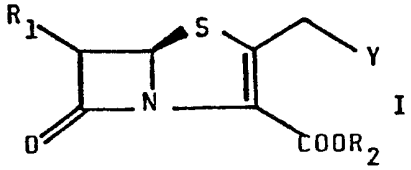
(12) UK Patent Application (19) GB (11) 2 131 432 A

(21) Application No **8332756**
(22) Date of filing **8 Dec 1983**
(30) Priority data
(31) **8235058**
(32) **8 Dec 1982**
(31) **8323129**
(32) **27 Aug 1983**
(33) **United Kingdom (GB)**
(43) Application published
20 Jun 1984
(51) **INT CL**^{3}
C07D 499/00 A61K 31/43
C07D 513/00
(52) Domestic classification
C2C 1310 1313 1315
1390 1464 1530 213 214
215 220 226 22Y 247 250
251 252 256 25Y 275
28X 290 292 29Y 305
30Y 311 313 314 31Y 330
332 335 337 339 340 34Y
351 352 354 357 358 360
361 362 363 366 367 368
36Y 370 373 37Y 387 389
43X 462 491 503 509
50Y 614 621 623 625 627
628 629 631 633 638 652
658 65X 661 678 681
695 699 70Y 72Y 761 762
801 AA AB KA KB MJ MM
QS RV TR YT YX
U1S 2410 C2C
(56) Documents cited
None
(58) Field of search
C2C
(71) Applicant
Farmitalia Carlo Erba SpA,
(Italy),
Via Imbonati 24 20159,
Milan,
Italy
(72) Inventors
Marco Alpegiani,
Angelo Bedeschi,
Maurizio Foglio,
Giovanni Franceschi,
Ettore Perrone
(74) Agent and/or address for service
Serjeants,
25 The Crescent,
King Street,
Leicester,
LE1 6RX

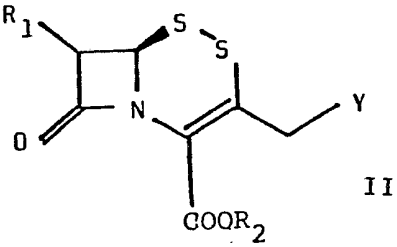
(54) **Preparation of (5R)-penem derivatives**

(57) (5R)-penem derivatives of the general formula I



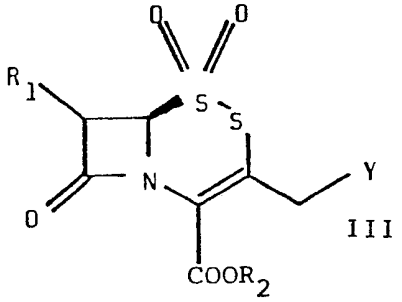
I

(R_1=H or an organic group, R_2=H or a carboxy protecting group and Y=H, halogen or an organic group) are prepared by oxidising 2-thiacephem derivatives of the general formula II



II

(R_1, R_2 and Y as above defined) by means of organic peracids, and submitting the resultant corresponding 1,1-dioxide of formula III to a desulphurative ring contraction with expulsion of SO_2.



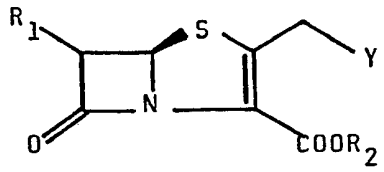
III

GB 2 131 432 A

SPECIFICATION

2-Thiacephems and (5R) penem derivatives

The invention relates to a new process for the preparation of (5R) penem compounds of the general formula I and their pharmaceutically and/or veterinarily acceptable salts.



I

In the general formula I, R_1 represents a hydrogen atom or an organic group; R_2 represents a hydrogen atom or a carboxy protecting group; and Y represents a hydrogen or halogen atom or an organic group.

Organic groups which R_1 may represent include optionally substituted aliphatic or cycloaliphatic groups. The aliphatic groups are preferably alkyl groups having from 1 to 12 carbon atoms and the optional substituents may be one or more hydroxy, amino, cyano and/or mercapto groups. The hydroxy, amino and mercapto groups may be free or protected. Particularly preferred alkyl groups are methyl and ethyl, especially the latter, and a preferred substituent for such a group is a hydroxy group, which may be free or protected. The 1-hydroxyethyl group in 6S, 8R or 6R, 8S configuration is most preferred. The cycloaliphatic groups are preferably monocycloalkyl groups having from 4 to 7 carbon atoms. Cyclopentyl and cyclohexyl groups are especially preferred. Optional substituents are preferably chosen from alkyl groups having from 1 to 6 carbon atoms, for example methyl or ethyl groups, hydroxy, amino and mercapto groups, the hydroxy, amino and mercapto groups being free or protected.

The carboxy protecting group R_2 may be any group which, together with the —COO— moeity, forms an esterified carboxy group. Examples of carboxy protecting groups R_2 are alkyl groups having from 1 to 6 carbon atoms, for instance methyl, ethyl or *t*-butyl; halo substituted alkyl groups having from 1 to 6 carbon atoms, for example 2,2,2-trichloroethyl; alkenyl groups having from 2 to 4 carbon atoms, for example allyl; optionally substituted aryl groups, for example phenyl and *p*-nitro-phenyl; aryl substituted alkyl groups, the alkyl part whereof has from 1 to 6 carbon atoms and the aryl part whereof is optionally substituted, for example benzyl, *p*-nitro-benzyl and *p*-methoxy-benzyl; aryloxy substituted alkyl groups, the alkyl part whereof has from 1 to 6 carbon atoms, for example phenoxy-methyl; or groups such as benzhydryl, *o*-nitro-benzhydryl, acetonyl, trimethylsilyl, diphenyl-*t*-butyl-silyl, and dimethyl-*t*-butyl-silyl. The definition of R_2 as a carboxy protecting group also includes any residue, such as acetoxymethyl, pivaloyloxymethyl or phthalidyl, leading to an ester group which is known to be hydrolyzed *"in vivo"* and to have favourably pharmacokinetic properties.

When Y represents a halogen atom, it is preferably a fluorine, chlorine or bromine atom.

When Y represents an organic group, it is preferably

a) a free or protected hydroxy group;

b) a formyloxy group or an acyloxy group having from 2 to 6 carbon atoms, optionally substituted by a halogen atom, by an acyl group having from 2 to 6 carbon atoms, or by an amino, hydroxy or mercapto group, the amino, hydroxy or mercapto group optionally being in a protected form;

c) an unsubstituted or N-alkyl or N-acyl substituted carbamoyloxy group;

d) an alkoxy group having from 1 to 12 carbon atoms or an alkylthio group having from 1 to 12 carbon atoms, either of which is optionally substituted by one or more halogen atoms, formyl groups, acyl groups having from 2 to 6 carbon atoms, and/or amino, hydroxy or mercapto groups, the amino, hydroxy or mercapto group optionally being in a protected form;

e) a 1-pyridinium group, unsubstituted or substituted in the meta or para position with the group $—CONH_2$;

f) a heterocyclylthio group —S—Het wherein Het, denoting a saturated or unsaturated heterocyclic ring containing at least one oxygen, sulphur and/or nitrogen heteroatom, is preferably:

A) a pentatomic or hexatomic heteromonocyclic ring, containing at least one double bond and at least one oxygen, sulphur and/or nitrogen heteroatom, unsubstituted or substituted by one or more

a') alkoxy groups having from 1 to 6 carbon atoms, aliphatic acyl groups having from 2 to 6 carbon atoms, hydroxy groups and/or halogen atoms;

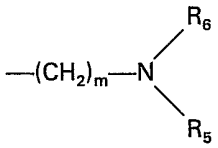
b') alkyl groups having from 1 to 6 carbon atoms, unsubstituted or substituted by one or more hydroxy groups and/or halogen atoms;

c') alkenyl groups having from 2 to 6 carbon atoms, unsubstituted or substituted by one or more hydroxy groups and/or halogen atoms;

d') groups of the general formula $—S—R_3$ wherein R_3 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms, or groups of the general formula $—S—CH_2—COOR_4$ wherein R_4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or a carboxy-protecting group;

e') groups of the general formulae $—(CH_2)_m—COOR_4$ or $—CH=CH—COOR_4$ or $—(CH_2)_m—CN$ or $—(CH_2)_m—CONH_2$ or $—(CH_2)_m—SO_3H$ wherein *m* is zero, 1, 2 or 3 and R_4 is as defined above;

f') groups of the general formula



wherein *m* is as defined above, and each of R_5 and R_6, which may be the same or different, represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aliphatic acyl group or when one of R_5 and R_6 is hydrogen, the other may be also an amino protecting group; or

B) a heterobicyclic ring, containing at least two double bonds wherein each of the condensed heteromonocyclic rings, being the same or different, is a pentatomic or hexatomic heteromonocyclic ring containing at least one oxygen, sulphur or nitrogen heteroatom, said heterobicyclic ring being unsubstituted or substituted by one or more substituents selected from a'), b'), c'), e') and f') as defined above.

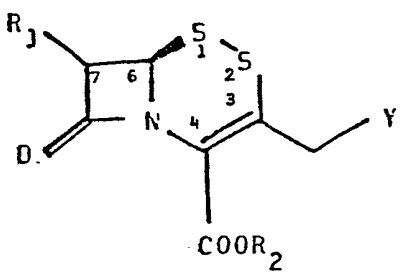
In the above definitions A) and B) preferred halogen atoms are chlorine, bromine and iodine; preferred alkyl groups are methyl and ethyl; a preferred alkenyl group is allyl; a preferred aliphatic acyl group is acetyl; a carboxy protecting group may be any of the groups previously indicated for the R_2 substituent; and the free sulpho and carboxy groups possibly present may be salified, e.g. as sodium or potassium salts. A heteromonocyclic ring of the above class A) may be, for example, an optionally substituted thiazolyl, triazolyl, thiadiazolyl, tetrazolyl or triazinyl ring. Preferred substituents on such rings are, for example, one or more substituents chosen from amino, hydroxy, oxo and a $C_1—C_6$-alkyl group, preferably methyl or ethyl, wherein the $C_1—C_6$-alkyl group may be optionally substituted by a substituent chosen from carboxy, sulpho, cyano, carbamoyl, amino, methylamino or dimethylamino. A heterobicyclic ring of the above class B) may be for example, a tetrazolopyridazinyl radical optionally substituted by amino or carboxy.

In the above formula I the amino, hydroxy or mercapto protecting groups possibly present may be those usually employed in the chemistry of penicillins and cephalosporins for these functions. They may be, for instance optionally substituted, especially halo-substituted, acyl groups, e.g. acetyl, monochloroacetyl, dichloroacetyl, trifluoroacetyl, benzoyl or *p*-bromophenacyl; triarylmethyl groups, in particular triphenylmethyl; silyl groups, in particular trimethylsilyl, dimethyl-*t*-butyl-silyl, diphenyl-*t*-butyl silyl; or also groups such as *t*-butoxycarbonyl, *p*-nitrobenzyloxycarbonyl, 2,2,2-trichloroethoxy-carbonyl, benzyl, pyranyl and nitro. When, in particular, the R_1 substituent in formula (I) is a hydroxyalkyl group, preferred protecting groups for the hydroxy function are *p*-nitro-benzyloxy-carbonyl; dimethyl-*t*-butyl-silyl; diphenyl-*t*-butylsilyl; trimethylsilyl; 2,2,2-trichloroethoxycarbonyl; benzyl; *p*-bromo-phenacyl; triphenylmethyl and pyranyl. All the alkyl and alkenyl groups, including the aliphatic hydrocarbon moiety of the alkoxy, alkylthio and acyloxy groups, may be branched or straight.

The pharmaceutically and/or veterinarily acceptable salts may be both salts with acids, either inorganic acids such as hydrochloric or sulphuric acid, or organic acids such as citric, tartaric, fumaric or methanesulphonic acid, and salts with bases, either inorganic bases such as alkali metal or alkaline-earth metal hydroxides, in particular sodium and potassium hydroxides, or organic bases such as triethylamine, pyridine, benzylamine or collidine. Preferred salts are the salts of the compounds of formula I wherein R_2 represents a hydrogen atom with one of the bases hereabove specified in particular with sodium hydroxide or potassium hydroxide.

The compounds of the general formula I obtainable by the process of the invention are known compounds, described in our British Patent Specifications Nos. 2043639A and 8210410. They are potent, broad-spectrum antimicrobial agents, and are therefore useful in the treatment of bacterial infections in warm-blooded animals, especially in humans, by enteral or parenteral administration.

Desulphurative ring contraction of 2-thiacephem of the general formula II

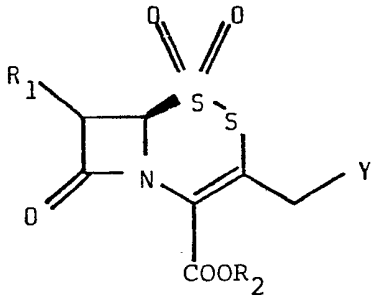


II

wherein R_1, R_2 and Y are as above defined is a known process for the preparation of penems, but it suffers from poor or adverse stereoselectivity. Although the carbon atom in position 6 has the R

configuration, the desulphurization usually gives (5S)-penems which are biologically inactive (H. R. Pfaendler et al., J. Am. Chem. Soc., 101, 1979, 6306) or a mixture of (5S)-and (5R)-penems (A. Henderson et al., J. Chem. Soc. Commun., 1982, 809). We have found and described in Tetrahedron Letters, *24*, pag. 3283 (1983) that (5R)-penems can be obtained from such desulphurative ring contractions if the substituents R_1, R_2 and Y and the solvent for the process are suitably selected. A more general stereoselective process, operable over the full range of values of the substituents R_1, R_2 and Y is, however, clearly desirable, as it would obviate the losses involved in the formation of the undesired (5S)-isomers and their separation from the desired (5R)-isomers.

The invention provides a process for the preparation of a (5R)-penem having the general formula I as above defined the process comprising oxidising a 2-thiacephem having the general formula II as above defined and wherein the carbon at position 6 has the R configuration to give a sulphone having the general formula III



III

wherein R_1, R_2 and Y are as above defined, and ring contracting the sulphone by extrusion of sulphur dioxide; and, if desired, converting the resultant (5R) penem of the general formula I into another compound of the general formula I; and/or, if desired, converting the resultant compound of the general formula I into a salt thereof; and/or, if desired, obtaining a free compound of the general formula I from a salt thereof.

The oxidation may be carried out using oxidizing agents usually used to convert an organic sulphide into the corresponding sulphone. Preferred oxidizing agents are peracids such as *m*-chloroperbenzoic acid or peracetic acid. The reaction is generally performed in an organic solvent, such as chloroform or benzene, at a temperature of from 0 to 60°C, preferably from 4 to 30°C.

The ring contraction of the sulphone, with loss of sulphur dioxide, may be effected simply by heating it in an inert organic solvent such as chloroform or benzene. The ring contraction may, in some cases, even occur spontaneously at room temperature. The R configuration of the carbon atom in position 6 in the 2-thiacephem II is retained throughout the process, so that (5R)-penems are obtained exclusively. It is noteworthy that, although loss of sulphur dioxide from thiosulphonates has occasionally been reported (see, for example, W. L. F. Armarego and E. E. Turner, J. Chem. Soc., 1956, 1665; A. Padwa and R. Gruber, J. Org. Chem., *35*, 1970, 1781), this reaction has hardly any precedent so far as yields and mildness of operative conditions are concerned and for the first time it has been applied in the synthesis of β-lactam compounds. The present invention also provides routes to obtain the required compounds of formula II possessing the (5R) configuration.

