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(54) Title: PROCESSES FOR PREPARING CLARITHROMYCIN AND CLARITHROMYCIN INTERMEDIATE, ESSENTIALLY OXIME-FREE CLARITHROMYCIN, AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

(57) Abstract: The present invention relates to processes for preparing protected silylated clarithromycin oxime, preferably 6-O-methy-2',4"-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime("S-MOP oxime"), and for converting protected silylated clarithromycin oxime, preferably S-MOP oxime, to clarithromycin. Processes for preparing protected silylated clarithromycin oxime according to the present invention, include reacting a silyl oxime derivative with methylating agent in the presence of at least one solvent and a base, where the solvent comprises methyl tertbutyl ether. Processes for converting protected silylated clarithromycin oxime to clarithromycin according to the present invention, include reacting protected silylated clarithromycin oxime with ethanol and water at an ethanol to water ratio of about 1:1, in the presence of an acid and a deoximating agent and cooling the reaction mixture prior to adding sodium hydroxide, where the process takes place without any additional water addition. Further processes for converting protected silylated clarithromycin oxime to clarithromycin, include heating a mixture of protected silylated clarithromycin oxime, acid, and deoximating agent in an ethanol/water solvent to reflux for more than 4 hours, with a two-fold addition of deoximating agent to produce essentially oxime-free clarithromycin.

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PROCESSES FOR PREPARING CLARITHROMYCIN AND CLARITHROMYCIN INTERMEDIATE, ESSENTIALLY OXIME-FREE CLARITHROMYCIN, AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

CROSS REFERENCE TO RELATED APPLICATION

The present application claims the benefit of U.S. Provisional Application Nos. 60/185,888 filed on February 29, 2000, 60/189,120 filed on March 14, 2000, and 60/213,239 filed on June 22, 2000.

FIELD OF THE INVENTION

The present invention relates to methods for preparing a protected silylated clarithromycin oxime, such as 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime (hereinafter "S-MOP oxime"), which include reacting a silyl oxime derivative with methylating agent while stirring in the presence of at least one solvent, where the solvent includes at least methyl tert-butyl ether (MTBE), and a base.

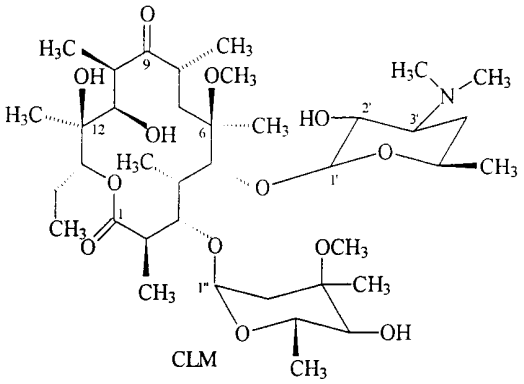
The present invention also relates to a method of converting the protected silylated clarithromycin oxime to clarithromycin, which includes reacting the protected silylated clarithromycin oxime with acid and deoximating agent in the presence of ethanol and water at an ethanol to water ratio of about 1:1. The reaction mixture is cooled to about 20°C and a base, preferably sodium hydroxide, is added. The method does not include any additional water addition to process clarithromycin.

The present invention further relates to a method of converting a protected silylated clarithromycin oxime, such as S-MOP oxime, to clarithromycin, which includes heating a mixture of the protected silylated clarithromycin oxime, acid, and deoximating agent in an ethanol/water solvent to reflux for more than 4 hours, with a two-fold addition of said deoximating agent. The invention further relates to the essentially oxime-free clarithromycin produced by such a method and pharmaceutical compositions containing the same.

BACKGROUND OF THE INVENTION

6-O-methyl erythromycin A (clarithromycin) is a semisynthetic macrolide antibiotic related to erythromycin A. It exhibits excellent antibacterial activity against gram-positive bacteria, some gram-negative bacteria, anaerobic bacteria, Mycoplasma, and Chlamydia. It is stable under acidic conditions and is efficacious when administered orally. Clarithromycin is a useful therapy for infections of the upper respiratory tract in children and adults. Clarithromycin is stable under acidic conditions and is efficacious when administered orally.

The chemical structure of clarithromycin is:



Various methods of preparing 6-O-methylerythromycin A from erythromycin A have been described in the patent literature. One of the most effective methods includes the following steps: 1) protecting the 9-oxo group with a substituted oxime group, 2) protecting the hydroxyl groups in positions 2' and 4'', 3) methylating the hydroxyl in position 6 to give a protected sililated clarithromycin oxime, and 4) removing the protecting groups at the 2', 4'' and 9 position.

The third step, which comprises methylating the hydroxyl group at position 6, is performed in the presence of a solvent. This 6-O-methylation of various erythromycin derivatives in converting erythromycin A to clarithromycin has been reported in several U.S. Patents including U.S. Patent Nos. 4,680,386 and 4,672,109.

