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(54) Title: ASPARTYL DIPEPTIDE ESTER DERIVATIVES AND SWEETENERS

(57) Abrégé/Abstract:
Novel aspartyl dipeptide ester derivatives (including salts thereof) having an excellent sweetening effect and usable as sweeteners such as N-[N-[3-(3-methyl-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1- methyl ester and N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1- methyl ester, and excellent sweeteners,etc. containing these novel derivatives are provided. A low-calory sweetener having especially an excellent sweetening potency can be provided in comparison with conventional ones.

ABSTRACT

Novel aspartyl dipeptide ester derivatives (including salts thereof) having an excellent sweetening effect and usable as sweeteners such as N-[N-[3-(3-methyl-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester and N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester, and excellent sweeteners,etc. containing these novel derivatives are provided.

A low-calory sweetener having especially an excellent sweetening potency can be provided in comparison with conventional ones.

ASPARTYL DIPEPTIDE ESTER DERIVATIVES AND SWEETENERS

TECHNICAL FIELD

The present invention relates to novel aspartyl dipeptide ester derivatives, and a sweetener and products such as foods having a sweetness, which contain the same as an active ingredient.

BACKGROUND ART

In recent years, as eating habits have been improved to a high level, fatness caused by excessive intake of sugar and diseases accompanied by fatness have been at issue. Accordingly, the development of a low-calory sweetener that replaces sugar has been in demand. As a sweetener that has been widely used at present, there is aspartame which is excellent in a safety and taste properties. However, this is somewhat problematic in the stability. In WO 94/11391, it is stated that derivatives in which an alkyl group is introduced in an amino group of aspartic acid constituting aspartame markedly improves sweetening potency and the stability is slightly improved. It is reported that the best compound described in this document is N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester having a 3,3-dimethylbutyl group as an alkyl group and the sweetening potency thereof is 10,000 times. Aspartame derivatives having introduced therein 20 types of substituents other than the 3,3-dimethylbutyl group are indicated therein, and the sweetening potency thereof is reported to be less than 2,500 times. Derivatives having a 3-(substituted phenyl)propyl group as an alkyl group are also shown. However, it is reported that the sweetening potency of N-[N-(3-phenylpropyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester is 1,500 times and that of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester is 2,500 times. Thus, these are far less than that (10,000 times) of N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester.

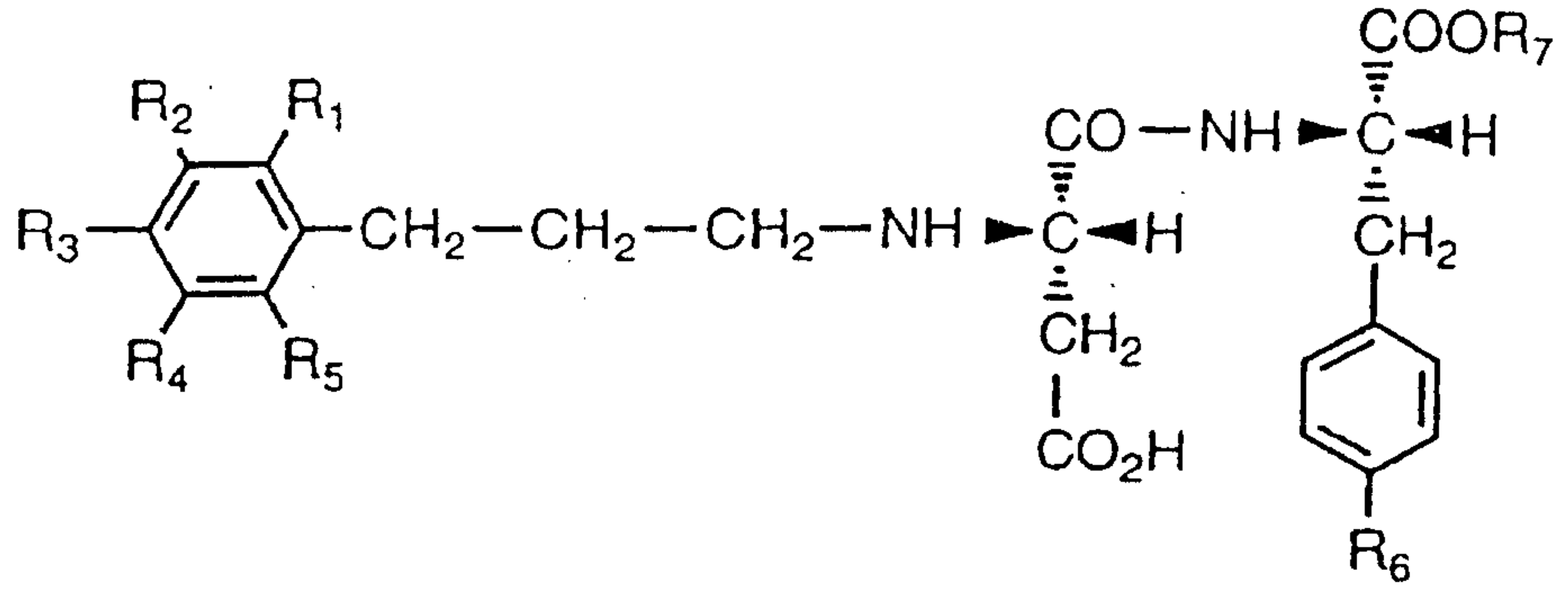
PROBLEMS INVENTION IS TO SOLVE, OBJECT THEREOF

It is an object of the invention to provide novel aspartyl dipeptide ester derivatives which are excellent in the safety and which have sweetening potency equal to or higher than that of the N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-mehtyl ester, and a low-calory sweetener containing the same as an active ingredient.

