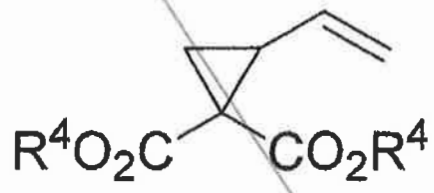
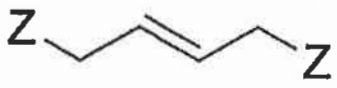
Claims

[Claim 1] A method for producing a compound represented by the following formula (4):
[Formula 2]



(4)

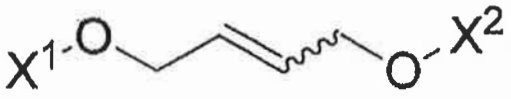
wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted, wherein
the method comprises a step (i) of allowing a compound represented by the following formula (3):
[Formula 1]



(3)

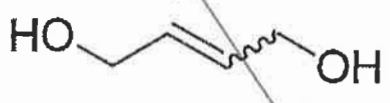
wherein Z represents a halogen atom or OR^3, wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms, an alkylsulfonyl group containing 1 to 10 carbon atoms or an aralkylsulfonyl group containing 7 to 20 carbon atoms, each of which may be optionally substituted,
to react with a malonic ester in the presence of an alkali metal alkoxide or alkali metal hydride, to produce the compound represented by the formula (4),
wherein, in the step (i), the alkali metal alkoxide or alkali metal hydride is used in an amount of 1.5 equivalents or more with respect to 1 equivalent of the compound represented by the above formula (3), and the malonic ester is used in an amount of 1 equivalent or more with respect to 1 equivalent of the alkali metal alkoxide or alkali metal hydride.

[Claim 2] The method according to claim 1, which further comprises, before the step (i), a step (ii) of hydrolyzing, with an acid or a base, a compound represented by the following formula (1):
[Formula 3]



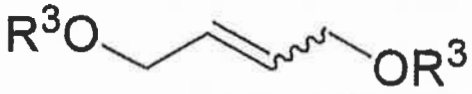
(1)

wherein X^1 represents a hydrogen atom or R^1, and X^2 represents a hydrogen atom or R^2, wherein R^1 and R^2 each independently represent an alkylcarbonyl group containing 2 to 11 carbon atoms, an aralkylcarbonyl group containing 8 to 21 carbon atoms or an arylcarbonyl group containing 7 to 13 carbon atoms, each of which may be optionally substituted, provided that X^1 and X^2 do not simultaneously represent hydrogen atoms,
so as to produce a compound represented by the following formula (2):
[Formula 4]



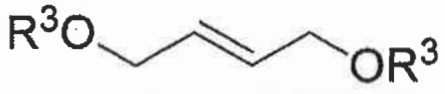
(2)

a step (iii) of allowing the compound represented by the above formula (2), which has been obtained by the above step (ii), to react with a compound represented by R^3X (wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms, an alkylsulfonyl group containing 1 to 10 carbon atoms or an aralkylsulfonyl group containing 7 to 20 carbon atoms, each of which may be optionally substituted; and X represents a halogen atom), so as to produce a compound represented by the following formula (3b):
[Formula 5]



(3b)

wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms, an alkylsulfonyl group containing 1 to 10 carbon atoms or an aralkylsulfonyl group containing 7 to 20 carbon atoms, each of which may be optionally substituted; and
a step (iv) of crystallizing the compound represented by the above formula (3b), which has been obtained by the above step (iii), so as to produce a compound represented by the following (3a):
[Formula 6]

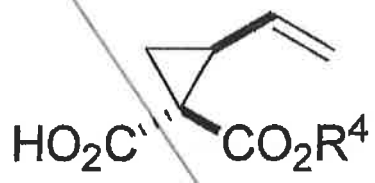


(3a)

wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms, an alkylsulfonyl group containing 1 to 10 carbon atoms or an aralkylsulfonyl group containing 7 to 20 carbon atoms, each of which may be optionally substituted.

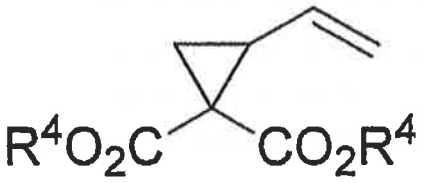
[Claim 3] The method according to claim 1 or 2, which comprises a step of purifying the compound represented by the formula (4) after performing the step (i).