U.S. Patent No. 4,680,386 for example, describes a method of methylating the hydroxyl group at the 6 position by reacting the compound with a methylating agent in the

presence of a base in an aprotic solvent at a temperature of between 0°C and room temperature. The '386 patent describes the use of solvents including N,N-dimethylformamide, dimethyl sulfoxide, hexamethylphosphoric triamide, and a mixture of one or more of these solvents. U.S. Patent No. 4,672,109 describes the use of solvents such as dimethyl sulfoxide, N,N-dimethylformamide, hexamethyl phosphoric triamide, a mixture of two or more of these solvents or a mixture of one of these solvents and tetrahydrofuran, 1, 2-dimethoxyethane and the like. The '109 patent further describes a preferred embodiment of this step using a mixture of dimethyl sulfoxide and tetrahydrofuran. WO 97/19096 describes a mixture of solvents including N,N-dimethylformamide, dimethyl sulfoxide, N-methyl-2-pyrrolidone, hexamethyl phosphoric triamide, tetrahydrofuran, 1,2-dimethoxyethane, acetonitrile and ethyl acetate for use in the methylating step.

However, several of the above-described solvents are expensive, do not enable selective methylation, produce significant unwanted side products and/or cause complications during later phase separation steps.

The fourth step includes removing the protecting groups, and thus, converts protected silylated clarithromycin oxime to clarithromycin. Described methods of converting a protected silylated clarithromycin oxime, such as S-MOP oxime, to clarithromycin include reacting the protected silylated clarithromycin oxime with ethanol in the presence of an acid and a deoximating agent. The product of the reaction is then washed with water one or more times. The ethanol generally also contains water.

U.S. Patent No. 4,990,602 has an ethanol to water ratio of 1:4 and does not involve cooling. U.S. Patent No. 4,670,549 adds sodium hydroxide after cooling at an ethanol to water ratio of 1:3. Neither of these methods lowers the impurity content of clarithromycin.

SUMMARY OF THE INVENTION

The present invention relates to methods for preparing a protected silylated clarithromycin oxime, such as 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime ("S-MOP oxime"), which include reacting a silyl oxime derivative with methylating agent while stirring in the presence of at least one solvent and

a base, where the solvent includes methyl tert-butyl ether (MTBE). In the method for preparing the protected silylated clarithromycin oxime, the methylating agent is preferably one or more of methyl iodide, methyl bromide, dimethylsulfate, methyl p-toluenesulfonate, or methanesulfonate. The base is preferably sodium hydride, potassium hydroxide, or sodium hydroxide.

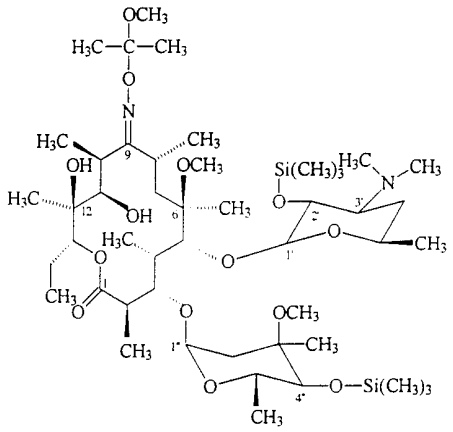
Further embodiments of the present invention relates to methods of converting a protected silylated clarithromycin oxime, such as S-MOP oxime, to clarithromycin. One such method includes reacting the protected silylated clarithromycin oxime with acid and a deoximating agent in the presence of ethanol and water at an ethanol to water ratio of about 1:1. The reaction mixture is cooled to about 20°C and a base, preferably sodium hydroxide solution, is added. In this method, no additional water is added to process clarithromycin. Another method of converting a protected silylated clarithromycin oxime to clarithromycin includes heating a mixture of the protected silylated clarithromycin oxime, acid, and deoximating agent in an ethanol/water solvent to reflux for more than 4 hours, with a two-fold addition of deoximating agent. In the latter method, essentially oxime-free clarithromycin is produced, which contains less than 40 ppm of the corresponding oxime intermediate.

DETAILED DESCRIPTION OF THE INVENTION

Clarithromycin is described, *inter alia*, in the following publications, which are hereby incorporated herein by reference: U.S. Patent Nos. 3,922,379, 4,331,803, 4,670,549, 4,672,109, 4,680,386, 4,808,411, 4,957,905, 4,990,602, 5,837,829, 5,844,105, 5,852,180, 5,858,986, 5,919,489, 5,932,710, and 5,945,405.

The terms "6-O-methylerythromycin A" and "clarithromycin" are used interchangeably herein and are meant to include clarithromycin in any form (such as crystalline Form 0, Form I, Form II or Form IV) or pharmaceutical salts thereof or mixtures thereof, as well as amorphous solids, syrups, or semisolids comprising clarithromycin in any state of purity, unless specified otherwise.

