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(54) Title: PROCESSES FOR PREPARING FLUOROKETOLIDES

(57) Abstract: Processes and intermediates for preparing fluoroketolide compounds are described herein.

PROCESSES FOR PREPARING FLUOROKETOLIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. § 119(e) of United States Provisional Application Serial Number 62/129,305, filed Mar 6, 2015, the disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

The invention described herein pertains to processes and intermediates for preparing fluoroketolide compounds.

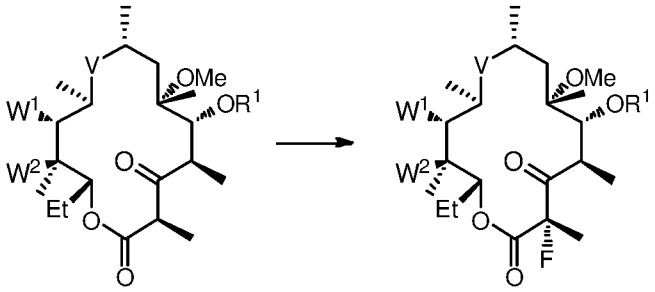
BACKGROUND AND SUMMARY OF THE INVENTION

Fluoroketolide compounds have been reported to be highly effective in treating bacterial and protozoal infections. Moreover, fluoroketolide compounds have been reported to be particular effective in treating resistant bacterial and protozoal infections compared to corresponding non-fluoroketolides, macrolides, and azalides. However, reported manufacturing processes for ketolides proceed with low conversion, which leads to sometimes insurmountable purification problems in separating the fluorinated product from the non-fluorinated starting material. In addition, reported manufacturing processes for ketolides tend to produce high amounts of unwanted side products, such as N-demethylated side products. Taken together, reported manufacturing processes for ketolides may be incapable of providing the needs of the world.

Due to the importance of these compounds for human and other animal health, alternative and/or improved processes for their preparation are needed. In particular, processes for preparing fluoroketolides at commercially relevant manufacturing scales are needed in order to satisfy the unmet need for these important human and animal health compounds.

It has been unexpectedly discovered herein that processes including amine bases provide high conversion rates to fluoroketolides, with fewer side products. Because of high conversion rates and fewer side products, processes described herein can be used to prepare multi-kilogram quantities of fluoroketlides, which may be isolated by simple precipitation, rather than by chromatography or fractional recrystallization, each of which are expensive and/or can lead to significant losses in isolated yield.

In one illustrative embodiment of the invention described herein, processes are described for preparing fluoroketolide compounds by fluorination at C2 of the macrocycle. In another embodiment, the processes described herein include the following step:



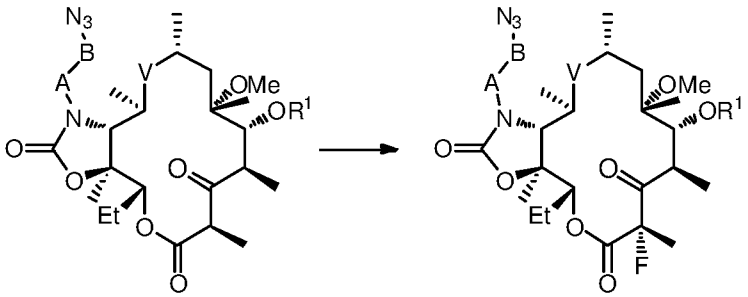
including salts of each of the foregoing, wherein:

R^1 is H or acyl, or R^1 is a monosaccharide, such as a methylamino or dimethylamino containing monosaccharide;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof; and

W^1 is hydroxy or a derivative thereof; and W^2 is H, or hydroxy or a derivative thereof; or W^1 and W^2 are taken together with the attached carbon atoms to form an oxygen and/or nitrogen containing heterocycle, each of which is optionally substituted.

In another embodiment, the processes include the following step:



including salts of each of the foregoing, wherein:

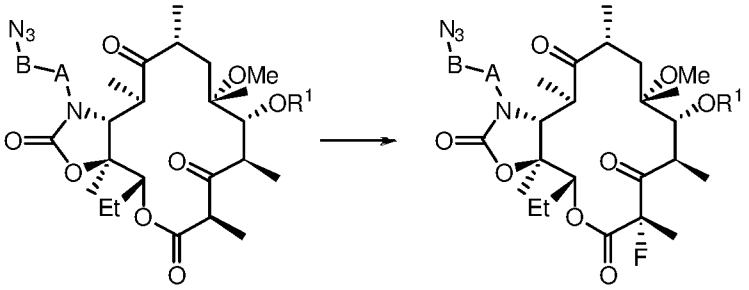
R^1 is H or acyl, or R^1 is a monosaccharide, such as a methylamino or dimethylamino containing monosaccharide;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof;

A is a bond, or A is an optional linker formed from O, C(O), CR, CR_2, and NR, and combinations thereof, where each R is independently selected in each instance from being absent to form a double or triple bond, being hydrogen, or being an optionally substituted alkyl; and

B is a bond, or B is an optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene.

In another embodiment, the processes include the following step:



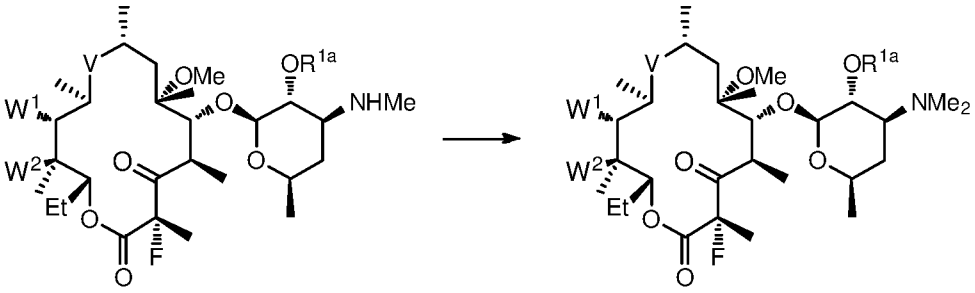
including salts of each of the foregoing, wherein:

R^1 is H or acyl, or R^1 is a monosaccharide, such as a methylamino or dimethylamino containing monosaccharide;

A is a bond, or A is an optional linker formed from O, C(O), CR, CR_2, and NR, and combinations thereof, where each R is independently selected in each instance from being absent to form a double or triple bond, being hydrogen, or being an optionally substituted alkyl; and

B is a bond, or B is an optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene.

In another embodiment, processes are described herein for preparing fluoroketolide compounds by *in situ* N-methylation. In another embodiment, the processes include the following step:



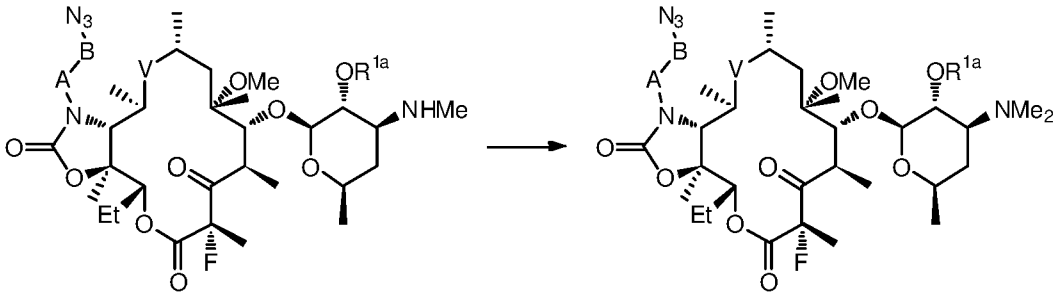
including salts of each of the foregoing, wherein:

R^{1a} is H or acyl;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof;

W^1 is hydroxy or a derivative thereof; and W^2 is H, or hydroxy or a derivative thereof; or W^1 and W^2 are taken together with the attached carbon atoms to form an oxygen and/or nitrogen containing heterocycle, each of which is optionally substituted.

In another embodiment, the processes include the following step:



including salts of each of the foregoing, wherein:

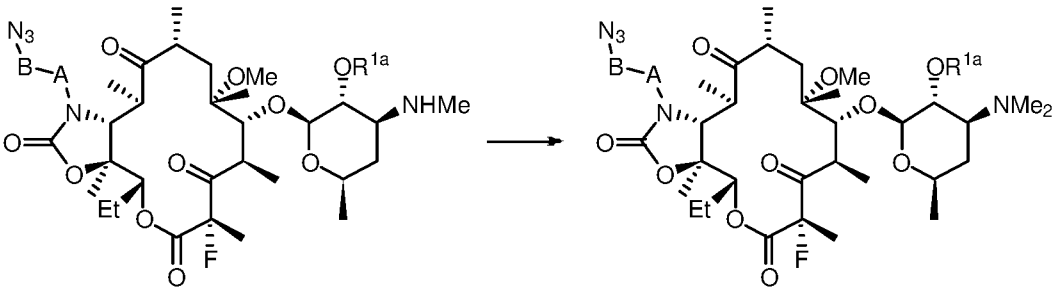
R^{1a} is H or acyl;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof;

A is a bond, or A is an optional linker formed from O, C(O), CR, CR_2, and NR, and combinations thereof, where each R is independently selected in each instance from being absent to form a double or triple bond, being hydrogen, or being an optionally substituted alkyl; and

B is a bond, or B is an optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene.

In another embodiment, the processes include the following step:



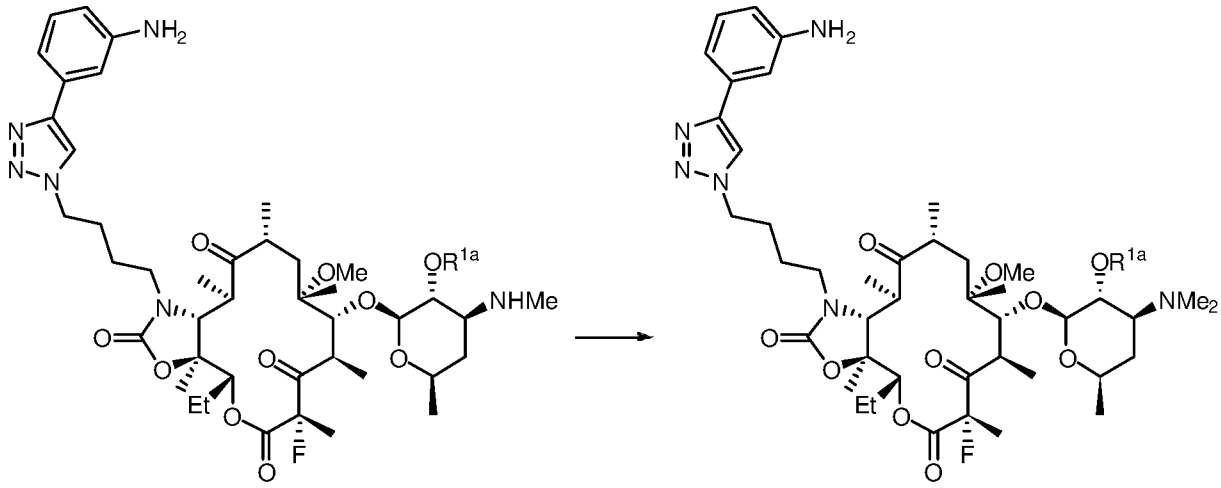
including salts of each of the foregoing, wherein:

R^{1a} is H or acyl;

A is a bond, or A is an optional linker formed from O, C(O), CR, CR_2, and NR, and combinations thereof, where each R is independently selected in each instance from being absent to form a double or triple bond, being hydrogen, or being an optionally substituted alkyl; and

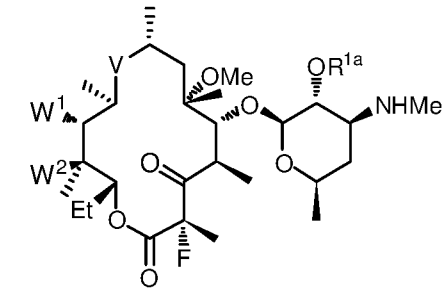
B is a bond, or B is an optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene.

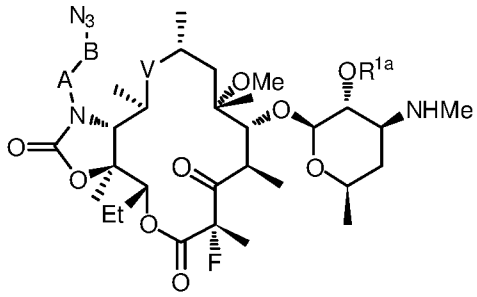
In another embodiment, the processes include the following step:

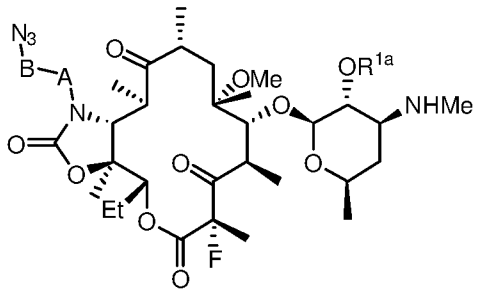


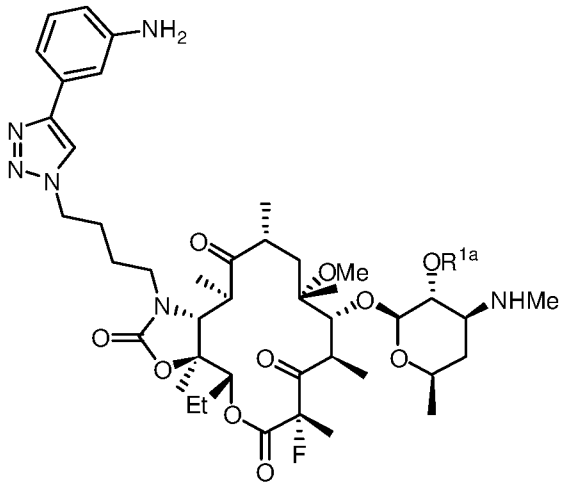
including salts of each of the foregoing, wherein R^{1a} is H or acyl.

In another embodiment, intermediates for preparing fluoroketolide compounds are described herein. Illustrative intermediates are of the formulae









and salts thereof, wherein R^{1a}, V, W^1, W^2, A, and B are as defined herein.

In another embodiment, pharmaceutical compositions containing one or more of the compounds are also described herein. It is to be understood that the compositions may include other components and/or ingredients, including, but not limited to, other therapeutically active compounds, and/or one or more carriers, diluents, excipients, and the like, and combinations thereof.

In another embodiment, methods for treating host animals with a bacterial or protozoal infection are also described herein, where the methods include administering one or more of the compounds and/or compositions described herein to the host animal. In another embodiment, uses of the compounds and compositions in the manufacture of a medicament for treating host animals with a bacterial or protozoal infection are also described herein. In another embodiment, the medicaments include a therapeutically effective amount of the one or more compounds and/or compositions for treating a host animal with a bacterial or protozoal infection.

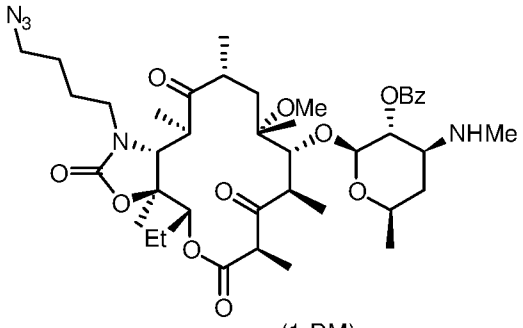
DETAILED DESCRIPTION

Certain fluoroketolides and processes for preparing fluoroketolides are described in WO 2004/080391. Processes for preparing fluoroketolides are also described in WO 2009/055557. It has been discovered that the processes described for fluorination at C2 of the macrolide core structure in the foregoing publications fail to go to completion. In addition, it has been discovered that attempts to effect complete fluorination at C2 leads to greater and greater amounts of side product formation, such as N-demethylation of sugars at C5, such as demethylation of desosamine, and decomposition as the reaction conditions become more vigorous. Thus, the quest to solve the problem of incomplete conversion, leads to at least two other problems, side product formation and lower overall yields. Moreover, it has also been unexpectedly discovered that the unfluorinated starting material and the fluorinated product are

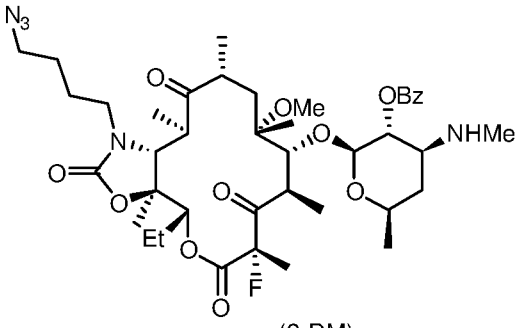
essentially inseparable, especially using commercially relevant purification techniques that are necessary for the large scales required to produce antibiotics for a worldwide market. Because the only difference between the starting material and the desired product is a single fluorine atom, separation of the two compounds is quite difficult, and can only be accomplished by careful column chromatography or fractional recrystallizations, which each result in substantial material loss, and consequentially, an overall loss in yield. It has also been unexpectedly discovered that the N-desmethyl side product is also very difficult to remove using commercially relevant purification techniques that are necessary for the large scales required to produce antibiotics for a worldwide market. Commercially relevant purification techniques include evaporations, precipitations, and crystallizations, whereas chromatography, or fractional crystallization, each of which is much more expensive and leads to substantial decreases in yield, are advantageously avoided.

In addition, it has been discovered that in many instances, the corresponding unfluorinated analog of the desired fluoroketolide is substantially less active than the desired fluorinated compound, especially against resistant pathogens. Similarly, it has been discovered that in nearly all instances the corresponding N-demethylated analog of the desired fluoroketolide is substantially less active than desired the N,N-dimethyl compound. Thus, it is understood that complete fluorination is desirable to ensure that the product is pure, and also, that it is not contaminated with less active analogs that might affect drug performance, especially when the relative amount of those less active analogs might vary from across multiple batches. Similarly, it is understood that averting demethylation is desirable to ensure that the product is pure, and also, that it is not contaminated with less active analogs that might affect drug performance, especially when the relative amount of those less active analogs might vary from across multiple batches.

Solving the problem of incomplete fluorination requires more vigorous reagents and reaction conditions, such as higher temperatures, more equivalents of base, and/or more equivalents of fluorinating agent. However, those same process modifications exacerbate the companion problem by increasing the amount of unwanted N-demethylated products, both of the starting unfluorinated compound, for example (1-DM), and the product fluorinated compound, for example (2-DM).



(1-DM)



(2-DM)

In addition, use of those same more vigorous reagents and reaction conditions leads to decomposition, other unwanted side products, and consequentially, an overall loss in yield.

Similarly, solving the problem of unwanted N-demethylation requires less vigorous reagents and reaction conditions. However, that same solution exacerbates the companion problem by decreasing the conversion of unfluorinated compound to the product fluorinated compound.

It has also been discovered that even when the process reported in WO 2009/055557 is modified to favor conversion, and concomitant N-demethylation, that *in situ* remethylation fails. Therefore, it is necessary to isolate the multiple products from the reaction mixture, and perform a separate remethylation step, which leads to additional material losses, an overall drop in yield, higher costs, and longer manufacturing times.

The need for fluoroketolides for treatment of bacterial and protozoal infections worldwide requires a manufacturing process that is both cost effective and can be performed on large scale. Without those attributes, supplies of fluoroketolides will be insufficient to meet the needs of world, and/or preclude the use of fluoroketolides in the poorer regions of the world, where bacterial or protozoal infections are often more prevalent, and lead to poorer outcomes.

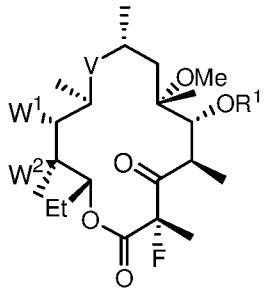
New processes for preparing fluoroketolides are needed. Without such improved processes that provide higher yields of highly pure fluoroketolide antibiotics, there is a risk that millions of patients having bacterial or protozoal infections will go untreated due to short supply, delayed manufacturing and/or treatment costs that are too high.

It has been unexpectedly discovered herein that the fluorination processes described herein provide substantially higher conversion of unfluorinated starting material to the needed fluoroketolides. It has also been unexpectedly discovered herein that the fluorination processes described herein provide substantially lower amounts of N-demethylated side products. In addition, it has unexpectedly discovered herein that the fluorination processes described herein can be adapted to include *in situ* remethylation to further improve overall yields by recapturing N-demethylated side products. Therefore, the unwanted N-demethylation products, including for example (1-DM) and (2-DM), are useful as starting materials for

preparing fluoroketolides. The processes described herein provide fluorinated ketolides in high yields, with high purity, and are adaptable to large multi-kilogram commercial manufacturing scales.

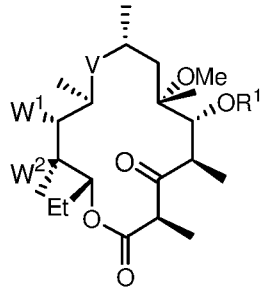
Several illustrative embodiments of the invention are described by the following clauses:

A process for preparing a fluoroketolide of formula (I)



(I)

the process comprising the step of contacting a compound of the formula



with a fluorinating agent and an amine base; wherein

R^1 is H or acyl, or R^1 is a monosaccharide, such as methylamino or dimethylamino containing monosaccharide;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof; and

W^1 is hydroxy or a derivative thereof; and W^2 is H, or hydroxy or a derivative thereof; or W^1 and W^2 are taken together with the attached carbon atoms to form an oxygen and/or nitrogen containing heterocycle, each of which is optionally substituted.

