Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
The present invention relates to novel compounds, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medical therapy, particularly antibacterial therapy.

Pleuromutilin, the compound of formula (A), is a naturally occurring antibiotic which has antmycoplasmal activity and modest antibacterial activity. It has been shown that the antimicrobial activity can be improved by replacing the glycolic ester moiety at position 14 by an R-X-CH₂-CO₂- group, where R is an aliphatic or aromatic moiety and X is O, S, or NR'. (H Egger and H Reinshagen, J Antibiotics, 1976, 29, 923). Tiamulin, the compound of formula (B), which is used as a veterinary antibiotic, is a derivative of this type (G Hogenauer in Antibiotics, Vol. V, part 1, ed. F E Hahn, Springer-Verlag, 1979, p.344).

In this application, the non-conventional numbering system which is generally used in the literature (G Hogenauer, loc.cit.) is used.

WO 97/25309 (SmithKline Beecham) describes further modification of the acyloxy group, disclosing 14-O-cabamoyl derivatives of mutilin or 19, 20-dihydromutilin, in which the N-atom of the carbamoyl group is unsubstituted, mono- or di-substituted.

WO 98/05659 (SmithKline Beecham) discloses 14-O-cabamoyl derivatives of mutilin or 19, 20-dihydromutilin, in which the N-atom of the carbamoyl group is acylated by a group which includes an azacyclic moiety.

WO 98/14189 (SmithKline Beecham, International Publication Date 9 April 1998) discloses the use of the topical antibacterial agent mupirocin for treating bacterial infections associated with the colonisation of the nasopharynx by pathogenic organisms, in particular, the prophylactic treatment of recurrent sinusitis and recurrent otitis media, especially with novel spray or cream formulations adpated for administration to the nasopharynx. In addition, Nsouli (Annals of Allergy, Asthma and Immunology, January 1996, 76(1), 117) has described a clinical study involving the use of a 0.2% aqueous solution of mupirocin in reducing the attacks of sinusitis.

US 4 060 542 describes 14-desoxy-14-thiocyanatoacetoxy-mutilin and its use as an animal feed additive to increase meat production and as an antibiotic in veterinary medicine.

GB 2 025 930 describes a process for producing pleuromutilin derivatives having a side-chain at the C14-position of the form -OCOCH₂-S-(CH₂)ₙ-NR₂R₃ wherein n is 2, 3, 4 or 5, and R₂ and R₃ are C₁-₄ alkyl or R₂ and R₃ together with the nitrogen atom to which they are attached form a heterocyclic ring optionally containing a second heteroatom selected from oxygen, sulfur or =N-R₅, in which R₅ is C₁-₄ alkyl.

EP 0 013 768 describes pleuromutilin derivatives having a side chain at the C14-position of the form -OCOCH₂S(CH₃)ₘ-R₂ in which m is 0 or 1 and R₂ is a heterocyclic radical in which a 5- or 6-membered unsaturated or saturated heterocyclic ring containing one or more heteroatoms selected from oxygen, sulfur and nitrogen is attached to the -S(CH₃)ₘ group, provided that when m is 0, R₂ is other than pyridyl.

EP 0 013 768 describes pleuromutilin derivatives having a side chain at the C14-position of the form -COCH₂SC(CH₃)₂CH₂NHCOR₂ wherein R₂ is an amino alkyl group or a five membered saturated heterocycle.

We have now found that further novel pleuromutilin derivatives have improved antimicrobial properties.

Accordingly, the present invention provides a compound of general formula (IA) or (IB):

\[
\begin{align*}
\text{(A)} & \quad \text{(B)} \\
\end{align*}
\]
in which:

\[ R_1 \text{ is vinyl or ethyl; } \]

\[ R_2 \text{ is a non-aromatic bicyclic group containing from 5 to 10 ring atoms in each ring, which group contains one or two basic nitrogen atoms, is attached through a ring carbon atom and is optionally substituted by up to 3 substituents selected from alkyl, alkoxy, alkenyl and alkenyloxy, which are optionally further substituted by one or more groups selected from aryl, heterocyclyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, aryloxy, (C_{1-6})alkylthio, amino, mono- or di-(C_{1-6})alkylamino, cycloalkyl, cycloalkenyl, carboxy and esters thereof, amides of carboxy, ureido, carbamimidoyl (amidino), guanidino, alkyl-sulfonfyl, amino-sulfonfyl (C_{1-6})acyloxy, (C_{1-6})acylamino, azido, hydroxy, and halogen; each of n and m is independently 0, 1 or 2; } \]

\[ X \text{ is selected from } -O-, -S-, -S(O)-, -SO_2-, -CO.O-, -NH-, -CONH-, -NHCONH- \text{ and a bond; and } \]

\[ R_3 \text{ is H or OH; or } \]

the moiety \( R^2(CH_2)_m X(CH_2)_n CH_2 COO \) at position 14 of (IA) or (IB) is replaced by \( R^a R^b C=CHCOO \) in which one of \( R^a \) and \( R^b \) is hydrogen and the other is \( R^2 \) or \( R^a \) and \( R^b \) together form \( R^2 \); or

a pharmaceutically acceptable salt thereof.

[0013] \( R^2 \) is bicyclic, contains from 5 to 10 ring atoms in each ring, and is optionally substituted by up to 3 substituents selected from alkyl, alkoxy, alkenyl and alkenyloxy, each of which may be carried by either a bridgehead or a non-bridgehead carbon atom. In addition, the or each nitrogen atom may be substituted by oxygen, to form an N-oxide, or by mono- or dialkyl, in which case it will be appreciated that a quaternary cation can be formed. The counterion may be a halide ion such as chloride or bromide, preferably chloride. The aza ring system additionally may contain one or more double bonds.

[0014] Representative bicyclic and monocyclic groups for \( R^2 \) include piperidinyl, pyrrolidyl, quinuclidinyl, azabicyclo[2.2.1]heptyl, azabicyclo[4.3.0]nonyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.0]octyl, azabicyclo[2.2.2]octyl, azabicyclo[3.2.1]octenyl, azabicyclo[3.3.1]nonyl and azabicyclo[4.4.0]decyl, all of which may be substituted or unsubstituted. Preferred examples for \( R^2 \) include quinuclidinyl.
The compounds of formula (IA) in which R^3 is hydroxy have the (2S) configuration at the carbon bearing this hydroxy group.

Preferably, n is 0. Preferably, m is 0 or 1.

Preferred compounds are those of formula (IA).

Alkyl and alkenyl groups referred to herein include straight and branched groups containing up to six carbon atoms and are optionally substituted by one or more groups selected from the group consisting of ary1, heterocyclyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, ary1(C_{1-6})alkoxy, ary1(C_{1-6})alkylthio, amino, mono- or di-(C_{1-6})alkylamino, cycloalkyl, cycloalkenyl, carboxy and esters thereof, amides of carboxy, ureido, carbamimidoyl (amidino), guanidino, alkyl-sulfonyl, amino-sulfonyl (C_{1-6})acyloy, (C_{1-6})acylamino, azido, hydroxy, and halogen.

Suitably any aryl group, including phenyl and naphthyl, may be optionally substituted by up to five, preferably up to three substituents. Suitable substituents include halogen, (C_{1-6})alkyl, ary1, ary1(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, hydroxy, nitro, cyan, azido, amino, mono- and di-N-(C_{1-6})alkylamino, no, acylamino, arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkoxy carbonyl, ary1oxy carbonyl, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkyl sulphynil, (C_{1-6})alkysulphonyl, heterocyclyl and heterocyclyl (C_{1-6})alkyl. In addition, two adjacent ring carbon atoms may be linked by a (C_{3-5})alkylene chain, to form a carbocyclic ring.

When used herein, the term "aryl" means single and fused rings suitably containing from 4 to 7, preferably 5 or 6, ring atoms in each ring, which rings may each be unsubstituted or substituted by, for example, up to three substituents. A fused ring system may include aliphatic rings and need include only one aromatic ring. Representative aryl groups include phenyl and naphthyl such as 1-naphthyl or 2-naphthyl.

Suitably any aryl group, including phenyl and naphthyl, may be optionally substituted by up to five, preferably up to three substituents. Suitable substituents include halogen, (C_{1-6})alkyl, ary1, ary1(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, hydroxy, nitro, cyan, azido, amino, mono- and di-N-(C_{1-6})alkylamino, no, acylamino, arylcarbonylamino, acyloxy, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkoxy carbonyl, ary1oxy carbonyl, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkyl sulphynil, (C_{1-6})alkysulphonyl, heterocyclyl and heterocyclyl (C_{1-6})alkyl. In addition, two adjacent ring carbon atoms may be linked by a (C_{3-5})alkylene chain, to form a carbocyclic ring.

When used herein the terms "heterocyclyl" and "heterocyclic" suitably include, unless otherwise defined, aromatic and non-aromatic, single and fused, rings suitably containing up to four heteroatoms in each ring, each of which is selected from oxygen, nitrogen and sulphur, which rings, may be unsubstituted or substituted by, for example, up to three substituents. Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Preferably substituents for a heterocyclyl group are selected from halogen, (C_{1-6})alkyl, ary1(C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{1-6})alkylthio, hydroxy, amino, mono- and di-N-(C_{1-6})alkylamino, acylamino, carboxy, carboxy salts, carboxy esters, carbamoyl, mono- and di-N-(C_{1-6})alkylcarbamoyl, (C_{1-6})alkoxy carbonyl, ary1oxy carbonyl, ureido, guanidino, sulphonylamino, aminosulphonyl, (C_{1-6})alkylthio, (C_{1-6})alkyl sulphynil, (C_{1-6})alkysulphonyl, heterocyclyl and heterocyclyl (C_{1-6})alkyl. In that situation the present invention includes the individual diastereoisomers and mixtures thereof.

Preferred examples of compounds of the invention include:

- Mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate;
- Mutilin 14-(quinuclid-4-ynethylsulfanyl)-acetate; and
- Mutilin 14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)-acetate.

The compounds of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be solvated, especially hydrated. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

The compounds according to the invention are suitably provided in substantially pure form, for example, at least 50% pure, suitable at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated as weight/weight.

The compounds of the invention may be in the form of free bases or acid addition salts. Compounds carrying a carboxy substituent may be in the form of zwitterions, or alkali metal salts (of the carboxy group). pharmaceutically acceptable salts are preferred.

Pharmaceutically acceptable acid-addition salts include those described by Berge, Bighley, and Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. Suitable salts include the hydrochloride, maleate, and methanesulphonate; particularly the hydrochloride.

Compounds of the present invention may be readily prepared from available starting materials by adapting synthetic processes well known in the art.

According to the present invention there is provided a process for preparing a compound according to the invention, or a pharmaceutically acceptable salt thereof, which comprises:

(a) coupling mutilin or epi-mutilin having a protected hydroxy group at position 11, with an active derivative, such
According to the present invention there is also provided a process for preparing a compound according to (b) above in which

(a) when X is O, S or NH, R^L is a leaving group and is reacted with

(i) the alcohol R^2-(CH\textsubscript{2})\textsuperscript{m}-OH;
(ii) the thiol R^2-(CH\textsubscript{2})\textsuperscript{m}-SH;
(iii) the amine R^2-(CH\textsubscript{2})\textsuperscript{m}-NH\textsubscript{2}.

(b) when X is CONH, R^L is amino and is reacted with the acid R^2A-(CH\textsubscript{2})\textsuperscript{m}-CO\textsubscript{2}H, or an acylating agent derived therefrom;
and
(c) when X is CO.O, R^L is hydroxy and is reacted with an acylating agent derived from the acid R^2A-(CH\textsubscript{2})\textsuperscript{m}-CO\textsubscript{2}H.

Accordingly, in a first aspect, the present invention provides a process for preparing a compound of formula (I) which comprises reacting a compound of formula (IIA) or (IIB):

\begin{align*}
\text{in which Y is hydrogen or a removable hydroxy-protecting group, and R}^{1A} \text{ and R}^{3A} \text{ are as defined for formulae (IA) and (IB) or groups convertible to R}^1 \text{ and R}^3, \\
\text{with an active derivative of a carboxylic acid of formula (III)}:
\end{align*}

\[ R^{2A}-(CH\textsubscript{2})\textsuperscript{m}-X-(CH\textsubscript{2})\textsuperscript{n}-CH\textsubscript{2}CO\textsubscript{2}H \] (III)

where R^2A is R^2 as defined for formulae IA and IB or a group convertible to R^2, under ester forming conditions and, where required or desired,

converting Y to hydrogen,

converting an R^{1A}, R^{2A} or R^{3A} group to a R^1, R^2 or R^3 group, and/or converting one R^1, R^2 or R^3 group to another R^1, R^2 or R^3 group.

Conventional methods for ester formation are described in the literature, for example in "Comprehensive Organic Functional Group Transformations", Vol. 5, ed. C J Moody, p. 123-130, Elsevier Scientific, Oxford, 1995. The active derivative used as an acylating agent may be for example an acid chloride, acid bromide, a mixed anhydride,
or an N-acyl-imidazole. The preferred agent is an acid chloride. General methods for forming such acylating agents are described in the chemical literature (see I O Sutherland, Comprehensive Organic Chemistry, Vol. 2, ed. I O Sutherland, pages 875-883 (Pergamon Press, Oxford, 1979), and references therein).

[0035] The ester-forming reaction can be carried out in the presence of an organic base, an inorganic base, or an acid. Organic bases include pyridine, 2,6-lutidine, triethylamine, and N,N-dimethylaniline. Inorganic bases include sodium hydride, lithium hydride, potassium carbonate, lithium hexamethyldisilazide, and sodium hexamethyldisilazide. Acids include p-toluenesulphonic acid, benzene sulphonic acid, and sulphuric acid. Optionally, when the reaction is carried out in the presence of a base, an acylation catalyst (G Hofle and W Steglich, Synthesis, 1972, 619) such as 4-dimethylamino-pyridine or 4-pyrrolidino-pyridine may also be added to the reaction mixture. Solvents for the ester forming reaction include tetrahydrofuran, 1,4-dioxane, acetonitrile, NN-dimethylformamide, diethyl ether, dichloromethane, and chloroform. A preferred solvent is tetrahydrofuran.

[0036] Useful methods for acylating the 14-hydroxyl in the present invention include the use of the following: acid chloride in N,N-dimethylformamide at elevated temperature (e.g. 100°C to 120°C); acid chloride in the presence of an organic base (e.g. pyridine, 2,6-lutidine, 2,4,6-collidine, di-iso-propylethylamine) or an inorganic base (e.g. sodium or lithium hexamethyldisilazide); carboxylic acid in the presence of dicyclohexylcarbodiimide and an acylation catalyst (e.g. 4-dimethylamino-pyridine, 4-pyrrolidino-pyridine); a mutilin 14-chloroformate derivative plus carboxylic acid, tertiary base (e.g. triethylamine, di-isopropyl-ethylamine), and an acylation catalyst (e.g. 4-dimethylamino-pyridine, 4-pyrrolidino-pyridine).

[0037] Conversions of an R1A, R2A or R3A group to a R1, R2 or R3 group typically arise when a protecting group is needed during the above coupling reaction or during the preparation of the reactants by the procedures described below. Interconversion of one R1, R2 or R3 group to another typically arises when one compound of formula IA/B is used as the immediate precursor of another compound of formula IA/B or when it is easier to introduce a more complex or reactive substituent at the end of a synthetic sequence.

[0038] Preferably Y is a hydroxyl protecting group such as an acyl group, for example so that -OY is trifluoroacetyl or dichloroacetyl. When the intended R3 is also hydroxyl, then R3A is also preferably acyloxy, for example acetyl or dichloroacetyl. Hydroxyl groups at positions 11 and 2 (as groups OY and R3A) may be protected using, for example, dichloroacetic anhydride and pyridine in tetrahydrofuran or N-trifluoroacetyl-imidazole in tetrahydrofuran at 0°C. After the reaction with the derivative of acid III is complete the protecting acyl groups may be removed to restore the hydroxyl groups by hydrolysis e.g. using NaOH in MeOH.

[0039] It may also be necessary to protect substituent groups in the acid component (III) prior to reaction with the the compound of formulae (IIA) or (IIIB), for example protecting N atoms with alkoxy carbonyl, for example t-butoxycarbonyl.

[0040] Suitable hydroxy, carboxy and amino protecting groups are those well known in the art and which may be removed under conventional conditions and without disrupting the remainder of the molecule. A comprehensive discussion of the ways in which hydroxy, carboxy and amino groups may be protected and methods for cleaving the resulting protected derivatives is given in for example "Protective Groups in Organic Chemistry" (T.W. Greene, Wiley-Interscience, New York, 2nd edition, 1991). Particularly suitable hydroxy protecting groups include, for example, triorganosilyl groups such as, for instance, trimethylsilyl and also organocarbonyl and organooxycarbonyl groups such as, for instance, acetyl, allyloxy carbonyl, 4-methoxybenzoylcarbonyl and 4-nitrobenzoylcarbonyl. Particularly suitable carboxy protecting groups include alkyl and aryl groups, for instance methyl, ethyl and phenyl. Particularly suitable amino protecting groups include alkoxy carbonyl, 4-methoxybenzoylcarbonyl and 4-nitrobenzoylcarbonyl.

[0041] R1A is typically the R1 group vinyl, and this may be converted to the alternative R1 ethyl group by hydrogenating the vinyl group to form an ethyl group, typically by hydrogenation over a palladium catalyst (e.g. 10% palladium-on-carbon) in a solvent such as ethyl acetate, ethanol, dioxane, or tetrahydrofuran.

[0042] R3A is typically hydrogen or protected hydroxyl, such as acyloxy. After the coupling reaction, protecting acyl groups may be removed to restore the hydroxyl groups by hydrolysis e.g. using NaOH in MeOH.

[0043] Alternatively a compound of formula (IA) in which R3 is hydrogen may be prepared by treating a compound of formula (IIC):
where $R_{1A}$ is as defined for formulae (IIA) and (IIB),
with an active derivative of the acid of formula (III) under ester forming conditions, and
then treating the product with an acid, and, where required or desired, converting an $R_{1A}$ or $R_{2A}$ group to a $R_1$ or $R_2$
group, and/or converting one $R_1$ or $R_2$ group to another $R_1$ or $R_2$ group.

The acid treatment indicated above converts the epi-mutilin configuration of formula (IIC) to the usual mutilin
nucleus of formula (IIA). Typically this conversion is carried out by treatment with conc. HCl or Lukas reagent (conc.
HCl saturated with $ZnCl_2$) in dioxane.

As in formulae (IIA) and (IIB), $R_{2A}$ is typically the $R_2$ group vinyl, and this may be converted to the alternative
$R_2$ group by hydrogenating the vinyl group to form an ethyl group. Also it may again be necessary to protect substituent
groups in the derivative of acid component (III) prior to reaction, for example protecting N atoms with, for example, t-
butoxycarbonyl

In cases where the intermediate of formula (IIA) and (IIB) (such as $Y=acetyl$) are used, a base-labile protecting
group may conveniently be removed at the same time as the group $Y$ is deprotected. In cases when the intermediate
formula (IIC) is used, an acid-labile protecting group may conveniently be removed at the same time as the acid
treatment that converts the epi-mutilin configuration into the desired configuration of the compounds of the invention.

The compounds of formulae (IIA), (IIB) and (IIC) may be prepared from compounds of formulae (IV) and (V)

Suitable compounds as formula (IV) include 11-O-acyl mutilin derivatives, e.g. mutilin 11-acetate (A J Birch,
C W Holzapfel, R W Richards, Tetrahedron (Suppl.), 1966, 8, Part II, 359) or mutilin 11-dichloroacetate or mutilin
11-trifluoroacetate. Formula (V) is (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epi-mutilin (H Berner, G Schulz and H

Compounds of formula (IIA) in which $R_{3A}$ is hydroxyl may be obtained by first preparing 2-hydroxymethylene
mutilin from a compound of formula (IV). Using procedures based on that described by A.J. Birch, C.W. Holzapfel and
R.W. Rickards (Tet (Suppl) 1996 B part III 359), a compound of formula (IV) in toluene and methyl formate is treated
with sodium methoxide and stirred under argon. The product is a mixture of the desired 2-hydroxymethylene compound
and corresponding compounds substituted by formate at position 11 (if $OY$ is OH) and/or position 14. The formate
groups may be removed when desired by treatment with potassium hydroxide in methanol.

The product mixture may however be used directly to prepare 2-diazo-mutilin derivatives using the method
described by H Berner, G Schulz, and G Fisher, Monatsh. Chem., 1981, 112, 1441, for example reacting a solution of
a 2-hydroxymethylene-mutilin and the formate derivatives in dichloromethane at -10 °C under argon with tosylazide and triethylamine. Removal of the formate groups as described above leaves 2-diazo-mutilin, which may be reacted with a carboxylic acid to give a 2-acyloxy-mutilin, effectively a compound of formula (IIA) in which R⁴A is protected hydroxyl. Suitably reaction with dichloroacetic acid gives 2-dichloroacetoxy-mutilin, which can be deprotected as described above to provide 2-OH, preferably after coupling with the derivative of acid (III). This reaction produces (2S)-2-hydroxy derivatives.

[0052] Compounds of formula (IIB) are either 1,2-didehydro-mutilin or obtainable therefrom by manipulation of OY and R¹A as described above. 1,2-Didehydro-mutilins may be prepared using the method described by G Schulz and H Berner in Tetrahedron, 1984, 40, 905.

[0053] The above described modifications to the mutilin nucleus may also be carried out after coupling of compounds of formula (IIA) and (IIC) where R³A is hydrogen (i.e. based on mutilin and epi-mutilin) with the active derivative of acid (III).

[0054] In another aspect, the present invention provides a method for preparing compounds of the invention in which X is O, S, NH, CO.O or CONH which comprises reacting a compound of formula VIA or VIB where Y is hydrogen or a removable hydroxy-protecting group, and R¹A and R³A are R¹ and R³ as defined for formulae IA and IB or groups convertible to R¹ and R³, n is as defined for formulae IA and IB, and R'L is a leaving group or OR or NH₂, with a compound of formula (VII):

\[
R²A-(CH₂)ₘ-XH
\]

where R²A is R² as defined for formulae (IA) and (IB) or a group convertible to R², and X and m are as defined for formulae IA and IB, or when X is CO.O with an active derivative of the acid of formula (VII), by one of the procedures set out below, and where required or desired converting Y to hydrogen, converting an R¹A, R²A or R³A group to an R¹, R² or R³ group, and/or converting one R¹, R² or R³ group to another R¹, R² or R³ group.

[0055] As in the method discussed above starting from compounds (IIA/B/C), preferably Y is a hydroxyl protecting group such as an acyl group, for example so that -OY is trifluoroacetyl or dichloroacetyl. When the intended R³ is also hydroxyl then R³A is also preferably acyloxy, for example acetyl or dichloroacetyl.

[0056] It may also be necessary to protect substituent groups in the compound of formula (VII) prior to reaction with the compound (VIA) or (VIB), for example protecting N atoms with alkoxy carbonyl, for example t-butoxycarbonyl.

[0057] Suitable hydroxy, carboxy and amino protecting groups are those well known in the art and are discussed above.

[0058] R¹A is typically the R¹ group vinyl, and this may be converted to the alternative R¹ ethyl group by hydrogenating the vinyl group to form an ethyl group, typically by hydrogenation over a palladium catalyst (e.g. 10% palladium-on-carbon) in a solvent such as ethanol, or tetrahydrofuran.

[0059] R³A is typically hydrogen or protected hydroxyl, such as acyloxy. After the coupling reaction, protecting acyl groups may be removed to restore the hydroxyl groups by hydrolysis e.g. using NaOH in MeOH.

