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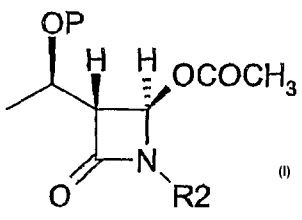
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(54) Title: PROCESSES FOR THE PREPARATION OF PENEMS AND ITS INTERMEDIATE



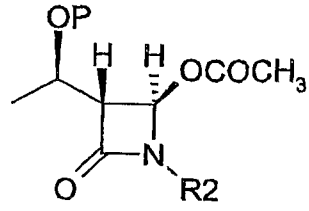
(I)

(57) Abstract: The present invention relates to a process for the preparation of 4-acetoxy azetidinone of Formula I, wherein R_2 is hydrogen or a suitable amino protecting group and P is suitable hydroxy protecting group, and to the use of these compounds as intermediates for the preparation of ß-lactam antibiotics that possess the carbapenem and penem ring systems. 4-acetoxy azetidinone of Formula I is a key intermediate in the synthesis of ß-lactam antibiotics which are commonly prescribed antimicrobial agents having activity against a wide range of both Gram-positive and Gram-negative bacteria.

PROCESSES FOR THE PREPARATION OF PENEMS AND ITS INTERMEDIATE

Field of the Invention

The field of the invention relates to a process for the preparation of 4-acetoxy azetidinone of Formula I,



Formula I

wherein R_2 is hydrogen or a suitable amino protecting group and P is suitable hydroxy protecting group, and to the use of these compounds as intermediates for the preparation of β-lactam antibiotics that possess the carbapenem and penem ring systems.

Background of the Invention

The compounds of Formula I are important synthetic intermediates of β-lactam antibiotics that possess the carbapenem and penem ring systems such as imipenem, ertapenem, faropenem, doripenem, meropenem, and the like. The β-lactam antibiotics are commonly prescribed antimicrobial agents with activity against a wide range of both Gram-positive and Gram-negative bacteria.

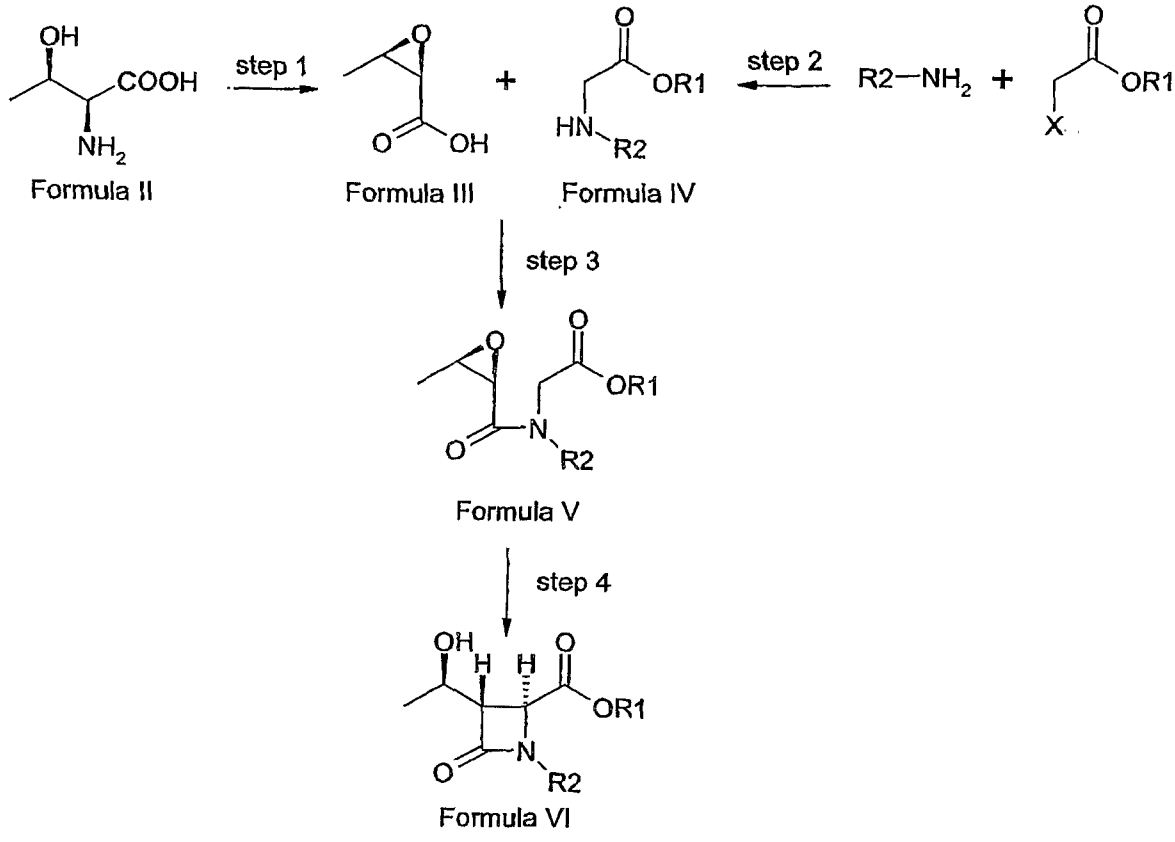
Several processes have been reported for the preparation of 4-acetoxy azetidinone for example, in U.S. Patent Nos. 5,081,239; 5,204,460; 4,861,877; *Journal of Chemical Society, Chemical Communication*, 1991, 662; International (PCT) Publication Nos. WO 98/07691; 98/07690.

U.S. Patent Nos. 5,081,239; and 5,204,460 disclose a process for the preparation of 4-acetoxy azetidinone of Formula I by acetoxylation using acetic acid and an oxidizing agent in the presence of Ruthenium compound as catalyst.

U.S. 4,861,377 discloses a process for the preparation of 4-acetoxy azetidinone by reaction of corresponding O-silyl protected compound with acetic anhydride in an organic solvent in the presence of a base.

Journal of Chemical Society, Chemical Communication, 1991, 662 discloses a process for the preparation of 4-acetoxy azetidinone from (3R)-butane-1,3-diol by reaction of corresponding enol-thioether with chlorosulphonyl isocyanate followed by acetoxylation of the azetidinone so formed at 4-position.

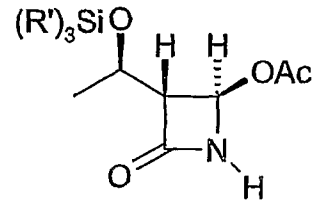
International (PCT) Publication No. WO 98/07691 discloses a process for the preparation of 4-alkoxycarbonyl-3-hydroxyethyl azetidinone of Formula VI from L-Threonine of Formula II by a series of reactions depicted in scheme 1 below:



Scheme 1

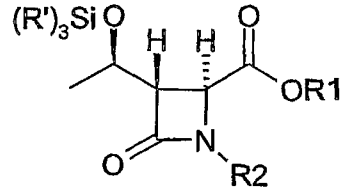
wherein R_1 represents a C_{1-4} alkyl group and R_2 is a protective group for β-lactam ring such as aryl or substituted aryl, particularly 4-methoxyphenyl or 2,4-dimethoxybenzyl.

