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### A PRACTICAL PREPARATION OF L-ASPARTYL-D-2-AMINO BUTYRIC ACID (S)- $\alpha$ -PHENYLPROPYLAMIDE, A NEW HIGH-POTENCY SWEETENER

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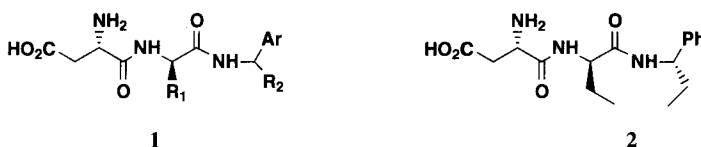
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**A PRACTICAL PREPARATION OF L-ASPARTYL-D-2-AMINOBTYRIC ACID  
(S)- $\alpha$ -PHENYLPROPYLAMIDE, A NEW HIGH-POTENCY SWEETENER**

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We have recently described a new series of L-aspartic acid amide sweeteners having the general structure **1**.<sup>1,2</sup> These materials are advantaged over aspartame (L-aspartyl-L-phenylalanine methyl ester), the most popular non-nutritive sweetener in use today, in that they are substantially more stable toward hydrolytic degradation and they possess much higher sweetness potencies. At the time of the original work, we prepared a number of these sweeteners using procedures that were fairly standard for small peptide synthesis. While these methods were useful for the preparation of many compounds on a laboratory scale, we felt that they would be less practical at a multikilogram level due to the expense of both excess protecting groups and reagents used for formation of the two amide bonds, as well as the need to isolate and purify the intermediates following several of the reaction steps. Some of these previous efforts had also suffered from unacceptably low yields and excessive racemization of the chiral amino acid centers. We describe here our work to overcome these problems

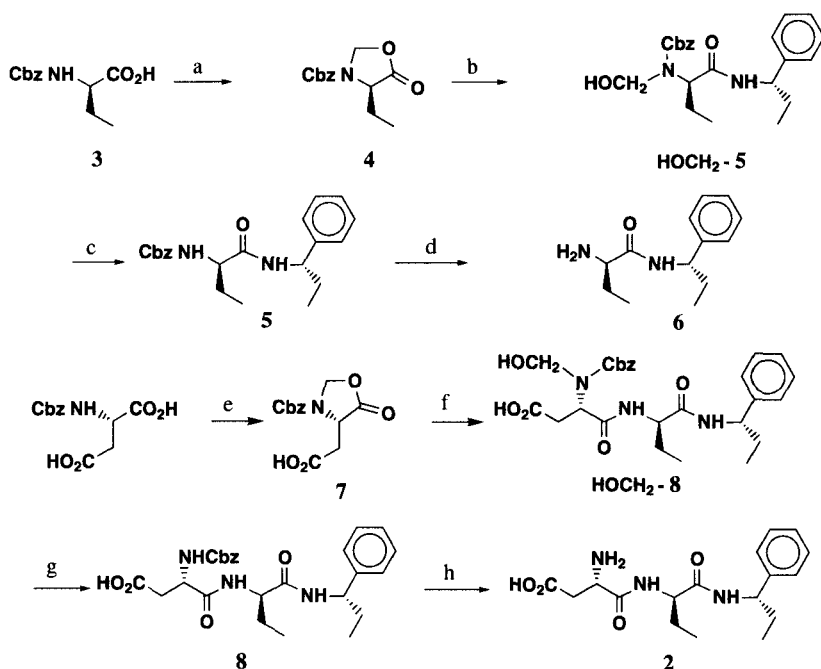


in developing a practical process that could be employed in the large-scale synthesis of L-aspartyl-D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (**2**), the most potent of this new series of L-aspartyl amide sweeteners. The sweetness potency of **2** is 2,000 times that of sucrose, relative to a 10% sucrose reference solution.

