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(54) Title: NOVEL ASPARTYLAMIDE DERIVATIVES AND SWEETENERS

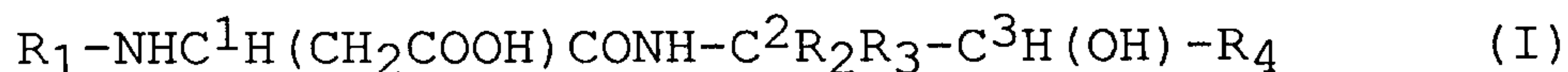
(57) **Abrégé/Abstract:**

The invention is concerned with novel aspartylamide derivatives having the general formula: $R_1-NHC^1H(CH_2COOH)CONH-C^2R_2$
 $R_3-C^3H(OH)-R_4$ (I) wherein R_1 represents a hydrogen atom, a saturated or unsaturated linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms or a mixed hydrocarbon group thereof; R_2 and R_3 each represent a hydrogen atom or a substituent selected from the group consisting of alkyl groups having from 1 to 6 carbon atoms, alkoxyalkyl groups having from 2 to 7 carbon atoms, hydroxyalkyl groups having from 2 to 7 carbon atoms, a phenyl group, a 2-furyl group, a dimethylene group, a trimethylene group, a tetramethylene group and a pentamethylene group; when R_1 is a saturated or unsaturated linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms or a mixed hydrocarbon group thereof, R_4 represents an alkyl group having from 1 to 12 carbon atoms or a substituent of formula (II) or (III), and when R_1 is a hydrogen atom, R_4 represents a substituent of formula (III):
 $-(CHR_5)_n-R_6$ (II) $-(CH_2)_m-C^4HR_7R_8$ (III) wherein, in formula (II), R_5 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R_6 represents a 3- to 10-membered cycloalkyl group having a total of 12 or less carbon atoms, a cycloalkenyl group, a cycloalkyl group which is substituted by an alkyl group, a cycloalkenyl group, a bicycloalkyl group, a bicycloalkenyl group, or a tricycloalkenyl group, and n represents 0 or 1; and in formula (III), R_7 and R_8 each represent a hydrogen atom, a cycloalkyl group having from 3 to 4 carbon atoms, an alkyl group having from 1 to 6 carbon atoms, an alkoxyalkyl group having from 2 to 7 carbon atoms, a phenyl group, a phenyl group having a substituent selected from the group consisting of fluorine, chlorine, bromine and iodine atoms, a hydroxy group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 2 to 7 carbon atoms, a cyano group, a nitro group, an acetyl group, an amino group and an acetylamino group in the 2-, 3- or 4-position, a phenyl group having a methylenedioxy group, a trimethylene group or a tetramethylene group in the 2- and 3-positions or in the 3- and 4-positions, a 2-, 3- or 4-pyridyl group, a 2- or 3-furyl group, or a 2- or 3-thienyl group, and m represents 0 or 1; and the C^1 -configuration is (S), and the C^2 -, C^3 - and C^4 -configurations are (R), (S) or (RS); and salts thereof. The compounds of formula (I) are useful as sweeteners which are excellent in terms of sweetness intensity, stability and sweetness properties.

NOVEL ASPARTYLAMIDE DERIVATIVES AND SWEETENERS

ABSTRACT

The invention is concerned with novel aspartylamide derivatives having the general formula:



wherein R_1 represents a hydrogen atom, a saturated or unsaturated linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms or a mixed hydrocarbon group thereof; R_2 and R_3 each represent a hydrogen atom or a substituent selected from the group consisting of alkyl groups having from 1 to 6 carbon atoms, alkoxyalkyl groups having from 2 to 7 carbon atoms, hydroxyalkyl groups having from 2 to 7 carbon atoms, a phenyl group, a 2-furyl group, a dimethylene group, a trimethylene group, a tetramethylene group and a pentamethylene group; when R_1 is a saturated or unsaturated linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms or a mixed hydrocarbon group thereof, R_4 represents an alkyl group having from 1 to 12 carbon atoms or a substituent of formula (II) or (III), and when R_1 is a hydrogen atom, R_4 represents a substituent of formula (III):



wherein, in formula (II), R_5 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R_6 represents a 3- to 10-membered cycloalkyl group having a total of 12 or less carbon atoms, a cycloalkenyl group, a cycloalkyl group which is substituted by an alkyl group, a cycloalkenyl group, a bicycloalkyl group, a bicycloalkenyl group, or a tricycloalkenyl group, and n represents 0 or 1; and in formula (III), R_7 and R_8 each represent a hydrogen atom, a cycloalkyl group having from 3 to 4 carbon atoms, an alkyl group having from 1 to 6 carbon atoms, an alkoxyalkyl group having from 2 to 7 carbon atoms, a phenyl group, a phenyl group having a

substituent selected from the group consisting of fluorine, chlorine, bromine and iodine atoms, a hydroxy group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 2 to 7 carbon atoms, a cyano group, a nitro group, an acetyl group, an amino group and an acetylamino group in the 2-, 3- or 4-position, a phenyl group having a methylenedioxy group, a trimethylene group or a tetramethylene group in the 2- and 3-positions or in the 3- and 4-positions, a 2-, 3- or 4-pyridyl group, a 2- or 3-furyl group, or a 2- or 3-thienyl group, and m represents 0 or 1; and the C¹-configuration is (S), and the C²-, C³- and C⁴-configurations are (R), (S) or (RS); and salts thereof. The compounds of formula (I) are useful as sweeteners which are excellent in terms of sweetness intensity, stability and sweetness properties.

NOVEL ASPARTYLAMIDE DERIVATIVES AND SWEETENERS

The present invention relates to novel aspartylamide derivatives and salts thereof as well as to a sweetener
5 containing the same as an active ingredient.