[0060] Procedures for coupling the group R¹(CH₂)ₙ(CH₂)CO.O- with compound R²A-(CH₂)ₘ-XH include the following:
(a) when R^L is a leaving group, such as 4-MeC_6H_4SO_3O, MeSO_3O, F_3CSO_2O, Br or Cl, and X is O, S or NH:

(i) where X = O, the alcohol R^2-(CH_2)_m-OH may be converted into the alkoxide by reaction with an inorganic base, such as sodium hydride, lithium hydride, sodium hexamethyldisilazide, or lithium hexamethyldisilazide, in a non-hydroxylic solvent, such as N,N-dimethylformamide or tetrahydrofuran, prior to reaction with the compound of formula VIA/B;

(ii) where X = S, the thiol R^2-(CH_2)_m-SH may be reacted with the compound of formula VIA/B in the presence of an inorganic base, such as sodium methoxide, sodium ethoxide, sodium hydride, sodium hexamethyldisilazide, or lithium hexamethyldisilazide, in a solvent such as 2-propanol, ethanol, methanol, N,N-dimethylformamide, or tetrahydrofuran.

(iii) where X = NH, the amine R^2-(CH_2)_m-NH_2 may be reacted with the compound of formula VIA/B in a solvent such as N,N-dimethylformamide or tetrahydrofuran, optionally in the presence of a base such as potassium carbonate, pyridine, N,N-di-(iso-propyl)-ethylamine, or triethylamine.

(b) when X is CONH, a compound of formula VIA/B in which R^L is amino may be reacted with a compound of formula R^{2A}-(CH_2)_m-CO_2H, or an acylating agent derived therefrom, using one of the general methods for amide formation that are described in the chemical literature. General methods for amide formation are described by B C Challis and J A Challis in *Comprehensive Organic Chemistry*, Vol. 2, ed. I O Sutherland, pages 959-964 (Pergamon Press, Oxford, 1979).

(c) when X is CO.O, a compound of formula VIA/B in which R^L is hydroxy may be reacted with an acylating agent derived from a compound of formula R^{2A}-(CH_2)_m-CO_2H, using one of the general methods that are described in the chemical literature, for example treating the acid with oxalyl chloride and reacting with R^L = hydroxy in a suitable solvent such as DMF.

[0061] Alternatively the above reactions may be carried out using a compound of formula (VIC):

\[ R^1A \]

where Y and R^{1A} are as defined for formulae IIA and IIB and R^L is as defined for formulae (VIA) and (VIB) with the compound (VII) by the procedures (a), (b) or (c) set out above, and then treating the product with an acid, and where required or desired converting an R^{1A} or R^{2A} group to a R^1 or R^2 group, and/or converting one R^1 or R^2 group to another R^1 or R^2 group.

[0062] As mentioned previously, the acid treatment indicated above converts the epi-mutilin configuration of formula (VIC) to the usual mutilin nucleus of formula (VIA). Typically this conversion is carried out by treatment with conc. HCl or Lukas reagent (conc. HCl saturated with ZnCl_2) in dioxane.

[0063] As in formulae (VIA) and (VIB), R^{1A} is typically the R^1 group vinyl, and this may be converted to the alternative R^1 group by hydrogenating the vinyl group to form an ethyl group. Also it may again be necessary to protect substituent groups in the compound (VII) prior to reaction, for example protecting N atoms with alkoxycarbonyl, for example t-butoxycarbonyl.

[0064] The compounds of formulae (VIA), (VIB) and (VIC) may be prepared by reacting the corresponding compounds of formula (IIA), (IIB) and (IIC) by conventional methodology to introduce acyl groups substituted by hydroxyl or amine or a leaving group.

[0065] Reference is directed to the preparation of the chloride and tosylate by K Riedl in *J. Antibiotics*, 1976, 29, 132; and the tosylate and mesylate described by H Egger and H Reinshagen in *J. Antibiotics*, 1976, 29, 915; starting from pleuromutilin or 19,20-dihydro-pleuromutilin (n=0). Also compounds where R^L is chloro or bromo may be prepared.
by reacting Br(CH₂)n(CH₂)COOCI or Cl(CH₂)n(CH₂)COOCI with compounds IV and V above. It will be appreciated that when n=0, compounds where R¹ is hydroxy are pleuromutilin and 19,20-dihydro-pleuromutilin. Compounds where R¹ is NH₂ may be prepared from the compound where R¹ is a leaving group, for example treating a tosylate with sodium azide, followed by treatment with triphenyl phosphate and a base.

[0066] Compounds of formula (IA) wherein X is S(O) or SO₂ may be obtained by preparing the corresponding compound in which X = S and treating it with an oxidising agent; for example, 2,3-dichloroperbenzoic acid in chloroform, or catalytic osmium tetroxide plus N-methylmorpholine N-oxide in tetrahydrofuran and tertiary-butanol.

[0067] It will be appreciated that it is also possible to carry out the reaction of the compounds VIA/B/C with compound VII with the substituents reversed, i.e. with -CH₂(CH₂)ₙXH as a 14-mutilin substituent and R¹ on the R²A-(CH₂)ₘ-R¹ residue. For example 22-deoxy-22-sulfanyl-pleuromutilin (US Patent 4130709) may be reacted with a compound of formula R²A-(CH₂)ₘ-R¹, where R¹ is a leaving group, such as 4-MeC₆H₄SO₂MeSO₂O, CF₃SO₂O, or Cl, in the presence of an inorganic base, such as sodium methoxide, sodium ethoxide, or sodium hydride, in a solvent such as 2-propanol, ethanol, methanol, or tetrahydrofuran.

[0068] The compounds (III) and (VII) are commercially available or may be formed by conventional methodology from starting materials that are commercially available compounds or described in the literature.

[0069] Where intermediates disclosed for the above processes are novel compounds, they also form part of this invention.

[0070] The compounds of the present invention may contain a chiral centre, and therefore the products of the above processes may comprise a mixture of diastereoisomers or a single diastereoisomer. A single diastereoisomer may be prepared by separating such a mixture of diastereoisomers which has been synthesised using a racemic starting material, or by synthesis using an optically pure starting material.

[0071] The products of the processes of this invention may be in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be present in the crystalline product. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

[0072] The compounds obtained according to the processes of the invention are suitably worked up to a substantially pure form, for example at least 50% pure, suitable at least 60% pure, advantageously at least 75% pure, preferably at least 85% pure, more preferably at least 95% pure, especially at least 98% pure, all percentages being calculated as weight/weight. An impure or less pure form of a compound according to the invention may, for example, be used in the preparation of a more pure form of the same compound or of a related compound (for example a corresponding derivative) suitable for pharmaceutical use.

[0073] The present invention also includes pharmaceutically acceptable salts and derivatives of the compounds of the invention. Salt formation may be possible when one of the substituents carries an acidic or basic group. Salts may be prepared by salt exchange in conventional manner.

[0074] Acid-addition salts may be pharmaceutically acceptable or non-pharmaceutically acceptable. In the latter case, such salts may be useful for isolation and purification of the compound of the invention, or intermediates thereto, and will subsequently be converted into a pharmaceutically acceptable salt or the free base. Pharmaceutically acceptable acid-addition salts include those described by Berge, Bighley, and Monkhouse, J. Pharm. Sci., 1977, 66, 1-19. Suitable salts include the hydrochloride, maleate, and methanesulphonate; particularly the hydrochloride.

[0075] It will also be understood that where the compound of the invention contains a free carboxy moiety, it can form a zwitterion.

[0076] The compounds of the present invention and their pharmaceutically acceptable salts or derivatives have antimicrobial properties and are therefore of use in therapy, in particular for treating microbial infections in animals, especially mammals, including humans, in particular humans and domesticated animals (including farm animals). The compounds may be used for the treatment of infections caused by, for example, Gram-positive and Gram-negative bacteria and mycoplasmas, including, for example, Staphylococcus aureus, Staphylococcus epidermidis, Enterococcus faecalis, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus pneumoniae, Haemophilus sp., Neisseria sp., Legionella sp., Chlamydia sp., Moraxella catarrhalis, Mycoplasma pneumoniae, and Mycoplasma gallisepti-

[0077] The present invention also provides the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof, or a composition according to the invention, in the manufacture of a medicament for treating microbial infections in animals, especially in humans and in domesticated mammals.

[0078] The invention further provides the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the preparation of a medicament for use in the treatment of microbial infections.

[0079] Compounds of the present invention may be used to treat skin and soft tissue infections and acne, by topical
application. Accordingly, in a further aspect the present invention provides the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the preparation of a medicament adapted for topical administration for use in the treatment of skin and soft tissue infections and also in the treatment of acne in humans.

[0080] Compounds of the present invention may be also used for the elimination or reduction of nasal carriage of pathogenic bacteria such as *S. aureus*, *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*, in particular colonisation of the nasopharynx by such organisms, by the administration of a compound of the present invention thereto. Accordingly, in a further aspect, the present invention provides for the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the manufacture of a medicament adapted for administration to the nasal cavity, for reducing or eliminating the nasal carriage of pathogenic organisms. Preferably, the medicament is adapted for focussed delivery to the nasopharynx, in particular the anterior nasopharynx.

[0081] Such reduction or elimination of nasal carriage is believed to be useful in prophylaxis of recurrent acute bacterial sinusitis or recurrent otitis media in humans, in particular in reducing the number of episodes experienced by a patient over a given period of time or reducing the time intervals between episodes. Accordingly, in a further aspect, the present invention provides for the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the manufacture of a medicament adapted for administration to the nasal cavity, for prophylaxis of recurrent acute bacterial sinusitis or recurrent otitis media.

[0082] Compounds of the present invention are also useful in treating chronic sinusitis. Accordingly, in a further aspect, the present invention provides for the use of a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof in the manufacture of a medicament, for treating of chronic sinusitis.

[0083] The compounds according to the invention may suitably be administered to the patient at a daily dosage of from 1.0 to 50 mg/kg of body weight. For an adult human (of approximately 70 kg body weight), from 50 to 3000 mg, for example about 1500 mg, of a compound according to the invention may be administered daily. Suitably, the dosage for adult humans is from 5 to 20 mg/kg per day. Higher or lower dosages may, however, be used in accordance with normal clinical practice.

[0084] To lessen the risk of encouraging the development of resistant organisms during prophylaxis of recurrent otitis media or recurrent acute bacterial sinusitis, it is preferred to administer the drug on an intermittent, rather than a continual, basis. In a suitable intermittent treatment regimen for prophylaxis of recurrent otitis media or recurrent sinusitis, drug substance is administered on a daily basis, for a small number of days, for instance from 2 to 10, suitably 3 to 8, more suitably about 5 days, the administration then being repeated after an interval, for instance, on a monthly basis over a period of months, for instance up to six months. Less preferably, the drug substance may be administered on a continuing, daily basis, over a prolonged period, for instance several months. Suitably, for prophylaxis of recurrent otitis media or recurrent sinusitis, drug substance is administered once or twice a day. Suitably, drug substance is administered during the winter months when bacterial infections such as recurrent otitis media and recurrent sinusitis tend to be more prevalent. The drug substance may be administered at a dosage of from 0.05 to 1.00mg, typically about 0.1 to 0.2mg, in each nostril, once or twice a day.

[0085] More generally, the compounds and compositions according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibiotics.

[0086] Accordingly, in a further aspect, the present invention provides a pharmaceutical composition comprising a compound of the invention or a pharmaceutically acceptable salt or derivative or solvate thereof together with a pharmaceutically acceptable carrier or excipient.

[0087] The compounds and compositions according to the invention may be formulated for administration by any route, for example oral, topical or parenteral. The compositions may, for example, be made up in the form of tablets, capsules, powders, granules, lozenges, creams, syrups, sprays or liquid preparations, for example solutions or suspensions, which may be formulated for oral use or in sterile form for parenteral administration by injection or infusion.

[0088] Tablets and capsules for oral administration may be in unit dosage form, and may contain conventional excipients including, for example, binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycerine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; and pharmaceutically acceptable wetting agents, for example sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice.

[0089] Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or another suitable vehicle before use. Such liquid preparations may contain conventional additives, including, for example, suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters (for example glycerine), propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and, if desired,
Conventional flavouring and colour agents.

- **Compositions according to the invention intended for topical administration may, for example, be in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, nose drops, nasal sprays, impregnated dressings, and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, ethanol or oleyl alcohol for lotions and aqueous bases for sprays. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.**

- **Compositions according to the invention intended for topical administration, in addition to the above, may also contain a steroidal anti-inflammatory agent; for example, betamethasone.**

- **Compositions according to the invention may be formulated as suppositories, which may contain conventional suppository bases, for example cocoa-butter or other glycerides.**

- **Compositions according to the invention intended for parenteral administration may conveniently be in fluid unit dosage forms, which may be prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, may be either suspended or dissolved in the vehicle. In preparing solutions, the compound may be dissolved in water for injection and filter-sterilised before being filled into a suitable vial or ampoule, which is then sealed. Advantageously, conventional additives including, for example, local anaesthetics, preservatives, and buffering agents can be dissolved in the vehicle. In order to enhance the stability of the solution, the composition may be frozen after being filled into the vial, and the water removed under vacuum; the resulting dry lyophilised powder may then be sealed in the vial and a accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions may be prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilisation cannot be accomplished by filtration. The compound may instead be sterilised by exposure to ethylene oxide before being suspended in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in such suspensions in order to facilitate uniform distribution of the compound.**

- **A compound or composition according to the invention is suitably administered to the patient in an antimicrobially effective amount.**

- **A composition according to the invention may suitably contain from 0.001 % by weight, preferably (for other than spray compositions) from 10 to 60% by weight, of a compound according to the invention (based on the total weight of the composition), depending on the method of administration.**

- **When the compositions according to the invention are presented in unit dosage form, for instance as a tablet, each unit dose may suitably comprise from 25 to 1000 mg, preferable from 50 to 500 mg, of a compound according to the invention.**

- **Preferred compositions of the present invention include those adapted for intranasal administration, in particular, those that will reach into the nasopharynx. Such compositions are preferably adapted for focussed delivery to, and residence within, the nasopharynx. The term 'focussed delivery' is used to mean that the composition is delivered to the nasopharynx, rather than remaining within the nares. The term 'residence' within the nasopharynx is used to mean that the composition, once delivered to the nasopharynx, remains within the nasopharynx over a course of several hours, rather than being washed away more or less immediately. Preferred compositions include spray compositions and creams. Representative spray compositions include aqueous compositions, as well as oily compositions which contain amphiphilic agents so that the composition increases in viscosity when in contact with moisture. Creams may also be used, especially creams having a rheology that allows the cream to spread readily in the nasopharynx.**

- **Preferred aqueous spray compositions include, in addition to water, further excipients including a tonicity modifier such as a salt, for instance sodium chloride; preservative, such as benzalkonium salt; a surfactant such as a non-ionic surfactant, for instance a polysorbate; and buffer, such as sodium dihydrogen phosphate; present in low levels, typically less than 1%. The pH of the composition may also be adjusted, for optimum stability of the drug substance during storage. For compounds of the present invention, a pH in the range 5 to 6, preferably about 5.3 to 5.8, typically about 5.5 is optimal.**

- **Representative oily spray and cream compositions are described in WO 98/14189 (SmithKline Beecham).**

- **Suitably, the drug substance is present in compositions for nasal delivery in between 0.001 and 5%, preferably 0.005 and 3%, by weight of the composition. Suitable amounts include 0.5% and 1% by weight of the composition (for oily compositions and creams) and from 0.01 to 0.2% (aqueous compositions).**

- **Preferably, an aqueous spray composition is used. Such compositions are found to show similar retention in the target area (nasal cavity and nasopharynx) in gamma scintigraphy studies and have superior release rates in synthetic membrane diffusion studies when compared to an oily composition as described in WO 98/14189. In addition, an aqueous base was found to be preferred to an oily base in sensory analysis studies.**

- **Spray compositions according to the present invention may be delivered to the nasal cavity by spray devices well known in the art for nasal sprays, for instance an air lift pump. Preferred devices include those which are metered...**
to provide a unit volume of composition, preferably about 100 µl, and optionally adapted for nasal administration by addition of a modified nozzle.

[0103] The following Examples illustrate the present invention and particularly the preparative procedures outlined above, by reference to the preparation of specific compounds within the scope of the present invention.

Note on naming of pleuromutilin analogues

[0104] In the Examples, compound (a), which in the IUPAC system has the systematic name (1S, 2R, 3S, 4S, 6R, 7R, 8R, 14R)-3,6-dihydroxy-2,4,7,14-tetramethyl-4-vinyltricyclo[5.4.3.0^1,8]tetradecan-9-one, is referred to using the trivial name mutilin and with the numbering system described by H Berner, G Schulz, and H Schneider in *Tetrahedron*, 1981, 37, 915-919.

![IUPAC numbering](image1)

![Mutilin numbering](image2)

[0105] Likewise, compound (b), which has the systematic name (1R, 2R, 4S, 6R, 7R, 8S, 9R, 14R)-6-hydroxy-9-methoxy-2,4,7,14-tetramethyl-4-vinyl-tricyclo[5.4.3.0^1,8]tetradecan-3-one, is named as (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epi-mutilin.

![Example 1 - Mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate](image3)

[0106] Quinuclidin-4-thiol hydrobromide (1.9 g, 0.009 mole) (W. Eckhardt and E.A. Grob, *Helvetica Chimica Acta* (1974), 57 (8) m 2339-2345) was added to a stirred solution of sodium ethoxide (1.72 g, 0.0253 mole) in ethanol (50 ml) under argon at room temperature. The mixture was stirred for 10 minutes before adding a solution of mutilin 14-toluenesulfonyloxyacetate (K. Ridel, *J. Antibiotics* (1976), 29m 132-139) (6.23 g, 0.0117 mole) in methyl ethyl ketone (20 ml). The mixture was stirred overnight at room temperature under argon, then concentrated in vacuo. The crude product was purified by chromatography on silica gel eluting with chloroform/methanol/35% ammonia solution (19:1:0.1) to give the title compound as a solid 1.8 g (40%); ^1^H NMR (CDCl₃) *inter alia* 0.75 (3H, d, J 6.7 Hz), 0.88 (3H, d, J 7 Hz), 1.25 (3H, s), 1.46 (3H, s), 1.68 (6H, t, J 7.6 Hz), 2.93 (6H, t, J 7.6 Hz), 3.18 (2H, ABq), 3.35 (1H, m), 5.19 (1H, dd, J 17.5 and ), 5.33 (1H, dd, 6.45 (1H, dd, J 17.4 and 11 Hz). MS (EI) m/z 504 (M^+^)
Example 2 - Mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate Hydrochloride

[0107] Mutilin 14-(quinuclidin-4-y1-sulfanyl)-acetate (1.0 g) was dissolved in a minimum volume of acetone and a 1M solution of HCl in ether was added. The heterogeneous mixture was concentrated in vacuo. The residue was triturated with ether (20 ml) and 1M HCl/ether (5 ml) to give the title compound as a beige solid (0.94 g); 1H NMR (D 2 O) inter alia 0.63 (3H, d, J 6 Hz), 0.86 (3H, d, J 6.8 Hz), 1.09 (3H, s), 1.36 (3H, s), 2.05 (6H, m), 3.40 (6H, m), 3.49 (1H, m), 5.10 (2H, m), 5.64 (1H, d, J 8.3 Hz), 6.29 (1H, dd, J 17.4 and 11 Hz). MS (EI) m/z 504 (M+ )

Example 3 - 19,20-Dihydromutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate

[0108] A solution of mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate (0.314 g, 0.00063 mole) in ethanol (30 ml) was hydrogenated over 10% Pd-C paste (50% moisture content) at room temperature for 1 hour. The catalyst was filtered off and the filtrate concentrated in vacuo. The residue was dissolved in chloroform and washed with saturated aqueous sodium carbonate and dried over magnesium sulphate. The resulting solution was evaporated to dryness in vacuo to give the title compound (0.18 g) (57%); 1 H NMR (CDCl 3 ) inter alia 0.71 (3H, 1d, J 6.6 Hz), 0.78 (3H, t, J 7.5 Hz), 0.94 (3H, d, J 7 Hz), 0.96 (3H, s), 1.43 (3H, s), 1.7 (6H, t, J 7 Hz), 2.40 (1H, m), 2.94 (6H, t, J 7.5 Hz), 3.19 (2H, s), 3.41 (1H, d, J 8.4 Hz), 5.60 (1H, d). MS (EI) m/z 506 (M+ )

Example 4 - Mutilin 14-(quinuclidin-3-yloxy)-acetate hydrochloride,

[0109] 3-Quinuclidinol (0.635 g) in dry DMF (4 ml) was stirred under argon and treated with sodium hydride (0.21 g of a 60% dispersion in oil). After 1 hour the mixture was cooled to -15°C and a solution of mutilin 14-methanesulfonyloxyacetate (2.28 g, see H. Egger and H. Reinshagen, J. Antibiotics 29 (9), 915) in dry DMF (4 ml) was added dropwise. The mixture was allowed to warm gradually to room temperature, left 1 hour and diluted with water (30 ml) and chloroform (30 ml). The layers were shaken and separated, the organic phase washed twice more with water, dried over MgSO4 and evaporated. The residue was chromatographed on silica, eluting with dichloromethane/methanol/35% ammonia solution (19:1:0.1) to isolate a compound at Rf approx. 0.45 on silica tlc, eluting with the same solvent mixture. A solution of this compound in chloroform (5 ml) was treated with 1N HCl in ether (2 ml) and evaporated to provide the title compound as a buff foam (0.339 g); υ max (CHCl 3 ) 3562, 3435 (broad), 2447 (broad), 1735 cm -1 ; 1 H NMR (CDCl 3 ) inter alia 0.71 (3H, d, J 6.7 Hz), 0.90 (3H, d, J 6.7 Hz), 3.1-3.6 (7H, m), 3.8-4.1 (3H, m), 5.22 (1H, d, 17.5 Hz), 5.38 (1H, d, J 10.8 Hz), 5.81 (1H, d, J 8.3 Hz), 6.48 (1H, dd, J 14.7 and 11.0 Hz), 12.3 (1H, broad s, disappears on D 2 O exchange); MS (+ve ion electrospray) m/z 488 (MH+ , 90%), 186 (100%).

Example 5 - Mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate

[0110] The preparation of quinuclidin-3-thiol was based on patent literature (J. Barriere, C. Cotret and J. Paris, E.P. 248703 [1987]). A solution of triphenylphosphine (12 g) in THF (85 ml) was ice-cooled under argon and treated dropwise with diisopropyl azodicarboxylate (9 ml). After 30 minutes a solution of 3-quinuclidinol (2.9 g) and thiolacetic acid (3.24 ml) in THF (170 ml) was added dropwise over 1 hour. The mixture was stirred overnight at room temperature, evaporated and the residue taken up in ether (250 ml). This solution was extracted with 1M hydrochloric acid (2 x 40 ml), the combined aqueous extracts washed twice more with ether (100 ml) and evaporated to dryness. The residue was desiccated under vacuum over P 2 O 5 for 4 days to provide a pale yellow solid. A portion of this solid (0.443 g) was dissolved in ethanol (10 ml) and treated with sodium methoxide (0.216 g). After 1 hour, mutilin 14-methanesulfonyloxyacetate (0.912 g) was added, the mixture stirred a further 1 hour, diluted with chloroform (30 ml) and water (30 ml), shaken and separated. The organic layer was washed with water (30 ml), dried over MgSO4 and evaporated. Chromatography of the residue on silica eluting with chloroform/methanol/35% ammonia solution (19:1:0.1) provided the title compound as a pale yellow foam, 0.62 g (62%); υ max (CHCl 3 ) 3563, 1730 cm -1 ; 1 H NMR (CDCl 3 ) inter alia 0.71 (3H, d, J 6.7 Hz), 0.90 (3H, d, J 6.7 Hz), 3.1-3.6 (7H, m), 3.8-4.1 (3H, m), 5.22 (1H, d, J 17.5 Hz), 5.38 (1H, d, J 10.8 Hz), 5.81 (1H, d, J 8.3 Hz), 6.48 (1H, dd, J 14.7 and 11.0 Hz), 12.3 (1H, broad s, disappears on D 2 O exchange); MS (+ve ion electrospray) m/z 504 (MH+ , 100%), 202 (55%).