According to the invention, the compounds of the general formula II are prepared by either of the routes shown in the following reaction scheme wherein:

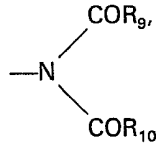
R_1, R_2 and Y are as defiend above,

Z represents

i) a group of the formula SR_7 wherein R_7 represents an alkyl group having from 1 to 8 carbon atoms, a phenyl or tolyl group, or, preferably, a heterocyclic group, especially a 2-benzothiazolylthio or 1-methyl-tetrazol-5-yl-thio group,

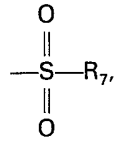
ii) a group of the formula $SCOR_8$ wherein R_8 represents an optionally substituted lower alkyl group, preferably a methyl group,

iii) a group of the formula



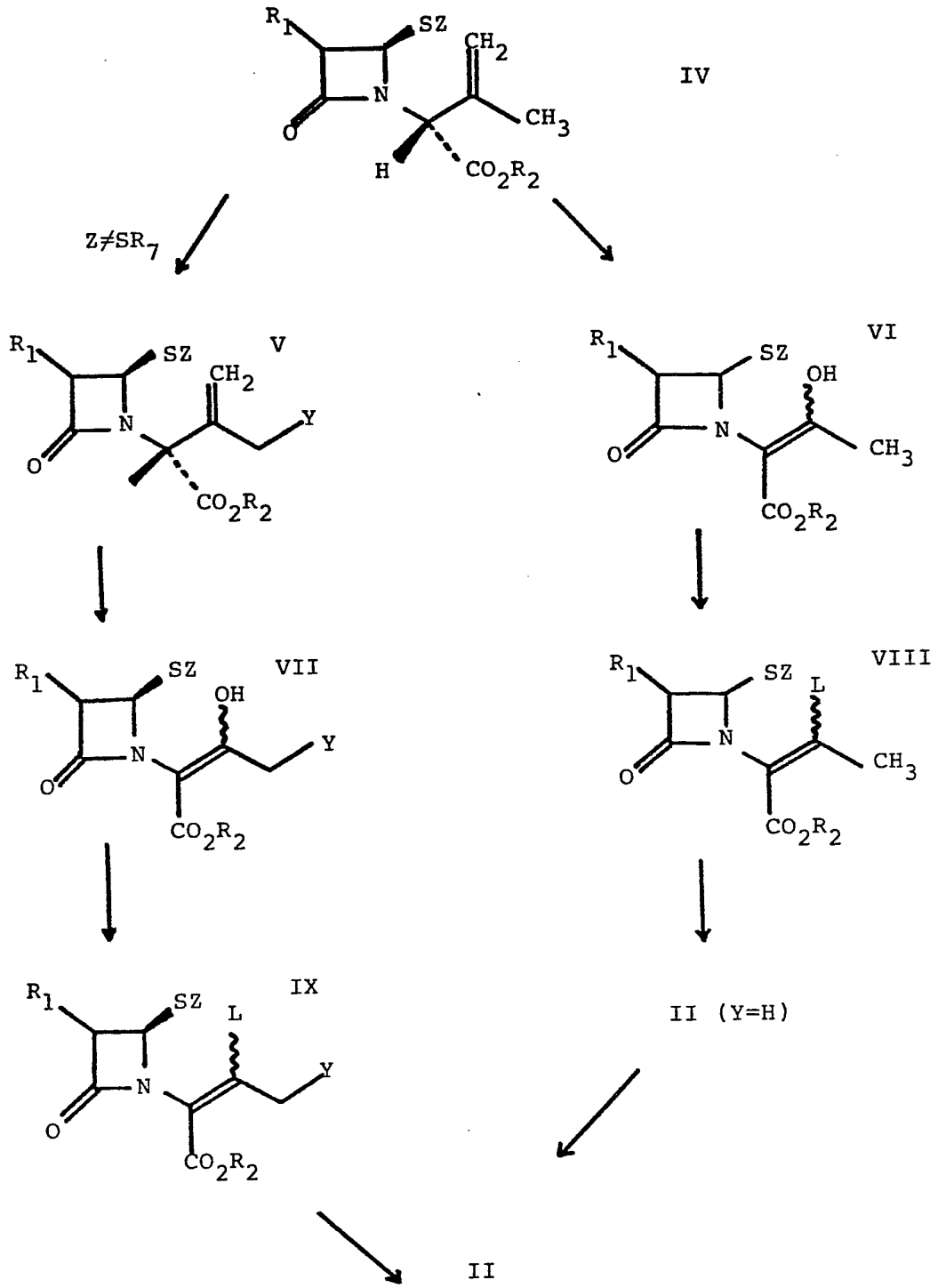
wherein R_9 and R_{10} independently represent lower alkyl or aryl groups, or together with the dicarboxyamino group form a heterocyclic ring, preferably a succinimido or phthalimido group, or

iv) a group of the formula



wherein R_7 represents an optionally substituted lower alkyl or aryl group, preferably a methyl, phenyl or *p*-tolyl group; and

L represents a halogen atom, an alkane sulphonyloxy group or an arene sulphonyloxy group, preferably a methanesulphonyloxy group.



Compounds of the general formula IV, which are used as starting materials, are known compounds or can be obtained from known compounds by *per se* known procedures; the preparation of some representative entities is described in the Examples.

The compound of the general formula IV is first ozonolysed to give a compound of the general formula VI. The hydroxy group is then converted into a group L and the resultant compound of the general formula VIII is cyclised to give a compound of the general formula II in which Y represents a hydrogen atom. If desired, the methyl group may then be halogenated to give a compound of the general formula II in which Y represents a halogen atom.

In an alternative process, the compound of the general formula IV may first be halogenated by methods known *per se* (allyl, ene-type, or electrochemical halogenation, see Tetrahedron Letters, *1980*, 71 and 351; *1981*, 3193; *1982*, 2187). The resultant compound of the general formula V is then ozonolysed; the hydroxy group of the resultant compound of the general formula VII is then transformed into a group L and the resultant compound of the general formula IX is cyclised to give a compound of the general formula II.

The group Y in the compounds of the general formulae V, VII, IX and II may, if it represents a halogen atom, be optionally transformed into any of the other groups, which Y may represent except a hydrogen atom. According to a preferred feature of the invention, this transformation is preferably carried out on the compounds of the general formula II.

The transformation into a group L of the hydroxy group in the enol VI or VIII, which may be in equilibrium with the corresponding keto-tautomer, is preferably a mesylation. We have surprisingly found that, when this reaction is carried out in tetrahydrofuran instead of the ubiquitously used halogenated hydrocarbons, mesylates IX or VIII having Z alkene geometry, which are the most suitable ones for the subsequent cyclization, are almost exclusively obtained (similar transformation performed in dichloromethane usually affords a 1:1 mixture of *E, Z* isomers: see T. W. Doyle et al., *Can. J. Chem.*, 1977, *55*, 2873; M. J. Pearson, *J. Chem. Soc., Chem. Comm.* 1981, 947; P. C. Cherry et al., *J. Chem. Soc., Chem. Comm.* 1979 663. Cyclisation of VIII or IX may be carried out in a single step, by reaction with a sulphide or hydrosulphide, such as Na_2S, NaHS, Bu_4NHS, or with H_2S in the presence of a base such as triethylamine or pyridine. The cyclisation of IX or VIII wherein Z represents a group other than SR_7 offers the clear advantage of releasing easily separable, usually water soluble by-products ZH (e.g. phenylsulphinic acid, succinimide), instead of by products R_3SH (e.g. mercaptobenzthiazole) which usually require chromatographic separation or precipitation as heavy metal salts (Ag^+, Pb^{2+}).

Against any reasonable expectation, which would rule out the possibility of halogenating the 3-methyl group of the compounds II (Y=H) owing to the presence of the disulphide moiety, we have found a method to effect such transformation in high yield. We can thus obtain the compounds II (Y=halogen), which are invaluable intermediates for the synthesis of highly active penem antibiotics I. A preferred halogenating reagent for such transformation is N-bromosuccinimide, which is best used in the presence of a radical initiator, such as azobisisobutyronitrile or benzoyl peroxide in the presence of acid scavengers, such as epoxides (e.g. propylene oxide), alkaline-earth oxides (e.g. calcium oxide), or molecular sieves, in solvents such as benzene, carbon tetrachloride or ethyl formate at a temperature ranging from 20°C to 130°C.

The compounds II (Y=halogen) can be converted into compounds II (Y=an organic group) by reactions known *per se;* e.g.

1) a compound II (Y=Br or Cl) can be converted into a compound II (Y=free or protected OH) by mild alkaline hydrolysis, or by reaction with cuprous oxide/dimethylsulphoxide/water or by reaction with a salt of a strong inorganic acid, e.g. a nitrate or a perchlorate, thus obtaining a labile ester with the said inorganic acid, which ester may be hydrolyzed, subsequently or in the same reaction medium, to the desired parent alcohol. Preferred salts of this type are $AgNO_3$, $AgClO_4$, $NaNO_3$;

2) a compound II (Y=Br or Cl) can be converted into a compound II (Y=an unsubstituted or N-alkyl substituted carbamoyloxy group) by conversion into a compound II (Y=OH) as described above followed by reaction with a suitable isocyanate; for example, trichloroacetyl isocyanate is a preferred reagent for obtaining compounds II ($Y=OCONH_2$), following deprotection of the trichloroacetyl moiety on the first formed urethane adduct;

3) a compound II (Y=Br or Cl) can be converted into a compound II (Y=acyloxy) by reaction with a suitable salt of the corresponding carboxylic acid in a suitable solvent or under phase-transfer catalysis; or by conversion into a compound II (Y=OH) followed by conventional acylation;

4) a compound II (Y=Br or Cl) can be converted into a compound II (Y=S—Het) by reaction with the corresponding HS—Het in the presence of a base, or with a preformed salt of HS—Het with a base, in a suitable solvent, such as tetrahydrofuran, acetone, acetonitrile, or dimethylformamide. A suitable base is triethylamine; a suitable preformed salt is a sodium salt, e.g. sodium 1-methyl-1,2,3,4-tetrazol-5-yl-mercaptide.

Owing to the pronounced propensity of 3-hydroxymethyl-2-thiacephem-4-carboxylates to lactonize, it is preferable that in the process 1) described above R_2 represents a somewhat bulky group, forming with the linked carboxy moiety an ester possessing a relative inertness towards nucleophilic attack by the neighbouring hydroxy group, e.g. a tert-butyl ester. Alternatively, it may be convenient to deprotect the hydroxy group from a protected form thereof after the ring-contraction step to the corresponding penem I, since 2-hydroxymethylpenemcarboxylates do not lactonize easily. For example, a compound II (Y=Br) may be converted into a compound II ($Y=ONO_2$), which may easily be isolated, purified if necessary, and desulphurized to the corresponding penem I whose reductive hydrolysis (e.g. Zn/CH_3COOH) affords without problems the free hydroxy derivative.

Owing to the different stability of the penem and 2-thiacephem nucleus towards the conditions required for —$COOR_2$ ester hydrolysis, a distinct advantage of the invention is that ester hydrolyses not compatible with a penem can be performed on the 2-thiacephem precursor, and the ring contraction may be performed on the free acid, or on a salt with an organic or inorganic base, or on a different

labile ester, which can be prepared in situ, if desired; e.g. a trimethylsilyl, *t*-butyldimethylsilyl, or *t*-butyldiphenylsilyl ester.

The following Examples illustrate the invention. The abbreviations Me, Bu^t, Ph, Ms, pNB, THF, EtOAc, DMSO, MeCN, stand respectively for methyl, *t*-butyl, phenyl, methanesulphonyl, *p*-nitrobenzyl, tetrahydrofuran, ethyl acetate, dimethylsulphoxide and acetonitrile. NMR spectra were taken either on a Hitachi-Perkin Elmer 60 MHz apparatus, or on a Brucker 90 MHz; separation of inner lines of AB quartets are referred to spectra taken on the latter.

Example 1
Diphenylmethyl 6,6-dibromopenicillanate

90 g of 6,6-dibromopenicillanic acid in 450 ml of acetonitrile was treated with a solution of 49 g of diphenyldiazomethane in 150 ml of acetonitrile. After 1 hour at 20°C the formed solid was collected by filtration and washed with small portions of cold diethyl ether, thus obtained 116 g of the title product. A second crop (9 g) was obtained by evaporation of the mother liquors and trituration with diethyl ether. The overall yield was 95%.

Analytical sample was obtained by crystallization from chloroform; mp 157—158°C; ν_{max} ($CHCl_3$ film) 1800, 1750 cm^{-1}; δ($CDCl_3$) 1.24 and 1.58 (each 3H, s, CMe_2), 4.61 (1H, s, N.CH.CO), 5.80 (1H, s, N.CH.S), 6.91 (1H, S. OCH), and 7.30 ppm (10H, s. Ar).

Found: C, 47.80; H, 3.63; N, 2.64; S, 5.95; Br, 30.49%. $C_{21}H_{19}Br_2NO_3S$ requires C, 48.02; H, 3.64; N, 2.67; S, 6.10; Br, 30.43%.

Example 2
t-Butyl 6,6-dibromopenicillanate
Method A

100 g of 6,6-dibromopenicillanic acid in 1 litre of diethyl ether at 0°C was sequentially treated with 37 ml of triethylamine and 56 g of phosphorus pentachloride. After 1 hour stirring, the reaction mixture was evaporated under *vacuum* (dry benzene added and removed). The crude acyl chloride was dissolved in 200 ml of dichloromethane and stirred for 24 hours with 500 ml of *t*-butanol in the presence of 50 g of calcium carbonate. The suspended salts were then filtered off, and the solution was washed with aqueous sodium bicarbonate solution (some unreacted starting material could be recovered by back-extraction of the acidified aqueous washings), decoloured with charcoal and evaporated to afford the title product, which was then crystallized from diisopropyl ether. Yield 69 g (60%); mp 120—121°C, ν_{max} ($CHCl_3$ film) 1800 and 1740 cm^{-1}; δ($CDCl_3$) 1.98 (15H, s, Bu^t and CH_3), 2.05 (3H, s, CH_3), 4.38 (1H, S, N.CH.CO) and 5.70 ppm (1H, s, N.CH.S).

Method B

15 g of 6,6-dibromopenicillanic acid in 300 ml of dichloromethane was stirred overnight with 25 g of O-*t*-butyl-N,N-diisopropyl-isourea. The reaction mixture was filtered and the solution washed with aqueous sodium bicarbonate solution. Crystallization of the product from diisopropyl ether gave the title compound, 8 g (47%).

Example 3
Diphenylmethyl 6α-bromo-6β-(1R-hydroxyethyl)-penicillanate

120 g of diphenylmethyl 6,6-dibromopenicillanate, prepared as described in Example 1, in 900 ml of dry distilled THF under nitrogen at —75°C was treated with 1 molar equivalent of a solution of ethylmagnesium bromide in diethyl ether. After 20 min at —75°C, 25.7 ml of acetaldehyde was added and the mixture was further stirred for 20 min at —75°C. After quenching with 400 ml of saturated aqueous ammonium chloride, partition between water and diethyl ether followed by removal of the solvent left the crude product. This was fractionated by silica gel chromatography (benzene:ethyl acetate) to afford the title compound, 67 g (60%), as a foam, crystallizable (diisopropyl ether) to a solid, mp 65—70°C; ν_{max} (film) 3450, 1785 and 1740 cm^{-1}; δ($CDCl_3$) 1.22 and 1.60 (each 3H, s, CMe_2), 1.29 (3H, d, J=6Hz, CH_3.CH), 2.90 (1H, d, OH), 4.17 (1H, m, CH_3.*CH*.OH), 4.58 (1H, s, N.CH.CO), 5.49 (1H, s, N.CH.S), 6.90 (1H, s, *OCH*Ph_2) and 7.3 ppm (10H, s. Ar).

Using *t*-butyl-6,6-dibromopenicillanate, prepared as described in Example 2, and proceeding similarly, there were obtained *t-butyl 6α-bromo-6β-(1R-hydroxyethyl)-penicillanate* in 65% yield after crystallization from diisopropyl ether: hexane; m.p. 93—95°C with decomposition; δ($CDCl_3$) 1.28 (3H, d, J=6Hz, CH_3.CH), 1.54 (12H, s, Bu^t and CH_3), 1.65 (3H, s, CH_3), 2.65 (1H, s, CH.O*H)*,4.25 (1H, m, CH_3.*CH*(OH).CH), 4.40 (1H, s, N—CH.CO) and 5.51 ppm (1H, s, N.CH.S).

Example 4
Diphenylmethyl 6α-(1R-hydroxyethyl)-penicillanate-1-oxide

52 g of diphenylmethyl 6α-bromo-6β-(1R-hydroxyethyl)-penicillanate, prepared as described in Example 3, in 400 ml of 95% ethanol was hydrogenated at 20700 pascals in the presence of 25 g of 10% by weight palladium-on-calcium carbonate and 11 g of calcium carbonate. The reaction mixture was filtered and evaporated to afford a residue which was partitioned between brine and

dichloromethane. Removal of the solvent left crude diphenylmethyl 6α-(1R-hydroxyethyl)-penicillanate, which was oxidized with 17 g of 85% MCPBA in 500 ml of chloroform at 0—5°C for 1 hour. The filtered solution was then washed with aqueous sodium bicarbonate solution and the solvent removed to leave 40 g (88%) of the crude title product as a foam, which can be used as such or purified by silica gel chromatography; ν_{max} ($CHCl_3$ film) 1790 and 1750 cm^{-1}; δ($CDCl_3$) 0.94 and 1.67 (each 3H, s, CMe_2), 1.37 (3H, d, J=6Hz), 3.55 (1H, dd, J=2 and 6.5Hz, CH.*CH*.CH), 4.25 (1H, m, CH_3.*CH*(OH).CH), 4.64 (1H, s, N.CH.CO), 4.98 (1H, d, J=2Hz, CH.C*H*.S), 6.98 (1H, s, O*CH*Ph_2) and 7.30 ppm (10H, s, Ar).

Using a similar procedure but starting from *t*-butyl 6α-bromo-6β-(1R-hydroxyethyl)-penicillanate, prepared as described in Example 3, there was obtained *t-butyl 6α-(1R-hydroxyethyl)-penicillanate-1-oxide:* yield 75%: ν_{max} (film) 3440, 1785 and 1740 cm^{-1}.

Example 5

Diphenylmethyl 6-(1R-t-butyldimethylsilyloxyethyl)penicillanate-1-oxide

40 g of crude diphenylmethyl 6α-(1R-hydroxyethyl)-penicillanate-1-oxide, prepared as described in Example 4, was dissolved in 350 ml of DMF and stirred for 3 hours at 50—55°C in the presence of 18.5 g of imidazole and 27 g of *t*-butyldimethylsilyl chloride. The reaction mixture was partitioned between diethyl ether and brine and the organic layer washed several times with water. Evaporation of the solvent and silica gel chromatography afforded the title product; yield 22 g; ν_{max} ($CHCl_3$ film) 1790 and 1755 cm^{-1}; δ($CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.88 (13H, s, Bu^t and CH_3), 1.3 (3H, d, J=6Hz, *CH_3*.CH), 1.7 (3H, s, CH_3), 3.4 (1H, dd, J=2 and 4.5Hz, CH.*CH*.CH), 4.40 (1H, m, CH_3—*CH*.CH) 4.55 (1H, s, N.CH.CO), 4.88 (1H, d, J=2, CH.*CH*.S), 6.9 (1H,SO*CH*Ph_2), and 7.25 ppm (10H, s. Ar).

By using a similar procedure, but starting from *t*-butyl 6α-(1R-hydroxyethyl)-penicillanate-1-oxide, prepared as described in Example 4, there was obtained *t-butyl 6-(1R-t-butyldimethylsilyloxyethyl)-penicillanate-1-oxide* in overall yield 55% from the 6α-bromoprecursor; ν_{max} ($CHCl_3$ film) 1785 and 1750 cm^{-1}; δ($CDCl_3$) 0.06 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiBu^t$), 1.25 and 1.66 (each 3H, s, CMe_2), 1.28 (3H, d, J=6Hz, *CH_3*.CH), 1.45 (9H, s, OBu^t), 3.5 (1H, dd, j=2 and 5Hz, CH.*CH*.CH), 4.4 (1H, s, N.CH.CO), 4.5 (1H, m, CH_3.*CH*.CH) and 4.9 ppm (1H, d, J=2Hz, CH.*CH*.S).