Any one of the preceding processes wherein the amine base is a cyclic, a non-aromatic amine base, or a base with a conjugate acid pKa of at least about 11, at least about 11.5, at least about 12, at least about 12.5, or at least about 13, or a combination of the foregoing.

Any one of the preceding processes wherein the base is a cyclic amine.

Any one of the preceding processes wherein the base is a bicyclic amine.

Any one of the preceding processes wherein the base is sterically hindered.

Any one of the preceding processes wherein the base is conformationally restricted.

Any one of the preceding processes wherein the base is a diamine.

Any one of the preceding processes wherein the base includes at least one nitrogen that does not have a hydrogen.

Any one of the preceding processes wherein the base does not include any NH groups.

Any one of the preceding processes wherein the base includes at least one C=N group.

Any one of the preceding processes wherein the base is selected from the group consisting of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and 3,3,6,9,9-pentamethyl-2,10-diazabicyclo[4.4.0]dec-1-ene (PMDBD), quinuclidine, and combinations thereof.

Any one of the preceding processes wherein the base is DBN or DBU, or a combination thereof.

Any one of the preceding processes wherein the base is DBU.

Any one of the preceding processes wherein the fluorinating agent is selected from the group consisting of NFSi, Selectfluor, and F-TEDA, and combinations thereof.

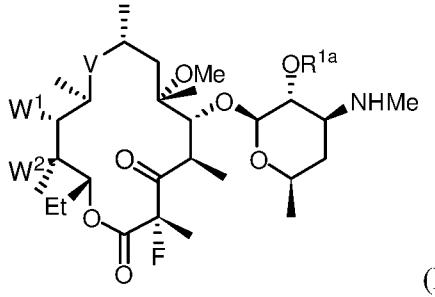
Any one of the preceding processes wherein the fluorinating agent is selected from the group consisting of NFSi and Selectfluor, and combinations thereof.

Any one of the preceding processes wherein the fluorinating agent is a combination of NFSi and Selectfluor.

Any one of the preceding processes wherein the fluorinating agent is NFSi.

Any one of the preceding processes wherein the temperature is between about -30°C and about -20°C. It has been observed that at temperatures closer to ambient temperatures, an increasing number of side products begin to form.

A process for preparing a compound of formula (I), the process comprising the step or further comprising the step of contacting a compound of the formula (DM)



(DM)

including salts of each of the foregoing, with a methylating agent; wherein:

R^{1a} is H or acyl;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof;

W^1 is hydroxy or a derivative thereof; and W^2 is H, or hydroxy or a derivative thereof; or W^1 and W^2 are taken together with the attached carbon atoms to form an oxygen and/or nitrogen containing heterocycle, each of which is optionally substituted.

Any one of the preceding processes wherein the methylating agent is CH_2O/HCO_2H.

Any one of the preceding processes performed in a solvent wherein the solvent comprises a ketone, such as acetone, MEK, or MTBK.

Any one of the preceding processes performed in a solvent wherein the solvent comprises an ether, such as MTBE, THF, Me-THF, or a glycol ether, such as dimethoxyethane, diethoxyethane, or a compound of the formula R^1O-$(CH_2)_2$-OR^2, where R^1 is alkyl, such as methyl, ethyl, propyl, isopropyl, or butyl; and R^2 is H, methyl, ethyl, propyl, isopropyl, or butyl; or a compound of the formula R^1[O-$(CH_2)_2$-]$_2OR^2$, where R^1 is alkyl, such as methyl, ethyl, propyl, isopropyl, or butyl; and R^2 is H, methyl, ethyl, propyl, isopropyl, or butyl.

Any one of the preceding processes performed in a solvent wherein the solvent comprises an ester, such as EtOAc, iPrOAc.

Any one of the preceding processes performed in a solvent wherein the solvent comprises an amide, such as DMF, DMA, NMP.

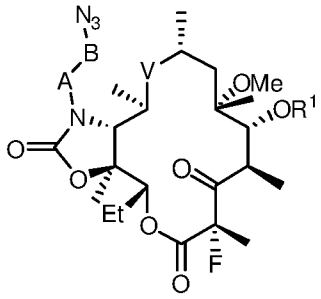
Any one of the preceding processes performed in a solvent wherein the solvent comprises a mixture of an amide and an ester, such as iPrOAc/DMF, or iPrOAc/DMF illustratively at a ratio in the range from about 1:2 to about 2:1, or about 3:2 to about 2:3, or about 1:1.

Any one of the preceding processes performed in a solvent wherein the solvent is substantially free of or free of chlorinated solvents, such as CH_2Cl_2 (DCM), $CHCl_3$, and/or CCl_4.

Any one of the preceding processes wherein W^1 and W^2 are taken together with the attached carbon atoms to form to carbamate where the nitrogen thereof is substituted with a radical of the formula N_3-B-A, where A is a bond, or A is an optional linker formed from O, C(O), CR, CR_2, and NR, and combinations thereof, where each R is independently selected in each instance from being absent to form a double or triple bond, being hydrogen, or being an optionally substituted alkyl; and B is a bond, or B is an optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene.

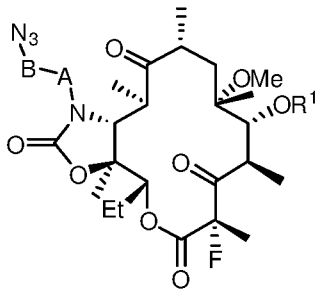
Any one of the preceding processes wherein W^1 and W^2 are taken together with the attached carbon atoms to form to carbamate where the nitrogen thereof is substituted with a radical of the formula T-B-A, where A is a bond, or A is an optional linker formed from O, C(O), CR, CR_2, and NR, and combinations thereof, where each R is independently selected in each instance from being absent to form a double or triple bond, being hydrogen, or being an optionally substituted alkyl; B is a bond, or B is an optionally substituted alkylene, optionally substituted alkenylene, or optionally substituted alkynylene; T is an optionally substituted aryl group, including but not limited to, imidazolyl, 1,2,3-triazolyl, phenyl, benzimidazolyl, benztriazolyl, and the like, and where the optional substitution, includes but is not limited to optionally substituted aryl, such as phenyl, aminophenyl, benzimidazolyl, benztriazolyl, benzimidazolylmethyl, benztriazolylmethyl, and the like.

Any one of the preceding processes wherein the compound of formula (I) is



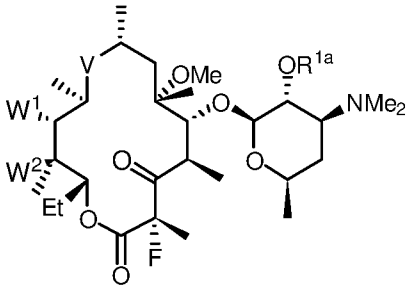
or a salt thereof.

Any one of the preceding processes wherein the compound of formula (I) is



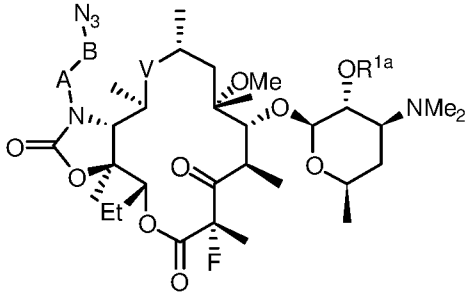
or a salt thereof.

Any one of the preceding processes wherein the compound of formula (I) is



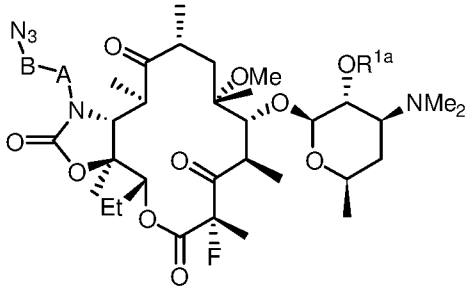
or a salt thereof.

Any one of the preceding processes wherein the compound of formula (I) is



or a salt thereof.

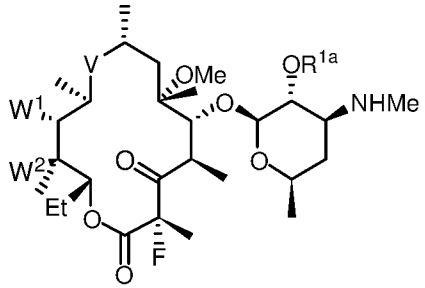
Any one of the preceding processes wherein the compound of formula (I) is



or a salt thereof.

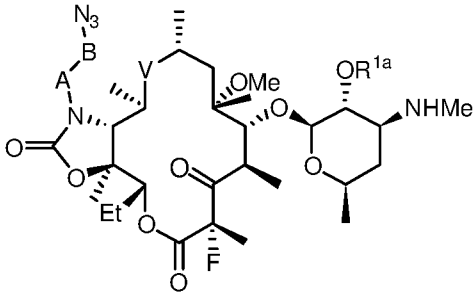
Any one of the preceding processes wherein the compound of formula (I) is solithromycin or a salt thereof.

Any one of the preceding processes wherein the compound of formula (DM) is



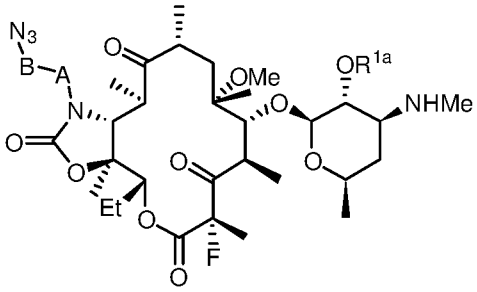
or a salt thereof.

Any one of the preceding processes wherein the compound of formula (DM) is



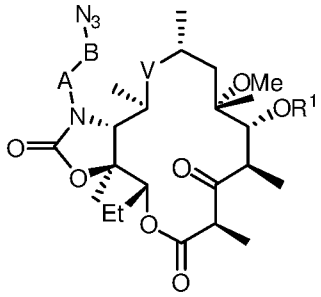
or a salt thereof.

Any one of the preceding processes wherein the compound of formula (DM) is



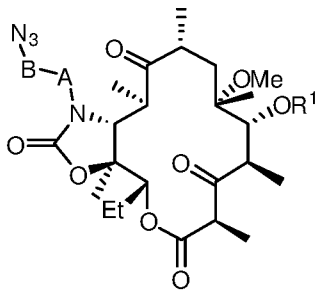
or a salt thereof.

Any one of the preceding processes wherein the starting compound is of the formula



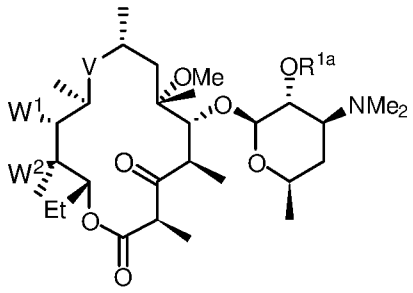
or a salt thereof.

Any one of the preceding processes wherein the starting compound is of the formula



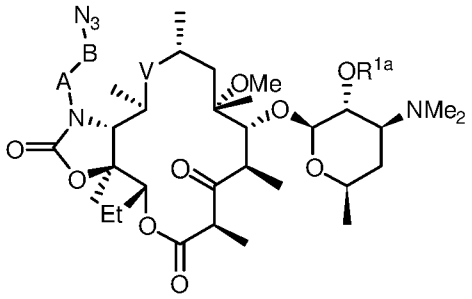
or a salt thereof.

Any one of the preceding processes wherein the starting compound is of the formula



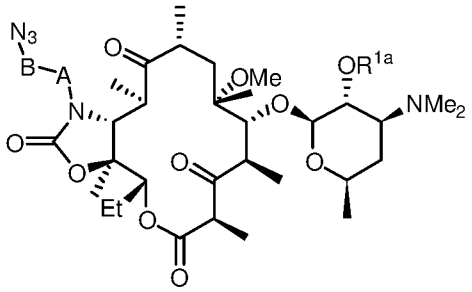
or a salt thereof.

Any one of the preceding processes wherein the starting compound is of the formula



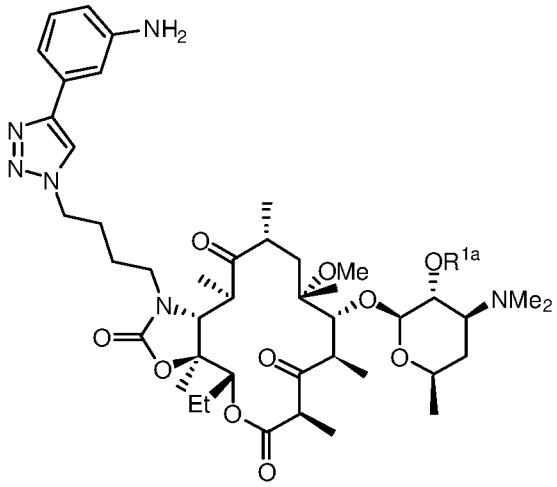
or a salt thereof.

Any one of the preceding processes wherein the starting compound is of the formula



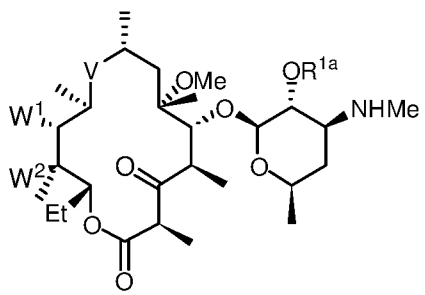
or a salt thereof.

Any one of the preceding processes wherein the starting compound is of the formula



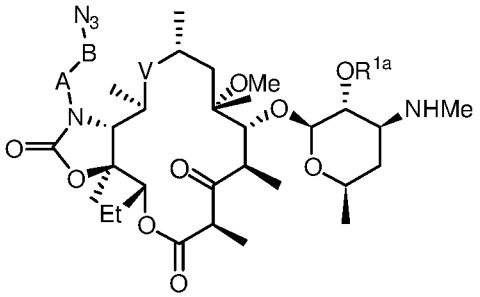
or a salt thereof.

Any one of the preceding processes wherein the starting compound is of the formula



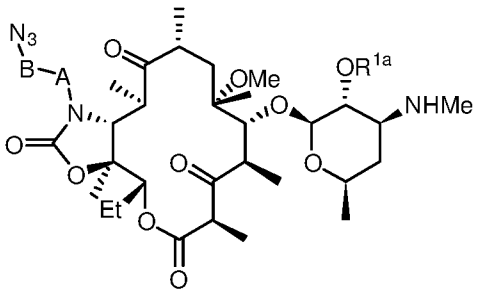
or a salt thereof, or the C2-fluoro analog of the foregoing.

Any one of the preceding processes wherein the starting compound is of the formula



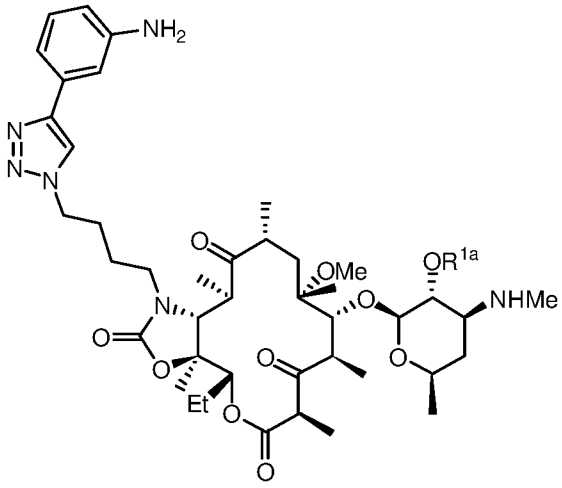
or a salt thereof, or the C2-fluoro analog of the foregoing.

Any one of the preceding processes wherein the starting compound is of the formula



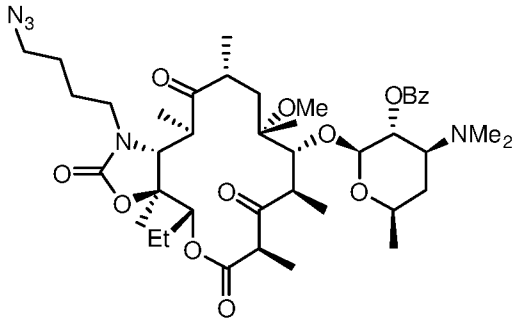
or a salt thereof, or the C2-fluoro analog of the foregoing.

Any one of the preceding processes wherein the starting compound is of the formula



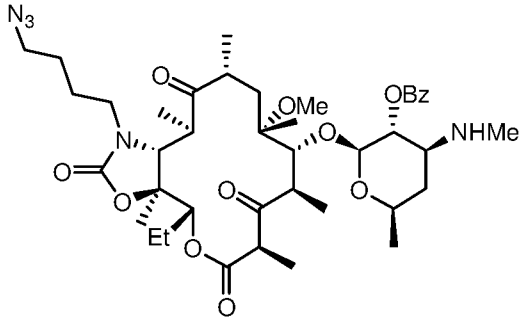
or a salt thereof, or the C2-fluoro analog of the foregoing.

Any one of the preceding processes wherein the compound is of the formula



or a salt thereof.

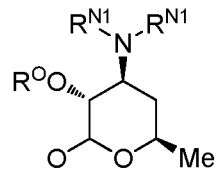
Any one of the preceding processes wherein the compound is of the formula



or a salt thereof.

Any one of the preceding processes wherein the monosaccharide is a hexose, such as D-glucose, D-mannose, D-xylose, D-galactose, L-fucose, and the like; a pentose such as D-ribose, D-arabinose, and the like; a ketose such as D-ribulose, D-fructose, and the like; including aminomethyl and dimethylamino derivatives thereof, such as glucosamine, galactosamine, acetylglucose, acetylgalactose, N-acetylglucosamine, N-acetyl-galactosamine, galactosyl-N-acetylglucosamine, N-acetylneuraminic acid (sialic acid), mycaminose, desosamine, L-vancosamine, 3-desmethyl-vancosamine, 3-epi-vancosamine, 4-epi-vancosamine, acosamine, 3-amino-glucose, 4deoxy-3-amino-glucose, actinosamine, daunosamine, 3-epi-daunosamine, ristosamine, N-methyl-D-glucamine, and the like; and aminomethyl and dimethylamino derivatives thereof.

Any one of the preceding processes wherein OR^1 is of the formula



where each R^{N1} is independently selected in each instance from H and acyl, and alkyl, cycloalkyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted; and R^O is H or acyl, or alkyl, cycloalkyl, arylalkyl, and heteroarylalkyl, each of which is optionally substituted. In another embodiment, at least one R^{N1} is methyl. In another embodiment, both R^{N1} are methyl. In another embodiment, R^O is H or acyl. In another embodiment, R^O is H.

Any one of the preceding processes wherein R^1 is desosaminyl.

Any one of the preceding processes wherein R^1 is N-desmethyl desosaminyl.

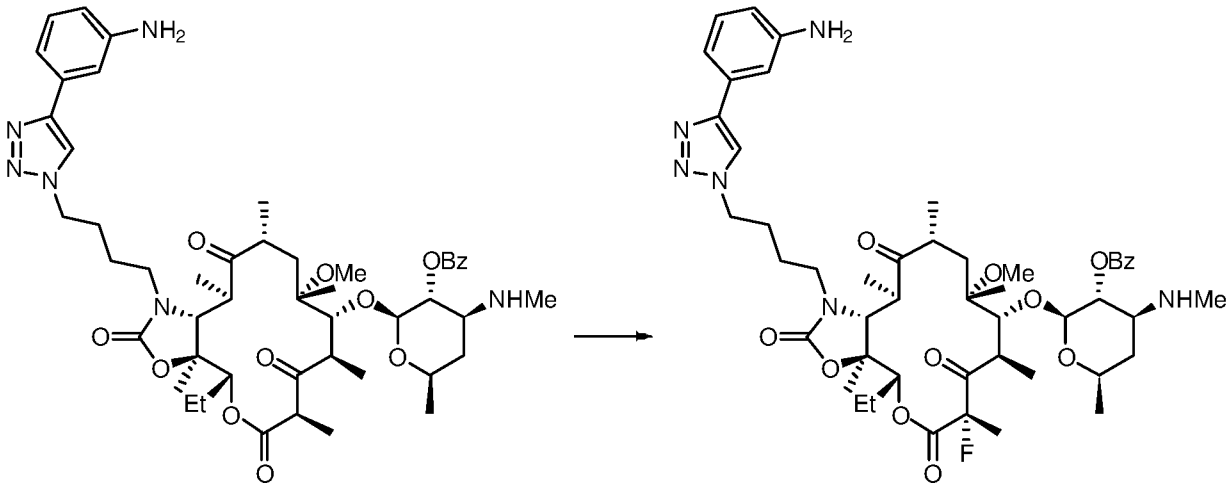
A composition comprising solithromycin that is substantially free of or free of desfluoro solithromycin.

A composition comprising solithromycin that comprises less than about 1%, less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.15%, less than about 0.1%, less than about 0.05%, or less than about 0.03% desfluoro solithromycin.

A composition comprising solithromycin that is substantially free of or free of N-desmethyl solithromycin.

A composition comprising solithromycin that comprises less than about 1%, less than about 0.5%, less than about 0.4%, less than about 0.3%, less than about 0.2%, less than about 0.15%, less than about 0.1%, less than about 0.05%, or less than about 0.03% N-desmethyl solithromycin.