In recent years, eating habits have been improved to a high level, and fatness caused by excessive intake of sugar and diseases accompanied by the fatness have been at issue. Therefore, the development of a low-calorie
10 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 terms of safety and sweetness properties. However, it involves a problem of stability. In order to improve the stability and the
15 sweetness intensity, an aspartylamide derivative which is a condensate of aspartic acid and β -amino-alcohol and which is free from an ester linkage was studied. Thus, the compounds described in U.S. Patent No. 4,423,029, European Patent No. 203,540, J. Med. Chem., 13, 1217
20 (1970) or Tetrahedron Letters, 35, 6891 (1994) were found. On the other hand, French Patent No. 2,697,844 discloses that aspartyldipeptide derivatives in which an alkyl group has been introduced into an amino group exhibits an extremely increased degree of sweetness.
25 However, these compounds do not satisfy the stability.

It is therefore an object of the present invention to provide novel aspartylamide derivatives and salts thereof which are obtained by using a readily available amino-alcohol component and which exhibit a high level of
30 safety and an excellent stability, as well as a low-calorie sweetener containing the same as an active ingredient.

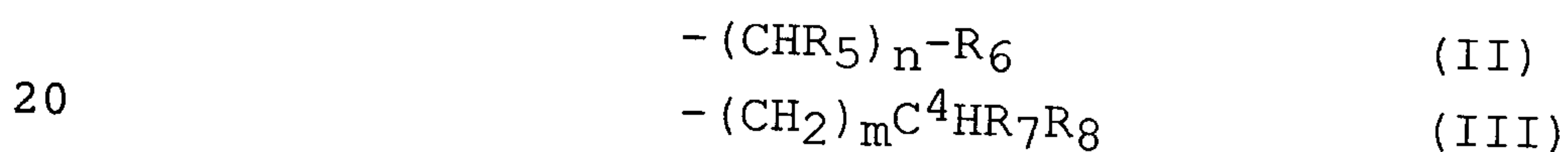
In accordance with the present invention, there are thus provided novel aspartylamide derivatives having the
35 general formula:



R₁ represents a hydrogen atom, a saturated or unsaturated linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms or a mixed hydrocarbon group thereof;

5 R₂ and R₃ each represent a hydrogen atom, or a substituent selected from the group consisting of alkyl groups having from 1 to 6 carbon atoms, alkoxyalkyl groups having from 2 to 7 carbon atoms, hydroxyalkyl groups having from 2 to 7 carbon atoms, a phenyl group, a
10 2-furyl group, a dimethylene group, a trimethylene group, a tetramethylene group and a pentamethylene group;

when R₁ is a saturated or unsaturated linear or cyclic hydrocarbon group having from 1 to 13 carbon atoms or a mixed hydrocarbon group thereof, R₄ represents an
15 alkyl group having from 1 to 12 carbon atoms or a substituent of formula (II) or (III), and when R₁ is a hydrogen atom, R₄ represents a substituent of formula (III):



wherein,

in formula (II):

R₅ represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms,

25 R₆ represents a 3- to 10-membered cycloalkyl group having a total of 12 or less carbon atoms, a cycloalkenyl group, a cycloalkyl group which is substituted by an alkyl group, a cycloalkenyl group, a bicycloalkyl group, a bicycloalkenyl group, or a tricycloalkenyl group, and

30 n represents 0 or 1; and
in formula (III):

R₇ and R₈ each represent a hydrogen atom, a cycloalkyl group having from 3 to 4 carbon atoms, an alkyl group having from 1 to 6 carbon atoms, an
35 alkoxyalkyl group having from 2 to 7 carbon atoms, a phenyl group, a phenyl group having a substituent selected from the group consisting of fluorine, chlorine,

bromine and iodine atoms, a hydroxy group, an alkyl group having from 1 to 6 carbon atoms, an alkoxy group having from 2 to 7 carbon atoms, a cyano group, a nitro group, an acetyl group, an amino group and an acetylamino group in the 2-, 3- or 4-position, a phenyl group having a methylenedioxy group, a trimethylene group or a tetramethylene group in the 2- and 3-positions or in the 3- and 4-positions, a 2-, 3-or 4-pyridyl group, a 2- or 3-furyl group, or a 2- or 3-thienyl group, and m represents 0 or 1; and the C¹-configuration is (S), and the C²-, C³- and C⁴-configurations are (R), (S) or (RS), and salts thereof.

In accordance with one embodiment of the present invention, there is an aspartylamide derivative that is selected from the group consisting of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3, 3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3, 3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide and salts thereof.

In accordance with yet another embodiment of the present invention, there is a sweetener containing, as the active ingredient, as aspartylamide derivative selected from the group consisting of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-

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phenylhexylamide, N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3, 3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide and salts thereof.

Examples of salts of the compounds of formula (I) according to the present invention include salts with alkali metals such as sodium and potassium; salts with alkaline-earth metals such as calcium and magnesium; salts with amines such as monoethanolamine; salts with inorganic acids such as hydrochloric acid and sulfuric acid; and salts with organic acids such as citric acid and acetic acid.

The aspartylamide derivatives of the present invention can be prepared by the usual peptide synthesis method (Izumiya et al., Basis of Peptide Synthesis and Experiments thereof, Maruzen, January 20, 1985). For example, a desired α -L-aspartylamide can be formed by first condensing an amino-alcohol with L-aspartic acid in which the carboxylic acid in the β -position and the amino group are protected to obtain an amide, and then removing the protective groups, or by first converting L-aspartic acid in which the carboxylic acid in the β -position and the amino group are protected into an active ester, reacting this ester with an amino-alcohol to obtain an amide, and then removing the protective groups.