The present invention relates to increasing the product yield and unwanted side effects produced various steps included in converting erythromycin A to clarithromycin. Clarithromycin is prepared from erythromycin A by a variety of synthetic routes. Some of these routes include oximation steps and the use of a protected silylated clarithromycin oxime, such as an S-MOP oxime intermediate.



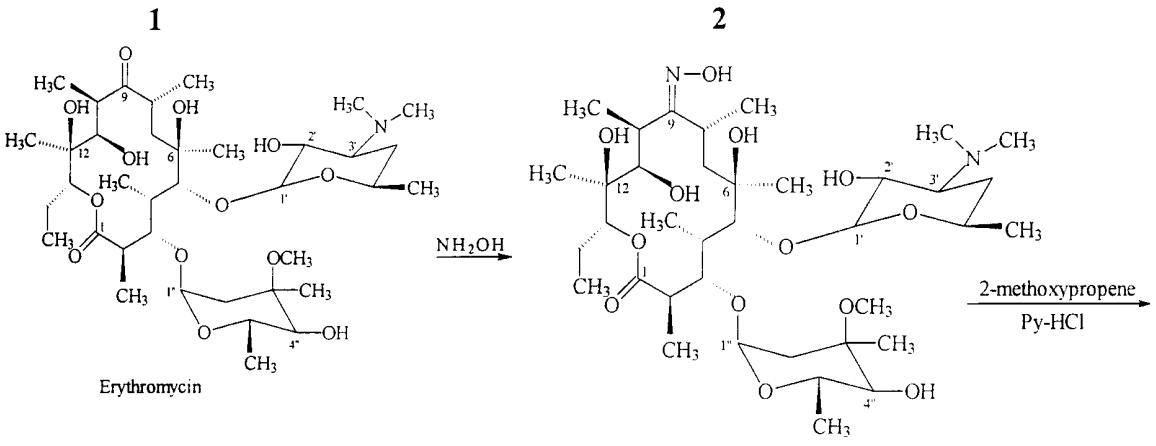
S-MOP Oxime

The synthetic routes of converting erythromycin A to clarithromycin that are improved herein, are those that utilize a protected silylated clarithromycin oxime intermediate, such an S-MOP oxime intermediate.

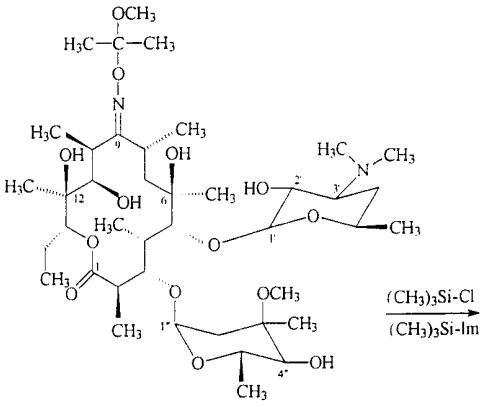
Synthetic routes of converting erythromycin A to clarithromycin include methylation of the 6-hydroxy group of erythromycin A. In the conversion process it is necessary to protect various groups, such as the hydroxy groups at the 2' and 4'' positions of erythromycin A, which are potentially reactive with alkylating agents, prior to alkylation of the 6-hydroxy group. Examples of methods of preparing clarithromycin using oxime intermediates are described for example, in U.S. Patent Nos. 4,990,602 and 5,858,986, which each describe a method of preparing clarithromycin from erythromycin A by oximation of the C-9 carbonyl, protection of the C-2' and C-4'' hydroxy groups, methylation of the C-6 hydroxy group, and deoximation and removal of the protecting groups.

An example of a synthetic route of converting erythromycin A to clarithromycin via oximation, that utilizes a protected silylated clarithromycin oxime, specifically S-MOP oxime, as an intermediate, is as follows in Scheme 1 (each compound in the process is numbered for ease of referencing them herein).

