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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 205/08	A1	(11) International Publication Number: WO 98/45260
		(43) International Publication Date: 15 October 1998 (15.10.98)

(21) International Application Number: PCT/KR97/00070

(22) International Filing Date: 30 April 1997 (30.04.97)

(30) Priority Data:
1997/13266 10 April 1997 (10.04.97) KR

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PROCESS FOR STEREOSELECTIVE PREPARATION OF AZETIDINONES

(57) Abstract

The present invention relates to a process for stereoselective preparation of (3S,4S)-3-[(1R)-hydroxyethyl]-4-acyl-1-p-methoxyphenyl-2-azetidinone which is a useful intermediate for preparing carbapenem and penem type antibiotics.

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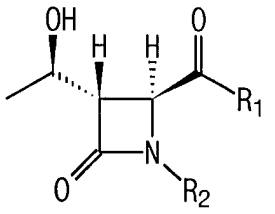
TITLE OF THE INVENTION

Process for stereoselective preparation of azetidinones

Technical Field

The present invention relates to a process for stereoselective preparation of (3S,4S)-3-[(1R)-hydroxyethyl]-4-acyl-1-p-methoxyphenyl-2-azetidinone (1) (here-in-after, abbreviated as "azetidinone") which is a useful intermediate for preparing carbapenem and penem type antibiotics.



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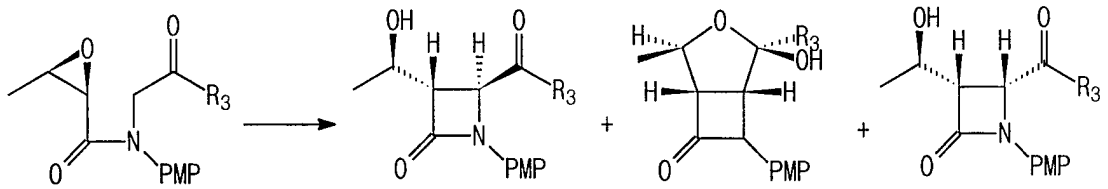
In the formula, R_1 represents a substituted or non-substituted aryl group, or a substituted or non-substituted lower alkyl group; and R_2, as a protective group for β-lactam ring, represents a substituted or non-substituted aryl group, or a substituted or non-substituted benzyl group.

Background Art

A process for preparation of the compound of general formula (1) has been reported in the literature [Synlett. Kugelmam et al., 431, 1990], wherein the object compound, trans-azetidinones (7a-c) are obtained by azetidinone ring formation with a yield of 67 to 89%, depending upon the substituents of the compound (See Scheme 1 below). However, the process has a problem in that by-products such as bicyclic hemiketal compound (8a-c) and cis-azetidinone (9a) occurs in an amount of 9% to 26%, depending on the substituents of each compound, as shown in Table

1.

Scheme 1



6 7a,7b,7c 8a,8b,8c 9a

Table 1 : Yield of azetidinone ring formation in the prior art

	7a	8a	9a	7b	8b	7c	8c
LiHMDS	67%	6%	3%	74%	26%	89%	11%
K_2CO_3	74%	7%	4%	81%	13%	69%	11%

In the above scheme and table, PMP represents p-methoxyphenyl group, LiHMDS represents Lithium hexamethyldisilazide, and R_3 represents phenyl or a substituted aryl group; a represents a compound wherein R_3 is phenyl, b represents a compound wherein R_3 is p-chlorophenyl, and c represents a compound wherein R_3 is p-methylphenyl.

