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(57) Abstract

A process of preparing a 6–O–alkyl derivative of erythromycin C is provided. The process includes the steps of protecting the 2',4''– and 9–oxime hydroxyls with acetyl and ketal protecting groups, alkylating the 6–hydroxyl, removing the protecting groups and deoximating. Intermediates used in the process are also provided.

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Chemical Synthesis of 6-O-Alkyl Erythromycin C

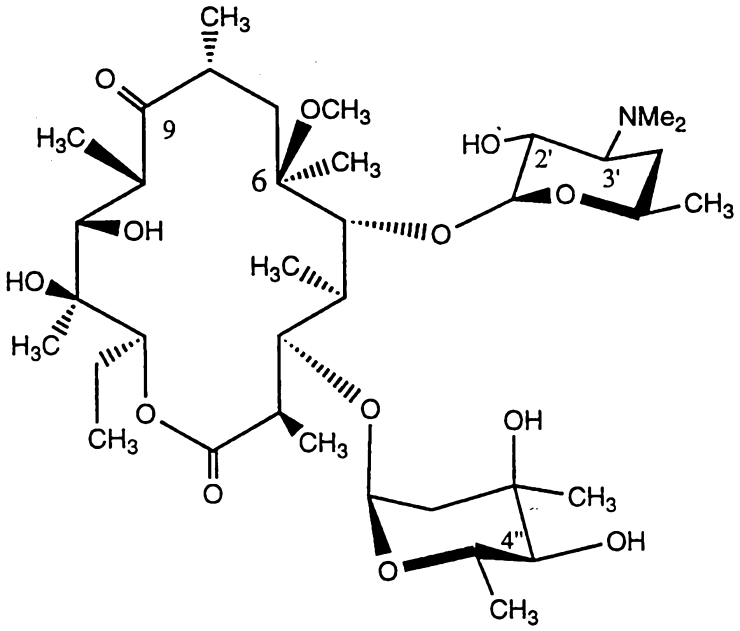
Description

Technical Field of the Invention

The present invention relates to erythromycin derivatives. More particularly, the present invention pertains to a process for the chemical synthesis of 6-O-alkyl derivatives of erythromycin C.

Background of the Invention

6-O-alkyl derivatives of erythromycin C have use as antibacterial agents. For example, 6-O-methyl erythromycin C (clarithromycin C), shown below, is a potent macrolide antibiotic.



6-O-methyl erythromycin C is a minor fermentation product of the microbial transformation of 6-O-methyl erythromycin A by *Mucor circinelloides* (McAlpine et al., 27th International Conference of Antimicrobial Agents and Chemotherapy, New York, October, 1987). There are, however, no reported methods for the chemical synthesis of 6-O-methyl erythromycin C. There is a need in the art, therefore, to provide a rapid, efficient method of chemically synthesizing 6-O-alkyl derivatives of erythromycin C and, in particular, 6-O-methyl erythromycin C.

Brief Summary of the Invention

The present invention provides an efficient and practical method of synthesizing a 6-O-alkyl erythromycin C derivative and, particularly 6-O-methyl erythromycin C. The synthetic process starts with the conversion of erythromycin C to 9-oxime erythromycin C. The oxime hydroxyl group (N-OH) of 9-oxime erthromycin C is protected. The 9-oxime protected derivative is O-protected at the 2'- and 4"- hydroxyl groups and the 6-hydroxyl group is alkylated. The 6-O-alkyl erythromycin C derivative is then obtained by deprotecting the 9-oxime hydroxyl group, deprotecting the 2'- and 4"- hydroxyl groups and deoximating the 9-oxime.

In a preferred embodiment, protection of the oxime hydroxyl group is accomplished by reacting 9-oxime erythromycin C with a ketalizing reagent such as a loweralkyl cycloalkyl ketal. O-Protection of the 2'- and 4"-hydroxyl groups is accomplished using an acyl protecting group. Acetyl is a most preferred acyl protecting group.

The 9-oxime derivative (oxime protected or unprotected) can be unsubstituted at the 3'-dimethylamino position or can contain a conventional N-protecting group at that position. Exemplary and preferred N-protecting groups are alkoxycarbonyl groups, alkoxyalkoxycarbonyl groups, haloalkoxycarbonyl groups, unsaturated alkoxycarbonyl groups, substituted benzyloxycarbonyl groups, substituted phenoxycarbonyl groups, and the like.

The present invention also relates to novel intermediates useful in the preparation of a 6-O-alkyl erythromycin C. Those intermediates are 9-oxime derivatives that are alkylated at the 6-position and unsubstituted or substituted at the 2'-, 3'- and/or 4"-positions.

Detailed Description of the Invention

I. Definitions

A number of defined terms are used herein to designate particular elements of the present invention. When so used, the following meanings are intended:

The term "alkyl" refers to saturated, straight or branched-chain hydrocarbon radicals containing between one and ten carbon atoms including, but not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl and neopentyl. More preferably, the alkyl is limited to lower alkyls having 1-6 carbons.