Example 6 - Mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate

Step 1. Quinuclidin-4-thiol hydrochloride

[0111] Crude quinuclidin-4-thiol hydroiodide (Eckharat et al., Helv. Chem. Acta, 57 (4), (1974) 2339-2345 (15.1 g, 0.057 mole) was dissolved in water (200 ml). Sodium carbonate (21.0 g, 0.2 mole) was added. The mixture was extracted with chloroform (200 ml x 7). The combined organic extract was dried over MgSO4 and concentrated in vacuo. To the concentrate was added 1M hydrogen chloride in ether (100 ml). The mixture was evaporated to dryness in vacuo
to yield the title compound as a white solid 7.135 g (71%); 1H NMR (D₂O) 2.18 (6H, t, J 8 Hz), 3.40 (6H, t, J 8 Hz), MS (EI) m/z 144 ([M-HCl]⁺, 100%).

Step 2 Mutilin 14-(quinuclidin-4-sulfanyl)-acetate

[0112] Quinuclidin-4-thiol hydrochloride (5 g) was stirred with ethanol (110 ml) under argon and solid sodium methoxide (3.15 g) added. After 30 minutes mutilin 14-methanesulfonyloxyacetate (12.7 g) was added, followed by ethanol (30 ml). After a further 30 minutes the mixture was diluted with chloroform (250 ml) and water (250 ml), shaken and separated. The organic layer was washed with water (200 ml), dried over MgSO₄ and evaporated. Chromatography of the residue on silica, eluting with chloroform/methanol/35% ammonia solution (19:1:0.1) provided the title compound as a pale coloured foam (12.24 g), identical by NMR with the product of Example 1.

Example 7 - Mutilin 14-[N-(2,2-dimethylazabicyclo[4.3.0]non-4-ylmethyl)]-aminoacetate

Step 1 (±) Equatorial 4-cyano-2,2-dimethylazabicyclo[4.3.0]nonane

[0113] To a mixture of (±) 2,2-dimethylazabicyclo[4.3.0]non-4-one (4.7 g, 0.028 mole), (F.D. King, J. Chem. Soc. Perkins. Trans 1, 447, 1986) and tosylmethyisocyanide (6.47 g, 0.033 mole) in dry dimethoxyethane (100 ml) at -10°C was added ethanol (3.4 ml) followed by potassium-tert-butoxide (7.21 g, 0.064 mole). The mixture was stirred at -10°C for 1 hour then warmed to 50°C for 2 hours. The mixture was allowed to cool and diethyl ether (500 ml) added. Filtration and concentration of the filtrate in vacuo gave an oil. Column chromatography on silica gel eluting with ethyl acetate gave the title compound as an oil 3.0 g (60%); 1H NMR (CDCl₃) 0.95 (3H, s), 1.21 (3H, s), 1.35-1.51 (1H, m), 1.61-1.91 (4H, m), 2.15-2.19 (1H, m), 2.28-2.39 (2H, m), 2.57-2.71 (1H, m), 2.89-2.98 (1H, m).

Step 2 (±) Equatorial aminomethyl-2,2-dimethylazabicyclo[4.3.0]nonane

[0114] (±) Equatorial 4-cyano-2,2-dimethylazabicyclo[4.3.0]nonane (1.0 g, 0.0056 mole) in tetrahydrofuran (50 ml) was treated with lithium aluminium hydride (1.07 g, 0.028 mole) and stirred at ambient temperature for 18 hours. Diethyl ether (50 ml) was then added followed by a mixture of water (4 ml) and 10% aqueous sodium hydroxide solution (1.5 ml). Filtration and concentration of the filtrate in vacuo gave the title compound 0.97 g (95%) as an oil; 1H NMR (CDCl₃) 0.95 (3H, s), 1.20 (3H, s), 1.25-1.95 (9H, m), 2.25-2.40 (2H, m), 2.55 (2H, d, J 6 Hz), 2.89-2.97 (1H, m).

Step 3 Mutilin 14-[N-(2,2-Dimethylazabicyclo[4.3.0]non-4-ylmethyl)]-aminoacetate

[0115] (±) Equatorial aminomethyl-2,2-dimethylazabicyclo[4.3.0]nonane (0.1 g, 0.0006 mole) was treated with mutilin 14-toluenesulfonyloxyacetate (0.25 g, 0.0005 mole), (K Riedl, J Antibiotics 29 (2), 133, 1976) and N,N-diisopropylethylamine (0.1 ml, 0.0006 mole) in ethanol (20 ml) and heated under reflux for 6 hours. The mixture was then concentrated in vacuo and the residue partitioned between saturated sodium hydrogen carbonate solution and dichloromethane. The organics were separated and dried (Na₂SO₄). Chromatography on silica gel eluting with chloroform/methanol/35% ammonia solution (90:9:1) gave the title compound 0.08 g, (31%); 1H NMR (CDCl₃) 0.71 (3H, d, J 6.5 Hz), 0.90 (3H, d, J 6.5 Hz), 0.95 (3H, s), 1.25-2.55 (38H, m), 2.85-2.97 (1H, m), 3.19-3.39 (2H, m), 5.15 (1H, d, J 16.5 Hz), 5.31 (1H, d, J 11.1 Hz), 5.78 (1H, d, J 8.6 Hz), 6.50 (1H, dd, J 15.0 and 11.1 Hz). MS (+ve ion electrospray) m/z 543 (MH⁺, 100%).

Example 8 - Mutilin 14-(quinuclidin-4-ylcarbonylamino)-acetate

Step 1. Mutilin 14-azidoacetate

[0116] To a stirred solution of mutilin 14-toluenesulfonyloxyacetate (5.33 g, 0.01 mole) in acetone (50 ml) was added a solution of sodium azide (0.7 g, 0.011 mole) in water (6.5 ml). A solid precipitated briefly then redissolved. The homogenous mixture was stirred for 2 hours at ambient temperature then heated to reflux for 3 hours. The mixture was concentrated in vacuo to low volume then diluted with chloroform. The resulting solution was washed three times with water then dried over magnesium sulfate. Concentration in vacuo gave a pale yellow foam which was purified by chromatography on silica gel. Elution with ethyl acetate/hexane mixtures provided the title compound as a white foam 3.3 g (82%); 1H NMR (CDCl₃) inter alia 0.73 (3H, d, J 6.8 Hz), 0.89 (3H, d, J 7.1 Hz), 1.23 (3H, s), 1.47 (3H, s), 3.77 (2H, s), 5.22 (1H, dd, J 17.4 and 1.3 Hz), 5.38 (1H, dd, J 11 and 1.3 Hz), 5.86 (1H, d, J 8.5 Hz), 6.49 (1H, dd, J 17.4 and 11 Hz).
Step 2. Mutilin 14-(triphenylphosphinimino)-acetate

[0117] Triphenylphosphine (0.275 g, 0.00105 mole) was added to a stirred solution of mutilin 14-azidoacetate (0.404 g, 0.001 mole) in dichloromethane maintained under an atmosphere of argon. The solution rapidly became homogenous and a gas was evolved. Stirring was continued for 17 hours; the mixture was then concentrated in vacuo to give the title compound as a white solid, obtained by filtration after trituration in petroleum ether 0.638 g (100 %); MS (+ve ion electrospray) m/z 638 (MH+, 100%)

Step 3. Mutilin 14-aminoacetate

[0118] Mutilin 14-(triphenylphosphinimino)-acetate (1 g, 0.00157 mole) was suspended in ethanol (25 ml) and potassium hydroxide (0.175 g, 0.00314 mole) was added. The mixture was stirred for 17 hours during which time it became homogeneous. 2M hydrochloric acid (1.7 ml) was then added, stirring continued for ten minutes and the mixture concentrated in vacuo. The residue was taken up in 2M hydrochloric acid and the solution washed three times with dichloromethane. The aqueous phase was then layered with dichloromethane and the pH adjusted to 11 by addition of solid potassium carbonate with vigorous stirring. The organic phase was then separated, the aqueous phase extracted with dichloromethane, the combined organic extract washed with brine, dried over magnesium sulfate and concentrated in vacuo. The title compound was obtained as a white foam 0.505 g (85 %); 1 H NMR (CDCl 3 ) inter alia 0.71 (3H, d, J 6.5 Hz), 0.89 (3H, d, J 6.9 Hz), 1.17 (3H, s), 1.45 (3H, s), 3.33 (3H, m), 5.21 (1H, d, J 17.4 Hz), 5.36 (1H, d, J 11 Hz), 5.78 (1H, d, J 11 Hz), 6.52 (1H, dd, J 17.4 and 11 Hz).

Step 4. Quinuclidin-4-ylcarbonyl chloride hydrochloride

[0119] Quinuclidine-4-carboxylic acid hydrochloride (0.192 g, 0.001 mole) was suspended in dichloromethane (5 ml) and dimethylformamide (1 drop) and oxalyl chloride (0.436 ml, 0.635 g, 0.005 mole) were added. The resulting suspension was heated to reflux under an atmosphere of argon for six hours. Following concentration of the suspension in vacuo the residue was suspended in dichloromethane, concentrated in vacuo and finally dried in vacuo to give the title compound as a pale brown solid.

Step 5. Mutilin 14-(quinuclidin-4-ylcarbonylamino)-acetate

[0120] Quinuclidin-4-ylcarbonyl chloride hydrochloride (0.001 mole theoretical, Step 4) was suspended in dichloromethane (6 ml) and mutilin 14-aminoacetate (0.126 g, 0.00033 mole) was added. To the stirred suspension, under an atmosphere of argon, was added triethylamine (0.278 ml, 0.202 g, 0.002 mole) and stirring continued for 18 hours. Chloroform and water were added and the pH of the aqueous phase adjusted to 11 by addition of solid potassium carbonate. After shaking, the phases were separated, the organic phase was washed once with saturated aqueous sodium hydrogen carbonate and once with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was repeatedly dissolved in chloroform with vigorous stirring. The product was dissolved in 2M hydrochloric acid, the solution washed twice with dichloromethane, then layered with dichloromethane. The pH of the aqueous phase was adjusted to 11 by addition of solid potassium carbonate. After shaking, the organic phase was separated, dried over magnesium sulfate and concentrated in vacuo. The residue was repeatedly dissolved in chloroform and concentrated in vacuo. Finally the residue was triturated with diethyl ether to give the title compound as an off-white solid. Purification by chromatography on silica gel eluting with chloroform/methanol/ammonia solution provided a pale yellow glass. The product was dissolved in 2M hydrochloric acid, the solution washed twice with dichloromethane, then layered with dichloromethane. The pH of the aqueous phase was adjusted to 11 by addition of solid potassium carbonate. After shaking, the organic phase was separated, dried over magnesium sulfate and concentrated in vacuo. The residue was repeatedly dissolved in chloroform and concentrated in vacuo. Finally the residue was triturated with diethyl ether to give the title compound as an off-white solid. MS (+ve ion electrospray) m/z 515 (MH+, 100%).

Example 9 - Mutilin 14-[(3R,4R)-Azabicyclo[2.2.1]hept-3ylcarbonylamino]-acetate Step 1. (3R,4R)-Azabicyclo[2.2.1]hept-3-ylcarbonyl chloride hydrochloride

[0121] 3R,4R-Azabicyclo[2.2.1]heptane-3-carboxylic acid hydrobromide (0.127 g, 0.0005 mole) was suspended in dichloromethane (2 ml) and dimethylformamide (1 drop) and oxalyl chloride (0.131 ml, 0.191 g, 0.0015 mole) were added. The mixture was stirred for 4 hours under an atmosphere of argon. The resulting homogenous solution was concentrated in vacuo, the residue was dissolved in dichloromethane, concentrated in vacuo and finally dried in vacuo to give the title compound as an off-white solid.
Step 2. Mutilin 14-[(3R,4R)Azabicyclo[2.2.1]hept-3-ylcarbonylamino]-acetate

[0122] (3R,4R)-Azabicyclo[2.2.1]hept-3-ylcarbonyl chloride hydrochloride (0.0005 mole theoretical, Step 1) was dissolved in dichloromethane (4 ml) and mutilin 14-aminoacetate (0.126 g, 0.00033 mole) was added. To the stirred solution under an atmosphere of argon was added triethylamine (0.134 ml, 0.101 g, 0.001 mole). The resulting solution was stirred for 17 hours. Chloroform and water were added and the pH of the aqueous phase adjusted to 11 by addition of solid potassium carbonate. After shaking, the phases were separated, the organic phase was washed once with saturated aqueous sodium hydrogen carbonate and once with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude product as an off-white foam. Purification by chromatography on silica gel eluting with chloroform/methanol/35% ammonia solution provided the product as a white foam 0.142 g (86 %); 1H NMR (CDCl₃) inter alia 0.72 (3H, d, J 6.9 Hz), 0.89 (3H, d, J 7 Hz), 1.18 (3H, s), 1.46 (3H, s), 3.37 (1H, m(br)), 3.96 (2H, d, J 5.1 Hz), 5.22 (1H, d, J 17.4 Hz), 5.36 (1H, d, J 11 Hz), 5.78 (1H, d, J 8.4 Hz), 5.96 (1H, m(br)), 6.47 (1H, dd, J 17.4 and 11 Hz); MS (+ve ion electrospray) m/z 501 (MH⁺, 40%).

Reference Example 1 - Mutilin 14-(1-methylpiperid-4-ylcarbonylamino)-acetate

Step 1.1-Methylpiperid-4-ylcarbonyl chloride hydrochloride

[0123] 1-Methylpiperidine-4-carboxylic acid hydrochloride (0.09 g, 0.0005 mole) was suspended in dichloromethane (5 ml) and dimethylformamide (1 drop) and oxalyl chloride (0.131 ml, 0.19 g, 0.0015 mole) were added. The mixture was stirred for 4 hours under an atmosphere of argon. The resulting homogenous solution was concentrated in vacuo, the residue was dissolved in dichloromethane, concentrated in vacuo and finally dried in vacuo to give the title compound as an off-white solid.

Step 2. Mutilin 14-(1-methylpiperid-4-ylcarbonylaminoacetate

[0124] 1-Methylpiperid-4-ylcarbonyl chloride hydrochloride (0.0005 mole theoretical, Step 1) was dissolved in dichloromethane (4 ml) and mutilin 14-aminoacetate (0.126 g, 0.00033 mole) was added. Triethylamine (0.139 ml, 0.101 g, 0.001 mole) was added to the stirred solution under an atmosphere of argon. After 2 hours chloroform and water were added and the pH of the aqueous phase adjusted to 11 by addition of solid potassium carbonate. After shaking, the phases were separated, the organic phase was washed once with saturated aqueous sodium hydrogen carbonate and once with brine, dried over magnesium sulfate and concentrated in vacuo to give the crude product as an off-white foam. Purification by chromatography on silica gel eluting with chloroform/methanol/35% ammonia solution provided the product as a white foam 0.150 g (90 %); 1H NMR (CDCl₃) inter alia 0.71 (3H, d, J 6.8 Hz), 0.89 (3H, d, J 7 Hz), 1.18 (3H, s), 1.45 (3H, s), 3.36 (1H, m), 3.94 (2H, d, J 5 Hz), 5.22 (1H, d, J 18.6 Hz), 5.35 (1H, d, J 12.2 Hz), 5.78 (1H, d, J 8.4 Hz), 5.99 (1H, m(br)), 6.47 (1H, dd, J 17.4 and 11 Hz); MS (+ve ion electrospray) m/z 503 (MH⁺, 25%).

Reference Example 2 - Mutilin 14-[(3-[1-methylpiperid-4-yl])-propionate

Step 1. 3-(1-Methylpiperid-4-yl)propionyl chloride

[0125] A suspension of 3-(1-methylpiperid-4-yl)propionic acid hydrochloride (WO 9620173 A1, Example 1)(0.33 g, 0.00159 mole) in dry dichloromethane (10 ml) was treated with dimethylformamide (1 drop) and oxalyl chloride (0.416 ml, 0.605 g, 0.00477 mole) under an atmosphere of argon. After stirring for 3½ hours the mixture was concentrated in vacuo. The residue was dissolved in dry dichloromethane and concentrated in vacuo and finally dried in vacuo to give the title compound as a white solid.

Step 2.

[0126] A solution of 3-(1-methylpiperid-4-yl)propionyl chloride (0.00159 mole theoretical, Step 1) and (3R)-3-deoxy-11-deoxy-11-oxo-4-epi-mutilin (H Berner, G. Schulz and H. Schneider, Tetrahedron, 1980, 36, 1807) in dry dimethylformamide was heated at 110°C under argon for 17 hours. The mixture was then concentrated in vacuo and the residue chromatographed on silica gel eluting with dichloromethane/methanol/35% ammonia solution mixtures. The title compound was obtained as a pale yellow oil 0.284g (49%); 1H NMR (CDCl₃) inter alia 0.79 (3H, d, J 6.4 Hz), 1.18 (3H, s), 1.24 (3H, s), 2.37 (3H, s), 2.97 (3H, m), 3.23 (3H, s), 3.48 (1H, m), 5.01 (1H, d, J 17.6 Hz), 5.30 (1H, d, J 10.7 Hz), 5.74 (1H, d, J 10 Hz), 6.67 (1H, dd, J 17.5 and 10.6 Hz); MS (+ve ion electrospray) m/z 488 (MH⁺, 100%).
Step 3. Mutilin 14-[3-(1-methylpiperid-4-yl)]-propionate

[0127] A solution of (3R)-3-deoxo-11-deoxy-11-methoxy-11-oxo-4-epi-mutilin (0.355 g, 0.000728 mole) in dioxan (3 ml) was treated with concentrated hydrochloric acid (3 ml). After 4 hours the mixture was diluted with water, layered with dichloromethane and the vigorously stirred mixture adjusted to pH 11 by addition of solid potassium carbonate. The phases were then separated and the aqueous phase extracted with dichloromethane. The combined organic extract was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel eluting with dichloromethane/methanol/35% ammonia solution (90:9:1) to give the title compound as a white foam 0.284 g (82%); 1H NMR (CDCl3) inter alia 0.70 (3H, d, J 6.6 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.45 (3H, s), 2.44 (3H, s), 3.05 (2H, m), 3.36 (1H, dd, J 11.4 and 8 Hz), 5.20 (1H, d, J 17.5 Hz), 5.36 (1H, d, J 11 Hz), 5.74 (1H, d, J 8.4 Hz), 6.51 (1H, dd, J 17.5 and 11 Hz); MS (+ve ion electrospray) m/z 474 (MH+ , 100%).

Example 10 - Mutilin 14-(quinuclidin-4-ylmethylsulfonyl)-acetate

[0128] An ice cooled solution of triphenylphosphine (1.19 g, 0.0042 mole) in dry tetrahydrofuran was treated dropwise with diisopropyl azodicarboxylate (0.85 g, 0.0042 mole). After 30 minutes a solution of quinuclidin-4-ylmethanol (0.565 g, 0.0042 mole) in dry tetrahydrofuran (100 ml) was treated with concentrated hydrochloric acid (3 ml). After 4 hours the mixture was diluted with water, layered with tert-butanol (0.2 ml) was treated with N-methylmorpholine oxide (0.036 g, 0.003 mole) and a catalytic amount of osmium tetroxide under argon for a period of 4.5 hours. The mixture was extracted with ethyl acetate. The organic solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate and evaporated to dryness. Chromatography of the residue on silica gel eluting with chloroform/methanol/35% ammonia solution provided the title compound as a foam, 0.48 g (31%); 1H NMR (CDCl3) inter alia 0.70 (3H, d, J 6.6 Hz), 0.88 (3H, d, J 7 Hz), 1.76 (3H, s), 1.44 (6H, t, J 7.7 Hz), 2.47 (2H, s), 2.87 (6H, t, J 7.5 Hz), 3.09 (2H, s), 3.36 (1H, m), 5.1-5.4 (2H, m), 5.75 (1H, d, J 8.3 Hz), 6.48 (1H, m); MS (+ve ion electrospray) m/z 518 (MH+, 100%).

Example 11 - 19,20-Dihydromutilin 14-(quinuclidin-4-ylthio)-acetate

[0129] A cooled solution of triphenylphosphine (1.19 g, 0.0042 mole) in dry tetrahydrofuran was treated dropwise with diisopropyl azodicarboxylate (0.85 g, 0.0042 mole). After 30 minutes a solution of quinuclidin-4-ylmethanol (0.565 g, 0.0042 mole) in dry tetrahydrofuran (100 ml) was treated with concentrated hydrochloric acid (3 ml). After 4 hours the mixture was diluted with water, layered with tert-butanol (0.2 ml) was treated with N-methylmorpholine oxide (0.036 g, 0.003 mole) and a catalytic amount of osmium tetroxide under argon for a period of 4.5 hours. The mixture was extracted with ethyl acetate. The organic solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate and evaporated to dryness. Chromatography of the residue on silica gel eluting with chloroform/methanol/35% ammonia solution provided the title compound as a foam, 0.48 g (31%); 1H NMR (CDCl3) inter alia 0.70 (3H, d, J 6.6 Hz), 0.88 (3H, d, J 7 Hz), 1.76 (3H, s), 1.44 (6H, t, J 7.7 Hz), 2.47 (2H, s), 2.87 (6H, t, J 7.5 Hz), 3.09 (2H, s), 3.36 (1H, m), 5.1-5.4 (2H, m), 5.75 (1H, d, J 8.3 Hz), 6.48 (1H, m); MS (+ve ion electrospray) m/z 518 (MH+, 100%).

Example 12 - 19,20-Dihydromutilin 14-(quinclidin-4-ylsulfoxy)-acetate

[0130] A solution of (3R)-3-deoxo-11-deoxy-11-methoxy-11-oxo-4-epi-mutilin (0.355 g, 0.000728 mole) in dioxan (3 ml) was treated with conentrated hydrochloric acid (3 ml). After 4 hours the mixture was diluted with water, layered with dichloromethane and the vigorously stirred mixture adjusted to pH 11 by addition of solid potassium carbonate. The phases were then separated and the aqueous phase extracted with dichloromethane. The combined organic extract was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel eluting with dichloromethane/methanol/35% ammonia solution (90:9:1) to give the title compound as a white foam 0.284 g (82%); 1H NMR (CDCl3) inter alia 0.70 (3H, d, J 6.6 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.45 (3H, s), 2.44 (3H, s), 3.05 (2H, m), 3.36 (1H, dd, J 11.4 and 8 Hz), 5.20 (1H, d, J 17.5 Hz), 5.36 (1H, d, J 11 Hz), 5.74 (1H, d, J 8.4 Hz), 6.51 (1H, dd, J 17.5 and 11 Hz); MS (+ve ion electrospray) m/z 474 (MH+, 100%).

Reference Example 3 - Mutilin 14-(1-methylpiperid-4-ylsulfonyl)-acetate

[0131] A solution of triphenylphosphine (5.51 g, 0.021 mole) in dry tetrahydrofuran (100 ml) was ice-cooled under argon and treated with diisopropyl azodicarboxylate (4.25 g, 0.021 mole). After 30 minutes a solution of 4-hydroxy-1-methylpiperidine (2.3 g, 0.02 mole) and thiolactic acid (1.54 g, 0.02 mole) in dry tetrahydrofuran (50 ml) was added over a period of 30 minutes. The mixture was stirred overnight at room temperature, evaporated in vacuo and the residue taken up in ether (200 ml). The etheral solution was extracted with 1M hydrochloric acid (50 ml x 4). The
combined aqueous extract was washed with ether, evaporated to dryness and dried in vacuo to give a yellow gum (2.4 g). A portion of this gum (0.517 g) was dissolved in ethanol and treated with potassium tert-butoxide (0.785 g) under argon for 30 minutes. Mutilin-14-methanesulfonyloxyacetate (0.92 g, 0.002 mole) was added and the mixture stirred overnight, then concentrated in vacuo. The residue was partitioned between chloroform and water. The organic layer was washed with brine, dried over magnesium sulfate and concentrated in vacuo. Chromatography on silica gel eluting with chloroform/methanol/35% ammonia solution provided the title compound as a foam, 0.557 g (57%); 1H NMR (CDCl$_3$) inter alia 0.73 (3H, d, J 6.5 Hz), 0.87 (3H, d, J 7 Hz), 1.30 (3H, s), 1.67 (3H, s), 2.25 (3H, s), 3.36 (1H, m), 5.28 (2H, m), 5.77 (1H, d, J 8.5 Hz), 6.47 (1H, m); MS (+ve ion electrospray) m/z 492 (MH$^+$, 100%).

