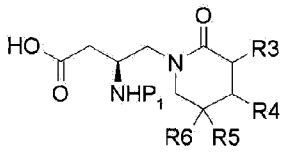
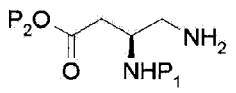
Claims

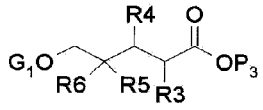
[Claim 1] A method for preparation of a compound of formula (2) characterized in that a compound of formula (4) is reacted with a compound of formula (5):



(2)



(4)



(5)

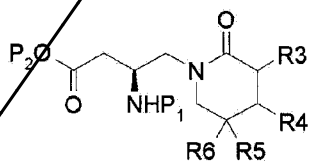
wherein each of R3, R4, R5 and R6 is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_4 alkyl; P_1 is an amine-protecting group; each of P_2 and P_3 is independently benzyl group, methyl group, ethyl group, i-propyl group or t-butyl group; and G_1O is a leaving group.

[Claim 2] The method according to claim 1, which comprises:

(a) the step of coupling reaction by addition of a base to the compound of formula (4) and the compound of formula (5),

(b) the step of cyclization by addition of an acid to obtain a compound of formula (2a), and

(c) the step of hydrolyzing the resulting compound of formula (2a) to obtain the compound of formula (2):



(2a)

wherein R3, R4, R5, R6, P_1 and P_2 are as defined in claim 1.

[Claim 3] The method according to claim 1 or 2, characterized in that P_2 is t-butyl group, and P_3 is methyl or ethyl group.

[Claim 4] The method according to claim 1 or 2, characterized in that G_1O is triflate, mesylate, tosylate, besylate or nonaflate.

[Claim 5] The method according to claim 1 or 2, characterized in that R3 and R4 are hydrogen, and R5 and R6 are fluorine.

[Claim 6] The method according to claim 2, characterized in that in step (a) C_1-C_4 trialkylamine is used as the base.

[Claim 7] The method according to claim 2, characterized in that in step (b) acetic acid is used as the acid.

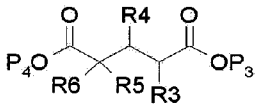
[Claim 8] The method according to claim 2, characterized in that in the case of the compound of formula (2a) wherein P_1 is Boc and P_2 is t-butyl, the hydrolysis of said step (c) is conducted under the basic condition to selectively remove only P_2 among the protecting groups P_1 and P_2 to provide the compound of formula (2).

[Claim 9] The method according to claim 8, characterized in that aqueous sodium hydroxide solution is used as the base.

[Claim 10] A method for preparation of the compound of formula (5) as defined in claim 1, which comprises:

(a) the step of reducing a compound of formula (7) to obtain a primary alcohol compound; and

(b) the step of reacting the alcohol compound obtained from the above with a G_1 compound corresponding to the portion G_1O of the compound of formula (2) to obtain the compound of formula (5):



(7)

wherein R3, R4, R5, R6 and P_3 are as defined above in claim 1, and P_4 is benzyl group, methyl group, ethyl group, i-propyl group or t-butyl group.

[Claim 11] The method according to claim 10, characterized in that in step (a) the reduction is conducted using $NaBH_4$.

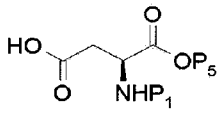
[Claim 12] The method according to claim 10, characterized in that in step (b) the G_1 compound is selected from the group consisting of trifluoromethane sulfonic acid anhydride (Tf_2O), trifluoromethane sulfonyl chloride (TfCl), methanesulfonyl chloride (MsCl), toluenesulfonyl chloride (TsCl), bromobenzenesulfonyl chloride (BsCl), $(CF_3(CF_2)_3SO_2)F$ and $(CF_3(CF_2)_3SO_2)_2O$.

