AUSTRALIA 663145

Patents Act 1990

NOTICE OF ENTITLEMENT

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the applicant and nominated person in respect of an application for a patent for an invention entitled 5-O-Desosaminylerythronolide derivatives

filed under Australian Application No. , state the following:

PART 1 - *Must be completed for all applications.*
The person(s) nominated for the grant of the patent
~~☐ is (are) the actual inventor(s)~~
~~or~~
☒ has, for the following reasons, gained entitlement from the actual inventor(s)
The nominated person is the assignee of the invention from the said actual inventor(s)

PART 2 - *Must be completed if the application is a Convention application.*
The person(s) nominated for the grant of the patent is (are):
☐ the applicant(s) of the basic application(s) listed on the patent request form
or
☐ entitled to rely on the basic application(s) listed on the patent request form by reason of the following:

The basic application(s) listed on the request form is (are) the first application(s) made in a Convention country in respect of the invention.

PART 3 - *Must be completed if the application was made under the PCT and claims priority.*
The person(s) nominated for the grant of the patent is (are):
~~☐ the applicant(s) of the application(s) listed in the declaration under Article 8 of the PCT~~
~~or~~
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The nominated person is the assignee of the basic application from the said actual inventor(s)

The basic application(s) listed in the declaration made under Article 8 of the PCT ~~is~~ (are) the first application(s) made in a Convention country in respect of the invention.

Dated this 21 day of June 19 94

Signed Status Patent Attorney

Signatory's Name Frederick Lyle SCHILLING

F.B. RICE & CO PATENT ATTORNEYS

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 663145

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5-O-DESOSAMINYLERYTHRONOLIDE DERIVATIVE

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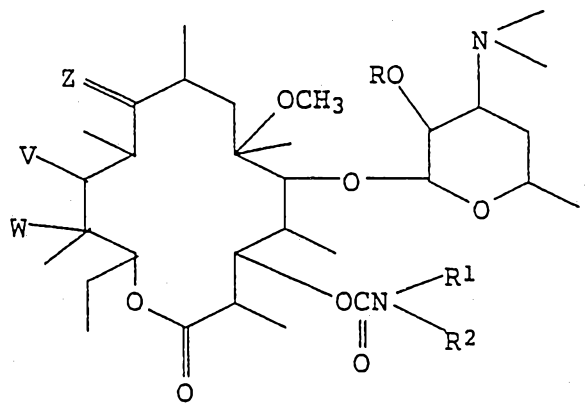
(56) Prior Art Documents
US 3923784

(57) Claim

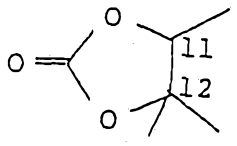
1. A 5-O-desosaminylerythronolide derivative represented by the formula:



(wherein each of R1 and R2 is a hydrogen atom; a phenyl group; a substituted phenyl group having 1 to 5 substituents selected from halogen atoms, nitro groups and amino groups; a C_1-C_{15} alkyl group; a C_2-C_{15} alkyl group

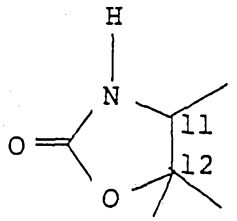
.../2

containing at least one nitrogen atom, oxygen atom or sulfur atom; a C_7-C_{10} aralkyl group; or a C_7-C_{10} aralkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; R^1 and R^2 being able to form a ring together with the adjacent nitrogen atom, Z is an oxygen atom or a group represented by the formula =N-O-R^3 (wherein R^3 is a hydrogen atom; a C_1-C_8 alkyl group; a C_1-C_{18} alkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; a benzyl group; or a substituted benzyl group having 1 to 5 substituents selected from halogen atoms and C_1-C_4 alkyl groups), V is a hydroxyl group and W is a hydrogen atom or a hydroxyl group, or V and W represent together with the carbon atoms at the 11- and 12-positions a group represented by the formula:



,

or a group represented by the formula:



,

R is a hydrogen atom, a C_2-C_{15} alkoxycarbonyl group, a C_2-C_{15} alkoxycarbonyl group containing at least one oxygen atom in its alkyl moiety, a C_2-C_{15} acyl group, a C_2-C_{15} acyl group containing at least one oxygen atom, or a pyridylcarbonyl group) and a pharmaceutically acceptable acid addition salt thereof.

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DE(欧州特許), DK(欧州特許), ES(欧州特許), FR(欧州特許),
GB(欧州特許), GR(欧州特許), IE(欧州特許), IT(欧州特許),
JP, KR, LU(欧州特許), MC(欧州特許), NL(欧州特許),
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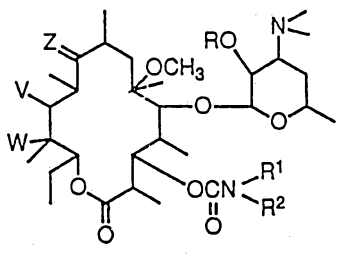
添付公開書類 国際調査報告書

(54) Title : 5-O-DESOSAMINYLERYTHRONOLIDE DERIVATIVE

(54) 発明の名称 5-O-デソサミニルエリスロノライド誘導体



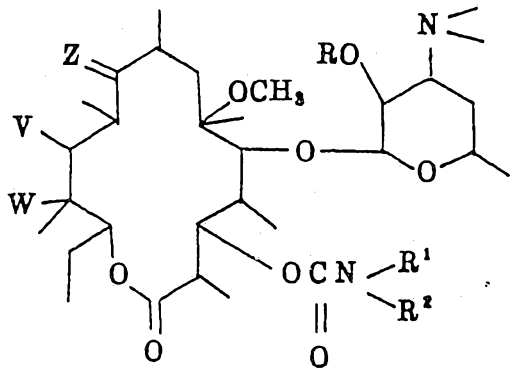
(I)

(57) Abstract

A 3-carbamoylated 5-O-desosaminyl-6-O-methylerythronolide derivative represented by general formula (I) and a pharmaceutically acceptable acid addition salt thereof, which are novel macrolide antibiotics with a potent antibacterial power, wherein R^1 and R^2 each represent hydrogen, phenyl optionally substituted by halogen, nitro or amino, alkyl optionally containing nitrogen, oxygen or sulfur, or aralkyl, or alternatively R^1 and R^2 are combined together with the nitrogen atom to form a nitrogenous ring; Z represents oxo or hydroxyimino; V represents hydroxy; W represents hydrogen or hydroxy, or alternatively V and W are combined together to form a cyclic carbonate group or an oxazoline ring; and R represents hydrogen or acyl.