The term "alkylating agent" refers to a reagent capable of placing an alkyl group onto a nucleophilic site, including, but not limited to, alkyl halides such as methyl bromide, ethyl bromide, n-propyl bromide, methyl iodide, ethyl iodide; and n-propyl bromide; dialkyl sulfates such as dimethyl sulfate, diethyl sulfate; and di-n-propyl sulfate; and alkyl or aryl sulfonates such as methyl-p-toluenesulfonate, ethyl methanesulfonate, n-propyl methanesulfonate, and the like.

The term "aryl(lower alkyl)" refers to a lower alkyl radical having appended thereto 1-3 aromatic hydrocarbon groups, as for example benzyl, diphenylbenzyl, trityl and phenylethyl.

The term "aryloxy" refers to an aromatic hydrocarbon radical which is joined to the rest of the molecule via an ether linkage (*i.e.*, through an oxygen atom), as for example phenoxy.

The term "cycloalkyl" refers to a saturated monocyclic hydrocarbon radical having from three to eight carbon atoms in the ring and optionally substituted with between one and three additional radicals selected from among lower alkyl, halo(lower alkyl), lower alkoxy, and halogen. Examples of cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 1-fluoro-cyclopropyl, and 2-fluorocyclopropyl.

The term "ketal" refers to a compound in which the carbonyl oxygen of a ketone has been replaced by two alkoxy groups.

The term "lower alkenyl" refers to a straight or branched-chain hydrocarbon radical containing between two and six carbon atoms and possessing at least one carbon-carbon double bond. Examples of lower alkenyl radicals include vinyl, allyl, 2- or 3-butenyl, 2-, 3- or 4-pentenyl, 2-, 3-, 4- or 5-hexenyl and isomeric forms thereof.

The term "lower alkoxy" refers to a lower alkyl radical which is joined to the rest of the molecule via an ether linkage (*i.e.*, through an oxygen atom). Examples of lower alkoxy radicals include, but are not limited to, methoxy and ethoxy.

The term "lower alkyl" refers to an alkyl radical containing one to six carbon atoms including, but not limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, *tert*-butyl and neopentyl.

The term "polar aprotic solvent" refers to polar organic solvents lacking an easily removable proton , including, but not limited to, N,N-dimethylformamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, acetonitrile, and the like.

The term "silyl" refers to a radical of the formula Si $(R^1)(R^2)(R^3)$ where each of R^1, R^2 and R^3 are independently hydrogen, lower alkyl, aryl, phenyl, phenylsubstituted lower alkyl, cycloalkyl or alkenyl.

The term "strong alkali metal base" refers to an alkali metal base having a weak conjugate acid, including, but not limited to, sodium hydroxide, potassium hydroxide, sodium hydride, potassium hydride, potassium t-butoxide, and the like.

The term "substituted aryl(lower alkyl)" refers to an aryl(lower alkyl) residue as defined above having between one and three non-hydrogen ring substituents, each independently selected from among halogen, lower alkoxy, lower alkyl, hydroxy-substituted lower alkyl, and (lower alkyl)amino. Examples of substituted aryl(lower alkyl) radicals include 2-fluorophenylmethyl, 4-fluorophenylethyl and 2,4-difluorophenylpropyl.

The term "weak organic amine base" refers to an organic amine base having a strong conjugate acid, including, but not limited to trimethylamine, triethylamine, tripropylamine, pyridine, 2-

methoxypyridine, 1-methylpyrrolidine, 1-methylpiperidine, and 1-ethylpiperidine, and the like.

II. Process of making a 6-O-Alkyl Erythromycin C

In one aspect, the present invention provides a process of preparing a 6-O-alkyl derivative of erythromycin C. That process includes the steps of converting erythromycin C to 9-oxime erythromycin C, protecting the oxime hydroxyl group (N-OH) and reacting the 9-oxime protected erythromycin C with an alkylating agent.

A process of the present invention begins with erythromycin C, typically produced using fermentation. Conversion to 9-oxime erythromycin C is accomplished using standard procedures well known in the art. Briefly, erythromycin C is reacted with either hydroxylamine hydrochloride and a base, free hydroxylamine in methanol or hydroxylamine and an organic acid (See, e.g., U.S. Patent No. 5,274,085, the disclosure of which is incorporated herein by reference). Preferably, oximation of erythromycin C is accomplished using hydroxylamine and formic acid.

The 9-oxime hydroxyl group (N-OH) of 9-oxime erythromycin C is then protected. Suitable protecting groups for the 9-oxime hydroxyl group are silyl and ketal groups. The 9-oxime erythromycin C can be silylated by reacting the compound with a silylating reagent. A preferred silylating reagent has the formula

$XSi(R')(R'')(R''')$

where R', R", and R"' are independently hydrogen, lower alkyl, aryl, phenyl, phenyl substituted lower alkyl, cycloalkyl or alkenyl and X is a halogen or a sulfonate (e.g., mesylate, tosylate). The silylating reaction is carried out in the presence of a suitable organic base such as triethylamine (Et_3N), pyridine, imidazole or di-trimethylsilyl amine [$HN(TMS)_2$]. The silylating reaction can also be carried out in the presence of a suitable acid such as HCO_2H.