DISCLOSURE OF INVENTION

In order to solve the problems, the present inventors have synthesized several aspartame derivatives in which various 3-(substituted phenyl)propyl groups are introduced in an amino group of aspartic acid constituting the aspartame derivatives by use of cinnamaldehyde having various substituents on 3-phenylpropianaldehyde having various substituents that can easily derived therefrom an precursor aldehydes, and have examined the sweetening potency of them. They have consequently found that with respect to the sweetening potency, the novel compounds that they have found are by far higher than not only N-[N-(3-phenylpropyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester which is reported to have the sweetening potency of 1,500 times in WO 94/11391 but also N-[N-(3,3-dimethylbutyl)-L-α-aspartyl]-L-phenylalanine 1-methyl ester which is reported therein to have the sweetening potency of 10,000 times, and that especially the compounds represented by the following formula (1) are excellent as a sweetener. These findings have led to the completion of the invention.

The present invention (Claim 1) is directed to novel aspartyl dipeptide ester derivatives (including those in the form of a salt) represented by the general formula (1):



(1)

wherein

R_1, R_2, R_3, R_4 and R_5, independently from each other, represent a substituent selected from a hydrogen atom (H), a hydroxyl group (OH), an alkoxy group (OR; methoxy group, ethoxy group, propoxy groups, or the like) having from 1 to 3 carbon atoms, an alkyl group (R; methyl group, ethyl group, propyl groups, or the like) having from 1 to 3 carbon atoms and a hydroxyalkyloxy group (for examples, $O(CH_2)_2OH$ or $OCH_2CH(OH)CH_3$) having 2 or 3 carbon atoms, or R_1 and R_2, or R_2 and R_3 together form a methylenedioxy group (OCH_2O) wherein R_4, R_5 and, R_1 or R_3 which does not form the methylenedioxy group as a part thereof, independently from each other, represent any substituents as mentioned above designated for the R_1, R_3, R_4 and R_5, respectively, provided the case where R_1 to R_5 are all hydrogen atoms and the case where R_2 is a methoxy group and R_3 is a hydroxyl group are excluded, R_6 represents a hydrogen atom or a hydroxyl group, and R_7 represents a substituent selected from a methyl group (CH_3), an ethyl group (CH_2CH_3), an isopropyl group ($CH(CH_3)_2$, an n-propyl group ($CH_2CH_2CH_3$) and a t-butyl group ($C(CH_3)_3$).

EMBODIMENTS OF INVENTION

The novel aspartyl dipeptide ester derivatives of the invention include the compounds represented by formula (1) and salts thereof.

Amino acids constituting the derivatives are preferably L-isomers in that these are present in nature.

With respect to the compounds of the invention, the following inventions are preferably included.

[1] Compounds of formula (1) wherein R_3 is a substituent selected from a hydroxyl group, an alkoxy group having from 1 to 3 carbon atoms, an alkyl group having from 1 to 3 carbon atoms and a hydroxyalkyloxy group having 2 or 3 carbon atoms, R_1, R_2, R_4 and R_5 are, independently from each other, each a substituent selected from a hydrogen atom, a hydroxyl group, an alkoxy group having from 1 to 3 carbon atoms, an alkyl group having from 1 to 3 carbon atoms and a hydroxyalkyloxy group having 2 or 3 carbon atoms, or R_1 and R_2, or R_2 and R_3 together form a methylenedioxy group (OCH_2O) wherein R_4, R_5 and, R_1 or R_3 which does not form the methylenedioxy group as a part thereof, independently from each other, represent any substituents as mentioned above for the R_1, R_3, R_4 and R_5, R_6 is a hydrogen atom or a hydroxyl group, and R_7 is a substituent selected from a methyl group, an ethyl group, an isopropyl group, an n-propyl group and a t-butyl group.

[2] Compounds of formula (1) wherein R_3 is a hydrogen atom, R_1, R_2, R_4 and R_5 are, independently from each other, each a substituent selected from a hydroxyl group, an alkoxy group having from 1 to 3 carbon atoms, an alkyl group having from

1 to 3 carbon atoms and a hydroxyalkyloxy group having 2 or 3 carbon atoms, or R_1 and R_2, or R_2 and R_3 together form a methylenedioxy group (OCH_2O) wherein R_4, R_5 and, R_1 or R_3 which does not form the methylenedioxy group as a part thereof, independently from each other, represent any substituents as mentioned above designated for the R_1, R_3, R_4 and R_5, respectively, R_6 is a hydrogen atom or a hydroxyl group, and R_7 is a substituent selected from a methyl group, an ethyl group, an isopropyl group, an n-propyl group and a t-butyl group.

[3] Compounds of formula (1) wherein R_3 is a hydroxyl group, R_1, R_2, R_4 and R_5 are each a substituent selected from a hydrogen atom, a hydroxyl group, an alkoxy group having from 1 to 3 carbon atoms, an alkyl group having from 1 to 3 carbon atoms and a hydroxyalkyloxy group having 2 or 3 carbon atoms, or R_1 and R_2, or R_2 and R_3 together form a methylenedioxy group (OCH_2O) wherein R_4, R_5, and R_1 or R_3 which does not form the methylenedioxy group as a part thereof, independently from each other, represent any substituents as mentioned above designated for the R_1, R_3, R_4 and R_5, respectively, R_6 is a hydrogen atom or a hydroxyl group, and R_7 is a substituent selected from a methyl group, an ethyl group, an isopropyl group, an n-propyl group and a t-butyl group.

[4] Compounds of formula (1) wherein R_2 is a hydroxyl group, R_3 is a methoxy group, R_1, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[5] Compounds of formula (1) wherein R_2 and R_3 are each a methoxy group, R_1, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[6] Compounds of formula (1) wherein R_2 and R_3 together form a methylenedioxy group, R_1, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[7] Compounds of formula (1) wherein R_3 is a hydroxyl group, R_1, R_2, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[8] Compounds of formula (1) wherein R_3 is a methoxy group, R_1, R_2, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[9] Compounds of formula (1) wherein R_3 is an ethoxy group, R_1, R_2, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[10] Compounds of formula (1) wherein R_2 is a hydroxyl group, R_1, R_3, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[11] Compounds of formula (1) wherein R_2 is a methoxy group, R_1, R_3, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[12] Compounds of formula (1) wherein R_3 is a methoxy group, R_2 and R_6 are each a hydroxyl group, R_1, R_4 and R_5 are each a hydrogen atom, and R_7 is a methyl group.