Scheme 1

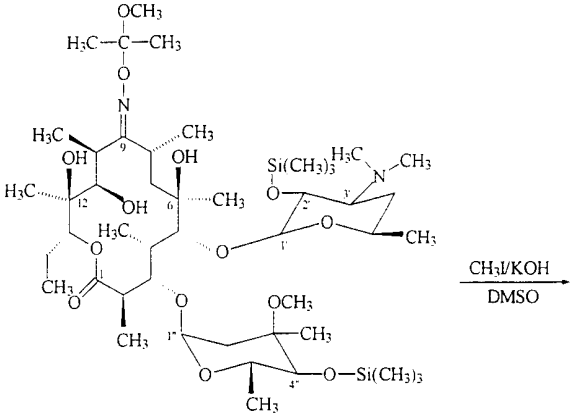


3



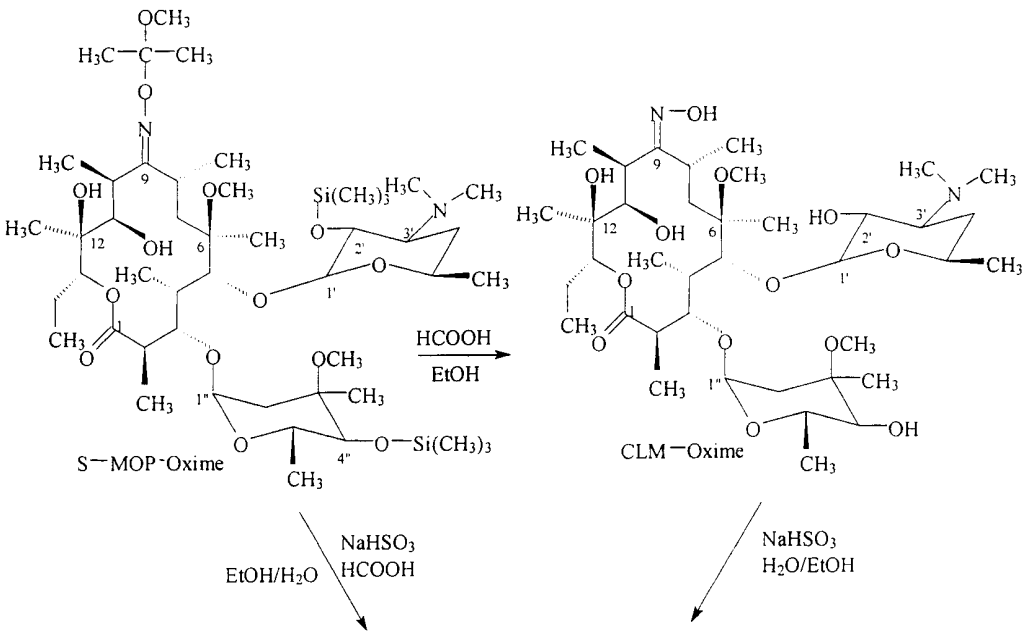
$(CH_3)_3Si\text{-}Cl$
$(CH_3)_3Si\text{-}Im$

4

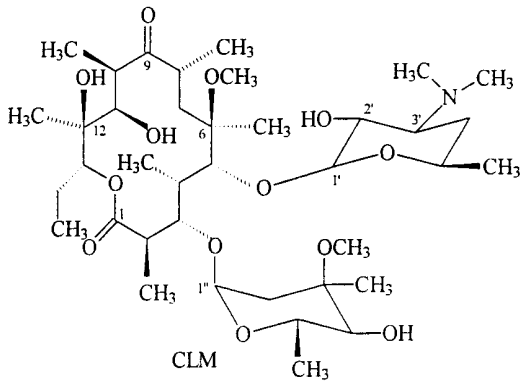


CH_3I/KOH
DMSO

5 6



7



The present invention is directed to improved methods of preparing a protected silylated clarithromycin oxime, preferably an S-MOP oxime (compound 5 in Scheme 1) from a 9-oxim silyl derivative (such as compound 4 in Scheme 1) and of converting a protected silylated clarithromycin oxime, preferably an S-MOP oxime (compound 7 in Scheme 1), to clarithromycin.

The methods described herein are not limited to use in the process shown in Scheme 1. Scheme 1 is provided as a representative scheme in which a protected silylated clarithromycin oxime, such as an S-MOP oxime, is prepared from a silyl derivative and another step includes converting the protected silylated clarithromycin oxime to clarithromycin. It would be understood by those in the art that the methods described herein may be used in various schemes for converting erythromycin A to clarithromycin, which employ a protected silylated clarithromycin oxime compound as an intermediate therein.

In the representative process of converting erythromycin A to clarithromycin shown above in Scheme 1, erythromycin A is first converted to a protected silylated oxime, such as 2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime (compound 4 in Scheme 1), by methods generally known in the art. As indicated above, protecting groups protect certain positions from potentially reacting with alkylating agents during the subsequent methylation of the 6-hydroxy group, and also protect 3'-dimethylamino groups from quaternary alkylation.

Although the conversion from erythromycin A to a protected silylated oxime (e.g., 2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime) may be accomplished by any methods known to those in the art, in a preferred method, erythromycin A is first oximated and subsequently protecting groups are added initially to the oxime group and then to the 2' and 4'' positions. Suitable methods for oximation and the addition of protecting groups are set forth in U.S. Patent Nos. 5,858,986 and 4,990,602, which teach general methods of oximation that may be used in accordance with the present invention, such as by reacting erythromycin A with the substituted hydroxylamine R^1ONH_2, or by reacting erythromycin A with hydroxylamine hydrochloride in the presence of base, or hydroxylamine in the presence of acid, followed by reaction with R^1X, where R^1 is alkoxyalkyl. U.S. Patent Nos. 5,858,986 and 4,990,602 further describe suitable methods for protecting the oxime group and two hydroxy groups (*i.e.*, at the 2' and 4'' positions) with silyl groups. The hydroxy groups may be protected simultaneously or in different steps from one another. Preferred methods of converting the silyl derivative to a protected silylated clarithromycin oxime and converting the protected silylated clarithromycin oxime to clarithromycin are set forth below.

