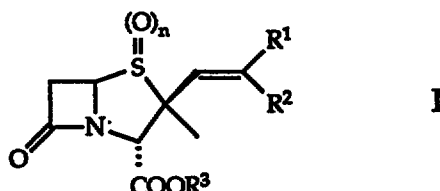


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RAN 4410/238

- 5 The present invention relates to penam derivatives, in particular it is concerned with 2 β -alkenyl-penam derivatives of the general formula



10

wherein

one of R¹ and R² signifies -COR⁴, -CN, -CH₂R⁵, halogen, -CH=CHR⁶ or Q and the other signifies hydrogen or lower alkyl or both together signify a γ -lactam ring,

- 15 R³ signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R⁴ signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino, lower alkylamino or lower alkyl-lower alkoxyamino,

- 20 R⁵ signifies hydroxy, -OCONHR⁷, -OCONH₂ or a five- or six-membered hetero-aromatic ring which contains N, S and/or O and which is linked via a nitrogen atom,

R⁶ signifies -CN or CHO,

R⁷ signifies -COCH₂Cl,

- 25 Q signifies a five- or six-membered hetero-aromatic ring which contains N, S and/or O and

n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

- 30 These compounds are novel and are distinguished by therapeutically valuable properties. In particular, they have pronounced β -lactamase inhibiting properties and are accordingly useful in combination with β -lactam antibiotics such as the penicillins and cephalosporins in the control of pathogens which form β -lactamase.

35

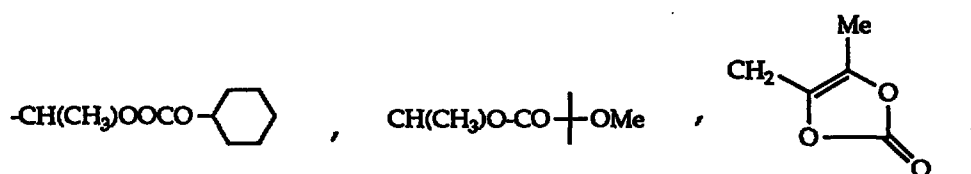
5 The term "lower alkyl", alone or in combination such as "lower alkoxy" or "lower alkylamino", signifies straight-chain or branched saturated hydrocarbon residues with a maximum of 7, preferably a maximum of 4, carbon atoms such as methyl, ethyl, isopropyl or t-butyl.

The term "aryl-alkyl" embraces benzyl, benzhydryl, p-methoxybenzyl or p-nitrobenzyl.

The term "halogen" embraces fluorine, chlorine, bromine or
15 iodine.

The term "five- or six-membered hetero-aromatic ring which contains N, S and/or O" preferably signifies 2-pyridyl, 1-methyl-pyridin-2-yl, 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl and the like.

25



or $-\text{CH}(\text{CH}_3)\text{OCO}-\text{CH}_3$.

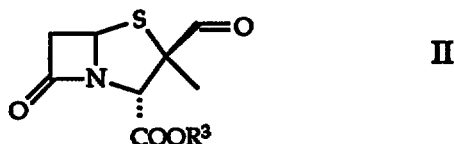
30 Objects of the present invention are 2 β -alkenyl-penam
derivatives of general formula I and pharmaceutically compatible
salts thereof per se and as pharmaceutically active substances,
the manufacture of these compounds, medicaments containing a
compound of general formula I or a pharmaceutically compatible
35 salt and, if desired, additionally a β -lactam antibiotic and the
manufacture of such medicaments, as well as the use of com-



pounds of general formula I and of pharmaceutically compatible salts thereof in the control or prevention of illnesses, especially of bacterial infections, and, respectively, for the manufacture of corresponding medicaments.

5

Furthermore, compounds of the general formula



10 wherein R³ has the above significance,
are an object of the invention.

These compounds of formula II are important intermediates for the manufacture of the compounds of general formula I.

15

Those compounds of general formula I in which R¹ = CN, halogen or COR⁴ and R⁴ = amino, methyl, lower alkoxy or benzyl-oxy and R² = hydrogen, e.g. the following compounds, are especially preferred:

20

Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

25

benzhydryl (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

sodium (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

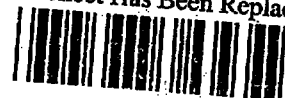
30

sodium (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium(E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

35

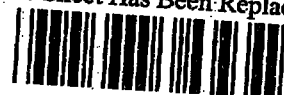


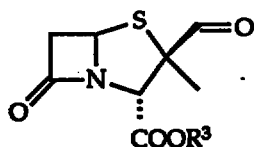
Furthermore, the following belong to the especially preferred compounds:

- Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
5 benzhydryl (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
10 sodium (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
sodium (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
15 benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
20 sodium (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
25 benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
sodium (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

The 2 β -alkenyl-penam derivatives of general formula I as well as their pharmaceutically compatible salts can be manufactured in accordance with the invention by

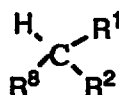
- a) reacting a compound of the general formula





II

wherein R³ has the significance given above,
5 with a compound of the general formula



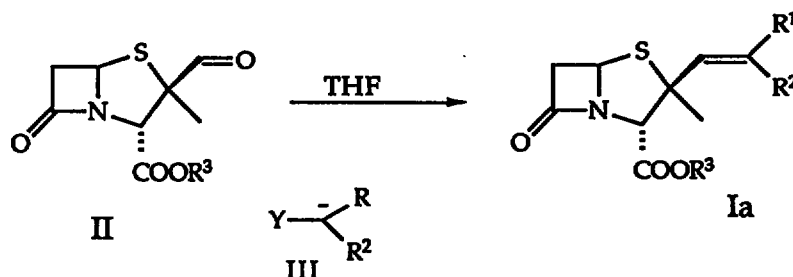
wherein R¹ and R² have the significance given above and R⁸
10 = P[⊕](aryl)₃, PO(Oalkyl)₂, Si(alkyl)₃ or halogen,
in the presence of an activating agent, or

- b) oxidizing a compound of general formula I in which n
signifies 0, or
15
c) converting a compound of general formula I in which R³ is
different from hydrogen into the corresponding free acid, and
d) if desired, converting an acidic compound of formula I into a
20 pharmaceutically acceptable salt.

Scheme 1 shows two known methods (Wittig or Horner
reaction) for carrying out process variant a).

25

Scheme 1



The substituents R¹, R² and R³ have the above significances.

30



The aldehyde of formula II is converted into the alkenyl-substituted penams of formula Ia by direct reaction with an alkylidene-triphenylphosphorane (III; $Y = P^{\oplus}(aryl)_3$, Wittig reaction) or with an alkylphosphonate (III, $Y = (alkylO)_2PO$, Horner reaction) in the presence of an activating agent, for example a base such as triethylamine, sodium methylate, lithium diisopropylamine or DBU (1,5-diaza-bicyclo[4.3.0]non-5-ene). Suitable solvents are e.g. tetrahydrofuran, toluene, dichloromethane, acetonitrile or benzene. The reaction temperature can vary between -30° and $80^{\circ}C$ depending on the solvent which is used.

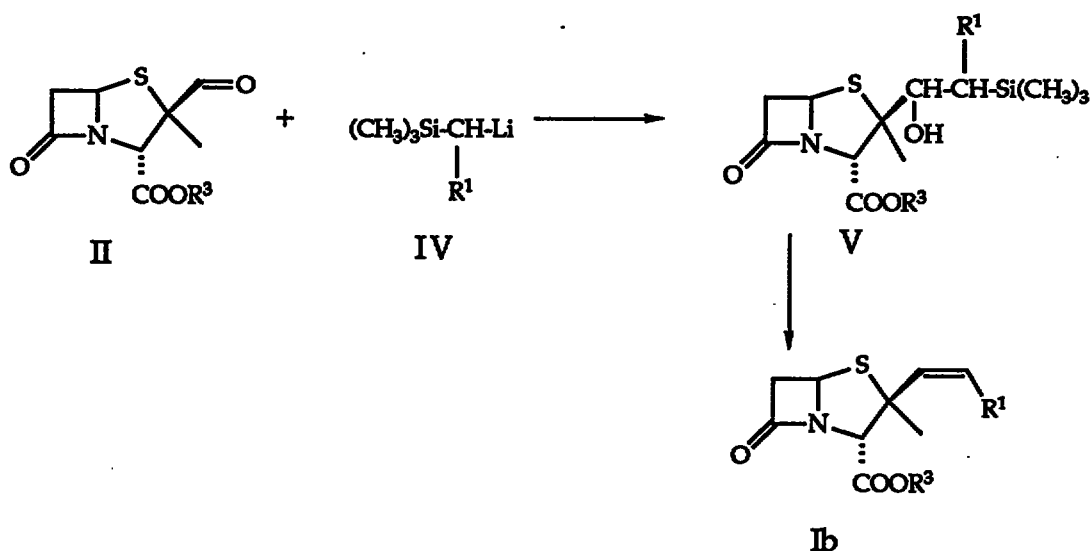
If desired, the compounds of formula I can also be manufactured by reacting correspondingly substituted triphenylphosphonium halides with 1,2-butylene oxide as the base and solvent. In this case the preferred reaction temperature lies between 50 and $70^{\circ}C$. Compounds of formula I in which n signifies 0 are obtained.

The Peterson olefination and the Reformatsky synthesis are further possibilities for carrying out process variant a). In the case of the Peterson olefination, lithium derivatives of trialkylsilanes are reacted with compounds of formula II in the presence of a base. Scheme 2 shows the reaction with a lithium trimethylsilane of formula IV in which R^1 and R^3 have the significances given above.

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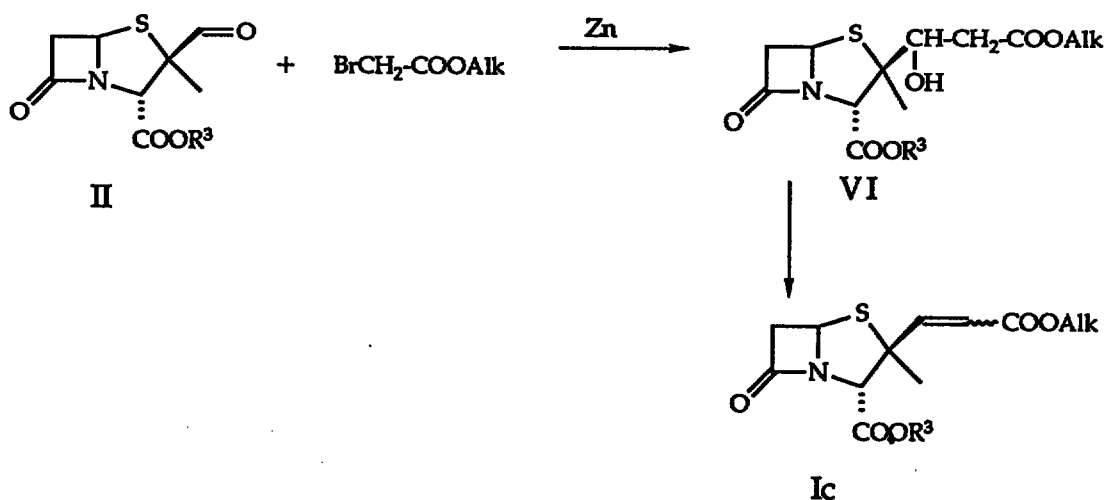
Scheme 2



5 The 2β-alkenyl-penam derivatives of formula Ib result from the compounds of formula V by spontaneous dehydration. Compounds of formula I in which n signifies 0 and R² signifies hydrogen are obtained. In the case of the Reformatsky synthesis, compounds of formula II are condensed with organo-zinc derivatives of α-halo esters to the corresponding β-hydroxyl esters of formula VI, from which compounds of formula I in which n signifies 0, R¹ signifies COR⁴, R⁴ signifies lower alkyl and R² signifies hydrogen result by water cleavage, corresponding to Scheme 3.

15

Scheme 3



R³ has the significance given above.



The oxidation of the sulphide group to the sulfoxide group or sulphone group is effected according to methods known per se. Reaction of the compounds of general formula I in which n signifies 0 in a two-phase system with ruthenium tetroxide or with an aqueous potassium permanganate solution and with a hydrogen peroxide solution has been found to be especially suitable.

Other oxidation reagents such as Na_2WO_4 or peracids can also be used for the preparation of the penam sulphones. Dichloromethane is an especially suitable solvent.

The compound of general formula I in which n signifies 0 is conveniently dissolved in dichloromethane and added to an aqueous suspension consisting of sodium (meta)periodate, sodium bicarbonate and ruthenium(IV) oxide. After completion of the reaction the organic phase is separated, purified and dried.

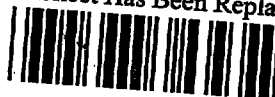
Whether a sulfoxide or a sulphone results from this oxidation depends on the nature and/or amount of oxidation agent.

The conversion of a compound of formula I in which R^3 is different from hydrogen into a free acid and the conversion of a free acid into a pharmaceutically acceptable salt can be effected according to methods known per se, in certain circumstances in a single procedure.

Ester groups, e.g. benzyl, p-nitrobenzyl, benzhydryl, p-methoxybenzyl or allyl, can be cleaved off as follows:

30

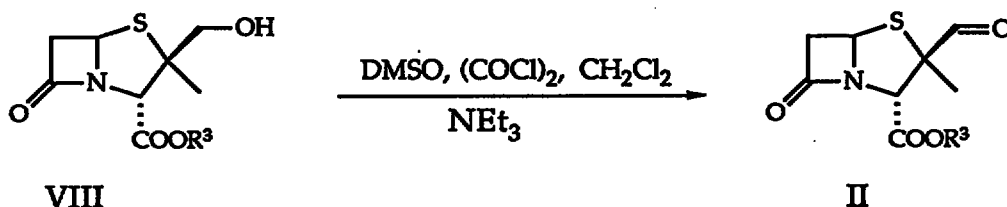
Benzyl and p-nitrobenzyl by hydrogenation over palladium-carbon at about 0°C to 80°C in an organic solvent such as ethyl acetate, methanol or water or by hydrolysis in the presence of sodium sulphide at about 0°C to room temperature in a solvent such as e.g. DMF. Allyl by palladium-(0)-catalyzed transallylation in the presence of a sodium or potassium salt of 2-ethylcaproic acid, benzhydryl with m-cresol at about 50°C within 4-5 hours.



The compounds of general formula II which are used as starting materials can be prepared from corresponding alcohols in analogy to the process described in Tetrahedron 43, No. 5, pp 1003-1012.

5

Scheme 4



10 In this, R³ has the significance given above.

Reaction with oxalyl chloride in dichloromethane has been found to be of advantage, with the following procedure conveniently being used: dichloromethane and the oxidation agent are cooled to about -60°C, treated with DMSO and a compound of
15 formula VIII and, after a reaction period of about 3 hours and addition of triethylamine, the cooling bath is removed. The thus-obtained aldehyde of formula II can be purified using usual methods.

20

Compounds of general formula II are obtained analogously by oxidation with PCC (pyridine chlorochromate), Dess-Martin reagent, MnO₂ and the like.

25 As mentioned earlier, the compounds of general formula I in accordance with the invention and pharmaceutically compatible salts thereof with bases exhibit pronounced β-lactamase-inhibiting activities against β-lactamases from various bacterial strains. As illustrated hereinafter, these therapeutically
30 valuable properties can be determined in vitro on isolated β-lactamases:

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A. Isolation of the β -lactamases

Various β -lactamases can be isolated from penicillin- or cephalosporin-resistant bacterial strains such as *Klebsiella pneumoniae* NCTC 418, *Proteus vulgaris* 1028, *Bacillus licheniformis* 749/C, *Escherichia coli* SN01 and *Citrobacter freundii* 1203. For this purpose, the corresponding strains are cultivated in Tryptic Soy Broth (Difco) and harvested by centrifugation in the last logarithmic growth phase (when necessary 50-100 mg/l of ampicillin are added to the medium towards the end of the log-phase in order to induce the β -lactamase). The thus-obtained bacterial mass is treated with 20 mM Tris-HCl buffer (pH 7.0); the cells are broken open with a French press while cooling. The mixture is centrifuged (20,000 r/min.) for 20-30 minutes and a clear crude extract is obtained. The purification of the proteins is effected according to the methods of Cartwright, S.J. & Waley, S.G. [Biochem. J. 221, 505-512 (1980)] and, for *B. licheniformis*, Ellerby, L.M. et al. [Biochemistry 29, 5797-5806 (1990)].

B. Determination of the β -lactamase activity

The determination of the activity of the isolated β -lactamases can be carried out according to the method of O'-Callaghan, C.H. et al. [Antimicrob. Agents Chemother. 1, 283-288 (1972)] using the chromogenic cephalosporin nitrocefin (87/312 from Glaxo). The requisite test batch contains per ml of water: 50 mM phosphate buffer (pH 7.0), 0.1 mM nitrocefin and sufficient enzyme (β -lactamase) to achieve a $\Delta A/\text{min.}$ of about 0.1. The cleavage of the substrate, which is accompanied by a change in colour, is effected at 37°C and is followed quantitatively at 482 nm using a spectral photometer.

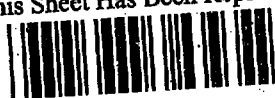
C. Determination of the β -lactamase-inhibiting activity of the compounds of general formula I

The above-described cleavage of the chromogenic substrate by β -lactamases (test B.) can be inhibited by the addition of compounds of general formula I (inhibitors). Since it has been found



- that the inhibitors irreversibly inactivate the β -lactamase in a time-dependent reaction, the reaction (cleavage of the substrate) is in each case started by addition of the substrate after a pre-incubation period of β -lactamase with inhibitor of 15 minutes.
- 5 As a measurement for the affinity of the particular tested inhibitor to the β -lactamase, which is a measurement of the strength of the inhibitor, there serves that concentration which inhibits by 50% (IC 50 in nM) the cleavage of the substrate (nitrocefin) effected under the above test conditions (test B) in
- 10 the absence of an inhibitor. 4 to 6 tests with different concentrations of inhibitor were carried out in order to determine the IC 50. The determination of the IC 50 was effected by means of a graph.
- 15 The results obtained in the above test (test C) are presented in Tables 1 to 3 hereinafter.

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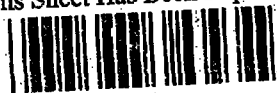


**Table 1**

The IC₅₀ value, given in nM, is a measurement of the β -lactamase inhibition. An IC₅₀ value of 5 μ M or less is considered to be significant.

β -Lactamase inhibiting activity of compounds of formula I

Examples of compound of formula I with reference	IC ₅₀ [μ M] <i>C. freundii</i> 1982	IC ₅₀ [μ M] <i>E. coli</i> CF 102
Tazobactam (reference)	0.900	0.015
6c (cis amide)	4.340	0.130
6c (trans amide)	2.250	0.054
5c (trans nitrile)	0.696	0.681
5c (cis nitrile)	0.210	0.126
2c (trans ethyl ester)	0.370	0.456
4c (trans benzyl ester)	0.478	0.444
8c (cis-chloro)	0.590	0.055
9c (trans COCH ₃)	0.147	0.417
11c (trans 1,2,4-oxadiazol-3-yl)	0.490	0.217
12c (trans 2-thiazolyl)	0.410	0.054
12c (cis 2-thiazolyl)	1.270	0.160
13c (trans 2-pyridinyl)	1.010	0.092
14c (trans-CONMe(OMe))	2.490	0.181
15 (trans 2-pyridinyl)	3.100	0.087
17b (trans CH=CH-CN(Z))	3.300	0.420
18c (gamma-lactam)	14.250	0.320
20c (trans CH ₂ OH)	6.92	0.590
22c (trans CH ₂ CONH ₂)	0.479	0.763
23c (trans CH ₂ -pyridinium)	15.700	0.142

**Table 2**

β -Lactamase inhibiting activity by combination of compounds of formula I with ceftriaxone

5

(1 part ceftriaxone + 4 parts inhibitor)

Examples of compounds of formula I with reference	IC [μ g/ml] C. freundii 1982	IC [μ g/ml] E. coli CF 102
Ceftriaxone	128	8
Ceftriaxone + Tazobactam (reference)	8	0.25
Ceftriaxone + 6c (cis amide)	4	0.12
Ceftriaxone + 6c (trans amide)	NA	0.12
Ceftriaxone + 5c (trans nitrile)	2	0.25
Ceftriaxone + 5c (cis nitrile)	1	0.25
Ceftriaxone + 2c (trans ethyl ester)	4	0.25
Ceftriaxone + 4c (trans benzyl ester)	16	2.00
Ceftriaxone + 8c (cis chloro)	4	0.25
Ceftriaxone + 9c (trans COCH ₃)	1	0.25
Ceftriaxone + 11c (trans 1,2,4-oxadiazol-3-yl)	4	0.5
Ceftriaxone + 12c (trans 2-thiazolyl)	8	1
Ceftriaxone + 12c (cis 2-thiazolyl)	16	0.5
Ceftriaxone + 13c (trans 2-pyridinyl)	8	1
Ceftriaxone + 14c (trans CONMe(OMe))	8	0.5
Ceftriaxone + 15 (trans 2-pyridinyl)	4	0.25
Ceftriaxone + 17b (trans CH=CH-CN(Z))	8	0.5

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Ceftriaxone + 18c (gamma-lactam)	16	1
Ceftriaxone + 20c (trans-CH ₂ OH)	8	0.5
Ceftriaxone + 22c (trans CH ₂ OCONH ₂)	2	1
Ceftriaxone + 23c (trans CH ₂ -pyridinium)	8	0.25

MIC signifies minimum inhibitory concentration.

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**Table 3**

In vitro activity of combinations of the penam sulphone derivative 5c with selected antibiotics against β -lactamase over-producer strains

5 (constant inhibitor concentration: 4 mg/l)

	MIC E.cloacae	MIC C.freundii	MIC Ps.aeru- ginosa	MIC E.coli
Ceftriaxone	>64	64	>64	16
Ceftriaxone + 5c (cis nitrile)	4	2	16	≤ 0.12
Ceftriaxone + tazobactam	64	32	>64	≤ 0.12
Ceftazidime	>64	>64	32	32.00
Ceftazidime + 5c (cis nitrile)	4	8	2	0.5
Ceftazidime + tazobactam	64	64	8	0.5
Piperacillin	>128	>128	>64	>64
Piperacillin + 5c (cis nitrile)	8	8	16	4
Piperacillin + tazobactam	128	64	64	4
Apalcillin	>128	>128	64	>64
Apalcillin + 5c (cis nitrile)	16	8	4	2
Apalcillin + tazobactam	>128	64	NA	2

The products in accordance with the invention can be used as medicaments, e.g. in the form of pharmaceutical preparations which contain them or their salts in admixture with a pharmaceutical, organic or inorganic inert carrier material which is suitable for parenteral or enteral administration, such as e.g. water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, Vaseline, etc. The pharmaceutical preparations can be present in solid form, e.g. as tablets, dragées, suppositories, capsules; or in liquid form, e.g. as solutions, suspensions or emulsions. They may be sterilized and/or may contain adjuvants such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure, anaesthetics or buffers. The compounds of formula I and their

salts preferably come into consideration for parenteral administration and, for this purpose, are preferably prepared as lyophilizates or dry powders for dilution with usual agents such as water or isotonic saline.

