HU000032484T2

(19) **HU**

(11) Lajstromszám: **E 032 484**

(13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 11 822081**
(22) A bejelentés napja: **2011. 08. 25.**

(96) Az európai bejelentés bejelentési száma:
EP 20110822081
(97) Az európai bejelentés közzétételi adatai:
EP 2611776 A2 **2012. 03. 08.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2611776 B1 **2016. 09. 21.**

(51) Int. Cl.: ***C07D211/36*** *(2006.01)*
A61K 31/45 *(2006.01)*
C07D211/76 *(2006.01)*
C07D471/04 *(2006.01)*
A61P 3/10 *(2006.01)*

(86) A nemzetközi (PCT) bejelentési szám:
PCT/KR 11/006260
(87) A nemzetközi közzétételi szám:
WO 12030106

(30) Elsőbbségi adatok:
20100086619 **2010. 09. 03.** **KR**

(72) Feltaláló(k):
KIM, Bong Chan, Daejeon 305-380 (KR)
KIM, Kyu Young, Daejeon 305-380 (KR)
LEE, Hee Bong, Daejeon 305-380 (KR)
AN, Ji Eun, Daejeon 305-380 (KR)
LEE, Kyu Woong, Daejeon 305-380 (KR)

(73) Jogosult(ak):
LG Life Sciences Ltd, Jongno-gu, Seoul 110-062 (KR)

(74) Képviselő:
ARINOVA Szabadalmi és Védjegy Iroda, Budapest

(54) **Intermedier-vegyület előállítási eljárása gyógyszer szintézise céljából**

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 611 776 B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
21.09.2016 Bulletin 2016/38

(21) Application number: **11822081.3**

(22) Date of filing: **25.08.2011**

(51) Int Cl.:
C07D 211/36 *(2006.01)* ***C07D 471/04*** *(2006.01)*
A61K 31/45 *(2006.01)* ***A61P 3/10*** *(2006.01)*
C07D 211/76 *(2006.01)*

(86) International application number:
PCT/KR2011/006260

(87) International publication number:
WO 2012/030106 (08.03.2012 Gazette 2012/10)

(54) **PRODUCTION METHOD OF INTERMEDIATE COMPOUND FOR SYNTHESIZING MEDICAMENT**

HERSTELLUNGSVERFAHREN FÜR EINE INTERMEDIATVERBINDUNG ZUR SYNTHESE EINES MEDIKAMENTS

PROCÉDÉ DE PRODUCTION D'UN COMPOSÉ INTERMÉDIAIRE POUR LA SYNTHÈSE D'UN MÉDICAMENT

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR

(30) Priority: **03.09.2010 KR 20100086619**

(43) Date of publication of application:
10.07.2013 Bulletin 2013/28

(73) Proprietor: **LG Life Sciences Ltd**
Jongno-gu, Seoul 110-062 (KR)

(72) Inventors:
- **KIM, Bong Chan**
  Daejeon 305-380 (KR)
- **KIM, Kyu Young**
  Daejeon 305-380 (KR)
- **LEE, Hee Bong**
  Daejeon 305-380 (KR)
- **AN, Ji Eun**
  Daejeon 305-380 (KR)
- **LEE, Kyu Woong**
  Daejeon 305-380 (KR)

(74) Representative: **Gillard, Richard Edward**
Elkington and Fife LLP
Thavies Inn House
3-4 Holborn Circus
London EC1N 2HA (GB)

(56) References cited:

EP-A2- 0 279 435
WO-A1-2006/104356
WO-A1-2006/104356
US-A- 5 556 982
US-A1- 2008 039 517

- **KIM S ET AL: "Free Radical-Mediated Carboxylation by Radical Reaction of Alkyl Iodides with Methyl Oxalyl Chloride", TETRAHEDRON LETTERS, PERGAMON, GB, vol. 39, no. 40, 1 October 1998 (1998-10-01), pages 7317-7320, XP004133669, ISSN: 0040-4039, DOI: 10.1016/S0040-4039(98)01568-8**
- **CHRISTOPHE MORIN ET AL: "Synthesis and Evaluation of Boronated Lysine and Bis(carboranylated)[gamma]-Amino Acids as Monomers for Peptide Assembly", EUROPEAN JOURNAL OF ORGANIC CHEMISTRY, vol. 2004, no. 18, 1 September 2004 (2004-09-01), pages 3828-3832, XP55090226, ISSN: 1434-193X, DOI: 10.1002/ejoc.200400342**
- **DAVID G. WASHBURN ET AL.: 'Discovery or orally active, pyrrolidinone-based progesterone receptor partial agonist' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS vol. 19, no. 16, 2009, pages 4664 - 4667, XP026419052**
- **MONICA LOPEZ-GARCIA ET AL.: 'Synthesis of (R)-3,4- diaminobutanoic acid by desymmetrization of dimethyl 3-(benzylamino)-glutarate through enzymatic ammonolysis' JOURNAL OF ORGANIC CHEMISTRY vol. 68, no. 2, 2003, pages 648 - 651, XP055105976**

EP 2 611 776 B1

Description

Technical Field

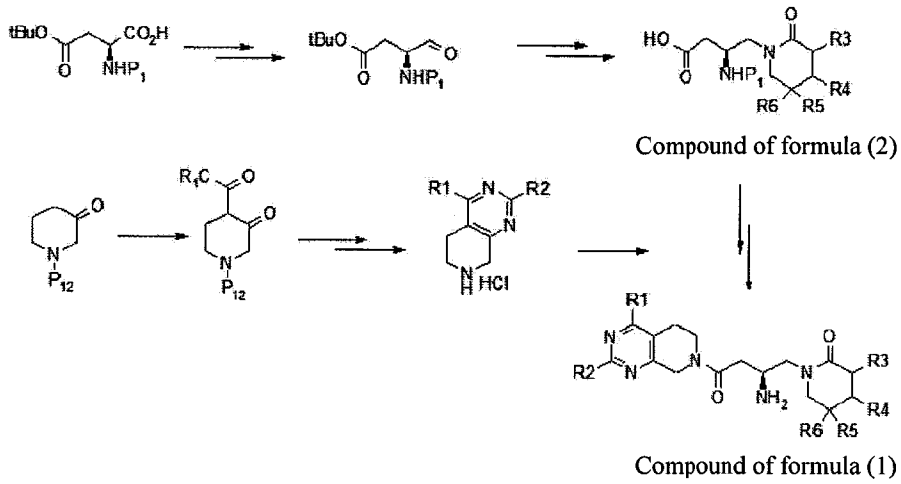
[0001] The present invention relates to a novel method for production of a compound of formula (2) as the major intermediate for synthesizing a compound of formula (1), which exhibits good inhibitory activity for Dipeptidyl Peptidase-IV (DPP-IV) and thus can be used as a medicinal product.

Background Art

[0002] The compound of formula (1), as the compound which has been disclosed in International Patent Publication WO 06/104356, exhibits a good inhibitory activity for Dipeptidyl Peptidase-IV enzyme, and therefore can be effectively used for treatment and prevention of diseases caused by the action of Dipeptidyl Peptidase-IV, including diabetes (particularly, type II diabetes), obesity, etc.

[0003] The methods for preparing the compound of formula (1) by means of the compound of formula (2) as the intermediate have been disclosed in WO 06/104356. Regarding said prior reference, the compounds of formulas (1) and (2) can be prepared by methods-for example, such as the following reaction scheme 1:

Reaction Scheme 1



[0004] However, in mass-scale production said prior method is difficult to obtain the compound of formula (2) having a high optical purity due to the racemization of a stereogenic center on which the amine group is present in the compound of formula (2) to some extent, and therefore it is also difficult to obtain the compound of formula (1) with a high optical purity.

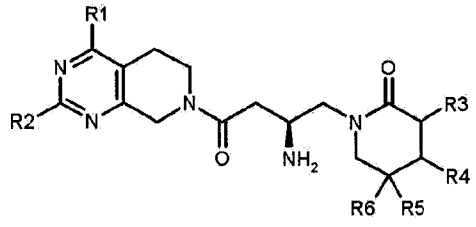
Disclosure of Invention

Technical Problem

[0005] The object of the present invention is to provide a novel method for preparing the compound of formula (2), with high optical purity, as the major intermediate for preparing the compound of formula (1), which can be medically used as an agent for inhibiting DPP-IV.

Solution to Problem

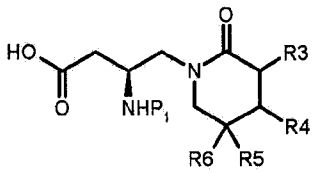
[0006] Therefore, the present invention provides a novel method for preparing the compound of formula (2) as the major intermediate, which can be effectively used for preparation of the compound of formula (1) as an agent for inhibiting DPP-IV:



(1)

[0007] In the above formula,

R1 is hydrogen or CF_3,
R2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_4 -C_8 aryl, and substituted or unsubstituted C_3-C_7 heteroaryl; and
each of R3, R4, R5 and R6 is independently hydrogen, halogen, or substituted or unsubstituted C_1-C_4 alkyl.

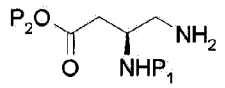


(2)

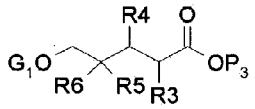
[0008] In the above formula, R3, R4, R5 and R6 are as defined above, and P_1 is an amine-protecting group. Preferably, P_1 is Boc (butyloxycarbonyl), Cbz (benzyloxycarbonyl) or Fmoc (9-fluorenylmethyloxycarbonyl) and more preferably, Boc.
[0009] In the above formulas (1) and (2), if C_1-C_4 alkyl is substituted, it can be preferably substituted with halogen, and more preferably, fluorine.

1. Preparation of the compound of formula (2)

[0010] The method for preparation of the compound of formula (2) according to the present invention is characterized in that a compound of formula (4) is reacted with a compound of formula (5) and further comprises the step of removing a carboxylic acid protecting group derived from the compound of formula (4) after the reaction of said two compounds.



(4)



(5)

[0011] In the above formulas,

P_1, R3, R4, R5 and R6 are as defined above;
each of P_2 and P_3 is independently benzyl group, methyl group, ethyl group, i-propyl group or t-butyl group;
G_1 functions as a good leaving group together with oxygen. G_1O is triflate (trifluoromethanesulfonate), mesylate, tosylate, besylate or nonaflate (nonafluorobutanesulfonate) and preferably triflate or nonaflate.

