A NOVEL PROCESS FOR THE PREPARATION OF PERAMIVIR AND INTERMEDIATES THEREOF

Abstract: The present invention relates to a novel process for preparing peramivir formula (I) or a pharmaceutically acceptable salt thereof, and to intermediates used therein.
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A NOVEL PROCESS FOR THE PREPARATION OF PERAMIVIR AND INTERMEDIATES THEREOF

Field of the Invention

[0001] The present invention relates to a novel process for the preparation of peramivir or a pharmaceutically acceptable salt thereof, and to novel intermediates thereof. In particular, this invention relates to a more efficient process for the preparation of peramivir or a pharmaceutically acceptable salt thereof, comprising highly diastereoselective reactions by utilizing less reaction steps to obtain peramivir.

Background of the Invention

[0002] Peramivir has the chemical name of

\[(1S,2S,3S,4R)-3-[\text{I}-\text{acetamido}-2\text{-ethyl-butyl}] -4-(\text{diaminomethylideneamino})-2\text{-hydroxy-cyclopentane-1-carboxylicacid}\]

and has the following structure:

![Chemical Structure of Peramivir]

[0003] Peramivir is currently being developed as an antiviral drug, and in particular, for treatment of influenza. Acting as a neuraminidase inhibitor, peramivir can efficiently inhibit the replication of all type of influenza viruses.
Peramivir can be administered via injection, and is known to be well-tolerated and cause only mild adverse effect.

[0004] Several processes relating to the preparation of peramivir are disclosed in CN1227466, CN1282316, and WO01/00577A1.

[0005] As shown in Scheme 1, CN1227466 discloses a process comprising ring-opening of chiral 2-azabicyclo [2.2.1] hept-5-en-3-one, followed by amino-protecting reaction, Diel-Alder conjugate cycloaddition, reduction, acetylation, guanidylation and finally hydrolyzation to yield peramivir. The major drawback of this process is the use of highly expensive starting material 1. In addition, this process is not suitable for scale-up.

\[ \text{Scheme 1} \]

[0006] WO2009021404 discloses a method comprising reacting N-Boc-protected chiral 2-azabicyclo [2.2.1] hept-5-en-3-one and 2-ethylbutylaldehyde as starting material to prepare peramivir as illustrated in
The major disadvantages of this process are long synthetic route, low yield and high production cost.

The present invention relates to a more efficient process for the preparation of peramivir, which comprises shorter synthetic route and higher overall yield. The process is free of chromatographic purification, and suitable for large scale production.

Summary of the Invention

In one aspect, the present invention provides a process for preparing peramivir (I),
comprising:

(a) reacting a compound of formula (II), or a pharmaceutically acceptable salt thereof,

\[
\begin{array}{c}
\text{H}_2\text{N} & \text{C} & \text{O} & \text{O} & \text{R}_1 \\
\text{N} & \text{C} & \text{H}_3 & \text{N} & \text{C} & \text{H}_3 \\
\text{H}_2 & \text{N} & \text{C} & \text{O} & \text{O} & \text{R}_1 \\
\text{H}_2 & \text{N} & \text{C} & \text{O} & \text{O} & \text{R}_1 \\
\end{array}
\]

(II)

wherein \( R_i \) is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen,

with an amidine compound of formula (III),

\[
\begin{array}{c}
\text{R}_2\text{N} & \text{C} & \text{N} & \text{R}_3 \\
\text{R}_2& \text{H} & \text{N} & \text{R}_3 \\
\end{array}
\]

(III)

wherein \( R_2 \) and \( R_3 \) are each independently a nitrogen-protecting group, and \( R_4 \) is a leaving group,

to provide a compound of formula (IV):

\[
\begin{array}{c}
\text{R}_3\text{N} & \text{C} & \text{N} & \text{R}_2 \\
\text{R}_3& \text{N} & \text{C} & \text{O} & \text{O} & \text{R}_1 \\
\end{array}
\]

(IV)

wherein \( R_i, R_2 \) and \( R_3 \) are defined as hereinabove;

(b) reacting the compound of formula (IV) with a compound of formula (V)
(V)

\[
\begin{align*}
\text{to produce a compound of formula (VI),} \\
\text{wherein } R_1, R_2 \text{ and } R_3 \text{ are defined as hereinabove;}
\end{align*}
\]

(c) reducing the compound of formula (VI) using a reducing agent, followed by acetylation to provide a compound of formula (VII),

(VII)

\[
\begin{align*}
\text{wherein } R_1, R_2 \text{ and } R_3 \text{ are defined as hereinabove;}
\end{align*}
\]

(d) hydrolyzing the compound of formula (VII), wherein \( R_i \) is not \( H \), with a base or an acid to provide a compound of formula (VIII),

(VIII)

\[
\begin{align*}
\text{wherein } R_2 \text{ and } R_3 \text{ are defined as hereinabove;}
\end{align*}
\]

(e) removing the nitrogen-protecting group \( (R_2 \text{ and } R_3) \) in the compound of formula (VII), wherein \( R_i \) is \( H \), or in the compound of formula (VIII), to provide
peramivir (I).

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

\[
\begin{align*}
R_3 & \equiv \text{hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; } R_2 \\
& \text{and } R_3 \text{ are each independently a nitrogen-protecting group, } \\
\text{the process comprising reacting a compound of formula (II), or a pharmaceutically acceptable salt thereof,} \\
\end{align*}
\]

\[
\begin{align*}
\text{(II)}
\end{align*}
\]

wherein \( R_1 \) is defined as hereinabove,

with an amidine compound of formula (III),

\[
\begin{align*}
\text{(III)}
\end{align*}
\]

wherein \( R_2 \) and \( R_3 \) are defined as hereinabove, and \( R_4 \) is a leaving group, to provide the compound of formula (IV).

[0011] In yet another aspect, the present invention provides a process for preparing a compound of formula (VI):
wherein \( R_i \) is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; \( R_2 \) and \( R_3 \) are each independently a nitrogen-protecting group.

the process comprising reacting a compound of formula (IV),

\[
\begin{align*}
R_3N &\equiv \text{NHR}_2 \\
&\equiv \text{HN} & \equiv \text{HN} \\
\text{HN} &\equiv \text{HN} & \equiv \text{HN} \\
\text{C} &\equiv \text{C} & \equiv \text{C} \\
\text{O} &\equiv \text{O} \\
\end{align*}
\]

(IV)

wherein \( R_i, R_2 \) and \( R_3 \) are defined as hereinabove,

with a compound of formula (V)

\[
\begin{align*}
\text{N} &\equiv \text{N} & \equiv \text{N} \\
\text{O} &\equiv \text{O} \\
\end{align*}
\]

(V)

to produce the compound of formula (VI).

