On Pyrrolidine Derivatives I.
An Efficient Synthesis of 3-Substituted (2S,5S)-Pyrrolidine-2,5-dicarboxylic Acids

Tsunetoshi Honma*, Yukio Tada, Ikuo Adachi, and Kikuo Igarashi

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku,
Osaka, 553, Japan
Received November 21, 1988

(2S,5S)-3-Alkylpyrrolidine-2,5-dicarboxylic acid derivatives I were stereoselectively synthesized by means of an efficient method starting from L-aspartic acid (1). Dieckmann reaction of 4-benzyl 1-t-butyl N-t-butyloxycarbonyl-N-ethoxycarbonylmethyl-L-aspartate (4) provided product 5 which consisted of a mixture of (2S,5S)- and (2R,5S)-1-t-butyloxycarbonyl-3-oxopyrrolidine-2,5-dicarboxylates in a ratio of 95:5. Treating 1-t-butyl 6-ethyl 2-L-(t-butyloxycarbonyl)amino-5-diazo-4-oxoadipate (8), prepared from 1, with rhodium(II) acetate dimer also afforded a good yield of 5. The Wittig reaction of 5, followed by catalytic hydrogenation and then deprotection provided compound I.

(2S,5S)-3-Alkylpyrrolidine-2,5-dicarboxylic acids I were prepared for studies on chemical modification of Enalapril [1], an antihypertensive drug with potent inhibitory activity on angiotensin converting enzyme (ACE). System I may couple with L-proline to provide compounds II, which structurally resemble Enalapril as a cyclic analog in the side chain with the same configuration and may be expected to exhibit potent inhibitory action on ACE (Chart 1).

Chart 1
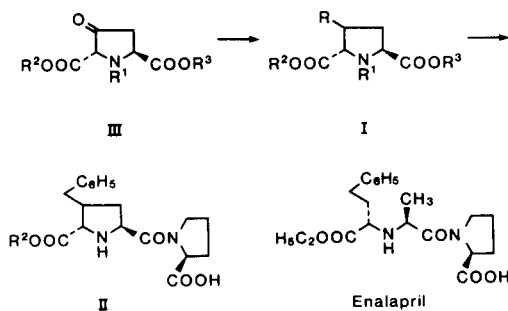
Although several studies have been conducted on the stereoselective synthesis of (2S,5S)-pyrrolidine-2,5-dicarboxylic acids [2], they have neglected the 3-substituted derivatives I. Here we report an efficient method for synthesizing system I stereoselectively through a course involving preparation of (2S,5S)-3-oxopyrrolidine-2,5-dicarboxylic acid derivatives III, starting from L-aspartic acid. For successful progress of the continuing reactions from III to II, we tried to prepare the unsymmetrical 2,5-diester derivatives, such as 5-t-butyl 2-ethyl 1-t-butyloxycarbonyl-3-oxopyrrolidine-2,5-dicarboxylate (5), which can be obtained by either Dieckmann reaction of the triester 4 (Method A) or cyclization of the diazo compound 8 (Method B), as shown in Chart 2. Compound 4 was obtained in 87% yield from the reaction of 4-benzyl 1-t-butyl L-aspartate (2) [3] with ethyl bromoacetate, followed by

treatment with di-t-butyldicarbonate. Compound 8 was obtained in quantitative yield from the diazotization of 1-t-butyl 6-ethyl 2-L-(t-butyloxycarbonyl)amino-4-oxoadipate (7), prepared from 1-t-butyl N-t-butyloxycarbonyl-L-aspartate (6) [4] by the ordinary methods [5] (Chart 2).

We first tried the Dieckmann reaction of compound 4 (Method A). Treating 4 with potassium t-butoxide in ether at -70° provided 5-t-butyl 2-ethyl 1-t-butyloxycarbonyl-3-oxopyrrolidine-2,5-dicarboxylate (5) in 36% yield. Another possible Dieckmann product, 3-benzyl 2-t-butyl 1-t-butyloxycarbonyl-4-oxopyrrolidine-2,3-dicarboxylate, was not obtained. The proposed structure of 5 agrees with the analytical data presented in the experimental. The ir spectrum of 5 in chloroform displayed a carbonyl band at 1778 cm^{-1} and no absorption in the enolate region, indicating that compound 5 mainly exists in the β-ketoester form in chloroform. The ^{1}H-nmr spectrum of 5 showed a pair of signals due to the C4 proton at δ 2.59 and 2.82 in a intensity ratio of 95:5, indicating that compound 5 exists as a mixture of C2 diastereoisomers, the major component of which is the 2S-enantiomer [6], in a ratio of 95:5. The specific rotation of 5 obtained by this method was $[\alpha]_D^{25}$ -9.6° (chloroform).