Another exemplary silylating reagent has the formula:

$HN[Si(R')(R'')(R''')]_2$

where R', R", and R"' are defined above.

Protection of the oxime hydroxyl group can also be accomplished by reacting 9-oxime erythromycin C with a suitable ketalizing reagent. An exemplary and preferred such ketalizing reagent is a lower alkyl cycloalkyl ketal. An especially preferred ketalizing reagent is isopropyl cyclohexyl ketal.

As is well known in the art, to efficiently and selectively alkylate erythromycin C at the 6-OH position, the hydroxyl groups at the 2'- and/or 4"- positions should be protected prior to methylation. It may also be desirable to protect the 3'-dimethylamino group. Such protection is accomplished by protecting those groups with conventional O- or N- protecting groups. The order of protection of 9-oxime and 2', 4"- OH groups can be exchanged.

Exemplary and preferred O-protecting groups are acyl groups or lower alkyl monocarbonyl groups such as acetyl, propionyl, butyryl, isobutyryl and the like. The use of O-protecting groups in the preparation of erythromycin derivatives has been described (See, e.g., U.S. Patent No. 4,672,109, and European Patent Application 0260938A2, the disclosures of which are incorporated herein by reference).

Conventional O-protecting groups, as set forth above, are positioned using standard procedures well known in the art. By way of example, an acetyl group can be positioned at the 2'- and 4"- positions by reacting erythromycin C (9-oxime or 9-oximketal) with an acetylating agent in an aprotic solvent. Suitable acetylating agents that can be used include anhydride and acid halide compounds of the formula $(R^4CO)_2O$ or R^4COCl, where R^4 is hydrogen or a substituent group such as lower alkyl (e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl and the like) or aryl (e.g., phenyl, p-methoxyphenyl, p-chlorophenyl, m-chlorophenyl, o-chlorophenyl, 2,4,-dichlorophenyl, p-bromophenyl, m-nitrophenyl, p-nitrophenyl, benzhydryl, 1-naphthyl and the like). Examples of aprotic solvents are dichloromethane, chloroform, DMF, tetrahydrofuran, dimethyl sulfoxide, ethyl acetate, N-methyl-2-

pyrrolidone, hexamethylphosphoric triamide, 1,2-dimethoxyethane, acetonitrile, and the like.

One of skill in the art will readily appreciate that it may be advantageous to also substitute for a methyl group of the dimethylamino moiety at the 3'-position of erythromycins using a conventional N-protecting group. Exemplary and preferred N-protecting groups are alkoxycarbonyl groups (e.g., a methoxycarbonyl group, an ethoxycarbonyl group, an isopropoxycarbonyl group, an n-propoxycarbonyl group, an n-butoxycarbonyl group, an isobutyloxycarbonyl group, a sec-butyloxycarbonyl group, a t-butyloxycarbonyl group, a 2-ethylhexyloxycarbonyl group, a cyclohexyloxycarbonyl group, a methyloxycarbonyl group and the like); alkoxyalkoxycarbonyl groups (e.g., a methoxymethoxycarbonyl group, an ethoxymethoxycarbonyl group, a 2-methoxyethoxycarbonyl group, a 2-ethoxyethylcarbonyl group, a 2-ethoxyethoxycarbonyl group, a 2-butoxyethoxycarbonyl group, a 2-methoxyethoxymethoxycarbonyl group and the like); haloalkoxycarbonyl groups (e.g., a 2-chloroethoxycarbonyl group, a 2-chloroethoxycarbonyl group, a 2,2,2-trichloroethoxycarbonyl group and the like), unsaturated alkoxycarbonyl groups (e.g., an allyloxycarbonyl group, a propargyloxycarbonyl group, a 2-butenoxycarbonyl group, a 3-methyl-2-butenoxycarbonyl group and the like), substituted benzyloxycarbonyl groups (e.g., a benzyloxycarbonyl group, a p-methylbenzyloxycarbonyl group, a p-methoxybenzyloxycarbonyl group, a p-nitrobenzyloxycarbonyl group, a 2,4-dinitrobenzyloxycarbonyl group, a 3,5-dimethylbenzyloxycarbonyl group, a p-chlorobenzyloxycarbonyl group, a p-bromobenzyloxycarbonyl group and the like), and substituted phenoxycarbonyl groups [e.g., a phenoxycarbonyl group, a p-nitrophenoxycarbonyl group, an o-nitrophenoxycarbonyl group, a 2,4-dinitrophenoxycarbonyl group, a p-methylphenoxycarbonyl group, an m-methylphenoxycarbonyl group, an o-bromophenoxycarbonyl group, a 3,5-dimethylphenoxycarbonyl group, a p-chloro-phenoxycarbonyl group, a 2-chloro-4-nitrophenoxycarbonyl group and the like (U.S. Patent No. 4,672,109)].

