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L-Aspartic Acid Bis(trimethylsilyl) Ester: A Convenient Starting Material for the Acylation of *L*-Aspartic Acid.

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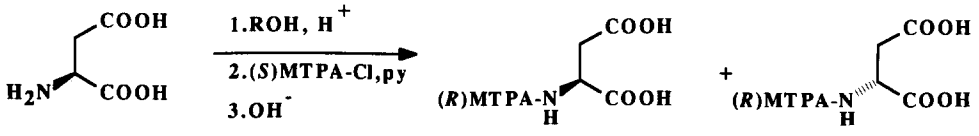
Abstract: *Reaction of L-aspartic acid with excess of bis(trimethylsilyl)amine under reflux provides optically pure L-aspartic acid bis(trimethylsilyl) ester in quantitative yield. This silyl ester reacts with a variety of acylating reagents in tetrahydrofuran to give N-protected aspartic acids and dipeptides in good yields without racemization.*

As part of a study on the synthesis of chiral nickelacycles, we have need of the preparation of a series of optically pure *N*-protected *L*-aspartic acids.[1] Although a variety of standard protective groups can be introduced by using the Schotten-Baumann procedure,[2] less reactive acylating agents such as (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride ((*S*)-MTPA-Cl) [3] fail to react with *L*-aspartic acid (**1**) under these reaction conditions. On the other hand, no reaction takes place between **1** and acylating agents in organic solvents because of the poor solubility of **1** or its salts. Alternatively, a circuitous route starting from the diester (dimethyl[4] or di-*n*-butyl ester[5]) followed by *N*-acylation with (*S*)-MTPA-Cl and saponification[6] gave a mixture of *N*-(*R*)-MTPA-*L*- and *N*-(*R*)-MTPA-*D*-aspartic acids (**2** and **3**) with low diastereomeric excess (de) (*ca.* 40 - 80 % de of the (*R*)-*L* derivative) (Eq 1).

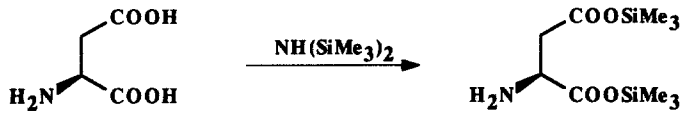


1 **2** **3**

(Eq 1)

In this paper we report the preparation of optically pure *L*-aspartic acid bis(trimethylsilyl) ester (**4**) by reaction of the free amino acid with bis(trimethylsilyl)amine (1,1,1,3,3,3-hexamethyldisilazane, HMDS).

This new derivative is a convenient starting material for the *N*-protection of aspartic acid in organic solvents under neutral and mild conditions. Silylation of α-amino acids has been carried out with trimethylsilyl chloride and triethylamine,[7] *N,N*-diethyltrimethylsilylamine (TMSDEA),[8] *N,O*-bis(trimethylsilyl)acetamide,[9] or trimethylsilyl cyanide.[10] However, reaction of *L*-aspartic acid (**1**) with TMSDEA, usually the most convenient trimethylsilylating reagent,[8] afforded a partially racemized tris(trimethylsilyl) derivative, which, after treatment with (*S*)-MTPA-Cl gave a 10:1 mixture of amides **2** and **3** (82 % de).



1 **4**

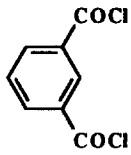
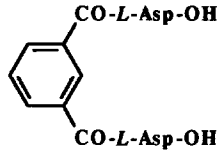
(Eq 2)

Although HMDS is a poor trimethylsilylating agent,[8c,11] the desired reactions have been promoted by addition of trimethylsilyl chloride[12] or an acid catalyst.[11,13] However, when a suspension of **1** was heated under reflux in neat HMDS, in the absence of additives, a clear solution was obtained, from which the desired pure bis(trimethylsilyl) ester (**4**) was isolated in quantitative yield as a colourless oil by evaporation of the solvent (Eq 2). This α-amino bis(trimethylsilyl) ester (**4**) can be distilled without polymerization and was found to be stable for several months at - 15 °C. Remarkably, none of the known tris(trimethylsilyl) derivative[14] was obtained under these reaction conditions. The ^{1}H NMR spectrum of **4** in deuteriochloroform showed a broad signal at δ 1.77 (2 H), corresponding to the NH_2 function, and two OTMS signals at δ 0.27 and 0.29. The presence of a free amino group was further demonstrated by the observation in the mass spectrum of a fragmentation corresponding to the loss of NH_2 (m/z 245, $[M^+ - CH_3] - NH_3$).