Disclosure of the invention

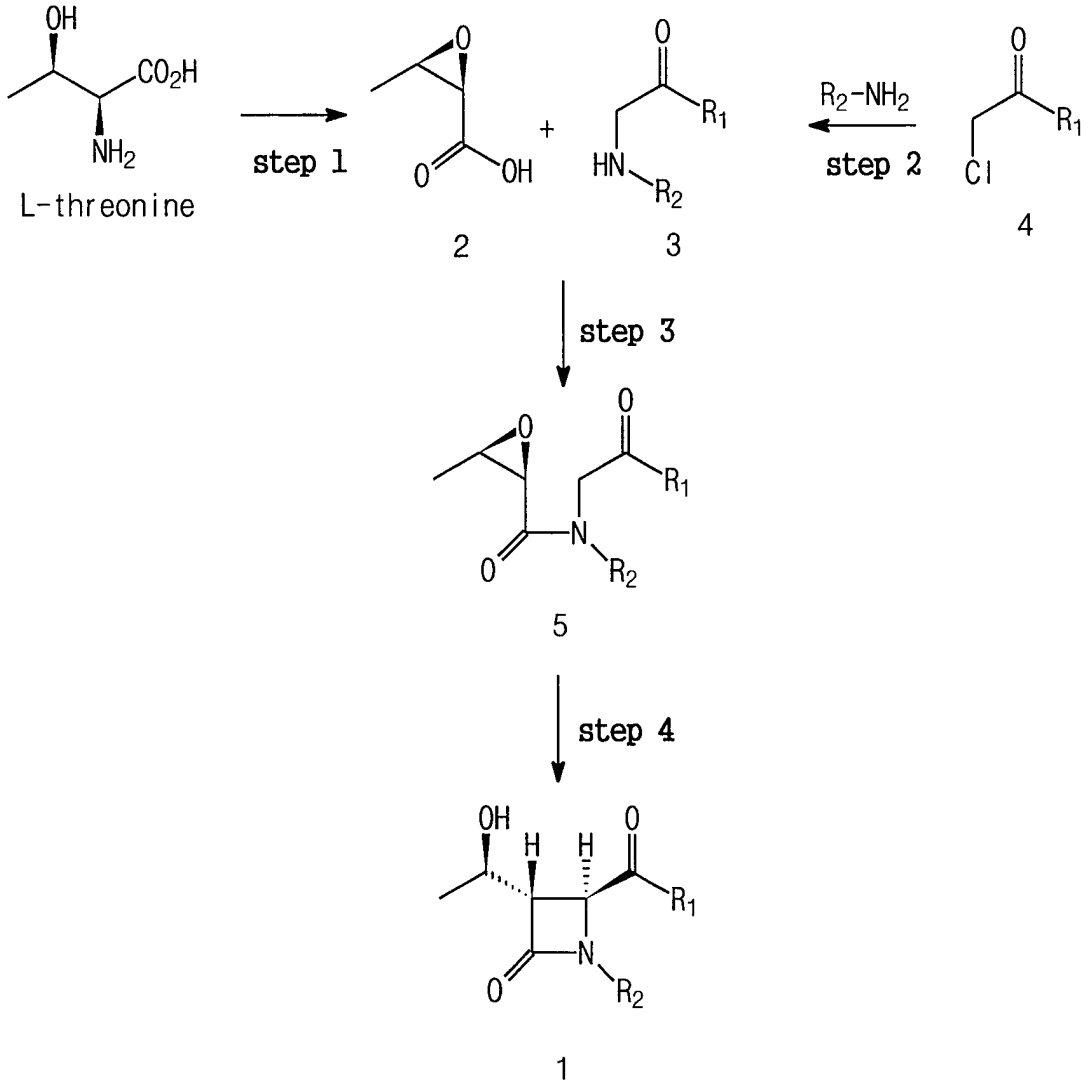
The present inventors have performed intensive studies to overcome the problem as mentioned above, and, as a result, developed a novel process for stereoselective preparation of trans-azetidinone by using intramolecular cyclization of an enamine.

The object of the present invention is to provide a process for stereoselective preparation of azetidinones (1).

According to the present invention, an azetidinone is stereoselectively prepared as shown in Scheme 2 below. First, L-threonine is converted to (2R,3R)- epoxybutyric acid (2) by the use of a known procedure [Tae-sub Hwang et al., Korean Patent Laid-Open No.

96-41161]; a secondary amine (3), obtained by reacting R_2-NH_2 with a compound of general formula (4), is reacted with the (2R,3R)-epoxybutyric acid (2) to obtain (2R,3R)- epoxyamide represented by formula (5); which is then reacted with amine compound, dehydrating agent and Lewis acid in the presence of benzene or dichloromethane as a solvent at a temperature between 0℃ and the reflux temperature of the solvent to stereoselectively give trans-azetidinone.