Example 6

Diphenyl 6α-(1R-p-nitrobenzyloxycarbonyloxyethyl)-penicillate-1-oxide

Diphenylmethyl 6α-(1R-hydroxyethyl)-penicillanate-1-oxide, prepared as described in Example 4, was acylated with *p*-nitrobenzylchlorocarbonate by using N, N-dimethylaminopyridine as a base and ethanol-free dichloromethane as solvent, according to a general method, thus obtaining the title product as a foam; δ($CDCl_3$) 0.96 and 1.70 (each 3H, s, CMe_2), 1.52 (3H, d, J=6Hz, *CH_3*.CH), 3.83 (1H, dd, J=2 and 6Hz, CH.*CH*.CH), 4.66 (1H, s, N.CH.CO), 4.99 (1H, d, J=2Hz, CH.*CH*.S), 5.28 (2H, s, O*CH_2*Ph), 5.35 (1H, m, CH_3.*CH*.CH), 7.01 (1H, s, OCHPh_2), 7.40 (10H, m, Ar), 7.55 and 8.26 ppm (each 2H, d, J=8Hz, Ar).

Following the same experimental procedure, there was obtained *t-butyl 6α-(1R-p-nitrobenzyloxycarbonyloxyethyl)-penicillanate-1-oxide.*

Following similar experimental procedures, but using trichloroethylchlorocarbonate instead of *p*-nitrobenzylchlorocarbonate, there were also obtained:

t-butyl-6α-(1R-trichloroethyloxycarbonyloxyethyl)-penicillanate-1-oxide

diphenylmethyl 6α-(1R-trichloroethyloxycarbonyloxyethyl)-penicillanate-1-oxide.

Example 7

3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one

A mixture of 5 g of methyl 6α-(1R-hydroxyethyl)-penicillanate-1-oxide and 3.04 g of 2-mercaptobenzthiazole was refluxed for 2 hours in dry toluene. The solvent was removed *in vacuo* and the crude product used as such for the next step.

Using similar procedures, there were obtained:

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, starting from methyl 6α-(1R-*t*-butyldimethylsilyloxyethyl)-penicillanate-1-oxide, and prolonging the reaction time up to 6 hours; ν_{max} ($CHCl_3$ film) 1770 and 1744 cm^{-1}, δ($CDCl_3$) 0.02 and 0.04 (each 3H, s, $SiMe_2$), 0.84 (9H, s, $SiBu^t$), 1.23 (3H, d, J=6Hz, *CH_3*.CH), 1.91 (3H, s, =C.CH_3), 3.38 (1H, dd, J=2 and 3.5Hz, CH.*CH*.CH), 3.69 (3H, s, OCH_3), 4.23 (1H, m, CH_3.*CH*.CH), 4.82 (1H, s, N.CH.CO), 5.07 (2H, m, CH_2=C), 5.42 (1H, d, J=2Hz, CH.*CH*.S) and 7.2—7.9 ppm (4H, m, Ar);

3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, starting from diphenylmethyl 6α-(1R-hydroxyethyl)-penicillanate-1-oxide; λ_{max} ($CHCl_3$ film) 3400, 1765 and 1740 cm^{-1}; δ($CDCl_3$) 1.22 (3H, d, J=6Hz, *CH_3*.CH), 1.60 (3H, s, =C.CH_3), 2.78 (1H, Br s, OH), 3.42 (1H, dd, J=2 and 6Hz, CH.*CH*.CH), 4.18 (1H, m, CH_3.*CH*OH.CH), 4.93 (1H, s, N.CH.CO), 4.90—5.10 (2H, m, CH_2=C), 5.38 (1H, d, J=2Hz, CH.*CH*.S), 6.89 (1H, s, O*CH*Ph_2) and 7.15—7.90 ppm (14H, m. Ar);

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzothiazolyldithio-1-(1-t-butoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, starting from *t*-butyl 6α-(1R-*t*-butyldimethylsilyloxyethyl)-penicillanate-1-oxide; reaction time 6 hours; $\delta(CDCl_3)$ 0.06 (6H, s, $SiMe_2$), 0.9 (9H, s, $SiBu^t$), 1.26 (3H, d, J=6Hz, CH_3.CH), 1.48 (9H, s, OBu^t), 1.95 (3H, s, =C.CH_3), 3.40 (1H, dd, J=2 and 4Hz, CH.*CH*.CH), 4.20 (1H, m, CH_3.*CH*.CH), 4.71 (1H, s, N.CH.CO), 5.1 2H, br s, CH_2=C), 5.42 (1H, d, J=2Hz, CH.*CH*.S) and 7.2—7.9 ppm (4H, m, Ar);

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, ν_{max} (film) 1722 and 1743 cm^{-1}; $\delta(CDCl_3)$ 0.05 (6H, s, $SiMe_2$), 0.80 (9H, s, $SiBu^t$), 1.29 (3H, d, J=6Hz, CH_3.CH), 1.95 (3H, s, =C.CH_3), 3.45 (1H, dd, J=2 and 4Hz, CH.*CH*.CH), 4.26 (1H, m, CH_3.*CH*.CH), 4.95 (1H, s, N.CH.CO), 5.08 (2H, ABq, separation of inner lines 5Hz, CH_2=C), 5.55 (1H, d, J=2Hz, CH.*CH*.S), 6.93 (1H, s, O*CH*Ph_2) and 7.1—8.0 ppm (14H, m, Ar);

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, starting from methyl 6α-(1R-trichloro ethoxycarbonyl-oxyethyl)-penicillanate-1-oxide: ν_{max} ($CHCl_3$) 1775 and 1745 cm^{-1}; $\delta(CDCl_3)$ 1.48 (3H, d, J=6Hz, CH_3.CH), 1.91 (3H, s, =C.CH_3), 3.69 (3H, s, OCH_3), 3.70 (1H, dd, CH.*CH*.CH), 4.68 (s, 2H, OCH_2), 4.76 (1H, s, N.CH.CO), 5.03—5.30 (2H, m, CH_2=C), 5.23 (1H, m, CH_3.*CH*.CH), 5.32 (1H, d, J=2Hz, CH.*CH*.S) and 7.10—7.96 ppm (4H, m, Ar);

and, in a likewise fashion, starting from the corresponding *t*-butyl and diphenyl methyl penicillanates,

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-t-butoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one;

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one;

and starting from methyl 6β-(1R-*t*-butyldimethylsilyloxyethyl)-penicillanate-1-oxide,

3R-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one.

Example 8

3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one

The crude 3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)azetidin-2-one obtained in Example 7 was dissolved in 300 ml of dry dichloromethane and treated with a stream of ozone at —70°C until TLC showed that all the starting material had reacted. The solution was purged with nitrogen and then 10 g of sodium metabisulphite was added at —30°C. The mixture was allowed to rise to room temperature under vigorous stirring, and then filtered. The solution was washed with 4% aqueous sodium bicarbonate solution, dried over anhydrous sodium sulphate and evaporated. The residue was taken up in diethyl ether, the undissolved matter was filtered off and the solution was evaporated to give the crude title product. An aliquot was purified by flash chromatography over silica gel (ethyl acetate:cyclohexane as eluant); $\delta(CDCl_3)$ 1.35 (3H, d, J=7Hz, CH_3.CH), 2.11 (3H, s, CH_3), 2.75 (1H, Br s, OH), 3.44 (1H, dd, J=2.0 and 5.0Hz, CH.*CH*.CH), 3.79 (3H, s, OCH_3), 4.26 (1H, m, CH_3.*CH*.CH), 5.29 (1H, d, J=2.0Hz, CH.*CH*.S) and 7.25—7.95 ppm (4H, m. Ar).

By using a similar procedure, there were obtained:

3S(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one, starting from crude 3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one; ν_{max} (film) 3350, 1770 and 1660 cm^{-1}; $\delta(CDCl_3)$ 0.05 and 0.07 (6H, each s, $SiMe_2$), 0.87 (9H, s, $SiBu^t$), 1.27 (3H, d, J=6.5Hz, CH_3.CH), 2.07 (3H, s, =C.CH_3), 3.33 (1H, dd, J=2.2 and 4.2Hz, CH.*CH*.CH), 3.74 (3H, s, OCH_3), 4.26 (1H, m, CH_3.*CH*.CH), 5.36 (1H, d, J=2.2Hz, CH.CH.S), 7.2—7.9 (4H, m, Ar) and 12.37 ppm (1H, br s, OH);

3R-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one, starting from 3R-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one; ν_{max} (film) 3200, 1773, 1710, 1665 and 1620 cm^{-1}. $\delta(CDCl_3)$ 0.20 (6H, s, $SiMe_2$), 0.94 (9H, s, $SiBu^t$), 1.52 (3H, d, J=6Hz, CH_3.CH), 2.17 (3H, br s, =C.CH_3), 3.6—3.7 (4H, s+dd, OCH_3 and CH.*CH*.CH), 4.4 (1H, m, CH_3.*CH*.CH), 5.25 (1H, d, CH.*CH*.S) and 7.3—7.9 ppm (4H, m, Ar);

3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one, starting from crude 3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-2-azetidin-2-one; ν_{max} ($CHCl_3$ film) 3400, 1770, 1730 and 1650 cm^{-1};

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one, starting from crude 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one; ν_{max} ($CHCl_3$ film) 3400, 1775, 1735, 1700 sh, 1655 and 1610 cm^{-1}; $\delta(CDCl_3)$ 0.06 (6H, s, $SiMe_2$), 0.82 (9H, s, Bu^t), 1.26 (3H, d, J=6Hz, CH_3.CH), 2.08 (3H, s, =C.CH_3), 3.33 (1H, dd, J=3 and 5.5 Hz,

CH.*CH*.CH), 4.18 (1H, m, CH_3.*CH*.CH), 5.22 (1H, d, J=2Hz, CH.*CH*.S), 6.86 (1H, s, O*CH*Ph_2) and 7.2—7.9 ppm (14H, m, Ar); and

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; $\delta(CDCl_3)$ 1.50 (3H, d, J=6Hz, CH_3.CH), 2.14 (3H, s, =C.CH_3), 3.67 (1H, dd, J=2.2 and 5.5Hz, CH.*CH*.CH), 3.82 (3H, s, OCH_3), 4.62 (2H, ABq, J=12Hz, separation of inner lines 2Hz, OCH_2), 5.10—5.40 (2H, m, CH_3.*CH*.CH and CH.*CH*.S), 7.20—8.00 (4H, m, Ar) and 12.40 ppm (1H, br s, OH);

and in likewise fashion, starting from the corresponding *t*-butyl and diphenylmethyl ester,

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-t-butoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one;

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; and

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-t-butoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one.

Example 9

3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one

A solution of 130 mg (0.03 mmol) of 3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one, prepared as described in Example 8, in 8 ml of anhydrous dichloromethane was sequentially treated at −40°C with 0.043 ml (0.3 mmol) of triethylamine and 0.024 ml (0.31 mmol) of methanesulphonyl chloride. The reaction was quenched after 5 minutes with cold 2% aqueous sodium bicarbonate solution. Removal of the solvent from the organic layer gave the crude title product (quantitative yield), which was used as such for the next step.

By following the same experimental procedure, there was obtained:

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one, starting from 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; an aliquot of this product was purifed by flash chromatography (silica gel; ethyl acetate-cyclohexane as eluant) to afford the pure title compound as a 1:1 mixture of *E* and *Z* isomers; ν_{max} (film) 1885, 1730, 1363 and 1165 cm^{-1}; $\delta(CDCl_3)$ 0.05 and 0.10 (each 3H, s, $SiMe_2$) 0.88 (9H, s, $SiBu^t$), 1.29 (3H, d, J=6.5Hz, CH_3.CH), 2.20 and 2.53 (3H, each s, =C.CH_3), 3.18 and 3.29 (3H, each s, SO_2CH_3), 3.42 (1H, m, CH.*CH*CH, 3.71 and 3.78 (3H, each s, OCH_3), 4.30 (1H, m, CH_3.*CH*.CH), 5.59 and 5.64 (1H, each d, J=2Hz, CH.*CH*.S) and 7.12—7.96 ppm (4H, m, Ar).

When tetrahydrofuran was used instead of dichloromethane as a solvent, the formation of the undesired *E* isomer was almost suppressed, and the pure *Z* isomer thus collected; $\delta(CDCl_3)$ 0.05 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiBu^t$), 1.29 (3H, d, J=6.5Hz, CH_3OH), 2.53 (3H, s, =C.CH_3), 3.29 (3H, s, SO_2CH_3), 3.42 (1H, dd, J=2 and 5Hz, CH.CH.CH), 3.71 (3H, s, OCH_3), 4.30 (1H, m, CH_3.*CH*.CH), 5.59 (1H, d, J=2Hz, CH.*CH*.S) and 7.12—7.95 ppm (4H, m. Ar).

By following this last procedure (tetrahydrofuran as a solvent in the mesylation step), there were obtained:

3R-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-[1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-(Z)-enyl]-azetidin-2-one, starting from 3R-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} ($CHCl_3$ film) 1775, 1735, 1365 and 1165 cm^{-1}; $\delta(CDCl_3)$ 0.18 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiBu^t$), 1.42 (3H, d, J=6.5Hz, CH_3.CH), 2.33 (3H, s, =C.CH_3), 3.05 (3H, s, SO_2CH_3), 3.45 (3H, s, OCH_3), 3.62 (1H, dd, CH.*CH*.CH), 4.3 (1H, m, CH_3.*CH*.CH), 5.40 (1H, d, J=5Hz, CH.*CH*.S) and 7.15—7.85 ppm (4H, m, Ar);

3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-[1-diphenylmethoxycarbonyl-2-methylsulphonyloxy-1-prop-1-(Z)-enyl]-azetidin-2-one, starting from 3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} (film) 3400, 1775, 1730, 1365 and 1170 cm^{-1}; δ ($CDCl_3$) 1.22 (3H, d, J=6.5Hz, CH_3.CH), 2.43 (3H, s, =C.CH_3), 3.13 (3H, s, SO_2CH_3), 3.35 (1H, dd, J=2.5 and 4Hz, CH.*CH*.CH), 4.1 (1H, m, CH_3.*CH*.CH), 5.40 (1H, d, J=2.5Hz, CH.*CH*.S), 6.85 (1H, s, O*CH*Ph_2) and 7.1—7.9 ppm (14H, m, Ar);

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-[1-diphenylmethoxycarbonyl-2-(Z)-methylsulphonyoxy-1-prop-1-enyl]-azetidin-2-one, starting from 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} ($CHCl_3$ film) 1775, 1725, 1370 and 1175 cm^{-1}; $\delta(CDCl_3)$ 0.1 (6H, s, $SiMe_2$), 0.9 (9H, s, $SiBu^t$), 1.28 (3H, d, J=6Hz, CH_3.CH), 2.5 (3H, s, =C.CH_3), 3.25 (3H, s, SO_2CH_3), 3.35 (1H, dd, J=2.5 and 5Hz, CH.*CH*.CH), 4.20 (1H, m, CH_3.*CH*.CH), 5.50 (1H, d, J=2.5Hz, CH.*CH*.S), 6.9 (1H, s, O*CH*Ph_2) and 7.1—7.9 ppm (14H, m, Ar);

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-[1-t-butoxycarbonyl-2-(Z)-methylsulphonyloxy-1-prop-1-enyl]-azetidin-2-one, starting from 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-*t*-butoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} (film) 1773, 1710, 1370 and 1165 cm^{-1}; $\delta(CDCl_3)$ 0.06 (6H, s, $SiMe_2$), 0.87 (9H, s, $SiBu^t$), 1.25 (3H, d, J=6Hz,

CH_3.CH), 1.49 (9H, si, OBu^t), 2.45 (3H, s, =C.CH_3), 3.25 (3H, s, SO_2CH_3), 3.35 (1H, dd, J=2.5 and 5Hz), 4.3 (1H, m, CH_3.*CH*.CH), 5.60 (1H, d, J=2.5Hz, CH.*CH*.S) and 7.1—7.9 ppm (4H, m, Ar); and

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-[1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1(Z)-enyl]-azetidin-2-one, starting from 3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} ($CHCl_3$ film) 1780, 1755 sh, 1730, 1380, 1250 and 1167 cm^{-1}; δ($CDCl_3$) 1.48 (3H, d, J=6Hz, *CH_3*.CH), 2.52 (3H, s, =C.CH_3), 3.25 (3H, s, SO_2CH_3), 3.72 (4H, s+dd, OCH_3 and CH.CH.CH), 4.68, (2H, s, OCH_2), 5.2 (1H, m, Ch_3.CH), 5.47 (1H, d, J=2.5Hz, CH.*C*HS) and 7.1—7.9 ppm (4H, m, Ar);

and likewise, starting from the corresponding *t*-butyl and diphenylmethyl esters, there was obtained:

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-[1-t-butoxycarbonyl-2-methylsulphonyloxy-1-prop-1(Z)-enyl]-azetidin-2-one; and

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-[1-diphenylmethoxycarbonyl-2-methylsulphonyloxy-1-prop-1(Z)-enyl]-azetidin-2-one.

Example 10

3S-(1R-methylsulphonyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one

When in the reaction described in Example 9 the starting material was exposed to an excess (2 molar equivalents) of methanesulphonylchloride and triethylamine, the title product was obtained as a foam in quantitative yield as a mixture of *E* (20%) and *Z* (80%) isomers; ν_{max} (film 1780, 1730, 1360 and 1170 cm^{-1}; δ($CDCl_3$) 1.58 (3H, d, J=6Hz, *CH_3*.CH), 2.22 and 2.56 (3H, each s, =C.CH_3 of *E* and *Z* isomers), 3.00 (3H, s, CH_3SO_2 on the hydroxyethyl chain), 3.20 (1H, dd, J=2.2 and 4.5Hz, CH.*CH*.CH), 3.28 (3H, s, CH_3SO_2 on the crotonic appendage), 3.76 (3H, s, OCH_3), 5.11 (1H, m, CH_3.*CH*.CH), 5.52 (1H, d, J=2.2Hz, CH.*CH*.S) and 7.30—7.95 ppm (4H, m, Ar).

