The present invention relates to a novel process for the preparation of the antiviral drug compound Entecavir, through novel intermediates.
PROCESS FOR THE PREPARATION OF ENTECAVIR THROUGH NOVEL INTERMEDIATES

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel process for the antiviral drug compound Entecavir.

BACKGROUND OF THE INVENTION

Entecavir (Formula I) is an antiviral drug used for the treatment of chronic hepatitis B. The chemical name of Entecavir is 2-amino-9-[(1S, 3R, 4S)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-6,9-dihydro-3H-purin-6-one. The trade name is Baraclude® and it is marketed as monohydrate by Bristol-Myers Squibb. Entecavir, being a nucleoside analog, acts as an inhibitor of reverse transcription, DNA replication and transcription in the viral process.

Several methods for the preparation of Entecavir are currently available in the literature. In EP0481754, the synthesis of Entecavir begins with the cyclopentadienyl anion. The carbocyclic core is built up to the point where all the oxygen substituents are protected and then, the coupling with the guanine base is accomplished via epoxide ring opening. The exocyclic methylene moiety may be formed under standard olefination conditions. The synthesis is completed with two deprotection steps.
The process exhibits some major drawbacks. All along the process, reagents difficult to handle are employed, namely metal sodium for the preparation of sodium cyclopentadienide (not shown in the scheme), Ipc₂BH for the stereoselective reaction hydroxylation and Dess-Martin reagent for the oxidation of the secondary alcohol to the ketone moiety. In addition, boron trichloride is employed in the last step of the process, a highly toxic and aggressive reagent, which also requires careful handling.
In WO2010074534 a cyclopentenone derivative is subjected to standard transformations and protections till a suitably protected carbocyclic key-intermediate is prepared, according to the above scheme. The key-intermediate is subjected to an olefination reaction, followed by coupling with a protected guanine-derivative. Two more steps are required for complete deprotection, which leads to compound of Formula I (Entecavir).

This process lines up a number of well-known synthetic transformations in an efficient way to reach the suitably protected cyclopentanone, as a key intermediate. What follows is an olefination reaction, coupling with a guanine derivative under Mitsunobu conditions and a two-step deprotection sequence. The process suffers from low yields at these crucial steps. The olefination reaction, performed with the use of Nysted reagent, affords, according to the experimental data provided in said application, the exomethylene product in 35% w/w yield. The Mitsunobu reaction proceeds also with a yield particularly low for a coupling reaction, namely 82% w/w.

In WO2012006964 the synthesis as shown in the scheme below, utilizes a suitably protected cyclic acetal derivative, prepared from Corey lactone diol. This cyclic derivative undergoes ring opening, to afford the respective product with the exocyclic double bond. After hydrolysis of the formyl moiety and partial deprotection a protected guanine derivative is attached and all the protecting groups are cleaved. In this process, highly toxic reagents which is considered to be a neurotoxin, namely lead tetraacetate [Pb(OAc)₄], is used for the double bond formation reaction. Such toxic
reagents are specifically unsuitable for industrial purposes, especially for the case of compounds intended to be used as drugs.

Accordingly, there is still a need for an industrially applicable, efficient and safe process for the production of Entecavir.

SUMMARY OF THE INVENTION

The present invention encompasses a process for the preparation of compound of formula II and its use for the preparation of Entecavir (formula I). The illustrated process holds a number of features suitable for industrial purposes, including high yields, efficient purification methods and reagents and conditions that are easy to use in an industrial process.

According to an aspect of the invention, there is provided a process for the preparation of entecavir from compound of formula III, characterized by an elimination reaction of compound of formula II or compound of formula IV.
According to another aspect of the invention, there is provided a process for the preparation of compound of formula II comprising:

a) subjecting compound of formula III to reaction with trimethylsilyl methyl magnesium halide (TMSCH$_2$MgX, wherein X is a halogen) or trimethylsilyl methyl lithium (TMSCH$_2$Li) to form compound of formula IV;

b) selective deprotection of compound of formula IV to form compound of formula II;

c) optional isolation and recrystallization of compound of formula II:
In the above structures \( R_1 \) and \( R_2 \) are independently selected from hydrogen or a hydroxyl-protecting group or \( R_1 \) and \( R_2 \) may together form a cyclic hydroxyl-protecting group and \( R_3 \) is selected from hydrogen or a hydroxyl-protecting group.

According to a further aspect of the invention, there is provided a process for the preparation of compound of formula II, wherein \( R_j \) and \( R_2 \) are t-butyldimethylsilyl (Formula Ila), according to the process described above. Said process comprises also compounds III and IV, wherein \( R_i \) and \( R_2 \) are t-butyldimethylsilyl and \( R_3 \) is benzyl and is depicted in the following scheme:

The invention also provides a process for the preparation of Entecavir (Formula I) from compounds of formula II, said process comprising:

a) elimination reaction and Mitsunobu coupling with a compound of formula VI, to yield compound of formula V, wherein \( R_1 \) and \( R_2 \) are defined as above, \( X \) may be a halogen, hydroxyl group or benzyloxy group and, \( R \) and \( R' \) are independently selected from amine-protecting groups or hydrogen;

b) deprotection of compound of formula V, to form Entecavir (Formula I).
According to another aspect of the invention, Entecavir is prepared according to the above process, from compound of formula II, wherein $R_1$ and $R_2$ are t-butyldimethylsilyl.

