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(21) International Application Number: PCT/US94/14770 (22) International Filing Date: 22 December 1994 (22.12.94) (30) Priority Data: 08/171,996 22 December 1993 (22.12.93) US (71) Applicant: THE COCA-COLA COMPANY [US/US]; P.O. Drawer 1734, Atlanta, GA 30301 (US). (72) Inventors: D'ANGELO, Lihong; 2245 Vistamont Drive, Decatur, GA 30033 (US). SWEENEY, James, G.; 2484 Oldfield Road, N.W., Atlanta, GA 30327 (US). KING, George, A., III; 858 Kings Court N.E., Atlanta, GA 30306 (US). (74) Agents: LANDGRAFF, Frank, A.; The Coca-Cola Company, Patent Dept., P.O. Drawer 1734, Atlanta, GA 30301 (US) et al.		(81) Designated States: AU, CA, CN, FI, JP, KR, NO, NZ, RU, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: NOVEL INTERMEDIATES FOR THE SYNTHESIS OF L-ASPARTYL-D- α -AMINOALKANOYL-(S)-N- α -ALKYLBENZYL AMIDES USEFUL AS ARTIFICIAL SWEETENERS (57) Abstract The present invention relates to chemical compounds that are useful for the preparation of artificial sweetener compounds, in particular, chemical intermediates that are useful for the preparation of L-aspartyl-D-α-aminoalkanoyl-(S)-N-α-alkylbenzyl amides.		

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NOVEL INTERMEDIATES FOR THE SYNTHESIS OF L-ASPARTYL-
D- α -AMINOALKANOYL-(S)-N- α -ALKYLBENZYL AMIDES
USEFUL AS ARTIFICIAL SWEETENERS

CROSS-REFERENCE TO RELATED APPLICATION

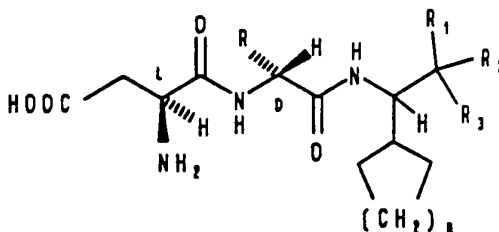
The subject application is a Continuation-in-
10 Part of Serial No. 07/902,310, filed June 22, 1992.

FIELD OF THE INVENTION

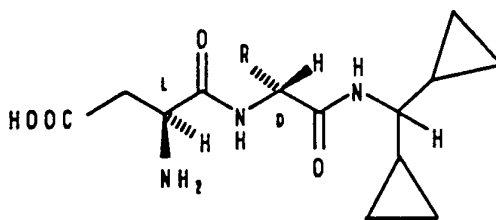
This invention relates to compounds that are useful for the synthesis of artificial sweetener compounds comprising L-aspartyl-D- α -aminoalkanoyl-(S)-N-
15 α -alkylbenzyl amides.

BACKGROUND OF THE INVENTION

L-aspartyl-D-alanine-N-alkyl amides, such as disclosed in U.S. Patent No. 4,411,925, are known to be useful as artificial sweeteners:



In the series of compounds described by the above structure, the most potent material reported was the L-aspartyl-D-alanine amide of (+/-) t-butyl-cyclopropyl methylamine ($R_1 = R_2 = R_3 = \text{CH}_3$, $n = 0$; wherein the
5 sweetness potency (SP) was reported to be 1200 times sucrose.) It was furthermore emphasized that the nature of R in the above structure was important for sweetness potency, with $R = \text{CH}_3$ (D-alanine) being especially preferred. In the typical case of the L-aspartyl-D-
10 alanine amides having the structure:



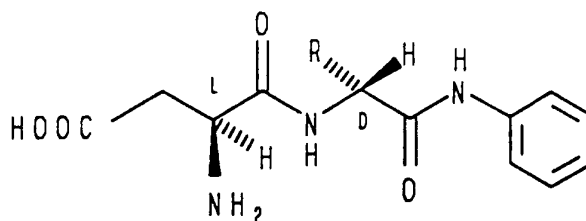
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the sweetness potency decreases as R is increased, that is, for $R = \text{methyl}$, $\text{SP} = 1200$, for $R = \text{ethyl}$, $\text{SP} = 500$, and for $R = \text{isopropyl}$, $\text{SP} = 110$.

20 Zeng et al., J. Agric. Food Chem. 39, 782-85 (1991), disclose L-aspartyl-D-alanine-N-phenyl amides wherein the benzene ring may have methyl-substituents:

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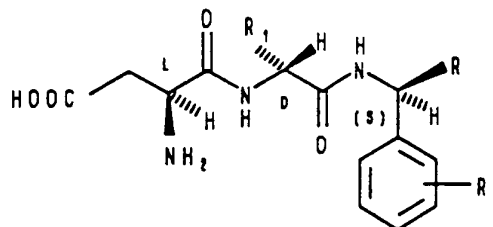
These compounds may be described as aniline amides of L-aspartyl-D-alanine. The individual members of this family of aniline amides were disclosed to have a sweetness potency that was at most 75 times that of sucrose except for the highly substituted 2,6-dimethylaniline amide which was disclosed to have a sweetness potency 500 times the sweetness of sucrose. In addition to the relatively low sweetness potency of most of the individual members of this series, these compounds have a potential for toxicity that is known for aniline derivatives.

In addition, Ariyoshi, Bull. Chem. Soc. Japan, 57, 3197 (1984), discloses a series of L-aspartyl-D-alanyl- α -amino acid esters and L-aspartyl-D-valinyl- α -amino acid esters that are tasteless, bitter or of sweetness potency less than 50 times sucrose.

Applicants' co-pending application having Serial No. 07/902,310 discloses the sweet taste and preparation of an artificial sweetener compound comprising an L-aspartyl-D- α -aminoalkanoyl-(S)- α -alkylbenzyl amide having the structure:

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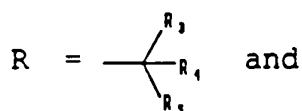


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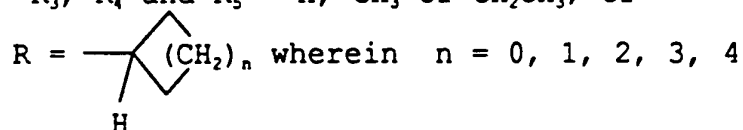
wherein $R_1 = \text{H}, \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_3, \text{CH}(\text{CH}_3)_2, -\text{C}(\text{CH}_3)_3, \text{CH}_2\text{OCH}_3, \text{CH}_2\text{OH}$ or ϕ

wherein $R_2 = \text{H}$ or CH_3 ;

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R_3, R_4 and $R_5 = \text{H}, \text{CH}_3$ or CH_2CH_3 ; or



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The sweetener compounds were prepared by coupling a (β -COOH/ α -NH₂)-diprotected L-aspartic acid with a second D-amino acid to give a (β -COOH/ α -NH₂)-diprotected L-aspartyl-D-amino acid. This material was in turn coupled with a (S)- α -alkylbenzylamine to give the (β -COOH/ α -NH₂)-diprotected L-aspartyl-D-amino acid amide. Removal of the protecting groups then produced the free sweetener 1.

Although this method of preparation of the new artificial sweetener compounds was effective on the laboratory scale, the method had the disadvantage of

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providing low yields in the preparation of the diprotected L-aspartyl-D-amino acid. The method had the further disadvantage of requiring the use of expensive reagents such as dicyclohexylcarbodiimide.

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OBJECTS AND SUMMARY OF THE INVENTION

An object of the present invention is to provide compounds that are useful for preparing chemically stable artificial sweeteners having high
10 sweetness potency.

More specifically, an object of the present invention is to provide compounds that may be used to prepare artificial sweeteners using economic reaction processes and inexpensive reagents.

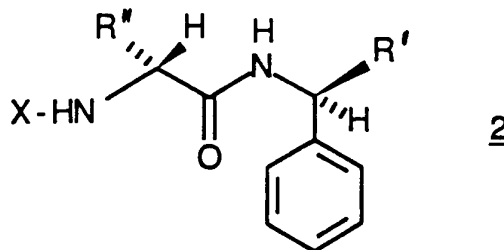
15 In particular, an object of the present invention is to provide compounds that may be used to produce artificial sweeteners using reaction processes having high yields using economic, safe and convenient reaction materials.

20 Another object of the present invention is to provide artificial sweeteners having high heat stability at temperatures typically used for preparing foods.

The present invention provides an N-protected-D-amino acid-(S)- α -alkylbenzyl amide having the

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structure:



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where $R'' = \text{CH}_3, \text{C}_2\text{H}_5, \text{or } \text{CH}(\text{CH}_3)_2;$

$R' = \text{CH}_3 \text{ or } \text{C}_2\text{H}_5, \text{ and}$

$X = \text{CO}_2\text{CH}_2\phi, \text{CHO or CO}_2\text{-tert-butyl}.$

10 The subject invention relates to adding the L-aspartic acid moiety to compound 2 followed by deprotection as the final steps in the preparation of the artificial sweetener. An additional subject of this invention relates to the addition of the (S)- α -

15 alkylbenzyl amine to a suitably protected dipeptide followed by deprotection as the final steps in the preparation of the artificial sweetener 1.

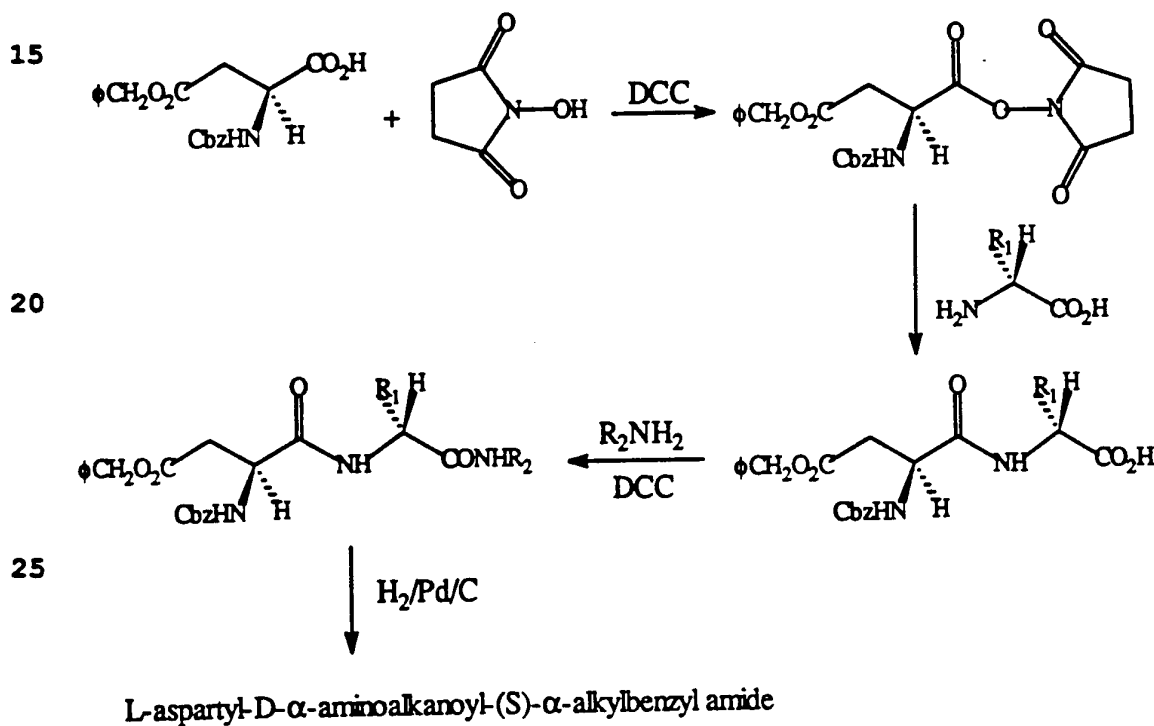
Detailed Description of the Invention

20 The methods by which the objects, features and advantages of the present invention are achieved will now be described in more detail. These particulars provide a more precise description of the invention for the purpose of enabling one skilled in the art to practice the

25 invention, but without limiting the invention to the specific embodiments described.

In one of the embodiments of the subject invention, the L-aspartyl-D-amino acid amides of the present invention may be obtained by preparing a suitably protected dipeptide using any of several known methods for the coupling of amino acids, (e.g., M. Bodansky, Principles of Peptide Synthesis, Berlin, (1984), Springer Verlag), and then coupling the dipeptide with an amine to produce the desired amide. This method is hereinafter referred to as the "dipeptide-intermediate" method.

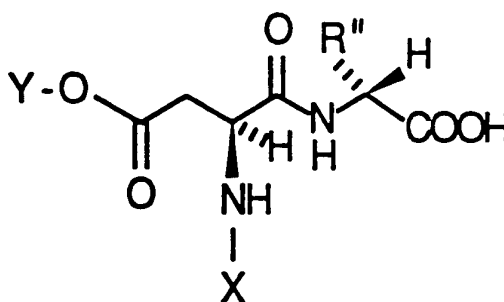
For example, the dipeptide-intermediate method outlined below has been found useful, where R_1 and R_2 are alkyl groups.