[Claim 13] A method for preparation of the compound of formula (4) as defined in claim 1, which comprises

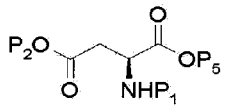
(a) the step of converting a carboxylic acid of a compound of formula (8) into an ester group by introducing P_2 group to obtain a compound of formula (9),

(b) the step of selectively reducing the ester group P_5 present in the

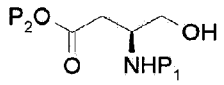
compound of formula (9) to obtain a compound of formula (10),
(c) the step of introducing G_2O leaving group into the compound of formula (10) to obtain a compound of formula (11),
(d) the step of reacting the compound of formula (11) with an azide compound to obtain a compound of formula (12), and
(e) the step of subjecting the compound of formula (12) to hydrogenation to obtain the compound of formula (4):



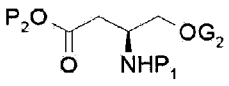
(8)



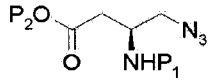
(9)



(10)



(11)

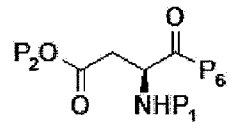


(12)

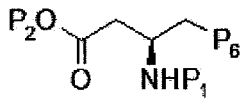
wherein P_1 and P_2 are as defined in claim 1, P_5 is methyl group, ethyl group, i-propyl group or t-butyl group, and G_2O is a leaving group.

[Claim 14] The method according to claim 13, characterized in that P_1 is Boc, P_2 is i-propyl group or t-butyl group, and G_2O is triflate or nonaflate.

[Claim 15] A method for preparation of the compound of formula (4) as defined in claim 1, which comprises:
(a) the step of converting a carboxylic acid compound of formula (13) into an activated ester, which is then reacted with a secondary amine compound to obtain an amide compound of formula (14),
(b) the step of reducing an amide group of the compound of formula (14) to obtain a tertiary amine compound of formula (15), and
(c) the step of subjecting the tertiary amine compound of formula (15) to debenzylation reaction to obtain the compound of formula (4):



(14)



(15)

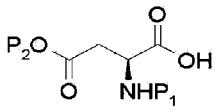
wherein P_1 and P_2 are as defined in claim 1, P_6 is monobenzylamine, dibenzylamine, monoallylamine or diallylamine.

[Claim 16] A method for preparation of the compound of formula (4) as defined in claim 1, which comprises:

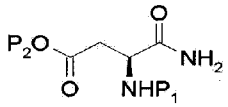
(a) the step of converting the carboxylic acid compound of formula (13) into an activated ester, which is then reacted with a nitrogen source compound to obtain an amide compound of formula (16),

(b) the step of reducing an amide group of the compound of formula (16) to obtain a nitrile compound of formula (17), and

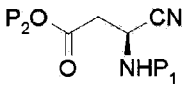
(c) the step of subjecting the nitrile compound of formula (17) to hydrogenation reaction to obtain the compound of formula (4):



(13)



(16)



(17)

wherein P_1 and P_2 are as defined in claim 1.

[Claim 17] The method according to claim 16, characterized in that P_1 is Boc, and P_2 is i-propyl or t-butyl.

[Claim 18] The method according to claim 16, characterized in that in step (a) chloroformate or Boc_2O is used as the activating agent.

[Claim 19] The method according to claim 16, characterized in that the nitrogen source compound used in step (a) is ammonia gas or ammonium salt.

[Claim 20] The method according to claim 16, characterized in that in step (b) the reduction is conducted using trifluoromethane sulfonic acid anhydride and Et_3N, or cyanuric chloride and DMF.

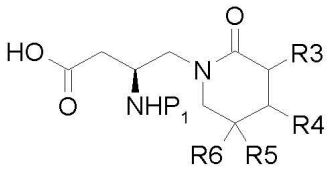
[Claim 21] The method according to claim 16, characterized in that in step (c) the hydrogenation is conducted using a metal selected from palladium, nickel(I) chloride, platinum(IV) oxide and palladium hydroxide.

[Claim 22] The method according to claim 16, characterized in that in step (c) the hydrogenation is conducted using palladium hydroxide metal, acetic

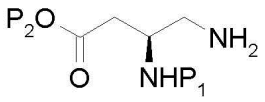
acid and hydrogen.

