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(56) Documents cited
None

(58) Field of search
C2C

(54) **Novel azetidinone intermediates and their use in the synthesis of 2-(substituted methyl) penem-3-carboxylates**

(57) 5R-2-(substituted methyl)penem-3-carboxylates are prepared from corresponding penicillanic acid S-oxide esters by a multistep process proceeding through a 3-methylenecepham 1-oxide ester and certain novel azetidinones of formulae
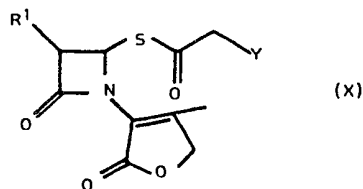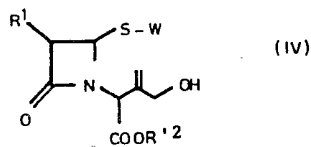
wherein W = SR^4 (R^4 = alkyl, aryl or heterocyclyl),   NCOR^5 (R^5, R^6

COR^6

independentyl = alkyl, aryl, heterocyclyl), phthalimido, succimimido, SO$_2$R^4; R^1 = organic group; W = SR^4 if R^1 = amino or substituted amino; R$^{\prime 2}$ = carboxylate protecting group; Y = a large range of substituents.

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SPECIFICATION

Novel azetidinone intermediates and their use in the synthesis of 2-(substituted methyl)-penem-3-carboxylates

DESCRIPTION
The invention relates to azetidinones, and to processes employing them in the preparation of penicillanic acid derivatives and pharmaceutically and/or veterinarily acceptable salts thereof.
The penicillanic acid derivatives which can be prepared by the process according to the invention have the general formula I

(I)

wherein:
R^1 represents an organic group, preferably an acylamino group or an optionally substituted aliphatic or cycloaliphatic hydrocarbon group, most preferably a C_1-C_{12} alkyl group optionally substituted by one or more hydroxy, amino, cyano or mercapto groups, the hydroxy, amino and mercapto groups being free or protected;
R^2 represents a hydrogen atom, a carboxy protecting group, a group forming, together with the linked oxycarbonyl group, an *in vivo* hydrolyzable ester, or an organic or inorganic cation, forming with the $-CO_2$ anion a carboxylate salt;
Y represents a substituent chosen from:
    a) a free or protected hydroxy group;
    b) a C_2-C_6 acyloxy group;
    c) a free or protected, unsubstituted or N-alkyl substituted carbamoyloxy group;
    d) a C_1-C_{12} alkoxy or C_1-C_{12} alkylthio group, either of which may be optionally substituted by one or more substituents selected from halogen, preferably fluorine, C_2-C_6 acyl, preferably acetyl, amino, hydroxy and mercapto, the amino, hydroxy or mercapto groups being free or protected;
    e) a heterocyclylthio group S–Het, wherein Het denotes a saturated or unsaturated heterocyclic ring containing at least one heteroatom selected from N, S and O, monocyclic or bicyclic, optionally substituted by one or more substituents selected from hydroxy, C_1-C_6 alkoxy, halogen, formyl, C_2-C_6 acyl, C_1-C_6 alkyl, amino, C_1-C_6 alkylthio, or $(CH_2)_n-Z$ or $CH = CH-Z$, wherein Z may be amino, dimethylamino, cyano, carbamoyl, sulphonyloxy or carboxy, the sulphonyloxy or carboxy groups being free, protected, esterified with a C_1-C_4 alkyl, or in the form of a salt with an organic or inorganic base.
The most preferred compounds of the general formula I are those wherein:
R^1 represents a 1-hydroxyethyl group,
R^2 represents a hydrogen, sodium or potassium atom or a chemically cleavable radical, such as *p*-nitrobenzyl, acetonyl or trimethylsilylethyl, or an *in vivo* hydrolyzable radical, such as pivaloyloxymethyl, acetoxymethyl or phthalidyl, and
Y represents an acetoxy or carbamoyloxy group, or a group S–Het, Het being as defined above.
Compounds of the general formula I, in the form of acids, pharmaceutically acceptable salts, or *in vivo* hydrolyzable esters, are potent, broad spectrum antimicrobial agents, described and claimed in our British Patent No 2043639 and in our copending British Patent Application No 8210410, useful in the treatment of bacterial infections in warm-blooded animals, especially in humans, by enteral or parenteral administration.
Flowsheet 1 shows in outline two prior art routes to the penem derivatives of the general formula I. In the formulae in Flowsheet 1, R^1, R^2 and Y can have some of the meanings hereinabove defined. Route B is by far the more common. The leading references to the prior art routes shown are
Route A: A. Henderson, G. Johnson, K.W. Moore, and B.C. Ross. *J. Chem. Soc., Chem. Commun.*, 1982, 809
Route B (leading reference): I. Ernest, J. Gosteli, G.W. Green grass, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, *J. Am. Chem. Soc.*, 1978, 100, 8214.
These prior art routes suffer from some drawbacks or limitations, which can be at least in part overcome by the invention.
Prior art route A has been described only for Y = H, and penem compounds wherein Y = H have been shown to possess greatly reduced activity in comparison with those wherein Y = $OCOCH_3$, $OCONH_2$ or SHet); the data reported in Table I, in spite of the unfortunate non-equivalence among bacteria strains available in different laboratories, can be considered illustrative. It should

be appreciated that functionalization of the previously known azetidinone intermediates wherein Y = H to give the corresponding compounds wherein Y has any of the other meanings hereabove stated is *not* trivial and, although highly desirable, it has never been accomplished.

TABLE 1

Comparison between the antibacterial activity of (8R, 5R, 6S) penem (I, Y= H[a,b]) and the 2-(functionalized methyl) analog (I, Y= OCOCH$_3$[c])

Strains		MIC (μg/ml)		
		(I),Y= H		(I),Y= OCOCH$_3$
Staphylococcus	A 9537	1	2	–
aureus	A 9606	2	4	–
	A15097	4	8	–
	209P	–		0.023
	Smith			
	ATCC 13709	–		0.046
	FI-PV 3	–		0.046
Streptococcus	A 9604	0.5	1	–
pyogenes	ATCC 12384	–		0.046
Streptococcus	A 20688	31	63	–
faecalis	ATCC 8043	–		3.12
Escherichia	A 15119	8	16	–
coli	A 20341-1	8	16	–
	B	–		0.39
	B Cef R	–		0.39
Enterobacter	A 9659	16	32	–
cloacae	A 9656	8	16	–
	P 99	–		3.12
	214	–		6.25
Klebsiella	A 15130	8	16	–
pneumoniae	ATCC 10031	–		0.39
Proteus	A 21559	8	16	–
vulgaris	ATCC 27973	–		0.39
Proteus	A 15153	16	32	–
morganii	ATCC 25830	–		0.78
Proteus	A 21203	8	16	–
rettgeri	ATCC 9250	–		0.78

[a]Data source: Nederland Terinzagelegging NL 7909056 (Bristol-Myers, 1980); Derwent No. 05333 C

[b]The highest figure of each couple is the one reported in the above patent. As they are relative to a racemic material, figures as low as the first ones of each couple can be inferred for the 5R stereomer, by considering the 5S compound devoid of significant activity
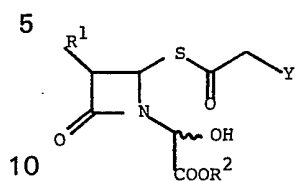
[c]Data source: *J. Antibiot.*, 1982, 35, 1248

Prior art route B entails the loss of all the carbon atom (and often of the sulphur atom as well) of the thiazolidine moiety of the starting penicillin, and the introduction of a glyoxylate synthon in order to build up the key intermediate of formula:
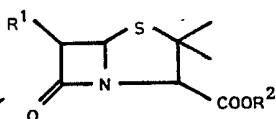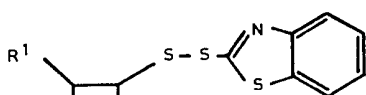
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Flowsheet 1

Prior Art Route to Penems

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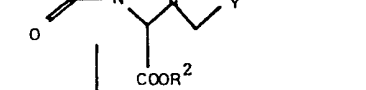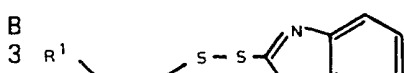
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B
3

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PRIOR ART
ROUTE A

(Y=H)

PRIOR ART
ROUTE B.
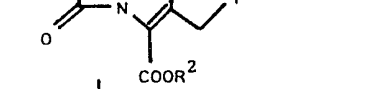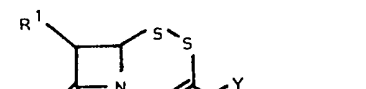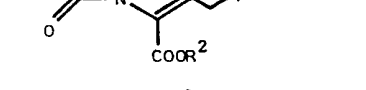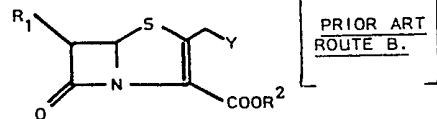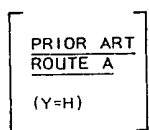
Flowsheet 2 shows the new routes provided by the invention to the penem derivatives of the
60 general formula I.
Invention Route A—This process, depicted on the lefthand side of Flowsheet 2, enables the conversion of a penicillanic acid sulphoxide of the general formula II into a 2-thiacephem derivative of general formula VII, wherein Y, being other than hydrogen, is preferably acetoxy, N-free or substituted carbamoyloxy, or lower alkoxy; the prior art route A shown in Flowsheet 1
65 leads only to 2-thiacephems wherein Y is hydrogen. The obtained 2-thiacephem intermediates

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VII are then desulphurized to afford the desired penem compounds I.