In the first step of the dipeptide-intermediate reaction sequence, a diprotected L-aspartic acid is condensed with N-hydroxysuccinimide to produce the activated L-aspartyl-N-hydroxysuccinimide ester. In this case the diprotected L-aspartic acid is a β -benzyl-N-carbobenzyloxy ("CBZ") derivative which is commercially available. Condensation of the CBZ-derivative with hydroxysuccinimide is achieved by use of dicyclohexylcarbodiimide (DCC) as the coupling agent. The DCC coupling agent is also readily available from known commercial sources.

In the second step of the dipeptide-intermediate method, the activated L-aspartyl succinimide ester may be reacted with an appropriate D-amino acid in dioxane-water with triethylamine to produce the β -benzyl-N-carbobenzyloxy-L-aspartyl-D-amino acid.

The preferred compounds that are useful for the preparation of artificial sweeteners using the dipeptide-intermediate method include compounds having the following structure:



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where X = $\text{CO}_2\text{CH}_2\phi$, CHO or CO_2 -tert-butyl;

R" = CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ ;

10 Y = CH_3 or $\text{CH}_2\phi$ or tert-butyl.

The preferred D-amino acids include D-alanine, D-valine, D- α -aminobutyric acid, D-phenylglycine and D- α -aminopentanoic acid. The most preferred D-amino acids of
15 this invention are D-alanine, D- α -amino-butyric acid and D-valine.

In the third step of the dipeptide-intermediate method, the reaction product of the second step may be activated with DCC and coupled in dioxane with an
20 appropriate amine to produce the β -benzyl-N-carbobenzyloxy-L-aspartyl-D-amino acid amide. The preferred amines of this invention include amines such as α -methylbenzylamine, α -ethylbenzylamine, α -isopropylbenzylamine, α -t-butylbenzylamine, α -n-propylbenzylamine, α -phenylbenzylamine, α -cyclopropyl
25 benzylamine, and α -isobutylbenzylamine. The (S)-

enantiomer or a racemic mixture of these amines may be used. Preferably the (S)-enantiomer is used. The most preferred amine of this invention is (S)- α -ethylbenzylamine.

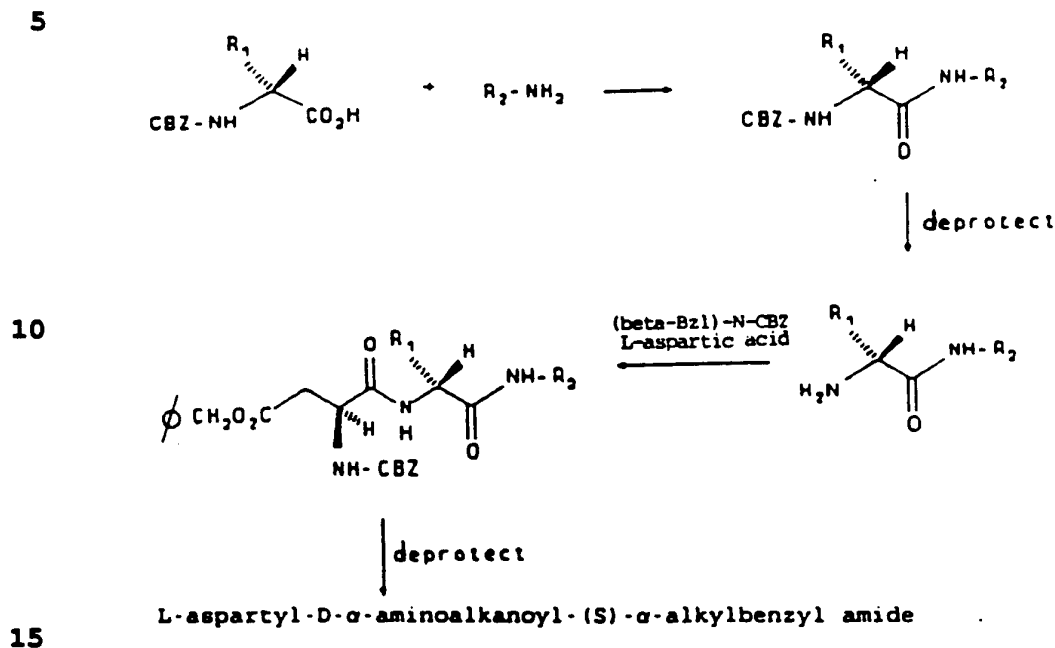
5 In the final step the sweetener compound is obtained by deprotection of the product of the third step by catalytic hydrogenation in an alcoholic solvent using Pd/C as catalyst.

 While the above steps of the dipeptide-
10 intermediate method have proven convenient and were used in preparation of all of the compounds described in the tables that follow, other steps may be envisioned which could prove equally advantageous. For example, as described in U.S. Patent No. 4,411,925, activation of the
15 acid groups of the first and third steps could be achieved using an alkyl chloroformate and a tertiary amine base in place of the DCC. In addition, the use of other protecting groups for the aspartic acid moiety, such as the combination of β -t-butyl ester and N-t-
20 butyloxycarbonyl can be envisioned. In this case, deprotection in step 4 would require acid catalysis rather than catalytic hydrogenation.

 In one of the preferred embodiments of the subject invention, preparation of the sweetener compounds
25 involves preparation of an amide-intermediate by coupling an N-protected α -amino acid with an (S)-alkylbenzylamine

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(R₂-NH₂) as a first step, as shown, wherein R₁ and R₂ are alkyl, phenyl or phenyl-containing alkyl groups.



This method is hereinafter referred to as the "amide-intermediate" method. The amide-intermediate method is distinguished from the dipeptide-intermediate method in that the D-amino acid group is combined with an amine before the D-amino acid group is combined with the L-aspartyl group. In the dipeptide-intermediate method, a dipeptide is formed first, that is, before it is combined with an amine.

In the second step of the amide-intermediate

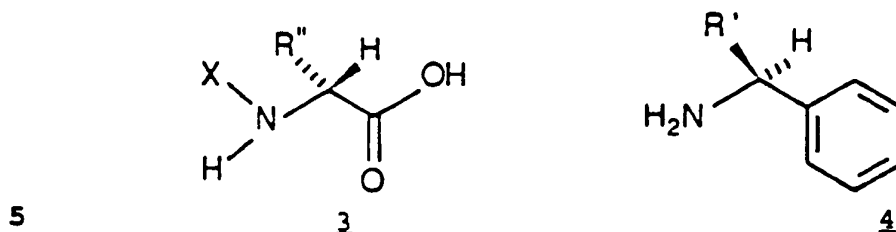
method, the protecting group of the N-protected D-amino acid group is removed to produce a free amine or amine salt. In the case of a carbobenzyloxy protecting group, this is achieved by catalytic hydrogenation. This new
5 amine is then reacted in a third step with N-carbobenzyloxy- β -benzyl-L-aspartic acid and a condensing agent such as DCC to produce a N-carbobenzyloxy- β -benzyl-L-aspartyl-D-amino acid-(S)- α -alkylbenzyl amide. The sweetener product is then obtained in a fourth step by
10 catalytic removal of the protecting groups using known methods of hydrogenation over Pd/C catalyst.

Although several methods for the synthesis of the amide intermediate, compound 2 above, can be envisioned, the preferred methods disclosed below have
15 been found to be especially effective in meeting the requirements for high yields and low cost of reagents.

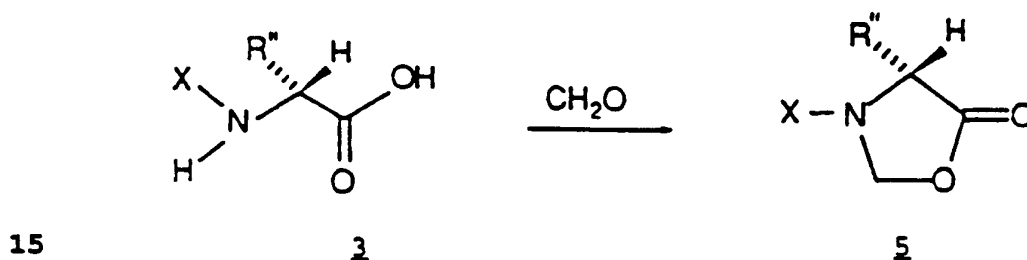
In the first preferred method for preparing the amide intermediate, an N-protected D-amino acid 3 is coupled to an (S)- α -alkylbenzylamine 4 using isobutyl
20 chloroformate and N-methylmorpholine at 0 °C in tetrahydrofuran as the activating reagent [M. Bodansky, "Principles of Peptide Synthesis", Springer Verlag, Berlin, 1984; pp. 21-27], (where X, R' and R" are as

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defined above):



The second preferred method for preparing the amide intermediate is the conversion of the N-protected D-amino acid 3 to the corresponding oxazolidinone 5,
 10 (where X and R'' are as defined above).

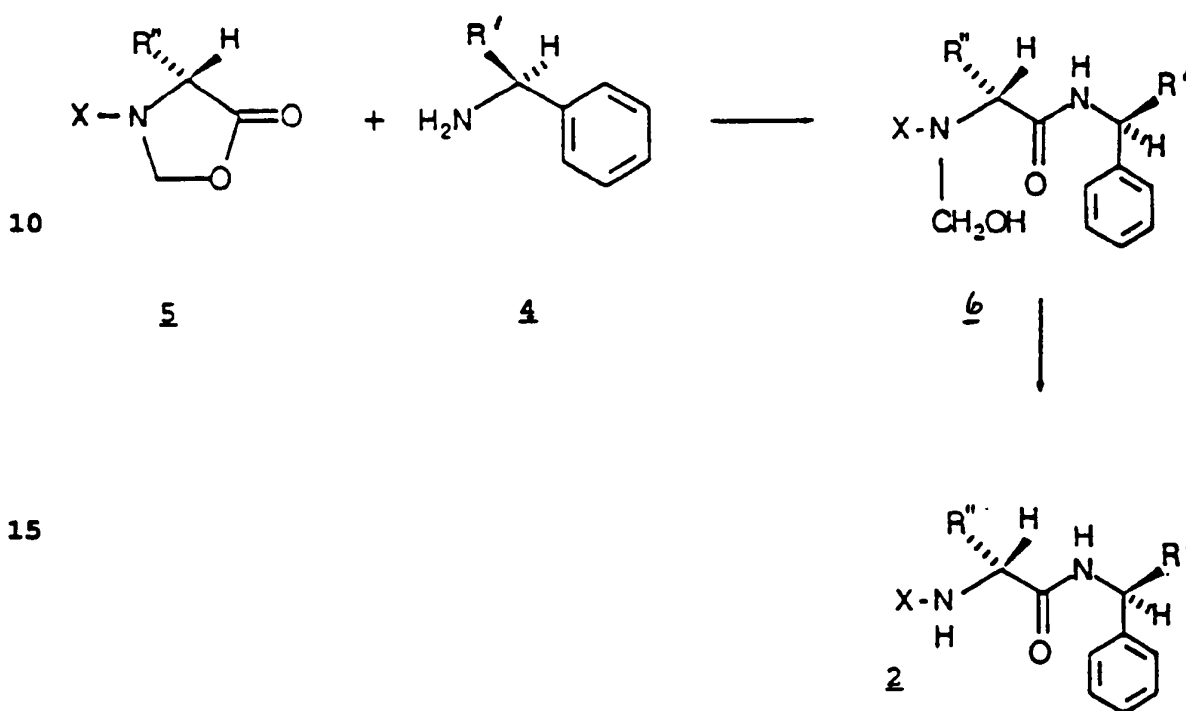


using formaldehyde and an acid catalyst with azeotropic removal of water [A.G. Shipov, N.A. Orlova I.A. Savostyanova, O.B. Artamkina and Y.I. Baukov, Zh. Obschch. Khim, 59, 1084-99 (1989); H. Bundgaard, G.J. Rasmussen, Pharm. Res., 8, 313-22 (1991); A. Buur, H. Bundgaard, Int. J. Pharm., 46, 159-67 (1988)]. The condensation of 5 with amine 4 in an appropriate solvent (e.g., benzene, toluene, isopropanol) at a moderate
 25 temperature produces the transient N-hydroxymethyl derivative 6, that is readily converted to the amide

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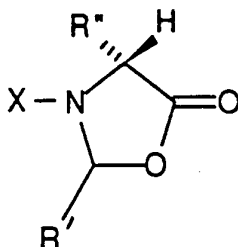
intermediate 2 in high yield by heating the reaction mixture at 80°C for one day, by stirring it with dilute acid at 50°C, or by treatment with aqueous base at pH = 12.5 (where X, R' and R'' are as defined above).

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The preferred oxazolidinones that may be useful for the preparation of artificial sweeteners include a D-amino acid oxazolidinone having the structure:

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where $X = \text{CO}_2\text{CH}_2\phi$, CHO or CO_2 -tert-butyl;

10 $R'' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ ; and

$R' = \text{H}$, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{C}(\text{CH}_3)_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, ϕ or CCl_3 .