We also tried to prepare 5 by cyclization of the diazo compound 8 in neutral medium (Method B). Treating 8 with rhodium(II) acetate dimer in dichloromethane at room temperature provided 5 in 85% yield (Chart 2). The ^{1}H-nmr spectrum of the product indicated that it was a mixture of the diastereoisomers in a ratio of 95:5, which was the same as the compound 5 obtained by Method A. High-performance liquid chromatographic (hplc) analysis of the product also exhibited two peaks in an area ratio of 96:4 in the chromatogram. The product showed $[\alpha]_D^{25}$ -12.4° (chloroform), which was more negative than that of the product 5 obtained by Method A [7]. For stereoselective synthesis of the product 5 with the 2S,5S-configuration, Method B gave better results than Method A with
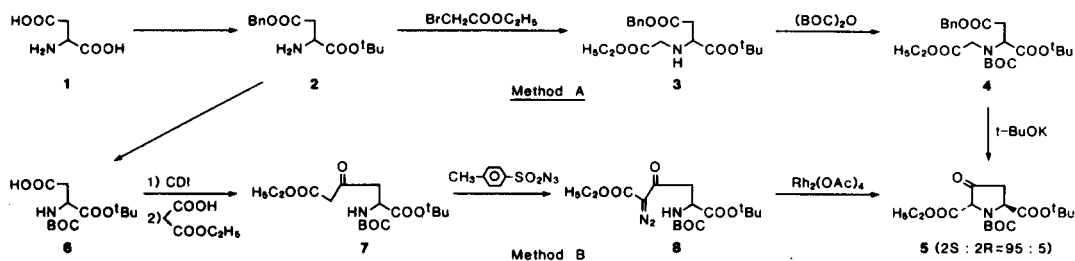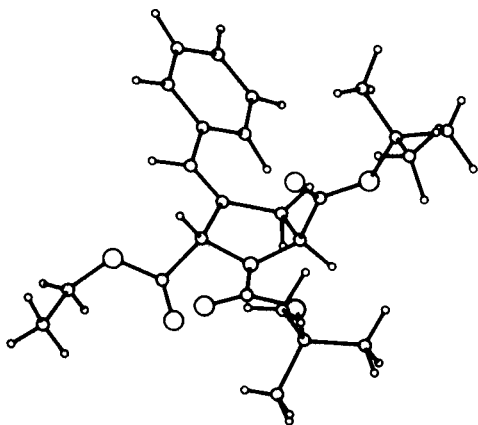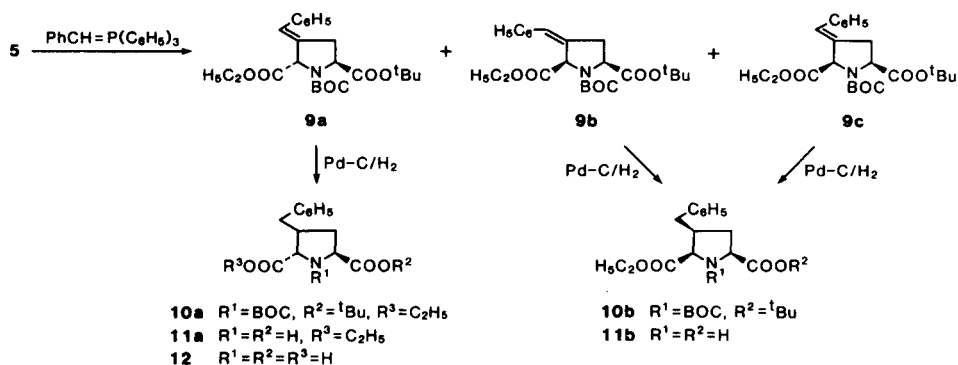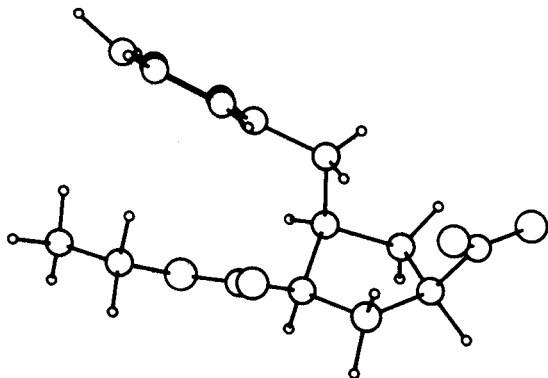
Chart 2

Chart 3

Fig. 1. X-ray crystal of **9a**.

respect to yield and optical purity. Further purification for the product from Method B by recrystallization from hexane gave a pure crystalline product which exhibited one peak in the hplc analysis and $[\alpha]_D^{25}$ -16.5° (chloroform).

Next, we tried to conduct the Wittig reaction of **5** with benzyltriphenylphosphonium chloride. The reaction readily proceeded at 0° to provide three products, **9a, b** and **c**, in 60, 11, and 8% yields, respectively (Chart 3). The structure of each product was proposed as shown in Chart 3 from the spectral data. The structure of **9a** was determined from X-ray crystallographic analysis to have the (2S,5S)(3E)-configuration (Figure 1). The minor products,

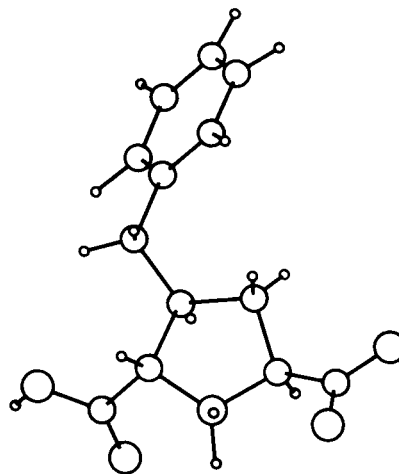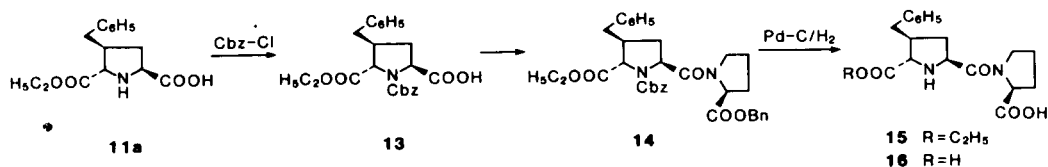Fig. 2. X-ray crystal of **11b**.