International (PCT) Publication No. WO 98/07690 discloses a process for preparation of 4-acetoxy azetidinone of Formula X,



Formula X

from 4-alkoxycarbonyl azetidinone of Formula VII,



Formula VII

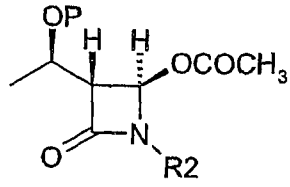
wherein R_2 is p-methoxyphenyl, and R_1 and R' each independently represent C_{1-4} alkyl group, by a series of reactions involving hydrolysis of the ester group at 4-position to carboxyl group followed by oxidation of the carboxyl group to acetoxy group and finally deprotection of the azetidinone ring nitrogen using ozone.

The processes reported in the prior art require extensive column chromatographic purification of intermediates and use of large quantities of solvents and reagents.

The present invention provides processes which do not involve tedious and costly chromatographic purification steps and are easily scalable. The yield and quality of the product is greatly improved when made by the processes of the present invention.

Summary of the Invention

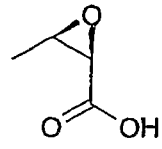
In one general aspect there is provided a process for the preparation of 4-acetoxy azetidinone of Formula I,



Formula I

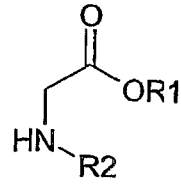
wherein R_2 is hydrogen or a suitable amino protecting group and P is suitable hydroxy protecting group.

In another general aspect there is provided a process for the preparation of (2R,3R)-epoxybutyric acid of Formula III.



Formula III

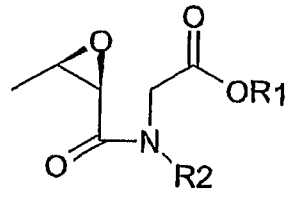
In another general aspect there is provided a process for the preparation of glycine ester of formula IV,



Formula IV

wherein R_1 is C_{1-4} alkyl group and R_2 is hydrogen or a suitable amino protecting group.

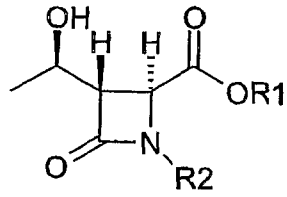
In another general aspect there is provided a process for the preparation of epoxyamide of Formula V,



Formula V

wherein R_1 is C_{1-4} alkyl group and R_2 is hydrogen or a suitable amino protecting group.

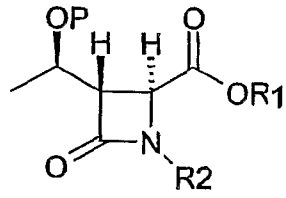
In another general aspect there is provided a process for the preparation of hydroxy azetidinone ester of Formula VIa,



Formula VIa

wherein R_1 is C_{1-4} alkyl group, and R_2 is hydrogen or a suitable amino protecting group.

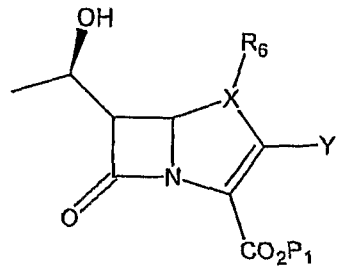
In another general aspect there is provided a process for the preparation of azetidinone ester of Formula VIb,



Formula VIb

wherein R_1 is C_{1-4} alkyl, P is a hydroxy protecting group and R_2 is hydrogen or a suitable amino protecting group.

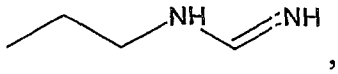
In another general aspect there is provided a process for the preparation of β-lactam compounds of Formula VIII,



Formula VIII

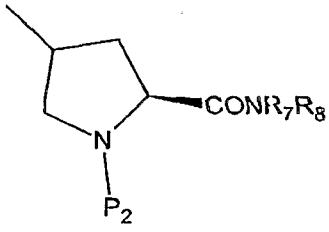
wherein P_1 is hydrogen or a carboxyl protecting group, R_6 is hydrogen or C_{1-5} alkyl and X is C or S, Y is a tetrahydrofuran ring connected via C_2 or Y represents a substituted thiol of Formula S-A, wherein A is selected from the group consisting of

a)



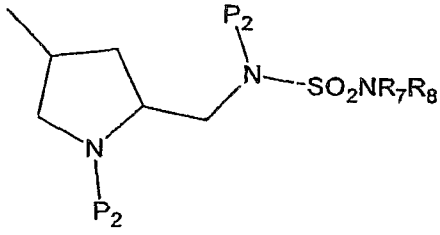
,

b)



, and

c)



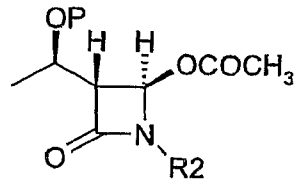
,

wherein P_2 is hydrogen or an amino protecting group, R_7 and R_8 are same or different and are hydrogen, C_{1-5} alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

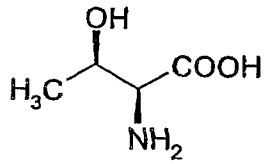
A first aspect of the present invention provides a process for the preparation of 4-acetoxy azetidinone of Formula I,



Formula I

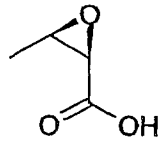
wherein R_2 is hydrogen or a suitable amino protecting group and P is a suitable hydroxy protecting group, the process comprising:

a) stirring a basified reaction mixture comprising L-threonine of Formula II,



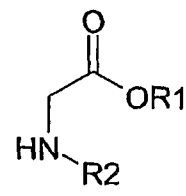
Formula II

an acid and an alkali metal nitrite, for 10 hours or less, to obtain (2R,3R)-epoxybutyric acid of Formula III;



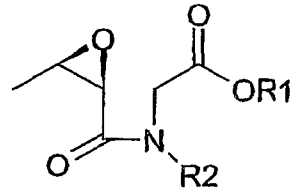
Formula III

b) condensing the epoxyacid of Formula III with glycine ester of Formula IV,



Formula IV

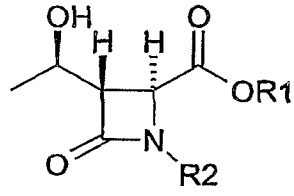
wherein R_1 is C_{1-4} alkyl group and R_2 is as described above, in the presence of a condensing agent in a halogenated solvent to obtain epoxyamide of Formula V,



Formula V

wherein R_1 and R_2 are as described above;

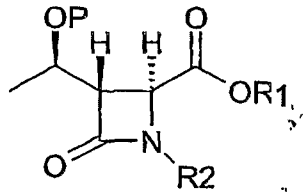
c) converting the epoxyamide of Formula V to hydroxy azetidinone ester of Formula VIa,



Formula VIa

wherein R_1, R_2 are as described above, by treatment with a base;

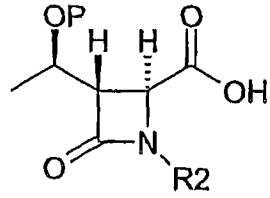
d) converting the hydroxy azetidinone ester of Formula VIa to azetidinone ester of Formula VIb,



Formula VIb

wherein R_1, R_2 are as described above, and P is a hydroxy protecting group, by treatment with a hydroxy protecting agent in the absence of a reaction solvent;

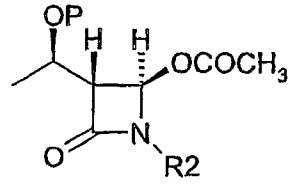
e) hydrolyzing azetidinone ester of Formula VIb to carboxy azetidinone of Formula VIIa,



Formula VIIa

wherein P and R_2 are as described above; and

f) oxidizing the carboxy azetidinone of Formula VIIa in the presence of an oxidizing agent to obtain 4-acetoxy azetidinone of Formula I,



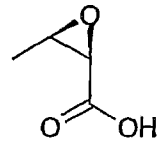
Formula I

wherein P and R_2 are as described above.

