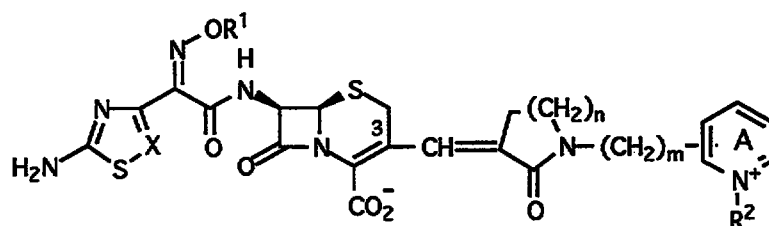


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RAN 4410/256

Cephalosporin Pyridinium Derivatives

The present invention relates to cephalosporin pyridinium derivatives of the general formula I



5

wherein

$R^1$  is hydrogen, lower alkyl, cycloalkyl or acetyl;

X is CH or N;

n is 0, 1 or 2;

10 m is 0 or 1;

$R^2$  is hydrogen, lower alkyl,  $\omega$ -hydroxy alkyl, benzyl or lower alkyl-heterocyclyl, the benzyl and the heterocyclyl group being unsubstituted or substituted with at least one of the groups amino, cyano, carboxy, halogen, hydroxy, lower alkyl, lower alkoxy or  $-\text{CONR}_2$ , R being hydrogen or lower alkyl; or  $R^2$  is  $-\text{CH}_2\text{CONR}^4\text{R}^5$ ; wherein

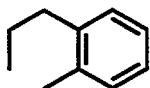
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$R^4, R^5$  are independently hydrogen,  $\omega$ -hydroxy-alkyl, phenyl, naphthyl or heterocyclyl, the phenyl, naphthyl or heterocyclyl being unsubstituted or substituted with at least one of the groups of optionally protected hydroxy, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy,  $\omega$ -hydroxyalkyl and/or cyano; or the groups  $R^4$  and  $R^5$

20



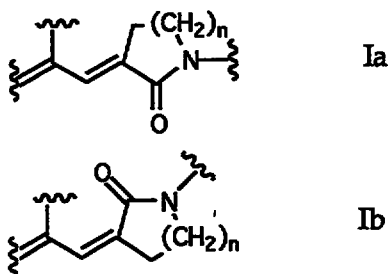
form together a group of formula



with the proviso that m is 1, when the pyridinium ring A is a pyridinium-4-yl;

- 5 as well as readily hydrolysable esters thereof, pharmaceutically acceptable salts of said compounds and hydrates of the compounds of formula I and of their esters and salts.

In above compounds of formula I the substituent in position 3 can be  
10 present in the E-form (formula Ia) or in the Z-form (formula Ib)



The pyridinium ring is attached in 2, 3 or 4 position to the  
15 cephalosporin moiety.

In a particular embodiment of the compounds of formula I n is 1. Moreover R<sup>1</sup> is preferably hydrogen or cyclopentyl and R<sup>2</sup> is lower alkyl, ω-hydroxy alkyl, benzyl, the benzyl group being unsubstituted or substituted with at least one of the groups amino, cyano, carboxy, halogen, hydroxy,  
20 lower alkyl, lower alkoxy or -CONR<sub>2</sub>, R being hydrogen or lower alkyl, preferably substituted with one of the groups cyano, carboxy or hydroxy. Examples of especially preferred R<sup>2</sup> are methyl, ethyl, 2-hydroxyethyl, benzyl, 2,3 or 4-hydroxybenzyl, 2,3 or 4-cyanobenzyl, 2,3 or 4-carboxybenzyl.

In yet another particular embodiment R<sup>2</sup> is -CH<sub>2</sub>CONR<sup>4</sup>R<sup>5</sup>. Especially  
25 preferred compounds of formula I wherein R<sup>2</sup> is -CH<sub>2</sub>CONR<sup>4</sup>R<sup>5</sup> are the compounds wherein R<sup>4</sup> is hydrogen and R<sup>5</sup> represents an optionally substituted phenyl, for example, hydroxyphenyl, 2-fluoro-4-hydroxy-phenyl, 3-fluoro-4-hydroxy-phenyl.

The compounds of the formula I are preferably in the Z-form at the  
30 oximino group and E-form for the substituent in position 3.

As used herein, the term "lower alkyl" refers to both straight and branched chain saturated hydrocarbon groups having 1 to 8 and preferably 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, tertiary butyl and the like.

5       The term "lower alkoxy" refers to ether groups wherein alkyl is defined as above.

By the term "cycloalkyl" is meant a 3-7 membered saturated carbocyclic moiety, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

By the term "optionally substituted lower alkyl, optionally substituted  
10 lower alkoxy" is understood both unsubstituted lower alkyl or lower alkoxy as defined above and lower alkyl or lower alkoxy substituted with at least one of halogen, especially fluorine, for example, fluoromethyl, trifluoromethyl, fluoroethyl, trifluoroethyl; or hydroxy, for example, 1-hydroxyethyl, 2-hydroxymethyl-propane-1,3-diol-2-yl; or amino or alkylamino, for example,  
15 1-aminoethyl, 2-aminoethyl, 1-methylaminoethyl etc.

By the term " $\omega$ -hydroxy alkyl" is meant straight chain or branched alkyl groups with hydroxy-substituted terminal carbon atoms. Such groups are, for example, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, propane-1,3-diol-2-yl, and the like.

20       By the term "lower alkylheterocyclyl" is meant a lower alkyl group as defined above substituted by a 4-, 5- or 6-membered heterocyclic ring, for example, azetidiny, pyrrolidinyl, piperidinyl, pyridinyl, pyrimidinyl, pyrazidinyl, imidazolyl, triazolyl, tetrazolyl, thiadiazolyl, isoxazolyl, oxazolyl etc.

25       Examples of "benzyl and heterocyclyl substituted with at least one of the groups of amino, cyano, carboxy, halogen, hydroxy, lower alkyl, lower alkoxy or -CONR<sub>2</sub>, R being hydrogen or lower alkyl" are 2-, 3- or 4-cyanobenzyl, 2-, 3- or 4-hydroxybenzyl, 2,4-dihydroxybenzyl, 3,4-dihydroxybenzyl, 2-, 3- or 4-carboxybenzyl.

30       Examples of "phenyl, naphthyl or heterocyclyl unsubstituted or substituted with at least one of the groups of optionally protected hydroxy, halogen, optionally substituted lower alkyl, optionally substituted lower alkoxy,  $\omega$ -hydroxyalkyl and/or cyano" are 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-chlorophenyl, 2-, 3- or 4-hydroxyphenyl, 2-, 3- or 4-methoxyphenyl, 2-fluoro-4-

hydroxyphenyl, 3-fluoro-4-hydroxyphenyl, 2-methoxy-4-hydroxyphenyl, 3-methoxy-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl and the like.

The term "optionally protected hydroxy" refers to hydroxy or hydroxy protected with, for example, t-butyloxycarbonyl, trimethylsilyl, t-butyl-  
5 dimethylsilyl, tetrahydropyranyl, trifluoroacetyl, or refers to an ester group, for example, phosphate, sulfonate and the like.

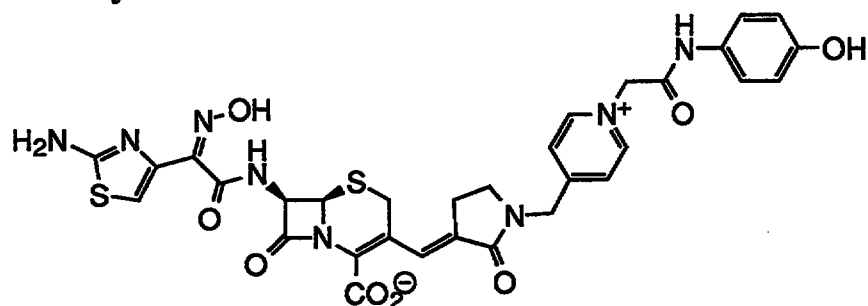
As used herein "pharmaceutically acceptable salts" useful in this invention include salts derived from metals, the ammonium salt, quaternary ammonium salts derived from organic bases and amino acid  
10 salts. Examples of preferred metal salts are those derived from the alkali metals, for example, lithium ( $\text{Li}^+$ ), sodium ( $\text{Na}^+$ ) and potassium ( $\text{K}^+$ ). Examples of quaternary ammonium salts derived from organic bases include tetramethylammonium ( $\text{N}^+(\text{CH}_3)_4$ ), tetraethylammonium ( $\text{N}^+(\text{CH}_2\text{CH}_3)_4$ ), benzyltrimethylammonium ( $\text{N}^+(\text{C}_6\text{H}_5\text{CH}_2)(\text{CH}_3)_3$ ),  
15 phenyltriethylammonium ( $\text{N}^+(\text{C}_6\text{H}_5)(\text{CH}_2\text{CH}_3)_3$ ), and the like. Those salts derived from amines include salts with N-ethylpiperidine, procaine, dibenzylamine, N,N'-dibenzylethylenediamine, alkylamines or dialkylamines as well as salts with amino acids such as, for example, salts with arginine or lysine. Further especially preferred salts are hydrochlorides,  
20 sulfates, phosphates, lactates, mesylates or the inner salt.

As readily hydrolysable esters of the compounds of formula I there are to be understood compounds of formula I, the carboxy group(s) of which (for example, the 2-carboxy group) is/are present in the form of readily hydrolysable ester groups. Examples of such esters, which can be of the  
25 conventional type, are the lower alkanoyloxy-alkyl esters (e.g., the acetoxymethyl, pivaloyloxymethyl, 1-acetoxyethyl and 1-pivaloyloxyethyl ester), the lower alkoxycarbonyloxyalkyl esters (e.g., the methoxycarbonyloxymethyl, 1-ethoxycarbonyloxyethyl and 1-isopropoxycarbonyloxyethyl ester), the lactonyl esters (e.g., the phthalidyl and thiophthalidyl ester), the  
30 lower alkoxymethyl esters (e.g., the methoxymethyl ester) and the lower alkanoylaminomethyl esters (e.g., the acetamidomethyl ester). Other esters (e.g., the benzyl and cyanomethyl esters) can also be used. Other examples of such esters are the following: (2,2-dimethyl-1-oxopropoxy)methyl ester; 2-[(2-methylpropoxy)carbonyl]-2-pentenyl ester; 1-[(1-methylethoxy)carbonyl]oxy] ethyl ester; 1-(acetyloxy) ethyl ester; (5-methyl-2-oxo-1,3-dioxol-4-yl) methyl  
35 ester; 1-[(cyclohexyloxy)carbonyl]oxy] ethyl ester; and 3,3-dimethyl-2-

oxobutyl ester. It will be appreciated by those of ordinary skill in the art that the readily hydrolysable esters of the compounds of the present invention can be formed at a free carboxy group of the compound, for example, at the carboxy group in position 1 or any other carboxy group.

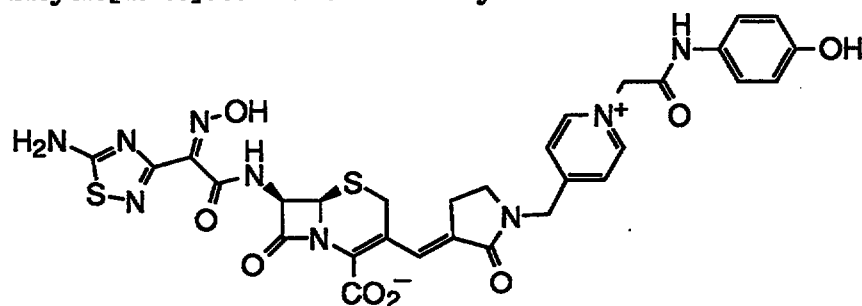
5 Preferred compounds of formula I include:

(6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



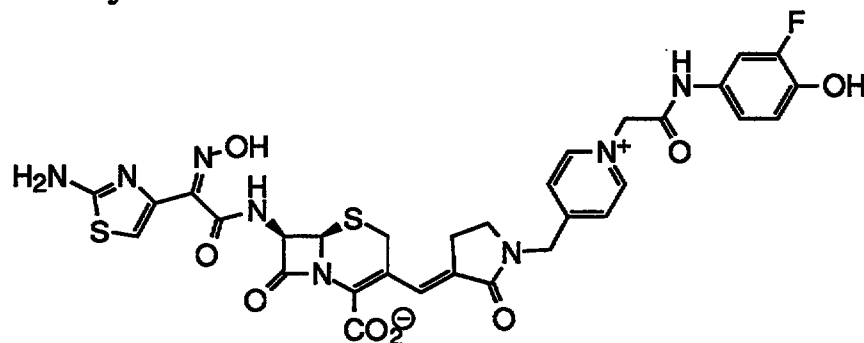
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(6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



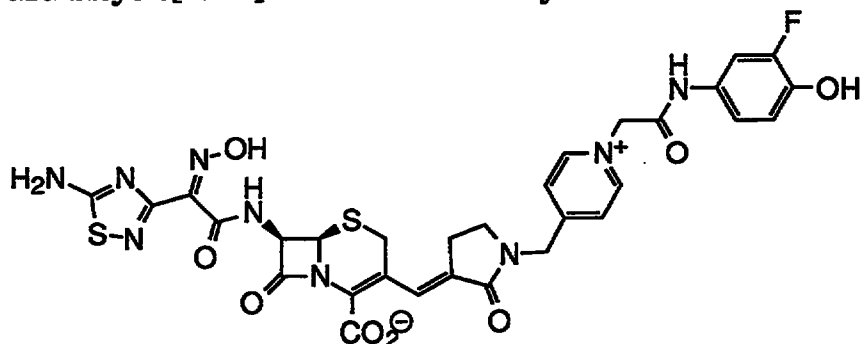
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(6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



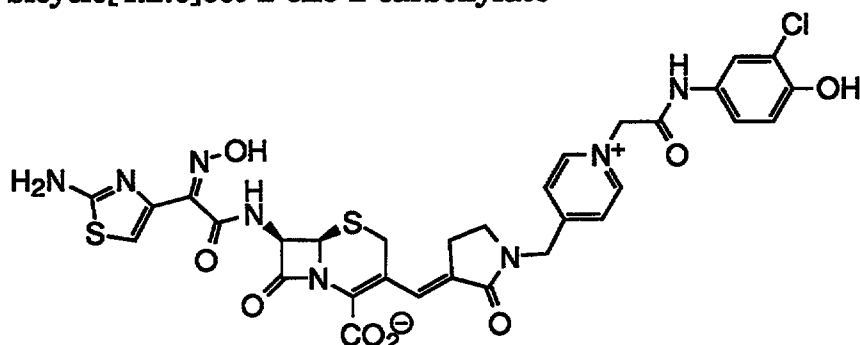
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(6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



