A compound of formula (I), wherein R¹, R² and R³ may be various substituents, and R⁴ may be hydrogen or a salt or ester-forming group and — indicates that the =CR¹R² side chain may be present as either (a) or (b) isomeric forms, or as a mixture of both isomers. The compounds have antibacterial activity.
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6-ETHYLIDENE PENEM DERIVATIVES

This invention relates to novel chemical compounds being penems, to methods for their preparation, to intermediate compounds in their preparation, to pharmaceutical formulations incorporating them, and to uses thereof.

Penems are a known class of compounds having antibiotic properties and in some cases also having β-lactamase inhibitory properties. Chem. Pharm. Bull. 23(10), 4371-4381, (1985) discloses 6-ethylidene penem compounds of formula (A):

\[
\begin{align*}
\text{OH} & \\
\text{CH}_3 & \\
\text{S} & \\
\text{X} & \\
\text{O} & \\
\text{CO}_2R & 
\end{align*}
\]

wherein X is -CH$_2$S-Het, where Het is a heteroaromatic ring system, thiazol-4-yl, 2-methylthiadiazol-4-yl, 1-hydroxyethyltetrazol-4-yl and 1-acetamidotetrazol-4-yl being exemplified, R being hydrogen, a cation or an ester forming group. Chem. Pharm. Bull. 23(10) 4382-4394 discloses compounds of formula (A) wherein X is -CH$_2$OCOCH$_3$. Further 6-ethylidene penems are disclosed in EP 0041768A and EP 0232966A.

A novel class of penem compounds has now been identified, and these compounds and their uses form the basis of this invention.

According to this invention are provided penem compounds of formula (I):

\[
\begin{align*}
\text{S} & \\
\text{R}^1 & \\
\text{R}^2 & \\
\text{R}^3 & \\
\text{R}^4 & \\
\text{CO}_2R^4 & 
\end{align*}
\]

(I)
wherein;
R¹ is (C₁₋₆) alkyl or substituted (C₁₋₆) alkyl;
R² is -CH₂X or -COY where;
X is halogen, COR, OCOR, NR₂, NR(COR), N(COR)₂,
5 CONR₂, CONR(COR), CON(COR)₂, OCONR₂, OCONR(COR),
OCON(COR)₂ SR or OR⁵;
Y is R, NR₂, NR(COR), N(COR)₂, or OR⁶;
each R being independently hydrogen, (C₁₋₆)alkyl, substituted (C₁₋₆)
alkyl, (C₁₋₁₂)heterocycyl or (C₁₋₁₂)aryl;
10 R³ is (CH₂)ₙR or (CH₂)ₙOR where n is O to 3 and R is hydrogen, (C₁₋₆)
alkyl, substituted (C₁₋₆)alkyl, (C₁₋₁₂) heterocycyl or (C₁₋₁₂)aryl;
R⁴ is hydrogen, a salt-forming cation or an ester-forming group;
R⁵ being R or a hydroxy-protecting group;
R⁶ being R or a carboxy-protecting group;
15 and = indicates that the =CR¹R² side chain may be present as either the

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^2
\end{array}
\quad \text{or} \quad
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{R}^1
\end{array}
\]

isomeric forms or as a mixture of both isomers.

The term 'alkyl' as used herein includes straight chain, branched chain
and cycloalkyl groups.

25 The term 'heterocycyl' as used herein includes aromatic and
non-aromatic, single and fused, rings containing up to 7 suitably 4-6
atoms in each ring and containing up to four hetero-atoms in each ring
selected from oxygen, nitrogen and sulphur, which rings may be
unsubstituted or substituted by up to three groups selected from halogen,
(C₁₋₆)alkanoyl, (C₁₋₆)alkanoyloxy, heterocycyl, amino, sulphonylamino
30 (ie - NHSO₂R where R is alkyl or aryl), (C₁₋₆) alkanoylamino, (mono or
di)-(C₁₋₆)alkylamino, hydroxy, (C₁₋₆)alkoxy, sulpho, mercapto, (C₁₋₆)
alkylthio, (C₁₋₆)alkylsulphinyl, (C₁₋₆)alkyl-sulphonyl, heterocyclylthio,
arylthio, sulphamoyl, carbamoyl, amidino, guanidino, nitro, halogen,
carboxy, carboxy salts, carboxy esters, arylcarbonyl, and
heterocyclic carbonyl and carboxyloxy groups, and also unsubstituted or substituted \((C_{1-6})\)alkyl, \((C_{2-6})\)alkenyl, \((C_{2-6})\)alkynyl, aryl, and aryl\((C_{1-6})\)alkyl groups.

The term 'aryl' as used herein includes phenyl and naphthyl, which may be unsubstituted or substituted by up to five, preferably up to three, groups selected from halogen, substituted or unsubstituted, \((C_{1-6})\)alkyl, phenyl, \((C_{1-6})\)alkoxy, halo\((C_{1-6})\)alkyl, hydroxy, amino, nitro, carboxy, \((C_{1-6})\)alkoxycarbonyl, \((C_{1-6})\)alkoxycarbonyl\((C_{1-6})\)alkyl, \((C_{1-6})\)alkylcarboxyloxy, \((C_{1-6})\)alkylcarbonyl \((C_{1-6})\)alkythio, arylthio, and mercapto groups.

Examples of suitable optional substituents for the above-mentioned \((C_{1-6})\)alkyl, \((C_{2-6})\)alkenyl, \((C_{2-6})\)alkynyl, aryl and aryl\((C_{1-6})\)alkyl (i.e. "hydrocarbon") substituents include \((C_{1-6})\)alkanoyl, \((C_{1-6})\)alkanoyloxy, heterocyclyl, amino, sulphonylamino, \((C_{1-6})\)alkanoylamino, \((\text{mono or di})-(C_{1-6})\)alkylamino, hydroxy, \((C_{1-6})\)alkylsulphinyl, \((C_{1-6})\)alkylsulphonyl, heterocyclylthio, arylthio, sulphanoyl, carbamoyl, amidino, guanidino, nitro, halogen, carboxy, carboxy salts, carboxy esters, arylcarbonyl and heterocyclylcarbonyl and carboxyloxy groups.

When the heterocyclyl or aryl group includes a carboxy salt or carboxy ester substituent, that substituent is suitably a pharmaceutically acceptable salt or pharmaceutically acceptable ester.

Preferably \(R^1\) is methyl.

When \(R^2\) is \(-\text{CH}_2\text{X}\), X is suitably halogen, typically fluorine, or OR, typically with R being hydrogen, or OCOR, typically with R being \((C_{1-6})\) alkyl such as methyl.

When \(R^5\) is a hydroxy-protecting group it may be a conventional protecting group such as an alkanoic ester group such as a \((C_{1-4})\) alkoxy carbonyl group such as tert-butylxycarbonyl, a \((C_{1-4})\) halogenoalkoxycarbonyl group such as 2-idoethylxycarbonyl or 2,2,2-trichloro-ethoxycarbonyl, an aralkoxyxcarbonyl group such as benzoxycarbonyl, a tri\((C_{1-4})\)alkylsilyl group such as tert-butyldimethylsilyl or trimethylsilyl, a \((C_4-10)\) tert-alkyl group such as
tert-butyl and a substituted or unsubstituted mono-, di or tri-
phenylmethyl group such as benzyl, p-methoxybenzyl, diphenylmethyl,
di(p-anisyl)methyl or trityl. Hydroxy-protecting groups R5 may be
removed by conventional methods which are appropriate to the R5 groups
concerned.

Typically when R3 is -(CH2)n-R, n is O and R is hydrogen (so that the 2-
position is unsubstituted), or n is O and R is heterocycl. Typical
heterocycl groups R when R3 is -(CH2)n-R are optionally substituted 5
or 6 membered heterocycl groups, for example containing one oxygen
atom as the sole hetero atom, such as 2-tetrahydro furanyl. Typically
when R3 is (CH2)nOR, n is O and R is (C1-6) alkyl, for example methyl.

When R4 is a salt-forming cation, preferably it is a pharmaceutically
acceptable salt forming cation.

Suitable pharmaceutically acceptable salts of the 3-carboxylic acid group
of the compound of formula I or of other carboxylic acid groups which may
be present as optional substituents include those in which R4 is a metal
ion e.g. aluminium salts, alkali metal salts (e.g. sodium, lithium or
potassium salts), alkaline earth metal salts (e.g. calcium or magnesium
salts), ammonium salts, and substituted ammonium salts, for example
those with lower alkylamines (e.g. triethylamine), hydroxy-lower
alkylamines (e.g. 2-hydroxyethylamine), di(2-hydroxyethyl)amine
tri(2-hydroxyethyl)amine, bis-(2-hydroxyethyl)amine, tris-(2-
hydroxyethyl)amine, lower-alkylamines (e.g. dicyclohexyl- amine), or with
procaine, dibenzylamine, N,N-dibenzyl- ethylenediamine, 1-ephenamine,
N-methylmorpholine, N-ethylpiperidine, N-benzyl-β-phenethylamine,
dehydroabietylamine, ethylenediamine,
N,N'-bishydroabietylethylenediamine, bases of the pyridine type (e.g.
pyridine, collidine and quinoline), and other amines which have been or
can be used to form quaternary ammonium salts with penicillins.

When R4 is an ester-forming group the compound of formula I may be a
pharmaceutically acceptable in vivo hydrolysable ester, being an ester
which hydrolyses in the human body to produce the parent acid or its salt.
Such esters may be identified by the test process of oral or intravenous
administration to a test animal, and subsequent examination of the test
animal's body fluids for the presence of the compound of the formula I or a salt thereof.

In some cases, the in vivo hydrolysable ester moiety may constitute a link between two different active ingredient moieties, one of which is a compound according to the invention and the other of which may be another therapeutically active compound, such that on in vivo hydrolysis of the ester moiety, the ester link breaks to give the two separate active compounds. The linked entity may be referred to as a 'mutual pro-drug'.

