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(54) **PROCESS FOR PREPARING CARBAMOYLPYRIDONE DERIVATIVES AND INTERMEDIATES**

VERFAHREN ZUR HERSTELLUNG VON CARBAMOYLPYRIDONDERIVATEN UND ZWISCHENPRODUKTE DAVON

PROCESSUS PERMETTANT DE PRÉPARER DES DÉRIVÉS ET DES PRODUITS INTERMÉDIAIRES DE CARBAMOYLPYRIDONE

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(56) References cited:
WO-A1-2010/011814
US-A- 4 524 149
US-A1- 2001 051 732
US-A1- 2006 019 996
US-A1- 2007 024 968
US-A1- 2009 318 421

- **KO ET AL.: 'A New and Facile Synthesis of 2-Pyridones.' BULL. KOREAN CHEM. SOC. vol. 22, no. 2, 2001, page 234**

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EP 2 549 870 B1

Description

Field of the Invention

[0001] The present invention relates to the preparation of carbamoylpyridone derivatives and intermediates which are useful as HIV integrase inhibitors.

Background of the Invention

[0002] Compounds having HIV integrase inhibitory activity are described in WO 2006/116764 (corresponding to U.S. Serial No. 11/919386 assigned to Shionogi & Co. Ltd.). The compounds are disclosed as polycyclic carbamoylpyridone deriviatives. Processes for making them are also disclosed. Among the examples of these compounds, the following polycyclic carbamoylpyridone derivatives are included:

[0003] The processes disclosed for preparing these compounds are quite arduous, involving as many as 14 steps. It would therefore be an advance in the art to find ways of making these compounds with greater efficiency.

Summary of the Invention

[0004] The present invention provides an improved process for preparing the following compounds:

[0005] In one aspect, the present invention is a method comprising contacting methyl 3-{[2,2-bis(methyloxy)ethyl]amino}-2-(methyloxy)acetyl]-2-propenoate (formula I): with an oxalate ester of formula II: in the presence of $M^+ {}^-OR$, where R is alkyl, aryl, or benzyl; and M^+ is an alkali metal cation; to form a pyridinone of formula III:

[0006] In a second aspect, the present invention method comprising selectively hydrolyzing a pyridinone of formula III: where R is alkyl, aryl, or benzyl
with a selective hydrolyzing reagent to form a pyridinone carboxylic acid of formula IV where R is alkyl, aryl, or benzyl: with greater than 90% selectivity.

[0007] In a third aspect, the present invention is a method comprising contacting a compound of formula VII: with a magnesium or lithium cation and a nucleophilic anion to form a compound of formula VIII:

[0008] The present disclosure encompasses a compound selected from the group consisting of:

[0009] In a fourth aspect, the present invention is a process comprising contacting a compound of formula IV where R is alkyl, aryl, or benzyl: with acetic acid and a catalytic amount of a strong protic acid to form a pyridinone carboxylic acid aldehyde of formula V where R is alkyl, aryl, or benzyl:

[0010] The process of the present invention is useful for the preparation of compounds with HIV integrase inhibitory activity.

Detailed Description of the Invention

[0011] The following schematic illustrates a general process for the preparation of the compound of formula VIII, ((3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo 2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide).

[0012] In the above schematic, 4-Methoxyacetoacetate is contacted with DMFDMA (*N*,*N*-dimethyl-1,1-bis(methyloxy)methanamine) under conditions sufficient to form methyl 3-(dimethylamino)-2-[(methyloxy)acetyl]-2-propenoate. Reaction of this intermediate with aminoacetaldehyde dimethyl acetal results in the formation of methyl 3-{[2,2-bis(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl] -2-propenoate (I).

[0013] Compound I is then contacted with oxalate ester (II) in the presence of $M^+ {}^-OR$ to form pyridinone (III). Each R is C_1-C_5-alkyl, aryl, or benzyl; M^+ is an alkali metal cation such as lithium, sodium, or potassium. Preferably, the alkali metal cation is lithium and the R group of the oxalate ester is the same as the R group from $M^+ {}^-OR$. Preferably R is a C_1-C_5-alkyl, especially a C_1-C_2-alkyl. Particularly preferred oxalate esters are dimethyl ethanedioate and diethyl ethanedioate. Particularly preferred alkali metal alkoxides are lithium methoxide and lithium ethoxide. Preferably, when the oxalate ester is dimethyl ethanedioate, the alkali metal alkoxide is lithium methoxide. Preferably, when the oxalate ester is diethyl ethanedioate, the alkali metal alkoxide is lithium ethoxide.

[0014] Pyridinone (III) is selectively hydrolyzed with LiOH to form pyridinone carboxylic acid (IV). Surprisingly, the methyl ester at the 5-position of pyridinone (III) is hydrolyzed with at least 90% selectivity over the ester at the 2-position.

[0015] Pyridinone carboxylic acid (IV) is contacted with acetic acid and a catalytic amount of a strong protic acid to form pyridinone carboxylic acid aldehyde (V). Examples of suitable strong protic acids include methanesulfonic acid, sulfuric acid, toluene sulfonic acid, and hydrochloric acid. Aldehyde (V) is then contacted with (2S)-2-amino-1-propanol to form ((3*S*,11a*R*)-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxylic acid) (VI).

[0016] Compound VI is contacted with 2.4-difluorobenzylamine under coupling conditions to form (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (VII).

[0017] Finally, compound VII is demethylated with a Lewis acid to form the product (3*S*,11a*R*)-*N*-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (VIII). Examples of suitable Lewis acids include magnesium, lithium, and calcium salts, as well as boron trihalides and trialkylsilyl halides. Preferred Lewis acids are magnesium and lithium salts. Magnesium salts include salts such as magnesium chloride, magnesium bromide, magnesium iodide, and mag-

nesium sulfide. Lithium salts include salts such as lithium chloride, lithium bromide, lithium iodide, and lithium sulfide. Lithium bromide is preferred.

