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(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF DIAZABICYCLOOCTANDERIVATER OG MELLEMPRODUKTER**

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WO-A1-2012/172368

DESCRIPTION

TECHNICAL FIELD

[0001] The present invention relates to a process for producing a diazabicyclooctane derivative represented by Formula (IV) and intermediates thereof.

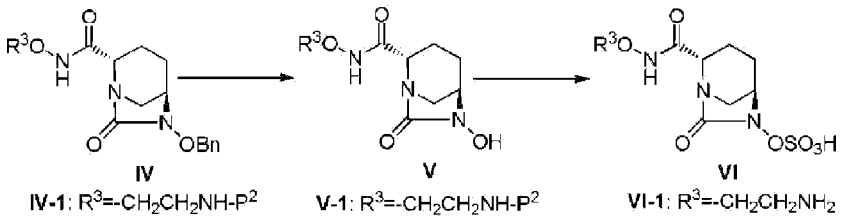
BACKGROUND ART

[0002] JP-B-4515704 indicates a novel heterocyclic compound, a production process thereof, and the medicinal use thereof, and discloses as a typical example of a compound thereof trans-7-oxo-6-(sulfooxy)- 1,6-diazabicyclo [3.2.1]octane-2-carboxamide (NXL104). Production processes of an intermediate in the form of a specific piperidine derivative are also indicated in JP-A-2010-138206 and JP-A-2010-539147 (Translation of PCT Application), while a production process of NXL104 and crystalline forms thereof is disclosed in WO 2011/042560.

[0003] In addition, JP-B-5038509 indicates (2S,5R)-7-oxo-N-(piperidin-4-yl)-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxa mide (MK-7655), while a production process of a specific piperidine derivative and MK7655 are disclosed in JP-A-2011-207900 and WO 2010/126820.

[0004] The inventors of the present invention also disclose novel diazabicyclooctane derivatives represented by Formulae (IV), (V) and (VI) and a production process thereof, and particularly a process for producing a compound of the following Formula (VI-1) in the following Scheme 1 in JP-A-2012-122603:

Scheme 1



IV

IV-1: R^3=-CH_2CH_2NH-P^2

V

V-1: R^3=-CH_2CH_2NH-P^2

VI

VI-1: R^3=-$CH_2CH_2NH_2$

(wherein OBn is benzyloxy, P^2 is tert-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz), and R^3 is same as will be subsequently described).

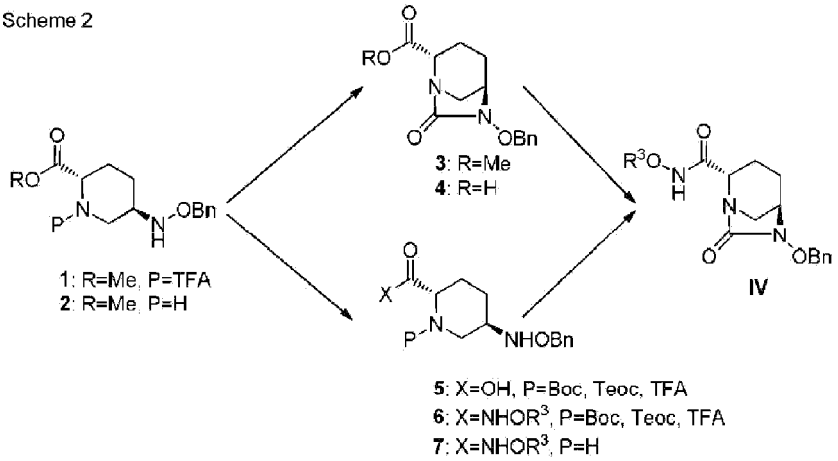
SUMMARY OF THE INVENTION

Problems to be Solved by the Invention

[0005] The inventors of the present invention previously disclosed a process that proceeds

from a compound of Formula (3) through a compound of Formula (4) and a process that proceeds from a compound of Formula (5) through a compound of Formula (6) and a compound of Formula (7) in the following Scheme 2 as a process for producing the aforementioned compound of Formula (IV), and particularly a compound of Formula (IV-1), but during the course of studying a process for enlarging the production scale of the development candidate, the processes were shown to not necessarily be industrially optimal process for reasons that, in addition to the former having only a moderate yield when proceeding from a compound of Formula (2) to the compound of Formula (3) and from the compound of Formula (3) to the compound of Formula (4), synthesis of the compound of Formula (IV) from the compound of Formula (4) did not have a satisfactory yield due to low reactivity attributed to steric hindrance of the environment surrounding the carboxyl group as well as purification loss during removal of byproduct, while the latter had low yield from the compound of Formula (7) to the compound of Formula (IV), and results in increased production costs due to the introduction of an R^3O-NH side chain early in the process:

Scheme 2

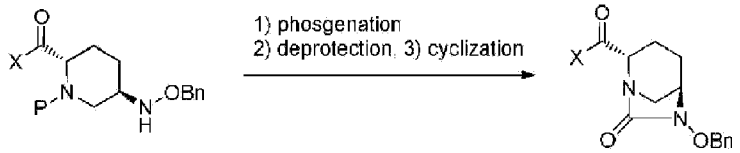


(wherein OBn is benzyloxy, TFA is 2,2,2-trifluoroacetyl, Boc is tert-butoxycarbonyl, Teoc is 2-trimethylsilylethoxycarbonyl, and R^3 is same as will be subsequently described).

[0006] While intramolecular ureation was attempted after using an active group as X of the compound of the aforementioned Formula (5) and deprotecting, the active group also ended up being removed under the conditions used for deprotection, or only a complex mixture was obtained due to the occurrence of decomposition caused by an intermolecular reaction occurring under the conditions of phosgenation. In addition, although an attempt was made to isolate an intermediate introduced with an active group from the compound of the aforementioned Formula (4), the desired compound was able to be obtained only in a moderate yield due to the low reactivity of the compound of Formula (4). Next, phosgenation, deprotection and then cyclization reaction were attempted on a compound of Formula (8) or a compound of Formula (9) in the following Scheme 3 as a preliminary study conducted for the purpose of obtaining the compound of Formula (IV) without proceeding from the compound of the aforementioned Formula (6) through the compound of Formula (7). As a result, although a compound of Formula (10) was able to be derived from the compound of Formula (8) without any problems without having to add an activating agent such as 4-dimethylaminopyridine during cyclization reaction, the desired compound of Formula (11) was indicated to be unable to be obtained at all from the compound of Formula (9).

[0007] With the foregoing in view, the inventors of the present invention conducted extensive studies on a novel and efficient process for producing a compound of the aforementioned Formula (IV) with the aim of developing a process for producing a compound of Formula (VI) industrially.

Scheme 3



8: X=NHBn, P=Boc
9: X=NHOBn, P=Boc

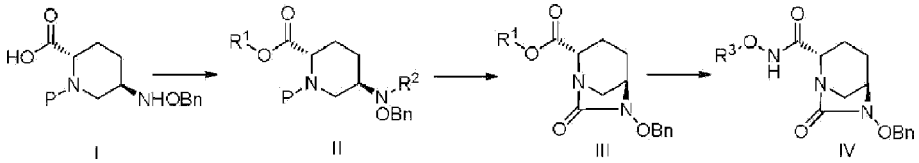
10: X=NHBn
11: X=NHOBn

(In the above formulas, OBn is benzyloxy, and Boc is tert-butoxycarbonyl.)

Means for Solving the Problems

[0008] The present inventors introduced various active groups employed in peptide synthesis for R^1 into the carboxyl group of a compound of Formula (I) of the following Scheme 4 instead of direct activation of the less reactive carboxyl group of the compound of the aforementioned Formula (4), and examined a synthetic process that goes through a compound of Formula (III) to a compound of Formula (IV). In particular, in the case of a compound having a 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl group as R^1 of Formula (II), the present inventors found that a protecting group P is selectively deprotected without having an effect on the active group under mildly acidic conditions following phosgenation, that the reaction subsequently proceeds continuously through the cyclization reaction by treating the reaction solution with a base, and that a compound of Formula (III) is obtained in a satisfactory yield. Moreover, the present inventors succeeded in deriving the compound of Formula (IV) without producing byproduct and in high yield by directly reacting the resulting compound of Formula (III) with R^3ONH_2 than the process that goes through the compound of the aforementioned Formula (4):

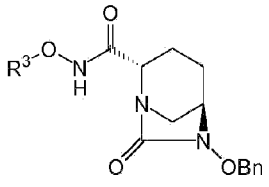
Scheme 4



I II III IV

(wherein P is an NH protecting group capable of being removed with an acid, R^1 is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl, R^2 is hydrogen, ClCO- or Cl_3COCO- and R^3 is same as will be subsequently described).

[0009] Hence, in one aspect the present invention relates to a process for r producing a compound of formula (IV):



(IV)

wherein

OBn
: is benzyloxy, and

R^3
: is C_{1-6}-alkyl or heterocyclyl, or forms a 3- to 7-membered heterocyclic ring together with the adjacent -O-NH-,

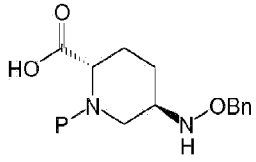
R^3 may be modified with 0-5 groups R^4 selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfonyl, heterocyclyl, heterocyclylcarbonyl, $R^5(R^6)N$- and a protecting group; and R^4 may be consecutively substituted ;

R^5 and R^6 each independently is H or C_{1-6} alkyl or together form a 3- to 7-membered heterocyclic ring;

and further, R^3, R^5 and R^6 can undergo ring closure at an arbitrary position;

comprising:

1. (i) reacting a compound of formula (I) wherein P is an NH protecting group capable of being removed with acid:

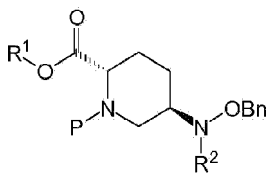


(I)

with R^1OH wherein

R^1
: is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2.6}$]dec-8-en-4-yl, followed by

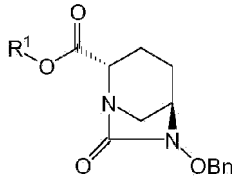
2. (ii) allowing a carbonylating agent selected from phosgene, diphosgene and triphosgene to act thereon to obtain a compound of formula (II) wherein R^2 is ClCO- or Cl_3COCO-,



(II),

3. (iii) removing the protecting group P and treating with a base to obtain a compound of

formula (III):

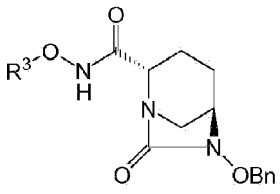


(III),

and

4. (iv) reacting with a compound R^3ONH_2 wherein R^3 is as defined above to produce the compound (IV).

[0010] In another aspect, the invention provides a process for producing a compound of formula (IV):



(IV)

wherein

OBn

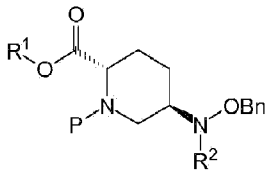
is benzyloxy, and

R^3

is C_{1-6}-alkyl or heterocyclyl, or forms a 3- to 7-membered heterocyclic ring together with the adjacent -O-NH-, R^3 may be modified with 0-5 groups R^4 selected from C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfonyl, heterocyclyl, heterocyclylcarbonyl, $R^5(R^6)N$- and a protecting group; and R^4 may be consecutively substituted ; R^5 and R^6 each independently is H or C_{1-6} alkyl or together form a 3- to 7-membered heterocyclic ring; and further, R^3, R^5 and R^6 can undergo ring closure at an arbitrary position;

comprising:

(ii) allowing a carbonylating agent selected from phosgene, diphosgene and triphosgene to act on a compound of formula (II),



(II)

wherein

R^1

is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-

dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl,

R^2

is H, and

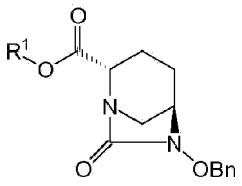
P

is an NH protecting group capable of being removed with acid;

followed by

(iii) removing the protecting group P, treating with a base and further reacting with a compound R^3ONH_2 wherein R3 is as defined above, to produce the compound of formula (IV).

[0011] In yet another aspect the invention provides a process for producing a compound of formula (III)



(III)

wherein

OBn

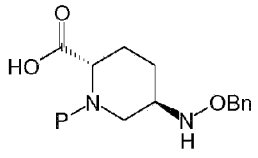
is benzyloxy, and

R^1

is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl,

comprising

1. (i) reacting a compound of formula (I), wherein P is an NH protecting group capable of being removed with acid:



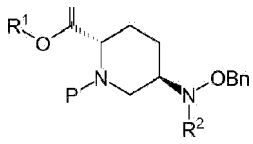
(I)

with R'OH wherein

R^1

is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl,

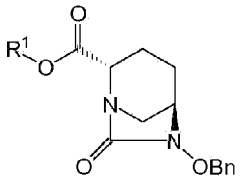
2. (ii) allowing a carbonylating agent selected from phosgene, diphosgene and triphosgene to act thereon to obtain a compound of formula (II) wherein R^2 is ClCO- or Cl_3COCO-:



(II),

3. (iii) removing the protecting group P and treating with a base to produce the compound of formula (III).

[0012] In yet a further aspect, the invention provides a process for producing a compound of Formula (III)



(III)

wherein

OBn

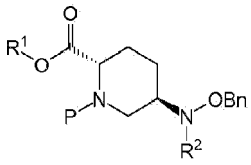
is benzyloxy, and

R^1

is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl,

comprising

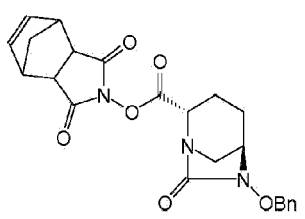
(ii) allowing a carbonylating agent selected from phosgene, diphosgene and triphosgene to act on a compound of formula (II), wherein R^2 is H and P is an NH protecting group capable of being removed with acid:

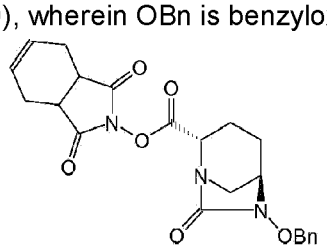


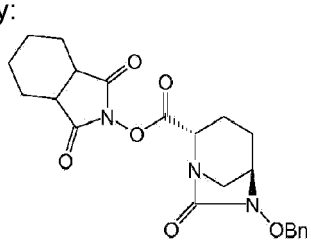
(II)

(iii) followed by removing the protecting group P and treating with a base to produce the compound of formula (III).

[0013] Also, the present invention provides a compound selected from the compounds of formulae (III-58) to (III-60), wherein OBn is benzyloxy:

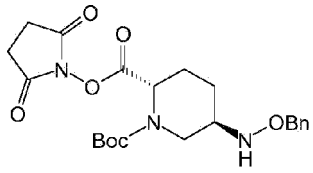




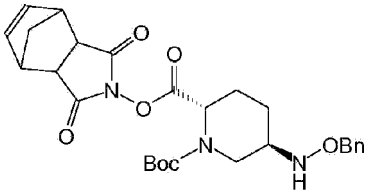


(III-58) (III-59) (III-60)

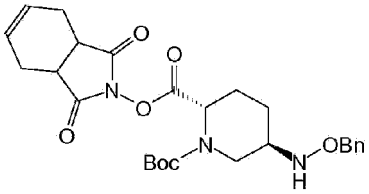
[0014] Even further, the present invention provides a compound selected from the compounds of formulae (II-30) to (II-33), wherein Boc is tert-butoxycarbonyl and OBn is benzyloxy:



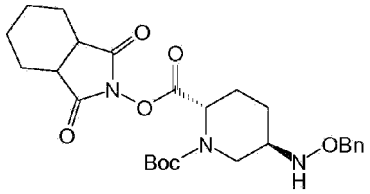
(II-30)



(II-31)



(II-32)



(II-33)

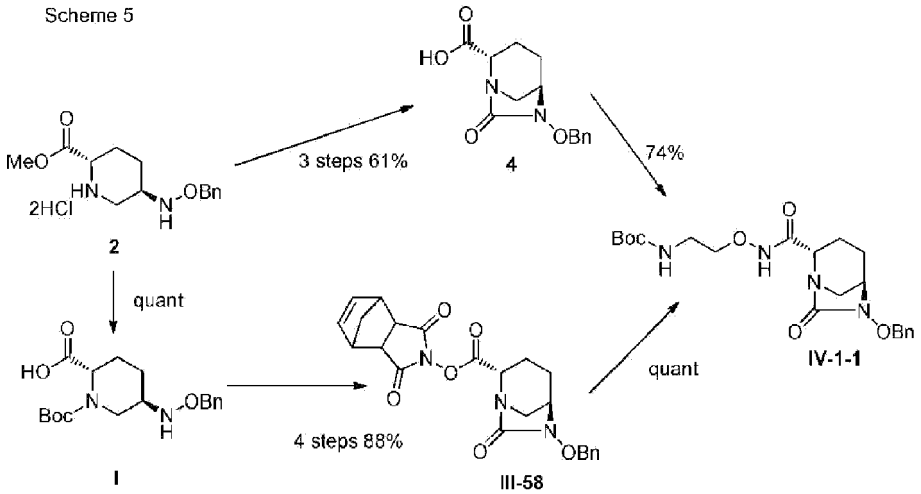
[0015] Preferred embodiments of the invention are as defined in the appended dependent claims and/or in the the following detailed description.

Effects of the Invention

[0016] The present production process is a process for efficiently obtaining a compound of the aforementioned Formula (IV) both more easily and in higher yield than by going through a compound of Formula (2) to a compound of Formula (4) of the aforementioned Scheme 2. The carboxyl group of the compound of the aforementioned Formula (I) can be more easily modified than the carboxyl group of a compound of Formula (4). Intramolecular ureation of a compound of Formula (II) easily proceeds in higher yield than a compound of Formula (2). In the reaction between the carboxyl group of the compound of the aforementioned Formula (4) and the R^3ONH_2 group, although a large amount of byproducts were formed and a satisfactory yield was unable to be obtained due to steric hindrance of the environment surrounding the carboxyl group even if carried out using a commonly employed dehydration condensation agent or mixed acid anhydride method, since an intermediate in the form of a compound of the aforementioned Formula (III) has an active ester, it is a highly versatile compound that enables the compound of the aforementioned Formula (IV) to be derived more selectively and directly. In particular, instead of going through the compound of Formula (4), the compound of the aforementioned Formula (III-58) can be obtained in high yield by continuously synthesizing from the compound of Formula (I) that is quantitatively obtained from the compound of Formula (2) without isolating the compound of Formula (II) as indicated in the following Scheme 5, demonstrates storage stability equal to that of the compound of Formula (4), and

allows the compound of Formula (IV), and particularly the compound of the following Formula (IV-1-1), to be obtained in high purity and high yield without forming byproduct simply by subjecting to extraction and washing treatment, thereby offering numerous advantages in terms of attempting to realize industrialization. The process for producing the compound of Formula (IV), and particularly the compound of Formula (IV-1-1), according to the present invention is highly useful as a production process suitable for commercialization of compounds of the aforementioned Formula (VI-1).

