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(54) **4"-SUBSTITUTED-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATIVES**

4"-SUBSTITUTIERTE-9-DEOXO-9A-AZA-9A-HOMOERYTHROMYCIN A DERIVATE

DERIVES DE HOMO-ERYTHROMYCINE -9-DEOXO-9A-AZA-9AA SUBSTITUTION EN POSITION 4

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(56) References cited:
EP-A- 0 508 699
EP-A- 0 549 040
US-A- 4 512 982
US-A- 5 441 939

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Description

Background of the Invention

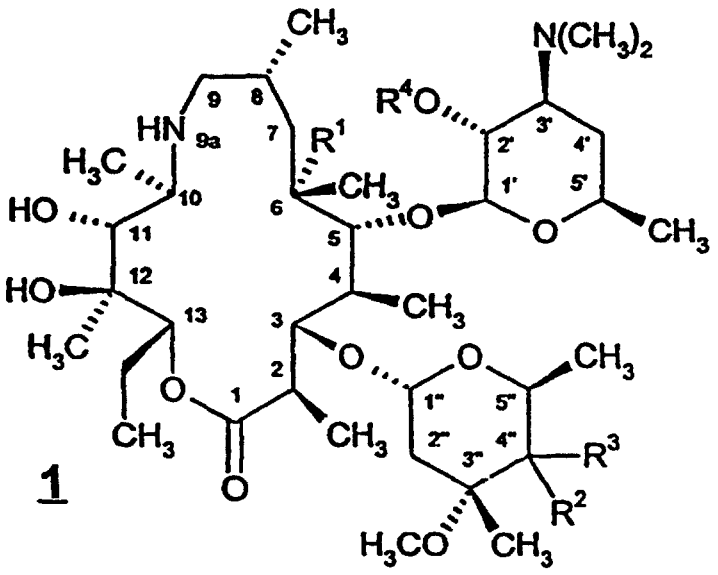
[0001] This invention relates to C-4" substituted derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A that are useful as antibacterial and antiprotozoa agents in mammals. induding man, as well as in fish and birds. This invention also relates to pharmaceutical compositions containing the compounds and to methods of treating bacterial infections and protozoa infections in mammals, fish and birds by administering the novel compounds to mammals, fish and birds requiring such treatment

[0002] Macrolide antibiotics are known to be useful in the treatment of a broad sprectrum of bacterial infections and protozoa infections in mammals, fish and birds. Such antibiotics include various derivatives of erythromycin A such as azithromycin which is commercially available and is referred to in United States patents 4.474.768 and 4,517,359,

[0003] Like azithromycin and other macrolide antibiotics, the macrolide compounds of the present invention possess potent activity against various bacterial infections and protozoa infections as described below.

Summary of the Invention

[0004] The present invention relates to compounds of the formula



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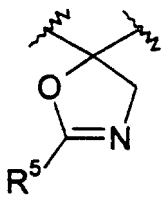
and to pharmaceutically acceptable salts thereof, wherein:

R^1 is H, hydroxy or methoxy:

R^2 is hydroxy:

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, $-CH_2S(O)_nR^8$ wherein n is an integer ranging from 0 to 2, $-CH_2OR^8$, $-CH_2N(OR^9)R^8$, $-CH_2NR^8R^{15}$, $-(CH_2)_m(C_6$-C_{10} aryl), or $(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^3 groups are optionally substituted by 1 to 3 R^{16} groups; or R^2 and R^3 are taken together to form an oxazolyl ring as shown below



R^4 is H, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^9R^{10}$ or a hydroxy protecting group;
R^5 is $-SR^8$, $-(CH_2)_nC(O)R^8$ wherein n is 0 or 1, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $(CH_2)_m(C_6$-C_{10} aryl), or $(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^5 groups are optionally substituted by 1 to 3 R^{16} groups;
each R^6 and R^7 is independently H, hydroxy, C_1-C_6 alkoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;
each R^8 is independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ wherein q and r are each independently an integer ranging from 0 to 3 except q and r are not both 0, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^8 groups, except H, are optionally substituted by 1 to 3 R^{16} groups;
or where R^8 is as $-CH_2NR^8R^{15}$, R^{15} and R^8 may be taken together to form a 4-10 membered monocyclic or polycydic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $-N(R^8)$-, in addition to the nitrogen to which R^{15} and R^8 are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;
each R^9 and R^{10} is independently H or C_1-C_6 alkyl;
each R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_m(C_6$-C_{10} aryl), and $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^{11}, R^{12}, R^{13} and R^{14} groups, except H, are optionally substituted by 1 to 3 R^{16} groups;
or R^{11} and R^{13} are taken together to form $-(CH_2)_p$- wherein p is an integer ranging from 0 to 3 such that a 4-7 membered saturated ring is formed that optionally includes 1 or 2 carbon-carbon double or triple bonds;
or R^{13} and R^{14} are taken together to form a 4-10 membered monocyclic or polycydic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $-N(R^8)$-, in addition to the nitrogen to which R^{13} and R^{14} are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;
R^{15} is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl, wherein the foregoing R^{15} groups are optionally substituted by 1 to 3 substituents independently selected from halo and $-OR^9$;
each R^{16} is independently selected from halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-OC(O)OR^{17}$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-(CH_2)_m(C_6$-C_{10} aryl), and $(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein said aryl and heteroaryl subsituents are optionally substituted by 1 or 2 substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-OC(O)OR^{17}$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;
each R^{17} is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_m(C_6$-C_{10} aryl), and $(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

with the proviso that R^8 is not H where R^3 is $-CH_2S(O)_nR^8$.

[0005] Preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$ or $-CH_2SR^8$, and R^4 is H.

[0006] Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^8R^{15}$, R^4 is H, R^{15} and R^8 are each selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^{15} and R^8 groups, except H, are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy. Speck preferred compounds having the foregoing general structure include those wherein R^{15} is either H or is selected from the following groups from which R^8 is also independently selected: methyl, ethyl, allyl, n-butyl, isobutyl, 2-methoxyethyl, cyclopentyl, 3-methoxypropyl, 3-ethoxypropyl, n-propyl, isopropyl, 2-hydroxyethyl, cyclopropyl, 2,2,2-trifluoroethyl, 2-propynyl, *sec*-butyl, *tert*-butyl, and n-hexyl.

[0007] Other preferred compounds of formula 1 indude those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NHR^8$, R^4 is H, and R^8 is $-(CH_2)_m(C_6$-C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^8 is phenyl or benzyl.

[0008] Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a saturated ring. Specific preferred compounds having the foregoing general structure include those wherein R^6 and R^8 are taken together to form a piperidino, trimethyleneimino, or morpholino ring.

[0009] Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$, R^4 is H, and R^{15} and R^8 are taken together to form a heteroaryl ring optionally substituted by 1 or 2 C_1-C_6 alkyl groups. Specific preferred compounds having the foregoing general structure include those wherein R^{15} and R^8 are taken together to form a pyrrolidino, triazolyl, or imidazolyl ring wherein said heteroaryl groups are optionally substituted by 1 or 2 methyl

groups.

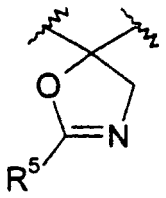
[0010] Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2SR^8$, R^4 is H, and R^8 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^8 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^8 is methyl, ethyl, or 2-hydroxyethyl.

[0011] Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^3 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C(O)R^{17}$, $-NF^6R^7$, halo, cyano, azido, 5-10 membered heteroaryl, and C_1-C_6 alkoxy. Specific preferred compounds having the foregoing general structure include those wherein R^3 is methyl, allyl, vinyl, ethynyl, 1-methyl-1-propenyl, 3-methoxy-1-propynyl, 3-dimethylamino-1-propynyl, 2-pyridylethynyl, 1-propynyl, 3-hydroxy-1-propynyl, 3-hydroxy-1-propenyl, 3-hydroxypropyl, 3-methoxy-1-propenyl, 3-methoxypropyl, 1-propynyl, n-butyl, ethyl, propyl, 2-hydroxyethyl, formylmethyl, 6-cyano-1-pentynyl, 3-dimethylamino-1-propenyl, or 3-dimethylaminopropyl.

[0012] Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is $-(CH_2)_m$(5-10 membered heteroaryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is 2-thienyl, 2-pyridyl, 1-methyl-2-imidazolyl, 2-furyl, or 1-methyl-2-pyrrolyl.

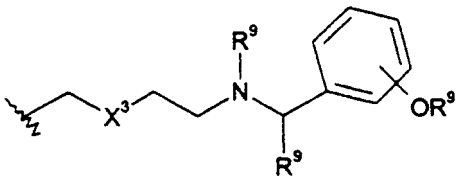
[0013] Other preferred compounds of formula 1 include those wherein R^1 is hydroxy, R^2 is hydroxy, R^4 is H, and R^3 is $-(CH_2)_m(C_6$-C_{10} aryl) wherein m is an integer ranging from 0 to 4. Specific preferred compounds having the foregoing general structure include those wherein R^3 is phenyl.

[0014] Specific compounds of formula 1 include those wherein R^2 and R^3 are taken together to form an oxazolyl ring as shown below



wherein R^5 is as defined above.

[0015] Specific compounds of formula 1 include those wherein R^3 is selected from the following:



wherein X^3 is O, S or $-N(R^{15})-$, and wherein the $-OR^9$ group may be attached at any available carbon on the phenyl group.

[0016] The invention also relates to a pharmaceutical composition for the treatment of a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises a therapeutically effective amount of a compound of formula 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

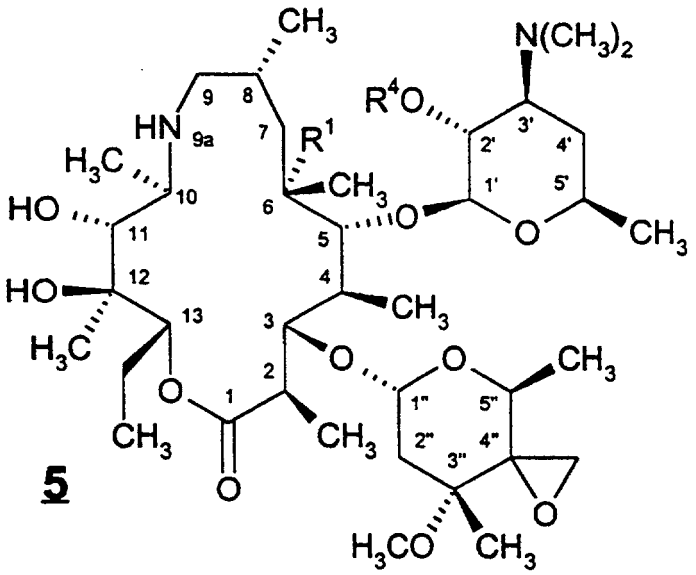
[0017] The invention also relates to a method of treating a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of a compound of formula 1 or a pharmaceutically acceptable salt thereof.

[0018] The term "treatment", as used herein, unless otherwise indicated, includes the treatment or prevention of a bacterial infection or protozoa infection as provided in the method of the present invention.

[0019] As used herein, unless otherwise indicated, the terms "bacterial infection(s)" and "protozoa infection(s)" include bacterial infections and protozoa infections that occur in mammals, fish and birds as well as disorders related to bacterial infections and protozoa infections that may be treated or prevented by administering antibiotics such as the compounds of the present invention. Such bacterial infections and protozoa infections, and disorders related to such infections, include the following: pneumonia, otitis media, sinusitis, bronchitis, tonsillitis, and mastoiditis related to infection by

Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, *Staphylococcus aureus,* or *Peptostreptococcus* spp.; pharynigitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes,* Groups C and G streptococci, *Clostridium diptheriae,* or *Actinobacillus haemolyticum;* respiratory tract infections related to infection by *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae, or Chlamydia pneumoniae;* uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by *Staphylococcus aureus,* coagulase-positive staphylococci (i.e., *S. epidermidis, S. hemolyticus,* etc.), *Streptococcus pyogenes , Streptococcus agalactiae,* Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum, Clostridium* spp., or *Bartonella henselae*; uncomplicated acute urinary tract infections related to infection by *Staphylococcus saprophyticus* or *Enterococcus* spp.; urethritis and cervicitis; and sexually transmitted diseases related to infection by *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum,* or *Neiserria gonorrheae;* toxin diseases related to infection by *S. aureus* (food poisoning and Toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori;* systemic febrile syndromes related to infection by *Borrelia recurrentis;* Lyme disease related to infection by *Borrelia burgdorferi;* conjunctivitis, keratitis, and dacrocystitis related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae,* or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium,* or *Mycobacterium intracellulare;* gastroenteritis related to infection by *Campylobacter jejuni;* intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis*; gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae.* Bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in animals include the following: bovine respiratory disease related to infection by *P. haem., P. multocida, Mycoplasma bovis,* or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella* spp., *Corynebacterium,* or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro., P. multocida,* or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli, Lawsonia intracellularis, Salmonella,* or *Serpulina hyodyisinteriae;* cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli;* cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus*; cow pink-eye related to infection by *Moraxella bovis;* cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by *E. coli;* skin and soft tissue infections in dogs and cats related to infection by *Staph. epidermidis, Staph. intermedius, coagulase neg. Staph.* or *P. multocida;* and dental or mouth infections in dogs and cats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium, Peptostreptococcus, Porphyromonas,* or *Prevotella.* Other bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

[0020] The present invention also relates to a method of preparing the above compound of formula 1, or a pharmaceutically acceptable salt thereof, wherein R^3 is $-CH_2S(O)_nR^8$, $-CH_2OR^8$ or $-CH_2NR^8R^{15}$, wherein n, R^{15} and R^8 are as defined above with the proviso that R^8 is not H where R^3 is $-CH_2S(O)_nR^8$, which comprises treating a compound of the formula



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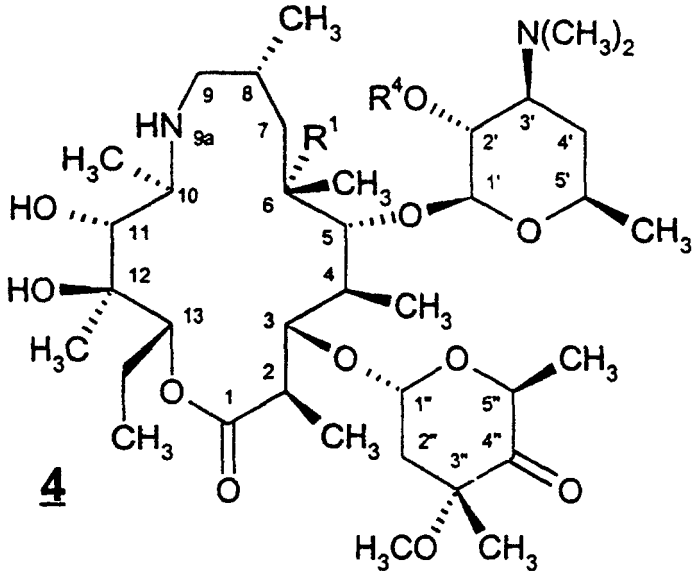
wherein R^1 and R^4 are as defined above, with a compound of the formula HSR^8, HOR^8 or $HNR^{15}R^8$, wherein n, R^{15} and R^8 are as defined above, optionally followed by oxidation of the $-SR^8$ substituent to form $-S(O)R^8$ or $-S(O)_2R^8$.

[0021] In a further aspect of the above process of preparing the compound of formula 1, or a pharmaceutically acceptable salt thereof, the above compound of formula 5 is prepared by treating a compound of the formula



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wherein R^1 and R^4 are as defined above, with $(CH_3)_3S(O)_nX^2$, wherein n is 0 or 1 and X^2 is halo, $-BF_4$ or $-PF_6$, preferably iodo or $-BF_4$, in the presence of a base such as as potassium tert-butoxide, sodium tert-butoxide, sodium ethoxide, sodium hydride, 1,1,3,3-tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicylo[4.3.0] non-5-ene, potassium hexamethyldisilazide (KHMDS), potassium ethoxide, or sodium methoxide, preferably KHMDS or a sodium-containing base such as sodium hydride.

[0022] The present invention also relates to the above compounds of formulas 4 and 5 which, as indicated above, are useful in the preparation of the above compounds of formula 1 and pharmaceutically acceptable salts thereof.

[0023] The term "hydroxy protecting group", as used herein, unless otherwise indicated, includes acetyl, benzyloxycarbonyl, and various hydroxy protecting groups familiar to those skilled in the art include the groups referred to in T. W. Greene, P. G. M. Wuts, "Protective Groups In Organic Synthesis," (J. Wiley & Sons, 1991).

[0024] The term "halo", as used herein, unless otherwise indicated, includes fluoro, chloro, bromo or iodo.

[0025] The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon

radicals having straight, cyclic or branched moieties, or mixtures thereof. It is to be understood that where cyclic moieties are intended, at least three carbons in said alkyl must be present. Such cydic moieties include cyclopropyl, cyclobutyl and cyclopentyl.

[0026] The term "alkoxy", as used herein, unless otherwise indicated, includes -O-alkyl groups wherein alkyl is as defined above.

[0027] The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

[0028] The term "5-10 membered heteroaryl", as used herein, unless otherwise indicated includes aromatic heterocyclic groups containing one or more heteroatoms each selected from O, S and N, wherein each heterocydic group has from 5 to 10 atoms in its ring system. Examples of suitable 5-10 membered heteroaryl groups include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, oxazolyl, pyrrolyl and thiazolyl.

[0029] The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups which may be present in the compounds of the present invention. The compounds of the present invention that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic adds. The **acids that** may be used to prepare pharmaceutically acceptable add addition salts of such bask compounds of the present invention are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. The compounds of the present invention that include an amino moiety may form pharmaceutically acceptable salts with various amino acids, in addition to the acids mentioned above.

[0030] Those compounds of the present invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and, particulary, the calcium, magnesium, sodium and potassium salts of the compounds of the present invention.

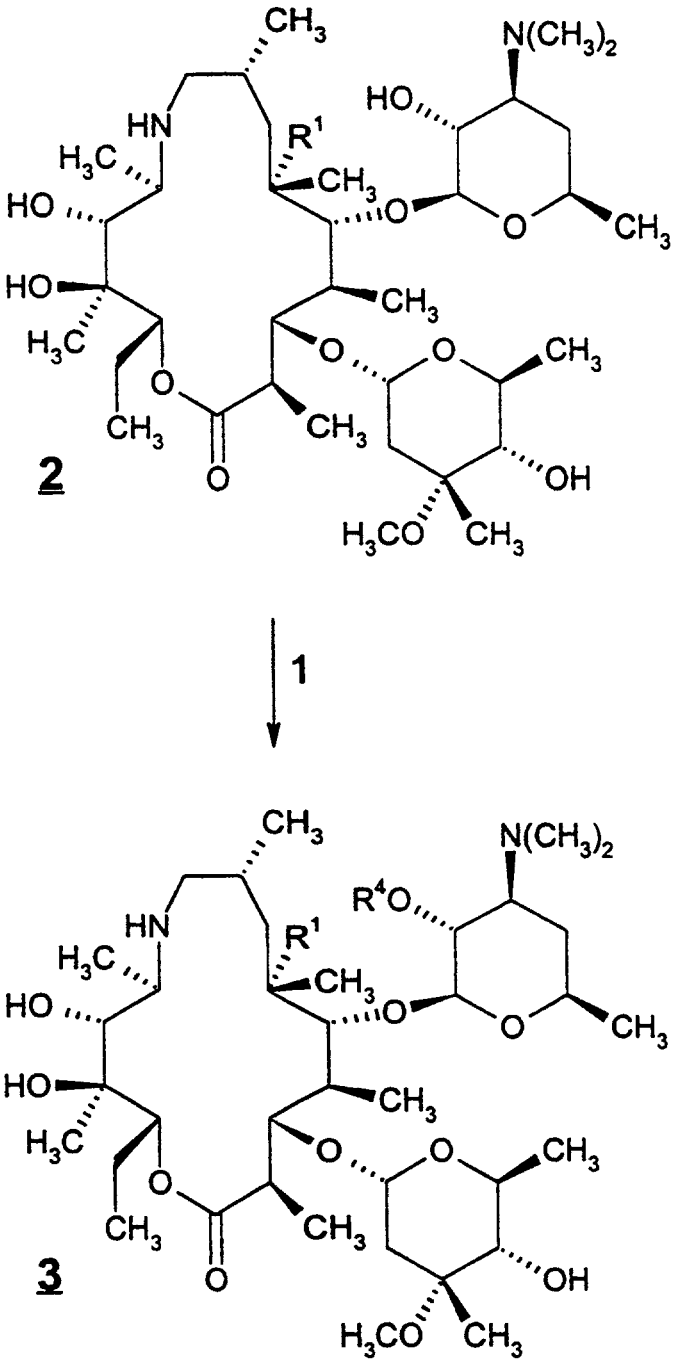
[0031] Certain compounds of the present invention may have asymmetric centers and therefore exist in different enantiomeric and diastereomic forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

[0032] The present invention includes the compounds of claim 1 and the pharmaceutically acceptable salts thereof, wherein one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism phamacokinetic studies and in binding assays.