[0018] Alternatively, and in another aspect of the present invention, compound V can be contacted with (3R)-3-amino-1-butanol to form a compound of formula VIa:

[0019] Compound VIa can be reacted with 2,4-difluorobenzylamine under coupling conditions to form a compound of formula VIIa:

[0020] Compound VIIa can be demethylated with MgX_n or LiX_n (wherein X is a halide, e.g., Br, Cl, F, or I) to form the compound of VIIIa:

Examples

[0021] The following example illustrates the process of the present invention. Solvents and reaction conditions are not intended to limit the scope of the invention. Starting materials are known in the art and are readily prepared or commercially available. Preferably, chemicals employed in the examples were obtained commercially (from Aldrich®, for example).

A. 1-[2,2-Bis(methyloxy)ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid

[0022] A mixture of methyl 4-methoxyacetoacetate (20 mL) and DMFDMA (24 mL) was stirred at room temperature for 1.5 h. The reaction mixture was diluted with MeOH (50 mL) and aminoacetaldehyde dimethyl acetal (16.7 mL) was added. The mixture was stirred for 1 h at room temperature, concentrated, and then diluted with MeOH (113 mL). Dimethyl oxalate (45.66 g) was charged followed by portion-wise addition of LiH (2.15 g) while maintaining the reaction temperature below 25 °C. The reaction content was heated to 40 °C for 14 h. The reaction mixture was cooled to -5 °C and LiOH (14.82 g) was added while maintaining the reaction temperature below 5 °C. When addition was complete, the mixture was stirred for a further 2 h at 3-5 °C for 1 h. The reaction mixture was quenched with aqueous HCl (2 N, 367 mL), maintaining the reaction temperature below 5 °C. When addition was complete, EtOAc (450 mL) was added and the mixture was warmed to 20 °C. The reaction mixture was filtered and the aqueous layer discarded. Water (225 mL) was added and the organic layer was removed under reduced pressure. The product was collected by filtration and dried in a vacuum oven overnight at 50 °C. The product was obtained as a solid.

B. (3S,11aR)-3-Methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxylic acid

[0023] **1-[2,2-bis(methyloxy)ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-**3-pyridinecarboxylic acid (22.54 g) was dissolved in 220 mL of CH_3CN. HOAc (20 mL) and CH_3SO_3H (1.4 mL) were added at room temperature and the mixture was heated to 58-65 °C for 19.5 h. Alaninol (7.511 g) in CH_3CN (15 mL) was added slowly and the resultant mixture was stirred at 64 °C for 18.5 h. The mixture was concentrated, and the residue was redissolved in CH_2Cl_2 (170 mL). HCl (1 N, 170 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (170 mL×2) and the organic layers were combined and concentrated. MeOH (50 mL) was added and the resultant mixture was again concentrated. MeOH (80 mL) was added and the resultant mixture was heated at reflux for 4 h, gradually cooled to 20 °C and held at 20 °C for 15 h. The product was collected by filtration and dried under vacuum.

C. (*3S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-*d*]pyrazine-8-carboxamide

[0024] (3S,11aR)-3-Methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxylic acid (3.00 g) and 1,1'-carbonyldiimidazole (CDI) (2.15 g) were slurried in 1,2-dimethoxyethane (DME) (30 mL). The mixture was heated to 80 °C for 1 h. The resulting solution was cooled to 20 °C, then treated with 2,4-difluorobenzylamine (1.45 mL). After stirring for 1 h, the mixture was quenched with water (30 mL) and DME was removed under reduced pressure. The product was collected by filtration and dried in a vacuum oven overnight at 50 °C. The product was obtained as a solid.

D. (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide

[0025] (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (193.1 mg) was dissolved in CH_3CN (4 mL) and $MgBr_2$ (206.3 mg) was added. The mixture was heated to 50 °C for 2 h and quenched with HCl (0.2 N, 10 mL). The mixture was diluted with CH_2Cl_2 and pH further adjusted to ~1. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The combined organic layers were dried and concentrated to afford the product.

[0026] Alternatively, the demethylation can be carried out with LiBr: (3*S*,11a*R*)-*N*-[(2,4-Difluorophenyl)methyl]-3-methyl-6-(methyloxy)-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (8.609 g) was dissolved in THF (90 mL) and LiBr (3.942 g) was added. The mixture was heated to reflux for 12 h and quenched with H_2SO_4 (0.5 M, 94.467 g). The resultant suspension was stirred at 20 °C for 2 h

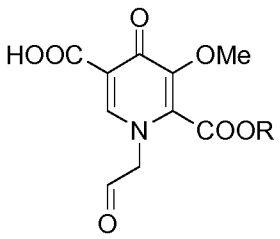
and filtered. The solid product was re-slurried in water-THF (50 mL-50 mL) at 20 °C for 2 h. The product was collected by filtration, rinsed with water-THF (1-1, 30 mL), and dried under vacuum to afford the product.

Claims

1. A method comprising contacting methyl 3-{[2,2-bis(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl]-2-propenoate (formula I): with an oxalate ester of formula II: in the presence of $M^+ {}^-OR$, where R is alkyl, aryl, or benzyl; and M^+ is an alkali metal cation; to form a pyridinone of formula III:

2. The method of Claim 1 wherein $M^+ {}^-OR$ is lithium methoxide or lithium ethoxide; and the oxalate ester is dimethyl ethanedioate or diethyl ethanedioate; wherein the compound of formula III is hydrolyzed in the presence of lithium hydroxide to form the pyridinone carboxylic acid of formula IV:

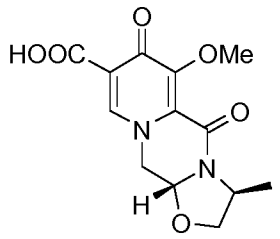
3. The method of Claim 2 wherein the pyridinone carboxylic acid is contacted with acetic acid and a catalytic amount of a strong protic acid to form a pyridinone carboxylic acid aldehyde of formula V:



V

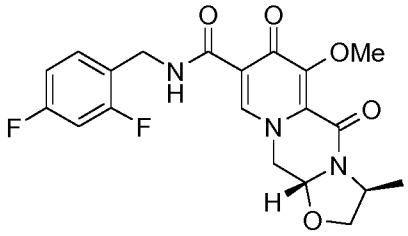
wherein R is alkyl, aryl, or benzyl.