5

As mentioned earlier, the compounds of general formula I and their pharmaceutically compatible salts can be used in accordance with the invention in the control or prevention of illnesses, especially in the control of β -lactamase-forming
10 pathogens in combination with β -lactam antibiotics, i.e. antibiotics which contain a β -lactam ring, for example penicillins such as piperacillin, mezlocillin, azlocillin, apalcillin, benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, tricarcillin, ampicillin, amoxycillin or mecillinam and
15 cephalosporins such as ceftriaxone, ceftazidime, cefetamet, cefatamet pivoxil, cefotaxime, cefmenoxime, ceftizoxime, cefuroxime, cephaloridine, cephalotin, cefazolin, cephalixin, cefoxitin, cephacetrile, cefamandole, cephapirin, cephradine, cephaloglycine, cefpirome or cefepime as well as penems and
20 carbapenems such as imipenem or meropenem. Thereby, the compounds of general formula I or pharmaceutically compatible salts thereof with bases can be administered before, simultaneously with or after the administration or intake of β -lactam antibiotics. Where the products in accordance with the invention
25 are administered simultaneously with a β -lactam antibiotic, then this can be effected by administration as an ad-hoc combination or in the form of a pharmaceutical combination which contains a compound of general formula I or a pharmaceutically compatible salt thereof with a base and a β -lactam antibiotic; such pharmaceutical combinations are also an object of the present invention.
30

The dosage of the compounds of general formula I and of the pharmaceutically compatible salts thereof with bases can vary within wide limits and will, of course, be fitted in each
35 particular case to the individual requirements and to the β -lactamase-producing pathogen to be controlled. In general, a daily dosage of about 0.1 to about 2.0 g should be appropriate. The ratio of β -lactamase inhibitor (compound of formula I or



pharmaceutically compatible salt thereof with a base) to β -lactam antibiotic can also vary within wide limits and will be fitted to the individual requirements in each particular case. In general, a ratio of about 1:20 to about 1:1 should be appropriate.

5

As mentioned earlier, medicaments containing a compound of general formula I or a pharmaceutically compatible salt thereof are also an object of the present invention, as is a process for the manufacture of such medicaments which comprises bringing
10 one or more compounds of general formula I or pharmaceutically compatible salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form; in this connection reference is again made to the pharmaceutical combinations referred to above, which are also an object
15 of the present invention. In particular, pharmaceutical combinations containing a compound of general formula I or a pharmaceutically compatible salt thereof and a β -lactam antibiotic, e.g. a penicillin such as piperacillin, mezlocillin, azlocillin, apalcillin, benzylpenicillin, phenoxymethylpenicillin,
20 carbenicillin, methicillin, propicillin, tricarcillin, ampicillin, amoxycillin or mecillinam, a cephalosporin such as ceftriaxone, ceftazidime, cefetamet, cefatamet pivoxil, cefotaxime, cefmenoxime, ceftizoxime, cefuroxime, cephaloridine, cephalotin, cefazolin, cephalixin, cefoxitin, cephacetrile, cefamandole,
25 cephapirin, cephradine, cephaloglycine, cefpirome or cefepime or a penem or carbapenem such as imipenem or meropenem, are an object of the present invention. Such combinations are suitable for the control of β -lactamase-forming pathogens.

30 The following Examples are intended to illustrate the present invention in more detail, but are not intended to limit its scope in any manner.

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Example 1

Benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

- 5 100 ml of dichloromethane are treated with 0.84 ml (9.6 mmol) of oxalyl chloride under argon and cooled to -60°C. Thereto there are added dropwise 0.73 ml (10.25 mmol) of DMSO, followed by
- 10 2.5 g (6.52 mmol) of benzhydryl (2S,3R,5R)-3-hydroxymethyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate dissolved in 100 ml of dichloromethane. The mixture is stirred at the same temperature for 3 hours and then 3.2 ml (23.0 mmol) of triethylamine are added. The cooling bath is removed and the mixture is left to warm to room temperature. The orange
- 15 solution is poured into 1000 ml of 0.2N hydrochloric acid and the aqueous phase is extracted twice with dichloromethane. The organic phases are washed with water and saturated, aqueous sodium chloride solution, dried over sodium sulphate, filtered and concentrated on a rotary evaporator. The thus-obtained product
- 20 (2.50 g, 100%) can be processed without further purification or can be recrystallized from diethyl ether.

Yield: 2.00 g (80%) of white crystal powder; m.p. 111.8-112.8°C

- 25 IR(KBr): 2720, 1788, 1743, 1718 cm⁻¹

MS: (M-CH₂CO) 339

- ¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.26(s,3H), 3.06(dd,1H,J=
- 30 16.2Hz, 2Hz, 6-H), 3.54(dd,1H,J=16.2Hz, 4Hz,6-H), 5.34(s,1H,2-H), 5.42(dd,1H,J=2Hz, 4Hz,5-H), 6.95(s,1H,CHPh₂), 7.30-7.38 (m,10H,Ph), 9.20(s,1H).

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Example 2

(a) Benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

500 mg (1.30 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 20 ml of THF under argon and treated with 500 mg (1.40 mmol) of ethoxycarbonylmethylene-triphenylphosphorane. The yellow solution is stirred at 50°C for 75 minutes and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with ethyl acetate:hexane 9:16 as the eluent.

Yield: 520 mg (88%) of yellow-orange resin;
IR (film): 1783, 1747, 1717, 1650 cm^{-1}

MS: (M-CONH) 406, (M-CHPh₂) 284

¹H-NMR (250MHz, CDCl₃): δ [ppm] = 1.31(t,3H,J=7Hz), 1.34(s,3H), 3.13(dd,1H,J=2Hz, 16Hz,6-H), 3.57(dd,1H,J=4Hz, 16Hz,6-H), 4.22(q,2H,J=7Hz), 4.78(s,1H,2-H), 5.30(dd,1H,J=4.2Hz, 5-H), 5.97(d,1H,J=15Hz,=CH), 6.94(s,1H,CHPh₂), 7.07(d,1H,J=15Hz,=CH), 7.30-7.38(m,10H,Ph).

(b) Benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

250 mg (0.55 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 10 ml of dichloromethane and treated with 6.5 ml of glacial acetic acid. 260 mg (1.66 mmol) of potassium permanganate in 25 ml of water are added dropwise to the yellow solution. After completion of the addition stirring is continued for a further 30 minutes and then the brown reaction mixture is treated with a 30% hydrogen per-



oxide solution until a colourless two-phase mixture forms. The phases are separated in a separating funnel and the aqueous phase is extracted twice with dichloromethane. The organic phase is washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. The residual oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:hexane 9:16 as the eluent.

10 Yield: 170 mg (60%) of colourless foam.

IR(KBr): 1802, 1757, 1721, 1653, 1331, 960 cm^{-1}

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MS: (M-H) 482.4

15

$^1\text{H-NMR}$ (250MHz, CDCl_3): $\delta[\text{ppm}] = 1.26(\text{s}, 3\text{H})$, $1.35(\text{t}, 3\text{H}, J=7\text{Hz})$, $3.44\text{--}3.59(\text{pseudo-m}, 2\text{H}, 6\text{-H})$, $4.29(\text{q}, 2\text{H}, J=7\text{Hz})$, $4.60(\text{dd}, 1\text{H}, J=4\text{Hz}, 2\text{Hz}, 5\text{-H})$, $4.61(\text{s}, 1\text{H}, 2\text{-H})$, $5.99(\text{d}, 1\text{H}, J=16\text{Hz}, =\text{CH})$, $6.94(\text{s}, 1\text{H}, \text{CHPh}_2)$, $7.07(\text{d}, 1\text{H}, J=16\text{Hz}, =\text{CH})$, $7.23\text{--}7.40(\text{m}, 10\text{H}, \text{Ph})$.

20

(c) Sodium (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

25 170 mg (0.35 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 3 ml of m-cresol under argon and stirred at 50°C for 4.5 hours. Thereafter, the mixture is treated with 12.5 ml of isobutyl methyl ketone and the

30 yellow-orange solution is extracted three times with 3 ml of saturated, aqueous sodium hydrogen carbonate solution each time. The aqueous phase is washed twice with 5 ml of isobutyl methyl ketone each time, filtered over a fluted filter and subsequently adjusted to $\text{pH} = 1$ with concentrated hydrochloric acid. The

35 mixture is extracted with ethyl acetate, the organic phase is washed with saturated, aqueous sodium chloride solution, dried over sodium sulphate, filtered and concentrated on a rotary evaporator. The residual yellow resin is dissolved in 0.5 ml of

ethyl acetate and treated with 108 μ l of sodium 2-ethylcaproate (2N solution in ethyl acetate). The mixture is concentrated, the residue is treated with 1.5 ml of water and extracted once with n-hexane. Subsequently, the aqueous phase is chromatographed
5 over polymeric hydrophobic gel with water as the eluent. The fractions containing the product are combined and lyophilized.

Yield: 60 mg (50%) of colourless lyophilizate

10 IR(KBr): 1782, 1715, 1627, 1396, 1192 cm^{-1}

MS: (M-Na)⁻ 316.1

¹H-NMR (250MHz, D₂O): δ [ppm] = 1.31(t,3H,J=7Hz), 1.66(s,3H),
15 3.46(dd,1H,J=16Hz, 2Hz,6-H), 3.71(dd,1H,J=16Hz, 4Hz,6-H),
4.28(q,2H,J=7Hz), 4.62(s,1H,2-H), 5.15(dd,1H,J=2Hz,4Hz,5-H),
6.35(d,1H,J=16Hz,=CH), 7.10(d,1H,J=16Hz,=CH).

Example 3

20

(a) Benzhydryl (E)-(2S,3S,5R)-3-(2-methoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

25 200 mg (0.52 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are converted into benzhydryl (E)-(2S,3S,5R)-3-(2-methoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate by reaction with 193 mg (0.58 mmol) of
30 methoxycarbonylmethylene-triphenylphosphorane according to Example 2.

Yield: 209 mg (91%) of colourless foam

IR (film): 1782, 1745, 1724, 1651 cm^{-1}

35 MS: (M+NH₄⁺) 455.3

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Example 4

- (a) Benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-
3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-
5 carboxylate

763 mg (2.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-
7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are
dissolved in 15 ml of THF under argon, treated with 821 mg (2.0
10 mmol) of benzyloxycarbonylmethylene-triphenylphosphorane and
the orange solution is stirred at 50°C for 2 hours. It is left to
cool to room temperature, the solvent is removed on a rotary
evaporator and the red-brown oil is chromatographed over silica
gel (particle size 0.040-0.063 mm) with ethyl acetate:hexane
15 9:16 as the eluent.

Yield: 800 mg (78%) of orange foam

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IR (film): 1782, 1746, 1721, 1649, 985 cm⁻¹

20

MS: (M+H)⁺ 514.3

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.33(s,3H), 3.11(dd,1H,J=16Hz,
1.6Hz, 6-H), 3.56(dd,1H,J=16Hz, 4.2Hz, 6-H), 4.78(s,1H,2-H),
25 5.20(s,2H), 5.36(dd,1H, J=1.6Hz, 4.2Hz, 5-H), 6.01(d,1H,J=
15Hz,=CH), 6.93(s,1H,CHPh₂), 7.12(d,1H,J=15Hz, =CH), 7.30-
7.43(m,15H,Ph).

- (b) Benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-
3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-
30 2-carboxylate

800 mg (1.56 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-benzyl-
oxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-
35 heptane-2-carboxylate are oxidized according to Example 2.

Yield: 255 mg (30%) of colourless foam

IR(KBr): 1802, 1757, 1723, 1650, 1332 cm^{-1}

MS: (M-H)⁻ 544.2

5 ¹H-NMR (250MHz, CDCl₃): δ [ppm] = 1.25(s,3H), 3.47(dd,1H,J=16Hz, 2Hz,6-H), 3.55(dd,1H,J=16Hz, 4Hz, 6-H), 4.66(dd,1H,J=2Hz, 4Hz,5-H), 4.81(s,1H,2-H), 5.26(s,2H), 6.02 (d,1H,J=16Hz,=CH), 6.93(s,1H, CHPh₂), 7.22(d,1H,J=16Hz,=CH), 7.13-7.14(m,15H,Ph).

10 (c) Sodium (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

250 mg (0.46 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-benzyl-
15 oxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

Yield: 54 mg (30%) of beige lyophilizate

20

IR (KBr): 1781, 1719, 1626, 1322, 1189, 979 cm^{-1}

MS: (M-H)⁻ 378.2

25 ¹H-NMR (250MHz, D₂O): δ [ppm] = 1.65(s,3H), 3.45(dd,1H,J=17Hz, 2Hz,6-H), 3.71(dd,1H,J=17Hz, 4Hz,6-H), 4.63(s,1H,2-H), 5.14 (dd,1H,J=4Hz, 2Hz,5-H), 5.29(s,2H), 6.42(d,1H,J=16Hz,=CH), 7.13(d,1H,J=16Hz,=CH), 7.42-7.55(m,5H,Ph).

30 Example 5

(a) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

35

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Method A:

1.0 g (2.62 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and
5 30 ml of toluene are added to 946 mg (3.14 mmol) of cyano-ethylene-triphenylphosphorane under argon. The brown suspension is stirred for 1 hour, concentrated and chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 3:1 as the eluent.

10

Yield: 1.0 g (94%) of isomer mixture, E:Z 3:1

Spectroscopic data of the mixture:

15 IR (film): 2224, 1781, 1744 cm^{-1}

MS: (M+Na⁺) 427.2

¹H-NMR (250MHz, CDCl₃) (E isomer): δ [ppm] = 1.32(s,3H),
20 3.13(dd,1H,J=16Hz, 1.6Hz, 6-H), 3.63(dd,1H,J=16Hz, 4.4Hz,6-H),
4.74(s,1H,2-H), 5.41(dd,1H,J=4.4Hz, 1.6Hz,5-H), 5.54(d,1H,J=15Hz,
=CH), 6.82(d,1H,J=15Hz,=CH), 6.95(s,1H,CHPh₂), 7.30-7.44(m,10H,
Ph).

25 ¹H-NMR (250MHz, CDCl₃) (Z isomer): δ [ppm] = 1.61(s,3H),
3.18(dd,1H,J=16Hz,1.5Hz,6-H), 3.64(dd,1H,J=16Hz, 4.6Hz,6-H),
4.86(s,1H,2-H), 5.41(d,1H,J=12Hz,=CH), 5.44(dd,1H,J=1.5Hz,
4.6Hz,5-H), 6.63(d,1H,J=12Hz,=CH), 6.95(s,1H,CHPh₂), 7.30-
7.44(m,10H,Ph).

30

Method B:

A suspension of 2.88 g (9.56 mmol) of cyanomethylene-triphenylphosphorane in 24 ml of lithium perchlorate solution (0.4M
35 in acetonitrile) is cooled to -20°C under argon. A solution of
3.32 g (8.70 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate
in 30 ml of acetonitrile is added dropwise thereto, the mixture

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is stirred at the same temperature for 4 hours and the solvent is removed on a rotary evaporator. The residue remaining behind is taken up in 100 ml of ethyl acetate, extracted three times with water and once with saturated sodium chloride solution, dried
5 over magnesium sulphate, filtered and concentrated. The residual oil is purified over silica gel (particle size 0.040-0.063 mm) with methylene chloride as the eluent.

Yield: 3.34 g (94%) of isomer mixture, E:Z 1:4

10

(b) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

15 Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate is prepared in the same manner as described in Example 2 by oxidizing benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

20 The two isomers can be separated by chromatography over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane (9:16). The Z isomer is eluted as the first component.

Yield: Z: 76 mg (7%) of colourless oil

25

E: 253 mg (23%) of colourless foam

Spectroscopic data E isomer:

MS: (M+NH₄)⁺ 454.2

30

IR (KBr): 2228, 1802, 1758, 1334, 1192, 990 cm⁻¹

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.24(s,3H), 3.50(dd,1H,J=16Hz, 2.2Hz,6-H), 3.60(dd,1H,J=16Hz, 4Hz,6-H), 4.65(dd,1H,J=2Hz, 4Hz,5-H), 4.75(s,1H,2-H), 5.37(d,1H,J=16Hz,=CH), 6.85(d,1H,J= 35 16Hz,=CH), 6.98(s,1H,CHPh₂), 7.25-7.45(m,10H,Ph).

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Spectroscopic data **Z isomer**:

MS: (M-H)⁻ 435.3

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5 IR (KBr): 2220, 1801, 1757, 1333, 1190 cm⁻¹

1H-NMR (250MHz, CDCl₃): δ[ppm] = 1.67(s, 3H), 3.48(dd, 1H, J=16Hz, 2.4Hz, 6-H), 3.64(dd, 1H, J=16Hz, 4.6Hz, 6-H), 4.72(dd, 1H, J=2.4Hz, 4.6Hz, 5-H), 4.85(s, 1H, 3-H), 5.90(d, 1H, J=12Hz, =CH),
10 6.41(d, 1H, J=12Hz, =CH), 6.97(s, 1H, CHPh₂), 7.26-7.44(m, 10H, Ph).

(c) Sodium (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

15

215 mg (0.5 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

20 Yield: 110 mg (82%) of white lyophilizate

IR (KBr): 2240, 1782, 1629, 1397, 1141 cm⁻¹

1H-NMR (250MHz, CDCl₃): δ[ppm] = 1.64(s, 3H), 3.47(dd, 1H, J=16Hz, 2Hz, 6-H), 3.72(dd, 1H, J=16Hz, 4Hz, 6-H), 4.62(s, 1H, 2-H), 5.15
25 (dd, 1H, J=2Hz, 4Hz, 5-H), 6.07(d, 1H, J=16Hz, =CH), 7.08(d, 1H, J=16Hz, =CH).

Sodium (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate
30

95 mg (0.2 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 3 ml of m-cresol and
35 stirred at 50°C for 45 minutes. The reaction mixture is treated with 10 ml of isobutyl methyl ketone and 120 µl of sodium 2-ethylcaproate (2N in ethyl acetate, 1.1 eq.). The mixture is extracted twice with 3 ml of water each time, the combined

aqueous phases are washed with 10 ml of isobutyl methyl ketone and lyophilized. The yellow lyophilizate is dissolved in 1.3 ml of water and chromatographed over polymeric hydrophobic gel.

5 Yield: 50mg (80%) of colourless lyophilizate

IR (KBr): 2222, 1782, 1626, 1395, 1323, 1141 cm^{-1}

^1H -NMR (250MHz, D_2O): $\delta[\text{ppm}] = 1.94(\text{s}, 3\text{H}), 3.47(\text{dd}, 1\text{H}, J=16\text{Hz}, 1.6\text{Hz}, 6\text{-H}), 3.73(\text{dd}, 1\text{H}, J=16\text{Hz}, 4.4\text{Hz}, 6\text{-H}), 4.80(\text{s}, 1\text{H}, 2\text{-H}),$
10 5.19(dd, 1H, $J=1.6\text{Hz}, 4.4\text{Hz}, 5\text{-H}), 6.15(\text{d}, 1\text{H}, J=12\text{Hz}, =\text{CH}), 6.68$
(d, 1H, $J=12\text{Hz}, =\text{CH})$.

Example 6

15

(a) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

20 2.60 g (6.86 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and 2.15 g (6.86 mmol) of carbamoylmethylene-triphenylphosphorane are suspended in 60 ml of THF under argon and stirred at 50°C for 45 minutes. Insoluble material is filtered off under suction and
25 the filtrate is concentrated on a rotary evaporator. The brown oil is chromatographed on silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:1 as the eluent and the two isomers are separated. The Z isomer is eluted before the E isomer, both can be obtained as crystalline solids from CH_2Cl_2 :n-hexane.

30

Z isomer:

Yield: 217 mg (7.5%) of colourless solid

35 IR (KBr): 3441, 1777, 1743, 1678, 986 cm^{-1}

MS: (M- CHPh_2) 255

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M.p.: 188-189°C

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.58(s,3H), 3.11(dd,1H,J=16Hz,
1.60Hz,6-H), 3.57(dd,1H,J=16Hz, 4.40Hz,6-H), 5.23(s,1H,2-H),
5 5.36(dd,1H,J=4.40Hz, 1.60Hz,5-H), 5.5(pseudo-d,2H,NH₂), 5.75
(d,1H,J=12Hz,=CH), 6.24(d,1H,J=12Hz,=CH), 6.92(s,1H,CHPh₂),
7.29-7.43(m,10H, Ph).

E isomer:

10

Yield: 347 mg (12%) of crystalline solid

IR (KBr): 3444, 1775, 1728, 1671 cm⁻¹

15 MS: (M+H)⁺ 423.4

M.p.: 142°C (dec.)

¹H-NMR (250MHz, CDCl₃): δ = 1.36(s,3H), 3.11(dd,1H,J=16Hz,
20 2.0Hz,6-H), 3.56(dd,1H,J=16Hz, 4.2Hz,6-H), 4.83(s,1H,2-H),
5.37(dd,1H,J=2.0Hz, 4.2Hz,5-H), 5.55(s,br,2H,NH₂), 5.97(d,1H,
J=15Hz,=CH), 6.94(s,1H,CHPh₂), 6.95(d,1H,J=15Hz,=CH), 7.28-
7.40(m,10H,Ph).

25 (b) Benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-
methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-
carboxylate

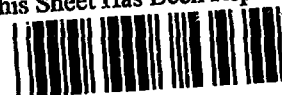
370 mg (0.875 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-
30 carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-
heptane-2-carboxylate are oxidized in accordance with Example
2. A mixture of ethyl acetate:n-hexane 1:1 is used as the eluent.

Yield: 225 mg (57%) of colourless foam

35

IR (KBr): 1799, 1750, 1678, 1326, 1188, 1140 cm⁻¹

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MS: (M+H)⁺ 455.2

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.50(s,3H), 3.45(dd,1H,J=16Hz, 2Hz,6-H), 3.56(dd,1H,J=16Hz, 4Hz,6-H), 4.67(dd,1H,J=4Hz, 2Hz,5-H), 5.28(s,1H,2-H), 5.63(s,br,1H,NH₂), 5.84(d,1H,J=13Hz,=CH), 6.69(s,br,1H,NH₂), 6.39(d,1H,J=13Hz,=CH), 6.93(s,1H,CHPh₂), 7.29-7.41(m,10H,Ph).

Benzhydryl (E)-(2S,3S,5R)-3-(2-Carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

0.64 g (1.51 mmol) of benzhydryl (E)-(2S,3R,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 30 ml of methylene chloride and cooled to 0°C. 1.86 g (7.55 mmol) of meta-chloroperbenzoic acid (content: 70-75%, 5 eq.) in 30 ml of methylene chloride are added dropwise thereto, the cooling bath is removed after completion of the addition and the mixture is stirred at room temperature for 6 hours. The reaction solution is extracted with sodium sulphite solution (30% in saturated aqueous sodium bicarbonate solution) and washed with saturated aqueous sodium chloride solution. The solution is dried over magnesium sulphate, filtered, the solvent is removed on a rotary evaporator and the residue remaining behind is recrystallized using methylene chloride:n-hexane.