The major challenges associated with the preparation of this group of sweeteners were first, activation of the L-aspartic acid and the D-2-aminobutyric acid carboxyl groups toward amide bond formation and second, regiospecific formation of the  $\alpha$ -amide bond with an L-aspartic acid moiety. In our solution for the synthesis of dipeptide amide **2**, we utilized an oxazolidinone chemistry which had been described earlier for the preparation of aspartame.<sup>3</sup> Using this methodology, we were able to address the above concerns while putting together a sequence of reactions which could be carried

forward with a minimum of product manipulation at the intermediate stages. First, the N-protected amino acids were efficiently converted to their corresponding N-protected oxazolidinones by treatment with paraformaldehyde. This activated the  $\alpha$ -carboxylic acid moieties, making them amenable to subsequent nucleophilic attack by alkyl amines.<sup>4,5</sup> The coupling reactions then resulted in the formation of mixtures of N-hydroxymethyl amide intermediates, accompanied by the free amides. Although it had been reported that the N-hydroxymethyl group could be removed directly during hydrogenolysis, we found that this also resulted in the formation of varying amounts of the corresponding N-methyl products in our case. Rather, the requisite complete removal of the hydroxymethyl groups, which was known to be very dependent on the pH,<sup>6,7</sup> was readily accomplished by treatment of the product mixtures with aqueous base prior to the hydrogenolytic removal of the carbobenzoxy (Cbz) protecting groups.

Our improved preparative method for **2** is summarized in the Scheme below, and will be described from the framework of the three key building blocks: Cbz-L-aspartic acid, Cbz-D-2-aminobutyric acid (**3**),<sup>8</sup> and (S)- $\alpha$ -phenylpropylamine.<sup>9</sup> Cbz-D-2-Aminobutyric acid was readily converted to its oxazolidinone (**4**) by refluxing in toluene with paraformaldehyde and a catalytic amount of *p*-TsOH while using a Dean-Stark trap to achieve the azeotropic removal of H<sub>2</sub>O. The *p*-TsOH and excess formaldehyde polymer were readily removed from the reaction mixture by filtration through a short silica gel pad and **4** was obtained as a clear oil, pure by HPLC, in essentially quantitative yield. The



- (a) Paraformaldehyde, *p*-TsOH, toluene, reflux (100%). (b) (S)- $\alpha$ -phenylpropylamine, toluene, 40°. (c) NaHCO<sub>3</sub>, EtOH/H<sub>2</sub>O, 65° (91%). (d) H<sub>2</sub>, 10% Pd/C, MeOH/H<sub>2</sub>O (100%). (e) Paraformaldehyde, *p*-TsOH, toluene, reflux (100%). (f) CH<sub>3</sub>CN, **6**, Et<sub>3</sub>N, 40°. (g) Na<sub>2</sub>CO<sub>3</sub>, MeOH/H<sub>2</sub>O, rt. (89%). (h) H<sub>2</sub>, 10% Pd/C, MeOH/H<sub>2</sub>O (91%).

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described procedure was a modification of one used previously with Cbz-L-aspartic acid.<sup>10,11</sup>

Oxazolidinone **4**, without further purification, was treated with (S)- $\alpha$ -phenyl-propylamine in the presence of 0.11 equiv of AcOH to give a mixture of Cbz-D-2-aminobutyric acid (S)- $\alpha$ -phenyl-propylamide (**5**) and the N-hydroxymethyl derivative of **5** (**HOCH<sub>2</sub>-5**) in a ratio of approximately 1:15. Originally, these oxazolidinone coupling reactions were carried out at temperatures of 50-80°, which resulted in significant loss of the hydroxymethyl groups as the reaction proceeded. However, we found that by carrying out these reactions at a lower temperature we gained several advantages. Even though the lower reaction temperature increased reaction times, the reactions were now much cleaner and proceeded to give higher conversions of the amines to the desired products. At higher temperatures, the greater loss of the hydroxymethyl group resulted in formation of free formaldehyde which was then capable of consuming the amine and producing later eluting (HPLC) impurities. We saw very little of these impurities when the coupling reactions were carried out at 20-40°. Also, as the presence of base catalyzed the loss of the hydroxymethyl group, another way to reduce the amount of these impurities was to add the (S)- $\alpha$ -phenylpropylamine very slowly. Reducing the amount of impurities present allowed us to carry forward the crude materials without the need for recrystallization or other purification steps at these intermediate stages. Complete removal of the hydroxymethyl group was accomplished by treatment with NaHCO<sub>3</sub> in aqueous EtOH, giving **5** as a white solid in 91% yield. Hydrogenolysis then provided D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (**6**) in quantitative yield as a thick oil.