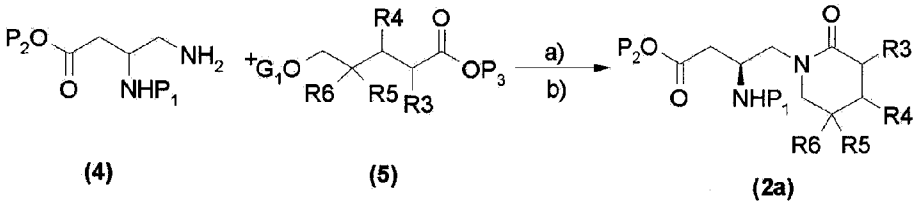
[0012] The method of the present invention produces the compound of formula (2) from the compound of formula (4) and the compound of formula (5) via a compound of formula (2a), and specifically comprises:

(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 the compound of formula (2a), and
(c) the step of removing the carboxylic acid protecting group by hydrolysis of the resulting compound of formula (2a) to obtain the compound of formula (2).

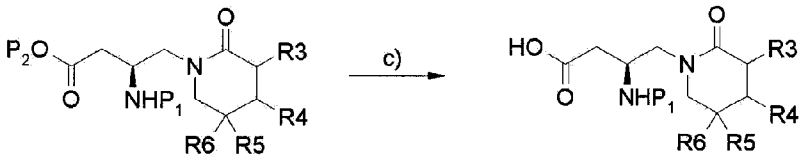
[0013] The method of the present invention can be represented as the following reaction schemes 2 and 3.

Reaction Scheme 2



(4) (5) (2a)

Reaction Scheme 3



(2a) (2)

[0014] In the above schemes,

a is a base such as Et_3N, Hunig's base, etc.;
b is an acid such as AcOH, etc., and an organic solvent such as CH_2Cl_2, etc.;
c varies with the protecting group and typically is selected from the conditions (1) a strong acid such as H_2SO_4, etc. and CH_2Cl_2, aq. NaOH, Boc_2O, and (2) NaOH, EtOH, H_2O, reflux, when P_1 is Boc and P_2 is t-butyl group or is the hydrolysis condition utilizing the base specified in the above condition (2), when P_1 is Boc and P_2 is benzyl group, methyl group, ethyl group and i-propyl group. R3, R4, R5, R6, P_1, P_2, P_3 and G_1 are as defined above.

[0015] Specifically, in step (a) the unprotected primary amine of the compound of formula (4) is coupled with a carbon atom having the leaving group in the compound of formula (5) under the basic condition, and $-OG_1$ is removed. This reaction uses C_1-C_4 trialkylamine, preferably triethylamine or diisopropylethylamine, as the base. As the reaction solvent, common organic solvents such as dichloroethane or dichloromethane, or cyclic ethers (e.g., tetrahydrofuran (THF) or dioxane) can be used. To facilitate the reaction, the base used alternatively serves as the solvent. The reaction can be conducted at any temperature between 0°C and the refluxing temperature.

[0016] In step (b), the compound of formula (2a) is synthesized through cyclization of the secondary amine group of the compound produced from said step (a), with the internal ester group under the acidic condition. In this reaction, as the acid inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, etc. or organic acids such as formic acid, acetic acid, tartaric acid, etc. can be used, with acetic acid being particularly preferable. The solvent and temperature conditions as described in the above step (a) can be used in this step. Said steps (a) and (b) are conducted in a continuous manner.

[0017] In step (c), the compound of formula (2a) obtained from step (b) is hydrolyzed to obtain the compound of formula (2). Specifically, in case of the compound of formula (2a) where P_1 is Boc and P_2 is t-butyl group, first a strong acid such as sulfuric acid, hydrochloric acid, phosphoric acid, TFA (trifluoroacetic acid), etc. can be used to remove both protecting groups and Boc protecting group can then be attached again to the amine group under the basic condition to obtain the desired compound of formula (2). Alternatively, the hydrolysis under the basic condition, rather than the acidic condition, can lead to selective removal of only P_2 among the protecting groups P_1 and P_2 to provide the compound of formula (2), and this manner of the procedure is more efficient. Preferably, sodium hydroxide solution is used as the base. Upon completion of the reaction, the compound of formula (2) can be obtained as a solid product through acidification using an acid.

[0018] In case of the compound where P_1 is Boc and P_2 is benzyl group, methyl group, ethyl group or i-propyl group, the hydrolysis can be conducted by means of a base. The deprotecting reaction is conducted using H_2/Pd-C when P_1 is Cbz, or using $Bu_4N^+F^-$ when P_1 is Fmoc.

[0019] Preferably, the compound of formula (2) can be obtained in a high yield when P_2 is t-butyl group or i-propyl group, more preferably t-butyl group, and P_3 is methyl group or ethyl group.

[0020] In addition, the present invention provides a method for preparation of the compounds of formulas (4) and (5) as the starting materials used for preparation of the compound of formula (2).

2. Preparation of the compound of formula (5)

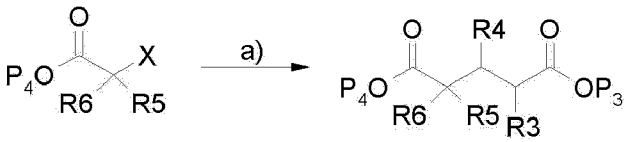
[0021] The compound of formula (5), as one of the starting materials used for preparation of the compound of formula (2), can be prepared from the known compound of formula (7), which can be obtained from a compound of formula (6) through the method shown in the following reaction scheme 4, as disclosed in WO 06/104356.

[0022] The method for preparation of the compound of formula (5) comprises

(a) the step of reducing the 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). This method can be represented as shown in the following reaction scheme 5.

Reaction Scheme 4



(6) **(7)**

[0023] In the above scheme,

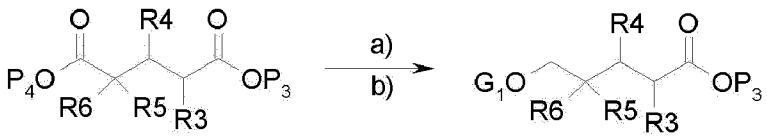
a is ethyl acrylate (where P_4 is ethyl), Cu powder, TMEDA (tetramethylethylenediamine) or THF;

X is a halogen such as Br, F or Cl, etc.;

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

R3, R4, R5, R6 and P_3 are as defined above.

Reaction Scheme 5



(7) **(5)**

[0024] In the above scheme,

a is $NaBH_4$, and EtOH or MeOH or i-PrOH;

b is trifluoromethane sulfonic acid anhydride (Tf_2O), trifluoromethane sulfonyl chloride (TfCl), methanesulfonyl chloride (MsCl), toluenesulfonyl chloride (TsCl), bromobenzenesulfonyl chloride (BsCl), $(CF_3(CF_2)_3SO_2)F$ or

$(CF_3(CF_2)_3SO_2)_2O$, pyridine or trialkylamine, and CH_2Cl_2;

R3, R4, R5, R6, P_3, P_4 and G_1 are as defined above.

[0025] Specifically, in the above step (a) sodium borohydride ($NaBH_4$) is used to selectively reduce only the ester group, P_4, protecting the carboxylic acid to obtain the primary alcohol compound, which in step (b) is then reacted with the G_1 compound corresponding to the portion G_1O of the compound of formula (5)-i.e., G_1 compound 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 $(CF_3(CF_2)_3SO_2)_2O$, in CH_2Cl_2 as the solvent in the presence of pyridine or trialkylamine to obtain the compound of formula (5). By way of example, when G_1O of the desired compound of formula (5) is triflate, the reaction is conducted using trifluoromethane sulfonic acid anhydride to obtain the compound of formula (5).

3. Preparation of the compound of formula (4)

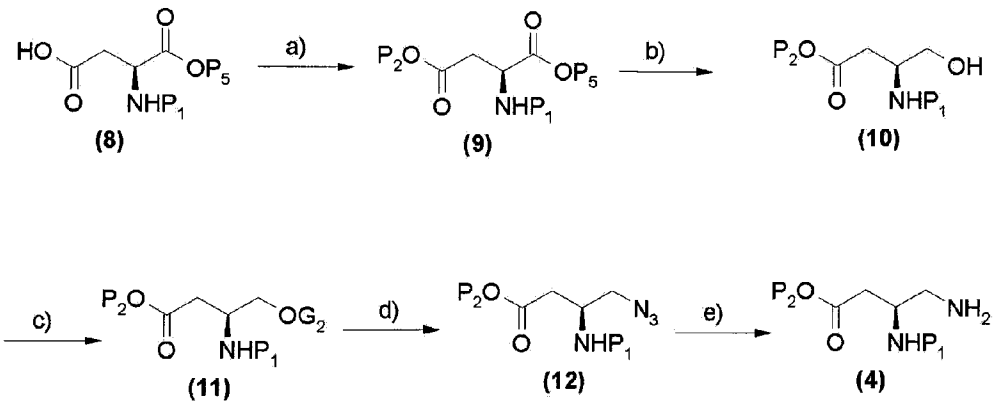
[0026] Meanwhile, the compound of formula (4) as the remaining one of the starting materials for preparing the compound of formula (2) can be prepared according to any one of the following methods.

[0027] The first method for preparing the compound of formula (4) comprises

(a) the step of converting a carboxylic acid group 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 an ester group P_5 present in the compound of formula (9) to obtain a compound of formula (10),
(c) the step of introducing a 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).

[0028] The first method for preparing the compound of formula (4) as described above comprises the procedures for introducing the amine group into the carbon atom to which the ester group is attached in the compound of formula (8) and can be represented as shown in the following reaction scheme 6.

Reaction Scheme 6



[0029] In the above scheme,

a is DMAP, Boc_2O (where P_2 is t-butyl group), and t-BuOH or THF;
b is $NaBH_4$, and MeOH or EtOH;
c is Tf_2O, MsCl, TsCl, $(CF_3(CF_2)_3SO_2)F$ or $(CF_3(CF_2)_3SO_2)_2O$ etc., pyridine or tri-alkylamine, CH_2Cl_2;
d is NaN_3, DMF or NMP or DMAc or DMAc/EtOAc or DMAc/H_2O or DMAc/ MeOH, heating;
e is selected from the conditions (1) H_2, Pd/C, MeOH or EtOH, (2) $NaBH_4$, Pd/C, MeOH, (3) PPh_3, H_2O, THF, and (4) trialkyl phosphine or trialkylphosphite, H_2O, THF;
P_5 is methyl group, ethyl group, i-propyl group or t-butyl group;

G_2 is together with oxygen a good leaving group including triflate, mesylate, tosylate, besylate, nonaflate, etc.;
P_1 and P_2 are as defined above.

[0030] In step (a) of said reaction, the carboxylic acid group of formula (8) is converted into the ester group by introducing P_2 to produce the compound of formula (9). In this reaction, t-BuOH or THF is used as the solvent, and a catalytic amount (0.5 mol% ~ 30 mol%) of 4-di(methylamino)pyridine (DMAP) is used. For example, if P_2 is introduced, when P_2 is t-butyl group, an equivalent of Boc_2O is used, and the reaction is conducted in the range between room temperature and about 40°C to obtain the desired ester compound of formula (9).

[0031] In step (b) of said reaction, the ester group which is originally present in the compound of formula (9)-i.e., the ester group present in the position of P_5-is selectively reduced with sodium borohyride ($NaBH_4$) to obtain the compound of formula (10) as the primary alcohol. In this reaction, methanol or ethanol is used as the solvent.