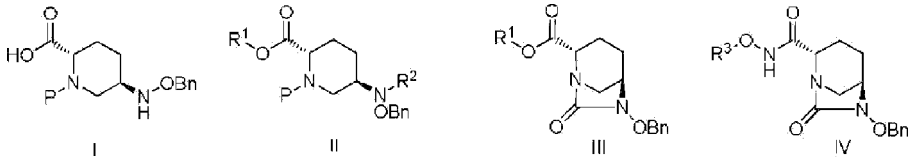
Scheme 5



(In the above formulas, Boc is tert-butoxycarbonyl and OBn is benzyloxy.)

MODE FOR CARRYING OUT THE INVENTION

[0017] As was previously described, the present invention provides a process for producing a diazabicyclooctane derivative of the following Formula (IV) and intermediates thereof:



(in the aforementioned Formulas (I), (II), (III) and (IV), OBn is benzyloxy, P is an NH protecting group capable of being removed with an acid, R^1 is 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, or 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl, R^2 is hydrogen, ClCO- or Cl_3COCO-, R^3 is C_{1-6} alkyl or heterocyclyl, or forms a 3- to 7-membered heterocyclic ring together with the adjacent -O-NH-, R^3 may be modified with 0 to 5 R^4, R^4 may be consecutively substituted. Here, R^4 is C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylsulfonyl, heterocyclyl, heterocyclylcarbonyl, $R^5(R^6)N$- or a protecting group. R^5 and R^6 each independently is hydrogen or C_{1-6} alkyl or together forms a 3- to 7-membered heterocyclic ring. Further, R^3, R^5 and R^6 can undergo ring closure at an arbitrary position).

[0018] Although the following provides a detailed explanation of the process of the present

invention for producing a diazabicyclooctane derivative of Formula (IV) and intermediates thereof, the present invention is not limited to the scope of the indicated specific examples thereof.

[0019] An "active group" and "active ester" refer to functional groups that fulfill the role of enhancing reaction yield and selectivity of the amine component by coupling to a carboxyl group.

[0020] "C_{1-6} alkyl" refers to an alkyl group having 1 to 6 carbon atoms which may be linear, branched or cyclic. "C_{1-6} alkoxy" refers to an alkoxy group having 1 to 6 carbon atoms which may be linear, branched or cyclic. "C_{1-6} alkylsulfonyl" refers to a sulfonyl group coupled to an alkyl group having 1 to 6 carbon atoms wherein the alkyl moiety may be linear, branched or cyclic.

[0021] "Heterocyclyl" refers to a 3- to 7-membered monocyclic heterocyclic saturated ring or non-aromatic ring having a total of 1 to 3 heteroatoms selected from a nitrogen atom, oxygen atom and sulfur atom as ring constituents thereof. "Heterocyclylcarbonyl" refers to a carbonyl group coupled to the heterocyclyl.

[0022] "$R^5(R^6)N$-" refers to an amino substituted with R^5 and R^6, namely an amino, mono-C_{1-6} alkylamino or di-C_{1-6} alkylamino. Alternatively, in "$R^5(R^6)N$-", R^5 and R^6 may together form a 3- to 7-membered heterocyclic ring.

[0023] "Modified" with respect to R^3 refers to a hydrogen in R^3 being substituted with or connected to R^4.

[0024] "R^3 may be modified with 0 to 5 R^4, and R^4 may be consecutively substituted" means that R^4 that modifies R^3 may be further modified with R^4, and examples thereof include R^3-$(R^4)_{0-5}$, R^3-$(R^4$-$R^4_{0-4})$, R^3-$(R^4$-$R^4_{0-3})_2$, R^3-$(R^4$-$R^4_{0-2})_3$ and R^3-$(R^4$-$R^4_{0-1})_4$.

[0025] Specific examples of protecting groups include carbamate-type protecting groups and trialkylsilyl groups that are protecting groups of amino groups and hydroxyl groups as described in Protective Groups in Organic Synthesis (T. W. Greene et al., Wiley, New York (1999)), and preferable examples thereof include triisopropylsilyl (TIPS), tert-butyldimethylsilyl (TBDMS or TBS), tert-butoxycarbonyl (Boc), trimethylsilylethoxycarbonyl (Teoc), 4-methoxybenzyloxycarbonyl (PMZ, Moz), allyloxycarbonyl (Alloc), diphenylmethoxycarbonyl, 9-fluororenylmethoxycarbonyl (Fmoc) and benzyloxycarbonyl (Cbz, Z).

[0026] Specific examples of "C_{1-6} alkyl" include C_{1-6} alkyl groups such as a methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, s-butyl, isobutyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, neopentyl, 1-methylbutyl, 2-methylbutyl, isopentyl and hexyl group, C_{3-6}

cycloalkyl groups such as a cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl group, and methyl groups substituted with a C_{3-5} cycloalkyl group such as a cyclopropylmethyl, cyclobutylmethyl or cyclopentylmethyl group, and preferably include methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopropylmethyl and cyclobutylmethyl groups.

[0027] Specific examples of "C_{1-6} alkoxy" include a variety of alkoxy having "C_{1-6} alkyl" specifically illustrated above.

[0028] Specific examples of "C_{1-6} alkylsulfonyl" include a variety of alkylsulfonyl having "C_{1-6} alkyl" specifically illustrated above.

[0029] Specific examples of "heterocyclyl" groups include aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, imidazolidine, oxazolidine, thiazolidine, pyrazolidine, piperidine, tetrahydro-2H-pyran, tetrahydro-2H-thiopyran, hexahydropyridazine, piperazine, morpholine, thiomorpholine, 1,2-oxazolidine, 1,3-oxazolidine, 1,2-oxazinane, 1, 3-oxazinane, 1,4-dioxane, 1,2-thiazolidine, 1,3-thiazolidine, 1,2-thiazinane, 1,3-thiazinane, azepane, oxepane, thiepane, 1,4-diazepane, 1,4-oxazepane, 1,4-thiazepane, 1,2,5-triazepane, 1,4,5-oxadiazepane, 1,2,5-oxadiazepane, 1,4,5-thiadiazepane, 1,5,2-dioxazepane, 1,5,2-oxathiazepane, 3,4-dihydro-2H-pyrrole, 4,5-dihydro-1H-pyrazole, 4,5-dihydro-1H-imidazole, 4,5-dihydro-1,2-oxazole, 4,5-dihydro-1,3-oxazole, 4,5-dihydro-1,3-thiazole, 2,3,4,5-tetrahydropyridine, 1,2,3,6-tetrahydropyrazine, 5,6-dihydro-4H-1,2-oxazine and 3,6-dihydro-2-H-1,4-oxazine and preferably include azetidine, pyrrolidine, tetrahydrofuran, piperidine, tetrahydro-2H-pyran, imidazolidine, 1,3-oxazolidine, 1,3-thiazolidine, hexahydropyridazine, piperazine, morpholine, 1,2-oxazinane, azepane, 1,4-diazepane or 1,2-oxazepane.

[0030] Specific examples of "heterocyclylcarbonyl" include a variety of heterocyclylcarbonyl having "heterocyclyl" specifically illustrated above.

[0031] Specific examples of "$R^5(R^6)N$-" groups include amino, methylamino, ethylamino, propylamino, isopropylamino, butylamino, tert-butylamino, s-butylamino, isobutylamino, pentylamino, 1,1-dimethylpropylamino, 1,2-dimethylpropylamino, neopentylamino, 1-methylbutylamino, 2-methylbutylamino, isopentylamino, hexylamino, N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino, N,N-di(isopropyl)amino, N,N-dibutylamino, N,N-di(tert-butyl)amino, N,N-di(s-butyl)amino, N,N-di(isobutyl)amino, N,N-dipentylamino, N,N-di(1,1-dimethylpropyl)amino, N,N-di(1 ,2-dimethylpropyl)amino, N,N-di(neopentyl)amino, N,N-di(1-methylbutyl)amino, N,N-di(2-methylbutyl)amino, N,N-di(isopentyl)amino and N,N-di(hexyl)amino and preferably include amino, methylamino, ethylamino, propylamino, isopropylamino, N,N-dimethylamino and N,N-diethylamino.

[0032] Specific examples of groups formed in the case of R^5 and R^6 of $R^5(R^6)N$-connecting to form a heterocyclyl group include azetidin-1-yl, pyrrolidin-1-yl, piperidin-1-yl and azepan-1-yl

groups. It goes without saying that the aforementioned specific examples include those connected with a protecting group in the form of a tert-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz, Z) group.

[0033] Specific examples of compounds of chemical Formula (II) provided by the present invention include:

1-tert-butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy)amino) piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy) ((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy) (chlorocarbonyl)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5 -((benzyloxy)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5 -((benzyloxy) ((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5 -((benzyloxy) (chlorocarbonyl)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5 -((benzyloxy)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5 -((benzyloxy) ((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5 -((benzyloxy) (chlorocarbonyl)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl) (2S,5R)-5 -((benzyloxy)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl) (2S,5R)-5 -((benzyloxy) ((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylate; and

1-tert-butyl 2-(3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl) (2S,5R)-5 -((benzyloxy) (chlorocarbonyl)amino)piperidine-1,2-dicarboxylate.

[0034] More preferably, these specific examples include:

1-tert-butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy)amino) piperidine-1,2-

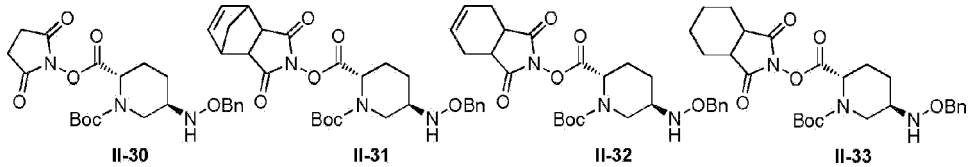
dicarboxylate;

1-tert-butyl2-(1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl) (2S,5R) -5-((benzyloxy)amino)piperidine-1,2-dicarboxylate;

1-tert-butyl 2-(1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5 -((benzyloxy)amino)piperidine-1,2-dicarboxylate; and

1-tert-butyl 2-(3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl) (2S,5R)-5 -((benzyloxy)amino)piperidine-1,2-dicarboxylate;

and they are of the following Formulas (II-30), (II-31), (II-32), and (II-33).



II-30 II-31 II-32 II-33

[0035] Specific examples of compounds of chemical Formula (III) provided by the present invention include:

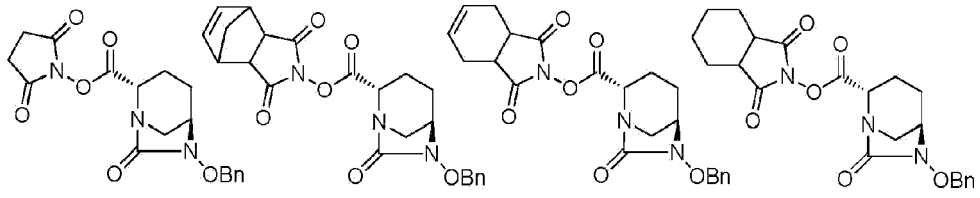
2,5-dioxopyrrolidin-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane-2-carboxylate;

1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7 -oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate;

1,3-dioxohexahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6 -diazabicyclo[3.2.1]octane-2-carboxylate; and

3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo -1,6-diazabicyclo[3.2.1]octane-2-carboxylate;

and they are of the following Formulas (III-57), (III-58), (III-59), and (III-60):



III-57 III-58 III-59 III-60

(wherein OBn is benzyloxy).

[0036] Continuing, specific examples of compounds formed in the case of a substituent defined by R^4 modifying a C_{1-6} alkyl or heterocyclyl that forms R^3O- are explained by listing even more specific typical examples thereof, but it goes without saying that these compounds are not limited to the scope of the indicated specific examples.

[0037] Specific examples of an amino group (H_2N-) of a typical example of $R^5(R^6)N$-modifying a "C_{1-6} alkyl" include 2-aminoethyl, 2-aminopropyl, 3-aminopropyl, 2-amino-1-methylethyl, 2-aminobutyl, 3-aminobutyl, 4-aminobutyl, 2-amino-1,1-dimethylethyl, 2-amino-1-methylpropyl, and 3-amino-2-methylpropyl. Here, it goes without saying that the aforementioned specific examples include those connected with a tert-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz, Z) protecting group contained in R^5OCO-.

[0038] Specific examples of a methyl group of a typical example of a C_{1-6} alkyl modifying a heterocyclyl include 1-methylazetidine, 3-methylazetidine, 1-methylpyrrolidine, 3-methylpyrrolidine, 1-methylimidazolidine, 3-methyloxazolidine, 1-methylpyrazolidine, 1-methylpiperidine, 4-methylpiperidine, 2-methyltetrahydro-2H-pyran, 4-methyltetrahydro-2H-pyran, 1-methylpiperazine, 1,4-dimethylpiperazine, 4-methylmorpholine, 4-methyl-thiomorpholine, 1-methylazepane, 1-methyl-1,4-diazepane and 1,4-dimethyl-1,4-diazepane. Here, it goes without saying that the aforementioned specific examples include those connected with a tert-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz, Z) protecting group.

[0039] Specific examples of an amino group (H_2N-) of a typical example of $R^5(R^6)N$-modifying a heterocyclyl include 3-aminoazetidine, 3-aminopyrrolidine, 3-amino-tetrahydrofuran, 3-amino-tetrahydrothiophene, 4-aminopyrazolidine, 4-aminopiperidine, 4-amino-tetrahydro-2H-pyran, 4-amino-tetrahydro-2H-thiopyran, 4-amino-hexahydropyridazine, 4-amino-1,2-oxazolidine, 4-amino-1,2-oxazinane, 4-aminoazepane, 4-aminooxepane and 6-amino-1,4-diazepane. Here, it goes without saying that the aforementioned specific examples include those connected with a tert-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz, Z) protecting group.

[0040] Specific examples of a heterocyclyl modifying a methyl or ethyl of a typical example of a C_{1-6} alkyl include azetidin-2-ylmethyl, azetidin-3-ylmethyl, pyrrolidin-2-ylmethyl, pyrrolidin-3-ylmethyl, tetrahydrofuran-3-ylmethyl, tetrahydrothiophen-3-ylmethyl, pyrazolidin-4-ylmethyl, 1,2-oxazolidin-3-ylmethyl, piperidin-2-ylmethyl, piperidin-3-ylmethyl, piperidin-4-ylmethyl, tetrahydro-2H-pyran-4-ylmethyl, tetrahydro-2H-thiopyran-4-ylmethyl, hexahydropyridazin-4-ylmethyl, piperazin-2-ylmethyl, 1,2-oxazinan-3-ylmethyl, morpholin-2-ylmethyl, morpholin-3-ylmethyl, thiomorpholin-2-ylmethyl, thiomorpholin-3-ylmethyl, azepan-2-ylmethyl, azepan-4-ylmethyl, oxepan-2-ylmethyl, oxepan-4-ylmethyl, 1,4-diazepan-2-ylmethyl, 1,4-diazepan-6-ylmethyl, 2-(azetidin-1-yl)ethyl, 2-(pyrrolidin-1-yl)ethyl, 2-(pyrazolidin-1-yl)ethyl, 2-(piperidin-1-yl)ethyl, 2-(hexahydropyridazin-1-yl)ethyl, 2-(piperazin-1-yl)ethyl, 2-(morpholin-4-yl)ethyl, 2-(thiomorpholin-4-yl)ethyl, 2-(1,2-oxazolidin-2-yl)ethyl, 2-(1,2-oxazinan-2-yl)ethyl, 2-(azepan-1-yl)ethyl, and 2-(1,4-diazepan-1-yl)ethyl. Here, it goes without saying that the aforementioned specific examples include those connected with a tert-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz, Z) protecting group.

[0041] Specific examples of compounds of chemical Formula (IV) provided by the present invention preferably include:

(2S,5R)-6-benzyloxy-N-methoxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2S,5R)-6-benzyloxy-N-ethoxy-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2S,5R)-6-benzyloxy-N-(cyclobutylmethoxy)-7-oxo-1,6-diazabicyclo[3.2.1] octane-2-carboxamide;

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} carbamate;

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1] oct-2-yl] carbonyl} amino)oxy] ethyl} (methyl)carbamate;

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1] oct-2-yl] carbonyl} amino)oxy] ethyl} (ethyl)carbamate;

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} (propyl)carbamate;

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} (propan-2-yl)carbamate;

(2S,5R)-6-benzyloxy-N-[2-(dimethylamino)ethoxy]-7-oxo-1,6-diazabicyclo[3. 2.1]octane-2-carboxamide;

tert-butyl {(2S)-1-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -yl] carbonyl} amino)oxy]propan-2-yl} carbamate;

tert-butyl {(2R)-1-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -yl] carbonyl} amino)oxy]propan-2-yl} carbamate;

tert-butyl {(2S)-2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -yl] carbonyl} amino)oxy]propyl} carbamate;

tert-butyl {3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -yl] carbonyl} amino)oxy]propyl} carbamate;

(2S,5R)-6-benzyloxy-2-(1,2-oxazolidin-2-ylcarbonyl)-1,6-diazabicyclo[3.2.1] octan-7-one;

(2S,5R)-6-benzyloxy-2-(1,2-oxazinan-2-ylcarbonyl)-1,6-diazabicyclo[3.2.1] octan-7-one;

(2S,5R)-6-benzyloxy-N-[2-(morpholin-4-yl)ethoxy]-7-oxo-1,6-diazabicyclo[3. 2.1]octane-2-carboxamide;

tert-butyl 4-{2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino) oxy]ethyl}piperazine-1-carboxylate;

tert-butyl 4-{2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -yl]carbonyl}amino)oxy]ethyl}-1,4-diazepane-1-carboxylate;

tert-butyl (2S)-2-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}azetidine-1-carboxylate;

tert-butyl (2S)-2-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}pyrrolidine-1-carboxylate;

tert-butyl (2R)-2-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}pyrrolidine-1-carboxylate;

tert-butyl (3R)-3-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}piperidine-1-carboxylate;

tert-butyl 3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]azetidine-1-carboxylate;

tert-butyl (3R)-3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]pyrrolidine-1-carboxylate;

tert-butyl (3S)-3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]pyrrolidine-1-carboxylate;

tert-butyl 3-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}azetidine-1-carboxylate;

tert-butyl (3R)-3-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}piperidine-1-carboxylate;

tert-butyl 4-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]piperidine-1-carboxylate;

tert-butyl 4-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}piperidine-1-carboxylate;

(2S,5R)-6-benzyloxy-N-[2-(1H-imidazol-1-yl)ethoxy]-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2S,5R)-6-benzyloxy-7-oxo-N-[2-(1H-pyrrol-1-yl)ethoxy]-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2S,5R)-6-benzyloxy-N-[2-(dimethylamino)-2-oxoethoxy]-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

tert-butyl 4-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]acetyl}piperazine-1-carboxylate;

(2S,5R)-6-benzyloxy-N-[2-(morpholin-4-yl)-2-oxoethoxy]-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

tert-butyl 4-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]

carbonyl}amino)oxy]acetyl}-1,4-diazepane-1-carboxylate;

(2S,5R)-6-benzyloxy-7-oxo-N-[2-(2-oxopyrrolidin-1-yl)ethoxy]-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2S,5R)-6-benzyloxy-7-oxo-N-[2-(2-oxoimidazolidin-1-yl)ethoxy]-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2S,5R)-6-benzyloxy-7-oxo-N-(2-triisopropylsilyloxyethoxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide;

(2S,5R)-6-benzyloxy-N-(2-methoxyethoxy)-7-oxo-1,6-diazabicyclo[3.2.1 octane-2-carboxamide;

(2S,5R)-6-benzyloxy-N-[2-(methylsulfonyl)ethoxy]-7-oxo-1,6-diazabicyclo[3. 2.1]octane-2-carboxamide; and

benzyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl} carbamate.

