ARTICLES

Discovery and Synthesis of a New Series of High-Potency L-Aspartyl-D-α-aminoalkanoyl-(S)-α-alkylbenzylamide Sweeteners

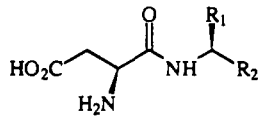
James G. Sweeny,* Lihong L. D'Angelo, Edith A. Ricks, and Guillermo A. Iacobucci†

Corporate Research and Development Department, The Coca-Cola Company, P.O. Drawer 1734, Atlanta, Georgia 30301

A new series of L-aspartyl-D-amino acid amide sweeteners is described in which the amide portion is prepared from an α-alkyl-substituted benzylamine. These materials show good taste characteristics and are 5 times more stable than aspartame at typical beverage pH (3–4). The most potent member of the series is L-aspartyl-D-α-aminobutyric acid (S)-α-ethylbenzylamide, having a sweetness potency 2000 times that of a 10% sucrose solution.

Keywords: *Artificial sweeteners; aspartic acid amides; aspartyl-D-amino acid amides; high-potency sweeteners*

In 1969, Mazur, Schlatter, and Goldkamp (Mazur et al., 1969) first reported on the sweetness of aspartame (**1**, R_1 = benzyl, R_2 = CO_2CH_3) and a related series of



1

aspartyl dipeptides. Since that time a large series of analogues have been prepared in an attempt to improve on both its sweetness potency (200 times that of sucrose) and stability (Walters et al., 1991).

The first significant potency increase in the area of aspartyl dipeptide sweeteners was reported by Fujino and co-workers (Fujino et al., 1973, 1975, 1976), who found that L-aspartyl aminomalonyl methyl fenchyl diester (**1**, R_1 = CO_2-fenchyl, R_2 = CO_2CH_3) was 50 000 times sweeter than sucrose. In a similar vein, workers at the Shanghai Institute of Organic Chemistry (Zeng and Wei, 1984), The Takasago Co. (Nagakura et al., 1986a,b), and General Foods (Zanno et al., 1988) prepared the related L-aspartyl-D-alanine β-fenchyl ester (**1**, R_1 = CO_2-fenchyl, R_2 = CH_3) having a potency of 5000 times that of sucrose, and Janusz (Janusz, 1987; Janusz et al., 1990) reported on L-aspartyl-D-phenylglycine β-fenchyl ester (**1**, R_1 = CO_2-β-fenchyl, R_2 = phenyl) also having a potency of 5000 times that of sucrose.

These compounds were found, unfortunately, to be slowly hydrolyzed at the acid pH (3–4) of soft drinks to give β-fenchyl alcohol, a compound that imparts an undesirable off-taste to the beverage at levels of less than 0.1 ppm (King et al., 1991).

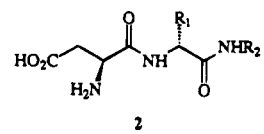
We have previously reported on one approach to solving this problem by attaching the bicycloalkyl unit of the fenchyl group directly to the alanine carbon (King et al., 1991). This gave compounds of type **1**, where R_1

fenchyl bornyl

= CH_2-bornyl and R_2 = CO_2CH_3, having sweetness potencies up to 4000 times that of sucrose. While solving the off-taste problems, these materials still had a stability no greater than that of aspartame as they were also methyl esters.

A very promising approach to the off-taste, stability, and potency problems was reported by Brennan and Hendrick of Pfizer, Inc., in 1983 (Brennan and Hendrick, 1983a,b, 1984, 1985). They found that an ester moiety was not required for sweetness in the aspartyl-D-alanine series. A group of the corresponding aspartyl-D-alanine amides (**2**) was found to have significant sweetness potency and was more stable than aspartame at beverage pH. In structure **2**, R_2 was described as any of a large series of branched or cyclic aliphatic groups.

In a related publication (Zeng et al., 1991), R_2 was described as a series of aromatic groups; the compound formed from 2,6-dimethylaniline had the highest potency of 500 times that of sucrose.

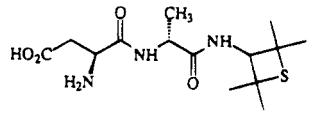


2

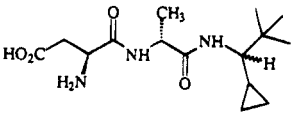
This potency was exceded, however, by the Brennan and Hendrick series with compound **3**, the tetramethylthietane analogue having a potency 2000 times that of sucrose. This material, under the trade name Alitame, is currently the subject of a new food ingredient application before the U.S. Food and Drug Administration. Compound **3** is 4–5 times more stable than aspartame at pH 3, due to the absence of the methyl ester group, and almost twice as potent as the (±)-α-cyclopropylneopentyl analogue **4** (**SP** = 1200 × sucrose), the second sweetest member of the series.

† Present address: Department of Chemistry, Emory University, 1515 Pierce Drive, Atlanta, GA 30322.

0021-8561/95/1443-1969$09.00/0

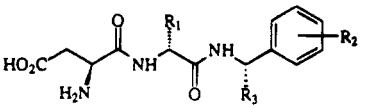


3



4

In this paper we describe our efforts to expand on the structures described in U.S. Patent 4,411,925 and the unexpected results obtained in our search (D'Angelo and Sweeny, 1994). We chose to prepare analogues of **4** as they would retain the desirable stability attributes of the series and hopefully be of improved sweetness potency. In particular, we decided to prepare a series of compounds in which the cyclopropyl ring of **4** is replaced by an aromatic group to give compounds of general structure **5**. The hope was that an aromatic



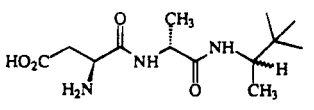
5

ring would show some of the electron donating ability of a sulfur atom and hence lead to enhanced receptor binding and presumably elevated potency. A series of analogues of **5** were therefore prepared in which the R_1, R_2, and R_3 groups were varied in a systematic manner.

The synthetic procedure selected involved a straight forward A → B → C approach (see Scheme 1) in which *N*-(carbobenzyloxy)-L-aspartic acid β-benzyl ester was converted to the α-*N*-hydroxysuccinimide ester using dicyclohexylcarbodiimide (DCC) as the coupling agent. The product was then reacted with a D-amino acid in dioxane–water to give a β-benzyl-*N*-CBZ-L-aspartyl-D-amino acid in moderate to good yields. This was in turn coupled with the desired α-alkylbenzylamine, again using DCC to afford the fully protected aspartyl amide. Finally, the sweetener was obtained by removing the benzyl ester and *N*-CBZ groups via catalytic hydrogenation over Pd/C.