Detailed Description of the Invention

[0033] The compounds of of the present invention may be prepared according to Schemes 1-3 below and the description that follows.

Scheme 1


CH3
N(CH3)2
HO
HN
R1
H3C
CH3
HO
O
O
CH3
HO
CH3
H3C
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O
CH3
O
CH3
CH3
2
OH
H3CO
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1
CH3
N(CH3)2
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R1
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CH3
HO
O
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CH3
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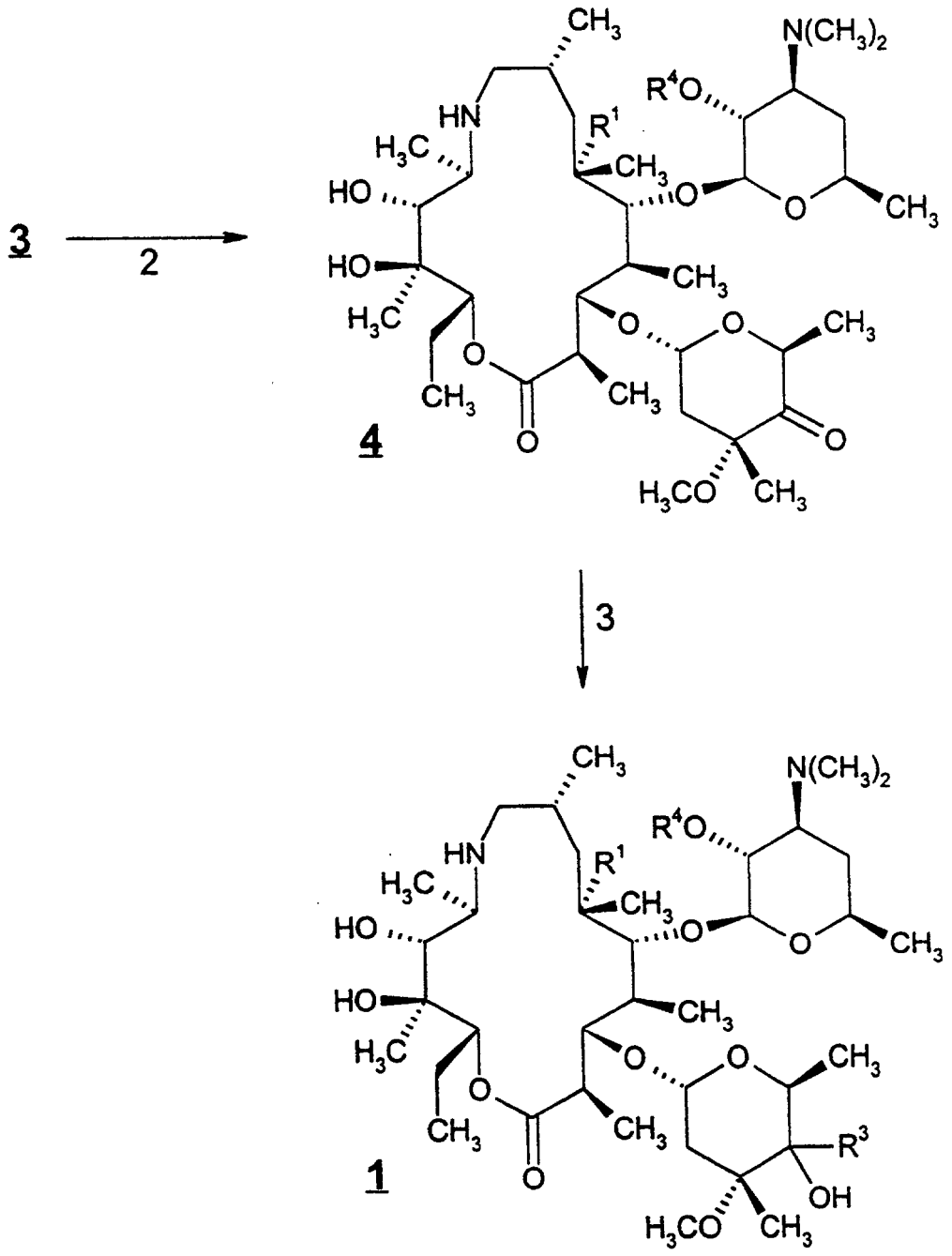
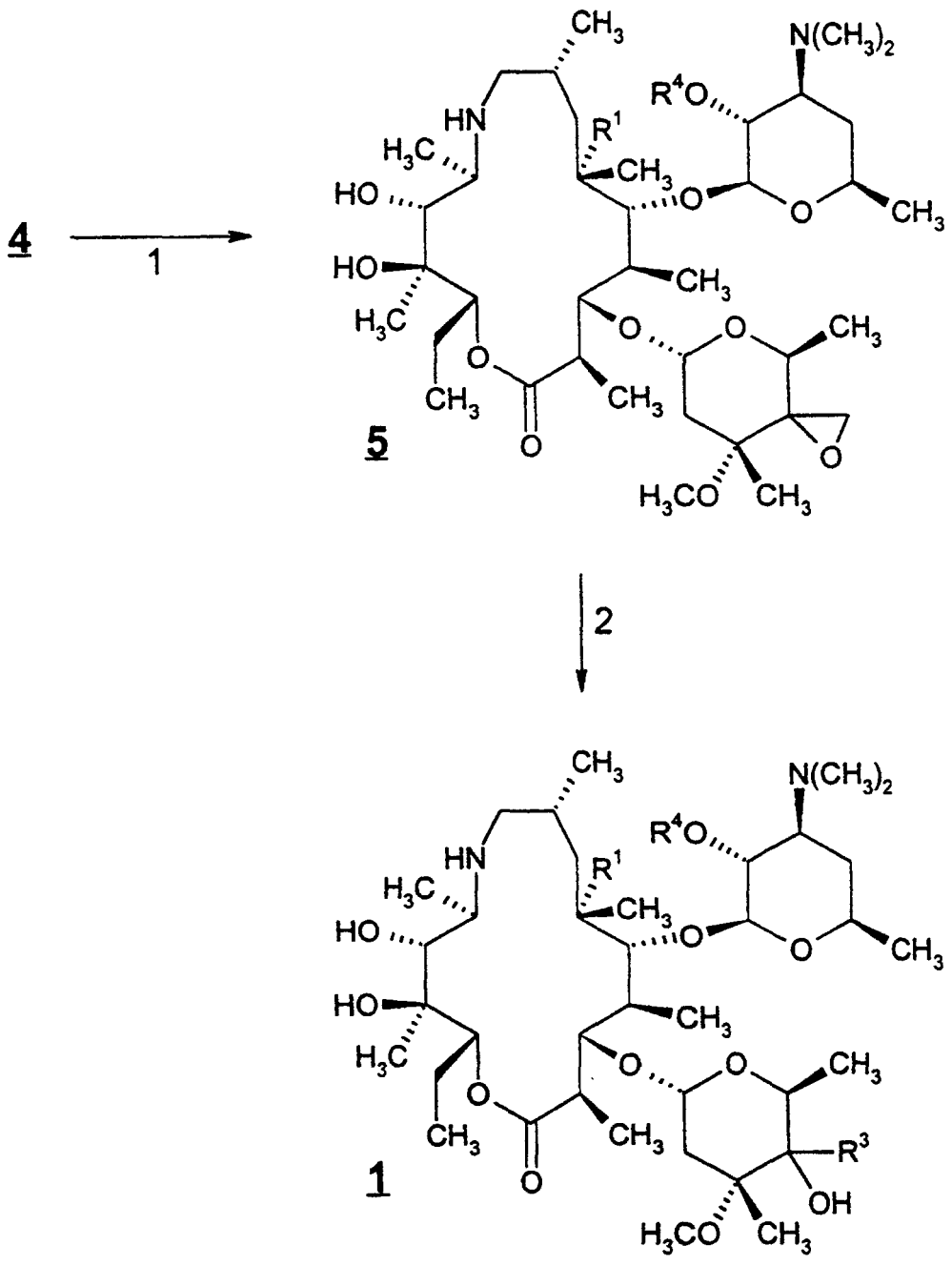
CH3

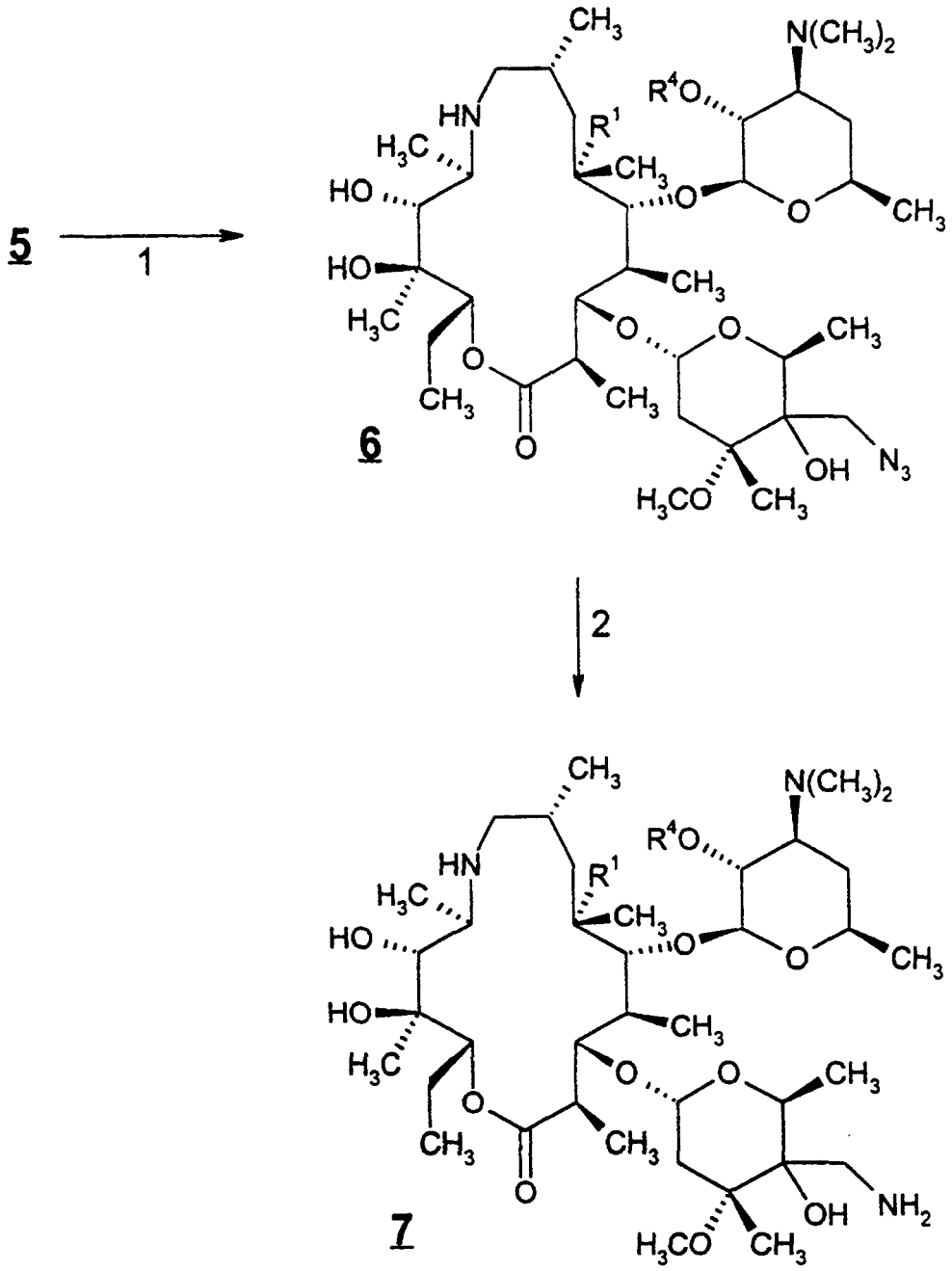
Scheme 1 continued



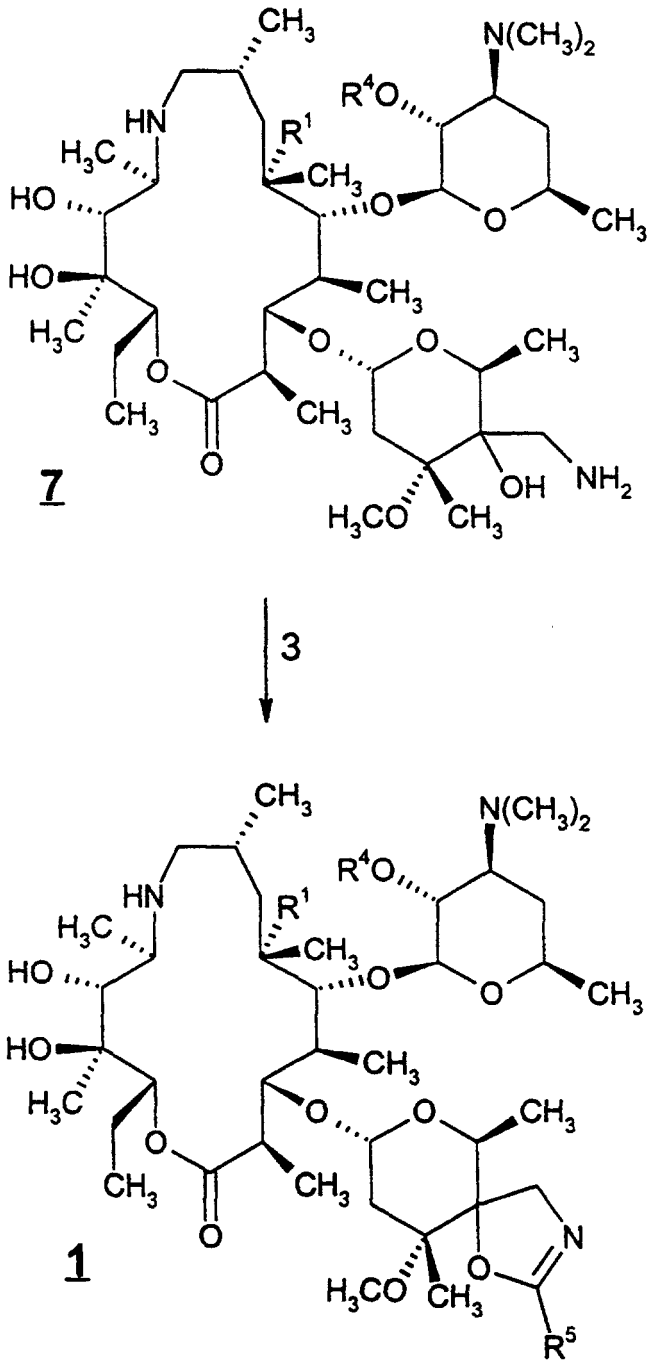
Scheme 2



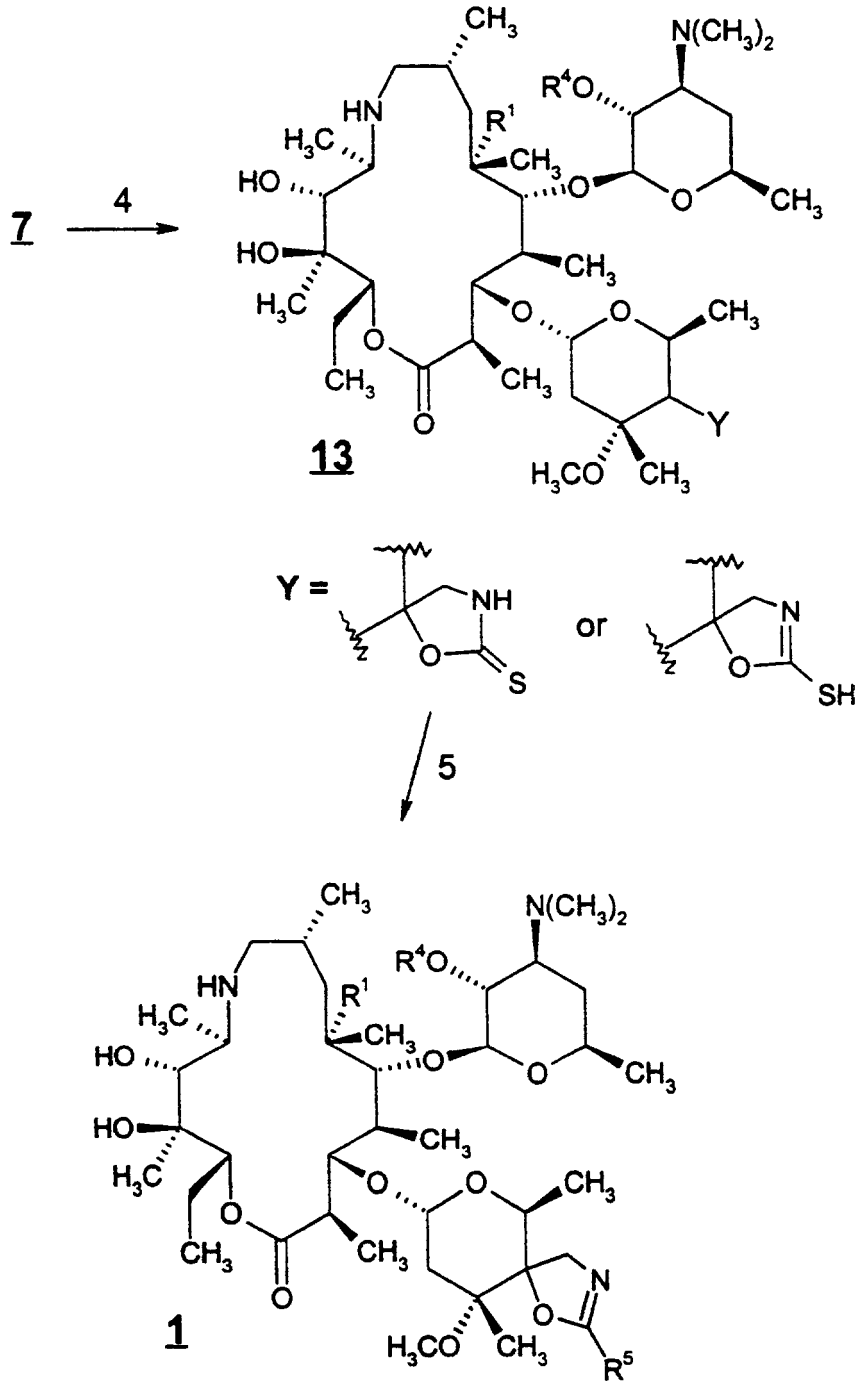
Scheme 3


5
1
6
2
7
CH3
N(CH3)2
R4O
HN
R1
H3C
HO
HO
H3C
CH3
O
CH3
CH3
CH3
CH3
OH
N3
H3CO
CH3
NH2

Scheme 3 continued



Scheme 3 continued

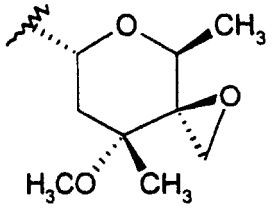


[0034] The compounds of the present invention are readily prepared. Referring to the Schemes illustrated above, the starting compound of formula 2 may be prepared according to one or more methods familiar to those skilled in the art including the synthetic methods described in United States patents 4,474,768 and 4,517,359, referred to above. In step 1 of Scheme 1, the C-2' hydroxy group may be selectively protected by treating the compound of formula 2 with one equivalent of acetic anhydride in dichloromethane in the absence of external base to provide the compound of formula 3 wherein R^4 is acetyl. The acetyl protecting group may be removed by treating the compound of formula 3 with methanol at 23-65°C for 10-48 hours. The C-2' hydroxy may also be protected with other hydroxy protecting groups familiar to

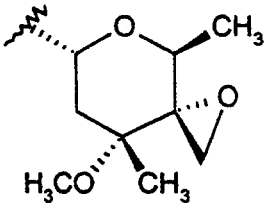
those skilled in the art, such as the benzytoxycarbonyl (Cbz) group. The C-9a amino group may also require protection before further synthetic modifications are performed. Suitable protecting groups for the amino moiety are Cbz and *t*-butyloxycarbonyl (Boc) groups. To protect the C-9a amino group, the macrolide may be treated with *t*-butyl dicarbonate in anhydrous tetrahydrofuran (THF) or benzyloxycarbonyl N-hydroxysuccinimide ester or benzylchloroformate to protect the amino group as its *t*-butyl or benzyl carbamate. Both the C-9a amino and C-2' hydroxy may be selectively protected with the Cbz group in one step by treating the compound of formula 2 with benzylchloroformate in THF and water. The Boc group may be removed by acid treatment and the Cbz group may be removed by conventional catalytic hydrogenation. In the following description, it is assumed that the C-9a amino moiety and the C-2' hydroxy group are protected and deprotected as would be deemed appropriate by those skilled in the art.

