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Stereoselective Reactions. IX.[1,2] Synthetic Studies on Optically Active β-Lactams. I. Chiral Synthesis of Carbapenam and Carbapenem Ring Systems Starting from (*S*)-Aspartic Acid[3,4]

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A chiral carbapenam ring system ((3*R*,5*R*)-(+)-**19** and -**20**) having the desired absolute configuration at C-5 was synthesized starting from (*S*)-aspartic acid, and the latter product was further transformed to a chiral carbapenem derivative ((5*S*,2′*R*)-(+)-**21**) having an (*R*)-cysteine moiety as a side chain.

Keywords——(*S*)-aspartic acid; thienamycin; β-lactam; chiral synthesis; carbapenam ring system; Arndt-Eistert synthesis; (*R*)-cysteine

Thienamycin (**1**)[6] and related natural products, novel β-lactam antibiotics with a highly potent antibacterial activity as well as a lack of susceptibility to β-lactamase, have been the subjects of considerable efforts directed at total syntheses. The syntheses of (+)-**1** and key intermediates for (+)-**1** from a variety of the starting materials including (*S*)-aspartic acid,[7a] dimethyl β-aminoglutarate (involving enzymatic asymmetric induction),[7b] penicillin,[7c] (*S*)-threonine,[7d] D-glucose,[7e] D-glucosamine,[7f] and by chemical asymmetric induction,[7g] have been reported.

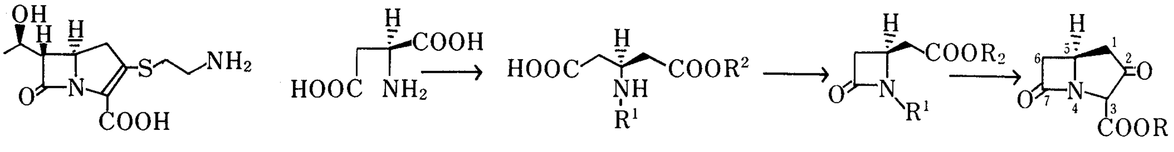

Chart 1

The carbapenam of type **5** having the fundamental skeleton of thienamycin is an attractive synthetic target since it should be convertible into useful thienamycin derivatives. We have already reported the chiral synthesis of a carbapenam ring system having the desired absolute configuration at C-5 starting from (*S*)-aspartic acid (**2**), as shown in Chart 1.[4] The (*S*)-4-methoxycarbonylmethyl-2-azetidinone derivative (**4**), prepared by cyclization of the (*S*)-β-amino acid ester (**3**), was considered to be a versatile intermediate of the carbapenam nucleus, and (*S*)-**3** could be obtained by the Arndt-Einstert synthesis from an (*S*)-aspartic acid derivative. The details of this work on the synthesis of the chiral carbapenam ring system and its derivatives are presented in this paper.

The synthetic scheme for the chiral carbapenam derivatives is illustrated in Chart 2. β-Benzyl *N*-*tert*-butoxycarbonyl(Boc)-(*S*)-aspartate ((*S*)-(−)-**6**)[8] was converted into the mixed anhydride with ethyl chloroformate in ether, followed by reaction with diazomethane in ether to give the diazoketone, which was then treated with silver benzoate and triethylamine (TEA) in methanol[9] at room temperature to afford benzyl (*R*)-3-*tert*-butoxycarbonylamino-4-

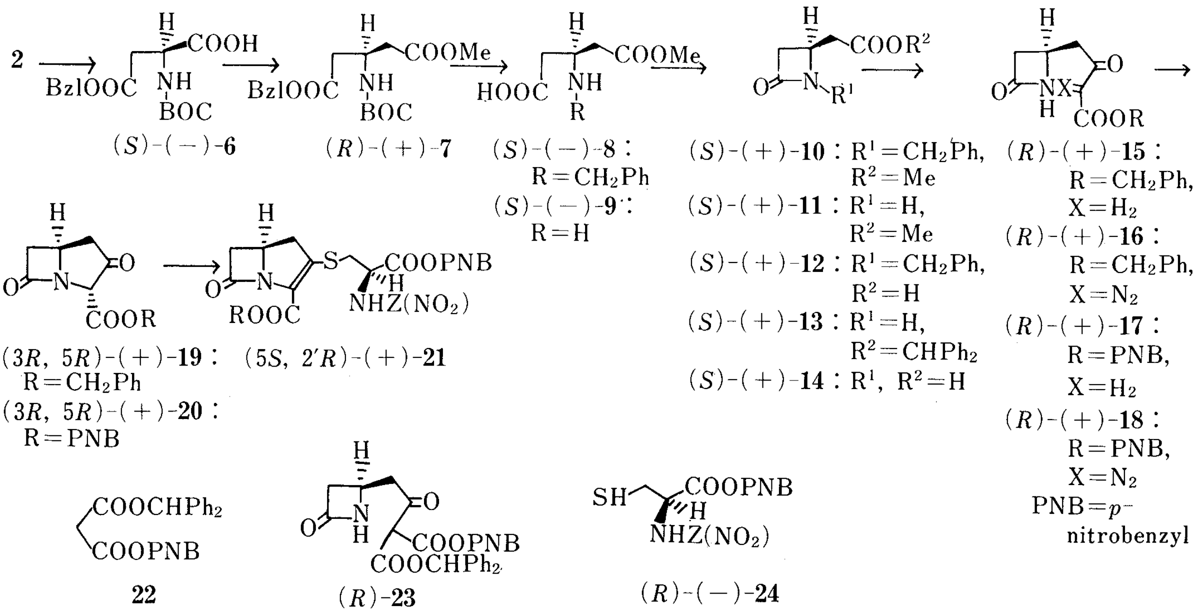

Chart 2

methoxycarbonylbutyrate ((*R*)-(+)-**7**) in 79% yield after column chromatography on silica gel. After cleavage of the Boc group by acidic treatment (2.5 N HCl–AcOEt), the Schiff base of the resulting free amino ester with benzaldehyde was catalytically hydrogenated in ethanol to furnish the *N*-benzyl *β*-amino acid ester ((*S*)-(−)-**8**) in 74% yield. Then (*S*)-(−)-**8** was treated with thionyl chloride at room temperature to provide the corresponding acid chloride hydrochloride, which was cyclized in benzene in the presence of TEA at room temperature to afford (*S*)-*N*-benzyl-4-methoxycarbonylmethyl-2-azetidinone ((*S*)-(+)-**10**, $[\alpha]_D^{20}$ +23.8° (c=1.0, benzene)) in 66% yield. The cyclization of the *N*-unsubstituted *β*-amino acid derivative ((*S*)-(−)-**9**), prepared in 50% yield from *β*-benzyl *N*-benzyloxycarbonyl (Z)-(*S*)-aspartate by the Arndt-Eistert synthesis followed by catalytic deprotection of the Z group and benzyl group, with thionyl chloride or dicyclohexylcarbodiimide gave the corresponding *β*-lactam ((*S*)-(+)-**11**) only in a poor yield (<5%).

