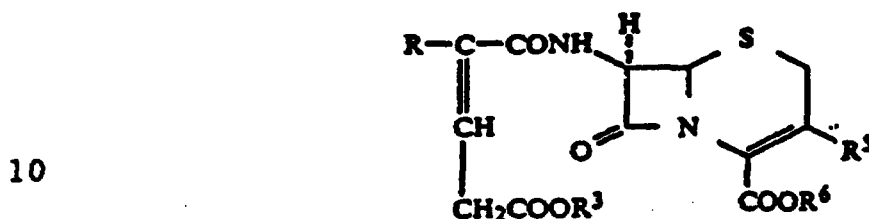


CARBOXYBUTENAMIDOCEPHALOSPORINS

This invention relates to antibacterial 7beta-(carboxybutenoylamino)-3-cephem-4-carboxylic acid
 5 represented by the following formula:



wherein:

15 R is optionally protected aminothiazolyl;
 R³ and R⁶ are each independently hydrogen,
 a carboxy-protecting group, a salt forming atom or
 group or a moiety forming a pharmaceutically
 available carboxy derivative; and

20 R⁵ is hydrogen or a 3-substituent of
 cephalosporins.

The groups R, R³, R⁵ and R⁶ are described
 in greater detail below:

R is optionally protected aminothiazolyl.
 25 Among the protecting groups in the protected amino,
 preferable are 7 to 20C optionally substituted
 aralkyl (e.g., benzyl, benzhydryl, trityl,
 methoxybenzyl, dimethoxybenzyl, nitrobenzyl,
 methylbenzyl, dimethylbenzyl), 1 to 8C optionally
 30 substituted alkyl (e.g., trichloromethyl,
 trichloroethyl, trifluoromethyl, tetrahydropyranyl),
 substituted phenylthio, 1 to 8C substituted
 alkylidene, 7 to 14C substituted aralkylidene, 5 to
 8C substituted cycloalkylidene, acyl [e.g. 1 to 8C
 35 optionally substituted alkanoyl (e.g., formyl,
 acetyl, chloroacetyl, trifluoroacetyl, 2 to 12C

optionally substituted lower alkoxy carbonyl (in which the alkyl part is methyl, ethyl, propyl, cyclopropylethyl, isopropyl, butyl, pentyl, hexyl, trichloroethyl, pyridylmethyl, cyclopentyl, cyclohexyl or quinolylmethyl), 8 to 15C optionally substituted aralkoxy carbonyl (in which the aralkyl part is benzyl, diphenylmethyl, or nitrobenzyl), succinyl, phthaloyl], trialkylsilyl, alkoxydialkylsilyl, and trialkylstannyl.

10 R^5 is a 3-substituent of cephalosporins and can be, among others, hydroxy, alkanoyloxy, halogen, alkoxy, alkylthio, alkenylthio, alkyl (e.g. methyl), alkenyl (e.g., vinyl, cyanovinyl, trifluoropropenyl), substituted methyl, or the like well known
15 3-substituents of cephalosporins. Here, the substituent in the said substituted methyl can be pyridinio, substituted pyridinio, halogen, hydroxy, alkoxy, acyloxy (e.g., acetoxy, carbamoyloxy), alkylthio, haloalkylthio, cyanoalkylthio,
20 heterocyclic thio (e.g., triazolylthio, methyltetrazolylthio, thiadiazolylthio optionally substituted by amino, aminomethyl, alkoxy, or methyl), triazolyl or tetrazolyl. Said alkyl part is preferably methyl. Preferably R^5 is hydrogen,
25 methyl, methoxymethyl, methylthiomethyl, cyanomethylthiomethyl, vinyl, cyanovinyl, fluoropropenyl, trifluoropropenyl, methoxy, chlorine, fluoroethylthio, trifluoroethylthio, acetoxymethyl, carbamoyloxymethyl, triazolylthiomethyl, methyl-
30 tetrazolylthiomethyl, or thiadiazolylthiomethyl, optionally substituted by amino, by aminomethyl or by methyl.

R^3 and R^6 as a carboxy-protecting group or a moiety forming a pharmaceutically available carboxy
35 derivative are preferably an ester-forming group or a salt forming atom or group.

The said salt forming moieties and carboxy-protecting groups which may constitute R^3 and/or R^6 are known in the penicillin and cephalosporin fields and can be introduced and removed without adverse effect on other parts of the molecule. Representative are an inorganic salt (e.g., lithium, sodium, potassium, magnesium, calcium, aluminium, or ammonium salt), organic base salt, for example, alkylamine salt (e.g., ethylamine, diethylamine, triethylamine, piperidine, morpholine, N-methyl-morpholine salt), aromatic amine salt (e.g., aniline, dimethylaniline salt), aromatic base salt (e.g., pyridine, picoline, lutidine, nicotinamide, quinoline salt), optionally substituted 1 to 8C alkyl ester (e.g., methyl, methoxymethyl, ethoxymethyl, ethyl, methoxyethyl, trichloroethyl, iodoethyl, propyl, isopropyl, ethoxyethyl, methylthioethyl, methanesulfonyl ethyl, methanesulfonmethyl, butyl, isobutyl, t-butyl, hexyl ester), 7 to 15C aralkyl ester (e.g., benzyl, methylbenzyl, dimethylbenzyl, methoxybenzyl, ethoxybenzyl, nitrobenzyl, aminobenzyl, phenethyl, diphenylmethyl, trityl, phthalidyl, phenacyl, di-t-butyl-hydroxybenzyl ester), 6 to 12C aryl ester (e.g., phenyl, tolyl, diisopropylphenyl, xylyl, trichlorophenyl, indanyl ester), 3 to 12C silyl ester (e.g., trimethylsilyl, t-butyldimethylsilyl, dimethylmethoxysilyl ester), 3 to 12C stannyl ester (e.g., trimethylstannyl ester), 1 to 12C N-hydroxyamino ester (ester with e.g., acetone oxim, acetophenone oxim, acetaldoxim, N-hydroxysuccinimide, N-hydroxyphthalimide) and 2 to 7C alkenyl ester (e.g., vinyl, propenyl, allyl ester). Anhydrides with carbonic or carboxylic acid, reactive amides, and the like are equivalent carboxy-protecting groups. Said protecting part may further be substituted.

Preferably R^3 and R^6 are hydrogen, sodium, potassium, methyl, t-butyl, phenyl, indanyl, benzyl, cyanobenzyl, halobenzyl, methylbenzyl, nitrobenzyl or phenylbenzyl.

5 The protecting group is absent in objective products. So, its structure has in itself no significance, so long as the group serves well for the protection and thus it can be replaced by a wide variety of equivalent groups.

10 Especially useful carboxy derivatives are medically available ones including light metal salts and pharmaceutically acceptable esters. The preferred light metals are those forming physiologically acceptable ions and belonging to the
15 1st to 3rd group, 2nd to 4th periods of the Periodic Table. Lithium, sodium, potassium, magnesium, calcium, and aluminium are preferable.

 The pharmacologically acceptable esters show antibacterial potency on oral or parenteral
20 administration and include well known 3 to 12C 1-substituted alkyl esters, for example, alkanoyloxyalkyl esters (e.g. acetoxymethyl, acetoxylethyl, propionyloxyethyl, pivaloyloxymethyl, pivaloyloxyethyl, tetrahydrofuryl or
25 tetrahydropyranyl ester), 3 to 8C alkoxyformyloxyalkyl esters (e.g. ethoxycarbonyloxyethyl ester), 7 to 15C substituted aralkyl esters (e.g., phenacyl or phthalidyl ester), 6 to 12C optionally substituted aryl esters (e.g.,
30 phenyl, xylyl or indanyl ester), and 2-alkenyl esters (e.g., allyl, 2-oxo-1,3-dioxolenylmethyl ester).

 It will be noted from comparison of the foregoing list of pharmacologically acceptable esters with the list of carboxy-protecting groups that some
35 groups (e.g. 6 to 12C aryl esters) fall in both categories, i.e. the two categories are not mutually

exclusive.

Both of the geometric isomers at the double bond in the 7-

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side chain are antibacterials. Among them, those having the R and H in the cis position are more potent antibacterials. The other geometric isomers (trans) are useful also as an intermediate for preparing the corresponding cis isomer.

5 Some of the representative Compounds (I) of this invention are listed below. These should not be taken as an exhaustive listing of the compounds of this invention.

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-cephem-4-carboxylic acid,

107beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-vinyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
15 3-trifluoropropenyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-acetoxymethyl-3-cephem-4-carboxylic acid,

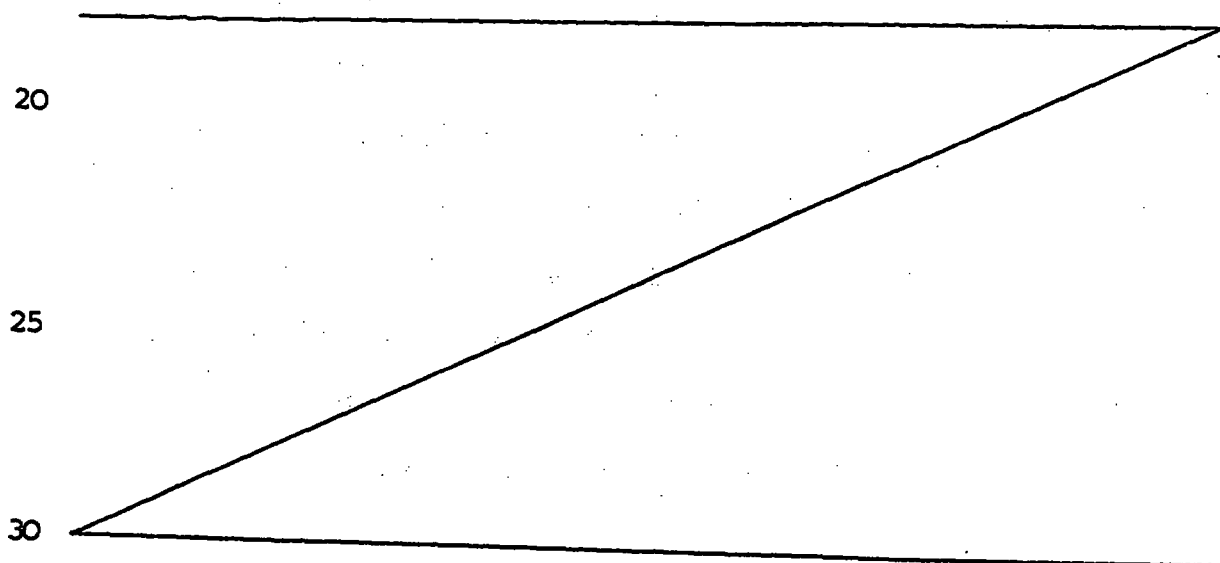
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-carbamoyloxymethyl-3-cephem-4-carboxylic acid,

20 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methoxymethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methylthiomethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
25 3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid,

- 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-pyridinioethyl-3-cephem-4-carboxylate,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-triazolylthiomethyl-3-cephem-4-carboxylic acid,
5 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-thiadiazolylthiomethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-methyltetrazolylthiomethyl-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
10 3-methoxy-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-chloro-3-cephem-4-carboxylic acid,
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-fluoroethylthio-3-cephem-4-carboxylic acid, and
15 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-
3-trifluoroethylthio-3-cephem-4-carboxylic acid,



Some compounds closely related to Compounds (I) are disclosed in Japanese patent publication Kokoku 10,996/1967, Kokai 57-93982, and Belgian Patent Nos. 816,408 and 888,389. 5 These are not superior to Compounds (I) in their antibacterial activity, enteral or parenteral absorbability, excretion, or the like characters.

Compounds (I) are antibacterials against aerobic Gram-positive bacteria (e.g., Bacillus cereus, Bacillus subtilis, 10 Corynebacterium diphtheriae, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus viridans, enterococci) and Gram-negative bacteria (e.g., Citrobacter diversus, Citrobacter freundii, Enterobacter aerogens, Enterobacter cloacae, Escheri- 15 chia coli, Haemophilus influenzae, Klebsiella pneumoniae, Neisseria gonorrhoeae, Neisseria meningitidis, Proteus mirabilis, Proteus morganii, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas aeruginosa, Salmonella paratyphi, Salmonella typhi, Serratia marcescens, Shigella sonnei, 20 Yersinia enterocolitica), including anaerobic bacteria (e.g., Bacteroides fragilis, Clostridium difficile, Clostridium perfringens, Eubacterium lentum, Fusobacterium nucleatum, Propionibacterium spp, peptostreptococci, Veillonella spp.).

Especially, high anti-Gram-negative potency, high 25 adsorption, excretion, and distribution are

remarkable. As a medicine for preventing or treating a bacterial infection, Compound (I) is administered orally, parenterally, or topically at a daily dose of 10 micrograms to 6 grams, if required formulating with conventional additives or 5coacting substances, e.g., other antibacterials.

They are useful as bacteriocidal, bacteriostatic, disinfecting, or antiperishable agents and useful for treating or preventing human, veterinary, or poultry infections caused by sensitive Gram-positive bacteria or Gram-negative bacteria, 10including anaerobic bacteria. Further, they are useful as bacterial growth inhibitors on human, animal, plant, or perishable subjects, human or animal growth promoting additives in foodstuff, or as an agents for testing sensitivity of bacteria to the antibacterial (I).

15 Protected compounds (I) are also useful as starting materials for synthesizing other antibacterials (I).

The compounds (I) may thus be used for treating or preventing human or veterinary bacterial infections (e.g., abscess, bronchitis, dermatitis, ear infections, empyema, 20 enteritis, gastroenteritis, nasopharyngitis, osteomyelitis, pneumonitis, pneumonia, pustulosis, pyelonephritis, respiratory tract infections, rhinitis, septicemia, tonsillitis, ulceration, urinary tract infections, wound and soft tissue infections) caused by sensitive bacteria by administering an 25 effective amount of Compound (I) at a typical daily dose of 10

micrograms to 1 gram externally, 0.2 to 5 grams intravenously, or 0.1 to 2 grams orally at an interval of 3 to 12 hours depending on the infecting bacteria and condition of the patient, if required formulating with a conventional additive.

5 Compound (I) as carboxylic acid or its light metal salt can be injected or infused intravenously, intramuscularly or subcutaneously (as e.g., injection, pellet), or given orally (as oral preparations, e.g., capsule, dry syrup, emulsion, granules, powder, solution, suspension, tablet, troche), if
10 required in admixture with an excipient (e.g., emulsifying agent). A pharmacological ester can be given intravenously, intramuscularly, subcutaneously, orally, externally, or topically (as e.g., ear, nasal, or ocular drug, ointment, inhalant, injection, pap preparation, spray, suppository).

15 When R is 2-amino-4-thiazolyl, R^3 , and R^6 are hydrogens, and R^1 is inter alia hydrogen, methyl, methoxymethyl, carbamoyloxymethyl, methylthiomethyl, cyanomethylthiomethyl, vinyl, fluoropropenyl, methoxy, chlorine, fluoroethylthio, or trifluoroethylthio, Compound (I) is absorbed orally as
20 well as subcutaneously. Its pharmaceutically acceptable esters are also absorbed through the digestive organs.

Further, this invention provides an antibacterial pharmaceutical composition containing Compound (I) in various enteral or parenteral dosage forms solely or in admixture with carriers
25 or coacting substances. The compositions may contain 0.01 to

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99 g of Compound (I) dissolved, dispersed, or suspended in solid or liquid pharmaceutical carriers.

The compositions may be solid preparations (e.g., capsule, dry syrup, granule, pellet, pill, powder, suppository, troche, 5 tablet) or liquid preparations (e.g., dispersion, elixir, emulsion, inhalant, injection, ointment, suspension, syrup, solution from ampoule or vial containing crystals, lyophilized material, or powder). They can be flavored or colored, and capsules, granules, and tablets may be coated. They can be in a 10 unit dosage form.

The carriers are harmless to both of Compound (I) and patients. Representative examples of such carriers are, among others, for solids, binders (e.g., acacia, carboxymethyl-cellulose, gelatin, glucose, polyvinylpyrrolidone, sodium 15 alginate, sorbitol, starch, syrup, tragacanth), bulking agents (e.g., bentonite, calcium carbonate, calcium phosphate, glycine, kaolin, lactose, polycarboxymethylene, salt, sorbitol, starch, sugar, talc), diluents (e.g., calcium carbonate, kaolin, lactose, starch, sucrose), disintegrators (e.g., agar, 20 carbonates, sodium laurylsulfate, starch), lubricants (e.g., boric acid, cacao oil, magnesium stearate, paraffin, polyethylene glycol, silica, sodium benzoate, stearic acid, talc), and wetting agents (e.g., hydroxypropyl cellulose); for solutions, solvents (e.g., alcohol, buffer, methyl oleate, 25 peanut oil, sesame oil, water), emulsifying

agents (e.g., acacia, lethicin, sorbitan monooleate), suspending agents (e.g., aluminum stearate gel, carboxymethyl cellulose, gelatin, glucose, hydrogenated fats, hydroxyethyl-cellulose, methyl cellulose, sorbitol, sugar syrup), buffers, dispersing agents, and solubilizing agents; and for both, preservatives (e.g., methyl or ethyl p-hydroxybenzoate, sorbic acid), absorption promoters (e.g., glycerin mono- or di-octanoate), antioxidants, aromatic substaces, analgesics, edible coloring agents, and stabilizing agents.

10 All of above pharmaceutical preparations can be prepared in conventional manners.

Patent Application No 8700123 (a divisional of the present application) relates to Carboxyalkenoic acids.



wherein R, R³ and R⁶ are as defined for Compound (I)

In the formula above, examples of preferable R are phenyl, thienyl, aminoisoxazolyl, thiadiazolyl, aminothiadiazolyl, and aminothiazolyl, said amino can be protected with benzyloxy-carbonyl, methylbenzyloxycarbonyl, t-butoxycarbonyl, methoxyethoxymethyl, formyl, chloroacetyl, benzylidene and dimethylaminomethylidene; and examples of preferable R³ and R⁶ are the same or different groups selected from hydrogen, methyl,

ethyl, t-butyl, trichloroethyl, benzyl, methylbenzyl, diphenylmethyl, and trityl.

Compounds of this invention can be synthesized, for example, by the following methods:

5(1) Salt formation

Compound (I) having carboxy on cephem nucleus at position 4 or in 7-substituent can form a light metal salt (I) by reacting with a base or by an exchange reaction with the corresponding light metal salt of other carboxylic acid. The procedure can be that conventional in the art, e.g., by neutralizing the free acid (with a base, e.g., light metal hydroxide, carbonate, or hydrogen carbonate) and evaporating the solvent, or by treating with light metal lower carboxylate in a polar organic solvent (e.g., alcohol, ketone, ester) and then adding a sparingly soluble less polar solvent to separate the salt. The solvent may be removed by filtering.

(2) Deprotection of carboxy-protecting groups etc.