(57) 要約

5－O－デソサミニル－6－O－メチルエリスロノライド誘導体の3位にカルバモイル基を導入した式



ただし、R^1, R^2 は水素、非置換またはハロゲン、ニトロまたはアミノ基で置換されたフェニル、アルキル、窒素、酸素または硫黄を含むアルキル、またはアラルキルであるかあるいは窒素原子を含む環を形成し、

Zはオキソまたはオキシイミノ基、Vは水酸基、Wは水素原子または水酸基を示し、あるいはVとWで環状カーボネートまたはオキサゾリン環を形成する。Rは水素またはアシル基を示す。

で表される化合物およびその医薬上許容される酸付加塩は強い抗菌力を有する新たなマクロライド系抗生物質である。

情報としての用途のみ

PCTに基づいて公開される国際出願のパンフレット第1頁にPCT加盟国を同定するために使用されるコード

AT オーストリア
AU オーストラリア
BB バルバドス
BE ベルギー
BF ブルキナ・ファソ
BG ブルガリア
BJ ベナン
BR ブラジル
CA カナダ
CF 中央アフリカ共和国
CG コンゴー
CH スイス
CI コート・ジボアール
CM カメルーン
CS チェッコスロヴァキア
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SE スウェーデン
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SN セネガル
SU ソヴィエト連邦
TD チャード
TG トーゴ
UA ウクライナ
US 米国
VN ヴェトナム

DESCRIPTION

5-O-DESOSAMINYLERYTHRONOLIDE DERIVATIVES

TECHNICAL FIELD

The present invention relates to novel derivatives of an antibiotic erythromycin. More particularly, it relates to novel derivatives of 5-O-desosaminylerythronolide derivatives and pharmaceutically acceptable acid addition salts thereof.

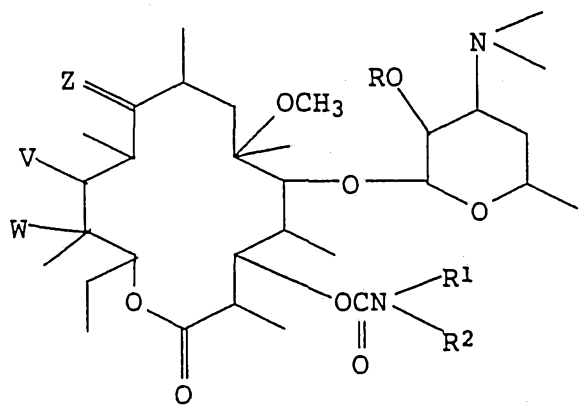
BACKGROUND ART

Erythromycin is an antibiotic clinically widely used as an agent for curing infectious diseases caused by Gram-positive bacteria, some Gram-negative bacteria, mycoplasmas, etc. Many derivatives of erythromycin have been produced for improving the biological and/or pharmacodynamic characteristics of erythromycin. As 5-O-desosaminylerythronolide derivatives, 3-O-acyl-5-O-desosaminylerythronolide derivatives, for example, have been disclosed in U.S. Patent 3,923,784. 5-O-desosaminylerythronolide derivatives, however, have been generally considered to be poor in antibacterial activity, and the antibacterial activity of the above-exemplified derivatives is also very weak. An object of the present invention is to provide novel antibiotics having a strong antibacterial activity.

DISCLOSURE OF THE INVENTION

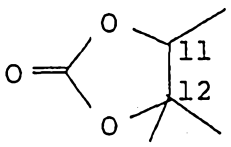
The present inventors conducted various researches on the antibacterial activity of 5-O-desosaminylerythronolide derivatives and consequently found that compounds obtained by introducing a carbamoyl group into 5-O-desosaminylerythronolide derivatives at the 3-position have an unexpectedly strong antibacterial activity, whereby the present invention has been accomplished.

The present invention is 5-O-desosaminyl-erythronolide derivatives represented by the formula:



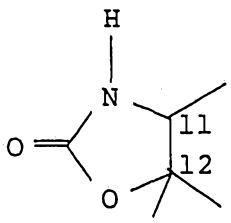
[wherein each of R^1 and R^2 is a hydrogen atom; a phenyl group; a substituted phenyl group having 1 to 5 substituents selected from halogen atoms, nitro groups and amino groups; a C_1-C_{15} alkyl group; a C_2-C_{15} alkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; a C_7-C_{15} aralkyl group; or a C_7-C_{15} aralkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; R^1 and R^2 being

able to be groups which form a ring together with the adjacent nitrogen atom, Z is an oxygen atom or a group represented by the formula =N-O-R^3 (wherein R^3 is a hydrogen atom; a C_1-C_8 alkyl group; a C_2-C_{18} alkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; a benzyl group; or a substituted benzyl group having 1 to 5 substituents selected from halogen atoms and C_1-C_4 alkyl groups), V is a hydroxyl group and W is a hydrogen atom or a hydroxyl group, or V and W represent together with the carbon atoms at the 11- and 12-positions a group represented by the formula:



,

or a group represented by the formula:



,

R is a hydrogen atom, a C_2-C_{15} alkoxycarbonyl group, a C_2-C_{15} alkoxycarbonyl group containing at least one oxygen atom in its alkyl moiety, a C_2-C_{15} acyl group, a C_2-C_{15} acyl group containing at least one oxygen atom,

or a pyridylcarbonyl group] and pharmaceutically acceptable acid addition salts thereof.

In the present invention, the halogen atoms are fluorine, chlorine, bromine and iodine atoms. The term "alkyl group" means a linear one or a branched one. As the C_2-C_{15} alkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom, there can be exemplified aminoethyl group, dimethylaminoethyl group, benzylaminoethyl group, N-benzyl-N-methylaminoethyl group, dibenzylaminoethyl group, 2,3-dihydroxypropyl group, 3-aminopropyl group and 2-hydroxy-3-aminopropyl group. As the C_7-C_{15} aralkyl group, there can be exemplified benzyl group, phenethyl group and diphenylmethyl group. As the C_7-C_{15} aralkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom, there can be exemplified nitrobenzyl group, methoxybenzyl group, methylthiobenzyl group, aminobenzyl group and dimethylaminobenzyl group. The term "C_2-C_{15} alkoxycarbonyl group" means a substituted carbonyl group having an alkoxy group as the substituent, and there can be exemplified methoxycarbonyl group and benzyloxycarbonyl group. An oxgen atom in the alkyl moiety, xycarobonyl group can be exemplified. As the C_2-C_{15} alkoxycarbonyl group containing at least one oxygen atom in its alkyl moiety, there can be exemplified methoxycarbonyl group, 2-methoxyethoxycarbonyl group, 2-[2-(2-methoxyethoxy)ethoxy]ethoxycarbonyl group, benzyloxycarbonyl group and 2-[2-(2-ethoxyethoxy)ethoxy]ethoxy-