Examples of suitable pharmaceutically acceptable in vivo hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Suitable ester groups of this type include those in which R⁴ has the formula (i), (ii), (iii) or (iv):

\[
\begin{align*}
\text{(i)} & \\
R^a & \quad \text{CH}_2\text{O.CO.R}^b
\end{align*}
\]

\[
\begin{align*}
\text{(ii)} & \\
-R^c & \quad \text{N}R^d
\end{align*}
\]

\[
\begin{align*}
\text{(iii)} & \\
\text{CH}_2 & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{(iv)} & \\
-R^g & \quad \text{CHOCO-} \quad \text{O} \quad \text{CO-CH-R}^g
\end{align*}
\]

wherein R⁴ is hydrogen, (C₁-₆) alkyl, (C₃-₇) cycloalkyl, methyl, or phenyl, R⁵ is (C₁-₆) alkyl, (C₁-₆) alkoxy, phenyl, benzyl, (C₃-₇) cycloalkyl, (C₁-₆) alkyl (C₃-₇) cycloalkyl, 1-amino (C₁-₆) alkyl, or 1-(C₁-₆ alkyl)amino (C₁-₆) alkyl; or R⁴ and R⁵ together form a 1,2-phenylene group optionally
substituted by one or two methoxy phenyl, benzyl, (C₃-7) cycloalkyl, (C₁-6) alkyl (C₃-7) cycloalkyl, 1-amino (C₁-6) alkyl, or 1-(C₁-6 alkyl)amino (C₁-6) alkyl; or R₈ and R₉ together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R₈ represents (C₁-6) alkylene optionally substituted with a methyl or ethyl group and R₉ and R₁₀ independently represent (C₁-6) alkyl; R₉ represents (C₁-6) alkyl; R₈ represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C₁-6) alkyl, or (C₁-6) alkoxy; and Q is oxygen or NH.

Examples of suitable in vivo hydrolysable ester groups include, for example, acyloxyalkyl groups such as acetoxyethyl, pivaloyloxyethyl, (1-acetoxy)ethyl, (1-pivaloyloxy)ethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; alkoxy carbonyloxyalkyl groups, such as ethoxycarbonyloxymethyl and α-ethoxycarbonyloxyethyl; dialkylaminoalkyl especially di-loweralkylamino alkyl groups such as dimethylaminomethyl, dimethylaminethyl, diethylaminomethyl or diethylaminethyl; lactone groups such as phthalidyl and dimethoxyphthalidyl; and esters linked to a second β-lactam antibiotic or to a β-lactamase inhibitor.

A further suitable pharmaceutically acceptable in vivo hydrolysable ester group is that in which R₄ has the formula:

\[
\begin{align*}
\text{CH}_2 & \quad \text{R} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O}
\end{align*}
\]

wherein R₈ is hydrogen, (C₁-6) alkyl or phenyl.

R₄ may also be a readily removable carboxy protecting ester group, other than a pharmaceutically acceptable in vivo hydrolysable ester group, or a non-pharmaceutically acceptable salt-forming cation. Such compounds of formula I are primarily useful as intermediates in the preparation of compounds of formula I and pharmaceutically acceptable salts and esters thereof.
Suitable ester-forming carboxy-protecting groups from which R^4 and R^6 may be selected include those which may be removed under conventional conditions. Such groups include benzyl, p-methoxybenzyl, benzoylmethyl, p-nitrobenzyl, 4-pyridylmethyl, 2,2,2-trichloroethyl, 2,2,2-tribromoethyl, t-butyl, t-amyl, allyl, diphenylmethyl, triphenylmethyl, adamantly, 2-benzoxoxygenyl, 4-methylthiophenyl, tetrahydrofur-2-yl, tetrahydropyran-2-yl, pentachlorophenyl, acetonyl, \( p \)-toluenesulphonyl-ethyl, methoxymethyl, a silyl, stannyl or phosphorus-containing group, an oxime radical of formula -N=CHR where R is aryl or heterocyclyl.

A CO\(_2\)R\(^4\) group in which R\(^4\) is hydrogen may be regenerated from any of the above-mentioned esters by usual methods appropriate to the particular R\(^4\) group, for example, acid- and base- catalysed hydrolysis, or by enzymically-catalysed hydrolysis, or by hydrogenolysis under conditions wherein the remainder of the molecule is substantially unaffected.

It will be appreciated that also included within the scope of the invention are salts and carboxy-protected derivatives, including in \textit{vivo} hydrolysable esters, of any carboxy groups that may be present as optional substituents in compounds of formula I.

Certain compounds of formula I may include an amino group which may be protected. Suitable amino protecting groups are those well known in the art which may be removed under conventional conditions if required without disruption of the remainder of the molecule.

Examples of amino protecting groups include (C\(_1\)-C\(_6\)) alkanoyl; benzoyl; benzyl optionally substituted in the phenyl ring by one or two substituents selected from (C\(_1\)-C\(_4\)) alkyl, (C\(_1\)-C\(_4\)) alkoxy, trifluoromethyl, halogen, or nitro; (C\(_1\)-C\(_4\)) alkoxy-carbonyl; benzoxycarbonyl or trityl substituted as for benzyl above; allyloxy-carbonyl, trifluoroethoxycarbonyl or chloroacetyl.

Amino or substituted amino group(s) that may be present as optional substituents on the compound of formula I, or of any heterocyclic group ring nitrogen atoms may also be present as acid addition salts, which may be pharmaceutically acceptable. Suitable salts include for example
hydrochlorides, sulphates, acetates, phosphates etc. and other pharmaceutically acceptable salts will be apparent to those skilled in the art. Preferred addition salts are the hydrochlorides.

The compound of formula (I), its salts and esters, may exist in a number of isomeric forms, all of which, including racemic and diastereoisomeric forms are encompassed within the scope of the present invention. A preferred isomeric form is the (5R) form. The orientation of the 6-position ethylenic side chain may be E or Z and the present invention includes both such forms or mixtures of these isomers in a 1:1 ratio or in which one such isomer predominates, although an isomerically pure compound is preferred. The Z-isomer is preferred.

From the foregoing it will be seen that one preferred subclass of compounds of formula (I) is that of formula (IA):

![Chemical Structure](image)

wherein R\(^{1A}\) is -CH\(_2\)-R wherein R is hydroxyl, (C\(_1\)-6) acyloxy, or halogen particularly fluorine, R\(^{3A}\) is hydrogen, -R where R is 5 or 6 membered heterocyclyl which has oxygen as its sole heteroatom or -CH\(_2\)O-R where R is (C\(_1\)-6) alkyl; and R\(^{4A}\) is hydrogen or a pharmaceutically acceptable salt-forming cation or pharmaceutically acceptable ester-forming group.

Some compounds of formula I and IA may be crystallised or recrystallised from solvents such as organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of solvents such as water that may be produced by processes such as lyophilisation.

Since the compounds of formula (I) and (IA) are antibiotics and are
intended for use in pharmaceutical compositions it will readily be understood that they are preferably each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85% pure, especially at least 95% pure particularly at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or (IA) or ester or salt thereof.

Accordingly, specific compounds of formula (I) include the following acids, and pharmaceutically acceptable salts (especially the sodium salt) and in vivo hydrolysable esters thereof:

(5R)-6-[(Z)-(1-methoxycarbonyl)ethylidene]-penem-3-carboxylic acid.

(5R)-6-[(E)-(1-fluoromethyl)ethylidene]-penem-3-carboxylic acid.

(5R)-6-[(Z)-(1-hydroxymethyl)ethylidene]penem-3-carboxylic acid.

(5R)-6-[(Z-1-(acetoxy)methyl)ethylidene]penem-3-carboxylic acid.

(5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[(Z-1-(hydroxymethyl)ethylidene)]penem-3-carboxylic acid.

(5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[(E-1-(fluoromethyl)ethylidene)]penem-3 carboxylic acid.

(5R)-2-(methoxymethyl)-6-[(Z-1-(hydroxymethyl)ethylidene)]penem-3-carboxylic acid.

(5R)-2-(methoxymethyl)-6-[(E-1-(fluoromethyl)ethylidene)]penem-3-carboxylic acid.

The present invention further provides a first process for the preparation of a compound of formula I as defined above, where R^2 is a group -CH_2OR^5 where R^5 is a hydroxy-protecting group or R^2 is a group -COOR^6
where R^6 is a carboxy-protecting group; wherein R^4 is a carboxy-protecting ester-forming group; which process comprises the step of removing at least one of protecting groups R^4, R^5 or R^6 and replacing them with at least one other group R^4, R^5 or R^6, so as to produce a compound of formula (I) in unprotected form.

The invention provides a further process for the preparation of compounds of formula (I), in which a compound of formula (II)

\[
\begin{align*}
W & \quad Z \\
R^1 & \quad S \\
R^2 & \quad N \\
& \quad CO_2R^4 \\
R^3 \\
\end{align*}
\]

in which R^1, R^2, R^3 and R^4 are as defined in formula (I); W and Z are substituents which may be eliminated together, is subjected to an elimination process to form a compound of formula (I); and thereafter if necessary or desired carrying out one or more of the following steps;

(i) removing any protecting groups,
(ii) converting the group CO_2R^4 into a different group CO_2R^4,
(iii) converting a group -OR^5 into a different group -OR^5,
(iv) converting a group -OR^6 into a different group -OR^6,
(v) converting the compound into a pharmaceutically acceptable salt or ester.

In one such elimination process, one of W and Z may be hydrogen (preferably Z being hydrogen) and the other may be hydroxy or a leaving group, such as a halogen atom or a leaving group of one of the formulae:

\[
\begin{align*}
-0\text{-SO}_2\text{-}(O)_nR^7 & \quad (i) \\
-0\text{-C}_0\text{-}(O)_n-R^7 & \quad (ii) \\
-0\text{-P}_0\text{-}(OR^8)_2 & \quad (iii)
\end{align*}
\]

in which n denotes 0 or 1, R^7 denotes (C_1-6) alkyl or substituted alkyl, aryl or aryl (C_1-6) alkyl, and R^8 denotes (C_1-6) alkyl or substituted alkyl.
or aryl.