[0042] More preferably, these specific examples include:

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl}carbamate;

benzyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl}carbamate;

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1] oct-2-yl]carbonyl}amino)oxy]ethyl}(methyl)carbamate;

tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl} (propan-2-yl)carbamate;

(2S,5R)-6-benzyloxy-N-[2-(dimethylamino)ethoxy]-7-oxo-1,6-diazabicyclo[3. 2.1]octane-2-carboxamide;

tert-butyl {(2S)-1-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -yl]carbonyl}amino)oxy]propan-2-yl}carbamate;

tert-butyl {(2R)-1-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -yl]carbonyl}amino)oxy]propan-2-yl}carbamate;

tert-butyl {3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]propyl}carbamate;

tert-butyl (2S)-2-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2 -

yl]carbonyl}amino)oxy]methyl}azetidine-1-carboxylate;

tert-butyl (2R)-2-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}pyrrolidine-1-carboxylate;

tert-butyl (3R)-3-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}piperidine-1-carboxylate;

tert-butyl (3S)-3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]pyrrolidine-1-carboxylate; and

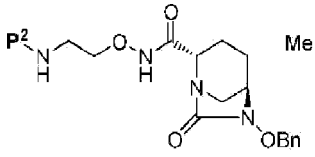
tert-butyl 3-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}azetidine-1-carboxylate;

and most preferably include compounds selected from

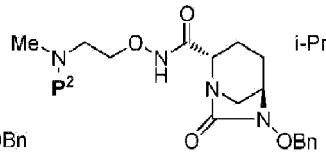
tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate; and

benzyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate;

and compounds of the following chemical formulas:



IV-1



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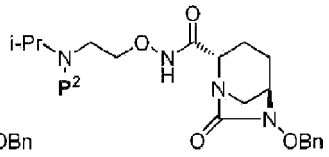

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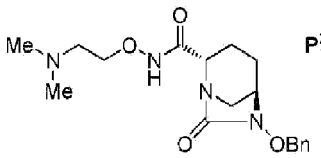

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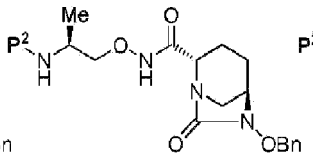

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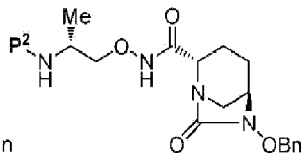

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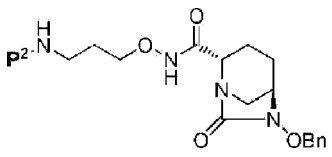

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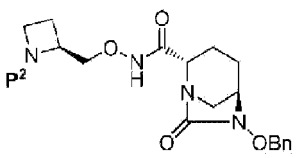

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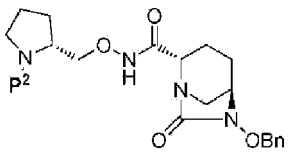

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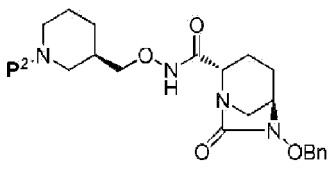

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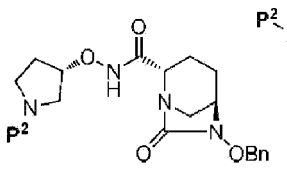

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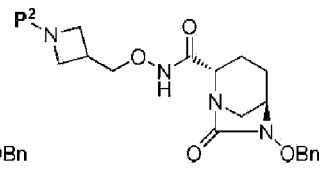
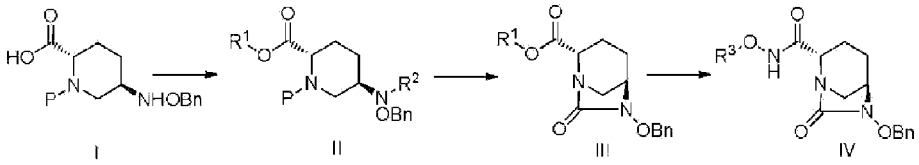


IV-12

(wherein P^2 is tert-butoxycarbonyl (Boc) or benzyloxycarbonyl (Cbz) and OBn is benzyloxy).

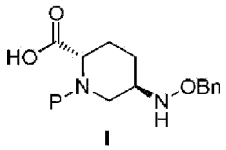
[0043] The following provides sequentially explanations of the processes for producing compounds of the following Formulas (II), (III) and (IV) provided by the present invention.

Scheme 6



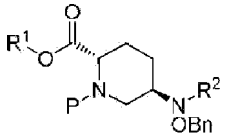
(In the aforementioned Formulas (I), (II), (III) and (IV), P, OBn, R^1, R^2 and R^3 are same as described above.)

[0044] A protecting group of an amino group able to be removed with an acid as described in Protective Groups in Organic Synthesis (T. W. Greene et al., Wiley, New York (1999)) can be employed as a suitable protecting group represented by P in the starting material of the following Formula (I) used as a starting material in the production process of the present invention:



(wherein OBn is benzyloxy and P is an NH protecting group capable of being removed with an acid). Specific examples thereof include tert-butoxycarbonyl (Boc), 2-trimethylsilylethoxycarbonyl (Teoc), 1-methyl-1-(4-biphenylyl)ethoxycarbonyl, 1-methylcyclobutoxycarbonyl, 1-adamantyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl (Alloc), cinnamyloxycarbonyl, 4-methoxybenzyloxycarbonyl (PMZ, Moz) and diphenylmethoxycarbonyl groups, and preferred is a tert-butoxycarbonyl (Boc) group.

[0045] The step for obtaining a compound of the following Formula (II):



(in the Formula (II), OBn, P and R^1 are same as described above) wherein R^2 is a hydrogen, from the compound of the aforementioned Formula (I), is carried out by esterification of the compound of the aforementioned Formula (I) with R'OH selected from 1-hydroxypyrrolidine-2,5-dione, 2-hydroxy-3a,4,7,7a-tetrahydro-1H-isoindol-1,3(2H)-dione, 2-hydroxyhexahydro-1H-isoindol-1,3(2H)-dione, or 4-hydroxy-4-azatricyclo[5.2.1.$0^{2.6}$]dec-8-ene-3,5-dione.

[0046] Esterification is carried out with a dehydration condensation agent or by a mixed acid anhydride method in the presence of a base.

[0047] Examples of reaction solvent used in esterification include ethyl acetate, toluene, tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, acetonitrile, dichloromethane, chloroform, dichloroethane, dimethylformamide and dimethylacetamide, preferable examples include ethyl

acetate, tetrahydrofuran, dichloromethane, chloroform, acetonitrile, dimethylformamide and dimethylacetamide, and these reaction solvents are used alone or as a mixture.

[0048] Examples of base used in the esterification reaction include sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, triethylamine, diisopropylethylamine, dimethylbutylamine, tributylamine, N-methylmorpholine, pyridine, N-methylimidazole and 4-dimethylaminopyridine, preferable examples include triethylamine, diisopropylethylamine and 4-dimethylaminopyridine, and the base is used as necessary within the range of 1 to 2 equivalents, and preferably 0.5 to 1.5 equivalents, based on the compound of Formula (I).

[0049] The R'OH selected from 1-hydroxypyrrolidine-2,5-dione, 2-hydroxy-3a,4,7,7a-tetrahydro-1H-isoindol-1,3(2H)-dione, 2-hydroxyhexahydro-1H-isoindol-1,3(2H)-dione, or 4-hydroxy-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione used in esterification is used as necessary within the range of 1 to 3 equivalents, and preferably 1 to 2 equivalents, based on the compound of Formula (I).

[0050] Examples of reagents used for the dehydration condensation agent and mixed acid anhydride method used in the esterification reaction include carbodiimides such as N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiiimide or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, propylphosphoric acid anhydride, diphenylphosphinyl chloride, bis(2-oxo-3-oxazolidinyl)phosphinyl chloride, ethyl chloroformate, isobutyl chloroformate, 2,4,6-trichlorobenzoyl chloride, methanesulfonyl chloride, 4-toluenesulfonyl chloride, dimethylsulfamoyl chloride, bis(2-pyridyl)carbonate or bis(2-thienyl)carbonate, and preferable examples include isobutyl chloroformate and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. The reagent used for the dehydration condensation agent and mixed acid anhydride method is used as necessary within the range of 0.8 to 2 equivalents, and preferably 1 to 1.5 equivalents, based on the compound of Formula (I).

[0051] The reaction temperature is within the range of -40 °C to room temperature and preferably within the range of -20 °C to room temperature. The reaction time is within the range of 30 minutes to 1 day and preferably within the range of 2 to 16 hours.

[0052] The compound of Formula (II) can be isolated following completion of the reaction by diluting the reaction solution with a suitable solvent and sequentially washing with water, diluted acid and an aqueous basic solution (such as diluted hydrochloric acid, potassium hydrogensulfate, citric acid and aqueous sodium bicarbonate or saturated brine) followed by concentrating by evaporating the solvent. Examples of organic solvents used for dilution include diethyl ether, ethyl acetate, butyl acetate, toluene, dichloromethane and chloroform, and ethyl acetate is preferable.

[0053] Carbonylation of a compound obtained by the aforementioned esterification is carried

out in the manner described below.

[0054] Examples of solvents used in the reaction include ethyl acetate, toluene, tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, acetonitrile, dichloromethane, chloroform, dichloroethane, dimethylformamide and dimethylacetamide, preferable examples include ethyl acetate, tetrahydrofuran, dichloromethane, chloroform and acetonitrile, and the solvents are used alone or as a mixture.

[0055] Carbonylation is preferably carried out in the presence of a base. Examples of base used in the reaction include triethylamine, diisopropylethylamine, dimethylbutylamine, tributylamine, N-methylmorpholine, pyridine, N-methylimidazole and 4-dimethylaminopyridine, preferable examples include triethylamine and diisopropylethylamine, and the base is used within the range of 1 to 6 equivalents, and preferably within the range of 2 to 3 equivalents, based on the compound obtained by esterification.

[0056] Examples of carbonylation agents used in the reaction include phosgene, diphosgene and triphosgene, triphosgene is preferable, and the carbonylation agent is used within the range of 0.33 to 2 equivalents, and preferably within the range of 0.33 to 1 equivalent, based on the compound obtained by esterification.

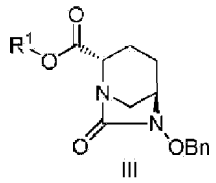
[0057] The reaction temperature is within the range of -25 to 50 °C and preferably within the range of -15 to 30 °C. The reaction time is 10 minutes to 24 hours and preferably 1 to 4 hours. Following completion of the reaction, the production process proceeds to the next step without isolating or purifying the reaction product after confirming the presence thereof in the form of trichloromethoxycarbamate or chlorocarbamate and completion of the reaction by an analytical means such as TLC.

[0058] Deprotection of the protecting group P of the compound of Formula (II) obtained by the aforementioned step under acidic conditions is carried out in the manner described below.

[0059] Examples of solvents used include water, methanol, ethanol, isopropanol, ethyl acetate, tetrahydrofuran, dioxane, dichloromethane, chloroform, 1,2-dichloroethane and 2,2,2-trifluoroethanol, preferable examples include ethyl acetate, dioxane, dichloromethane, chloroform and dichloroethane, and the solvents are used alone or as a mixture. Examples of acids used for deprotection include hydrochloric acid, sulfuric acid, phosphoric acid, formic acid, trifluoroacetic acid, methanesulfonic acid, trifluoromethanesulfonic acid, chloromethanesulfonic acid and tetrafluoroboric acid, and preferable examples include hydrochloric acid, sulfuric acid, trifluoroacetic acid, methanesulfonic acid and tetrafluoroboric acid. Methanesulfonic acid is more preferable. The acid is used within the range of 1 equivalent based on the compound of Formula (II) to the amount of solvent, and preferably within the range of 5 to 20 equivalents, based on the compound of Formula (II). The reaction temperature is within the range of -25 to 50 °C and preferably within the range of -10 to 30 °C. The reaction time is within the range of 1 minute to 1 hour and preferably within the range of 5 to 30 minutes. Following completion of the reaction, the production process proceeds to the

next step without isolating or purifying the reaction product after confirming the presence thereof in the form of a salt of the acid used and completion of the reaction by an analytical means such as TLC.

[0060] Continuing, a cyclization reaction for obtaining a compound of the following Formula (III):



III

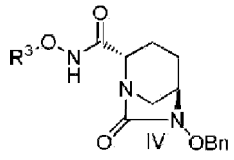
(wherein OBn and R^1 are same as described above) from a compound of the aforementioned Formula (II) following removal of the protecting group P is carried out in the manner described below.

[0061] The reaction is carried out by continuously treating the reaction solution of a compound of the aforementioned Formula (II) with a base.

[0062] Examples of base used in the reaction include sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, triethylamine, diisopropylethylamine, dimethylbutylamine, tributylamine, N-methylmorpholine, pyridine, N-methylimidazole and 4-dimethylaminopyridine, preferable examples include sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine and diisopropylethylamine, and an aqueous solution can be used in the case of using an inorganic base. The base is used in slight excess based on the acid used to deprotect Formula (II), and is preferably used at 5 to 20 times the amount of the compound of Formula (II). The reaction temperature is within the range of -25 to 50 °C and preferably within the range of -10 to 10 °C. The reaction time is within the range of 0.5 to 3 hours and preferably within the range of 0.5 to 1 hour.

[0063] The compound of Formula (III) can be isolated by diluting the reaction solution with a suitable solvent following completion of the reaction, and sequentially washing with water, diluted acid and an aqueous basic solution (such as dilute hydrochloric acid, potassium hydrogensulfate, citric acid and aqueous sodium bicarbonate or saturated brine) followed by concentrating by evaporating the solvent. Examples of organic solvents used for dilution include diethyl ether, ethyl acetate, butyl acetate, toluene, dichloromethane and chloroform, and ethyl acetate is preferable. Purification is carried out by an ordinary procedure such as silica gel column chromatography, precipitation or crystallization.

[0064] Continuing, synthesis of a compound of the following Formula (IV):



IV

(wherein OBn and R^3 are same as described above) from a compound of the aforementioned

Formula (III) is carried out in the manner described below.

[0065] Examples of solvents used in the reaction include water, methanol, ethanol, isopropanol, ethyl acetate, tetrahydrofuran, dioxane, dichloromethane, chloroform, 1,2-dichloroethane and 2,2,2-trifluoroethanol, preferable examples include ethyl acetate, dioxane, dichloromethane, chloroform and dichloroethane, and the solvents are used alone or as a mixture.

[0066] The compound: R^3ONH_2 used in the reaction can be preferably selected from those listed in the specific examples of R^3, and is used within the range of 1 to 2 equivalents, and preferably within the range of 1 to 1.3 equivalents, based on a compound of Formula (III).

[0067] Examples of base used in the reaction include sodium hydrogencarbonate, potassium hydrogencarbonate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydroxide, potassium hydroxide, triethylamine, diisopropylethylamine, dimethylbutylamine, tributylamine, N-methylmorpholine, pyridine, N-methylimidazole and 4-dimethylaminopyridine, preferable examples include sodium hydrogencarbonate, potassium hydrogencarbonate, triethylamine and diisopropylethylamine, and an aqueous solution can be used in the case of using an inorganic base. The base is used within the range of 0 to 2 equivalents and preferably within the range of 0 to 1.5 equivalents based on a compound of Formula (III). R^3ONH_2 is used within the range of 0 to 2 equivalents and preferably within the range of 0 to 1.5 equivalents based on a compound of Formula (III). The reaction temperature is within the range of -25 to 50 °C and preferably within the range of -10 to 10 °C. The reaction time is within the range of 1 to 24 hours and preferably within the range of 1 to 16 hours.

[0068] The compound of Formula (IV) can be isolated by diluting the reaction solution with a suitable solvent following completion of the reaction, and sequentially washing with water, diluted acid and an aqueous basic solution (such as dilute hydrochloric acid, potassium hydrogensulfate, citric acid and aqueous sodium bicarbonate or saturated brine) followed by concentrating by evaporating the solvent. Examples of organic solvents used for dilution include diethyl ether, ethyl acetate, butyl acetate, toluene, dichloromethane and chloroform, and ethyl acetate is preferable. Purification is carried out by an ordinary procedure such as silica gel column chromatography, precipitation or crystallization.

EXAMPLES

[0069] The present invention will be described below in more detail by way of Examples.

Reference Example 1

carboxamide (VI-1)

Step 1

tert-Butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} carbamate (IV-1-1)

[0070] A solution of (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (4.30 g, 15.56 mmol) in dehydrated ethyl acetate (47 mL) was cooled to -30 °C, and isobutyl chloroformate (2.17 g, washed with 1 mL of dehydrated ethyl acetate) and triethylamine (1.61 g, washed with 1 mL of dehydrated ethyl acetate) were added dropwise sequentially, followed by stirring at -30 °C for 1 hour. To the reaction solution was added a solution of tert-butyl 2-(aminooxy)ethylcarbamate (3.21 g) in dehydrated ethyl acetate (4 mL) (washed with 1 mL of dehydrated ethyl acetate), and the temperature was elevated to 0 °C over 1.5 hours, followed by further stirring overnight. The mixture was washed sequentially with 8% citric acid (56 mL), saturated sodium bicarbonate (40 mL) and saturated brine (40 mL), dried over anhydrous magnesium sulfate, subsequently filtered, concentrated to 5 mL, and further substitution-concentrated with ethanol (10 mL) to 6 mL. To the resulting solution were added ethanol (3 mL) and hexane (8 mL), followed by ice cooling, seeding, and stirring for 15 minutes. To the mixture was added dropwise hexane (75 mL) over 2 hours, followed by stirring overnight. The precipitated crystalline solid was filtered, washed with hexane, and dried in vacuo to afford 5.49 g of the title compound (net 4.98 g, yield 74%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.56-1.70 (m, 1H), 1.90-2.09 (m, 2H), 2.25-2.38 (m, 1H), 2.76 (d, J = 11.6 Hz, 1H), 3.03 (br.d., J = 11.6 Hz, 1H), 3.24-3.47 (m, 3H), 3.84-4.01 (m, 3H), 4.90 (d, J = 11.6 Hz, 1H), 5.05 (d, J = 11.6 Hz, 1H), 5.44 (br.s., 1H), 7.34-7.48 (m, 5H), 9.37 (br.s., 1H); MS m/z 435 $[M+H]^+$.

Step 2

tert-Butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl}carbamate (V-1)

[0071] To a solution of tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo [3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate (3.91 g, 9.01 mmol) in methanol (80 mL) was added a 10% palladium carbon catalyst (50% wet, 803 mg), followed by stirring under a hydrogen atmosphere for 45 minutes. The reaction solution was filtered through a Celite pad and

concentrated under reduced pressure, and then 3.11 g of the title compound was afforded (quantitative).