Fig. 3. X-ray crystal of **12**.

Chart 4

9b and **c**, were assigned as stereoisomer of **9a** with a 3-(Z)-and 3-(E)-benzylidene substituent, respectively, according to their ^{1}H-nmr spectra, which displayed each signal due to the vinyl proton at δ 6.52 for **9b** and 6.68 for **9c** [8]. They were also characterized as having the (2R,5S)-configuration because catalytic hydrogenation of each compound, **9b** and **c**, followed by treatment with trifluoroacetic acid provided the same product **11b** in excellent yields. The structure of **11b** was determined to be (2R,3S,5S)-3-benzylpyrrolidine-2,5-dicarboxylic acid 2-ethyl ester by X-ray crystallographic analysis (Chart 3 and Figure 2).

Thus, although the ratio for S:R in the C2 position slightly shifted to the R side in the course of the Wittig reaction from **5** to **9**, the 3-substituted (2S,5S)-pyrrolidine-2,5-dicarboxylic acid derivatives **I** could be stereoselectively synthesized.

Catalytic hydrogenation of **9a** with palladium on carbon provided an oily product **10a**, which when deprotected with trifluoroacetic acid afforded a crystalline product (Chart 3). Its ^{1}H-nmr spectrum indicated that it consisted of a mixture of the C3 diastereoisomers in a ratio of 85:15 on the basis of the intensities of the signals at δ 4.11 and 4.56 due to the C2 proton. Recrystallization from ethanol provided the enantiomerically pure compound **11a** in 72% yield. Alkalline hydrolysis of **11a** afforded an excellent yield of **12**, which was determined to be (2S,3S,5S)-3-benzylpyrrolidine-2,5-dicarboxylic acid by X-ray crystallographic analysis (Figure 3).

The present trials on pyrrolidine formation offered an efficient and convenient method for stereoselective synthesis of the (2S,5S)-3-alkylpyrrolidine-2,5-dicarboxylic acid derivatives **I**, starting from the readily available L-aspartic acid (**1**).

Finally, we synthesized the compounds **II** shown in Chart 1 and tested their ACE inhibitory activity. The reactions were conducted via the course shown in Chart 4 and the products **15** and **16**, were obtained in good yields. In ordinary tests [9] for evaluating the inhibitory effect on ACE, compounds **15** and **16** exhibited no activity.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus and were not corrected. Specific rotations were measured with a Perkin-Elmer Model 141 polarimeter.

Column chromatography was performed on column of silica gel Merck (70-230 mesh; E. Merck, Darmstadt, Germany) or prepacked LiChroprep Si 60 Merck (40-63 μm; E. Merck, Darmstadt, Germany). The ^{1}H-nmr spectra were recorded with a Varian EM-390 or VXR-200 nmr spectrometer, using TMS as an internal standard. The infrared spectra were measured using JASCO A-702 spectrometer. High-performance liquid chromatography (hplc) was carried out on a Shimadzu hplc system (LC-3A pump, SPD-2A detector).

4-Benzyl 1-t-Butyl N-Ethoxycarbonylmethyl-L-aspartate (3).

A solution of ethyl bromoacetate (30.0 g, 178 mmoles) in dimethylformamide (5 ml) was added dropwise to a solution of 4-benzyl 1-t-butyl L-aspartate (**2**) [3] (21.8 g, 78 mmoles) and triethylamine (23 ml, 165 mmoles) in dimethylformamide (65 ml). After stirring at room temperature for 30 minutes, the mixture was poured into water and the aqueous solution was extracted with benzene. The extract was washed with water, dried over magnesium sulfate and concentrated in vacuo to give an oil, which was chromatographed on silica gel eluting with benzene-acetone (19:1) to give **3** (25.92 g, 91%) as colorless oil; $[\alpha]_D^{25}$ -4.2° (c 1.51, chloroform); ir (chloroform): 3300, 1730 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, J = 7.1 Hz, 3H, ethyl CH$_3$), 1.42 (s, 9H, t-C$_4$H$_9$), 2.26 (s, 1H, NH), 2.75 (d, J = 6.0 Hz, 2H, H-3), 3.45 (s, 2H, N-CH$_2$), 3.60 (t, J = 6.0 Hz, 1H, H-2), 4.18 (q, J = 7.1 Hz, 2H, ethyl CH$_2$), 5.13 (s, 2H, benzyl CH$_2$), 7.35 (s, 5H, Ar H).

4-Benzyl 1-t-Butyl N-t-Butyloxycarbonyl-N-ethoxycarbonyl-methyl-L-aspartate (4).