25

Yield: 210 mg (30%) of colourless solid

IR (KBr): 1799, 1756, 1686, 1329, 1143, 1191 cm⁻¹

30 MS: (M+H)⁺ 455.3

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M.p.: 186-188°C

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.30(s,3H), 3.47(dd,1H,J=16Hz, 3.0Hz,6-H), 3.61(dd,1H,J=16Hz, 4.4Hz,6-H), 4.67(dd,1H,J=3.0Hz, 4.4Hz,5-H), 4.82(s,1H,2-H), 5.53(s,br,2H,NH₂), 6.03(d,1H, J=16Hz,=CH), 6.98(d,1H,J=16Hz,=CH), 6.94(s,1H,CHPh₂), 7.26-7.40(m,10H,Ph).

(c) Sodium (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5

135 mg (0.30 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

10

Yield: 67 mg (70%) of colourless lyophilizate

IR (KBr): 3434, 1781, 1668, 1626, 1397, 1317, 1139 cm^{-1}

15 MS: (M-Na)⁻ 287.2

¹H-NMR (250MHz, D₂O): δ [ppm] = 1.76(s,3H), 3.44(dd,1H,J=16Hz, 1.2Hz,6-H), 3.69(s,1H,J=16Hz, 4Hz,6-H), 4.68(s,1H,2-H), 5.10 (dd,1H,J=4Hz, 1.2Hz,5-H), 5.94(d,1H,J=13Hz,=CH), 6.53 (d,1H, J=13Hz,=CH).

20

Sodium (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

25 350 mg (0.78 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

30 Yield: 190 mg (80%)

IR (KBr): 1782, 1684, 1622, 1398, 1318, 1140 cm^{-1}

MS: (M-Na)⁻ 287.2

35

¹H-NMR (250MHz, D₂O): δ [ppm] = 1.66(s,3H), 3.46(dd,1H,J=17Hz, 1.4Hz, 6-H), 3.71(dd, 1H, J=17Hz, 4.0Hz,6-H), 4.62(s,1H,2-H),

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5.14(dd,J=1.4Hz, 4.0Hz,5-H), 6.46(d,1H,J=16Hz,=CH),
6.88(d,1H,J=16Hz,=CH).

Example 7

5

(a) Benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-propenyl)-
3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-
carboxylate

10 286 mg (0.75 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-
methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptan-2-carboxylate
are dissolved in 12 ml of THF under argon and treated with
271 mg (0.75 mmol) of (1-ethoxycarbonylethylidene)-triphenyl-
phosphorane. The yellow solution is stirred at 70°C for 6 hours
15 and subsequently concentrated. The residue remaining behind is
chromatographed over silica gel (0.040-0.063 mm particle size)
with ethyl acetate:hexane 9:16 as the eluent.

Yield: 157 mg (45%) of pale yellow solid

20

IR (film): 1788, 1754, 1704, 1642 cm⁻¹

MS: (M+NH₄⁺)483.4

25 ¹H-NMR (400MHz, CDCl₃): δ[ppm] = 1.32(t,3H,J=7.1Hz) ,1.38(s,3H),
2.03(d,3H,J=1.5Hz), 3.05(dd,1H,J=1.8Hz, 16Hz,6-H), 3.57(dd,1H,
J=4.3Hz, 16Hz,6-H), 4.23(q,2H,J=7.1Hz), 4.89(s,1H,2-H), 5.29(dd,
1H,J=4.3, 1.8Hz,5-H), 6.94(s,1H,CHPh₂), 7.20(d,1H,J=1.5Hz,=CH),
7.30-7.36(m,10H,Ph).

30

Example 8

(a) Benzhydryl (E,Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-
7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

35

A suspension of 1.37 g (4.40 mmol) of chloromethylene-
triphenylphosphorane in 25 ml of diethyl ether is cooled to 0°C
and treated with 1.60 g (4.20 mmol) of benzhydryl (2S,3R,5R)-3-

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formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate. The cooling bath is removed and the mixture is stirred at room temperature for a further 3 hours. The orange suspension is filtered and subsequently concentrated. The
5 residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with ethyl acetate:hexane 1:2 as the eluent.

Yield: 1.20 g (69%) of yellow isomer mixture, E:Z 7:9

10

Spectroscopic data of the mixture:

IR (film): 1782, 1747, 1590, 1496, 1251 cm^{-1}

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15 MS: ($\text{M}+\text{NH}_4^+$) 413

(b) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

20

2.98 g (14.05 mmol) of sodium metaperiodate are dissolved in 30 ml of water under argon and cooled to 0°C. The solution is treated with 0.93 g (11.17 mmol) of sodium bicarbonate followed by 45 ml of acetonitrile as well as 60 ml of methylene
25 chloride. 9 mg (0.070 mmol) of ruthenium dioxide and subsequently the solution of 1.20 g (2.90 mmol) of benzhydryl (E/Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are added to the two-phase mixture. The cooling bath is removed and the reaction mixture is
30 stirred until the reaction has finished (tlc control). Subsequently, the mixture is treated with 2 g of active charcoal and 20 ml of saturated sodium chloride solution, stirred for 5 minutes and suction filtered over Dicalite. The phases are separated in a separating funnel, the aqueous phase is extracted
35 twice with methylene chloride and the combined organic extracts are washed with water and saturated sodium chloride solution, dried over magnesium sulphate/fuller's earth, filtered and evaporated. The residual oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:2

as the eluent, the two isomers being separated in this manner.
The Z isomer is eluted as the first component.

Yield: Z: 495 mg (38%) of colourless foam

5

E: 385 mg (30%) of colourless foam

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Spectroscopic data E isomer:

10 MS: (M+NH₄)⁺ 463.4

IR (KBr): 1800, 1756, 1612, 1331, 1143, 700 cm⁻¹

Spectroscopic data Z isomer:

15

MS: (M+NH₄)⁺ 463.4

IR (KBr): 1800, 1755, 1630, 1330, 1143, 700 cm⁻¹

20 (c) Sodium (E)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

385 mg (0.86 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]-

25 heptane-2-carboxylate are dissolved in 2.3 ml of m-cresol under argon and stirred at 50°C for 4 hours. Subsequently, the mixture is diluted with 15 ml of isobutyl methyl ketone, treated with 0.50 ml of sodium 2-ethylcaproate (2N solution in ethyl acetate) and extracted three times with 8 ml of water each time. The
30 combined aqueous phases are washed once with 10 ml of isobutyl methyl ketone, lyophilized and the lyophilizate obtained is chromatographed over polymeric hydrophobic gel with water as the eluent.

35 Yield: 57 mg (32%)

MS: (M-Na)⁻ 278.2

IR (KBr): 1780, 1626, 1564, 1417, 1329, 1145 cm⁻¹

40

Sodium (Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

400 mg (0.90 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 176 mg (65%) of colourless lyophilizate

10 MS: (M-Na)⁻ 278.2

IR (KBr): 1779, 1626, 1398, 1321, 1142 cm⁻¹

15 Elementary analysis: C₉H₉ClNO₅SNa (301.676)

Calc. C 35.83 H 3.01 N 4.64

Found#) C 35.72 H 3.04 N 4.65

20 #) anhydrous, calculated with 5.53 % water

Example 9

25 (a) (E)-(2S,3S,5R)-3-methyl-7-oxo-3-(3-oxo-but-1-enyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

381 mg (1.00 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 12 ml of THF under argon and treated with
30 350 mg (1.10 mmol) of acetylmethylene-triphenylphosphorane. The mixture is stirred at 50°C for 6 days and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with ethyl acetate:methylene chloride 95:5 as the eluent.

35

Yield: 221 mg (52%) of white resin

IR (film): 1782, 1681, 1627, 1319, 1141, 980 cm⁻¹

40 MS: (M-Na)⁻ 286.1

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(b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5

221 mg (0.49 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-7-oxo-3-(3-oxo-but-1-enyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out once over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent and crystallization is carried out from methylene chloride/n-hexane.

Yield: 95 mg (40%) of colourless crystals

15 MS: (M+NH₄)⁺ 471.2

IR (KBr): 1798, 1760, 1682, 1627, 1330, 1193, 1142, 976 cm⁻¹

M.p.: 183-184°C

20

(c) Sodium (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

25 250 mg (0.55 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 47 mg (27%) of colourless lyophilizate

30

MS: (M-Na)⁻ 286.1

IR (KBr): 1782, 1681, 1627, 1394, 1319, 1141, 980 cm⁻¹

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Example 10

(a) (E)-(2S,3S,5R)-3-(2-Formyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5

3.81 g (10.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 40 ml of methylene chloride under argon and treated with 3.34 g (11.0 mmol) of formylmethylene-triphenyl-phosphorane. The yellow solution is stirred at room temperature for 3 days and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with tert.butyl methyl ether:n-hexane 2:3 as the eluent.

15

Yield: 528 mg (13%) of colourless resin

IR (film): 2738, 1781, 1744, 1717, 1690, 1496, 1178, 986 cm⁻¹

20 MS: (M+MH₄⁺) 425.6

Example 11

(a) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

25

1.14 g (3.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 15 ml of 1,2-butylene oxide, treated with 1.38 g (3.6 mmol) of (1,2,4-oxadiazol-3-yl)methyl-triphenylphosphonium chloride and refluxed for 10 hours. Subsequently, the mixture is filtered, the filtrate is evaporated and the residual brown oil is chromatographed over silica gel (0.040-0.063 mm particle size) with methylene chloride as the eluent.

30

35

Yield: 280 mg (21%) of colourless crystals

MS: (M+NH₄⁺) 465.3



IR (KBr): 1792, 1753, 1658, 1492, 1200, 991 cm^{-1}

(b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-
5 oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-
bicyclo[3.2.0]heptane-2-carboxylate

280 mg (0.63 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-
[2-(1,2,4-oxadiazol-3-yl)-vinyl]-7-oxo-4-thia-1-aza-bicyclo-
10 [3.2.0]heptane-2-carboxylate are oxidized according to Example 8.
Chromatography is carried out once over silica gel (particle size
0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent
and crystallization is carried out from methylene chloride/n-
hexane.

15

Yield: 95 mg (40%) of colourless crystals

MS: (M-H)⁻ 478.3

20 IR (KBr): 1805, 1758, 1650, 1334, 1196 cm^{-1}

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M.p.: 157°C

Elementary analysis: $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_6\text{S}$ (479.507)

25

Calc. C 60.12 H 4.41 N 8.76

Found C 59.94 H 4.26 N 8.55

(c) (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-
vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-
30 carboxylic acid

355 mg (0.74 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-
(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-
bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 3 ml of m-
cresol and stirred at 50°C for 4 hours. 20 ml of n-hexane are
35 added to the pale brown solution, the separated crystals are
filtered off under suction and rinsed with n-hexane. The crude
crystallizate is recrystallized from ethyl acetate/n-hexane.

Yield: 170 mg (73%) of colourless crystals

MS: (M-H)⁻ 312.2

5

IR (KBr): 2900(br), 1811, 1714, 1660, 1331, 1194, 980 cm⁻¹

M.p.: 161°C (dec.)

10 Elementary analysis: C₁₁H₁₁N₃O₆S (313.284)

Calc. C 42.17 H 3.54 N 13.41

Found C 42.41 H 3.64 N 13.18

15 (c) Sodium (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

85 mg (0.27 mmol) of (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo-
20 [3.2.0]heptane-2-carboxylic acid are added in one portion to a clear solution of 23 mg (0.27 mmol) of sodium hydrogen carbonate in 10 ml of water, the mixture is stirred for about 10 minutes, filtered and lyophilized.

25 Yield: 90 mg (91%) of colourless lyophilizate

MS: (M-Na)⁻ 312.2

IR (KBr): 1787, 1627, 1395, 1321, 1192, 970 cm⁻¹

30

Elementary analysis: C₁₁H₁₀N₃O₆SNa (335.266)

Calc. C 39.41 H 3.01 N 12.53

Found#) C 39.86 H 3.04 N 12.51

#) anhydrous, calculated with 5.82% water

35

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REPLACED

Example 12

(a) Benzhydryl (E) and (Z)-(2S,3S,5R)-3-methyl-3-(2-thiazol-
2-yl-vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-
5 carboxylate

1.14 g (3.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-
7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are
dissolved in 50 ml of 1,2-butylene oxide, treated with 1.53 g
10 (3.86 mmol) of (thiazol-2-yl)methyl-triphenylphosphonium
chloride and refluxed for 40 hours. Subsequently, the mixture is
filtered, evaporated and the brown residue remaining behind is
chromatographed over silica gel (0.040-0.063 mm particle size)
with methylene chloride:ethyl acetate 95:5 as the eluent. The
15 two isomers are separated in this manner, the Z isomer being
eluted as the first component.

Z isomer:

20 Yield: 240 mg (17%) of yellow oil

IR (film): 1778, 1743, 1493, 1197, 986 cm^{-1}

MS: (M+H⁺) 463.5

25

E isomer:

Yield: 855 mg (62%) of yellow resin

30 IR (KBr): 1779, 1746, 1492, 1292, 988 cm^{-1}

MS: (M+H)⁺ 463.5

This Sheet Has Been Replaced



(b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5 200 mg (0.43 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-thiazol-2-yl-vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with methylene chloride:ethyl acetate 95:5 as
10 the eluent.

Yield: 72 mg (33%) colourless foam

MS: (M+H)⁺ 495.4

15

IR (KBr): 1799, 1756, 1329, 1192, 1142, 963 cm⁻¹

Benzhydryl (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

20

210 mg (0.45 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out over silica gel (particle size
25 0.040-0.063 mm) with methylene chloride:ethyl acetate 95:5 as the eluent.

Yield: 72 mg (33%) of colourless foam

30 MS: (M+H)⁺ 495.4

IR (KBr): 1793, 1754, 1490, 1328, 1184, 1142, 963 cm⁻¹

(E)-(2S,3S,5R)-3-Methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-
35 4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

200 mg (0.40 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-thiazol-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo-

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[3.2.0]heptane-2-carboxylate are deprotected analogously to
Example 11.

Yield: 53 mg (40%) of colourless crystals

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MS: (M+H)⁺ 329.4

IR (KBr): 2800(br), 1791, 1740, 1634, 1321, 1142, 965 cm⁻¹

10 Sodium (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

53 mg (0.16 mmol) of (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-

15 carboxylic acid are converted into the corresponding sodium salt analogously to Example 11.

Yield: 55 mg (98%) of colourless lyophilizate

20 IR (KBr): 1778, 1627, 1392, 1318, 1192, 1141, 955 cm⁻¹

Elementary analysis: C₁₂H₁₁N₂O₅S₂Na (350.339)

Calc. C 41.14 H 3.16 N 8.00

25

Found#) C 40.73 H 3.51 N 7.92

#) anhydrous, calculated with 5.9% water

30 Sodium (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

160 mg (0.32 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo-

35 [3.2.0]heptane-2-carboxylate are converted into the corresponding sodium salt analogously to Example 8.

Yield: 60 mg (57%) of colourless lyophilizate

IR (KBr): 1781, 1623, 1398, 1320, 1193, 1140, 950 cm^{-1}

$^1\text{H-NMR}$ (250MHz, CDCl_3): $\delta[\text{ppm}]$ = 1.52(s,3H), 3.42(dd,1H, $J=16\text{Hz}$,
5 1.2Hz,6-H), 3.58(dd,1H, $J=16\text{Hz}$, 4.1Hz,6-H), 5.04(dd,1H, $J=1.2\text{Hz}$,
4.1Hz,5-H), 5.19(s,1H,2-H), 6.06(d,1H, $J=12.5\text{Hz}$,=CH), 7.14(d,1H, $J=$
12.5Hz,=CH), 7.75(AB system,2H, $J=3.5\text{Hz}$, thiazole-H).

Example 13

10

(a) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-
vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-
carboxylate

15 A suspension of 353 mg (1.0 mmol) of (2-picolyl)methylene-
triphenylphosphorane and 381 mg (1.00 mmol) of benzhydryl
(2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo-
[3.2.0]heptane-2-carboxylate in 10 ml of diethyl ether is stirred
at room temperature under argon for 2 hours. The mixture is
20 treated with 10 ml of methylene chloride, insoluble material is
removed by suction filtration and the filtrate is concentrated.
The residue remaining behind is chromatographed over silica gel
(particle size 0.040-0.063 mm) with methylene chloride:ethyl
acetate 95:5 as the eluent.

25

Yield: 128 mg (28%) of a colourless foam

MS: (M^+) 456

This Sheet Has Been Replaced



30 IR (KBr): 1779, 1747, 1634, 1291, 988 cm^{-1}

(b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-
vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-
carboxylate

35

196 mg (0.43 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-
(2-pyridin-2-yl-vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-
heptane-2-carboxylate are oxidized according to Example 8.

Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with methylene chloride:ethyl acetate 95:5 as the eluent.

5 Yield: 130 mg (62%) of colourless foam

This Sheet Has Been Replaced



MS: (M+H)⁺ 489.4

IR (KBr): 1799, 1756, 1580, 1490, 1327, 1184, 1141, 969 cm⁻¹

10

(c) (E)-(2S,3S,5R)-3-Methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

15 200 mg (0.41 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected analogously to Example 10.

20 Yield: 85 mg (65%) of pale beige crystal powder

MS: (M+H)⁺ 323.3

IR (KBr): 2700(br), 1790, 1720, 1621, 1318, 1140, 978 cm⁻¹

25

Sodium (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

30 83 mg (0.17 mmol) of (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid are converted into the corresponding sodium salt analogously to Example 10.

Yield: 89 mg (100%) of colourless lyophilizate

35

IR (KBr): 1784, 1629, 1587, 1478, 1396, 1320, 1187, 1141, 980 cm⁻¹

Elementary analysis: $C_{14}H_{13}N_2O_5SNa$ (344.317)

Calc. C 48.84 H 3.81 N 8.14

5 Found#) C 49.18 H 4.23 N 8.17

#) anhydrous, calculated with 6.86% water

Example 14

10

(a) Benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate

15 An orange solution of 1.14 g (3.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and 1.14 g (3.15 mmol) of (N-methoxymethylaminocarbonylmethylene)-triphenylphosphorane is stirred at room temperature under argon for 3 days. The solvent
20 is removed on a rotary evaporator and the residue is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:1 as the eluent.

Yield: 1.12 g (80%) of colourless foam

25

MS: (M+H)⁺ 467.4

IR (KBr): 1781, 1744, 1662, 1629, 995 cm^{-1}

30 (b) Benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

0.69 g (1.48 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate is oxidized in analogy to
35 Example 8. Chromatography is carried out over silica gel

This Sheet Has Been Replaced



(particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 3:2 as the eluent.

Yield: 405 mg (55%) of colourless foam

5

MS: (M+H)⁺ 499.4

IR (KBr): 1807, 1753, 1662, 1624, 1318, 1140, 1000 cm⁻¹

- 10 (c) Sodium (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate.

- 15 200 mg (0.40 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 95 mg (67%) of colourless lyophilizate

20

MS: (M+H)⁺ 355.3

IR (KBr): 1785, 1650, 1626, 1390, 1322, 1191, 1141, 980 cm⁻¹

- 25 Elementary analysis: C₁₂H₁₅N₂O₇SNa (354.309)

Calc. C 40.68 H 4.27 N 7.91

Found#) C 40.37 H 4.35 N 7.84

30

#) anhydrous, calculated with 2.74% water

This Sheet Has Been Replaced



Example 15

(E)-(2S,3S,5R)-3-Methyl-3-[2-(1-methyl-pyridin-2-yl)-vinyl]-
4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptan-2-carboxylic
5 acid

150 mg (0.31 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-
(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo-
[3.2.0]heptane-2-carboxylic acid are dissolved in 3 ml of
10 methylene chloride, cooled to 0°C and treated with 56 µl
(0.51 mmol) of methyl trifluoromethylsulphonate. The cooling
bath is removed and the mixture is stirred at room temperature
for 2 days. The solvent is removed on a rotary evaporator and the
residue is dried in a high vacuum. The thus-obtained product
15 (200 mg, 100%) is processed without further purification. The
brown resin is dissolved in 2 ml of m-cresol and stirred at 50°C
for 2 hours. Thereafter, the mixture is treated with 10 ml of
isobutyl methyl ketone as well as 5 ml of water, shaken, the
phases are separated and the organic phase is extracted twice
20 with 5 ml of water. The aqueous phases are washed twice with
10 ml of isobutyl methyl ketone each time, filtered and lyoph-
ilized. The yellowish lyophilizate is chromatographed over
polymeric hydrophobic gel with water as the eluent.

25 Yield: 105 mg (72%) of orange lyophilizate

IR (KBr): 1778, 1627, 1377, 1185, 970 cm⁻¹

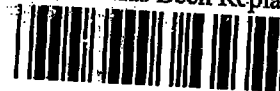
MS: (M⁺) 337.4

30

Example 16

(a) Benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-formyl-buta-1,3-
dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-
35 heptane-2-carboxylate

Benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-formyl-buta-1,3-dienyl)-3-
methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate



is prepared in analogy to Example 9 from 3.81 g (10.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and 4.55 g (15.0 mmol) of formylmethylene-triphenylphosphorane. Chromatography is
5 carried out over silica gel (0.040-0.063 mm particle size) with methylene chloride:ethyl acetate 98:2 as the eluent.

Yield: 347 mg (8%) of yellowish resin

10 MS: (M+NH₄)⁺ 451.4

IR (KBr): 1779, 1745, 1680, 1637, 1201, 988 cm⁻¹

Example 17

15

(a) Benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

20 Benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate is prepared in analogy to Example 4, Method B, from 815 mg (2.14 mmol) of benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-formyl-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo-
25 [3.2.0]heptane-2-carboxylate. The residual oil is purified over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:2 as the eluent.

Yield: 820 mg (89%) of isomer mixture, E:Z 2:3

30

Spectroscopic data of the isomer mixture:

IR (film): 2215, 1780, 1745, 1202, 989 cm⁻¹

35 MS: (M+NH₄)⁺ 448.5

This Sheet Has Been Replaced



(b) Benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5 770 mg (1.79 mmol) of benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. The two isomers can be separated by chromatography over silica gel (particle size 0.040-0.063 mm)
10 with ethyl acetate:n-hexane 9:16 as the eluent. The Z isomer is eluted as the first component.

Yield: Z: 430 mg (52%) of colourless oil

15 E: 280 mg (34%) of colourless foam

Spectroscopic data E isomer:

MS: (M+NH₄)⁺ 480.5

20

IR (KBr): 2219, 1800, 1756, 1329, 1191, 994 cm⁻¹

Spectroscopic data Z isomer:

25 MS: (M+NH₄)⁺ 435.3

IR (KBr): 2210, 1800, 1756, 1330, 1192, 993 cm⁻¹

(c) Sodium (1E,3E)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-
30 3 - methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

250 mg (0.54 mmol) of benzhydryl(1E,3E)-(2S,3S,5R)-3-(4-
35 cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8.

