpha]^{25}_D$ −9.2° (*c*, 1.0, MeOH); optical purity 97% ee (HPLC: CHIRAL PAC OJ (Daicel), *n*-hexane:2-propanol = 65:35, 0.5 mL/min, 30 °C, 254 nm). Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.72; H, 6.32; N, 6.76. Found: C, 63.87; H, 6.54; N, 6.56.

(*R*)-4-Benzylthiopyrrolidine-2-thione (18). A mixture of **16** (20 g, 0.0964 mol) and phosphorus pentasulfide (4.88 g, 0.0212 mol) in chloroform (64 mL) was stirred at 25 °C for 5 h. The mixture was poured into saturated aqueous sodium bicarbonate (20 mL), extracted with chloroform, washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was crystallized from toluene to afford **18** (17.65 g, 82%) as colorless crystals: mp 86−88 °C; IR (Nujol) 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.41 (br s, 1H), 7.20−7.40 (m, 5H), 3.76 (s, 2H), 3.70−3.90 (m, 1H), 3.40−3.60 (m, 2H), 3.10 (ABqd, J = 6.5, 8.4, 18.1, 49.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 203.7, 137.5 (2s), 128.8, 128,7, 127.5 (3d), 55.9, 50.2 (2t), 39.4 (d), 36.2 (t); SIMS m/z 224 ($M^+ + 1$); $[\alpha]^{25}_D$ −13.7° (*c*, 1.0, MeOH); optical purity >99.9% ee (HPLC: CHIRAL PAC OJ (Daicel), *n*-hexane:2-propanol = 3:7, 0.5 mL/min, 30 °C, 215 nm). Anal. Calcd for $C_{11}H_{13}NS_2$: C, 59.15; H, 5.87; N, 6.27. Found: C, 59.16; H, 5.88; N, 6.22.

(*R*)-4-Mercaptopyrrolidine-2-thione (2). Compound **18** (1 g, 4.48 mmol) was dissolved in liquid ammonia (20 mL). To the solution was added sodium (225 mg, 14.5 mmol) over 20 min, and the mixture was stirred for 20 min. Ammonium chloride (5 g) was added to the reaction mixture, and ammonia was removed. The residue was acidified (pH 1) with 1 N aqueous HCl and extracted with chloroform. The combined extracts were dried over anhydrous magnesium sulfate and evaporated in vacuo. The crystals formed were collected by adding *n*-hexane to afford **2** (507 mg, 85%) as colorless crystals: mp 47−48 °C; IR (Nujol) 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.71 (brs, 1H), 4.00−4.15 (s, 1H), 3.65−3.85 (m, 1H), 3.52−3.65 (m, 1H), 2.93 (dd, J = 8. 18 Hz, 1H), 2.87 (dd, J = 6. 18 Hz, 1H), 2.00 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 203.3 (s), 59.1, 53.7 (2t), 34.6 (d); SIMS m/z 134 ($M^+ + 1$); $[\alpha]^{25}_D$ −109.56° (*c*, 1.07, MeOH). Anal. Calcd for $C_4H_7NS_2$: C, 36.06; H, 5.30; N, 10.51. Found: C, 36.26; H, 5.23; N, 10.72. The product thiol **2** was converted back to the corresponding benzyl thioether by treatment with benzyl bromide and *i*-Pr_2EtN and was shown to be optically pure (>99.9% ee) by HPLC (CHIRAL PAC OJ (Daicel), *n*-hexane:2-propanol = 3:7, 0.5 mL/min, 30 °C, 215 nm).

Allyl (4*R*,5*R*,6*S*)-6-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)-ethyl]-3-[(*R*)-pyrrolidine-2-thion-4-ylthio)]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6). To a solution of **5**[5] (6.01 g, 9.8 mmol) in DMF (12 mL) were added **2** (1.43 g, 10.8 mmol) and *N*,*N*-diisopropylethylamine (2.22 mL, 12.7 mmol) at −30 °C, and the mixture was stirred at 0−5 °C for 2 h. Phosphate buffer (0.1 M, K_2HPO_4, pH 7.0, 50 mL) was added to the reaction mixture, and it was extracted with AcOEt (2 × 50 mL). The combined extracts were washed with brine (80 mL), dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was crystallized from a mixed solvent of *n*-hexane and AcOEt (10:1) to afford **6** (4.18 g, 78%) as colorless crystals: mp 130−133 °C; IR (Nujol) 1766, 1708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.58 (s, 1H), 5.77−5.93 (m, 1H), 5.14−5.40 (m, 2H), 4.55−4.75 (m, 2H), 3.56−4.19 (m, 4H), 3.45−3.60 (m, 1H), 2.85−3.35 (m, 4H), 1.16 (d, J = 6.3 Hz, 6H), 0.80 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 210.6, 180.4, 168.2, 153.2 (4s), 139.2 (d), 135.4 (s), 126.3 (t), 73.7 (d), 73.7 (t), 68.3, 63.7 (2d), 62.2, 59.6 (2t), 51.7, 47.7 (2d), 33.5, 30.2 (2q), 25.7 (s), 24.7, 3.6, 2.8 (3q); SIMS m/z 497 ($M^+ + 1$); $[\alpha]^{25}_D$ +1.4° (*c*, 1.2, MeOH). Anal. Calcd for $C_{23}H_{36}N_2O_4S_2Si$: C, 55.61; H, 7.30; N, 5.64. Found: C, 55.43; H, 7.22; N, 5.81.