Suitable hydroxy and amino protecting groups include, but are not limited to, lowertrialkylsilyl groups, lowerdialkylhalosilyl groups, nitrogen containing silyl groups, lower alkoxymethyl groups, aralkyl groups, acyl groups, lower alkoxycarbonyl groups, alkenyloxycarbonyl groups and aralkyloxycarbonyl groups, aryl or substituted aryl group for example, 4-methoxyphenyl or 2,4-dimethoxybenzyl. The silyl groups described above can be introduced using silylating agents. Examples include trimethylchlorosilane, tert-butyldimethylchlorosilane, 1,1,1,3,3,3,-hexamethyl disilazane, n-trimethylsilylacetamide, tetramethyldisilazane, bis(trimethylsilyl)acetamide, vinyltriacetoxysilane, dimethylchlorosilane, bromomethyldimethylchlorosilane, di(chloromethyl)tetramethyldisilazane, vinyltriethoxysilane, and the like.

Suitable condensing agents include 1,3-dicyclohexylcarbodiimide (DCC), 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), and the like.

A second aspect of the present invention provides a process for the preparation of (2R,3R)-epoxybutyric acid of Formula III,



Formula III

the process comprising stirring a basified reaction mixture comprising L-threonine of Formula I, an acid and an alkali metal nitrite, which is acidified with an acid at a temperature less than 20°C.

The reaction mixture containing the (2R,3R)-epoxybutyric acid of Formula III may be extracted with an organic solvent comprising one or more of C_{4-8} ethers; C_{1-4} alcohols; C_{3-8} ketones; halogenated solvents; polar aprotic solvents, hydrocarbons, or a mixture thereof; with a proviso that the organic solvent is not an ester.

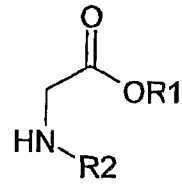
The (2R,3R)-epoxybutyric acid of Formula III can be converted to 4-acetoxy azetidinone of Formula I by the process disclosed in the present invention. The inventors have found that the yield of (2R,3R)-epoxybutyric acid obtained by stirring the reaction mixture for less than 10 hours at 25°C after addition of 40% w/v sodium hydroxide is comparable to the yield obtained by practicing Example 1 of WO 98/07691.

Examples of suitable acids include hydrochloric acid, hydrobromic acid, nitric acid, p-toluene sulphonic acid, and the like. Examples of suitable alkali metal nitrites include sodium nitrite, potassium nitrite, and the like. Suitable bases include alkali metal amides, hydrides, hydroxides, metal alkyls, tertiary amines and bicyclic amines. The tertiary amines may include triethylamine, pyridine, 4-N,N-dimethylamino pyridine, N-methylmorpholine, and the like. The bicyclic amines may include 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), and the like.

Suitable solvents include C_{4-8} ethers; C_{1-4} alcohols; C_{3-8} ketones; halogenated solvents; polar aprotic solvents; and hydrocarbon solvents. Examples of halogenated solvents include

dichloromethane, dichloroethane, chloroform, carbon tetrachloride, ethylene bromide, and the like. A suitable polar aprotic solvent includes one or more of tetrahydrofuran, dimethylformamide, dimethylacetamide, and the like. Suitable hydrocarbon solvents include benzene, toluene, xylene, and the like. Mixtures of all of these solvents are also contemplated. The solvents described above do not cause undesired side reactions and also can be recovered and reused in the present process without purification.

A third aspect of the present invention provides a process for the preparation of glycine ester of formula IV,



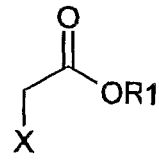
Formula IV

wherein R_1 is C_{1-4} alkyl group and R_2 is hydrogen or a suitable amino protecting group, the process comprising reacting a compound of Formula A,

$R2—NH_2$

Formula A

wherein R_2 is as described above, with 2-halo acetic acid ester of Formula B,



Formula B

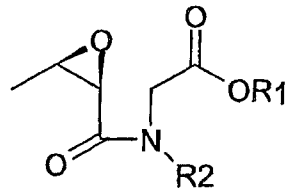
wherein X is a leaving group and R_1 is as described above, in the presence of a base at about 80-100°C.

The glycine ester of Formula IV can be converted to 4-acetoxy azetidinone of Formula I by the process of the present invention. Suitable bases include alkali metal amides, hydrides, hydroxides, metal alkyls, tertiary amines and bicyclic amines. The tertiary amines may include

triethylamine, pyridine, 4-N,N-dimethylamino pyridine, N-methylmorpholine, and the like. The bicyclic amines may include 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), and the like.

Suitable leaving groups represented by X in Formula B above can be chlorine, bromine, iodine, mesyl, tosyl, and the like. The present inventors have found that the process for the preparation of glycine derivative of Formula IV reported in Example 7 of WO 98/07691 failed to initiate at the reported temperature of 50°C leading to consumption of a large amount of ethylchloroacetate. The reaction suddenly got initiated whereby the high exothermicity led to a runaway condition and consequently resulted in low yield of the glycine derivative of Formula IV.

A fourth aspect of the present invention provides a process for the preparation of epoxyamide of Formula V,



Formula V

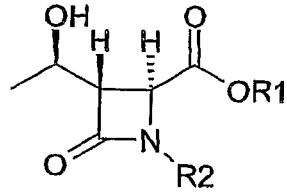
wherein R_1 is C_{1-4} alkyl group and R_2 is hydrogen or a suitable amino protecting group, the process comprising condensing (2R,3R)-epoxybutyric acid of Formula III with glycine ester of Formula IV in the presence of a condensing agent in a halogenated solvent.

The epoxyamide Formula V can be converted to 4-acetoxy azetidinone of Formula I by the process of the present invention. Epoxybutyric acid of Formula III and glycine ester of Formula IV can be prepared by methods known in the art or according to the processes disclosed in the present invention. Examples of halogenated solvents include dichloromethane, dichloroethane, chloroform, carbon tetrachloride, ethylene bromide, and the like.