[0035] In step 2 of Scheme 1, the C-4" hydroxy group of the compound of formula 3 is oxidized to the corresponding ketone by methods familiar to those skilled in the art, including one or more methods described in the Journal of Antibiotics, 1988, pages 1029-1047. For example, the ketone of formula 4 may be prepared with DMSO and an appropriate activating agent. Typical reaction conditions for the oxidation include: (a) Moffatt oxidation which employs N-ethyl-N'-(N,N-dimethylaminopropy))carbodiimide and DMSO in the presence of pyridinium trifluoroacetate; or (b) Swem oxidation in which oxalyl chloride and DMSO in CH_2Cl_2 is followed by the addition of triethylamine or alternatively trifluoracetic anhydride and DMSO in CH_2Cl_2 is followed by the addition of triethylamine. In step 3 of Scheme 1, the compound of formula 4 is treated with R^3MgX^1 or R^3-Li and $Mg(X^1)_2$, wherein X^1 is a halide such as chloro or bromo, in a solvent such as THF, ethytene glycol dimethyl ether (DME), diisopropyl ether, toluene, diethyl ether, or tetramethylethylenediamine (TMEDA), hexanes, or a mixture of two or more of the foregoing solvents, preferably an ether solvent, at a temperature ranging from about -78°C to about room temperature (20-25°C), to provide the compound of formula 1 wherein R^2 is hydroxy and R^1, R^3 and R^4 are as defined above.

[0036] Scheme 2 illustrates the preparation of compounds of formula 1 through use of an epoxide intermediate. In step 1 of Scheme 2, the compound of formula 5 may be generated by two methods. In one method (Method A), the compound of formula 4 is treated with $(CH_3)_3S(O)X^2$, wherein X^2 is halo, $-BF_4$ or $-PF_6$, preferably iodo, in the presence of a base such as as potassium tert-butoxide, sodium tert-butoxide, sodium ethoxide, sodium hydride, 1,1,3,3-tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicylo[4.3.0]non-5-ene, potassium ethoxide, or sodium methoxide, preferably a sodium-containing base such as sodium hydride, in a solvent such as THF, an ether solvent, dimethylformamide (DMF), or methyl sulfoxide (DMSO), or a mixture of two or more of the foregoing solvents, at a temperature within the range of about O° to about 60°C, the compound of formula 5 is generated in which the following configuration of the epoxide moiety may predominate



[0037] In a second method (Method B), the compound of formula 4 is treated with $(CH_3)_3SX^2$, wherein X^2 is halo, $-BF_4$ or $-PF_6$, preferably $-BF_4$, in the presence of a base such as as potassium tert-butoxide, sodium ethoxide, sodium tert-butoxide, sodium hydride, 1,1,3,3-tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicylo[4.3.0]non-5-ene, potassium ethoxide, potassium hexamethyldisilazide (KHMDS) or sodium methoxide, preferably KHMDS, in a solvent such as THF, an ether solvent, DMF, or DMSO, or a mixture of two or more of the foregoing solvents, at a temperature within the range of about -78°C to about 60°C, to provide the compound of formula 5 in which the following configuration of the epoxide moiety predominates



[0038] In step 2 of Scheme 2, the compound of formula 5 may be converted to a compound of formula 1 wherein R^2 is hydroxy and R^3 is a group that is attached to the C-4" carbon through a methylene group, such as where R^3 is $CH_2NR^{15}R^8$ or $-CH_2S(O)_nR^8$ wherein n, R^{15} and R^8 are as defined above. To prepare a compound of formula 1 wherein R^3 is $-CH_2NR^{15}R^8$, the compound of formula 5 may be treated with a compound of the formula $HNR^{15}R^8$, wherein R^{15} and R^8 are as defined above, in the absence or presence of a polar solvent such as water, methanol, or THF, or a mixture of the foregoing solvents, at a temperature ranging from about room temperature to about 100°C, preferably about 60°C, optionally in the presence of a halide reagent such as potassium iodide, lithium perchlorate, magnesium perchlorate, lithium tetrafluoroborate, pyridinium hydrochloride, or a tetraalkylammonium halide reagent such as tetrabutylammonium iodide. To prepare a compound of formula 1 wherein R^3 is $-CH_2S(O)_nR^8$ wherein n and R^8 are as defined above, the compound of formula 5 may be treated with a compound of the formula HSR^8 in the presence of K_2CO_3, KI, or sodium methoxide, in an aromatic solvent such as methanol, benzene or toluene at a temperature ranging from about room temperature to about 120°C. As appropriate, the sulfur moiety may be oxidized to -SO- or $-SO_2-$ according to methods familiar to those skilled in the art. To prepare a compound of formula 1 wherein R^3 is $-CH_2SR^8$ and R^8 is $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$, wherein the substituents of said R^8 group are as defined above, the compound of formula 5 may be treated with a compound of the formula $HS-(CH_2)_qCR^{11}R^{12}(CH_2)_r$-NPhth, wherein NPhth represents phthalimido, and potassium iodide to provide the compound of formula 1 wherein R^3 is $-CH_2S(CH_2)_qCR^{11}R^{12}(CH_2)_rNH_2$, after removal of the phthalimido moiety, which may be further modified as necessary. Using the same or an analogous method, a compound of formula 1 wherein R^3 is $-CH_2NR^{15}R^8$ and R^8 is $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ may be prepared by treating the compound of formula 5 with either a compound of the formula $HNR^9-(CH_2)_qCR^{11}R^{12}(CH_2)_r-NR^{13}R^{14}$ or a compound of the formula $H_2N-(CH_2)_qCR^{11}R^{12}(CH_2)_rNH_2$ followed by reductive alkylation of the nitrogen atoms. Using the same or an analogous method, a compound of formula 1 wherein R^3 is $-CH_2OR^8$ and R^8 is as defined above may be prepared by treating a compound of formula 5 with a compound of the formula HOR^8.

[0039] Scheme 3 illustrates the preparation of compounds of formula 1 in which R^2 and R^3 are taken together to form an oxazolyl moiety. In step 1 of Scheme 3, the compound of formula 5 is treated with sodium azide in the presence of NH_4Cl in methanol or water, or a mixture of the two solvents, at a temperature ranging from about 0°C to about 100°C, preferably about 80°C, to provide the compound of formula 6. In step 2 of Scheme 3, the compound of formula 6 may be converted to the corresponding amine of formula Z via conventional catalytic hydrogenation. Preferably, such hydrogenation is done using Pd (10% on carbon) powder under an H_2 atmosphere (1 atm). The resulting amine of formula 7 may be converted to various compounds of formula 1 wherein R^3 is $-CH_2NR^{15}R^8$ using conventional synthetic methods such as reductive amination.

[0040] In step 3 of Scheme 3, the compound of formula 7 may be converted to the compound of formula 1 wherein R^2 and R^3 are taken together as shown by treating the compound of formula 7 with a compound of formula R^5-CN, R^5-C=N(OCH_3), R^5-C=N(OC_2H_5), R^5-C(O)Cl, or R^5-CO_2H, wherein R^5 is as defined above, except it is not NH_2, in the presence or absence of an acid, such as HCl, or a Lewis acid, such as $ZnCl_2$ or BF_4Et_3O, or a base, such as NaOH or TEA, in a solvent such as THF, a chlorohydrocarbon (such as CH_2Cl_2 or chlorobenzene), at a temperature ranging from about room temperature to reflux. In the altemative, the compound of formula 7 may proceed as indicated in steps 4 and 5 of Scheme 3. In step 4 of Scheme 3, the compound of formula 7 is treated with thiocarbonyldiimidazole in methylene chloride at a temperature ranging from about 0°C to room temperature to provide the compound of formula 13. In step 5 of Scheme 3, the compound of formula 13, is treated with R^5-X^1, wherein X^1 is a halide such as bromo or iodo, and a base such as sodium methoxide in a solvent such as methanol or acetone, or a mixture of the two solvents, at a temperature ranging from about 0°C to room temperature.

[0041] The compounds of the present invention may have asymmetric carbon atoms and therefore exist in different enantiomeric and diastereomeric forms. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers may be separated by converting the enantiomeric mixtures into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. The use of all such isomers, including diastereomer mixtures and pure enantiomers, are considered to be part of the present invention.

[0042] The compounds of the present invention that are basic in nature are capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to mammals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The desired salt can also be precipitated from a solution of the free base in an organic solvent

by adding to the solution an appropriate mineral or organic acid.

[0043] Those compounds of the present invention that are acidic in nature are capable of forming base salts with various cations. For compounds that are to be administered to mammals, fish or birds such salts must be pharmaceutically acceptable. Where a pharmaceutically acceptable salt is required, it may be desirable to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter to a pharmaceutically acceptable salt in a process analogous to that described above relating to the conversion of pharmaceutically unacceptable acid addition salts to pharmaceutically acceptable salts. Examples of base salts include the alkali metal or alkaline-earth metal salts and particularly the sodium, amine and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of the present invention. Such non-toxic base salts include those derived from such pharmacologically acceptable cations as sodium, potassium, calcium, magnesium, various amine cations, etc. These salts can easily be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable bases with cations such as sodium, potassium, calcium, magnesium, various amine cations, etc., and then evaporating the resulting solution to dryness, preferably under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are preferably employed in order to ensure completeness of reaction and maximum yields of the desired final product.

[0044] The antibacterial and antiprotozoa activity of the compounds of the present invention against bacterial and protozoa pathogens is demonstrated by the compound's ability to inhibit growth of defined strains of human (Assay I) or animal (Assays II and III) pathogens.

Assay I

[0045] Assay I, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to compounds that circumvent defined mechanisms of macrolide resistance. In Assay I, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of macrolide resistance mechanisms that have been characterized. Use of this panel enables the chemical structure/activity relationship to be determined with respect to potency, spectrum of activity, and structural elements or modifications that may be necessary to obviate resistance mechanisms. Bacterial pathogens that comprise the screening panel are shown in the table below. In many cases, both the macrolide-susceptible parent strain and the macrolide-resistant strain derived from it are available to provide a more accurate assessment of the compound's ability to circumvent the resistance mechanism. Strains that contain the gene with the designation of *ermA*/*ermB*/*ermC* are resistant to macrolides, lincosamides, and streptogramin B antibiotics due to modifications (methylation) of 23S rRNA molecules by an Erm methylase, thereby generally prevent the binding of all three structural classes. Two types of macrolide efflux have been described; *msrA* encodes a component of an efflux system in staphylococci that prevents the entry of macrolides and streptogramins while *mefA*/*E* encodes a transmembrane protein that appears to efflux only macrolides. Inactivation of macrolide antibiotics can occur and can be mediated by either a phosphorylation of the 2'-hydroxyl *(mph)* or by cleavage of the macrocyclic lactone (esterase). The strains may be characterized using conventional polymerase chain reaction (PCR) technology and/or by sequencing the resistance determinant. The use of PCR technology in this application is described in J. Sutcliffe et at., "Detection Of Erythromycin-Resistant Determinants By PCR", Antimicrobial Agents and Chemotherapy, 40(11), 2562-2566 (1996). The assay is performed in microtiter trays and interpreted according to Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition: Approved Standard, published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. Compounds are initially dissolved in dimethylsulfoxide (DMSO) as 40 mg/ml stock solutions.

Strain Designation	Macrolide Resistance Mechanism(s)
Staphylococcus aureus 1116	susceptible parent
Staphylococcus aureus 1117	*ermB*
Staphylococcus aureus 0052	susceptible parent
Staphylococcus aureus 1120	*ermC*
Staphylococcus aureus 1032	*msrA, mph,* esterase
Staphylococcus hemolyticus 1006	*msrA, mph*

Table continued

Strain Designation	Macrolide Resistance Mechanism(s)
Streptococcus pyogenes 0203	susceptible parent
Streptococcus pyogenes 1079	*ermB*
Streptococcus pyogenes 1062	susceptible parent
Streptococcus pyogenes 1061	*ermB*
Streptococcus pyogenes 1064	ermB
Streptococcus agalactiae 1024	susceptible parent
Streptococcus agalactiae 1023	*ermB*
Streptococcus pneumoniae 1016	susceptible
Streptococcus pneumoniae 1046	*ermB*
Streptococcus pneumoniae 1095	*ermB*
Streptococcus pneumoniae 1175	*mefE*
Streptococcus pneumoniae 0085	susceptible
Haemophilus influenzae 0131	susceptible
Moraxella catarrhalis 0040	susceptible
Moraxella catarrhalis 1055	erythromycin intermediate resistance
Escherichia coli 0266	susceptible

[0046] Assay II is utilized to test for activity against *Pasteurella multocida* and Assay III is utilized to test for activity against *Pasteurella haemolytica.*

Assay II

[0047] This assay is based on the liquid dilution method in microliter format. A single colony of *P. multocida* (strain 59A067) is inoculated into 5 ml of brain heart infusion (BHI) broth. The test compounds are prepared by solubilizing 1 mg of the compound in 125 μl of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated BHI broth. The concentrations of the test compound used range from 200 μg/ml to 0.098 μg/ml by two-fold serial dilutions. The *P. multocida* inoculated BHI is diluted with uninoculated BHI broth to make a 10^4 cell suspension per 200 μl. The BHI cell suspensions are mixed with respective serial dilutions of the test compound, and incubated at 37°C for 18 hours. The minimum inhibitory concentration (MIC) is equal to the concentration of the compound exhibiting 100% inhibition of growth of P. multocida as determined by comparison with an uninoculated control.

Assay III

[0048] This assay is based on the agar dilution method using a Steers Replicator. Two to five colonies isolated from an agar plate are inoculated into BHI broth and incubated overnight at 37°C with shaking (200 rpm). The next morning, 300 μl of the fully grown *P. haemolytica* preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37°C with shaking (200 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two ml of the respective serial dilution is mixed with 18 ml of molten BHI agar and solidified. When the inoculated *P. haemolytica* culture reaches 0.5 McFarland standard density, about 5 μl of the *P. haemolytica* culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and incubated for 18 hours at 37°C. Initial concentrations of the test compound range from 100-200 μg/ml. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of *P. haemolytica* as determined by comparison with an uninoculated control.

[0049] The in vivo activity of the compounds of formula (I) can be determined by conventional animal protection studies well known to those skilled in the art, usually gamed out in mice.

[0050] Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Animals are inoculated with 0.5 ml of a 3 x 10^3 CFU/ml bacterial suspension (*P. multocida* strain

59A006) intraperitoneally. Each experiment has at least 3 non-medicated control groups including one infected with 0.1X challenge dose and two infected with 1X challenge dose; a 10X challenge data group may also be used. Generally, all mice in a given study can be challenged within 30-90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of 30 minutes. The routes of administration are subcutaneous or oral doses. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. Compounds are administered 30 minutes, 4 hours, and 24 hours after challenge. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded. The *P. multocida* model monitoring continues for 96 hours (four days) post challenge.

[0051] The PD_{50} is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection which would be lethal in the absence of drug treatment.

[0052] The compounds of formula 1, and the pharmaceutically acceptable salts thereof (hereinafter "the active compounds"), may be adminstered through oral, parenteral, topical, or rectal routes in the treatment of bacterial and protozoa infections. In general, these compounds are most desirably administered in dosages ranging from about 02 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 4 mg/kg/day to about 50 mg/kg/day is most desirably employed. Variations may nevertheless occur depending upon the species of mammal, fish or bird being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

[0053] The active compounds may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the active compounds may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compounds are present in such dosage forms at concentration levels ranging from about 5.0% to about 70% by weight.

[0054] For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably com, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral adinistration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

[0055] For parenteral administration, solutions of an active compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques will known to those skilled in the art.

[0056] Additionally, it is also possible to administer the active compounds of the present invention topically and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

[0057] For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

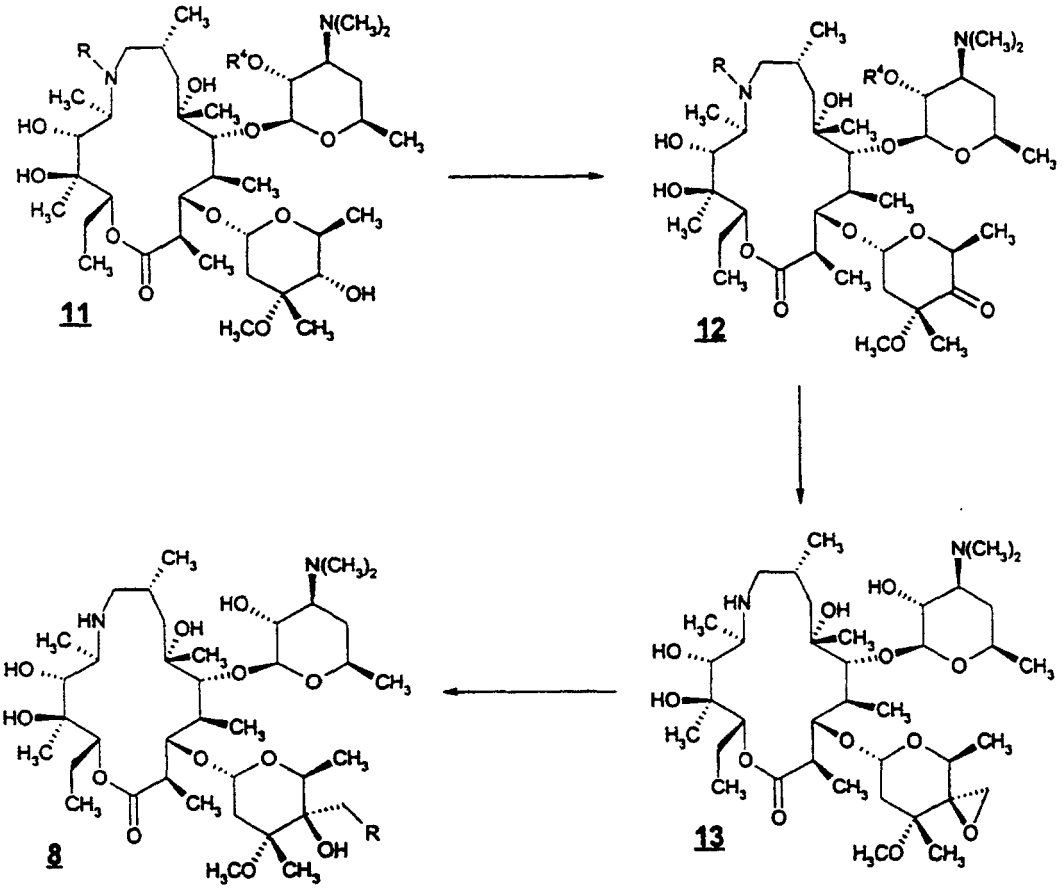
[0058] The active compounds may also be adminstered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesides. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

[0059] The active compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide phenyl, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoylresidues. Furthermore, the active compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

[0060] The following Examples further illustrate the method and intermediates of the present invention. It is to be understood that the present invention is not limited to the specific details of the Examples provided below.

Table 1

The compounds of Examples 1-32 have the general formula 8 below with the R substituents indicated in the table below. The compounds were prepared as described in Preparations 1-7 below. In the table, the yield and mass spectra ("Mass Spec") data apply to the final product.