***S*-[(*R*)-Pyrrolidine-2-thion-4-yl]-(*R*)-2-{(3*S*,4*S*)-1-allyloxycarbonylmethyl-3-[(1*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-2-oxoazetidin-4-yl}thiopropionate (8).** To a solution of compound **20**[6] (1 g, 2.5 mmol) in CH_3CN were added *N*,*N*-dimethylaminopyridine (30 mg, 0.25 mmol), compound **2** (336 mg, 2.53 mmol), and dicyclohexylcarbodiimide (632 mg, 3.06 mmol) at 10 °C, and the mixture was stirred at 10 °C for 20 h. The mixture was filtered to remove insoluble materials, and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (*n*-hexane:$CHCl_3$:AcOEt = 5:5:4) to afford **8** (1.07 g, 83%) as a colorless oil: IR (Nujol) 1747, 1676 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.47 (s, 1H), 5.75−5.92 (m, 1H), 5.17−5.34 (m, 2H), 4.55−4.59 (m, 2H), 4.20 (d, J = 17.9 Hz, 1H), 4.01−4.24 (m, 4H), 3.79 (d, J = 17.9 Hz, 1H), 3.22−3.50 (m, 2H), 2.74−3.02 (m, 3H), 1.16−1.20 (m, 6H), 0.80 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.2, 200.0, 167.2 (3s), 130.7 (d), 110.3 (t), 85.6 (d), 85.2 (t), 60.4, 56.3 (2d), 55.1 (t), 48.5 (d), 47.7, 41.9 (2t), 38.1 (d), 25.0, 21.9 (2q), 17.1 (s), 11.6 (q); SIMS m/z 515 ($M^+ + 1$); $[\alpha]^{25}_D$ −3.9° (*c*, 1.5, MeOH).

Allyl (4*R*,5*R*,6*S*)-6-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)-ethyl]-3-[(*R*)-pyrrolidine-2-thion-4-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6) (Counter-attack Method). To a solution of $NaN(TMS)_2$ (1 M in THF, 6.6 mL, 6.6 mmol) was added the compound **8** (1.03 g, 2 mmol) in THF (6 mL) at −60 to −50 °C over 5 min, and the mixture was stirred at −50 °C for 10 min. Chlorotrimethylsilane (0.58 mL, 4.6 mmol) was added at −60 °C, and the mixture was stirred at −60 °C for 15 min. Diphenyl phosphorochloridate (0.44 mL, 2.1 mmol) was added at −60 °C, and the mixture was stirred at 0 °C for 1.5 h. To the mixture was added DMF (10 mL) at 0 °C followed by *n*-Bu_4NF (1 M in THF, 1.6 mL) at −60 °C. The mixture was stirred at −50 °C for 30 min and gradually warmed to −20 °C for 1 h. The mixture was poured into phosphate buffer (0.2 M, K_2HPO_4, pH 7.0, 10 mL), extracted with AcOEt, washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$:*n*-hexane:AcOEt = 5:5:4) to afford **6** (575 mg, 58%) as colorless crystals.

Allyl (4*R*,5*R*,6*S*)-6-[(*R*)-1-(Hydroxy)ethyl]-3-[(*R*)-pyrrolidine-2-thion-4-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (24). To a solution of **6** (69 g, 0.134