Scheme 2



In the formula, R_1 and R_2 are defined as above.

Now, the process according to the present invention (Scheme 2) is described step by step, in more detail.

Step 1

The procedure of <Step 1> has been disclosed by the present inventors et al., in Korea Patent Laid-Open No. 96-41161.

Step 2

It is a process for preparing the secondary amine represented by general formula (3) by reacting the compound of general formula (4) and a compound represented by R_2-NH_2 with a dehalogenating agent in the presence or absence of an inert organic solvent.

The compounds represented by R_2-NH_2 include aniline, p- anisidine, 2,4-dimethoxy aniline, 3,4-dimethoxy aniline, 2,4- dimetoxybenzylamine, or the like. Among these, p-anisidine is preferably used.

The compounds of general formula (4) include chloroacetone, chloroacetophenone, 2,4'-dichloroacetophenone, 2,4'-dibromoacetophenone, 2-bromo-4'-methylacetophenone, or the like. Among these, preferable are chloroacetone and chloroacetophenone. The inert solvents used in the step include any organic solvent which can dissolve every compounds involved in the reaction, without participating the reaction under the given reaction condition or lowering the reactivity, and minimize the side reaction. Preferable solvents include hydrocarbons such as hexane and benzene; ethers such as diethyl ether and tetrahydrofuran (THF); halogenated hydrocarbons such as dichloromethane, carbon tetrachloride, 1,2-dichloroethane and chloroform; esters such as methyl acetate and ethyl acetate; lower alcohols such as methanol and ethanol; and other solvents such as acetonitrile, toluene, N,N-dimethylformamide (DMF), and so on. Among these, benzene is preferably used.

The dehalogenating agents which can be used in this step include alkali metal bases such as n-butyl lithium, lithium amide, sodium amide, sodium hydride and potassium hydride; organic tertiary amines such as triethylamine, pyridine, DBN and DBU; ammonium hydroxide and alkali metal hydroxides such as sodium hydroxide, potassium hydroxide. It is preferable to use triethyl amine in an amount of 1 to 5 equivalents. The reaction temperature is properly selected between room temperature and the reflux temperature.

Step 3

It is a process for reacting (2R,3R)-epoxybutyric acid (2) from <Step 1> and the secondary amine (3) from <Step 2> by using an amide bond coupling agent to synthesize (2R,3R)-epoxyamide compound of general formula (5).

As the amide coupling process in this step, an acid halide process, a mixed anhydride process and an active ester process can be generally mentioned. Among them, the active ester process is preferable as it minimizes the side reactions and increases the reaction yield under a mild reaction condition. The activating agents for the active ester process include ethyl chloroformate, isopropylchloroformate, and isobutyl chloroformate. Ethylchloroformate in an amount of 1 to 3 equivalents is preferably used.

While the inert organic solvents mentioned in <Step 2> may be used in this step, preferable are dichloromethane and chloroform.

As a compound for removing hydrochloric acid (HCl) which is generated during this step, tertiary amines such as triethylamine, pyridine, N,N-dimethylaminopyridine, N-methylmorpholine, and bicyclic amines (e.g. DBN, DBU) can be used. It is preferable to use 1 to 5 equivalents of triethylamine or N-methylmorpholine.

The reaction temperature is preferably selected between -40℃ and room temperature.

Step 4

According to this step, (2R,3R)-epoxyamide compound of general formula (5) obtained from <Step 3> is reacted with an amine compound, a dehydrating agent and a Lewis acid. Firstly, in a reactor, the ketone group of (2R,3R)-epoxyamide compound (5) is substituted by an enamine, which then goes through intramolecular cyclization with Lewis acid to stereoselectively give trans-azetidinone.

As an amine compound, a dialkyl amine such as dimethylamine, diethylamine, dipropylamine or diisobutylamine; or a heterocyclic secondary amine such as pyrrolidine, piperidine, hexamethylene imine, morpholine, N-methyl piperazine, N-phenyl piperazine, azetidine or aziridine can be used. Pyrrolidine in an amount of 1 to 10 equivalents is preferably used.