A protected-carboxy in Compound (I) can conventionally be deprotected, for example, as follows:

- 20 a) A highly reactive ester or anhydride as a carboxy-protecting group can be deprotected by contacting in an aqueous solvent with an acid, base, buffer solution, or ion exchange resin. When its reactivity is insufficient, one can increase it in a conventional manner to deprotect more easily (e.g., by activating of a trichloroethyl ester with metal and acid;
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p-nitrobenzyl ester with hydrogen and catalyst (e.g., palladium, nickel), dithionate, or metal and acid; and phenacyl ester with irradiation).

b) An aralkyl ester can be deprotected by a conventional catalytic reduction with hydrogen in the presence of a catalyst (e.g., platinum, palladium, nickel).

c) An aralkyl, cyclopropylmethyl, sulfonylethyl, or the like ester can be deprotected by solvolyzing [with a mineral acid, Lewis acid (e.g., aluminium chloride, tin chloride, titanium tetrachloride), sulfonic acid (e.g., methanesulfonic acid, trifluoromethanesulfonic acid), or strong carboxylic acid (trifluoroacetic acid), if required in the presence of a cation scavenger.

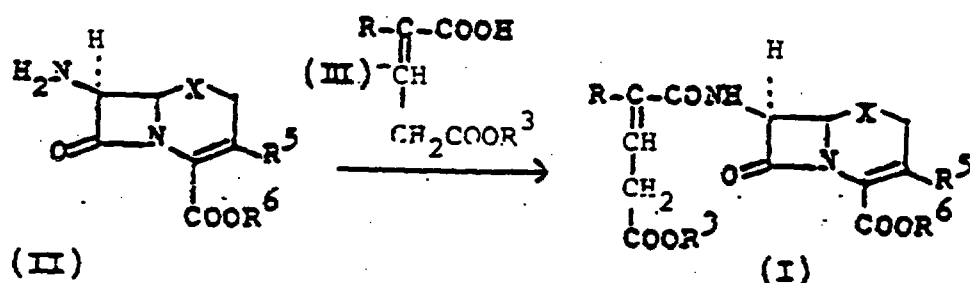
An amino-protecting group in Compound (I) can conventionally be deprotected, for example, as follows: substituted alkyl (e.g., tetrahydropyranyl), aralkyl group (e.g., trityl), alkylidene, aralkylidene, alkanoyl (e.g. formyl), trialkylsilyl, trialkylstannyl, or the like can be deprotected with an aqueous or nonaqueous acid; an alkoxyformyl (e.g., t-butoxycarbonyl), aralkoxyformyl (e.g., benzyloxycarbonyl, methylbenzyloxycarbonyl), aralkyl (e.g., trityl), or the like can be deprotected with a Lewis acid in the presence of an acid scavenger; haloalkoxycarbonyl (e.g., trichloroethyl, iodoethoxycarbonyl) or aralkoxycarbonyl (e.g., benzyloxycarbonyl), can be deprotected by reduction; and phenylthio or

acyl (e.g., alkanoyl, succinyl, phthaloyl) can be deprotected with a base.

Deprotection of other protecting groups for hydroxy or the like functional groups in Compound (I) can be carried out according to methods well known in the field of penicillin and cephalosporin chemistry as described in various scientific and patent literatures.

(3) Amidation

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A conventional reaction of Amine (II) or its reactive derivative with Carboxylic acid (III) or its reactive derivative gives Compound (I) or its derivatives.

The reactive derivative of Amine (II) is that having 7-amino activated by silyl (e.g., trimethylsilyl, methoxydimethylsilyl, t-butyldimethylsilyl), stannyl (e.g., trimethylstannyl), alkylene (as a part of enamino of the amino with e.g., aldehyde, acetone, acetylacetone, acetoacetate, acetoacetonitrile, acetoacetanilide, cyclopentanedicone, acetylbutyrolactone), alkylidene (e.g., 1-haloalkylidene,

1-haloaralkylidene, 1-alkoxyalkylidene, 1-alkoxyaralkylidene, 1-alkoxy-1-phenoxyalkylidene, alkylidene, aralkylidene), acid (e.g., mineral acid, carboxylic acid, sulfonic acid as a salt of the amino), or easily removable acyl (e.g., alkanoyl),

5 or that protected at other functions of the molecule.

Free acid (III) is reacted in the presence of a condensing reagent [carbodiimide (e.g., N,N'-diethylcarbodiimide, N,N'-dicyclohexylcarbodiimide), carbonyl compound (e.g., carbonyl diimidazole), isoxazolinium salt, acylamino compound (e.g., 10 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline), etc.].

The reactive derivative of Carboxylic acid (I) can be an acid anhydride, e.g., symmetric anhydride or mixed anhydride [with mineral acid (e.g., phosphoric acid, sulfuric acid, hydrohalogenic acid, carbonic half ester), organic acid (e.g., 15 alcanoic acid, aralkanoic acid, sulfonic acid), intramolecular anhydride (e.g., ketene, isocyanate), etc.], acid halide, reactive ester [enol ester (e.g., vinyl ester, isopropenyl ester), aryl ester (e.g., phenyl ester, halophenyl ester, nitrophenyl ester), heterocyclic ester (e.g., pyridyl ester, 20 benzotriazolylester), an ester with N-hydroxy compound, diacylhydroxylamine ester (e.g. N-hydroxysuccinimide ester, N-hydroxyphthalimide ester), thioester (e.g., aralkyl thiol ester, heterocyclic thiol ester) or the like], or reactive amide [aromatic amide (amide with e.g., imidazole, triazole, 25 2-ethoxy-1,2-dihydroquinoline), diacylanilide]. The acid

scavenger to be used with the said derivative is, for example, inorganic base (e.g., oxide, hydroxide, carbonate, hydrogen carbonate, of alkali metal or alkaline earth metal, etc.), organic base (e.g., tertiary amine, aromatic base), oxirane, 5 (e.g., alkylene oxide, aralkylene oxide), pyridinium salt (e.g., tripyridiniumtriazine trichloride), or adsorbent (e.g., Celite), CELITE is a Trade Mark.

(4) Introduction of 3-function

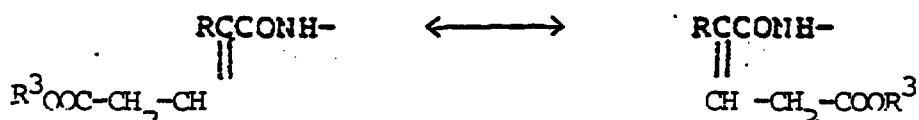
Compound (I) having 3-nucleophile substituted-methyl can be 10 prepared by reacting an analog of Compound (I) having a leaving group-substituted methyl at the 3 position on cephem ring with a heterocyclic thiol, aromatic base, or its reactive derivatives. Here, the leaving group can be, among others, halogen, sulfonyloxy, alkanoyloxy, dihaloalkanoyloxy, or 15 trihaloacetoxo.

The said reactive derivative of thiol can be among others, alkali metal salt, ammonium salt, or carboxylate ester. The reaction can be carried out well in a dry or wet solvent at 0°C to 60°C. This reaction can be promoted with eg. a dehydrating reagent, phosphoryl chloride 20 compound or rhodanate.

Compound (I) having 3-acyloxymethyl (e.g., alkanoyloxy-methyl, carbamoyloxymethyl) can be made from the corresponding 4-protected carboxy-3-hydroxymethyl-3-cephem derivative by the action of an acylating reagent for introducing the correspond- 25 ing acyl group.

Compound (I) having no carbon linked to the 3 position can be made from the corresponding 3-hydroxy-3-cephem or its oxo form, for example, by activating the 3-hydroxy (e.g., acylating or halogenating), and then substituting it with a nucleophilic reagent to give a 3-nucleophile substituted compound; a basic or thermal elimination reaction of the corresponding 3-(hydroxy, acyloxy, or halo)cepham compounds or a reduction of 3-(acyloxy or halo)-3-cephem compounds to give a 3-hydrogen-3-cephem compound; or the like conventional 3-modification.

10 (5) Isomerization at the 7-side chain double bond



The said geometric isomers are interconvertible by isomerization. This reaction is preferably carried out in a protic solvent by the action of acid, base, or light. The acid can be a mineral acid (e.g., hydrochloric acid, sulfuric acid, phosphoric acid), carboxylic acid (e.g., formic acid, trifluoroacetic acid), sulfonic acid (e.g., methanesulfonic acid, benzenesulfonic acid), or the like. The base can be inorganic base (e.g., sodium hydroxide, sodium hydrogen carbonate, potassium carbonate), or organic base (e.g., triethylamine, potassium t-butoxide),

Compound (I) easily isomerizes under various conditions.

25 In a typical condition, Compound (I) as free carboxylic

acid is dissolved in water at pH 8, acidified to pH 0 to 1, kept at 0°C to 100°C for 1 to 10 hours to obtain an epimic mixture. Thermally stable isomer is in trans form. Usual separation (e.g., crystallization, precipitation, high precision liquid chromatography, adsorption and elution) gives the geometric isomers in a pure form.

(6) Other synthetic methods

a) Sulfoxide formation:--- Cephem compound (I) is conventionally oxidized with an oxidizing reagent (e.g., hydrogen peroxide, percarboxylic acid, iodobenzene dichloride) in an inert solvent at 0 to 60°C for 0.2 to 5 hours to give the corresponding Cephem-1-oxide (I).

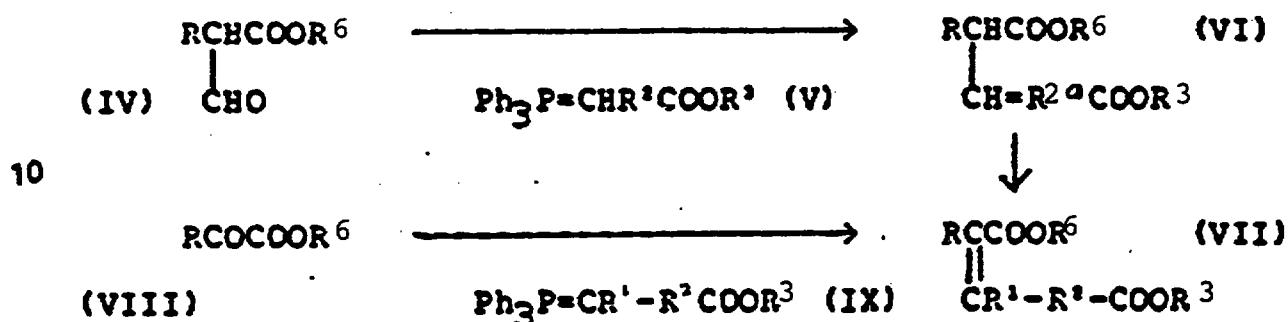
b) Sulfoxide reduction:--- Cephem-1-oxide compound (I) is reduced conventionally with a trivalent phosphorus compound, lower valent metal compound, or hydrogen iodide in an inert solvent at 0 to 80°C for 0.1 to 10 hours giving the corresponding Cephem compound (I).

c) Double bond migration:--- The 2-double bond of the corresponding 2-cephem compound is conventionally migrated with base at 0 to 80°C for 1 to 10 hours to give 3-Cephem compound (I).

d) Ring closure:--- Compound (I) may be synthesized by a conventional ring closure reaction forming a heterocyclic R group in a manner analogous to those described above under the section of (7) Synthesis of the side chain acids.

(7) Synthesis of the side chain fragment acids

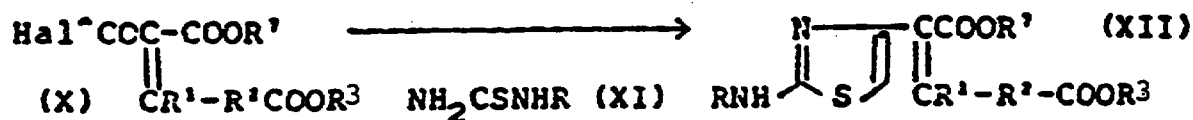
The 7-side chain acids are novel compounds prepared by Wittig type reaction of Formylacetate (IV) or its enol or acetal with Alkylidenetriarylphosphorane (V) by heating, e.g., 5 at 30°C to 120°C for 1 to 10 hours, to give Nonconjugated ester (VI) the double bond of which migrates to give Conjugate ester (VII):



(wherein and $\text{R}^{1,2}$ is alkylene or a single bond, R^1 is H and R^2 is CH_2) or of Oxalate (VIII) with Alkylidenetriarylphosphorane (IX), 15 e.g., at 30°C to 120°C for 1 to 10 hours to give Conjugate ester (VII).

Alternatively, it is produced by a ring closure of Haloacetylcarboxylic acid (X) with optionally N-protected thiourea (XI) in alcohol at 30°C to 90°C for 1 to 5 hours giving

20 Aminothiazole ester (XII):



(wherein $\text{R}^{1,2}$ is hydrogen or amino protecting group, R^1 is H and R^2 is CH_2) When R^3 and/or R^6 of Conjugated acid (XII) or (XII) is a 25 carboxy protecting group, it may be deprotected conventionally

by treating with acid, base, Lewis acid and cation scavenger or hydrogen and catalyst, to give the corresponding Free acid, preferably in an inert solvent at -60°C to 100°C for 1/6 to 10 hours.

5 Representative synthesis of the side chain carboxylic acids are given under the section of Preparations.

(8) Reaction Conditions

The said reactions (1) to (7) can usually be carried out at -60°C to 120°C , preferably at -20°C to 80°C for 10 minutes to 10 10 hours depending on the type of reaction. These are done in a solvent. Other conventional conditions (e.g., stirring, shaking, inert gas sealing, drying) may be used.

Examples of typical reaction solvents are hydrocarbons (e.g., pentane, hexane, octane, benzene, toluene, xylene), 15 halohydrocarbons (e.g., dichloromethane, chloroform, carbon tetrachloride, dichloroethane, trichloroethane, chlorobenzene), ethers (e.g., diethyl ether, methyl isobutyl ether, dioxane, tetrahydrofuran), ketones (e.g., acetone, methyl ethyl ketone, cyclohexanone), esters (e.g., ethyl acetate, isobutyl 20 acetate, methyl benzoate), nitrohydrocarbons (e.g., nitromethane, nitrobenzene), nitriles (e.g., acetonitrile, benzonitrile), amides (e.g., formamide, acetamide, dimethylformamide, dimethylacetamide, hexamethylphosphorotriamide), sulfoxides (e.g., dimethyl sulfoxide), carboxylic acids (e.g., 25 formic acid, acetic acid, propionic acid), organic bases (e.g.,

diethylamine, triethylamine, pyridine, picoline, collidine, quincline), alcohols (e.g., methanol, ethanol, propanol, hexanol, octanol, benzyl alcohol), water, and other industrial solvents and mixtures thereof.

5 (9) Work up

The products can be obtained from a reaction mixture by removing contaminants (e.g., solvents, unreacted starting materials, by-products) by a conventional method (e.g., extracting, evaporating, washing, concentrating, precipitating, 10 filtrating, drying), and isolating the product by a usual work up (e.g., adsorbing, eluting, distilling, precipitating, separating, chromatographing), or a combination of said procedures.

(10) Oral availability

15 Compounds (I) are absorbed well

through digestive organ and available as oral cephalosporins. Especially efficient are those having hydrogen, vinyl, cyano-vinyl, trifluoropropenyl, acetoxymethyl, carbamoyloxymethyl, and thiadiazolylthiomethyl as R'. It is to be noted that

20 compounds (I) having a single bond, dimethylene, or

trimethylene in place of the methylene group in the carboxylic γ -side chain or that having no carboxylic γ -side chain are practically unabsorbed enterally. The amino group of the aminothiazolyl group can form a salt by mixing with an acid, e.g., mineral acid (e.g. HCl), carboxylic acid (TFA).

Examples

Following examples illustrate the embodiments of this invention.

In the Examples, "part" shows part by weight and 5 "equivalent" shows molar equivalent of the beta-lactam starting material. Symbols "cis" and "trans" show relative position of amido and carboxylic substituents attaching to the side chain double bond. Physicochemical constants of the products are summarized in Tables in which IR shows cm^{-1} value, 10 NMR shows δ -value, and J value shows coupling constants in Hz scale. In NMR of a geometric isomer mixture, signals splitting into two or more are shown by chemical shifts separating with comma and splitting number and "X" before multiplicity mark.

Usually the reaction mixture is, if required after adding 15 a solvent (e.g., water, acid, dichloromethane), washed, dried, and concentrated, and the product is separated. All concentrating are done in reduced pressure.

(Abbreviations) AOM = acetoxymethyl; BE = diphenylmethyl; Bu = butyl; BOC = t-butoxycarbonyl; Bzl = benzyl; Cbz = benzyloxy- 20 carbonyl; circle in a hetero ring of the structural formula = the ring is aromatic; exo = 3,4-double bond position isomer in the 7-side chain acyl; Me = methyl; MEM = methoxyethoxymethyl; Ph = phenyl; PMB = p-methoxybenzyl; PNB = p-nitrobenzyl; and POM = pivaloyloxymethyl.

Example 1 (Sodium salt)

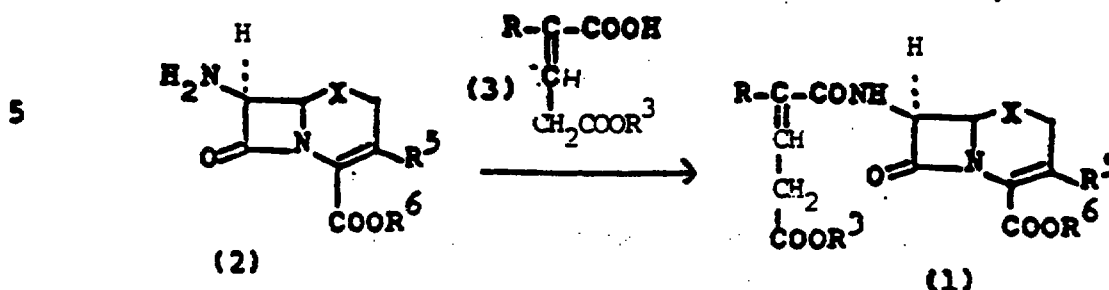
- 1) A solution of carboxylic acid (1) in Table 2 (1 g) in aqueous 0.5% sodium hydrogen carbonate (6 ml) adjusted to pH 7 with hydrochloric acid is washed with ethyl acetate, desalted, and poured into a 10 ml vial. This is lyophilized conventionally to give the corresponding sodium salt (2) as powder.
 - 2) Similarly, to a suspension of carboxylic acid (I) (1 g) of Table 2 in water is added aqueous sodium carbonate to make a solution of pH 6.5. The solution is desalted and poured into 10 ml vials, and lyophilized to give a sodium salt preparation same to above.
 - 3) The sodium salt (1 g) produced under sterile condition is dissolved in sterile water (4 g) and is given twice a day orally or intravenously to a patient suffering from
- 15 Staphylococcus aureus infection for treating said disease.
- 4) Each one of the carboxylic acids on Table 2 are dissolved in aqueous sodium hydrogen carbonate and assayed as the sodium salts for MIC by the standard method of Japan Society of Chemotherapy to give values of 3.1 to 0.2 microgram/ml against
- 20 Streptococcus pyogenes C-203 and 0.8 to 0.025 microgram/ml against Escherichia coli H.

