COMMONWEALTH OF AUSTRALIA

Patents Act 1952

Form 1
Regulation 9

APPLICATION FOR A STANDARD PATENT OR A STANDARD PATENT OF ADDITION

60706

LODGED AT SUB-OFFICE
11 AUG 1987
Melbourne

Insert full name(s) of applicant(s)

(71) I/We GENERAL FOODS CORPORATION

Insert address(es) of applicant(s)

of 250 North Street, White Plains, New York, United States of America

Insert title of invention

(54) hereby apply for the grant of a ☑ standard patent ☐ patent of addition for an invention entitled

L-AMINODICARBOXYLIC ACID ESTERS

(tick appropriate box)

which is described in the accompanying ☐ provisional ☑ complete specification.

PATENT OFFICE
325216
Collector of Public Moneys

Insert name of actual inventor

(72) The actual inventor(s) of the said invention ~~is~~/are PAUL ROBERT ZANNO, GLENN MICHAEL ROY, RONALD EDWARD BARNETT

Insert address for service of notices in Australia

(74) My/our address for service is SANDERCOCK, SMITH & BEADLE, 207 Riversdale Road, (P.O. Box 410) Hawthorn, Victoria, 3122 Attorney Code SA

(ONLY TO BE USED IN THE CASE OF A CONVENTION APPLICATION)

Details of basic application(s) –

NUMBER	COUNTRY	DATE OF APPLICATION	ISO Code
898063	United States of America	19 August 1986	US

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 12-12-90

Insert day, month and year form signed

Dated this 11th day of August, 1987

Signature of applicant or Australian attorney

GENERAL FOODS CORPORATION
Charles Sandercock
(Signature)
SANDERCOCK, SMITH & BEADLE

TO

THE COMMISSIONER OF PATENTS

This form must be accompanied by either a provisional specification (Form 9 and true copy) or by a complete specification (Form 10 and true copy).

FORM 7 & 8

PATENTS ACT 1952

AUSTRALIA

PATENT DECLARATION FORM (CONVENTION OR NON-CONVENTION)

5822ZY

DECLARATION IN SUPPORT OF APPLICATION FOR A PATENT

Insert name of applicant.

In support of the application made by GENERAL FOODS CORPORATION

Insert title of invention.

for a patent for an invention entitled: L-AMINODICARBOXYLIC ACID ESTERS

Insert full name(s) and address(es) of person(s) making declaration. If applicant a company, person must be authorised to make declaration.

I, Thomas E. McIntyre of

~~I/We~~ GENERAL FOODS CORPORATION, a corporation organized and existing under the laws of the State of Delaware having a place of business at 250 North Street, White Plains, New York, United States of America

do solemnly and sincerely declare as follows:

* 1. (a) ~~I am/We are the applicant(s) for the patent.~~

* OR (b) I am authorized by the abovementioned applicant to make this declaration on its behalf.

* 2. (a) ~~I am/We are the actual inventor(s) of the invention.~~

* OR (b) Paul Robert Zanno, Glenn Michael Roy and Ronald Edward Barnett, all United States Citizens, residing at 2 April Lane, Nanuet; 16 Trimble Street, Garnerville; and 73 E. Maple Avenue, Suffern; respectively New York, United States of America

* Delete alternatives which do not apply

Insert name(s) and address(es) of actual inventor(s).

x is/are the actual inventor(s) of the invention and the facts upon which the applicant~~(s)~~ is/~~are~~ entitled to make the application are as follows:—

Applicant is the Assignee of the actual inventor(s)

3. The basic application~~(s)~~ as defined by Section 141 of the Act was/~~were~~ made in the following country or countries on the following date~~(s)~~ by the following applicant(s)

in United States of on 19
~~by~~ America
~~by~~ BY: Paul Robert Zanno on 19
by Glenn Michael Roy
by Ronald Edward Barnett on August 19, 1986 19
by
in on 19
by

4. The basic application~~(s)~~ referred to in paragraph 3 of this Declaration was/~~were~~ the first application~~(s)~~ made in a Convention country in respect of the invention the subject of the application.

Place and date of Signature.

