Sterically Controlled Synthesis of Aspartic Acid by Addition of Dialkyl Malonate to *N*-Benzyloxycarbonyl-L-alanyl-2-chloroglycine Methyl Ester

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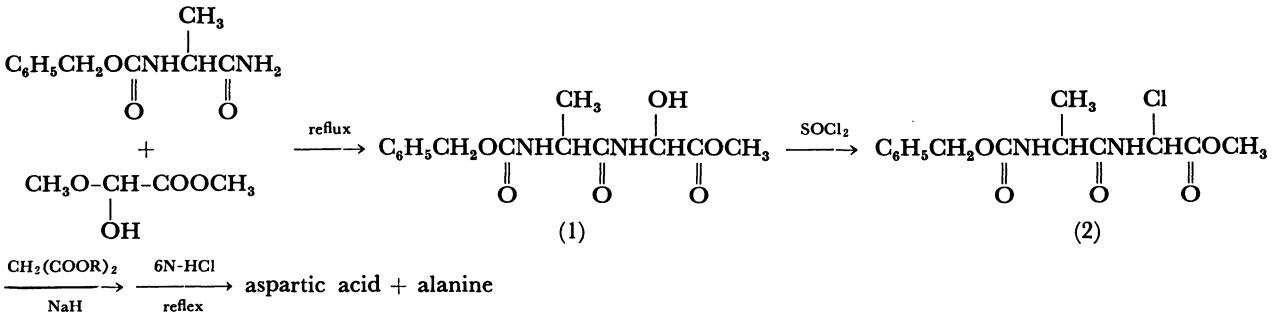
Synopsis. Aspartic acid was synthesized stereoselectively by addition of dialkyl malonate to *N*-benzyloxycarbonyl-L-alanyl-2-chloroglycine methyl ester, followed by hydrolysis. Substituent effect of the alkyl group of dialkyl malonate on the stereoselectivity was observed. Higher optical purity of aspartic acid was obtained as the alkyl group of dialkyl malonate became bulkier.

Several studies on the asymmetric addition reactions of malonic acid ester have been reported.[1-3] Recently, the preparation of *N*-benzyloxycarbonyl-3-carboxy-aspartic acid derivatives from *N*-benzyloxycarbonyl-2-chloroglycine methyl ester was reported.[4] In the present paper, we describe a sterically controlled synthesis of aspartic acid by the addition of dialkyl malonate to *N*-benzyloxycarbonyl-L-alanyl-2-chloroglycine methyl ester (Z-L-Ala-Cl-Gly-OMe)(**2**), which was obtained from *N*-benzyloxycarbonyl-L-alanyl-2-hydroxyglycine methyl ester (Z-L-Ala-OH-Gly-OMe) (**1**) by treatment with thionyl chloride, followed by hydrolysis (Scheme 1).

The results are summarized in Table 1. Dimethyl malonate reacted with compound **2** in THF at −10 °C and aspartic acid was obtained with 29% enantiomeric excess after hydrolysis (Table 1, entry 1). Substituent effect of the ester residue of malonic acid on the stereoselectivity was observed. As the ester residue of malonic acid became bulkier, the optical purity of aspartic acid obtained became higher. When di-*t*-butyl malonate was used, the optical purity of the resulting aspartic acid reached 48% enantiomeric excess (Table 1, entry 6).

The sterically controlled synthesis of aspartic acid shown in Scheme 1 involves three stereochemical steps in which the configuration of the product would be controlled by each reaction. These are: 1) the condensation reaction between *N*-benzyloxycarbonyl-L-alaninamide with methyl glyoxylate hemiacetal to form compound **1**, 2) the chlorination reaction of compound **1** to form compound **2**, and 3) the coupling reaction of compound **2** with dialkyl malonate.

In order to examine the asymmetric induction in the condensation reaction between *N*-benzyloxycarbonyl-L-alaninamide with methyl glyoxylate hemiacetal, the diastereomeric ratio of synthesized compound **1** was determined by HPLC. Though the configuration of each diastereomer, which was separated by HPLC, was unknown, the diastereomer eluted first on HPLC ver-



Scheme 1.

TABLE 1. ASPARTIC ACID OBTAINED BY SUCCESSIVE REACTIONS FROM **1**

Entry	d.r.[a]	Ester residue[b]	Temp/°C[c]	Solvent[d]	c.y./%[e]	e.e/%[f]	Confign.[g]
1	56 : 44	Me	−10	THF	48	29	S
2	74 : 26	Me	−10	THF	37	32	S
3	56 : 44	Me	−30	THF	57	32	S
4	56 : 44	Me	−10	diglyme	65	37	S
5	56 : 44	Et	−10	THF	41	33	S
6	56 : 44	*t*-Bu	−10	THF	37	48	S

a) Diastereomeric ratio of Z-L-Ala-OH-Gly-OMe. b) Ester residue of malonic acid. c) Reaction temperature in the addition reaction of dialkyl malonate. d) Solvent used in the addition reaction of dialkyl malonate. e) Chemical yield based on Z-L-Ala-OH-Gly-OMe. f) Enantiomeric excess of aspartic acid obtained. g) Configuration of aspartic acid.

sus that eluted second was 54:46. Compound **1** was recrystallized twice, and the diastereomeric ratios after first and second recrystallization were found to be 56:44 and 74:26, respectively. These were converted to compound **2**, and **2** was allowed to react with sodium salt of dimethyl malonate without purification to avoid diastereomeric fractionation. The enantiomeric excess of the resulting aspartic acid was 29% and 32%, respectively (Table 1, entry 1 and 2). These results indicate that the enantiomeric ratio of aspartic acid does not depend strongly on the diastereomeric ratio of Z-L-Ala-OH-Gly-OMe.

