COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT
Melbourne

(1) Here insert (in full) Name or Names of Applicants, followed by Address (a).

We

Hoechst UK Limited

of Hoechst House, Salisbury Road, Hounslow Middlesex

TW 6JH, Great Britain

&

hereby apply for the grant of a Patent for an invention entitled:

(2)

7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPT-2-ENE DERIVATIVES

which is described in the accompanying complete specification. This application is a

Convention application and is based on the application numbered

(3)

8520631

for a patent or similar protection made in

(4) United Kingdom

on 16th August 1985

My address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys,

50 Queen Street, Melbourne, Victoria, Australia.

DATED this 14th day of August 1986,

(5)

Hoechst UK Limited

By

James Murray

Registered Patent Attorney

To:

THE COMMISSIONER OF PATENTS
In support of the Convention application made under Part XVI.
of the Patents Act 1952 by HOECHST UK LIMITED, Hoechst House,
Salisbury Road, Hounslow Middx. TW4 6JH, Great Britain for a
patent for an invention entitled:

7-OXO-4-THIA-1 AZABICYCLO[3.2.0]HEPT-2-ENE DERIVATIVES

I, Kenneth Frederick Kinch, Secretary of Hoechst UK Limited
of Hoechst House, Salisbury Road, Hounslow Middx. TW4 6JH
Great Britain
do solemnly and sincerely declare as follows:

1. I am authorized by HOECHST UK LIMITED the applicant
for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was
made in Great Britain
under No. 8520631 on August 16, 1985
by HOECHST UK LIMITED

3. a) Michael David Cooke, 10 Westbury Lane, Newport Pagnell, Bucks.
   b) Stephen Connolly, 19 Page Hill Avenue, Buckingham, Bucks.
   a) and b) Great Britain

4. The basic application referred to in paragraph 2 of this
   Declaration was the first application made in a Convention
country in respect of the invention the subject of the application.

DECLARED at Hounslow
this 1st day of July 1986

To the Commissioner of Patents

PAT 510
1. A compound of formula I

in which

R represents a hydrogen atom or a carboxylic acid esterifying group;

R¹ represents

(i) one of the following groups
(11) AU-A-61510/86

in which Ra and Rb, which may be the same or different, each represents an alkyl group having from 1 to 4 carbon atoms, or

(ii) a \( \text{CONH(CH}_2\text{)}_m\text{Q} \) or \( \text{NECO(CH}_2\text{)}_m\text{Q} \) group in which

\( m \)

represents an integer of from 1 to 3, and

Q represents one of the following groups

- \( \text{CONH}_2 \)
- \( \text{CONHCH}_3 \)
- \( \text{CONHOH} \)
- \( \text{SO}_2\text{Rc} \)
- \( \text{CH}_3 \)
- \( \text{NHRC} \)
- \( \text{OCNH}_2 \)
- \( \text{NHCH=NH} \)
- \( \text{NHC=NH} \)
- \( \text{SO}_2\text{NH}_2 \)

\( \text{SCH}_3 \)

\( \text{NHRc} \)

\( \text{Rc} \)

S

in which \( \text{Rc} \) represents a methyl or ethyl group, or

(iii) a \( \text{CO}_2\text{Rd} \) group, in which \( \text{Rd} \) represents a methyl or ethyl group which is unsubstituted or is substituted by one or more substituents, which may be the same or different; selected from

(a) halogen atoms and vinyl groups,

(b) phenyl groups which are unsubstituted or are substituted by one or more groups selected from alkoxy groups having from 1 to 4 carbon atoms, nitro groups and halogen atoms,

(c) silyl groups \( \text{SiR}_e\text{R}_f\text{R}_g \), the groups \( \text{R}_e, \text{R}_f \) and \( \text{R}_g \) being the same or different, each representing a phenyl group or an alkyl group having from 1 to 4 carbon atoms, and

(d) groups Q as defined above; or

(iv) a \( \text{CO}_2\text{SiR}_e\text{R}_f\text{R}_g \) group, in which \( \text{R}_e, \text{R}_f \) and \( \text{R}_g \) are defined as in (c) above, or

(v) a \( \text{CO}_2\text{-phenyl} \)

group, in which the phenyl moiety is unsubstituted or substituted as defined in (b) above;

\( \text{R}_2 \)

represents (i) a hydrogen atom,
(ii) a group as defined above for $R^1$ ($R^1$ and $R^2$ being the same or different), or
(iii) a chlorine, bromine or iodine atom, an alkyl group having from 1 to 4 carbon atoms, an $-\text{NH}_2$, $-\text{NRa}$ or $-\text{NHaRb}$ group, an $-\text{OH}$ or $-\text{ORa}$ group, or an $-\text{OCOCH}_3$ group, Ra and Rb being defined as above, and

$R^3$ represents a hydrogen atom or a hydroxy protecting group; and in which $R^1$ and $R^2$, independently of each other, may be present at any position on the phenyl ring; and salts thereof, especially physiologically tolerable salts; and isomers thereof.

20. A compound of formula II

$$
\begin{align*}
&\text{II} & \text{O} & \text{H} & \text{H} & \text{R}^3 & \text{O} & \text{OOC} & \text{R}^4 & \text{R}^5 & \text{R}^6 & \text{R}^7
\end{align*}
$$

in which $R^3$ is defined in claim 1 and $R^4$, $R^5$, $R^6$, $R^7$ and $R^8$ are as defined in claim 8.

21. A compound of formula XXVII

$$
\begin{align*}
&\text{XXVII} & \text{O} & \text{H} & \text{H} & \text{SR}^9 & \text{N} & \text{R}^4 & \text{OOC} & \text{R}^5 & \text{R}^6 & \text{R}^7
\end{align*}
$$

in which $R^3$ is as defined in claim 1, $R^4$, $R^5$ and $R^6$ are as defined in claim 12,
R³ is an alkyl group having 1 to 8 carbon atoms, an alkenyl group having 2 to 4 carbon atoms, or a phenyl group, and Ry is SCOR⁷, OH or OR¹⁰ in which R⁷ is as defined in claim 12 and R¹⁰ is a group -SO₂Rh or -CORh in which Rh is an alkyl group having from 1 to 4 carbon atoms, an optionally substituted phenyl group, or a polyfluoroalkyl group.

22. A compound of formula XXVIII

\[
\text{XXVIII}
\]

in which Rₓ is H or a group

\[
\begin{align*}
\text{P(Z)}_3 & \quad \text{COOR}^4 \\
\text{COOR}^4 & \quad \text{CH}\sim\text{R}^8 \\
\text{COOR}^4 & \quad \text{CH}\sim\text{Bh}
\end{align*}
\]

in which

R³ is as defined in claim 1,
X, R⁴, R⁵, R⁶, R⁷, R⁸, and P(Z)₃ are as defined in claim 12.
COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952-

COMPLETE SPECIFICATION
(ORIGINAL)

Application Number: 61510/86

Class

Int. Class

Complete Specification Lodged:

Accepted:

Published:

Priority:

Related Art:

Name of Applicant: HOECHST UK LIMITED

Address of Applicant: Hoechst House, Salisbury Road, Hounslow, Middlesex TW4 6JH, Great Britain

Actual Inventor: MICHAEL DAVID COOKE, and STEPHEN CONNOLLY

Address for Service: EDWD. WATERS & SONS, 50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

7-OXO-4-THIA-1-AZABICYCLO[3.2.0]HEPT-2-ENE DERIVATIVES

The following statement is a full description of this invention, including the best method of performing it known to us.

1.
This invention relates to 7-oxo-4-thia-1-azabicyclo[3,2,0]hept-2-ene derivatives, to a process for their preparation, to pharmaceutical preparations comprising them, and to intermediates for use in the preparation of substances having antibacterial activity and/or \( \beta \)-lactamase inhibitory and/or inactivating activity.

The penicillins as a class have in common the \( \beta \)-lactam structure A known semi-systematically as the "penam" nucleus. The introduction of a double bond between carbon atoms 2 and 3 in this structure gives rise to the "penem" nucleus B.

The penem nucleus B is given the systematic name "7-oxo-4-thia-1-azabicyclo[3,2,0]hept-2-ene", with the numbering as shown in formula C. A side chain at position 6 is numbered as shown in formula D.

It is well known that penicillin antibiotics have been used extensively for many years to combat bacterial infections in humans and other animals. The first of the penicillin antibiotics to come into general therapeutic use was benzylpenicillin, and this compound still finds widespread use today.

There is, however, a continuing need for new antibiotics, not only to combat bacterial pathogens that do not respond satisfactorily to treatment with conventional penicillins, but also to combat those strains of bacteria which, although once susceptible to penicillin treatment, are now resistant to such therapy. Accordingly, in the search for new types of antibiotics, the discovery of compounds which possess a wide spectrum of activity together with an ability to combat infections caused by penicillin-resistant organisms is an important goal.
Various specifications disclose penem derivatives having a phenyl or substituted phenyl group at the 2-position. EP 0 002 210A describes penem derivatives having a wide selection of substituents at the 2- and 6-positions, as does GB 2 042 515A. EP 0 002 210A includes in a Table of compounds those having a 1-hydroxyethyl group at position 6 and a phenyl, aminomethylphenyl, aminophenyl or trifluoromethylphenyl group at position 2. GB 2 042 515A similarly includes in a Table of compounds a 6-hydroxyethyl penem derivative having a phenyl group at position 2, that phenyl group being unsubstituted. EP 0 070 204A discloses penems with certain very specific substituted phenyl groups at the 2-position in combination with a hydrogen atom or an optionally protected hydroxyethyl group at position 6. Those Examples that relate to substituted phenyl groups at position 2 do so in combination with a hydrogen atom at position 6.

We have made and tested certain 6-hydroxyethyl-2-substituted phenyl derivatives disclosed generally in the prior art, and we have found that although they have activity in a representative antibacterial screen, there remains a need for compounds having higher activities.

The present invention provides a compound of formula I

\[
\text{CH}_3\text{CH}-\text{S}-\text{R}^1-\text{R}^2-\text{COOR}
\]

in which
\( R \) represents a hydrogen atom or a carboxylic acid esterifying group;
\( R^1 \) represents

(i) one of the following groups

\[
\begin{align*}
\text{-CN} & \quad \text{-CONH}_2 \\
\text{-NO}_2 & \quad \text{-CONHR} \\
\text{-NHCO}_2 & \quad \text{-CONHHR} \\
\text{-SO}_2NH_2 & \quad \text{-CONHR}_1RH_2 \\
\text{-SO}_2NH & \quad \text{-CONHR}_1RHR_2 \\
\text{-SO}_2NRH & \quad \text{-CONHR}_1RHR_3 \\
\text{-SO}_2NRHR & \quad \text{-CONHR}_1RHR_4 \\
\end{align*}
\]

Such groups may be removed by acid hydrolysis, for example, using 0.1 to 2M, preferably 0.5M hydrochloric acid.
in which Ra and Rb, which may be the same or different, each represents an alkyl group having from 1 to 4 carbon atoms, or

(ii) a -CONH(CH₂)ₘQ or -NHCO(CH₂)ₘQ group, in which

<table>
<thead>
<tr>
<th>Ra</th>
<th>Rb</th>
</tr>
</thead>
<tbody>
<tr>
<td>-CN</td>
<td>-SO₂NH₂</td>
</tr>
<tr>
<td>-SO₃Rc</td>
<td>-SO₂Rc</td>
</tr>
<tr>
<td>-NH₂</td>
<td>-NHCH=NH</td>
</tr>
<tr>
<td>-CONH₂</td>
<td>-CONHCH₃</td>
</tr>
<tr>
<td>-NHRC</td>
<td>-OCNH₂</td>
</tr>
</tbody>
</table>

in which Rb represents a methyl or ethyl group, or

(iii) a -CO₂Rd group, in which Rd represents a methyl or ethyl group which is unsubstituted or is substituted by one or more substituents, which may be the same or different, selected from

(a) halogen atoms and vinyl groups,
(b) phenyl groups which are unsubstituted or are substituted by one or more groups selected from alkoxy groups having from 1 to 4 carbon atoms, nitro groups and halogen atoms,
(c) silyl groups SiReRfRg, the groups Re, Rf and Rg being the same or different, each representing a phenyl group or an alkyl group having from 1 to 4 carbon atoms, and
(d) groups Q as defined above; or

(iv) a -CO₂SiReRfRg group, in which Re, Rf and Rg are
defined as in (c) above, or (v) a -CO₂-phenyl group, in which the phenyl moiety is unsubstituted or substituted as defined in (b) above;

R² represents (i) a hydrogen atom,

(ii) a group as defined above for R¹ (R¹ and R² being the same or different), or

(iii) a chlorine, bromine or iodine atom, an alkyl group having from 1 to 4 carbon atoms, an -NH₂, -NRa or -NRaRb group, an -OH or -ORa group, or an -OCOC₃ group,

Ra and Rb being defined as above, and

R³ represents a hydrogen atom or a hydroxy protecting group; and in which R¹ and R², independently of each other, may be in any position on the phenyl ring; and salts thereof; and isomers thereof.

In a compound of formula I, a protected carboxy group -COOR is preferably an esterified carboxy group that can be converted by hydrolysis, by photolysis, by oxidation, by reduction or, especially, by esterase enzyme action, to give the free acid of formula I. Moreover, in a compound of formula I, a hydroxy protecting group R³ is preferably a group that can be converted by hydrolysis, by photolysis, by reduction or, especially, by esterase enzyme action, to give a compound of formula I having a free 8-hydroxy group.

Details of such carboxy and hydroxy protecting groups are given below.

Groups that can be removed by esterase action are groups that can be cleaved in vivo. Compounds having such groups are known as "prodrugs". Preferred compounds of formula I are those in which, independently, R represents a hydrogen atom, a physiologically tolerable salt-forming group, or a group that can be cleaved in vivo to give the free carboxy group or a carboxylate group, and R³ represents a hydrogen atom or a group that can be cleaved in vivo to give the free hydroxy group.

The present invention provides salts of a compound of formula I, especially physiologically tolerable salts thereof. A salt may be formed at the 2-carboxylic acid group or at any acidic or basic centre present. Moreover,
when both an acidic centre and a basic centre are present, a compound of formula I may exist in a zwitterionic form. A carboxylic acid salt of a compound of formula I is preferable to the free acid if solubility is important.

In the definitions of \( R^1 \) and \( R^2 \), an alkyl group \( R^a \) or \( R^b \) is preferably a methyl or ethyl group, especially a methyl group. The symbol "m" preferably denotes the integer 1 or 2.

Of the groups \( R^1 \) given above, the following are preferred:

\[
\begin{align*}
-\text{CONH}_2 & \quad -\text{CONH}R^a & \quad -\text{NHCO(CH}_2\text{)}_m\text{Q} \\
-\text{CONH(CH}_2\text{)}_m\text{Q} & \quad -\text{NHCNH}_2 & \quad -\text{CNH}_2 \\
-\text{NHCHO} & \quad -\text{NHCOR}^a & \\
-\text{SOR}^a & \quad -\text{SO}_2\text{NH}_2 & \quad -\text{SO}_2\text{NH}R^a
\end{align*}
\]

\( R^a, Q \) and \( m \) being as defined above, and especially having the preferred meanings given above. Particularly preferred as \( R^1 \) are \(-\text{CONH}_2, -\text{CONHCH}_3, -\text{NHCHO} \) and \(-\text{NHCOCH}_3 \) groups.

A compound of formula I may exist in various isomeric forms, all of which are part of the present invention, for example, a substituent \( R^1 \) may be present at any position on the phenyl ring when \( R^2 \) represents a hydrogen atom. When \( R^2 \) represents other than a hydrogen atom, \( R^1 \) and \( R^2 \) may occupy any two positions on the ring, subject to known constraints regarding, for example, stereochemical considerations. Moreover, some substituents \( R^1 \) and \( R^2 \) may themselves exist in various tautomeric and/or geometric isomeric forms, for example, an oxime may be in \textit{syn} or \textit{anti} form. As mentioned above, all isomers are part of the present invention.

The stereochemistry at positions 5, 6 and 8 of a compound of formula I can be \( R \) or \( S \), independently (\( R \) and \( S \) being as defined by the Cahn-Ingold-Prelog system of nomenclature). The preferred stereochemistry at position 5 is \( R \), at position 6 is \( S \), and at position 8 is \( R \). 5R, 6S, 8R-stereochemistry is particularly preferred.

The present invention also provides a process for the production of a compound of formula I, which comprises (A) treating a compound of formula II
in which $R^3$ is as defined above,

$R^4$ represents a carboxy protecting group,

$R^5$ represents a group $R^1$ as defined above or a group that
can be converted into a group $R^1$,

$R^6$ represents a group $R^2$ as defined above or a group that
can be converted into a group $R^2$,

$R^7$ represents a phenyl group or an alkyl group having from 1 to 4 carbon atoms, and

$R^8$ represents a bromine or chlorine atom, especially a
carbon atom,

with a base; or

(B) effecting cyclisation of a compound of formula III

\[
\begin{align*}
\text{CH}_3 \text{CH} & \text{CH}\text{NH} \text{SCOR}^7 \\
\text{R}^6 \text{DOC} & \text{R}^5 \text{R}^7
\end{align*}
\]

(III)

in which $R^3$, $R^4$, $R^5$ and $R^6$ are defined as above, $X$
represents an oxygen or sulphur atom, and the group $P\{Z\}_3$
represents a group derived from a trivalent organo-
phosphorus reagent, or

(C) treating a compound of formula IV or V

\[
\begin{align*}
\text{CH}_3 \text{CH} & \text{CH}\text{NH} \text{SCOR}^7 \\
\text{R}^6 \text{DOC} & \text{R}^5 \text{R}^7
\end{align*}
\]

(IV)

(\text{V})

in which $X$, $R^3$, $R^4$, $R^5$, $R^6$ and $R^8$ are defined as above,
with a trivalent organophosphorus compound and effecting
cyclisation, or

an ether, for example, diethyl ether, dioxane or
(D) reacting a compound of formula VI

![Chemical Structure VI](image)

in which $R^3$, $R^4$ and the group $P(Z)_3$ are defined as above, and $R^{19}$ represents Cu(II), Pb(II) or Hg(II), in which case $n$ represents 2, or $R^{19}$ represents Ag(I), in which case $n$ represents 1, with a compound of formula VII

![Chemical Structure VII](image)

in which $R^{11}$ represents an activating group, for example, an activating ester group or, preferably a halogen atom, and especially a chlorine atom, and $X$, $R^5$ and $R^6$ are defined as above, and effecting cyclisation, and

(E) in an appropriate compound in which $R^5$ and/or $R^6$ represent a group that can be converted into a group $R^1$ and/or $R^2$, respectively, converting such a group or groups $R^5$ and/or $R^6$ into such a group or groups $R^1$ and/or $R^2$ and,

(F) if desired or required, in an appropriate compound converting a group $R^1$ and/or a group $R^2$ into another group $R^1$ and/or $R^2$, respectively; and

(G) if desired or required, carrying out any one or more of the following steps in any desired order:

a) hydrolysing a 2-carboxylic ester group in an appropriate compound to give the corresponding free acid,

b) treating an appropriate free acid or a salt thereof with an agent capable of forming a 2-carboxylic acid ester, for example, with an alcohol, a phenol or a reactive derivative thereof, to give a 2-carboxylic acid ester thereof,

c) carrying out an acid- or base-catalysed ester interchange on an appropriate 2-carboxylic acid ester to give a different ester of that compound,

d) treating an appropriate free acid compound with a base
to give a salt at the carboxy group at position 2,
e) treating an appropriate free acid or 2-carboxylic acid
ester having a basic group present with an acid to give an
acid addition salt thereof,
f) treating a salt of an appropriate compound with an acid
to give a free acid of that compound,
g) removing a hydroxy protecting group from an appropriate
compound having a protected 8-hydroxy group to give the
responding compound having a free 8-hydroxy group,
h) treating an appropriate compound having a free hydroxy
group at the 8-position with an organic acid derivative to
form an ester at the 8-position, and
i) treating an appropriate compound to effect a change in
the stereochemical configuration.

In formula I, R³ may represent a hydrogen atom or a
protecting group. In certain of the processes involved in
the production of a compound of formula I, it may be
preferable to protect the 8-hydroxy group. Similarly, it
may be preferable or essential to protect the 2-carboxy
group during the formation of a compound of formula I.
Hydroxy and carboxy protecting groups and methods for their
introduction and removal are known (that is to say, in
actual use in the art or described in the literature of the
art) see, for example, McOmie, Protecting Groups in Organic
Chemistry, Plenum Press, London, 1973 and T.W. Greene,
Protective Groups in Organic Synthesis, J. Wiley & Sons
Inc. 1981. Hydroxy and carboxy protecting groups
preferably used in the present invention and methods for
their introduction and removal are described in more detail
below.

Hydroxy and carboxy protecting groups may be present
independently of each other in a compound of formula I or
in any intermediate involved in the formation thereof.
Moreover, protecting groups may be introduced and removed
at any appropriate point in a reaction sequence.

A compound of formula II is treated with a base to
give a compound of formula I or a precursor thereof. The

- 8 -

- 21a -
The carboxy group in the compound of formula I is protected, but the hydroxy group may be free or protected. The base may be inorganic or organic, for example, ammonia, or an alkali metal, especially a sodium or potassium, carbonate, bicarbonate, or hydroxide; a primary amine, for example, methylamine, ethylamine, aniline or benzylamine; an alkali metal alkoxide, for example, sodium methoxide; or a heterocyclic base, for example, having a pK\textsubscript{a} within the range of from 5 to 9, for example, imidazole, pyridine or a substituted pyridine, for example, an alkyl-, amino-, monoalkylamino- or dialkylamino-substituted pyridine, for example, 4-methylpyridine or 4-dimethylaminopyridine. Imidazole is particularly preferred.

The reaction is generally carried out in a solvent or diluent, the choice of which is wide, provided that it is inert under the reaction conditions. Examples of solvents and diluents are oxygenated hydrocarbons, for example, ethers, for example, having up to 4 carbon atoms, for example, diethyl ether, also tetrahydrofuran and dioxane; ketones, for example, having up to 4 carbon atoms, for example, acetone and methyl ethyl ketone; esters, for example, methyl acetate and ethyl acetate; and amides, for example, dimethylformamide and dimethylacetamide; also chlorinated hydrocarbons, for example, chloroform, methylene chloride and carbon tetrachloride; aromatic hydrocarbons, for example, benzene and toluene; and other solvents for example, acetonitrile and nitromethane. A mixture of two or more solvents may be used, and solvents are preferably used in admixture with water; preferably a water-miscible solvent is used in admixture with 5 to 20\% (v/v) water.

The reaction is generally carried out at a temperature within the range of from 0 to 40°C, preferably from 0 to 20°C.

A compound of formula Ia, that is to say, a compound analogous to compound I but having groups R\textsuperscript{5} and R\textsuperscript{6}, may be prepared as shown in the following Reaction Scheme I:
REACTION SCHEME I

from 1 to 4 carbon atoms, for example, C6-furane.
in which \( R^3, R^4, R^5, R^6, R^7 \) and \( R^8 \) are defined as above, 
\( R^9 \) represents an alkyl group having from 1 to 8, preferably from 1 to 4 carbon atoms, an alkenyl group having from 2 to 4 carbon atoms, or a phenyl group, and 
\( R^{10} \) represents a group \(-SO_2-Rh\) or \(-CORh\) in which Rh represents an alkyl group having from 1 to 4 carbon atoms, an optionally substituted phenyl group, or a polyfluoralkyl group, especially a trifluoromethyl group.

Some compounds of formula VIII are known, see for example, GB 2 102 798A and Belgian Patent 887,886. Other compounds of formula VIII may be prepared analogously.

To obtain compound IX, compound VIII is reacted, in the presence of a base, with an activated carboxylic acid derivative of formula VIIa

\[
\text{(VIIa)}
\]

in which \( R^5, R^6 \) and \( R^{11} \) are as defined above.

Many compounds of formula VIIa are known, and the others may be prepared by methods analogous to those described for the preparation of the known compounds, see for example, Organic Syntheses, Collective Volume 4, page 715, Wiley, New York, 1963, or Collective Volume 2, page 328, 1943.

The reaction between compound VIII and compound VIIa is carried out in the presence of a base, preferably having a \( pK_a \approx 20 \), preferably a metallated amine, and examples of preferred bases are lithium diisopropylamide, lithium hexamethyldisilazide, lithium 2,2,6,6-tetramethylpiperidide, lithium cyclohexyl isopropylamide, and sodamide.

The reaction is generally carried out in an aprotic solvent, for example, an oxygenated hydrocarbon, preferably an ether, for example, diethyl ether, tetrahydrofuran, dioxane, glyme or diglyme. The reaction temperature is,
for example, from -120 to +30°C, preferably from -78 to  
-20°C.

The amount of base used is, for example, from 1 to 3  
moles, calculated per mole of compound VIII, preferably  
from 1.5 to 2.5 moles of base. The compound of formula  
VIIa is preferably used in an amount of from 1 to 1.5 moles  
per mole of compound VIII, preferably from 1 to 1.1 moles  
of compound VIIa per mole of compound VIII.

The reaction may be carried out as follows: The base  
may be added to a stirred solution of compounds VIII and  
VIIa. Alternatively, to a stirred solution of compound  
VIII under an inert atmosphere is added the base and  
subsequently a solution of compound VIIa in the same or a  
different solvent.

Compound IX is generally obtained in the form of a  
mixture of isomers generally comprising the E, Z and oxo  
isomers. Such isomers may be separated, but this is not  
generally necessary. (The terms E and Z are as defined on  
page 142 of Allinger et al., "Organic Chemistry" 1971,  
Worth, New York.)

Compound IX is reacted, in the presence of a base,  
with a compound of formula XII

\[ R^{10} - R^{11} \] (XII)  

in which \( R^{10} \) is as defined above, and represents, for  
example, a methylsulphonyl, phenylsulphonyl or poly-  
fluoroalkylsulphonyl group, especially a trifluoromethyl-  
sulphonyl group, or a trifluoroacety group and \( R^{11} \)  
represents an activating group as defined above, to produce  
a compound of formula X.

The base used in the reaction between compounds IX and  
XII may be organic or inorganic and is, for example, a  
tertiary amine, for example, a trialkylamine, especially  
triethylamine or ethyldiisopropylamine, or a heterocyclic  
base, for example, pyridine or an alkyl-, dialkyl-, amino,  
monoalkylamino- or dialkylamino-substituted pyridine, for
example, 4-dimethylaminopyridine. The reaction is generally carried out in a solvent or diluent, for example, a chlorinated hydrocarbon, for example, dichloromethane, an ether, for example, diethyl ether or tetrahydrofuran, or an ester, for example, ethyl acetate. The temperature of the reaction is generally within the range of from -80 to +20°C. Compound X is generally produced in the form of a mixture of isomers generally comprising the E- and Z-isomers. Such isomers may be separated, but this is not generally necessary.

Compound X is converted into compound XI by reaction with a compound of formula XIII

\[
R^7\text{COSH}
\]  

(XIII)

in which \(R^7\) is as defined above and preferably represents a methyl or, especially, t-butyl group. Compound XIII is preferably in the form of a reactive derivative thereof, for example, as an alkali metal, alkaline earth metal or organic amine salt. Compound XIII may be converted into salt form in situ.

The reaction between compound X and compound XIII is generally carried out in a polar solvent, for example, acetonitrile, dimethylformamide or dimethyl sulfoxide. The reaction temperature is generally within the range of from 0 to 40°C, conveniently room temperature.

The \(-\text{SCOR}_4\) group in the resulting compound of formula XI may be E or Z to the \(-\text{COOR}_4\) group. The isomers may be separated for the subsequent reaction, but this is not generally necessary, and the isomeric mixture is generally used as both isomers give a compound of formula I.

The resulting compound XI is then halogenated to give a compound of formula II, using an agent capable of splitting a carbon-sulphur bond and of introducing a halogen atom. Such agents are well known in the art and include, for example, molecular chlorine, sulphuryl
chloride, t-butyl hypochlorite, cyanogen chloride and molecular bromine.

The reaction is generally carried out at a temperature within the range of from -60 to +20°C. The reaction is generally carried out in a solvent or diluent that is non-protic, and is inert under the reaction conditions, for example, an ether, a hydrocarbon or a halogenated hydrocarbon, for example, dioxane, benzene, chloroform or dichloromethane. A mixture of two or more solvents may be used. Examples of halogenating systems are: chlorine in chloroform, chlorine in benzene and t-butyl hypochlorite in benzene. In the latter two cases, the temperature is preferably from 5 to 20°C, and normally from 5 to 10°C. Generally, 1 to 2 moles of the halogenating agent are used per mole of compound VIIa, cf. S. Kukolja, J. Amer. Chem. Soc. (1971), 93, 6267 and P.C. Cherry, C.E. Newall and N.S. Watson, J.C.S. Chem. Comm. 1979 p. 663.

The resulting compound of formula II may be converted into a compound of formula I as described above.

In the Reaction Scheme I described above, it is preferable that the 8-hydroxy group in compound VIII is protected, to prevent it from reacting with the activated acid derivative of formula VIIa. The hydroxy group is also preferably protected during the reaction between compound IX and compound XII. A hydroxy protecting group may be retained in compounds XI and II, but it has been found that if a compound of formula XI having S-stereochemistry at position 3 and having a protected hydroxy group at position 8 is halogenated, the resulting compound of formula I has the less desirable 5S stereochemistry, and it is then necessary to change the stereochemistry at position 5, for example, by heating under reflux, if the 5R stereochemistry is wanted.

Accordingly, it is generally preferable to protect the 8-hydroxy group until compound X has been formed, and to remove the hydroxy protecting group before halogenating compound XI to give compound II. A hydroxy protecting
group may be removed from compound X before it is converted into compound XI, or it may be removed after formation of compound XI.