[0032] In step (c) of said reaction, the leaving group G_2O is introduced through reaction with trifluoromethane sulfonic acid anhydride (Tf_2O), trifluoromethane sulfonyl chloride (TfCl), methanesulfonyl chloride (MsCl), toluenesulfonyl chloride (TsCl), bromobenzenesulfonyl chloride (BsCl), $(CF_3(CF_2)_3SO_2)F$ or $(CF_3(CF_2)_3SO_2)_2O$, in CH_2Cl_2 as the solvent in the presence of pyridine or trialkylamine to obtain the compound of formula (11).

[0033] In step (d) of said reaction, the compound of formula (11) is reacted with 1.0 to 2.0 equivalents of sodium azide under warming condition (60°C to 80°C) to obtain the compound of formula (12).

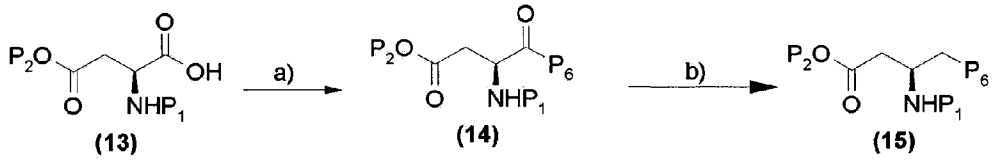
[0034] The azide group of the compound of formula (12) thus obtained can be converted into the amine group through hydrogenation reaction under various reaction conditions (e) to obtain the compound of formula (4).

[0035] Particularly, when P_1 is Boc, P_2 is i-propyl group or t-butyl group and G_2O is triflate or nonaflate, the compound of formula (4) can be obtained in a high yield.

[0036] The second method for preparation of the compound of formula (4) 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). This method can be represented as shown in the following reaction scheme 7.

Reaction Scheme 7



(13) (14) (15)

[0037] In the above scheme,

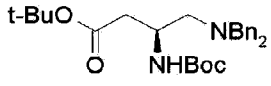
a is selected from the conditions (1) i-BuOCOCl, NMM (N-methylmorpholine), Bn_2NH or $BnNH_2$ or diallylamine or allylamine; and (2) i-BuOCOCl, NMM, diallylamine;
b is selected from the conditions (1) $Os(CO)_{12}$, $Ru(CO)_{12}$, $RuCl_2(CO)_2(PPh_3)_2$ or $RuH_2(CO)_2(PPh_3)_2$ as the reaction catalyst, Et_3SiH, toluene, reflux, (2) $RuH(CO)(PPh_3)_3$, $Ru_3(CO)_{12}$ or $RuCl(PPh_3)_3$ as the reaction catalyst, Ph_2SiH_2, PMHS (polydimethylsiloxane), THF or 2-Me THF, 1,4-dioxane, ethyl ether, toluene, (3) 9-BBN (9-Borabicyclo[3,3,1]nonane), THF, reflux, and (4) BH_3.DMS or BH_3.THF, toluene, heating;
P_6 is monobenzylamine or dibenzylamine or monoallylamine or diallylamine,
P_1 and P_2 are as defined above.

[0038] In step (a) of said reaction, the amide compound of formula (14) can be conveniently obtained by converting the carboxylic acid compound of formula (13) into the activated ester with the action of isobutyl chloroformate and a base, and then reacting with a secondary amine such as Bn_2NH, diallylamine, etc.

[0039] In step (b) of said reaction, the amide group of the amide compound of formula (14) can be reduced through various methods known in the relevant technical field to obtain the tertiary amine compound of formula (15). For example, the methods for converting amide group into amine have been known as follows: Method b-1: see, for example, Tetrahydron Lett. 2001, 42, 1945; Method b-2: see, for example, Tetrahydron Lett. 1998, 39, 1017; Method b-3: see, for example, Org. Lett. 1999, 1, 799, and Tetrahydron Lett. 1999, 40, 3673; Method b-3: see, for example, Bioorg. Med.

Chem. 2006, 14, 6586, and Chem. Eur. J. 2006, 12, 6910, and Synthesis 2005, 2281.

[0040] By way of example, in case of the compound of formula (14) where P_1 is Boc and P_2 is t-butyl, the desired compound of formula (15) can be obtained under various catalytic conditions of said b-1. In addition, the catalysts and conditions described in the above b-2 can be used to obtain the desired compound of formula (15). Particularly, when Ph_2SiH_2 is used under the catalyst $Ru_3(CO)_{12}$, the reaction can be conducted using 0.5 mol% ~ 30 mol% of $Ru_3(CO)$ and 5.0 equivalents of Ph_2SiH_2 in the presence of THF solvent at 80°C to obtain the desired compound of formula (15). The progress rate of the reduction under condition b-3 as defined above is somewhat low (maximum 25% progress rate). Under reaction condition b-4 as defined above, the best result in terms of the yield can be obtained when the reaction is conducted using 2.0 equivalents of BH_3.DMS in toluene solvent at 50°C (14: 15: 15a = 11.4: 61.2: 10.7). Among them, a compound of formula (15a) can be debenzylated by hydrogenation in the presence of Pd/C-based catalysts to obtain the compound of formula (4) as defined above.



(15a)

[0041] In reaction step (c), the compound of formula (15) can be debenzylated, for example, through debenzylation reaction using H_2 and Pd/C for benzyl protecting group or deaiylation reaction using $PdCl_2$/1,3-dimethylbarbituric acid to obtain the compound of formula (4).

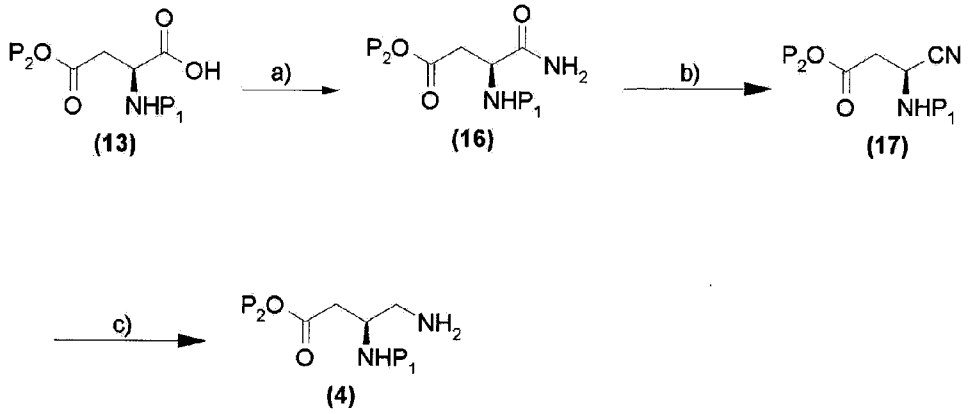
[0042] The third method for preparation of the compound of formula (4) comprises

(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 amide 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). This method can be represented as shown in the following reaction scheme 8.

Reaction Scheme 8



[0043] In the above scheme,

a is selected from the conditions (1) EtOCOCl, NMM, NH3(g), and (2) Boc_2O, NH_4HCO_3, pyridine, DMF;

b is selected from the conditions (1) $(CF_3CO)_2O$, Et_3N, and (2) cyanuric acid, DMF;

c is selected from the conditions (1) Pd/C, H_2, AcOH, 45 psi, (2) NiCl.$6H_2O$, $NaBH_4$, (3) CF_3CO_2H, $NaBH_4$, (4) PtO_2, H_2, AcOH, (5) PtO_2, H_2, EtOH, $CHCl_3$, (6) $Pd(OH)_2$, H_2, MeOH: AcOH (1:1) or AcOH:toluene (1:1), and (7) $Pd(OH)_2$, H_2, AcOH;

P_1 and P_2 are as defined above.

[0044] Specifically, in step (a) the carboxylic acid group of the starting compound of formula (13) is converted into the activated ester group using chloroformate or Boc_2O as an activating agent under the base condition and then reacted with a nitrogen source compound such as ammonia gas or ammonium salt (e.g., ammonium bicarbonate or ammonium

carbonate, etc.) to obtain the amide compound of formula (16). In this case, when in the compound of formula (13) P_1 is Boc and P_2 is i-propyl group or t-butyl group, the result of the reaction is preferable in terms of the yield.

[0045] In step (b), the amide group of the compound of formula (16) thus obtained is reacted with trifluoromethane sulfonic acid anhydride/Et_3N or cyanuric acid/DMF to obtain the compound of formula (17) having a nitrile group (-CN).

[0046] In step (c), hydrogenation can be conducted utilizing a metal selected from palladium, nickel(I) chloride, platinum(IV) oxide or palladium hydroxide to obtain the primary amine compound of formula (4).

[0047] The present invention is illustrated in further detail by means of the following Preparations and Examples. However, it is not intended that the scope of the present invention is limited in any manner by these Preparations and Examples.

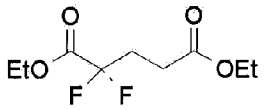
Advantageous Effects of Invention

[0048] The method of the present invention can produce the compound of formula (2) having high optical purity as the intermediate for preparing the compound of formula (1), which can be used as a medicine for treatment or prevention of diseases, including diabetes, caused by the action of dipeptidyl peptidase IV, with high optical purity.

Mode for the Invention

PREPARATION 1: Synthesis of diethyl 2.2-difluoropentanedioate

[0049]

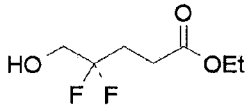


[0050] To a solution of ethyl bromodifluoroacetate (33.2 g) in tetrahydrofuran (94.0 g) was added ethyl acrylate (8.2 g) and copper powder (10.9 g). After heating to 50°C, TMEDA (9.5 g) was added dropwise and the reaction mixture was then stirred for 3 hours at the same temperature. Upon disappearance of ethyl acrylate as the starting material, to the reaction solution was added methyl t-butyl ether (MTBE, 73.7 g) followed by addition of 10% aqueous ammonium chloride solution (49.8 g) dropwise, and the mixture was then stirred for 30 minutes. The remaining copper residue was removed by filtration through a celite, and methyl t-butyl ether (MTBE, 66.3 g) was added to separate the layers. The separated organic layer was washed successively with 10% aqueous NH_4Cl solution (66.3 g) and 3 N aqueous hydrochloric acid solution (99.6 g) in order and then distilled under reduced pressure to obtain 55.0 g of the desired title compound.

[0051] ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J=7.2 Hz, 3H), 1.37 (t, J=7.2 Hz, 3H), 2.37-2.49 (m, 2H), 2.55 (t, J=7.2 Hz, 2H), 4.16 (q, J=7.2 Hz, 2H), 4.29 (q, J=7.2 Hz, 2H).

