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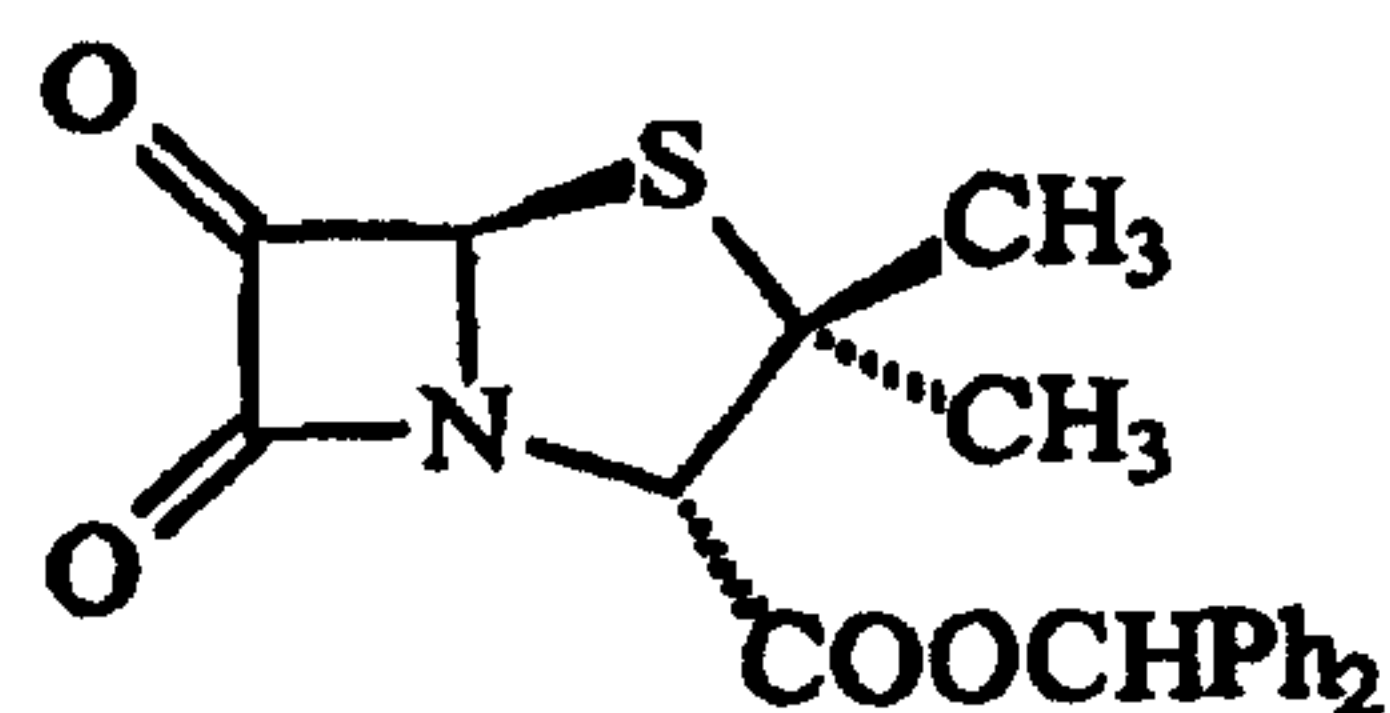
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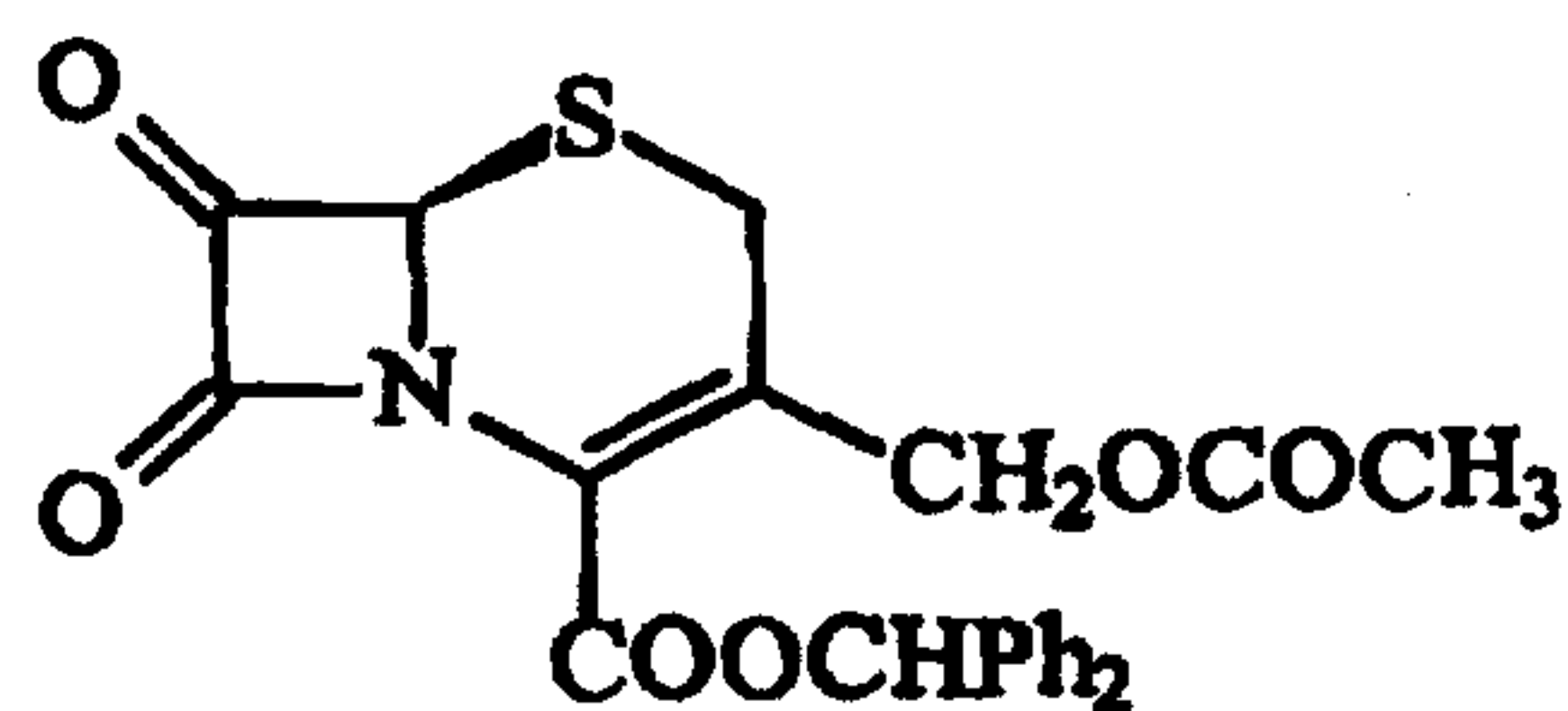
(30) 1997/12/29 (60/068,927) US

(54) **PROCEDE DE PREPARATION D' α -OXOLACTAMES**

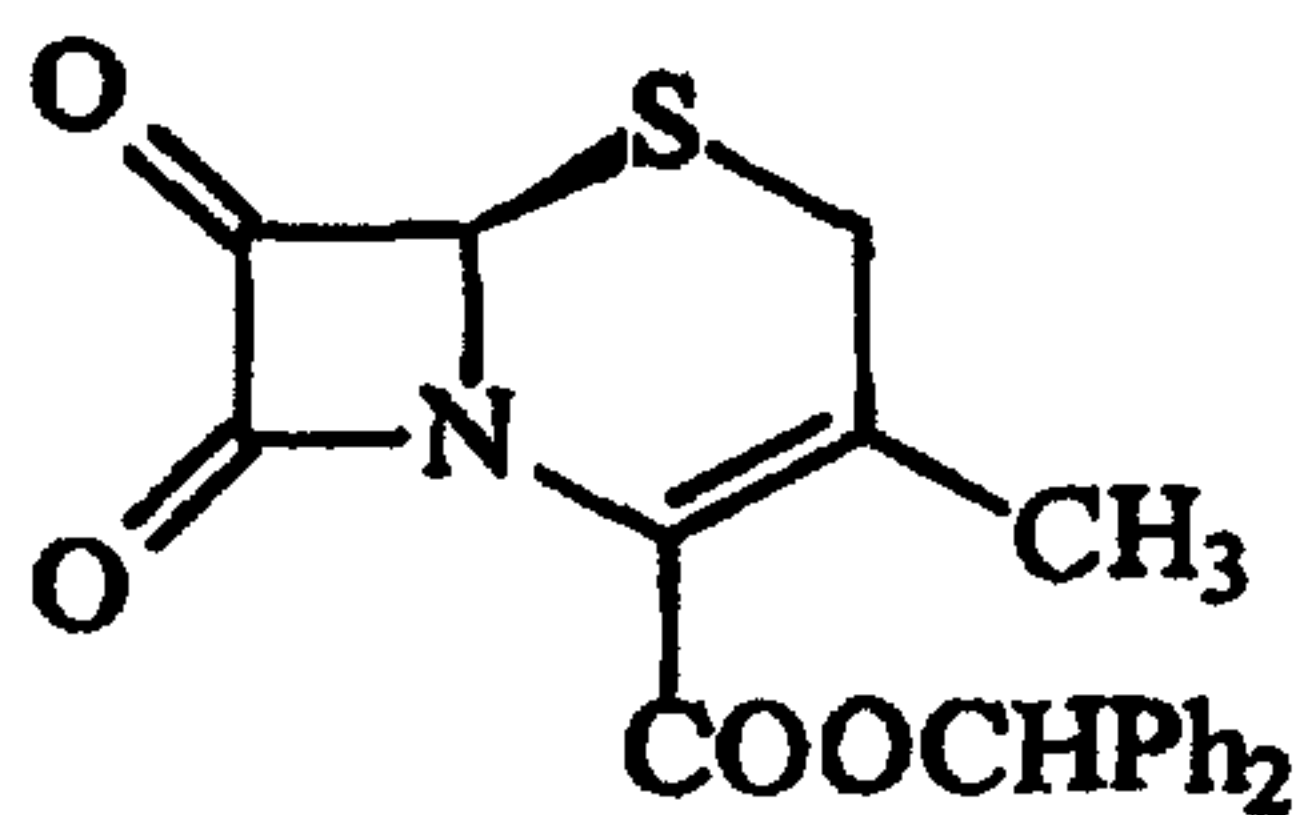
(54) **PROCESS FOR THE PREPARATION OF α -OXOLACTAMS**



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(57) L'invention concerne un procédé de préparation d'un α -oxolactame, ce procédé consistant à faire réagir un α -diazolactame correspondant avec un vecteur d'oxygène, en présence d'un catalyseur de métal de transition, de manière à produire l' α -oxolactame correspondant.