The N-alkylaspartylamide derivatives can be prepared by forming an amide of L-aspartic acid having protective groups and an amino-alcohol, then selectively removing

the N-protective group, alkylating through reduction the resulting compound with an aldehyde [A. F. Abdel-Magid et al., Tetrahedron Letters, 31, 5595 (1990)], and further removing the remaining protective group. For example, an amino-alcohol is first condensed with L-aspartic acid in which the carboxylic acid in the β -position and the amino group are protected to obtain an amide, or L-aspartic acid in which a carboxylic acid in the β -position and the amino group are protected is first converted into an active ester, and this active ester is then reacted with an amino-alcohol to obtain an amide. The N-protective group of this protected aspartylamide is selectively removed, the resulting substance is alkylated through reduction with an aldehyde and a reducing agent [for example, $\text{NaB}(\text{OAc})_3\text{H}$], and the remaining protective group is then removed to obtain N-alkyl- α -L-aspartylamide. The N-alkyl- α -L-aspartylamide can also be obtained by alkylating through reduction the above-mentioned α -L-aspartylamide with an aldehyde and a reducing agent (for example, palladium on carbon). The amino-alcohol which is used to produce the compounds of the present invention can easily be obtained from an amino acid as an optically active substance by methods described in the literature [Tetrahedron Letters, by M. W. Holladay et al., 24, 4401 (1983), or Angew. Chem. Int. Ed. Engle., by M. T. Reets et al., 26, 1141 (1987)].

As a result of the sensory evaluation, it was found that the compounds of the present invention and the salts thereof have a strong sweetness and their sweetness qualities are similar to that of sugar. For example, the degree of sweetness of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide was approximately 2,500 times that of sugar, the degree of sweetness of N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide was approximately 1,500 times that of sugar, the degree of sweetness of N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide was approximately

2,300 times that of sugar, the degree of sweetness of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide was approximately 5,500 times that of sugar, the degree of sweetness of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide was approximately 3,000 times that of sugar), the degree of sweetness of N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide was approximately 3,000 times that of sugar, and the degree of sweetness of N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide was approximately 4,000 times that of sugar.

The half-life (in a phosphate buffer of pH 3 at 70°C) of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide in an acidic aqueous solution was approximately 289 hours, and it was by far more stable than aspartame having a half-life of approximately 24 hours.

Further, N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide was subjected to a toxicity test in one oral administration (2.0 g/kg) using ICR-strain mice. It was found that this compound did not present any problem with respect to safety.

The structures of the aspartylamide derivatives of formula (I) which were subjected to a sensory evaluation and the results of the sensory evaluation thereof are shown in Table 1.

TABLE 1
Structures of aspartylamide derivatives and degrees of sweetness thereof

R ₁	R ₂	R ₃	C ² - config- uration	C ³ - config- uration S:R	R ₄	Degree of sweet- ness ¹⁾
H	H	Me	R	>5:1	(S)-2- phenyl- butyl	2500
H	H	Me	R	>9:1	(R)-2- phenyl- butyl	1500
H	H	Me	R	>9:1	(RS)-2- phenyl- butyl	2300
H	H	Me	R	3:7	(RS)-2- phenyl- butyl	1000
H	H	Me	R	3:7	(R)-2- phenyl- butyl	800
H	H	Me	R	7:3	(RS)-2- phenyl- propyl	700
H	H	Me	R	7:3	(RS)-2- phenyl-3- methoxy propyl	100
H	H	Et	R	>9:1	(RS)-2- phenyl- butyl	250

Table 1 - Continued

H	H	MeCH-(OH)	R	9:1	(RS)-2-phenyl-butyl	100
H	Me	Me	-	1:1	(RS)-2-phenyl-butyl	250
H	H	Me	R	9:1	(2)-phenyl-ethyl	50
3,3-dimethyl-butyl	H	Me	R	>5:1	(S)-2-phenyl-butyl	5500
3,3-dimethyl-butyl	H	Me	R	>9:1	(R)-2-phenyl-butyl	3000
2-ethyl-butyl	H	Me	R	>5:1	(S)-2-phenyl-butyl	3000
3-methyl-butyl	H	Me	R	>5:1	(S)-2-phenyl-butyl	4000
3-3-dimethyl-butyl	H	Me	R	>9:1	cyclo-hexyl-methyl	100
3,3-dimethyl-butyl	H	Me	R	3:7	cyclo-hexyl-methyl	750

1) Relative to a degree of sweetness of a 4% sucrose aqueous solution.

2) The C¹-configuration is (S).

When the compounds of the present invention or the salts thereof are used as sweeteners, the compounds may be used in combination with other sweeteners unless problems arise.

5 EXAMPLE 1

Synthesis of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide

LAH (0.73 g, 19.25 mmols) was suspended in 50 ml of ether, and the suspension was maintained at 0°C. To this
10 suspension were added 3.44 g (11.0 mmols) of N-methoxy-N-methylcarboxamide of N,N-dibenzyl- α -D-alanine. The mixture was stirred at 0°C for 1 hour, and 50 ml of a 1M potassium hydrogensulfate aqueous solution were added thereto. The reaction solution was extracted twice with
15 50 ml of ether. The organic layer was washed with 50 ml of a 5% sodium hydrogencarbonate aqueous solution and with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was
20 concentrated to obtain 2.76 g (10.9 mmols) of (R)-2-N,N-dibenzylaminopropyl aldehyde.

Magnesium (0.24 g, 9.9 mmols) was suspended in 1 ml of THF, and a solution of 1.41 g (6.6 mmols) of (R)-2-phenylbutyl bromide in 2 ml of THF was added dropwise to
25 the suspension. The reaction solution was stirred at room temperature for 1 hour, and 5 ml of THF were added thereto. The mixed solution was cooled to 0°C. To the reaction solution was added a solution obtained by dissolving 1.37 g (5.5 mmols) of the above-obtained (R)-
30 2-N,N-dibenzylaminopropyl aldehyde in 10 ml of THF, and the mixture was stirred at 0°C for 1 hour. To this reaction solution were added 50 ml of a saturated aqueous solution of ammonium chloride, and the mixture was extracted twice with 50 ml of ether. The organic layer
35 was washed with 5% sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate

was removed by filtration, and the filtrate was concentrated. The residue was purified by PTLC to give 1.46 g (3.77 mmols) of N,N-dibenzyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamine (2S:2R = >5:1).