Also described herein is a process for preparing solithromycin benzoate, or a salt thereof, where the process includes the step



including salts of each of the foregoing.

Also described herein is a process for preparing solithromycin, or a salt thereof, where the process includes preparing a fluorinated compound described herein, and converting that fluorinated compound into solithromycin, or a salt thereof.

In each of the foregoing and each of the following embodiments, unless otherwise indicated, it is to be understood that the formulae include and represent not only all pharmaceutically acceptable salts of the compounds, but also include any and all hydrates and/or solvates of the compound formulae. It is appreciated that certain functional groups, such as the hydroxy, amino, and like groups form complexes and/or coordination compounds with water and/or various solvents, in the various physical forms of the compounds. Accordingly,

the above formulae are to be understood to be a description of such hydrates and/or solvates, including pharmaceutically acceptable solvates.

In each of the foregoing and each of the following embodiments, unless otherwise indicated, it is also to be understood that the formulae include and represent any and all crystalline forms, partially crystalline forms, and non-crystalline and/or amorphous forms of the compounds.

In each of the foregoing and each of the following embodiments, unless otherwise indicated, it is also to be understood that the formulae include and represent each possible isomer, such as stereoisomers and geometric isomers, both individually and in any and all possible mixtures.

As used herein, the term "solvates" refers to compounds described herein complexed with a solvent molecule. It is appreciated that compounds described herein may form such complexes with solvents by simply mixing the compounds with a solvent, or dissolving the compounds in a solvent. It is appreciated that where the compounds are to be used as pharmaceuticals, such solvents are pharmaceutically acceptable solvents. It is further appreciated that where the compounds are to be used as pharmaceuticals, the relative amount of solvent that forms the solvate should be less than established guidelines for such pharmaceutical uses, such as less than International Conference on Harmonization (ICH) Guidelines. It is to be understood that the solvates may be isolated from excess solvent by evaporation, precipitation, and/or crystallization. In some embodiments, the solvates are amorphous, and in other embodiments, the solvates are crystalline.

It is to be understood that each of the foregoing embodiments may be combined in chemically relevant ways to generate subsets of the embodiments described herein. Accordingly, it is to be further understood that all such subsets are also illustrative embodiments of the invention described herein.

The compounds described herein may contain one or more chiral centers, or may otherwise be capable of existing as multiple stereoisomers. It is to be understood that in one embodiment, the invention described herein is not limited to any particular sterochemical requirement, and that the compounds, and compositions, methods, uses, and medicaments that include them may be optically pure, or may be any of a variety of stereoisomeric mixtures, including racemic and other mixtures of enantiomers, other mixtures of diastereomers, and the like. It is also to be understood that such mixtures of stereoisomers may include a single stereochemical configuration at one or more chiral centers, while including mixtures of stereochemical configuration at one or more other chiral centers.

Similarly, the compounds described herein may include geometric centers, such as cis, trans, E, and Z double bonds. It is to be understood that in another embodiment, the invention described herein is not limited to any particular geometric isomer requirement, and that the compounds, and compositions, methods, uses, and medicaments that include them may be pure, or may be any of a variety of geometric isomer mixtures. It is also to be understood that such mixtures of geometric isomers may include a single configuration at one or more double bonds, while including mixtures of geometry at one or more other double bonds.

As used herein, the term "alkyl" includes a chain of carbon atoms, which is optionally branched. As used herein, the terms "alkenyl" and "alkynyl" each include a chain of carbon atoms, which is optionally branched, and include at least one double bond or triple bond, respectively. It is to be understood that alkynyl may also include one or more double bonds. It is to be further understood that in certain embodiments, alkyl is advantageously of limited length, including C_1-C_{24}, C_1-C_{12}, C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and the like Illustratively, such particularly limited length alkyl groups, including C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_8, C_2-C_6, and C_2-C_4, and the like may be referred to as lower alkyl. It is to be further understood that in certain embodiments alkenyl and/or alkynyl may each be advantageously of limited length, including C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_{24}, C_3-C_{12}, C_3-C_8, C_3-C_6, and C_3-C_4, and the like Illustratively, such particularly limited length alkenyl and/or alkynyl groups, including C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_8, C_3-C_6, and C_3-C_4, and the like may be referred to as lower alkenyl and/or alkynyl. It is appreciated herein that shorter alkyl, alkenyl, and/or alkynyl groups may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkyl refers to alkyl as defined herein, and optionally lower alkyl. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkenyl refers to alkenyl as defined herein, and optionally lower alkenyl. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkynyl refers to alkynyl as defined herein, and optionally lower alkynyl. Illustrative alkyl, alkenyl, and alkynyl groups are, but not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, neopentyl, hexyl, heptyl, octyl, and the like, and the corresponding groups containing one or more double and/or triple bonds, or a combination thereof.

As used herein, the term "alkylene" includes a divalent chain of carbon atoms, which is optionally branched. As used herein, the term "alkenylene" and "alkynylene" includes a divalent chain of carbon atoms, which is optionally branched, and includes at least one double

bond or triple bond, respectively. It is to be understood that alkynylene may also include one or more double bonds. It is to be further understood that in certain embodiments, alkylene is advantageously of limited length, including C_1-C_{24}, C_1-C_{12}, C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and the like. Illustratively, such particularly limited length alkylene groups, including C_1-C_8, C_1-C_6, and C_1-C_4, and C_2-C_8, C_2-C_6, and C_2-C_4, and the like may be referred to as lower alkylene. It is to be further understood that in certain embodiments alkenylene and/or alkynylene may each be advantageously of limited length, including C_2-C_{24}, C_2-C_{12}, C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_{24}, C_3-C_{12}, C_3-C_8, C_3-C_6, and C_3-C_4, and the like. Illustratively, such particularly limited length alkenylene and/or alkynylene groups, including C_2-C_8, C_2-C_6, and C_2-C_4, and C_3-C_8, C_3-C_6, and C_3-C_4, and the like may be referred to as lower alkenylene and/or alkynylene. It is appreciated herein that shorter alkylene, alkenylene, and/or alkynylene groups may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior. In embodiments of the invention described herein, it is to be understood, in each case, that the recitation of alkylene, alkenylene, and alkynylene refers to alkylene, alkenylene, and alkynylene as defined herein, and optionally lower alkylene, alkenylene, and alkynylene. Illustrative alkyl groups are, but not limited to, methylene, ethylene, n-propylene, isopropylene, n-butylene, isobutylene, sec-butylene, pentylene, 1,2-pentylene, 1,3-pentylene, hexylene, heptylene, octylene, and the like.

As used herein, the term "cycloalkyl" includes a chain of carbon atoms, which is optionally branched, where at least a portion of the chain in cyclic. It is to be understood that cycloalkylalkyl is a subset of cycloalkyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkyl include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, 2-methylcyclopropyl, cyclopentyleth-2-yl, adamantyl, and the like. As used herein, the term "cycloalkenyl" includes a chain of carbon atoms, which is optionally branched, and includes at least one double bond, where at least a portion of the chain in cyclic. It is to be understood that the one or more double bonds may be in the cyclic portion of cycloalkenyl and/or the non-cyclic portion of cycloalkenyl. It is to be understood that cycloalkenylalkyl and cycloalkylalkenyl are each subsets of cycloalkenyl. It is to be understood that cycloalkyl may be polycyclic. Illustrative cycloalkenyl include, but are not limited to, cyclopentenyl, cyclohexylethen-2-yl, cycloheptenylpropenyl, and the like. It is to be further understood that chain forming cycloalkyl and/or cycloalkenyl is advantageously of limited length, including C_3-C_{24}, C_3-C_{12}, C_3-C_8, C_3-C_6, and C_5-C_6. It is appreciated herein that shorter alkyl and/or alkenyl chains forming cycloalkyl and/or cycloalkenyl, respectively, may add less lipophilicity to the compound and accordingly will have different pharmacokinetic behavior.

As used herein, the term "heteroalkyl" includes a chain of atoms that includes

both carbon and at least one heteroatom, and is optionally branched. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain variations, illustrative heteroatoms also include phosphorus, and selenium. As used herein, the term "cycloheteroalkyl" including heterocyclyl and heterocycle, includes a chain of atoms that includes both carbon and at least one heteroatom, such as heteroalkyl, and is optionally branched, where at least a portion of the chain is cyclic. Illustrative heteroatoms include nitrogen, oxygen, and sulfur. In certain variations, illustrative heteroatoms also include phosphorus, and selenium. Illustrative cycloheteroalkyl include, but are not limited to, tetrahydrofuryl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, morpholinyl, piperazinyl, homopiperazinyl, quinuclidinyl, and the like.

As used herein, the term "aryl" includes monocyclic and polycyclic aromatic carbocyclic groups, each of which may be optionally substituted. Illustrative aromatic carbocyclic groups described herein include, but are not limited to, phenyl, naphthyl, and the like. As used herein, the term "heteroaryl" includes aromatic heterocyclic groups, each of which may be optionally substituted. Illustrative aromatic heterocyclic groups include, but are not limited to, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, quinolinyl, quinazolinyl, quinoxalinyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, benzisoxazolyl, benzisothiazolyl, and the like.

As used herein, the term "amino" includes the group NH_2, alkylamino, and dialkylamino, where the two alkyl groups in dialkylamino may be the same or different, i.e. alkylalkylamino. Illustratively, amino includes methylamino, ethylamino, dimethylamino, methylethylamino, and the like. In addition, it is to be understood that when amino modifies or is modified by another term, such as aminoalkyl, or acylamino, the above variations of the term amino are included therein. Illustratively, aminoalkyl includes H_2N-alkyl, methylaminoalkyl, ethylaminoalkyl, dimethylaminoalkyl, methylethylaminoalkyl, and the like. Illustratively, acylamino includes acylmethylamino, acylethylamino, and the like.

As used herein, the term "amino and derivatives thereof" includes amino as described herein, and alkylamino, alkenylamino, alkynylamino, heteroalkylamino, heteroalkenylamino, heteroalkynylamino, cycloalkylamino, cycloalkenylamino, cycloheteroalkylamino, cycloheteroalkenylamino, arylamino, arylalkylamino, arylalkenylamino, arylalkynylamino, heteroarylamino, heteroarylalkylamino, heteroarylalkenylamino, heteroarylalkynylamino, acylamino, and the like, each of which is optionally substituted. The term "amino derivative" also includes urea, carbamate, and the like.

As used herein, the term "hydroxy and derivatives thereof" includes OH, and alkyloxy, alkenyloxy, alkynyloxy, heteroalkyloxy, heteroalkenyloxy, heteroalkynyloxy,

cycloalkyloxy, cycloalkenyloxy, cycloheteroalkyloxy, cycloheteroalkenyloxy, aryloxy, arylalkyloxy, arylalkenyloxy, arylalkynyloxy, heteroaryloxy, heteroarylalkyloxy, heteroarylalkenyloxy, heteroarylalkynyloxy, acyloxy, and the like, each of which is optionally substituted. The term "hydroxy derivative" also includes carbamate, and the like.

As used herein, the term "thio and derivatives thereof" includes SH, and alkylthio, alkenylthio, alkynylthio, heteroalkylthio, heteroalkenylthio, heteroalkynylthio, cycloalkylthio, cycloalkenylthio, cycloheteroalkylthio, cycloheteroalkenylthio, arylthio, arylalkylthio, arylalkenylthio, arylalkynylthio, heteroarylthio, heteroarylalkylthio, heteroarylalkenylthio, heteroarylalkynylthio, acylthio, and the like, each of which is optionally substituted. The term "thio derivative" also includes thiocarbamate, and the like.

As used herein, the term "acyl" includes formyl, and alkylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, heteroalkylcarbonyl, heteroalkenylcarbonyl, heteroalkynylcarbonyl, cycloalkylcarbonyl, cycloalkenylcarbonyl, cycloheteroalkylcarbonyl, cycloheteroalkenylcarbonyl, arylcarbonyl, arylalkylcarbonyl, arylalkenylcarbonyl, arylalkynylcarbonyl, heteroarylcarbonyl, heteroarylalkylcarbonyl, heteroarylalkenylcarbonyl, heteroarylalkynylcarbonyl, acylcarbonyl, and the like, each of which is optionally substituted.

As used herein, the term "carbonyl and derivatives thereof" includes the group C(O), C(S), C(NH) and substituted amino derivatives thereof.

As used herein, the term "carboxylic acid and derivatives thereof" includes the group CO_2H and salts thereof, and esters and amides thereof, and CN.

As used herein, the term "sulfinic acid or a derivative thereof" includes SO_2H and salts thereof, and esters and amides thereof.

As used herein, the term "sulfonic acid or a derivative thereof" includes SO_3H and salts thereof, and esters and amides thereof.

As used herein, the term "sulfonyl" includes alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, heteroalkylsulfonyl, heteroalkenylsulfonyl, heteroalkynylsulfonyl, cycloalkylsulfonyl, cycloalkenylsulfonyl, cycloheteroalkylsulfonyl, cycloheteroalkenylsulfonyl, arylsulfonyl, arylalkylsulfonyl, arylalkenylsulfonyl, arylalkynylsulfonyl, heteroarylsulfonyl, heteroarylalkylsulfonyl, heteroarylalkenylsulfonyl, heteroarylalkynylsulfonyl, acylsulfonyl, and the like, each of which is optionally substituted.

As used herein, the term "phosphinic acid or a derivative thereof" includes $P(R)O_2H$ and salts thereof, and esters and amides thereof, where R is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heteroalkyl, heteroalkenyl, cycloheteroalkyl, cycloheteroalkenyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, each of which is optionally substituted.

As used herein, the term "phosphonic acid or a derivative thereof" includes

PO_3H_2 and salts thereof, and esters and amides thereof.

As used herein, the term "hydroxylamino and derivatives thereof" includes NHOH, and alkyloxylNH alkenyloxylNH alkynyloxylNH heteroalkyloxylNH heteroalkenyloxylNH heteroalkynyloxylNH cycloalkyloxylNH cycloalkenyloxylNH cycloheteroalkyloxylNH cycloheteroalkenyloxylNH aryloxylNH arylalkyloxylNH arylalkenyloxylNH arylalkynyloxylNH heteroaryloxylNH heteroarylalkyloxylNH heteroarylalkenyloxylNH heteroarylalkynyloxylNH acyloxy, and the like, each of which is optionally substituted.

As used herein, the term "hydrazino and derivatives thereof" includes alkylNHNH, alkenylNHNH, alkynylNHNH, heteroalkylNHNH, heteroalkenylNHNH, heteroalkynylNHNH, cycloalkylNHNH, cycloalkenylNHNH, cycloheteroalkylNHNH, cycloheteroalkenylNHNH, arylNHNH, arylalkylNHNH, arylalkenylNHNH, arylalkynylNHNH, heteroarylNHNH, heteroarylalkylNHNH, heteroarylalkenylNHNH, heteroarylalkynylNHNH, acylNHNH, and the like, each of which is optionally substituted.

The term "optionally substituted" as used herein includes the replacement of hydrogen atoms with other functional groups on the radical that is optionally substituted. Such other functional groups illustratively include, but are not limited to, amino, hydroxyl, halo, thiol, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxyl, thiol, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is optionally substituted.

As used herein, the terms "optionally substituted aryl" and "optionally substituted heteroaryl" include the replacement of hydrogen atoms with other functional groups on the aryl or heteroaryl that is optionally substituted. Such other functional groups, also referred to herein as aryl substituents or heteroaryl substituents, respectively, illustratively include, but are not limited to, amino, hydroxy, halo, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, nitro, sulfonic acids and derivatives thereof, carboxylic acids and derivatives thereof, and the like. Illustratively, any of amino, hydroxy, thio, alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl, heteroarylheteroalkyl, and/or sulfonic acid is optionally substituted.

Illustrative substituents include, but are not limited to, a radical $-(CH_2)_xZ^X$, where x is an integer from 0-6 and Z^X is selected from halogen, hydroxy, alkanoyloxy, including C_1-C_6 alkanoyloxy, optionally substituted aroyloxy, alkyl, including C_1-C_6 alkyl,

alkoxy, including C_1-C_6 alkoxy, cycloalkyl, including C_3-C_8 cycloalkyl, cycloalkoxy, including C_3-C_8 cycloalkoxy, alkenyl, including C_2-C_6 alkenyl, alkynyl, including C_2-C_6 alkynyl, haloalkyl, including C_1-C_6 haloalkyl, haloalkoxy, including C_1-C_6 haloalkoxy, halocycloalkyl, including C_3-C_8 halocycloalkyl, halocycloalkoxy, including C_3-C_8 halocycloalkoxy, amino, C_1-C_6 alkylamino, (C_1-C_6 alkyl)(C_1-C_6 alkyl)amino, alkylcarbonylamino, N-(C_1-C_6 alkyl)alkylcarbonylamino, aminoalkyl, C_1-C_6 alkylaminoalkyl, (C_1-C_6 alkyl)(C_1-C_6 alkyl)aminoalkyl, alkylcarbonylaminoalkyl, N-(C_1-C_6 alkyl)alkylcarbonylaminoalkyl, cyano, and nitro; or Z^X is selected from $-CO_2R^4$ and $-CONR^5R^6$, where R^4, R^5, and R^6 are each independently selected in each occurrence from hydrogen, C_1-C_6 alkyl, aryl-C_1-C_6 alkyl, and heteroaryl-C_1-C_6 alkyl.

The term "protecting group" as used herein general refers to any radical that is reversibly bonded to a functional group and is used to block or partially block the reactivity of that functional group to a predetermined set of conditions, such as reaction conditions. Illustratively, nitrogen protecting groups are reversibly bonded to amines to block or partially block the reactivity of the amine under a predetermined set of conditions. Illustrative nitrogen protecting groups include, but are not limited to, carbamates, such as t-Boc, Fmoc, and the like.

As used herein, the term "leaving group" refers to a reactive functional group that generates an electrophilic site on the atom to which it is attached such that nucleophiles may be added to the electrophilic site on the atom. Illustrative leaving groups include, but are not limited to, halogens, optionally substituted phenols, acyloxy groups, sulfonoxy groups, and the like. It is to be understood that such leaving groups may be on alkyl, acyl, and the like. Such leaving groups may also be referred to herein as activating groups, such as when the leaving group is present on acyl. In addition, conventional peptide, amide, and ester coupling agents, such as but not limited to PyBop, BOP-Cl, BOP, pentafluorophenol, isobutylchloroformate, and the like, form various intermediates that include a leaving group, as defined herein, on a carbonyl group.

It is to be understood that in every instance disclosed herein, the recitation of a range of integers for any variable describes the recited range, every individual member in the range, and every possible subrange for that variable. For example, the recitation that n is an integer from 0 to 8, describes that range, the individual and selectable values of 0, 1, 2, 3, 4, 5, 6, 7, and 8, such as n is 0, or n is 1, or n is 2, etc. In addition, the recitation that n is an integer from 0 to 8 also describes each and every subrange, each of which may for the basis of a further embodiment, such as n is an integer from 1 to 8, from 1 to 7, from 1 to 6, from 2 to 8, from 2 to 7, from 1 to 3, from 2 to 4, etc.

As used herein, the terms "treating", "contacting" or "reacting" when referring to

a chemical reaction generally mean to add or mix two or more reagents under appropriate conditions that allows a chemical transformation or chemical reaction to take place, and/or to produce the indicated and/or the desired product. It is to be understood that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added. In other words, there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

As used herein, the term "composition" generally refers to any product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. It is to be understood that the compositions described herein may be prepared from isolated compounds described herein or from salts, solutions, hydrates, solvates, and other forms of the compounds described herein. It is also to be understood that the compositions may be prepared from various amorphous, non-amorphous, partially crystalline, crystalline, and/or other morphological forms of the compounds described herein. It is also to be understood that the compositions may be prepared from various hydrates and/or solvates of the compounds described herein. Accordingly, such pharmaceutical compositions that recite compounds described herein are to be understood to include each of, or any combination of, the various morphological forms and/or solvate or hydrate forms of the compounds described herein. In addition, it is to be understood that the compositions may be prepared from various co-crystals of the compounds described herein.

Illustratively, compositions may include one or more carriers, diluents, and/or excipients. The compounds described herein, or compositions containing them, may be formulated in a therapeutically effective amount in any conventional dosage forms appropriate for the methods described herein. The compounds described herein, or compositions containing them, including such formulations, may be administered by a wide variety of conventional routes for the methods described herein, and in a wide variety of dosage formats, utilizing known procedures (see generally, Remington: The Science and Practice of Pharmacy, (21st ed., 2005)).

The term "therapeutically effective amount" as used herein, refers to that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. In one aspect, the therapeutically effective amount is that which may treat or alleviate the disease or symptoms of the disease at a reasonable benefit/risk ratio applicable to

any medical treatment. However, it is to be understood that the total daily usage of the compounds and compositions described herein may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient: the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known to the researcher, veterinarian, medical doctor or other clinician of ordinary skill.

It is also appreciated that the therapeutically effective amount, whether referring to monotherapy or combination therapy, is advantageously selected with reference to any toxicity, or other undesirable side effect, that might occur during administration of one or more of the compounds described herein. Further, it is appreciated that the co-therapies described herein may allow for the administration of lower doses of compounds that show such toxicity, or other undesirable side effect, where those lower doses are below thresholds of toxicity or lower in the therapeutic window than would otherwise be administered in the absence of a cotherapy.

