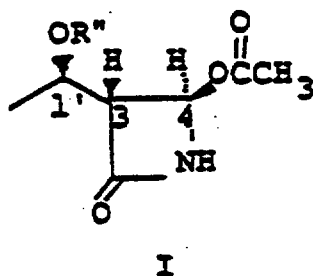


Anhydropenicillins and a Stereocontrolled Process for Producing AzetidinoneBACKGROUND OF THE INVENTION1. Field of the Invention

The present invention is directed to a novel stereocontrolled process for producing a key intermediate used in the synthesis of carbapenem and penem antibiotics.

2. Description of the Prior Art

The present invention is directed to a novel stereocontrolled process for converting 6-aminopenicillanic acid to an optically active azetidinone intermediate of the formula

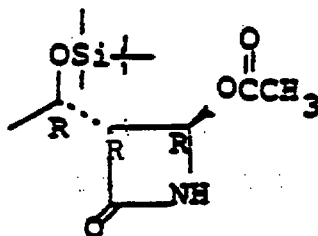


wherein R' is a conventional hydroxy-protecting group and wherein the absolute configuration at carbons 1', 3 and 4 is R, R and R. Intermediates of formula I, which are known per se, are key intermediates in the synthesis of carbapenem and penem antibiotics having an (R)-hydroxyethyl substituent at the 6-position of the carbapenem or penem nucleus and the absolute configuration R and S at the 5 and 6 positions, respectively. A wide variety of such compounds, including the natural fermentation product thienamycin, have been reported in the patent and scientific literature as having exceptional antibacterial activity.

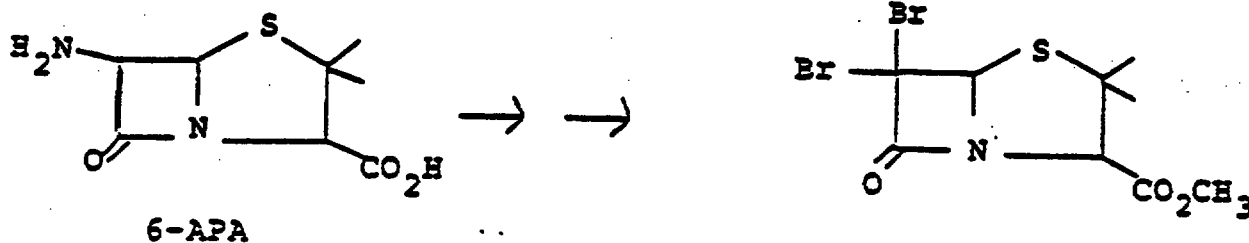
Several total synthesis procedures have been reported for preparation of the above-described penem and carbapenem antibiotics, but to date such procedures have been unsatisfactory

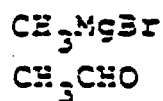
from a commercial standpoint due to the large number of steps required and the necessity of separating diastereomer mixtures formed in such procedures.

One approach to synthesis of carbapenems and penems of the above-described type has been to use as a starting material, 6-aminopenicillanic acid (6-APA), a readily-available substance easily obtained by fermentation procedures. Hirai, et al. in Heterocycles 17: 201-207 (1982) report a process for converting 6-APA to the optically active 4-acetoxy-3-azetidinone of the formula

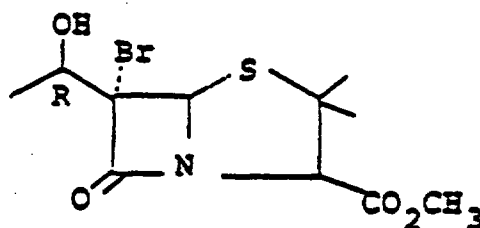


which can be converted, by known procedures, to biologically active penems and carbapenems. In this process 6-APA is converted to the above-indicated azetidinone by the following scheme:

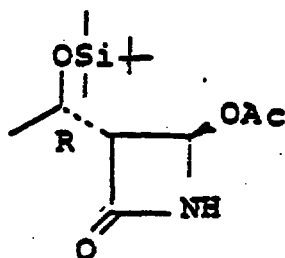
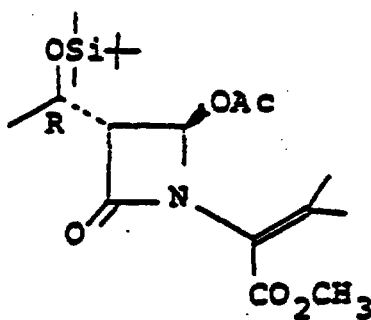
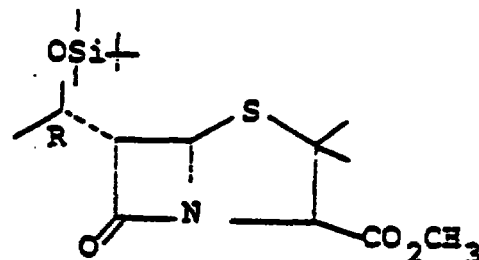
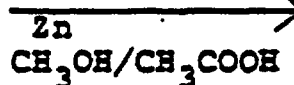
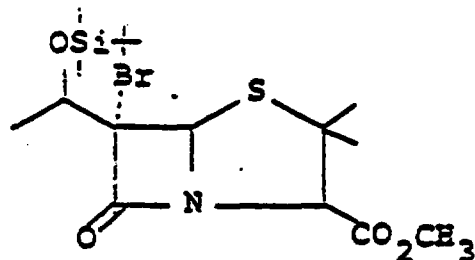




-60°C



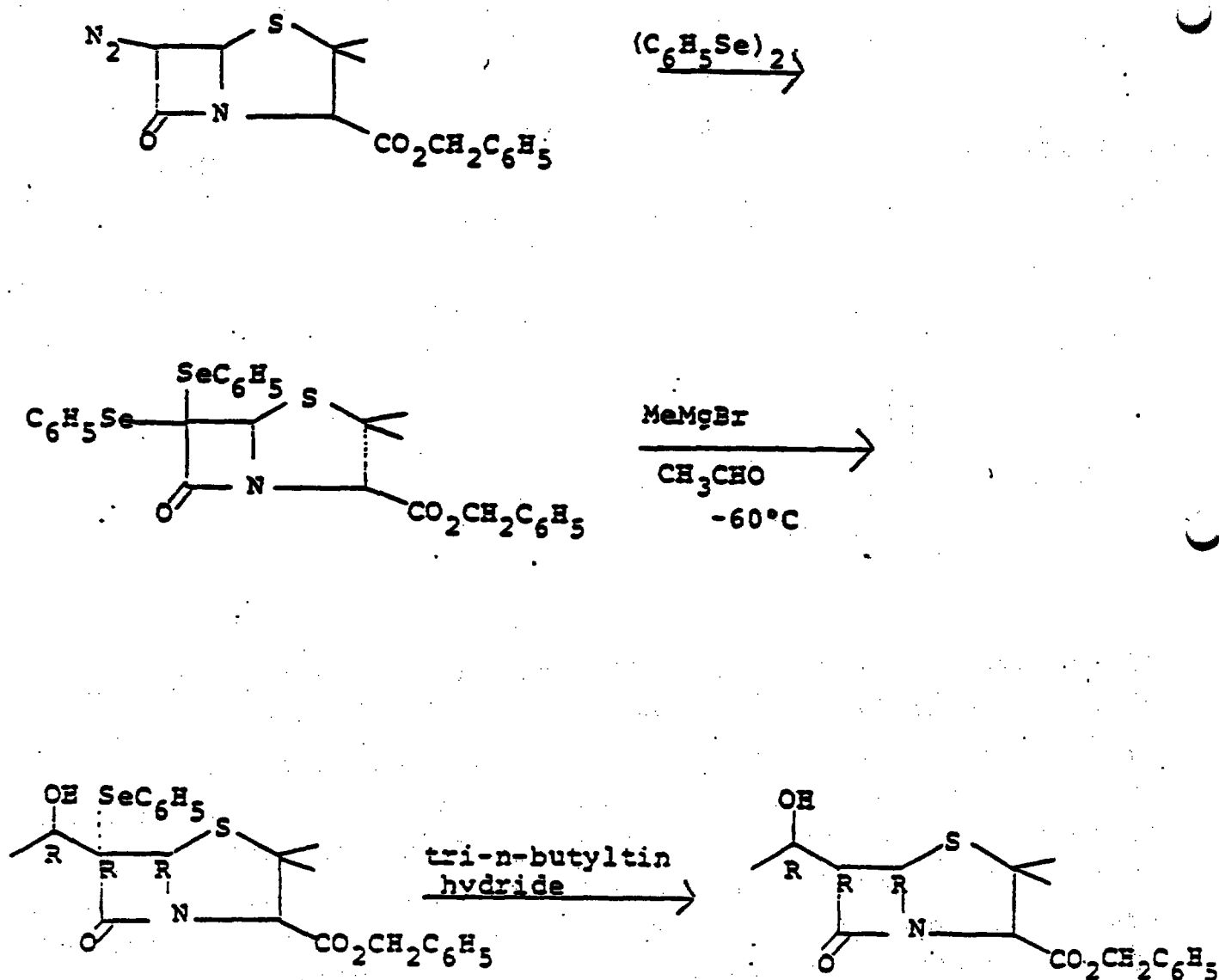
silylation



To elaborate, 6-APA is esterified to give the methyl ester and then converted by known methods, e.g. those described in U.K. 2,045,755A, to give the methyl ester of 6,6-dibromopenicillin. This ester is then hydroxyethylated by the metal-halogen exchange process described in J. Org. Chem. 42: 2960-2965 (1977) to give a mixture of cis and trans diastereomers which, at least on a small scale, can be chromatographically separated to yield the desired (R)-hydroxyethyl cis-isomer. This isomer is silylated with t-butyldimethylchlorosilane to give the corresponding hydroxy-protected intermediate which is then subjected to reductive debromination with Zn to give a mixture of the cis and trans

(R)-hydroxyethyl products from which the desired trans isomer can be separated. The hydroxyethylated penicillin ester is then treated with $\text{Hg}(\text{OAc})_2$ in acetic acid to cleave the thiazolidine ring and form a 4-acetoxiazetidinone intermediate which is oxidized with KMnO_4 to remove the β -methylcrotonate moiety and form the desired optically active 4-acetoxiazetidinone intermediate.

Tetrahedron Letters 23(39): 4021-4024 (1982) describes the following reaction scheme:



Thus, the diazopenicillin ester starting material was converted

to benzyl 6,6-bis(phenylselenyl)penicillinate which was hydroxyethylated with MeMgBr and CH_3CHO at -60°C to give a mixture of diastereomers from which the desired cis isomer can be isolated.

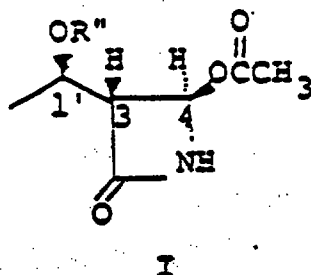
The optically active 4-acetoxazetidinone can be used in known procedures in the synthesis of carbapenem and penem antibiotics. For example, Tetrahedron Letters 23(22): 2293-2296 (1982) describes conversion of this intermediate to thienamycin and Chem. Pharm. Bull. 29(11): 3158-3172 (1981) describes use of this intermediate to prepare penem antibiotics.