The invention also provides a process for the preparation of compound of formula VIII, comprising the following steps:

a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide ($\text{TMSCH}_2\text{MgX}$, wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV:

\[
\begin{align*}
\text{III} & \quad \text{IV} \\
R_1O & \quad R_1O \\
R_2O & \quad R_2O \\
\text{TMS} & \quad \text{TMS} \\
\text{OR}_3 & \quad \text{OR}_3 \\
\end{align*}
\]

b) subjecting compound of formula IV to elimination reaction, to form compound of formula VII:

\[
\begin{align*}
\text{IV} & \quad \text{VII} \\
R_1O & \quad R_1O \\
R_2O & \quad R_2O \\
\text{TMS} & \quad \text{TMS} \\
\text{OR}_3 & \quad \text{OR}_3 \\
\end{align*}
\]

c) deprotection of compound of formula VII to form compound of formula VIII.

In the above structures $R_1$ and $R_2$ are independently selected from hydrogen or a hydroxyl-protecting group or $R_1$ and $R_2$ may together form a cyclic hydroxyl-protecting group and $R_3$ is selected from hydrogen or a hydroxyl-protecting group.

The invention further provides a process for the preparation of Entecavir (Formula I) from compounds of formula III, said process comprising:
a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide (TMSCH$_2$MgX, wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV;

\[
\begin{align*}
\text{III} & \quad \text{IV} \\
R_1O & \quad R_2O \\
R_2O & \quad \text{OH}_{\text{TMS}} \\
\text{OR}_3 & \quad \text{OR}_3 \\
\end{align*}
\]

b) subjecting compound of formula IV to elimination reaction, to form compound of formula VII;

\[
\begin{align*}
\text{IV} & \quad \text{VII} \\
R_1O & \quad R_2O \\
\text{OH}_{\text{TMS}} & \quad \text{OR}_3 \\
\text{OR}_3 & \quad \text{OR}_3 \\
\end{align*}
\]

c) deprotection of compound of formula VII to form compound of formula VIII;

\[
\begin{align*}
\text{VII} & \quad \text{VIII} \\
R_1O & \quad R_2O \\
\text{OR}_3 & \quad \text{OR}_3 \\
\end{align*}
\]

d) optional isolation and recrystallization of compound of formula VIII;

e) Mitsunobu coupling with a compound of formula VI, to yield compound of formula V, wherein X may be halogen, benzyloxy group (-OBn) or hydroxyl group; R and R’ are independently selected from amine protecting groups or hydrogen;

\[
\begin{align*}
\text{VI} & \\
\end{align*}
\]

f) conversion of compound of formula V to Entecavir (Formula I).

\[
\begin{align*}
\text{V} & \quad \text{I} \\
R_1O & \quad \text{OH} \\
R_2O & \quad \text{OH} \\
\text{NRR'} & \quad \text{NH}_2 \\
\end{align*}
\]
DEFINITIONS

The term "hydroxyl protecting group" refers to protecting groups known in the art and exemplified such as in Greene's Protective Groups on Organic Synthesis 4th Edition, John Wiley & Son, Peter G. M. Wuts, Theodora W. Greene, Print ISBN: 9780471697541. Preferred hydroxyl protecting groups are alkyl and aryl ethers, silyl ethers, esters, carbonates, sulfonates. More preferred hydroxyl protecting groups are allyl (All), methoxymethyl (MOM), 2-methoxyethoxymethyl (MEM), methylthiomethyl (MTM), benzoxymethyl (BOM), 2-(trimethylsilyl)ethoxymethyl (SEM), tetrahydropyranyl (THP), 2,4-dinitrobenzyl, diphenylmethyl (DPM), trityl (Tr), p-methoxyphenyldiphenylmethyl (MMTr), benzyl (Bn), naphthyl (NAP), p-methoxybenzyl (PMB), p-nitrobenzyl, formyl, acyl (Ac), chloroacetyl, methoxyacetyl, pivaloyl (Piv), benzoyl (Bz), p-nitrobenzoyl, p-methoxybenzoyl, p-bromobenzoyl, p-phenylbenzoyl, trimethylsilyl (TMS), tnethylsilyl (TES), isopropylidemethylsilyl (IPDMS), triisopropylsilyl (TIPS), tert-butylidemethylsilyl (TBS), tert-butylidiphenylsilyl (TBDPS), methyldiphenylsilyl (TDS), methyl carbonate, ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), allyl carbonate (Alloc), 9-(Fluoromethyl) carbonate (Fmoc), benzyl carbonate (Cbz), t-butyloxycarbonyl (Boc), sulfates, allylsulfonate, methanesulfonate, benzylsulfonate, tosylate.

The term "cyclic hydroxyl-protecting group" refers, also, to hydroxyl protecting groups exemplified in the textbook mentioned above. Preferred cyclic hydroxyl protecting groups are cyclic acetals, cyclic ketals, cyclic ortho esters, cyclic carbonate, silyl derivatives. More preferred cyclic hydroxyl-protecting group are isopropylidene, pentyldene, hexyldene, benzylidene, p-methoxybenzylidene, naphthylidene, 4-phenylbenzylidene, methoxymethylene, ethoxymethylene, cyclic carbonate, 1,3-(1,1,3,3-tetraisopropyl)disiloxanediyl (TIPDS).

The term "amine protecting group" refers, also, to protecting groups exemplified in the textbook mentioned above. Preferred amine protecting groups are carbamates, amides, N-alkyl, N-aryl, N-silyl amino and N-sulfonyl derivatives. More preferred amine protecting groups are tert-butoxycarbonyl (Boc), benzoyloxycarbonyl (Cbz), allyloxy carbonyl (Alloc), 9-fluorenylmethoxycarbonyl (Fmoc), 2,2,2-trichloroethyl...
carbonate (Troc), formyl, acetyl, trifluoroacetyl, benzyl (Bn), allyl (All), trityl (Tr), trimethoxyphenylmethylene, trimethylsilyl (TMS), tert-butyldimethylsilyl, (TBS), p-methoxybenzyl (PMB), p-halo-benzyl, diphenylmethyl, naphthylmethyl, benzenesulfonate, tosylate.