Example 2 (Amidation)

A 7-beta-amino compound (2) (1 equivalent) is treated with carboxylic acid corresponding to the 7-beta-side chain (3) or

25 its reactive derivative to give amide (1), for

example, by a method as exemplified below:



1) In a mixture of dichloromethane (10 volumes), 2-ethoxy-101-ethoxycarbonyl-1,2-dihydroquinoline (1.1 equivalents), N,N'-dicyclohexylcarbodiimide (1.1 equivalents), pyridine (1.5 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 1 to 6 hours at 0°C to room temperature.

2) In a mixture of ethyl acetate (10 volumes), di-2-15 pyridyl disulfide (1.1 equivalents), triphenylphosphine (1.1 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 2 to 6 hours at 10 to 50°C.

3) In a mixture of dichloromethane (3 volumes), 1,3,5-tripyridiniumtriazine trichloride (4 equivalents), and Example 20 carboxylic acid (3) (1.1 equivalents), stirred for 1 to 5 hours at -10 to 10°C.

4) In a mixture of carbon tetrachloride (30 volumes), 4-methylmorpholine (1.5 equivalents), trisdiethylaminophosphine (1.1 equivalents) and carboxylic acid (3) (1.1 equivalents), 25 kept at -20 to 10°C for 1 to 5 hours.

5) In a mixture of chloroform (10 volumes) and dimethoxyethane (10 volumes), triethylamine (1.5 moles), and a mixed anhydride of carboxylic acid (3) and isobutoxyformic acid, stirred at a temperature between -5 to 10°C over a 30 5 minutes and 6 hours time.

6) In a mixture of ethyl acetate (10 volumes), 1,2-dichloroethane (10 volumes), 4-methylmorpholine (1.5 equivalents), and the symmetric anhydride of carboxylic acid (3) (1.1 equivalents), refluxed for 10 minutes to 2 hours.

10 7) In a mixture of dichloromethane (10 volumes), pyridine (1.5 equivalents), and mixed anhydride of carboxylic acid (3) and methanesulfonic acid (1.1 equivalents), stirred for 1 to 3 hours at between -70°C and room temperature.

8) In a mixture of ethyl acetate (10 volumes), pyridine 15 (1.5 equivalents) and a mixed anhydride of diethyl hydrogen phosphate and carboxylic acid (3) (1.5 equivalents), stirred at 0°C to 10°C for 1 to 5 hours.

9) In a mixture of ethyl acetate (10 volumes), dichloromethane (10 volumes), N-methylmorpholine (1 equivalent), and 20 mixed anhydride of carboxylic acid (3) and dichlorophosphoric acid (1.1 equivalents), stirred for 1 to 3 hours at 0°C to room temperature.

10) In a mixture of lutidine (1.5 equivalents), dichloromethane (10 volumes), and the mixed anhydride (1.1 to 2 25 equivalents) of carboxylic acid (3) and monochlorophosphoric

acid dimethylamide, stirred for 1 to 4 hours at 0 to 30°C.

11) In a mixture of dichloromethane (5 volumes), trifluoroacetic anhydride (1.5 equivalents), pyridine (3 equivalents), and carboxylic acid (3) (1.5 equivalents), stirred for 1 to 5 hours at 0°C to room temperature.

12) In a mixture of dichloromethane (10 volumes), bromide of diethyl hydrogen phosphate (1.2 equivalents), 4-methylmorpholine (2.5 equivalents), and carboxylic acid (3) (1.2 equivalents), stirred for 1 to 3 hours at 0°C to room temperature.

13) Amine (2) having carboxy at position 4 of cephem ring is dissolved in aqueous (10 volumes) sodium hydrogen carbonate (2.5 equivalents). Carboxylic acid (3) chloride (1.1 equivalents) is dropwise added thereto. The mixture is kept at 15-5°C to room temperature for 30 minutes to 2 hours.

14) Amine (2) having carboxy at position 4 of cephem ring is treated with trimethylsilyl chloride and triethylamine (1.2 equivalents each), and then treated with pyridine (4 equivalents) and carboxylic acid (3) chloride (1.1 equivalents) at 20-30°C for between 30 minutes and 2 hours, and then the resulting silyl ester is hydrolyzed with acid.

15) In a solution of picoline (4 equivalents) and carboxylic acid (3) chloride (1.2 equivalents) in dichloromethane (20 volumes) at 0°C to -30°C over 30 minutes and 2 hours.

16) In a mixture of dimethylformamide (2 volumes) and ethyl acetate (10 volumes), stirred with triethylamine (1.1 equivalents) and carboxylic acid (3) chloride (1.1 equivalents) at 0°C to 20°C for between 30 minutes and 3 hours.

5 17) In a mixture of dichloromethane (30 volumes), cyanuric chloride (1.1 equivalents), pyridine (4 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 5 minutes to 2 hours at -30°C to 10°C.

18) In a mixture of dichloromethane (3 volumes), 10 phosphorus oxychloride (1.1 equivalents), triethylamine (1.5 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 20 minutes to 2 hours at -10°C to 10°C.

19) Amine (2) is treated with trimethylsilyl chloride and an acid scavenger to obtain the corresponding N-trimethylsilyl 15 compound, and this is treated with phosphorus oxychloride (1.5 equivalents), carboxylic acid (3) (1.2 equivalents), and dimethylaniline (4 equivalents) in dichloromethane (5 parts) for 30 minutes to 2 hours at 0°C to room temperature.

20) In a mixture of dichloromethane (8 volumes), 20 thionylchloride (1.5 equivalents), pyridine (2.5 equivalents), and carboxylic acid (3) (1.1 equivalents), stirred for 1 to 5 hours at -30 to 0°C.

21) In a mixture of chloroform (3 volumes), toluene (1 volume), picoline (2 equivalents), oxalyl chloride (1 25 equivalent), and carboxylic acid (3) (1.1 equivalents),

stirred for 10 minutes to 2 hours at -50°C to 10°C .

22) In a mixture of dichloromethane (20 volumes), pyridine (3 equivalents), and benzotriazolyl ester of carboxylic acid (3) (3 equivalents), stirred for 5 to 30 hours at 10 to 50°C .

5 23) In a mixture of dichloromethane (20 volumes), 1-ethoxycarbonyl-1,2-dihydroquinoline (2.5 equivalents) and carboxylic acid (3) (2 equivalents), stirred at room temperature for 1 to 15 hours.

24) In a mixture of dioxane (10 volumes) and phthalimido ester of carboxylic acid (3) (2 equivalents), stirred for 2 to 8 hours at 10 to 50°C .

25) In a mixture of methyl isobutyl ketone (10 volumes) and succinimido ester of carboxylic acid (3) (1.5 equivalents), stirred for 2 to 9 hours at 0 to 40°C .

15 26) In a mixture of carbonyldiimidazole (1.1 equivalents), tetrahydrofuran (10 volumes), dimethylacetamide (5 volumes), and carboxylic acid (3) (1.1 equivalents), stirred for 1 to 5 hours at 0°C to room temperature.

27) In a mixture of dimethylformamide (5 volumes), 20 dimethylaniline (1.3 equivalents) carboxylic acid (3) and the Vilsmeier reagent made from dimethylformamide (1.1 equivalents), stirred at room temperature for 1 to 5 hours.

28) In a mixture of dichloromethane (10 volumes), dimethylformamide (5 volumes), N,N-dicyclohexylcarbodiimide

(1.1 equivalents), picoline (1.2 equivalents), and carboxylic acid (3) (1.1 equivalents), reacted for 2 hours to 24 hours.

29) To a solution of 7-amino-3-(1-methyl-5-tetrazolyl)-thiomethyl-3-cephem-4-carboxylic acid diphenylmethyl ester in 5-dichloromethane (50 parts) containing 2-(2-benzyloxycarbonylamido-4-thiazolyl)-4-benzyloxycarbonyl-2-butenic acid (1 equivalent) is added N,N'-dicyclohexylcarbodiimide (1 equivalent). After stirring for 2 hours at room temperature, the mixture is concentrated. The residue is triturated in ethyl acetate, filtered to remove solid, and purified by column chromatography to give 7-[2-(2-benzyloxycarbonylamino-4-thiazolyl)-4-benzyloxycarbonyl-2-butenoylamino]-3-(1-methyl-5-tetrazolyl)thiomethyl-3-cephem-4-carboxylic acid diphenylmethyl ester. Yield: 90 %.

15 30) To a solution of 7-amino-3-pyridinylmethyl-3-cephem-4-carboxylic acid chloride hydrochloride in a mixture of water (10 parts) and dioxane (15 parts) are added at 0°C sodium hydrogen carbonate (2 equivalents), 2-(2-benzyloxycarbonylamino-4-thiazolyl)-4-benzyloxycarbonyl-2-butenic acid (1.2
20 equivalents), 1-hydroxybenzotriazole (1.2 equivalents), N,N'-dicyclohexylcarbodiimide (1.2 equivalents), and dioxane (5 parts) at 0°C. After stirring at 0°C for 3.5 hours, the mixture is acidified with 1N-hydrochloric acid (5 parts) and filtered. The filtrate and acetone (50 parts) washing of the
25 solid are combined, purified by silica gel chromatography, and

lyophilized to give 7-[2-(2-benzyloxycarbonylamino-4-thiazol-yl)-4-benzyloxycarbonyl-2-butenoylamino]-3-pyridiniummethyl-3-cephem-4-carboxylate. Yield: 50.8 %.

Example 3 (Carboxy-Deprotection)

- 5 1) A solution of a t-butyl, p-methoxybenzyl, or diphenylmethyl ester of Table 1 in a mixture of dichloromethane (0.3 to 3 parts), trifluoroacetic acid (0.3 to 3 parts), and anisole (0.5 to 5 parts) is stirred for 10 minutes to 3 hours at between -10 and 40°C. The solution is concentrated to
10 remove the solvent and reagent. The residue is washed with benzene or ether to give the corresponding acid in 70 to 90 % yield.
- 2) To a solution of a t-butyl, benzyl, p-methylbenzyl, p-methoxybenzyl, or diphenylmethyl ester listed on Table 1 in
15 a mixture of dichloromethane (5 to 9 parts) and anisole (2 to 8 parts) is added aluminum chloride, tin tetrachloride, or titanium tetrachloride (3 to 12 equivalents) at between -10 and 10°C, and the mixture is stirred for 1 to 24 hours. The mixture is washed with diluted hydrochloric acid and water,
20 dried and concentrated to give the corresponding free acid in 80 to 95 % yield. t-Butoxycarbonylamino, N-t-butoxycarbonyl-N-methoxyethoxymethylamino, or benzyloxycarbonylamino group when present, is deprotected to give amino group.
- 3) To a solution of a t-butyl, benzyl, p-methylbenzyl,
25 p-methoxybenzyl, or diphenylmethyl ester listed on of Table 1

are added 90 % formic acid (5 to 6 parts) and anisole (2 to 3 parts). The mixture is stirred at 50 to 60°C for 1 to 4 hours to give the corresponding carboxylic acid in 40 to 50 % yield.

4) To a solution of a p-nitrobenzyl ester of Table 1 in 5 dichloromethane (60 parts) are added acetic acid (10 parts) and zinc powder (2 parts). After stirring for 2 hours at 0°C, the mixture is filtered to remove solid, diluted with water, and extracted with dichloromethane. The extract solution is washed with water and extracted with aqueous sodium hydrogen 10 carbonate. The aqueous layer is washed with hydrochloric acid to pH 2, and extracted with dichloromethane. This organic layer is washed with water, dried, and vacuum concentrated to give the corresponding free acid in 60 to 80 % yield.

5) The same ester can be deesterified by shaking with 15 hydrogen in the presence of the same amount of 5% palladium charcoal in dioxane at room temperature for 2 hours.

6) To a solution of 7-[2-(2-benzyloxycarbonylamino-4-thiazol-yl)-4-benzyloxycarbonyl-2-butenoylamino]-3-(1-methyl-5-tetra- 20 zolyl)thiomethyl-3-cephem-4-carboxylic acid diphenylmethyl ester in anisole (12 parts) is added aluminum chloride (9 equivalents). After stirring for 4 hours at 0°C, the mixture is neutralized with aqueous 5 % sodium hydrogen carbonate, filtered to remove solid, and washed with ethyl acetate. Aqueous layer is acidified with hydrochloric acid, washed with 25 ethyl acetate, and passed through a column of HP 20 or SP 207

(synthetic adsorbent produced by Mitsubishi Chemical K.K.). Adsorbed material is eluted with 80 % methanol to afford 7-[2-(2-amino-4-thiazolyl)-4-carboxy-2-butenoylamino]-3-(1-methyl-5-tetrazolyl)thiomethyl-3-cephem-4-carboxylic acid.

Yield: 65 %.

7) To a suspension of 7-[2-(2-benzyloxycarbonylamino-4-thiazolyl)-4-benzyloxycarbonyl-2-butenoylamino]-3-pyridinium-methyl-3-cephem-4-carboxylic acid in anisole (2 parts) is added a solution of aluminium chloride (9 equivalents) in anisole (20 parts) at 0°C. After stirring for 3.5 hours, the mixture is acidified with 10 % hydrochloric acid and washed with ethyl acetate. Aqueous layer is passed through a column of Diaion HP-20. Adsorbed material is eluted with aqueous 5 % acetone and the eluate lyophilized to give 7-[2-(2-amino-4-thiazolyl)-3-carboxymethylacrylamido]-3-pyridinylmethyl-3-cephem-4-carboxylic acid. Yield: 55 %.

8) In a manner similar to that of above 1) to 7), a free carboxy compound of Table 2 are prepared from the corresponding carboxy-protected compound of Table 1.

20 Example 4 (Amino deprotection)

1) A solution of a t-butoxycarbonylamino compound listed on Table 1 in a mixture of dichloromethane (0.3 to 3 parts), trifluoroacetic acid (0.3 to 3 parts), and anisole (0.5 to 5 parts) is stirred for 10 minutes to 3 hours at between -10 and 25 40°C. The solution is concentrated to remove the solvent and

reagent. The residue is washed with benzene to give the corresponding amino compound listed on Table 1 or 2 in 70 to 80 % yield.

2) To a solution of a t-butoxycarbonylamino, benzyloxy-5 carbonylamino, methylbenzyloxycarbonylamino, methoxyethoxymethylamino, or trityl amino compound listed on Table 1 (1 part) in a mixture of dichloromethane (5 to 9 parts) and anisole (2 to 8 parts) is added aluminum chloride, tin tetrachloride, or titanium tetrachloride (3 to 12 equivalents) 10 at between -10 and 10°C, and the mixture is stirred for 1 to 24 hours. The mixture is extracted with diluted hydrochloric acid and water, the aqueous layer is passed through a column of HP-20 absorbent to give the corresponding free amino compound listed on Table 1 or 2 in 60 to 80 % yield. A t-butyl, benzyl, 15 p-methylbenzyl, p-methoxybenzyl, or diphenylmethyl ester group when present, is deprotected to give free carboxy.

3) To a solution of a chloroacetamido compound of Table 1 in a mixture of tetrahydrofuran (15 parts) and methanol (15 parts) are added thiourea or N-methyldithiocarbamate (4 equivalents) 20 and sodium acetate (2 equivalents). After one night at room temperature, the mixture is concentrated, diluted with ethyl acetate, washed with saline, dried, and concentrated. The residue is chromatographed to give the corresponding amino compound.

25 4) To a solution of a formamido, Schiff base, silylamino, or

tritylamino compound listed on Table 1 in formic acid, acetic acid, or ethanol (10 parts) is added 1 to 3N-hydrochloric acid (0.1 to 3 parts), and the mixture is stirred for 1 to 3 hours at room temperature. The reaction mixture is concentrated, diluted with dichloromethane, washed with aqueous sodium hydrogen carbonate and water, dried and concentrated. The residue is purified in a conventional manner to give the corresponding free amino compound listed on Table 1 or 2.

5) To a solution of a benzyloxycarbonylamino compound listed on Table 1 in a mixture of ethanol and ethyl acetate (30 parts : 1:1) is added 5 % palladium charcoal (0.5 parts), and the mixture is shaken under hydrogen until the starting material is consumed. The reaction mixture is filtered to remove solid and concentrated to give the corresponding amino compound listed on Table 1 or 2.

Example 5 (Esterification)

(R³ and/or R⁶ = diphenylmethyl)

1) To a solution of compound (I) in which R³ and/or R⁶ is hydrogen in a mixture of dichloromethane and methanol (10 weights each) is added diphenyldiazomethane (2 equivalents). After stirring for 1 hour, the mixture is washed with hydrochloric acid and water, dried, and concentrated. The residue is crystallized from ethyl acetate to give the corresponding diphenylmethyl ester.

25 (R³ and/or R⁶ = POM)

2) To a solution of compound (I) wherein R^1 and/or R^2 is potassium in N,N-dimethylformamide (2 to 5 parts) is added iodomethyl pivalate (1 to 2 equivalents) under ice-salt cooling. After 15 minutes to 2 hour's stirring, the mixture is diluted with ethyl acetate, washed with ice water and aqueous sodium hydrogen carbonate, dried, and concentrated in vacuum. The residue is recrystallized from ethyl acetate to give the pivaloyloxymethyl ester of the carboxylic acid of Table 3.

3) The potassium salt of above section 2) is replaced by sodium salt to give the same products under the same condition.

4) The pivaloyloxymethyl ester of above section 2) (250 mg), corn starch (150 mg), and magnesium stearate (5 mg) are mixed, granulated, and encapsulated in a conventional manner. This capsule (2 to 3 capsules) are given orally to treat a patient suffering from infection caused by sensitive E. coli.

(R^1 and/or R^2 = AOM)

5) In place of iodomethyl pivalate of above 1), iodomethyl acetate is used under the same reaction condition to give the corresponding acetoxymethyl ester of Table 3.

Example 6 (Introduction of 3-substituents)

(R^3 = H)

1) To a solution of a compound listed on Table 1 and having methanesulfonyloxy or chlorine as R^1 in dichloromethane (13 parts) are added acetic acid (10 part) and zinc powder (2.5 parts) and the mixture is heated at 50°C for 5 hours. The

reaction mixture is filtered to remove solid, diluted with ethyl acetate, washed with diluted hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The residue is purified by silica gel chromatography eluting with a mixture of benzene and ethyl acetate to give the corresponding compound listed on Table 1 or 2 having hydrogen as R⁵ in 50 to 80 % yield.

2) Above reaction 1) is carried out at room temperature for 5 to 10 hours in the presence of a diluent isopropanol (4 parts) to give the same product in 40 to 60 % yield.

