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(71) **Applicant** *(for all designated States except US)*: **GLAXOSMITHKLINE LLC** [US/US]; GlaxoSmithKline LLC, One Franklin Plaza, 200 North 1th Street, Philadelphia, Pennsylvania 19102 (US).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **WANG, Huan** [CN/US]; GlaxoSmithKline, c/o Global Patents, 709 Swedeland Road, King of Prussia, Pennsylvania 19406 (US). **GOODMAN, Steven N** [US/US]; GlaxoSmithKline, c/o Global Patents, 709 Swedeland Road, King of Prussia, Pennsylvania 19406 (US). **MANS, Douglas** [US/US]; GlaxoSmithKline, c/o Global Patents, 709 Swedeland Road, King of Prussia, Pennsylvania 19406 (US). **KOWALSKI, Matthew** [US/US]; GlaxoSmithKline, c/o Global Patents, 709 Swedeland Road, King of Prussia, Pennsylvania 19406 (US).

(74) **Agent**: **DEPPENBROCK, Bonnie**; GlaxoSmithKline, c/o Global Patents, Five Moore Drive, C.2111.2F, PO Box 13398, Research Triangle Park, North Carolina 27709 (US).

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

(57) **Abstract**: The present invention relates to the preparation of carbamoylpyridone derivatives and intermediates.

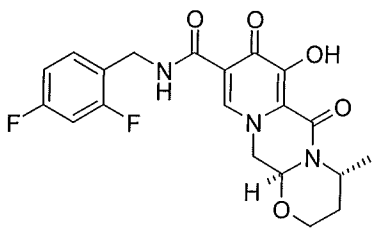
PROCESS FOR PREPARING CARBAMOYLPYRIDONE DERIVATIVES AND INTERMEDIATES

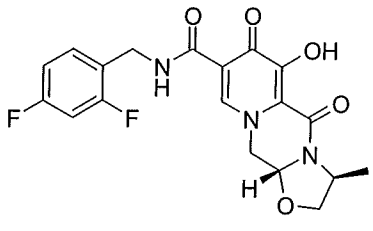
Field of the Invention

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

Background of the Invention

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:

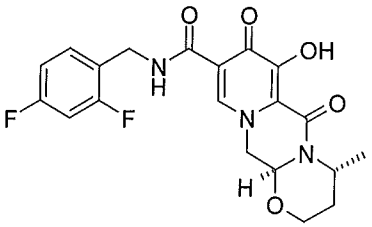


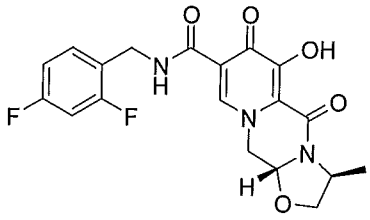


The processes disclosed for preparing these compounds are quite arduous, involving as many as 14 steps. It would therefore be an advance in the art to find ways of making these compounds with greater efficiency.

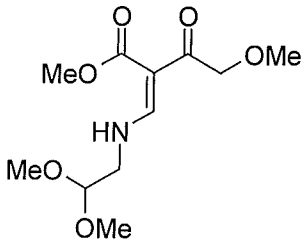
Summary of the Invention

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



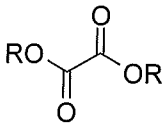


In one aspect, the present invention is a method comprising contacting methyl 3-{[2,2-bis(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl]-2-propenoate (formula I):



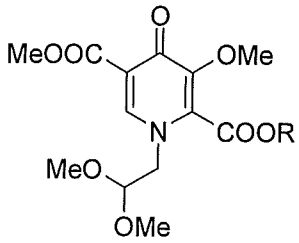
I

with an oxalate ester of formula II:



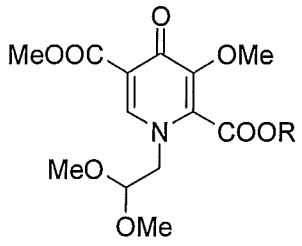
II

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:



III.