[0012] In a further aspect, the present invention provides a compound of formula (IV),

\[
\begin{align*}
R_3N &\equiv \text{NHR}_2 \\
&\equiv \text{HN} & \equiv \text{HN} \\
\text{HN} &\equiv \text{HN} & \equiv \text{HN} \\
\text{C} &\equiv \text{C} & \equiv \text{C} \\
\text{O} &\equiv \text{O} \\
\end{align*}
\]

(IV)

wherein \( R_i \) is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; and \( R_2 \) and \( R_3 \) are each independently a nitrogen-protecting group.

[0013] In another aspect, the present invention provides a compound of formula
wherein $R_i$ is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; $R_2$ and $R_3$ are each independently a nitrogen-protecting group.

**Brief Description of the Drawings**

[0014] Figure 1 depicts $^\wedge$-NMR for compound 13.

[0015] Figure 2 depicts $^\wedge$-NMR for compound 15.

[0016] Figure 3 depicts $^\wedge$-NMR for compound 16.

[0017] Figure 4 depicts $^\wedge$-NMR for compound 17.

[0018] Figure 5 depicts $^\wedge$-NMR for compound peramivir.

**Detailed Description of the Invention**

[0019] The present invention relates to a novel process for preparation of peramivir (I), or a pharmaceutically acceptable salt thereof:

$$\text{Peramivir (I)}$$

[0020] The process comprises:
(a) reacting a compound of formula (II), or a pharmaceutically acceptable salt thereof,

\[
\begin{align*}
\text{H}_2\text{N}\cdots\text{O} \quad \text{O} \quad \text{R}_1
\end{align*}
\]

(II)

wherein \( R_i \) is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen,

with an amidine compound of formula (III),

\[
\begin{align*}
\text{R}_2\text{HN} & \quad \text{R}_4 \\
\text{NR}_3
\end{align*}
\]

(III)

wherein \( R_2 \) and \( R_3 \) are each independently a nitrogen-protecting group, and \( R_4 \) is a leaving group,

to provide a compound of formula (IV):

\[
\begin{align*}
\text{R}_3\text{NN} & \quad \text{NHR}_2 \\
\text{HN} & \quad \text{O} \quad \text{O} \quad \text{R}_1
\end{align*}
\]

(IV)

wherein \( R_i, R_2 \) and \( R_3 \) are defined as hereinabove;

(b) reacting the compound of formula (IV) with a compound of formula (V)

\[
\begin{align*}
\text{Cl} & \quad \text{N} \quad \text{O} \quad \text{H}
\end{align*}
\]

(V)

to produce a compound of formula (VI),
(c) reducing the compound of formula (VI) using a reducing agent, followed by acetylation to provide a compound of formula (VII),

(VII),

wherein R₁, R₂ and R₃ are defined as hereinabove; (d) hydrolyzing the compound of formula (VII), wherein Rᵢ is not H, with a base or an acid to provide a compound of formula (VIII),

(VIII),

wherein R₂ and R₃ are defined as hereinabove;

(e) removing the nitrogen-protecting group (R₂ and R₃) in the compound of formula (VII), wherein Rᵢ is H, or in the compound of formula (VIII), to provide peramivir (I).

[0021] Starting material compound (II) can be conveniently synthesized...
according to known literature procedure.

In certain embodiments, Ri is hydrogen, (C\textsubscript{i}-C\textsubscript{4})alkyl, (C\textsubscript{3}-C\textsubscript{7})cycloalkyl, phenyl, or (C\textsubscript{i}-C\textsubscript{4})alkyl-phenyl, in which said (C\textsubscript{i}-C\textsubscript{4})alkyl is optionally substituted with one or more halogen.

In certain embodiments, the leaving group is alkylthio, arylthio, pyrazolyl, imidazole, cyano or triazolyl. In certain other embodiments, the leaving group is (C\textsubscript{i}-C\textsubscript{4})alkylthio, phenylthio, pyrazolyl, imidazole, cyano or triazolyl.

In certain other embodiments, the reducing agent is selected from: (1) alkali metal borohydride in combination with transition metal chloride, transition metal sulfate, or transition metal phosphate; (2) Pt\textsubscript{0}/H\textsubscript{2}, Raney Ni/ H\textsubscript{2}, Pd/C/H\textsubscript{2}, or Rh/ H\textsubscript{2}; (3) transition metal such as Zn and Fe in acids such as acetic acid; (4) Red-Al; and (5) NaBH\textsubscript{4}/Me\textsubscript{2}S\textsubscript{0}\textsubscript{4}.

In yet other embodiments, the alkali metal borohydride is selected from NaBH\textsubscript{4}, KBH\textsubscript{4}, LiBH\textsubscript{4}, NaBH\textsubscript{3}CN, and NaBH(OAc)\textsubscript{3}.

In yet other embodiments, the transition metal chloride is selected from NiCl\textsubscript{2}, CoCl\textsubscript{2}, and ZnCl\textsubscript{2}.

In certain embodiments, the acetylation step is achieved using acetic anhydride, acetyl chloride, or acetyl mixed anhydrides (e.g. acetic formic anhydride). In certain other embodiments, the acetylation step is achieved using a carboxylic anhydride of formula R\textsubscript{a}(C=0)0(C=0)R\textsubscript{b}, wherein R\textsubscript{a} and R\textsubscript{b} may be same or different and are each independently H or (C\textsubscript{i}-C\textsubscript{4})alkyl.

In another aspect, the present invention provides a process for preparing a
compound of formula (IV):

\[
\begin{align*}
\text{R}_2\text{N} & = \text{NHR}_2 \\
\text{HN} & \text{O} \\
\text{OR}_1 \\
\text{(IV)}
\end{align*}
\]

wherein \(\text{R}_1\) is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; \(\text{R}_2\) and \(\text{R}_3\) are each independently a nitrogen-protecting group.

the process comprising reacting a compound of formula (II), or a pharmaceutically acceptable salt thereof,

\[
\begin{align*}
\text{H}_2\text{N} & \text{O} \\
\text{OR}_1 \\
\text{(II)}
\end{align*}
\]

wherein \(\text{R}_1\) is defined as hereinabove,

with an amidine compound of formula (III),

\[
\begin{align*}
\text{R}_2\text{HN} & \text{NR}_3 \\
\text{R}_4 \text{(III)}
\end{align*}
\]

wherein \(\text{R}_2\) and \(\text{R}_3\) are defined as hereinabove, and \(\text{R}_4\) is a leaving group, to provide the compound of formula (IV).

[0029] In certain embodiments, \(\text{R}_1\) is hydrogen, \((\text{C}_1-\text{C}_4)\)alkyl, \((\text{C}_3-\text{C}_7)\)cycloalkyl, phenyl, or \((\text{C}_1-\text{C}_4)\)alkyl-phenyl, in which said \((\text{C}_1-\text{C}_4)\)alkyl is optionally substituted with one or more halogen.