A mixture of **3** (575 mg, 1.57 mmoles), di-t-butyldicarbonate (1.118 g, 5.1 mmoles) and triethylamine (0.24 ml, 1.73 mmoles) in 50% aqueous dioxane (3 ml) was stirred at 50° for 8 hours, and then poured into ice-water. The aqueous solution was extracted with benzene. The extract was washed with water, dried over magnesium sulfate and concentrated to give an oil, which was chromatographed on silica gel eluting with n-hexane-acetone (9:1) to give **4** (704 mg, 96%) as a colorless oil, $[\alpha]_D^{25}$ -15.7° (c 1.05, chloroform); ir (chloroform): 1750, 1735, 1703 cm^{-1}. The ^{1}H-nmr spectrum (deuteriochloroform) indicated that it consisted of a mixture of the syn and anti rotamers: δ 1.24, 1.25 (2t, J = 7.1 Hz, 6H, ethyl CH$_3$), 1.42, 1.44, 1.46 (3s, 36H, t-C$_4$H$_9$), 2.91 (dd, J = 7.1 and 5.0 Hz, 1H, H-3a), 2.92 (dd, J = 17.1 and 6.4 Hz, 1H, H-3a), 3.14 (dd, J = 17.1 and 6.4 Hz, 1H, H-3b), 3.18 (dd, J = 17.1 and 7.9 Hz, 1H, H-3b), 3.87, 3.92, 4.06, 4.27 (4d, J = 17.9 Hz, 4H, N-CH$_2$), 4.13, 4.15 (2q, J = 7.1 Hz, 4H, ethyl CH$_2$), 4.48 (dd, J = 7.9 and 5.0 Hz, 1H, H-2), 4.75 (t, J = 6.4 Hz, 1H, H-2), 5.07, 5.09, 5.15, 5.18 (4d, J = 12.1 Hz, 4H, benzyl CH$_2$), 7.34, 7.35 (2s, 10H, Ar H).

Anal. Calcd. for C$_{24}$H$_{35}$NO$_8$: C, 61.92; H, 7.58; N, 3.01. Found: C, 61.98; H, 7.45; N, 2.98.

1-t-Butyl 6-Ethyl 2-L(t-Butyloxycarbonyl)amino-4-oxoadipate (7).

A solution of 1-t-butyl N-t-butyloxycarbonyl-L-aspartate (**6**) [4]

(7.275 g, 25.1 mmoles) and N,N'-carbonyldiimidazole (4.893 g, 30.2 mmoles) in anhydrous tetrahydrofuran (100 ml) was kept at room temperature for 12 hours to give an imidazolide solution. To a solution of isopropylmagnesium bromide in tetrahydrofuran, prepared from isopropyl bromide (7.32 ml, 77.9 mmoles), metal magnesium (1.833 g, 75.4 mmoles) and tetrahydrofuran (50 ml) by the ordinary method, a solution of hydrogen ethyl malonate (4.982 g, 37.7 mmoles) in tetrahydrofuran (5 ml) was added dropwise at 0°. The mixture was stirred successively at 0° for 30 minutes, at room temperature for 30 minutes and at 40° for 30 minutes. To this solution was added dropwise the imidazolide solution at 0°. The mixture, after stirring at 0° for 30 minutes and then at room temperature for 18 hours, was diluted with chloroform (150 ml) and poured into ice-water. The solution was acidified with 10% hydrochloric acid to pH 2.8 and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel eluting with *n*-hexane-ethyl acetate (6:1) to give **7** (7.786 g, 86%) as a crystalline solid. Recrystallization from *n*-hexane-ether gave pure **7** (7.473 g, 83% as a colorless needles, mp 57-58°; $[\alpha]_D^{22}$ +21.4° (c 1.01, chloroform); ir (Nujol): 3410, 1753, 1733, 1720, 1518 cm^{-1}; ^{1}H-nmr (deuteriochloroform-deuteriomethanol): δ 1.28 (t, J = 7.1 Hz, 3H, ethyl CH$_3$), 1.45 (s, 18H, t-C$_4$H$_9$), 3.03, 3.23 (2dd, J = 18.2 and 4.5 Hz, 2H, H-3), 3.45 (s, 2H, H-5), 4.20 (q, J = 7.1 Hz, 2H, ethyl CH$_2$), 4.39 (t, J = 4.5 Hz, 1H, H-2).

Anal. Calcd. for C$_{17}$H$_{29}$NO$_7$: C, 56.81; H, 8.13; N, 3.90. Found: C, 56.61; H, 8.17; N, 3.95.

1-*t*-Butyl 6-Ethyl 2-L-(*t*-Butyloxycarbonyl)amino-5-diazo-4-oxo-adipate (8).

A solution of **7** (7.313 g, 20.4 mmoles) in acetonitrile (37 ml) was added to a solution of *p*-toluenesulfonyl azide (4.415 g, 22.4 mmoles) and triethylamine (4.12 g, 40.7 mmoles) in acetonitrile (8 ml) and the mixture was stirred for 1 hour. The reaction mixture was poured into ice-water and the aqueous solution was extracted with ether. The extract was washed successively with water, 10% hydrochloric acid, and water, dried over magnesium sulfate and concentrated *in vacuo* to give **8** (7.843 g, quantitative yield) as a yellow oil, which was used for the following reaction without further purification. A small amount of this product was purified by column chromatography on silica gel eluting with *n*-hexane-ethyl acetate (8:1) to give a yellow oil, $[\alpha]_D^{25}$ +42.3° (c 1.34, chloroform); ir (chloroform): 3440, 2140, 1710, 1622 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.31 (t, J = 7.1 Hz, 3H, ethyl CH$_3$), 1.43 (s, 18H, t-C$_4$H$_9$), 3.22, 3.52 (2dd, J = 18.2 and 4.5 Hz, 2H, H-3), 4.31 (q, J = 7.1 Hz, 2H, ethyl CH$_2$), 4.56 (t, J = 4.5 Hz, 1H, H-2), 5.44 (broad s, 1H, NH).

5-*t*-Butyl 2-Ethyl (2S,5S)-1-*t*-Butyloxycarbonyl-3-oxopyrrolidine-2,5-dicarboxylate (5).

Method A.