The other starting material for the synthesis of **2** was Cbz-L-aspartic acid, which was readily converted to the corresponding oxazolidinone **7** using a procedure similar to that described for **4**. Following the azeotropic removal of H<sub>2</sub>O, the solution was cooled, at which point the *p*-TsOH separated as a thick oil. The toluene solution was then decanted and concentrated, giving the desired product in very high yield and purity, ready to use directly in coupling with aminoamide **6**.

The second amide bond was then formed when oxazolidinone **7** was condensed with aminoamide **6** in the presence of 0.5 equivalents of Et<sub>3</sub>N. This reaction gave a mixture of **8** and the N-hydroxymethyl derivative of **8** (**HOCH<sub>2</sub>-8**) in a ratio of approximately 1:25. Complete removal of the hydroxymethyl group was achieved by treatment of an aqueous methanolic solution of the mixture with Na<sub>2</sub>CO<sub>3</sub>. This procedure gave Cbz-L-aspartyl-D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (**8**) as a white solid in 89% yield. The major advantage of this particular procedure, and one of the reasons that we preferred to use oxazolidinone chemistry, was that we were not required to use a protecting group for the L-aspartyl- $\beta$ -carboxylate.

In the final step, hydrogenolysis of **8** resulted in the formation of **2** as a white solid which had a purity by HPLC of 95%. The major impurities were determined to be L-aspartyl-L-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (1.4%), which was formed due to a small amount of racemization of the 2-aminobutyric acid moiety, and  $\beta$ -L-aspartyl-D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (3.4%), which was a rearrangement product of the corresponding  $\alpha$ -product. This mixture was recrystallized to give **2** having an HPLC purity of >99%. Thus, using the improved process described

above, the new high-potency sweetener L-aspartyl-D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (**2**) was synthesized in 70% overall yield *via* a multi-step sequence which required only a minimum of product manipulation.

## EXPERIMENTAL SECTION

All chemicals were reagent grade and used as received from the supplier. D-2-aminobutyric acid was purchased from Synthetech, Inc., Albany, OR. and (S)- $\alpha$ -phenylpropylamine was purchased from Celgene Corp., Warren, N.J. IR spectra were determined on a Perkin Elmer 281 spectrophotometer. Optical rotations were run on a Rudolph Autopol® III polarimeter. Ultraviolet spectra were measured on a Cary IE UV-visible spectrophotometer. Mass spectra were taken on a Kratos MS25RFA using EI (70 mV) with direct sample injection.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Microanalyses were carried out by Atlantic Microlab, Norcross, GA.

HPLC analyses were performed on a Beckman System Gold chromatograph using a Beckman Vetrasphere 4.6 x 150 mm ODS-C18 analytical column and a diode array detector set at 210 nm. Two isocratic eluent systems were employed: (1) 20%  $\text{CH}_3\text{CN}$  in 0.05M  $(\text{NH}_4)_2\text{H}_2\text{PO}_4$  solution adjusted to a final pH 3.8 and (2) 50%  $\text{CH}_3\text{CN}$  in 0.05M  $(\text{NH}_4)_2\text{H}_2\text{PO}_4$  solution adjusted to a final pH 3.8. Using eluent system (1), the  $k'$  values determined are 5.94 for **2** and 5.41 for **6**. Using eluent system (2), the  $k'$  values determined are 5.19 for **4**, 6.38 for **HOCH<sub>2</sub>-5**, 6.88 for **5**, 2.16 for **7**, 3.09 for **HOCH<sub>2</sub>-8** and 3.28 for **8**.

