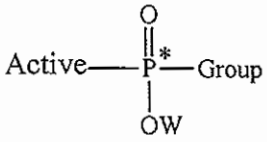
Claims

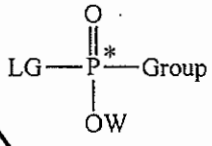
1. A process for preparing a composition comprising an enantiomerically- or a diastereomerically-enriched phosphorus-containing active, salt, or pharmaceutically acceptable salt thereof, of formula **I**:



I

which comprises

a) reacting a protected or unprotected Active with a base to form a salt of said active and then reacting said salt with an enantiomerically- or a diastereomerically enriched compound of formula **II**



II

wherein Group is as defined herein, W is an aryl or $-(CH_2)_nSC(O)C(CH_3)_m(CH_2OH)_{3-m}$, where n is 2 or 3 and m is 0, 1, 2, or 3, and LG is a leaving group;

b) optionally deprotecting the compound obtained in step a) and

c) optionally subjecting the compound obtained in step a) or the compound obtained in step b) to chromatography, extraction, or crystallization to obtain the active.

2. The process of claim 1, wherein the base is a basic reagent.

3. The process of claim 1, wherein the Active is a nucleoside, a nucleoside-analog, or a non-nucleoside compound.

4. The process of claim 3, wherein the nucleoside is selected from among compounds 1-8, 10-13, 15-20, 22, 24-26, 28-32, 39, and 41-43.

5. The process of claim 3, wherein the nucleoside-analog is selected from among compounds 33-38 and 40.

6. The process of claim 3, wherein the non-nucleoside compound is selected from among compounds 44-90.

7. The process of claim 1, wherein the compound of formula II is obtained by a process that comprises:

1) reacting $(LG)P(O)(LG')_2$, wherein LG', independent of LG, is a leaving group, with

(i) a Group-precursor, as defined herein, and a first base to obtain (LG)P(O)(LG')(Group) followed by reacting (LG)P(O)(LG')(Group) with HOW and a second base to obtain a mixture comprising (LG)P(O)(OW)(Group), wherein the first base and the second base are the same or different,

(ii) HOW and a first base to obtain (LG)P(O)(LG')(OW) followed by reacting (LG)P(O)(LG')(OW) with a Group-precursor and a second base to obtain a mixture comprising (LG)P(O)(OW)(Group), wherein the first base and the second base are the same or different, or

(iii) combining a Group-precursor, HOW, and at least one base to obtain a mixture comprising (LG)P(O)(OW)(Group); or

2) reacting $(WO)P(O)(LG')_2$, wherein LG' is a leaving group, with

(i) a Group-precursor and a first base to obtain (WO)P(O)(LG')(Group) followed by reacting (WO)P(O)(LG')(Group) with a leaving group precursor and a second base to obtain a mixture comprising (LG)P(O)(OW)(Group), wherein the first base and the second base are the same or different.

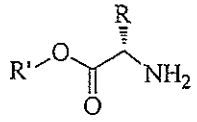
8. The process of claim 1, wherein the compound of formula II is obtained by a process that comprises:

reacting $(WO)P(O)(LG')_2$, wherein LG' is a leaving group, with (i) a Group-precursor and a first base to obtain (WO)P(O)(LG')(Group) followed by reacting

(WO)P(O)(LG')(Group) with a leaving group precursor and a second base to obtain a mixture comprising (LG)P(O)(OW)(Group), wherein the first base and the second base are the same or different.

9. The process of claim 8, wherein LG' is chloride and W is an aryl or $-(CH_2)_nSC(O)C(CH_3)_m(CH_2OH)_{3-m}$, where n is 2 or 3 and m is 0, 1, 2, or 3.

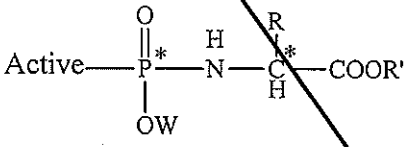
10. The process of claim 9, wherein the Group is derived from an amino-acid derivative or acid-addition salt (HX) thereof having the following structure:



wherein R is a substituent found in a naturally occurring amino acid and R' is a C_{1-6}alkyl or C_{3-7}cycloalkyl.