By following the same procedure, but using THF as a solvent, *3S-(1R-methylsulphonyloxyethyl)-4R-benzthiazolyldithio-1-[1-diphenylmethoxycarbonyl-2-methylsulphonyloxy-1-prop-1-(Z)-enyl]-azetidin-2-one* was prepared and displayed the following spectral data: ν_{max} (film) 1777, 1728, 1360 and 1170 cm^{-1}; δ($CDCl_3$) 1.50 (3H, d, J=6Hz, *CH_3*.CH), 2.52 (3H, s, =C.CH_3), 2.9 (3H, s, CH_3SO_2 on the hydroxyethyl chain), 3.23 (3H, s, CH_3SO_2 on the crotonic appendage), 3.62 (1H, dd, J=2.5 and 5.5Hz, CH.*CH*.CH), 5.05 (1H, m, CH_3.*CH*.CH), 5.45 (1H, d, J=2.5Hz, CH.*CH*.S), 6.95 (1H, s, O*CH*Ph_2) and 7.10—7.95 ppm (14H, m, Ar).

Example 11

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-methoxycarbonyl-2-trifluoromethylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one

300 mg of crude 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one in 5 ml of THF at —40°C was sequentially treated with 0.170 ml of triethylamine and 0.180 ml of trifluoromethanesulphonic anhydride. Work-up and chromatography gave the two separate geometric isomers of the title product, as foams: *E* isomer: ν_{max} ($CHCl_3$) 1778, 1730, 1420, 1215 and 1135 cm^{-1}; δ($CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.86 (9H, s, SiBu^t), 1.26 (3H, d, J=6Hz, *CH_3*.CH), 2.05 (3H, s, =C.CH_3), 3.46 (1H, dd, 2.2 and 4Hz, CH.*CH*.CH), 3.81 (3H, s, OCH_3), 4.28 (1H, m, CH_3.*CH*.CH), 5.76 (1H, d, J=2.2Hz, CH.*CH*.S) and 7.25—7.90 (4H, m, Ar); Z isomer *(inter alia)* δ($CDCl_3$) 2.45 (3H, s =C.CH_3), 3.40 (1H, dd, J=2 and 4Hz, CH.*CH*.CH), 3.64 (3H, s, OCH_3), 4.30 (1H, m, CH_3.CH.CH) and 5.65 ppm (1H, d, J=2Hz, CH.*CH*.S).

Example 12

Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate

A solution of 0.5 ml of triethylamine in 10 ml of dichloromethane was saturated at —50°C with hydrogen sulphide. After purging with nitrogen, 0.34 ml of this solution was added to a cold (—50°C) solution of 75 mg (0.121 mmol) of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one. The mixture was allowed to warm up to room temperature and then washed with water, dried on anhydrous sodium sulphate and evaporated. Separation of the new compound from the formed 2-mercaptobenzthiazole and minor impurities was achieved by silica gel chromatography (ethyl acetate; cyclohexane as eluant), thus obtained the title compound as white crystals (19 mg, 20%), mp 85—87°C, λ_{max} (EtOH) 223 (ε=4,773), 277 (6,335), and 326 (2,922) nm, ν_{max} ($CHCl_3$ film) 1785 and 1730 cm^{-1}; δ($CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.88 (9H, s, SiBu^t), 1.25 (3H, d, J=6Hz, *CH_3*.CH), 2.22 (3H, s, CH_3), 3.07 (1H, dd, J=2.2 and 3.5Hz,CH.*CH*.CH), 3.8 (3H, s, OMe), 4.36 (1H, m. CH_3.*CH*.CH) and 4.62 ppm (1H, d, J=2.2Hz, CH.*CH*.S).

Found: C, 49.08; H, 6.96; N, 3.52; S, 15.16. $C_{16}H_{27}NO_4SiS_2$ requires C, 49.32; H, 6.99; N, 3.60; S, 16.46%.

When, instead of hydrogen sulphide and triethylamine, a solution of NaHS (0.9 mol equiv) in DMF was used, and quenching (partition between water and ethyl acetate) followed within 1 minute at 0°C, the isolated yield of the pure title product was raised to 40—45%.

When the above process was performed on the geometrical *Z* isomer of the starting material, the yield was further enhanced (up to 60—65%). On the contrary, the *E* isomer afforded only a very low amount of the title product.

By following the same experimental procedure, *methyl (7R,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate was obtained* starting from 3R-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} (film) 1785 and 1725 cm^{-1}; $\delta(CD_3COCD_3)$ 0.03 and 0.05 (each 3H, s, $SiMe_2$), 0.84 (9H, s, $SiBu^t$), 1.19 (3H, d, 6.5Hz, *CH*$_3$.CH), 2.08 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 4.11 (1H, dd, J=5.5 and 8.0Hz, CH.*CH*.CH), 4.20 (1H, m, CH_3.*CH*.CH) and 5.01 ppm (1H, d, J=5.5Hz, CH.*CH*.S).

Example 13

Methyl (7S,6R)-7-(1R-hydroxyethyl)-3-methyl-2-thiacephem-4-carboxylate

145 mg (0.287 mmol) of crude 3S-(1R-hydroxyethyl)-4R-benzothiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one, prepared as described in Example 9, was dissolved in 2 ml of anhydrous dimethylformamide and treated at +20°C with a freshly prepared solution of 16 mg (0.287 mmol) of NaHS in 1.6 ml of the same solvent. The mixture was stirred for 2 minutes and then partitioned between ethyl acetate and water.

After repeated washings with water, the solvent was removed leaving a residue which was purified by pressure chromatography on silica gel (ethyl acetate:cyclohexane as eluant) to give the pure title product in 45% yield as a white powder; ν_{max} (nujol) 3400, 1770 and 1720 cm^{-1}; $\delta(CDCl_3)$ 1.37 (3H, d, J=7Hz, *CH*$_3$.CH); 2.22 (3H, s, CH_3), 2.40 (1H, br s, OH), 3.12 (1H, dd, J=2.0 and 4.5Hz, CH.*CH*.CH), 3.86 (3H, s, OCH_3), 4.35 (1H, m, CH_3.*CH*.CH) and 4.65 ppm (1H, d, J=2.0Hz, CH.*CH*.S).

By following a similar experimental procedure, there were obtained:

Diphenylmethyl (7S,6R)-7-(1R-hydroxyethyl)-3-methyl-2-thiacephem-4-carboxylate, starting from 3S-(1R-hydroxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; λ_{max} (EtOH) 281 (ε=5,900) and 326 (3,670) nm; ν_{max} (KBr) 3550—3250, 3080, 3060, 3020, 2960, 2920, 2840, 1775, 1720, 1660 and 1490 cm^{-1}; $\delta(CDCl_3)$ 1.36 (3H, d, J=6.5Hz, *CH*$_3$.CH), 2.17 (3H, s, CH_3), 3.12 (1H, dd, J=2.0 and 5Hz, CH.*CH*.CH), 4.36 (1H, m, CH_3.*CH*.CH), 4.76 (1H, d, J=2.0Hz, CH.*CH*.S), 6.97 (1H, s, OCH_2Ph) and 7.30 (10H, m, Ar);

Diphenylmethyl (7S,6S)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate, starting from 3S-(1R-t-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; $\delta(CDCl_3)$ 0.06 (6H, s, $SiMe_2$); 0.83 (9H, s, $SiBu^t$); 1.27 (3H, d, J=6.5Hz, *CH*$_3$.CH), 2.05 (3H, s, CH_3), 3.08 (1H, dd, J=3.0 and 5.0Hz, CH.*CH*.CH), 4.32 (1H, m, CH_3.CH.CH), 4.60 (1H, d, J=3.0Hz, CH.*CH*.S), 7.02 (1H, s, O*CH*Ph_2) and 7.30 ppm (10H, s, Ar);

t-Butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate, starting from 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-*t*-butoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; λ_{max} ($CHCl_3$) 278 (ε=6,300) and 327 nm (ε=2,560); ν_{max} ($CHCl_3$ film) 1780 and 1720 cm^{-1}; $\delta(CDCl_3)$ 0.12 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiBu^t$), 1.25 (3H, d, J=6Hz, CH_3.CH), 1.52 (9H, s, OBu^t), 2.10 (3H, s, CH_3), 3.02 (1H, dd, J=2.5 and 5Hz, CH.*CH*.CH), 4.28 (1H, m, CH_3.*CH*.CH) and 4.53 ppm (1H, d, J=2.5Hz, CH.*CH*.S);

Methyl (7S,6R)-7-(1R-methylsulphonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate, starting from 3S-(1R-methylsulphonyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} 1780, 1725, 1360 and 1175 cm^{-1}; $\delta(CDCl_3)$ 1.60 (3H, d, J=6.5Hz, *CH*$_3$.CH), 2.25 (3H, s, CH_3), 3.07 (3H, s, CH_3SO_2), 3.27 (1H, dd, J=2.2 and 5Hz, CH.*CH*.CH), 3.83 (3H, s, OCH_3), 4.70 (1H, d, J=2.2Hz, CH.*CH*.S) and 5.24 ppm (1H, m, CH_3*CH*.CH);

Diphenylmethyl (7S,6R)-7-(1R-methylsulphonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate, starting from 3S-(1R-methylsulphonyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; λ_{max} ($CHCl_3$) 282 (ε=7,080) and 330 (3,966) nm; ν_{max} ($CHCl_3$ film) 1778, 1720, 1255 and 1170 cm^{-1}; $\delta(CDCl_3)$ 1.53 (3H, d, J=6Hz, *CH*$_3$.CH), 2.10 (3H, s, CH_3), 2.71 (3H, s, CH_3SO_2), 3.22 (1H, dd, J=2.5 and 5.5 Hz, CH.*CH*.CH), 4.67 (1H, d, J=2.5Hz, CH.*CH*.S), 5.05 (1H, m, CH_3.*CH*.CH); 6.90 (1H, s, O*CH*Ph_2) and 7.25 (10H, s, Ar);

Methyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate, starting from 3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} (film) 1787, 1760 sh, 1725 and 1250 cm^{-1}; $\delta(CDCl_3)$ 1.54 (3H, d, J=5.5Hz, *CH*$_3$.CH), 2.23 (3H, s, CH_3), 3.30 (1H, dd, J=2 and 7.5Hz, CH.*CH*.CH), 3.84 (3H, s, OCH_3), 4.68 (1H, d, J=2Hz, CH.*CH*.S), 4.78 (2H, s, OCH_2) and 5.37 ppm (1H, m, CH_3.*CH*.CH); and

Diphenylmethyl (7S,6R)-7-(1R-p-nitrobenzyloxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate, starting from (3S)-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-diphenylmethoxycarbonyl-2-methylsulphonyloxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} 1787, 1745, 1720 sh cm^{-1}; $\delta(CDCl_3)$ 1.53 (3H, d, *CH*$_3$CH), 2.17 (3H, s, CH_3), 3.28 (1H, dd, J=2 and 6.5Hz, CH—

CH—CH), 4.65 (1H, d, J=2Hz, CH.*CH*.S), 5.15 (2H, s, OCH_2), 5.28 (1H, m, CH_2.*CH*.CH), 6.97 (1H, s, O*CH*Ph_2), 7.2—7.5 (12H, m, Ar) and 8.17 ppm (2H, d, J=9Hz, Ar); and, likewise, there were obtained:

t-butyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate;

diphenylmethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate;

trichloroethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate;

trichloroethyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate;

acetoxymethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate;

acetoxymethyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate; and

acetoxymethyl (7S,6R)-7-(1R-trimethylsilyloxyethyl)-3-methyl-2-thiacephem-carboxylate.

Example 14

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-succinimidothio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one

A solution of 2.32 g of methyl 6α-(1R-*t*-butyldimethylsilyloxyethyl)-penicillanate-1-oxide in 35 ml of dimethylacetamide was treated with 0.15 ml of acetic acid, purged with nitrogen, and heated for $3\frac{1}{2}$ hours at 105°C in the presence of 5 g of N-trimethylsilylsuccinimide. After cooling to room temperature, the reaction mixture was partitioned between ethyl acetate and cold water. Fractionation of the material obtained from the organic layer (silica gel chromatography, ethyl acetate:cyclohexane) afforded the title product as a white foam, 1.2 g (43%); ν_{max} ($CHCl_3$ film) 1770, 1735, 1710 sh and 1680 cm^{-1}. δ($CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.87 (9H, s, $SiBu^t$), 1.32 (3H, d, J=6.5Hz, CH_3.CH), 1.84 (3H, s, =C.CH_3), 2.85 (4H, s, CO.CH_2.CH_2.CO), 3.29 (1H, dd, J=3 and 4.5Hz, CH.*CH*.CH), 3.73 (3H, s, OMe), 4.24 (1H, m, CH_3.*CH*.CH), 4.66 (1H, s, N.CH.CO), 4.85 (1H, d, J=2.5Hz, CH.*CH*.S) and 5.00 ppm (2H, br s, CH_2=C).

By following a similar experimental procedure, there were also obtained:

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-succinimidothio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, and

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phthalimidothio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, both isolated as crude materials and used as such in the following steps.

Example 15

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phthalimidothio-1-[1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-(Z)-enyl]-azetidin-2-one

A solution of 100 mg of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzothiazolyldithio-1-[1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-(Z)-enyl]-azetidin-2-one in 9 ml of acetone was treated with 34 mg of silver nitrate, soon followed by an ethanolic slurry of 30 mg of potassium phthalimide. After 30 minutes stirring at room temperature, the precipitate was collected partitioned between water and ethyl acetate, and purified by short silica gel chromatography to afford the title product (55%); ν_{max} (film) 1780, 1745 and 1725 cm^{-1}; δ($CDCl_3$) 0.1 (6H, s, $SiMe_2$), 0.89 (9H, s, Bu^t), 1.4 (3H, d, CH_3.CH), 2.2 (3H, s, =C.CH_3), 3.05 (3H, s, SO_2.CH_3), 3.4 (1H, m, CH.*CH*.CH), 3.6 (3H, s, OCH_3), 4.2 (1H, m. CH_3.*CH*.CH), 5.45 (1H, d, J=2Hz, CH.*CH*.S) and 7.8 ppm (4H, m, Ar).

Example 16

3S-(1R-t-butyldimethylsilyloxyethyl-4R-succinimidothio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one

The title product was obtained by ozonolysis of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-succinimidothio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one in dichloromethane according to the procedure described in Example 8, and used as such for further reactions. A sample was characterized as its dimethylketal (MeOH/dry HCl): ν_{max} 1770, 1730 and 1715 sh cm^{-1}; δ($CDCl_3$) 0.04 and 0.09 (each 3H, s, $SiMe_2$), 0.90 (9H, s, $SiBu^t$), 1.31 (3H, d, J=5Hz, CH_3.CH), 1.49 (3H, s, CH_3), 2.84 (4H, s, $COCH_2$.CH_2CO), 3.21 and 3.26 (each 3H, s, ketal OCH_3), 3.24 (1H, dd, J=2.5 and 5Hz), 3.73 (3H, s, ester OCH_3), 4.20 (1H, m, CH_3.*CH*.CH), 4.43 (1H, s, N.CH.CO) and 4.94 ppm (1H, d, J=2.5Hz).

Likewise, *3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phthalimidothio-1-(1-diphenylmethoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one* was obtained starting from 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-phthalimidothio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one.

Example 17

Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate

A solution of 400 mg of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-phthalimidothio-1-[1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-(Z)-enyl]-azetidin-2-one in 4 ml of dimethyl-

formamide was treated with 50 g of finely ground NaHS under vigorous stirring. As soon as the last reagent was dissolved, the reaction was quenched by partition between diethyl ether and water. Work-up gave the title compound, identical with the sample described in Example 12.

Example 18

Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate

0.8 g of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-succinimidothio-1-(1-methoxycarbonyl-1-prop-2-enyl)-azetidin-2-one in dichloromethane was ozonized at −70°C until tlc showed complete conversion. Excess ozone was purged with nitrogen and 1 ml of dimethylsulphide was added. After 1 hour at room temperature, any volatile material was removed *in vacuo* and the residue reacted in dichloromethane at −20°C to 0°C with equimolar amounts of triethylamine and mesyl chloride until conversion of the enol into the mesylates was judged complete by tlc. The mixture was concentrated *in vacuo* and partitioned between ethyl acetate and a cold, aqueous solution of sodium bicarbonate. The organic layer was evaporated to afford the crude mixture of *E,Z* mesylates which without purification was treated with NaHS in DMF according to the procedure described in Example 13. Purification of the resulting product by silica gel chromatography afforded the title compound, identical with the material obtained according to Example 12.

By a similar procedure,

Diphenylmethyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate was obtained, starting from 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-phthalimidothio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, and showed the same spectral properties as the material previously described (Example 13).

Example 19

Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate

120 mg of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-(1-methyl-5-tetrazolyldithio)-1-{1-methoxycarbonyl-2-[(1-methyl-5-tetrazolylthio)-methyl]-1-prop-2-enyl}-azetidin-2-one in dichloromethane was subjected to the reaction sequence reported in Examples 8, 9 and 17 (ozonolysis, mesylation, reaction with NaHS). The crude product was partitioned between ethyl acetate and aqueous sodium bicarbonate solution, thus removing the liberated mercaptotetrazole; the organic layer was washed several times with water, evaporated and the residue fractionated by silica gel chromatography to afford the title product, 17 mg (17%; ν_{max} (film) 1787, 1725, 1587, 1360 and 1250 cm^{-1}; $\delta(CDCl_3)$ 0.10 (6H, s, $SiMe_2$), 0.89 (9H, s, $SiBu^t$), 1.26 (3H, d, J=6Hz, *CH_3*—CH), 3.15 (1H, dd, J=2.2 and 3.5Hz CH.*CH*.CH), 3.88 (3H, s, OMe), 3.92 (3H, s, NMe), 4.38 (1H, m, CH_3.*CH*.CH), 4.46 (2H, ABq, J=14Hz, separation of inner lines 14Hz) and 4.68 ppm (1H, d, J=2.2Hz, CH.*CH*.S).