This Sheet Has Been Replaced



Yield: 55 mg (41%) of yellowish lyophilizate

IR (KBr): 2221, 1781, 1631, 1397, 1319, 1139, 992 cm^{-1}

5 MS: $(\text{M}+\text{Na})^+$ 341.2

Sodium (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

10

230 mg (0.49 mmol) of benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8.

15

Yield: 84 mg (58%) of yellowish lyophilizate

This Sheet Has Been Replaced



IR (KBr): 2219, 1780, 1625, 1396, 1316, 1138, 951 cm^{-1}

20 MS: $(\text{M}+\text{H})^+$ 319.3

Elementary analysis: $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_5\text{SNa}$ (318.279)

25

Calc. C 45.28 H 3.48 N 8.80

Found#) C 45.29 H 3.63 N 8.82

#) anhydrous, calculated with 6.93% water

30 Example 18

(a) Benzhydryl (E/Z)-(2S,3S,5R)-3-methyl-7-oxo-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenmethyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

35

762 mg (2.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are reacted with 1.02 g (2.0 mmol) of rac-[2-oxo-1-(2,2,2-

trifluoroethyl)-2-pyrrolidiny]-triphenylphosphonium bromide according to Example 12. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

5

Yield: 763 mg (71%) of isomer mixture, E:Z 5:1

Spectroscopic data of the mixture:

This Sheet Has Been Replaced



10 IR (film): 1782, 1748, 1702, 1664, 1158 cm⁻¹

MS: (M-CPh₂) 363

15 (b) Benzhydryl (E) und (Z)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

20 763 mg (1.42 mmol) of benzhydryl (E/Z)-(2S,3S,5R)-3-methyl-7-oxo-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidene-methyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. The two isomers can be separated by chromatography over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:2 as the eluent.

25 Yield: E: 192 mg (24%) of colourless foam

Z: 32 mg (4%) of colourless foam

Spectroscopic data E isomer:

30

MS: (M+NH₄)⁺ 580.4

IR (KBr): 1801, 1759, 1706, 1667, 1329, 1144 cm⁻¹

35 Spectroscopic data Z isomer:

MS: (M+NH₄)⁺ 580.4

IR (KBr): 1798, 1755, 1694, 1327, 1142 cm^{-1}

(c) (E)-(2S,3S,5R)-3-Methyl-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-
5 aza-bicyclo[3.2.0]heptane-2-carboxylic acid

192 mg (0.34 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate
10 are deprotected analogously to Example 11.

Yield: 78 mg (59%) of colourless crystal powder

This Sheet Has Been Replaced



MS: $(\text{M}+\text{NH}_4)^+$ 414.4

15

IR (KBr): 2800(br), 1790, 1729, 1674, 1646, 1321, 1166 cm^{-1}

Sodium (E)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-
20 bicyclo[3.2.0]heptane-2-carboxylate

50 mg (0.13 mmol) of (E)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid are
25 converted into the corresponding sodium salt analogously to Example 11.

Yield: 52 mg (98%) of colourless lyophilizate

30 IR (KBr): 1780, 1699, 1628, 1478, 1396, 1323, 1140 cm^{-1}

Elementary analysis: $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_6\text{F}_3\text{SNa}$ (418.318)

35

Calc. C 40.20 H 3.37 N 6.70

Found#) C 39.80 H 3.28 N 6.62

#) anhydrous, calculated with 7.24% water

Example 19

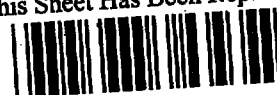
- 5 (a) Benzhydryl (E/Z)-(2S,3S,5R)-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

381 mg (1.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate
10 are reacted with 495 mg (1.1 mmol) of rac-[1-cyclopropyl-2-oxo-3-pyrrolidinyl]-triphenylphosphonium bromide according to Example 18. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

15

Yield: 362 mg (74%) of isomer mixture, E:Z 5:1

This Sheet Has Been Replaced



Spectroscopic data of the mixture:

20 IR (film): 1780, 1750, 1692, 1661, 1195, 1118 cm⁻¹

MS: (M+H)⁺ 489.4

Example 20

25

- (a) Benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxy-propen-1-yl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

30 5.80 g (14.2 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-formyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 240 ml of toluene under argon and cooled to 0°C. Then, 14.2 ml (21.3 mmol) of a 20% diisobutyl-aluminium hydride solution (in toluene) are added dropwise and
35 the cooling bath is removed. The reaction mixture is stirred at room temperature for 6 hours, poured into 150 ml of saturated ammonium chloride solution and extracted three times with 200 ml of methylene chloride each time. The combined organic

extracts are washed once with 300 ml of water as well as saturated sodium chloride solution, dried over magnesium sulphate, filtered and freed from solvent on a rotary evaporator. The residual yellow oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 1.90 g (32%) of colourless resin

10 IR (film): 3480(br), 1778, 1750, 1202, 1080, 988 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 427.6

15 (c) Sodium (E)-(2S,3S,5R)-3-(3-hydroxy-propen-1-yl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

500 mg (0.95 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-[3-[(R)- and (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 165 mg (62%) of colourless lyophilizate

25 MS: $(\text{M}-\text{Na})^-$ 274.3

IR (KBr): 3428, 1780, 1622, 1398, 1311, 1192, 1139, 1082 cm^{-1}

Elementary analysis: $\text{C}_{10}\text{H}_{12}\text{NO}_6\text{SNa}$ (297.257)

30

Calc.	C 40.41	H 4.07	N 4.71
-------	---------	--------	--------

Found#)	C 40.44	H 4.48	N 4.79
---------	---------	--------	--------

35

#) anhydrous, calculated with 8.73% water

This Sheet Has Been Replaced



Benzhydryl (E)-(2S,3S,5R)-3-methyl-7-oxo-3-[3-[(R)- and (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5 620 mg (1.50 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxy-propenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 30 ml of methylene chloride and treated with 4.5 mg (0.024 mmol) of p-toluenesulphonic acid monohydrate. Subsequently, 0.25 ml (2.70 mmol) of 3,4-di-
10 hydro-2H-pyran is added and the mixture is stirred for a further 1 hour. The solvent is removed on a rotary evaporator and chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

15 Yield: 700 mg (93%) colourless oil, diastereomer mixture (1:1)

IR (film): 3031, 1782, 1749, 1257, 1134, 967 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 511.6

20

Benzhydryl (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-[3-[(R)- und (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

25 585 mg (1.18 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-7-oxo-3-[3-[(R)- and (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-
30 hexane 9:16 as the eluent.

Yield: 525 mg (84%) of colourless foam, diastereomer mixture (1:1)

35 IR (KBr): 1800, 1756, 1327, 1189, 1141, 969 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 543.5

This Sheet Has Been Replaced



Example 21

- (a) Benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetyl-amino-carbonyloxy)-propenyl]-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

300 mg (0.73 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxy-propenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 10 ml of tetrahydrofuran under argon and treated with 90 μ l (1.05 mmol) of chloroacetyl isocyanate. The mixture is stirred for 3 hours, evaporated and chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 300 mg (77%) of colourless foam

IR (KBr): 3300(br), 1779, 1753, 1730, 1495, 1203 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 546.4

20

- (b) Benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetyl-amino-carbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

295 mg (0.57 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized analogously to Example 8. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

30

Yield: 216 mg (68%) of colourless foam

IR (KBr): 3413(br), 1798, 1758, 1730, 1705, 1326, 1198, 991 cm^{-1}

35

MS: $(\text{M}+\text{NH}_4)^+$ 578.4

This Sheet Has Been Replaced



(c) Sodium (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5 195 mg (0.35 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8 and converted into the corresponding sodium salt.

10

Yield: 60 mg (49%) of colourless lyophilizate

MS: (M-COCH₂Cl-Na)⁻ 317.3

15 IR (KBr): 3435, 1781, 1721, 1622, 1533, 1396, 1314, 1192, 1139 cm⁻¹

¹H-NMR (250MHz, D₂O): δ[ppm] = 1.61(s,3H), 3.42(dd,1H,J=16Hz, 1.6Hz, 6-H), 3.69(dd, 1H, J=16Hz, 4.0Hz, 6-H), 4.43(s,2H,CH₂Cl),
20 4.49(s,1H,2-H), 4.84(d,2H,J=4.4Hz,CH₂O), 5.08(dd,J=1.6Hz, 4.0Hz, 5-H), 6.08(d(br),1H,J=16Hz,=CH), 6.22(dt,1H,J=16Hz, 4.4Hz, =CH)

Example 22

25 Benzhydryl (E)-(2S,3S,5R)-3-(carbamoyloxy-propenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

450 mg (0.80 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are
30 dissolved in 5 ml of tetrahydrofuran under argon and treated with 1.7 ml of methanol. 135 mg (1.61 mmol) of sodium hydrogen carbonate in 2.8 ml of water are added to this solution. After completion of the reaction (tlc control) the solvent mixture
35 is removed on a rotary evaporator, the residual yellow oil is taken up in 15 ml of ethyl acetate as well as 15 ml of saturated sodium chloride solution, shaken and the phases are separated. The aqueous phase is back-extracted twice with 15 ml of ethyl



acetate each time and the combined organic extracts are washed once with 15 ml of saturated sodium chloride solution. They are dried over magnesium sulphate, concentrated on a rotary evaporator and the residual oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 2:1 as the eluent.

Yield: 200 mg (78%) of colourless foam

IR (KBr): 3481, 1799, 1749, 1731, 1601, 1329, 1191, 996 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 484

(c) Sodium (E)-(2S,3S,5R)-3-(carbamoyloxy-propenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

190 mg (0.60 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(carbamoyloxypropenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8.

Yield: 82 mg (62%) of colourless lyophilizate

$^1\text{H-NMR}$ (250MHz, D_2O): $\delta[\text{ppm}]$ = 1.61(s,3H), 3.42(dd,1H, J =17Hz, 1.6Hz,6-H), 3.69(dd,1H, J =17Hz,4Hz,6-H), 4.48(s,1H,2-H), 4.70(d,2H, J =4.6Hz, CH_2), 5.08(dd,1H, J =4Hz, 1.6Hz,5-H), 5.97(d,1H, J =16Hz,=CH), 6.19(dt,1H, J =16Hz, 4.6Hz,=CH).

Example 23

(a) (2S,3S,5R)-1-[3-(2-Benzhydryloxycarbonyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluormethanesulphonate

410 mg (1.0 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxypropenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 6 ml of methylene chloride,



cooled to -40°C and treated with $250\ \mu\text{l}$ ($1.5\ \text{mmol}$) of trifluoromethanesulphonic anhydride. After 5 minutes $200\ \mu\text{l}$ ($2.50\ \text{mmol}$) of pyridine are added, the mixture is stirred at the same temperature for a further hour and subsequently the cooling bath is removed. The solvent is removed on a rotary evaporator at room temperature, the reaction mixture is taken up in $20\ \text{ml}$ of methylene chloride and washed twice with $10\ \text{ml}$ of saturated sodium chloride solution each time. Drying over magnesium sulphate, filtration and concentration on a rotary evaporator are carried out. The residual red resin is oxidized without further purification.

Yield: $600\ \text{mg}$ (97%) of red resin

MS: (M^+) 471.6

IR (KBr): $1777, 1743, 1630, 1160, 987\ \text{cm}^{-1}$

(b) (2S,3S,5R)-1-[3-(2-Benzhydryloxycarbonyl-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluoromethanesulphonate

$600\ \text{mg}$ ($0.97\ \text{mmol}$) of (2S,3S,5R)-1-[3-(2-benzhydryloxy-carbonyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluoromethanesulphonate are oxidized in analogy to Example 8.

Yield: $440\ \text{mg}$ (70%) of green resin

MS: (M^+) 503.3

IR (KBr): $1797, 1753, 1632, 1167\ \text{cm}^{-1}$

(E)-(2S,3S,5R)-3-Methyl-4,4,7-trioxo-3-(3-pyridin-1-ylpropenyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

A solution of $440\ \text{mg}$ ($0.67\ \text{mmol}$) of (2S,3S,5R)-1-[3-(2-benzhydryloxycarbonyl-3-methyl-4,4,7-trioxo-4-thia-1-aza-

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bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluoromethane-sulphonate in 3 ml of m-cresol is stirred at 50°C for 1.5 hours. The mixture is diluted with 10 ml of isobutyl methyl ketone at room temperature and extracted three times with 8 ml of water
5 each time. The combined aqueous extracts are washed twice with 10 ml of isobutyl methyl ketone each time, filtered over a paper filter and lyophilized. The brown lyophilizate is subsequently chromatographed over polymeric hydrophobic gel with water as the eluent.

10

Yield: 125 mg (55%) of beige lyophilizate

IR (KBr): 1780, 1625, 1485, 1372, 1312, 980 cm^{-1}

15 MS: $\text{M}+\text{H}^+$ 337.4

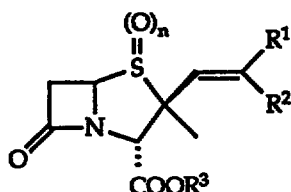
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Claims

1. 2β -Alkenyl-penam derivatives of the general formula



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wherein

one of R^1 and R^2 signifies $-\text{COR}^4$, $-\text{CN}$, $-\text{CH}_2\text{R}^5$, halogen, $-\text{CH}=\text{CHR}^6$ or Q and the other signifies hydrogen or lower alkyl or both together signify a γ -lactam ring,

10

R^3 signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R^4 signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino, lower alkylamino or lower alkyl-lower alkoxyamino,

15

R^5 signifies hydroxy, $-\text{OCONHR}^7$, $-\text{OCONH}_2$ or a five- or six-membered hetero-aromatic ring which contains N, S and/or O and which is linked via a nitrogen atom,

R^6 signifies $-\text{CN}$ or CHO ,

R^7 signifies $-\text{COCH}_2\text{Cl}$,

20

Q signifies a five- or six-membered hetero-aromatic ring which contains N, S and/or O and

n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

25

2. Compounds according to claim 1,

wherein

one of R^1 and R^2 signifies $-\text{COR}^4$, $-\text{CN}$ or $-\text{CH}_2\text{OR}^5$ and the other signifies hydrogen or lower alkyl,

30

R^3 signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R^4 signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino or lower alkylamino,

R^5 signifies hydroxy or $-\text{CONH}_2$,

R^6 signifies lower alkyl and

35

n signifies 0, 1 or 2.



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3. Compounds according to claim 1 or 2, wherein R¹ signifies CN, halogen or COR⁴, R² signifies hydrogen and R⁴ signifies methyl, lower alkoxy, benzyloxy or amino.

5

4. Compounds according to any one of claims 1 to 3, wherein n signifies 0 or 2.

5. Compounds according to any one of claims 1 to 4,
10 wherein R³ signifies hydrogen or benzhydryl.

6. Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

15 7. Benzhydryl (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

8. Benzhydryl (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-
20 methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

9. Sodium (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

25

10. Sodium (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

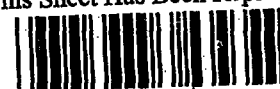
11. Sodium (E)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-
30 4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

12. Sodium (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

35

13. Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

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benzhydryl (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

5

benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

10 sodium (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

15

benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

20 benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

25 sodium (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

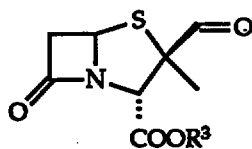
30 benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

35 sodium (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.



14. Compounds of the general formula



II



5 wherein R³ has the significance given in claim 1.

15. Benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

10 16. Compounds according to any one of claims 1 to 13 for use as therapeutically active substances.

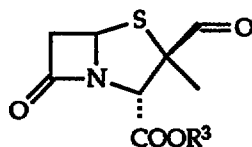
17. Compounds according to any one of claims 1 to 13 for use as β -lactamase inhibitors.

15

18. A process for the manufacture of compounds according to any one of claims 1 to 13, which process comprises

a) reacting a compound of the general formula

20



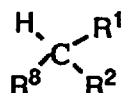
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wherein R³ has the significance given in claim 1, with a compound of the general formula

25



wherein R¹ and R² have the significance given in claim 1 and R⁸ = P[⊕](aryl)₃, PO(Oalkyl)₂, Si(alkyl)₃ or halogen,

30 in the presence of an activating agent, or

b) oxidizing a compound of general formula I in which n signifies 0, or



c) converting a compound of general formula I in which R^3 is different from hydrogen into the corresponding free acid, and

5 d) if desired, converting an acidic compound of formula I into a pharmaceutically acceptable salt.

19. A medicament containing a compound according to any one of claims 1 to 13.

10

20. A β -lactamase-inhibiting medicament containing a compound according to any one of claims 1 to 13.

21. A medicament according to claim 19 or 20 which
15 additionally contains a β -lactam antibiotic.

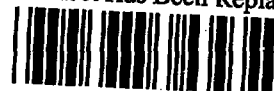
22. A medicament according to claim 21 containing a penicillin, cephalosporin, penem or cabapenem as the β -lactam antibiotic.

20

23. A medicament according to claim 22 containing piperacillin, mezlocillin, azlocillin, apalcillin, benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, ticarcillin, ampicillin, amoxicillin, mecillinam, ceftriaxone,
25 ceftazidime, cefetamet, cefetamet pivoxil, cefotaxime, cefmenoxime, ceftizoxime, cefuroxime, cephaloridine, cephalotin, cefazolin, cephalixin, cefoxitin, cephacetrile, cefamandole, cephapirin, cephradine, cephaloglycine, cefpirone, cefepime, imipenem or meropenem or a pharmaceutically compatible salt of
30 one of these compounds.

24. A medicament according to claim 22 containing ceftriaxone or one of its pharmaceutically compatible salts.

35 25. A medicament according to any one of claims 21 to 24 as a combination preparation for the simultaneous, separate or chronologically stepwise use in antibacterial therapy.



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26. The use of compounds according to any one of claims 1 to 13 in the control or prevention of illnesses.

27. The use of compounds according to any one of claims 1 to 13 in the control or prevention of bacterial infections.

28. The use of compounds according to any one of claims 1 to 13 for the manufacture of antibacterially-active medicaments.

10 29. Compounds in accordance with any one of claims 1-15, whenever prepared according to the process as claimed in claim 18 or by an obvious chemical equivalent thereof.

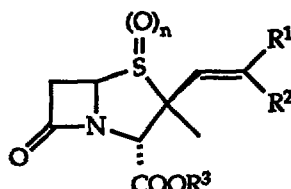


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Abstract

5 The present invention is concerned with penam derivatives, in particular it is concerned with 2 β -alkenyl-penam derivatives of the general formula



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10

wherein

one of R¹ and R² signifies -COR⁴, -CN, -CH₂R⁵, halogen, -CH=CHR⁶ or Q and the other signifies hydrogen or lower alkyl or both together signify a γ -lactam ring,

15 R³ signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R⁴ signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino, lower alkylamino or lower alkyl-lower alkoxyamino,

20 R⁵ signifies hydroxy, -OCONHR⁷, -OCONH₂ or a five- or six-membered hetero-aromatic ring which contains N,S and/or O and which is linked via a nitrogen atom,

R⁶ signifies -CN or CHO,

R⁷ signifies -COCH₂Cl,

25 Q signifies a five- or six-membered hetero-aromatic ring which contains N, S and/or O and

n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

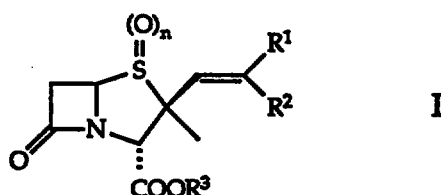
30 These compounds are good β -lactamase inhibitors. They can be used for the prevention or treatment of bacterial infections, optionally together with a β -lactam antibiotic.

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2- β -ALKENYL PENAM SULFONES AS β -LACTAMASE INHIBITORS

The present invention relates to penam derivatives, in particular it is concerned with 2 β -alkenyl-penam derivatives of the general formula



wherein

one of R¹ and R² signifies -COR⁴, -CN, -CH₂R⁵, halogen, -CH=CHR⁶ or Q and the other signifies hydrogen or lower alkyl or both together signify a γ -lactam ring,

R³ signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R⁴ signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino, lower alkylamino or lower alkyl-lower alkoxyamino,

R⁵ signifies hydroxy, -OCONHR⁷, -CONH₂ or a five- or six-membered hetero-aromatic ring which contains N, S and/or O and which is linked via a nitrogen atom,

R⁶ signifies -CN or CHO,

R⁷ signifies -COCH₂Cl,

Q signifies a five- or six-membered hetero-aromatic ring which contains N, S and/or O and

n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

These compounds are novel and are distinguished by therapeutically valuable properties. In particular, they have pronounced β -lactamase inhibiting properties and are accordingly useful in combination with β -lactam antibiotics such as the penicillins and cephalosporins in the control of pathogens which form β -lactamase.

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Furthermore, they have an antibacterial activity of their own against certain bacterial strains, such as e.g. *Acinetobacter* spp.

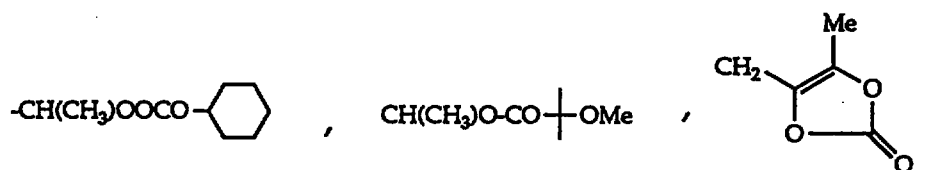
The term "lower alkyl", alone or in combination such as "lower alkoxy" or "lower alkylamino", signifies straight-chain or branched saturated hydrocarbon residues with a maximum of 7, preferably a maximum of 4, carbon atoms such as methyl, ethyl, isopropyl or t-butyl.

The term "aryl-alkyl" embraces benzyl, benzhydryl, p-methoxybenzyl or p-nitrobenzyl.

The term "halogen" embraces fluorine, chlorine, bromine or iodine.

The term "five- or six-membered hetero-aromatic ring which contains N, S and/or O" preferably signifies 2-pyridyl, 1-methyl-pyridin-2-yl, 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl and the like.

A residue which is cleavable in vivo signifies a residue which is suitable for oral administration and which preferably contains an ester group such as, for example, $-\text{CH}_2\text{OOC}(\text{CH}_3)_3$.



or $-\text{CH}(\text{CH}_3)\text{OCO}-\text{CH}_3$.

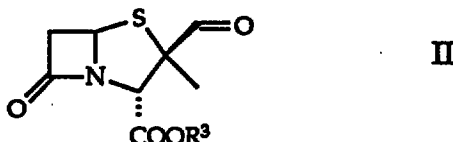
Objects of the present invention are 2 β -alkenyl-penam derivatives of general formula I and pharmaceutically compatible salts thereof per se and as pharmaceutically active substances, the manufacture of these compounds, medicaments containing a compound of general formula I or a pharmaceutically compatible salt and, if desired, additionally a β -lactam antibiotic and the manufacture of such medicaments, as well as the use of com-

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pounds of general formula I and of pharmaceutically compatible salts thereof in the control or prevention of illnesses, especially of bacterial infections, and, respectively, for the manufacture of corresponding medicaments.