The dehydrating agents include phosphorus pentoxide, molecular sieve, magnesium sulfate, sodium sulfate and calcium chloride. As a chemical dehydrating agent, calcium hydride, titanium(IV) chloride or tris-dialkylaminoborane can be used.

The Lewis acids which can be used in this step include zinc chloride, zinc bromide, tin(IV) chloride, boranetrifluoride ethyl ether compound, aluminum chloride, lithium chloride, thallium chloride or titanium(IV) chloride and chlorotrimethylsilane. Titanium(IV) chloride is preferably used in an amount of 0.5 to 5 equivalents as a dehydrating agent and, at the same time, a Lewis acid.

The reaction temperature is preferably selected between 0℃ and reflux temperature.

As an organic solvent, benzene, dichloromethane, acetonitrile or tetrahydrofuran may be used. In particular, benzene or dichloromethane is preferably used.

In case that zinc chloride or zinc bromide is used as a Lewis acid, the reaction may be performed in a milder condition as compared to the

reaction using titanium(IV) chloride, but shows lower stereoselectivity. If 0.1 to 10 equivalent of zinc chloride or zinc bromide is used, the reaction is preferably carried out by using 1 - 10 equivalents of pyrrolidine as an amine compound and 0.5 to 5 equivalents of phosphorus pentoxide as a dehydrating agent at a temperature between room temperature and reflux temperature in the presence of reaction solvent such as benzene, chloroform and acetonitrile.

As the present invention provides a process for stereoselective preparation of azetidinone ring starting from L-threonine which can be abundantly supplied from the nature, it is economically advantageous. According to the invention, azetidinones can be prepared in a high yield and high stereoselectivity.

Best Mode for Carrying out the Invention

The present invention is described in more detail with reference to the Examples. It should be noted that the scope of the present invention is not restricted to those Examples.

Example 1: (2R,3R)-Epoxybutyric acid

After chilling 7.5N-HCl (90 ml), L-threonine (17.86 g, 0.15 mol) was added thereto and dissolved therein. As maintaining the reaction temperature at room temperature, $NaNO_2$ (18.2 g) was added thereto in small portions over 5 hours. After cooling the interior temperature of the reactor to 0℃, 40% solution of NaOH was slowly added dropwise, and the mixture stirred at room temperature for 15 hours. As restraining the elevation of the reaction temperature, the reaction mixture was acidified (to pH 2.0) with 6N-HCl, and then extracted from ethyl acetate (twice with each 400 ml). The combined organic layer was dried over anhydrous sodium sulfate (10 g), and concentrated under reduced pressure to obtain relatively pure title compound (14.3 g, yield: 93%). The product can be directly used in the next step without further

purification.

^{1}H-NMR(300MHz, $CDCl_3$, δ) ; 1.44(d, J=5.33Hz, 3H), 3.38(m, 1H), 3.57(d, J=4.72Hz, 1H), 9~10(brs, 1H)ppm.

Example 2: N-p-Methoxyphenyl-N-(acetyl)methylamine

To benzene (10 ml), p-anisidine (10 g, 0.08 mol), triethylamine (14.8 ml, 0.104 mol) and chloroacetone (8.4 ml, 0.14 mol) were added and the mixture was stirred under reflux condition for 30 minutes. After the reaction has been completed, the reaction mixture was cooled and extracted from dichloromethane (100 ml) and water (100 ml). The aqueous layer was extracted again with dichloromethane (50 ml). The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crude solid product. The crude product was purified by a column chromatography (eluent: n-hexane/ethyl acetate = 2/1) to give pure yellow brown title compound (25.84 g, yield: 90%).

^{1}H-NMR(300MHz, $CDCl_3$, δ) ; 2.24(s, 3H), 3.74(s, 3H), 3.97(s, 2H), 4.28(brs, 1H), 6.57(d, J=6.7Hz, 2H), 6.79(d, J=6.7Hz, 2H)ppm.