The dimethylamino moiety at the 3'-position may also be protected as a quaternary salt by reacting with a 3'-dimethylamino derivative A-X, wherein A is a 2-alkenyl group, a benzyl group or a substituted benzyl group; and X is a halogen atom (See, e.g., U.S. Patent No. 4,670,549). The 9-oximesilyl, 2'- and 4"-substituted erythromycin C derivative is then selectively alkylated at the 6-position. Procedures and reagents for alkylating the 6-position of erythromycin A derivatives are well known in the art (See, e.g., U.S. Patent Nos. 4,672,109 and 4,670,549).

Following protection, the 6-hydroxyl group is selectively alkylated. Briefly, the hydroxyl-protected compound is reacted with a suitable alkylating agent in the presence of a base. Exemplary and preferred alkylating agents are alkyl halides such as methyl bromide, ethyl bromide, n-propyl bromide, methyl iodide, ethyl iodide, n-propyl iodide, dimethyl sulfate, diethyl sulfate, di-n-propyl sulfate, methyl-p-toluenesulfonate, ethyl methanesulfonate, and n-propyl methanesulfonate.

Exemplary and preferred bases are a strong alkali metal base, preferably selected from the group consisting of an alkali metal hydride, alkali metal hydroxide or alkali metal alkoxide, and a weak organic amine base, preferably selected from the group consisting of trimethylamine, triethylamine, tripropylamine, pyridine, 2-methoxypyridine, 1-methylpyrrolidine, 1-methylpiperidine, and 1-ethylpiperidine.

The alkylation step is carried out in a suitable solvent that includes methyl-t-butyl ether. Exemplary and preferred solvents are polar aprotic solvents such as N, N-dimethylformamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethylphosphoric triamide, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile or ethyl acetate, or a mixture of such polar aprotic solvents maintained at a reaction temperature and for a period of time sufficient to effect alkylation, preferably from -15°C to room temperature for a period of 1 to 8 hours.

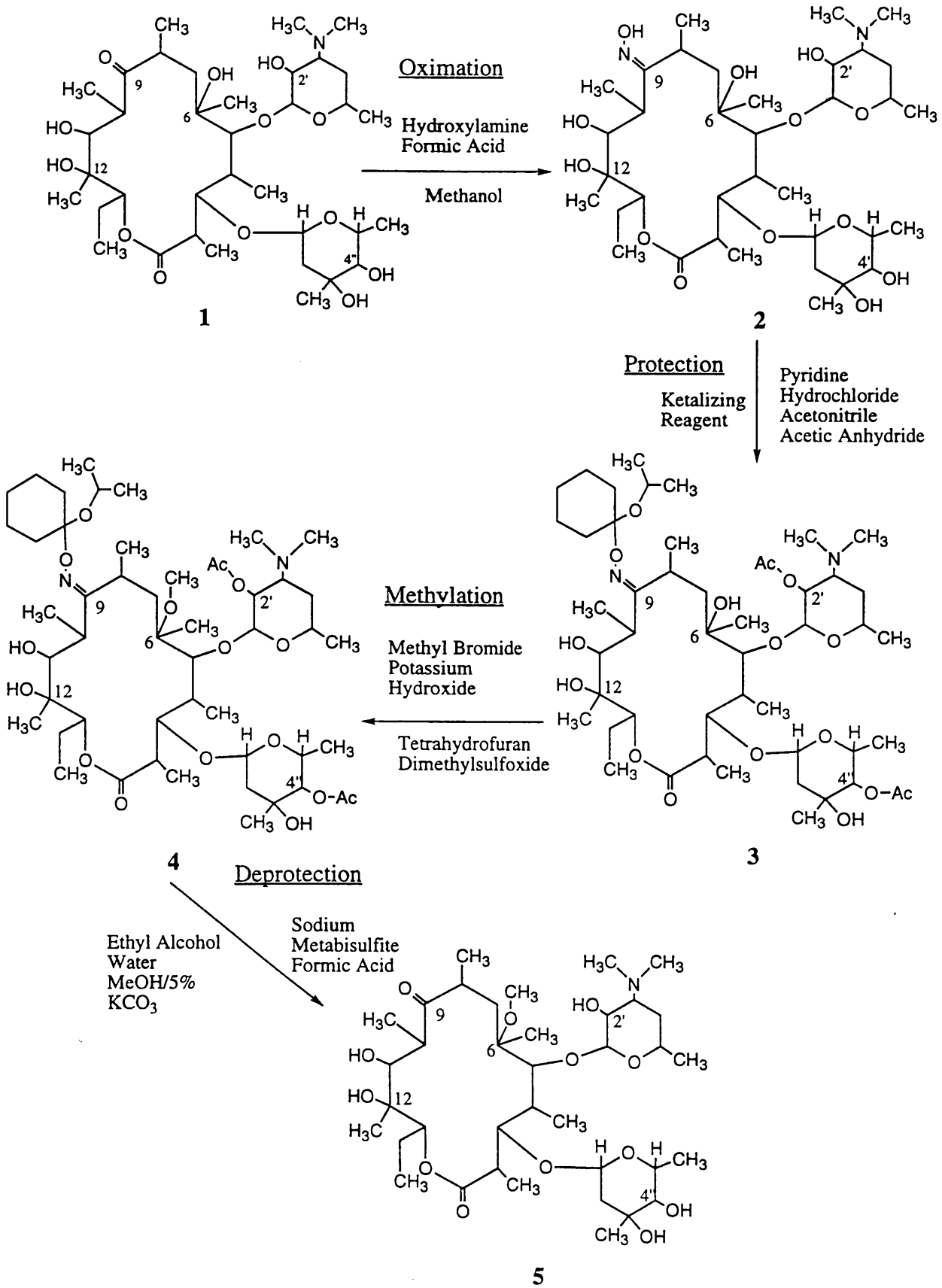
The preparation of 6-O-alkyl erythromycin C proceeds by removing the O-protecting groups from the 2'- and 4"-positions and the ketal group from the 9-oximeketal and then deoximating the 9-oxime. Means for removing the O-protecting groups at the 2'- and 4"-positions are well known in the art and depend upon the nature of the protecting group.