[Claim 4] A method for producing a compound represented by the following formula (5):
[Formula 8]



(5)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted, wherein the method comprises:
a step (v) of producing a compound represented by the following formula (4) by the method according to any one of claims 1 to 3:
[Formula 7]



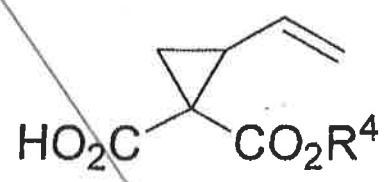
(4)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and
a step (vi) of subjecting the compound represented by the above formula (4), which has been obtained by the above step (v), to hydrolysis, or to hydrolysis and optical resolution, to produce the compound represented by the formula (5).

[Claim 5] The method according to claim 4, wherein the step (vi) is a step (vi-1) of allowing the compound represented by the formula (4), which has been obtained by the step (v), to react with an enzyme, cells containing the enzyme, a preparation of the cells, or a culture solution obtained by culturing the cells, so as to produce an optically active compound represented by the formula (5).

[Claim 6] The method according to claim 4, wherein the step (vi) is a step (vi-2) of hydrolyzing the compound represented by the formula (4) obtained by the step (v) to produce a compound represented by the following formula (5a):

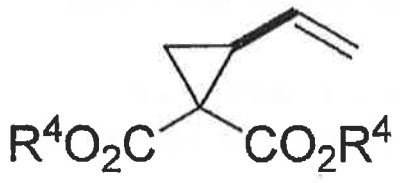
[Formula 9]



(5a)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted,
and then subjecting the compound represented by the formula (5a) to optical resolution using an enzyme, cells containing the enzyme, a preparation of the cells, or a culture solution obtained by culturing the cells, or to optical resolution using an optically active basic compound or by chromatography, to produce an optically active compound represented by the formula (5).

[Claim 7] The method according to claim 4, wherein the step (vi) is a step (vi-3) of subjecting the compound represented by the formula (4) obtained by the step (v) to optical resolution using an enzyme, cells containing the enzyme, a preparation of the cells, or a culture solution obtained by culturing the cells, or to optical resolution by chromatography, to produce a compound represented by the following formula (4a):
[Formula 10]



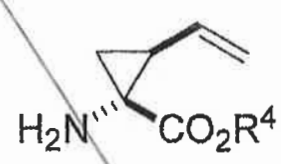
(4a)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted,
and then hydrolyzing the compound represented by the formula (4a), to produce an optically active compound represented by the formula (5).

[Claim 8] The method according to any one of claims 4 to 7, wherein the absolute stereochemistry of the compound represented by the formula (5) is (1S,2S).

[Claim 9] A method for producing a compound represented by the following formula (7):

[Formula 13]

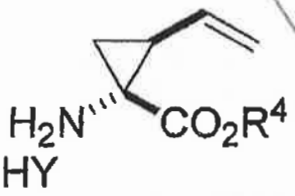


(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms, or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted,

or by the following formula (8):

[Formula 14]



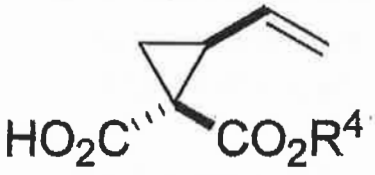
(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms, or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and HY represents an inorganic acid, sulfonic acid, or carboxylic acid,

wherein the method comprises:

a step (vi) of producing a compound represented by the following formula (5) by the method according to any one of claims 4 to 7:

[Formula 11]

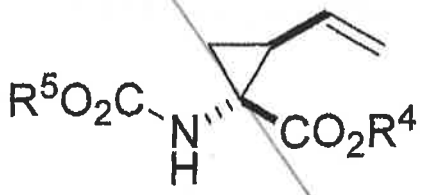


(5)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted;

a step (vii), in which (vii-1) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a condensation agent or an acid halogenating agent to obtain a reaction intermediate, and the reaction intermediate is then allowed to react with a metal azide compound or a trialkylsilyl azide, or

(vii-2) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a phosphoric acid ester-azide,
so as to obtain an acid azide, and the acid azide is then converted to an isocyanate, and the isocyanate is further allowed to react with an alcohol, thereby producing a compound represented by the following formula (6):
[Formula 12]



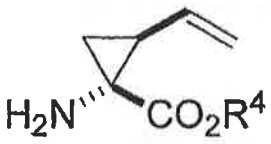
(6)

wherein R^4 and R^5 each independently represent an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms, or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and
a step (viii) of allowing the compound represented by the above formula (6) obtained by the above step (vii) to react with an acid or a base, or subjecting the compound represented by the formula (6) to a catalytic hydrogenation reaction, so as to produce the compound represented by the formula (7) or the formula (8).