When one or W and Z is hydrogen the elimination reaction may be carried out as described in EP 041768A and 0150781A.

For example if Z is hydrogen and W is hydroxy the elimination may be carried out by subjecting the compound of formula (II) to to dehydration elimination process as described in EP 041768A P7 line 24 - P9 line 8 or EP 0150781A P11 line 14 - P17 line 28, the contents of which are included by reference.

For example when Z is hydrogen and W is a leaving group such as halogen or (i), (ii), or (iii) above, the elimination may be carried out by subjecting the compound of formula (II) to an elimination process as described in EP 041768A P9 line 10 - P11 line 6 or EP 0150781 A P17 line 30 - p 18 line 36, the contents of which are included by reference.

Further examples of suitable leaving groups will be apparent to those skilled in the art and include sulphoxide, selenoxide and xanthate groups, which can be eliminated by known methods, see for example W. Carruthers 'Some modern methods of organic synthesis' Cambridge Univ. Press 1978 (2nd edition) P93-103.

In a preferred elimination process, in the compound of formula (II) Z is a halogen, particularly bromine, and W is a leaving group which is preferably a halogen atom, a hydroxy group, a substituted hydroxy group, an \(-S(\text{0})_n R^9\) or an \(-\text{Se}(\text{0})_m R^9\) group; in which n is 0, 1 or 2, m is 0 or 1, and \(R^9\) is hydrogen, a hydrocarbon group or a heterocycl group and the elimination reaction is a reductive elimination reaction.

Preferred substituted hydroxy groups are the leaving groups of formula (i), (ii) and (iii) referred to above. A particular preferred substituted hydroxy group is one of formula (ii) above having n as zero and \(R^7\) as alkyl i.e an acyloxy group, preferably an acetoxy group.

The reductive elimination step may be carried out in a manner which is generally known pere se for such elimination reactions. For example the reductive elimination may be carried out by reaction of the compound of
formula (II) with a metal, such as zinc, magnesium, aluminium or iron, in
the presence of an acid, such as acetic acid or a mineral acid, or by
reaction with a triorganophosphous compound such as
triphenylphosphine, suitably at a temperature between -20°C and +40°C,
preferably from 0° to 20°C. The reaction may be carried out in the
presence of a solvent, which may be polar or non-polar, protic or aprotic,
for example an organic solvent such as dioxane, dimethoxyethane or
tetrahydrofuran, or alternatively the neat acid and metal may be used.

Compounds of formula (II) exist in various isomers and any may be used
in the above described elimination processes. The product compound of
formula (I) may be formed as a pure isomer about the double bond, or may
be formed as a mixture of isomers which may be separated by conventional
techniques such as chromatography or crystallisation.

During these elimination processes it is desirable that carboxylic acid,
amino and hydroxy groups in the compound of formula (II) are protected
as will be understood by those skilled in the art.

Compounds of formula (II) may be prepared from 6-halo penem
compounds of formula (III):

\[ \text{(III)} \]

in which \( R^3 \) and \( R^4 \) are as defined in formula (I), and \( Z \) is as defined in
formula (II), by first forming the corresponding anion (IIIA):

\[ \text{(IIIA)} \]

followed by reaction with a ketone compound of formula (IV):
in which $R^1$ and $R^2$ are as defined in formula (I).

The anion of formula (IIIA) may be prepared from the compound of formula (III) by reaction of the compound of formula (III) with an organometallic compound of the formula $M-R^{10}$ where $M$ is an alkali metal, especially lithium, and $R^{10}$ is the residue of an organic base such as diphenylamine. The compound of $M-R^{10}$ may for example be prepared by reaction of a metal alkyl such as n-butyllithium with the corresponding base such as diphenylamine in a suitable organic solvent such as tetrahydrofuran at a temperature of for example -20°C to +20°C under an inert atmosphere.

Methods of preparing compounds of formula $M-R$ are generally known. The compound of formula (III) may then be reacted with the compound $M-R^{10}$ in situ, for example in a suitable solvent such as tetrahydrofuran at a temperature of -100°C to 20°C under an inert atmosphere.

Ketone compounds of formula (IV) are generally known or may be prepared from standard literature routes. The reaction between the anion of formula (IIIA), and ketone (IV) may be carried out using the anion in situ as prepared above, for example by mixing the anion (IIIA) and ketone (IV) in a suitable solvent such as tetrahydrofuran at a temperature from -100°C to +20°C under an inert atmosphere.

The product of the reaction between the anion of formula (IIIA) and the compound of formula (IV) is a compound of formula (II) having $W$ as hydroxy, and this hydroxy group $W$ may be converted into a leaving group such as (i), (ii) or (iii) above by reaction with a suitable acid or acid derivative such as an acid halide or anhydride. For example to prepare a preferred compound of formula (II) having $W$ as an acyloxy group the hydroxy compound product may be reacted with an acid anhydride such as
acetic anhydride, which may conveniently be done with the hydroxy compound of formula (II) in situ prepared as described above.

Compounds of formula (III) are known, or else may be prepared by cyclisation from compounds of formula (V):

![Chemical Structure](image)

in which $R^3$ and $R^4$ are as defined in formula (I), $R^{11}$ denotes oxygen, sulphur or a phosphorylidene group, and $R^{12}$ is a phosphoranylidene group, $=C(CH_3)_2$, oxygen or sulphur.

Suitable phosphorylidene groups are those of formula $=PR_3^{13}$ where $R^{13}$ is an organic group, especially aryl or (C$_1$-C$_6$)alkoxy.

The cyclisation may be carried out in a generally known manner. General methods of carrying out this cyclisation are for example described in EP 0232966, with reference to routes A to F on P 13-25 thereof.

Suitably $R^{12}$ may be a phosphoranylidene group $=PR_3^{13}$ in which $R^{13}$ is phenyl or (C$_1$-C$_6$)alkoxy, and $R^{11}$ is oxygen. Such a compound of formula (V) may conveniently cyclise spontaneously or by heating in an inert solvent such as toluene either under reflux or at a sub-reflux temperature preferably in an inert atmosphere optionally in the presence of a trivalent phosphorus compound.

When in formula (V) $R^{11}$ is oxygen and $R^{12}$ is $C(CH_3)_2$, i.e. compounds of formula (VA):
where $R^{12}$ is $C(CH_3)_2$, then this cyclisation may suitably be carried out by ozonolysis to form a compound of formula (VA) in which $R^{12}$ is oxygen, followed by reaction with a tri-organo phosphorus compound, such as $PR^{13}$ where $R^{13}$ is as defined above, to form the phosphorane, i.e. a compound of formula (VA) having $R^{12}$ as $= PR^{13}$. Suitable methods of ozonolysis and of forming a phosphorane of formula (V) are for example described in EP 0232966 A.

Compounds of formula (V) and (VA) may in turn be prepared from compounds of formula (VI):

![Diagram of chemical structure VI]

where $R^4$ and $R^{12}$ are as defined in formula (V) $M$ is a metal, especially silver, and $a$ is the ionic charge of the cation of metal $M$, by reaction with an acyl halide of formula $R^3 COX$ where $X$ is a halogen especially chlorine.

Compounds of formula (VI) and halides of formula $R^3 COX$, and suitable reaction conditions are known, for example in EPO232966, for example see Example 3 thereof, which discloses a compound of formula (VI) in which $Z$ is bromine, $M$ is silver, $R^4$ is para-methoxy benzyl and $R^{12}$ is triphenylphosphoranylidene.

Compounds of formula (VI) in which $Z$ is bromine, $M$ is silver and $R^{12}$ is $= C(CH_3)_2$ may for example be prepared starting from known 6-$\beta$-bromopenicillanic acid (VII):
by protection of the acid group, eg with a group R⁴, such as p-
methoxybenzyl, followed by treatment with a silver salt, for example of an
inorganic or (C₁₋₁₀) alkanolic acid, such as silver acetate, typically in the
presence of β-picoline and a base, suitably 1,8-diazabicyclo [5,4,0]undec-7-
ene. Suitably this reaction is carried out in an organic solvent, for
example acetonitrile, at a low temperature, suitably 3°C to -15°C,
preferably in the dark. Suitably the silver salt and the picoline are first
reacted together in a solvent, then the base is added. To this reaction
mixture is then added the compound of formula (VII). When the
compound of formula (VI) is prepared in this way it may be used in-situ
without subsequent isolation, i.e. the acyl halide R³COX may be added
directly to the solution resulting from the above process.

Protecting groups may be removed from protected positions such as R⁴
and -OR⁵ (when R⁵ is a hydroxy-protecting group) by methods which are
conventional in the art. For example when R⁴ is the carboxy-protecting
group paramethoxybenzyl it may for example be removed by reaction with
aluminium chloride or a mono- or di-alkylaluminium chloride and anisole
in a suitable solvent such as dichloromethane, followed by addition of a
suitable buffer such as sodium citrate or sodium phosphate. For example
when R⁵ is the hydroxy-protecting group trialkylsilyl, e.g. trimethylsilyl,
this may be removed by reaction with tetra-n-butylammonium fluoride
under acid conditions, e.g. using acetic acid. For example if R⁵ is the
hydroxy-protecting group acyl, e.g. acetyl, this may be removed by reaction
with diisobutyl aluminium hydride, e.g. at -70°C.

It will be appreciated that in compounds of formula (I) when R² contains a
functional group, e.g. when X is halogen, and where R is hydrogen, the
presence of these functional groups such as halo, hydroxy, carboxylate or
amino can be used as the basis of reactions for the preparation of other
compounds within the scope of formula (I) using reactions which are
evident to those skilled in the art. For example hydroxyl and amino functional groups in \( R^2 \) may be acylated using acids or conventional acylating derivatives thereof, carboxylate functional group \( R^2 \) may acylate hydroxyl or amino groups either directly or via conventional acylating derivatives thereof, and halogen atoms may be replaced by amino or substituted amino groups.