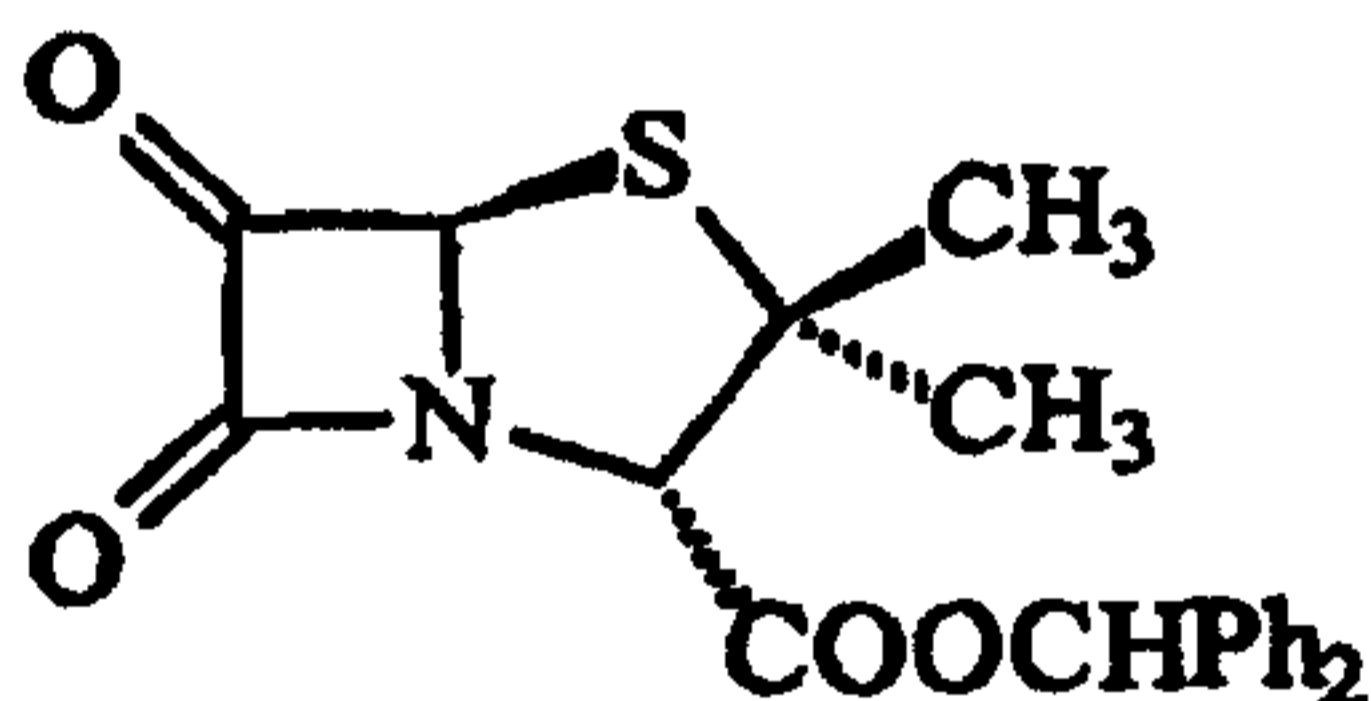
(57) A method for preparing a α -oxolactam comprising, reacting a corresponding α -diazolactam with an oxygen donor, in the presence of a transition metal catalyst, to yield the corresponding α -oxolactam.

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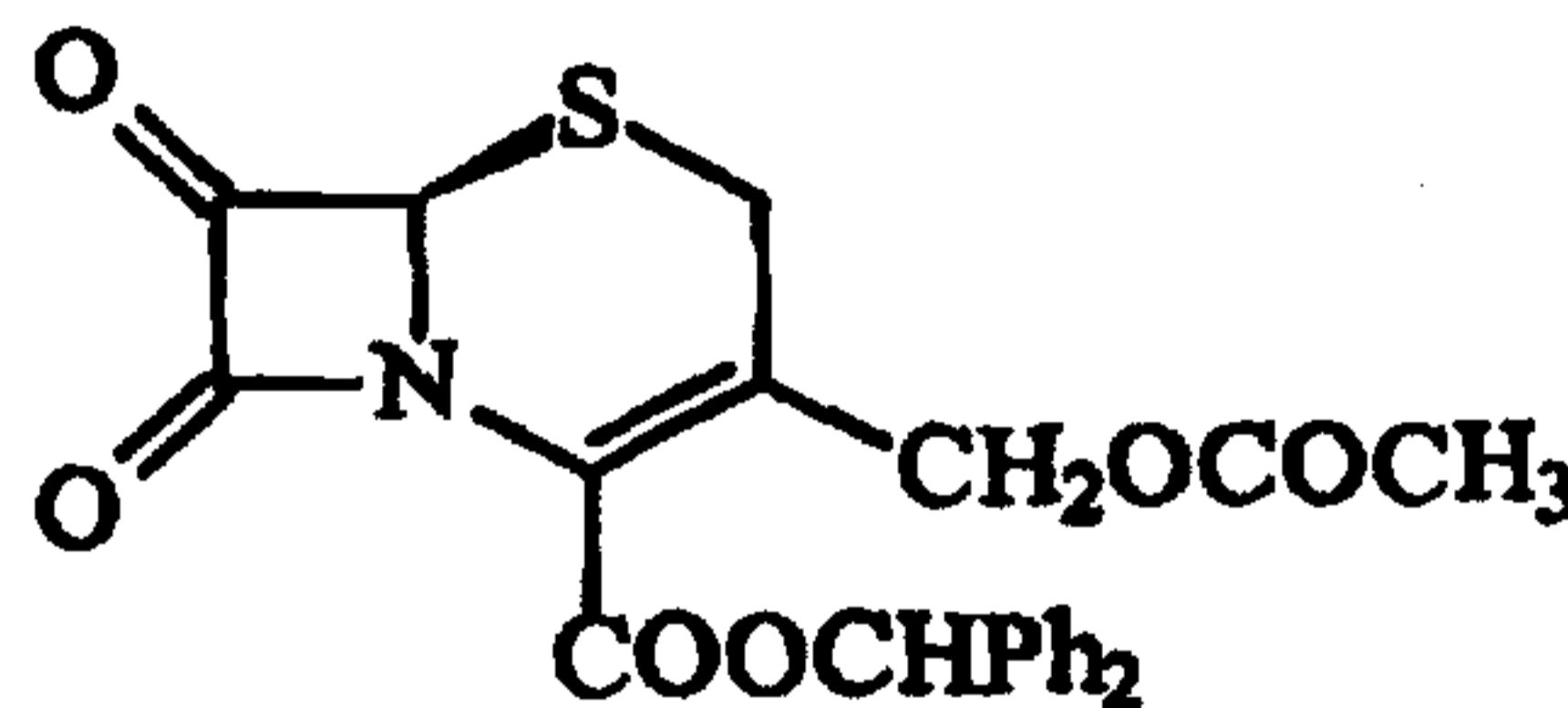
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

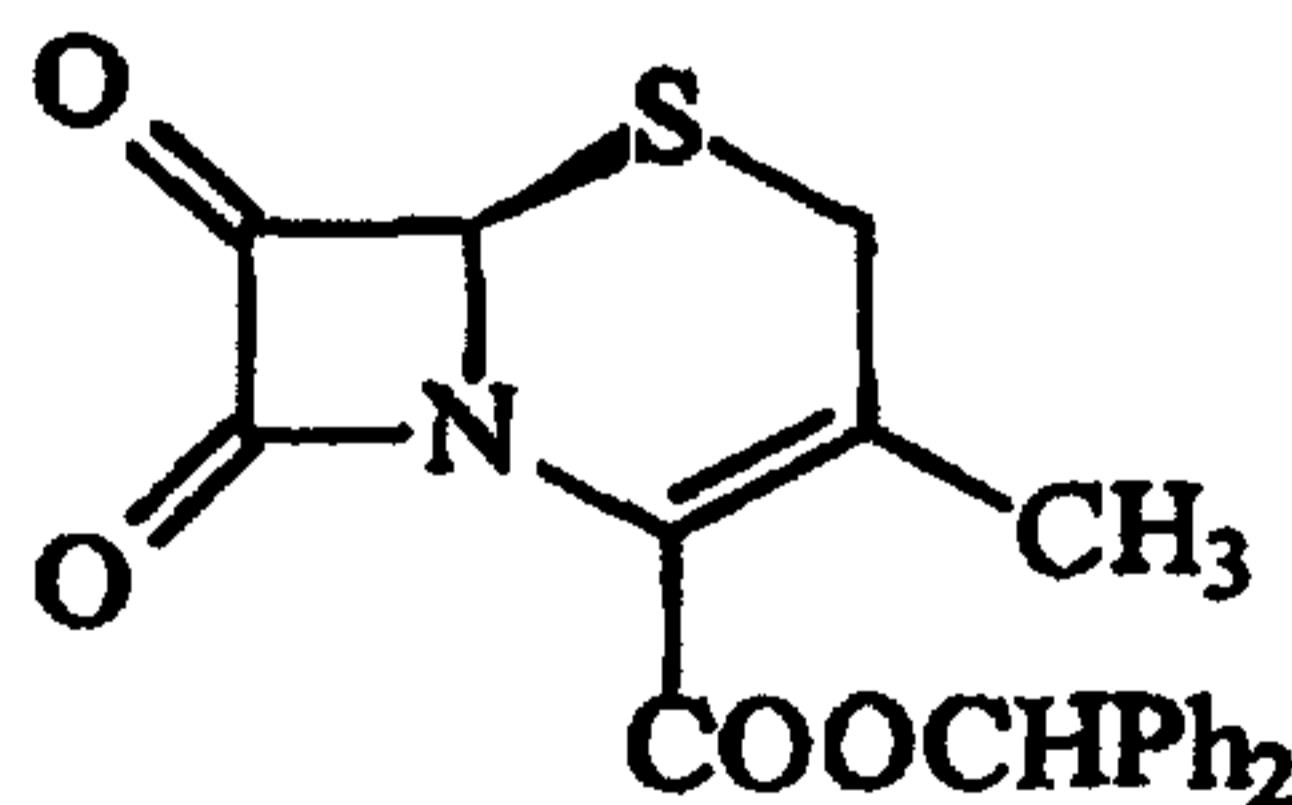
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<p>(21) International Application Number: PCT/US98/27636 (22) International Filing Date: 29 December 1998 (29.12.98) (30) Priority Data: 60/068,927 29 December 1997 (29.12.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/068,927 (CIP) Filed on 29 December 1997 (29.12.97) (71) Applicant (for all designated States except US): RESEARCH CORPORATION TECHNOLOGIES, INC. [US/US]; Suite 600, 101 North Wilmot Road, Tucson, AZ 85711-3335 (US). (71)(72) Applicants and Inventors: BUYNAK, John, D. [US/US]; 10842 Hayfield Drive, Dallas, TX 75238 (US). RAO, Akireddy, Srinivasa [IN/US]; Apartment 125, 1230 South White Oak Drive, Waukegan, IL 60085 (US). (74) Agent: VIKSNINS, Ann, S.; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).</p>		<p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.</p>

(54) Title: PROCESS FOR THE PREPARATION OF α -OXOLACTAMS

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(57) Abstract

A method for preparing a α -oxolactam comprising, reacting a corresponding α -diazolactam with an oxygen donor, in the presence of a transition metal catalyst, to yield the corresponding α -oxolactam.

**PROCESS FOR THE PREPARATION OF
 α -OXOLACTAMS**

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Background of the Invention

α -Oxolactams are useful synthons for preparing a variety of natural products and biologically active compounds (for example see A. Hisham *Tetrahedron*, 1997, 53, no. 5, 1813-1822). They can also be used to prepare synthetically useful α -substituted ω -amino carboxylic acids, and to prepare a variety of isoindigoide dyes (G. Kollenz, et al. *Tetrahedron*, 1996, 52, no. 15, 5427-5440).

α -Oxo- β -lactams, such as 6-oxopenams, 7-oxocephems and 6-oxopenems, are also useful for preparing α -alkylidene- β -lactams and α -vinylidene- β -lactams, both important classes of β -lactamase inhibitors (U.S. Patent Number 5,597,817, issued January 29, 1997 ("817"); U.S. Patent Number 5,629,306, issued May 13, 1997 ("306"); Buynak et al., *J. Org. Chem.*, 1993, 58, 1325.; Buynak et al., *J. Am. Chem. Soc.*, 1994, 116, 10955; Buynak et al., *J. Med. Chem.*, 1995, 38, 1022; Buynak et al., *Bioorg. Med. Chem. Lett.*, 1995, 5, 1513; Arisawa et al., *J. Antibiot.*, 1982, 35, 1578; Brenner et al., *Biochemistry*, 1984, 23, 5839; Chen et al., *Tetrahedron Lett.*, 1986, 27, 3449; Bennet et al., *J. Antibiot.*, 1991, 44, 969).

α -Oxo- β -lactams have also been used to prepare cytotoxic analogs of paclitaxel (J. Kant et al. *Tetrahedron Letters*, 1996, 37, 6495-6498); and to prepare α -aminoacid N-carboxy anhydrides and their corresponding α -amino acid derivatives (C. Palomo *J. Org. Chem.*, 1994, 59, 3123-3130).