Furthermore, compounds of the general formula



wherein R^3 has the above significance, are an object of the invention.

These compounds of formula II are important intermediates for the manufacture of the compounds of general formula I.

Those compounds of general formula I in which $R^1 = \text{CN}$, halogen or COR^4 and $R^4 = \text{amino}$, methyl, lower alkoxy or benzyl-oxy and $R^2 = \text{hydrogen}$, e.g. the following compounds, are especially preferred:

Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
 benzhydryl (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
 benzhydryl (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate
 sodium (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate
 sodium (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
 sodium (Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,
 sodium(E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

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Furthermore, the following belong to the especially preferred compounds:

Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

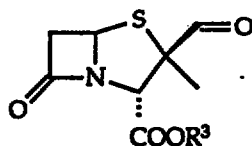
sodium (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

The 2 β -alkenyl-penam derivatives of general formula I as well as their pharmaceutically compatible salts can be manufactured in accordance with the invention by

a) reacting a compound of the general formula

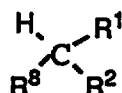
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II

wherein R^3 has the significance given above,
with a compound of the general formula

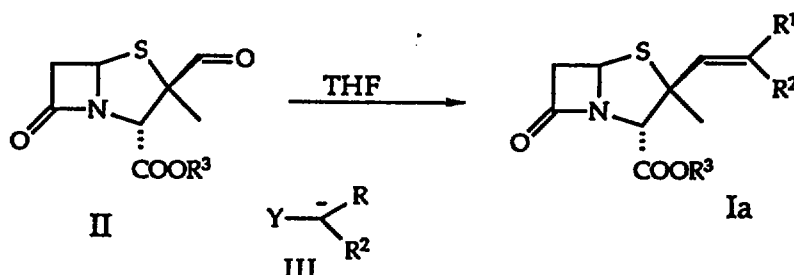


wherein R^1 and R^2 have the significance given above and R^8
= $P^{\oplus}(\text{aryl})_3$, $PO(\text{Oalkyl})_2$, $Si(\text{alkyl})_3$ or halogen,
in the presence of an activating agent, or

- b) oxidizing a compound of general formula I in which n signifies 0, or
- c) converting a compound of general formula I in which R^3 is different from hydrogen into the corresponding free acid, and
- d) if desired, converting an acidic compound of formula I into a pharmaceutically acceptable salt.

Scheme 1 shows two known methods (Wittig or Horner reaction) for carrying out process variant a).

Scheme 1



The substituents R^1 , R^2 and R^3 have the above significances.

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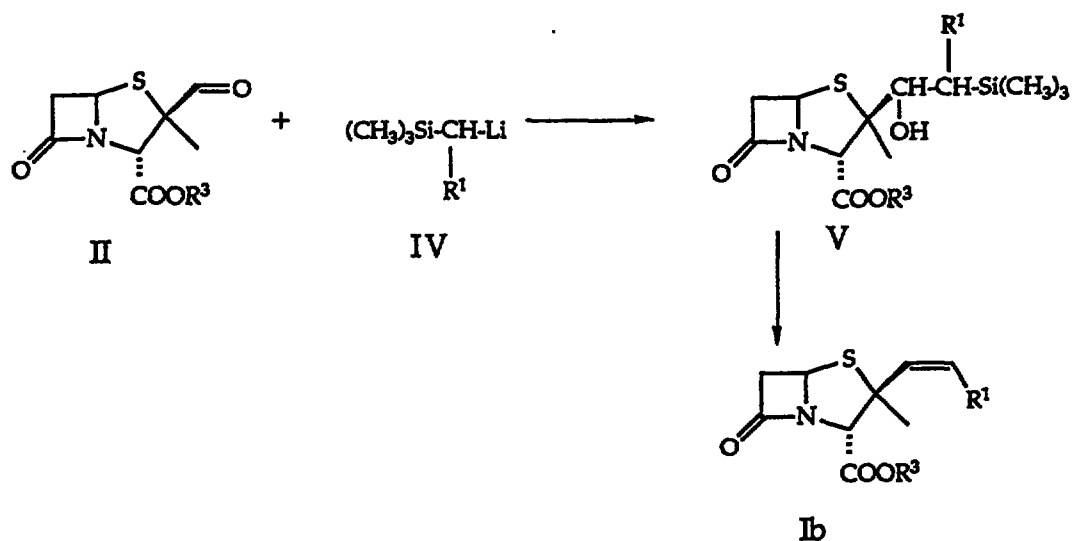
The aldehyde of formula II is converted into the alkenyl-substituted penams of formula Ia by direct reaction with an alkylidene-triphenylphosphorane (III; $Y = P^{\oplus}(aryl)_3$, Wittig reaction) or with an alkylphosphonate (III, $Y = (alkylO)_2PO$, Horner reaction) in the presence of an activating agent, for example a base such as triethylamine, sodium methylate, lithium diisopropylamine or DBU (1,5-diaza-bicyclo[4.3.0]non-5-ene). Suitable solvents are e.g. tetrahydrofuran, toluene, dichloromethane, acetonitrile or benzene. The reaction temperature can vary between -30° and $80^{\circ}C$ depending on the solvent which is used.

If desired, the compounds of formula I can also be manufactured by reacting correspondingly substituted triphenylphosphonium halides with 1,2-butylene oxide as the base and solvent. In this case the preferred reaction temperature lies between 50 and $70^{\circ}C$. Compounds of formula I in which n signifies 0 are obtained.

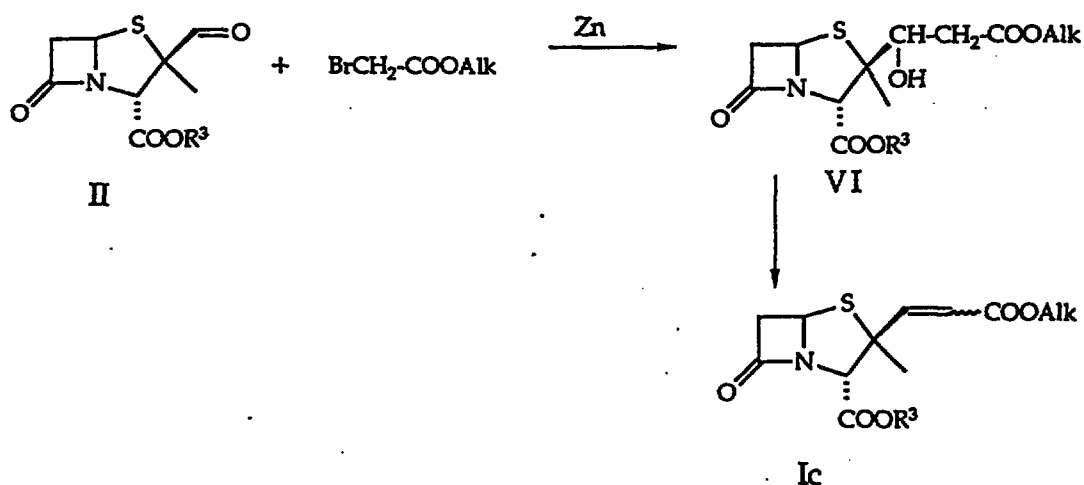
The Peterson olefination and the Reformatsky synthesis are further possibilities for carrying out process variant a). In the case of the Peterson olefination, lithium derivatives of trialkylsilanes are reacted with compounds of formula II in the presence of a base. Scheme 2 shows the reaction with a lithium trimethylsilane of formula IV in which R^1 and R^3 have the significances given above.

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Scheme 2

The β -alkenyl-penam derivatives of formula **Ib** result from the compounds of formula **V** by spontaneous dehydration. Compounds of formula **I** in which n signifies 0 and R^2 signifies hydrogen are obtained. In the case of the Reformatsky synthesis, compounds of formula **II** are condensed with organo-zinc derivatives of α -halo esters to the corresponding β -hydroxyl esters of formula **VI**, from which compounds of formula **I** in which n signifies 0, R^1 signifies COR^4 , R^4 signifies lower alkyl and R^2 signifies hydrogen result by water cleavage, corresponding to Scheme 3.

Scheme 3

R^3 has the significance given above.

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The oxidation of the sulphide group to the sulfoxide group or sulphone group is effected according to methods known per se. Reaction of the compounds of general formula I in which n signifies 0 in a two-phase system with ruthenium tetroxide or with an aqueous potassium permanganate solution and with a hydrogen peroxide solution has been found to be especially suitable.

Other oxidation reagents such as Na_2WO_4 or peracids can also be used for the preparation of the penam sulphones. Dichloromethane is an especially suitable solvent.

The compound of general formula I in which n signifies 0 is conveniently dissolved in dichloromethane and added to an aqueous suspension consisting of sodium (meta)periodate, sodium bicarbonate and ruthenium(IV) oxide. After completion of the reaction the organic phase is separated, purified and dried.

Whether a sulfoxide or a sulphone results from this oxidation depends on the nature and/or amount of oxidation agent.

The conversion of a compound of formula I in which R^3 is different from hydrogen into a free acid and the conversion of a free acid into a pharmaceutically acceptable salt can be effected according to methods known per se, in certain circumstances in a single procedure.

Ester groups, e.g. benzyl, p-nitrobenzyl, benzhydryl, p-methoxybenzyl or allyl, can be cleaved off as follows:

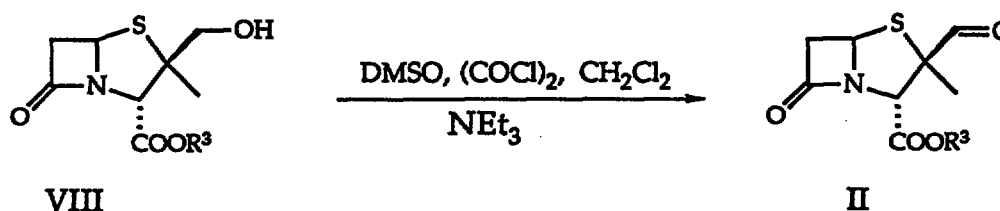
Benzyl and p-nitrobenzyl by hydrogenation over palladium-carbon at about 0°C to 80°C in an organic solvent such as ethyl acetate, methanol or water or by hydrolysis in the presence of sodium sulphide at about 0°C to room temperature in a solvent such as e.g. DMF. Allyl by palladium-(0)-catalyzed transallylation in the presence of a sodium or potassium salt of 2-ethylcaproic acid, benzhydryl with m-cresol at about 50°C within 4-5 hours.

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The compounds of general formula II which are used as starting materials can be prepared from corresponding alcohols in analogy to the process described in Tetrahedron 43, No. 5, pp 1003-1012.

Scheme 4



In this, R³ has the significance given above.

Reaction with oxalyl chloride in dichloromethane has been found to be of advantage, with the following procedure conveniently being used: dichloromethane and the oxidation agent are cooled to about -60°C, treated with DMSO and a compound of formula VIII and, after a reaction period of about 3 hours and addition of triethylamine, the cooling bath is removed. The thus-obtained aldehyde of formula II can be purified using usual methods.

Compounds of general formula II are obtained analogously by oxidation with PCC (pyridine chlorochromate), Dess-Martin reagent, MnO₂ and the like.

As mentioned earlier, the compounds of general formula I in accordance with the invention and pharmaceutically compatible salts thereof with bases exhibit pronounced β -lactamase-inhibiting activities against β -lactamases from various bacterial strains. As illustrated hereinafter, these therapeutically valuable properties can be determined in vitro on isolated β -lactamases:

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A. Isolation of the β -lactamases

Various β -lactamases can be isolated from penicillin- or cephalosporin-resistant bacterial strains such as *Klebsiella pneumoniae* NCTC 418, *Proteus vulgaris* 1028, *Bacillus licheniformis* 749/C, *Escherichia coli* SN01 and *Citrobacter freundii* 1203. For this purpose, the corresponding strains are cultivated in Tryptic Soy Broth (Difco) and harvested by centrifugation in the last logarithmic growth phase (when necessary 50-100 mg/l of ampicillin are added to the medium towards the end of the log-phase in order to induce the β -lactamase). The thus-obtained bacterial mass is treated with 20 mM Tris-HCl buffer (pH 7.0); the cells are broken open with a French press while cooling. The mixture is centrifuged (20,000 r/min.) for 20-30 minutes and a clear crude extract is obtained. The purification of the proteins is effected according to the methods of Cartwright, S.J. & Waley, S.G. [Biochem. J. 221, 505-512 (1980)] and, for *B. licheniformis*, Ellerby, L.M. et al. [Biochemistry 29, 5797-5806 (1990)].

B. Determination of the β -lactamase activity

The determination of the activity of the isolated β -lactamases can be carried out according to the method of O'-Callaghan, C.H. et al. [Antimicrob. Agents Chemother. 1, 283-288 (1972)] using the chromogenic cephalosporin nitrocefin (87/312 from Glaxo). The requisite test batch contains per ml of water: 50 mM phosphate buffer (pH 7.0), 0.1 mM nitrocefin and sufficient enzyme (β -lactamase) to achieve a $\Delta A/\text{min.}$ of about 0.1. The cleavage of the substrate, which is accompanied by a change in colour, is effected at 37°C and is followed quantitatively at 482 nm using a spectral photometer.

C. Determination of the β -lactamase-inhibiting activity of the compounds of general formula I

The above-described cleavage of the chromogenic substrate by β -lactamases (test B.) can be inhibited by the addition of compounds of general formula I (inhibitors). Since it has been found

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that the inhibitors irreversibly inactivate the β -lactamase in a time-dependent reaction, the reaction (cleavage of the substrate) is in each case started by addition of the substrate after a pre-incubation period of β -lactamase with inhibitor of 15 minutes. As a measurement for the affinity of the particular tested inhibitor to the β -lactamase, which is a measurement of the strength of the inhibitor, there serves that concentration which inhibits by 50% (IC 50 in nM) the cleavage of the substrate (nitrocefin) effected under the above test conditions (test B) in the absence of an inhibitor. 4 to 6 tests with different concentrations of inhibitor were carried out in order to determine the IC 50. The determination of the IC 50 was effected by means of a graph.

The results obtained in the above test (test C) are presented in Tables 1 to 3 hereinafter.

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Table 1

The IC₅₀ value, given in nM, is a measurement of the β -lactamase inhibition. An IC₅₀ value of 5 μ M or less is considered to be significant.

β -Lactamase inhibiting activity of compounds of formula I

Examples of compound of formula I with reference	IC ₅₀ [μ M] C. freundii 1982	IC ₅₀ [μ M] E. coli CF 102
Tazobactam (reference)	0.900	0.015
6c (cis amide)	4.340	0.130
6c (trans amide)	2.250	0.054
5c (trans nitrile)	0.696	0.681
5c (cis nitrile)	0.210	0.126
2c (trans ethyl ester)	0.370	0.456
4c (trans benzyl ester)	0.478	0.444
8c (cis-chloro)	0.590	0.055
9c (trans COCH ₃)	0.147	0.417
11c (trans 1,2,4-oxadiazol-3-yl)	0.490	0.217
12c (trans 2-thiazolyl)	0.410	0.054
12c (cis 2-thiazolyl)	1.270	0.160
13c (trans 2-pyridinyl)	1.010	0.092
14c (trans-CONMe(OMe))	2.490	0.181
15 (trans 2-pyridinylio)	3.100	0.087
17b (trans CH=CH-CN(Z))	3.300	0.420
18c (gamma-lactam)	14.250	0.320
20c (trans CH ₂ OH)	6.92	0.590
22c (trans CH ₂ OCONH ₂)	0.479	0.763
23c (trans CH ₂ -pyridinium)	15.700	0.142

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Table 2

β -Lactamase inhibiting activity by combination of compounds of formula I with ceftriaxone

(1 part ceftriaxone + 4 parts inhibitor)

Examples of compounds of formula I with reference	IC [μ g/ml] C. freundii 1982	IC [μ g/ml] E. coli CF 102
Ceftriaxone	128	8
Ceftriaxone + Tazobactam (reference)	8	0.25
Ceftriaxone + 6c (cis amide)	4	0.12
Ceftriaxone + 6c (trans amide)	NA	0.12
Ceftriaxone + 5c (trans nitrile)	2	0.25
Ceftriaxone + 5c (cis nitrile)	1	0.25
Ceftriaxone + 2c (trans ethyl ester)	4	0.25
Ceftriaxone + 4c (trans benzyl ester)	16	2.00
Ceftriaxone + 8c (cis chloro)	4	0.25
Ceftriaxone + 9c (trans COCH ₃)	1	0.25
Ceftriaxone + 11c (trans 1,2,4-oxadiazol-3-yl)	4	0.5
Ceftriaxone + 12c (trans 2-thiazolyl)	8	1
Ceftriaxone + 12c (cis 2-thiazolyl)	16	0.5
Ceftriaxone + 13c (trans 2-pyridinyl)	8	1
Ceftriaxone + 14c (trans CONMe(OMe))	8	0.5
Ceftriaxone + 15 (trans 2-pyridinyl)	4	0.25
Ceftriaxone + 17b (trans CH=CH-CN(Z))	8	0.5

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Ceftriaxone + 18c (gamma-lactam)	16	1
Ceftriaxone + 20c (trans-CH ₂ OH)	8	0.5
Ceftriaxone + 22c (trans CH ₂ OCONH ₂)	2	1
Ceftriaxone + 23c (trans CH ₂ -pyridinium)	8	0.25

MIC signifies minimum inhibitory concentration.

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Table 3

In vitro activity of combinations of the penam sulphone derivative 5c with selected antibiotics against β -lactamase over-producer strains

(constant inhibitor concentration: 4 mg/l)

	MIC E.cloacae	MIC C.freundii	MIC Ps.aeru- ginosa	MIC E.coli
Ceftriaxone	>64	64	>64	16
Ceftriaxone + 5c (cis nitrile)	4	2	16	≤ 0.12
Ceftriaxone + tazobactam	64	32	>64	≤ 0.12
Ceftazidime	>64	>64	32	32.00
Ceftazidime + 5c (cis nitrile)	4	8	2	0.5
Ceftazidime + tazobactam	64	64	8	0.5
Piperacillin	>128	>128	>64	>64
Piperacillin + 5c (cis nitrile)	8	8	16	4
Piperacillin + tazobactam	128	64	64	4
Apalcillin	>128	>128	64	>64
Apalcillin + 5c (cis nitrile)	16	8	4	2
Apalcillin + tazobactam	>128	64	NA	2

The products in accordance with the invention can be used as medicaments, e.g. in the form of pharmaceutical preparations which contain them or their salts in admixture with a pharmaceutical, organic or inorganic inert carrier material which is suitable for parenteral or enteral administration, such as e.g. water, gelatine, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, Vaseline, etc. The pharmaceutical preparations can be present in solid form, e.g. as tablets, dragées, suppositories, capsules; or in liquid form, e.g. as solutions, suspensions or emulsions. They may be sterilized and/or may contain adjuvants such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure, anaesthetics or buffers. The compounds of formula I and their

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salts preferably come into consideration for parenteral administration and, for this purpose, are preferably prepared as lyophilizates or dry powders for dilution with usual agents such as water or isotonic saline.

As mentioned earlier, the compounds of general formula I and their pharmaceutically compatible salts can be used in accordance with the invention in the control or prevention of illnesses, especially in the control of β -lactamase-forming pathogens in combination with β -lactam antibiotics, i.e. antibiotics which contain a β -lactam ring, for example penicillins such as piperacillin, mezlocillin, azlocillin, apalcillin, benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, tricarcillin, ampicillin, amoxycillin or mecillinam and cephalosporins such as ceftriaxone, ceftazidime, cefetamet, cefatamet pivoxil, cefotaxime, cefmenoxime, ceftizoxime, cefuroxime, cephaloridine, cephalotin, cefazolin, cephalixin, cefoxitin, cephacetrile, cefamandole, cephapirin, cephradine, cephaloglycine, cefpirome or cefepime as well as penems and carbapenems such as imipenem or meropenem. Thereby, the compounds of general formula I or pharmaceutically compatible salts thereof with bases can be administered before, simultaneously with or after the administration or intake of β -lactam antibiotics. Where the products in accordance with the invention are administered simultaneously with a β -lactam antibiotic, then this can be effected by administration as an ad-hoc combination or in the form of a pharmaceutical combination which contains a compound of general formula I or a pharmaceutically compatible salt thereof with a base and a β -lactam antibiotic; such pharmaceutical combinations are also an object of the present invention.

The dosage of the compounds of general formula I and of the pharmaceutically compatible salts thereof with bases can vary within wide limits and will, of course, be fitted in each particular case to the individual requirements and to the β -lactamase-producing pathogen to be controlled. In general, a daily dosage of about 0.1 to about 2.0 g should be appropriate. The ratio of β -lactamase inhibitor (compound of formula I or

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pharmaceutically compatible salt thereof with a base) to β -lactam antibiotic can also vary within wide limits and will be fitted to the individual requirements in each particular case. In general, a ratio of about 1:20 to about 1:1 should be appropriate.

As mentioned earlier, medicaments containing a compound of general formula I or a pharmaceutically compatible salt thereof are also an object of the present invention, as is a process for the manufacture of such medicaments which comprises bringing one or more compounds of general formula I or pharmaceutically compatible salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical administration form; in this connection reference is again made to the pharmaceutical combinations referred to above, which are also an object of the present invention. In particular, pharmaceutical combinations containing a compound of general formula I or a pharmaceutically compatible salt thereof and a β -lactam antibiotic, e.g. a penicillin such as piperacillin, mezlocillin, azlocillin, apalcillin, benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, tricarcillin, ampicillin, amoxycillin or mecillinam, a cephalosporin such as ceftriaxone, ceftazidime, cefetamet, cefatamet pivoxil, cefotaxime, cefmenoxime, ceftizoxime, cefuroxime, cephaloridine, cephalotin, cefazolin, cephalixin, cefoxitin, cephacetrile, cefamandole, cephapirin, cephradine, cephaloglycine, cefpirome or cefepime or a penem or carbapenem such as imipenem or meropenem, are an object of the present invention. Such combinations are suitable for the control of β -lactamase-forming pathogens.

The following Examples are intended to illustrate the present invention in more detail, but are not intended to limit its scope in any manner.

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Example 1

Benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

100 ml of dichloromethane are treated with 0.84 ml (9.6 mmol) of oxalyl chloride under argon and cooled to -60°C . Thereto there are added dropwise 0.73 ml (10.25 mmol) of DMSO, followed by 2.5 g (6.52 mmol) of benzhydryl (2S,3R,5R)-3-hydroxymethyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate dissolved in 100 ml of dichloromethane. The mixture is stirred at the same temperature for 3 hours and then 3.2 ml (23.0 mmol) of triethylamine are added. The cooling bath is removed and the mixture is left to warm to room temperature. The orange solution is poured into 1000 ml of 0.2N hydrochloric acid and the aqueous phase is extracted twice with dichloromethane. The organic phases are washed with water and saturated, aqueous sodium chloride solution, dried over sodium sulphate, filtered and concentrated on a rotary evaporator. The thus-obtained product (2.50 g, 100%) can be processed without further purification or can be recrystallized from diethyl ether.