[13] Compounds of formula (1) wherein R_1 is a hydroxyl

group, R_3 is a methoxy group, R_2, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[14] Compounds of formula (1) wherein R_1 is a hydroxyl group, R_2 is a methoxy group, R_3, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[15] Compounds of formula (1) wherein R_1 is a hydroxyl group, R_4 is a methoxy group, R_2, R_3, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[16] Compounds of formula (1) wherein R_1 is a hydroxyl group, R_3 and R_7 are each a methyl group, and R_2, R_4, R_5 and R_6 are each a hydrogen atom.

[17] Compounds of formula (1) wherein R_1 and R_3 are each a methoxy group, R_2, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[18] Compounds of formula (1) wherein R_1 is an ethoxy group, R_3 is a methoxy group, R_2, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[19] Compounds of formula (1) wherein R_2 and R_7 are each a methyl group, R_3 is a hydroxyl group, and R_1, R_4, R_5 and R_6 are each a hydrogen atom.

[20] Compounds of formula (1) wherein R_2 is a hydroxyl group, R_3 and R_7 are each a methyl group, and R_1, R_4, R_5 and R_6 are each a hydrogen atom.

[21] Compounds of formula (1) wherein R_2 and R_7 are each a methyl group, R_3 is a methoxy group, and R_1, R_4, R_5 and R_6 are

each a hydrogen atom.

[22] Compounds of formula (1) wherein R_2 and R_4 are each a methoxy group, R_1, R_3, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[23] Compounds of formula (1) wherein R_3 is a 2-hydroxyethoxy group, R_1, R_2, R_4, R_5 and R_6 are each a hydrogen atom, and R_7 is a methyl group.

[24] Compounds of formula (1) wherein R_3 and R_7 are each a methyl group, and R_1, R_2, R_4, R_5 and R_6 are each a hydrogen atom.

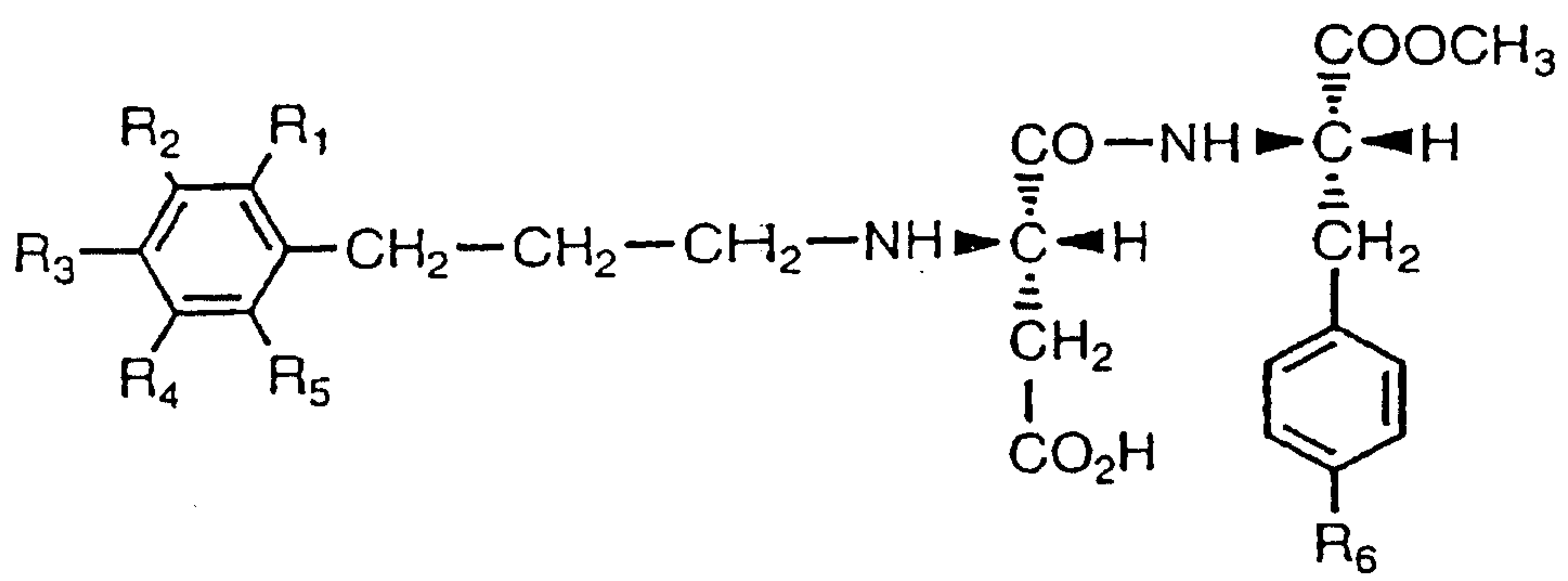
Examples of the salts of the compounds in the invention include salts with alkali metals such as sodium and potassium; salts with alkaline earth metals such as calcium and magnesium; ammonium salts with ammonia; salts with amino acids such as lysine and arginine; salts with inorganic acids such as hydrochloric acid and sulfuric acid; and salts with organic acids such as citric acid and acetic acid. These are included in the derivatives of the invention as described above.

