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(21) International Application Number: PCT/US94/10046 (22) International Filing Date: 7 September 1994 (07.09.94) (30) Priority Data: 118,188 9 September 1993 (09.09.93) US (60) Parent Application or Grant (63) Related by Continuation US 118,188 (CON) Filed on 9 September 1993 (09.09.93) (71) Applicant (for all designated States except US): THE GILLETTE COMPANY [US/US]; Prudential Tower Building, Boston, MA 02199 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): LANEY, Judith, Wolfe [US/US]; 12018 Auth Lane, Silver Spring, MD 20902 (US). (74) Agents: HANDELMAN, Joseph, H. et al.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: O-ACYL SERINES AS DEODORANTS (57) Abstract The invention relates to a method of suppressing human body malodor by utilizing a deodorant composition containing a competitive substrate for the enzymatic creation of axillary body malodor. The compound is present in a dermatologically acceptable vehicle, and in an amount effective to reduce the conversion of malodor producing precursor. The present invention also relates to novel O-acylated serine compounds and method for the production thereof.		

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O-ACYL SERINES AS DEODORANTS

The present invention relates to deodorants, a method of suppressing human body odor, compounds useful as deodorants and method
5 for the production thereof.

The eccrine and apocrine sweat glands are the structures of the human body responsible for sweat. The apocrine glands become active at puberty and produce an odorless proteinaceous
10 secretion. Axillary bacteria act on the apocrine secretions to produce the pungent odor known as axillary malodor.

Current deodorants are generally of three types: odor maskers, antiperspirants, and
15 germicides. Despite the many disclosures in the art pertaining to deodorant compositions, current products are not sufficient to suppress odor in a significant proportion of the population, particularly during periods of
20 "stress." There remains a need for new deodorant compositions and methods which are effective, safe and economical.

The present invention relates to a deodorant composition comprising a compound
25 which is capable of serving as an alternative substrate to the naturally occurring malodor producing precursor. The compound is present in

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a dermatologically acceptable vehicle, and in an amount effective to reduce the conversion of malodor producing precursor.

5 The present invention further relates to a method for suppressing body malodor which includes the application to the skin of the deodorant composition of the present invention.

10 The present invention also relates to novel O-acylated serine compounds and a method for the production thereof.

15 The current invention is a novel method of suppressing body odor by the topical application of compounds which compete with the naturally occurring malodor producing precursor. The compounds are O-acylated serine derivatives. Deodorant compositions containing at least one compound from the specified group of O-acylated serine derivatives in an effective concentration will serve to suppress axillary malodor when
20 applied to the underarm. Tests indicate that these compositions significantly attenuate the body odors formed in the axilla. In a preferred embodiment, the O-acylated serine derivatives may generate pleasant odors in the axilla
25 concomitant with suppressing the malodor.

Axillary malodor is generated by certain skin bacteria in the presence of apocrine secretion. Two strains of bacteria which produce axillary malodor when incubated
30 with human apocrine secretions are Staphylococcus and several Coryneform isolates. Production of human axillary malodor can be assayed from these strains of bacteria by incubating cells with apocrine secretions
35 collected from human axilla that has been sterilized in a phosphate buffer at pH 6.8. The volatile malodor compound is extracted into

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chloroform and smelled after spotting on filter paper.

The conversion of the naturally occurring apocrine precursor to axillary malodor occurs within the bacterial cells. Extracts of bacteria are capable of converting the precursor to the malodor compound in an enzymatic process. The enzyme which is designated as the malodor-forming enzyme has been found to be a pyridoxal phosphate dependent amino acid lyase. The enzyme acts to cleave amino acids with the general structure $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-X}$ where X is S-R or O-R. The products of the reaction are pyruvate, ammonia, and XH.

The naturally occurring apocrine precursor to axillary malodor is a sulfur containing amino acid. It has now been found that the production of axillary malodor is blocked if an alternative substrate for the malodor-forming enzyme is provided, so that the alternative substrate is cleaved instead of the apocrine precursor. The alternative substrates produce either a neutral odor or a pleasant odor upon cleavage.