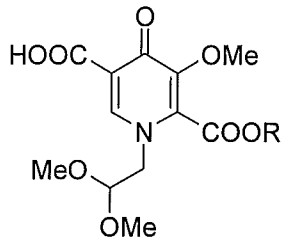
In a second aspect, the present invention method comprising selectively hydrolyzing a pyridinone of formula III:



III

where R is alkyl, aryl, or benzyl

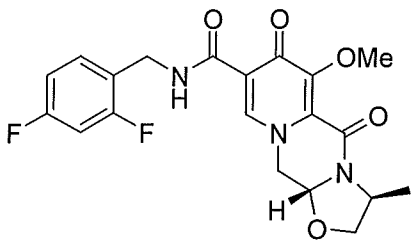
with a selective hydrolyzing reagent to form a pyridinone carboxylic acid of formula IV where R is alkyl, aryl, or benzyl:



IV

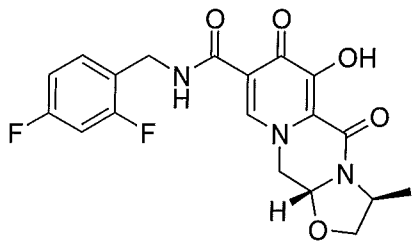
with greater than 90% selectivity.

In a third aspect, the present invention is a method comprising contacting a compound of formula VII:



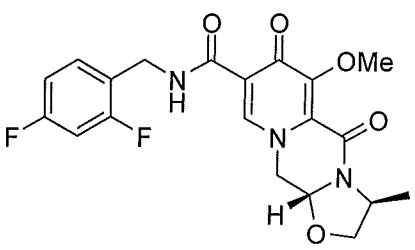
VII

with a magnesium or lithium cation and a nucleophilic anion to form a compound of formula VIII:

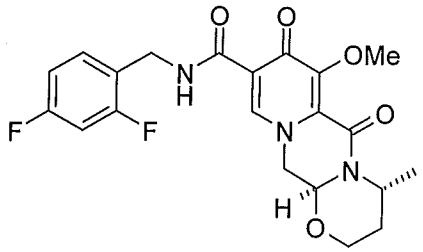


VIII.

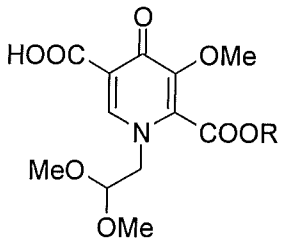
In a fourth aspect, the present invention is a compound selected from the group consisting of:



and

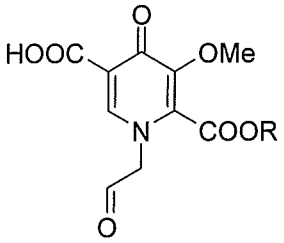


In a fifth aspect, the present invention is a process comprising contacting a compound of formula IV where R is alkyl, aryl, or benzyl:



IV

with acetic acid and a catalytic amount of a strong protic acid to form a pyridinone carboxylic acid aldehyde of formula V where R is alkyl, aryl, or benzyl:



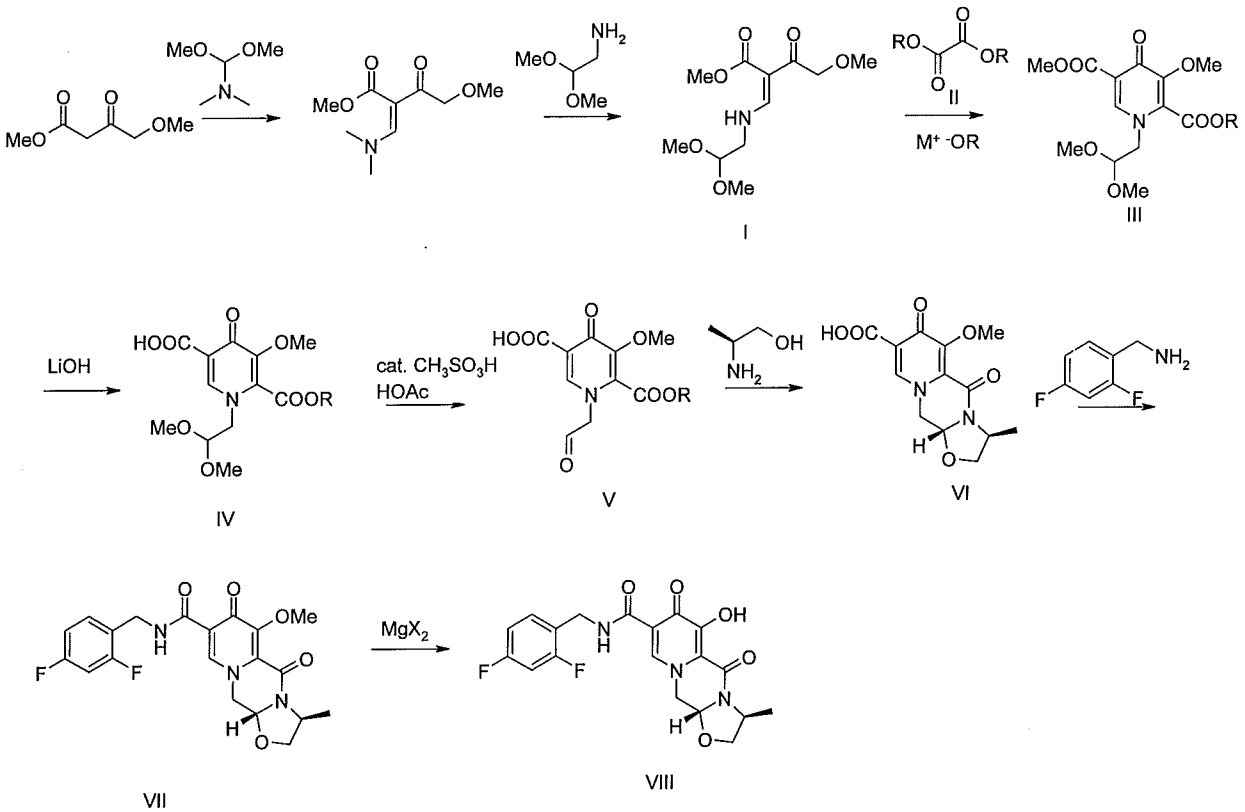
V.

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

Detailed Description of the Invention

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).

Scheme:



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).

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.

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.

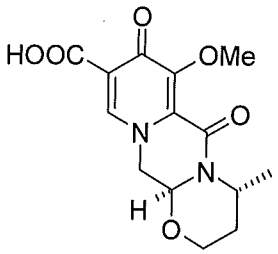
Pyridinone carboxylic acid (IV) is contacted with acetic acid and a catalytic amount of a strong protic acid to form pyridinone carboxylic acid aldehyde (V). Examples of suitable strong protic acids include methanesulfonic acid, sulfuric acid, toluene sulfonic acid, and hydrochloric acid. Aldehyde (V) 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).

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).

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-

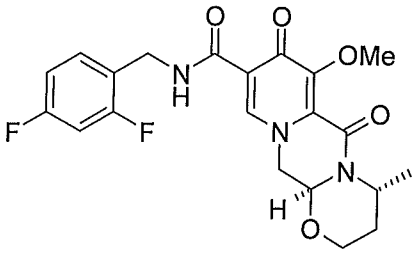
hexahydro[1,3]oxazolo[3,2-*a*]pyrido[1,2-*d*]pyrazine-8-carboxamide (VIII). Examples of suitable Lewis acids include magnesium, lithium, and calcium salts, as well as boron trihalides and trialkylsilyl halides. Preferred Lewis acids are magnesium and lithium salts. Magnesium salts include salts such as magnesium chloride, magnesium bromide, magnesium iodide, and magnesium sulfide. Lithium salts include salts such as lithium chloride, lithium bromide, lithium iodide, and lithium sulfide. Lithium bromide is preferred.