4. The method of Claim 3 wherein the pyridinone carboxylic acid aldehyde of formula V is contacted with (2S)-2-amino-1-propanol to form the compound of formula VI:



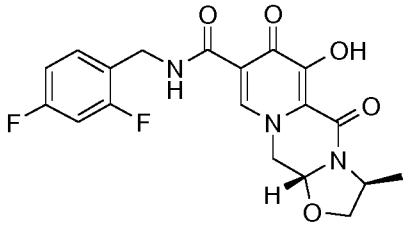
VI.

5. The method of Claim 4 wherein the compound of formula VI is contacted with 2,4-difluorobenzylamine under coupling conditions to form a compound of formula VII:



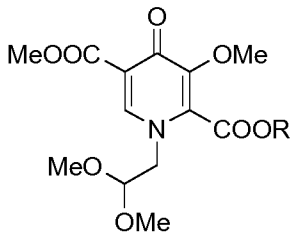
VII.

6. The method of Claim 5 wherein the compound of formula VII is contacted with a magnesium halide or lithium halide to form a compound of formula VIII:



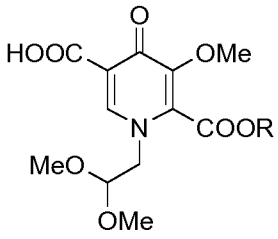
VIII.

7. A method comprising selectively hydrolyzing a pyridinone of formula III:



III

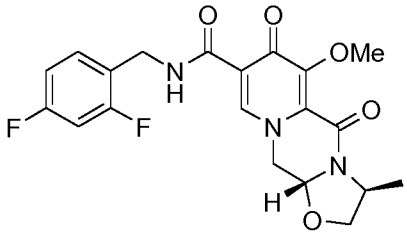
with a selective hydrolyzing reagent to form a pyridinone carboxylic acid of formula IV where R is alkyl, aryl, or benzyl:



IV

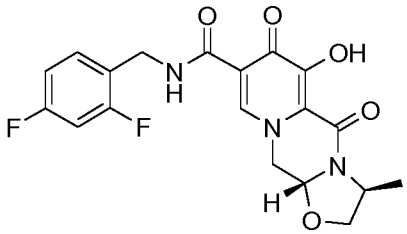
with greater than 90% selectivity.

8. A method comprising contacting a compound of formula VII:



VII

with a Lewis acid to form a compound of formula VIII:



VIII.

9. A method according to claim 8 comprising the steps of:

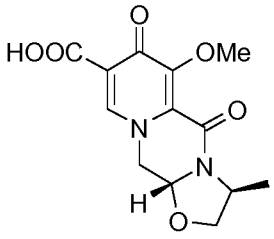
a) contacting methyl-4-methoxyacetoacetate with N,N-dimethyl-1,1-bis(methyloxy)methanamine under suitable conditions to form methyl 3-(dimethylamino)-2-[(methyloxy)acetyl]-2-propenoate;

b) contacting the methyl 3-(dimethylamino)-2-[(methyloxy)acetyl]-2-propenoate with 2,2-bis(methyloxy)ethanamine to form methyl 3-{[2,2-bis(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl]-2-propenoate;

c) contacting the methyl 3-{[2,2-bis(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl]-2-propenoate with dimethylethanedioate in the presence of lithium methoxide to form dimethyl 1-[2,2-bis(methyloxy)ethyl]-3-(methyloxy)-4-oxo-1,4-dihydro-2,5-pyridinedicarboxylate;

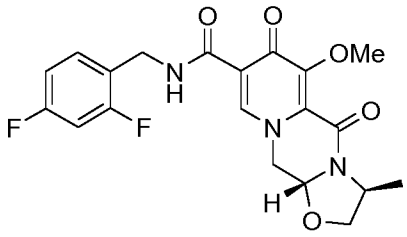
d) hydrolyzing the dimethyl 1-[2,2-bis(methyloxy)ethyl]-3-(methyloxy)-4-oxo-1,4-dihydro-2,5-pyridinedicarboxylate in the presence of lithiumhydroxide to form 1-[2,2-bis(methyloxy)ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid;

e) contacting the 1-[2,2-bis(methyloxy)ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid with (2S)-2-amino-1-propanol in the presence of acetic acid and a catalytic amount of methanesulfonic acid to form a compound of formula VI:



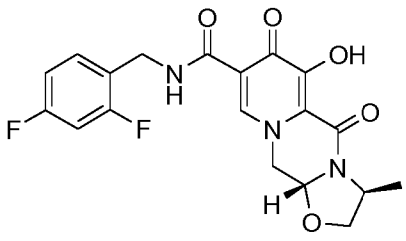
VI

f) contacting the compound of formula VI with 2,4-difluorobenzylamine under coupling conditions to form a compound of formula VII:



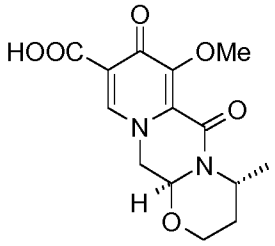
VII; and

g) contacting the compound of formula VII with magnesium bromide to form a compound of formula VIII:



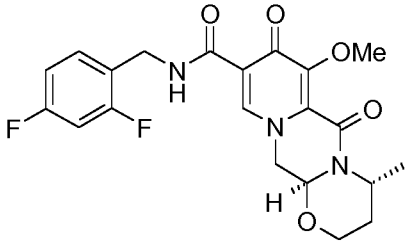
VIII.

10. The method of Claim 3 wherein the pyridinone carboxylic acid aldehyde of formula V is contacted with (3R)-3-amino-1-butanol to form the compound of formula VIa:



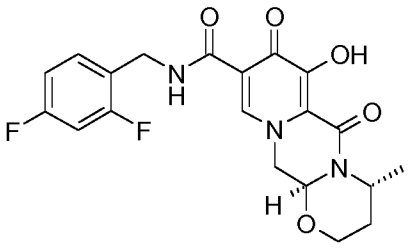
VIa.

11. The method of Claim 10 wherein the compound of VIa is contacted with 2,4-difluorobenzylamine under coupling conditions to form a compound of formula VIIa:



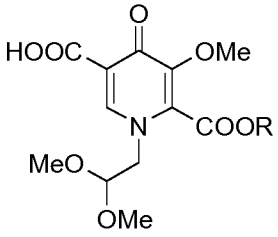
VIIa.