While the above-described procedures are potentially useful for large scale synthesis of (8R)-hydroxyethyl penem and carbapenem antibiotics, they suffer from a lack of stereospecificity in the aldol condensation step and in the reduction step, i.e. hydroxyethylation of the dibromopenicillin or bis-(phenylselenyl)penicillin ester and reduction of such hydroxyethylated intermediates to remove the bromo or phenylseleno group gives a mixture of diastereomers which must be separated to give the desired optically active product. Such a separation, particularly on a commercial scale, results in the procedures being much less efficient than they might otherwise be.

SUMMARY OF THE INVENTION

The present invention provides a novel stereocontrolled process for converting 6-aminopenicillanic acid to the known

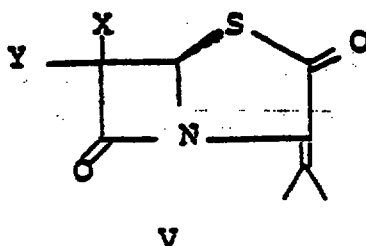
optically active azetidinone intermediate of the formula



wherein R'' is a conventional hydroxy-protecting group and wherein the absolute configuration at carbons 1', 3 and 4 is R, R and R. Such intermediates are key intermediates in the synthesis of a wide variety of previously disclosed carbapenem and penem antibiotics having an (R)-hydroxyethyl substituent at the 6-position of the carbapenem or penem nucleus and the absolute configuration R and S (trans) at the 5 and 6 positions, respectively. Also provided are certain novel intermediates used in such process.

More specifically the present invention provides an improved process for preparing the optically active azetidinone intermediate I which involves the steps of

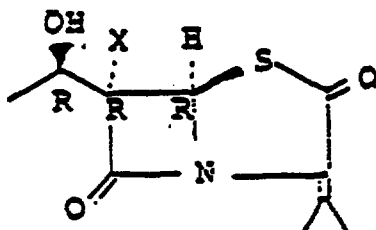
(a) converting by per se known procedures 6-aminopenicillanic acid to an anhydropenicillin of the formula



wherein X and Y are each independently chloro, bromo, iodo or phenylseleno (SeC_6H_5);

(b) reacting intermediate V with a reagent selected from a Grignard reagent of the formula R_1MgX or an organolithium compound of the formula R_1Li in which R_1

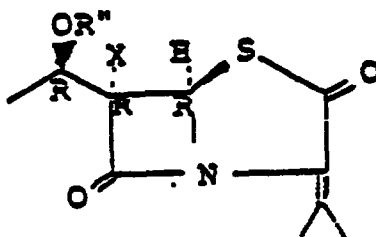
is (lower)alkyl or aryl and X is as defined above in an anhydrous inert organic solvent and at a temperature in the range of about 0° to -78°C and subsequently adding acetaldehyde to produce exclusively the intermediate of the formula



IIa

wherein X is as defined above;

(c) converting intermediate IIa to the corresponding intermediate of the formula

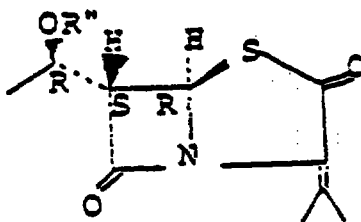


IIb

wherein R' is a conventional hydroxy-protecting group, most preferably a bulky triorganosilyl group such as t-butyldimethylsilyl, t-butyldiphenylsilyl or triisopropylsilyl, and X is as defined above;

(d) subjecting intermediate IIb to reduction in an inert solvent and isolating the so-produced 5,6-trans

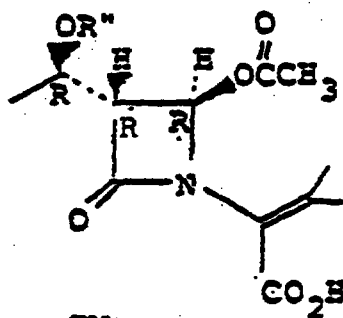
isomer of the formula



IIIb

wherein R' is as defined above;

(e) cleaving the thiazolidine ring of intermediate IIIb to produce an acetoxызetidinone intermediate of the formula

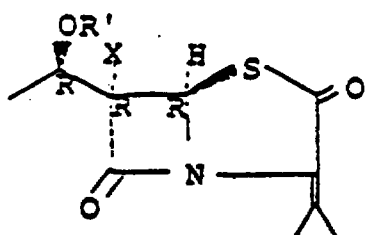


IV

; and

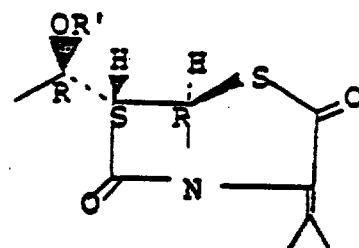
(f) oxidizing intermediate IV to remove the β -methylcrotonate moiety and produce the desired optically active intermediate I. In a variant of the above-described process, intermediate IIa may be reduced prior to protection of the hydroxy functional group.

Intermediates of the formulae



II

and

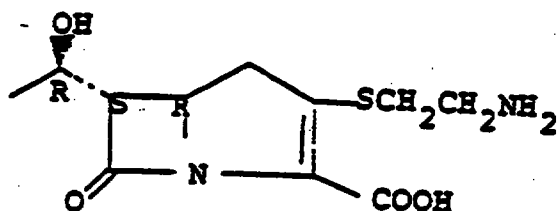


III

wherein X is chloro, bromo, iodo or phenylseleno and R' is hydrogen or a conventional hydroxy-protecting group are novel compounds and are included within the scope of the present invention.

DETAILED DESCRIPTION

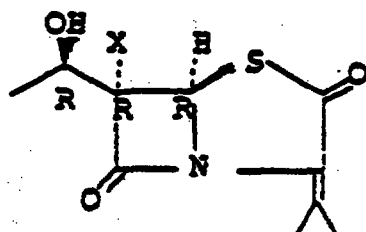
The present invention provides a significant improvement in the prior art method of converting 6-aminopenicillanic acid to the key optically active acetoxызetidinone intermediate I which is used to synthesize various carbapenem and penem antibiotics including the broad-spectrum carbapenem, thienamycin, of the formula



As noted above, prior art procedures for preparing (8R)-hydroxyethyl carbapenem and penem compounds via the 6-APA route involve an aldol condensation reaction to introduce the desired 6-hydroxyethyl substituent. One literature procedure involves converting 6-APA to the 6-acetyl derivative and then

reducing this derivative to give the hydroxyethyl penicillin product (JACS 103: 6765-6767, 1981). The reduction step, however, is not stereospecific and the desired optical isomer must be separated from a mixture of diastereomers. Direct hydroxyethylation of a 6-halopenicillin, 6,6-dihalopenicillin or 6,6-bis(phenylselenenyl)penicillin is disclosed, for example, in Chem. Pharm. Bull. 29(10): 2899-2909 (1981), J. Org. Chem. 42: 2960-2965 (1977), Heterocycles 17: 201-207 (1982) and Tetrahedron Letters 23(39): 4021-4024 (1982), but this procedure suffers from the fact that the aldol reaction on the penicillin intermediate is not stereospecific and it is necessary to separate out the desired (8R)-hydroxyethyl isomer before proceeding with the remaining steps of the synthesis.

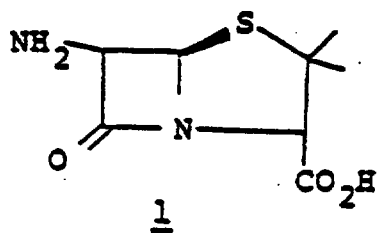
The present invention is based on the unexpected discovery that an aldol condensation reaction on certain 6,6-disubstituted anhydropenicillins results in exclusive formation of only one stereoisomer, i.e. the isomer of the formula



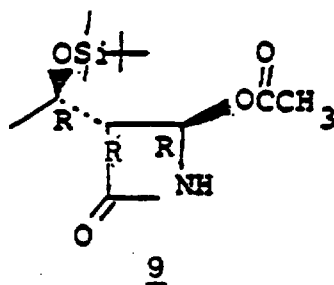
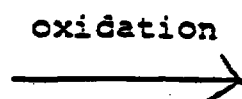
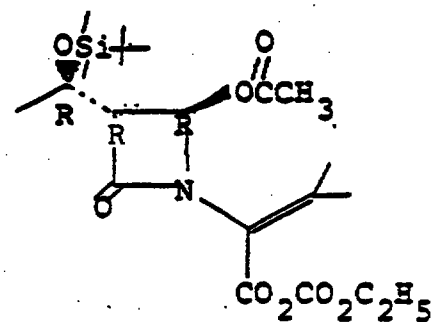
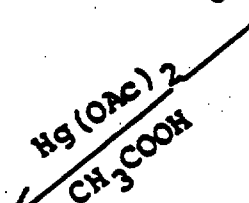
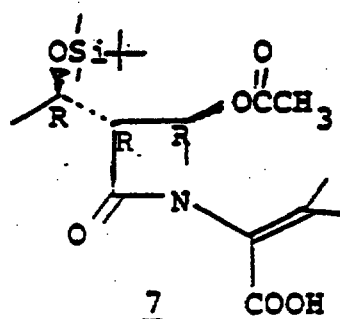
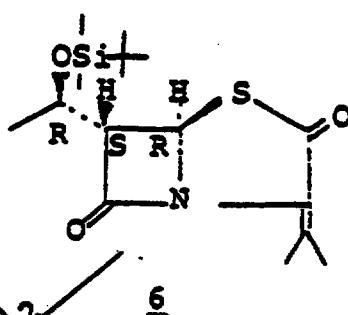
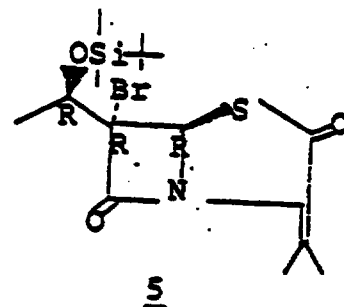
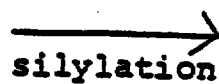
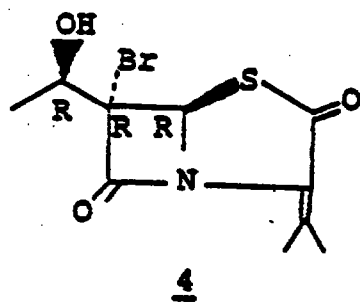
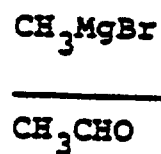
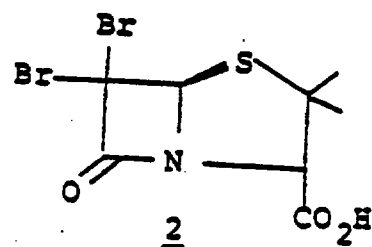
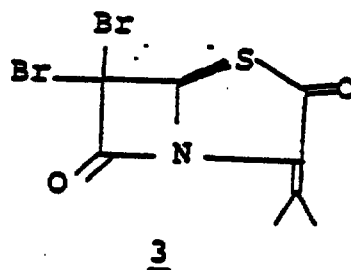
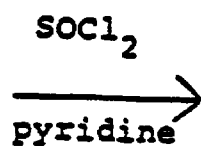
X = halo or
phenylseleno

which has the desired 5R, 6R, 8R stereochemistry. This stereospecific hydroxyethylation eliminates the necessity of separating stereoisomers following this step and, coupled with the stereoselective reductive removal of X under the preferred conditions of the present invention, greatly improves the usefulness of the 6-APA route for synthesis of penem and carbapenem antibiotics.