The term "amine base" may refer to compounds of formula NR₄R₅R₆, wherein R₄, R₅ and R₆ are selected from hydrogen, alkyl or substituted alkyl groups, aminoacids, heterocyclic bases, such as monocyclic, bicyclic or tricyclic amine bases, protected or unprotected DNA bases and their derivatives;

It will be acknowledged from the person skilled in the art, that in the case of the preparation of compounds of formulae IV and II, two possible diastereomers may form, with respect to the newly-formed quaternary carbon. Depending on the nature of the protecting groups, the result of the reactions may differ, in terms of the ratio of the diastereomers. By careful selection of the bulkiness and stereoelectronic effects of the protecting groups, it may be also possible to control the diastereoselectivity of the reaction with trimethylsilyl methyl magnesium halide or trimethylsilyl methyl lithium. The scope of the invention may be considered to include these variations also.

DETAILED DESCRIPTION OF THE INVENTION

According to a first aspect of the invention, there is provided a process for the preparation of entecavir from compound of formula III, characterized by an elimination reaction of compound of formula II or compound of formula IV.

According to one aspect, the present invention provides a process for the preparation of compounds of formula II comprising:

a) subjecting compound of formula III to reaction with trimethylsilyl methyl magnesium halide (TMSCH₂MgX, wherein X is a halogen) or trimethylsilyl methyl lithium (TMSCH₂Li) to form compound of formula IV;
wherein $R_1$, $R_2$ and $R_3$ are defined as above and

b) selective deprotection of the $R_3$ group of compound of formula IV to form compound of formula II:

\[ \text{IV} \rightarrow \text{II} \]


c) isolation and optional recrystallization of compound of formula II.

Step a) may be performed in a polar aprotic solvent or a non-polar solvent. Preferred solvents are halogenated hydrocarbons, ethers, ketones and aromatic hydrocarbons.

The reaction may be performed at temperatures that range from -20°C to the boiling point of the solvent used in the reaction. Preferred temperature range is from -20°C to 120°C. More preferred temperature range is from 0°C to 80°C.

Step b) is a typical deprotection reaction. The step may be performed according to methods described in Greene's Protective Groups on Organic Synthesis 4th Edition mentioned above.

Step c) is a recrystallization procedure that may be performed in an organic solvent. Preferred solvents are alcohols, ketones, esters, ethers, aromatic and aliphatic hydrocarbons or mixtures thereof. More preferred solvents are methanol, ethanol, 2-propanol, dichloromethane, chloroform, tetrahydrofuran, 2-methyl-tetrahydrofuran, diethyl ether, 1,4-dioxane, toluene, acetone, methyl isobutyl ketone.

According to another aspect of the present invention, there is provided a process for the preparation of compound of formula II, wherein $R_i$, $R_2$ and $R_3$ are representing hydroxyl protecting groups, or $R_i$ and $R_2$ together form a cyclic hydroxyl protecting
group and \( R_3 \) represents a hydroxyl protecting groups, wherein the hydroxyl protecting groups are preferably selected from alkyl and aryl ethers, silyl ethers, esters and carbonates.

More preferred hydroxyl protecting groups are allyl (All), methoxymethyl (MOM), 2-methoxyethoxymethyl (MEM), methylthiomethyl (MTM), benzoyxymethyl (BOM), 2-(trimethylsilyl)ethoxymethyl (SEM), tetrahydropropyranyl (THP), 2,4-dinitrobenzyl, diphenylmethyl (DPM), trityl (Tr), \( p \)-methoxyphenyldiphenylmethyl (MMTr), benzyl (Bn), naphthyl (NAP), \( p \)-methoxybenzyl (PMB), \( p \)-nitrobenzyl, formyl, acyl (Ac), chloroacil, methoxyacil, pivaloyl (Piv), benzoyl (Bz), \( p \)-nitrobenzoyl, \( p \)-methoxybenzoyl, \( p \)-bromobenzoyl, \( p \)-phenylbenzoyl, trimethylsilyl (TMS), triethylsilyl (TES), isopropylidemethylsilyl (IPDMS), triisopropylsilyl (TIPS), tert-butylidemethylsilyl (TBS), tert-butylidiphenylsilyl (TBDPS), methyldiphenylsilyl, thexylidemethylsilyl (TDS), methyl carbonate, ethyl carbonate, 2,2,2-trichloroethyl carbonate (Troc), allyl carbonate (Alloc), 9-(Fluoromethyl) carbonate (Fmoc), benzyl carbonate (Cbz), \( t \)-butyl carbonate (Boc), sulfate, allylsulfonate, methanesulfonate, benzylsulfonate, tosylate.

Even more preferred hydroxyl protecting groups are allyl (All), methoxymethyl (MOM), tetrahydropropyranyl (THP), diphenylmethyl (DPM), trityl (Tr), \( p \)-methoxyphenyldiphenylmethyl (MMTr), benzyl (Bn), \( p \)-methoxybenzyl (PMB), acetyl (Ac) pivaloyl (Piv), benzoyl (Bz), \( p \)-nitrobenzoyl, \( p \)-phenylbenzoyl, triethylsilyl (TES), triisopropylsilyl (TIPS), tert-butylidemethylsilyl (TBS), tert-butylidiphenylsilyl (TBDPS).