**3-Cbz-4-(R)-Ethyl Oxazolidin-5-one (4).**- To a solution of 19.4 g (81.9 mmol) of Cbz-D-2-aminobutyric acid (**3**) in 400 mL of toluene was added 2.8 g (93.3 mmol) of paraformaldehyde and 0.40 g (2.5 mol%) of *p*-TsOH $\cdot$ H<sub>2</sub>O. The resultant mixture was heated to 95° over a period of 1 hr and kept at this temperature until the solid paraformaldehyde had disappeared. The mixture was then refluxed for 60 min with azeotropic removal of H<sub>2</sub>O using a Dean-Stark trap (2.5% Cbz-D-2-aminobutyric acid remained after this initial treatment). The reaction mixture was cooled to 70°, an additional 0.2 g (6.7 mmol) of paraformaldehyde added, and heating repeated as above. Upon completion of the reaction, as determined by HPLC analysis (0.2% Cbz-D-2-aminobutyric acid remaining), the solution was cooled to rt and filtered through a short silica gel pad to remove the remaining formaldehyde polymer and *p*-TsOH. Concentration of the filtrate *in vacuo* gave 20.7 g (quantitative) of **4** as a colorless oil. This residue contained a small amount of toluene. An analytical sample was prepared by chromatography on silica gel using EtOAc/hexane as the eluent:  $[\alpha]_{\text{D}}^{24} = -92.3^\circ$  (*c* 1.20, MeOH); IR (Neat, KBr plates): 3040, 2980, 2950, 2880, 1810, 1720, 1500, 1450, 1415, 1360, 1315, 1235, 1165, 1135, 1040, 955, 915, 765, and 695  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.3 (s, 5H), 5.5 (br s, 1H), 5.2 (m, 3H), 4.3 (t, *J* = 4.8 Hz, 1H), 1.8-2.2 (m, 2H) and 0.96 (t, *J* = 7.4 Hz, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  172.5, 164.2, 135.6, 128.5, 128.4, 128.3, 78.0, 67.7, 55.5, 23.6 and 8.1; MS *m/z* (rel. int.): 249(8, M<sup>+</sup>), 107(3), 92(8), 91(100), 70(7), 65(9), 61(5), 56(5), 45(7), 43(51).

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{15}\text{NO}_4$ : C, 62.65; H, 6.02; N, 5.62. Found: C, 62.64; H, 6.09; N, 5.61

**Cbz-D-2-Aminobutyric Acid (S)- $\alpha$ -Phenylpropylamide (5).**- The 20.7 g of 3-Cbz-4-(R)-ethyl oxazolidin-5-one (**4**) from the above reaction was dissolved in 30 mL of toluene, 0.5 mL (11 mol%)