CLAIMS

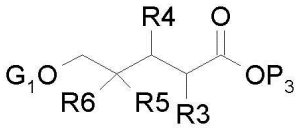
1. A method for preparation of a compound of formula (2) comprising reacting a compound of formula (4) with a compound of formula (5):



(2)



(4)



(5)

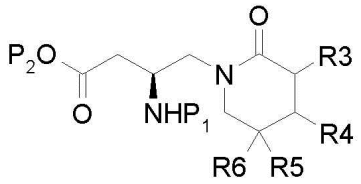
wherein each of R3, R4, R5 and R6 is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_4 alkyl; P_1 is an amine-protecting group; each of P_2 and P_3 is independently benzyl group, methyl group, ethyl group, i-propyl group or t-butyl group; and G_1O is a leaving group.

2. The method according to claim 1, which comprises:

(a) the step of coupling reaction by addition of a base to the compound of formula (4) and the compound of formula (5),

(b) the step of cyclization by addition of an acid to obtain a compound of formula (2a), and

(c) the step of hydrolyzing the resulting compound of formula (2a) to obtain the compound of formula (2):



(2a)

wherein R3, R4, R5, R6, P_1 and P_2 are as defined in claim 1.

3. The method according to claim 1, wherein P_2 is t-butyl group, and P_3 is methyl or ethyl group.

4. The method according to claim 1, wherein G_1O is triflate, mesylate, tosylate, besylate or nonaflate.

5. The method according to claim 1, wherein R3 and R4 are hydrogen, and R5 and R6 are fluorine.

6. The method according to claim 2, wherein in step (a) C_1-C_4 trialkylamine is used as the base.

7. The method according to claim 2, wherein in step (b) acetic acid is used as the acid.

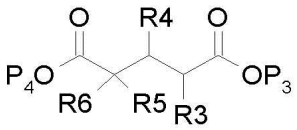
8. The method according to claim 2, wherein in the case of the compound of formula (2a) wherein P_1 is Boc and P_2 is t-butyl, the hydrolysis of said step (c) is conducted under the basic condition to selectively remove only P_2 among the protecting groups P_1 and P_2 to provide the compound of formula (2).

9. The method according to claim 8, wherein aqueous sodium hydroxide solution is used as the base.

10. The method according to claim 1 wherein the compound of formula (5) is prepared by a method comprising:

(a) the step of reducing a compound of formula (7) to obtain a primary alcohol compound; and

(b) the step of reacting the alcohol compound obtained from the above with a G_1 compound corresponding to the portion G_1O of the compound of formula (5) to obtain the compound of formula (5):



(7)

wherein each of R3 and R4 is independently hydrogen or substituted or unsubstituted C_1-C_4 alkyl;

each of R5 and R6 is independently halogen; and

P_4 is benzyl group, methyl group, ethyl group, i-propyl group or t-butyl group.

11. The method according to claim 10, wherein in step (a) the reduction is conducted using $NaBH_4$.

12. The method according to claim 10, wherein in step (b) the G_1 compound is selected from the group consisting of trifluoromethane sulfonic acid anhydride (Tf_2O), trifluoromethane sulfonyl chloride (TfCl), methanesulfonyl chloride (MsCl), toluenesulfonyl chloride (TsCl), bromobenzenesulfonyl chloride (BsCl), $(CF_3(CF_2)_3SO_2)F$ and $(CF_3(CF_2)_3SO_2)_2O$.

13. The method according to claim 1 wherein the compound of formula (4) is prepared by a method comprising:

(a) the step of converting a carboxylic acid of a compound of formula (8) into an ester group by introducing P_2 group to obtain a compound of formula (9),

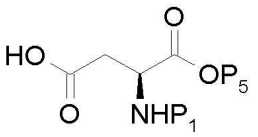
(b) the step of selectively reducing the ester group P_5 present in the compound of formula (9) to obtain a compound of formula (10),

(c) the step of introducing G_2O leaving group into the compound of formula (10) to

