Efficient Preparation of D-Aspartic Acid β-Methyl Ester as an Aspoxicillin Material by Optical Resolution, Epimerization, and Asymmetric Transformation

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A practical preparation of D-aspartic acid β-methyl ester [D-Asp(OMe)], a raw material for the antibiotic aspoxicillin, has been developed by the use of a second-order asymmetric transformation. The diastereomeric resolution of DL-Asp(OMe) with (−)-1-phenylethanesulfonic acid (PES) resulted in salt formation of less soluble D-·(−) and more soluble L-·(−) in acetonitrile. The soluble L-·(−) was easily epimerized into DL-·(−) by heating it in acetonitrile in the presence of catalysts. Attempted fractional crystallization of DL-·(−) or L-·(−) under such epimerizing conditions led to the desired D-·(−) in 90% yield *via* equilibrium asymmetric transformation in a solid–liquid heterogeneous system. Details of optimum techniques for the asymmetric transformation are presented.

From these results, unique preparation processes of both D-Asp(OMe) and D-*p*-hydroxyphenylglycine, important intermediate materials for aspoxicillin, have been achieved by asymmetric transformation using chiral PES as the resolving agent.

Keywords asymmetric transformation; optical resolution; epimerization; aspartic acid; aspoxicillin; 1-phenylethanesulfonic acid; diastereomeric salt; *p*-hydroxyphenylglycine

Aspoxicillin,[1] which is a new semisynthetic penicillin with a broad spectrum of antibacterial activities, has a unique chemical structure with two D-amino acids in its side chain, *i.e.*, D-*p*-hydroxyphenylglycine (D-HPG) and N^4-methyl-D-asparagine (N^4-Me-D-Asn). In order to produce this aspoxicillin on commercial scale, it became necessary to develop useful procedures for the practical production of the above two D-amino acids. Our previous studies[2,3] have led to the development of a convenient process for producing D-HPG by asymmetric transformation of DL-HPG with (+)-1-phenylethanesulfonic acid [(+)-PES] on a large scale. Fortunately, we have also found now that a precursor of N^4-Me-D-Asn, D-aspartic acid β-methyl ester [D-Asp(OMe)], could be prepared by the asymmetric transformation of DL- or L-Asp(OMe) with (−)-PES. Herein, we report an efficient preparation of D-Asp(OMe) by means of a second-order asymmetric transformation between the diastereomeric salts.

Recently, D-amino acids have become increasingly important in the pharmaceutical field, *e.g.*, in peptide analogues, β-lactam antibiotics, and anticancer drugs. However, D-amino acids are still difficult to obtain on commercial scale, although the natural L-amino acids are easily available. It is therefore necessary to develop facile methods for producing the D-amino acids inexpensively and in large amounts.

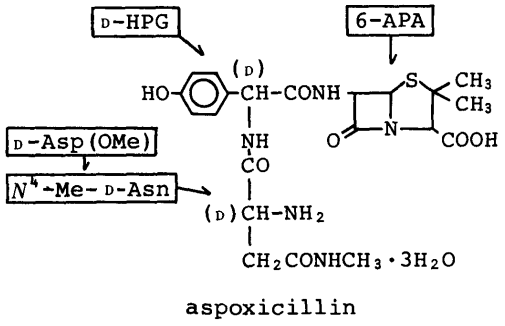


Fig. 1. Aspoxicillin and Its Starting Materials

D-Amino acids can generally be obtained through optical resolution of the racemic (DL-) isomers. That is, physicochemical, chemical, and enzymatic resolution methods have been employed for the purpose of practical production of L-amino acids,[4] and are also applicable to the production of D-amino acids by the opposite treatment. Among the various techniques employed, preferential crystallization and diastereomer formation may be more favorable for the above purpose since they have been extensively utilized not only in the laboratory but also in industry.[5] However, even these resolution techniques have an inevitable disadvantage that the maximal yield of the desired isomer (*e.g.*, D-) is theoretically only half of the corresponding DL-isomer, and the other undesired isomer (L-) must be racemized into DL-isomer to reuse in the next optical resolution, particularly when industrial applications are contemplated. Such a disadvantage of optical resolution and tedious racemization, and the increasing demand for optically active amino acids, have prompted us to study a second-order asymmetric transformation: all of the DL-isomer may be theoretically transformed into the desired isomer by a combination of optical resolution and simultaneous racemization (or epimerization) in a system.[5,6] Elegant examples were presented in our previous papers[2,3,7] and elsewhere.[8] These successful results further motived us to take up the asymmetric transformation of DL- or L-Asp(OMe) in connection with the development of

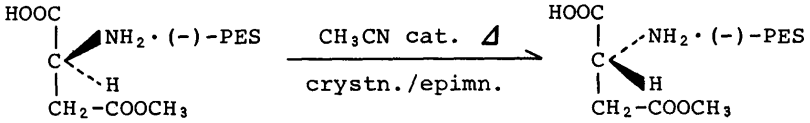


Chart 1

aspoxicillin.