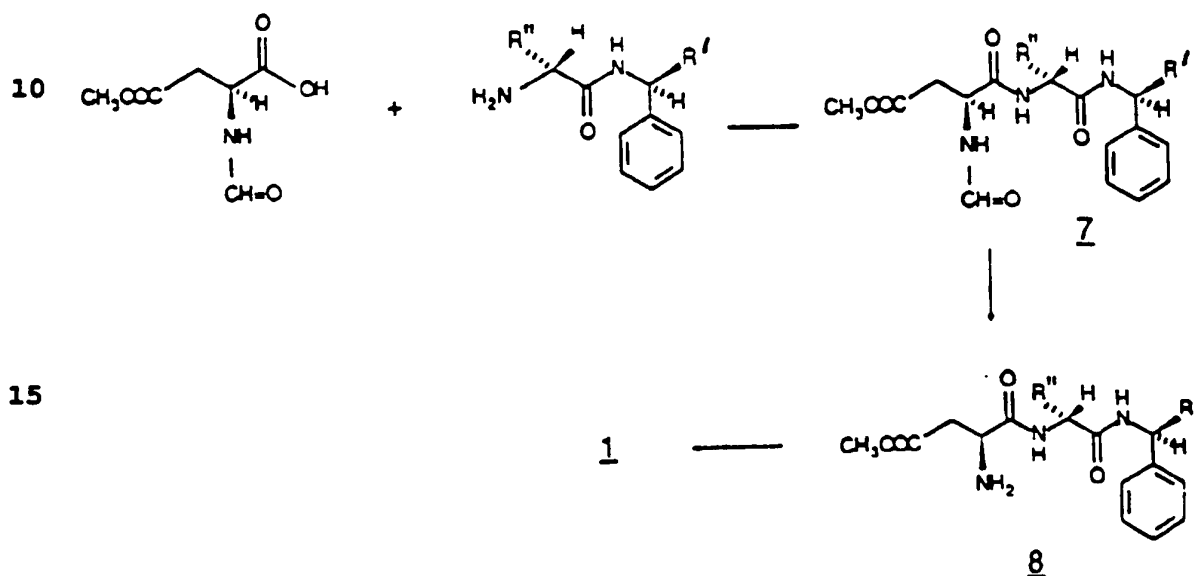
Having prepared intermediate 2, the N-protecting group may then be removed to produce a free amine or a amine salt prior to its conversion to the sweetener compound, (for the free amine, $X = \text{H}$ in the amide-intermediate compound 2). This may be accomplished by using acid hydrolysis for $X = \text{CHO}$ and CO_2 -tert-butyl, and catalytic hydrogenation on Pd/C for $X = \text{CO}_2\text{CH}_2\phi$.

The coupling of the free amine to a suitably protected L-aspartic acid may be achieved, for example, by using any of the following different routes. In the first amine-aspartic acid coupling reaction, N-formyl-(β -methyl)-L-aspartic acid may be used as the mixed anhydride that is prepared in situ with isobutyl

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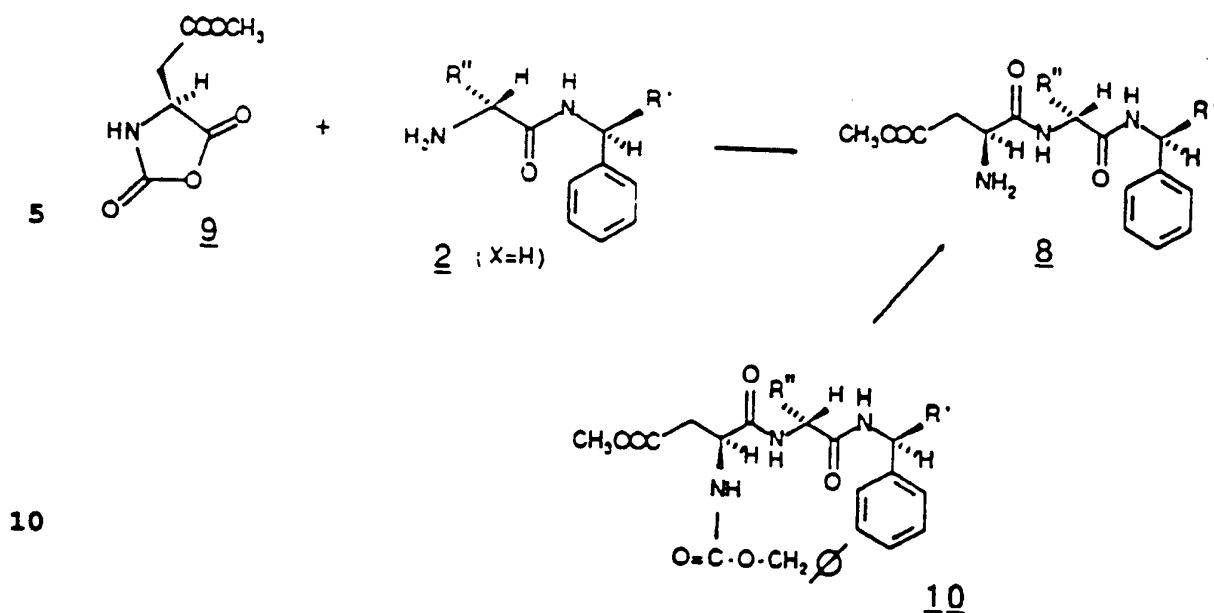
chloroformate/N-methylmorpholine, to which the free amine of 2 may be added. The coupled product 7 that results may be readily hydrolyzed to the sweetener 1 by stirring with 5N HCl at 50 °C for 2 hours. During the hydrolysis, the (β-methyl)-protected intermediate 8 may be observed as a transient species, (where R' and R'' are as defined above):



20 Intermediate 8 may in principle also be obtained from the coupling of (β-methyl)-L-aspartic acid-N-carboxyanhydride 9 [J.S. Tou and B.D. Vineyard, J. Org. Chem., 50, 4982-4984 (1985)] to the free amine obtained from the amide-intermediate compound 2. Alternatively, a sample of 8

25 may be prepared by hydrogenation of the N-carbobenzyloxy derivative 10, (where R' and R'' are as defined above).

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Another procedure for activating the N-protected

15 aspartic acid involves formation of the anhydride.

Coupling of amines with aspartic anhydrides may give some of the unwanted β -aspartyl amides, but they can be removed from the final product by fractional crystallization. For use of N-carbobenzyloxy-L-aspartic

20 acid anhydride, see C.P. Yang and C.S. Su, J. Org. Chem. 51 5186 (1986). For the N-formyl-L-aspartic anhydride, see U.S. Patent No. 3,879,372 or U.S. Patent No. 3,933,781.

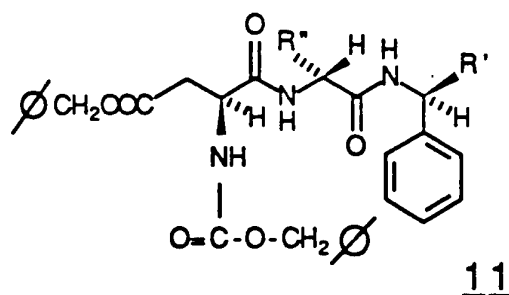
In another preferred method for coupling the

25 free amine obtained from the amide-intermediate compound 2 with the aspartic acid group, the N-carbobenzyloxy-L-

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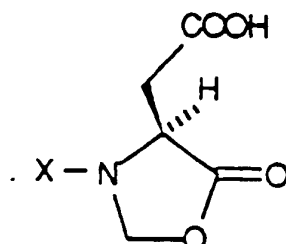
aspartic acid- β -benzyl ester is the preferred diprotected derivative. As above, this ester is coupled to the free amine of 2 by adding isobutyl chloroformate/N-methyl morpholine as the coupling agent. The resulting compound 11 may be converted to the sweetener 1 by catalytic hydrogenation (Pd/C).

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Still another preferred method for coupling the free amine obtained from the amide-intermediate compound 2 with the aspartic acid group comprises using the N-protected L-aspartic acid oxazolidinone 12 as the activated form of L-aspartic acid:

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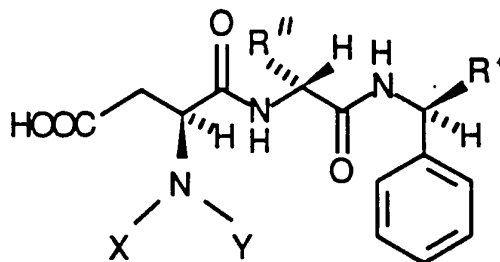
X = CO₂CH₂ϕ, CHO and CO₂-tert-butyl.

Compound 12 (X= CO₂CH₂ϕ) has been prepared previously for the synthesis of the artificial sweetener aspartame [K.I. Lee, J.H. Kim, K.Y. Ko and W.J. Kim, Synthesis, 935-936 (1991); J.M. Scholtz and P.A. Bartlett, Synthesis, 542-544 (1989); T. Fujii, K. Yanagiuchi, S. Mitsunobu, S. Aoki and M. Tsuda, U.S. Patent No. 4,730,076 (1988); C. Higuchi, T. Kato, T. Ora, M. Ajioko, T. Yamaguchi and H. Yamashita, Jpn. Kokai Tokkyo Koho, JP 03,255,093 (1991).] As with compound 5, compound 12 may be prepared by reaction of the N-protected aspartic acid with paraformaldehyde and an acid catalyst in benzene or toluene, with azeotropic removal of water. The reaction of 12 (X= CO₂CH₂ϕ) with the free amine of 2 in an appropriate solvent (benzene, toluene,

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and isopropanol) at 50°C for 10 hours, produces a mixture of N-protected derivative 13 and its hydroxymethyl analogue 14, (where X, R' and R'' are as defined above):

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10 For 13, Y = H and for 14, Y = CH₂OH (R'', R' and X as in 2)

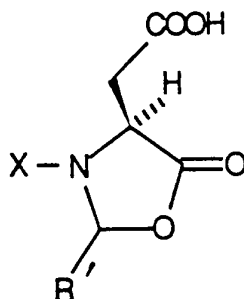
The sweetener compound 1 may then be obtained by heating in dilute acid or by mild base treatment of the 13/14 mixture to obtain pure 13, followed by removal of the X-protecting group. In the case of the N-carbobenzyloxy group, this may be achieved by catalytic hydrogenation in methanol using 10% Pd/C. For the removal of the N-tert-butoxycarbonyl and N-formyl groups, acid hydrolysis is used.

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The preferred oxazolidinones that may be useful for the preparation of artificial sweeteners also include an L-aspartic acid oxazolidinone having the structure:

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where $X = \text{CO}_2\text{CH}_2\phi$, CHO or CO_2 -tert-butyl;

$R' = \text{H}$, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{C}(\text{CH}_3)_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$,
 10 $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, ϕ or CCl_3 .

The practice of the present invention is described in the examples for the case of the sweetener 1 where $R'' = R' = \text{ethyl}$.

15 The α -alkylbenzylamines used with the present invention are known in the prior art, and may be prepared by reduction of the corresponding ketoxime with sodium in ethanol. The ketoximes may be obtained from the corresponding ketones, which are commercially available.
 20 The amines used in the examples had boiling points corresponding to literature values and ^1H and ^{13}C NMR spectra consistent with their assigned structures.

Except for the case of the (R)- α - and (S)- α -methylbenzylamines which were purchased as such, the α -
 25 alkylbenzylamines were prepared as racemic mixtures. One of the synthetic amines, the α -ethylbenzylamine, was

resolved and resulted in a showing that predominantly the (S)-isomer invokes sweetness in the dipeptide amide products. Resolution was achieved by five recrystallizations of the L-(+)-tartaric acid salt of the racemic amine from 95% ethanol.

The other materials, N-carbobenzyloxy-L-aspartic acid, N-carbobenzyloxy- β -benzyl-L-aspartic acid, the N-hydroxysuccinimide, isobutylchloroformate, N-methylmorpholine, dicyclohexylcarbodiimide (DCC), and the D-amino acids, including D-alanine, D-valine, D- α -aminobutyric acid, D-phenylglycine and D- α -aminopentanoic acid are all readily available commercially.

The results of the sweetness potency measurements for the disclosed sweeteners of this invention are summarized in Tables 1-4. The sweetness potency was determined by having four tasters compare the sweetness of various dilutions of the test compound with a 200 ppm solution of aspartame, at which concentration the sweetness potency of aspartame was taken to be 180 times sucrose.

For the L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amides, the presence of the benzyl group produces a high sweetness potency for the various analogues. For example, the results in Table 1 show an increased sweetness potency for the S-enantiomer over the R-enantiomer and a high sweetness potency for the (R,S)

mixtures of ethyl-, propyl-, and t-butyl-, α -alkylbenzyl substituents as well as for the compound having an additional phenyl group at the α -benzyl position. Furthermore, contrary to the compounds of U.S. Patent No. 4,411,925, the data presented in Table 2 generally indicate that increasing the size of the R_1 group of the chemical structure shown in Table 2 results in an increase in the sweetness potency. However, the n-propyl-group derivative was found to be less sweet than the methyl-, ethyl- or isopropyl-group derivatives, showing that there are limits on the size of R_1 .

The combination of the highest potency of D-amino acid from Table 2, valine, with the highest potency of α -alkylbenzyl substituent from Table 1, (S)- α -ethylbenzyl, should produce a compound having the highest overall sweetness potency. Indeed, Table 3 shows that L-aspartyl-D-valine-(S)- α -ethylbenzyl amide has a sweetness potency of 1500 times sucrose. However, Table 3 also shows an unexpectedly higher sweetness potency of 2500 times sucrose for L-aspartyl-D- α -aminobutyric-acid-(S)- α -ethylbenzyl amide. The results in Table 3, thus, indicate L-aspartyl-D- α -aminobutyric-acid-(S)- α -ethylbenzyl amide and L-aspartyl-D-valine-(S)- α -ethylbenzyl amide to be the more preferred sweeteners of the present invention.