By way of example, where the 2' and/or 4"-positions are acetylated, the acetyl group can be removed by reacting the acetylated derivative with a compound of the formula R^5OH, where R^5 is alkyl (e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, t-butyl and the like). The reaction can take place in the absence or presence of an acid (e.g., formic acid, acetic acid) or water, or can take place in the absence or presence of a base (e.g., KCO_3, $NaCO_3$, $KHCO_3$, $NaHCO_3$).

Removal of the ketal group from the 9-oximeketal is accomplished using acidification. A final step in the preparation of a 6-O-alkyl erythromycin C is deoximation. Deoximation is carried out in accordance with standard procedures well known in the art (See e.g., U.S. Patent No. 4,672,109). Briefly, 9-oxime erythromycin C is reacted with sodium hydrogen sulfite in alcohol (e.g., ethanol) and refluxed. The solution is cooled, alkalinized and precipitated with aqueous alkali metal bicarbonate. The precipitate formed in the above reaction is collected by filtration, washed and recrystallized with alcohol.

A detailed description of the synthesis of 6-O-methyl erythromycin C using a process of the present invention is set forth hereinafter in the Examples. A schematic illustration of one embodiment of a synthetic scheme in accordance with the present invention is set forth below in Scheme 1.

Scheme 1


Oximation
Hydroxylamine
Formic Acid
Methanol
1
2
Protection
Ketalizing
Reagent
Pyridine
Hydrochloride
Acetonitrile
Acetic Anhydride
Methylation
Methyl Bromide
Potassium
Hydroxide
Tetrahydrofuran
Dimethylsulfoxide
3
4
Deprotection
Ethyl Alcohol
Water
MeOH/5%
KCO3
Sodium
Metabisulfite
Formic Acid
5

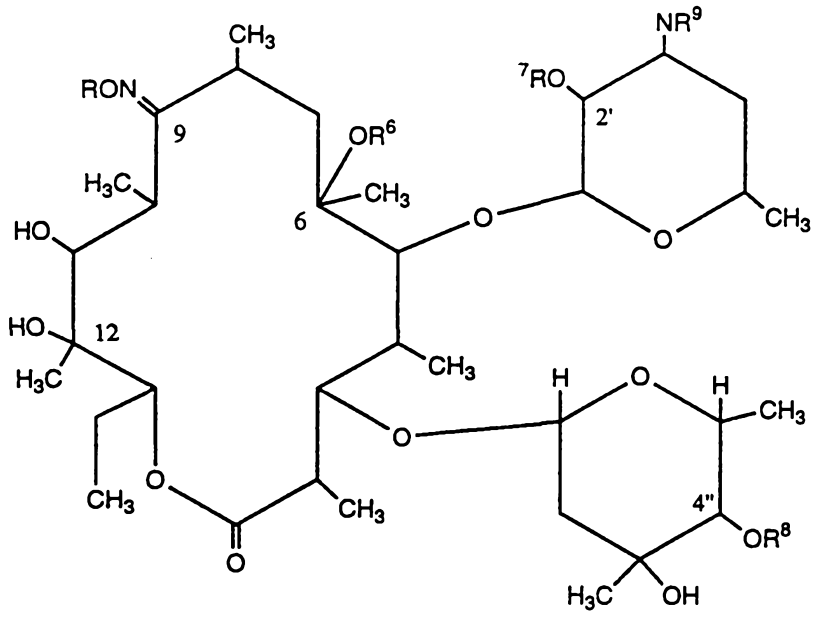
With reference to Scheme 1, erythromycin C (**Compound 1**) is reacted with hydroxylamine in the presence of formic acid and methanol to form 9-oxime erythromycin C (**Compound 2**).

Compound 2 is then reacted with a ketalizing reagent followed by reaction with pyridine hydrochloride and acetic anhydride in acetonitrile to form 2', 4"-diacetyl-9-oximeketal erythromycin C (**Compound 3**).