Declared at Rye Brook, New York this 25th day of June 19 87

GENERAL FOODS CORPORATION

By : [signature]

CORPORATE SEAL

NO ATTESTATION OR SEAL

Name Typewritten : Thomas E. McIntyre

Title : Assistant Secretary

To: The Commissioner of Patents, Australia

(12) PATENT ABRIDGMENT (11) Document No. AU-B-76829/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 607706

(54) Title
BETA(+) FENCHYL ESTERS OF ALPHA-L-ASPARTYL-D-ALAININE AND ALPHA-L-ASPARTYLMETHYL+ALANINE

International Patent Classification(s)
(51)[4] C07K 005/06 A23L 001/236

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898063 19.08.86 US UNITED STATES OF AMERICA

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GENERAL FOODS CORPORATION

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PAUL ROBERT ZANNO; GLENN MICHAEL ROY; RONALD EDWARD BARNETT

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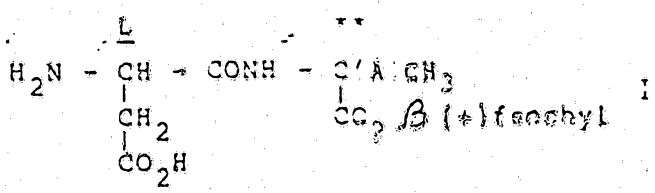
SMITH SHELSTON BEADLE, PO Box 410, HAWTHORN VIC 3122

(56) Prior Art Documents
EP 199257

(57) Claim

1. A compound represented by the formula:



I

and food acceptable salts thereof, wherein

A is hydrogen or methyl,

with the proviso that when the double asterisked carbon is an asymmetric or chiral center, the configuration around said carbon is in the D form.

2. The compound according to Claim 1 which is α-L-Aspartyl-D-alanine [β (+)fenchyl]ester.

.../2

3. The compound according to Claim 1 which α-L-Aspartyl-2-methylalanine [β(+)fenchyl]ester.

5. An edible composition according to Claim 4 which further comprises a food acceptable carrier.

11. A method of sweetening an edible composition which comprises adding to the edible composition a sweetening amount of a compound according to Claim 1.

12. A process for the preparation of a compound of Formula I herein which comprises reacting a carboxylic acid or derivatives thereof of Formula II herein with an amine of Formula III herein under amide forming conditions and removing the protecting groups when present and optionally forming pharmaceutically acceptable salts of said compounds.

607706

COMMONWEALTH OF AUSTRALIA

Form 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Class Int. Class

Application Number:
Lodged:

Complete Specification—Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

TO BE COMPLETED BY APPLICANT

Name of Applicant: GENERAL FOODS CORPORATION

Address of Applicant: 250 North Street, White Plains, New York, United States of America

Actual Inventor: PAUL ROBERT ZANNO
GLENN MICHAEL ROY
RONALD EDWARD BARNETT

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207 Riversdale Road, (P.O. Box 410)
Hawthorn, Victoria, 3122

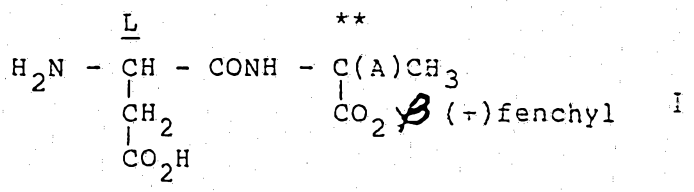
Complete Specification for the invention entitled:

L-AMINOCARBOXYLIC ACID ESTERS

The following statement is a full description of this invention, including the best method of performing it known to me:—

This invention relates to a novel group of compounds and more particularly to a novel group of compounds particularly well suited as sweeteners in edible foodstuffs.

This invention provides new sweetening compounds represented by the formula:



I

and food acceptable salts thereof, wherein

A is hydrogen or methyl,

with the proviso that when the double asterisked carbon is an asymmetric or chiral center, the configuration around said carbon is in the D form. The specific compounds of this invention are β (+) fenchyl esters of α-L-aspartyl-D-alanine and α-L-aspartylmethyl-alanine.