Certain amino acids and amino acid analogues can serve as deodorants in this fashion, i.e., these amino acids and amino acid analogues serve as alternative substrates for the malodor-forming enzyme and produce a neutral or pleasant odor. As stated above, the malodor-forming enzyme cleaves amino acids and amino acid analogues having the general structure, $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-X}$ where X is S-R or O-R.

In the present invention, O-acylated serine derivatives are employed with an R group which results in the production of neutral or pleasant odors. The general structure of the O-

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acyl serines of the present invention is $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-R}$. The R group may be a) a branched or straight alkyl, alkenyl, or alkynyl chain of one to about seventeen carbon atoms
5 that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, carboxyl, or phenyl that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, or carboxyl; or b) a phenyl
10 that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, or carboxyl, or an aliphatic carbon chain of one to about eight carbon atoms that is unsubstituted or substituted with one or more halo, hydroxyl,
15 amino, nitro, amide, carboxyl, or phenyl that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, or carboxyl.

Suitable substrates include compounds
20 such as O-succinyl serine, O-benzoyl serine, O-phenylacetyl serine, O-malonyl serine, O-acetyl serine, O-oleoyl serine, O-palmitoyl serine, O-cinnamoyl serine, O-p-aminobenzoyl serine, O-lactoyl serine, O-salicyloyl serine, O-
25 sarcosinoyl serine, O-2-ethyl hexanoyl serine, and the like.

For example, the malodor-forming enzyme cleaves O-benzoyl serine (i.e., where X is O-benzoyl) to produce non-odorous benzoic
30 acid. Suitable R groups of the O-acyl serines of the present invention include $-\text{CH=CH-C}_6\text{H}_5$ which is cleaved to produce cinnamic acid; $-\text{C}_6\text{H}_4\text{NH}_2$ which is cleaved to produce p-aminobenzoic acid; $-\text{CH(OH)CH}_3$ which is cleaved
35 to produce lactic acid; $-\text{C}_6\text{H}_4\text{OH}$ which is cleaved to produce salicylic acid; $-\text{C}_2\text{H}_4\text{NH}_2$ which is cleaved to produce sarcosine; and

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-CH(C₂H₅)-(CH₂)₃-CH₃ which is cleaved to produce 2-ethyl hexanoic acid.

Suitable O-acyl serines of the present invention can be prepared by the following procedure. Initially, protected serine is esterified with the desired R group compound, such as by esterification mediated by dicyclohexylcarbodiimide. The intermediate product may then be purified according to conventional purification techniques and recrystallized. The recrystallized intermediate product is then hydrogenated in the presence of an appropriate catalyst, e.g., palladium/carbon, to remove the protecting groups and yield the corresponding O-acyl serine.

The presence of the O-acyl serine in adequate quantities will compete with the natural precursor and at least reduce, if not almost entirely prevent the conversion of the natural precursor to the malodor compound.

In addition, when certain of these alternative substrates are cleaved, pleasant odors are produced. These O-acylated serine derivatives are generally those in which the R group is an aromatic or branched chain aliphatic group. The acid that results from cleavage is pleasant smelling. The compound O-phenylacetyl serine is converted to phenylacetic acid, a compound that smells of honey, which is an example of such a cleavage product.

The presence of an alternative substrate such as the above compound in moderate quantities competes with the natural precursor which is present in low quantities, typically about one nanomole/axilla. Such competition almost completely prevents the malodor precursor from being converted. These compounds therefore

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serve as deodorants.

Although deodorancy is the most important concern for the consumer of underarm products, many also choose a product with antiperspirant activity. Current antiperspirant compounds, which are aluminum salts, also function as deodorants by virtue of their germicidal properties. Thus, if desired, the deodorants of the present invention can be employed with the antiperspirant salts well known in the art. In such formulations, the O-acylated serine derivatives can be incorporated into a deodorant or antiperspirant formulation along with an antiperspirant salt, wherein the antiperspirant salt may be employed in a perspiration reducing effective concentration, e.g., 6 to 30% or in a deodorant effective concentration, e.g., 1 to 6%.