Presumably the acid functionality of aspartic acid promotes the smooth silylation reaction. Accordingly, neutral amino acids such as *L*-Ala, *L*-Val, and *D*-Phegly did not yield silyl esters after heating in HDMS for several hours under reflux. On the other hand, silylation of glutamic acid under the same conditions gave a more labile derivative, which reacted with benzyloxycarbonyl chloride (Z-Cl) to yield mixtures of Z-*L*-Glu-OH and Z-*L*-pyroglutamic acid in variable yields.[13]

The results of the reaction of **4** with a variety of acylating reagents in tetrahydrofuran (THF) are summarized in Table I. The reactions proceeded in good to excellent yields at 23 °C with acid chlorides (entries 1 - 3), including a diacid dichloride (entry 4), and chloroformates (entries 5 - 8). On the other hand, the less reactive di-*t*-butyl dicarbonate ($(BOC)_2O$) required heating at 60°C (entry 9). The reaction can also be employed for the preparation of dipeptides EOC-*L*-Ala-Asp-OH (**5**) and Z-*L*-Asp(*L*-Asp-OH)-OBn (**6**) by reaction with EOC-*L*-Ala-Cl[15] and the acid fluoride derived from Z-*L*-Asp-OBn,[16] respectively (entries 10 and 11).

Table I[a]

entry	RCOX	product	yield (%)	$[\alpha]_D^{23}$
1	*t*-BuCOCl	*t*-BuCO-*L*-Asp-OH	83	-38.1° (c 1, EtOH)
2	PhCOCl	PhCO-*L*-Asp-OH	92	+37.4° (c 6.7, aq KOH)[b]
3	(*S*)-MTPA-Cl	(*R*)-MTPA-*L*-Asp-OH	100	+27.7° (c 1, THF)
4			93	+4.1° (c 1, EtOH)
5	Z-Cl	Z-*L*-Asp-OH	91	+8.4° (c 1, AcOH)[c]
6	TROC-Cl	TROC-*L*-Asp-OH	94	-34.6° (c 2.5, DMF)[d]
7	ALOC-Cl	ALOC-*L*-Asp-OH	96	-40.5° (c 2.2, DMF)
8	Ment-Cl	Ment-*L*-Asp-OH	83	-71.6° (c 0.8, DMF)
9	$(BOC)_2O$	BOC-*L*-Asp-OH	67	-5.6° (c 1, MeOH)[e]
10	EOC-*L*-Ala-Cl	EOC-*L*-Ala-*L*-Asp-OH	79	+9.0° (c 3, THF)
11	Z-*L*-Asp(F)-OBn	Z-*L*-Asp(*L*-Asp)-OBn	75	+2.0° (c 1, EtOH)

[a] Abbreviations: MTPA = α-methoxy-α-trifluoromethylphenyl acetyl; Z = benzyloxycarbonyl; TROC = trichloroethoxycarbonyl; ALOC = allyloxycarbonyl; Ment = (1*R*,2*S*,5*R*)-menthyloxycarbonyl; BOC = *t*-butoxycarbonyl; EOC = ethoxycarbonyl; Bn = benzyl. [b] lit[2] +37.4° (c 1, aq KOH). [c] lit[2,17] +9.25 ± 0.5° (c 1, HOAc). [d] lit[18] -32.0° (c 3.5, DMF). [e] lit[2] -6.2°(c 1, MeOH).