Synthesis and Resolution of DL-Asp(OMe) DL-Asp(OMe) was easily obtained by dehydrochlorination of DL-Asp(OMe)·HCl, prepared by β-esterification of DL-aspartic acid with thionyl chloride in methanol.

A resolving agent for DL-Asp(OMe) was sought through fractional crystallization of diastereomeric salts formed from it with 1 mol eq of various acidic resolving agents in several solvents. This screening procedure led to the selection of optically active PES. The (−)-PES was prepared through diastereomeric resolution of synthetic (±)-PES with L-*p*-hydroxyphenylglycine in aqueous solvent. By use of this (−)-PES as a resolving agent, optical resolution of DL-Asp(OMe) was examined under various conditions. As a result, when salt formation of DL-Asp(OMe) was done with (−)-PES in acetonitrile, D-Asp(OMe)·(−)-PES was fractionally crystallized as the less soluble diastereomeric salt in a good yield (40% based on DL-·(−) salt), while soluble L-Asp(OMe)·(−)-PES remained in the mother liquor. This successful resolution was based on the difference in the properties of the two diastereomeric salts as listed in Table I. The difference in the solubilities of the two salts increased with increasing temperature, which led to an advantage for carrying out resolution–epimerization (asymmetric transformation) under heating.

Epimerization of L-Asp(OMe)·(−)-PES To achieve asymmetric transformation, we looked for conditions under which L-Asp(OMe)·(−)-PES is easily epimerized into DL-Asp(OMe)·(−)-PES under the above-mentioned resolution conditions.

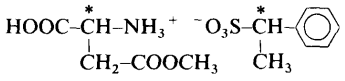
Our previous work[9] and the literature[10] indicated that free optically active amino acids and their derivatives (salts and esters) could be readily racemized by heating them in various solvents in the presence of a catalytic amounts of aldehydes. This concept led us to test the epimerization of L-Asp(OMe)·(−)-PES in acetonitrile medium. Figure 2 shows the time course of epimerization of L-Asp(OMe)·(−)-PES by heating it in acetonitrile with catalysts in a sealed vessel. The result suggested that the presence of salicylaldehyde as a catalyst may accelerate the epimerization with increase in temperature and then further addition of free L-Asp(OMe) should make it more effective. This more rapid epimerization should be ascribed to the catalytic formation of the Schiff base of excess free L-Asp(OMe) itself with salicylaldehyde in the reaction system, since the free optically active amino acids can be racemized more easily than their salts.[9] On the other hand, during such epimerization, (−)-PES itself was found to be chemically and optically stable,[2] because no DL-Asp(OMe)·(−)-PES was epimerized into DL-Asp(OMe)·(±)-PES under the same conditions.

The rapid epimerization and optically stability of (−)-PES were favorable for the intended asymmetric transformation.

Asymmetric Transformation of L-Asp(OMe)·(−)-PES A second-order asymmetric transformation (diastereomeric resolution) has the characteristic that two diastereomers are transformed into the one component through both crystallization and epimerization. To achieve a higher yield of asymmetric transformation therefore, it is necessary to increase the amount of the desired diastereomer [D-Asp(OMe)·(−)-PES] crystallizing in the reaction system. For this purpose, the kinds and amounts of solvent and additives, and heating temperature for epimerization were examined in detail.