In addition to the illustrative dosages and dosing protocols described herein, it is to be understood that an effective amount of any one or a mixture of the compounds described herein can be readily determined by the attending diagnostician or physician by the use of known techniques and/or by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician or physician, including, but not limited to the species of mammal, including human, its size, age, and general health, the specific disease or disorder involved, the degree of or involvement or the severity of the disease or disorder, the response of the individual patient, the particular compound administered, the mode of administration, the bioavailability characteristics of the preparation administered, the dose regimen selected, the use of concomitant medication, and other relevant circumstances.

The dosage of each compound of the claimed combinations depends on several factors, including: the administration method, the condition to be treated, the severity of the condition, whether the condition is to be treated or prevented, and the age, weight, and health of the person to be treated. Additionally, pharmacogenomic (the effect of genotype on the pharmacokinetic, pharmacodynamic or efficacy profile of a therapeutic) information about a particular patient may affect the dosage used.

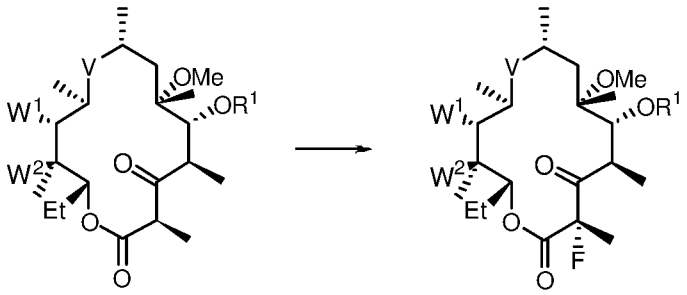
The term "administering" as used herein includes all means of introducing the compounds and compositions described herein to the host animal, including, but are not limited to, oral (po), intravenous (iv), intramuscular (im), subcutaneous (sc), transdermal, inhalation, buccal, ocular, sublingual, vaginal, rectal, and the like. The compounds and compositions described herein may be administered in unit dosage forms and/or formulations containing conventional nontoxic pharmaceutically-acceptable carriers, adjuvants, and/or vehicles.

Illustrative formats for oral administration include tablets, capsules, elixirs, syrups, and the like.

Illustrative routes for parenteral administration include intravenous, intraarterial, intraperitoneal, epidurial, intraurethral, intrasternal, intramuscular and subcutaneous, as well as any other art recognized route of parenteral administration.

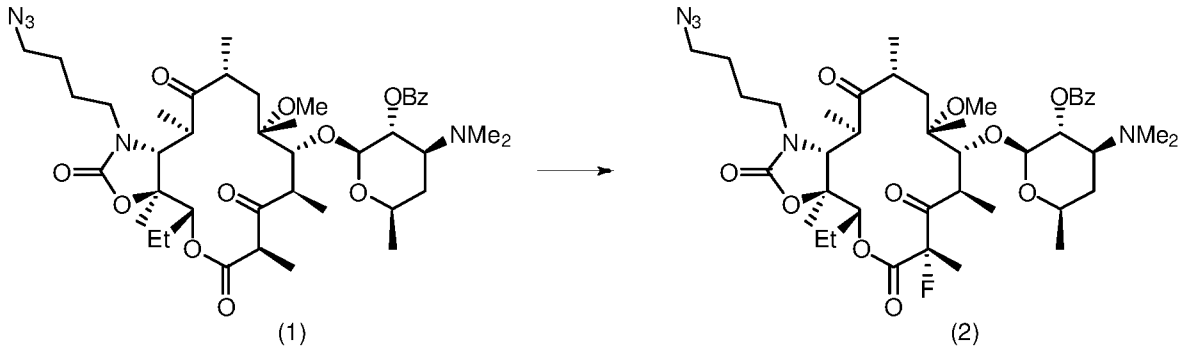
The following examples further illustrate specific embodiments of the invention; however, the following illustrative examples should not be interpreted in any way to limit the invention.

EXAMPLES



(I)

EXAMPLE. General procedure for preparing fluoroketolides. A solution of starting material is cooled to a temperature in the range from about -15°C to about -40°C. An amine base described herein (2-3 eq) is added. A fluorinating reagent (1-2 eq), or solution of a fluorinating agent is added. After acceptable or complete conversion, the reaction is quenched with water. The compound of formula (I) is isolated from the organic layer, and optionally precipitated from an alcohol/water mixture.



(1) (2)

EXAMPLE. (11-N-(4-azido-butyl)-5-(2'-benzoyl-desosaminyl)-3-oxo-2-fluoro-

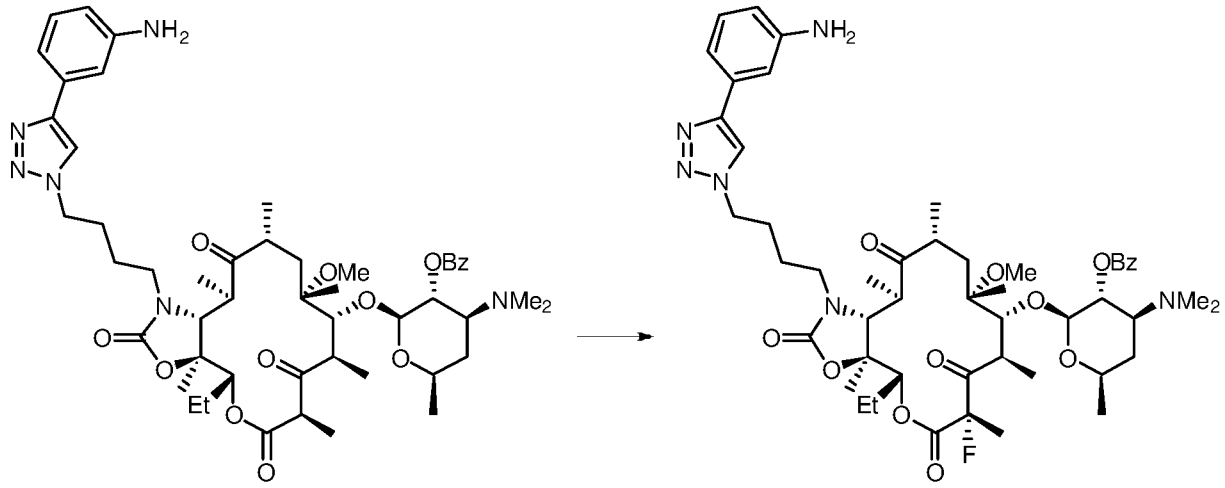
6-O-methyl-erythronolide A, 11,12-cyclic carbamate) (CEM-276, compound (2)). CEM-275 (compound (1), 1.0 eq) is added to DMF, isopropyl acetate, or a mixture of DMF/isopropyl acetate (2-10 volumes) and stirred at ambient temperature to give a clear solution. It is to be understood that the foregoing concentrations are not critical. The solution is cooled to and maintained at -20°C to -30°C with stirring. DBU (2-3 eq) is added, then a solution of NFSI (1.1-1.5 eq) in DMF, isopropyl acetate, or a mixture of DMF/isopropyl acetate (1-3 volumes) is added. The mixture is stirred until acceptable or complete conversion is observed, such as by TLC, HPLC, and the like. Isopropyl acetate (2-7 volumes) and chilled water (2-10 volumes) are added, optionally in stages. The organic layer is removed, and the aqueous layer is extracted with isopropyl acetate. The combined organic layers are washed with water. Formaldehyde (0.1-0.3 eq) and formic acid (0.5-1.0 eq) are added to the solution at ambient temperature, then the mixture is heated to 45-50°C until acceptable or complete conversion is observed, such as by TLC, HPLC, and the like. The solution is cooled to ambient temperature, water is added, and the pH is adjusted to 7-8 with aqueous ammonia. The aqueous layer is removed, and the organic layer is washed with water. The organic layer is concentrated under vacuum. Isopropanol (IPA) is added and the mixture is heated. Water is added, and the resulting slurry is cooled to ambient temperature, and filtered. The resulting solid is washed with water and dried under vacuum to give CEM-276.

EXAMPLE. The general process described herein was performed on a scale of 50 g (2 independent runs) followed by *in situ* methylation to provide (2) in 90-92% isolated yield with 98% HPLC purity, with (1) in the range of about 0.05-0.1%. Neither (1-DM) nor (2-DM) were detected.

EXAMPLE. The general process described herein was performed on a commercial scale of 100 g (3 independent runs) followed by *in situ* methylation to provide (2) in a 89-90% isolated yield with 98-99% HPLC purity, with (1) in the range of about 0.07-0.18%. Neither (1-DM) nor (2-DM) were detected.

EXAMPLE. The general process described herein was performed on a commercial scale of 200 g (2 independent runs) followed by *in situ* methylation to provide (2) in a consistent 88% isolated yield with 98-99% HPLC purity, with (1) consistently at 0.07%, and (1-DM) and (2-DM) consistently not detectable.

EXAMPLE. The general process described herein was performed on a commercial scale of 3 kg followed by *in situ* methylation to provide (2) in 93% isolated yield with 98.4% HPLC purity.



EXAMPLE. 11-N-(3-amino-phenyl-1-yl-[1,2,3]-triazole-1-yl]butyl)-5-(2'-benzoyldesosaminyl)-3-oxo-2-fluoro-erythronolide A, 11,12-cyclic carbamate. 11-N-(3-amino-phenyl-1-yl-[1,2,3]-triazole-1-yl]butyl)-5-(2'-benzoyldesosaminyl)-3-oxo-erythronolide A, 11,12-cyclic carbamate was prepared according to WO 2009/055557 from (1) and 3-ethynylphenylamine. The general process described herein was performed to provide a 97% conversion, 90% isolated yield of the title compound, only 0.36% remaining unfluorinated starting material, and 2.3% N-desmethyl before *in situ* methylation.

EXAMPLE. 11-N-(3-amino-phenyl-1-yl-[1,2,3]-triazole-1-yl]butyl)-5-(2'-benzoyldesosaminyl)-3-oxo-2-fluoro-erythronolide A, 11,12-cyclic carbamate. 11-N-(4-azidobutyl)-5-(2'-benzoyldesosaminyl)-3-oxo-2-fluoro-6-O-methylerythronolide A, 11,12-cyclic carbamate, 3-ethynylphenylamine, copper iodide, and diisopropylethylamine are reacted in acetonitrile as described in WO 2009/055557 to prepare 11-N-(3-amino-phenyl-1-yl-[1,2,3]-triazole-1-yl]butyl)-5-(2'-benzoyldesosaminyl)-3-oxo-2-fluoro-erythronolide A, 11,12-cyclic carbamate.

EXAMPLE. Solithromycin. 11-N-(3-amino-phenyl-1-yl-[1,2,3]-triazole-1-yl]butyl)-5-(2'-benzoyldesosaminyl)-3-oxo-2-fluoro-erythronolide A, 11,12-cyclic carbamate is dissolved in methanol and heated at reflux, as described in WO 2009/055557 to prepare solithromycin.

COMPARATIVE EXAMPLE. A process for preparing (2) from (1) is disclosed in WO 2009/055557. The process was performed as described on a scale of 10 g (2 independent runs) to provide a 65% yield of (2) having 89% HPLC purity, and contaminated with 9.9% unreacted starting material (1).

EXAMPLE. The foregoing process was adapted by using NFSI and lithium tert-butoxide as the base. Conversion to (2) was incomplete with 9-11% remaining (1).

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using potassium pentoxide as the base. Conversion to (2) was very low or not

observed. In addition, one or more unknown side products was formed.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using lithium tert-butoxide as the base. Conversion to (2) was very low with 9-11% unreacted (1) remaining. In addition, unknown side products was also formed.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using NaH as the base. Conversion to (2) was very low with significant decomposition to unknown side products.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using Selectfluor as the fluorinating agent. Conversion to (2) was comparable with 29% unreacted (1) remaining.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using NaHMDS as the base. Conversion to (2) was very low with significant decomposition to unknown side products.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using K_2CO_3 as the base. Conversion to (2) was not observed. Instead, significant decomposition to one or more unknown side products was observed.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using K_2CO_3 as the base in toluene/water with tetra-n-butylammonium bromide (TBAB) phase transfer catalyst. Conversion to (2) was not observed. In addition, one or more unknown side products was formed.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using NFSI or Selectfluor and a Lewis Acid or transition metal catalyst, such as $MgClO_4$, $Ti(iOPR)_4$, $Pd(OAc)_2$, and the like, in place of the base. Conversion to (2) was not observed. In addition, one or more unknown side products was formed.

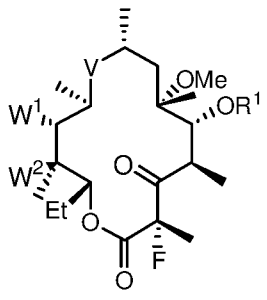
COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using DMF as the solvent. Conversion to (2) was low with 24% unreacted (1) remaining.

COMPARATIVE EXAMPLE. The process disclosed in WO 2009/055557 was modified by using 1:1 THF/DCM as the solvent. Conversion to (2) was low with 12-15% unreacted (1) remaining. In addition, unknown side products was also formed.

Each publications cited herein is incorporated herein by reference.

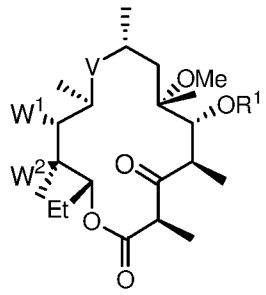
WHAT IS CLAIMED IS:

1. A process for preparing a fluoroketolide of formula (I)



(I)

the process comprising contacting a compound of the formula



with a fluorinating agent and an amine base; wherein

R^1 is H or acyl, or R^1 is a monosaccharide, such as methylamino or dimethylamino containing monosaccharide;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof; and

W^1 is hydroxy or a derivative thereof; and W^2 is H, or hydroxy or a derivative thereof; or W^1 and W^2 are taken together with the attached carbon atoms to form an oxygen and/or nitrogen containing heterocycle, each of which is optionally substituted.

2. The process of claim 1 wherein the amine base is a cyclic, a non-aromatic amine base, or a base with a conjugate acid pKa of at least about 11, at least about 11.5, at least about 12, at least about 12.5, or at least about 13, or a combination of the foregoing.

3. The process of claim 1 wherein the base is sterically hindered.

4. The process of claim 1 wherein the base is a diamine.

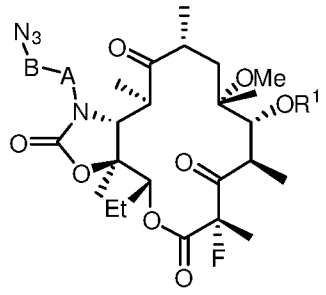
5. The process of claim 1 wherein the base includes at least one nitrogen that does not have a hydrogen.

6. The process of claim 1 wherein the base includes at least one C=N group.

7. The process of claim 1 wherein the base is DBN or DBU, or a combination thereof.

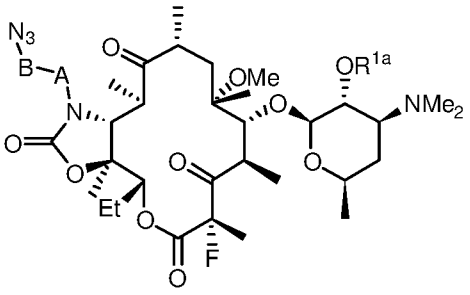
8. The process of any one of claims 1 to 7 wherein the fluorinating agent is selected from the group consisting of NFSi, Selectfluor, and F-TEDA, and combinations thereof.

9. The process of claim 8 wherein the compound of formula (I) is



or a salt thereof.

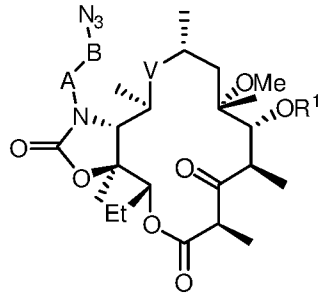
10. The process of claim 8 wherein the compound of formula (I) is



or a salt thereof.

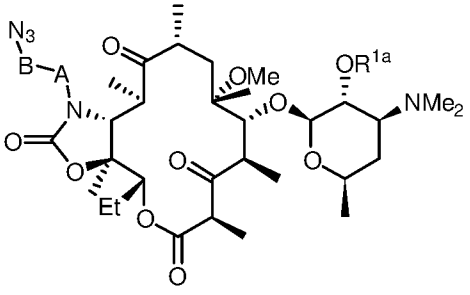
11. The process of claim 8 wherein the compound of formula (I) is solithromycin or a salt thereof.

12. The process of claim 8 wherein the starting compound is of the formula



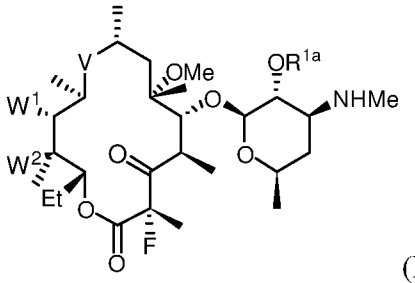
or a salt thereof.

13. The process of claim 8 wherein the starting compound is of the formula



or a salt thereof.

14. A process for preparing a compound of formula (I), the process comprising or further comprising contacting a compound of the formula (DM)



(DM)

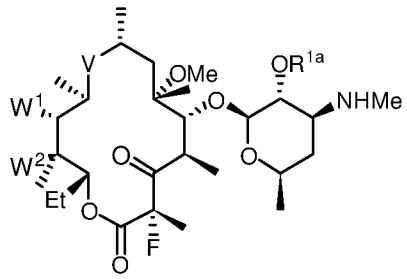
including salts of each of the foregoing, with a methylating agent; wherein:

R^{1a} is H or acyl;

V is CH_2-N(R), C=Q or C=NQ^1; where Q is O or (NR, H); where R is hydrogen or optionally substituted alkyl; and Q^1 is hydroxy or a derivative thereof or amino or a derivative thereof;

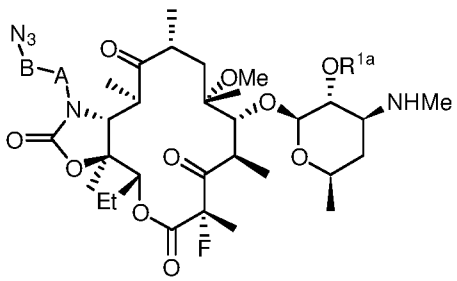
W^1 is hydroxy or a derivative thereof; and W^2 is H, or hydroxy or a derivative thereof; or W^1 and W^2 are taken together with the attached carbon atoms to form an oxygen and/or nitrogen containing heterocycle, each of which is optionally substituted.

15. The process of claim 14 wherein the compound of formula (DM) is



or a salt thereof.

16. The process of claim 14 wherein the compound of formula (DM) is



or a salt thereof.