RESULTS AND DISCUSSION

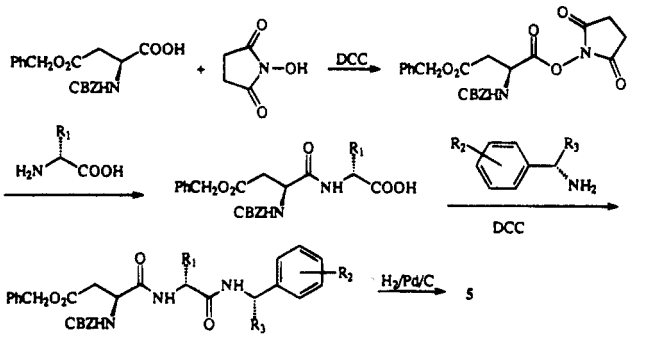
The first two compounds prepared as new sweetener candidates were L-aspartyl-D-alanine (*R*)- (**14**) and (*S*)- (**13**) α-methylbenzylamides as the two chiral α-methylbenzylamines are readily available commercially. These two materials had sweetness potencies of 10 and 180 times that of sucrose, respectively (see Table 1). The sweetness potency of the (*S*)-amine isomer and the relative lack of sweetness of the (*R*)-amine isomer is in keeping with the results of Brennan and Hendrick (1983), who found that the *S* isomer of **6** exhibits a potency of 375 while the *R* isomer is tasteless.



6

The other compounds (**15**–**20**) prepared via the systematic variation of R_3 in structure **5** are listed in Table 1. The most potent compound of this series was the α-cyclopropylbenzylamide (**20**). Further work on this compound was not pursued however, as it was felt that the cyclopropylcarbinylamine group may present synthetic, stability, or toxicological problems. Among the simple aliphatic substituents, the (*R*,*S*)-α-ethylbenzylamide substituent (**15**) showed the highest potency of 270 that of sucrose.

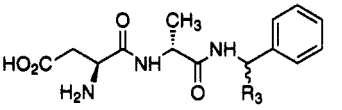
Scheme 1



As this potency was somewhat disappointing, an attempt was made to increase the potency by methylation of the aromatic ring. As shown in Table 2, however, all three methylated α-methylbenzylamides (**21**–**23**) showed potencies lower than that of the parent compound.

The final part of structure **5** to be varied was the R_1 group, i.e., the replacement of the D-alanine moiety with higher homologues. This approach did not at first

Table 1. Effect of Amine Structure on the Sweetness Potency of L-Aspartyl-D-alanine Amides



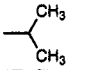
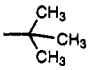
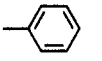
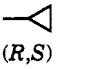
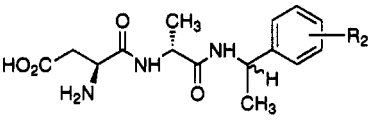
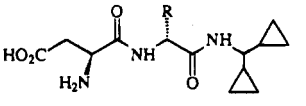
compd	R_3	SP (× 10% sucrose)
13	$-CH_3$ (*S*)	180
14	$-CH_3$ (*R*)	<10
15	$-CH_2CH_3$ (*R*,*S*)	270
16	 (*R*,*S*)	180
17	$-CH_2CH_2CH_3$ (*R*,*S*)	135
18	 (*R*,*S*)	150
19		180
20	 (*R*,*S*)	1080

Table 2. Effect of Aromatic Methylation on the Sweetness of L-Aspartyl-D-alanine (*R*,*S*)-α-Methylbenzylamides

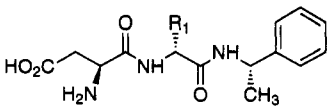


compd	R_2	SP (× 10% sucrose)
13 + **14**	H	90
21	*o*-CH_3	40
22	*m*-CH_3	40
23	*p*-CH_3	80



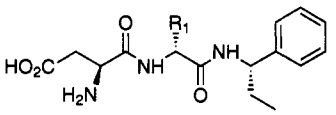
7

Table 3. Effect of the D-Amino Acid Structure upon the Sweetness Potency of the L-Aspartyl-D-amino Acid (S)-α-Methylbenzylamides



compd	R_1	SP (× 10% sucrose)
13	$-CH_3$	180
24	$-CH_2CH_3$	360
25	$-CH_2CH_2CH_3$	90
26		540
27		270

Table 4. Effect of the Variation of the D-Amino Acid on the Sweetness Potency of L-Aspartyl-D-amino Acid (S)-α-Ethylbenzylamides



compd	R_1	SP (× 10% sucrose)
28	$-CH_2CH_3$	2000
29		1500

appear to be promising as Brennan and Hendrick had tried a similar substitution in the case of compound **7** and found that the sweetness decreased in the order R = methyl (SP = 1200), R = ethyl (SP = 500), and R = isopropyl (SP = 110). In our case, however, we were pleasantly surprised to find an increase in potency from methyl (**13**, SP = 180) to ethyl (**24**, SP = 360) to isopropyl (**26**, SP = 540) in the case of the (*S*)-α-methylbenzylamides (see Table 3).

The reason for this surprising difference in properties between compounds of type **5** and **7** is not quite clear. However, molecular modeling work has provided some insights into how these differences can be rationalized (D'Angelo and Iacobucci, unpublished results, 1995). Other work on sweetener structure–activity relationships using computer-aided molecular modeling (Walters et al., 1991; Yamazaki et al., 1994) has also appeared recently.

It remained, of course, to prepare the analogues containing the sweetest isomer from Table 1 [the (*S*)-α-ethylbenzylamide] and the sweetest isomers from Table 3 (the D-homoalanine and D-valine analogues). As anticipated, L-aspartyl-D-valine (*S*)-α-ethylbenzylamide] (**29**, SP = 1500) and L-aspartyl-D-homoalanine (*S*)-α-ethylbenzylamide (**28**, SP = 2000) gave very high sweetness potencies. Also as expected, a storage study of **28** in pH 3.0 buffer showed only 10% hydrolysis after 6 months at 30 °C. The only detected degradation products were L-aspartic acid, D-homoalanine (*S*)-α-ethylbenzylamide and the β-aspartyl isomer of the starting sweetener.

MATERIALS AND METHODS

Taste tests were conducted with a panel of four tasters using a range of sample dilutions in distilled water versus aspartame at 200 ppm. Sweetener potencies were then calculated versus sucrose by using an aspartame potency of 180 times sucrose.

With the exception of tetrahydrofuran, which was distilled from lithium aluminum hydride, all chemicals were of reagent grade and used as received from the supplier. Melting points are uncorrected. Optical rotations were determined on a Perkin-Elmer 241 polarimeter, GC analysis was performed on a Varian 2700 gas chromatograph, and ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. The complete ^1H and ^{13}C NMR data for all of the compounds described below are given in Tables 5–10.

The α-alkylbenzylamines used in preparing the sweeteners were synthesized via reduction of the corresponding ketoximes with sodium ethanol as described by Brennan and Hendricks (1983a,b). The product amines had boiling points and NMR spectra consistent with those reported in the literature (Rinaldi et al., 1982; Alcaide et al., 1986; Brunner et al., 1986).