The present inventors have found that this amide coupling reaction when carried out in the presence of a condensing agent DCC in a halogenated solvent at a temperature of about –

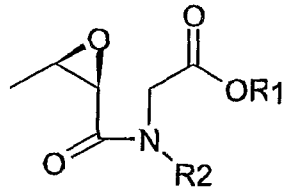
20°C to about 30°C proceeds with nearly 100% conversion as determined by Thin Layer Chromatography. The process of the present invention does not require tedious column chromatography for isolation of the final product and provides good yield of the epoxyamide. The product can be used as such in the subsequent reaction step and the halogenated solvent used can be recovered and reused without purification.

A fifth aspect of the present invention provides a process for the preparation of hydroxy azetidinone ester of Formula VIa,



Formula VIa

wherein R_1 is C_{1-4} alkyl group, R_2 is hydrogen or a suitable amino protecting group, the process comprising; treating epoxyamide of Formula V,



Formula V

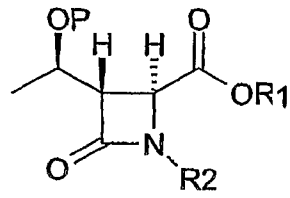
wherein R_1 and R_2 are as described above, with a base.

The hydroxy azetidinone ester of Formula VIa can be converted to 4-acetoxy azetidinone of Formula I by the process of the present invention. The epoxyamide of Formula V can be prepared by methods known in the art or according to the processes described in the present invention.

The present inventors have found that the above cyclization of epoxyamide of Formula V when carried out under reduced quantities of tetrahydrofuran proceeds with nearly 100% conversion as determined by Thin Layer Chromatography. The process of the present invention does not require tedious column chromatography purification, provides good yield

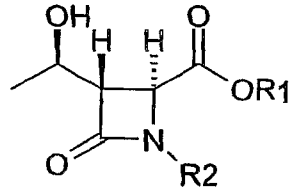
of the hydroxy azetidinone of Formula VIa, which can be used as such in the subsequent reaction step.

A sixth aspect of the present invention provides a process for the preparation of azetidinone ester of Formula VIb,



Formula VIb

wherein R_1 is C_{1-4} alkyl, P is a hydroxy protecting group and R_2 is hydrogen or a suitable amino protecting group, the process comprising treating hydroxy azetidinone ester of Formula VIa,



Formula VIa

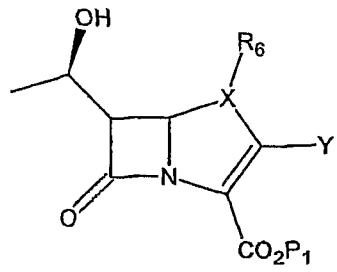
wherein R_1 and R_2 are as described above, with a hydroxy protecting agent in the absence of a reaction solvent.

The hydroxy azetidinone ester of Formula VIa, wherein R_1 and R_2 are as described above, can be prepared by methods known in the art or according to the process disclosed in the present invention. The hydroxy azetidinone ester of Formula VIa described above was treated with a hydroxy protecting agent for example, a silylating agent in the absence of a reaction solvent, to obtain O-silyl protected azetidinone ester which can be converted to 4-acetoxy azetidinone of Formula I, by the process of the present invention.

The present inventors have surprisingly found that the silyl protection of side chain hydroxy group in azetidinone ester of Formula VIa, wherein R_1 and R_2 are as described above, can be carried out without solvent with good yield and the product can be used as such in the subsequent reaction step. Further, the present inventors have found that the reaction times are

greatly reduced when solvent is not used and the process of the present invention does not require tedious column chromatography for isolation of the product.

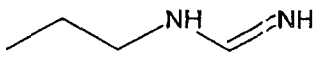
4-acetoxy azetidinone of Formula I prepared by the process of the present invention can be further converted to β-lactam compounds of Formula VIII,



Formula VIII

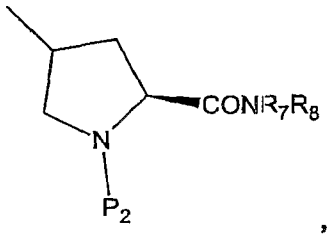
wherein P_1 is hydrogen or a carboxyl protecting group, R_6 is hydrogen or C_{1-5} alkyl and X is C or S, Y is a tetrahydrofuran ring connected via C_2 or Y represents a substituted thiol of Formula S-A wherein A is selected from the group consisting of

a)



,

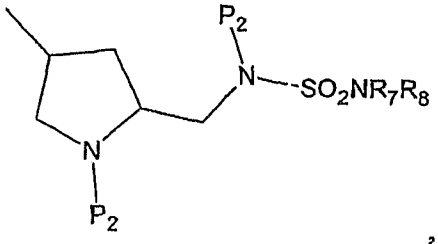
b)



,

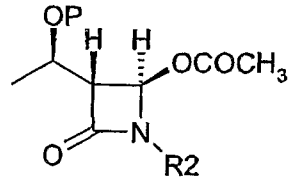
and

c)



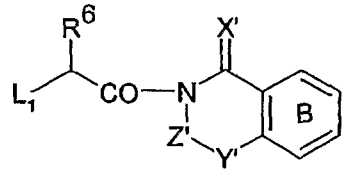
wherein P_2 is hydrogen or an amino protecting group, R_7 and R_8 are same or different and are hydrogen, C_{1-5} alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, by processes known to one skilled in the art. For example, compound of Formula I can be converted to compound of Formula VIII by processes disclosed in U.S. Patent Nos. 4,943,569; 5,478,820; 5,317,016; 5,652,233; 5,856,321; 4,997,829; and 5,998,612. For example, 4-acetoxy azetidinone of Formula I can be converted to β-lactam compounds of Formula VIII by the following steps:

a) reacting 4-acetoxy azetidinone of Formula I



Formula I

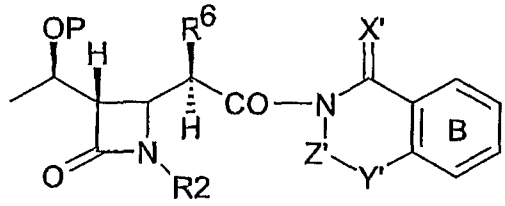
wherein R_2 is hydrogen or a suitable amino protecting group and P is a suitable hydroxy protecting group, with α-haloacetamide derivative of Formula IX,



Formula IX

wherein R_6 is as described above; Ring B is a benzene ring which may be substituted by one to four group(s) selected from halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy and phenyl which may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino; X' is O or S; Y' is O, S, CH_2 or an imino group which may be substituted by C_{1-6}-alkyl or an acyl group selected from C_{2-8}-alkanoyl, (C_{1-6}alkoxy)carbonyl, or phenylcarbonyl or phenyl(C_{1-6}-

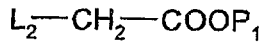
alkoxy)carbonyl, the phenyl group of which each may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino; Z is a methylene group which may be substituted by one to two group(s) selected from C_{3-7}-alkylene, C_{1-20}-alkyl, C_{4-7}-cycloalkyl, phenyl, each of these substituents may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino, phenyl-C_{1-6}-alkyl, the phenyl group of which may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino, or a heterocyclic group; and L_1 is a halogen atom, to obtain a compound of Formula X,