[0030] In certain embodiments, the leaving group is alkylthio, arylthio, pyrazolyl, imidazole, cyano or triazolyl. In certain other embodiments, the leaving group is \((\text{C}_1-\text{C}_4)\)alkylthio, phenylthio, pyrazolyl, imidazole, cyano or triazolyl. In certain
embodiments, R<sub>2</sub> and R<sub>3</sub> are defined as hereinabove.

[0031] As described herein, for the synthesis of intermediate IV, the reaction solvent can be selected from, but not limited to acetonitrile, dichloroethane, tetrahydrofuran or other suitable solvents. The reaction temperature can be from room temperature to about 80°C. If R<sub>4</sub> represents alky! or aryi sulfide, the reaction rate and yield can be improved by elevated temperature or addition of sulfide precipitation reagent such as HgCl<sub>2</sub>, AgNO<sub>3</sub>, and so on. If R<sub>4</sub> represents pyrazolyl or triazolyl, the reaction rate and yield can be improved by addition of an organic base such as trimethylamine, triethylamine, tributylamine, N,N-diisopropylethylamine, N-methylpiperidme, pyridine, N,N-dimethylaniline, DBU and so on.

[0032] At the end of the reaction, compound (IV) can be obtained by general purification methods, such as extraction, washing, crystallization, re-crystallization and so on.

[0033] In certain embodiments, the process further comprises reacting the compound of formula (IV) with a compound of formula (V)

![image](image)

(V)

to produce a compound of formula (VI),

![image](image)

(VI)
wherein \(R_1, R_2\) and \(R_3\) are defined as hereinabove.

[0034] In yet another aspect, the present invention provides a process for preparing a compound of formula (VI):

\[
\begin{align*}
\text{R}_3\text{N} & \equiv \text{NHR}_2 \quad \text{O} \quad \text{R}_1 \\
\text{HN} & \equiv \text{HN} \\
\text{O} & \equiv \text{O} \\
\text{N} & \equiv \text{N}
\end{align*}
\]

(VI)

wherein \(R_1\) is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; \(R_2\) and \(R_3\) are each independently a nitrogen-protecting group,

the process comprising reacting a compound of formula (IV),

\[
\begin{align*}
\text{R}_3\text{N} & \equiv \text{NHR}_2 \quad \text{O} \quad \text{R}_1 \\
\text{HN} & \equiv \text{HN} \\
\text{O} & \equiv \text{O} \\
\text{N} & \equiv \text{N}
\end{align*}
\]

(IV)

wherein \(R_1, R_2\) and \(R_3\) are defined as hereinabove,

with a compound of formula (V)

\[
\begin{align*}
\text{N} & \equiv \text{O} \\
\text{OH} & \equiv \text{OH} \\
\text{Cl} & \equiv \text{Cl}
\end{align*}
\]

(V)

to produce the compound of formula (VI).

[0035] Compound (V) can be conveniently prepared by known literature procedure. As used herein, the reaction solvent can be selected from toluene, tetraliydrofuran or other suitable organic solvents. The reaction temperature for the synthesis of compound (VI) can be from room temperature to about 100°C. The reaction can be carried out under basic conditions, for example, in presence of
trimethylamine, triethylamine, tributylamine, N,N-diisopropylethylamine, N-methylpiperidine, pyridine, N,N-dimethylaniline, DBU and so on.

[0036] Applicants have surprisingly found that the formation of diasteromeric side-product of formula (VI-1) is greatly reduced, if a bulky group is used for R₂ and/or R₃. For example, when teri-butyloxy carbonyl group is used for both R₂ and/or R₃, the formation of the side-product is significantly reduced. Without being bound by a particular theory, it is believed that the steric hindrance of the teri-butyloxy carbonyl group helps minimize the formation of the undesired side-product. Compound (VI) can be obtained by general purification methods, such as extraction, washing, crystallization, re-crystallization and so on.

![Diagram of compound (VI-1)]

[0037] In certain embodiments, the process further comprises reducing the compound of formula (VI) using a reducing agent, followed by acetylation to provide a compound of formula (VII),

![Diagram of compound (VII)]

wherein R₁, R₂ and R₃ are defined as hereinabove.

[0038] In certain embodiments, the reducing agent is selected from: (1) alkali
metal borohydride in combination with transition metal chloride, transition metal sulfate, or transition metal phosphate; (2) Pt\( 
\text{H}_2 \), Raney Ni/\( \text{H}_2 \), Pd/C/\( \text{H}_2 \), or Rh/\( \text{H}_2 \); (3) transition metal such as Zn and Fe in acids such as acetic acid; (4) Red-Al; and (5) NaBH\(_4\)/Me\(_2\)SO\(_4\).

[0039] In certain embodiments, the alkali metal borohydride is selected from NaBH\(_4\), KBH\(_4\), LiBH\(_4\), NaBH\(_3\)CN, and NaBH(OAc)\(_3\). In certain other embodiments, the transition metal chloride is selected from NiCl\(_2\), CoCl\(_2\), and ZnCl\(_2\).

[0040] When using alkali metal borohydride and transition metal chloride as a reductive system, the reaction solvent is selected from, but not limited to, protic solvents such as methanol, ethanol and so on. The reaction temperature can be from about -78°C to room temperature, for example at 0°C.

[0041] The resulting reductive reaction mixture can be directly quenched with an acetylation reagent. The molar equivalent ratio between acetylating reagent and compound (VI) can be ranged from about 1 to about 50, for example at about 5 molar equivalents, 10 molar equivalents, 15 molar equivalents, or 20 molar equivalents. The reaction temperature can be from about -78°C to room temperature, for example at about 0°C.

[0042] In certain embodiments, the acetylation step is achieved using acetic anhydride, acetyl chloride, or acetyl mixed anhydrides (e.g. acetic formic anhydride). In certain other embodiments, the acetylation step is achieved using a carboxylic anhydride of formula R\(_a\)(C=0)O(C=0)R\(_b\), wherein R\(_a\) and R\(_b\) may be
same or different and are each independently H or (Ci-C₄)alkyl.

[0043] Compound (VII) can be obtained by general purification methods, such as extraction, washing, crystallization, re-crystallization and so on.

[0044] In certain embodiments, the process further comprises hydrolyzing the compound of formula (VII), wherein Rᵢ is not H, with a base or an acid to provide a compound of formula (VIII),

\[
\begin{align*}
R \equiv N = \equiv N H R \equiv \\
\overset{\text{O}}{\text{H}}
\end{align*}
\]

(VIII),

wherein R₂ and R₃ are defined as hereinabove.