Flowsheet 2

Invention Routes to Penems

INVENTION ROUTE A

INVENTION ROUTE B

(II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, I)
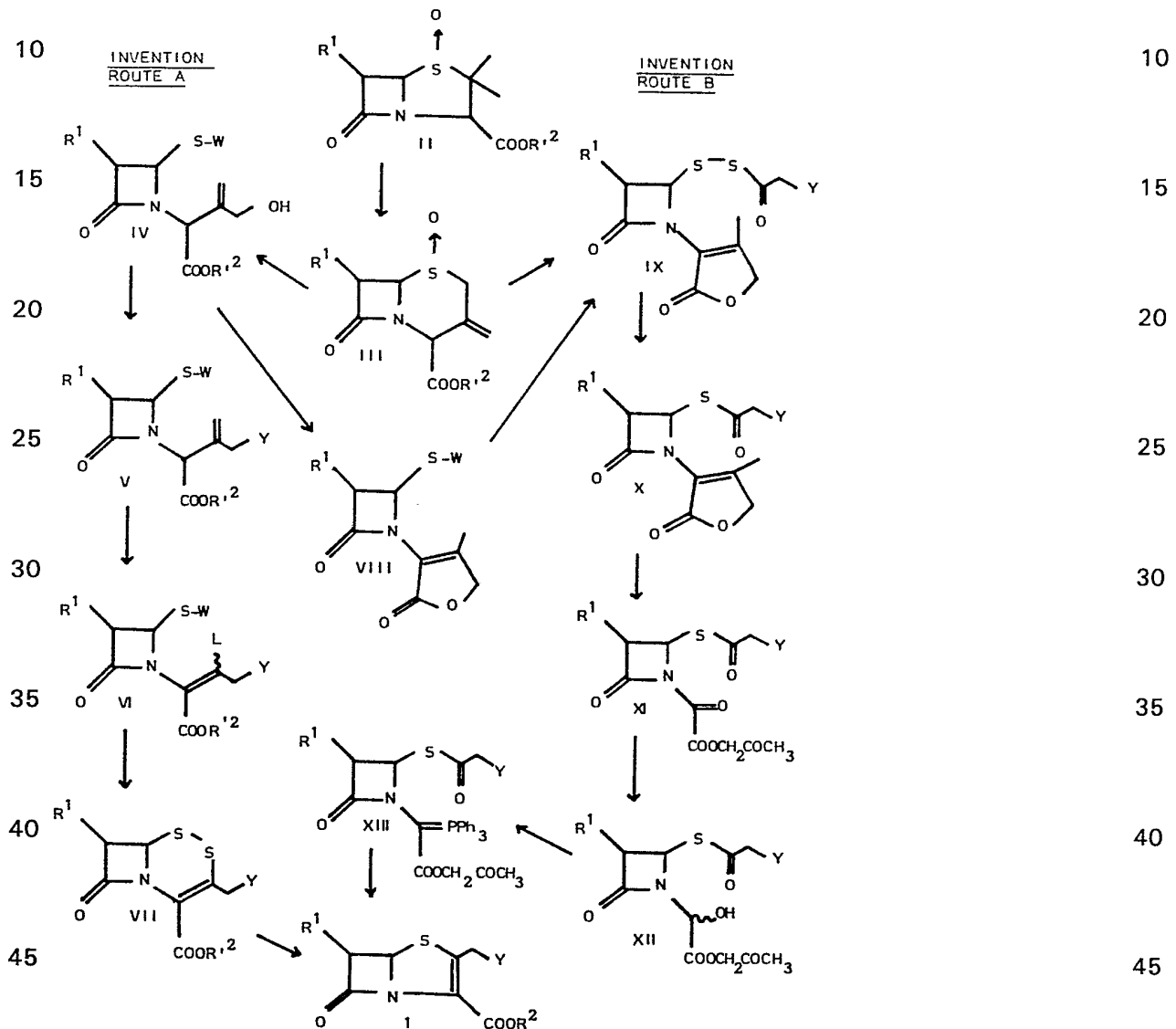
Invention Route B—This process, depicted on the righthand side of Flowsheet 2, provides acetonyl esters of the desired penem carboxylic acid (I, $R^2 = CH_2COCH_3$) starting from cheap and chemically stable esters, e.g. methyl esters, of the starting penicillanic acid sulphoxide II. The route proceeds through novel azetidinone lactones of the general formula X, and incorporates all the carbon atoms of the penicillanic acid II in the penem ester I. Acetonyl esters of penem compounds can be easily hydrolyzed (J. Am. Chem. Soc., 1979, 101, 6306) and, in some instance, are well adsorbed orally *in vivo*, thus being intermediate precursors of therapeutically useful compounds or even therapeutically useful compounds as such. Acetonyl esters are unstable in the conditions usually required for the introduction of the R^1 group into a penicillanic nucleus when R^1, according to a particularly preferred embodiment of the invention, is 1-hydroxyethyl (e.g. a Grignard-type reaction): this invention provides a method for achieving the conversion of a cheap methyl penicillinate into an acetonyl 6-hydroxy-ethyl-penem-3-carboxylate, by exploiting all the carbon atoms of the penicillanic precursors. Compared to the prior art route B (Flowsheet 1), this process reduces to a minimum the use of external synthons.

The aforesaid Invention Routes A and B are better specified as follows. According to Invention Route A, a penicillanic acid derivative II wherein R'^2 is a carboxylate protecting group,

preferably p-nitrobenzyl or trimethylsilylethyl, is heated in an anhydrous, inert solvent, in the
presence of a positive halogen source, to form a sulphinyl halide of the following formula
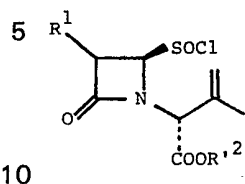
which is then reacted, in the same or in a different solvent, or in a mixture of solvents, with an
acid, preferably a Lewis acid, to yield a 3-methylenecepham sulphoxide of formula (III), in a
manner substantially similar to that described by S. Kukolja for related "classical" penicillin
derivatives (II) wherein R^1 is phthalimido or an acylamino group (J. Am. Chem. Soc., 1976, 98,
5040). Compounds of formula (III) wherein, according to a preferred embodiment of the present
invention, R^1 is an optionally substituted alkyl group, such as free or protected 1-hydroxyethyl,
are novel. Suitable solvents for the above reaction are 1,2-dichloroethane, benzene, toluene and
carbon tetrachloride. The reaction may be carried out at temperatures ranging from about 60° to
about 120°C. Suitable positive halogen sources are sulphuryl chloride, N-chlorophthalimide, N-
bromosuccinimide, and especially N-chlorosuccinimide. A preferred Lewis acid is tin tetrachlo-
ride. In the preferred case of $R^1 =$ (protected) hydroxyethyl group, we have found that high
yields are obtained in benzene, preferably after azeotropic removal of any trace of water from
the reagents, and by using freshly recrystallized samples of N-chlorosuccinimide. When
concentrated solutions are used, the presence of added acid acceptors, such as resin-linked
tertiary amines (e.g. Hünig base), or propylene oxide, or suspended inorganic salts, may be of
advantage.
    Subsequently, the obtained compound III is converted into a compound IV, wherein R^1, R'^2
are as above defined and W is a leaving group selected from;
    a) a group $S-R^4$, wherein R^4 represents an alkyl or aryl group or, preferably, a heterocyclyl
radical, especially 2-benzothiazolyl; or
    b) a group
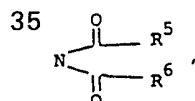
wherein R^5 and R^6, which may be the same or different, are defined as R^4 above, or preferably,
are such that the whole group is a phthalimido or succinimido group; or
    c) a group
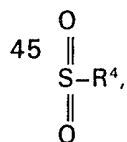
wherein R^4 is as above defined, and is preferably a phenyl or p-tolyl radical. To achieve the
conversion, the compound III is heated at a suitable temperature in a suitable solvent. An
equilibrium between the allyl sulphoxide III and a sulphenate of formula:
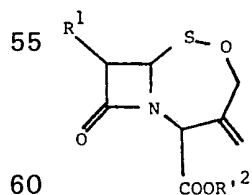
is set up and the latter can be trapped by a compound of formula HW, W being as defined
above, or a salt or a silylated derivative thereof, which is added to the reaction mixture. A
preferred solvent is toluene, at reflux or near reflux temperatures.

The preparation of allyl alcohols from β,γ unsaturated sulphoxides, through not popular, is a general method in organic chemistry (J. March, "Advanced Organic Chemistry", McGraw-Hill Kogakusha, Tokyo 1977, p. 1056). In the field of β-lactam antibiotics, it has been exploited very recently over compounds of formula (III) wherein R^1 is an α-oriented benzamido group, in a
5 synthesis of 1-oxa-1-dethiacephem derivatives (H. Yanagisawa and A. Ando, Tetrahedron Lett., 1982, 23, 3379; Jpn Kokai Tokkyo Koho JP 82 38,769 (Sankyo, 1982), Derwent No. 29389 E). Compounds IV wherein R^1 is other than unsubstituted or substituted amino are novel, as is any compound IV wherein W is a group

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$$\begin{array}{c} O \\ \parallel \\ S{-}R^4, \\ \parallel \\ O \end{array}$$
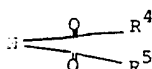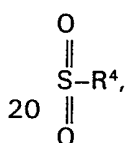
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as specified above. In particular, compounds IV wherein R^1 is 1-hydroxyethyl, which are part of a particularly preferred embodiment of the present invention, are novel. The philosophy of
25 incorporating *both* the sulphur and oxygen atom of the intermediate sulphenate in the molecule of the desired compound is also novel; since in the general allyl alcohol synthesis and in the particular 1-oxa-1-dethiacephem preparation (*vide supra*) the sulphur atom, after being intercepted by the group W or other nucleophiles, is lost. Next, the compound IV is converted into a compound of formula V, wherein R^1 and R'^2 are as above defined, and Y, among the meanings
30 above defined for the compounds I, may have the ones of a protected hydroxy, a lower alkoxy, an acyloxy, or a free, N-protected or N-alkyl substituted carbamoyloxy group. The preferred protected hydroxy groups are tetrahydropyranyloxy or a silyloxy group, such as *t*-butyldimethylsilyloxy, or a carbonate group RO.CO.O, such as *p*-nitrobenzyloxycarbonyloxy; a preferred acyloxy group is acetoxy; a preferred carbamoyloxy group is $OCONH_2$. The compounds V as thus
35 defined are novel. The conversion of a compound IV into a compound V is carried out conventionally, for example by reaction with a substituted silyl chloride, a chloroformate or with a diazoalkane, or with an acyl chloride or an anhydride, e.g. acetyl chloride or acetic anhydride, or an isocyanate, e.g. ethyl isocyanate or trichloroacetylisocyanate. It should be noted that a compound V may be sometimes obtained directly from the compound III, if the latter is treated
40 with a mixture of the above described reagents and the compound HW, or with a reactive derivative thereof; e.g. 2-acetylthio-benzothiazole may effect the conversion of a compound III into a compound V wherein Y is acetyl and W is 2-benzothiazolylthio.