The aspartyl dipeptide ester derivatives of the invention can easily be formed by reductively alkylating aspartame derivatives with cinnamaldehydes having various substituents and a reducing agent (for example, hydrogen/palladium carbon catalyst). Alternatively, the derivatives can be formed by subjecting aspartame derivatives (for example, β-O-benzyl-α-L-aspartyl-L-phenylalanine methyl ester) having a protective group in a carboxylic acid in the β-position which derivatives can be obtained by the usual peptide synthesis method (Izumiya et al., Basis of Peptide Synthesis and Experiments Thereof, Maruzen, published January 20, 1985) to reductive alkylation with cinnamaldehydes having various substituents and a reducing agent (for example, $NaB(OAc)_3H$) (A. F. Abdel-Magid et al., Tetrahedron Letters, 31, 5595 (1990)), and then removing the protective group. However, the method of forming the compounds of the invention is not limited thereto. 3-Phenylpropionaldehydes having various substituents or acetal derivatives thereof can of course be used as precursor aldehydes in the reductive alkylation instead of cinnamaldehydes having various substituents.

As a result of a sensory evaluation, the compounds and the salts thereof in the invention were found to have a strong sweetening potency and have taste properties similar to that of sugar. For example, the sweetening potency of N-[N-[3-(3-methyl-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was approximately 35,000 times (relative to sugar), that of N-[N-[3-(2-hydroxy-4-methylphenyl)propyl]-L-α-aspartyl]-L-α-phenylalanine 1-methyl ester was approximately 30,000 times (relative to sugar), that of N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was approximately

20,000 times, that of N-[N-[3-(2-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was approximately 20,000 times (relative to sugar), that of N-[N-[3-(3-hydroxy-4-methylphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was approximately 15,000 times (relative to sugar), that of N-[N-[3-(3-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was approximately 8,000 times (relative to sugar), that of N-[N-[3-(4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was approximately 6,500 times (relative to sugar), and that of N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-tyrosine 1-methyl ester was approximately 16,000 times (relative to sugar).

With respect to the aspartyl dipeptide derivatives (represented by formula (2)) formed, the structures and the results of the sensory evaluation are shown in Table 1.



(2)

Table 1

Structures and sweetening potency of aspartyl dipeptide ester derivatives

Compound No.	R_1	R_2	R_3	R_4	R_5	R_6	sweetening potency*)
1	H	OH	OCH_3	H	H	H	20000
2	H	OCH_3	OCH_3	H	H	H	2500
3	H	OCH_2O		H	H	H	5000
4	H	H	OH	H	H	H	5000
5	H	H	OCH_3	H	H	H	6500
6	H	H	OCH_2CH_3	H	H	H	1500
7	H	OH	H	H	H	H	8000
8	H	OCH_3	H	H	H	H	3500
9	H	OH	OCH_3	H	H	OH	16000
10	OH	H	OCH_3	H	H	H	20000
11	OH	OCH_3	H	H	H	H	10000
12	OH	H	H	OCH_3	H	H	1500
13	OH	H	CH_3	H	H	H	30000
14	OCH_3	H	OCH_3	H	H	H	4000
15	OCH_2CH_3	H	OCH_3	H	H	H	2500
16	H	CH_3	OH	H	H	H	35000
17	H	OH	CH_3	H	H	H	15000
18	H	CH_3	OCH_3	H	H	H	8000
19	H	OCH_3	H	OCH_3	H	H	800
20	H	H	OCH_2CH_2OH	H	H	H	1000
21	H	H	CH_3	H	H	H	4000

*) Relative to sweetening potency of a 4% sucrose aqueous solution

As understood from the results of Table 1, the novel derivatives in the present invention are excellent in sweetening potency.

When the compounds (including those in the form of a salt) of the invention are used as a sweetener, these may of course be used in combination with other sweeteners unless inviting any special troubles.

When the derivatives of the invention are used as a sweetener, an appropriate carrier and/or an appropriate bulking agent may be used as required. For example, a carrier which has been so far used is available.

The derivatives of the invention can be used as a sweetener or an ingredient therefor, and further as a sweetener for products such as foods and the like to which a sweetness has to be imparted, for example, confectionary, chewing gum, hygiene products, toiletries, cosmetics, pharmaceutical products and veterinary products for animals. Still further, they can be used in a method of imparting a sweetness to the products. This method can be, for example, a conventional method for using a sweetening ingredient for a sweetener in the sweeteners or the method of imparting a sweetness.

PREFERRED EMBODIMENTS OF INVENTION

The invention is illustrated specifically by referring to the following Examples.

EXAMPLE 1

Synthesis of N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Five milliliters of a solution of 4N-HCl and dioxane were added to 485 mg (1.0 mmol) of N-t-butoxycarbonyl-β-O-benzyl-α-L-aspartyl-L-phenylalanine methyl ester, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure. Thirty milliliters of a 5% sodium hydrogencarbonate aqueous solution were added to the residue, and the mixture was extracted twice with 30 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate. Then, magnesium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 385 mg of β-O-benzyl-α-L-aspartyl-L-phenylalanine methyl ester as a viscous oil.

The β-O-benzyl-α-L-aspartyl-L-phenylalanine methyl ester (385 mg, 1.0 mmol) was dissolved in 15 ml of THF, and the solution was maintained at 0°C. To this were added 268 mg (1.0 mmol) of 3-benzyloxy-4-methoxycinnamaldehyde, 0.060 ml (1.0 mmol) of acetic acid and 318 mg (1.5 mmol) of $NaB(OAc)_3H$. The mixture was stirred at 0°C for 1 hour and further overnight at room temperature. To the reaction solution were added 50 ml of a saturated aqueous solution of sodium hydrogen carbonate, and the mixture was extracted twice with 30 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and dried over anhydrous magnesium sulfate. Then, magnesium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified with PTLC (Preparative Thin Layer Chromatography) to obtain 523 mg (0.82 mmol) of N-[N-[3-(3-benzyloxy-4-methoxyphenyl)propenyl]-β-O-benzyl-L-α-aspartyl]-L-phenylalanine 1-methyl ester as a viscous oil.