Methylation of the 6-OH group is then carried out by reacting **Compound 3** with a methylating agent (methyl bromide) and potassium hydroxide in an appropriate solvent [dimethylsulfoxide (DMSO) and tetrahydrofuran (THF)] to form 2', 4"-diacetyl-6-O-methyl-9-oximeketal erythromycin C (**Compound 4**). The ketal group at the 9-position is removed by reacting **Compound 4** with formic acid. The resulting 9-oxime is deoximated with sodium metabisulfide. The acetyl groups at the 2'- and 4"-positions are removed by reaction with ethyl alcohol, water, methanol (MeOH) and potassium carbonate (K_2CO_3) to yield 6-O-methyl erythromycin C (**Compound 5**).

III. 6-O-Alkyl-9-Oxime Erythromycin C Derivatives

The present invention also provides 9-oxime derivatives of erythromycin C, which derivatives are intermediates in the synthesis of a 6-O-alkyl erythromycin C. A 9-oxime derivative of the present invention is alkylated at the 6-position and unsubstituted (i.e., 2'-OH, 4"-OH, 3'-dimethyl) or substituted at the 2', 4" or 3'-positions with a conventional protecting group as set forth above. A 9-oxime erythromycin C derivative of the present invention corresponds to the structure I below:



I

wherein R is hydrogen, ketal or silyl, R^6 is hydrogen or alkyl, R^7 and R^8 are each independently hydrogen or a conventional O-protecting group, and R^9 is $-NR^{10}CH_3$, where R^{10} is methyl (CH_3) or a conventional N-protecting group or $-N^+(CH_3)_2R^{11}X$, where R^{11} is 2-alkenyl, benzyl or substituted benzyl, and X is a halogen such as Br, Cl or I.

The compound of structure I is shown without spatial bond orientation. Structure I, thus, defines all combinations of bond orientation and is intended to cover all possible stereo-configurations (e.g., epimers). In a preferred embodiment, the bond orientations of Structure I are the same as shown above for 6-O-methyl erythromycin C.

In one embodiment, 9-oxime erythromycin C is unsubstituted (unprotected) at the 2'-, 3' and 4"-positions. Ketalation of such a derivative results in formation of a 9-oximeketal derivative of structure I, where R^7 and R^8 are both hydrogen and R^6 is methyl.

In another embodiment, 9-oxime erythromycin C used in the synthetic process has conventional O-protecting groups at the 2'- and/or 4"- positions. Conventional O-protecting groups for protecting hydroxyls from alkylation are well known in the art and include silyl, acyl, lower alkenyl monocarbonyl, alkoxycarbonyl, alkylcarbonyl, lower alkoxycarbonylalkylcarbonyl, and arylcarbonyl groups.

The following Examples illustrate preferred embodiments of the present invention and are not limiting of the specification and claims in any way.

Example 1: Preparation of 9-Oxime Erythromycin C

Erthromycin C, 15.38 g (21.4 m mole) was dissolved in 150 mL methanol, and 46.6 g 50% w/w hydroxylamine and 14.5 g formic acid (88%) were added at room temperature; the temperature rose to 36ºC and external heating was started. The solution was refluxed for 16 hours and then cooled to ambient temperature. The volume of the solution was reduced to half under vacuum distillation and 200 mL ethyl acetate was added to extract the product. After the layers were separated, the lower aqueous layer was re-extracted once more with 200 mL ethyl acetate. The two ethyl acetate layers were combined and washed with 50 mL water. The organic layer was dried with magnesium sulfate, and the solids were removed by filtration, providing a clear solution, which was stripped on Rotavap to give 15.06 g of the title compound.

Example 2: Preparation of 9-Oximeketal Erythromycin C

9-Oxime erthromycin C from Example 1, (3.1 g) (4.2 m mole) was dissolved in 12 mL acetonitrile and 5.4 g diisopropylcyclohexyl ketal was added followed by the addition of 12 mL pyridine hydrochloride in acetonitrile (1.0 m solution). The reaction mixture was quenched with 100 mL heptane and 20 ml of 2 N NaOH. The layers were separated and the product in the heptane layer was collected by filtration to give 1.9 g of the title compound.

Example 3: Preparation of 2',4"-Diacetyl-9-Oxime Erythromycin C

The product from Example 2 was dissolved in 20 mL pyridine into which 2 mL acetic anhyride was added. The mixture was stirred for 26 hours and quenched with 100 mL ether and 50 g ice. Then, 20 mL of 2N sodium hydroxide and 10 g of sodium chloride were added. The layers were separated and the upper organic layer was washed with 15 mL saturated salt solution. The organic layer was dried with

magnesium sulfate and the solids were removed by filtration. The solvent was distilled under vacuum and the residual oil chased three ties with 15 mL toluene each time; 2.0 g of the title product was obtained.

Example 4: Preparation of 2',4"-Diacetyl-6-O-Methyl-9-Oximeketal Erythromycin C

1.8 g of the product from Example 3 was dissolved in 14 mL tetrahydrofuran, and 18 mL dimethyl sulfoxide and cooled to 0-5ºC, followed by 5 ml methyl bromide and 0.1 g powder KOH. The mixture was stirred at this temperature for 10 minutes and quenched with 110 mL heptane and 10 mL 2 N sodium hydroxide. The layers were separated and the upper heptane layer was dried with magnesium sulfate and the solvent was removed to give 1.2 g of the title compound.