Example 13 - Mutilin 14-{(3RS,4SR)-1-aza-bicyclo[2.2.1]hept-3-yl-sulfanyl}-acetate

[0132] The title compound was prepared in 32% overall yield from endo-3-hydroxy-azabicyclo[2.2.1]heptane (S.M. Jenkins et al, J. Med. Chem.; 1992, 35, 2392-2406) using the procedure described in Example 5. The title compound was isolated as a colourless solid, in the 1H NMR spectrum the 8 line multiplets at δ 3.05-3.40 and 6.43-6.56 indicate a 1:1 mixture of diastereoisomers; 1H NMR (CDCl$_3$) inter alia 0.74 (3H, d, J 6.4 Hz), 0.88 (3H, d, J 7.0 Hz), 3.05-3.40 (2H, m), 5.21 (1H, d, J 17.5 Hz), 5.35 (1H, d, J 11.0 Hz), 5.75-5.80 (1H, m), 6.43-6.56 (1H, m); MS (+ve electrospray) m/z 490 (MH$^+$).

Example 14 - Mutilin 14-{(3RS,4SR)-1-aza-bicyclo[2.2.1]hept-3-yl-sulfanyl}-acetate hydrochloride

[0133] The title compound was prepared from mutilin 14-{(3RS,4SR)-1-azabicyclo[2.2.1] hept-3-yl-sulfanyl}-acetate using the procedure described in Example 2. The title compound was isolated as a colourless solid, 1:1 mixture of diastereoisomers; 1H NMR (DMSO-d$_6$) inter alia 0.65 (3H, d, J 6.4 Hz), 0.84 (3H, d, J 6.8 Hz), 1.09 (3H, s), 1.39 (1H, s), 4.61 (1H, d, J 5.2Hz, exchanged with D$_2$O), 5.05-5.12 (2H, m), 5.60 (1H, d, J 7.9 Hz), 6.14 (1H, dd, J 18 and 10.7 Hz), 10.4-10.6 (1H, br, exchanged with D$_2$O); MS (+ve electrospray) m/z 490 (MH$^+$ of free base).

Example 15 - Mutilin 14-(quinuclidin-3-ylidene)-acetate hydrochloride (both geometric isomers)

Step 1. Methyl quinuclidin-3-ylidene acetate hydrochloride

[0134] A suspension of quinuclidin-3-one hydrochloride (3.23 g) in DMF (20 ml) was treated with sodium methoxide (1.08 g) and stirred vigorously for 30 minutes. A solution of trimethyl phosphonoacetate (4.05 ml) and sodium methoxide (1.35 g) in DMF (20 ml) was added dropwise over 15 minutes and stirred a further 2 hours. The DMF was evaporated and the residue treated with dry ether (100 ml), triturated and filtered. The filtrate was treated with 1N HCl in ether (30 ml), the resulting solid triturated and the ether decanted. Ether (200 ml) was added, the suspension stirred vigorously for 30 minutes, the solid filtered off and heated at 60°C under vacuum for 2 days. The resulting methylquinuclidin-3-ylideneacetate hydrochloride (3.93 g) was a ca. 1:1 mixture of geometric isomers; 1H NMR (D$_2$O) inter alia 5.84 (broad s) and 5.94 (t, J 2.5 Hz) (vinyl protons of the two geom. isomers).

Step 2. Quinuclidin-3-ylideneacetic acid hydrochloride

[0135] Methyl quinuclidin-3-ylideneacetate hydrochloride (1g) was heated in concentrated hydrochloric acid (10 ml) at 60°C for 18 hrs and the solution evaporated to dryness. The residue was kept under vacuum over P$_2$O$_5$ for 3 days to give quinuclidin-3-ylidene acetic acid hydrochloride, 0.91 g (97%) as a white solid; 1H NMR (D$_2$O) inter alia 5.77 (broad s) and 5.86 (broad s) (ca. 1:1, vinyl protons of the two geom. isomers).

Step 3. (3R)-3-deoxo-11-deoxy-3-methoxy-11-ozo-4-epimutilin 14-(quinuclidin-3-ylidene)-acetate

[0136] Quinuclidin-3-ylideneacetic acid hydrochloride (0.204 g) was suspended in chloroform (5 ml), stirred under argon and treated with 1 drop DMF and oxalyl chloride (0.87 ml). After 2 hours the solvent was evaporated, toluene (10 ml) added to the residue and evaporated. The residue was taken up in DMF (2 ml), treated with (3R)-3-deoxo-11-deoxy-3-methoxy-11-ozo-4-epimutilin (0.334 g, prepared according to H. Berner, G. Schulz and H. Schneider, Tetrahedron (1980) 36 1807) and heated at 100°C under argon for 3 hours. After leaving at room temperature overnight, the mixture was diluted with chloroform (20 ml), washed with aqueous NaHCO$_3$ and water, dried and evaporated to dryness. Chromatography on silica, eluting with chloroform/methanol/35% ammonia solution (19:1:0.1) separated the 2 geometric isomers of the title compound. Less polar isomer, 0.1 g (20%); 1H NMR (CDCl$_3$) inter alia 3.23 (3H, s), 3.4-3.6 (1H, m), 3.96 (2H, ABq, J 20 Hz), 5.02 (1H, d, J 17.5Hz), 5.34 (1H, d, J 10.5 Hz), 5.64 (1H, t, J 2.5 Hz), 5.81 (1H, d, J 10 Hz), 6.74 (1H, dd, J 17.5 and 10.5 Hz); MS (+ve ion electrospray) m/z 484 (MH$^+$, 100%).
More polar isomer, 0.234 g (48%); ¹H NMR (CDCl₃) *inter alia* 3.12 (2H, s), 3.23 (3H, s), 3.4-3.5 (1H, m), 5.01 (1H, d, J 17.5 Hz), 5.30 (1H, d, J 10.5 Hz), 5.78 (1H, d, J 10 Hz), 6.37 (1H, d, J 0.95 Hz), 6.65 (1H, dd, J 17.5 and 10.5 Hz); MS (+ve ion electrospray) m/z 484 (MH⁺, 100%).

**Step 4. Mutilin 14-(quinuclidin-3-ylidene)-acetate hydrochloride**

[0137] The less polar geometric isomer of (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin 14-(quinuclidin-3-ylidene)-acetate (0.1 g) was dissolved in dioxan (3 ml), briefly cooled in ice-water and treated with conc. HCl (2 ml). After 5 hours at room temperature CHCl₃ (10 ml) and water (20 ml) were added, followed by solid NaHCO₃ until basic. The layers were separated, the aqueous re-extracted with CHCl₃ and the combined organic dried and evaporated. The residue was chromatographed, eluting with chloroform/methanol/35% ammonia solution 97:3:0.3 and the product in chloroform solution treated with 1M HCl in ether (1 ml). Evaporation gave the less polar geometric isomer of the title compound as a white foam, 0.105 g; ¹H NMR (CD₃SOCD₃) *inter alia* 2.85 (1H, s), 4.38 (2H, ABq, J 19 Hz), 4.59 (1H, d, J 6 Hz, disappears on D₂O exchange), 5.0-5.2 (2H, m), 5.64 (1H, d, J 8 Hz), 6.27 (1H, dd, J 17.5 and 11 Hz), 10.7 (1H, broad s, disappears on D₂O exchange); MS (+ve ion electrospray) m/z 470 (MH⁺ - HCl, 100%).

In the same manner, the more polar geometric isomer of (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin 14-(quinuclidin-3-ylidene)-acetate (0.116 g) was converted into the more polar geometric isomer of the title compound (0.096 g) as an off-white foam; ¹H NMR (CD₃SOCD₃) 4.62 (1H, d, J 6 Hz, disappears on D₂O exchange), 5.0-5.2 (2H, m), 5.65 (1H, d, J 8 Hz), 6.18 (1H, dd, J 17.5 and 11 Hz), 6.64 (1H, s), 11.42 (1H, broad s, disappears on D₂O exchange); MS (+ve ion electrospray) m/z 470 (MH⁺ - HCl, 100%).

**Example 16 - Mutilin 14-[(±)-quinuclidin-3-yl]-acetate hydrochloride**

**Step 1. (±)-Quinuclidine-3-acetic acid hydrochloride**

[0138] A mixture of methyl quinuclidin-3-ylideneacetate hydrochloride (Example 15, Step 1) (2g), ethanol (50 ml), 2M hydrochloric acid (5 ml) and 10% Pd/C (1 g) was stirred for 24 hours under H₂ at atmospheric pressure, filtered through celite and evaporated to dryness. The residue was dissolved in concentrated hydrochloric acid (10 ml), heated at 60°C for 18 hours, treated with a further 10 ml of concentrated hydrochloric acid, heated at 80°C for 6 hours and evaporated to dryness. The residue was kept under vacuum over P₂O₅ for 3 days to give the title compound as a white solid (1.8 g); MS (+ve ion electrospray) m/z 170 (MH⁺, 100%).

**Step 2. (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin 14-[(±)-quinuclidin-3-yl]-acetate**

[0139] (±)-Quinuclidine-3-acetic acid hydrochloride was converted into acid chloride and reacted with (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin in the manner of Example 15, Step 3. Chromatography of the product gave the title compound as a white foam (68%); ¹H NMR (CDCl₃) *inter alia* 3.23 (3H, s), 3.4-3.5 (1H, m), 5.01 (1H, d, J 17.5 Hz), 5.32 (1H, d, J 10.5 Hz), 5.75 (1H, d, J 9.8 Hz), 6.68 and 6.69 (1H, 2 dd, J 17.5 and 10.5 Hz); MS (+ve ion electrospray) m/z 486 (MH⁺, 100%).

**Step 3. Mutilin 14-[(±)-quinuclidin-3-yl]-acetate hydrochloride**

[0140] Rearrangement of (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin 14-[(±)-quinuclidin-3-yl]acetate in the manner of Example 15, Step 4 gave the title compound as a white foam (95%); ¹H NMR (CDCl₃) *inter alia* 5.1-5.4 (2H, m), 5.74 (1H, d, J 8.3 Hz), 6.43 and 6.47 (1H, 2 dd, J 17.5 and 10.5 Hz); MS (+ve ion electrospray) m/z 472 (MH⁺, 100%).

**Example 17 - Mutilin 14-[(±)-quinuclidin-3-ylacetoxyl-acetate hydrochloride**

[0141] (±)-Quinuclidine-3-acetic acid hydrochloride (0.206 g) was suspended in chloroform (5 ml) under argon, treated with DMF (1 drop) and oxalyl chloride (0.87 ml) and stirred 1 hour. The solution was evaporated, toluene was added and evaporated and the residue taken up in DMF (2 ml). Pleuromutilin (0.378 g) was added and the mixture stirred under argon for 18 hours, then heated at 110°C for 30 minutes. It was diluted with chloroform (10 ml), washed with aqueous NaHCO₃ (twice) and water, dried and evaporated. The residue was chromatographed, eluting with chloroform/methanol/35% ammonia solution (9:1:0.1). A chloroform solution of the material obtained was treated with 1M HCl in ether (2 ml) and evaporated. Trituration under ether and filtration gave the title compound as an off-white solid, 0.22 g (42%); ¹H NMR (CD₃SOCD₃) *inter alia* 4.5-4.7 (3H, m, reduces to 2H, m on D₂O exchange); 5.0-5.2 (2H, m), 5.59 (1H, d, J 8 Hz), 6.10 (1H, dd, J 17.5 and 10.5 Hz), 10.06 (1H, broad s, disappears on D₂O exchange); MS (+ve ion electrospray) m/z 472 (MH⁺, 100%).
Example 18 - Mutilin 14-(quinuclidin-3-ylmethylsulfanyl)-acetate

Step 1. Mixture of (±)-quinuclidin-3-ylmethylsulfanylacetate hydrochloride and (±)-quinuclidin-3-ylmethanethiol hydrochloride

[0142] (±)-Quinuclidine-3-methanol (L.I. Mastafonova, L.N Yakhontov, M.V. Rubtsov, Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR. 1965(6), 858-863) was converted into the title mixture using the procedure of Example 5. MS (+ve ion electrospray) m/z 200 (MH+ for thioacetate, 100%), 158 (MH+ for thiol, 40%).

Step 2. Mutilin 14-(±-quinuclidin-3-ylmethylsulfanyl)-acetate

[0143] The mixture from Step 1 was reacted with mutilin 14-methanesulfonyloxyacetate in the manner described in Example 5 to provide the title compound as an off-white foam (28%); 1 H NMR (CDCl 3 ) inter alia 0.75 (3H, d, J 6.7 Hz), 0.89 (3H, d, J 7 Hz), 3.12 (2H, s), 3.37 (1H, broad, becomes d, J 6.3 Hz on D2O exchange), 5.21 (1H, d, J 17.5 Hz), 5.36 (1H, d, J 8.4 Hz), 6.51 (1H, dd, J 17.5 and 11 Hz); MS (positive ion electrospray) m/z 518 (MH+, 100%).

Example 19 - 1,2-Didehydromutilin 14-(quinuclidin-4-ylsulfanyl)-acetate

Step 1. 1,2-Didehydromutilin-14-methanesulfonyloxyacetate

[0144] 1,2-Didehydropleuromutilin (0.2g, 0.00053 mole) (G. Schulz and H. Berner, Tetrahedron, (1984) 40, 905-17) was converted to 1,2-didehydromutilin-14-methanesulfonyloxyacetate by the method previously described for pleuromutilin (H. Egger and H. Reinshagen, J. Antibiotics (1976), 29, 915-22) providing the product as a yellow foam, (100%); 1 H NMR (CDCl 3 ) inter alia 0.80 (3H, d, J 6.4 Hz), 1.08 (3H, d, J 7 Hz), 1.15 (3H, s), 1.55 (3H, s), 3.20 (2H, ABq), 5.20 (1H, dd, J 17.4 and 1.4 Hz), 5.35 (1H, dd, J 11 and 1.4 Hz), 5.74 (1H, d, J 8.7 Hz), 6.04 (1H, d, J 6.1 Hz), 6.47 (1H, d, J 6.1 Hz), 7.74 (1H, d, J 6.1 Hz).

Step 2. 1,2-Didehydromutilin 14-(quinuclidin-4-ylsulfanyl)-acetate

[0145] A solution of 1,2-didehydromutilin 14-methanesulfonyloxyacetate (0.00053 moles) in ethanol was treated with quinuclidin-4-thiol hydrochloride (0.105 g, 0.000583 mole). After 15 minutes sodium methoxide (0.057 g, 0.00106 mole) was added to the stirred solution. After 1 hour the mixture was concentrated in vacuo to a slurry. Chloroform and water were then added. The pH of the aqueous phase was adjusted to 11-12 by addition of solid potassium carbonate. The phases were separated and the aqueous re-extracted with chloroform. The combined organic extract was dried over magnesium sulfate and concentrated in vacuo. Purification by chromatography on silica gel eluting with chloroform/methanol/35% ammonia solution provided the product as an off-white foam 0.19 g (72%); 1 H NMR (CDCl 3 ) inter alia 0.80 (3H, d, J 6.4 Hz), 1.08 (3H, d, J 7 Hz), 1.15 (3H, s), 1.55 (3H, s), 3.20 (2H, ABq), 5.20 (1H, dd, J 17.4 and 1.4 Hz), 5.35 (1H, dd, J 11 and 1.4 Hz), 5.74 (1H, d, J 8.7 Hz), 6.04 (1H, d, J 6.1 Hz), 6.47 (1H, dd, J 17.3 and 11 Hz), 7.74 (1H, d, J 6.1 Hz); MS (-ve ion electrospray) m/z 500 ([M-H]-, 50%).

Example 20 - 2α-Hydroxymutilin 14-(quinuclidin-4-ylsulfanyl)-acetate

Step 1. 2-Diazomutilin 14-methanesulfonyloxyacetate

[0146] 2-Diazopleuromutilin (0.809 g, 0.002 mole) (G. Schulz and H. Berner, Tetrahedron (9184), 40, 905-17) was converted to 2-diazomutilin-14-methanesulfonyloxyacetate by the method described for pleuromutilin (H. Egger and H. Reinshagen, J. Antibiotics (1976), 29, 915-22) providing the product as a bright yellow gum (100%); 1 H NMR (CDCl 3 ) inter alia 0.80 (3H, d, J 6.4 Hz), 1.08 (3H, d, J 7 Hz), 1.15 (3H, s), 1.55 (3H, s), 3.20 (2H, ABq), 5.20 (1H, dd, J 17.4 and 1.4 Hz), 5.35 (1H, dd, J 11 and 1.4 Hz), 5.74 (1H, d, J 8.7 Hz), 6.04 (1H, d, J 6.1 Hz), 6.47 (1H, dd, J 17.3 and 11 Hz), 7.74 (1H, d, J 6.1 Hz); MS (-ve ion electrospray) m/z 500 ([M-H]-, 50%).
dichloromethane and washed twice with saturated aqueous sodium hydrogen carbonate and once with brine. After
drying over magnesium sulfate concentration in vacuo gave the product as a pale yellow foam (100%); 1H NMR (CDCl₃)
inter alia 0.76 (3H, d, J 6 Hz), 0.93 (3H, d, J 7 Hz), 1.12 (3H, s), 1.49 (3H, s), 3.20 (3H, s), 4.66 (2H, s), 5.05 (1H, t, J
9 Hz), 5.25 (1H, d, J 17.3 Hz), 5.38 (1H, d, J 11 Hz), 5.83 (1H, d, J 8.5 Hz), 5.97 (1H, s), 6.43 (1H, dd, J 17.4 and 11 Hz).

Step 3. 2α-Hydroxymutilin 14-(quinuclidin-4-ylsulfanyl)-acetate

[0148] 2-Dichloroacetoxymutilin-14-methanesulfonyloxyacetate (0.001 mole theoretical) from Step 2 in ethanol (2
ml) was added to a pre-mixed solution of quinuclidine-4-thiol hydrochloride (0.27 g, 0.0015 mole) and sodium methoxide
(0.162 g, 0.003 mole) in ethanol (8 ml). After stirring for 1 hour the mixture was diluted with chloroform, washed twice
with saturated sodium hydrogen carbonate and once with brine, then dried over magnesium sulfate. Concentration in
vacuo was followed by silica gel chromatography, eluting with chloroform/methanol/35% ammonia solution. The product
was obtained as a white foam 0.2 g (38% overall, 3 steps); 1H NMR (CDCl₃) inter alia 0.75 (3H, d, J 6.5 Hz), 0.92 (3H,
d, J 7 Hz), 1.17 (3H, s), 1.48 (3H, s), 3.19 (2H, ABq), 3.99 (1H, t, J 8.7 Hz), 5.20 (1H, d, J 17.3 Hz), 5.33 (1H, d, J 11
Hz), 5.75 (1H, d, J 8.4 Hz), 6.45 (1H, dd, J 17.3 and 11 Hz); MS (+ve ion electrospray) m/z 520 (MH⁺, 100%).

Example 21- Mutilin 14-(quinuclidin-4-yl)-acetate

Step 1. Quinuclidin-4-ylmethanol

[0149] Quinuclidine-4-carboxylic acid hydrochloride (6.0 g, 0.031 mmoles) in tetrahydrofuran (300 ml) was treated
with lithium aluminium hydride (5.0 g, 0.137 mmoles) at ambient temperature for 18 hours. Water (20 ml) and 10%
aqueous sodium hydroxide (7.5 ml) was added carefully and the mixture filtered, washing with diethyl ether. The com-
bined filtrates were evaporated to dryness to give the title compound as a white solid 4.04 g, (91%); MS (+ve ion
electrospray) m/z 142 (MH⁺, 100%)

Step 2. Quinuclidin-4-ylacetonitrile

[0150] Quinuclidin-4-ylmethanol (2.19 g, 0.015 moles) was converted to the corresponding mesylate by treatment
with triethylamine/methanesulphonyl chloride in chloroform. Washing the organics with saturated potassium carbonate,
drying over sodium sulphate and evaporation to dryness gave the mesylate 3.24 g (95%). The mesylate was dissolved
in dry dimethyl formamide (50 ml) and treated with sodium cyanide (2.26 g, 0.046 moles) and heated to 130°C for 18
hours. The mixture was evaporated to dryness and the residue partitioned between saturated potassium carbonate
and chloroform. The organics were dried (Na₂SO₄) and chromatographed on silica gel eluting with 0-10% methanol/
chloroform. This gave the title compound 1.1 g (50%); 1H NMR (CDCl₃) 1.45 (6H, t, J 9 Hz), 2.12 (2H, s), 2.85 (6H, t,
J 9 Hz); MS (+ve ion electrospray) m/z 151 (MH⁺, 100%).

Step 3. Ethyl quinuclidin-4-ylacetate

[0151] Hydrogen chloride gas was bubbled through a solution of quinuclidin-4-ylacetonitrile (1.1 g, 0.007 moles) in
ethanol (40 ml) at reflux for 48 hours. The mixture was concentrated in vacuo and treated with saturated potassium carbonate.
Extraction with chloroform (4x50 ml), drying and chromatography on silica gel eluting with 0-10% methanol/
chloroform gave the title compound 1.0 g (69%); 1H NMR (CDCl₃) 1.45 (6H, t, J 9 Hz), 1.45 (6H, t, J 9 Hz), 2.08 (2H,
s), 2.85 (6H, t, J 9 Hz), 4.05 (2H, q, J 8 Hz).

Step 4. Quinuclidin-4-ylacetic acid hydrochloride

[0152] Ethyl quinuclidin-4-ylacetate (1.0 g, 0.005 moles) was heated under reflux in 5M hydrochloric acid (60 ml) for
18 hours. Evaporation to dryness and trituration with acetone gave the title compound 0.93 g (89%); 1H NMR (CD₃SOCD₃)
1.71 (6H, t, J 9 Hz), 2.15 (2H, s), 3.05 (6H, t, J 9 Hz), 10.35-10.55 (1H, br s), 12.19-12.29 (1H, br s).

Step 5. Quinuclidin-4-ylaceetyl chloride hydrochloride

[0153] Quinuclidine-4-acetic acid hydrochloride (0.5 g, 0.0024 moles) was converted to the title compound using the
method of Example 8, Step 4. MS (+ve ion electrospray in methanol) m/z 183 (MH⁺ for methyl ester, 100% showing complete conversion)
Step 6. (3R)-3-Deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin 14-(quinuclidin-4-yl)-acetate

[0154] Quinuclidin-4-ylacetyl chloride hydrochloride (0.54 g, 0.0024 moles) and (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin (0.84 g, 0.0025 moles) were heated together in dry dimethylformamide (15 ml) at 100°C for 6 hours. The mixture was evaporated to dryness and the residue partitioned between saturated sodium hydrogen carbonate and chloroform. The organic layer was dried and chromatographed on silica gel eluting with 0-6% methanol/chloroform to give the title compound 0.4 g (39%) as a foam; 1H NMR (CDCl3) 0.87 (3H, d, J 7 Hz), 0.98 (3H, d, J 7 Hz), 1.05-1.70 (19 H, m), 1.95-2.03 (2H, m), 2.15 (2H, d, J 5 Hz), 2.17-2.21 (1H, m), 2.35-2.45 (1H, m), 2.85-2.97 (8H, m), 3.15 (3H, s), 3.35-3.45 (1H, m), 4.95 (1H, d, J 17 Hz), 5.30 (1H, d, J 12 Hz), 5.70 (1H, d, J 12 Hz), 6.67 (1H, dd, J 17 Hz and J 10 Hz); MS (+ve ion electrospray) m/z 486 (MH+, 100%).

