New High-Potency L-Aspartyl-3-bicycloalkyl-L-alanine Methyl Ester Sweeteners

George A. King, III, James G. Sweeny,* and Guillermo A. Iacobucci

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

A new series of high-intensity sweeteners was prepared in which the phenyl ring of aspartame is replaced by a substituted bicycloalkyl unit. In the case of the L-aspartyl-3-(2-norbornyl)-L-alanine methyl esters, methyl substitution of the norbornyl ring increased sweetness potency except in the case of the 1,3,3-trimethylnorbornyl analogue, where a great reduction was found. The two sweetest compounds prepared were the 1,7,7-trimethylnorbornyl and the 7,7-dimethylnorbornyl analogues. For these compounds, the four possible ring stereoisomers were synthesized, and in each case only the 2*R*-exo and 2*R*-endo isomers were intensely sweet.

Since the original discovery of the sweetness of L-aspartyl-L-phenylalanine methyl ester [aspartame (1)] (Figure 1) by Mazur et al. in 1969, a large number of analogues have been prepared in an attempt to improve on its sweetness potency and/or chemical stability (Iwamura, 1981; Brussel et al., 1975; Miyoshita et al., 1986; Janusz, 1987; Tsang et al., 1984; Zanno et al., 1986a–e, 1987a,b).

In the absence of any knowledge defining the dimensions and shape of the human sweet taste receptor(s), the search for new N-substituted L-aspartylamides has been conducted over a period of 20 years by the conventional trial and error approach. From the wealth of information thus obtained, a general structure **2** (Figure 2) can be formulated to encompass the topographical characteristics considered essential for the induction of sweetness. Besides the requirement for the L-aspartyl moiety [only replaceable by L-aminomalonyl (Briggs and Morley, 1972)], the substituent on the amide nitrogen must conform to the depicted geometry, in which three nonpolar groups of different size (L, large; M, medium; S, small) are attached to a chiral carbon with the absolute configuration shown in structure **2**. The configuration of the chiral carbon can, of course, be either *R* or *S* depending on the nature of the L, M, and S groups. In aspartame, for instance, the carbon has the *S* configuration with L = benzyl, M = carbomethoxy, and S = H. In Alitame (Brennan and Hendrick, 1983, 1984, 1985) the configuration is *R* with L = CONH-tetramethylthietanyl, M = CH_3, and S = H.

Our efforts in the field have focused on the replacement of the phenyl ring of aspartame with saturated, bicyclic alkyl substituents. This approach was suggested by the results obtained by scientists at the Takeda Chemical Co. (Nakajima et al., 1976; Fujino et al., 1973, 1975, 1976), who found that the L-aspartylamide of 2-aminomalonic acid methyl fenchyl diester **3** (Figure 3) was 20 000 times as sweet as sucrose. This makes compound **3** the sweetest aspartylamide yet discovered. In fact, more recent work (Yin-Zeng et al., 1980) describing the synthesis of the four fenchyl alcohol isomers of **3** found that the 2*R*-exo (+)-β-fenchyl ester was 50 000 times as sweet as sucrose, and the 2*R*-endo (−)-α isomer 30 000 times as sweet. The 2*S*-endo (+)-α and the 2*S*-exo (−)-β isomers showed intensities of 1000 and 2500 times sucrose, respectively. The exact configuration of the large, hydrophobic groups L in structure **2** is therefore very important in determining how well they interact with the sweetness receptor sites and thus effect the sweetness potency.

Although extremely potent, fenchyl esters of type **3** have

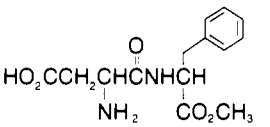

Figure 1. Structure 1.

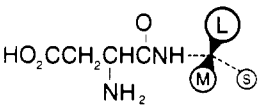

Figure 2. Structure 2.