The results in Table 4 show that methylation of

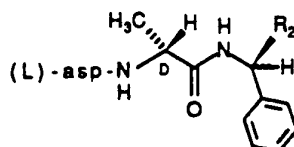
the aromatic ring of the benzyl group produces a decrease in sweetness potency for each of the compounds shown.

25

TABLE 1

Effect of amine structure upon the sweetness potency of
(L)-aspartyl-(D)-alanine amides.

5



10

<u>R₂</u>	<u>SP (x Sucrose)</u>
-CH ₃ (S)	180
-CH ₃ (R)	<10
-CH ₂ CH ₃ (R,S)	270
(R,S)	180

15

-CH ₂ CH ₂ CH ₃ (R,S)	135
(R,S)	150
	180

20

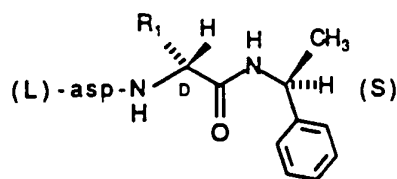
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25

TABLE 2

Effect of the (D)-amino acid structure upon the sweetness potency of the (L)-aspartyl-(D)-amino acid-(S)- α -methyl benzyl amides.

5



10

<u>R₁</u>	<u>SP (x Sucrose)</u>
—CH ₃	180

—CH ₂ CH ₃	360
----------------------------------	-----

—CH ₂ CH ₂ CH ₃	90
--	----

15

—CH(CH ₃) ₂	540
------------------------------------	-----

20

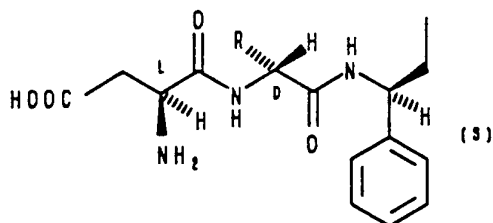
—C ₆ H ₅	270
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25

TABLE 3

Effect of the variation of the D-amino acid on the sweetness potency of L-aspartyl-D-amino acid-(S)- α -ethylbenzyl amides.

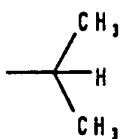
5



10

- R -

SP--(x-succrose)



1,500

15

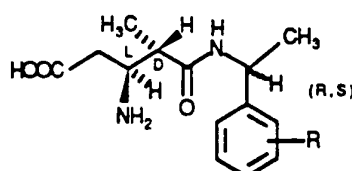
-CH₂CH₃

2,500

TABLE 4

Effect of aromatic methylation on the sweetness of (L)-aspartyl-D-alanine-(R,S)- α -methylbenzyl amides.

5



10

<u>R</u>	<u>SP (x sucrose)</u>
H	90
ortho CH ₃	40
meta CH ₃	40
para CH ₃	80

15

The sweetener compounds of the present invention, including the physiologically acceptable salts thereof, provide advantages as sweetening agents in view of their high sweetness potency, their physical form and stability. They are, ordinarily, crystalline, non-hygroscopic, water soluble solids. They are characterized by possessing a sweet taste, devoid of undesirable harsh or bitter flavor qualities at ordinary use levels.

25

The compounds of the invention can be prepared in a variety of forms suitable for utilization as

sweetening agents. Typical forms that can be employed are solids, such as powders, tablets, granules and dragees, and liquid forms, such as solutions, suspensions, syrups, emulsions, as well as other commonly employed forms that are particularly suited for combination with edible materials. These forms can be comprised of the compounds of the present invention, or of their physiologically acceptable salts, either apart or in association with non-toxic sweetening agent carriers, e.g., non-toxic substances commonly employed in association with sweetening agents. Such suitable carriers include liquids such as water, ethanol, glycerol, corn oil, peanut oil, soybean oil, sesame oil, propylene glycol, corn syrup, maple syrup and liquid paraffin, and solids such as sorbitol, citric acid, lactose, cellulose, starch, dextrin, modified starches, polysaccharides such as polydextrose (see, e.g. U.S. Pat. No. 3,766,165 and 3,876,794), calcium phosphate (mono-, di- or tri-basic) and calcium sulfate.

The sweeteners of this invention may be used to provide desirable properties of sweetness in any orally ingestible product. Examples of specifically ingestible materials include: fruits, vegetables, juices, meat products such as ham, bacon and sausage; egg products, fruit concentrates, gelatins and gelatin-like products such as jams, jellies, preserves, and the like; milk

products such as ice cream, sour cream and sherbet;
icings, syrups including molasses; corn, wheat, rye,
soybean, oat, rice and barley products, nut meats and nut
products, beverages such as coffee, tea, carbonated and
5 non-carbonated soft drinks, beers, wines and liquors;
confections such as candy and fruit flavored drops,
condiments such as herbs, spices and seasonings, flavor
enhancers such as monosodium glutamate and chewing gum.
The sweeteners may also be useful in prepared packaged
10 products such as dietetic sweeteners, liquid sweeteners,
granulated flavor mixes which upon reconstitution with
water provide non-carbonated drinks, instant pudding
mixes, instant coffee and tea, coffee whiteners, malted
milk mixes, pet foods, livestock feed, tobacco and
15 personal care products such as mouth washes and
toothpaste as well as proprietary and non-proprietary
pharmaceutical preparations and other products of the
food, pharmaceutical and sundry industries. Because of
their high heat stability at pH 7, these sweeteners are
20 adept for baking applications such as powdered baking
mixes for the preparation of breads, cookies, cakes,
pancakes, donuts and the like. Especially preferred
sweetened edible compositions are carbonated beverages
containing one or more of the subject sweeteners. The
25 sweeteners could also be used in frozen desserts, chewing
gum, dentifrices, medications or any other orally

ingestible substance.

The sweeteners of this invention may also be blended with other sweeteners known to the art, such as, for example, sucrose, fructose and other polyols, as well as other high potency non-nutritive sweeteners including but not limited to saccharin, cyclamate, aspartame, acesulfame-K, alitame, sucralose, stevioside and the like, which are useful for sweetening edible materials. Especially useful are the blends of the sweeteners of this invention and saccharin or physiologically acceptable salts thereof. Examples of saccharin salts include the sodium, potassium, calcium and ammonium salts. Examples of the sweeteners of this invention also include their sulfates, malates, hydrochlorides, carbonates, phosphates, citrates, acetates, tartrates, benzoates and the like. In blends with saccharin the compounds of this invention may reduce or completely mask the well known, undesirable bitter aftertaste of the saccharin.

The invention is further illustrated by the following non-limiting examples.

EXAMPLES

Example 1. N-carbobenzyloxy- β -benzyl-L-aspartyl-D-alanine

This example describes the preparation of the protected dipeptide utilized in subsequent examples.

A mixture of 5.0 g N-carbobenzyloxy- β -benzyl-L-aspartic acid (14 mmoles), 100 ml tetrahydrofuran, 2.88 g (14 mmoles) dicyclohexylcarbodiimide and 1.61 g (14 mmoles) N-hydroxysuccinimide were 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 dioxane followed by a solution of 1.5 g (16.6 mmoles) D-alanine, 10 ml dioxane, 20 ml H₂O and 1.85 ml (1.34 g, 13.3 mmoles) triethylamine.

The mixture was stirred again at room temperature overnight. The solution was filtered and the filtrate concentrated to approximately 25 ml. The residue was diluted with 100 ml H₂O, acidified to pH 2.0 with 10% H₃PO₄ and extracted twice with 100 ml ethyl acetate. The combined ethyl acetate layers were backwashed with 100 ml H₂O and 50 ml brine. After drying over Na₂SO₄, 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 (U.S. Patent No. 4,411,925) gives mp 158-59°C.

N-carbobenzyloxy- β -benzyl-L-aspartyl-D-valine (57%, mp 93-96°C); N-carbobenzyloxy- β -benzyl-L-aspartyl-D- α -amino butyric acid (57%, mp 151-53°C) [U.S. Patent No. 4,571,345, mp 150-52°C], N-carbobenzyloxy- β -benzyl-L-

aspartyl-D-phenylglycine (54%, mp. 64-67°C) and N-carbobenzyloxy- β -benzyl-L-aspartyl-D- α -aminopentanoic acid (73%, mp 91-95°C) were prepared in a similar procedure substituting equivalent weights of the appropriate D-amino acid for the D-alanine.

Example 2. Synthesis of L-aspartyl-D-alanine-N-(S)- α -methylbenzylamide.

(a) In a 50 ml flask was mixed 500 mg (1.17 mmoles) N-carbobenzyloxy- β -benzyl-L-aspartyl-D-alanine, 0.16 ml (150 mg., 1.24 mmoles) (S)- α -methyl-benzylamine, 241 mg (1.17 mmoles) dicyclohexylcarbodiimide, 210 mg (1.17 mmoles) N-hydroxy-5-norbornene-2,3-dicarboximide and 25 ml 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 ethyl acetate, washed twice with 30 ml, 5% aqueous citric acid, twice with 30 ml 4% aqueous NaHCO₃, and twice with 30 ml brine, dried over MgSO₄, and evaporated to give 0.66 g white solid. This was recrystallized from ethyl acetate/hexane to give 0.55 g (1.04 mmoles, 89%) white crystals, mp 168-70°C.

¹H NMR (200 MHz, CDCl₃), δ : 7.27-7.33 (m, Ar-H, 15H), 7.2 (d, -N-H, 1H), 7.0 (d, -NH, 1H), 6.0 (d, -NH, 1H), 5.07 (s, -O-CH₂-, 2H), 5.05 (s, -OCH₂-, 2H), 4.4-4.6 (m, N-CH-, 3H), 2.65-3.1 (dd, -CH₂-, 2H), 1.4 (d, C-CH₃, 3H), 1.3 (d, C-

CH₃, 3H)

¹³C NMR (50 MHz, CDCl₃), δ: 173.6 (-COO-), 173.0 (-CON-), 172.6 (-CON), 158.0 (-OCON-), 145.6 (-Ar-), 137.9 (-Ar), 137.3 (-Ar), 130.2-130.7 (m, -Ar), 69.3, (-O-CH₂-), 68.8 (-CH₂-O), 53.4 (Ar-CH-N), 51.1 (-CH-N), 50.7 (-CH-N), 38.1 (-CH₂-), 23.8 (-CH₃), 19.5 (-CH₃)

10

(b) L-aspartyl-D-alanine-N-(S)-α-methylbenzyl amide
0.55 g (1.04 mmoles) N-carbobenzyloxy-β-benzyl-L-aspartyl-D-alanine-(S)-α-methylbenzyl amide was dissolved in 50 ml methanol. To this was added 0.06 g
15 10% Pd on activated carbon. The mixture was hydrogenated at 40 psi overnight. The catalyst was removed by filtration through a Celite® filter material (available from Celite Corporation, Lompoc, CA) and the filtrate was evaporated to give 0.43 g solid. This was then dissolved
20 in 200 ml water and filtered to remove a small amount of the dicyclohexylurea that was carried over. The filtrate was freeze-dried to give 0.26 g (0.85 mmoles, 82%) white solid. mp 194-96°C. [α]_D = +41.5° (13.0 mg in 1.00 ml methanol).

25

¹H N (200 MHz, CD₃OD), δ: 7.26-7.4 (m, -Ar-H,

35

5H), 5.00 (m, N-CH-, 1H), 4.37-4.42 (m, N-CH-, 1H), 3.95-4.1 (m, N-CH-, 1H), 2.60-2.71 (m, -CH₂-, 2H), 1.44 (d, -CH₃, 3H), 1.38 (d, -CH₃, 3H).

5

¹³C NMR (50 MHz, D₂O), δ: 180.5 (CO), 178.7 (CO), 173.8 (CO), 148.0 (Ar), 133.4, 132.0, 130.4 (Ar), 54.9, 54.4, 53.9 (CHN) 41.6 (CH₂CO), 25.5 (CH₃) and 21.1 (CCH₃).

10

Sweetness - 180 times sucrose. (The sweetness potency was determined by comparison, using well known methods, against 200 ppm aspartame solution, adopting for aspartame the sweetness potency value of 180 times

15 sucrose.)

Example 3. Synthesis of L-aspartyl-D-α-aminobutyric acid N-(S)-α-methylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D-α-aminobutyric acid-N-(S)-α-methylbenzyl amide was synthesized using N-carbobenzyloxy-β-benzyl-L-aspartyl-D-α-aminobutyric acid in place of the N-carbobenzyloxy-β-benzyl-L-aspartyl-D-alanine.

25

Yield of protected intermediate - 56%,
mp. 167-9°

Yield of sweetener - 99%, mp. 185-9°

Sweetness - 360 times sucrose

Example 4. Synthesis of L-aspartyl-D- α -aminopentanoic acid-N-(S)- α -methylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D- α -aminopentanoic acid-N-(S)- α -methylbenzyl
5 amide was synthesized using N-carbobenzyloxy- β -benzyl-L-aspartyl-D- α -aminopentanoic acid in place of the N-carbobenzyloxy- β -benzyl-L-aspartyl-D-alanine.

Yield of protected intermediate - 69%, mp. 158-61°C

Yield of sweetener - 36%, mp. 203-05°C

10 Sweetness - 90 times sucrose

Example 5. Synthesis of L-aspartyl-D-valine-N-(S)- α -methylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D-valine-N-(S)- α -methylbenzyl amide was
15 synthesized using N-carbobenzyloxy- β -benzyl-L-aspartyl-D-valine in place of the N-carbobenzyloxy- β -benzyl-L-aspartyl-D-alanine.