17. A composition comprising solithromycin that is substantially free of or free of desfluoro solithromycin.

18. A composition comprising solithromycin that is substantially free of or free of N-desmethyl solithromycin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US16/21085

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/706; A61P 31/04; C07H 17/08 (2016.01)
CPC - A61K 31/706; C07H 17/08
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)
IPC(8): A61K 31/706; A61P 31/04, 31/10; C07H 17/08 (2016.01)
CPC: A61K 31/706; C07H 17/08

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)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; Pubmed; EBSCO; SureChEMBL; Cempra Pharmaceuticals, Pereira, Schneider, solithromycin, desfluoro, N-desmethyl, amine, azide, methylation, fluorination, macrolide, ketolide, antibacterial, NFSi, Selectfluor, F-TEDA, DBU, DBN, diamine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/165792 A2 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 9 October 2014; figure 2; paragraphs [0003], [0030]-[0031], [0034], [00643], [00661], [00666], [00691], [00697]-[00698], [00719]	1-3, 5-7, 8/1-3, 8/5-7, 9/8/1-3, 9/8/5-7, 10/8/1-3, 10/8/5-7, 11/8/1-3, 11/8/5-7, 12/8/1-3, 12/8/5-7, 13/8/1-3, 13/8/5-7, 17
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Y		4, 8/4, 9/8/4, 10/8/4, 11/8/4, 12/8/4, 13/8/4, 14-16, 18
Y	US 3,668,282 A (BELOW, JF) 6 June 1972; column 1, lines 30-40	4, 8/4, 9/8/4, 10/8/4, 11/8/4, 12/8/4, 13/8/4
Y	MORIMOTO, S et al. Chemical Modification of Erythromycins. I. Synthesis and Antibacterial Activity of 6-O-Methylerythromycins A. The Journal of Antibiotics, Vol. XXXVII No. 2, February 1984, pp. 187-189; page 187, column 1, paragraph 1; page 187, column 1, formula; page 187, column 1, paragraph 4; page 187, column 2, paragraph 1	14-16, 18
A	WO 2014/145210 A1 (CEMPRA PHARMACEUTICALS, INC) 18 September 2014; entire publication	1-7

☐ 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 application or patent 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
"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
"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
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2016 (29.04.2016)	17 MAY 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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(19)中华人民共和国国家知识产权局

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A61P 31/04(2006.01)
C07H 17/08(2006.01)

权利要求书3页 说明书22页

(54)发明名称

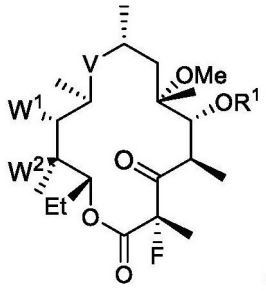
用于制备氟酮内酯的方法

(57)摘要

本文描述了用于制备氟酮内酯化合物的方法和中间体。

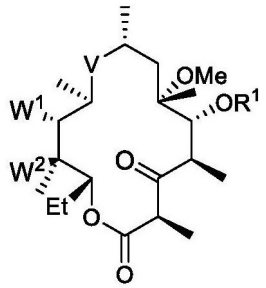
CN 107405355 A

1.一种用于制备式(I)的氟酮内酯的方法



(I)

所述方法包括使下式化合物



与氟化剂和胺碱接触;其中

R^1是H或酰基,或R^1是单糖,如含甲基氨基或二甲基氨基的单糖;

V是CH_2-N(R)、C＝Q或C＝NQ^1;其中Q是O或(NR,H);其中R是氢或任选取代的烷基;并且Q^1是羟基或其衍生物或氨基或其衍生物;并且

W^1是羟基或其衍生物;并且W^2是H或羟基或其衍生物;或W^1和W^2与所连接的碳原子一起形成含有氧和/或氮的杂环,其各自被任选取代。

2.如权利要求1所述的方法,其中所述胺碱是环状非芳族胺碱,或共轭酸pKa为至少约11、至少约11.5、至少约12、至少约12.5或至少约13或前述的组合的碱。

3.如权利要求1所述的方法,其中所述碱是空间位阻的。

4.如权利要求1所述的方法,其中所述碱是二胺。

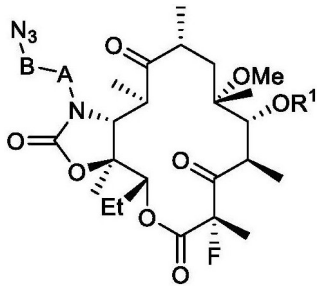
5.如权利要求1所述的方法,其中所述碱包含至少一个不具有氢的氮。

6.如权利要求1所述的方法,其中所述碱包含至少一个C＝N基团。

7.如权利要求1所述的方法,其中所述碱是DBN或DBU或其组合。

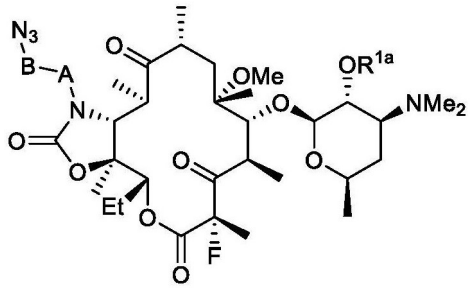
8.如权利要求1至7中任一项所述的方法,其中所述氟化剂选自由以下组成的组:NFSi、Selectfluor和F-TEDA以及其组合。

9.如权利要求8所述的方法,其中所述式(I)化合物是



或其盐。

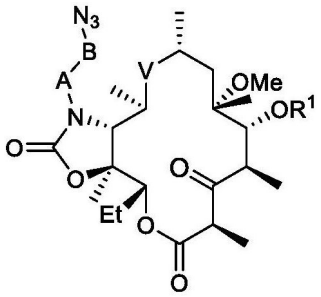
10.如权利要求8所述的方法,其中所述式(I)化合物是



或其盐。

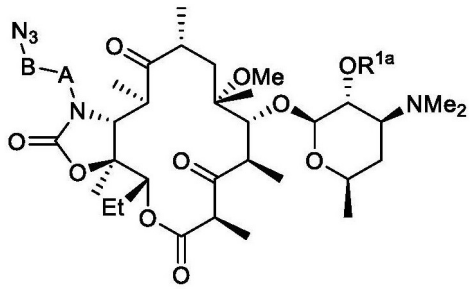
11.如权利要求8所述的方法,其中所述式(I)化合物是索利霉素或其盐。

12.如权利要求8所述的方法,其中所述起始化合物具有式



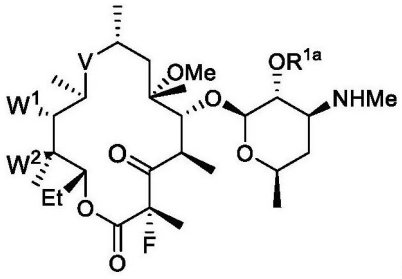
或其盐。

13.如权利要求8所述的方法,其中所述起始化合物具有式



或其盐。

14.一种用于制备式(I)化合物的方法,所述方法包括或还包括使式(DM)化合物



(DM)

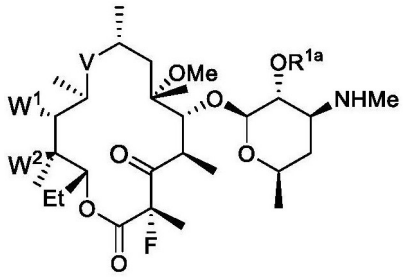
包括前述中的每一种的盐,与甲基化剂接触;其中:

R^{1a}是H或酰基;

V是CH_2-N(R)、C=Q或C=NQ^1;其中Q是O或(NR,H);其中R是氢或任选取代的烷基;并且Q^1是羟基或其衍生物或氨基或其衍生物;

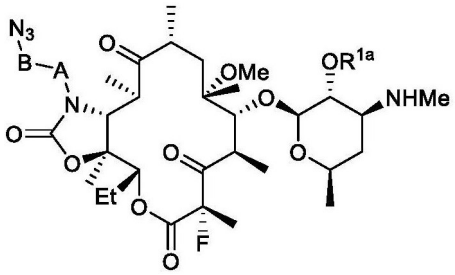
W^1是羟基或其衍生物;并且W^2是H或羟基或其衍生物;或W^1和W^2与所连接的碳原子一起形成含有氧和/或氮的杂环,其各自被任选取代。

15.如权利要求14所述的方法,其中所述式(DM)化合物是



或其盐。

16.如权利要求14所述的方法,其中所述式(DM)化合物是



或其盐。

17.一种组合物,其包含基本上不含或不含脱氟索利霉素的索利霉素。

18.一种组合物,其包含基本上不含或不含N-去甲基索利霉素的索利霉素。

用于制备氟酮内酯的方法

[0001] 相关申请的交叉引用

[0002] 本申请根据美国法典第35篇第119条(e)款要求2015年3月6日提交的美国临时申请序列号62/129,305的权益,所述临时申请的公开内容以引用的方式并入本文。

技术领域

[0003] 本文描述的发明涉及用于制备氟酮内酯化合物的方法和中间体。

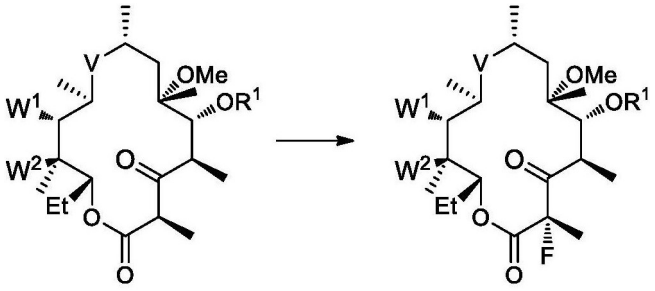
[0004] 发明背景和概述

[0005] 据报道氟酮内酯化合物在治疗细菌感染和原生动物感染方面非常有效。此外,据报道与对应的非氟酮内酯类、大环内酯类和氮杂内酯类相比,氟酮内酯化合物在治疗抗性细菌感染和原生动物感染方面特别有效。然而,所报道的用于酮内酯的制备方法以低转化率进行,这有时会导致在分离氟化产物与非氟化起始材料时不可克服的纯化问题。此外,所报道的用于酮内酯的制备方法往往会产生大量不想要的副产物,如N-去甲基化副产物。总而言之,所报道的用于酮内酯的制造方法可能无法满足世界的需求。

[0006] 由于这些化合物对人和其他动物健康的重要性,所以需要用于其制备的替代方法和/或改进的方法。具体地说,为了满足这些重要的人和动物健康化合物的未满足的需求,需要用于在商业上相关的制造规模下制备氟酮内酯的方法。

[0007] 在本文中已经意外地发现,包括胺碱的方法提供氟酮内酯的高转化率,具有较少副产物。由于高转化率和较少副产物,本文所述的方法可用于制备数千克量的氟酮内酯,所述氟酮内酯可通过简单沉淀分离,而不是通过色谱法或分级重结晶分离,色谱法或分级重结晶各自均是昂贵的和/或可导致分离产率的显著损失。

[0008] 在本文描述的发明的一个说明性实施方案中,描述了用于通过在大环的C2处氟化来制备氟酮内酯化合物的方法。在另一个实施方案中,本文所述的方法包括以下步骤:

[0009] 

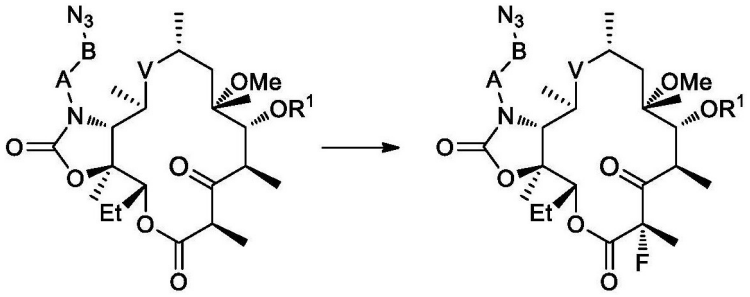
[0010] 包括前述中的每一种的盐,其中:

[0011] R^1是H或酰基,或R^1是单糖,如含甲基氨基或二甲基氨基的单糖;

[0012] V是CH_2-N(R)、C=Q或C=NQ^1;其中Q是O或(NR,H);其中R是氢或任选取代的烷基;并且Q^1是羟基或其衍生物或氨基或其衍生物;并且

[0013] W^1是羟基或其衍生物;并且W^2是H或羟基或其衍生物;或W^1和W^2与所连接的碳原子一起形成含有氧和/或氮的杂环,其各自被任选取代。

[0014] 在另一个实施方案中,所述方法包括以下步骤:

[0015] 

[0016] 包括前述中的每一种的盐，其中：

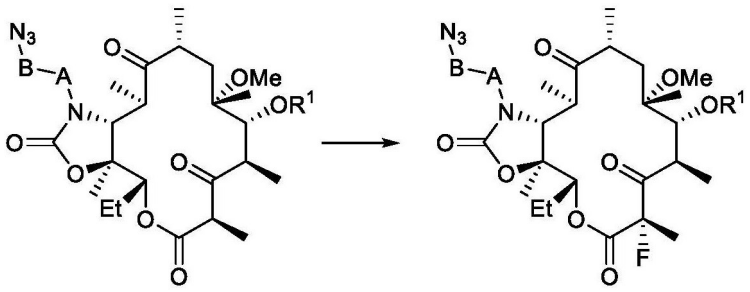
[0017] R^1是H或酰基，或R^1是单糖，如含甲基氨基或二甲基氨基的单糖；

[0018] V是CH_2-N(R)、C＝Q或C＝NQ^1；其中Q是O或(NR,H)；其中R是氢或任选取代的烷基；并且Q^1是羟基或其衍生物或氨基或其衍生物；

[0019] A是键，或A是由O、C(O)、CR、CR_2和NR以及其组合形成的任选的接头，其中每个R在每种情况下独立地选自不存在以形成双键或三键，氢或任选取代的烷基；并且

[0020] B是键，或B是任选取代的亚烷基、任选取代的亚烯基或任选取代的亚炔基。

[0021] 在另一个实施方案中，所述方法包括以下步骤：

[0022] 

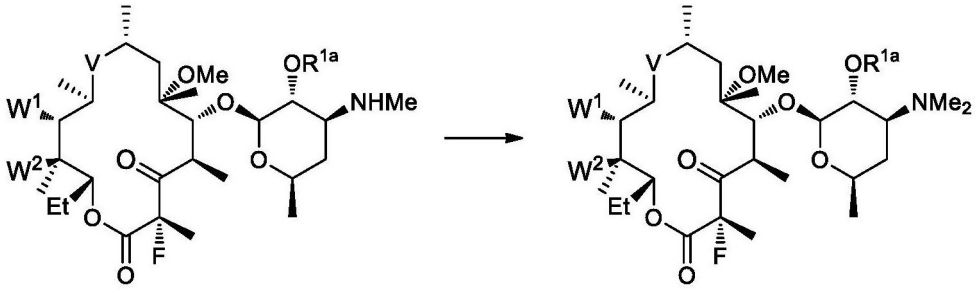
[0023] 包括前述中的每一种的盐，其中：

[0024] R^1是H或酰基，或R^1是单糖，如含甲基氨基或二甲基氨基的单糖；

[0025] A是键，或A是由O、C(O)、CR、CR_2和NR以及其组合形成的任选的接头，其中每个R在每种情况下独立地选自不存在以形成双键或三键，氢或任选取代的烷基；并且

[0026] B是键，或B是任选取代的亚烷基、任选取代的亚烯基或任选取代的亚炔基。

[0027] 在另一个实施方案中，本文描述用于通过原位N-甲基化制备氟酮内酯化合物的方法。在另一个实施方案中，所述方法包括以下步骤：

[0028] 

[0029] 包括前述中的每一种的盐，其中：

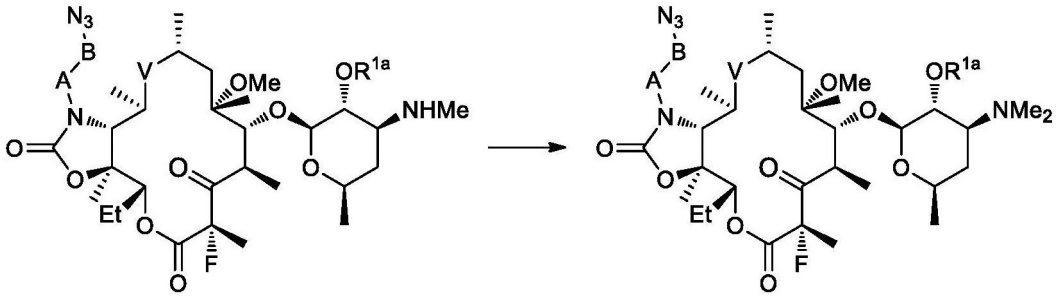
[0030] R^{1a}是H或酰基；

[0031] V是CH_2-N(R)、C＝Q或C＝NQ^1；其中Q是O或(NR,H)；其中R是氢或任选取代的烷基；并且Q^1是羟基或其衍生物或氨基或其衍生物；

[0032] W^1是羟基或其衍生物；并且W^2是H或羟基或其衍生物；或W^1和W^2与所连接的碳原子

一起形成含有氧和/或氮的杂环，其各自被任选取代。

[0033] 在另一个实施方案中，所述方法包括以下步骤：

[0034] 

[0035] 包括前述中的每一种的盐，其中：

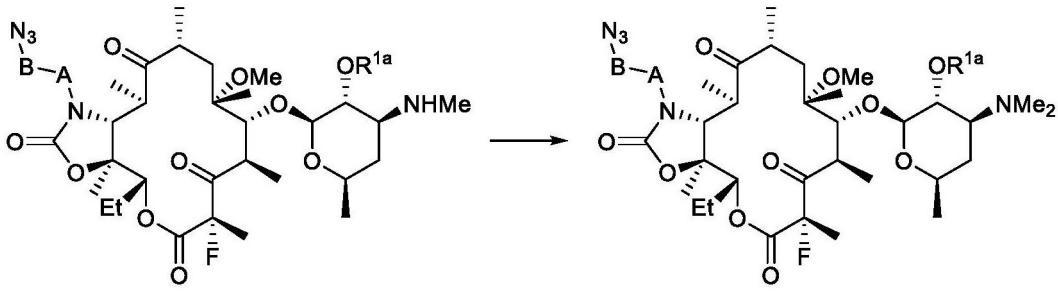
[0036] R^{1a}是H或酰基；

[0037] V是CH_2-N(R)、C＝Q或C＝NQ^1；其中Q是O或(NR,H)；其中R是氢或任选取代的烷基；并且Q^1是羟基或其衍生物或氨基或其衍生物；

[0038] A是键，或A是由O、C(O)、CR、CR_2和NR以及其组合形成的任选的接头，其中每个R在每种情况下独立地选自不存在以形成双键或三键，氢或任选取代的烷基；并且

[0039] B是键，或B是任选取代的亚烷基、任选取代的亚烯基或任选取代的亚炔基。

[0040] 在另一个实施方案中，所述方法包括以下步骤：

[0041] 

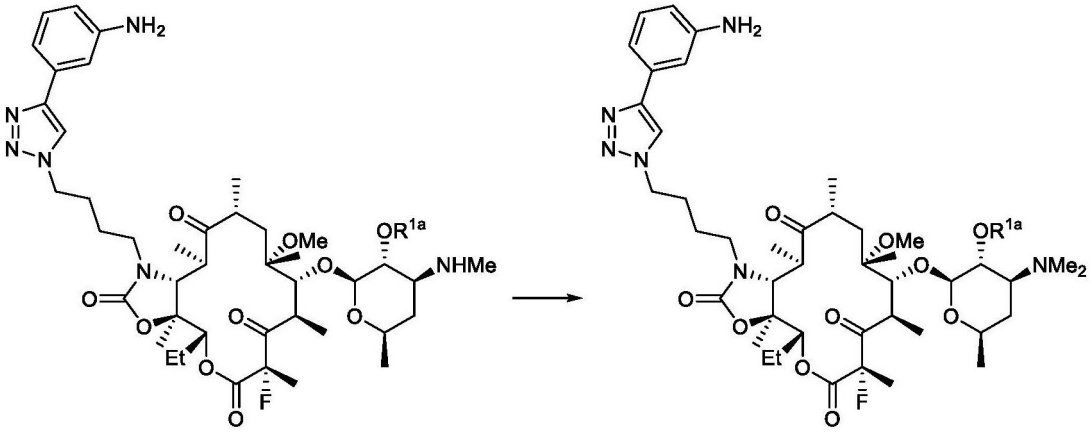
[0042] 包括前述中的每一种的盐，其中：

[0043] R^{1a}是H或酰基；

[0044] A是键，或A是由O、C(O)、CR、CR_2和NR以及其组合形成的任选的接头，其中每个R在每种情况下独立地选自不存在以形成双键或三键，氢或任选取代的烷基；并且

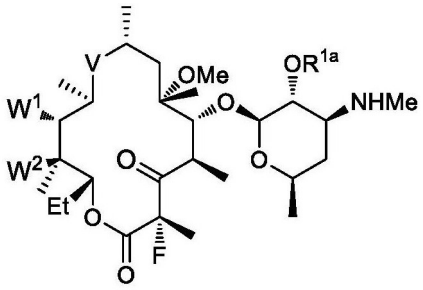
[0045] B是键，或B是任选取代的亚烷基、任选取代的亚烯基或任选取代的亚炔基。

[0046] 在另一个实施方案中，所述方法包括以下步骤：

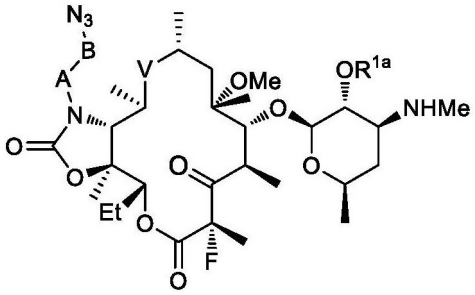
[0047] 

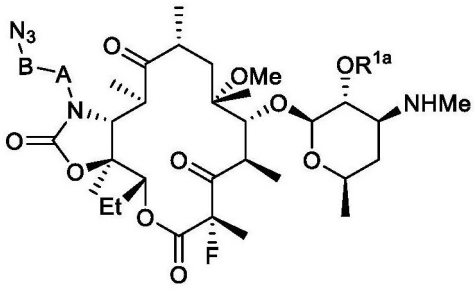
[0048] 包括前述中的每一种的盐，其中R^{1a}是H或酰基。

[0049] 在另一个实施方案中，本文描述了用于制备氟酮内酯化合物的中间体。说明性中间体具有式

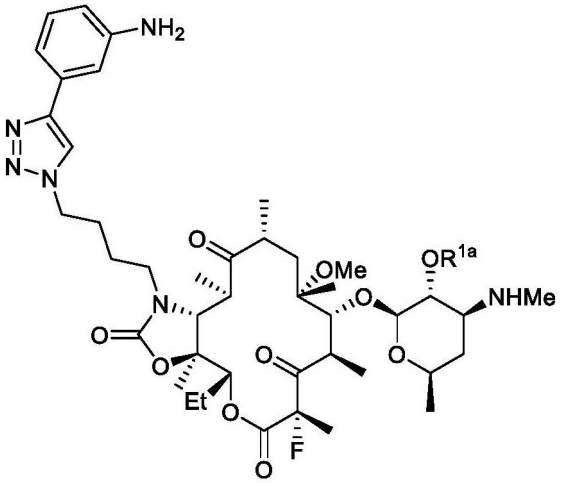


[0050]





[0051]



[0052] 及其盐，其中R^{1a}、V、W^1、W^2、A和B是如本文所定义。

[0053] 在另一个实施方案中，本文还描述了含有所述化合物中的一种或多种的药物组合物。应理解，所述组合物可包含其他组分和/或成分，包括但不限于其他治疗活性化合物和/或一种或多种载体、稀释剂、赋形剂等以及其组合。

[0054] 在另一个实施方案中，本文还描述了用于治疗患有细菌或原生动物感染的宿主动物的方法，其中所述方法包括向所述宿主动物施用一种或多种本文所述的化合物和/或组

合物。在另一个实施方案中，本文还描述了所述化合物和组合物在制造用于治疗患有细菌或原生动物感染的宿主动物的药物中的用途。在另一个实施方案中，所述药物包括用于治疗患有细菌或原生动物感染的宿主动物的治疗有效量的一种或多种化合物和/或组合物。