Formula X

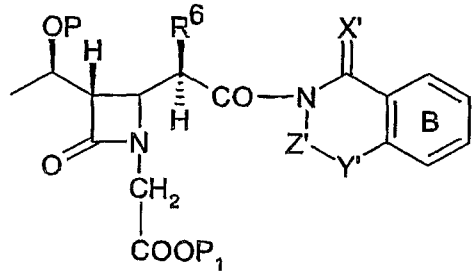
wherein P, R_2, R_6, X', Y' and Z' are as described above;

b) deprotecting the compound of Formula X wherein R_2 is a suitable amino protecting group and reacting the deprotected compound with acetic acid derivative of Formula XI,



Formula XI

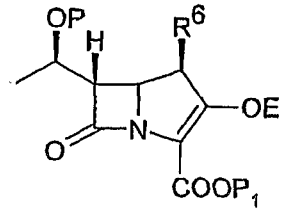
wherein P_1 is as described above and L_2 is a leaving group, to obtain N-substituted azetidinone compound of Formula XII,



Formula XII

wherein P, P_1, R_6, X', Y' and Z' are as described above;

c) subjecting the compound of Formula XII to intramolecular cyclization and esterification to obtain a compound of Formula XIII,



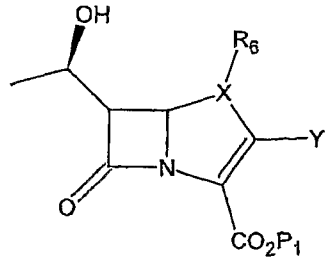
Formula XIII

wherein P, P_1, R_6 are as described above and OE is an esterified hydroxy group; and

d) reacting the compound of Formula XIII with a thiol of Formula,

HS—A

wherein A is as described above and deprotecting the hydroxy protecting group P, to obtain the compound of Formula VIII,



Formula VIII

wherein P_1 and R_6 are as described above, X is Carbon and Y represents a thiol of formula S—A wherein A is as described above.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example 1: Preparation of ethyl N-p-methoxyphenylglycinate

p-Anisidine (100 g) was dissolved in triethylamine (500 ml) at about 50°C under nitrogen atmosphere. The solution was warmed to 90°C and ethylchloroacetate was added slowly over 2-3 hours. The reaction mixture was refluxed for 0.5 hours and cooled to 40°C and washed with water at the same temperature. The organic layer was cooled to 0°C slowly and stirred for 1 hour and filtered to collect the solids. The solids were washed with 2 x 100 ml of 1:1 of

methanol: water mixture and dried under vacuum to obtain the title compound in high purity. Yield =135 g

Example 2: Preparation of (2R,3R)-epoxybutyric acid

L-Threonine (100 g) was dissolved in 7.5 N HCl (546 ml) at 0-5°C. To this solution, 40% w/v aqueous sodium nitrite (240 ml) was added in 5 hours maintaining temperature at –2 to +2°C. The reaction mixture was stirred for 0.5 hours at 0°C, warmed to 25°C, vigorously stirred for 2 hours and then cooled to 0°C. A 40% w/v solution of sodium hydroxide (504 ml) was added maintaining the temperature at 0-5°C and stirred for 1-2 hours at 25°C. pH of the solution of was adjusted to 1-1.2 with concentrated hydrochloric acid at 0-5°C. The reaction mass was saturated with sodium chloride and extracted with 3 x 500 ml tetrahydrofuran at pH 1-1.2. Tetrahydrofuran was recovered from the combined extracts under vacuum at less than 15°C. To the residue so obtained, dichloromethane (700 ml) was added followed by the addition of anhydrous sodium sulfate (100 g). The reaction mixture was stirred for 0.5 to 1 hour and filtered to remove the solids. Dichloromethane (100 ml) washings were added to the above filtrate. This combined filtrate was concentrated under vacuum at less than 15°C to obtain the product. Alternatively, the filtrate was concentrated to half its volume and the solution was used as such for the next step.

Yield =74 g

Example 3: Preparation of (2R,3R)-N-(ethoxycarbonyl)methyl-N-p-methoxyphenyl-2,3-epoxybutyric amide

To a stirred solution of (2R,3R)-epoxybutyric acid (50 g) in dichloromethane, was added ethyl N-p-methoxyphenyl glycinate (92.2 g) at 0-5°C. A solution of dicyclohexylcarbodiimide (101 g) in dichloromethane (75 ml) was added to the reaction mass in 1.5 hours at 0-5°C. To this reaction mixture, water (75 ml) was added at 0-5°C followed by stirring at 20-25°C for 1 hour. The reaction mass was filtered to remove solids. The solids were washed with dichloromethane (2 x 75 ml) and the washings added to the filtrate. The filtrate was washed with 2 x 150 ml 3N HCl and 1 x 50 ml saturated sodium bicarbonate solution at 15°C. Dichloromethane was recovered under vacuum to obtain the title compound as a thick oil which can be used as such in the next step.

Yield =145 g

Example 4: Preparation of (3S,4S)-3-[(1'R)-1'-hydroxyethyl]-4-ethoxycarbonyl]-1-p-methoxyphenyl-2-azetidinone

Method 1:

To (2R,3R)-N-(ethoxycarbonyl)methyl-N-p-methoxyphenyl-2,3-epoxybutyric amide (100 g), was added tetrahydrofuran (500 ml) followed by zinc chloride (7 g) at room temperature. The reaction mass was stirred to dissolve the solids and then cooled to $-15^{o}C$. Lithium hexamethyldisilazane solution in tetrahydrofuran (20%, 385 ml) was added at $-15^{o}C$. The reaction mass was brought to $0^{o}C$ and stirred to completion. The reaction was then quenched in 2:1 mixture of dichloromethane:dilute hydrochloric acid. The reaction mass was filtered over HYFLO® and the layers separated. The organic layer was washed with water and concentrated under reduced pressure to afford the title compound as thick oil, which was used as such in the next step.

Yield = 98 g

Method 2:

Part I:

To a stirred solution of Lithium amide (14.23 g) in tetrahydrofuran (230 ml), was added hexamethyldisilazane (126.7 g) at $25^{o}C$. The resulting solution was refluxed for 3 hours and cooled to $25^{o}C$ and stored under nitrogen atmosphere.

Part II:

To a stirred solution of (2R,3R)-N-(ethoxycarbonyl)methyl-N-p-methoxyphenyl-2,3-epoxybutyric amide (115 g) in tetrahydrofuran (345 ml), was added zinc chloride (8.05 g) at $25^{o}C$. The reaction mixture was stirred for 10 minutes at $25^{o}C$ and cooled to $-15^{o}C$. The solution prepared in part I was slowly added into the above reaction mixture at -10 to $-15^{o}C$ in 15 minutes. The resultant mass was stirred at $0^{o}C$ till the reaction was complete and quenched in a mixture of dichloromethane:dilute hydrochloric acid (575 ml + 719 ml) at $0\text{-}2^{o}C$ and then filtered through HYFLO®. The layers were separated and the organic layer was washed with

water and concentrated under vacuum to afford the title compound as a brown solid, which was taken as such to the next step.