J.M. van der Veen et al. *J. Org. Chem.*, 1989, 54, 5758-5762 disclose the preparation of specific α -oxo- β -lactams by hydrolysis of the corresponding α -chloro- α -phenylthio- β -lactams, which are prepared by the treatment of α -phenylthio- β -lactams with N-chlorosuccinimide. C. Palomo et al. *J. Org. Chem.*, 1994, 59, 3123-3130, disclose the preparation of specific α -oxo- β -lactams by oxidation of the corresponding α -hydroxy- β -lactams using $\text{Me}_2\text{SBr}_2\text{-NEt}_3$, CrO_3 -pyridine, or $\text{DMSO-P}_2\text{O}_5$. U.S. Patents '817 and '306 disclose the preparation of specific α -oxo- β -lactams by treatment of the corresponding α -amino- β -lactams

with trifluoromethanesulfonic anhydride and triethylamine, followed by aqueous acid.

Existing methods for preparing α -oxolactams are limited because they require the use of toxic or corrosive reagents, produce hazardous side products, require starting materials that are difficult or expensive to prepare, or yield products that can not be easily isolated or purified. Additionally, existing methods can not conveniently be performed to yield products on a commercially useful (e.g. kilogram) scale. Therefore, there is a need for improved methods for preparing α -oxolactams, which overcome one or more of the limitations of the existing synthetic methods.

Summary of the Invention

The present invention provides a method comprising reacting an α -diazolactam with an oxygen donor, in the presence of a transition metal catalyst to yield the corresponding α -oxolactam. The method utilizes non-toxic reagents, does not produce hazardous side products, and yields a product that can be easily isolated. Additionally, the method is mild and selective, and allows for the preparation of the α -oxolactam functionality in the presence of a wide variety of other functional groups.

The method may also further comprise the step of preparing the α -diazolactam from a corresponding α -aminolactam by diazotization.

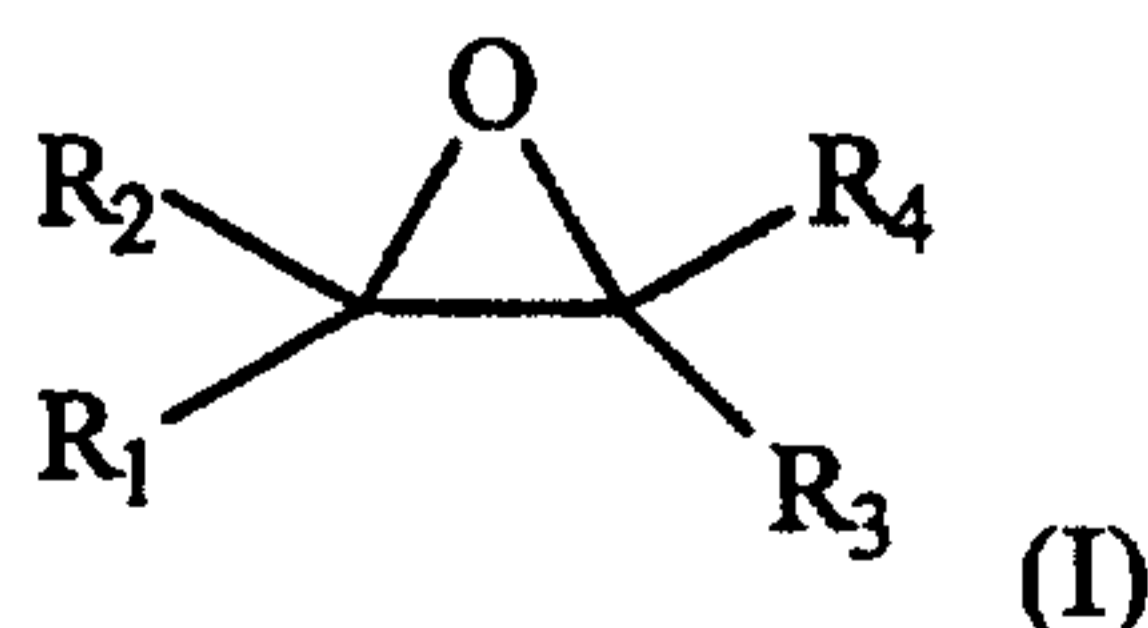
Brief Description of the Figures

Figure 1 shows the α -oxo- β -lactams prepared in Example 1, Example 2, and Example 3.

Detailed Description of the Invention

Oxygen Donors

The method of the instant invention may be practiced using any suitable oxygen donor. Preferably, the oxygen donor is an epoxide. For example, the method may be carried out using an epoxide of formula (I):



wherein

a) R_1 , R_2 , R_3 , and R_4 are each independently hydrogen, or (C_1-C_{10}) alkyl;

or

b) R_1 and R_3 , or R_1 and R_2 , together with the carbon atoms to which they
5 are attached form a five to eight membered carbocyclic ring; or

c) R_2 and R_4 , or R_3 and R_4 , together with the carbon atoms to which they
are attached form a five to eight membered carbocyclic ring; or

d) any possible combination of a), b), and c).

The nature of the organic epoxide is not critical to the practice of the
10 present method, so long as it is compatible with the reactants to which it is
exposed. Preferably, the epoxide is ethylene oxide, propylene oxide, 1-butylene
oxide, 2-butylene oxide, isobutylene oxide, 1-pentene oxide, 2-pentene oxide, 1-
isopentene oxide, 2-isopentene oxide, 3-isopentene oxide, 1-hexene oxide, 2-
hexene oxide, 3-hexene oxide, cyclopentene oxide, cyclohexene oxide,
15 cycloheptene oxide, or cyclooctene oxide.

The method may also be carried out using the epoxides described in M.G.
Martin and B. Ganem, *Tetrahedron Letters*, 1984, 25, 251-254, or using
epoxides similar thereto.

20 Transition Metal Catalyst

The invention may be practiced using any suitable transition metal
catalyst, such as an inorganic or organic salt of a group VIII, VIIB, IB, or IIB
metal. The catalyst may conveniently comprise rhodium (II), rhenium (V),
rhenium (VII), copper (I), or copper (II).

25 Suitable catalysts comprising copper are well known in the art and
include the copper catalysts disclosed to be useful for carrying out intramolecular
insertion reactions by S.D. Burke, and P.A. Grieco, *Org. React.* 26, 361-474
(1979). Specific copper catalysts include copper (II) acetylacetonate, copper (I)
iodide, copper (I) trifluoromethanesulfonate, copper (II)
30 trifluoromethanesulfonate, copper (II) sulfate, copper (I) oxide, copper (II) oxide,
copper powder, copper (I) bromide, and copper (I) chloride.

In a preferred embodiment of the invention, the catalyst comprises
rhodium (II). More preferably, the catalyst comprises a binuclear rhodium (II)

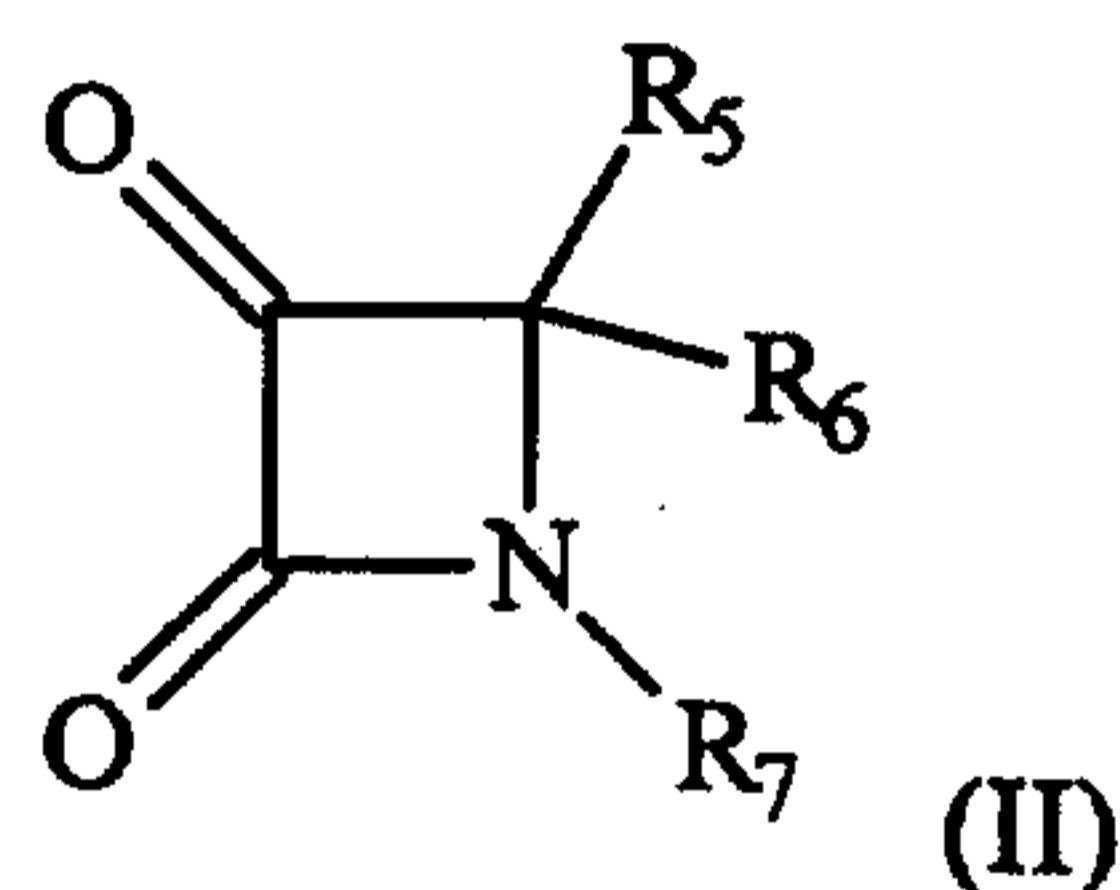
carboxylate salt, for example, $\text{Rh}_2(\text{OAc})_4$, rhodium octanoate dimer, or rhodium pivalate dimer.

In another preferred embodiment of the invention, the catalyst comprises rhenium (V) or rhenium (VII). More preferably, the catalyst comprises MeReO_3 or $\text{ReOCl}_3(\text{PPh}_3)_2$ (B.E. Ledford and E.M. Carreira *Tetrahedron Letters*, 1997, 38, 8125-8128).

α -Oxolactams

Because of the mild reaction conditions involved, the method of the invention is generally useful for preparing α -oxolactams (e.g. α -oxo- β -lactams, α -oxo- γ -lactams and α -oxo- δ -lactams).

Specifically, the method of the invention is useful for preparing α -oxo- β -lactams of formula II:



wherein R_5 , R_6 and R_7 , either alone or in any combination, are organic moieties compatible with the reaction conditions of the method of the invention.

The method of the invention is also specifically useful for preparing an α -oxo- β -lactam of formula (II) wherein R_5 , R_6 and R_7 are each individually hydrogen, $(\text{C}_1\text{-C}_{10})$ alkyl, aryl, heteroaryl, or any combination thereof.

The method of the invention is also specifically useful for preparing an α -oxo- β -lactam of formula II wherein R_5 , R_6 and R_7 together with the α -oxo- β -lactam ring to which they are attached, form an α -oxopenam, α -oxopenem, α -oxocarbapenam, α -oxocephem, α -oxocarbacephem or α -(oxo)oxacephem ring system, or an intermediate useful (or subsequently used) for preparing such a ring system. Compounds comprising such a ring system can be used for preparing antibiotics or β -lactamase inhibitors, such as those disclosed in U.S. Patents '817 and '306 cited hereinabove, and those disclosed by I. Heinze-Krauss et al. *J. Med. Chem.* 1996, 39, 1864-1871. In particular, the method is useful for

preparing 6-oxopenams, 7-oxocephems and 6-oxopenems, because it allows for the introduction of the α -oxo-substituent in the presence of the reactive sulfide sulfur of these ring systems.

The method of the invention is also specifically useful for preparing an α -oxo- β -lactam intermediate of formula II wherein R_5 is phenyl, R_6 is hydrogen and R_7 is tert-butyl-dimethylsilyl. This compound is a useful intermediate for preparing taxol analogs (J. Kant *Tetrahedron Letters*, 1996, 37, 6495-6498).