3) To a solution of 7beta-[2-(2-benzyloxycarbonylaminothiazol-4-yl)-4-benzyloxycarbonylbut-2-enoylamino]-3-hydroxycepham-4-carboxylic acid diphenylmethyl ester sulfoxide in dichloromethane (13 parts) are added pyridine (6 equivalents) and acetic anhydride (6 equivalents). After 13 hours' stirring at 0°C, the mixture is mixed with triethylamine (3 equivalents) and stirred for 24 hours. The reaction mixture is washed with water, aqueous sodium hydrogen carbonate, and water, dried, and concentrated to give 7beta-[2-(2-benzyloxycarbonylaminothiazol-204-yl)-4-benzyloxycarbonyl-2-butenoylamino]-3-cephem-4-carboxylic acid diphenylmethyl ester sulfoxide in 40 to 60 % yield.

(R⁵ = cyanomethylthiomethyl)

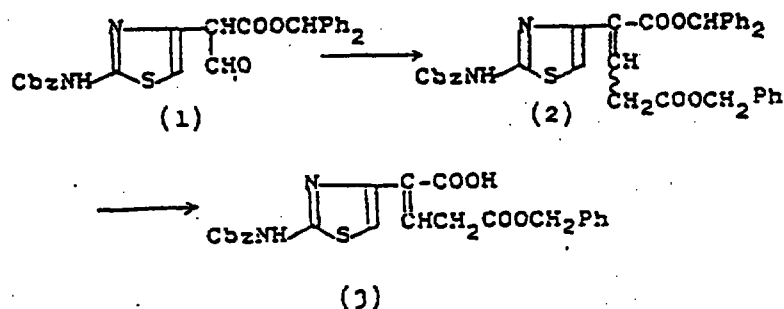
4) In the manner as given in Preparation B-4 a compound having bromomethyl as R⁵ is treated with sodium cyanomethyl mercaptide at -65°C to 70°C for 2 hours to give the corresponding compound

Preparations A Preparation of Carboxylic acids

Preparation A-1

2-(2-Benzyloxycarbonylaminothiazol-4-yl)-4-benzyloxycarbonyl-2-butenic acid (3)

5



10 1) A solution of formylacetate (1) and benzyloxycarbonyl-methylidenetriphenylphosphorane (1.3 equivalents) in dioxane or toluene (8 parts) is stirred for 1 to 6 hours at 80 to 120°C. After cooling, the mixture is concentrated, and the residue is purified by silica gel chromatography to give 15 propenedicarboxylate (2). Yield: 87 %. This is a mixture of 34 % cis and 53 % trans geometric isomers which can be separated after repeated chromatography.

IR (CHCl₃) ν : 3410, 1730 cm⁻¹ (trans).

IR (CHCl₃) ν : 3400, 1730 cm⁻¹ (cis).

20 2) To a solution of this product (2) in dichloromethane (10 parts) are added anisole (2 parts) and trifluoroacetic acid (2 parts). After stirring for 2 hours, the reaction mixture is concentrated, and the residue washed with a mixture of ether and hexane to give monobenzyl ester of the dicarboxylic acid 25 (3). Yield: 89 %. These geometric isomers can be separated by

listed on Table 1 having cyanomethylthiomethyl as R' in 50 to 60 % yield.

Example 7 (Sulfoxide reduction)

In a manner similar to that of Preparation B-4 2) using the same ratio of the reagents and solvents, the corresponding sulfoxide is reduced to give the cephem (sulfide) compounds of Table 1.

Example 8 (Double bond migration)

To a solution of 7beta-[2-(2-t-butoxycarbonylaminothiazol-4-yl)-4-benzyloxycarbonyl-2-butenoylamino]-3-chloro-2-cephem-4-carboxylic acid diphenylmethyl ester is reduced according to the method of Example 6 1) to induce concomitant double bond migration affording 7beta-[2-(2-aminothiazolyl-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid diphenylmethyl ester in 53% yield.

Example 9. (Amine salt)

To a solution of an amino compound listed on Table 2 in diluted hydrochloric acid is added acetonitrile. The precipitated material is collected by filtration to give the corresponding hydrochloric acid addition salt in good yield.

chromatography.

NMR (CDCl_3 - CD_3OD) δ : 3.51 (d, $J=7\text{Hz}$, 2H), 5.13 (s, 2H), 5.26 (s, 2H), 7.06 (s, 1H), 7.0 - 7.5 (m, 11H) (trans).

NMR (CDCl_3 - CD_3OD): δ 3.73 (d, $J=7\text{Hz}$, 2H), 5.13 (s, 2H), 7.10 (s, 1H), 7.0 - 7.5 (m, 11H) (cis).

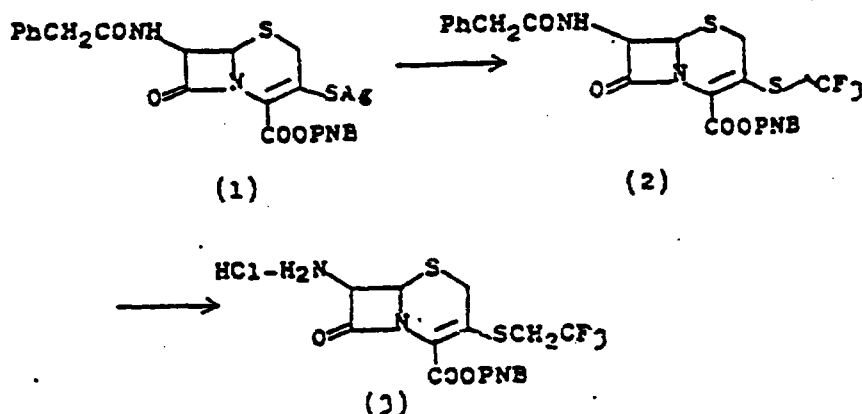
In a manner similar to that of Preparation A-1, a butenoic acid diester listed on Table 4 are prepared from the corresponding formylacetate using the same ratios of reactants and solvents at the same temperature for the same reaction 10 time. The obtained ester is, if required, totally or partially deesterified using a conventional reagent, e.g., sodium hydroxide for alkyl esters and a Lewis acid (e.g., aluminum, titanium, or tin halide) for t-alkyl or aralkyl esters, to give free acids.

Preparation B (Introduction of 3-substituents)

Preparation B-1

7beta-Amino-3-(2,2,2-trifluoroethylthio)-3-cephem-4-carboxylic acid p-nitrobenzyl ester (3)

5



10

1) To a suspension of silver mercaptide (1) (1.86 g) in hexamethylphosphorotriamide (45 ml) is added sodium iodide 15 (0.96 g). After stirring at room temperature for 50 minutes under nitrogen, the mixture is mixed with trifluoromethanesulfonic acid trifluoroethyl ester (2.95 g). After stirring at room temperature for 1 hour, the reaction mixture is poured into ice water and extracted with ethyl acetate. The extract 20 is washed with water, dried, and concentrated. The residue is purified by silica gel chromatography (eluting with benzene-ethyl acetate (2:1) mixture) to give sulfide (2) (1.03 g). mp. 159-160°C.

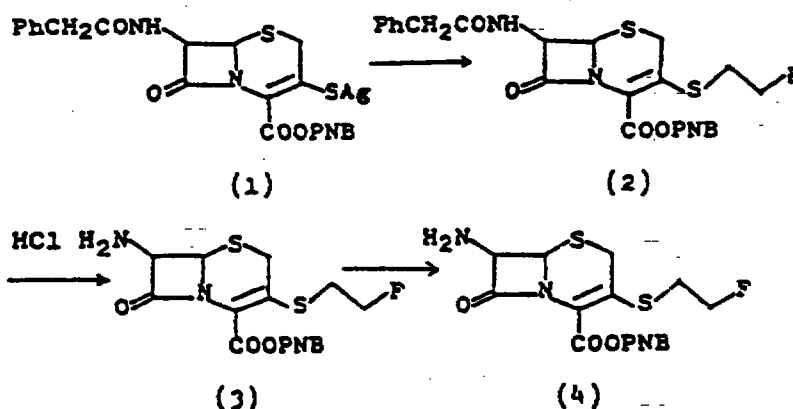
2) To an ice cold solution of sulfide (2) (690 mg) in 25 dichloromethane (22 ml) are added phosphorus pentachloride

(675 mg) and pyridine (0.288 ml). After stirring at room temperature for 2 hours, the mixture is cooled to -40°C , diluted with methanol (22 ml), stirred at 0°C for 2 hours, mixed with water (0.5 ml), and concentrated. The residue is triturated in ether to separate solid, which is suspended in dichloromethane, washed with aqueous sodium hydrogen carbonate and water, and concentrated to give amine (3) (562 mg).

IR (CHCl_3) ν : 3300br, 1775, 1735 cm^{-1} .

Preparation B-2

10 7beta-Amino-3-(2-fluoroethylthio)-3-cephem-4-carboxylic acid p-nitrobenzyl ester (4)



(1) To a suspension of silver mercaptide (1) (2 g) in hexamethylphosphorotriamide (60 ml) are added p-toluene-sulfonic acid 2-fluoroethyl ester (2.95 g) and sodium iodide (2.02 g). After keeping at room temperature for 4.5 hours, the mixture is poured into ice water (100 ml) and extracted with ethyl acetate. The extract is washed with water, dried, concentrated, dissolved in dichloromethane, and diluted with ether to separate thioether (2). mp. $144-149^{\circ}\text{C}$.

Yield: 87.8 %.

IR (CHCl_3) ν : 3400, 1780, 1720, 1680, 1630 cm^{-1} .

2) To a solution of thioether (2) (1.54 g) in dichloromethane (38.5 ml) are added pyridine (0.52 ml) and phosphorus pentachloride (1.207 g). After keeping at room temperature for 2.5 hours, the reaction mixture is cooled at -40°C , diluted with isobutanol (38.5 ml), kept at 0°C for 3 hours, and filtered to collect separated crystals of amine hydrochloride (3). Yield: 91 %.

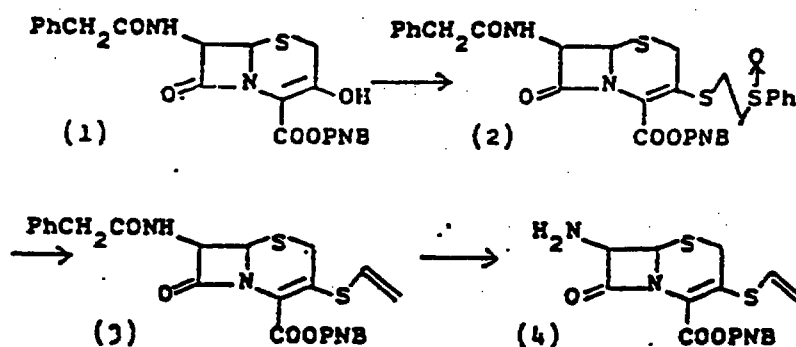
10 IR (Nujol) ν : 3140, 2645, 2585, 1773, 1604, 1600, 1512, 1492, 1460 cm^{-1} .

3) A mixture of amine hydrochloride (3) (1.186 g), ethyl acetate (50 ml), sodium hydrogen carbonate (1.107 g), and water (30 ml) is stirred at 0°C . Organic layer is washed with 15 aqueous sodium hydrogen carbonate and water, dried, and concentrated to give amine (4). Yield: 94.2 %.

IR (CHCl_3) ν : 3400, 1772, 1726, 1602 1513 cm^{-1} .

Preparation B-3

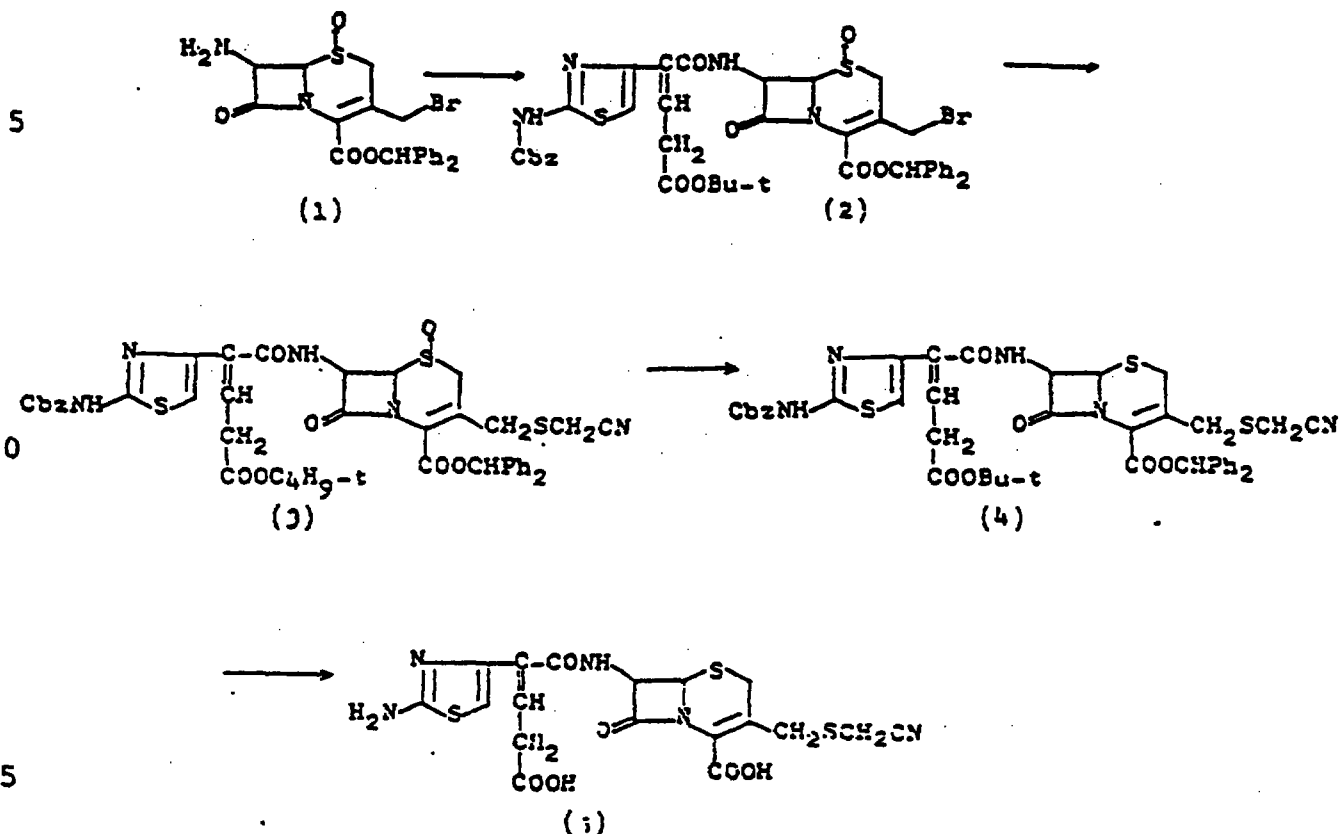
7beta-Amino-3-vinylthio-3-cephem-4-carboxylic acid p-nitro-20 benzyl ester (4)



- 1) To a solution of 3-enol (1) (9.38 g) in acetonitrile (120 ml) are added diphenyl chlorophosphinate (6.57 g) and diisopropylaminoethane (2.97 g). After stirring for 2 hours, this is mixed with 2-(benzenesulfinyl)ethanethiol (3.16 g),
5 diisopropylaminoethane (2.19 g), and acetonitrile (6 ml), and stirred at -40°C to -25°C for 2.5 hours. The mixture is poured into iced hydrochloric acid and extracted with dichloromethane. The extract is washed with water, dried, and concentrated. The residue is crystallized from ethyl
10 acetate-ether to give sulfoxide (2) (6.84 g). mp. $174-176^{\circ}\text{C}$.
- 2) A solution of sulfoxide (2) (2 g) in 1,1,2-trichloroethane (40 ml) is refluxed for 11 hours under nitrogen. The reaction mixture is concentrated, and crystallized from ether to give vinyl thioether (3) (1.38 g). mp. $193-194^{\circ}\text{C}$.
- 15 3) To a stirred and ice cold solution of vinyl thioether (3) (440 mg) in dichloromethane (15 ml) are added phosphorus pentachloride (358 mg) and pyridine (149 mg) under nitrogen. After stirring at room temperature for 2 hours, the reaction mixture is cooled to -40°C , diluted with methanol (15 ml), and
20 stirred for 2 hours at 0°C . The mixture is mixed with water (1 ml), concentrated, washed with ether, suspended in dichloromethane, and washed with aqueous 10 % sodium hydrogen carbonate and water, dried, and concentrated. The residue is crystallized from a mixture of dichloromethane and ether to
25 give amine (4) (204 mg). mp. $152-154^{\circ}\text{C}$.

Preparation B-4

7beta-[2-(2-Aminothiazol-4-yl)-4-carboxy-2-butenamidol]-3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid (5)



1) To a solution of bromomethyl compound (2) (340 mg) (prepared by amidating Amine (1) in a manner similar to Example 2) in *N,N*-dimethylformamide (3 ml) is added at -70°C an ethanol solution of sodium cyanomethylmercaptide (prepared from cyanomethyl thiolacetate (71 mg) and sodium ethylate in ethanol). After 2 hours' stirring at -65°C to -70°C , the mixture is poured into ethyl acetate, washed with water, dried and concentrated. The residue is purified by silica gel

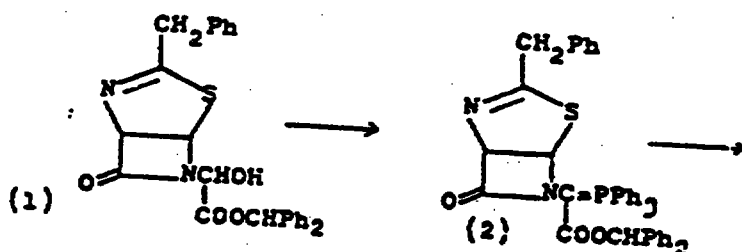
chromatography (eluting with a mixture of benzene and ethyl acetate (3:1) to give oxide (3). Yield: 57.2 %.

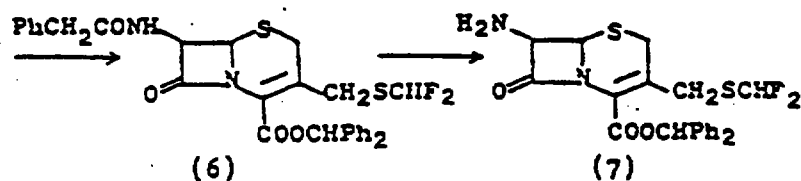
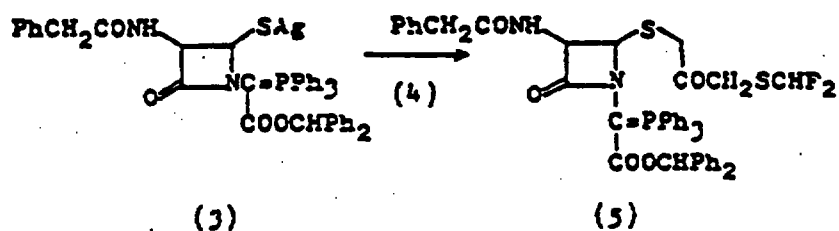
2) To a solution of oxide (3) (690 mg) in acetone (10 ml) are added potassium iodide (883 mg) and acetyl chloride (0.339 ml) at -35°C . After 90 minutes' stirring at -20°C to -25°C , the mixture is diluted with ethyl acetate, washed with diluted sodium thiosulfate, and aqueous sodium hydrogen carbonate, dried, and concentrated to give sulfide (4). Yield: 85.6 %.