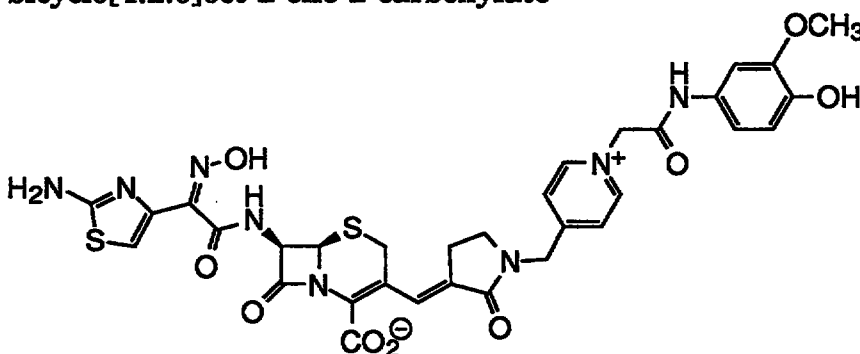
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(6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-chloro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



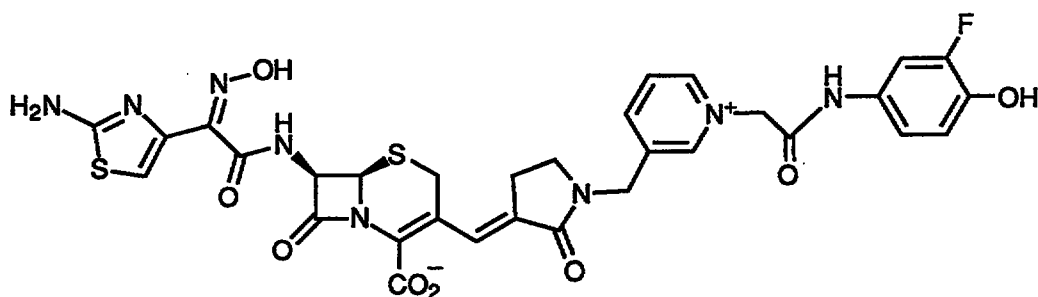
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(6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-3-methoxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



15

(6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate



The invention also relates to pharmaceutical compositions and methods of use of the above.

The compounds of formula I as well as their salts and readily  
5 hydrolysable esters can be hydrated. The hydration can be effected in the course of the manufacturing process or can occur gradually as a result of hygroscopic properties of an initially anhydrous product.

The compounds of the present invention are useful as antibiotics having potent and broad antibacterial activity, especially against methicillin-  
10 resistant staphylococci (MRSA), enterococci and pneumococci.

The products in accordance with the invention can be used as medicaments, for example, in the form of pharmaceutical preparations for parenteral administration, and for this purpose are preferably made into preparations as lyophilisates or dry powders for dilution with customary  
15 agents, such as water or isotonic common salt solution.

Depending on the nature of the pharmacologically active compound the pharmaceutical preparations can contain the compound for the prevention and treatment of infectious diseases in mammals, human and non-human, a daily dosage of about 10 mg to about 4000 mg, especially about 50 mg to  
20 about 3000 mg, is usual, with those of ordinary skill in the art appreciating that the dosage will depend also upon the age, conditions of the mammals, and the kind of diseases being prevented or treated. The daily dosage can be administered in a single dose or can be divided over several doses. An average single dose of about 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, and  
25 2000 mg can be contemplated.

Representative compounds of the present invention were tested.

In vitro activity was determined by minimum inhibitory concentration in a microorganism spectrum by the agar dilution method in Mueller Hinton agar.

The following compounds were tested:

A: (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
[(E)-1-[1-[(4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-  
oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-  
5 carboxylate

B: (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-  
amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
10 oct-2-ene-2-carboxylate

C: (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
15 oct-2-ene-2-carboxylate

D: (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-  
amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-  
ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
20 bicyclo[4.2.0]oct-2-ene-2-carboxylate

E: (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
[(E)-1-[1-[(3-chloro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
25 oct-2-ene-2-carboxylate

F: (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
[(E)-1-[1-[(4-hydroxy-3-methoxy-phenylcarbonyl)-methyl]-pyridin-1-ium-4-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
30 oct-2-ene-2-carboxylate

G: (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-3-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
35 oct-2-ene-2-carboxylate

The antibacterial Spectrum appears below:

MIC : Minimum Inhibiting Concentration Values

***In vitro* activity against sensitive and resistant *S. aureus***

|                                    | A   | B   | C | D | E   | F | G   |
|------------------------------------|-----|-----|---|---|-----|---|-----|
| MIC <i>S. aureus</i> 6538 (MSSA)*  | 0.5 | 0.5 | 1 | 1 | 0.5 | 1 | 0.5 |
| MIC <i>S. aureus</i> 42080 (MRSA)* | 4   | 4   | 4 | 4 | 4   | 8 | 4   |
| MIC90 MRSA (n=17)**                | 8   | 4   | 4 | 4 | 8   | 8 | 8   |

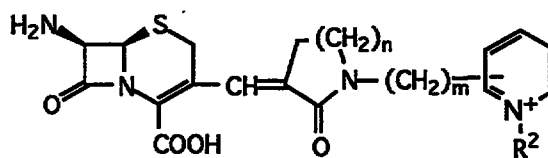
MIC [ $\mu\text{g/ml}$ ]; agar dilution method on Mueller-Hinton agar.

\* inoculum  $10^4$  CFU/spot

5 \*\* inoculum  $10^5$  CFU/spot

The compounds of the formula I in accordance with the invention as well as their pharmaceutical acceptable salts, hydrates, or readily hydrolyzable esters can be manufactured in accordance with the invention by

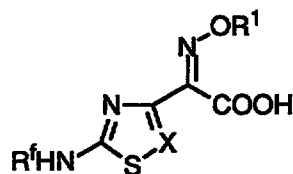
10 (a) treating a compound having the formula II



II

in which  $R^2$ , m and n are defined above,

15 or an ester or salt thereof, with a carboxylic acid of the general formula III

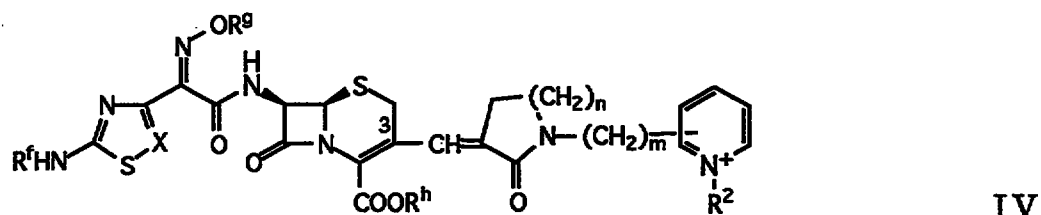


III

in which  $R^f$  is hydrogen or an amino protecting group,  $R^1$  and X are defined above, or a reactive functional derivative thereof, or

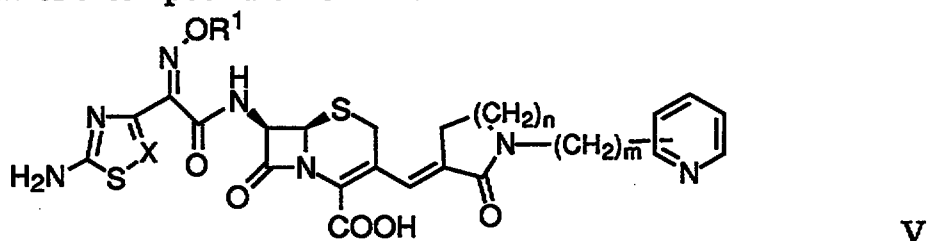
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(b) cleaving off the amino, hydroxy and/or carboxy protecting group in a compound having the formula IV



in which  $R^2$ ,  $m$  and  $n$  are defined above,  $R^f$  is hydrogen or an amino protecting group,  $R^g$  is hydrogen or a hydroxy protecting group,  $R^h$  is hydrogen or a carboxy protecting group, provided that at least one of  $R^f$ ,  $R^g$  and  $R^h$  is a corresponding protecting group or a salt thereof, or

(c) alkylation of a compound of formula



wherein  $R^1$ ,  $X$ ,  $m$  and  $n$  are as defined above,

with a alkylating agent such a methyl iodide, dimethyl sulfate, trimethyloxonium tetrafluoroborate, bromo-, iodoacetamide or  $\text{Br-CH}_2\text{-CONR}^4\text{R}^5$ , wherein  $R^4$  and  $R^5$  are as defined above, or

(d) for the manufacture of a readily hydrolysable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding esterification, or

(e) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts converting a compound of formula I into a salt or hydrate or into a hydrate of said salts.

The reaction of compounds of formula II and III or a reactive derivative of of formula III according to embodiment (a) can be carried out in a manner known per se. The carboxy group in compounds of formula II can be protected; for example, by esterification to form a readily cleavable ester such as a silyl ester (e.g. the trimethylsilyl ester) p-methoxybenzyl or benzhydryl ester.

The amino group present in the acylating agent of formula III can be protected. Possible protecting groups  $R^f$  are, for example, protecting groups

which are cleavable by acid hydrolysis (e.g. the tert.butoxycarbonyl or trityl groups), by basic hydrolysis (e.g. the trifluoroacetyl group) or by hydrazinolysis (e.g. the phthalimido group). Preferred protecting groups are the t-butyloxy-carbonyl, phenylacetyl, the chloroacetyl, bromoacetyl and  
5 iodoacetyl groups, especially the chloroacetyl group. These last-mentioned protecting groups can be cleaved off by treatment with thiourea. The 7-amino group in compounds II can be protected, for example, by a silyl protecting group such as the trimethylsilyl group.

In reacting a 7-amino compound of formula II with a carboxylic acid of  
10 formula III or a reactive functional derivative thereof, for example, a free carboxylic acid can be reacted with an aforementioned ester of a compound of formula II in the presence of a carbodiimide such as dicyclohexylcarbodiimide in an inert solvent such as ethyl acetate, acetonitrile, dioxane, chloroform, methylene chloride, benzene or dimethylformamide, and  
15 subsequently the ester group can be cleaved off.

According to another embodiment, a salt of an acid of formula II (e.g. a trialkylammonium salt such as the triethylammonium salt) is reacted with a reactive functional derivative of a carboxylic acid of formula III in an inert solvent (e.g. tetrahydrofuran, dichloromethane, dimethylformamide and  
20 dimethylsulfoxide).

According to a further embodiment, preferred acylation, where the amino group present in the acylating agent of formula III need not be protected, involves the use of a 2-benzothiazolyl thioester, a 1-hydroxybenzotriazole ester or a mixed anhydride of thiophosphoric acid of the carboxylic  
25 acid. For instance, the 2-benzthiazolyl thioester may be reacted with the compound II in an inert organic solvent such as a chlorinated hydrocarbon e.g. methylene chloride, or in dimethylformamide, dimethyl-sulfoxide, acetone, ethyl acetate or in a mixture of such solvents with water. The 1-hydroxybenzotriazole ester can be employed by reacting the carboxylic acid  
30 with 1-hydroxybenzotriazole and a carbodiimide, especially N,N'-dicyclohexylcarbodiimide or N,N'-diisopropylcarbodiimide in an inert organic solvent, preferably methylene chloride, dimethylformamide, dimethyl-sulfoxide, tetrahydrofuran, acetonitrile or ethyl acetate.

The reaction of a 7-amino compound of formula II with the carboxylic  
35 acid of formula III or a reactive derivative thereof can conveniently be

carried out at a temperature between about  $-40^{\circ}\text{C}$  and  $+60^{\circ}\text{C}$ , e.g. at room temperature.

Embodiment (b) of the process of the present invention involves deprotection (removal) of protected amino, hydroxy or carboxylic groups  
5 present in a compound of formula IV and can be carried and as follows:

Removal of amino protecting groups

Possible amino-protecting groups are those employed in peptide chemistry, such as an alkoxycarbonyl group, e.g., t-butoxycarbonyl, allyloxy carbonyl etc., a substituted alkoxycarbonyl group, e.g., trichloroethoxy-  
10 carbonyl etc., an optionally substituted aralkyloxycarbonyl group, e.g., p-nitrobenzyloxycarbonyl or benzyloxycarbonyl, an aralkyl group such as trityl or benzhydryl or a halogen-alkanoyl group such as chloroacetyl, bromoacetyl, iodoacetyl or trifluoroacetyl.

Preferred protecting groups are t-butoxycarbonyl (t-BOC) and trityl.

15 The amino protecting groups may be cleaved off by acid hydrolysis (e.g. the t-butoxycarbonyl or trityl group), e.g. aqueous formic acid, trifluoroacetic acid or by basic hydrolysis (e.g. the trifluoroacetyl group). The chloroacetyl, bromoacetyl and iodoacetyl groups are cleaved off by treatment with thiourea.

20 Amino-protecting groups which are cleavable by acid hydrolysis are preferably removed with the aid of a lower alkanecarboxylic acid which may be halogenated. In particular, formic acid or trifluoroacetic acid is used. The reaction is carried out in the acid or in the presence of a co-solvent such as a halogenated lower alkane, e.g. methylene chloride. The acid hydrolysis is  
25 generally carried out at room temperature, although it can be carried out at a slightly higher or slightly lower temperature (e.g. a temperature in the range of about  $-30^{\circ}\text{C}$  to  $+40^{\circ}\text{C}$ ). Protecting groups which are cleavable under basic conditions are generally hydrolyzed with dilute aqueous caustic alkali at  $0^{\circ}\text{C}$  to  $30^{\circ}\text{C}$ . The chloroacetyl, bromoacetyl and iodoacetyl protecting  
30 groups can be cleaved off using thiourea in acidic, neutral or alkaline medium at about  $0^{\circ}\text{C}$ - $30^{\circ}\text{C}$ .

Removal of hydroxy protecting groups

Possible hydroxy protecting groups are such as are commonly known in the art, e.g.