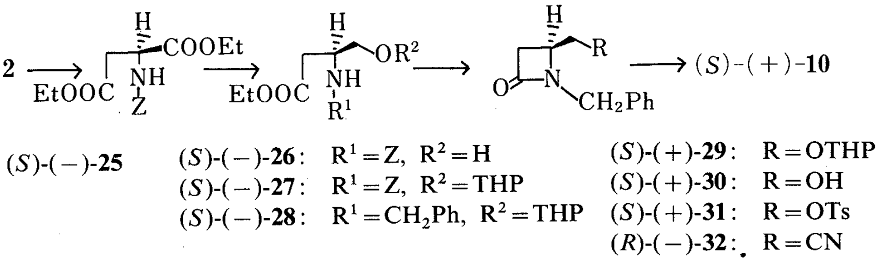

Chart 3

An alternative route for (*S*)-(+)-**10** is shown in Chart 3. Diethyl *N*-benzyloxycarbonyl-(*S*)-aspartate ((*S*)-(−)-**25**) was treated with sodium borohydride in ethanol at 0 °C to afford the corresponding alcohol ((*S*)-(−)-**26**) in 60% yield.[10] After the protection of the free hydroxyl of (*S*)-(−)-**26** as its tetrahydropyranyl (THP) ether and reductive removal of the Z group, the resulting free amino ester was treated in the same manner as described for the preparation of (*S*)-(−)-**8** to furnish the *N*-benzyl *β*-amino ester ((*S*)-(−)-**28**) in 76% yield. Reaction of (*S*)-(−)-**28** with ethylmagnesium bromide (1 eq.) in ether at room temperature resulted in cyclization to yield the corresponding *β*-lactam ((*S*)-(+)-**29**) in 60% yield. After removal of the THP group by acidic treatment (cat. *p*-TsOH–MeOH), the tosylate ((*S*)-(+)-**31**) obtained from the resulting hydroxy derivative ((*S*)-(+)-**30**) was treated with potassium cyanide in the presence of 18-crown-6 in acetonitrile at 60 °C for 2 d to yield (*R*)-*N*-benzyl-4-cyanomethyl-2-azetidinone ((*R*)-(−)-**32**), which was then treated with methanolic hydrogen chloride at 0 °C to afford (*S*)-(+)-**10** in 22% yield from (*S*)-(+)-**29**. The spectral and physical data of the product were identical with those of the sample prepared as described above.

After alkaline hydrolysis of the methyl ester of (*S*)-(+)-**10**, the *N*-benzyl group of (*S*)-(+)-**12** was reductively removed with metallic sodium in liquid ammonia to afford (*S*)-(+)-**14**, which was isolated and purified as its benzhydryl ester ((*S*)-(+)-**13**) due to the high solubility of (*S*)-(+)-**14** in water. After removal of the benzhydryl group by catalytic hydrogenation, the resulting carboxylic acid ((*S*)-(+)-**14**) was converted into the mixed anhydride with isobutyl chloroformate in tetrahydrofuran (THF), and then condensed with the lithium enolate of benzyl acetate (10 eq.) to give the desired *β*-keto ester ((*R*)-(+)-**15**), $[\alpha]_D^{20}$ +43.2° ($c = 1.37$, benzene)) in 26% yield after chromatography. Chiral syntheses of (*R*)-(−)-**10** and (*R*)-(+)-**15** from D-glyceraldehyde acetonide,[11a] and (*S*)-glutamic acid[11b] and D-glucosamine,[7f] respectively, have also been reported recently. The construction of the carbapenam ring system was achieved by using the carbene insertion reaction.[12] The diazo derivative ((*R*)-(+)-**16**) obtained from (*R*)-(+)-**15** by diazo exchange with *p*-carboxybenzenesulfonyl azide was treated with rhodium acetate in benzene at 80 °C to give the bicyclic keto ester ((3*R*,5*R*)-(+)-**19**) in 72% yield from (*R*)-(+)-**15**.

In order to improve the yield in the synthesis of *β*-keto ester and to introduce the *p*-nitrobenzyl group into the ester moiety, the malonic acid derivative (**22**) was used for the preparation of the *β*-keto ester. The mixed anhydride prepared from (*S*)-(+)-**14** with isobutyl chloroformate in THF was reacted with the sodium salt of **22** in THF to afford (*R*)-**23** (a mixture of keto and enol tautomers), which was then treated with trifluoroacetic acid in the presence of anisole to cleave the benzhydryl group followed by decarboxylation to give the desired *β*-keto ester ((*R*)-(+)-**17**) in 74% yield. The bicyclic keto ester ((3*R*,5*R*)-(+)-**20**) was obtained as described above for the preparation of (3*R*,5*R*)-(+)-**19** in 81% yield.

Since the concentration-dependent instability of thienamycin might be due to intermolecular aminolysis of the azetidinone by the cysteamine side chain,[13] the synthesis of the carbapenem derivative having an (*R*)-cysteine moiety[14] as a side chain (expected to be a less nucleophilic species) was undertaken.

The bicyclic keto ester ((3*R*,5*R*)-(+)-**20**) was converted to the enol phosphate by treatment with diphenyl phosphorochloridate and *N*,*N*-diisopropylethylamine in acetonitrile,[15] and then reacted with the bis-protected (*R*)-cysteine derivative ((*R*)-(−)-**24**) in acetonitrile to provide (5*S*,2′*R*)-(+)-**21**, which was precipitated directly from the reaction mixture in 48% yield; pure (5*S*,2′*R*)-(+)-**21** was obtained by chromatography on a short Florisil column.