11. The process of claim 10, wherein R is methyl or isopropyl.

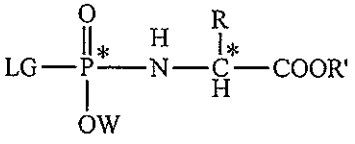
12. A process for preparing a composition comprising an enantiomerically- or a diastereomerically enriched phosphorus-containing active, salt, or pharmaceutically acceptable salt thereof, of formula **I-1**:



I-1

which comprises

a) reacting a protected or unprotected Active with a base to form a salt of said active and then reacting said salt with a compound of formula **II-1**



II-1

wherein

the Active is a nucleoside, a nucleoside-analog, or a non-nucleoside compound; W is an aryl or $-(CH_2)_nSC(O)C(CH_3)_m(CH_2OH)_{3-m}$, where n is 2 or 3

and m is 0, 1, 2, or 3; LG is a leaving group; R is a radical observed in any one of the naturally occurring amino acids, or R is a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted alkaryl, a substituted or unsubstituted alkenyl, a substituted or unsubstituted alkoxide, a substituted or unsubstituted aryl; and R' is a substituted or unsubstituted alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted alkaryl, or a substituted or unsubstituted aryl;

b) optionally deprotecting the compound obtained in step a) and

c) optionally subjecting the compound obtained in step a) or the compound obtained in step b) to chromatography, extraction, or crystallization to obtain compound **II-1**.

13. The process of claim 12, wherein the base is a basic reagent.

14. The process of claim 12, wherein the Active is a nucleoside, a nucleoside-analog, or a non-nucleoside compound.

15. The process of claim 14, wherein the nucleoside is selected from among compounds 1-8, 10-13, 15-20, 22, 24-26, 28-32, 39, and 41-43.

16. The process of claim 15, wherein R is a radical observed in any one of the naturally occurring amino acids and R' is a C_{1-6}alkyl or C_{3-7}cycloalkyl.

17. The process of claim 15, wherein R is methyl or isopropyl and R' is a C_{1-6}alkyl or C_{3-7}cycloalkyl.

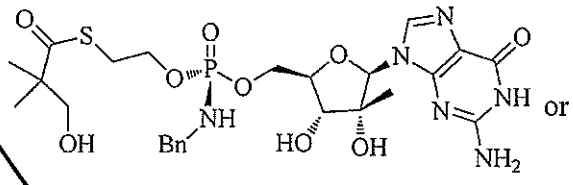
18. The process of claim 17, wherein the LG is an aryloxide substituted with at least one electron withdrawing group.

19. The process of claim 17, wherein the LG is selected from among 2-nitrophenoxide, 4-nitrophenoxide, 2,4-dinitrophenoxide, pentafluorophenoxide, 2-chloro-4-nitrophenoxide, 2,4-dichlorophenoxide, and 2,4,6-trichlorophenoxide.

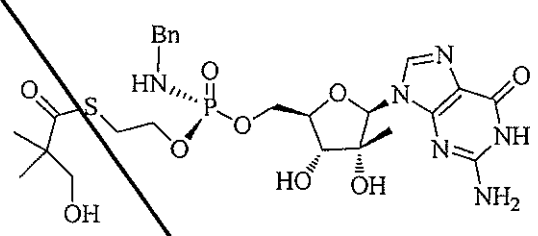
20. The process of claim 14, wherein the nucleoside-analog is selected from among compounds 33-38 and 40.

21. The process of claim 14, wherein the non-nucleoside compound is selected from among compounds 44-90.

22. A process for preparing a compound having the structure:

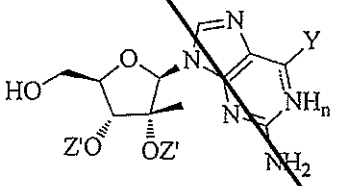


or



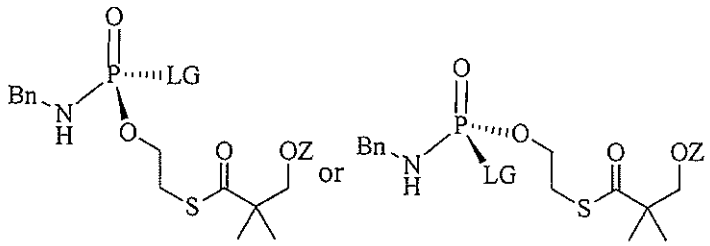
which comprises:

a) reacting a first compound having the structure



with a basic reagent to form a salt of the first compound, where Z' is hydrogen or a protecting group and Y is =O or $-OC_{1-6}$alkyl, with proviso that ---- is a single bond and n is 1 when Y is =O, and ---- is a double bond and n = 0 when Y is $-OC_{1-6}$alkyl;

b) reacting the salt of the first compound with a second compound having the structure,



where LG is a leaving group, Z is hydrogen or a protecting group, and Bn is $-CH_2Ph$; and

c) optionally deprotecting.

23. The process of claim 22, wherein Z is hydrogen and Z' is hydrogen.

24. The process of claim 23, wherein LG is an aryloxide having at least one electron withdrawing group.

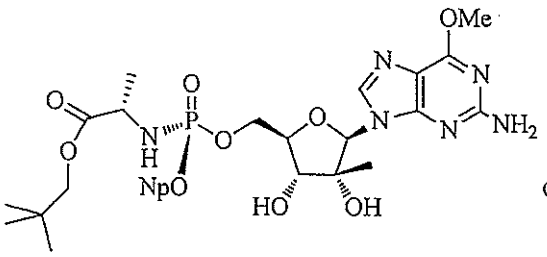
25. The process of claim 23, wherein LG is selected from among 2-nitrophenoxide, 4-nitrophenoxide, 2,4-dinitrophenoxide, pentafluorophenoxide, 2-chloro-4-nitrophenoxide, 2,4-dichlorophenoxide, and 2,4,6-trichlorophenoxide.

26. The process of claim 25, wherein the basic reagent is a Grignard reagent.

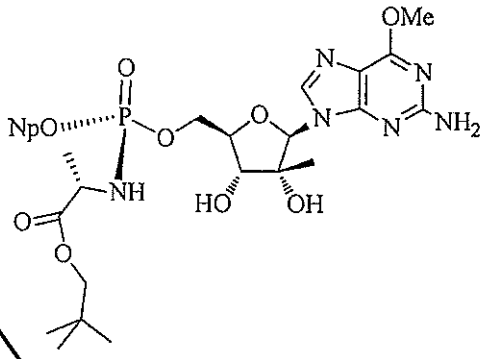
27. The process of claim 26, wherein the basic reagent is a t-butylmagnesium halide.

28. The process of claim 26, wherein the basic reagent is t-butylmagnesium bromide or t-butylmagnesium chloride.

29. A process for preparing a compound having the structure

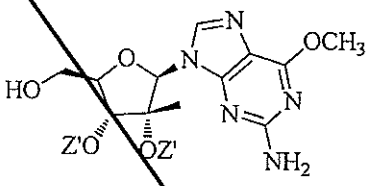


or



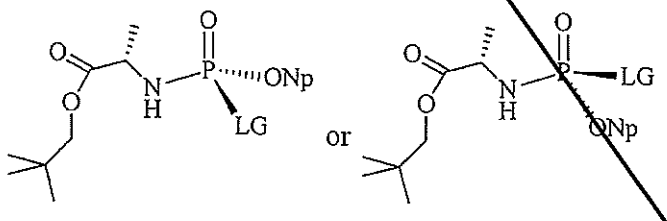
which comprises:

a) reacting a first compound having the structure



with a basic reagent to form a salt of the first compound, where Z' is hydrogen or a protecting group;

b) reacting the salt of the first compound with a second compound having the structure



where LG is a leaving group and Np is naphthalen-1-yl; and

c) optionally deprotecting.