PREPARATION 2: Synthesis of ethyl 4,4-difluoro-5-hydroxypentanoate

[0052]

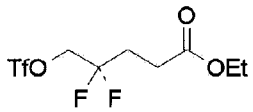


[0053] 14.8 g of the compound obtained from the above Preparation 1 was diluted with ethanol (20.4 g) and tetrahydrofuran (69.1 g) and then cooled to 0°C. To this solution was slowly added sodium borohydride ($NaBH_4$, 3.5 g) stepwise while keeping the internal temperature below 30°C. After confirming completion of the reaction by ^1H NMR, the reaction solution was cooled to the temperature of 10°C and 10% aqueous ammonium chloride solution (77.7 g) was slowly added. The remaining boron compound was filtered through celite, and the filtrate was distilled under reduced pressure to remove tetrahydrofuran. Then, ethyl acetate (105.2 g) was added to separate the layers, and the organic layer was distilled under reduced pressure to obtain 10.8 g of the title compound.

[0054] ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J=7.2 Hz, 3H), 2.15-2.29 (m, 2H), 2.49 (t, J=7.2 Hz, 2H), 3.69 (t, J=12.0 Hz, 2H), 4.12 (q, J=4.0 Hz, 2H).

EXAMPLE 1: Synthesis of ethyl 4,4-difluoro-5-{[(trifluoromethyl)sulfonyl]oxy}-pentanoate

[0055]

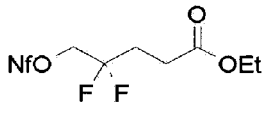


[0056] To the solution of 10.8 g of the compound, as obtained from the above Preparation 2, dissolved in dichloromethane (100.2 g) was added pyridine (7.0 g), and then the mixture was cooled to -5.0°C. After completion of cooling, trifluoromethane sulfonic acid anhydride (20.1 g) was slowly added dropwise while keeping the reaction temperature below 6.3°C. After stirring the reaction solution for 30 minutes, 1.5 N hydrochloric acid solution was added dropwise at 0°C to separate the layers. The aqueous layer as separated was back-extracted twice with dichloromethane (33.4 g), and the extracts were combined with the organic layer separated from the above and then distilled under reduced pressure to obtain 19.7 g of the title compound as a yellow oil.

[0057] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J=7.2 Hz, 3H), 2.29-2.39 (m, 2H), 2.59 (t, J=7.6 Hz, 2H), 4.18 (q, J=7.2 Hz, 2H), 4.55 (t, J=11.6 Hz, 2H).

EXAMPLE 2-1: Synthesis of ethyl 4,4-difluoro-5-{[(nonafluorobutyl)sulfonyl]-oxy}pentanoate

[0058]



Nf= $CF_3(CF_2)_3SO_2$

[0059] To the solution of 100.0 g of the compound, as obtained from the above Preparation 2, dissolved in dichloromethane (300.0 ml) was added pyridine (65.7 g), and the mixture was then cooled to -10.0°C. After completion of cooling, nonafluorobutane-sulfonic anhydride (477.4 g) was slowly added dropwise. After stirring the reaction solution for 3 hours, 1.0 N hydrochloric acid solution (300.0 ml) was added dropwise to separate the layers. The aqueous layer as separated was back extracted once with dichloromethane (500.0 ml), and the extracts were combined with the organic layer separated from the above and then distilled under reduced pressure to obtain 177.5 g of the title compound.

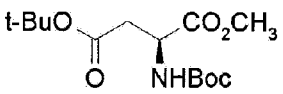
[0060] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, 3H, J=7.3 Hz), 2.30-2.36 (m, 2H), 2.58 (t, 2H, J=7.4 Hz), 4.16 (q, 2H, J=7.3 Hz), 4.57 (t, 2H, J=11 Hz).

EXAMPLE 2-2: Synthesis of ethyl 4,4-difluoro-5-{[(nonafluorobutyl)sulfonyl]-oxy}pentanoate

[0061] To the solution of 500.0 g of the compound, as obtained from the above Preparation 2, dissolved in dichloromethane (1000.0 ml) was added triethylamine (389.0 g), and the mixture was then cooled to 0°C. After completion of cooling, perfluorobutanesulfonyl chloride (948.80 g) was slowly added dropwise. The reaction solution was stirred for 3 hours at room temperature, distilled under reduced pressure, dissolved in methyl t-butyl ether (MTBE, 3000.0 ml) and then washed three times with water. The organic layer thus obtained was dehydrated with magnesium sulfate, filtered through a celite and then distilled under reduced pressure to obtain 960.0 g of the title compound.

EXAMPLE 3: Synthesis of methyl (2S)-2-[(tert-butoxycarbonyl)amino]-4-oxo-pentanoate

[0062]



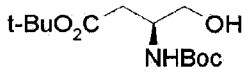
[0063] To 25.0 g of the starting material, (3S)-3-[(t-butoxycarbonyl)amino]-4-oxo-pentanoic acid, was added t-butanol (96.9 g) followed by the addition of Boc_2O (25.4 g) and dimethylaminopyridine (DMAP, 62.0 g, 0.5 mol%) at room temperature, and the reaction mixture was then stirred for 23 hours at 40°C. Upon completion of the reaction, ethylene

dichloride (62.3 g) in t-butanol was added, and the mixture was then distilled under reduced pressure to obtain 30.7 g of the title compound.

[0064] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.47 (s, 9H), 2.71 (dd, J=4.8, 16.4 Hz, 1H), 2.88 (dd, J=4.4, 16.4 Hz, 1H), 3.75 (s, 3H), 4.53 (m, 1H), 5.44 (br d, J=8.0 Hz, 1H).

EXAMPLE 4: Synthesis of tert-butyl (3S)-3-[(tert-butoxycarbonyl)aminol]-4-hydroxy-butanoate

[0065]

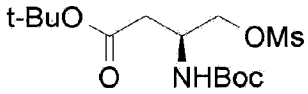


[0066] 30.7 g of the compound obtained from the above Example 3 was dissolved in ethanol (112.3 g) and, after lowering the internal temperature to 10.5°C sodium borohydride ($NaBH_4$, 5.7 g) was slowly added dropwise. This reaction solution was stirred while maintaining the temperature below 22°C. After confirming completion of the reaction by ^{1}H NMR and TLC, to the reaction solution was slowly added 3.0 N hydrochloric acid solution (30.7 g) dropwise at the internal temperature of 10°C followed by addition of diluted 0.2% hydrochloric acid solution (100.0 g). The reaction solution was adjusted to pH 3~4 with addition of 9.0% aqueous hydrochloric acid solution, and then back-extracted twice with ethyl acetate (100.0 g) and toluene (44.0 g). The organic layer thus obtained was distilled under reduced pressure to obtain 25.1 g of the title compound.

[0067] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.45 (s, 9H), 2.48-2.57 (m, 2H), 3.69 (d, J=4.9 Hz, 1H), 3.97 (m, 1H), 5.22 (bs, 1H).

EXAMPLE 5: tert-butyl (3S)-[(tert-butoxycarbonyl)amino]-4-[(methylsulfonyl)oxy]-butanoate

[0068]

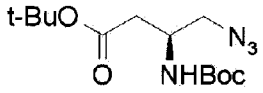


[0069] To 25.1 g of the compound obtained from the above Example 4 was added dichloromethane (133.0 g) and triethylamine (148.0 g), and the mixture was then cooled to 0°C. To this reaction solution was slowly added methanesulfonyl chloride (11.8 g) diluted with dichloromethane (39.9 g) dropwise for 50 minutes while maintaining the internal temperature below 12°C. After completion of the reaction, the reaction solution was washed with 0.5 N aqueous hydrochloric acid solution (120.0 g) and water (100.4 g), and then distilled under reduced pressure to obtain 31.5 g of the title compound.

[0070] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.46 (s, 9H), 2.62 (d, J=6.0 Hz, 2H), 3.04 (s, 3H), 4.21 (m, 1H), 4.30 (d, J=5.2 Hz, 2H), 5.16 (br d, J=7.2 Hz, 1H).

EXAMPLE 6: Synthesis of tert-butyl (3S)-4-azido-3-[(tert-butoxycarbonyl)amino]-butanoate

[0071]

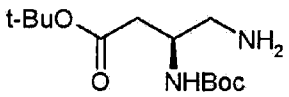


[0072] Sodium azide (NaN_3, 11.6 g) was diluted with dimethylacetamide (DMAc, 260.0 g). After elevating the internal temperature to 80°C, a solution of 31.5 g of the compound, as obtained from the above Example 5, diluted with dimethylacetamide (DMAc, 45.0 g) was added thereto. The reaction proceeded at 80°C for 2 hours. To the reaction solution were added toluene (251.0 g) and water (320.0 g) to separate the layers. The organic layer thus obtained was distilled under reduced pressure to obtain 24.0 g of the title compound.

[0073] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.49 (s, 9H), 2.49 (d, J=6.0 Hz, 2H), 3.44-3.55 (m, 2H), 4.09 (br s, 1H), 5.14 (br s, 1H).

EXAMPLE 7: Synthesis of tert-butyl (3S)-4-amino-3-[(tert-butoxycarbonyl)amino]-butanoate

[0074]

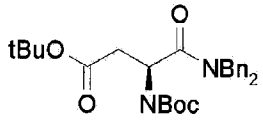


[0075] To 21.0 g of the compound obtained from the above Example 6 was added tetrahydrofuran (93.3 g) followed by the addition of triphenylphosphine (PPh_3, 21.0 g) at 40°C, the mixture was stirred for 2 hours at the same temperature, and water (3.8 g) was then added thereto. The reaction solution was distilled under reduced pressure, and the resulting triphenylphosphine oxide solid was diluted with toluene (26.0 g) and n-hexane (41.0 g), and then filtered off. The filtrate was adjusted to pH 2~3 with 1.0 N aqueous hydrochloric acid solution (110.0 g) and then subjected to separation of the layers. To remove any residual triphenylphosphine oxide solid, the aqueous layer obtained above was washed with dichloromethane (100.0 g) and then adjusted to pH 8~9 with 28% aqueous ammonia solution (7.6 g). The aqueous solution thus obtained was extracted with dichloromethane (100.0 g) and distilled under reduced pressure to obtain 8.5 g of the title compound as a white solid.

[0076] ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.45 (s, 9H), 2.45 (d, J=6.1 Hz, 2H), 2.77 (d, J=5.5 Hz, 2H), 3.87 (br s, 1H), 5.22 (br s, 1H).