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of AcOH added and followed by 11.1 g (82.2 mmoles) of (S)- $\alpha$ -phenylpropylamine added portion wise, under N<sub>2</sub>, during 8 hrs. The reaction flask was flushed with N<sub>2</sub>, stoppered, and heated at 40° for 24 hrs. The toluene was removed under reduced pressure giving 31.8 g of an oily residue consisting of HOCH<sub>2</sub>-**5** and **5** in a ratio of approximately 15:1. A small amount of unreacted starting materials also remained. This crude product was dissolved in 200 mL of 95% EtOH and 50 mL of an aqueous 5% NaHCO<sub>3</sub> solution added. It was then reacted for 2 hrs at 65° followed by the addition of 1.5 mL of AcOH and 200 mL of H<sub>2</sub>O, during which time the product started to come out of solution. The mixture was cooled, filtered, and the solid washed with H<sub>2</sub>O. The solid was then dried at 40° in a vacuum oven until it reached a constant weight of 26.6 g (75.1 mmol, 91%). Purity by HPLC 99%: mp. 129.5-130.5°; [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -40.1° (c 1.0, MeOH); IR (KBr): 3300, 2970, 2930, 1690, 1645, 1545, 1530, 1445, 1390, 1300, 1270, 1240, 1130, 1120, 1080, 1055, 775, 740 and 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.2-7.33 (m, 10H), 6.60 (d, J = 8.4 Hz, 1H), 5.42 (d, J = 7.4 Hz, 1H), 5.07 (s, 2H), 4.84 (q, J = 8 Hz, 1H), 4.14 (q, J = 6.7 Hz, 1H), 1.6-1.9 (m, 4H) and 0.92 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  173.0, 158.4, 144.0, 138.2, 128.5-130.6, 68.9, 58.1, 56.8, 31.0, 27.7, 12.4 and 11.5; MS m/z (rel. int.): 354 (1, M<sup>+</sup>), 325 (4), 246 (2), 217 (8), 148 (9), 134 (9), 132 (8), 119 (10), 106 (19), 102 (24), 91 (100), 79 (14), 77 (14), 65 (7), 58 (10), 51 (9).

*Anal.* Calcd for C<sub>21</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>: C, 71.16; H, 7.39; N, 7.90. Found: C, 70.95; H, 7.44; N, 7.86

**D-2-Aminobutyric Acid (S)- $\alpha$ -Phenylpropylamide (6).**- A suspension of 26.6 g (75.1 mmol) of Cbz-D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (**5**) in 150 mL of MeOH was sparged with N<sub>2</sub> and 0.5 g of 10% Pd/C added. The mixture was then hydrogenated at 35-40 psi H<sub>2</sub> overnight on a Parr Shaker, during which time the product went into solution. The catalyst was removed by filtration through Celite® and the solvent evaporated. Drying overnight *in vacuo* gave 16.8 g (quantitative) of **6** as a thick oil. Purity by HPLC 98%: [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -125.6° (c 1.20, MeOH); IR (Neat, KBr plates): 3295, 2970, 2930, 2870, 1645, 1550, 1510, 1450, 1380, 1125, 1025, 750, and 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.78 (br d, 1H), 7.15-7.3 (m, 5H), 4.82 (dd, J = 7.2, 8.4 Hz, 1H), 3.35 (m, 1H), 2.30 (br s, 2H), 1.4-1.9 (m, 4H) and 0.86 (t, J = 7.4 Hz, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  174.0, 142.6, 128.5, 127.1, 126.6, 56.0, 54.3, 29.2, 27.5, 10.4, and 9.6; MS m/z (rel. int.): 220 (2, M<sup>+</sup>), 119 (4), 106 (15), 104 (8), 91 (20), 77 (8), 59 (10), 58 (100).

For further characterization, an analytical sample was prepared by crystallization of the D-tartrate salt from EtOH: mp. 185-187°; [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -94.5° (c 1.02, MeOH).

*Anal.* Calcd for C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>O<sub>7</sub>: C, 55.14; H, 7.02; N, 7.57. Found: C, 55.25; H, 7.15; N, 7.61

**3-Cbz-4-(S)-Carboxymethyl Oxazolidin-5-one (7).**- To 21.0 g (78.7 mmol) of Cbz-L-aspartic acid was added 400 mL of toluene, followed by 2.7 g (90 mmol) of paraformaldehyde and 0.4 g (2.7 mol%) of *p*-TsOH•H<sub>2</sub>O. The mixture was heated to 95° and held at this temperature for 1 hr until the solid had disappeared. It was then heated to reflux and refluxed for 1 hr with azeotropic removal of H<sub>2</sub>O using a Dean-Stark trap (5% Cbz-L-aspartic acid remained at this point). The mixture was cooled to 70°, 0.3 g (10 mmol) of para-formaldehyde added, and heating repeated as above. The mixture was then cooled and the pale yellow solution (1% Cbz-L-aspartic acid remaining) decanted from the

brownish gum (0.7 g, which was mostly *p*-TsOH). The toluene solution was concentrated under reduced pressure to give 22.4 g (quantitative) of a reddish gum (7).