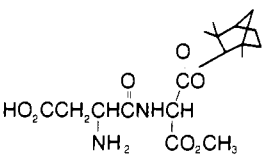

Figure 3. Structure 3.

an inherent drawback. On standing in solution at the acid pH range (3–5) common to fruit juices, soft drinks, and similar products, fenchyl alcohol is slowly released by ester hydrolysis. Due to the low taste thresholds (0.03–0.10 ppm) of the four isomeric fenchyl alcohols and their dominant camphoraceous/musty taste (B. C. Clark, Jr., The Coca-Cola Co., personal communication), their release negatively affects the flavor characteristics of products containing sweeteners of type **3**.

As a result of the above analysis we have prepared a series of compounds containing a bicyclic ring system in place of the aromatic ring in aspartame. With the bicyclic ring system attached directly to the amino acid center via a methylene bridge, these compounds no longer present the possibility of the formation of undesirable bicyclic alcohols through ester hydrolysis.

MATERIALS AND METHODS

Taste tests were conducted with a panel of six tasters using a range of sample dilutions in distilled water versus aspartame at 250 ppm. Sweetness potencies were then calculated vs sucrose by using an aspartame potency of 180 times sucrose. All samples had solubilities greater than 2000 ppm, so that solutions equivalent to 10% sucrose could be readily prepared. In the case of the sweetest compounds, the bornyl derivatives **16** and **19** and the 7,7-dimethylnorbornyl derivatives **20** and **23**, a slight lingering of the sweetness was also noted.

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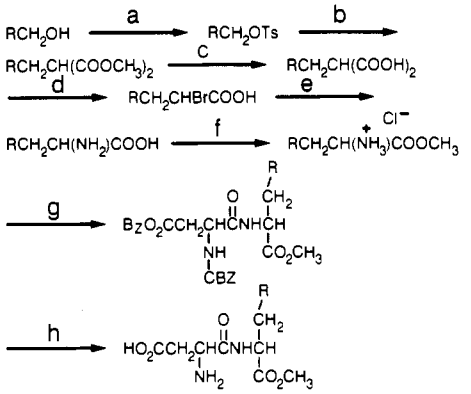
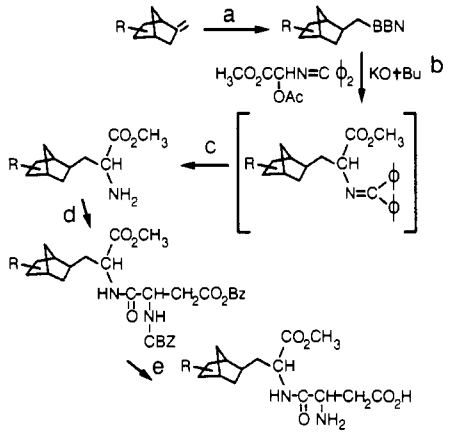
Scheme I. Procedure A



[a] *p*-Toluenesulfonyl chloride/pyridine, 18 h, R.T. [b] $NaCH(CO_2CH_3)_2$, methanol, 48 h, reflux. [c] KOH, methanol/H_2O, 6 h, reflux. [d] Br_2, R. T.; then 140–150 °C, 5 h. [e] NH_4OH, 7 days, R.T. [f] HCl/methanol, 15 h, reflux. [g] *N*-CBZ-L-aspartic acid β-benzyl ester, *i*-BuOCOCl, 4-methylmorpholine, −20 °C, then R.T., 18 h. [h] 10% Pd/C, methanol, H_2.

Scheme II. Procedure B



[a] 9-BBN, THF, R.T., 2 h. [b] Methyl *N*-(diphenylmethylene)-2-acetoxyglycinate, KOtBu, THF, 0 °C; then 23 °C, 18 h. [c] 1 N HCl, R.T., 18 h. [d] *N*-CBZ-L-aspartic acid β-benzyl ester, DCC, *N*-hydroxy-5-norbornene-2,3-dicarboximide, dioxane; R.T. 18 h. [e] 10% Pd/C, methanol, H_2.

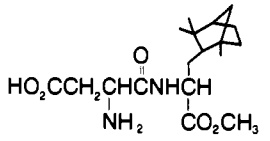


Figure 4. Structure 4.