The optical purity of the α-methyl- and α-ethylbenzylamine was determined by GC on a 12 m, 0.32 mm i.d.; SE 30 column programmed at 4 °C/min from 40 to 180 °C after an initial 4 min hold. The amines were derivatized with trifluoroacetylprolyl chloride in CH_2Cl_2 (Aldrich) prior to injection on the column.

***N*-(Carbobenzyloxy)-β-benzyl-L-aspartyl-D-alanine (8).** A mixture of 5.0 g of *N*-(carbobenzyloxy)-β-benzyl-L-aspartic acid (14 mmol), 100 mL of tetrahydrofuran, 2.88 g (14 mmol) of dicyclohexylcarbodiimide; and 1.61g (14 mmol) of *N*-hydroxysuccinimide was stirred at room temperature overnight. The solution was then filtered and the filtrate evaporated to give a thick oil. To this oil was added 80 mL of dioxane followed by a solution of 1.5 g (16.6 mmol) of D-alanine, 10 mL of dioxane, 20 mL of H_2O, and 1.85 mL (1.34 g, 13.3 mmol) of triethylamine.

The mixture was stirred at room temperature overnight. The solution was filtered and the filtrate concentrated to approximately 25 mL. The residue was diluted with 100 mL of H_2O, acidified to pH 2.0 with 10% H_3PO_4, and extracted twice with 100 mL of ethyl acetate. The combined ethyl acetate layers were backwashed with 100 mL of H_2O and 50 mL of brine. After drying over Na_2SO_4, the ethyl acetate layer was evaporated to give a white solid. This was crystallized from ethyl acetate/hexane to give 4.2 g, mp 165–67 °C. A second crop of 303 mg was obtained at 5 °C from the mother liquors to give a total yield of 4.5 g (75%). The literature (Brennan and Hendrick, 1983a,b) gives mp 158–59 °C.

N-(Carbobenzyloxy)-β-benzyl-L-aspartyl-D-valine (**9**, 57%, mp 93–96 °C); *N*-(carbobenzyloxy)-β-benzyl-L-aspartyl-D-α-aminobutyric acid (**10**, 57%, mp 151–53 °C) [lit. mp 150–52 °C (Verlander et al., 1986)], *N*-(carbobenzyloxy)-β-benzyl-L-aspartyl-D-phenylglycine (**11**, 54%, mp 64–67 °C), and *N*-(carbobenzyloxy)-L-aspartyl-D-α-aminopentanoic acid (**12**, 73%, mp 91–95 °C) were prepared in a similar procedure by substituting equivalent weights of the appropriate D-amino acid for the D-alanine.

β-Benzyl-*N*-CBZ-L-aspartyl-D-alanine (*S*)-α-Methylbenzylamide (13A). In a 50 mL flask was mixed 500 mg (1.17 mmol) of *N*-(carbobenzyloxy)-β-benzyl-L-aspartyl-D-alanine, 0.16 mL (150 mg, 1.24 mmol) of (*S*)-α-methylbenzylamine, 241 mg (1.17 mmol) of dicyclohexylcarbodiimide, 210 mg (1.17 mmol) of *N*-hydroxy-5-norbornene-2,3-dicarboximide, and 25 mL of dioxane. The solution was stirred at room temperature overnight and filtered. The filtrate was then evaporated to a solid. This was dissolved in 50 mL of ethyl acetate, washed twice with 30 mL of 5% aqueous citric acid, twice with 30 mL of 4% aqueous $NaHCO_3$, and twice with 30 mL of brine, dried over $MgSO_4$, and evaporated to give 0.66 g of white solid. This was recrystallized from ethyl acetate/hexane to give 0.55 g (1.04 mmol, 89%) of white crystals, mp 168–70 °C.

N-CBZ-β-benzyl-L-aspartyl-D-alanine (*R*)-α-methylbenzylamide (**14A**), 88%, mp 167–9 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-alanine (*R,S*)-α-ethylbenzylamide (**15A**), 86%, mp 133–34.5 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-alanine (*R,S*)-α-isopropylbenzylamide (**16A**), 78%, mp 135–9 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-alanine (*R,S*)-α-*n*-propylbenzylamide (**17A**), 84%, mp 153–55 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-alanine (*R,S*)-α-*tert*-butylbenzylamide (**18A**), 77%, amorphous; *N*-CBZ-β-benzyl-L-aspartyl-D-alanine α-phenylbenzyl amide (**19A**), 83%, mp 165–68 °C; *N*-CBZ-β-benzylaspartyl-D-alanine α-cyclopropyl-

Table 5. ^{1}H NMR Spectral Data for Sweetener Intermediates 8–12

sample	solvent	ArH	NH	CH_2O	NCH	NCH	CH_2CO	CH	CH_3
8	$CDCl_3$ + CD_3OD	7.15–7.5 (m, 10H)	6.25 (m, 1H)	5.05 (bs, 4H)	4.63 (m, 1H)	4.43 (m, 1H)	2.75–2.97 (m, 2H)		1.35 (d, 3H)
9	CD_3OD	7.27–7.33 (m, 10H)	7.09 (d, 1H) 6.12 (d, 1H)	5.10 (m, 4H)	4.63–4.86 (m, 1H)	4.46–4.52 (m, 1H)	2.72–3.02 (m, 2H)	2.09–2.28 (m, 1H)	0.88 (d, 6H)
10	$CDCl_3$ + CD_3OD	7.2–7.4 (bs, 10H)	6.40 (d, 1H)	5.05 (bs, 4H)	4.60 (m, 1H)	4.38 (m, 1H)	2.75–2.90 (m, 2H)	1.55–1.90 (m, 2H)	0.82 (t, 3H)
11	$CDCl_3$	7.27–7.30 (m, 15H)	7.82 (d, 1H) 6.15 (d, 1H) 5.55 (d, 1H)	5.16 (m, 2H) 5.09 (m, 2H)	5.01 (m, 1H)	4.80 (m, 1H)	2.60–2.98 (m, 2H)		
12	CD_3OD	7.27–7.33 (m, 10H)	7.09 (d, 1H) 6.12 (d, 1H)	5.10 (m, 4H)	4.63–4.80 (m, 1H)	4.48–4.60 (m, 1H)	2.71–3.06 (m, 2H)	1.47–1.98 (m, 2H) 1.12–1.42 (m, 2H)	0.89 (t, 3H)