Example 5: Preparation of 6-O-Methyl Erythromycin C

The deketalization and deoximation reaction of the product from Example 4 was accomplished by acid hydrolysis of the ketal functionality followed by sodium bisulfite treatment. Thus, 1.2 g of the product from Example 4 was dissolved in 60 mL 3A alcohol and 60 mL water with 0.31 g formic acid (88%). The solution was heated to 60-65°C for two hours. 3.0 grams of sodium bisulfite was added and the mixture stirred for 2 hours. The solution was cooled to room temperature and the volume reduced to half under vacuum distillation. Methylene chloride (100 mL) was used to extract the product. After removal of the solvent, 0. 82 g of 2'-acetyl erythromycin C was obtained. This solid was dissolved in 20 mL methanol and 10 mL 5% potassium carbonate and stirred at room temperature for three hours. This solution was stripped to an oil under vacuum and the oil dissolved in 50 mL methylene chloride, dried with magnesium sulfate and filtered. After solvent removal, 0.66 g of 6-O-methyl erythromycin C was obtained. Anlytical samples was obtained by preparatory HPLC using YMC column and 50/50 acetonnitrile/buffer. Confirmation of structure of the formed product was obtained by NMR. The buffer contained 0.25 % KH_2P0_4 at 7.0. The results of the NMR analysis are set forth in the Table below.

^{1}H and ^{13}C NMR Assignments for Example 5

Position	^{13}C (ppm) [a]	^{1}H (ppm) [b]
Erythronolide		
1	175.8	-
2	45.4	2.86
2-Me	16.1	1.22
3	81.7	3.88
4	39.6	1.92
4-Me	9.1	1.08
5	82.1	3.61
6	78.7	-
6-Me	19.7	1.46
7	39.5	1.83, 1.77
8	45.1	2.60
8-Me	18.0	1.15
9	220.9	-
10	37.2	3.01
10-Me	12.2	1.14
11	69.0	3.74
12	74.2	-
12-Me	16.0	1.11
13	77.0	5.05
14	20.9	1.94, 1.49
15	10.6	0.85
Ome	50.6	3.03
Desosamine		
1'	104.5	4.27
2'	70.8	3.19
3'	65.5	2.44
4'	28.3	1.67, 1.24
5'	69.4	3.50
6'	21.4	1.25
NmE_2	40.2	2.27
Cladinose		
1"	98.5	5.03
2"	40.3	2.21, 1.84
3"	69.5	-
3"-Me	25.6	1.27
4"	76.4	3.00
5"	66.3	3.91
6"	18.5	1.36

[a] Relative to $CHCl_3$ assigned as 77.0 ppm.

[b] Relative to $CHCl_3$ assigned as 7.27 ppm.

Example 6: Anti-bacterial activity of 6-0-Methyl Ethromycin C

6-O-Methyl erythromycin C prepared in accordance with Examples 1-5 was assayed *in vitro* for antibacterial activity as follows: Twelve petri dishes containing successive aqueous dilutions of the test compound mixed with 10mL of sterilized Brain Heart Infusion (BHI) agar (Difco 0418-01-5) were prepared. Each plate was inoculated with 1:100 (or 1:10 for slow-growing strains, such as *Micrococcus* and *Streptococcus*) dilutions of up to 32 different micoorganisms, using a Steers replicatore block. The inoculated plates were incubated at 35-37° for 20 to 24 hours. In addition, a control plate, using BHI agar containing no test compound, was prepared and incubated at the beginning and end of each test.

An additional plate containing a compound having known susceptibility patterns for the organisms being tested and belonging to the same antibiotic clas as the test compound was also prepared and incubated as further control, as well as to provide test-to-test comparability.

After incubation, each disk was read. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of drug yielding no growth, a slight haze, or sparsely isolated colonies on the inoulum spot as compared to the growth control. The results of this assay, shown below in Tables 2 and 3, support the conclusion that 6-O-meythylerythromycin C is an effective antibacterial agent.

TABLE 2

MICROBIOLOGICAL DATA

ORGANISM MIC (μg/ml)

	6-OMeA	14-OH	15-OH	6-OMeC	14-OH-C
STAPHYLOCOCCUS AUREUS ATCC 6538P	.1	.78	.78	.2	.39
STAPHYLOCOCCUS AUREUS A5177	.78	3.1	6.2	1.56	1.56
STAPHYLOCOCCUS AUREUS 45	.1	.39	.78	.2	.39
STAPHYLOCOCCUS AUREUS 45 RAR2	.2	.78	.78	.2	.39
STAPHYLOCOCCUS AUREUS CMX 503A		.78	.78	.2	.39
STAPHYLOCOCCUS AUREUS CMX 553		.78	.78	.2	.39
STAPHYLOCOCCUS EPIDERMIDIS 3519	.1	.78	.78	.2	.39
MICORCOCCUS LUTEUS ATCC 9341	.1	.1	.2	.02	.05
MICORCOCCUS LUTEUS ATCC 4698	.2	.39	.78	.2	.39
ENTEROCOCCUS FAECIUM ATCC 8043	.05	.2	.39	.1	.2
STREPTOCOCCUS BOVIS A5169	.005	.02	.05	.01	.02
STREPTOCOCCUS AGALACTIAE CMX 508	.02	.1	.2	.05	.1
STREPTOCOCCUS PYOGENES EES61	.01	.39	.39	.1	.2
STREPTOCOCCUS PYOGENES 930 CONST	>100.	>25.	>25.	>25.	>25.
STREPTOCOCCUS PYOGENES 2548 INDUC		12.5	25.	3.1	6.2
ESCHERICHIA COLI JUHL	25.	>25.	>25.	>25.	>25.
ACINETOBACTER SP CMX 669	6.2	12.5	>25.	12.5	6.2