Yield =112.7 g

Example 5: Preparation of (3S,4S)-3-{[(1'R)-1'-t-butyldimethylsilyloxy] ethyl}-4-ethoxy carbonyl-1-p-methoxyphenyl-2-azetidinone

To (3S,4S)-3-[(1'R)-1'-hydroxyethyl]-4-ethoxycarbonyl]-1-p-methoxyphenyl-2-azetidinone (100g), tert-butyldimethylsilylchloride (56.5 g) and imidazole (27.8 g) were added under stirring at 20°C. The reaction was exothermic and the temperature rose to about 45°C. The reaction mass was slowly warmed to 90°C when the reaction was complete. The reaction mass was cooled to room temperature and 400 ml of dichloromethane was added. The separated solids (imidazole hydrochloride) were filtered and the filtrate was washed with water. Dichloromethane was then recovered from the organic layer by distillation and the product was obtained as thick oil, which was used as such in the next step.

Yield =135 g

Example 6: Preparation of (3S,4S)-3-{[(1'R)-1'-t-butyldimethyl silyloxy]ethyl}-4-carboxy-1-p-methoxyphenyl-2-azetidinone

To (3S,4S)-3-{[(1'R)-1'-t-butyldimethylsilyloxy] ethyl}-4-ethoxycarbonyl-1-p-methoxyphenyl-2-azetidinone (100g), methanol (500ml) was added. To the methanolic solution, was added 245 ml of 1N sodium hydroxide and the reaction mixture was stirred at room temperature till the starting material was completely consumed as determined by Thin Layer Chromatography. Methanol was then recovered under reduced pressure at 30°C. The reaction mass was then diluted with water (1 L), washed with ethyl acetate and further diluted with water (1 L). The pH of the solution was adjusted to 3.5 at 0-5°C and the solids obtained were filtered and washed with water. The solids were then dissolved in 250 ml of acetone at 35°C and 250 ml of water was added slowly. The reaction mass was cooled slowly to 20°C and filtered and the solids washed with 1:1 acetone: water. The solids were dried to obtain the product as off-white to light brown powder, which was used as such in the next step.

Yield =64g

Purity ~95%

Reference example 1: (3R,4R)-4-acetoxy-3-(((1'R)-1'-t-butyldimethylsilyloxyethyl}-1-p-ethoxy phenyl-2-azetidinone

Method 1:

To a mixed solution of dimethylformamide and acetic acid (3/1, 300 ml), (3S,4S)-3-{[(1'R)-1'-t-butyldimethylsilyloxy]ethyl}-4-carboxy-1-p-methoxyphenyl-2-azetidinone (15 g, 39.5 mmol) was added followed by tetravalent lead acetate (24.5 g, 55.3 mmol) and the reaction mixture was stirred for 2 hours while maintaining the reaction temperature at 60°C. To the reaction mixture, a mixed solution of ethyl acetate and n-hexane (1:1, 800 ml), and brine (500 ml) were added. The reaction mass was stirred for 30 minutes at room temperature and insoluble materials were filtered off. The filtrate containing the organic layer was washed with brine (400 ml), 10% sodium bicarbonate solution (400 ml) and brine (400 ml) sequentially and concentrated under reduced pressure. The residue was purified by a short column chromatography (eluent: ethyl acetate: hexane = 1:6) to obtain pure title compound as brown oil.

Method 2:

(3S,4S)-3-{[(1'R)-1'-t-butyldimethylsilyloxy]ethyl}-4-carboxy-1-p-methoxyphenyl-2-azetidinone) (15 g, 39.5 mmol) was dissolved in glacial acetic acid (100 ml). To this solution, lead tetraoxide (29.4 g, 43 mmol) was added in small portions at the reaction temperature of 60°C. The reaction temperature slowly rose as the reaction was exothermic. The reaction mixture was vigorously stirred for 30 minutes. After completion of reaction, a small amount of ethylene glycol was added and the solvent removed by evaporation under reduced pressure. The reaction mixture was worked-up as the procedure described in (Method A) to obtain the title compound

Reference example 2: (3R,4R)-4-acetoxy-3-{[(1'R)-1'-t-butyldimethylsilyloxylethyl)-2-azetidinone

Method 1:

(3R,4R)-4-acetoxy-3-(((1'R)-1'-t-butyldimethylsilyloxylethyl}-1-p-ethoxy phenyl-2-azetidinone (26 g, 66 mmol) was dissolved in methanol (500 ml). The internal temperature of the reactor was lowered to $-20^{O}C$ and the reaction was performed for 3 hours with slowly incorporating ozone. After the reaction was completed, 10% solution of sodium thiosulphate and thiourea were added sequentially and the resultant mixture was vigorously stirred for 30 minutes at room temperature. The reaction mixture was concentrated to 1/3 of the initial volume of the mixture. The concentrate was chilled to $-10^{O}C$ to produce white crystalline powder. The powder was filtered, dried and recrystallized from n-hexane to obtain pure title compound as white crystals.

Method 2:

To lithium perchlorate solution (0.1 M; 45 ml) in mixed solvent of acetonitrile and distilled water (10:1), (3R,4R)-4-acetoxy-3-(((1'R)-1'-t-butyldimethylsilylofylethyl}-1-p-ethoxy phenyl-2-azetidinone (349 mg, 1 mmol) was added and dissolved. The mixture was poured in a non-dividable electrolysis vessel with connecting an amorphous carbon anode and a cathode plate, and a Ag/Ag^{+} reference electrode to a Potentiostat (EG & G 273). Under 1.8 V constant voltage, the mixture was electrolysed until all the starting material disappeared. The organic solvent was removed by evaporation under reduced pressure and the residue was dissolved in ethyl acetate. The solution was washed with 10% aqueous sodium sulfite solution and saturated brine sequentially and evaporated under reduced pressure. The residue was purified by a short column chromatography (eluent: ethyl acetate: hexane = 1:4) to obtain pure title compound as white crystals.