In the following step of invention route A, a compound V is converted into a compound of formula VI, wherein R^1, R'^2, W and Y are as defined above, and L is a leaving group selected
45 from chloro, bromo, optionally substituted alkanesulphonyloxy or arenesulphonyloxy, such as mesyloxy, tosyloxy or trifluoromethanesulphonyloxy. The wavy line $\wr$ denotes that the group L may be either *cis* or *trans* with respect to the azetidinyl group. The conversion may be carried out by first ozonolysing the compound V to obtain an enol of the following formula

50
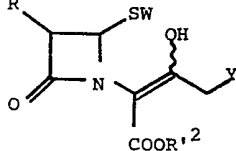
55

or the keto tautomer thereof, which is then reacted with reagents known *per se* to be suitable for the transformation of the hydroxy substituent into the group L. Preferred reagents of this
60 type are oxalyl choride (L = Cl), mesyl chloride or anhydride (L = OSO_2CH_3), trifluoromethanesulphonyl anhydride (L = OSO_2CF_3). They are preferably used in the presence of a base, such as triethylamine or pyridine, and in a suitable solvent, such as dichloromethane or tetrahydrofuran. A preferred group L is mesyloxy, and the preferred geometrical arrangement with respect to the azetidinyl group is the *cis* one (alkene Z geometry), herebelow depicted:

$$\begin{array}{c} \underset{O}{\overset{\cdot R^1}{\underset{}{\bigsqcup}}} \end{array}$$
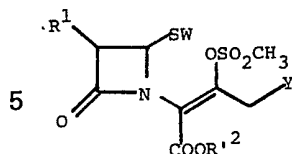
Next, the compound VI is cyclized to afford a 2-thiacephem VII wherein R^1, R'^2 and Y are as
10   defined above. This cyclization is carried out in a single step, by reaction of (VI) with a sulphide   10
or hydrosulphide, such as sodium sulphide, NaHS, Bu_4NHS or with hydrogen sulphide in the
presence of a base, such as triethylamine or pyridine, in a suitable solvent, such as dimethyl-
formamide, dimethylsulphoxide, acetonitrile or ethanol, optionally in admixture with water; best
yields are obtained when the reagents are allowed to react, at a temperature of from $-10°$ to
15   $+30°C$, for no longer than the time required to consume the starting material. Finally, the   15
compounds VII are desulphurized to a penem of formula (I), wherein R^2 is R'^2, and R^1, R'^2 and Y
are as above defined, by reaction with a tervalent organophosphorous reagent, preferably
triphenylphosphine, in a suitable solvent, which is preferably selected from chloroform,
acetonitrile, tetrahydrofuran, ethanol, dimethylsulphoxide and acetone. The type of solvent may
20   have a pronounced effect on the configuration of the 5-C atom of the resulting penem (VIII),   20
depending on the groups R^1, R'^2, Y and it must be selected with care in order to achieve the
highest yield of the $5R$ penem diastereomer. In the process of the invention, the obtained
compound I may be converted, if desired, into another compound I; preferred conversions of
this type comprise standard reactions such as deprotection of a functional group on the R^1
25   group; or the deprotection of a protected hydroxy group Y; or the conversion of the R'^2 group   25
into a different R^2 group, being R^2 as above defined. In particular, when $-CO_2R'^2$ is an ester
radical, such as a p-nitrobenzylester, it may be converted into a group $-CO_2R^2$, wherein R^2 is
hydrogen, sodium or potassium. Interconversions of this type between a R'^2 group and a
different R^2 group or atom above defined, and/or between different accepted meanings of R^1,
30   R^2, can be performed, if desired, on the 2-thiacephem intermediates VII. Owing to the good   30
stability of the 2-thiacephem nucleus towards acid conditions, a distinct advantage of route A,
as compared with other classical routes to penems, is that ester hydrolyses not compatible with
a penem ring system (e.g., cleavage of a t-butyl or diphenylmethyl ester) can be performed on
the 2-thiacephem precursors, while the final ring-contraction, which is a particularly mild and
35   facile reaction, may be carried out even on the free acid, or on a salt thereof with an organic or   35
inorganic base, or on a different, labile ester (e.g., trimethylsilyl ester), thus directly obtaining
the desired compound, even if highly functionalized and relatively unstable.
    According to Invention Route B, a compound III, wherein R^1 is as defined above, and R'^2 is
preferably methyl, or another residue forming with the $-CO_2$ moiety an ester group cheaply
40   introduced and conveniently carried on (for what concerns yields, purification, etc.) from a   40
penicillin precursor to the level of said intermediate (III), is first converted into the key lactone
intermediate of formula IX, wherein R^1 and Y are as above defined.
    The conversion can be carried out in three separate steps, i.e.:
    1) the compound III is first converted into a compound IV as hereinabove described;
45   2) the compound IV is allowed to lactonize, affording an intermediate of formula VIII. Such   45
lactonization is facilitated by prolonged heating, and/or by exposure to basic or acid catalysts. A
preferred basic catalyst is triethylamine, with or without the presence of an inert organic solvent
such as dichloromethane or tetrahydrofuran. Under these conditions the process is very rapid at
room temperature or below, and affords the compound VIII in almost quantitative yield;
50   3) displacement of HW or of a salt thereof, W being as above defined, with   50

$$YCH_2C\overset{\displaystyle O}{\underset{\displaystyle SH}{\diagup}}$$
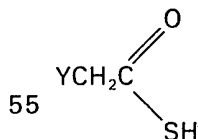
55   55

or a salt thereof, Y being as above defined, finally affords the compound IX, again under
extremely simple operative conditions (inert solvent such as dichloromethane, at room tempera-
60   ture or below) and in excellent yields.   60
    It should be mentioned that the conversion of compound III into compound IX can be
performed in two steps or even one step. Thus, prolonged heating of a compound III in the
presence of HW usually affords VIII directly, instead of IV. Moreover, heating a compound III in
the presence of the compound

$$Y-CH_2-C \begin{array}{c} \diagup O \\ \diagdown SH \end{array}$$
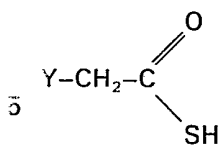
usually gives IX in good yields; we believe that this straightforward result stems from the (previously unreported) trapping of a thermally-generated sulphenate, in this instance the one of
10 the following formula
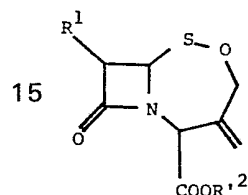
with said thioacid, followed by spontaneous or acid-catalyzed lactonization.

Thereafter, the acyldithioazetidinyl lactone IX is desulphurized with a tervalent organophosphorous reagent, preferably triphenyl phosphine, to give the corresponding thioester lactone X. Again, this process is rapid at room temperature (an inert organic solvent such as dichloromethane is preferably employed), gives good yield, and proceeds with substantial retention of the
25 original azetidinone C–4 configuration (beyond any reasonable expectation, even when R^1 and

$$S-S-C-CH_2Y$$
$$\parallel$$
$$O$$
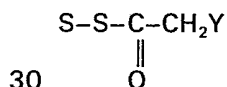
are *cis* arranged to each other); this is crucial in conferring to Invention Route B the ability of converting a natural penicillanic acid precursor into a penem compound I possessing the desired 5R configuration (an essential stereochemical requirement for antibiotic activity: H.R. Pfaendler
35 et al., *J. Am. Chem. Soc.*, 1979, 101, 6306). Compound IX need not be isolated before desulphurisation; thus, a single-pot conversion of III into X is possible.

It should be mentioned that it may be convenient in particular instances to reverse the operative sequence lactonization/group W displacement/desulphurization. Thus, reaction of (IV) with the compound of formula

$$Y-CH_2-C-SH,$$
$$\parallel$$
$$O$$
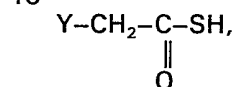
45 wherein Y is as defined above; in the same experimental conditions described for the reaction of (VIII) to give (IX), affords a compound of formula

(IXa)
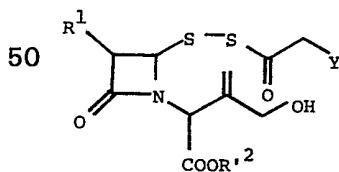
or, alternatively, said compound may be obtained directly from (III) and the compound

$$Y-CH_2-C-SH$$
$$\parallel$$
$$O$$
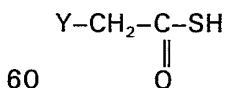
hereabove defined, in variable amounts together or instead of its lactone of formula (IX), depending on the nature of the substituents, particularly of R′, and on the reaction conditions.
Said compound of formula (IXa) may then be lactonized into a compound of formula (IX), in the
65 same experimental conditions described for the conversion of (IV) into (VIII), or may be

desulphurised into a compound of formula

5

(Xa)

5

10
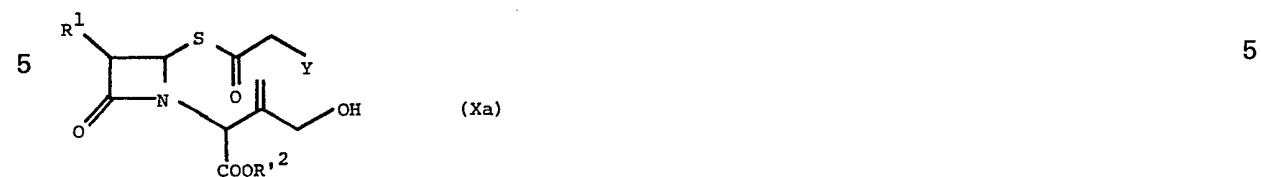
10   by using the experimental conditions described for the desulphurization of (IX) into (X), and then
converted into its lactone (X), again under the conditions reported for the conversions of (IV) into
(VIII); the final outcome of all these routes being the key intermediate (X).
      The next step comprises the ozonolysis of a compound X at temperatures between −70° and
15   about 0°C, in a suitable solvent, such as dichloromethane, to give an oxalimide XI. This reaction   15
not only provides the useful

$$-N-C-CO_2-$$
$$\qquad \| $$
20    $$\qquad O$$

20
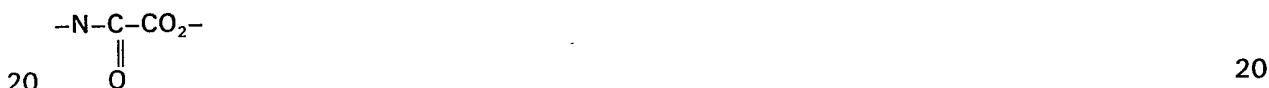
      moiety, but generates an acetonyl ester which is bound in the following steps to be incorporated
in the penem compound I. The compound XI can be converted into the penem compound I by
Wittig-type ring closure of a phosphorane XIII. To this end, the compound XI is first reduced
25   into a carbinol XII; this can be achieved by a variety of reducing agents, such as boranes (e.g.   25
B_2H_6), hydrides (e.g. $NaBH_4$, $NaBH_3CN$) or metals (e.g. Al/Hg, Zn). A preferred reagent is zinc
dust in the presence of an organic acid, preferably acetic acid, in which case the reaction is
conveniently carried out in the same ozonlysis vessel (solvent: dichloromethane) by adding said
reagent and stirring at temperatures ranging from 0°C to +30°C.
30   The next steps leading to the penem compound I call for little description, as they follow the   30
very popular route described by Woodward (J. Am. Chem. Soc., 1978, 100, 8214). The
carbinol XII is converted into the corresponding chloride (preferred reagent: thionyl chloride in
pyridine or lutidine) and thence into the phosphorane (reagent: triphenylphosphine, optionally in
the presence of a base and/or silica gel) which is then thermolyzed in an inert solvent (such as
35   benzene, toluene or xylene) to yield penem compound I (R^1 and Y as defined above,   35
R^2 = acetonyl). The compounds I thus obtained can optionally be converted into different
compounds I as above described. In particular the acetonyl ester can be easily cleaved to afford
the sodium salt of the parent penem acid, by simple tritation with a dilute solution of sodium
hydroxide (see J. Am. Chem. Soc., 1979, 101, 6306).
40   40