These novel compounds are effective sweetness agents when used alone or in combination with other sweeteners in an ingesta, e.g., foodstuffs or pharmaceuticals. For example, other natural and/or artificial sweeteners which may be used with the novel compounds of the present invention include sucrose, fructose, corn syrup solids, dextrose, xylitol, sorbitol, mannitol, acetosulfam, thaumatin, invert sugar, saccharin, thiophene saccharin, meta-aminobenzoic acid,

meta-hydroxybenzoic acid, cyclamate, chlorosucrose, dihydrochalcone, hydrogenated glucose syrups, aspartame (L-aspartyl-L-phenylalanine methyl ester) and other dipeptides, glycyrrhizin and stevioside and the like. These sweeteners, when employed with the sweetness agents of the present invention, it is believed could produce synergistic sweetness responses.

Furthermore, when the sweetness agents of the present invention are added to ingesta, the sweetness agents may be added alone or with nontoxic carriers such as the abovementioned sweeteners or other food ingredients such as acidulants, natural and artificial gums, bulking agents such as polycarbohydrates, dextrins, and other food approved carbohydrates and derivatives. Typical foodstuffs, and pharmaceutical preparations, in which the sweetness agents of the present invention may be used are, for example, beverages including soft drinks, carbonated beverages, ready to mix beverages and the like, infused foods (e.g. vegetables or fruits), sauces, condiments, salad dressings, juices, syrups, desserts, including puddings, gelatin and frozen desserts, like ice creams, sherbets, icings and flavored frozen desserts on sticks, confections, chewing gum, cereals, baked goods, intermediate moisture foods (e.g. dog food), toothpaste, mouthwash and the like.

In order to achieve the effects of the present invention, the compounds described herein are generally added to the food product at a level which is effective to perceive sweetness in the foodstuff and suitably is in an amount in the range of from about 0.0005 to 2% by weight based on the consumed product. Greater amounts are operable but not practical.

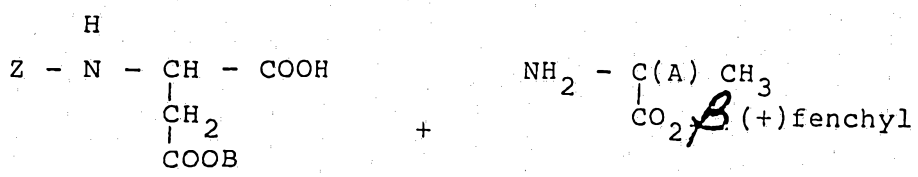
Preferred amounts are in the range of from about 0.001 to about 1% of the foodstuff. Generally, the sweetening effect provided by the present compounds are experienced over a wide pH range, e.g., 2 to 10, preferably 3 to 7, and in buffered and unbuffered formulations.

More preferably, if α- L-aspartyl-D-alaine [β(+)fenchyl] ester is used as a sweetener, the amount of sweetener can range from about 0.0005 to 0.005% by weight of the foodstuff. When α-L-aspartyl-2-methylalanine [β(+)fenchyl] ester is used as a sweetener, the amounts used can fall in a broader range described above but it is highly preferred to be used in amounts from about 0.0005 to about 0.01% by weight of the foodstuff.

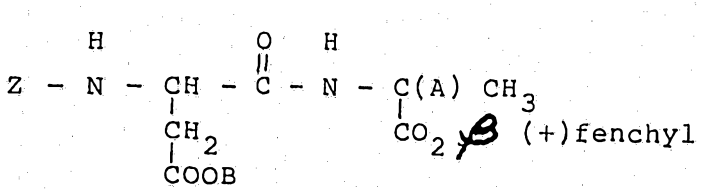
It is desired that when the sweetness agents of this invention are employed alone or in combination with another sweetener, the sweetener or combination of sweeteners provide a sucrose equivalent in the range of from about 2 weight percent to about 40 weight percent and more preferably from about 3 weight percent to about 15 weight percent in the foodstuff or pharmaceutical.

A taste procedure for determination of sweetness merely involves the determination of sucrose equivalency. Sucrose equivalence for sweeteners are readily determined. The amount of a sweetener that is equivalent to a given weight percent sucrose can be determined by having a panel of tasters taste solutions of a sweetener at known concentrations and match its sweetness to standard solutions of sucrose.