Step 7. Mutilin 14-(quinuclidin-4-yl)-acetate

[0155] (3R)-3-Deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin-14-(quinuclidin-4-yl)-acetate (0.37 g, 0.008 moles) in 1,4-dioxan (5 ml) was treated with concentrated hydrochloric acid (5 ml) and stirred at ambient temperature for 4 hours. Water (20 ml) was added and the mixture basified with sodium hydrogen carbonate. The product was extracted into chloroform (2 x 25 ml), dried (Na2SO4), filtered and evaporated to dryness to give the title compound as a white foam 0.33 g (92%); 1H NMR (CDCl3) inter alia 0.7 (1H, d, J 7 Hz), 0.85 (1H, d, J 7 Hz) 1.1 (3H, s), 1.4 (3H, s), 2.85 (6H, t, J 9 Hz), 3.30-3.45 (1H, br s), 5.18 (1H, d, J 17 Hz), 5.31 (1H, d, J 10 Hz), 5.75 (1H, J, J 10 Hz), 6.50 (1H, dd, J 17 and J 10 Hz). MS (+ve ion electrospray) m/z 472 (MH+, 100%).

Example 22 - Mutilin 14-(quinuclidin-4-ylmethyl)-aminoacetate

Step 1. 4-Cyanoquinuclidine

[0156] Quinuclidin-4-ylcarbonyl chloride hydrochloride (Example 8, Step 4) (3.4 g; 0.016 moles) was dissolved in acetonitrile (150 ml) and treated with 35% ammonia solution (50 ml). The mixture was stirred for 18 hours at ambient temperature then concentrated to dryness in vacuo. 1 g of the residue was then treated with phosphorus oxychloride (8 ml) at reflux for 5 hours. The mixture was then concentrated in vacuo and the residue partitioned between saturated potassium carbonate and diethylether (4 x 50 ml). The combined organic extracts were dried (Na2SO4), filtered and concentrated. Column chromatography on silica gel eluting with 0-5% methanol/chloroform gave the title compound 0.34 g (75%); 1H NMR (CDCl3) 1.85 (6H, t, J 10 Hz), 2.91 (6H, t, J 10 Hz).

Step 2. 4-Aminomethylquinuclidine

[0157] 4-Cyanoquinuclidine (0.31 g, 0.0028 moles) was reduced with lithium aluminium hydride (0.45 g, 0.012 moles) in tetrahydrofuran (20 ml) at ambient temperature for 18 hours. Diethyl ether (20 mls) was added followed by water (1.8 ml) and 10% w/v aqueous sodium hydroxide (0.68 ml) and the mixture stirred for 30 minutes. The mixture was then filtered and the filtrate concentrated in vacuo to give the title compound 0.3 g (94%).

Step 3. Mutilin 14-(quinuclidin-4-ylmethyl)-aminoacetate

[0158] 4-Aminomethylquinuclidine (0.2 g, 0.0014 moles) in chloroform (20 ml) was treated with diisopropylethylamine (0.54 g, 0.0042 moles) and mutilin 14-methanesulphonyloxyacetate (0.65 g, 0.0014 moles). The mixture was heated under reflux for 4 hours then allowed to cool. The solution was washed with saturated sodium hydrogen carbonate solution (2 x 20 ml). The organic phase was separated and dried (Na2SO4) and concentrated. Chromatography on a Sep-Pak silica gel (10 g) cartridge eluting with 0-10% (9:1 methanol/35% ammonia solution) in chloroform gave the title compound 0.0065 g (1%); 1H NMR (CDCl3) inter alia 0.71 (3H, d, J 7 Hz), 0.89 (3H, d, J 7 Hz), 1.1 (3H, s), 1.41 (3H, s), 2.80 (6H, t, J 10 Hz), 3.28 (2H, q, J 21 Hz), 5.20 (1H, d, J 17 Hz), 5.35 (1H, d, J 11 Hz), 5.75 (1H, d, J 8 Hz), 6.52 (1H, dd, J 17 and 11 Hz). MS (+ve ion electrospray) m/z 501 (MH+, 30%).

Example 23 - Mutilin 14-[3-(quinuclidin-4-yl)-acrylate]

Step 1. N',O-Dimethylquinuclidin-4-yl amide

[0159] Quinuclidin-4-ylcarbonyl chloride hydrochloride (Example 8, Step 4) (16.5 g; 0.079 moles) in acetonitrile (600 ml) at 0°C was treated with N,O-Dimethylhydroxylamine hydrochloride (8.8g, 0.09 moles) and pyridine (20 ml, 0.24 moles) and stirred at ambient temperature for 18 hours. The mixture was concentrated in vacuo and the residue par-
partitioned between saturated potassium carbonate and diethyl ether. The organics were dried (Na₂SO₄) filtered and evaporated to dryness to give the title compound 8.8 g (57%); ¹H NMR (CDCl₃) 1.88 (6H, t, J 10 Hz), 2.91 (6H, t, J 10 Hz), 3.13 (3H, s), 3.65 (3H, s).

Step 2. Quinuclidine-4-carboxaldehyde

[N0160] N.O-Dimethylquinuclidin-4-yl amide (8.77 g, 0.044 moles) in dry toluene at -70°C was treated with 1.5 molar diisobutylaluminiumhydride (45 ml, 0.067 moles) and allowed to warm to ambient temperature over 2 hours. The reaction was quenched with excess 5M hydrochloric acid, basified with potassium carbonate and extracted into diethyl ether. The organics were dried (Na₂SO₄), filtered and concentrated. Chromatography on silica gel eluting with 0-10% (9:1 methanol/880 ammonia) in chloroform gave the title compound 1.3 g (21%); ¹H NMR (CDCl₃) 1.59 (6H, t, J 10 Hz), 2.90 (6H, t, J 10 Hz), 9.40 (1H, s).

Step 3. Ethyl [3-(quinuclidin-4-yl)-acrylate]

[N0161] Triethylphosphonoacetate (1.6 ml, 0.0077 moles) in dimethoxyethane (50 ml) was treated with sodium hydride 60% dispersion in oil (0.35 g, 0.0088 moles) at ambient temperature for 1 hour. Quinuclidine-4-carboxaldehyde (1.0 g, 0.0072 moles) was then added and the mixture heated under reflux for 2 hours, allowed to cool and concentrated in vacuo. Chromatography of the residue on silica gel, eluent as in Step 2, gave the title compound 0.71 g (47%); ¹H NMR (CDCl₃) 1.29 (3H, t, J 10 Hz), 1.55 (6H, t, J 10 Hz), 2.99 (6H, t, J 10 Hz), 4.18 (2H, q, J 10 Hz), 5.65 (1H, d, J 19 Hz), 6.79 (1H, d, J 19 Hz).

Step 4. 3-(Quinuclidin-4-yl)-acrylic acid hydrochloride

[N0162] Ethyl 3-(quinuclidin-4-yl)-acrylate (0.7 g, 0.0033 moles) was heated under reflux in 5 molar hydrochloric acid (30 ml) for 18 hours, cooled then concentrated in vacuo to an oil. Trituration with acetone gave the title compound as an off-white solid 0.43 g (60%). MS (+ve ion electrospray) m/z 182 (MH⁺, 100%).

Step 5. 3-(Quinuclidin-4-yl)-propionate hydrochloride

[N0163] The title compound was prepared from 3-(quinuclidin-4-yl)-acrylic acid as in the method of Example 8, Step 4 (0.24 g, 100%). MS (+ve ion electrospray) m/z 196 (MH⁺, 100% - methyl ester from reaction with methanol).

Step 6. (3R)-3-Deoxy-11-deoxy-3-methoxy-11-oxo-4-epimutilin-14-[3’-(quinucHdin-4-yl)-acrylate]

[N0164] (3R)-3-Deoxy-11-deoxy-3-methoxy-11-oxo-4-epimutilin (0.24 g, 0.001 moles) and (3R)-3-deoxy-11-deoxy-3-methoxy-11-oxo-4-epimutilin (0.34 g, 0.001 moles) were heated together in dimethylformamide (15 ml) at 110°C for 18 hours. The mixture was allowed to cool and concentrated in vacuo. The residue was partitioned between chloroform and saturated sodium hydrogen carbonate solution. The organic layer was dried (Na₂SO₄), filtered and evaporated to dryness. Chromatography on Sep-Pak silica gel 10 g cartridge eluting with 0-10% (9:1 methanol / 35% ammonia solution) in chloroform gave the title compound 0.035 g (6.5%); MS (+ve ion electrospray) m/z 498 (MH⁺, 100%).

Step 7. Mutilin 14-[3-(quinuclidin-4-yl)-propionate]

[N0165] The title compound was prepared from (3R)-3-Deoxy-11-deoxy-3-methoxy-11-oxo-4-epimutilin-14-[3’-(quinucHdin-4-yl)-acrylate] (0.035 g, 0.00007 moles) as in the method of Example 21, Step 7 0.026 g, (76%); ¹H NMR (CDCl₃) inter alia 0.61 (3H, d, J 7 Hz), 0.8 (3H, d, J 7 Hz), 1.1 (3H, s), 2.80 (6H, t, J 10 Hz), 5.12 (1H, d, J 17 Hz), 5.28 (1H, d, J 11 Hz), 5.49 (1H, d, J 15 Hz), 5.70 (1H, d, J 8 Hz), 6.49 (1H, dd, J 17 and 11 Hz), 6.64 (1H, d, J 15 Hz); MS (+ve ion electrospray) m/z 484 (MH⁺, 85%).

Example 24 - Mutilin 14-[3-(Quinuctidin-4-yl)]-propionate

Step 1. 3-(Quinuclidin-4-yl)-propionic acid hydrochloride

[N0166] 3-(Quinuclidin-4-yl)-acrylic acid (Example 23, Step 4) (0.2 g, 0.0009 moles) was hydrogenated at atmospheric pressure and ambient temperature over 10% palladium on charcoal (0.05 g) for 18 hours. The catalyst was filtered off and the filtrate evaporated to dryness to give the title compound 0.18 g (89%); MS (+ve ion electrospray) m/z 184 (MH⁺, 100%).
Step 2. 3-(Quinuclidin-4-yl)-propionylchloride hydrochloride

[0167] The title compound was prepared from 3-(quinuclidin-4-yl)-propionic acid hydrochloride (0.18 g, 0.0008 moles) as in the method of Example 8, Step 4. 0.19 g (100%). MS (+ve ion electrospray) m/z 198 (MH+, 100%)-methyl ester from reaction with methanol.

Step 3. (3R)-3-Deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin 14-[3'-(quinuclidin-4-yl)-propionate]

[0168] The title compound was prepared from 3-(quinuclidin-4-yl)-propionyl chloride hydrochloride (0.19 g, 0.0008 moles) and (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin (0.27 g, 0.0008 moles) as in the method of Example 21, Step 6. 0.19 g (48%). MS (+ve ion electrospray) m/z 500 (MH+, 100%).

Step 4. Mutilin 14-[3'-quinuclidin-4-yl-propionate]

[0169] The title compound was prepared from (3R)-3-deoxo-11-deoxy-3-methoxy-11-oxo-4-epimutilin 14-[3'-quinuclidin-4-yl-propionate] (0.18 g, 0.0004 moles) as in the method of Example 21, Step 7. 0.15 g (83%); 1H NMR (CDCl3) inter alia 0.69 (3H, d, J 7 Hz), 0.87 (3H, d, J 7 Hz), 1.14 (3H, s), 1.45 (3H, s), 2.85 (6H, t, J 10 Hz), 5.17 (1H, d, J 17 Hz), 5.31 (1H, d, J 11 Hz), 5.69 (1H, d, J 8 Hz), 6.51 (1H, dd, J 17 and 11 Hz). MS (+ve ion electrospray) m/z 486 (MH+, 100%).

Example 25 - Mutilin 14-(quinuclidin-4-ylmethyloxy)-acetate

Step 1. Quinuclidin-4-ylmethanol

[0170] Quinuclidine-4-carboxylic acid hydrochloride (3.0 g, 0.016 moles) was treated with lithium aluminium hydride (2.5 g, 0.066 moles) in tetrahydrofuran (150 ml) at ambient temperature for 18 hours. The reaction was worked up as in the method of Example 22, Step 1 to give the title compound 2.24 g (100%). MS (+ve electrospray) m/z 142 (MH+, 100%).

Step 2. Mutilin 14-(quinuclidin-4-ylmethyloxy)-acetate

[0171] Quinuclidin-4-ylmethanol (0.3 g, 0.002 moles) in dry dimethylformamide (5 ml) was treated with sodium hydride 60% dispersion in oil (0.095 g, 0.0022 moles) at ambient temperature for 1 hour. The mixture was then cooled to -10°C and mutilin 14-methanesulphonyloxyacetate (1.0 g, 0.002 moles) was added. The mixture was stirred for 4 hours at ambient temperature then concentrated in vacuo. The residue was partitioned between saturated sodium hydrogen carbonate and chloroform. The organic layer was dried (Na2SO4), filtered and evaporated to dryness. Chromatography on Sep-Pak silica gel (10 g) cartridge eluting with 0-10% (9:1 methanol/880 ammonia) in chloroform gave the title compound 0.12 g (12%); 1H NMR (CDCl3) inter alia 0.71 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.16 (3H, s), 1.42 (3H, s), 2.85 (6H, t, J 10 Hz), 3.14 (2H, dd, J 10 and J 2.6 Hz), 3.93 (2H, q, J 17 Hz), 5.20 (1H, d, J 17 Hz), 5.35 (1H, d, J 11 Hz), 5.78 (1H, d, J 8 Hz), 6.52 (1H, dd, J 17 and J 11 Hz), 6.52 (1H, dd, J 17 and J 11 Hz). MS (+ve ion electrospray) m/z 502 (MH+, 100%).

Example 26 - Mutilin 14-[(3R)-quinuclidin-3-ylamino]-acetate

[0172] The title compound was prepared from (R)-(+)-3-aminoquinuclidine dihydrochloride and mutilin 14-methanesulphonyloxyacetate as in the method of Example 25, Step 2. 0.05 g (9%); 1H NMR (CDCl3) inter alia 0.71 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.18 (3H, s), 1.45 (3H, s), 2.85 (6H, t, J 17 Hz), 5.17 (1H, d, J 17 Hz), 5.35 (1H, d, J 11 Hz), 5.81 (1H, d, J 8 Hz), 6.52 (1H, dd, J 17 and J 11 Hz), 6.52 (1H, dd, J 17 and J 11 Hz). MS (+ve ion electrospray) m/z 487 (MH+, 82%).

Example 27 - Mutilin 14-(quinuclidin-4-yl-amino)-acetate

Step 1. 4-Aminoquinuclidine dihydrochloride

[0173] Quinuclidin-4-ylcarbonylchloride (Example 8, Step 4) (1.0 g, 0.0048 moles) was treated with sodium azide (0.34 g, 0.005 moles) in dimethylformamide (10 ml) at 50°C for 18 hours. The mixture was concentrated in vacuo and the residue partitioned between saturated potassium carbonate and toluene. The toluene solution was separated, dried (Na2SO4), filtered and the filtrate was heated under reflux for 1 hour to give the isocyanate. The mixture was allowed to cool and then extracted with 5 M hydrochloric acid (3 x 20 ml). The combined acid extracts were then heated under
reflux for 1 hour, cooled then evaporated to dryness. Trituration with acetone gave the title compound as a white solid 0.56 g (60%). M.S. (+ve ion electrospray) m/z 127 (MH+, 100%).

Step 2. Mutilin 14-(quinuclidin-4-ylamino)-acetate

[0174] The title compound was prepared from 4-aminoquinuclidine dihydrochloride and mutilin 14-methanesulphonyloxacetate as in the method of Example 25 Step 2 0.023 g (3%); 1H NMR (CDCl3) inter alia 0.7 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.48 (3H, s), 2.95 (6H, t, J 10 Hz), 5.20 (1H, d, J 17 Hz), 5.35 (1H, d, J 11 Hz), 5.75 (1H, d, J 8 Hz), 6.49 (1H, dd, J 17 and J 11 Hz). M.S. (+ve ion electrospray) m/z 487 (MH+, 100%).

Example 28 - Mutilin 14-[4-(quinuclidin-4-yl)]-butyrate

Step 1. Quinuclidin-4-acetonitrile

[0175] Quinuclidin-4-ylmethanol (1.94 g, 0.014 moles) was converted to the corresponding mesylate by treatment with methane sulphonyl chloride and triethylamine in chloroform. The mesylate was dissolved in dimethylformamide (50 ml) and treated with sodium cyanide (1.4 g, 0.028 moles) at 120°C for 18 hours. The mixture was cooled and concentrated in vacuo. The residue was partitioned between saturated potassium carbonate and chloroform. The organic layer was separated and dried (Na2SO4), filtered and evaporated to dryness. Chromatography on silica gel eluting with 0-10% methanol/chloroform gave the title compound 1.5 g (72%). M.S. (+ve electrospray) m/z 151 (MH+, 100%).

Step 2. Quinuclidin-4-acetaldehyde

[0176] Quinuclidin-4-ylacetonitrile (3.0 g, 0.02 moles) in dry toluene (100 ml) was treated with 1.5 molar diisobutyl aluminium hydride (19.7 ml, 0.03 moles) at ambient temperature for 5 hours. The mixture was quenched by adding 2 M hydrochloric acid (50 ml) and stirring for 30 minutes. The mixture was then basified with potassium carbonate and extracted with chloroform. The organics were separated, dried (Na2SO4), filtered and evaporated to dryness to give the title compound as an oil 2.2 g (72%). M.S. (+ve ion electrospray) m/z 154 (MH+, 100%).

Step 3. Mutilin 14-[4-(quinuclidin-4-yl)]-butyrate

[0177] The title compound was prepared in 6 steps from quinuclidin-4-ylacetaldehyde analogously to Example 23 Steps 3-4 and Example 24 Steps 1-4 0.08 g (3% overall, 6 steps); 1H NMR (CDCl3) inter alia 0.65 (3H, d, J 7 Hz), 0.81 (3H, d, J 7 Hz), 1.10 (3H, s), 1.18 (3H, s), 2.95 (6H, t, J 10 Hz), 5.12 (1H, d, J 17 Hz), 5.27 (1H, d, J 11 Hz), 5.65 (1H, d, J 8 Hz), 6.43 (1H, dd, J 17 and J 11 Hz). M.S. (+ve ion electrospray) m/z 500 (MH+, 100%).

Example 29

(±) Mutilin 14-(1-azabicyclo[3,3,0]oct-4-ylmethylsulfanyl)-acetate

[0178] The title compound was prepared as in the method of Reference Example 3 from (±)-1-azabicyclo[3,3,0]octan-4-ylmethanol (1.85 g, 0.007 moles) (Pizzorno, M.T., Albornico S.M., J. Org. Chem. (1974) 39, 731). This gave 1.3 g (71%); 1H NMR (CDCl3) inter alia 0.75 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.45 (3H, s), 5.20 (1H, d, J 17 Hz), 5.74 (1H, d, J 8 Hz), 6.50 (1H, dd, J 17 and J 11 Hz). M.S. (+ve ion electrospray) m/z 518 (MH+, 100%).

Example 30 - (±) Mutilin 14-(1-azabicyclo[3,3,0]oct-3-ylsulfanyl)-acetate

[0179] The title compound was prepared as in the method of Reference Example 3 from (±)-1-azabicyclo[3,3,0]octan-3-ol (0.6 g, 0.0047 moles) (Schnekenburger, J. Pharm. Inst., Univ. Kiel, Kiel, D-2300, Fed. Rep. Ger. Arch. Pharm. (1988), 321 (12), 925-9). This gave 0.21 g (9%); 1H NMR (CDCl3) inter alia 0.72 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.18 (3H, s), 1.45 (3H, s), 5.20 (1H, d, J 17 Hz), 5.34 (1H, d, J 11 Hz), 5.74 (1H, d, J 8 Hz), 6.46 (1H, dd, J 17 and J 11 Hz). M.S. (+ve ion electrospray) m/z 504 (MH+, 35%).

Example 31 - Mutilin 14-(endo)-8-methyl-8-azabicyclo[3,2,1]oct-3-ylsulfanyl)-acetate

[0180] The title compound was prepared as in the method of Reference Example 3 from exo-8-methyl-8-azabicyclo[3,2,1]octan-3-ol (1.8 g, 0.0127 moles) (Nicken, A., Fieser, L.F., J. American. Chem. Soc. (1952) 74, 5566). This gave
Example 32 - (±) Mutilin 14-(1-azabicyclo[4,3,0]non-4-ylsulfanyl)-acetate

Step 1. (±) 1-Azabicyclo[4,3,0]nonan-4-ol

0.73 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.47 (3H, s), 5.18 (1H, d, J 17 Hz), 5.32 (1H, d, J 11 Hz), 5.75 (1H, d, J 8 Hz). M.S. (+ve ion electrospray) m/z 518 (MH+, 100%).

Step 2. (±) Mutilin 14-(1-azabicyclo[4,3,0]non-4-ylsulfanyl)-acetate

0.72 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.20 (3H, s), 1.45 (3H, s), 5.21 (1H, d, J 17 Hz), 5.34 (1H, d, J 11 Hz), 5.77 (1H, d, J 8 Hz). M.S. (+ve ion electrospray) m/z 518 (MH+, 100%).

Example 33 - (±) 19,20-Dihydromutilin 14-(1-azabicyclo[4,3,0]non-4-ylsulfanyl)-acetate

0.71 (3H, d, J 7 Hz), 0.8 (3H, t, J 9 Hz), 1.45 (3H, s), 3.15 (2H, s). M.S. (+ve ion electrospray) m/z 520 (MH+, 100%).

Reference Example 4 - Mutilin 14-(1-carboxymethylpiperidin-4-ylsulfanyl)-acetate

Step 1. tert-Butyl (piperidin-4-one-1-yl)-acetate

1.45 (9H, s), 2.45 (4H, t, J 7 Hz), 2.3-2.4 (4H, m), 3.29 (2H, s).

Step 2. tert-Butyl (piperidin-4-ol-1-yl)-acetate

2.9g (96%). M.S. (+ve ion electrospray) m/z 216 (MH+, 100%).

Step 3. Mutilin (1-carboxymethylpiperidin-4-ylsulfanyl)-acetate

0.7 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.47 (3H, s), 5.22 (1H, d, J 17 Hz), 5.35 (1H, d, J 11 Hz), 5.75 (1H, d, J 8 Hz). M.S. (+ve ion electrospray) m/z 536 (MH+, 100%).

Reference Example 5 - Mutilin 14-(piperidin-4-ylsulfanyl)-acetate

Step 1. 1(tert.Butoxycarbonyl)piperidin-4-ol

1(tert-Butoxycarbonyl)-4-piperidone (5 g, 0.025 moles) was treated with sodium borohydride (1.13 g, 0.028 moles) in methanol (150 ml) at ambient temperature for 1 hour. Glacial acetic acid (1.68 g, 0.028 moles) was added and the mixture stirred for 15 minutes. The mixture was concentrated in vacuo and the residue partitioned between saturated sodium carbonate solution and ethyl ether. The organics were separated, dried (Na₂SO₄), filtered and evaporated to dryness to give the title compound 7.36 g (94%); 1H NMR (CDCl₃) 1.45 (9H, s), 2.45 (4H, t, J 7 Hz), 2.3-2.4 (4H, m), 3.29 (2H, s).

Step 2. tert-Butyl (piperidin-4-ol-1-yl)-acetate

3 g, 96%. M.S. (+ve ion electrospray) m/z 216 (MH+, 100%).

Step 3. Mutilin (1-carboxymethylpiperidin-4-ylsulfanyl)-acetate

0.7 (3H, d, J 7 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.47 (3H, s), 5.22 (1H, d, J 17 Hz), 5.35 (1H, d, J 11 Hz), 5.75 (1H, d, J 8 Hz). M.S. (+ve ion electrospray) m/z 536 (MH+, 100%).
inter alia 1.45 (9 H, s), 1.29-1.41 (2 H, m), 2.42-3.05 (2H, m), 3.75-3.99 (3H, m).