Table 6. ^{1}H NMR Spectral Data for Sweetener Intermediates 13A–29A

sample	solvent	ArH	NH	$ArCH_2O$	CHN	CH_2CO	CH	CH_3	CH_3Ar
13A	$CDCl_3$	7.27–7.33 (m, 15H)	7.2 (d, 1H) 7.0 (d, 1H) 6.0 (d, 1H)	5.07 (s, 2H) 5.05 (s, 2H)	4.4–4.6 (m, 3H)	2.65–3.1 (dd, **2H**)		1.3 (d, 3H) 1.4 (d, 3H)	
14A	$CDCl_3$	7.24–7.29 (m, 15H)	7.2 (d, 1H) 7.1 (d, 1H) 6.05 (d, 1H)	5.1 (s, 2H) 5.0 (s, 2H)	4.29–4.73 (m, 3H)	2.6–3.05 (dd, 2H)		1.5 (d, 3H) 1.3 (d, 3H)	
15A	$CDCl_3$	7.15–7.40 (m, 15H)	6.8–7.0 (m, 2H) 5.80–5.95 (m, 1H)	5.10 (d, 4H)	4.4–4.65 (m, 2H) 4.75–5.05 (m, 1H)	2.70–3.20 (m, 2H)	1.79 (q, 2H)	0.87 (t, 3H) 1.33 (d, 3H)	
16A	$CDCl_3$	7.15–7.40 (m, 15H)	6.8–7.0 (m, 2H) 5.80–5.95 (q, 1H)	5.10 (m, 4H)	4.40–4.75 (m, 3H)	2.70–3.20 (m, 2H)	2.0 (m, 1H)	0.75 (dd, 3H) 0.90 (dd, 3H) 1.32 (t, 3H)	
17A	$CDCl_3$	7.10–7.40 (m, 15H)	6.75–6.95 (m, 2H) 5.70–5.90 (m, 1H)	5.10 (m, 4H)	4.40–4.65 (m, 2H) 4.85–5.05 (m, 1H)	2.70–3.20 (m, 2H)	1.75 (m, 2H) 1.1–1.4 (m, 2H)	1.33 (d, 3H) 0.90 (m, 3H)	
18A	$CDCl_3$	7.15–7.40 (m, 15H)	6.9–7.2 (m, 2H) 5.90–6.05 (m, 1H)	5.10 (m, 4H)	4.30–4.55 (m, 1H) 4.60–4.85 (m, 2H)	2.70–3.10 (m, 2H)		0.90 (d, 9H) 1.30 (t, 3H)	
19A	$CDCl_3$	7.1–7.40 (m, 20H)	6.8 (d, 1H) 6.25 (d, 1H)	5.04 (d, 2H) 4.7–4.95 (m, 2H)	4.5–4.7 (m, 2H) 5.75 (m, 1H)	2.65–3.25 (dd, 2H)		1.38 (d, 3H)	
20A	$CDCl_3$	7.2–7.5 (m, 15H)	6.8–7.1 (m, 2H) 5.8–5.95 (m, 1H)	5.10 (m, 4H)	4.30–4.65 (m, 3H)	2.70–3.2 (m, 2H)	1.0–1.2 (m, 1H) 0.3–0.65 (m, 4H)	1.37 (t, 3H)	
21A	$CDCl_3$	7.10–7.40 (m, 14H)	6.8–7.05 (dd, 2H) 5.8–5.95 (m, 1H)	5.0–5.15 (m, 4H)	4.4–4.65 (m, 2H) 5.15–5.3 (m, 1H)	2.70–3.2 (m, 2H)		1.34 (d, 3H) 1.42 (d, 3H)	2.36 (s, 3H)
22A	$CDCl_3$	7.10–7.40 (m, 14H)	6.75–7.1 (m, 2H) 5.75–5.95 (m, 1H)	4.95–5.15 (m, 4H)	4.4–4.65 (m, 2H) 4.8–5.1 (m, 1H)	2.70–3.25 (m, 2H)		1.35 (dd, 3H) 1.44 (dd, 3H)	2.31 (s, 3H)
23A	$CDCl_3$	7.10–7.40 (m, 14H)	6.75–7.0 (m, 2H) 5.75–5.90 (m, 1H)	5.0–5.15 (m, 4H)	4.4–4.65 (m, 2H) 4.8–5.1 (m, 1H)	2.70–3.25 (m, 2H)		1.35 (dd, 3H) 1.43 (dd, 3H)	2.28 (s, 3H)
24A	$CDCl_3$	7.26–7.34 (m, 15H)	6.69–6.8 (dd, 2H) 5.75 (d, 1H)	5.09 (s, 2H) 5.07 (s, 2H)	4.57 (m, 1H) 4.32 (m, 1H) 5.15 (m, 1H)	2.71–3.6 (m, 2H)	1.52–2.08 (m, 2H)	1.45 (d, 3H) 0.86 (t, 3H)	
25A	$CDCl_3$	7.23–7.36 (m, 15H)	6.64–6.70 (m, 2H) 5.73 (d, 1H)	5.06–5.18 (m, 5H)	4.49–4.62 (m, 1H) 4.28-4.44 (m, 1H)	2.69–3.22 (m, 2H)	1.80–2.01 (m, 2H) 1.1-1.2 (m, 2H)	1.4 (d, 3H) 0.9 (t, 3H)	
26A	CDCl3	7.23–7.34 (m, 15H)	6.80 (d, 1H) 6.67 (d, 1H) 5.80 (d, 1H)	5.09 (s, 2H) 5.06 (s, 2H)	4.51–4.68 (m, 1H) 4.15–4.29 (m, 1H) 5.15 (m, 1H)	2.68–3.19 (m, 2H)	2.22–2.40 (m, 1H)	1.4 (d, 3H) 0.77–0.92 (m, 6H)	
27A	$CDCl_3$	7.2–7.3 (m, 20H)	6.69–6.80 (m, 1H) 6.26 (d, 1H) 5.91 (d, 1H)	5.09–5.11 (m, 4H)	4.03–4.15 (m, 1H) 4.52–4.68 (m, 1H) 5.31–5.39 (m, 1H)	2.60–3.17 (m, 2H)		1.40 (m, 3H)	
28A	$CDCl_3$	7.15–7.45 (m, 15H)	5.85 (m, 1H) 6.75–6.9 (t, 2H)	5.10 (m, 4H)	4.60 (m, 1H) 4.85 (m, 1H) 4.35 (q, 1H)	2.70–3.15 (m, 2H)	1.55–2.05 (m, 4H)	0.86 (bt, 6H)	
29A	$CDCl_3$	7.21–7.33 (m, 15H)	6.85 (d, 1H) 6.69 (d, 1H) 5.82 (d, 1H)	5.06 (s, 2H) 5.09 (s, 2H)	4.79–4.92 (m, 1H) 4.51–4.66 (m, 1H) 4.20–4.31 (m, 1H)	2.70–3.17 (m, 2H)	2.18–2.40 (m, 1H) 1.68–1.88 (m, 2H)	0.70–0.97. (m, 9H)	

benzylamide (**20A**), 62%, mp 162–6 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-alanine (*R,S*)-α,2-dimethylbenzylamide (**21A**), 89%, mp 136–8 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-alanine (*R,S*)-α,3-dimethylbenzylamide (**22A**), 86%, mp 123–5 °C, *N*-CBZ-β-benzyl-L-aspartyl-D-alanine (*R,S*)-α,4-dimethylbenzylamide (**23A**), 89%, mp 146–8 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-α-aminobutyric acid (*S*)-α-methylbenzylamide (**24A**), 56%, mp 167–69 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-α-aminopentanoic acid (*S*)-α-methylbenzylamide (**25A**), 69%, mp 158–61 °C; *N*-CBZ-β-benzyl-L-aspartyl-D-valine-(*S*)-α-methylbenzylamide (**26A**), 71%, mp 178–80 °C; and *N*-CBZ-β-benzyl-L-aspartyl-D-phenylglycine (*S*)-α-methylbenzylamide (**27A**), 45%, mp 160–4 °C, were prepared from the corresponding β-benzyl-*N*-CBZ-aspartyl-D-amino acids and benzylamines as described above.