The subsequent work-up and purification of compounds of formula (I) after the preparative methods described above may be by essentially conventional methods such as solvent extraction, aqueous washing, chromatography, recrystallisation etc., as will be well understood by those skilled in the art.

The intermediate compounds of formula (II) are believed to be novel and as such form part of this invention.

The present invention also provides a pharmaceutical composition which comprises a compound of formula (I), particularly (IA) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier. The compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The antibiotic compounds 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.

The composition may be formulated for administration by any route, such as oral, topical or parenteral. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.
The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tablettng lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. 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 other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as 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 such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.
Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (IA) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof is administered in the above-mentioned dosage range.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibiotics or with a β-lactamase inhibitor may be employed.

Advantageously, the compositions also comprise a compound of formula (VIII) or a pharmaceutically acceptable salt or ester thereof:
wherein
R¹ is hydroxyl, substituted hydroxyl, thiol, substituted thiol, amino, mono- or di-hydrocarbyl-substituted amino, or mono- or di-acylamino; an optionally substituted triazolyl group; or an optionally substituted tetrazolyl group as described in EP O 053 893.

A further advantageous composition comprises an antibiotic compound of formula (I) or (IA) according to the invention and a pharmaceutically acceptable carrier or excipient together with a β-lactamase inhibitor of formula (IX) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof:

wherein R² is hydrogen, halogen (especially chlorine) or a group of formula:

in which R⁰ and R¹ are the same or different and each is hydrogen, (C₁-₆) alkoxy carbonyl, or carboxy or a pharmaceutically acceptable salt thereof.
Further suitable β-lactamase inhibitors include 6-alkylidene penems of formula (X) below:

![Chemical Structure](image)

(X)

or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, wherein \( R^m \) and \( R^n \) are the same or different and each represents hydrogen, or a C\(_{1-10}\) hydrocarbon or heterocyclic group optionally substituted with a functional group; and \( R^{16} \) represents hydrogen or a group of formula \( R \) or \(-SR\) where \( R \) is an optionally substituted (C\(_{1-10}\)) hydrocarbon or heterocyclic group, as described in EP 041 768A.

Further suitable β-lactamase inhibitors include 6β-bromopenicillanic acid and pharmaceutically acceptable salts and in vivo hydrolysable esters thereof and 6β-iodopenicillanic acid and pharmaceutically acceptable salts and in vivo hydrolysable esters thereof described in, for example, EP-A-0 410 768 and EP-A-0 154 132 (both Beecham Group).

Such compositions of this invention which include a β-lactamase inhibitory amount of a β-lactamase inhibitor are formulated in a conventional manner using techniques and procedures per se known in the art.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use as a therapeutic agent.

The present invention further provides a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use in the treatment of bacterial infections.

The present invention also includes a method of treating bacterial infections in humans and animals which comprises the administration of a therapeutically effective amount of an antibiotic compound of this
invention of the formula (I) or a pharmaceutically acceptable in vivo hydrolysable ester thereof.

In addition, the present invention includes the use of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, in the manufacture of a medicament for the treatment of bacterial infections.

The antibiotic compounds of the present invention are active against a wide range of organisms including both Gram-negative organisms and Gram-positive organisms.

The following Examples illustrate compounds of the present invention.

EXAMPLE 1

Sodium (5R)-6-Z-1-(methoxycarbonyl)ethylidenelpenem-3-carboxylate

(a) 4-Methoxybenzyl (5R)-6-bromo-6-(1-acetoxy-1-methoxycarbonyl)-ethylpenem-3-carboxylate, isomers

A solution of diphenylamine (0.169g, 1mmol) in anhydrous tetrahydrofuran (THF; 2ml) was stirred under argon at -10°C and treated with 1.46M n-butyllithium in hexane (0.68ml). The resulting solution was stirred at ambient temperature for 10min., then cooled to -70°C and treated with a solution of 4-methoxybenzyl (5R,6S)-6-bromopenem-3-carboxylate [J. Chem. Soc., Chem. Commun., 1989, 371 and refs. therein]; 0.370g, 1mmol) in THF (7ml) added dropwise. After a further 10min. a solution of methyl pyruvate (0.102g, 1mmol) in THF (1ml) was added and stirring was continued at -70°C for 1h, after which time no starting material was visible by TLC. Acetic anhydride (0.15ml) was then added and the solution allowed to warm to -10°C, then quenched by addition of saturated ammonium chloride (20ml). The mixture was diluted with ethyl acetate (20ml), then the organic phase was separated and the aqueous phase washed with a little more ethyl acetate. The combined organic extracts were washed with water and brine, dried and evaporated to crude product (0.77g). Chromatography on silica gel, eluting with ethyl acetate-hexane mixtures, afforded on evaporation of appropriate fractions (TLC)
the title compounds (isomers; 0.453g, 88%) as an oil (Found: M, 513.0099. C_{20}H_{20}BrNO_8S requires M, 513.0093); \nu_{\text{max}} (\text{CHCl}_3)/\text{cm}^{-1} 1805, 1755(\text{sh}), 1730(\text{br}), and 1610(\text{w}); \delta (90\text{MHz, CDCl}_3) 1.90 (3H, s), 2.10 (3H, s), 3.76 (6H, 2s), 5.16 (2H, s), 6.44 (1H, s), 6.85, 7.31 (4H, ABq), and 7.18 (1H, s); largely one isomer by N.M.R.; m/e 513, 515 (M^+ for 79Br, 81Br, both 15-20%).

(b) 4-Methoxybenzyl (5R)-6-Z-1-(methoxycarbonyl)-ethylidene]-penem-3-carboxylate

The bromo-acetoxy isomers from part (a) (0.450g, 0.88mmol) in THF (15ml) were treated with glacial acetic acid (0.2ml) and zinc powder (0.25g) and stirred vigorously at ambient temperature. After 1h, no starting material was visible (TLC); the mixture was filtered through Kieselguhr, and the precipitate washed with ethyl acetate (20ml). The total organic solution was washed with brine, saturated aqueous sodium hydrogen carbonate (2x) and brine (2x), dried and evaporated to an orange gum (0.31g). Chromatography on silica, applying in toluene and eluting with ethyl acetate-hexane mixtures, afforded the title ester as an orange oil (0.182g, 55%) (Found: M, 375.0753. C_{18}H_{17}NO_6S requires M, 375.0777); \nu_{\text{max}} (\text{KBr})/\text{cm}^{-1} 1779, 1718, 1611(\text{m}), 1586(\text{w}), and 1553(\text{m}); \delta (250\text{MHz, CDCl}_3) 2.24 (3H, s), 3.81, 3.84 (6H, 2s), 5.20 (2H, ABq), 6.38 (1H, s), 6.90, 7.36 (4H, ABq), and 7.30 (1H, s); NOE studies established the Z-geometry of the double bond; m/e 375 (M^+, ca. 5%).

(c) Sodium (5R)-6-Z-1-(methoxycarbonyl)ethylidene]-penem-3-carboxylate

Freshly-ground aluminium trichloride (0.078g, 0.58mmol) was dissolved in anhydrous dichloromethane (DCM, 1ml) and anisole (3ml) and stirred under argon at -40°C. A solution of the ester from part (b) (0.088g, 0.23mmol) in DCM (3ml) was added dropwise and the temperature maintained at -40°C; TLC showed complete disappearance of ester in 15min. After addition of 0.5M trisodium citrate (7.5ml), the mixture was stirred vigorously and allowed to regain ambient temperature. The organic phase was removed, then the aqueous was washed again with DCM and evaporated to dryness. Purification was effected by chromatography on a column of HP20SS resin ('Diaion') eluting with
acetone-water mixtures containing 0-10% acetone. Appropriate fractions (HPLC) were combined, concentrated and lyophilised to afford the penem (0.041g, 63%) as a fluffy yellow solid; ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 1753, 1727, 1693(w), 1602, and 1557; δ (250MHz, D<sub>2</sub>O) 2.12 (3H, s), 3.78 (3H, s), 6.42 (1H, s), and 7.06 (1H, s); m/e 278 (MH<sup>+</sup>, 30%).

**EXAMPLE 2**

**Sodium (5R)-6-[E]-1-(fluoromethyl)ethylidenepenem-3-carboxylate and the 6Z-isomer**

(a) 4-Methoxybenzyl (5R)-6-bromo-6-(1-acetoxy-1-fluoromethyl)ethylidene-penem-3-carboxylate, isomers

Fluoroacetone (0.152g, 2mmol) in THF (0.65ml) was added to a THF solution of the anion of 4-methoxybenzyl (5R,6S)-6-bromopenem-3-carboxylate (from 0.74g, 2mmol of the ester) prepared as in Example 1(a). After 0.5h at -70°C acetic anhydride (0.4ml) was added and the reaction worked up as above, giving after chromatography the *title compounds* (0.746g, 76%) as a gum (Found: M<sup>+</sup>, 487.0109. C<sub>19</sub>H<sub>19</sub>BrFNO<sub>6</sub>S requires M<sup>+</sup>, 487.0100); ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 1799, 1746, 1712, 1611(m), 1586(w), 1558, and 1514; δ (90MHz, CDCl<sub>3</sub>) 1.70-1.85 (3H, m), 2.00-2.10 (3H, m), 3.76 (3H, s), 4.30-5.10 (2H, m), 5.16 (2H, s), 6.30-6.40 (1H, m), 6.85, 7.32 (4H, ABq), 7.18, and 7.22 (1H, 2s); m/e 487, 489 (M<sup>+</sup>, 79Br and 81Br, ca. 7%).

b) 4-Methoxybenzyl (5R)-6-[E]-1-(fluoromethyl)ethylidenepenem-3-carboxylate, E and Z