Step 2. Mutilin 14-(1-tertbutoxycarbonylpiperid-4-ythio)-acetate

[0188] The title compound was prepared as in the method of Reference Example 3 from 1-(tert-butoxycarbonyl)piperidin-4-ol (2.5 g, 0.012 moles). M.S. (-ve ion electrospray) m/z 576 (M-H, 100%).

Step 3. Mutilin 14-(piperidin-4-ylsulfanyl)-acetate

[0189] The product from Step 2 was treated with trifluoroacetic acid (10 ml) in dichloromethane (100 ml) at 0°C for 2 hours. The mixture was concentrated in vacuo and the residue partitioned between saturated sodium hydrogen carbonate and chloroform. The organic layer was separated, dried (Na₂SO₄) filtered and evaporated to dryness. Chromatography on silica gel eluting with 0-10% (9:1 methanol/880 ammonia) in chloroform gave the title compound 1.01 g (26%); 1 H NMR (CDCl₃) inter alia 0.75 (3H, d, J 7 Hz), 0.9 (3H, d, J 7 Hz), 1.18 (3H, s), 1.45 (3H, s), 5.20 (1H, d, J 17 Hz), 5.35 (1H, d, J 11 Hz), 5.80 (1H, d, J 8 Hz), 6.52 (1H, dd, J 17 and 11 Hz). M.S. (+ve ion electrospray) m/z 478 (MH⁺, 65%).

Reference Example 6 - Mutilin 14-(1-methylpiperidin-4-ylmethylsulfanylacetate hydrochloride

Step 1. 1-Methyl4-Chydroxymethyl)piperidine

[0190] 1-Methylpiperidine-4-carboxylic acid hydrochloride (J. Med. Chem. 1988, 31, 812) (1 g, 0.007 mole) was added portionwise to a suspension of lithium aluminium hydride (1.3 g, 0.035 mole) in dry tetrahydrofuran (100 ml) under argon at 0°C. The mixture was heated under reflux overnight after which it was cooled to 0°C and treated dropwise with water (1.3 ml), 10% sodium hydroxide solution (1.95 ml) and water (3.25 ml) and stirred for 1 hour at room temperature. The resulting slurry was filtered through celite and the filtrate evaporated in vacuo to afford the title compound 0.90 g (99.7%) as a pale orange oil; 1 H NMR (CDCl₃) 1.18-1.53 (3H, m), 1.67-1.81 (2H, m), 1.83-2.12 (3H, m), 2.28 (3H, s), 2.79-2.94 (2H, m), 3.50 (2H, d, J 7 Hz); MS (+ve ion electrospray) m/z 130 (MH⁺).

Step 2. (1-Methylpiperidin-4-ylmethylsulfanyl)-acetate

[0191] Triphenylphosphine (3.67 g, 0.014 mole) was dissolved in dry tetrahydrofuran (25 ml) and cooled to 0°C under argon. Diisopropyl azodicarboxylate (2.75 ml, 0.014 mole) was added dropwise and the mixture was stirred at 0°C for 0.5 hour. The product of Step 1 (0.90 g, 0.007 mole) and thiolacetic acid (1.0 ml, 0.014 mole) in dry tetrahydrofuran (50 ml) were added dropwise and the mixture stirred at room temperature overnight. The solvent was removed in vacuo and the residue was partitioned between 1M hydrochloric acid and diethyl ether. The aqueous layer was washed with diethyl ether until all triphenylphosphine oxide had been removed, basified with solid potassium carbonate, extracted into dichloromethane, dried (magnesium sulfate) and evaporated in vacuo to afford the title compound 0.60 g (46%) as a pale yellow oil; 1 H NMR (CDCl₃) 1.22-1.59 (3H, m), 1.72-1.85 (2H, m), 1.95 (2H, dt, J 13 and 3 Hz), 2.28 (3H, s), 2.35 (3H, s), 2.80-2.98 (4H, m); MS (+ve ion electrospray) m/z 188 (MH⁺).

Step 3. Mutilin 14-(1-methylpiperidin-4-ylmethylsulfanyl)-acetate hydrochloride

[0192] The product of Step 2 (0.19 g, 0.001 mole) was dissolved in dry ethanol (10 ml) under argon and treated with sodium methoxide (0.054 g, 0.001 mole). The mixture was stirred for 1 hour and mutilin 14-methanesulfonyloxyacetate (0.456 g, 0.001 mole) was added. The mixture was stirred at room temperature overnight. The solvent was removed in vacuo and the residue partitioned between water and dichloromethane. The organic layer was dried (magnesium sulfate) and evaporated in vacuo to afford the title compound 0.17 g (34%) as a white foam; 1 H NMR (CDCl₃) 0.73 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 5.23 (1H, dd, J 17 and 3 Hz), 5.35 (1H, d, J 13 and 3 Hz), 5.73 (1H, d, J 7 Hz), 6.48 (1H, q, J 17 and 10 Hz), 12.26-12.69 (1H, br s); MS (+ve ion electrospray) m/z 506 (MH⁺ free base).

Example 34 - Mutilin 14-[(3S,4R)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl]-acetate

Step 1. (3S,4R)-1-Azabicyclo[2.2.1]hept-3-ylmethanol

[0193] The title compound 0.60 g (84%) was prepared from (3S,4R)-1-azabicyclo[2.2.1]heptane-3-carboxylic acid...
hydrochloride (WO 98/05659, SmithKline Beecham) using the method of Example 1 Step 1; 1H NMR (CDCl₃) 1.38-1.65 (1H, m), 1.83-2.00 (1H, m), 2.12-2.66 (7H, m), 2.78-3.05 (2H, m), 3.49-3.81 (2H, m); MS (+ve ion electrospray) m/z 128 (MH⁺).

Step 2. [(3S, 4R)-1-Azabicyclo[2.2.1]hept-3-ylmethylsulfonyl]acetate

[0194] The title compound, 0.58g (66%) was prepared from the product of Step 1 using the method of Example 1 Step 2; 1H NMR (CDCl₃) 1.36-1.63 (2H, m), 1.90-2.01 (1H, m), 2.10-2.29 (1H, m), 2.34 (3H, s), 2.40-2.58 (4H, m), 2.78-2.96 (2H, m), 3.00-3.13 (2H, m); MS (+ve ion electrospray) m/z 186 (MH⁺).

Step 3. Mutilin 14-[(3S,4R)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfonyl]acetate

[0195] The title compound, 0.21 g (42%) was prepared from the product of Step 2 using the method of Example 1 Step 3. Purification of the compound was achieved by flash column chromatography on silica gel eluting with 10% methanol/dichloromethane; 1H NMR (CDCl₃) 0.76 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 5.37 (1H, dd, J 12 and 2 Hz), 5.78 (1H, d, J 7 Hz), 6.50 (1H, q, J 18 and 13 Hz); MS (+ve ion electrospray) m/z 504 (MH⁺).

Example 35 - Mutilin 14-(quinuclidin-2-ylmethylsulfonyl)-acetate

Step 1. (Quinuclidin-2-ylmethylsulfonyl)acetate

[0196] The title compound, 0.78 g (55%) was prepared from quinuclidin-2-ylmethanol (J. Am. Chem. Soc., 1988, 116, 1278) using the method of Example 1 Step 2; 1H NMR (CDCl₃) 1.08-1.22 (1H, m), 1.40-1.58 (4H, m), 1.73-1.90 (2H, m), 2.35 (3H, s), 2.66-3.28 (7H, m); MS (+ve ion electrospray) m/z 158 (MH⁺ thiol).

Step 2. Mutilin 14-(quinuclidin-2-ylmethylsulfonyl)-acetate

[0197] The title compound, 0.20 g (39%) was prepared from the product of Step 1 using the method of Example 1 Step 3; 1H NMR (CDCl₃) inter alia 1.75 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 3.18 (2H, d, J 7 Hz), 5.21 (1H, dd, J 18 and 2 Hz), 5.37 (1H, dd, J 12 and 2 Hz), 5.75 (1H, d, J 7 Hz), 6.50 (1H, q, J 18 and 12 Hz); MS (+ve ion electrospray) m/z 518 (MH⁺).

Example 36 - Mutilin 14-{(3S,4R)-1-azabicyclo[2.2.1]hept-4-ylmethylsulfonyl}-acetate

Step 1. (1-Azabicyclo[2.2.1]hept-4-ylmethylsulfonyl)acetate

[0198] The title compound, 0.55 g (42%) was prepared from 1-azabicyclo[2.2.1]hept-4-yl methanol (WO 93/15080) using the method of Example 1 Step 2; 1H NMR (CDCl₃) 1.21-1.35 (2H, m), 1.50-1.68 (2H, m), 2.29 (2H, s), 2.38 (3H, s), 2.53-2.70 (2H, m), 2.99-3.05 (2H, m), 3.28 (2H, s); MS (+ve ion electrospray) m/z 186 (MH⁺).

Step 2. Mutilin 14-{(3S,4R)-1-azabicyclo[2.2.1]hept-4-ylmethylsulfonyl}-acetate

[0199] The title compound, 0.14 g (28%) was prepared from the product of Step 1 using the method of Example 1 Step 3; 1H NMR (CDCl₃) inter alia 0.78 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 3.16 (2H, s), 5.22 (1H, dd, J 18 and 2 Hz), 5.37 (1H, dd, J 12 and 2 Hz), 5.78 (1H, d, J 8 Hz), 6.50 (1H, q, J 18 and 12 Hz); MS (+ve ion electrospray) m/z 504 (MH⁺).

Example 37 - Mutilin 14-[(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfonyl]-acetate

Step 1. (3R, 4S)-1-Azabicyclo[2.2.1]hept-3-yl methanol

[0200] The title compound, 0.68 g (95%) was prepared from (3R,4S)-1-azabicyclo[2.2.1] heptane-carboxylic acid using the method of Example 1 Step 1; 1H NMR (CDCl₃) 1.37-1.71 (2H, m), 1.82-2.00 (1H, m), 2.10-2.72 (6H, m), 2.77-3.05 (2H, m), 3.47-3.76 (2H, m); MS (+ve ion electrospray) m/z 128 (MH⁺).

Step 2. [(3R,4S)-1-Azabicyclo[2.2.1]hept-3-ylmethylsulfonyl]-acetate

[0201] The title compound, 0.22 g (25%) was prepared from the product of Step 1 using the method of Example 1
Step 2; $^1$H NMR (CDCl$_3$) 1.40-1.70 (2H, m), 1.93-2.09 (1H, m), 2.12-2.31 (1H, m), 2.35 (3H, s), 2.51-2.70 (4H, m), 2.78-2.98 (2H, m), 3.0-3.15 (2H, m); MS (+ve ion electrospray) m/z 186 (MH$^+$).

Step 3. Mutilin 14-{(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl}-acetate

[0202] The title compound 0.12 g (20%) was prepared from the product of Step 2 using the method of Example 1 Step 3; $^1$H NMR (CDCl$_3$) $^{inter alia}$ 0.72 (3H, d, J 7 Hz), 0.89 (3H, d, J 7 Hz), 3.13 (2H, s), 5.21 (1H, dd, J 18 and 2 Hz), 5.35 (1H, dd, J 12 and 2 Hz), 5.76 (1H, d, J 7 Hz), 6.50 (1H, q, J 18 and 12 Hz); MS (+ve ion electrospray) m/z 504 (MH$^+$).

Example 38 - Mutilin 14-{(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl}-acetate

Step 1. 1-Azabicyclo[3.2.1]oct-5-ylmethanol

[0203] The title compound, 2.05 g (93%) was prepared from 1-azabicyclo[3.2.1]octane-5-carboxylic acid hydrochloride (J. Med. Chem., 1991, 34, 2726-2735) using the method of Example 1 Step 1; $^1$H NMR (CDCl$_3$) 1.39-1.90 (5H, m), 2.61 (2H, s), 2.70 (4H, m), 3.35 - 3.75 (4H, m); MS (+ve ion electrospray) m/z 142 (MH$^+$).

Step 2. [1-Azabicyclo[3.2.1]oct-5-ylmethylsulfanyl]-acetate

[0204] The title compound, 1.0 g (35%) was prepared from the product of Step 1 using the method of Example 1 Step 2; $^1$H NMR (CDCl$_3$) 1.45-1.89 (6H, m), 2.47 (3H, s), 2.60 (2H, s), 2.70-2.94 (3H, m), 3.00-3.17 (3H, m); MS (+ve ion electrospray) m/z 200 (MH$^+$).

Step 3. Mutilin 14-{(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl}-acetate

[0205] The title compound, 0.19 g (7%) was prepared from the product of Step 2 using the method of Example 1 Step 3; $^1$H NMR (CDCl$_3$) $^{inter alia}$ 0.73 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 5.20 (1H, dd, J 18 and 2 Hz), 5.37 (1H, dd, J 12 and 2 Hz), 5.76 (1H, d, J 7 Hz), 6.48 (1H, q, J 18 and 12 Hz); MS (+ve ion electrospray) m/z 518 (MH$^+$).

Reference Example 7 - Mutilin 14-{(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl}-acetate

Step 1. (R)-1-Ethylcarbamoylpiperidine-2-carboxylic acid

[0206] L-Pipocolinic acid (0.50 g, 0.004 mole) in dry dichloromethane (10 ml) was cooled to 0°C under argon and treated with triethylamine (0.65 ml, 0.0046 mole) followed dropwise by ethyl chloroformate (0.37 ml, 0.004 mole) in dry dichloromethane (2 ml). The mixture was stirred overnight at room temperature after which it was diluted with dichloromethane, washed with 5M hydrochloric acid and the organic layer dried (magnesium sulfate) and evaporated in vacuo to afford the title compound 0.60 g (77%) as an orange oil; $^1$H NMR (CDCl$_3$) 1.12-1.84 (8H, m), 2.15-2.40 (1H, m), 2.88-3.20 (1H, m), 3.90-4.28 (3H, m), 4.77-5.07 (1H, m), 5.68-6.82 (1H, br s).

Step 2. (R)-1-Methylpiperidin-2-ylmethanol

[0207] The product of Step 1 (0.60 g, 0.003 mole) in dry tetrahydrofuran (10 ml) was added dropwise to a suspension of lithium aluminium hydride (0.57 g, 0.015 mole) in dry tetrahydrofuran (20 ml). The mixture was heated under reflux for 2 hours and stirred at room temperature overnight. The reaction mixture was cooled to 0°C and water (0.5 ml) was added dropwise, followed by 10% sodium hydroxide solution (0.9 ml) and water (1.4 ml). The mixture was stirred for 1 hour, filtered through Celite and the filtrate evaporated in vacuo to afford the title compound 0.06 g (77%) as an orange oil; $^1$H NMR (CDCl$_3$) 1.12-1.84 (8H, m), 2.15-2.40 (1H, m), 2.88-3.20 (1H, m), 3.90-4.28 (3H, m), 4.77-5.07 (1H, m), 5.68-6.82 (1H, br s).

Step 3. ((R)-1-Methylpiperidin-2-ylmethylsulfanyl]-acetate

[0208] The title compound, 0.30 g (71%) was prepared from the product of Step 2 using the method of Example 1 Step 2; $^1$H NMR (CDCl$_3$) 1.16-1.76 (6H, m), 2.00-2.18 (2H, m), 2.29 (3H, s), 2.35 (3H, s), 2.80-2.92 (1H, m), 3.00-3.23 (2H, m).
Step 4. Mutilin 14-{(R)-1-Methylpiperid-2-ylmethylsulfanyl}-acetate

[0209] The title compound, 0.19 g (22%) was prepared from the product of Step 3 using the method of Example 1 Step 3; 1H NMR (CDCl3) inter alia 0.75 (3H, d, J 7 Hz), 0.89 (3H, d, J 7 Hz), 3.11 (2H, s), 3.36 (1H, q, J 12 and 7 Hz), 5.19 (1H, dd, J 18 and 2 Hz), 5.35 (1H, dd, J 12 and 2 Hz), 5.75 (1H, d, J 7 Hz), 6.50 (1H, q, J 18 and 12 Hz); MS (+ve ion electrospray) m/z 506 (MH+).

Reference Example 8 - Mutilin 14-{(S)-1-Methylpyrrolid-2-ylmethylsulfanyl}-acetate

Step 1. [(S)-1-Methylpyrrolid-2-ylmethylsulfanyl] -acetate

[0210] The title compound, 0.64 g (85%) was prepared from (S)(−)-1-methyl-2-pyrrolid-2-ylmethanol using the method of Example 1 Step 2; 1H NMR (CDCl3) 1.44-1.61 (1H, m), 1.65-1.85 (2H, m), 1.87-2.04 (1H, m), 2.15-2.42 (2H, m), 2.35 (3H, s), 2.38 (3H, s), 2.82-2.94 (1H, m), 3.05-3.14 (1H, m), 3.28 (1H, dd, J 13 and 7 Hz); MS (-ve ion electrospray) m/z 130 (M-H for thiol).

Step 2. Mutilin 14-{(S)-1-Methylpyrrolid-2-ylmethylsulfanyl}-acetate

[0211] The title compound, 0.17 g (23%) was prepared from the product of Step 1 using the method of Example 1 Step 3; 1H NMR (CDCl3) inter alia 0.76 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 3.18 (2H, s), 3.35 (1H, q, J 10 and 7 Hz), 5.20 (1H, dd, J 18 and 2 Hz), 5.35 (1H, dd, J 12 and 2 Hz), 5.75 (1H, d, J 7 Hz), 6.50 (1H, q, J 18 and 12 Hz); MS (+ve ion electrospray) m/z 492 (MH+).

Reference Example 9 - Mutilin 14-1{(R)-1-methylpiperid-3-ylmethylsulfanyl}-acetate

Step 1. (R)-Ethyl 1-ethylcarbamoylpiperidine-3-carboxylate

[0212] (R)-Ethynipecotate (J.Org. Chem., 56, 1991, 1166-1170) (3.0 g, 0.019 mole) in dry dichloromethane (50 ml) was cooled to 0°C under argon. Triethylamine (3.19 ml, 0.023 mole) was added, followed dropwise by ethyl chlorofor-mate (1.83 ml, 0.019 mole) in dry dichloromethane (6 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with dichloromethane, washed with water, dried (magnesium sulfate) and evaporated in vacuo to afford the title compound 3.45 g (79%) as a colourless oil; 1H NMR (CDCl3) 1.28 (6H, t, J 7 Hz), 1.38-1.82 (3H, m), 2.00-2.15 (1H, m), 2.38-2.55 (1H, m), 2.77-3.13 (2H, m), 3.91-4.04 (1H, m), 4.07-4.35 (5H, m)

Step 2. (R)-1-Methylpiperid-3-ylmethanol

[0213] The title compound, 1.8 g (92%) was prepared from the product of Step 1 using the method of Example 7 Step 2; 1H NMR (CDCl3) 0.90-1.12 (1H, m), 1.50-1.90 (5H, m), 1.94-1.99 (1H, m), 2.25 (3H, s), 2.57-2.74 (1H, m), 2.79-2.92 (1H, m), 3.14-3.71 (3H, m); MS (+ve ion electrospray) m/z 130 (MH+).

Step 3. (R)-1-Methylpiperid-3-ylmethylsulfanyl]-acetate

[0214] The title compound, 0.59 g (81%) was prepared from the product of Step 2 using the method of Example 1 Step 3; 1H NMR (CDCl3) 0.87-1.06 (1H, m), 1.44-1.94 (6H, m), 2.27 (3H, s), 2.34 (3H, s), 2.62-2.92 (4H, m); MS (+ve ion electrospray) m/z 188 (MH+).

Step 4. Mutilin 14-{(R)-1-methylpiperid-3-ylmethylsulfanyl}-acetate

[0215] The title compound, 0.26 g (34%) was prepared from the product of Step 3 using the method of Example 1 Step 3; 1H NMR (CDCl3) inter alia 0.74 (3H, d, J 7 Hz), 0.90 (3H, d, J 7 Hz), 3.12 (2H, d, J 2 Hz), 3.30-3.44 (1H, m), 5.22 (1H, dd, J 18 and 2 Hz), 5.38 (1H, dd, J 12 and 2 Hz), 5.76 (1H, d, J 7 Hz), 6.50 (1H, q, J 18 and 12 Hz); MS (+ve ion electrospray) m/z 506 (MH+).

Example 39 - Mutilin 14-(quinuclidin-4-ylmethylsulfanyl)-acetate

[0216] A solution of triphenylphosphine (1.1 g, 0.0042 mole) in dry tetrahydrofuran (50 ml) was ice-cooled under argon and treated with diisopropyl azodicarboxylate (0.85 g, 0.0042 mole). After 30 minutes a solution of thiolacetic acid (0.315 ml, 0.0042 mole) and quinuclidin-4-ylmethanol (0.565 g, 0.0042 mole) in dry tetrahydrofuran was added
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dropwise. The mixture was then allowed to stand at 5°C for 72 hours. Following concentration in vacuo the residue was partitioned between diethyl ether and 1M hydrochloric acid. The aqueous phase was washed with diethyl ether then concentrated in vacuo to give a solid (0.65 g). The solid was dissolved in ethanol and treated with potassium tert-butoxide (0.785 g, 0.007 mole). After stirring for 30 minutes mutilin 14-methanesulfonyloxyacetate (1.38 g, 0.003 mole) was added. The mixture was stirred under argon for 18 hours then concentrated in vacuo. The residue was partitioned between chloroform and water. The organic phase was washed with brine, dried over magnesium sulfate and concentrated in vacuo. Chromatography on silica gel eluting with chloroform / methanol / 35% ammonia solution (10/1/0.1) provided the title compound 0.478 g (31%); 1H NMR (CDCl_3) _inter alia_ 0.74 (3H, d, J 6.5 Hz), 0.88 (3H, d, J 7 Hz), 1.17 (3H, s), 1.40 (6H, t, J 8 Hz), 2.47 (2H, s), 2.87 (6H, t, J 8 Hz), 3.0 (2H, s), 3.36 (1H, m), 5.1 to 5.4 (2H, m), 5.75 (1H, d, J 8.3 Hz), 6.48 (1H, m); MS (+ve ion electrospray) m/z 518 (MH^+, 100%).

**Example 40 - Mutilin 14-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylmethylsulfanyl)-acetate**

**Step 1. (8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methanol**

[0217] The title compound was prepared from 8-methyl-8-azabicyclo[3.2.1]octane-3-carboxylic acid hydrochloride salt (WO 98/05659 Example 25, Step 3) using the process described in Example 21 Step 1 0.78 g (100%); 1H NMR (CDCl_3) _inter alia_ 1.3-2.0 (9H, m), 2.25 (3H, s), 3.16 (2H, m), 3.44 (2H, d, J 6.3 Hz); MS (+ve ion electrospray) m/z 156 (MH^+, 100%).

**Step 2. Mutilin 14-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylmethylsulfanyl)-acetate**

[0218] The title compound was prepared from (8-methyl-8-azabicyclo[3.2.1]oct-3-yl)methanol and mutilin 14-methanesulfonyloxyacetate using the process described in Reference Example 3 0.101 g (19%); 1H NMR (CDCl_3) _inter alia_ 0.74 (3H, d, J 6.5 Hz), 0.88 (3H, d, J 7 Hz), 1.25 (3H, s), 1.49 (3H, s), 2.34 (3H, s), 2.48 (2H, d, J 6.3 Hz), 3.1 (2H, s), 3.15 (2H, m), 3.36 (1H, m), 5.1-5.4 (2H, m), 5.74 (1H, d, J 8.5 Hz), 6.48 (1H, m); MS (+ve ion electrospray) m/z 533 (MH^+, 85%).

**Example 41 - Mutilin 14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)-acetate**

[0219] The title compound was prepared from _endo_-8-methyl-8-azabicyclo[3.2.1]octan-3-ol and mutilin 14-methanesulfonyloxyacetate using the process described in Reference Example 3 0.09 g (17%); 1H NMR (CDCl_3) _inter alia_ 0.74 (3H, d, J 6.7 Hz), 0.99 (3H, d, J 7.5 Hz), 1.18 (3H, s), 1.63 (3H, s), 2.28 (3H, s), 3.0 (1H, m), 3.13 (2H, s), 3.16 (2H, m), 3.36 (1H, m), 5.15 to 5.37 (2H, m), 5.77 (1H, d, J 8.3 Hz), 6.49 (1H, m); MS (+ve ion electrospray) m/z 518 (MH^+, 100%).