[Claim 10] The method according to claim 9, wherein, in the step (vii-1), the reaction intermediate is allowed to react with a metal azide compound or a trialkylsilyl azide in the presence of an acid.

[Claim 11] The method according to claim 9 or 10, wherein the absolute stereochemistry of the compound represented by the formula (5) is (1S,2S), and the absolute stereochemistry of each of the compounds represented by the formula (6), the formula (7) and the formula (8) is (1R,2S).

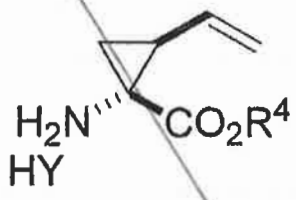
[Claim 12] A method for producing a compound represented by the following formula (7):
[Formula 16]



(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which

may be optionally substituted,
or by the following formula (8):
[Formula 17]



(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms, or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and HY represents an inorganic acid, sulfonic acid, or carboxylic acid,
wherein the method comprises:
a step (vi) of producing a compound represented by the following formula (5) by the method according to any one of claims 4 to 7:
[Formula 15]



(5)

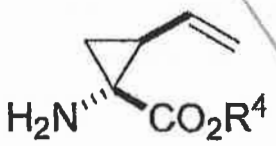
wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and
a step (ix), in which
(ix-1) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a condensation agent or an acid halogenating agent to obtain a reaction intermediate, and the reaction intermediate is then allowed to react with a metal azide compound or a trialkylsilyl azide, or
(ix-2) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a phosphoric acid ester-azide,
so as to obtain an acid azide, and the acid azide is then converted to an isocyanate, and the isocyanate is further allowed to react with water in the presence of an acid, thereby producing the compound represented by the formula (7) or the formula (8).

[Claim 13] The method according to claim 12, wherein, in the step (ix-1), the reaction

intermediate is allowed to react with a metal azide compound or a trialkylsilyl azide in the presence of an acid.

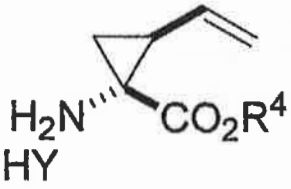
[Claim 14] The method according to claim 12 or 13, wherein the absolute stereochemistry of the compound represented by the formula (5) is (1S,2S), and the absolute stereochemistry of each of the compounds represented by the formula (7) and the formula (8) is (1R,2S).

[Claim 15] A method for producing a compound represented by the following formula (7):
[Formula 19]



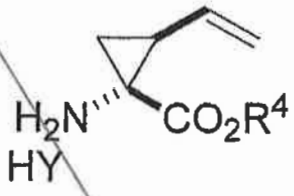
(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted, wherein the method comprises:
a step (x) of producing a compound represented by the following formula (8) by the method according to any one of claims 9 to 14:
[Formula 18]



(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and HY represents an inorganic acid, sulfonic acid, or carboxylic acid; and
a step (xi) of allowing the compound represented by the formula (8) obtained by the above step (x) to react with a base.
[Claim 16] A method for producing a compound represented by the following formula (8):
[Formula 21]



(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and HY represents an inorganic acid, sulfonic acid, or carboxylic acid,

wherein the method comprises:

a step (xii) of producing a compound represented by the following formula (7) by the method according to any one of claims 9 to 15:

[Formula 20]



(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, an aralkyl group containing 7 to 20 carbon atoms or an aryl group containing 6 to 12 carbon atoms, each of which may be optionally substituted; and

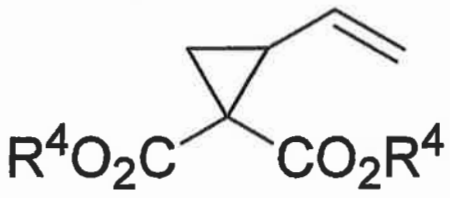
a step (xiii) of allowing the compound represented by the formula (7) obtained by the above step (xii) to react with an inorganic acid, sulfonic acid, or carboxylic acid.