L-Aspartyl-D-alanine (S)-α-Methylbenzylamide (13). *N*-(carbobenzyloxy)-β-benzyl-L-aspartyl-D-alanine (*S*)-α-methylbenzylamide (0.55 g, 1.04 mmol) was dissolved in 50 mL of methanol. To this was added 0.06 g of 10% Pd on activated carbon. The mixture was hydrogenated at 40 psi overnight.

Table 7. ^{1}H NMR Spectral Data for Sweetener Compounds 13–29

sample	solvent	ArH	NCH	NCH	NCH	CH_2CO	CH	CH_3	CH_3Ar
13	CD_3OD	7.26–7.4 (m, 5H)	5.0 (m, 1H)	4.37–4.42 (m, 1H)	3.95–4.1 (m, 1H)	2.60–2.71 (m, 2H)		1.44 (d, 3H) 1.38 (d, 3H)	
14	CD_3OD	7.23–7.33 (m, 5H)	4.90 (m, 1H) (in HOD peak)	4.30–4.43 (m, 1H)	3.9–4.1 (m, 1H)	2.59–2.67 (m, 2H)		1.45 (d, 3H) 1.36 (d, 3H)	
15	CD_3OD	7.20–7.40 (m, 5H)	4.75 (m, 1H)	4.40 (m, 1H)	4.05 (m, 1H)	2.55–2.70 (m, 2H)	1.80 (m, 2H)	1.40 and 1.30 (dd, 3H) 0.93 (t, 3H)	
16	CD_3OD	7.15–7.35 (m, 5H)		4.35–4.60 (m, 2H)	4.05 (m, 1H)	2.55–2.75 (m, 2H)	2.05 (m, 1H)	1.40 and 1.24 (dd, 3H) 1.00 (t, 3H) 0.77 (t, 3H)	
17	CD_3OD	7.20–7.40 (m, 5H)	4.90 (m, 1H) (in HOD peak)	4.40 (m, 1H)	4.05 (m, 1H)	2.60–2.75 (m, 2H)	1.75 (m, 2H) 1.25–1.45 (m, 2H)	1.42 and 1.31 (dd, 3H) 0.96 (t, 3H)	
18	CD_3OD	7.20–7.40 (m, 5H)	4.80 (m, 1H)	4.55 (m, 1H)	4.10 (m, 1H)	2.60–2.80 (m, 2H)		0.93 (s, 9H) 1.41 and 1.24 (dd, 3H)	
19	CD_3OD	7.23–7.38 (m, 10H)	6.17 (s, 1H)	4.45 (q, 1H)	3.95 (m, 1H)	2.50–2.65 (m, 2H)		1.37 (d, 3H)	
20	CD_3OD	7.25–7.45 (m, 5H)	4.80 (m, 1H) (in HOD peak)	4.30 (q, 1H)	4.05 (m, 1H)	2.63 (m, 2H)	1.20 (m, 1H) 0.61 (m, 2H) 0.39 (m, 2H)	1.40 and 1.32 (dd, 3H)	
21	CD_3OD	7.1–7.4 (m, 4H)	5.18 (m, 1H)	4.35 (q, 1H)	4.05 (m, 1H)	2.60–2.75 (m, 2H)		1.41 (d, 3H) 1.34 (m, 3H)	2.36 (s, 3H)
22	CD_3OD	7.0–7.25 (m, 4H)	4.90 (m, 1H) (in HOD peak)	4.35 (q, 1H)	4.05 (m, 1H)	2.60–2.75 (m, 2H)		1.44 (d, 3H) 1.35 (dd, 3H)	2.33 (s, 3H)
23	CD_3OD	7.0–7.3 (m, 4H)	4.90 (m, 1H) (in HOD peak)	4.35 (q, 1H)	4.05 (m, 1H)	2.55–2.70 (m, 2H)		1.43 (d, 3H) 1.35 (dd, 3H)	2.30 (s, 3H)
24	D_2O	7.34–7.38 (m, 5H)	4.88–4.93 (m, 1H)		4.12–4.19 (m, 2H)	2.66–2.73 (m, 2H)	1.61–1.83 (m, 2H)	1.46 (m, 3H) 0.87 (t, 3H)	
25	CD_3OD	7.21–7.38 (m, 5H)	5.0 (m, 1H)	4.36 (m, 1H)	4.03 (m, 1H)	2.48–2.78 (m, 2H)	1.59–1.85 (m, 2H) 1.22–1.43 (m, 2H)	1.47 (d, 3H) 0.97 (t, 3H)	
26	D_2O	7.28–7.39 (m, 5H)	4.89 (m, 1H)	4.2 (t, 1H)	4.06 (d, 1H)	2.76 (m, 2H)	2.02 (m, 1H)	1.41 (d, 3H) 0.92 (m, 6H)	
27	CD_3OD	7.2–7.4 (m, 10H)	5.3–5.4 (m, 1H)	4.87–4.96 (m, 1H)	3.95–4.08 (m, 1H)	2.35–2.62 (m, 2H)		1.2–1.3 (m, 3H)	
28	CD_3OD	7.1–7.4 (m, 5H)	4.80 (m, 1H)	4.30 (m, 1H)	4.05 (m, 1H)	2.50–2.70 (m, 2H)	1.76 (m, 4H)	0.93 (m, 6H)	
29	D_2O	7.26–7.37 (m, 5H)	4.55–4.69 (m, 1H)	4.23–4.40 (m, 1H)	4.06–4.12 (m, 1H)	2.99–3.08 (m, 2H)	1.83–2.02 (m, 1H) 1.58–1.82 (m, 2H)	0.72–0.93 (m, 9H)	