- for protection of hydroxyimino groups ( $R^1$  = hydrogen in compounds of formula I), usually trityl, lower alkanoyl, preferably acetyl, tetrahydropyranyl protecting groups are employed.

These protecting groups are e.g. removed as follows:

- |    |                    |                                                                                                                                                                                               |
|----|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5  | -trityl            | in acidic solvents like 90% formic acid at about 0 to 50°C or triethylsilane in trifluoroacetic acid at about -20 to 25°C;<br>in organic solutions of hydrochloric acid at about -50 to 25°C; |
| 10 | -acetyl            | with weak inorganic bases like sodium bicarbonate in methanol or ethanol/water at about 0 to 50°C;                                                                                            |
|    | -tetrahydropyranyl | with weak organic acids like p-toluenesulfonic acid in an alcohol, e.g. ethanol, at about 0°C to the boiling point of the mixture.                                                            |

15 Removal of protecting groups at the carboxy function

As carboxyl protecting groups one may utilize an ester form which can be easily converted into a free carboxyl group under mild conditions, for example, benzhydryl, t-butyl, p-nitrobenzyl, p-methoxybenzyl, allyl, etc.

These protecting groups may be removed as follows:

- |    |                 |                                                                                                                                                                                                                                             |
|----|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 | benzhydryl      | trifluoroacetic acid with anisol, phenol, cresol or triethylsilane at about -40°C to room temperature; hydrogen with Pd/C in an alcohol such as ethanol or in tetrahydrofuran; BF <sub>3</sub> -etherate in acetic acid at about 0 to 50°C; |
| 25 | t-butyl         | formic acid or trifluoroacetic acid with or without anisol, phenol, cresol or triethylsilane and a solvent such as dichloromethane at about -10°C to room temperature;                                                                      |
|    | p-nitrobenzyl   | sodium sulfide in acetone/water at about 0 to room temperature; or hydrogen with Pd/C in an alcohol such as ethanol or in tetrahydrofuran;                                                                                                  |
| 30 | p-methoxybenzyl | formic acid at about 0 to 50°C; or trifluoroacetic acid and anisol, phenol or triethylsilane at about -40°C to room temperature;                                                                                                            |
| 35 | allyl           | palladium(O) catalyzed transalkylation reaction in the presence of sodium or potassium salt of 2-ethyl hexanoic acid, see for example J. Org. Chem. 1982, <u>47</u> , 587.                                                                  |

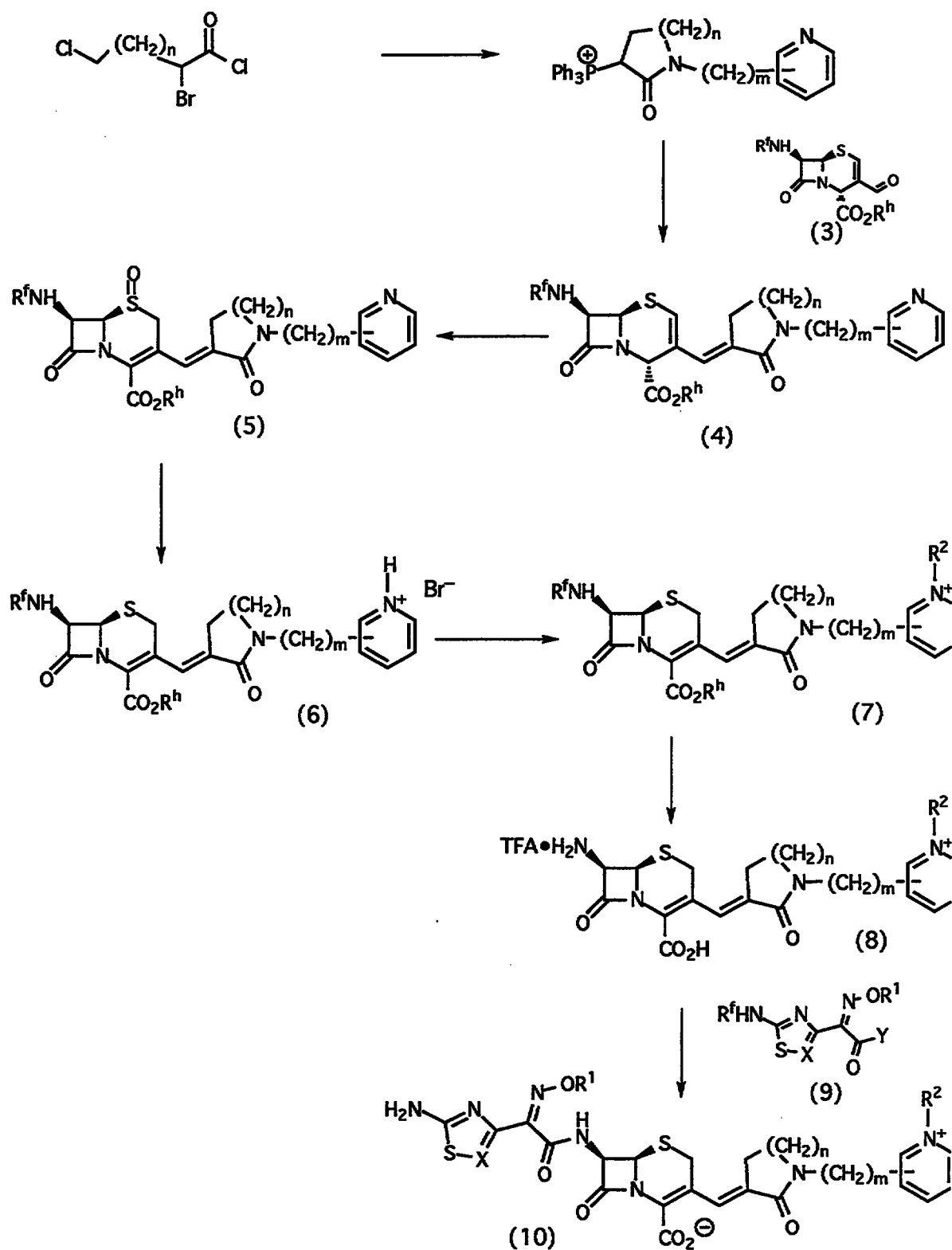
In order to manufacture a readily hydrolysable ester of the carboxylic acids of formula I in accordance with embodiment (c) of the process provided by the present invention, a carboxylic acid of formula I is preferably reacted with a corresponding halide, preferably an iodide, containing the desired ester group. The reaction can be accelerated with the aid of a base such as an alkali metal hydroxide, an alkali metal carbonate or an organic amine such as triethylamine. The esterification is preferably carried out in an inert organic solvent such as dimethylacetamide, hexamethylphosphoric acid triamide, dimethyl sulfoxide or, especially, dimethylformamide. The reaction is preferably carried out at a temperature in the range of about 0-40°C.

The manufacture of the salts and hydrates of the compounds of formula I or the hydrates of said salts in accordance with embodiment (d) of the process provided by the present invention can be carried out in a manner known per se; for example, by reacting a carboxylic acid of formula I or a salt thereof with an equivalent amount of the desired base, conveniently in a solvent such as water or an organic solvent (e.g. ethanol, methanol, acetone and the like). Correspondingly, salt formation is brought about by the addition of an organic or inorganic salt or acid. The temperature at which the salt formation is carried out is not critical. The salt formation is generally carried out at room temperature, but it can be carried out at a temperature slightly above or below room temperature, for example in the range of 0°C to +50°C.

The manufacture of the hydrates usually takes place automatically in the course of the manufacturing process or as a result of the hygroscopic properties of an initially anhydrous product. For the controlled manufacture of a hydrate, a completely or partially anhydrous carboxylic acid of formula I or salt thereof can be exposed to a moist atmosphere (e.g. at about +10°C to +40°C).

Exemplary of the process for obtaining products in accordance with the invention are the following reaction schemes 1 and 2 below.

Scheme 1

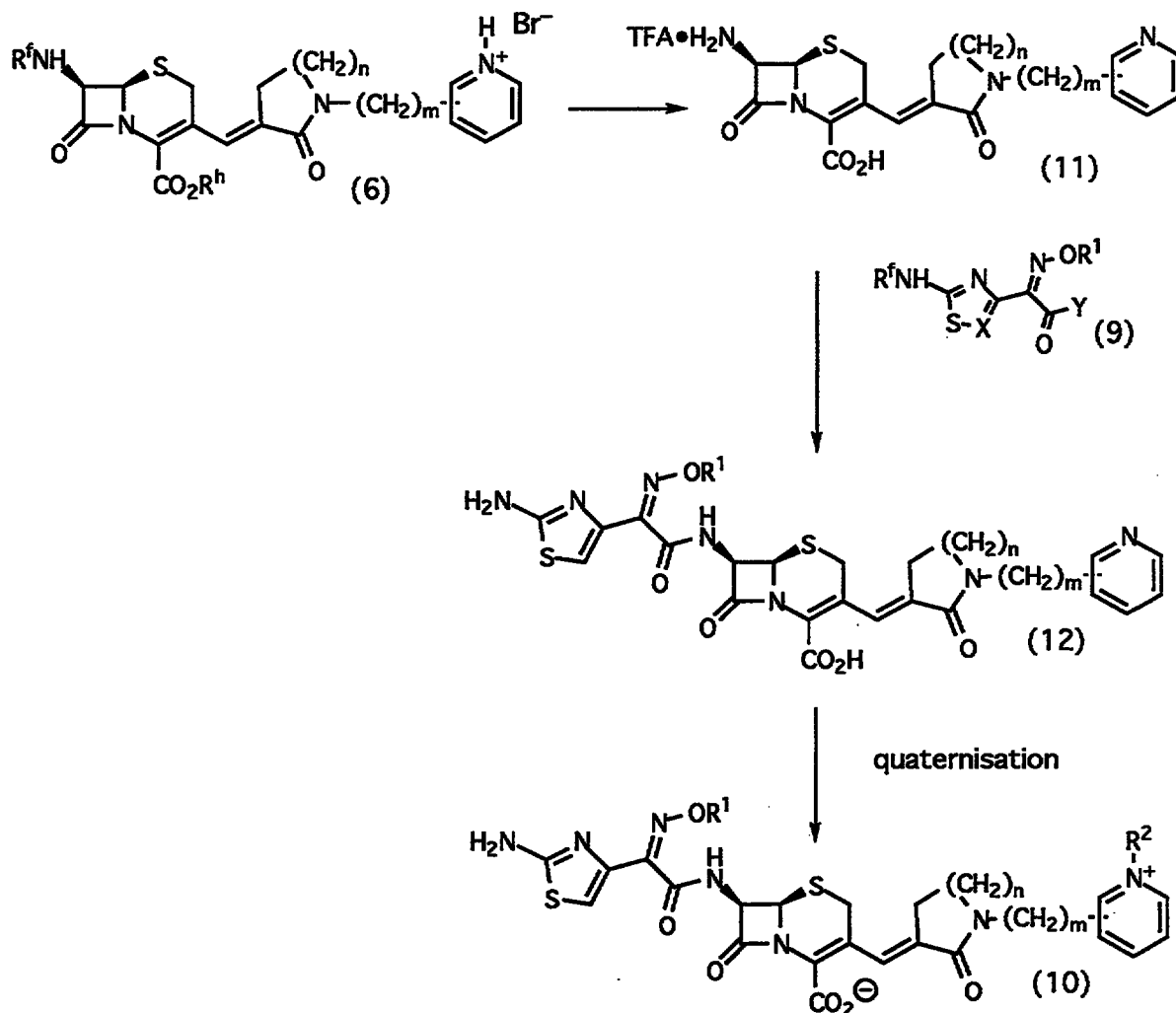


wherein  $n$  is 1 or 2,  $Y$  is OH, halogen or an activating group, for example,  
 5 the 2-benzothiazolythioester, the 1-hydroxybenzotriazole or a mixed

anhydride of thiophosphonic acid and the remaining symbols are as defined above.

Scheme 2

5



(1) → (2)

The known  $\alpha$ -bromo- $\omega$ -chloro acid chloride (1) is converted into a  
 10 Wittig reagent (2) by firstly reacting it with a amino-pyridine (for  $m = 0$ ) or a  
 picolylamine (for  $m = 1$ ) to form the corresponding bromolactam which is  
 subsequently treated with triphenylphosphine in solvents like tetrahydro-  
 furan (THF), dimethylformamide (DMF) or the like.

(2) → (4)

15 The reaction of known 2-cephem aldehyde (3) where  $\text{R}^h$  is a carboxy  
 protecting group as defined above, e.g. benzhydryl ester, and  $\text{R}^f$  is an amino  
 protecting group as defined above, e.g. tert. butyloxycarbonyl, with a Wittig

reagent, exemplified by structure (2), yields the cephalosporin moiety (4). The reaction is carried out in the presence of a base which is either an inorganic base (sodium or potassium hydroxide, sodium or potassium carbonate etc.), an organic base (tertiary amines, potassium tert.butoxide),  
5 an organolithium such as butyl lithium or phenyllithium or an epoxide such as 1,2-butyleneoxide. The reaction in presence of an epoxide is preferred. The preferred solvents, in the case of inorganic base being used, are water and water-miscible solvent (acetone, tetrahydrofuran, or alcohols etc.); in the case of organic base being used, an inert solvent such as methylene chloride,  
10 dicloroethane, chloroform, benzene, tetrahydrofuran; in the case of organolithium being used, benzene or tetrahydrofuran; and in the case an epoxide being used, the epoxide itself (e.g. 1,2-butyleneoxide or in mixture with e.g. dichloroethane). The temperature for the reaction ranges from -20°C to 80°C. The preferred conditions are exemplified in the examples.

15 In the normal Wittig reaction according to scheme 1, the E isomer is the predominant product. Invariably, less than 10% Z-isomer is formed, the amount depending on the reagents and conditions.

(4) → (5)

Compound (4) is converted to the sulfoxide (5) with an oxidizing agent,  
20 for example, hydrogen peroxide or a peracid, preferably 3-chloroperbenzoic acid. The temperature ranges from -20°C to room temperature and any suitable solvent, preferably chlorinated hydrocarbon or benzene can be used.

(5) → (6)

The de-oxygenation of the sulfoxide (5) is carried out in the presence of  
25 phosphorus tribromide in dimethylformamide or in the mixed solvent of dimethylformamide and N-methylacetamide. The reaction temperature for the reaction is from about -78°C to about 0°C.