12. The method of Claim 11 wherein the compound of formula VIIa is contacted with a Lewis acid to form a compound of formula VIIIa:



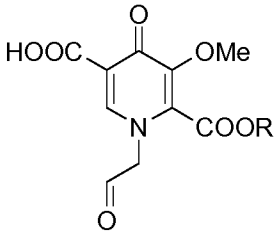
VIIIa.

13. A process comprising contacting a compound of formula IV where R is alkyl, aryl, or benzyl:



IV

with acetic acid and a catalytic amount of a strong protic acid to form a pyridinone carboxylic acid aldehyde of formula V:

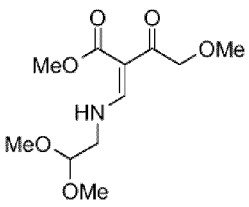


V

wherein R is selected from the group consisting of alkyl, aryl, and benzyl.

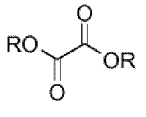
Patentansprüche

1. Verfahren, umfassend das In-Kontakt-Bringen von Methyl-3-{[2,2-Bis(methyloxy)ethyl]amino}-2-[(methyloxy)-acetyl]-2-propenoat (Formel I):



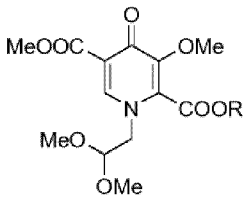
(I)

mit einem Oxalatester der Formel (II):



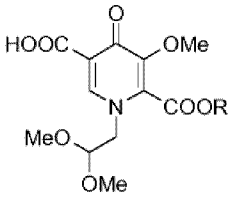
(II)

in Gegenwart von $M^+ {}^-OR$, worin R Alkyl, Aryl oder Benzyl ist und M^+ ein Alkalimetallkation ist, um ein Pyridinon der Formel (III) zu bilden:



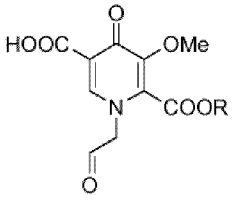
(III).

2. Verfahren gemäss Anspruch 1, worin $M^+ {}^-OR$ Lithiummethoxid oder Lithiumethoxid ist und der Oxalatester Dimethylethandioat oder Diethylethandioat ist; wobei eine Verbindung der Formel (III) in Gegenwart von Lithiumhydroxid hydrolysiert wird, um die Pyridinoncarbonsäure der Formel (IV) zu bilden:



(IV).

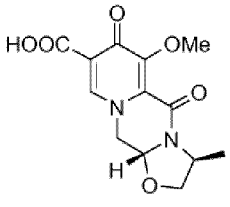
3. Verfahren gemäss Anspruch 2, wobei die Pyridinoncarbonsäure mit Essigsäure und einer katalytischen Menge einer starken Protonensäure in Kontakt gebracht wird, um einen Pyridinoncarbonsäurealdehyd der Formel (V) zu bilden:



(V)

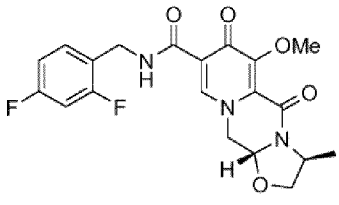
worin R Alkyl, Aryl oder Benzyl ist.

4. Verfahren gemäss Anspruch 3, wobei der Pyridinoncarbonsäurealdehyd der Formel (V) mit (2S)-2-Amino-1-propanol in Kontakt gebracht wird, um eine Verbindung der Formel (VI) zu bilden:



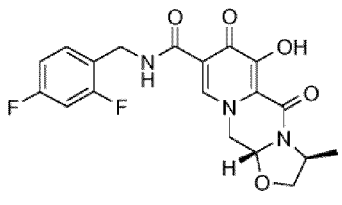
(VI).

5. Verfahren gemäss Anspruch 4, wobei eine Verbindung der Formel (VI) mit 2,4-Difluorbenzylamin unter Kupplungsbedingungen in Kontakt gebracht wird, um eine Verbindung der Formel (VII) zu bilden:



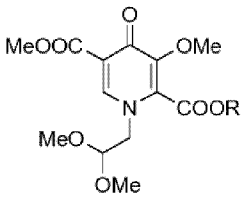
(VII).

6. Verfahren gemäss Anspruch 5, wobei eine Verbindung der Formel (VII) mit einem Magnesiumhalogenid oder Lithiumhalogenid in Kontakt gebracht wird, um eine Verbindung der Formel (VIII) zu bilden:



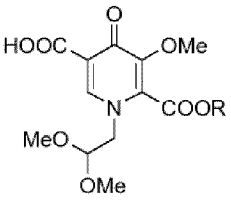
(VIII).

7. Verfahren, umfassend das selektive Hydrolysieren eines Pyridinons der Formel (III):



(III)

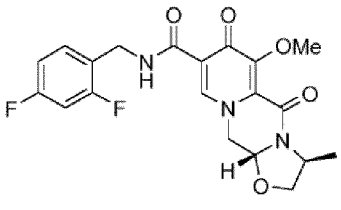
mit einem selektiven Hydrolysierungsreagens, um eine Pyridinoncarbonsäure der Formel (IV), worin R Alkyl, Aryl oder Benzyl ist:



(IV)

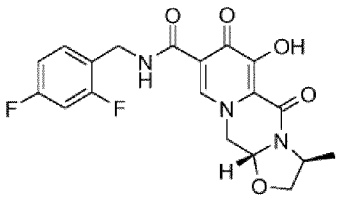
mit einer Selektivität von grösser als 90 % zu bilden.

8. Verfahren, umfassend das In-Kontakt-Bringen einer Verbindung der Formel (VII):



(VII)

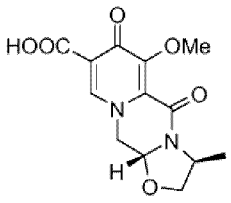
mit einer Lewis-Säure, um eine Verbindung der Formel (VIII) zu bilden:



(VIII).