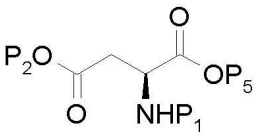
obtain a compound of formula (11),

(d) the step of reacting the compound of formula (11) with an azide compound to obtain a compound of formula (12), and

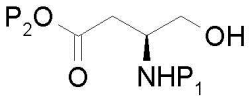
(e) the step of subjecting the compound of formula (12) to hydrogenation to obtain the compound of formula (4):



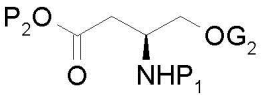
(8)



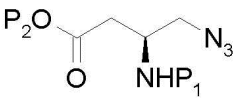
(9)



(10)



(11)



(12)

wherein P_1 is an amine-protecting group;

P_2 is benzyl group, i-propyl group or t-butyl group;

P_5 is methyl group, ethyl group, i-propyl group or t-butyl group~~,~~; and

G_2O is a leaving group~~,~~;

provided that P_5 is methyl group or ethyl group, when P_2 is i-propyl group;

P_5 is methyl group, ethyl group or i-propyl group, when P_2 is t-butyl group; and

P_5 is methyl group, ethyl group, i-propyl group or t-butyl group, when P_2 is benzyl group.

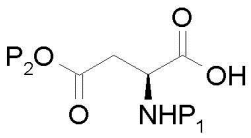
14. The method according to claim 13, wherein P_1 is Boc, P_2 is i-propyl group or t-butyl group, and G_2O is triflate or nonaflate.

15. The method according to claim 1 wherein the compound of formula (4) is prepared by a method comprising:

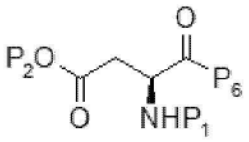
(a) the step of converting a carboxylic acid compound of formula (13) into an activated ester, which is then reacted with an amine compound to obtain an amide compound of formula (14),

(b) the step of reducing an amide group of the compound of formula (14) to obtain an amine compound of formula (15), and

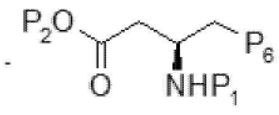
(c) the step of subjecting the amine compound of formula (15) to debenzylation or deallylation reaction to obtain the compound of formula (4):



(13)



(14)



(15)

wherein P_1 and P_2 are as defined in claim 1, P_6 is monobenzylamine, dibenzylamine, monoallylamine or diallylamine.

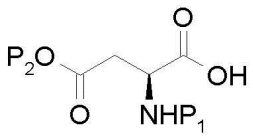
16. The method according to claim 1 wherein the compound of formula (4) is prepared by a method comprising:

(a) the step of converting the carboxylic acid compound of formula (13) into an activated ester, which is then reacted with a nitrogen source compound to obtain

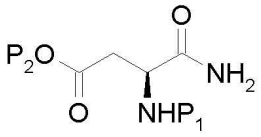
an amide compound of formula (16),

(b) the step of dehydrating an amide group of the compound of formula (16) to obtain a nitrile compound of formula (17), and

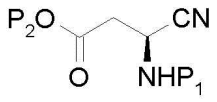
(c) the step of subjecting the nitrile compound of formula (17) to hydrogenation reaction to obtain the compound of formula (4):



(13)



(16)



(17)

wherein P_1 and P_2 are as defined in claim 1.

17. The method according to claim 16, wherein P_1 is Boc, and P_2 is i-propyl or t-butyl.

18. The method according to claim 16, wherein in step (a) chloroformate or Boc_2O is used as the activating agent.

19. The method according to claim 16, wherein the nitrogen source compound used in step (a) is ammonia gas or ammonium salt.

20. The method according to claim 16, wherein in step (b) the dehydration is conducted using trifluoromethane sulfonic acid anhydride and Et_3N, or cyanuric chloride and DMF.

21. The method according to claim 16, wherein in step (c) the hydrogenation is conducted using a metal selected from palladium, nickel(I) chloride, platinum(IV) oxide and palladium hydroxide.

22. The method according to claim 16, wherein in step (c) the hydrogenation is conducted using palladium hydroxide metal, acetic acid and hydrogen.