(6) → (7) and (12) → (10) (see Scheme 2)

The N-alkylation of (6) resp. (12) is preferably performed in an inert  
30 solvent, for example, dimethylformamide (DMF) using an appropriate halogeno-derivative.

(7) → (8)

The protecting groups R<sup>f</sup> and R<sup>h</sup> are removed and the reaction conditions used are depending on the nature of the protecting groups. In the  
35 case of R<sup>f</sup> being tert-butoxycarbonyl and R<sup>h</sup> being benzhydryl, trifluoroacetic

acid and anisole or triethylsilane is employed, at temperature of about -20°C to about room temperature (about 22°C).

(8) → (10) and (11) → (12)

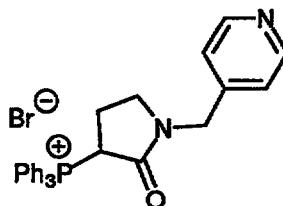
The acylation of compound (8), respectively (11) can be carried out with  
5 an organic acid (9) which is activated with known reagents Y, preferably thionyl chloride, oxalyl chloride, dicyclohexylcarbodiimide, bis-[benz-thiazolyl-(2)]disulfide, N-hydroxy-benzotriazole, a 2-halo N-methyl-pyridinium salt or a mixed anhydride of thiophosphoric acid e.g. of  
10 diethylthiophosphoric acid. The reaction is carried out with or without the base (inorganic or organic bases) depending on the method of activation and a wide range of solvents, from water and water-miscible solvent to inert solvents such as chloroform, dichloroethane, dimethylformamide (DMF) or dimethylsulfoxide (DMSO) can be used. The substituents in the R<sup>1</sup> group, if  
15 necessary, can be further deprotected with a reaction condition suitable for the removal of the protecting group.

(12) → (10)

The quaternisation of the pyridyl ring may be performed subsequent to the isomerisation steps (4) → (6) as described above or subsequent to the acylation step (11) → (12) (scheme 2). However, quaternisation after acylation  
20 requires intermediate protection of the other sensitive groups in compound (12).

**Example 1**

preparation (1) → (2), scheme 1



**1.1. (RS)-(2-Oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-yl)-triphenyl-phosphonium bromide**

A stirred solution of 4-picolylamine (6.7 ml, 0.067 mol) and triethylamine (9.3 ml, 0.067 mol) in 400 ml dichloromethane was treated within 30 min at  
30 -55°C with a solution of 2-bromo-4-chloro-butanoyl chloride (14.67 g, 0.067 mol) in 100 ml dichloromethane. The reaction mixture was stirred at -50°C to -10°C for 3.5 h and then poured on 200 ml ice/water. The phases were

separated, the organic phase was washed once with 200 ml ice/water before it was concentrated to a volume of about 400 ml.

To the organic phase was added 1.2 g Dowex 2x10 and the vigorously stirred mixture was treated within 20 min at 0°C with 170 ml 50% aqueous sodium  
5 hydroxide solution. The mixture was allowed to warm up to room temperature and was stirred for 18 h. The phases were separated, the aqueous phase was extracted once with 170 ml dichloromethane. The combined organic phases were washed twice with 200 ml ice/water, once with brine and were dried over magnesium sulfate. After filtration they  
10 were reduced to a volume of about 30 ml and purified by column chromatography (50 g SiO<sub>2</sub>, ethyl acetate). The fractions containing pure material were combined and reduced to a volume of 300 ml.

Triphenylphosphine (17.5 g, 0.067 mol) and 50 ml DMF were added to the solution before dichloromethane was removed *in vacuo*. The residual  
15 solution was heated at 80°C for 4 h. The residue was dissolved in dichloromethane and water, the phases were separated and the aqueous phase was extracted thrice with dichloromethane. The combined organic phases were washed once with water, dried over magnesium sulfate and after filtration concentrated to a volume of 200 ml. This solution was added dropwise with  
20 stirring to 1000 ml diethylether upon which the product separated. It was collected by filtration, washed with diethylether and dried *in vacuo*, yielding 10.3 g (30%) colourless crystals.

IR(KBr) 1689, 1641 cm<sup>-1</sup>; MS(ISP) 437.4 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the  
25 following compounds were prepared:

**1.2. (RS)-(2-Oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-yl)-triphenyl-phosphonium bromide**

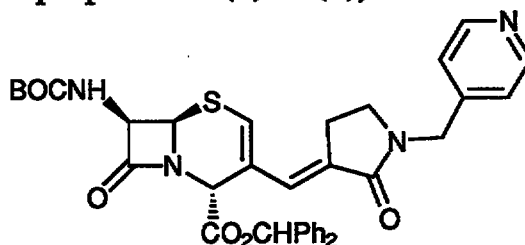
IR (KBr) 1686 cm<sup>-1</sup>, MS (ISP) 438.6 (M-H)<sup>+</sup>

**1.3. (RS)-(2-Oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-yl)-triphenyl-phosphonium  
30 bromide**

IR (KBr) 1687 cm<sup>-1</sup>, MS (ISP) 437.5 M<sup>+</sup>

**Example 2**

preparation (2) → (4), scheme 1



5 **2.1. (E)-(2R,6R,7R)-7-tert-Butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-3-ene-2-carboxylic acid benzhydryl ester**

A suspension of (RS)-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-yl)-triphenylphosphonium bromide (62.0 g, 0.12 mol) and (2R,6R,7R)-tert-butoxycarbonyl-  
10 amino-3-formyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-3-ene-2-carboxylic acid benzhydryl ester (65.3 g, 0.13 mol) in a mixture of 300 ml butylenoxide and 300 ml dichloroethane were refluxed for 3.5 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography (1000 g SiO<sub>2</sub>, ethyl acetate) yielding 70.0 g (89%) of the product as a orange-red foam.

15 IR(KBr) 1780, 1743, 1714 cm<sup>-1</sup>; MS(ISP) 653.4 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

20 **2.2. (E)-(2R,6R,7R)-7-tert-Butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-3-ene-2-carboxylic acid benzhydryl ester**

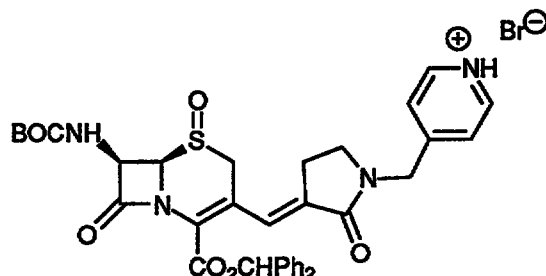
IR (KBr) 1781, 1743, 1716 cm<sup>-1</sup>, MS (ISP) 653.2 (M+H)<sup>+</sup>

**2.3. (E)-(2R,6R,7R)-7-tert-Butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-3-ene-2-carboxylic acid benzhydryl ester**

25 IR (KBr) 1781, 1744 cm<sup>-1</sup>, MS (ISP) 653.4 (M+H)<sup>+</sup>

### Example 3

preparation (4) → (5), scheme 1



#### 3.1. Mixture of (E)-(5R,6R,7R)- and -(5S,6R,7R)-7-tert-butoxycarbonylamino-5,8-dioxo-3-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate acid benzhydryl ester

A solution of (E)-(2R,6R,7R)-7-tert-butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-3-ene-2-carboxylic acid benzhydryl ester (70.0 g, 0.11 mol) in 700 ml dichloromethane was cooled to -10°C. To this was added dropwise a solution of m-chloroperbenzoic acid (70%, 29.0 g, 0.12 mol) in 400 ml dichloromethane. After 4.5 h at -10°C, 400 ml aqueous sodium thiosulfate solution (10%) was added and the mixture was stirred for 15 min. The phases were separated and the organic phase was washed with each 400 ml of aqueous solutions of sodium thiosulfate (10%), sodium bicarbonate (10%) and finally brine. The solution was dried over magnesium sulfate, concentrated after filtration and purified by column chromatography (1000 g SiO<sub>2</sub>, gradient of ethyl acetate and methanol). The fractions containing the pure product were collected, concentrated and added dropwise to hexane. The product separated yielding 45.0 g (61%) beige crystals.  
IR(KBr) 1794, 1720 cm<sup>-1</sup>; MS(ISP) 669.4 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

#### 3.2. Mixture of (E)-(5R,6R,7R)- and -(5S,6R,7R)-7-tert-butoxycarbonylamino-5,8-dioxo-3-(2-oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-ylidenemethyl)-4-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester

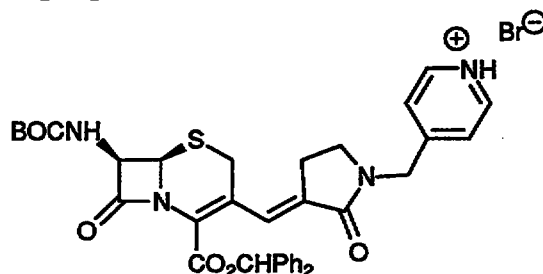
IR (KBr) 1795, 1721 cm<sup>-1</sup>, MS (ISP) 669.3 (M+H)<sup>+</sup>

#### 3.4. Mixture of (E)-(5R,6R,7R)- and -(5S,6R,7R)-7-tert-butoxycarbonylamino-5,8-dioxo-3-(2-oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester

IR (KBr) 1795, 1721 cm<sup>-1</sup>, MS (ISP) 669.3 (M+H)<sup>+</sup>

#### Example 4

preparation (5) → (6), scheme 1



5 **4.1. (E)-(6R,7R)-7-tert-Butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester hydrobromide**

A solution of a mixture of (E)-(5R,6R,7R)- and -(5S,6R,7R)-7-tert-butoxycarbonylamino-5,8-dioxo-3-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate acid  
10 benzhydryl ester (45 g, 0.067 mol) in 600 ml dichloromethane, 60 ml DMF and 40 ml N-methylacetamide was treated at -78°C with phosphorous tribromide (26 ml, 0.269 mol). After 3.5 h the mixture was allowed to warm up to -5°C, quenched with 500 ml water and the pH was adjusted to 3.5 using 4 N sodium hydroxide solution. The phases were separated, the aqueous phase  
15 was extracted once with 600 ml dichloromethane, the combined organic phases were washed once with 500 ml water and dried over magnesium sulfate. After concentration, the solution was added dropwise into 1500 ml hexane, upon which the product separated, yielding 40.1 g (92%) yellowish crystals.

20 IR(KBr) 1784, 1719 cm<sup>-1</sup>; MS(ISP) 653.5 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

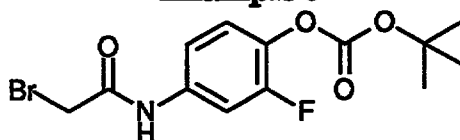
25 **4.2. (E)-(6R,7R)-7-tert-Butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester**

IR (KBr) 1784, 1718 cm<sup>-1</sup>, MS (ISP) 675.3 (M+Na)<sup>+</sup>

**4.3. (E)-(6R,7R)-7-tert-Butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester**

30 IR (KBr) 1783, 1720 cm<sup>-1</sup>, MS (ISP) 653.4 (M+H)<sup>+</sup>

**Example 5**



**5.1. Carbonic acid 4-(2-bromo-acetylamino)-2-fluoro-phenyl ester tert-butyl ester**

- 5 A solution of carbonic acid 4-amino-2-fluoro-phenyl ester tert-butyl ester (3 g, 13.2 mmol, synthesized according to Can. J. Chem. **63**, 153 (1985)) and triethylamine (1.8 ml, 13.2 mmol) in 50 ml dichloromethane was treated with bromoacetyl bromide (1.1 ml, 13.2 mmol) at 0-5°C. After 1 h, the reaction mixture was extracted with water, dried over magnesium sulfate and
- 10 concentrated *in vacuo*. The oily residue was triturated with hexane, yielding 4.2 g (91%) of a beige solid.

IR(KBr) 1769  $\text{cm}^{-1}$ ; MS(EI) 348 ( $\text{M}+\text{H}$ ) $^{\circ}$ .

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

- 15 **5.2. Carbonic acid 4-(2-bromo-acetylamino)-phenyl ester tert-butyl ester**

**5.3. Carbonic acid 3-(2-bromo-acetylamino)-phenyl ester tert-butyl ester**

IR (KBr) 1751  $\text{cm}^{-1}$ , MS (EI) 329  $\text{M}^{\circ}$

**5.4. Carbonic acid 2-(2-bromo-acetylamino)-phenyl ester tert-butyl ester**

IR (KBr) 1770  $\text{cm}^{-1}$ , MS (EI) 229  $\text{M}^{\circ}$

- 20 **5.5. Carbonic acid 4-(2-bromo-acetylamino)-3-fluoro-phenyl ester tert-butyl ester**

IR (KBr) 1770, 1740  $\text{cm}^{-1}$ , MS (ISP) 367.2 ( $\text{M}+\text{NH}_4$ ) $^{+}$

**5.6. Carbonic acid 4-(2-bromo-acetylamino)-2-chloro-phenyl ester tert-butyl ester**

- 25 IR (KBr) 1770  $\text{cm}^{-1}$ , MS (EI) 348 ( $\text{M}-\text{CH}_3$ ) $^{\circ}$

**5.7. Carbonic acid 4-(2-bromo-acetylamino)-2-methoxy-phenyl ester tert-butyl ester**

IR (KBr) 1759  $\text{cm}^{-1}$ , MS (EI) 286 ( $\text{M}-\text{OtBu}$ ) $^{\circ}$

**5.8. 2-Bromo-N-(3,4-difluoro-phenyl)-acetamide**

- 30 IR (KBr) 1666  $\text{cm}^{-1}$ , M (EI) 249  $\text{M}^{\circ}$

**5.9. 2-Bromo-N-(3-hydroxy-benzyl)-acetamide**

IR (KBr) 1678 cm<sup>-1</sup>, M (EI) 245 M<sup>•</sup>

**5.10. 2-Bromo-N-[2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-acetamide**

IR (KBr) 1659 cm<sup>-1</sup>, M (EI) 280 (M-CH<sub>3</sub>)<sup>•</sup>

5 **5.11. 2-Bromo-N-(5-methyl-1,3,4-thiadiazol-2-yl)-acetamide**

IR (KBr) 1606 cm<sup>-1</sup>, MS (EI) 235 M<sup>•</sup>

**5.12. 2-Bromo-N-(4-methoxy-phenyl)-acetamide**

**5.13. 2-Bromo-1-(2,3-dihydro-indol-1-yl)-ethanone**

IR (KBr) 1660 cm<sup>-1</sup>, MS (EI) 239 M<sup>•</sup>

10 **5.14. N-(3-Acetylamino-4-hydroxy-phenyl)-2-bromo-acetamide**

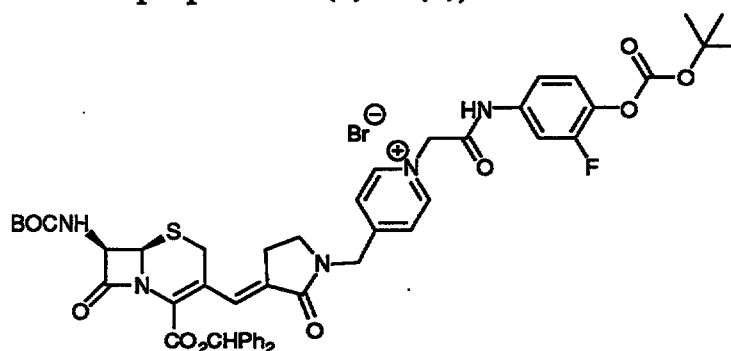
**5.15. (R)-3-(2-Bromo-acetylamino)-pyrrolidine-1-carboxylic acid allyl ester**

IR (KBr) 1674 cm<sup>-1</sup>, MS (ISP) 308.1 (M+NH<sub>4</sub>)<sup>+</sup>

**Example 6**

preparation (6) → (7), scheme 1

15



**6.1. (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-tert-butoxycarbonyloxy-3-fluoro-phenylcarbamoyl)-methyl]-pyridinium bromide**

20

(E)-(6R,7R)-7-tert-Butoxycarbonylamino-8-oxo-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid benzhydryl ester (1 g, 1.53 mmol) in 25 ml DMF was treated with carbonic acid 4-(2-bromo-acetylamino)-2-fluoro-phenyl ester tert-butyl ester (1.06 g, 3.00 mmol) for 25 h at room temperature. The solvent was removed *in vacuo* and the residue was triturated with diethylether yielding 1.1 g (72%) of

25

the product as a beige powder.