The results of tests of antimicrobial activity will be reported in due course.[16]

Experimental[17]

1-Benzyl 5-Methyl (*R*)-3-*tert*-Butoxycarbonylaminoglutarate ((*R*)-(+)-7)——Ethyl chloroformate (8.95 ml, 94 mmol) was added to a solution of *β*-benzyl *N*-*tert*-butoxycarbonyl-(*S*)-aspartate ((*S*)-(−)-**6**) (20.0 g, 61.9 mmol) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (4.66 ml, 30.9 mmol) in ether (200 ml) at −10—−20 °C. After being stirred at −10—−20 °C for 1 h, the mixture was added dropwise to a solution of diazomethane in ether (prepared from 43 g of nitrosomethylurea) at −10 °C. After being stirred at 0—5 °C for 1 h, the reaction mixture was allowed to come to room temperature. Excess diazomethane was removed, the insoluble materials were filtered off and the filtrate was concentrated *in vacuo* to give the crude diazoketone (23 g), which was dissolved in methanol (100 ml). To this solution was added a mixture of silver benzoate (0.44 g) and TEA (4 ml). After being stirred at room temperature for 1 h, the mixture was concentrated *in vacuo* to afford an oily residue, which was dissolved in ether (150 ml) and successively washed with water, 10% aq. citric acid, satd. aq. $NaHCO_3$, and satd. aq. NaCl. Drying followed by

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evaporation gave an oily residue, which was purified by column chromatography (silica gel, benzene : AcOEt = 35 : 1) to give pure (*R*)-(+)-**7** (17.1 g, yield 79%) as a pale yellow oil, $[\alpha]_D^{20}$ +3.4° (c=4.1, benzene). IR ν_{max}^{film} cm^{-1}: 3360, 1730—1680. NMR ($CDCl_3$): 1.43 (9H, s, $(CH_3)_3$), 2.55—2.85 (4H, m, 2 × CH_2), 3.65 (3H, s, $COOCH_3$), 4.3 (1H, m, CH), 5.13 (2H, s, $\underline{CH_2}C_6H_5$), 5.35 (1H, NH), 7.35 (5H, s, C_6H_5). *Anal.* Calcd for $C_{18}H_{25}N_1O_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.22; H, 7.18; N, 3.82.

5-Methyl 1-Hydrogen (*S*)-3-Benzylaminoglutarate ((*S*)-(−)-8)——(*R*)-(+)-**7** (52.5 g, 149 mmol) was treated with 2.5 N HCl–AcOEt (183 ml) at room temperature for 2 h, then the mixture was extracted with water (100 ml). The aqueous layer was basified with K_2CO_3, and extracted with AcOEt. The organic layer was washed with satd. aq. NaCl. Drying followed by evaporation gave an oily residue (34.9 g), which was dissolved in benzene (310 ml). To this solution were added benzaldehyde (15.5 g, 146 mmol) and molecular sieve 4A (34 g). The mixture was stirred at room temperature for 2 h, then the molecular sieve 4A was removed by filtration, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was catalytically hydrogenated with 5% Pd–C (10 g) in methanol (30 ml). After removal of the catalyst, the filtrate was concentrated *in vacuo* to give a solid, which was recrystallized from MeOH–ether to afford pure (*S*)-(−)-**8** (27.6 g, yield 74%) as colorless prisms, mp 114—115.5 °C, $[\alpha]_D^{20}$ −16.1° (c=0.98, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1740, 1580. NMR ($CDCl_3$): 2.35—3.05 (4H, m, 2 × CH_2), 3.4—3.95 (1H, m, CH), 3.72 (3H, s, OCH_3), 4.11 (2H, s, $\underline{CH_2}C_6H_5$), 7.45 (5H, s, C_6H_5). *Anal.* Calcd for $C_{13}H_{17}N_1O_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.85; H, 6.85; N, 5.62.

(*S*)-*N*-Benzyl-4-methoxycarbonylmethyl-2-azetidinone ((*S*)-(+)-10)——A mixture of (*S*)-(−)-**8** (3.2 g, 12.8 mmol) and thionyl chloride (15 ml) was stirred at room temperature for 1.5 h, and then excess thionyl chloride was removed *in vacuo*. After repeated evaporation with benzene, the vesulting oily residue was dissolved in benzene (200 ml). To this solution was added dropwise a solution of TEA (3.6 ml) in benzene (200 ml) at room temperature over a period of 5 h. After being stirred at room temperature for 3 h, the mixture was successively washed with 0.5 N aq. HCl, water, satd. aq. $NaHCO_3$, and satd. aq. NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, benzene : AcOEt = 5 : 1) to give (*S*)-(+)-**10** (1.96 g, yield 66%) as crystals. Recrystallization from ether–hexane gave pure (*S*)-(+)-**10** as colorless prisms, mp 43.5—44.5 °C $[\alpha]_D^{20}$ +23.8° (c=1.0, benzene). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755, 1745. NMR ($CDCl_3$): 2.45—2.85 (3H, m, $\underline{CH_2}COOCH_3$, C-3-H_β), 3.16 (1H, dd, J=5, 15 Hz, C-3-H_α), 3.59 (3H, s, OCH_3), 3.9 (1H, m, C-4-H), 4.25 and 4.45 (2H, AB, J=15 Hz, $\underline{CH_2}C_6H_5$), 7.25 (5H, s, C_6H_5). *Anal.* Calcd for $C_{13}H_{15}N_1O_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.74; H, 6.51; N, 5.99.

5-Methyl 1-Hydrogen (*S*)-3-Aminoglutarate ((*S*)-(−)-9)——This sample (mp 186—187 °C (dec.) (MeOH), $[\alpha]_D^{20}$ −13.3° (c=1.8, 67% aq. MeOH), lit.[5b] mp 175—177 °C, $[\alpha]_D^{25}$ −5.52° (c=3.26, H_2O)) was obtained in 84% yield by catalytic deprotection (5% Pd–C, MeOH) of (*S*)-3-*N*-benzyloxycarbonylamino-4-methoxycarbonylbutyrate (mp 48—49 °C (ether–hexane), $[\alpha]_D^{20}$ +0.52° (c=3.2, benzene), prepared in 59% yield from *β*-benzyl *N*-benzyloxycarbonyl-(*S*)-aspartate[18] as described above for the preparation of (*R*)-(+)-**7**).