carbonyl group. As the C_2-C_{15} acyl group, there can be exemplified acetyl group, propionyl group and benzoyl group. The term "C_2-C_{15} acyl group containing at least one oxygen atom" means a substituted acyl group having, for example, an alkoxycarbonyl group as the substituent, and ethylsuccinyl group can be exemplified. As the pharmaceutically acceptable acid addition salts, there can be exemplified acetates, propionates, butyrates, formates, trifluoroacetates, maleates, tartarates, citrates, stearates, succinates, ethylsuccinates, lactobionates, gluconates, glucoheptonates, benzoates, methanesulfonates, ethanesulfonates, 2-hydroxyethanesulfonates, benzenesulfonates, p-toluenesulfonates, laurylsulfates, malates, aspartates, glutaminates, adipates, cysteine salts, hydrochlorides, hydrobromides, phosphates, sulfates, hydroiodides, nicotinates, oxalates, picrates, thiocyanates, undecanoates, polyacrylates and carboxyvinyl polymer salts.

The compounds of the present invention include both those in which the coordination at the 3-position is natural (3S forms) and those in which the coordination at the 3-position is not natural (3R forms).

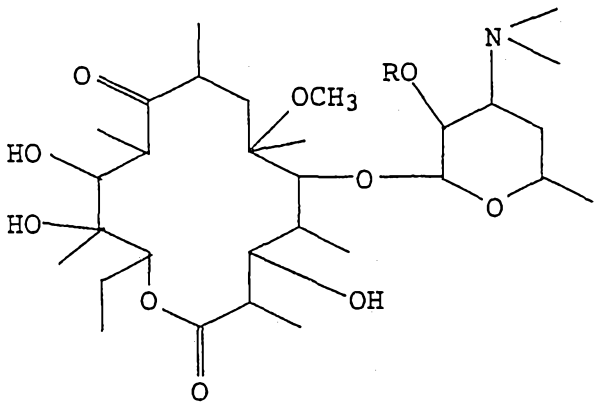
The compounds of the present invention can be produced, for example, as follows.

[Production process 1]

Process using 5-O-desosaminyl-6-O-methylerythronolide A as a starting material

Step (1) ;

5-O-desosaminyl-6-O-methylerythronolide A is reacted with an acid anhydride of the formula R_2O (wherein R is as defined above except for hydrogen atom) or a halide of the formula R-X (wherein R is as defined above except for hydrogen atom, and X is an optional halogen atom) and a base in an inert solvent at 0°C to 30°C, whereby there can be obtained a compound of the formula (a):

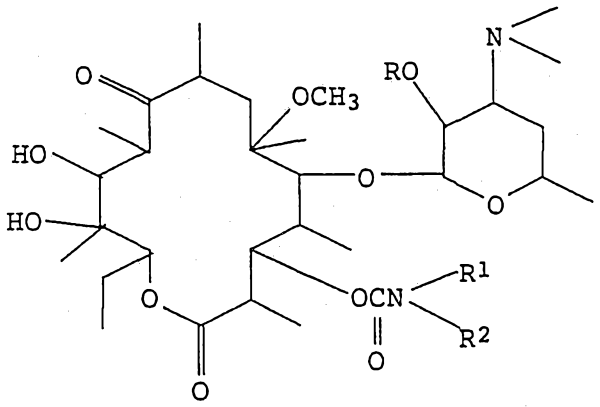


(a)

wherein R is as defined above. Here, as the suitable inert solvent, there are used dichloromethane, dichloroethane, acetone, pyridine, ethyl acetate, tetrahydrofuran, etc. As the acid anhydride or the halide, there are used anhydrides and halides of acetic acid, propionic acid, benzoic acid and pyridinecarboxylic acid, and carbonic acid ester halides such as 2-[2-(2-methoxyethoxy)ethoxy]ethyl chloroformate. As the base, there are used sodium hydrogencarbonate, sodium carbonate, potassium carbonate, triethylamine, pyridine, tributylamine, etc.

Step (2) ;

The compound obtained in step (1) is reacted with 1,1'-carbonyldiimidazole in an inert solvent at 0°C to 80°C, after which an amine of the formula (wherein R^1 and R^2 are as defined above) is added and the reaction is carried out at 0°C to 30°C, whereby there can be obtained a compound of the present invention of the formula (b):

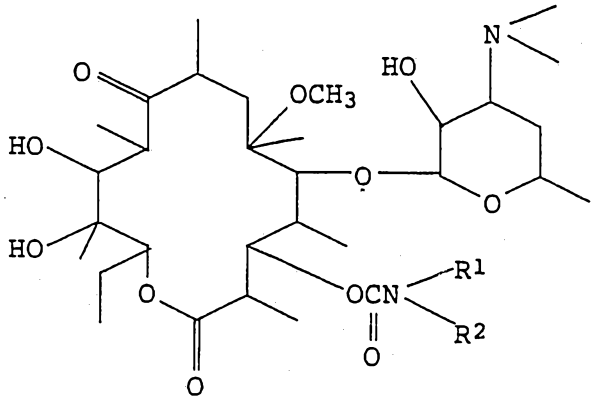


(b)

wherein R is as defined above. The compound of the formula (b) can be obtained also by using a suitable isocyanate and a base.

Step (3) ;

The compound obtained in step (2) is reacted in a lower alcohol at room temperature to 100°C, whereby there can be obtained a compound of the present invention of the formula (c):

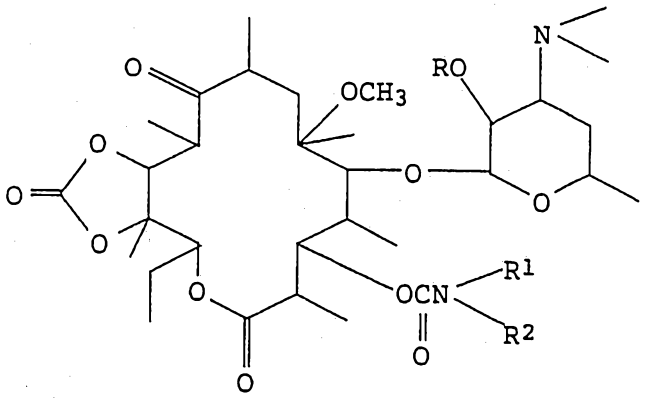


(c)

Here, as the lower alcohol, there are used methanol, ethanol, propanol, butanol, etc.