Yield: 2.00 g (80%) of white crystal powder; m.p. $111.8-112.8^{\circ}\text{C}$

IR(KBr): 2720, 1788, 1743, 1718 cm^{-1}

MS: (M-CH₂CO) 339

¹H-NMR (250MHz, CDCl₃): $\delta[\text{ppm}] = 1.26(\text{s}, 3\text{H})$, $3.06(\text{dd}, 1\text{H}, J=16.2\text{Hz}, 2\text{Hz}, 6\text{-H})$, $3.54(\text{dd}, 1\text{H}, J=16.2\text{Hz}, 4\text{Hz}, 6\text{-H})$, $5.34(\text{s}, 1\text{H}, 2\text{-H})$, $5.42(\text{dd}, 1\text{H}, J=2\text{Hz}, 4\text{Hz}, 5\text{-H})$, $6.95(\text{s}, 1\text{H}, \text{CHPh}_2)$, $7.30-7.38(\text{m}, 10\text{H}, \text{Ph})$, $9.20(\text{s}, 1\text{H})$.

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Example 2

- (a) Benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

500 mg (1.30 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 20 ml of THF under argon and treated with 500 mg (1.40 mmol) of ethoxycarbonylmethylene-triphenylphosphorane. The yellow solution is stirred at 50°C for 75 minutes and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with ethyl acetate:hexane 9:16 as the eluent.

Yield: 520 mg (88%) of yellow-orange resin;
IR (film): 1783, 1747, 1717, 1650 cm^{-1}

MS: (M-CONH) 406, (M-CHPh₂) 284

¹H-NMR (250MHz, CDCl₃): δ [ppm] = 1.31(t,3H,J=7Hz), 1.34(s,3H), 3.13(dd,1H,J=2Hz, 16Hz,6-H), 3.57(dd,1H,J=4Hz, 16Hz,6-H), 4.22(q,2H,J=7Hz), 4.78(s,1H,2-H), 5.30(dd,1H,J=4.2Hz, 5-H), 5.97(d,1H,J=15Hz,=CH), 6.94(s,1H,CHPh₂), 7.07(d,1H,J=15Hz,=CH), 7.30-7.38(m,10H,Ph).

- (b) Benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

250 mg (0.55 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 10 ml of dichloromethane and treated with 6.5 ml of glacial acetic acid. 260 mg (1.66 mmol) of potassium permanganate in 25 ml of water are added dropwise to the yellow solution. After completion of the addition stirring is continued for a further 30 minutes and then the brown reaction mixture is treated with a 30% hydrogen per-

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oxide solution until a colourless two-phase mixture forms. The phases are separated in a separating funnel and the aqueous phase is extracted twice with dichloromethane. The organic phase is washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated. The residual oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:hexane 9:16 as the eluent.

Yield: 170 mg (60%) of colourless foam.

IR(KBr): 1802, 1757, 1721, 1653, 1331, 960 cm^{-1}

MS: (M-H) 482.4

$^1\text{H-NMR}$ (250MHz, CDCl_3): $\delta[\text{ppm}] = 1.26(\text{s}, 3\text{H})$, $1.35(\text{t}, 3\text{H}, J=7\text{Hz})$, $3.44\text{--}3.59(\text{pseudo-m}, 2\text{H}, 6\text{-H})$, $4.29(\text{q}, 2\text{H}, J=7\text{Hz})$, $4.60(\text{dd}, 1\text{H}, J=4\text{Hz}, 2\text{Hz}, 5\text{-H})$, $4.61(\text{s}, 1\text{H}, 2\text{-H})$, $5.99(\text{d}, 1\text{H}, J=16\text{Hz}, =\text{CH})$, $6.94(\text{s}, 1\text{H}, \text{CHPh}_2)$, $7.07(\text{d}, 1\text{H}, J=16\text{Hz}, =\text{CH})$, $7.23\text{--}7.40(\text{m}, 10\text{H}, \text{Ph})$.

(c) Sodium (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

170 mg (0.35 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 3 ml of m-cresol under argon and stirred at 50°C for 4.5 hours. Thereafter, the mixture is treated with 12.5 ml of isobutyl methyl ketone and the yellow-orange solution is extracted three times with 3 ml of saturated, aqueous sodium hydrogen carbonate solution each time. The aqueous phase is washed twice with 5 ml of isobutyl methyl ketone each time, filtered over a fluted filter and subsequently adjusted to $\text{pH} = 1$ with concentrated hydrochloric acid. The mixture is extracted with ethyl acetate, the organic phase is washed with saturated, aqueous sodium chloride solution, dried over sodium sulphate, filtered and concentrated on a rotary evaporator. The residual yellow resin is dissolved in 0.5 ml of

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ethyl acetate and treated with 108 μ l of sodium 2-ethylcaproate (2N solution in ethyl acetate). The mixture is concentrated, the residue is treated with 1.5 ml of water and extracted once with n-hexane. Subsequently, the aqueous phase is chromatographed over polymeric hydrophobic gel with water as the eluent. The fractions containing the product are combined and lyophilized.

Yield: 60 mg (50%) of colourless lyophilizate

IR(KBr): 1782, 1715, 1627, 1396, 1192 cm^{-1}

MS: (M-Na)⁻ 316.1

¹H-NMR (250MHz, D₂O): δ [ppm] = 1.31(t,3H,J=7Hz), 1.66(s,3H), 3.46(dd,1H,J=16Hz, 2Hz,6-H), 3.71(dd,1H,J=16Hz, 4Hz,6-H), 4.28(q,2H,J=7Hz), 4.62(s,1H,2-H), 5.15(dd,1H,J=2Hz,4Hz,5-H), 6.35(d,1H,J=16Hz,=CH), 7.10(d,1H,J=16Hz,=CH).

Example 3

(a) Benzhydryl (E)-(2S,3S,5R)-3-(2-methoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

200 mg (0.52 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are converted into benzhydryl (E)-(2S,3S,5R)-3-(2-methoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate by reaction with 193 mg (0.58 mmol) of methoxycarbonylmethylene-triphenylphosphorane according to Example 2.

Yield: 209 mg (91%) of colourless foam

IR (film): 1782, 1745, 1724, 1651 cm^{-1}

MS: (M+NH₄⁺) 455.3

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Example 4

- (a) Benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

763 mg (2.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 15 ml of THF under argon, treated with 821 mg (2.0 mmol) of benzyloxycarbonylmethylene-triphenylphosphorane and the orange solution is stirred at 50°C for 2 hours. It is left to cool to room temperature, the solvent is removed on a rotary evaporator and the red-brown oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:hexane 9:16 as the eluent.

Yield: 800 mg (78%) of orange foam

IR (film): 1782, 1746, 1721, 1649, 985 cm⁻¹

MS: (M+H)⁺ 514.3

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.33(s,3H), 3.11(dd,1H,J=16Hz, 1.6Hz, 6-H), 3.56(dd,1H,J=16Hz, 4.2Hz, 6-H), 4.78(s,1H,2-H), 5.20(s,2H), 5.36(dd,1H, J=1.6Hz, 4.2Hz, 5-H), 6.01(d,1H,J=15Hz,=CH), 6.93(s,1H,CHPh₂), 7.12(d,1H,J=15Hz, =CH), 7.30-7.43(m,15H,Ph).

- (b) Benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

800 mg (1.56 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 2.

Yield: 255 mg (30%) of colourless foam

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IR(KBr): 1802, 1757, 1723, 1650, 1332 cm^{-1}

MS: (M-H)⁻ 544.2

¹H-NMR (250MHz, CDCl₃): δ [ppm] = 1.25(s,3H), 3.47(dd,1H,J=16Hz, 2Hz,6-H), 3.55(dd,1H,J=16Hz, 4Hz, 6-H), 4.66(dd,1H,J=2Hz, 4Hz,5-H), 4.81(s,1H,2-H), 5.26(s,2H), 6.02 (d,1H,J=16Hz,=CH), 6.93(s,1H, CHPh₂), 7.22(d,1H,J=16Hz,=CH), 7.13-7.14(m,15H,Ph).

(c) Sodium (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

250 mg (0.46 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

Yield: 54 mg (30%) of beige lyophilizate

IR (KBr): 1781, 1719, 1626, 1322, 1189, 979 cm^{-1}

MS: (M-H)⁻ 378.2

¹H-NMR (250MHz, D₂O): δ [ppm] = 1.65(s,3H), 3.45(dd,1H,J=17Hz, 2Hz,6-H), 3.71(dd,1H,J=17Hz, 4Hz,6-H), 4.63(s,1H,2-H), 5.14 (dd,1H,J=4Hz, 2Hz,5-H), 5.29(s,2H), 6.42(d,1H,J=16Hz,=CH), 7.13(d,1H,J=16Hz,=CH), 7.42-7.55(m,5H,Ph).

Example 5

(a) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

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Method A:

1.0 g (2.62 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and 30 ml of toluene are added to 946 mg (3.14 mmol) of cyano-ethylene-triphenylphosphorane under argon. The brown suspension is stirred for 1 hour, concentrated and chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 3:1 as the eluent.

Yield: 1.0 g (94%) of isomer mixture, E:Z 3:1

Spectroscopic data of the mixture:

IR (film): 2224, 1781, 1744 cm^{-1}

MS: (M+Na⁺) 427.2

¹H-NMR (250MHz, CDCl₃) (E isomer): δ [ppm] = 1.32(s,3H), 3.13(dd,1H,J=16Hz, 1.6Hz, 6-H), 3.63(dd,1H,J=16Hz, 4.4Hz,6-H), 4.74(s,1H,2-H), 5.41(dd,1H,J=4.4Hz, 1.6Hz,5-H), 5.54(d,1H,J=15Hz, =CH), 6.82(d,1H,J=15Hz,=CH), 6.95(s,1H,CHPh₂), 7.30-7.44(m,10H, Ph).

¹H-NMR (250MHz, CDCl₃) (Z isomer): δ [ppm] = 1.61(s,3H), 3.18(dd,1H,J=16Hz,1.5Hz,6-H), 3.64(dd,1H,J=16Hz, 4.6Hz,6-H), 4.86(s,1H,2-H), 5.41(d,1H,J=12Hz,=CH), 5.44(dd,1H,J=1.5Hz, 4.6Hz,5-H), 6.63(d,1H,J=12Hz,=CH), 6.95(s,1H,CHPh₂), 7.30-7.44(m,10H,Ph).

Method B:

A suspension of 2.88 g (9.56 mmol) of cyanomethylene-triphenylphosphorane in 24 ml of lithium perchlorate solution (0.4M in acetonitrile) is cooled to -20°C under argon. A solution of 3.32 g (8.70 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate in 30 ml of acetonitrile is added dropwise thereto, the mixture

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is stirred at the same temperature for 4 hours and the solvent is removed on a rotary evaporator. The residue remaining behind is taken up in 100 ml of ethyl acetate, extracted three times with water and once with saturated sodium chloride solution, dried over magnesium sulphate, filtered and concentrated. The residual oil is purified over silica gel (particle size 0.040-0.063 mm) with methylene chloride as the eluent.

Yield: 3.34 g (94%) of isomer mixture, E:Z 1:4

(b) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate is prepared in the same manner as described in Example 2 by oxidizing benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate. The two isomers can be separated by chromatography over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane (9:16). The Z isomer is eluted as the first component.

Yield: Z: 76 mg (7%) of colourless oil
 E: 253 mg (23%) of colourless foam

Spectroscopic data E isomer:

MS: (M+NH₄)⁺ 454.2

IR (KBr): 2228, 1802, 1758, 1334, 1192, 990 cm⁻¹

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.24(s,3H), 3.50(dd,1H,J=16Hz, 2.2Hz,6-H), 3.60(dd,1H,J=16Hz, 4Hz,6-H), 4.65(dd,1H,J=2Hz, 4Hz,5-H), 4.75(s,1H,2-H), 5.37(d,1H,J=16Hz,=CH), 6.85(d,1H,J=16Hz,=CH), 6.98(s,1H,CHPh₂), 7.25-7.45(m,10H,Ph).

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Spectroscopic data **Z** isomer:

MS: (M-H)⁻ 435.3

IR (KBr): 2220, 1801, 1757, 1333, 1190 cm⁻¹

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.67(s, 3H), 3.48(dd, 1H, J=16Hz, 2.4Hz, 6-H), 3.64(dd, 1H, J=16Hz, 4.6Hz, 6-H), 4.72(dd, 1H, J=2.4Hz, 4.6Hz, 5-H), 4.85(s, 1H, 3-H), 5.90(d, 1H, J=12Hz, =CH), 6.41(d, 1H, J=12Hz, =CH), 6.97(s, 1H, CHPh₂), 7.26-7.44(m, 10H, Ph).

(c) Sodium (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

215 mg (0.5 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

Yield: 110 mg (82%) of white lyophilizate

IR (KBr): 2240, 1782, 1629, 1397, 1141 cm⁻¹

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.64(s, 3H), 3.47(dd, 1H, J=16Hz, 2Hz, 6-H), 3.72(dd, 1H, J=16Hz, 4Hz, 6-H), 4.62(s, 1H, 2-H), 5.15(dd, 1H, J=2Hz, 4Hz, 5-H), 6.07(d, 1H, J=16Hz, =CH), 7.08(d, 1H, J=16Hz, =CH).

Sodium (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

95 mg (0.2 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 3 ml of m-cresol and stirred at 50°C for 45 minutes. The reaction mixture is treated with 10 ml of isobutyl methyl ketone and 120 µl of sodium 2-ethylcaproate (2N in ethyl acetate, 1.1 eq.). The mixture is extracted twice with 3 ml of water each time, the combined

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aqueous phases are washed with 10 ml of isobutyl methyl ketone and lyophilized. The yellow lyophilizate is dissolved in 1.3 ml of water and chromatographed over polymeric hydrophobic gel.

Yield: 50mg (80%) of colourless lyophilizate

IR (KBr): 2222, 1782, 1626, 1395, 1323, 1141 cm^{-1}

$^1\text{H-NMR}$ (250MHz, D_2O): $\delta[\text{ppm}]$ = 1.94(s,3H), 3.47(dd,1H, $J=16\text{Hz}$, 1.6Hz, 6-H), 3.73(dd, 1H, $J=16\text{Hz}$, 4.4Hz, 6-H), 4.80(s,1H,2-H), 5.19(dd, 1H, $J=1.6\text{Hz}$, 4.4Hz,5-H), 6.15(d,1H, $J=12\text{Hz}$,=CH), 6.68 (d,1H, $J=12\text{Hz}$,=CH).

Example 6

(a) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

2.60 g (6.86 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and 2.15 g (6.86 mmol) of carbamoylmethylene-triphenylphosphorane are suspended in 60 ml of THF under argon and stirred at 50°C for 45 minutes. Insoluble material is filtered off under suction and the filtrate is concentrated on a rotary evaporator. The brown oil is chromatographed on silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:1 as the eluent and the two isomers are separated. The Z isomer is eluted before the E isomer, both can be obtained as crystalline solids from CH_2Cl_2 :n-hexane.

Z isomer:

Yield: 217 mg (7.5%) of colourless solid

IR (KBr): 3441, 1777, 1743, 1678, 986 cm^{-1}

MS: (M-CHPh₂) 255

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M.p.: 188-189°C

$^1\text{H-NMR}$ (250MHz, CDCl_3): δ [ppm] = 1.58(s,3H), 3.11(dd,1H, J =16Hz, 1.60Hz,6-H), 3.57(dd,1H, J =16Hz, 4.40Hz,6-H), 5.23(s,1H,2-H), 5.36(dd,1H, J =4.40Hz, 1.60Hz,5-H), 5.5(pseudo-d,2H, NH_2), 5.75(d,1H, J =12Hz,=CH), 6.24(d,1H, J =12Hz,=CH), 6.92(s,1H, CHPh_2), 7.29-7.43(m,10H, Ph).

E isomer:

Yield: 347 mg (12%) of crystalline solid

IR (KBr): 3444, 1775, 1728, 1671 cm^{-1}

MS: $(\text{M}+\text{H})^+$ 423.4

M.p.: 142°C (dec.)

$^1\text{H-NMR}$ (250MHz, CDCl_3): δ = 1.36(s,3H), 3.11(dd,1H, J =16Hz, 2.0Hz,6-H), 3.56(dd,1H, J =16Hz, 4.2Hz,6-H), 4.83(s,1H,2-H), 5.37(dd,1H, J =2.0Hz, 4.2Hz,5-H), 5.55(s,br,2H, NH_2), 5.97(d,1H, J =15Hz,=CH), 6.94(s,1H, CHPh_2), 6.95(d,1H, J =15Hz,=CH), 7.28-7.40(m,10H,Ph).

(b) Benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

370 mg (0.875 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate are oxidized in accordance with Example 2. A mixture of ethyl acetate:n-hexane 1:1 is used as the eluent.

Yield: 225 mg (57%) of colourless foam

IR (KBr): 1799, 1750, 1678, 1326, 1188, 1140 cm^{-1}

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MS: (M+H)⁺ 455.2

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.50(s,3H), 3.45(dd,1H,J=16Hz, 2Hz,6-H), 3.56(dd,1H,J=16Hz, 4Hz,6-H), 4.67(dd,1H,J=4Hz, 2Hz,5-H), 5.28(s,1H,2-H), 5.63(s,br,1H,NH₂), 5.84(d,1H,J=13Hz,=CH), 6.69(s,br,1H,NH₂), 6.39(d,1H,J=13Hz,=CH), 6.93(s,1H,CHPh₂), 7.29-7.41(m,10H,Ph).

Benzhydryl (E)-(2S,3S,5R)-3-(2-Carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

0.64 g (1.51 mmol) of benzhydryl (E)-(2S,3R,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 30 ml of methylene chloride and cooled to 0°C. 1.86 g (7.55 mmol) of meta-chloroperbenzoic acid (content: 70-75%, 5 eq.) in 30 ml of methylene chloride are added dropwise thereto, the cooling bath is removed after completion of the addition and the mixture is stirred at room temperature for 6 hours. The reaction solution is extracted with sodium sulphite solution (30% in saturated aqueous sodium bicarbonate solution) and washed with saturated aqueous sodium chloride solution. The solution is dried over magnesium sulphate, filtered, the solvent is removed on a rotary evaporator and the residue remaining behind is recrystallized using methylene chloride:n-hexane.

Yield: 210 mg (30%) of colourless solid

IR (KBr): 1799, 1756, 1686, 1329, 1143, 1191 cm⁻¹

MS: (M+H⁺) 455.3

M.p.: 186-188°C

¹H-NMR (250MHz, CDCl₃): δ[ppm] = 1.30(s,3H), 3.47(dd,1H,J=16Hz, 3.0Hz,6-H), 3.61(dd,1H,J=16Hz, 4.4Hz,6-H), 4.67(dd,1H,J=3.0Hz, 4.4Hz,5-H), 4.82(s,1H,2-H), 5.53(s,br,2H,NH₂), 6.03(d,1H,J=16Hz,=CH), 6.98(d,1H,J=16Hz,=CH), 6.94(s,1H,CHPh₂), 7.26-7.40(m,10H,Ph).

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(c) Sodium (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

135 mg (0.30 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

Yield: 67 mg (70%) of colourless lyophilizate

IR (KBr): 3434, 1781, 1668, 1626, 1397, 1317, 1139 cm^{-1}

MS: (M-Na)⁻ 287.2

¹H-NMR (250MHz, D₂O): δ [ppm] = 1.76(s,3H), 3.44(dd,1H,J=16Hz, 1.2Hz,6-H), 3.69(s,1H,J=16Hz, 4Hz,6-H), 4.68(s,1H,2-H), 5.10(dd,1H,J=4Hz, 1.2Hz,5-H), 5.94(d,1H,J=13Hz,=CH), 6.53 (d,1H, J=13Hz,=CH).

Sodium (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

350 mg (0.78 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 2.

Yield: 190 mg (80%)

IR (KBr): 1782, 1684, 1622, 1398, 1318, 1140 cm^{-1}

MS: (M-Na)⁻ 287.2

¹H-NMR (250MHz, D₂O): δ [ppm] = 1.66(s,3H), 3.46(dd,1H,J=17Hz, 1.4Hz, 6-H), 3.71(dd, 1H, J=17Hz, 4.0Hz,6-H), 4.62(s,1H,2-H),

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5.14(dd, J=1.4Hz, 4.0Hz, 5-H), 6.46(d, 1H, J=16Hz, =CH),
6.88(d, 1H, J=16Hz, =CH).

Example 7

(a) Benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-propenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

286 mg (0.75 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptan-2-carboxylate are dissolved in 12 ml of THF under argon and treated with 271 mg (0.75 mmol) of (1-ethoxycarbonylethylidene)-triphenylphosphorane. The yellow solution is stirred at 70°C for 6 hours and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with ethyl acetate:hexane 9:16 as the eluent.

Yield: 157 mg (45%) of pale yellow solid

IR (film): 1788, 1754, 1704, 1642 cm^{-1}

MS: (M+NH₄⁺)483.4

¹H-NMR (400MHz, CDCl₃): δ [ppm] = 1.32(t, 3H, J=7.1Hz), 1.38(s, 3H), 2.03(d, 3H, J=1.5Hz), 3.05(dd, 1H, J=1.8Hz, 16Hz, 6-H), 3.57(dd, 1H, J=4.3Hz, 16Hz, 6-H), 4.23(q, 2H, J=7.1Hz), 4.89(s, 1H, 2-H), 5.29(dd, 1H, J=4.3, 1.8Hz, 5-H), 6.94(s, 1H, CHPh₂), 7.20(d, 1H, J=1.5Hz, =CH), 7.30-7.36(m, 10H, Ph).

Example 8

(a) Benzhydryl (E,Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

A suspension of 1.37 g (4.40 mmol) of chloromethylene-triphenylphosphorane in 25 ml of diethyl ether is cooled to 0°C and treated with 1.60 g (4.20 mmol) of benzhydryl (2S,3R,5R)-3-

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formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate. The cooling bath is removed and the mixture is stirred at room temperature for a further 3 hours. The orange suspension is filtered and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with ethyl acetate:hexane 1:2 as the eluent.

Yield: 1.20 g (69%) of yellow isomer mixture, E:Z 7:9

Spectroscopic data of the mixture:

IR (film): 1782, 1747, 1590, 1496, 1251 cm^{-1}

MS: ($\text{M}+\text{NH}_4^+$) 413

(b) Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

2.98 g (14.05 mmol) of sodium metaperiodate are dissolved in 30 ml of water under argon and cooled to 0°C. The solution is treated with 0.93 g (11.17 mmol) of sodium bicarbonate followed by 45 ml of acetonitrile as well as 60 ml of methylene chloride. 9 mg (0.070 mmol) of ruthenium dioxide and subsequently the solution of 1.20 g (2.90 mmol) of benzhydryl (E/Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are added to the two-phase mixture. The cooling bath is removed and the reaction mixture is stirred until the reaction has finished (tlc control). Subsequently, the mixture is treated with 2 g of active charcoal and 20 ml of saturated sodium chloride solution, stirred for 5 minutes and suction filtered over Dicalite. The phases are separated in a separating funnel, the aqueous phase is extracted twice with methylene chloride and the combined organic extracts are washed with water and saturated sodium chloride solution, dried over magnesium sulphate/fuller's earth, filtered and evaporated. The residual oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:2

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as the eluent, the two isomers being separated in this manner.
The Z isomer is eluted as the first component.