One type of preferred protected group \(-\text{OR}^3\) is that from which the protecting group \(\text{R}^3\) can be removed under acidic conditions. Such protected groups are well known in the art and are, for example, tetrahydropyranloxy and tetrahydrofuranyloxy groups; acetal and ketal groups, for example, of formula

\[
\begin{align*}
\text{OR}^4 \\
\text{O-} & - \text{C-} \text{R}^3 \\
\text{R}^2
\end{align*}
\]

in which \(\text{R}^{12}\) and \(\text{R}^{13}\), which may be the same or different, each represents a hydrogen atom or a lower alkyl group, preferably a methyl group, or \(\text{R}^{12}\) and \(\text{R}^{13}\) together with the carbon atoms to which they are attached, represent a cycloalkyl ring having from 4 to 7 carbon atoms, and \(\text{R}^{14}\) represents a lower alkyl group, preferably a methyl or ethyl group, or \(\text{R}^{12}\) and \(\text{R}^{14}\), together with the carbon atom and the oxygen atom to which they are attached, respectively, represent a tetrahydropyranyl ring; also silyl ethers, for example, having three substituents on the silicon atom, and preferably up to 24 carbon atoms in total, the three substituents being the same or different, and selected from alkoxy, alkenyl and cycloalkyl groups, and phenyl and rhenalkyl groups which may be unsubstituted or substituted as defined above, for example, \(-\text{OSiReRfRg}\) groups, in which \(\text{Re}, \text{Rf}\) and \(\text{Rg}\) are as defined above, that is to say, they may be the same or different, and each represents an alkyl group having from 1 to 4 carbon atoms or a phenyl group, for example, giving trimethylsilyloxy, triethylsilyloxy, diphenyl-t-butyilsilyloxy, dimethyl-t-butyilsilyloxy, and methyldiphenylsilyloxy groups.

Prefered hydroxy protecting groups \(\text{R}^3\) are tetrahydropyranyl, 2-methoxyprop-2-yl, trimethylsilyl and, especially, triethylsilyl and t-butyldimethylsilyl groups.

A compound of formula Ia may be produced from a compound of formula III, IV, V or VI, as shown in the following Reaction Scheme II:

A compound of formula III will cyclise to give a compound of formula I at room temperature if left for sufficient time, but generally heat is applied to accelerate the reaction. The cyclisation is preferably carried out in a solvent, for example, an ether, for example, diethyl ether, dioxane or tetrahydrofuran, an aromatic hydrocarbon, for example, benzene, toluene or xylene, a halogenated hydrocarbon, for example, chloroform or dichloromethane, or dimethylformamide or dimethyl sulfoxide. The temperature used may be from room temperature to the reflux temperature of the reaction mixture.

A compound of formula III may be produced from a compound of formula IV, V or VI, as shown in Reaction Scheme II, and may be isolated, if desired. Each of compounds IV, V and VI may, however, give a compound of formula Ia directly, also as shown in Reaction Scheme II.

In general, if a compound of formula IV, V or VI is reacted at lower temperatures, a compound of formula III is formed, and may be isolated and then preferably heated as described above to give a compound of formula Ia. If higher reaction temperatures are used, a compound of formula Ia is the reaction product obtained. The latter reaction may proceed via a compound of formula III or via another intermediate. Further details of these procedures are given below.
REACTION SCHEME II

(XIV) → (XV) → (XVI)

(IV) → (V) → (III) → (Ia)

(VI)
In Reaction Scheme II $R^3$, $R^4$, $R^5$, $R^6$, $R^8$, $X$ and $Z$ are defined as above, and $L$ represents a leaving group, that is to say, a group that can be replaced in a nucleophilic displacement reaction, for example, a halogen atom, especially a chlorine atom; an alkylcarbonyloxy group in which the alkyl moiety has from 1 to 4 carbon atoms, has a straight or branched chain, and may be substituted by an electron-withdrawing group, for example, a halogen atom, especially a fluorine atom, for example, an acetoxy or trifluoroacetoxy group; a phenylcarbonyloxy group, for example a benzyloxy group; or an $-\text{SO}_2\text{R}_j$ group in which $\text{R}_j$ represents an alkyl group having from 1 to 4 carbon atoms or a phenyl group. $L$ preferably represents an acetoxy group.

Certain compounds of formula XIV are known, for example, when $R^3$ represents a dimethyl-t-butylsilyloxy group (Belgian Patent Specification No. 882 764), and when $R^3$ represents a p-nitrobenzylcarbonyl group (EP 0 002 210A). Other compounds of formula XIV may be prepared analogously.

A compound of formula XV may be prepared by reacting a compound of formula XIV with a compound of formula XVII

\[
\text{MS} - \text{C} - \text{R}^5 - \text{R}^6
\]

(XVII)

in which $X$, $R^5$ and $R^6$ are defined as above, and $M$ represents a hydrogen atom or an alkali metal or alkaline earth metal atom, or an ammonium group that is unsubstituted or substituted by, for example, one to four groups selected from alkyl groups having from 1 to 4 carbon atoms. (When $M$ represents hydrogen the reaction is carried out in the presence of a base, see below).

Compound XVII is generally prepared in situ and is not generally isolated before reaction with compound XIV.

A compound XVII may be prepared (i) by reacting a compound of formula VII.
in which \( X, R^5, R^6 \) and \( R^{11} \) are defined as above, with a compound of formula \( MSH \) or \( M_2S \), in which \( M \) is as defined above, (when \( M \) represents hydrogen the reaction is carried out in the presence of a base, for example, pyridine or a tri-alkylamine in which each alkyl moiety has from 1 to 4 carbon atoms); or

(ii) by reacting a compound of formula XVIII

In each of the processes (i) and (ii) above, the reaction is generally carried out in a solvent that is inert under the reaction conditions, for example, in
an ether, for example, diethyl ether, dioxane or tetrahydrofuran, an aromatic hydrocarbon, for example, benzene, toluene or xylene, or a halogenated hydrocarbon, for example, chloroform, carbon tetrachloride or dichloromethane.

A compound of formula XV is then acylated using a compound of formula XIX

\[
\begin{align*}
\text{COR}^5 \\
\text{COOR}^4
\end{align*}
\]

in which \( R^4 \) is as defined above and \( R^{15} \) represents a group that can be displaced by the azetidinone nitrogen in the compound of formula XV to give a compound of formula IV.

A group \( R^{15} \) is, for example, a halogen atom, an imidazolidine group, or a mixed anhydride group, for example, a group -OCORk or -OC(O)ORk in which \( Rk \) represents a straight or branched chain alkyl group having from 1 to 4 carbon atoms. \( R^{15} \) preferably represents a halogen atom, especially a chlorine atom.

The reaction between compound XV and the acylating agent of formula XIX is carried out in the presence of a base, for example, a tertiary amine, preferably a trialkylamine (each alkyl moiety having from 1 to 4 carbon atoms and having a straight or branched chain, the three alkyl moieties being the same or different), and especially triethylamine or ethyldiisopropylamine; or pyridine or a substituted pyridine, for example, 4-dimethylaminopyridine.

Particularly preferred bases are triethylamine and ethyldiisopropylamine. A mixture of two or more bases may be used, and a base may be polymer-bound.

In addition to an organic base as described above, it is preferable to include an acid binding agent in the reaction mixture. Examples of acid binding agents are alkali metal and alkaline earth metal carbonates and bicarbonates, and organic epoxides, for example, propylene
oxide. Calcium carbonate is a commonly-used binding agent.

In general, for each mole of compound XV there is used from 1 to 2 moles of the acylating agent XIX, from 1 to 4 moles of an amine base (or a total of from 1 to 4 moles of a mixture of amine bases), and from 0 to 10 moles of the acid binding agent, if present.

The compound of formula XV and the acylating agent of formula XIX are generally reacted in a solvent or diluent that is inert to the reaction, for example, in a halogenated hydrocarbon, for example, dichloromethane or chloroform, in an oxygenated hydrocarbon, for example, an ether, for example, tetrahydrofuran, dioxane or diethyl ether, or in an aromatic hydrocarbon, for example, benzene or toluene. The reaction is generally carried out at a temperature within the range of from -20 to +60°C, preferably from 0 to 20°C.

Compound IV, the product of the acylation reaction, may be isolated if desired, but is generally reacted without further purification with a trivalent organophosphorus reagent to give a compound of formula III or to give a compound of formula Ia directly.

Compound IV may also be obtained by oxidation of a compound formula XXVII
in which \( R^3 \), \( R^4 \), \( R^5 \), \( R^6 \) and \( X \) are defined as above.

A suitable oxidising agent is ozone or a higher oxide of a metal for example a higher oxide of a metal selected from one of Groups Ia, Vb, VIb, VIIb or VIII of the periodic table of the elements (see the CRC Handbook of Chemistry and Physics, 52nd Ed., CRC Press, Cleveland, 1971), for example osmium tetroxide, ruthenium tetroxide, an alkali metal peroxide, for example potassium superoxide; a periodate, for example an alkali metal periodate, for example sodium periodate; or an alkali metal permanganate, for example potassium permanganate. A combination of two or more oxidising agents, for example selected from those particularly described above, may also be used. The reaction is generally carried out at a temperature within the range of from -80 to +50°C. An inert solvent or diluent may also be used, for example water; a halogenated hydrocarbon, for example dichloromethane; or acetonitrile. Particularly preferred conditions are ozone in dichloromethane at a temperature of -80 to 0°C, and potassium permanganate in water at a temperature within the range 0°C to +40°C.

A compound of formula XXVII may be obtained by reacting a compound of formula XXVIII

\[
\begin{align*}
\text{XXVII} & \quad \text{XXVIII}
\end{align*}
\]
in which \( n, R^3, R^4 \) and \( R^{19} \) are defined as above, with a compound of formula VII in an inert solvent or diluent, for example an ether, for example diethyl ether, tetrahydrofuran or dioxane; a halogenated hydrocarbon, for example chloroform or dichloromethane; acetonitrile; an ester, for example ethyl acetate; or an aromatic hydrocarbon, for example toluene. The reaction is generally carried out at a temperature within the range -80°C to +60°C, preferably from -40 to 20°C. Optionally a base may also be used: examples are triethylamine, pyridine, and 4-dimethylaminopyridine.

Some compounds of formula XXVIII are known (M. Alpegiani et al., J. Amer. Chem. Soc., 107, 6398 (1985)), and others may be prepared analogously.

Examples of trivalent organophosphorus reagents which may be used to convert compound IV to compound III or compound 1a are phosphites and phosphoramides, for example, of the following formulae XX and XXI, and phosphines of formula XXII in combination with phosphites of formula XX

\[
\begin{align*}
&\text{OR}^7 \\
R^6O-P-OR^8 \\
(\text{XX})
\end{align*}
\]

\[
\begin{align*}
&\text{OR}^7 \\
R^6O-P-NR^8R^9 \\
(\text{XXI})
\end{align*}
\]

\[
\begin{align*}
&R^7 \\
R^6-P-R^8 \\
(\text{XXII})
\end{align*}
\]

in which formulae \( R^{16}, R^{17}, R^{18} \) and \( R^{19} \), which may be the same or different, each represents a straight or branched chain alkyl group having from 1 to 6 carbon atoms or a phenyl group which may be unsubstituted or substituted, for example, by a methyl group, especially a para-methyl group; also cyclic trialkyl phosphites, each alkyl moiety having

followed by page 22
from 1 to 4 carbon atoms, for example, of formula XXIII

$$\text{CH}_3\text{A-O-P}$$

(XXIII)

in which each group A denotes an alkylene group having from 1 to 4 carbon atoms; and also catechol phosphites and catechol dimer phosphites, for example, of the following formulae XXIV and XXV, respectively:

$$\text{O-P-OR}^5$$

(XXIV)

$$\text{O-P-A-P}$$

(XXV)

in which R$^1$ and A are defined as above. A trivalent organophosphorus compound may be bound to an inert polymer.

A preferred trivalent organophosphorus reagent is a phosphite or phosphoramidite of formula XX or XXI respectively, or a combination of a phosphine of formula XXII with a phosphite of formula XX. Particularly preferred are the trialkyl phosphites, and especially trimethyl phosphate and triethyl phosphate.

When the organophosphorus reagent used is a phosphite or phosphoramidite, generally from 2 to 3 moles thereof are used per mole of compound IV. When a phosphine is chosen, from 1 to 3 moles are generally used per mole of compound IV, in combination with a phosphite, generally 1 mole thereof. The phosphite is preferably added slowly to a mixture of the phosphine and the compound IV.

As described above, a resulting compound of formula III may be isolated and then cyclised to a compound of formula IA, or a compound of formula IV may be reacted with the organophosphorus reagent and cyclised in situ to give a compound IA. In the latter case, the reaction may proceed via compound III or via another intermediate.

The cyclisation reaction is generally carried out in a refluxing solvent. When X in compound IV or compound III represents a sulphur atom, preferred solvents are aromatic hydrocarbons, for example, benzene, toluene and xylene, and
halogenated hydrocarbons, for example, dichloromethane, chloroform and 1,2-dichloroethane. When X in compound III or IV represents an oxygen atom, preferred solvents are benzene, toluene and xylene.

In a compound of formula III, it can be seen that the group \(-\text{P}(\text{Z})_3\) is derived from the trivalent organophosphorus reagent or mixture of reagents used, which reagent or mixture of reagents is preferably selected from the reagents of formulae XX to XXVI described above. As mentioned above, the organophosphorus reagent may be polymer-bound, in which case a resulting compound of formula III will also be polymer-bound.

Compound Ia may be produced from compound XV by an alternative route via compounds XVI, V, and optionally III as shown in Reaction Scheme II.

By this route, a compound of formula XV is reacted with a glyoxylic ester of formula XXVI

\[
\begin{array}{c}
\text{O} \\
\text{O}
\end{array}
\begin{array}{c}
\text{HC} \quad \text{C} \\
\text{OR}^4
\end{array}
\]

(XXVI)

in which \(R^4\) is as defined above, or with a reactive derivative thereof, for example, a hydrate or hemiacetal, a hemiacetal preferably being formed with an alcohol having from 1 to 4 carbon atoms, for example, ethanol.

When a hydrate of a compound of formula XXVI is used, the water formed during the reaction is preferably removed, for example, azeotropically or by use of a dehydrating agent, for example, a molecular sieve.

The reaction is generally carried out in a solvent or diluent that is inert under the reaction conditions, for example, an ether, for example, tetrahydrofuran, dioxane or diethyl ether, an aprotic solvent, for example, dimethylacetamide or dimethylformamide, or an aromatic hydrocarbon, for example, benzene or toluene. A mixture of two or more solvents may be used. The reaction is generally carried out at a temperature within the range of from 0 to 100°C. Preferably from 1 to 2 moles of the glyoxylate derivative
are used per mole of compound XXII.

The resulting compound of formula XVI is obtained as a mixture of the R- and S-isomers at the >CH-OH group. These isomers may be separated, if desired, but the R,S-mixture is generally used for the next reaction.

In the next step, the alcohol of formula XVI is converted into a halide of formula V. The halogenation may be carried out in a conventional manner using an appropriate agent, for example, thionyl chloride or bromide, phosphorus oxychloride or oxybromide, or a phosphorus halide, for example, phosphorus pentachloride or pentabromide, or a mixture of two or more thereof.

The reaction is preferably carried out in the presence of a base, for example, a heterocyclic base, for example, pyridine, 4-dimethylaminomethylpyridine, or lutidine, or atrialkylamine, for example, triethylamine or diisopropyl-ethylamine. The base may be polymer-bound.

The reaction is generally carried out in a solvent, for example, an ether, for example, diethyl ether or dioxane. The reaction temperature is generally within the range of from -40 to +40°C, preferably room temperature and, if desired, the reaction may be carried out under an inert atmosphere.

The resulting compound of formula V is obtained as a mixture of the R- and S-isomers at the >CH-Cl or >CH-Br group. As in the case of compound XVI, the isomeric mixture may be separated into the individual isomers, but generally the R,S-mixture is used.

A compound of formula V may be converted into a compound of formula Ia. This reaction may proceed via a compound of formula III or via another intermediate. If desired, a compound of formula V may be phosphorylated to give a compound of formula III, which may then be isolated and cyclised to give a compound of formula Ia.

A compound of formula V may be converted into a compound of formula Ia or of formula III by reaction at an appropriate temperature with a trivalent organophosphorus reagent, for example, a compound of formula XX, XXI, XXII,
XXIII, XXIV or XXV as described above. (In the present case, a phosphine of formula XX may be used alone.)

The reaction is preferably carried out in the presence of a base, for example, an organic amine, for example, a tertiary amine, for example, pyridine or a pyridine derivative, or a trialkylamine, for example, triethylamine or diisopropylethylamine. The reaction is generally carried out in a solvent that is inert under the reaction conditions, for example, an aromatic hydrocarbon, for example, benzene or toluene, or an ether, for example, diethyl ether, tetrahydrofuran or dioxane.

The reaction temperature is generally within the range of from -10 to 150°C. As mentioned above, the use of lower temperatures, for example, room temperature or below, generally enables a compound III to be isolated, whereas higher temperatures, for example, above room temperature, generally lead to compound Ia directly.

A compound of formula Ia may be produced by a third method, which is also shown in Reaction Scheme II. This method comprises reacting a heavy metal mercaptide of formula VI

\[
\begin{align*}
\text{VI} & \\
\begin{array}{c}
\text{R}^2 \text{O} \\
\text{CH}_3 \text{CH} \\
\text{N} \text{P} \text{Z}^3 \text{R}^3 \text{R}^4 \\
\text{COOR}^4 \\
\end{array}
\end{align*}
\]

in which \(\text{=P} \text{Z}^3 \text{R}^3 \text{R}^4 \) are defined as above, and \(\text{R}^{19}\) represents \text{Cu(II)}, \text{Pb(II)} or \text{Hg(II)} in which case \(n\) represents the integer 2, or \(\text{R}^{19}\) represents \text{Ag(I)}, in which case \(n\) represents the integer 1, with a compound of formula VII

\[
\begin{align*}
\text{VII} & \\
\begin{array}{c}
\text{R}^{11} \text{C} \text{R}^5 \text{R}^6 \\
\text{X} \\
\end{array}
\end{align*}
\]

in which \(\text{R}^5, \text{R}^6, \text{R}^{11}\) and \(X\) are defined as above.

A compound of formula VI in which \(Z\) represents a
phenyl group is described in GB 2 042 515A, which also
described a process for the production thereof. Other
compounds of formula VI may be produced analogously, using
the appropriate trivalent organophosphorus reagent.

Compounds VI and VII are generally reacted in a
solvent, for example, an ether, for example, diethyl ether
or dioxane, an aromatic hydrocarbon, for example, benzene,
toluene or xylene, an ester, for example, ethyl acetate, a
halogenated hydrocarbon, for example, dichloromethane or
chloroform, or an aprotic solvent, for example,
dimethylformamide or dimethylacetamide. The reaction
temperature is generally within the range of from -40 to
100°C, preferably from 0 to 40°C.

Compound VI may be converted to compound Ia either via
compound III or via another intermediate, or compound VI
may be converted into compound III, which may then be
isolated and converted to compound Ia. Lower temperatures,
for example, from -40°C to room temperature, generally
enable compound III to be isolated, whereas higher
temperatures, for example, from room temperature to 150°C,
generally lead to compound Ia.

In all the various intermediates involved in the
production of a compound of formula Ia by the procedures
described in Reaction Scheme II, the 8-hydroxy group and
the 2-carboxy group, when present, are preferably
protected, with removal of the protecting groups preferably
being delayed until after compound Ia has been formed and,
if appropriate, until any conversions of groups R5 and/or
R6, and any interconversions of groups R1 and/or R2 have
been carried out.

As mentioned above, a final product of formula I may
have R- or S-stereochemistry at position 5, 5R-stereo-
chemistry being preferred. The stereochemistry at the
6-position is preferably S.

In process (A), the stereochemistry at position 5 in
compound I is predominantly inverse to that at position 4
in the precursor azetidinone compound II. In the preceding
reaction steps shown in Reaction Scheme I, halogenation of
compound XI when R³ represents a radical other than a hydrogen atom gives a compound of formula II with a mainly trans relationship between R⁸ and the protected hydroxyethyl group at the 8-position. The resulting penem compound of formula I then has a predominantly cis relationship between the ring sulphur atom and the protected hydroxyethyl group. Conversely, halogenation of a compound of formula XI in which R³ represents hydrogen generally yields a compound of formula II with R⁸ mainly cis to the free hydroxyethyl group, the resulting compound of formula I being predominantly trans.

In processes (B), (C) and (D), the stereochemistry of compound I at position 5 is predominantly determined by the stereochemistry of the attachment of the sulphur atom at position 4 of the azetidinone ring in the precursor compounds III, IV, V and VI. In these compounds, and in the precursor compounds shown in Reaction Scheme II, this sulphur atom is generally almost always trans to the optionally protected hydroxyethyl group at position 3, implying also a trans relationship at the hydrogen atoms at positions 3 and 4. Thus, in Reaction Scheme II, compound I with 6S-stereochemistry will naturally acquire 5R-stereochemistry, with the hydrogen atoms at positions 5 and 6 being trans.

In the formation of a compound of formula I, some degree of thermal equilibration at position 5 does occur, and this effect can be used in the production of compounds having a different relationship between the hydrogen atoms at positions 5 and 6. In particular, the equilibration process is facilitated, for example, by heating, for example, in a solvent or diluent at a temperature generally within the range of from 60 to 150°C, especially at the reflux temperature of the solvent system used.

As mentioned above, R⁵ and/or R⁶ may represent a group that can be converted into a group R¹ and/or R², respectively. Such a group R⁵ and/or R⁶ may be converted into the appropriate group R¹ and/or R² in any compound in which it appears, such a conversion being part of the
Moreover, a group R\textsubscript{1} and/or a group R\textsubscript{2} may be converted into another group R\textsubscript{1} and/or R\textsubscript{2}. As described above for R\textsubscript{5} and R\textsubscript{6}, such a conversion may be carried out on any of the compounds containing such groups, and such a conversion is also part of the present invention.

The possibility of modifying substituents on the phenyl ring is particularly useful for the production of compounds of formula I having a substituent R\textsubscript{1} and/or R\textsubscript{2} that is potentially unstable in any of the reactions involved in the production of compound I, or incompatible with any of the reagents used. In such a case, a group R\textsubscript{5} and/or R\textsubscript{6}, or another group R\textsubscript{1} and/or R\textsubscript{2}, may function as a protected form of the desired group, or there may be used a different but stable or compatible group that can be converted into the desired group. The conversion step is, accordingly, carried out after the reaction or reactions in which the desired substituent is potentially unstable or incompatible.

Although a conversion may be carried out, if appropriate, on a precursor of a compound of formula I, it is generally preferable to retain convertible group(s) until after formation of a compound of formula I or formula Ia. (As shown above, a compound of formula Ia is a compound analogous to compound I but having groups R\textsubscript{5} and/or R\textsubscript{6} that can be converted into groups R\textsubscript{1} and/or R\textsubscript{2}, respectively.)

In a compound of formula I or Ia, a conversion may be carried out before or after the removal of a protecting group from the 8-hydroxy group, and before or after the removal of a 2-carboxy protecting group, having regard to the potential reactivity of a free hydroxy group and of a free carboxy group in the reaction under consideration.

Examples of such conversions (including conversions of radicals forming a part of a larger group) are the following:

(i) -COORD, -COOSiReRfRg or -COO-phenyl to -COOH
(ii) -COOH to -CONH\textsubscript{2}, -CONHRa or -CONH(CH\textsubscript{2})\textsubscript{m}Q
(iii) -COOH to -COOR or -CO₂CH₂Q or -CO₂CH₂CH₂Q or -CO₂CH(CH₃)Q
(iv) -COOH to -COR
(v) -NHRₘ or -NRₘRₙ in which Rₘ and Rₙ are protecting groups, to -NH₂

(vi) -NH₂ to
- NH=NH₂
- NH=NH₂
- NH=NHRₘ
- NH=NRₘRₙ

(vii) -CONRₘRₙ, Rₘ being a protecting group, to -CONHR₁
(viii) -N₃ to -NH₂, which is then optionally converted to a group R₁ as described in (v) above,

(ix) halogen to -CN or -COOH
(x) -SRₐ to -SORₐ or -SO₂Rₐ
(xi) -CN to -CH₂NH₂, which is then optionally converted to a group as defined in (v) above.
(xii) -SORₐ to -SO₂Rₐ
(xiii) -NO₂ to -NH₂, which may then converted further as described in (vi) above.

The conversions described above may be used in any appropriate combination, for example, conversion of a halogen atom to a nitrile group which may then be converted into an aminomethyl group, which may be reacted further. In some cases, the group that is converted may not be a group R₁ or R₅ itself, but may be a moiety forming part of such a group, for example, an -NH₂ group may be a group Q as defined above or the terminal moiety of a group Q.

Many of the methods for carrying out such reactions are known per se in the art, for example,
(i) a carboxy protecting group may be removed by conventional methods, for more details, see below;
(ii) a carboxy group may be amidated using an amine and a condensing agent, for example, a carbodiimide, or by reacting an amine with an activated carboxylic acid derivative, for example, an active ester or an anhydride
(symmetrical or asymmetrical), or an acid chloride;
(iii) a carboxylic acid group may be esterified using an
alcohol and an activated carboxylic acid derivative, for
example, an active ester, acid anhydride or acid chloride;
(iv) a carboxy group may be converted to a ketone by
reaction with an alkyllithium compound, for example, RaLi;
(v) and (vii) a protected amine group may be deprotected by
conventional methods, for example, as described in McOmie,
loc. cit., and in Greene, loc. cit.;
(vi) substitution of the amine group by an acyl group or an
alkyl or substituted alkyl group as defined in (vi) may be
carried out conventionally, for example, an amino group may
be acylated with, for example, an acid chloride or an acid
anhydride, for example, acetyl chloride or acetic
anhydride, or with the appropriate acid derivative;
(viii) an azide group may be converted into an amino group
by catalytic reduction;
(ix) a halide, especially an iodide, may be treated with an
organometallic compound, for example, an organolithium
compound, especially t-butyllithium, the resulting complex
being treated with cyanogen to give the -CN group;
(x) an alkylthio group may be oxidised, preferably with a
carboxylic peracid, especially m-chloroperbenzoic acid, to
give the corresponding alkylsulphinyl or alkylsulphonyl
group;
(xi) a cyano group may be converted to an amino group by
reduction, for example, using a metal hydride, which amimo
group is then reacted further as described above
(xii) an alkylsulphinyl group may be oxidised to an
alkylsulphonyl group as described in (x) above;
(xiii) a nitro group may be reduced to an amino group by
noble metal catalysed hydrogenation, for example, using
platinum or 10% palladium on carbon, c.f. M. Freifelder,
Catalytic Hydrogenation in Organic Synthesis, Wiley
Interscience, 1978, page 26, and P.N. Rylander, Catalytic
Hydrogenation over Platinum Metals, Academic Press, 1967,
Chapter 11, and the amino group is then reacted further as
In process (A), and in Reaction Scheme I, it is not generally necessary to protect the 8-hydroxy group, and the special considerations regarding protection and deprotection of the 8-hydroxy group in the formation of a compound of formula II are discussed above. In processes (B), (C) and (D), and in Reaction Scheme II, however, it is generally preferable to protect the 8-hydroxy group, and to remove the protecting group as one of the last steps in the formation of compound I. Accordingly, in compounds of formulae III, IV, V, VI, XIV, XV and XVI, R₃ preferably represents a hydroxy protecting group.

As mentioned above, hydroxy protecting groups and methods for their introduction and removal are well known. Particularly useful hydroxy protecting groups R₃ and methods for their removal are described in detail above.

In a compound of formula I, the 8-hydroxy group, if esterified, is preferably esterified with a group that can be removed in vivo to give the free hydroxy group, that is to say, an ester group that can be removed under physiological conditions. Examples of suitable esterifying groups are carboxylic acid acyl groups of the formula R₂₀CO⁻ in which R₂₀ represents a hydrogen atom or a straight or branched chain alkyl group having from 1 to 6 carbon atoms, especially a methyl, ethyl or t-butyl group, or represents a phenyl group or a phenoxyalkyl group in which the alkyl moiety is straight-chained or branched and has from 1 to 4 carbon atoms, and is especially a methylene group.

A non-physiologically removable protecting group R₃ is generally removed from a resulting compound of formula I, and may be replaced by a physiologically removable group, if desired. In some cases, a carboxylic acid acyl group R₃ may fulfill a protective role during the synthesis of compound I. Such a dual function protective group may be removed, retained or replaced in formula I, as desired.
An ester group at the 8-position may be the only ester group present, or it may be present in addition to an ester group at the 2-carboxyl group. As mentioned above, a physiologically removable group may be present as a protecting group R³ during the formation of a compound of formula I, or it may be introduced at the free 8-hydroxy group of a compound of formula I, after removal of a non-physiologically removable hydroxy protecting group, if present. An esterifying group may be introduced at the 8-hydroxy group by a reaction with an organic acid derivative in known manner. A particularly convenient method is to react a compound of formula I with an activated acid derivative, for example, an acid anhydride in the presence of an organic base, for example, 4-dimethylaminopyridine.

As indicated above, a compound of formula I may be in the form of an ester at the carboxy group at position 2. Such an ester is particularly one that can be converted into the free acid by hydrolysis, photolysis, reduction oxidation or esterase enzyme action. Examples of such esters are those formed with unsubstituted or substituted aliphatic alcohols or phenols having up to 20 carbon atoms in total. In an esterified carboxy group -COOR, the group R may be, for example, a straight or branched chain substituted or unsubstituted alkyl, alkenyl or alkynyl group having up to 18 carbon atoms, preferably up to 8 carbon atoms, and especially up to 6 carbon atoms, for example, a methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, n-hexyl, allyl or vinyl group. An aliphatic group R, especially a methyl or ethyl group, may be substituted, for example, by an acyloxy group (further details of such groups are given below); by an aminoalkanoyloxy group; by an optionally substituted amino group; or, in the case of a methyl group, by one or more unsubstituted or substituted phenyl groups. A phenyl group, either as a phenol or as a substituent of a methyl group, may be substituted, for example, by one or
more substituents, selected especially from methoxy and nitro groups and halogen atoms. Examples of phenyl substituted-aliphatic groups, are benzyl, nitrobenzyl, methoxybenzyl, dimethoxybenzyl, benzhydryl and trityl groups.

As indicated above, an ester group is especially one that can be removed by hydrolysis, photolysis, oxidation, reduction or enzyme action, or two or more of these methods may be used, for example, reduction followed by hydrolysis. A group \( R \) that can be removed readily without substantial degradation of the rest of the molecule is particularly useful as a carboxy protecting group. Examples of esters that are readily split by reduction are trichloroethyl esters, and phenyl substituted-methyl esters, which may be unsubstituted or substituted, for example, benzyl \( p \)-nitrobenzyl, benzhydryl and trityl esters.