The N-[N-[3-(3-benzyloxy-4-methoxyphenyl)propenyl]-β-O-benzyl-L-α-aspartyl]-L-phenylalanine 1-methyl ester (523 mg, 0.82 mmol) was dissolved in a mixed solvent of 30 ml of methanol and 1 ml of water, and 200 mg of 10% palladium carbon (water content 50%) were added thereto. The mixture was reduced under a hydrogen stmosphere at room temperature for 3 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. In order to remove an odor adsorbed, the residue was purified with PTLC to obtain 228 mg (0.48 mmol) of N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.50-1.60 (m, 2H), 2.15-2.40 (m, 6H), 2.87-2.97 (dd, 1H), 3.05-3.13 (dd, 1H), 3.37-3.43 (m, 1H), 3.62 (s, 3H), 3.71 (s, 3H), 4.50-4.60 (m, 1H), 6.52 (d, 1H), 6.60 (s, 1H), 6.79 (d, 1H), 7.18–7.30 (m, 5H), 8.52 (d, 1H), 8.80 (brs, 1H).

ESI–MS 459.2 (MH^+)

Sweetening potency (relative to sugar): 20,000 times

EXAMPLE 2

Synthesis of N-[N-[3-(3,4-dimethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3,4-dimethoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(3,4-dimethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 48.7% as a solid.

^{1}HNMR (DMSO–d_6) δ: 1.52–1.62 (m, 2H), 2.18–2.50 (m, 6H), 2.86–2.76 (dd, 1H), 3.04–3.12 (dd, 1H), 3.37–3.44 (m, 1H), 3.62 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 4.52–4.62 (m, 1H), 6.66 (d, 1H), 6.76 (s, 1H), 6.83 (d, 1H), 7.18–7.30 (m, 5H), 8.50 (d, 1H).

ESI–MS 473.2 (MH^+)

Sweetening potency (relative to sugar): 2,500 times

EXAMPLE 3

Synthesis of N-[N-[3-(3,4-methylenedioxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3,4-methylenedioxycinnamaldehyde was used instead of 3-

benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(3,4-methylenedioxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 42.1% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.48-1.60 (m, 2H), 2.14-2.48 (m, 6H), 2.86-2.96 (dd, 1H), 3.03-3.12 (dd, 1H), 3.37-3.43 (m, 1H), 3.62 (s, 3H), 4.54-4.59 (m, 1H), 5.94 (s, 1H), 5.95 (s, 1H), 6.61 (d, 1H), 6.74 (s, 1H), 6.78 (d, 1H), 7.15-7.30 (m, 5H), 8.47 (d, 1H).

ESI-MS 457.2 (MH^+)

Sweetening potency (relative to sugar): 5,000 times

EXAMPLE 4

Synthesis of N-[N-[3-(4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 4-benzyloxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 40.6% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.48-1.60 (m, 2H), 2.14-2.43 (m, 6H), 2.86-2.96 (dd, 1H), 3.04-3.14 (dd, 1H), 3.37-3.42 (m, 1H), 3.62 (s, 3H), 4.52-4.62 (m, 1H), 6.65 (d, 2H), 6.93 (d, 2H), 7.16-7.29 (m, 5H), 8.49 (d, 1H), 9.12 (brs, 1H).

ESI-MS 429.2 (MH^+)

Sweetening potency (relative to sugar): 5,000 times

EXAMPLE 5

Synthesis of N-[N-[3-(4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester (1)

Example 1 was repeated except that 4-methoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 50.0% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.50-1.62 (m, 2H), 2.16-2.48 (m, 6H), 2.84-2.94 (dd, 1H), 3.04-3.12 (dd, 1H), 3.38-3.44 (m, 1H), 3.62 (s, 3H), 3.71 (s, 3H), 4.52-4.62 (m, 1H), 6.83 (d, 2H), 7.08 (d, 2H), 7.17-7.29 (m, 5H), 8.50 (d, 1H).

ESI-MS 443.3 (MH^+)

Sweetening potency (relative to sugar): 6,500 times

EXAMPLE 6

Synthesis of N-[N-[3-(4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester (2)

4-Methoxycinnamaldehyde (405 mg, 2.5 mmol), 735 mg (2.5 mmols) of aspartame and 350 mg of 10% palladium carbon (water content 50%) were added to a mixed solvent of 15 ml of methanol and 5 ml of water, and the mixture was stirred under a hydrogen atmosphere overnight at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added 30 ml of ethyl acetate, and the mixture was stirred for a while. Then, the insoluble material was collected by filtration. The insoluble material collected was washed with a small amount of ethyl acetate. To this were added 50 ml of a mixed solvent of ethyl acetate and methanol (5:2), and the mixture was stirred for a while. The insoluble material was removed by filtration, and the filtrate was concentrated. Then, the overall residue was solidified. This was dried under reduced pressure, and then recrystallized from a mixed solvent of methanol and water to obtain N-[N-[3-(4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 43.4% as a solid.

EXAMPLE 7

Synthesis of N-[N-[3-(4-ethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 4-ethoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(4-ethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 57.1% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.30 (t, 3H), 1.50-1.62 (m, 2H), 2.16-2.48 (m, 6H), 2.85-2.95 (dd, 1H), 3.02-3.12 (dd, 1H), 3.39-3.44 (m, 1H), 3.62 (s, 3H), 3.96 (q, 2H), 4.52-4.59 (m, 1H), 6.81 (d, 2H), 7.05 (d, 2H), 7.17-7.28 (m, 5H), 8.50 (d, 1H).