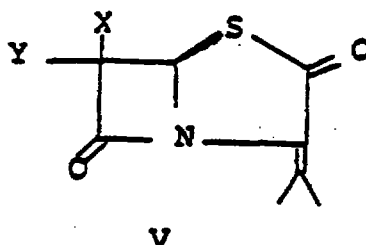
The general reaction scheme for the present process is illustrated below for the case in which a 6,6-dibromopenicillin starting material is used:



6-APA

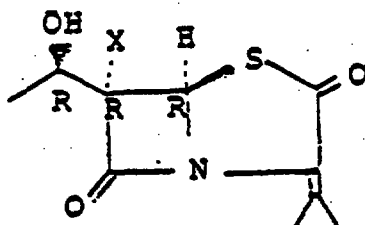


To elaborate on the above process, 6-APA is first converted by known procedures to a 6,6-dihaloanhydropenicillin or 6,6-bis(phenylselenyl)anhydropenicillin intermediate of the formula



wherein X and Y are each independently chloro, bromo, iodo or phenylseleno. Intermediates of formula V, the starting materials for the novel reaction steps of the present invention, are known compounds or are prepared by known methods. These intermediates may be prepared by converting 6-APA to the corresponding 6,6-dihalopenicillanic acid or 6,6-bis(phenylselenyl)penicillanic acid, forming an acid halide or mixed anhydride thereof and then reacting such acid halide or anhydride with a tertiary amine to give the anhydropenicillin. U.K. Patent 2,405,755A discloses preparation of various 6,6-dihalopenicillanic acids such as 6,6-dibromopenicillanic acid, 6-chloro-6-iodopenicillanic acid, 6-bromo-6-iodopenicillanic acid and 6,6-diiodopenicillanic acid. Tetrahedron Letters 23(39): 4021-4024 (1982) discloses preparation of 6,6-bis(phenylselenyl)penicillins. Conversion of 6,6-dihalopenicillanic acids to the corresponding anhydropenicillin is taught, for example, in J. Chem. Soc. (C): 2123-2127, 1969 where preparation of 6,6-dibromoanhydropenicillin is specifically disclosed. U.S. Patent 3,311,638 teaches general procedures for converting penicillins to anhydropenicillins. The most preferred anhydropenicillin starting materials for use in the process of the present invention are 6,6-dihaloanhydropenicillins preferably 6,6-dibromoanhydropenicillin and 6-bromo-6-iodoanhydropenicillin, and most preferably 6,6-dibromoanhydropenicillin.

The anhydropenicillin starting material is subjected to an aldol condensation reaction to provide the desired hydroxyethylated intermediate of the formula



IIa

wherein X is chloro, bromo, iodo or phenylseleno, most preferably bromo, and wherein the absolute configuration is 5R, 6R, 8R. This is the key step in the present process as the aldol condensation on the anhydropenicillin intermediate results in exclusive formation of the desired optically active isomer, i.e. the stereoisomer having a cis-configuration at carbons 5 and 6 and an (8R)-hydroxyethyl substituent at position 6. This unexpected stereospecific aldol condensation eliminates the need for separation of diastereomers as required in prior art procedures and, therefore, greatly increases the practical utility of the 6-APA route for synthesis of carbapenem and penem end-products.

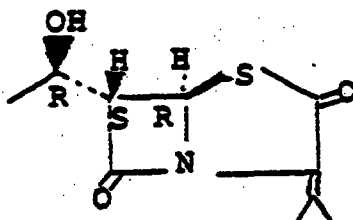
The aldol condensation may be carried out in essentially the same manner as in prior art reactions with penicillins, e.g. see J. Org. Chem. 42(18): 2960-2965, (1977). An enolate is first generated from the 6,6-dihaloanhydropenicillin by a metal-halogen exchange process at temperatures below about 0°C, e.g. 0° to -78°C, using an organolithium reagent or a Grignard reagent and the so produced enolate then reacted in situ with excess acetaldehyde to form the hydroxyethylated product.

The aldol reaction step is carried out in an inert anhydrous organic solvent, e.g. methylene chloride, chloroform, tetrahydrofuran, diethyl ether, toluene, dioxane, dimethoxyethane or mixtures thereof, at temperatures below 0°C and preferably below about -20°C. The enolate is generated by use of

about a molar equivalent of organolithium reagent or Grignard reagent.

Preferred organolithium reagents are those of the type R_1Li in which R_1 is (lower)alkyl, i.e. C_1-C_6 alkyl, or aryl, i.e. C_6-C_{10} aryl such as phenyl. An example of a suitable organolithium reagent is n-butyllithium. The Grignard reagent is preferably a reagent of the type R_1MgX where R_1 is C_1-C_6 alkyl or C_6-C_{10} aryl and X is chloro, bromo or iodo. Preferred Grignard reagents are CH_3MgBr and CH_3MgCl . A preferred embodiment comprises use of CH_3MgCl at a temperature of about $-40^\circ C$ to $-45^\circ C$. Another preferred embodiment comprises use of CH_3MgBr at a temperature of about $-20^\circ C$. After formation of the enolate a molar excess of acetaldehyde is added to form the desired hydroxyethylated isomer.

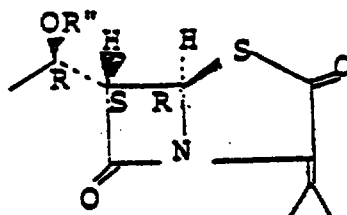
Intermediate IIa may next be subjected to reduction to form the intermediate



IIIa

or, alternatively and preferably, intermediate IIa may first be converted to the corresponding anhydropenicillin intermediate in which the hydroxyl group is protected by a conventional hydroxy-protecting group and then reduced to form the hydroxyl-protected

Intermediate



IIIb

where R' is a conventional hydroxy-protecting group. If reduction is carried out directly on intermediate IIa, the hydroxyl group of product IIIa is protected to form intermediate IIIb before the subsequent thiazolidine ring cleavage step.

Hydroxyl protection is achieved according to known procedures using conventional hydroxy-protecting groups known to those skilled in the art. Protection of the hydroxyl functional group of intermediate IIa or IIIa is desirable to prevent side reactions and reduced yields in later steps of the reaction sequence, e.g. the ring degradation step with mercuric salt. Suitable hydroxy groups may be, for example, acyl groups such as benzyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, p-nitrobenzyloxycarbonyl and 2,2,2-trichloroethoxycarbonyl, aralkyl groups such as benzyl, benzhydryl, trityl or p-nitrobenzyl or triorganosilyl groups such as tri(C₁-C₆)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, triisopropylsilyl, isopropyldimethylsilyl, t-butyldimethylsilyl, methyldiisopropylsilyl or methyldi-t-butylsilyl), triarylsilyl (e.g. triphenylsilyl, tri-p-xylylsilyl) or triaralkylsilyl (e.g. tribenzylsilyl). Examples of these and other suitable hydroxy-protecting groups and methods for their formation and removal are known in the art, e.g. see Protective Groups in Organic Synthesis, T. W. Greene, John Wiley & Sons, New York, 1981, Chapter 2.

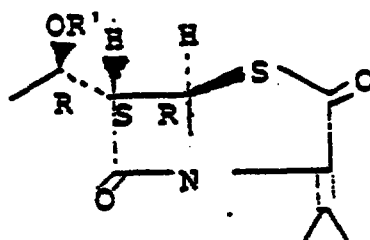
While any conventional hydroxyl protecting group may be utilized in the reductive removal of substituent X, it was unexpectedly found that use of a bulky triorganosilyl hydroxy

protecting group such as t-butyldimethylsilyl, t-butyldiphenylsilyl or triisopropylsilyl results in essentially exclusive formation (e.g. ~ 95%) of the desired trans isomer IIb, while use of other hydroxy protecting groups or unprotected intermediate IIa results in co-production of the undesired cis isomer in sufficient amounts to require a separation step. Thus, it is a preferred embodiment of the present invention that intermediate IIa be converted to the corresponding hydroxyl-protected intermediate IIb where R² is a bulky triorganosilyl group, most preferably t-butyldimethylsilyl, t-butyldiphenylsilyl or triisopropylsilyl, and then this intermediate be subjected to the reduction step so as to provide essentially stereoselective formation of the trans intermediate IIb.

The hydroxy protecting group selected should be one that is readily removable at a later stage of the reaction process. Triorganosilyl protecting groups are advantageously used (in addition to certain of these groups, i.e. the bulky triorganosilyl groups such as triisopropylsilyl, t-butyldiphenylsilyl or t-butyldimethylsilyl being preferred for an essentially stereocontrolled reduction step) since such groups can be readily removed under mild conditions, e.g. by treatment with methanolic HCl or with fluoride ion (e.g. tetra-n-butylammonium fluoride/tetrahydrofuran), without destroying the sensitive β -lactam nucleus. Silylation may be accomplished by use of a suitable silylating agent (e.g. silylchloride or silyltriflate) in an inert organic solvent such as methylene chloride, tetrahydrofuran, dioxane, dimethoxyethane, chloroform or diethyl ether and in the presence of base, e.g. an organic base such as pyridine, 2,6-lutidine, imidazole or triethylamine. While silylation can be carried out over a wide temperature range, it is preferred to use temperatures in the range of about -40°C up to about +5°C. In a preferred embodiment the hydroxy group of intermediate IIa or IIIa is silylated with triisopropylsilyltriflate, t-butyldiphenylsilyltriflate or t-butyldimethylsilyltriflate in methylene chloride, tetrahydrofuran, chloroform, toluene or diethyl ether,

most preferably tetrahydrofuran or methylene chloride, at a temperature around 0°C.

Intermediate IIa or hydroxy-protected intermediate IIb is subjected to reduction so as to remove the halogen or phenyl-seleno group and produce the desired 5R, 6S product

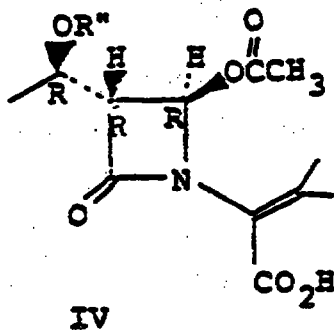


III

wherein R' is hydrogen or a conventional hydroxy-protecting group, most preferably a bulky triorganosilyl group such as triisopropylsilyl, t-butyldiphenylsilyl or t-butyldimethylsilyl. Reduction may be carried out with a chemical reducing agent such as zinc-silver couple, zinc-copper couple, SnI_2 , tin hydride, zinc amalgam, zinc or zinc activated with acid (e.g. HCl or CH_3COOH) or by means of catalytic hydrogenation. An inert solvent is generally employed such as tetrahydrofuran, diethyl ether, methanol, ethanol, isopropanol, acetic acid, mixtures of ether and alcoholic solvents, etc. In a preferred embodiment zinc-silver couple is used in a THF/ CH_3OH solvent system. Another preferred embodiment involves use of zinc activated with acid, preferably HCl or acetic acid. Reduction may be achieved over a wide temperature range, e.g. -45°C up to room temperature. Generally the reduction step provides the most desired trans (5R, 6S) isomer as the predominant product with only minor amounts of the less desired cis isomer. As mentioned above, if intermediate IIa is converted to a hydroxy-protected intermediate IIb wherein R' is a bulky triorganosilyl group such as triisopropylsilyl, t-butyldimethylsilyl or t-butyldiphenylsilyl, reduction of IIb is essentially stereospecific with the desired trans isomer being almost exclusively formed. Thus, under such preferred conditions, the product of the reduction step can be used

directly in the subsequent reaction steps without the necessity of first separating out the undesired cis isomer co-product.