Step (4) ;

The compound obtained in step (2) is reacted with a reagent such as phosgene dimer or phosgene trimer under ice-cooling in a suitable inert solvent by the use of a base such as pyridine, whereby there can be obtained a compound of the formula (d):

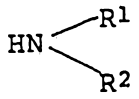


(d)

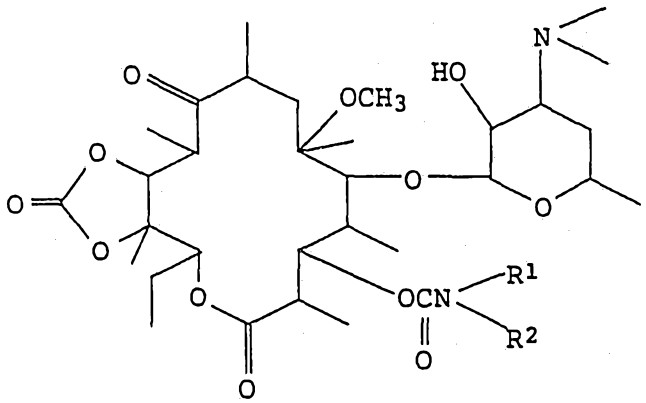
wherein R is as defined above. Here, the suitable inert solvent is the same as used in step (1).

Step (5) ;

The compound of the formula (d) can be produced also by reacting the compound obtained in step (1), in the same manner as in step (4), adding an amine of the formula:



(wherein R^1 and R^2 are as defined above) in the same reactor, and then carrying out the reaction at 0°C to room temperature. Then, the compound (d) is reacted in the same manner as in step (3), whereby there can be produced a compound of the present invention of the formula (e):



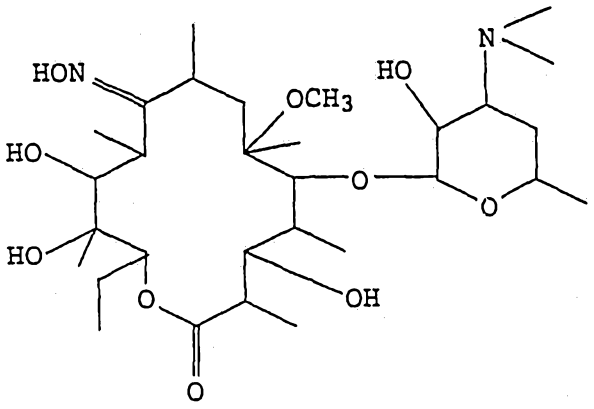
(e)

[Production process 2]

Process using 6-O-methylerythromycin A 9-oxime as a starting material

Step (6) ;

6-O-methylerythromycin A 9-oxime is reacted with an acid in a lower alcohol at 0°C to 30°C to obtain a compound of the formula (f):

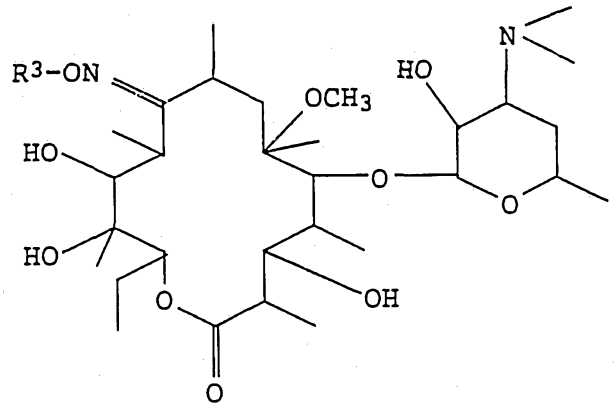


(f)

Here, the lower alcohol is the same as used in step (3). As the acid, there are used hydrochloric acid, hydrobromic acid, sulfuric acid, etc.

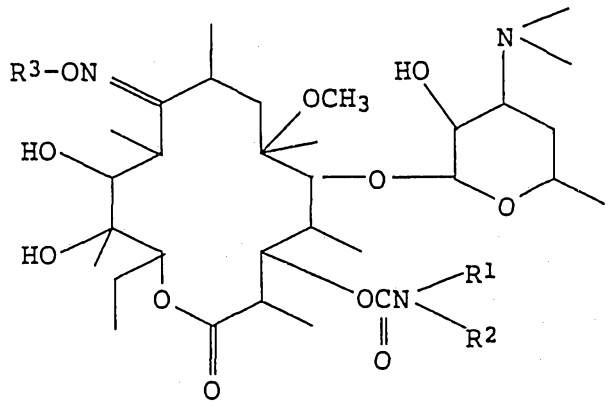
Step (7) ;

The compound obtained in step (6) is reacted with a reagent of the formula R^3D (wherein R^3 is as defined above, and D is an optional halogen atom) and a base in an inert solvent at 0°C to 30°C to obtain a compound of the formula (g):



(g)

wherein R^3 is as defined above. Subsequently, this compound is reacted in the same manner as in steps (1), (2) and (3), whereby there can be produced a compound of the present invention of the formula (h):

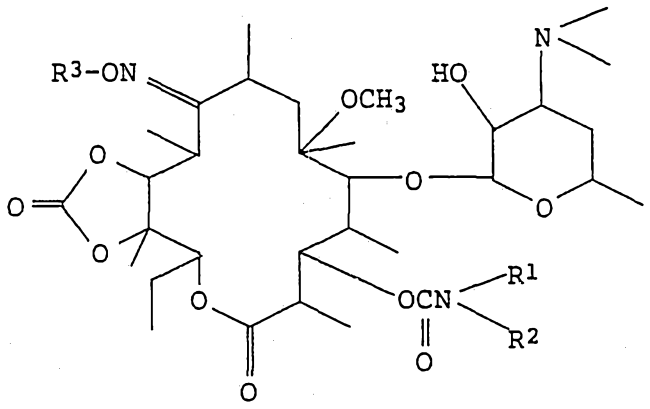


(h)

wherein R^3 is as defined above. Here, as the inert solvent, there are used dimethylformamide, N-methylpyrrolidone, tetrahydrofuran, acetonitrile and mixed solvents thereof. As the base, there are used sodium hydride, potassium hydroxide, sodium bistrimethylsilylamide, etc.

Step (8) ;

The compound of the formula (g) is reacted in the same manner as in steps (1) and (2) and then in the same manner as in step (4) to be converted into a 11,12-cyclic carbonate, which is reacted in the same manner as in step (3), whereby there can be produced a compound of the present invention of the formula (i):

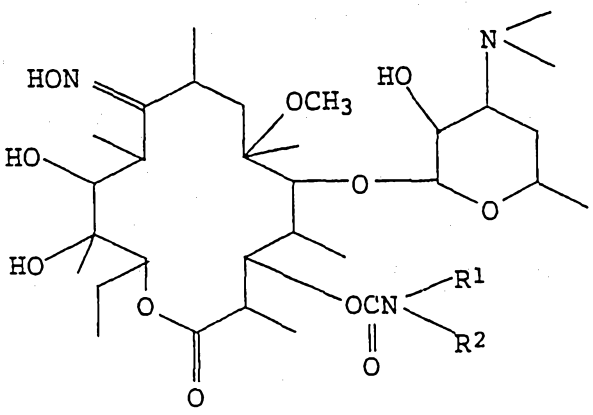


(i)

wherein R^3 is as defined above.