mol) in a mixture of DMF (518 mL) and *N*-methylpyrrolidone (173 mL) was added ammonium bifluoride (30.6 g, 0.536 mol) at 20 °C, and the mixture was stirred at 20 °C for 108 h. Phosphate buffer (0.2 M, K_2HPO_4, pH 7.0, 2 L) was added to the reaction mixture and extracted with AcOEt. The combined organic phases were washed with water (1 L), dried over anhydrous magnesium sulfate, and evaporated in vacuo. The crystals formed were collected by adding *n*-hexane to afford **24** (47.8 g, 90%) as colorless crystals: mp 144−145 °C; IR (Nujol) 1749, 1688 cm^{-1}; ^1H NMR (DMSO-d_3) δ 10.37, 5.82−6.01 (m, 1H), 5.07−5.46 (m, 2H), 4.55−4.79 (m, 2H), 3.97−4.27 (m, 4H), 3.23−3.46 (m, 5H), 2.67−2.78 (m, 1H), 1.15 (d, J = 6.1 Hz, 6H); ^{13}C NMR (DMSO-d_3) δ 214.1, 186.9, 173.0, 162.1 (4s), 145.2 (d), 138.1 (s), 130.8, 77.8 (2t), 77.2, 72.6, 68.5 (3d), 67.1, 65.3 (2t), 56.1, 52.6 (2d), 34.8, 29.9 (2q); SIMS *m*/*z* 383 ($M^+ + 1$); $[\alpha]_D^{25}$ +4.3° (*c*, 0.88, MeOH). Anal. Calcd for $C_{17}H_{22}N_2O_4S_2$: C, 53.38; H, 5.80; N, 7.32. Found: C, 53.42; H, 5.63; N, 7.44.

Sodium (4*R*,5*R*,6*S*)-6-[(*R*)-1-(Hydroxy)ethyl]-3-[(*R*)-pyrrolidine-2-thion-4-ylthio)]-4-methyl-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (25). A mixture of sodium bicarbonate (10.2 g, 0.121 mol) and dimedone (10.2 g, 0.0725 mol) in water (121 mL) was sonicated for 10 min. Compound **24** (46.3 g, 0.121 mol), triethyl phosphite (7.02 g, 0.0402 mol), palladium acetate (1.33 g, 5.9 mmol), and THF (968 mL) were added, and the mixture was stirred at 35−37 °C for 45 min. To the mixture was added THF (968 mL), and the resulting mixture was stirred at 0 °C for 1 h. The crystals formed were collected, washed with THF, and dried at 25 °C for 4 h under reduced pressure to afford **25** (45.48 g, 87% (net yield); the crystals contained water (12.86%) and THF (2.8%)) as colorless crystals: mp 140−150 °C dec; IR (Nujol) 1746, 1594 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.09−4.32, 3.28−3.71 (m, 4H), 2.91−3.01 (m, 1H), 1.30 (d, J = 6.4 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 205.0, 179.1, 170.4, 141.9, 136.0 (5s), 67.9, 61.2, 60.2 (3d), 57.8, 54.4 (2t), 45.5, 42.0 (2d), 22.9, 18.8 (2q); SIMS *m*/*z* 365 ($M^+ + 1$); $[\alpha]_D^{25}$ +1.7° (*c*, 1.0, H_2O).

Isobutyryloxymethyl (4*R*,5*R*,6*S*)-6-[(*R*)-1-(Hydroxy)-ethyl]-3-[(*R*)-pyrrolidine-2-thion-4-ylthio)]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate, TA-949 (1). To a solution of **25** (2 g, content: 88.1%, 4.84 mmol) in DMF (13.2 mL) and *N*-methylpyrrolidone (4.4 mL) was added 4 Å molecular sieves (3.2 g), and the mixture was stirred for 30 min. *N*,*N*-Diisopropylethylamine (189 mg, 1.46 mmol) and isobutyryloxymethyl iodide (1.27 g, 5.57 mmol) were added at −15 °C, and the mixture was stirred at −10 °C for 1.5 h. The reaction mixture was poured into a mixture of phosphate buffer (0.2 M, K_2HPO_4, pH 7.0, 50 mL) and ice (50 g) and extracted with AcOEt (2 × 30 mL). The combined organic phases were washed with water (2 × 50 mL), dried over anhydrous magnesium sulfate, and evaporated in vacuo. The residue was crystallized from AcOEt (2 mL) and diisopropyl ether (50 mL) to afford **1** (1.77 g, 83%) as colorless crystals: mp 153.9 °C; IR (Nujol) 1750, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.36 (s, 1H), 5.87 (d, J = 5.9 Hz, 1H), 5.74 (d, J = 5.9 Hz, 1H), 5.09 (d, J = 5 Hz, 1H), 3.94−4.35 (m, 4H), 3.24−3.50 (m, 4H), 2.47−2.80 (m, 2H), 1.14 (d, J = 11.1 Hz, 3H), 1.10 (d, J = 12.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 200.7, 174.5, 173.6, 158.7, 151.3, 123.8 (6s), 78.8 (t), 63.8, 59.5, 55.1 (3d), 53.7, 52.0 (2t), 43.0, 39.3, 32.7 (3d), 21.4, 18.1, 16.5 (3q); SIMS *m*/*z* 444 ($M^+ + 1$); $[\alpha]_D^{25}$ +14.2° (*c*, 1.0, MeOH). Anal. Calcd for $C_{19}H_{26}N_2O_6S_2$: C, 51.57; H, 5.92; N, 6.33. Found: C, 51.66; H, 5.88; N, 6.32.

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