IR(KBr) 1770, 1698  $\text{cm}^{-1}$ ; MS(ISP) 920.5  $\text{M}^+$ .

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

- 5 **6.2.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-tert-butoxycarbonyloxy-phenylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1783, 1758  $\text{cm}^{-1}$ , MS (ISP) 902.6  $(\text{M}+\text{H})^+$
- 10 **6.3.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(3-tert-butoxycarbonyloxy-phenylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1781, 1761  $\text{cm}^{-1}$ , MS (ISP) 902.5  $\text{M}^+$
- 15 **6.4.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(2-tert-butoxycarbonyloxy-phenylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1779, 1712  $\text{cm}^{-1}$ , MS (ISP) 902.6  $\text{M}^+$
- 20 **6.5.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-tert-butoxycarbonyloxy-2-fluoro-phenylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1781, 1712  $\text{cm}^{-1}$ , MS (ISP) 920.5  $\text{M}^+$
- 25 **6.6.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-tert-butoxycarbonyloxy-3-chloro-phenylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1772, 1701  $\text{cm}^{-1}$ , MS (ISP) 936.5  $\text{M}^+$
- 30 **6.7.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-tert-butoxycarbonyloxy-3-methoxy-phenylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1783, 1770  $\text{cm}^{-1}$ , MS (ISP) 932.5  $\text{M}^+$

- 6.8.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(3,4-difluoro-phenylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1783, 1697  $\text{cm}^{-1}$ , MS (ISP) 822.4  $\text{M}^+$
- 5 **6.9.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(3-hydroxy-benzylcarbamoyl)-methyl]-pyridinium bromide  
IR (KBr) 1781, 1691  $\text{cm}^{-1}$ , MS (ISP) 816.5  $\text{M}^+$
- 6.10.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[[2-(tert-butyl-dimethyl-silanyloxy)-ethylcarbamoyl]-methyl]-pyridinium bromide  
10 IR (KBr) 1784, 1718  $\text{cm}^{-1}$ , MS (ISP) 868.6  $\text{M}^+$
- 6.11.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(5-methyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-pyridinium bromide  
15 IR (KBr) 1783, 1712  $\text{cm}^{-1}$ , MS (ISP) 808.3 ( $\text{M}+\text{H}$ ) $^+$
- 6.12.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-methoxy-phenylcarbamoyl)-methyl]-pyridinium bromide  
20 IR (KBr) 1789, 1716  $\text{cm}^{-1}$ , MS (ISP) 816.5  $\text{M}^+$
- 6.13.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[2-(2,3-dihydro-indol-1-yl)-2-oxo-ethyl]-pyridinium bromide  
25 IR (KBr) 1782, 1717  $\text{cm}^{-1}$ , MS (ISP) 812.6  $\text{M}^+$
- 6.14.** (E)-(6R,7R)-1-[(1-Allyloxycarbonyl-pyrrolidin-3-ylcarbamoyl)-methyl]-4-[3-(2-benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-pyridinium bromide  
30 IR (KBr) 1783, 1687  $\text{cm}^{-1}$ , MS (ISP) 863.5  $\text{M}^+$
- 6.15.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-

ylmethyl]-1-methyl-pyridinium sulfate

IR (KBr) 1778, 1714  $\text{cm}^{-1}$ , MS (ISP) 667.5 (M)<sup>+</sup>

**6.16.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-

5 ylmethyl]-1-carbamoylmethyl-pyridinium bromide

IR (KBr) 1780, 1695  $\text{cm}^{-1}$ , MS (ISP) 710.4 (M+H)<sup>+</sup>

**6.17.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-benzyl-pyridinium bromide

10 IR (KBr) 1781, 1717  $\text{cm}^{-1}$ , MS (ISP) 743.4 M<sup>+</sup>

**6.18.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-(4-cyano-benzyl)-pyridinium bromide

IR (KBr) 1781, 1717  $\text{cm}^{-1}$ , MS (ISP) 768.4 M<sup>+</sup>

**6.19.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-(3-hydroxy-benzyl)-pyridinium bromide

IR (KBr) 1781, 1717  $\text{cm}^{-1}$ , MS (ISP) 759.2 (M+H)<sup>+</sup>

**6.20.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-(4-carboxy-benzyl)-pyridinium bromide

IR (KBr) 1781, 1715  $\text{cm}^{-1}$ , MS (ISP) 787.4 M<sup>+</sup>

**6.20a.** (E)-(6R,7R)-4-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-tert-butoxycarbonyloxy-2-trifluoromethyl-phenylcarbamoyl)-methyl]-pyridinium bromide

IR (KBr): 1780, 1766  $\text{cm}^{-1}$ , MS (ISP) 970,5 M<sup>+</sup>

The following compounds were prepared in the same way using (E)-(6R,7R)-7-tert-butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid  
30 benzhydryl ester

**6.21.** (E)-(6R,7R)-3-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-

ylmethyl]-1-[(5-methyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-pyridinium  
bromide

IR (KBr) 1771, 1713  $\text{cm}^{-1}$ , MS (ISP) 920.5  $\text{M}^+$

5 **6.22.** (E)-(6R,7R)-3-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-  
8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-  
ylmethyl]-1-[(3-tert-butoxycarbonyloxy-phenylcarbamoyl)-methyl]-  
pyridinium bromide

IR (KBr) 1784, 1714  $\text{cm}^{-1}$ , MS (ISP) 902.7  $\text{M}^+$

10 **6.23.** (E)-(6R,7R)-3-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-  
8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-  
ylmethyl]-1-[(4-tert-butoxycarbonyloxy-phenylcarbamoyl)-methyl]-  
pyridinium bromide

IR (KBr) 1784, 1759  $\text{cm}^{-1}$ , MS (ISP) 902.5  $\text{M}^+$

15 **6.24.** (E)-(6R,7R)-3-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-  
8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-  
ylmethyl]-1-[(4-tert-butoxycarbonyloxy-3-fluoro-phenylcarbamoyl)-methyl]-  
pyridinium bromide

IR (KBr) 1783, 1716  $\text{cm}^{-1}$ , MS (ISP) 808.4  $\text{M}^+$

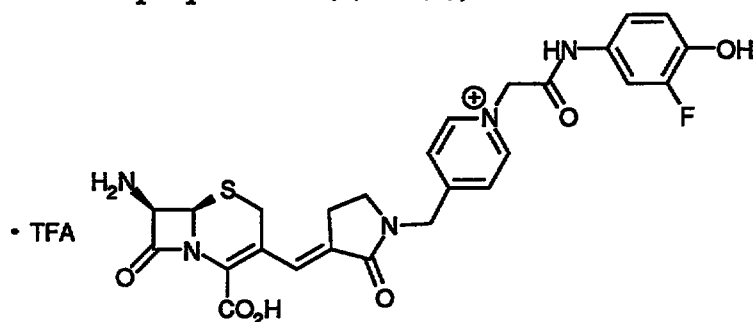
20 The following compound was prepared in the same way using (E)-(6R,7R)-7-  
tert-butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-  
ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid  
benzhydryl ester

25 **6.25.** (E)-(6R,7R)-2-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-  
8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-  
ylmethyl]-1-methyl-pyridinium tetrafluoroborate

IR (KBr) 1782, 1716  $\text{cm}^{-1}$ , MS (ISP) 667.3  $(\text{M}+\text{H})^+$

**Example 7**

preparation (7) → (8), scheme 1



**7.1. (E)-(6R,7R)-7-Amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt**

A solution of (E)-(6R,7R)-4-[3-(2-benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-ylmethyl]-1-[(4-tert-butoxycarbonyloxy-3-fluoro-phenylcarbamoyl)-methyl]-pyridinium bromide (1.1 g, 1.09 mmol) in 25 ml dichloromethane was treated with 1.2 ml anisol and 5 ml trifluoroacetic acid at 0-5°C. After 3 h stirring at room temperature, the mixture was concentrated and triturated with diethylether yielding 697 mg (96%) of a beige solid.

IR(KBr) 1782, 1678  $\text{cm}^{-1}$ ; MS(ISP) 554.3 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

**7.2. (E)-(6R,7R)-7-Amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt**

IR (KBr) 1782, 1678  $\text{cm}^{-1}$ , MS (ISP) 558.2 (M+Na<sup>+</sup>)

**7.3. (E)-(6R,7R)-7-Amino-3-[1-[1-[(3-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoro-acetic acid salt**

IR (KBr) 1781, 1680  $\text{cm}^{-1}$ , MS (ISP) 536.3 (M+H)<sup>+</sup>

**7.4. (E)-(6R,7R)-7-Amino-3-[1-[1-[(2-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt**

IR (KBr) 1782, 1679  $\text{cm}^{-1}$ , MS (ISP) 536.3 (M+H)<sup>+</sup>

- 7.5.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(2-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1785, 1680  $\text{cm}^{-1}$ , MS (ISP) 554.2 (M+H)<sup>+</sup>
- 5 **7.6.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(3-chloro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1783, 1689  $\text{cm}^{-1}$ , MS (ISP) 570.2 (M+H)<sup>+</sup>
- 10 **7.7.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(4-hydroxy-3-methoxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1782, 1679  $\text{cm}^{-1}$ , MS (ISP) 566.3 (M+H)<sup>+</sup>
- 15 **7.8.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(3,4-difluoro-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1780, 1682  $\text{cm}^{-1}$ , MS (ISP) 556.1 (M+H)<sup>+</sup>
- 7.9.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(3-hydroxy-benzylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
20 IR (KBr) 1783, 1681  $\text{cm}^{-1}$ , MS (ISP) 550.4 (M+H)<sup>+</sup>
- 7.10.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(2-hydroxy-ethylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1783, 1680  $\text{cm}^{-1}$ , MS (ISP) 488.4 (M+H)<sup>+</sup>
- 25 **7.11.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(5-methyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1781, 1681  $\text{cm}^{-1}$ , MS (ISP) 542.3 (M+H)<sup>+</sup>
- 30 **7.12.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(4-methoxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoro-acetic acid salt  
IR (KBr) 1783, 1681  $\text{cm}^{-1}$ , MS (ISP) 550.2 (M+H)<sup>+</sup>

- 7.13.** (E)-(6R,7R)-7-Amino-3-[1-[1-[2-(2,3-dihydro-indol-1-yl)-2-oxo-ethyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1783, 1675 cm<sup>-1</sup>, MS (ISP) 546.3 (M+H)<sup>+</sup>
- 5 **7.14.** (E)-(6R,7R)-3-(1-{1-[(1-Allyloxycarbonyl-3-methyl-pyrrolidin-3-ylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl}-2-oxo-pyrrolidin-3-ylidenemethyl)-7-amino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1790, 1691 cm<sup>-1</sup>, MS (ISP) 597.2 (M+H)<sup>+</sup>
- 10 **7.15.** (E)-(6R,7R)-7-Amino-3-[1-(1-methyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1784, 1677 cm<sup>-1</sup>, MS (ISP) 401.3 M<sup>+</sup>
- 7.16.** (E)-(6R,7R)-7-Amino-3-[1-(1-carbamoylmethyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
15 IR (KBr) 1779, 1683 cm<sup>-1</sup>, MS (ISP) 444.4 M<sup>+</sup>
- 7.17.** (E)-(6R,7R)-7-Amino-3-[1-(1-benzyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
20 IR (KBr) 1782, 1690 cm<sup>-1</sup>, MS (ISP) 477.3 (M+H)<sup>+</sup>
- 7.18.** (E)-(6R,7R)-7-Amino-3-[1-[1-(4-cyano-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
25 IR (KBr) 1781, 1679 cm<sup>-1</sup>, MS (ISP) 502.0 (M+H)<sup>+</sup>
- 7.19.** (E)-(6R,7R)-7-Amino-3-[1-[1-(3-hydroxy-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1774, 1676 cm<sup>-1</sup>, MS (ISP) 493.3 (M+H)<sup>+</sup>
- 30 **7.20.** (E)-(6R,7R)-7-Amino-3-[1-[1-(4-carboxy-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1780, 1680 cm<sup>-1</sup>, MS (ISP) 543.3 (M+Na<sup>+</sup>)