The step of converting a silyl derivative such as compound 4 to a protected silylated clarithromycin oxime (such as S-MOP oxime) is a methylation step. In this methylation step, one or more hydroxy groups, such as that at the 6-position, is methylated. One embodiment of the present invention relates to methods for preparing a protected silylated clarithromycin oxime, which includes reacting a silyl oxime derivative with a methylating agent while stirring in the presence of a solvent and a base.

The solvent in this embodiment includes MTBE (methyl tertbutyl ether), preferably along with another aprotic solvent(s). The most preferable solvent is a mixture of DMSO (dimethyl sulfoxide) and MTBE. The present inventors have found the MTBE is more selective, cheaper and easier to recover than solvents described in the literature, including the primarily used combination of DMSO with THF (tetrahydrofuran).

In this embodiment, the silyl derivative is stirred in a solvent at about ambient temperature until the silyl derivative is dissolved. For purposes of this specification, ambient temperature is from about 20°C to about 25°C. A further solvent may then be added. The solution is cooled to a temperature of between about 0°C and about 20°C, preferably between about 5 and about 15°C, even more preferably about 10°C.

In this embodiment, a methylating agent is added while stirring the solution. The methylating agent is preferably an agent such as methyl iodide, methyl bromide, dimethylsulfate, methyl p-toluenesulfonate, methyl methanesulfonate, dimethyl sulfate, and the like. The methylating agent is most preferably methyl iodide. Although 1.0 to 10 molar equivalents of methylating agent can be used per mole of silyl derivative, it is sufficient to use between about 1.0 and about 3.0 molar equivalents of methylating agent per mole of silyl oxime derivative.

A base is added to the solution of silyl oxime derivative, solvent(s) and methylating agent in this embodiment, and stirred at a temperature of between about 9°C and about 25°C, preferably between about 9°C and about 15°C until the reaction is essentially completed. The base is preferably one or more of sodium hydride, potassium hydroxide, sodium hydroxide, sodium hydride, potassium tert-butoxide, potassium hydride, and the like. Most preferably, the base is powdered potassium hydroxide, which is added to the solution and stirred at about 10°C.

The amount of base used is usually from about 1 to about 3 molar equivalents of the silyl oxime derivative.

Preferably the temperature is maintained at about 10°C to about 12°C while stirring is taking place and the reaction is occurring. The progress of the reaction is monitored by HPLC.

When MTBE is used as a solvent in this embodiment, two phases may form, making it easier to separate the protected silylated clarithromycin oxime, than if other solvents are used that form a single phase. The separation of protected silylated clarithromycin oxime may be performed by conventional methods. For example, once the reaction is complete, the workup of the reaction mixture may include phase separation, washing of the MTBE layer with water and evaporation to dryness.

Another embodiment of the present invention relates to converting a protected silylated clarithromycin oxime, preferably S-MOP oxime, (whether it is arrived at by the method of the above embodiment or by another method) to clarithromycin, by reacting the protected silylated clarithromycin oxime with an acid and a deoximating agent in the presence of aqueous ethanol where the ethanol to water ratio is about 1:1. The reaction of the protected silylated clarithromycin oxime with deoximating agent and acid brings about deoximation together with elimination of the protecting groups. The reaction mixture is then cooled to between about 15°C and about 25°C, more preferably about 20°C, and subsequently a base, preferably sodium hydroxide solution, is added.

Previously described methods of converting a protected silylated clarithromycin oxime to clarithromycin include introducing the protected silylated clarithromycin oxime into a water/ethanol system in the presence of an acid and a deoximating agent and refluxing at 80°C. Subsequently, a large amount of water is added. According to this process, the mass ratio between the protected silylated clarithromycin oxime:ethanol:water is about 1:5:5 before the addition of the large amount of water. The ratio of ethanol to water is about 1:1, before adding additional water and about 1:4 after adding additional water. Then, NaOH is added and the solution is cooled to 0°C. This method results in the precipitation of clarithromycin. However, this process is disadvantageous because it doesn't allow purification of the product from an impurity, the 11-methyl derivative of clarithromycin. This impurity is referred to as the

"dimethyl" form of clarithromycin, which is difficult to remove. When the ethanol to water ratio is 1:3 or 1:4 for example, it is difficult to remove the impurity. If the reaction mixture is not cooled prior to addition of sodium hydroxide, the impurity content may not decrease.

The present invention relates to an improved process for obtaining clarithromycin from a protected silylated clarithromycin oxime, such as S-MOP oxime, in which the obtained clarithromycin contains significantly reduced amounts of the "dimethyl" impurity. The method includes reacting a protected silylated clarithromycin oxime with an acid (such as formic acid) and a deoximating agent in the presence of aqueous ethanol at an ethanol/water ratio of about 1:1, refluxing the solution at 80°C, cooling the solution to about 20°C, and adding NaOH.