According to a further aspect of the present invention, there is provided a process for the preparation of compound of formula II, wherein \( R_1 \) and \( R_2 \) are \( t \)-butylidemethylsilyl, according to the above described process, through Formulae III and IV, wherein \( R_i \) and \( R_2 \) are \( t \)-butylidemethylsilyl and \( R_3 \) is benzyl. The inventors have found that compound Ila, being a solid, can easily be purified from undesirable impurities, through techniques known in the art, such as recrystallization. The present invention enables efficient purification at this step of the process, namely prior to attachment of the guanine moiety, which affords a final product with fine purity.
Moreover, although this process may form compound of formula IIa in variable ratios of diastereomers, with respect to the stereochemistry of the carbon bearing the -CH₂TMS group, this feature does not have an impact to the scope of the invention. Any ratio of diastereomers, regarding this stereogenic center, is within the scope of the present invention. The described process is shown in the scheme below:

Step a) may be performed in a polar aprotic solvent. Preferred solvents are defined as above.

The reaction may be performed at temperatures that range from -20 °C to the boiling point of the solvent used in the reaction. Preferred temperature range is from 0 °C to 80 °C.

Step b) is a typical deprotection reaction. The cleavage of the benzyl group may be achieved according to procedures described in Greene’s Protective Groups on Organic Synthesis 4th Edition. Preferred conditions for this step are catalytic hydrogenation conditions. More preferred conditions are a palladium-based catalyst and a hydrogen source.

Step c) is a recrystallization procedure that may be performed in an organic solvent or a mixture of organic solvents, as described above.

According to another aspect of the present invention there is provided a compound of formula II, wherein R₁ and R₂ are defined as above. R₁ and R₂ are preferably alkyl and aryl ethers, silyl ethers, esters, carbonates, or R₁ and R₂ together form a cyclic hydroxyl protecting group. More preferably, R₁ and R₂ are silyl ethers, esters, alkyl and aryl esters. Even more preferably, R₁ and R₂ are silyl protecting groups.
According to still another aspect of the present invention there is provided a compound of formula Ila, where $R_1$ and $R_2$ are t-butyldimethylsilyl.

According to a further aspect of the present invention there is provided a compound of formula IV, wherein $R_1$, $R_2$ and $R_3$ are defined as above. $R_1$ and $R_2$ are preferably alkyl and aryl ethers, silyl ethers, esters, carbonates, or $R_1$ and $R_2$ together form a cyclic hydroxyl protecting group. More preferably, $R_1$ and $R_2$ are silyl ethers, esters, alkyl and aryl esters. $R_3$ is preferably a hydroxyl protecting group that can be cleaved in the presence of hydroxyl protecting groups $R_1$ and $R_2$.

According to still another aspect of the present invention there is provided a compound of formula IV, where $R_1$, $R_2$ and $R_3$ represent hydroxyl protecting groups, or $R_1$ and $R_2$ together form a cyclic hydroxyl protecting group and $R_3$ represents a hydroxyl protecting group, wherein the hydroxyl protecting groups are selected from alkyl and aryl ethers, silyl ethers, esters, carbonates.

According to another aspect of the present invention there is provided a compound of formula IVa, where $R_1$ and $R_2$ are t-butyldimethylsilyl and $R_3$ is Bn.

According to still another aspect of the present invention, there is provided a process for the preparation of Entecavir from compound of formula II, said process comprising:

a) elimination reaction and Mitsunobu coupling with compound of formula VI, to yield compound of formula V, wherein $R_1$ and $R_2$ are defined as above, $X$ may be a
halogen, OH or OBn and, R and R' are independently selected from amine protecting groups or hydrogen, as defined above:

\[
\begin{align*}
\text{halogen, } & \text{OH or OBn and, R and R'} \\
\text{are independently } & \text{selected from amine protecting groups or hydrogen, as defined above;}
\end{align*}
\]

b) deprotection and/or hydrolysis of compound of formula V, to form Entecavir (Formula I).

\[
\begin{align*}
\text{Step a) comprises of a Mitsunobu reaction and an elimination reaction in one chemical step. The skilled person can perform this step by following procedures exemplified in prior art.}
\end{align*}
\]

Mitsunobu reactions are performed in the presence of a phosphine and an azo-based compound. Several procedures are available in prior art and scientific literature, for example, review article *Chemical Reviews* 2009, 109, 2551. Preferred phosphines are trialkyl and triarylphosphines and their polymer-supported analogues. More preferred phosphines are triphenylphosphine, trimethylphosphine, tributylphosphine. Preferred azo-based compounds are diethylazodicarboxylate (DEAD), diisopropylazodicarboxylate (DIAD), di-t-butylazodicarboxylate, 2-(phenylazo)pyridine, di-/?-chlorobenzylazodicarboxylate (DCAD), 1,1'- (azodicarboxyl)dipepine. Mitsunobu reactions are also carried out with the employment of phosphorane ylides. Preferred phosphorane ylides are (cyanomethylene)trimethylphosphorane or tributylphosphorane.

The elimination reaction is performed according to procedures exemplified in prior art and scientific literature, for example review articles *Org. Reactions* 1990, 38, 1 and *Chem. Soc. Rev.* 2003, 31, 195. Such procedures may employ base or acid catalyzed conditions.
Base catalyzed conditions may refer to organic or inorganic bases. Organic bases may be amine bases, hydrocarbon or alkoxide alkali metal salts or alkali metal amine salts. Inorganic bases may be alkali metal hydrides, alkali metal hydroxides, salts thereof or quaternary ammonium salts or non-nucleophilic bases such as silyl amides.

Acid catalyzed conditions may refer to strong inorganic acids, Lewis acids or organic acids.

By combining the conditions required for the performance of these two reactions, step a) may be performed in a single chemical step.