Yield of protected intermediate - 71%, mp. 178-80°C

20 Yield of sweetener - 45%, mp. 235°C (dec.)

Sweetness - 540 times sucrose

Example 6. Synthesis of L-aspartyl-D-phenylglycine-N-(S)- α -methylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D-phenylglycine-N-(S)- α -methylbenzyl amide was
25 synthesized using N-carbobenzyloxy- β -benzyl-L-aspartyl-D-phenylglycine in place of the N-carbobenzyloxy- β -benzyl-

L-aspartyl-D-alanine.

Yield of protected intermediate- 46%, mp. 160-64°C

Yield of sweetener - 44%, mp. 211-13°C

Sweetness - 270 times sucrose

5

Example 7. Synthesis of L-aspartyl-D-alanine-N-(R)- α -methylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D-alanine-N-(R)- α -methylbenzyl amide was

10 synthesized using (R)- α -methylbenzylamine in place of the (S)-isomer.

Yield of protected intermediate - 88%, mp. 167-69°C

Yield of sweetener - 82% mp. 198-200°C

Sweetness - less than 10 times sucrose

15

Example 8. Synthesis of L-aspartyl-D-alanine-N-(R,S)- α -ethylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D-alanine-N-(R,S)- α -ethylbenzyl amide was

20 synthesized using (R,S)- α -ethylbenzylamine in place of (S)- α -methylbenzylamine.

Yield of protected intermediate - 86%, mp. 133-34.5°C

Yield of sweetener - 87%, mp. 180-83°

25

Sweetness - 270 times sucrose

Example 9. Synthesis of L-aspartyl-D-alanine-N-(R,S)- α -isopropylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D-alanine-N-(R,S)- α -isopropylbenzyl amide was synthesized using (R,S)- α -isopropylbenzylamine in place of (S)- α -methylbenzylamine.

- 5 Yield of protected intermediate - 78%, mp. 135-39°C
Yield of sweetener - 90%, mp. 187-91°C
Sweetness - 180 times sucrose

10 Example 10. Synthesis of L-aspartyl-D-alanine-N-(R,S)- α -t-butylbenzyl amide.

Following the procedure of Example 2, L-aspartyl-D-alanine-N-(R,S)- α -t-butylbenzyl amide was synthesized using (R,S)- α -t-butylbenzylamine in place of (S)- α -methylbenzylamine.

- 15 Yield of protected intermediate - 77%,
mp. (amorphous)
Yield of sweetener - 90%, mp. 158-63°C
Sweetness - 150 times sucrose

20 Example 11. Synthesis of L-aspartyl-D-alanine-N-(R,S)- α -n-propylbenzyl amide.

- 25 Following the procedure of Example 2, L-aspartyl-D-alanine-N-(R,S)- α -n-propylbenzyl amide was synthesized using (R,S)- α -n-propylbenzylamine in place of (S)- α -methylbenzylamine.

Yield of protected intermediate - 84%, mp. 153-55°C
Yield of sweetener - 83% mp. 184-6°C

Sweetness - 90 times sucrose

Example 12. Synthesis of L-aspartyl-D-alanine-N- α -phenylbenzyl amide.

5 Following the procedure of Example 2, L-aspartyl-D-alanine-N- α -phenylbenzyl amide was synthesized using α -phenylbenzylamine in place of (S)- α -methylbenzylamine.

Yield of protected intermediate - 83% mp. 165-68°C

10 Yield of sweetener - 51%, mp. 193-95°C

Sweetness - 180 times sucrose

Example 13. Synthesis of L-aspartyl-D-alanine-N- α -cyclopropylbenzyl amide.

15 Following the procedure of Example 2, L-aspartyl-D-alanine-N- α -cyclopropylbenzyl amide was synthesized using (R,S)- α -cyclopropylbenzylamine in place of (S)- α -methylbenzylamine.

20 Yield of protected intermediate - 62%, mp. 162-6°C

Yield of sweetener - 93%, mp. 188-90°C

Sweetness - 1,080 times sucrose

25 Example 14. Synthesis of L-aspartyl-D- α -aminobutyric acid-N-(S)- α -ethylbenzyl amide.

(a) N-carbobenzyloxy- β -benzyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide.

To 250 ml 4% aqueous sodium carbonate was added 3.22 g (11.3 mmoles) (S)- α -ethylbenzylamine L-(+)-

tartrate (mp. 176-79°C). The mixture was extracted twice with 125 ml methylene chloride, the combined methylene chloride extracts dried over Na₂SO₄ and evaporated at <25°C and 20 mm to give a liquid. This was dissolved in 10 ml dioxane and added to a stirred mixture of 5.0 g (11.3 mmol) N-carbobenzyloxy-β-benzyl-L-aspartyl-D-α-aminobutyric acid, 200 ml dioxane, 2.5 g (12.1 mmol) dicyclohexylcarbodiimide and 1.25 g (7.0 mmol) N-hydroxy-5-norbornene 2,3-dicarboximide. The mixture was stirred at room temperature overnight, then filtered and the filtrate evaporated to a thick oil. The oil was dissolved in 300 ml chloroform and washed twice with 200 ml 4% aqueous citric acid, three times with 150 ml 4% aqueous NaHCO₃ and with 100 ml H₂O. Drying the chloroform layer over Na₂SO₄ 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 protected sweetener, mp. 134-36°C.

20 (b) L-aspartyl-D-α-aminobutyric acid-N-(S)-α-ethylbenzyl amide.

To a solution of 5.25g (9.4 mmol) of the product of step (a), described above, in 100 ml methanol was added 400 mg of 10% Pd/C catalyst and the mixture 25 hydrogenated at 40 psi H₂ on a Parr shaker for 3 hours at room temperature. The catalyst was removed by filtration

through a bed of a 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 mmols, 49.6% mp. 197-98°C) of L-aspartyl-D-
5 α -aminobutyric acid-N-(S)- α -ethylbenzyl amide. A second crop was also obtained: 0.397 g (1.18 mmols, 12.6%, mp 195-97°C).

^1H NMR (200 MHz, CD_3OD) δ : 7.2 (m, ArH, 5H): 4.60 (m, -N-CH(R)CO-, 1H), 4.20 (m, -NCH(R)(CO), 1H), 3.94
10 (m, -CH(R) Ar, 1H), 2.5 (m, CH_2 -CO₂H, 2H), 1.55-1.85 (m, CH_2 , 4H) and 0.83 (2t, CH_3 , 6H).

^{13}C NMR (50 MHz, CD_3OD) δ : 175.1, 178.2 and 180.9 (CO), 132.3, 132.6, 134.0, 148.7 (Ar), 61.1
15 (NHCH(R)Ar), 60.7 (NHCHCO), 56.7 (NCHCO), 42.8 (CH_2CO), 34.7 (CH_2), 31.3 (CH_2), 15.8 (CH_3), and 15.0 (CH_3).

Sweetness - 2500 times Sucrose

20 Example 15. Synthesis of L-aspartyl-D-valine-N-(S)- α -ethylbenzyl amide.

Following the procedure of Example 14, L-aspartyl-D-valine-N-(S)- α -ethylbenzyl amide was synthesized using N-carbobenzyloxy- β -benzyl-L-aspartyl-D-
25 valine in place of N-carbobenzyloxy- β -benzyl-L-aspartyl-D- α -aminobutyric acid.

Yield of protected intermediate - 54%, mp. 180-2°

42

Yield of sweetener - 42%, mp. 220-40°

Sweetness - 1500 times sucrose.

Example 16. Cola Beverage

5 L-aspartyl-D- α -aminobutyric acid-N-(S)-
ethylbenzylamide (0.16 g) is dissolved in 500 ml water
and the volume adjusted to one liter. Citric acid (1 g),
phosphoric acid (2 g), caramel color (10 g), cola
flavoring (10 g) and a benzoate preservative (2 g) are
10 dissolved in the liter solution of sweetener. The
resulting cola concentrate is diluted with 3 liters of
water to provide a single strength beverage. Carbonation
produces a satisfying effervescent carbonated cola drink
having a palatable sweetness.

15

Example 17. Citrus Beverage

160 mg of L-aspartyl-D- α -aminobutyric acid-N-
(s)- α -ethylbenzylamide is dissolved in 1 liter of water.
To this 4.5 g citric acid, 2 g sodium benzoate and 10 g
20 of citrus flavoring are added. The resulting citrus
concentrate is diluted with 3 liters of water to provide
a single strength beverage. Carbonation as desired gives
a satisfactory effervescent beverage having a palatable
sweetness.

25

Example 18. Dietetic Hard Candy

A hard candy is prepared according to the following formulation and procedure:

	Ingredients	% by weight (approximate)
5	A sweetener	---
	FD and C Red #40 (10% aqueous)	0.05
	Cherry Flavor	0.1
	Citric acid	1.0
10	Polydextrose*	70
	Water	30

*U.S. Pat. No. 3,766,165

15 The sweetener is an L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl amide. The quantity of sweetener added is varied
20 depending on the sweetness potency of the sweetener.

In a small beaker dissolve the sweetener in water, add color, flavor and citric acid and mix well to dissolve. In a separate beaker combine polydextrose and water. Stir while heating to 140°C, then allow to cool
25 to 120°-125°C. Add other ingredients from a small beaker and mix or knead thoroughly. Transfer the material to an oil coated marble slab and allow to cool to 75°-80°C. Extract the material through an oil coated impression roller.

Example 19. Gelatin Dessert

A gelatin dessert is prepared according to the following composition and procedure.

5	Ingredients	% by weight (approximate)
	Gelatin 225 Bloom	1.5
	Citric acid	0.36
	Sodium citrate	0.26
10	Strawberry flavor	0.06
	A sweetener	---
	Boiling water	49
	Cold Water	49

15 The sweetener is an L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl
20 amide. The quantity of sweetener added is varied depending on the sweetness potency of the sweetener.

Premix the first five ingredients, add to boiling water and stir to dissolve completely. Add cold water and stir briskly. Transfer to serving dishes and
25 refrigerate until set.

Example 20. Low Calorie Table Sweetener

Low calorie table sweeteners are prepared according to the following formulations:

30 A. A powder form of sweetener is prepared by blending the following ingredients.

	Ingredients	% by weight (approximate)
	A sweetener	---
5	Crystalline sorbitol	49.5
	Dextrin (dextrose equivalent 10)	50
	Monosodium glutamate	0.02
	Glucono-delta-lactone	0.02
	Sodium Citrate	0.02
10		

The sweetener is an L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl amide. The quantity of sweetener added is varied depending on the sweetness potency of the sweetener.

B. A table sweetener in liquid form is prepared as follows.

20	Ingredients	% by weight (approximate)
	A sweetener	--
	Water	99
25	Sodium benzoate	0.10

The sweetener is an L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl amide. The quantity of sweetener added is varied depending on the sweetness potency of the sweetener.

35 Example 21. Frozen Dessert

A vanilla sugarless frozen dessert is prepared

according to the following formulation by conventional practice.

	Ingredients	% by weight (approximate)
5	Heavy cream (35% butterfat)	23
	Nonfat milk solids	10
	Mono- and diglyceride emulsifier	0.25
	Polydextrose*	11
10	Water	54
	A sweetener	0.06
	Gelatin (225 Bloom)	0.5

*U.S. Pat. No. 3,766,165

15

The sweetener is an L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl
20 amide. The quantity of sweetener added is varied depending on the sweetness potency of the sweetener.

Example 22. Canned Pears

Fresh Pears are washed, peeled, cored, sliced
25 into pieces and immersed in an aqueous solution containing 0.05% by weight of ascorbic acid. The sliced fruit is packed into screw-cap jars and the jars filled with a syrup containing the following ingredients:

	Ingredients	% by weight (approximate)
5	Sorbitol	25
	A sweetener	--
	Citric acid	0.12
	Water	75

- 10 The sweetener is an L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl amide. The quantity of sweetener added is varied
- 15 depending on the sweetness potency of the sweetener.

The jars are capped loosely and placed in an autoclave containing hot water and processed at 100°C for 45 minutes. The jars are removed, immediately sealed by tightening the caps and allowed to cool.

20

Example 23. Powder Beverage Concentrate

	Ingredients	% by weight (approximate)
25	Citric acid	32
	Sodium citrate	5
	Strawberry flavor	58
	Strawberry FD and C color	0.5
	A sweetener	---
30	Carboxymethyl cellulose	2.4

- The sweetener is an L-aspartyl-D- α -aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed
- 35 herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl

amide. The quantity of sweetener added is varied depending on the sweetness potency of the sweetener.

Combine all ingredients in a blender and blend until homogeneous. For use, 1.73 g. of powder beverage
 5 concentrate is dissolved in 4 fluid ounces (118 ml.) of water.

Example 24. Baked Cake

A vanilla cake may be prepared employing the
 10 following recipe:

	Ingredients	% by weight (approximate)
	Emulsified shortening	7.9
15	Water	9.9
	Eggs	11.3
	Sodium bicarbonate	0.5
	Vanilla extract, single fold	0.1
	Glucono-delta-lactone	0.8
20	Polydextrose*, 70% aqueous solution	39.5
	Nonfat dry milk	1.2
	Cake flour	27.6
	Whole milk powder	0.4
	Wheat starch	0.7
25	A sweetener	---

U.S. Pat. No. 3,766,165

The sweetener is an L-aspartyl-D- α -
 30 aminoalkanoyl-(S)-N- α -alkylbenzyl amide as disclosed herein, e.g. L-aspartyl-D- α -aminobutyric acid-S- α -ethylbenzyl amide or L-aspartyl-D-valine-S- α -ethylbenzyl amide. The quantity of sweetener added is varied depending on the sweetness potency of the sweetener.