In order to prepare compounds of the present invention, several reaction schemes may be employed. In one reaction scheme, compounds of general formula II (protected α-aminodicarboxylic acid) and III (amino-ester compound) are condensed to form compounds of general formula IV. Subsequent removal of protecting groups B and Z from compounds of general formula IV give the desired compounds of general formula I:



II + III



IV

In these, group Z is an amino protecting group, B is a carboxyl protecting group, and A has the same meaning as previously described. A variety of protecting groups known in the art may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis" by T.W. Green, John Wiley and Sons, 1981. Among the preferred groups that may be employed are benzyloxycarbonyl for A and benzyl for B.

Coupling of compound with general formula III to compounds having general formula II employs established techniques in peptide chemistry. One such technique uses dicyclohexylcarbodiimide (DCC) as the coupling agent. The DCC method may be employed with or without additives such as 4-dimethylaminopyridine or copper (II). The DCC coupling reaction generally proceeds at room temperature, however, it may be carried out from about -20° to 50°C. in a variety of solvents inert to the reactants. Thus suitable solvents include, but are not limited to, N,N-dimethyl-formamide, methylene chloride, toluene and the like. Preferably the reaction is carried out under an inert atmosphere such as argon or nitrogen. Coupling usually is complete within 2 hours but may take as long as 24 hours depending on reactants.

Various other methods can be employed to prepare the desired compounds. The following illustrates such methods.

For example, U.S. Patents 3,786,039; 3,833,553; 3,879,372 and 3,933,781 disclose the reaction of N-protected aspartic anhydrides with amino acids and amino acid derivatives to yield the desired products. These N-protected aspartic anhydrides can be reacted with compounds of formula III by methods disclosed in the above patents. As described in U.S. Patent 3,786,039 compounds of formula III can be reacted directly in inert organic solvents with L-aspartic anhydride having its amino group protected by a formyl, carbobenzyloxy, or p-methoxycarbobenzyloxy group which is subsequently removed after coupling to give compounds of general formula I. The N-acyl-L-aspartic anhydrides are prepared by reacting the corresponding acids with acetic anhydride in amounts of 1.0 -1.2 moles per mole of the N-acyl-L-aspartic acid at 0° to 60°C. in an inert solvent. The N-acyl-aspartic anhydrides are reacted with preferably 1 to 2 moles of compounds of formula III in an organic solvent capable of dissolving both and inert to the same. Suitable solvents are, but not limited to, ethyl acetate, methyl propionate, tetrahydrofuran, dioxane, ethyl ether, N,N-dimethylformamide and benzene. The reaction proceeds smoothly at 0° to 30°C. The N-acyl group is removed after coupling by catalytic hydrogenation with palladium on carbon with HBr or HCl in a conventional manner. U.S. Patent No. 3,879,372 discloses that this coupling method can also be performed in an aqueous solvent at a temperature of -10° to 50°C. and at a pH of 4-12.

Another method for the synthesis of the desired compounds is the reaction of compounds of formula III with suitable aspartic acid derivatives in which protecting groups have been attached to the amino and beta-carboxy groups and the alpha carboxy group has been converted to a reactive ester function. As disclosed in U.S. Patent 3,475,403 these coupled products may be deprotected as described to yield the desired compounds of formula I.

An alternative scheme to the desired coupled compounds involves reaction of compounds of formula III with L-aspartic acid N-thiocarboxyanhydride by the method of Vinick and Jung, Tet. Lett. 23, 1315-18 (1982). An additional coupling method is described by T. Miyazawa, Tet. Lett., 25, 771 (1984).

Compounds of general formula III are synthesized using art recognized techniques. For example compounds of formula III can be synthesized by standard esterification methods known in the art by reacting the free acid or acid functional equivalents, such as esters or anhydrides, with the corresponding alcohols under ester-forming conditions, as for example in the presence of mineral acids, such as hydrochloric or sulfuric acids or organic acids, such as p-toluene-sulfonic acids. Reaction temperatures are in the range of -78° to reflux. The reaction is carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to methylene chloride, diethyl ether, tetrahydrofuran, dimethylsulfoxide, N,N-dimethylformamide, and the like.