Potassium *t*-butoxide (2.03 g, 18.1 mmoles) was added portion-wise to a solution of **4** (6.74 g, 14.5 mmoles) in anhydrous ether (111 ml) under stirring at -70°. The mixture, after stirring at -70° for 45 minutes, was quenched with acetic acid (1.086 g, 18.1 mmoles) and poured into ice-water. The aqueous solution was extracted with *n*-hexane. The extract was washed successively with water, saturated sodium bicarbonate solution and water, dried over magnesium sulfate, and concentrated *in vacuo* to give **5** (1.868 g, 36%) as a colorless oil, $[\alpha]_D^{25}$ -9.6° (c 1.07, chloroform);

ir (chloroform): 1778, 1742, 1710 cm^{-1}; the ^{1}H-nmr spectrum (deuteriochloroform) indicated that it consisted of a mixture of the diastereomeric and rotational isomers: δ 1.30, 1.31 (2t, J = 7.1 Hz, 6H, ethyl CH$_3$), 1.44, 1.45, 1.46, 1.47 (4s, 36H, t-C$_4$H$_9$), 2.59 (dd, J = 18.6 and 2.8 Hz, 1.9H, H-4a), 2.82 (m, 0.2H, H-4a and b), 3.02, 3.07 (2dd, J = 18.6 and 10.2 Hz, 1.9H, H-4b), 4.18-4.34 (m, 4H, ethyl CH$_2$), 4.56, 4.61 (2s, 2H, H-2), 4.64, 4.70 (2dd, J = 10.2 and 2.8 Hz, 2H, H-5).

Method B.

A solution of **8** (7.843 g, 20.35 mmoles) and rhodium(II) acetate dimer (157 mg) in dry dichloromethane (200 ml) was stirred at room temperature for 2.5 hours, and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel eluting with dichloromethane-acetonitrile (97:3) to give **5** (6.197 g, 85%) as a crystalline solid, mp 52-60°; $[\alpha]_D^{25}$ -12.4° (c 1.27, chloroform); hplc (TSK gel ODS-120T column, 4.6 mm x 25 cm; acetonitrile-water, 4:1; 1.0 ml/minute) t$_R$: 5.0 minutes (the 2S-enantiomer), 4.9 minutes (the 2R-enantiomer) (ratio of both peaks, 96:4); ^{1}H-nmr and ir spectrum of this compound were identical with those of **5** prepared by the Method A. Recrystallization from *n*-hexane gave the 2S-enantiomer as a colorless needles, mp 69-70°; $[\alpha]_D^{22}$ -16.4° (c 1.09, chloroform); hplc t$_R$: 5.0 minutes.

Anal. Calcd. for C$_{17}$H$_{27}$NO$_7$: C, 57.13; H, 7.62; N, 3.92. Found: C, 57.01; H, 7.60; N, 4.00.

The mother liquid was concentrated and the crystalline solid was recrystallized from *n*-hexane to give the 2R-enantiomer as a colorless prisms, mp 92-95°; $[\alpha]_D^{24}$ +16.2° (c 1.01, chloroform); ir (chloroform): 1770, 1751, 1708 cm^{-1}; hplc t$_R$: 4.9 minutes.

Anal. Calcd. for C$_{17}$H$_{27}$NO$_7$: C, 57.13; H, 7.62; N, 3.92. Found: C, 57.08; H, 7.53; N, 3.92.

Reaction of **5** with Benzyltriphenylphosphorane.

Potassium *t*-butoxide (2.714 g, 24.18 mmoles) was added portionwise to a solution of benzyltriphenylphosphonium chloride (10.447 g, 26.9 mmoles) in dry dichloromethane (220 ml) under stirring, and the mixture was stirred at room temperature for 1 hour. The insoluble materials were filtered off and washed with a small amount of dichloromethane. To the combined filtrate and washing, a solution of **5** (4.801 g, 13.43 mmoles), prepared from **8**, in dichloromethane (10 ml) was added dropwise at 0° and the mixture was stirred at 0° for 4 hours and then poured into ice-water. After extracting with dichloromethane, the extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo* to give an oil. The oily residue was dissolved in a small amount of chloroform and the solution was diluted with *n*-hexane to deposit crystalline triphenylphosphine oxide. After removal of the precipitates by filtration, the filtrate was concentrated *in vacuo* to dryness. The residue was purified by repeating chromatography on silica gel eluting with *n*-hexane-ethyl acetate (12:1). The first fraction gave 5-*t*-butyl 2-ethyl (2R,5S)-1-*t*-butyl-oxycarbonyl-(3Z)-benzylidenepyrrolidine-2,5-dicarboxylate (9b) (618 mg, 11%) as a colorless oil; $[\alpha]_D^{23}$ -250.8° (c 1.25, chloroform); ir (chloroform): 1737, 1700 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.2-1.3 (m, 3H, ethyl CH$_3$), 1.30, 1.41, 1.44, 1.51 (4s, 18H, t-C$_4$H$_9$), 2.9-3.2 (m, 2H, H-4a and b), 4.1-4.3 (m, 3H, ethyl CH$_2$ and H-5), 5.03, 5.24 (2s, 1H, H-2), 6.52 (s, 1H, CH=), 7.2-7.5 (m, 5H, Ar H).

The second fraction gave 5-*t*-butyl 2-ethyl (2R,5S)-1-*t*-butyloxy-carbonyl(3E)-benzylidenepyrrolidine-2,5-dicarboxylate (9c) (449 mg, 8%) as a colorless oil; $[\alpha]_D^{23}$ -1.0° (c 1.23, chloroform); ir

(chloroform): 1750, 1701 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 1.2-1.4 (m, 3H, ethyl CH₃), 1.47, 1.50, 1.51 (3s, 18H, t-C₄H₉), 2.9-3.3 (m, 2H, H-4a and b), 4.1-4.4 (m, 3H, ethyl CH₂ and H-5), 4.89, 4.99 (2s, 1H, H-2), 6.68 (broad s, 1H, CH=), 7.24-7.4 (m, 5H, Ar H).