[0045] In certain embodiments, the process further comprises removing the nitrogen-protecting group (R₂ and R₃) in the compound of formula (VII), wherein Rᵢ is H; or removing the nitrogen-protecting group (R₂ and R₃) in the compound of formula (VIII), to provide peramivir (I):

\[
\begin{align*}
H₂N = \equiv N H \equiv \\
\overset{\text{O}}{\text{H}}
\end{align*}
\]

(I)

[0046] In certain embodiments, the nitrogen-protecting group used herein is t-butyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, 9-fluorenylmethoxycarbonyl, 9-(2-sulfo)fluorenylmethoxycarbonyl, 9-(2,7-dibromo)fluorenylalkylmethoxycarbonyl,
17-tetrabenzo[a,c,g,i]fluorenylmethoxycarbonyl,
2-chloro-3-indenylmethoxycarbonyl, benz[f]inden-3-ylmethoxycarbonyl,
2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)] methoxycarbonyl, 1,1-dioxobenzothiophene-2-ylmethoxycarbonyl,
2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl,
2-phenylethoxycarbonyl, 1-(1-adamantyl)-1-methylethoxycarbonyl,
2-chloroethoxycarbonyl, 1,1-dimethyl-2-haloethoxycarbonyl,
1,1-dimethyl-2,2-dibromoethoxycarbonyl,
1,1-dimethyl-2,2,2-trichloroethoxycarbonyl,
1,1-methyl-1-(4-biphenylyl)ethoxycarbonyl,
1-(3,5-di-t-butylphenyl)-1-methylethoxycarbonyl, 2-(2'- and 4'-pyridyl)ethoxycarbonyl, 2,2-bis(4'-nitrophenyl)ethoxycarbonyl,
N-(2-pivaloylamino)-1,1-dimethylethoxycarbonyl,
2-[(2-nitrophenyl)dithio]-1-phenylethoxycarbonyl,
2-(2-(N,N-dicyclohexylcarboxamido) ethoxycarbonyl, t-butyloxycarbonyl,
1-adamantyloxycarbonyl, 2-adamantyloxycarbonyl, vinyloxycarbonyl,
allyloxycarbonyl, 1-isopropylallyloxycarbonyl, cinnamylloxycarbonyl,
4-nitrocinnamylloxycarbonyl, 3-(3'-pyridyl)prop-2-enyloxycarbonyl,
8-quinolylloxycarbonyl, N-hydroxypiperdiny1, alkylidithiooxycarbonyl,
benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl,
p-bromobenzyloxycarbonyl, p-chlorobenzyloxycarbonyl,
2,4-dichlorobenzyloxycarbonyl, 4-methylsulfmylbenzyloxycarbonyl,
9-anthrylmethyloxycarbonyl, diphenylmethyloxycarbonyl, N-formyl, N-acetyl, N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, N-phenylacetyl, N-3-phenylpropionyl, N-4-pentenoyl, N-picolinoyl, N-3-pyridylcarboxamido, N-benzooylphenylalanyl, N-benzoyl, or N-p-phenylbenzoyl.

[0047] In certain other embodiments, the nitrogen-protecting group is t-butyloxycarbonyl, ethoxycarbonyl, benzyloxy carbonyl, substituted benzyloxy carbonyl (e.g., p-methoxybenzyloxy carbonyl, p-nitrobenzyloxy carbonyl, p-bromobenzyloxy carbonyl, p-chlorobenzyloxy carbonyl, 2,4-dichlorobenzyloxy carbonyl, 4-methylsulfmylbenzyloxy carbonyl), allyloxy carbonyl, trimethylsilylethoxycarbonyl, acetyl, substituted acetyl (e.g., N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, or N-phenylacetyl), N-benzoyl, or N-p-phenylbenzoyl. In yet other embodiments, the nitrogen-protecting group is t-butyloxycarbonyl.

[0048] In certain embodiments, the nitrogen-protecting group is removed using an organic or inorganic acid, or a mixture thereof. In certain other embodiments, the nitrogen-protecting group is removed using TFA/Et₃SiH, HCl, HBr, or a mixture thereof.

[0049] Peramivir can be obtained by general purification methods, such as extraction, washing, crystallization, re-crystallization and so on, for example, re-crystallization from mixture of alcohol and water. In certain embodiments, the re-crystallization solvent is a mixture of methanol and water.

[0050] In a further aspect, the present invention provides a compound of formula
wherein $R_i$ is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; $R_2$ and $R_3$ are each independently a nitrogen-protecting group. In certain embodiments, $R_i$ is hydrogen, (C$_i$-C$_4$)alkyl, (C$_3$-C$_7$)cycloalkyl, phenyl, or (C$_i$-C$_4$)alkyl-phenyl, in which said (C$_i$-C$_4$)alkyl is optionally substituted with one or more halogen.

[0051] In certain embodiments, the nitrogen-protecting group ($R_2$ and $R_3$ in formula IV) is described as hereinabove.

[0052] In certain embodiments, the present invention provides a compound of the formula

$$\text{BocHN} \equiv \begin{array}{c} N \cr \text{NBoc} \end{array} \equiv \text{O}$$

[0053] In another aspect, the present invention provides a compound of formula (VI),

wherein $R_i$ is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; $R_2$ and $R_3$ are each independently a nitrogen-protecting group. In certain embodiments, $R_i$ is hydrogen, (C$_i$-C$_4$)alkyl, (C$_3$-C$_7$)cycloalkyl, phenyl, or (C$_i$-C$_4$)alkyl-phenyl, in
which said (C1-C4)alkyl is optionally substituted with one or more halogen.

[0054] In certain embodiments, the nitrogen-protecting group (R2 and R3 in formula VI) is described as hereinabove.

[0055] In certain embodiments, the present invention provides a compound of

\[
\begin{align*}
\text{BocHN} & \quad \text{N}\text{Boc} \\
\text{N} & \quad \text{COOMe}
\end{align*}
\]

formula .

**Definition**

[0056] Throughout the present application, unless otherwise noted, the term "alkyl" whether used alone or as part of a substituent group, includes straight and branched chains containing one to eight carbon atoms, preferably one to three carbon atoms, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, i-butyl, i-ptyl and the like.

[0057] The term "cycloalkyl" means cyclic aliphatic groups containing three to eight carbon atoms, including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

[0058] The term "aryl" means non-substituted aromatic groups, such as phenyl, naphthyl, and the like, preferably phenyl.

[0059] The term "Ar-alkyl" means any alkyl group substituted with an aryl group, such as benzyl, phenylethyl, and so on.

[0060] As used herein, unless otherwise noted, substituents on the aryl or
Ar-alkyl group are one or more, preferably one or two of halogen.

[0061] In certain embodiments, the present invention provides a process for the preparation of peramivir (I) as shown in Scheme 3:

Scheme 3

[0062] Certain specific aspects and embodiments of present invention are described in further detail by the examples below. The illustrated examples are not intended to limit the scope of this invention.