After reduction the anhydropenicillin intermediate III, following hydroxy group protection if required, is converted by per se known reaction steps to the desired acetoxyazetidinone intermediate I. Thus, in the most preferred embodiment, the hydroxy-protected intermediate IIb, having the desired chirality at carbons 5, 6 and 8, is subjected to thiazolidine ring degradation, e.g. with $\text{Hg}(\text{OAc})_2$ in acetic acid, to produce the intermediate

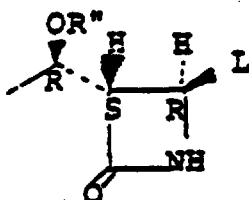


wherein R^* is a conventional hydroxy-protecting group and this intermediate IV is then oxidized to form the desired optically active intermediate I. Thiazolidine ring degradation is described in the literature and may be accomplished, for example, by reacting intermediate IIb in acetic acid or a mixture of acetic acid and an inert organic solvent such as tetrahydrofuran or dioxane with a mercuric salt such as $\text{Hg}(\text{OAc})_2$ or HgCl_2 at a temperature between about 0° and 40°C .

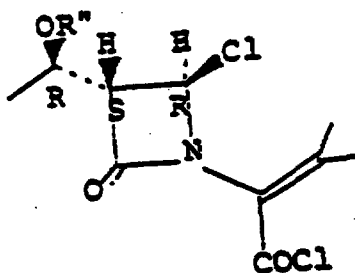
Removal of the crotonate moiety is accomplished by oxidation of intermediate IV. Use of ozonolysis (e.g. O_3 in CH_3OH) allows acid IV to be directly oxidized to intermediate I. Chemical oxidizing agents such as KMnO_4 , KMnO_4 with phase transfer catalysts, $\text{KMnO}_4/\text{NaIO}_4$ and $\text{RuO}_4/\text{NaIO}_4$ generally require that the carboxylic acid functional group of IV be protected prior to oxidation, e.g. by conversion to an ester or anhydride.

The above-described reaction can of course, with judicious selection of solvents, be carried out without isolation of one or more intermediates in the sequence. Alternatively, where possible, intermediates may be isolated as crystalline materials and optionally purified as by recrystallization before proceeding with subsequent reaction steps.

It will be apparent to those skilled in the art that the present process, although described in terms of producing acetoxyazetidinone I, can be readily modified to provide other useful azetidinone intermediates of the type

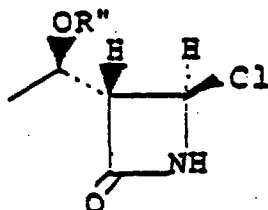


where L represents a conventional leaving group. For example, intermediate IIIf above may be subjected to chlorinolysis ($\text{Cl}_2/\text{CH}_2\text{Cl}_2$, -15°C) to give



which may be oxidized, after conversion to the corresponding acid or ester, as described above for the corresponding acetoxy

derivative to give the chloro intermediate

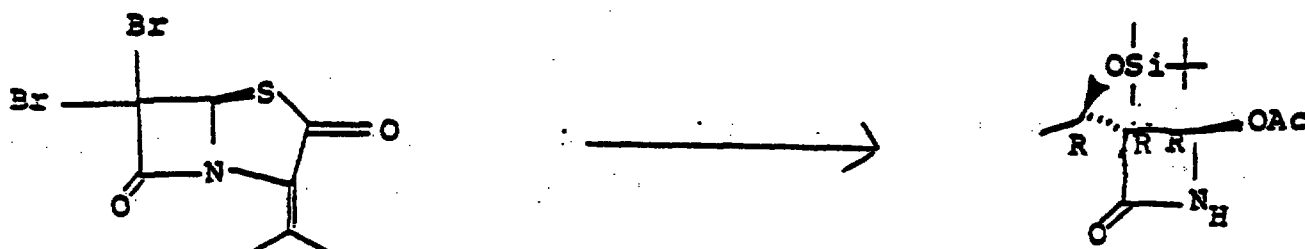


The (R)-hydroxyethyl azetidinone intermediates produced according to the present invention, i.e. intermediate I or an analog thereof such as the above-mentioned chloro compound, are readily converted by known methods to thienamycin and other carbapenem and penem derivatives having useful antibacterial activity.

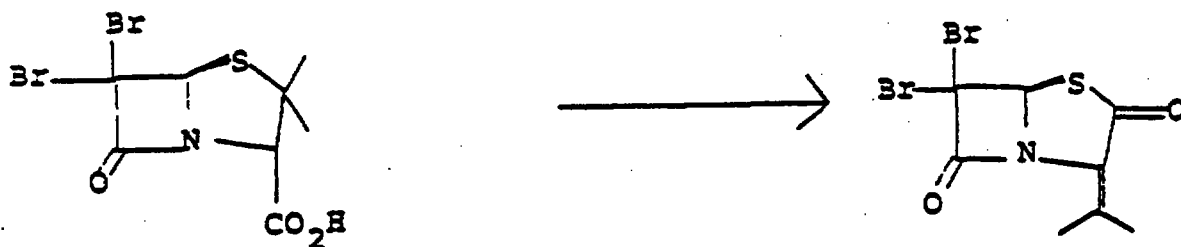
The following examples illustrate but do not limit the scope of the present invention. All temperatures referred to below are in degrees Celsius unless otherwise indicated.

Example 1

Preparation of (4R)-acetoxy-(3R)-[(1'R)-(tert-butyl-dimethylsilyl-oxy)ethyl]-2-azetidinone from anhydro-6,6-dibromopenicillin

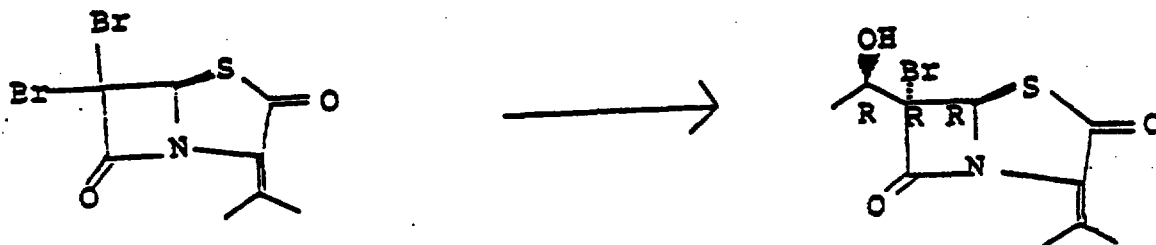


A. Anhydro-6,6-dibromopenicillin



A cold (ice-methanol bath) solution of 6,6-dibromopenicillanic acid (20.00 g, 55.56 mmol) in CH_2Cl_2 (200 mL) was treated dropwise with triethylamine (58.4 mmol, 8.00 mL) and stirred for 15 min. To the solution was added dropwise trifluoroacetic anhydride (8.40 mL, 61.2 mmol). It was stirred for 30 min, then treated dropwise with pyridine (4.8 mL, 61.2 mmol). The mixture was stirred for 30 min at -10°C and then for 18 h at 5° . The mixture was successively washed with 1N aqueous HCl, water, 1M aqueous NaHCO_3 and brine and dried (MgSO_4). The residue obtained upon solvent evaporation was redissolved in ethyl acetate (EtOAc), and treated with activated charcoal to give title compound: mp $102-103^\circ\text{C}$ (CH_3OH), (16.1 g, 47.2 mmol, yield 85%); ^1Hmr (CDCl_3 , 80 MHz) δ : 5.80 (1H, s, H-5), 2.21 (3H, s, CH_3), and 2.15 ppm (3H, s, CH_3); ir (CH_2Cl_2) ν_{max} : 1800 (s, β -lactam C=O), 1708 (s, lactone C=O) and 1640 cm^{-1} (w, olefin); $[\alpha]_D^{22} + 88.9^\circ$ (c 0.144, CH_3OH); Anal. calcd. for $\text{C}_8\text{H}_7\text{NO}_2\text{SBr}_2$: C 28.17, H 2.07, N 4.10; found C 28.08, H 1.98, N 4.06.

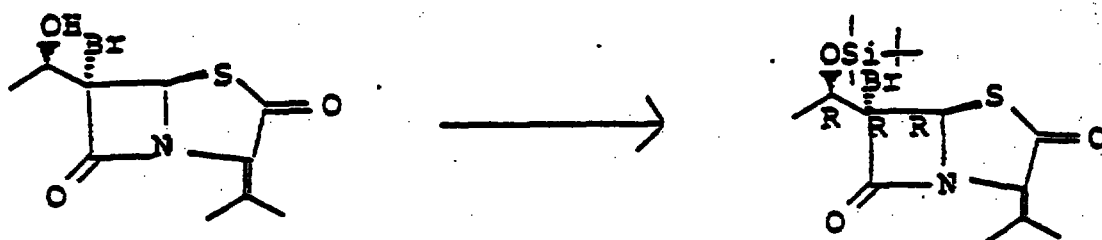
B. Anhydro-6 α -bromo-6 β -[(1' R)-hydroxyethyl]penicillin



Anhydro-6,6-dibromopenicillin (15.02 g, 44 mmol) was dissolved in cold (-78°) THF (450 mL), treated dropwise with a 2.85 M solution of MeMgBr (18.0 mL, 51.3 mmol) in ether and

stirred for 20 min at -78°C . The resulting magnesium enolate was trapped with excess acetaldehyde (25 mL, 0.45 mol) and stirred for 20 min. The cooling bath was removed and to the reaction mixture was added 1N aqueous HCl (70 mL) and ether (300 mL). The aqueous phase was removed and extracted with ether (2 x 200 mL). The organic phases were combined, washed successively with 1N aqueous HCl, water, 1M aqueous NaHCO_3 and brine and dried (MgSO_4). The solvent was removed to give title compound (13.08 g; 42.7 mmol; yield 97%) as an oil: ^1Hmr (CDCl_3) δ : 5.61 (1H, s, H-5), 4.28 (1H, q, $J=6.0$, H-1'), 2.21 (3H, s, CH_3) 2.16 (3H, s, CH_3), 1.64 (1H, bs, OH), and 1.31 ppm (3H, d, $J=6.0$ Hz, CH_3); ir (CH_2Cl_2) ν_{max} : 3560 (m, OH), 1785 (s, β -lactam C=O), 1710 (s, lactone C=O) and 1635 cm^{-1} (m, olefin); $[\alpha]_D^{22} + 83.8^{\circ}$ (c 0.128, MeOH); Anal. calcd. for $\text{C}_{10}\text{H}_{12}\text{NO}_3\text{SBr}$: C 39.23, H 3.95, N 4.57; found C 38.31, H 4.63, N 4.61.