The method of the invention is also specifically useful for preparing α -oxo- β -lactam intermediates of formula II wherein R_5 is hydrogen, phenyl, methyl, (tert-butyl-diphenylsilyloxy)methyl, (1-tert-butoxycarbonylamino)ethyl, or α -(tert-butyl-dimethylsilyloxy)benzyl; R_6 is hydrogen; and R_7 is 4-methoxyphenyl or benzyl. These compounds are useful for preparing α -amino acid N-carboxy anhydrides and their corresponding α -amino acid derivatives (C. Palomo *J. Org. Chem.*, 1994, 59, 3123-3130).

The method of the invention is also specifically useful for preparing α -oxo- β -lactam intermediates of formula II wherein R_5 is phenyl, optionally substituted with one or two substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₃)alkoxy, hydroxyl, and cyano; R_6 is hydrogen; and R_7 is (C₁-C₄)alkyl, cyclopentyl, cyclohexyl, 1-naphthylmethyl, 1-phenethyl, 1-carboxy-2-phenethyl, phenyl, benzyl, or 3-[(C₁-C₄)alkoxycarbonyl]-1-[(C₁-C₄)alkoxy-carbonyl]propyl, wherein any phenyl or benzyl may optionally be substituted on the phenyl ring with one or two substituents independently selected from the group consisting of halogen, (C₁-C₄)alkyl, (C₁-C₃)alkoxy, dimethylamino, carboxy, dichloroacetyl and trifluoromethyl. These compounds are useful for preparing 2-azetidinone blood aggregation inhibitors (Y. Kawashima Japanese Patent Application Publication Number JP 01135763; and European Patent Application Publication Number 264231).

The method of the invention is also specifically useful for preparing an α -oxo- β -lactam of formula (II) wherein R_5 and R_6 are each hydrogen; and R_7 is phenyl. This compound is a useful intermediate for preparing antibiotics (I. Heinze-Krauss et al. *J. Med. Chem.* 1996, 39, 1864-1871).

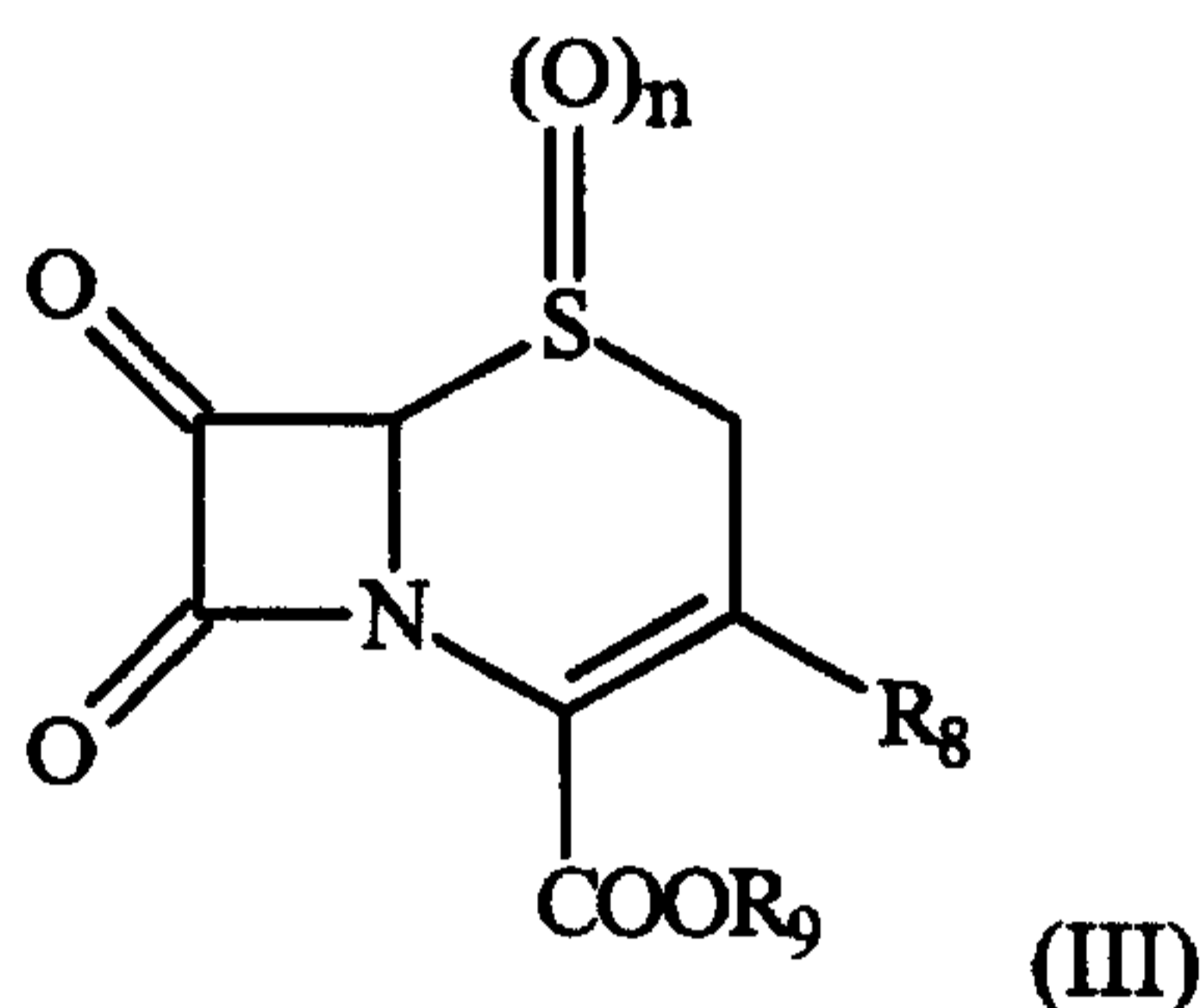
The method of the invention is also specifically useful for preparing an α -oxo- β -lactam of formula (II) wherein R_5 is phenyl, 4-methoxyphenyl, 2-

bromophenyl, or styryl; R_6 is hydrogen; and R_7 is 4-methoxyphenyl. These compounds are useful for preparing α -allyl- β -lactams which can be used to prepare a variety of heterocyclic compounds including pyrrolidine and piperidine alkaloids (M. Jayaraman et al. *Tetrahedron Letters*, 1997, 38, 709-712; A.K.

5 Bose et al. *Tetrahedron Letters*, 1986, 27, 5955).

The method of the invention may also specifically be useful for preparing the aldose reductase inhibitor 1-benzyl-3-hydroxy-2(5H)-oxopyrrole-4-carboxylate as well as other biologically active compounds and intermediates disclosed by B.L. Mylari, *J. Med. Chem.*, 1991, 34, 1011-1018.

10 Preferrably, the α -oxo- β -lactam prepared by the method of the invention is a compound of formula (III):



wherein

n is 0, 1, or 2;

15 R_8 is hydrogen, carboxy, chloro, fluoro, trifluoromethyl, formyl, or -
CH₂M;

M is

hydrogen;

halo;

20 hydroxy;

(C₁-C₁₀)alkoxy;

aryloxy;

aryl(C₁-C₁₀)alkoxy;

mercapto;

25 mercapto substituted with (C₁-C₁₀)alkyl, aryl, or aryl(C₁-C₁₀)alkyl;

(C₂-C₁₀)alkanoylthio;

(C₂-C₁₀)alkanoyloxy;

(C₂-C₁₀)carbamoyloxy;

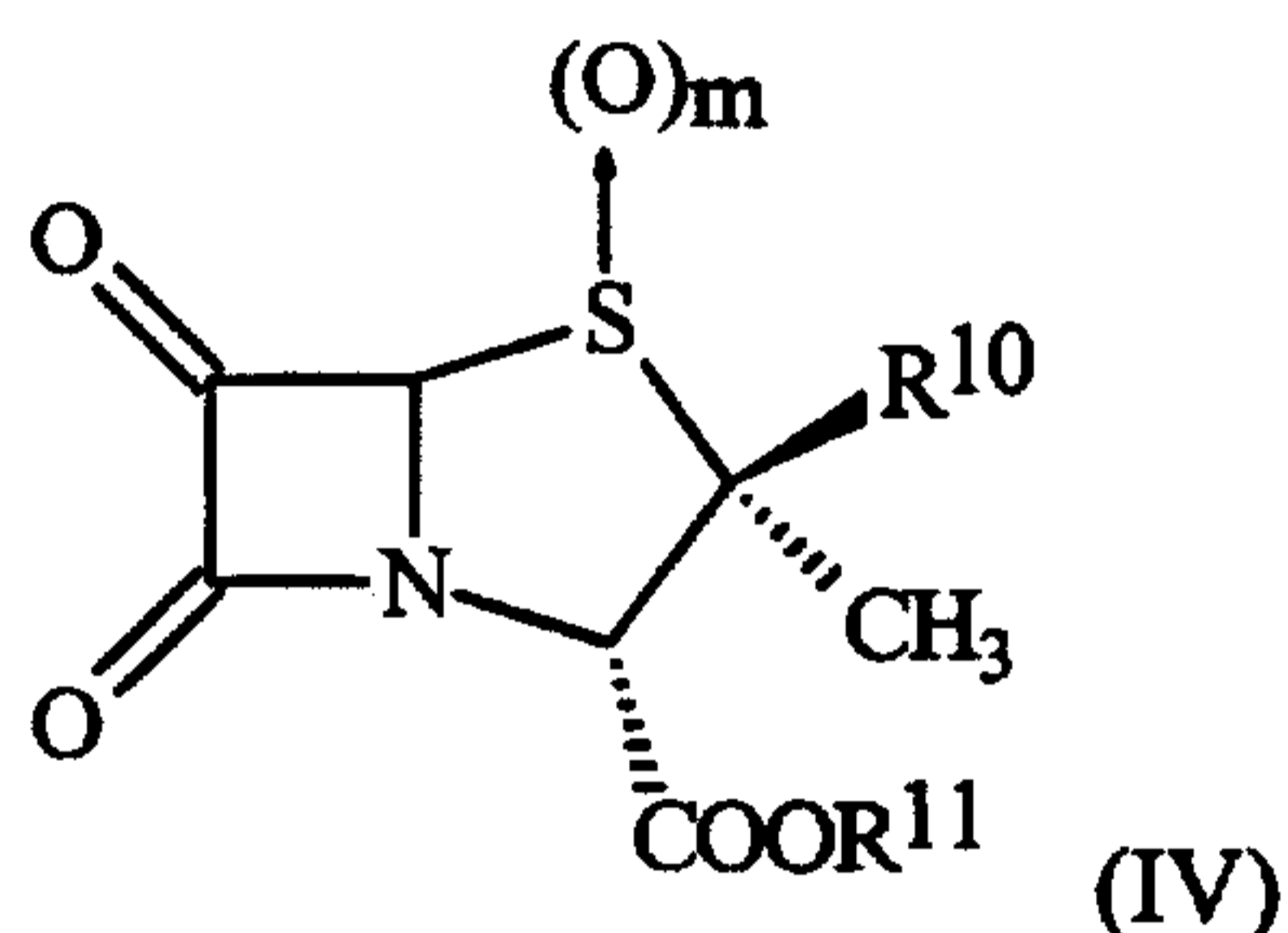
(C₂-C₁₀)alkanoyloxy or (C₂-C₁₀)carbamoyloxy, substituted with one or more carboxy, aminophenyl, phenyl, (C₁-C₆)alkyl, chloro, bromo or fluoro; or

5 N(R)₂, wherein each R is independently selected from hydrogen, (C₁-C₁₀)alkyl, or (C₁-C₁₀)alkanoyl; and

R₉ is hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, C₃-C₈cycloalkyl(C₁-C₁₀)alkyl, aryl, aryl(C₁-C₁₀)alkyl, or diaryl(C₁-C₁₀)alkyl;

or a salt thereof.