EXAMPLE 8: Synthesis of N,N-dibenzyl-L-N(Boc)-aspartamide 4-tert-butyl ester

[0077]



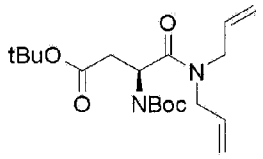
[0078] N-Boc-L-aspartic acid 4-t-butyl ester (29.0 g, 0.10 mol) was added to THF (200 ml). After cooling to temperature below -5°C, to the reaction solution was added isobutylchloroformate (13.0 ml, 0.10 mol) followed by addition of N-methyl morpholine (12.0 ml, 0.10 mol) dropwise, and the reaction mixture was stirred for over 30 minutes. To the reaction mixture was added dropwise dibenzylamine (21.1 ml, 0.11 mol), and the mixture was then stirred for over 3 hours and monitored for the reaction progress by TLC (EtOAc: Hexane=1:4). Upon completion of the reaction, the reaction solution was stirred with addition of ethyl acetate (300.0 mL) and 1 N hydrochloric acid to separate the layers, and distilled under reduced pressure to precipitate a solid. The solid was filtered and washed with ethyl acetate (100 ml), and then the washings were concentrated by distillation again under reduced pressure. The residue was then subjected to silica gel column to obtain the purified desired product (41.7 g, 0.89 mol).

[0079] ^1H NMR (400 MHz, $CDCl_3$) δ: 7.32 (m, 5H), 7.20 (m, 5H), 5.39 (d, J=7.2 Hz, 1H), 5.30 (m, 1H), 4.87-4.77 (m, 2H), 4.48-4.39 (m, 2H), 2.72 (dd, J=15.8 Hz, J=8.0 Hz, 1H), 2.56 (dd, J=15.8 Hz, J=6.4 Hz, 1H), 1.43 (s, 9H), 1.37 (s, 9H).

[0080] Mass (ESI, m/z): 491 (M+Na), 469 (M+H), 413 (M-55).

EXAMPLE 9: Synthesis of N, N-diallyl-L-N(Boc)-aspartamide 4-tert-butyl ester

[0081]



[0082] L-N(Boc)-aspartic acid 4-t-butyl ester (5.00 g, 17.3 mol) was added to THF (50 ml). After cooling to temperature below -5°C, to the reaction solution was added isobutylchloroformate (2.26 ml, 17.3 mol) followed by addition of N-methyl morpholine (1.90 ml, 17.3 mol) dropwise, and the reaction mixture was stirred for over 30 minutes. To the reaction mixture was added dropwise diallylamine (2.35 ml, 19.0 mol), and the mixture was then stirred for over 3 hours and

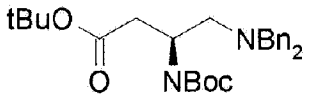
monitored for the reaction progress by TLC (EtOAc: Hexane=1:4). Upon completion of the reaction, the reaction solution was stirred with addition of ethyl acetate (60 ml) and 1 N hydrochloric acid and, after separating the layers, concentrated by distillation under reduced pressure. The residue was then subjected to silica gel column to obtain the purified desired product (6.0 g, 16.3 mol).

[0083] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.78 (m, 2H), 5.30 (m, 1H), 5.23-5.11 (m, 1H), 5.30 (m, 1H), 4.93 (m, 1H), 4.11-3.84 (m, 4H), 2.68 (dd, J=15.8 Hz, J=8.0 Hz, 1H), 2.51 (dd, J=15.8 Hz, J=8.0 Hz, 1H), 1.44 (s, 9H), 1.42 (s, 9H).

[0084] Mass (ESI, m/z): 391 (M+Na), 369 (M+H), 313 (M-55).

EXAMPLE 10: Synthesis of N,N-dibenzyl-4-amino-3(S)-N(Boc)-aminobutanoic acid 4-tert-butyl ester

[0085]



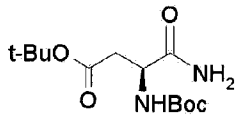
[0086] 10.0 g of the compound obtained from the above Example 8, $Ru_3(CO)_{12}$ (136 mg, 1mol%), and diphenylsilane (19.7 ml, 106.7 mmol) were added to tetrahydrofuran (50 ml), and the reaction solution was stirred under reflux for over 40 hours. The reaction solution was extracted with ethyl acetate (200 ml) and concentrated by distillation under reduced pressure. The residue was then subjected to silica gel column to obtain the purified desired product (4.7 g, 10.5 mmol).

[0087] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31-7.20 (m, 10H), 5.12 (bs, 1H), 3.90 (bs, 1H), 3.63 (d, J=12.0 Hz, 2H), 3.48 (d, J=12.0 Hz, 2H), 3.24 (m, 1H), 3.16 (bs, 1H), 2.42 (m, 2H), 1.81 (m, 1H), 1.59 (m, 9H), 1.46 (s, 9H), 1.06 (s, 9H).

[0088] Mass (ESI, m/z): 455 (M+H), 441 (M-13).

EXAMPLE 11: Synthesis of tert-butyl (3S)-4-amino-3-[(tert-butoxycarbonyl)amino]-4-oxobutanoate

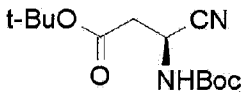
[0089]



[0090] 360.0 g of the starting material, N-Boc-Asp(O-t-Bu)OH, together with Boc_2O (353.0 g) and ammonium bicarbonate (NH_4HCO_3, 123.9 g) was added to dimethylformamide (1174.6 g), and pyridine (61.0 g) was added dropwise thereto at room temperature, and the reaction mixture was then stirred for about 3 hours. Upon completion of the reaction, water (1440 ml) and toluene (1800 ml) were added to the reaction solution and stirred for 30 minutes to separate the layers. The organic layer thus obtained was distilled under reduced pressure to remove t-butanol and toluene to obtain the title compound, which was directly used in the next reaction.

EXAMPLE 12: Synthesis of (S)-tert-butyl 3-(tert-butoxycarbonylamino)-3-cyanopropanoate

[0091]

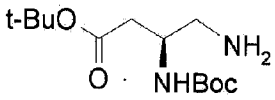


[0092] To the compound obtained from Example 11 was added dimethylformamide (1019.5 g) followed by addition of cyanuric chloride (112.0 g) dropwise for 1.5 hours at temperature below 25°C. The reaction solution was stirred for one hour at room temperature, and then 0.1 N aqueous sodium hydroxide solution (1850.0 g) and toluene (1860 ml) were added thereto to separate the layers. The organic layer thus obtained was washed once again with water (700 ml) and then distilled under reduced pressure to obtain 318.3 g of the title compound.

[0093] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.45 (s, 9H), 2.45 (d, J=6.1 Hz, 2H), 2.77 (d, J=5.5 Hz, 2H), 3.87 (br s, 1H), 5.22 (br s, 1H).

EXAMPLE 13: Synthesis of tert-butyl (3S)-4-amino-3-[(tert-butoxycarbonyl)amino]-butanoate

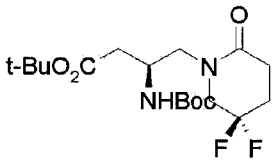
[0094]



[0095] To 212.1 g of the compound obtained from the above Example 12 was added acetic acid (4000 ml) followed by addition of 20 wt% $Pd(OH)_2$ (1.1 g) at 40°C. The mixture was stirred for 8 hours while keeping the internal temperature below 45°C and 3 atmospheric pressure of hydrogen. Upon completion of the reaction, the reaction solution was distilled under reduced pressure to remove acetic acid, diluted with toluene (640 L) and then filtered through a celite. To the filtrate was added 0.25 N aqueous hydrochloric acid solution (1060 ml) to separate the layers. The aqueous layer thus obtained was basified with aqueous ammonia solution (543.1 g) and then extracted with methyl t-butyl ether (MTBE, 1000 ml). The organic layer thus obtained was distilled under reduced pressure to obtain 185.0 g of the title compound.

EXAMPLE 14: Synthesis of 3-t-butoxycarbonylamino-4-(5,5-difluoro-2-oxo-piperidin-1-yl)-butyric acid t-butyl ester

[0096]

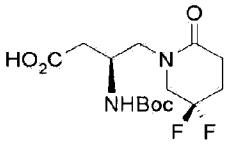


[0097] Triethylamine (13.2 g) was added to 16.0 g of the compound obtained from the above Example 1 or 2-1 or 2-2, and 14.1 g of the compound obtained from the above Example 7 or 13, and the mixture was then stirred for 21 hours at 40°C. Then, dichloromethane (154.8 g) and acetic acid (18.3 g) were added, and the mixture was stirred for 5 hours at room temperature. To the resulting reaction solution was added 0.5 N aqueous hydrochloric acid solution (116.8 g) and then, the mixture was stirred for 30 minutes to separate the layers. The organic layer thus obtained was distilled under reduced pressure to obtain 23.6 g of the title compound.

[0098] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.42 (s, 9H), 1.46 (s, 9H), 2.27 (m, 2H), 2.40-2.64 (m, 4H), 3.20 (dd, J=4.3, 13.5 Hz, 1H), 3.56-3.70 (m, 2H), 3.76-3.91 (m, 2H), 4.16 (m, 1H), 5.20 (d, J=8.6 Hz, 1H).

EXAMPLE 15: Synthesis of 3-t-butoxycarbonylamino-4-(5,5-difluoro-2-oxo-piperidin-1-yl)-butyric acid

[0099]



[0100] 23.6 g of the compound obtained from the above Example 14 was added to dichloromethane (20.0 g) followed by addition of H_3PO_4 (30.0 g), and the mixture was stirred for 16 hours at room temperature. After confirming the detachment of all of t-butyl group and t-butyloxycarbonyl group, the reaction solution was adjusted to pH 7.0~8.0 with 10 N aqueous hydrogen peroxide, and Boc_2O (16.0 g) was added thereto. After completion of the addition, 10 N aqueous hydrogen peroxide was used to maintain the pH of the reaction solution at 8.0~9.0. After stirring for 3 hours, the resulting sodium phosphate was filtered off, and the filtrate was then adjusted to pH 2.0~3.0 with 3.0 N aqueous hydrochloric acid solution. The resulting solid was filtered and dried under nitrogen to obtain 14.5 g of the title compound.

[0101] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (s, 9H), 2.20-2.43 (m, 6H), 3.26-3.31 (m, 2H), 3.61 (m, 1H), 3.81 (m, 1H), 4.02 (m, 1H), 6.73 (d, J=8.6 Hz, 1H), 12.16 (s, 1H).

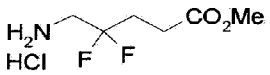
[0102] For the title compound resulting from the above, its enantiomeric isomers-i.e. S-form and R-form-were measured by HPLC (high-performance liquid chromatography), and an excess of the enantiomeric isomers (S vs. R form) (enan-

tiomeric excess; ee) was then calculated as being ee > 99%. On the other hand, in case of the Comparative Example prepared according to the prior method based on WO 06/104356, as described below, the excess (ee) of enantiomeric isomers (S vs. R form) was 80%. From this, it can be identified that the compound of formula (2) having an optically high purity could be obtained according to the method of the present invention.