Example 1
4-(R)-Benzothiazolyldithio-1-(2-hydroxymethyl-1-p-nitrobenzyloxycarbonyl-1-prop-2-enyl)-3(R)-
phthalimido-azetidin-2-one
      A solution of 495 mg of 7(R)-phthalimido-3-methylene-cepham-1-oxide *p*-nitrobenzyl ester in
45   50 ml of dry toluene was refluxed with 250 mg of 2-mercaptobenzothiazole for 1 hour.   45
Removal of the solvent left a foam, consisting of the title product (85%) accompanied by a
minor amount of 4(R)-benzothiazolyldithio-1-(4-methyl-2-oxo-2,5-dihydro-furan-3-yl)-3(R)phthal-
imidoazetidin-2-one and the excess 2-mercaptobenzothiazole. This mixture can be conveniently
used as such for the following steps. A pure sample of the title product can be obtained after
50   silica gel chromatography; ν_{max} (CHCl$_3$ film) 1780, 1745, 1720, 1605 cm^{-1}; δ (CDCl$_3$) 3.20 br   50
(1H, s,OH), 4.47 (2H, s, *CH*$_2$OH), 5.22 (1H, s, N*CH*CO), 5.31 (2H, s, O*CH*$_2$Ar), 5.47 (2H, m,
C:CH$_2$), 5.78 (1H, d, J = 4.0Hz, H–*CH*.CH), 7.2–8.0 (10H, m, *Ar*), 8.19 (2H, d, *Ar*) ppm.

Example 2
55   *4(R)-Benzothiazolyldithio-1-(2-acetoxymethyl-1-p-nitrobenzyloxycarbonyl-1-prop-2-enyl)-4(R)-*   55
phthalimido-azetidin-2-one
Method A
      A solution of 663 mg of 4(R)-benzothiazolyldithio-1-(2-hydroxymethyl-1-*p*-nitrobenzyloxycarbo-
nyl-1-prop-2-enyl)-3(R)-phthalimido-azetidin-2-one, prepared as described in Example 1, in 7 ml
60   of dry dichloromethane was sequentially treated at 0°C with 0.11 ml of acetyl chloride and 0.1   60
ml of pyridine. After a few minutes the mixture was washed with water and the dried organic
layer evaporated to give the title product; ν_{max} (film) 1785, 1770 sh, 1740, 1720, 1605 cm^{-1};
δ (CDCl$_3$) 2.17 (3H, s, COCH$_3$), 4.85 (2H, br s, CH$_2$O), 5.19 (1H, br s, NCHCO), 5.34 (3H, br
s, O*CH*$_2$Ar and C:CH.*H*), 5.54 (1H, br s, C:*CH*.H), 5.81 (2H, ABq, J = 5.5Hz, separation of
65   inner lines 9 Hz, β-lactam protons), 7.2–8.0 (10H, m, *Ar*), 8.19 2H, d, *Ar*) ppm.   65

Method B

The two-step conversion described in Example 1 and in Method A of this Example can be conveniently carried out in a single pot. Thus, 1.5 g of 7(R)-phthalimido-3-methylene-cepham-1-
5   oxide p-nitrobenzyl ester was refluxed for 1.5 hours in toluene with 506 mg of mercaptobenzo-   5
thiazole. After cooling, the mixture was diluted with dichloromethane and treated at 0°C
sequentially with 0.32 ml of acetyl chloride and 0.29 ml of pyridine. The reaction was followed
by tlc, repeating the addition of acetyl chloride and pyridine if necessary. Washing with water
and then with aqueous hydrogen carbonate, and removal of the solvent left the title product (2
10 g) which can be used as such for the following steps.   10

Method C

When the 7-phthalimido-3-methylenecepham sulphoxide (0.5 g) was refluxed in dry toluene
(24 ml) containing acetic anhydride (4 ml) for 1 hour, the title compound was obtained in good
15 yield.   15

Method D

Refluxing 7-phthalimido-3-methylene-cepham-1-oxide with 2-acetylthiobenzothiazole in tolu-
ene afforded the title product.
20   20

Example 3
*4(R)-Benzothiazolyldithio-1-[2-(N-ethylcarbamoyloxy-methyl)-1-p-nitrobenzyloxycarbonyl-1-prop-2-
enyl]-3(R)-phthalimido-azetidin-2-one*

A solution of 665 mg of 4(R)-benzothiazolyldithio-1-(2-hydroxy-methyl-1-p-nitrobenzyloxycar-
25 bonyl-1-prop-2-enyl)-3(R)-phthalimido-azetidin-2-one, prepared as described in Example 1, in dry   25
toluene was treated with 1 ml of ethyl isocyanate overnight at room temperature. Removal of
the solvent left the title product in virtually quantitative yield; ν_{max} (CHCl$_3$ film) 3410, 1785,
1770 sh, 1720 br, 1610 cm^{-1}; δ (CDCl$_3$ + D$_2$O) 1.15 (3H, t, CH$_2$CH$_3$), 3.2 (2H, q, CH$_2$.CH$_3$),
4.8 (2H, br s, CH$_2$O), 5.25 (4H, br s, NCHCO + OCH$_2$Ar + C:CH.H), 5.50 (1H, br s, C:CH.H),
30 5.80 (2H, ABq, J = 5 Hz, β-lactam protons), 7.2–7.9 (10H, m, Ar), 8.15 (2H, d, J = 8Hz, Ar)   30
ppm.

The reaction can conveniently be carried out starting from 7(R)-phthalimido-3-methylene-
cepham-1-oxide p-nitrobenzylester and 2-mercaptobenzothiazole, without isolating the intermedi-
ate carbinol. Column chromatography then afforded the pure title product in more than 70%
35 overall yield.   35

Example 4
*4(R)-Benzothiazolyldithio-1-[2-(N-trichloroacetyl)-carbamoyloxymethyl-1-p-nitrobenzyloxycarbonyl-
1-prop-2-enyl]-3(R)-phthalimido-azetidin-2-one*
40   Operating as described in Example 3, but using trichloroacetyl isocyanate instead of ethyl   40
isocyanate, the title product was obtained; ν_{max} (CHCl$_3$ film) 1800 sh, 1785 sh, 1775, 1750,
1725, 1660, 1610 cm^{-1}; δ (CDCl$_3$) 4.95 (2H, br s, CH$_2$O), 5.3 (4H, m, OCH$_2$Ar + NCH-
CO + C:CH.H), 5.55 (1H, br s, C:CH.H), 5.82 (2H, s, β-lactam protons), 7.2–7.9 (10H, m, Ar),
8.18 (2H, d, J = 8Hz, Ar) ppm.
45   45

Example 5
*4(R)-Benzothiazolyldithio-1-[2-(2-tetrahydropyranyloxymethyl)-1-p-nitrobenzyloxycarbonyl-1-prop-
2-enyl]-3(R)-phthalimido-azetidin-2-one*

A solution of 665 mg of 4(R)-benzothiazolyldithio-1-(2-hydroxymethyl-1-p-nitrobenzyloxycarbo-
50 nyl-1-prop-2-enyl)-3(R)-phthalimido-azetidin-2-one, prepared as described in Example 1, in dry   50
dichloromethane was allowed to react overnight with a large excess of dihydropyrane in the
presence of a catalytic amount of pyridinium p-toluenesulphonate. Aqueous work-up and
evaporation *in vacuo* left the title product; ν_{max} (film) 1785, 1775 sh, 1740, 1720, 1610 cm^{-1};
δ (CDCl$_3$) 1.64 (6H, m, pyranyl CH$_2$.CH$_2$.CH$_2$), 3.4–4.0 (2H, m, OCH$_2$, pyranyl), 4.30 and 4.41
55 (2H, centre of ABq + s, CH$_2$O), 4.70 (1H, m, pyranyl O.CH.O), 5.20 and 5.25 (1H, each s,   55
N.CH.CO), 5.32 (2H, s, OCH$_2$Ar), 5.44 (2H, m, C:CH$_2$), 5.71 and 5.74 (1H, each d, J = 5.0
Hz, CH.CH.S), 5.82 and 5.84 (1H, each d, J = 5.0 Hz, N.CH.CH), 7.20–8.25 (12H, m, Ar)
ppm.

Alternatively, without isolating the carbinol, 7(R)-phthalimido-3-methylene-cepham-1-oxide p-
60 nitrobenzyl ester can be convered into the title product (70% yield after silica gel chromato-   60
graphy) by sequential reaction with 2-mercaptobenzothiazole in toluene under reflux and
dihydropyrane in toluene and dichloromethane at room temperature.

Example 6
65 *(E)-1-(3-Acetoxy-2-methanesulphonyloxy-1-p-nitrobenzyloxycarbonyl-1-prop-1-enyl)-4(R)-benzothi-*   65

azolyldithio-3(R)-phthalimido-azetidin-2-one

A solution of crude 4(R)-benzothiazolyldithio-1-(2-acetoxymethyl-1-*p*-nitrobenzyloxycarbonyl-1-prop-2-enyl)-3(R)-phthalimido-azetidin-2-one, prepared as described in Example 2, Method B, in a dichloromethane:methanol mixture was treated with ozone at $-70°C$ (tlc monitoring). 1 ml of
5 dimethylsulphide was then added and the mixture stirred for 30 minutes at room temperature.   5
Removal of the solvent left the crude intermediate enol, which was reacted with mesyl chloride/pyridine (molar equivalent amounts) in dry distilled tetrahydrofuran. Further amounts of mesyl chloride and pyridine were added, if necessary, until tlc showed complete conversion.
After partial evaporation *in vacuo* the reaction mixture was partitioned between water and ethyl
10 acetate.   10
The organic layer was evaporated and the residue passed through a silica gel column to afford the title product; ν_{max} (film) 1790 sh, 1770, 1750 sh, 1720, 1380, 1170 cm^{-1}.