[Claim 17] The method according to claim 16, wherein the step (xiii) is a step of allowing the compound represented by the formula (7) obtained by the above step (xii) to react with sulfuric acid in the presence of an organic solvent.

[Claim 18] The method according to any one of claims 9 to 17, which comprises a step of recrystallizing the compound represented by the formula (8).

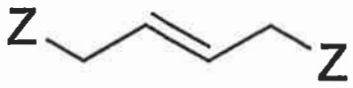
CLAIMS:

[Claim 1] A method for producing a compound represented by the following formula (4):
[Formula 2]



(4)

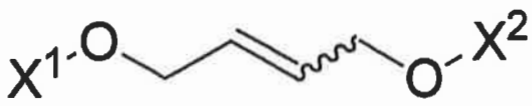
wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, wherein
the method comprises a step (i) of allowing a compound represented by the following formula (3):
[Formula 1]



(3)

wherein Z represents a halogen atom or OR^3, wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms,
to react with a malonic ester in the presence of an alkali metal alkoxide or alkali metal hydride, to produce the compound represented by the formula (4),
wherein, in the step (i), the alkali metal alkoxide or alkali metal hydride is used in an amount of 1.5 equivalents or more with respect to 1 equivalent of the compound represented by the above formula (3), and the malonic ester is used in an amount of 1 equivalent or more with respect to 1 equivalent of the alkali metal alkoxide or alkali metal hydride.

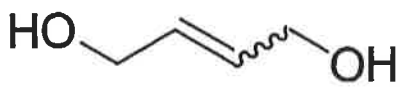
[Claim 2] The method according to claim 1, which further comprises, before the step (i), a step (ii) of hydrolyzing, with an acid or a base, a compound represented by the following formula (1):
[Formula 3]



(1)

wherein X^1 represents a hydrogen atom or R^1, and X^2 represents a hydrogen atom or R^2, wherein R^1 and R^2 each independently represent an alkylcarbonyl group containing 2 to 11 carbon atoms, provided that X^1 and X^2 do not simultaneously represent hydrogen atoms,
so as to produce a compound represented by the following formula (2):

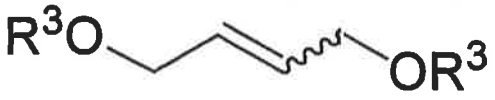
[Formula 4]



(2)

a step (iii) of allowing the compound represented by the above formula (2), which has been obtained by the above step (ii), to react with a compound represented by R^3X (wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms, and X represents a halogen atom), so as to produce a compound represented by the following formula (3b):

[Formula 5]

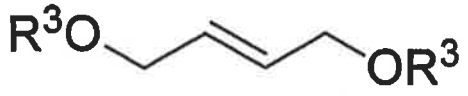


(3b)

wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms; and

a step (iv) of crystallizing the compound represented by the above formula (3b), which has been obtained by the above step (iii), so as to produce a compound represented by the following (3a):

[Formula 6]



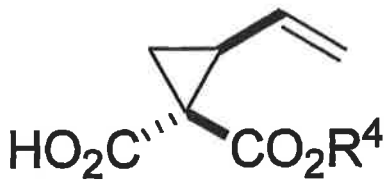
(3a)

wherein R^3 represents an arylsulfonyl group containing 6 to 12 carbon atoms.

[Claim 3] The method according to claim 1 or 2, which comprises a step of purifying the compound represented by the formula (4) after performing the step (i).

[Claim 4] A method for producing a compound represented by the following formula (5):

[Formula 8]

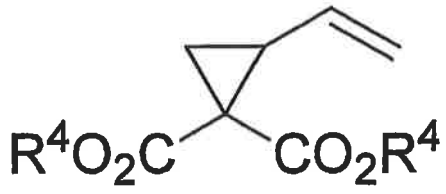


(5)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, wherein the method comprises:

a step (v) of producing a compound represented by the following formula (4) by the method according to any one of claims 1 to 3:

[Formula 7]

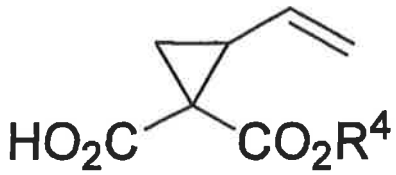


(4)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms; and
a step (vi) of subjecting the compound represented by the above formula (4), which has been obtained by the above step (v), to hydrolysis, or to hydrolysis and optical resolution, to produce the compound represented by the formula (5).