^{1}H NMR (400 MHz, CD_3OD) δ 1.44 (s, 9H), 1.73-1.83 (m, 1H), 1.86-1.99 (m, 1H), 2.01-2.12 (m, 1H), 2.22 (br.dd., J = 15.0, 7.0 Hz, 1H), 3.03 (d, J = 12.0 Hz, 1H), 3.12 (br.d., J = 12.0 Hz, 1H), 3.25-3.35 (m, 2H), 3.68-3.71 (m, 1H), 3.82-3.91 (m, 3H); MS m/z 345 $[M+H]^+$.

Step 3

(2S,5R)-N-(2-Aminoethoxy)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane -2-carboxamide (VI-1)

[0072] To a solution of tert-butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo [3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate (3.09 g, 8.97 mmol) in dichloromethane (80 mL) were added 2,6-lutidine (3.20 mL) and sulfur trioxide-pyridine complex (3.58 g), followed by stirring at room temperature overnight. The reaction solution was poured into semi-saturated sodium bicarbonate, the aqueous layer was washed with chloroform, and subsequently to the aqueous layer were added tetrabutylammonium hydrogen sulfate (3.47 g) and chloroform (30 mL), followed by stirring for 10 minutes. After the aqueous layer was extracted with chloroform, the resulting organic layer was dried over anhydrous sodium sulfphate, filtered, and then concentrated under reduced pressure to afford 5.46 g of tetrabutylammonium tert-butyl {2-[({[(2S,5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate (yield 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.4 Hz, 12H), 1.37-1.54 (m, 8H), 1.45 (s, 9H), 1.57-1.80 (m, 9H), 1.85-1.98 (m, 1H), 2.14-2.24 (m, 1H), 2.30-2.39 (m, 1H), 2.83 (d, J = 11.6 Hz, 1H), 3.20-3.50 (m, 11H), 3.85-3.99 (m, 3H), 4.33-4.38 (m, 1H), 5.51 (br s, 1H), 9.44 (br.s., 1H); MS m/z 425 $[M\text{-}Bu_4N+2H]^+$.

[0073] To a solution of this tetrabutylammonium salt (5.20 g, 7.82 mmol) in dichloromethane (25 mL) was added trifluoroacetic acid (25 mL) under ice cooling, followed by stirring at 0 °C for 1 hour. The reaction solution was concentrated under reduced pressure, the resulting residue was washed with diethyl ether, subsequently the pH was adjusted to 7 with a sodium bicarbonate aqueous solution, and octadecyl silica gel column chromatography purification (water) was carried out. After lyophilization, 1.44 g of the title compound was obtained (yield 57%).

^{1}H NMR (400 MHz, D_2O) δ 1.66-1.76 (m, 1H), 1.76-1.88 (m, 1H), 1.91-2.00 (m, 1H), 2.00-2.08 (m, 1H), 3.02(d, J = 12.0 Hz, 1H), 3.15 (t, J = 5.0 Hz, 2H), 3.18 (br d, J = 12.0 Hz, 1H), 3.95 (dd, J = 7.8, 2.2 Hz, 1H), 4.04 (t, J = 5.0 Hz, 2H), 4.07 (dd, J = 6.4&3.2 Hz, 1H); MS m/z 325 $[M+H]^+$.

Reference Example 2

(2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (I)

[0074] Methyl (2S,5R)-5-(benzyloxyamino)piperidine-2-carboxylate, dihydrochloride (65.4 g, 200 mmol) was dissolved in water (400 mL) and 1,4-dioxane (270 mL), followed by ice cooling. 5 M sodium hydroxide (132 mL) was added, followed by stirring for 1 hour. To the reaction solution were added 5 M hydrochloric acid (12 mL), potassium carbonate (27.6 g) and di-tert-butyl dicarbonate (48 g), and the temperature was elevated to room temperature, followed by stirring overnight. The aqueous solution obtained by concentration of the reaction solution was washed with ethyl acetate, adjusted to pH 3.3 with citric acid·monohydrate, extracted twice with ethyl acetate (500 mL), washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The solvent was concentrated under reduced pressure, and further solvent-switched to ethyl acetate yielded 68.7 g of the title compound (quantitative). This compound was used in the next step without purification. A portion thereof was crystalized from ethyl acetate/hexane to confirm the structure.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.50-1.72 (m, 2H), 1.98-2.10 (m, 2H), 3.12-3.19 (m, 2H), 4.13-4.20 (m, 1H), 4.76 (d, J = 11.5 Hz), 4.70 (d, J = 11.5 Hz), 4.85-4.92 (m, 1H), 7.26-7.35 (m, 5H); MS m/z 351 $[M+H]^+$.

Reference Example 3

tert-Butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} carbamate (V-1)

Step 1

(2S,5R)-N-(2-benzyloxycarbonylaminoethoxy)-5-(benzyloxyamino)-1-(tert-butoxycarbonyl)piperidine-2-carboxamide

[0075] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (1.879 g, 5.362 mmol), benzyl 2-(aminooxy)ethylcarbamate (1.41 g, 6.707 mmol) and 1-hydroxybenzotriazole-monohydrate (220 mg) were dissolved in dichloromethane (20 mL), followed by stirring under ice cooling.

N-Ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.29 g) was added thereto and the temperature was elevated to room temperature, followed by stirring overnight. The mixture

was diluted with dichloromethane (20 mL), washed sequentially with water, 10% citric acid, saturated sodium bicarbonate and saturated brine, and dried over magnesium sulfate. The solvent was concentrated under reduced pressure to afford 2.91 g of the title compound (quantitative).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.50-1.93 (m, 4H), 3.40 (m, 2H), 3.89 (m, 2H), 4.15-4.21 (m, 1H), 4.61 (m, 1H), 4.69 (d, J = 11.6 Hz, 1H), 4.76 (d, J = 11.6 Hz, 1H), 5.11 (s, 2H), 5.86 (s, 1H), 7.27-7.36 (m, 5H), 9.28 (s, 1H); MS m/z 543 $[M+H]^+$.

Step 2

(2S,5R)-N-(2-Benzyloxycarbonylaminoethoxy)-5-(benzyloxyamino)piperidine -2-carboxamide

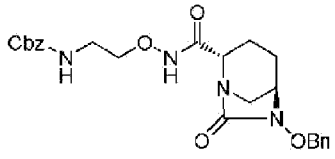
[0076] (2S,5R)-N-(2-Benzyloxycarbonylaminoethoxy)-5-(benzyloxyamino)-1-(tert-butoxycarbonyl)piperidine-2-carboxamide (2.91 g, 5.362 mmol) was dissolved in 1,4-dioxane (5 mL), and 4 M hydrogen chloride in dioxane (10 mL) was added under ice cooling. After stirring for 2 hours, the mixture was concentrated under reduced pressure, dissolved in water (30 mL), and washed with ether. The aqueous layer was ice cooled and the pH was adjusted to about 7 with 5 M sodium hydroxide and acetic acid, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (chloroform → chloroform/methanol = 3/1) to afford 2.27 g of the title compound (yield 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22-1.34 (m, 1H), 1.50-1.58 (m, 1H), 1.89-1.92 (m, 1H), 1.92-2.06 (m, 1H), 2.43-2.48 (m, 1H), 2.95 (m, 1H), 3.23-3.27 (m, 1H), 3.40-3.42 (m, 2H), 3.71-3.73 (m, 2H), 3.89-3.92 (m, 2H), 4.66 (s, 2H), 5.11 (s, 2H), 5.91 (s, 1H), 7.26-7.52 (m, 10H); MS m/z 443 $[M+H]^+$.

Step 3

Benzyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} carbamate (IV-1-2)

[0077]



IV-1-2

[0078] A solution of (2S,5R)-N-(2-benzyloxycarbonylaminoethoxy)-5-(benzyloxyamino)piperidine-2-carboxamide (642 mg, 1.451 mmol) in acetonitrile (66 mL) was ice cooled, and triethylamine (709 µL) and chlorotrimethylsilane (203 µL) were added, followed by stirring for 1 hour. To this reaction solution was added diphosgene (105 µL), followed by stirring at the same temperature for 20 minutes. Then, to this reaction solution was added 4-(dimethylamino)pyridine (18 mg), and the temperature was elevated to room temperature, followed by stirring overnight. The reaction mixture was concentrated under reduced pressure, the resulting residue was diluted with ethyl acetate and washed sequentially with water, 5% citric acid, 6.5% sodium bicarbonate and saturated brine, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 1/3) to afford 407 mg of the title compound (yield 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59-1.65 (m, 1H), 1.91-2.02 (m, 2H), 2.26-2.31 (m, 1H), 2.71-2.74 (d, J = 11.6 Hz, 1H), 2.99-3.02 (br.d, J = 11.2 Hz, 1H), 3.28 (s, 1H), 3.31-3.39 (m, 1H), 3.46-3.49 (m, 1H), 3.88-3.97 (m, 3H), 4.88-4.91 (d, J =11.6 Hz, 1H), 5.03-5.06 (d, J = 11.6 Hz, 1H), 5.11 (s, 2H), 5.83 (br.s., 1H), 7.27-7.43 (m, 10H), 9.36 (br.s., 1H); MS m/z 469 $[M+H]^+$.

Step 4

tert-Butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} carbamate (V-1)

[0079] Benzyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy]ethyl} carbamate (468 mg, 1.00 mmol) and di-tert-butoxycarbonyl dicarbonate (240 mg) were dissolved in tetrahydrofuran (6.6 mL), and 10% Pd/C (93 mg, 50% wet) was added, followed by vigorous stirring under an hydrogen atmosphere for 3 hours. TLC confirmed the end point, and the catalyst was filtered through a Celite pad. The filtrate was concentrated under reduced pressure to afford 403.7 mg of the title compound (quantitative). Instrumental data were consistent with those of Reference Example 1, Step 2.

Reference Example 4

(2S,5R)-N-[2-(Methylamino)ethoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2. 1]octane-2-carboxamide (VI-2)

Step 1

tert-Butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl}(methyl)carbamate (IV-2)

[0080] In a similar manner to Reference Example 1, (2S,5R)-6-(benzyloxy)-7-oxo-1,6 -diazabicyclo[3.2.1]octane-2-carboxylic acid (390 mg, 1.41 mmol) and tert-butyl (2-(aminooxy)ethyl)(methyl)carbamate (436 mg) gave 347.8 mg of the title compound (yield 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.58-1.70 (m, 1H), 1.88-2.07 (m, 2H), 2.25-2.36 (m, 1H), 2.70-3.08 (m, 2H), 2.88 (s, 3H), 3.23-3.41 (m, 2H), 3.51-3.68 (m, 1H), 3.83-4.10 (m, 3H), 4.90 (d, J = 11.4 Hz, 1H), 5.06 (d, J = 11.4 Hz, 1H), 7.32-7.47 (m, 5H), 10.11 (br s, 1H); MS m/z 449 $[M+H]^+$.

Step 2

tert-Butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl}(methyl)carbamate (V-2)

[0081] In a similar manner to Reference Example 1, the total amount of the compound in Step 1 above gave the title compound (quantitative).

^{1}H NMR (400 MHz, CD_3OD) δ 1.46 (s, 9H), 1.73-1.83 (m, 1H), 1.86-2.00 (m, 1H), 2.01-2.13 (m, 1H), 2.14-2.28 (m, 1H), 2.93 (s, 3H), 3.04 (d, J = 10.8 Hz, 1H), 3.08-3.18 (m, 1H), 3.43-3.55 (m, 2H), 3.65-3.72 (m, 1H), 3.79-3.88 (m, 1H), 3.92-4.05 (m, 2H); MS m/z 359 $[M+H]^+$.

Step 3

(2S,5R)-N-[2-(Methylamino)ethoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2. 1]octane-2-carboxamide (VI-2)

[0082] In a similar manner to Reference Example 1, the total amount of the compound in Step 2 above gave tetrabutylammonium tert-butyl {2-[({[(2S,5R)-7-oxo-6-(sulfooxy) -1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}(methyl)carbamate (quantitative).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 12H), 1.36-1.53 (m, 8H), 1.47 (s, 9H), 1.57-1.77 (m, 9H), 1.83-1.98(m, 1H), 2.13-2.25 (m, 1H), 2.28-2.40 (m, 1H), 2.82-2.96 (m, 4H), 3.22-

3.42 (m, 11H), 3.60-4.08 (m, 3H), 4.34 (br.s., 1H), 10.15 (br.s., 1H); MS m/z 437 $[M-Bu_4N]^-$.

[0083] The total amount of the tetrabutylammonium salt above was deprotected with trifluoroacetic acid and purified by octadecyl silica gel column chromatography, and then 149.4 mg of the title compound was afforded (3 step yield 57%). ^1H NMR (500 MHz, D_2O) δ 1.73-1.97 (m, 2H), 1.98-2.07 (m, 1H), 2.08-2.18 (m, 1H), 2.74 (s, 3H), 3.09 (d, J = 12.0 Hz, 1H), 3.21-3.32 (m, 3H), 4.04 (dd, J = 7.5, 2.0 Hz, 1H), 4.10-4.23 (m, 3H); MS m/z 337 $[M-H]^-$.

Reference Example 5

(2S,5R)-7-Oxo-N-[2-(propan-2-ylamino)ethoxy]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1]octane-2-carboxamide (VI-3)

Step 1

tert-Butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl}(propan-2-yl)carbamate (IV-3)

[0084] A solution of (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (414 mg, 1.50 mmol) in dehydrated dichloromethane (14.1 mL) was cooled under an argon atmosphere to 0 °C, isobutyl chloroformate (245.9 mg) was slowly added so as not to exceed 0 °C. Triethylamine (197 mg) was then slowly added so as not to exceed 0 °C, followed by stirring for 30 minutes, and thus mixed acid anhydride was prepared in the reaction system. To this reaction mixture was slowly added tert-butyl (2-(aminooxy)ethyl)(isopropyl) carbamate (596 mg). After the completion of the introduction, the temperature was elevated to room temperature, followed by stirring for 1 hour. This reaction mixture was washed sequentially with 0.5 M hydrochloric acid and saturated brine, the organic layer was dried over magnesium sulfate, and subsequently the residue resulted from distillation off under reduced pressure was subjected to silica gel column chromatography to afford 578.4 mg of the title compound (yield 81%).

^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 6.8 Hz, 6H), 1.46 (s, 9H), 1.55-1.70 (m, 1H), 1.89-2.07 (m, 2H), 2.25-2.37 (m, 1H), 2.73-2.90 (m, 1H), 2.98-3.08 (m, 1H), 3.22-3.38 (m, 2H), 3.40-3.60 (m, 1H), 3.83-4.06 (m, 4H), 4.90 (d, J = 11.2 Hz, 1H), 5.06 (d, J = 11.2 Hz, 1H), 7.35-7.46 (m, 5H), 10.29 (br.s., 1H); MS m/z 477 $[M+H]^+$.

Step 2

tert-Butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]ethyl}(propan-2-yl)carbamate (V-3)

[0085] In a similar manner to Reference Example 1, the total amount of the compound in Step 1 above gave the title compound (quantitative).

^{1}H NMR (400 MHz, CD_3OD) δ 1.09-1.23 (m, 6H), 1.46 (s, 9H), 1.73-2.27 (m, 4H), 3.06 (d, J = 11.6 Hz, 1H), 3.08-3.50 (m, 4H), 3.64-3.73 (m, 1H), 3.79-3.98 (m, 3H); MS m/z 387 $[M+H]^+$.

Step 3

(2S,5R)-7-Oxo-N-[2-(propan-2-ylamino)ethoxy]-6-(sulfooxy)-1,6-diazabicyclo [3.2.1]octane-2-carboxamide (VI-3)

[0086] In a similar manner to Reference Example 1, the total amount of the compound in Step 2 above gave tetrabutylammonium tert-butyl {2-[({[(2S,5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}(propan-2-yl)carbamate (quantitative).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J = 7.4 Hz, 12H), 1.10-1.20 (m, 6H), 1.33-1.77 (m, 17H), 1.46 (s, 9H), 1.84-1.97 (m, 1H), 2.12-2.25 (m, 1H), 2.28-2.40 (m, 1H), 2.79-2.95 (m, 1H), 3.17-3.45 (m, 9H), 3.50-3.67 (m, 1H), 3.80-4.07 (m, 5H), 4.34 (br.s., 1H), 10.36 (br.s., 1H); MS m/z 465 $[M\text{-}Bu_4N]^-$.

[0087] The total amount of the tetrabutylammonium salt above was deprotected with trifluoroacetic acid and purified by octadecyl silica gel column chromatography, and then 252.1 mg of the title compound was afforded (3 step yield 57%). ^{1}H NMR (500 MHz, D_2O) δ 1.28 (d, J = 6.5 Hz, 6H),1.74-1.83 (m, 1H), 1.85-1.96 (m, 1H), 1.98-2.14 (m, 2H), 3.11 (d, J = 12.5 Hz, 1H), 3.22-3.30 (m, 3H), 3.40 (quint, J = 6.5 Hz, 1H), 4.01 (br d, J = 5.5 Hz, 1H), 4.09-4.18 (m, 3H); MS m/z 367 $[M+H]^+$.

Reference Example 6

(2S,5R)-N-(3-aminopropoxy)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1] octane-2-carboxamide (VI-7)

Step 1

tert-Butyl {3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]propyl}carbamate (IV-7)

[0088] In a similar manner to Reference Example 1, (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (390 mg, 1.41 mmol) and tert-butyl (3-(aminooxy)propyl)carbamate (730 mg) gave 398.1 mg of the title compound (yield 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.50-1.67 (m, 1H), 1.75-1.86 (m, 2H), 1.88-2.07 (m, 2H), 2.28-2.37 (m, 2H), 2.77 (d, J = 11.0 Hz, 1H), 3.01 (br.d., J = 11.0 Hz, 1H), 3.20-3.38 (m, 3H), 3.89-4.04 (m, 3H), 4.90 (d, J = 11.4 Hz, 1H), 5.05 (d, J = 11.4 Hz, 1H), 5.17 (br.s., 1H), 7.36-7.45 (m, 5H), 9.21 (br.s., 1H); MS m/z 449 $[M+H]^+$.

Step 2

tert-Butyl {3-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]propyl}carbamate (V-7)

[0089] In a similar manner to Reference Example 1, the compound in Step 1 above (392.8 mg, 876 μmol) gave the title compound (quantitative).

^{1}H NMR (400 MHz, CD_3OD) δ 1.43 (s, 9H), 1.73-1.99 (m, 4H), 2.01-2.12 (m, 1H), 2.13-2.24 (m, 1H), 3.07 (d, J = 11.6 Hz, 1H), 3.09-3.21 (m, 3H), 3.69 (br.s., 1H), 3.80-3.96 (m, 3H); MS m/z 359 $[M+H]^+$.