With regard to the removal of protecting groups from compounds of formula IV and N-protected precursors of formula III, a number of deprotecting techniques are known in the art and can be utilized to advantage depending on the nature of the protecting groups. Among such techniques is catalytic hydrogenation utilizing palladium on carbon or transfer hydrogenation with 1,4-cyclohexadiene. Generally, the reaction is carried out at room temperature but may be conducted from 5 to 65°C. Usually the reaction is carried out in the presence of a suitable solvent which may include, but are not limited to water, methanol, ethanol, dioxane, tetrahydrofuran, acetic acid, t-butyl alcohol, isopropanol or mixtures thereof. The reaction is usually run at a positive hydrogen pressure of 50 psi but can be conducted over the range of 20 to 250 psi. Reactions are generally quantitative taking 1 to 24 hours for completion.

In any of the previous synthetic methods the desired products are preferably recovered from reaction mixtures by crystallization. Alternatively, normal or reverse-phase chromatography may be utilized as well as liquid/liquid extraction or other means.

The desired compounds of formula I are usually obtained in the free acid form; they may also be recovered as their physiologically acceptable salts, i.e., the corresponding amino salts such as hydrochloride, sulfate, hydrosulfate, nitrate, hydrobromide, hydroiodide, phosphate or hydrophosphate; or the alkali metal salts such as the sodium, potassium,

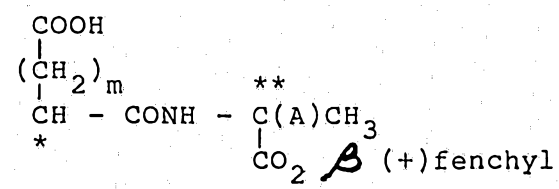
lithium, or the alkaline earth metal salts such as calcium or magnesium, as well as aluminum, zinc and like salts.

Conversion of the free peptide derivatives of formula I into their physiologically acceptable salts is carried out by conventional means, as for example, bringing the compounds of formula I into contact with a mineral acid, an alkali metal hydroxide, an alkali metal oxide or carbonate or an alkaline earth metal hydroxide, oxide, carbonate or other complexed form.

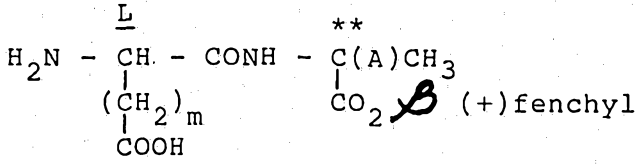
These physiologically acceptable salts can also be utilized as sweetness agents usually having increased solubility and stability over their free forms.

It is known to those skilled in the art that the compounds of the present invention having asymmetric carbon atoms may exist in racemic or optically active forms.

The compounds of the present invention have one asymmetric site, which is designated by an asterisk (*) in the formula below, and one pseudoasymmetric site which is designated by a double asterisk (**).



All of the stereochemical configurations are encompassed within the above formula. However, the present invention is directed to only compounds of the formula:



in which the dicarboxylic acid group is in the L-configuration as depicted in formula I and, when A is H, the pseudo-asymmetric center is in the D-form.

In the production of compounds of formula I, the L, L diastereomer, though not sweet itself, may be admixed with the L, D stereoisomer. The admixture of the L, L and L, D stereoisomers exhibits sweetness, but said mixture is not as sweet as the L, D stereoisomer in its pure form.

The following examples further illustrate the invention. In the following examples, the sensory evaluation was obtained by a panel of experts using known weight percent aqueous solutions of the exemplified compounds which were matched to sucrose standard solutions.

EXAMPLE 1

α - L-Aspartyl-2-methylalanine [β(+)Fenchyl] ester

N-CBZ- protected amino isobutyric acid (Chemical Dynamics, Inc.) was dissolved in 1,2-dichloroethane (50 mL) at 0°C under argon. A solution of N,N-dimethylaminopyridine (0.5 equiv.) and β(+) fenchyl alcohol (1 equiv.) in 1,2-dichloroethane (10 mL) was added. Lastly, dicyclohexylcarbodiimide (1.1 equiv.) was added as a solid. After five days of stirring at room temperature the urea was removed by filtration and the filtrate was diluted with petroleum ether (50 mL). The solution was clarified again by filtration and the filtrate was hi-vacuum rotary evaporated to a paste. Column chromatography on silica gel with 15:1 petroleum ether/ethyl acetate gave the pure product in 75-79% yield as a white crystalline solid. NMR ($CDCl_3$): δ0.90 (s,3H), 1.05 (s,3H) 1.10(s,3H), 1.20-1.80(m,7H), 1.60(s,6H), 4.20(s,1H), 5.10(s,2H), 5.55(s,1H), 7.40(s,5H). $[\alpha]_D^{25} = -11.65°$ (MeOH) mp. 83-85°C.