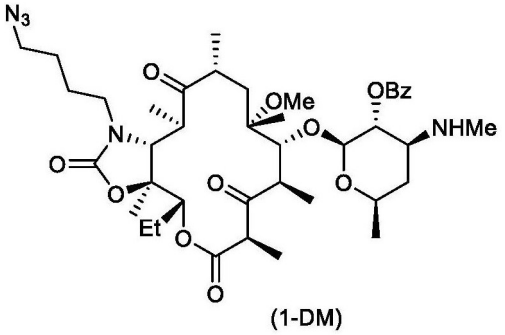
[0055] 详述

[0056] WO 2004/080391中描述了某些氟酮内酯和用于制备氟酮内酯的方法。WO 2009/055557中也描述了用于制备氟酮内酯的方法。已经发现，在前述公布中针对在大环内酯核心结构的C2处氟化描述的方法未能进行到完成。此外，已经发现，在C2处实现完全氟化的尝试导致越来越多量的副产物形成，如C5处的糖的N-去甲基化，如脱氧糖胺的去甲基化；以及当反应条件变得更剧烈时的分解。因此，解决不完全转化的问题的探索导致至少两个其他问题，即副产物形成和总产率较低。此外，还已经意外地发现，未氟化起始材料和氟化产物基本上是不可分离的，尤其是使用对于生产用于全球市场的抗生素所需的大规模来说必需的商业上相关的纯化技术不可分离的。由于起始材料与所需产物之间的唯一不同之处是单一氟原子，所以两种化合物的分离是相当困难的，并且只能通过仔细的柱色谱法或分级重结晶来实现，所述柱色谱法或分级重结晶各自导致显著材料损失，并且因此导致总体产率损失。还已经意外地发现，N-去甲基副产物也非常难以使用对于生产用于全球市场的抗生素所需的大规模来说必需的商业上相关的纯化技术除去。商业上相关的纯化技术包括蒸发、沉淀和结晶，而有利地避免了色谱法或分级结晶，所述色谱法或分级结晶各自更昂贵并且导致显著产率降低。

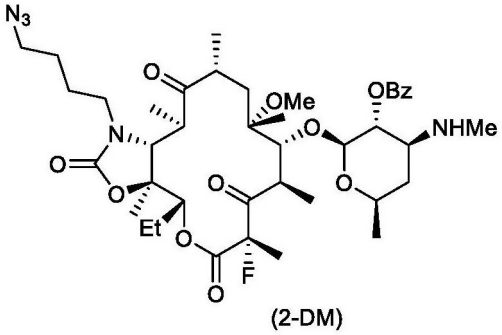
[0057] 此外，已经发现，在许多情况下，所需氟酮内酯的对应未氟化类似物比所需的氟化化合物活性显著更低，尤其是针对抗性病原体。类似地，已经发现，在几乎所有情况下，所需氟酮内酯的对应N-去甲基化类似物比所需N,N-二甲基化合物活性显著更低。因此，应理解，希望完全氟化以确保产物是纯的并且此外它不会被可能影响药物性能的较低活性的类似物污染，特别是当这些较低活性的类似物的相对量可跨多个批次变化时。类似地，应理解，希望避免去甲基化以确保产物是纯的并且此外它不会被可能影响药物性能的较低活性的类似物污染，特别是当这些较低活性的类似物的相对量可跨多个批次变化时。

[0058] 解决不完全氟化的问题需要更剧烈的试剂和反应条件，如更高温度、更多当量的碱和/或更多当量的氟化剂。然而，这些相同方法修改通过增加不想要的N-去甲基化产物(起始未氟化化合物例如(1-DM)和产物氟化化合物例如(2-DM)两者)的量而加剧伴随的问题。

[0059]



(1-DM)



(2-DM)

[0060] 此外，使用这些相同的更剧烈的试剂和反应条件导致分解、其他不想要的副产物且因此导致总体产率损失。

[0061] 类似地，解决不想要的N-去甲基化的问题需要不那么剧烈的试剂和反应条件。然

而，同样的解决方案通过降低未氟化合物至产物氟化化合物的转化而加剧伴随的问题。

[0062] 还已经发现，即使在WO 2009/055557中报道的方法被修改以有利于转化和伴随的N-去甲基化时，原位再甲基化也失败。因此，有必要将多种产物与反应混合物分离，并且进行单独的再甲基化步骤，这导致额外的材料损失、总体产率下降、更高的成本和更长的制造时间。

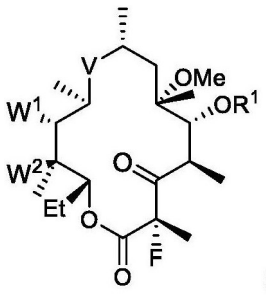
[0063] 在全世界对用于治疗细菌和原生动物感染的氟酮内酯的需要要求具有成本效益并且可大规模进行的制造方法。在没有这些属性的情况下，氟酮内酯的供应将不足以满足世界的需要，和/或妨碍在世界的欠发达地区使用氟酮内酯，在所述欠发达地区中细菌或原生动物感染通常更普遍并导致较差的结果。

[0064] 需要用于制备氟酮内酯的新方法。在没有提供更高产率的高纯度氟酮内酯类抗生素的此类改进方法的情况下，由于供应不足、延迟制造和/或治疗成本太高，存在数百万患有细菌或原生动物感染的患者将遭受未治疗的风险。

[0065] 在本文中已经意外地发现，本文所述的氟化方法提供未氟化起始材料至所需氟酮内酯的显著更高转化率。在本文中还已经意外地发现，本文所述的氟化方法提供基本上较少量的N-去甲基化副产物。此外，在本文中已经意外地发现，本文所述的氟化方法可适于包括原位去甲基化，以通过重新捕获N-去甲基化副产物来进一步提高总产率。因此，包括例如(1-DM)和(2-DM)的不想要的N-去甲基化产物适用作用于制备氟酮内酯的起始材料。本文所述的方法以高产率提供具有高纯度的氟化酮内酯，并且可适于大的数千克商业制造规模。

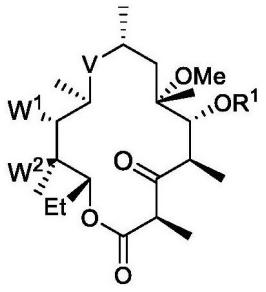
[0066] 本发明的若干说明性实施方案通过以下条款来描述：

[0067] 一种用于制备式(I)的氟酮内酯的方法

[0068] 

(I)

[0069] 所述方法包括以下步骤：使下式化合物

[0070] 

[0071] 与氟化剂和胺碱接触；其中，

[0072] R^1是H或酰基，或R^1是单糖，如含甲基氨基或二甲基氨基的单糖；

[0073] V是CH_2-N(R)、C＝Q或C＝NQ^1；其中Q是O或(NR,H)；其中R是氢或任选取代的烷基；并且Q^1是羟基或其衍生物或氨基或其衍生物；并且

[0074] W^1是羟基或其衍生物；并且W^2是H或羟基或其衍生物；或W^1和W^2与所连接的碳原子

一起形成含有氧和/或氮的杂环,其各自被任选取代。

[0075] 前述方法中的任一种,其中所述胺碱是环状非芳族胺碱,或共轭酸pKa为至少约11、至少约11.5、至少约12、至少约12.5或至少约13或前述的组合的碱。

[0076] 前述方法中的任一种,其中所述碱是环胺。

[0077] 前述方法中的任一种,其中所述碱是双环胺。

[0078] 前述方法中的任一种,其中所述碱是空间位阻的。

[0079] 前述方法中的任一种,其中所述碱是构象限制的。

[0080] 前述方法中的任一种,其中所述碱是二胺。

[0081] 前述方法中的任一种,其中所述碱包含至少一个不具有氢的氮。

[0082] 前述方法中的任一种,其中所述碱不包含任何NH基团。

[0083] 前述方法中的任一种,其中所述碱包含至少一个C=N基团。

[0084] 前述方法中的任一种,其中所述碱选自由以下组成的组:1,8-二氮杂双环[5.4.0]十一-7-烯(DBU)、1,5-二氮杂双环[4.3.0]壬-5-烯(DBN)和3,3,6,9,9-五甲基-2,10-二氮杂双环[4.4.0]癸-1-烯(PMDBD)、奎宁环以及其组合。

[0085] 前述方法中的任一种,其中所述碱是DBN或DBU,或其组合。

[0086] 前述方法中的任一种,其中所述碱是DBU。

[0087] 前述方法中的任一种,其中所述氟化剂选自由以下组成的组:NFSi、Selectfluor和F-TEDA以及其组合。

[0088] 前述方法中的任一种,其中所述氟化剂选自由以下组成的组:NFSi和Selectfluor以及其组合。

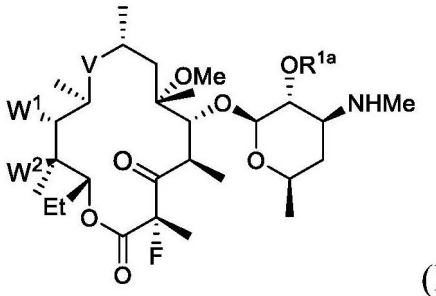
[0089] 前述方法中的任一种,其中所述氟化剂是NFSi与Selectfluor的组合。

[0090] 前述方法中的任一种,其中所述氟化剂是NFSi。

[0091] 前述方法中的任一种,其中温度介于约-30℃与约-20℃之间。已经观察到,在更接近环境温度的温度下,越来越多的副产物开始形成。

[0092] 一种用于制备式(I)化合物的方法,所述方法包括以下步骤或还包括以下步骤:使式(DM)化合物

[0093]



(DM)

[0094] 包括前述中的每一种的盐,与甲基化剂接触;其中:

[0095] R^{1a}是H或酰基;

[0096] V是CH_2-N(R)、C=Q或C=NQ^1;其中Q是O或(NR,H);其中R是氢或任选取代的烷基;并且Q^1是羟基或其衍生物或氨基或其衍生物;

[0097] W^1是羟基或其衍生物;并且W^2是H或羟基或其衍生物;或W^1和W^2与所连接的碳原子一起形成含有氧和/或氮的杂环,其各自被任选取代。

[0098] 前述方法中的任一种，其中所述甲基化剂是CH_2O/HCO_2H。

[0099] 前述方法中的任一种，其在溶剂中进行，其中所述溶剂包含酮，如丙酮、MEK或MTBK。

[0100] 前述方法中的任一种，其在溶剂中进行，其中所述溶剂包含醚，如MTBE、THF、Me-THF或二醇醚，如二甲氧基乙烷、二乙氧基乙烷或式$R^1O-(CH_2)_2-OR^2$的化合物，其中R^1是烷基，如甲基、乙基、丙基、异丙基或丁基；并且R^2是H、甲基、乙基、丙基、异丙基或丁基；或式$R^1[O-(CH_2)_2-]_2OR^2$的化合物，其中R^1是烷基，如甲基、乙基、丙基、异丙基或丁基；并且R^2是H、甲基、乙基、丙基、异丙基或丁基。

[0101] 前述方法中的任一种，其在溶剂中进行，其中所述溶剂包含酯，如EtOAc、iPrOAc。

[0102] 前述方法中的任一种，其在溶剂中进行，其中所述溶剂包含酰胺，如DMF、DMA、NMP。

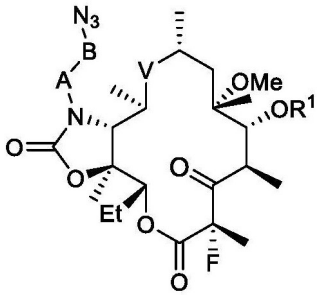
[0103] 前述方法中的任一种，其在溶剂中进行，其中所述溶剂包含说明性地在约1:2至约2:1或约3:2至约2:3的范围内或约1:1的比率下的酰胺与酯的混合物，如iPrOAc/DMF或iPrOAc/DMF。

[0104] 前述方法中的任一种，其在溶剂中进行，其中所述溶剂基本上不含或不含氯化溶剂，如CH_2Cl_2(DCM)、$CHCl_3$和/或CCl_4。

[0105] 前述方法中的任一种，其中W^1和W^2与所连接的碳原子一起形成氨基甲酸酯，其中其氮被式N_3-B-A的基团取代，其中A是键，或者A是由O、C(O)、CR、CR_2和NR以及其组合形成的任选的接头，其中每个R在每次出现时独立地选自不存在以形成双键或三键，氢或任选取代的烷基；并且B是键，或B是任选取代的亚烷基、任选取代的亚烯基或任选取代的亚炔基。

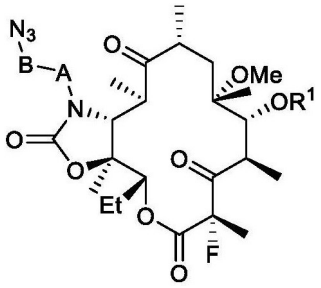
[0106] 前述方法中的任一种，其中W^1和W^2与所连接的碳原子一起形成氨基甲酸酯，其中其氮被式T-B-A的基团取代，其中A是键，或者A是由O、C(O)、CR、CR_2和NR以及其组合形成的任选的接头，其中每个R在每次出现时独立地选自不存在以形成双键或三键，氢或任选取代的烷基；B是键，或B是任选取代的亚烷基、任选取代的亚烯基或任选取代的亚炔基；T是任选取代的芳基，包括但不限于咪唑基、1,2,3-三唑基、苯基、苯并咪唑基、苯并三唑基等，并且其中所述任选的取代包括但不限于任选取代的芳基、苯基、氨基苯基、苯并咪唑基、苯并三唑基、苯并咪唑基甲基、苯并三唑基甲基等。

[0107] 前述方法中的任一种，其中所述式(I)化合物是

[0108] 

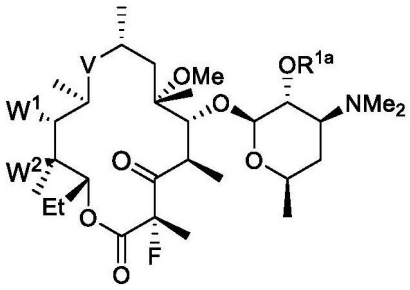
[0109] 或其盐。

[0110] 前述方法中的任一种，其中所述式(I)化合物是

[0111] 

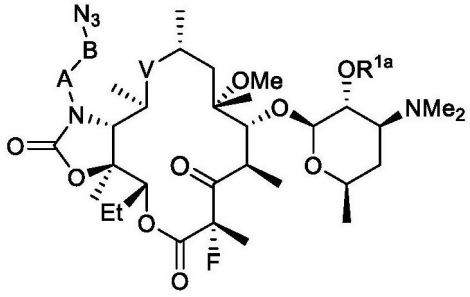
[0112] 或其盐。

[0113] 前述方法中的任一种，其中所述式(I)化合物是

[0114] 

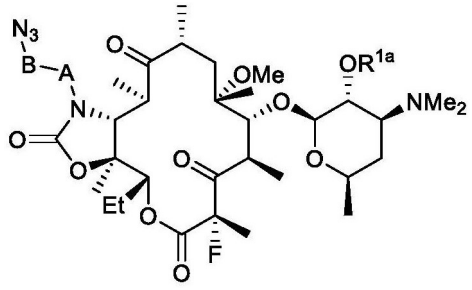
[0115] 或其盐。

[0116] 前述方法中的任一种，其中所述式(I)化合物是

[0117] 

[0118] 或其盐。

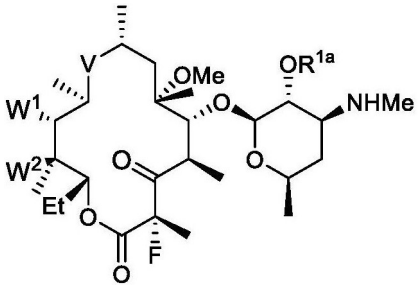
[0119] 前述方法中的任一种，其中所述式(I)化合物是

[0120] 

[0121] 或其盐。

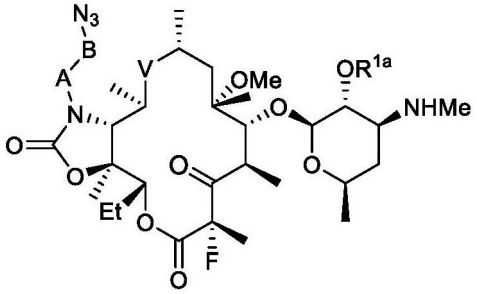
[0122] 前述方法中的任一种，其中所述式(I)化合物是索利霉素或其盐。

[0123] 前述方法中的任一种，其中所述式(DM)化合物是

[0124] 

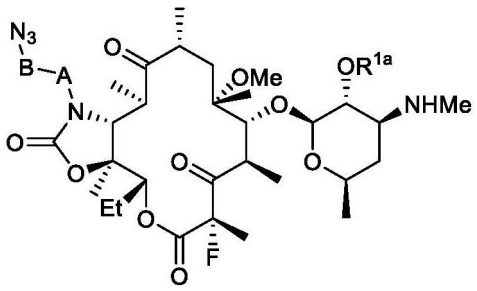
[0125] 或其盐。

[0126] 前述方法中的任一种，其中所述式(DM)化合物是

[0127] 

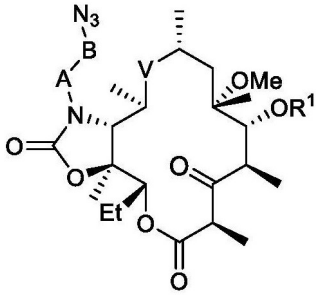
[0128] 或其盐。

[0129] 前述方法中的任一种，其中所述式(DM)化合物是

[0130] 

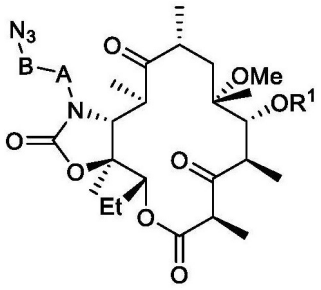
[0131] 或其盐。

[0132] 前述方法中的任一种，其中起始化合物具有式

[0133] 

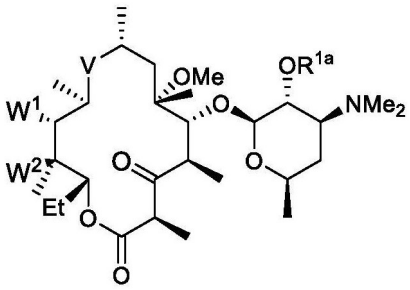
[0134] 或其盐。

[0135] 前述方法中的任一种，其中起始化合物具有式

[0136] 

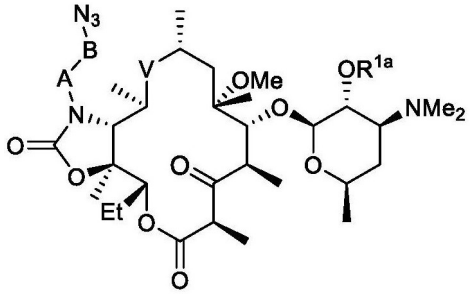
[0137] 或其盐。

[0138] 前述方法中的任一种，其中起始化合物具有式

[0139] 

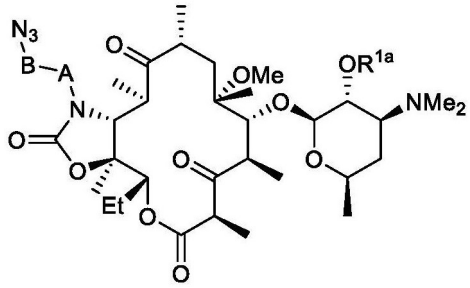
[0140] 或其盐。

[0141] 前述方法中的任一种，其中起始化合物具有式

[0142] 

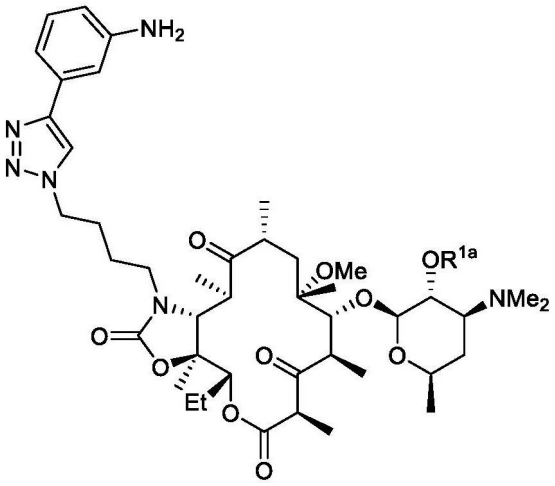
[0143] 或其盐。

[0144] 前述方法中的任一种，其中起始化合物具有式

[0145] 

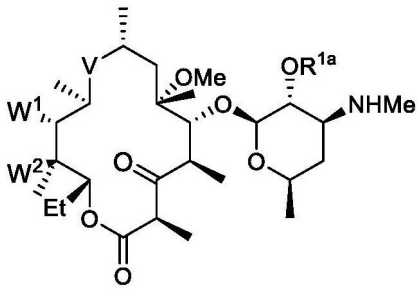
[0146] 或其盐。

[0147] 前述方法中的任一种，其中起始化合物具有式

[0148] 

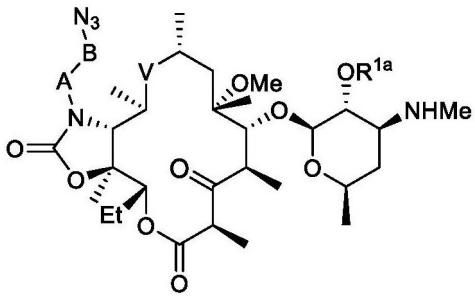
[0149] 或其盐。

[0150] 前述方法中的任一种,其中起始化合物具有式

[0151] 