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:



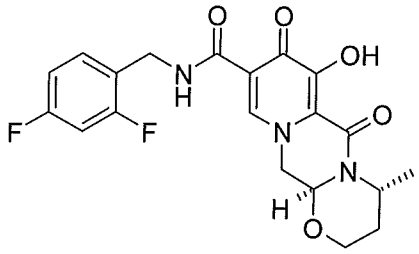
VIa

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



VIIa.

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:



VIIIa.

Examples

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

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

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 (7.511g) 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. (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

(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

(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

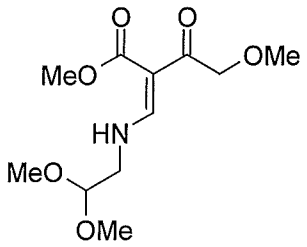
50 °C for 2 h and quenched with HCl (0.2 N, 10 mL). The mixture was diluted with CH_2Cl_2 and pH further adjusted to ~1. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The combined organic layers were dried and concentrated to afford the product.

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:

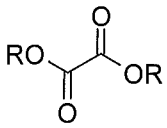
What is claimed is:

1. A method comprising contacting methyl 3-{[2,2-bis(methyloxy)ethyl]amino}-2-[(methyloxy)acetyl]-2-propenoate (formula I):



I

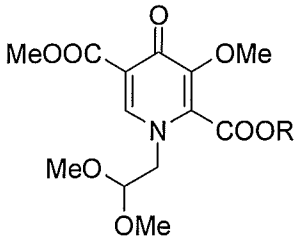
with an oxalate ester of formula II:



II

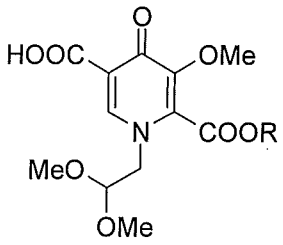
in the presence of $M^+ {}^-OR$, where R is alkyl, aryl, or benzyl; and M^+ is an alkali metal cation;

to form a pyridinone of formula III:



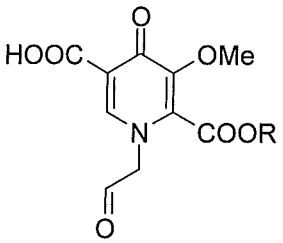
III.

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:



IV.

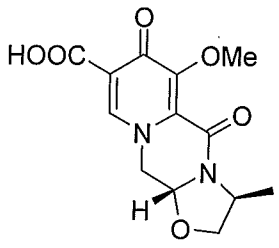
3. The method of Claim 2 wherein the pyridinone carboxylic acid is contacted with acetic acid and a catalytic amount of a strong protic acid to form a pyridinone carboxylic acid aldehyde of formula V:



V

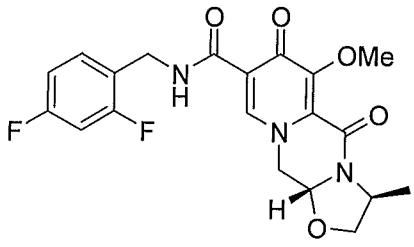
wherein R is alkyl, aryl, or benzyl.

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:



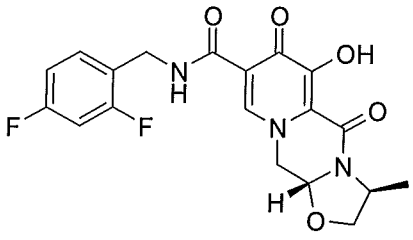
VI.

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:



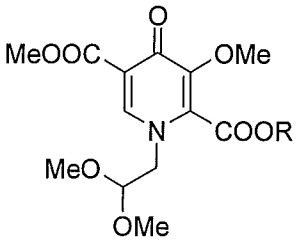
VII.

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:



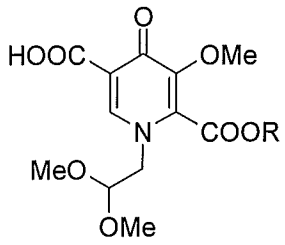
VIII.