The antiperspirant salt used in the present invention may be any of those which contain aluminum, either alone or in combination with other materials such as zirconium. Typical aluminum salts, although not all-inclusive, include:

Aluminum chlorohydrate;
Aluminum sesquichlorohydrate;
Aluminum dichlorohydrate;
Aluminum chlorohydrate PG or PEG;
Aluminum sesquichlorohydrate PG or PEG;
Aluminum dichlorohydrate PG or PEG;
Aluminum zirconium trichlorohydrate;
Aluminum zirconium tetrachlorohydrate;
Aluminum zirconium tetrachlorohydrate PG or PEG;
Aluminum zirconium pentachlorohydrate;
Aluminum zirconium octachlorohydrate;
Aluminum zirconium trichlorohydrate-

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gly;

Aluminum zirconium tetrachlorohydrate;

gly;

Aluminum zirconium pentachlorohydrate;

5

gly;

Aluminum zirconium octachlorohydrate;

gly;

Aluminum zirconium chloride;

Aluminum zirconium sulfate;

10

Potassium aluminum sulfate;

Sodium aluminum chlorohydroxyacetate;

Aluminum bromohydrate.

In general, the active antiperspirant salt is present in the same amounts at which such materials are employed in prior art compositions. As a general rule, such compositions contain from about 3% to about 30%, preferably from about 10% to about 25%, of the active antiperspirant salt component.

15

20

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given. It is understood that these examples are intended only to be illustrative without serving to limit the scope of the present invention.

25

Evaluation of O-acyl serines that produce neutral or odorless products

Example 1

As a representative of the class, O-benzoyl serine was evaluated and was found to be effective as a substrate of the malodor enzyme at concentrations of 0.5 millimolar and above. When tested as described above for the ability to block malodor formation by bacterial cells, the minimum concentration needed for complete inhibition was 25 millimolar.

30

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Example 2

O-succinyl serine was evaluated and was found to be effective as a substrate of the malodor enzyme at concentrations of 1 millimolar and above. When tested as described above for the ability to block malodor formation by bacterial cells, the minimum concentration needed for complete inhibition was 150 millimolar.

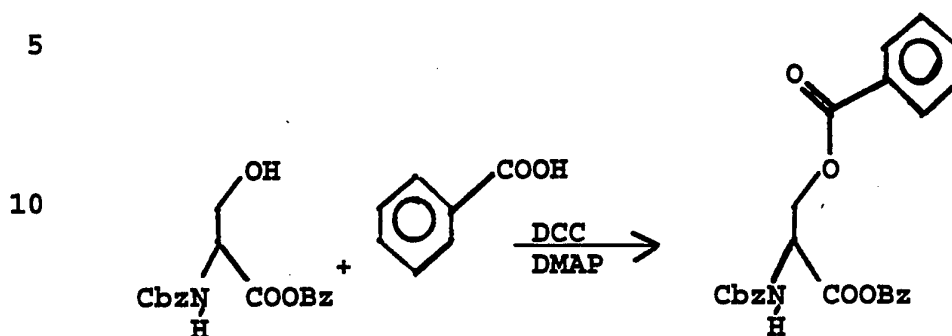
10 Evaluation of O-acyl serines
 that produce a pleasant odor

Example 3

15 O-phenylacetyl serine was tested as described above for the ability to inhibit malodor in vitro while producing in its place a pleasant odor. The compound blocked malodor production at a concentration of 25 millimolar while producing a pleasant, honey-like fragrance.