- 7.21.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(2-methyl-benzooxazol-5-ylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1764, 1679  $\text{cm}^{-1}$ , MS (ISP) 575.3 (M+H)<sup>+</sup>
- 5 **7.22.** (E)-(6R,7R)-7-Amino-3-[1-[1-(2-hydroxy-ethyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1778, 1678  $\text{cm}^{-1}$ , MS (ISP) 453.3 (M+Na<sup>+</sup>)
- 7.23.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
10 IR (KBr) 1782, 1680  $\text{cm}^{-1}$ , MS (ISP) 554.1 (M+H)<sup>+</sup>
- 7.24.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
15 IR (KBr) 1780, 1670  $\text{cm}^{-1}$ , MS (ISP) 558.1 (M+Na<sup>+</sup>)
- 7.25.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(3-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
20 IR (KBr) 1781, 1680  $\text{cm}^{-1}$ , MS (ISP) 536.2 (M+H)<sup>+</sup>
- 7.26.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(5-methyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1783, 1679  $\text{cm}^{-1}$ , MS (ISP) 564.1 (M+Na<sup>+</sup>)
- 25 **7.27.** (E)-(6R,7R)-7-Amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-2-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
IR (KBr) 1780, 1681  $\text{cm}^{-1}$ , MS (ISP) 536.3 (M+H)<sup>+</sup>
- 7.28.** (E)-(6R,7R)-7-Amino-3-[1-[1-(3-hydroxy-benzyl)-pyridin-1-ium-2-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt  
30 IR (KBr) 1784, 1677  $\text{cm}^{-1}$ , MS (ISP) 493.3 (M+H)<sup>+</sup>

**7.29. (E)-(6R,7R)-7-Amino-3-[1-(1-methyl-pyridin-1-ium-2-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt**

IR (KBr) 1782, 1680  $\text{cm}^{-1}$ , MS (ISP) 401.2 (M+H)<sup>+</sup>

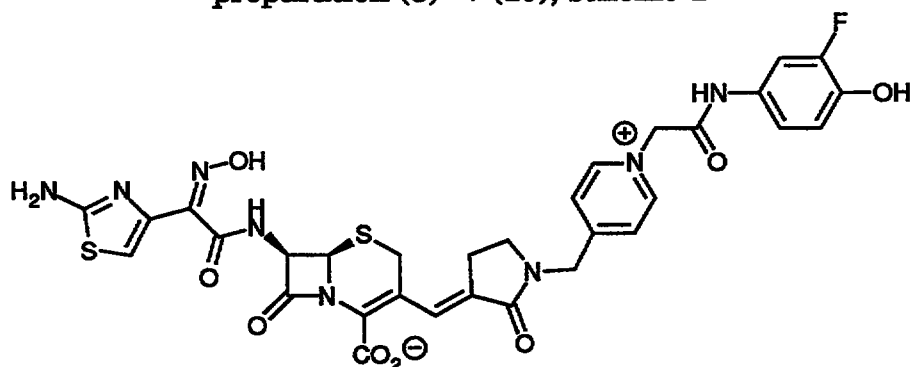
5 **7.30. (E)-(6R,7R)-7-Amino-3-[1-[1-[(4-hydroxy-2-trifluoromethyl-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetate (1:1)**

IR (KBr): 1782, 1679  $\text{cm}^{-1}$ , MS(ISP): 604.2 (M+H<sup>+</sup>)

10

### Example 8

preparation (8)  $\rightarrow$  (10), scheme 1



**8.1. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate**

A suspension of (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt (400 mg, 0.72 mmol) in 10 ml DMF was treated with (Z)-(2-aminothiazol-4-yl)-trityloxyimino-acetic acid 1-benzotriazolyl ester (394 mg, 0.72 mmol) for 24 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue triturated with ethyl acetate yielding 461 mg (60%) of a beige solid. The solid was treated with 3 ml trifluoroacetic acid and triethylsilane (0.2 ml, 0.85 mmol) at 0-5°C for 30 min. The reaction mixture was added dropwise into diethylether upon which the product separated as a beige solid. It was purified by gel chromatography (MCI Gel 75-150 $\mu$ , using a gradient of water with increasing concentrations of

acetonitrile). Yield: 380 mg (28%).

IR(KBr) 1767, 1672  $\text{cm}^{-1}$ ; MS(ISP) 723.4 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

- 5    **8.2.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1766  $\text{cm}^{-1}$ , MS (ISP) 727.4 (M+Na<sup>+</sup>)
- 10    **8.3.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1765, 1665  $\text{cm}^{-1}$ , MS (ISP) 705.3 (M+H)<sup>+</sup>
- 15    **8.4.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(2-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1770, 1669  $\text{cm}^{-1}$ , MS (ISP) 705.3 (M+H)<sup>+</sup>
- 20    **8.5.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(2-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1765, 1625  $\text{cm}^{-1}$ , MS (ISP) 723.3 (M+H)<sup>+</sup>
- 25    **8.6.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-chloro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1766, 1675  $\text{cm}^{-1}$ , MS (ISP) 739.2 (M+H)<sup>+</sup>
- 30    **8.7.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-3-methoxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1769, 1671  $\text{cm}^{-1}$ , MS (ISP) 735.5 (M+H)<sup>+</sup>

**8.8.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3,4-difluoro-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

5 IR (KBr) 1766, 1675  $\text{cm}^{-1}$ , MS (ISP) 725.0 (M+H)<sup>+</sup>

**8.9.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-hydroxy-benzylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

10 IR (KBr) 1766, 1688  $\text{cm}^{-1}$ , MS (ISP) 657.3 (M+H)<sup>+</sup>

**8.10.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(2-hydroxy-ethylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

15 IR (KBr) 1769, 1675  $\text{cm}^{-1}$ , MS (ISP) 719.3 (M+H)<sup>+</sup>

**8.11.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-(5-methyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

20 IR (KBr) 1766, 1665  $\text{cm}^{-1}$ , MS (ISP) 711.3 (M+H)<sup>+</sup>

**8.12.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-methoxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

25 IR (KBr) 1770, 1680  $\text{cm}^{-1}$ , MS (ISP) 719.4 (M+H)<sup>+</sup>

**8.13.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[2-(2,3-dihydro-indol-1-yl)-2-oxo-ethyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

30 IR (KBr) 1771, 1670  $\text{cm}^{-1}$ , MS (ISP) 715.4 (M+H)<sup>+</sup>

**8.14.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-(1-methyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

IR (KBr) 1767, 1666  $\text{cm}^{-1}$ , MS (ISP) 592.3 (M+Na<sup>+</sup>)

- 8.15.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-(1-carbamoylmethyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1764, 1672  $\text{cm}^{-1}$ , MS (ISP) 613.3 (M+H)<sup>+</sup>
- 5 **8.16.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-(1-benzyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1768, 1639  $\text{cm}^{-1}$ , MS (ISP) 646.4 (M+H)<sup>+</sup>
- 10 **8.17.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-(4-cyano-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1775, 1677  $\text{cm}^{-1}$ , MS (ISP) 671.3 (M+H)<sup>+</sup>
- 15 **8.18.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-(3-hydroxy-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1774, 1676  $\text{cm}^{-1}$ , MS (ISP) 662.3 (M+H)<sup>+</sup>
- 20 **8.19.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-(4-carboxy-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
sodium salt  
IR (KBr) 1767, 1694  $\text{cm}^{-1}$ , MS (ISP) 690.2 (M+H)<sup>+</sup>
- 25 **8.20.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(2-methyl-benzooxazol-5-ylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1766, 1668  $\text{cm}^{-1}$ , MS (ISP) 744.6 (M+H)<sup>+</sup>
- 30 **8.21.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1767, 1668  $\text{cm}^{-1}$ , MS (ISP) 723.4 (M+H)<sup>+</sup>
- 8.22.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

carboxylate

IR (KBr) 1766, 1671  $\text{cm}^{-1}$ , MS (ISP) 705.2 (M+H)<sup>+</sup>

5 **8.23.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

IR (KBr) 1766, 1664  $\text{cm}^{-1}$ , MS (ISP) 705.3 (M+H)<sup>+</sup>

10 **8.24.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(5-methyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

IR (KBr) 1766, 1669  $\text{cm}^{-1}$ , MS (ISP) 711.2 (M+H)<sup>+</sup>

15 **8.25.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-(3-hydroxy-benzyl)-pyridin-1-ium-2-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

IR (KBr) 1771, 1672  $\text{cm}^{-1}$ , MS (ISP) 662.2 (M+H)<sup>+</sup>

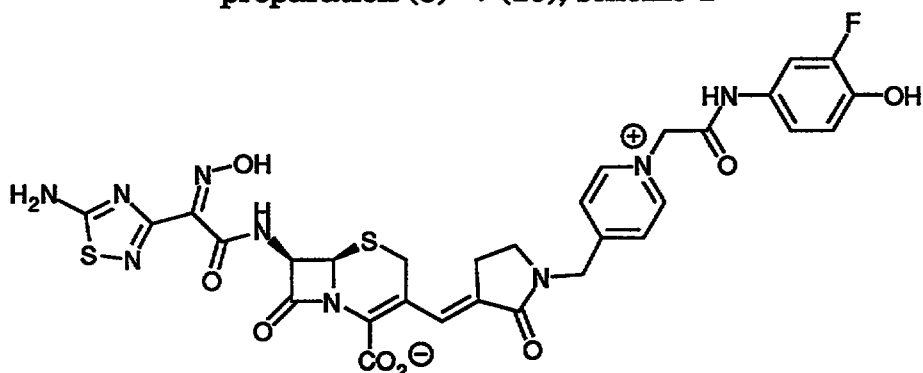
**8.26.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-(1-methyl-pyridin-1-ium-2-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

20 IR (KBr) 1775, 1678  $\text{cm}^{-1}$ , MS (ISP) 570.1 (M+H)<sup>+</sup>

**8.27** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-2-trifluoromethyl-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

25 IR (KBr) 1769, 1672  $\text{cm}^{-1}$ , MS (ISP) 773.4 (M+H)<sup>+</sup>

**Example 9**  
preparation (8) → (10), scheme 1



5 **9.1. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate**

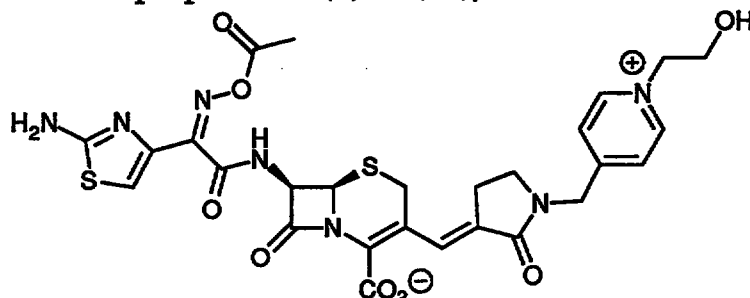
A suspension of (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt (500 mg, 0.74 mmol) ) in 20 ml DMF was treated with (Z)-(5-amino-[1,2,4]thiadiazol-3-yl)-trityloxyimino-thioacetic acid 2-mercaptobenzothiazolyl ester (434 mg, 0.74 mmol) for 21 h at room  
10 temperature. The reaction mixture was concentrated *in vacuo* and the residue triturated with ethyl acetate and diethylether. The solid was treated with 5 ml trifluoroacetic acid and triethylsilane (0.2 ml, 1.06 mmol) at 0-5°C for 30 min. The reaction mixture was added dropwise into diethylether upon which the product separated as a beige solid. It was purified by gel  
15 chromatography (MCI Gel 75-150μ, using a gradient of water with increasing concentrations of acetonitrile). Yield: 182 mg (47%).  
20 IR(KBr) 1767, 1673 cm<sup>-1</sup>; MS(ISP) 724.2 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

25 **9.2. (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate**  
IR (KBr) 1780, 1671 cm<sup>-1</sup>, MS (ISP) 706.3 (M+H)<sup>+</sup>

**Example 10**

preparation (8) → (10), scheme 1

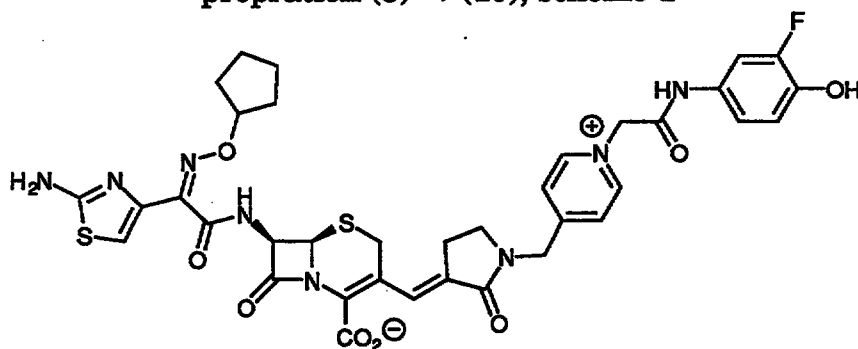


5 **(6R,7R)-7-[(Z)-2-Acetoxyimino-2-(2-amino-thiazol-4-yl)-acetyl-amino]-3-[(E)-1-[1-(2-hydroxy-ethyl)-pyridin-1-ium-1-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate**

A solution of (E)-(6R,7R)-7-amino-3-[1-[1-(2-hydroxy-ethyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt (600 mg, 1.1 mmol) in 20 ml DMF was treated with (Z)-(2-amino-thiazol-4-yl)-acetoxyimino-acetic acid diethoxy-thiophosphoryl ester (420 mg, 1.1 mmol) for 24 h at room temperature. The reaction mixture was concentrated *in vacuo* and the residue triturated with ethyl acetate. The resulting solid was purified by gel chromatography (MCI Gel 75-150 $\mu$ , using a gradient of water with increasing concentrations of acetonitrile). Yield: 67 mg (9%). IR(KBr) 1768, 1669  $\text{cm}^{-1}$ ; MS(ISP) 664.2 ( $\text{M}+\text{Na}^+$ ).