Example 20

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one

2.6 g of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, prepared as described in Example 7, in 160 ml of acetone and 18 ml of water was treated under vigorous stirring with 0.98 g of silver nitrate, immediately followed by 0.79 g of sodium benzenesulphinate in 60 ml of water. After 1 hour at room temperature the white precipitate was filtered off, and the filtrate concentrated *in vacuo* and then partitioned between water and ethyl acetate. Removal of the solvent from the organic layer left the title product as a yellowish powder (2.43 g, 98%), recrystallizable from cyclohexane (white leaflets, mp 105—106°C); ir (KBr) 3080, 3020, 2960, 2930, 2900, 2860, 1770, 1750, 1330 and 1145 cm^{-1}; $\delta(CDCl_3)$ 0.05 (6H, s, $SiMe_2$), 0.98 (12H, s+d, $SiBu^t$ and *CH_3*.CH), 1.84 (3H, s, =C.CH_3), 3.22 (1H, dd, J=2 and 2.5Hz, CH.*CH*.CH), 3.75 (3H, s, OMe), 4.19 (1H, m, CH_3.*CH*.CH), 4.58 (1H, s, N.CH.CO), 5.00 (2H, m, C=CH_2), 5.37 (1H, d, J=2Hz, CH.*CH*.S), 7.60 and 7.96 ppm (3 and 2H, each m, Ar).

Found: C, 53.69; H, 6.99; N, 2.70; S, 12.42%, $C_{23}H_{35}NO_6SiS_2$ requires C, 53.77, H, 6.87; N, 2.74; S 12.48%.

By following the same procedure, there were also obtained:

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-(1-t-butoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one;

3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-(1-diphenylmethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one;

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-phenylsulphonylthio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one;

3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-phenylsulphonylthio-1-(1-trichloroethoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one.

Example 21
3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-[1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1-(Z)-enyl]-azetidin-2-one
Procedure A

1 g of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-(1-methoxycarbonyl-2-methyl-1-prop-2-enyl)-azetidin-2-one, prepared as described in Example 20, in dry dichloromethane was ozonized at —70°C. After purging with nitrogen, 3.5 ml of dimethylsulphide was added and the mixture was stirred for 3 hours at room temperature. After removal of any volatile material *in vacuo,* the residue was partitioned between ethyl acetate and water. Evaporation of the solvent left the intermediate 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-(1-methoxycarbonyl-2-hydroxy-1-prop-1-enyl)-azetidin-2-one; ν_{max} 3450, 1778, 1658 and 1620 cm^{-1}; δ ($CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.90 (9H, s, $SiBu^t$), 1.13 (3H, d, J=6Hz, CH_3.CH), 1.90 (3H, s, =C.CH_3), 3.12 (1H, dd, J=2.5 and 4Hz, CH.*CH*.CH), 3.72 (3H, s, OMe), 4.2 (1H, m, CH_3.*CH*.CH), 5.52 (1H, d, J=2.5Hz, CH.*CH*.S), 7.4—8.0 (5H, m, Ar) and 13 ppm (1H, s, OH).

This material was mesylated with 0.272 ml of triethylamine and 0.151 ml of mesyl chloride in 10 ml of dry THF according to the procedure of Example 10, thus obtaining the title product as a foam, 550 mg after silica gel chromatography; ir (film) 1780, 1730, 1640, 1370 and 1145 cm^{-1}; δ($CDCl_3$) 0.05 (6H, s, $SiMe_2$), 0.80 (9H, s, $SiBu^t$), 0.97 (3H, d, J=6Hz, CH_3.CH), 2.50 (3H, s, =C.CH_3), 3.15 (4H, m, SO_2CH_3 and CH.*CH*.CH), 3.76 (3H, s, OCH_3), 4.13 (1H, m, CH_3.*CH*.CH), 5.7 (1H, d, J=2.8Hz, CH.*CH*.S) and 7.6—8.0 ppm (5H, m, Ar).

Procedure B

100 mg of 3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-benzthiazolyldithio-1-[1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1(Z)-enyl]-azetidin-2-one in 9 ml of acetone and 1 ml of water was sequentially treated under stirring with 34.3 mg of silver nitrate and 26.6 mg of sodium benzenesulphinate in 4 ml of water. After 15 minutes at room temperature the precipitated silver benzthiazolemercaptide was removed by filtration and the solution partitioned between dichloromethane and water. Removal of the solvent left the title product as a syrup (quantitive yield), having the same spectral properties as the sample from procedure A.

According to the same methodology, there were obtained:
3S-(1R-t-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-[1-t-butoxycarbonyl-2-methylsulphonyloxy-1-prop-1(Z)-enyl]-azetidin-2-one; and
3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-phenylsulphonylthio-1-[1-trichloroethoxycarbonyl-2-methylsulphonyloxy-1-prop-1(Z)-enyl]-azetidin-2-one.

Example 22
Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate

3S-(1R-*t*-butyldimethylsilyloxyethyl)-4R-phenylsulphonylthio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1Z-enyl)-azetidin-2-one was allowed to react with NaHS in DMF following the procedure described in Example 13 thereby obtaining the title product, identical with the material previously described. This preparation allows for a simpler purification of the product, since the by-product, sodium benzenesulphinate, is soluble in water and does not need chromatographic separation or fractional crystallization to be removed (unlike, e.g. mercaptobenzthiazole).

According to the same methodologies, there were obtained:
t-Butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate; and
Trichloroethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate.

Example 23
3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-acetyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1Z-enyl)-azetidin-2-one

A solution of 340 mg of 3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-benzthiazolyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1Z-enyl)-azetidin-2-one in 5 ml of THF was treated with 0.043 ml of thioacetic acid. Five minutes later the mixture was evaporated and the crude reaction product freed from 2-mercaptobenzthiazole by chromatography to obtain the pure title compound as a colourless syrup, 280 mg (96%); ν_{max} (film) 1775, 1760 sh, 1730 br cm^{-1}; δ($CDCl_3$) 1.50 (3H, d, CH_3.CH), 2.48 (3H, s, =C.CH_3), 2.62 (3H, s, $COCH_3$), 3.29 (3H, s, SO_2CH_3), 3.44 (1H, dd, CH.*CH*.CH), 3.83 (3H, s, OMe), 4.77 (2H, ABq, J=11.5Hz, separation of inner lines 2Hz), 5.24 (1H, d, CH.*CH*.S) and 5.25 (1H, m, CH_3.*CH*.CH).

Example 24
Methyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate

A solution of 140 mg of 3S-(1R-trichloroethoxycarbonyloxyethyl)-4R-acetyldithio-1-(1-methoxycarbonyl-2-methylsulphonyloxy-1-prop-1Z-enyl)-azetidin-2-one, prepared as described in

Example 23, in 10 ml of THF was treated at 0°C with a solution of 65 mg of tetrabutylammonium hydrogen sulphide in the same solvent.

Work-up and chromatography afforded the title product: λ_{max} (EtOH) 280 (ε4,974) and 327 nm (2,262); ν_{max} (film) 1787, 1769 sh, 1725 cm^{-1}; $\delta(CDCl_3)$ 1.54 (3H, d, CH_3.CH), 2.23 (3H, s, CH_3), 3.30 (1H, dd, 2 and 7.5Hz, CH.*CH*.CH), 3.84 (3H, s, OMe), 4.68 (1H, d, CH.*CH*.S), 4.78 (2H, s, OCH_2CCl_3) and 5.3H ppm (1H, m, CH_3.*CH*.CH), followed by some recovered starting material.

Example 25

Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate

0.52 g of methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate, 0.95 ml of propylene oxide, 0.52 g of N-bromosuccinimide and 0.05 g of azobisisobutyronitrile in 40 ml of carbon tetrachloride were refluxed for six hours. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated *in vacuo* and the residue was purified by silica gel column eluting with ethyl acetate: hexane mixtures, thus obtaining the title product as a yellowish oil (80%); λ_{max} ($CHCl_3$) 282 and 336 nm; ν_{max} ($CHCl_3$ film) 1785, 1730 cm^{-1}; $\delta(CDCl_3)$ 0.10 (6H, s, $SiMe_2$), 0.89 (9H, s, $SiBu^t$), 1.28 (3H, d, CH_3.CH.OSi), 3.23 (1H, dd, J=2.0 and 3.5Hz, CH.*CH*.CH), 3.87 (3H, s, OCH_3), 4.65 (2H, center ABq, s.i.l. 4Hz, J=11.5Hz, CH_2Br), 4.30 (1H, m, CH_3.*CH*.CH) and 4.76 ppm (1H, d, J=2.0Hz, CH.*CH*.S).

Found: C, 41.1; H, 5.64; N, 3.01; S, 13.55; Br, 17.20; $C_{16}H_{26}BrNO_4SiS_2$ requires C, 41.02; H, 5.59; N, 2.99; S, 13.69; Br, 17.06.

By following a similar procedure, there were obtained:

t-butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate; λ_{max} ($CDCl_3$) 283 and 332 nm; ν_{max} (film) 1787 and 1720 cm^{-1}; $\delta(CDCl_3)$ 0.9 (6H, s, $SiMe_2$), 0.9 (9H, $SiBu^t$), 1.28 (3H, d, CH_3.CH), 1.55 (9H, s, Obu^t), 3.18 (1H, dd, J=2.5 and 4.5Hz, CH.*CH*.CH), 4.35 (3H, m, CH_2Br) and CH_3.CH.CH) and 4.71 ppm (1H, d, J=2.5Hz, CH.*CH*.S);

p-nitrobenzyl (7S,6R)-7-(1R-p-nitrobenzyloxycarbonyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate;

$\delta(CDCl_3)$ 1.45 (3H, d, CH_3.CH), 3.43 (1H, dd, J=2.5 and 6Hz, CH.*CH*.CH), 4.45 (2H, ABq, J=12Hz, CH_2Br), 4.80 (1H, d, J=2.5Hz, CH.*CH*.S), 5.2, 5.5 (5H, m, two OCH_2Ar) and CH_3.*CH*.CH); 7.47 and 7.60 (each 2H, d, J=8.5Hz, Ar), and 8.20 ppm (4H, d, J=8.5Hz, Ar);

diphenylmethyl (7S,6R)-7-(1R-p-nitrobenzyloxycarbonyloxyethyl)-3-bromoethyl-2-thiacephem-4-carboxylate;

$\delta(CDCl_3)$ 1.45 (3H, d, CH_3.CH), 3.32 (1H, dd, J=3 and 6Hz, CH.*CH*.CH), 4.18 (2H, ABq, J=11Hz, CH_2Br), 4.70 (1H, d, J=3Hz, CH.*CH*.S), 5.20 (2H, s, OCH_2Ar), 5.30 (1H, m, CH_3.*CH*.CH), 6.97 (1H, s, O*CH*Ph_2), 7.10—7.40 (10H, br s, Ar), 7.45 and 8.15 ppm (each 2H, d, J=9Hz, Ar);

diphenyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate; ν_{max} (film) 1790 and 1730 cm^{-1}; $\delta(CDCl_3)$ 0.05 (6H, s, $SiMe_2$), 0.8 (9H, s, $SiBu^t$), 1.22 (3H, d, J=6.5Hz, CH_3.CH), 3.10 (1H, dd, J=2.7 and 4.5Hz, CH.*CH*.CH), 4.05 (2H, s, CH_2Br), 4.2 (1H, m, CH_3.*CH*.CH), 4.63 (1H, d, J=2.7Hz, CH.*CH*.S), 6.92 (1H, s, O*CH*Ph_2), and 7.05—7.40 ppm (10H, m, Ar); λ_{max} ($CHCl_3$) 283 (ε=7,867) and 336 nm (ε=3,533);

trichloroethyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate; and

trichloroethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate.

Example 26

Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate

A THF solution of crude methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate was kept overnight in the presence of sodium 1-methyl-tetrazole-5-mercaptide bihydrate (3 mol equiv). Work-up and chromatography afforded the title product as an oil in 85% yield; λ_{max} (EtOH) 281 and 333 nm; ν_{max} (film) 1790 and 1725 cm^{-1}; $\delta(CDCl_3)$ 0.10 (6H, s, $SiMe_2$), 0.89 (9H, s, Bu^t), 1.26 (3H, d, CH_3.CH), 3.15 (1H, dd, J=2.2 and 3.5Hz, CH.*CH*.CH), 3.88 (3H, s, OMe), 3.92 (3H, s, N.CH_3), 4.38 (1H, m, CH_3.*CH*.CH), 4.46 (2H, Abq. sep. of inner lines 14Hz, J=14Hz) and 4.68 ppm (1H, d, CH.*CH*.S, J=2.2Hz).

By following a similar procedure, there were obtained:

t-butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate, starting from *t*-butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl-3-bromomethyl-2-thiacephem-4-carboxylate; and

diphenylmethyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-{(8-aminotetrazolo[1,5-b]pyridazin-6-ylthio)-methyl}-2-thiacephem-4-carboxylate

Example 27
(5aR,6S)-6-(1R-t-butyldimethylsilyloxyethyl)-5a,6-dihydro-3H,7H-azeto[2,1-c]furo[3,4-e]1,2,4-dithiazine-1,7-dione
Procedure A

A solution of 15 mg of methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate in 2 ml of DMSO and 1.5 ml of water was stirred with 50 mg of cuprous oxide at 50°C for 2½ hours. The reaction mixture was partitioned between water and ethyl acetate. Evaporation and chromatography of the organic extracts afforded the title product as a white powder; ν_{max} ($CHCl_3$ film) 1800—1760 br cm^{-1}; δ($CDCl_3$) 0.06 (3H, s, $SiCH_3$), 0.11 (3H, s, $SiCH_3$), 0.90 (9H, s, Bu^t), 1.33 (3H, d, CH_3.CH), 3.33 1H, dd, J=2.5 and 4.5Hz, CH.*CH*.CH), 4.44 (1H, m, CH_3.*CH*.CH), 4.62 (1H, d, J=2.5Hz, CH.*CH*.S) and 4.98 ppm (2H, s, CH_2O).

Procedure B

250 mg of the 2-bromomethyl precursor in 35 ml of acetone:water (2:1 by volume) was stirred for 15 minutes at 0°C with 153 mg of silver perchlorate. The reaction mixture was partitioned between water and ethyl acetate and the organic layer was evaporated off to leave a residue. Silica gel chromatography afforded the title product, identical with the sample described above under A).

Example 28
t-Butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-hydroxymethyl-2-thiacephem-4-carboxylate

300 mg of *t*-Butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate in 10 ml of a 2:1 by volume acetone:water mixture was stirred for 15 minutes at 0°C with 150 mg of silver perchlorate. Removal of the solvent, followed by water:ethyl partition and work-up of the organic layer, gave 250 mg (96%) of the title product; λ_{max} ($CHCl_3$) 281 and 335 nm; ν_{max} (film) 3450, 1785 and 1712 cm^{-1}; δ($CDCl_3$) 0.1 (6H, s, $SiMe_2$), 0.86 (9H, s, $SiBu^t$), 1.25 (3H, d, CH_3CH), 1.50 (9H, s, OBu^t), 3.13 (1H, dd, J=2.5 and 4.5Hz, CH.*CH*.CH), 4.25 (centre of ABq, J=13Hz, CH_2OH), 4.37 (1H, m, CH_3.*CH*.CH) and 4.60 ppm (1H, d, J=2.5Hz, CH.*CH*.S).

Example 29
t-Butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-(N-trichloroacetylcarbamoyloxymethyl)-2-thiacephem-4-carboxylate

250 mg of *t*-Butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-hydroxymethyl-2-thiacephem-4-carboxylate in 2.5 ml of ethanol-free dichloromethane was treated at —40°C with 0.080 ml of trichloroacetylisocyanate. The mixture was allowed to rise to room temperature and then sequentially washed with 2% aqueous sodium bicarbonate solution and brine. Evaporation of the solvent from the organic layer gave the title product in quantitative yield: λ_{max} (EtOH) 275 and 329 nm; ν_{max} 1795 and 1725 br cm^{-1}; δ(CD_3CN), 0.1 (6H, s, $SiMe_2$), 0.9 (9H, s, $SiBu^t$), 1.3 (3H, d, CH_3.CH), 1.5 (9H, s, OBu^t), 3.40 (1H, dd, J=3 and 4Hz, CH.*CH*.CH), 4.35 (1H, m, CH_3.*CH*.CH), 4.80 (1H, d, J=3Hz, CH.*CH*.S) and 5.0 ppm (centre of Abq, CH_2OCO).

Example 30
t-Butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-carbamoyloxymethyl-2-thiacephem-4-carboxylate

A methanolic solution of *t*-butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-(N-trichloroacetylcarbamoyloxymethyl)-2-thiacephem-4-carboxylate, prepared as described in Example 29, was stirred with silica gel for 20 hours. The slurry was then charged onto a silica gel column and the product eluted with ethyl acetate; δ($CDCl_3$) 0.1 (6H, s, $SiMe_2$), 0.9 (9H, s, $SiBu^t$), 1.35 (3H, d, CH_3.CH), 1.60 (9H, s, OBu^t), 3.1 (1H, dd, CH.*CH*.CH), 4.3 (1H, m, CH_3.*CH*.CH) 4.75 (1H, d, J=3Hz, CH.*CH*.S) and 5.0 ppm (centre of ABq, OCH_2CO).