In most cases, the acylation was carried out in a one-pot operation. The acylated products were optically pure compounds, as determined by comparison of the optical rotations with literature values[2,17,18] and by the observation of a single diastereomer by NMR (^1H, ^{13}C and/or ^{19}F)[19] for the derivatives of entries 3, 4, 8, 10, and 11. The BOC derivative (entry 9) gave a lower optical rotation than that reported in the literature.[2] However, in our hands, reaction of **1** with $(BOC)_2O$ in aqueous $NaHCO_3$ solution at 23°C gave the protected amino acid with a similar optical rotation ($[\alpha]_D$ -5.2 ± 0.3°).

Application of the recently introduced modified Mosher's method to the (*R*)- and (*S*)-MTPA derivatives of aspartic acid gave results in agreement with the model proposed by Kakisawa.[20] However, this method gave the wrong predictions when applied to the cyclic MTPA-Asp anhydrides . Although failure of this method has been noted for secondary alcohols with sterically hindered OH groups,[20b] this is the first report of an anomaly with an amine derivative.

In summary, the described synthesis of bis(trimethylsilyl) ester **4** should prove useful for the preparation of *N*-functionalized derivatives of α-aspartic acid (**1**) with labile acylating reagents as well as for the coupling of peptides with with the unprotected amino acid.

EXPERIMENTAL SECTION

Optical rotations were measured on a Perkin-Elmer 241 MC Polarimeter with a path-length of 10 cm at 23 ± 1°C. Infrared spectra were obtained on a Perkin-Elmer 681 spectrophotometer. NMR spectra were recorded on a Bruker AM 200 or a Varian XL-300 spectrometer with TMS (^{1}H), $CFCl_3$ (^{19}F) or the solvent (^{13}C) as internal standard. Low-resolution mass spectra (LRMS) were obtained on a VG-12-250 spectrometer. Elemental analyses were performed at the CSIC.

***L*-Aspartic acid bis(trimethylsilyl) ester (4).** (*L*)-Aspartic acid (506 mg, 3.80 mmol) was suspended in HMDS (5 mL) and heated under reflux for 5 h to give a colourless solution. The solvent was evaporated to yield the title compound **4** as a colourless oil (1.070 g, quantitative yield after distillation) [bp (Kugelrhor) 130 - 140°C, 0.5 mm Hg]; $[\alpha]_D$ -16.1, $[\alpha]_{436}$ -34.0 (c 3.8, THF) [hydrolysis gave H-Asp-OH, $[\alpha]_D$ +25° (c 2, 5M HCl)]; IR (neat) 2960, 1710, 1670 - 1550 (br), 1400, 1305, 1060, 850 (br), 755 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.69 (dd, J = 6.6, 4.6 Hz, H-2), 2.81 (dd, J = 17.0, 4.7 Hz, H-3), 2.69 (dd, J = 17.0, 6.6 Hz, H-3'), 1.77 (br, NH_2), 0.29 (s, OTMS), 0.27 (s, OTMS); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.74, 171.79, 52.14, 40.42, -0.28, -0.36; LRMS m/z 278 (M^++1, 2), 262 (2), 245 (7), 234 (4), 202 (2), 160 (51), 147 (51), 130 (21), 73 (100).

Anal. Calcd for $C_{10}H_{23}NO_4Si_2$: C, 43.28; H, 8.35; N, 5.05.
Found: C, 43.60; H, 8.73; N, 5.00.

***N*-Acylation of 4. General Procedure (Table I).** Bis(trimethylsilyl) ester **4** (1.56 mmol) was treated with a solution of acylating reagent (0.90 - 0.95 equiv) in THF (3 mL) (exothermic reaction). The mixture was stirred at 23 °C for 5 - 20 h and then treated with ethanol (3 equiv). The excess of aspartic acid (**1**) was filtered off and the filtrate was evaporated to yield the *N*-acyl derivatives in the stated yields. Alternatively (entries 2, 3, 7, and 8) the mixture was partitioned between water and ethyl acetate. The ethyl acetate solution was extracted with 5 % aqueous sodium bicarbonate. Acidification with 1.2 M HCl, extraction with ethyl acetate and evaporation of the solvent provides the *N*-acylated derivatives.