Reduction of an ester, for example, a phenyl substituted-methyl ester, for example, a \( p \)-nitrobenzyl ester, may be carried out using hydrogen and a metal catalyst, for example, a noble metal catalyst, for example, platinum, palladium or rhodium, which catalyst may be supported, for example, on charcoal or kieselguhr. Such reductions may be carried out in the presence of a salt forming agent, for example, sodium or potassium bicarbonate, if it is desired to form directly a salt at the 2-carboxylic acid group of formula I.

Alternatively, a \( p \)-nitrobenzyl ester may be converted into the corresponding free acid by a two-step method, with an initial reduction of the nitro group followed by hydrolysis. The nitro group may be reduced by noble metal catalysed hydrogenation, for example, using platinum, or palladium on carbon, or by a metal reducing agent, for example, zinc in acetic acid. Other metal reducing agents are, for example, aluminium amalgam, and iron and ammonium chloride, see for example, British Patent Specification No. 1,582,960. Reduction of the nitro group is followed by hydrolysis which may occur in situ during reduction of
the nitro group or which may be carried out subsequently by treatment with an acid or a base.

An o-nitrobenzyl ester may be converted into the corresponding free acid by photolysis.

Certain ester groups may be split off by base hydrolysis, for example, acetylmethyl, acetoxyethyl and phenoxethyl esters.

Some ester groups may be cleaved by oxidative hydrolysis, for example, the dimethoxybenzyl group.

Other cleavable esters include, for example, silyl esters, for example, trialkylsilyl and trialkylsilylalkyl esters, in which alkyl moieties have, independently, from 1 to 4 carbon atoms, for example, trimethylsilyl and trimethylsilylalkyl esters.

In the above process, removal of esterifying groups by oxidative and reductive processes may be achieved electrochemically.

There may be used an esterifying group that is removable under physiologic conditions, that is to say, the esterifying group is split off in vivo to give the free acid or a carboxylate, for example, an acyloxyethyl ester having from 2 to 12 carbon atoms in the acyl moiety, for example, an acyloxyethyl, 1′-(acetoxy)ethyl or pivaloyloxyethyl ester, a 5-methyl-1,3-dioxalen-2-on-4-yl-methyl ester, an aminoalkanoyloxyethyl ester having from 2 to 12 carbon atoms in the alkanooy moiety, for example, a glycyloxyethyl, L-valinloyloxymethyl or L-leucylloxymethyl ester, or a phthalidyl ester, or a 1′-(alkoxy carbonyloxy)ethyl ester, for example, a 1′-(methoxy carbonyloxy)ethyl or 1′-(ethoxy carbonyloxy)ethyl ester, or an optionally substituted 2-aminoethyl ester, for example, a 2-diethylaminomethyl or 2-(1-morpholino)-ethyl ester.

Preferred esters are the p-nitrobenzyl, phthalidyl, pivaloyloxymethyl, ethoxycarbonyloxymethyl, 5-methyl- dioxalen-2-on-4-yl-methyl, acetylmethyl, acetoxyethyl, 1′-(acetoxy)ethyl, 1′(acetyl)ethyl and 1′(ethoxy carbonyloxy)ethyl esters.

An ester at any position in a compound of formula I or of any other free acid described herein, may be prepared
by reaction of the appropriate free acid or activated derivative thereof with an alcohol, a phenol or a reactive derivative thereof. The reaction is preferably carried out under mild conditions in order to prevent rupture of the ring system, for example, under neutral or mild acidic or basic conditions, and at temperatures within the range of from -70 to +35°C.

An ester derived from an alcohol may also be produced by reaction of a reactive derivative of the alcohol, for example, a halide, for example, a chloride, bromide or iodide, or hydrocarbonsulphonyl derivative, for example, a mesyl or tosyl ester, with a salt of an acid of formula I or of another free acid described herein, for example, an alkali or alkaline earth metal salt, for example, a lithium, sodium, potassium, calcium or barium salt, or an amine salt, for example, a triethylammonium salt. The reaction is preferably carried out in a substituted sulphoxide or amide solvent, for example, in dimethyl sulphoxide, dimethylformamide, or hexamethylphosphoramide or, alternatively, an ester may be prepared by reaction of an alcohol or phenol with the acid, for example, in an activated form, for example, in the presence of a condensing agent, for example, dicyclohexylcarbodiimide.

The present invention also provides salts of those compounds of formula I that have salt-forming groups, especially the salts of a free acid of formula I and acid addition salts of compounds of formula I having a basic group. The salts are especially physiologically tolerable salts, for example, alkali metal and alkaline earth metal salts, for example, sodium, potassium, lithium, calcium, and magnesium salts, ammonium salts, and salts with organic amines; also physiologically tolerable acid addition salts. These may be formed with a suitable inorganic or organic acid, for example, hydrochloric acid, sulphuric acid, or an organic carboxylic or organic sulphonlic acid, for example, p-toluene-sulphonic acid.

A salt of a free acid of formula I may be produced by reacting the free acid with the appropriate base in a solvent, preferably under those conditions under which
The cyclisation reaction is generally carried out in a refluxing solvent. When X in compound IV or compound III represents a sulphur atom, preferred solvents are aromatic hydrocarbons, for example, benzene, toluene and xylene, and the salt precipitates. A preferred base is potassium 2-ethylhexanoate.

A salt may be produced directly from an ester by splitting off the ester group under suitable reaction conditions, for example, catalytic reduction of an ester, for example, a p-nitrobenzyl ester, in an aqueous/organic solvent, for example, comprising water and ethyl acetate, dioxane or tetrahydrofuran, in the presence of a metal salt, especially a metal bicarbonate, for example, in an equivalent amount or in a slight excess, yields the salt directly.

When an acidic centre and a basic centre are both present in a compound of formula I, the compound may exist in zwitterionic form.

Protecting groups may be introduced or removed at any appropriate point in the reactions involved in the production of a compound of formula I.

At any stage in the production of a compound of formula I, a compound produced may be isolated from the reaction mixture in which it was prepared and, if desired, purified by the appropriate techniques used for the purification of organic compounds, for example, chromatography and crystallisation.

As indicated above, various intermediates may be produced in the form of mixtures of isomers of various kinds. Such mixtures may be separated or resolved at any stage, or an isomeric mixture may be used per se for subsequent reactions.

A compound of formula I may have the R or S stereochemistry independently at positions 5, 6 and 8. Any mixture of two or more isomeric forms may be resolved, if desired, or a compound of formula I can be used in the form of an isomeric mixture. The preferred stereochemistry at position 5 in compound I is generally R, corresponding to that in naturally occurring penicillins and cephalosporins, at position 6 is S and at position 8 is R.

Compounds of formula I possess excellent activity
against gram positive bacteria and gram negative bacteria. Moreover, the compounds of formula I and salts thereof show activity against these organisms in the presence of \( \beta \)-lactamase enzymes produced by both gram positive organisms, for example, Staphylococcus aureus and gram negative organisms, for example, Enterobacter cloacae, thus indicating resistance to these enzymes. 

Compounds of formula I are also inhibitors of \( \beta \)-lactamase enzymes.

The compounds of formula I and physiologically tolerable salts thereof may be used in humans and other animals to treat, for example, bacterial infections caused by both gram positive and gram negative bacteria, for example, Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Bacillus subtilis and Proteus morganii, some strains of which are resistant to conventional penicillin therapy.

It has been found that compounds of formula I (and esters thereof at the 2-carboxylic acid group) having an esterified hydroxy group at the 8-position also have antibacterial and/or \( \beta \)-lactamase inhibiting properties, in particular since the 8-ester group can be cleaved \textit{in vivo} by esterases. In addition, esterification at the 8-hydroxy group can enhance the degree of absorption on oral administration.

Compounds of the present formula I have certain advantages with respect to antimicrobial activity compared with the corresponding unsubstituted phenyl and also the 4-chloro-, 4-fluoro-, 4-methoxy-, 4-methylthio- and 3-methylthiophenyl compounds for example, 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate and the corresponding (4-aminocarbonylphenyl), (3-formylaminophenyl) and (4-formylaminophenyl) compounds have greater antibacterial activity against a variety of microorganisms, particularly \( \beta \)-lactamase producing organisms than do the above comparison compounds, as shown in the Table below.
The antimicrobial activity was determined by measuring the Minimum Inhibitory Concentration (MIC). The MIC of the compounds was determined by a standard test, the "agar dilution test" according to Lorian (Antibiotics in Laboratory Medicine, Williams and Wilkins, Baltimore/London 1980) as follows:

A two-fold decreasing concentration series of each compound was prepared in Petri dishes containing 15 ml of Mueller Hinton agar (Difco). One Petri dish containing only the Mueller Hinton agar served as control for bacterial growth. Each Petri dish was inoculated with a multi-point inoculator (Denley), which transferred 0.6μl of a 1:100 diluted 18 hours culture of the appropriate test bacterium. After 16 to 18 hours of incubation at 37°C the Petri dishes were examined for growth of bacteria. The lowest concentration of the compound which causes complete inhibition of growth is taken as the MIC except that the growth of a single colony or a haze is not taken as evidence of growth.

Table of antimicrobial activity (mg/l)

In all the compounds in the Table below, R³ is hydrogen, R² is hydrogen, and the stereochemistry is 5R, 6S, 8R.
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ND implies not determined
The present invention accordingly provides a pharmaceutical preparation which comprises a compound of formula I, or a physiologically tolerable salt thereof, or a mixture of two or more such substances as active ingredient, in admixture or conjunction with a pharmaceutically suitable carrier. The preparation may also comprise one or more other pharmaceutically active substances, for example another antibacterial substance, especially one having a β-lactam ring. The preparations may be in a form suitable for enteral or parenteral administration, for example, for oral, intravenous or intramuscular administration, for example, as tablets, capsules, syrups, or sterile injectable or infusion solutions. The preparations are advantageously in unit dosage form and preferably comprise from 10 to 2000 mg of the active ingredient per unit dose. The daily dosage of the active ingredient is generally from 20 to 8000 mg, in divided doses, generally up to 4 doses.

The invention also provides the use of a compound of formula I or a physiologically tolerable ester or salt thereof for the manufacture of a medicament for the treatment of bacterial infections.

The invention further provides a method of treating mammals, especially humans, to combat a bacterial infection, which comprises administering to the mammal a compound of formula I or a physiologically tolerable ester or salt thereof.

The invention further provides a pharmaceutical preparation which comprises an active ingredient as defined above, in unit dosage form.

The invention also provides a pharmaceutical preparation which comprises an active ingredient as defined above, or a physiologically tolerable salt thereof or a mixture of two or more such substances, and one or more further pharmaceutically active substances, in unit dosage form. Unit dosages are preferably as described above.

Compounds of formula I are also useful in the production of the antibacterially active compounds.
Particularly interesting compounds of formula I are

(i) 3-(3-aminocarbonylphenyl)-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene 2-carboxylic acid;
(ii) 3-(4-aminocarbonylphenyl)-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene 2-carboxylic acid;
(iii) 3-(3-formylaminophenyl)-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene 2-carboxylic acid;
(iv) 3-(4-formylaminophenyl)-6-(1-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene 2-carboxylic acid.

Of these compounds, the 3-aminocarbonylphenyl compound (i) and the 4-formylaminophenyl compound (iv) are particularly preferred.

In each of compounds (i) to (iv) above, 5R,6S,8R-stereochemistry is preferred. The compounds may be in the form of esters or salts as described above.

The present invention also provides compounds of formulae II, III, IV, V, IX, X, XI, XV and XVI.

The following Examples illustrate the invention, but are not limiting.

In the Examples, temperatures are given in degrees Celsius, and ratios of solvents are calculated by volume.
Example 1

4-Nitrobenzyl 3-(4-cyanophenyl)-2-{3S-[1R-(dimethyl(2-
methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-
2-on-1-yl}-3-hydroxypropenoate

A mixture of 4-nitrobenzyl 2-{3S-[1R-(dimethyl(2-
methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-2-
on-1-yl}acetate (9.65g) and 4-cyanobenzoyl chloride
(3.97g) in tetrahydrofuran (10ml) was cooled to -40°
and treated with a solution of lithium
hexamethyldisilazide [prepared from n-butyl lithium in
tetrahydrofuran (1.6M, 28.10ml) and
hexamethyldisilazane (10.46ml)]. The mixture was
stirred for 1 hour then glacial acetic acid (4.80g) was
added. Evaporation gave a residue which was
partitioned between ethyl acetate and water. The
organic layer was separated, washed with saturated
aqueous sodium bicarbonate and brine and evaporated.
Chromatography of the resulting oil with ethyl acetate-
hexane mixtures over silica gel afforded the title
compound as a brown gum (10.18g) whose 1H n.m.r.
spectrum showed it was a complex mixture of E and Z
isomers and the corresponding keto-tautomer.

δ (CDCl₃) inter alia 3.02 (1H,m)
4.26 (1H,m), 5.62 (1H,d, J = 1.5Hz).

Example 2

4-Nitrobenzyl 3-(4-cyanophenyl)-2-{3S-[1R-(dimethyl(2-
methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-
2-on-1-yl}-3-(methylsulphonyloxy)propenoate

A solution of 4-nitrobenzyl 3-(4-cyanophenyl)-2-
{3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-
ethylthioazetidin-2-on-1-yl}3-hydroxypropenoate (4.04g)
in dichloromethane (100ml) was cooled to -60°,
treated with triethylamine (1.00g) followed by
methanesulphonyl chloride (1.13g) and stirred for 1
hour. The solution was washed successively with 0.5M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, and evaporated. The resulting gum was chromatographed with ethyl acetate-hexane mixtures over silica gel to give the product as a pale yellow foam (2.29g) as a mixture of E and Z isomers.

\[ \delta (\text{CDCl}_3) \quad 0.00-0.01 (6H, m); \quad 0.96-1.06 (9H, 2xs); \]
\[ 2.16-2.46 (6H, m); \quad 2.50 \text{ and } 2.77 (2H, 2q, J = 8.4Hz); \]
\[ 3.08 (3H, 2xs); \quad 3.10 \text{ and } 3.40 (1H, 2xdd, J = 2.6 \text{ and } 3.0Hz); \]
\[ 4.26 \text{ and } 4.43 (1H, m); \quad 5.07 \text{ and } 5.40 (2H, 2xAB, J_{gem} = 12.9Hz); \]
\[ 7.23-7.27 (1H, m); \quad 7.56-8.14 (5H, m); \]
\[ 8.21-8.27 (2H, 2xJ, J = 8.9Hz). \]

Example 3

4-Nitrobenzyl 3-(4-cyanophenyl)-2-[4R-ethylthio-3S-(1R-
hydroxyethyl)azetidin-2-on-1-yl]-3-(methylsulphonyloxy)-propanoate.

A solution of 4-nitrobenzyl 3-(4-cyanophenyl)-2-
{3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-
ethylthioazetidin-2-on-1-yl}-3-(methylsulphonyloxy)-
propenoate (4.36g) in tetrahydrofuran (60m1) was
treated with water (2.0ml) and concentrated (35%)
ydrochloric acid (1.94g) and stirred at room
temperature for 22 hours. The tetrahydrofuran was
removed in vacuo and the aqueous residue was
neutralised with saturated aqueous sodium bicarbonate.
After extraction with ethyl acetate, the organic
extract was dried over anhydrous magnesium sulphate and
evaporated, and the residue was chromatographed with
ethyl acetate-hexane mixtures over silica gel to give the
title compound (2.26g) as a mixture of E and Z isomers.

\[ \delta (\text{CDCl}_3) \quad 0.96-1.30 (6H, m); \quad 2.30 \text{ and } 2.60 (2H, 2xs); \]
\[ 2.10 (3H, s); \quad 2.98 \text{ and } 3.28 (1H, 2xdd, J = 2.6 \text{ and } 4.3Hz); \]
\[ 4.15 \text{ and } 4.30 (1H, 2xm); \quad 5.05 \text{ and } 5.31 (2H, 2xAB, J = 13.2Hz); \]
\[ 4.74 \text{ and } 5.33 (1H, 2xd, J = 2.6Hz); \quad 8.22-8.80 (6H, m); \]
Example 4
4-Nitrobenzyl 3-(4-cyanophenyl)-3-(2,2-dimethylpropanoylthio)-2-[4R-ethylthio-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]propenoate.

A stirred solution of 4-nitrobenzyl 3-(4-cyanophenyl)-2-[4R-ethylthio-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]propenoate (1.32g) in acetonitrile (100ml) was treated with potassium 2,2-(dimethyl)thiopropanoate (0.54g). After 4.5 hours the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulphate and evaporated. The resulting gum was chromatographed with ethyl acetate-hexane mixtures over silica gel to afford the title compound as a yellow gum (0.57g) which was a mixture of E and Z isomers.

δ (CDCl₃) 1.00-1.40 (15H, m);
2.45 and 2.68 (2H, 2xm); 3.15 and 3.37 (1H, 2xdd, J=2.9 and 4.3Hz); 4.23 and 4.31 (1H, 2xm); 4.93, 5.13 and 5.27, 5.44 (2H, 2xAB, Jgem = 13.0Hz); 4.43 and 5.45 (1H, 2xd, J= 2.7Hz); 7.18-7.30 7.40-7.68 (2H, m);
8.10-8.26 (2H, m).

Example 5
4-Nitrobenzyl 2-[4S-chloro-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]-3-(4-cyanophenyl)-3-(2,2-dimethylpropanoylthio)propenoate.

A solution of 4-nitrobenzyl 3-(4-cyanophenyl)-3-(2,2-dimethylpropanoylthio)-2-[4R-ethylthio-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]propenoate (0.57g) in CDCl₃ (15ml) was cooled to -60° treated with a
solution of chlorine in carbon tetrachloride (30mg/ml, 2.5ml) and stirred for 1 hour. The mixture was evaporated and the resulting gum was chromatographed with ethyl acetate-hexane mixtures over silica gel to afford the title compound as a yellow foam (0.34g) as a mixture of E and Z isomers.

\[ \delta (CDCl_3) \]
1.10-1.50 (12H, m);
3.47 and 3.58 (1H, 2xdd, J = 4.0Hz and 9.5Hz);
4.25 and 4.49 (1H, 2xm);
5.04 and 5.44 (2H, 2xAB, Jgem=12.7Hz);
5.28 and 6.31 (1H, 2xH, J = 4.0Hz);
7.18-7.80 (6H, m);
8.16-8.27 (2H, m).

Example 6
4-Nitrobenzyl 5R,3-(4-cyanophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-carboxylate.

To a solution of 4-nitrobenzyl 2-[4S-chloro-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]-3-(4-cyanophenyl)-3-(2,2-dimethylpropanoylthio)propenoate (0.04g) in dioxane (5ml) was added a solution of imidazole (7 mg) in water (0.5ml) and the mixture was stirred at room temperature for 3 hours. The reaction mixture was chromatographed directly with ethyl acetate-hexane mixtures over silica gel to afford the title compound as a yellow gum (0.03g).

\[ \nu_{\text{max}} (CDCl_3) \]
3400 br, 1790 and 1720 cm\(^{-1}\)

\[ \delta (CDCl_3) \]
1.41 (3H, d, J = 6.3Hz);
3.89 (1H, dd, J = 1.6 and 6.3Hz);
4.32 (1H, m);
5.12, 5.33 (2H, AB, Jgem = 13.6Hz);
5.80 (1H, d, J = 1.6Hz);
7.55, 7.66 (4H, AA'BB', J = 8.5Hz);
7.50, 8.20 (4H, AA'BB', J = 8.5Hz).

Example 7
Potassium 5R,3-(4-cyanophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
4-Nitrobenzyl 5R-3-(4-cyanophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.11g) was dissolved in dioxane (10ml) and mixed with a solution of potassium hydrogen carbonate (24mg) in water (10ml). The mixture was hydrogenated at 375kPa (4 atm) over 10% palladium-on-charcoal (0.11g) for 1 hour then filtered through Hyflo*. The filtrate was freeze-dried. The residue was dissolved in water, washed with ethyl acetate and freeze-dried to give the title compound as a pale yellow powder (0.08g).

\[ \delta (D_2O) \ 1.31 \ (3H, d, J = 6.5Hz); \ \ 4.02 \ (1H, m); \ \ 4.25' \ (1H, m); \ \ 5.82 \ (1H, d, J = 1.4Hz); \ \ 7.55, 7.75 \ (4H, AJIBB', J = 8.1Hz). \]

(*Hyflo is a Trade Mark.)

Example 8

4-Nitrobenzyl 3-(3-cyanophenyl)-2-{3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-2-on-1-y1}-3-hydroxypropenoate.

By a method analogous to that described in Example 1, and using 4-nitrobenzyl 2-{3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-2-on-1-y1}acetate (14.48g), 3-cyanobenzoyl chloride (5.96g), n-butyl lithium in tetrahydrofuran (1.6M, 42.2ml), hexamethyldisilazane (15.70ml), glacial acetic acid (7.20g) and tetrahydrofuran (200ml), the title compound was obtained as a brown foam (19.47g) whose \[^1H\ n.m.r.\] spectrum showed it was a complex mixture of E and Z isomers and the corresponding keto-tautomer.

\[ \nu_{\text{max}} \ (CDCl_3) \ 1800, 1750 \text{ and } 1700 \ \text{cm}^{-1} \]

\[ \delta (CDCl_3) \ \text{inter alia} \ 3.04 \ (1H, m); \ \ 4.25 (1H, m); \ \ 5.60 \ (1H, d, J = 5.6Hz). \]
Example 9

4-Nitrobenzyl 3-(3-cyanophenyl)-2-{3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-2-on-1-yl}-3-(methylsulphonyl oxy)propenoate.

According to the method of Example 2 and using 4-nitrobenzyl 3-(3-cyanophenyl)-2-{3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-2-on-1-yl}-3-hydroxypropenoate (19.47g), triethylamine (4.85g), methanesulphonyl chloride (5.50g) and dichloromethane (150ml) the title compound was obtained as an orange gum (20.47g) comprising a mixture of E and Z isomers.

δ (CDCl₃) 0.00-0.10 (6H,m); 0.81-0.91 (9H,2xs); 1.09-1.31 (6H,m); 2.41 and 2.66 (2H,2xq, J = 7.5Hz); 3.06 and 3.08 (3H,2xs); 2.94 and 3.28 (1H,2xdd, J = 2.7 and 4.3Hz); 4.13 and 4.31 (1H,2xm); 5.08 and 5.41 (2H,2xs); 5.01 and 5.43 (1H,2xdd, J = 2.7Hz); 7.24-7.28 (1H,m); 7.43-7.74 (4H,m); 7.94-8.28 (3H,m).

Example 10

4-Nitrobenzyl 3-(3-cyanophenyl)-2-[4R-ethylthio-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]-3-(methylsulphonyloxy)propenoate.

According to the method of Example 3 and using 4-nitrobenzyl 3-(3-cyanophenyl)-2-[3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-ethylthioazetidin-2-on-1-yl]-3-(methylsulphonyloxy)propenoate (20.47g), water (18.2ml), concentrated (35%) hydrochloric acid (18.15g) and tetrahydrofuran (174ml) the title compound was obtained as a mixture of E and Z isomers in the form of an orange foam.

δ (CDCl₃) 1.03-1.38 (6H,m); 2.40 and 2.70 (2H,2xm); 3.19 (3H,s); 3.07 and 3.33 (2H,2xdd, J = 2.7 and 4.3Hz); 4.24 and 4.38 (2H,2xm); 5.13 and 5.39 (2H,2xs); 4.75 and 5.40 (1H,2xd, J = 2.7Hz);
Example 11

4-Nitrobenzyl 3-(3-cyanophenyl)-3-(2,2-dimethyl-propanoylthio)-2-[4R-ethylthio-3S-(1R-hydroxyethyl)-azetidin-2-on-1-yl]propenoate.

According to the method of Example 4 and using 4-nitrobenzyl 3-(3-cyanophenyl)-3-(2,2-dimethyl-propanoylthio)-2-[4R-ethylthio-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]propenoate (5.76g), potassium 2,2-(dimethyl)thiopropanoate (2.34g) and acetonitrile (250ml) the title compound was obtained as an orange gum (2.65g) comprising a mixture of E and Z isomers.

$\delta$ (CDCl$_3$) 1.40 (15H, m); 2.50 and 2.75 (2H, 2xq, $J$ = 7.5Hz); 3.13 and 3.42 (1H, 2xdd, $J$ = 2.7 and 4.3Hz); 4.25 and 4.35 (1H, 2xm); 5.04, 5.15 and 5.27, 5.40 (2H, 2xAB, Jgem = 13.0Hz); 5.43 and 5.44 (1H, 2xd, $J$ = 2.7Hz); 7.26-7.40 (3H, m); 7.45-7.84 (8H, m); 8.14-8.20 (2H, 2xd, $J$ = 8.7Hz).

Example 12

4-Nitrobenzyl 2-[4S-chloro-3S-(1R-hydroxyethyl)-azetidin-2-on-1-yl]3-(3-cyanophenyl)-3-(2,2-dimethyl-propanoylthio)propenoate.

According to the method of Example 5 and using 4-nitrobenzyl 3-(3-cyanophenyl)-3-(2,2-dimethylpropanoylthio)-2-[4R-ethylthio-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]propenoate (1.39g), chlorine in carbon tetrachloride (33mg/ml, 5.76ml) and CDCl$_3$ (30ml), the title compound was obtained as a yellow gum (0.53g) comprising a mixture of E and Z isomers.

$\nu$ max (CDCl$_3$) 1780 and 1700 cm$^{-1}$

$\delta$ (CDCl$_3$) 1.10-1.50 (12H, m); 3.36 and 3.58 (1H, 2xdd, $J$ = 4.3 and 9.3Hz); 4.20 and 4.50 (1H, 2xm); 5.07 and 5.37 (2H, 2xAB, Jgem = 13.6Hz); 5.42 and 6.32 (1H,
Example 13
4-Nitrobenzyl 5R,3-(3-cyanophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclonor3.2.0]-hept-2-ene-2-carboxylate.

According to the method of Example 6 and using 4-nitrobenzyl 2-[4S-chloro-3S-(1R-hydroxyethyl)azetidin-2-on-1-yl]-3-(4-cyanophenyl)-3-(2,2-dimethylpropanoylthio)-propenoate (0.53g), dioxane (10ml), imidazole (95mg) and water (1ml) the title compound was obtained as a yellow gum (0.16g).

\[ \nu_{\text{max}} \text{ (Nujol mull)} * 3440, 2220, 1770, \text{ and } 1700 \text{ cm}^{-1} \]
\[ \delta \text{ (CDCl}_3) 1.40 (3H, d, J = 6.3Hz); 3.90 (1H, dd, J = 1.6 \text{ and } 6.3Hz); 4.31 (1H, m); 5.13, 5.32 (2H, AB, J_{gem}=13.6Hz); 5.80 (1H, d, J = 1.6Hz); 7.43-7.52 (3H, m); 7.66-7.74 (3H, m); 8.18 (2H, d, J = 8.8Hz). \]
(* Nujol is a Trade Mark).

Example 14
Potassium 5R,3-(3-cyanophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

According to the method of Example 7 and using 4-nitrobenzyl 5R,3-(3-cyanophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.16g), dioxane (10ml), potassium bicarbonate (35mg) water (10ml) and palladium-on-charcoal (0.16g) the title compound was obtained as a pale yellow powder (0.09g).

\[ \delta \text{ (D}_2\text{O)} 1.27 (3H, d, J = 5.8Hz); 7.97 (1H, dd, J = 1.4 \text{ and } 4.2Hz); 4.26 (1H, m); 5.76 (1H, d, J = 1.4Hz); 7.43-7.97 (4H, m). \]
position 5 in compound I is generally R, corresponding to that in naturally occurring penicillins and cephalosporins, at position 6 is S and at position 8 is R.

Compounds of formula I possess excellent activity

Example 15
4-Methylthio-thiobenzoic acid.

To a stirred solution of 4-methylthiobenzoyl chloride (9.82g) in dichloromethane (150ml) at 0°C was added dropwise pyridine (8.5ml); then after the mixture had been stirred for a further 10 minutes hydrogen sulphide (excess) was bubbled through. After a further 60 minutes stirring the mixture was extracted with saturated aqueous sodium bicarbonate. The aqueous extract was washed with dichloromethane, then acidified to pH 2 with dilute hydrochloric acid, and extracted with ethyl acetate. The organic extract was washed with water, and brine, dried over anhydrous sodium sulphate and evaporated in vacuo to afford the title compound as a yellow solid (5.2g).

δ (CDCl₃): 2.53 (3H, s); 5.40 (1H, bs);
7.28, 7.83 (4H, AA'BB', J = 8.0Hz).

Example 16
3S-([R]-(2-methylprop-2-yl)silyloxy)ethyl)-
4R-(4-methylthiobenzoylthio)azetidin-2-one.

To a stirred solution of 4-methylthio-thiobenzoic acid (5.7g) in 100ml acetone was added 1M sodium hydroxide until the pH was 8.5 followed by a solution of 4-acetoxy-3R-([R]-(2-methylprop-2-yl)-silyloxy)ethyl)azetidin-2-one (7.41g) in acetone (100ml). After having been stirred for a further 1 hour, the mixture was partitioned between ethyl acetate and water; the organic phase was washed with water, with saturated aqueous sodium bicarbonate, with water, and with brine, was dried over anhydrous magnesium sulphate, and evaporated in vacuo to afford a yellowish solid (11g) chromatography over silica gel, and elution with ethyl acetate-hexane mixtures afforded the title compound (9.9g).
Example 17

4-Nitrobenzyl (3S-[1R-(dimethyl(2-methylprop-2-yl)-
silyloxy)ethyl]-4R-(4-methylthiobenzoylthio)azetidin-
2-on-1-yl)oxoacetate.