30. The process of claim 29, wherein Z' is hydrogen.

31. The process of claim 30, wherein LG is an aryloxide having at least one electron withdrawing group.

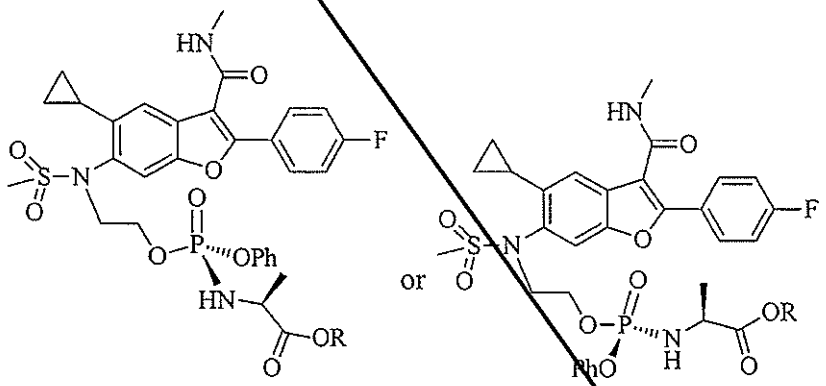
32. The process of claim 30, wherein LG is selected from among 2-nitrophenoxide, 4-nitrophenoxide, 2,4-dinitrophenoxide, pentafluorophenoxide, 2-chloro-4-nitrophenoxide, 2,4-dichlorophenoxide, and 2,4,6-trichlorophenoxide.

33. The process of claim 32, wherein the basic reagent is a Grignard reagent.

34. The process of claim 32, wherein the basic reagent is a t-butylmagnesium halide.

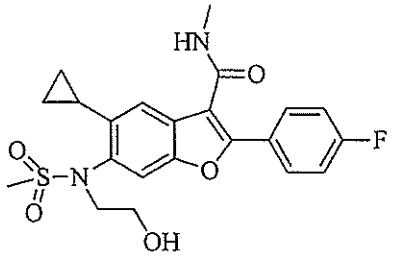
35. The process of claim 32, wherein the basic reagent is t-butylmagnesium bromide or t-butylmagnesium chloride.

36. A process process for preparing a compound having the structure



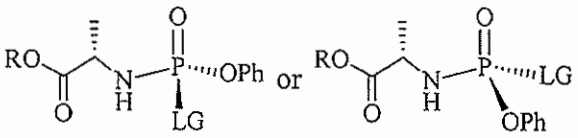
which comprises:

a) reacting a first compound having the structure



with a basic reagent to form a salt of the first compound,

b) reacting the salt of the first compound with a second compound having the structure



where LG is a leaving group and R is a C_{1-6}alkyl or a C_{3-7} cycloalkyl.

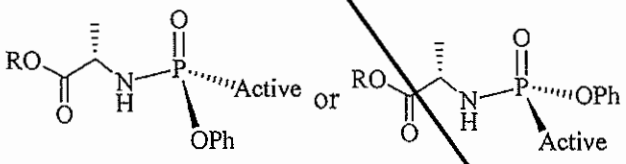
37. The process of claim 36, wherein LG is an aryloxide having at least one electron withdrawing group.

38. The process of claim 36, LG is selected from among 2-nitrophenoxide, 4-nitrophenoxide, 2,4-dinitrophenoxide, pentafluorophenoxide, 2-chloro-4-nitrophenoxide, 2,4-dichlorophenoxide, and 2,4,6-trichlorophenoxide.

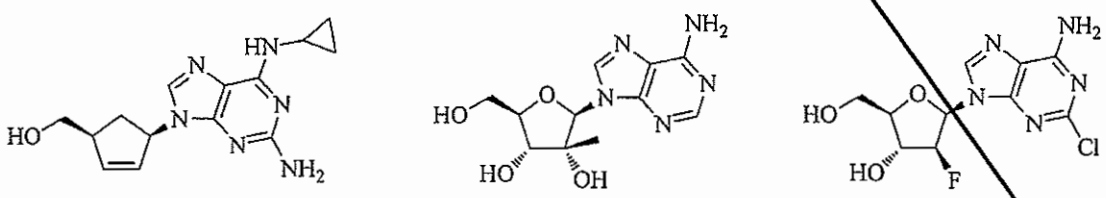
39. The process of claim 38, wherein the basic reagent is a t-butylmagnesium halide.