The ester from above was deprotected in the usual manner by hydrogenation with palladium on carbon (10%) in methanol to give a quantitative yield of the free-amino ester.

The amine was immediately dissolved in DMF and coupled to an aspartic acid precursor by the Copper (II) chloride procedure to give a 90% yield of N-CBZα-L-aspartic acid β-benzylesterα2-methyl-alanine[β(+)Fenchyl]ester. NMR ($CDCl_3$):δ0.90 (s,3H), 1.05 (s,3H), 1.10 (s,3H), 1.20-1.80 (m, 7H), 1.6 (d, 6H) 2.70-3.15 (m,2H),4.1-4.2 (m, 1H), 4.20 (s, 1H), 4.60 (s, 1H), 5.10 (s,4H), 5.60 (d, 1H), 5.90 (d, 1H), 5.90 (d, 1H), 7.40 (s, 10H).
The product was deprotected by hydrogenation and purified by Rp C_{18} column chromatography with 85:15 methanol: water eluant, $[\alpha]_{D=}^{25}$- 3.30°(MeOH) mp. 121 - 3°C.

Sweetness determination with this compound gave the following results:

Concentration	Sucrose Equivalents	Sweetness relative to Sucrose (X Sucrose)
0.00750	8.5%	1133
0.00375	6.0%	1600
0.00185	5.7%	3100
0.00692	3.5%	3800
0.0025	6.0%	2400
0.0025	4.3%	1733
0.0025	4.25%	1700
0.005	7.37%	1475
0.005	7.0%	1400
0.005	6.0%	1200
0.01	9.25%	925
0.01	9.0%	900

EXAMPLE 2

α-L-Aspartyl- D - alanine [β (+) Fenchyl] ester

A. exo-β - (+) - Fenchol

To a refluxing suspension of 72.65g aluminum isopropoxide in 300 ml of freshly distilled isopropyl alcohol, was added dropwise, 27.1g R-(-)- fenchone in 50 ml isopropanol. The reaction was halted after six days when it was determined by gas chromatography (Carbowax 20 M) that more than 50% of the ketone was reduced. It was also determined by capillary chromatography (Supelcowax 10) that the exo/endo ratio for the fenchol was 3/1. Upon cooling, the mixture was filtered and washed thoroughly with dichloromethane. The precipitate was dissolved in 5% HCl (100 ml) and extracted with dichloromethane (50 ml). The combined dichloromethane solutions were washed with 5% HCl (50 ml), saturated $NaHCO_3$ (50 ml) and water (50 ml) and dried over Mg SO_4. Filtration and removal of the solvent afforded 23.44 g of an oil that was 40% unreacted fenchone and 60% α and β fenchol isomers.

A mixture of 12 g (0.78mol) β and α - fenchols, 11.9 ml (1.1 eq) triethylamine and 15.9 g p-nitrobenzoyl chloride (1.1 g) in 500 mls dry dichloromethane was refluxed for 24 hours. The mixture of β/α esters was separated by silica gel flash chromatography using hexane: ethyl acetate (40:1). 6.0 g of the exo-fenchyl para-nitrobenzate was isolated. ($[\alpha]^{25}$= - 17.1° (in benzene). 3 g of fenchol (9/1; β/α^{D}) was obtained upon basic hydrolysis of the nitrobenzate ester (refluxing excess NaOH in methanol). β - (+)-fenchol; $[\alpha]_D^{25}$= + 23.4° (neat),

NMR: δ 0.95-1.8 (16 H, m, CH_2, CH_3); 3.0 ppm (1H, s, CH-O).