10 In another preferred embodiment of the invention, the α-oxo-β-lactam prepared by the method of the invention is a compound of formula (IV):



wherein

R¹⁰ is (C₃-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl,
 15 (C₁-C₁₀)alkanoyl, (C₃-C₈)cycloalkyl, aryl, heteroaryl, aryl(C₁-C₁₀)alkyl, heteroaryl(C₁-C₁₀)alkyl, or -CH₂R_a, wherein R_a is halo, cyano, cyanato, -OR_b, -NR_cR_d, azido, -SR_e, or (C₃-C₈)cycloalkyl;

R¹¹ is hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, aryl, or heteroaryl;

20 m is 0, 1, or 2;

R_b is hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, -C(=O)N(R_g)₂, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, or (C₁-C₁₀)alkanoyl, wherein each R_g is independently hydrogen, (C₁-C₁₀)alkyl, aryl, benzyl, phenethyl, or heteroaryl;

25 each R_c or R_d is independently hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)alkanoyl, -C(=O)N(R_h)₂, aryl, benzyl, phenethyl, heteroaryl oxazolidinyl, isoxazolidinyl,

or morpholinyl; wherein each R_h is independently hydrogen, (C_1-C_{10}) alkyl, aryl, benzyl, phenethyl, or heteroaryl; or R_c and R_d together with the nitrogen to which they are attached are triazolyl, imidazolyl, oxazolidinyl, isoxazolidinyl, pyrrolyl, morpholino, piperidino, pyrrolidino, pyrazolyl, indolyl, or tetrazolyl; and

5 R_e is hydrogen, (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, cyano, aryl, benzyl, phenethyl, heteroaryl, oxazolidinyl, isoxazolidinyl, or morpholinyl;

wherein any (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, (C_1-C_{10}) alkanoyl, aryl, benzyl, phenethyl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, oxazolidinyl, isoxazolidinyl, or morpholinyl of R^{10} , R^{11} , R_a-R_e , or R_g-R_h , may optionally be substituted with 1, 2, or 3 Z; and each Z is independently halo, nitro, cyano, hydroxy, (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, (C_2-C_{10}) alkanoyloxy, trifluoromethyl, aryl, aryloxy, heteroaryl, or $-SR_f$ wherein R_f is hydrogen, $(C_1-$
15 $C_{10})$ alkyl, (C_3-C_8) cycloalkyl, aryl, benzyl, phenethyl, or heteroaryl;

and further wherein any aryl, aryloxy, heteroaryl, benzyl, or phenethyl of Z may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, $(C_2-$
20 $C_{10})$ alkanoyloxy, benzyloxy, 4-methoxybenzyloxy, and trifluoromethyl; or a salt thereof.

The invention also provides novel compounds of formulae III and IV.

The following definitions apply herein unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, alkenyl, alkynyl etc. denote
25 both straight and branched groups, but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached
30 via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C_1-C_4) alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic

heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

It will be appreciated by those skilled in the art that α -oxolactams having one or more chiral centers may exist in and be prepared in optically active and racemic forms. The present invention provides a method which is generally useful for preparing any racemic, optically-active, or stereoisomeric form of a given α -oxolactam.

Specifically, (C₁-C₁₀)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, hexyl, heptyl, octyl, nonyl or decyl; (C₃-C₈)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; (C₁-C₁₀)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, or decyloxy; (C₂-C₁₀)alkenyl can be vinyl, allyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 4-octenyl, 5-octenyl, 6-octenyl, 7-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 4-nonenyl, 5-nonenyl, 6-nonenyl, 7-nonenyl, 8-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl, 4-decenyl, 5-decenyl, 6-decenyl, 7-decenyl, 8-decenyl, or 9-decenyl; (C₂-C₁₀)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 3-butylnyl, 1-pentylnyl, 2-pentylnyl, 3-pentylnyl, 4-pentylnyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl, 1-heptylnyl, 2-heptylnyl, 3-heptylnyl, 4-heptylnyl, 5-heptylnyl, 6-heptylnyl, 1-octynyl, 2-octynyl, 3-octynyl, 4-octynyl, 5-octynyl, 6-octynyl, 7-octynyl, 1-nonylnyl, 2-nonylnyl, 3-nonylnyl, 4-nonylnyl, 5-nonylnyl, 6-nonylnyl, 7-nonylnyl, 8-nonylnyl, 1-decynyl, 2-decynyl, 3-decynyl, 4-decynyl, 5-decynyl, 6-decynyl, 7-decynyl, 8-decynyl, or 9-decynyl; (C₁-C₁₀)alkanoyl can be acetyl, propanoyl, butanoyl, isobutanoyl, pentanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, or decanoyl; and (C₂-C₁₀)alkanoyloxy can be acetoxyl, propanoyloxy, butanoyloxy, isobutanoyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, or decanoyloxy. Likewise, aryl can be phenyl, indenyl, or naphthyl. Heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl,

isoxazolyl, thiazolyl, isothiazoyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide), thiadiazolyl, thiazotriazolyl, oxadiazolyl, or quinolyl (or its N-oxide).

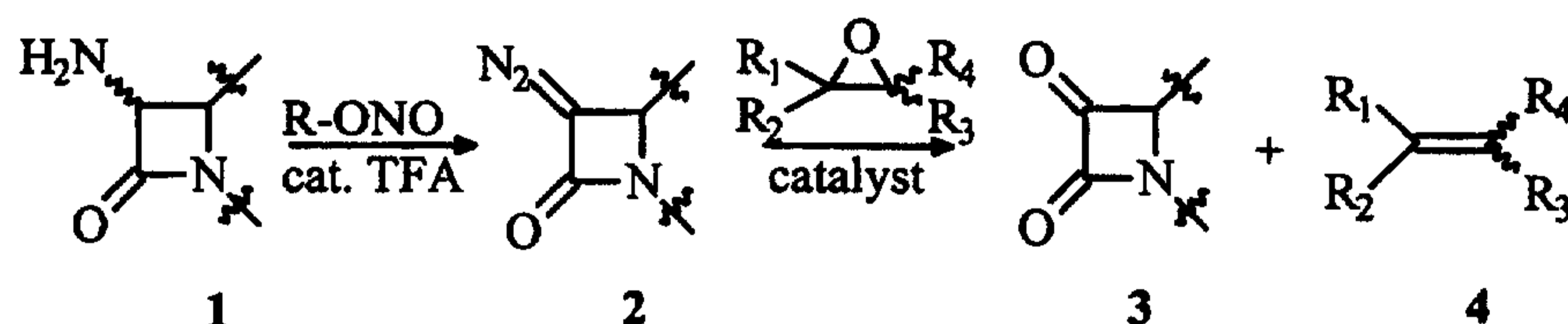
- 5 Specific and preferred values given herein for radicals, substituents, and ranges, are for illustration only and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Starting Materials

- 10 The requisite α -diazolactam starting materials can be prepared from a corresponding α -aminolactams by diazotization using techniques which are well known to the art. The diazotization of an α -amino- β -lactam 1, is illustrated in Scheme I.

Scheme I

15



- Treatment of amine 1 with isopropyl or isoamyl nitrite (R-ONO) in the presence of trifluoroacetic acid gives α -diazo- β -lactam 2. Suitable conditions for diazotizing amines are well known in the art; see for example J. March *Advanced*
- 20 *Organic Chemistry*, John Wiley & Sons, 4ed., 1992; or H.O. House *Modern Synthetic Reactions*, W.A. Benjamin, Inc., 2ed., 1972. Diazo compound 2 can be treated with an epoxide in the presence of a transition metal catalyst to yield α -oxo- β -lactam 3 and an olefin 4.

25 Salts

In cases where the α -oxolactam product (such as for example a compound of formula III or IV) is sufficiently basic or acidic to form a stable acid or base salt, the invention may further comprise the preparation of such a salt. Examples of acceptable salts are organic acid addition salts formed with

acids which form an acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording an acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Summary

The invention provides a method for the synthesis of an α -oxolactam. It allows for the selective oxidation of an α -diazolactam to the corresponding α -oxolactam in the presence of other easily oxidizable groups. The invention also provides a method that can conveniently and cost effectively yield α -oxolactams on a commercial scale.

The invention will now be illustrated by the following non-limiting Examples.

20

EXAMPLE 1

Benzhydryl 6-oxopenicillanate

To a solution of benzhydryl 6-aminopenicillanate (2 g, 5.23 mmol) in ethyl acetate (20 mL) were added isopropyl nitrite (1.8 mL, 7.85 mmol, 40 % solution in CH_2Cl_2) and trifluoroacetic acid (18 mg, 0.16 mmol) and the reaction was allowed to stir for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure and redissolved in benzene (15 mL). To this solution was added propylene oxide (30 g, 0.52 mol) followed by rhodium octanoate dimer (5 mg) and the reaction was stirred for 15 minutes (until evolution of nitrogen ceases). Volatiles were removed to yield the title compound (5, Figure 1) (2 g, quantitative, 95% pure). IR (CHCl_3): 1820, 1775, 1730 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.38 (10 H, bs), 7.00 (1H, s), 5.83 (1 H, s), 4.91 (1 H, s), 1.56 (3 H, s), 1.36 (3 H, s); ^{13}C NMR (CDCl_3): δ 190.4 (s), 168.0 (s),

165.8 (s), 139.1 (s), 138.6 (s), 128.5, 128.2, 127.6, 127.4, 127.1, 126.8, 126.5, 78.8 (d), 76.8 (d), 71.5 (d), 64.2 (s), 34.1 (q), 24.7 (q).

The starting material, benzhydryl 6-aminopenicillanate, can be readily prepared from 6-aminopenicillanic acid, which is available from Aldrich

5 Chemical Company, Inc. Milwaukee, Wisconsin, USA.

EXAMPLE 2

Benzhydryl 7-oxocephalosporanate

To a solution of benzhydryl 7-aminocephalosporanate (0.5 g, 1.146 mmol) in ethyl acetate (5 mL) were added isopropyl nitrite (0.38 mL, 1.71 mmol, 40 % solution in CH₂Cl₂) and trifluoroacetic acid (6.5 mg, 0.05 mmol) and the reaction was allowed to stir for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure and redissolved in benzene (5 mL). To this solution was added propylene oxide (6.7 g, 0.114 mol) followed by rhodium octanoate dimer (2 mg) and the reaction was stirred for 15 minutes (until evolution of nitrogen ceases). Volatiles were removed to produce the title compound (6, Figure 1) (0.5 g, quantitative, 90% pure). IR (CHCl₃) 3005, 1830, 1790, 1740 cm⁻¹; ¹H NMR (CDCl₃) δ 7.39 (10 H, m), 7.05 (1 H, s), 5.32 (1 H, s), 5.07 (1 H, d, A of ABq, J = 13.9 Hz), 4.85 (1 H, d, B of ABq, J = 14.0 Hz), 3.64 (1 H, d, A of ABq, J = 18.5 Hz), 3.44 (1 H, d, B of ABq, J = 18.6 Hz), 2.05 (3 H, s); ¹³C NMR (CDCl₃) δ 188.4 (s), 170.3 (s), 160.1 (s), 158.7 (s), 138.8 (s), 138.6 (s), 128.4, 128.2, 128.1, 127.7, 126.9, 126.2, 80.1 (d), 65.8 (d), 62.6 (t), 27.7 (t), 20.4 (q).

The starting material benzhydryl 7-aminocephalosporanate can be readily prepared from 7-aminocephalosporanic acid, which is available from Aldrich Chemical Company, Inc. Milwaukee, Wisconsin, USA.

EXAMPLE 3

Benzhydryl 7-oxo-3'-(desacetoxy)cephalosporanate

To a solution of benzhydryl 7-amino-3'-desacetoxycephalosporanate (15 g, 39.47 mmol) in ethyl acetate (300 mL) were added isopropyl nitrite (13.26 mL, 59.21 mmol, 40 % solution in CH₂Cl₂) and trifluoroacetic acid (0.134 g, 1.184 mmol) and the reaction was stirred for 1 hour at room temperature, concentrated under reduced pressure, and redissolved in benzene (75 mL). Propylene oxide (150 mL) oxide was added, followed by rhodium octanoate

dimer (100 mg) and the reaction was stirred for 15 minutes (until evolution of nitrogen gas ceased). Volatiles were removed under reduced pressure to give the title compound in quantitative yield (15 g, >90% purity); ¹H NMR (CDCl₃) δ 7.97-7.25 (m, 10H), 6.99 (s, 1H), 5.29 (s, 1H), 3.47 (d, J=17.86 Hz, 1H), 3.29 (d, J=17.86 Hz, 1H), 2.18 (s, 3H).