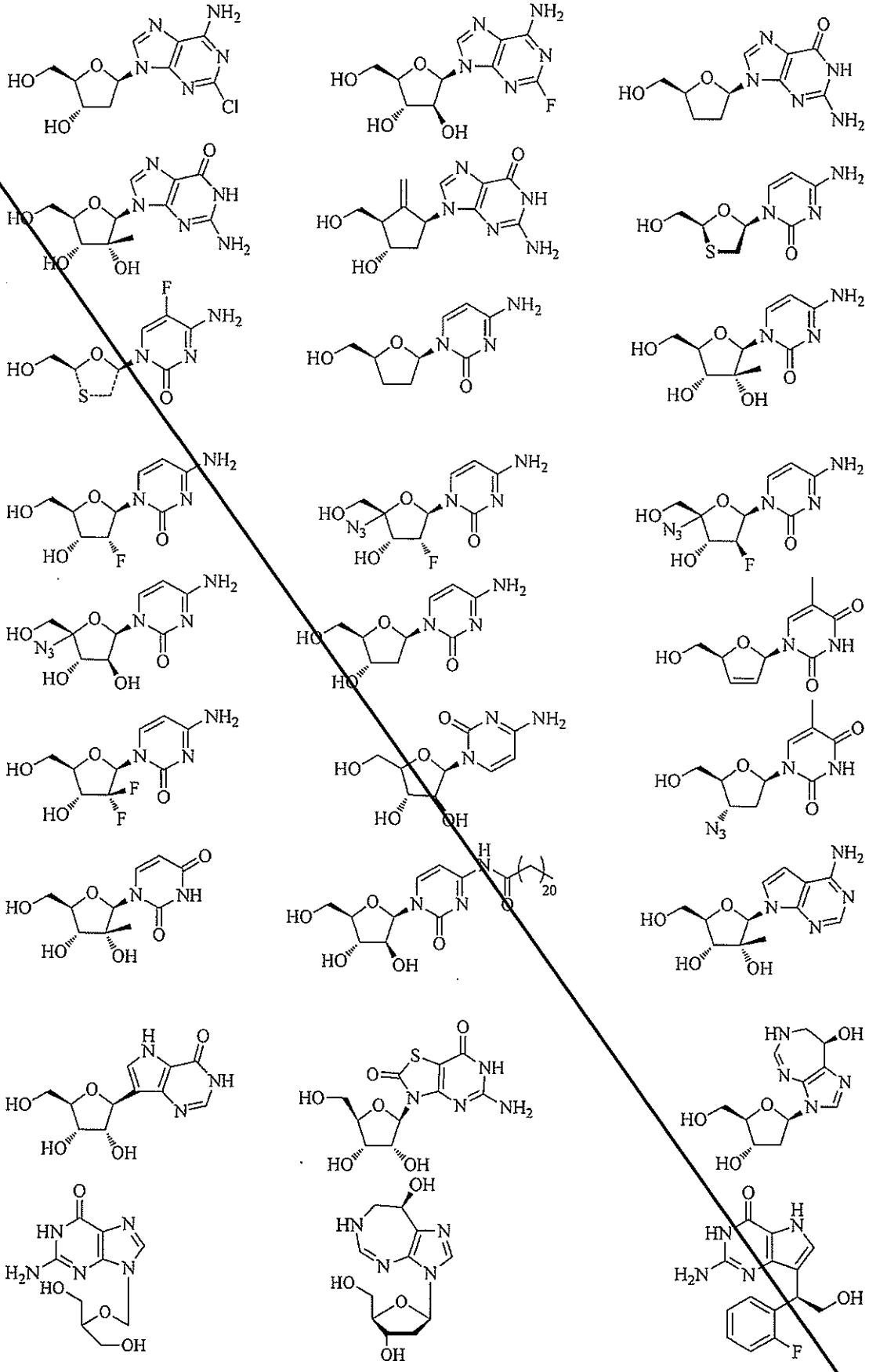
40. The process of claim 38, wherein the basic reagent is t-butylmagnesium bromide or t-butylmagnesium chloride.