B. N-Cbz-D-alanine, β -(+)-fenchyl ester

To a stirred solution of 1.3 g β-(+)-fenchol in 20 ml dry dichloromethane was added 1.9 g (.0084 mol) N-Cbz D-alanine, and the solution was cooled to 0°C. Then, 0.113 g p-dimethylaminopyridine and 1.91 g dicyclohexylcarbodiimide were added. After 24 hours, the reaction was stopped and filtered. The solvent was evaporated and the oily residue was dissolved in diethyl ether, washed with 5% HCl (25 ml), saturated $NaHCO_3$ (25 ml), water (25 ml) and dried over $MgSO_4$. After filtration and solvent evaporation, the product was purified by silica gel chromatography to yield 1.86 g N-Cbz-D-alanine, β - (+)-fenchyl ester; $[\alpha]^{25}_D$ = +3.86°. NMR: δ 0.8-1.8 ppm (19H, m, CH_2, CH_3); 4.2 ppm (1 H, s, CH-O); 4.4 ppm (1H, m, CH-C(=O)-O); 5.1 ppm (2 H, s, CH_2-Ph) 5.4 ppm (1 H, d, NH); 7.4 ppm (5H, s, Ph).

C. D-alanine, β -fenchyl ester

The N-Cbz-D-alanine, β-(+)-fenchyl ester, (1.86 g) was dissolved in 50 ml methanol and hydrogenated over 0.1 g 5% Pd/C in a Paar shaker. After 2 hours the reaction was over; it was filtered through Celite, washed with methanol, concentrated and the crystallized residue was dissolved in dichloromethane.

D. N-Cbz-β-benzyl-L-aspartyl-D-alanine, β-(+)fenchyl ester

To the dichloromethane solution containing the D-alanine ester (0.00355 mol) was added an equimolar amount of B-benzyl-N-Cbz-L-aspartic acid (1.27 g) and 0.526 g $Cu(II)Cl_2$. Upon solution of the $CuCl_2$, DCC (0.81 g) was added. After 24 hours, the reaction was complete, the urea was filtered and the solvent was evaporated. The yellow oil was dissolved in diethyl ether (25 ml) and washed with 5% HCl (25 ml), saturated $NaHCO_3$ (25 ml), and H_2O (25 ml). The ether layer was dried over $MgSO_4$ and evaporated to yield 0.95 g of product. NMR: δ 0.85-1.80 (19 H, m, CH_2, CH_3), 4.2 ppm (1 H, s, CH-O); 4.5-4.7 ppm (2 H, m, N-CH-C); 5.1 ppm (4 H, s, OCH_2- Ph); 5.95 ppm (1 H, d, NH); 7.05 ppm (1 H, d, NH); 7.4 ppm (10 H, s, Ph).

E. α-L-aspartyl-D-alanine, β-(+)-fenchyl ester

0.95 g protected dipeptide was dissolved in 50 ml methanol to which 0.1 g 10% Pd/C was added. This was hydrogenated in Paar shaker for 2 hours. The solution was filtered and evaporated to dryness to yield 0.194 g solid; $[\alpha]_D^{25} = -0.867^\circ$.

The product was purified on reverse phase HPLC (85% methanol/water) to yield 75 mg L-aspartyl-D-alanine, β-(+)Fenchyl ester. NMR: δ 0.8-1.8 (19 H, m, CH_2, CH_3); 2.3-2.4 ppm (2 H, m, CH_2 - C); 4.2 ppm (1 H, s, OCH); 4.5 ppm (2H, m, N-CH); 8.8 ppm (1H, s, NH-C).

Sweetness determination with this compound gave the following results:

Concentration	Sucrose Equivalence	Sweetness relative to Sucrose (X Sucrose)
0.00012	0.6%	5000
0.00024	1.42%	5900
0.00047	2.28%	4900
0.00092	4.7%	5100
0.00185	6.5%	3500
0.0025	6.0%	2400
0.00375	8.6%	2300
0.005	9.3%	1860
0.005	10.0%	2000
0.0075	9.0%	1200
0.01	11.0%	1100

The compounds of this invention possess greater sweetness and higher stability in comparison to corresponding esters of the prior art.