COMPARATIVE EXAMPLE 1: Synthesis of 3-t-butoxycarbonylamino-4-(5,5-difluoro-2-oxo-piperidin-1-yl)-butyric acid t-butyl ester

COMPARATIVE EXAMPLE 1-1: Synthesis of methyl 5-amino-4,4-difluoro-pentanoate HCl

[0103]



[0104] To 10.0 g of the compound obtained from Example 1 was added 40 ml of anhydrous ammonia solution (7 M solution in methanol), and the mixture was stirred for 3 hours. The reaction solution was distilled and 30 ml of hydrochloric acid solution saturated with methanol was added dropwise thereto. The reaction mixture was stirred at room temperature and then distilled to obtain 7.2 g of the title compound as a white solid.

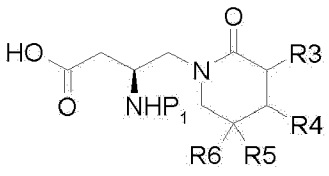
[0105] ^{1}H NMR (500 MHz, CD_3OD) δ: 2.35 (m, 2H), 2.59 (t, J=7.6 Hz, 2H), 3.49 (t, J=15.3 Hz, 2H), 3.68 (s, 3H).

COMPARATIVE EXAMPLE 1-2: Synthesis of 3-t-butoxycarbonylamino-4-(5,5-difluoro-2-oxo-piperidin-1-yl)-butyric acid t-butyl ester

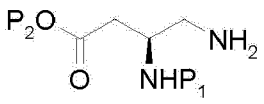
[0106] To the solution of the compound (1.93 g), as obtained from the above Example 4, dissolved in dichloromethane (20.0 g) and H_2O (4.0 g) were added NaBr (0.8 g) and TEMPO (11 mg, 1 mol%). To this reaction solution was slowly added a solution of 5% NaOCl (11.5 g) and $NaHCO_3$ (1.7 g) dissolved in H_2O (12.0 g) dropwise for about 2 hours while maintaining the temperature below 5°C. Upon completion of dropwise addition, the reaction solution was stirred for 30 minutes to separate the layers. To the organic layer thus obtained was added the compound (1.6 g) obtained from the above Comparative Example 1-1. After stirring for 15 minutes at room temperature, $NaBH(OAc)_3$ (2.23 g) was added to the reaction solution. After stirring for about 19 hours, 10% aqueous $NaHCO_3$ solution (20.0 g) and 0.5 N aqueous hydrochloric acid solution (20.0 g) were added dropwise to the reaction solution to separate the layers. The organic layer thus obtained was dehydrated under anhydrous $MgSO_4$ to obtain 2.0 g (yield 73%) of the same title compound as Example 14, as a yellow solid. For the title compound resulting from the above, its enantiomeric isomers-i.e., S-form and R-form-were measured by HPLC (high-performance liquid chromatography), and an excess (ee) of the enantiomeric isomers (S vs. R form) was then calculated as being ee = 80%.

Claims

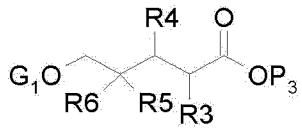
1. A method for preparation of a compound of formula (2) **characterized in that** a compound of formula (4) is reacted with a compound of formula (5):



(2)



(4)

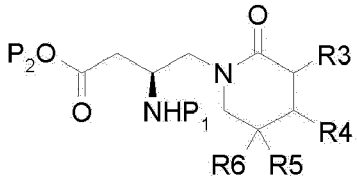


(5)

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.

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 or 2, **characterized in that** P_2 is t-butyl group, and P_3 is methyl or ethyl group.

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

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

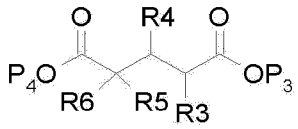
6. The method according to claim 2, **characterized in that** in step (a) C_1-C_4 trialkylamine is used as the base.

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

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), preferably wherein aqueous sodium hydroxide solution is used as the base.

9. The method according to claim 1, wherein the method further comprises:

(a) the step of reducing a compound of formula (7):



(7)

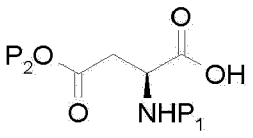
wherein R3, R4, R5, R6 and P_3 are as defined above in claim 1, and P_4 is benzyl group, methyl group, ethyl group, i-propyl group or t-butyl group, to obtain a primary alcohol compound; and
(b) the step of reacting the alcohol compound obtained from the above with a G_1 compound corresponding to the portion G_1O of the compound of formula (5) to obtain the compound of formula (5).

10. The method according to claim 9, **characterized in that** in step (a) the reduction is conducted using $NaBH_4$.

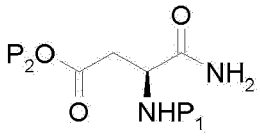
11. The method according to claim 9, **characterized in that** in step (b) the G_1 compound is selected from the group consisting of trifluoromethane sulfonic acid anhydride (Tf_2O), trifluoromethane sulfonyl chloride (TfCl), methanesulfonyl chloride (MsCl), toluenesulfonyl chloride (TsCl), bromobenzenesulfonyl chloride (BsCl), $(CF_3(CF_2)_3SO_2)F$ and $(CF_3(CF_2)_3SO_2)_2O$.

12. The method according to claim 1, wherein the method further comprises:

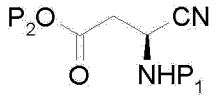
(a) the step of converting the carboxylic acid compound of formula (13) into an activated ester, which is then reacted with a nitrogen source compound to obtain an amide compound of formula (16),
(b) the step of reducing an amide group of the compound of formula (16) to obtain a nitrile compound of formula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

13. The method according to claim 12, **characterized in that** P_1 is Boc, and P_2 is i-propyl or t-butyl.

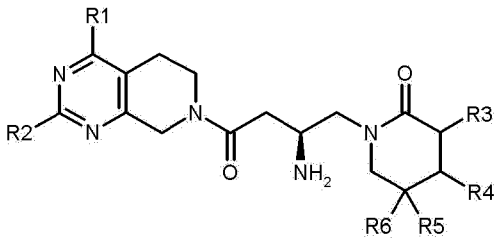
14. The method according to claim 12, **characterized in that** in step (a) chloroformate or Boc_2O is used as the activating agent.

15. The method according to claim 12, **characterized in that** the nitrogen source compound used in step (a) is ammonia gas or ammonium salt.

16. The method according to claim 12, **characterized in that** in step (b) the reduction is conducted using trifluoromethane sulfonic acid anhydride and Et_3N, or cyanuric chloride and DMF.

17. The method according to claim 12, **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, preferably wherein the hydrogenation is conducted using palladium hydroxide metal, acetic acid and hydrogen.

18. A method for preparation of a compound of formula (1):

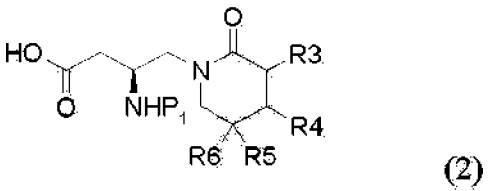


(1)

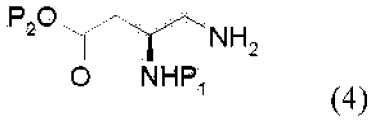
wherein R1 is hydrogen or CF_3, and
R2 is selected from the group consisting of hydrogen, substituted or unsubstituted C_1-C_{10} alkyl, substituted or unsubstituted C_3-C_{10} cycloalkyl, substituted or unsubstituted C_4-C_8 aryl, and substituted or unsubstituted C_3-C_7 heteroaryl,
comprising the method according to claim 1.

Patentansprüche

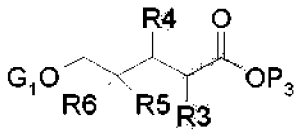
1. Verfahren zur Vorbereitung einer Verbindung der Formel (2), **dadurch gekennzeichnet, dass** eine Verbindung der Formel (4) mit einer Verbindung der Formel (5) umgesetzt wird:



(2)



(4)

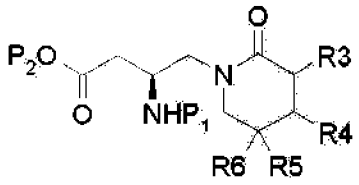


(5)

wobei jedes von R3, R4, R5 und R6 eigenständig Wasserstoff, Halogen oder substituiertes oder unsubstituiertes C_1-C_4-Alkyl ist, P_1 eine Aminschutzgruppe ist, jedes von P_2 und P_3 eigenständig Benzylgruppe, Methylgruppe, Ethylgruppe, i-Propylgruppe oder t-Butylgruppe ist und G_1O eine Abgangsgruppe ist.

2. Verfahren nach Anspruch 1, welches Folgendes umfasst:

(a) den Kupplungsreaktionsschritt durch Zugabe einer Base zu der Verbindung der Formel (4) und der Verbindung der Formel (5),
(b) den Zyklisierungsschritt durch Zugabe einer Säure, um eine Verbindung der Formel (2a) zu erhalten und
(c) den Schritt der Hydrolyse der sich ergebenden Verbindung der Formel (2a), um die Verbindung der Formel (2) zu erhalten:



(2a)

wobei R3, R4, R5, R6, P_1 und P_2 wie in Anspruch 1 definiert sind.

3. Verfahren nach Anspruch 1 oder 2, **dadurch gekennzeichnet, dass** P_2 t-Butylgruppe ist und P_3 Methyl- oder Ethylgruppe ist.

4. Verfahren nach Anspruch 1 oder 2, **dadurch gekennzeichnet, dass** G_1O Triflat, Mesylat, Tosylat, Besylat oder Nonaflat ist.

5. Verfahren nach Anspruch 1 oder 2, **dadurch gekennzeichnet, dass** R3 und R4 Wasserstoff, und R5 und R6 Fluor sind.

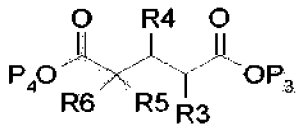
6. Verfahren nach Anspruch 2, **dadurch gekennzeichnet, dass** in Schritt (a) C_1-C_4-Trialkylamin als Base verwendet wird.

7. Verfahren nach Anspruch 2, **dadurch gekennzeichnet, dass** in Schritt (b) Essigsäure als Säure verwendet wird.

8. Verfahren nach Anspruch 2, **dadurch gekennzeichnet, dass** im Fall der Verbindung der Formel (2a), wobei P_1 Boc ist und P_2 t-Butyl ist, die Hydrolyse des genannten Schrittes (c) unter der Grundbedingung durchgeführt wird, selektiv nur P_2 unter den Schutzgruppen P_1 und P_2 zu entfernen, um die Verbindung der Formel (2) bereitzustellen, vorzugsweise wobei eine wässrige Natriumhydroxidlösung als Base verwendet wird.

9. Verfahren nach Anspruch 1, wobei das Verfahren ferner Folgendes umfasst:

(a) den Schritt der Reduktion einer Verbindung der Formel (7):



(7)

wobei R3, R4, R5, R6 und P_3 wie oben in Anspruch 1 definiert sind und P_4 Benzylgruppe, Methylgruppe, Ethylgruppe, i-Propylgruppe oder t-Butylgruppe ist, um eine primäre Alkoholverbindung zu erhalten, und
(b) den Schritt der Umsetzung der von den oben genannten erhaltenen Alkoholverbindung mit einer dem Teil G_1O der Verbindung der Formel (5) entsprechenden G_1-Verbindung, um die Verbindung der Formel (5) zu erhalten.