Among the various solvents, acetonitrile was the most suitable one, but 1,4-dioxane was comparatively desirable. It was also found that absolute acetonitrile was more favorable since the desired D-Asp(OMe)·(−)-PES was very soluble in water, and its optimum level was 1.5 times the volume of L-Asp(OMe)·(−)-PES. The catalytic additives for epimerization could be used in the range of salicylaldehyde 0.05—0.2 and of L-Asp(OMe) 0.05—0.1 mol eq, respectively, without decreasing the yield. The reaction temperature required for rapid epimerization was 80 °C for 2 h and that for epimerization–fractional crystallization was

TABLE I. Properties of D- and L-Asp(OMe)·(−)-PES



[Asp(OMe)·(−)-PES]

Analyses		D-Asp(OMe)·(−)-PES	L-Asp(OMe)·(−)-PES
mp (°C)		176—177	134—135
$[\alpha]_D^{25}$ (°) (c=1, MeOH)		−18.9	+0.3
Solubility	40 °C	<0.2	0.5
(g/100 ml CH_3CN)	60 °C	<0.2	1.5
	70 °C	0.2	5.2
IR ν_{max}^{Nujol} (cm^{-1})		3050, 1730, 1600, 1520, 1205	3150, 1750, 1725, 1580, 1500, 1200
^{1}H-NMR (in DMSO-d_6) δ		1.45 (3H, d, J=7, CH_3), 2.85 (2H, d, J=7, CH_2), 3.6—3.9 (4H, m, CH_3, CH), 4.12 (1H, t, J=7, CH), 7.0—7.4 (5H, m, ArH), 8.4 (3H, br s, NH_3^+)	1.44 (3H, d, J=7, CH_3), 2.86 (2H, d, J=7, CH_2), 3.6—3.9 (4H, m, CH_3, CH), 4.11 (1H, t, J=7, CH), 7.0—7.4 (5H, m, ArH), 8.35 (3H, br s, NH_3^+)
Analysis (%)	C:	46.84	46.92	46.96
Calcd for	H:	5.75	5.76	5.73
$C_{13}H_{19}NO_7S$	N:	4.20	4.19	4.18
	S:	9.62	9.44	9.40

Coupling constants (J) are given in Hz.

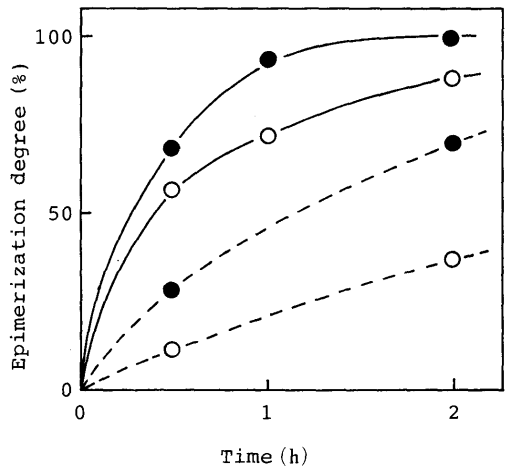


Fig. 2. Effect of Addition and Temperature on Epimerization of L-Asp(OMe)·(−)-PES

The L-Asp(OMe)·(−)-PES/CH_3CN system was stirred in the presence of additives (mol eq) at a prescribed temperature.
Additives: ○, salicylaldehyde (0.2); ●, salicylaldehyde (0.2) and L-Asp(OMe) (0.05). Temperature: ——, 80 °C; ------, 70 °C.

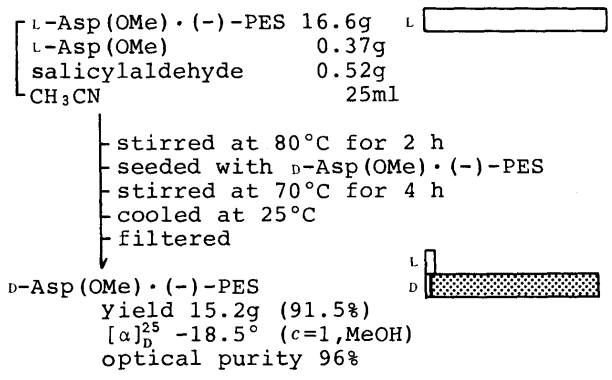


Fig. 3. Asymmetric Transformation of L-Asp(OMe)·(−)-PES
▦, crystals of salt; □, salt in solution.

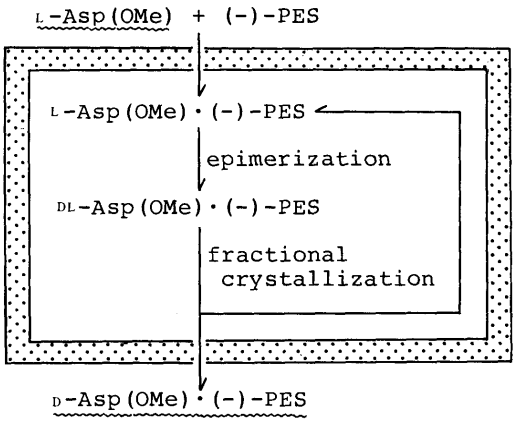


Fig. 4. Reaction Pathway of Asymmetric Transformation of L-Asp(OMe) with (−)-PES
▦, liquid phase; ～～, solid state.