Example 31
Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-nitrooxymethyl-2-thiacephem-4-carboxylate

A solution of 200 mg of methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate in 20 ml of acetone was stirred for 20 minutes in the presence of 100 mg of silver nitrate. The filtered reaction mixture was fractionated by silica gel chromatography to obtain the title product, 120 mg; λ_{max} ($CHCl_3$) 280 and 337 nm; ν_{max} (film) 1790, 1730, 1640 and 1280 cm^{-1}; δ($CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.87 (9H, s, $SiBu^t$), 1.38 (3H, d, CH_3.CH), 3.18 (1H, dd, J=2.5 and 5.5Hz, CH.*CH*.CH), 3.85 (3H, s, OMe), 4.38 (1H, m, CH_3.*CH*.CH), 4.73 (1H, d, J=2.5Hz, CH.*CH*.S) and 5.36 ppm (2H, ABq, J=13.5Hz, s.i.l. 29.5Hz, CH_2ONO_2); further elution then afforded some of the lactone described in Example 27.

Example 32
Methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-formyloxymethyl-2-thiacephem-4-carboxylate

200 mg of methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate in dichloromethane was treated at daily intervals with tetrabutylammonium formate (3×600 mg). After 3 days at 5°C, tlc showed 80% conversion in the product (ethyl acetate:light petroleum 1:2 by volume). Elution through a short silica gel column gave the title material; $\delta(CDCl_3)$ 0.1 (6H, s, $SiMe_2$), 0.9 (9H, s, $SiBu^t$), 1.35 (3H, d, CH_3.CH), 3.20 (1H, dd, 2.5 and 7Hz, CH.*CH*.CH), 3.9 (3H, s, OMe), 4.5 (1H, m, CH_3.*CH*.CH), 4.74 (1H, d, 2.5Hz, CH.*CH*.S) and 5.13 ppm (centre of ABq, CH_2O).

In a similar way, starting from the corresponding *t*-butyl and diphenylmethyl esters, there were obtained:

t-butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-formyloxymethyl-2-thiacephem-4-carboxylate; and

diphenylmethyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-formyloxymethyl-2-thiacephem-4-carboxylate

and, in a likewise fashion, the corresponding acetates were obtained.

methyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate;

t-butyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate;

diphenylmethyl (7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate; and

trichloroethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate.

Example 33
Methyl (7S,6R)-7-(1R-hydroxyethyl)-3-methyl-2-thiacephem-4-carboxylate

0.75 g of methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate was added to a solution of 2.03 g of tetrabutylammonium fluoride trihydrate in 1.23 ml of acetic acid and 10 ml of THF. Work-up after 20 hours gave the title compound (virtually quantitative yield), showing the spectral properties described for the sample obtained in Example 13.

By similar experimental procedures, there were obtained:

Methyl (7S,6R)-7-(1R-hydroxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate, starting from methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate; ν_{max} (film) 1775, 1730 cm^{-1}; $\delta(CDCl_3)$ 1.35 (3H, d, CH_3.CH), 3.38 (1H, dd, CH.*CH*.CH), 3.60 (1H, br s, OH), 3.97 (3H, s, OMe), 4.33 (1H, m, CH_3.*CH*.CH), 4.46 (2H, centre of ABq, J=11Hz, sep. of inner lines 4Hz, CH_2Br)) and 4.88 ppm (1H, d, J=2.2Hz, CH.*CH*.S);

Methyl (7S,6R)-7-(1R-hydroxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate, starting from methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate; ν_{max} (KBr) 1765 and 1707 cm^{-1}; $\delta(CD_3COCD_3)$, 1.30 (3H, d, CH_3.CH), 3.39 (1H, dd, CH.*CH*.CH), 3.79 (3H, s, NCH_3), 3.97 (3H, s, OCH_3), 4.0 (1H, m, CH_3.*CH*.CH), 4.38 (2H, centre of ABq, J=16Hz, separation of inner lines 13Hz, CH_2.S), 4.77 (1H, d, J=2.2Hz, CH.*CH*.S) and 5.0 ppm (1H, br s, OH); and, analogously, the corresponding *t*-butyl, diphenylmethyl and trichloroethyl esters were also prepared.

Example 34
(7S,6R)-7-(1R-methylsulphonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylic acid

Diphenylmethyl (7S,6R)-7-(1R-methylsulphonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate was dissolved in cold trifluoroacetic acid (0°C, neat). After 15 minutes stirring at the same temperature, carbon tetrachloride was added and the solution thoroughly evaporated *under vacuum* without external heating. The residue was triturated in carbon tetrachloride and collected, thus obtaining the title product; λ_{max} ($CHCl_3$) 281 and 326 nm; ν_{max} ($CHCl_3$) 3000—2300, 2970, 2930, 2850, 1775, 1710, 1530 and 1170 cm^{-1}; $\delta(CD_3COCD_3)$ 1.58 (3H, d, CH_3.CH), 2.23 (3H, s, Me), 3.16 (3H, s, SO_2Me), 3.66 (1H, dd, J=2 and 6Hz, CH.*CH*.CH), 4.85 (1H, d, J=2Hz, CH.*CH*.S) and 5.30 ppm (1H, m, CH_3.*CH*.CH).

The same material was obtained by trifluoroacetic acid hydrolysis of the corresponding *t*-butyl ester, but prolonging the reaction time to about 1 hour.

Similarly hydrolyses of the *t*-butyl or diphenylmethyl precursors gave the following products:

(7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-2-thiacephem-4-carboxylic acid;

(7S,6R)-7-(1R-hydroxyethyl)-3-methyl-2-thiacephem-4-carboxylic acid;

(7S,6R)-7-(1R-hydroxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylic acid;

(7S,6R)-7-(1R-hydroxyethyl)-3-carbamoyloxymethyl-2-thiacephem-4-carboxylic acid; and

(7S,6R)-7-(1R-hydroxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylic acid.

Example 35
(7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-3-methyl-4-methoxycarbonyl-2-thiacephem-1,1-dioxide
Procedure A

A solution of 117 mg of (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-methyl-4-methoxycarbonyl-2-thiacephem in 5 ml of chloroform was treated with 220 mg of *m*-chloroperbenzoic acid at 0°C under stirring. After 30 minutes the reaction mixture was partitioned between dichloromethane and a 2% by weight aqueous sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and the solvent was evaporated off. The residue was purified by short-path chromatography to afford the title product (89 mg) as a syrup; ν_{max} (CH_2Cl_2 film) 1800, 1735 cm^{-1}; $\delta(CDCl_3)$ 0.10 (6H, s, Me_2Si), 0.90 (9H, s, Bu^tSi), 1.27 (3H, d, CH_3—CH), 2.18 (3H, s, CH_3), 3.81—3.83 (1H, dd, +3H, s, CH—*CH*—CH and OCH_3), 4.35 (1H, m, CH_3—*CH*—CH) and 5.05 ppm (1H, d, J=2.0 Hz, CH—*CH*—S); λ_{max} (hexane) 276 (ε=5,084) and 297 (sh, ε=3,745) nm.

Procedure B

A solution of 500 mg of (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-methyl-4-methoxycarbonyl-2-thiacehem in 25 ml of chloroform was treated with 276 mg of 80% *m*-chloroperbenzoic acid at —20°C. The temperature was allowed to rise to +20°C within 30 minutes and 4% by weight aqueous sodium bicarbonate solution was then added. The organic layer was dried over anhydrous sodium sulphate, and the solvent was evaporated off. The residue was separated by silica gel chromatography to afford in the following order:— 1,1-dioxide, syrup, 35 mg; NMR and IR data as above;— the 2-oxide, syrup, 60 mg; ν_{max} (CH_2Cl_2 film) 1795, 1740 cm^{-1}; $\delta(CDCl_3)$ 0.10 (6H, s, Me_2Si); 0.90 (9H, s, Bu^tSi), 1.24 (3H, d, CH_3—CH), 2.35 (3H, s, CH_3); 2.85—3.90 (1H, dd, +3H, s, CH—*CH*—CH and OCH_3), 4.35 (1H, m, CH_3—*CH*—CH) and 5.27 ppm (1H, d, J=2.5Hz, CH—*CH*—S); λ_{max} (hexane) 276 (ε=5,092) nm;— the 1-oxide, white powder, mp 90—93°C, 330 mg; ν_{max} (CH_2Cl_2 film) 1790, 1730 cm^{-1}; δ0.10 (6H, s, Me_2Si), 0.90 (9H, s Bu^tSi) 1.28 (3H, d, CH_3—CH), 2.24 (3H, s, CH_3), 3.60 (1H, dd, J=2.0 and 4.0Hz, CH—*CH*—CH), 3.87 (3H, s, OCH_3), 4.35 (1H, m, CH_3—*CH*—CH) and 4.67 ppm (1H, d, J=2.0HZ CH—*CH*—S); λ_{max} (hexane) 273 (ε=4.862), 309 (sh, ε=2,721) nm.

The solution of 300 mg of the 1-oxide in 30 ml of chloroform was stirred for 1 hour at room temperature in the presence of 160 mg of *m*-chloroperbenzoic acid. The reaction mixture was washed with aqueous sodium bicarbonate solution, concentrated and purified by flash chromatography (silica gel, cyclohexane:ethyl acetate as eluent) thus obtaining a further 280 mg of the title product.

Example 36
Methyl (6S,5R)-6-[1(R)-tert-butyldimethylsilyloxyethyl]-2-methylpenem-3-carboxylate

A chloroform solution of 300 mg of the 1,1-dioxide prepared in Example 35 was heated at 50°C for 5 hours. Removal of the solvent afforded the title compound, free of stereoisomers, in nearly quantitative yield (250 mg); ν_{max} ($CHCl_3$) 1795 1715 cm^{-1}; $\delta(CDCl_3)$ 0.08 (6H, s, Me_2Si), 0.89 (9H, s, Bu^tSi), 1.23 (3H, d, CH_3—CH); 2.33 (3H, s, CH_3), 3.61 (1H, dd, J=1.8 and 5.0Hz, CH—*CH*—CH), 3.75 (3H s, OCH_3), 4.21 (1H, m, CH_3—*CH*—CH) and 5.50 ppm (1H, d, J=1.8Hz, CH—*CH*—S); λ_{max} (EtOH) 257, 314 nm.

The above reaction occurred even at room temperature; e.g. after 16 hours standing in chloroform, NMR analysis revealed a mixture 1:2 of the title product and the starting material.

Example 37
(7S,6R)-7-(1R-hydroxyethyl)-3-methyl-4-methoxycarbonyl-2-thiacephem-1,1-dioxide

A solution of 40 mg of (7S,6R)-7-(1R-hydroxyethyl)-3-methyl-4-methoxycarbonyl-2-thiacephem in 1 ml of chloroform was stirred at 0°C for 15 minutes in the presence of 60 mg of *m*-chloroperbenzoic acid. Partition between ethyl acetate and an aqueous solution of sodium bicarbonate and removal of the solvent left the title compound, which was further purified by silica gel chromatography; $\delta(CDCl_3)$ 1.36 (3H, d, J=6.4Hz, CH_3—CH), 2.21 (3H, s, CH_3), 3.80—3.88 (4H, m, CH—*CH*—CH and OCH_3), 4.40 (1H, m, CH_3—*CH*—CH) and 5.08 ppm (1H, d, J=1.6Hz, CH—*CH*—S).

Example 38
Methyl (6S,5R)-6-(1R-hydroxyethyl)-2-methylpenem-3-carboxylate

When a solution of the 1,1-dioxide prepared in Example 37 in an inert solvent (e.g. chloroform or benzene) was allowed to stand for a few days, or briefly heated at 50—80°C, the title compound was formed, free of diastereoisomers, in virtually quantitative yield. $\delta(CDCl_3)$ 1.34 (3H, d, J=6.4Hz, CH_3—CH), 2.35 (3H, s, CH_3), 3.68 (1H, dd, J=6.6 and 1.5Hz, CH—*CH*—CH), 3.80 (3H, s, OCH_3), 4.40 (1H, m, CH_3—*CH*—CH) and 5.56 ppm (1H, d, J=1.5Hz, CH—*CH*—S).

Example 39
Methyl (6S,5R)-6-(1R-t-butyldimethylsilyloxyethyl)-2-[(1-methyl-5-tetrazolylthio)-methyl]-penem-3-carboxylate

A solution of methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate in chloroform was stirred at 0°C with *m*-chloroperbenzoic acid

(2.5 molar equivalent) for 30 minutes, and then washed with aqueous sodium bicarbonate solution. The dried organic layer was refluxed for a few hours (tlc monitoring).

Evaporation of the solvent and silica gel chromatography afforded the title product: $\delta(CDCl_3)$ 0.07 (6H, s, $SiMe_2$) 0.82 (9H, s, $SiBu^t$), 1.20 (3H, d, CH_3—CH), 3.68 (1H, dd, 1.8 and 4Hz, CH.CH.CH), 3.80 (3H, s, N—Me), 3.81 (3H, s, OMe), 4.22 (1H, m, CH_3—CH—CH), 4.69 (2H, centre of ABq, J=14Hz, separation of inner lines 11.5Hz, CH_2S) and 5.54 ppm (1H, d, J=1.8Hz, CH—CH—S).

Example 40
p-Nitrobenzyl (7S,6R)-7-(1R-p-nitrobenzyloxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate

A solution of 200 mg of diphenylmethyl (7S,6R)-7-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-3-methyl-2-thiacephem-4-carboxylate in 25 ml of dichloromethane was treated for 30 min at 0°C with 0.4 ml of trifluoroacetic acid. Evaporation under vacuum in the cold left the crude 2-thiacephem-4-carboxylic acid, which was dissolved in 10 ml of acetonitrile:dimethylformamide (2:1 by volume) and treated with 0.050 ml of triethylamine and 100 mg of *p*-nitrobenzylbromide. After 1 hour at 25°C, the mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer, dried over anhydrous magnesium sulphate, was concentrated and the residue passed through a short silica column (ethyl acetate: light petrol as eluants) to afford the pure title product, 150 mg (79%); $\delta(CDCl_3)$ 1.45 (3H, d, CH_3.CH), 3.43 (1H, dd, J=2.5 and 6Hz, CH—CH—CH), 4.45 (2H, ABq, J=12Hz, CH_2Br), 4.80 (1H, d, J=2.5Hz, CH—CH—S), 5.2—5.5 (5H, m), 7.47 and 7.60 (each 2H, d, Ar) and 8.20 ppm (4H, d, Ar).

Example 41
(7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-4-diphenylmethoxycarbonyl-3-(pyridinium-methyl)-2-thiacephem bromide

A solution of 310 mg of diphenylmethyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate in 15 ml of dry acetone was treated with 0.4 ml of pyridine. After 20 hours at room temperature the solvent was distilled off and the residue purified by silica gel chromatography. The product-containing fractions (eluted with dichloromethane:acetic acid: methanol 70:15:15 by volume) were collected and freed from the solvents to leave the title compound as a syrup; ν_{max} ($CHCl_3$ film) 1790, 1715 cm^{-1}; $\delta(CDCl_3)$ (inter alia) 1.32 (3H, d, J=6.5Hz), 3.33 (1H, dd), 4.45 (1H, m), 5.0 (1H, d, J<2Hz) and 7.11 ppm (1H, s); λ_{max} ($CHCl_3$) 283 and 337 nm (ε=4,060). In a likewise manner, and starting from *p*-nitrobenzyl (7S,6R)-7-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate, there was obtained:

(7S,6R)-7-(1R-p-nitrobenzyloxycarbonyloxyethyl)-4-p-nitrobenzyloxycarbonyl-3-(pyridinium-methyl)-2-thiacephem bromide.

Example 42
(7S,6R)-7-(1R-t-butyldimethylsilyloxyethyl)-4-carboxy-3-(pyridinium-methyl)-2-thiacephem trifluoroacetate

A solution of (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-4-diphenylmethoxycarbonyl-3-(pyridinium-methyl)-2-thiacephem bromide, prepared as described in Example 41, in 10 ml of dichloromethane was treated with 2 ml of trifluoroacetic acid at 0°C for 15 minutes. After evaporation in vacuo, the residue was taken up in a small amount of chloroform. Diethyl ether was added under stirring and then decanted off, to leave the crude title product; ν_{max} ($CHCl_3$ film) 3420, 1785, 1715 and 1635 br cm^{-1}; $\delta(CDCl_3)$ (inter alia) 1.30 (3H, d, J=6.5Hz), 3.23 (1H, dd), 4.38 (1H, m) and 4.76 ppm (1H, d); λ_{max} ($CHCl_3$) 262 and 334 nm.

Example 43
(7S,6R)-7-(1R-p-nitrobenzyloxycarbonyloxyethyl)-4-p-nitrobenzyloxycarbonyl-3-(3-carbamoylpyridinium-methyl)-2-thiacephem bromide

A solution of 460 mg of *p*-nitrobenzyl (7S,6R)-7-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate in 5 ml of DMF was stirred overnight in the dark in the presence of 200 mg of nicotinamide. Most of the solvent was distilled off and the residue taken up in 150 ml of tetrahydrofuran. This solution was washed with a solution of sodium chloride in 0.1 N hydrochloric acid (2×50 ml) and with brine (2×50 ml), dried on anhydrous sodium sulphate and evaporated to dryness. The residue was charged to the top of a column packed with silanised silica gel (Merck, Art. 7719). Excess nicotinamide and impurities were eluted with ethyl acetate, and the product was then collected by eluting with ethyl acetate:acetic acid (9:1 by volume). Evaporation in vacuo left the title product; ν_{max} ($CHCl_3$) 1800, 1725, 1695 cm^{-1}; δ(Deuteroacetone; 200 MHz) 1.67 (3H, d, J=6.4Hz, CH_3—CH), 4.14 (1H, dd, J=2.5 and 4.7Hz, CH—CH—CH), 5.30 (1H, d, J=2.5Hz, CH—CH—S), 5.4—5.7 (7H, m, 2×CH_2OAr, CH_2N^+, and CH_3—CH—CH), 7.7—8.4 (8H, m, Ar), and 8.0, 8.7, 9.5 and 9.7 ppm (each 1H, br s, pyridinium). Analogously, by using isonicotinamide instead of nicotinamide, there was obtained:

(7S,6R)-7-(1R-p-nitrobenzyloxycarbonyloxyethyl)-4-p-nitrobenzyloxycarbonyl-3-(4-carbamoyl-pyridinium-methyl)-2-thiacephem bromide.