**Example 42 -Mutilin 14-[(3-(quinuclidin-4-ylsulfanyl)]-propionate**

**Step 1. Mutilin 14-acrylate-11-trifluoroacetate**

[0220] Mutilin 11-trifluoroacetate (WO 97/25309 Example 85 step 2) (3.0 g, 0.0072 mole), triethylamine (3.74 g, 0.037 mole) and a catalytic amount of 4-dimethylaminopyridine in dichloromethane (100 mls) was treated with acryloyl chloride (3.33 g, 0.037 mole) overnight at room temperature under argon. The reaction mixture was partitioned between water and dichloromethane. The organic layer was dried over magnesium sulfate and the solvents removed in vacuo. Chromatography of the residue gel eluting with ethylacetate / petroleum ether 40-60° (1:10) provided the title compound 1.25 g (37%); 1H NMR (CDCl_3) _inter alia_ 0.69 (3H, d, J 6.6 Hz), 0.84 (3H, d, J 7 Hz), 1.06 (3H, s), 1.52 (3H, s), 2.1 to 2.4 (4H, m), 2.65 (1H, m), 5.0 (1H, d, J 6.9 Hz), 5.20-5.37 (2H, m), 5.72-5.86 (2H, m), 6.0-6.1 (1H, m), 6.3-6.5 (2H, m).

**Step 2. Mutilin 14-[(3-quinuclidin4-ylsulfanyl)]-propionate**

[0221] Mutilin 14-acrylate-11-trifluoroacetate (0.376 g, 0.008 mole) was treated with prepared potassium quinuclidin-4-sulfanate from quinuclidin-4-thiol hydrochloride (0.145 g, 0.0008 mole) and potassium tert-butoxide (0.094 g, 0.000838 mole) in ethanol (15 ml) under argon at room temperature overnight. Solvents were removed in vacuo and the residue chromatographed on silica gel using chloroform/methanol/35% ammonia solution (10:1:0.1) mixture. This chromatographed product (0.262 g) was dissolved in tetrahydrofuran/water (5:1) (6 ml) and treated with 0.5 M sodium hydroxide solution (1 ml) for 3 hours at room temperature. The reaction mixture was concentrated in vacuo. The residue was chromatographed on silica gel using chloroform/methanol/35% ammonia solution (9:1:0.1) mixture to provide the
Example 43 Mutilin 14-[3-(quinuclidin-4-ylmethylsulfanyl)]-propionate

[0222] To an ice-cooled solution of triphenylphosphine (1.1 g, 0.0042 mole) in dry tetrahydrofuran (50 ml) was added dropwise diisopropyl azodicarboxylate (0.85 g, 0.0042 mole). After 30 mins a solution of thiolacetic acid (0.335 g, 0.0042 mole) and quinuclidin-4-ylmethanol (Example 25, Step 1) (0.565 g, 0.004 mole) in dry tetrahydrofuran (20 ml) was added dropwise. The mixture was stirred under argon for 72 hours, evaporated in vacuo and taken up in ether. The ethereal solution was extracted with 1M hydrochloric acid. The aqueous extract was washed with ether and evaporated to give a solid (0.65 g). The title compound was prepared from the latter solid and mutilin 14-acrylate-11-trifluoroacetate (Example 42, Step 1) according to the procedure of Example 42, Step 2 0.41 g (80%); 1H NMR (CDCl₃) inter alia 0.72 (3H, d, J 6.8 Hz), 0.87 (3H, d, J 7.0 Hz), 1.17 (3H, s), 1.46 (3H, s), 2.18 (2H, m), 2.25 (2H, s), 2.95 (6H, t, J 7.8 Hz), 3.35 (1H, m), 5.27 (2H, m), 5.74 (1H, d, J 8.3 Hz), 6.52 (1H, m); MS (+ve ion electrospray) m/z 532 (MH⁺, 100%).

Reference Example 10 - Mutilin 14-[3-(1-methylpiperid-4-ylsulfanyl)]-propionate

[0223] A solution of triphenylphosphine (5.51 g, 0.021 mole) in dry tetrahydrofuran (100 ml) treated with diisopropyl azodicarboxylate (4.25 g, 0.021 mole). After 30 minutes a solution of 1-methylpiperidin-4-ol (2.3 g, 0.02 mole) and thiolacetic acid (1.54 g, 0.02 mole) in dry tetrahydrofuran (50 ml) was added over a period of 30 minutes. The mixture was stirred overnight, concentrated in vacuo and the residue taken up in ether. The ethereal solution was extracted with 1M hydrochloric acid. The aqueous extract was washed with ether, evaporated to dryness and dried in vacuo to give a yellow gum (2.4 g). A portion of the gum (0.252 g) was treated with sodium methoxide (0.120 g) in ethanol and subsequently with mutilin 14-acrylate-11-trifluoroacetate (Example 42, Step 1) according to the procedure of Example 42, Step 2 to give the title compound 0.3 g (74%); 1H NMR (CDCl₃) inter alia 0.71 (3H, d, J 6.8 Hz), 0.78 (3H, t, J 7.6 Hz), 0.94 (3H, d, J 7.6 Hz), 0.97 (3H, s), 1.43 (3H, s), 2.25 (2H, s), 2.42 (1H, m), 2.81 (2H, m), 3.42 (1H, t, J 6 Hz), 5.63 (1H, d, J 8 Hz); MS (+ve ion electrospray) m/z 494 (MH⁺, 75%).

Reference Example 11 - 19,20-Dihydromutilin 14-(1-methylpiperidin-4-ylsulfanyl)-acetate

Step 1. 19,20-Dihydromutilin 14-methanesulfonyloxyacetate

[0224] The title compound was prepared from 19,20-dihydropleuromutilin (A. Birch et al, Terthahedron (1966) Suppl. 8 part II, 359-387) using the literature process for pleuromutilin (H. Egger and H. Reinschagen, J. Antibiotics 29 (9), 915); 1H NMR (CDCl₃) inter alia 0.71 (3H, d, J 7 Hz), 0.77 (3H, t, 7.5 Hz), 0.95 (3H, d, J 8.5 Hz), 0.97 (3H, s), 1.42 (3H, s), 3.21 (3H, s), 3.42 (1H, m), 4.66 (2H, m), 5.72 (1H, d, 8.2 Hz).

Step 2. 19,20-Dihydromutilin 14-(1-methylpiperidin-4-ylsulfanyl)-acetate

[0225] The title compound was prepared from 4-hydroxy-1-methylpiperidine and 19,20-dihydromutilin 14-methanesulfonyloxyacetate using the process described in Reference Example 3 0.42 g (83%); 1H NMR (CDCl₃) inter alia 0.71 (3H, d, J 6.8 Hz), 0.78 (3H, t, J 7.6 Hz), 0.94 (3H, d, J 7.6 Hz), 0.97 (3H, s), 1.43 (3H, s), 2.25 (2H, s), 2.42 (1H, m), 2.81 (2H, m), 3.42 (1H, t, J 6 Hz), 5.63 (1H, d, J 8 Hz); MS (+ve ion electrospray) m/z 494 (MH⁺, 75%).

Example 44 - 19,20-Dihydromutilin 14-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylmethylsulfanyl)-acetate

[0226] The title compound was prepared from 19,20-dihydromutilin 14-methanesulfonyloxyacetate (Reference Example 11, step 1) and 8-methyl-8-azabicyclo[3.2.1]oct-3-ylmethyl methanol using the process described in Reference Example 3 0.335 g (45%); 1H NMR (CDCl₃) inter alia 0.71 (3H, d, J 6.5 Hz), 0.79 (3H, t, J 7.3 Hz), 0.93 (3H, d, J 7.0 Hz), 0.97 (3H, s), 1.0 to 2.2 (27H, m), 2.28 (3H, s), 2.41 (1H, m), 3.11 (2H, s), 3.17 (2H, m), 3.42 (1H, m), 5.62 (1H, d, J 8.3 Hz); MS (+ve ion electrospray) m/z 520 (MH⁺, 60%).
Example 45 - Mutilin 14-[4-(quinuclidin-4-ylsulfanyl)]-butyrate

Step 1. Mutilin 14-(4-bromobutyrate)-11-trifluoroacetate

[0227] Mutilin 11-trifluoroacetate (WO 97/25309, Example 85, Step 2) (1.25 g, 0.003 mole) and pyridine (0.237 g, 0.003 mole) in dry dichloromethane (20 ml) were treated with 4-bromobutyroyl chloride (0.56 g, 0.003 mole) for 72 hours. The mixture was concentrated in vacuo and the resulting residue chromatographed on silica gel using dichloromethane, providing the title compound, 1.5 g (93%); 1 H NMR (CDCl 3 ) inter alia 0.72 (3H, d, J 6.7 Hz), 0.83 (3H, d, J 7 Hz), 1.05 (3H, s), 1.43 (3H, s), 2.62 (1H, t, J 7 Hz), 3.46 (2H, t, J 6 Hz), 5.0 (1H, d, J 6.7 Hz), 5.3 (2H, m), 5.69 (1H, d, J 8 Hz), 6.37 (1H, m); MS (+ve ion electrospray) m/z 532 (MH+, 40%).

Step 2. Mutilin 14-[4-(quinuclidin-4-ylsulfanyl)]-butyrate

[0228] Quinuclidin-4-thiol hydrochloride (0.359 g, 0.002 mole) in ethanol (10 ml) was treated with sodium methoxide (0.216 g, 0.004 mole). After 30 minutes mutilin 14-(4-bromobutyrate) (0.565 g, 0.001 mole) was added and the mixture allowed to stand overnight under argon. The reaction mixture was concentrated in vacuo and the residue partitioned between water and chloroform. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel using chloroform/methanol/35% ammonia solution (10:1:0.1) to give title compound, 0.190 g (35%); 1 H NMR (CDCl 3 ) inter alia 0.71 (3H, d, J 6.5 Hz), 0.87 (3H, d, J 6.8 Hz), 1.16 (3H, s), 1.59 (3H, s), 1.81 (14H, m) 2.06 (2H, t, J 8.5 Hz), 2.49 (2H, t, J 7.3 Hz), 2.94 (6H, t, J 7.3 Hz), 3.35 (1H, m), 5.29 (2H, m), 5.75 (1H, d, J 8.5 Hz), 6.52 (1H, m); MS (+ve ion electrospray) m/z 532 (MH+, 100%).

Reference Example 12

1,2-Didehydromutilin 14-(1-methylpiperidin-4-ylmethylsulfanyl)acetate

Step 1. 1,2-Didehydromutilin 11-dichloroacetate

[0229] A solution of 1,2-didehydromutilin (1.41 g, 0.0044 mole) (prepared by analogy to the procedure described for 1,2-didehydropleuromutilin, G. Schulz and H. Berner, Tetrahedron, 1984, 40, 905-17), pyridine (0.56 ml, 0.0066 mole) and N,N-dimethylaminopyridine (0.02 g) in tetrahydrofuran (30 ml) was treated with dichloroacetic anhydride (1.16 g, 0.0048 mole) in tetrahydrofuran (5ml). After 18 hours the mixture was concentrated in vacuo and the residue partitioned between ethyl acetate and dilute hydrochloric acid. The organic phase was separated, washed with water and brine, dried over magnesium sulphate and the solvent removed in vacuo. Chromatography of the residue on silica gel eluting with 20% ethyl acetate in hexanes gave the title compound (1.3 g, 69%) as a colourless solid; 1 H NMR (CDCl 3 ) inter alia 4.33 (1H, d, J 7.7Hz), 4.57 (1H, d, J 7.0Hz), 5.34 (1H, d, J 11.2Hz), 5.48 (1H, d, J 17.8Hz), 5.99 (1H, s), 6.10 (1H, d, J 6.1Hz), 6.11 (1H, dd, J 17.8 and 11.2 Hz), 7.67 (1H, d, J 6.1 Hz).

Step 2. 1,2-Didehydromutilin 11 dichloroacetate-14-chloroacetate

[0230] A solution of 1,2-didehydromutilin 11 dichloroacetate (1.2 g, 0.0028 mole), pyridine (0.7 ml) and N,N-dimethylaminopyridine (0.01 g) in dichloromethane (10 ml) at 0°C was treated with chloroacetyl chloride (0.33 ml, 0.0042 mole). After stirring at room temperature for 18 hours the mixture was concentrated in vacuo and the residue partitioned between ethyl acetate and dilute hydrochloric acid. The organic phase was separated, washed with water and brine, dried over magnesium sulphate and the solvent removed in vacuo. Chromatography of the residue on silica gel eluting with 20% ethyl acetate in hexanes gave the title compound (0.7 g, 50%) as a colourless solid; 1 H NMR (CDCl 3 ) inter alia 0.79 (3H, d, J 6.8Hz), 1.04 (3H, d, J 7.1Hz), 1.10 (3H, s), 1.58 (3H, s), 4.00 (2H, s), 4.60 (1H, d, J 7.0Hz), 5.30 (1H, d, J 17.7Hz) 5.36 (1H, d, J 10.7Hz), 5.70 (1H, d, J 8.8Hz), 5.97 (1H, s), 6.10 (1H, d, J 6.2Hz), 6.34 (1H, dd, J 17.7 and 11.7Hz), 7.66 (1H, d, J 6.2Hz).

Step 3. 1,2-Didehydromutilin 11-dichloroacetate-14-(1-methylpiperidin-4-ylmethylsulfanyl)-acetate

[0231] The title compound (0.36 g, 49%) was prepared from 1,2-didehydromutilin 11-dichloroacetate-14-chloroacetate (0.7 g, 0.0012 mole) and (1-methylpiperidin-4-ylmethylsulfanyl)-acetate (0.224 g, 0.0012 mole) using the process described in Reference Example 6 Step 3. 1 H NMR (CDCl 3 ) inter alia 0.80 (3H, d, J 6.3Hz), 1.03 (3H, d, J 7.0Hz), 1.09 (3H, s), 1.56 (3H, s), 2.26 (3H, s), 3.13 (2H, s), 4.60 (1H, d, J 6.8Hz), 5.30 (1H, d, J 17.5 Hz), 5.34 (1H, d, J 10.7Hz), 5.66 (1H, d, J 8.4Hz), 5.97 (1H, s), 6.09 (1H, d, J 6.1 Hz), 6.34 (1H, dd, J 17.5 and 10.7Hz), 7.65 (1H, d, J 6.1Hz); MS (+ve ion electrospray) 616 and 614 (MH+).
Step 4. 1,2-Didehydromutilin 14-(1-methylpiperidin-4-ylmethylsulfanyl)-acetate

[0232] A solution of 1,2-didehydromutilin 11-dichloroacetate-14-(1-methylpiperidin-4-ylmethylsulfanyl)-acetate (0.18 g, 0.0003 mole) in dioxane (3 ml) was treated with a aqueous potassium hydroxide (1M, 0.36ml). After stirring at room temperature for 1 hour the mixture was neutralised with dilute hydrochloric acid and the solvent evaporated in vacuo. The residue was partitioned between ethyl acetate and sodium hydrogen carbonate solution. The organic phase was separated, washed with water and brine, dried over magnesium sulphate and the solvent removed in vacuo. Chromatography on silica gel eluting with dichloromethane/methanol/35% ammonia solution (20:1:0.1) gave the title compound (0.12 g, 80%) as a colourless solid; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \textit{inter alia} 0.81 (3H, d, J 6.5Hz), 1.08 (3H, d, J 7.1Hz), 1.15 (3H, s), 1.55 (3H, s), 2.26 (3H, s), 3.12 (2H, s), 5.20 (1H, dd, J 17.5 and 1.4Hz), 5.36 (1H, dd, J 10.9 and 1.4Hz), 5.72 (8.6Hz), 6.04 (1H, d, J 6.1Hz), 6.47 (1H, dd, J 17.5 and 10.9Hz), 7.73 (1H, d, J 6.1Hz); MS (+ve ion electrospray) 504 (MH\textsuperscript{+}).

Example 46 - Mutilin 14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)-acetate

[0233] 22-Deoxy-22-sulfanylpleuromutilin (US Patent 4130709, 1978) (0.1 g, 0.00025 mole) in ethanol (4 ml) was treated with sodium methoxide (0.014 g, 0.0026 mole) and the resulting mixture stirred for 30 minutes. A solution of endo-3-methanesulfonyloxy-8-methyl-8-azabicyclo [3.2.1] octane (prepared from endo-8-methyl-8-azabicyclo [3.2.1] octan-3-ol and methanesulfonyl chloride) (0.061 g, 0.00028 mole) in ethanol (1 ml) was then added. Stirring was continued for 68 hours; a further portion of endo-3-methanesulfonyloxy-8-methyl-8-azabicyclo [3.2.1] octane (0.061 g, 0.00028 mole) was then added and stirring continued for a further 18 hours. The mixture was then diluted with dichloromethane, washed twice with aqueous potassium carbonate, once with brine, dried over magnesium sulfate and concentrated in vacuo. Chromatography on silica gel eluting with chloroform/methanol/35% ammonia solution (9:1:0:1) gave the title compound 0.035 g (27%), identical to the compound described in Example 41.

Reference Example 13 - Mutilin 14-(1-carbozamidomethylpiperidin-4-ylsulfanyl)-acetate

[0234] Mutilin (1-carboxymethylpiperidin-4-ylsulfanyl)-acetate (Reference Example 4) (0.08 g, 0.00015 mole) in dichloromethane (3 ml) was treated with oxalyl chloride (0.032 ml, 0.00036 moles) and dimethylformamide (1 drop) and stirred at ambient temperature for 2 hours. The mixture was then evaporated to dryness and the residue suspended in tetrahydofuran (3 ml) and treated with 35% aqueous ammonia solution (25 ml) and stirred for 2 hours. The mixture was evaporated to dryness and the residue positioned between saturated sodium bicarbonate and chloroform. The organic layer was separated and dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and evaporated to dryness. Chromatography was saturated on silica gel eluting with chloroform/methanol/35% ammonia solution (90:9:1). Trituration of the residue obtained with methanol/diethyl ether gave the title compound 0.035 g; M.S. (+ve ion electrospray) m/z 535(MH\textsuperscript{+},88%).

Antibacterial Activity

[0235] The following Table illustrates the antibacterial activities of representative mutilin 14-esters. Activities are given as minimum inhibitory concentrations in micrograms per millilitre (10\textsuperscript{-6} g/ml), and were determined using a standard broth dilution method in microtitre.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Pleuromutilin</th>
<th>Tiamulin</th>
<th>Compound from Example 1</th>
<th>Compound from Reference Example 3</th>
<th>Compound from Example 41</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.a.</td>
<td>2</td>
<td>0.25</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
</tr>
<tr>
<td>S.p.</td>
<td>8</td>
<td>0.25</td>
<td>≤ 0.06</td>
<td>≤5 0.06</td>
<td>≤ 0.06</td>
</tr>
<tr>
<td>E.c.</td>
<td>&gt; 64</td>
<td>&gt; 64</td>
<td>16</td>
<td>64</td>
<td>32</td>
</tr>
<tr>
<td>H.i.</td>
<td>2</td>
<td>2</td>
<td>0.25</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>M.c.</td>
<td>0.5</td>
<td>0.125</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
</tr>
</tbody>
</table>

S.a. = Staphylococcus aureus; S.p. = Streptococcus pneumoniae 1629; E.c. =Escherichia coli DC0; H. i. =Haemophilus influenzae Q1; M.c. = Moraxella catarrhalis Ravasio
Pharmaceutical Compositions

Example 1 - Oily Spray Formulation

[0236] A carrier for a nasal spray formulation was prepared by forming a blend of 67% w/w fractionated coconut oil (medium chain length)* and 33% w/w of glyceryl mono-oleate **. To this blend was added 0.2% w/w of powdered lemon juice flavour, followed by 0.5 or 1.0% w/w of drug substance (either in solution or, if insoluble, micronized)***.

[0237] The resultant formulation has a viscosity which is sprayable at 20°C or above. When sprayed into the nose of a patient, the liquid coats the nasal passages and contact with moisture inside the nose (from the mucous membranes, and the humid environment generally) causes the carrier to thicken. This prolongs the residence time of the sprayed formulation on the nasal surfaces. A spray volume of about 100 µl contains approximately 0.5 or 1mg of drug substance.

Example 2 - Aqueous Spray formulation

[0238] [0239] Hydrochloric acid and sodium hydroxide were used to adjust the pH of the composition to about pH 5.5. The drug molecule shows optimum stability at this pH.

Claims

1. A compound of general formula (IA) or (IB):

```
R² — (CH₂)ₘ — X — (CH₂)ₙ — CH₂CO₂
R¹
```

*Commercial product Miglyol, obtainable from Condea.
** Commercial product Myverol 18-99, obtainable from Eastman.
*** for example, the compound of Example 1 or Example 8.
in which:

R¹ is vinyl or ethyl;

R² is a non-aromatic bicyclic group containing from 5 to 10 ring atoms in each ring, which group contains one or two basic nitrogen atoms, is attached through a ring carbon atom and is optionally substituted by up to 3 substituents selected from alkyl, alkoxy, alkenyl and alkenoxy, which are optionally further substituted by one or more groups selected from aryl, heterocyclyl, (C₁₋₆)alkoxy, (C₁₋₆)alkythio, aryloxy, aryloxy(C₁₋₆)alkylthio, amino, mono- or di-(C₁₋₆)alkylamino, cycloalkyl, cycloalkylthio, carboxy and esters thereof, amides of carboxy, ureido, carbamimidoyl (amidino), guanidino, alkyl-sulfonyl, amino-sulfonyl (C₁₋₆)acyloxy, (C₁₋₆)acylamino, azido, hydroxy, and halogen;

each of n and m is independently 0, 1 or 2;

X is selected from -O-, -S-, -S(O)-, -SO₂-, -CO.O-, -NH-, -CONH-, -NHCONH- and a bond; and

R³ is H or OH; or

the moiety R²(CHₙ)mX(CH₂)nCH₂COO at position 14 of (IA) or (IB) is replaced by RᵃRᵇC=CHCOO in which one of Rᵃ and Rᵇ is hydrogen and the other is R² or R² and Rᵇ together form R²; or

a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which R² is selected from optionally substituted quinuclidinyl, azabicyclo[2.2.1]heptyl, azabicyclo[4.3.0]nonyl, azabicyclo[3.2.1]octyl, azabicyclo[3.3.0]octyl, azabicyclo[2.2.2]octyl, azabicyclo[3.2.1]octenyl, azabicyclo[3.3.1]nonyl and azabicyclo[4.4.0]decal.

3. A compound according to claim 1 or 2 in which R² is substituted by alkyl, alkoxy, alkenyl or alkenoxy, which are optionally further substituted by one or more groups selected from aryl, heterocyclyl, (C₁₋₆)alkoxy, (C₁₋₆)alkythio, aryloxy, aryloxy(C₁₋₆)alkythio, amino, mono- or di-(C₁₋₆)alkylamino, cycloalkyl, cycloalkylthio, carboxy and esters thereof, amides of carboxy, ureido, carbamimidoyl (amidino), guanidino, alkyl-sulfonyl, amino-sulfonyl (C₁₋₆)acyloxy, (C₁₋₆)acylamino, azido, hydroxy, and halogen.