70 °C for 4 h.

The foregoing reaction conditions resulted in a satisfactory stirring state and good yield. A typical procedure of asymmetric transformation is briefly summarized in Fig. 3. This reaction proceeded smoothly in a solid–liquid heterogeneous system (slurry) through the pathway shown in Fig. 4. L-Asp(OMe)·(−)-PES was transformed into D-Asp(OMe)·(−)-PES in up to *ca.* 90% yield, as also illustrated graphically in Fig. 3.

The resulting D-Asp(OMe)·(−)-PES could be effectively decomposed to optically pure D-Asp(OMe) by neutralizing it with triethylamine (Et_3N) in isopropanol without further purification. The (−)-PES·Et_3N that remained in the mother liquor was passed through a column of Amberlite IR-120 (H^+ form), and could be easily reused as the resolving agent for the next asymmetric transformation.

Conclusion

A second-order asymmetric transformation as described above is an attractive technique for preparing optically active compounds. The mechanism is diastereomeric isomerization–crystallization based on displacement of the solid–liquid equilibrium in the reaction system. However, it is necessary to find limited conditions under which fractional crystallization can be simultaneously successfully performed under severe epimerizing conditions, and in many cases, the yield is low.

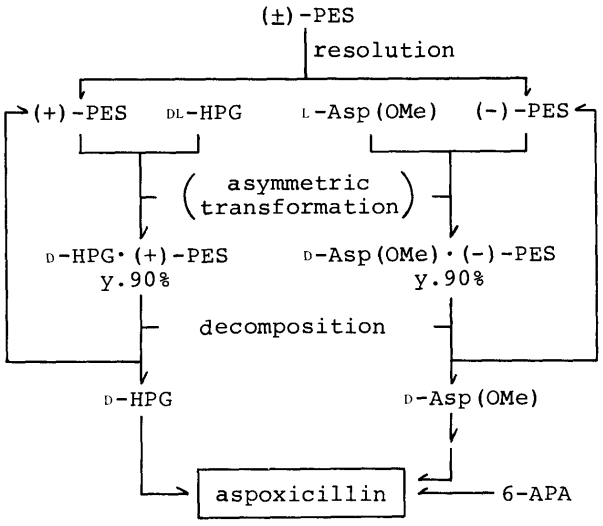


Chart 2. Flowsheet for Preparation of D-*p*-Hydroxyphenylglycine (HPG) and D-Asp(OMe) by Asymmetric Transformation

We fortunately achieved the preparation of both D-HPG and D-Asp(OMe) by asymmetric transformation using antagonistic chiral PES as the resolving agent. The combination of two asymmetric transformations is a unique and advantageous procedure, since the two D-amino acids required to synthesize aspoxicillin can be prepared by the use of one resolving agent pair (Chart 2). The proposed processes are, therefore, expected to be advantageous procedures for economical production of aspoxicillin.

Experimental

Analyses Melting points were determined with a Yamato Mp-21 melting point apparatus; they are uncorrected. Infrared (IR) spectra were obtained in nujol mulls with a Shimadzu IR-420 infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi Perkin-Elmer R-40 high-resolution ^{1}H-NMR spectrometer at 90 MHz using tetramethylsilane as an internal standard. Elemental analyses were carried out with a Perkin-Elmer 240 elemental analyzer. Optical rotations were determined on a Perkin-Elmer 243 automatic polarimeter using a 10 cm water-jacketed cell. Solubility was determined by approaching saturation equilibrium from both undersaturation and supersaturation. Solute concentrations were measured with a Carl Zeiss immersion refractometer.

Materials L- and DL-Aspartic acid and L-HPG were produced by Tanabe Seiyaku Co., Ltd. The (−)-PES was prepared by the method described below. Other chemicals were commercially obtained from Katayama Chemical Industries Co., Ltd. and Tokyo Kasei Kogyo Co., Ltd.