For further characterization, an analytical sample was obtained by crystallization from EtOAc/hexane: mp. 86-87°. lit.<sup>10</sup> mp. 87-88.5°;  $[\alpha]_D^{24} = +134.0^\circ$  (c 1.0, MeOH). lit.<sup>10</sup>  $[\alpha]_D^{24} = +125.7^\circ$  (c 3.53, MeOH); IR (KBr): 3140, 2920, 1820, 1800, 1735, 1665, 1435, 1355, 1200, 1170, 1145, 1055, 1035, 995, 810, 765, 745, and 695  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.4 (s, 5H), 5.55 (br m, 1H), 5.1-5.35 (m, 3H), 4.4 (m, 1H), 3-3.3 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  175.1, 171.6, 152.9, 135.2, 128.8, 128.6, 128.4, 78.4, 68.1, 51.2, 34.1; MS *m/z* (rel. int.): 279 (1, M<sup>+</sup>), 235 (3), 144 (3), 126 (4), 107 (13), 104 (10), 92 (10), 91 (100), 77 (5), 65 (12), 51 (6), 44 (19), 43 (22).

*Anal.* Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>6</sub>: C, 55.91; H, 4.66; N, 5.02. Found: C, 55.96, H, 4.74, N, 4.98

**Cbz-L-Aspartyl-D-2-aminobutyric Acid (S)- $\alpha$ -Phenylpropylamide (8).**- A solution of 22.4 g of 3-Cbz-4-(S)-carboxymethyl oxazolidin-5-one (7) dissolved in 75 mL of CH<sub>3</sub>CN was added to the 16.8 g (75.1 mmol) of D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (6) from above (this gave slight warming of the solution). After the material was all in solution 5.2 mL of Et<sub>3</sub>N (50 mol%) was added, the head space flushed with N<sub>2</sub>, and the reaction vessel stoppered and heated at 40° for 24 hrs. This resulted in a product mixture consisting of HOCH<sub>2</sub>-8 and 8 in a ratio of approximately 25:1. A small amount of starting materials also remained. This solution was concentrated to a thick oil and the residue dissolved in 200 mL of MeOH, 120 mL of an aqueous 5% Na<sub>2</sub>CO<sub>3</sub> solution added and the mixture reacted at 30° for 24 hrs. The small amount of solid material which appeared during the reaction was removed by filtration and was washed with 200 mL of 70% MeOH/H<sub>2</sub>O. Removal of the hydroxymethyl group was complete at this point. Then 180 mL of 1N H<sub>2</sub>SO<sub>4</sub> was added to the above combined filtrate with vigorous stirring, lowering the pH of the mixture to 2.6, and the mixture kept overnight at 3°. The solid product was removed by filtration, washed with H<sub>2</sub>O, and dried *in vacuo* at 40-45° to constant weight. This gave 31.4 g (67.0 mmol, 89%) of 8 as a whitish solid. Purity by HPLC 94%: mp. 184.5-186.5°;  $[\alpha]_D^{24} = -11.3^\circ$  (c 1.5, MeOH).