Step b) is performed with respect to the protecting groups present on intermediate V. The person skilled in the art is enabled to perform this step by referring to textbooks such as Greene's Protective Groups on Organic Synthesis 4th Edition. When X is halogen, the conversion to the free guanine moiety involves a hydrolysis reaction under acidic conditions, which also leads to deprotection of acid labile protecting groups. More specific examples can also be found in prior art, such as WO2010074534 or EP0481754.

According to still another aspect of the present invention, Entecavir may be prepared according to the above described process, wherein Ri and R₂ are representing hydroxyl protecting groups, or R₁ and R₂ together form a cyclic hydroxyl protecting group, wherein the hydroxyl protecting groups are selected from silyl ethers, esters, alkyl and aryl ethers, carbonates.

According to still another aspect of the present invention, Entecavir may be prepared according to the above described process, wherein R₁ and R₂ are t-butyldimethyl silyl, X is halogen, R is t-butoxycarbonyl (Boc) and R' is H.

According to still another aspect of the present invention, Entecavir may be prepared according to the above described process, wherein Ri and R₂ are t-butyldimethylsilyl, X is halogen and R and R' are H.
The person skilled in the art will acknowledge that step b) should be interpreted as a deprotection step with respect to all the protecting groups. It can be performed as a global deprotection step, or a suitable sequence of deprotection reactions can be selected. The person skilled in the art can perform this step according to procedures described in Greene's Protective Groups on Organic Synthesis 4th Edition.

According to a further aspect of the present invention, there is provided a process for the preparation of compound of formula VIII, comprising:

10 a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide (TMSCH₂MgX, wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV as a single diastereomer or a mixture of diastereomers;

\[
\text{III} \rightarrow \text{IV}
\]

15 b) subjecting compound of formula IV to elimination reaction, to form compound of formula VII;

\[
\text{IV} \rightarrow \text{VII}
\]

c) deprotection of compound of formula VII to form compound of formula VIII,

\[
\text{VII} \rightarrow \text{VIII}
\]

wherein R₁ and R₂ are independently selected from hydrogen, hydroxyl-protecting group or R₁ and R₂ may together form a cyclic hydroxyl-protecting group and R₃ is a hydroxyl protecting group.

Steps a)-c) may be performed as already described above.
According to another aspect of the present invention there is provided a process for the preparation of entecavir, comprising the following steps:

a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide \((\text{TMSCH}_2\text{MgX})\), wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV as a single diastereomer or a mixture of diastereomers;

\[
\begin{align*}
\text{III} & \quad \text{IV} \\
\begin{array}{c}
\text{R}_1 \text{O} \\
\text{R}_2 \text{O} \\
\text{OR}_3 \\
\end{array} & \quad \text{R}_1 \text{O} \\
\begin{array}{c}
\text{R}_2 \text{O} \\
\text{OR}_3 \\
\end{array}
\end{align*}
\]

b) subjecting compound of formula IV to elimination reaction, to form compound of formula VII;

\[
\begin{align*}
\text{IV} & \quad \text{VII} \\
\begin{array}{c}
\text{R}_1 \text{O} \\
\text{R}_2 \text{O} \\
\text{OR}_3 \\
\end{array} & \quad \text{R}_1 \text{O} \\
\begin{array}{c}
\text{R}_2 \text{O} \\
\text{OR}_3 \\
\end{array}
\end{align*}
\]

c) deprotection of compound of formula VII to form compound of formula VIII;

\[
\begin{align*}
\text{VII} & \quad \text{VIII} \\
\begin{array}{c}
\text{R}_1 \text{O} \\
\text{R}_2 \text{O} \\
\text{OR}_3 \\
\end{array} & \quad \text{R}_1 \text{O} \\
\begin{array}{c}
\text{R}_2 \text{O} \\
\text{OR}_3 \\
\end{array}
\end{align*}
\]

d) optional isolation and recrystallization of compound of formula VIII;

e) Mitsunobu coupling with a compound of formula VI, to yield compound of formula V, wherein X may be halogen, benzyloxy group \((-\text{OBn})\) or OH; R and R' are independently selected from amine protecting groups or hydrogen;

\[
\begin{align*}
\text{VI} & \quad \text{V} \\
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{NRR'} \\
\end{array} & \quad \text{R}_1 \text{O} \\
\begin{array}{c}
\text{R}_2 \text{O} \\
\text{X} \\
\text{NRR'} \\
\end{array}
\end{align*}
\]

f) conversion of compound of formula V to Entecavir (Formula I).

\[
\begin{align*}
\text{V} & \quad \text{I} \\
\begin{array}{c}
\text{R}_1 \text{O} \\
\text{R}_2 \text{O} \\
\text{X} \\
\end{array} & \quad \text{R}_1 \text{O} \\
\begin{array}{c}
\text{R}_2 \text{O} \\
\text{X} \\
\text{NH}_2 \\
\end{array}
\end{align*}
\]
Steps a)-f) may be performed as already described above.

According to still another aspect of the present invention there is provided compound of formula IX, which can be prepared by global deprotection of compound of formula II, according to textbooks discussed above.

![Formula IX](image)

EXPERIMENTAL

**EXAMPLE 1: Preparation of compound of formula IVa**

![Formula IVa](image)

Dissolve 1.1 g of compound of formula Ilia in 37 ml dichloromethane, add 10.6 ml (3.0 eq) of a solution of 1.0 M trimethylsilylmethylmagnesium chloride in diethyl ether and stir at ambient temperature till reaction completion. Add 90 ml of saturated aqueous solution of ammonium chloride and 65 ml dichloromethane, separate layers and extract aqueous layer twice with 90 ml dichloromethane. Wash combined organic extracts with 20 ml of a 20% w/v aqueous solution of sodium chloride. Dry organic layer over 0.5 g of anhydrous sodium sulfate, evaporate solvent and separate residue by column chromatography to get 770 mg of compound of formula IVa as an oil.