***N*-2,2-Dimethylpropanoyl-*L*-aspartic acid** (Table I, entry 1): white solid; mp 142 - 143°C (Et_2O), lit[21] 145 - 147°C; $[\alpha]_D$ -38.1°, $[\alpha]_{436}$ -83.1° (c 1, DMF); IR (KBr) 3480 - 2700 (br), 3390, 2980, 1750, 1720, 1630, 1550, 1420, 1290, 1180 cm^{-1}; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 12.5 (br, 2 H), 7.59 (d, J = 8.0 Hz, 1 H), 4.52 (m, 1 H), 2.72 (dd, J = 16.3, 5.9 Hz, 1 H), 2.57 (dd, J = 16.4, 7.1 Hz, 1 H), 1.06 (s, 9 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 177.22, 172.68, 171.97, 48.78, 37.88, 35.84, 27.19.

Anal. Calcd for $C_9H_{15}NO_5$: C, 49.75; H, 6.69; N, 6.45.
Found: C, 49.93; H, 6.96; N, 6.71.

***N*-Benzoyl-*L*-aspartic acid** (Table I, entry 2): white solid; mp 173 - 174°C (EtOAc-hexane), lit[2] 184 - 185°C; $[\alpha]_D$ +37.4° (c 6.7, H_2O + 2 equiv KOH), lit[2] $[\alpha]_D$ +37.4° (c 9, H_2O + 2 equiv KOH); ^{13}C NMR (DMSO-d_6) δ 172.60, 171.86, 166.19, 133.89, 131.50, 128.35, 127.38, 49.44, 35.87.

Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.67; N, 5.90.
Found: C, 56.00; H, 5.01; N, 6.10.

(*R*)-2-Methoxy-2-phenyl-3-trifluoropropanoyl-*L*-aspartic acid [(*R*)-MTPA-*L*-AspOH, **2**, Table I, entry 3]: semisolid; $[\alpha]_D$ +27.7° (c 1, THF); IR (KBr) 3400 - 2900 (br), 1750 - 1650 (br), 1510, 1380, 1260, 1160, 1090, 970, 945, 750, 705, 680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.93 (d, J = 8.5 Hz, 1 NH), 7.74 - 7.53 (m, 2 H Ph), 7.44 - 7.37 (m, 3H Ph), 4.5 - 3.8 (br, 2 COOH), 4.92 (m, H-2), 3.34 (q, $^5J(^1H-^{19}F)$ = 1.0 Hz, OMe), 3.12 (dd, J = 17.6, 4.2 Hz, H-3), 2.93 (dd, J = 17.4, 4.9 Hz, H-3'); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.95, 173.75, 166.99, 131.46, 129.65, 128.58, 127.98, 123.67 [q, $^1J(^{13}C-^{19}F)$ = 290.0 Hz)], 84.07 [q, $^2J(^{13}C-^{19}F)$ = 26.6 Hz], 54.79, 48.33, 35.44; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -73.77.

Anal. Calcd for $C_{14}H_{14}F_3NO_6$: C, 48.14; H, 3.98; N, 4.01.
Found: C, 48.00; H, 4.10; N, 3.80.

(*S*)-2-Methoxy-2-phenyl-3-trifluoropropanoyl-*L*-asparticacid [(*S*)-MTPA-*L*-AspOH]: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.69 (d, J = 8.1 Hz, 1 NH), 7.52 - 7.43 (m, 2 H Ph), 7.40 - 7.36 (m, 3H Ph), 4.5 - 3.8 (br, 2 H COOH), 4.92 (m, H-2), 3.47 (q,$^5J(^1H-^{19}F)$ = 1.4 Hz, OMe), 3.07 (dd, J = 17.5, 4.3 Hz, H-3), 2.91 (dd, J = 17.5, 4.9 Hz, H-3').

The anhydrides were prepared in quantitative yield by reaction with dicyclohexylcarbodiimide (1 equiv) at 23°C in CH_2Cl_2 (4 - 6 h), followed by filtration of the insoluble urea and evaporation of the solvent.