The bromo-acetoxyl isomers from part (a) (0.74g, 1.52mmol) were treated with zinc according to the procedure of Example 1(b). Careful chromatography of the crude product (0.53g, red oil) using 20-50% ethyl acetate-hexane afforded firstly the title E-ester (0.083g, 16%) as a yellow gum (Found: M<sup>+</sup>, 349.0802. C<sub>17</sub>H<sub>16</sub>FNO<sub>4</sub>S requires M<sup>+</sup>, 349.0784); ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 1779, 1710, 1611, 1586(w), 1555, and 1514; δ (250MHz, CDCl<sub>3</sub>) 1.91 (3H, s), 3.81 (3H, s), 5.10-5.45 (4H, m), 6.24 (1H, s), 6.89, 7.36 (4H, ABq), and 7.28 (1H, s); m/e 349 (M<sup>+</sup>, 7%). Further elution gave the Z-ester (0.212g, 40%), also a yellow gum (Found: M<sup>+</sup>, 349.0782. C<sub>17</sub>H<sub>16</sub>FNO<sub>4</sub>S requires M<sup>+</sup>, 349.0784); ν<sub>max</sub> (KBr)/cm<sup>-1</sup> 1779, 1711, 1611,
Sodium (5R)-6-[E-1-(fluoromethyl)ethylidene]penem-3-carboxylate

(c) The E-ester from part (b) (0.076g, 0.22mmol) was deprotected with aluminium trichloride-anisole as described in Example 1(c). Following chromatography there was obtained the title penem (0.023g, 42%); ν max (KBr/cm⁻¹) 1762, 1710(w), 1616, 1559, and 1496(w); δ (250MHz, D₂O) 1.88 (3H, s), 5.14, 5.32 (2H, 2dd, J 46 and 12Hz), 6.36 (1H, s), and 7.09 (1H, s); m/e 274 (MNa⁺, 18%) and 252 (MH⁺, 20%). The E-geometry was established by N.O.E. studies.

Sodium (5R)-6-[Z-1-(fluoromethyl)ethylidene]penem-3-carboxylate

(d) In a similar manner, the Z-ester from part (b) (0.100g, 0.29mmol) afforded the title penem (0.038g, 53%); ν max (KBr/cm⁻¹) 1761, 1713, 1616, 1559, 1442, and 1398; δ (250MHz, D₂O) 1.95 (3H, s), 4.99, 5.18 (2H, 2ABq, J 46 and 16Hz), 6.42 (1H, d, J 3.5Hz), and 7.03 (1H, s); m/e 274 (MNa⁺, base peak) and 252 (MH⁺, 30%).

EXAMPLE 3

Sodium (5R)-6-[Z-1-(hydroxymethyl)ethylidene]penem-3-carboxylate

(a) 4-Methoxybenzyl (5R)-6-[Z-1-[(trimethylsilyloxy)-methyl]ethylidene]penem-3-carboxylate

1-Trimethylsilyloxy-2-propanone (M. Reetz and H. Keimbach, Chem. Ber., 1983, 116, 3702; 0.295g, 2mmol) in THF (1ml) was added at -70°C to the anion derived from 4-methoxybenzyl (5R,6S)-6-bromopenem-3-carboxylate (0.74g, 2mmol) as in Example 1(a). After 3h. acetic anhydride (0.5ml) was added, the solution was allowed to regain ambient temperature and treated with acetic acid (0.5ml) and zinc (0.75g) with vigorous stirring. The reaction was worked up after 0.75h as in Example 1(b); chromatography, applying the crude product in toluene and eluting with 10-50% ethyl acetate in hexane, afforded the title compound (0.086g, 10%);
vmax (KBr/cm⁻¹ 1778, 1710, 1611(m), 1586(w), 1554, and 1513; δ
(250MHz, CDCl₃) 0.16 (9H, s), 1.98 (3H, s), 3.81 (3H, s), 4.22 (2H, brs,
5.19 (2H, ABq, J 12Hz), 6.43 (1H, s, 5-H), 6.89, 7.36 (4H, 2d), and 7.23
(1H, s); m/e 419 (M⁺, 2%) and 420 (M⁺, base peak, by chemical
ionisation). Again N.O.E. measurements confirmed the Z-geometry.

(b) 4-Methoxybenzyl (5R)-6-[Z-1-(hydroxymethyl) ethylidenelenpenem-3-
  carboxylate

The product from part (a) (0.080g, 0.19mmol) in THF (2.5ml) was stirred
at ambient temperature with acetic acid (0.1ml) and tetra-n-butyl-
ammonium fluoride trihydrate (0.157g, 0.50mmol). After 5 min. no
starting material was visible by TLC; the solution was diluted with ethyl
acetate (15ml) and washed sequentially with brine, saturated aqueous
sodium hydrogen carbonate (2x) and brine (2x). Drying and evaporation
gave crude product (0.065g) which was chromatographed on silica gel,
applying in toluene and eluting with 10-50% ethyl acetate-hexane.
Appropriate fractions (TLC) were pooled and evaporated to give the title
alcohol as a gum (0.046g, 70%) (Found: M, 347.0827. C₁₇H₁₇NO₅S
requires M, 347.0827); vmax (KBr/cm⁻¹ 3466, 1774, 1707, 1611, 1586(w),
1552, and 1514; δ (250MHz, CDCl₃) 1.79 (1H, brs, D₂O exch.), 2.01 (3H,
s), 3.81 (3H, s), 4.35 (2H, ABq, J 17Hz), 5.19 (2H, ABq, J 12Hz), 6.49 (1H,
s), 6.89, 7.36 (4H, ABq), and 7.24 (1H, s); m/e 347 (M⁺, 5%).

(c) Sodium (5R)-6-[Z-1-(hydroxymethyl) ethylidenelenpenem-3-
carboxylate

The hydroxy-ester from part (b) (0.037g, 0.275mmol) was deprotected
using aluminium trichloride-anisole as in Example 1(c), affording after
chromatography the title penem (0.008g, 30%); vmax (KBr/cm⁻¹ 3387(br),
1752, 1713(w), 1609, 1555, and 1399; δ (250MHz, D₂O) 1.94 (3H, s), 4.24
(2H, ABq, J 18Hz), 6.48 (1H, s), and 7.01 (1H, s); m/e, no M⁺. The product
was contaminated with a little trisodium citrate.

EXAMPLE 4

Sodium (5R)-6-[Z-1-[(acetoxy)methyl] ethylidenelenpenem-3-carboxylate
(a) **(2-Acetoxy)acetone**

Acetol (6.84ml=7.4g, 0.1mol) was added to a vigorously stirred mixture of anhydrous potassium carbonate (20.7g, 0.15mol) and ether (50ml) at 0°C. Acetyl chloride (7.11ml=7.85g, 0.1mol) was added dropwise over 0.25h and the mixture was allowed to regain ambient temperature. After 4.5h the solid was filtered off and washed with ether, then the combined filtrate and washings were evaporated. Distillation of the residue afforded the title compound (see, e.g., P.A. Levene and A. Walti, *J. Biol. Chem.*, 1928, 79, 363) (5.02g, 43%, in two fractions); ν<sub>max</sub> (CHCl<sub>3</sub>) cm<sup>-1</sup> 3500, 1830(sh), and 1735; δ (90MHz, CDCl<sub>3</sub>) 2.15 (6H, s) and 4.62 (2H, s). The first fraction contained ca. 15% unreacted acetol and was not retained.

(b) **4-Methoxybenzyl (5R)-6-[[acetoxymethyl]ethyldiene]penem-3-carboxylate**

(2-Acetoxy)acetone (0.232g, 2mmol) in THF (1.06ml) was added at -70°C to the anion derived from 4-methoxybenzyl (5R,6S)-6-bromopenem-3-carboxylate (0.74g, 2mmol) as in Example 1(a). After 4h acetic anhydride (0.4ml) was added and the reaction worked up as above. Without purification this material was redissolved in THF (15ml) and subjected to zinc-acetic acid reduction as in Example 1(b); after work up as described therein, chromatography afforded the title compound (0.177g, 23%); ν<sub>max</sub> (KBr) cm<sup>-1</sup> 1780, 1746, 1711, 1611(m), 1586 (w), 1553(m), 1514, and 1442; δ (250MHz, CDCl<sub>3</sub>) 2.10 (3H, s), 2.15 (3H, s), 3.81 (3H, s), 4.67 (2H, ABq, J 17Hz), 5.20 (2H, ABq, J 12Hz), 6.39 (1H, s), 6.90, 7.36 (4H, ABq), and 7.24 (1H, s); m/e 412 (M<sup>Na</sup>+, 79%).

(c) **Sodium (5R)-6-[[acetoxymethyl]ethyldiene]penem-3-carboxylate**

The ester from part (b) (0.088g, 0.23mmol) was deprotected using aluminium trichloride-anisole as in Example 1(c) to give, after chromatography, the title penem (0.013g, 20%); ν<sub>max</sub> (KBr) cm<sup>-1</sup> 1752, 1710(w), 1620, and 1561; δ (250MHz, D<sub>2</sub>O) 2.02 (3H, s), 2.16 (3H, s), 4.74 (2H, ABq, J 17Hz), 6.49 (1H, s), and 7.04 (1H, s); m/e 292 (M<sup>Na</sup>+, 14%) and 314 (M<sup>Na</sup>+, 9%).
EXAMPLE 5

Sodium (5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[1-(hydroxymethyl)ethyl]penem-3-carboxylate

(a) (3S,4R)-3-Bromo-4-(mercapto-1-(4-methoxy)benzyl-oxycarbonyl-2-methylprop-1- enyl)azetidin-2-one

A stirred suspension of silver acetate (10.0g, 0.05 mole) in acetonitrile (100ml) and protected from light was treated with α-picoline (35ml) and the resultant solution cooled to 0°C. 1,8-diazabicyclo[5.4.0]undec-7-ene (9.0ml, 0.06 moles) was added and the mixture stirred at 0-3°C for 30 mins. A suspension of p-methoxybenzyl 6-α-bromopencillanate (20.0g, 0.05 moles) in acetonitrile was added at 0-3°C and the reaction stirred at 3°C for 14 hours. This silver compound was not isolated but was used in situ below.