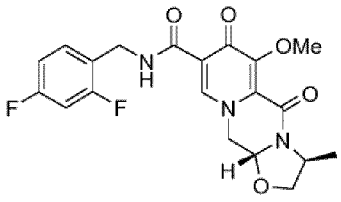
9. Verfahren gemäss Anspruch 8, umfassend die Schritte:

(a) In-Kontakt-Bringen von Methyl-4-methoxyaceto-acetat mit N,N-Dimethyl-1,1-bis(methyloxy)methanamin unter geeigneten Bedingungen, um Methyl-3-(dimethyl-amino)-2-[(methyloxy)acetyl]-2-propenoat zu bilden;
(b) In-Kontakt-Bringen von Methyl-3-(dimethylamino)-2-[(methyloxy)acetyl]-2-propenoat mit 2,2-Bis(methyloxy)ethanamin, um Methyl-3-{(2,2-bis-(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl]-2-propenoat zu bilden;
(c) In-Kontakt-Bringen von Methyl-3-{(2,2-bis-(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl]-2-propenoat mit Dimethylethandioat in Gegenwart von Lithiummethoxid, um Dimethyl-1-[2,2-bis(methyloxy)-ethyl]-3-(methyloxy)-4-oxo-1,4-dihydro-2,5-pyridindicarboxylat zu bilden;
(d) Hydrolysieren von Dimethyl-1-[2,2-bis-(methyloxy)ethyl]-3-(methyloxy)-4-oxo-1,4-dihydro-2,5-pyridindicarboxylat in Gegenwart von Lithiumhydroxid, um 1-[2,2-Bis(methyloxy)ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridin-carbonsäure zu bilden;
(e) In-Kontakt-Bringen von 1-[2,2-Bis(methyloxy)-ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridincarbonsäure mit (2S)-2-Amino-1-propanol in Gegenwart von Essigsäure und einer katalytischen Menge an Methansulfonsäure, um eine Verbindung der Formel (VI) zu bilden:



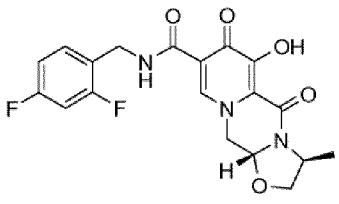
(VI);

(f) In-Kontakt-Bringen einer Verbindung der Formel (VI) mit 2,4-Difluorbenzylamin unter Kupplungsbedingungen, um eine Verbindung der Formel (VII) zu bilden:



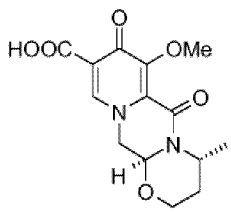
(VII)

und
(g) In-Kontakt-Bringen einer Verbindung der Formel (VII) mit Magnesiumbromid, um eine Verbindung der Formel (VIII) zu bilden:



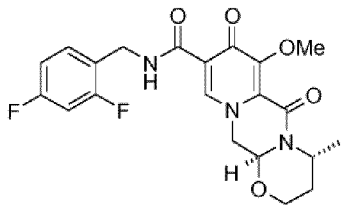
(VIII).

10. Verfahren gemäss Anspruch 3, wobei der Pyridincarbonsäurealdehyd der Formel (V) mit (3R)-3-Amino-1-butanol in Kontakt gebracht wird, um eine Verbindung der Formel (VIa) zu bilden:



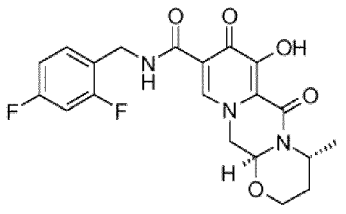
(VIa).

11. Verfahren gemäss Anspruch 10, wobei eine Verbindung der Formel (VIa) mit 2,4-Difluorbenzylamin unter Kupplungsbedingungen in Kontakt gebracht wird, um eine Verbindung der Formel (VIIa) zu bilden:



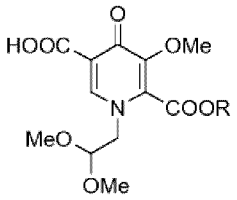
(VIIa).

12. Verfahren gemäss Anspruch 11, wobei eine Verbindung der Formel (VIIa) mit einer Lewis-Säure in Kontakt gebracht wird, um eine Verbindung der Formel (VIIIa) zu bilden:



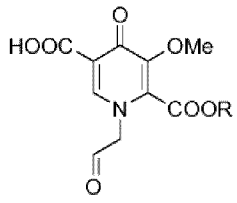
(VIIIa).

13. Verfahren, umfassend das In-Kontakt-Bringen einer Verbindung der Formel (IV), worin R Alkyl, Aryl oder Benzyl ist:



(IV)

mit Essigsäure und einer katalytischen Menge einer starken Protonensäure, um einen Pyridinoncarbonsäurealdehyd der Formel (V) zu bilden:

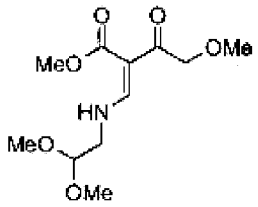


(V)

worin R aus der Gruppe bestehend aus Alkyl, Aryl und Benzyl ausgewählt ist.

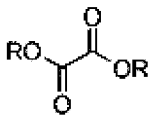
Revendications

1. Procédé comprenant la mise en contact du 3-{[2,2-bis(méthyloxy)éthyl]amino}-2-[(méthyloxy)acétyl]-2-propénoate de méthyle (formule I) :



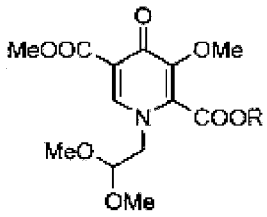
I

avec un ester d'oxalate de formule II :



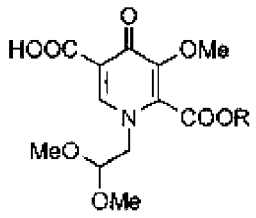
II

en présence de $M^+ {}^-OR$, où R représente un alkyle, un aryle, ou un benzyle ; et M^+ est un cation de metal alcalin ;
afin de former une pyridinone de formule III :