Step 3

(2S,5R)-N-(3-aminopropoxy)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1] octane-2-carboxamide (VI-7)

[0090] In a similar manner to Reference Example 1, the total amount of the compound in Step 2 above gave tetrabutylammonium tert-butyl {3-[({[(2S,5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]propyl}carbamate (quantitative).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.4 Hz, 12H), 1.33-1.53 (m, 8H), 1.47 (s, 9H), 1.55-1.96 (m, 12H), 2.14-2.23 (m, 1H), 2.31-2.41 (m, 1H), 2.85 (br.d., J= 11.2 Hz, 1H), 3.15-3.42 (m, 11H), 3.88-4.07 (m, 3H), 4.35 (br.s., 1H), 5.27 (br s, 1H), 9.26 (br.s., 1H); MS m/z 437 $[M-Bu_4N]^-$.

[0091] The total amount of the tetrabutylammonium salt above was deprotected with trifluoroacetic acid and purified by octadecyl silica gel column chromatography, and then 138.4 mg of the title compound was afforded (3 step yield 47%). ^{1}H NMR (400 MHz, D_2O) δ 1.67-2.05 (m, 6H), 3.00-3.19 (m, 4H), 3.82-3.94 (m, 3H), 4.05-4.10 (m, 1H); MS m/z 337 $[M-H]^-$.

Reference Example 7

(2S,5R)-N-[(2S)-Azetidin-2-ylmethoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide (VI-8)

Step 1

tert-Butyl (2S)-2-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}azetidine-1-carboxylate (IV-8)

[0092] In a similar manner to Reference Example 5, (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (553 mg, 2.00 mmol) and (S)-tert-butyl 2-((aminooxy)methyl)azetidine-1-carboxylate (578 mg) gave 760.1 mg of the title compound (yield 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.56-1.70 (m, 1H), 1.88-2.07 (m, 3H), 2.23-2.34 (m, 2H), 2.84 (d, J = 11.6 Hz, 1H), 3.02 (d, J = 11.6 Hz, 1H), 3.28 (br s, 1H), 3.77-4.03 (m, 4H), 4.06-4.15 (m, 1H), 4.37-4.48 (m, 1H), 4.89 (d, J =11.6 Hz, 1H), 5.04 (d, J = 11.6 Hz, 1H), 7.34-7.44 (m, 5H), 10.63 (br.s., 1H); MS m/z 461 $[M+H]^+$.

Step 2

tert-Butyl (2S)-2-{[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}azetidine-1-carboxylate (V-8)

[0093] In a similar manner to Reference Example 1, the compound in Step 1 above (699 mg, 1.52 mmol) gave the title compound (quantitative).

^{1}H NMR (400 MHz, CD_3OD) δ 1.44 (s, 9H), 1.74-1.85 (m, 1H), 1.86-1.99 (m, 1H), 2.02-2.14 (m, 1H), 2.16-2.40 (m, 3H), 3.06 (d, J = 11.6 Hz, 1H), 3.10-3.17 (m, 1H), 3.67-3.74 (m, 1H),

3.75-3.93 (m, 3H), 4.01 (dd, J = 10.6, 10.6 Hz, 1H), 4.14 (dd, J = 10.6, 10.6 Hz, 1H), 4.37-4.47 (m, 1H); MS m/z 371 $[M+H]^+$.

Step 3

(2S,5R)-N-[(2S)-Azetidin-2-ylmethoxy]-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]octane-2-carboxamide (VI-8)

[0094] In a similar manner to Reference Example 1, the total amount of the compound in Step 2 above gave tetrabutylammonium tert-butyl (2S)-2-{[({[(2S,5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}azetidine-1-car boxylate (quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 12H), 1.30-2.10 (m, 19H), 1.46 (s, 9H), 2.12-2.39 (m, 3H), 2.89 (br.d., J = 12.0 Hz, 1H), 3.23-3.39 (m, 9H), 3.76-3.93 (m, 3H), 3.95-4.06 (m, 1H), 4.08-4.18 (m, 1H), 4.33 (br.s., 1H), 4.37-4.50 (m, 1H); MS m/z 449 $[M-Bu_4N]^-$.

[0095] The total amount of the tetrabutylammonium salt above was deprotected with trifluoroacetic acid and purified by octadecyl silica gel column chromatography, and then 172.3 mg of the title compound was afforded (3 step yield 32%). ^{1}H NMR (500 MHz, D_2O) δ 1.71-1.83 (m, 1H), 1.84-1.97 (m, 1H), 1.98-2.16 (m, 2H), 2.36-2.49 (m, 1H), 2.50-2.61 (m, 1H), 3.10 (d, J = 12.0 Hz, 1H), 3.22-3.30 (m, 1H), 3.92-4.12 (m, 5H), 4.25-4.36 (m, 1H), 4.68-4.77 (m, 1H); MS m/z 351 $[M+H]^+$.

Reference Example 8

(2S,5R)-7-Oxo-N-[(3S)-pyrrolidin-3-yloxy]-6-(sulfooxy)-1,6-diazabicyclo[3.2. 1]octane-2-carboxamide (VI-11)

Step 1

tert-Butyl (3S)-3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]pyrrolidine-1-carboxylate (IV-11)

[0096] In a similar manner to Reference Example 1, (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (553 mg, 2.00 mmol) and (S)-tert-butyl 3-

(aminooxy)pyrrolidine-1-carboxylate (606 mg) gave 920.4 mg of the title compound (quantitative).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.61-1.68 (m, 1H), 1.89-2.09 (m, 3H), 2.15-2.19 (m, 1H), 2.28-2.34 (m, 1H), 2.75 (d, J = 11.6 Hz, 1H), 2.95-3.06 (m, 1H), 3.31 (br s, 1H), 3.35-3.68 (m, 4H), 3.97 (d, J = 7.6 Hz, 1H), 4.60 (br.d., J= 23.2 Hz, 1H), 4.90 (d, J = 11.6 Hz, 1H), 5.05 (d, J = 11.6 Hz, 1H), 7.26-7.43 (m, 5H), 9.08 (br.d., J = 23.2 Hz, 1H); MS m/z 461 $[M+H]^+$.

Step 2

tert-Butyl (3S)-3-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]pyrrolidine-1-carboxylate (V-11)

[0097] In a similar manner to Reference Example 1, the compound in Step 1 above (869 mg, 1.89 mmol) gave the title compound (quantitative).

^{1}H NMR (400 MHz, CD_3OD) δ 1.47 (s, 9H), 1.75-2.12 (m, 4H), 2.13-2.25 (m, 2H), 3.05 (d, J = 12.0 Hz, 1H), 3.13 (br.d., J = 12.0 Hz, 1H), 3.25-3.50 (m, 2H), 3.61 (br.d., J = 13.2 Hz, 1H), 3.70 (br.s., 1H), 3.86 (br d, J = 7.2 Hz, 1H), 4.32-4.38 (m, 1H), 4.54-4.62 (m, 1H); MS m/z 371 $[M+H]^+$.

Step 3

(2S,5R)-7-Oxo-N-[(3S)-pyrrolidin-3-yloxy]-6-(sulfooxy)-1,6-diazabicyclo[3.2. 1]octane-2-carboxamide (VI-11)

[0098] In a similar manner to Reference Example 1, the total amount of the compound in Step 2 above gave tetrabutylammonium tert-butyl (3S)-3-[({[(2S,5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]pyrrolidine-1-carboxyl ate (quantitative). MS m/z 449$[M-Bu_4N]^-$.

[0099] The total amount of the tetrabutylammonium salt above was deprotected with trifluoroacetic acid and purified by octadecyl silica gel column chromatography, and then 170.7 mg of the title compound was afforded (3 step yield 26%). ^{1}H NMR (400 MHz, D_2O) δ 1.71-1.92 (m, 2H), 1.95-2.18 (m, 3H), 2.21-2.30 (m, 1H), 3.07 (d, J = 12.2 Hz, 1H), 3.24 (br.d., J = 12.2 Hz, 1H), 3.31-3.45 (m, 3H), 3.51 (d, J = 13.6 Hz, 1H), 3.99 (br.d., J = 6.0 Hz, 1H), 4.10-4.14 (m, 1H), 4.72-4.77 (m, 1H); MS m/z 349 $[M-H]^-$.

Reference Example 9

(2S,5R)-N-(Azetidin-3-ylmethoxy)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1] octane-2-carboxamide (VI-12)

Step 1

tert-Butyl 3-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]methyl}azetidine-1-carboxylate (IV-12)

[0100] In a similar manner to Reference Example 5, (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (553 mg, 2.00 mmol) and tert-butyl 3-((aminooxy)methyl)azetidine-1-carboxylate (564 mg) gave 699.7 mg of the title compound (yield 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.54-1.70 (m, 1H), 1.87-2.06 (m, 2H), 2.27-2.35 (m, 1H), 2.75 (d, J = 11.6 Hz, 1H), 2.80-2.90 (m, 1H), 3.01 (br.d., J = 11.6 Hz, 1H), 3.32 (br.s., 1H), 3.68-3.76 (m, 2H), 3.94 (br.d., J = 7.6 Hz, 1H), 4.00-4.15 (m, 4H), 4.90 (d, J = 11.8 Hz, 1H), 5.05 (d, J = 11.8 Hz, 1H), 7.35-7.44 (m, 5H), 9.08 (br s, 1H); MS m/z 461 $[M+H]^+$.

Step 2

tert-Butyl 3-{[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl}amino)oxy]methyl}azetidine-1-carboxylate (V-12)

[0101] In a similar manner to Reference Example 1, the compound in Step 1 above (642 mg, 1.39 mmol) gave the title compound (quantitative).

^{1}H NMR (400 MHz, CD_3OD) δ 1.43 (s, 9H), 1.74-1.85 (m, 1H), 1.86-1.97 (m, 1H), 2.04-2.13 (m, 1H), 2.16-2.24 (m, 1H), 2.84-2.94 (m, 1H), 3.05 (d, J = 11.6 Hz, 1H), 3.13 (br.d., J = 11.6 Hz, 1H), 3.68-3.82 (m, 3H), 3.83 (br.d., J = 6.8 Hz, 1H), 3.97-4.06 (m, 4H); MS m/z 371 $[M+H]^+$.

Step 3

(2S,5R)-N-(azetidin-3-ylmethoxy)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1] octane-2-carboxamide (VI-12)

[0102] In a similar manner to Reference Example 1, the total amount of the compound in Step 2 above gave tetrabutylammonium tert-butyl 3-{[({[(2S,5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]methyl}azetidine-1-carboxylate (quantitative).

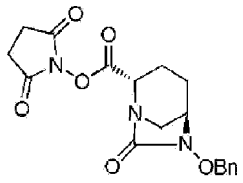
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 12H), 1.37-1.51 (m, 8H), 1.46 (s, 9H), 1.54-1.75 (m, 9H), 1.82-1.97 (m, 1H), 2.13-2.25 (m, 1H), 2.29-2.40 (m, 1H), 2.77-2.95 (m, 2H), 3.24-3.40 (m, 9H), 3.64-4.16 (m, 7H), 4.36 (br.s., 1H), 9.16 (br.s., 1H); MS m/z 449 $[M\text{-}Bu_4N]^-$.

[0103] The total amount of the tetrabutylammonium salt above was deprotected with trifluoroacetic acid and purified by octadecyl silica gel column chromatography, and then 164.7 mg of the title compound was afforded (3 step yield 34%). ^{1}H NMR (400 MHz, D_2O) δ 1.65-1.89 (m, 2H), 1.92-2.06 (m, 2H), 3.06 (d, J = 12.4 Hz, 1H), 3.10-3.22 (m, 2H), 3.90-4.00 (m, 5H), 4.07-4.14 (m, 3H); MS m/z 351 $[M+H]^+$.

Reference Example 10

2,5-Dioxopyrrolidin-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1] octane-2-carboxylate (III-57)

[0104]



III-57

[0105] (2S,5R)-6-(Benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (201 mg, 0.758 mmol) was dissolved in dehydrated dichloromethane (3.6 mL), and N-methylmorpholine (162 mg) was added, followed by cooling to 0 °C. To the mixture was added isobutyl chloroformate (198.8 mg), followed by stirring for 10 minutes. Subsequently, 1-hydroxypyrrolidine-2,5-dione (167 mg) was added, followed by stirring for another 0.5 hours. The reaction mixture was washed with water and dried over anhydrous magnesium sulfate, and the filtrate was concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 1/2) to afford 161 mg of the title compound as a colorless solid (yield 57%).

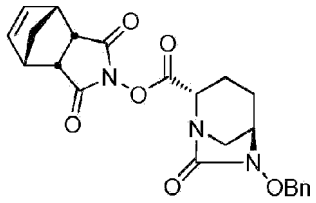
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70-1.77 (m, 1H), 2.04-2.27 (m, 3H), 2.80-2.90 (m, 4H), 3.09-3.19 (m, 2H), 3.35 (br.s., 1H), 4.48 (d, J = 6.9 Hz, 1H), 4.92 (d, J = 11.3 Hz, 1H), 5.07 (d, J =

11.3 Hz, 1H), 7.35-7.45 (m, 5H); MS m/z 374 $[M+H]^+$.

Reference Example 11

(1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6 -(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-58)

[0106]



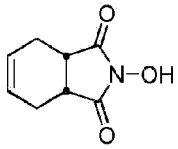
III-58

[0107] (2S,5R)-6-(Benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (529 mg, 1.918 mmol) was dissolved in dehydrated tetrahydrofuran (5.5 mL), followed by cooling to -20 °C. To the mixture was added N-methylmorpholine (445 mg) and isobutyl chloroformate (300 mg), followed by stirring for 15 minutes. Subsequently, (1R,2S,6R,7S)-4-hydroxy-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (394 mg) was added, followed by stirring for 0.5 hours and then at room temperature for another 0.5 hours. The reaction mixture was diluted with chloroform (50 mL), washed sequentially with 1 M hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL) and saturated brine (20 mL) and dried over anhydrous magnesium sulfate, and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in chloroform (4 mL), and hexane (4 mL) was added, followed by stirring for 5 minutes. Further, hexane (4 mL) was added, followed by stirring and aging for 1.5 hours. The precipitated solid was filtered, washed with a mixed solution of chloroform/hexane (2/3) and dried under reduced pressure to afford 678 mg of the title compound as a colorless crystalline-powder (yield 81%).
HPLC: COSMOSIL 5C18 MS-II 4.6X150mm, 35 °C, 0.02M TFA/CH3CN = 50/50, 1.0 ml/min, UV 210 nm, RT 7.1 min; enantiomeric excess 99.9 %ee or more: CHIRALPAK AD-H, 4.6 x 150 mm, 40 °C, Hexane/EtOH = 1/1, UV 210 nm, 1 mL/min, RT 37.3 min (cf. enantiomer 16.5 min); Mp 196 °C; $[\alpha]^{26}_D$ +12.686 ° (c 0.885, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 9.1 Hz, 1H), 1.70 (m, 1H), 1.78 (d, J = 9.1 Hz, 1H), 2.01-2.26 (m, 3H), 3.04-3.17 (m, 2H), 3.32 (m, 3H), 3.45 (br.s., 2H), 4.41 (d, J = 6.7 Hz, 1H), 4.91 (d, J = 11.4 Hz, 1H), 5.06 (d, J = 11.4 Hz, 1H), 6.19 (br.s., 2H), 7.33-7.46 (m, 5H); MS m/z 438 $[M+H]^+$.

Reference Example 12

(3aR,7aS)-2-Hydroxy-3a,4,7,7a-tetrahydro-1H-isoindol-1,3(2H)-dione

[0108]



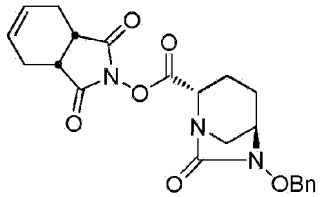
[0109] Hydroxylamine sulfate (24.975 g, 0.152 mol) was dissolved in water (100 mL), and (3aR,7aS)-3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (45.228 g) was added. To the mixture was added 25% sodium hydroxide aqueous solution (50 g) over 15 minutes in small portions, followed by stirring at 90 °C for 2 hours. The mixture was cooled to room temperature, and the precipitated crystalline-solid was suction-filtered, followed by deliquoring for 30 minutes. The wet crystals were dried in vacuo at 50 °C for 2 days to afford 42.87 g of the title compound (yield 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20-2.31 (m, 2H), 2.56-2.65 (m, 2H), 3.08-3.14 (m, 2H), 5.91 (dt, J = 0.9, 2.7 Hz, 2H); MS m/z 166 $[M-H]^-$.

Reference Example 13

(3aR,7aS)-1,3-Dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-59)

[0110]



III-59

[0111] (2S,5R)-6-(Benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (1.831 g, 5 mmol) was dissolved in dehydrated tetrahydrofuran (15 mL), followed by cooling to -20 °C. To the mixture were added isobutyl chloroformate (751 mg) and triethylamine (1.111 g), followed by stirring for 15 minutes. Subsequently, (3aR,7aS)-2-hydroxy-3a,4,7,7a-tetrahydro-1H-isoindol-1,3(2H)-dione (Reference Example 12, 919 mg) was added, followed by stirring for 0.5 hours and then at room temperature for another 0.5 hours. The reaction mixture was diluted with chloroform (150 mL), washed sequentially with 1 M hydrochloric acid (60 mL), saturated

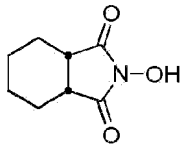
sodium bicarbonate (60 mL) and saturated brine (60 mL) and dried over anhydrous magnesium sulfate, and the filtrate was concentrated under reduced pressure. The resulting residue was dissolved in chloroform (4 mL), and hexane (4 mL) was added, followed by stirring for 30 minutes. Further, hexane (2 mL) was added, followed by stirring and aging for 30 minutes. The precipitated solid was filtered, washed with a mixed solution of chloroform/hexane (2/3) and dried under reduced pressure to afford 1.419 g of the title compound as a colorless crystalline-powder (yield 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.77 (m, 1H), 2.08 (d, J = 14.2 Hz, 1H), 2.14-2.26 (m, 2H), 2.30 (d, J = 13.8 Hz, 2H), 2.55-2.66 (m, 2H), 3.10-3.24 (m, 4H), 3.34 (bs, 1H), 4.45 (d, J = 6.4 Hz, 1H), 4.91 (d, J = 11.2 Hz, 1H), 5.06 (d, J = 11.4 Hz, 1H), 5.97 (bs, 2H), 7.34-7.45 (m, 5H); MS m/z 426 $[M+H]^+$.

Reference Example 14

(3aR,7aS)-2-Hydroxyhexahydro-1H-isoindol-1,3(2H)-dione

[0112]



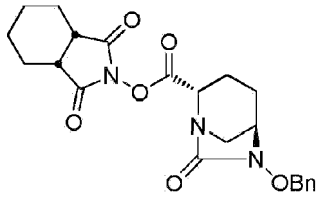
[0113] Hydroxylamine sulfate (24.975 g, 0.152 mol) was dissolved in water (75 mL) and (3aR,7aS)-hexahydroisobenzofuran-1,3-dione (48.000 g) was added. To the mixture was added 25% sodium hydroxide aqueous solution (50 g) over 15 minutes in small portions, followed by stirring at 90 °C for 1 hour. The mixture was cooled to room temperature, extracted twice with chloroform 50 mL, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, the residue was dissolved in chloroform, insoluble was filtered, and the solvent was concentrated under reduced pressure. The residue was dissolved by adding ethyl acetate, the solvent was concentrated under reduced pressure and dried in vacuo for further 2 days to afford 49.35 g of the title compound as a colorless solid (yield 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (dt, J = 3.0, 5.9 Hz, 4H), 1.71-1.90 (m, 4H), 2.84-2.92 (m, 2H), 6.01 (b rs, 1H); MS m/z 168 $[M-H]^-$.