EXAMPLES

Example 1

1 (1S,4R)-methyl-4-(2,3-bis(leri-butoxycarbonyl)guanidino)cyclopent-2-ene-carboxylate (13)
To a mixture of \((1S,4R^methyl\) 4-aminocyclopent-2-enecarboxylate tartaric acid salt 11 (7.29 g, 25 mmol) in dichloromethane (150 mL), was added Et₃N (9 mL, 65 mmol) at 0 °C, and the resulting mixture was stirred for 15 min. To this, tert-butyl (lH-pyrazol-l-yl)methylene dicarbamate 12 was added. After addition, the reaction was monitored for completion by TLC (PE: EtOAc=5:1). The organic layers were washed with water and brine and dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated to give 13 as a white solid, which was used in the next step without further purification.

\[ \text{MS (M+)}: 384. \]

\[ \text{H NMR (400 MHz, CDC1₃) } \delta 11.49 (s, 1H), 8.53 (d, J = 8.4 Hz, 1H), 5.94 - 5.83 (m, 2H), 5.38 - 5.31 (m, 1H), 3.73 (s, 3H), 3.56 - 3.44 (m, 1H), 2.60 (dt, J = 14.0, 8.5 Hz, 1H), 1.94 (dt, J = 13.9, 4.7 Hz, 1H), 1.50 (d, J = 7.4 Hz, 18H) \]

(See attached Chart 1)

**Example 2**

\( 2 (3aR,4R,6S,6aS)-methyl-4-(2,3-bis(ieri-butoxycarbonyl)guanidino)-3-(pentan-3-yl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-6-carboxylate \) (5)
a) Preparation of 2-Ethyl-N-hydroxybutanimidoyl chloride (14):

[0066] Hydroxylamine hydrochloride (7.2g, 0.1 mol) was dissolved in water (7 mL). Toluene (27 mL) was added, followed by addition of 2-ethylbutylaldehyde (10g, 0.1 mol). The two-phase mixture was stirred vigorously while cooling. Sodium hydroxide solution (ca.30%, 14.6g, 0.1 mol) was added slowly (addition is very exothermic) to maintain a temperature between 15-25 °C. The mixture was stirred for 60 min, then allowed to stand to separate the layers. The organic extract was washed with water and brine, dried over Na₂SO₄, and directly used in the next step.

[0067] N-Chlorosuccinimide (NCS) (13.3g, 0.1 mol) was suspended in dimethylformamide (DMF) (17ml) and cooled to about 10 °C. The toluene solution prepared above (3.15 mol) was added dropwise with sufficient cooling to maintain the reaction temperature between 10-25°C. After addition, the reaction was monitored by TLC until completion of the reaction. Water (100ml) was added slowly (slightly exothermic) while maintaining the temperature at 15-25 °C. The two-phase mixture was stirred for 15 min at 15-25 °C and the layers were separated. The water layer was extracted with toluene (10ml) and the organic layer washed with water (3 X 20ml) and brine, dried over Na₂SO₄, and directly used in the next step.

b) Preparation of (3aR,4R,6S,6aS)-methyl-4-(2,3-bis(ieryl-butoxycarbonyl)-guan
idine)-3-(pentan-3-yl)-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-6-carboxylate (15)

[0068] 13 (from example 1, 9.2g, 0.024 mol) was dissolved in toluene (100 mL) and triethylamine (10.0g, 0.099 mol) and the reaction mixture was heated to 60-70 °C. 2-Ethyl-N-hydroxylbutanimidoyl chloride 14 (from example 2a, 14.8 g, 0.099 mol) in toluene (40 mL) was added to the above solution. A white solid (triethylammonium chloride) was formed. After addition, the reaction was monitored for completion by TLC (PE: EtOAc=3:1. The reaction mixture was cooled to 20-25°C, the precipitate was removed by filtration and the filter cake was washed with toluene (50 g). The organic filtrate was washed with water, brine, and dried over anhydrous Na2SO4. The mixture was filtered and concentrated by rotary evaporation. The resulting residue was purified by silica gel flash column chromatography using PE/EtOAc (30:1-4:1, v/v) to give 15 as a white solid.

[0069] Yield: 10.0 g (85%).


[0071] 1H NMR (400 MHz, CDCl3) δ 11.29 (s, 1H), 8.55 (d, J = 6.4 Hz, 1H), 5.30 (dd, J = 9.1, 1.5 Hz, 1H), 4.53 (d, J = 4.8 Hz, 1H), 3.78 (s, 3H), 3.70 (d, J = 9.1 Hz, 1H), 3.25 (t, J = 5.4 Hz, 1H), 2.93 - 2.84 (m, 1H), 2.20 (dd, J = 7.6, 3.7 Hz, 2H), 1.87 - 1.60 (m, 4H), 1.49 (d, J = 6.0 Hz, 1H), 0.95 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H). (See attached Chart 2)

Example 3
3. (1\(^1\), 2\(^2\), 3\(^3\), 4\(^4\))-ιηι1-3-(1-306ι αιδοι-2-6ι γιβιυи1)-4-(2,3-5ιιει-бутокарб-онил) гуанидино)-2-гидроксициклоценекарбоксилат (16):

[0072] Compound **15** (from example 2, 5.0 g, 10.08 mmol) and nickel chloride hexahydrate (2.5 g, 10.5 mmol) were dissolved in methanol (40 mL). The green solution was cooled to -15 °C, while a suspension formed. Sodium borohydride (0.456 g, 12 mmol) was added to the reaction mixture at -10 to -5 °C (reaction is highly exothermic). A black suspension was formed along with gas evolution. After complete addition of the sodium borohydride solution, the reaction mixture was stirred until TLC showed **15** was fully consumed. A solution of acetic anhydride (15 g, 0.13 mol) was added slowly and maintained the reaction temperature at 0-5 °C, the reaction mixture was stirred for 2-12 h at 0 °C (The black solution change into green solution ). The pH of the mixture was adjusted to ~9 by addition of 25% aq. ammonium hydroxide. The mixture was concentrated by rotary evaporator. The resulting residue was diluted with water (30 mL) and extracted with EtOAc (50 mL<<3). The combined organic extracts were washed with water and brine and dried over anhydrous Na\(_2\)SO\(_4\). The mixture was filtered and concentrated by rotary evaporation. The residue was purified by flash chromatography using DCM/Methanol (100:0 to 100:2, v/v) to give **16** as a white solid.
Yield: 3.8 g (71%).