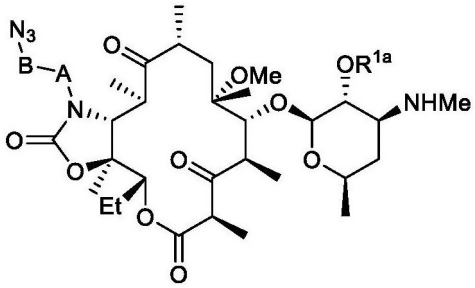
[0152] 或其盐,或前述的C2-氟代类似物。

[0153] 前述方法中的任一种,其中起始化合物具有式

[0154] 

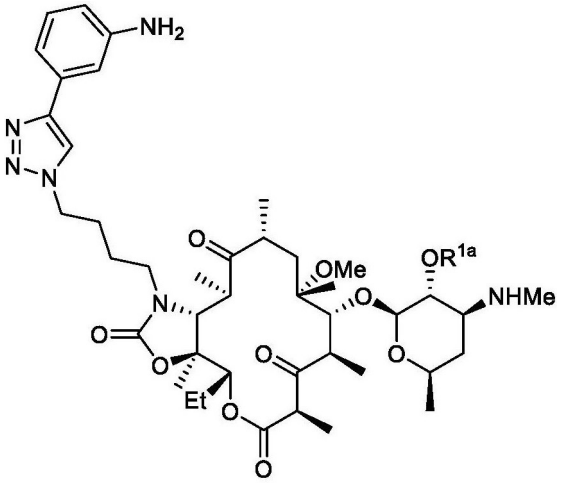
[0155] 或其盐,或前述的C2-氟代类似物。

[0156] 前述方法中的任一种,其中起始化合物具有式

[0157] 

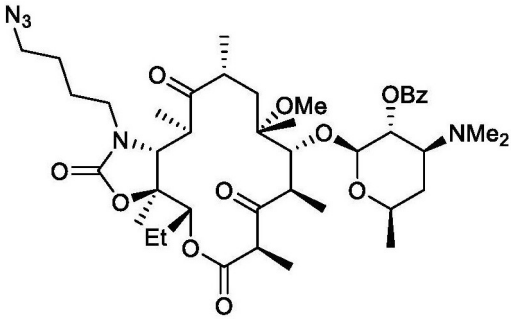
[0158] 或其盐,或前述的C2-氟代类似物。

[0159] 前述方法中的任一种,其中起始化合物具有式

[0160] 

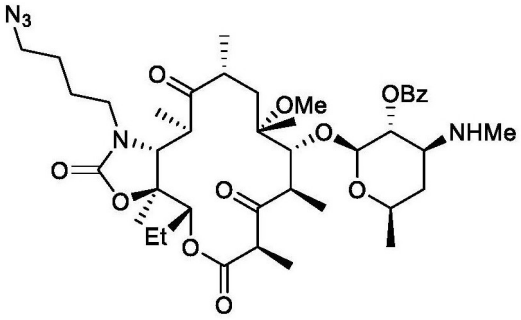
[0161] 或其盐,或前述的C2-氟代类似物。

[0162] 前述方法中的任一种,其中所述化合物具有式

[0163] 

[0164] 或其盐。

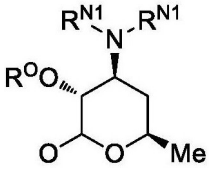
[0165] 前述方法中的任一种,其中所述化合物具有式

[0166] 

[0167] 或其盐。

[0168] 前述方法中的任一种,其中所述单糖是己糖,如D-葡萄糖、D-甘露糖、D-木糖、D-半乳糖、L-岩藻糖等;戊糖,如D-核糖、D-阿拉伯糖等;酮糖,如D-核酮糖、D-果糖等;包括其氨基甲基和二甲基氨基衍生物,如葡糖胺、半乳糖胺、乙酰葡萄糖、乙酰半乳糖、N-乙酰葡糖胺、N-乙酰基-半乳糖胺、半乳糖基-N-乙酰葡糖胺、N-乙酰神经氨酸(唾液酸)、碳霉糖、脱氧糖胺、L-万古糖胺、3-去甲基-万古糖胺、3-表-万古糖胺、4-表-万古糖胺、acosamine、3-氨基-葡萄糖、4脱氧-3-氨基-葡萄糖、actinosamine、道诺糖胺、3-表-道诺糖胺、瑞斯托糖胺、N-甲基-D-葡糖胺等;以及其氨基甲基和二甲基氨基衍生物。

[0169] 前述方法中的任一种,其中OR^1具有式

[0170] 

[0171] 其中每个R^{N1}在每种情况下独立地选自H和酰基以及烷基、环烷基、芳基烷基和杂芳基烷基，其各自被任选取代；并且R^0是H或酰基或烷基、环烷基、芳基烷基和杂芳基烷基，其各自被任选取代。在另一个实施方案中，至少一个R^{N1}是甲基。在另一个实施方案中，两个R^{N1}是甲基。在另一个实施方案中，R^0是H或酰基。在另一个实施方案中，R^0是H。

[0172] 前述方法中的任一种，其中R^1是脱氧糖胺基。

[0173] 前述方法中的任一种，其中R^1是N-去甲基脱氧糖胺基。

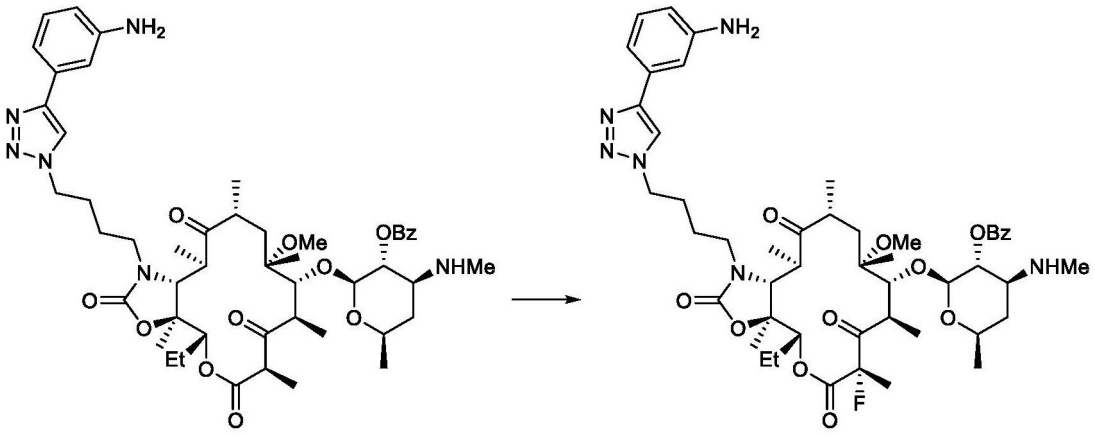
[0174] 一种组合物，其包含基本上不含或不含脱氟索利霉素的索利霉素。

[0175] 一种组合物，其包含含有少于约1％、少于约0.5％、少于约0.4％、少于约0.3％、少于约0.2％、少于约0.15％、少于约0.1％、少于约0.05％或少于约0.03％脱氟索利霉素的索利霉素。

[0176] 一种组合物，其包含基本上不含或不含N-去甲基索利霉素的索利霉素。

[0177] 一种组合物，其包含含有少于约1％、少于约0.5％、少于约0.4％、少于约0.3％、少于约0.2％、少于约0.15％、少于约0.1％、少于约0.05％或少于约0.03％N-去甲基索利霉素的索利霉素。

[0178] 本文还描述了一种用于制备苯甲酸索利霉素或其盐的方法，其中所述方法包括以下步骤

[0179] 

[0180] 包括前述中的每一种的盐。

[0181] 本文还描述了一种用于制备索利霉素或其盐的方法，其中所述方法包括制备本文所述的氟化化合物，并将所述氟化化合物转化成索利霉素或其盐。

[0182] 在每个前述实施方案和每个以下实施方案中，除非另外指明，否则应理解，所述式不仅包括并表示所述化合物的所有药学上可接受的盐，而且包括所述化合物式的任何和所有水合物和/或溶剂化物。应了解，某些官能团如羟基、氨基等基团与水和/或各种溶剂形成复合物和/或配位化合物，所述化合物呈不同的物理形式。因此，以上式应被理解为是此类水合物和/或溶剂化物的描述，包括药学上可接受的溶剂化物。

[0183] 在每个前述实施方案和每个以下实施方案中，除非另外指明，否则还应理解，所述式包括并表示所述化合物的任何和所有结晶形式、部分结晶形式和非结晶形式和/或非晶

形式。

[0184] 在每个前述实施方案和每个以下实施方案中，除非另外指明，否则还应理解，所述式包括并表示每种可能的异构体，如单独地以及呈任何和所有可能的混合物形式两者的立体异构体和几何异构体。

[0185] 如本文所用，术语“溶剂化物”是指与溶剂分子复合的本文所述的化合物。应了解，本文所述的化合物可通过将所述化合物与溶剂简单地混合或将所述化合物溶解在溶剂中而与溶剂形成此类复合物。应了解，当所述化合物待用作药物时，此类溶剂是药学上可接受的溶剂。还应了解，当所述化合物待用作药物时，形成溶剂化物的溶剂的相对量应小于此类药物用途的确立的指南，如小于国际协调会议(ICH)指南。应理解，溶剂化物可通过蒸发、沉淀和/或结晶从过量溶剂中分离。在一些实施方案中，溶剂化物是非晶形的，并且在其他实施方案中，溶剂化物是结晶的。

[0186] 应理解，前述实施方案中的每一个可以化学相关的方式组合以产生本文描述的实施方案的子集。因此，应进一步理解，所有此类子集也是本文描述的发明的说明性实施方案。

[0187] 本文所述的化合物可含有一个或多个手性中心，或者可另外能够作为多种立体异构体存在。应理解，在一个实施方案中，本文所述的发明并不限于任何特定的立体化学要求，并且所述化合物和包含所述化合物的组合物、方法、用途以及药物可以是光学纯的，或者可以是多种立体异构体混合物中的任一种，包括外消旋和对映异构体的其他混合物、非对映异构体的其他混合物等。还应理解，此类立体异构体的混合物可在一个或多个手性中心处包含单一立体化学构型，同时在一个或多个其他手性中心处包含立体化学构型的混合物。

[0188] 类似地，本文所述的化合物可包含多个几何中心，如顺式、反式、E、以及Z双键。应理解，在另一个实施方案中，本文描述的发明并不限于任何特定的几何异构体要求，并且所述化合物和包含所述化合物的组合物、方法、用途以及药物可以是纯的，或者可以是多种几何异构体混合物中的任一种。还应理解，此类几何异构体的混合物可在一个或多个双键处包含单一构型，同时在一个或多个其他双键处包含几何结构的混合物。

[0189] 如本文所用，术语“烷基”包含任选支化的碳原子链。如本文所用，术语“烯基”和“炔基”各自包含任选支化的碳原子链，并且分别包含至少一个双键或三键。应理解，炔基还可包含一个或多个双键。应进一步理解，在某些实施方案中，烷基有利地具有有限的长度，包括C_1-C_{24}、C_1-C_{12}、C_1-C_8、C_1-C_6和C_1-C_4以及C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6和C_2-C_4等。说明性地，包括C_1-C_8、C_1-C_6和C_1-C_4以及C_2-C_8、C_2-C_6和C_2-C_4等的此类具体有限长度的烷基可被称为低级烷基。应进一步理解，在某些实施方案中，烯基和/或炔基可各自有利地具有有限的长度，包括C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6和C_2-C_4以及C_3-C_{24}、C_3-C_{12}、C_3-C_8、C_3-C_6和C_3-C_4等。说明性地，包括C_2-C_8、C_2-C_6和C_2-C_4以及C_3-C_8、C_3-C_6和C_3-C_4等的此类具体有限长度的烯基和/或炔基可被称为低级烯基和/或炔基。在本文中应了解，较短的烷基、烯基和/或炔基可向化合物添加较少亲脂性且因此将具有不同的药物动力学行为。在本文所述的发明的实施方案中，应理解在每种情况下，烷基的叙述是指如本文定义的烷基以及任选的低级烷基。在本文所述的发明的实施方案中，应理解在每种情况下，烯基的叙述是指如本文定义的烯基以及任选的低级烯基。在本文所述的发明的实施方案中，应理解在每种情况下，炔基的叙述是指如本文

定义的炔基以及任选的低级炔基。说明性烷基、烯基和炔基是但不限于甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、戊基、2-戊基、3-戊基、新戊基、己基、庚基、辛基等，以及含有一个或多个双键和/或三键的相应基团，或其组合。

[0190] 如本文所用，术语“亚烷基”包含任选支化的二价碳原子链。如本文所用，术语“亚烯基”和“亚炔基”包含任选支化的二价碳原子链，并且分别包含至少一个双键或三键。应理解，亚炔基还可包含一个或多个双键。应进一步理解，在某些实施方案中，亚烷基有利地具有有限的长度，包括C_1-C_{24}、C_1-C_{12}、C_1-C_8、C_1-C_6、和C_1-C_4、和C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6以及C_2-C_4等。说明性地，包括C_1-C_8、C_1-C_6和C_1-C_4以及C_2-C_8、C_2-C_6和C_2-C_4等的此类具体有限长度的亚烷基可被称为低级亚烷基。应进一步理解，在某些实施方案中，亚烯基和/或亚炔基可各自有利地具有有限的长度，包括C_2-C_{24}、C_2-C_{12}、C_2-C_8、C_2-C_6和C_2-C_4以及C_3-C_{24}、C_3-C_{12}、C_3-C_8、C_3-C_6和C_3-C_4等。说明性地，包括C_2-C_8、C_2-C_6和C_2-C_4以及C_3-C_8、C_3-C_6和C_3-C_4等的此类具体有限长度的亚烯基和/或亚炔基可被称为低级亚烯基和/或亚炔基。在本文中应了解，较短的亚烷基、亚烯基和/或亚炔基可向化合物添加较少亲脂性且因此将具有不同的药物动力学行为。在本文所述的发明的实施方案中，应理解在每种情况下，亚烷基、亚烯基和亚炔基的叙述是指如本文定义的亚烷基、亚烯基和亚炔基以及任选的低级亚烷基、亚烯基和亚炔基。说明性烷基是但不限于亚甲基、亚乙基、亚正丙基、亚异丙基、亚正丁基、亚异丁基、亚仲丁基、亚戊基、1,2-亚戊基、1,3-亚戊基、亚己基、亚庚基、亚辛基等。

[0191] 如本文所用，术语“环烷基”包含任选支化的碳原子链，其中所述链的至少一部分为环状。应理解，环烷基烷基是环烷基的子集。应理解，环烷基可以是多元环。说明性环烷基包括但不限于，环丙基、环戊基、环己基、2-甲基环丙基、环戊基乙-2-基、金刚烷基等。如本文所用，术语“环烯基”包含任选支化的碳原子链，并且包含至少一个双键，其中所述链的至少一部分为环状。应理解，一个或多个双键可处于环烯基的环部分和/或环烯基的非环部分中。应理解，环烯基烷基和环烷基烯基各自是环烯基的子集。应理解，环烷基可以是多元环。说明性环烯基包括但不限于，环戊烯基、环己基乙烯-2-基、环庚烯基丙烯基等。应进一步理解，链形成环烷基和/或环烯基有利地具有有限的长度，包括C_3-C_{24}、C_3-C_{12}、C_3-C_8、C_3-C_6以及C_5-C_6。在本文中应了解，分别形成环烷基和/或环烯基的较短烷基和/或烯基链可向化合物添加较小亲脂性且因此将具有不同药物动力学行为。

[0192] 如本文所用，术语“杂烷基”包含含有碳和至少一个杂原子二者且任选支化的原子链。说明性杂原子包括氮、氧和硫。在某些变化形式中，说明性杂原子还包括磷和硒。如本文所用，术语“环杂烷基”(包括杂环基和杂环)包含含有碳和至少一个杂原子二者(如杂烷基)且任选支化的原子链，其中所述链的至少一部分是环状的。说明性杂原子包括氮、氧和硫。在某些变化形式中，说明性杂原子还包括磷和硒。说明性环杂烷基包括但不限于，四氢呋喃基、吡咯烷基、四氢吡喃基、哌啶基、吗啉基、哌嗪基、高哌嗪基、奎宁环基等。

[0193] 如本文所用，术语“芳基”包含单环和多环芳族碳环基团，其各自可被任选取代。本文所述的说明性芳族碳环基团包括但不限于苯基、萘基等。如本文所用，术语“杂芳基”包含芳族杂环基团，其各自可被任选取代。说明性芳族杂环基团包括但不限于，吡啶基、嘧啶基、吡嗪基、三嗪基、四嗪基、喹啉基、喹唑啉基、喹喔啉基、噻吩基、吡唑基、咪唑基、噁唑基、噻唑基、异噁唑基、异噻唑基、噁二唑基、噻二唑基、三唑基、苯并咪唑基、苯并噁唑基、苯并噻唑基、苯并异噁唑基、苯并异噻唑基等。

[0194] 如本文所用，术语“氨基”包括基团NH_2、烷基氨基和二烷基氨基，其中二烷基氨基中的两个烷基可相同或不同，即烷基烷基氨基。说明性地，氨基包括甲基氨基、乙基氨基、二甲基氨基、甲基乙基氨基等。此外，应理解，当氨基修饰另一术语或由另一术语修饰时，如氨基烷基或酰基氨基，术语氨基的以上变化形式包括在其中。说明性地，氨基烷基包括H_2N-烷基、甲基氨基烷基、乙基氨基烷基、二甲基氨基烷基、甲基乙基氨基烷基等。说明性地，酰基氨基包括酰基甲基氨基、酰基乙基氨基等。

[0195] 如本文所用，术语“氨基及其衍生物”包括如本文所述的氨基，以及烷基氨基、烯基氨基、炔基氨基、杂烷基氨基、杂烯基氨基、杂炔基氨基、环烷基氨基、环烯基氨基、环杂烷基氨基、环杂烯基氨基、芳基氨基、芳基烷基氨基、芳基烯基氨基、芳基炔基氨基、杂芳基氨基、杂芳基烷基氨基、杂芳基烯基氨基、杂芳基炔基氨基、酰基氨基等，其各自被任选取代。术语“氨基衍生物”还包括脲、氨基甲酸酯等。

[0196] 如本文所用，术语“羟基及其衍生物”包括OH以及烷基氧基、烯基氧基、炔基氧基、杂烷基氧基、杂烯基氧基、杂炔基氧基、环烷基氧基、环烯基氧基、环杂烷基氧基、环杂烯基氧基、芳基氧基、芳基烷基氧基、芳基烯基氧基、芳基炔基氧基、杂芳基氧基、杂芳基烷基氧基、杂芳基烯基氧基、杂芳基炔基氧基、酰基氧基等，其各自被任选取代。术语“羟基衍生物”还包括氨基甲酸酯等。

[0197] 如本文所用，术语“硫基及其衍生物”包括SH以及烷基硫基、烯基硫基、炔基硫基、杂烷基硫基、杂烯基硫基、杂炔基硫基、环烷基硫基、环烯基硫基、环杂烷基硫基、环杂烯基硫基、芳基硫基、芳基烷基硫基、芳基烯基硫基、芳基炔基硫基、杂芳基硫基、杂芳基烷基硫基、杂芳基烯基硫基、杂芳基炔基硫基、酰基硫基等，其各自被任选取代。术语“硫基衍生物”还包括硫代氨基甲酸酯等。

[0198] 如本文所用，术语“酰基”包括甲酰基以及烷基羰基、烯基羰基、炔基羰基、杂烷基羰基、杂烯基羰基、杂炔基羰基、环烷基羰基、环烯基羰基、环杂烷基羰基、环杂烯基羰基、芳基羰基、芳基烷基羰基、芳基烯基羰基、芳基炔基羰基、杂芳基羰基、杂芳基烷基羰基、杂芳基烯基羰基、杂芳基炔基羰基、酰基羰基等，其各自被任选取代。

[0199] 如本文所用，术语“羰基及其衍生物”包括基团C(O)、C(S)、C(NH)以及其取代的氨基衍生物。

[0200] 如本文所用，术语“羧酸及其衍生物”包括基团CO_2H及其盐，以及其酯和酰胺，以及CN。

[0201] 如本文所用，术语“亚磺酸或其衍生物”包括SO_2H及其盐，以及其酯和酰胺。

[0202] 如本文所用，术语“磺酸或其衍生物”包括SO_3H及其盐，以及其酯和酰胺。

[0203] 如本文所用，术语“磺酰基”包括烷基磺酰基、烯基磺酰基、炔基磺酰基、杂烷基磺酰基、杂烯基磺酰基、杂炔基磺酰基、环烷基磺酰基、环烯基磺酰基、环杂烷基磺酰基、环杂烯基磺酰基、芳基磺酰基、芳基烷基磺酰基、芳基烯基磺酰基、芳基炔基磺酰基、杂芳基磺酰基、杂芳基烷基磺酰基、杂芳基烯基磺酰基、杂芳基炔基磺酰基、酰基磺酰基等，其各自被任选取代。

[0204] 如本文所用，术语“次膦酸或其衍生物”包括P(R)O_2H及其盐，以及其酯和酰胺，其中R是烷基、烯基、炔基、环烷基、环烯基、杂烷基、杂烯基、环杂烷基、环杂烯基、芳基、杂芳基、芳基烷基或杂芳基烷基，其各自被任选取代。