**Example 11,**

preparation (8) → (10), scheme 1



20 **11.1. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenyl)carbamoyl]-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate**

25 A suspension of (E)-(6R,7R)-7-amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenyl)carbamoyl]-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-

ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt (180mg, 0.26 mmol) ) in 5 ml DMF was treated with (Z)-(2-aminothiazol-4-yl)-cyclopentyloxyimino-acetic acid 2-mercaptobenzothiazolyl ester (109 mg, 0.72 mmol) for 24 h at room  
5 temperature. The reaction mixture was concentrated *in vacuo* and the residue triturated with ethyl acetate. The resulting solid was purified by reversed phase chromatography (MERCK Lichroprep RP-18 silicagel, 25-40 $\mu$ , using a gradient of water with increasing concentrations of acetonitrile). Yield: 64 mg (31%).  
10 IR(KBr) 1768, 1671  $\text{cm}^{-1}$ ; MS(ISP) 791.3 (M+H)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

**11.2.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-  
15 ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1769, 1674  $\text{cm}^{-1}$ , MS (ISP) 773.4 (M+H)<sup>+</sup>

**11.3.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-  
20 ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1770, 1677  $\text{cm}^{-1}$ ; MS (ISP) 773.3 (M+H)<sup>+</sup>

**11.4.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-[(2-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-  
25 ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1769, 1676  $\text{cm}^{-1}$ ; MS (ISP) 773.4 (M+H)<sup>+</sup>

**11.5.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-[(2-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-  
30 pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1767, 1673  $\text{cm}^{-1}$ ; MS (ISP) 791.4 (M+H)<sup>+</sup>

**11.6.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-chloro-4-hydroxy-phenylcarbamoyl)-methyl]-

pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-  
aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1775, 1680  $\text{cm}^{-1}$ ; MS (ISP) 807.3 (M+H)<sup>+</sup>

11.7. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-  
5 acetylamino]-3-[(E)-1-[1-[(4-hydroxy-3-methoxy-phenylcarbamoyl)-methyl]-  
pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-  
aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1769, 1672  $\text{cm}^{-1}$ ; MS (ISP) 803.4 (M+H)<sup>+</sup>

11.8. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-  
10 acetylamino]-3-[(E)-1-[1-[(3,4-difluoro-phenylcarbamoyl)-methyl]-pyridin-1-  
ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1770, 1673  $\text{cm}^{-1}$ ; MS (ISP) 793.3 (M+H)<sup>+</sup>

11.9. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-  
15 acetylamino]-3-[(E)-1-[1-[(3-hydroxy-benzylcarbamoyl)-methyl]-pyridin-1-  
ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1768, 1674  $\text{cm}^{-1}$ ; MS (ISP) 787.7 (M+H)<sup>+</sup>

11.10. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-  
20 acetylamino]-3-[(E)-1-[1-[(2-hydroxy-ethylcarbamoyl)-methyl]-pyridin-1-ium-  
4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1778, 1675  $\text{cm}^{-1}$ ; MS (ISP) 725.5 (M+H)<sup>+</sup>

11.11. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-  
25 acetylamino]-3-[(E)-1-[1-[(5-methyl-[1,3,4]thiadiazol-2-ylcarbamoyl)-methyl]-  
pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-  
aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1780, 1675  $\text{cm}^{-1}$ ; MS (ISP) 779.5 (M+H)<sup>+</sup>

11.12. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-  
30 acetylamino]-3-[(E)-1-[1-[(4-methoxy-phenylcarbamoyl)-methyl]-pyridin-1-  
ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-  
bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1771, 1676  $\text{cm}^{-1}$ ; MS (ISP) 787.5 (M+H)<sup>+</sup>

- 11.13.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-[2-(2,3-dihydro-indol-1-yl)-2-oxo-ethyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
5 IR (KBr) 1770, 1669  $\text{cm}^{-1}$ ; MS (ISP) 783.5 (M+H)<sup>+</sup>
- 11.14.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-(1-methyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1768, 1668  $\text{cm}^{-1}$ ; MS (ISP) 638.4 (M+H)<sup>+</sup>
- 10 **11.15.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-(2-hydroxy-ethyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1769, 1670  $\text{cm}^{-1}$ ; MS (ISP) 690.4 (M+Na)<sup>+</sup>
- 15 **11.16.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino]-acetyl-amino]-3-[(E)-1-(1-carbamoylmethyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1766, 1665  $\text{cm}^{-1}$ ; MS (ISP) 681.4 (M+H)<sup>+</sup>
- 20 **11.17.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-(1-benzyl-pyridin-1-ium-4-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
trifluoroacetic acid salt  
IR 1777, 1676  $\text{cm}^{-1}$ ; MS (ISP) 714.4 (M+H)<sup>+</sup>
- 25 **11.18.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-(4-cyano-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1769, 1670  $\text{cm}^{-1}$ ; MS (ISP) 739.3 (M+H)<sup>+</sup>
- 30 **11.19.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-3-[(E)-1-[1-(3-hydroxy-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1769, 1664  $\text{cm}^{-1}$ ; MS (ISP) 730.4 (M+H)<sup>+</sup>

**11.20.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentylloxyimino-acetyl-amino]-3-[(E)-1-[1-(4-carboxyl-benzyl)-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate sodium salt

5 IR (KBr) 1765, 1668  $\text{cm}^{-1}$ ; MS (ISP) 758.4 (M+H)<sup>+</sup>

**11.21.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentylloxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

10 IR (KBr) 1769, 1674  $\text{cm}^{-1}$ ; MS (ISP) 791.5 (M+H)<sup>+</sup>

**11.22.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentylloxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

15 IR (KBr) 1767, 1672  $\text{cm}^{-1}$ ; MS (ISP) 773.3 (M+H)<sup>+</sup>

**11.23.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentylloxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-hydroxy-phenylcarbonyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

20 IR (KBr) 1770, 1665  $\text{cm}^{-1}$ ; MS (ISP) 773.3 (M+H)<sup>+</sup>

**11.24.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentylloxyimino-acetyl-amino]-3-[(E)-1-[1-[(5-methyl-[1,3,4]thiadiazol-2-ylcarbonyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

25 IR (KBr) 1769, 1671  $\text{cm}^{-1}$ ; MS (ISP) 779.2 (M+H)<sup>+</sup>

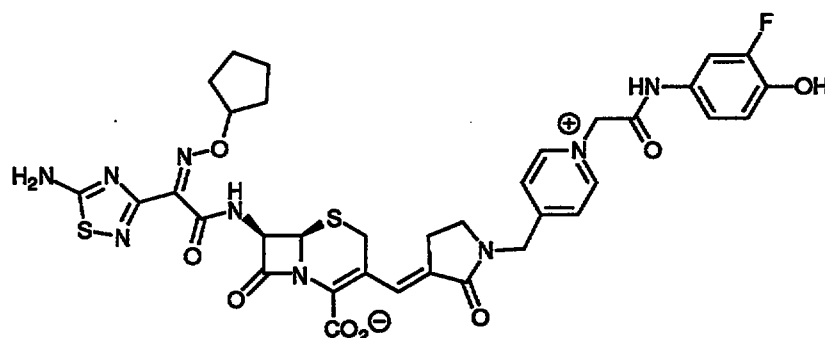
**11.25.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentylloxyimino-acetyl-amino]-3-[(E)-1-(1-methyl-pyridin-1-ium-2-ylmethyl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate

IR (KBr) 1775, 1675  $\text{cm}^{-1}$ ; MS (ISP) 638.3 (M+H)<sup>+</sup>

30

### Example 12

preparation (8) → (10), scheme 1

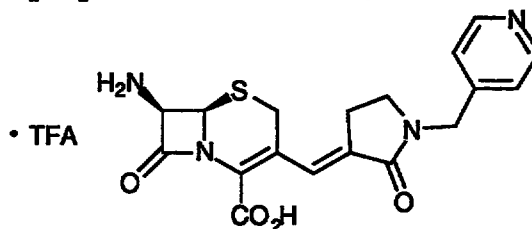


**(6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-cyclopentyloxyimino-acetylamino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate**

A solution of (Z)-(5-amino-[1,2,4]thiadiazol-3-yl)-cyclopentyloxyimino-acetate 1-allyl-1-methyl-pyrrolidinium salt in 10 ml DMF was treated with HBTU (170 mg, 0.45 mmol) for 1.5 h at room temperature. (E)-(6R,7R)-7-Amino-3-[1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt (300 mg, 0.45 mmol) was added and the mixture was stirred for 78 h before it was concentrated *in vacuo*. The residue was dissolved in ethylacetate and extracted with water. The organic phase was evaporated and the residue triturated with diethylether. The product was purified by gel chromatography (MCI-gel, using a gradient of water with increasing concentrations of acetonitrile). Yield: 40 mg (11%).  
IR(KBr) 1767, 1670  $\text{cm}^{-1}$ ; MS(ISP) 792.4 (M+H)<sup>+</sup>.

### Example 13

preparation (6) → (11), scheme 2



The following compounds were synthesized using the procedure described in example 7.

**13.1. (E)-(6R,7R)-7-Amino-8-oxo-3-(2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid trifluoroacetic acid salt**

IR (KBr) 1782, 1679  $\text{cm}^{-1}$ ; MS (ISP) 387.2 (M+H)<sup>+</sup>

**13.2. (E)-(6R,7R)-7-Amino-8-oxo-3-(2-oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid**  
trifluoroacetic acid salt  
IR (KBr) 1782, 1677  $\text{cm}^{-1}$ ; MS (ISP) 387.2 (M+H)<sup>+</sup>

5 **13.3. (E)-(6R,7R)-7-Amino-8-oxo-3-(2-oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid**  
trifluoroacetic acid salt  
IR (KBr) 1787, 1682  $\text{cm}^{-1}$ ; MS (ISP) 387.2 (M+H)<sup>+</sup>

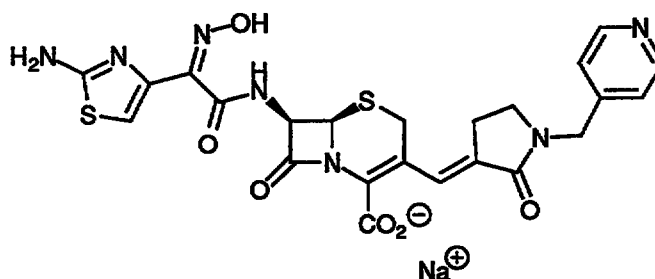
10

### Example 14

preparation (11) → (12), scheme 2

The following compounds were synthesized using the procedure described in example 8. They were converted into their sodium salts by adjusting the aqueous suspension of the acid with 1 N sodium hydroxide solution to pH 6.

15 Purification was accomplished by reversed phase chromatography (MERCK Lichroprep RP-18 silicagel, 25-40 $\mu$ , using a gradient of water with increasing concentrations of acetonitrile).



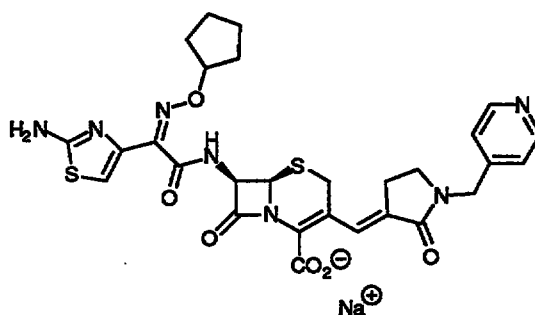
**14.1. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetylamin]-8-oxo-3-[(E)-2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt**  
20 IR (KBr) 1765, 1666  $\text{cm}^{-1}$ ; MS (ISP) 600.3 (M+2Na-H)<sup>+</sup>

**14.2. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetylamin]-8-oxo-3-[(E)-2-oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid**  
25 IR (KBr) 1769, 1666  $\text{cm}^{-1}$ ; MS (ISN) 554.1 (M-H)<sup>-</sup>

**14.3. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetylamin]-8-oxo-3-[(E)-2-oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid**  
30 IR (KBr) 1775, 1668  $\text{cm}^{-1}$ ; MS (ISP) 556.2 (M+H)<sup>+</sup>

### Example 15

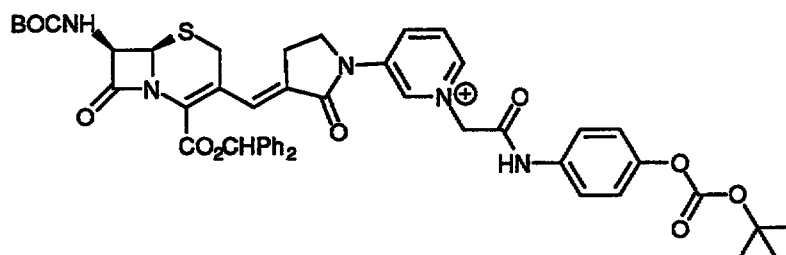
The following compounds were synthesized using the procedure described in example 11. They were converted into their sodium salts by adjusting the aqueous suspension of the acid with 1 N sodium hydroxide solution to pH 6. Purification was accomplished by reversed phase chromatography (MERCK Lichroprep RP-18 silicagel, 25-40 $\mu$ , using a gradient of water with increasing concentrations of acetonitrile).



- 10 **15.1.** (6R,7R)-7-[(Z)-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-8-oxo-3-[(E)-2-oxo-1-pyridin-4-ylmethyl-pyrrolidin-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt  
IR (KBr) 1763 cm<sup>-1</sup>; MS (ISP) 624.3 (M-Na+2H)<sup>+</sup>
- 15 **15.2.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-8-oxo-3-[(E)-(2-oxo-1-pyridin-3-ylmethyl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid sodium salt  
IR (KBr) 1770, 1671 cm<sup>-1</sup>; MS (ISP) 624.2 (M+H)<sup>+</sup>
- 20 **15.3.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-amino]-8-oxo-3-[(E)-2-oxo-1-pyridin-2-ylmethyl-pyrrolidin-3-ylidenemethyl]-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylic acid  
IR (KBr) 1776, 1669 cm<sup>-1</sup>; MS (ISP) 624.2 (M+H)<sup>+</sup>

### Example 16

preparation (6) → (7) scheme 1



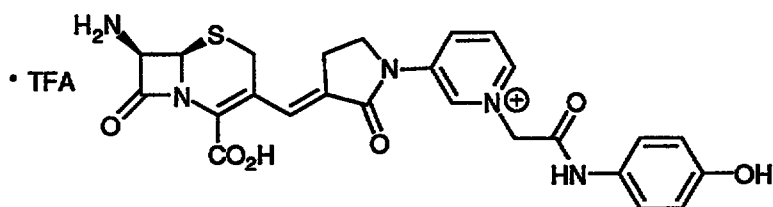
- 5 **16.1. (E)-(6R,7R)-3-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-yl]-1-[(4-tert-butoxycarbonyloxy-phenylcarbamoyl)-methyl]-pyridinium bromide**  
A solution of (E)-(6R,7R)-7-tert-butoxycarbonylamino-8-oxo-3-(2-oxo-1-pyridin-3-yl-pyrrolidin-3-ylidenemethyl)-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-  
10 carboxylic acid benzhydryl ester (see EP 620225-A1) (639 mg, 1.0 mmol) in 10 ml dichloromethane/acetonitrile (1:1) was treated with carbonic acid 4-(2-bromo-acetyl-amino)-phenyl ester tert-butyl ester (494 mg, 1.5 mmol) for 48 h. The solvent was removed *in vacuo* and the residue triturated with diethylether. Yield: 857 mg (88%)  
15 IR(KBr) 1786, 1758  $\text{cm}^{-1}$ ; MS(ISP) 888.4 (M)<sup>+</sup>.