ESI-MS 457.2 (MH^+)

Sweetening potency (relative to sugar): 1,500 times

EXAMPLE 8

Synthesis of N-[N-[3-(3-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3-benzyloxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(3-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 46.6% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.50-1.62 (m, 1H), 2.10-2.48 (m, 6H), 2.87-2.96 (dd, 1H), 3.40-3.12 (dd, 1H), 3.33-3.38 (m, 1H), 3.62 (s, 3H), 4.52-4.60 (m, 1H), 6.53-6.60 (m, 3H), 7.04 (t, 1H), 7.17-7.30 (m, 5H), 8.50 (d, 1H), 9.40 (brs, 1H).

ESI-MS 429.2 (MH^+)

Sweetening potency (relative to sugar): 8,000 times

EXAMPLE 9

Synthesis of N-[N-[3-(3-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3-methoxycinnamaldehyde was used instead of 3-benzyloxy-4-

methoxycinnamaldehyde to obtain N-[N-[3-(3-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 55.6% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.54-1.66 (m, 2H), 2.18-2.50 (m, 6H), 2.86-2.96 (dd, 1H), 3.02-3.12 (dd, 1H), 3.40-3.46 (m, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.53-4.61 (m, 1H), 6.70-6.78 (m, 3H), 7.13-7.30 (m, 5H), 8.50 (d, 1H).

ESI-MS 443.1 (MH$^+$)

Sweetening potency (relative to sugar): 3,500 times

EXAMPLE 10

Synthesis of N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-tyrosine 1-methyl ester

Example 1 was repeated except that N-t-butoxycarbonyl-β-O-benzyl-α-L-aspartyl-L-tyrosine methyl ester was used instead of N-t-butoxycarbonyl-β-O-benzyl-α-L-aspartyl-L-phenylalanine methyl ester to obtain N-[N-[3-(3-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-tyrosine 1-methyl ester in a total yield of 45.4% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.52-1.64 (m, 2H), 2.24-2.48 (m, 6H), 2.74-2.84 (dd, 1H), 2.91-2.99 (dd, 1H), 3.47-3.54 (m, 1H), 3.61 (s, 3H), 3.72 (s, 3H), 4.45-4.53 (m, 1H), 6.54 (d, 1H), 6.60 (s, 1H), 6.65 (d, 2H), 6.79 (d, 1H), 6.98 (d, 2H), 8.54 (d, 1H), 8.78 (brs, 1H), 9.25 (brs, 1H).

ESI-MS 475.2 (MH^+)

Sweetening potency (relative to sugar): 16,000 times

EXAMPLE 11

Synthesis of N-[N-[3-(2-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 2-benzyloxy-4-methoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(2-hydroxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 54.4% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.52-1.57 (m, 2H), 2.20-2.31 (m, 2H), 2.26-2.41 (m, 4H), 2.88-3.11 (m, 2H), 3.41-3.44 (m, 1H), 3.62 (s, 3H), 3.65 (s, 3H), 4.53-4.59 (m, 1H), 6.28-6.36 (m, 2H), 6.88-6.90 (d, 1H), 7.19-7.29 (m, 5H), 8.55 (d, 1H).

ESI-MS 459.3 (MH^+)

Sweetening potency (relative to sugar): 20,000 times

EXAMPLE 12

Synthesis of N-[N-[3-(2-hydroxy-3-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 2-benzyloxy-3-methoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(2-hydroxy-3-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-

methyl ester in a total yield of 33.4% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.53-1.58 (m, 2H), 2.04-2.25 (m, 2H), 2.26-2.32 (m, 4H), 2.90-3.12 (m, 2H), 3.51-3.53 (m, 1H), 3.61 (s, 3H), 3.76 (s, 3H), 4.52-4.58 (m, 1H), 6.64-6.78 (m, 3H), 7.18-7.29 (m, 5H), 8.52 (d, 1H).

ESI-MS 459.4 (MH$^+$)

Sweetening potency (relative to sugar): 10,000 times

EXAMPLE 13

Synthesis of N-[N-[3-(2-hydroxy-5-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 2-benzyloxy-5-methoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(2-hydroxy-5-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 57.6% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.52-1.63 (m, 2H), 2.19-2.35 (m, 2H), 2.27-2.47 (m, 4H), 2.89-3.14 (m, 2H), 3.47-3.50 (m, 1H), 3.62 (s, 3H), 3.65 (s, 3H), 4.50-4.58 (m, 1H), 6.57-6.71 (m, 3H), 7.19-7.30 (m, 5H), 8.62 (d, 1H). 8.84 (brs, 1H).

ESI-MS 459.3 (MH$^+$)

Sweetening potency (relative to sugar): 1,500 times

EXAMPLE 14

Synthesis of N-[N-[3-(2-hydroxy-4-methylphenyl)propyl]-L-α

-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 2-benzyloxy-4-methylcinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(2-hydroxy-4-methylphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 35.7% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.52-1.58 (m, 2H), 2.17 (s, 3H), 2.19-2.32 (m, 2H), 2.37-2.44 (m, 4H), 2.87-3.11 (m, 2H), 3.39-3.42 (m, 1H), 3.62 (s, 3H), 4.53-4.58 (m, 1H), 6.50 (d, 2H), 6.58 (s, 1H), 6.80 (d, 1H), 7.15-7.29 (m, 5H), 8.54 (d, 1H).

ESI-MS 443.3 (MH$^+$)

Sweetening potency (relative to sugar): 30,000 times

EXAMPLE 15

Synthesis of N-[N-[3-(2,4-dimethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 2,4-dimethoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(2,4-dimethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 32.4% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.50-1.54 (m, 2H), 2.20-2.31 (m, 2H), 2.25-2.43 (m, 4H), 2.88-3.12 (m, 2H), 3.44-3.82 (m, 1H), 3.62 (s, 3H), 3.72 (s, 3H), 3.75 (s, 3H), 4.54-4.59 (m, 1H), 6.40−6.50 (m, 2H), 6.96−6.98 (m, 1H), 7.19−7.29 (m, 5H), 8.51 (d, 1H).