In the present method, acid is added to the mixture of protected silylated clarithromycin oxime, ethanol, water and deoximating agent and the mixture is heated at reflux (about 80°C.) Heating is then continued and the suspension is stirred for an amount of time sufficient to finish the reaction. The mixture is then cooled to about 20°C and sodium hydroxide solution having a concentration of from about 20% to about 47%, preferably 47%, is added at this temperature until the pH of the reaction mixture reaches about 10 to about 11, preferably about 10.2 to about 10.5. Crystalline clarithromycin is then isolated, preferably by filtration, with no further water addition. The obtained clarithromycin may subsequently be further purified and/or isolated and the crystalline form of clarithromycin may be altered to the desired form (such as crystal form 0, I, II, or IV) for use.

There is need to add no additional water in the method of the present invention. Since additional water (that is, water other than the water present with the ethanol in a ratio of about 1:1 and in sodium hydroxide solution) is not required in the present method, clarithromycin may be formed with a significant decrease in the amount of impurities.

The advantages of the present method are *inter alia* that the clarithromycin produced contains about 50% less of the dimeric impurity than clarithromycin produced by other processes, and the working volumes are lower. Preferably, the volume ratio of protected silylated clarithromycin oxime oxime:water:ethanol is about 1:3:3.

Another embodiment of the present invention also relates to converting a protected silylated clarithromycin oxime, such as S-MOP oxime, (whether it is arrived at by the method

described hereinabove or by another method) to clarithromycin, by heating a mixture of a protected silylated clarithromycin oxime, acid, and two-fold addition of deoximating agent in an ethanol/water solvent to reflux for more than 4 hours. Essentially oxime-free clarithromycin, that is clarithromycin, which contains less than 40 ppm of the corresponding oxime intermediate, may be produced by this method.

As in the previous embodiment, the reaction of protected silylated clarithromycin oxime with deoximating agent and acid brings about deoximation together with elimination of the protecting groups. The reaction mixture is then cooled to between about 15°C and about 25°C, more preferably about 20°C, and subsequently a base, preferably sodium hydroxide solution, is added.

Previously described methods of converting a protected silylated clarithromycin oxime to clarithromycin include introducing the protected silylated clarithromycin oxime into a water/ethanol system in the presence of an acid and a deoximating agent and refluxing for 2 hours in an ethanol/water solvent. The product of this process contains clarithromycin oxime as an impurity.

By two-fold addition of deoximating agent refluxing for over four hours, the clarithromycin oxime impurity is largely removed, resulting in relatively pure (essentially oxime-free) clarithromycin. Accordingly, the present invention is also directed to this essentially oxime-free clarithromycin and pharmaceutical compositions containing the essentially oxime-free clarithromycin. Pharmaceutical compositions containing clarithromycin are described for example in US Patent No. 5,858,986.

In the present method, acid is added to the mixture of S-MOP oxime, ethanol, water and deoximating agent and the mixture is heated at reflux (about 80°C). Heating is then continued and the suspension is stirred for at least four hours. The mixture is then cooled, preferably to about 20°C. and sodium hydroxide solution having a concentration of from about 20% to about 47%, preferably 47%, is added at this temperature until the pH of the reaction mixture reaches about 10 to about 11, preferably about 10.2 to about 10.5. Crystalline clarithromycin is then isolated, preferably by filtration, with no further water addition. The obtained clarithromycin may subsequently be further purified and/or isolated and the crystalline form of clarithromycin

may be altered to the desired form (such as crystal form 0, I, II, or IV) for use.

Examples of suitable deoximating agents for use in the methods of producing clarithromycin according to the present invention include inorganic sulfur oxide compounds such as sodium hydrogen sulfite, sodium pyrosulfate, sodium thiosulfate, sodium sulfite, sodium hydrosulfite, sodium metabisulfite, sodium dithionate, postassium hydrogen sulfite, potassium thiosulfate, potassium metabisulfite and the like. A particularly preferred deoximating agent is sodium metabisulfite. The amount of deoximating agent is about 1 to 10 molar equivalents, preferably 4 to 7 molar equivalents relative to the protected silylated clarithromycin oxime.

A non-limiting example of a suitable acid for use in the present invention is formic acid. The amount of formic acid added to the mixture of protected silylated clarithromycin oxime is about 1.5 to 10 molar equivalents, preferably 2 to 5 equivalents relative to the protected silylated clarithromycin oxime.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the claims.

Example 1

This example is directed to a method for preparing a protected silylated clarithromycin oxime, particularly the preferred S-MOP oxime, according to the present invention. The example involves reacting a silylated erythromycin A oxime derivative with a methylating agent while stirring in the presence of at least one solvent and a base.

MTBE is charged at about ambient temperature (12 liters) and a 9-oxime silyl derivative (1 kg) is charged at about ambient temperature, stirring the 9-oxime silyl derivative in the MTBE solvent for several minutes until the silyl derivative is dissolved and a clear solution is obtained. DMSO (10.0 liters) is added to the clear solution and the solution is cooled to about 10°C. Methyl iodide (0.218 kg) is added to the solution while stirring. Powdered potassium hydroxide (0.1 kg) is also added at 10°C with stirring.