Reference Example 15

(3aR,7aS)-1,3-Dioxohexahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-60)

[0114]



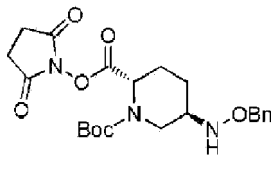
III-60

[0115] (2S,5R)-6-(Benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylic acid (1.831 g, 5 mmol) was dissolved in dehydrated tetrahydrofuran (15 mL), followed by cooling to -20 °C. To the mixture were added isobutyl chloroformate (751 mg) and triethylamine (1.111 g), followed by stirring for 15 minutes. Subsequently, (3aR,7aS)-2-hydroxyhexahydro-1H-isoindol-1,3(2H)-dione (Reference Example 14, 919 mg) was added, followed by stirring for 0.5 hours and then at room temperature for another 0.5 hours. The reaction mixture was diluted with chloroform (150 mL), washed sequentially with 1M hydrochloric acid (60 mL), saturated sodium bicarbonate (60m L), and saturated brine (60 mL), and dried over anhydrous magnesium sulfate, and the filtrate was concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (chloroform/ethyl acetate = 6/1) to afford 1.294 g of the title compound as a colorless solid (yield 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ1.50 (bs, 4H), 1.62 (bs, 1H), 1.68-1.84 (m, 1H), 1.91 (bs, 4H), 2.04-2.27 (m, 2H), 3.02 (bs, 2H), 3.15 (s, 2H), 3.35 (bs, 1H), 4.47 (d, J = 6.6 Hz, 1H), 4.92 (d, J = 11.2 Hz, 1H), 5.07 (d, J = 11.4 Hz, 1H), 7.34-7.45 (m, 5H); MS m/z 428 $[M+H]^+$.

Example 1

tert-Butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy)amino) piperidine-1,2-dicarboxylate (II-30)

[0116]



II-30

[0117] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 6.75 g, 19.26 mmol) was dissolved in dehydrated dichloromethane (80 mL), and 1-hydroxypyrrolidine-2,5-dione (6.65 g) was added, followed by ice cooling. To the

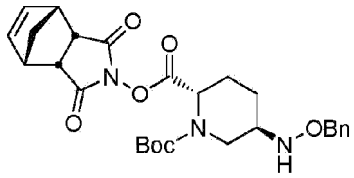
mixture were sequentially added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (4.62 g) and 4-dimethylaminopyridine (1.2 g), followed by stirring at room temperature overnight. The residue resulted from concentration of the reaction solution under reduced pressure was diluted with ethyl acetate, washed sequentially with ice-cold 10% citric acid, saturated sodium bicarbonate and saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 1/1) to afford 5.61 g of the title compound (yield 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.54 (m, 9H), 1.70-1.77 (m, 2H), 2.09-2.21 (m, 2H), 2.84 (br.s., 4H), 3.13-3.26 (m, 1H), 3.29 (br.s., 1H), 4.18-4.27 (m, 1H), 4.67-4.78 (m, 2H), 5.06 (br.s., 0.5H), 5.35 (br.s., 0.5H), 5.46 (br.s., 1H), 7.28-7.39 (m, 5H); MS m/z 448 $[M+H]^+$.

Example 2

1-tert-Butyl 2-((1R,2S,6R,7S)-3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl) (2S,5R)-5-((benzyloxy)amino)piperidine-1,2-dicarboxylate (II-31)

[0118]



II-31

[0119] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 1.40 g, 4.0 mmol) was dissolved in dehydrated dichloromethane (15 mL), and (1R,2S,6R,7S)-4-hydroxy-4-azatricyclo[5.2.1.0^{2,6}] dec-8-ene-3,5-dione (859 mg) was added, followed by ice cooling. To the mixture were sequentially added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (920 mg) and 4-dimethylaminopyridine (244 mg), followed by stirring at room temperature overnight. The residue resulted from concentration of the reaction solution under reduced pressure was diluted with ethyl acetate, washed sequentially with ice-cold 10% citric acid, saturated sodium bicarbonate and saturated brine, dried over anhydrous magnesium sulfate and filtered, and the solvent was distilled off under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford 1.87 g of the title compound as a colorless crystalline powder (yield 92%).

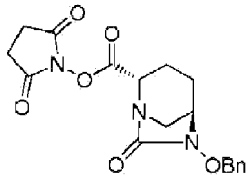
^{1}H NMR (400 MHz, $CDCl_3$) δ1.46 (s, 9H), 1.52 (m, 1H), 1.65-1.83 (m, 3H), 1.93-2.19 (m, 2H), 3.09-3.23 (m, 2H), 3.26 (m, 1H), 3.32 (br.s., 2H), 3.44 (br.s., 2H), 4.12-4.24 (m, 1H), 4.68 (d, J = 11.5 Hz, 1H), 4.74 (d, J = 11.5 Hz, 1H), 4.99 (br.s., 0.5H), 5.28 (br.s., 0.5H), 5.44 (br.s., 1H),

6.20 (br.s., 2H), 7.24-7.40 (m, 5H); MS m/z 512 $[M+H]^+$.

Example 3a

2,5-Dioxopyrrolidin-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1] octane-2-carboxylate (III-57)

[0120]



III-57

Step 1

1-tert-Butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy) ((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylate or 1-tert-butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino) piperidine-1,2-dicarboxylate

[0121] tert-Butyl 2-(2,5-dioxopyrrolidin-1-yl) (2S,5R)-5-((benzyloxy)amino) piperidine-1,2-dicarboxylate (Example 1, 447 mg, 1 mmol) was dissolved in dehydrated dichloromethane (8 mL), and diisopropylethylamine (259 mg) was added, followed by ice cooling. To the mixture was added triphosgene (169 mg), followed by stirring for 1.5 hours, and the completion of the reaction for the title compounds was confirmed by TLC. The compounds were subjected to the next step without purification and isolation.

Step 2

2,5-Dioxopyrrolidine-1-yl (2S,5R)-5-((benzyloxy)((trichloromethoxy) carbonyl)amino)piperidine-2-carboxylate or 2,5-dioxopyrrolidine-1-yl (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino)piperidine-2-carboxylate, methanesulfonate

[0122] To the mixture in Step 1 above was added methanesulfonic acid (961 mg) under ice

cooling, followed by stirring for 5 minutes, and the completion of the reaction for the title compounds was confirmed by TLC. The compounds were subjected to the next step without purification and isolation.

Step 3

2,5-Dioxopyrrolidine-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane-2-carboxylate

[0123] To the mixture in Step 2 above was added dropwise diisopropylethylamine (1.43 g), followed by stirring for 0.5 hours. The reaction solvent was concentrated under reduced pressure. The residue was diluted with ethyl acetate (65 mL), washed sequentially with 1 M hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL) and saturated brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The solid in the residue was washed sequentially with hexane/ethyl acetate (1/1, 2 mL), hexane/ethyl acetate (2/1, 2 mL) and hexane (2 mL) and dried in vacuo to afford 274 mg of the title compound as a colorless crystalline powder (total yield over three steps: 73%). Instrumental data were consistent with those of Reference Example 10.

Example 3b

2,5-Dioxopyrrolidine-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane-2-carboxylate (III-57) Sequential synthesis 1

[0124] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 354 mg, 1 mmol) was dissolved in dehydrated acetonitrile (8 mL), and diisopropylethylamine (194 mg) and 4-dimethylaminopyridine (12 mg) were added, followed by ice cooling. To the mixture was added bis (2,5-dioxopyrrolidine-1-yl)carbonate (384 mg), followed by stirring at room temperature for 3 hours. The residue resulted from concentration of the reaction solution under reduced pressure was diluted with ethyl acetate (65 mL), washed with 10% citric acid (20 mL), and subsequently stirred with saturated sodium bicarbonate (20 mL) for 15 minutes. The organic layer was separated, washed with saturated brine (20 mL), dried over anhydrous magnesium sulfate and filtered. The solvent was distilled off under reduced pressure to give 436 mg of the residue (step yield 98%). The total amount of the residue was dissolved in dehydrated dichloromethane (8 mL), and diisopropylethylamine (259 mg) was added, followed by ice cooling. To the mixture was added triphosgene (169 mg), followed by stirring for 1 hour. Methanesulfonic acid (961 mg) was then added, followed by stirring for 5 minutes. The mixture was added dropwise to ice-cold 1 M potassium bicarbonate (1.1 g/9 mL), followed by stirring for 0.5 hours. Ethyl acetate (65 mL) was added and the layers

were separated. The organic layer was washed sequentially with 1 M hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL) and saturated brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The solid in the residue was washed sequentially with hexane/ethyl acetate (1/1, 2 mL), hexane/ethyl acetate (2/1, 2 mL) and hexane (2 mL) to afford 260 mg of the title compound as crystalline solid (total yield 58%). Instrumental data were consistent with those of Reference Example 10.

Example 3c

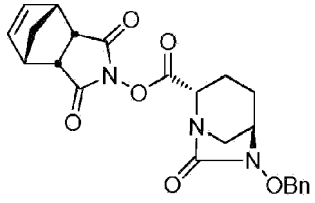
2,5-Dioxopyrrolidine-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane-2-carboxylate (III-57) Sequential synthesis 2

[0125] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 700 mg, 2 mmol) was dissolved in dehydrated tetrahydrofuran (10 mL), followed by cooling to -20 °C. To the mixture were sequentially added dropwise isobutyl chloroformate (300 mg) and triethylamine (444 mg), followed by stirring for 15 minutes. To the reaction solution was added 1-hydroxypyrrolidine-2,5-dione (253 mg), followed by stirring for 30 minutes and stirring for another 30 minutes at room temperature. The reaction solution was diluted with ethyl acetate (35 mL), washed sequentially with 10% citric acid (10 mL), saturated sodium bicarbonate (10 mL) and saturated brine (10 mL), dried over anhydrous magnesium sulfate and filtered, and the solvent was distilled off under reduced pressure to give 985 mg of the residue. The total amount of the residue was dissolved in dehydrated chloroform (10 mL), and triethylamine (303 mg) was added, followed by ice cooling. To the mixture was added triphosgene (237 mg), followed by stirring for 30 minutes. Methanol (0.1 mL) was added, followed by stirring for 30 minutes. A solution of methanesulfonic acid (1.3 mL) in dichloromethane (4.0 mL) was then added dropwise, followed by further stirring for 30 minutes. The mixture was added dropwise to ice-cold 1 M potassium bicarbonate (2.4 g/20 mL), followed by stirring for 30 minutes. Chloroform (10 mL) was added and the layers were separated. The organic layer was washed sequentially with 1 M hydrochloric acid (10 mL), saturated sodium bicarbonate (10 mL) and saturated brine (10 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Seeding was carried out to the residue, and to the solid was added hexane/ethyl acetate (1/2, 3 mL), stirred, filtered, washed sequentially with hexane/ethyl acetate (1/1, 3 mL) and hexane (3 mL) to afford 556 mg of the title compound as crystals (total yield 75%). Instrumental data were consistent with those of Reference Example 10.

Example 4a

(1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-58)

[0126]



III-58

Step 1

1-tert-Butyl 2-((1R,2S,6R,7S)-3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl) (2S,5R)-5-((benzyloxy)((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylat e or 1-tert-butyl 2-((1R,2S,6R,7S)-3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl) (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino)piperidine-1,2-dicarboxylate

[0127] 1-tert-Butyl 2-((1R,2S,6R,7S)-3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl) (2S,5R)-5-((benzyloxy)amino)piperidine-1,2-dicarboxylate (Example 2, 512 mg, 1 mmol) was dissolved in dehydrated dichloromethane (8 mL), and diisopropylethylamine (260 mg) was added, followed by ice cooling. To the mixture was added triphosgene (169 mg), followed by stirring for 0.5 hours, and the completion of the reaction for the title compounds was confirmed by TLC (MS m/z 575 $[M+H]^+$). The compounds were subjected to the next step without purification and isolation.

Step 2

(1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl (2S,5R)-5-((benzyloxy)((trichloromethoxy)carbonyl)amino)piperidine-2-carboxylate or (1R,2S,6R,7S)-3,5-dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino)piperidine-2-carboxylate, methanesulfonate

[0128] To the mixture in Step 1 above was added methanesulfonic acid (0.65 mL) under ice cooling, followed by stirring for 5 minutes, and the completion of the reaction for the title compounds was confirmed by TLC. The compounds were subjected to the next step without purification and isolation.

Step 3

(1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate

[0129] The mixture in Step 2 above was added dropwise to ice-cold 1 M potassium bicarbonate (1.1 g/9 mL), followed by stirring for 0.5 hours. Ethyl acetate (65 mL) was added and the layers were separated. The organic layer was washed sequentially with 1 M hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL) and saturated brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The solid in the residue was washed with ethyl acetate/hexane (1:2) and dried to afford 346 mg of the title compound as a colorless crystalline powder (total yield over three steps: 79%). Instrumental data were consistent with those of Reference Example 11.

Example 4b

(1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-58) Sequential synthesis 1

[0130] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 368 mg, 1.05 mmol) was dissolved in dehydrated dichloromethane (4 mL), and (1R,2S,6R,7S)-4-hydroxy-4-azatricyclo[5.2.1.$0^{2,6}$] dec-8-ene-3,5-dione (207 mg) was added, followed by ice cooling. To the mixture were sequentially added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (221 mg) and 4-dimethylaminopyridine (13 mg), followed by stirring at room temperature overnight. The residue resulted from concentration of the reaction solution under reduced pressure was diluted with ethyl acetate (30 mL), washed sequentially with ice-cold 10% citric acid (10 mL), saturated sodium bicarbonate (10 mL) and saturated brine (10 mL), dried over anhydrous magnesium sulfate, and filtered. The total amount of the residue 541 mg obtained by distilling off the solvent under reduced pressure was dissolved in dehydrated dichloromethane (8 mL), and diisopropylethylamine (155 mg) was added, followed by ice cooling. To the mixture was added triphosgene (119 mg), followed by stirring for 0.5 hours. Methanesulfonic acid (0.52 mL) was then added, followed by stirring for 5 minutes. The mixture was added dropwise to ice-cold 1 M potassium bicarbonate (801 mg/9 mL), followed by stirring for 0.5 hours. Ethyl acetate (65 mL) was added and the layers were separated. The organic layer was washed sequentially with 1 M hydrochloric acid (20 mL), saturated sodium bicarbonate (20 mL) and saturated brine (20 mL), dried over anhydrous magnesium sulfate, and filtered. The solid in the residue resulted from concentration of the solvent under reduced pressure was washed with hexane/ethyl

acetate (1/3), filtered and dried to afford 346 mg of the title compound (total yield 75%). Instrumental data were consistent with those of Reference Example 11.

Example 4c

(1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-58) Sequential synthesis 2

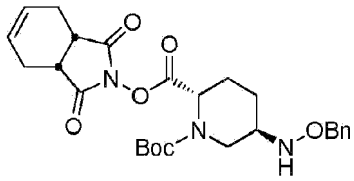
[0131] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 14.0 g, 41.09 mmol) was dissolved in dehydrated tetrahydrofuran (200 mL), followed by cooling to around -20 °C. To the mixture were added dropwise isobutyl chloroformate (6.11 g) and then triethylamine (8.86 g), followed by stirring at the same temperature for 15 minutes. Then, to the reaction solution was added (1R,2S,6R,7S)-4-hydroxy-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (7.87 g), followed by stirring at the same temperature for 30 minutes and then at room temperature for 30 minutes. The reaction solution was diluted with ethyl acetate (700 mL), washed sequentially with ice-cold 10% citric acid (200 mL), saturated sodium bicarbonate (200 mL) and saturated brine (200 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent was distilled off under reduced presssure, substitution-concentration was again carreid out with ethyl acetate, the total amount of the resulting residue 25.1 g (net yield 92%) was dissolved in dehydrated chloroform (180 mL), and triethylamine (5.5 g) was added, followed by ice cooling. To the mixture was added triphosgene (4.29 g), followed by stirring for 30 minutes. Methanol (1 mL) was then added, followed by stirring for 30 minutes. To the reaction solution was added dropwise a solution of methanesulfonic acid (23.5 mL) in dichloromethane (30 mL), followed by stirring for another 30 minutes. The mixture was added dropwise to ice-cold 1 M potassium bicarbonate (43.5 g/200 ml), followed by stirring for 30 minutes. Chloroform (100 ml) was added and the layers were separated. The organic layer was washed sequentially with 1 M hydrochloric acid (200 mL), saturated sodium bicarbonate (200 mL) and saturated brine (200 mL). Each aqueous layer was back-extracted with chloroform (100 mL) sequentially. The organic layers was combined, dried over anhydrous magnesium sulfate, and filtered. The residue obtained by concentration of the solvent under reduced pressure was dissolved in chloroform (70 mL), hexane (100 mL) was added, followed by stirring for 30 minutes for crystallization. Further, hexane (100 mL) was added for stirring and aging for 1 hour. The crystalline solid was filtered and dried to afford 15.4 g of the title compound (content 100%, total yield 88%). Instrumental data were consistent with those of Reference Example 11. As a result of evaluation of the stability of this product, it remained stable in a refrigerator for one month.

Example 5

1-tert-Butyl

2-((3aR,7aS)-1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5-((benzyloxy)amino)piperidine-1,2-dicarboxylate (II-32)

[0132]



II-32

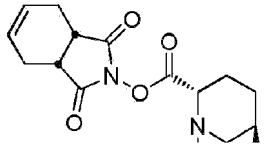
[0133] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 3.504 g, 10 mmol) was dissolved in dehydrated tetrahydrofuran (50 mL), followed by cooling to around -20 °C. To the mixture were added dropwise isobutyl chloroformate (1.51 g) and then triethylamine (2.17 g), followed by stirring at the same temperature for 15 minutes. Then, to the reaction solution was added (3aR,7aS)-2-hydroxy-3a,4,7,7a-tetrahydro-1H-isoindol-1,3(2H)-dione (Reference Example 12, 1.84 g), followed by stirring at the same temperature for 30 minutes and then at room temperature for 30 minutes. The reaction solution was diluted with ethyl acetate (200 mL), washed sequentially with ice-cold 10% citric acid (60 mL), saturated sodium bicarbonate (60 mL) and saturated brine (60 mL), dried over anhydrous magnesium sulfate, and filtered. The residue obtained by concentration of the filtrate under reduced pressure was subjected to silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford 4.689 g of the title compound as a colorless foamy solid (yield 94 %).

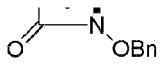
^{1}H NMR (400 MHz, $CDCl_3$) δ1.47 (bs, 9H), 1.59-1.75 (m, 2H), 2.04-2.32 (m, 2H), 2.16-2.35 (m, 2H), 2.61 (d, J=15.2 Hz, 2H), 3.14-3.24 (m, 4H), 4.15-4.22 (m, 1H), 4.71 (q, J=11.6 Hz, 2H), 5.03 (bs, 1H), 5.97 (bs, 2H), 7.26-7.38 (m, 5H); MS m/z 500 $[M+H]^+$.