MS (M+1 ) : 543.

\[ ^1H \text{ NMR (400 MHz, CDCl}_3 \] \( \delta \) 11.39 (s, 1H), 8.72 (d, J = 9.9 Hz, 1H), 8.59 (d, J = 8.5 Hz, 1H), 4.53 - 4.39 (m, 1H), 4.26 (d, J = 16.4 Hz, 2H), 3.96 (t, J = 10.2 Hz, 1H), 3.71 (s, 3H), 2.90 - 2.75 (m, 1H), 2.53 (dt, J = 13.6, 8.8 Hz, 1H), 2.10 (s, 3H), 2.03 (d, J = 6.3 Hz, 1H), 1.90 - 1.76 (m, 1H), 1.38 (dd, J = 73.9, 7.9 Hz, 18H), 1.25 (ddd, J = 15.2, 13.1, 7.3 Hz, 4H), 0.79 (t, J = 7.3 Hz, 3H), 0.75 (dd, J = 14.1, 6.9 Hz, 3H). (See attached Chart 3)

**Example 4**

4. \((1^\text{,}2^\text{,}3^\text{,}4^)\)-3-(1-306 iau\id{0}-2-6i hylbui\iy1)-4-(2,3-5is(ier\-butoxycarbonyl)gu -anidino)-2-hydroxycyclopentanecarboxylic acid (17)

![Chemical Structure]

To a mixture of compound 16 (from example 3, 2.0 g, 3.69 mmol) in MeOH/THF (1:1, v/v, 12 mL), was added aq. NaOH (IN, 7 mL) at room temperature. After completion of the reaction (monitored by TLC, DCM:MeOH=10: 1, the mixture was concentrated by rotary evaporation. The resulting solution was neutralized to pH 7 using ice-cold 1 N HCl aq. solution and quickly extracted with EtOAc twice. The combined organic extracts were washed with water, brine, and dried over anhydrous \( \text{Na}_2\text{SO}_4 \). The mixture was filtered and
the filtrate was concentrated by rotary evaporation. The resulting white foam was washed triturated by hexane, filtered, dried to give 17 as a white solid

[0077] Yield: 1.6 g (84%).


[0079] ^1H NMR (400 MHz, CDCl3) δ 11.41 (s, 1H), 8.80 (d, J = 9.8 Hz, 1H), 8.62 (d, J = 8.3 Hz, 1H), 4.43 (dd, J = 23.3, 14.3 Hz, 2H), 4.00 (t, J = 9.8 Hz, 1H), 2.83 (s, 1H), 2.53 (dt, J = 16.9, 8.4 Hz, 1H), 2.14 (s, 3H), 1.91 (dd, J = 12.5, 6.0 Hz, 1H), 1.46 (dd, J = 30.1, 9.5 Hz, 18H), 1.47 - 1.14 (m, 6H), 0.97 - 0.69 (m, 6H).

(See attached Chart 4)

Example 5

5. (1^,2^,3^,4^)-3-(1-hydroxy-2-hydroxycyclopent-4^)-4\^\text{ua\eta\idio-2-6\^\text{hy\l\bul\y1}-}\text{anecarboxylic acid (Peramivir I)}

[0080] Compound 17 (from example 4, 1.1 g, 2 mmol) was dissolved in aq. HCl (6N, 6 mL, 36 mmol) at 0 °C. The mixture was stirred at room temperature overnight. The resulting solution was neutralized to pH 6-7 using ice-cold 1 N NaOH aq. solution. The mixture was concentrated to 1.5 ml by rotary evaporation. To this, methanol (20 mL) was added. The precipitate was filtered, and the filtrate
was concentrated. The resulting white solid was recrystallized from methanol/water (1:1, v/v) to give Peramivir I as a white solid.

[0081] Yield: 500 mg (73%).

[0082] MS (M+1) : 329.

[0083] $^1$H NMR (400 MHz, D$_2$O) δ 4.21 (d, J = 10.6 Hz, 2H), 3.70 (dd, J = 14.6, 9.0 Hz, 1H), 2.57 (d, J = 4.8 Hz, 1H), 2.40 (dt, J = 17.7, 8.9 Hz, 1H), 2.14 - 2.01 (m, 1H), 1.81 (s, 3H), 1.75 - 1.58 (m, 1H), 1.31 (s, 3H), 0.78 (ddd, J = 21.6, 18.6, 6.8 Hz, 8H). (See attached Chart 5)
WE CLAIM:

1. A process for preparing a compound of formula (IV):

\[
R_3N^\text{\textendash}NHR_2\xrightarrow{HNR^-\circ\text{OR}_1}(IV)
\]

wherein R_i is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; R_2 and R_3 are each independently a nitrogen-protecting group, the process comprising reacting a compound of formula (II), or a pharmaceutically acceptable salt thereof,

\[
\xrightarrow{H_2N^-\circ\text{OR}_1}(II)
\]

wherein R_i is defined as hereinabove, with an amidine compound of formula (III),

\[
\xrightarrow{R_2^\text{\textendash}NR^-\circ\text{R}_4^\text{\textendash}NR_3^\text{\textendash}R_4}(III)
\]

wherein R_2 and R_3 are defined as hereinabove, and R_4 is a leaving group, to provide the compound of formula (IV).

2. The process of claim 1, wherein said leaving group is alkylthio, arylthio, pyrazolyl, imidazole, cyano, or triazolyl.

3. The process of claim 1 or 2, further comprising reacting the compound of formula (IV) with a compound of formula (V)

\[
\xrightarrow{\text{Cl}^-\text{OH}}(V)
\]
to produce a compound of formula (VI),

\[
\begin{array}{c}
\text{R}_1 \text{HN}\text{N} \text{NH} \text{N} \\
\text{HN} \text{C} \text{O} \text{R}_2 \text{N} \text{N} \text{N} \text{C} \text{O} \\
\text{R}_3 \text{N} \text{N} \text{C} \text{O} \text{R}_1 \\
\end{array}
\]

(VI)

wherein \( \text{R}_1, \text{R}_2 \) and \( \text{R}_3 \) are defined as hereinabove.

4. A process for preparing a compound of formula (VI):

\[
\begin{array}{c}
\text{R}_1 \text{HN}\text{N} \text{NH} \text{N} \\
\text{HN} \text{C} \text{O} \text{R}_2 \text{N} \text{N} \text{N} \text{C} \text{O} \\
\text{R}_3 \text{N} \text{N} \text{C} \text{O} \text{R}_1 \\
\end{array}
\]

(VI)

wherein \( \text{R}_1 \) is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; \( \text{R}_2 \) and \( \text{R}_3 \) are each independently a nitrogen-protecting group,

the process comprising reacting a compound of formula (IV),

\[
\begin{array}{c}
\text{R}_1 \text{HN}\text{N} \text{NH} \text{N} \\
\text{HN} \text{C} \text{O} \text{R}_2 \text{N} \text{N} \text{N} \text{C} \text{O} \\
\text{R}_3 \text{N} \text{N} \text{C} \text{O} \text{R}_1 \\
\end{array}
\]

(IV)

wherein \( \text{R}_1, \text{R}_2 \) and \( \text{R}_3 \) are defined as hereinabove,

with a compound of formula (V)

\[
\begin{array}{c}
\text{Cl} \text{OH} \text{N} \\
\text{N} \text{C} \text{O} \text{R}_1 \\
\end{array}
\]

(V)

to produce the compound of formula (VI).

5. The process of claim 3 or 4, further comprising reducing the compound of formula (VI) using a reducing agent, followed by acetylation to provide a
compound of formula (VII),

wherein \( R_i, R_2 \) and \( R_3 \) are defined as hereinabove.