(*S*)-4-Methoxycarbonylmethyl-2-azetidinone ((*S*)-(+)-11)——The acid chloride hydrochloride prepared from (*S*)-(−)-**9** (0.32 g, 2 mmol) by reaction with thionyl chloride was dissolved in dioxane (50 ml). This solution was added to a solution of TEA (0.55 ml) in dioxane (50 ml) at room temperature over a period of 4 h, then the mixture was stirred overnight. After removal of the insoluble materials, the filtrate was evaporated *in vacuo* to give an oily residue, which was subjected to chromatography on a short silica gel column ($CHCl_3$: acetone = 5 : 1). The fractions containing the desired *β*-lactam were further purified by preparative thin layer chromatography on silica gel (benzene : AcOEt = 1 : 3) to afford pure (*S*)-(+)-**11** (10 mg, yield 3.5%) as crystals, mp 66—68 °C, $[\alpha]_D^{20}$ +63° (c=0.2, benzene), (lit.[7b] mp 67.5—68 °C, $[\alpha]_D^{25}$ +65.34° (c=1.11, $CHCl_3$)). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 1760, 1735. NMR ($CDCl_3$): 2.55—2.7 (2H, m, $\underline{CH_2}COOMe$), 2.6 (1H, ddd, C-3-H_β), 3.2 (1H, ddd, J=2, 5, 15 Hz, C-3-H_α), 3.7 (3H, s, OCH_3), 4.0 (1H, m, C-4-H), 6.6 (1H, br s, NH).

Ethyl (*S*)-3-*N*-Benzyloxycarbonylamino-4-hydroxybutyrate ((*S*)-(−)-26)——$NaBH_4$ (0.3 g, 7.94 mmol) was added to a solution of diethyl *N*-benzyloxycarbonyl-(*S*)-aspartate ((*S*)-(−)-**25**) (2.0 g, 6.2 mmol, prepared from diethyl (*S*)-aspartate[19] by reaction with ZCl in satd. aq. $NaHCO_3$, mp 42—43 °C (AcOEt–hexane), $[\alpha]_D^{20}$ −18.3° (c=1.6, EtOH)) in EtOH (20 ml) at 0 °C. After being stirred at 0 °C for 8 h, the mixture was diluted with AcOEt (150 ml) and washed with satd. aq. NaCl (× 5). Drying followed by evaporation afforded an oily residue, which was purified by column chromatography (silica gel, $CHCl_3$: AcOEt = 1 : 1) to give (*S*)-(−)-**26** (1.04 g, yield 60%) as crystals. Recrystallization from ether–hexane gave pure (*S*)-(−)-**26** as colorless prisms, mp 65 °C, $[\alpha]_D^{20}$ −9.3° (c=1.16, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3320, 1730, 1680. NMR ($CDCl_3$): 1.15 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 2.6 (2H, d, J=6 Hz, $\underline{CH_2}COOEt$), 3.7 (2H, m, $\underline{CH_2}OH$), 3.6 (1H, br s, OH), 4.1 (2H, q, J=7 Hz, $\underline{CH_2}CH_3$), 4.0—4.3 (1H, m, CH), 5.1 (2H, s, $\underline{CH_2}C_6H_5$), 5.8 (1H, NH), 7.3 (5H, s, C_6H_5). *Anal.* Calcd for $C_{14}H_{19}N_1O_5$: C, 59.77; H, 6.81; N, 4.98. Found: C, 59.99; H, 6.78; N, 4.92.

Ethyl (*S*)-3-*N*-Benzyloxycarbonylamino-4-2′-tetrahydropyranoxybutyrate ((*S*)-(−)-27)——A mixture of (*S*)-(−)-**26** (2.5 g, 8.9 mmol), dihydropyran (2.24 g, 26.7 mmol), and a catalytic amount of *p*-toluenesulfonic acid in ether (30 ml) was stirred at room temperature for 6 h, and then washed with satd. aq. $NaHCO_3$ and water. Drying followed by evaporation gave an oily residue, which was purified by column chromatography (silica gel, $CHCl_3$: AcOEt = 10 : 1) to afford pure (*S*)-(−)-**27** (3.0 g, yield 93%) as an oil, $[\alpha]_D^{20}$ −8.6° (c=2.2, EtOH). IR ν_{max}^{film} cm^{-1}: 1720, 1690.

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NMR ($CDCl_3$): 1.2 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.2—2.0 (6H, m, $(CH_2)_3$), 2.6 (2H, d, $J=6$ Hz, $C\underline{H}_2COOEt$), 3.2—4.0 (4H, m, $2\times CH_2$), 4.1 (2H, q, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.0—4.3 (1H, m, CH), 4.6 (1H, br s, OCHO), 5.1 (2H, s, $C\underline{H}_2C_6H_5$), 5.5 (1H, NH), 7.3 (5H, s, C_6H_5).

Ethyl (*S*)-3-Benzylamino-4-2′-tetrahydropyranoxybutyrate ((*S*)-(−)-28)——After catalytic removal of the Z group of (*S*)-(−)-**27** (2.9 g, 7.95 mmol) with 5% Pd–C (0.7 g) in EtOH (30 ml), (*S*)-(−)-**28** (2.1 g, oil, yield 82% after column chromatography (silica gel, $CHCl_3$: ether = 10 : 1)) was obtained as described above for the preparation of (*S*)-(−)-**8**, $[\alpha]_D^{20}$ −7.0° ($c=2$, EtOH). IR ν_{max}^{film} cm^{-1}: 1720. NMR ($CDCl_3$): 1.2 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.2—2.0 (6H, m, $(CH_2)_3$), 2.5 (2H, d, $J=6$ Hz, $C\underline{H}_2COOEt$), 3.0—4.1 (5H, m, $2\times CH_2$, CH), 3.8 (2H, s, $C\underline{H}_2C_6H_5$), 4.1 (2H, t, $J=7$ Hz, $C\underline{H}_2CH_3$), 4.65 (1H, br s, OCHO), 7.25 (5H, s, C_6H_5).