(*R*)-2-Methoxy-2-phenyl-3-trifluoropropanoyl-*L*-asparticanhydride: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, J = 6.8 Hz, NH), 7.49 - 7.45 (m, 2 H Ph), 7.49 - 7.45 (m, 3H Ph), 4.72 (m, H-2), 3.43 (br s, OMe), 3.23 (dd, J = 18.5, 9.9 Hz, H-3), 3.00 (dd, J = 18.5, 7.0 Hz, H-3').

(*S*)-2-Methoxy-2-phenyl-3-trifluoropropanoyl-*L*-asparticanhydride: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91 (d, J = 6.7 Hz, NH), 7.59 - 7.41 (m, 5 H Ph), 4.53 (m, H-2), 3.34 (br s, OMe), 3.20 (dd, J = 18.6, 9.9 Hz, H-3), 3.07 (dd, J = 18.8, 7.3 Hz, H-3').

Δδ values [$\Delta\delta = \delta_S - \delta_R$][21] (ppm, $CDCl_3$) obtained for (*R*) and (*S*) amides of (*L*)-Asp-OH and its anhydride (anh):

MTPA-(*S*)-Asp-OH: H-2 (0.00), H-3 (-0.05), H-3' (-0.03), NH (-0.24), MeO (0.13).
MTPA-(*S*)-Asp-anh: H-2 (-0.19), H-3 (-0.03), H-3' (0.07), NH (0.04), MeO (-0.15).

***N*-Isophthaloyl bis *L*-aspartic acid** (Table I, entry 4). This bisamide was isolated by treatment of the reaction mixture with ethanol (3 equiv), evaporation of the solvent, and addition of THF. The solid (excess of aspartic acid) was filtered off and the filtrate was evaporated to yield pure compound as a white solid: mp 148 -149 °C (EtOAc-EtOH; hexane); $[\alpha]_D$ +4.1°, $[\alpha]_{436}$ +3.6 (c 1, EtOH); IR (KBr) 3540 - 2820 (br), 1720 (br), 1645, 1540, 1420, 1305 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.60 (br, 4 H), 8.92 (d, J = 7.8 Hz, 1 N), 8.33 (s, 1H), 8.00 (dd, J = 7.8, 1.7 Hz, 2H), 7.59 (t, J = 7.7 Hz, 1 H), 4.77 (m, 2 H), 2.86 (dd, J = 16.5, 5.7 Hz, 2 H), 2.72 (dd, J = 16.4, 8.0 Hz, 2 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 172.37,

171.68, 165.65, 134.09, 130.06, 128.34, 126.53, 49.42, 35.69.

Anal. Calcd for $C_{16}H_{16}N_2O_{10}$: C, 48.49; H, 4.07; N, 7.07.
Found: C, 48.20; H, 4.20; N, 7.25.

***N*-Benzyloxycarbonyl-*L*-aspartic acid** (Table I, entry 5): white solid; mp 115 - 116°C (Et_2O-hexane), lit[2] 112 - 113°C; $[\alpha]_D$ +8.4° (c 1 HOAc), lit[2,17] $[\alpha]_D$ 9.2 ± 0.5° (c 1, HOAc); IR (KBr) 3360, 3200 - 2600 (br), 1735 - 1685, 1535, 1420, 1325, 1310, 1280, 1235, 1195, 1065, 920, 905, 778, 740, 700, 640 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 12.5 (br, 2 H), 7.58 (d, J = 8.4 Hz, 1 H), 7.35 (br, 5 H), 5.04 (s, 2 H), 4.35 (m, 1 H), 2.74 (dd, J = 16.5, 5.5 Hz, 1 H), 2.56 (dd, J = 16.4, 8.0 Hz, 1 H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 172.63, 171.61, 155.86, 136.92, 128.34, 127.80, 127.68, 65.49, 50.50, 36.01.

Anal. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24.
Found: C, 53.57; H, 5.02; N, 5.33.