To a stirred mixture of 3S-[1R-[dimethyl(2-
methylprop-2-yl)silyloxy]ethyl]-4R-(4-
methylthiobenzoylthio)azetidin-2-one (9.89 g), calcium
carbonate (10 g) and diisopropylethylamine (6.27 ml) at
0°C was added a solution of 4-nitrobenzyl
chlorooxoacetate (6.99 g) in dichloromethane (150 ml).
After the mixture had been stirred for a further 30
minutes, it was partitioned between water and
dichloromethane; the organic layer was washed
successively with dilute hydrochloric acid, with water,
and with brine, and was dried over anhydrous sodium
sulphate. Evaporation of the solvent afforded the
title compound (15.6 g) as an orange oil.

\[ \delta (\text{CDCl}_3) 0.09 (6H, s); 0.82 (9H, s); 1.26 (3H, d, J = 6.4 \text{ Hz}); \]
\[ 2.53 (3H, s); 3.63 (1H, t, J = 3.0 \text{ Hz}); 4.40 (1H, m); \]
\[ 5.39 (2H, AB, J_{\text{gem}} = 13.0 \text{ Hz}); 6.20 (1H, d, J = 3.0 \text{ Hz}); \]
\[ 7.25 \text{ and } 7.63 (4H, AA'BB', J = 8.6 \text{ Hz}); 7.56 \text{ and } 8.21 \]
\[ (4H, AA'BB', J = 8.8 \text{ Hz}). \]

Example 18

4-Nitrobenzyl 5R,6S-[1R-[dimethyl(2-methylprop-2-yl)-
silyloxy]ethyl]-3-(4-methylthiophenyl)-7-oxo-4-thia-
1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

A mixture of 4-nitrobenzyl (3S-[1R-(dimethyl(2-
methylprop-2-yl)silyloxy)ethyl]-4R-(4-methylthiobenzoylthio)-
azetidinyl-2-on-1-yl)oxoacetate (15.6g), triethyl phosphite (8.23ml) and o-xylene (100ml) were heated under reflux (bath temperature 130°C) for 12 hours, and then evaporated in vacuo. Chromatography of the residue over silica gel, and elution with diethyl ether-hexane mixtures afforded the title compound (6.87g).

\[ \text{max (CDCl}_3 \text{)} 1783 \text{ cm}^{-1} \]

\[ \delta (\text{CDCl}_3) 0.06 (3H, s); 0.08 (3H, s); 0.85 (9H, s) \]

1.27 (3H, d, J = 6.3Hz); 2.48 (3H, s);
3.80 (1H, dd, J = 1.6 and 4.2Hz); 4.30 (1H, m);
5.21 (2H, AB, J grenades = 13.8Hz); 5.68 (1H, d, J = 1.6Hz);
7.18 (2H, d, J = 8.5Hz); 7.41 (4H, m); 8.16 (2H, d, J = 8.8Hz).

**Example 19**

4-Nitrobenzyl 5R,6S-(1R-hydroxyethyl)-(4-methylthio-phenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

To a stirred solution of 4-nitrobenzyl 5R,6S-(1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-3-(4-methylthiophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (6.87g) in dry tetrahydrofuran (100ml) was added glacial acetic acid (9.37ml) and a 1M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (35ml). After the mixture had been stirred for 16 hours it was partitioned between ethyl acetate and water; the organic layer was successively washed with saturated aqueous sodium bicarbonate, with water, with brine, was dried over anhydrous magnesium sulphate and evaporated in vacuo. Chromatography of the crude residue over silica gel, and elution with ethyl acetate-hexane mixtures afforded the title compound as a yellow solid (3.3g).

\[ \delta (\text{CDCl}_3) 1.19 (3H, d, J = 6.3Hz); 2.38 (3H, s); \]
3.78 (1H, dd, J = 1.5 and 6.3Hz); 4.08 (1H, m);
5.14 (2H, AB, J grenades = 14.0Hz); 5.71 (1H, d, J = 1.5Hz);
Example 20
4-Nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-methylsulphinyl-phenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

To a mixture of 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)(4-methylthiophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (306mg), ethyl acetate (10ml) and acetone (10ml) at -40°C was added a solution of 80% 3-chloroperbenzoic acid (154mg) in ethyl acetate (10ml). After the mixture had been warmed over two hours to 0°C, and this stirred for a further one hour at room temperature, it was partitioned between ethyl acetate and 5% aqueous potassium metabisulphite. The organic layer was washed with saturated aqueous sodium bicarbonate, with water and with brine, and then evaporated to dryness.

Chromatography over silica gel, and elution with ethylacetate-hexane mixtures afforded the title compound (143mg).

\[ \lambda_{\text{max}} (\text{CDCl}_3) 1780 \text{ cm}^{-1} \]
\[ \delta (\text{acetone-d}_6) 1.19 (3H,d,J = 6.3Hz); \]
\[ 2.59 (3H,s); \quad 3.84 (1H,dd,J = 1.5 \text{ and } 6.1Hz); \]
\[ 4.09 (1H,m); \quad 5.07,5.22 (2H,AB,J_{gem} = 13.8Hz); \]
\[ 5.79 (1H,d, J = 1.5Hz); \quad 7.41,8.06 (4H,AA'BB',J = 8.4Hz); \]
\[ 7.56 (4H,s). \]

Example 21
Potassium 5R,6S-(1R-hydroxyethyl)-3-(4-methylsulphinyl-phenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (140mg) was obtained by a procedure analogous to that described in Example 7 and
using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-methylsulphinylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (170mg), potassium bicarbonate (35.3mg), 10% palladium on charcoal (170mg), dioxane (5ml) and water (5ml).

\[ \delta (D_2O) 1.26 (3H,d,J = 6.3Hz); 2.83 (3H,s); \]
3.96 (1H,dd,J = 1.5 and 5.8Hz); 4.22 (1H,m);
5.76 (1H,d,J = 1.5Hz); 7.56,7.64 (4H,AA'BB', J = 8.2Hz)

Example 22

4-Nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-methyl-sulphonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (148mg) was obtained by a procedure analogous to that described in Example 20 by using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-methylthiophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.00g), 80% 3-chloroperbenzoic acid (1.00g), ethyl acetate (35ml) and acetone (15ml).

\[ \gamma_{max} (CDCl_3) 1780 \text{ cm}^{-1} \]
\[ \delta \text{(acetone-d}_6) 1.31 (3H,d, J = 6.3Hz); 3.13 (3H,s); \]
3.98 (1H,dd,J = 1.6 and 6.0Hz); 4.22 (1H,m);
5.26 (2H,AB, Jgem = 13.8Hz); 5.94 (1H,d,J = 1.6Hz);
7.52,7.93 (4H,AA'BE',J = 8.4Hz);
7.73,8.18 (4H,AA'BB',J = 8.7Hz).

Example 23

Potassium 5R,6S-(1R-hydroxyethyl)-3-(4-methylsulphonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (91mg) was obtained by a procedure analogous to that described in Example 7 by using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-
methylsulphonyl-phenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (148mg), potassium bicarbonate (29.7mg) 10% palladium on charcoal (70mg), water (5ml) and dioxane (5ml).

Example 24

4-Cyanothiobenzoic acid

A solution of 4-cyanobenzoyl chloride (1.66g) in dichloromethane (50ml) was treated with pyridine (0.81ml) and saturated with hydrogen sulphide for 30 minutes. The mixture was flushed with nitrogen then evaporated and the residue was partitioned between ethyl acetate and 2M aqueous hydrochloric acid. The organic layer was separated and extracted with saturated aqueous sodium bicarbonate. The basic aqueous extract was acidified with 2M aqueous hydrochloric acid and extracted with ethyl acetate. After drying over anhydrous magnesium sulphate the organic extract was evaporated to give 4-cyanothiobenzoic acid as a yellow solid (1.25g).

max (Nujol mull) 2500, 2230 and 1700 cm⁻¹

(acetone-d₆) 7.90, 8.20 (4H, AA'BB', J = 8.0Hz)

Example 25

4R-(4-Cyanobenzoylthio)-3S-[1R-(dimethyl(2-methylprop-2-y1)siloxyl)ethyl]azetidin-2-one.

A solution of 4-cyanothiobenzoic acid (0.34g) in acetone (5ml) was treated with 1M aqueous sodium hydroxide (2.1ml) and the mixture was added dropwise to a cooled (0⁰) solution of 4R-acetoxy-3R-[1R-(dimethyl (2-methylprop-2-y1)siloxyl)ethyl]azetidin-2-one (0.58g) in acetone-water (70:30) (10ml). The mixture was stirred
for 45 minutes then partitioned between ethyl acetate and brine. The organic phase was separated, dried over anhydrous magnesium sulphate and evaporated. Chromatography of the resulting oil with ethyl acetate-hexane mixtures over silica gel afforded the title compound as a colourless oil (0.56g).

\[ \delta (\text{CDCl}_3) 0.07 (6\text{H},\text{s}); 0.89 (9\text{H},\text{s}); 1.25 (3\text{H},\text{d,} J = 6.2\text{Hz}); 3.32 (1\text{H},\text{m}); 4.32 (1\text{H},\text{m}); 5.50 (1\text{H},\text{d,} J = 2.3\text{Hz}); 6.46 (1\text{H},\text{bs}); 7.80, 8.00 (4\text{H},\text{AA'BB',} J = 8.5\text{Hz}). \]

Example 26
4-Nitrobenzyl 4R-(4-cyanobenzoylthio)-3S-[1R-
[dimethyl(2-methylprop-2-yl)silyloxyethyl]-azetidin-
2-on-1-yl-oxoacetate.

A solution of 4R-(4-cyanobenzoylthio)-3S-[1R-
dimethyl(2-methylprop-2-yl)silyloxyethyl]-azetidin-2-one (0.76g) in dichloromethane (15ml) was cooled (0°C) and stirred. Solid calcium carbonate (0.49g) was added followed by diisopropylethylamine (0.51ml). A solution of 4-nitrobenzyl chlorooxocacetate (0.57g) in dichloromethane (6ml) was introduced dropwise and stirring was continued for 30 minutes. The mixture was filtered and the filtrate was washed with 0.1M aqueous hydrochloric acid, dried over anhydrous magnesium sulphate and evaporated to afford the title compound as a yellow foam (1.16g).

\[ \delta (\text{CDCl}_3) 0.03 (3\text{H},\text{s}); 0.09 (3\text{H},\text{s}); 0.87 (9\text{H},\text{s}); 1.26 (3\text{H},\text{d,} J = 6.4\text{Hz}); 3.63 (1\text{H},\text{m}); 4.41 (1\text{H},\text{m}); 5.43 (2\text{H},\text{s}); 6.17 (1\text{H},\text{d,} J = 3.5\text{Hz}); 7.57, 8.04 (4\text{H},\text{AA'BB',} J = 8.8\text{Hz}); 7.80, 8.23 (4\text{H},\text{AA'BB',} J = 8.8\text{Hz}). \]
Example 27

4-Nitrobenzyl 5R,3-(4-cyanophenyl)-6S-(1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

A solution of 4-nitrobenzyl 4R-(4-cyanobenzoylthio) 3S-(1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-azetidin-2-on-1-yl-oxoacetate (1.16g) in xylene (25ml) was warmed to 70° and treated with triethyl phosphite (0.67ml). The mixture was heated to reflux for 1 hour then evaporated and the residue was chromatographed in ether-hexane over silica to afford the product as a yellow oil (0.61g).

\[(\text{CDCl}_3)\] 0.05 (3H,s); 0.09 (3H,s); 0.89 (9H,s); 1.27 (3H,d, J = 6.2Hz); 3.86 (1H,dd, J = 1.6 and 3.8Hz);
4.33 (1H,m); 5.12,5.31 (2H,AB,Jgem = 13.6Hz);
5.79 (1H,dd,J = 1.6Hz); 7.50,7.66 (4H,AA'BB',J = 8.5Hz);
7.56,8.18 (4H,AA'BB',J = 8.5Hz).

Example 28

4-Nitrobenzyl 5R,3-(4-cyanophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

To a stirred solution of 4-nitrobenzyl 5R,3-(4-cyanophenyl)-6S-(1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.29g) in tetrahydrofuran (10ml), cooled to 0°, was added glacial acetic acid (0.30g). A solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 1.47ml) was introduced dropwise and the stirring was continued for 65 hours. Evaporation gave a residue which was dissolved in ethyl acetate, washed with saturated aqueous sodium bicarbonate, water and brine. The organic extract was dried over anhydrous magnesium sulphate evaporated and
the resulting gum was chromatographed with ethyl acetate-hexane mixtures over silica gel to afford the title compound as a yellow gum (0.11g). This compound had IR and $^1$H n.m.r. spectra identical to that of the compound prepared in Example 6.

**Example 29**

**4-(2,4-Dimethoxybenzylcarbonyl)thiobenzoic acid**

A solution of terephthaloyl chloride (20.30g) in dioxane (250ml) was treated dropwise with a solution of 2,4-dimethoxybenzyl alcohol (20.18g) in dioxane (40ml). Triethylamine (16.70ml) was added and the mixture was stirred for 1 hour before being filtered. The filtrate was evaporated and the resulting gum was dissolved in dichloromethane (200ml), treated with pyridine (9.71ml) and saturated with hydrogen sulphide for 40 minutes. The mixture was flushed with nitrogen then evaporated and the residue was partitioned between ethyl acetate and 2M aqueous hydrochloric acid. The organic layer was separated and extracted with saturated aqueous sodium bicarbonate. The basic aqueous extract was acidified with 2M aqueous hydrochloric acid and extracted with ethyl acetate. After drying over anhydrous magnesium sulphate the organic extract was evaporated to afford the title compound as a yellow solid (18.00g).

$\nu_{\text{max}}$ (CDCl$_3$) 2580, 1720, and 1700 cm$^{-1}$

$\delta$ (CDCl$_3$) 3.85 (6H, s); 5.39 (2H, s); 6.53 (3H, m); 7.40 (1H, d, $J = 9.0$Hz); 8.10 (4H, m).

**Example 30**

**4R-[4-(2,4-Dimethoxybenzylcarbonyl)benzoylthio]-3S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-azetidin-2-one.**
A solution of 4-(2,4-dimethoxybenzyloxycarbonyl)-thiobenzoic acid (16.2g) in acetone (150ml) was treated with 1M aqueous sodium hydroxide (62ml) and the mixture was added dropwise to a cooled (0°) solution of 4R-acetoxy-3R-([dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-azetidin-2-one (11.5g) in acetone water (70:30) (100ml). The mixture was stirred for 45 minutes then partitioned between ethyl acetate and brine. The organic phase was separated, dried over anhydrous magnesium sulphate and evaporated. Chromatography of the resulting oil with ethyl acetate-hexane mixtures over silica gel gave the title compound as a colourless foam (17.40g).

\[ \text{max (CDCl}_3\text{) } 3420, 1775 \text{ and } 1720 \text{ cm}^{-1} \]

\[ \delta (\text{CDCl}_3) \quad 0.07 (6H,s); 0.87 (9H,s); 1.24 (3H,d,J = 6.3Hz); 3.82 (6H,s); 4.30 (1H,m); 5.34 (2H,s); 5.49 (1H,d,J = 2.4Hz); 6.49 (2H,m); 6.61 (1H,bs); 7.32 (1H,d,J = 8.9Hz); 7.93,8.13 (4H,AA'BB',J = 8.5Hz). \]

Example 31

4-Nitrobenzyl 4R-[4-(2,4-dimethoxybenzyloxycarbonyl)benzoylthio]-3S-([dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-azetidin-2-one-oxoacetate.

To a cooled (0°), stirred solution of 4R-[4-(2,4-dimethoxybenzyloxycarbonyl)benzoylthio]-3S-([dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-azetidin-2-one (5.60g) in dichloromethane (50ml) was added calcium carbonate (2.50g) followed by diisopropylethylamine (2.61ml). A solution of 4-nitrobenzyl chloro-oxoacetate (2.92g) in dichloromethane (10ml) was added dropwise and after 30 minutes the mixture was filtered, washed with 0.1M aqueous hydrochloric acid, dried over anhydrous magnesium sulphate and evaporated to afford the title compound as a pale yellow foam.
Example 32
4-Nitrobenzyl 5R,3R-\{4-(2,4-dimethoxybenzyl)oxycarbonyl\}-3S-\{1R-\{dimethyl(2-methylprop-2-yl)silyloxylethyl\}\} oxoacetate

A solution of 4-nitrobenzyl 4R-\{4-(2,4-dimethoxybenzyl)oxycarbonyl\} benzoylthio]-3S-\{1R-\{dimethyl(2-methylprop-2-yl)silyloxylethyl\}\} azetidin-2-one (7.67 g) in xylene (100 ml) was warmed to 70\(^\circ\)C and treated with triethyl phosphite (3.43 ml). The mixture was heated to reflux for 4 hours then evaporated and the residue was chromatographed with ether-hexane mixtures over silica gel to afford the product as a yellow foam (4.38 g).

\(\delta (\text{CDCl}_3)\) 0.07 (3H, s); 0.08 (3H, s); 0.85 (9H, s); 1.27 (3H, d, J = 6.2 Hz); 3.82 (7H, m); 4.30 (1H, m); 5.09, 5.27 (2H, AB, J\_{\text{gem}} = 13.6 Hz); 5.34 (2H, s);

5.75 (1H, d, J = 1.5 Hz); 6.48 (2H, m); 7.32 (1H, d, J = 8.4 Hz); 7.48, 8.03 (4H, AA'BB', J = 8.6 Hz); 7.48, 8.13 (4H, AA'BB', J = 8.7 Hz).

Example 33
4-Nitrobenzyl 5R,3\{4-carboxyphenyl\}-6S-\{1R-\{dimethyl(2-methylprop-2-yl)silyloxy\}ethyl\}-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

A solution of 4-nitrobenzyl 5R,3\{4-(2,4-dimethoxy-
benzyloxycarbonyl)phenyl]-6S-{1R-[dimethyl(2-
methylprop-2-yl)silyloxy]ethyl]-7-oxo-4-thia-1-
azabicyclo[3.2.0]hept-2-ene-2-carboxylate (2.02g) in
dichloromethane (100ml) containing water (1ml) was
treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
(DDQ) (1.63g). The mixture was stirred at room
temperature for 30 hours then evaporated and the
residue was chromatographed with ethyl acetate-hexane
mixtures over silica gel to afford the title compound as a
brown foam (1.11g).

\[ \text{\(J_{\text{max}}(\text{CDCl}_3)\) 3660 br, 1790, 1720 and 1700 cm}^{-1}\]

\[ \delta \text{(acetone-d}6)\ 0.07 \ (3H,s); \ 0.10 \ (3H,s);
0.66 \ (9H,s); \ 1.29 \ (3H,d, J = 6.3Hz); \ 4.04 \ (1H,dd, J = 1.6
and 3.5Hz); \ 4.36 \ (1H,dd, J = 3.5 and 6.3Hz);
5.15,5.31 \ (2H,AB, J_{\text{gem}} = 13.7Hz); \ 5.91 \ (1H,d, J=1.6Hz);
7.59,7.98 \ (4H,AA'BB', J = 8.6Hz); \ 7.52,8.14 \ (4H,AA'BB',
J = 8.9Hz).\]

Example 34

4-Nitrobenzyl 5R,3-(4-aminocarbonylphenyl)-6S-{1R-
[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-7-oxo-4-
thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

To a stirred solution of 4-nitrobenzyl 5R,3-(4-
carboxyphenyl)-6S-{1R-[dimethyl(2-methylprop-2-yl)
silyloxy]ethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-
e-2-carboxylate (0.41g) in acetonitrile (10ml) was
added a solution of 1-hydroxybenzotriazole hydrate
(HOBt) (0.19g) in tetrahydrofuran (2ml) followed by
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
hydrochloride (0.20g). After 20 minutes a solution of
ammonia in ethanol (39mg ml \(^{-1}\), 1ml) was introduced
and the mixture was stirred for a further 10 minutes.
Evaporation and chromatography of the resulting residue
over silica gel and elution with ethyl acetate-hexane
mixtures gave the product as a yellow oil
\( \text{CDCl}_3 \) 1.10-1.50 (12H, m); 3.36 and 3.58 (1H, 2xdd, \( J = 4.3 \) and \( 9.3 \text{Hz} \)); 4.20 and 4.50 (1H, 2xm); 5.07 and 5.37 (2H, 2xAB, \( J_{\text{gem}} = 13.6 \text{Hz} \)); 5.42 and 6.32 (1H,
Example 35

4-Nitrobenzyl 5R,3-(4-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

A solution of 4-nitrobenzyl 5R,3-(4-aminocarbonylphenyl)-6S-(1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.41g) in tetrahydrofuran (20ml) cooled (0°C) and treated with glacial acetic acid (0.42g) followed by a solution of tetra-n-butyrammonium fluoride in tetrahydrofuran (1M, 2.1ml). The mixture was stirred for 45 hours then evaporated and the resulting gum was chromatographed with ethyl acetate over silica gel to afford the title compound as a pale yellow powder (0.13g).

$\lambda_{\text{max}}$ (Nujol mull) 3460-3260 br, 1775, 1705 and 1650 cm$^{-1}$
$\delta$ (acetone-$d_6$) 1.31 (3H, d, $J = 6.3$Hz); 3.94 (1H, dd, $J = 1.6$ and 6.2Hz); 4.21 (1H, m); 5.18, 5.33 (2H, AB, Jgem = 13.9Hz); 5.89 (1H, d, $J = 1.6$Hz); 6.73 (1H, bs); 7.54, 7.90 (4H, AA'BB', J = 8.4Hz); 7.46, 8.14 (4H, AA'BB', J = 8.9Hz).

Example 36

Potassium 5R,3-(4-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

7.40, 7.80 (4H, AA'BB', J = 9Hz); 7.56, 7.77 (4H, AA'BB', J = 8Hz).
4-Nitrobenzyl 5R,3-(4-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.12g) was dissolved in dioxane (10ml), potassium hydrogen carbonate (25mg) was dissolved in water (10ml) and the two solutions were mixed and hydrogenated at 375KPa (4 atm) over 10% palladium-on-charcoal (0.12g) for 1 hour. The mixture was filtered through Hyflo and the filtrate was freeze-dried. The residue was dissolved in water, washed with ethyl acetate and freeze-dried to give the title compound as a pale yellow powder (0.09g).

\[
\delta (D_2O) \quad 1.30 (3H, d, J = 6.3Hz); \quad 3.99 (1H, dd, J = 1.1 and 5.9Hz); \quad 4.26 (1H, m); \quad 5.79 (1H, d, J = 1.1Hz); \\
7.50, 7.80 (4H, AB'BB', J = 8.3Hz).
\]

Example 37

4-Nitrobenzyl 5R,3-(4-carboxyphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

A solution of 4-nitrobenzyl 5R,3-(4-carboxyphenyl)-6S-(1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.20g) in tetrahydrofuran (10ml) was cooled (0°C) and treated with glacial acetic acid (0.20g) followed by a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 1.02ml). The mixture was stirred for 24 hours then evaporated and the residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The basic aqueous layer was separated, carefully acidified to pH6 with 2M aqueous hydrochloric acid and extracted with ethyl acetate.

Evaporation of the extract afforded the title compound as a brown oil (0.08g).

\[
\nu_{\text{max}} \quad (\text{Nujol mull}) \quad 1770 \text{ and } 1700 \text{ cm}^{-1} \\
\delta \quad (\text{acetone}-d_6) \quad 1.31 (3H, d, J = 6.3Hz);
\]
3.95 (1H, d, J = 1.6 and 6.4Hz); 4.21 (1H, m);
5.16, 5.30 (2H, AB, Jgem = 13.8Hz); 5.94 (1H, d, J = 1.6Hz);
7.55, 7.98 (4H, AA'BB', J = 8.4Hz); 7.47, 8.13 (4H, AA'BB',
J = 8.8Hz).

Example 38
4-Nitrobenzyl 5R,3-(4-aminocarbonylphenyl)-6S-(1R-
hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate.

A solution of 4-nitrobenzyl 5R,3-(4-carboxyphenyl) -
6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-
azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.08g) in acetonitrile (10ml) was stirred and treated with a solution of 1-hydroxybenzotriazole (HBT) (0.04g) in tetrahydrofuran (2ml) followed by 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (0.05g). After 1 hour a solution of ammonia in ethanol (50mgm⁻¹, 0.5ml) was added and stirring was continued for a further 10 minutes. The mixture was evaporated and the residue dissolved in dichloromethane, washed with 1M aqueous citric acid, saturated aqueous sodium bicarbonate and brine. Evaporation of the organic extract afforded the title compound (0.07g) with properties identical to those of the compound prepared in Example 35.

Example 39
4-Nitrobenzyl 5R,3-[4-(2,4-dimethoxybenzylloxycarbonyl)-
phenyl]-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo-
[3.2.0]hept-2-ene-2-carboxylate.

A solution of 4-nitrobenzyl 5R,3-[4-(2,4-dimethoxy-
benzylloxycarbonyl)phenyl]-6S-(1R-[dimethyl(2-methylprop-
2-yl)silyl]oxy)ethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0] hept-2-ene-2-carboxylate (1.00g) in tetrahydrofuran
(40ml) was cooled (0°C) and treated with glacial acetic acid (0.82g) followed by a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 4.1ml). The mixture was stirred for 24 hours then evaporated and the residue was chromatographed over silica gel and eluted with ethyl acetate-hexane mixtures to give the title compound as a yellow oil (0.27g).

δ (CDCl₃) 1.38 (3H, d, J = 5.3Hz); 3.87 (1H, t, J = 5.3Hz); 4.30 (1H, m); 5.08, 5.25 (2H, AB, Jgem = 13.6Hz); 5.33 (2H, s); 7.45, 7.99 (4H, AA'BB', J = 8.5Hz); 8.11 (2H, d, J = 8.7Hz).

**Example 40**

4-Nitrobenzyl 3R,3-(4-carboxyphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

A solution of 4-nitrobenzyl 3R,3-(4-(2,4-dimethoxybenzylxycarbonyl)phenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.27g) in dichloromethane (20ml) containing water (1ml) was stirred and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.20g). After 24 hours the mixture was evaporated and the residue partitioned between ethyl acetate and water. The organic layer was separated, dried over anhydrous magnesium sulphate, evaporated and the resulting gum was chromatographed over silica gel with ethyl acetate-hexane mixtures to afford the title compound (0.13g) with properties identical to the compound prepared in Example 37.

**Example 41**

4-Nitrobenzyl 3R,3-(4-[N-(cyanomethyl)aminocarbonyl]-
phenyl]-6S-{1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl}-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

To a stirred solution of 4-nitrobenzyl 5R,3-{4-carboxyphenyl]-6S-{1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl}-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.36g) in acetonitrile (10ml) was added a solution of 1-hydroxybenzotriazole (HOBT) (0.17g) in tetrahydrofuran (2ml) followed by 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.18g). After 30 minutes aminoacetonitrile hydrochloride (0.7g) was added followed by triethylamine (0.26ml), and stirring was continued for a further 30 minutes. The mixture was evaporated, the residue was dissolved in ethyl acetate and washed with 2M aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, and evaporation of the organic phase gave a brown gum which was chromatographed with ethyl acetate-hexane mixtures over silica gel to afford the product as a yellow foam (0.24g).

$\nu$ max (Nujol mull) 3400-3300br, 1790, 1720 and 1665cm$^{-1}$
$\delta$ (CDCl$_3$) 7.04 (3H, s); 0.06 (3H, s); 0.84 (9H, s);
1.25 (3H, d, J = 6.3Hz); 3.82 (1H, d, J = 1.6 and 3.9Hz);
4.28 (1H, dq, J = 3.9 and 6.3Hz); 4.35 (2H, d, J = 5.9Hz);
5.08, 5.26 (2H, AB, Jgem = 13.6Hz); 5.75 (1H, d, J = 1.6Hz);
6.67 (1H, br, J = 5.9Hz); 7.51, 7.72 (4H, AA'BB', J = 8.5Hz);
7.43, 8.12 (4H, AA'BB', J = 8.7Hz).

Example 42
4-Nitrobenzyl 5R,3-{4-[N-(cyanomethyl)aminocarbonyl]-phenyl]-6S-{1R-[hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

To a cooled (0$^\circ$C) solution of 4-nitrobenzyl 5R,3-{4-[N-(cyanomethyl)aminocarbonyl]phenyl]-6S-{1R-
[dimethyl(2-methylprop-2-y1)silyloxy]ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.23g) in tetrahydrofuran (50ml) was added glacial acetic acid (0.22g) and a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 1.1ml). The mixture was stirred for 40 hours then evaporated and the residue was chromatographed with ethanol-ethyl acetate mixtures over silica gel to afford the title compound as a pale yellow solid (0.10g).

\[(\text{acetone-d}_6) 1.31 (3H, d, J = 6.3Hz); 3.95 (1H, dd, J = 1.7 and 6.2Hz); 4.21 (1H, m); 4.41 (2H, d, J = 3.3Hz); 5.17, 5.31 (2H, AB, J_{gem} = 13.8Hz); 5.90 (1H, d, J = 1.7Hz); 7.57, 7.68 (4H, AA'BB', J = 8.5Hz); 7.49, 8.15 (4H, AA'BB', J = 8.8Hz); 8.51 (1H, bt, J = 3.3Hz).\]

**Example 63**

Potassium 5R,3-\{N-(cyanomethyl)aminocarbonyl\}phenyl-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate.

4-Nitrobenzyl 5R,3-\{N-(cyanomethyl)aminocarbonyl\}phenyl-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.10g) was dissolved in dioxane (10ml), potassium hydrogen carbonate (19mg) was dissolved in water (10ml) and the two solutions were mixed and hydrogenated at about 375 pKa (4 atmospheres) over 10% palladium-on-charcoal (0.10g) for 1 hour. The mixture was filtered through Hyflo (Trade Mark) and the filtrate was freeze-dried. The residue was dissolved in water, washed with ethyl acetate and freeze-dried to afford the title compound as a pale yellow powder (0.07g).

\[(\text{D}_2\text{O}) 1.30 (3H, d, J = 6.4Hz); 4.00 (1H, dd, J=1.4 and 5.9Hz); 4.25 (1H, m); 4.36 (2H, s); 5.79 (1H, d, J = 1.4Hz); 7.51 and 7.75 (4H, AA'BB', J = 8.5Hz).\]
Example 44

4-(Methoxyaminocarbonyl)thiobenzoic acid

To a solution of terephthalyl chloride (7.0g) in dichloromethane (250ml) was added a 25% aqueous solution of methoxyamine hydrochloride (15ml) followed by a solution of triethylamine (12.5ml) in dichloromethane (250ml). After the mixture had been stirred for 1 hour, pyridine (4.2ml) was added, and then gaseous hydrogen sulphide (excess) was bubbled through over 30 minutes. After it had been stirred for a further 30 minutes the mixture was flushed with nitrogen, and partitioned between ethyl acetate and aqueous citric acid. The organic layer was washed with water and then extracted with saturated aqueous sodium bicarbonate. This aqueous extract was washed with ethyl acetate, and then reacidified to pH2 with 11M hydrochloric acid. Extraction with ethyl acetate, gave giving an organic extract which was then washed with water and with brine, and evaporated in vacuo, to afford a residue, which was chromatographed over silica gel. Elution with ethyl acetate-hexane mixtures afforded the title compound (2.0g).