Example 3: N-p-Methoxyphenyl-N-(benzoyl)methylamine

To benzene (2.5 ml), p-anisidine (5 g, 40.6 mmol), triethylamine (7.4 ml, 52.8 mmol) and chloroacetophenone (6.9 g, 44.5 mmol) were added and the mixture was stirred under reflux condition for 30 minutes. After the reaction has been completed, the reaction mixture was cooled and extracted from dichloromethane (100 ml) and water (100 ml). The aqueous layer was extracted again with dichloromethane (50 ml). The combined organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crude solid product. The crude product was purified by a column chromatography (eluent: n-hexane/ethyl acetate = 2/1) to give pure title compound as yellow solid (7.82 g, yield: 85%).

^{1}H-NMR(300MHz, $CDCl_3$, δ) ; 3.76(s, 3H), 4.59(s, 3H),
6.71(d, J=9.4Hz, 2H), 6.78(d, J=9.4Hz, 2H), 7.49(m, 2H),
7.63(m, 1H), 8.02(m, 2H)ppm.

Example 4: (2R,3R)-N-(Acetyl)methyl-N-p-methoxyphenyl- 2,3-epoxy butyric amide

(2R,3R)-Epoxybutyric acid (14.3 g, 0.14 mol) was dissolved in chloroform (150 ml), and the solution chilled to -30℃. N-methylmorpholine (20 ml, 0.18 mol) was added and ethylchloroformate (17.4 ml, 0.18 mol) was slowly added dropwise thereto. The mixture was stirred vigorously for 30 minutes. To the reaction mixture, N-p-methoxyphenyl-N-(acetyl)methyl-amine (22.58 g, 0.126 mol) prepared in Example 2 was added, and the reaction temperature was raised to room temperature. Then the reaction mixture was stirred for 2 hours. After the completion of the reaction, the organic layer was washed with 2N-HCl and saturated solution of sodium bicarbonate, sequentially, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crude title compound. The crude product was purified by a column chromatography (eluent: n-hexane/ethyl acetate = 1/2) to obtain pure title compound (28.16 g, yield: 86%) as brown oil.

^{1}H-NMR(300MHz, $CDCl_3$, δ) ; 1.42(d, J=5.37Hz, 3H), 2.16(s, 3H),
3.05(m, 1H), 3.30(d, J=4.5Hz, 1H), 3.83(s, 3H),
4.23(d, J=17.7Hz, 1H), 4.72(d, J=17.7Hz, 1H), 6.92(d, J=10Hz,
2H), 7.25(d, J=10Hz, 2H)ppm.

Example 5: (2R,3R)-N-(Benzoyl)methyl-N-p-methoxyphenyl-2,3-epoxy butyric amide

(2R,3R)-Epoxybutyric acid (11 g, 0.109 mol) was dissolved in chloroform (100 ml), and the solution chilled to -30℃. N-methylmorpholine (15.4 ml, 0.14 mol) was added and ethylchloroformate

(13.4 ml, 0.14 mol) was slowly added dropwise thereto. The mixture was stirred vigorously for 30 minutes. To the reaction mixture, N-p-methoxyphenyl-N-(benzoyl)methyl-amine (22.2 g, 0.098 mol) prepared in Example 3 was added, and the reaction temperature was raised to room temperature. Then the reaction mixture was stirred for 2 hours. After the completion of the reaction, the organic layer was washed with 2N-HCl and saturated solution of sodium bicarbonate, sequentially, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crude title compound. The crude product was purified by a column chromatography (eluent: n-hexane/ethyl acetate = 1/2) to obtain pure title compound (25.78 g, yield: 85%) as yellow foam.

^{1}H-NMR(300MHz, $CDCl_3$, δ) ; 1.47(d, J=5.35Hz, 3H), 3.09(m, 1H), 3.37(d, J=4.48Hz, 1H), 3.81(s, 3H), 4.86(d, J=17.3Hz, 1H), 5.42(d, J=17.3Hz, 1H), 6.92(d, J=9Hz, 2H), 7.34(d, J=9Hz, 2H), 7.45(m, 2H), 7.56(m, 1H), 7.92(m, 2H)ppm.

