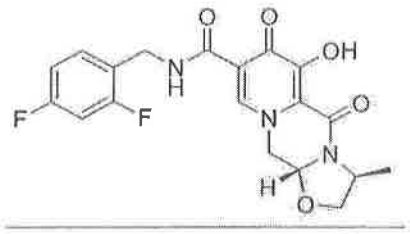
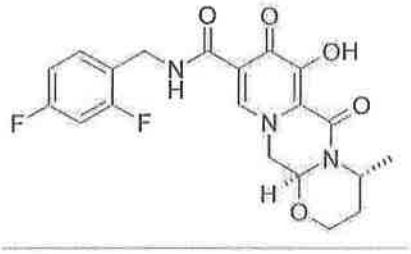
Claims:

What is claimed is:

1. A method suitable for preparing a compound of formula VIII or VIIIa:

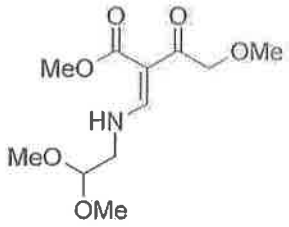


VIII



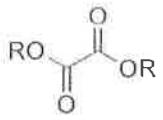
VIIIa,

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



I

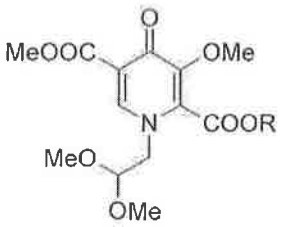
with an oxalate ester of formula II:



II

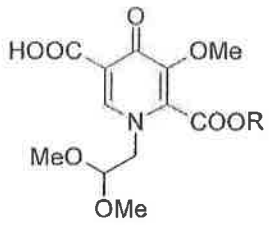
in the presence of $M^+ {}^-OR$, where R is C_{1-5}alkyl, aryl, or benzyl; and M^+ is an alkali metal cation;

to form a pyridinone of formula III:



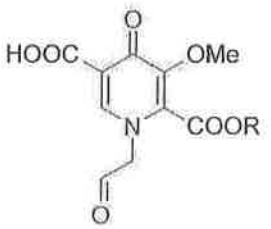
III.

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.

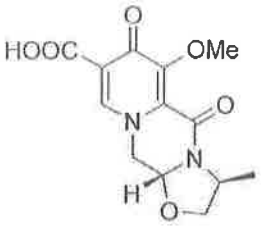
3. The method of Claim 2 wherein the pyridinone carboxylic acid is contacted with acetic acid and a catalytic amount of a strong protic acid to form a pyridinone carboxylic acid aldehyde of formula V:



V

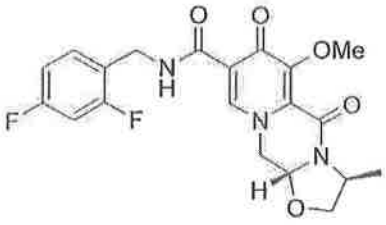
wherein R is $\underline{C_{1\text{-}5}}$alkyl, aryl, or benzyl.

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:



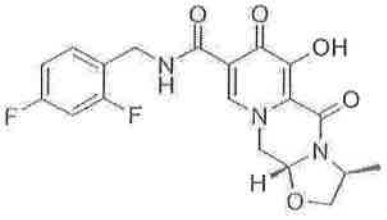
VI.

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:



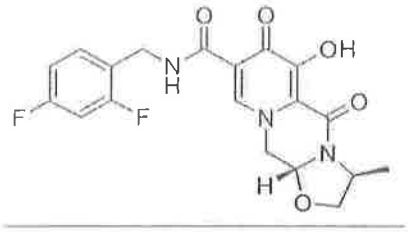
VII.

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:

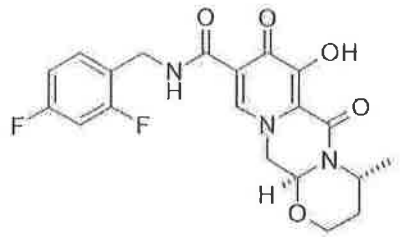


VIII.

7. A method suitable for preparing a compound of formula VIII or VIIIa:

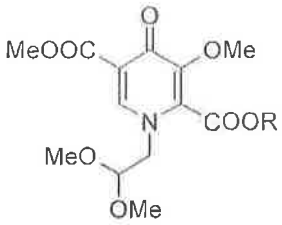


VIII



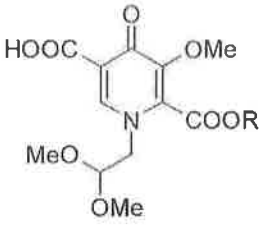
VIIIa.

the 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 C_{1-5}alkyl, aryl, or benzyl:

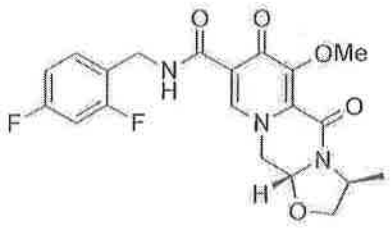


IV

with greater than 90% selectivity.

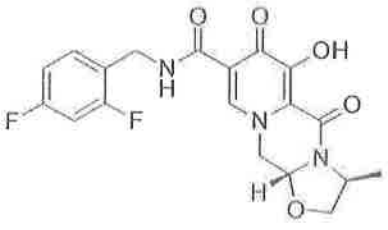
8. The method of Claim 7 wherein the hydrolyzing reagent is LiOH.