3) To a solution of sulfide (4) (550 mg) in anisole (10 ml) is added a solution of aluminium chloride (1.24 g) in anisole (5 ml) at -30°C . After 3 hours' stirring, the mixture is diluted with hydrochloric acid and washed with ethyl acetate. Aqueous layer is purified with synthetic adsorbent HP 20 (Mitsubishi Chemical K.K.) and eluted to give aminocarboxylic acid (5). Yield: 74.4 %.

Preparation B-5

7beta-Amino-3-difluoromethylthio-3-cephem-4-carboxylic acid diphenylmethyl ester (7)



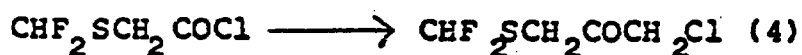


- 1) To a suspension of glycolate (1) (22.8 g) in dichloro-
 10 methane (300 ml) are added pyridine (4.63 ml) and thionyl
 chloride (4 ml) at -20°C to -23°C over a 24 minutes period.
 After stirring for 10 minutes at -20°C and for 30 minutes at
 0°C , the reaction mixture is washed with ice water and dried
 over magnesium sulfate. To the solution are added pyridine
 15 (4.63 ml) and triphenylphosphine (13 g). After stirring at
 room temperature for 2 hours and refluxing for 2 hours, the
 mixture is washed with water, and purified by silica gel
 chromatography (eluting with benzene-ethyl acetate (2:1)
 mixture) to give phosphoranilidene ester (2) (20.13 g).
- 20 2) To a solution of phosphoranilidene ester (2) (16.65 g) in
 dioxane (80 ml) are added a solution of 99 % silver perchlor-
 ate monohydrate (5.87 g) in water (19 ml) and aqueous 60 %
 perchloric acid (7.96 ml) at room temperature. After stirring
 for 1 hour, the mixture is diluted with dichloromethane and
 25 iced water. Organic layer is taken, washed with water, dried,

and concentrated to give silver mercaptide (3).

3) To a solution of silver mercaptide (3) in hexamethylphosphorotriamide (100 ml) are added 1-(difluoromethylthio)-3-chloroacetone (4) (3.95 g) and sodium iodide (3.55 g). After 52 hour stirring at room temperature, the reaction mixture is diluted with ethyl acetate and water. Organic layer is taken, washed with water, dried, and evaporated. The residue is purified by silica gel chromatography (eluting with benzene-ethyl acetate (1:1) mixture) to give ketone (5).

10 Above 1-(difluoromethylthio)-3-chloroacetone (4) can be prepared as follows;



To a solution of diazomethane in ether (200 ml) prepared from N-nitrosomethylurea (20.6 g) is added dropwise a solution 15 of difluoromethylthioacetyl chloride (10 g) in ether (20 ml) under ice cooling over 20 minutes period. After stirring at 0°C for 20 minutes and at room temperature for 2 hours, the mixture is saturated with hydrogen chloride under ice cooling 20 over 30 minutes. The reaction mixture is diluted with ice water, ether layer is taken, washed with water, dried, concentrated, and distilled to give (4) from fractions evaporating at bp (1 mmHg) 52-53°C as colorless liquid.

4) To a solution of ketone (5) (8.388 g) in toluene (200 ml) is added hydroquinone (180 mg) and refluxed for 14 hours.

25 After evaporating toluene, the mixture is purified by silica

gel chromatography (eluting with benzene-ethyl acetate (2:1) mixture) to give cephem (6) (4.42 g).

NMR (CDCl_3) δ : 3.58 (s, 2H), 3.73 (s, 2H).

5) To an ice cold solution of cephem (6) (4.42 g) in 5 dichloromethane (80 ml) are added pyridine (1.35 ml) and phosphorus pentachloride (3.17 g). After stirring at 0°C for 10 minutes and at room temperature for 90 minutes, the mixture is cooled to -45°C to -55°C, mixed with cold methanol (110 ml), stirred at 0°C for 30 minutes, diluted with ice water, 10 and neutralized. Organic layer is taken, washed with water, dried, and concentrated. The residue is purified by silica gel chromatography (eluting with benzene-ethyl acetate (2:1) mixture to give amine (7) (2.686 g).

NMR (CDCl_3) δ : 1.73 (brs, 2H) ppm.

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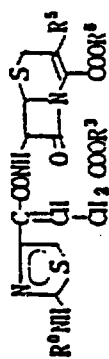


Table 1 (I) Esters

No	cis: trans	R ⁰	R ¹	R ²	R ³	R ⁴	IR(CKCl, cm ⁻¹)	NMR(CDCl ₃) δ : ppm	Example No.
1		H	H	Me		H	nd	3.70-4.30(m, 4H), 4.13, 4.16(2xs, 3H), 5.56, 5.62(2xd, J=5Hz, 1H), 6.20, 6.26(2xd, J=5Hz, 1H), 6.66-6.83(m, 1H), 6.90, 7.26(2xt, J=9Hz, 1H), 7.06, 7.13(2xs, 1H) [D ₂ O].	3-1)
2	cis	H	H	Me		BH	1787, 1731, 1680, 1280.	3.35-3.47(m, 2H), 3.58(d, J=8Hz, 2H), 3.70(s, 3H), 4.98(d, J=5Hz, 1H), 5.44(lrs, 2H), 5.95, 6.04(dd, J=5Hz, J=9Hz, 1H), 6.47(s, 1H), 6.61(t, J=8Hz, 1H), 6.56-6.66(m, 1H), 6.95(s, 1H), 7.24-7.48(m), 8.56(d, J=9Hz, 1H).	4-4)
3	trans	H	H	Me		BH	1785, 1730, 1678, 1280.	3.40(d, J=8Hz, 2H), 3.35-3.47(m, 2H), 3.68(s, 3H), 4.92(d, J=5Hz, 1H), 5.59(lrs, 2H), 5.94, 6.03(dd, J=5Hz, J=9Hz, 1H), 6.48(s, 1H), 6.53-6.63(m, 1H), 6.90(s, 1H), 7.14(t, J=8Hz, 1H), 7.23-7.45(m, 1H), 8.65(d, J=9Hz, 1H).	4-4)
4	cis	H	H	Bzl		H	3270, 1770, 1735, 1722 [NaJ].	3.44(d, J=7.5Hz, 2H), 3.54-3.67(m, 2H), 5.10(d, J=5Hz, 1H), 5.17(s, 2H), 5.80, 5.89(dd, J=5Hz, J=8Hz, 1H), 6.40(s, 1H), 6.42-6.59(m, 2H), 7.41(s, 5H), 9.39(d, J=8Hz, 1H) [CD ₃ SOCD ₃].	3-1)
5	trans	H	H	Bzl		H	3280, 1772, 1735, 1725 [NaJ].	3.54-3.69(m, 4H), 5.15(d, J=5Hz, 1H), 5.15(s, 2H), 5.78, 5.88(dd, J=5Hz, J=8Hz, 1H), 6.45-6.53(m, 1H), 6.66(s, 1H), 6.78(t, J=7.5Hz, 1H), 7.40(s, 5H), 9.25(d, J=8Hz, 1H) [CD ₃ SOCD ₃].	3-1)

Table 1 (II) Esters (No. 2)

No	cis: trans	R ⁰	R ³	R ⁴	R ⁵	IR(CHCl ₃) ν : cm ⁻¹	NMR(CHCl ₃) δ : ppm	Example No.
6	cis	H	Bzl	H	BH	1782, 1722, 1670, 1278.	3.32-3.46(m, 2H), 3.62(d, J=8Hz, 2H), 4.95(d, J=5Hz, 1H), 5.13(s, 2H), 5.31(brs, 2H), 5.92, 6.02(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.46(s, 1H), 6.53-6.61(m, 1H), 6.63(t, J=8Hz, 1H), 6.94(s, 1H), 7.21-7.47(m), 8.67(d, J=8Hz, 1H).	4-3)
7	trans	H	Bzl	H	BH	1780, 1721, 1670, 1280.	3.30-3.45(m, 4H), 4.88(d, J=5Hz, 1H), 5.11(s, 2H), 5.52(brs, 2H), 5.92, 6.02(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.41(s, 1H), 6.50-6.65(m, 1H), 6.88(s, 1H), 7.15(t, J=7.5Hz, 1H), 7.16-7.48(m), 8.61(d, J=8Hz, 1H).	4-3)
8	1:4	Clz	Bzl	H	H	nd	3.00-3.90(m, 4H), 4.96, 5.00(2x d, J=5Hz, 1H), 5.13(s, 2H), 5.23(s, 2H), 5.73-5.88(m, 1H), 5.76, 5.86(dd, J ₁ =5Hz, J ₂ =9Hz, 1H), 6.50-6.60(m, 1H), 6.93(s, 1H), 7.11(t, J=8Hz, 1H), 7.33(s, 5H), 7.36(s, 5H) [CDCl ₃ -OD ₂ CD].	2-7), 14), 3-1).
9		Clz	Bzl	H	H	3160, 1775, 1720, 1670, 1630.	3.34-3.50(m, 4H), 4.95(d, J=5Hz, 1H), 5.13(s, 2H), 5.23(s, 2H), 5.80(d, J=5Hz, 1H), 6.48-6.60(m, 1H), 6.94(s, 1H), 7.03-7.40(m, 1H).	2-7), 14), 3-1).
10	trans	Clz	t-Bu	H	BH	3330, 1775, 1725, 1670, 1630, mp. 162-164°C.	1.34(s, 9H), 2.58-3.26(m, 4H), 4.70(d, J=5Hz, 1H), 5.07, 5.51(ABq, J=13H z, 2H), 5.68, 5.76(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.30-6.39(m, 1H), 6.61(s, 1H), 6.75(s, 1H), 7.10-7.57(m, 15H), 7.67(d, J=8Hz, 1H).	2-1), 15), 5-1), 6-1), 3).
11	1:4	Clz	Bzl	H	BH	3340, 1775, 1725, 1670.	3.04(s, 2H), 3.6-4.1(m, 2H), 4.58(d, J=5Hz, 1H), 4.8-5.6(m, 4H), 5.68(d, J=5Hz, 1H), 6.25(m, 1H), 6.59, 6.67(2x s, 1H), 6.63(s, 1H), 7.0-7.9(m, 22H).	2-1), 15), 21), 6-1).

Table 1 (I) Esters (No. 3)

No	cis: trans	R ⁰	R ²	R ¹	R ⁰	IR(COCl ₂) ν : cm ⁻¹	NMR(COCl ₂) δ : ppm	Example No.
12	trans	Clz	Bz1	H	DH	3830, 1780, 1725, 1675, 1630. mp. 131-133°C.	2.68-3.36(m, 4H), 4.69(d, J=5Hz, 1H), 4.98(s, 2H), 5.03, 5.46(ABq, J=12H z, 2H), 5.65, 5.74(dd, J=5Hz, J=8Hz, 1H), 6.29-6.40(m, 1H), 6.60(s, 1H) 6.64(s, 1H), 7.10-7.47(m, 15H), 7.63(d, J=8Hz, 1H).	2-5), 21). 6-2), 7.
13		Clz	MeBz1	H	DH	3340, 1775, 1725, 1670, 1630, 1560.	2.30(s, 3H), 2.70-3.37((m, 4H), 4.71(d, J=5Hz, 1H), 4.95(d, 2H), 5.04, 5.49(ABq, J=12Hz, 2H), 5.67, 5.76(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.30-6.40(m, 1H), 6.62(s, 1H), 6.69(s, 1H), 7.05-7.47(m, 20H), 7.66(d, J=8Hz, 1H).	2-7)
14		Clz	PrB	H	DH	3325, 1770, 1720, 1665, 1625, 1605, 1505, 1400.	2.60-3.65(m, 4H), 3.74(s, 3H), 4.67, 4.75(2x d, J=5Hz, 1H), 4.86-5.53(m, 4H), 5.65, 5.73, 5.82(2x d, J ₁ =5Hz, J ₂ =7Hz, 1H), 6.25-6.50(m, 1H), 6.50-6.95(m, 4.5H), 7.05-7.50(m, 18.5H), 7.65, 7.90(2x d, J=7Hz, 1H).	2-15), 18).
15	trans	DOC	Bz1	H	DH	3400, 3330, 1773, 1720, 1668, 1278, 1152.	1.50(s, 9H), 3.16(d, J=4.5Hz, 2H), 3.29(d, J=8Hz, 2H), 4.73(d, J=5Hz, 1H), 5.04(s, 2H), 5.68, 5.77(dd, J ₁ =5Hz, J ₂ =7.5Hz, 1H), 6.35(t, J=4.5Hz, 1H), 6.64(s, 1H), 6.71(s, 1H), 7.17-7.48(m), 7.79(d, J=7.5Hz, 1H).	2-23)
16	cis	BOC	Bz1	H	DH	3410, 3340, 1780, 1725, 1675, 1282, 1154.	1.53(s, 9H), 3.15-3.37(m, 2H), 3.86(d, J=7Hz, 2H), 4.85(d, J=5Hz, 1H), 5.17(s, 2H), 5.82, 5.91(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.43-6.54(m, 1H), 6.70 (t, J=7Hz, 1H), 6.79(s, 1H), 6.83(s, 1H), 7.15-7.49(m), 8.14(d, 1H).	2-23)
17		HCO	H	H	H	nd	5.02(d, J=5Hz, 1H), 5.86(d, J=5Hz, 1H), 6.54-6.64(m, 1H), 7.04(t, J=8Hz, 1H), 7.16(s, 1H), 8.51(s, 1H) [COCl ₂ , -O, O].	3-1), 2), 3).
18	trans	HCO	t-Bu	H	DH	3420, 1770, 1715, 1665, 1625.	1.39(s, 9H), 3.12(br d, 2H), 3.27(d, J=7Hz, 2H), 4.67(d, J=5Hz, 1H), 5.74, 5.83(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.29-6.38(m, 1H), 6.62(s, 1H), 6.83 (s, 1H), 7.20-7.47(m, 11H), 7.68(d, J=8Hz, 1H), 8.51(s, 1H).	2-18)

Table 1 (I) Esters (No. 4)

No	cis: trans	R ⁰	R ¹	R ²	R ³	R ⁴	IR(CHCl ₃) ν : cm ⁻¹	NMR(CHCl ₃) δ : ppm	Example No.
19	1:2	HCO	H	DH		BH	1775, 1772, 1672, 1280, 1152.	3.60-3.16(m, 2H), 3.46, 3.87(2x d, J=8Hz, 2H), 4.65, 4.70(2x d, J=5Hz, 1H), 5.72, 5.81: 5.77, 5.86(2x dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.26-6.45(m, 1H), 6.61, 6.76(2x s, 1H), 6.66(s, 1H), 6.87, 6.95(2x s, 1H), 7.10-7.47(m), 7.64, 7.86(2x d, J=2Hz, 1H), 8.40, 8.43(2x s, 1H), 11.27, 11.51(2x hrs, 1H).	5-1)
20	1:2	Cl CH ₃ CO	H	H	H	H	1761, 1720, 1700 [No Jol]	4.61, 4.75(2x s, 2H), 5.45, 5.51(2x d, J=5Hz, 1H), 6.08, 6.19(2x dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 7.01, 7.30(2x t, J=8Hz, 1H), 7.60, 7.72(2x s, 1H), 8.26, 8.74(2x d, J=8Hz, 1H) [CD ₃ SOCD ₃].	3-2)
21		Cl CH ₃ CO	H	Bz1		H	3150, 1770, 1718, 1680, 1278, 1152 [No Jol].	3.38-3.70(m, 4H), 4.38(s, 2H), 5.06(d, H=5Hz, 1H), 5.13(s, 2H), 5.73, 5.82(dd, J ₁ =5Hz, J ₂ =8Hz, 1H), 6.41-6.52(m, 1H), 6.62(t, J=7.5Hz, 1H), 7.24(s, 1H), 7.38(s, 5H), 9.00(d, J=8Hz, 1H), 12.57(hrs, 1H) [CD ₃ SOCD ₃].	3-1)
22	5:6	Cl CH ₃ CO	H	Bz1		DH	3320, 1780, 1732, 1727, 1680.	3.13, 3.26(m, 2H), 3.36, 3.76(2x d, J=8Hz, 2H), 3.87, 4.69: 4.16, 4.32(2x ABq, J=17Hz, 2H), 4.70, 4.79(2x d, J=5.0Hz, 1H), 5.06, 5.17(2x s, 2H), 5.69, 5.78: 5.78, 5.87(2x dd, J ₁ =5.0Hz, J ₂ =9.0Hz, 1H), 6.31-6.48(m, 1H), 6.66, 6.75(2x s, 1H), 6.72, 6.83(2x s, 1H), 6.67(t, 8Hz, 5H/11), 7.18-7.49(m), 7.73, 7.94(2x d, J=9Hz, 1H).	2-18)
23	trans	tBuSi- Me,	H	Bz1		DH	3400, 1785, 1725, 1670, 1630.	0.28(s, 6H), 0.93(s, 9H), 3.18-3.78(m, 2H), 3.47(d, J=7.5Hz, 2H), 4.79(s, 1H), 4.98(d, H=5Hz, 1H), 5.16(s, 2H), 6.00, (dd, J ₁ =5Hz, J ₂ =9Hz, 1H), 6.48(s, 1H), 6.57-6.67(m, 1H), 6.98(s, 1H), 7.17(t, J=7.5Hz, 1H), 7.2-7.6(m, 15H), 8.65(d, J=9Hz, 1H).	2-1)