(b) (3S,4R)-3-Bromo-1-[1-(4-methoxy)benzyloxy carbonyl-2-methylprop-1-enyl]-4-[[2R,2S]-tetrahydrofuran-2-yl]carbonylthiol]azetidin-2-one

A solution of (3S,4R)-3-bromo-4-mercapto-1-[1-(4-methoxy)benzyloxy carbonyl-2-methylprop-1-enyl]azetidin-2-one, silver salt (5.07g, 10mmol) in anhydrous DCM (50ml) and pyridine (0.8ml) was stirred at 0°C and treated with a solution of (2R,2S)-tetrahydro-2-furoyl chloride (prepared from the acid and thionyl chloride in a standard procedure; 1.34g, 10mmol) in anhydrous DCM (10ml) added dropwise over 10min. The resulting dark solution was allowed to regain ambient temperature, stirred for 0.5h and diluted with ethyl acetate (60ml). Following filtration through Celite and washing of the precipitate with ethyl acetate (120ml), the combined organic solutions were washed with 5% aqueous citric acid solution (2x), brine, saturated NaHCO₃ solution and brine, then dried and evaporated to give the title compound as a near-colourless oil (4.08g, 81%) which was virtually homogeneous by t.l.c. (Found: M, 497.0505. C₂₁H₂₄BrNO₅S requires M, 497.0508); νmax (CHCl₃/cm⁻¹) 1780, 1710, and 1615; δ (90MHz, CDCl₃) 1.70-2.30 (4H, m), 1.93, 2.23 (6H, 2s), 3.77 (3H, s), 3.80-4.10 (2H, m), 4.30-4.50 (1H, m), 4.72, 5.56 (2H, 2m), 5.16 (2H, brs), 6.85 and 7.35 (4H, ABq). This material could be purified by silica-gel chromatography, eluting with ethyl acetate-hexane mixtures, but was
suitable for progression without purification.

(c) \((3S,4R)-3\text{-Bromo-1-}\{1-(4\text{-methoxy} \text{benzyloxy})\text{oxaly}l\}-4-\text{f}[(2R,2S)\text{-tetrahydrofuran-2-yl}]\text{carbonylthiolazetidin-2-one}\)

5
Ozonised oxygen was passed through a solution of the product from part (b) (4.08g, 8.19mmol) in ethyl acetate (50ml) at -70°C; after 1.5h, no starting material was visible by t.l.c. Excess ozone was removed by passage of argon for 0.5h, then the mixture was diluted with ethyl acetate (25ml), washed with 10% aqueous sodium metabisulphite solution and brine, dried and evaporated to give the title compound (3.38g, 87%) as an oil sufficiently pure for further use; \(v_{\text{max}}\) (CHCl\(_3\)) cm\(^{-1}\) 1820, 1750, 1720, and 1610; n.m.r. analysis showed complete loss of the 2-methylprop-1-enyl group from the starting material; \(\delta\) (90MHz, CDCl\(_3\)) \text{inter alia}, 3.77 (3H, s), 4.95, 5.63 (2H, 2m), and 5.26 (2H, s).

(d) \((3S,4R)-3\text{-Bromo-1-}\{1-(4\text{-methoxy} \text{benzyloxyl})\} \text{carbonylthiolazetidin-2-one}\)

20
A solution of the oxalimide from part (c) (3.38g, 7.16mmol) in toluene (50ml) was stirred at ambient temperature with triphenylphosphine (4.29g, 16.38mmol) and triethyl phosphite (1.40ml=1.36g, 8.19mmol). After 16h the near-solution was diluted with ethyl acetate and washed with water, then the aqueous phase was backwashed with a little ethyl acetate. The combined organic extracts were washed with water and brine, dried and evaporated to an oil which was chromatographed on silica gel, eluting with ethyl acetate-hexane mixtures. Appropriate fractions were pooled and evaporated to give the title phosphorane (3.16g, 61%); \(v_{\text{max}}\) (KBr) cm\(^{-1}\) 1775, 1692, 1655(sh), 1625, and 1511; m/e 742 (MNa\(^{+}\)), 720 (M+). The n.m.r. spectrum was very complex, but showed the presence of (triethoxy)phosphoranyliden compound in addition to the title compound; both these compounds cyclised to the desired penem in the next step.

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(e) \(4\text{-Methoxybenzyl (5R,6S)-2-}\{(2R,2S)\text{-tetrahydrofuran-2-yl}\}6\text{-bromopenem-3-carboxylate}\)
A solution of the product from part (d) (3.15g, 4.39mmol) in toluene (1.2l) was heated at reflux for 1.5h, very little starting material then being visible by t.l.c. The yellow solution was then evaporated to dryness and chromatographed on silica gel, being applied in toluene-chloroform for solubility and eluted with mixtures containing up to 50% ethyl acetate in hexane. Pooling and evaporation of appropriate early fractions afforded the title penem as a white solid (0.58g, 30%), m.p. 105-110° C (Found: M, 439.0097. C_{18}H_{18}BrNO_{5}S requires M, 439.0089); \nu_{\text{max}} \text{(KBr)/cm}^{-1} 1788, 1708, 1612(m), 1571, and 1516; \delta \text{(250MHz, CDCl}_{3}) 1.65-2.05, 2.30-2.45 (4H, 3m), 3.75-4.00 (2H, m), 3.81 (3H, s) 5.07, 5.08 (1H, 2d, J 1.5 and 1.4Hz), 5.19 (3H, m), 5.25-5.40 (1H, m), 5.53, 5.60 (1H, 2m, J 1.3 and 1.4Hz), 6.90, and 7.36 (4H, ABq). Later-eluting fractions on evaporation afforded 4-methoxybenzyl 5-(2R,2S)-tetrahydrofuran-2-ylthiazole-4-carboxylate (0.28g, 20%) as a yellow semi-solid (Found: M, 319.0881).

C_{16}H_{17}NO_{4}S requires M, 319.0878; \nu_{\text{max}} \text{(KBr)/cm}^{-1} 1786, 1702, 1612, 1587(w), 1516, 1464, and 1431; \delta \text{(90MHz, CDCl}_{3}) 1.60-2.20, 2.40-2.70 (4H, 2m), 3.76 (3H, s), 3.85-4.20 (2H, m), 5.30 (2H, s), 5.64 (1H, approx. t), 6.85, 7.35 (4H, A_{3}q), and 8.57 (1H, s). By performing the cyclisation at 80° C for 15h., the yield of the desired penem was increased to 41% and the yield of thiazole reduced.

(f) 4-Methoxybenzyl (5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[(Z-1-[(acetoxy)methyl]ethylidene)penem-3-carboxylate

A solution of the 6-bromopenem from part (e) (0.27g, 0.61mmol) in THF (4.5ml) was converted to its anion using diphenylamine/n-butyllithium at -70° C as described in Example 1(a). To this solution under argon was added a solution of 2-acetoxyacetone (0.071g, 0.61mmol) in THF (1ml). After 1.5h acetic anhydride (0.15ml) was added, then the solution was allowed to regain ambient temperature and treated with zinc and acetic acid as described in Example 3(a); workup after 0.75h as given in Example 1(b) afforded crude product (0.39g). Chromatography on silica gel, applying in toluene and eluting with up to 50% ethyl acetate in hexane, afforded the title compound (0.13g, 45%); \nu_{\text{max}} \text{(KBr)/cm}^{-1} 1774, 1750(sh), 1700, 1611, 1576, and 1514; \delta \text{(250MHz, CDCl}_{3}) 1.70-2.50 (4H, 2m), 2.08 (3H, s), 2.15, 2.16 (3H, 2s), 3.70-4.00 (2H, m), 3.81 (3H, s), 4.50-4.80 (2H, m), 5.10-5.40 (3m, m), 6.12, 6.20 (1H, 2s), 6.90, and 7.37 (4H, ABq); m/e 482 (MNa\textsuperscript{+}, 26%).
(g) 4-Methoxybenzyl (5R)-2-[(2R,2S)-tetrahydrofuran-2-yll]-6-[Z-1-]
(hydroxymethyl)ethylidene]penem-3-carboxylate

A solution of the acetoxymethyl derivative from part (f) (0.056g, 0.12mmol) in dry THF (5ml) was stirred under argon at -70°C and treated with a 1.5M solution of diisobutylaluminium hydride in toluene (DIBAL; 0.16ml). After 2h., further reagent (0.1ml) was added, maintaining the same temperature; after a total of 3h., when very little starting material was visible by t.l.c., the reaction was quenched by addition of methanol (0.5ml) and saturated aqueous sodium sulphate solution (20ml). The mixture was allowed to regain ambient temperature and filtered, washing the precipitate with THF and water; the combined filtrate and washings were diluted with ethyl acetate, then the organic phase was separated, washed again with water and brine, dried and evaporated to crude product (0.048g). Chromatography on silica (ethyl acetate-hexane elution) afforded the title hydroxy compound (0.029g, 58%) (Found: M, 417.1238. C_{21}H_{23}NO_{6}S requires M, 417.1246); v_{max} (KBr)/cm\(^{-1}\) 1768, 1699, 1611, 1570, and 1514; δ (250MHz, CDCl\(_3\)) 1.40-2.50 (5H, m, 4H on D\(_2\)O exchange), 1.99 (3H, s), 3.40-4.00 (2H, m), 3.81 (3H, s), 4.31 (2H, m), 5.10-5.40 (3H, m), 6.22, 6.29 (1H, 2s), 6.89, and 7.38 (4H, ABq); m/e 417 (M\(^+\), 13%; electron impact) and 435 (MNH\(_4^+\), 2%), 418 (MH\(^+\), 25%; chemical ionisation, NH\(_3\)).