Yield: Z: 495 mg (38%) of colourless foam

 E: 385 mg (30%) of colourless foam

Spectroscopic data E isomer:

MS: (M+NH₄)⁺ 463.4

IR (KBr): 1800, 1756, 1612, 1331, 1143, 700 cm⁻¹

Spectroscopic data Z isomer:

MS: (M+NH₄)⁺ 463.4

IR (KBr): 1800, 1755, 1630, 1330, 1143, 700 cm⁻¹

(c) Sodium (E)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

385 mg (0.86 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate are dissolved in 2.3 ml of m-cresol under argon and stirred at 50°C for 4 hours. Subsequently, the mixture is diluted with 15 ml of isobutyl methyl ketone, treated with 0.50 ml of sodium 2-ethylcaproate (2N solution in ethyl acetate) and extracted three times with 8 ml of water each time. The combined aqueous phases are washed once with 10 ml of isobutyl methyl ketone, lyophilized and the lyophilizate obtained is chromatographed over polymeric hydrophobic gel with water as the eluent.

Yield: 57 mg (32%)

MS: (M-Na)⁻ 278.2

IR (KBr): 1780, 1626, 1564, 1417, 1329, 1145 cm⁻¹

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Sodium (Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

400 mg (0.90 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 176 mg (65%) of colourless lyophilizate

MS: (M-Na)⁻ 278.2

IR (KBr): 1779, 1626, 1398, 1321, 1142 cm⁻¹

Elementary analysis: C₉H₉ClNO₅Na (301.676)

Calc.	C	35.83	H	3.01	N	4.64
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Found#)	C	35.72	H	3.04	N	4.65
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#) anhydrous, calculated with 5.53 % water

Example 9

(a) (E)-(2S,3S,5R)-3-methyl-7-oxo-3-(3-oxo-but-1-enyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

381 mg (1.00 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 12 ml of THF under argon and treated with 350 mg (1.10 mmol) of acetylmethylene-triphenylphosphorane. The mixture is stirred at 50°C for 6 days and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm. particle size) with ethyl acetate:methylene chloride 95:5 as the eluent.

Yield: 221 mg (52%) of white resin

IR (film): 1782, 1681, 1627, 1319, 1141, 980 cm⁻¹

MS: (M-Na)⁻ 286.1

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- (b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

221 mg (0.49 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-7-oxo-3-(3-oxo-but-1-enyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out once over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent and crystallization is carried out from methylene chloride/n-hexane.

Yield: 95 mg (40%) of colourless crystals

MS: (M+NH₄)⁺ 471.2

IR (KBr): 1798, 1760, 1682, 1627, 1330, 1193, 1142, 976 cm⁻¹

M.p.: 183-184°C

- (c) Sodium (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

250 mg (0.55 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 47 mg (27%) of colourless lyophilizate

MS: (M-Na)⁻ 286.1

IR (KBr): 1782, 1681, 1627, 1394, 1319, 1141, 980 cm⁻¹

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Example 10

- (a) (E)-(2S,3S,5R)-3-(2-Formyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

3.81 g (10.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 40 ml of methylene chloride under argon and treated with 3.34 g (11.0 mmol) of formylmethylene-triphenylphosphorane. The yellow solution is stirred at room temperature for 3 days and subsequently concentrated. The residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with tert.butyl methyl ether:n-hexane 2:3 as the eluent.

Yield: 528 mg (13%) of colourless resin

IR (film): 2738, 1781, 1744, 1717, 1690, 1496, 1178, 986 cm^{-1}

MS: (M+MH₄⁺) 425.6

Example 11

- (a) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

1.14 g (3.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 15 ml of 1,2-butylene oxide, treated with 1.38 g (3.6 mmol) of (1,2,4-oxadiazol-3-yl)methyl-triphenylphosphonium chloride and refluxed for 10 hours. Subsequently, the mixture is filtered, the filtrate is evaporated and the residual brown oil is chromatographed over silica gel (0.040-0.063 mm particle size) with methylene chloride as the eluent.

Yield: 280 mg (21%) of colourless crystals

MS: (M+NH₄)⁺ 465.3

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IR (KBr): 1792, 1753, 1658, 1492, 1200, 991 cm^{-1}

(b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

280 mg (0.63 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out once over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent and crystallization is carried out from methylene chloride/n-hexane.

Yield: 95 mg (40%) of colourless crystals

MS: (M-H)⁻ 478.3

IR (KBr): 1805, 1758, 1650, 1334, 1196 cm^{-1}

M.p.: 157°C

Elementary analysis: $\text{C}_{24}\text{H}_{21}\text{N}_3\text{O}_6\text{S}$ (479.507)

Calc.	C 60.12	H 4.41	N 8.76
Found	C 59.94	H 4.26	N 8.55

(c) (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

355 mg (0.74 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 3 ml of m-cresol and stirred at 50°C for 4 hours. 20 ml of n-hexane are added to the pale brown solution, the separated crystals are filtered off under suction and rinsed with n-hexane. The crude crystallizate is recrystallized from ethyl acetate/n-hexane.

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Yield: 170 mg (73%) of colourless crystals

MS: (M-H)⁻ 312.2

IR (KBr): 2900(br), 1811, 1714, 1660, 1331, 1194, 980 cm⁻¹

M.p.: 161°C (dec.)

Elementary analysis: C₁₁H₁₁N₃O₆S (313.284)

Calc.	C 42.17	H 3.54	N 13.41
Found	C 42.41	H 3.64	N 13.18

(c) Sodium (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

85 mg (0.27 mmol) of (E)-(2S,3S,5R)-3-methyl-3-[2-(1,2,4-oxadiazol-3-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid are added in one portion to a clear solution of 23 mg (0.27 mmol) of sodium hydrogen carbonate in 10 ml of water, the mixture is stirred for about 10 minutes, filtered and lyophilized.

Yield: 90 mg (91%) of colourless lyophilizate

MS: (M-Na)⁻ 312.2

IR (KBr): 1787, 1627, 1395, 1321, 1192, 970 cm⁻¹

Elementary analysis: C₁₁H₁₀N₃O₆SNa (335.266)

Calc.	C 39.41	H 3.01	N 12.53
Found#)	C 39.86	H 3.04	N 12.51

#) anhydrous, calculated with 5.82% water

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Example 12

- (a) Benzhydryl (E) and (Z)-(2S,3S,5R)-3-methyl-3-(2-thiazol-2-yl-vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

1.14 g (3.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 50 ml of 1,2-butylene oxide, treated with 1.53 g (3.86 mmol) of (thiazol-2-yl)methyl-triphenylphosphonium chloride and refluxed for 40 hours. Subsequently, the mixture is filtered, evaporated and the brown residue remaining behind is chromatographed over silica gel (0.040-0.063 mm particle size) with methylene chloride:ethyl acetate 95:5 as the eluent. The two isomers are separated in this manner, the Z isomer being eluted as the first component.

Z isomer:

Yield: 240 mg (17%) of yellow oil

IR (film): 1778, 1743, 1493, 1197, 986 cm^{-1}

MS: (M+H⁺) 463.5

E isomer:

Yield: 855 mg (62%) of yellow resin

IR (KBr): 1779, 1746, 1492, 1292, 988 cm^{-1}

MS: (M+H)⁺ 463.5

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- (b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

200 mg (0.43 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-thiazol-2-yl-vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with methylene chloride:ethyl acetate 95:5 as the eluent.

Yield: 72 mg (33%) colourless foam

MS: (M+H)⁺ 495.4

IR (KBr): 1799, 1756, 1329, 1192, 1142, 963 cm⁻¹

Benzhydryl (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

210 mg (0.45 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with methylene chloride:ethyl acetate 95:5 as the eluent.

Yield: 72 mg (33%) of colourless foam

MS: (M+H)⁺ 495.4

IR (KBr): 1793, 1754, 1490, 1328, 1184, 1142, 963 cm⁻¹

(E)-(2S,3S,5R)-3-Methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

200 mg (0.40 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-thiazol-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo-

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[3.2.0]heptane-2-carboxylate are deprotected analogously to Example 11.

Yield: 53 mg (40%) of colourless crystals

MS: (M+H)⁺ 329.4

IR (KBr): 2800(br), 1791, 1740, 1634, 1321, 1142, 965 cm⁻¹

Sodium (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

53 mg (0.16 mmol) of (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid are converted into the corresponding sodium salt analogously to Example 11.

Yield: 55 mg (98%) of colourless lyophilizate

IR (KBr): 1778, 1627, 1392, 1318, 1192, 1141, 955 cm⁻¹

Elementary analysis: C₁₂H₁₁N₂O₅S₂Na (350.339)

Calc.	C 41.14	H 3.16	N 8.00
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Found#)	C 40.73	H 3.51	N 7.92
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#) anhydrous, calculated with 5.9% water

Sodium (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

160 mg (0.32 mmol) of benzhydryl (Z)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-(2-thiazol-2-yl-vinyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are converted into the corresponding sodium salt analogously to Example 8.

Yield: 60 mg (57%) of colourless lyophilizate

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IR (KBr): 1781, 1623, 1398, 1320, 1193, 1140, 950 cm^{-1}

$^1\text{H-NMR}$ (250MHz, CDCl_3): δ [ppm] = 1.52(s,3H), 3.42(dd,1H, J =16Hz, 1.2Hz,6-H), 3.58(dd,1H, J =16Hz, 4.1Hz,6-H), 5.04(dd,1H, J =1.2Hz, 4.1Hz,5-H), 5.19(s,1H,2-H), 6.06(d,1H, J =12.5Hz,=CH), 7.14(d,1H, J =12.5Hz,=CH), 7.75(AB system,2H, J =3.5Hz, thiazole-H).

Example 13

(a) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

A suspension of 353 mg (1.0 mmol) of (2-picolyl)methylene-triphenylphosphorane and 381 mg (1.00 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate in 10 ml of diethyl ether is stirred at room temperature under argon for 2 hours. The mixture is treated with 10 ml of methylene chloride, insoluble material is removed by suction filtration and the filtrate is concentrated. The residue remaining behind is chromatographed over silica gel (particle size 0.040-0.063 mm) with methylene chloride:ethyl acetate 95:5 as the eluent.

Yield: 128 mg (28%) of a colourless foam

MS: (M^+) 456

IR (KBr): 1779, 1747, 1634, 1291, 988 cm^{-1}

(b) Benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

196 mg (0.43 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8.

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Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with methylene chloride:ethyl acetate 95:5 as the eluent.

Yield: 130 mg (62%) of colourless foam

MS: (M+H)⁺ 489.4

IR (KBr): 1799, 1756, 1580, 1490, 1327, 1184, 1141, 969 cm⁻¹

(c) (E)-(2S,3S,5R)-3-Methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

200 mg (0.41 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected analogously to Example 10.

Yield: 85 mg (65%) of pale beige crystal powder

MS: (M+H)⁺ 323.3

IR (KBr): 2700(br), 1790, 1720, 1621, 1318, 1140, 978 cm⁻¹

Sodium (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

83 mg (0.17 mmol) of (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid are converted into the corresponding sodium salt analogously to Example 10.

Yield: 89 mg (100%) of colourless lyophilizate

IR (KBr): 1784, 1629, 1587, 1478, 1396, 1320, 1187, 1141, 980 cm⁻¹

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Elementary analysis: $C_{14}H_{13}N_2O_5SNa$ (344.317)

Calc. C 48.84 H 3.81 N 8.14

Found#) C 49.18 H 4.23 N 8.17

#) anhydrous, calculated with 6.86% water

Example 14

- (a) Benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate

An orange solution of 1.14 g (3.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and 1.14 g (3.15 mmol) of (N-methoxymethylaminocarbonylmethylene)-triphenylphosphorane is stirred at room temperature under argon for 3 days. The solvent is removed on a rotary evaporator and the residue is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:1 as the eluent.

Yield: 1.12 g (80%) of colourless foam

MS: (M+H)⁺ 467.4

IR (KBr): 1781, 1744, 1662, 1629, 995 cm^{-1}

- (b) Benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

0.69 g (1.48 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate is oxidized in analogy to Example 8. Chromatography is carried out over silica gel

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(particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 3:2 as the eluent.

Yield: 405 mg (55%) of colourless foam

MS: (M+H)⁺ 499.4

IR (KBr): 1807, 1753, 1662, 1624, 1318, 1140, 1000 cm⁻¹

(c) Sodium (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate.

200 mg (0.40 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[2-(methoxy-methyl-carbamoyl)-vinyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 95 mg (67%) of colourless lyophilizate

MS: (M+H)⁺ 355.3

IR (KBr): 1785, 1650, 1626, 1390, 1322, 1191, 1141, 980 cm⁻¹

Elementary analysis: C₁₂H₁₅N₂O₇SNa (354.309)

Calc.	C 40.68	H 4.27	N 7.91
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Found#)	C 40.37	H 4.35	N 7.84
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#) anhydrous, calculated with 2.74% water

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Example 15

(E)-(2S,3S,5R)-3-Methyl-3-[2-(1-methyl-pyridin-2-yl)-vinyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptan-2-carboxylic acid

150 mg (0.31 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-(2-pyridin-2-yl-vinyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid are dissolved in 3 ml of methylene chloride, cooled to 0°C and treated with 56 μ l (0.51 mmol) of methyl trifluoromethylsulphonate. The cooling bath is removed and the mixture is stirred at room temperature for 2 days. The solvent is removed on a rotary evaporator and the residue is dried in a high vacuum. The thus-obtained product (200 mg, 100%) is processed without further purification. The brown resin is dissolved in 2 ml of m-cresol and stirred at 50°C for 2 hours. Thereafter, the mixture is treated with 10 ml of isobutyl methyl ketone as well as 5 ml of water, shaken, the phases are separated and the organic phase is extracted twice with 5 ml of water. The aqueous phases are washed twice with 10 ml of isobutyl methyl ketone each time, filtered and lyophilized. The yellowish lyophilizate is chromatographed over polymeric hydrophobic gel with water as the eluent.

Yield: 105 mg (72%) of orange lyophilizate

IR (KBr): 1778, 1627, 1377, 1185, 970 cm^{-1}

MS: (M⁺) 337.4

Example 16

(a) Benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-formyl-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]-heptane-2-carboxylate

Benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-formyl-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

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is prepared in analogy to Example 9 from 3.81 g (10.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate and 4.55 g (15.0 mmol) of formylmethylene-triphenylphosphorane. Chromatography is carried out over silica gel (0.040-0.063 mm particle size) with methylene chloride:ethyl acetate 98:2 as the eluent.

Yield: 347 mg (8%) of yellowish resin

MS: (M+NH₄)⁺ 451.4

IR (KBr): 1779, 1745, 1680, 1637, 1201, 988 cm⁻¹

Example 17

(a) Benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

Benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate is prepared in analogy to Example 4, Method B, from 815 mg (2.14 mmol) of benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-formyl-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate. The residual oil is purified over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:2 as the eluent.

Yield: 820 mg (89%) of isomer mixture, E:Z 2:3

Spectroscopic data of the isomer mixture:

IR (film): 2215, 1780, 1745, 1202, 989 cm⁻¹

MS: (M+NH₄)⁺ 448.5

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- (b) Benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

770 mg (1.79 mmol) of benzhydryl (1E,3E) and (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. The two isomers can be separated by chromatography over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent. The Z isomer is eluted as the first component.

Yield: Z: 430 mg (52%) of colourless oil

E: 280 mg (34%) of colourless foam

Spectroscopic data E isomer:

MS: (M+NH₄)⁺ 480.5

IR (KBr): 2219, 1800, 1756, 1329, 1191, 994 cm⁻¹

Spectroscopic data Z isomer:

MS: (M+NH₄)⁺ 435.3

IR (KBr): 2210, 1800, 1756, 1330, 1192, 993 cm⁻¹

- (c) Sodium (1E,3E)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

250 mg (0.54 mmol) of benzhydryl(1E,3E)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8.

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Yield: 55 mg (41%) of yellowish lyophilizate

IR (KBr): 2221, 1781, 1631, 1397, 1319, 1139, 992 cm^{-1}

MS: $(\text{M}+\text{Na})^+$ 341.2

Sodium (1E,3Z)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

230 mg (0.49 mmol) of benzhydryl (1E,3E)-(2S,3S,5R)-3-(4-cyano-buta-1,3-dienyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8.

Yield: 84 mg (58%) of yellowish lyophilizate

IR (KBr): 2219, 1780, 1625, 1396, 1316, 1138, 951 cm^{-1}

MS: $(\text{M}+\text{H})^+$ 319.3

Elementary analysis: $\text{C}_{12}\text{H}_{11}\text{N}_2\text{O}_5\text{SNa}$ (318.279)

Calc.	C	45.28	H	3.48	N	8.80
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Found#)	C	45.29	H	3.63	N	8.82
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#) anhydrous, calculated with 6.93% water

Example 18

(a) Benzhydryl (E/Z)-(2S,3S,5R)-3-methyl-7-oxo-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenmethyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

762 mg (2.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are reacted with 1.02 g (2.0 mmol) of rac-[2-oxo-1-(2,2,2-

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trifluoroethyl)-2-pyrrolidiny]-triphenylphosphonium bromide according to Example 12. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 763 mg (71%) of isomer mixture, E:Z 5:1

Spectroscopic data of the mixture:

IR (film): 1782, 1748, 1702, 1664, 1158 cm^{-1}

MS: (M-CPh₂) 363

(b) Benzhydryl (E) und (Z)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

763 mg (1.42 mmol) of benzhydryl (E/Z)-(2S,3S,5R)-3-methyl-7-oxo-3-[2-oxo-1-(2,2,2-trifluoro-ethyl)-pyrrolidin-3-ylidene-methyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. The two isomers can be separated by chromatography over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 1:2 as the eluent.

Yield: E: 192 mg (24%) of colourless foam

Z: 32 mg (4%) of colourless foam

Spectroscopic data E isomer:

MS: (M+NH₄)⁺ 580.4

IR (KBr): 1801, 1759, 1706, 1667, 1329, 1144 cm^{-1}

Spectroscopic data Z isomer:

MS: (M+NH₄)⁺ 580.4

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IR (KBr): 1798, 1755, 1694, 1327, 1142 cm^{-1}

(c) (E)-(2S,3S,5R)-3-Methyl-3-[2-oxo-1-(2,2,2-trifluoroethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid

192 mg (0.34 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoroethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected analogously to Example 11.

Yield: 78 mg (59%) of colourless crystal powder

MS: $(\text{M}+\text{NH}_4)^+$ 414.4

IR (KBr): 2800(br), 1790, 1729, 1674, 1646, 1321, 1166 cm^{-1}

Sodium (E)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoroethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

50 mg (0.13 mmol) of (E)-(2S,3S,5R)-3-methyl-3-[2-oxo-1-(2,2,2-trifluoroethyl)-pyrrolidin-3-ylidenemethyl]-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylic acid are converted into the corresponding sodium salt analogously to Example 11.

Yield: 52 mg (98%) of colourless lyophilizate

IR (KBr): 1780, 1699, 1628, 1478, 1396, 1323, 1140 cm^{-1}

Elementary analysis: $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_6\text{F}_3\text{SNa}$ (418.318)

Calc.	C 40.20	H 3.37	N 6.70
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Found#)	C 39.80	H 3.28	N 6.62
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#) anhydrous, calculated with 7.24% water

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Example 19

- (a) Benzhydryl (E/Z)-(2S,3S,5R)-3-(1-cyclopropyl-2-oxo-pyrrolidin-3-ylidenemethyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

381 mg (1.0 mmol) of benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are reacted with 495 mg (1.1 mmol) of rac-[1-cyclopropyl-2-oxo-3-pyrrolidinyl]-triphenylphosphonium bromide according to Example 18. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 362 mg (74%) of isomer mixture, E:Z 5:1

Spectroscopic data of the mixture:

IR (film): 1780, 1750, 1692, 1661, 1195, 1118 cm^{-1}

MS: (M+H)⁺ 489.4

Example 20

- (a) Benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxy-propen-1-yl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

5.80 g (14.2 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(2-formyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 240 ml of toluene under argon and cooled to 0°C. Then, 14.2 ml (21.3 mmol) of a 20% diisobutyl-aluminium hydride solution (in toluene) are added dropwise and the cooling bath is removed. The reaction mixture is stirred at room temperature for 6 hours, poured into 150 ml of saturated ammonium chloride solution and extracted three times with 200 ml of methylene chloride each time. The combined organic

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extracts are washed once with 300 ml of water as well as saturated sodium chloride solution, dried over magnesium sulphate, filtered and freed from solvent on a rotary evaporator. The residual yellow oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 1.90 g (32%) of colourless resin

IR (film): 3480(br), 1778, 1750, 1202, 1080, 988 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 427.6

(c) Sodium (E)-(2S,3S,5R)-3-(3-hydroxy-propen-1-yl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

500 mg (0.95 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-[3-[(R)- and (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected according to Example 8.

Yield: 165 mg (62%) of colourless lyophilizate

MS: $(\text{M}-\text{Na})^-$ 274.3

IR (KBr): 3428, 1780, 1622, 1398, 1311, 1192, 1139, 1082 cm^{-1}

Elementary analysis: $\text{C}_{10}\text{H}_{12}\text{NO}_6\text{SNa}$ (297.257)

Calc.	C	40.41	H	4.07	N	4.71
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Found#)	C	40.44	H	4.48	N	4.79
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#) anhydrous, calculated with 8.73% water

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Benzhydryl (E)-(2S,3S,5R)-3-methyl-7-oxo-3-[3-[(R)- and (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

620 mg (1.50 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxy-propenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 30 ml of methylene chloride and treated with 4.5 mg (0.024 mmol) of p-toluenesulphonic acid monohydrate. Subsequently, 0.25 ml (2.70 mmol) of 3,4-dihydro-2H-pyran is added and the mixture is stirred for a further 1 hour. The solvent is removed on a rotary evaporator and chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 700 mg (93%) colourless oil, diastereomer mixture (1:1)

IR (film): 3031, 1782, 1749, 1257, 1134, 967 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 511.6

Benzhydryl (E)-(2S,3S,5R)-3-methyl-4,4,7-trioxo-3-[3-[(R)- und (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

585 mg (1.18 mmol) of benzhydryl (E)-(2S,3S,5R)-3-methyl-7-oxo-3-[3-[(R)- and (S)-tetrahydro-pyran-2-yloxy]-propenyl]-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are oxidized according to Example 8. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 525 mg (84%) of colourless foam, diastereomer mixture (1:1)

IR (KBr): 1800, 1756, 1327, 1189, 1141, 969 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 543.5

Example 21

- (a) Benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

300 mg (0.73 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxypropenyl)-3-methyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate are dissolved in 10 ml of tetrahydrofuran under argon and treated with 90 μ l (1.05 mmol) of chloroacetyl isocyanate. The mixture is stirred for 3 hours, evaporated and chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 300 mg (77%) of colourless foam

IR (KBr): 3300(br), 1779, 1753, 1730, 1495, 1203 cm^{-1}

MS: (M+NH₄)⁺ 546.4

- (b) Benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

295 mg (0.57 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate are oxidized analogously to Example 8. Chromatography is carried out over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 9:16 as the eluent.