Step (9) ;

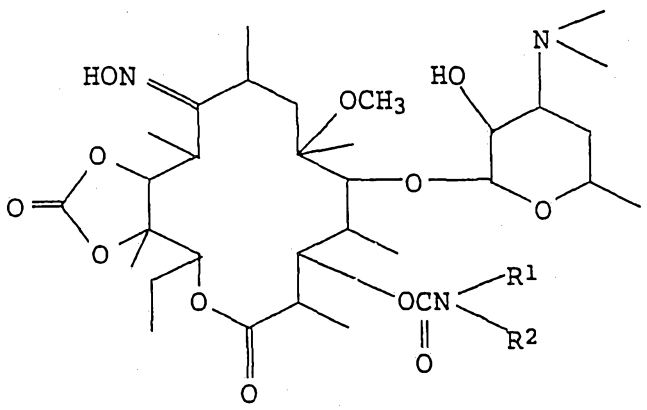
The compound obtained in step (6) is reacted in the same manner as in step (1) to protect the hydroxyl group at the 2'-position and the hydroxyl group of the oxime at the 9-position, after which the reaction product is reacted in the same manner as in steps (2) and then (3), whereby there can be produced a compound of the present invention of the formula (j):



(j)

Step (10) ;

The compound obtained in step (6) is reacted in the same manner as in step (1) to protect the hydroxyl group at the 2'-position and the hydroxyl group of the oxime at the 9-position, after which the reaction product is reacted in the same manner as in steps (2), (4) and then (3), whereby there can be produced a compound of the present invention of the formula (k):



(k)

The compounds of the present invention can be administered orally or parenterally. Their pharmaceutical forms for administration are tablets, capsules,

powders, troches, ointments, suspensions, suppositories, injections, etc. These can be prepared by conventional preparation techniques.

INDUSTRIAL APPLICABILITY

The compounds of the present invention have a strong antibacterial activity against erythromycin-sensitive bacteria and resistant bacteria. Therefore, the compounds of the present invention are useful as antibacterial agents for curing infectious diseases caused by bacteria in human beings and animals (including farm animals).

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated below in further detail with examples.

Example 1

Production of 3-O-(2,3,4,5,6-pentafluorophenyl)aminocarbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate

(1) 2.27 Milliliters (0.024 mole) of 5-O-desosaminyl-6-O-methylerythronolide A acetic anhydride was added, followed by stirring at room temperature for 6 hours. Acetone was evaporated under reduced pressure and the residue was extracted with dichloromethane. The dichloromethane layer was washed with a saturated sodium hydrogencarbonate solution and then a

saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate, after which the solvent was evaporated under reduced pressure. The residue was recrystallized from ether-n-hexane to obtain 12.17 g of 2'-O-acetyl-5-O-desosaminyl-6-O-methyl-erythronolide as white powder.

mp ; 158 - 160°C

Mass (FAB) m/z; 632 $[MH]^+$

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm); 2.07 (3H, s), 2.26 (6H, s), 2.95 (3H, s), 3.26 (1H, s), 3.96 (1H, s)

IR (KBr, cm^{-1}); 3469, 1750, 1733, 1693

(2) In 25 ml of dichloromethane was dissolved 1.90 g (3.0 mmoles) of the compound obtained in (1) above, and 3.63 ml (45 mmoles) of pyridine and 0.90 ml (7.5 mmoles) of trichloromethyl chloroformate were added under ice-cooling and stirred for 3 hours. After 2.75 g (15 mmoles) of 2,3,4,5,6-pentafluoroaniline was added, the resulting mixture was stirred at room temperature for 15 hours. A piece of ice and 0.5 g of sodium hydrogencarbonate were added, followed by extraction with ethyl acetate. The extract was purified by a silica gel column chromatography (eluent; hexane : acetone : triethylamine = 10 : 6 : 0.2) to obtain 1.29 g of 2'-O-acetyl-3-O-(2,3,4,5,6-pentafluorophenyl)amino-carbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate.

(3) In 30 ml of methanol was dissolved 450 mg (0.52 mmole) of the compound obtained in (2) above and the resulting solution was stirred for 24 hours, after which the solvent was evaporated to obtain 375 mg of the title compound.

mp ; 227 - 229°C (crystallized from methanol)

Mass (FAB) m/z; 825 $[MH]^+$

^1H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.30 (6H, s), 2.99 (3H, s)

IR (KBr, cm^{-1}); 3420, 1813, 1747, 1721

Example 2

Production of 3-O-imidazolylcarbonyl-5-O-desosaminyl-6-O-methylerythronolide A 9-[O-(2,4,6-trimethylbenzyl)oxime]

(1) In 1 liter of 1N hydrochloric acid was dissolved 500 g (0.655 mole) of 6-O-methylerythromycin A 9-oxime, and the solution was allowed to stand at room temperature for 24 hours. Then, the solution was adjusted to pH 10 with an aqueous sodium hydroxide solution, and the crystals precipitated were collected by filtration. The crystals were dissolved in dichloromethane and the resulting solution was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. Subsequently, the dichloromethane was evaporated under reduced pressure and the residue was crystallized

from methanol to obtain 259.8 g of 5-O-descsaminyl-6-O-methylerythronolide A 9-oxime as white powder.

mp ; 257 - 260°C

Mass (FAB) m/z; 605 $[MH]^+$

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 1.42 (3H, s), 2.34 (6H, s), 2.99 (3H, s), 3.26 (1H, s), 3.57 (1H, s), 4.37 (1H, s), 4.42 (1H, d, J=7Hz), 5.23 (1H, dd, J=11Hz, 2Hz), 7.43 (1H, broad-s)

IR (KBr, cm^{-1}); 3523, 3370, 1712, 1188, 1169, 1085

(2) In 20 ml of N,N-dimethylformamide were dissolved 1.73 g (2.87 mmoles) of the compound obtained in (1) above and 7.26 mg (4.30 mmoles) of 2,4,6-trimethylbenzyl chloride, followed by adding thereto 138 mg (344 mmoles) of 60% sodium hydride, and the reaction was carried out at room temperature for 6 hours to obtain 2.34 g of 5-O-desosaminyl-6-O-methylerythronolide A 9-[O-(2,4,6-trimethylbenzyl)oxime] as a white foamy substance.