Example 7
15 *4(R)-Benzothiazolyldithio-1-[3-(N-ethylcarbamoyloxy)-2-methanesulphonyloxy-1-p-nitrobenzyloxy-*   15
carbonyl-1-prop-1-enyl]-3(R)-phthalimido-azetidin-2-one
A solution of 600 g of 4(R)-benzothiazolyldithio-1-[2-(N-ethyl-carbamoyloxymethyl)-1-prop-2-enyl]-3(R)-phthalimido-azetidin-2-one, prepared as described in Example 3, in 3:2 by volume methanol:dichloromethane was ozonized at $-70°C$ until the starting material was no longer
20 detectable by tlc. The solution was purged with nitrogen and then allowed to warm up to room   20
temperature in the presence of 1 ml of dimethylsulphide. Removal of the solvent and flash chromatography afforded some 4(R)-benzothiazolyldithio-3(R)-phthalimido-azetidin-2-one, followed by 4(R)-benzothiazolyldithio-1-[3-(N-ethyl-carbamoyloxy)-2-hydroxy-1-*p*-nitrobenzyloxycarbonyl-1-prop-1-enyl]-3(R)-phthalimido azetidin-2-one; ν_{max} (CHCl$_3$ film) 3350, 1785, 1770,
25 1720, 1650 cm^{-1}.   25
400 mg of the latter material in 4 ml of dry distilled tetrahydrofuran was treated with 0.42 ml of mesyl chloride and 0.44 ml of pyridine. After stirring for 10 minutes at room temperature, the solvent was removed. The residue was taken up in ethyl acetate and washed with dilute aqueous hydrochloric acid. The solvent was again evaporated off to give the crude title product.
30 A pure sample was obtained after flash chromatography; ν_{max} (CHCl$_3$ film) 1790, 1770, 1725,   30
1365, 1170 cm^{-1}; δ (CDCl$_3$ + D$_2$O) 1.05 (3H, t, CH$_3$), 3.20 (2H, q, NCH$_2$CH$_3$), 3.4 (3H, s, SO$_2$CH$_3$), 5.1–5.4 (5H, m, OCH$_2$Ar + CH$_2$OCO + NCHCO), 5.85 (2H, s, β-lactam protons), 7.2–8.2 (12H, m, Ar) ppm.

35 *Example 8*   35
4(R)-Benzothiazolyldithio-1-[3-(2-tetrahydropyranyloxy)-2-methanesulphonyloxy-1-p-nitrobenzylox-
ycarbonyl-1-prop-1-enyl]-3(R)-phthalimido-azetidin-2-one
Following the experimental procedure described in Example 6, 4(R)benzothiazolyldithio-1-[2-(2-tetrahydro-pyranyloxymethyl)-1-*p*-nitrobenzyloxycarbonyl-1-prop-2-enyl]-3(R)-phthalimido-azeti-
40 din-2-one, prepared as described in Example 5, was converted first into the enol intermediate   40
(ν_{max} (nujol) 1785 sh, 1770, 1720, 1660 cm^{-1}), and thence into the title product; ν_{max} (CHCl$_3$
film) 1795, 1775, 1725, 1390, 1170 cm^{-1}.

Example 9
45 *p-Nitrobenzyl (7R,6R)-7-phthalimido-3-(N-ethylcarbamoyloxymethyl)-2-thiacephem-4-carboxylate*   45
A solution of 150 mg of 4(R)-benzothiazolyldithio-1-[3-(N-ethyl-carbamoyloxy)-2-methanesulphonyloxy-1-*p*-nitrobenzyloxycarbonyl-1-prop-1-enyl]-3(R)-phthalimido-azetidin-2-one, prepared as described in Example 7, in 5 ml of dimethylformamide treated with a solution of 14 mg sodium hydrosulphide monohydrate in dimethylformamide. After 20 seconds at room tempera-
50 ture the mixture was poured in a mixture of ethyl acetate and water. The organic layer was   50
washed several times with water, dried, evaporated and passed through a silica gel column to afford 54 mg of the title product as a waxy solid; ν_{max} (CHCl$_3$ film) 3400, 1800, 1775, 1725, 1610 cm^{-1}; δ (CDCl$_3$) 1.14 (3H, t, CH$_2$CH$_3$), 3.20 (2H, m, NHCH$_2$CH$_3$), 5.13 (1H, d, J = 5Hz, CH.CH.S), 5.20–5.18 (4H, m, CH$_2$.O), 6.10 (1H, d, J = 5Hz, N.CH.CH), 7.60 and 8.20 (each
55 2H, d, Ar.NO$_2$), 7.82 (4H, m, Ft) ppm; λ_{max} (CHCl$_3$) 269 and 337 nm.   55
Following the same experimental procedures, but starting from the intermediates described in Examples 6 and 8, there were obtained:
p-nitrobenzyl (7R,6R)-7-phthalimido-3-acetoxymethyl-2-thiacephem-4-carboxylate;
p-nitrobenzyl (7R,6R)-7-phthalimido-3-(2-tetrahydropyranyloxymethyl)-2-thiacephem-4-carboxyl-
60 ate.   60

Example 10
p-Nitrobenzyl 6-phthalimido-2-(N-ethylcarbamoyloxymethyl)-penem-3-carboxylate
A solution of 200 mg of *p*-nitrobenzyl 7-phthalimido-3-(N-ethyl-carbamoyloxymethyl)-2-thiace-
65 phem-4-carboxylate in chloroform was treated with 120 mg of triphenylphosphine. The reaction   65

(tlc monitoring) is immediately over. Removal of the solvent and purification from triphenylphos-
phine sulphide and excess reagent afforded the title product in almost quantitative yield as a 1:9
mixture of 5,6-*cis* and *trans* isomers; ν_{max} (CHCl₃ film) 3400, 1800, 1780 sh, 1720 cm⁻¹; λ_{max}
(CHCl₃) 267, 305 sh, 324 nm. Improved amounts of the *cis* isomer could be obtained by
5 performing the desulphuration in a more polar solvent (in particular, tetrahydrofuran or   5
acetonitrile).

Example 11
(6R,5S)-6-Phthalimido-2-(N-ethylcarbamoyloxymethyl-penem-3-carboxylic acid
10   2 ml of water and 50 mg of 5% by weight palladium on charcoal were added to a solution of   10
20 mg of (6R,5S)-*p*-nitrobenzyl 6-phthalimido-2-(N-ethylcarbamoyloxymethyl)-penem-3-carboxyl-
ate in 2 ml of ethyl acetate. The mixture was stirred for 1 hour at room temperature under
hydrogen, and then for a further 30 minutes after more catalyst was added. After filtration, the
mixture was partitioned between ethyl acetate and dilute acetic acid. Removal of the solvent
15 from the organic layer left a residue which was collected as a white powder (10 mg) after   15
trituration with diethyl ether; ν_{max} (CHCl₃ film) 3320, 1795 sh, 1775, 1720, 1700 sh cm⁻¹; δ
(CDCl₃ + D₂O) 1.15 (3H, t, CH₂CH₃), 4.25 (2H, q, CH₂CH₃), 5.34 (2H, ABq, J = 16Hz,
separation of inner lines 40 Hz (200 MHz apparatus), CH₂O), 5.82 and 5.98 (each 1H, d,
J = 1.5Hz), 7.9 (4H, m, Ar) ppm. The same reaction, performed on the (6R, 5R) isomer of the
20 starting material, afforded the (6R, 5R) isomer of the title product; λ_{max} (CHCl₃) 244, 304 and   20
318 nm.

Example 12
4(R)-Benzothiazolyldithio-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3(R)-phthalimido-azetidin-2-
25 *one*   25
    A solution of 750 mg of 7(R)-phthalimido-3-methylene-cepham-1-oxide *p*-nitrobenzyl ester in
30 ml of benzene was refluxed with 253 mg of 2-mercaptobenzothiazole for 15 hours.
Chromatography over silica gel afforded in sequence *p*-nitrobenzyl alcohol and the title product;
ν_{max} (CHCl₃ film) 1790, 1775, 1760, 1720 cm⁻¹; δ (CDCl₃) 2.35 (3H, s, CH₃), 4.6 (2H, br s,
30 CH₂O), 5.9 and 6.25 (2H, each d, J = 5Hz, β-lactam protons), 7.2–8.0 (4H, m, Ar) ppm.   30

Example 13
4(R)-Acetyldithio-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3(R)-phthalimido-azetidin-2-one
Method A
35   A solution of 100 mg of 7(R)-phthalimido-3-methylene-cepham-1-oxide *p*-nitrobenzyl ester in   35
5 ml of toluene was refluxed with an excess (0.07 ml) of thioacetic acid. When the starting
material had disappeared (tlc monitoring) the mixture was cooled, treated with 0.1 ml of
triethylamine, evaporated, and then chromatographed on silica gel to yield *p*-nitrobenzyl alcohol
and the title product (65 mg); ν_{max} (CHCl₃ film) 1790, 1775, 1760, 1725 cm⁻¹; δ (CDCl₃) 2.3
40 and 2.35 (each 3H, s, CH₃), 4.85 (2H, br s, CH₂O), 5.8 (2H, br, s, β-lactam protons), 7.2–7.9   40
(4H, m, Ar) ppm.

Method B
    A solution of 300 mg of 4(R)-benzothiazolyldithio-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-
45 3(R)-phthalimido-azetidin-2-one, prepared as described in Example 12, in 20 ml of dichloro-   45
methane was treated at room temperature with 0.043 ml of thioacetic acid. An instantaneous
reaction leading to the title product and 2-mercaptobenzothiazole took place. The former could
be isolated by chromatography or, more conveniently, used as such for the following steps.