Yield: 216 mg (68%) of colourless foam

IR (KBr): 3413(br), 1798, 1758, 1730, 1705, 1326, 1198, 991 cm^{-1}

MS: (M+NH₄)⁺ 578.4

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(c) Sodium (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

195 mg (0.35 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8 and converted into the corresponding sodium salt.

Yield: 60 mg (49%) of colourless lyophilizate

MS: (M-COCH₂Cl-Na)⁻ 317.3

IR (KBr): 3435, 1781, 1721, 1622, 1533, 1396, 1314, 1192, 1139 cm⁻¹

¹H-NMR (250MHz, D₂O): δ[ppm] = 1.61(s,3H), 3.42(dd,1H,J=16Hz, 1.6Hz, 6-H), 3.69(dd, 1H, J=16Hz, 4.0Hz, 6-H), 4.43(s,2H,CH₂Cl), 4.49(s,1H,2-H), 4.84(d,2H,J=4.4Hz,CH₂O), 5.08(dd,J=1.6Hz, 4.0Hz, 5-H), 6.08(d(br),1H,J=16Hz,=CH), 6.22(dt,1H,J=16Hz, 4.4Hz, =CH)

Example 22

Benzhydryl (E)-(2S,3S,5R)-3-(carbamoyloxy-propenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

450 mg (0.80 mmol) of benzhydryl (E)-(2S,3S,5R)-3-[3-(2-chloro-acetylaminocarbonyloxy)-propenyl]-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 5 ml of tetrahydrofuran under argon and treated with 1.7 ml of methanol. 135 mg (1.61 mmol) of sodium hydrogen carbonate in 2.8 ml of water are added to this solution. After completion of the reaction (tlc control) the solvent mixture is removed on a rotary evaporator, the residual yellow oil is taken up in 15 ml of ethyl acetate as well as 15 ml of saturated sodium chloride solution, shaken and the phases are separated. The aqueous phase is back-extracted twice with 15 ml of ethyl

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acetate each time and the combined organic extracts are washed once with 15 ml of saturated sodium chloride solution. They are dried over magnesium sulphate, concentrated on a rotary evaporator and the residual oil is chromatographed over silica gel (particle size 0.040-0.063 mm) with ethyl acetate:n-hexane 2:1 as the eluent.

Yield: 200 mg (78%) of colourless foam

IR (KBr): 3481, 1799, 1749, 1731, 1601, 1329, 1191, 996 cm^{-1}

MS: $(\text{M}+\text{NH}_4)^+$ 484

(c) Sodium (E)-(2S,3S,5R)-3-(carbamoyloxy-propenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

190 mg (0.60 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(carbamoyloxypropenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are deprotected in analogy to Example 8.

Yield: 82 mg (62%) of colourless lyophilizate

$^1\text{H-NMR}$ (250MHz, D_2O): $\delta[\text{ppm}] = 1.61(\text{s}, 3\text{H})$, $3.42(\text{dd}, 1\text{H}, J=17\text{Hz}, 1.6\text{Hz}, 6\text{-H})$, $3.69(\text{dd}, 1\text{H}, J=17\text{Hz}, 4\text{Hz}, 6\text{-H})$, $4.48(\text{s}, 1\text{H}, 2\text{-H})$, $4.70(\text{d}, 2\text{H}, J=4.6\text{Hz}, \text{CH}_2)$, $5.08(\text{dd}, 1\text{H}, J=4\text{Hz}, 1.6\text{Hz}, 5\text{-H})$, $5.97(\text{d}, 1\text{H}, J=16\text{Hz}, =\text{CH})$, $6.19(\text{dt}, 1\text{H}, J=16\text{Hz}, 4.6\text{Hz}, =\text{CH})$.

Example 23

(a) (2S,3S,5R)-1-[3-(2-Benzhydryloxycarbonyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluormethanesulphonate

410 mg (1.0 mmol) of benzhydryl (E)-(2S,3S,5R)-3-(3-hydroxypropenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate are dissolved in 6 ml of methylene chloride,

cooled to -40°C and treated with 250 μl (1.5 mmol) of trifluoromethanesulphonic anhydride. After 5 minutes 200 μl (2.50 mmol) of pyridine are added, the mixture is stirred at the same temperature for a further hour and subsequently the cooling bath is removed. The solvent is removed on a rotary evaporator at room temperature, the reaction mixture is taken up in 20 ml of methylene chloride and washed twice with 10 ml of saturated sodium chloride solution each time. Drying over magnesium sulphate, filtration and concentration on a rotary evaporator are carried out. The residual red resin is oxidized without further purification.

Yield: 600 mg (97%) of red resin

MS: (M⁺) 471.6

IR (KBr): 1777, 1743, 1630, 1160, 987 cm^{-1}

(b) (2S,3S,5R)-1-[3-(2-Benzhydryloxy-carbonyl-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluoromethanesulphonate

600 mg (0.97 mmol) of (2S,3S,5R)-1-[3-(2-benzhydryloxy-carbonyl-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluoromethanesulphonate are oxidized in analogy to Example 8.

Yield: 440 mg (70%) of green resin

MS: (M⁺) 503.3

IR (KBr): 1797, 1753, 1632, 1167 cm^{-1}

(E)-(2S,3S,5R)-3-Methyl-4,4,7-trioxo-3-(3-pyridin-1-ylpropenyl)-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate

A solution of 440 mg (0.67 mmol) of (2S,3S,5R)-1-[3-(2-benzhydryloxy-carbonyl-3-methyl-4,4,7-trioxo-4-thia-1-aza-

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bicyclo[3.2.0]heptan-3-yl)-allyl]-pyridinium trifluoromethane-sulphonate in 3 ml of m-cresol is stirred at 50°C for 1.5 hours. The mixture is diluted with 10 ml of isobutyl methyl ketone at room temperature and extracted three times with 8 ml of water each time. The combined aqueous extracts are washed twice with 10 ml of isobutyl methyl ketone each time, filtered over a paper filter and lyophilized. The brown lyophilizate is subsequently chromatographed over polymeric hydrophobic gel with water as the eluent.

Yield: 125 mg (55%) of beige lyophilizate

IR (KBr): 1780, 1625, 1485, 1372, 1312, 980 cm^{-1}

MS: $\text{M}+\text{H}^+$ 337.4

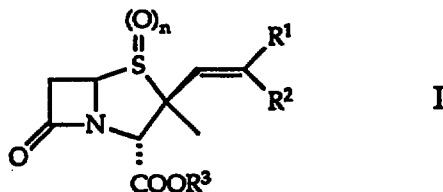
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Claims

1. 2β -Alkenyl-penam derivatives of the general formula



wherein

one of R^1 and R^2 signifies $-\text{COR}^4$, $-\text{CN}$, $-\text{CH}_2\text{R}^5$, halogen, $-\text{CH}=\text{CHR}^6$ or Q and the other signifies hydrogen or lower alkyl or both together signify a γ -lactam ring,

R^3 signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R^4 signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino, lower alkylamino or lower alkyl-lower alkoxyamino,

R^5 signifies hydroxy, $-\text{OCONHR}^7$, $-\text{OCONH}_2$ or a five- or six-membered hetero-aromatic ring which contains N, S and/or O and which is linked via a nitrogen atom,

R^6 signifies $-\text{CN}$ or CHO ,

R^7 signifies $-\text{COCH}_2\text{Cl}$,

Q signifies a five- or six-membered hetero-aromatic ring which contains N, S and/or O and

n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

2. Compounds according to claim 1,

wherein

one of R^1 and R^2 signifies $-\text{COR}^4$, $-\text{CN}$ or $-\text{CH}_2\text{OR}^5$ and the other signifies hydrogen or lower alkyl,

R^3 signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R^4 signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino or lower alkylamino,

R^5 signifies hydroxy or $-\text{CONH}_2$,

R^6 signifies lower alkyl and

n signifies 0, 1 or 2.

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3. Compounds according to claim 1 or 2, wherein R¹ signifies CN, halogen or COR⁴, R² signifies hydrogen and R⁴ signifies methyl, lower alkoxy, benzyloxy or amino.
4. Compounds according to any one of claims 1 to 3, wherein n signifies 0 or 2.
5. Compounds according to any one of claims 1 to 4, wherein R³ signifies hydrogen or benzhydryl.
6. Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
7. Benzhydryl (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
8. Benzhydryl (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
9. Sodium (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
10. Sodium (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
11. Sodium (E)-(2S,3S,5R)-3-(2-chloro-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
12. Sodium (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
13. Benzhydryl (E/Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

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benzhydryl (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

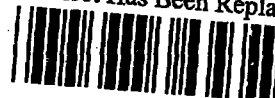
sodium (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.

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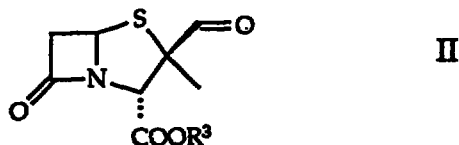
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14. Compounds of the general formula



wherein R^3 has the significance given in claim 1.

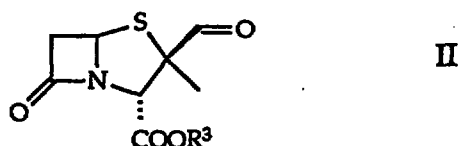
15. Benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate.

16. Compounds according to any one of claims 1 to 13 for use as therapeutically active substances.

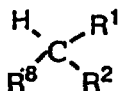
17. Compounds according to any one of claims 1 to 13 for use as β -lactamase inhibitors.

18. A process for the manufacture of compounds according to any one of claims 1 to 13, which process comprises

a) reacting a compound of the general formula



wherein R^3 has the significance given in claim 1,
with a compound of the general formula



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wherein R^1 and R^2 have the significance given in claim 1
and $R^8 = P^{\oplus}(\text{aryl})_3$, $PO(\text{Oalkyl})_2$, $Si(\text{alkyl})_3$ or halogen,
in the presence of an activating agent, or

b) oxidizing a compound of general formula I in which n
signifies 0, or



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- c) converting a compound of general formula I in which R^3 is different from hydrogen into the corresponding free acid, and
- d) if desired, converting an acidic compound of formula I into a pharmaceutically acceptable salt.

19. A medicament containing a compound according to any one of claims 1 to 13.

20. A β -lactamase-inhibiting medicament containing a compound according to any one of claims 1 to 13.

21. A medicament according to claim 19 or 20 which additionally contains a β -lactam antibiotic.

22. A medicament according to claim 21 containing a penicillin, cephalosporin, penem or cabapenem as the β -lactam antibiotic.

23. A medicament according to claim 22 containing piperacillin, mezlocillin, azlocillin, apalcillin, benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, ticarcillin, ampicillin, amoxicillin, mecillinam, ceftriaxone, ceftazidime, cefetamet, cefetamet pivoxil, cefotaxime, cefmenoxime, ceftizoxime, cefuroxime, cephaloridine, cephalotin, cefazolin, cephalexin, cefoxitin, cephacetrile, cefamandole, cephapirin, cephradine, cephaloglycine, cefpirone, cefepime, imipenem or meropenem or a pharmaceutically compatible salt of one of these compounds.

24. A medicament according to claim 22 containing ceftriaxone or one of its pharmaceutically compatible salts.

25. A medicament according to any one of claims 21 to 24 as a combination preparation for the simultaneous, separate or chronologically stepwise use in antibacterial therapy.





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26. The use of compounds according to any one of claims 1 to 13 in the control or prevention of illnesses.

27. The use of compounds according to any one of claims 1 to 13 in the control or prevention of bacterial infections.

28. The use of compounds according to any one of claims 1 to 13 for the manufacture of antibacterially-active medicaments.

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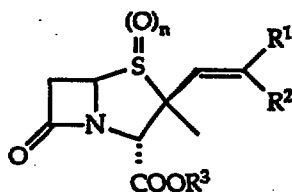
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2- β -ALKENYL PENAM SULFONES AS β -LACTAMASE INHIBITORS

Abstract

The present invention is concerned with penam derivatives, in particular it is concerned with 2 β -alkenyl-penam derivatives of the general formula



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wherein

one of R¹ and R² signifies -COR⁴, -CN, -CH₂R⁵, halogen, -CH=CHR⁶ or Q and the other signifies hydrogen or lower alkyl or both together signify a γ -lactam ring,

R³ signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R⁴ signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino, lower alkylamino or lower alkyl-lower alkoxyamino,

R⁵ signifies hydroxy, -OCONHR⁷, -OCONH₂ or a five- or six-membered hetero-aromatic ring which contains N,S and/or O and which is linked via a nitrogen atom,

R⁶ signifies -CN or CHO,

R⁷ signifies -COCH₂Cl,

Q signifies a five- or six-membered hetero-aromatic ring which contains N, S and/or O and

n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

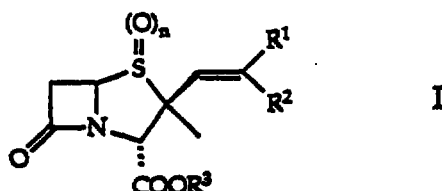
These compounds are good β -lactamase inhibitors. They can be used for the prevention or treatment of bacterial infections, optionally together with a β -lactam antibiotic.



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Claims

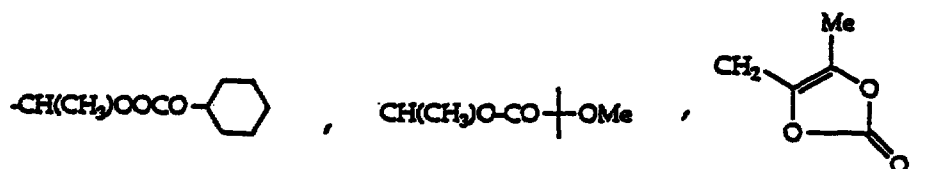
1. β -Alkenyl-penam derivatives of the general formula



wherein

one of R^1 and R^2 signifies $-\text{COR}^4$, $-\text{CN}$, $-\text{CH}_2\text{R}^5$, halogen, $-\text{CH}=\text{CHR}^6$ or Q and the other signifies hydrogen or C_1 - C_7 -alkyl or both together signify a γ -lactam ring,

R^3 signifies hydrogen, C_1 - C_7 -alkyl, benzyl, benzhydryl, p-methoxybenzyl, p-nitrobenzyl, ally or a residue which is cleavable in vivo and which contains an ester group, such as $-\text{CH}_2\text{OCCC}(\text{CH}_3)_3$,



or $-\text{CH}(\text{CH}_3)\text{OCO}-\text{CH}_3$,

- R^4 signifies hydrogen, C_1 - C_7 -alkyl, C_1 - C_7 -alkoxy, benzyloxy, amino, C_1 - C_7 -alkylamino or C_1 - C_7 -alkyl- C_1 - C_7 -alkoxyamino,
- R^5 signifies hydroxy, $-\text{OCONHR}^7$, $-\text{OCONH}_2$, or a five- or six-membered hetero-aromatic ring which contains N,S and/or O and which is linked via a nitrogen atom,
- R^6 signifies $-\text{CN}$ or $-\text{CHO}$,
- R^7 signifies $-\text{COCH}_2\text{Cl}$,
- Q signifies 2-pyridyl, 1-methyl-pyridin-2-yl, 1,3-thiazol-2-yl, 1,2,4-oxadiazol-3-yl and
- n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

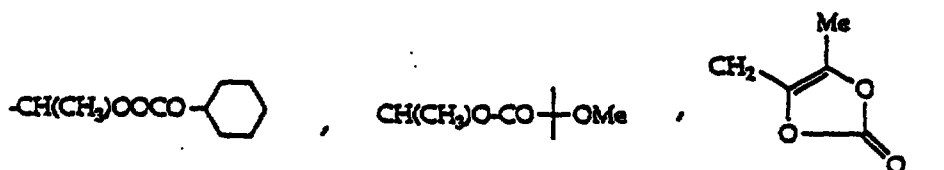


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2. Compounds according to claim 1, wherein

one of R^1 and R^2 signifies $-\text{COR}^4$, $-\text{CN}$ or $-\text{CH}_2\text{R}^5$ and the other signifies hydrogen or C_1 - C_7 -alkyl,

R^3 signifies hydrogen, C_1 - C_7 -alkyl, benzyl, benzhydryl, p-methoxybenzyl, p-nitrobenzyl, allyl or a residue which is cleavable in vivo and which contains an ester group, such as $-\text{CH}_2\text{O}(\text{COCH}_3)_3$,



or $-\text{CH}(\text{CH}_3)\text{OCO-CH}_3$,

R^4 signifies hydrogen, C_1 - C_7 -alkyl, C_1 - C_7 -alkoxy, benzyloxy, amino or C_1 - C_7 -alkylamino,

R^5 signifies hydroxy or $-\text{CONH}_2$ and

n signifies 0, 1 or 2

3. Compounds according to claim 1 or 2, wherein R^1 signifies CN , halogen or COR^4 , R^2 signifies hydrogen and R^4 signifies methyl, C_1 - C_7 -alkoxy, benzyloxy or amino.
4. Compounds according to any one of claims 1 to 3, where n signifies 0 or 2.
5. Compounds according to any of claims 1 to 4, wherein R^3 signifies hydrogen or benzhydryl.
6. The compound according to claim 1, benzhydryl (E/Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
7. The compound according to claim 1, benzhydryl (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.



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8. The compound according to claim 1, benzhydryl (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
9. The compound according to claim 1, sodium (E)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
10. The compound according to claim 1, sodium (Z)-(2S,3S,5R)-3-(2-cyanoethenyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
11. The compound according to claim 1, sodium (E)-(2S,3S,5R)-3-(2-chlorovinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
12. The compound according to claim 1, sodium (E)-(2S,3S,5R)-3-methyl-3-(3-oxo-but-1-enyl)-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate.
13. The compounds according to claim 1, benzhydryl (E/Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate,

sodium (E)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (Z)-(2S,3S,5R)-3-(2-carbamoyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,



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benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

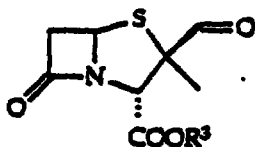
sodium (E)-(2S,3S,5R)-3-(2-ethoxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-7-oxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

benzhydryl (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

sodium (E)-(2S,3S,5R)-3-(2-benzyloxycarbonyl-vinyl)-3-methyl-4,4,7-trioxo-4-thia-1-aza-bicyclo[3.2.0]heptane-2-carboxylate,

14. Compounds of the general formula



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wherein R³ has the significance given in claim 1.

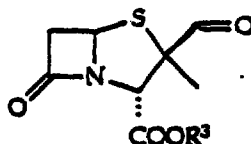
15. The compound according to claim 14, benzhydryl (2S,3R,5R)-3-formyl-3-methyl-7-oxo-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate.
16. Compounds according to any one of claims 1 to 13 for use as therapeutically active substances.
17. Compounds according to any one of claims 1 to 13 for use as β -lactamase inhibitors.



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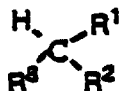
18. A process for the manufacture of compounds according to any one of claims 1 to 13, characterized by

a) reacting a compound of the general formula



II

wherein R^3 has the significance given in claim 1, with a compound of the general formula



wherein R^1 and R^2 have the significance given in claim 1 and R^3 signifies $P^{\oplus}(\text{aryl})_3$, $PO(\text{Oalkyl})_2$, $Si(\text{alkyl})_3$ or halogen, in the presence of an activating agent, or

b) oxidizing a compound of general formula I in which n signifies 0, or

c) converting a compound of general formula I in which R^3 is different from hydrogen into the corresponding free acid, and

d) if desired, converting an acidic compound of formula I into a pharmaceutically acceptable salt.

19. A medicament containing a compound according to any one of claims 1 to 13.
20. A β -lactamase-inhibiting medicament containing a compound according to any one of claims 1 to 13.
21. A medicament according to claim 19 or 20 which additionally contains a β -lactam antibiotic.



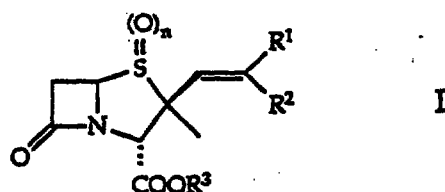
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22. A medicament according to claim 21 containing a penicillin, cephalosporin, penem or cabapenem as the β -lactam antibiotic.
23. A medicament according to claim 22 containing piperacillin, mezlocillin, azocillin, apalcillin, benzylpenicillin, phenoxymethylpenicillin, carbenicillin, methicillin, propicillin, ticarcillin, ampicillin, amoxicillin, mecillinam, ceftriaxone, ceftazidime, cefetamet, cefetamet pivoxil, cefotaxime, cefmenoxime, ceftizoxime, cefuroxime, cephaloridine, cephalotin, cefazolin, cephalixin, cefoxitin, cephaceterile, cefamandole, cephapirin, cephradine, cephaloglycine, cefpirone, cefepime, imipenem or meropenem or a pharmaceutically compatible salt of one of these compounds.
24. A medicament according to claim 22 containing ceftriaxone or one of its pharmaceutically compatible salts.
25. A medicament according to any one of claims 21 to 24 as a combination preparation for the simultaneous, separate or chronologically stepwise use in antibacterial therapy.
26. The use of compounds according to any one of claims 1 to 13 for the manufacture of a medicament for the control or prevention of illnesses.
27. The use of compounds according to any one of claims 1 to 13 for the manufacture of a medicament for the control or prevention of bacterial infections.
28. The use of compounds according to any one of claims 1 to 13 for the manufacture of antibacterially-active medicaments.

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2- β -ALKENYL PENAM SULFONES AS β -LACTAMASE INHIBITORSAbstract

The present invention is concerned with penam derivatives, in particular it is concerned with 2 β -alkenyl-penam derivatives of the general formula



wherein

one of R¹ and R² signifies -COR⁴, -CN, -CH₂R⁵, halogen, -CH=CHR⁶ or Q and the other signifies hydrogen or lower alkyl or both together signify a γ -lactam ring,

R³ signifies hydrogen, lower alkyl, aryl-alkyl, allyl or a residue which is cleavable in vivo,

R⁴ signifies hydrogen, lower alkyl, lower alkoxy, benzyloxy, amino, lower alkylamino or lower alkyl-lower alkoxyamino,

R⁵ signifies hydroxy, -OCONHR⁷, -CONH₂ or a five- or six-membered hetero-aromatic ring which contains N, S and/or O and which is linked via a nitrogen atom,

R⁶ signifies -CN or CHO,

R⁷ signifies -COCH₂Cl,

Q signifies a five- or six-membered hetero-aromatic ring which contains N, S and/or O and

n signifies 0, 1 or 2,

as well as pharmaceutically compatible salts of these compounds.

These compounds are good β -lactamase inhibitors. They can be used for the prevention or treatment of bacterial infections, optionally together with a β -lactam antibiotic.