5 N,N-dibenzyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamine (1.46 g, 3.77 mmols) was dissolved in 25 ml of methanol, and 0.43 ml (7.53 mmols) of acetic acid and 0.6 g of 5% palladium on carbon (water content 50%) were added thereto. The reaction solution was stirred
10 under a hydrogen atmosphere at 50°C for 16 hours. Subsequently, the catalyst was removed by filtration, and the filtrate was concentrated. To the residue were added 15 ml of a saturated aqueous solution of sodium hydrogencarbonate, and the mixture was extracted twice
15 with 50 ml of methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, and magnesium sulfate was then removed by filtration. The filtrate was concentrated to obtain 0.61 g (2.96 mmols) of (1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamine.

20 To 30 ml of methylene chloride were added 1.17 g (3.26 mmols) of N-benzyloxycarbonyl-L-aspartic acid-β-benzyl ester and 0.61 g (2.96 mmols) of (1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamine. The reaction solution was cooled to 0°C, and 0.63 g (3.26 mmols) of water-soluble carbodiimide hydrochloride and 0.44 g (3.26
25 mmols) of HOBt were added thereto. The mixture was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, 50 ml of water were
30 added to the residue, and the mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed twice with a 5% citric acid aqueous solution, with 50 ml of water, twice with 50 ml of a 5% sodium hydrogen-carbonate aqueous solution and with 50 ml of a saturated
35 aqueous solution of sodium chloride. After the organic layer was dried over anhydrous magnesium sulfate, magnesium sulfate was removed by filtration. The filtrate

was concentrated under reduced pressure, and was purified with PTLC to obtain N- α -L-(N'-benzyloxycarbonyl- β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide as a viscous oil.

5 N- α -L-(N'-benzyloxycarbonyl- β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide (1.32 g, 2.42 mmols) was dissolved in 40 ml of methanol, and 5 ml of water and 0.85 g of 5% palladium on carbon (water content 50%) were added thereto. The mixed solution was
10 reduced under a hydrogen atmosphere overnight at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was then dried to give 0.72 g (2.23 mmols) of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenyl-
15 hexylamide (2S:2R = 5:1).

^1H NMR(DMSO- d_6) δ : 0.67 (t, 3H), 0.99 (d, 3H), 1.38-1.60 (m, 2H), 1.63-1.76 (m, 2H), 2.53-2.65 (m, 1H), 2.60-2.80 (2dd, 2H), 3.49 (m, 1H), 3.74 (m, 1H), 3.94 (t, 1H), 7.14-7.31 (m, 5H), 8.32 (d, 1H)

20 ESI-MS 323.2 (MH^+)

Degree of sweetness: 2,500 times that of sugar.

EXAMPLE 2

Synthesis of N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide

25 Example 1 was repeated except that (S)-2-phenylbutyl bromide was used instead of (R)-2-phenylbutyl bromide to give N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide (2S:2R = >9:1) as a solid in a total yield of 54.2%.

30 ^1H NMR(DMSO- d_6) δ : 0.69 (t, 3H), 0.93 (d, 3H), 1.45-1.68 (m, 4H), 2.64-2.77 (m, 3H), 3.10 (m, 1H), 3.57 (m, 1H), 3.94 (t, 1H), 7.14-7.31 (m, 5H), 8.28 (d, 1H)

ESI-MS 322.9 (MH^+)

Degree of sweetness: 1,500 times that of sugar.

EXAMPLE 3Synthesis of N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide

Example 1 was repeated except that (RS)-2-phenyl-
5 butyl bromide was used instead of (R)-2-phenylbutyl
bromide to give N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-
hydroxy-4-phenylhexylamide as a solid in a total yield of
16.7%.

¹NMR (DMSO-d₆) δ : 0.66 (t, 1.5H), 0.70 (d, 1.5H), 0.93 (d, 1.5H),
10 0.97 (d, 1.5H), 1.40-1.75 (m, 4H), 2.10-2.65 (m, 3H), 3.00
(m, 0.5H), 3.40 (m, 0.5H), 3.55-3.90 (m, 2H), 7.13-7.29
(m, 5H), 8.07 (brd, 0.5H), 8.17 (brd, 0.5H)

ESI-MS 322.8 (MH⁺)

Degree of sweetness: 2,300 times that of sugar.

15 EXAMPLE 4Synthesis of N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylpentylamide

Example 1 was repeated except that (RS)-2-phenyl-
propyl bromide was used instead of (R)-2-phenylbutyl
20 bromide to give N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-
hydroxy-4-phenylpentylamide (2S:2R = 7:3) as a solid in a
total yield of 29.3%.

¹HNMR (DMSO-d₆) δ : 0.94 (d, 1.5H), 1.00 (d, 1.5H), 1.16
(d, 1.5H), 1.18 (d, 1.5H), 1.46-1.72 (m, 2H), 2.33-2.60 (m, 2H),
25 2.92 (m, 0.5H), 3.06 (m, 0.5H), 3.45-3.83 (m, 2H), 7.12-7.38
(m, 5H), 8.14 (d, 0.5H), 8.24 (d, 0.5H)

ESI-MS 309.3 (MH⁺)

Degree of sweetness: 700 times that of sugar.

EXAMPLE 530 Synthesis of N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenyl-5-methoxypentylamide

Example 1 was repeated except that (RS)-2-phenyl-3-
methoxypropyl bromide was used instead of (R)-2-
phenylbutyl bromide to give N- α -L-aspartyl-(1R, 2S, 4RS)-
35 1-methyl-2-hydroxy-4-phenyl-5-methoxypentylamide (2S:2R =
7:3) as a solid in a total yield of 34.5%.

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$^1\text{H NMR}$ (DMSO- d_6) δ : 0.93 (d, 1.5H), 0.98 (d, 1.5H), 1.46-1.84 (m, 2H), 2.68-2.80 (m, 2H), 2.94-3.22 (m, 2H), 3.18 (s, 3H), 3.29-3.53 (m, 2H), 3.53-3.78 (m, 1H), 3.90-4.00 (m, 1H), 7.14-7.32 (m, 5H), 8.30 (d, 0.5H), 8.39 (d, 0.5H)

5 ESI-MS 339.1 (MH^+)

Degree of sweetness: 100 times that of sugar.