δ (acetone-d₆) 3.80 (3H, s); 7.79-8.30 (4H, m).

Example 45

3S-1R-[Dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-4R-(4-methoxyaminocarbonylbenzoylthio)-azetidin-2-one

The title compound (1.85g) was prepared by a procedure analogous to that described in Example 16 by using 4-acetoxy-3R-[1R-[dimethyl(2-methylprop-2-yl)-silyloxy]ethyl]azetidinone (21.9g), 4-(methoxyaminocarbonyl)thiobenzoic acid (1.9g), 1M sodium hydroxide (8.7ml) and acetone (10ml).

max (film) 1758, 1665 cm⁻¹
Example 46

4-Nitrobenzyl \{3S-[1R-(dimethyl(2-methylprop-2-yl)-
silyloxy)ethyl]-4R-[4-(methoxy-(4-nitrobenzyloxy-
carbonyl-carbonyl)-aminocarbonyl)benzoylthio]-
azetidin-2-on-1-yl\}oxoacetate.

The title compound (4.1 mmol) was prepared by a procedure analogous to that described in Example 17 by using 3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)-
ethyl]-4R-(4-methoxyaminocarbonylbenzozylthio)azetidin-
2-one (1.8 g), 4-nitrobenzyl chlorooxocetate (2.5 g),
calcium carbonate (1.8 g), diisopropylethylene
(2.2 ml) and dichloromethane (20 ml).

\[ \delta_{(CDCl_3)} \text{max (CDCl}_3 \text{) 1815 cm}^{-1} \]
\[ \delta_{(CDCl_3)} 0.10 (6H, s); 0.84 (9H, s); \]
1.27 (3H, d, J = 6.3 Hz); 3.64-3.69 (1H, m); 3.90 (3H, s);
4.40-4.43 (1H, m); 5.39-5.44 (4H, m); 6.19 (1H, d, J = 3.4 Hz);
7.55-8.26 (12H, m).

Example 47

4-Nitrobenzyl 5R,6S-[1R-[dimethyl(2-prop-2-yl)silyloxy]-
ethyl]-3-[4-(methoxy-(4-nitrobenzyloxy carbonyl carbonyl)-
aminocarbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]
hept-2-ene-2-carboxylate.

The title compound (113 mg) was obtained by a procedure analogous to that described in Example 18 by using 4-nitrobenzyl \{3S-[1R-(dimethyl(2-methylprop-2-yl)-
silyloxy)ethyl]-4R-[4-(methoxy-(4-nitrobenzyloxy carbonyl-
carbonyl)-aminocarbonyl)benzoylthio]-azetidin-2-on-1-yl\}-
oxoacetate (1.25 mmol), triethyl phosphite (428 μl) and
xylene (5ml).

\[ \text{max (film) 1775, 1748 and 1725 cm}^{-1} \]
\[ \delta (\text{CDCl}_3) 0.07 (6H, s); 0.83 (9H, s); \]
1.25 (3H, d, J=6.3Hz); 3.80-3.83 (1H, m); 3.89 (3H, s);
4.30-4.38 (1H, m); 5.07,5.20 (2H, AB, J = 13.6Hz);
5.37 (2H, s); 5.75 (1H, d, J = 1.5Hz);
7.39, 7.98 (4H, AA'BB', J = 8.6Hz); 7.45, 8.09 (4H, AA'
BB', J = 8.3Hz); 7.50, 8.22 (4H, AA'BB', J = 8.7Hz).

**Example 48**

4-Nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-methoxyamino-
carbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-
en-2-carboxylate.

The title compound (250mg) was obtained by a
procedure analogous to that described in Example 19,
using 4-nitrobenzyl 5R,6S-{1R-[dimethyl(2-prop-2-yl)-
silyloxy]ethyl}-3-(4-[methoxy-(4-nitrobenzyloxy-
carbonyl-carbonyl)-aminocarbonyl]phenyl)-7-oxo-4-thia-1-
azabicyclo[3.2.0]hept-2-ene-2-carboxylate (670mg),
acetic acid (570μl), 1M tetra-n-butylammonium fluoride
in tetrahydrofuran (2.88ml), and tetrahydrofuran
(10ml).

\[ \text{max (film) 1788, 1722 cm}^{-1} \]
\[ \delta (\text{CDCl}_3) 1.41 (3H, d, J = 6.3Hz); \]
3.88 (1H, dd, J = 1.6 and 6.4Hz); 3.94 (3H, s); 4.28-4.35
(1H, m); 5.10, 5.26 (2H, AB, Jgem = 13.5Hz); 5.79 (1H, d, J=1.6Hz);
7.32, 7.98 (4H, AA'BB', J = 8.5Hz);
7.47, 8.13 (4H, AA'BB', J = 8.7Hz).

**Example 49**

Potassium 5R,6S-(1R-hydroxyethyl)-3-(4-methoxyamino-
carbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate.
The title compound (28mg) was obtained by a procedure analogous to that described in Example 7 by using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-methoxyaminocarbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (60mg), 10% palladium-on-charcoal (60mg), potassium bicarbonate (12mg), dioxane (5ml) and water (5ml).

δ (D2O) 1.29 (3H, d, J = 6.4Hz); 3.90 (3H, s); 4.00 (1H, dd, J = 1.5 and 5.9Hz); 4.21-4.28 (1H, m); 5.79 (1H, d, J = 1.5Hz); 7.49, 7.97 (4H, AA'BB', J=8.5Hz).

Example 50

4-(Methylaminocarbonyl)thiobenzoic acid.

The title compound (3.1g) was obtained by a procedure analogous to that described in Example 44 by using terephthaloyl chloride (10.0g), dichloromethane (300ml), methylene hydrochloride (4.2g), triethylamine (17.4ml), pyridine (7.76ml), and excess hydrogen sulphide.

δ (acetone-d6) 2.90 (3H, s); 7.96, 8.10 (4H, AA'BB', J = 8.4Hz).

Example 51

3S-[1R-[Dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-4R-(4-methylaminocarbonylbenzoylthio)-azetidin-2-one.

The title compound (1.7g) was obtained by a procedure analogous to that described in Example 16, by using 4-acetoxy-3R-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-azetidin-2-one (3.0g), 4-(methylaminocarbonyl)thiobenzoic acid (3.0g), 1M sodium hydroxide (15.6ml), and acetone (50ml).

max (film) 1765, 1660 cm⁻¹

δ (CDCl3) 0.08 (6H, s); 0.88 (9H, s); 1.23 (3H, d, J = 6.3Hz); 3.03 (3H, d, J = 4.8Hz);
3.28 (1H, dd, J = 2.4 Hz and 3.8 Hz); 4.28-4.32 (1H, m); 5.47 (1H, d, J = 2.4 Hz); 6.37 (1H, dd, J = 4.8 Hz); 6.54 (1H, bs); 7.83, 7.94 (4H, AA'BB', J = 8.5 Hz).

Example 52

4-Nitrobenzyl [3S-(1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-[4-(methylaminocarbonyl)benzoylthio]-azetidin-2-on-1-yl]oxoacetate.

The title compound (2.5g) was obtained by a procedure analogous to that used in Example 17 by using 4-nitrobenzyl chlorooxocacetate (1.17g), 3S-1R-{dimethyl-(2-methylprop-2-yl)silyloxy}ethyl]-4R-(4-methylaminocarbonylbenzoylthio)-azetidin-2-one (1.7g), calcium carbonate (1.7g), diisopropylethylamine (1.05ml), and dichloromethane (15ml).

δ (CDCl₃) 0.09 (6H, s); 0.86 (9H, s); 1.27 (3H, d, J = 6.3 Hz); 3.54 (3H, m, J = 4.9 Hz); 3.63 (1H, dd, J = 3.4 and 2.7 Hz); 4.39-4.43 (1H, m); 5.35, 5.43 (2H, AB, Jgem = 13.7 Hz); 6.19 (1H, d, J = 3.4 Hz); 7.57, 7.97 (4H, AA'BB', J = 8.1 Hz); 7.86, 8.22 (4H, AA'BB', J = 8.7 Hz).

Example 53

4-Nitrobenzyl 5R,6S-{1R-{dimethyl(2-methylprop-2-yl)silyloxy}ethyl}-3-(4-methylaminocarbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (0.66g) was obtained by a procedure analogous to that used in Example 18 by using 4-nitrobenzyl [3S-1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-[4-(methylaminocarbonyl)benzoylthio]-azetidin-2-on-2-yl]oxoacetate (2.5g), triethyl phosphite (1.37ml), hydroquinone (5mg), o-xylene (15ml).
\( \nu_{\text{max}} \) (film) 1778, 1715 cm\(^{-1}\)
\( \delta \) (CDCl\(_3\)) 0.082 (6H, s); 0.90 (9H, s);
1.22 (3H, d, \( J = 6.3 \text{ Hz} \)); 3.01 (3H, d, \( J = 4.6 \text{ Hz} \));
3.83 (1H, dd, \( J = 1.5 \) and \( 4.2 \text{ Hz} \)); 4.12–4.19 (1H, m);
5.10, 5.27 (2H, AB, \( J_{\text{gem}} = 13.6 \text{ Hz} \)); 5.76 (1H, d, \( J = 1.5 \text{ Hz} \));
6.15 (1H, dd, \( J = 4.6 \text{ Hz} \)); 7.43, 7.71 (4H, AA'BB', \( J = 8.4 \text{ Hz} \));
7.46, 8.14 (4H, AA'BB', \( J = 8.7 \text{ Hz} \)).

**Example 54**

4-Nitrobenzyl 5R,6S-(1R-hydroxyethyl)-(4-methylamino-carbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (175mg) was obtained by a procedure analogous to that used in Example 19 by using 4-nitrobenzyl 5R,6S-{1R-dimethyl(2-methylprop-2-yl)-silyloxy}ethyl]-3-(4-methylaminocarbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (660mg), glacial acetic acid (660µl), 1M tetra-n-butylammonium fluoride in tetrahydrofuran (3.3ml), and tetrahydrofuran (5ml).

\( \nu_{\text{max}} \) (KBr) 1770 cm\(^{-1}\)
\( \delta \) (DMSO-d\(_6\)) 1.17 (3H, d, \( J = 6.1 \text{ Hz} \));
2.78 (3H, d, \( J = 4.5 \text{ Hz} \)); 3.96–4.02 (2H, m); 5.2C (2H, m);
5.82 (1H, d, \( J = 1.5 \text{ Hz} \)); 7.32, 7.76 (4H, AA'BB', \( J = 7.2 \text{ Hz} \));
7.46, 8.10 (4H, AA'BB', \( J = 8.6 \text{ Hz} \)); 8.49 (1H, dd, \( J = 4.0 \text{ Hz} \)).

**Example 55**

Potassium 5R,6S-(1R-hydroxyethyl)-3-(4-methylamino-carbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (117mg) was obtained by a procedure analogous to that used in Example 7 by using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-methylamino-
carbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-one-2-carboxylate (175mg), 10% palladium on charcoal (175mg), potassium bicarbonate (36.2mg), dioxane (5ml) and water (5ml).

\[ \delta (D_2O) \]
- 1.26 (3H, d, J = 6.4Hz); 2.86 (3H, s); 3.96 (1H, dd, J = 1.3 and 6.0Hz); 4.19-4.26 (1H, m); 5.75 (1H, d, J = 1.3Hz); 7.44, 7.64 (4H, AA'BB', J = 8.3Hz).

Example 56

4-(Propylaminocarbonyl)-thiobenzoic acid

The title compound (3.4g) was obtained by a procedure analogous to that used in Example 44 by using terephthaloyl chloride (10.0g), propylamine (4.84ml), triethylamine (10.2ml), pyridine (8.36ml), excess hydrogen sulphide and dichloromethane (300ml).

\[ \delta (acetone-d_6) \]
- 0.93 (3H, t, J = 7.4Hz); 1.60 (2H, m); 3.30-3.40 (2H, m); 7.96-8.13 (4H, m).

Example 57

3B-\{1R-[Dimethyl(2-methylprop-2-yl)silyloxy]ethyl\}-4R-(4-propylaminocarbonylbenzoylthio)azetidin-2-one

The title compound (250mg) was obtained by a procedure analogous to that used in Example 16 by using 4-(propylaminocarbonyl)-thiobenzoic acid (330mg), 4-acetoxy-3R-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]azetidin-2-one (280mg) 1M sodium hydroxide solution (1.46ml), water (1.5ml), and acetone (7ml).

\[ \text{max (film) 1758, 1660 cm}^{-1} \]

\[ \delta (CDCl_3) \]
- 0.10 (6H, s); 0.90 (9H, s); 0.93 (3H, t, J = 7.3Hz); 1.19 (3H, d, J = 6.2Hz); 1.43-1.63 (2H, m); 3.23 (1H, dd, J = 2.4 and 3.8Hz); 3.34 (2H, m); 4.23-4.27 (1H, m); 5.42 (1H, d, J = 2.4Hz); 6.18 (1H, bs); 6.41 (1H, bs); 7.78, 7.91 (4H, AA'BB').
$J = 8.6\text{Hz}$.

**Example 58**

4-Nitrobenzyl $[3S-[1R-(\text{dimethyl}(2-\text{methylprop-2-yl})-\text{silyloxy})\text{ethyl}]-4R-[\text{(4-propylaminocarbonylbenzoylthio)}\text{azetidin-2-on-1-yl}]\text{oxoacetate.}$

The title compound (361mg) was obtained by a procedure analogous to that used in Example 17 by using $3S-[1R-(\text{dimethyl}(2-\text{methylprop-2-yl})-\text{silyloxy})\text{ethyl}]-4R-(\text{4-propylaminocarbonylbenzoylthio)}\text{azetidin-2-one}$ (250mg), 4-nitrobenzyl chlorooxocacetate (162mg), diisopropylethylamine (6.145m1), calcium carbonate (250mg), and dichloromethane (5m1).

$\delta$ (CDCl$_3$) 0.11 (6H,s); 0.92 (9H,s); 1.01 (3H,t, $J = 7.3\text{Hz}$); 1.27 (3H,d, $J = 6.3\text{Hz}$); 1.53-1.65 (2H,m); 3.46-3.51 (2H,m); 3.66 (1H,dd,$J = 2.8$ and 3.5Hz); 4.32-4.39 (2H,s); 5.43 (2H,s); 6.22 (1H,d, $J = 3.5\text{Hz}$); 7.57-8.30 (8H,m).

**Example 59**

4-Nitrobenzyl $5R,6S-[1R-(\text{dimethyl}(2-\text{methylprop-2-yl})-\text{silyloxy})\text{ethyl}]-7\text{-oxo-3-[4-(propylaminocarbonyl)phenyl]-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.}$

The title compound (45mg) was obtained by a procedure analogous to that used in Example 18 by using 4-nitrobenzyl $[3S-[1R-(\text{dimethyl}(2-\text{methylprop-2-yl})-\text{silyloxy})\text{ethyl}]-4R-(\text{4-propylaminocarbonylbenzoylthio)}\text{azetidin-2-on-1-yl}]\text{oxoacetate}$ (361mg), triethyl phosphite (0.185m1), and o-xylene (5m1).

$\nu_{\text{max}}$ (film) 1789 cm$^{-1}$

$\delta$ (CDCl$_3$) 0.90 (6H,s); 0.94 (9H,s); 1.04 (3H,t, $J = 7.4\text{Hz}$); 1.23 (3H,d, $J = 6.3\text{Hz}$); 1.27-1.34 (2H,m); 3.44-3.52 (2H,m); 3.89 (1H,dd, $J = 1.6$ and 4.2Hz); 4.19-4.30 (1H,m); 5.15 and 5.34 (2H,AB, $J_{\text{gem}} = 13.6\text{Hz}$); 5.81 (1H,d, $J = 1.6\text{Hz}$); 6.10 (1H,bs);
Example 60

4-Nitrobenzyl 5R,6S-(1R-hydroxyethyl)-7-oxo-3-[4-
(propylaminocarbonyl)phenyl]-4-thia-1-azabicyclo[3.2.0]-
hept-2-ene-2-carboxylate.

The title compound (50mg) was obtained by a
procedure analogous to that used in Example 19 by using
4-nitrobenzyl 5R,6S-(1R-[dimethyl(2-methylprop-2-yl)-
silyloxy]ethyl)-7-oxo-3-[4-(propylaminocarbonyl)phenyl]-
4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
(670mg), glacial acetic acid (0.67ml), tetrahydrofuran
(5ml), and 1M tetra-n-butylammonium fluoride in
tetrahydrofuran (3.2ml).

Example 61

Potassium 5R,6S-(1R-hydroxyethyl)-7-oxo-3-[4-(propyl-
aminocarbonyl)phenyl]-4-thia-1-azabicyclo[3.2.0]hept-2-
ene-2-carboxylate.

The title compound (30mg) was obtained by a
procedure analogous to that used in Example 7 by using
4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-7-oxo-3-[4-
(propylaminocarbonyl)phenyl]-4-thia-1-azabicyclo[3.2.0]-
hept-2-ene-2-carboxylate (50mg), 10% palladium on
charcoal (50mg), potassium bicarbonate (9.8mg), dioxane
(5ml), and water (5ml).

6 (D2O) 0.91 (3H,t, J = 7.3Hz); 1.28 (3H,d, J= 6.4Hz);
Example 62.

4-(Acetlylamino)-thiobenzoic acid.

To a stirred suspension of 4-acetylaminobenzoic acid (10.0g) in dry dichloromethane (50ml) at -15°C was added triethylamine (6ml) followed by ethyl chloroformate (6ml). After 3 hours hydrogen sulphide was bubbled through; the mixture was warmed to room temperature, treated with 2M hydrochloric acid and filtered. The filtrate was partitioned and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with water, with brine, were dried and were evaporated in vacuo. Chromatography of the residue over silica gel and elution with ethyl acetate-hexane mixtures afforded the title compound (2.2g).

δ (acetone-d₆) 2.17 (3H,s); 3.42 (1H,bs);
7.90,8.01 (4H,AA'BB',J = 8.8Hz).

Example 63

4R-(4-Acetylaminobenzoylthio)-3R-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-azetidin-2-one.

The title compound (0.85g) was obtained by a procedure analogous to that used in Example 16 by using 4-(acetlylamino)-thiobenzoic acid (2.0g), 4-acetoxy-3R-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-azetidin-2-one (2.2g) sodium hydroxide (0.44g), water (2ml), dichloromethane (5ml) and tetrahydrofuran (2ml).

ν max (CDCl₃) 1769, 1700, 1655 cm⁻¹

δ (CDCl₃) 0.09 (6H,s); 0.89 (9H,s);
1.24 (3H, J = 6.3Hz); 2.23 (3H,s);
3.28 (1H,dd, J = 2.4 and 4.0Hz); 4.24-4.36 (1H,m);
Example 64

4-Nitrobenzyl [4R-[4-(acetylamino)benzoylthio]-3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-azetidin-2-on-1-yl]oxoacetate.

The title compound (151mg) was obtained by a procedure analogous to that used in Example 17 by using 4R-[4-(acetylaminobenzoylthio)]-3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-azetidin-2-one (100mg), 4-nitrobenzyl chloro-oxoacetate (69mg), calcium carbonate (100mg), diisopropylethylamine (49ul), and dichloromethane (4ml).

\[ \nu_{\text{max}} (\text{CDCl}_3) 1813, 1760 \text{ cm}^{-1} \]

\[ \delta (\text{CDCl}_3) 0.09 (6H, s); 0.83 (9H, s); 1.26 (3H, d, J = 6.3Hz); 2.22 (3H, s); 3.60 (1H, dd, J = 3.0 and 3.4Hz); 4.35 (1H, m); 5.41 (2H, s); 6.15 (1H, d, J = 3.4Hz); 7.4-8.3 (8H, m). \]

Example 65

4-Nitrobenzyl 5R,3-(4-acetylaminophenyl)-6S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-7-oxo-4-thia-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (430mg) was obtained by a procedure analogous to that used in Example 18 by using 4-nitrobenzyl [4R-[4-(acetylamino)benzoylthio)-3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-azetidin-2-on-1-yl]oxoacetate (1.0g), triethyl phosphate (0.566ml), and o-xylene (8ml).

\[ \nu_{\text{max}} (\text{CDCl}_3) 1785, 1705 \text{ cm}^{-1} \]

\[ \delta (\text{CDCl}_3) 0.08 (6H, s); 0.85 (9H, s); 1.27 (3H, d, J = 6.3Hz); 2.19 (3H, s); 3.78 (1H, dd, J = 1.6 and 4.2Hz); 4.30 (1H, m); 5.10, 5.30 (2H, AB, J_{\text{gem}} = 13.7Hz); 5.65 (1H, d, J = 1.6Hz); 7.29-8.19 (8H, m). \]
Example 66

4-Nitrobenzyl 5R,3-(4-acetylamino'phenyl)-6S-(1R-
hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-
2-ene-2-carboxylate.

The title compound (131mg) was obtained by a
procedure analogous to that used in Example 19 by using
4-nitrobenzyl 5R,3-(4-acetylamino'phenyl)-6S-(1R-[dimethyl-
(2-methylprop-2-yl)-silyloxy]ethyl)-7-oxo-4-thia-1-aza-
bicyclo[3.2.0]hept-2-ene-2-carboxylate (430mg), glacial
acetic acid (0.534ml), tetrahydrofuran (10ml), and
1m tetra-n-butylammonium fluoride in tetrahydrofuran
(2.7ml).

\( \delta_{\text{max}} (\text{CDCl}_3) 1786 \text{ cm}^{-1} \).

\( \delta (\text{CDCl}_3) 1.40 (3H, d, J = 6.3\text{Hz}); 1.63 (1H, bs);
2.20 (3H, s); 3.60 (1H, dd, J = 1.6 and 6.6\text{Hz}); 4.2 (1H, m);
5.10, 5.29 (2H, AB, J_{\text{gem}}=13.7\text{Hz}); 5.70 (1H, d, J = 1.6\text{Hz});
7.23-8.16 (8H, m). \)

Example 67

Potassium 5R,3-(4-acetylamino'phenyl)-6S-(1R-hydroxyethyl)-
7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

The title compound (65mg) was obtained by a
procedure analogous to that used in Example 7 by using
4-nitrobenzyl 5R,3-(4-acetylamino'phenyl)-6S-(1R-hydroxy-
ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-
carboxylate (123mg), 10\% palladium on charcoal (123mg),
potassium bicarbonate (33.3mg), dioxane (5ml) and water
(5ml).

\( \delta (\text{D}_2\text{O}) 1.34 (3H, d, J = 6.4\text{Hz}); 2.19 (3H, s);
4.00 (1H, dd, J = 1.6 and 6.1\text{Hz}); 4.17-4.28 (1H, m);
5.79 (1H, d, J = 1.6\text{Hz}); 7.46 (4H, s). \)
Example 68
3-(Methylaminocarbonyl)-thiobenzoic acid

The title compound (4.5g) was obtained by a procedure analogous to that used in Example 44 by using isophthaloyl chloride (10.0g), triethylamine (17.8m1), methylamine hydrochloride (5g), dichloromethane (200m1), pyridine (7.5m1), and hydrogen sulphide (excess).

$\delta$ (acetone-$d_6$) 2.91 (3H, d, $J = 1.2$Hz); 7.5-8.3 (4H, m).

Example 69
3S-[1R-(Dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-[3-(methylaminocarbonyl)benzoylthio]azetidin-2-one.

The title compound (1.0g) was obtained by a procedure analogous to that used in Example 16 by using 4-acetoxy-3R-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]azetidin-2-one (2.04g), 3-(methylaminocarbonyl)-thiobenzoic acid (4.5g), 1M sodium hydroxide (21m1), and acetone (50m1).

$\gamma$ max (film) 1768, 1655 cm$^{-1}$

$\delta$ (CDCl$_3$) 0.10 (6H, s); 0.89 (9H, s);

1.24 (3H, d, $J = 6.3$Hz); 3.03 (3H, d, $J = 4.8$Hz);
3.29 (1H, dd, $J = 2.4$ anf; 3.8Hz); 4.30-4.36 (1H, m);
5.49 (1H, d, $J = 2.4$Hz); 6.96 (1H, bs, $J = 4.8$Hz);
7.14 (1H, bs); 7.53-8.30 (4H, m).

Example 70
4-Nitrobenzyl [3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-[3-(methylaminocarbonyl)benzoylthio]azetidin-2-oneyl]oxoacetate.

The title compound (1.43g) was obtained by a procedure analogous to that used in Example 17 by using 3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-(3-methylaminocarbonylbenzoylthio)azetidin-2-one (1.0g), 4-nitrobenzyl chloro-oxoacetate (720mg),
dichloromethane (10ml), calcium carbonate (1.0g), and diisopropylethylamine (0.60ml).

δ (CDCl₃) 0.09 (6H, s); 0.83 (9H, s); 1.25 (3H, d, J = 6.3Hz); 3.04 (3H, d, J = 4.9Hz); 3.60-3.66 (1H, m); 4.30-4.40 (1H, m); 5.38-5.42 (2H, AB, J = 13.0Hz); 6.19 (1H, d, J = 3.4Hz); 7.53-8.26 (8H, m).

Example 71

4-Nitrobenzyl 5R,6S-{1R-[dimethyl(2-methylprop-2-yl)-silyloxy]ethyl}-3-[(3-(methylaminocarbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (0.48g) was obtained by a procedure analogous to that used in Example 18 by using 4-nitrobenzyl {3S-[1R-(dimethyl(2-methylprop-2-yl)-silyloxy)ethyl]-4R-[3-(methylaminocarbonyl)benzoylthio]-azetidin-2-on-1-yl}oxacetate (1.43g), triethyl phosphite (0.78ml), hydroquinone (5mg), and o-xylene (10ml).

ν max (film) 1779 cm⁻¹

δ (CDCl₃) 0.08 (6H, s); 0.86 (9H, s); 1.25 (3H, d, J = 6.4Hz); 3.01 (3H, d, J = 4.9Hz); 3.81 (1H, dd, J = 1.6 and 4.2Hz); 4.10-4.25 (1H, m); 5.20, 5.28 (2H, AB, J = 13.6Hz); 5.74 (1H, d, J = 1.6Hz); 6.11 (1H, bd, J = 4.9Hz); 7.39-8.29 (8H, m).

Example 72

4-Nitrobenzyl 5R,6S-{1R-[hydroxyethyl]-3-[3-(methylaminocarbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (160mg) was obtained by a procedure analogous to that used in Example 19 by using 4-nitrobenzyl 5R,6S-{1R-[dimethyl(2-methylprop-2-yl)-silyloxy]ethyl}-3-[3-(methylaminocarbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.
(480mg), glacial acetic acid (0.48ml), tetrahydrofuran (10ml) and 1N tetra-n-butylammonium fluoride in tetrahydrofuran (2.4ml).

\[ \text{max (KBr)} 1785 \text{ cm}^{-1} \]

\( \delta (\text{CDCl}_3) 1.41 (3H, d, J = 6.3Hz); 1.68 (1H, bs); 3.01 (3H, d, J = 4.9Hz); 3.87 (1H, dd, J = 1.6 and 6.5Hz); 4.28-4.35 (1H, m); 5.13, 5.30 (2H, AB, J = 13.6Hz); 5.77 (1H, d, J = 1.6Hz); 6.08 (1H, bs); 7.37-8.17 (8H, m). 

**Example 73**

**Potassium 5R,6S-(1R-hydroxyethyl)-3-[3-(methylamino-carbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.**

The title compound (80mg) was obtained by a procedure analogous to that used in Example 7 by using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-[3-(methylamino-carbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (160mg), 10\% palladium on charcoal (160mg), potassium bicarbonate (33.1mg), water (5ml) and dioxane (5ml).

\( \delta (\text{D}_2\text{O}) 1.30 (3H, d, J = 6.4Hz); 2.89 (3H, s); 3.99 (1H, dd, J = 1.2 and 5.8Hz); 4.21-4.29 (1H, m); 5.78 (1H, d, J = 1.2Hz); 7.44-7.79 (8H, m). 

**Example 74**

**4-(Nitro)-thiobenzoic acid**

The title compound (9.8g) was obtained by a procedure analogous to that used in Example 24 by using 4-nitrobenzoyl chloride (10.0g), dichloromethane (200ml), pyridine (8.6ml); and hydrogen sulphide (excess).

\( \delta (\text{acetone-}d_6) 4.30 (1H, bs); 8.30, 8.37 (4H, AA'BB', J = 9.9Hz). 


Example 75

3S-{1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl}-4R-(4-nitrobenzoylthio)azetidin-2-one.

The title compound (2.6g) was obtained by a procedure analogous to that used in Example 16 by using 4-acetoxy-3R-{1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl}azetidin-2-one (2.0g), 4-(nitro)-thiobenzoic acid (1.7g), dichloromethane (50ml), water (50ml), and sodium hydroxide (0.36g).

\[ \text{Nmax (CDCl3) } 1775 \text{ cm}^{-1} \]
\[ \delta (CDCl3) \text{ } 0.10 \text{ (6H, s), } 0.89 \text{ (9H, s); } 1.27 \text{ (3H, d, } J = 6.3 \text{ Hz); } 3.32 \text{ (1H, dd, } J = 2.3 \text{ and } 3.8 \text{ Hz); } 4.30 \text{ (1H, m); } 5.51 \text{ (1H, d, } J = 2.3 \text{ Hz); } 6.50 \text{ (1H, bs); } 8.07,8.32 \text{ (4H, AA'BB', } J = 9.0 \text{ Hz).} \]

Example 76

4-Nitrobenzyl {3S-{1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl}-4R-(4-nitrobenzoylthio)azetidin-2-one-1-yl}loxoacetate.