(h) Sodium (5R)-2-[(2R,2S)-tetrahydrofuran-2-yll]-6-[Z-1-]
(hydroxymethyl)ethylidene]penem-3-carboxylate

The hydroxy-ester from part (g) (0.049g) was deprotected using aluminium trichloride-anisole as described in Example 1(c); following chromatography, there was obtained the title penem (0.024g, 65%); v_{max} (KBr)/cm\(^{-1}\) 1748, 1700(sh), 1670(sh), and 1617; δ (250MHz, D\(_2\)O) 1.60-2.35 (4H, m), 1.93 (3H, s), 3.70-3.95 (2H, m), 4.23 (2H, dd), 5.47 (1H, approx. dd), 6.26, and 6.30 (1H, 2s). Diastereoisomeric ratio ca. 2:1; m/e 320 (MH\(^+\), 3%). Prolonged reaction times and/or allowing the temperature to rise above -40°C in this reaction led to the production of a β-lactam ring-opened product of a type known from the literature (see J. Antibiotics, 1990, 43, 901). This could be avoided by using dimethylaluminium chloride, as described in later examples.
EXAMPLE 6

Sodium (5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[(E)-1-(fluoromethyl)ethylidene]penem-3-carboxylate and the 6Z-isomer

(a) 4-Methoxybenzyl (5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[(1-fluoromethyl)ethylidene]penem-3-carboxylate, E and Z

4-Methoxybenzyl (5R,6S)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-bromopenem-3-carboxylate [Example 5(e); 0.384g, 0.87mmol] was converted into its anion as described in Example 1(a), then reacted with fluoroacetone (0.066g, 0.87mmol) followed by acetylation and zinc reduction as in Example 5(f). Chromatography of the crude product (0.504g) on silica (ethyl acetate-hexane) afforded firstly the E-ester (0.044g, 12%) (Found: M, 419.1177. C_{21}H_{22}FNO_{5}S requires M, 419.1222; ν_{max} (KBr)/cm^{-1} 1762, 1699, 1611(w), 1570, and 1512; δ (250MHz, CDCl_{3}) 1.70-2.05, 2.30-2.45 (4H, 2m), 1.88, 1.89 (3H, 2s), 3.75-4.05 (2H, m), 3.81 (3H, s), 5.05-5.45 (5H, m), 5.96, 6.03 (1H, 2s), 6.90, and 7.36 (4H, ABq). Further elution afforded the Z-ester (0.160g, 44%) (Found: M, 419.1181. C_{21}H_{22}FNO_{5}S requires M, 419.1202; ν_{max} (KBr)/cm^{-1} 1772, 1700, 1611(m), 1572, 1514, and 1443; δ (250MHz, CDCl_{3}) 1.55-2.05, 2.30-2.45 (4H, 2m), 2.01 (3H, s), 3.75-4.05 (2H, m), 3.81 (3H, s), 4.88, 5.06 (2H, 2dd, J = 46 and 3.5Hz), 5.10-5.40 (3H, m), 6.11, 6.18 (1H, 2d, J = 3.5Hz), 6.89, and 7.36 (4H, ABq).

(b) Sodium (5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[(E)-1-(fluoromethyl)ethylidene]penem-3-carboxylate

A solution of the E-ester from part (a) (0.037g, 0.088mmol) in DCM (1ml) and anisole (1ml) was stirred under argon at -40°C and treated with 1M dimethylaluminium chloride in hexane (0.20ml). After 0.75h, when no starting material was visible by t.l.c., the reaction was worked up as in Example 1(c); following chromatography there was obtained the title penem (0.024g, 87%); ν_{max} (KBr)/cm^{-1} 1757, 1695(sh), 1669, and 1617; δ (250MHz, D_{2}O) 1.85 (3H, s), 1.80-2.40 (4H, m), 3.75-3.95 (2H, m), 5.05-5.20, 5.25-5.40 (2H, approx. 2dd, J = 46.5 and 12.5Hz), 5.45-5.55 (1H, m), and 6.16 (1H, 2s). Diastereoisomeric ratio 4:1; m/e 322 (MH^{+}, 8%) and 299 (M^{+}, free acid).
(c) Sodium (5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[[Z]-1-
(fluoromethyl)ethylidene]penem-3-carboxylate

The Z-ester from part (a) (0.153g, 0.37mmol) was deprotected using
dimethylaluminium chloride as described in part (b). Following
chromatography there was obtained the penem (0.019g, 16%); νmax
(KBr/cm⁻¹) 1757, 1670(sh), 1611, 1575(sh), and 1443; δ (250MHz, D₂O)
1.70-2.10, 2.20-2.40 (4H, 2m), 1.93 (3H, s), 3.75-3.95 (2H, m), 5.00, 5.18
(4H, 2dd, J 46 and 24Hz), 5.49 (1H, dd), 6.22, and 6.26 (1H, 2d, J 3.5Hz);
diastereoisomeric ratio 3:4; m/e 322 (MH⁺, 42%) and 300 (MH⁺, free acid).

EXAMPLE 7

15 Sodium (5R)-2-(methoxymethyl)-6-[[Z]-1-(hydroxymethyl)ethylidene]penem-
3-carboxylate

(a) (3S,4R)-3-Bromo-1-[(4-methoxy)benzylloxycarbonyl-2-methylprop-
1-eny]l-4-[(methoxymethyl)carbonyl]-thiolazetidin-2-one

A solution of (3S,4R)-3-bromo-4-mercapto-1-[(4-methoxy)benzylloxycar-
bonyl-2-methylprop-1-eny]lazetidin-2-one, silver salt (Example 5(a))
(5.07g, 10mmol) was S-acylated using methoxycetyl chloride
(0.91ml=1.085g, 10mmol) as described in Example 5(b). Chromatography
of crude product (3.8g) on silica, eluting with up to 50% ethyl acetate in
hexane, afforded the thiol ester (2.85g, 60%) as a colourless oil (Found: M,
471.0330. C₁₁H₂₂BrNO₆S requires M, 471.0351); νmax (CHCl₃/cm⁻¹)
1785, 1720, 1615(w), and 1515(w); δ (90MHz, CDCl₃) 1.94, 2.23 (6H, 2s),
3.43, 3.78 (6H, 2s), 4.03 (2H, s), 4.74 (1H, d, J 2Hz), 5.17 (2H, s), 5.65 (1H,
d, J 2Hz), 6.86, and 7.34 (4H, ABq).

(b) (3S,4R)-3-Bromo-1-[(4-methoxy)benzylloxalyl]-4-[(methoxy-
methyl)carbonyl]thiolazetidin-2-one

The thiol ester from part (a) (5.55g, 11.76mmol) was ozonised as described
in Example 5(c), giving after workup the title oxalimide (4.92g, 94%, not
rigorously dried); νmax (CHCl₃/cm⁻¹) 1825, 1755(sh), 1725, 1615, 1590(w),
and 1515(w); δ (90MHz, CDCl₃) no signals @ δ <3.0; the material was used
without further purification.

(c) \((3S,4R)-3\text{-Bromo-1-}[1-(4\text{-methoxy} benzyl)oxy]carbonyl-1-(\text{triphenylphosphoranylidene})\text{methyl-4-}[\text{(methoxymethyl)}-\text{carbonylthio}]lazetidin-2\text{-one}\)

A solution of the oxalimide from part (b) (4.92g, 11.03mmol) in toluene (35ml) was treated with triethyl phosphite-triphenylphosphine as described in Example 5(d) but using a greater excess of phosphine (5:1). Workup and chromatography as described therein afforded the title compound (3.60g, 47%); \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 1774, 1694, 1660(sh), 1623, 1586(w), 1510, 1482, and 1436; m/e 612 (M-Br\(^+\), 15%), by electron impact; m/e 692, 694 (M\(^+\), 79Br, 81Br, ca. 5%) by chemical ionisation (NH\(_3\)). The n.m.r. was complex, but compared to Example 5(d) showed a much increased triphenyltrioethoxy ratio, about 9:1.

(d) \(4\text{-Methoxybenzyl (5R,6S)-2-[(methoxymethyl)6-bromopenem-3-carboxylate}\)

The product from part (c) (1.53g, 2.30mmol) was cyclised by heating in toluene (600ml) at 70\(^\circ\)C for 6h. Workup as in Example 5(e), including chromatography, afforded the title penem (0.75g, 81%) as a colourless oil (Found: M, 412.9906. C\(_{16}\)H\(_{16}\)BrNO\(_5\)S requires M, 412.9933); \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 1796, 1702, 1610, 1585, 1512, and 1451; \(\delta\) (250MHz, CDCl\(_3\)) 3.38 (3H, s), 3.81 (3H, s), 4.62 (2H, ABq, \(\delta\) 16Hz), 5.09 (1H, d, \(\delta\) 1.1Hz), 5.21 (2H, narrow ABq), 5.62 (1H, d, \(\delta\) 1.1Hz), 6.90, and 7.37 (4H, ABq). The material was unstable on standing, even at -10\(^\circ\)C, and was best prepared immediately before use in the next step.

(e) \(4\text{-Methoxybenzyl (5R)-2-[(methoxymethyl)6-[(acetoxymethyl)ethylidene]penem-3-carboxylate}\)

The bromopenem from part (d) (0.370g, 0.89mmol) was converted to its anion and reacted with 2-acetoxyacetone (0.103g, 0.87mmol) as described in Example 5(f). Workup and chromatography as described therein afforded the title compound (0.202g, 52%) (Found: M, 433.1191. C\(_{21}\)H\(_{23}\)NO\(_7\)S requires M, 433.1195); \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 1787, 1751, 1701, 1611, 1591, 1513, and 1450; \(\delta\) (250MHz, CDCl\(_3\)) 2.08 (3H, s), 2.15 (3H, s),
3.38 (3H, s), 3.81 (3H, s), 4.45-4.80 (4H, 2ABq), 5.20 (2H, ABq), 6.22 (1H, s), 6.90, and 7.38 (4H, ABq); m/e 433 (M⁺, very weak), electron impact; m/e 434 (MH⁺, 2%), chemical ionisation (NH₃).