1H-NMR (500MHz, CDCl₃) δ 7.26-7.33 (m, 5H), 4.55 (d, J = 11.7 Hz, 1H), 4.49 (td, J = 8.7, 5.6 Hz, 1H), 4.36 (d, J = 11.8 Hz, 1H), 4.06 (dd, J = 10.5, 2.4 Hz, 1H), 3.95 (dd, J = 10.5, 1.7 Hz, 1H), 3.58 (dd, J = 6.1, 2.0 Hz, 1H), 2.50 (ddd, J = 14.5, 8.4, 6.2 Hz, 1H), 1.74 (d, J = 9.0 Hz, 1H), 1.65 - 1.56 (m, 2H), 1.29 (d, J = 14.5 Hz, 1H), 0.99 - 0.95 (m, 1H), 0.88 (dd, J = 8.1, 5.1 Hz, 18H), 0.13 (s, 3H), 0.10 (s, 3H), 0.06 - 0.02 (m, 12H).
**13C NMR (126 MHz, CDCl₃) δ 139.07, 128.35, 128.16, 127.47, 127.38, 84.47, 84.41, 70.77, 70.04, 59.86, 58.79, 26.03, 25.96, 25.91, 25.79, 23.03, 18.16, 18.05, 0.74, -4.12, -4.67, -5.59, -5.67.**

**LC-MS (ESI positive) m/z: 575 [M+Na]⁺, 403 [M-OH-OTBS] +**

**EXAMPLE 2:** Preparation of compound of formula Ila

![Diagram of compound Ila]

Dissolve 300 mg of compound of formula IVa in 18 ml methanol, add 548 mg (16.0 eq) ammonium formate and then, portionwise, 864 mg palladium on carbon 10% (50% wet). Heat to reflux and stir till reaction is completed. Cool to ambient temperature, filter through celite pad, distill off methanol. Dissolve residue in 3 ml dichloromethane, add 1 ml of saturated aqueous solution of ammonium chloride, dry organic layer over sodium sulfate, evaporate solvent to obtain crude Ha. Further separation, either by column chromatography or crystallization provides the diastereomERICally pure compound as a white solid.

**1H-NMR (500 MHz, CDCl₃) δ 4.33 (td, J = 7.2, 4.1 Hz, 1H), 4.12 (s, 1H), 4.04 (dd, J = 10.5, 2.9 Hz, 1H), 3.92 (dd, J = 10.5, 3.4 Hz, 1H), 3.80 (d, J = 4.9 Hz, 1H), 2.57 - 2.48 (m, 1H), 1.99 (s, 1H), 1.78 (dt, J = 6.4, 3.1 Hz, 1H), 1.53 - 1.46 (m, 1H), 1.16 (d, J = 14.8 Hz, 1H), 1.04 (d, J = 14.8 Hz, 1H), 0.87 (dd, J = 15.6, 7.0 Hz, 18H), 0.12 (s, 3H), 0.09 (s, 3H), 0.08 - 0.04 (m, 12H).**

**13C NMR (126 MHz, CDCl₃) δ 85.04, 78.82, 72.38, 60.47, 56.82, 42.26, 25.97, 25.89, 24.1 1, 18.09, 0.66, -4.33, -4.70, -5.55, -5.58, -5.62.**

**LC-MS (ESI positive) m/z: 485 [M+Na]⁺**

mp 183.1-183.8 °C
EXAMPLE 3: Preparation of compound of formula Va

Method A:
Dissolve 50 mg of compound of formula Ila in 1.5 ml dichloromethane, add 113 mg (4.0eq) triphenylphosphine and cool to 0°C. Add 0.096 ml (4.5eq) diisopropylazodicarboxylate dropwise, stir for 30 minutes at 0°C, then allow to warm to ambient temperature and further stir for 30 minutes. Cool again to 0°C, add 117 mg (3.0eq) of Via (N2-Boc-2-amino-6-iodopurine) in three portions, every 30 minutes. After the end of the addition further stir for 30 min, then allow the mixture to reach ambient temperature. After further addition of 43 mg (1.5eq) of triphenylphosphine, 60 mg (1.5eq) Via and 0.034 ml (2.0eq) diethylazodicarboxylate at -15°C the conversion by TLC is complete. Evaporation of volatiles provides 35mg of compound of formula Va as an oil, which may be used without further purification.

EXAMPLE 4: Preparation of compound of formula I (Entecavir)
Dissolve 53 mg of compound of formula Va in 0.1 ml tetrahydrofuran, add 0.1 ml 2N hydrochloric acid, heat to reflux and maintain this temperature for 2-4 hours, till reaction is completed. Cool at ambient temperature, add 0.08 ml of 10% w/v aqueous solution of sodium hydroxide and distill off solvent. Purification by flash column chromatography affords 7 mg of Entecavir. The analytical data, including NMR, LCMS and HPLC, are confirmed with a reference sample.

EXAMPLE 5: Preparation of compound of formula IX

Dissolve 200 mg of compound of formula Ila in 10 ml THF and add 600 mg TBAF.3H₂O. Stir the mixture at room temperature until TLC shows complete consumption of the starting material. Distill off THF under reduced pressure and add 30 ml AcOEt to the residue. Wash the mixture with water and brine, dry with anhydrous Na₂SO₄, filter and distill off organic solvents. Column chromatography provides 85 mg (83%) of compound of compound of formula IX.
CLAIMS

1. A process for the preparation of entecavir from compound of formula III, as defined in claim 2, characterized by an elimination reaction of an intermediate, said intermediate selected from compounds of formulae II or IV, as defined in claim 2.