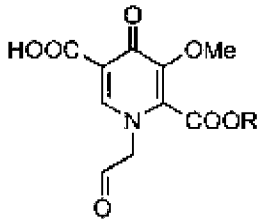
III

2. Procédé selon la revendication 1, dans lequel $M^+ {}^-OR$ est le méthoxyde de lithium ou l'ethoxyde de lithium ; et l'ester d'oxalate est l'éthanedioate de diméthyle ou l'éthanedioate de diéthyle ; dans lequel le compose de formule III est hydrolysé en présence d'hydroxyde de lithium afin de former l'acide carboxylique de pyridinone de formule IV :



IV

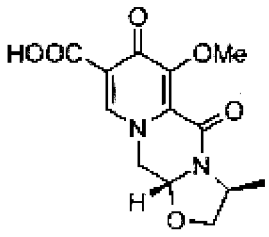
3. Procédé selon la revendication 2, dans lequel l'acide carboxylique de pyridinone est mis en contact avec de l'acide acétique et une quantité catalytique d'un acide protique fort afin de former un aldehyde d'acide carboxylique de pyridinone de formule V :



V

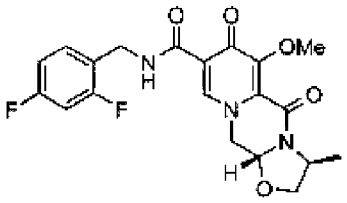
dans laquelle R représente un alkyle, un aryle, ou un benzyle.

4. Procédé selon la revendication 3, dans lequel l'aldéhyde d'acide carboxylique de pyridinone de formule V est mis en contact avec le (2S)-2-amino-1-propanol afin de former le composé de formule VI :



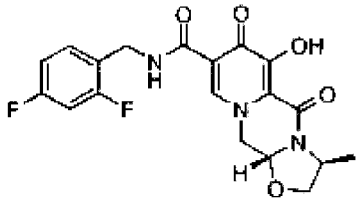
VI

5. Procédé selon la revendication 4, dans lequel le composé de formule VI est mis en contact avec la 2,4-difluorobenzylamine dans des conditions de couplage afin de former un compose de formule VII :



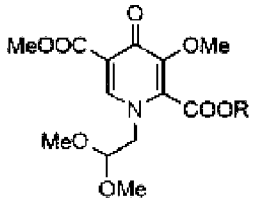
VII

6. Procédé selon la revendication 5, dans lequel le composé de formule VII est mis en contact avec un halogénure de magnésium ou un halogénure de lithium afin de former un compose de formule VIII :



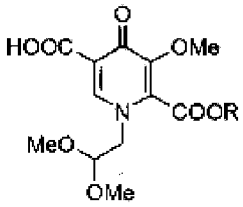
VIII

7. Procédé comprenant l'hydrolyse sélective d'une pyridinone de formule III :



III

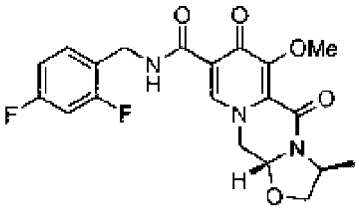
avec un réactif d'hydrolyse sélective afin de former un acide carboxylique de pyridinone de formule IV dans laquelle R représente un alkyle, un aryle, ou un benzyle :



IV

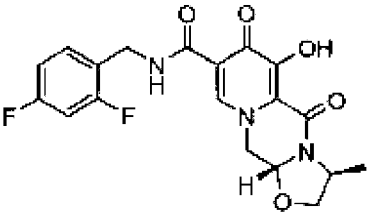
avec une sélectivité supérieure à 90 %.

8. Procédé comprenant la mise en contact d'un composé de formule VII :



VII

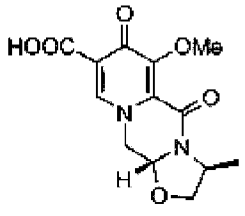
avec un acide de Lewis afin de former un composé de formule VIII :



VIII

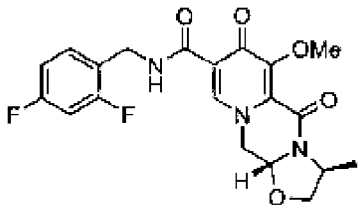
9. Procédé selon la revendication 8, comprenant les étapes de :

a) mise en contact du 4-méthoxyacétoacétate de méthyle avec la N,N-diméthyl-1,1-bis(méthyloxy)méthanamine dans des conditions appropriées pour former le 3-(diméthylamino)-2-[(méthyloxy)acétyl]-2-propénoate de méthyle ;
b) mise en contact du 3-(diméthylamino)-2-[(méthyloxy)acétyl]-2-propénoate de méthyle avec la 2,2-bis(méthyloxy)éthanamine afin de former le 3-{[2,2-bis(méthyloxy)éthyl]amino}-2-[(méthyloxy)acétyl]-2-propénoate de méthyle ;
c) mise en contact du 3-{[2,2-bis(méthyloxy)éthyl]amino}-2-[(méthyloxy)acétyl]-2-propénoate de méthyle avec de l'éthanedioate de diméthyle en présence de méthoxyde de lithium afin de former le 1-[2,2-bis(méthyloxy)éthyl]-3-(méthyloxy)-4-oxo-1,4-dihydro-2,5-pyridinedicarboxylate de diméthyle ;
d) hydrolyse du 1-[2,2-bis(méthyloxy)éthyl]-3-(méthyloxy)-4-oxo-1,4-dihydro-2,5-pyridine dicarboxylate de diméthyle en présence d'hydroxyde de lithium afin de former l'acide 1-[2,2-bis(méthyloxy)éthyl]-5-(méthyloxy)-6-[(méthyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridine carboxylique ;
e) mise en contact de l'acide 1-[2,2-bis(méthyloxy)éthyl]-5-(mééthyloxy)-6-[(méthyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridine carboxylique avec le (2S)-2-amino-1-propanol en présence d'acide acétique et d'une quantité catalytique d'acide métane sulfonique afin de former un composé de formule VI :



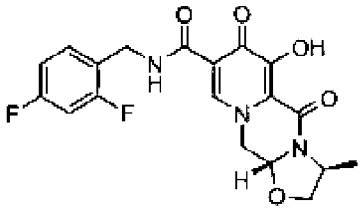
VI

f) mise en contact du composé de formule VI avec la 2,4-difluorobenzylamine dans des conditions de couplage afin de former un composé de formule VII :