ESI−MS 473.3 (MH^+)

Sweetening potency (relative to sugar): 4,000 times

EXAMPLE 16

Synthesis of N-[N-[3-(2-ethoxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 2-ethoxy-4-methoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(2-ethoxy-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 35.6% as a solid.

^{1}HNMR (DMSO−d_6) δ: 1.30−1.34 (t, 3H), 1.50−1.57 (m, 2H), 2.19−2.41 (m, 2H), 2.24−2.43 (m, 4H), 2.87−3.11 (m, 2H), 3.38−3.42 (m, 1H), 3.62 (s, 3H), 3.71 (s, 3H), 3.70−4.03 (q, 2H), 4.53−4.60 (m, 1H), 6.40−6.48 (m, 2H), 6.96−6.98 (m, 1H), 7.19−7.29 (m, 5H), 8.51 (d, 1H).

ESI−MS 487.4 (MH^+)

Sweetening potency (relative to sugar): 2,500 times

EXAMPLE 17

Synthesis of N-[N-[3-(3-methyl-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3-methyl-4-benzyloxycinnamaldehyde was used instead of 3-benzyloxy-4-

methoxycinnamaldehyde to obtain N-[N-[3-(3-methyl-4-hydroxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 32.2% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.50-1.58 (m, 2H), 2.08 (s, 3H), 2.09-2.30 (m, 2H), 2.26-2.38 (m, 4H), 2.89-3.09 (m, 2H), 3.35-3.42 (m, 1H), 3.62 (s, 3H), 4.54-4.59 (m, 1H), 6.65-6.83 (m, 3H), 7.19-7.28 (m, 5H), 8.52 (d, 1H). 9.04 (brs, 1H).

ESI-MS 443.4 (MH^+)

Sweetening potency (relative to sugar): 35,000 times

EXAMPLE 18

Synthesis of N-[N-[3-(3-hydroxy-4-methylphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3-benzyloxy-4-methylcinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(3-hydroxy-4-methylphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 46.9% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.51-1.58 (m, 2H), 2.06 (s, 3H), 2.18-2.32 (m, 2H), 2.24-2.39 (m, 4H), 2.87-3.11 (m, 2H), 3.39-3.43 (m, 1H), 3.62 (s, 3H), 4.54-4.60 (m, 1H), 6.47-6.58 (m, 2H), 6.90-6.93 (m, 1H), 7.12-7.29 (m, 5H), 8.52 (d, 1H). 9.12 (brs, 1H).

ESI-MS 443.4 (MH^+)

Sweetening potency (relative to sugar): 15,000 times

EXAMPLE 19

Synthesis of N-[N-[3-(3-methyl-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3-methyl-4-methoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(3-methyl-4-methoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 34.0% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.52-1.59 (m, 2H), 2.11 (s, 3H), 2.20-2.38 (m, 2H), 2.26-2.43 (m, 4H), 2.89-3.10 (m, 2H), 3.39-3.43 (m, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.52-4.59 (m, 1H), 6.79-6.82 (m, 1H), 6.92-6.94 (m, 2H), 7.19-7.28 (m, 5H), 8.53 (d, 1H).

ESI-MS 457.4 (MH^+)

Sweetening potency (relative to sugar): 8,000 times

EXAMPLE 20

Synthesis of N-[N-[3-(3,5-dimethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 3,5-dimethoxycinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(3,5-dimethoxyphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 41.0% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.56-1.62 (m, 2H), 2.18-2.38 (m, 2H), 2.25-2.47 (m, 4H), 2.88-3.11 (m, 2H), 3.38-3.44 (m, 1H), 3.62 (s, 3H), 3.71 (s, 6H), 4.53-4.59 (m, 1H), 6.30-6.35 (m, 3H), 7.19-7.28 (m, 5H), 8.55 (d, 1H).

ESI-MS 473.3 (MH^+)

Sweetening potency (relative to sugar): 800 times

EXAMPLE 21

Synthesis of N-[N-[3-(4-(2-hydroxyethoxy)phenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 4-(2-hydroxyethoxy)cinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(4-(2-hydroxyethoxy)phenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 33.8% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.52-1.60 (m, 2H), 2.18-2.35 (m, 2H), 2.24-2.47 (m, 4H), 3.38-3.43 (m, 1H), 3.62 (s, 3H), 3.67-3.71 (m, 2H), 3.92-3.95 (m, 2H), 4.53-4.59 (m, 1H), 6.82-6.85 (d, 2H), 7.05-7.07 (d, 2H), 7.19-7.29 (m, 5H), 8.51 (d, 1H).

ESI-MS 473.3 (MH^+)

Sweetening potency (relative to sugar): 1,000 times

EXAMPLE 22

Synthesis of N-[N-[3-(4-methylphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester

Example 1 was repeated except that 4-methylcinnamaldehyde was used instead of 3-benzyloxy-4-methoxycinnamaldehyde to obtain N-[N-[3-(4-methylphenyl)propyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester in a total yield of 54.1% as a solid.

^{1}HNMR (DMSO-d_6) δ: 1.50-1.63 (m, 2H), 2.18-2.39 (m, 2H), 2.25 (s, 3H), 2.29-2.46 (m, 4H), 2.87-3.11 (m, 2H), 3.41-3.47 (m, 1H), 3.61 (s, 3H), 4.53-4.61 (m, 1H), 7.03-7.09 (m, 4H), 7.17-7.29 (m, 5H), 8.58 (d, 1H).