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Preparation of
O-benzoyl Serine

Example 4

Step 1

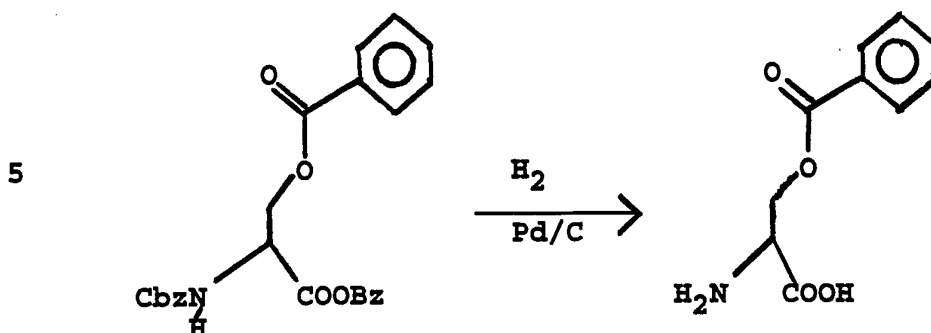
<u>Ingredient</u>	<u>Amount</u>
Cbz-serine-benzyl ester	12.72 g (0.039 mol)
benzoic acid	4.5 g (0.037 mol)
dimethyl amino pyridine ("DMAP")	0.382 g (0.003 mol)
dicyclohexylcarbodiimide ("DCC")	7.6 g (0.037 mol)

25 Dissolve benzoic acid in CH_2Cl_2 (200 mL). Add carbobenzyloxy-serine-benzyl ester and DMAP. Cool on ice bath. Add DCC. Keep on ice bath for 5 minutes, then remove ice and stir at room temperature under N_2 for 4 hours.

30 Filter to remove precipitated dicyclohexyl urea. Concentrate to dryness, then re-dissolve in CH_2Cl_2 and filter to remove any new precipitate. Wash twice with 1N HCl then once with saturated NaHCO_3 . Dry organic layer over MgSO_4 and concentrate in vacuo. The crude product is recrystallized from 2-propanol to give carbobenzyloxy-benzoyl-serine-benzyl ester as a white solid, m.p. 94-95°C.

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10 Step 2

<u>Ingredient</u>	<u>Amount</u>
Cbz-PhCO-serine-benzyl ester	10.8 g (0.25 mol)
10% Pd/carbon	3 g

The protected amino acid, carbobenzyloxy-benzoyl-serine-benzyl ester, is placed in a large flask and dissolved in methanol (500 mL) with stirring. Stirring is stopped, and the Pd/C catalyst added slowly. The vessel is purged with H_2 for 1 minute. The reaction is then stirred under H_2 (1 atmosphere) overnight. The reaction mixture is filtered through a pad of Celite, the pad is rinsed with MeOH, and the combined filtrate and rinsings are concentrated in vacuo to give the product O-benzoyl serine as a white solid, m.p. 125-130 (decomposed).

Formulations for Deodorant Use

The concentration of O-acylated serine derivative employed in topical applications should be consistent with efficacy, economy and safety. The O-acylated serine derivatives of the present invention are employed in a malodor precursor competing amount in a dermatologically acceptable vehicle, and are efficacious at concentrations between about 5 micromolar and about 500 millimolar, i.e., about 0.01% to about 10% by weight. The most preferred range is from

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about 50 micromolar to about 100 millimolar. This constitutes a weight percent of about 0.1% to about 2% by weight as the most preferred range of active ingredient.

5 If desired, the O-acylated serine derivatives of the present invention can also be employed in combination with an antiperspirant salt. In such case, the O-acylated serine derivative is added to a standard deodorant or
10 antiperspirant formulation containing the antiperspirant salt in the same concentrations as set forth above.

Examples of various formulations are given below:

15 Example 5

Deodorant Stick

	<u>Ingredient</u>	<u>% by weight</u>
	propylene glycol	78
	sodium stearate C-1	7.9
20	fragrance	0.1
	water	13
	O-phenylacetyl serine	1

Procedure: Mix propylene glycol and sodium stearate C-1 at room temperature and stir.
25 Increase the temperature to about 70°C. and continue agitation to obtain a clear and uniform solution. Add the water followed by the O-phenylacetyl serine. Lower the temperature to 55°C. and add the fragrance. Pour into molds
30 and cool to room temperature.