VII

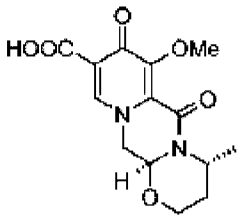
g) mise en contact du composé de formule VII avec un bromure de magnésium afin de former un composé de formule VIII :



VIII

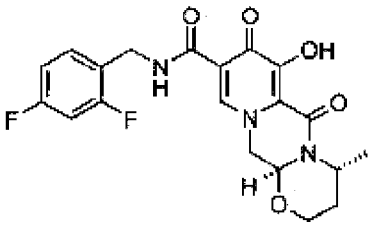
10. Procédé selon la revendication 3, dans lequel l'aldéhyde d'acide carboxylique de pyridinone de formule V est mis en contact avec le (3R)-3-amino-1-butanol afin de former le composé de formule VIa :

11. Procédé selon la revendication 10, dans lequel le composé de formule VIa est mis en contact avec la 2,4-difluorobenzylamine dans des conditions de couplage afin de former un compose de formule VIIa :



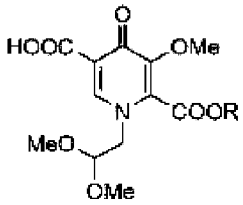
VIa

12. Procédé selon la revendication 11, dans lequel le composé de formule VIIa est mis en contact avec un acide de Lewis afin de former un composé de formule VIIIa :



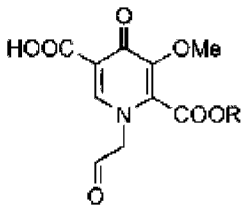
VIIIa

13. Procédé comprenant la mise en contact d'un composé de formule IV où R représente un alkyle, un aryle, ou un benzyle :



IV

avec de l'acide acétique et une quantité catalytique d'un acide protique fort afin de former un aldéhyde d'acide carboxylique de pyridinone de formule V :



V

dans laquelle R est choisi dans le groupe consistant en un alkyle, un aryle, et un benzyle.

REFERENCES CITED IN THE DESCRIPTION

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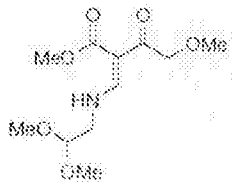
Patent documents cited in the description

- WO 2006116764 A **[0002]**
- US 11919386 B **[0002]**

SZTNH-100057311

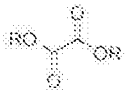
Szabadalmi igénypontok

1. Eljárás, amely tartalmazza metil-3-{[2,2-bisz(metiloxi)etil]amino}-2-[(metiloxi)acetil]-2-propenoát (I képlet)



I

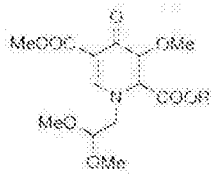
érintkeztetését II képletű oxalátészterrel



II

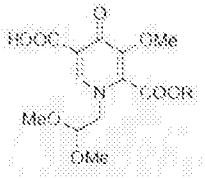
M^+ ^-OR jelenlétében, ahol R jelentése alkil, aril vagy benzil; és M^+ jelentése alkálifém kation;

és így III képletű piridinont alakítunk ki:



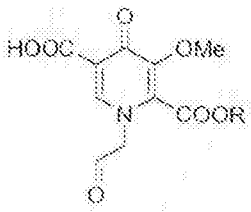
III

2. Az 1. igénypont szerinti eljárás, ahol az M^+ ^-OR jelentése lítium-metoxid vagy lítium-etoxid; és az oxalátészter a dimetil-etándioát vagy dietil-etándioát; ahol a III képletű vegyületet lítium-hidroxid jelenlétében hidrolizáljuk, és így IV képletű piridinon-karbonsavat alakítunk ki:



IV

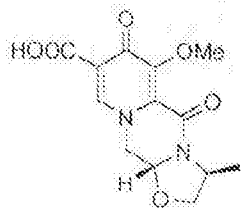
3. A 2. igénypont szerinti eljárás, ahol a piridinon-karbonsavat érintkeztetjük ecetsavval és erős protikus sav katalitikus mennyiségével, és így V képletű piridinon-karbonsav-aldehidet alakítunk ki:



V

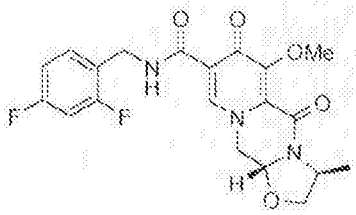
ahol R jelentése alkil, aril vagy benzil.

4. A 3. igénypont szerinti eljárás, ahol az V képletű piridinon-karbonsav-aldehidet érintkeztetjük (2S)-2-amino-1-propanollal, és így VI képletű vegyületet alakítunk ki:



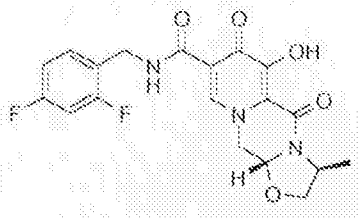
VI.

5. A 4. igénypont szerinti eljárás, ahol a VI képletű vegyületet kapcsolási körülmények között érintkeztetjük 2,4-difluorbenzilaminnal, és így VII képletű vegyületet alakítunk ki:



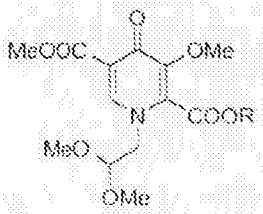
VII.

6. Az 5. igénypont szerinti eljárás, ahol a VII képletű vegyületet érintkeztetjük magnézium-halogeniddel vagy lítium-halogeniddel, és így VIII képletű vegyületet alakítunk ki:



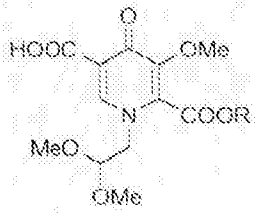
VIII.