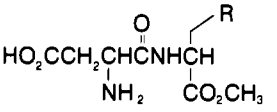
Detailed examples of the two basic synthetic procedures (procedures A and B given in Schemes I and II, respectively) and the preparation of the individual stereoisomers of the 2-bornyl- and 2-(7,7-dimethylnorbornyl)-D,L-alanine sweeteners as well as the spectral and analytical data on all the compounds listed in Tables I–III are included in the supplementary material.

RESULTS AND DISCUSSION

Several previous publications deal with aliphatic amino acid analogues of aspartame (Grosch and Belitz, 1977; Iwamura, 1981; Mazur et al., 1973; Brussel et al., 1975), but none of the analogues contained a bicyclic ring or showed a potency greater than that of aspartame itself.

Our first synthetic target was compound 4, in which the phenyl ring of aspartame was replaced with the fenchyl group. Two materials were actually prepared by starting with (+)- and (−)-fenchone as described in the supplementary material. One was a mixture of the 2*R*-exo and 2*S*-endo isomers at the ring juncture [from (−)-fenchone] and the other a mixture of the 2*R*-endo and 2*S*-exo isomers [from (+)-fenchone].

Table I. Sweetness of L-Aspartyl-3-(bicycloalkyl)-D,L-alanine Methyl Esters



synthetic method		R	no. of isomers	sweetness (× sucrose w/w)
A, B	(5)	2(*R*)-*exo*/2(*S*)-*endo*-fenchyl	4	20
A	(6)	2-norbornyl	8	225
A	(7)	2-(3-methylnorbornyl)	8	250
A	(8)	2-camphanyl	8	300
A	(9)	2-(bicyclo[2.2.2]octyl)	4	340
A, B	(10)	2-bornyl	8	810
A	(11)	2-(1-methylnorbornyl)	8	450
A	(12)	2(*R*,*S*)-*exo*-norbornyl	4	200
A	(13)	2(*R*,*S*)-*endo*-norbornyl	4	290
B	(14)	10-[(1*R*)-*exo*/*endo*-pinanyl]	4	160
B	(15)	2(*R*)-*exo*/2(*S*)-*endo*-7,7-dimethylnorbornyl	4	900

When these compounds were tasted in water, the panel found them to be only 20–30 times as sweet as sucrose. This finding was surprising not only in view of the Takeda results but also when compared to those recently announced by Janusz (1987), who described the preparation of a series of L-aspartyl-D-phenylglycine fenchyl esters. In this series the (+)-β-fenchyl (5000 times sucrose) and the (−)-α-fenchyl (1750 times sucrose) esters were the sweetest compounds found.

Even more recently, workers at General Foods (Zanno et al., 1988) and the Takasago Co. (Nagakura et al., 1986a,b) described the preparation of a series of L-aspartyl-D-alanine esters in which the sweetest reported compound (2000–5000 times sucrose) was once again the (+)-β-fenchyl ester.

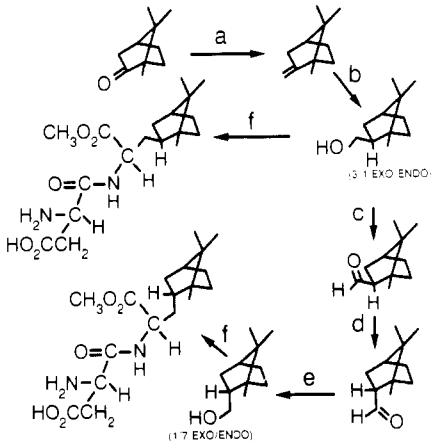
To determine if the low sweetness potency of 4 was a general characteristic of these bicycloalkyl compounds, several more analogues were prepared as shown in Table I. All of the compounds prepared contained at least two isomers as they were all racemic at the alanine center. In addition, the norbornyl ring itself was racemic, and a varying ratio of exo and endo isomers was seen. The listing in the table under number of isomers, therefore, gives the maximum number of isomers possibly present on the basis of the method of synthesis.