4. A compound according to any one of claims 1 to 3 in which n is 0.

5. A compound according to any one of claims 1 to 4 in which m is 0 or 1.

6. A compound according to any one of claims 1 to 5 in which R² is quinuclidinyl.

7. A compound according to any one of claims 1 to 6 which has the formula (IA).

8. A compound according to claim 1 selected from mutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate; 19,20-dihydromutilin 14-(quinuclidin-4-yl-sulfanyl)-acetate;
mutilin 14-(quinuclidin-3-yloxy)-acetate;
mutilin 14-(quinuclidin-3-ylsulfanyl)-acetate;
mutilin 14-[N-(2,2-dimethylazabicyclo[4.3.0]non-4-ylmethyl)]-aminoacetate;
mutilin 14-(quinuclidin-4-ylcarbonylamino)-acetate;
mutilin 14-[(3R,4R)-azabicyclo[2.2.1]hept-3-ylcarbonylamino]-acetate;
mutilin 14-(quinuclid-4-ylmethylsulfanyl)-acetate;
19,20-dihydromutilin 14-(quinuclidin-4-ylsulfanyl)acetate;
19,20-dihydromutilin 14-(quinuclidin-4-ylsulfoxyl)acetate;
mutilin 14- [(3RS,4SR)-1-aza-bicyclo[2.2.1]hept-3-yl-sulfanyl]-acetate;
mutilin 14-(quinuclidin-3-yldene)-acetate;
mutilin 14-[quinuclidin-3-yl]-acetate;
mutilin 14-[quinuclidin-3-ylacetoxyl]-acetate;
mutilin 14-(quinuclidin-3-ylmethyl)-aminoacetate;
mutilin 14-[3-(quinuclidin-4-yl)-acrylate];
mutilin 14-[3-(quinuclidin-4-yl)-propionate;
mutilin 14-(quinuclidin-4-ylmethyloxy)-acetate;
mutilin 14-[3-(quinuclidin-4-ylamino)-acetate;
mutilin 14-[4-(quinuclidin-4-yl)]-butyrate;
mutilin 14-(1-azabicyclo[3,3,0]oct-4-yhnethylsulfanyl)-acetate;
mutilin 14-(1-azabicyclo[3,3,0]oct-3-ylsulfanyl)-acetate;
mutilin 14-(endol 8-methyl-8-azabicyclo[3,2.1]oct-3-ylsulfanyl)-acetate;
mutilin 14-(1-azabicyclo[4,3,0]non-4-ylsulfanyl)-acetate;
19,20-dihydromutilin 14-(1-azabicycl[4,3,0]non-4-ylsulfanyl)-acetate;
mutilin 14- [(3S,4R)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl] -acetate;
mutilin 14-(quinuclidin-2-ylmethyloxyl)-acetate;
mutilin 14-(1-azabicyclo[2.2.1]hept-4-ylmethylsulfanyl)-acetate;
mutilin 14- [(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl}-acetate;
mutilin 14-(1-azabicyclo[3,2.1]oct-5-ylmethylsulfanyl)-acetate;
mutilin 14-(quinuclidin-4-ylmethylsulfanyl)-acetate;
mutilin 14-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylmethylsulfanyl)-acetate;
mutilin 14-[3-(quinuclidin-4-ylsulfanyl)]-propionate;
mutilin 14-[3-(quinuclidin-4-ylmethylsulfanyl)]-propionate;
19,20-dihydromutilin 14-(8-methyl-8-azabicyclo[3.2.1]oct-3-ylmethylsulfanyl)-acetate;
mutilin 14-[4-(quinuclidin-4-ylsulfanyl)]-butyrate; and
mutilin 14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)-acetate, or a pharmaceutically acceptable salt thereof.

A compound according to claim 1 which is mutilin 14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)-acetate, or a pharmaceutically acceptable salt thereof.

A process for preparing a compound according to any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, which comprises:

(a) coupling mutilin or epi-mutilin having a protected hydroxy group at position 11, with an active derivative, such as an acid chloride, of a carboxylic acid R 2A -(CH 2 ) m -X-(CH 2 ) n -CH 2 CO 2 H, where R 2A is R 2 as defined in claim 1 or a group convertible thereto, and n, m, and X are as defined in claim 1, and if necessary converting the epi-mutilin to mutilin, and where necessary or desired, before or after the coupling, modifying the mutilin nucleus to introduce 2-OH; 19,20-dihydro; or 1,2-dehydro substituents; or

(b) providing a mutilin or epi-mutilin derivative having (CH 2 ) n CH 2 CO as an O-acyl group at position 14, where the acyl group is substituted with R L , which is a leaving group, OH or NH, coupling the 14-O-acyl-(epi)mutilin derivative with a compound R 2A (CH 2 ) m XH or an active derivative therof, and if necessary converting the epi-mutilin configuration to mutilin, and where necessary or desired, before or after the coupling, modifying the
mutilin nucleus to introduce 2-OH; 19,20-dihydro; or 1,2-dehydro substituents.

11. A process for preparing a compound according to claim 10(b) in which

   (a) when X is O, S or NH, R₂⁻ is a leaving group and is reacted with
   
   (i) the alcohol R²-(CH₂)m-OH;
   (ii) the thiol R²-(CH₂)m-SH;
   (iii) the amine R²-(CH₂)m-NH₂;

   (b) when X is CONH, R₂⁻ is amino and is reacted with the acid R²A-(CH₂)m-CO₂H, or an acylating agent derived therefrom;

   (c) when X is CO.O, R₂⁻ is hydroxy and is reacted with an acylating agent derived from the acid R²A-(CH₂)m-CO₂H.

12. A pharmaceutical composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition according to claim 12 in the form of a spray adapted for administration to the nasal cavity.

14. A pharmaceutical composition according to claim 13 in which the spray is an aqueous spray.

15. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, for use in therapy.

16. The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of microbial infections.

17. The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament adapted for administration to the nasal cavity for reducing or eliminating the nasal carriage of pathogenic organisms.

18. The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament adapted for administration to the nasal cavity for prophylaxis of recurrent otitis media or recurrent acute bacterial sinusitis.

19. The use of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating skin and soft tissue infections and acne.

Patentansprüche

1. Verbindung der allgemeinen Formel (IA) oder (IB):
worin:

R\(^1\) Vinyl oder Ethyl ist;

R\(^2\) eine nicht-aromatische bicyclische Gruppe ist, die 5 bis 10 Ringatome in jedem Ring enthält, wobei die Gruppe ein oder zwei basische Stickstoffatome enthält, über ein Ring-Kohlenstoffatom gebunden ist und gegebenenfalls mit bis zu 3 Substituenten substituiert ist, die aus Alkyl, Alkoxy, Alkenyl und Alkenyloxy ausgewählt sind, die gegebenenfalls weiter substituiert sind mit einer oder mehreren Gruppen, die ausgewählt sind aus Aryl, Heterocycl, (C\(_1\)-C\(_6\))-Alkoxy, (C\(_1\)-C\(_6\))-Alkylthio, Amino, Mono- oder Di(C\(_1\)-C\(_6\))-alkylamino, Carboxyl, Cycloalkyl, Cycloalkenyl, Carboxy und Estern davon, Amid von Carboxy, Ureido, Carbamimidoyl (Amidino), Guanidino, Alkylsulfon, Aminosulfon(C\(_1\)-C\(_6\))-acyloxy, (C\(_1\)-C\(_6\))-Acylamino, Azido, Hydroxy und Halogen;

die Einheit R\(^2\)(CH\(_2\))\(_m\)X(CH\(_2\))\(_n\)CH\(_2\)COO in der Position 14 von (IA) oder (IB) durch R\(^a\)R\(^b\)C=CHCOO ersetzt ist, worin eines aus R\(^a\) und R\(^b\) Wasserstoff ist und das andere R\(^2\) ist oder R\(^a\) und R\(^b\) zusammen R\(^2\) bilden; oder ein pharmazeutisch akzeptables Salz davon.


3. Verbindung gemäß Anspruch 1 oder 2, worin R\(^2\) mit Alkyl, Alkoxy, Alkenyl oder Alkenyloxy substituiert ist, die gegebenenfalls weiter substituiert sind mit einer oder mehreren Gruppen, die ausgewählt sind aus Aryl, Heterocycl, (C\(_1\)-C\(_6\))-Alkoxy, (C\(_1\)-C\(_6\))-Alkylthio, Amino, Mono- oder Di(C\(_1\)-C\(_6\))-alkylamino, Cycloalkyl, Cycloalkenyl, Carboxy und Estern davon, Amid von Carboxy, Ureido, Carbamimidoyl (Amidino), Guanidino, Alkylsulfon, Aminosulfon(C\(_1\)-C\(_6\))-acyloxy, (C\(_1\)-C\(_6\))-Acylamino, Azido, Hydroxy und Halogen.

4. Verbindung gemäß einem der Ansprüche 1 bis 3, worin n 0 ist.

5. Verbindung gemäß einem der Ansprüche 1 bis 4, worin m 0 oder 1 ist.

6. Verbindung gemäß einem der Ansprüche 1 bis 5, worin R\(^2\) Chinuclidinyl ist.

7. Verbindung gemäß einem der Ansprüche 1 bis 6, die die Formel (IA) hat.

8. Verbindung gemäß Anspruch 1, ausgewählt aus:
Mutilin-14-(chinuclidin-4-yl-sulfanyl)-acetat; 19,20-Dihydromutilin-14-(chinuclidin-4-yl-sulfanyl)-acetat;
Mutilin-14-(chinuclidin-3-yloxy)-acetat;
Mutilin-14-(chinuclidin-3-ylsulfanyl)-acetat;
Mutilin-14-[N-(2,2-dimethylazabicyclo[4.3.0]non-4-ylmethyl)]-aminoacetat;
Mutilin-14-(chinuclidin-4-ylcarbonylamino)-acetat;
19,20-Dihydromutilin-14-(chinuclidin-4-ylsulfonyl)-acetat; 19,20-Dihydromutilin-14-(chinuclidin-4-ylsulfoxy)-acetat;
Mutilin-14-((3R,4SR)-1-azabicyclo[2.2.1]hept-3-yl)-acetat;
Mutilin-14-(chinuclidin-3-yliden)-acetat;
Mutilin-14-[chinuclidin-3-yl]-acetat;
Mutilin-14-[chinuclidin-3-ylacetoxyl]-acetat;
1,2-Dideshydromutilin-14-(chinuclidin-4-ylsulfanyl)-acetat;
2α-Hydroxymutilin-14-(chinuclidin-4-ylsulfanyl)-acetat;
Mutilin-14-(chinuclidin-4-yl)-acetat;
Mutilin-14-(chinuclidin-4-ylmethyl)-aminoacetat;
Mutilin-14-[3-(chinuclidin-4-yl)-acrylat];
Mutilin-14-[3-(chinuclidin-4-yl)]-propionat;
Mutilin-14-(chinuclidin-4-ylmethylthio)-acetat;
Mutilin-14-[(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl)sulfanyl]-acetat;
Mutilin-14-(1-azabicyclo[3.3.0]oct-4-ylmethylsulfanyl)-acetat; 19,20-Dihydromutilin-14-(1-azabicyclo[3.3.0]oct-4-ylmethylsulfanyl)-acetat;
Mutilin-14-(1-azabicyclo[3.3.0]oct-4-yl)-acetat; 19,20-Dihydromutilin-14-(1-azabicyclo[3.3.0]oct-4-yl)-acetat;
Mutilin-14-((3S,4R)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl)-acetat;
Mutilin-14-(1-azabicyclo[2.2.1]hept-4-ylmethylsulfanyl)-acetat;
Mutilin-14-[(3R,4S)-1-azabicyclo[2.2.1]hept-3-ylmethylsulfanyl]-acetat;
Mutilin-14-(1-azabicyclo[3.2.1]oct-5-ylmethylsulfanyl)-acetat;
Mutilin-14-(1-azabicyclo[3.2.1]oct-5-ylmethylsulfanyl)-acetat; 19,20-Dihydromutilin-14-(1-azabicyclo[3.2.1]oct-5-ylmethylsulfanyl)-acetat;
Mutilin-14-[4-(chinuclidin-4-yl)-butyrat; und
Mutilin-14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)-acetat,
oder ein pharmaceutisch akzeptables Salz davon.

9. Verbindung gemäß Anspruch 1, die Mutilin-14-(exo-8-methyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl)-acetat oder ein pharmaceutisch akzeptables Salz davon ist.

10. Verfahren zur Herstellung einer Verbindung gemäß einem der Ansprüche 1 bis 9 oder eines pharmaceutisch akzeptablen Salzes davon, welches umfasst:

(a) Kuppeln von Mutilin oder epi-Mutilin mit einer geschützten Hydroxygruppe in der Position 11 mit einem aktiven Derivat, wie einem Säurechlorid, einer Carbonsäure R2A(CH2)mX-(CH2)nCH2CO2H, worin R2A R2 wie in Anspruch 1 definiert oder eine dazu umwandeltbare Gruppe ist und n, m und X wie in Anspruch 1 definiert sind, und, falls erforderlich, Umwandeln des epi-Mutilins zu Mutilin, und nach Bedarf oder Wunsch, vor oder nach dem Kuppeln, Modifizieren des Mutilinkerns zur Einführung von 2-OH-, 19,20-Dihydro- oder 1,2-Deshydro-Substituenten; oder

(b) Bereitstellen eines Mutilin- oder epi-Mutilinderivats mit (CH2)nCH2CO als O-Acylgruppe in der Position 14,
worin die Acylgruppe mit R², das eine Abgangsgruppe ist, OH oder NH substituiert ist, Kuppeln des 14-O-Acyl-(epi)mutilin-derivats mit einer Verbindung R²⁻(CH₂)ₘ⁻XH oder einem aktiven Derivat davon und, falls erforderlich, Umwandeln der epi-Mutilin-Konfiguration zu Mutilin und, falls notwendig oder gewünscht, vor oder nach dem Kuppeln, Modifizieren des Mutilinkerns zur Einführung von 2-OH-, 19,20-Dihydro- oder 1,2-Deshydro-Substituenten.

11. Verfahren zur Herstellung einer Verbindung gemäß Anspruch 10(b), worin
   (a) wenn X O, S oder NH ist, R¹ eine Abgangsgruppe ist und mit
      (i) dem Alkohol R²⁻(CH₂)ₘ⁻OH;
      (ii) dem Thiol R²⁻(CH₂)ₘ⁻SH;
      (iii) dem Amin R²⁻(CH₂)ₘ⁻NH₂
      umgesetzt wird;
   (b) wenn X CONH ist, R¹ Amino ist und mit der Säure R²⁻(CH₂)ₘ⁻CO₂H oder einem daraus abgeleiteten Acylierungsmittel umgesetzt wird;
   (c) wenn X CO.O ist, R¹ Hydroxy ist und mit einem aus der Säure R²⁻(CH₂)ₘ⁻CO₂H abgeleiteten Acylierungsmittel umgesetzt wird.

12. Pharmazeutische Zusammensetzung, die eine Verbindung gemäß Anspruch 1 oder ein pharmazeutisch akzeptables Salz davon und einen pharmazeutisch akzeptablen Träger umfasst.

13. Pharmazeutische Zusammensetzung gemäß Anspruch 12 in Form eines zur Verabreichung in die Nasenhöhle angepassten Sprays.


15. Verbindung gemäß Anspruch 1 oder ein pharmazeutisch akzeptables Salz davon zur Verwendung in der Therapie.


17. Verwendung einer Verbindung gemäß Anspruch 1 oder eines pharmazeutisch akzeptablen Salzes davon in der Herstellung eines Medikaments, das zur Verabreichung in die Nasenhöhle angepasst ist, zur Reduzierung oder Eliminierung des nasalen Transports von pathogenen Organismen.

18. Verwendung einer Verbindung gemäß Anspruch 1 oder eines pharmazeutisch akzeptablen Salzes davon in der Herstellung eines Medikaments, das zur Verabreichung in die Nasenhöhle angepasst ist, zur Prophylaxe von wiederkehrender Mittellohrentzündung oder wiederkehrender, akuter, bakterieller Sinusitis.


Revendications

1. Composé de formule générale (IA) ou (IB) :
dans lesquelles :

\[ R_1 \] est un groupe vinyle ou éthyle ;

\[ R_2 \] est un groupe bicyclique non aromatique contenant de 5 à 10 atomes dans chaque noyau, ledit groupe contenant un ou deux atomes d'azote basiques, il est lié par un atome de carbone du noyau et éventuellement substitué par jusqu'à 3 substituants choisis parmi les groupes alkyle, alkyloxy, alcényle et alcényloxy, qui sont éventuellement substitués en outre par un ou plusieurs groupes choisis parmi les groupes aryle, hétérocyclyle, alcoxy en \( C_{1-6} \), alkylthio en \( C_{1-6} \), aroyl alcoxy en \( C_{1-6} \), aroyl alkylthio en \( C_{1-6} \), amino, mono- ou di-alkylamino en \( C_{1-6} \), cycloalkyl, cycloalcényle, carboxy et des esters de ceux-ci, des amides de groupes carboxy, uréido, carbamidiméthyle (amidino), guanidino, alkylsulfonyle, aminosulfonylexy en \( C_{1-6} \), acylamino en \( C_{1-6} \), azido, hydroxy et un halogène ;

chacun de \( n \) et \( m \) est indépendamment 0, 1 ou 2 ;

\[ X \] est choisi parmi -O-, -S-, -S(O)-, -SO2-, -CO.O-, -NH-, -CONH-, -NHCONH- et une liaison ; et

\[ R_3 \] est H ou OH ; ou

le radical \( R_2 (CH_2)_m X (CH_2)_n CH_2 COO \) en position 14 de (IA) ou de (IB) est remplacé par \( R^a R^b C=CHCOO \)
dans lequel l'un de \( R^a \) et \( R^b \) est l'hydrogène et l'autre est \( R^2 \), ou \( R^a \) et \( R^b \) forment ensemble \( R^2 \) ; ou

un sel pharmaceutiquement acceptable de celui-ci.

2. Composé selon la revendication 1, dans lequel \( R^2 \) est choisi parmi les groupes quinuclidinyle, azabicyclo[2.2.1] heptyle, azabicyclo[4.3.0]nonyle, azabicyclo[3.2.1]octyle, azabicyclo[3.3.0]octyle, azabicyclo[2.2.2]octyle, azabicyclo[3.3.1]octényle, azabicyclo[3.3.1]nonyle et azabicyclo[4.4.0]décyle éventuellement substitués.

3. Composé selon la revendication 1 ou 2, dans lequel \( R^2 \) est substitué par des groupes alkyle, alkyloxy, alcényle ou alcényloxy, qui sont éventuellement substitués, en outre, par un ou plusieurs groupes choisis parmi les groupes aryle, hétérocyclyle, alcoxy en \( C_{1-6} \), alkylthio en \( C_{1-6} \), aroyl alcoxy en \( C_{1-6} \), aroyl alkylthio en \( C_{1-6} \), amino, mono- ou di-alkylamino en \( C_{1-6} \), cycloalkyl, cycloalcényle, carboxy et des esters de ceux-ci, des amides de groupes carboxy, uréido, carbamiméthyle (amidino), guanidino, alkylsulfonyle, aminosulfonylexy en \( C_{1-6} \), acylamino en \( C_{1-6} \), azido, hydroxy et un halogène.

4. Composé selon l'une quelconque des revendications 1 à 3, dans lequel \( n \) vaut 0.
5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel m vaut 0 ou 1.

6. Composé selon l'une quelconque des revendications 1 à 5, dans lequel R² est un groupe quinuclidinyle.

7. Composé selon l'une quelconque des revendications 1 à 5, qui a la formule (IA).

8. Composé selon la revendication 1 choisi parmi
   14-(quinuclidin-4-yl-sulfanyl)-acétate de mutiline ;
   14-(quinuclidin-4-yl-sulfanyl)-acétate de 19,20-dihydromutiline ;
   14-(quinuclidin-3-yloxy)-acétate de mutiline ;
   14-(quinuclidin-3-ylsulfanyl)-acétate de mutiline ;
   14-[N-(2,2-diméthylazabicyclo[4.3.0]non-4-ylméthyl)]-aminoacétate de mutiline ;
   14-(quinuclidin-4-ylcarbonylamino)-acétate de mutiline ;
   14-(quinuclidin-4-yl-sulfanyl)-acétate de 19,20-dihydromutiline ;
   14-(quinuclidin-4-ylsulfanyl)-acétate de 1,2-didéhydro-mutiline ;
   14-(quinuclidin-4-ylsulfonyl)-acétate de 1,2-didéhydro-mutiline ;
   14-(quinuclidin-4-ylamino)-acétate de mutiline ;
   14-(quinuclidin-4-ylméthyl)-aminoacétate de mutiline ;
   14-[3-(quinuclidin-4-yl)-propionate de mutiline ;
   14-(quinuclidin-4-ylméthyl)-aminoacétate de mutiline ;
   14-

9. Composé selon la revendication 1, qui est du 14-(exo-8-méthyl-8-azabicyclo[3.2.1]oct-3-ylsulfanyl]-acétate de mutiline ou un sel pharmaceutiquement acceptable de celui-ci.

10. Procédé de préparation d'un composé selon l'une quelconque des revendications 1 à 9, ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant les étapes consistant à :

    (a) coupler de la mutiline ou de l'épi-mutiline ayant un groupe hydroxy protégé en position 11 avec un dérivé
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actif, comme un chlorure d'acide, d'un acide carboxylique R²A-(CH₂)ₘ-X-(CH₂)ₙ-CH₂CO₂H dans lequel R²A est R² tel que défini dans la revendication 1 ou un groupe pouvant être transformé en celui-ci, et n, m et X sont tels que définis dans la revendication 1, et si nécessaire, transformer l'épimutiline en mutiline, et quand cela est nécessaire ou désirable, avant ou après le couplage, modifier le noyau de mutiline pour introduire des substituants 2-OH ; 19,20-dihydro ou 1,2-déhydro ; ou

(b) fournir un dérivé de mutiline ou d'épi-mutiline ayant (CH₂)ₙCH₂CO en tant que groupe O-acylé en position 14, dans lequel le groupe acylé est substitué par R²⁻, qui est un groupe sortant, OH ou NH, coupler le dérivé de 14-O-acyl(épi)mutiline avec un composé R²A-(CH₂)ₘXH ou un dérivé actif de celui-ci, et si nécessaire, transformer la configuration épi-mutiline en mutiline, et quand cela est nécessaire ou désirable, avant ou après le couplage, modifier le noyau de mutiline pour introduire des substituants 2-OH ; 19,20-dihydro ou 1,2-déhydro.

11. Procédé de préparation d'un composé selon la revendication 10(b), dans lequel

(a) quand X est O, S ou NH, R²⁻ est un groupe sortant et est mis en réaction avec

(i) l'alcool R²-(CH₂)ₘ-OH ;
(ii) le thiol R²-(CH₂)ₘ-SH ;
(iii) l'amino R²-(CH₂)ₘ-NH₂ ;

(b) quand X est CONH, R²⁻ est un groupe amino et est mis en réaction avec l'acide R²A-(CH₂)ₘ-CO₂H ou un agent acylant dérivé de celui-ci ;
(c) quand X est CO₂, R²⁻ est un groupe hydroxy et est mis en réaction avec un agent acylant dérivé de l'acide R²A-(CH₂)ₘ-CO₂H.

12. Composition pharmaceutique comprenant un composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, et un support pharmaceutiquement acceptable.

13. Composition pharmaceutique selon la revendication 12 sous la forme d'un produit à pulvériser adapté pour une administration dans la cavité nasale.

14. Composition pharmaceutique selon la revendication 13, ledit produit à pulvériser étant un produit aqueux à pulvériser.

15. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, à utiliser dans une thérapie.

16. Utilisation d'un composé selon la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, dans la fabrication d'un médicament destiné à être utilisé dans le traitement d'infections microbiennes.

17. Utilisation d'un composé selon la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, dans la fabrication d'un médicament adapté pour une administration dans la cavité nasale pour réduire ou éliminer le transport nasal d'organismes pathogènes.

18. Utilisation d'un composé selon la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, dans la fabrication d'un médicament adapté pour une administration dans la cavité nasale pour la prophylaxie d'une otite moyenne récurrente, ou d'une sinusite bactérienne aiguë récurrente.

19. Utilisation d'un composé selon la revendication 1, ou d'un sel pharmaceutiquement acceptable de celui-ci, dans la fabrication d'un médicament pour traiter des infections de la peau et des tissus mous, et l'acné.