2. A process for the preparation of compound of formula II,

\[
\begin{align*}
&\text{II} \\
&\text{III} \\
\end{align*}
\]

wherein \( R_1 \) and \( R_2 \) are independently selected from hydrogen, hydroxyl-protecting group or \( R_1 \) and \( R_3 \) may together form a cyclic hydroxyl-protecting group, comprising the following steps:

a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide (TMSCH\(_2\)MgX, wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV as a single diastereom or a mixture of diastereomers,

\[
\begin{align*}
&\text{III} \\
&\text{IV} \\
\end{align*}
\]

wherein \( R_3 \) is a hydroxyl protecting group;

b) deprotection of compound of formula IV to form compound of formula II;

\[
\begin{align*}
&\text{IV} \\
&\text{II} \\
\end{align*}
\]

c) isolation and optional recrystallization of compound of formula II.

3. A process, according to claim 2, wherein \( R_1, R_2 \) and \( R_3 \) are representing hydroxyl protecting groups, or \( R_1 \) and \( R_2 \) together may form a cyclic hydroxyl protecting group and \( R_3 \) represents a hydroxyl protecting group, wherein the hydroxyl
protecting groups are selected from silyl ethers, esters, alkyl and aryl ethers and carbonates.

4. A process, according to claim 2, for the preparation of compound of formula \( \text{IIa} \), wherein \( R_1 \) and \( R_2 \) are t-butyldimethylsilyl, \( R_3 \) is benzyl, said process comprising the following steps:
   a) subjecting compound of formula \( \text{IIa} \) to reaction with trimethylsilylmethylmagnesium halide or trimethylsilyl methyl lithium to form compound of formula \( \text{IVa} \) as a single diastereomer or a mixture of diastereomers;
   
   \[
   \text{IIIa} \quad \overset{TBSO}{\text{TBSO}} \quad \text{O} \quad \text{Bn} \quad \rightarrow \quad \text{IVa} \quad \overset{TBSO}{\text{TBSO}} \quad \text{OH} \quad \text{TMS} \quad \text{OBn}
   \]

   b) deprotection of compound of formula \( \text{IVa} \) to form compound of formula \( \text{IIa} \);
   
   \[
   \text{IVa} \quad \overset{TBSO}{\text{TBSO}} \quad \text{OH} \quad \text{TMS} \quad \text{OBn} \quad \rightarrow \quad \text{IIa} \quad \overset{TBSO}{\text{TBSO}} \quad \text{OH} \quad \text{TMS} \quad \text{OH}
   \]

   c) isolation and optional recrystallization of compound of formula \( \text{IIa} \).

5. A compound of formula \( \text{II} \), wherein \( R_1 \) and \( R_2 \) are defined as in claim 2.

6. A compound of formula \( \text{II} \), wherein \( R_1 \) and \( R_2 \) are representing hydroxyl protecting groups, or \( R_1 \) and \( R_2 \) together may form a cyclic hydroxyl protecting group, wherein the hydroxyl protecting groups are selected from silyl ethers, esters, alkyl and aryl ethers, carbonates.

7. A compound of formula \( \text{II} \), wherein \( R_1 \) and \( R_2 \) are t-butyldimethylsilyl (Formula \( \text{IIa} \)).
8. A compound, according to claim 7, which is either a single diastereomer or includes a mixture of two diastereomers, with respect to the stereocenter formed in carbon No 1 as numbered in the below scheme, in any proportion

9. A compound, according to claim 7, having the absolute configuration shown below

10. A compound of formula IV, wherein \( R_1, R_2 \) and \( R_3 \) are defined as in claim 2 or 3.

11. A compound of formula IV, wherein \( R_1 \) and \( R_2 \) are t-butyldimethylsilyl groups and \( R_3 \) is benzyl group (Formula IVa).

12. A process for the preparation of Entecavir (Formula I), from compound of formula II, said process comprising:

a) elimination reaction and Mitsunobu coupling of a compound of formula II with a compound of formula VI, to yield compound of formula V, wherein \( X \) may be halogen, benzyl group (-OBn) or OH; \( R \) and \( R' \) are independently selected from amine protecting groups or hydrogen;
b) conversion of compound of formula V to Entecavir (Formula I)

wherein $R_1$ and $R_2$ are defined as in claims 2 or 3.

13. A process, according to claim 12, wherein $R_1$ and $R_2$ are representing hydroxyl protecting groups, or $R_1$ and $R_2$ together may form a cyclic hydroxyl protecting group, wherein the hydroxyl protecting groups are selected from silyl ethers, esters, alkyl and aryl ethers, carbonates.

14. A process, according to claim 12, wherein $R_1$ and $R_2$ are t-butyldimethylsilyl, X is halogen, R is t-butoxycarbonyl and $R'$ is H.

15. A process, according to claim 12, wherein $R_1$ and $R_2$ are t-butyldimethylsilyl, X is halogen and R and $R'$ are H.