Table 8. ^{13}C NMR Spectral Data for Sweetener Intermediates 8–12

sample	solvent	CO	OCON	Ar	$ArCH_2O$	COCHN	CH_2CO	CH	CH_3
8	$CDCl_3 + CD_3OD$	176.7, 173.3, 172.3	159.0	138.0, 137.4, 130.6, 130.4, 130.3, 130.1	69.2 68.7	52.0 50.2	38.2		19.5
9	CD_3OD	174.3, 172.8, 169.4	158.5	127.3, 130.1–130.7	69.4 68.9	59.1 53.0	35.3	26.5	20.7
10	$CDCl_3 + CD_3OD$	176.5, 173.1, 172.6	159.0	138.0, 137.4, 130.5, 130.4, 130.2, 130.1, 129.9	69.1 68.9	55.3 52.3	38.3	26.7	11.0
11	$CDCl_3$	175.1, 173.4, 172.1	158.6	138.2, 137.2, 130.9, 130.6, 130.4, 130.2, 130.1, 129.3	69.3 68.9	58.5 53.0	38.5		
12	CD_3OD	177.6, 173.5, 172.6	158.5	137.3, 134.0, 132.7, 130.8, 130.1–130.6	69.3 68.9	54.0 52.9	38.9	26.3 20.2	15.3

The catalyst was removed by filtration through a Celite filter, and the filtrate was evaporated to give 0.43 g of solid. This was then dissolved in 200 mL of water and filtered to remove a small amount of dicyclohexylurea which was carried over from the previous step. The filtrate was freeze-dried to give 0.26 g (0.85 mmol, 82%) of white solid: mp 194–96 °C; $[\alpha]_D$ = +41.5° (c = 1.3, MeOH).

L-Aspartyl-D-alanine (*R*)-α-methylbenzylamide (**14**), 82%, mp 198–200 °C; L-aspartyl-D-alanine (*R,S*)-α-ethylbenzylamide (**15**), 87%, mp 180–3 °C; L-aspartyl D-alanine (*R,S*)-α-isopropylbenzylamide (**16**), 90%, mp 187–91 °C; L-aspartyl-D-alanine (*R,S*)-α-*n*-propylbenzyl amide (**17**), 83%, mp 184–6 °C; L-aspartyl-D-alanine (*R,S*)-α-*tert*-butylbenzylamide (**18**), 90%, mp 158–63 °C; L-aspartyl-D-alanine-α-phenylbenzylamide (**19**), 51%, mp 193–5 °C; L-aspartyl-D-alanine (*R,S*)-α-cyclopropylbenzylamide (**20**), 93%, mp 188–90 °C; L-aspartyl-D-alanine (*R,S*)-α,2-dimethylbenzylamide (**21**), 77%, mp 185–7 °C; L-aspartyl-D-alanine (*R,S*)-α,3-dimethylbenzylamide (**22**), 94%, mp 177–9 °C; L-aspartyl-D-alanine (*R,S*)-α,4-dimethylbenzylamine (**23**), 99%, mp 172–5 °C; L-aspartyl-D-α-aminobutyric acid (*S*)-α-methylbenzylamide (**24**), 99%, mp 185–9 °C; L-aspartyl-D-α-aminopentanoic acid (*S*)-α-methylbenzylamide (**25**), 35%, mp 203–5 °C; L-aspartyl-D-valine (*S*)-α-methylbenzylamide (**26**), 45%, mp >230 °C; and L-aspartyl-D-phenylglycine (*S*)-α-methylbenzylamide (**27**), 44%, mp 211–13 °C, were prepared as described above via reduction of the *N*-CBZ, β-benzyl derivatives.

(*S*)-α-Ethylbenzylamine L-(+)-Tartrate. Racemic α-ethylbenzylamine was treated with 1 molar equiv of L-(+)-tartaric acid in 95% ethanol. The product was then recrystallized five times from the same solvent (concentration ≈ 10%) to give the (*S*)-α-ethylbenzylamine tartrate (*S*/*R* = 20/1) in 11% yield: mp 176–9 °C; $[\alpha]_D$ +22° (c 1.0, H_2O). The optical isomer ratio was

Table 9. ^{13}C NMR Spectral Data for Sweetener Intermediates 13A–29A (Values in Parentheses Represent Diastereoisomer Peaks for Compounds Prepared from Racemic Amines)

sample	solvent	CO	OCON	Ar	OCH_2Ar	ArCHN	COCHN	CH_2CO	CH	CH_3
13A	$CDCl_3$	173.6, 173.0, 172.6	158.0	145.6, 137.9, 137.3, 130.2–130.7	69.3 68.8	53.4	51.1 50.7	38.1		23.8 19.5
14A	$CDCl_3$	173.9, 172.8, 173.2	159.2	145.5, 137.9, 137.3, 130.9, 130.7, 130.1, 129.2, 128.2	69.4 68.7	53.3	51.0 50.5	38.3		23.3 19.2
15A	$CDCl_3$	173.8, 173.0, 172.6	158.2	144.5, 144.3, 137.7, 137.2, 128.5–130.7	69.4 68.9	56.8	53.1 51.1	38.0	31.2	19.4 12.5
16A	$CDCl_3$	173.8 (173.7) 172.9 (173.1) 172.6 (172.7)	158.2	143.8, 143.5, 137.8, 137.3, 128.9–131.0	69.4 68.9	61.4 (61.1)	53.2 51.0	37.9	35.4 (35.0)	21.6 20.7 (20.5) 19.3 (19.2)
17A	$CDCl_3$	173.9 (173.8) 173.0 (172.9) 172.5 (172.4)	158.2	144.8, 144.6, 137.8, 137.1, 128.4–130.7	69.5 69.0	55.1	53.2 51.1	40.4 (38.0)	21.3 21.1	19.4 15.5
18A	$CDCl_3$	173.4 172.9 172.7	158.2	141.9, 137.9, 137.3, 129.7–130.7, 129.0	69.3 68.8	63.9 (63.8)	53.2 51.2 (51.0)	37.9	35.7	28.4 19.0 (18.7)
19A	$CDCl_3$	170.1, 168.9, 168.8	157.5	139.7, 139.6, 125.3–126.8	65.6 65.0	54.6	49.3 47.3	33.8		15.3
20A	$CDCl_3$	173.7, 172.9, 172.4	159.4	144.1, 137.8, 137.2, 128.5–130.7	69.5 68.8	58.9	53.2 51.1	38.0	5.6, 5.2 18.4	19.4
21A	$CDCl_3$	173.7, 172.6, 172.5	158.2	143.5, 143.4, 137.8, 137.2, 132.6, 126.7–130.7	69.4 68.8	53.2	51.0 (50.9) 47.4 (47.2)	38.1		23.0 (22.9) 20.9 19.5 (19.4)
22A	$CDCl_3$	174.1 (173.9) 172.8 (172.7) 172.5 (172.4)	158.2	145.4, 145.3, 140.1, 137.7, 124.9–130.7	69.5 68.9	53.2	51.0 (50.7) 50.5	38.0		23.7 (23.6) 23.2
23A	$CDCl_3$	174.0 172.9 172.5	158.2	142.3, 138.7, 137.8, 137.1, 127.9–131.3	69.5 68.5	53.2	51.0 50.4 (50.3)	38.0		19.4 (19.3) 23.7 22.7 19.4
24A	$CDCl_3$	178.8, 172.7, 172.0	154.4	128.2–130.4	69.5 68.9	56.7	53.3 50.7	36.5	26.6	19.8 11.7
25A	$CDCl_3$	173.9, 172.6, 172.2	158.2	145.4, 143.1, 130.2–130.6, 129.3, 128.2	69.5 68.9	55.3	51.0 50.7	35.7	26.7 23.7	20.6 15.4
26A	$CDCl_3$	173.6, 172.8, 171.8	158.1	145.3, 137.9, 137.2, 130.4–130.7, 129.3, 128.2	69.3 68.9	60.6	53.3 50.7	38.3	31.7 23.6	21.0 19.2
27A	$CDCl_3$	172.7, 171.9, 170.5		144.8, 138.0, 139.5, 136.5, 131.2, 130.2–130.7, 129.6, 128.2,	69.4 68.8	59.7	53.2 51.0	37.9		
28A	$CDCl_3$	173.6, 172.8 172.4	158	144.4, 128.6–130.7	69.3 68.8	56.8	56.7 53.3	39.1	26.7 31.1	11.6 12.5
29A	$CDCl_3$	173.7, 172.8, 172.0	158.5	144.4, 130.3, 130.5–130.7, 128.6	69.4 68.9	60.7	56.9 53.3	35.4	26.6 21.1	19.1 12.5