(f) Sodium (5R)-2-(methoxymethyl)-6-[Z]-1-(hydroxymethyl)ethylidenepenem-3-carboxylate

A solution of the product from part (e) (0.169g, 0.39mmol) in anhydrous DCM (8ml) was reduced with Dibal according to Example 5(g). Workup and chromatography as described therein gave hydroxy-ester (0.031g) which was deprotected using dimethylaluminium chloride as described in Example 6(b). Following chromatography there was finally obtained the title penem (0.012g, 11%); ν_max (KBr)/cm⁻¹ 1751, 1610, 1576, and 1438(w); δ (250MHz, D₂O) 1.93 (3H, s), 3.33 (3H, s), 4.23 (2H, ABq, J 18Hz), 4.59 (2H, ABq, J 14Hz), and 6.35 (1H, s); m/e 294 (MH⁺, 78%) and 272 (MH⁺, free acid, 18%).

EXAMPLE 8

Sodium (5R)-2-(methoxymethyl)-6-[E]-1-(fluoromethyl)ethylidenepenem-3-carboxylate and the 6Z-isomer

(a) 4-Methoxybenzyl (5R)-2-(methoxymethyl)-6-[1-(fluoromethyl)-ethylidenepenem-3-carboxylate, E and Z

4-Methoxybenzyl (5R,6S)-2-(methoxymethyl)-6-bromopenem-3-carboxylate [Example 7(d); 0.400g, 0.97mmol] was converted into its anion as in Example 1(a), then reacted with fluoroacetone (0.074g, 0.97mmol) followed by subsequent reaction and workup as in Example 5(f). Following chromatography as described therein, the first-eluted product was the E-ester (0.020g, 5%) [assigned by analogy with Example 6(a), but not characterised in view of the small amount of material]; further elution afforded the Z-ester (0.095g, 25%) (Found: M, 333.1031. C₁₉H₂₀FNO₅S requires M, 393.1046; ν_max (KBr)/cm⁻¹ 1772, 1700, 1611(m), 1584, 1514, and 1443(m); δ (250MHz, CDCl₃) 2.01 (3H, s), 3.37 (3H, s), 3.80 (3H, s), 4.62 (2H, ABq, J 15.5Hz), 4.98 (2H, 2dd, J 46.5 and 3.4Hz), 5.20 (2H, ABq, J 12Hz), 6.20 (1H, d, J 3.4Hz), 6.89, and 7.38 (4H, ABq).
(b) Sodium (5R)-2-(methoxymethyl)-6-[E-1-(fluoromethyl)ethylidenel- penem-3-carboxylate

The E-ester from part (a) (0.020g, 0.051mmol) was deprotected using dimethylaluminium chloride as given in Example 6(b). Ether (3 vols.) was added during the partition-workup to ensure better separation of the product into the aqueous phase; apart from this modification, workup and chromatography were performed as in Example 1(c) to give the title penem (0.011g, 73%); νmax (KBr)/cm⁻¹ 1751, 1616, 1586, 1440(w), and 1388; δ (250MHz, D₂O) 1.85 (3H, s), 3.33 (3H, s), 4.60 (2H, ABq, J 14Hz), 5.20 (2H, 2dd, J 46.5 and 12.5Hz), and 6.20 (1H, s); m/e 296 (MH⁺, 73%) and 318 (MNa⁺, 30%).

(c) Sodium (5R)-2-(methoxymethyl)-6-[Z-1-(fluoromethyl)ethylidenel- penem-3-carboxylate

The Z-ester from part (a) (0.085g, 0.22mmol) was deprotected using dimethylaluminium chloride with the modification given in part (b); following chromatography there was obtained the title penem (0.032g, 50%); νmax (KBr)/cm⁻¹ 1763, 1629, 1585, 1444(m), and 1390; δ (250MHz, D₂O) 1.94 (3H, s), 3.33 (3H, s), 4.43 (2H, ABq), 5.08 (2H, 2dd, J 46 and 16Hz), and 6.29 (1H, d, J 3.5Hz); m/e 296 (MH⁺, 65%).
CLAIMS

1. A compound of formula (I):

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \quad \text{N} \quad \text{R}^3 \\
\text{O} \quad \text{CO}_2 \text{R}^4
\end{array}
\]

wherein;
R\(^1\) is (C\(_{1-6}\)) alkyl or substituted (C\(_{1-6}\)) alkyl;
R\(^2\) is -CH\(_2\)X or -COY where;
X is halogen, COR, OCOR, NR\(_2\), NR(COR), N(COR)\(_2\),
CONR\(_2\), CONR(COR), CON(COR)\(_2\), OCONR\(_2\), OCON(COR),
OCON(COR)\(_2\) SR or OR\(^5\);
Y is R, NR\(_2\), NR(COR), N(COR)\(_2\), or OR\(^6\);
each R being independently hydrogen, (C\(_{1-6}\))alkyl, substituted (C\(_{1-6}\))
alkyl, (C\(_{1-12}\))heterocycl or (C\(_{1-12}\))aryl;
R\(^3\) is (CH\(_2\))^\(_n\)R or (CH\(_2\))^\(_n\)OR where n is 0 to 3 and R is hydrogen, (C\(_{1-6}\))alkyl, substituted (C\(_{1-6}\))alkyl, (C\(_{1-12}\))heterocycl or (C\(_{1-12}\))aryl;
R\(^4\) is hydrogen, a salt-forming cation or an ester-forming group;
R\(^5\) being R or a hydroxy-protecting group;
R\(^6\) being R or a carboxy-protecting group;
and \(=\) = indicates that the \(=\text{CR}^1\text{R}^2\) side chain may be present as either
the

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2
\end{array}
\]  

or

\[
\begin{array}{c}
\text{R}^1 \\
\text{R}^2
\end{array}
\]

isomeric forms or as a mixture of both isomers.

2. A compound according to claim 1 in which R\(^1\) is methyl.
3. A compound according to claim 1 or 2 in which R² is -CH₂ₓ where x is halogen or -OR, where R is hydrogen, or -OCOR where R is (C₁-₆) alkyl.

4. A compound according to claim 1 or 2 in which R² is -COY where Y is -OR⁶, R⁶ being (C₁-₆) alkyl.

5. A compound according to any one of the preceding claims in which R³ is -(CH₂)ₙ-R where n is O and R is hydrogen, or n is O and R is heterocyclyl.

6. A compound according to claim 5 wherein n is O and R is tetrahydrofuranyl.

7. A compound according to any one of the preceding claims selected from the list consisting of:

(5R)-6-(Z-(1-methoxycarbonyl)ethylidene)penem-3-carboxylic acid,

(5R)-6-(E-(1-fluoromethyl)ethylidene)penem-3-carboxylic acid,

(5R)-6-(Z-(1-hydroxymethyl)ethylidene)penem-3-carboxylic acid,

(5R)-6-(Z-1-(acetoxy)methyl)ethylidene)penem-3-carboxylic acid,

(5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[Z-1-(hydroxymethyl)ethylidene]penem-3-carboxylic acid,

(5R)-2-[(2R,2S)-tetrahydrofuran-2-yl]-6-[E-1-(fluoromethyl)ethylidene]penem-3-carboxylic acid,

(5R)-2-(methoxymethyl)-6-[Z-1-(hydroxymethyl)ethylidene]penem-3-carboxylic acid,

(5R)-2-(methoxymethyl)-6-[E-1-(fluoromethyl)ethylidene]penem-3-carboxylic acid.

8. A compound according to any one of the preceding claims,
substantially as hereinbefore described with reference to any one of the accompanying examples.

9. A process for the preparation of compounds of formula (I), in which a compound of formula (II)

\[
\begin{array}{c}
R^1 \\
R^2 \\
S \\
R^3 \\
R^4 \\
\text{CO}_2R^4 \\
\end{array}
\]

(II)

in which \(R^1, R^2, R^3\) and \(R^4\) are as defined in formula (I); \(W\) and \(Z\) are substituents which may be eliminated together, is subjected to an elimination process to form a compound of formula (I); and thereafter if necessary or desired carrying out one or more of the following steps;

(i) removing any protecting groups,
(ii) converting the group \(\text{CO}_2R^4\) into a different group \(\text{CO}_2R^4\),
(iii) converting a group \(-\text{OR}^5\) into a different group \(-\text{OR}^5\),
(iv) converting a group \(-\text{OR}^6\) into a different group \(-\text{OR}^6\),
(v) converting the compound into a pharmaceutically acceptable salt or ester

10. A compound of formula (II) as defined in claim 9.

11. A pharmaceutical composition which comprises a compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof and a pharmaceutically acceptable carrier.

12. A compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use as a therapeutic agent.

13. A compound of formula (I) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use in the treatment of bacterial infections.
14. A method of treating bacterial infections in humans and animals which comprises the administration of a therapeutically effective amount of an antibiotic compound of this invention of the formula (I) or a pharmaceutically acceptable in vivo hydrolysable ester thereof.

15. The use of a compound of formula (Ia) or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, in the manufacture of a medicament for the treatment of bacterial infections.
INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D499/88; A61K31/43

II. FIELDS SEARCHED

Minimum Documentation Searched

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Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>X</td>
<td>GB, A, 2 144 126 (SHIONOGI SEIYAKU K. K.) 27 February 1985 see claims</td>
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<td>X</td>
<td>CHEMICAL &amp; PHARMACEUTICAL BULLETIN vol. 33, no. 10, 1985, pages 4371 - 4381 MITSURO IMUTA cited in the application see the whole document</td>
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<td>Y</td>
<td>EP, A, 0 002 210 (MERCK &amp; CO., INC.) 13 June 1979 see page 134 - page 135; claims</td>
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* Special categories of cited documents:
* A: document defining the general state of the art which is not considered to be of particular relevance
* E: earlier document but published on or after the international filing date
* L: document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
* O: document referring to an oral disclosure, use, exhibition or other means
* T: document published prior to the international filing date but later than the priority date claimed

IV. CERTIFICATION

Date of the Actual Completion of the International Search 01 OCTOBER 1992

Date of Mailing of this International Search Report 30.10.92

International Searching Authority EUROPEAN PATENT OFFICE

Signature of Authorized Officer CHOLLY J.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 92/01306

Box I  Observations where certain claims were found unsearable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark: Although claim 14 is directed to a method of treatment of diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.
This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. Date: 01/10/92

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82