The third fraction gave 5-t-butyl 2-ethyl (2S,5S)-1-t-butyloxycarbonyl-(3E)-benzylidenepyrrolidine-2,5-dicarboxylate (**9a**) (3.468 g, 60%) as a crystalline solid. Recrystallization from *n*-hexane gave colorless prisms, mp 91-92°; [α]_D²³ +13.5° (c 1.14, chloroform); ir (Nujol): 1755, 1741, 1705 cm⁻¹; the ¹H-nmr spectrum (deuteriochloroform) indicated that it consisted of a mixture of the *syn* and *anti* rotamers; δ 1.27, 1.29 (2t, J = 7.0 Hz, 6H, ethyl CH₃), 1.37, 1.45, 1.46 (3s, 36H, t-C₄H₉), 2.86, 2.94 (broad d, J = 16.2 Hz, 2H, H-4a), 3.15-3.4 (m, 2H, H-4b), 4.1-4.35 (m, 4H, ethyl CH₂), 4.52 (dd, J = 10.0 and 1.7 Hz, 1H, H-5), 4.60 (dd, 9.6 and 2.2 Hz, 1H, H-5), 4.92 (t, J = 1.7 Hz, 1H, H-2), 4.98 (t, J = 2.2 Hz, 1H, H-2), 6.70 (broad s, 2H, CH=), 7.2-7.4 (m, 10H, Ar H).

Anal. Cald. for C₂₄H₃₃NO₆: C, 66.80; H, 7.71; N, 3.25. Found: C, 66.83; H, 7.72; N, 3.22.

Hydrogenation of 9a.

A solution of **9a** (500 mg, 1.16 mmoles) in ethanol (13.6 ml) was hydrogenated over 10% palladium on carbon (50 mg) for 30 minutes at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give 5-t-butyl 2-ethyl (2S,5S)-1-t-butyloxycarbonyl-3-benzylpyrrolidine-2,5-dicarboxylate (**10a**) (502 mg) as an oil, the hplc analysis of which showed that it was a mixture of the C3 diastereoisomers in a ratio of 85:15; hplc (LiChrosorb₅ Si, 60; 4.6 mm x 2.5 cm; *n*-hexane-ethyl acetate, 9:1; 1.0 ml/minute) t_R: 12.6 minutes (the 3S-enantiomer), 12.0 minutes (the 3R-enantiomer); [α]_D²³ −23.4° (c 1.22, chloroform); (3S)-isomer; the ¹H-nmr spectrum (deuteriobenzene) indicated that it considered of a mixture of the *syn* and *anti* rotamers: δ 0.92, 0.94 (2t, J = 7.0 Hz, 6H, ethyl CH₃), 1.38, 1.43, 1.44, 1.49 (4s, 36H, t-C₄H₉), 1.6-1.75 (m, 2H, H-4a), 2.0-2.3 (m, 2H, H-4b), 2.35-2.55 (m, 2H, H-3), 2.55-2.9 (m, 4H, benzyl CH₂), 3.8-4.05 (m, 4H, ethyl CH₂), 4.33 (d, J = 4.2 Hz, 1H, H-2), 4.46 (dd, J = 10.3 and 3.6 Hz, 1H, H-5), 4.57 (d, J = 3.0 Hz, 1H, H-2), 4.58 (dd, J = 9.3 and 5.3 Hz, 1H, H-5), 6.9-7.1 (m, 10H, Ar H); (3R)-isomer; the ¹H-nmr spectrum (deuteriobenzene) indicated that it consisted of a mixture of the *syn* and *anti* rotamers: δ 0.96, 0.93 (2t, J = 7.0 Hz, 6H, ethyl CH₃), 1.25, 1.27, 1.42, 1.45 (4s, 36H, t-C₄H₉), 1.6-1.9 (m, 2H, H-4a), 2.0-2.3 (m, 2H, H-4b), 2.8-3.0 (m, 6H, benzyl CH₂ and H-3), 3.9-4.1 (m, 4H, ethyl CH₂), 4.57 (d, J = 8.8 Hz, 1H, H-5), 4.63 (d, J = 8.4 Hz, 1H, H-2), 4.77 (dd, J = 9.6 and 0.9 Hz, 1H, H-5), 4.87 (d, J = 8.2 Hz, 1H, H-2), 6.8-6.9 (m, 10H, Ar H).

(2S,3S,5S)-3-Benzylpyrrolidine-2,5-dicarboxylic Acid 2-Ethyl Ester (11a).

A solution of **10a** (139 mg, 0.32 mmole) in trifluoroacetic acid (2.8 ml) was stirred at room temperature for 5 hours, and then concentrated *in vacuo*. The residue was adsorbed on a HP-20 resin column previously equilibrated with water, and eluted successively with water and 50% aqueous methanol. The eluates from 50% aqueous methanol were concentrated *in vacuo* to give a crystalline solid. Recrystallization from ethanol gave **11a** (64 mg, 72%) as colorless needles, mp 161-162°; [α]_D²⁴ −4.3° (c 1.02, methanol); ir (Nujol): 3200-2000, 1760, 1740, 1639, 1600 cm⁻¹; ¹H-nmr (deuteriochloroform-deuteriomethanol): δ 1.27 (t, J = 7.1 Hz, 3H, ethyl CH₃), 1.87 (dt, J = 12.8 and 8.4 Hz, 1H, H-4a), 2.34 (dt, J = 12.8 and 8.4 Hz, 1H, H-4b), 2.5-2.75 (m, 2H, H-3 and ben-

zyl CH₂), 3.08 (dd, J = 12.6 and 4.2 Hz, 1H, benzyl CH₂), 4.06 (t, J = 8.4 Hz, 1H, H-5), 4.11 (d, J = 7.3 Hz, 1H, H-2), 4.22 (q, J = 7.1 Hz, 2H, ethyl CH₂), 7.1-7.35 (m, 5H, Ar H).