C. Anhydro-6 α -bromo-6 β -[(1'R)-(tert-butyldimethylsilyloxy)-ethyl]penicillin

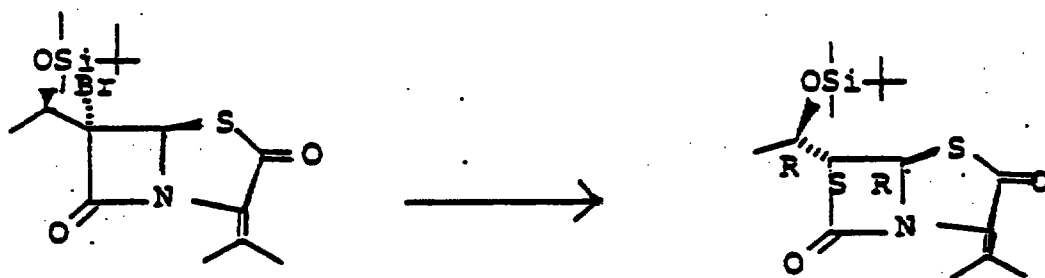


To a cold (ice bath) methylene chloride (60 mL) solution of anhydro-6 α -bromo-6 β -[(1'R)-hydroxyethyl]penicillin (6.0 g, 19.6 mmol) was added first 2,6-lutidine (4.50 mL, 39 mmol) followed by the dropwise addition of tert-butyldimethylsilyl triflate (7.8 mL, 34 mmol). The mixture was stirred (5°C) for 1 h, then washed with 1N aqueous HCl, water, 1M aqueous NaHCO_3 and brine. The resulting organic phase was dried (MgSO_4), diluted with an equal volume of a mixture of ether-petroleum ether(1:2) and treated with activated charcoal. The solid residue upon solvent evaporation was redissolved in hot hexane and allowed to crystallize to give title compound, 5.35 g. The

mother liquor was concentrated, treated with activated charcoal and allowed to crystallize in the cold (5°C, 1.28 g).

Combination of the two crops gave the protected hydroxyl derivative (6.63 g, 15.7 mmol, yield 80.6%) mp 116-117°C (MeOH): ^1Hmr (CDCl_3) δ : 5.53 (1H, s, H-5), 4.27 (1H, q, $J=6.1$ Hz, H-1'), 2.20 (3H, s, CH_3), 2.13 (3H, s, CH_3) 1.28 (3H, d, $J=6.1$ Hz, CH_3), 0.91 (9H, s, tert-butyl), 0.09 (3H, s, CH_3) and 0.07 (3H, s, CH_3); ir (CH_2Cl_2) ν_{max} : 1785 (s, β -lactam C=O), 1700 (s, lactone C=O) and 1635 cm^{-1} (m, olefin); $[\alpha]_{\text{D}}^{22} + 119.6^\circ$ (c 0.14 MeOH); .
Anal. calcd. for $\text{C}_{16}\text{H}_{27}\text{NO}_3\text{SBrSi}$: C 45.60, H 6.45, N 3.32; found: C 46.38, H 6.02, N 3.23.

D. Anhydro-6 α -(1'R)-(tert-butyldimethylsilyloxy)ethyl]penicillin



To a solution of anhydro-6 α -bromo-6 β -[(1'R)-(tert-butyldimethylsilyloxy)ethyl]penicillin (1.00 g, 2.38 mmol) in a 25% mixture of THF-MeOH (25 mL) cooled at -45°C was added Zn (Ag)* (10 g). The mixture was stirred until all the starting material was consumed (TLC plate, R_f 0.4, 2% $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ and then filtered through CELITE** pad into a cold 1M aqueous NH_4Cl solution. The phases were shaken, separated and the aqueous phase was extracted with ether (3 x 10 mL). The organic phases were combined and successively washed with 1N aqueous HCl, water, 1M aqueous NaHCO_3 , brine and dried (MgSO_4). Evaporation of the solvent afforded an oil that crystallized under vacuum (815 mg, 2.38 mmol, yield 99.6%). HPLC analysis of the solid showed the following ratio: Starting material 0.70%, the cis isomer 2.51% and title compound 96.79%; mp 56-7°C (MeOH); ^1Hmr (CDCl_3) δ : 5.29 (1H, d, $J=1.8$, H-5), 4.34 (1H, dq, $J=6.3$, $J=3.5$ Hz, H-1'), 3.52 (1H, dd, $J=3.5$ Hz, $J=1.8$ Hz, H-6), 2.17 (3H, s, CH_3), 2.08 (3H,

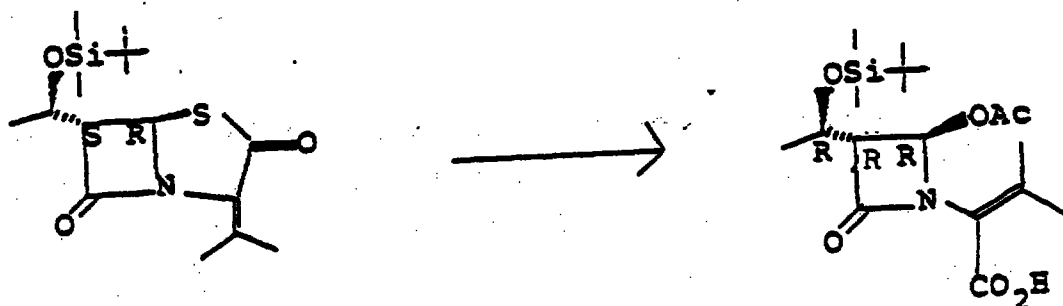
** Registered Trade Mark

s, CH₃), 1.25 (3H, d, $J=6.3$ Hz, CH₃), 0.89 (9H, s, tert-butyl), and 0.09 ppm (6H, s, CH₃); ir (CH₂Cl₂) $\nu_{\max}$: 1775 (s, β -lactam C=O), 1695 (s, lactone C=O) and 1635 cm⁻¹ (m, olefin); $[\alpha]_D^{22} + 42.8^\circ$ (c 0.114, MeOH); Anal. calcd. for C₁₆H₂₇NO₃SSi: C 56.10, H 8.24, N 4.09, S 9.38; found: C 56.65, H 7.82, N 4.07, S 9.04.

The corresponding 6-S-(1'R) isomer was isolated as an oil: ¹Hmr (CDCl₃) δ : 5.35 (1H, d, $J=4.6$, H-5), 4.31 (1H, dq, $J=6.0$, $J=9.4$, H-1'), 3.83 (1H, dd, $J=4.6$, $J=9.4$, H-6), 2.18 (3H, s, CH₃), 2.08 (3H, s, CH₃), 1.23 (3H, d, $J=6.0$, CH₃), 0.89 (9H, s, tert-butyl), 0.10 (3H, s, CH₃) and 0.06 ppm (3H, s, CH₃); ir (CH₂Cl₂) $\delta_{\max}$: 1785 (s, β -lactam C=O), 1695 (s, lactone C=O), and 1635 cm⁻¹ (m, olefin); $[\alpha]_D^{22} + 171.2^\circ$ (c 0.084, MeOH).

* Zinc silver couple was prepared from one part of silver acetate and 11.7 parts of Zn.

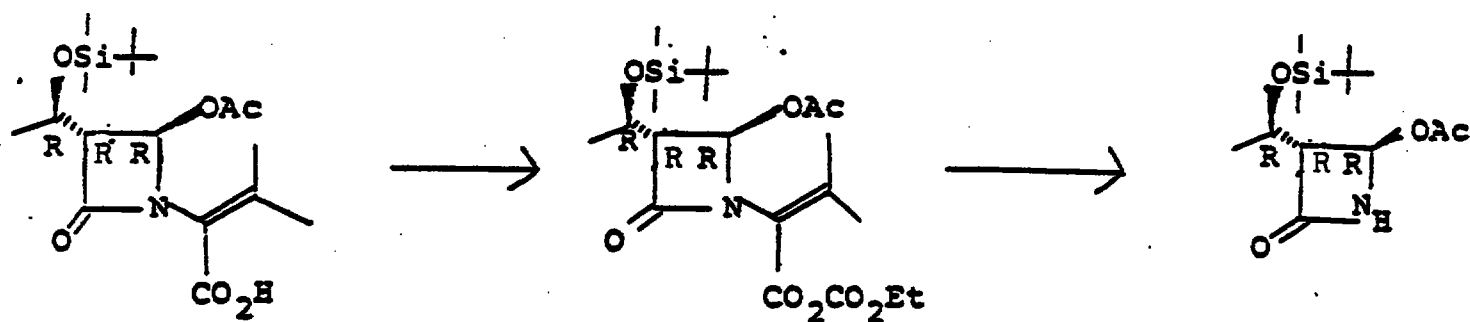
E. α -[(3R)-[(1'R)-(tert-butyldimethylsilyloxy)ethyl]-(4R)-acetoxy-2-azetidinon -1-yl]- β -methylcrotonic acid



A solution of anhydro-6 α -[(1'R)-(tert-butyldimethylsilyloxy)ethyl]penicillin (5.00 g, 14.6 mmol) in acetic acid (75 mL) was treated at 22° C with mercuric acetate (14 g, 44 mmol) and stirred for 24 h. To the mixture was added additional mercuric acetate (9.3 g, 29 mmol) and the stirring was continued for 24 more hours. The reaction mixture was filtered through a CELITE pad and the solid was washed with acetic acid. The filtrate was diluted with water (150 mL) and extracted with ether (5 x 40 mL). The organic extracts were combined, washed with water (3 x 40 mL) brine, dried (MgSO₄) and treated with charcoal.

Solvent evaporation gave an oil which crystallized under vacuum (5.33 g, 13.8 mmol, yield 95%), mp 119–20°C (CH₂Cl₂/pet. ether, 9/1); ¹Hmr (CDCl₃) δ: 6.32 (1H, d, *J*=1.4, H-4), 4.24 (1H, center of 5 lines, *J*=6.0, H-1'), 3.20 (1H, dd, *J*=1.4, *J*=5.8, H-3), 2.24 (3H, s, CH₃), 2.05 (3H, s, CH₃CO₂), 1.97 (3H, s, CH₃), 1.29 (3H, d, *J*=6.3, CH₃), 0.86 (9H, s, *tert*-butyl), 0.08 (3H, s, CH₃), and 0.05 ppm (3H, s, CH₃); ir (CH₂Cl₂) *v*_{max}: 1770 (s, β-lactam C=O), 1745 (m, CH₃C=O); 1690 (m, CO₂H), and 1620 cm⁻¹ (w, olefin); [α]_D²² + 18.9° (c 0.088, MeOH); Anal. calcd. for C₁₈H₃₁NO₆Si: C 56.07, H 8.10, N 3.63; found: C 56.00, H 8.25, N 3.73.