Example	R Substituent	Preparation	Yield	Mass Spec
1	n-butylamino	1	48%	820
2	2-methoxyethylamino	1	52%	822
3	piperidino	1	61%	832
4	morpholino	1	39%	834
5	t-butylamino	1	23%	821
6	benzylamino	1	34%	854
7	cyclopentylamino	2	23%	832
8	propylamino	2	11%	806
9	anilino	1	21%	841
10	2-methoxypropylamino	1	46%	835

Example	R Substituent	Preparation	Yield	Mass Spec
11	azido	3	46%	790
12	hexylamino	1	56%	847
13	3-ethoxypropylamino	1	52%	851
14	diethylamino	2	53%	821
15	N-methylbutylamino	1	76%	835
16	N-methylpropylamino	2	59%	819
17	ethylamino	5	18%	792
18	cyclopropylamino	2	50%	804
19	ethylmethylamino	2	92%	806
20	2,2,2-trifluoroethylamino	2	67%	846
21	allylamino	1	59%	804
22	2-hydroxyethylthio	6	44%	826
23	dimethylamino	1	71%	793
24	imidazol-1-yl	4	42%	815
25	bis(2-hydroxyethyl)amino	7	21%	853
26	pyrrolidino	2	40%	818
27	2-hydroxy-ethylmethylamino	2	23%	822
28	1,2,3-triazol-1-yl	4	69%	817
29	2-propynylamino	2	51%	802
30	2-methylimidazol-1-yl	4	14%	829
31	diallylamino	2	29%	844
32	1,2,4-triazol-1-yl	4	34%	816

Preparation Methods for Table 1

[0061] With reference to the Scheme illustrated above, the compound of formula 11 wherein R is H and R^4 is H (25 g (34.01 mmol, 1.0 equiv)) was mixed in a solution with phenol red in 250 mL THF and 125 mL water. To this pink solution was slowly added 29 mL (204.1 mmol, 6.0 equiv) benzylchloroformate and 2N NaOH to keep the solution basic. The reaction was allowed to stir at room temperature overnight The reaction mixture was concentrated to remove the THF and the aqueous phase was adjusted to the pH of 9.5 and extracted 3 X 500 mL EtOAc. The combined organic layers were washed with 500 mL brine and then dried over Na_2CO_3. Filtration, concentration of the filtrate, and drying afforded a crude material. Further purification was done by column chromatography (100% CH_2Cl_2 to remove impurities and then 5% MeOH/CH_2Cl_2 to remove product) to yield 32.6 g (96%) of a yellowish solid which was the compound of formula 11 wherein R and R^4 were both Cbz (MS (FAB) m/z 1003). 32.6 g (32.49 mmol, 1.0 equiv) of this product was dissolved in 216.6 mL CH_2Cl_2 and 27.3 mL of DMSO. To this solution, 21.2 g (110.5 mmol, 3.4 equiv) of EDC and 24.1 g (124.8 mmol, 3.8 equiv) PTFA were added. After stirring overnight the reaction was quenched with 150 mL of water and the pH was adjusted to 9.5 with the addition of 2N NaOH. The organic layer was extracted 3 X 150 mL CH_2Cl_2 and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying afforded a crude yellow oil. Further purification on a silica gel column (2% MeOH/$CHCl_3$) to give 25.6 g (79%) of a yellowish solid which was the compound of formula 12 wherein both R and R^4 were Cbz.

[0062] 14 g (13.98 mmol, 1.0 equiv) of the compound of formula 12 prepared as described above was dissolved in 1 L of 2-propanol and to this was added 14 g of 10% Pd/C. The mixture was hydrogenated at 345KPa (50 psi) for three days. 14 g of 10% Pd/C was added to the reaction and allowed to stir for another day. This was repeated again and stirred for another day. The catalyst was removed by filtration through Celite and a minimal wash of 2-propanol to yield 4.8 g (47%) of the compound of formula 12 wherein both R and R^4 were H (MS (APCi) m/z 734).

[0063] 6.7 g (169.17 mmol. 6.2. equiv) of NaH (60% in oil dispersion) was washed twice with 150 mL hexanes to remove the mineral oil. The solid was diluted in 335 mL of DMSO and 38.4 g (174.62 mmol, 6.4 equiv) of Me_3SOI was added in three portions. The soution was stirred for an hour or until it turned dear. 20 g (27.29 mmol, 1.0 equiv) of the compound of formula 12 wherein both R and R^4 were H was dissolved in 200 mL of THF. The ketone was transferred via cannula to the reaction flask and allowed to stir for 20 minutes. The reaction was quenched with 500 mL saturated $NaHCO_3$. extracted 4 X 500 mL EtOAc, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave the crude oil. Further purification on 750 g of silica gel (5% MeOH/$CHCl_3$, 0.3 % NH_4OH) afforded 8.8 g (43%) of a white

solid which was the compound of formula 13 (MS (TS) m/z 747).

Preparation 1

[0064] 250-500 mg of the above compound of formula 13 was dissolved in 1-2 mL of an amine corresponding to the R substituent specified in Table 1. A catalytic amount (20 mg) of pyridinium hydrochloride was added and the solution was heated to 50-45°C for one to seven days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3 x 50 mL CH_2Cl_2, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2-4% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 2

[0065] 250-500 mg of the above compound of formula 13 was dissolved in 1-2 mL of an amine corresponding to the R substituent specified in Table 1 in a sealed tube. A catalytic amount (20 mg) of pyridinium hydrochloride was added and the solution was heated to 50-75°C for one to five days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3 x 50 mL CH_2Cl_3, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2-4% MeOH/$CHCl_3$, 02.% NH_4OH) afforded the final product

Preparation 3

[0066] 100 mg of the above compound of formula 13 was dissolved in MeOH/H_2O (8:1). Sodium azide (7 equiv) and ammonium chloride (5.5 equiv) were added and the solution was heated to 60°C for two days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3 x 50 mL CH_2Cl_2, and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 4

[0067] 150-250 mg of the above compound of formula 13 was dissolved in 1-2 mL MeOH/H_2O or MeOH. To this was added the heteroaromatic reagent corresponding to the R substituent specified in Table 1 (10-50 equiv) and a catalytic amount (20 mg) of pyridinium hydrochloride. The reaction mixture was heated at 45-50°C for one to three days. The reaction was then quenched with 100 mL saturated $NaHCO_3$, extracted with 3 x 25 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to a solid. The solid was re-dissolved in 100 mL EtOAc and washed with 3 x 25 mL 2N NaOH to remove the excess reagent. Further purification on a silica gel column (2-5% MeOH/$CHCl_3$, 02% NH_4OH) afforded the final product.

Preparation 5

[0068] 50 mg of the above compound of formula 13 was dissolved in 1mL of an amine corresponding to the R substituent specified in Table 1. A small scoop of neutral alumina was added and the mixture was stirred at room temperature for seven days. The reaction was worked up by filtering through Celite™ (diatomaceous earth) and concentrated to a crude solid. Further purification on a silica gel column (5% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

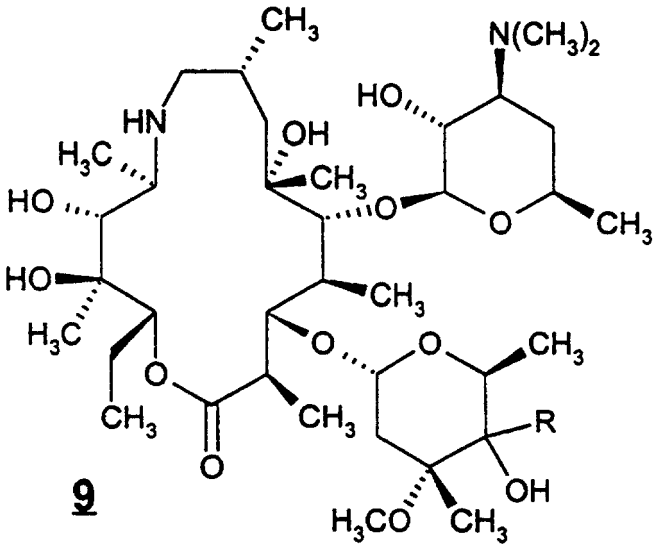
Preparation 6

[0069] 270 mg of the above compound of formula 13 was dissolved in 4 mL benzene. To this was added excess K_2CO_3 and 0.5 mL of thiol. The mixture stirred at room temperature for 16 hours. The reaction was quenched with 100 mL saturated $NaHCO_3$, extracted with 3 x 25 mL CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to a solid. Further purification on a silica gel column (2%MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

Preparation 7

[0070] 250 mg of the above compound of formula 13 was dissolved in 0.5 mL bis(2-hydroxyethyl)amine and 2 mL 2-propanol in a sealed tube. A catalytic amount (20 mg) of pyridinium hydrochloride was added and the solution was heated to 75°C for seven days. The reaction was worked up by quenching with 50 mL saturated $NaHCO_3$, extracted with 3 x 50 mL CH_2Cl_2 and dried over Na_2SO_4. Filtration, concentration of the filtrate, and drying gave a crude oil or solid. Further purification on a silica gel column (2% MeOH/$CHCl_3$, 0.2% NH_4OH) afforded the final product.

[0071] Examples 33-68 below describe the preparation of compounds having the general structure of formula 9 below wherein R is as defined in the examples.



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Example 33

[0072] To a solution of the compound of formula 4 wherein R^4 is H (0.059 g, 0.08 mmol) in THF (2 mL) at 0 °C was added allylmagnesium bromide in Et_20 (1.0 M, 0.5 mL). After 2 hours at 0°C, stirring was continued at room temperature for 12 hours. The reaction was diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (2 x 15 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2 :$NH_4$0H (6:93:1 to 10:89:1) afforded 0.011 g (18% yield) of the compound of formula 9 wherein R is allyl: MS: 776 (TS).

Example 34

[0073] To a solution of the compound of formula 4 wherein R^4 is H (0.059 g, 0.08 mmol) in DME (3 mL) at 0 °C was added vinylmagnesium bromide in THF (1.0 M, 0.56 mL). After stirring at 0 °C for 1 hour and at room temperature for 1 hour, the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and EtOAc (10 mL). After separation, the aqueous layer was washed with EtOAc (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (15 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1) afforded 0.016 g (26% yield) of the compound of formula 9 wherein R is vinyl: MS: 762 (FAB).

Example 35

[0074] To a flask containing $MgCl_2$ (0.095 g, 1 mmol) and DME (1 mL) at 0 °C was added 2-thienyl lithium (1.0 M, 1.0 mL). After 0.5 hour, a solution of the compound of formula 4 wherein R^4 is H (0.073 g, 0.1 mmol) in DME (2 mL) was introduced and stirring was continued at 0°C for 1 hour, then at room temperature for 0.5 hour. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (10 mL) and EtOAc (15 mL). After separation, the aqueous layer was washed with EtOAc (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (15 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1) afforded 0.012 g (15% yield) of the compound of formula 9 wherein R is 2-thienyl: MS: 817 (TS).

Example 36

[0075] To a solution of the compound of formula 4 wherein R^4 is H (0.147 g, 0.2 mmol) in DME (10 mL) at 0 °C was added ethynylmagnesium bromide in THF (0.5 M, 2.8 mL). After stirring at 0°C for 1 hour and at room temperature for

1 hour, the reaction mixture was diluted with water (20 mL) and EtOAc (35 mL). After separation, the aqueous layer was washed with EtOAc (3 x 25 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.068 g (45% yield) of the compound of formula 9 wherein R is ethynyl: MS: 759 (API).

Example 37

[0076] To a solution of the compound of formula 4 wherein R^4 is H (0.220 g, 0.3 mmol) in DME (15 mL) at 0°C was added 1-methyl-1-propenylmagnesium bromide in THF (0.5 M, 4.2 mL). After stirring at room temperature for 3 hours, the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (20 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (25 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.068 g (26% yield) of the compound of formula 9 wherein R is 1-methyl-1-propenyl: MS: 790 (API).

Example 38

[0077] To a solution of butylmagnesium bromide in THF (2.0 M, 1.0 mL) at 0°C was added a solution of methyl propargyl ether (0.154 g, 0.2 mmol) in DME (3 mL). After stirring at 0°C for 0.5 hour, a solution of the compound of formula 4 wherein R^4 is H (0.147 g, 0.2 mmol) in DME (7 mL) was added. After stirring at 0°C for 0.5 hour and room temperature for 4 hours, the reaction mixture was diluted with water (20 mL) and EtOAc (25 mL). After separation, the aqueous layer was washed with EtOAc (3 x 20 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.081 g (50% yield) of the compound of formula 9 wherein R is 3-methoxy-1-propynyl: MS: 803 (API).

Example 39

[0078] To a solution of methylmagnesium bromide in Et_2O (3.0 M, 1.8 mL) at 0°C was added a solution of 1-dimethylamino-2-propyne (0.154 g, 0.2 mmol) in THF (5 mL). After stirring at 0°C for 6 hours, a solution of the compound of formula 4 wherein R^{13} is H (0.147 g, 0.2 mmol) in DME (10 mL) was added at room temperature. After stirring at room temperature for 3 hours, the reaction mixture was diluted with water (40 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (40 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.140 g (57% yield) of the compound of formula 9 wherein R is 3-dimethylamino-1-propynyl: MS: 817 (API).

Example 40

[0079] To a solution of methylmagnesium bromide in Et_2O (3.0 M, 1.8 mL) and DME (1 mL) at 0°C was added a solution of 2-ethynylpyridine (0.186 g, 1.8 mmol) in DME (2 mL). After stirring at 0°C for 1 hour and room temperature for 1 hour, a solution of the compound of formula 4 wherein R^4 is H (0.110 g, 0.15 mmol) in DME (7 mL) was added at room temperature. After stirring at room temperature for 3 hours, the reaction mixture was diluted with water (20 mL) and EtOAc (40 mL). After separation, the aqueous layer was washed with EtOAc (3 x 30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.066 g (53% yield) of the compound of formula 9 wherein R is 2-pyridylethynyl: MS: 836 (API).

Example 41

[0080] To a round bottomed flask containing $MgBr_2$ (0.552 g, 3.0 mmol) and propynyl lithium (0.069 g, 1.5 mmol) at 0°C was added THF (5 mL). After 4 hours, a solution of the compound of formula 4 wherein R^4 is H (0.110 g, 0.15 mmol) in DME (10 mL) was introduced at room temperature and stirring was continued for 3 hours. The reaction mixture was diluted with water (30 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3 x 40 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 7:92:1) afforded 0.060 g (52% yield) of the compound of formula 9 wherein R is 1-propynyl: MS: 817 (TS).

Example 42

[0081] To a solution of methylmagnesium bromide in Et_2O (3.0 M, 0.6 mL) mL) at 0°C was added a solution of propargyl alcohol (0.346 mL, 0.289 g, 2.25 mmol) in THF (5 mL). After stirring at 0°C for 3 hours, a solution of the compound of formula 4 wherein R^4 is H (0.110 g, 0.15 mmol) in DME (10 mL) was added at room temperature. After stirring at room temperature for 2 hours, the reaction mixture was diluted with water (35 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3 x 40 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1) afforded 0.038 g (32% yield) of the compound of formula 9 wherein R is 3-hydroxy-1-propynyl: MS: 790 (API).

Example 43

[0082] Palladium catalyst (20 mg, 10% Pd/C) was added to a solution of the compound from example 42 in isopropanol (8 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Filtration of an aliquot of the reaction mixture through Celite™ and concentration under vacuum afforded the compound of formula 9 wherein R is 3-hydroxy-1 -propenyl: MS: 791 (API).

Example 44

[0083] Palladium catalyst (20 mg, 10% Pd/C) was added to the remaining solution from example 43 and the reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 48 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.018 g (57% yield) of the compound of formula 9 wherein R is 3-hydroxypropyl: MS: 793 (API)

Example 45

[0084] Palladium catalyst (15 mg, 10% Pd/C) was added to a solution of the title compound from example 38 in isopropanol (8 mL). The reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 24 hours. Filtration of an aliquot of the reaction mixture through Celite™ and concentration under vacuum afforded the compound of formula 9 wherein R is 3-methoxy-1-propenyl: MS: 806 (API).

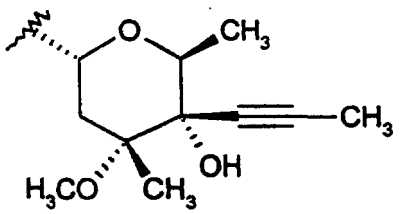
Example 46

[0085] Palladium catalyst (15 mg, 10% Pd/C) was added to the remaining solution from example 45 and the reaction vessel was flushed and filled with hydrogen (50 psi) and shaken at room temperature for 48 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 7:92:1) afforded 0.017 g (73% yield) of the compound of formula 9 wherein R is 3-methoxy-propyl: MS: 808 (API)

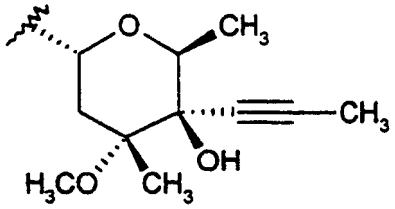
Sample 47

[0086] To a solution of the compound of formula 4 wherein R^4 is benzyloxycarbonyl (0.520 g, 0.6 mmol) in DME (6 mL) and TMEDA (2 mL) at -40°C was added propynyl lithium (0.414 g, 9.0 mmol). After stirring at -40 °C for 2.5 hours, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (30 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (25 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.6:0.4) afforded 0.157 g (29% yield) of the faster eluting diastereomer, along with 0.071 g (13% yield) of the slower eluting diastereomer and 0.070 g (13% yield) of a mixture of the diastereomers.

[0087] A solution of the faster eluting diastereomer (0.157 g. 0.17 mmol) in MeOH (5 mL) was allowed to stir at 30°C for 6 days. Upon concentration under vacuum, silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6: 93.6:0.4) afforded 0.102 g (78% yield) of the compound of formula 9 wherein R is 1-propynyl according to the following configuration at the C-4" carbon (MS: 774 (API)):



[0088] A solution of the slower eluting diastereomer (0.071 g, 0.078 mmol) in MeOH (3 mL) was allowed to stir at 30°C for 6 days. Upon concentration under vacuum, silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.6:0.4) afforded 0.041 g (68% yield) of material identical to that described by the compound of Example 41 which corresponds to the compound of formula 9 wherein R is 1-propynyl according to the following configuration at the C-4" carbon (MS: 774 (API)):

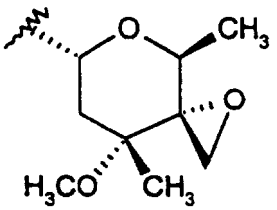


Example 48

[0089] To a suspension of trimethylsulfonium tetrafluoroborate (1.03 g, 6.3 mmol) in THF (40 mL) at -10°C was added KHMDS (1.20 g, 6.0 mmol). After stirring below 0°C for 0.5 hour, the reaction vessel was cooled to -78°C and a solution of the compound of formula 4 wherein R^{13} is benzyloxycarbonyl (2.60 g, 3 mmol) in DME (10 mL) was added. After 0.5 hour, the reaction mixture was diluted with a saturated aqueous solution of ammonium chloride (40 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH: CH_2Cl_2:NH_4OH (2:97.6:0.4 to 4:95.5:0.4) afforded 0.834 g (32% yield) of the compound of formula 5 wherein R^4 is benzyloxycarbonyl (MS: 881 (API)).