[0205] 如本文所用，术语“膦酸或其衍生物”包括PO_3H_2及其盐，以及其酯和酰胺。

[0206] 如本文所用，术语“羟基氨基及其衍生物”包括NHOH以及烷基氧基NH、烯基氧基NH、炔基氧基NH、杂烷基氧基NH、杂烯基氧基NH、杂炔基氧基NH、环烷基氧基NH、环烯基氧基NH、环杂烷基氧基NH、环杂烯基氧基NH、芳基氧基NH、芳基烷基氧基NH、芳基烯基氧基NH、芳基炔基氧基NH、杂芳基氧基NH、杂芳基烷基氧基NH、杂芳基烯基氧基NH、杂芳基炔基氧基NH、酰基氧基等，其各自被任选取代。

[0207] 如本文所用，术语“肼基及其衍生物”包括烷基NHNH、烯基NHNH、炔基NHNH、杂烷基NHNH、杂烯基NHNH、杂炔基NHNH、环烷基NHNH、环烯基NHNH、环杂烷基NHNH、环杂烯基NHNH、芳基NHNH、芳基烷基NHNH、芳基烯基NHNH、芳基炔基NHNH、杂芳基NHNH、杂芳基烷基NHNH、杂芳基烯基NHNH、杂芳基炔基NHNH、酰基NHNH等，其各自被任选取代。

[0208] 如本文所用的术语“任选被取代”包括在任选被取代的基团上用其它官能团置换氢原子。此类其他官能团说明性地包括但不限于，氨基、羟基、卤素、巯基、烷基、卤代烷基、杂烷基、芳基、芳烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基、硝基、磺酸及其衍生物、羧酸及其衍生物等。说明性地，任何氨基、羟基、巯基、烷基、卤代烷基、杂烷基、芳基、芳烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基和/或磺酸是被任选取代的。

[0209] 如本文所用，术语“任选被取代的芳基”和“任选被取代的杂芳基”包括在任选被取代的芳基或杂芳基上用其它官能团置换氢原子。此类其他官能团(在本文中还被称为芳基取代基或杂芳基取代基)说明性地包括但不限于，氨基、羟基、卤代、硫基、烷基、卤代烷基、杂烷基、芳基、芳烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基、硝基、磺酸及其衍生物、羧酸及其衍生物等。说明性地，氨基、羟基、硫基、烷基、卤代烷基、杂烷基、芳基、芳基烷基、芳基杂烷基、杂芳基、杂芳基烷基、杂芳基杂烷基和/或磺酸中的任一者被任选取代。

[0210] 说明性取代基包括但不限于基团$-(CH_2)_xZ^X$，其中x是0-6的整数，并且Z^X选自卤素、羟基、烷酰氧基(包括C_1-C_6烷酰氧基)、任选取代的芳酰氧基、烷基(包括C_1-C_6烷基)、烷氧基(包括C_1-C_6烷氧基)、环烷基(包括C_3-C_8环烷基)、环烷氧基(包括C_3-C_8环烷氧基)、烯基(包括C_2-C_6烯基)、炔基(包括C_2-C_6炔基)、卤代烷基(包括C_1-C_6卤代烷基)、卤代烷氧基(包括C_1-C_6卤代烷氧基)、卤代环烷基(包括C_3-C_8卤代环烷基)、卤代环烷氧基(包括C_3-C_8卤代环烷氧基)、氨基、C_1-C_6烷基氨基、(C_1-C_6烷基)(C_1-C_6烷基)氨基、烷基羰基氨基、N-(C_1-C_6烷基)烷基羰基氨基、氨基烷基、C_1-C_6烷基氨基烷基、(C_1-C_6烷基)(C_1-C_6烷基)氨基烷基、烷基羰基氨基烷基、N-(C_1-C_6烷基)烷基羰基氨基烷基、氰基和硝基；或Z^X选自$-CO_2R^4$和$-CONR^5R^6$，其中R^4、R^5和R^6在每次出现时各自独立地选自氢、C_1-C_6烷基、芳基-C_1-C_6烷基和杂芳基-C_1-C_6烷基。

[0211] 如本文所用的术语“保护基团”是指可逆地键合至官能团并且用于阻断或部分阻断所述官能团对一组预定条件(如反应条件)的反应性的任何基团。说明性地，氮保护基团可逆地键合至胺以阻断或部分阻断胺在一组预定条件下的反应性。示例性氮保护基团包括但不限于氨基甲酸酯，如t-Boc、Fmoc等。

[0212] 如本文所用，术语“离去基团”是指在其所连接的原子上生成亲电子位点以使得亲核试剂可添加至所述原子上的亲电子位点的反应性官能团。说明性离去基团包括但不限于卤素、任选取代的苯酚、酰氧基、磺酰氧基等。应理解，此类离去基团可处于烷基、酰基等上。此类离去基团在本文中也可称为活化基团，如当离去基团存在于酰基上时。此外，常规肽、酰胺以及酯偶联剂(如但不限于，PyBop、BOP-C1、BOP、五氟苯酚、异丁基氯甲酸酯等)形成在

羰基上包含如本文定义的离去基团的不同中间体。

[0213] 应理解，在本文所公开的每种情况下，任何变量的整数范围的叙述描述了所叙述范围、所述范围内的每个单个成员、以及所述变量的每个可能的子范围。例如，n是0至8的整数的叙述描述了所述范围，单个以及可选择的值是0、1、2、3、4、5、6、7以及8，如n是0或n是1或n是2等。此外，n是0至8的整数的叙述也描述了每一个子范围，所述子范围各自在另一个实施方案的基础上可以是如n是1至8、1至7、1至6、2至8、2至7、1至3、2至4等的整数。

[0214] 如本文所用，当提及化学反应时，术语“处理”、“接触”或“反应”通常意味着在允许发生化学转化或化学反应的适当条件下添加或混合两种或更多种试剂，和/或产生所指示和/或所需的产物。应理解，产生所指示和/或所需产物的反应可能不一定直接来自最初加入的两种试剂的组合。换句话说，可能存在在最终导致所指示和/或所需产物的形成的混合物中产生的一种或多种中间体。

[0215] 如本文所用，术语“组合物”通常是指含有指定量的指定成分的任何产物以及由指定量的指定成分的组合直接或间接得到的任何产物。应理解，本文所述的组合物可由本文所述的分离的化合物或者由本文所述的化合物的盐、溶液、水合物、溶剂化物以及其他形式制备。还应理解，所述组合物可由本文所述的化合物的各种非晶、非非晶、部分结晶、结晶和/或其他形态学形式制备。还应理解，所述组合物可由本文所述的化合物的各种水合物和/或溶剂化物制备。因此，叙述本文所述的化合物的此类药物组合物应理解为包括本文所述的化合物的各种形态学形式和/或溶剂化物或水合物形式的每一种或任何组合。此外，应理解，所述组合物可由本文所述的化合物的各种共晶制备。

[0216] 说明性地，组合物可包含一种或多种载体、稀释剂和/或赋形剂。本文所述的化合物或含有它们的组合物可以治疗有效量以适于本文所述的方法的任何常规剂型加以配制。本文所述的化合物或含有它们的组合物(包括此类制剂)可利用已知程序，通过各种各样用于本文所述的方法的常规途径，且以各种各样的剂型施用(总体上参见Remington:The Science and Practice of Pharmacy,(第21版,2005))。

[0217] 如本文所用的术语“治疗有效量”是指研究员、兽医、医师或其他临床医生寻找的在组织系统、动物或人中引发生物学或医学反应的活性化合物或药物试剂的量，所述反应包括减轻所治疗的疾病或病症的症状。一方面，治疗有效量是可以可适用于任何医学治疗的合理益处/风险比下治疗或减轻疾病或疾病的症状的量。然而，应理解，本文所述的化合物和组合物的总每日用量可由主治医师在合理的医学判断范围内决定。用于任何特定患者的特定治疗有效剂量水平将取决于多种因素，包括所治疗的病症和病症的严重程度；所用特定化合物的活性；所用特定组合物；患者的年龄、体重、总体健康状况、性别和膳食；所用特定化合物的施用时间、施用途径和排泄速率；治疗的持续时间；与所用特定化合物组合或同时使用的药物；以及为研究者、兽医、医生或具有一般技能的其他临床医师所熟知的类似因素。

[0218] 也应了解的是关于单药疗法或组合疗法的治疗有效量都是关于可能在施用一种或多种本文所述的化合物期间存在的任何毒性或其它不合需要的副作用加以有利地选择。此外，应了解的是本文所述的共同疗法可允许施用较低剂量的示出所述毒性或其它不合需要的副作用的化合物，其中那些较低剂量低于毒性阈值或治疗窗低于将另外在不存在共同疗法下施用的治疗窗。

[0219] 除本文所述的说明性剂量和给药方案之外，应理解，本文所述的化合物的任一种或混合物的有效量可易于由照护诊断医师或医师通过使用已知技术和/或通过观察在类似情况下获得的结果来确定。在确定有效量或剂量时，照护诊断医师或医师要考虑许多因素，包括但不限于哺乳动物的种类(包括人)、它的身材、年龄和总体健康状况、涉及的特定疾病或病症、疾病或病症的程度或牵连或严重性、个别患者的反应、施用的特定化合物、施用模式、施用的制剂的生物可用度特征、选择的剂量方案、相伴药物的使用、和其他相关事项。

[0220] 所要求的组合的各化合物的剂量取决于若干因素，包括：施用方法、待治疗的病状、病状的严重程度、病状是待治疗抑或预防、以及待治疗的人士的年龄、重量和健康状况。另外，关于特定患者的药物基因组学(基因型对治疗剂的药物动力学、药效学或功效分布的影响)信息可影响所用剂量。

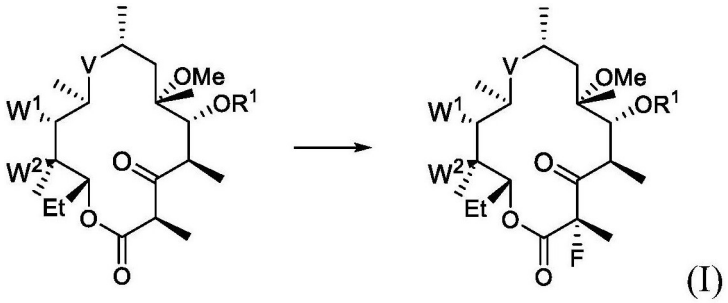
[0221] 如本文所用的术语“施用”包括将本文所述的化合物和组合物引入患者中的所有方式，包括但不限于经口(po)、静脉内(iv)、肌肉内(im)、皮下(sc)、经皮、吸入、经颊、眼部、舌下、经阴道、经直肠等。本文所述的化合物和组合物可以含有常规无毒的药学上可接受的载体、佐剂以及媒介物的单位剂型和/或制剂施用。

[0222] 用于口服施用的说明性剂型包括片剂、胶囊、酏剂、糖浆等。

[0223] 用于胃肠外施用的说明性途径包括静脉内、动脉内、腹膜内、硬膜外、尿道内、胸骨内、肌肉内和皮下途径以及任何其他本领域认可的胃肠外施用途径。

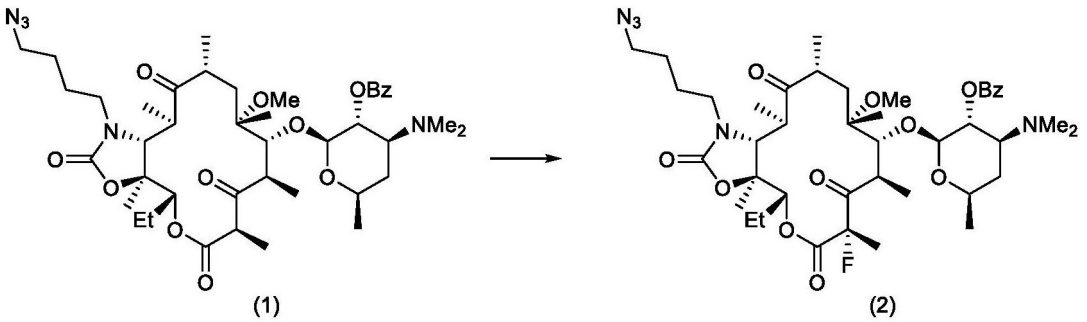
[0224] 以下实施例进一步说明本发明的特定实施方案；然而，以下说明性实施例无论如何都不应解释为限制本发明。

实施例

[0225] 

(I)

[0226] 实施例.用于制备氟酮内酯的一般程序。将起始材料的溶液冷却至约-15℃至约-40℃范围内的温度。添加本文所述的胺碱(2-3当量)。添加氟化试剂(1-2当量)或氟化剂的溶液。在可接受或完全转化后，用水淬灭反应。将式(I)化合物与有机层分离，并且任选地从醇/水混合物中沉淀出来。

[0227] 

(1) (2)

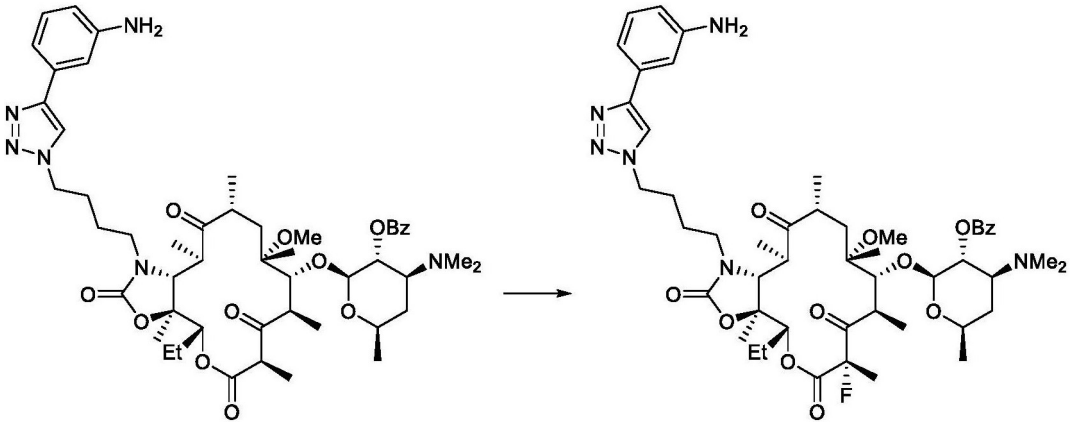
[0228] 实施例.(11-N-(4-叠氮基-丁基)-5-(2'-苯甲酰基-脱氧糖胺基)-3-氧代-2-氟-6-O-甲基-红霉内酯A,11,12-环状氨基甲酸酯)(CEM-276,化合物(2))。将CEM-275(化合物(1),1.0当量)添加至DMF、乙酸异丙酯或DMF/乙酸异丙酯的混合物(2-10体积),并在环境温度下搅拌以得到澄清溶液。应理解,前述浓度不是关键的。将溶液在搅拌下冷却至-20℃至-30℃并且维持在-20℃至-30℃下。添加DBU(2-3当量),然后添加NFSI(1.1-1.5当量)于DMF、乙酸异丙酯或DMF/乙酸异丙酯混合物(1-3体积)中的溶液。搅拌混合物直到如通过TLC、HPLC等观察到可接受或完全转化。任选地分阶段添加乙酸异丙酯(2-7体积)和冷水(2-10体积)。除去有机层,并且用乙酸异丙酯萃取水层。用水洗涤合并的有机层。在环境温度下将甲醛(0.1-0.3当量)和甲酸(0.5-1.0当量)添加至溶液,然后将混合物加热至45℃-50℃,直到如通过TLC、HPLC等观察到可接受或完全转化。将溶液冷却至环境温度,添加水,并且用氨水将pH调节至7-8。除去水层,并且用水洗涤有机层。在真空下浓缩有机层。添加异丙醇(IPA),并且加热混合物。添加水,并且将所得浆液冷却至环境温度并过滤。将所得固体用水洗涤并在真空下干燥以得到CEM-276。

[0229] 实施例.本文描述的一般方法以50g(2次独立运行)的规模进行,然后进行原位甲基化以提供具有98%HPLC纯度的90%-92%分离产率的(2),其中(1)在约0.05%-0.1%的范围内。(1-DM)和(2-DM)两者都未检测到。

[0230] 实施例.本文描述的一般方法以100g(3次独立运行)的商业规模进行,然后进行原位甲基化以提供具有98%-99%HPLC纯度的89%-90%分离产率的(2),其中(1)在约0.07%-0.18%的范围内。(1-DM)和(2-DM)两者都未检测到。

[0231] 实施例.本文描述的一般方法以200g(2次独立运行)的商业规模进行,然后进行原位甲基化以提供具有98%-99%HPLC纯度的一致88%分离产率的(2),其中(1)一致地在0.07%下,并且(1-DM)和(2-DM)一致地不可检测到。

[0232] 实施例.本文描述的一般方法以3kg的商业规模进行,然后进行原位甲基化以提供具有98.4%HPLC纯度的93%分离产率的(2)。

[0233] 

[0234] 实施例.11-N-(3-氨基-苯基-1-基-[1,2,3]-三唑-1-基]丁基)-5-(2'-苯甲酰基脱氧糖胺基)-3-氧代-2-氟-红霉内酯A,11,12-环状氨基甲酸酯。11-N-(3-氨基-苯基-1-基-[1,2,3]-三唑-1-基]丁基)-5-(2'-苯甲酰基脱氧糖胺基)-3-氧代-红霉内酯A,11,12-环状氨基甲酸酯根据WO2009/055557由(1)和3-乙炔基苯胺制备。进行本文所述的一般方法以在原位甲基化之前提供97%转化率、90%分离产率的标题化合物,仅0.36%剩余的未氟化起始材料和2.3%N-去甲基。

[0235] 实施例.11-N-(3-氨基-苯基-1-基-[1,2,3]-三唑-1-基]丁基)-5-(2'-苯甲酰基脱氧糖胺基)-3-氧代-2-氟-红霉内酯A,11,12-环状氨基甲酸酯。如WO 2009/055557中所描述使11-N-(4-叠氮基丁基)-5-(2'-苯甲酰基脱氧糖胺基)-3-氧代-2-氟-6-O-甲基红霉内酯A,11,12-环状氨基甲酸酯、3-乙炔基苯胺、碘化铜和二异丙基乙胺在乙腈中反应以制备11-N-(3-氨基-苯基-1-基-[1,2,3]-三唑-1-基]丁基)-5-(2'苯甲酰基脱氧糖胺基)-3-氧代-2-氟-红霉内酯A,11,12-环状氨基甲酸酯。

[0236] 实施例.索利霉素如WO 2009/055557中所描述将11-N-(3-氨基-苯基-1-基-[1,2,3]-三唑-1-基]丁基)-5-(2'苯甲酰基脱氧糖胺基)-3-氧代-2-氟-红霉内酯A,11,12-环状氨基甲酸酯溶解于甲醇中并在回流下加热以制备索利霉素。

[0237] 比较实施例.用于由(1)制备(2)的方法在WO 2009/055557中公开。所述方法以10g(2次独立允许)的规模如所描述进行以提供具有89％HPLC纯度并混杂有9.9％未反应的起始材料(1)的65％产率的(2)。

[0238] 实施例.前述方法通过使用NFSI和叔丁醇锂作为碱进行修改。向(2)的转化不完全,具有9％-11％剩余的(1)。

[0239] 比较实施例.WO 2009/055557中公开的方法通过使用五氧化钾作为碱进行修改。向(2)的转化非常低或未观察到。此外,形成一种或多种未知副产物。

[0240] 比较实施例.WO 2009/055557中公开的方法通过使用叔丁醇锂作为碱进行修改。向(2)的转化非常低,具有9％-11％未反应的(1)剩余。此外,还形成了未知的副产物。

[0241] 比较实施例.WO 2009/055557中公开的方法通过使用NaH作为碱进行修改。向(2)的转化非常低,具有显著分解为未知副产物。

[0242] 比较实施例.WO 2009/055557中公开的方法通过使用Selectfluor作为氟化剂进行修改。向(2)的转化是可比较的,具有29％未反应的(1)剩余。

[0243] 比较实施例.WO 2009/055557中公开的方法通过使用NaHMDS作为碱进行修改。向(2)的转化非常低,具有显著分解为未知副产物。

[0244] 比较实施例.WO 2009/055557中公开的方法通过使用K_2CO_3作为碱进行修改。未观察到向(2)的转化。相反,观察到显著分解为一种或多种未知的副产物。

[0245] 比较实施例.WO 2009/055557中公开的方法通过在具有溴化四正丁基铵(TBAB)相转移催化剂的甲苯/水中使用K_2CO_3作为碱进行修改。未观察到向(2)的转化。此外,形成一种或多种未知副产物。

[0246] 比较实施例.WO 2009/055557中公开的方法通过使用NFSI或Selectfluor和路易斯酸或过渡金属催化剂(如$MgClO_4$、$Ti(iOPR)_4$、$Pd(OAc)_2$等)代替碱进行修改。未观察到向(2)的转化。此外,形成一种或多种未知副产物。

[0247] 比较实施例.WO 2009/055557中公开的方法通过使用DMF作为溶剂进行修改。向(2)的转化较低,具有24％未反应的(1)剩余。

[0248] 比较实施例.WO 2009/055557中公开的方法通过使用1:1THF/DCM作为溶剂进行修改。向(2)的转化较低,具有12％-15％未反应的(1)剩余。此外,还形成了未知的副产物。

[0249] 本文引用的每个公布均以引用的方式并入本文。