50 *Example 14*   50
4(R)-Acetylthio-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3(R)-phthalimido-azetidin-2-one
    A solution of 0.59 g of 4(R)-acetyldithio-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3(R)-phthal-
imido-azetidin-2-one, prepared as described in Example 13, in 10ml of chloroform was treated
with 160 mg of triphenylphosphine. Removal of the solvent left a mixture of triphenylphosphine
55 sulphide and the title product. The latter could be isolated pure in almost quantitative yield after 55
silica gel chromatography, or the reaction mixture used as such for the following step; ν_{max}
(CHCl₃ film) 1790, 1775, 1765, 1725 cm⁻¹; δ (CDCl₃) 2.2 and 2.3 (each 3H, s, CH₃), 4.75
(2H, br s, CH₂O), 5.85 (1H, d, J = 5.5Hz, N.CH.CH), 6.58 (1H, d, J = 5.5Hz, CH.CH.S),
7.3–7.9 (4H, m, Ar) ppm.
60   60
Example 15
1-Acetonyloxyoxalyl-4(R)-acetylthio-3(R)-phthalimido-azetidin-2-one
    A stream of ozone in dry oxygen was passed through a solution of 400 mg of 4(R)-acetylthio-
1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3(R)-phthalimido-azetidin-2-one, prepared as described
65 in Example 14, in 20 ml of dichloromethane at − 70°C, until the starting material was no   65

longer detectable by tlc. The mixture was purged with a stream of nitrogen and the solution,
containing the title product in almost quantitative yield, normally used as such for the following
steps. The title product, if desired, can be isolated by adding a large excess of solid sodium
metabisulphite and, when the temperature rises to + 5°C, adding water, separating the organic
5 layer and removing the solvent, ν_{max} (CHCl$_3$ film) 1830, 1780 sh, 1760, 1720, 1700 sh cm^{-1}.   5

Example 16
Acetonyl (5R,6R)-6-phthalimido-2-methyl-penem-3-carboxylate
   The crude ozonolysis mixture obtained as described in Example 15 was treated with 400 mg
10 of activated zinc dust and 0.4 ml of acetic acid. After stirring for 1 hour at room temperature,   10
the mixture was filtered and the liquors washed with water and then aqueous hydrogen
carbonate. Removal of the solvent left crude 1-(1-acetonyloxycarbonyl-1-hydroxy-methyl)-4(R)-
acetylthio-3(R)-phthalimido-azetidin-2-one. Without purification, this material was dissolved in
dry distilled tetrahydrofuran and allowed to react at − 5°C under nitrogen with 0.08 ml of
15 pyridine and 0.072 ml of thionyl chloride. After ten minutes the salts were filtered off and any   15
volatile material removed in vacuo at 25°C to obtain crude 1-(1-acetonyloxycarbonyl-1-chloro-
methyl)-4(R)-acetylthio-3(R)-phthalimido-azetidin-2-one as a foam, which was immediately dis-
solved in a solution of 0.26 g of triphenylphosphine in tetrahydrofuran. 5 g of silica gel was
added and the solvent removed. The dried material was left standing overnight, then charged to
20 the top of a silica gel column. Elution with ethyl acetate:cyclohexane mixtures gave 200 mg of   20
1-(1-acetonyloxycarbonyl-1-phosphoranylidene-methyl)-4(R)-acetylthio-3(R)-phthalimido-azetidin-
2-one as a foam. Heating a toluene solution of this product at about 115°C for 48 hours (about
50% conversion) followed by silica gel chromatography, gave the title product, 25 mg
(crystallizing directly from the cyclohexane:ethyl acetate mixture used as eluant), triphenylphos-
25 phine oxide and then the starting phosphorane (which could be recycled); mp 176–178°C ν_{max} 25
(CHCl$_3$) 1795, 1770, 1727, 1720, 1705 cm^{-1}; δ (CDCl$_3$) 2.24 (3H, s, COCH$_3$), 2.42 (3H, s,
CH$_3$), 2.79 (2H, s, OCH$_2$CO), 5.98 (2H, s, β-lactam protons), 7.82 (4H, m, Ar) ppm; λ_{max}
(CHCl$_3$) 292 sh, 308, 324 sh nm.

30 *Example 17*   30
7(S)-[1(R)-t-butyldimethylsilyloxyethyl]-3-methylene-cepham-1-oxide methyl ester
   A mixture of 4 g of 6(S)-[1(R)-t-butyldimethylsilyloxyethyl]-penicillanate-1-oxide methyl ester,
1 g of N-chlorosuccinimide and 8 g of sodium sulphite in 125 ml of dry benzene was refluxed
for 10 hours. The cooled reaction mixture was then treated with 0.5 ml of diethyl ether and
35 1.26 ml of tin tetrachloride. After 2 hours stirring, ethyl acetate and dilute hydrochloric acid   35
were added. The separated organic layer was dried and evaporated to afford a residue which
crystallized from diisopropyl ether; mp 120–122°; ν_{max} (KBr) 1775, 1740, 1265 cm^{-1}; δ
(CDCl$_3$) 0.06 and 0.11 (each 3H, s, SiMe$_2$), 0.89 (9H, s, Bu^t), 1.32 (3H, d, J = 6.5Hz, CH$_3$CH),
3.58 (1H, dd, J = 2 and 4Hz, CH.CH.CH), 3.8 (5H, br s, CH$_2$S and OCH$_3$), 4.3 (1H, m,
40 CH$_3$.CH.CH), 4.75 (1H, d, J = 2Hz, CH.CH.S), 5.0 (1H, s, N.CH.CO), 5.25 and 5.50 (2H, each   40
s, = CH$_2$) ppm.

Example 18
4(R)-benzothiazolyldithio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(2-hydroxymethyl-1-methoxy-
45 *carbonyl-1-prop-2-enyl)-azetidin-2-one*   45
   A solution of 250 mg of 7(S)-[1(R)-t-butyldimethylsilyloxyethyl]-3-methylene-cepham-1-oxide
methyl ester, prepared as described in Example 17, and 110 mg of 2-mercaptobenzothiazole
was refluxed for 5 hours in toluene. Removal of the solvent left a residue consisting mainly of
the title material. The latter can be obtained pure by flash chromatography, although partial
50 conversion into the corresponding lactone (see Example 19) occurs on silica gel; ν_{max} (CHCl$_3$ film)   50
3400, 1765 and 1740 cm^{-1}; δ (CDCl$_3$) 0.08 (6H, s, SiMe$_2$) 0.9 (9H, s, Bu^t), 1.3 (3H, d,
J = 6Hz, CH$_3$.CH), 3.45 (1H, dd, J = 2 and 3.5 Hz, CH.CH.CH), 4.35 (3H, m, CH$_3$.CH.CH and
CH$_2$OH), 5.0 (1H, s, N.CH.CO), 5.2 and 5.35 (2H, each s, = CH$_2$), 5.38 (1H, d, J = 2Hz,
CH.CH.S), 7.1–7.9 (4H, m, Ar) ppm.

55   55
Example 19
4(R)-Benzothiazolyldithio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(4-methyl-2-oxo-2,5-dihydrofu-
ran-3-yl)-azetidin-2-one
Method A
60   A solution of 800 mg of 7(R)-(1-t-butyldimethylsilyloxyethyl)-3-methylene-cepham-1-oxide   60
methyl ester and 335 mg of 2-mercaptobenzothiazole in 10 ml of toluene was refluxed for 5
hours. The cooled reaction mixture was treated with 0.01 ml of triethylamine. After 1 hour, the
solvent was removed in vacuo and the residue crystallized from diethyl ether to give the title
product as a white powder (600 mg).

Method B

A solution of 100 mg of 4(R)-benzothiazolyldithio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(2-hydroxymethyl-1-methoxycarbonyl-1-prop-2-enyl)-azetidin-2-one, prepared as described in Example 18, in 25 ml of dichloromethane was stirred for 3 hours in the presence of 0.01 ml of
5 triethylamine. Removal of the solvent left the title product; ν_{max} (CHCl$_3$ film) 1775, 1760 cm^{-1};   5
δ (CDCl$_3$) 0.06 and 0.1 (6H, each s, SiMe$_2$), 0.88 (9H, s, Bu^t), 1.3 (3H, d, CH_3.CH), 1.8 (3H, s, CH$_3$), 3.5 (1H, dd, J = 2 and 3Hz, CH.CH.CH), 4.15 (2H, ABq, J = 18Hz, CH$_2$O), 4.3 (1H, m, CH$_3$.CH.CH), 5.9 (1H, d, J = 2Hz, CH.CH.S), 7.0–7.8 (4H, m, Ar) ppm.

10 *Example 20*   10
4(R)-Acetylthio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one

A solution of 220 mg of 4(R)-benzothiazolyldithio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one, prepared as described in Example 19, in 2
15 ml of chloroform was treated in sequence with 0.03 ml of thioacetic acid and 130 mg of   15
triphenylphosphine. Removal of the solvent and purification from mercaptobenzothiazole and triphenylphosphine sulphide (silica gel chromatography) afforded the title product; ν_{max} (CHCl$_3$ film) 1775 sh, 1760, 1700 cm^{-1}; δ (CDCl$_3$) 0.06 and 0.1 (each 3H, s, SiMe$_2$), 0.85 (9H, s, Bu^t), 1.25 (3H, d, J = 6.5Hz, CH_3.CH), 2.15 and 2.30 (each 3H, s, CH$_3$), 3.45 (1H, dd,
20 J = 2.5 and 3.5Hz, CH.CH.CH), 4.3 (1H, m, CH$_3$.CH.CH), 4.67 (2H, s, CH$_2$O), 5.5 (1H, d,   20
J = 2.5Hz, CH.CH.S) ppm.

Example 21
1-Acetonyloxyoxalyl-4(R)-acetylthio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-azetidin-2-one
25 This material was obtained from 4(R)-acetylthio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(4-   25
methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one, prepared as described in Example 20, according to the experimental procedure described in Example 15.

Example 22
30 *Acetonyl (5R,6S)-6-[1(R)-t-butyldimethylsilyloxyethyl]-2-methyl-penem-3-carboxylate*   30
Starting from 100 mg of 4(R)-acetylthio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one, prepared as described in Example 20 and by using the ozonolysis procedure described in Example 15, directly followed by the sequence of operations described in Example 16 (reduction with 0.5 g of zinc and 0.5 ml of acetic acid; chlorination
35 with 0.017 ml of thionyl chloride and 0.019 ml of pyridine; reaction with 0.062 g of   35
triphenylphosphine, on 3 g of silica gel; elution and thermolysis in refluxing toluene for 6 hours) afforded, after silica gel chromatography, the title product (50 mg, 54% overall yield); ν_{max} (CHCl$_3$ film) 1785, 1710, 1590 cm^{-1}; δ (CDCl$_3$) 0.07 (6H, s, SiMe$_2$), 0.84 (9H, s, Bu^t), 1.22 (3H, d, J = 6.5Hz CH_3.CH), 2.15 (3H, s, COCH$_3$), 2.32 (3H, s, CH$_3$), 3.58 (1H, dd, J = 2 and
40 5Hz), 4.2 (1H, m, CH$_3$.CH.CH), 4.60 (2H, s, OCH$_2$), 5.48 (1H, d, J = 2Hz, CH.CH.S) ppm; λ_{max} 40
(CHCl$_3$) 271 sh, 321 nm.