(*S*)-*N*-Benzyl-4-2′-tetrahydropyranoxymethyl-2-azetidinone ((*S*)-(+)-29)——An ethereal solution of EtMgBr (6.2 ml, 1.3 eq.) was added dropwise to a stirred solution of (*S*)-(−)-**28** (1.6 g, 4.98 mmol) at 0 °C over a period of 10 min, then the mixture was stirred at room temperature for 3 h. After the addition of 10% aq. NH_4Cl (10 ml), the organic layer was separated and washed with satd. aq. NaCl. Drying followed by evaporation *in vacuo* afforded an oily residue, which was purified by column chromatography (silica gel, $CHCl_3$: ether = 10 : 1) to give pure (*S*)-(+)-**29** (0.95 g, yield 60%) as an oil, $[\alpha]_D^{20}$ +5.4° ($c=1.8$, EtOH). IR ν_{max}^{film} cm^{-1}: 1760. NMR ($CDCl_3$): 1.4—2.0 (6H, m, $(CH_2)_3$), 1.7—3.0 (2H, m, C-3-H_{ab}), 3.1—4.1 (5H, m, C-4-H, $2\times CH_2$), 4.3 and 4.7 (2H, AB, $J=15$ Hz, $C\underline{H}_2C_6H_5$), 4.5 (1H, m, OCHO), 7.3 (5H, s, C_6H_5).

(*S*)-*N*-Benzyl-4-hydroxymethyl-2-azetidinone ((*S*)-(+)-30)——A mixture of (*S*)-(+)-**29** (0.9 g, 3.3 mmol) and a catalytic amount of *p*-TsOH in MeOH (9 ml) was stirred at room temperature for 3 h, and then diluted with ether (50 ml). After washing of the organic layer with satd. aq. $NaHCO_3$ and water, drying followed by evaporation gave a solid, which was recrystallized from AcOEt–hexane to afford pure (*S*)-(+)-**30** (0.5 g, yield 80%) as colorless prisms, mp 110 °C, $[\alpha]_D^{20}$ +80.5° ($c=1.2$, EtOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700. NMR ($CDCl_3$): 2.5 (1H, br s, OH), 2.6—2.9 (2H, m, C-3-H_{ab}), 3.4—3.8 (3H, m, $C\underline{H}_2OH$, C-4-H), 4.3 and 4.65 (2H, AB, $J=15$ Hz, $C\underline{H}_2C_6H_5$), 7.3 (5H, s, C_6H_5). *Anal.* Calcd for $C_{11}H_{23}N_1O_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.86; H, 6.87; N, 7.09.

(*S*)-*N*-Benzyl-4-tosyloxymethyl-2-azetidinone ((*S*)-(+)-31)——A mixture of (*S*)-(+)-**30** (0.6 g, 3.18 mmol) and *p*-toluenesulfonyl chloride (0.73 g, 3.8 mmol) in pyridine (10 ml) was stirred at room temperature overnight, and then diluted with AcOEt (80 ml). After washing of the organic layer with 10% HCl, satd. aq. NaCl, and water, drying followed by evaporation gave a solid, which was recrystallized from AcOEt–hexane to afford pure (*S*)-(+)-**31** (0.99 g, yield 90%) as colorless prisms, mp 96—97 °C, $[\alpha]_D^{20}$ +11.6° ($c=2$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745. NMR ($CDCl_3$): 2.45 (3H, s, CH_3), 2.6 (1H, dd, $J=2$, 15 Hz, C-3-H_β), 3.0 (1H, dd, $J=5$, 15 Hz, C-3-H_α), 3.6 (1H, m, C-4-H), 4.0 (2H, m, CH_2OTs), 4.05 and 4.5 (2H, AB, $J=15$ Hz, $C\underline{H}_2C_6H_5$), 7.2 (5H, s, C_6H_5), 7.3 (2H, d, $J=8$ Hz, aromatic protons), 7.6 (2H, d, $J=8$ Hz, aromatic protons). *Anal.* Calcd for $C_{18}H_{19}N_1O_4S_1$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.57; H, 5.55; N, 4.24.

(*R*)-*N*-Benzyl-4-cyanomethyl-2-azetidinone ((*R*)-(−)-32)——A mixture of (*S*)-(+)-**31** (0.4 g, 1.16 mmol), KCN (0.15 g, 2.32 mmol), and 18-crown-6 (0.31 g, 1.16 mmol) in CH_3CN (5 ml) was heated at 60 °C for 2 d, and then diluted with ether (100 ml) followed by successive washing with satd. aq. NaCl and water. Drying followed by evaporation gave an oily residue, which was purified by column chromatography (silica gel, $CHCl_3$: ether = 9 : 1) to afford pure (*S*)-(−)-**32** (0.17 g, yield 75%) as a pale yellow oil, $[\alpha]_D^{20}$ −14.3° ($c=2.8$, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 2240, 1740. NMR ($CDCl_3$): 2.55 (2H, d, $J=6$ Hz, CH_2CN), 2.8 (1H, dd, $J=2$, 15 Hz, C-3-H_β), 3.2 (1H, dd, $J=5$, 15 Hz, C-3-H_α), 3.7 (1H, m, C-4-H), 4.2 and 4.5 (2H, AB, $J=15$ Hz, $C\underline{H}_2C_6H_5$), 7.3 (5H, s, C_6H_5). MS *m*/*e*: 200 (M^+).

(*S*)-*N*-Benzyl-4-methoxycarbonylmethyl-2-azetidinone ((*S*)-(+)-10)——HCl gas was bubbled into a solution of (*R*)-(−)-**32** (0.14 g, 0.7 mmol) in MeOH (5 ml) at 0 °C for 10 min. After being stirred at room temperature for 1 h, the mixture was diluted with ether (100 ml) and washed with satd. aq. $NaHCO_3$ and satd. aq. NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, $CHCl_3$: ether = 5 : 1) to afford pure (*S*)-(+)-**10** (0.07 g, yield 40%) as crystals, mp 42—44 °C, $[\alpha]_D^{20}$ +21° ($c=1$, benzene). Its IR and NMR spectra were identical with those of the product obtained from (*S*)-(−)-**8**.