Method 3:

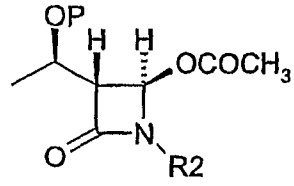
3R,4R)-4-acetoxy-3-(((1'R)-1'-t-butyldimethylsilyloxyethyl}-1-p-ethoxy phenyl-2-azetidinone (5 g, 12.7 mmol) was dissolved in acetonitrile (100 ml). After chilling the solution to $-15^{O}C$, a solution of ceric ammonium nitrate (34.8 g, 63.5 mmol) dissolved in water (150 ml) was added dropwise. The resultant mixture was stirred for 30 minutes. After the completion of the reaction, the mixture was extracted from ethyl acetate (300 ml), and the organic layer was washed with

water (200 ml), 10% sodium thiosulphate solution, 10% sodium bicarbonate solution and saturated brine, sequentially and then concentrated under reduced pressure. The brown residue obtained was recrystallized from n-hexane to obtain the title compound as white crystalline powder.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

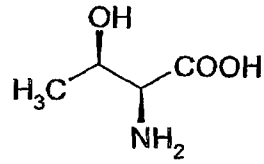
1. A process for the preparation of 4-acetoxy azetidinone of Formula I,



Formula I

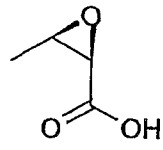
wherein R_2 is hydrogen or a suitable amino protecting group and P is a suitable hydroxy protecting group, the process comprising:

a) stirring a basified reaction mixture comprising L-threonine of Formula II,



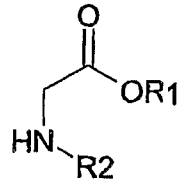
Formula II

an acid and an alkali metal nitrite, for 10 hours or less, to obtain (2R,3R)-epoxybutyric acid of Formula III;



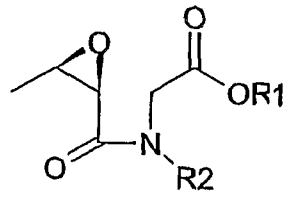
Formula III

b) condensing the epoxyacid of Formula III with glycine ester of Formula IV,



Formula IV

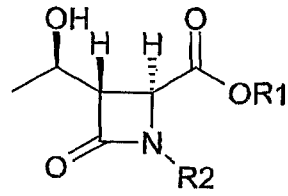
wherein R_1 is C_{1-4} alkyl group, R_2 is as described above, in the presence of a condensing agent in a halogenated solvent to obtain epoxyamide of Formula V,



Formula V

wherein R_1 and R_2 are as described above;

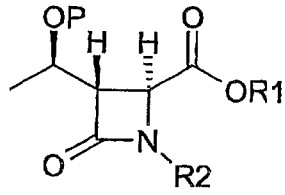
c) converting the epoxyamide of Formula V to hydroxy azetidinone ester of Formula VIa,



Formula VIa

wherein R_1, R_2 are as described above, by treatment with a base;

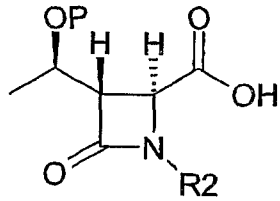
d) converting the hydroxy azetidinone ester of Formula VIa to azetidinone ester of Formula VIb,



Formula VIb

wherein R_1, R_2 are as described above, and P is a hydroxy protecting group, by treatment with a hydroxy protecting agent in the absence of a reaction solvent;

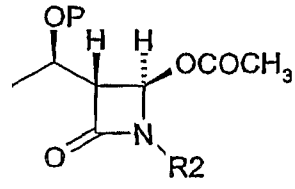
e) hydrolyzing the azetidinone ester of Formula VIb to carboxy azetidinone of Formula VIIa,



Formula VIIa

wherein R_2 is as described above and P is a hydroxy protecting group; and

f) oxidizing the carboxy azetidinone of Formula VIIa in the presence of an oxidizing agent to obtain 4-acetoxy azetidinone of Formula I,



Formula I

wherein P and R_2 are as described above.

2. The process according to claim 1, wherein the basified reaction mixture is acidified with an acid at a temperature less than 20°C.

3. The process according to claim 2, further comprising extracting with organic solvent comprising one or more of C_{4-8} ethers; C_{1-4} alcohol; C_{3-8} ketones; halogenated solvents; polar aprotic solvents, and hydrocarbons with a proviso that the organic solvent is not an ester.

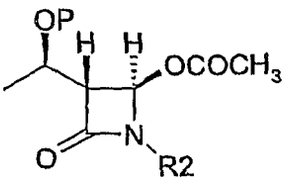
4. The process according to claim 1 step b), wherein the condensation is carried out in the presence of dicyclohexylcarbodiimide in dichloromethane.

5. The process according to claim 1 step d), wherein the hydroxy azetidinone ester of Formula VIa is treated with a silylating agent.

6. The process according to claim 5, wherein the silylating agent comprises one or more of trimethylchlorosilane, tert-butyldimethylchlorosilane, 1,1,1,3,3,3,-hexamethyldisilazane, n-trimethylsilylacetamide, tetramethyldisilazane, bis(trimethylsilyl)acetamide, vinyltriacetoxysilane, dimethylchlorosilane, bromomethyldimethylchlorosilane, di(chloromethyl)tetra methyldisilazane, and vinyltriethoxysilane.

7. The process for the preparation of 4-acetoxy azetidinone of Formula I according to claim 1, wherein the process does not employ chromatographic purification.

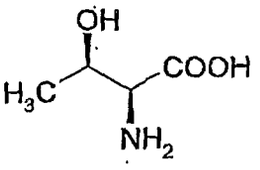
8. A process for the preparation of 4-acetoxy azetidinone of Formula I,



Formula I

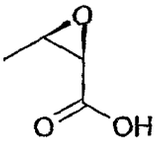
wherein R_2 is hydrogen or a suitable amino protecting group and P is a suitable hydroxy protecting group, the process comprising:

a) stirring a basified reaction mixture of L-threonine of Formula II,



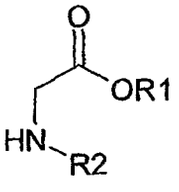
Formula II

an acid and an alkali metal nitrite, to obtain (2R,3R)-epoxybutyric acid of Formula III;



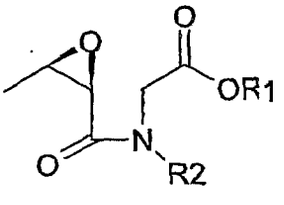
Formula III

b) condensing the epoxyacid of Formula III with glycine ester of Formula IV,



Formula IV

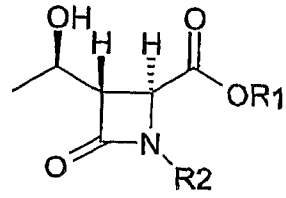
wherein R_1 is C_{1-4} alkyl group, R_2 is as described above, to obtain epoxyamide of Formula V,



Formula V

wherein R_1 and R_2 are as described above;

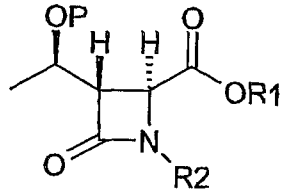
c) converting the epoxyamide of Formula V to hydroxy azetidinone ester of Formula VIa by treatment with a base,



Formula VIa

wherein R_1, R_2 and P are as described above;

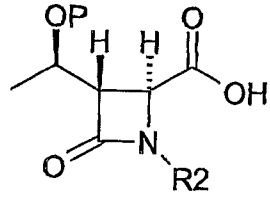
d) converting the hydroxy azetidinone ester of Formula VIa to azetidinone ester of Formula VIb,



Formula VIb

wherein R_1, R_2 are as described above, and P is a hydroxy protecting group, by treatment with a hydroxy protecting agent;

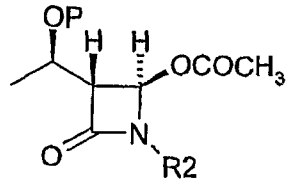
e) hydrolyzing the hydroxy azetidinone of Formula VIb to carboxy azetidinone of Formula VIIa,



Formula VIIa

wherein P and R_2 are as described above; and

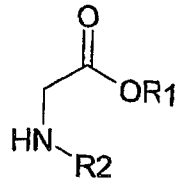
f) oxidizing the carboxy azetidinone of Formula VIIa in the presence of an oxidizing agent to obtain 4-acetoxy azetidinone of Formula I,



Formula I

wherein P and R_2 are as described above, wherein the process does not employ chromatographic purification at any stage.