The starting material benzhydryl 7-amino-3'-desacetoxycephalosporanate can be readily prepared from 7-amino-3'-desacetoxycephalosporanic acid, which is available from Gist-brocades BV, a division of Gist-brocades international, Holland.

10 All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and
15 scope of the invention.

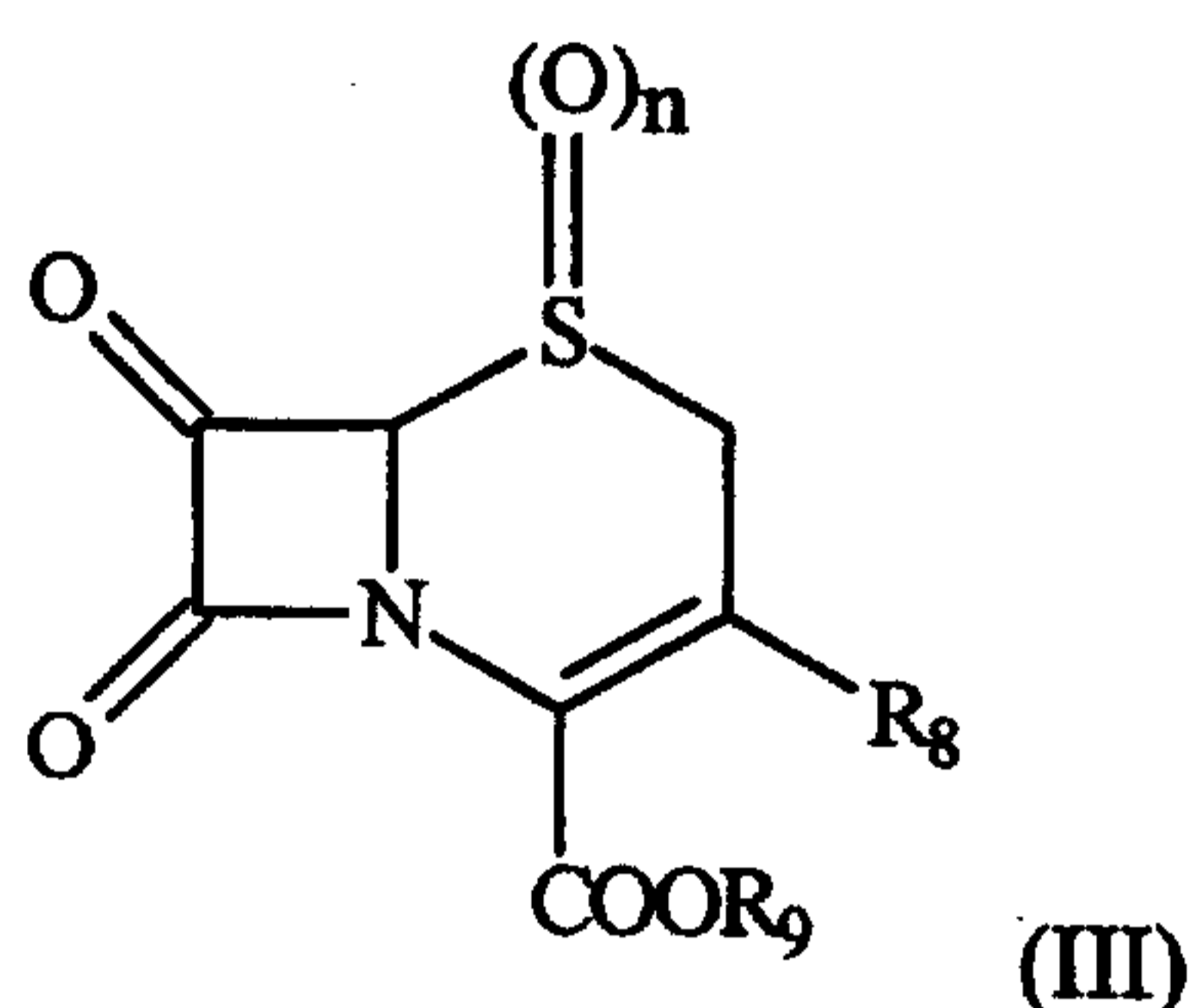
What is claimed is:

1. A method for preparing an α -oxolactam comprising reacting a corresponding α -diazolactam with an oxygen donor, in the presence of a transition metal catalyst, to yield the α -oxolactam.
2. The method of claim 1, wherein the oxygen donor is an epoxide.
3. The method of claim 2, wherein the epoxide is ethylene oxide, propylene oxide, 1-butylene oxide, 2-butylene oxide, isobutylene oxide, 1-pentene oxide, 2-pentene oxide, 1-isopentene oxide, 2-isopentene oxide, 3-isopentene oxide, 1-hexene oxide, 2-hexene oxide, 3-hexene oxide, cyclopentene oxide, cyclohexene oxide, cycloheptene oxide, or cyclooctene oxide.
4. The method of claim 1, wherein the catalyst comprises rhodium (II), copper (I), copper (II), rhenium (V), or rhenium (VII).
5. The method of claim 1, wherein the catalyst comprises rhodium (II).
6. The method of claim 5, wherein the catalyst is $\text{Rh}_2(\text{OAc})_4$, rhodium octanoate dimer, or rhodium pivalate dimer.
7. The method of claim 1 wherein the catalyst comprises rhenium (V) or rhenium (VII).
8. The method of claim 1 wherein the catalyst comprises MeReO_3 or $\text{ReOCl}_3(\text{PPh}_3)_2$.
9. The method of claim 1 wherein the α -oxolactam is a α -oxo- β -lactam, α -oxo- γ -lactam, or an α -oxo- δ -lactam.
10. The method of claim 1 wherein the α -oxolactam is a α -oxo- β -lactam.

11. A method for preparing an α -oxo- β -lactam comprising reacting a corresponding α -diazo- β -lactam with an epoxide in the presence of a catalyst comprising rhodium (II), copper (I), copper (II), rhenium (VII), or rhenium (V).

5 12. The method of claim 11 wherein the catalyst comprises rhodium (II).

13. The method of claim 1, wherein the α -oxolactam is a compound of formula (III):



wherein

10 n is 0, 1, or 2;

R₈ is carboxy, chloro, fluoro, trifluoromethyl, formyl, or -CH₂M;

M is

hydrogen;

halo;

15 hydroxy;

(C₁-C₁₀)alkoxy;

aryloxy;

aryl(C₁-C₁₀)alkoxy;

mercapto;

20 mercapto substituted with (C₁-C₁₀)alkyl, aryl, or aryl(C₁-C₁₀)alkyl;

(C₂-C₁₀)alkanoylthio;

(C₂-C₁₀)alkanoyloxy;

(C₂-C₁₀)carbamoyloxy;

(C₂-C₁₀)alkanoyloxy or (C₂-C₁₀)carbamoyloxy, substituted with

25 one or more carboxy, aminophenyl, phenyl, (C₁-C₆)alkyl, chloro, bromo or fluoro; or

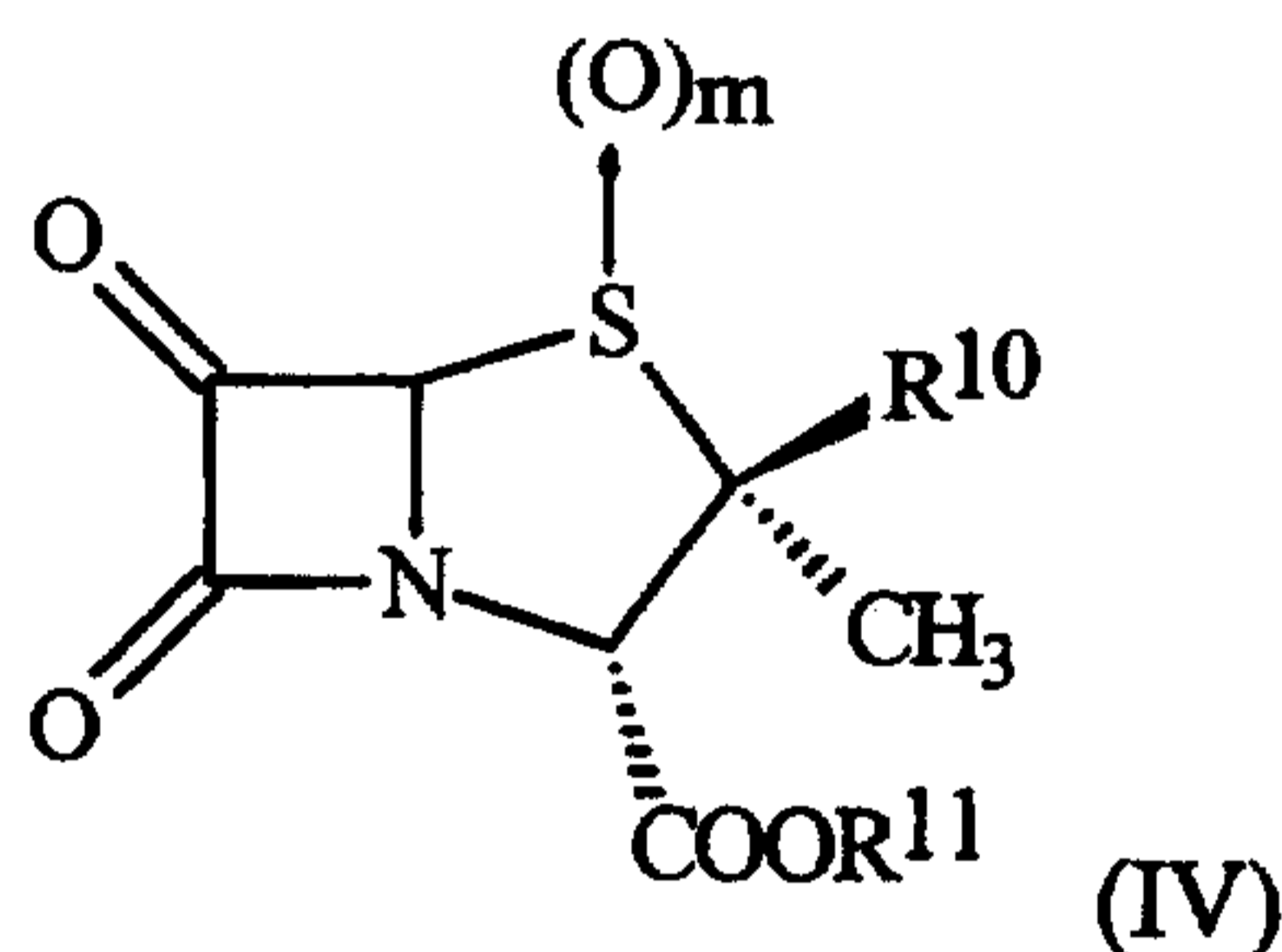
$N(R)_2$, wherein each R is independently selected from hydrogen, (C₁-C₁₀)alkyl, or (C₁-C₁₀)alkanoyl; and

R₉ is hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkyl(C₁-C₁₀)alkyl, aryl, aryl(C₁-C₁₀)alkyl, or diaryl(C₁-C₁₀)alkyl;

5 or a salt thereof.