7. Eljárás, amely tartalmazza a III képletű piridinon szelektív hidrolizálását.



III

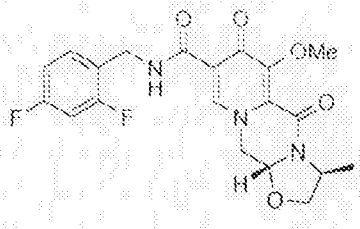
szelektív hidrolizáló reagenssel, és így IV képletű piridinon-karbonsavat alakítunk ki, ahol R jelentése alkil, aril vagy benzil:



IV

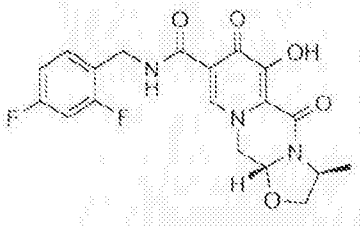
90 %-nál nagyobb szelektivitással.

8. Eljárás, amely tartalmazza VII képletű vegyület



VII

érintkeztetését egy Lewis-savval, és így VIII képletű vegyületet alakítunk ki:



VIII.

9. A 8. igénypont szerinti eljárás, amely tartalmazza a következő lépéseket:

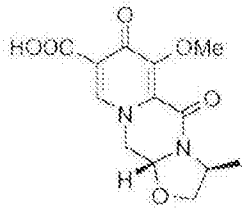
a) metil-4-metoxiacetoacetát érintkeztetését N,N-dimetil-1,1-bisz(metiloxi)metánaminnal ahhoz megfelelő körülmények között, hogy metil-3-(dimetilamino)-2-[(metiloxi)acetil]-2-propenoátot alakítsunk ki;

b) a metil-3-(dimetilamino)-2-[(metiloxi)acetil]-2-propenoát érintkeztetését 2,2-bisz(metiloxi)etánaminnal, és így metil-3-{[2,2-bisz(metiloxi)etil]amino}-2-[(metiloxi)acetil]-2-propenoátot alakítunk ki;

c) a metil-3-{[2,2-bisz(metiloxi)etil]amino}-2-[(metiloxi)acetil]-2-propenoát érintkeztetését dimetiletándioáttal lítium-metoxid jelenlétében, és így dimetil-1-[2,2-bisz(metiloxi)etil]-3-(metiloxi)-4-oxo-1,4-dihidro-2,5-piridindikarboxilátot állítunk elő;

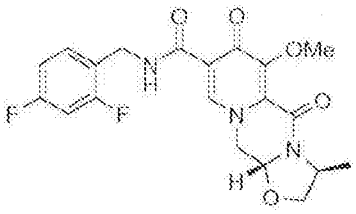
d) a dimetil-1-[2,2-bisz(metiloxi)etil]-3-(metiloxi)-4-oxo-1,4-dihidro-2,5-piridindikarboxilát hidrolízálását lítium-hidroxid jelenlétében, és így 1-[2,2-bisz(metiloxi)etil]-5-(metiloxi)-6-[(metiloxi)karbonil]-4-oxo-1,4-dihidro-3-piridinkarbonsavat alakítunk ki;

e) az 1-[2,2-bisz(metiloxi)etil]-5-(metiloxi)-6-[(metiloxi)karbonil]-4-oxo-1,4-dihidro-3-piridinkarbonsav érintkeztetését (2S)-2-amino-1-propanollal ecetsav és metánszulfonsav katalitikus mennyiségének jelenlétében, és így VI képletű vegyületet alakítunk ki:



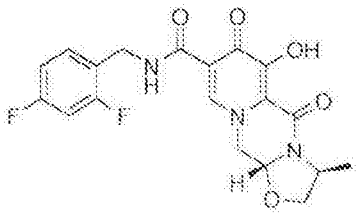
VI

f) a VI képletű vegyület érintkeztetését 2,4-difluorbenzilaminnal kapcsolási körülmények között, és így VII képletű vegyületet alakítunk ki:



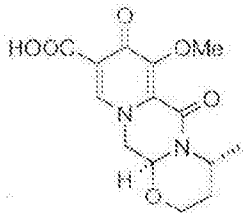
VII; és

g) a VII képletű vegyület érintkeztetését magnézium-bromiddal, és így VIII képletű vegyületet alakítunk ki:



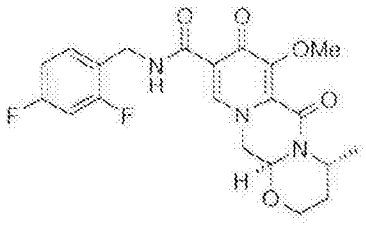
VIII.

10. A 3. igénypont szerinti eljárás, ahol az V képletű piridinon-karbonsav-aldehidet érintkeztetjük (3R)-3-amino-1-butanollal, és így VIa képletű vegyületet alakítunk ki:



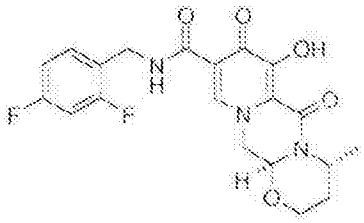
VIa.

11. A 10. igénypont szerinti eljárás, ahol a VIa képletű vegyületet érintkeztetjük 2,4-difluorbenzilaminnal kapcsolási körülmények között, és így VIIa képletű vegyületet alakítunk ki:



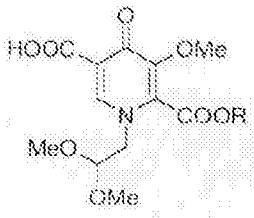
VIIa.

12. A 11. igénypont szerinti eljárás, ahol a VIIa képletű vegyületet érintkeztetjük egy Lewis-savval, és így VIIIa képletű vegyületet alakítunk ki:



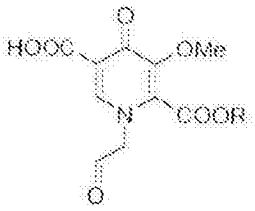
VIIIa.

13. Eljárás, amely tartalmazza IV képletű vegyület, ahol R jelentése alkil, aril vagy benzil:



IV

érintkeztetését ecetsavval és erős protikus sav katalitikus mennyiségével, és így V képletű piridinon-karbonsav-aldehidet alakítunk ki:



V

ahol R a következők alkotta csoportból választott: alkil, aril és benzil.