***N*-Tricloroethoxycarbonyl-*L*-aspartic acid** (Table I, entry 6): white solid; mp 148 - 149°C (Et_2O-hexane or EtOAc-hexane), lit[18] 146 - 147°C; $[\alpha]_D$ -34.6°, $[\alpha]_{436}$ -73.0° (c 2.5, DMF), lit[19] $[\alpha]_D$ -32.0°, $[\alpha]_{436}$ -68.4 (c 3.5, DMF); IR (KBr) 3400 - 3080 (br), 3220, 1760, 1740, 1695, 1530, 1415, 1390, 1290, 1240, 1185, 1170, 1095, 1040, 820, 795 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 12.5 (br, 2 H), 8.01 (d, J = 8.3 Hz, 1 H), 4.79 (s, 2 H), 4.34 (m, 1 H), 2.74 (dd, J = 16.5, 5.5 Hz, 1 H), 2.57 (dd, J = 16.5, 8.2 Hz, 1 H) [the *cis* isomer showed the NH d at 7.60 ppm; the ratio *trans*:*cis* changes from 11:1 at 20°C to 15:1 at 50°C; coalescence was observed at *ca.* 85°C in DMSO-d_6 (δ 7.70, br)]; ^{13}C NMR (DMSO-d_6, 50 MHz) δ 172.39, 171.67, 154.37, 96.14, 73.73, 50.84, 35.93.

Anal. Calcd for $C_7H_8NO_6Cl_3$: C, 27.25; H, 2.61; N, 4.54.
Found: C, 27.12; H, 2.59; N, 4.45.

***N*-Allyloxycarbonyl-*L*-aspartic acid** (Table I, entry 7): white solid; mp 135 - 136°C (Et_2O-hexane); $[\alpha]_D$ -40.5° (c 2.2, DMF); IR (KBr) 3540 - 2500 (br), 3320, 1705, 1550, 1425, 1310, 1280, 1195, 1070 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.5 (br, 2 H), 7.48 (d, J = 8.4 Hz, 1 H), 5.88 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H), 5.27 (dq, J = 17.2, 1.7 Hz, 1 H), 5.16 (dd, J = 10.4, 1.4 Hz, 1 H), 4.46 (d, J = 5.3 Hz, 2 H), 4.31 (m, 1 H), 2.70 (dd, J = 16.4, 5.4 Hz, 1 H), 2.54 (dd, J = 16.4, 8.0 Hz, 1 H) [the *cis* isomer (*ca.* 10%) showed the NH d at 7.03 ppm]; ^{13}C NMR (DMSO-d_6, 50 MHz) δ 172.68, 171.66, 155.66, 133.46, 117.05, 64.52, 50.47, 36.04.

Anal. Calcd for $C_8H_{11}NO_6$: C, 42.24; H, 5.11; N, 6.45.
Found: C, 44.50; H, 4.90; N, 6.25.

***N*-(*1R, 2S, 5R*)-Menthyloxycarbonyl-*L*-aspartic acid** (Table I, entry 8): white solid: 157 - 158.5 °C (Et_2O-hexane); $[\alpha]_D$ -71.6°, $[\alpha]_{436}$ -143.1°, $[\alpha]_{546}$ -120.1° (c 0.8, DMF); IR (KBr) 3500 - 2840 (br), 3380, 2960, 1710, 1535, 1420, 1300, 1280, 1200, 640 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 12 - 11 (br, 2 H), 7.22 (d, J = 8.5 Hz, 1 H), 4.40 (td, J = 10.7, 4.1 Hz, 1 H), 4.29 (m, 1 H), 2.68 (dd, J = 16.3, 5.6 Hz, 1 H), 2.52 (dd, J = 16.3, 7.9 Hz, 1 H), 1.95 - 1.84 (m, 2 H), 1.63 - 1.58 (m, 2 H), 1.39 - 1.21 (m, 2 H), 1.04 - 0.70 (m, 3 H), 0.86 (d, J = 6.4 Hz, 3 H), 0.84 (d, J = 7.0 Hz, 3 H), 0.71 (d, J = 6.9 Hz, 3 H) [the *cis* isomer (*ca.* 13%) showed the NH d at 6.95 ppm]; ^{13}C NMR (DMSO-d_6, 50 MHz) δ 172.76,

171.69, 155.86, 73.31, 50.42, 46.92, 41.23, 36.01, 33.80, 30.89, 25.63, 23.12, 21.92, 20.54, 16.35.

Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.12; H, 7.99; N, 4.44.
Found: C, 56.91; H, 7.82; N, 4.53.

***N*-*t*-Butoxycarbonyl-*L*-aspartic acid** (Table I, entry 9): white solid; mp 118.5 -119.5°C (Et_2O-hexane), lit[2] 118-119°C; $[\alpha]_D$ -5.6 ± 0.2°, $[\alpha]_{436}$ -13.9° (c 1.3, MeOH), lit[2] $[\alpha]_D$ -6.2 (c 1, MeOH) [a sample prepared by Schotten-Baumann acylation gave $[\alpha]_D$ -5.2 ± 0.3°, $[\alpha]_{436}$ -13.9° (c 1.3, MeOH) ; ^1H NMR (DMSO-d_6, 300 MHz) δ 12.5 (br, 2 H), 6.97 (d, J = 8.4 Hz, 1 H), 4.24 (m, 1 H), 2.65 (dd, J = 16.3, 5.6 Hz, 1 H), 2.50 (dd, J = 16.0, 7.9 Hz, 1 H), 1.36 (s, 9 H) [the *cis* isomer (*ca.* 10%) showed the NH d at 6.70 ppm].

***N*-Ethoxycarbonyl-*L*-alanyl-*L*-aspartic acid** (Table I, entry 10): hygroscopic white solid; $[\alpha]_D$ +9.0°, $[\alpha]_{436}$ +13.0 (c 3, THF); ^1H NMR (DMSO-d_6, 200 MHz) δ 12.5 (br, 2 COOH), 8.02 (d, J = 8.0 Hz, NH), 7.15 (d, J = 7.3 Hz, NH), 4.51 (q, J = 6.7 Hz, H-2 Asp), 4.06 - 3.95 (m, H-2 Ala), 3.96 (q, J = 7.1 Hz, CH_2 EtO), 2.73 - 2.59 (m, H-3 and H-3' Asp), 1.17 (d, J = 7.1 Hz, CH_3 Ala), 1.13 (t, J = 7.0 Hz, CH_3 EtO); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 172.54, 172.35, 171.75, 155.81, 59.90, 49.84, 48.56, 36.06, 18.20, 14.63.

Anal. Calcd for $C_{10}H_{16}N_2O_7$: C, 43.48; H, 5.84; N, 10.14.
Found: C, 43.70; H, 6.10; N, 9.97.

***N*-Benzyloxycarbonyl-*L*-aspartyl(α-benzyl ester)-Cβ-*L*-aspartic acid** (table I, entry 11): white solid; mp 148.5 - 150°C (CH_2Cl_2-hexane); $[\alpha]_D$ +2.0°, $[\alpha]_{436}$ +2.1 (c 1, EtOH); IR (KBr) 3500-3250 (br), 3400, 1750, 1715, 1160, 1630, 1435, 1420, 1360, 1210, 1195, 730 cm^{-1}; ^1H NMR (DMSO-d_6, 200 MHz) δ 12.5 (br, 2 COOH), 8.28 (d, J = 7.8 Hz, NH), 7.56 (d, J = 8.0 Hz, NH), 7.32 (br s, 10 H Ph), 5.10 (br s, CH_2 Bn), 5.01 (br s, CH_2 Bn), 4.53 - 4.46 (m, 2 H-2), 2.67 - 2.53 (m, 2 H-3 and 2 H-3'); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.37, 171.68, 171.42, 168.73, 155.88, 136.86, 135.94, 128.43, 128.03, 127.88, 127.73, 66.13, 65.61, 50.72, 48.67, 36.62, 36.14.

Anal. Calcd for $C_{23}H_{24}N_2O_9$: C, 58.47; H, 5.12; N, 5.93.
Found: C, 58.24; H, 5.05; N, 5.89.

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