6. The process of claim 5, wherein said reducing agent is selected from: (1) alkali metal borohydride in combination with transition metal chloride, transition metal sulfate, or transition metal phosphate; (2) \( \text{PtO}_2 / \text{H}_2 \), Raney Ni / \( \text{H}_2 \), \( \text{Pd/C/H}_2 \), or Rh/ \( \text{H}_2 \); (3) transition metal such as Zn and Fe in acids such as acetic acid; (4) Red-Al; and (5) \( \text{NaBH}_4 / \text{Me}_2\text{SO}_4 \).

7. The process of claim 6, wherein said alkali metal borohydride is selected from \( \text{NaBH}_4, \text{KBH}_4, \text{LiBH}_4, \text{NaBH}_3\text{CN}, \) and \( \text{NaBH(OAc)}_3 \).

8. The process of claim 6 or 7, wherein said transition metal chloride is selected from \( \text{NiCl}_2, \text{CoCl}_2, \) and \( \text{ZnCl}_2 \).

9. The process of claim 5, wherein said acetylation is achieved using acetic anhydride, acetyl chloride, or acetyl mixed anhydrides.

10. The process of any one of claims 5-9, further comprising hydrolyzing the compound of formula (VII), wherein \( R_1 \) is not \( \text{H} \), with a base or an acid to provide a compound of formula (VIII),
wherein $R_2$ and $R_3$ are defined as hereinabove.

11. The process of any one of claims 5-10, further comprising removing the nitrogen-protecting group ($R_2$ and $R_3$) in the compound of formula (VII), wherein $R_i$ is H; or removing the nitrogen-protecting group ($R_2$ and $R_3$) in the compound of formula (VIII), to provide peramivir (I)

12. The process of any one of claims 1-11, wherein said nitrogen-protecting group is t-butyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, 9-fluorenylmethoxycarbonyl, 9-(2-sulfo)fluorenylmethoxycarbonyl, 9-(2,7-dibromo)fluorenylmethoxycarbonyl, 17-tetrabenzo[a,c,g,i]fluorenylmethoxycarbonyl, 2-chloro-3-indenylmethoxycarbonyl, benz[ffinden-3-ylmethoxycarbonyl, 2,7-di-t-butyl-[9-(10, 10-dioxo- 10, 10, 10-tetrahydrothioxanthyl)] methoxycarbonyl, 1, 1-dioxobenzo[b]thiophene-2-ylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, 2-phenylethoxycarbonyl, 1-(1-adamantyl)- 1-methylethoxycarbonyl,
2-chloroethoxycarbonyl, 1,1-dimethyl-2-haloethoxycarbonyl,  
1,1-dimethyl-2,2-dibromoethoxycarbonyl,  
1,1-dimethyl-2,2,2-trichloroethoxycarbonyl,  
1,1-methyl-1-(4-biphenylyl)ethoxycarbonyl,  
1-(3,5-di-t-butylphenyl)-l-methylethoxycarbonyl,  
2-(2’-and 4’-pyridyl)ethoxycarbonyl,  
2,2-bis(4’-nitrophenyl)ethoxycarbonyl,  
N-(2-pivaloylamino)-l,1-dimethylethoxycarbonyl,  
2-[(2-nitrophenyl)dithio]-l-phenylethoxycarbonyl,  
2-(2-(N,N-dicyclohexylcarboxamido)ethoxycarbonyl, t-butyloxycarbonyl,  
1-adamantyloxycarbonyl, 2-adamantyloxycarbonyl, vinyloxycarbonyl,  
allyloxycarbonyl, 1-isopropylallyloxycarbonyl, cinnamyloxycarbonyl,  
4-nitrocinnamyloxycarbonyl, 3-(3’-pyridyl)prop-2-enyloxycarbonyl,  
8-quinolyloxycarbonyl, N-hydroxypiperdiny1, alkylthiooxycarbonyl,  
benzylloxycarbonyl, p-methoxybenzylxycarbonyl, p-nitrobenzylxycarbonyl,  
p-bromobenzylxycarbonyl, p-chlorobenzylxycarbonyl,  
2,4-dichlorobenzylxycarbonyl, 4-methylsulfilmbenzylxycarbonyl,  
9-anthrylmethoxycarbonyl, diphenylmethoxycarbonyl, N-formyl, N-acetyl,  
N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, N-phenylacetyl,  
N-3-phenylpropionyl, N-4-pentenoyl, N-picolinoyl, N-3-pyridylcarboxamido,  
N-benzoxyphenylalanyl, N-benzoyl, or N-p-phenylbenzoyl.

13. The process of claim 11 or 12, wherein the nitrogen-protecting group is removed using an organic or inorganic acid, or a mixture thereof.
14. The process of claim 11 or 12, wherein the nitrogen-protecting group is removed using TFA/Et$_3$SiH, HCl, HBr, or a mixture thereof.

15. A process for preparing Peramivir (I),

![Chemical Structure](I)

comprising:

(a) reacting a compound of formula (II), or a pharmaceutically acceptable salt thereof,

![Chemical Structure](II)

wherein R$_1$ is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen,

with an amidine compound of formula (III),

![Chemical Structure](III)

wherein R$_2$ and R$_3$ are defined as hereinabove, and R$_4$ is a leaving group,

to provide a compound of formula (IV):

![Chemical Structure](IV)

wherein R$_1$, R$_2$ and R$_3$ are defined as hereinabove;
(b) reacting the compound of formula (IV) with a compound of formula (V)

\[ \text{(V)} \]

\[ \text{(VI)} \]

wherein R₁, R₂ and R₃ are defined as hereinabove;

(c) reducing the compound of formula (VI) using a reducing agent, followed by acetylation to provide a compound of formula (VII),

\[ \text{(VII)} \]

wherein R₁, R₂ and R₃ are defined as hereinabove;

(d) hydrolyzing the compound of formula (VII), wherein R₁ is not H, with a base or an acid to provide a compound of formula (VIII),

\[ \text{(VIII)} \]

wherein R₂ and R₃ are defined as hereinabove;
(e) removing the nitrogen-protecting group (R_2 and R_3) in the compound of formula (VII), wherein R_1 is H, or in the compound of formula (VIII), to provide peramivir (I).

16. The process of claim 15, wherein said leaving group is alkylthio, arylthio, pyrazolyl, imidazole, cyano or triazolyl.

17. The process of claim 15 or 16, wherein said reducing agent is selected from: (1) alkali metal borohydride in combination with transition metal chloride, transition metal sulfate, or transition metal phosphate; (2) PtO_2/H_2, Raney Ni/H_2, Pd/C/H_2, or Rh/H_2; (3) transition metal such as Zn and Fe in acids such as acetic acid; (4) Red-Al; and (5) NaBH_4/Me_2SO_4.

18. The process of claim 17, wherein said alkali metal borohydride is selected from NaBH_4, KBH_4, LiBH_4, NaBH_3CN, and NaBH(OAc)_3.