Stirring is continued while maintaining the temperature at about 10°C to about 12°C. The progress of the reaction is monitored by HPLC. The reaction is completed after about 60

min. After the reaction is completed it is quenched by adding dimethyl amine solution (40%, 0.6 liters) at 10-12°C and stirring for 30 min. The stirring is then stopped and the layers are separated. The lower layer is extracted out with MTBE (4.0 liters). Both MTBE layers, from reaction and from extraction, are combined and washed with water (5.0 liters). The MTBE layer is distilled under reduced pressure to dryness to receive S-MOP oxime (crude), yield: 1.05 kg. The DMSO layer is taken for recovery.

Examples 2 and 3 are directed to methods of converting a protected silylated clarithromycin oxime, particularly the preferred S-MOP oxime, to clarithromycin.

Example 2

S-MOP oxime (20 g) is mixed with aqueous ethanol (120 ml) where the water to ethanol ratio is about 1:1 and sodium metabisulfite (13.6 g). Formic acid (2.6 g) is added and the mixture is stirred at about 80°C to the reflux temperature to give clarithromycin. Heating is continued and the suspension is stirred for 2 hours. The mixture is then cooled to about 20°C and sodium hydroxide solution in a concentration of about 47% is added at about this temperature until the pH reaches about 10.5. The solid is filtered and dried to give 8.3 g of clarithromycin, (about 78% based on assay).

Example 3

S-MOP-oxime (20 g) was mixed with aqueous ethanol (120 ml) where the water to ethanol ratio is about 1:1 and sodium metabisulfite (13.6 g). Formic acid (2.6 g) was added and the mixture was stirred at reflux temperature for 3-4 hours. The second portion of sodium metabisulfite (13.6 g) was added and the reflux was continued for an additional 3-4 hours. The work up procedure was performed as described in Example 2. The crude clarithromycin was obtained (8.7g, 82% based on assay) which after crystallization from ethanol gives essentially pure clarithromycin, which does not contain any detectable amount of clarithromycin oxime.

The present invention provides methods for preparing a protected silylated clarithromycin oxime and for converting a protected silylated clarithromycin oxime to clarithromycin. The invention further provides essentially oxime-free clarithromycin and compositions containing essentially oxime-free clarithromycin. Although the present invention has been described with respect to certain exemplary embodiments, such as those in which the method of preparing a protected silylated clarithromycin oxime includes reaction in the presence of specific solvents, bases, or methylating agents, there are many other variations of the above-described embodiments which will be apparent to those skilled in the art, even where elements or steps have not explicitly been designated as exemplary. It is understood that these modifications are within the teaching of the present invention.

CLAIMS

We claim:

1. A method for preparing a protected silylated clarithromycin oxime comprising reacting a silylated erythromycin A oxime derivative with methylating agent while stirring in the presence of a base and a solvent comprising methyl tertbutyl ether.

2. The method of claim 1, wherein the methylating agent is selected from the group consisting of methyl iodide, methyl bromide, dimethylsulfate, methyl p-toluenesulfonate, and methanesulfonate.

3. The method of claim 1, wherein the base is selected from the group consisting of sodium hydride, potassium hydroxide, and sodium hydroxide.

4. The method of claim 1, wherein the solvent further comprises dimethyl sulfoxide.

5. The method of claim 1, wherein the protected silylated clarithromycin oxime is 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime and the silyl oxime derivative is 2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime.

6. A method of converting a protected silylated clarithromycin oxime to clarithromycin comprising

a) reacting the protected silylated clarithromycin oxime with acid and deoximating agent in the presence of ethanol and water at an ethanol to water ratio of about 1:1 to obtain a solution,

b) refluxing the solution obtained by step a),

c) cooling the solution obtained after step b) to about 15°C to about 25°C, and

d) adding NaOH.

7. The method of claim 6, wherein the cooling is to about 20°C.

8. The method of claim 6, wherein the acid is formic acid.

9. The method of claim 6, wherein the deoximating agent is sodium metabisulfite.

10. The method of claim 6, wherein the protected silylated clarithromycin oxime is 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl)oxime.

11. A method of converting protected silylated clarithromycin oxime to clarithromycin including

reacting the protected silylated clarithromycin oxime with acid and deoximating agent in the presence of ethanol and water at an ethanol to water ratio of about 1:1 to form a reaction mixture;

cooling the reaction mixture to about 15°C to about 25°C; and

adding sodium hydroxide solution to the reaction mixture;

wherein essentially no additional water to process clarithromycin.

12. The method of claim 10 wherein the protected silylated clarithromycin oxime is 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxy prop-2-yl) oxime.