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:

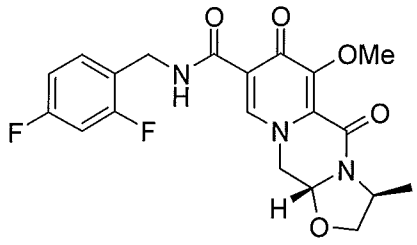


IV

with greater than 90% selectivity.

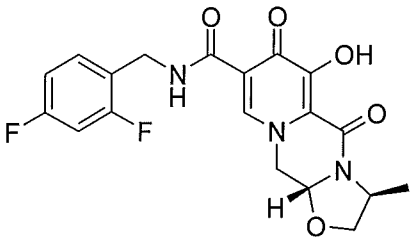
8. The method of Claim 7 wherein the hydrolyzing reagent is LiOH.

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



VII

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



VIII.

10. The method of Claim 9 wherein the Lewis acid is a magnesium halide or a lithium halide.

11. A method comprising the steps of:

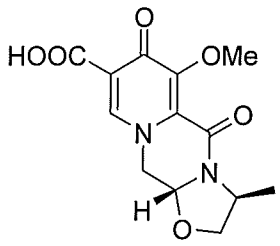
a) contacting methyl-4-methoxyacetoacetate with N,N-dimethyl-1,1-bis(methyloxy)methanamine under suitable conditions to form methyl 3-(dimethylamino)-2-[(methyloxy)acetyl]-2-propenoate;

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;

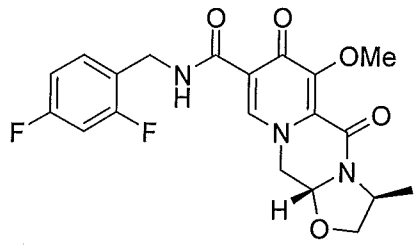
d) hydrolyzing the dimethyl 1-[2,2-bis(methyloxy)ethyl]-3-(methyloxy)-4-oxo-1,4-dihydro-2,5-pyridinedicarboxylate in the presence of lithium hydroxide to form 1-[2,2-bis(methyloxy)ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid;

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:



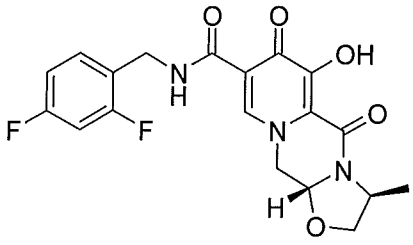
VI

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



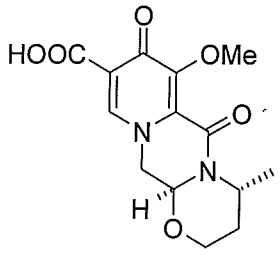
VII; and

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



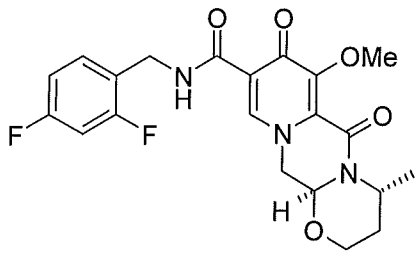
VIII.

12. 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:



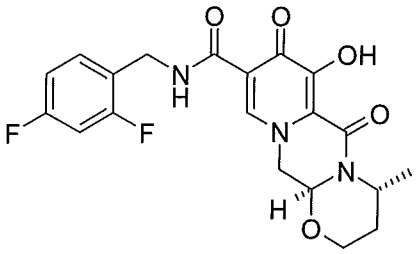
VIa.

13. The method of Claim 12 wherein the compound of VIa is contacted with 2,4-difluorobenzylamine under coupling conditions to form a compound of formula VIIa:



VIIa.

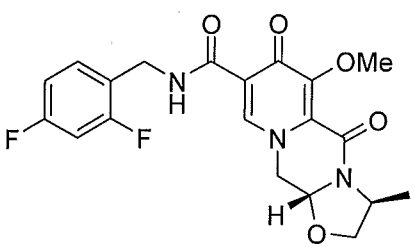
14. The method of Claim 13 wherein the compound of formula VIIa is contacted with a Lewis acid to form a compound of formula VIIIa:



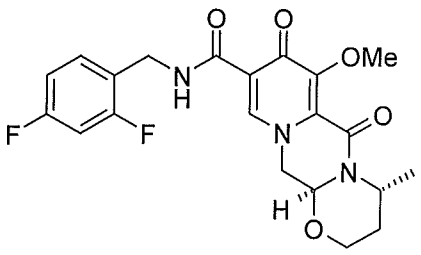
VIIIa.