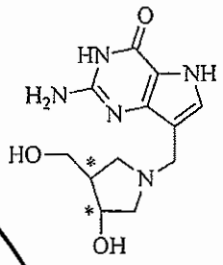
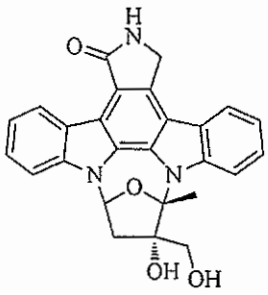
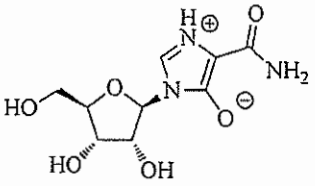
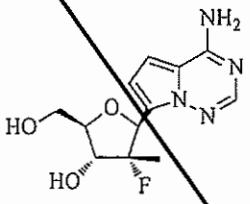
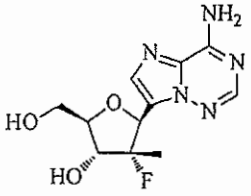
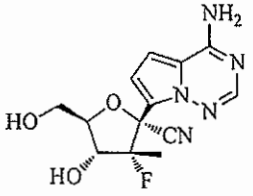
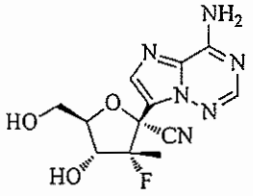
41. A compound having the following structure:



wherein R is a C_{1-6}alkyl or a C_{3-7} cycloalkyl and the Active is comprised of any one of the following chemical structures less at least one hydrogen on a primary or secondary hydroxyl group



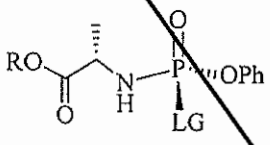


42. A process for preparing the compound of claim 41, which comprises

a) reacting any one of the so-noted compounds with basic reagent to obtain a salt of any one of the compounds; and

b) reacting the salt of any one of the compounds with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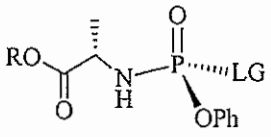


43. The process of claim 42, wherein LG is an aryloxide having at least one electron withdrawing group.

44. The process of claim 43, wherein the basic reagent is a Grignard reagent.

45. The process of claim 44, wherein the Grignard reagent is a t-butylmagnesium halide.

46. The process of claim 45, wherein the t-butylmagnesium halide is present in a mole equivalent amount of about 1 to about 2.5 relative to any one of the compounds.

47. The process of claim 46, wherein the t-butylmagnesium halide is present in a mole equivalent amount of about 1, about 1.1, about 1.2, about 1.3, about 1.4,

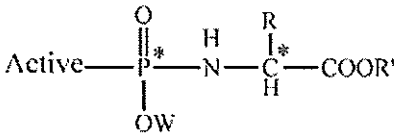
about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0 about 2.1, about 2.2, about 2.3, about 2.4, or about 2.5 relative to any one of the compounds.

48. The process of claim 46, wherein the t-butylmagnesium halide is present in a mole equivalent amount of about 1 to about 1.1 relative to any one of the compounds.

49. The process of claim 46, wherein the t-butylmagnesium halide is present in a mole equivalent amount of about 2 to about 2.1 relative to any one of the compounds.

Claims

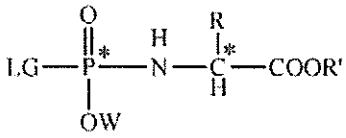
1. A process for preparing an enantiomerically- or a diastereomerically enriched phosphorus-containing active, salt, or pharmaceutically acceptable salt thereof, of formula I-1:



I-1

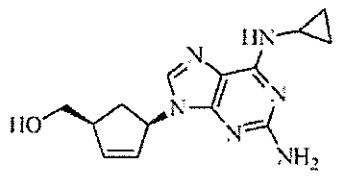
which comprises the steps of:

(a) reacting a protected or unprotected Active with a base to form a salt of said active and then reacting said salt with an enantiomerically- or a diastereomerically enriched compound of formula II-1



II-1

wherein the Active is a nucleoside, a nucleoside-analog, or a non-nucleoside; wherein the nucleoside is selected from



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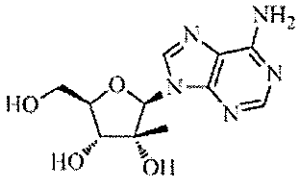