35 Combine nonfat dry milk, whole milk powder,

polydextrose solution and emulsified shortening. Mix at low speed until creamy and smooth (about 3 minutes), add eggs and beat until a homogeneous creamy mix is obtained. Dissolve sweetener in water, add to creamy homogenate and
5 mix 2-3 minutes. Add remaining ingredients and mix until creamy and smooth (3-5 minutes). Place 120 g. of batter in small pregreased pan and bake at 350°F. (176°C.) for 30 minutes.

10 Example 25. (S)- α -Ethylbenzylamine L-tartrate

A mixture of 20.6 g of (R,S)- α -ethylbenzylamine, b.p. 108-12°/33-38 mm [P.L. Rinaldi, M.S.R. Naidu & W.E. Conaway, J. Org. Chem. 47, 3987-91 (1982) give b.p. 87-90° (15 mm.)] and 22.9 g L-(+)-
15 tartaric acid was reacted at reflux in 350 ml of 95% ethanol, then allowed to cool for 18 hours at room temperature. This produced 13.01 g amine tartrate with (S/R) = 2.75/1. Recrystallization then produced fractions as follows:
20 13.01g (S/R = 2.75/1) plus 130 ml EtOH gave 8.42g (S/R = 6.25/1);
8.42g (S/R = 6.25/1) plus 84 ml EtOH produced 6.41g (S/R = 12.7/1);
6.41g (S/R = 12.7/1) plus 64 ml EtOH produced 4.66g
25 (S/R = 15.8/1), mp. 176-9°C, $[\alpha]_D = +24^\circ$, (C = 1.15, H₂O).

Example 26. N-carbobenzyloxy-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide

To a solution of 5.0 g N-CBZ-D- α -aminobutyric acid in 150 ml dry tetrahydrofuran was added 2.4 ml N-methyl morpholine at 0 °C under nitrogen. While stirring, 2.8 ml isobutyl chloroformate was added in three portions over five minutes. Reaction was continued for twenty minutes at 0 °C after which a solution of 2.84g (S)- α -ethylbenzylamine in 40 ml THF was added dropwise over a ten minute interval. The reaction mixture was allowed to warm to room temperature for three hours. Thereafter, solvent was removed in vacuo to give a white solid which was stirred for five minutes with 100 ml of 1% phosphoric acid and then filtered. The precipitate was washed with 3 x 25 ml deionized water. The product was dried overnight in vacuo and recrystallized from ethyl acetate-hexane. Yield - 6.35 g (85%), mp 126-30°C.

¹H-NMR (CDCl₃), δ : 7.2 - 7.33 (m, ArH, 10H); 6.50 (d, NH, 1H); 5.42 (d, NH, 1H); 5.07 (s, CH₂O, 2H); 4.84 (q, CH-N, 1H); 4.14 (q, CH-N, 1H); 1.79 (m, CH₂, 4H) and 0.91 (m, CH₃, 6H).

¹³C-NMR (CDCl₃), δ : 173.0 (CO); 158.4 (CONH); 144.0 (Ar); 138.2 (Ar); 128.5 -130.6 (6 peaks, Ar); 68.9 (CH₂O); 58.1 (CH-N); 56.8 (CH-N); 31.0 (CH₂); 27.7

(CH₂); 12.4 (CH₃) and 11.5 (CH₃).

Example 27. D- α -aminobutyric acid-(S)- α -ethylbenzyl amide, (D)-(-)-tartrate

- 5 a) To a solution of 4.0 g N-CBZ-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide in 100 ml methanol was added 400 mg 10% Pd/C and the mixture hydrogenated at 40 psi H₂ on a Parr shaker for 4 hours. The catalyst was removed by filtration through Celite®
10 and the filtrate evaporated to a thick oil.
[α]_D - 125.6° (C = 1.2, MeOH)

¹H NMR (CDCl₃) δ : 7.78 (d, NH, 1H), 7.15-7.3 (m, ArH, 5H), 4.82 (dd, CH-N, 1H), 3.35 (m, CH-N, 1H), 2.30
15 (br s, NH₂, 2H), 1.4-1.9 (m, CH₂, 4H), 0.86 (t, CH₃, 6H).

¹³C NMR (CDCl₃) δ : 174.0 (CO), 142.6, 128.5, 127.1, 126.6 (Ar), 56.0 (CH-N), 54.3 (CH-N), 29.2 (CH₂),
20 27.5 (CH₂), 10.4 (CH₃), 9.6 (CH₃).

b) To the oil was added 1.70 g D-tartaric acid and the mixture crystallized from 50 ml 95% ethanol. This produced 2.45 g colorless crystals, mp. 185-7°C.

25 ¹H-NMR (D₂O) δ : 7.36 (m, 5H, ArH); 4.76 (s, HOD); 4.69 (t, 1H, CH-N); 3.92 (t, 1H, CH-N); 1.93 (m, 2H, CH₂); 1.80 (m, 2H, CH₂); 1.00 (t, 3H, CH₃) and 0.89

(t, 3H, CH₃).

¹³C-NMR (D₂O) δ : 181.1, 174.0 (C=O); 146.8 (Ar);
133.4, 132.2, 131.0 (Ar); 77.2 (CH-O); 60.62, 58.78
5 (CH-N); 33.1 and 28.9 (CH₂); 14.6 and 12.7 (CH₃).

Example 28. β -methyl-N-formyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide

A solution of 5.0 g N-CBZ-D- α -aminobutyric
10 acid-(S)- α -ethylbenzyl amide in 100 ml methanol was
treated with 400 mg of 10% palladium/carbon and then
hydrogenated on a Parr shaker at 40 psi H₂ for three
hours. The catalyst was removed by filtration through
Celite® and the filtrate evaporated to a thick oil
15 (compound A).

Separately, 5.0 g N-formyl- β -methyl-L-aspartic
acid and 1.8 ml N-methylmorpholine in 100 ml dry
tetrahydrofuran were cooled in an ice bath under
nitrogen. To this solution was added two 1 ml portions
20 of isobutyl chloroformate and the solution was stirred at
0° under nitrogen for twenty minutes. Next, compound (A)
in 40 ml tetrahydrofuran was added dropwise at 0 °C under
nitrogen over a ten minute interval. The reaction
mixture was stirred for three hours at room temperature,
25 after which it was concentrated in vacuo to a white
solid, which was suspended in 75 ml of 1% phosphoric acid
and then filtered. The precipitate was washed twice with

50 ml deionized water. Drying the precipitate in vacuo produced 4.32 g. This was recrystallized from ethyl acetate-hexane to produce 2.93 g, having a melting point range of 167-168 °C.

5

$^1\text{H-NMR}$ (CDCl_3), δ : 8.02 (s, CHO, 1H); 7.16-7.32 (m, ArH +NHCO, 6H); 6.97 (t, NHCO, 2H); 4.66 (m, CH-N), 2H); 4.34 (m, CH-N), 1H); 3.64 (s, CH_3O , 3H); 2.76 (m, CH_2CO , 2H); 1.78 (m, CH_2 , 4H) and 0.88 (2t, CH_3 , 6H).

10

$^{13}\text{C-NMR}$ (CDCl_3), δ : 173.8, 172.6, 172.2 and 163.4 (CO); 144.3 (Ar); 130.6, 129.3, 128.6 (Ar); 56.9, 56.8 (CH-N); 53.9 (CH-N); 49.7 (OCH_3); 37.6 (CH_2CO); 31.6 (CH_2); 27.0 (CH_2); 12.5 (CH_3) and 11.6 (CH_3).

15

Example 29. β -Methyl-N-carbobenzyloxy-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide

To a solution of 500 mg N-CBZ-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide in 40 ml methanol was added 100 mg of 10% Pd/C and the mixture hydrogenated at 40 psi for 4 hours. The catalyst was removed by filtration through Celite® and the filtrate evaporated to a thick oil. This was dissolved in 10 ml dioxane and added to a solution of 400 mg N-CBZ-(β -methyl)-L-aspartic acid (SIGMA®), 290 mg dicyclohexylcarbodiimide and 145 mg N-hydroxy-5-norbornene-2,3-dicarboximide in 25 ml dioxane.

25

After stirring overnight at room temperature, the mixture was filtered and the filtrate evaporated to give an amorphous solid. This was dissolved in 60 ml CHCl_3 and washed twice with 25 ml 5% aq. citric acid, three times with 30 ml 5% aq. NaHCO_3 and 25 ml H_2O . Drying (Na_2SO_4) and evaporating the CHCl_3 produced a white solid. Recrystallization from ethyl acetate-hexane produced 520 mg of a product having a mp. 189-90 °C.

- 10 ^1H -NMR (CDCl_3), δ : 7.2-7.4 (m, 10H, ArH); 6.79 (t, 2H, 2NH); 5.83 (d, 1H, NH); 5.10 (s, 2H, CH_2O); 4.85 (q, 1H, CH-N); 4.56 (q, 1H, CH-N); 4.33 (q, 1H, CH-N); 3.64 (s, 3H, OCH_3); 2.65-3.14 (m, 2H, CH_2CO); 1.55-2.05 (m, 4H, CH_2); and 0.87 (b.t., 6H, CH_3).
- 15 ^{13}C -NMR (CDCl_3), δ : 174.3, 172.7, 172.3, 158.2 (CO); 144.4, 137.8 (ArH); 128.5-130.7 (m, Ar); 69.4 (ArCH_2O); 56.9, 56.7 (CH-N); 53.9 (CH_3O); 53.5 (CH-N); 37.9 (CH_2CO); 31.1 (CH_2); 26.6 (CH_2); 12.5 (CH_3) and 11.6 (CH_3).
- 20

Example 30. β -Methyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide acetate.

To a solution of 400 mg β -methyl-N-CBZ-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide in 50 ml methanol was added 100 mg of 10% Pd/C and 100 ml acetic acid and the mixture hydrogenated at 40 psi H_2 on a

55

Parr shaker for four hours. The catalyst was then removed by filtration through Celite® and the solvent evaporated to produce a thick oil. The product was dried in vacuo and produced 310 mg.

5

¹H-NMR (CDCl₃), δ: 8.08 (m, 1H, NH); 7.52 (d, 1H, NH); 7.20 (m, 5H, ArH); 5.80 (m, 3H, NH₃); 4.78 (q, 1H, CH-N); 4.37 (m, 1H, CH-N); 3.71 (m, 1H, CH-N); 3.59 (s, 3H, OCH₃); 2.72 (m, 2H, CH₂CO); 1.60-2.0 (m, 7H, CH₂ and CH₃CO₂) and 0.84 (2t, 6H, CH₃).

10

¹³C-NMR (CDCl₃), δ: 178.4 (CH₃CO₂H); 175.0; 174.3, 173.3 (CO); 144.6 (Ar); 130.4, 129.0, 128.6 (Ar); 56.9, 56.7 (CH-N); 53.7 (CH₃O); 52.9 (CH-N); 40.0 (CH₂CO); 31.0 (CH₂); 27.0 (CH₂); 23.6 (CH₃CO₂H); 12.6, 11.7 (CH₃).

15

Example 31. Synthesis of (D)-3-carbobenzyloxy-4-ethyl-5-oxazolidinone.

20

To a solution of 48.5 g of N-carbobenzyloxy-D-α-aminobutyric acid in 700 ml of toluene was added 12.2 g of paraformaldehyde and 2.0 g of p-TsOH.H₂O. The mixture was heated at reflux for 80 minutes with Dean-Stark trap removal of water. This was then cooled, passed through a short pad of silica gel and the solvent removed under reduced pressure to give 49.1 g of a clear oil (96%).