EXAMPLE 6

Synthesis of N- α -L-aspartyl-(1R, 2S, 4RS)-1-ethyl-2-hydroxy-4-phenylhexylamide

10 Example 1 was repeated except that (RS)-2-phenylbutyl bromide was used instead of (R)-2-phenylbutyl bromide and N-methoxy-N-methylcarboxyamide of N,N-dibenzyl- α -D-aminobutyric acid instead of N-methoxy-N-methylcarboxyamide of N,N-dibenzyl- α -D-alanine respectively. Consequently, N- α -L-aspartyl-(1R, 2S, 4RS)-1-ethyl-2-hydroxy-4-phenylhexylamide (2S:2R = >9:1) was obtained as a solid in a total yield of 35.3%.

15 $^1\text{H NMR}$ (DMSO- d_6) δ : 0.60-0.84 (m, 6H), 1.15-1.78 (m, 6H), 2.33-2.75 (m, 3H), 2.97 (m, 1H), 3.45 (m, 1H), 3.59 (m, 1H), 3.77 (m, 1H), 7.13-7.38 (m, 5H), 7.95-8.23 (brd, 1H)

20 ESI-MS 337.5 (MH^+)

Degree of sweetness: 250 times that of sugar.

EXAMPLE 7

Synthesis of N- α -L-aspartyl-(1R, 2S, 4RS)-1- α -hydroxyethyl-2-hydroxy-4-phenylhexylamide

25 Example 1 was repeated except that (RS)-2-phenylbutyl bromide was used instead of (R)-2-phenylbutyl bromide and N-methoxy-N-methylcarboxyamide of N,N-dibenzyl-O-benzyl- α -D-threonine instead of N-methoxy-N-methylcarboxyamide of N,N-dibenzyl- α -D-alanine respectively. Consequently, N- α -L-aspartyl-(1R, 2S, 4RS)-1- α -hydroxyethyl-2-hydroxy-4-phenylhexylamide (2S:2R = 9:1) was obtained as a solid in a total yield of 16.7%.

30 $^1\text{H NMR}$ (DMSO- d_6) δ : 0.60-0.72 (m, 3H), 0.82-0.98 (m, 3H), 1.30-1.84 (m, 4H), 2.24-2.40 (m, 2H), 2.50-2.60 (m, 1H), 2.66-2.80 (m, 1H), 2.35-3.65 (m, 1H), 3.65-3.90 (m, 1H), 4.00-4.40 (m, 1H), 7.12-7.34 (m, 5H), 8.06 (brs, 1H)

ESI-MS 353.6 (MH⁺)

Degree of sweetness: 100 times that of sugar.

EXAMPLE 8

Synthesis of N- α -L-aspartyl-(1R, 2S)-1-methyl-2-hydroxy-4-phenylbutylamide

Example 1 was repeated except that 2-phenylethyl bromide was used instead of (R)-2-phenylbutyl bromide to give N- α -L-aspartyl-(1R, 2S)-1-methyl-2-hydroxy-4-phenylbutyl-amide (2S:2R = 9:1) as a solid in a total yield of 28.5%.

¹HNMR (DMSO-d₆) δ : 1.00 (d, 3H), 1.46-1.65 (m, 1H), 1.65-1.73 (m, 1H), 2.19 (dd, 1H), 2.39 (dd, 1H), 2.55-2.60 (m, 1H), 2.69-2.80 (m, 1H), 3.30-3.38 (m, 1H), 3.58-3.64 (m, 1H), 3.66-3.74 (m, 1H)

ESI-MS 295.2 (MH⁺)

Degree of sweetness: 50 times that of sugar.

EXAMPLE 9

Synthesis of N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide

LAH (0.40 g, 10.5 mmols) was suspended in 20 ml of ether, and the suspension was maintained at 0°C. To this suspension were added 1.63 g (7.0 mmols) of N-methoxy-N-methylcarboxamide of N-tert-butoxycarbonyl- α -D-alanine. The mixture was stirred at 0°C for 1 hour, and 25 ml of a 1M potassium hydrogensulfate aqueous solution were added thereto. The reaction solution was extracted twice with 50 ml of ether. The organic layer was washed with 50 ml of a 5% sodium hydrogencarbonate aqueous solution and with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was concentrated to obtain 1.21 g (7.0 mmols) of (R)-2-N-tert-butoxycarbonylaminopropyl aldehyde as a solid.

Magnesium (0.63 g, 26.3 mmols) was suspended in 2 ml of THF, and a solution of 3.73 g (17.5 mmols) of (RS)-2-phenylbutyl bromide in 3 ml of THF was added dropwise to the suspension. The reaction solution was stirred at room

temperature for 1 hour, and 5 ml of THF were then added thereto. The mixed solution was cooled to -78°C . To the reaction solution was added a solution obtained by dissolving 1.21 g (7.0 mmols) of the above-obtained (R)-
5 2-N-tert-butoxycarbonylaminopropyl aldehyde in 10 ml of THF. The temperature was gradually elevated from -78°C , and the mixture was then stirred at room temperature for 15 hours. To this reaction solution were added 50 ml of a saturated aqueous solution of ammonium chloride, and the
10 mixture was extracted twice with 50 ml of ether. The organic layer was washed with 5% sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was
15 concentrated. The residue was purified with PTLC to obtain 0.91 g (2.96 mmols) of (1R, 2S, 4RS)-N-tert-butoxycarbonyl-1-methyl-2-hydroxy-4-phenylhexylamine (2S:2R = 3:7) as an oil.