14. The method of claim 13 wherein R₈ is acetoxymethyl.

15. The method of claim 1, wherein the α -oxo-lactam is a compound of
10 formula (IV):



wherein

R¹⁰ is (C₃-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)alkanoyl, (C₃-C₈)cycloalkyl, aryl, heteroaryl, aryl(C₁-C₁₀)alkyl, heteroaryl(C₁-C₁₀)alkyl, or -CH₂R_a, wherein R_a is halo, cyano, cyanato, -OR_b, -NR_cR_d, azido, -SR_e, or (C₃-C₈)cycloalkyl;

R¹¹ is hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, aryl, or heteroaryl;

m is 0, 1, or 2;

20 R_b is hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, -C(=O)N(R_g)₂, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, or (C₁-C₁₀)alkanoyl, wherein each R_g is independently hydrogen, (C₁-C₁₀)alkyl, aryl, benzyl, phenethyl, or heteroaryl;

25 each R_c or R_d is independently hydrogen, (C₁-C₁₀)alkyl, (C₃-C₈)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₁-C₁₀)alkanoyl, -C(=O)N(R_h)₂, aryl, benzyl, phenethyl, heteroaryl oxazolidinyl, isoxazolidinyl, or morpholinyl; wherein each R_h is independently hydrogen, (C₁-C₁₀)alkyl, aryl,

benzyl, phenethyl, or heteroaryl; or R_c and R_d together with the nitrogen to which they are attached are triazolyl, imidazolyl, oxazolidinyl, isoxazolidinyl, pyrrolyl, morpholino, piperidino, pyrrolidino, pyrazolyl, indolyl, or tetrazolyl; and

R_e is hydrogen, (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, cyano, aryl, benzyl, phenethyl, heteroaryl, oxazolidinyl, isoxazolidinyl, or morpholinyl;

wherein any (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_2-C_{10}) alkenyl, (C_2-C_{10}) alkynyl, (C_1-C_{10}) alkanoyl, aryl, benzyl, phenethyl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, oxazolidinyl, isoxazolidinyl, or morpholinyl of R^{10} , R^{11} , R_a-R_e , or R_g-R_h , may optionally be substituted with 1, 2, or 3 Z; and each Z is independently halo, nitro, cyano, hydroxy, (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, (C_2-C_{10}) alkanoyloxy, trifluoromethyl, aryl, aryloxy, heteroaryl, or $-SR_f$, wherein R_f is hydrogen, (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, aryl, benzyl, phenethyl, or heteroaryl;

and further wherein any aryl, aryloxy, heteroaryl, benzyl, or phenethyl of Z may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, nitro, cyano, hydroxy, (C_1-C_{10}) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_{10}) alkoxy, (C_1-C_{10}) alkanoyl, (C_2-C_{10}) alkanoyloxy, benzyloxy, 4-methoxybenzyloxy, and trifluoromethyl.

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16. The method of claim 15 wherein R_{10} is acetoxymethyl.

17. The method of claim 1 further comprising, first preparing the α -diazolactam, by diazotizing a corresponding α -aminolactam.

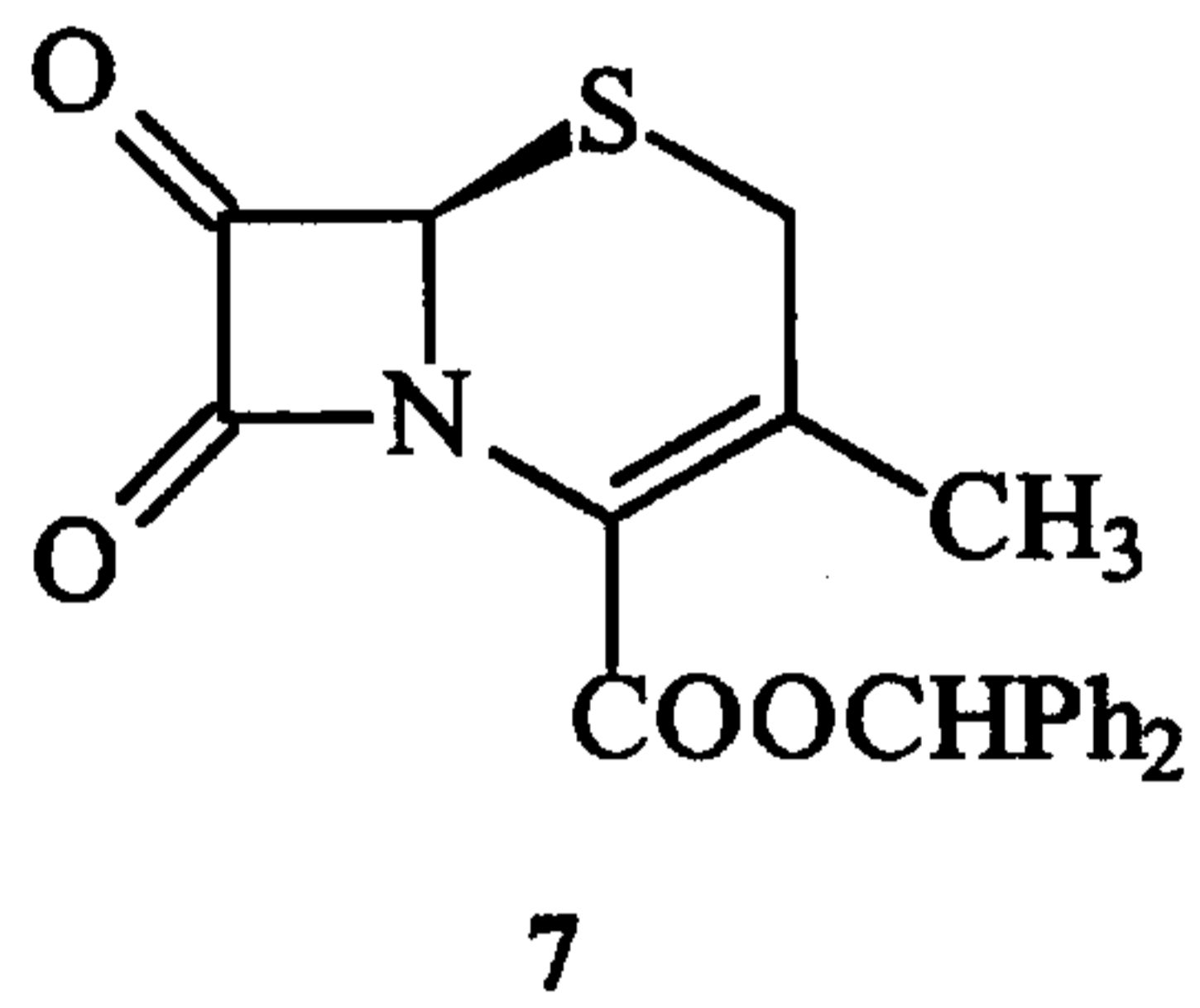
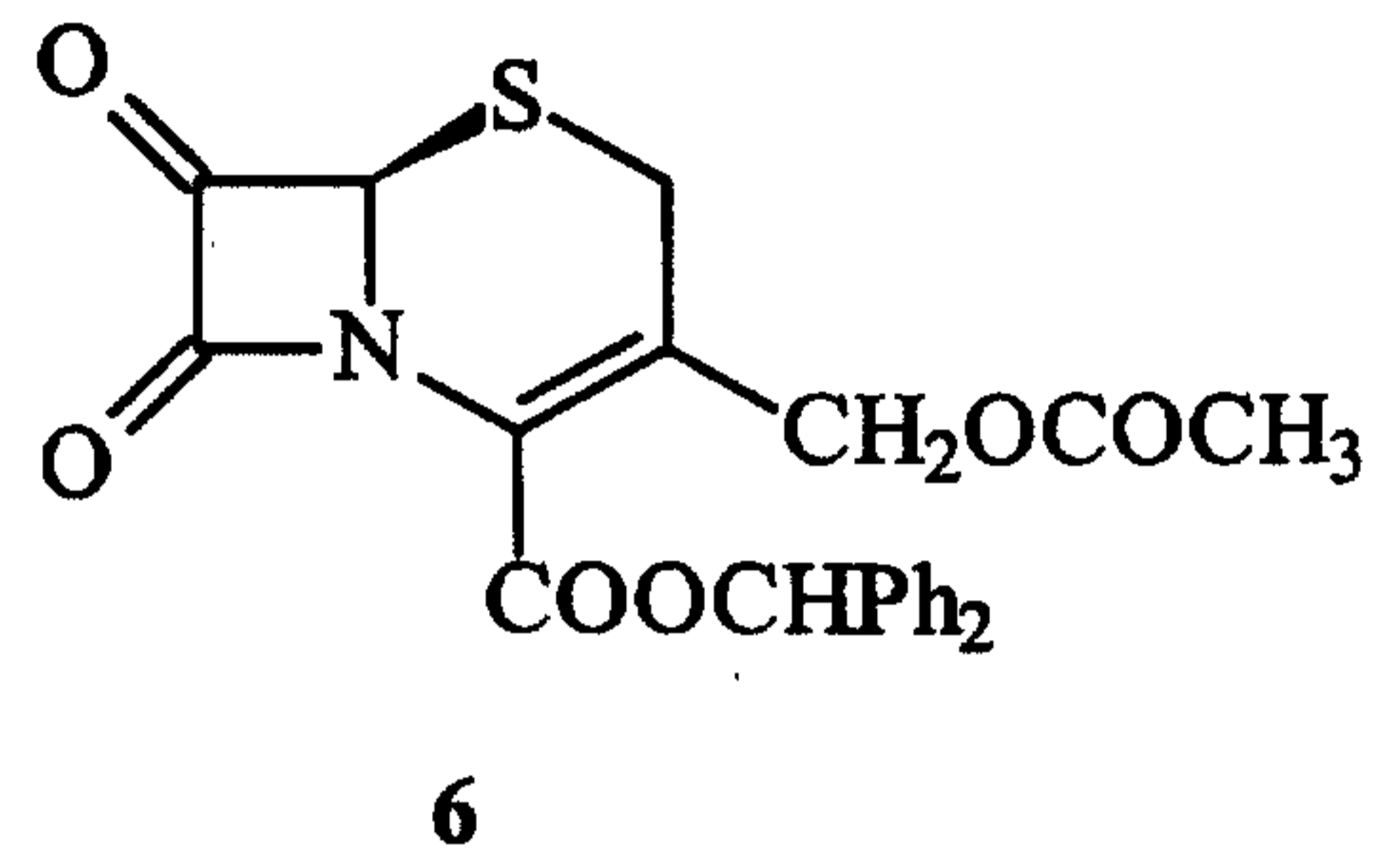
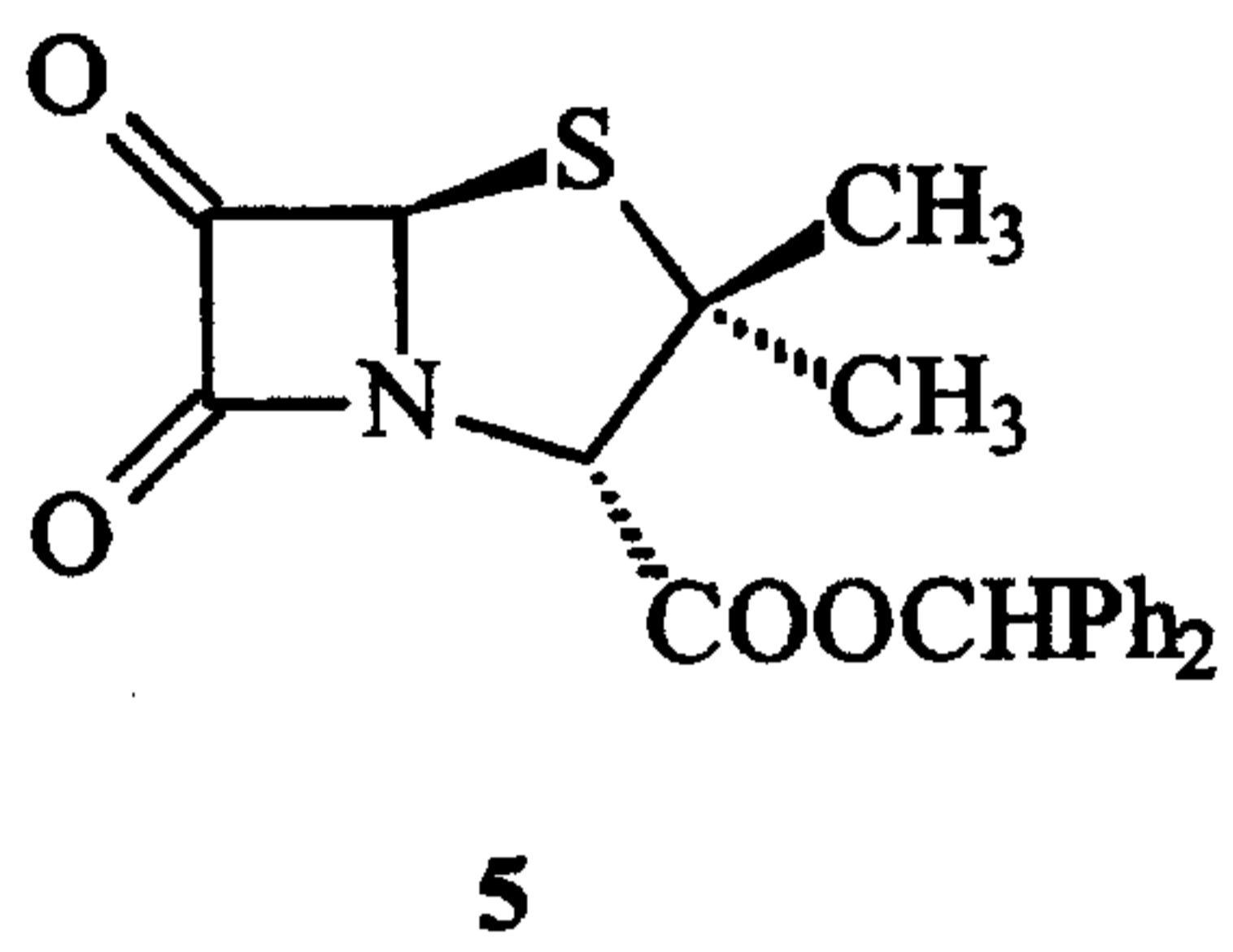
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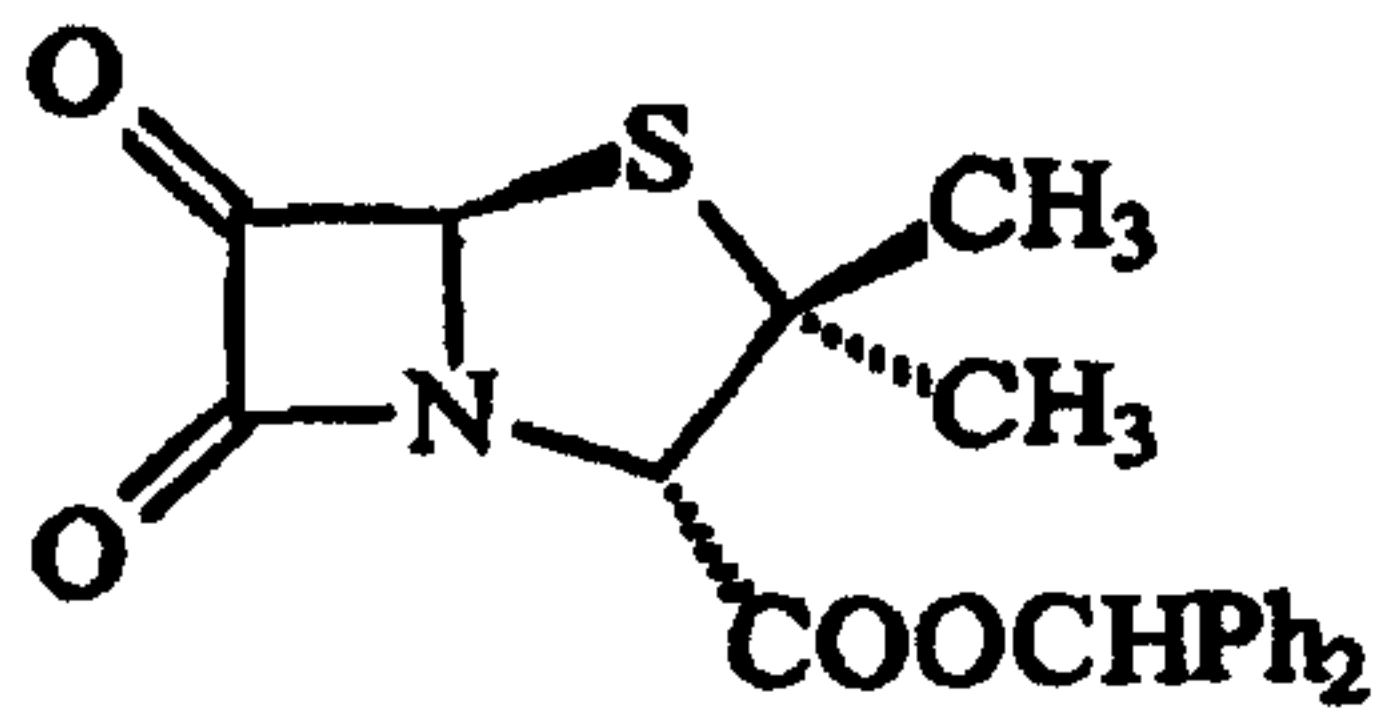
18. The method of claim 17 wherein the α -aminolactam is diazotized by treatment with isopropyl or isoamyl nitrite in the presence of an acid catalyst.