Example 49

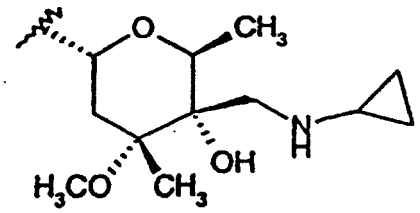
[0090] A solution of the compound of Example 48 (0.176 g, 0.2 mmol) in MeOH (5 mL) was allowed to stir at 50°C for 4 days. Upon concentration, silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.5:0.4) afforded 0.107 g (72% yield) of the compound of formula 5 wherein R^4 is hydrogen and the epoxide moiety at C-4" has the following configuration (MS: 748 (API)):



Example 50

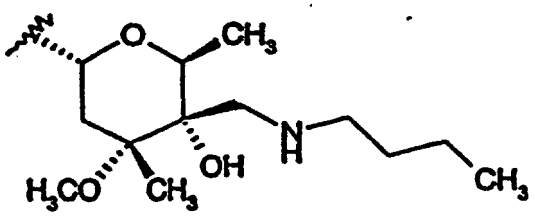
[0091] A solution of the compound of Example 48 (0.176 g, 02 mmol), potassium iodide (2.32 g, 14 mmol) and cydopropytamine (2.43 mL, 2.00 g, 35 mmol) in MeOH (30 mL) was allowed to stir at 50°C for 2 days. Upon concentration, the residue was dissolved in water (50 mL) and EtOAc (100 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate

(50 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH: CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.5:0.4) afforded 0.377 g (69% yield) of the compound of formula 9 wherein R is cyclopropylaminomethyl according to the following configuration at the C-4" carbon (MS: 805 (API)):



Example 51

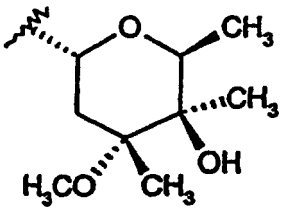
[0092] A solution of the compound of Example 48 (0.176 g, 0.2 mmol), tetrabutytammonium iodide (0.739 g, 2.0 mmol) and butylamine (0.395 mL, 0.293 g, 4 mmol) in MeOH (5 mL) was allowed to stir at 50°C for 2 days. Upon concentration, the residue was dissolved in water (20 mL) and EtOAc (20 mL). After separation, the aqueous layer was washed with EtoAc (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.6:0.4 to 6:93.5:0.4) afforded 0.088 g (54% yield) of the compound of formula 9 wherein R is propylaminomethyl according to the following configuration at the C-4''carbon (MS: 821 (API)):



Example 52

[0093] To a solution of a compound of formula 4 wherein R^4 is benzyloxycarbonyl and the hydrogen attached to the C-9a nitrogen is replaced by benzyloxycarbonyl (0.500 g. 0.499 mmol) in THF (15 mL) 0°C was added methylmagnesium bromide in Et_20 (3.0 M. 1.2 mL). After 20 minutes, the reaction was diluted with EtOAc (30 mL) and water (50 mL). After separation, the aqueous layer was washed with EtOAc (3 x 35 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (120 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.500 g (98% yield) of an off-white foam. (MS: 1017,845 (API)).

[0094] Palladium catalyst (0.250 g. 10% Pd/C) was added to a solution of the compound described above (0.500 g 0.491 mmol) in isopropanol (50 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 48 hours. Additional palladium catalyst (0.250 g. 10% Pd/C) was added and hydrogenation was continued at 345KPa (50 psi) for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. The resulting oil was dissolved in isopropanol (50 mL), palladium catalyst was added (0.312 g, 10% Pd/C), and hydrogenation was continued at 50 psi for 24hours. Additional palladium catalyst (0.170 g, 10% Pd/C) was added and hydrogenation was continued at 345KPa (50 psi) for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (8:91:1 to 10:89:1) afforded 0.120 g (33% yield) of the compound of formula 9 wherein R is methyl according to the following configuration at the C-4" carbon (MS: 749 (API)):



Example 53

[0095] To a solution of a compound of formula 4 wherein R^4 is benyloxycarbonyl and the hydrogen attached to the C-9a nitrogen is replaced by benzyloxycarbonyl (0.101 g. 0.101 mmol) in THF (2 mL) at -78°C was added phenylmagnesium bromide in THF (1.01 M, 1.0 mL). After 15 minutes, stirring was continued 0°C for 1 hour, then at room temperature for 12 hours. The reaction was diluted with a 10% aqueous solution of sodium bicarbonate (10 mL) and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3x15 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (5:94:1 to 25:74:1) afforded 0.048 g (45% yield) of a white foam (MS: 1080 (LSIMS)).

[0096] Palladium catalyst (0.024 g. 10% Pd/C) was added to a solution of the compound described above (0.024 9, 0.022 mmol) in methanol (15 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (5:94.5:1 to 10:89:1) afforded 0.010 g (28% yield) of the compound of formula 9 wherein R is phenyl: MS: 811 (LSIMS).

Example 54

[0097] To a solution of the starting compound used in Example 53 (0.300 g. 0.30 mmol) in ThF (3 mL) at 0°C was added n-butylmagnesium chloride in THF (2.0 M. 1.5 mL). After 20 minutes the reaction was diluted with water and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (55 mL), dried over Na_2SO_4, and concentrated under vacuum to afford 0.295 g (93% yield) of an off-white foam (MS: 1060 (FAB)).

[0098] Palladium catalyst (0.087 g, 10% Pd/C) was added to a solution of the compound described above (0.087 g. 0.082 mmol) in isopropanol (15 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.087 g. 10% Pd/C) was added and hydrogenation was continued at 345KPa (50 psi) for 60 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (5:94.5:0.5 to 10:89:1) afforded 0.010 g (28% yield) of the compound of formula 9 wherein R is n-butyl: MS: 792 (API).

Example 55

[0099] To a solution of the starting compound used in Example 53 (0.200 g. 020 mmol) in THF (2 mL) at 0°C was added ethylmagnesium bromide in THF (1.0 M. 2.0 mL). After 20 minutes the reaction was diluted with water and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3 x 30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (55 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (5:94.5:0.5 to 20:79:1) afforded 0.079 g (38% yield) of a white foam (MS: 1033 (LSIMS)).

[0100] Palladium catalyst (0.035 g, 10% Pd/C) was added to a solution of the compound described above (0.079 g, 0.077 mmol) in ethanol (20 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.036 g. 10% Pd/C) was added and hydrogenation was continued at 345KPa (50psi) or 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum, affording 0.056 g (96% yield) of the compound of formula 9 wherein R is ethyl: MS: 763 (TS).

Example 56

[0101] To a solution of the starting compound used in Example 53 (0.300 g. 0.30 mmol) in THF (3 mL) at 0°C was added isopropenylmagnesium chloride in THF (0.5 M. 6.0 mL). After 20 minutes the reaction was diluted with water and EtOAc (20 mL). After separation, the aqueous layer was washed with EtOAc (3 x 30 mL). The combined organic extracts

were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (55 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (3:96.9:0.1 to 20:79.9:0.1) afforded 0.063 9 (20% yield) of a white foam (MS: 1045 (LSIMS)).

[0102] Palladium catalyst (0.075 g. 10% Pd/C) was added to a solution of the compound described above (0.150 g, 0.165 mmol) in ethanol (30 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.075 g. 10% Pd/C) was added and hydrogenation was continued at 345KPa(50 psi) for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.024 g (19% yield) of the compound of formula 9 wherein R is isopropenyl: MS: 775 (TS).

Example 57

[0103] To a solution of the starting compound used in Example 53 (0.750 g. 0.75 mmol) in THF (12 mL) at 0 °C was added allylmagnesium chloride in THF (2.0 M, 3.0 mL). After 15 minutes the reaction was diluted with water and EtOAc (40 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1) afforded 0.530 g (68% yield) of an off-white foam (MS: 1044, 910 (API)).

[0104] Palladium catalyst (0.175 g, 10% Pd/C) was added to a solution of the compound described above (0.350 g, 0.335 mmol) in isopropanol (100 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.150 g, 10% Pd/C) was added and hydrogenation was continued at for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.148 g (57% yield) of the compound of formula 9 wherein R is propyl: MS: 778 (API).

Example 58

[0105] To a solution of the compound used as a starting material in Example 53 (0.750 g, 0.75 mmol) in THF (12 mL) at 0°C was added allylmagnesium chloride in THF (2.0 M, 3.0 mL). After 15 minutes the reaction was diluted with water and EtOAc (40 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL). dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1) afforded 0.530 g (68% yield) of an off-white foam (MS: 1044 (API)).

[0106] A solution of the compound described above (0.104 g, 0.100 mmol) and (1S)-(+)-10-camphor sulfonic acid (0.046 g, 0.200 mmol) in MeOH (4 mL) was cooled to -78°C and treated with ozone until a deep blue color persisted. The reaction was purged with oxygen, dimethylsulfide (0.13 mL, 1.76 mmol) and pyridine (0.20 mL, 2.42 mmol) were added and stirring was continued for 12 hours. CH_2Cl_2 (30 mL) and 10% aqueous solution of sodium bicarbonate (10 mL) were added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL). dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.024 g (23% yield) of an off-white foam (MS: 912 (API)).

[0107] To a solution of the compound described above (0.022 g, 0.024 mural) in MeOH (1 mL) was added sodium borohydride (0.001 g, 0.024 mmol). Additional sodium borohydride (0.004 g, 1.00 mmol) was added over a period of 3 hours. The reaction mixture was diluted with CH_2Cl_2 (30 mL) and 10% sodium bicarbonate solution (20 mL). After separation, the aqueous layer was extracted with CH_2Cl_2 (3x 30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.022 g (100% yield) of a yellow foam (MS: 914 (API)).

[0108] Palladium catalyst (0.012 g, 10% Pd/C) was added to a solution of the compound described above (0.022 g, 0.024 mmol) in isopropanol (10 mL). The reaction vessel was flushed and filed with hydrogen 345 KPa (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.020 g, 10% Pd/C) was added and hydrogenation was continued at 345KPa (50 psi) for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:$CH_2Cl_2NH_4OH$ (8:91:1 to 10:89:1) afforded 0.005 mg (23% yield) of the compound of formula 9 wherein R is 2-hydroxyethyl: MS: 779 (API).

Example 59

[0109] To a solution of the starting compound used in Example 53 (0.750 g, 0.75 mmol) in THF (12 mL) at 0°C was added allylmagnesium chloride in THF (2.0 M, 3.0 mL). After 15 minutes the reaction was diluted with water and EtOAc

(40 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 15:84:1) afforded 0.530 g (68% yield) of an off-white foam (MS: 1044 (API)).

[0110] A solution of the compound described above (0.104 g. 0.100 mural) and (1S)-(+)-10-camphor sulfonic acid (0.046 g, 0.200 mmol) in MeOH (4 mL) was cooled to -78°C and treated with ozone until a deep blue color persisted. The reaction was purged with oxygen, dimethylsulfide (0.13 mL, 1.76 mmol) and pyridine (0.20 mL, 2.42 mmol) were added and stirring was continued for 12 hours. CH_2Cl_2 (30 mL) and 10% aqueous solution of sodium bicarbonate (10 mL) were added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x 30 mL). The combined organic extracts were washed with a 10% aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.024 g (23% yield) of an off-white foam (MS: 912 (API)).

[0111] Palladium catalyst (0.040 g. 10% Pd/C) was added to a solution of the compound described above (0.057 g. 0.063 mmol) in isopropanol (15 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Additiona palladium catalyst (0.040 g. 10% Po/C) was added and hydrogenation was continued at 345KPa (50 psi) for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.010 g (15% yield) of the compound of formula 9 wherein R is formylmethyl: MS: 777 (API).

Example 60

[0112] To a solution of 2-bromopyridine (0.474 g. 3.0 mmol) in THF (5 mL) at -78°C was added n-butyl lithium (3.0 M, 1-2 mL) at -78 °C. After 40 minutes, the solution was transferred via a cannula cooled with a dry ice jacket to a flask containing $MgCl_2$ (0.428 g. 4.5 mmol) and ether (4 mL) at -78°C. After 15 minutes, a solution of a compound of formula 4 wherein R^4 is benzytoxycarbonyl (0.260 g, 0.3 mmol) in THF (3 mL) at -78°C was introduced and stirring was continued allowing the reaction to warm to room temparature over several hours. Alter 3.5 hours. the reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (20 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL), The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (60 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93.3:0.7 to 10:89:1) afforded 0.023 g (9.5% yield) of the compound of formula 9 wherein R is 2-pyridyl: MS: 812 (API).

Example 61

[0113] To a round bottom flask containing n-butyl lithium (3.0 M, 1.62 ml) in diethyl ether (15 mL) at -78°C was added chilled (-78°C) 3-bromopyridine (0.790 g, 5 mural) via a cannula codec with a dry ice jacket Stirring continued at -78°C for 35 minutes. A suspension of $MgBr_2$ diethyl ethereate (0.114 g, 0.440 mmol) in diethyl ether (3 mL) at -78°C was added via a cannula cooled with a dry ice jacket to the 3-pyridyl lithium solution. A solution of a compound of formula 4 wherein R^4 is benzyloxycarbonyl (0.347 g. 0.400 mmol) in diethyl ether (3 mL) at -78°C was introduced via cannula. Stirring continued at -78°C for 2 hours and slowly allowed to warm to 0°C over 3 hours. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (20 mL) and EtOAc (30 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (60 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95.4:0.6 to 20:79:1) afforded 0.075 g (26% yield) of a while foam (MS: 947, 812 (API)).

[0114] Palladium catalyst (0.073 g, 10% Pd/C) was added to a solution of the compound described above (0.073 g. 0.077 mmol) in isopropanol (30 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 48 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.032 g (51% yield) of the compound of formula 9 wherein R is 3-pyridyl: MS: 812 (API).

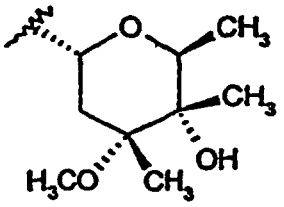
Example 62

[0115] To a solution of methyl magnesium bromide in diethyl ether (3.0 M, 1.8 mL) at 0°C was added a solution of 5-hexynenitrile (0.63 mL, 6.00 mmol) in THF (5 mL). After stirring at 0°C for 6 hours, a solution of the compound of formula 4 wherein R^4 is H (0.220 g. 0.300 mmol) in DME (10 mL) was added and storing was continued at 0°C for 0.5 hour. then at room temperature for 4 hours. The reaction mixture was diluted with water (20 mL) and EtOAc (25 mL), the layers were separated and the aqueous layer was washed with EtOAc (3 x 20 mL). The combined organic extracts

were washed with a saturated aqueous solution of sodium bicarbonate (20 mL) and brine (25 mL), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 10:89:1) afforded 0.035 g (14% yield) of the compound of formula 9 wherein R is 6-cyano-1-pentynyl: MS: 827 (API).

Example 63

[0116] To a solution of the compound of Example 49, except wherein R^4 is benzyloxycarbonyl. (0.101 g, 0.115) in DME (3 mL) was added $LiAlH_4$ (1.0 M. 2.1 mL) dropwise. After 10 minutes the reaction mixture was treated sequentially with water (0.044 mL), 15% NaOH solution (0.044 mL), and water (0.132 mL). then stirred at rt for 0.5 hour. The mixture was diluted with EtOAc (20 mL) and water (20 mL). After separation the aqueous layer was extracted with EtOAc (3x30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (60 mL). dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (3:96.5:0.5 to 3.5:95:0.5) afforded 0.042 g (49% yield) of the compound of formula 9 wherein R is methyl according to the following configuration at the C-4" carbon (MS: 749 (API)):



Example 64

[0117] To a solution of 1-methylimidazole (0.41 g. 4.99 mmol) in THF (5 ml) at -78°C was added n-butyl lithium (2.5M, 2.02ml). After 45 minutes at -78°C the solution was added via cannula to a flask containing $MgCl_2$ (0.71 g, 7.49 mmol) and THF (5 mL) at 0°C. After 1.5 hours at 0°C, a solution of the starting compound used in Example 53 (0.500 g, 0.499 mmol) in DME (2 mL) was introduced and stirring was continued at 0°C for 1 hour. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (100 mL) and EtOAc (100 mL). After separation, the aqueous layer was washed with EtOAc (3 x 100 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 mL). dried over Na_2SO_4 and concentrated under vacuum to afford 0.660 g of a yellow foam (MS: 949 (API)).

[0118] Palladium catalyst (0.700 g. 10% Pd/C) was added to a solution of the compound decribed above in isopropanol (60 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Addtional palladium catalyst (0.500 g. 10% Pd/C) was added and hydrogenation was continued at 345KPa (50 psi) for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (1:98:1 to 8:91:1) afforded 0.052 g (13% yield) of the compound of formula 9 wherein R is 1-methylimldazol-2-yl- MS: 816 (API).

Example 65

[0119] To a solution of furan (0.34g, 4.99 mmol) in THF (5ml) at -78°C was added n-butyl lithium (2.5M, 1.98ml). After 0.5 hour at -78°C the solution was added to a flask containing $MgCl_2$ (0.71 g, 7.49 mmol) and THF (5 mL) at 0°C. After 1.5 hours at 0 °C, a solution of the starting compound used in Example 53 (0.500 g, 0.499 mmol) in DME (2 mL) was introduced and stirring was continued at 0°C for 1 hour, then at room temperature for 1 hour. The reaction mixture was diluted wi th a saturated aqueous solution of sodium bicarbonate (100 mL) and EtOAc (100 mL). After separation, the aqueous layer was washed with EtOAc (3 x 100 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (100 mL) and brine (100 ml), dried over Na_2SO_4 and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (1:98:1 to 8:91:1) afforded 0.096 g (24% yield) of a white foam (MS: 935 (API)).

[0120] Palladium catalyst (0.100 g. 10% Pd/C) was added to a solution of the compound described above in isopropanol (15 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 72 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (1:98:1 to 8:91:1) afforded 0.053 g (13% yield) of the compound of formula 9 wherein R is 2-furyl: MS: 802 (API).

Example 66

[0121] To a solution of N-methylpyrrole (0.184 g, 2.31 mmol) in THF (4 ml) at -78°C was added n-butyl lithium (2.5M, 0.93 ml). The solution was warmed to room temperature over 1 hour and then added via cannula to a flask containing $MgCl_2$ (0.329 g, 3.46 mmol) and Et_2O (4 mL) at room temperature. After 1 hour, a solution of the compound of formula 4 wherein R^4 is benzyloxycarbonyl (0.200 g, 0.231 mmol) in THF (2 mL) was introduced and stirring was continued at room temperature for 45 minutes. The reaction mixture was diluted with a saturated aqueous solution of sodium bicarbonate (50 mL) and EtOAc (50 mL). After separation, the aqueous layer was washed with EtOAc (3 x 50 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum to afford 0.293 g of a yellow foam (MS: 949 (API)).

[0122] Palladium catalyst (0.324 g, 10% Pd/C) was added to a solution of the compound decribed above in isopropanol (30 mL). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Additional palladium catalyst (0.300 g, 10% Pd/C) was added and hydrogenation was continued at 345KPa (50 psi) for 24 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (6:93:1 to 8:91:1) afforded 0.033 g (18% yield) of the compound of formula 9 wherein R is 1-methyl-2-pyrrolyl: MS: 814 (API).

Example 67

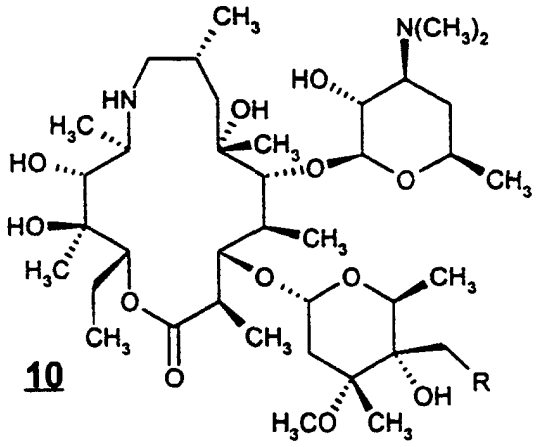
[0123] To a solution of unpurified compound prepared as described in Example 39 (0.480 g) in isopropanol (40 mL) was added platinum oxide (0.115 g, 0.505 mmol). The reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 24 hours. Filtration of an aliquot of the reaction mixture through Celite™ and concentration under vacuum afforded the compound of formula 9 wherein R is 3-dimethylamino-1-propenyl: MS: 819 (API).

Example 68

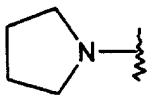
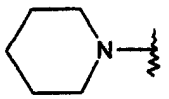
[0124] Platinum oxide (0.076 g, 0.335 mmol) was added to the remaining solution from Example 67 and the reaction vessel was flushed and filled with hydrogen 345KPa (50 psi) and shaken at room temperature for 96 hours. The reaction mixture was filtered through Celite™ and concentrated under vacuum. Silica gel chromatography with MeOH:CH_2Cl_2:NH_4OH (4:95:1 to 6:93:1) afforded 0.069 g (15% yield) of the compound of formula 9 wherein R is 3-dimethylpropyl: MS: 821 (API).