EXAMPLE 3

α-L-Aspartyl-2-methylalanine[β(+)fenchyl]ester (Example 1), α-L-Aspartyl-D-alanine-[β(+)fenchyl]ester (Example 2) and aspartame (L-aspartyl-L-phenylalanine methyl ester) were studied for stability at pH 3, 5 and 7 in buffer solutions maintained at 50°C, 75°C. or 100°C., the following results were obtained:

Half Life Hours

at 100°C.

	pH3	pH5	pH7
Example 1	8.4	33	67
Example 2	3.9	14	10
Aspartame	5.3	5.3	$<<1$

Half Life, Days

at 75°C.

	pH3	pH5
Example 1	3.0	15.0
Example 2	1.3	5.1
Aspartame	0.9	1.1

Half Life, Days

at 50°C.

	pH3	pH5
Example 1	64	150
Example 2	22	131

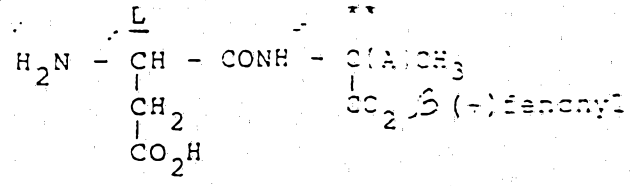
The sweeteners of Example 1 and Example 2 have outstanding stability in buffered solutions at pH's 3, 5, and 7. Example 1 and Example 2 compounds have better stability in the buffered solutions studied than does aspartame, except at pH3 @10°C. where aspartame

has an intermediate stability between Example 1 and Example 2 compounds. The compound of Example 1 is more stable than the compound of Example 2. The half life of the Example 1 compound is 2 to 3 times longer in buffered solutions at 75°C. and 100°C. at pH 3 and pH 5 than that of Example 2. The half life of the Example 1 compound in a buffered solution at 50°C. and a pH 5 is about 1.1 to about 2.9 times longer than that of Example 2.

The claims form part of the disclosure of this specification.

The claims defining the invention are as follows:

1. A compound represented by the formula:



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and food acceptable salts thereof, wherein

A is hydrogen or methyl,

with the proviso that when the double asterisked carbon is an asymmetric or chiral center, the configuration around said carbon is in the D form.

2. The compound according to Claim 1 which is α-L-Aspartyl-D-alanine [β(+)fenchyl]ester.

3. The compound according to Claim 1 which α-L-Aspartyl-2-methylalanine [β(+)fenchyl]ester.

4. An edible composition comprising a sweetening effective amount of a compound according to any of Claims 1-3.

5. An edible composition according to Claim 4 which further comprises a food acceptable carrier.

6. An edible composition according to Claim 4 which is a beverage.

7. An edible composition according to Claim 4 which is a gelatin dessert.

8. An edible composition according to Claim 4 which is a milk-based composition.

9. An edible composition according to any of Claims 4-8 which further comprises an additional sweetener.

10. An edible composition according to Claim 9 wherein the additional sweetener is sucrose, fructose, corn syrup solids, dextrose, xylitol, sorbitol, mannitol, acetosulfam, thaumatin, invert sugar, saccharin, thiophene-saccharin, meta-aminobenzoic acid, meta-hydroxybenzoic acid, cyclamate, chlorosucrose, dihydrochalcone, hydrogenated glucose syrup, aspartame or other dipeptides, glycyrrhizin or stevioside or mixtures thereof.

11. A method of sweetening an edible composition which comprises adding to the edible composition a sweetening amount of a compound according to Claim 1.

12. A process for the preparation of a compound of Formula I herein which comprises reacting a carboxylic acid or derivatives thereof of Formula II herein with an amine of Formula III herein under amide forming conditions and removing the protecting groups when present and optionally forming pharmaceutically acceptable salts of said compounds.

13. The process of Claim 12 wherein the compound formed is:

α-L-Aspartyl-D-alanine[β (+)fenchyl]ester.

14. The process of Claim 12 wherein the compound formed is:

α-L-Aspartyl-2-methylalanine[β (+)fenchyl]ester.

15. An edible composition comprising a sweetening effective amount of a compound produced in accordance with the process of any of Claims 12-14.

16. A compound in accordance with claim 1, an edible composition containing same, a method of sweetening using same and a process for preparing same substantially as hereinbefore described with reference to any one of the Examples.

~~17. The articles, things, parts, elements, steps,~~ features, methods, processes, compounds ~~and~~ compositions referred to or indicated in ~~the~~ specification and/or claims of the ~~application~~ individually or collectively, and any and ~~all combinations of any two or more of such.~~

DATED THIS 11th August, 1987
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