(3) In 20 ml of acetone, 2.34 g (3.18 mmoles) of the compound obtained in (2) above was reacted with 0.39 ml (4.13 mmoles) of acetic anhydride to obtain 1.74 g of 2'-O-acetyl-5-O-desosaminyl-6-O-methylerythronolide A 9-[O-(2,4,6-trimethylbenzyl)oxime] as a white foamy substance.

(4) In 12 ml of dichloromethane was dissolved 900 mg (1.16 mmoles) of the compound obtained in (3) above, followed by adding thereto 40 mg (5.8 mmoles) of 1,1'-carbonyldiimidazole and 156 mg (1.28 mmoles) of 4-

dimethylaminopyridine, and the resulting mixture was heated under reflux for 7.5 hours. Purification by a silica gel column chromatography (eluent; chloroform : methanol : ammonia = 20 : 1 : 0.3) gave 117 mg of the title compound and 290 mg of 2'-O-acetyl-3-O-imidazolylcarbonyl-5-O-desosaminyl-6-O-methylerythronolide A 9-[O-(2,4,6-trimethylbenzyl)oxime] as white foamy substances. The title compound:

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm); 2.26 (3H, s), 2.37 (9H, s), 2.41 (3H, s), 2.99 (3H, s), 4.06 (1H, s), 5.70 (2H, s), 6.85 (2H, s), 7.11 (1H)

2'-O-acetyl-3-O-imidazolylcarbonyl-5-O-desosaminyl-6-O-methylerythronolide A 9-[O-(2,4,6-trimethylbenzyl)-oxime]:

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm); 2.20 (3H, broad-s), 2.26 (3H, s), 2.36 (12H, s), 2.98 (3H, s), 3.29 (1H, s), 4.60 (1H, s), 5.70 (2H, s), 6.84 (2H, s), 7.19 (1H), 7.49 (1H), 8.20 (1H)

Example 3

Production of 3-O-(2,4-difluorophenyl)amino-carbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate

(1) In 500 ml of dichloromethane was dissolved 50 g (84.8 mmoles) of the compound obtained in Example 1, (1), and 102.6 ml (1.27 moles) of pyridine was added under ice-cooling. At the same temperature, 40 ml of a solution of 25.4 ml (212 mmoles) of trichloromethyl

chloroformate in dichloromethane was added dropwise, and the resulting mixture was stirred for 5.5 hours. Small amounts of cold water and a saturated sodium hydrogencarbonate solution were added to the reaction mixture, followed by extraction with dichloromethane. The dichloromethane layer was washed with a saturated sodium hydrogencarbonate solution and then a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate, after which the solvent was evaporated under reduced pressure.

The residue was purified by a silica gel column chromatography (eluent; acetone : n-hexane : triethylamine = 6-10 : 10 : 0.2) to obtain 41.93 g of 2'-O-acetyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate as a white foamy substance.

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm); 2.05 (3H, s), 2.25 (6H, s), 2.92 (3H, s), 4.57 (1H, d, J=9Hz), 4.74 (1H, s), 4.75 (1H, dd, J=10Hz, 9Hz), 5.13 (1H, dd, J=12Hz, 2Hz)

(2) In 10 ml of tetrahydrofuran was dissolved 450 mg (0.685 mmole) of the compound obtained in (1) above, followed by adding thereto 0.41 ml (3.425 mmoles) of 2,4-difluorophenyl isocyanate and 0.08 ml (1.028 mmoles) of pyridine, and the resulting mixture was stirred at room temperature for 18 hours. The reaction mixture was extracted with ethyl acetate, and the extract was washed with a saturated aqueous sodium chloride solution and then purified by a silica gel column chromatography

(eluent; chloroform : methanol : 25% aqueous ammonia = 20 : 1 : 0.1).

(3) In methanol, 40 mg of the compound obtained in (2) was heated under reflux for 3 hours to remove the acetyl group, whereby 40 mg of the title compound was obtained as a white foamy substance.

^{1}H-NMR (200 MHz, $CDCl_3$) δ(ppm); 1.30 (3H, s), 2.22 (6H, s), 3.03 (3H, s), 4.03 (1H, d, J=7Hz), 4.76 (1H, s), 5.02 (1H, d, J=9Hz), 6.82-6.95 (2H), 7.18 (1H, broad-s), 8.02-8.15 (1H)

Example 4

Production of 3-O-(3-nitrophenyl)amino-carbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate

1.65 Grams of the title compound was obtained by using a combination of 1.90 g (3.0 mmoles) of the compound obtained in Example 1, (1), 3.63 ml (45 mmoles) of pyridine and 0.90 ml (7.5 mmoles) of trichloromethyl chloroformate, and then 2.07 g (15 mmoles) of 3-nitroaniline, and reacting them in the same manner as in Example 1.

Mass (FAB) m/z; 780 [MH]+

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.18 (6h, s), 3.04 (3H, s), 7.79 (1H, broad-s), 7.51 (1H, m), 7.88 (1H, m), 7.93 (1H, m), 8.38 (1H, m)

IR (KBr, cm^{-1}); 3346, 1818, 1742, 1706

Example 5

Production of 3-O-[2-(dimethylamino)ethyl]-aminocarbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate

0.86 Gram of the title compound was obtained by using a combination of 1.90 g (3.0 mmoles) of the compound obtained in Example 1, (1), 3.63 ml (45 mmoles) of pyridine and 0.90 ml (7.5 mmoles) of trichloromethyl chloroformate, and then 1.63 g (15 mmoles) of N,N-dimethylethylenediamine, and reacting them in the same manner as in Example 1.

Mass (FAB) m/z; 730 $[MH]^+$

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.26 (6H, s), 2.30 (6H, s), 3.02 (3H, s), 5.43 (1H, t)

IR (KBr, cm^{-1}); 3387, 1815, 1738, 1713

Example 6

Production of 3-O-[2-(dimethylamino)ethyl]-aminocarbonyl 5-O-desosaminyl-6-methylerythronolide A

In 25 ml of tetrahydrofuran was dissolved 2.95 g (5.0 mmoles) of 5-O-desosaminyl-6-O-methylerythronolide A, followed by adding thereto 2.43 g (15 mmoles) of N,N'-carbonyldiimidazole, and the resulting mixture was refluxed for 5 hours. After extraction with ethyl acetate, the solvent was evaporated and the excess N,N'-carbonyldiimidazole was removed by a silica gel column chromatography (eluent; acetone : chloroform). In 20 ml of ethyl acetate was dissolved

2.96 g of the thus obtained colorless caramel, followed by adding thereto 1.09 g (10.0 mmoles) of N,N-dimethylethyldiamine, and the resulting mixture was stirred at room temperature for 3 days. After extraction with ethyl acetate, the extract was purified by a silica gel column chromatography (eluent; 8-15% methanol-chloroform) to obtain 0.53 g of the title compound as colorless crystalline powder.