Example 44
(6S,5R)-6-(1R-hydroxyethyl)-2-(pyridinium-methyl)-penem-3-carboxylate

A solution of (7S,6R)-7-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-4-*p*-nitrobenzyloxycarbonyl-3-(pyridinium-methyl)-2-thiacephem acetate (prepared from the corresponding bromide by conventional treatment with silver acetate or an ion-exchange resin) in chloroform was treated with 2 mol equivalents of peracetic acid at 0°C. Workup and gentle heating, according to the general procedure described in Examples 37—39, gave (6S,5R)-6-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-3-*p*-nitrobenzyloxycarbonyl-2-(pyridinium-methyl)-penem acetate: ν_{max} (KBr) 1795, 1740, 1705 cm^{-1}; δ($CDCl_3$+deuteroacetone) 1.4 (3H, d, J=6.5Hz, CH_3—CH), 4.10 (1H, dd, J=1.7 and 8Hz, CH—*CH*—CH), 5.20 and 5.31 (each 2H, s, OCH_2Ar), 5.2 (1H, m, CH_3—*CH*—CH), 5.77 (1H, d, J=1.7Hz, CH—*CH*—S), 6.05 (2H, ABq, J=15Hz, CH_2N), 7.4—8.3 (11H, m, Ar) and 9.15 ppm (2H, d, J=6Hz, o-Pyr).

300 mg of this material in 40 ml of tetrahydrofuran:water (1:1 by volume) was treated with 5 g of ammonium chloride under stirring to obtain a clear solution. After cooling to about 10°C, 2.5 g of iron powder was added under vigorous stirring; the reaction could be monitored by TLC (water:methanol:sodium chloride 9:1:1 by volume) by following the development of the product as a faster running spot. After about one hour, 3 g of celite was added and the whole filtered through a glass septum, washing with demineralised water. Removal of the organic solvent, followed by washings with diethyl ether, left an aqueous solution of the title product and inorganic salts. The former was obtained in pure form after reverse-phase chromatography and freeze-drying; δ(D_2O, 200 MHz) 1.27 (3H, d, J=6.5Hz, CH_3CH), 3.98 (1H, dd, J=1.4 and 5.8 Hz, CH—*CH*—CH), 4.24 (1H, m, CH_3—*CH*—CH), 5.69 (1H, d, J=1.4Hz, CH—*CH*—S), 5.94 (2H, ABq, J=14.9Hz, CH_2N), 8.10 (2H, t, J=6.6Hz, pyridinium m—H), 8.61 (1H, bd, J=7.7Hz, pyridinium p—H) and 8.95 ppm (2H, d, J=6.6Hz, pyridinium o—H).

In a likewise manner, starting from the compounds described in Example 43, there were obtained:

(6S,5R)-6-(1R-hydroxyethyl)-2-(3-carbamoylpyridinium-methyl)-penem-3-carboxylate; and
(6S,5R)-6-(1R-hydroxyethyl)-2-(4-carbamoylpyridinium-methyl)-penem-3-carboxylate.

Example 45
(6S,5R)-6-(1R-hydroxyethyl)-2-[(1-methyl-5-tetrazolylthio)-methyl]-penem-3-carboxylic acid, sodium salt

A solution of *p*-nitrobenzyl (7S,6R)-7-(1R-*p*-nitrobenzyloxy-carbonyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate in chloroform was oxidized with *m*-chloroperbenzoic acid, as described in Example 37, to give the corresponding sulphone. Without purification, this material was heated at 60°C in dry distilled tetrahydrofuran under a stream of nitrogen until expulsion of sulphur dioxide was complete. Removal of the solvent and silica gel chromatography gave *p*-nitrobenzyl (6S,5R)-6-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-2-[(1-methyl-5-tetrazolylthio)-methyl]-penem-3-carboxylate; δ($CDCl_3$) 1.48 (3H, d, J=7Hz, CH_3—CH), 3.84 (1H, dd, J=2 and 5.5Hz, CH—*CH*—CH), 3.96 (3H, s, NCH_3), 4.69 (2H, ABq, J=14Hz, CH_2S), 5.20 (1H, m, CH_3—*CH*—CH), 5.24 (2H, s, OCH_2Ar), 5.27 (2H, ABq, J=13Hz, OCH_2Ar), 5.61 (1H, d, J=2Hz), 7.51 and 7.82 (each 2H, d, J=8Hz, Ar) and 8.02 ppm (4H, d, J=8Hz, Ar). Reaction of the above material with iron and ammonium chloride, according to the procedure described in Example 44, afforded the title product; δ(D_2O) 1.28 (3H, d, J=6.5Hz), 3.87 (1H, dd, J=1.4 and 6.3 Hz, CH—*CH*—CH), 4.10 (3H, s, NCH_3), 4.19 (1H, m, CH_3—CH—CH), 4.40 (2H, ABq, J=16Hz, CH_2S) and 5.59 ppm (1H, d, J=1.4Hz, CH—*CH*—S); λ_{max} (H_2O) 315 nm.

Example 46
Methyl (6S,5R)-6-(1R-t-butyldimethylsilyloxyethyl)-2-nitrooxymethyl-penem-3-carboxylate

A solution of methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-nitrooxymethyl-2-thiacephem-4-carboxylate, prepared as described in Example 31, in chloroform was treated with 2 mol. equiv. of *m*-chloroperbenzoic acid at 0°C to give the 1-sulphone. Aqueous carbonic acid was added to extract the *m*-chlorobenzoic acid, and then the dried organic solution was gently refluxed (tlc monitoring) to give a solution of the title compound; δ($CDCl_3$) (inter alia) 5.64 (1H, d, J=2Hz, CH—*CH*—S) and 5.65 ppm (2H, ABq, J=15Hz, sep. of inner line 46Hz, CH_2ONO_2) ν_{max} ($CHCl_3$) 1790 and 1710 cm^{-1}. In a likewise manner, starting from trichloroethyl (7S,6R)-7-(1R-trichloroethoxycarbonyl-oxyethyl)-3-nitrooxymethyl-2-thiacephem-4-carboxylate, there was obtained:

Trichloroethyl (6S,5R)-6-(1R-trichloroethoxycarbonyloxyethyl)-2-nitrooxymethyl-penem-3-carboxylate

Example 47
Methyl (6S,5R)-6-(1R-t-butyldimethylsilyloxyethyl)-2-hydroxymethyl-penem-3-carboxylate

A solution of crude methyl (6S,5R)-6-(1R-*t*-butyldimethylsilyloxyethyl-2-nitrooxymethyl-penem-3-carboxylate, prepared as described in Example 46, in 2 ml of dichloromethane was stirred for 5 minutes at 0°C with 0.1 g of zinc dust and 0.1 ml of acetic acid. The reaction mixture was filtered and the solution was evaporated to give the crude title product, which was purified by silica gel

chromatography (ethyl acetate:light petrol, from 1:4 to 1:1 by volume); ν_{max} ($CHCl_3$ film) 1785, 1710 cm^{-1}; δ($CDCl_3$) 0.07 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiBu^t$), 1.23 (3H, d, CH_3—CH), 3.70 (1H, dd, J=1.8 and 4.5Hz, CH—*CH*—CH), 4.25 (1H, m, CH_3—*CH*—CH), 4.59 (2H, s, CH_2OH) and 5.57 ppm (1H, d, J=1.8 Hz, CH—*CH*—S).

Operating in an analogous way on trichloroethyl (6S,5R)-6-(1R-trichloroethoxycarbonyloxyethyl)-2-nitrooxymethyl-penem-3-carboxylate, complete deblocking of the protecting groups was achieved, thus obtaining after aqueous sodium bicarbonate work up and reverse phase chromatography (water as eluant); (6S,5R)-6-(1R-hydroxyethyl)-2-hydroxymethyl-penem-3-carboxylic acid, sodium salt; $\delta(D_2O)$ 1.30 (3H, d, CH_3—CH), 3.88 (1H, dd, J=1 and 6.3Hz, CH—*CH*—CH), 4.23 (1H, m, CH_3—*CH*—CH), 4.63 (2H, ABq, J=14.5Hz, separation of inner lines 4Hz, CH_2OH) and 5.62 ppm (1H, d, J=1Hz, CH—*CH*—S); λ_{max} (KBr) 1765 and 1610—1590 cm^{-1}.

Example 48

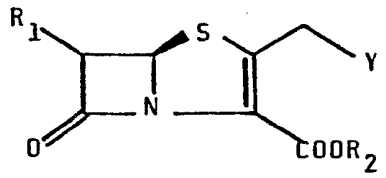
(6S,5R)-6-(1R-hydroxyethyl)-2-carbamoyloxymethyl-penem-3-carboxylic acid, sodium salt

A chloroform solution of trichloroethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-carbamoyloxymethyl-2-thiacephem-4-carboxylate was treated with *m*-chloroperbenzoic acid according to the general procedure of Example 37. After work-up brief heating of the resulting 1-sulphone in benzene gave trichloroethyl (6S,5R)-6-(1R-trichloroethoxycarbonyloxyethyl)-2-carbamoyloxymethyl-penem-3-carboxylate; $\delta(CDCl_3)$ 1.5 (3H, d, CH_3—CH), 3.94 (1H, dd, J=2 and 8Hz, CH—*CH*—CH), 4.73 and 4.82 (each 2H, s, OCH_2CCl_3), 4.8 (1H, m, CH_3—*CH*—CH), 5.25 (2H, ABq, J=10Hz, CH_2OCONH_2) and 5.62 (1H, d, J=2Hz, CH—*CH*—S).

A THF solution of this material was treated with zinc dust (approx. 6 parts by weight) and 1M aqueous sodium bihydrogen phosphate under stirring. After 3 hours stirring at 25°C, another portion of zinc was added and the mixture kept under stirring for 3 hours. Work-up and reverse-phase chromatography afforded the title product; $\delta(D_2O)$ 1.31 (3H, d, J=6.5Hz, CH_3—CH), 3.91 (1H, dd, J=1.5 and 6Hz, CH—*CH*—CH), 4.25 (1H, m, CH_3—*CH*—CH), 5.19 (2H, ABq, J=14.5Hz, CH_2OCO) and 5.66 ppm (1H, d, J=1.5Hz, CH—*CH*—S).

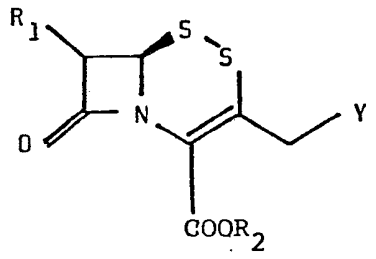
Claims

1. A process for the preparation of a (5R)-penem derivative of the general formula I



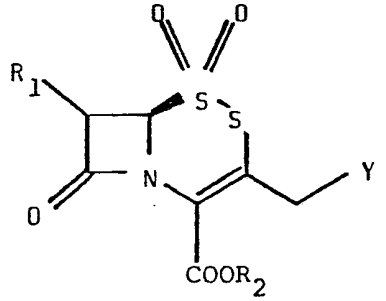
I

wherein R_1 represents a hydrogen atom or an organic group, R_2 represents a hydrogen atom or a carboxy protecting group and Y represents a hydrogen or halogen atom or an organic group, the process comprising oxidising a 2-thiacephem derivative of the general formula II



II

wherein R_1, R_2 and Y are as above defined to give a sulphone of the general formula III



III

wherein R_1, R_2 and Y are as above defined, and ring contracting the sulphone by extrusion of sulphur dioxide; and, if desired, converting the resultant (5R)-penem of the general formula I into another compound of the general formula I; and/or, if desired, converting the resultant compound of the general formula I into a salt thereof; and/or, if desired, obtaining a free compound of the general formula I from a salt thereof.

2. A process according to claim 1 in which the oxidation is carried out with a peracid.

3. A process according to claim 2 in which the peracid is *m*-chloroperbenzoic acid or peracetic acid.

4. A process according to any preceding claim in which the oxidation is carried out in an inert organic solvent at from 0°C to 60°C.

5. A process according to any preceding claim in which the oxidation is carried out in an inert organic solvent at from 4°C to 30°C.

6. A process according to claim 4 or claim 5 in which the inert organic solvent is chloroform or benzene.

7. A process according to any preceding claim in which the ring contraction is carried out in an inert organic solvent at ambient temperature.

8. A process according to any preceding claim in which the ring contraction is carried out in an inert organic solvent under gentle heating.

9. A process according to claim 7 or claim 8 in which the inert organic solvent for the ring contraction is chloroform or benzene.

10. A (5R)-penem derivative of the general formula I wherein R_1 represents an optionally substituted aliphatic or cycloaliphatic group, and R_2 and Y are as defined in claim 1 prepared by a process according to any preceding claim.

11. A (5R)-penem derivative of the general formula I wherein R_1 represents a straight or branched alkyl group having from 1 to 12 carbon atoms optionally substituted by one or more free or protected mercapto, amino or hydroxy groups or by a cyano group, and R_2 and Y are as defined in claim 1 prepared by a process according to any of claims 1 to 9.

12. A (5R)-penem derivative of the general formula I wherein R_1 represents a hydroxymethyl, hydroxyethyl or hydroxyisopropyl group, free or protected by a *p*-nitrobenzyloxycarbonyl, dimethyl-*t*-butyl-silyl, diphenyl-*t*-butyl-silyl, trimethylsilyl, 2,2,2-trichloroethoxycarbonyl, benzyl, *p*-bromophenacyl, triphenylmethyl or pyranyl group, and R_2 and Y are as defined in claim 1 prepared by a process according to any of claims 1 to 9.

13. A (5R)-penem derivative of the general formula I wherein R_1 represents a monocycloalkyl group having from 4 to 7 carbon atoms, unsubstituted or substituted by one or more alkyl groups having from 1 to 6 carbon atoms and/or by one or more free or protected mercapto, amino or hydroxy groups and R_2 and Y are as defined in claim 1 prepared by a process according to any of claims 1 to 9.

14. A (5R)-penem derivative of the general formula I wherein R_2 represents a straight or branched alkyl group having from 1 to 6 carbon atoms, a halo-substituted alkyl group having from 1 to 6 carbon atoms, an alkenyl group having from 2 to 4 carbon atoms, an optionally substituted aryl group, an aryl substituted alkyl group the alkyl part whereof has from 1 to 6 carbon atoms and the aryl part whereof is optionally substituted, an aryloxy substituted alkyl group the alkyl part whereof has from 1 to 6 carbon atoms, or a benzhydryl, *o*-nitrobenzhydryl, acetonyl, trimethylsilyl, diphenyl-*t*-butyl-silyl-dimethyl-*t*-butyl-silyl, acetoxymethyl, pivaloyloxymethyl or phthalidyl group and R_1 and Y are as defined in claim 1 prepared by a process according to any of claims 1 to 9.

15. A (5R)-penem derivative of the general formula I wherein Y represents a fluorine, chlorine or bromine atom, and R and R_2 are as defined in claim 1, prepared by a process according to any of claims 1 to 9.

16. A (5R)-penem derivative of the general formula I wherein Y represents

a) a free or protected hydroxy group;

b) a formyloxy group or an acyloxy group having from 2 to 6 carbon atoms, optionally substituted by a halogen atom, by an acyl group having from 2 to 6 cabon atoms, or by an amino, hydroxy or mercapto group, the amino, hydroxy or mercapto group optionally being in a protected form;

c) an unsubstituted or N-alkyl substituted carbamoyloxy group;

d) an alkoxy group having from 1 to 12 carbon atoms or an alkylthio group having from 1 to 12 carbon atoms, either of which is optionally substituted by one or more halogen atoms, formyl groups, acyl groups having from 2 to 6 carbon atoms, and/or amino, hydroxy or mercapto groups optionally being in a protected form;

e) a 1-pyridinium group, unsubstituted or substituted in the meta or para position with the group $—CONH_2$; or

f) a heterocyclylthio group —S—Het wherein Het, denoting a saturated or unsaturated heterocyclic ring containing at least one oxygen, sulphur and/or nitrogen heteroatom, is preferably:

A) a pentatomic or hexatomic heteromonocyclic ring, containing at least one double bond and at least one oxygen, sulphur and/or nitrogen heteroatom, such as a thiazolyl, triazolyl, thiadiazolyl, tetrazolyl, triazinyl group, unsubstituted or substituted by one or more

a') alkoxy groups having from 1 to 6 carbon atoms, aliphatic acyl groups having from 2 to 6 carbon atoms, hydroxy groups and/or halogen atoms;

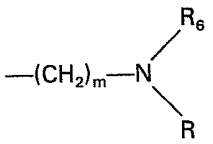
b') alkyl groups having from 1 to 6 carbon atoms, unsubstituted or substituted by one or more hydroxy groups and/or halogen atoms;

c') alkenyl groups having from 2 to 6 carbon atoms, unsubstituted or substituted by one or more hydroxy groups and/or halogen atoms;

d') groups of the general formula —S—R_3 wherein R_3 represents a hydrogen atom or an alkyl group having from 1 to 6 carbon atoms; or groups of the general formula —S—CH_2—$COOR_4$ wherein R_4 represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or a carboxy-protecting group;

e') groups of the general formula —$(CH_2)_m$—$COOR_4$ or —CH=CH—$COOR_4$ or —$(CH_2)_m$—CN or —$(CH_2)_m$—$CONH_2$ or —$(CH_2)_m$—SO_3H wherein *m* is zero, 1, 2 or 3 and R_4 is as defined above;

f') groups of the general formula



wherein *m* is as defined above, and each of R_5 and R_6, which may be the same or different, represents a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms or an aliphatic acyl group or when one of R_5 and R_6 is hydrogen, the other may be also an amino protecting group; or

B) a heterobicyclic ring, containing at least two double bonds wherein each of the condensed heteromonocyclic rings, being the same or different, is a pentatomic or hexatomic heteromonocyclic ring containing at least one oxygen, sulphur or nitrogen heteroatom, said heterobicyclic ring being unsubstituted or substituted by one or more substituents selected from a'), b'), c'), e') and f') as defined above, and R_1 and R_2 are as defined in claim 1 prepared by a process according to any of claims 1 to 9.