Example 6: (3S,4S)-3-[(1R)-Hydroxyethyl]-4-acetyl-1-p-methoxyphenyl-2-azetidinone

(Method A)

(2R,3R)-N-(Acetyl)methyl-N-p-methoxyphenyl-2,3-epoxy butyric amide (5 g, 19 mmol) prepared in Example 4 was dissolved in benzene (50 ml). The interior temperature of the reactor is lowered to 0℃, and pyrrolidine (7.8 ml, 94.9 mmol) was added to the mixture. After stirring the reaction mixture for 5 minutes, titanium(IV) chloride (2.7 ml, 24.7 mmol) was slowly added dropwise. Upon the addition, a vigorous exothermic reaction occurred. After vigorously stirring the mixture for about 10 minutes, the reaction was quenched by adding 1N-HCl (50 ml) at 10℃. The separated organic layer was washed with saturated solution of sodium bicarbonate and saturated brine sequentially, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give crude product (5.2 g). The crude product was purified

by a column chromatography (eluent: n-hexane/ethyl acetate = 1/1) to obtain pure title compound (4.25 g, yield: 85%) as solid.

^{1}H-NMR (300MHz, $CDCl_3$, δ) ; 1.39(d, J= 6.37Hz, 3H), 2.25(s, 3H), 2.33(brs, 1H), 3.16(dd, J=2.64 and 5.26Hz, 1H), 3.78(s, 3H), 4.32(m, 1H), 4.56(d, J=2.64Hz, 1H), 6.87(d, J=6.87Hz, 2H), 7.2(d, J=6.8Hz, 2H)ppm.

(Method B)

N-(Acetyl)methyl-N-p-methoxyphenyl-2,3-epoxy butyric amide (4 g, 15.19 mmol) prepared in Example 4 was dissolved in chloroform (40 ml). Sodium sulfate (2.16 g, 15.19 mmol), zinc chloride (3.73 g, 27.34 mmol) and pyrrolidine (2.66 ml, 31.9 mmol) were added thereto. The reaction temperature was then slowly raised to 60℃, and the mixture was stirred for 3.5 hours. After cooling the reaction mixture to room temperature, the reaction was quenched by adding 2N-HCl (40 ml). The separated organic layer was washed with saturated solution of sodium bicarbonate and saturated brine sequentially, and concentrated under reduced pressure to give crude product (5.2 g). The crude product was purified by a column chromatography (eluent: n-hexane/ethyl acetate = 1/1) to obtain pure title compound (4.0 g, yield: 80%) as solid, and bicyclic hemiketal compound (265 mg, 5.3 %).

Title compound :

^{1}H-NMR(300MHz, $CDCl_3$, δ) : identical to Example 6

Bicyclic hemiketal compound

^{1}H-NMR(300MHz, $CDCl_3$, δ) ; 1.41(s, 3H), 1.42(d, J=6.7Hz, 3H), 2.57(s, 1H), 3.65(d, J=4.3Hz, 1H), 3.79(s, 3H), 3.60(d, J=4.3Hz, 1H), 4.71(m, 1H), 6.88(d, J=10.1Hz, 2H), 7.33(d, J=10.1Hz, 2H)ppm.

Example 7: (3S,4S)-3-[(1R)-Hydroxyethyl]-4-benzoyl-1-p-methoxyphenyl-2-azetidinone

The reaction was performed according to the same procedure described in Example 6, Method A, to give white solid product (4.35 g, yield: 86%).

^{1}H-NMR(300MHz, $CDCl_3$, δ) ; 1.36(d, J=6.37Hz, 3H),
2.31(d, J=4.99Hz, 1H), 3.21(dd, J=2.37 and 6.33Hz, 1H),
3.70(s, 3H), 4.35(m, 1H), 5.53(d, J=2.37Hz, 1H),
4.80(d, J=6.8Hz, 2H), 7.18(d, J=6.8Hz, 2H), 7.55(m, 2H),
7.65(m, 1H), 8.18(m, 2H)ppm.