9. A process for the preparation of glycine ester of formula IV,



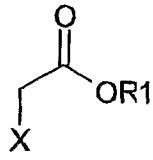
Formula IV

wherein R_1 is C_{1-4} alkyl group and R_2 is hydrogen or a suitable amino protecting group, the process comprising reacting a compound of Formula A,

$R2—NH_2$

Formula A

wherein R_2 is as described above, with 2-halo acetic acid ester of Formula B,



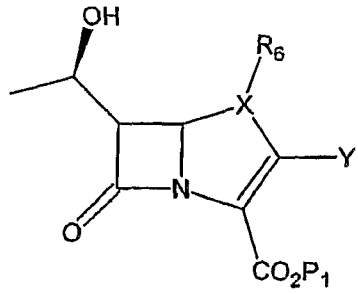
Formula B

wherein X is a leaving group and R_1 is as described above, in the presence of a base at about 80-100°C.

10. The process according to claim 9 further comprising converting the glycine ester of Formula IV to 4-acetoxy azetidinone of Formula I by the process of claim 1.

11 The process according to claims 1, 8 or 9 wherein the base comprises one or more of alkali metal amides, hydrides, hydroxides, metal alkyls, tertiary amines and bicyclic amines.

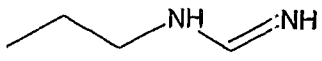
12. A process for the preparation of β-lactam compounds of Formula VIII,



Formula VIII

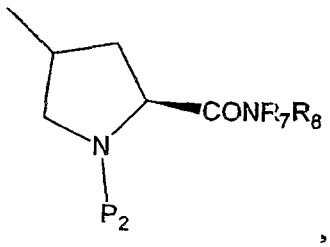
wherein P_1 is hydrogen or a carboxyl protecting group, R_6 is hydrogen or C_{1-5} alkyl and X is C or S, Y is a tetrahydrofuran ring connected via C_2 or Y represents a substituted thiol of Formula S-A, wherein A is selected from the group consisting of

a)



,

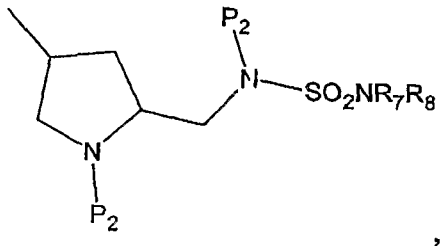
b)



,

and

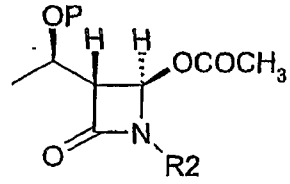
c)



,

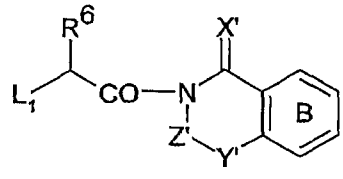
wherein P_2 is hydrogen or an amino protecting group, R_7 and R_8 are same or different and are hydrogen, C_{1-5} alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, the process comprising:

a) reacting 4-acetoxy azetidinone of Formula I prepared by the process of claim 1 or 8,



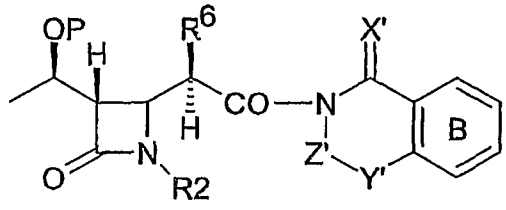
Formula I

wherein R_2 is hydrogen or a suitable amino protecting group and P is a suitable hydroxy protecting group, with α-haloacetamide derivative of Formula IX,



Formula IX

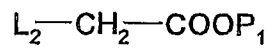
wherein R^6 is as described above; Ring B is a benzene ring which may be substituted by one to four group(s) se ected from halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy and phenyl which may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino; X' is O or S; Y' is O, S, CH_2 or an imino group which may be substituted by C_{1-6}-alkyl or an acyl group selected from C_{2-8}-alkanoyl, (C_{1-6}-alkoxy)carbonyl, or phenylcarbonyl or phenyl(C_{1-6}-alkoxy)carbonyl, the phenyl group of which each may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino; Z is a methylene group which may be substituted by one to two group(s) selected from C_{3-7}-alkylene, C_{1-20}-alkyl, C_{4-7}-cycloalkyl, phenyl, each of these substituents may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino, phenyl-C_{1-6}-alkyl, the phenyl group of which may be substituted with C_{1-6}-alkyl, C_{1-6}-alkoxy, halogen or optionally protected amino, or a heterocyclic group; and L_1 is a haloger atom, to obtain a compound of Formula X,



Formula X

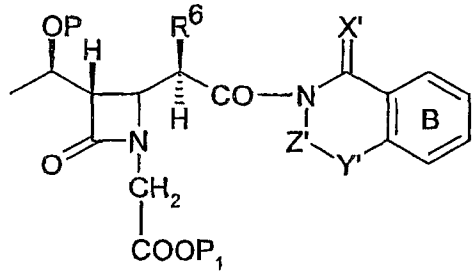
wherein P, R_2, R_6, X', Y' and Z' are as described above;

b) deprotecting the compound of Formula X wherein R_2 is a suitable amino protecting group and reacting the deprotected compound with acetic acid derivative of Formula XI,



Formula XI

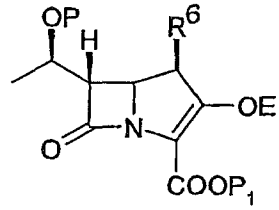
wherein P_1 is as described above and L_2 is a leaving group, to obtain N-substituted azetidinone compound of Formula XII,



Formula XII

wherein P, P_1, R_6, X', Y' and Z' are as described above;

c) subjecting the compound of Formula XII to intramolecular cyclization and esterification to obtain a compound of Formula XIII,



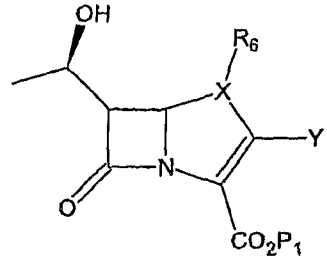
Formula XIII

wherein P, P_1, R_6 are as described above and OE is an esterified hydroxy group; and

d) reacting the compound of Formula XIII with a thiol of Formula,

HS—A

wherein A is as described above and deprotecting the hydroxy protecting group P, to obtain the compound of Formula VIII,



Formula VIII

wherein P_1 and R_6 are as described above, X is Carbon and Y represents a thiol of formula S—A, wherein A is as described above.