17. Methyl (6S,5R)-6-(1R-*t*-butyldimethylsilyloxyethyl)-2-methyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

18. Methyl (6S,5R)-6-(1R-hydroxyethyl)-2-methyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

19. *p*-Nitrobenzyl (6S,5R)-6-(1R-hydroxyethyl)-2-acetoxymethyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

20. *p*-Nitrobenzyl (6S,5R)-6-(1R-hydroxyethyl)-2-[(1-methyl-5-tetrazolylthio)-methyl]-penem-3-carboxylate prepared according to any of claims 1 to 9.

21. Methyl (6S,5R)-6-(1R-*t*-butyldimethylsilyloxyethyl)-2-[(1-methyl-5-tetrazolylthio)-methyl]-penem-3-carboxylate prepared according to any of claims 1 to 9.

22. (6S,5R)-6-(1R-Hydroxyethyl)-2-(pyridinium-methyl)-penem-3-carboxylate prepared according to any of claims 1 to 9.

23. (6S,5R)-6-(1R-Hydroxyethyl)-2-[(3-carbamoyl-pyridinium)-methyl]-penem-3-carboxylate prepared according to any of claims 1 to 9.

24. (6S,5R)-6-(1R-Hydroxyethyl)-2-[(4-carbamoyl-pyridinium)-methyl]-penem-3-carboxylate prepared according to any of claims 1 to 9.

25. Sodium (6S,5R)-6-(1R-hydroxyethyl)-2-[(1-methyl-5-tetrazolylthio)-methyl]-penem-3-carboxylate prepared according to any of claims 1 to 9.

26. Methyl (6S,5R)-6-(1R-*t*-butyldimethylsilyloxyethyl)-2-nitrooxymethyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

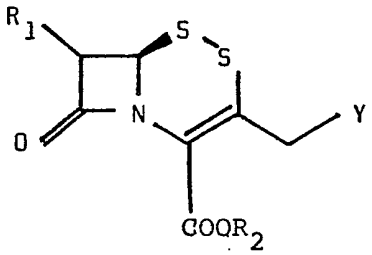
27. Trichloroethyl (6S,5R)-6-(1R-trichloroethoxycarbonyloxyethyl)-2-nitrooxymethyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

28. Methyl (6S,5R)-6-(1R-*t*-butyldimethylsilyloxyethyl)-2-hydroxyethyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

29. Sodium (6S,5R)-6-(1R-hydroxyethyl)-2-hydroxymethyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

30. Sodium (6S,5R)-6-(1R-hydroxyethyl)-2-carbamoyloxymethyl-penem-3-carboxylate prepared according to any of claims 1 to 9.

31. A process for the preparation of a 2-thiacephem derivative of the general formula II:



II

wherein R_1 and R_2 are as defined in claim 1 and Y represents a halogen atom, the process comprising halogenating a 2-thiacephem derivative of the general formula II wherein R_1 and R_2 are as above defined and Y represents a hydrogen atom in an inert organic solvent, at a temperature of from 20° to 130°C in the presence of a radical initiator and an acid scavenger.

32. A process according to claim 31 in which the halogenation is effected with N-bromosuccinimide or N-chlorosuccinimide.

33. A process according to claim 31 or claim 32 in which the radical initiator is azobisisobutyronitrile or benzoyl peroxide.

34. A process according to any of claims 31 or 33 in which the acid scavenger is an epoxide, an alkaline earth oxide or a molecular sieve.

35. A process according to any of claims 31 to 34 in which the solvent is benzene, carbon tetrachloride or ethyl formate.

36. Methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

37. Diphenylmethyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromo-methyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

38. Trichloroethyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

39. Trichloroethyl (7S,6R)-7-(1R-trichloroethoxycarbonyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

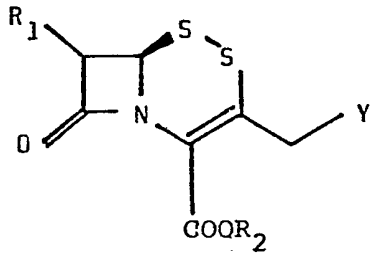
40. *t*-Butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

41. *p*-Nitrobenzyl (7S,6R)-7-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

42. Diphenylmethyl (7S,6R)-7-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

43. Diphenylmethyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-bromomethyl-2-thiacephem-4-carboxylate prepared according to any of claims 31 to 35.

44. A process for the preparation of a 2-thiacephem derivative of the general formula II



II

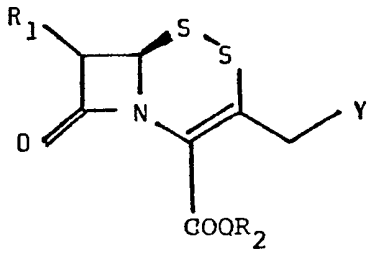
wherein R_1 and R_2 are as defined in claim 1 and Y represents a hydroxy group, the process comprising reacting a 2-thiacephem derivative of the general formula II wherein R_1 and R_2 are as above defined and Y represents a halogen atom with a salt of a strong inorganic acid and hydrolysing the resultant labile ester of the inorganic acid.

45. A process according to claim 44 in which the salt is silver nitrate, silver perchlorate or sodium nitrate.

46. A process according to claim 44 or claim 45 in which the reaction is carried out in an acetone: water mixture at 0°C for 15 minutes, and the subsequent hydrolysis is carried out in the same reaction medium.

47. *t*-Butyl-(7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-hydroxymethyl-2-thiacephem-4-carboxylate prepared according to any of claims 44 to 46.

48. A process for the preparation of a 2-thiacephem derivative of the general formula II



II

wherein R_1 and R_2 are as defined in claim 1 and Y represents an unsubstituted or substituted N-alkyl or N-acyl carbamoyloxy group, the process comprising reacting a 2-thiacephem derivative of the general formula II wherein R_1 and R_2 are as above defined and Y represents a hydroxy group with an alkylisocyanate or an acylisocyanate and, if desired, deprotecting the carbamoyloxy group.

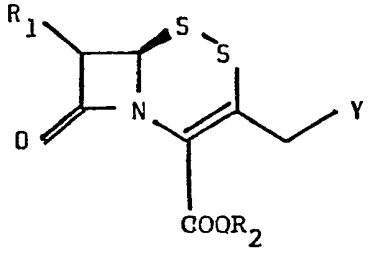
49. A process according to claim 48 in which the reaction is carried out in dichloromethane at −40°C.

50. A process according to claim 48 or claim 49 in which the deprotection is carried out by stirring with silica gel in methanol for 20 hours.

51. *t*-Butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxymethyl)-3-(N-trichloroacetylcarbamoyloxymethyl-2-thiacephem-4-carboxylate prepared according to any of claims 48 to 50.

52. *t*-Butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-carbamoyloxymethyl-2-thiacephem-4-carboxylate prepared according to any of claims 48 to 50.

53. A process for the preparation of a 2-thiacephem derivative of the general formula II



II

wherein R_1 and R_2 are as defined in claim 1 and Y represents an acyloxy group, the process comprising reacting a 2-thiacephem derivative of the general formula II wherein R_1 and R_2 are as above defined and Y represents a halogen atom with a carboxylic acid salt.

54. A process according to claim 53 in which the reaction is carried out in dichloromethane at 5°C with addition of the salt portionwise over 3 days.

55. Methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-formyloxymethyl-2-thiacephem-4-carboxylate prepared according to claim 53 or claim 54.

56. *t*-Butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-formyloxymethyl-2-thiacephem-4-carboxylate prepared according to claim 53 or claim 54.

57. Diphenylmethyl (7S,6R)-(1R-*t*-butyldimethylsilyloxyethyl)-3-formyloxymethyl-2-thiacephem-4-carboxylate prepared according to claim 53 or claim 54.

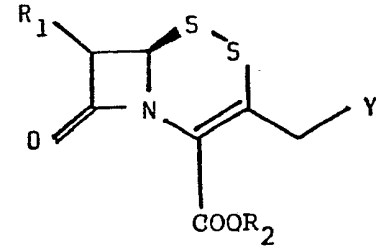
58. Methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate prepared according to claim 53 or claim 54.

59. *t*-Butyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate prepared according to claim 53 or claim 54.

60. Diphenylmethyl (7S,6R)-7-(1R-*t*-butyldimethyl siloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate prepared according to claim 53 or claim 54.

61. Trichloroethyl (7S,6R)-6-(1R-trichloroethoxycarbonyloxyethyl)-3-acetoxymethyl-2-thiacephem-4-carboxylate prepared according to claim 53 or claim 54.

62. A process for the preparation of a 2-thiacephem derivative of the general formula II



II

wherein R_1 and R_2 are as defined in claims 1 to 6 and Y represents a —S—Het group as defined in claim 16, the process comprising reacting a 2-thiacephem derivative of the general formula II wherein R_1 and R_2 are as above defined and Y represents a halogen atom in an organic solvent with a compound of the formula HS—Het in the presence of a base or with a preformed sodium salt of the compound HS—Het.

63. A process according to claim 62 in which the solvent is tetrahydrofuran, acetone, acetonitrile or dimethylformamide.

64. A process according to claim 62 or claim 63 in which the reaction is carried out overnight at room temperature.

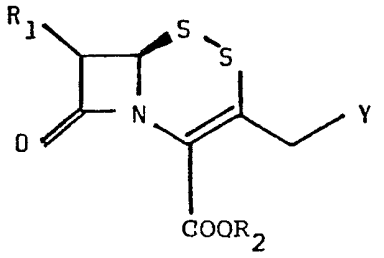
65. A process according to any of claims 62 to 64 in which the base is triethylamine.

66. Methyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate prepared according to any of claims 62 to 65.

67. *t*-Butyl (7S,6R)-1R-*t*-butyldimethylsilyloxyethyl)-3-[(1-methyl-5-tetrazolylthio)-methyl]-2-thiacephem-4-carboxylate prepared according to any of claims 62 to 65.

68. Diphenylmethyl (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-[(8-aminotetrazol-[1,5-b]-pyridazin-6-ylthio)-methyl]-2-thiacephem-4-carboxylate prepared according to any of claims 62 to 65.

69. A process for the preparation of a 2-thiacephem derivative of the general formula II



II

wherein R_1 and R_2 are as defined in claim 1 and Y is a 1-pyridinium group, unsubstituted or substituted in the meta or para position with a carbamoyl group, the process comprising reacting a 2-thiacephem derivative of the general formula II wherein R_1 and R_2 are as above defined and Y represents a halogen atom with pyridine, nicotinamide or isonicotinamide.

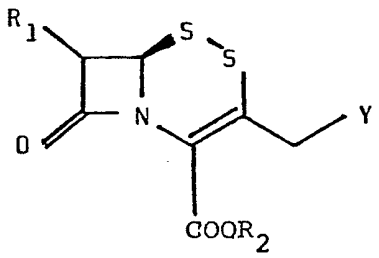
70. (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-4-diphenylmethoxycarbonyl-3-(pyridinium-methyl)-2-thiacephem bromide prepared according to claim 69.

71. (7S,6R)-7-(1R)-*p*-nitrobenzyloxycarbonyloxyethyl)-4-*p*-nitrobenzyloxycarbonyl-3-(pyridinium-methyl)-2-thiacephem bromide prepared according to claim 69.

72. (7S,6R)-7-(1R-*p*-nitrobenzyloxycarbonyloxyethyl)-4-*p*-nitrobenzyloxycarbonyl-3-(3-carbamoylpyridinium-methyl)-2-thiacephem bromide prepared according to claim 69.

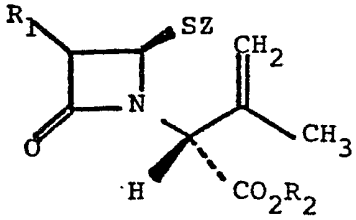
73. (7S,6R)-7-(1R)-*p*-nitrobenzyloxycarbonyloxyethyl)-4-*p*-nitrobenzyloxycarbonyl-3-(4-carbamoylpyridinium-methyl)-2-thiacephem-bromide prepared according to claim 69.

74. A process for the preparation of a 2-thiacephem derivative of the general formula II



II

wherein R_1 and R_2 are as defined in claim 1 and Y is as defined in claim 8, the process comprising halogenating a compound of the general formula IV



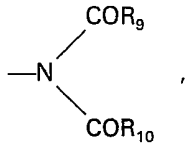
IV

wherein R_1 and R_2 are as above defined and Z represents

i) a group of the formula SR_7 wherein R_7 represents an alkyl group having from 1 to 8 carbon atoms, a phenyl or tolyl group, or preferably, a heterocyclic group, especially a 2-benzothiazolylthio or 1-methyl-5-tetrazolylthio group,

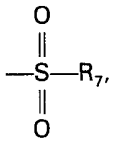
ii) a group of the formula $SCOR_8$ wherein R_8 represents an optionally substituted lower alkyl group, preferably a methyl group,

iii) a group of the formula



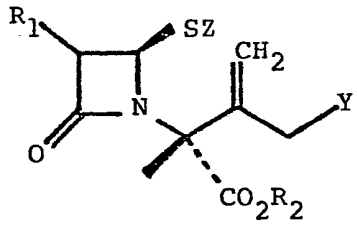
wherein R_9 and R_{10} independently represent lower alkyl or aryl groups, or together with the dicarboxyamino group form a heterocyclic ring, preferably a succinimido or phthalimido group, or

iv) a group of the formula



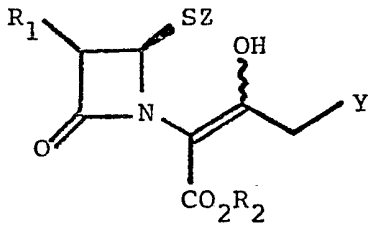
wherein R_7 represents an optionally substituted lower alkyl or aryl group, preferably a methyl, phenyl or *p*-tolyl group;

ozonolysing the resultant compound of the general formula V



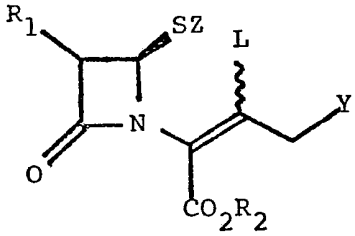
V

wherein R_1, R_2 and Z are as above defined and Y represents a halogen atom; and transforming the resultant compound of the general formula VII



VII

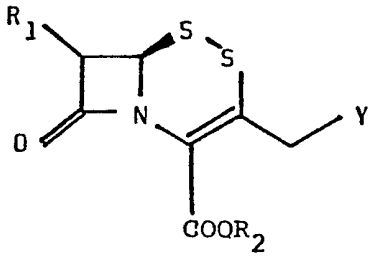
wherein R_1, R_2, Y and Z are as above defined into a compound of the general formula IX



IX

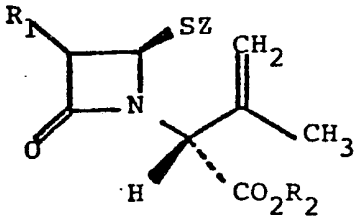
wherein R_1, R_2, Y and Z are as above defined, and L represents a halogen atom, an alkane sulphonyloxy group or an arenesulphonyloxy group; and cyclizing the compound of the general formula IX.

75. A process for the preparation of a 2-thiacephem derivative of the general formula II



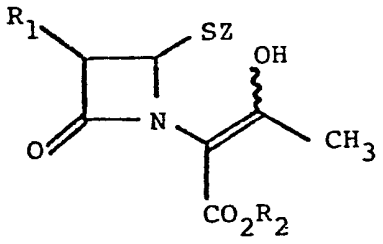
II

wherein R_1 and R_2 are as defined in claim 1 and Y represents a hydrogen atom, the process comprising ozonolysing a compound of the general formula IV



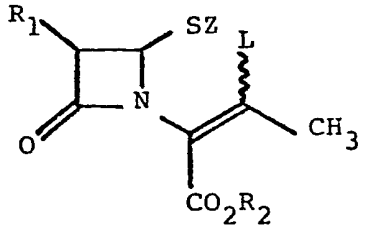
IV

wherein R_1 and R_2 are as defined in claim 1 and Z is as defined in claim 74, converting the resultant compound of the general formula VI



VI

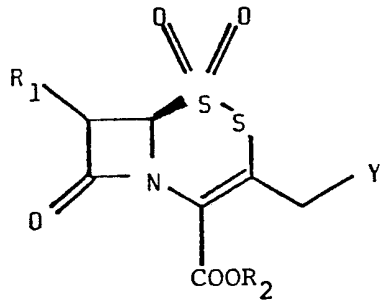
into a compound of the general formula VIII



VIII

wherein R_1, R_2, L and Z are as defined in claim 74, and cyclizing the compound of the general formula VIII by treatment with a salt of hydrogen sulphide with an organic or inorganic base.

76. A 2-thiacephem-1,1-dioxide of the general formula III:



III

wherein R_1, R_2 and Y are as defined in claim 1.

77. (7S,6R)-7-(1R-*t*-butyldimethylsilyloxyethyl)-3-methyl-4-methoxycarbonyl-2-thiacephem-1,1-dioxide.

78. (7S,6R)-7-(1R-hydroxyethyl)-3-methyl-4-methoxycarbonyl-2-thiacephem-1,1-dioxide.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1984. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.