According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

- 16.2. (E)-(6R,7R)-3-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-yl]-1-carbamoylmethyl-pyridinium bromide**  
20 IR (KBr) 1783, 1703  $\text{cm}^{-1}$ ; MS (ISP) 696.4 (M)<sup>+</sup>.
- 16.3. (E)-(6R,7R)-3-[3-(2-Benzhydryloxycarbonyl-7-tert-butoxycarbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-yl]-1-methyl-pyridinium iodide**  
25 IR (KBr) 1782, 1712  $\text{cm}^{-1}$ ; MS (ISP) 653.5 (M)<sup>+</sup>.

### Example 17

preparation (7)→ (8) scheme 1



**17.1. (E)-(6R,7R)-7-Amino-3-[1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-yl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt**

5 A solution of (E)-(6R,7R)-3-[3-(2-benzhydryloxycarbonyl-7-tert-butoxy-carbonylamino-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-en-3-ylmethylene)-2-oxo-pyrrolidin-1-yl]-1-carbamoylmethyl-pyridinium bromide (840 mg, 0.867 mmol) in 10 ml dichloromethane and 0.84 ml anisole was treated at 0-5°C with 4.2 ml trifluoroacetic acid. After stirring for 2 h at room temperature, the mixture was concentrated *in vacuo* and the residue poured on 200 ml cold diethylether. The precipitate was collected by filtration yielding 518 mg (94%) of the product as a beige powder.

IR(KBr) 1776, 1683  $\text{cm}^{-1}$ ; MS(ISP) 522.3 (M+H)<sup>+</sup>.

15 According to the procedure set forth in the preceeding example, the following additional compounds were prepared:

**17.2. (E)-(6R,7R)-7-Amino-3-[1-(1-carbamoylmethyl-pyridin-1-ium-3-yl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate trifluoroacetic acid salt**

IR (KBr) 1780, 1692  $\text{cm}^{-1}$ ; MS (ISP) 430.3 (M+H)<sup>+</sup>

20 **17.3. (E)-(6R,7R)-7-Amino-3-[1-(1-methyl-pyridin-1-ium-3-yl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate**

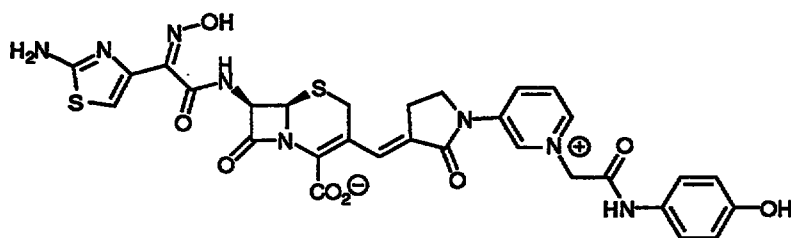
IR (KBr) 1756, 1617  $\text{cm}^{-1}$ ; MS (ISP) 387.4 (M+H)<sup>+</sup>

**Example 18**

preparation (8) → (10) scheme 1

25

The following compounds were synthesized using the procedure described in example 8.



**18.1.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
 [(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-yl]-2-oxo-  
 pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-  
 5 carboxylate  
 IR (KBr) 1769, 1678  $\text{cm}^{-1}$ ; MS (ISP) 691.2 (M+H)<sup>+</sup>

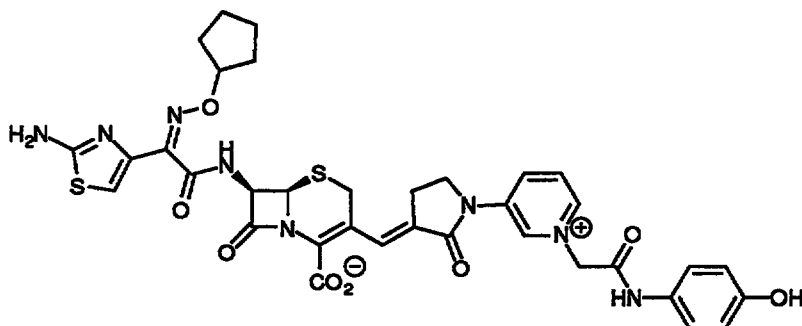
**18.2.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
 [(E)-1-(1-carbamoylmethyl-pyridin-1-ium-3-yl)-2-oxo-pyrrolidin-3-  
 ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
 10 trifluoroacetic acid salt  
 IR (KBr) 1769, 1692  $\text{cm}^{-1}$ ; MS (ISP) 599.3 (M+H)<sup>+</sup>

**18.3.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
 [(E)-1-(1-methyl-pyridin-1-ium-3-yl)-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-  
 5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
 15 IR (KBr) 1767, 1618  $\text{cm}^{-1}$ ; MS (ISP) 556.0 (M+H)<sup>+</sup>

### Example 19

preparation (8) → (10) scheme 1

The following compounds were synthesized using the procedure described in  
 20 example 11.



**19.1.** (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-  
 amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-yl]-  
 2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-

carboxylate

IR (KBr) 1770, 1676  $\text{cm}^{-1}$ ; MS (ISP) 759.5 (M+H)<sup>+</sup>

19.2. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-acetyl-  
amino]-3-[(E)-1-(1-carbamoylmethyl-pyridin-1-ium-3-yl)-2-oxo-pyrrolidin-3-  
5 ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
IR (KBr) 1773, 1688  $\text{cm}^{-1}$ ; MS (ISP) 667.4 (M+H)<sup>+</sup>

19.3. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-cyclopentyloxyimino-  
acetyl-amino]-3-[(E)-1-(1-methyl-pyridin-1-ium-3-yl)-2-oxo-pyrrolidin-3-  
ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate  
10 IR (KBr) 1775, 1679  $\text{cm}^{-1}$ ; MS (ISP) 624.2 (M+H)<sup>+</sup>

### Example 20

20.1. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-  
15 ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
oct-2-ene-2-carboxylate dihydrochloride

To a suspension of (6R,7R)-7-[(Z)-2-(2-amino-thiazol-4-yl)-2-hydroxyimino-  
acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-  
pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-  
20 aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate (578.2 mg, 0.8 mmol) in 32 ml  
methanol was added 1ml of a saturated solution of HCl in diethylether. The  
resulting solution was added with stirring into 500 ml diethylether. The solid  
material was collected by filtration, washed with diethylether and dried.

Yield: 564 mg beige powder

25 Microanalysis: calculated for  $\text{C}_{31}\text{H}_{27}\text{FN}_8\text{O}_8\text{S}_2 \cdot 2 \text{HCl}$   
calc. C 46.80 H 3.67 N 14.08 S 8.06 Cl 8.91  
found C 46.93 H 3.36 N 14.17 S 8.18 Cl 9.02

According to the procedure set forth in the preceeding example, the  
30 following additional compounds were prepared:

20.2. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-  
[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
35 oct-2-ene-2-carboxylate methanesulfonate

Microanalysis: calculated for  $\text{C}_{31}\text{H}_{27}\text{FN}_8\text{O}_8\text{S}_2 \cdot 2 \text{CH}_3\text{SO}_3\text{H}$

calc. C 43.52 H 3.94 N 12.14 S 13.89  
found C 43.61 H 3.66 N 11.93 S 13.95

20.3. (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetylamino]-3-  
5 [(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-  
ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]-  
oct-2-ene-2-carboxylate hydrogensulfate

Microanalysis: calculated for  $C_{31}H_{27}FN_8O_8S_2 \cdot 2 H_2SO_4$

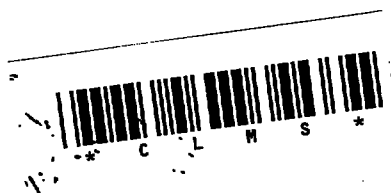
calc. C 40.52 H 3.40 N 12.20 S 13.96  
10 found C 42.02 H 3.42 N 11.99 S 13.96

2

\* \* C L M S \*

2

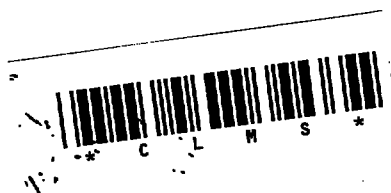
\* \* C L M S \*



2

\* \* C L M S \*

- 2
- \* \* C L M S \*



2

\* \* C L M S \*

2

\* \* C L M S \*

2

\* \* C L M S \*



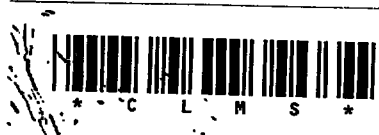
3. Compounds according to claims 1 or 2, wherein R<sup>1</sup> is hydrogen or cyclopentyl.

4. Compounds according to anyone of claims 1 to 3 wherein R<sup>2</sup> is lower alkyl, ω-hydroxy alkyl, benzyl, the benzyl group being unsubstituted or substituted with at least one of the groups cyano, carboxy or hydroxy.

5. Compounds according to anyone of claims 1 to 4 wherein R<sup>2</sup> is -CH<sub>2</sub>CONR<sup>4</sup>R<sup>5</sup> and R<sup>4</sup> is hydrogen and R<sup>5</sup> represents an optionally substituted phenyl.

6. The compounds

- 10 (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate;
- (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-
- 15 amino]-3-[(E)-1-[1-[(4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate;
- (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-
- 20 2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate;
- (6R,7R)-7-[(Z)-2-(5-Amino-[1,2,4]thiadiazol-3-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-
- 25 aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate;
- (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(3-chloro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate;
- 30 (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-[1-[(4-hydroxy-3-methoxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-4-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-carboxylate;
- (6R,7R)-7-[(Z)-2-(2-Amino-thiazol-4-yl)-2-hydroxyimino-acetyl-amino]-3-[(E)-1-
- 35 [1-[(3-fluoro-4-hydroxy-phenylcarbamoyl)-methyl]-pyridin-1-ium-3-ylmethyl]-2-oxo-pyrrolidin-3-ylidenemethyl]-8-oxo-5-thia-1-aza-bicyclo[4.2.0]oct-2-ene-2-



carboxylate;

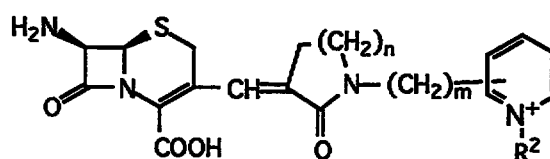
as well as pharmaceutically acceptable salts of this compound and hydrates of said compounds and salts.

7. Compounds as in any one of claims 1 to 6 for use as pharmaceutically active substances, particularly for the treatment and prophylaxis of infectious diseases.

8. Process for the manufacture of the compounds according to any one of claims 1 to 6, which process comprises

(a) treating a compound having the formula II

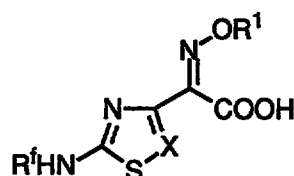
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II

in which  $R^2$ ,  $m$  and  $n$  are as defined in claim 1, or an ester or salt thereof, with a carboxylic acid of the general formula III

15

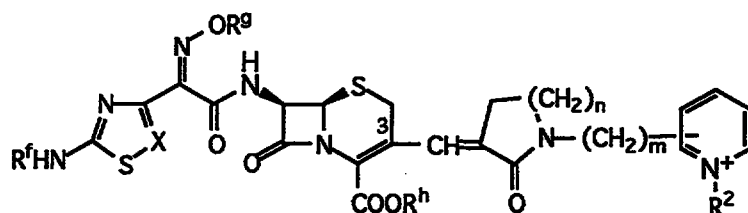


III

in which  $R^f$  is hydrogen or an amino protecting group,  $R^1$  and  $X$  are defined above, or a reactive functional derivative thereof, or

(b) cleaving off the amino, hydroxy and/or carboxy protecting group in a compound having the formula IV

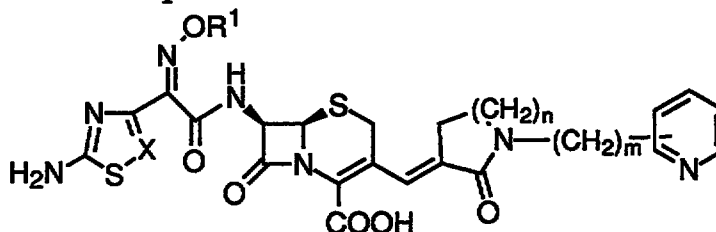
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IV

in which  $R^2$ ,  $m$  and  $n$  are defined above,  $R^f$  is hydrogen or an amino protecting group,  $R^g$  is hydrogen or a hydroxy protecting group,  $R^h$  is hydrogen or a carboxy protecting group, provided that at least one of  $R^f$ ,  $R^g$  and  $R^h$  is a corresponding protecting group or a salt thereof, or

(c) alkylation of a compound of formula



wherein  $R^1$ , X, m and n are as defined above,

5 with a alkylating agent, or

(d) for the manufacture of a readily hydrolysable ester of a compound of formula I subjecting a carboxylic acid of formula I to a corresponding esterification, or

10

(e) for the manufacture of salts or hydrates of a compound of formula I or hydrates of said salts converting a compound of formula I into a salt or hydrate or into a hydrate of said salts.

15 9. A pharmaceutical preparation containing a compound according to any one of claims 1 to 6 and a therapeutically inert carrier, particularly for the treatment and prophylaxis of infectious diseases.

20 10. Compounds according to any one of claims 1 to 6, whenever prepared according to the process claimed in claim 8 or by an obvious chemical equivalent thereof.

11. The use of the compounds according to any one of claims 1 to 6 in the treatment and prophylaxis of infectious diseases or for the manufacture of medicaments for the treatment and prophylaxis of infectious diseases.

25 12. The novel compounds, formulations, processes and methods substantially as described herein.

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