The title compound (754mg) was obtained by a procedure analogous to that used in Example 17 by using 3S-{1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl}-4R-(4-nitrobenzoylthio)azetidin-2-one (0.5g), calcium carbonate (0.5g), 4-nitrobenzyl chlorooxoacetate (0.36g), dichloromethane (10ml) and diisopropylethylamine (0.255ml).

\[ \text{Nmax (film) } 1817,1712 \text{ cm}^{-1} \]
\[ \delta (CDCl3) \text{ } 0.10 \text{ (6H, s), } 0.84 \text{ (9H, s); } 1.28 \text{ (3H, d, } J = 6.3 \text{ Hz); } 3.64 \text{ (1H, dd, } J = 3.0 \text{ and } 3.4 \text{ Hz); } 4.38-4.47 \text{ (1H, m); } 5.41 \text{ (2H, s); } 6.18 \text{ (1H, d, } J = 3.4 \text{ Hz); } 7.75,8.22 \text{ (4H, AA'BB', } J = 8.8 \text{ Hz); } 8.08,8.33 \text{ (4H, AA'BB', } J = 8.9 \text{ Hz).} \]
Example 77

4-Nitrobenzyl 5R,6S-[1R-[dimethyl(2-methylprop-2-yl)-silyloxy]ethyl]-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (215mg) was obtained by a procedure analogous to that used in Example 18 by using 4-nitrobenzyl[3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-(4-nitrobenzoylthio)azetidin-2-on-1-yl]-oxoacetate (754mg), triethyl phosphite (0.418 ml), and o-xylene (5ml).

\[ \text{max (CDCl}_3\text{)} 1778 \text{ cm}^{-1} \]

\[ \text{max (CDCl}_3\text{) 0.09 (6H,s); 0.86 (9H,s);} \]

1.27 (3H, d, J = 6.3Hz); 3.87 (1H, dd, J = 1.5 and 4.0Hz);
4.29 (1H, m); 5.12, 5.30 (2H, AB, Jgem = 13.6Hz);
5.81 (1H, d, J = 1.5Hz); 7.51, 8.16 (4H, AA'BB', J=8.6Hz);
7.62, 8.20 (4H, AA'BB', J = 8.8Hz).

Example 78

4-Nitrobenzyl 5R,6S-[1R-hydroxyethyl]-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (106mg) was obtained by a procedure analogous to that used in Example 19 by using 4-nitrobenzyl 5R,6S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (200mg), glacial acetic acid (0.204ml), tetrahydrofuran (5ml), and 1M tetra-n-butylammonium fluoride in tetrahydrofuran (1.02ml).

\[ \text{max (film) 1790, 1712 cm}^{-1} \]

\[ \text{(CDCl}_3\text{) 1.41 (3H,d, J = 6.3Hz); 1.61 (1H,bs);} \]

3.91 (1H, dd, J = 1.6, 6.4Hz); 4.20-4.39 (1H, m);
5.12, 5.31 (2H, AB, Jgem = 13.5Hz);
5.82 (1H, d, J = 1.6Hz); 7.47, 8.17 (4H, AA'BB', J=8.7Hz);
7.58, 8.21 (4H, AA'BB', J = 8.9Hz).
Example 79
Potassium 5R,3-(4-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

The title compound (44mg) was obtained by a procedure analogous to that used in Example 7 by using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (100mg), 10% palladium on charcoal (100mg), potassium bicarbonate (21.2 mg), water (5ml), and dioxane (5ml).

\[ \delta (D_2O) 1.33 \text{ (3H,d,} J = 6.3Hz); \]
\[ 3.93 \text{ (1H,dd,} J = 1.4 \text{, and 5.3Hz); 4.23 \text{ (1H,m); 5.70 \text{ (1H,d,} J = 1.4Hz); 6.80,7.30 \text{ (4H,AA'BB',} J = 8.4Hz).} \]

Example 80
Potassium 5R-3-(4-acetylaminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

A solution of 4-nitrobenzyl 5R,3-(4-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (33mg) in water (0.5ml) and dioxane (0.5ml) was treated at 0° with acetic anhydride (0.05ml). The mixture was warmed over 30 minutes to room temperature and stirred a further hour. Lyophilisation followed by partition of the solid between ethyl acetate and water, and lyophilisation of the aqueous layer afforded the title compound (29mg) with properties identical to those given in Example 67.

Example 81
2-(Trimethylsilyl)ethyl chlorooxoxacetate.

To a stirred solution of oxalyl chloride (12.7g) in dry diethyl ether (25ml) at 0°C was added dropwise 2-(trimethylsilyl)ethanol (11.8g). The mixture was stirred for a further 16 hours, and then distilled to afford the title compound (19.9g) bp 80°/8mm.
Example 82

2-(Trime:thylsilyl)ethyl [3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-4R-(4-nitrobenzoylthio)azetidin-2-on-1-yl]oxoacetate.

The title compound (8.0g) was obtained by a procedure analogous to that used in Example 17 by using 4-cetoxyl-3S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-azetidin-2-one (5.0g), calcium carbonate (5.0g), 2-(trimethylsilyl)ethyl chlorooxooacetate (3.35ml), dichloromethane (100ml) and diisopropylethylamine (4.2ml).

δ (CDCl₃) 0.07 (9H,s); 0.12 (6H,8); 0.88 (9H,s); 1.11 (2H,t,J 8.4Hz); 1.29 (3H,d,J = 6.3Hz); 3.62 (1Hdt,J = 3.3Hz); 4.40 (6.18 (1H,d,J = 3.3Hz); 8.11, 8.7 (AA'BB',J = 8.8Hz).

Example 83

2-(Trime:thylsilyl)ethyl 5R,6S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (2.86g) was obtained by a procedure analogous to that used in Example 18 by using 2-(trimethylsilyl)ethyl [3S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-4R-(4-nitrobenzoylthio)azetidin-2-on-1-yl]oxoacetate (8.0g), triethyl phosphite (4.2ml), o-xylene (100ml), and hydroquinone (10mg).

max (film) 1796, 1711 cm⁻¹

δ (CDCl₃) 0.01 (9H,s); 0.11 (3H,s); 0.12 (3H,s); 0.91 (11H,m); 1.28 (3H,d,J = 6.3Hz); 3.82 (1H,dd,J = 1.6 and 4.6Hz); 4.18 (2H,m); 4.29 (1H,m); 5.76 (1H,d,J = 1.6Hz); 7.64, 8.23 (4H,AA'BB',J=8.9Hz).
Example 84

2-(Trimethylsilyl)ethyl 5R,6S-(1R-hydroxyethyl)-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

The title compound (142mg) was obtained by a procedure analogous to that used in Example 19 by using prop-2-yl) silyloxy)]ethyl)-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (360mg), glacial acetic acid (0.4mI), tetrahydrofuran (10ml), and 1M tetra-n-butylammonium fluoride in tetrahydrofuran (2ml).

\[ \begin{align*}
\text{max (CDCl}_3 \text{) } & 1789, 1710 \text{ cm}^{-1} \\
\delta (\text{CDCl}_3) & 0.01 (9H, s); 0.92 (2H, m); 1.40 (3H, d, J = 6.3Hz); 3.86 (1H, dd, J = 1.6 and 6.6Hz); 4.20 (2H, m); 4.30 (1H, m); 5.79 (1H, d, J = 1.6Hz).
\end{align*} \]

Example 85

2-(Trimethylsilyl)ethyl 5R,6S-(1R-hydroxyethyl)-3-(4-hydroxyaminophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate.

A mixture of 2-(trimethylsilyl)ethyl 5R,6S-(1R-hydroxyethyl)-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (2.1g), 10% palladium on charcoal (2.1g) and dioxane (50ml) was hydrogenolysed at 375 kPa (4 atm) for 2 hours, was filtered through diatomaceous earth and evaporated in vacuo. Chromatography at the residue over silica gel and elution with ethyl acetate-hexane mixtures afforded the title compound (1.5g).

\[ \begin{align*}
\delta (\text{acetone-}d_6) & 0.02 (9H, s); 0.95 (2H, m); 1.31 (3H, d, J = 6.3Hz); 3.76 (1H, dd, J = 1.5 and 7.0Hz); 4.17 (3H, m); 4.42 (1H, d, J = 4.9Hz); 5.69 (1H, d, J = 1.5Hz); 6.95 and 7.43 (4H, AA''BB'', J = 8.6Hz); 7.90 (1H, broad).
\end{align*} \]
Example 86

2-(Trimethylsilyl)ethyl 5R,3-(4-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate.

A mixture of 2-(trimethylsilyl)ethyl 5R,6S-(1R-hydroxyethyl)-3-(4-hydroxyaminophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.4g), platinum dioxide (500mg), and dry ethyl acetate (30ml) was hydrogenolysed at 375 kPa (4 atm) at 20°C, and then filtered and evaporated in vacuo. Chromatography of the residue over silica gel and elution with ethyl acetate-hexane mixtures afforded the title compound (1.06g).

Example 87

2-(Trimethylsilyl)ethyl 5R,3-(4-formylaminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate.

To a stirred solution of 2-(trimethylsilyl)ethyl 5R,3-(4-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (200mg) in deuterochloroform (5ml) at 0°C was added formic acid (22.3μl), followed by 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (113mg). The mixture was stirred a further 15 minutes, and was then partitioned between water and chloroform. The organic layer was washed with 1M citric acid, with water, with saturated aqueous sodium bicarbonate, with brine, was
dried over anhydrous sodium sulphate and was evaporated in vacuo. Chromatography of the residue over silica gel and elution with ethyl acetate-hexane mixtures afforded the title compound (162mg).

\[ \delta \] (KBr) 1777, 1702 and 1623 cm\(^{-1}\) 

\( \gamma \) \( \nu \) (DMSO-\( d_6 \)) 0.01 (9H, s); 0.84 (2H, m); 

1.18 (3H, d, J = 6.3 Hz); 3.85 (1H, dd, J = 1.5 and 6.3 Hz); 

4.00 (1H, m); 4.10 (2H, m); 5.23 (1H, d, J = 4.8 Hz); 

5.73 (1H, d, J = 1.5 Hz); 

7.42 and 7.61 (\( 4\)H, AA'BB', J = 8.5 Hz); 8.31 (1H, s); 

10.31 (1H, broad).

**Example 88**

Potassium 5R,3-(4-formylaminophenyl)-6S-(1R-hydroxy-ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

To a stirred solution of 2-(trimethylsilyl)ethyl 5R,3-(4-formylaminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (80mg) in tetrahydrofuran (3ml) at 0°C was added a solution of a 1M tetra-n-butylammonium fluoride in tetrahydrofuran (0.184ml) which had been dried over 4Å molecular sieves. After 16 hours the mixture was treated with an aqueous solution of potassium bicarbonate (18.4mg). The aqueous solution was washed with ethyl acetate, and then lyophilised to afford a crude product (110mg). Purification either by chromatography over HP20A resin or by acidification/neutralisation or preparative high pressure liquid reverse phase chromatography (C\( 18 \)-silica gel) and elution with water-acetonitrile-formic acid mixtures afforded, after lyophilisation and reneutralisation with potassium bicarbonate the title compound (50mg).

\[ \delta \] (D\( 2 \)O) 1.35 (3H, d, J = 6.3 Hz); 

3.95 (1H, dd, J = 1.5 and 5.5 Hz); 4.25 (1H, m);
Example 89

2-(Trimethylsilyl)ethyl 5R,6S-(1R-hydroxyethyl)-3-[4-[methylamino]carbonylaminophenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

A mixture of 2-(trimethylsilyl)ethyl 5R,3-(4-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (200mg), dry tetrahydrofuran (5ml) and methyl isocyanate (0.3ml) was stirred at room temperature for 16 hours, and then partitioned between ethyl acetate and water. The organic layer was washed with water and with brine, was dried over anhydrous sodium sulphate and evaporated in vacuo. Chromatography of the residue over silica gel, and elution with ethyl acetate-hexane mixtures afforded the title compound (86 mg).

\[ \text{max (film) 1785 cm}^{-1} \]
\[ \delta (\text{acetone-d}_6) 0.01 (6H, s); 0.93 (2H, m); \]
\[ 1.29 (3H, d, J = 6.3Hz); 2.73 (3H, d, J = 4.6Hz); \]
\[ 3.77 (1H, dd, J = 1.6 and 6.9Hz); 4.15 (3H, m); \]
\[ 4.37 (1H, d, J = 5.0Hz); 5.70 (1H, d, J = 1.6Hz); \]
\[ 5.78 (1H, broad); 7.41 and 7.52 (4H, AA'BB', J = 8.8Hz); \]
\[ 8.21 (1H, broad). \]

Example 90

Potassium 5R,6S-(1R-hydroxyethyl)-3-{4-[methylamino]carbonylaminophenyl}-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate.

The title compound (55mg) was obtained by a procedure analogous to that used in Example 88, using 2-(trimethylsilyl)ethyl 5R,6S-(1R-hydroxyethyl)-3-[4-[methylamino]carbonylaminophenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (80mg), a
dried solution of 1M tetra-n-butylammonium fluoride in tetrahydrofuran (0.17ml), tetrahydrofuran (5ml) and potassium bicarbonate (17.3mg).

$^1$H NMR (D$_2$O) 1.3 (3H, d, J=6.3Hz); 2.71 (3H, s); 3.91 (1H, dd, J=1.5 and 5.8Hz); 4.23 (1H, m); 5.70 (1H, d, J=1.5Hz); 7.26 and 7.36 (4H, AA'BB', J=8.7Hz).

**Example 91**

4-Nitrobenzyl 5R,3-(3-carboxyphenyl)-6S-[L-[dimethyl-
(2-methylprop-2-yl)silyloxy]ethyl]-7-oxo-4-thia-1-aza-
bicyclo[3.2.0]hept-2-ene-2-carboxylate.

By a procedure analogous to that used in Example 29, but starting from a solution of isophthaloyl chloride (10.15g) in dioxane (150ml), a solution of 2,4-
dimethoxybenzyl alcohol (10.09g) in dioxane (20ml),
triethylamine (8.35ml), dichloromethane (100ml),
pyridine (4.85ml), and hydrogen sulphide (excess), there
was obtained
3-(2,4-dimethoxybenzylloxycarbonyl)thiobenzoic acid
(11.6g);

$\nu$ max 2550, 1721, 1675 and 1615 cm$^{-1}$;
$^1$H NMR (acetone-d$_6$) 3.72 (3H, s); 3.77 (3H, s); 5.26 (2H, s); 6.44 (1H, dd, J=2.4 and 8.3Hz); 6.50 (1H, d, J=2.3Hz); 7.28 (1H, d, J=8.3Hz); 7.60 (1H, m); 8.16 (2H, m); 8.53 (1H, m).

A solution of this thiobenzoic acid (10.9g) in
acetone (70ml) was treated in a procedure analogous to
that used in Example 30 with 1M-sodium hydroxide (43ml)
and a solution of 4-acetoxy-3R-[1R-[dimethyl(2-methyl-
prop-2-yl)silyloxy]ethyl]-azetidin-2-one (7.85g) in
acetone-water (3:1) (100ml) to afford
4R-[3-(2,4-dimethoxybenzylloxycarbonyl)benzoylethio]-3S-
[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]azetidin-
2-one (7.66g);
A solution of this azetidinone (2.8g) in dichloromethane (20mL) was treated in a procedure analogous to that used in Example 31 with calcium carbonate (1.25g), diisopropylethylamine (0.97g), and a solution of 4-nitrobenzyl chlorooxalate (1.46g) in dichloromethane (5mL) to afford as a yellow foam 4-nitrobenzyl 4R-3-[2,4-dimethoxybenzylloxy carbonyl]-benzoylthio]-3S-[1R-[dimethyl(2-methylprop-2-yl)silyl-oxyllethylacetidin-2-on-1-yl]oxyacetate (3.8g).

\[ \text{\( \gamma_{\text{max}} (\text{CDCl}_3) \)) = 3418, 1772, 1719 \text{ cm}^{-1}; \]
\[ \delta (\text{CDCl}_3) = 0.07 (6H, s); 0.86 (9H, s); 1.22 (3H, d, J=6.3Hz); \]
3.27 (1H, dd, J=2.5 and 4Hz); 3.80 (3H, s); 3.81 (3H, s); 4.29 (3H, m); 5.34 (2H, s); 5.46 (1H, d, J=2.5Hz);
5 6.47 (2H, m); 6.54 (1H, s); 7.30 (1H, d, J=8.9Hz);
7.51 (1H, t, J=7.8Hz); 8.05 (1H, dd, J=1.4 and 7.8Hz);
8.25 (1H, dd, J=1.4 and 7.8Hz); 8.54 (1H, t, J=1.4Hz).

A solution of this foam (3.8g) in xylene (100mL) was treated in a procedure analogous to that used in Example 32 with triethyl phosphite (1.66g) in xylene (10mL) to afford 4-nitrobenzyl 5S,6S-[1R-[dimethyl(2-methylprop-2-yl)silyl-oxy)]ethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.84g):

\[ \text{\( \gamma_{\text{max}} (\text{CDCl}_3) \)) = 1790 and 1721 \text{ cm}^{-1}; \]

\[ \delta (\text{CDCl}_3) = 0.01 (3H, s); 0.09 (3H, s); 0.83 (9H, s); 1.26 (3H, d, J=6.3Hz); 3.64 (1H, t, J=3Hz); 3.82 (3H, s); 4.83 (3H, s); 5.36 (2H, s); 5.40 (2H, s);
6.19 (1H, d, J=3.4Hz); 6.50 (1H, m); 7.32 (1H, d, J=8.9Hz);
7.55 (3H, m); 8.09 (1H, d, J=7.9Hz); 8.21 (2H, d, J=8.8Hz);
8.29 (1H, d, J=7.9Hz); 8.57 (1H, d, J=1.7Hz).\]
A solution of this 4-nitrobenzyl carboxylate (1.84g) in dichloromethane (100ml) was treated in a procedure analogous to that used in Example 33 with water (1ml) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (1.14g) to afford the title 3-carboxyphenyl compound (0.98g):

$$\delta\ (CDCl_3)\ 0.07\ (3H, s); 0.08\ (3H, s); 0.85\ (9H, s); 3.82\ (3H, s+m); 4.30\ (1H, m); 5.08, 5.25\ (2H, AB, J_{gem}=13.7Hz); 5.32\ (2H, s); 5.74, (1H, d, J=1.5Hz); 6.48\ (2H, m); 7.31\ (1H, d, J=8.9Hz); 7.40\ (3H, m); 7.59\ (1H, m); 8.08\ (4H, m);$$

Example 92

4-Nitrobenzyl 5R,3-[3-(2,4-dimethoxybenzyloxy carbonyl)-phenyl]-6S-[1R-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

The title compound (6.6g) was prepared by a procedure analogous to that used in Example 37 by using 4-nitrobenzyl 5R,3-[3-(2,4-dimethoxybenzyloxy carbonyl)-phenyl]-6S-[1R-[dimethyl(2-methylprop-2-yl)silyloxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.8g), glacial acetic acid (6.5g) and a 1M solution of tetra-n-butylammonium fluoride in tetrahydrofuran (32.6ml).

$$\delta\ (CDCl_3)\ 1.31\ (3H, d, J=6Hz); 3.75\ (6H, s); 3.80\ (1H, dd, J=1.2 and 6.5Hz); 4.03\ (1H, m); 5.00, 5.17\ (2H, AB, J_{gem}=13.6Hz); 5.25\ (2H, s); 5.69\ (1H, d, J=1.2Hz); 6.42\ (2H, m); 7.2-7.5\ (5H, m); 7.9-8.2\ (4H, m).$$
Example 93
4-Nitrobenzyl 5R,3-(3-carboxyphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

The title compound (1.39g) was obtained by a procedure analogous to that used in Example 40 using 4-nitrobenzyl 5R,3-[3-(2,4-dimethoxybenzoylcarbonyl)phenyl]-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (6.2g), dichloromethane (200ml), water (10ml) and DDQ (4.54g):

δ (acetone-d₆) 1.20 (3H,d,J=6.3Hz); 3.84 (1H,dd,J=1.7 and 4.10 5.06, 5.19 (2H,AB,J=13.8Hz); 5.79 (1H,d,J=1.7Hz); 7.35-7.45 (4H,m); 7.61 (1H,dd,J=7.8 and 1.4Hz); 7.90-8.06 (4H,m).

Example 94
4-Nitrobenzyl 5R,3-(3-aminocarbonylphenyl)-6S-(1R-[dimethyl-(2-methylprop-2-yl)silyloxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

By a procedure analogous to that used in Example 34, but using 4-nitrobenzyl 5R,3-(3-carboxyphenyl)-6S-[1R-[dimethyl-(2-methylprop-2-yl)silyloxyethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (786mg), HOBt (365mg), acetonitrile 840ml, tetrahydrofuran (4ml), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (389mg) and a solution of ammonia in ethanol (36 g,1.0, 2ml) the title compound was obtained:

δ (acetone-d₆) 0.08 (3H,s); 0.10 (3H,s); 0.93 (9H,s); 1.28 (3H,d,J=6.3Hz); 4.02 (1H,dd,J=1.7 and 3.6Hz); 4.35 (1H,dq,J=3.6 and 6.3Hz); 5.30, 5.15 (2H,AB,J=13.9Hz); 5.87 (1H,d,J=1.7Hz); 6.92 (1H,bs); 7.47 (1H,t,J=7.8Hz); 7.54, 8.13 (4H,AA'BB',J=8.6Hz); 7.64 (1H,dt,J=1.4 and
Example 95

4-Nitrobenzyl 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

By a process analogous to that used in Example 38, but using 4-nitrobenzyl 5R,3-(3-carboxyphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (492mg), 1-hydroxybenzotriazole (HOBT) (283mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (830mg) and a solution of ammonia in ethanol (29.8 g l⁻¹, 1.78ml), acetonitrile (50ml) and tetrahydrofuran (82ml), the title compound (392mg) was obtained:

δ (acetone-d₆) 1.30 (3H,d,J=6.3Hz); 3.93 (1H,dd,J=1.6 and 6.3Hz); 4.18 (1H,m); 5.16, 5.29 (2H,AB,J_gem=14.0Hz); 5.88 (1H,d,J=1.6Hz); 6.79 (1H,bs); 7.48 (3H,m); 7.62 (1H,dt,J=1.3Hz and 7.8Hz); 7.97 (1H,dt,J=1.3 and 7.8Hz); 8.03 (1H,t,J=1.3Hz); 8.13 (2H,d,J=8.8Hz).

Alternatively, the title compound (314mg) was obtained from the corresponding dimethyl-(2-methylprop-2-yl)silyloxyethyl compound (744mg) prepared in Example 94 by a procedure analogous to that used in Example 35 by using glacial acetic acid (766mg) and a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 3.84ml).
Example 96

Potassium 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

By a procedure analogous to that used in Example 36, and using 4-nitrobenzyl 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (250mg), dioxane (1ml), potassium bicarbonate (51mg), water (10ml) and 10% palladium-on-charcoal (250mg), the title compound (125mg) was obtained.

\[ \delta (\text{D}_2\text{O}) \]

1.30 (3H, d, J=6.3Hz); 3.98 (1H, dd, J=1.3 and 5.9Hz); 4.25 (1H, m); 5.78 (1H, d, J=1.5Hz);
7.48 (1H, t, J=8.0Hz); 7.60 (1H, dt, J=1.4 and 7.9Hz);
7.75-7.79 (2H, m).

Example 97

4-Nitrobenzyl 5R,3-(3-aminocarbonylmethylaminocarboxyphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

By a process analogous to that used in Example 38, but using 4-nitrobenzyl 5R,3-(3-carboxyphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (243mg), HOBT (140mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (148mg), acetonitrile (20ml), tetrahydrofuran (2ml), glycineamide hydrochloride (285mg) and triethylamine (261mg) the title compound was obtained as a yellow solid (132mg).

\[ \delta (\text{acetone-}d_6) \]

1.32 (3H, d, J=6.3Hz); 3.96 (1H, dd, J=1.7 and 6.3Hz); 4.03 (2H, d, J=5.6Hz); 4.22 (1H, m); 4.47 (1H, d, J=4.8Hz); 5.18 and 5.31 (2H, AB, J_{gem}=13.8Hz); 5.91 (1H, d, J=1.6Hz); 6.44 (1H, bs); 7.05 (1H, bs); 7.49 and 8.16 (4H, AA'BB', J=8.8Hz); 7.52 (1H, m); 7.64 (1H, dt, J=1.3 and 7.8Hz); 7.97 (1H, dt, J=1.4 and 7.8 Hz); 8.04 (1H, m).
Example 98
Potassium 5R, 3-(3-aminocarbonylmethylaminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

By a procedure analogous to that used in Example 36, and using 4-nitrobenzyl 5R, 3-(3-aminocarbonylmethylaminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (130mg), dioxane (10m1), potassium bicarbonate (24.7mg), water (10m1) and 10% palladium on-charcoal (130mg), the title compound (102mg) was obtained.

(D₂O) 1.30 (3H,d,J=6.4Hz); 4.00 (1H,dd,J=1.4 and 5.9Hz); 4.08 (2H,s); 4.24 (1H,m); 5.80 (1H,d,J=1.4Hz); 7.48-7.82 (4H,m).

Example 99.
5R, 3-(3-Cyanomethylaminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

By a procedure analogous to Example 34, but using 4-nitrobenzyl 5R,3-(3-carboxyphenyl)-6S-[1R-[dimethyl-(2-methylprop-2-yl)silyloxy]ethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (186mg), HOBT (186mg), acetonitrile (10m1), tetrahydrofuran (2m1) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (190mg), triethylamine (209mg), and aminoacetonitrile hydrochloride (192mg), there was obtained 4-nitrobenzyl 5R, 3-(3-cyanomethylaminocarbonylphenyl)-6S-[1R-[dimethyl-(2-methylprop-2-yl)silyloxy]ethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (165mg).

(CDCl₃) 0.05 (3H,s); 0.08 (3H,s); 0.84 (9H,s); 1.26 (3H,d,J=6Hz); 3.03 (1H,m); 4.27 (1H,m); 4.33 (2H,d,J=5.7Hz); 5.08 and 5.25 (2H,AB,J₆=13.7Hz);
This product (159mg) was treated by a process analogous to that used in Example 35 but using glacial acetic acid (187mg) and a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 0.93ml) and tetrahydrofuran (5ml) to afford 4-nitrobenzyl 5R,3-(3-cyanomethylaminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate as a viscous yellow oil (89mg):

(acetone-\(d_6\)) 1.22 (3H,d,\(J=6.3\)Hz); 3.86 (1H,dd,\(J=1.6\) and 6.3Hz); 4.13 (1H,m); 4.31 (2H,d,\(J=5.7\)Hz); 4.50 (1H,broad); 5.08 and 5.21 (2H,AB,\(J_{gem}=13.8\)Hz); 5.81 (1H,d,\(J=1.6\)Hz); 7.39 and 8.05 (4H,AA'BB',\(J=8.5\)Hz); 7.44 (1H,m); 7.59 (1H,dt,\(J=1.5\) and 7.6Hz); 7.86 (1H,dt,\(J=1.5\) and 7.6Hz); 7.92 (1H,t,\(J=1.5\)Hz).

This 4-nitrobenzyl ester (89mg) was treated in a process analogous to that used in Example 36 with water (10ml), dioxane (10ml), potassium bicarbonate (17.5mg) and 10% palladium-on-charcoal (90mg) to afford the corresponding potassium salt (66mg). This crude product was chromatographed over a silylated silica gel, and elution with acetonitrile-water-formic acid mixtures afforded the title carboxylic acid (20mg).

(\(D_2O\) containing KHCO\(_3\)) 1.30 (3H,d,\(J=6.4\)Hz); 3.99 (1H,dd,\(J=1.5\) and 4.8Hz); 4.25 (1H,m); 4.36 (2H,s); 5.78 (1H,d,\(J=1.5\)Hz); 7.50 (1H,t,\(J=8\)Hz); 7.63 (1H,d,\(J=8\)Hz); 7.77 (2H,m).

Example 100.

Potassium 5R,6S-(1R-hydroxyethyl)-3-[4-(2-hydroxyethyl)-aminocarbonylphenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.
By a procedure analogous to that used in Example 34 and using 4-nitrobenzyl 5R,3-(4-carboxyphenyl)-6S-[1R-
[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
(117mg), acetonitrile (10ml), HOBT (54mg), tetrahydro-
furan (2ml) and 1-(3-dimethylaminopropyl)-3-ethyl-
carbodiimide hydrochloride (58mg) and ethanediamine
(13.4mg) there was obtained as a yellow foam
4-nitrobenzyl 5R,6S-[1R-[dimethyl-(2-methylprop-2-yl)]-
silyloxy]ethyl]-3-[4-(2-hydroxyethyl)aminocarbonyl-
phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-
carboxylate (94mg).

(CDCl₃) 0.06 (3H,s); 0.08 (3H,s); 0.85 (9H,s);
1.27 (3H,d,J=6.3Hz); 3.58 (2H,m); 3.78 (2H,m);
3.84 (1H,dd,J=1.6 and 4Hz); 4.29 (1H,m); 5.08 and 5.26
(2H,AB,J gem =13.7Hz); 5.76 (1H,d,J=1.6Hz); 7.06
(1H,broad m); 7.41 (2H,d,J=8.7Hz); 7.46 (2H,d,J=8.4Hz);
7.73 (2H,d,J=8.4Hz); 8.13 (2H,d,J=8.7Hz).

This product (94mg) was treated by a process
analogous to that used in Example 35 using acetic acid (90mg), a solution of tetra-n-butylammonium
fluoride in tetrahydrofuran (1M, 0.45 ml) and tetra-
hydrofuran (10ml) to afford 4-nitrobenzyl 5R,6S-(1R-
hydroxyethyl)-3-[4-(2-hydroxyethyl)aminocarbonylphenyl]-
7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate
(30mg).

(acetone-d₆) 1.31 (3H,d,J=6Hz); 3.53 (2H,m);
3.70 (2H,m); 3.95 (1H,dd,J=1.3 and 6.3Hz); 4.22 (1H,m);
5.18 and 5.31 (2H,AB,J gem =14Hz); 5.90 (1H,d,J=1.3Hz);
7.46 (2H,d,J=8.7Hz); 7.53 (2H,d,J=8.3Hz);
7.89 (2H,d,J=8.3Hz); 8.15 (2H,d,J=8.7Hz).

This product (30mg) was treated in a process
analogous to that used in Example 36 but using dioxane
(5ml), water (5ml), potassium bicarbonate (5.9mg) and
10% palladium-on-charcoal (30 mg) to afford the title potassium salt (24 mg).

$^6$ (D$_2$O) 1.30 (3H, d, $J$=6.4 Hz); 3.53 (2H, m); 3.76 (2H, m); 3.94 (1H, m); 4.28 (1H, m); 5.01 (1H, d, $J$=1.5 Hz); 7.51 and 7.73 (4H, AA'BB', $J$=8.3 Hz).