19. The process of claim 17, wherein said transition metal chloride is selected from NiCl_2, CoCl_2, and ZnCl_2.

20. The process of any one of claims 15-19, wherein said acetylation is achieved using acetic anhydride, acetyl chloride, or acetyl mixed anhydrides.

21. The process of any one of claims 15-20, wherein said nitrogen-protecting group is t-butyloxy carbonyl, methoxycarbonyl, ethoxycarbonyl, 9-fluorenymethoxycarbonyl, 9-(2-sulfo)fluorenymethoxycarbonyl, 9-(2,7-dibromo)fluorenymethoxycarbonyl, 17-tetrabenzo[a,c,g,i]fluorenymethoxycarbonyl, 2-chloro-3-indenymethoxycarbonyl, benz[f]inden-3-ylmethoxycarbonyl,
2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)] methoxycarbonyl, 1,1-dioxobenzo[b]thiophene-2-ylmethoxycarbonyl,
2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl,
2-phenylethoxycarbonyl, 1-(1-adamantyl)-1-methylethoxycarbonyl,
2-chloroethoxycarbonyl, 1,1-dimethyl-2-haloethoxycarbonyl,
1,1-dimethyl-2,2-dibromoethoxycarbonyl,
1,1-dimethyl-2,2,2-trichloroethoxycarbonyl,
1,1-dimethyl-2-(1-(4-biphenylyl)methylethoxycarbonyl,
1,1-dimethyl-2-(2'-pyridyl)ethoxycarbonyl, 2,2-bis(4'-nitrophenyl)ethoxycarbonyl,
N-(2-pivaloylamino)-1,1-dimethylethoxycarbonyl,
2-[(2-nitrophenyl)dithio]-1-phenylethoxycarbonyl,
2-(2-(N,N-dicyclohexylcarboxamido)ethoxycarbonyl, t-butyloxycarbonyl,
1-adamantyloxycarbonyl, 2-adamantyloxycarbonyl, vinyloxycarbonyl,
allyloxycarbonyl, 1-isopropylallyloxycarbonyl, cinnamyloxycarbonyl,
4-nitrocinnamyloxycarbonyl, 3-(3'-pyridyl)prop-2-enyloxycarbonyl,
8-quinoloxycarbonyl, N-hydroxypiperdiny1, alkylthiooxycarbonyl,
benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl,
p-bromobenzyloxycarbonyl, p-chlorobenzyloxycarbonyl,
2,4-dichlorobenzyloxycarbonyl, 4-methylsulfmethylbenzyloxycarbonyl,
9-anthryloxycarbonyl, diphenylmethyloxycarbonyl, N-formyl, N-acetyl,
N-chloroacetetyl, N-trichloroacetyl, N-trifluoroacetyl, N-phenylacetyl,
N-3-phenylpropionyl, N-4-pentenoyl, N-picolinoyl, N-3-pyridylcarboxamido, N-benzoylphenylalanyl, N-benzoyl, or N-p-phenylbenzoyl.

22. The process of any one of claims 15-20, wherein the nitrogen-protecting group is removed using an organic or inorganic acid, or a mixture thereof.

23. The process of any one of claims 15-20, wherein the nitrogen-protecting group is removed using TFA/Et₃SiH, HCl, HBr, or a mixture thereof.

24. A compound of formula (IV),

![IV](image)

wherein R₁ is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen;

R₂ and R₃ are each independently a nitrogen-protecting group.

25. The compound of claim 24, wherein said nitrogen-protecting group is t-butyloxy carbonyl, ethoxycarbonyl, benzyloxycarbonyl, substituted benzyloxycarbonyl (e.g., p-methoxybenzyloxy carbonyl, p-nitrobenzyloxy carbonyl, p-bromobenzyloxy carbonyl, p-chlorobenzyloxy carbonyl, 2,4-dichlorobenzyloxy carbonyl, 4-methylsulfanyl benzyloxy carbonyl), allyloxy carbonyl, trimethylsilyl ethoxycarbonyl, acetyl, substituted acetyl (e.g., N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, or N-phenylacetyl), N-benzoyl, or N-p-phenylbenzoyl.
26. The compound of claim 24, having the following structure:

![Structure](image)

27. A compound of formula (VI),

![Structure](image)

(VI),

wherein R₁ is hydrogen, alkyl, cycloalkyl, aryl, or alkyl-aryl, in which said alkyl is optionally substituted with one or more halogen; R₂ and R₃ are each independently a nitrogen-protecting group.

28. The compound of claim 27, wherein said nitrogen-protecting group is t-butyloxycarbonyl, ethoxycarbonyl, benzyloxy carbonyl, substituted benzyloxy carbonyl (e.g., p-methoxy benzyloxy carbonyl, p-nitro benzyloxy carbonyl, p-bromobenzyloxy carbonyl, p-chlorobenzyloxy carbonyl, 2,4-dichlorobenzyloxy carbonyl, 4-methylsulfonylbenzyloxy carbonyl), allyloxy carbonyl, trimethylsilyl ethoxycarbonyl, acetyl, substituted acetyl (e.g., N-chloroacetyl, N-trichloroacetyl, N-trifluoroacetyl, or N-phenylacetyl), N-benzoyl, or N-p-phenyl benzoyl.

29. The compound of claim 27, having the following structure:

![Structure](image)
INTERNATIONAL SEARCH REPORT

International application No. PCT/CN2011/073575

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07C 279/-; C07C 277/-

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

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

WPI EPDOC CNPAT CNKI CA: peramivir acetylamino ethyl butyl hydroxy aminoiminomethyl cyclopentyl carboxylic guanidine aminoimino cyclopetenyl cyclopentyl 330600-85-6 229614-55-5

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO9933781 A1 (BIOCRYST PHARMACEUTICALS, INC.) 08 July 1999 (08.07.1999) pages 31-33, 11 1-170 of the description, examples 102-209</td>
<td>1-29</td>
</tr>
<tr>
<td>A</td>
<td>CN10538228A (BEIJING PUSHIKANG MEDICINE TECHNOLOGY CO. LTD.) 23 Sept. 2009 (23.09.2009) pages 4-7, 9-15 of the description, examples 1-16</td>
<td>1-29</td>
</tr>
<tr>
<td>A</td>
<td>CN1986521A (SOUTH CHINA AGRICULTURAL UNIVERSITY) 27 June 2007 (27.06.2007) pages 3-6 of the description</td>
<td>1-29</td>
</tr>
</tbody>
</table>

1-29 Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search 15 Dec. 2011 (15.12.2011)

Date of mailing of the international search report 08 Mar. 2012 (08.03.2012)

Name and mailing address of the ISA/CN
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Authorized officer XIA, Fengjuan
Telephone No. (86-10) 82246747

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## A. CLASSIFICATION OF SUBJECT MATTER

C07C 279/16(2006.01)i
C07C 277/08(2006.01)i
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