25

$[\alpha]_D - 83.6^\circ$ (C = 1.0, i-PrOH)

^1H NMR (CDCl_3), δ : 7.3 (s, Ar-H, 5H), 5.5 (br s, CH_2 , 1H), 5.2 (d, CH_2 , 1H), 5.2 (s, ArCH_2 -, 2H), 4.3 (t, H-4, 1H), 1.8-2.2 (br m, H α , 2H), 0.9 (t, CH_3 , 3H)

5

^{13}C NMR (CDCl_3) δ : 172.5 (CO), 164.2 (CO), 135.6, 128.5, 128.4, 128.3 (Ar), 78.0 ($\text{O-CH}_2\text{N}$), 67.7 (ArCH_2 -), 55.5 (NCHCO) 23.6 (CH_2), 8.1 (CH_3)

10 Example 32. Synthesis of N-carbobenzyloxy-D- α -aminobutyric acid-(S)- α -ethylbenzylamide.

a) To a solution of 4.2 g of

D-3-carbobenzyloxy-4-ethyl-5-oxazolidinone in 30 ml of toluene was added 3.0 g of (S)- α -ethylbenzylamine. This
15 was heated to 60-5°C and stirred overnight. The solution was concentrated under reduced pressure and taken up in 200 ml of EtOAc. This was washed twice with 50 ml of 10% citric acid, brine, and then concentrated to give 6.2 g of a mixture of the desired product and the labile

20 intermediate N-carbobenzyloxy-N-hydroxymethyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide:

^1H NMR (CDCl_3), δ : 7.32, 7.25 (s, ArH, 10H), 4.95-5.2 (m, CH_2O , 4H), 4.4-4.95 (m, CH-N , 1H), 4.1-4.4 (m,
25 CH-N , 1H), 1.5-2.1 (m, CH_2 , 4H), 0.7-1.0 (m, CH_3 , 6H)

b) The above residue was taken up in 200 ml

of 50% MeOH and the solution adjusted to pH 12.5 with 50% NaOH. It was then adjusted back to pH 6 using H_3PO_4 . The solution was concentrated to remove the MeOH and then extracted twice with 100 ml of EtOAc. The organic extract
5 was dried over $MgSO_4$ and the solvent removed to give 5.4 g of a yellow solid (90%). This was recrystallized from hexane/EtOAc, giving 4.9 g of a pale yellow solid. mp 128-30°C $[\alpha]_D - 38.6^\circ$ (C=1.3, MeOH)

10 Example 33. Synthesis of N-carbobenzyloxy-N-hydroxymethyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide.

To 1.7 g of D- α -aminobutyric acid-(S)- α -ethylbenzylamide in 10 ml of toluene was added 1.9 g of
15 N-CBZ-L-aspartic acid oxazolidinone. This solution was stirred for 1 hour at 23°C followed by the addition of 0.70 ml of Et_3N and heating at 50-5°C for 8 hours. The mixture was cooled and the toluene decanted from the gummy product. This gum was taken up in 200 ml of EtOAc
20 and washed twice with 100 ml of 10% citric acid, water, brine and dried over $MgSO_4$. This gave 3.3 g of a white glassy solid (>95%) which contained a small amount of N-carbobenzyloxy-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide.

25 An aliquot of this mixture was chromatographed on RPC-18 (CH_3CN/H_2O) to give a product which upon drying in vacuo was a white foam, having mp 65-8°C.

$[\alpha]_D -76.1^\circ$ (C=1.0, MeOH)

^1H NMR (CDCl_3), δ : 7.4-7.9 (br s(2), -NH, 1H),
7.0-7.4 (m, ArH, 10H), 4.8-5.2 (m, CH_2O , 4H), 4.78
5 (t, ArCHN, 1H), 4.70 (m, CH-N, 1H), 4.23 (m, CH-N,
1H), 2.7-3.4 (m, HO_2CCH_2 , 2H), 1.5-1.9 (m, CH_2 , 4H),
0.7-1.0 (m, CH_3 , 6H)

^{13}C NMR (CDCl_3) δ : 174.9, 171.8, 171.4, 155.8 (CO),
10 142.3, 135.6, 128.6-126.6 (Ar), 72.1 (CH_2O), 67.8
(CH_2O), 58.1 (CH-N), 55.4 (CH-N), 55.1 (CH-N), 34.4
(CH_2), 28.8 (CH_2), 24.6 (CH_2), 10.6 (CH_3), 9.5 (CH_3)

15 Example 34. Synthesis of N-carbobenzyloxy-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide.

2.6 g of the impure N-carbobenzyloxy-N-hydroxymethyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide was taken up in 100 ml of 50% MeOH and the solution adjusted to pH 12.3 using 50%
20 NaOH. It was then acidified to pH 3.5 using H_3PO_4 , the MeOH removed under reduced pressure and the resulting white solid taken up in 200 ml of EtOAc. The organic solution was washed with 50 ml of 10% citric acid, brine, and dried over MgSO_4 , to give 2.3 g of a white solid (94%)
25 which was recrystallized from EtOAc/Hexane. mp $187-8^\circ\text{C}$
 $[\alpha]_D -11.0^\circ$ (C=1.0, MeOH)

^1H NMR (CD_3OD), δ : 8.05-8.27 (m, -NH, 1H), 7.15-7.40

(m, ArH, 10H), 5.08 (s, CH₂O, 2H), 4.77 (dd, ArCHN, 1H), 4.47 (t, CH-N, 1H), 4.27 (dd, CH-N, 1H), 2.77 (m, HO₂CCH₂-, 2H), 1.5-2.0 (m, CH₂, 4H), 0.88 (q, CH₃, 6H).

5

¹³C NMR (CD₃OD) δ : 174.4, (CO), 173.7 (CO), 159.7 (CO), 144.4, 139.3, 129.7, 129.3, 129.0, 128.4, 128.0 (Ar), 68.0 (CH₂O), 56.8 (CH-N), 56.7 (CH-N), 53.4 (CH-N), 36.9 (CH₂), 30.5 (CH₂), 26.0 (CH₂), 11.4 (CH₃), 10.7 (CH₃).

10

Example 35. Synthesis of L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide.

1.5 g of N-carbobenzyloxy-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide was dissolved in 100 ml of MeOH, 0.12 g of 10% Pd/C added and the mixture hydrogenated overnight at 30 psi H₂. The catalyst was removed by filtration through a short Celite® plug and the filtrate concentrated under reduced pressure. The resulting white solid was then dried in vacuo to give 1.1 g (>95%) of a white solid. This was recrystallized from 95% EtOH. mp 198-9°C. [α]_D -28.8° (C = 1.0, HOAc)

20

Example 36. β -Methyl-N-formyl-L-aspartyl-D- α -aminobutyric acid.

25

A solution of 1.20 g (6.86 mmol) β -methyl-N-formyl-L-aspartic acid and 1.28 ml (9.15 mmol)

- triethylamine in 50 ml THF was cooled at 0 °C. To this was added 1.25 g (9.15 mmol) isobutyl chloroformate in three portions with stirring. The mixture was stirred at 0°C for 20 minutes, then 0.95 g (9.2 mmol) D- α -
- 5 aminobutyric acid (Aldrich) in 9.2 ml 1 N NaOH was added to the above solution. After stirring overnight at 4°C, THF was evaporated under 35°C. The aqueous phase was extracted by 30 ml ethyl acetate, acidified to pH = 2 with 6 N HCl, and then extracted twice with 30 ml ethyl
- 10 acetate. The combined organic layers were washed with brine, and dried over MgSO₄. Ethyl acetate was removed in vacuo to give 0.88 g thick oil. Crystalization with ethyl acetate/hexane gave 0.79 g white solid. mp. 110-112°C.
- 15 ¹H NMR (200 MHz, CD₃OD), δ : 8.1 (s, 1H, -COH), 4.9 (m, 1H, -CH-), 4.3 (m, 1H, -CH-), 3.69 (s, 3H, -OCH₃), 2.8 (m, 2H, -CH₂-), 1.8 (m, 2H, -CH₂-), 0.9 (m, 3H, -CH₃).
- 20 ¹³C NMR (50 MHz, CD₃OD), δ : 179.6 (-COOH), 177.0 (-COO-), 171.8 (-CON-), 168.4 (-COH), 59.5 (-CH-), 56.8 (-CH-), 41.4 (-CH₂-), 30.1 (-CH₂-), 14.6 (-CH₃).

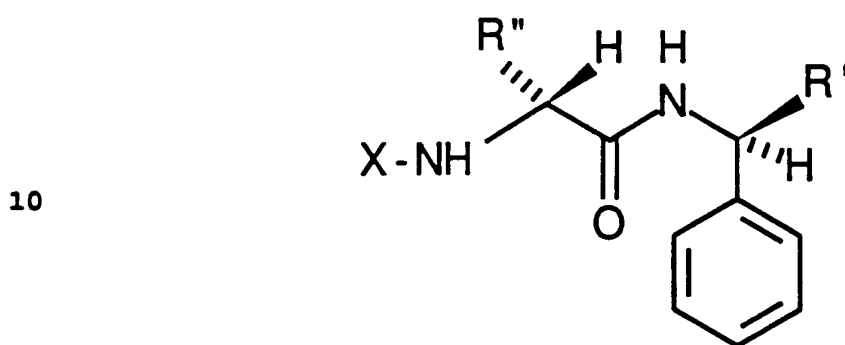
25 Example 37. Acid Hydrolysis of β -methyl-N-formyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide.

Into 2 ml of 5N HCl containing 250 mg β -methyl-N-formyl-L-aspartyl-D- α -aminobutyric acid-

(S)- α -ethylbenzyl amide were added four 230 mg portions of the same protected sweetener at 30 minute intervals, at which time previously added material was in solution. Hydrolysis was continued for 2 hours at 50°C subsequent
5 to the last addition of material. Thereafter, the preparation, diluted to 5 ml with deionized water, was placed in a room temperature water bath and adjusted to pH 7.0 with 33% (w/w) sodium hydroxide solution while stirring rapidly. The opaque, white viscous mass that
10 resulted was dispersed gently with a spatula and collected over a sintered glass funnel using lab aspiration, oven dried at 25°C in vacuo and recrystallized from 95% ethanol/water. The melting point for the preparation was observed to be 197-8°. The
15 material was identical by NMR comparison with the product of Example 14.

WHAT IS CLAIMED IS:

1. A chemical compound useful for the preparation of artificial sweeteners comprising a D-amino acid-(S)- α -alkylbenzyl amide having the structure:



- 15 where X = H, CO₂CH₂ ϕ , CHO or CO₂-tert-butyl;

R'' = CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃ or ϕ ; and

R' = CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃, CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃ or ϕ .

20

2. The chemical compound of claim 1 wherein said D-amino acid (S)- α -alkylbenzylamide is selected from the group consisting of said structure with X = H, and R'' = R' = CH₂CH₃, said structure with X = H, R'' = CH₃ and R' = CH₂CH₃, said structure with X = H, R'' = CH₂CH₃ and R' = CH₃, said structure with X = H, R'' = CH(CH₃)₂ and R' = CH₃,
- 25

said structure with $X = H$, $R'' = CH(CH_3)_2$ and $R' = CH_2CH_3$,
said structure with $X = CO_2CH_2\phi$ and $R'' = R' = CH_2CH_3$, said
structure with $X = CO_2CH_2\phi$, $R'' = CH_3$ and $R' = CH_2CH_3$, said
structure with $X = CO_2CH_2\phi$, $R'' = CH_2CH_3$ and $R' = CH_3$, said
5 structure with $X = CO_2CH_2\phi$, $R'' = CH(CH_3)_2$ and $R' = CH_3$,
said structure with $X = CO_2CH_2\phi$, $R'' = CH(CH_3)_2$ and $R' =$
 CH_2CH_3 , said structure with $X = CHO$ and $R'' = R' = CH_2CH_3$,
said structure with $X = CHO$, $R'' = CH_3$ and $R' = CH_2CH_3$,
said structure with $X = CHO$, $R'' = CH_2CH_3$ and $R' = CH_3$,
10 said structure with $X = CHO$, $R'' = CH(CH_3)_2$ and $R' = CH_3$
and said structure with $X = CHO$, $R'' = CH(CH_3)_2$ and $R' =$
 CH_2CH_3 .

3. The chemical compound of claim 1 where $X =$
15 H ; and $R'' = R' = CH_2CH_3$.

4. The chemical compound of claim 1 where $X =$
 H ; $R'' = CH_3$; and $R' = CH_2CH_3$.

20 5. The chemical compound of claim 1 where $X =$
 H ; $R'' = CH_2CH_3$; and $R' = CH_3$.

6. The chemical compound of claim 1 where $X =$
 H ; $R'' = CH(CH_3)_2$; and $R' = CH_3$.

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7. The chemical compound of claim 1 where $X =$

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H; $R'' = \text{CH}(\text{CH}_3)_2$; and $R' = \text{CH}_2\text{CH}_3$.

8. The chemical compound of claim 1 where $X = \text{CHO}$; and $R'' = R' = \text{CH}_2\text{CH}_3$.

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9. The chemical compound of claim 1 where $X = \text{CHO}$; $R'' = \text{CH}_3$; and $R' = \text{CH}_2\text{CH}_3$.

10. The chemical compound of claim 1 where $X = \text{CHO}$; $R'' = \text{CH}_2\text{CH}_3$; and $R' = \text{CH}_3$.

11. The chemical compound of claim 1 where $X = \text{CHO}$; $R'' = \text{CH}(\text{CH}_3)_2$; and $R' = \text{CH}_3$.

12. The chemical compound of claim 1 where $X = \text{CHO}$; $R'' = \text{CH}(\text{CH}_3)_2$; and $R' = \text{CH}_2\text{CH}_3$.

13. The chemical compound of claim 1 where $X = \text{CO}_2\text{CH}_2\phi$; and $R'' = R' = \text{CH}_2\text{CH}_3$.

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14. The chemical compound of claim 1 where $X = \text{CO}_2\text{CH}_2\phi$; $R'' = \text{CH}_3$; and $R' = \text{CH}_2\text{CH}_3$.

15. The chemical compound of claim 1 where $X = \text{CO}_2\text{CH}_2\phi$; $R'' = \text{CH}_2\text{CH}_3$; and $R' = \text{CH}_3$.

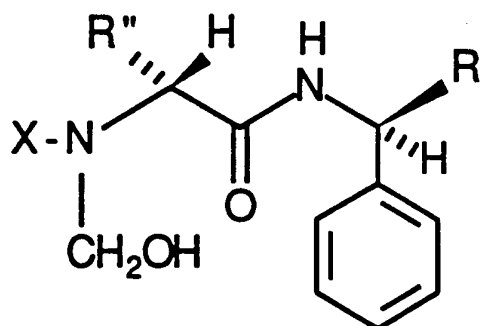
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16. The chemical compound of claim 1 where $X = \text{CO}_2\text{CH}_2\phi$; $R'' = \text{CH}(\text{CH}_3)_2$; and $R' = \text{CH}_3$.