Fifteen milliliters of a solution containing 4N HCl
20 and dioxane were added to 0.91 g (2.96 mmols) of (1R, 2R, 4RS)-N-tert-butoxycarbonyl-1-methyl-2-hydroxy-4-phenylhexylamine, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was
25 further concentrated after the addition of 25 ml of ether. The resulting residue was dissolved in 25 ml of methylene chloride. The reaction solution was cooled to 0°C , and 1.17 g (3.26 mmols) of N-benzyloxycarbonyl-L-aspartic acid- β -benzyl ester, 0.45 ml (3.26 mmols) of
30 triethylamine, 0.63 g (3.26 mmols) of water-soluble carbodiimide and 0.44 g (3.26 mmols) of HOBt were added thereto. The reaction solution was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction solution was concentrated
35 under reduced pressure, 50 ml of water were added to the residue, and the resulting solution was extracted twice with 50 ml of ethyl acetate. The organic layer was washed

twice with 50 ml of a 5% citric acid aqueous solution, with 50 ml of water, with 50 ml of a 5% sodium hydrogencarbonate aqueous solution and with 50 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and magnesium sulfate was then removed by filtration. The filtrate was concentrated under reduced pressure, and was purified with PTCL to obtain 1.15 g (2.11 mmols) of N- α -L-(N'-benzyloxycarbonyl- β -O-benzylaspartyl)-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide as a viscous oil.

N- α -L-(N'-benzyloxycarbonyl- β -O-benzylaspartyl)-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide (1.15 g, 2.11 mmols) was dissolved in 35 ml of methanol, and 5 ml of water and 0.35 g of 5% palladium on carbon (water content 50%) were added thereto. The mixed solution was reduced under a hydrogen atmosphere overnight at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was then dried to give 0.59 g (1.84 mmols) of N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide (2S:2R = 3:7) as a solid.

$^1\text{H NMR}$ (DMSO- d_6) δ : 0.67 (t, 1.5H), 0.69 (t, 1.5H), 0.91 (d, 1.5H), 0.96 (d, 1.5H), 1.40-1.75 (m, 4H), 2.40-2.70 (m, 3H), 2.95-3.90 (m, 3H), 7.10-7.35 (m, 5H), 8.07 (brs, 1H)

ESI-MS 323.1 (MH^+)

Degree of sweetness: 1,000 times that of sugar.

EXAMPLE 10

Synthesis of N- α -L-aspartyl-(1R, 2R, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide

Example 9 was repeated except that (S)-2-phenylbutyl bromide was used instead of (RS)-2-phenylbutyl bromide to give N- α -L-aspartyl-(1R, 2R, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide (2S:2R = 3:7) as a solid in a total yield of 38.6%.

¹HNMR (DMSO-d₆) δ: 0.58-0.73 (m, 3H), 0.88-1.00 (m, 3H), 1.35-1.75 (m, 4H), 2.45-2.75 (m, 3H), 3.05-3.95 (m, 3H), 7.13-7.32 (m, 5H), 8.07 (d, 1H)

ESI-MS 323.1 (MH⁺)

5 Degree of sweetness: 800 times that of sugar.

EXAMPLE 11

Synthesis of N- α -L-aspartyl-(2RS, 4RS)-1,1-dimethyl-2-hydroxy-4-phenylhexylamide

Example 9 was repeated except that N-methoxy-N-methylcarboxyamide of N-tert-butoxycarbonyl- α,α -dimethylglycine was used instead of N-methoxy-N-methylcarboxyamide of N-tert-butoxycarbonyl- α -D-alanine to give N- α -aspartyl-(2RS, 4RS)-1,1-dimethyl-2-hydroxy-4-phenylhexylamide as a solid in a total yield of 8.3%.

15 ¹HNMR (DMSO-d₆) δ: 0.64-0.75 (m, 3H), 1.05-1.25 (m, 6H), 1.25-1.90 (m, 4H), 2.10-2.50 (m, 2H), 2.58 (m, 1H), 3.05 (m, 1H), 3.45-3.90 (m, 2H), 7.13-7.30 (m, 5H), 7.93 (brs, 0.5H), 8.07 (brd, 0.5H)

ESI-MS 337.6 (MH⁺)

20 Degree of sweetness: 250 times that of sugar.

EXAMPLE 12

Synthesis of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide

N-tert-butoxycarbonyl-L-aspartic acid- β -benzyl ester (0.91 g, 2.80 mmols) and 0.58 g (2.80 mmols) of (1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamine (0.58 g, 2.80 mmols) which had been prepared as in Example 1 were added to 30 ml of methylene chloride. The reaction solution was cooled to 0°C, and 0.59 g (3.08 mmols) of water-soluble carbodiimide hydrochloride and 0.42 g (3.08 mmols) of HOBT were added thereto. The mixed solution was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction mixture was concentrated under reduced pressure, 50 ml of water were added to the residue, and the mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed twice with a 5% citric acid aqueous solution, with 50 ml of water,

twice with a 5% sodium hydrogencarbonate aqueous solution and with 50 ml of a saturated aqueous solution of sodium chloride. After the organic layer was dried over anhydrous magnesium sulfate, magnesium sulfate was removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 1.43 g (2.78 mmols) of N- α -L-(N'-tert-butoxycarbonyl- β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenyl-hexylamide as a viscous oil.

10 Seven milliliters of a solution containing 4-N HCl and dioxane were added to 1.43 g (2.78 mmols) of N- α -L-(N'-tert-butoxycarbonyl- β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, and the mixture was stirred at room temperature for 1 hour. The reaction
15 solution was concentrated under reduced pressure, and 50 ml of a 5% sodium hydrogencarbonate aqueous solution were added to the residue. The mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and
20 was dried over anhydrous magnesium sulfate. Magnesium sulfate was then removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 1.13 g (2.73 mmols) of N- α -L-(β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide as a pale yellow
25 oil.

N- α -L-(β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide (1.13 g, 2.73 mmols) was suspended in 20 ml of THF, and the suspension was maintained at 0°C. To this suspension were added 0.16 ml
30 (2.73 mmols) of acetic acid, 0.34 ml (2.73 mmols) of 3,3-dimethylbutyl aldehyde and 0.87 g (4.10 mmols) of NaB(OAc)₃H. The mixture was stirred at 0°C for 1 hour and then overnight at room temperature. To the reaction solution were added 30 ml of a saturated aqueous solution
35 of sodium hydrogencarbonate, and the mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of

sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was then removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified with PTLC to
 5 obtain 1.04 g (2.09 mmols) of N- α -L-(N'-3,3-dimethylbutyl- β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide as a pale yellow oil.