[Claim 5] The method according to claim 4, wherein the step (vi) is a step (vi-1) of allowing the compound represented by the formula (4), which has been obtained by the step (v), to react with an enzyme, cells containing the enzyme, a preparation of the cells, or a culture solution obtained by culturing the cells, so as to produce an optically active compound represented by the formula (5).

[Claim 6] The method according to claim 4, wherein the step (vi) is a step (vi-2) of hydrolyzing the compound represented by the formula (4) obtained by the step (v) to produce a compound represented by the following formula (5a):
[Formula 9]

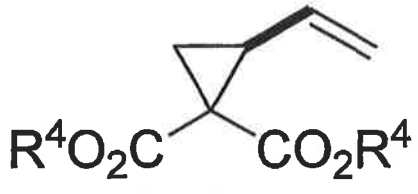


(5a)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms,
and then subjecting the compound represented by the formula (5a) to optical resolution using an enzyme, cells containing the enzyme, a preparation of the cells, or a culture solution obtained by culturing the cells, or to optical resolution using an optically active basic compound or by chromatography, to produce an optically active compound represented by the formula (5).

[Claim 7] The method according to claim 4, wherein the step (vi) is a step (vi-3) of subjecting the compound represented by the formula (4) obtained by the step (v) to optical resolution using an enzyme, cells containing the enzyme, a preparation of the cells, or a culture solution obtained

by culturing the cells, or to optical resolution by chromatography, to produce a compound represented by the following formula (4a):
[Formula 10]

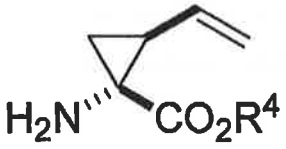


(4a)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms,
and then hydrolyzing the compound represented by the formula (4a), to produce an optically active compound represented by the formula (5).

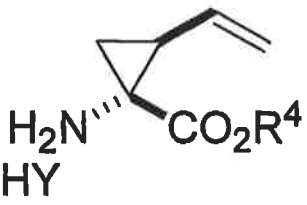
[Claim 8] The method according to any one of claims 4 to 7, wherein the absolute stereochemistry of the compound represented by the formula (5) is (1S,2S).

[Claim 9] A method for producing a compound represented by the following formula (7):
[Formula 13]



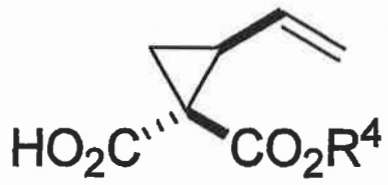
(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms,
or by the following formula (8):
[Formula 14]



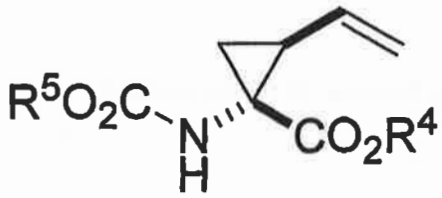
(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms; and HY represents an inorganic acid, sulfonic acid, or carboxylic acid,
wherein the method comprises:
a step (vi) of producing a compound represented by the following formula (5) by the method according to any one of claims 4 to 7:
[Formula 11]



(5)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms;
a step (vii), in which (vii-1) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a condensation agent or an acid halogenating agent to obtain a reaction intermediate, and the reaction intermediate is then allowed to react with a metal azide compound or a trialkylsilyl azide, or
(vii-2) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a phosphoric acid ester-azide,
so as to obtain an acid azide, and the acid azide is then converted to an isocyanate, and the isocyanate is further allowed to react with an alcohol, thereby producing a compound represented by the following formula (6):
[Formula 12]



(6)

wherein R^4 and R^5 each independently represent an alkyl group containing 1 to 10 carbon atoms; and
a step (viii) of allowing the compound represented by the above formula (6) obtained by the above step (vii) to react with an acid or a base, or subjecting the compound represented by the formula (6) to a catalytic hydrogenation reaction, so as to produce the compound represented by the formula (7) or the formula (8).