13. The method of claim 11, wherein the cooling is to about 20°C.

14. The method of claim 11, wherein the acid is formic acid.

15. The method of claim 11, wherein the deoximating agent is sodium metabisulfite.

16. Clarithromycin formed by a process comprising

converting erythromycin A to 2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl) oxime;

reacting 2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl) oxime with methylating agent while stirring in the presence of at least one solvent and a base, wherein the at least one solvent comprises methyl tertbutyl ether, to form 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl) oxime; and

reacting the 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl) oxime with an acid and a deoximating agent in the presence of aqueous ethanol to form clarithromycin.

17. The clarithromycin of claim 16, wherein the methylating agent is selected from the group consisting of methyl iodide, methyl bromide, dimethylsulfate, methyl p-toluenesulfonate, and methanesulfonate.

18. The clarithromycin of claim 16, wherein the base is selected from the group consisting of sodium hydride, potassium hydroxide, and sodium hydroxide.

19. Clarithromycin formed by a process comprising

converting erythromycin A to protected silylated clarithromycin oxime;

reacting the protected silylated clarithromycin oxime with acid and deoximating agent in the presence of ethanol and water at an ethanol to water ratio of about 1:1 to form a reaction mixture;

cooling the reaction mixture to about 15°C to about 25°C; and

adding sodium hydroxide solution to the reaction mixture.

20. The method of claim 19, wherein the protected silylated clarithromycin oxime is 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxy prop-2-yl) oxime.

21. The clarithromycin of claim 19, wherein the cooling is to about 20°C.

22. The clarithromycin of claim 19, wherein the acid is formic acid.

23. The clarithromycin of claim 19, wherein the deoximating agent is sodium metabisulfite.

24. A method of converting erythromycin A to clarithromycin comprising

converting erythromycin A to protected silylated clarithromycin oxime;

reacting protected silylated clarithromycin oxime with methylating agent while stirring in the presence of at least one solvent, wherein the at least one solvent comprises methyl tertbutyl ether, and a base to form 6-O-methyl protected silylated clarithromycin oxime; and

reacting the 6-O-methyl- protected silylated clarithromycin oxime with acid and a deoximating agent in the presence of aqueous ethanol to form clarithromycin.

25. A method of converting erythromycin A to clarithromycin comprising

converting erythromycin A to protected silylated clarithromycin oxime; and

reacting the protected silylated clarithromycin oxime with an acid and deoximating agent in the presence of ethanol and water at an ethanol to water ratio of about 1:1, cooling to about 20°C, and adding sodium hydroxide solution, wherein essentially no additional water is added to process clarithromycin.

26. The method of claim 25, wherein the protected silylated clarithromycin oxime is 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxy prop-2-yl) oxime.

27. A process for preparing essentially oxime-free clarithromycin, which comprises heating a mixture of protected silylated clarithromycin oxime, formic acid and a deoximating agent in a ethanol/water solvent to reflux for more than 4 hours, with a two-fold addition of said deoximating agent.

28. The method of claim 27, wherein the protected silylated clarithromycin oxime is 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxy prop-2-yl) oxime.

29. Clarithromycin comprising less than 40 ppm of its corresponding oxime intermediate formed by heating a mixture of protected silylated clarithromycin oxime, formic acid and deoximating agent in an ethanol/water solvent to reflux for more than 4 hours, with a two-fold addition of said deoximating agent.

30. Clarithromycin comprising less than 40 ppm of its corresponding oxime intermediate formed by a method that includes converting a clarithromycin oxime intermediate to clarithromycin.

31. Clarithromycin comprising less than 40 ppm of its corresponding oxime intermediate formed by a method that includes converting 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxy prop-2-yl) oxime intermediate to clarithromycin.

32. Clarithromycin comprising less than 40 ppm of its corresponding oxime intermediate formed by heating a mixture of protected silylated clarithromycin oxime, formic acid and deoximating agent in an ethanol/water solvent to reflux for more than 4 hours, with a two-fold addition of said deoximating agent.

33. Clarithromycin comprising less than 40 ppm of clarithromycin-S-MOP-Oxime intermediate formed by a method that includes converting a clarithromycin oxime intermediate to clarithromycin.

34. Clarithromycin comprising less than 40 ppm of its corresponding oxime intermediate formed by heating a mixture of 6-O-methyl-2', 4''-bis(trimethylsilyl)-erythromycin A 9-O-(2-methoxyprop-2-yl) oxime, formic acid and deoximating agent in an ethanol/water solvent to reflux for more than 4 hours, with a two-fold addition of said deoximating agent.

35. A pharmaceutical composition comprising the product of claim 29, 30, 31, 32, 33 or 34.

INTERNATIONAL SEARCH REPORT

Inte. .tional application No.
PCT/US00/33843

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/70; C07H 1/00, 17/08
US CL :514/29; 538/7.2, 18.5

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. : 514/29; 538/7.2, 18.5

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.
X	US 5,837,829 A (KU) 17 November 1998, column 2, lines 65-68 and column 3, lines 1-5.	1-35

☐ 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
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"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)	"&"	document member of the same patent family
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