Table 2

The compounds of Examples 69-81 have the general structure of formula 10 below with the R substituents indicated in the table below. The compounds of Examples 69-82 were prepared following the procedures of Examples 50 and 51, referred to above, with the reaction period specified in the table below. In the table, the yield and mass spectra ("Mass Spec") data apply to the final product.



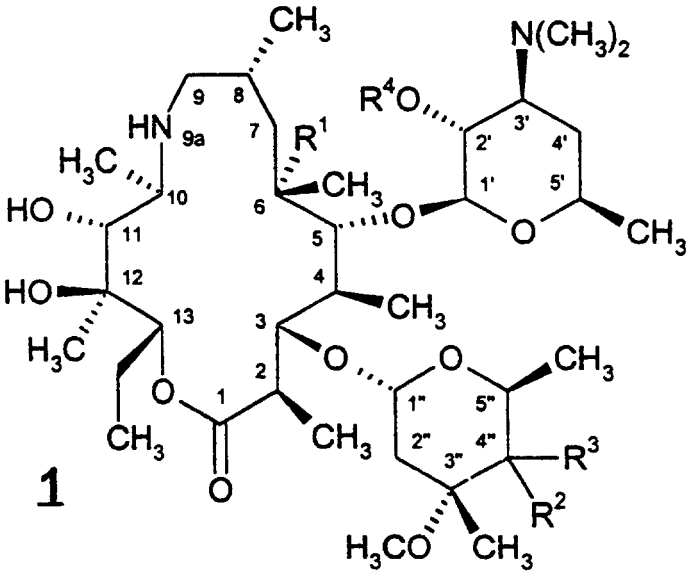
10

Example	R	Reaction Time (hours)	Yield (%)	Mass Spec
69	1-imidazolyl	72	60	816
70	n-propylamino	48	55	807
71	dimethylamino	24	42	793
72	methylamino	120	55	779
73	ethylamino	120	58	793
74	isopropylamino	48	44	806
75	isobutylamino	48	27	821
76	trimethyleneimino	24	31	804
77	allylamino	24	22	804
78	cyclopropylmethylamino	24	34	818
79	N-ethylmethylamino	48	16	820
80	t-butylamino	96	30	821
81	diethylamino	168	25	820
81(a)		48	75	818.5
81(b)		96	95	832.6
82	4-methoxybenzylamino	48	21.7	884.6
83	4-nitrobenzylamino	48	8	899.7
84	4-chlorobenzylamino	48	25.5	888.6
85	3,4-difluorobenzylamino	48	14.5	890.6

85	3-pyridylmethylamino	48	21.0	855.6
86	4-trifluoromethylbenzyl-amino	48	16.5	922.6
87	2,6-difluorobenzylamino	48	11.0	890.6
88	benzylamino	96	62	854.7
89	4-fluorobenzylamino	48	50.9	872.7
90	3-fluorobenzylamino	48	32.7	872.7
91	2-fluorobenzylamino	48	39.6	872.7
92	2,4-difluorobenzylamino	48	24.6	890.1
93	2,5-difluorobenzylamino	48	28.1	890.1
94	3,5-difluorobenzylamino	48	35.6	890.1
95	1-(4-fluorophenyl)piperazine	48	44.7	927.6
96	2-trifluoromethylbenzyl-amino	48	32.7	922.5
97	4-trifluoromethylbenzyl-amino	48	28.6	938.1
98	3-trifluoromethylbenzyl-amino	48	26.2	922.6
99	2-fluorophenylethylamino	48	33.5	886.2
100	3-fluorophenylethylamino	48	28.7	886.1
101	4-pyridylmethylamino	48	46	855.2
102	methyl,3-pyridylmethylamino	72	28.8	869.6
103	4-hydroxy-3-methoxybenzylamino	48	12.0	900.1
104	piperonylamino	48	14.0	898.1
105	3-methoxybenzylamino	48	33.0	884.1
106	2-methoxybenzylamino	48	24.0	884.5
107	2-pyridylmethylamino	48	28.9	855.1

Claims

1. A compound of the formula



1

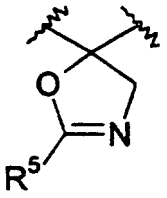
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, hydroxy or methoxy;

R^2 is hydroxy;

R^3 is C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, cyano, $-CH_2S(O)_nR^8$ wherein n is an integer ranging from 0 to 2, $-CH_2OR^8$, $-CH_2N(OR^9)R^8$, $-CH_2NR^8R^{15}$, $(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^3 groups are optionally substituted by 1 to 3 R^{16} groups;

or R^2 and R^3 are taken together to form an oxazolyl ring as shown below



R^4 is H, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^9R^{10}$ or a hydroxy protecting group;

R^5 is $-SR^8$, $-(CH_2)_nC(O)R^8$ wherein n is 0 or 1, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^5 groups are optionally substituted by 1 to 3 R^{16} groups;

each R^6 and R^7 is independently H, hydroxy, C_1-C_8 alkoxy, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $-(CH_2)_m$ (C_6-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

each R^8 is independently H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ wherein q and r are each independently an integer ranging from 0 to 3 except q and r are not both 0, $-(CH_2)_m(C_6$-C_{10} aryl), or $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^8 groups, except H, are optionally substituted by 1 to 3 R^{16} groups;

or where R^8 is as $-CH_2NR^8R^{15}$, R^{15} and R^8 may be taken together to form a 4-10 membered monocydic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $-N(R^8)$-, in addition to the nitrogen to which R^{15} and R^8 are attached, said saturated ring optionally includes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;

each R^9 and R^{10} is independently H or C_1-C_6 alkyl;

each R^{11}, R^{12}, R^{13} and R^{14} is independently selected from H, C_1-C_{10} alkyl, $-(CH_2)_m(C_6$-C_{10} aryl), and $-(CH_2)_m$ (5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein the foregoing R^{11}, R^{12},

R^{13} and R^{14} groups, except H, are optionally substituted by 1 to 3 R^{16} groups;
or R" and R^{13} are taken together to form $-(CH_2)_p-$ wherein p is an integer ranging from 0 to 3 such that a 4-7 membered saturated ring is formed that optionally includes 1 or 2 carbon-carbon double or triple bonds;
or R^{13} and R^{14} are taken together to form a 4-10 membered monocydic or polycyclic saturated ring or a 5-10 membered heteroaryl ring, wherein said saturated and heteroaryl rings optionally include 1 or 2 heteroatoms selected from O, S and $-N(R^8)-$, in addition to the nitrogen to which R^{13} and R^{14} are attached, said saturated ring optionally indudes 1 or 2 carbon-carbon double or triple bonds, and said saturated and heteroaryl rings are optionally substituted by 1 to 3 R^{16} groups;
R^{15} is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, or C_2-C_{10} alkynyl, wherein the foregoing R^{15} groups are optionally substituted by 1 to 3 substituents independently selected from halo and $-OR^9$;
each R^{16} is independently selected from halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-OC(O)OR^{17}$, $-NR^6C(O)R^7$, $C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, $-(CH_2)_m(C_6$-C_{10} aryl), and $(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4, and wherein said aryl and heteroaryl subsituents are optionally substituted by 1 or 2 substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, C_1-C_6 alkyl, and C_1-C_6 alkoxy;
each R^{17} is independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl,- $(CH_2)_m(C_6$-C_{10} aryl), and $-(CH_2)_m$(5-10 membered heteroaryl), wherein m is an integer ranging from 0 to 4;

with the proviso that R^8 is not H where R^3 is $-CH_2S(O)_nR^8$.

2. The compound of claim 1 wherein R^4 is H, acetyl, or benzyloxycarbonyl.

3. The compound of claim 2 wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$ or $-CH_2SR^8$.

4. The compound of claim 3 wherein R^3 is $-CH_2NR^{15}R^8$ and R^{15} and R^8 are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein the foregoing R^{15} and R^8 groups, except H, are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy.

5. The compound of claim 4 wherein R^{15} and R^8 are each independently selected from H, methyl, ethyl, allyl, n-butyl, isobutyl, 2-methoxyethyl, cyclopentyl, 3-methoxypropyl, 3-ethoxypropyl, n-propyl, isopropyl, 2-hydroxyethyl, cyclopropyl, 2,2,2-trifluoroethyl, 2-propynyl, *sec*-butyl, *tert*-butyl, and n-hexyl.

6. The compound of claim 2 wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NHR^8$, and R^8 is $-(CH_2)_m(C_6$-C_{10} aryl) wherein m is an integer ranging from 0 to 4.

7. The compound of claim 6 wherein R^8 is phenyl or benzyl.

8. The compound of claim 2 wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$, and R^{15} and R^8 are taken together to form a 4-10 membered saturated ring.

9. The compound of claim 8 wherein R^{15} and R^8 are taken together to form a piperidino, trimethyleneimino, or morpholino ring.

10. The compound of claim 2 wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2NR^{15}R^8$, and R^{15} and R^8 are taken together to form a 5-10 membered heteroaryl ring optionally substituted by 1 or 2 C_1-C_6 alkyl groups.

11. The compound of claim 10 wherein R^{15} and R^8 are taken together to form a pyrrolidino, triazolyl, or imidazolyl ring wherein said heteroaryl groups are optionally substituted by 1 or 2 methyl groups.

12. The compound of claim 2 wherein R^1 is hydroxy, R^2 is hydroxy, R^3 is $-CH_2SR^8$, and R^8 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^8 groups are optionally substituted by 1 or 2 substituents independently selected from hydroxy, halo and C_1-C_6 alkoxy.

13. The compound of claim 12 wherein R^8 is methyl, ethyl, or 2-hydroxyethyl.

14. The compound of daim 2 wherein R^1 is hydroxy, R^2 is hydroxy, and R^3 is selected from C_1-C_{10} alkyl, C_2-C_{10} alkenyl, and C_2-C_{10} alkynyl, wherein said R^3 groups are optionally substituted by 1 or 2 substituents independently selected

from hydroxy, -C(O)R^{17}, -NR^6R^7, halo, cyano, azido, 5-10 membered heteroaryl, and C_1-C_6 alkoxy.

15. The compound of claim 14 wherein R^3 is methyl, allyl, vinyl, ethynyl, 1-(methyl-1-propenyl, 3-methoxy-1-propynyl, 3-dimethylamino-1-propynyl, 2-pyridylethynyl, 1-propynyl, 3-hydroxy-1-propynyl, 3-hydroxy-1-propenyl, 3-hydroxy-propyl, 3-methoxy-1-propenyl, 3-methoxypropyl, 1-propynyl, n-butyl,ethyl, propyl, 2-hydroxyethyl, azidomethyl, formylmethyl, 6-cyano-1-pentynyl, 3-dimethylamino-1-propenyl, or 3-dimethylaminopropyl.

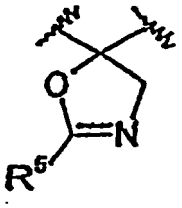
16. The compound of claim 2 wherein R^1 is hydroxy, R^2 is hydroxy, and R^3 is -$(CH_2)_m$(5-10 membered heteroaryl) wherein m is an integer ranging from 0 to 4.

17. The compound of claim 16 wherein R^3 is 2-thienyl, 2-pyridyl, 1-methyl-2-imidazolyl, 2-furyl, or 1-methyl-2-pyrrolyl.

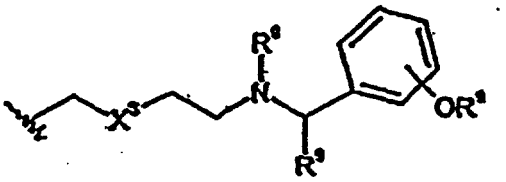
18. The compound of claim 2 wherein R^1 is hydroxy, R^2 is hydroxy, and R^3 is -$(CH_2)_m$(C_6-C_{10} aryl) wherein m is an integer ranging from 0 to 4.

19. The compound of claim 18 wherein R^3 is phenyl.

20. The compound of claim 2 wherein R^2 and R^3 are taken together to form an oxazolyl ring as shown below



21. The compound of claim 2 wherein R^3 is selected from the following:



wherein X^3 is O, S or -N(R^{15})-. R^9 and R^{15} are as defined in claim 1, and the -OR^9 group may be attached at any available carbon on the phenyl group.

22. 11-(4-Dimethylamino- 3-hydroxy- 6-methyl-tetrahydro-pyran- 2-yloxy)- 2-ethyl- 3,4,10-trihydroxy- 13-(5-hydroxy- 4-methoxy- 4,8-dimethy)- 5-propylaminomethy) -tetrahydro-pyran- 2-yloxy)- 3,5,8,10,12,14-hexamethyl- 1-oxa- 6-aza-cyclapentadecan-15-ore

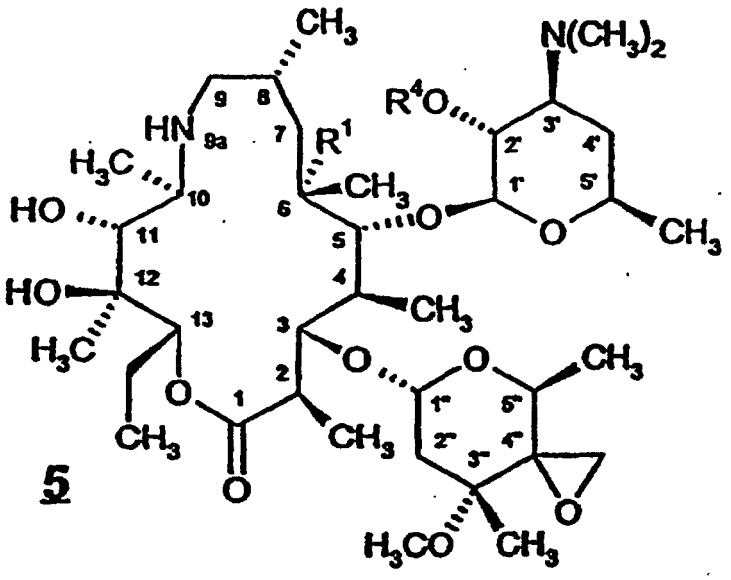
23. A compound as claimed in any of claims 1 to 22 for use as a medicament.

24. The use of a compound as claimed in any of claims 1 to 22 for the manufacture of a medicament for the treatment of a bacterial or protozoal infection in a mammal, fish or bird.

25. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 22 and a pharmaceutically acceptable carrier.

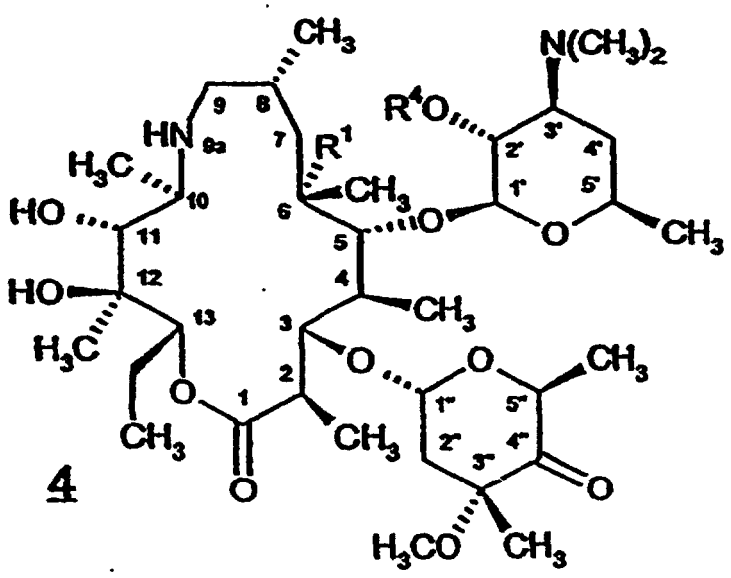
26. A composition as claimed in claim 25, wherein said composition is for the treatment of a bacterical or protozoal infection in a mammal, fish or bird.

27. A method of preparing a compound of the formula (1) as described in claim 1. which comprises treating a compound of the formula



wherein R^1 and R^4 are as defined above, with a compound of the formula HOR^8, HSR^8 or $HNR^{15}R^8$, wherein n, R^{15} and R^8 are as defined in claim 1, wherein if said compound of formula HSR^8 is used the resulting R^3 group of formula $-CH_2SR^8$ is optionally oxidised to $-CH_2S(O)R^8$ or $-CH_2S(O)_2R^8$.

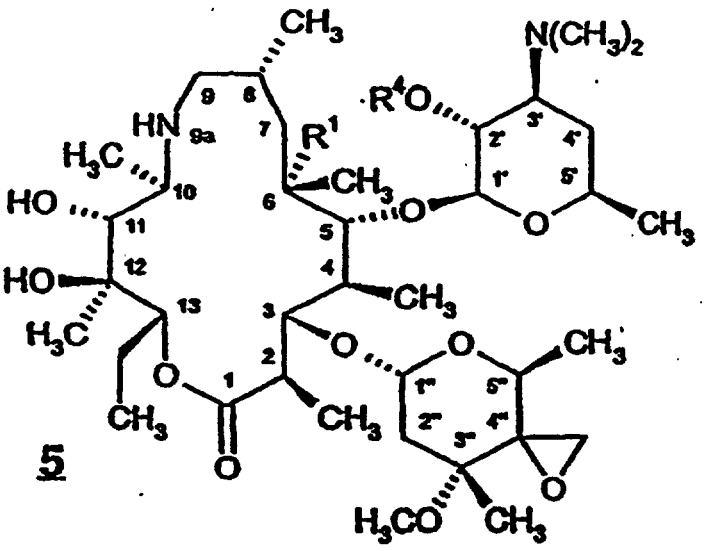
28. The method of claim 27 wherein the compound of formula 5 is separated by treating a compound of the formula



wherein R^1 and R^4 are as defined in **claim** 1, with $(CH_3)_3S(O)_nX^2$, wherein n is 0 or 1 and X^2 is halo, $-BF_4$ or $-PF_6$, in the presence of a base.

29. The method of claim 28 wherein X^2 is iodo or BF_4 and said base is selected from potassium tert-butoxide, sodium tert-butoxide, sodium ethoxide, sodium hydride, 1.1,3,3-tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicylo[4.3.0]non-5-ene, potassium hexamethyldisilazide (KHMDS), potassium ethoxide, and sodium methoxide.

30. A compound of the formula



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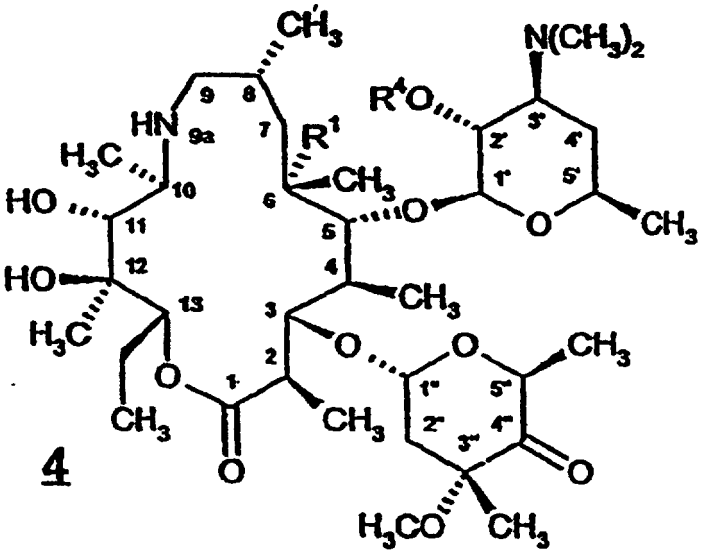
or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, hydroxy or methoxy; and,
R^4 is H, -C(O)R^9.-C(O)OR^9,-C(O)NR^9R^{10} or a hydroxy protecting group; and,
each R^9 and R^{10} is independently H or C_1-C_6 alkyl.

31. A compound of the formula

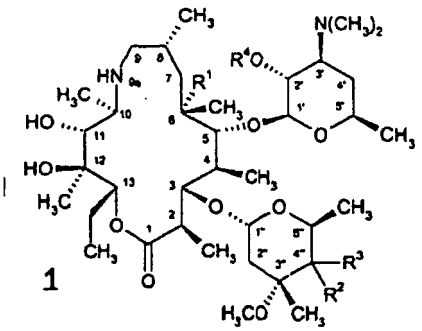


or a pharmaceutically acceptable salt thereof, wherein:

R^1 is H, hydroxy or methoxy; and,
R^4 is H, -C(O)R^9, -C(O)OR^9, -C(O)NR^9R^{10} or a hydroxy protecting group; and, each R^9 and R^{10} is independently H or C_1-C_6 alkyl.