For further characterization, an analytical sample was prepared by crystallization from EtOAc/hexane: mp. 187-188°;  $[\alpha]_D^{24} = -11.0^\circ$  (c 1.0, MeOH); IR (KBr): 3290, 3050, 2970, 2920, 1725, 1695, 1645, 1525, 1225, 1045, 740, and 695  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.05-8.27 (m, 1H), 7.15-7.40 (m, 10H), 5.08 (s, 2H), 4.77 (br q, J = 8.1 Hz, 1H), 4.47 (dd, J = 5.2, 4.7 Hz, 1H), 4.27 (dd, J = 7.6, 5.8 Hz, 1H), 2.77 (m, 2H), 1.5-2.0 (m, 4H) and 0.88 (m, 6H); <sup>13</sup>C NMR (CD<sub>3</sub>OD):  $\delta$  174.4, 173.7, 173.5, 159.7, 144.4, 139.3, 129.7, 129.3, 129.0, 128.4, 128.0, 68.0, 56.8, 53.4, 36.9, 30.5, 26.0, 11.4 and 10.7; MS *m/z* (rel. int.): 451 (2, M<sup>+</sup>-H<sub>2</sub>O), 423 (2), 289 (2), 199 (3), 155 (4), 134 (21), 108 (19), 107 (18), 106 (18), 91 (100), 79 (21), 77 (16), 58 (83).

*Anal.* Calcd for C<sub>25</sub>H<sub>31</sub>N<sub>3</sub>O<sub>6</sub>: C, 63.95; H, 6.65; N, 8.95. Found: C, 63.69; H, 6.65, N, 8.93

**L-Aspartyl-D-2-aminobutyric Acid (S)- $\alpha$ -Phenylpropylamide (2).**- A suspension of 16.0 g (34.1 mmol) of Cbz-L-aspartyl-D-2-aminobutyric acid (S)- $\alpha$ -phenylpropylamide (8) in 260 mL of 60% MeOH/H<sub>2</sub>O was sparged with N<sub>2</sub> and then 0.4 g of 10% Pd/C added. The mixture was hydrogenated at 40 psi H<sub>2</sub> on a Parr Shaker for eight hrs at rt. This gave the product as a suspension which was

## PREPARATION OF L-ASPARTYL-D-2-AMINO BUTYRIC ACID (S)- $\alpha$ -PHENYLPROPYLAMIDE

dissolved by adding 150 mL of H<sub>2</sub>O and then heating the mixture to 40-50°. The solution was filtered through Celite® to remove the catalyst and the crude filtrate (purity by HPLC 95%) concentrated *in vacuo*, giving 11.6 g of crude **2** as a white solid. This material was recrystallized from H<sub>2</sub>O/MeOH and dried *in vacuo* at 40° to give 10.6 g (31.2 mmol, 91%). Purity by HPLC 99%; mp. 198-199°; lit.<sup>1</sup> mp. 197-198°;  $[\alpha]_D^{24} = -28.8^\circ$  (c 1.0, AcOH); IR (KBr): 3270, 3050, 2960, 2920, 2860, 1640, 1530, 1445, 1375, 1265, 1210, 1120, 735 and 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (CD<sub>3</sub>OD):  $\delta$  7.2 (m, 5H), 4.60 (m, 1H), 4.20 (m, 1H), 3.94 (m, 1H), 2.5 (m, 2H), 1.55-1.85 (m, 4H) and 0.83 (m, 6H); <sup>13</sup>C NMR (CD<sub>3</sub>OD):  $\delta$  180.9, 178.2, 175.1, 148.7, 134.0, 132.6, 132.3, 61.1, 60.7, 56.7, 42.8, 34.7, 31.3, 15.8 and 15.0; MS *m/z* (rel. int.): 220 (1), 182 (2), 168 (5, (M<sup>+</sup>+1)/2), 122 (6), 110 (16), 107 (14), 95 (54), 91 (14), 77 (8), 70 (14), 59 (43), 58 (100), 55 (15), 43 (92); Moisture by Karl Fisher titration = 4%.

*Anal.* Calcd for C<sub>17</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> + 4% H<sub>2</sub>O: C, 58.44; H, 7.65; N, 12.03. Found: C, 58.59; H, 7.65; N, 11.99

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