Anal. Calcd. for C₁₅H₁₉NO₄: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.96; H, 7.01; N, 4.98.

(2S,3S,5S)-3-Benzylpyrrolidine-2,5-dicarboxylic Acid (12).

A solution of **11a** (85 mg, 0.31 mmole) in 1 *N* aqueous sodium hydroxide (0.93 ml) was stirred at room temperature for 30 minutes, and then quenched with 1 *N* hydrochloric acid (0.93 ml). The precipitated crystalline solid was collected by filtration, washed with water and recrystallized from water give **12** (69 mg, 91%) as colorless plates, mp 276-277° dec; [α]_D²³ +36.3° (c, 0.68, 1 *N* hydrochloric acid); ir (Nujol): 3160, 3040, 1710, 1582 cm⁻¹; ¹H-nmr (diluted deuteriosulfuric acid): δ 1.78 (dt, J = 13.9 and 9.2 Hz, 1H, H-4a), 2.28 (dt, J = 13.9 and 8.0 Hz, 1H, H-4b), 2.54 (dd, J = 13.0 and 9.2 Hz, 1H, benzyl CH₂), 2.6-2.8 (m, 1H, H-3), 2.97 (dd, J = 13.0 and 4.4 Hz, 1H, benzyl CH₂), 4.04 (d, J = 8.4 Hz, 1H, H-2), 4.29 (dd, J = 9.2 and 8.0 Hz, 1H, H-5), 7.0-7.3 (m, 5H, Ar H).

Anal. Calcd. for C₁₃H₁₅NO₄: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.52; H, 6.23; N, 5.78.

Hydrogenation of 9b and 9c.

Compound **9b** (100 mg) was hydrogenated in a manner similar to that described above for preparing **10a** to give the (2R,5S)-isomer of **10a** (**10b**) (89 mg, 89%) as a crystalline solid, mp 76-80°. Recrystallization from *n*-hexane gave colorless needles, mp 85-86°; [α]_D³¹ −10.7° (c 1.24, chloroform); ir (Nujol): 1748, 1700 cm⁻¹; the ¹H-nmr spectrum (deuteriochloroform) indicated that it consisted of a mixture of the *syn* and *anti* rotamers: δ 1.29, 1.32 (2t, J = 7.1 Hz, 6H, ethyl CH₃), 1.43, 1.46, 1.48, 1.49 (4s, 36H, t-C₄H₉), 1.9-2.3 (m, 4H, H-4), 2.3-2.45, 2.8-3.0 (m, 4H, benzyl CH₂), 2.5-2.8 (m, 2H, H-3), 4.0-4.15 (m, 2H, H-5), 4.15-4.3 (m, 4H, ethyl CH₂), 4.38 (d, J = 8.2 Hz, 1H, H-2), 4.50 (d, J = 8.0 Hz, 1H, H-2), 7.1-7.4 (m, 10H, Ar H).

Anal. Calcd. for C₂₄H₃₅NO₆: C, 66.49; H, 8.14; N, 3.24. Found: C, 66.49; H, 8.06; N, 3.32.

Treatment of **9c** in a manner similar to that described above gave 89% yield of **10b**, which was identical with the sample obtained from **9b** by comparison of their ir and ¹H-nmr spectra.

(2R,3S,5S)-3-Benzylpyrrolidine-2,5-dicarboxylic Acid 2-Ethyl Ester (11b).

Compound **10b** (164 mg) was treated in a manner similar to that described above for preparing **11a** to give **11b** (90 mg, 86%) as a crystalline solid. Recrystallization from ethanol gave colorless prisms, mp 171-172°; [α]_D²¹ −5.5° (c 1.06, methanol); ir (Nujol): 3060, 1733, 1727, 1620, 1598 cm⁻¹; ¹H-nmr (deuteriomethanol): δ 1.30 (t, J = 7.0 Hz, 3H, ethyl CH₃), 1.8-3.2 (m, 5H, H-3, H-4a, b and benzyl CH₂), 4.05 (dd, J = 9.0 and 6.0 Hz, 1H, H-5), 4.30 (q, J = 7.0 Hz, 2H, ethyl CH₂), 4.52 (d, J = 7.0 Hz, 1H, H-2), 7.1-7.4 (m, 5H, Ar H).

Anal. Calcd. for C₁₅H₁₉NO₄: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.82; H, 6.87; N, 5.11.

(2S,3S,5S)-1-Benzyloxycarbonyl-3-benzylpyrrolidine-2,5-dicarboxylic Acid 2-Ethyl Ester (13).

A solution of benzyloxycarbonyl chloride (215 mg, 1.25 mmoles) in dioxane (1 ml) was added to a solution of **11a** (250 mg, 0.76 mmole) and sodium bicarbonate (132 mg, 1.57 mmoles) in 37% aqueous dioxane (9.7 ml). After stirring at room tempera-

ture for 2 hours, the reaction mixture was poured into ice-water. The aqueous solution was acidified to pH 1 with 10% hydrochloric acid and extracted with benzene. The extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo* to give an oil, which was chromatographed on silica gel eluting with chloroform-methanol (9:1) to give **13** (279 mg, 90%) as a colorless amorphous solid; $[\alpha]_D^{24}$ -22.4° (c 1.27, methanol); ir (chloroform): 3600-2300, 1735, 1703 cm^{-1}.