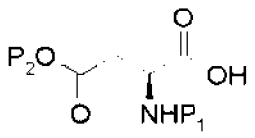
10. Verfahren nach Anspruch 9, **dadurch gekennzeichnet, dass** in Schritt (a) die Reduktion mit $NaBH_4$ durchgeführt wird.

11. Verfahren nach Anspruch 9, **dadurch gekennzeichnet, dass** in Schritt (b) die G_1-Verbindung aus der Gruppe bestehend aus Trifluormethansulfonsäureanhydrid (Tf_2O), Trifluonnethansulfonylchlorid (TfCl), Methansulfonylchlorid (MsCl), Toluolsulfonylchlorid (TsCl), Brombenzolsulfonylchlorid (BsCl), $(CF_3(CF_2)_3SO_2)F$ und $(CF_3(CF_2)_3SO_2)_2O$ ausgewählt wird.

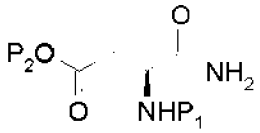
12. Verfahren nach Anspruch 1, wobei das Verfahren ferner Folgendes umfasst:

(a) den Schritt der Umwandlung der Carbonsäureverbindung der Formel (13) in einen aktivierten Ester, der anschließend mit einer Stickstoffquellen-Verbindung umgesetzt wird, um eine Amid-Verbindung der Formel (16) zu erhalten,

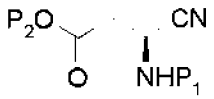
(b) den Schritt der Reduktion einer Amid-Gruppe der Verbindung der Formel (16), um eine Nitril-Verbindung der Formel (17) zu erhalten und
(c) den Schritt der Unterwerfung der Nitril-Verbindung der Formel (17) einer Hydrierungsreaktion, um die Verbindung der Formel (4) zu erhalten:



(13)



(16)



(17)

wobei P_1 und P_2 wie in Anspruch 1 definiert sind.

13. Verfahren nach Anspruch 12, **dadurch gekennzeichnet, dass** P_1 Boc ist und P_2 i-Propyl oder t-Butyl ist.

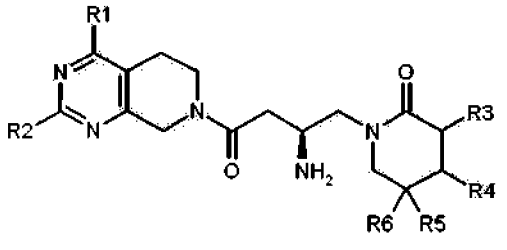
14. Verfahren nach Anspruch 12, **dadurch gekennzeichnet, dass** in Schritt (a) Chlorformiat oder Boc_2O als Aktivierungsmittel verwendet wird.

15. Verfahren nach Anspruch 12, **dadurch gekennzeichnet, dass** die in Schritt (a) verwendete Stickstoffquellen-Verbindung Ammoniakgas oder Ammoniumsalz ist.

16. Verfahren nach Anspruch 12, **dadurch gekennzeichnet, dass** in Schritt (b) die Reduktion mit Trifluormethansulfonsäureanhydrid und Et_3N, oder Cyanurchlorid und DMF durchgeführt wird.

17. Verfahren nach Anspruch 12, **dadurch gekennzeichnet, dass** in Schritt (c) die Hydrierung mit einem aus Palladium, Nickel(I)-Chlorid, Platin(IV)-Oxid und Palladiumhydroxid ausgewählten Metall durchgeführt wird, vorzugsweise wobei die Hydrierung mit Palladiumhydroxid-Metall, Essigsäure und Wasserstoff durchgeführt wird.

18. Verfahren zur Vorbereitung einer Verbindung der Formel (1):

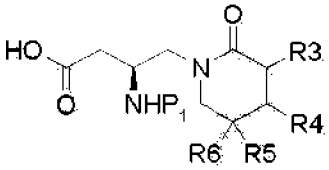


(1)

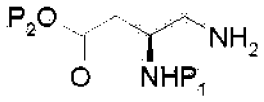
wobei R1 Wasserstoff oder CF_3 ist und
R2 aus der Gruppe bestehend aus Wasserstoff, substituiertes oder unsubstituiertes C_1-C_{10}-Alkyl, substituiertes oder unsubstituiertes C_3-C_{10}-Zykloalkyl, substituiertes oder unsubstituiertes C_4-C_8-Aryl und substituiertes oder unsubstituiertes C_3-C_7-Heteroaryl ausgewählt wird, das Verfahren nach Anspruch 1 umfassend.

Revendications

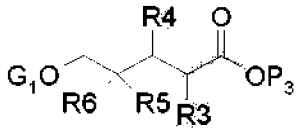
1. Procédé de préparation d'un composé de formule (2) **caractérisé en ce qu'**un composé de formule (4) est mis à réagir avec un composé de formule (5) :



(2)



(4)

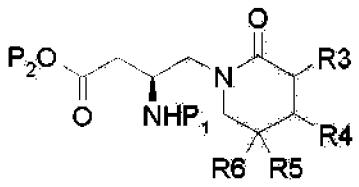


(5)

dans lesquels chaque groupe parmi R3, R4, R5 et R6 représente indépendamment un atome d'hydrogène, d'halogène ou un groupe alkyle en C_1 à C_4 substitué ou non substitué ; P_1 représente un groupe protecteur d'amine ; chaque groupe parmi P_2 et P_3 représente indépendamment un groupe benzyle, un groupe méthyle, un groupe éthyle, un groupe i-propyle ou un groupe t-butyle ; et G_1O représente un groupe partant.

2. Procédé selon la revendication1, qui comprend :

(a) l'étape de réaction de couplage par addition d'une base au composé de formule (4) et au composé de formule (5),
(b) l'étape de cyclisation par addition d'un acide pour obtenir un composé de formule (2a), et
(c) l'étape d'hydrolyse du composé résultant de formule (2a) pour obtenir le composé de formule (2) :



(2a)

dans lequel R3, R4, R5, R6, P_1 et P_2 sont tels que définis dans la revendication 1.

3. Procédé selon la revendication 1 ou 2, **caractérisé en ce que** P_2 représente un groupe t-butyle et P_3 représente un groupe méthyle ou éthyle.

4. Procédé selon la revendication 1 ou 2, **caractérisé en ce que** G_1O représente un groupe triflate, mésylate, tosylate, bésylate ou nonaflate.

5. Procédé selon la revendication 1 ou 2, **caractérisé en ce que** R3 et R4 représentent un atome d'hydrogène, et R5 et R6 représentent un atome de fluor.

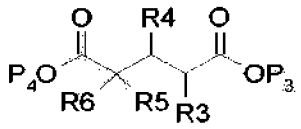
6. Procédé selon la revendication 2, **caractérisé en ce que** dans l'étape (a) un groupe trialkylamine en C_1 à C_4 est utilisé comme base.

7. Procédé selon la revendication 2, **caractérisé en ce que** dans l'étape (b) l'acide acétique est utilisé comme acide.

8. Procédé selon la revendication 2, **caractérisé en ce que** dans le cas du composé de formule (2a) dans lequel P_1 représente un groupe Boc et P_2 représente un groupe t-butyle, l'hydrolyse de ladite étape (c) est effectuée dans la condition basique pour enlever de manière sélective uniquement P_2 parmi les groupes de protection P_1 et P_2 pour donner le composé de formule (2), de préférence une solution aqueuse d'hydroxyde de sodium étant utilisée comme base.

9. Procédé selon la revendication 1, ledit procédé comprenant en outre :

(a) l'étape de réduction d'un composé de formule (7) :



(7)

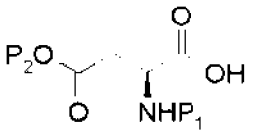
dans lequel R3, R4, R5, R6 et P_3 sont tels que définis ci-dessus dans la revendication 1 et P_4 représente un groupe benzyle, un groupe méthyle, une groupe éthyle, un groupe i-propyle ou un groupe t-butyle, pour obtenir un composé alcool primaire ; et
(b) l'étape de réaction du composé alcool obtenu à partir de ci-dessus avec un composé G_1 correspondant à la partie G_1O du composé de formule (5) pour obtenir le composé de formule (5).

10. Procédé selon la revendication 9, **caractérisé en ce que** dans l'étape (a) la réduction est effectuée en utilisant $NaBH_4$.

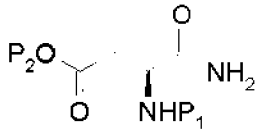
11. Procédé selon la revendication 9, **caractérisé en ce que** dans l'étape (b) le composé G_1 est choisi dans le groupe constitué par l'anhydride d'acide trifluorométhanesulfonique (Tf_2O), le chlorure de trifluorométhanesulfonyle (TfCl), le chlorure de méthanesulfonyle (MsCl), le chlorure de toluènesulfonyle (TsCl), le chlorure de bromobenzènesulfonyle (BsCl), $(CF_3(CF_2)_3SO_2)F$ et $(CF_3(CF_2)_3SO_2)_2O$.

12. Procédé selon la revendication 1, ledit procédé comprenant en outre :

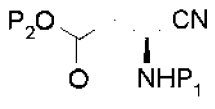
(a) l'étape de conversion du composé acide carboxylique de formule (13) en ester activé, qui est ensuite mis à réagir avec un composé source d'azote pour obtenir un composé amide de formule (16),
(b) l'étape de réduction d'un groupe amide du composé de formule (16) pour obtenir un composé nitrile de formule (17), et
(c) l'étape de soumission du composé nitrile de formule (17) à une réaction d'hydrogénation pour obtenir le composé de formule (4) :



(13)



(16)



(17)

dans lesquels P_1 et P_2 sont tels que définis dans la revendication 1.

13. Procédé selon la revendication 12, **caractérisé en ce que** P_1 représente un groupe Boc et P_2 représente un groupe i-propyle ou t-butyle.

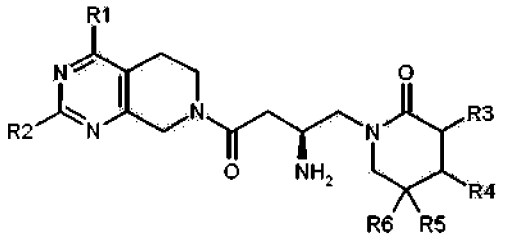
14. Procédé selon la revendication 12, **caractérisé en ce que** dans l'étape (a) le chloroformate ou le Boc_2O est utilisé comme agent activateur.

15. Procédé selon la revendication 12, **caractérisé en ce que** le composé source d'azote utilisé dans l'étape (a) est l'ammoniac gazeux ou le sel d'ammonium.