Two basic synthetic schemes were used—the malonate pathway (A) and the iminoglycinate pathway (B). The method used for each compound prepared is given in Table I, and typical examples of each process are described in the supplementary material. The process ultimately used in each case was determined by the availability of the various bicyclic starting materials.

The sweetness potency of each compound mixture prepared was then determined in water by a panel of six tasters using aspartame at 250 ppm as a reference. The results shown in Table I indicate that, even as mixtures of isomers, several compounds have been found which are considerably sweeter than aspartame.

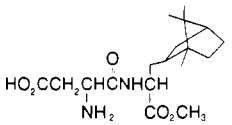
The very low level of sweetness found for the fenchyl derivative appears to derive from the high degree of crowding in close proximity to the point of attachment to the alanine moiety. Relief of this steric clutter at the carbon of the bicyclic ring bearing the alanine substituent, either by removing the angular methyl group (fenchyl → camphanyl) or the *gem*-dimethyl group (fenchyl →

Scheme III



[a] Methyltriphenylphosphonium bromide, THF, *n*-butyllithium, 18 h, reflux. [b] B_2H_6, THF, R.T., 1 h; then NaOH, H_2O_2, 1 h, R.T. [c] Pyridinium chlorochromate, CH_2Cl_2, 1.5 h, R.T. [d] 1,8-Diazabicyclo[5.4.0]undec-7-ene, THF, R.T., 48 h. [e] $NaBH_4$, ethanol, 2 h, R.T. [f] Procedure A.

Table II. Sweetness Potencies of Isomeric L-Aspartyl-3-(2-bornyl)-D,L-alanine Methyl Esters



	no. of isomers	sweetness (× sucrose)
2(*R*)-*exo*-bornyl (**16**)	2	1690
2(*S*)-*endo*-bornyl (**17**)	2	70
2(*S*)-*exo*-bornyl (**18**)	2	350
2(*R*)-*endo*-bornyl (**19**)	2	1930

1-methylnorbornyl) or by shifting the *gem*-dimethyl group from C3 to C7 (fenchyl → bornyl), results in a greater than 10-fold increase in sweetness.

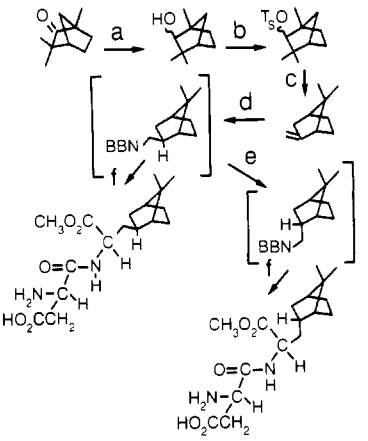
The presence of methyl groups on the bicyclic ring system, therefore, tends to increase the sweetness potency over the unsubstituted norbornyl compound but *only* if they do not introduce excessive crowding near the point of attachment to the alanine C3. That is, substitution cannot occur at the norbornyl C1 and C3 simultaneously.

As stated above, the compounds of Table I were prepared as a mixture of isomers about the bicyclic ring due to the racemic nature of the starting materials. To gain further insight on the structure/potency relationships, the preparation of the individual isomers of the bornyl- and (7,7-dimethylnorbornyl)alanines was investigated.

The bornyl isomers were prepared from (+) and (−)-camphor. Wittig reaction of (1*R*)-(+)-camphor gave the corresponding methylenebornane (see Scheme III). Hydroboration–oxidation of the methylene compound then afforded a 3/1 ratio of the exo/endo alcohols (Brown and Kawakami, 1970). This mixture could be converted to a 7/1 ratio of the endo/exo alcohols by oxidation to the aldehyde with pyridinium chlorochromate, epimerization of the aldehyde with DBU, and reduction with sodium borohydride. The predominantly exo and endo alcohols were then converted to the corresponding 3-[2(*R*)-*exo* and 2(*S*)-*endo*-bornyl]alanine sweeteners via procedure A. The 2*R*-endo and 2*S*-exo isomers were prepared in the same way by using (1*S*)-(−)-camphor as the starting material.