No	cis: trans	R ⁰	R ³	R ⁵	R ⁸	IR(CCl ₄) ν : cm ⁻¹	NMR(CCl ₄) δ : ppm	Example No.
24	cis	cH ₃ Si- H ₂	Bz1	H	BH	3390, 1780, 1720, 1670, 1630.	0.28(s, 6H), 0.94(s, 9H), 3.17-3.75(m, 2H), 3.66(d, J=7.5Hz, 2H), 4.68 (s, 1H), 4.99(d, J=5Hz, 1H), 5.16(s, 2H), 6.00(d, J=5Hz, J=9Hz, 1H), 6.50(s, 1H), 6.57-6.65(m, 1H), 6.68(t, J=7.5Hz, 1H), 6.97(s, 1H), 7.1-7.6 (m, 15H), 8.35(d, J=9Hz, 1H).	2-1)
25	1:3	CH ₂	Bz1	Me	BH	3320, 1765, 1725, 1675.	2.00(s, 3H), 2.27, 2.77(ABq, J=17Hz, 2H), 3.03, (AB part of ABX, J=16Hz, 3/2H), 3.63(AB part of ABX, J=16Hz, 1/2H), 4.77(d, J=4Hz, 1H), 4.9-5.6 (m, 5H), 6.61, 6.66(2xs, 1H), 6.69, 6.75(2xs, 1H), 6.9-7.5(m, 21H), 7.70 -7.89(2xd, J=7Hz, 1H).	2-5)
26	1:2	CH ₂	Bz1	CH=CH ₂	BH	3330, 1770, 1725, 1675, 1620.	2.70-3.94(m, 4H), 4.73, 4.79(2xd, J=4Hz, 1H), 4.90-5.30(m, 7H), 6.56- 6.64(m, 2H), 6.90-7.50(m, 22H), 7.74, 7.92(2xd, J=7Hz, 1H).	2-15)
27	2:1	CH ₂	Bz1	CH=CHCH(Z)	BH	3407, 3345, 2210, 1783, 1728, 1679, 1631.	2.7-4.2(m, 4H), 4.85, 4.92(2xd, J=4.5Hz, 1H), 5.07(s, 2H), 5.13(s, 2H), 5.20, 5.39(2xd, J=12Hz, 1H), 5.70(m, 1H), 6.49, 6.76(2xs, 1H), 6.63, 6.67(2xs, 1H), 6.5-8.1(m, 23H).	2-3)
28	2:1	CH ₂	Bz1	CH=CHCH(Z)	H	3168, 2193, 1785, 1726, 1672 [Naip1].	3.50(m, 2H), 4.02(m, 2H), 5.13(d, J=4.5Hz, 1H), 5.17(s, 2H), 5.28(s, 2H), 5.45(d, J=12.5Hz, 1H), 5.90(d, J=4.5Hz, 1H), 6.95, 7.07(2xm, 1H), 6.98(s, 1H), 7.1-7.7(m, 11H) [OCl, -O, O].	3-1)
29		CH ₂	Bz1	CH=CHCO ₂ -Bu (E)	BH	3391, 1779, 1728, 1618.	1.41(s, 9H), 2.3-4.2(m, 4H), 5.04, 5.08(2xd, J=4.5Hz, 1H), 5.10(s, 2H), 5.17(s, 2H), 5.67(2xm, 1H), 5.94(d, J=16Hz, 1H), 6.63, 6.89(2xs, 1H), 6.72, 6.76(2xs, 1H), 6.4-7.7(m, 17H), 7.86(d, J=16Hz, 1H).	2-7)

Table 1 (I) Esters (No. 6)

No	cis: trans	R ⁰	R ¹	R ²	R ³	R ⁴	IR(CCl ₄) ν : cm ⁻¹	NMR(CCl ₄) δ : ppm	Example No.
30		CH ₂		Bz-1	Bz-1	CH=CHCOOEt-Bz ₁ (E)	3170, 1780, 1730, 1613, 1302, 1229 [No sol.]	1.49(s, 9H), 3.3-4.2(m, 4H), 5.03, 5.07(2xd, J=4.5Hz, 1H), 5.14(s, 2H), 5.23(s, 2H), 5.82(2xm, 1H), 5.96(d, J=16Hz, 1H), 6.65(m, 0.5H), 6.91(s, 1H), 7.0-7.5(m, 10.5H), 7.86(d, J=16Hz, 1H).	3-1)
31		CH ₂		Bz-1	Bz-1	CH=CHCF ₃ (5E:2Z)	3330, 1775, 1725, 1675, 1620.	2.7-3.6(m, 4H), 4.75-4.95(m, 1H), 4.95-6.0(m, 6H), 6.4-6.8(m, 2H), 7.05- 7.85(m, 23H).	2-16)
32		CH ₂		Bz-1	Bz-1	CH=CHCF ₃ (Z)	3325, 3390, 1775, 1725, 1672, 1625.	2.7-3.8(m, 4H), 4.8-5.9(m, 7H), 6.55-6.85(m, 3H), 7.0-7.7((m, 22H).	2-16)
33	1:2	CH ₂		Bz-1	Bz-1	CH ₂ N ⁺ CC ₅ H ₅ Cl ⁻	nd	3.16, 3.68(ABq, J=18Hz, 2H), 3.51(d, J=8Hz, 2H), 5.12(s, 2H), 5.28(s, 2H), 5.20(d, J=5Hz, 1H), 5.82(d, J=5Hz, 1H), 5.37, 5.76(ABq, J=20Hz, 2H), 7.00, 7.15(2xs, 1H), 7.35(s, 5H), 7.42(s, 5H), 6.8-7.5(m, 1H), 8.0-9.3 (m, 5H) [CD ₃ CO-CD ₃ COO ₃ -D ₂ O].	2-30)
34	cis	CH ₂		Bz-1	Bz-1	CH ₂ CH ₂	3390, 1780, 1728, 1675, 1304, 1168, 1092.	3.16(s, 3H), 3.25(s, 2H), 3.54, 3.68(AB parts of ABX, J ₁ =19.2Hz, J ₂ = 7Hz, 2H), 4.14, 4.28(ABq, J=15.5Hz, 2H), 4.91(d, J=4.5Hz, 1H), 5.12(s, 2H), 5.16, 5.34(ABq, J=18Hz, 2H), 5.65(dd, J ₁ =4.5Hz, J ₂ =8.5Hz, 1H), 6.62 (t, J=7Hz, 1H), 6.75(s, 1H), 6.79(s, 1H), 7.23-7.40(m, 2H), 8.10(d, J= 8.5Hz, 1H).	2-0)

Table 1 (I) Esters (No. 7)

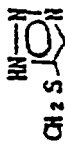
No	cis: trans	R ⁰	R ¹	R ²	R ³	R ⁴	IR(CCl ₄) ν : cm ⁻¹	NMR(CCl ₄) δ : ppm	Example No.
35	trans	CH ₃	CH ₂ CH ₃	Bz1	BH	BH	3425, 1778, 1726, 1675, 1302, 1220, 1090.	2.95, 3.19(AB parts of AX, J=8.1Hz, 2H), 3.14(s, 3H), 3.18(s, 2H), 4.09, 4.27(ABq, J=13.5Hz, 1H), 4.80(d, J=4.5Hz, 1H), 5.02(s, 2H), 5.09, 5.37(ABq, J=12.6Hz, 2H), 5.50(dd, J=4.5Hz, J=7Hz, 1H), 6.57(s, 1H), 6.63(s, 1H), 7.10(t, J=8.1Hz, 1H), 7.20-7.42(m, 2H), 7.74(d, J=7Hz, 1H).	2-9)
36		CH ₃	CH ₂ COCH ₃	Bz1	BH	BH	3400, 3330, 1775, 1725, 1670, 1625.	1.95(s, 3H), 2.82-3.70(m, 4H), 4.56-5.73(m, 8H), 6.60-6.77: 7.04-7.50 (2m, 23H).	2-11)
37	1:10	CH ₃	CH ₂ COCH ₂ CH ₃	Bz1	BH	BH	3320, 1775, 1720, 1710 [NaJO1].	3.49, 3.64(ABq, J=18Hz, 2H), 3.57(d, J=8Hz, 2H), 4.75, 4.97(ABq, J=12Hz, 2H), 5.15(s, 2H), 5.20(d, J=4Hz, 1H), 5.28(s, 2H), 5.75-6.30(m, 3H), 6.93(s, 1H), 7.10(t, J=8Hz, 1H), 7.20(s, 1H), 7.2-7.7(m, 20H) [O, OXO], J	2-1)
38		CH ₃	CH ₂ SH ₂	Bz1	BH	BH	1770, 1750, 1720, 1670.	1.82(s, 3H), 3.3-3.7(m, 6H), 5.03(d, J=5Hz, 1H), 5.12(s, 2H), 5.25(s, 2H), 5.6-5.75(m, 1H), 6.89(s, 1H), 6.90(s, 1H), 6.66, 7.11(2xt, J=8Hz, 1H), 7.2-7.5(m, 20H) [OXI, -CO, O].	2-18)
39		CH ₃	CH ₂ SCH ₂ CH ₃	Bz1	BH	BH	3230, 2245, 1785, 1730, 1680, 1620, 1560.	2.7-3.4(m, 6H), 3.57, 3.77(ABq, J=14Hz, 2H), 4.93(d, J=4Hz, 1H), 5.06(s, 2H), 5.18, 5.27(2s, 2H), 5.48(dd, J=4Hz, J=9Hz, 1H), 6.69(s, 1H), 6.76(s, 1H), 7.1-7.5(m, 20H), 8.46(d, J=9Hz, 1H).	6-4)
40		CH ₃	CH ₂ SOH ₂	Bz1	BH	BH	3400, 3330, 1775, 1735, 1725, 1675, 1630.	3.14(t, J=9Hz, 2H), 4.87(d, J=5Hz, 1H), 5.05(s, 2H), 5.44(dd, J=5Hz, J=8Hz, 2H), 6.60(t, J=56Hz, 1H), 6.15(s, 1H), 6.18(s, 1H), 7.10(t, J=9Hz, 1H), 7.2-7.4(m, 20H), 7.74(d, J=8Hz, 1H).	2-27)
41	2:3	CH ₃		Bz1	BH	BH	3380, 3160, 1775, 1723, 1675, 1220.	3.16-4.20(m, 6H), 4.81-5.26(m, 6H), 5.39-6.19(m, 1H), 6.63-6.85, 7.05-7.36(m, 24H), 7.47(s, 1H), 8.18, 8.48(2xt, J=8Hz, 1H).	2-7)

Table 1 (I) Esters (No. 8)

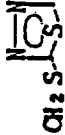
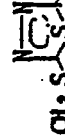
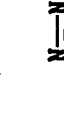
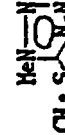
No	cis:trans	R ⁶	R ³	R ⁵	R ⁶	IR(CHCl ₃) ν : cm ⁻¹	NMR(CDCl ₃) δ : ppm	Example No.
42	3:5	MeOAc	MeBz1		BH	1780, 1722, 1672.	2.30(s, 6H), 2.77-3.27, 3.90-3.60, 4.17-4.57(3 ^m , 6H), 4.35(d, J=5Hz, 1H), 4.90-5.50(m, 5H), 6.60(s, 1H), 6.73(s, 1H), 7.00-7.50(m, 13H), 8.37(s, 1H).	2-10)
43	1:1	OAc	Bz1		BH	3403, 3175, 1775, 1721, 1670, 1621, 1542.	3.36(d, J=8Hz, 2H), 3.59(brs, 2H), 4.36(ABq, J=14Hz, 2H), 4.98, 5.01(2 ^x d, J=4Hz, 1H), 5.10(s, 2H), 5.22(s, 2H), 5.68, 5.78(2 ^x d, J=4Hz, 1H), 6.87, 6.89, 6.91(3 ^s , 2H), 7.1-7.6(m, 2H), 8.93, 8.94(2 ^s , 1H) [OAc, -CD ₃ CO(10:1)].	2-8).18).
44		OAc	Bz1		BH	3385, 3160, 1773, 1720, 1668, 1620, 1541.	2.61(s, 3H), 3.36(d, J=8Hz, 2H), 3.54(brs, 2H), 4.30(ABq, J=14Hz, 2H), 4.96, 5.00(2 ^x d, J=4Hz, 1H), 5.11(s, 2H), 5.23(s, 2H), 5.68, 5.77(2 ^x d, J=4Hz, 1H), 6.88(s, 2H), 7.00-7.55(m, 2H) [OAc, -CD ₃ CO(10:1)].	2-28), 2-18).
45	1:1	OAc	Bz1		BH	3380, 3170, 1780, 1725, 1675, 1603, 1564.	3.47(d, J=8Hz, 2H), 3.52(brs, 2H), 4.09(brs, 2H), 4.97, 5.01(2 ^x d, J=4Hz, 1H), 5.11, 5.13(2 ^s , 2H), 5.23(s, 2H), 5.72, 5.78(2 ^x d, J=4Hz, 2H), 6.86, 6.89, 6.90(3 ^s , 2H), 7.00-7.60(m, 2H), 6.65, 7.12(2 ^s , J=8Hz, 1H) [OAc, -CD ₃ CO(10:1)].	2-25)
46	1:1	OAc	Bz1		BH	3385, 3170, 1779, 1723, 1673, 1620, 1560.	3.38(d, J=8Hz, 2H), 3.51(brs, 2H), 4.06(brs, 2H), 4.23(brs, 2H), 4.98, 5.01(2 ^x d, J=4Hz, 1H), 5.11(s, 2H), 5.20(s, 2H), 5.78(d, J=4Hz, 1H), 6.87(s, 1H), 6.90(s, 1H), 7.00-7.60(m, 2H) [OAc, -CD ₃ CO(10:1)].	2-15)
47	cis	OAc	Bz1		BH	3400, 1785, 1725, 1670.	3.40(s, 2H), 3.61(d, J=7Hz, 2H), 3.73(s, 3H), 4.11, 4.43(ABq, J=14Hz, 2H), 4.91(d, J=5Hz, 1H), 5.11(s, 2H), 5.14, 5.24(ABq, J=12Hz, 2H), 5.65(d, J=8Hz, 1H), 5.5Hz, 1H), 6.62(t, J=7Hz, 1H), 6.78(s, 1H), 6.81(s, 1H), 7.1-7.6(m, 2H), 8.27(d, J=8Hz, 1H).	2-20)

Table 1 (I) Esters (No. 9)

No	cis: trans	R ⁰	R ¹	R ²	R ⁶	IR(NCl ₃) ν : cm ⁻¹	NMR(CDCl ₃) δ : ppm	Exmple No.
48	trans	Cl ₂	Bz1		BH	1785, 1730, 1675.	2.98(d, J=8Hz, 2H), 3.23(s, 2H), 3.76(s, 3H), 3.98, 4.52(ABq, J=14Hz, 2H), 4.80(d, J=5Hz, 1H), 5.06(s, 2H), 5.10(s, 2H), 5.40(dd, J=5Hz, J=, 6Hz, 1H), 6.52(s, 1H), 6.77(s, 1H), 7.08(t, J=8Hz, 1H), 7.1-7.6(m, 20H), 7.77(d, J=6Hz, 1H).	2-29)
49		Cl ₂	Bz1	OMe	DH	3325, 1760, 1715, 1670, 1625.	1.98, 2.69(ABq, J=16Hz, 2H), 2.76-4.01(m, 2H), 3.52(s, 3H), 4.92-5.54(m, 6H), 6.66(s, 1H), 6.88(s, 1H), 7.01-7.50(m, 21H).	2-15)
50		Cl ₂	Bz1	OSO ₂ Me	BH	3340, 1785, 1735, 1675, 1630.	2.65-3.75(m, 2H), 2.94(s, 3H), 3.51(brs, 2H), 4.86(d, J=5Hz, 1H), 5.03(s, 2H), 5.02, 5.49(ABq, J=13Hz, 2H), 5.61, 5.70(s, 2H), 5.02, 5.49(ABq, J=13Hz, 2H), 5.61, 5.70(dd, J=5Hz, J=8Hz, 1H), 6.50, 6.53, 6.60(3xs, 2H).	2-12)
51	1:2	Cl ₂	Bz1	Cl	DH	3350, 1785, 1740, 1685, 1635.	2.64-3.95(m, 2H), 3.37(brs, 2H), 4.78, 4.80(2xs, J=6Hz, 1H), 4.94-5.13(m, 2H), 5.00, 5.10(2xs, 2H), 5.58(dd, J=8Hz, J=6Hz, 1H), 6.55-6.67: 6.95-7.50(2xm, 23H).	2-28)
52		BOC	Bz1	Cl	PMB	1778, 1745, 1727, 1675, 1350, 1150.	1.52(s, 9H), 3.38(d, J=8Hz, 2H), 4.89(d, J=2Hz, 1H), 5.13(s, 2H), 5.28(d, J=4Hz, 1H), 5.31(s, 2H), 5.43, 5.51(dd, J=4Hz, J=7Hz, 1H), 6.35(d, J=2Hz, 1H), 6.93(s, 1H), 7.18(t, J=8Hz, 1H), 7.33(s, 5H), 7.52(d, J=8Hz, 2H), 8.20(d, J=7Hz, 1H), 8.23(d, J=8Hz, 2H), 8.99(brs, 1H).	2-24)
53		MeCl ₂	MeBz1	SOCH ₂ CH ₂ F	PMB	3340, 1780, 1732, 1676, 1620, 1606.	2.32(s, 6H), 2.7-3.3(m, 4H), 3.39(s, 2H), 4.49(dt, J=47Hz, J=6Hz, 2H), 4.82(d, J=4Hz, 1H), 5.02(s, 2H), 4.68, 5.48(ABq, J=19Hz, 2H), 5.21(s, 2H), 6.83(s, 1H), 7.0-7.3(m, 9H), 7.46(d, J=9Hz, 1H), 7.67(d, 8Hz, 1H), 8.14(d, J=9Hz, 2H).	2-17)

Table 1 (1) Esters (No. 10)

No	cis: trans	R ⁰	R ³	R ⁵	R ⁶	IR(CCl ₄) ν : cm ⁻¹	NMR(CCl ₄) δ : ppm	Example No.
54		HCO ₂	HCO ₂ Ph	CH ₂ CH ₂ F	DH	3345, 1757, 1730, 1672, 1630, 1557, 1528.	2.26(s, 6H), 2.1-2.7(m, 2H), 2.7-3.3(m, 4H), 4.31(dt, J, =6Hz, J, =4Hz, 2H), 4.8-4.5(m, 6H), 6.65(s, 1H), 6.80(s, 1H), 7.0-7.7(m, 2H).	2-5)
55	1:1	CO ₂	Ph	CH ₂ CF ₃	PMB	3330, 1775, 1725, 1665.	2.8-3.7(m, 6H), 4.75-5.75(m, 8H), 6.82(s, 1H), 7.0-7.7(m, 12H), 7.45, 8.15(ABq, J=9Hz, 4H).	2-22)
56		CO ₂	Ph	CH ₂ CF ₃	H	3170br 1775, 1725, 1670.	nd	3-1)
57		CO ₂	Ph	CH=CH ₂	DH	3320, 1770, 1750, 1720, 1670.	2.5-3.8(m, 4H), 4.7-5.8(m, 8H), 5.9-8.0(m, 2H).	2-17)
58		CO ₂	Ph	CH=CH ₂	PMB	3325, 1775, 1720, 1670.	2.7-3.8(m, 2H), 3.43(s, 2H), 4.75-5.70(m, 10H), 6.25-8.3(m, 19H).	2-17)

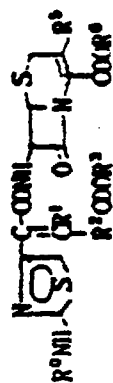
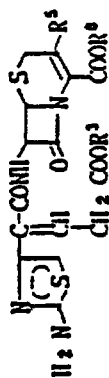