**EXAMPLE 101**

2-(Triethylsilyl) ethyl 5R,3-(3-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

By a process analogous to that used in Example 24 and using 3-nitrobenzoyl chloride (10 g), dichloromethane (200 ml), pyridine (8.7 ml) and hydrogen sulphide (excess) there was obtained 3-(nitro)-thiobenzoic acid as a pale yellow solid (9.3 g).

$^8$ (CDCl$_3$) 4.8 (1H, broad); 7.72 (1H, $t$, $J$=8.0 Hz); 8.23 (1H, $dt$, $J$=1.4 and 7.8 Hz); 8.47 (1H, $dt$, $J$=1.2 and 8.2 Hz); 8.74 (1H, $t$, $J$=1.8 Hz).

This 3-(nitro)-thiobenzoic acid (9.3 g) was reacted by a procedure analogous to that used in Example 16 with a mixture of 4-acetoxy-3R-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-azetidin-2-one (10 g), and sodium hydroxide (2.08 g) in acetone (250 ml) and water (52 ml) to afford 3S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-4R-(3-nitrobenzoylthio)azetidin-2-one (13 g)

$\nu_{\text{max}}$ (film) 1770 cm$^{-1}$

$^9$ (CDCl$_3$) 0.10 (6H, s); 0.90 (9H, s); 1.26 (3H, d, $J$=6.3 Hz); 3.34 (1H, $t$, $J$=3 Hz); 4.33 (1H, m); 5.53 (1H, d, $J$=2.4 Hz); 6.54 (1H, s); 7.72 (1H, $t$, $J$=8 Hz); 8.25 (1H, $dd$, $J$=1.2 and 8 Hz); 8.49 (1H, $ddd$, $J$=1, 2 and 8 Hz); 8.76 (1H, $t$, $J$=2 Hz).

Treatment of this azetidinone (13 g) in a procedure analogous to that used in Example 17 by using dichloromethane (300 ml), calcium carbonate (13 g), diisopropylethylamine (11 ml) and 2-(triethylsilyl)ethyl
chlorooxooacetate (8.9 ml) afforded 2-(trimethylsilyl)-
ethyl (3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)-
ethyl]-4R-(3-nitrobenzoylthio)azetidin-2-oxo-1-yl]-

-98-

oxoacetate

$\delta$ (CDCl$_3$) 0.08 (6H, s); 0.09 (9H, s); 0.91 (11H, s and m);
1.27 (3H, d, J=6.7 Hz); 3.65 (1H, t, J=3 Hz); 4.42 (3H, m);
6.23 (1H, d, J=3 Hz); 7.72 (1H, t, J=8 Hz); 8.28 (1H, ddd, J=1, 2 and 8 Hz); 8.49 (1H, ddd, J=1, 2 and 8 Hz);
8.80 (1H, t, J=2 Hz).

This oxoacetate was immediately treated in a
procedure analogous to that used in Example 18 with
triethyl phosphite (10.8 ml), hydroquinone (10 mg) and o-
xylene (300 ml) to afford 2-(trimethylsilyl)ethyl 5R,6S-
[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-3-(3-
nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-
2-carboxylate (10.5 g)

$\nu$ max (CDCl$_3$) 1792, 1710, 1535 cm$^{-1}$;
$\delta$ (CDCl$_3$) 0.01 (9H, s); 0.10 (3H, s); 0.12 (3H, s); 0.94
(11H, s and m); 1.28 (3H, d, J=6.3 Hz); 3.82 (1H, ddd, J = 1.6
and 4.6 Hz); 4.15-4.42 (3H, m); 5.75 (1H, d, J=1.6 Hz);
7.57 (1H, t, J=8 Hz); 7.80 (1H, dt, J=1 and 8 Hz);
8.25 (1H, ddd, J=1, 2 and 8 Hz); 8.36 (1H, t, J=2 Hz).

Treatment of this silylated penem (1g) in a
procedure analogous to that used in Example 19 with
glacial acetic acid (1ml), tetrahydrofuran (20ml) and a
solution of tetra-n-butylammonium fluoride in
tetrahydrofuran (1M, 5.6ml) afforded 2-(trimethylsilyl)-
ethyl 5R,6S-(1R-hydroxyethyl)-3-(3-nitrophenyl)-7-oxo-4-
thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (300mg)

$\nu$ max (CDCl$_3$) 1785, 1710, 1532 cm$^{-1}$
$\delta$ (CDCl$_3$) 0.01 (9H, s); 0.91 (2H, m); 1.39 (3H, d, J=6.3 Hz);
3.86 (1H, ddd, J=1.6 and 6.6 Hz); 4.1-4.3 (3H, m); 5.78
(1H, d, J=1.6 Hz); 7.57 (1H, t, J=8 Hz); 7.79 (1H, dt, J=1 and
8 Hz); 8.26 (1H, ddd, J=1, 2 and 8 Hz); 8.35 (1H, t, J=2 Hz).
A solution of this 3-nitrophenyl-penem-carboxylate (4.5g) in dry ethyl acetate (100ml) was hydrogenolysed at 375 kPa (4 atm) at 20°C in the presence of platinum dioxide (1.1g), was filtered and evaporated in vacuo.

Chromatography of the residue over silica gel, and elution with ethyl acetate - hexane mixtures afforded the title 3-aminophenyl compound

$$\nu_{\text{max}} (\text{CDCl}_3) 3600(\text{broad}), 3400(\text{broad}), 3178, 1710, 1621 \text{cm}^{-1}$$

$$\delta (\text{CDCl}_3) 0.01 (9H, s); 0.93 (2H, m); 1.36 (3H, d, J=6.3Hz);$$

2.84 (2H, broad); 3.78 (1H, dd, J=1.5 and 6.6Hz);

4.18 (3H, m); 5.67 (1H, d, J=1.5Hz);

6.70 (1H, dd, J=2.2 and 7.3Hz); 6.77 (1H, m);

6.83 (1H, dd, J=7.7 and 1Hz); 7.14 (1H, t, J=7.7Hz).

Example 102

Potassium 5R,3-(3-formylaminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylate.

By a procedure analogous to that used in Example 87 and using 2-((trimethylsilyl)ethyl 5R,3-(3-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylate (200mg) in dry dichloromethane (5ml), formic acid (0.022ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (113mg) there was obtained 2-((trimethylsilyl)ethyl 5R,3-(3-formylaminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylate (171mg):

$$\nu_{\text{max}} (\text{CDCl}_3) 3500(\text{sh}), 3320(\text{broad}), 1787, 1695 \text{ cm}^{-1};$$

$$\delta (\text{CDCl}_3) [\text{observed as a mixture of both formamide conformers}] (a) 0.01 (6H, s); 0.91 (2H, m); 1.36 (3H, d, J=6.3Hz); 2.73 (1H, broad); 3.80 (2H, m); 4.17 (3H, m);

5.70 (1H, d, J=1.4Hz); 7.1-7.6 (4H, m); 7.81 (1H, d, J=1.6Hz); 8.33 (1H, d, J=1.6Hz); and

(b) 0.01 (6H, s); 0.91 (2H, m); 1.37 (3H, d, J=6.3Hz);
A solution of this product (168mg) in tetrahydrofuran (5ml) was then treated by a process analogous to that used in Example 88 with a dry solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 0.387ml) and finally with potassium hydrogen carbonate (38.7mg) to afford the crude product (218mg). Purification as in Example 88 then afforded the title compound (37mg).

Example 103

Potassium 5R,3-(3-acetylanilinophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylate.

A mixture of 2-(trimethylsilyl)ethyl 5R,3-(3-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[

[3,2,0]hept-2-ene-2-carboxylate (200mg), tetrahydrofuran (3ml), acetic anhydride (0.051ml) and N-methylmorpholine (0.06ml) was stirred at 200 for 1 hour, was then partitioned between ethyl acetate and water. The organic layer was washed with water, with 1M-citric acid, with saturated sodium bicarbonate solution, and dried. Evaporation in vacuo and chromatography of the residue over silica gel, and elution with ethyl acetate - hexane mixtures afforded 2-(trimethylsilyl)ethyl 5R,3-(3-acetylanilinophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3,2,0]hept-2-ene-2-carboxylate (210mg); $\nu_{\text{max}}$ (CDCl$_3$) 3356 (broad), 1782, 1680 cm$^{-1}$; $\delta$ (CDCl$_3$) 0.01 (9H, s); 0.95 (2H, m); 1.39 (3H, d, J=6.3Hz); 2.18 (3H, s); 3.81 (1H, d, J=1.5 and 6.8Hz); 4.1-4.3 (3H, m); 5.70 (1H, d, J=1.5Hz); 7.1-7.7 (5H, m).
This material (194mg) was treated in a process analogous to that used in Example 88 with dry tetrahydrofuran (5ml), a solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1M, 0.433ml) and potassium hydrogen carbonate (43.3mg), to afford crude title compound (260mg). Purification as in Example 88 afforded pure title compound (47mg).

Example 104

To a stirred solution of 2-(trimethylsilyl)ethyl 5R,3-(4-aminophenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (400mg) in tetrahydrofuran (20ml) was added cyanoacetic acid (126mg) and dicyclohexylcarbodiimide (304mg). After 30 minutes, the mixture was filtered; the filtrate was partitioned between ethyl acetate and water. The organic layer was washed with 1M-citric acid, with saturated aqueous sodium bicarbonate and brine, was dried and evaporated in vacuo. Chromatography of the residue over silica gel and elution with hexane-ethyl acetate mixtures afforded 2-(trimethylsilyl)ethyl 5R,3-(4-[cyanacetamido]phenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (177mg):

\[
\delta_{\text{max}}(\text{CDCl}_3) 1788 \text{ and } 1710 \text{ cm}^{-1};
\]

\[
\delta \text{ (CDCl}_3\text{) } 0.01 (9H,s); 0.98 (2H,m); 1.38 (3H,d,J=6.3Hz); 3.59 (2H,s); 3.80 (1H,dd,J=1.6 \text{ and } 7.1 \text{ Hz}); 4.20 (3H,m); 5.68 (1H,d,J=1.6Hz); 7.53 (4H,m); 8.14 (1H,s).\]
In a process analogous to that used in Example 88, a solution of this ester (177mg) in dry tetrahydrofuran (5ml) was treated with a 1M solution of dry tetrabutylammonium fluoride (0.374ml), with addition of potassium hydrogen carbonate (37mg) to afford a crude product (145mg) which was purified by reverse-phase HPLC to afford the title acid (9mg):

$\delta$ (D$_2$O, containing a trace of KHCO$_3$) 1.30 (3H,d, J=6.4Hz); 3.96 (1H,dd,J=1.4 and 6.0Hz); 4.25 (1H,m); 5.75 (1H,d,J=1.4Hz); 7.44 (4H,s).

Example 105
5R,6S-[(R)-Hydroxyethyl]-3-(4-methylaminothioformsylaminophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

A mixture of 2-(trimethylsilyl)ethyl 5R,3-([4-amino-phenyl]-6S-[(R)-hydroxyethyl]-7-oxo-4-thia-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (200mg), tetrahydrofuran (5ml) and methyl isothiocyanate (72mg) was stirred for 16 hours, and was then partitioned between ethyl acetate and water. The organic layer was washed with water, with cold 1M-hydrochloric acid, with water, with saturated aqueous sodium bicarbonate, with brine and was evaporated in-vacuo. Chromatography of the residue over silica gel and elution with ethyl acetate - hexane mixtures afforded 2-(trimethylsilyl)ethyl 5R,6S-[(R)-hydroxyethyl]-3-(4-methylaminothioformsylaminophenyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (80mg):

$\nu_{\text{max}}$(CDCl$_3$) 3600, 3410, 1788, 1708 cm$^{-1}$;

$\delta$(CDCl$_3$) 0.01 (9H,s); 0.99 (2H,m); 1.39 (3H,d,J=6.3Hz); 1.96 (1H,broad); 3.16 (3H,d,J=4.5Hz); 3.81 (1H,dd,J=1.6 and 6.6Hz); 4.23 (3H,m); 5.71 (1H,d,J=1.6Hz); 6.24 (1H,broad); 7.20 and 7.55 (4H,AA'BB',J=8.5Hz); 7.74 (1H,s).
This ester (200mg) was treated in a process analogous to that used in Example 88 with tetrahydrofuran (10ml) and a solution of dry tetrabutylammonium fluoride in tetrahydrofuran (1M, 0.417ml), with addition of potassium bicarbonate (42mg). After ion-exchange and reverse-phase chromatography there was obtained the title acid (16mg):

\[ \delta \text{(D}_2\text{O, containing KHCO}_3) \] 1.29 (3H, d, J=6.4Hz); 2.96 (3H, s); 3.96 (1H, dd, J=1.3 and 5.9Hz); 4.24 (1H, m); 5.75 (1H, d, J=1.3Hz); 7.23 and 7.43 (4H, AA'BB', J=8.6Hz).

Example 106

Potassium 5R,6S-(1R-hydroxyethyl)-3-(3-methylsulphinylphenyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate.

By procedures analogous to those used in Examples 15,16,17,18 and 19, and starting from 3-(methylthio)benzoic acid there was obtained 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(3-methylthiophenyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate as a yellow foam:

\[ \delta \text{(CDCl}_3) \] 1.40 (3H, d, J=6.4Hz); 2.10 (1H, d, J=4.3Hz); 2.44 (3H, s); 3.86 (1H, dd, J=1.5 and 6.4Hz); 4.31 (1H, m); 5.12 and 5.28 (2H, AB, J=13.8Hz); 5.75 (1H, d, J=1.5Hz); 7.17 (1H, m); 7.28 (3H, m); 8.13 (2H, d, J=8.8Hz).

This sulphide (183mg) was treated by a process analogous to that used in Example 20 with 80% 3-chloroperbenzoic acid (92mg) to afford 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(3-methylsulphinylphenyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]hept-2-ene-2-carboxylate (107mg)

\[ \delta \text{(acetone-d}_6) \] 1.33 (3H, d, J=6.3Hz); 2.67 (3H, s); 3.98 (1H, dd, J=1.7 and 6.2Hz); 4.23 (1H, m); 4.48 (1H, d, J=4.9Hz); 5.21 and 5.35 (2H, AB, J=14.2Hz); 5.93 (1H, d, J=1.7Hz); 7.51 and 8.16 (4H, AA'BB', J=8.5Hz); 7.6-7.8 (4H, m).
this sulphoxide (107mg) was hydrogenolysed in the presence of 10% palladium-on-charcoal (100mg), potassium hydrogen carbonate, dioxane (6ml) and water (6ml) to afford the title compound (65mg):

$^1$H NMR of (D$_2$O) 1.29 (3H, d, J=6.5Hz); 2.85 (3H, s); 3.99 (1H, dd, J=1.5 and 6Hz); 4.25 (1H, m); 5.79 (1H, d, J=1.5Hz); 7.58-7.80 (4H, m).

Example 107

Potassium 5R,6S-(1R-hydroxyethyl)-3-(3-methylsulphonyl-phenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

By a procedure analogous to that used in Example 22, and using 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(3-methylsulphonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (414mg), 80% 3-chloroperbenzoic acid (165mg) and ethyl acetate (40ml), there was obtained 4-nitrobenzyl 5R,6S-(1R-hydroxyethyl)-3-(3-methylsulphonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (76mg):

$^1$H NMR of (acetone-d$_6$) 1.33 ((3H, d, J=6.3Hz); 2.84 (3H, s); 4.00 (1H, dd, J=1.7 and 6.1Hz); 4.23 (1H, m); 4.47 (1H, d, J=4.9Hz); 5.20 and 5.35 (2H, AB, J$_{gem}$=14Hz); 5.95 (1H, d, J=1.7Hz); 7.52 and 8.18 (4H, AB, J=8.9Hz);

$^1$H NMR of (acetone-d$_6$) 7.70 (1H, t, J=7.6Hz); 7.85 (1H, dd, J=7.4Hz); 8.00 (1H, dd, J=1.2 and 7.3Hz); 8.06 (1H, m).

In a procedure analogous to that used in Example 7, this sulphoxide (76mg) was hydrogenolysed in the presence of 10% palladium-on-charcoal (75mg), potassium hydrogen carbonate (15.3mg), dioxane (4ml) and water (4ml) to afford the title potassium salt (39mg):

$^1$H NMR of (D$_2$O) 1.31 (3H, d, J=6.4Hz); 3.25 (3H, s); 4.00 (1H, dd, J=1.4 and 5.9Hz); 4.26 (1H, m); 5.80 (1H, d, J=1.4Hz); 7.63 (1H, t, J=7.8Hz); 7.77 (1H, m); 7.91 (1H, dm, J=7.8Hz); 7.98 (1H, t, J=1.6Hz).
Example 108

2-(Trimethylsilyl)ethyl 5R,6S-(1R-acetoxyethyl)-3-(4-formylaminophenyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-hept-2-ene-2-carboxylate

A mixture of 2-(trimethylsilyl)ethyl 5R,3-(4-formylamino)phenyl-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (500mg), tetrahydrofuran (10ml), 4-dimethylaminopyridine (15mg) and acetic anhydride (1.09ml) was stirred at room temperature for 30 min., and then partitioned between ethyl acetate and water. The organic layer was washed with saturated aqueous sodium bicarbonate, with brine, was dried over anhydrous sodium sulphate, and evaporated in vacuo. Chromatography on silica gel and elution with ethyl acetate-hexane mixtures afforded the title compound (210mg):

δ (CDCl₃) 0.00 (9H, s); 0.97 (2H, m); 1.42 (3H, d, J=6.4Hz); 2.08 (3H, s); 3.90 (1H, d, J=1.5 and 7.6Hz); 4.20 (2H, m); 5.29 (1H, m); 5.64 and 5.62 (1H, 2d, J=1.5Hz); 7.06 (–0.8H, d, J=8.6Hz); 7.4 –7.6 (–3.8H, m); 7.88 (–0.4H, d, J=11.4Hz); 8.37 (–0.6H, d, J=1.6Hz) and 8.75 (–0.4H, d, J=11.4Hz).

δ (DMSO-d₆) 0.00 (9H, s); 0.84 (2H, t, J=7.5Hz); 1.30 (3H, d, J=6.3Hz); 2.03 (3H, s); 4.12 (2H, m); 4.21 (1H, d, J=1.5 and 5.5Hz); 5.17 (1H, m); 5.78 (1H, d, J=1.5Hz); 7.43 and 7.62 (4H, AA'BB' ,J_AB=8.8Hz); 8.31 (–0.8H, d, J=1.5Hz); 8.89 (–0.2H, d, J=11.5Hz); 9.36 (–0.2H, d, J=11.5Hz) and 10.44 (–0.8H, d, J =1.5Hz).

Example 109

5R,6S-(1R-Acetoxyethyl)-3-(4-formylaminophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

The crude product obtained by a procedure analogous to that used in Example 88 but using 2-(trimethylsilyl)ethyl 5R,6S-(1R-acetoxyethyl)-3-(4-formylaminophenyl)-7-
oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (200 mg), tetrahydrofuran (10ml) and a solution of dry tetrabutylammonium fluoride in tetrahydrofuran (1M, 41ml), with addition of potassium bicarbonate (41mg), was purified by ion-exchange and reverse-phase chromatography to afford the pure title compound (49mg).

Example 110

4-nitrobenzyl 5S,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

A mixture of 4-nitrobenzyl 5S,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (120mg) and acetonitrile (7.5ml) was heated in a sealed flask at 85°C for 20 hours, and was then evaporated in vacuo. Chromatography of the residue afforded some starting trans-penen, and the title compound (20mg):

δ (DMSO-d6) 1.48 (3H,d,J=6.3Hz); 4.02 (1H,dd,J=3.8 and 5.5Hz); 4.30 (1H,m); 5.15 and 5.30 (2H,AB,Jgem=13.8Hz); 5.95 (1H,d,J=3.8Hz); 7.2-8.1 (10H,m).

Example 111

Potassium 5S,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

By a procedure analogous to that used in Example 36, and using 4-nitrobenzyl 5S,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (50mg), dioxane (5ml), water (5ml), potassium bicarbonate (10mg) and 10%
palladium-on-charcoal (50mg), the title compound 27mg) was obtained (27mg):

$\delta (D_2O)$ 1.42 (3H, d, J=6.3Hz); 4.05 (1H, dd, J=4 and 6 Hz); 4.26 (1H, m); 5.90 (1H, d, J=4Hz); 7.4-7.8 (4H, m).

**Example 112**

4-Nitrobenzyl 5R, 3-[[3-(allyloxy carbonyl)phenyl]-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

By a procedure analogous to that used in Example 39, but starting from a solution of isophthaloyl chloride (60.9g) in dioxane (400ml), allyl alcohol (20.9g), triethylamine (36.4g), dichloromethane (600ml), pyridine (28.5g) and hydrogen sulphide (excess) there was obtained 3-(allyloxy carbonyl)thiobenzoic acid:

$\nu_{max}$ 2550, 1725 cm$^{-1}$;

$\delta$ (CDCl$_3$) 5.0 (2H, m); 5.5 (3H, broad m); 6.0 (1H, m); 7.5-9.1 (4H, m).

A solution of this thiobenzoic acid (5g) in acetone (35ml) was treated in a procedure analogous to that used in Example 30 with a mixture of 1M sodium hydroxide solution (22ml) and a solution of 4-acetoxy-3R-[1R-[dimethyl(2-methyl-prop-2-yl)silyloxyethyl]azetidin-2-one (4.3g) in acetone:water (3:1) (50ml) to afford 4R-[3-(allyloxy carbonyl)benzoylthio]-3S-[1R-[dimethyl(2-methylprop-2-yl)silyloxyethyl]azetidin-2-one (4.3g):

$\delta$ (CDCl$_3$) 0.00 (6H, s); 0.80 (9H, s); 1.15 (3H, d, J=6.3Hz); 3.22 (1H, dd, J=2.5 and 3.6Hz); 4.22 (1H, m); 4.76 (1H, dd, J=1.1 and 6.8Hz); 5.2-5.4 (2H, m); 5.41 (1H, d, J=2.5Hz); 5.92 (1H, m); 6.64 (1H, s); 7.5-8.6 (4H, m).

A solution of this azetidinone (22.1g) in dichloromethane (250ml) was treated in a procedure
analogous to that used in Example 31 with calcium carbonate (12.3g), and diisopropylethylamine (9.5g) and a solution of 4-nitrobenzyl chlorooxalate (14.4g) in dichloromethane (25ml) to afford as a yellow oil 4-nitrobenzyl-[4R,3-[3-(allyloxycarbonyl)benzoylthio]-3S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-azetidin-2-on-1-yl]oxoacetate

$^6$(CDCl$_3$) 0.00 (3H,s); 0.09 (3H,s); 0.83 (9H,s); 1.26 (3H,d,J=6.3Hz); 3.65 (1H,t,J=3.5Hz); 4.41 (1H,m); 4.85 (2H,d,J=5.8Hz); 5.30-5.45 (4H,m); 6.02 (1H,m); 6.20 (1H,d,J=3.5Hz); 7.5-7.6 (3H,m); 8.09-8.3 (4H,m); 8.60 (1H,t,J=1.6Hz).

A solution of this oil in xylene (500ml) was treated in a procedure analogous to that used in Example 32 with a solution of triethyl phosphite (16.3g) in xylene (100ml) to afford 4-nitrobenzyl-[5R,3-[3-(allyloxycarbonyl)phenyl]-6S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (25.3g)

$^6$(CDCl$_3$) 0.06 (3H,s); 0.08 (3H,s); 0.85 (9H,s); 1.27 (3H,d,J=6.3Hz); 3.83 (1H,dd,J=1.3 and 3.9Hz); 4.28 (1H,m); 4.81 (2H,d,J=5.5Hz); 5.09 (1H,d,J=13.7Hz); 5.2-5.4 (3H,m); 5.75 (1H,d,J=1.3Hz); 6.00 (1H,m); 7.3-7.6 (4H,m); 8.1-8.3 (4H,m).

A solution of this 4-nitrobenzyl carboxylate (34.2g) in tetrahydrofuran (70ml) was treated in a procedure analogous to that used in Example 37 with glacial acetic acid (32.8g) and a 1M solution of tetrabutylammonium fluoride in tetrahydrofuran (163ml) to afford the title hydroxyethyl compound (20.4g):

$^6$(CDCl$_3$) 1.40 (3H,d,J=6.3Hz); 3.88 (1H,dd,J=1.6 and 6.5Hz); 4.31 (1H,m); 4.80 (2H,m); 5.10 (1H,d,J=13.7Hz);
Example 113

4-Nitrobenzyl 5R,6S-(1R-acetoxyethyl)-3-[3-(allyloxycarbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

A mixture of 4-nitrobenzyl 5R,3-[3-(allyloxycarbonyl)phenyl]-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.0g) dry tetrahydrofuran (15ml), acetic anhydride (1.0g) and 4-dimethylaminopyridine (23mg) was stirred under a nitrogen atmosphere for 30 min., and then partitioned between ethyl acetate and water. The organic layer was washed with water, with saturated aqueous sodium bicarbonate solution and was then dried and evaporated in vacuo. Chromatography of the residue over silica gel and elution with ethyl acetate – hexane mixtures afforded the title compound (0.9g):

δ (CDCl₃) 1.45 (3H, d, J=6.3Hz); 2.09 (3H, s); 3.99 (1H, dd, J=1.8 and 5.8Hz); 4.81 (2H, d, J=5.8Hz); 5.13 (1H, d, J=13.7Hz); 5.2-5.4 (4H, m); 5.73 (1H, d, J=1.8Hz); 6.01 (1H, m); 7.35 (2H, d, J=8.7Hz); 7.45 (1H, t, J=7.9Hz); 7.62 (1H, m); 8.07-8.16 (4H, m).

Example 114

4-Nitrobenzyl 5R,6S-(1R-acetoxyethyl)-3-(3-carboxyphenyl)-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

A mixture of 4-nitrobenzyl 5R,6S-(1R-acetoxyethyl)-3-[3-(allyloxycarbonyl)phenyl]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.9g), dichloromethane (10ml), potassium 2-ethylhexanoate
(0.46g), triphenylphosphine (17mg) and tetakis-(triphenylphosphine)palladium (38mg) was stirred at room temperature for one hour, and the pH was then adjusted to 4.4 by addition of potassium dihydrogen phosphate solution. The resulting mixture was extracted with ethyl acetate, which was then dried and evaporated in vacuo. Chromatography of the residue and elution with hexane - ethyl acetate - formic acid mixtures afforded the title compound:

\[
\begin{align*}
7 & \text{(CDCl}_3) 1.45 (3H, d, J=6.4Hz); 2.09 (3H, s); 3.99 (1H, dd, J=1.5 and 7.5Hz); 5.13 and 5.26 (2H, AB, J \text{ gem }=13.1Hz); 5.31 (1H, m); 5.73 (1H, d, J=1.5Hz); 7.36 (2H, d, J=8.8Hz); 7.45-7.72 (2H, m); 7.9-8.2 (4H, m).
\end{align*}
\]

**Example 115**

4-Nitrobenzyl 5R,6S-(1R-acetoxyethyl)-3-(3-amino-carbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

To a stirred suspension of 4-nitrobenzyl 5R,6S-(1R-acetoxyethyl)-3-(3-carboxyphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (200mg) in dry dichloromethane (10ml) at 0 was added triethylamine (0.11ml) and ethyl chloroformate (47mg), followed after one hour by a solution of ammonia (20mg) in ethanol (1ml). The mixture was stirred a further hour, and was then evaporated in vacuo. The residue was chromatographed on silica gel. Elution with ethyl acetate - hexane mixtures afforded the title compound (98mg):

\[
\begin{align*}
& S (\text{DMSO-d}_6) 1.42 (3H, d, J=6.3Hz); 2.13 (3H, s); 4.22 (1H, dd, J=1.5 and 6 Hz); 5.15 and 5.30 (2H, AB, J \text{ gem }=13.8Hz); 5.14 (1H, d, J=6Hz); 5.92 (1H, d, J=1.5Hz); 6.85 (1H, bs); 7.47-7.8 (4H, m); 7.99 (1H, dt, J=1 and 8Hz); 8.03 (1H, t, J=1Hz); 8.13 (2H, d, J=8.8Hz).
\end{align*}
\]
Alternatively, the title compound (83mg) was obtained by a procedure analogous to that used in Example 113 by using 4-nitrobenzyl 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (200mg), dry tetrahydrofuran (3ml), acetic anhydride (0.2ml) and 4-dimethylaminopyridine (10mg).

Example 116
Potassium 5R,6S-(1R-acetoxyethyl)-3-(3-aminocarbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

By a procedure analogous to that used in Example 36, and using 4-nitrobenzyl 5R,6S-(1R-acetoxyethyl)-3-(3-aminocarbonylphenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (100mg), dioxane (1ml), potassium bicarbonate (19mg), water (1ml) and 10% palladium-on-charcoal (100mg), the title compound (57mg) was obtained:

$^6$(D<sub>2</sub>O) 1.38 (3H, d, J=6.3Hz); 2.13 (3H, s); 4.20 (1H, dd, J=1.4 and 5.9Hz); 5.31 (1H, m); 5.88 (1H, d, J=1.4Hz); 7.48 (1H, t, J=8Hz); 7.60 (1H, dt, J=1.4 and 8Hz); 7.7-7.8 (2H, m).
Example 117
2-(Trimethylsilyl)ethyl-2-(3S-\{7R-(dimethyl(2-methyl-prop-2-y1)silyloxy)ethyl\}-4R-\{3-nitrobenzoylthio\}azetidin-2-on-1-yl)-3,3-triethoxy-3-phospha-propenoate

To a solution of 2-(trimethylsilyl)ethyl \{3S-\{7R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl\}-4R-\{3-nitrobenzoylthio\}azetidin-2-on-1-yl\} oxoacetate (330 mg) in toluene (5 ml) at 100° was added dropwise over 30 minutes a solution of triethyl phosphite (0.24 ml) in toluene (1 ml). After the mixture had been heated at 100° for a further hour, it was evaporated in vacuo to afford a residue which was chromatographed over silica gel. Elution with hexane - ethyl acetate mixtures afforded the title compound (150 mg) as a yellow gum. 