determined using GC analysis of the *N*-(trifluoroacetyl)-L-proline derivative as described in the general section above.

***N*-(Carbobenzyloxy)-β-benzyl-L-aspartyl-D-α-aminobutyric Acid (*S*)-α-Ethylbenzylamide (28A).** To 250 mL of 4% aqueous sodium carbonate was added 3.22 g (11.3 mmol) (*S*)-α-ethylbenzylamine L-(+)-tartrate. The mixture was extracted twice with 125 mL of methylene chloride, and the combined methylene chloride extracts were dried over Na_2SO_4 and evaporated at <25 °C and 20 mm to give a liquid. This was dissolved in 10 mL of dioxane and added to a stirred mixture of 5.0 g (11.3 mmol) of *N*-(carbobenzyloxy)-β-benzyl-L-aspartyl-D-α-aminobutyric acid, 200 mL of dioxane, 2.33 g of dicyclohexylcarbodiimide (11.3 mmmol), and 2.5 g (7.0 mmol) of *N*-hydroxy-5-norbornene-2,3-dicarboximide. The mixture was stirred at room temperature overnight and then filtered, and the filtrate was evaporated to a thick oil. The oil was dissolved in 300 mL of chloroform and washed twice with 200 mL of 4% aqueous citric acid, three times with 150 mL of 4% aqueous $NaHCO_3$, and with 100 mL of H_2O. Drying the chloroform layer over Na_2SO_4 and evaporation of the solvent gave an amorphous solid. Crystallization from ethyl acetate and hexane yielded 5.55 g (9.93 mmol, 88%) of the title compound, mp 134–36 °C.

L-Aspartyl-D-α-aminobutyric Acid (*S*)-α-Ethylbenzylamide (28). To a solution of 5.25 g (9.4 mmol) of *N*-CBZ-β-benzyl-L-aspartyl-D-α-aminobutyric acid (*S*)-α-ethylbenzylamide in 100 mL of methanol was added 400 mg of 10% Pd/C catalyst, and the mixture was hydrogenated at 40 psi of H_2 on a Parr shaker for 3 h at room temperature. The catalyst was removed by filtration through a bed of Celite filter material and the filtrate evaporated to give a white solid. This was crystallized from 95% ethanol and acetonitrile to give 1.56 g (4.66 mmol, 49.6%, mp 197–98 °C) of L-aspartyl-D-α-aminobutyric acid (*S*)-α-ethylbenzylamide. A second crop was also obtained: 0.397 g (1.18 mmol, 12.6%, mp 195–7 °C).

***N*-CBZ-β-benzyl-L-aspartyl-D-valine (*S*)-Ethylbenzylamide (29A).** Following the procedure described above, the title compound was prepared in 54% yield using *N*-CBZ-β-benzyl-L-aspartyl-D-valine and (*S*)-α-ethylbenzylamine, mp 180–2 °C.

L-Aspartyl-D-valine (*S*)-α-Ethylbenzylamide (29). Reduction of **29A** using 10% Pd/C in methanol at 40 psi of H_2 as described gave the title compound in 42% yield, mp 220–40 °C.

LITERATURE CITED

Alcaide, B.; Domiguez, G.; Lopez-Mardomingo, C.; Perez-Ossorio, R.; Plumet, J. Stereochemistry of imino group reduction. Part 6. Stereochemistry of reduction of 1, 2 imino ketones having a preexisting chiral center. Synthesis of aminoalcohols with three chiral centers. *J. Chem. Soc., Perkin Trans. 2*, **1986**, 99–103.

Table 10. ^{13}C NMR Spectral Data for Sweetener Compounds 13–29 (Values in Parentheses Represent Diastereoisomer Peaks for Compounds Prepared from Racemic Amines)