(*S*)-4-(Diphenylmethyloxycarbonyl)methyl-2-azetidinone ((*S*)-(+)-13)——A 1 N aq. NaOH solution (7.3 ml) was added to a stirred solution of (*S*)-(+)-**10** (1.62 g, 6.95 mmol) in MeOH (16 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h, then the methanol was removed *in vacuo*. The aqueous layer was acidified with 1 N aq. HCl and extracted with AcOEt. The organic layer was washed with satd. aq. NaCl. Drying followed by evaporation gave a solid, which was recrystallized from benzene to afford pure (*S*)-*N*-benzyl-4-carboxymethyl-2-azetidinone ((*S*)-(+)-**12**) (1.33 g, yield 87%) as colorless prisms, mp 109—110 °C, $[\alpha]_D^{20}$ +12.2° ($c=0.87$, EtOH). Next, Na (0.15 g) was added in small pieces to liquid ammonia (150 ml), and the whole was stirred for 20 min. To this solution was added (*S*)-(+)-**12** (0.31 g, 1.42 mmol) over a period of 5 min. The mixture was stirred for 5 min, and the ammonia was evaporated off to leave a white solid, to which a solution of EtOH (30 ml) and 1 N aq. HCl (7.8 ml) was added at −20 °C. This mixture was allowed to come to room temperature, and diphenyldiazomethane (3.0 g) was added. The whole was stirred at room temperature for 1 h, then the solvent was evaporated off *in vacuo* and the residue was extracted with AcOEt (30 ml). The organic layer was washed with water and satd. aq. NaCl. Drying followed by evaporation gave a residue, which was purified by column chromatography (silica gel, benzene : AcOEt = 10 : 1) to afford (*S*)-(+)-**13** (0.355 g, yield 74%) as crystals. Recrystallization from ether gave pure (*S*)-(+)-**13** as colorless needles, mp 65.5—66.5 °C, $[\alpha]_D^{20}$

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+46.6° (c=0.96, benzene). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3310, 1760, 1735. NMR ($\mathrm{CDCl_3}$): 2.4—3.35 (4H, m, $2\times\mathrm{CH_2}$), 3.9 (1H, m, C-4-H), 6.4 (1H, m, NH), 6.96 (1H, s, $\mathrm{C\underline{H}(C_6H_5)_2}$), 7.40 (10H, s, $2\times\mathrm{C_6H_5}$). *Anal.* Calcd for $\mathrm{C_{18}H_{17}N_1O_3}$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.04; H, 5.81; N, 4.87.

(*S*)-4-Carboxymethyl-2-azetidinone ((*S*)-(+)-14)——(*S*)-(+)-**13** (0.3 g, 1 mmol) was hydrogenated with 5% Pd-C (90 mg) in ethanol (8 ml) at room temperature for 1.5 h. After the removal of the catalyst, the filtrate was concentrated *in vacuo* to give a solid, which was recrystallized from THF to afford pure (*S*)-(+)-**14** (0.115 g, yield 88%) as colorless prisms, mp 169—171 °C (dec.), $[\alpha]_D^{20}$ +12.3° (c=0.5, EtOH). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3250, 1735, 1715. NMR ($\mathrm{D_2O}$): 2.5—2.9 (3H, m, $\mathrm{C\underline{H}_2COOH}$, C-3-H$_\beta$), 3.16 (1H, m, C-3-H$_\alpha$), 3.95 (1H, m, C-4-H). *Anal.* Calcd for $\mathrm{C_5H_7N_1O_3}$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.77; H, 5.49, N, 10.86.

(*R*)-4-3′-Benzyloxycarbonyl-2′-oxopropyl-2-azetidinone ((*R*)-(+)-15)——Isobutyl chloroformate (0.51 ml, 3.88 mmol) was added to a stirred solution of (*S*)-(+)-**14** (0.452 g, 3.5 mmol) and TEA (0.51 ml, 3.67 mmol) in THF (35 ml) at −20 °C under an argon atmosphere. The mixture was stirred at −20 °C for 1 h. To this solution was added the lithium enolate of benzyl acetate (35 mmol, prepared from lithium diisopropylamide (35 mmol) and benzyl acetate (35 mmol) in THF (49 ml)) at −78 °C. The mixture was stirred at −78 °C for 5 min, then 15 ml of satd. aq. $\mathrm{NH_4Cl}$ was added and the whole was extracted with AcOEt (120 ml). The organic layer was successively washed with dil. aq. HCl, water, satd. aq. $\mathrm{NaHCO_3}$, and satd. aq. NaCl. Drying followed by evaporation gave an oily residue, which was purified by column chromatography (silica gel, benzene : AcOEt = 2 : 1) to afford (*R*)-(+)-**15** (0.236 g, yield 26%) as a pale yellow oil, $[\alpha]_D^{20}$ +43.2° (c=0.37, benzene). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3420, 1758, 1720. NMR ($\mathrm{CDCl_3}$): 2.3—3.35 (4H, m, C-3-H$_{ab}$, C-1′-H$_{ab}$), 3.48 (2H, s, C-3′-H$_{ab}$), 3.9 (1H, m, C-4-H), 5.15 (2H, s, $\mathrm{C\underline{H}_2C_6H_5}$), 6.30 (1H, NH), 7.33 (5H, s, $\mathrm{C_6H_5}$). MS *m/e*: 261 ($\mathrm{M^+}$).

(*R*)-4-3′-Benzyloxycarbonyl-3′-diazo-2′-oxopropyl-2-azetidinone ((*R*)-(+)-16)——TEA (0.13 ml, 0.95 mmol) was added to a stirred solution of (*R*)-(+)-**15** (83 mg, 0.318 mmol) and *p*-carboxybenzenesulfonyl azide (76 mg, 0.33 mmol) in $\mathrm{CH_3CN}$ (1.5 ml) at 0 °C, then the mixture was stirred at room temperature for 1 h. After filtration to remove insoluble materials, the filtrate was diluted with ether (10 ml), and successively washed with water, satd. aq. $\mathrm{NaHCO_3}$, and satd. aq. NaCl. Drying followed by evaporation gave a solid, which was recrystallized from ether to give pure (*R*)-(+)-**16** (79 mg, yield 87%) as crystals, mp 99—102 °C, $[\alpha]_D^{20}$ +68.8° (c=0.28, benzene). IR $\nu_{\max}^{\mathrm{CH_2Cl_2}}$ cm^{-1}: 3405, 2140, 1765, 1715, 1647. NMR ($\mathrm{CDCl_3}$): 2.5—3.35 (3H, m, C-3-H$_{ab}$, C-1′-H$_a$), 3.38 (1H, dd, J=4, 18 Hz, C-1′-H$_b$), 4.0 (1H, m, C-4-H), 5.26 (2H, s, $\mathrm{C\underline{H}_2C_6H_5}$), 6.05 (1H, NH), 7.37 (5H, s, $\mathrm{C_6H_5}$). MS *m/e*: 259 ($\mathrm{M^+}-28$).