9. A method suitable for preparing a compound of formula VIII, the 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:

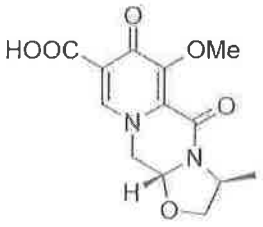
a) contacting methyl-4-methoxyacetoacetate with N,N-dimethyl-1,1-bis(methyloxy)methanamine ~~under suitable conditions~~ to form methyl 3-(dimethylamino)-2-[(methyloxy)acetyl]-2-propenoate;

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;

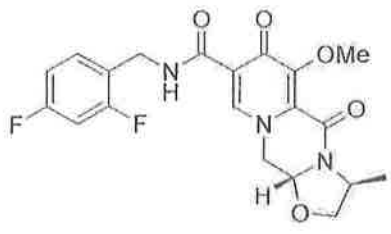
d) hydrolyzing the dimethyl 1-[2,2-bis(methyloxy)ethyl]-3-(methyloxy)-4-oxo-1,4-dihydro-2,5-pyridinedicarboxylate in the presence of lithium hydroxide to form 1-[2,2-bis(methyloxy)ethyl]-5-(methyloxy)-6-[(methyloxy)carbonyl]-4-oxo-1,4-dihydro-3-pyridinecarboxylic acid;

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:



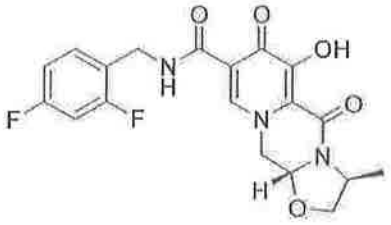
VI

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



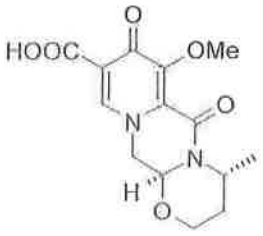
VII; and

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



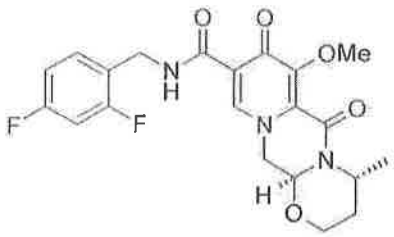
VIII.

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:



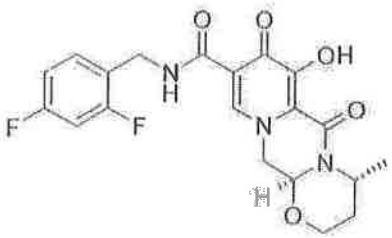
VIa.

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.

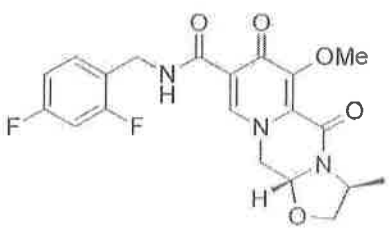
14. The method of Claim 13 wherein the compound of formula VIIa is contacted with a Lewis acid to form a compound of formula VIIIa:



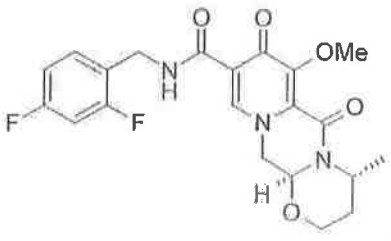
VIIIa.

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

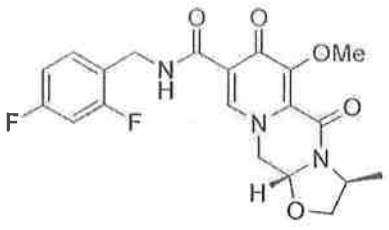
16. A compound selected from the group consisting of:



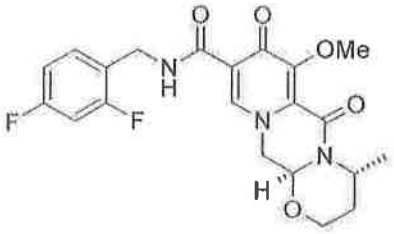
and



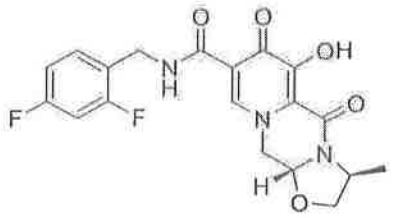
17. A compound according to Claim 16 having the formula:



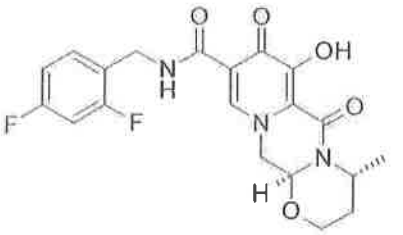
18. A compound of Claim 16 having the formula:



19. A process suitable for preparing a compound of formula VIII or VIIIa:

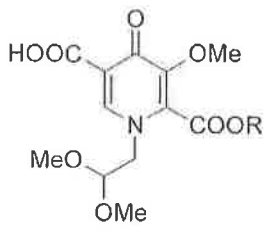


VIII



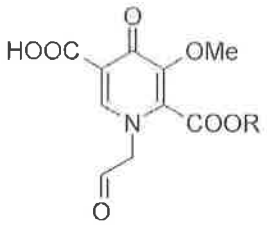
VIIIa.

the process comprising contacting a compound of formula IV where R is C_{1-5}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 C_{1-5}alkyl, aryl, and benzyl.