F. (4R)-Acetoxy-(3R)-[(1'R)-(tert-butyldimethylsilyloxy)ethyl]-2-azetidinone



To a solution of α-(3R)-[(1'R)-(tert-butyldimethylsilyloxy)ethyl]-(4R)-acetoxy-2-azetidinone-1-yl]-β-methyl crotonic acid (2.0 g, 5.2 mmol) in CH₂Cl₂ (30 mL) was added at -15°C (ice-MeOH bath) EEDQ (1.63 g, 6.20 mmol). The cooling bath was removed and the reaction mixture was stirred for 18 h at 22°C. It was successively washed with 1N aqueous HCl, water, 1M aqueous NaHCO₃, brine and dried (MgSO₄). Evaporation of the solvent afforded a mixed anhydride (2.14 g, yield 93.3%) as a carboxylic acid-protected derivative; ¹Hmr (CDCl₃) δ: 6.23 (1H, d, *J*=1.4, H-4), 4.32 (2H, q, *J*=7.1, CH₂CH₃), 4.05–4.39 (1H, m, *J*=6.1, H-1'), 3.23 (1H, dd, *J*=1.4, *J*=6.1, H-3), 2.25 (3H, s, CH₃), 2.06 (3H, s, CH₃CO), 1.17 (3H, s, CH₃), 1.35 (3H, t, *J*=7.1, CH₃CH₂), 1.29 (3H, d, *J*=6.1, CH₃), 0.86 (9H, s, *tert*-butyl), 0.08 (3H, s, CH₃) and 0.05 ppm (3H, s, CH₃); ir (CH₂Cl₂) *v*_{max}: 1800

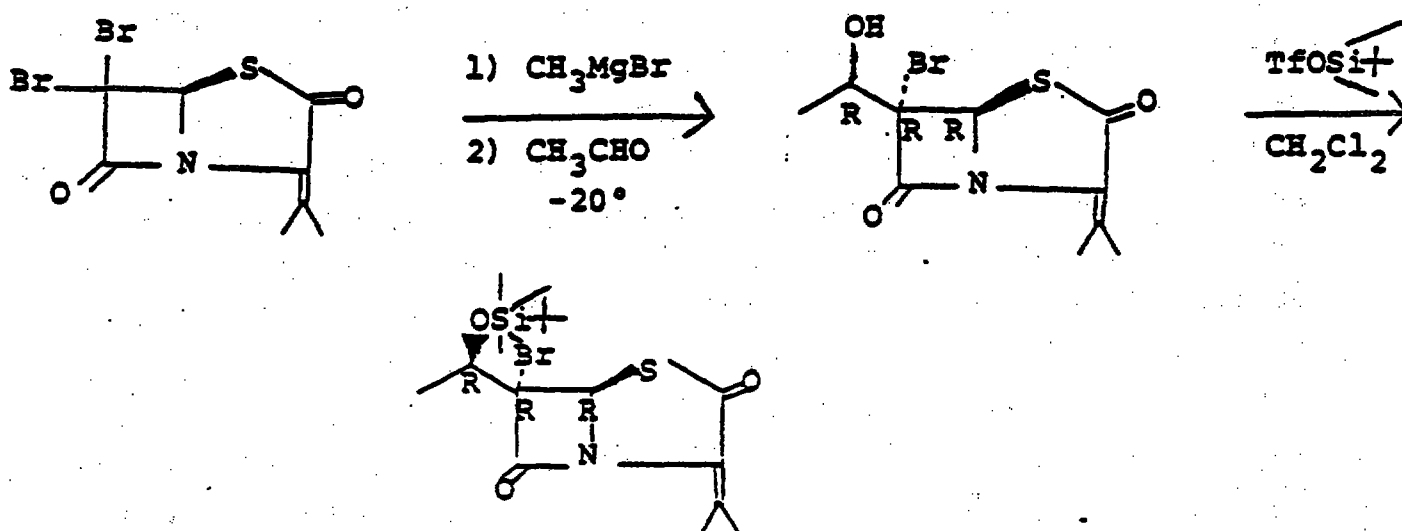
(s, mixed anhydride), 1775 (s, β -lactam C=O), 1750 (s, Acetate C=O) and 1625 cm^{-1} (w, olefin).

The mixed anhydride (2.10 g, 4.76 mmol) so obtained was dissolved in CH_2Cl_2 (30 mL) cooled to -78°C (acetone-dry ice bath) and ozonolyzed until all starting material disappeared (1.5 h). The cold (-78°C) solution of ozonide was reduced with $(\text{CH}_3)_2\text{S}$ (6 mL) and stirred at room temperature for 1.5 h. Methanol (30 mL) was added followed by 2,6-lutidine (1.2 mL). The mixture was stirred at 22°C for 2 h, diluted with ether, washed with 1N aqueous HCl, water, 1M aqueous NaHCO_3 , brine and dried (MgSO_4). Evaporation of the solvent gave title compound (1.31 g, 4.56 mmol, yield 95%) as a white solid; mp $104\text{--}106^\circ\text{C}$ ether/pet. ether: 1/1 [literature* mp $104\text{--}106^\circ\text{C}$]; $[\alpha]_D^{22} + 47.4^\circ$ (c 0.136, CHCl_3). [literature* $[\alpha]_D + 48.8^\circ$ (c 0.41, CHCl_3)].

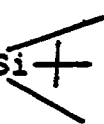
*Chem. Pharm. Bull (Tokyo) 29 2899 (1981).

Example 2

6 α -Bromo-6 β -[(1' R -hydroxyethyl)anhydropenicillin and 6 α -bromo-6 β -[(1' R -t-butyldimethylsilyloxy)ethyl]anhydropenicillin-illustrates aldol condensation reaction at relatively high (-20°C) temperature



REAGENTS:

anhydropenicillin	10.23 g (0.03 mole)
CH ₃ MgBr	12.21 mL (0.0348 mole, 16% excess, 2.85M solution in ether, Aldrich)
CH ₃ CHO	6.6 g = 8.4 mL (0.15 mole, d. 0.788, Aldrich)
THF	150 mL (dried over molecular sieves)
TfOSi 	11.54 g = 10.02 mL (0.0436 mole, d. 1.151 distd)
2,6-lutidine	6.42 g = 6.98 mL (0.06 mole, d. 0.92, Aldrich)
CH ₂ Cl ₂	100 mL (dried over molecular sieves)

PROCEDURE:

To a solution of anhydro-6,6-dibromopenicillin (10.23 g) in dry THF (150 mL) cooled to -20°, there was added dropwise methylmagnesium bromide (12.21 mL) over 10 min. while maintaining the temperature at -15° ~ -20°. The resulting solution was stirred at -20° for 10 min., and then acetaldehyde (8.4 mL) was, initially dropwise, added over 5 min., maintaining the temperature at -15° ~ -20°. The solution was stirred at -20° for 15 min. To the reaction mixture was added saturated ammonium chloride (10 mL) followed by water (80 mL). The mixture was then extracted with ethyl acetate (150 mL, 50 mL). The ethyl acetate extract was washed with brine (twice, 100 mL each), dried over anhydrous sodium sulfate and concentrated to give an oil (8.9 g, 97%). HPLC* 92% of cis, no trans isomer, 8% of impurities.

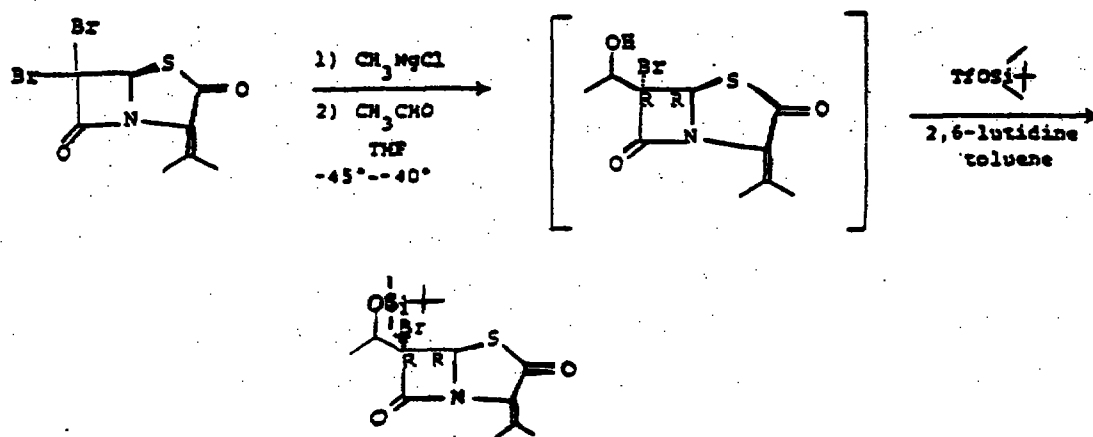
*Column: μ Porasil (Waters)
 Solvent: 3% $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$
 Flow: 90 mL/h
 Detection: uv 275 nm
 Attenuation: 0.2

("Porasil" is a registered Trade Mark)

The above crude oil was dissolved in dry CH_2Cl_2 (100 mL) cooled to 0° . There was added 2,6-lutidine (6.98 mL) followed by dropwise addition of t-butyldimethylsilyl trifluoromethylsulfonate (10.02 mL) over 20 min., maintaining the temperature at 0° - 5° . The resulting solution was stirred at 0° - 5° for 1 hour. TLC (silica, ether-pet. ether 1:1, I_2 showed completion of reaction. The reaction mixture was washed with 1N HCl (100 mL), saturated NaHCO_3 (100 mL) and brine (100 mL) respectively, dried over anhydrous Na_2SO_4 and concentrated to give a dark oil that gradually solidified. This oil was dissolved in warm pet. ether, carbon-treated and concentrated to dryness (14 g). This crude solid was redissolved in warm isopropanol (70 mL), diluted with water (35 mL) while the solution was warm, cooled to 0° and filtered. The cake was washed with isopropanol/ H_2O 2:1 and dried in a vacuum desiccator. Yield 7.0 g (55.5% over 2 steps).

Example 3

6 α -Bromo-6 β -[(1'R)-(t-butyldimethylsilyloxy)ethyl]anhydropenicillin-illustrates use of CH_3MgCl as Grignard reactant



REAGENTS:

anhydropenicillin	34.1 g (0.1 mole)
CH ₃ MgCl	39.6 mL (0.116 mole, 16% excess, 2.9 M solution in THF)
CH ₃ CHO	28 mL = 22 g (0.5 mole, d.0.788)
THF	350 mL (dried over molecular sieves)
2,6-lutidine	23.3 mL = 21.4 g (0.2 mole, d.0.92, dried over KOH)
TfOSi $\leftarrow$	32 g = 27.6 mL (0.12 mole, d.1.151)
toluene	800 mL

PROCEDURE:

A solution of anhydro-6,6-dibromopenicillin (34.1 g) in dry THF (350 mL) was cooled to -45° and there was added dropwise methylmagnesium chloride (39.6 mL) over 20 min., maintaining the temperature below -40°. The resulting solution was stirred at -45° ~ -40° for 10 min. and acetaldehyde (28 mL) was, initially dropwise, added over 5 min. while maintaining the temperature below -30°. The solution was stirred at -40° for 15 min. To the reaction mixture was added saturated ammonium chloride (35 mL), followed by addition of water (400 mL). The mixture was extracted with toluene (350 mL and 150 mL). The toluene extract was washed with brine (2 x 300 mL), dried over anhydrous magnesium sulfate and concentrated until the volume became ~100 mL. To the concentrated solution was added toluene (300 mL) followed by continued concentration to ~300 mL¹.

The toluene solution was cooled to 0° and there was added 2,6-lutidine (23.3 mL) followed by dropwise addition of

triflate (27.6 mL) over 15 min. while maintaining the temperature at 0-5°. The resulting solution was stirred at 0° for 1 h.² To the reaction mixture was added water (250 mL) and the pH was adjusted to 2.5 from 5.0 with conc. hydrochloric acid (~8 mL). The organic layer was separated. To the organic layer was added water (250 mL) and the pH was adjusted to 8.0 with 1% sodium hydroxide (~10 mL). The organic layer was washed with brine (2 x 250 mL), carbon-treated (15 g) and concentrated to ~50 mL. To the concentrate were added isopropanol (200 mL) and water (dropwise) (100 mL) under stirring. 100 mL of solvent was removed under reduced pressure to give a slurry that was cooled to 0°, stirred for 0.5 h and filtered. The cake was washed with ice-cold isopropanol-water 2:1 (80 mL) and dried in a vacuum desiccator. Yield 29.0 g (69%) mp 95°-100°. The crude product was recrystallized as follows: dissolved in toluene (150 mL), carbon-treated, concentrated as much as possible, isopropanol (200 mL) added, followed by dropwise addition of water (100 mL) under ice-cooling and stirring. The precipitated product was filtered off, washed with ice-cold isopropanol-water 2:1 and dried in a vacuum desiccator. Yield 21.0 g (50%); mp 104-108°.