Benzyl (3*R*,5*R*)-1-Carba-2-oxopenam-3-carboxylate ((3*R*,5*R*)-(+)-19)——A solution of the diazocompound ((*R*)-(+)-**16**) (59 mg, 0.21 mmol) in dry benzene (20 ml) in the presence of a catalytic amount of $\mathrm{Rh_2(OAc)_4}$ was stirred at 80—85 °C (bath temperature) for 45 min, then this solution was concentrated *in vacuo* to half of its original volume. After the addition of ether (15 ml), the insoluble materials were filtered off, and the filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography (silica gel, benzene : AcOEt = 10 : 1) to afford (3*R*,5*R*)-(+)-**19** (44 mg, yield 83%) as crystals. Recrystallization from ether gave pure (3*R*,5*R*)-(+)-**19** as colorless needles, mp 68—69 °C, $[\alpha]_D^{20}$ +298° (c=1.54, benzene). IR $\nu_{\max}^{\mathrm{CH_2Cl_2}}$ cm^{-1}: 1775, 1745. NMR ($\mathrm{CDCl_3}$): 2.35 (1H, dd, J=8, 19 Hz, C-1-H$_a$), 2.74—3.04 (2H, m, C-1-H$_b$, C-6-H$_\beta$), 3.62 (1H, dd, J=6, 16 Hz, C-6-H$_\alpha$), 4.12 (1H, m, C-5-H), 4.70 (1H, s, C-3-H), 5.19 (2H, s, $\mathrm{C\underline{H}_2C_6H_5}$), 7.32 (5H, s, $\mathrm{C_6H_5}$). *Anal.* Calcd for $\mathrm{C_{14}H_{13}N_1O_4}$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.91; H, 5.10; N, 5.41.

(*R*)-4-3′-*p*-Nitrobenzyloxycarbonyl-2′-oxopropyl-2-azetidinone ((*R*)-(+)-17)——A solution of *p*-nitrobenzyl (diphenylmethyloxycarbonyl)acetate [**22**, 1.14 g, 2.81 mmol, prepared by successive treatments of malonic acid with 1 eq of diphenyl diazomethane (ether, room temperature) and 1 eq of *p*-nitrobenzyl bromide (TEA (1 eq) in dioxane), mp 66.5—68.5 °C] in THF (95 ml) was added to a suspension of sodium hydride (0.135 g (50% oil suspension), 2.8 mmol, washed with hexane) in THF (5 ml) at −10 °C. The mixture was stirred at −10—−5 °C for 20 min, then a solution of mixed anhydride of (*S*)-(+)-**14** (1 mmol, prepared in the same manner as described for the preparation of (*R*)-(+)-**15**) in THF (10 ml) was added at −15 °C. The reaction mixture was stirred at −5—5 °C for 1 h, and then AcOEt (50 ml) and 10% aq. citric acid (5 ml) were added. The organic layer was separated and washed with water and satd. aq. NaCl. Drying followed by evaporation gave an oily residue, which was purified by column chromatography (silica gel, benzene : AcOEt = 3 : 1) to afford (*R*)-4-3′-diphenylmethyloxycarbonyl-3′-*p*-nitrobenzyloxycarbonyl-2′-oxopropyl-2-azetidinone ((*R*)-**23**, 0.42 g, yield 81%, a mixture of keto and enol tautomers) as a pale yellow oil. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3420, 1762, 1738, 1720, 1525, 1352. NMR ($\mathrm{CDCl_3}$): 2.4—3.4 (4H, m, C-3-H$_{ab}$, C-1′-H$_{ab}$), 3.9 (1H, m, C-4-H), 4.6 (s, C-3′-H), 5.31 (2H, s, $\mathrm{C\underline{H}_2C_6H_4NO_2}$-*p*), 6.2 (1H, NH), 6.97 (1H, s, $\mathrm{C\underline{H}(C_6H_5)_2}$), 7.26 (10H, s, $2\times\mathrm{C_6H_5}$), 7.2—7.65 (2H, aromatic protons), 7.9—8.3 (2H, aromatic protons). A mixture of (*R*)-**23** (0.37 g, 0.72 mmol), anisole (1.9 ml), and trifluoroacetic acid (1.9 ml) was stirred at −5—−2 °C for 20 min, then the anisole and trifluoroacetic acid were removed *in vacuo* to give a residue, which was dissolved in AcOEt (25 ml). The mixture was washed with satd. aq. $\mathrm{NaHCO_3}$ and satd. aq. NaCl. Drying followed by evaporation gave a solid, which was purified by column chromatography (silica gel, $\mathrm{CHCl_3}$: acetone = 9 : 1) to afford (*R*)-(+)-**17** (0.2 g, yield 91%) as crystals. Recrystallization from benzene gave pure (*R*)-(+)-**17** as colorless needles, mp 78—79 °C, $[\alpha]_D^{20}$ +43.1° (c=2, $\mathrm{CHCl_3}$). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3420, 1765, 1720, 1525, 1350. NMR ($\mathrm{CDCl_3}$): 2.4—3.35 (4H, m, C-3-H$_{ab}$, C-1′-H$_{ab}$), 3.56 (2H, s, C-3′-H$_{ab}$), 3.95 (1H, m, C-4-H), 5.24 (2H, s, $\mathrm{C\underline{H}_2C_6H_4NO_2}$-*p*), 6.1 (1H, NH), 7.48 (2H, d, J=8 Hz, aromatic protons), 8.18 (2H, d, $J=8$ Hz, aromatic protons). *Anal.* Calcd for $C_{14}H_{14}N_2O_6$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.60; H, 4.62; N, 9.22.