Preparation of L- and DL-Asp(OMe) L-Aspartic acid (100 g, 0.75 mol) was added to a solution of thionyl chloride (54 ml, 0.75 mol) in MeOH (500 ml) at 0—10 °C with stirring. After stirring at the same temperature for 0.5 h, the solution was quickly concentrated at 40 °C under reduced pressure. The resulting residue was taken up in MeOH (50 ml) and EtOAc (200 ml), and the mixture was then permitted to stand at 5—10 °C overnight. The crystals which separated were filtered off, washed with EtOAc, and dried at 90—95 °C to give L-Asp(OMe)·HCl (105 g, 76.1% yield). mp 194—195 °C (dec.), $[\alpha]_D^{25}$ +16.4° (*c*=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1930, 1730, 1570, 1500, 1205.

Triethylamine (75.6 ml, 0.54 mol) was added dropwise to a suspension mixture of L-Asp(OMe)·HCl (100 g, 0.54 mol) in EtOH (900 ml) at 60 °C with stirring. After stirring at 25 °C for 2 h, the resulting product was collected by filtration, washed with EtOH, and dried at 70 °C to give L-Asp(OMe) (72.8 g, 91.0% yield). mp 188—189 °C (dec.), $[\alpha]_D^{25}$ +21.8° (*c*=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1750, 1600, 1560, 1500, 1300. ^{1}H-NMR (DMSO-d_6 +CF_3COOD) δ: 2.95 (2H, d, J=7 Hz, CH_2), 3.65 (3H, s, CH_3), 4.22 (1H, t, J=7 Hz, CH).

DL-Asp(OMe) was prepared in the almost same yield by the same

procedure as described above. DL-Asp(OMe)·HCl: mp 105—107 °C. IR ν_{max}^{Nujol} cm^{-1}: 3150, 1950, 1760, 1710, 1600, 1490, 1290. DL-Asp(OMe): mp 191—193 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1735, 1600, 1520, 1300. ^{1}H-NMR (CF_3COOD) δ: 3.46 (2H, d, J=7 Hz, CH_2), 3.93 (3H, s, CH_3), 4.75 (1H, t, J=7 Hz, CH).

Preparation of (−)-PES (±)-1-Phenylethyl bromide (185 g, 1 mol) was added to a stirred solution of a 50% aqueous ammonium hydrogensulfite solution (317 g, 1.6 mol) and 28% aqueous ammonia (97 g, 1.6 mol), and the mixture was stirred at 30—40 °C for 6 h. After the oil layer of the reaction mixture had been removed by toluene extraction, 21% sulfuric acid (750 g) was added and simultaneously sulfur dioxide (gas) evolved was boiled off. L-HPG (35 g) was added to the aqueous solution (contained (±)-PES 74 g) at 70 °C and the mixture was allowed to cool to 20 °C with stirring. The resulting crystals were filtered off, washed cold water, and dried to give crude (−)-PES·L-HPG (63.2 g, 45% yield based on (±)-PES in the solution). $[\alpha]_D^{25}$ +79.6° (c=1, MeOH). This crude product (63 g) was recrystallized from 1% sulfuric acid (540 g) giving optically pure (−)-PES·L-HPG (56.7 g, 90% yield). $[\alpha]_D^{25}$ +78.9° (c=1, MeOH).

Aqueous ammonia (23 ml, 6 N) was added dropwise to a suspension of the present (−)-PES·L-HPG (50 g, 0.14 mol) in water (50 ml) at 60 °C over a period of 0.5 h, and then the mixture was adjusted to neutrality. After the addition, the whole was stirred at 5 °C for 2 h. A crystalline solid that separated which was filtered off, washed with cold water, and dried to give L-HPG (21.6 g, 91.5% recovery yield). The filtrate was passed through a column packed with Amberlite IR-120 resin (200 ml, H^+ form) using water as an eluent, and the effluent was concentrated to obtain (−)-PES (free acid 25.5 g, 98% yield) as pasty crystals. $[\alpha]_D^{25}$ −6.2° (c=3, H_2O). ^{1}H-NMR (D_2O) δ: 1.71 (3H, d, J=7 Hz, CH_3), 4.24 (1H, q, J=7 Hz, CH), 7.55 (5H, s, Ar H).

Optical Resolution of DL-Asp(OMe) with (−)-PES A solution of DL-Asp(OMe) (14.7 g, 0.1 mol) in 50% aqueous (−)-PES solution (37.2 g, 0.1 mol) was concentrated under reduced pressure. The resulting oil was dissolved in acetonitrile (CH_3CN, 300 ml) with heating and then the solution was slowly cooled to 25 °C with stirring. After stirring at the same temperature for 2 h, the resulting crystals were filtered off, washed with CH_3CN and dried to give D-Asp(OMe)·(−)-PES (12.0 g, 36.0% yield based on DL-·(−) salt). $[\alpha]_D^{25}$ −18.5° (c=1, MeOH), optical purity 96%.