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Example 6Deodorant Roll-On Emulsion

	<u>Ingredient</u> <u>weight</u>	<u>% by</u>
5	hydrogenated palm oil glycerides and sodium cetyl sulfate	3.0
	steareth-7	1.0
	octyldodecanol	4.0
	glyceryl laurate	2.0
10	octyl palmitate	4.0
	dimethicone	1.0
	propylparaben	0.1
	methylparaben	0.2
	imidazolidinyl urea	0.3
15	glycerin	5.0
	allantoin	0.5
	PEG-35 lanolin	0.5
	fragrance	0.3
20	2 wt. % O-benzoyl serine in 80% propylene glycol/20% water at neutral pH	78.1

Procedure: Mix and stir the ingredients except
the fragrance at 80°C. Decrease the temperature
to 40°C. and add the fragrance. Decrease the
25 temperature to room temperature.

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Example 7Aerosol Deodorant

	<u>Ingredient</u>	<u>% by weight</u>
	zinc phenolsulfonate	1.7
5	quaternium 18 hectorite	1.0
	dioctyl succinate	10.0
	SDA 40 ethanol, anhydrous	20.0
	fragrance	0.1
10	1 wt. % O-succinyl serine in 50% ethanol/water at neutral pH	10.0
	propellant	57.2

Procedure: Dissolve all ingredients in the alcohol, add the propellant, and cold or pressure fill.

15 Example 8Roll-on Antiperspirant and Deodorant

	<u>Ingredient</u>	<u>% by weight</u>
	PPG-15 stearyl ether	4.0
	steareth-21	0.6
20	steareth-2	2.6
	aluminum zirconium pentachlorohydrate, 10:1 (a 25% solution)	32.0
	fragrance	0.1
25	1.8 wt. % O-oleoyl serine in 80% propylene glycol/water at neutral pH	60.7

Procedure: Mix all the ingredients except the fragrance at 70°C. with agitation. Add the fragrance at 45°C. Stir and cool to room temperature.

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Example 9Aerosol Antiperspirant and Deodorant

	<u>Ingredient</u>	<u>% by weight</u>
	O-palmitoyl serine	1.0
5	isopropyl myristate	13.4
	aluminum chlorohydrate	10.0
	quaternium-18 hectorite	0.8
	SDA 40 ethanol, anhydrous	0.8
	fragrance	0.1
10	propellant	73.9

Procedure: Mix the isopropyl myristate and quaternium-18 hectorite together for 30 minutes with an Eppenbach Homomixer. Add aluminum chlorohydrate and mix 15 minutes. Add the O-palmitoyl serine and SDA 40 and mix 10 minutes. Homogenize the suspension using a Manton-Gaulin homogenizer set at 6000 psi. Add fragrance and mix on a Hobart Mixer set at moderate speed. Mix 10 minutes. Charge with propellant.

20 Example 10Stick Antiperspirant and Deodorant

	<u>Ingredient</u>	<u>% by weight</u>
	aluminum chlorohydrate	16.0
	SDA 40 ethanol, anhydrous	30.0
25	sorbitol, 70%	3.0
	sodium stearate C-1	5.0
	sodium ceteth-13 carboxylate	3.0
	stearyl alcohol	1.0
	cyclomethicone	15.0
30	fragrance	0.1
	2 wt. % O-malonyl serine in 80% propylene glycol/water at neutral pH	26.9

Procedure: Mix the aluminum chlorohydrate, SDA 40 ethanol and the O-malonyl serine and heat to 65°C. Add sorbitol and then sodium stearate C-1 and sodium ceteth-13 carboxylate, and mix until a complete solution is obtained. Add the

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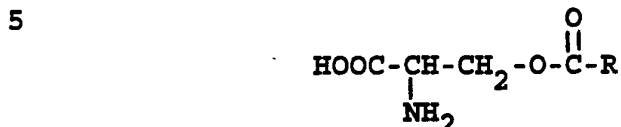
remaining ingredients and mix for 5 minutes.
Cool to 50°C. and add to containers.