19. The method of claim 1 wherein the α -oxo- β -lactam is benzhydryl 6-oxopenicillanate, benzhydryl 7-oxocephalosporanate, or benzhydryl 7-oxo-3'-(desacetoxy)cephalosporanate.

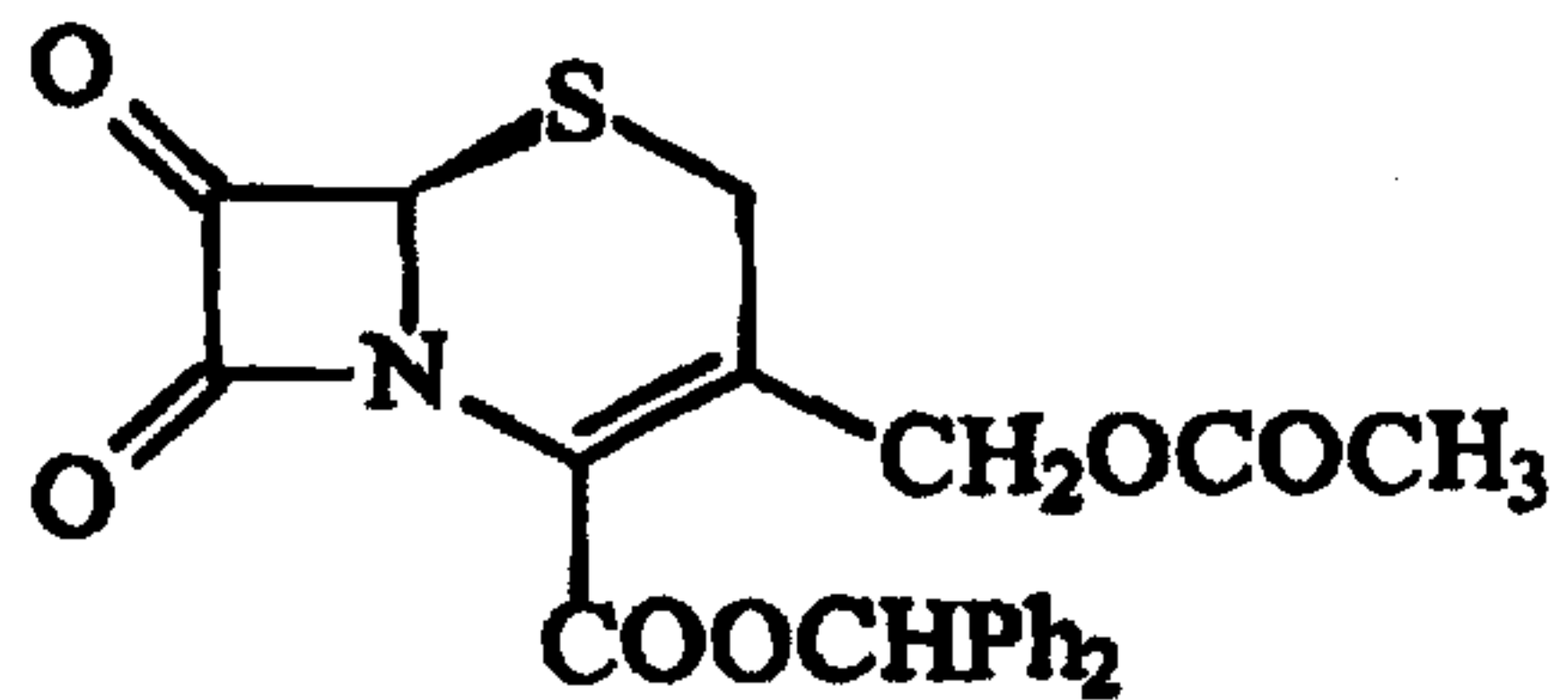
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Figure 1

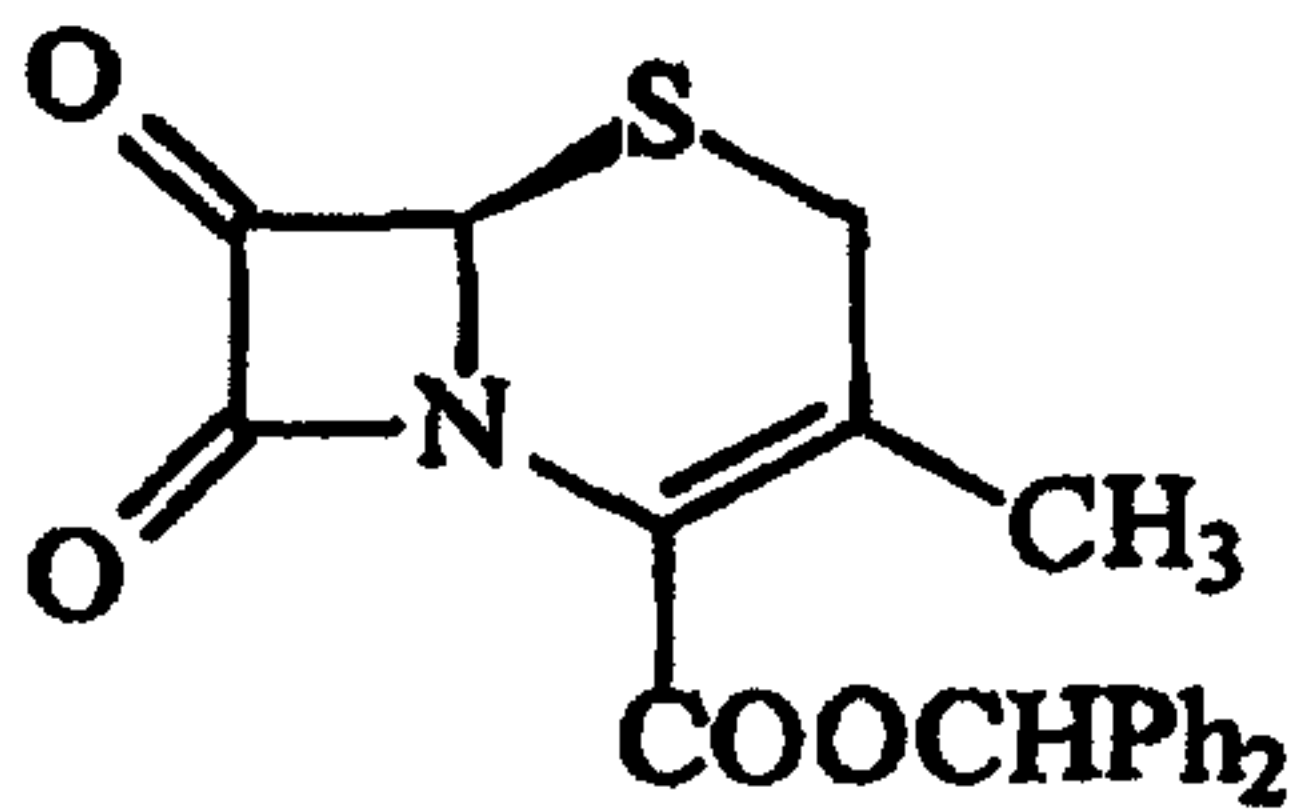




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