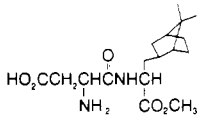
The four isomeric compounds were tasted in water and the sweetness potencies calculated from the results (Table II). The two sweetest isomers were the 2*R*-exo (1690 times sucrose) and the 2*R*-endo (1930 times sucrose) isomers,

Scheme IV



[a–c] Hückel and Volkmann (1963). [d] 9-BBN, THF, R.T., 1 h. [e] 150 °C, 3 h. [f] Procedure B.

Table III. Sweetness Potencies of Isomeric L-Aspartyl-3-(7,7-dimethyl-2-norbornyl)-D,L-alanine Methyl Esters



	no. of isomers	sweetness (× sucrose)
2(*R*)-*exo* (**20**)	2	985
2(*S*)-*endo* (**21**)	2	150
2(*S*)-*exo* (**22**)	2	45
2(*R*)-*endo* (**23**)	2	1115

both as D,L mixtures at the alanine amino acid center. This means that pure L-aspartyl-3-[2(*R*)-*endo*-(1,7,7-trimethylnorbornyl)]-L-alanine methyl ester should be 3860 times as sweet as sucrose, as only the L-alanine isomers in this series are sweet. This particular orientation at the point of ring substitution for the two most potent bornyl derivatives is also seen in the series of aminomalonate fenchyl esters (Yin-Zeng et al., 1980), where the two sweetest compounds derive from (+)-β- and (−)-α-fenchyl alcohols, having 2*R*-exo and 2*R*-endo orientations at the ring junctures, respectively.

The synthesis of the four ring isomers of the (7,7-dimethylnorbornyl)alanine sweetener was undertaken by a different route (Scheme IV). Starting with (1*R*)-(−)-fenchone, the corresponding (1*S*)-(α)-fenchene was prepared by sodium borohydride reduction, tosylation of the resulting alcohol with *p*-toluenesulfonyl chloride and pyridine, and rearrangement of the tosylate with acetic acid–sodium acetate (Hückel and Volkmann, 1963). The resulting α-fenchene was then treated with 9-BBN in THF to give the exo hydroboration product. This was then converted to the 2(*R*)-*exo*-(7,7-dimethylnorbornyl)alanine sweetener via procedure B. The 2*S*-endo isomer was prepared by isomerization of the *exo*-(α-fenchene)–BBN adduct to the endo form by heating it neat at 150 °C for 2 h (Braun and Fisher, 1960). The isomerized product was then converted via procedure B as above to afford the 2(*S*)-*endo*-(7,7-dimethylnorbornyl)alanine sweetener.

A similar sequence starting with (1*S*)-(+)-fenchone gave the corresponding 2*R*-endo and 2*S*-exo isomers. Sweetness evaluation as previously described showed the potency values listed in Table III. Once again, the 2R-exo and 2R-endo isomers had the highest potency.

CONCLUSION

These results lead to the conclusion that it is possible to replace the phenyl ring of the phenylalanine moiety in aspartame by a bicyclic aliphatic ring system without destroying its inherent sweet taste characteristics. This replacement is subject to structural and stereochemical requirements that, when fulfilled, have resulted in derivatives up to 22 times sweeter than aspartame. In the case of the sweetest bornyl and 7,7-dimethylnorbornyl derivatives, the preference for 2*R*-exo and 2*R*-endo substitution at the bicyclic ring reflects a topographical requirement of the receptor's binding site. It is expected that this spatial arrangement will also be shared by the other sweeteners of this series.

ABBREVIATIONS USED

DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; 9-BBN, 9-borabicyclo[3.3.1]nonane; THF, tetrahydrofuran; DCC, dicyclohexylcarbodiimide.

Supplementary Material Available: Details of the synthesis of and spectral and analytical data for the new sweeteners described in this paper (28 pages). Ordering information is given on any current masthead page.