Other objects, features and advantages
of the present invention will become apparent
5 from the foregoing detailed description and
accompanying examples. It should be understood,
however, that the detailed description and
specific examples, while indicating various
embodiments of the invention, are given by way
10 of illustration only, since various changes and
modifications within the spirit and scope of the
invention will become apparent to those skilled
in the art from this detailed description.

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C L A I M S

1. A deodorant composition comprising a malodor reducing effective amount of a compound of the structure



wherein R is a substituent which when cleaved from said compound produces an acid having a neutral or pleasant odor, in a dermatologically acceptable vehicle.

2. The deodorant composition of claim 1, wherein R is a) a branched or straight alkyl, alkenyl, or alkynyl chain of one to about seventeen carbon atoms that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, carboxyl, or phenyl that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, or carboxyl; or b) a phenyl that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, or carboxyl, or an aliphatic carbon chain of one to about eight carbon atoms that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, or carboxyl.

3. The deodorant composition of claim 1, wherein said compound is O-benzoyl serine, O-phenylacetyl serine, O-succinyl serine, O-malonyl serine, O-acetyl serine, O-oleoyl serine, O-palmitoyl serine, O-cinnamoyl serine, O-p-aminobenzoyl serine, O-lactoyl serine, O-salicyloyl serine, O-sarcosinoyl serine, O-2-ethyl hexanoyl serine.

4. The deodorant composition of claim 1, wherein said compound is present at a concentration of at least about 0.01% by

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weight.

5. The deodorant composition of claim 1, wherein said compound is present at a concentration of between about 5 micromolar and about 500 millimolar.

6. The deodorant composition of claim 1, wherein said compound is present at a concentration of between about 50 micromolar to about 100 millimolar.

7. The deodorant composition of claim 1, further comprising an antiperspirant salt.

8. A method of suppressing body malodor comprising the application to skin of the deodorant composition of claim 1.

9. A method of generating a pleasant odor comprising the application to skin of the deodorant composition of claim 1.

10. A method for making an O-acyl serine comprising:

a) esterifying a protected serine with a compound of the formula $R-COOH$, wherein R is i) a branched or straight alkyl, alkenyl, or alkynyl chain of one to about seventeen carbon atoms that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, carboxyl, or phenyl that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, or carboxyl; or ii) a phenyl that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, or carboxyl, or an aliphatic carbon chain of one to about eight carbon atoms that is unsubstituted or substituted with one or more halo, hydroxyl, amino, nitro, amide, or carboxyl and

b) hydrogenating the product of a) in the presence of a suitable hydrogenation catalyst to remove the serine protecting groups.

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11. The method of claim 10, wherein the compound of the formula R-COOH is phenylacetic acid.
12. The method of claim 10, wherein the compound of the formula R-COOH is benzoic acid.
13. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-C}_6\text{H}_5$.
14. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-CH}_2\text{-C}_6\text{H}_5$.
15. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-CH=CH-C}_6\text{H}_5$.
16. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-C}_6\text{H}_4\text{NH}_2$.
17. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-CH(OH)CH}_3$.
18. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-C}_6\text{H}_4\text{OH}$.
19. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-C}_2\text{H}_4\text{NH}_2$.
20. A compound of the formula $\text{HOOC-CH(NH}_2\text{)-CH}_2\text{-O-C(O)-CH(C}_2\text{H}_5\text{)-(CH}_2\text{)}_3\text{-CH}_3$.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10046

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 7/32; C07C 229/00

US CL :424/065; 562/553

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/065; 562/553

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 02-017156 (Nagao et al)orin) 22 January 1990, see Chemical Abstract 113-4962 only.	1-20
A	JP, A, 43-020165 (AJINOMOTO KK) 14 OCTOBER 1966, see Derwent Abstract 66-67582 only.	10



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

06 DECEMBER 1994

Date of mailing of the international search report

11 JAN 1995

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10046

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☒

No protest accompanied the payment of additional search fees.