Mass (FAB) m/z; 704 $[MH]^+$

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.23 (6H, s), 2.28 (6H, s), 3.06 (3H, s)

IR (KBr, cm^{-1}); 3455, 3327, 1738, 1723, 1697

Example 7

Production of 3-O-(3-aminopropyl)amino-carbonyl-5-O-desosaminyl-6-O-methylerythronolide A

(1) In a mixed solution of 15 ml of dichloroethane and 10 ml of tetrahydrofuran was dissolved 1.26 g (2.0 mmoles) of the compound obtained in Example 1, (1), followed by adding thereto 1.30 g (8 mmoles) of N,N'-carbonyldiimidazole, and the resulting mixture was heated under reflux for 8 hours. The solvent was evaporated and the residue was subjected to a silica gel column chromatography (eluent; acetone : hexane : triethylamine = 5 : 10 : 0.1) to obtain 1.14 g of 2'-O-acetyl-3-O-imidazolylcarbonyl-5-O-desosaminyl-6-O-methylerythronolide A.

(2) In 10 ml of tetrahydrofuran was dissolved 1 g of the compound obtained in (1) above, followed by adding thereto 0.22 ml (2.5 mmoles) of 1,3-diaminopropane, and the resulting mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure, and the residue was extracted with methylene chloride. Then, the extract was purified by a silica gel column chromatography (eluent; chloroform : methanol : aqueous ammonia = 100 : 20 : 0.5) to obtain 0.74 g of the title compound which was colorless and foamy.

Mass (FAB) m/z; 690 $[MH]^+$

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.28 (6H, s), 3.05 (3H, s)

IR (KBr, cm^{-1}); 3414, 1724

Example 8

Production of 3-O-(2,3-dihydroxypropyl)aminocarbonyl-5-O-desosaminyl-6-O-methylerythronolide A

In a mixed solution of 15 ml of tetrahydrofuran and 10 ml of N,N-dimethylformamide was dissolved 1.81 g (2.5 mmoles) of a compound obtained in the same manner as in Example 7, (1), followed by adding thereto 683 mg (7.5 mmoles) of 3-amino-1,2-propanediol, and the resulting mixture was stirred at room temperature for 20 hours. The solvent was evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The solvent was evaporated and 1.72 g of the colorless

and foamy compound thus obtained was dissolved in 10 ml of methanol, after which the resulting solution was stirred for 15 hours. The solvent was evaporated and the residue was purified by a silica gel column chromatography (eluent; chloroform : methanol : aqueous ammonia = 100 : 10 : 0.1) to obtain 1.17 g of the title compound which was colorless and foamy.

Mass (FAB) m/z; 707 $[MH]^+$

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.48 (6H, s), 3.04 (3H, s)

IR (KBr, cm^{-1}); 3436, 1735

Example 9

Production of 3-O-[(3-amino-2-hydroxy)propyl]-aminocarbonyl-5-O-desosaminyl-6-O-methylerythronolide A

0.82 Gram of the title compound which was colorless and foamy was obtained by using 1.5 g (2.07 mmoles) of a compound obtained in the same manner as in Example 7, (1) and 372 mg (4.13 mmoles) of 1,3-diamino-2-propanol, and reacting them in the same manner as in Example 8.

Mass (FAB) m/z; 706 $[MH]^+$

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.30 (6H, s), 3.04 (3H, s), 5.71 (1H, broad-s)

IR (KBr, cm^{-1}); 3437, 1808, 1736

Example 10

Production of 3-O-(1-methylpiperazin-4-yl)-

carbonyl-5-O-desosaminyl-6-O-methylerythronolide A

1.43 Grams of the title compound was obtained by using 3.2 g (4.41 mmoles) of a compound obtained in the same manner as in Example 7, (1) and 1.94 ml (17.6 mmoles) of 1-methylpiperazine, and reacting them in the same manner as in Example 8.

Mass (FAB) m/z; 716 $[MH]^+$

^1H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.33 (9H, s), 3.06 (3H, s)

IR (KBr, cm^{-1}); 3459, 1814, 1737, 1703

Example 11

Production of 3-O-(1-methylpiperazin-4-yl)-carbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate

(1) In 15 ml of acetone was dissolved 1.26 g of the compound obtained in Example 10, followed by adding thereto 0.25 ml (2.64 mmoles) of acetic anhydride, and the resulting mixture was stirred at room temperature for 20 hours. Extraction with ethyl acetate gave 1.31 g of anhydrous and foamy 2'-O-acetyl-3-O-(1-methyl-piperazin-4-yl)carbonyl-5-O-desosaminyl-6-O-methyl-erythronolide A.

(2) In 20 ml of dichloromethane was dissolved 1.31 g of the compound obtained in (1) above, and 2.13 ml (26.4 mmoles) of pyridine and 0.53 ml (4.4 mmoles) of trichloromethyl chloroformate were added under ice-cooling and stirred for 3 hours. A piece of ice and

sodium hydrogencarbonate powder were added and the pH of the aqueous layer was adjusted to 7, after which the solvent was evaporated under reduced pressure. After extraction with ethyl acetate, the solvent was again evaporated under reduced pressure. The residue was purified by a silica gel column chromatography (eluent; 5-10% methanol-chloroform) to obtain 0.81 g of 2'-O-acetyl-3-O-(1-methylpiperazin-4-yl)carbonyl-5-O-desosaminyl-6-O-methylerythronolide A 11,12-cyclic carbonate.

(3) 0.54 Gram of the title compound was obtained by dissolving 0.81 g of the compound obtained in (2) above, in 20 ml of methanol, and stirring the resulting solution for one day.

Mass (FAB) m/z; 742 $[MH]^+$

^{1}H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.30 (6H, s), 2.32 (3H, s), 3.02 (3H, s)

IR (KBr, cm^{-1}); 3459, 1814, 1742, 1704

Example 12

Production of 3-O-(2-cyanoimino-1,3-oxazolidin-4-yl)methylaminocarbonyl-5-O-desosaminyl-6-O-methylerythronolide A

In 10 ml of ethanol was dissolved 353 mg (0.5 mmole) of the compound obtained in Example 9, and 146 mg (1.0 mmole) of S,S'-dimethyl-N-cyanodithioiminocarbonate was added and then stirred for 7 hours. The solvent was evaporated under reduced pressure, and the residue was

extracted with ethyl acetate. By a silica gel column chromatography (eluent; chloroform : methanol : aqueous ammonia =) 20 : 1 : 0.1), 318 mg of the title compound was obtained.