Preparation of Pure L- and D-Asp(OMe)·(−)-PES The title compounds were prepared by salt formation of optically pure Asp(OMe) and (−)-PES: L-Asp(OMe) (14.7 g, 0.1 mol) and (−)-PES (free acid 20 g, 0.11 mol) were dissolved in MeOH (100 ml), and the MeOH solution was evaporated to dryness under reduced pressure. CH_3CN (100 ml) was added to the resulting residue, and the mixture was allowed to stand in an ice box for 2 d. The crystals which precipitated were collected by filtration, washed with CH_3CN, and dried *in vacuo* at 70 °C to afford crude L-Asp(OMe)·(−)-PES (23.5 g, 70.5% yield). This crude product was then recrystallized several times from an CH_3CN–MeOH solution to give optically pure L-Asp(OMe)·(−)-PES. Optically pure D-Asp(OMe)·(−)-PES was prepared in a similar manner. The properties of two products are summarized in Table I.

Epimerization of L-Asp(OMe)·(−)-PES The following procedure is typical. A mixture of L-Asp(OMe)·(−)-PES (0.5 g, 1.5 mmol), DL-Asp(OMe) (11 mg, 1.5×0.05 mmol), salicylaldehyde (15.7 μl, 1.5×0.1 mmol), and CH_3CN (0.75 ml) was sealed in a glass vessel. After heating at 70 or 80 °C for the prescribed time, the reaction solution was diluted with MeOH (7 ml), and its optical rotation was measured. The resulting degree of epimerization was evaluated from the following formula:

$$\frac{\text{initial optical rotation} - \text{final optical rotation}}{\text{initial optical rotation}} \times 100\%$$

Figure 1 shows the results together with those without free L-Asp(OMe).

Typical Procedure for Asymmetric Transformation of DL- or L-Asp(OMe) with (−)-PES A mixture of dry L-Asp(OMe)·(−)-PES (16.6 g, 50 mmol), salicylaldehyde (0.52 ml, 5 mmol), and DL-Asp(OMe) (0.37 g, 2.5 mmol) in dry CH_3CN (25 ml) was dissolved by heating it in a flask fitted with a mechanical stirrer and a condenser. After stirring at 80 °C for 2 h, the reaction solution was seeded with crystals of D-Asp(OMe)·(−)-PES and slowly stirred for 4 h at 70 °C. During this period the reaction system was a stirred solid–liquid heterogeneous slurry. The resulting solid was filtered by suction, washed with CH_3CN, and dried to obtain D-Asp(OMe)·(−)-PES (15.2 g, 91.5% yield based on L-·(−) salt). $[\alpha]_D^{25}$ −18.5° (c=1, MeOH), optical purity 96%. The ^{1}H-NMR and IR spectra were in agreement with those of an authentic sample. The asymmetric transformation of DL-Asp(OMe)·(−)-PES was also achieved in a similar manner and yield.

Purification of Optically Impure D-Asp(OMe)·(−)-PES Although D-Asp(OMe)·(−)-PES obtained by the above procedure was highly optically pure, if further optical purification is required, it is possible in the following manner. Optically crude D-Asp(OMe)·(−)-PES (10 g, optical purity 90%) was dissolved in CH_3CN–H_2O (180/4 ml) with heating. The solution was gradually cooled to 5 °C, and stirred at the same temperature for 2 h. The residual crystals were filtered out, washed with CH_3CN, and dried under reduced pressure to give optically pure D-Asp(OMe)·(−)-PES (8.6 g, 90.5% yield based on D-·(−) moiety in the starting optically crude D-Asp(OMe)·(−)-PES). $[\alpha]_D^{25}$ −18.9° (c=1, MeOH).

Preparation of Pure D-Asp(OMe) Triethylamine (4.2 ml, 30 mmol) was added dropwise to a suspension mixture of D-Asp(OMe)·(−)-PES (10 g, 30 mmol, optical purity 96%) in isopropanol (60 ml) at 50 °C, and then the mixture was stirred at the same temperature for 0.5 h. The suspension was accurately adjusted to neutrality, and stirred at 5—10 °C for 2 h. The resulting crystals were collected by filtration, and washed with isopropanol to afford D-Asp(OMe) (4.2 g, 95.1% yield). mp 188—190 °C (dec), $[\alpha]_D^{25}$ −21.7° (c=1, MeOH).

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