Benzyl (2S,3S,5S)-N-(1-Benzyloxycarbonyl-3-benzyl-2-carbo-ethoxypyrrolidine-5-carbonyl)-L-prolinate (14).

A solution of N,N'-dicyclohexylcarbodiimide (228 mg, 1.1 mmoles) in tetrahydrofuran (3 ml) was added to a solution of **13** (279 mg, 0.68 mmole), benzyl L-prolinate hydrochloride (185 mg, 0.77 mmole), 1-hydroxybenzotriazole (9 mg) and triethylamine (78 mg, 0.77 mmole) in dimethylformamide (5.2 ml) with stirring at room temperature, and the mixture was stirred for 5 hours. After removal of the precipitated crystalline solid by filtration, the filtrate was dissolved in benzene. The solution was washed successively with water, 10% hydrochloric acid and water, dried over magnesium sulfate and concentrated to dryness. The residue was chromatographed on silica gel eluting with *n*-hexane-acetone (4:1) to give **14** (326 mg, 80%), $[\alpha]_D^{22}$ -67.3° (c 1.39, methanol); ir (chloroform): 1740, 1703, 1660 cm^{-1}.

Anal. Calcd. for $C_{35}H_{38}N_2O_7 \cdot 2H_2O$: C, 69.79; H, 6.43; N, 4.65. Found: C, 69.78; H, 6.50; N, 4.73.

(2S,3S,5S)-N-(3-Benzyl-2-ethoxycarbonylpyrrolidine-5-carbonyl)-L-proline Hydrochloride (15).

A solution of **14** (206 mg, 0.34 mmole) in 0.1 N hydrochloric acid (3.4 ml) and dioxane (7 ml) was hydrogenated over 10% palladium on carbon (30 mg) for 1 hour at room temperature under atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give **15** (135 mg, 95%) as a colorless amorphous solid; $[\alpha]_D^{20}$ -39.9° (c 1.04, methanol).

(2S,3S,5S)-N-(3-Benzyl-2-carboxypyrrolidine-5-carbonyl)-L-proline (16).

A solution of **15** (135 mg, 0.33 mmole) in 1 N aqueous sodium hydroxide (1.4 ml) was stirred at room temperature for 1 hour, then acidified to pH 1 with 1N hydrochloric acid, adsorbed on a HP-20 resin column, previously equilibrated with water, and

eluted successively with water and 50% aqueous methanol. The eluates from 50% aqueous methanol were concentrated *in vacuo* to give **16** (83 mg, 74%) as a colorless amorphous solid; $[\alpha]_D^{23}$ -58.5° (c 0.66, water); ir (potassium bromide): 3700, 1720, 1640 cm^{-1}.

Anal. Calcd. for $C_{18}H_{22}N_2O_5 \cdot 0.7H_2O$: C, 60.22; H, 6.57; N, 7.80. Found: C, 60.27; H, 6.59; N, 7.82.

REFERENCES AND NOTES

[1] A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, M. T. Wu, D. Taub, E. R. Peterson, T. J. Ikeler, J. Ten Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N. S. Lohr, R. D. Hoffsommer, H. Joshua, W. V. Ruyle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson and R. Hirschmann, *Nature* (London) **288**, 280 (1980).

[2a] G. Impellizzeri, S. Mangiafico, G. Oriente, M. Piattelli, S. Sciuto, E. Fattorusso, S. Magno, C. Santacroce and D. Sica, *Phytochemistry*, **14**, 1549 (1975); [b] T. Ohta, A. Hosoi, T. Kimura and S. Nozoe, *Chem. Letters*, 2091 (1987); [c] Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki and M. Yamaguchi, *Tetrahedron Letters*, **25**, 857 (1987); [d] Y. Morimoto, Y. Terao and K. Achiwa, *Chem. Pharm. Bull.*, **35**, 2266 (1987); [e]F. Björkling, J. Boutelje, M. Hjalmarsson K. Hult and T. Norin, *J. Chem. Soc., Chem. Commun.*, 1041 (1987).

[3] R. Roeske, *J. Org. Chem.*, **28**, 1251 (1963).

[4] C. C. Yang and R. B. Merrifield, *J. Org. Chem.*, **41**, 1032 (1976).

[5] M. P. Moyer, P. L. Feldman and H. Rapoport, *J. Org. Chem.*, **50**, 5223 (1985).

[6] The (2S,5S)-enantiomer may have sterically more stable form than that of the (2R,5S)-isomer, because the steric interaction between the C2 and C5 ester groups is less in the 2S,5S configuration than that of the 2R,5S. So it may result in the dominant formation of the (2S)-enantiomer.

[7] Increasing value in the special optical rotation of the product **5** obtained by Method A suggests that partial racemization at the C5 position of **5** occurs under the strong alkaline condition employed.

[8] It has been known that the signal due to a vinyl proton near the carbonyl group appears in the lower fields in the ^{1}H-nmr spectrum. See: A. P. Morgenstern, C. Schutij and W. Th. Nauta, *Chem. Commun.*, 321 (1969).

[9] M. Hayakari, T. Kondo and H. Izumi, *Anal. Biochem.*, **84**, 361 (1978).