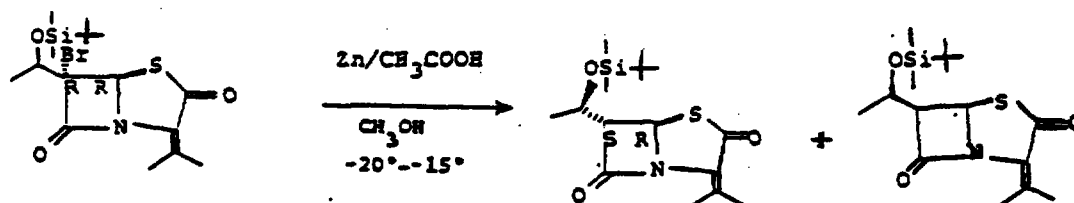
¹HPLC* showed 92% purity, no trans isomer.

*Column:	Porasil (Waters)
Solvent:	3% CH ₃ CN/CH ₂ Cl ₂
Flow:	90 mL/h
Detection:	uv 275 nm
Attenuation:	0.2

²TLC: silica gel, ether-pet. ether 1:1, I₂

Example 4

6 α -[(1'R)-(t-butyltrimethylsilyloxy)ethyl]anhydropenicillin - illustrates use of zinc/acetic acid reduction



REAGENTS:

anhydropenicillin	42.0 g (0.1 mole)
zinc dust	42.0 g (0.65 mole, Anachemia)
acetic acid	11 mL $\pm$ 11.54 g (0.19 mole, d 1.049, glacial)
CH ₃ OH	1000 mL

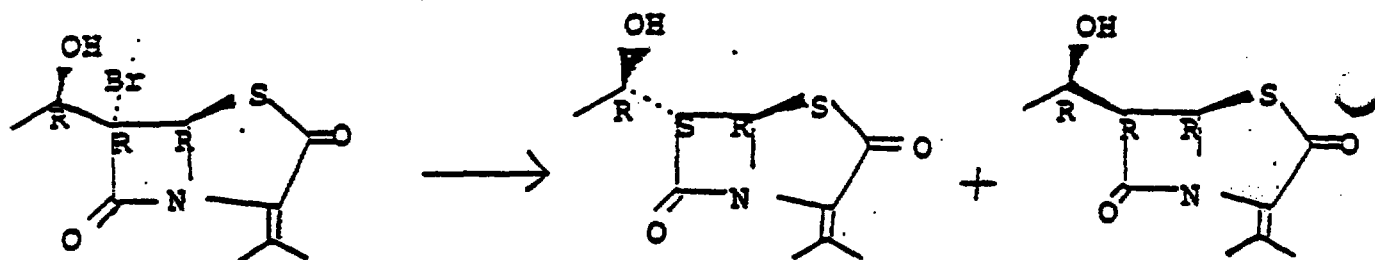
PROCEDURE:

In a 2 L 3-necked flask fitted with a mechanical stirrer, a thermometer, a dropping funnel and nitrogen inlet and outlet tubes was suspended anhydro-6 α -bromo-6 β -[(1'R)- t-butyl-trimethylsilyloxyethyl]penicillin (42 g) in methanol (100 mL). The reaction mixture was cooled to -20° and there was added zinc dust (42 g) followed by slow addition of acetic acid (11 mL). The resulting mixture was stirred at -25° ~ -15° for 0.5 h. TLC (silica, ether-pet. ether 1:3, I₂ or molybdate solution) showed completion of reaction. The reaction mixture was filtered on CELITE into saturated ammonium chloride (100 mL) and the CELITE was washed with methylene chloride. The filtrate was diluted with water

(500 mL) and extracted with methylene chloride (1000 mL and 500 mL). The methylene chloride extract was washed with brine (1000 mL), dried over anhydrous magnesium sulfate and concentrated to give an oil (34 g, 100% crude) that gradually crystallized. Analysis showed trans 83.3%, cis 5.7%, impurities: 11%.

Example 5

Preparation of Anhydro 6 α -and 6 β -[(1' R)-hydroxyethyl]penicillin



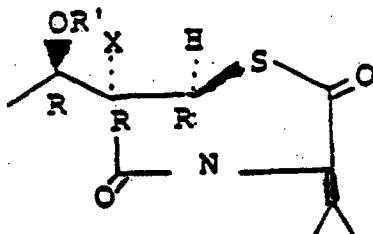
A cold (ice-methanol bath) solution of anhydro-6 α -bromo-6 β -[(1' R)-hydroxyethyl]penicillin (4.20 g, 13.7 mmol) in methanol (40 mL) was treated with Zn(Ag) (4.2 g) and stirred for 15 min. More Zn(Ag) (1.1 g) was added and the mixture was stirred for 10 min. The cold suspension was filtered through a CELITE pad into cold concentrated aqueous NH_4Cl . The solid was washed with ether and the two phases were separated. The aqueous phase was extracted with ether (2 x 20 mL). The ether extracts were combined and successively washed with 1N aqueous HCl, water, 1M aqueous NaHCO_3 and brine and then dried. The residue upon solvent evaporation was triturated with a cold mixture of petroleum ether/ether: 9/1 to give the 6 α -isomer (1.3 g, 5.7 mmol, yield 42%)* as a white solid: mp 173-4°C (CH_2Cl_2 /ether: 2/8); ^1Hmr (CDCl_3) δ : 5.28 (1H, d, $J=1.7$, H-5), 4.35 (1H, quintet, $J=6.2$, H-1'), 3.57 (1H, dd, $J=6.2$, $J=1.7$, H-6), 2.19 (3H, s, CH_3), 2.11 (3H, s, CH_3), 1.72 (1H, bs, OH) and 1.40 ppm (3H, d, $J=6.3$, CH_3); ir (CH_2Cl_2) ν_{max} : 3500 (w, OH), 1775 (s, β -lactam C=O), 1695 (s, lactone C=O) and 1635 cm^{-1} (m, olefin); Anal. calcd. for $\text{C}_{10}\text{H}_{13}\text{NO}_3\text{S}$: C 52.84, H 5.76, N 6.16; found: C 52.86, H 5.72, N 6.08.

The cold ether/petroleum ether: 1/9 mixture was evaporated and the pure 6 β -isomer separated on preparative TLC (2% CH₃CN/CH₂Cl₂); ¹Hmr (CDCl₃) δ : 5.40 (1H, d, J =4.6, H-5), 4.36 (1H, dq, J =6.1, J =9.0, H-1'), 3.74 (1H, dd, J =9.0, J =4.6, H-6), 2.19 (3H, s, CH₃), 2.25-1.90 (1H, bs, OH), 2.09 (3H, s, CH₃) and 1.27 ppm (3H, d, J =6.0, CH₃); ir (CH₂Cl₂) ν_{max} : 3580 (w, OH), 1770 (s, β -lactam C=O), 1700 (s, lactone C=O) and 1640 cm⁻¹ (m, olefin).

*Reaction conditions not optimized; when repeated at -50°C it gave a 56.6% yield of the 6 α -isomer

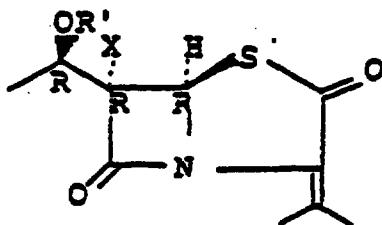
CLAIMS

1. A compound having the formula



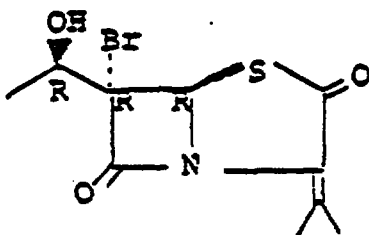
II

- wherein X is chloro, bromo, iodo or phenylseleno and R' is hydrogen or a conventional hydroxyl-protecting group.
2. A compound of Claim 1 wherein R' is a bulky triorganosilyl hydroxy-protecting group.
3. A compound of Claim 2 wherein R' is triisopropylsilyl, t-butyldimethylsilyl or t-butyldiphenylsilyl.
4. A compound of having the formula

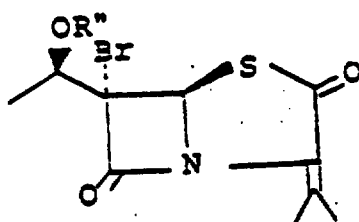


wherein X is bromo and R' is hydrogen or a conventional hydroxy-protecting group.

5. The compound of Claim 4 having the formula

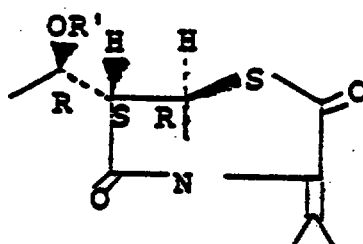


A compound of Claim 4 having the formula



wherein R'' is a conventional hydroxyl-protecting group.

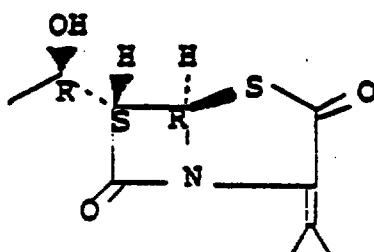
7. A compound of Claim 6 wherein R'' is a bulky triorganosilyl protecting group.
8. The compound of Claim 7 wherein R'' is t-butyldimethylsilyl, triisopropylsilyl or t-butyldiphenylsilyl.
9. A compound having the formula



III

wherein R' is hydrogen or a conventional hydroxyl-protecting group.

10. The compound of Claim 9 having the formula

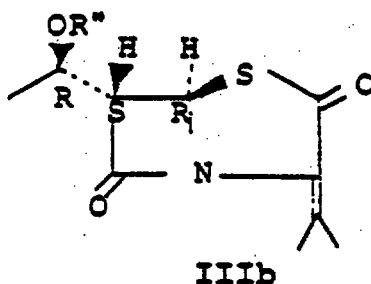


IIIa

W C L N S W

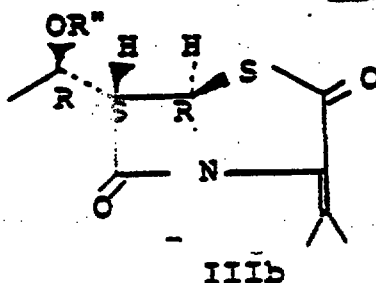


11. A compound of Claim 9 having the formula



wherein R' is a conventional hydroxyl-protecting group.