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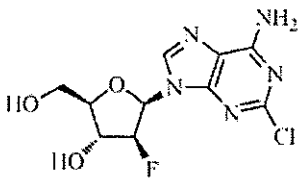

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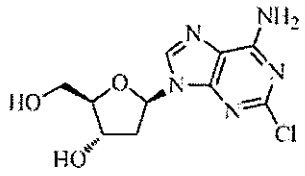

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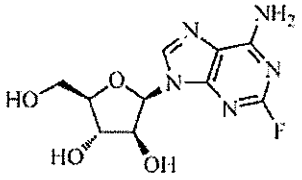

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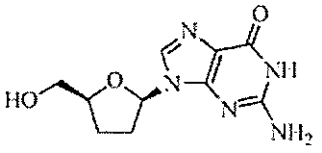

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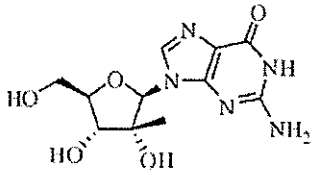

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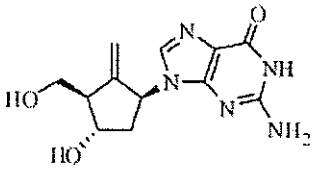

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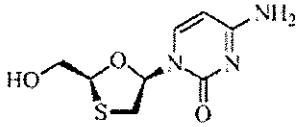

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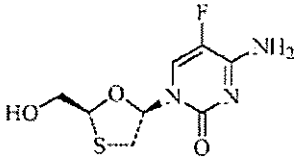

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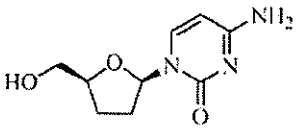

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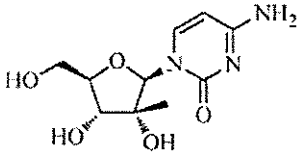

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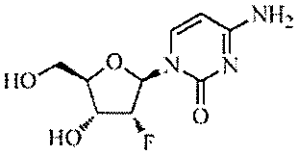

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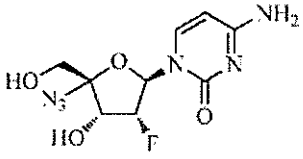

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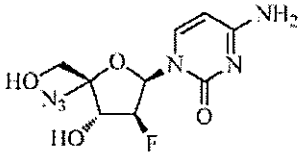

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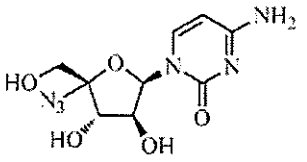

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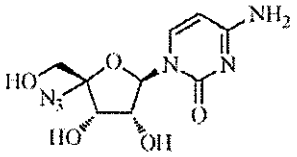

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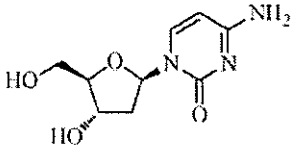

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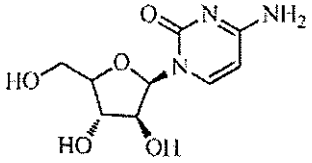

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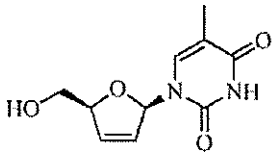

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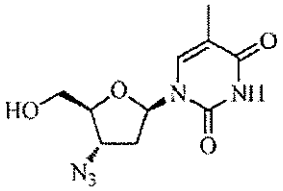

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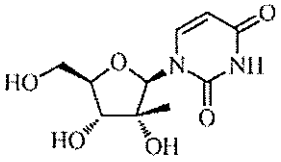

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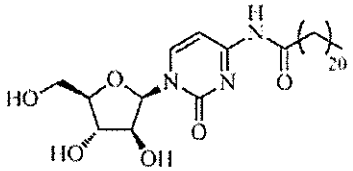

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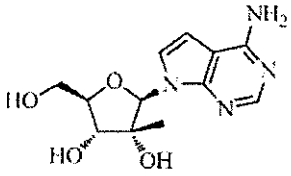

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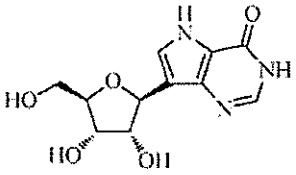