Table 1 (2) Esters (No. 2)

No	cis: trans	R	R ²	R ⁴	IR (CHCl ₃) ν: cm ⁻¹	NMR (CHCl ₃) δ: ppm	Example No.
1	trans	NO ₂ -p H ₂ C=CH	CH ₃	H	1780, 1720, 1670, 1620, 1515, 1340.	3.13-3.73(m, 2H), 3.50(d, J=7.5Hz, 2H), 5.02(d, J=5Hz, 1H), 5.17(s, 2H), 5.99 (dd, J ₁ =5Hz, J ₂ =14Hz, 1H), 6.57-6.68(m, 1H), 6.99(s, 1H), 7.2-7.6(m, 17H), 8.07, 8.21(ABq, J=9Hz, 4H), 8.71(d, J=8Hz, 1H), 9.20(s, 1H).	2-27)
2	cis	NO ₂ -p H ₂ C=CH	CH ₃	H	1780, 1720, 1665, 1625, 1515, 1340.	3.13-3.75(m, 2H), 3.77(d, J=7Hz, 2H), 5.03(d, J=5Hz, 1H), 5.18(s, 2H), 5.98 (dd, J ₁ =5Hz, J ₂ =14Hz, 1H), 6.60-6.70(m, 1H), 6.92(t, J=7Hz, 1H), 7.01(s, 1H), 7.2-7.6(m, 16H), 8.09, 8.23(ABq, J=8Hz, 4H), 8.83(d, J=8Hz, 1H), 9.21(s, 1H).	2-27)
3	1:1	NO ₂ -p O ₂ CNH	CH ₃	H	1780, 1730, 1540, 1280.	3.91-3.31(m, 1H), 3.64, 3.50(ABq, J=10Hz, 1H), 3.67, 3.81(2x d, J=7Hz, 2H), 4.71, 4.84(2x d, J=5Hz, 1H), 5.04, 5.11(2xs, 1H), 5.22, 5.29(ABq, J=12Hz, 1H), 5.22(m, 1H), 5.6-6.1(m, 0.5H), 6.3-6.7(m, 1H), 6.22, 6.87(2xs, 1H), 7.2-7.7(m, 23H), 8.33, 9.07(2x d, J=8Hz, 1H).	2-1)
4	cis	NO ₂ -p O ₂ CNH	-	H	3200, 1770, 1730, 1690, 1550, 1290.	2.78-3.24(m, 2H), 4.88(d, J=5Hz, 1H), 5.11(s, 2H), 5.17, 5.32(ABq, J=13Hz, 2H), 6.09, 6.19(dd, J ₁ =8Hz, J ₂ =5Hz, 1H), 6.52(m, 1H), 6.86(s, 1H), 7.01(s, 1H), 7.27(m, 20H), 8.46(d, J=8Hz, 1H).	2-1)

Table 2 (1) Carboxylic acids



No	cis: trans	R ⁵	R ⁶	IR ν : cm^{-1}	NMR δ : ppm	Example No.
1	1:1	H	H	1763, 1705, 1630 [KBr].	3.22(d, J=7Hz, 1H), 3.42(d, J=7Hz, 1H), 3.60(s, 2H), 5.07, 5.11(2xd, J=5Hz, 1H), 5.81(d, J=5Hz, 1H), 6.31, 6.57(2xs, 1H), 6.3-6.8(m, 2H) [CD ₃ COOD, -CD ₃ O, D ₂ O].	3-1), 4-1).
2	cis	H (HCl salt)	H	3425, 3300, 3260, 1760, 1715, 1657, 1620, 1548 [NaJol]	3.31(d, J=7Hz, 2H), 3.54-3.63(brs, 2H), 5.21(d, J=5Hz, 1H), 5.79(d, J=5Hz, 1H), 6.54 -6.83(m, 2H), 6.63(s, 1H) [CD ₃ COOD, -CD ₃ O].	3-1), 2), 4-1), 2), 9.
3	cis	H	H	3580, 3260, 1770, 1700, 1650, 1572, 1546, 1362 [NaJol]	3.68(d, J=8Hz, 2H), 3.93(A part of ABX, J ₁ =5.5Hz, J ₂ =20Hz, 1H), 4.13(B part of ABX, J ₁ =3.5Hz, J ₂ =20Hz, 1H), 5.65(d, J=5Hz, 1H), 6.30(d, J=5Hz, 1H), 6.78(X part of ABX, J ₁ =3.5Hz, J ₂ =5.5Hz, 1H), 6.95(t, J=8Hz, 1H), 7.05(s, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-1), 4-1), 8.
4	1:1	H	H	1760, 1710, 1630 [KBr].	2.13(s, 3H), 3.39(d, J=7Hz, 2H), 5.03(d, J=4.5Hz, 1/2H), 5.08(d, J=4Hz, 1/2H), 5.73(d, J=4.5Hz), 5.76(d, J=4Hz, 1/2H), 6.43, 6.54(2xs, 1H), 6.61, 6.94(2xt, 7Hz, 1H) [CD ₃ COOD, -CD ₃ O, -CD ₃ O].	1-4), 3-2), 4-2).
5	1:1	H	H	3280, 1760, 1630 [NaJol].	3.66(d, J=8Hz, 2H), 4.10(brs, 2H), 5.62-5.96(m, 3H), 6.16, 6.22(2xd, J=4Hz, 1H), 6.85-7.46(m, 3H) [D ₂ O].	1-4), 3-2), 4-2).
6	1:1	H	H	3195, 2205, 1764, 1611 [NaJol].	3.3-4.2(m, 4H), 5.08, 5.15(2xd, J=4.5Hz, 1H), 5.26(d, J=12Hz, 1H), 5.63, 5.71(2xd, J=4.5Hz, 1H), 6.35, 6.43(2xs, 1H), 6.53, 6.78(m, 1H), 6.98(d, J=12Hz, 1H) [NaHCO ₃ - D ₂ O].	1-4), 3-2), 4-2).

Table 2 (1) Carboxylic acids (No. 2)

No	cis: trans	R ³	R ⁴	R ⁵	R ⁶	IR ν : cm^{-1}	NMR δ : ppm	Example No.
7	1 : 1	H	H	CH=CHCOOH (E)	H	3267, 1770, 1612 [NaJol]	2.8-3.4 (m, 2H), 3.42, 3.72 (ABq, J=14.5 Hz, 2H), 5.10, 5.15 (2xd, J=4.5 Hz, 1H), 5.63, 5.69 (2xd, J=4.5 Hz, 1H), 5.90 (d, J=16 Hz, 1H), 6.36, 6.76 (2xs, 1H), 6.45, 6.53 (2xs, 1H), 7.23 (d, J=16 Hz, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
8	1 : 1	H	H	CH=CHCF ₃ (1Z:2E)	H	3340, 1770, 1708, 1640, 1530 [KBr].	3.67 (d, J=7.8 Hz, 2H), 3.75-4.3 (m, 2H), 5.67, 5.73 (2xd, J=4.5 Hz, 1H), 6.15-6.70 (m, 2H), 6.96, 7.24 (2xt, 7.8 Hz, 1H), 7.05, 7.13 (2xs, 1H), 7.20, 7.68 (2xd, J=10 Hz, J=16.5 Hz, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
9	1 : 1	H	H	CH=CHCF ₃ (Z)	H	3360, 1772, 1708, 1655, 1628, 1532 [KBr].	3.68 (d, J=7.8 Hz, 2H), 3.99, 4.19 (ABq, J=18 Hz, 2H), 5.18, 5.73 (2xd, J=4.5 Hz, 1H), 6.17, 6.27 (2xd, J=4.5 Hz, 1H), 6.1-6.7 (m, 1H), 7.05, 7.34 (2xt, 7.8 Hz, 1H), 7.07, 7.15 (2xs, 1H), 7.23 (d, J=12.8 Hz, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
10	1 : 2	H	$\ominus$	CH ₂ N $\oplus$ C ₆ H ₅	$\ominus$	3380, 1770, 1620, 1525 [KBr].	3.66, 4.08 (ABq, J=18 Hz, 2H), 3.78 (d, J=8 Hz, 2H), 5.66, 5.71 (2xd, J=5 Hz, 1H), 5.80, 6.00 (ABq, J=15 Hz, 2H), 6.20, 6.26 (2xd, J=5 Hz, 1H), 7.11, 7.24 (2xs, 1H), 6.8-7.5 (m, 1H), 8.4-9.5 (m, 5H) [D ₂ O].	3-7), 4-2)
11	2 : 3	H	H	CH ₂ OHc	H	3170br, 1760, 1622 [NaJol].	nd	1-4), 3-2), 4-2).
12	3 : 5	H	H	CH ₂ OCOHc	H	3275, 1770, 1720, 1630 [NaJol].	2.75 (s, 3H), 3.70 (d, J=8 Hz, 2H), 3.86, 4.13 (ABq, J=18 Hz, 2H), 5.60, 5.70 (2xd, J=6 Hz, 1H), 6.22, 6.28 (2xd, J=6 Hz, 1H), 6.98, 7.38 (2xt, J=8 Hz, 1H), 7.07, 7.16 (2xs, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).

Table 2 (I) Carboxylic acids (No. 3)

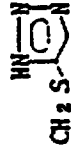
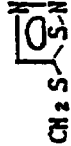
No	cis: trans	R ³	R ⁴	R ⁵	IR ν : cm ⁻¹	NMR δ : ppm	Example No.
13	2:3	H	CH ₂ OC(=O)NH ₂	H	3250, 1760, 1720, 1700 [Nu jo1].	3.66(d, J=8Hz, 2H), 3.83, 4.08(ABq, J=18Hz, 2H), 5.12, 5.31(ABq, J=12Hz, 2H), 5.61, 5.67(2xd, J=4Hz, 1H), 6.19, 6.24(2xd, J=4Hz, 1H), 7.00, 7.14(2xs, 1H), 6.95, 7.36 (2xt, J=8Hz, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
14	1:1	Na	CH ₂ SHc	Na	3370, 1755, 1590, 1525 [KBr].	2.46(s, 3H), 3.67(d, J=8Hz, 2H), 3.7-4.3(m, 4H), 5.62(d, J=5Hz, 1/2H), 5.66(d, J=4Hz, 1/2H), 6.12(d, J=5Hz, 1/2H), 6.17(d, J=4Hz, 1/2H), 6.94, 7.35(2xt, J=8Hz, 1H), 7.05, 7.14(2xs, 1H) [D ₂ O].	1-2), 3-2), 4-2).
15		H	CH ₂ SCH ₂ CN	H	3300, 2240, 1765, 1625, 1530 [Nu jo1].	3.68(d, J=8Hz, 2H), 3.91, 4.20(ABq, J=13Hz, 2H), 4.01(s, 2H), 4.20(s, 2H), 5.65, 5.71(2xd, J=5Hz, 1H), 6.19, 6.23(2xd, J=5Hz, 1H), 6.97, 7.38(2xt, J=8Hz, 1H), 7.07, 7.15(2xs, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
16		H	CH ₂ SCH ₂ F	H	3275br, 1765, 1660 sh, 1625 [Nu jo1].	nd	1-4), 3-2), 4-2).
17	2:3	Na		Na	1748 [Nu jo1].	3.67(d, J=8Hz, 2H), 3.65-4.37(m, 2H), 4.50, 4.71(ABq, J=21Hz, 2H), 5.54, 5.59(2xd, J=4.5Hz, 1H), 6.09, 6.15(2xd, J=4.5Hz, 1H), 6.95, 7.35(2xt, J=8Hz, 1H), 7.04, 7.14 (2xs, 1H), 8.41(s, 1H) [D ₂ O].	1-1), 3-2), 4-2).
18	3:5	Na		Na	1770, 1662, 1630 [KBr].	3.60, 3.69(2xd, J=7Hz, 2H), 3.91-4.10(m, 2H), 4.17-4.41(m, 2H), 5.04, 5.61(2xd, J=5 Hz, 1H), 6.10, 6.17(2xd, J=5Hz, 1H), 6.93, 7.33(2xt, J=7Hz, 1H), 7.03, 7.12(2xs, 1H), 9.15(s, 1H) [NaHCO ₃ -D ₂ O].	1-1), 3-2), 4-2).

Table 2 (1) Carboxylic acids (No. 4)

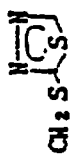
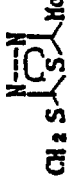
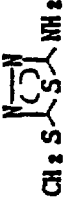
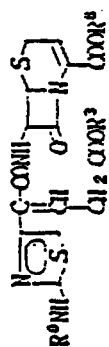
No	cis: trans	R ²	R ³	R ⁶	IR ν : cm^{-1}	NMR δ : ppm	Example No.
19	1 : 1	H		H	3300, 1764, 1627, 1529, 1367 [KBr].	3.69(d, J=8Hz, 2H), 4.07(ABq, J=17Hz, 2H), 4.75(ABq, J=12Hz, 2H), 5.58, 5.62(2x d, J=4Hz, 1H), 6.18, 6.20(d, J=4Hz, 1H), 6.98, 7.40(2xt, J=8Hz, 1H), 7.03, 7.13(2xs, 1H), 9.88(s, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
20	1 : 1	H		H	3390, 1763, 1622, 1523, 1376 [KBr].	3.18(s, 3H), 3.68(d, J=8Hz, 2H), 4.03(ABq, J=17Hz, 2H), 4.67(ABq, J=14Hz, 2H), 5.57, 5.61(2x d, J=4Hz, 1H), 6.14, 6.17(2x d, J=4Hz, 1H), 6.94, 7.37(2xt, J=8Hz, 1H), 7.01, 7.11(2xs, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
21	1 : 1	H		H	3300, 1763, 1621, 1511, 1382, 1355 [KBr].	3.69(d, J=8Hz, 2H), 4.16(ABq, J=18Hz, 2H), 4.53(ABq, J=13.5Hz, 2H), 5.58, 5.62(2x d, J=4Hz, 1H), 6.14, 6.19(2x d, J=4Hz, 1H), 6.97, 7.38(2xt, J=8Hz, 1H), 7.04, 7.13(2xs, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
22	1 : 1	H		H	3410, 1762, 1615, 1528, 1361 [KBr].	3.68(d, J=8Hz, 2H), 4.06(ABq, J=18Hz, 2H), 4.65(ABq, J=14Hz, 2H), 4.87, 5.01(2xs, 2H), 5.58, 5.62(2x d, J=4Hz, 1H), 6.14, 6.19(2x d, J=4Hz, 1H), 6.70-7.50(m, 1H), 7.04, 7.13(2xs, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).
23	1 : 1	H		H	1765, 1710, 1630 [KBr].	3.37(d, J=8Hz, 2H), 3.69(s, 2H), 3.95(s, 3H), 4.35(s, 2H), 5.03, 5.07(2x d, J=5Hz, 1H), 5.82(d, J=5Hz, 1H), 6.41, 6.53(2xs, 1H), 6.61, 6.93(2xt, J=8Hz, 1H) [CD ₃ SOCD ₃ -CD ₃ OD-CDCl ₃].	1-4), 3-6).
24	3 : 5	H	OMe	H	3275, 1760, 1620 [Na ₂ SO ₄].	3.68, 3.72(2x d, J=8Hz, 2H), 3.73-4.25(m, 2H), 4.21, 4.23(2xs, 3H), 5.64, 5.70(2x d, J=6Hz, 1H), 6.00, 6.05(2x d, J=6Hz, 1H), 6.97, 7.37(2xt, J=8Hz, 1H), 7.10, 7.16(2xs, 1H) [NaHCO ₃ -D ₂ O].	1-4), 3-2), 4-2).

Table 2 (1) Carboxylic acids (No. 5)

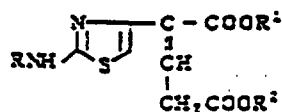
No	cis: trans	R ³	R ²	R ¹	IR ν : cm ⁻¹	NMR δ : ppm	Example No.
25	3 : 5	H	Cl	H	3275, 1760, 1625 [Nu jo1].	3.64, 3.65(2x1, J=8Hz, 1H), 3.97, 4.34(4.00, 4.37(2xAlq, J=18Hz, 2H), 5.68, 5.71(2x d, J=6Hz, 1H), 6.17, 6.22(2x d, J=6Hz, 1H), 6.94, 7.33(2xt, J=8Hz, 1H), 7.03, 7.13(2x s, 1H) [NaHCO ₃ -D ₂ O].	1-4). 3-2). 4-2).
26	1 : 2	H	SCN ₂ CH ₂ F	H	3300, 1763, 1660, 1629, 1531 [KBr].	3.52(dt, J ₁ =22.5Hz, J ₂ =6Hz, 2H), 3.67(d, J=7.5Hz, 2H), 3.83, 4.41(ABq, J=17.1Hz, 2H), 5.07(dt, J ₁ =47.7Hz, J ₂ =6Hz, 2H), 5.63, 5.69(2x d, J=5Hz, 1H), 6.15, 6.21(2x d, J= 5Hz, 1H), 6.96, 7.36(2xt, J=7.5Hz, 1H), 7.06, 7.15(2xs, 1H) [NaHCO ₃ -D ₂ O].	1-4). 3-4). 3-5).
27	3 : 7	Na	SCN ₂ CF ₃	Na	nd	3.70(d, J=7Hz, 2H), 3.6-4.4(m, 2H), 4.30, 4.85(ABq, J=15Hz, 2H), 5.67, 5.74(2x d, J= 4Hz, 1H), 6.20, 6.27(2x d, J=4Hz, 1H), 7.00, 7.38(2xt, J=7Hz, 1H), 7.07, 7.17(2xs, 1H) [D ₂ O].	3-2).4). 1-2).
28	4 : 5	H	SCN=CH ₂	H	3150, 1760, 1705 [Nu jo1].	3.68(d, J=7Hz, 2H), 4.15(brs, 2H), 5.6-6.2(m, 1H), 6.35(q, J ₁ =16Hz, J ₂ =8Hz, 1H), 6.8-7.6(m, 2H) [NaHCO ₃ -D ₂ O].	1-4). 3-4).