Example 6a

(3aR,7aS)-1,3-Dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-59)

[0134]





III-59

Step 1

1-tert-Butyl 2-((3aR,7aS)-1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5-((benzyloxy)((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylate or 1-tert-butyl 2-((3aR,7aS)-1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2 (3H)-yl) (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino)piperidine-1,2-dicarboxylate

[0135] 1-tert-Butyl 2-((3aR,7aS)-1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5-((benzyloxy)amino)piperidine-1,2-dicarboxylate (Example 5, 4.689 g, 9.386 mmol) was dissolved in dehydrated chloroform (50 mL), and triethylamine (1.40 g) was added, followed by ice cooling. To the mixture was added triphosgene (1.09 g), followed by stirring for 0.5 hours, and the completion of the reaction for the title compounds was confirmed by TLC. The compounds were subjected to the next step without purification and isolation.

Step 2

(3aR,7aS)-1,3-Dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-5-((benzyloxy)((trichloromethoxy)carbonyl)amino)piperidine-2-carboxylate or (3aR,7aS)-1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino)piperidine-2-carboxylate, methanesulfonate

[0136] To the mixture in Step 1 above was added methanol (0.255 mL) under ice cooling, followed by stirring for 30 minutes. Subsequently, methanesulfonic acid (8.89 g) was added, followed by stirring for 30 minutes, and the completion of the reaction for the title compounds was confirmed by TLC. The compounds were subjected to the next step without purification and isolation.

Step 3

(3aR,7aS)-1,3-Dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate

[0137] The mixture in Step 2 above was added dropwise to ice-cold 1 M potassium bicarbonate (11.1 g/100 mL), followed by stirring for 0.5 hours. Chloroform (30 mL) was added, layers are separated, the organic layer was washed sequentially with 1 M hydrochloric acid (70 mL), saturated sodium bicarbonate (70 mL) and saturated brine (70 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in chloroform (16 mL), hexane (24 mL) was added, followed by stirring for 15 minutes. Further, hexane (8 mL) was added, followed by stirring and aging for 15 minutes. The precipitated solid was filtered, washed with a mixed solution of chloroform/hexane (2/3) and dried under reduced pressure to afford 3.51 g of the title compound as a colorless crystalline-powder (total yield over three steps: 88%). Instrumental data were consistent with those of Reference Example 13.

Example 6b

(3aR,7aS)-1,3-Dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy) -7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-59) Sequential synthesis

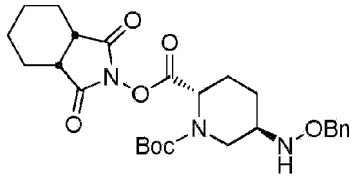
[0138] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 3.504 g, 10 mmol) was dissolved in dehydrated tetrahydrofuran (50 mL), followed by cooling to around -20 °C. To the mixture were added dropwise isobutyl chloroformate (1.157 g) and then triethylamine (2.17 g), followed by stirring at the same temperature for 15 minutes. Then, to the reaction solution was added (3aR,7aS)-2-hydroxy -3a,4,7,7a-tetrahydro-1H-isoindol-1,3(2H)-dione (Reference Example 12, 1.84 g), followed by stirring at the same temperature for 30 minutes and then at room temperature for 30 minutes. The reaction solution was diluted with ethyl acetate (200 mL), washed sequentially with ice-cold 10% citric acid (60 mL), saturated sodium bicarbonate (60 mL) and saturated brine (60 mL), dried over anhydrous magnesium sulfate, and filtered. The total amount of the residue 5.21 g (quantitative) obtained by concentration of the filtrate under reduced pressure was dissolved in dehydrated chloroform (50 mL), and triethylamine (1.5 g) was added, followed by ice cooling. To the mixture was added triphosgene (1.157 g), followed by stirring for 30 minutes. Methanol (0.27 mL) was then added, followed by stirring for 30 minutes. To the reaction solution was added dropwise a solution of methanesulfonic acid (9.47 g) in dichloromethane (8 mL), followed by stirring for another 30 minutes. The mixture was added dropwise to ice-cold 1 M potassium bicarbonate (11.84 g/100 ml), followed by stirring for 30 minutes. Chloroform (30 ml) was added and the layers were separated. The organic layer was washed sequentially with 1 M hydrochloric acid (70 mL), saturated sodium bicarbonate (70 mL) and saturated brine (70 mL). Each aqueous layer was back-extracted with chloroform (33 mL) sequentially. The organic layers were combined, dried over anhydrous magnesium sulfate, and filtered. The total amount of the residue obtained by concentration of the solvent under reduced pressure was dissolved in chloroform (16 mL), hexane (29 mL) was added, followed by stirring for 15 minutes. Further, hexane (5 mL) was added, followed by stirring and aging for

15 mimutes. The precipitated solid was washed, filtered and dried to afford 3.37 g of the title compound (total yield 79%). Instrumental data were consistent with those of Reference Example 13.

Example 7

1-tert-Butyl 2-((3aR,7aS)-1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R) -5-((benzyloxy)amino)piperidine-1,2-dicarboxylate (II-33)

[0139]



II-33

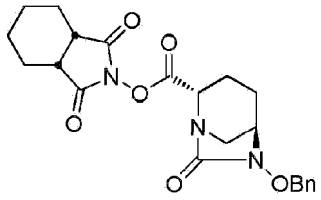
[0140] (2S,5R)-5-((Benzyloxy)amino)-1-(tert-butoxycarbonyl)piperidine-2-carboxylic acid (Reference Example 2, 3.504 g, 10 mmol) was dissolved in dehydrated tetrahydrofuran (50 mL), followed by cooling to around -20 °C. To the mixture were added dropwise isobutyl chloroformate (1.51 g) and then triethylamine (2.17 g), followed by stirring at the same temperature for 15 minutes. Then, to the reaction solution was added (3aR,7aS)-2-hydroxyhexahydro-1H-isoindol-1,3(2H)-dione (Reference Example 14, 1.86 g), followed by stirring at the same temperature for 30 minutes and then at room temperature for 30 minutes. The reaction solution was diluted with ethyl acetate (200 mL), washed sequentially with ice-cold 10% citric acid (60 mL), saturated sodium bicarbonate (60 mL) and saturated brine (60 mL), dried over anhydrous magnesium sulfate, and filtered. The residue obtained by concentration of the filtrate under reduced pressure was subjected to silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford 4.521 g of the title compound as a colorless foamy solid (yield 90%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35-1.58 (m, 13H), 1.62 (bs, 1H), 1.76 (bs, 2H), 1.90 (bs, 4H), 1.95-2.15 (m, 2H), 3.00 (bs, 2H), 3.15-3.30 (m, 2H), 4.16-4.25 (m, 1H), 4.72 (q, J = 11.6 Hz, 2H), 5.30-5.53 (m, 1H), 7.26-7.38 (m, 5H); MS m/z 502 $[M+H]^+$.

Example 8

(3aR,7aS)-1,3-Dioxohexahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (III-60)

[0141]



III-60

Step 1

1-tert-Butyl 2-((3aR,7aS)-1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5-((benzyloxy)((trichloromethoxy)carbonyl)amino)piperidine-1,2-dicarboxylat e or 1-tert-butyl 2-((3aR,7aS)-1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino)piperidine-1,2-dicarboxylate

[0142] 1-tert-Butyl 2-((3aR,7aS)-1,3-dioxohexahydro-1H-isoindol-2(3H)-yl) (2S,5R)-5-((benzyloxy)amino)piperidine-1,2-dicarboxylate (Example 7, 4.521 g, 9.01 mmol) was dissolved in dehydrated chloroform (50 mL), and triethylamine (1.350 g) was added, followed by ice cooling. To the mixture was added triphosgene (1.043 g), followed by stirring for 0.5 hours, and the completion of the reaction for the title compounds was confirmed by TLC. The compounds were subjected to the next step without purification and isolation.

Step 2

(3aR,7aS)-1,3-Dioxohexahydro-1H-isoindol-2(3H)-yl (2S,5R)-5-((benzyloxy)((trichloromethoxy)carbonyl)amino)piperidine-2-carboxylate or (3aR,7aS)-1,3-dioxohexahydro-1H-isoindol-2(3H)-yl (2S,5R)-5-((benzyloxy)(chlorocarbonyl)amino)piperidine-2-carboxylate, methanesulfonate

[0143] To the mixture in Step 1 above was added methanol (0.245 mL) under ice cooling, followed by stirring for 30 minutes. Subsequently, methanesulfonic acid (8.53 g) was added, followed by stirring for 30 minutes, and the completion of the reaction for the title compounds was confirmed by TLC. The compounds were subjected to the next step without purification and isolation.

Step 3

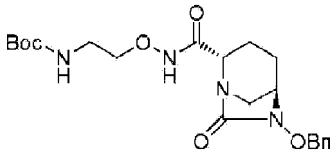
(3aR,7aS)-1,3-Dioxohexahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7 -oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate

[0144] The mixture in Step 2 above was added dropwise to ice-cold 1 M potassium bicarbonate (10.668 g/90 mL), followed by stirring for 0.5 hours. Chloroform (33 mL) was added, layers are separated, the organic layer was washed sequentially with 1 M hydrochloric acid (70 mL), saturated sodium bicarbonate (70 mL) and saturated brine (70 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (chloroform/ethyl acetate = 6/1) to afford 3.106 g of the title compound as a colorless solid (total yield over three steps: 81%). Instrumental data were consistent with those of Reference Example 15.

Example 9

tert-Butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate (IV-1-1)

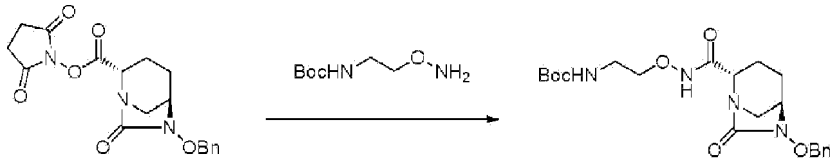
[0145]



IV-1-1

Example 9a

[0146]

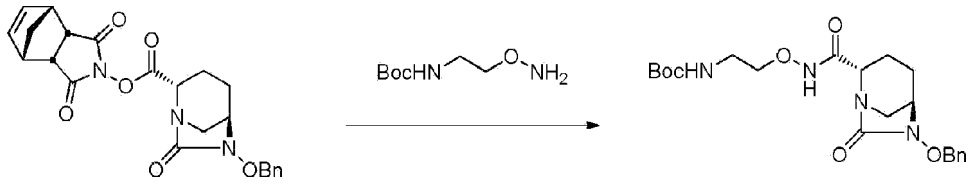


[0147] 2,5-Dioxopyrrolidine-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane-2-carboxylate (Example 3a-c, 373 mg, 1 mmol) was dissolved in dehydrated dichloromethane (5 mL), and a solution of tert-butyl 2-(aminooxy) ethylcarbamate (194 mg) in dehydrated dichloromethane (2 mL, washed with 1 mL) was added under ice cooling, followed by stirring for 1 hour. The reaction solution was diluted with ethyl acetate (65 mL), washed sequentially

with 10% citric acid (20 mL), saturated sodium bicarbonate (20 mL) and saturated brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford 362 mg of the title compound (yield 83%). Instrumental data were consistent with those of Reference Example 1, Step 1.

Example 9b

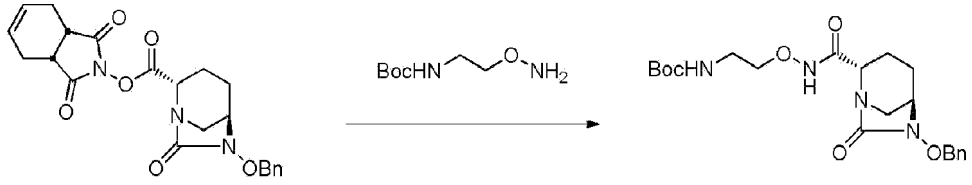
[0148]



[0149] (1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Examples 4a-c, 49.7 g, 113.6 mmol) was suspended in dehydrated ethyl acetate (650 mL), and a solution of tert-butyl 2-(aminooxy)ethylcarbamate (24.2 g) in dehydrated ethyl acetate (134 mL) and triethylamine (13.8 g) were added at room temperature, followed by stirring for 2.5 hours. The reaction solution was diluted with ethyl acetate (0.8 L), washed sequentially with ice-cold 0.25 M hydrochloric acid (1 L), saturated sodium bicarbonate (1 L) and water (1 L), and concentrated under reduced pressure to afford 50.67 g of the title compound (net 48.08 g, yield 98%, HPLC area ratio 99% or more). Instrumental data were consistent with those of Reference Example 1, Step 1.

Example 9c

[0150]

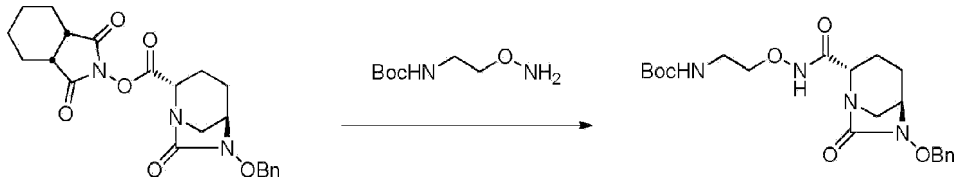


[0151] (3aR,7aS)-1,3-Dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Examples 6a-b, 425 mg, 1 mmol) was dissolved in dehydrated chloroform (5 mL), and a solution of tert-butyl 2-(aminooxy)ethyl carbamate (211 mg) in dehydrated ethyl acetate (1.41 g) and triethylamine (121 mg) were added under ice cooling, followed by stirring for 30 minutes. The reaction solution was diluted with ethyl acetate (75 mL), washed sequentially with 10% citric acid aqueous solution (35 mL), saturated sodium bicarbonate (35 mL) and saturated brine (35 mL),

and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 1/2) to afford 481 mg of the title compound (quantitative). Instrumental data were consistent with those of Reference Example 1, Step 1.

Example 9d

[0152]

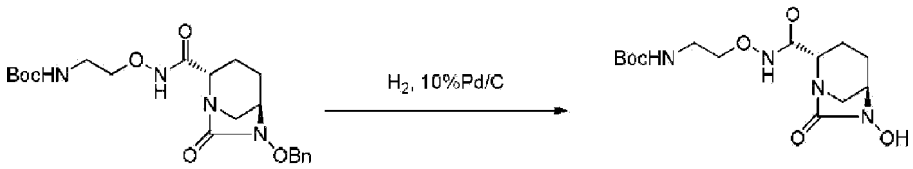


[0153] (3aR,7aS)-1,3-Dioxohexahydro-1H-isoindol-2(3H)-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Example 8, 427 mg, 1 mmol) was dissolved in dehydrated chloroform (5 mL), and a solution of tert- butyl 2-(aminooxy)ethyl carbamate (211 mg) in dehydrated ethyl acetate (1.41 g) and triethylamine (121 mg) were added under ice cooling, followed by stirring for 30 minutes. The reaction solution was diluted with ethyl acetate (75 mL), washed sequentially with 10% citric acid aqueous solution (35 mL), saturated sodium bicarbonate (35 mL) and saturated brine (35 mL), and dried over anhydrous magnesium sulfate. The filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 1/2) to afford 418 mg of the title compound (yield 96%). Instrumental data were consistent with those of Reference Example 1 Step 1.

Example 10

tert-Butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} carbamate (V-1)

[0154]



[0155] To a solution of tert-butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo [3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate (Example 9b, net 156.42 g, 360 mmol) in methanol

(2.4 L) was added a 10% palladium carbon catalyst (50% water content, 15.64 g), followed by stirring under a hydrogen atmosphere for 1.5 hours. The catalyst was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure to 450 mL, and subsequently acetonitrile (1.5 L) was added, followed by concentration to 450 mL. The mixture was ice cooled and stirred for 30 minutes, and the precipitated crystalline solid was filtered, washed with acetonitrile, and dried in vacuo to afford 118.26 g of the title compound (net 117.90 g, yield 95%). Instrumental data were consistent with those of Reference Example 1, Step 2.

Example 11

(2S,5R)-N-(2-Aminoethoxy)-7-oxo-6-(sulfoxy)-1,6-diazabicyclo[3.2.1]octane -2-carboxamide (VI-1)

[0156]

[0157] To a solution of tert-butyl {2-[({[(2S,5R)-6-hydroxy-7-oxo-1,6-diazabicyclo [3.2.1]oct-2-yl]carbonyl}amino)oxy]ethyl}carbamate (Example 10, 537.61 g, 1.561 mol) in acetonitrile (7.8 L) were added 2,6-lutidine (512.08 g) and sulfur trioxide-pyridine complex (810.3 g), followed by stirring at room temperature overnight. The mixture was filtered to remove insolubles, and the filtrate was concentrated to 2.5 L and diluted with ethyl acetate (15.1 L). The mixture was extracted with 20% sodium dihydrogen phosphate (7.8 L), to the resulting aqueous layer were added ethyl acetate (15.1 L) and tetrabutylammonium hydrogen sulfate (567.87 g), followed by stirring for 20 minutes. The organic layer was separated, dried over anhydrous magnesium sulfate (425 g), filtered, subsequently concentrated under reduced pressure, and solvent-switched to dichloromethane (3.1 L) to afford 758 g of tetrabutylammonium tert-butyl {2-[({[(2S,5R)-7-oxo-6-(sulfooxy)-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} amino)oxy]ethyl}carbamate (net 586.27 g, yield 84%).

[0158] A solution of 719 g of the tetrabutylammonium salt (net 437.1 g, 0.656 mol) in dichloromethane (874 mL) was cooled to -20 °C, trifluoroacetic acid (874 mL) was added dropwise for 15 minutes, and the temperature was elevated to 0 °C, followed by stirring for 1 hour. The reaction solution was cooled to -20 °C, diisopropyl ether (3.25 L) was added dropwise, the temperature of the mixture was elevated to 0 °C, followed by stirring for 1 hour. The precipitates was filtered, washed with diisopropyl ether, and dried in vacuo to afford 335.36 g of the crude title compound (net 222.35 g, yield 99%).

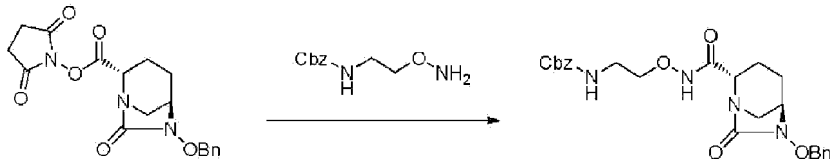
[0159] The crude title compound (212.99 g, net 133.33 g) and an ice-cold 0.2 M phosphate

buffer (pH 6.5, 4.8 L) were mixed alternately in small portions to give a solution having pH 5.3. The solution was concentrated under reduced pressure to 3.6 L, and the pH was again adjusted to pH 5.5 using a 0.2 M phosphate buffer (pH 6.5, 910 mL). The solution was subjected to resin purification (Mitsubishi Kasei, SP207, water to 10% IPA-water) and active fractions were collected, concentrated and lyophilized. 128.3 g of the title compound was then obtained (yield 96%). Instrumental data were consistent with those of Reference Example 1, Step 3.