15. The method of Claim 14 wherein the Lewis acid is a magnesium halide or a lithium halide.

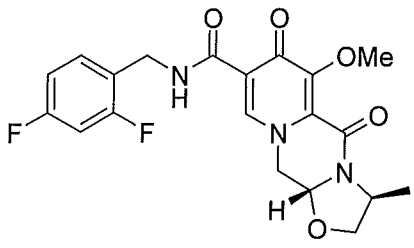
16. A compound selected from the group consisting of:



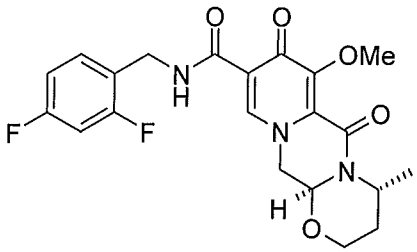
and



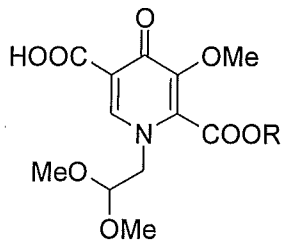
17. A compound according to Claim 16 having the formula:



18. A compound of Claim 16 having the formula:

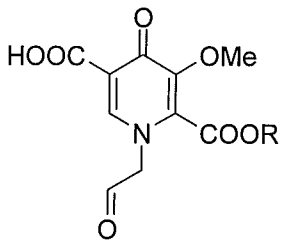


19. A process comprising contacting a compound of formula IV where R is alkyl, aryl, or benzyl:



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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/29369

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/42; A61K 31/44 (2011.01)
USPC - 514/290-294
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)
USPC: 514/290-294

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/81, 211.08, 214.02, 220, 229.2,230.2, 233.2, 243, 249-250, 348, 374-375, 432, 459; 540/545, 559, 579; 544/95, 101, 112, 115, 117, 183, 230, 250, 342-343, 346, 350; 546/296; 549/28, 418 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PUBWEST (PGPUB, EPAB, JPAB, USPT), Google. THOMSON INNOVATION (US Grant, GB App, US App, FR App, WO App, DE Util, EP Grant, DE Grant, EP App, DE App, JP App, KR Grant, KR App, Other, JP Grant, CN App, CN Util, JP Util, KR Util). Search Terms Used methyl-4-methoxyacetoacetate, Pyridinone, methyl-4-methoxyacetoacetate, d

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- A	US 2009/0318421 A1 (Johns et al.) 24 December 2009 (24.12.2009) entire document especially para [0354]-[0355], [0565], [0715]	9-10 and 16-18 ---------- 1-8, 11-15 and 19
A	US 2001/0051732 A1 (Muraoka et al.) 13 December 2001 (13.12.2001) especially para [0012]-[0020]	1-19
A	US 2007/0249687 A1 (Yoshida) 25 October 2007 (25.10.2007) especially para [0118]	1-19
A	US 2006/0019996 A1 (Tucci et al.) 26 January 2006 (26.01.2006) especially para [0048]-[0053]	1-19
A	WO 2010/011814 A1 (Johns et al.) 28 January 2010 (28.01.2010) entire document	1-19
A	Ko et al. A New and Facile Synthesis of 2-Pyridones. Bull. Korean Chem. Soc., 2001, Vol 22, No 2, pg 234	1-19
A	US 4,524,149 A (Lesher et al.) 18 June 1985 (18.06.1985) especially col 8, ln 33 to col 9, ln 7	1-19

☐ Further documents are listed in the continuation of Box C. ☐

* 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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 2011 (20.04.2011)	17 MAY 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)