Table 3 Pharmaceutical esters



No	cis: trans	R ²	R ³	R ⁴	IR(CMCL ₃) ν: cm ⁻¹	NMR(CMCL ₃) δ: ppm	Example No.
1	cis	H	H	POH	3420, 2980, 1780, 1750, 1660, 1630, 1530, 1480, 1390[KBr].	1.20(s, 9H), 3.15-3.75(m, 4H), 5.04(d, J=5Hz, 1H), 5.81, 5.92(ABq, J=6Hz, 2H), 5.90(d, J=5Hz, 1H), 6.40-6.70(m, 2H), 7.35(s, 1H).	3-2), 4-2), 5-2).
2	1:1	H	H	POH	3420, 2980, 1780, 1750, 1660, 1630, 1530, 1480, 1390[KBr].	1.20(s, 9H), 3.15-3.75(m, 4H), 5.04, 5.06(2x d, J=5Hz, 1H), 5.81, 5.92(ABq, J=6Hz, 2H), 5.85-5.95(m, 1H), 6.40-6.70: 6.83-7.03(2xm, 2H), 7.37(s, 1H) [CMCL ₃ -CD ₃ OD].	3-2), 4-2), 5-2).
3	1:1	H	POH	POH	3395, 3320, 1790, 1753, 1685, 1110, 988.	nd	4-3), 5-2).
4	1:1	H	AOH	AOH	3380, 3310, 1790, 1741, 1687, 1150, 985.	nd	4-2), 5-5).
5	1:1	Clz	Bz1	POH	nd	1.20(s, 9H), 3.00-3.90(m, 4H), 5.13(s, 2H), 5.10, 5.33: 5.15, 5.37(2x ABq, J=12Hz, 2H), 5.55-6.00(m, 3H), 5.85, 5.92(2x d, J=5Hz, 1H), 6.36-6.53(m, 1H), 6.65, 7.07(2xt, J=8Hz, 1H), 6.94, 6.96(2xs, 1H), 7.20-7.50(m, 10H), 7.66, 8.05(2x d, J=8Hz, 1H).	4-2).

Table 4 Side chain acids and derivatives



	R	R ¹	R ²	IR(Nujol) ν : cm^{-1}	NMR δ : ppm
1	BOC (cis)	H	H	3120. 1700. 1675. dp 153-154°C	1.50(s. 9H). 3.45(d. J=7.5Hz. 2H). 7.00(t. J=7.5 Hz. 1H). 7.13(s. 1H) [O,SOO,].
2	BOC (trans)	H	H	3150. 1700. 1630. 1600. dp 165-167°C.	1.49(s. 9H). 3.41(d. J=7.5Hz. 2H). 6.89(t. J=7.5 Hz. 1H). 7.08(s. 1H) [O,SOO,].
3	Cbz	H	H	3200. 1733. 1715. 1690. dp 169-172°C.	3.44. 3.50. (2xd. J=5Hz. 2H). 5.25(s. 2H). 7.07. 7.35(2xt. J=5Hz. 1H). 7.12(s. 1H). 7.33(brs. 5H) [OCl,-O,CO].
4	HCO	H	H	3400. 1718. 1690. 1630. 1550. dp 156°C.	3.45. 3.63(2xd. J=7.5Hz. 2H). 7.14. 7.32(2xt. J=7.5Hz. 1H). 7.23. 7.25(2xs. 1H). 8.51(s. 1H) [OCl,-O,CO].
5	ClCH ₂ CO	H	H	3100. 1720. 1635. 1620. dp 153-155°C.	3.45(d. J=5Hz. 2H). 4.37(s. 2H). 6.97. 7.05(2xt. J=5Hz. 1H). 7.23. 7.27(2xs. 1H) [O,SOO,].
6	BOC	H	Bzl	3160. 1740. 1724. 1700. 1673. 1255. 1163.	3.95(d. J=7.5Hz. 2H). 5.50(s. 2H). 7.25(t. J=7.5 Hz. 1H). 7.30(brs. 1H). 7.49(s. 1H). 7.75(s. 5H). 11.86(brs. 1H) [O,SOO,].
7	HCO (2 cis: 1 trans)	H	t-Bu	3150. 3100. 1720. 1690. 1635. mp. 165-168°C	1.40(s. 9H). 3.43(d. J=7Hz. 2H). 6.89. 7.00(2xt. J=7Hz. 1H). 7.20. 7.26(2xs. 1H). 8.48(s. 1H) [O,SOO,].
8	HCO	H	Bzl	1735. 1660. 1620. dp 153-155°C.	3.69(d. J=7Hz. 2H). 5.12(s. 2H). 7.17(t. J=7Hz. 1H). 7.21(s. 1H). 7.32(s. 5H). 8.46(s. 1H) [O,SOO,].
9	ClCH ₂ CO	H	Me	nd	3.39(d. J=7.5Hz. 2H). 3.70(s. 3H). 4.24(s. 2H). 7.11(s. 1H). 7.23(t. J=7.5Hz. 1H). 9.37(brs. 2H) [OCl,].
10	ClCH ₂ CO	H	Bzl	1725. 1635. 1160. dp 155°C.	3.95. 4.01(2xd. J=7.5Hz. 2H). 4.71(s. 2H). 5.45. 5.47(2xs. 2H). 7.28. 7.40(2xt. J=7.5Hz. 1H). 7.58. 7.65(2xs. 1H). 7.70(s. 5H). 12.9(brs. 1H) [O,SOO,].
11	Cbz	H	Me	3400-2300. 1740. 1550.	3.53-3.73(m. 2H). 3.63(s. 3H). 5.27(s. 2H). 7.03-7.46(m. 7H) [O,SOO,].
12	Cbz (trans)	H	t-Bu	3160-2200. 1720. 1660. 1635. mp. 169-171°C	1.42(s. 9H). 3.53(d. J=7Hz. 2H). 5.29(s. 1H). 7.27(t. J=7Hz. 1H). 7.35(s. 1H). 7.30-7.50(m. 5H) [O,COO,].
13	Cbz (cis)	H	t-Bu	nd	1.44(s. 9H). 3.53(d. J=7Hz. 2H). 5.27(s. 2H). 7.13(t. J=7Hz. 1H). 7.24(s. 1H). 7.30-7.47(m. 5H) [OCl,].
14	Cbz (2 cis: 1 trans)	H	Me- Bzl	3150-2050. 1720. 1670. 1620. 1570. mp. 160-163°C.	2.33(s. 3H). 2.53. 2.70(2xd. J=8Hz. 2H). 5.11(s. 2H). 5.25(s. 2H). 6.99-7.40(m. 10H) [OCl,-O,CO].
15	Cbz (2 cis: 3 trans)	H	Bzl	1725. 1675. 1620. 1575. mp. 164-166°C.	3.51. 3.73(2xd. J=7Hz. 2H). 5.13(s. 2H). 5.26(s. 2H). 7.06. 7.10(2xs. 1H). 7.0-7.5(m. 11H) [OCl,-O,CO].

Table 4 Side chain acids and derivatives (No. 2)

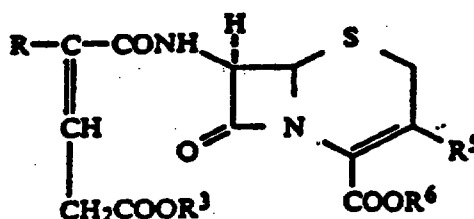
	R	R ¹	R ²	IR(Nujol) ν : cm ⁻¹	NMR δ : ppm
16	H (HCl salt)	Me	H	3330-2450. 1720. 1680. 1630.	3.39(d. J=7Hz. 2H). 3.73(s. 3H). 6.88(s. 1H). 7.25(t. J=7Hz. 1H) [O,SO ₂].
17	Cbz	H	Ph	1720. 1575. 1515. mp. 145-148°C.	3.80(d. J=8Hz. 2H). 3.90(s. 3H). 5.20(s. 2H). 5.33(s. 2H). 7.00(s. 1H). 6.95-7.60(m. 10H) [OCl, -O,CO].
18	H (HCl salt)	Me	Me	3200. 1720. 1625. 1605. [CHCl ₃].	3.44(d. J=7Hz. 2H). 3.75(s. 3H). 3.85. 3.88(2xs. 3H). 6.70. 6.75(2xs. 1H). 6.97. 7.43(2xt. J=7Hz. 1H) [OCl, -O,CO].
19	BOC (trans)	Me	Me	3415. 1720. 1541. 1155 [CHCl ₃].	1.52(s. 9H). 3.54(d. J=5.5Hz. 2H). 3.64(s. 3H). 3.76(s. 3H). 7.11(s. 1H). 7.18(t. J=5.5Hz. 1H). 9.12(brs. 1H) [OCl ₂].
20	BOC (cis)	Me	Me	3410. 1720. 1541. 1150 [CHCl ₃].	1.51(s. 9H). 3.54(d. J=5.5Hz. 2H). 3.69(s. 3H). 3.83(s. 3H). 7.03(s. 1H). 7.08(t. J=5.5Hz. 1H). 9.12(brs. 1H) [OCl ₂].
21	Cbz	Me	Me	3390. 1720. 1540 [CHCl ₃].	3.41. 3.48(2xd. J=8Hz. 2H). 3.65. 3.73. 3.69. 3.83(4xs. 6H). 5.24(s. 2H). 7.00-7.37(m. 7H) [OCl ₂].
22	Cbz	Et	Et	3395. 1720 [CHCl ₃].	1.19. 1.20. 1.22. 1.30(4xt. J=8Hz. 6H). 3.34. 3.42(2xd. J=8Hz. 2H). 4.08. 4.12. 4.15. 4.24(4xs. J=8Hz. 4H). 5.21. 5.22. 5.24(3xs. 2H). 7.03. 7.13(2xt. J=8Hz. 1H). 7.03(s. 1H). 7.31(s. 5H). 10.15(brs. 1H) [OCl ₂].
23	Cbz	Bzl	Bzl	3400. 1725 [CHCl ₃].	3.31. 3.42(2xd. J=7Hz. 2H). 5.01. 5.03. 5.11. 5.17(4xs. 6H). 6.95-7.30(m. 17H). 10.19(brs. 1H) [OCl ₂].
24	Cbz	Ph	Bzl	nd	3.40(d. J=7Hz. 2H). 3.75(s. 3H). 5.10(s. 2H). 5.15(s. 2H). 5.20(s. 2H). 6.5-7.4(m. 16H) [OCl ₂].
25	Cbz	BH	Bzl	3490. 1725 [OCl ₂].	3.34. 3.40(2xd. J=7Hz. 2H). 5.02. 5.05. 5.09. 5.17(4xs. 4H). 6.8-7.4(m. 23H). 9.90(brs. 1H) [OCl ₂].
26	HCO (trans)	Me	Me	3380. 3140. 1722. 1705. 1695 [CHCl ₃] mp. 100°C.	3.46(d. J=7.5Hz. 2H). 3.66(s. 3H). 3.78(s. 3H). 7.05(s. 1H). 7.24(t. J=7.5Hz. 1H). 8.49(s. 1H) [OCl ₂].
27	HCO (cis)	Me	Me	3390. 3150. 1715. 1700. 1635 [CHCl ₃].	3.56(d. J=7.0Hz. 2H). 3.73(s. 3H). 3.84(s. 3H). 7.02(t. J=7Hz. 1H). 7.12(s. 1H). 8.55(s. 1H) [OCl ₂].
28	HCO (cis)	Me	t-Bu	3380. 1710. 1540 [CHCl ₃]. mp. 101-104°C	1.47(s. 9H). 3.50(d. J=7Hz. 2H). 3.86(s. 3H). 7.07(t. J=7Hz. 1H). 7.13(s. 1H). 8.60(s. 1H) [OCl ₂].
29	HCO (trans)	Me	t-Bu	nd	1.44(s. 9H). 3.27(d. J=7Hz. 2H). 3.80(s. 3H). 7.05(s. 1H). 7.31(t. J=7Hz. 1H). 8.52(s. 1H) [OCl ₂].
30	ClCH ₂ CO (trans)	Me	Me	nd	3.50(d. J=6.5Hz. 2H). 3.68(s. 3H). 3.79(s. 3H). 4.25(s. 2H). 7.24(s. 1H). 7.24(t. J=6.5Hz. 1H) [OCl ₂].
31	ClCH ₂ CO (cis)	Me	Me	3470. 1725. 1715. 1680. 1535 [CHCl ₃].	3.60(d. J=7Hz. 2H). 3.75(s. 3H). 3.87(s. 3H). 4.27(s. 2H). 7.18(s. 1H). 7.18(t. J=7Hz. 1H) [OCl ₂].
32	Ph ₃ C (3 cis: 2 trans)	Me	Me	3380. 1720. 1703. 1500. 1480. 1425 [CHCl ₃].	3.43(d. J=6.5Hz. 2H). 3.26. 3.64(2xs. 3H). 3.70. 3.75(2xs. 3H). 6.44. 6.63(2xs. 1H). 6.54. 6.70(2xs. 1H). 7.01(t. J=6.5Hz. 1H). 7.25(s. 15H) [OCl ₂].



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CLAIMS

1. A compound of the formula:



wherein:

- 15 R is optionally protected aminothiazolyl;
R³ and R⁶ are each independently hydrogen,
a carboxy-protecting group, a salt forming atom or
group or a moiety forming a pharmaceutically
available carboxy derivative; and
20 R⁵ is hydrogen or a 3-substituent of
cephalosporins.

2. A compound as claimed in claim 1, wherein the
7-acylamido double bond has the amido and carboxylic
25 substituents in the cis position.

3. A compound as claimed in claim 1 or claim 2,
wherein R is optionally protected 2-aminothiazol-4-yl.

30 4. A compound as claimed in any one of claims 1 to
3, wherein R⁵ is hydrogen, methyl, methoxymethyl,
methylthiomethyl, cyanomethylthiomethyl, vinyl,
cyanovinyl, fluoropropenyl, trifluoropropenyl,
methoxy, chlorine, fluoroethylthio,
35 trifluoroethylthio, acetoxymethyl,
carbamoyloxymethyl, triazolylthiomethyl,



methyltetrazolylthiomethyl, or thiadiazolylthiomethyl optionally substituted by amino, by aminomethyl or by methyl.

5 5. A compound as claimed in claim 4 wherein R^5 is hydrogen, vinyl, cyanovinyl, trifluoropropenyl, acetoxymethyl, carbamoyloxymethyl, thiadiazolylthiomethyl, methyl, methoxymethyl, methylthiomethyl, cyanomethylthiomethyl,
10 fluoropropenyl, methoxy, chlorine, fluoroethylthio or trifluoroethylthio.

6. A compound as claimed in any one of claims 1 to 3 wherein R^5 is one of the R^5 groups exemplified
15 hereinbefore in the Examples (including Tables 1 and 2).

7. A cephem compound exemplified hereinbefore in any one of Tables 1, 2 or 3.
20

8. A compound as claimed in any one of claims 1 to 6 wherein R^3 and/or R^6 are/is independently a salt forming atom or group or an ester-forming group.
25

9. A compound as claimed in any of the claims 1 to 6, wherein R^3 and/or R^6 are/is independently hydrogen, an alkali metal or a pharmaceutically acceptable ester-forming group.
30

10. A compound as claimed in any one of claims 1 to 6, wherein R^3 and/or R^6 are/is independently an alkyl or aralkyl ester-forming group.

35 11. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid.



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12. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methyl-3-cephem-4-carboxylic acid.

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13. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-vinyl-3-cephem-4-carboxylic acid.

14. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-trifluoropropenyl-3-cephem-4-carboxylic acid.

15. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-acetoxymethyl-3-cephem-4-carboxylic acid.

16. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-carbamoyloxymethyl-3-cephem-3-carboxylic acid.

17. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxymethyl-3-cephem-4-carboxylic acid.

18. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methylthiomethyl-3-cephem-4-carboxylic acid.

19. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid.

20. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-pyridinoethyl-3-cephem-4-carboxylate.

21. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-triazolylthiomethyl-3-cephem-4-carboxylic acid.

22. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-thiadiazolylthiomethyl-3-cephem-4-carboxylic acid.

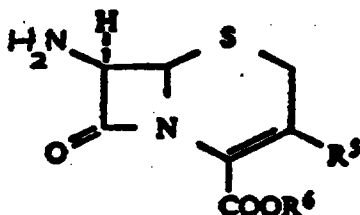


23. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methyltetrazolylthiomethyl-3-cephem-4-carboxylic acid.
- 5
24. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxy-3-cephem-4-carboxylic acid.
25. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-chloro-3-cephem-4-carboxylic acid.
- 10
26. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-fluoroethylthio-3-cephem-4-carboxylic acid.
- 15
27. 7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-trifluoroethylthio-3-cephem-4-carboxylic acid.
- 20
28. A compound as claimed in any one of claims 7 or 11 to 27, wherein one or both of the 4-position carboxyl group on the cephem ring and the 4-position carboxyl group on the 7β-butenoyl side chain is/are modified by being bonded to another moiety than that of the compound as claimed, said other moiety being hydrogen, a carboxy-protecting group, a salt forming atom or group, or a moiety forming a pharmaceutically available carboxy derivative, and/or wherein one or more of any other protected groups is not protected or is protected by a different protecting group and/or one or more of any unprotected protectable groups is protected.
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29. A compound as claimed in claim 1 or claim 6, wherein R, R³ and/or R⁶ are/is selected from examples thereof given hereinbefore
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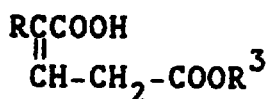
30. A process for preparing a compound as claimed in claim 1, which process comprises either: (a) amidating a 7beta-amino-3-cephem-4-carboxylic acid derivative of the formula:



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- or a reactive derivative thereof, with a carboxyalkenoic acid of the formula:

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- 20 or a reactive derivative thereof; or (b) neutralizing a compound as claimed in claim 1 wherein at least one of R^3 and R^6 is hydrogen, or a reactive derivative thereof, with a base; or (c) introducing a 3-function into an analog of a compound as claimed in claim 1 by 3-double bond introduction by basic or thermal elimination of the corresponding 3-(hydroxy, acyloxy or halo)cepham, by sulfoxide reduction, by reduction of a 3-(halo or sulfonyloxy)cephem or by displacement of a 3-(leaving group
- 25 substituted)methyl-3-cephem with a nucleophilic reagent; or (d) deprotecting a compound as claimed in claim 1 having a protected amino or protected carboxy group, or a reactive derivative thereof.

30

- 35 31. A process for preparing a compound as claimed in claim 1 and substantially as hereinbefore



described under any one of methods (1) to (7).

32. A process for preparing a compound as claimed
in claim 1 and substantially as hereinbefore
5 described.

33. A process for preparing a compound as claimed
in claim 1 and substantially as hereinbefore
described in any one of the runs of any one of
10 Examples 2 to 9.

34. A compound as claimed in any one of claims 1 to
29 whenever prepared by a process as claimed in any
one of claims 30 to 33.

15 35. An antibacterial formulation comprising a
compound as claimed in any one of claims 1 to 29 or
34 and wherein R^3 and R^6 are each independently
hydrogen or a moiety forming a pharmaceutically
20 available carboxy derivative (which may be a salt
forming atom or group), the compound being formulated
for therapeutic antibacterial use.

36. A formulation as claimed in claim 35 and also
25 comprising a therapeutically acceptable diluent,
carrier or excipient.

37. A formulation as claimed in claim 35 or claim
36 and in unit dosage form.

30 38. A method for combating bacteria or inhibiting
their presence in an environment other than the human
or animal body which comprises treating the
environment with a compound as claimed in any one of
35 claims 1 to 29 or 30 or a formulation as claimed in
any one of claims 35 to 37.