Example 23
Acetonyl (5R,6S)-6-[1(R)-hydroxyethyl]-2-methyl-penem-3-carboxylate
45 A solution of 30 mg of acetonyl (5R,6S)-6-[1(R)-t-butyldimethylsilyloxyethyl]-2-methyl-penem-   45
3-carboxylate, prepared as described in Example 22, in 2 ml of tetrahydrofuran was treated with 0.045 ml of acetic acid and 71 mg of tetrabutylammonium fluoride trihydrate. After stirring for 20 hours, column chromatography afforded the title product (18 mg) as a white solid; ν_{max} (CHCl$_3$) 1780, 1735, 1710 cm^{-1}; δ (CDCl$_3$) 1.32 (3H, d, CH_3.CH), 2.21 (3H, s, COCH$_3$), 2.37
50 (3H, s, CH$_3$), 2.55 (1H, s, OH), 3.70 (1H, dd, J = 2.0 and 6.5Hz, CH.CH.CH), 4.13 (1H, m,   50
CH$_3$.CH.CH), 4.73 (2H, s, OCH$_2$CO), 5.61 (1H, d, J = 2.0Hz, CH.CH.S) ppm: λ_{max} (CHCl$_3$) 265 and 319 nm.

Example 24
55 *3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-4(R)-t-butyldiphenylsilyloxyacetylthio-1-(4-methyl-2-oxo-*   55
2,5-dihydrofuran-3-yl)-azetidin-2-one
Method A

A solution of 97 mg of 7(S)-[1(R)-t-butyldimethylsilyloxyethyl]-3-methylene-cepham-1-oxide methyl ester, prepared as described in Example 17, in 5 ml of toluene was refluxed with 98 mg
60 of t-butyldiphenylsilyloxythioacetic acid for 16 hours. The reaction mixture was cooled to 10°C,   60
2 drops of triethylamine were added and then removed with the solvent in vacuo. The crude product was dissolved in chloroform, treated with triphenylphosphine and then purified by silica gel chromatography, thus eluting the title compound; ν_{max} (CHCl$_3$ film) 1778, 1765, 1700 cm^{-1}; δ (CDCl$_3$) 0.06 and 0.1 (each 3H, s, SiMe$_2$), 0.85 and 1.10 (each 9H, s, Bu^t), 1.23 (3H,
65 d, J = 6Hz, CH_3.CH), 2.05 (3H, s, CH$_3$), 3.40 (1H, dd, J = 2.2 and 3Hz, CH.CH.CH), 4.12   65

(2H, s, OCH$_2$CO), 4.25 (1H, m, CH$_3$.CH.CH), 4.53 (2H, s, OCH$_2$C:), 5.92 (1H, d, J = 2.2Hz, CH.CH.S), 7.0–7.6 (10H, m, Ar) ppm.

Method B

5   A solution of 0.75 g of 4(R)-benzothiazolyldithio-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one, prepared as described in Example 19, in 50 ml of dichloromethane was treated sequentially with 0.47 g of t-butyldiphenylsilyloxythioacetic acid and 0.37 g of triphenylphosphine. Removal of the solvent and chromatography afforded the title product (0.64g).

Example 25
1-Acetonyloxyoxalyl-3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-4(R)-t-butyldiphenylsilyloxyacetylthio-azetidin-2-one
    This material was obtained from 3(S)-[1(R)-t-butyldimethylsilyloxyethyl]-4(R)-t-butyldiphenylsi-
15 lyloxyacetylthio-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one, prepared as described in   15
Example 24, according to the experimental procedure described in Example 15.

Example 26
Acetonyl (5R,6S)-6-[1(R)-t-butyldimethylsilyloxyethyl]-2-(t-butyldiphenylsilyloxymethyl)-penem-3-
20 *carboxylate*   20
    Ozonolysis in dichloromethane at − 70°C, reduction with 1g of zinc and 1 ml of acetic acid, chlorination with 0.02 ml of thionyl chloride and 0.023 ml of pyridine, displacement with 0.15 g of triphenylphosphine on 2 g of silica gel, elution from the silica and thermolysis in toluene for 8 hours at reflux, as described in Example 16, converted 150 mg of 1-acetonyloxyoxalyl-3(S)-
25 [1(R)-t-butyldimethylsilyloxyethyl]-4(R)-t-butyldiphenylsilyloxyacetylthio-azetidin-2-one, prepared   25
as described in Example 25, into 45 mg of the title penem; ν_{max} (CHCl$_3$) 1785, 1720 sh, 1708, 1575 cm^{-1}; δ (CDCl$_3$) 0.80 and 0.98 (each 9H, s, Bu^t), 1.20 (3H, d, J = 6Hz, CH$_3$.CH), 2.08 (3H, s, COCH$_3$), 3.68 (1H, dd, J = 2 and 4Hz, CH.CH.CH), 4.20 (1H, m, CH$_3$.CH.CH), 4.53 (2H, ABq, J = 16Hz), 4.84 (2H, s, OCH$_2$CO), 5.55 (1H, d, J = 2Hz, CH.CH.S), 7.3–7.66
30 (10H, m, Ar) ppm.   30

Example 27
Acetonyl (5R,6S)-6-[1(R)-t-butyldimethylsilyloxyethyl]-2-hydroxymethyl-penem-3-carboxylate
    A solution of 30 mg of acetonyl (5R,6S)-6-[1(R)-t-butyldimethylsilyloxyethyl]-2-(t-butyldiphe-
35 nylsilyloxymethyl)-penem-3-carboxylate, prepared as described in Example 26, in 1 ml of   35
tetrahydrofuran was treated with 0.01 ml of acetic acid and then 0.02 g of tetrabutylammonium fluoride trihydrate. After stirring for 15 minutes the solvent was removed and passed through a short silica gel column, thus obtaining the title product; ν_{max} (CHCl$_3$) 3400, 1785, 1715 sh, 1700 cm^{-1}; δ (CDCl$_3$) 0.07 (6H, s, SiMe$_2$), 0.87 (9H, s, Bu^t), 1.27 (3H, d, J = 6Hz, CH$_3$.CH),
40 2.23 (3H, s, CH$_3$), 3.77 (1H, dd, J = 2 and 5 Hz, CH.CH.CH), 4.25 (1H, m, CH$_3$.CH.CH), 4.62   40
(2H, br s, CH$_2$OH), 4.76 (2H, s, OCH$_2$CO), 5.64 (1H, d, J = 2 Hz) ppm.

Example 28
Sodium (5R,6S)-6-[1(R)-hydroxyethyl]-2-carbamoyloxymethyl-penem-3-carboxylate
45   A solution of 0.3 g of acetonyl (5R,6S)-6-[1(R)-t-butyldimethylsilyloxyethyl]-2-hydroxymethyl-   45
penem-3-carboxylate, prepared as described in Example 27, in 1 ml of dichloromethane was treated at − 10°C with 0.13 ml of trichloroacetylisocyanate. The reaction mixture was concentrated in vacuo and the residue dissolved in 4 ml of tetrahydrofuran containing 0.44 ml of acetic acid and 0.7 g of tetrabutylammonium fluoride trihydrate. This mixture was stirred for
50 24 hours under nitrogen. The solvent was then removed and the residue partitioned between   50
ethyl acetate and aqueous sodium hydrogen carbonate. The dried organic extracts were concentrated and then diluted with toluene to precipitate acetonyl (5R, 6S)-6-[1(R)-hydroxye-thyl]-2-carbamoyloxymethyl-penem-3-carboxylate (0.18 g) as a white solid. This material was dissolved in 5 ml of acetonitrile and 2.5 ml of degassed water and under nitrogen treated
55 dropwise at + 5°C with 5.5 ml of 0.1 M sodium hydroxide. Powdered dry ice was added and   55
the mixture was freeze dried to afford the title compound; δ (D$_2$O) 1.31 (3H, d, J = 6.5Hz, CH$_3$.CH), 3.91 (1H, dd, J = 1.5 and 6.0Hz, CH.CH.CH), 4.25 (1H, m, CH$_3$.CH.CH), 5.02 and 5.36 (2H, each d, J = 14.5Hz, CH$_2$O), 5.66 (1H, d, J = 1.5Hz, CH.CH.S) ppm; λ_{max} (H$_2$O) 258 and 306 nm.
60   60
Example 29
1-Acetonyloxyoxalyl-4(R)-carbamoyloxyacetylthio-3(S)-[1(R)-(2,2,2-trichloro-ethoxycarbonyloxy)-ethyl]-azetidin-2-one
Part A.
65   4.29 g of Methyl 6α-[1(R)-(2,2,2-trichloroethoxycarbonyloxy)-ethyl]-penicillinate-1-oxide dis-   65

solved in 15 ml of dry toluene was added to a refluxing mixture of 10 ml of propylene oxide, 1 g of calcium oxide and 2 g of anhydrous sodium sulphide in 125 ml of dry toluene. 1.47 g of commercial N-chlorosuccinimide was then added. The mixture was stirred for 4 hours in an oil bath at 125°C, and then concentrated under reduced pressure to a volume of about 20 ml and cooled to room temperature. 1.5 ml of diethyl ether was added and then 1.2 ml of anhydrous tin tetrachloride was added under stirring. After 45 minutes a further 1.2 ml of tin tetrachloride was added. 20 minutes later the solvent (containing minor amounts of impurities) was decanted off and the sticky syrupy residue covered with ethyl acetate and treated under vigorous stirring with 1N hydrochloric acid. The organic layer was washed in sequence with aqueous solutions of sodium chloride, sodium bicarbonate, and sodium chloride, and the solvent was then removed in vacuo to yield 3.95 g (92%) of pure 7(S)-[1(R)-(2,2,2-trichloroethoxycarbonyloxy)-ethyl]-3-methylene-cephem-1-oxide methyl ester as a colourless foam. ν_{max} (CHCl$_3$) 1775, 1740, br cm^{-1}, δ (CDCl$_3$) 1.53 (3H, d, CH_3CH), 3.69 (2H, s, endocyclic CH$_2$), 3.80 (4H, m, OCH$_3$ and CH-CH-CH), 4.78 (3H, m, CH$_2$CCl$_3$ and CH-CH-S), 5.10 (1H, s, N-CH-CO$_2$), 5.20 (1H, m, CH$_3$-CH-CH), 5.40 and 5.66 (2H, each s, exocyclic CH$_2$) ppm.