Comparative Example 1: (3S,4S)-3-[(1R)-Hydroxyethyl]-4- acetyl-1-p-methoxyphenyl-2-azetidinone

(Method A)

(2R,3R)-N-(Acetyl)methyl-N-p-methoxyphenyl-2,3-epoxy butyric amide (1 g, 3.8 mmol) prepared in Example 4 was dissolved in tetrahydrofuran (5 ml). The interior temperature of the reactor is lowered to 0℃. By adding 1M-lithium hexamethyldisilazide (1M-LiHMDS) (4.94 ml, 4.94 mmol), the temperature was slowly raised to room temperature with stirring for 30 minutes. After the completion of the reaction, ethyl ether (10 ml) and saturated solution of ammonium chloride was added and the organic and aqueous layer was separated. The aqueous layer was extracted again with ethyl ether (10 ml). The combined organic layer was concentrated under reduced pressure, and the crude product was purified by column chromatography (eluent : n-hexane/ethyl acetate = 1/1) to obtain pure solid title compound (560 mg, yield: 56%) and bicyclic hemiketal compound 112 mg (yield: 11.2 %).

Title compound :

^{1}H-NMR(300MHz, $CDCl_3$, δ) : identical to Example 6

Bicyclic hemiketal compound :

^{1}H-NMR(300MHz, $CDCl_3$, δ) : identical to Example 6

(Method B)

(2R,3R)-N-(Acetyl)methyl-N-p-methoxyphenyl-2,3-epoxy butyric amide (1 g, 3.8 mmol) prepared in Example 4 was dissolved in DMF (5 ml). Anhydrous potassium carbonate (683 mg, 4.94 mmol) was added thereto, and the mixture was reacted at 60℃ for 1 hour. After cooling the reaction mixture to room temperature, saturated ammonium chloride solution was added, and the resultant mixture was extracted from ethyl ether (10 ml). The separated aqueous layer was extracted again from ethyl ether (10 ml). The combined organic layer was concentrated under reduced pressure to give crude product. The crude product was purified by a column chromatography (eluent: n-hexane/ethyl acetate = 1/1) to obtain pure title compound (600 mg, yield: 60%) as solid, and bicyclic hemiketal compound (125 mg, 12.5 %).

Title compound :

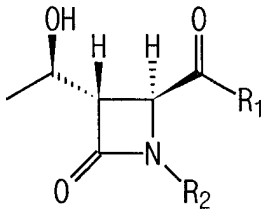
^{1}H-NMR(300MHz, $CDCl_3$, δ) : identical to Example 6

Bicyclic hemiketal compound

^{1}H-NMR(300MHz, $CDCl_3$, δ) : identical to Example 6

CLAIMS

1. A process for stereoselective preparation of azetidinone represented by general formula (1):



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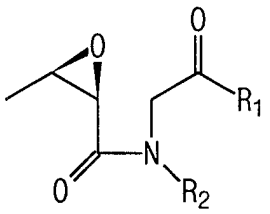
wherein, R_1 represents a substituted or non-substituted aryl group, or a substituted or non-substituted lower alkyl group; and R_2, as a protective group for β-lactam ring, represents a substituted or non-substituted aryl group, or a substituted or non-substituted benzyl group, which comprises reacting the compound of general formula (5) with an amine compound, a dehydrating agent and a Lewis acid at a temperature between 0℃ to the reflux temperature in the presence of benzene or dichloromethane solvent.



5

2. A process according to claim 1, wherein the amine compound is selected from the group consisting of dimethylamine, diethylamine, dipropylamine, diisobutylamine, pyrrolidine, piperidine, hexamethylene imine, morpholine, N-methyl piperazine, N-phenyl piperazine, azetidine and aziridine.

3. A process according to claim 1, wherein the amine compound is pyrrolidine in an amount of 1 to 10 equivalents.

4. A process according to claim 1, wherein the dehydrating agent is phosphorus pentoxide, molecular sieve, magnesium sulfate, sodium sulfate, calcium chloride, calcium hydride, titanium(IV) chloride or tris-dialkylaminoborane.

5. A process according to claim 1, wherein the dehydrating agent is titanium(IV) chloride or phosphorus pentoxide in an amount of 0.5 to 5 equivalent, respectively.