N- α -L-(N'-3,3-dimethylbutyl- β -O-benzylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide (1.04 g, 2.09 mmols) was dissolved in 40 ml of methanol, and 5 ml
 10 of water and 0.50 g of 5% palladium on carbon (water content 50%) were added thereto. The solution was reduced under a hydrogen atmosphere overnight at room temperature. The catalyst was removed by filtration, and
 15 the filtrate was concentrated under reduced pressure. The residue was then dried to give 0.74 g (1.81 mmols) of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide (2S:2R = >5:1) as a solid.

$^1\text{H NMR}$ (DMSO- d_6) δ : 0.66 (t, 3H), 0.83 (s, 9H), 1.00 (d, 3H),
 20 1.35-1.56 (m, 4H), 1.63-1.76 (m, 2H), 2.55-2.72 (m, 5H), 3.40-3.48 (m, 1H), 3.75-3.88 (m, 2H), 4.70 (brs, 1H), 7.10-7.30 (m, 5H), 8.34 (d, 1H)

ESI-MS 407.4 (MH^+)

Degree of sweetness: 5,500 times that of sugar.

25 EXAMPLE 13

Synthesis of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide

Example 12 was repeated except that (S)-2-phenylbutyl bromide was used instead of (R)-2-phenylbutyl
 30 bromide to give N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide (2S:2R = >9:1) as a solid in a total yield of 52.2%.

$^1\text{H NMR}$ (DMSO- d_6) δ : 0.69 (t, 3H), 0.85 (s, 9H), 0.93 (d, 3H),
 35 1.38-1.66 (m, 6H), 2.60-2.78 (m, 5H), 3.00-3.10 (m, 1H), 3.58-3.67 (m, 1H), 3.81 (t, 1H), 7.10-7.30 (m, 5H), 4.60 (brs, 1H), 8.26 (d, 1H)

ESI-MS 407.4 (MH⁺)

Degree of sweetness: 3,000 times that of sugar.

EXAMPLE 14

Synthesis of N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide

Example 12 was repeated except that 2-ethylbutyl aldehyde was used instead of 3,3-dimethylbutyl aldehyde to give N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide as a solid in a total yield of 30.6%.

¹HNMR(DMSO-d₆) δ : 0.66(t, 3H), 0.79(t, 6H), 1.00(d, 3H), 1.22-1.36(m, 4H), 1.36-1.54(m, 3H), 1.64-1.77(m, 2H), 2.50-2.66(m, 5H), 3.38(brs, 1H), 3.67(t, 1H), 3.73-3.83(m, 1H), 4.66(brs, 1H), 7.10-7.23(m, 5H), 8.17(d, 1H)

ESI-MS 407.4 (MH⁺)

Degree of sweetness: 3,000 times that of sugar.

Example 15

Synthesis of N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide

Example 12 was repeated except that 3-methylbutyl aldehyde was used instead of 3,3-dimethylbutyl aldehyde to give N- α -L-(N'-3-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide as a solid in a total yield of 25.4%.

¹HNMR(DMSO-d₆) δ : 0.66(t, 3H), 0.83(d, 3H), 0.84(d, 3H), 1.00(d, 3H), 1.30-1.62(m, 5H), 1.62-1.76(m, 2H), 2.40-2.54(m, 3H), 2.60(t, 2H), 3.34-3.44(m, 1H), 3.64(t, 1H), 3.70-3.80(m, 1H), 4.67(brs, 1H), 7.12-7.32(m, 5H), 8.14(d, 1H)

ESI-MS 393.4 (MH⁺)

Degree of sweetness: 4,000 times that of sugar.

EXAMPLE 16

Synthesis of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S)-1-methyl-2-hydroxy-3-cyclohexylpropylamide

Example 12 was repeated except that cyclohexylmethyl bromide was used instead of (R)-2-phenylbutyl bromide to give N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S)-1-

methyl-2-hydroxy-3-cyclohexylpropylamide as a solid in a total yield of 11.3%.

¹HNMR (DMSO-d₆) δ: 0.88 (s, 9H), 0.99 (d, 3H), 0.80-1.80 (m, 15H), 2.60 (d, 2H), 2.69 (t, 2H), 3.41-3.48 (m, 1H), 3.62-3.72 (m, 1H), 3.77 (t, 1H), 4.57 (brs, 1H), 8.25 (d, 1H)

ESI-MS 371.4 (MH⁺)

Degree of sweetness: 100 times that of sugar.

EXAMPLE 17

Synthesis of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexylpropylamide

LAH (0.66 g, 17.5 mmols) was suspended in 40 ml of ether, and the suspension was maintained at 0°C. To this suspension were added 2.32 g (10.0 mmols) of N-methoxy-N-methylcarboxamide of N-tert-butoxycarbonyl- α -D-alanine. The mixture was stirred at 0°C for 1 hour, and 25 ml of a 1M potassium hydrogensulfate aqueous solution were then added thereto. The reaction solution was extracted twice with 50 ml of ether. The organic layer was washed with 50 ml of a 5% sodium hydrogencarbonate aqueous solution and with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was concentrated to obtain 1.29 g (7.43 mmols) of (R)-2-N-tert-butoxycarbonylaminopropyl aldehyde as a solid.

Magnesium (0.68 g, 27.8 mmols) was suspended in 2 ml of THF, and a solution of 3.29 g (18.6 mmols) of cyclohexylmethyl bromide in 3 ml of THF was added dropwise to the suspension. The reaction solution was stirred at room temperature for 1 hour, and 5 ml of THF were added thereto. The mixed solution was cooled to -78°C. To the reaction solution was added a solution obtained by dissolving 1.29 g (7.43 mmols) of the above-obtained (R)-2-N-tert-butoxycarbonylaminopropyl aldehyde in 10 ml of THF. The temperature was gradually elevated from -78°C, and the mixture was then stirred at room temperature for 15 hours. To this reaction solution were added 50 ml of a saturated aqueous solution of ammonium

chloride, and the mixture was extracted twice with 50 ml of ether. The organic layer was washed with 5% sodium hydrogencarbonate and with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was removed by filtration, and the filtrate was concentrated. The residue was purified with PTLC to obtain 0.88 g (3.25 mmols) of (1R, 2R)-N-tert-butoxycarbonyl-1-methyl-2-hydroxy-3-cyclohexylpropylamine (2S:2R = 3:7) as an oil.