Patentansprüche

1. Verbindung der Formel



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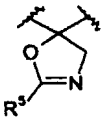
oder ein pharmazeutisch verträgliches Salz davon, worin: R^1 H, Hydroxy oder Methoxy darstellt; R^2 Hydroxy darstellt; R^3 C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl, C_2-C_{10}-Alkinyl, Cyano, $-CH_2S(O)_nR^8$, worin n eine ganze Zahl im Bereich von 0 bis 2 ist, $-CH_2OR^8$, $-CH_2N(OR^9)R^8$, $-CH_2NR^8R^{15}$, $-(CH_2)_m(C_6$-C_{10}-Aryl) oder $-(CH_2)_m$(5-10-gliedriges Heteroaryl), worin m eine ganze Zahl im Bereich von 0 bis 4 ist, darstellt und wobei die vorangehenden Gruppen R^3 gegebenenfalls mit 1 bis 3 Gruppen R^{16} substituiert sind; oder R^2 und R^3 zusammengenommen, einen wie nachstehend gezeigten Oxazolylring bilden,



R^4 H, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^9R^{10}$ oder eine Hydroxyschutzgruppe darstellt; R^5 $-SR^8$, $-(CH_2)_nC(O)R^8$, worin n 0 oder 1 ist, C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl, C_2-C_{10}-Alkinyl, $-(CH_2)_m(C_6$-C_{10}-Aryl) oder $-(CH_2)_m$(5-10-gliedriges Heteroaryl), worin m eine ganze Zahl im Bereich von 0 bis 4 ist, darstellt und worin die vorangehenden Gruppen R^5 gegebenenfalls mit 1 bis 3 Gruppen R^{16} substituiert sind; jedes R^6 und R^7 unabhängig H, Hydroxy, C_1-C_6-Alkoxy, C_1-C_6-Alkyl, C_2-C_6-Alkenyl, C_2-C_6-Alkinyl, $(CH_2)_m(C_6$-C_{10}-Aryl) oder $-(CH_2)_m$(5-10-gliedriges Heteroaryl), worin m eine ganze Zahl im Bereich von 0 bis 4 ist, darstellt; jedes R^8 unabhängig H, C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl, C_2-C_{10}-Alkinyl, $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$, worin q und r jeweils unabhängig eine ganze Zahl im Bereich von 0 bis 3 sind, mit der Ausnahme, dass q und r nicht beide 0 sind, $-(CH_2)_m(C_6$-C_{10}-Aryl) oder $-(CH_2)_m$(5-10-gliedriges Heteroaryl), worin m eine ganze Zahl im Bereich von 0 bis 4 ist, darstellt, und worin die vorangehenden Gruppen R^8, ausgenommen H, gegebenenfalls mit 1 bis 3 Gruppen R^{16} substituiert sind; oder worin R^8 wie $-CH_2NR^8R^{15}$ ist, R^{15} und R^8 zusammengenommen werden können, um einen 4-10-gliedrigen monocyclischen oder polycyclischen gesättigten Ring oder einen 5-10-gliedrigen Heteroarylring zu bilden, wobei die gesättigten und Heteroarylringe gegebenenfalls 1 oder 2 Heteroatome, ausgewählt aus O, S und $-N(R^8)$-, einschließen, zusätzlich zu dem Stickstoff, an den R^{15} und R^8 gebunden sind, der gesättigte Ring gegebenenfalls 1 oder 2 Kohlenstoff-Kohlenstoff-Doppel- oder -Dreifachbindungen einschließt und die gesättigten und Heteroarylringe gegebenenfalls mit 1 bis 3 Gruppen R^{16} substituiert sind; jedes R^9 und R^{10} unabhängig H oder C_1-C_6-Alkyl darstellt; jedes R^{11}, R^{12}, R^{13} und R^{14} unabhängig ausgewählt ist aus H, C_1-C_{10}-Alkyl, $-(CH_2)_m(C_6$-C_{10}-Aryl) und $-(CH_2)_m$(5-10-gliedrigem Heteroaryl), worin m eine ganze Zahl im Bereich von 0 bis 4 ist, und worin die vorangehenden Gruppen R^{11}, R^{12}, R^{13} und R^{14}, ausgenommen H, gegebenenfalls mit 1 bis 3 Gruppen R^{16} substituiert sind; oder R^{11} und R^{13} zusammengenommen werden, um $-(CH_2)_p$- zu bilden, worin p eine ganze Zahl im Bereich von 0 bis 3 ist, sodass ein 4-7-gliedriger gesättigter Ring gebildet wird, der gegebenenfalls 1 oder 2 Kohlenstoff Kohlenstoff Doppel- oder -Dreifachbindungen einschließt; oder R^{13} und R^{14} zusammengenommen werden, um einen 4-10-gliedrigen monocyclischen oder polycyclischen gesättigten Ring oder einen 5-10-gliedrigen Heteroarylring zu bilden, worin die gesättigten und Heteroarylringe gegebenenfalls 1 oder 2 Heteroatome, ausgewählt aus O, S und $-N(R^8)$-, zusätzlich zu dem Stickstoff, an den R^{13} und R^{14} gebunden sind, einschließen, wobei der gesättigte Ring gegebenenfalls 1 oder 2 Kohlenstoff-Kohlenstoff-Doppel- oder -Dreifachbindungen einschließt und die gesättigten und Heteroarylringe gegebenenfalls mit 1 bis 3 Gruppen R^{16} substituiert sind; R^{15} H, C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl oder C_2-C_{10}-Alkinyl darstellt, worin die vorangehenden Gruppen R^{15} gegebenenfalls mit 1 bis 3 Substituenten, unabhängig ausgewählt aus Halogen und $-OR^9$, substituiert sind; jedes R^{16} unabhängig ausgewählt ist aus Halogen, Cyano, Nitro, Trifluormethyl, Azido, $-C(O)R^{17}$,

-C(O)OR^{17}, -C(O)OR^{17}, -OC(O)OR^{17}, -NR^{6}C(O)R^7, -C(O)NR^{6}R^7, -NR^{6}R^7, Hydroxy, C_1-C_6-Alkyl, C_1-C_6-Alkoxy, $(CH_2)_m$(C_6-C_{10}-Aryl) und -$(CH_2)_m$(5-10-gliedrigem Heteroaryl), worin m eine ganze Zahl im Bereich von 0 bis 4 ist, und worin die Aryl- und Heteroarylsubstituenten gegebenenfalls mit 1 oder 2 Substituenten, unabhängig ausgewählt aus Halogen, Cyano, Nitro, Trifluormethyl, Azido, -C(O)R, -C(O)OR, -C(O)OR, -OC(O)OR^{17}, -NR^{6}C(O)R^7, -C(O)NR^{6}R^7, -NR^{6}R^7, Hydroxy, C_1-C_6-Alkyl und C_1-C_6-Alkoxy, substituiert sind; jedes R^{17} unabhängig ausgewählt ist aus H, C_1-C_{10}-Alkyl, C_2-C_{10}—Alkenyl, C_2-C_{10}-Alkinyl, $(CH_2)_m$(C_6-C_{10}-Aryl) und -$(CH_2)_m$(5-10-gliedrigem Heteroaryl), worin m eine ganze Zahl im Bereich von 0 bis 4 ist; mit der Maßgabe, dass R^8 nicht H darstellt, wenn R^3 -$CH_2S(O)_nR^8$ darstellt.

2. Verbindung nach Anspruch 1, worin R^4 H, Acetyl oder Benzyloxycarbonyl darstellt.

3. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt, R^3 -$CH_2NR^{15}R^8$ oder -CH_2SR^8 darstellt.

4. Verbindung nach Anspruch 3, worin R^3 -$CH_2NR^{15}R^8$ darstellt und R^{15} und R^8 unabhängig ausgewählt sind aus H, C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl und C_2-C_{10}-Alkinyl, worin die vorangehenden Gruppen R^{15} und R^8, ausgenommen H, gegebenenfalls mit 1 oder 2 Substituenten, unabhängig ausgewählt aus Hydroxy, Halogen und C_1-C_6-Alkoxy, substituiert sind.

5. Verbindung nach Anspruch 4, worin R^{15} und R^8 jeweils unabhängig ausgewählt sind aus H, Methyl, Ethyl, Allyl, n-Butyl, Isobutyl, 2-Methoxyethyl, Cyclopentyl, 3-Methoxypropyl, 3-Ethoxypropyl, n-Propyl, Isopropyl, 2-Hydroxyethyl, Cyclopropyl, 2,2,2-Trifluorethyl, 2-Propinyl, sec-Butyl, tert-Butyl und n-Hexyl.

6. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt, R^3 -CH_2NHR^8 darstellt und R^8 -$(CH_2)_m$(C_6-C_{10}-Aryl) darstellt, worin m eine ganze Zahl im Bereich von 0 bis 4 ist.

7. Verbindung nach Anspruch 6, worin R^8 Phenyl oder Benzyl darstellt.

8. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt, R^3 -$CH_2NR^{15}R^8$ darstellt und R^{15} und R^8 zusammengenommen werden, um einen 4-10-gliedrigen gesättigten Ring zu bilden.

9. Verbindung nach Anspruch 8, worin R^{15} und R^8 zusammengenommen werden, um einen Piperidino-, Trimethylenimino- oder Morpholinoring zu bilden.

10. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt, R^3 -$CH_2NR^{15}R^8$ darstellt und R^{15} und R^8 zusammengenommen werden, um einen 5-10-gliedrigen Heteroarylring, gegebenenfalls substituiert mit 1 oder 2 C_1-C_6-Alkylgruppen, zu bilden.

11. Verbindung nach Anspruch 10, worin R^{15} und R^8 zusammengenommen werden, um einen Pyrrolidino-, Triazolyl- oder Imidazolylring zu bilden, worin die Heteroarylgruppen gegebenenfalls mit 1 oder 2 Methylgruppen substituiert sind.

12. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt, R^3 -CH_2SR^8 darstellt und R^8 aus C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl und C_2-C_{10}-Alkinyl ausgewählt ist, worin die Gruppen R^8 gegebenenfalls mit 1 oder 2 Substituenten, unabhängig ausgewählt aus Hydroxy, Halogen und C_1-C_6-Alkoxy, substituiert sind.

13. Verbindung nach Anspruch 12, worin R^8 Methyl, Ethyl oder 2-Hydroxyethyl darstellt.

14. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt und R^3 ausgewählt ist aus C_1-C_{10}-Alkyl, C_2-C_{10}-Alkenyl und C_2-C_{10}-Alkinyl, worin die Gruppen R^3 gegebenenfalls mit 1 oder 2 Substituenten, unabhängig ausgewählt aus Hydroxy, -C(O)R^{17}, -NR^{6}R^7, Halogen, Cyano, Azido, 5-10-gliedrigem Heteroaryl und C_1-C_6-Alkoxy, substituiert sind.

15. Verbindung nach Anspruch 14, worin R^3 Methyl, Allyl, Vinyl, Ethinyl, 1-Methyl-1-propenyl, 3-Methoxy-1-propinyl, 3-Dimethylamino-1-propinyl, 2-Pyridylethinyl, 1-Propinyl, 3-Hydroxy-1-propinyl, 3-Hydroxy-1-propenyl, 3-Hydroxypropyl, 3-Methoxy-1-propenyl, 3-Methoxypropyl, 1-Propinyl, n-Butyl, Ethyl, Propyl, 2-Hydroxyethyl, Azidomethyl, Formylmethyl, 6-Cyano-1-pentinyl, 3-Dimethylamino-1-propenyl oder 3-Dimethylaminopropyl darstellt.

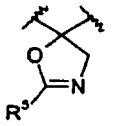
16. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt und R^3 $-(CH_2)_m$(5-10-gliedriges Heteroaryl) darstellt, worin m eine ganze Zahl im Bereich von 0 bis 4 ist.

17. Verbindung nach Anspruch 16, worin R^3 2-Thienyl, 2-Pyridyl, 1-Methyl-2-imidazolyl, 2-Furyl oder 1-Methyl-2-pyrrolyl darstellt.

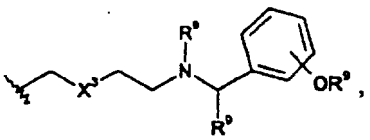
18. Verbindung nach Anspruch 2, worin R^1 Hydroxy darstellt, R^2 Hydroxy darstellt und R^3 $-(CH_2)_m(C_6\text{-}C_{10}$-Aryl) darstellt, worin m eine ganze Zahl im Bereich von 0 bis 4 ist.

19. Verbindung nach Anspruch 18, worin R^3 Phenyl darstellt.

20. Verbindung nach Anspruch 2, worin R^2 und R^3 zusammengenommen einen wie nachstehend gezeigten Oxazolylring bilden.



21. Verbindung nach Anspruch 2, worin R^3 ausgewählt ist aus dem Nachstehenden:



worin X^3 O, S oder $-N(R^{15})$- darstellt, R^9 und R^{15} wie in Anspruch 1 definiert sind und die Gruppe $-OR^9$ an jedes beliebige verfügbare Kohlenstoffatom an der Phenylgruppe gebunden sein kann.

22. 11-(4-Dimethylamino- 3-hydroxy- 6-methyl-tetrahydro-pyran- 2-yloxy)- 2-ethyl- 3,4,10-trihydroxy- 13-(5-hydroxy-4-methoxy-4,6-dimethyl-5-propylaminomethyl-tetrahydro-pyran-2-yloxy)-3,5,8,10,12,14-hexamethyl-1-oxa-6-aza-cyclapentadecan-15-or.

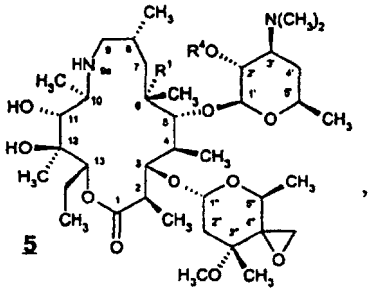
23. Verbindung nach einem der Ansprüche 1 bis 22 zur Verwendung als Arzneimittel.

24. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 22 zur Herstellung eines Arzneimittels für die Behandlung von bakterieller oder Protozoeninfektion bei einem Säuger, Fisch oder Vogel.

25. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der Ansprüche 1 bis 22 und einen pharmazeutisch verträglichen Träger.

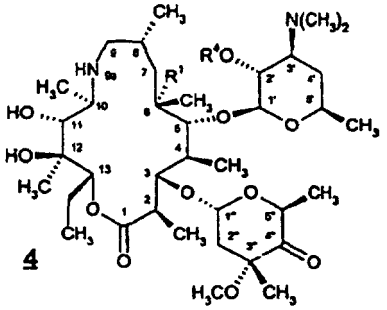
26. Zusammensetzung nach Anspruch 25, wobei die Zusammensetzung für die Behandlung einer bakteriellen oder Protozoeninfektion bei einem Säuger, Fisch oder Vogel vorgesehen ist.

27. Verfahren zur Herstellung einer Verbindung der Formel (1), wie in Anspruch 1 beschrieben, das Behandeln einer Verbindung der Formel



worin R^1 und R^4 wie vorstehend definiert sind, mit einer Verbindung der Formel HOR^8, HSR^8 oder $HNR^{15}R^8$, worin n, R^{15} und R^8 wie in Anspruch 1 definiert sind, wobei, wenn die Verbindung der Formel HSR^8 verwendet wird, die erhaltene Gruppe R^3 der Formel $-CH_2SR^8$ gegebenenfalls zu $-CH_2S(O)R^8$ oder $-CH_2S(O)_2R^8$ oxidiert wird, umfasst.

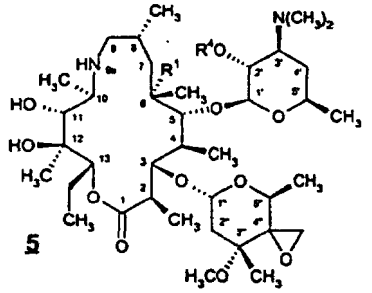
28. Verfahren nach Anspruch 27, wobei die Verbindung der Formel **5** durch Behandeln einer Verbindung der Formel



worin R^1 und R^4 wie in Anspruch 1 definiert sind, mit $(CH_3)_3S(O)_nX^2$, worin n 0 oder 1 ist und X^2 Halogen, $-BF_4$ oder $-PF_6$ darstellt, in Gegenwart einer Base hergestellt wird.

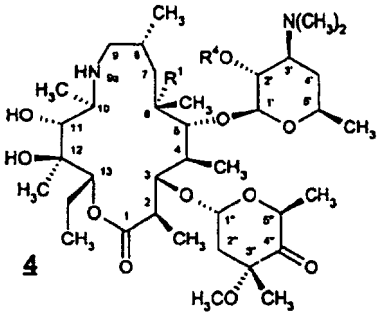
29. Verfahren nach Anspruch 28, wobei X^2 Jod oder BF_4 darstellt und die Base ausgewählt ist aus Kaliumtert-butoxid, Natrium-tert-butoxid, Natriumethoxid, Natriumhydrid, 1,1,3,3-Tetramethylguanidin, 1,8-Diazabicyclo[5.4.0]undec-7-en, 1,5-Diazabicyclo[4.3.0]non-5-en, Kaliumhexamethyldisilazid (KHMDS), Kaliumethoxid und Natriummethoxid.

30. Verbindung der Formel



oder ein pharmazeutisch verträgliches Salz davon, worin: R^1 H, Hydroxy oder Methoxy darstellt; und R^4 H, $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^9R^{10}$ oder eine Hydroxyschutzgruppe darstellt; und jedes R^9 und R^{10} unabhängig H oder C_1-C_6-Alkyl darstellt.

31. Verbindung der Formel



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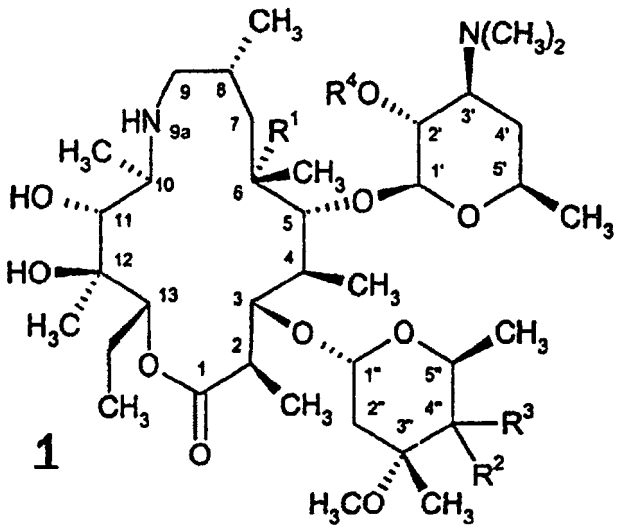
oder ein pharmazeutisch verträgliches Salz davon, worin: R^1 H, Hydroxy oder Methoxy darstellt; und R^4 H, -C(O) R^9, -C(O)OR^9, -C(O)NR^9R^{10} oder eine Hydroxyschutzgruppe darstellt; und jedes R^9 und R^{10} unabhängig H oder C_1-C_6-Alkyl darstellt.