Part B

A solution of 3.95 g of the product of Part A in 150 ml of benzene was refluxed with 148 mg of 2-mercaptobenzothiazole for 32 hours. The solvent was removed in vacuo and the residue taken up on acetone, whereupon 2.86 g of 4(R)-benzothiazolyldithio-3(S)-[1(R)-(2,2,2-trichloroethoxycarbonlyoxy)-ethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one crystallized out. mp 190–191°C, ν_{max} (KBr) 1775, 1750, 1740 sh cm^{-1}; δ (CDCl$_3$), 1.50 (3H, d, CH_3CH), 1.80 (3H, s, CH$_3$), 3.62 (1H, dd, J = 2.5 and 6.5 Hz, CH-CH-CH), 4.20 (2H, centre of ABq, J = 17Hz, lactone CH$_2$), 4.72 (2H, s, CH$_2$CCl$_3$), 5.20 (1H, m, CH$_3$$CH$CH), 5.90 (1H, d, J = 2.5Hz, CHCHS), 7.2–7.9 (4H, m, Ar) ppm. The mother liquors could be recovered and heated again for several hours to afford more of the product obtained in this step.

Part C

A suspension of 3.10 g of the product of Part B in 100 ml of chloroform was treated with 810 mg of carbamoyloxythioacetic acid under vigorous stirring. After 30 minutes, 100 ml of diethyl ether was added, and the solid collected by filtration, thus obtaining 4(R)-carbamoyloxyacetyldithio-3(S)-[1(R)-(2,2,2-trichloroethoxycarbonyloxy)-ethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one (2.85 g, 94%) as a white solid, m.p. 197–199°C (with decomposition); ν_{max} (KBr) 1755 br, 1720, 1600 cm^{-1}; δ (CDCl$_3$) 1.51 (3H, d, J = 6.5Hz, CH_3-CH), 2.16 (3H, s,CH$_3$), 3.46 (1H, dd, J = 2.5 and 6.2Hz, CH-CH-CH), 4.77 (2H, centre of ABq, J = 12Hz, CH$_2$CCl$_3$), 4.81 (2H, s, OCH$_2$), 5.23 (1H, m, CH$_3$-CH-CH), 5.75 (1H, d, J = 2.5Hz, CH-CH-S) ppm.

Part D

2.85 g of the product of Part C was stirred overnight with 1.75 g of triphenylphosphine in 300 ml of chloroform to give a clear solution. Removal of excess reagent and triphenylphosphine sulphide (filtration over a silica gel septum, elution with neat benzene and then with ethyl acetate:benzene) gave pure 4(R)-carbamoyloxyacetylthio-3(S)-[1(R)-(2,2,2-trichloroethoxycarbonyloxy)ethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one. 2.28 g (85%) as a white foam; ν_{max} (CHCl$_3$ film) 1780sh, 1755, 1710 sh cm^{-1}; δ (CDCl$_3$) 1.51 (3H, d, J = 6.4Hz, CH_3-CH); 2.16 (3H, s, CH$_3$), 3.73 (1H, dd, J = 2.6 and 6.2Hz, CH-CH-CH), 4.71 (2H, centre of ABq, CH$_2$CCl$_3$), 4.77 (2H, s, OCH$_2$), 5.30 (1H, m, CH$_3$-CH-CH), 5.94 (1H, d, J = 2.6Hz, CH-CH-S) ppm. The crude material, however, could be used as such in the following step.

Part E

Dry ozone was passed through a cold solution of 2.28g of the material from Part D in 250 ml of dichloromethane at − 70°C until the starting material had disappeared. The excess ozone was flushed out with nitrogen, and 10 g of sodium bisulphite was added in portions.

The cooling bath was removed and the temperature allowed to rise to + 5°C under stirring. Water was then added and the organic layer collected. Evaporation *in vacuo* left the compound: 1-acetonyloxyoxalyl-4(R)-carbamoyloxyacetylthio-3(S)-[1(R)-(2,2,2-trichloroethoxycarbonyloxy)-ethyl]-azetidin-2-one. 2.25 g (93%) as a white foam; ν_{max} 1825, 1765, 1715 cm^{-1}; δ (CDCl$_3$) (3H, d, J = 6.5Hz, CH_3CH), 2.21 (3H, s, CH$_3$), 3.78 (1H, dd, J = 3.7 and 6Hz, CH-CH-CH), 4.70–4.84 (6H, m, OCH$_2$), 5.27 (1H, m, CH$_3$-CH-CH), 5.45 (2H, bs, NH$_2$), 5.90 (1H, d, J = 3.7 Hz, CH-CH-S) ppm.
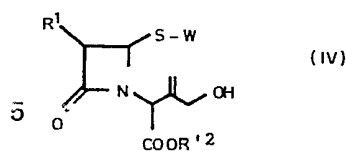
CLAIMS

1. A process for the preparation of a 2-(substituted methyl)-penem-3-carboxylate of the general formula I as herein defined, the process comprising heating a penicillanic acid S-oxide ester of the general formula II as herein defined in an anhydrous inert solvent in the presence of

a positive halogen source, reacting the resultant sulphinyl halide with an acid in an inert solvent
to obtain a 3-methylenecepham sulphoxide of the general formula III as herein defined,
converting the 3-methylenecepham sulphoxide III into either a compound of the general formula
IV as herein defined or a compound of the general formula X as herein defined, the conversion
5 to the compound IV being effected by heating the compound III in a solvent in the presence of   5
a compound having the general formula HW as herein defined or a salt or silylated derivative
thereof, the conversion to the compound X being effected by
      (a) heating the compound III in the presence of a compound of the general formula
YCH$_2$.COSH as herein defined or a salt of such a compound to obtain a compound of the
10 general formula IX as herein defined or a compound of the general formula IXa as herein   10
defined, or a mixture thereof, according to the substituents and the reaction conditions, and
proceeding from the compound IX to the compound X as described in (b) below or from the
compound IXa to the compound X as described in (d) or (e) below
      (b) obtaining the compound IV as above described, lactonising it by prolonged heating
15 and/or exposure to basic or acid catalysts, displacing the group W from the resultant compound   15
of the general formula VIII as herein defined by the reaction with a compound of the general
formula YCH$_2$.COSH as herein defined or a salt of such a compound in an inert solvent and
desulphurizing the resultant compound IX by reaction with a tervalent organophosphorus
reagent,
20   (c) prolonged heating of the compound III in a solvent in the presence of a compound of the   20
general formula HW as herein defined or a salt or silylated derivative thereof to obtain the
compound VIII and proceeding from the compound VIII to the compound X as described in (b)
above
      (d) obtaining the compound IV as above described, displacing the group W from it by
25 reaction with a compound of the general formula YCH$_2$.COSH as herein defined or a salt of such   25
a compound in an inert solvent, lactonising the resultant compound IXa by prolonged heating
and/or exposure to basic or acid catalysts, and desulphurizing the resultant compound IX as
described in (b) above, or
      (e) obtaining the compound IXa as described in (d) above, desulphurizing it by reaction with a
30 tervalent organophosphorus reagent, and lactonising the resultant compound of the general   30
formula Xa as herein defined by prolonged heating and/or exposure to basic or acid catalysts,
and converting the compound IV or the compound X to the compound I,
      the conversion of the compound IV being effected by reacting it with a substituted silyl
chloride, a chloroformate, a diazoalkane, an acyl chloride or anhydride or an isocyanate to give a
35 compound of the general formula V as herein defined, ozonolyzing the compound V and   35
reacting the resultant intermediate with a reagent containing a group L as herein defined to
obtain a compound of the general formula VI as herein defined, cyclising the compound VI with
a sulphide or hydrosulphide in a solvent, and desulphurizing the resultant compound of the
general formula VII as herein defined by reaction with a tervalent organophosphorus reagent in
40 an organic solvent,   40
      the conversion of the compound X being effected by ozonolysing it at from − 70°C to 0°C in
an organic solvent, reducing the resultant compound of the general formula XI, as herein
defined converting the resultant carbinol of the general formula XII as herein defined into the
corresponding chloride and thence to the corresponding phosphorane of the general formula XIII
45 as herein defined by reaction with triphenylphosphine, and thermolysing the phosphorane XIII,   45
      and optionally converting the resultant compound I into another compound I by subjecting the
R^1, R^2 and Y substituents to known conversions such as deprotection.
      2.   A 3-methylenecepham sulphoxide of the general formula III

50   50

(III)

55   55

60 wherein R$_1$ represents an alkyl group or a substituted alkyl group and R$^{'2}$ represents a   60
carboxylate protecting group.
      3.   7(S)-[1(R)-t-Butyldimethylsilyloxyethyl]-3-methylenecepham-1-oxide methyl ester.
      4.   A compound of the general formula IV

(IV)

5

wherein R_1 represents an organic group and W represents
10 (a) a group SR_4 wherein R_4 represents an alkyl or aryl group of a heterocyclyl radical   10
(b) a group

$$\underset{\diagdown}{\overset{\diagup}{N}}\overset{COR_5}{\underset{COR_6}{}}$$

15 N   15

wherein each of R_5 and R_6 independently represents a group as defined by R_4 or the whole
20 group is a succinimido or phthalimido group, or   20
(c) a group SO_2R_4 wherein R_4 is as defined in (a) above
with the proviso that if R_1 represents an amino or substituted amino group then W does not
have the value given in (a) above.
5. 4(R)-Benzothiazolyldithio-3(S)-[1(R)-*t*-butyldimethylsilyloxyethyl]-1-(2-hydroxymethyl-1-me-
25 thoxycarbonyl-1-prop-2-enyl)-azetidin-2-one.   25
6. An azetidinone lactone of the general formula X as herein defined.
7. 4(R)-Acetylthio-1-(4-methyl-2-oxo-2,5-dihydrofuran-3-yl)-3(R)-phthalimido-azetidin-2-one.
8. 4(R)-Acetylthio-3(S)-[1(R)-*t*-butyldimethylsilyloxyethyl]-1-(4-methyl-2-oxo-2,5-dihydrofuran-
3-yl)-azetidin-2-one.
30 9. 4(R)-*t*-Butyldiphenylsilyloxyacetylthio-3(S)-[1(R)-*t*-butyldimethylsilyloxyethyl]-1-(4-methyl-2- 30
oxo-2,5-dihydrofuran-3-yl)-azetidin-2-one.