(*R*)-4-3′-Diazo-3′-*p*-nitrobenzyloxycarbonyl-2′-oxopropyl-2-azetidinone ((*R*)-(+)-18)——This sample (0.15 g, yield 90%) was obtained from (*R*)-(+)-**17** (0.153 g, 0.5 mmol) as described above for the preparation of (*R*)-(+)-**16**, mp 80—81 °C, $[\alpha]_D^{20}$ +66.3° ($c=0.53$, benzene). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3420, 2145, 1765, 1720, 1525, 1350. NMR ($CDCl_3$): 2.66 (1H, dd, $J=2$, 15 Hz, C-3-H_β), 3.00 (1H, dd, $J=9$, 18 Hz, C-1′-H_a), 3.0—3.32 (1H, m, C-3-H_α), 3.37 (1H, dd, $J=4$, 18 Hz, C-1′-H_b), 3.95 (1H, m, C-4-H), 5.32 (2H, s, $C\underline{H}_2C_6H_4NO_2$-*p*), 6.1 (1H, NH), 7.50 (2H, d, $J=8$ Hz, aromatic protons), 8.19 (2H, d, $J=8$ Hz, aromatic protons). *Anal.* Calcd for $C_{14}H_{12}N_4O_6$: C, 50.61; H, 3.64; N, 16.89. Found: C, 50.72; H, 3.67; N, 16.97.

***p*-Nitrobenzyl (3*R*,5*R*)-1-Carba-2-oxopenam-3-carboxylate ((3*R*,5*R*)-(+)-20)**——This sample (0.14 g, oil, yield 92%) was obtained from (*R*)-(+)-**18** (0.16 g, 0.5 mmol) as described above for the preparation of (3*R*,5*R*)-(+)-**19**, $[\alpha]_D^{20}$ +270° ($c=0.44$, benzene). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1775, 1750, 1525, 1350. NMR ($CDCl_3$): 2.42 (1H, dd, $J=8$, 19 Hz, C-1-H_a), 2.75—3.1 (2H, m, C-1-H_b, C-6-H_β), 3.66 (1H, dd, $J=6$, 16 Hz, C-6-H_α), 4.1 (1H, m, C-5-H), 4.74 (1H, s, C-3-H), 5.22 and 5.29 (2H, AB, $J=15$ Hz, $C\underline{H}_2C_6H_4NO_2$-*p*), 7.46 (2H, d, $J=8$ Hz, aromatic protons), 8.14 (2H, d, $J=8$ Hz, aromatic protons).

***p*-Nitrobenzyl *N*-*p*-Nitrobenzyloxycarbonyl-(*R*)-cysteinate ((*R*)-(−)-24)**——This sample (mp 105.5—107 °C, $[\alpha]_D^{20}$ −13.1° ($c=0.95$, benzene)) was prepared in 41% yield by successive treatments of *S*-trityl-(*R*)-cysteine[20] with *p*-nitrobenzyl chloroformate (1 eq, dioxane–aq. NaOH), *p*-nitrobenzyl bromide (1 eq, TEA (1 eq), AcOEt, 80 °C), and 0.2 N HBr–AcOH (room temperature) followed by neutralization with $NaHCO_3$.

***p*-Nitrobenzyl (5*S*,2′*R*)-2-2′-*p*-nitrobenzyloxycarbonyl-2′-*p*-nitrobenzyloxycarbonylaminoethylthio-1-carba-2-penem-3-carboxylate ((5*S*,2′*R*)-(+)-21)**——A solution of *N*,*N*-diisopropylethylamine (0.068 ml, 0.39 mmol) in CH_3CN (0.5 ml) was added to a stirred solution of (3*R*,5*R*)-(+)-**20** (0.103 g, 0.34 mmol) in CH_3CN (2.5 ml) at −10—−8 °C over a period of 3 min followed by the addition of a solution of diphenyl phosphorochloridate (0.077 ml) in CH_3CN (0.5 ml) at the same temperature over a period of 3 min. The mixture was stirred at −10—−8 °C for 1 h, then a solution of *N*,*N*-diisopropylethylamine (0.077 ml) in CH_3CN (0.5 ml) and a solution of (*R*)-(−)-**24** (0.162 g, 0.373 mmol) in CH_3CN (3 ml) were added. Stirring was continued at −10 °C for 10 min, then 10 ml of ether was added and the whole was stirred at −5—0 °C for 2 h. The precipitate was collected and washed with ether to afford (5*S*,2′*R*)-(+)-**21** (0.118 g, yield 48%) as crystals, which were subjected to column chromatography (Florisil, benzene : AcOEt = 2 : 1) to give pure (5*S*,2′*R*)-(+)-**21** as a crystals, mp 143—147 °C (dec.), $[\alpha]_D^{20}$ +3° ($c=0.61$, DMF). IR ν_{max}^{KBr} cm^{-1}: 3320, 1790, 1735, 1690. NMR ($CDCl_3$): 2.9—3.75 (6H, m, C-1-H_{ab}, C-6-H_{ab}, S-$C\underline{H}_2CH$), 4.25 (1H, m, C-5-H), 4.7 (1H, m, $SCH_2C\underline{H}$), 5.29 (2H, s, $C\underline{H}_2C_6H_4NO_2$-*p*), 5.39 (2H, s, $C\underline{H}_2C_6H_4NO_2$-*p*), 5.31 and 5.52 (2H, AB, $J=15$ Hz, C-3-$COOC\underline{H}_2C_6H_4NO_2$-*p*), 7.32 (1H, NH), 7.55—8.4 (12H, aromatic protons). *Anal.* Calcd for $C_{32}H_{27}N_5O_{13}S_1$: C, 53.26; H, 3.77; N, 9.70. Found: C, 52.97; H, 3.73; N, 9.47.

References and Notes

1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
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17) All melting points are uncorrected. Infrared (IR) spectral measurements were performed with a JASCO DS-402G or a JASCO IRA-1 grating infrared spectrometer. Nuclear magnetic resonance (NMR) spectra were measured with a JNM-PS 100 (100 MHz) or a Hitachi R-24 (60 MHz) spectrometer. Data are reported in parts per million (ppm) downfield from internal tetramethylsilane. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were determined with a Yanaco OR-50 automatic polarimeter or a JASCO DIP-181. Mass spectrum (MS) were recorded with a JEOL JMS-01 SG-Z mass spectrometer. The organic solutions were dried over $MgSO_4$ before vacuum evaporation.

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