ESI-MS 427.4 (MH^+)

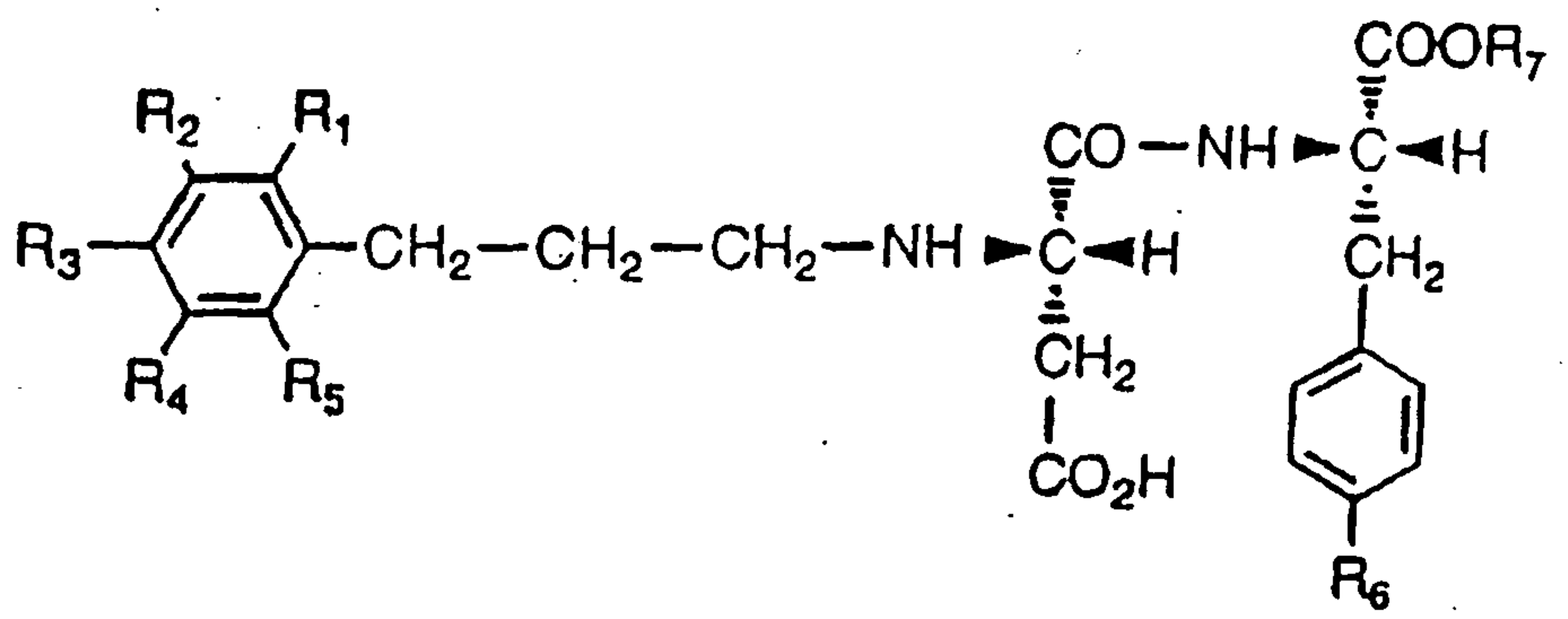
Sweetening potency (relative to sugar): 4,000 times

EFFECTS OF INVENTION

The novel aspartyl dipeptide ester derivatives of the invention have especially an excellent sweetening potency in comparison with conventional sweeteners. The invention can provide novel chemical substances having excellent taste properties as a sweetener. Accordingly, such novel derivatives in the present invention can be used as a sweetener, and also can impart a sweetness to products such as beverages and foods requiring a sweetness.

-CLAIMS :

1. An aspartyl dipeptide ester derivative represented by formula (1) :



(1)

or a salt thereof wherein

R_1, R_2, R_4 and R_5, independently from each other, represent a substituent selected from a hydrogen atom, a hydroxyl group, an alkoxy group having from 1 to 3 carbon atoms, an alkyl group having from 1 to 3 carbon atoms and a hydroxyalkyloxy group having 2 or 3 carbon atoms, or R_1 and R_2 together form a methylenedioxy group wherein R_4 and R_5, independently from each other, represent any substituents as mentioned above designated for the R_4 and R_5 respectively,

R_6 represents a hydrogen atom or a hydroxyl group;

R_3 is a methoxy; and

R_7 represents a substituent selected from a methyl group, an ethyl group, an isopropyl group, an n-propyl group and a t-butyl group.

2. The derivative of claim 1, or a salt thereof wherein R_2 is a hydroxyl group, R_1, R_4, R_5 and R_6 are hydrogen atoms, and R_7 is a methyl group.

3. The derivative of claim 1, or a salt thereof wherein R_2 is a methoxy group, R_1, R_4, R_5 and R_6 are hydrogen atoms, and R_7 is a methyl group.

4. The derivative of claim 1, or a salt thereof wherein R_1, R_2, R_4, R_5 and R_6 are hydrogen atoms, and R_7 is a methyl group.

5. The derivative of claim 1, or a salt thereof wherein R_2 and R_6 are hydroxyl groups, R_1, R_4 and R_5 are hydrogen atoms, and R_7 is a methyl group.

6. The derivative of claim 1, or a salt thereof wherein R_1 is a hydroxyl group, R_2, R_4, R_5 and R_6 are hydrogen atoms, and R_7 is a methyl group.

7. The derivative of claim 1, or a salt thereof wherein R_1 is a methoxy group, R_2, R_4, R_5 and R_6 are hydrogen atoms and R_7 is a methyl group.

8. The derivative of claim 1, or a salt thereof wherein R_1 is an ethoxy group, R_2, R_4, R_5 and R_6 are hydrogen atoms, and R_7 is a methyl group.

9. The derivative of claim 1, or a salt thereof wherein R_2 and R_7 are methyl groups and R_1, R_4, R_5 and R_6 are hydrogen atoms.

10. A sweetener or products comprising at least one derivative as defined in any one of claims 1 to 9 or a salt thereof.

11. The sweetener or products according to claim 10, further comprising a carrier, a bulking agent for sweeteners or mixtures thereof.

12. Use of a derivative as defined in any one of claims 1 to 9 or a salt thereof as a sweetener.