Revendications

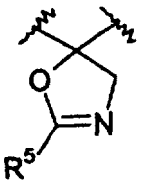
1. Composé de formule



1

ou un de ses sels pharmaceutiquement acceptables, formule dans laquelle :

R^1 représente H, un groupe hydroxy ou méthoxy ;
R^2 représente un groupe hydroxy ;
R^3 représente un groupe alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10}, alcynyle en C_2 à C_{10}, cyano, $-CH_2S(O)_nR^8$ dans lequel n représente un nombre entier de 0 à 2, $-CH_2OR^8$, $-CH_2N(OR^9)R^8$, $-CH_2NR^8R^{15}$, $(CH_2)_m$ (aryle en C_6 à C_{10}) ou $-(CH_2)_m$(hétéroaryle penta- à décagonal), dans lequel m représente un nombre entier de 0 à 4, les groupes R^3 précités étant facultativement substitués avec 1 à 3 groupes R^{16} ;
ou bien R^2 et R^3 sont pris conjointement pour former un noyau oxazolyle représenté ci-dessous



R^4 représente H, un groupe $-C(O)R^9$, $-C(O)OR^9$, $-C(O)NR^9R^{10}$ ou un groupe protecteur de la fonction hydroxy ;
R^5 représente un groupe $-SR^8$, $-(CH_2)_nC(O)R^8$ dans lequel n est égal à 0 ou 1, alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10}, alcynyle en C_2 à C_{10}, $-(CH_2)_m$(aryle en C_6 à C_{10}) ou $-(CH_2)_m$(hétéroaryle penta- à décagonal) dans lequel m représente un nombre entier de 0 à 4, les groupes R^5 précités étant facultativement substitués avec 1 à 3 groupes R^{16} ;
chacun des groupes R^6 et R^7 représente, indépendamment, H, un groupe hydroxy, alkoxy en C_1 à C_6, alkyle en C_1 à C_6, alcényle en C_2 à C_6, alcynyle en C_2 à C_6, $-(CH_2)_m$(aryle en C_6 à C_{10}) ou -(CH2)$_m$(hétéroaryle penta- à décagonal), dans lequel m représente un nombre entier de 0 à 4 ;
chaque groupe R^8 représente, indépendamment, H, un groupe alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10}, alcynyle en C_2 à C_{10}, $-(CH_2)_qCR^{11}R^{12}(CH_2)_rNR^{13}R^{14}$ dans lequel q et r représentent chacun, indépendamment, un nombre entier de 0 à 3, sauf que q et r ne sont pas l'un et l'autre égaux à 0, $-(CH_2)_m$(aryle en C_6 à C_{10}) ou $-(CH_2)_m$(hétéroaryle penta- à décagonal), dans lequel m représente un nombre entier de 0 à 4, les groupes R^8 précités, à l'exception de H, étant facultativement substitués avec 1 à 3 groupes R^{16} ;
ou bien, lorsque R^8 est sous forme d'un groupe $-CH_2NR^8R^{15}$, R^{15} et R^8 peuvent être pris conjointement pour former un noyau saturé monocyclique ou polycyclique tétra-à décagonal ou un noyau hétéroaryle penta- à décagonal, lesdits noyaux saturés et noyaux hétéroaryle comprenant facultativement 1 ou 2 hétéroatomes choisis entre O, S et $-N(R^8)-$, en plus de l'atome d'azote auquel R^{15} et R^8 sont fixés, ledit noyau saturé comprenant facultativement 1 ou 2 doubles ou triples liaisons carbone-carbone, et lesdits noyaux saturés et noyaux hétéroaryle étant facultativement substitués avec 1 à 3 groupes R^{16} ;
chacun des groupes R^9 et R^{10} représente, indépendamment, H ou un groupe alkyle en C_1 à C_6 ;
chacun des groupes R^{11}, R^{12}, R^{13} et R^{14} est choisi, indépendamment, entre H, des groupes alkyle en C_1 à C_{10}, $-(CH_2)_m$(aryle en C_6 à C_{10}) et $-(CH_2)$ m (hétéroaryle penta- à décagonal), dans lesquels m représente un nombre entier de 0 à 4, les groupes R^{11}, R^{12}, R^{13} et R^{14} précités, à l'exception de H, étant facultativement substitués avec 1 à 3 groupes R^{16} ;
ou bien R^{11} et R^{13} sont pris conjointement pour former un groupe $-(CH_2)_p-$ dans lequel p représente un nombre entier de 0 à 3 de manière à former un noyau saturé tétra-à heptagonal qui comprend facultativement 1 ou 2 doubles ou triples liaisons carbone-carbone ;
ou bien R^{13} et R^{14} sont pris conjointement pour former un noyau saturé monocyclique ou polycyclique tétra- à décagonal ou un noyau hétéroaryle penta- à décagonal, lesdits noyaux saturés et noyaux hétéroaryle comprenant facultativement 1 ou 2 hétéroatomes choisis entre O, S et $-N(R^8)-$, en plus de l'atome d'azote auquel R^{13} et R^{14} sont fixés, ledit noyau saturé comprenant facultativement 1 ou 2 doubles ou triples liaisons carbone-carbone, et lesdits noyaux saturés et noyaux hétéroaryle étant facultativemenet substitués avec 1 à 3 groupes R^{16} ;
R^{15} représente H, un groupe alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10} ou alcynyle en C_2 à C_{10}, les groupes R^{15} précités étant facultativement substitués avec 1 à 3 substituants choisis, indépendamment, entre des groupes halogéno et $-OR^9$;
chaque groupe R^{16} est choisi, indépendamment, entre des groupes halogéno, cyano, nitro, trifluorométhyle, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-OC(O)OR^{17}$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, alkyle en C_1 à C_6, alkoxy en C_1 à C_6, $-(CH_2)_m$(aryle en C_6 à C_{10}) et $-(CH_2)_m$ (hétéroaryle penta- à décagonal), dans lesquels m représente un nombre entier de 0 à 4, et dans lesquels lesdits substituants aryle et hétéroaryle sont facultativement substitués avec 1 ou 2 substituants choisis, indépendamment, entre des groupes halogéno, cyano, nitro, trifluorométhyle, azido, $-C(O)R^{17}$, $-C(O)OR^{17}$, $-C(O)OR^{17}$, $-OC(O)OR^{17}$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, hydroxy, alkyle en C_1 à C_6 et alkoxy en C_1 à C_6 ;
chaque groupe R^{17} est choisi, indépendamment, entre H, des groupes alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10}, alcynyle en C_2 à C_{10}, $-(CH_2)_m$(aryle en C_6 à C_{10}) et $-(CH_2)_m$(hétéroaryle penta- à décagonal), dans lesquels m représente un nombre entier de 0 à 4 ;
sous réserve que R^8 ne représente pas H lorsque R^3 représente un groupe $-CH_2S(O)_nR^8$.

2. Composé suivant la revendication 1, dans lequel R^4 représente H, un groupe acétyle ou benzyloxycarbonyle.

3. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy, R^3 représente un groupe $-CH_2NR^{15}R^8$ ou $-CH_2SR^8$.

4. Composé suivant la revendication 3, dans lequel R^3 représente un groupe $-CH_2NR^{15}R^8$ et R^{15} et R^8 sont choisis, indépendamment, entre H, des groupes alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10} et alcynyle en C_2 à C_{10}, les groupes R^{15} et R^8 précités, à l'exception de H, étant facultativement substitués avec 1 ou 2 substituants choisis, indépendamment, entre des groupes hydroxy, halogéno et alkoxy en C_1 à C_6.

5. Composé suivant la revendication 4, dans lequel R^{15} et R^8 sont choisis chacun, indépendamment, entre H, des groupes méthyle, éthyle, allyle, n-butyle, isobutyle, 2-méthoxyéthyle, cyclopentyle, 3-méthoxypropyle, 3-éthoxypropyle, n-propyle, isopropyle, 2-hydroxyéthyle, cyclopropyle, 2,2,2-trifluoréthyle, 2-propynyle, sec.-butyle, tertio-butyle et n-hexyle.

6. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy, R^3 représente un groupe $-CH_2NHR^8$ et R^8 représente un groupe- $(CH_2)_m$(aryle en C_6 à C_{10}) dans lequel m représente un nombre entier de 0 à 4.

7. Composé suivant la revendication 6, dans lequel R^8 représente un groupe phényle ou benzyle.

8. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy, R^3 représente un groupe $-CH_2NR^{15}R^8$, et R^{15} et R^8 sont pris conjointement pour former un noyau saturé tétra-à décagonal.

9. Composé suivant la revendication 8, dans lequel R^{15} et R^8 sont pris conjointement pour former un noyau pipéridino, triméthylène-imino ou morpholino.

10. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy, R^3 représente un groupe $-CH_2NR^{15}R^8$, et R^{15} et R^8 sont pris conjointement pour former un noyau hétéroaryle penta- à décagonal facultativement substitué avec 1 ou 2 groupes alkyle en C_1 à C_6.

11. Composé suivant la revendication 10, dans lequel R^{15} et R^8 sont pris conjointement pour former un noyau pyrrolidino, triazolyle ou imidazolyle, lesdits groupes hétéroaryle étant facultativement substitués avec 1 ou 2 groupes méthyle.

12. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy, R^3 représente un groupe $-CH_2SR^8$, et R^8 est choisi entre des groupes alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10} et alcynyle en C_2 à C_{10}, lesdits groupes R^8 étant facultativement substitués avec 1 ou 2 substituants choisis, indépendamment, entre des groupes hydroxy, halogéno et alkoxy en C_1 à C_6.

13. Composé suivant la revendication 12, dans lequel R^8 représente un groupe méthyle, éthyle ou 2-hydroxyéthyle.

14. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy et R^3 est choisi entre des groupes alkyle en C_1 à C_{10}, alcényle en C_2 à C_{10} et alcynyle en C_2 à C_{10}, lesdits groupes R^3 étant facultativement substitués avec 1 ou 2 substituants choisis, indépendamment, entre des groupes hydroxy, $-C(O)R^{17}$, $-NR^6R^7$, halogéno, cyano, azido, hétéroaryle penta- à décagonal et alkoxy en C_1 à C_6.

15. Composé suivant la revendication 14, dans lequel R^3 représente un groupe méthyle, allyle, vinyle, éthynyle, -méthyl-1-propényle, 3-méthoxy-1-propynyle, 3-diméthylamino-1-propynyle, 2-pyridyléthynyle, 1-propynyle, 3-hydroxy-1-propynyle, 3-hydroxy-1-propényle, 3-hydroxypropyle, 3-méthoxy-1-propényle, 3-méthoxypropyle, 1-propynyle, n-butyle, éthyle, propyle, 2-hydroxyéthyle, azidométhyle, formylméthyle, 6-cyano-1-pentynyle, 3-diméthylamino-1-propényle ou 3-diméthylaminopropyle.

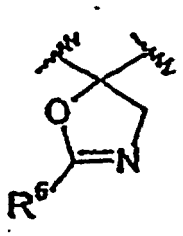
16. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy et R^3 représente un groupe $-(CH_2)_m$(hétéroaryle penta- à décagonal) dans lequel m représente un nombre entier de 0 à 4.

17. Composé suivant la revendication 16, dans lequel R^3 représente un groupe 2-thiényle, 2-pyridyle, 1-méthyl-2-imidazolyle, 2-furyle ou 1-méthyl-2-pyrrolyle.

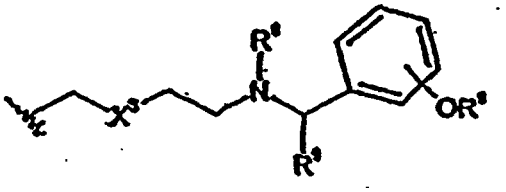
18. Composé suivant la revendication 2, dans lequel R^1 représente un groupe hydroxy, R^2 représente un groupe hydroxy et R^3 représente un groupe $-(CH_2)_m$(aryle en C_6 à C_{10}) dans lequel m représente un nombre entier de 0 à 4.

19. Composé suivant la revendication 18, dans lequel R^3 représente un groupe phényle.

20. Composé suivant la revendication 2, dans lequel R^2 et R^3 sont pris conjointement pour former un noyau oxazolyle représenté ci-dessous



21. Composé suivant la revendication 2, dans lequel R^3 est choisi parmi les groupes suivants :



dans lesquels X^3 représente O, S ou un groupe $-N(R^{15})-$, R^9 et R^{15} répondent aux définitions suivant la revendication 1 et le groupe $-OR^9$ peut être fixé à n'importe quel atome de carbone disponible sur le groupe phényle.

22. La 11-(4-diméthylamino-3-hydroxy-6-méthyltétrahydropyranne-2-yloxy)-2-éthyl-3,4,10-trihydroxy-13-(5-hydroxy-4-méthoxy- 4,6-diméthyl- 5-propylaminométhyltétrahydropyranne- 2-yloxy)- 3,5,8,10,12,14-hexaméthyl- 1-oxa-6-aza-cyclapentadécane-15-one.

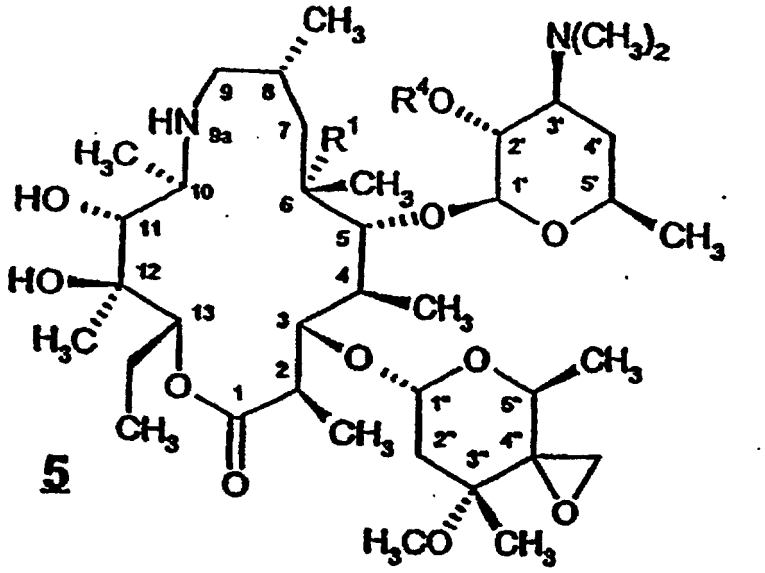
23. Composé suivant l'une quelconque des revendications 1 à 22, destiné à être utilisé comme médicament.

24. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 22 pour la production d'un médicament destiné au traitement d'une infection par des bactéries ou protozoaires chez un mammifère, un poisson ou un oiseau.

25. Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 1 à 22 et un support pharmaceutiquement acceptable.

26. Composition suivant la revendication 25, qui est destinée au traitement d'une infection par des bactéries ou protozoaires chez un mammifère, un poisson ou un oiseau.

27. Procédé pour la préparation d'un composé de formule (1) tel que décrit dans la revendication 1, qui comprend le traitement d'un composé de formule



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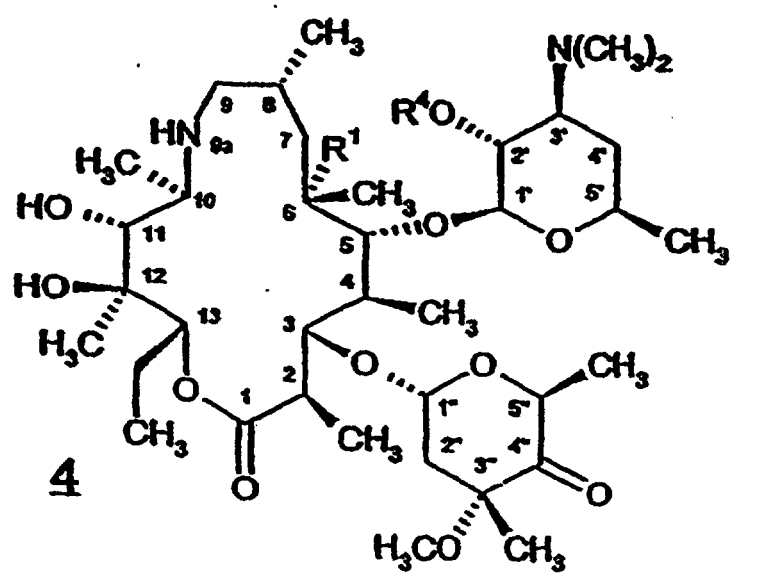
dans laquelle R^1 et R^4 répondent aux définitions précitées, avec un composé de formule HOR^8, HSR^8 ou $HNR^{15}R^8$, dans laquelle n, R^{15} et R^8 répondent aux définitions suivant la revendication 1, dans lequel, si. ledit composé de formule HSR^8 est utilisé, le groupe R^3 résultant de formule $-CH_2SR^8$ est facultativement oxydé en un groupe $-CH_2S(O)R^8$ ou - $CH_2S(O)_2R^8$.

28. Procédé suivant la revendication 27, dans lequel le composé de formule 5 est préparé en traitant un composé de formule



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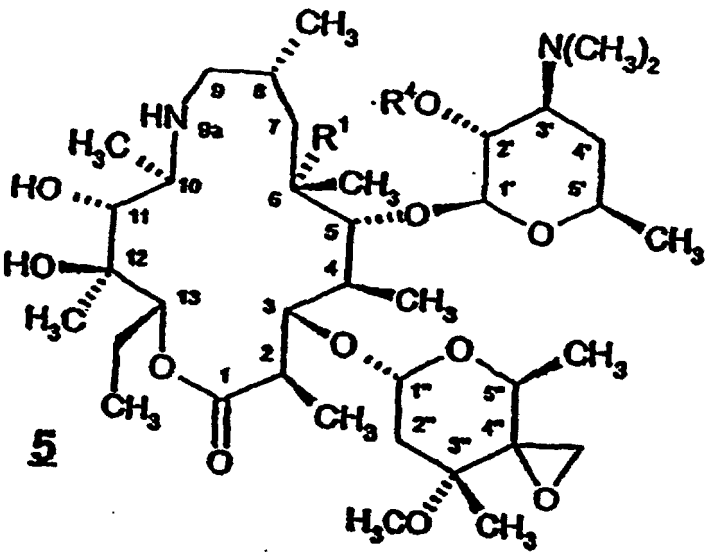
dans laquelle R^1 et R^4 répondent aux définitions suivant la revendication 1, avec un composé de formule $(CH_3)_3(O)_nX^2$, dans laquelle n est égal à 0 ou 1 et X^2 représente un groupe halogéno, $-BF_4$ ou $-PF_6$, en présence d'une base.

29. Procédé suivant la revendication 28, dans lequel X^2 représente un groupe iodo ou BF_4 et ladite base est choisie entre le tertio-butylate de potassium, le tertio-butylate de sodium, l'éthylate de sodium, l'hydrure de sodium, la 1,1,3,3-tétraméthylguanidine, le 1,8-diazabicyclo[5.4.0]undéc-7-ène, le 1,5-diazabicyclo[4.3.0]non-5-ène, l'hexa-

méthyldisilazoture de potassium (KHMDS), l'éthylate de potassium et le méthylate de sodium.

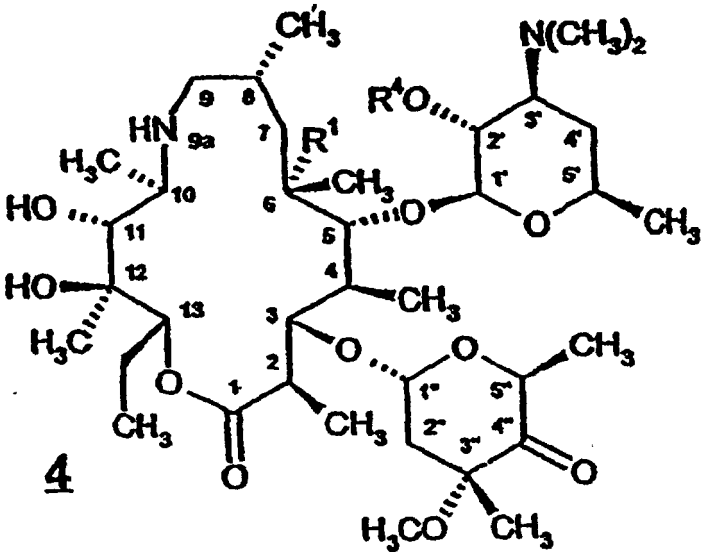
30. Composé de formule



ou un de ses sels pharmaceutiquement acceptables, formule dans laquelle :

R^1 représente H, un groupe hydroxy ou méthoxy ; et
R^4 représente H, un groupe -C(O)R^9, -C(O)OR^9, -C(O)NR^9R^{10} ou un groupe protecteur de la fonction hydroxy ; et
chacun des groupes R^9 et R^{10} représente, indépendamment, H ou un groupe alkyle en C_1 à C_6.

31. Composé de formule



ou un de ses sels pharmaceutiquement acceptables, formule dans laquelle :

R^1 représente H, un groupe hydroxy ou méthoxy ; et
R^4 représente H, un groupe -C(O)R^9, -C(O)OR^9, - C(O)NR^9R^{10} ou un groupe protecteur de la fonction hydroxy ;

et
chacun des groupes R^9 et R^{10} représente, indépendamment, H ou un groupe alkyle en C_1 à C_6.