12. A compound of Claim 11 wherein R' is a bulky triorganosilyl protecting group.
13. The compound of Claim 12 wherein R' is t-butyldimethylsilyl, triisopropylsilyl or t-butyldiphenylsilyl.
14. A process for the preparation of an intermediate of the formula

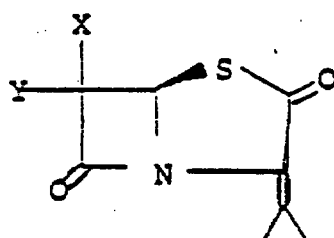


wherein R' is a conventional hydroxy-protecting group, which comprises the steps of

- (a) reacting a 6,6-disubstituted anhydropenicillin of

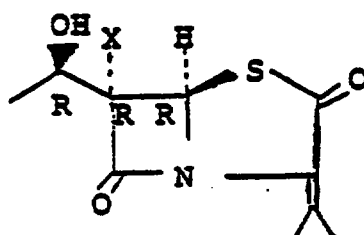


the formula



V

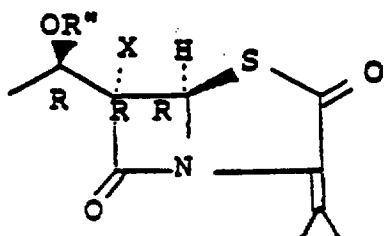
wherein X and Y are each independently chloro, bromo, iodo or phenylseleno with a reagent selected from a Grignard reagent of the formula R_1MgX or an organolithium compound of the formula R_1Li in which R_1 is (lower)alkyl or aryl and X is as defined above in an anhydrous inert organic solvent and at a temperature in the range of 0° to $-78^\circ C$ and subsequently adding acetaldehyde to exclusively produce the cis isomer of the formula



IIa

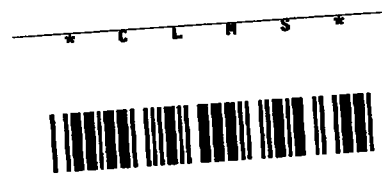
wherein X is as defined above;

(b) converting intermediate IIa to the corresponding intermediate of the formula

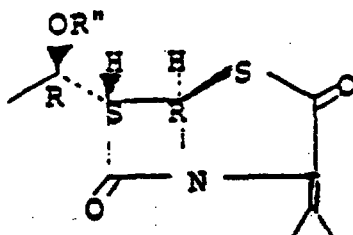


IIb

wherein R^* is a conventional hydroxy-protecting group and X is as defined above; and



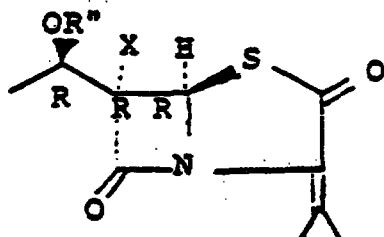
(c) subjecting intermediate IIb to reduction in an inert solvent and isolating the so-produced 5,6-trans isomer of the formula



IIIb

wherein R'' is as defined above.

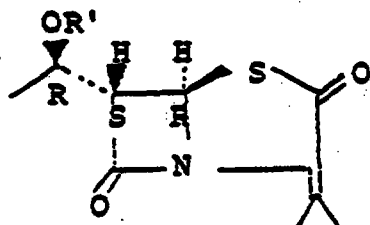
15. The process according to Claim 14 wherein in step (b) intermediate IIa is converted to the intermediate of the formula



IIb

wherein R'' is a bulky triorganosilyl hydroxy-protecting group.

16. A process for the preparation of an intermediate of the formula

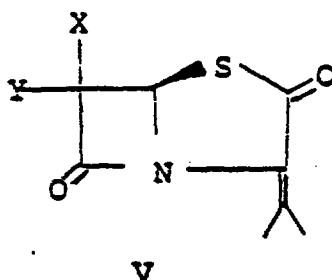


III

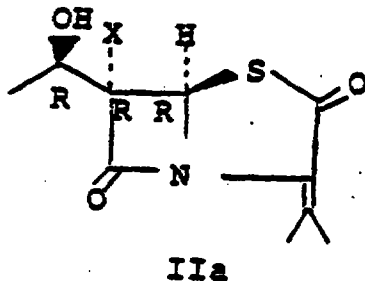
wherein R' is hydrogen or a conventional hydroxy-protecting group, which comprises the steps of



(a) reacting a 6,6-disubstituted anhydropenicillin of the formula

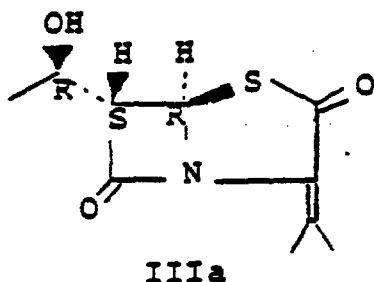


wherein X and Y are each independently chloro, bromo, iodo or phenylseleno with a reagent selected from a Grignard reagent of the formula R_1MgX or an organolithium compound of the formula R_1Li in which R_1 is (lower)alkyl or aryl and X is as defined above in an anhydrous inert organic solvent and at a temperature in the range of 0° to $-78^\circ C$ and subsequently adding acetaldehyde to exclusively produce the cis isomer of the formula



wherein X is as defined above;

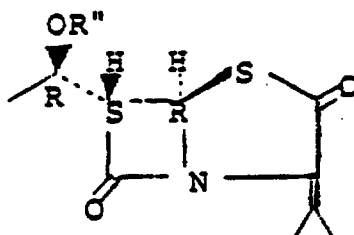
(b) subjecting intermediate IIa to reduction in an inert solvent and isolating the so-produced 5,6-trans isomer of the formula



; and, if desired,



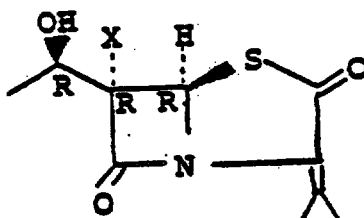
(c) converting intermediate IIIa to the corresponding intermediate of the formula



IIIb

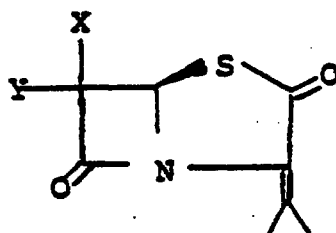
wherein R'' is a conventional hydroxyl-protecting group.

17. A process for the preparation of a compound of the formula



IIa

wherein X is chloro, bromo, iodo or phenylseleno which comprises reacting an intermediate of the formula

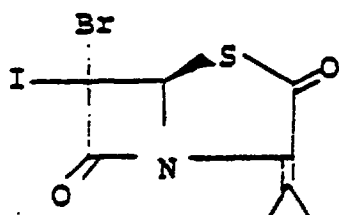


V

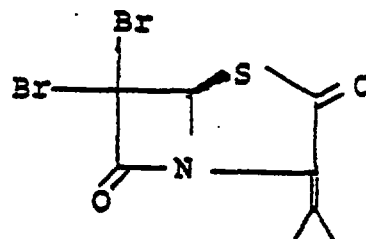
wherein X and Y are each independently chloro, bromo, iodo or phenylseleno with a reagent selected from a Grignard reagent of the formula R_1MgX or an organolithium compound of the formula R_1Li in which R_1 is (lower)alkyl or aryl and X is as defined above in an anhydrous inert organic solvent and at a temperature in the range of 0° to $-78^\circ C$ and subsequently adding acetaldehyde to exclusively produce the desired (8R)-hydroxyethyl cis isomer of formula II.



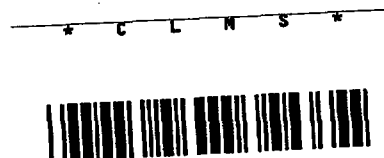
18. The process of Claim 17 wherein the starting material is



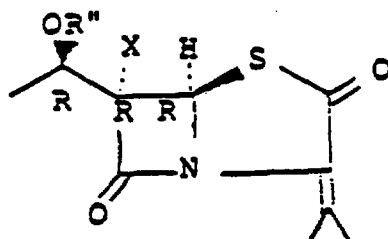
or



19. The process of Claim 17 wherein the starting material is 6,6-dibromoanhydropenicillin.
20. The process of Claim 17, 18 or 19 wherein the Grignard reagent CH_3MgBr is used.
21. The process of Claim 17, 18 or 19 wherein the Grignard reagent CH_3MgCl is used.
22. The process of Claim 17 wherein 6,6-dibromoanhydropenicillin is reacted in an inert organic solvent with about a molar equivalent of methylmagnesium chloride at a temperature in the range of about -45°C to -40°C followed by addition of a molar excess of acetaldehyde.
23. The process of Claim 17 wherein 6,6-dibromoanhydropenicillin is reacted in an inert organic solvent with about a molar equivalent of methylmagnesium bromide at a temperature of about -20°C followed by addition of a molar excess of acetaldehyde.

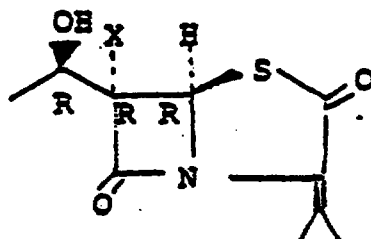


24. A process for preparing a compound having the formula



I Ib

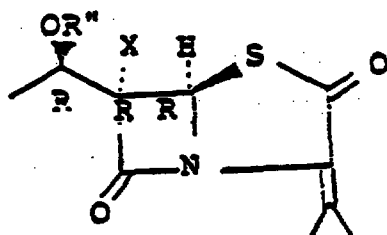
wherein X is chloro, bromo, iodo or phenylseleno and R^{*} is a conventional hydroxyl-protecting group, which comprises converting the intermediate of the formula



I Ia

wherein X is as defined above into the corresponding intermediate wherein the hydroxyl group is protected by a conventional hydroxyl-protecting group.

25. The process according to Claim 24 wherein intermediate I Ia is converted to an intermediate of the formula

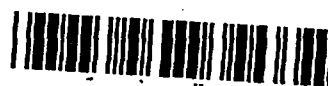


I Ib

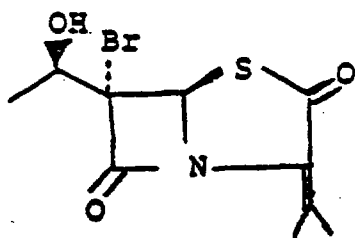
wherein R^{*} is a bulky triorganosilyl hydroxy-protecting group.

26. The process according to Claim 25 wherein the hydroxy-protecting group is triisopropylsilyl, t-butyldimethylsilyl or t-butyldiphenylsilyl.

* C L N S *



27. The process according to Claim 25 or 26 wherein the compound of the formula



- is reacted in an inert organic solvent at a temperature in the range of about -40°C to room temperature with a bulky triorganosilylating agent in the presence of base.
28. The process of Claim 27 wherein the reaction is carried out with t-butyldimethylsilyltriflate, t-butyldiphenylsilyltriflate or triisopropylsilyltriflate in a solvent selected from methylene chloride, tetrahydrofuran, chloroform, toluene or diethyl ether and in the presence of an organic base.



29. A process according to claim 14 employing a procedure substantially as described in the foregoing Examples section.

30. A process according to claim 16 employing a procedure substantially as described in the foregoing Examples section.

31. A process according to claim 17 employing a procedure substantially as described in the foregoing Examples section.

32. A process according to claim 24 employing a procedure substantially as described in the foregoing Examples section.

33. A compound of the formula IIIb specified in claim 14, prepared by a process according to claim 14, 15 or 29.

34. A compound of the formula III specified in claim 16, prepared by a process according to claim 16 or 30.

35. A compound of the formula IIa specified in claim 17, prepared by a process according to any of claims 17 to 23, or claim 31.

36. A compound of the formula IIb specified in claim 24, prepared by a process according to any of claims 24 to 28, or claim 32.

* C L N S *