Mass (FAB) m/z; 757 $[MH]^+$

^1H-NMR (300 MHz, $CDCl_3$) δ(ppm); 2.30 (6H, s), 3.05 (3H, s), 5.55 (1H, broad-s)

IR (KBr, cm^{-1}); 3424, 2195, 1738, 1656

Test Example (in vitro antibacterial activity)

The in vitro antibacterial activity of the compound of the present invention against various test bacteria was measured according to the MIC measuring method of Japanese Chemotherapeutic Association by using sensitive disc media (available from Eiken Chemical, Co.). 6-O-methylerythromycin A was used as a reference agent. The results are expressed in MIC values (minimum inhibitory concentration; mcg/ml).

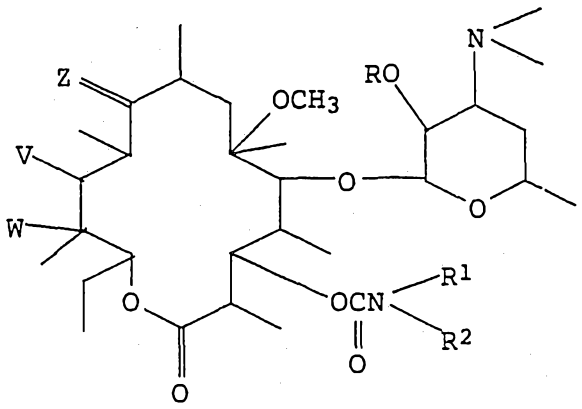
Table 1

in vitro Antibacterial activity MIC value (mcg/ml)

Microorganism \ Compound	Example 1	Reference agent
S. aureus 209P-JC	0.05	0.10
S. aureus Smith 4	0.10	0.10
S. epidermides IID 866	0.10	0.10
E. faecalis CSJ 1212	0.39	0.78
S. aureus J-109	100	>100
S. aureus B1	0.78	>100
S. aureus C1	0.78	>100

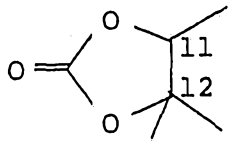
CLAIMS

1. A 5-O-desosaminylerythronolide derivative represented by the formula:



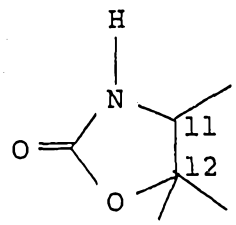
(wherein each of R' and R2 ~~R1~~ is a hydrogen atom; a phenyl group; a substituted phenyl group having 1 to 5 substituents selected from halogen atoms, nitro groups and amino groups; a C_1-C_{15} alkyl group; a C_2-C_{15} alkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; a C_7-C_{10} aralkyl group; or a C_7-C_{10} aralkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; R^1 and R^2 being able to form a ring together with the adjacent nitrogen atom, Z is an oxygen atom or a group represented by the formula =N-O-R^3 (wherein R^3 is a hydrogen atom; a C_1-C_8 alkyl group; a C_1-C_{18} alkyl group containing at least one nitrogen atom, oxygen atom or sulfur atom; a benzyl group; or a substituted benzyl group having 1 to 5 substituents selected from halogen atoms and C_1-C_4 alkyl groups), V

is a hydroxyl group and W is a hydrogen atom or a hydroxyl group, or V and W represent together with the carbon atoms at the 11- and 12-positions a group represented by the formula:



,

or a group represented by the formula:



,

R is a hydrogen atom, a C_2-C_{15} alkoxycarbonyl group, a C_2-C_{15} alkoxycarbonyl group containing at least one oxygen atom in its alkyl moiety, a C_2-C_{15} acyl group, a C_2-C_{15} acyl group containing at least one oxygen atom, or a pyridylcarbonyl group) and a pharmaceutically acceptable acid addition salt thereof.

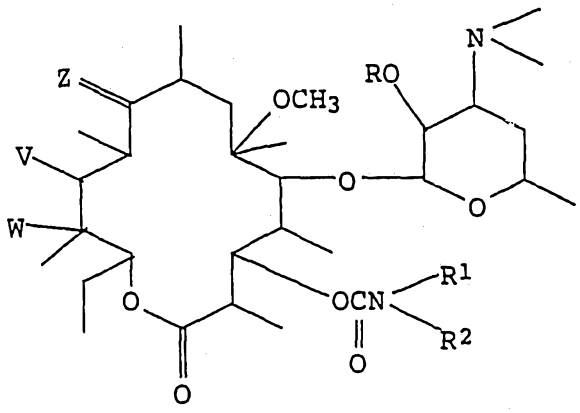
ABSTRACT

Object:

Provision of novel macrolide antibiotics having a strong antibacterial activity.

Construction:

Compounds represented by the formula:



which are obtained by introducing a carbamoyl group into 5-O-desosaminyl-6-O-methylerythronolide derivatives at the 3-position; and pharmaceutically acceptable acid addition salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP92/01713

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl^5 C07H17/08//A61K31/71

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)

Int. Cl^5 C07H17/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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.
P	JP, A, 4-290893 (Roussel Huchaf), October 15, 1992 (15. 10. 92), Compound of example 46, page 29 & EP, A1, 487411 & AU, A, 9187986 & FR, A, 2669337 & BR, A, 9105062	1
A	US, A, 3923784 (Hoffmann-La Roche Inc.), February 19, 1974 (19. 02. 74), (Family: none)	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"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

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Date of the actual completion of the international search	Date of mailing of the international search report
March 17, 1993 (17. 03. 93)	April 6, 1993 (06. 04. 93)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

国際調査報告

国際出願番号 PCT/JP 92/01713

A. 発明の属する分野の分類（国際特許分類（IPC））

Int. Cl[5] C07H17/08//A61K31/71

B. 調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl[5] C07H17/08

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAS ONLINE

C. 関連すると認められる文献

引用文献のカテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
P	JP, A, 4-290893（ルセル・ユクラフ）, 15. 10月. 1992（15. 10. 92） 29頁 例46の化合物 &EP, A1, 487411 &AU, A, 9187986 &FR, A, 2669337 &BR, A, 9105062	1
A	US, A, 3923784（Hoffmann-La Roche Inc.） 19. 2月. 1974（19. 02. 74）（ファミリーなし）	1

☐ C欄の続きにも文献が列挙されている。

☐ パテントファミリーに関する別紙を参照。

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「A」特に関連のある文献ではなく、一般的技術水準を示すもの
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「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
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国際調査を完了した日
17. 03. 93

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