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Received for review April 5, 1990. Revised manuscript received July 31, 1990. Accepted August 9, 1990.

Registry No. **5**, 130609-50-6; (2*S*)-*endo*-**S**, 130551-68-7; **6**, 120439-16-9; **7**, 130551-69-8; **8**, 130551-70-1; **9**, 130551-71-2; **11**, 130551-72-3; **14**, 130551-73-4; **15**, 130551-74-5; **16**, 130693-98-0; **17**, 130693-99-1; **18**, 130694-00-7; **19**, 130790-14-6; **20**, 130694-01-8; **21**, 130694-02-9; **22**, 130694-03-0; **23**, 130694-04-1; (2*R*,*S*)--norbornylmethanol, 69831-11-4; (2*R*,*S*)-*endo*-norbornylmethyl tosylate, 130609-51-7; dimethyl malonate, 108-59-8; dimethyl [(2*R*,*S*)-*endo*-norbornylmethyl]malonate, 130551-75-6; (2*R*,*S*)--*endo*-norbornylmethylmalonic acid, 130551-76-7; 2-bromo-3-[-(2*R*,*S*)-*endo*-norbornyl]propionic acid, 120439-19-2; 3-[(2*R*,*S*)-*endo*-norbornyl]-D,L-alanine, 120439-20-5; 3-[(2*R*,*S*)-*endo*-norbornyl]-D,L-alanine methyl ester hydrochloride, 120439-21-6; *N*-carbobenzyloxy-L-aspartic acid-β-benzyl ester, 3479-47-8; *N*-carbobenzyloxy-β-*O*-benzyl-L-aspartyl-3-[(2*R*,*S*)-*endo*-norbornyl]--D,L-alanine methyl ester, 130694-05-2; diethyl malonate, 105-53-3; (+)-α-fenchene, 116724-26-6; (−)-α-fenchene, 7378-37-2; methyl-*N*-(diphenylmethylene)-2-acetoxyglycinate, 130551-77-8; 3-(7,7-dimethylnorbornyl)-D,L-alanine methyl ester hydrochloride, 130551-78-9; *N*-carbobenzyloxy-L-aspartyl-β-*O*-benzyl-3-(2*R*-*exo*-7,7-dimethylnorbornyl)-D,L-alanine methyl ester, 130573-23-8; *N*-carbobenzyloxy-L-aspartyl-β-*O*-benzyl-3-(2*R*-*endo*-7,7-

dimethylnorbornyl)-D,L-alanine methyl ester, 130694-06-3; methyltriphenylphosphonium bromide, 1779-49-3; (−)-camphor, 464-48-2; (+)-2-methylene-1,7,7-trimethylnorbornane, 130790-15-7; 2*R*-*exo*-1,7,7-trimethylnorbornyl methanol, 130693-83-3; 2*R*-*exo*-1,7,7-trimethylnorbornyl methanol tosylate, 130609-52-8; (2*R*-*exo*-1,7,7-trimethylnorbornyl)methylmalonate, 130551-79-0; 2-bromo-3-(1,7,7-trimethylnorbornyl)propionic acid, 130551-80-3; (2*R*-*exo*-1,7,7-trimethylnorbornyl)-methylmalonic acid, 130551-81-4; 3-(1,7,7-trimethylnorbornyl)-D,L-alanine, 130551-82-5; 3-(1,7,7-trimethylnorbornyl)-D,L-alanine methyl ester, 130551-83-6; *N*-carbobenzyloxy-L-aspartyl-β-*O*-benzyl-3-(2*R*-*exo*-1,7,7-trimethylnorbornyl)-D,L-alanine methyl ester, 130573-24-9; [2*R*-*exo*-1,7,7-trimethylnorbornyl]-2-carboxyaldehyde, 130609-53-9; [2*S*-*endo*-1,7,7-trimethylnorbornyl]-2-carboxyaldehyde, 60244-29-3; pyridinium chlorochromate, 26299-14-9.