sample	solvent	CO	Ar	ArCHN	COCHN	CH_2CO	CH	CH_3
13	D_2O	180.6, 178.7, 173.8	148.0, 133.4, 131.9, 130.4,	54.9	54.4 53.9	41.6		25.5 21.0
14	D_2O	180.9, 178.4, 174.5	148.1, 133.4, 131.9, 130.2	55.1	54.2 53.9	41.8		25.5 21.0
15	D_2O	180.8, 179.0, 175.0	147.0, 133.3, 131.4, 130.9	60.2	55.06 54.2 (54.4)	41.6	33.0 (33.1)	21.3 (21.0) 14.5
16	D_2O	180.8, 178.9, 174.0	146.1, 133.1, 131.9, 131.7	64.9 (64.8)	55.0 (54.3) 54.2 (54.5)	41.6	36.9 (36.8)	23.3 (22.8) 21.3 (20.9)
17	D_2O	181.0, 179.0, 174.6	147.3, 133.1, 191.9, 130.8	58.1	55.1 54.4 (54.5)	41.9	23.3 23.2	21.2 (21.0) 17.3
18	D_2O	179.3, 178.9, 173.3	144.3 (144.2) 133.0 (132.9) 132.7 (132.5) 132.4 (131.9)	67.4	54.5 (54.3) 54.2 (54.1)	40.5 (40.3)	38.5 (38.3)	21.5 (20.9) 30.1
19	D_2O	184.0, 179.1, 177.8	145.3 (145.1) 133.4, 132.4, 132.3, 132.1, 131.9	61.9	56.2 54.3	45.5		20.9
20	D_2O	181.0, 178.8 (178.5) 174.8	146.5, 133.3, 132.1, 130.9	63.0	55.2 54.4 (54.2)	42.0	7.60 (7.40)	21.2 (21.0) 20.5 (20.3)
21	D_2O	174.7, 178.3, 181.0	146.1, 140.1, 135.1, 131.9, 131.1, 129.0	55.1	54.1 (54.2) 50.5 (50.6)	41.9		24.0 (24.2) 22.2 (20.85) 20.9
22	D_2O	174.3, 178.4, 180.8	148.1, 143.5, 133.4, 132.5, 130.9, 127.2	55.2	54.2 (54.4) 53.8 (54.1)	41.7		25.5 24.7 21.0
23	D_2O	174.3, 178.5, 180.8	144.9, 142.1, 133.9, 130.3	55.2	54.4 53.6	41.6		25.5 24.3 21.0
24	D_2O	180.9, 177.8, 174.8	148.0, 133.4, 132.0, 130.4	60.1	55.2 54.0	42.0	29.1	25.6 13.8
25	D_2O	181.4, 178.1, 176.3	148.0, 133.3, 131.9, 130.4	58.5	55.5 53.9	43.1	37.6 25.5	22.7 (22.8) 17.0 (16.9)
26	D_2O	180.6, 177.1, 174.3	148.0, 133.4, 133.3, 131.9, 130.6, 130.5	64.2	55.0 53.9	41.8	34.6	25.6, 22.7 21.9
27	DMSO (CORR)	172.7 171.0 168.5	144.1, 138.6, 128.2, 127.5, 126.6, 126.0	55.9	50.6 47.9	39.5		21.8
28	D_2O	180.9, 178.2, 175.1	132.3, 132.6, 134.0, 148.7	61.1	60.7 56.7	42.8	34.7 31.3	15.8 15.0
29	D_2O	177.1, 177.0, 173.0	133.2, 131.9, 131.1, 130.8, 146.8	63.9	60.3 53.7	39.2	34.7 33.1	14.6 14.4

Brennan, T. M.; Hendrick, M. E. Branched amides of L-aspartyl-D-amino acid dipeptides. U.S. Pat. 4,399,163, Aug 16, 1983a.

Brennan, T. M.; Hendrick, M. E. Branched amides of L-aspartyl-D-amino acid dipeptides. U.S. Pat. 4,411,925, Oct 25, 1983b.

Brennan, T. M.; Hendrick, M. E. Branched amides of L-aspartyl-D-amino acid dipeptides. U.S. Pat. 4,454,328, June 12, 1984.

Brennan, T. M.; Hendrick, M. E. Branched amides of L-aspartyl-D-amino acid dipeptides. U.S. Pat. 4,517,379, May 14, 1985.

Brunner, H.; Becker, R.; Gauder, S. Asymmetric catalysis. 29 optically active primary amines by enantioselective catalytic hydrosilylation of ketoximes. *Organometallics* **1986**, *5*, 739–746.

D'Angelo, L. L.; Sweeny, J. G. L-aspartyl-D-alpha-aminoalkanoyl-N-alpha-alkyl-benzyl amides useful as artificial sweeteners. U.S. Pat. 5,286,509, Feb 15, 1994.

Fujino, M.; Wakimasu, M.; Mano, M.; Tanaka, K.; Nakajima, N.; Aoki, H. L-aspartyl-aminomalonic acid diesters. *Naturwissenshaften* **1973**, *60*, 351–52.

Fujino, M.; Wakimasu, M.; Nakajima, N.; Aoki, H. L-aspartyl-aminomalonic acid diester. U.S. Pat. 3,907,766, Sept 23, 1975.

Fujino, M.; Wakimasu, M.; Mano, M.; Tanaka, K.; Nakajima, N.; Aoki, N. Structure-taste relationships of L-aspartyl-aminomalonic acid diesters. *Chem. Pharm. Bull.* **1976**, *24*, 2112–2117.

Janusz, J. M. Alpha-L-aspartyl-D-phenylglycine esters and amides useful as high intensity sweeteners. U.S. Pat. 4,692,512, Sept 8, 1987.

Janusz, J. M.; Gardlik, J. M.; Young, P. A.; Burkes, R. V.; Stoll, S. J.; Estelle, A. F.; Riley, C. M. High potency dipeptide sweeteners 1. L-Aspartyl-D-phenylglycine esters. *J. Med. Chem.* **1990**, *33*, 1052–1061.

King, G. A., III; Sweeny, J. G.; Iacobucci, G. A. New high potency L-aspartyl-3-bicycloalkyl-L-alanine methyl ester sweeteners. *J. Agric. Food Chem.* **1991**, *39*, 52–56.

Mazur, R. H.; Schlatter, J. M.; Goldkamp, A. H. Structure-taste relationships of some dipeptides. *J. Am. Chem. Soc.* **1969**, *91*, 2684–2691.

Nagakura, A.; Yuasa, Y.; Tsuruta, H.; Akutagawa, S. Pinanyl and fenchyl esters of aspartylalanine. Jpn. Kokai Tokkyo Koho 61,200,999, Sept 5, 1986a; *Chem. Abstr.* **1987**, *106*, 156864c.

Nagakura, A.; Yuasa, Y.; Tsuruta, H.; Akutagawa, S. L-Aspartyl-D-alanine-(+)-β-fenchyl ester as a sweetener Jpn. Kokai Tokkyo Koho 61,291,596, Dec 22, 1986b; *Chem. Abstr.* **1987**, *106*, 176872g.

Rinaldi, P. L.; Naidu, M. S. R.; Conaway, W. E. Absolute configuration determination of chiral α-substituted benzylamines using liquid crystal induced circular dichroism. *J. Org. Chem.* **1982**, *47*, 3987–3991.

Verlander, M. S.; Fuller, W. D.; Goodman, M. 1,1-Diaminoalkane derived sweeteners U.S. Pat. 4,571,345, Feb 14, 1986.

Walters, D. E.; Orthoefer, F. T.; DuBois, G. E. Sweeteners—discovery, molecular design and chemoreception. *ACS Symp. Ser.* **1991**, *No. 450*.

Yamazaki, T.; Beneditti, E.; Kent, D.; Goodman, M. Conformational requirements for sweet-tasting peptides and peptidomimetics. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1437–1451.

Zanno, P. R.; Barnett, R. E.; Roy, G. M. L-Aminodicarboxylic acid esters. U.S. Pat, 4,766,246, Aug 23, 1988.
Zeng, G.-Z.; Wei, S.-T. *Molecular Recognition of Taste*; Science Press: Beijing, 1984; p 26.
Zeng, G.-Z.; Chen, J.-T.; He, H.-Z.; Wang, Z.-Q.; Yan, J.-S. In pursuit of a better sweetener. *J. Agric. Food Chem.* **1991**, *39*, 782–785.

Received for review January 9, 1995. Revised manuscript received April 27, 1995. Accepted May 26, 1995.[⊗]

JF950016M

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1995.