Fifteen milliliters of a solution containing 4-N HCl and dioxane were added to 0.88 g (3.25 mmols) of (1R, 2R)-N-tert-butoxycarbonyl-1-methyl-2-hydroxypropylamine, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the residue was further concentrated after the addition of 25 ml of ether. The resulting residue was dissolved in 30 ml of methylene chloride, and the solution was cooled to 0°C. N-tert-butoxycarbonyl-L-aspartic acid- β -benzyl ester 1.11 g (3.42 mmols), 0.50 ml (3.58 mmols) of triethylamine, 0.69 g (3.58 mmols) of water-soluble carbodiimide and 0.48 g (3.58 mmols) of HOBt were added to the above-obtained solution. The mixture was stirred for 1 hour while being cooled and then overnight at room temperature. After the reaction solution was concentrated under reduced pressure, 50 ml of water were added to the residue, and the mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed twice with 50 ml of a 5% citric acid aqueous solution, with 50 ml of water, twice with a 5% sodium hydrogencarbonate aqueous solution and with 50 ml of a saturated aqueous solution of sodium chloride. The organic layer was dried over anhydrous magnesium sulfate, and magnesium sulfate was then removed by filtration. The filtrate was concentrated under reduced pressure, and was purified through PTLC to obtain 0.81 g (1.69 mmols) of N- α -L-(N'-tert-

butoxycarbonyl- β -O-benzylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexyl-propylamide as a viscous oil.

Eight milliliters of a solution containing 4-N HCl and dioxane were added to 0.81 g (1.69 mmols) of N- α -L-(N'-tert-butoxycarbonyl- β -O-benzylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexylpropylamide, and the mixture was stirred at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and 50 ml of a 5% sodium hydrogencarbonate aqueous solution were added to the residue. The mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was then removed by filtration, and the filtrate was concentrated under reduced pressure to obtain 0.60 g (1.60 mmols) of N- α -L-(β -O-benzylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexylpropylamide as a pale yellow viscous oil.

N- α -L-(β -O-benzylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexylpropylamide (0.60 g, 1.60 mmols) was suspended in 12 ml of THF, and the suspension was maintained at 0°C. To this suspension were added 0.092 ml (1.60 mmols) of acetic acid, 0.20 ml (1.60 mmols) of 3,3-dimethylbutyl aldehyde and 0.51 g (2.41 mmols) of NaB(OAc)₃H. The mixture was stirred at 0°C for 1 hour and then overnight at room temperature. Twenty milliliters of a saturated aqueous solution of sodium hydrogencarbonate were added to the reaction solution, and the mixture was extracted twice with 50 ml of ethyl acetate. The organic layer was washed with a saturated aqueous solution of sodium chloride, and was dried over anhydrous magnesium sulfate. Magnesium sulfate was then removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified with PTLC to obtain 0.50 g (1.09 mmols) of N- α -L-(N'-3,3-dimethylbutyl- β -O-benzylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexylpropylamide as a pale yellow oil.

N- α -L-(N'-3,3-dimethylbutyl- β -O-benzylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexylpropylamide (0.50 g, 1.09 mmols) was dissolved in 30 ml of methanol, and 5 ml of water and 0.25 g of 5% palladium on carbon (water content 50%) were added thereto. The solution was reduced under a hydrogen atmosphere at room temperature for 4 hours. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was then dried to give 0.36 g (0.98 mmols) of N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2R)-1-methyl-2-hydroxy-3-cyclohexylpropylamide as a solid.

¹HNMR (DMSO-d₆) δ : 0.86 (s, 9H), 1.02 (d, 3H), 0.80-1.74 (m, 15H), 2.48-2.56 (m, 2H), 2.60-2.70 (m, 2H), 3.40-3.55 (m, 1H), 3.63-3.83 (m, 2H), 4.53 (brs, 1H), 8.06 (d, 1H)

ESI-MS 371.4 (MH⁺)

Degree of sweetness: 750 times that of sugar.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. An aspartylamide derivative selected from the group consisting of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide and salts thereof.
2. The aspartylamide derivative according to claim 1, which is N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.
3. The aspartylamide derivative according to claim 1, which is N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.
4. The aspartylamide derivative according to claim 1, which is N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.
5. The aspartylamide derivative according to claim 1, which is N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.
6. The aspartylamide derivative according to claim 1, which is N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

7. The aspartylamide derivative according to claim 1, which is N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

8. The aspartylamide derivative according to claim 1, which is N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

9. The aspartylamide derivative according to claim 1, which is N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

10. A sweetener containing, as the active ingredient, an aspartylamide derivative selected from the group consisting of N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide, N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide and salts thereof.

11. The sweetener according to claim 10, wherein the active ingredient is N- α -L-aspartyl-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

12. The sweetener according to claim 10, wherein the active ingredient is N- α -L-aspartyl-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

13. The sweetener according to claim 10, wherein the active ingredient is N- α -L-aspartyl-(1R, 2S, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

14. The sweetener according to claim 10, wherein the active ingredient is N- α -L-aspartyl-(1R, 2R, 4RS)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

15. The sweetener according to claim 10, wherein the active ingredient is N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

16. The sweetener according to claim 10, wherein the active ingredient is N- α -L-(N'-3,3-dimethylbutylaspartyl)-(1R, 2S, 4R)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

17. The sweetener according to claim 10, wherein the active ingredient is N- α -L-(N'-2-ethylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.

18. The sweetener according to claim 10, wherein the active ingredient is N- α -L-(N'-3-methylbutylaspartyl)-(1R, 2S, 4S)-1-methyl-2-hydroxy-4-phenylhexylamide or salt thereof.