Example 12

Benzyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} carbamate (IV-1-2)

[0160]



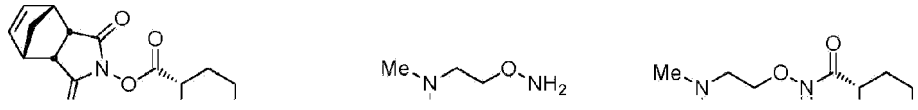
IV-1-2

[0161] 2,5-Dioxopyrrolidine-1-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo [3.2.1]octane-2-carboxylate (Example 3a-c, 201 mg, 0.538 mmol) was dissolved in dehydrated dichloromethane (4 mL), and a solution of benzyl 2-(aminooxy) ethylcarbamate (128 mg) in dehydrated dichloromethane (0.5 mL, washed with 0.5 mL) was added under ice cooling, followed by stirring for 1.5 hours. The reaction solution was diluted with ethyl acetate (30 mL), washed sequentially with 10% citric acid (15 mL), saturated sodium bicarbonate (15 mL) and saturated brine (15 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford 222 mg of the title compound (yield 88%). Instrumental data were consistent with those of Reference Example 3, Step 3.

Example 13

tert-Butyl {2-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy] ethyl} (methyl) carbamate (IV-2)

[0162]

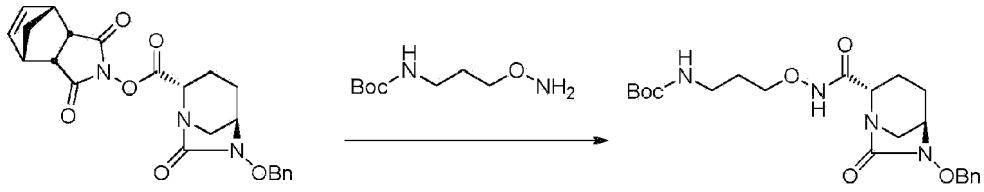


[0163] (1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Example 4a-c, 144 mg, 0.329 mmol) was dissolved in dehydrated dichloromethane (2.5 mL), and a solution of tert-butyl (2-(aminooxy)ethyl)(methyl)carbamate (88.8 mg) in dehydrated dichloromethane (0.5 mL) was added, followed by stirring at room temperature for 18 hours. The reaction solution was diluted with ethyl acetate (10 mL), washed sequentially with 0.25 M hydrochloric acid, saturated sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 132 mg of the title compound (yield 89%). Instrumental data were consistent with those of Reference Example 4, Step 1.

Example 14

tert-Butyl {3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy]propyl} carbamate (IV-7)

[0164]

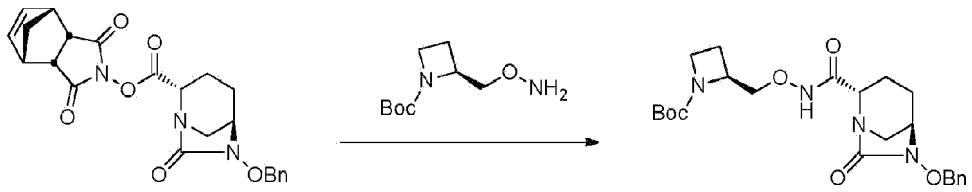


[0165] (1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Example 4a-c, 148 mg, 0.339 mmol) was dissolved in dehydrated dichloromethane (2.5 mL), and a solution of tert-butyl 3-(aminooxy)propylcarbamate (90.9 mg) in dehydrated dichloromethane (0.5 mL) was added, followed by stirring at room temperature for 18 hours. The reaction solution was diluted with ethyl acetate (10 mL), washed sequentially with 0.25 M hydrochloric acid, saturated sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 134 mg of the title compound (yield 88%). Instrumental data were consistent with those of Reference Example 6, Step 1.

Example 15

tert-Butyl (2S)-2-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl} amino)oxy]methyl} azetidine-1 -carboxylate (IV-8)

[0166]

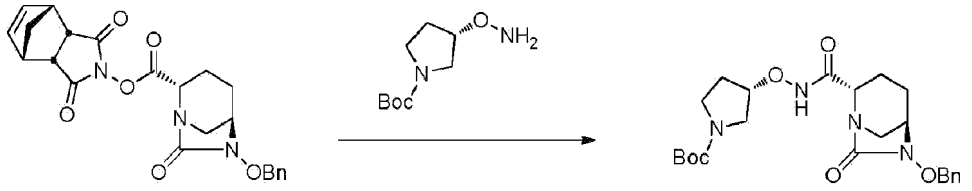


[0167] (1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Example 4a-c, 145 mg, 0.331 mmol) was dissolved in dehydrated dichloromethane (2.5 mL), and a solution of (S)-tert-butyl 2-((aminooxy)methyl)azetidine-1-carboxylate (93.2 mg) in dehydrated dichloromethane (0.5 mL) was added, followed by stirring at room temperature for 21 hours. The reaction solution was diluted with ethyl acetate (10 mL), washed sequentially with 0.25 M hydrochloric acid, saturated sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 127 mg of the title compound (yield 83%). Instrumental data were consistent with those of Reference Example 7, Step 1.

Example 16

tert-Butyl (3S)-3-[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl]carbonyl}amino)oxy]pyrrolidine-1-carboxylate (IV-11)

[0168]



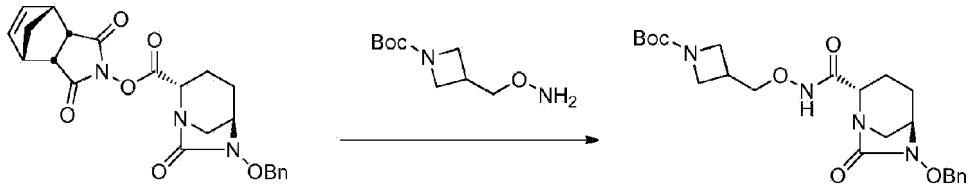
[0169] (1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Example 4a-c, 145 mg, 0.332 mmol) was dissolved in dehydrated dichloromethane (2.5 mL), and a solution of (S)-tert-butyl 3-(aminooxy)pyrrolidine-1-carboxylate (91.6 mg) in dehydrated dichloromethane (0.5 mL) was added, followed by stirring at room temperature for 19 hours. The reaction solution was diluted with ethyl acetate (10 mL), washed sequentially with 0.25 M hydrochloric acid, saturated sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 145 mg of the title compound (yield 95%).

Instrumental data were consistent with those of Reference Example 8, Step 1.

Example 17

tert-Butyl 3-{[({[(2S,5R)-6-benzyloxy-7-oxo-1,6-diazabicyclo[3.2.1]oct-2-yl] carbonyl} amino)oxy]methyl} azetidine-1 -carboxylate (IV-12)

[0170]



[0171] (1R,2S,6R,7S)-3,5-Dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl (2S,5R)-6-(benzyloxy)-7-oxo-1,6-diazabicyclo[3.2.1]octane-2-carboxylate (Example 4a-c, 140 mg, 0.320 mmol) was dissolved in dehydrated dichloromethane (2.5 mL), and a solution of tert-butyl 3-((aminooxy)methyl)azetidine-1-carboxylate (91.5 mg) in dehydrated dichloromethane (0.5 mL) was added, followed by stirring at room temperature for 20 hours. The reaction solution was diluted with ethyl acetate (10 mL), washed sequentially with 0.25 M hydrochloric acid, saturated sodium bicarbonate and saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 132 mg of the title compound (yield 90%). Instrumental data were consistent with those of Reference Example 9, Step 1.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- JP4515704B [0002]
- JP2010138206A [0002]
- JP2010539147A [0002]
- WO2011042560PCT [0002]

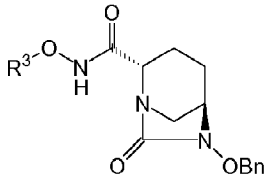
- JP5038509B [0003]
- JP2011207900A [0003]
- WO2010126820A [0003]
- JP2012122603A [0004]

Non-patent literature cited in the description

- Protective Groups in Organic SynthesisWiley19990000 [0025]
- **T. W. GREENE et al.**Protective Groups in Organic SynthesisWiley19990000 [0044]

Patentkrav

1. Fremgangsmåde til fremstilling af en forbindelse med formel (IV):



(IV)

hvor

OBn er benzyloxy, og

R^3 er C_{1-6}-alkyl eller heterocyclyl, eller danner en 3- til 7-leddet heterocyklisk ring sammen med den tilstødende -O-NH-,

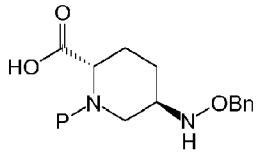
R^3 kan modificeres med 0-5 grupper R^4 valgt fra C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfonyl, heterocyclyl, heterocyclylcarbonyl, $R^5(R^6)N$- og en beskyttelsesgruppe; og R^4 kan efterfølgende substitueres;

R^5 og R^6 er hver uafhængigt H eller C_{1-6}-alkyl eller danner sammen en 3- til 7-leddet heterocyklisk ring;

og yderligere, R^3, R^5 og R^6 kan gennemgå ringlukning ved en vilkårlig position;

omfattende:

(i) at reagere en forbindelse med formel (I) hvor P er en NH-beskyttelsesgruppe, som kan fjernes med syre:



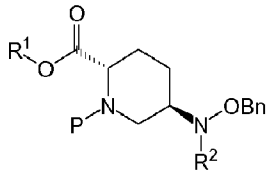
(I)

med R^1OH hvor

R^1 er 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, eller 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2.6}$]dec-8-en-4-yl, efterfulgt af

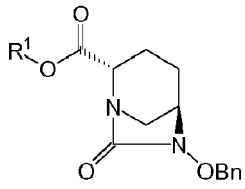
(ii) at lade et carbonyleringsmiddel valgt fra phosgen, diphosgen og triphosgen indvirke derpå for at opnå en forbindelse med formel (II), hvor

R^2 er ClCO- eller Cl_3COCO-,



(II),

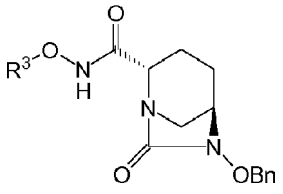
(iii) at fjerne beskyttelsesgruppen P og behandle med en base for at opnå en forbindelse med formel (III):



(III), og

(iv) at reagere med en forbindelse R^3ONH_2, hvor R^3 er som defineret ovenfor for at fremstille forbindelsen (IV).

2. Fremgangsmåde til fremstilling af en forbindelse med formel (IV):



(IV)

hvor

OBn er benzyloxy, og

R^3 er C_{1-6}-alkyl eller heterocyclyl, eller danner en 3- til 7-leddet heterocyklisk ring sammen med den tilstødende -O-NH-,

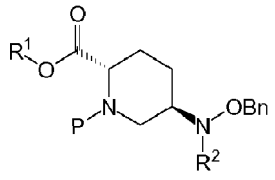
R^3 kan modificeres med 0-5 grupper R^4 valgt fra C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylsulfonyl, heterocyclyl, heterocyclylcarbonyl, $R^5(R^6)N$- og en beskyttelsesgruppe; og R^4 kan efterfølgende substitueres;

R^5 og R^6 er hver uafhængigt H eller C_{1-6}-alkyl eller danner sammen en 3- til 7-leddet heterocyklisk ring;

og yderligere, R^3, R^5 og R^6 kan gennemgå ringlukning ved en vilkårlig position;

omfattende:

(ii) at lade et carbonyleringsmiddel valgt fra phosgen, diphosgen og triphosgen indvirke på en forbindelse med formel (II),



(II)

hvor

R^1 er 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, eller 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-4-yl,

R^2 er H, og

P er en NH-beskyttelsesgruppe, som kan fjernes med syre;

efterfulgt af

(iii) at fjerne beskyttelsesgruppen P, at behandle med en base og yderligere at reagere med en forbindelse R^3ONH_2, hvor R^3 er som defineret ovenfor, for at fremstille forbindelsen med formel (IV).

3. Fremgangsmåde ifølge krav 1 eller 2, hvor R^3 er

2-(tert-butoxycarbonylamino)ethyl;

2-((tert-butoxycarbonyl)(methyl)amino)ethyl;

2-((tert-butoxycarbonyl)(isopropyl)amino)ethyl;

2-(dimethylamino)ethyl;

(2S)-2-((tert-butoxycarbonyl)amino)propyl;

(2R)-2-((tert-butoxycarbonyl)amino)propyl;

3-((tert-butoxycarbonyl)amino)propyl;

(2S)-tert-butoxycarbonylazetidin-2-ylmethyl;

(2R)-tert-butoxycarbonylpyrrolidin-2-ylmethyl;

(3R)-tert-butoxycarbonylpiperidin-3-ylmethyl;

(3S)-tert-butoxycarbonylpyrrolidin-3-yl;

1-(tert-butoxycarbonyl)azetidin-3-yl;

2-(benzyloxycarbonylamino)ethyl;

2-((benzyloxycarbonyl)(methyl)amino)ethyl;

2-((benzyloxycarbonyl)(isopropyl)amino)ethyl;

2-(dimethylamino)ethyl;

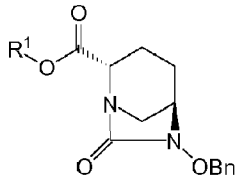
(2S)-2-((benzyloxycarbonyl)amino)propyl;

(2R)-2-((benzyloxycarbonyl)amino)propyl;

3-((benzyloxycarbonyl)amino)propyl;

(2S)-benzyloxycarbonylazetidin-2-ylmethyl;
(2R)-benzyloxycarbonylpyrrolidin-2-ylmethyl;
(3R)-benzyloxycarbonylpiperidin-3-ylmethyl;
(3S)-benzyloxycarbonylpyrrolidin-3-yl; eller
1-(benzyloxycarbonyl)azetidin-3-yl;
fortrinsvis 2-(tert-butoxycarbonylamino)ethyl eller
2-(benzyloxycarbonylamino)ethyl; og
mere fortrinsvis 2-(tert-butoxycarbonylamino)ethyl.

4. Fremgangsmåde til fremstilling af en forbindelse med formel (III)



(III)

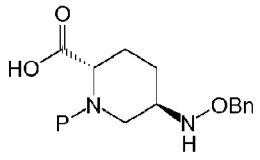
hvor

OBn er benzyloxy, og

R^1 er 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, eller 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2.6}$]dec-8-en-4-yl,

omfattende

(i) at reagere en forbindelse med formel (I), hvor P er en NH-beskyttelsesgruppe, som kan fjernes med syre:



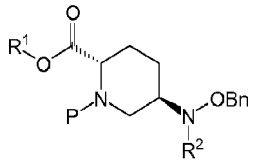
(I)

med R^1OH hvor

R^1 er 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, eller 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2.6}$]dec-8-en-4-yl,

(ii) at lade et carbonyleringsmiddel valgt fra phosgen, diphosgen og triphosgen indvirke derpå for at opnå en forbindelse med formel (II), hvor

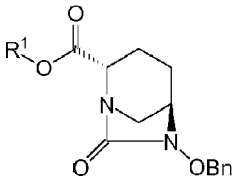
R^2 er ClCO- eller Cl_3COCO-:



(II),

(iii) at fjerne beskyttelsesgruppen P og behandle med en base for at fremstille forbindelsen med formel (III).

5. Fremgangsmåde til fremstilling af en forbindelse med formel (III)



(III)

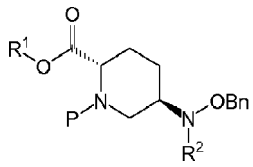
hvor

OBn er benzyloxy, og

R^1 er 2,5-dioxopyrrolidin-1-yl, 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl, 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl, eller 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2.6}$]dec-8-en-4-yl,

omfattende

(ii) at lade et carbonyleringsmiddel valgt fra phosgen, diphosgen og triphosgen indvirke på en forbindelse med formel (II), hvor R^2 er H, og P er en NH-beskyttelsesgruppe, som kan fjernes med syre:



(II)

efterfulgt af

(iii) at fjerne beskyttelsesgruppen P og behandle med en base for at fremstille forbindelsen med formel (III).

6. Fremgangsmåde ifølge et hvilket som helst af kravene 1-5, hvor P er tert-butoxycarbonyl (Boc).

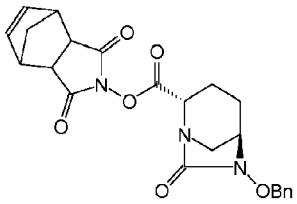
7. Fremgangsmåde ifølge et hvilket som helst af kravene 1-6, hvor R^1 er 2,5-dioxopyrrolidin-1-yl.

8. Fremgangsmåde ifølge et hvilket som helst af kravene 1-6, hvor R^1 er 1,3-dioxo-3a,4,7,7a-tetrahydro-1H-isoindol-2(3H)-yl.

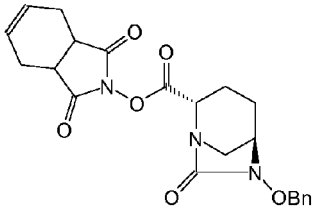
9. Fremgangsmåde ifølge et hvilket som helst af kravene 1-6, hvor R^1 er 1,3-dioxohexahydro-1H-isoindol-2(3H)-yl.

10. Fremgangsmåde ifølge et hvilket som helst af kravene 1-6, hvor R^1 er 3,5-dioxo-4-azatricyclo[5.2.1.$0^{2,6}$] dec-8-en-4-yl.

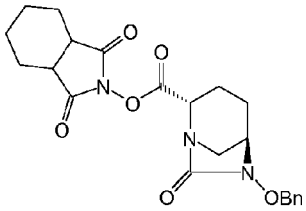
11. Forbindelse valgt fra forbindelserne med formlerne (III-58) til (III-60), hvor OBn er benzyloxy:



(III-58)

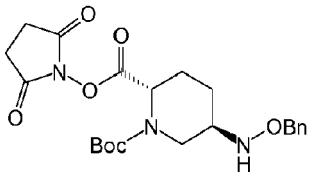


(III-59)

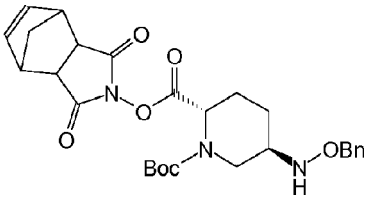


(III-60)

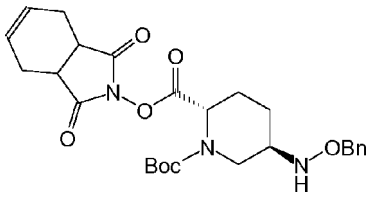
12. Forbindelse valgt fra forbindelserne med formlerne (II-30) til (II-33), hvor Boc er tert-butoxycarbonyl, og OBn er benzyloxy:



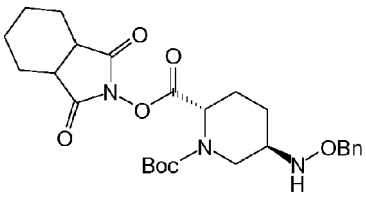
(II-30)



(II-31)



(II-32)



(II-33)