\( \gamma (\text{CDCl}_3) 1752, 1670 \text{ and } 1620 \text{ cm}^{-1} \)

\( \delta (\text{CDCl}_3) 0.10 \text{ (6H, s); } 0.84 \text{ (11H, m); } 1.22 \text{ (3H, d, } J=6.3 \text{ Hz); } 1.33 \text{ (9H, t, } J=7 \text{ Hz); } 3.27 \text{ (1H, m); } 4.21 \text{ (9H, m); } 5.81 \text{ (1H, broad); } 8.10 \text{ and } 8.33 \text{ (4H, AA'BB'; } J_{AB}= 8.8 \text{ Hz).} \)

A mixture of this phosphorane (150 mg) and o-xylene (3 ml) was heated at 140° for one hour, and then evaporated in vacuo. Chromatography of the residue over silica gel and elution with hexane - ethyl acetate mixtures afforded 2-(trimethylsilyl) 5R,6S-\{7R-(dimethyl(2-methylprop-2-yl)-silyloxy)ethyl\}-3-(4-nitrophenyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (97 mg) with properties identical to those described in Example 83.
Example 118

4-Nitrobenzyl 2-{4R-[3-aminocarbonylbenzoylthio]-3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-azetidin-2-on-1-yl}-3-methylpropenoate.

A solution of silver 3S-[1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl-1-[2-methyl-1-(4-nitrobenzoylcarbonyl)propenyl]-azetidin-2-one-4R-thiolate (400 mg) in acetonitrile (10 ml) was added dropwise to a stirred solution of isophthaloyl chloride (612 mg) in acetonitrile (29 ml) at 0°C. After 30 minutes a solution of ammonia (90 mg) in chloroform (5 ml) was added; the mixture was filtered and the filtrate evaporated in vacuo. Chromatography of the residue on silica gel, and elution with hexane-ethyl acetate mixtures afforded the title compound (206 mg).

δ: (CDCl₃) 0.03 (3H,s); 0.06 (3H,s); 0.82 (9H,s); 1.26 (3H,d,J=6.3Hz); 2.03 (3H,s); 2.21 (3H,s); 3.36 (1H,dd,J=2.6 and 5.6 Hz); 4.25 (1H,m); 5.34 (2H,s); 5.90 (1H,d,J=2.6 Hz); 6.2 (2H, broad); 7.50-7.61 (3H,m); 8.17-8.36 (5H,m).
Example 119

4-Nitrobenzyl 2-\{4R-[3-aminocarbonylbenzoylthio]-3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-azetidin-2-on-1-yl\}oxoacetate.

A solution of 4-nitrobenzyl 2-\{4R-[3-aminocarbonylbenzoylthio]-3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-azetidin-2-on-1-yl\}-3-methylpropenoate (182 mg) in dry dichloromethane (30 ml) was treated at -78°C with ozone (excess); oxygen was then bubbled through the mixture for 5 minutes, and dimethyl sulphide (excess) was added. The mixture was warmed to room temperature, was evaporated in vacuo. The resulting oil was partitioned between ethyl acetate and water; the organic layer was separated, was washed with water, with brine, was dried and evaporated in vacuo to afford the title compound (140 mg).

5 (CDCl₃) 0.03 (3H, s); 0.06 (3H, s); 0.82 (9H, s); 1.27 (3H, d, J=6Hz); 3.64 (1H, t, J=3Hz); 4.40 (1H, m); 5.36 and 5.43 (2H, AB, J=12.9Hz); 6.20 (1H, d, J=3.5Hz); 6.2 (2H, broad); 7.5-7.7 (3H, m); 8.1-8.4 (5H, m).
$\delta$ (CDCl$_3$) 0.01 (9H, s); 0.98 (2H, m); 1.38 (3H, d, J=6.3Hz); 3.59 (2H, s); 3.80 (1H, dd, J=1.6 and 7.1 Hz); 4.20 (3H, m); 5.68 (1H, d, J=1.6Hz); 7.53 (4H, m); 8.14 (1H, s).

Example 120

4-Nitrobenzyl 5R,3-(3-aminocarbonylphenyl)-6S-(1R-[dimethyl(2-methylprop-2-yl)silyloxy]ethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

To a mixture of 4-nitrobenzyl 2-{4R-[3-aminocarbonylbenzyloxythio]-3S-[1R-(dimethyl(2-methylprop-2-yl)silyloxy)ethyl]-azetidin-2-on-1-yl}oxoacetate (140 mg) in xylene (15 ml) at 130° was added a mixture of triethyl phosphite (0.073 ml) in xylene (5 ml). The mixture was heated a further hour at 130°, and then cooled and evaporated in vacuo. Chromatography of the residue on silica gel, and elution with hexane-ethyl acetate mixtures afforded the title compound (100 mg) with properties identical to those described in Example 94.
Example 121

1-(Acetoxethyl) 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate.

Under a nitrogen atmosphere a stirred mixture of potassium 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (100 mg), sodium iodide (80 mg) and dry dimethylformamide (2.5 ml) was treated at room temperature with a solution of 1-chloroethyl acetate (164 mg) in chloroform (0.76 ml). After 18 hours the mixture was partitioned between ethyl acetate and water; the organic layer was evaporated to dryness and chromatographed on silica gel. Elution with ethyl acetate - ethanol mixtures afforded the title compound (16 mg) as a yellow gum as a mixture of diastereoisomers.

δ(CDCls) 1.37 (6H, d, J=6.5 Hz); 2.01 (3H, s); 3.02 (1H, dd, J=1.8 and 6.7 Hz); 4.27 (1H, m); 5.73 (1H, d, J=1.5 Hz); 5.95 (1H, broad); 6.57 (1H, broad); 6.79 (1H, m); 7.48 (1H, t, J=7.8 Hz); 7.60 (1H, m); 7.91 (1H, m).
Example 122

Acetoxymethyl 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate.

By a procedure analogous to that used in Example 121, but using potassium 5R,3-(3-aminocarbonylphenyl)-6S-(1R-hydroxyethyl)-7-oxo-4-thia-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (100 mg), sodium iodide (80 mg), dry dimethylformamide (2 ml) and chloromethyl acetate (150 mg), the title compound (75 mg) was obtained as a yellow gum.

δ(CD3CN) 1.22 (3H, d, J=0.3 Hz); 2.01 (3H, s); 3.85 (1H, dd, J=14.5 and 6 Hz); 4.2 (1H, m); 5.75 (1H, d, J=1.5 Hz); 5.72 and 5.80 (2H, AB, J=6 Hz); 6.80 and 6.9 (2H, broad s); 7.50 (1H, t, J=8 Hz); 7.50 (1H, m) and 7.97 (1H, m).
CLAIMS
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of formula I

   \[
   \begin{align*}
   &\text{CH}_3\text{O} \\
   &\text{N} \\
   &\text{S} \\
   &\text{R}^2 \\
   &\text{R}^1
   \end{align*}
   \]

in which

- \( R \) represents a hydrogen atom or a carboxylic acid esterifying group;
- \( R^1 \) represents
  - (i) one of the following groups
    \[
    \begin{align*}
    &\text{-OH} \\
    &\text{-S(O)\text{CH}_3} \\
    &\text{-SO_3\text{H}} \\
    &\text{CONH\text{CH}_3} \\
    &\text{CONH\text{NHC\text{CH}_3}} \\
    \end{align*}
    \]
  - in which \( R_a \) and \( R_b \), which may be the same or different, each represents an alkyl group having from 1 to 4 carbon atoms, or
  - (ii) a \(-\text{CONH(\text{CH}_2)}_m\text{O}\) or \(-\text{NRCO(\text{CH}_2)}_m\text{O}\) group in which \( m \) represents an integer of from 1 to 3, and
  - \( R^2 \) represents one of the following groups
    \[
    \begin{align*}
    &\text{-OH} \\
    &\text{-SO_3\text{H}} \\
    &\text{CONH\text{CH}_3} \\
    &\text{CONH\text{NHC\text{CH}_3}} \\
    \end{align*}
    \]
  - in which \( R_c \) represents a methyl or ethyl group, or
  - (iii) a \(-\text{CO}_2\text{Rd}\) group, in which \( R_d \) represents a methyl or ethyl group which is unsubstituted or is substituted

The crude product obtained by a procedure analogous to that used in Example 88 but using 2-(trimethylsilyl)ethyl 5R,6S-(1R-acetoxyethyl)-3-(4-formylaminophenyl)-7-
by one or more substituents, which may be the same or
different, selected from

(a) halogen atoms and vinyl groups;
(b) phenyl groups which are unsubstituted or are
substituted by one or more groups selected from
alkoxy groups having from 1 to 4 carbon atoms,
nitro groups and halogen atoms,
(c) silyl groups SiReRfRg, the groups Re, Rf and
Rg being the same or different, each representing
a phenyl group or an alkyl group having from 1 to
4 carbon atoms, and
(d) groups Q as defined above; or
(iv) a \(-\text{CO}_2\text{SiReRfRg}\) group, in which Re, Rf and Rg
are defined as in (c) above, or
(v) a \(\text{CD}_2\)-phenyl
group, in which the phenyl moiety is unsubstituted
or substituted as defined in (b) above;

\(R^2\) represents (i) a hydrogen atom,
(ii) a group as defined above for \(R^1\) (\(R^1\) and
\(R^2\) being the same or different), or
(iii) a chlorine, bromine or iodine atom, an alkyl
group having from 1 to 4 carbon atoms, an \(-\text{NH}_2,\)
\(-\text{NH}Ra\) or \(-\text{NR}a\text{R}b\) group, an \(-\text{OH}\) or \(-\text{OR}a\) group, or an
\(-\text{OCOCH}_3\) group, Ra and Rb being defined as above,
and
\(R^3\) represents a hydrogen atom or a hydroxy protecting
group; and in which \(R^1\) and \(R^2\), independently
of each other, may be present at any position on
the phenyl ring;
and salts thereof, especially physiologically
tolerable salts; and isomers thereof.

2. A compound of formula I as claimed in claim 1,
wherein in a group containing an alkyl group Ra or
Rb, Ra or Rb denotes a methyl or ethyl group; in a
group containing the symbol \(m\), \(m\) denotes the
integer 1 or 2.

3. A compound of formula I as claimed in claim 1, wherein R represents one of the following groups: -NHCO(CH₂)ₘQ

-CONH(CH₂)ₘQ  -NHCONH₂  -CONH₂  -CONH₂Ra

-NHCHO  -NHCORa

-SO₂Ra  -SO₂NH₂  -SO₂NH₂Ra  -CNH₂

wherein Q is as defined in claim 1 and Ra and m are as defined in claim 2.

4. A compound of formula I as claimed in any one of claims 1 to 3, wherein a protected carboxy group -COOR is an esterified carboxy group that can be converted by hydrolysis, by photolysis, by oxidation, by reduction or by esterase action to give the free acid of formula I or a carboxylate, for example the group R is a phenyl group or a methyl group substituted by one or more unsubstituted or substituted phenyl groups; and wherein a phenyl group, either as R or as a substituent of a methyl group, is optionally substituted by one or more substituents selected from methoxy and nitro groups and halogen atoms, for example, R represents a benzyl, nitrobenzyl, methoxybenzyl, dimethoxybenzyl, phthalidyl, benzhydryl or trityl group; or R represents a phenoxyethyl or trichloroethyl group; or R represents a methyl or ethyl group optionally substituted by an acyl or acyloxy group, by an alkoxyacarbonyloxy group, by an aminoalkanoyloxy group or by an optionally substituted amino group, for example, R represents an acyloxymethyl or acyloxyethyl group having from 2 to 12 for example 2 to 6 carbon atoms in the acyl moiety, an aminoalkanoyloxymethyl group having from 2 to 12 for example 2 to 6 carbon
atoms in the alkanoyl moiety, a 1'-alkoxy-
carbonyloxyethyl group, or an optionally substituted 2-
aminoethyl group, especially a glycoloxymethyl, L-
valinylxoxymethyl or L-leucinylxoxymethyl group, a 1'-
(methoxycarbonyloxy)ethyl group, a pivaloyloxymethyl,
ethoxycarbonyloxymethyl, acetylmethyl, acetoxyxoxymethyl,
1'-acetoxyethyl, 1'-acetyl)ethyl or 1'-ethoxy-
carbonyloxyethyl)ethyl group or a 2-diethylaminomethyl or 2-
(1-morpholino)-ethyl group; or R represents a 5-
methyldioxalen-2-on-4-yl-methyl group; or R represents
a trialkylsilyl or trialkylsilylalkyl group, in which
groups alkyl moieties have from 1 to 4 carbon atoms.

5. A compound of formula I as claimed in any one of
claims 1 to 4, wherein a hydroxy protecting group R³
is a group that can be converted by hydrolysis, by
protolysis, by reduction or by esterase enzyme action
to give a compound of formula I having a free 8-hydroxy
group, for example R³ is a carboxylic acid acyl group
of the formula R²COO⁻ in which R² represents a
hydrogen atom or a straight or branched chain alkyl
group having from 1 to 6 carbon atoms, or represents a
phenyl group or a phenoxyalkyl group in which the alkyl
moiety is straight-chained or branched and has from 1
to 4 carbon atoms, for example, R² represents a
methyl, ethyl or t-butyl group, or a phenoxyethyl
group.

6. A compound of formula I as claimed in any one of
claims 1 to 5, wherein R represents a hydrogen atom or
a physiologically tolerable salt forming group or
a group that can be cleaved in vivo to give a free
carboxy group or a carboxylate group, and R³
represents a hydrogen atom or a group that can be
cleaved in vivo to give a free hydroxy group.
7. A compound as claimed in any one of claims 1 to 6, having, independently or in any combination, 5R-stereochemistry, 6S-stereochemistry and 8R-stereochemistry, especially having 5R, 6S, 8R-stereochemistry.

8. A compound as claimed in claim 1 which is 5R,3-[(4-Aminocarbonylphenyl)-6S-(1R-hydroxyethyl)]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, or an ester thereof at the 8- and/or 2-position, or a salt thereof, especially a physiologically tolerable salt.

9. A compound as claimed in claim 1 which is 5R,3-[(3-Aminocarbonylphenyl)-6S-(1R-hydroxyethyl)]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, or an ester thereof at the 8- and/or 2-position, or a salt thereof, especially a physiologically tolerable salt.

10. A compound as claimed in claim 1 which is 5R,3-[(4-Formylaminophenyl)-6S-(1R-hydroxyethyl)]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, or an ester thereof at the 8- and/or 2-position, or a salt thereof, especially a physiologically tolerable salt.

11. A compound as claimed in claim 1 which is 5R,3-[(3-Formylaminophenyl)-6S-(1R-hydroxyethyl)]-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, or an ester thereof at the 8- and/or 2-position, or a salt thereof, especially a physiologically tolerable salt.

12. A process for the production of a compound of formula I as claimed in claim 1, which comprises (A) reacting a compound of formula II
in which $R^3$ is as defined in claim 1, $R^4$ represents a carboxy protecting group, $R^5$ represents a group $R^1$ as defined in claim 1 or a group that can be converted into a group $R^1$, $R^6$ represents a group $R^2$ as defined in claim 1 or a group that can be converted into a group $R^2$, $R^7$ represents a phenyl group or an alkyl group having from 1 to 4 carbon atoms, and $R^8$ represents a bromine or chlorine atom, with a base for example, ammonia, an alkali metal carbonate, bicarbonate or hydroxide; a primary amine, an alkali metal alkoxide or a heterocyclic base having a $pK_a$ within the range of from 5 to 9; or

(B) effecting cyclisation of a compound of formula III

\[
\begin{align*}
\text{(III)} \\
\end{align*}
\]

in which $R^3$, $R^4$, $R^5$ and $R^6$ are defined as above, $X$ represents an oxygen or sulphur atom, and the group $P(Z)_3$ represents a group derived from a trivalent organophosphorus reagent, by allowing compound III to stand at room temperature or by heating compound III, or

(C) reacting a compound of formula IV or V

\[
\begin{align*}
\text{(IV)} \\
\text{(V)}
\end{align*}
\]
in which \(X, R^3, R^4, R^5, R^6,\) and \(R^8\) are defined as above, with a trivalent organophosphorus compound and effecting cyclisation of the reaction product by heating it or allowing it to stand, or (D) reacting a compound of formula VI

\[
\begin{array}{c}
\text{R}^3 \text{O} \\
\text{CH}_2 \text{CH} \\
\text{H} \\
\text{H} \\
\text{S} \\
\text{R}^{19} \\
\text{n}
\end{array}
\]

(VI)

in which \(R^3, R^4\) and the group \(P(\text{Z})_3\) are defined as above, and \(R^{19}\) represents Cu(II), Pb(II) or Bi(II), in which case \(n\) represents 2, or \(R^{19}\) represents Ag(I), in which case \(n\) represents 1, with a compound of formula VII

\[
\begin{array}{c}
\text{R}^3 \text{C} \\
\text{O} \\
\text{R}^5 \\
\text{R}^6
\end{array}
\]

(VII)

in which \(R^{11}\) represents an activating ester group or a halogen atom, and \(X, R^5\) and \(R^6\) are defined as above, and effecting cyclisation of the reaction product by heating it or allowing it to stand, and (E) in an appropriate compound in which \(R^5\) and/or \(R^6\) represents a group that can be converted into a group \(R^1\) and/or \(R^2\), respectively, converting such a group or groups \(R^5\) and/or \(R^6\) into such a group or groups \(R^1\) and/or \(R^2\) and,

(F) if desired or required, in an appropriate compound converting a group \(R^1\) and/or a group \(R^2\) into another group \(R^1\) and/or \(R^2\), respectively; and

(G) if desired or required, carrying out any one or
more of the following steps in any desired order:

a) hydrolysing a 2-carboxylic ester group in an appropriate compound to give the corresponding free acid,

b) treating an appropriate free acid or a salt thereof with an agent capable of forming a 2-carboxylic acid ester to give a 2-carboxylic acid ester thereof,

c) carrying out an acid- or base-catalysed ester interchange on an appropriate 2-carboxylic acid ester to give a different ester of that compound,

d) treating an appropriate free acid compound with a base to give a salt at the carboxy group at position 2,

e) treating an appropriate free acid or 2-carboxylic acid ester having a basic group present with an acid to give an acid addition salt thereof,

f) treating a salt of an appropriate compound with an acid to give a free acid of that compound,

g) removing a hydroxy protecting group from an appropriate compound having a protected 8-hydroxy group to give the corresponding compound having a free 8-hydroxy group,

h) treating an appropriate compound having a free hydroxy group at the 8-position with an organic acid derivative to form an ester at the 8-position, and

i) treating an appropriate compound to effect a change in the stereochemical configuration.

13. A process as claimed in claim 12(a), wherein a compound of formula II is produced by halogenating a compound of formula XI

\[ \text{XI} \]
in which $R^3$ is as defined in claim 1 and is especially a hydrogen atom, and $R^4$, $R^5$, $R^6$ and $R^7$ are as defined in claim 12, and $R^5$ represents an alkyl group having from 1 to 8 carbon atoms, an alkenyl group having from 2 to 4 carbon atoms, or a phenyl group, using an agent capable of splitting a carbon sulphur bond and of introducing a halogen atom, for example, molecular chlorine, sulphuryl chloride, t-butyl hypochlorite, cyanogen chloride or molecular bromine.

14. A process as claimed in claim 12 or claim 13, wherein a compound of formula XI is produced by reacting a compound of formula X

$$\text{R}^3\text{O} \quad \text{H} \quad \text{H} \quad \text{SR}^9 \quad \text{CH}_3\text{CH} \quad \text{N} \quad \text{OR}^{10} \quad \text{R}^6 \quad \text{R}^5$$  \quad (X)

in which $R^3$ is as defined in claim 1. $R^4$, $R^5$ and $R^6$ are defined as in claim 12, $R^9$ is defined as in claim 13, and $R^{10}$ represents a group $-\text{SO}_2\text{R}$, or $-\text{COR}$ in which $\text{R}$ represents an alkyl group having from 1 to 4 carbon atoms, an optionally substituted phenyl group, or a polyfluoroalkyl group, with a compound of formula XIII

$$\text{R}^7\text{COSH}$$  \quad (XIII)

in which $R^7$ is as defined in claim 12; and wherein a compound of formula X is preferably produced by reacting a compound of formula IX or a tautomer thereof

$$\text{R}^3\text{O} \quad \text{H} \quad \text{H} \quad \text{SR}^9 \quad \text{CH}_3\text{CH} \quad \text{N} \quad \text{O} \quad \text{R}^6 \quad \text{R}^5$$  \quad (IX)
in which \( R^3 \) is as defined in claim 1, \( R^4, R^5 \) and \( R^6 \) defined as in claim 12 and \( R^9 \) is defined as in claim 13, in the presence of a base with a compound of formula XII

\[
\begin{align*}
R^{10} & \quad R^{11} \\
(XII)
\end{align*}
\]

in which \( R^{10} \) is as defined above, and \( R^{11} \) represents an activating group; and

wherein a compound of formula IX is preferably produced by reacting a compound of formula VIII

\[
\begin{align*}
\text{formula VIII}
\end{align*}
\]

in which \( R^3 \) is as defined in claim 1, \( R^4 \) is defined as in claim 12 and \( R^9 \) is defined as in claim 13, in the presence of a base with an activated carboxylic acid derivative of formula VIIa

\[
\begin{align*}
\text{formula VIIa}
\end{align*}
\]

in which \( R^5 \) and \( R^6 \) are defined as in claim 12, and \( R^{11} \) is defined as above.

15. A process as claimed in claim 12(C),
(i) wherein a compound of formula IV is produced by reacting a compound of formula XV
in which R³ is defined as in claim 1, and R⁵ and R⁶ and X are defined as in claim 12, with a compound of formula XIX

\[
\text{XIX}
\]

in which R⁴ is as defined in claim 12 and R¹⁵ represents a group that can be displaced by the azetidinone nitrogen in the compound of formula XV, for example, a halogen atom, an imidazolidine group or a mixed anhydride group, to give a compound of formula IV, or

(ii) wherein a compound of formula V is produced by halogenating a compound of formula XVI

\[
\text{XVI}
\]

in which R³ is defined as in claim 1, and R⁴, R⁵, R⁶ and X are defined as in claim 12 using a halogenating agent for example, thionyl chloride or bromide, phosphorus oxychloride or oxybromide, or a phosphorus halide, or a mixture of two or more thereof, and wherein a compound of formula XVI is preferably produced by reacting a compound of formula XV as defined in (i) above with a glyoxylic ester of formula XXVI

\[
\text{XXVI}
\]
in which \( R^4 \) is as defined in claim 9, or with a reactive derivative thereof, and

(iii) wherein a compound of formula XV is preferably produced by reacting a compound of formula XIV

\[
\text{XIV}
\]

in which \( R^3 \) is as defined in claim 1, and \( L \) represents a leaving group, for example, a halogen atom, an alkylcarbonyloxy group in which the alkyl moiety has from 1 to 4 carbon atoms, has a straight or branched chain, and may be substituted by an electron-withdrawing group, for example, a halogen atom, especially a fluorine atom, a phenylcarbonyloxy group, or an \(-\text{SO}_2\text{R}^j\) group in which \( \text{R}^j \) represents an alkyl group having from 1 to 4 carbon atoms or a phenyl group, and is preferably an acetoxy group, with a compound of formula XVII

\[
\text{XVII}
\]

in which \( R^5, R^6 \) and \( X \) are defined as in claim 12, and \( M \) represents a hydrogen atom or an alkali metal or alkaline earth metal atom, or an ammonium group that is unsubstituted or substituted (when \( M \) represents hydrogen the reaction is carried out in the presence of a base), and

wherein a compound of formula XVII is preferably produced

(a) by reacting a compound of formula VII

\[
\text{VII}
\]

in which \( X, R^5, R^6 \) are defined as in claim 12 and \( R^{11} \)
is defined as in claim 12 with a compound of formula MSH or M₂S, in which M is as defined above, (when M represents hydrogen the reaction is carried out in the presence of a base); or
(b) by reacting a compound of formula XVII

\[ \text{M} - \text{R}^5 \]  \hspace{1cm} \text{(XVII)}

in which \( \text{M} \) represents an alkali metal or alkaline earth metal radical, together with a counter-ion, if required in the case where \( \text{M} \) represents a divalent metal ion, with carbon disulphide or carbon oxysulphide, giving a compound of formula XVII in which \( \text{M} \) represents an alkali metal or alkaline earth metal atom.

16. A process as claimed in any one of claims 12 to 15 wherein a protected group \(-\text{OR}^3\) is that from which the protecting group \( \text{R}^3 \) can be removed under acidic conditions, for example, a tetrahydropyranloxy or tetrahydrofuranyloxy group; an acetal or ketal group; or a silyl ether, wherein an acetal or ketal group preferably has the formula

\[ \text{O}-\text{C}^\text{\textminus} \text{R}^1_{14} \]

\[ \text{O} - \text{C} - \text{R}^1_{13} \]

\[ \text{R}^1_{12} \]

in which \( \text{R}^1_{12} \) and \( \text{R}^1_{13} \), which may be the same or different, each represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, or \( \text{R}^1_{12} \) and \( \text{R}^1_{13} \) together with the carbon atoms to which they are attached, represent a cycloalkyl ring having from 4 to 7 carbon atoms, and \( \text{R}^1_{14} \) represents an alkyl group.
having from 1 to 4 carbon atoms, or R12 and R14,
together with the carbon atom and the oxygen atom to
which they are attached, respectively, represent a
tetrahydropyranyl ring; and a silyl ether has three
substituents on the silicon atom and up to 24 carbon
atoms in total, the three substituents being the same
or different, and selected from alkyl, alkenyl and
cycloalkyl groups, and phenyl and phenalkyl groups
which may be unsubstituted or substituted, and
wherein a silyl ether is preferably a -OSiReRfRg
group in which Re, Rf and Rg are as defined in claim 1,
and wherein a hydroxy protecting group R3 is
especially a tetrahydropyranyl, 2-methoxyprop-2-yl,
trimethylsilyl, triethylsilyl or t-butyldimethyl-
silyl group.

17. A process as claimed in any one of claims 12 to claim 16,
wherein in a compound of formula I or any appropriate
precursor thereof, any one or more of the following
conversions are carried out:
(a) a group R5 to a group R1 or to another group
R5, (including conversion of a radical present as
part of a group R5);
(b) a group R6 to a group R2 or to another group
R6, (including conversion of a radical present as
part of a group R6);
(c) a group R1 to another group R1, (including
conversion of a radical present as part of a group
R1);
(d) a group R2 to a group R2, (including conversion
of a radical present as part of a group R2);
the conversion being carried out as follows:
(i) \(-\text{COO}R_d, \text{COO}Ph\text{Rg} \text{ or } \text{COO}-\text{phenyl} \text{ to } \text{COOH}\)
(ii) \(-\text{COOH} \text{ to } \text{CONH}_2, \text{CONHRA} \text{ or } \text{CONH}(\text{CH}_2)_n\text{O} \text{ or } \text{CO}_2\text{CH}(\text{CH}_3)\text{O}\)
(iii) \(-\text{COOH} \text{ to } \text{COOR}^4, \text{CO}_2\text{CH}_2\text{O} \text{ or } \text{CO}_2\text{CH}_2\text{CH}_2\text{O}\)
(iv) \(-\text{COOH} \text{ to } \text{COR}_a\)
(v) \(-\text{NHR}_m \text{ or } -\text{NR}_m\text{R}_n \text{ in which } R_m \text{ and } R_n \text{ are protecting groups}, \text{ to } \text{NH}_2\)
(vi) \(-\text{NH}_2 \text{ to }\)
\[\text{NHCH}_2\text{NH} \quad \text{NHSO}_2\text{R}_a \quad -\text{NH}_2\]
(vii) \(-\text{CONHR}_m, R_m \text{ being a protecting group, to }\)
\[-\text{CONHRA}\]
(viii) \(-\text{N}_3 \text{ to } -\text{NH}_2\), which is then optionally converted to a group \(R^1\) as described in (vi) above,
(ix) halogen to \(-\text{CN} \text{ or } -\text{COOH}\)
(x) \(-\text{SR}_a \text{ to } -\text{SOR}_a \text{ or } -\text{SO}_2\text{R}_a\)
(xi) \(-\text{CN} \text{ to } \text{CH}_2\text{NH}_2, \text{ which is then optionally converted to a group as defined in (vi) above,}\)
(xii) \(-\text{SOR}_a \text{ to } -\text{SO}_2\text{R}_a\)
(xiii) \(-\text{NO}_2 \text{ to } \text{NB}_2, \text{ which is then optionally converted further as described in (vi) above.}\)

18. A pharmaceutical preparation which comprises a compound of formula I as claimed in any one of claims 1 to 11 or a physiologically tolerable salt thereof, or a mixture of two or more such substances as active ingredient, in admixture or conjunction with a pharmaceutically suitable carrier.

19. A compound of formula I as claimed in any one of claims 1 to 11 or a physiologically tolerable salt
thereof for use in the manufacture of a medicament for the treatment of bacterial infections.

20. A compound of formula II

\[
\text{(II)}
\]

in which \( R^3 \) is defined in claim 1 and \( R^4, R^5, R^6, R^7 \) and \( R^8 \) are as defined in claim 8.

21. A compound of formula XXVII

\[
\text{(XXVII)}
\]

in which:
- \( R^3 \) is as defined in claim 1,
- \( R^4, R^5 \) and \( R^6 \) are as defined in claim 12,
- \( R^9 \) is an alkyl group having 1 to 6 carbon atoms, an alkenyl group having 2 to 4 carbon atoms, or a phenyl group, and
- \( \text{Ry} \) is \( \text{SCOR}^7, \text{OH} \) or \( \text{OR}^{10} \) in which
  - \( R^7 \) is as defined in claim 12 and
  - \( R^{10} \) is a group \(-\text{SO}_2\text{R}^h \) or \(-\text{COR}^h \) in which \( \text{R}^h \) is an alkyl group having from 1 to 4 carbon atoms, an optionally substituted phenyl group, or a polyfluoro-alkyl group.

22. A compound of formula XXVIII
in which $R_x$ is $\text{H}$ or a group,

$$
\text{P}(\text{II})_3 \quad \text{COOR}^4 \quad \text{COOR}^4 \quad \text{CH} \quad \text{CH}^{\sim} \quad \text{R}^4 \quad \text{R}^4
$$

in which

$R^3$ is as defined in claim 1,

$X$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, and $\text{P}(\text{II})_3$ are as defined in claim 12.

DATED this 14th day of August 1986.

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