MEDIUM: MHA+LYHB+N

TABLE 3

ORGANISM MIC (μg/ml)

	6-OMeA	14-OH	15-OH	6-OMeC	14-OH-C
HAEMOPHILUS INFLUENZAE 503B	1	4	2	4	2
HAEMOPHILUS INFLUENZAE 504	2	16	4	8	4
HAEMOPHILUS INFLUENZAE 1177	1	1	.5	1	.5
HAEMOPHILUS INFLUENZAE ATCC 19418	1	2	2	8	2

WHAT IS CLAIMED IS

1. A process of preparing a 6-O-alkyl derivative of erythromycin C comprising the steps of:

a) oximating erythromycin C to form 9-oxime erythromycin C;

b) ketalizing the 9-oxime erythromycin C to form 9-oximeketal erythromycin C;

c) acylating the 9-oximeketal erythromycin C to form 2',4"-diacyl-9-oximeketal erythromycin C;

d) alkylating the 6-hydroxyl group of the 2',4"-diacyl-9-oximeketal erythromycin C to form a 2',4"-diacyl-6-O-alkyl-9-oximeketal erythromycin C derivative; and

e) deprotecting the 9-oxime hydroxyl, the 2'- and 4"-hydroxyl groups and deoximating the 9-oxime erythromycin C to provide the 6-O-alkyl erythromycin C derivative.

2. The process of claim 1 wherein erythromycin C is reacted with hydroxylamine in the presence of a organic acid.

3. The process of claim 2 wherein the organic acid is formic acid.

4. The process of claim 1 wherein 9-oxime erythromycin C is reacted with a lower alkyl cycloalkyl ketal.

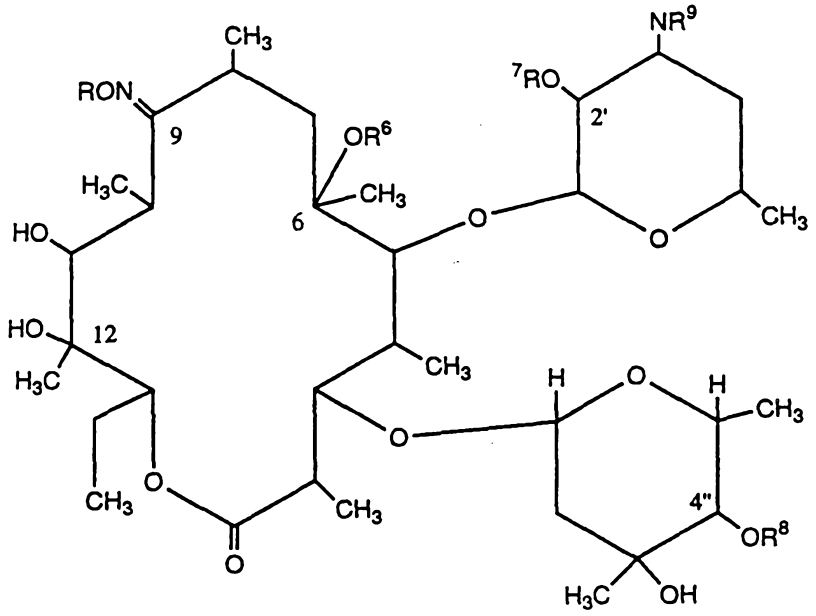
5. The process of claim 4 wherein the lower alkyl cycloalkyl ketal is isopropyl cyclohexyl ketal.

6. The process of claim 1 wherein the 9-oximeketal erythromycin C derivative is reacted with acetic anhydride in pyridine.

7. The process of claim 1 wherein the 2',4"- diacyl-9-oximeketal erythromycin C is reacted with an alkyl halide.

8. The process of claim 7 wherein the alkyl halide is methyl bromide.

9. A compound having the structure I, below:



I

where R is hydrogen, ketal or silyl, R^6 is hydrogen or alkyl, R^7 and R^8 are each independently hydrogen or a conventional O-protecting group, and R^9 is $-NR^{10}CH_3$, where R^{10} is methyl (CH_3) or a conventional N-protecting group or $-N^+(CH_3)_2R^{11}X^-$, where R^{11} is 2-alkenyl, benzyl or substituted benzyl, and X is a halogen.

10. The compound of claim 9 where R is isopropyl cyclohexyl ketal.

11. The compound of claim 9 where R^7 and R^8 are both acetyl and R^9 is dimethyl.