16. A process for the preparation of entecavir, comprising the following steps:

a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide (TMSCH$_2$MgX, wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV as a single diastereomer or a mixture of diastereomers,
wherein $R_1$ and $R_2$ are independently selected from hydrogen, hydroxyl-protecting group or $R_1$ and $R_2$ may together form a cyclic hydroxyl-protecting group and $R_3$ is a hydroxyl protecting group;

b) deprotection of compound of formula IV to form compound of formula II;

\[
\begin{array}{c}
\text{IV} \\
\text{R}_1O \quad \text{TMS} \\
\text{OH} \\
\text{R}_2O \\
\text{OR}_3
\end{array}
\quad \rightarrow
\begin{array}{c}
\text{II} \\
\text{R}_1O \quad \text{TMS} \\
\text{OH} \\
\text{R}_2O \\
\text{OR}_3
\end{array}
\]

c) optional isolation and recrystallization of compound of formula II;

d) elimination reaction and Mitsunobu coupling of a compound of formula II with a compound of formula VI, to yield compound of formula V, wherein $X$ may be halogen, benzyloxy group (-OBn) or hydroxyl group; $R$ and $R'$ are independently selected from amine protecting groups or hydrogen;

e) conversion of compound of formula V to Entecavir (Formula I).

17. A process, according to claim 16, wherein $R_1$ and $R_2$ are independently selected from hydrogen, hydroxyl-protecting group or $R_1$ and $R_2$ may together form a cyclic hydroxyl-protecting group and $R_3$ is a hydroxyl protecting group, wherein the hydroxyl protecting groups are selected from silyl ethers, esters, alkyl and aryl ethers, carbonates.

18. A process, according to claim 16, wherein $R_1$ and $R_2$ are t-butyldimethylsilyl, $R_3$ is benzyl, $X$ is halogen, $R$ is t-butoxycarbonyl and $R'$ is H.

19. A process, according to claim 16, wherein $R_1$ and $R_2$ are t-butyldimethylsilyl, $R_3$ is benzyl, $X$ is halogen, $R$ and $R'$ are H.
20. A process for the preparation of compound of formula VIII from compound of formula III, comprising the following steps:

a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide (TMSCH$_2$MgX, wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV as a single diastereomer or a mixture of diastereomers;

\[ \text{III} \rightarrow \text{IV} \]

b) subjecting compound of formula IV to elimination reaction, to form compound of formula VII;

\[ \text{IV} \rightarrow \text{VII} \]

c) deprotection of compound of formula VII to form compound of formula VIII,

\[ \text{VII} \rightarrow \text{VIII} \]

wherein R$_1$, R$_2$ and R$_3$ are defined as in claim 2 or 3.

21. A process for the preparation of entecavir, comprising the following steps:

a) subjecting compound of formula III to reaction with trimethylsilylmethylmagnesium halide (TMSCH$_2$MgX, wherein X is halogen) or trimethylsilylmethyl lithium, to form compound of formula IV as a single diastereomer or a mixture of diastereomers;

\[ \text{III} \rightarrow \text{IV} \]
b) subjecting compound of formula IV to elimination reaction, to form compound of formula VII;

\[
\text{IV} \rightarrow \text{VII}
\]

c) deprotection of compound of formula VII to form compound of formula VIII;

\[
\text{VII} \rightarrow \text{VIII}
\]

d) optional isolation and recrystallization of compound of formula VIII;
e) Mitsunobu coupling of a compound of formula VIII with a compound of formula VI, to yield compound of formula V, wherein X may be halogen, benzyloxy group (-OBn) or hydroxyl group; R and R’ are independently selected from amine protecting groups or hydrogen;

f) conversion of compound of formula V to Entecavir (Formula I).

22. Use of compound of formula II, as defined in claim 2, for the preparation of any other compound, preferably Entecavir.

23. Use of compound of formula IIa, as defined in claim 4, for the preparation of any other compound, preferably Entecavir.

24. Use of compound of formula III, as defined in claim 2, for the preparation of any other compound, preferably Entecavir, with the proviso that R3 is not alkylsilyl or allylsilyl:
25. Use of compound of formula IIa, as defined in claim 4, for the preparation of any other compound, preferably Entecavir.

26. Use of compound of formula IV, as defined in claim 2, for the preparation of any other compound, preferably Entecavir.

27. Use of compound of formula IVa, as defined in claim 4, for the preparation of any other compound, preferably Entecavir.

28. Compound of formula IX.

29. Use of compound of formula DC, as defined in claim 28, for the preparation of any other compound, preferably Entecavir.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. C07D473/18 C07F7/18
ADD.

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)
C07D C07F

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 practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>WO 2010/074534 A2 (HANMI PHARM IND CO LTD [KR]; LEE JAEHEON [KR]; PARK GHA-SEUNG [KR]; KI) 1 July 2010 (2010-07-01) cited in the application on Reacti on scheme 3; claims 1-9</td>
<td>1-4, 12-21</td>
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**X** Further documents are listed in the continuation of Box C.  
**X** See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

**Date of the actual completion of the international search**  
19 January 2015

**Date of mailing of the international search report**  
29/01/2015

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**Authorized officer**  
Rufet, Jacques

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>A</td>
<td>EP 2 474 548 AI (ESTEVE QUIMICA SA [ES]) 11 July 2012 (2012-07-11) Scheme I; claims 1-10</td>
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<td>A</td>
<td>CN 102 417 506 A (HANGZHOU SAILI PHARMACEUTICAL INST CO LTD; HAINAN POLY PHARM CO LTD; Z) 18 April 2012 (2012-04-18) Scheme of page 7; claim 1</td>
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<td>A</td>
<td>JOSE L. CHIARA ET AL.: &quot;l-Silyl-2,6-diketones: Versatile intermediates for the divergent synthesis of five- and six-membered carbocycles under radical and ionic conditions&quot;, ORGANIC LETTERS, vol. 8, no. 18, 8 August 2006 (2006-08-08), pages 3935-3938, XP002734623, USAMERICAN CHEMICAL SOCIETY ISSN: 1523-7060 Scheme 1; compounds F, G</td>
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