[Claim 10] The method according to claim 9, wherein, in the step (vii-1), the reaction intermediate is allowed to react with a metal azide compound or a trialkylsilyl azide in the presence of an acid.

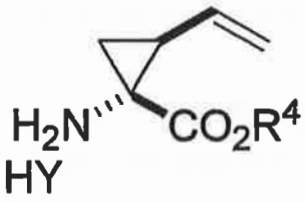
[Claim 11] The method according to claim 9 or 10, wherein the absolute stereochemistry of the compound represented by the formula (5) is (1S,2S), and the absolute stereochemistry of each of the compounds represented by the formula (6), the formula (7) and the formula (8) is (1R,2S).

[Claim 12] A method for producing a compound represented by the following formula (7):
[Formula 16]



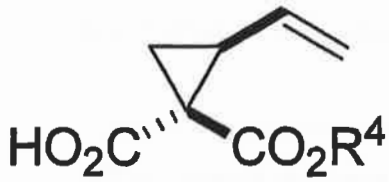
(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms,
or by the following formula (8):
[Formula 17]



(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms; and HY represents an inorganic acid, sulfonic acid, or carboxylic acid,
wherein the method comprises:
a step (vi) of producing a compound represented by the following formula (5) by the method according to any one of claims 4 to 7:
[Formula 15]



(5)

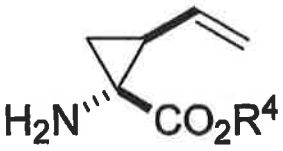
wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms; and
a step (ix), in which
(ix-1) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a condensation agent or an acid halogenating agent to obtain a reaction intermediate, and the reaction intermediate is then allowed to react with a metal azide compound or a trialkylsilyl azide, or
(ix-2) the compound represented by the formula (5) obtained by the above step (vi) is allowed to react with a phosphoric acid ester-azide,

so as to obtain an acid azide, and the acid azide is then converted to an isocyanate, and the isocyanate is further allowed to react with water in the presence of an acid, thereby producing the compound represented by the formula (7) or the formula (8).

[Claim 13] The method according to claim 12, wherein, in the step (ix-1), the reaction intermediate is allowed to react with a metal azide compound or a trialkylsilyl azide in the presence of an acid.

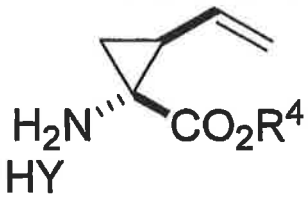
[Claim 14] The method according to claim 12 or 13, wherein the absolute stereochemistry of the compound represented by the formula (5) is (1S,2S), and the absolute stereochemistry of each of the compounds represented by the formula (7) and the formula (8) is (1R,2S).

[Claim 15] A method for producing a compound represented by the following formula (7):
[Formula 19]



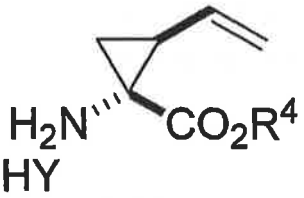
(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms, wherein the method comprises:
a step (x) of producing a compound represented by the following formula (8) by the method according to any one of claims 9 to 14:
[Formula 18]



(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms; and
a step (xi) of allowing the compound represented by the formula (8) obtained by the above step (x) to react with a base.
[Claim 16] A method for producing a compound represented by the following formula (8):
[Formula 21]



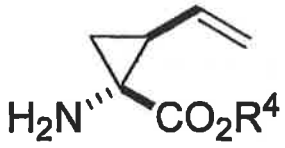
(8)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms; and HY represents an inorganic acid, sulfonic acid, or carboxylic acid,

wherein the method comprises:

a step (xii) of producing a compound represented by the following formula (7) by the method according to any one of claims 9 to 15:

[Formula 20]



(7)

wherein R^4 represents an alkyl group containing 1 to 10 carbon atoms; and

a step (xiii) of allowing the compound represented by the formula (7) obtained by the above step (xii) to react with an inorganic acid, sulfonic acid, or carboxylic acid.

[Claim 17] The method according to claim 16, wherein the step (xiii) is a step of allowing the compound represented by the formula (7) obtained by the above step (xii) to react with sulfuric acid in the presence of an organic solvent.

[Claim 18] The method according to any one of claims 9 to 17, which comprises a step of recrystallizing the compound represented by the formula (8).