The stereochemistry of the chlorination reaction of compound **1** was not examined. The chemical property of compound **2** was too labile to determine the diastereomeric ratio by using HPLC. Therefore, the stereochemical relation between compound **2** and aspartic acid was unknown.

The substituent effect of the alkyl group of dialkyl malonate on the stereoselectivity shown in Table 1 indicates that the reaction with dialkyl malonate could be an important stereochemical step in the synthesis of optically active aspartic acid.

Experimental

All the melting points were uncorrected. NMR spectra were obtained with a Hitachi R-24A spectrometer and the chemical shifts were given in δ values (ppm) from tetramethylsilane (TMS). All the gas chromatographic analyses were carried out with a Hitachi 163 gas chromatograph. HPLC was carried out on a Jasco component consisting of a TRI ROTAR-V pump and a UVIDEC-100-IV UV spectrometer using a OA-1000 column. Amino acid analyses were carried out with a Hitachi 835-50 instrument.

Preparation of Z-L-Ala-OH-Gly-OMe (1). *N*-Benzyloxycarbonyl-L-alaninamide (0.88 g, 4×10^{-3} mol) was suspended in 10 ml of benzene, and methyl glyoxylate hemiacetal (0.48 g, 4×10^{-3} mol) was added to the suspension. The reaction mixture was refluxed for 3 d and then concentrated *in vacuo*. The residue was purified by column chromatography on silica gel using $CHCl_3$–MeOH (19:1 v/v) as an eluent. The solid obtained was recrystallized from hexane–ethyl acetate, yield 0.77 g (62%), mp 105—110 °C, ^{1}H NMR (CD_3OD): δ=1.33 (d, 3H), 3.69 (s, 3H), 4.12 (q, 1H), 5.02 (s, 2H), 5.53 (s, 1H), 7.24 (s, 5H). Found: C, 53.98; H, 5.86; N, 9.04%. Calcd for $C_{14}H_{18}N_2O_6$: C, 54.18; H, 5.84; N, 9.02%. Diastereomeric ratio of compound **1** was determined by HPLC using hexane–2-propanol (12:1 v/v) as an eluent.

Preparation of Z-L-Ala-Cl-Gly-OMe (2). Z-L-Ala-OH-Gly-OMe (**1**)(783 mg, 2.53×10^{-3} mol) was suspended in 10 ml of CH_2Cl_2, and 1 ml of thionyl chloride was added to the suspension. The reaction mixture was refluxed for 1 h and then concentrated *in vacuo*. The crude product obtained was recrystallized from CH_2Cl_2–hexane, yield 671 mg (81%), mp 120—124 °C, ^{1}H NMR ($CDCl_3$): δ=1.37 (d, 3H), 3.81 (s, 3H), 4.27 (m, 1H), 5.10 (s, 2H), 5.42 (d, 1H), 6.35 (d, 1H), 7.29 (s, 5H), 7.60 (d, 1H). Found: C, 51.20; H, 5.20; N, 8.40%. Calcd for $C_{14}H_{17}N_2O_5Cl$: C, 51.14; H, 5.21; N, 8.52%.

Reaction of Z-L-Ala-OH-Gly-OMe with Thionyl Chloride Followed by Addition of Dialkyl Malonate. General Procedure: Z-L-Ala-OH-Gly-OMe (**1**)(31 mg, 1×10^{-4} mol) was suspended in 1 ml of CH_2Cl_2, and 1 ml of thionyl chloride was added to the suspension. The reaction mixture was refluxed for 1 h and then concentrated *in vacuo*. The residue was dissolved in 1 ml of THF, and a suspension of sodium salt of dimethyl malonate in 1 ml of THF (prepared from 13 mg of dimethyl malonate and 4 mg of NaH (60%)) was added to the solution at −10 °C. After stirring for 2 h at −10 °C, 3 ml of MeOH saturated with hydrogen chloride was added to the mixture, and the mixture was concentrated *in vacuo*. The residue was refluxed with 6 M HCl (1 M=1 mol dm^{-3}) for 10 h and the hydrolyzate was concentrated *in vacuo*. A part of the residue was diluted appropriately and analyzed with an amino acid analyzer to determine the chemical yield of aspartic acid (48%, based on **1**). A part of the resulting aspartic acid was converted to *N*-(trifluoroacetyl)aspartic acid diisopropyl ester in the usual manner and then subjected to gas chromatographic analysis employing a chiral stationary phase (Chirasil-Val[5]).

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