6. A process according to claim 1, wherein the Lewis acid is borane trifluoride ethyl ether, zinc chloride, zinc bromide, tin(IV) chloride, aluminum chloride, lithium chloride, thallium chloride or titanium(IV) chloride.

7. A process according to claim 1, wherein the Lewis acid is zinc chloride or zinc bromide in an amount of 0.1 to 10 equivalents.

8. A process according to claim 1, wherein 0.5 to 5 equivalents of titanium(IV) chloride is used as the dehydrating agent and, at the same time, the Lewis acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00070

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 205/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 205/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem.Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

QUESTEL: CAS, WPIL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 276 993 A1 (IMPERIAL CHEM. IND.) 03 August 1988 (03.08.88), claim 1, formula X.	1-8
A	EP 0 181 831 A2 (CIBA-GEIGY AG) 21 May 1986 (21.05.86), claim 20, example 2.	1-8
A	EP 0 240 164 (SCHERING CORPORATION) 07 October 1987 (07.10.87), page 10, formula 10.	1-8
A	Chemical Abstracts, Vol. 114, No.3, 21 January 1991, (Columbus, OHIO, USA) page 669, column 2, abstract No. 23601h, KUGELMANN, M. et al., "Synthesis of azetidinones from L-threonine: formation of unusually stable bicyclic hemiketals and cis-azetidinones" Synlett 1990, (7),431-2 (Eng).	1-8
A	Chemical Abstracts, Vol. 122, No.13, 27 March 1995, (Columbus, OHIO, USA) page 929, column 1, abstract No. 159898h, GROSJEAN, F., "Molecular modeling study of the regioselectivity of the opening of glycidic acids by aliphatic amines" Tetrahedron 1994, 50(31), 9325-34 (Fr).	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 November 1997 (13.11.97)	20 November 1997 (20.11.97)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hammer Telephone No. 1/53424/374

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 97/00070

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol. 116, No.25, 22 June 1992, (Columbus, OHIO, USA) page 766, column 2, abstract No. 255396q, UENO, TSUNEMASA et al.,"Preparation of 2-azetidinone derivatives", Appl 90/78,893.	1-8
A	Chemical Abstracts, Vol. 102, No.13, 01 April 1985, (Columbus, OHIO, USA) page 676, column 2, abstract No. 113 121h, HANESSIAN, ST., "A new synthetic strategy for the penems. Total synthesis of (5R,6S,8R)-6-(α-hydroxymethyl)-2-(hydroxymethyl)penem-3-carboxylic acid" J.Am.Chem.Soc. 1985, 107(5), 1438-9 (Eng.)	1-8

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 97/00070

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A1 276993	03-08-88	AT E 109771	15-08-94
		DE C0 3850977	15-09-94
		DE T2 3850977	15-12-94
		EP B1 276993	10-08-94
		GB A0 8702139	04-03-87
		JP A2 63246363	13-10-88
		US A 4940788	10-07-90
EP A2 181831	21-05-86	AT E 93520	15-09-93
		DE C0 3587546	30-09-93
		DK A0 4422/85	30-09-85
		DK A 4422/85	02-04-86
		DK A 9/93	05-01-93
		DK A0 9/93	05-01-93
		EP A3 181831	13-08-86
		EP B1 181831	25-08-93
		ES A1 547464	16-01-87
		ES A5 547464	16-02-87
		ES A1 8702887	01-04-87
		ES A1 557111	16-05-88
		ES A5 557111	16-06-88
		ES A1 8802380	16-08-88
		FI A0 853737	27-09-85
		FI A 853737	02-04-86
		FI B 84716	30-09-91
		FI C 84716	10-01-92
		HU A2 41005	30-03-87
		HU A2 42437	28-07-87
		HU B 194821	28-03-88
		HU B 198011	28-07-89
		IE B 60388	13-07-94
		JP A2 61087661	06-05-86
		JP A2 6016622	25-01-94
		KR B1 9305983	01-07-93
		PT A 81226	01-10-85
		PT B 81226	22-01-88
		DD A5 250532	14-10-87
EP A2 240164	07-10-87	EP A3 240164	09-12-87
		JP A2 63253064	20-10-88
		US A 4882429	21-11-89