16. Procédé selon la revendication 12, **caractérisé en ce que** dans l'étape (b) la réduction est effectuée en utilisant de l'anhydride d'acide trifluorométhanesulfonique et de l'Et_3N, ou du chlorure cyanurique et du DMF.

17. Procédé selon la revendication 12, **caractérisé en ce que** dans l'étape (c) l'hydrogénation est effectuée en utilisant un métal choisi parmi le palladium, le chlorure de nickel(I), l'oxyde de platine(IV) et l'hydroxyde de palladium, de préférence ladite hydrogénation étant effectuée en utilisant du métal d'hydroxyde de palladium, de l'acide acétique et de l'hydrogène.

18. Procédé de préparation d'un composé de formule (1) :



(1)

dans lequel R1 représente un atome d'hydrogène ou un groupe CF_3, et
R2 est choisi dans le groupe constitué par un atome d'hydrogène, un groupe alkyle en C_1 à C_{10} substitué ou non substitué, un groupe cycloalkyle en C_3 à C_{10} substitué ou non substitué, un groupe aryle en C_4 à C_8 substitué ou non substitué et un groupe hétéroaryle en C_3 à C_7 substitué ou non substitué, comprenant le procédé selon la revendication 1.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO 06104356 A **[0002] [0003] [0021] [0102]**

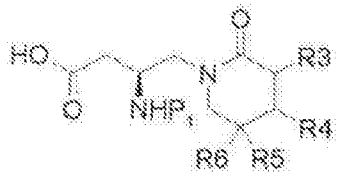
Non-patent literature cited in the description

- *Tetrahydron Lett.,* 2001, vol. 42, 1945 **[0039]**
- *Tetrahydron Lett.,* 1998, vol. 39, 1017 **[0039]**
- *Org. Lett.,* 1999, vol. 1, 799 **[0039]**
- *Tetrahydron Lett.,* 1999, vol. 40, 3673 **[0039]**
- *Bioorg. Med. Chem.,* 2006, vol. 14, 6586 **[0039]**
- *Chem. Eur. J.,* 2006, vol. 12, 6910 **[0039]**
- *Synthesis,* 2005, 2281 **[0039]**

INTERMEDIER-VEGYÜLET ELŐÁLLÍTÁSI ELJÁRÁSA GYÓGYSZER SZINTÉZISE CÉLJÁBÓL

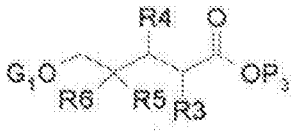
Szabadalmi igénypontok

1. Eljárás egy (2) képletű vegyület előállítására, **azzal jellemezve, hogy** egy (4) képletű vegyület van reagáltatva egy (5) képletű vegyülettel:



(2)

(4)



(5)

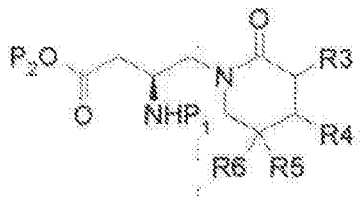
ahol R3, R4, R5 és R6 közül mindegyik jelentése egymástól függetlenül hidrogén, halogén, vagy szubsztituált vagy szubsztituálatlan C_1-C_6-alkil; P_1 jelentése egy amin-védőcsoport (angolul: „amine-protecting group"); P_2 és P_3 közül mindegyik jelentése egymástól függetlenül benzil-csoport, metil-csoport, etil-csoport, i-propil-csoport vagy t-butil-csoport; és G_1O jelentése egy távozó-csoport (leváló-csoport, angolul: „leaving group").

2. Eljárás az 1. igénypont szerint, amely magában foglalja a következőket:

   (a) a lépést, amely összekapcsolási reakcióból áll azáltal, hogy egy bázis van hozzáadva a (4) képletű vegyülethez és az (5) képletű vegyülethez,

   (b) a lépést, amely ciklizációból (angolul: „cyclization") áll azáltal, hogy egy sav van hozzáadva, hogy legyen előállítva egy (2a) képletű vegyület, és

   (c) a lépést, amely a kapott (2a) képletű vegyület hidrolíziséből áll, hogy legyen előállítva a (2) képletű vegyület:



(2a)

ahol R3, R4, R5, R6, P_1 és P_2 jelentése az 1. igénypontban meghatározottak szerinti.

3. Eljárás az 1. vagy 2. igénypont szerint, **azzal jellemezve, hogy** P_2 jelentése t-butil-csoport és P_3 jelentése metil-csoport vagy etil-csoport.

4. Eljárás az 1. vagy 2. igénypont szerint, **azzal jellemezve, hogy** G_1O jelentése triflát, mezilát, tozilát, bezilát vagy nonaflát.

5. Eljárás az 1. vagy 2. igénypont szerint, **azzal jellemezve, hogy** R3 és R4 jelentése hidrogén, és R5 és R6 jelentése fluor.

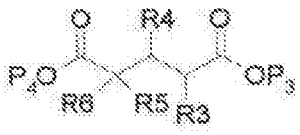
6. Eljárás a 2. igénypont szerint, **azzal jellemezve, hogy** az (a) lépésben C_1-C_4-trialkil-amin van alkalmazva a bázisként.

7. Eljárás a 2. igénypont szerint, **azzal jellemezve, hogy** a (b) lépésben ecetsav van alkalmazva a savként.

8. Eljárás a 2. igénypont szerint, **azzal jellemezve, hogy** a (2a) képletű vegyületnek az esetében, ahol P_1 jelentése Boc és P_2 jelentése t-butil, a nevezett (c) lépés szerinti hidrolízis azon alapfeltétel alatt van megvalósítva, hogy szelektív módon csak a P_2 legyen eltávolítva a P_1 és P_2 védőcsoportok közül, hogy rendelkezésre álljon (adva legyen) a (2) képletű vegyület, előnyösen ahol vizes nátrium-hidroxid oldat van alkalmazva a bázisként.

9. Eljárás az 1. igénypont szerint, ahol az eljárás továbbá magában foglalja a következőket:

   (a) a lépést, amely egy (7) képletű vegyület redukciójából áll:



(7)

   ahol R3, R4, R5, R6 és P_3 jelentése fennebb, az 1. igénypontban meghatározottak szerinti és P_4 jelentése benzil-csoport, metil-csoport, etil-csoport, i-propil-csoport vagy t-butil-csoport, hogy legyen előállítva egy primer alkohol-vegyület; és

   (b) a lépést, amely abból áll, hogy a fennebb megnevezettek szerint előállított alkohol-vegyület reagáltatva van egy G_1-vegyülettel, amely megfelel az (5) képletű vegyületnek a G_1O-részének, hogy legyen előállítva az (5) képletű vegyület.

10. Eljárás a 9. igénypont szerint, **azzal jellemezve, hogy** az (a) lépésben a redukció $NaBH_4$ alkalmazásával van megvalósítva.

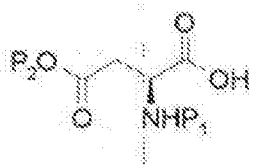
11. Eljárás a 9. igénypont szerint, **azzal jellemezve, hogy** a (b) lépésben a G_1-vegyület a következőkből álló csoportból van választva: trifluor-metán-szulfonsav-anhidrid (Tf_2O), trifluor-metán-szulfonil-klorid (TfCl), metán-szulfonil-klorid (MsCl), toluol-szulfonil-klorid (TsCl), bróm-benzol-szulfonil-klorid (BsCl), $(CF_3(CF_2)_3SO_2)F$ és $(CF_3(CF_2)_3SO_2)_2O$.

12. Eljárás az 1. igénypont szerint, ahol az eljárás továbbá magában foglalja a következőket:

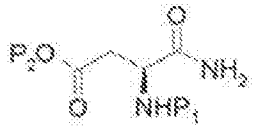
   (a) a lépést, amely abból áll, hogy a (13) képletű karbonsav-vegyület egy aktivált észterré van átalakítva, amely ezt követően reagáltatva van egy nitrogén-eredetű vegyülettel (angolul: „nitrogen source compound"), hogy legyen előállítva egy (16) képletű amid-vegyület,

   (b) a lépést, amely abból áll, hogy a (16) képletű vegyület egy amid-csoportja van redukálva, hogy legyen előállítva egy (17) képletű nitril-vegyület, és

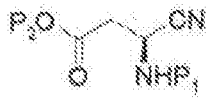
   (c) a lépést, amely abból áll, hogy a (17) képletű nitril-vegyület hidrogénezési reakciónak van alávetve, hogy legyen előállítva a (4) képletű vegyület:



(13)



(16)



(17)

ahol P_1 és P_2 jelentése az 1. igénypontban meghatározottak szerinti.

13. Eljárás a 12. igénypont szerint, **azzal jellemezve, hogy** P_1 jelentése Boc és P_2 jelentése i-propil vagy t-butil.

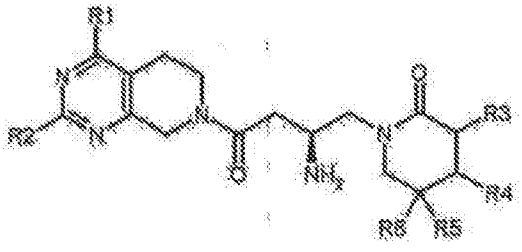
14. Eljárás a 12. igénypont szerint, **azzal jellemezve, hogy** az (a) lépésben klór-formiát vagy Boc_2O van alkalmazva az aktiváló szerként.

15. Eljárás a 12. igénypont szerint, **azzal jellemezve, hogy** az (a) lépésben alkalmazott nitrogén-eredetű vegyület a következő: ammóniagáz vagy ammóniumsó.

16. Eljárás a 12. igénypont szerint, **azzal jellemezve, hogy** a (b) lépésben a redukció trifluor-metán-szulfonsav-anhidrid és Et_3N, vagy cianur-klorid és DMF alkalmazásával van megvalósítva.

17. Eljárás a 12. igénypont szerint, **azzal jellemezve, hogy** a (c) lépésben a hidrogénezés egy fém alkalmazásával van megvalósítva, amely a következők közül van választva: palládium, nikkel(I)-klorid, platina(IV)-oxid és palládium-hidroxid, előnyösen ahol a hidrogénezés a következők alkalmazásával van megvalósítva: palládium-hidroxid-fém, ecetsav és hidrogén.

18. Eljárás egy (1) képletű vegyület előállítására:



(1)

ahol R1 jelentése hidrogén vagy CF_3, és

R2 jelentése a következőkből álló csoportból van választva: hidrogén, szubsztituált vagy szubsztituálatlan C_1-C_{10}-alkil, szubsztituált vagy szubsztituálatlan C_3-C_{10}-cikloalkil, szubsztituált vagy szubsztituálatlan C_4-C_8-aril és szubsztituált vagy szubsztituálatlan C_3-C_7-heteroaril,

ahol az magában foglalja z 1. igénypont szerinti eljárást.