17. The chemical compound of claim 1 where $X =$
 5 $\text{CO}_2\text{CH}_2\phi$; $R'' = \text{CH}(\text{CH}_3)_2$; and $R' = \text{CH}_2\text{CH}_3$.

18. A chemical compound useful for the
 preparation of artificial sweeteners comprising a D-amino
 acid-(S)- α -alkylbenzyl amide having the structure:

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where $X = \text{CO}_2\text{CH}_2\phi$, CHO or CO_2 -tert-butyl;

$R'' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 20 $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ ; and

$R' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ .

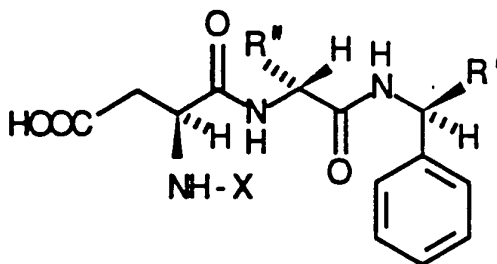
19. The chemical compound of claim 18 wherein
 25 said (S)- α -alkylbenzyl amide is selected from the group
 consisting of said structure with $X = \text{CO}_2\text{CH}_2\phi$ and $R'' = R'$

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- = CH_2CH_3 , said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' = \text{CH}_3$ and $\text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' = \text{CH}_2\text{CH}_3$ and $\text{R}' = \text{CH}_3$, said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' = \text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_3$, said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' =$
- 5 $\text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CHO}$ and $\text{R}'' = \text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CHO}$, $\text{R}'' = \text{CH}_3$ and $\text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CHO}$, $\text{R}'' = \text{CH}_2\text{CH}_3$ and $\text{R}' = \text{CH}_3$, said structure with $\text{X} = \text{CHO}$, $\text{R}'' = \text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_3$ and said structure with $\text{X} = \text{CHO}$, $\text{R}'' =$
- 10 $\text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_2\text{CH}_3$.

20. A chemical compound useful for the preparation of artificial sweeteners comprising a L-aspartyl-D-amino acid-(S)- α -alkylbenzyl amide having the
- 15 structure:

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- where $\text{X} = \text{CO}_2\text{CH}_2\phi$, CHO or CO_2 -tert-butyl;
- $\text{R}'' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
- 25 $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ ; and
- $\text{R}' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,

$\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ .

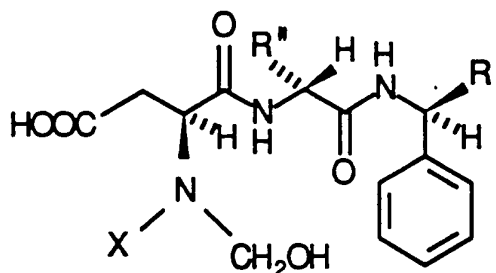
21. The chemical compound of claim 20 wherein said (S)- α -alkylbenzyl amide is selected from the group
- 5 consisting of said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$ and $\text{R}'' = \text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' = \text{CH}_3$ and $\text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' = \text{CH}_2\text{CH}_3$ and $\text{R}' = \text{CH}_3$, said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' = \text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_3$, said structure with $\text{X} = \text{CO}_2\text{CH}_2\phi$, $\text{R}'' =$
- 10 $\text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CHO}$ and $\text{R}'' = \text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CHO}$, $\text{R}'' = \text{CH}_3$ and $\text{R}' = \text{CH}_2\text{CH}_3$, said structure with $\text{X} = \text{CHO}$, $\text{R}'' = \text{CH}_2\text{CH}_3$ and $\text{R}' = \text{CH}_3$, said structure with $\text{X} = \text{CHO}$, $\text{R}'' = \text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_3$ and said structure with $\text{X} = \text{CHO}$, $\text{R}'' =$
- 15 $\text{CH}(\text{CH}_3)_2$ and $\text{R}' = \text{CH}_2\text{CH}_3$.

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22. A chemical compound useful for the preparation of artificial sweeteners comprising a L-aspartyl-D-amino acid (S)- α -alkylbenzyl amide having the structure:

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where X = CO₂CH₂ϕ, CHO or CO₂-tert-butyl;

R'' = CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃,
 15 CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃ or ϕ; and

R' = CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃,
 CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃ or ϕ.

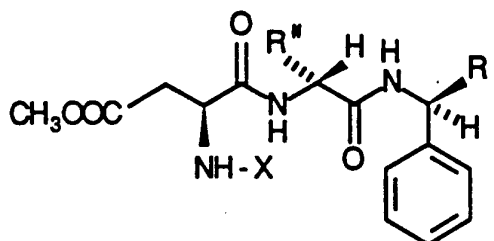
23. The chemical compound of claim 22 wherein
 20 said (S)- α -alkylbenzyl amide is selected from the group
 consisting of said structure with X = CO₂CH₂ϕ and R'' = R'
 = CH₂CH₃, said structure with X = CO₂CH₂ϕ, R'' = CH₃ and R'
 = CH₂CH₃, said structure with X = CO₂CH₂ϕ, R'' = CH₂CH₃ and
 R' = CH₃, said structure with X = CO₂CH₂ϕ, R'' = CH(CH₃)₂
 25 and R' = CH₃, said structure with X = CO₂CH₂ϕ, R'' =
 CH(CH₃)₂ and R' = CH₂CH₃, said structure with X = CHO and

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- $R'' = R' = \text{CH}_2\text{CH}_3$, said structure with $X = \text{CHO}$, $R'' = \text{CH}_3$
 and $R' = \text{CH}_2\text{CH}_3$, said structure with $X = \text{CHO}$, $R'' = \text{CH}_2\text{CH}_3$
 and $R' = \text{CH}_3$, said structure with $X = \text{CHO}$, $R'' = \text{CH}(\text{CH}_3)_2$
 and $R' = \text{CH}_3$ and said structure with $X = \text{CHO}$, $R'' =$
 5 $\text{CH}(\text{CH}_3)_2$ and $R' = \text{CH}_2\text{CH}_3$.

24. A chemical compound useful for the
 preparation of artificial sweeteners comprising a
 protected L-aspartyl-D-amino acid (S)- α -alkylbenzylamide
 10 having the structure:

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- where $X = \text{H}$, $\text{CO}_2\text{CH}_2\phi$, CHO or CO_2 -tert-butyl;
 $R'' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 20 $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ ; and
 $R' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$,
 $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ .

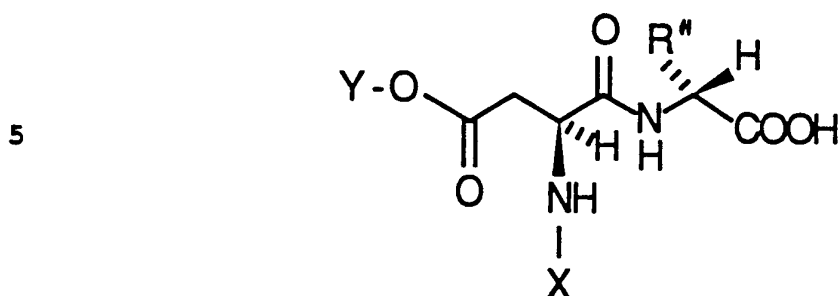
25. The chemical compound of claim 24 wherein
 25 said (S)- α -alkylbenzyl amide is selected from the group
 consisting of said structure with $X = \text{H}$, and $R'' = R' =$

- CH₂CH₃, said structure with X = H, R" = CH₃ and R' = CH₂CH₃, said structure with X = H, R" = CH₂CH₃ and R' = CH₃, said structure with X = H, R" = CH(CH₃)₂ and R' = CH₃, said structure with X = H, R" = CH(CH₃)₂ and R' = CH₂CH₃,
- 5 said structure with X = CO₂CH₂ϕ and R" = R' = CH₂CH₃, said structure with X = CO₂CH₂ϕ, R" = CH₃ and R' = CH₂CH₃, said structure with X = CO₂CH₂ϕ, R" = CH₂CH₃ and R' = CH₃, said structure with X = CO₂CH₂ϕ, R" = CH(CH₃)₂ and R' = CH₃, said structure with X = CO₂CH₂ϕ, R" = CH(CH₃)₂ and R' =
- 10 CH₂CH₃, said structure with X = CHO and R" = R' = CH₂CH₃, said structure with X = CHO, R" = CH₃ and R' = CH₂CH₃, said structure with X = CHO, R" = CH₂CH₃ and R' = CH₃, said structure with X = CHO, R" = CH(CH₃)₂ and R' = CH₃ and said structure with X = CHO, R" = CH(CH₃)₂ and R' =
- 15 CH₂CH₃.

26. A chemical compound useful for the preparation of artificial sweeteners comprising an L-

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aspartyl-D-amino acid having the structure:



10 where X = CO₂CH₂ϕ, CHO or CO₂-tert-butyl;

R'' = CH₃, CH₂CH₃, CH(CH₃)₂, CH₂CH₂CH₃, CH₂CH₂CH₂CH₃,
CH₂CH(CH₃)₂, CH(CH₃)CH₂CH₃ or ϕ;

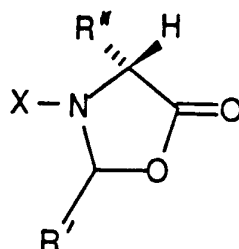
Y = CH₃, CH₂ϕ or tert-butyl; and X is not equal to
CO₂CH₂ϕ when Y = CH₂ϕ.

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27. The chemical compound of claim 26 wherein
said L-aspartyl-D-amino acid is selected from the group
consisting of said structure with X = CHO and R'' = CH₂CH₃
and Y = CH₃, said structure with X = CHO, R'' = CH₃ and Y =
20 CH₃, and said structure with X = CHO, R'' = CH(CH₃)₂ and Y =
CH₃.

28. A chemical compound useful for the
preparation of artificial sweeteners comprising a D-amino
25 acid oxazolidinone having the structure:

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where $X = \text{CO}_2\text{CH}_2\phi$, CHO or $\text{CO}_2\text{-tert-butyl}$;

$R'' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$ or ϕ ; and

10 $R' = \text{H}$, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, $\text{C}(\text{CH}_3)_3$, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, ϕ or CCl_3 .

29. The chemical compound of claim 28

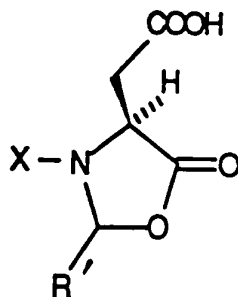
where $X = \text{CO}_2\text{CH}_2\phi$;

15 $R'' = \text{CH}_3$, CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$; and

$R' = \text{H}$, $\text{C}(\text{CH}_3)_3$, ϕ or CCl_3 .

30. A chemical compound useful for the preparation of artificial sweeteners comprising an L-

20 aspartic acid oxazolidinone having the structure:



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where $X = \text{CO}_2\text{CH}_2\phi$, CHO or CO_2 -tert-butyl;

$R' = \text{H}, \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}(\text{CH}_3)_2, \text{C}(\text{CH}_3)_3, \text{CH}_2\text{CH}_2\text{CH}_3, \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3, \text{CH}_2\text{CH}(\text{CH}_3)_2, \text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3, \phi$ or CCl_3 .

5 31. The chemical compound of claim 30

where $X = \text{CO}_2\text{CH}_2\phi$ and

$R' = \text{H}, \text{C}(\text{CH}_3)_3, \phi$ or CCl_3 .

32. The chemical compound of claim 30

10 where $X = \text{CO}_2\text{CH}_2\phi$ and

$R' = \text{C}(\text{CH}_3)_3, \phi$ or CCl_3 .

33. A chemical compound useful for the preparation of artificial sweeteners comprising a

15 compound selected from the group consisting of N-carbobenzyloxy-N-hydroxymethyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide, N-carbobenzyloxy-D- α -aminobutyric acid-(S)- α -ethylbenzylamide, D- α -aminobutyric acid-(S)- α -ethylbenzyl amide, β -methyl-N-formyl-L-aspartyl-D- α -
20 aminobutyric acid-(S)- α -ethylbenzyl amide, β -Methyl-N-carbobenzyloxy-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide, β -Methyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide, (D)-3-carbobenzyloxy-4-ethyl-5-oxazolidinone,
25 N-carbobenzyloxy-N-hydroxymethyl-L-aspartyl-D- α -aminobutyric acid-(S)- α -ethylbenzyl amide,

N-carbobenzyloxy-L-aspartyl-D- α -aminobutyric
acid-(S)- α -ethylbenzyl amide, L-aspartyl-D- α -aminobutyric
acid-(S)- α -ethylbenzylamide, β -Methyl-N-formyl-L-
aspartyl-D- α -aminobutyric acid.

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34. A salt of the chemical compound of claims
1-17 where X = H, wherein the salt is selected from the
group consisting of a sulfate, a malate, a hydrochloride,
a carbonate, a phosphate, a citrate, an acetate, a
10 tartrate and a benzoate, or other salts as appropriate.

35. A salt of the chemical compound of claim
24 and 25 where X = H, wherein the salt is selected from
the group consisting of a sulfate, a malate, a
15 hydrochloride, a carbonate, a phosphate, a citrate, an
acetate, a tartrate and a benzoate and other salts as
appropriate.