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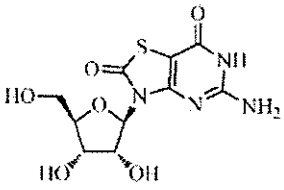

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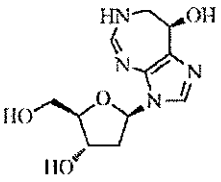

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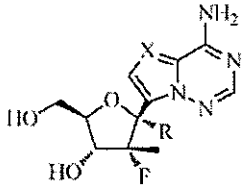

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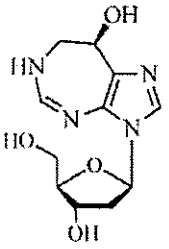

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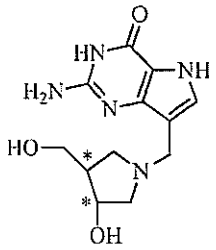

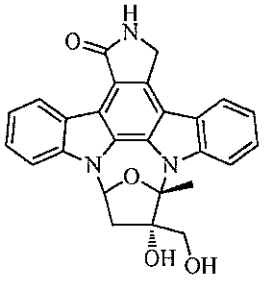

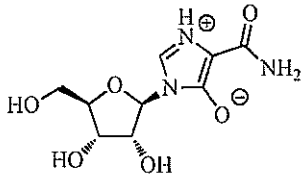

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(R,R)-41 ;

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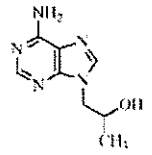

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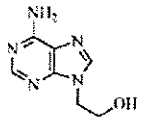

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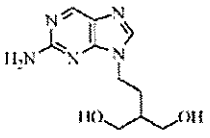

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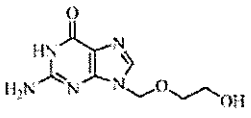

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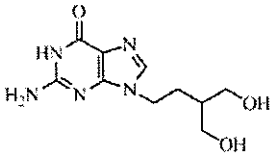

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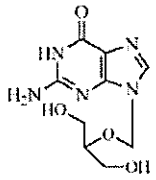

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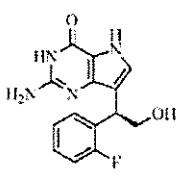

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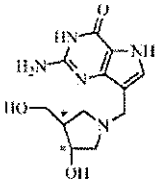

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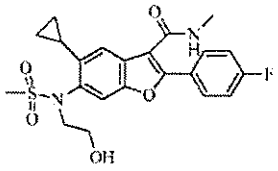

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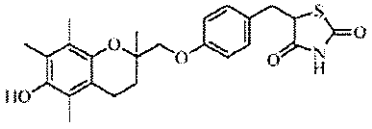

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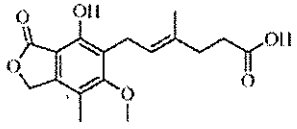

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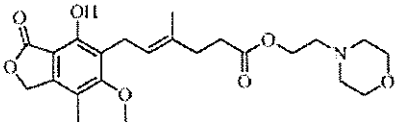

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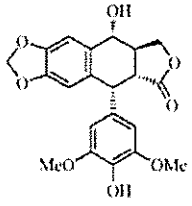

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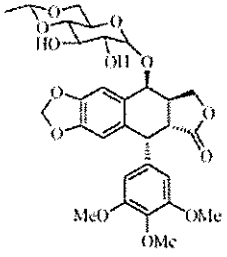

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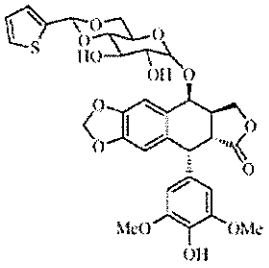

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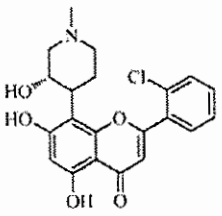

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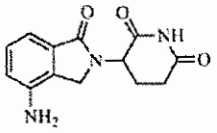

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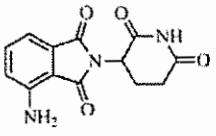

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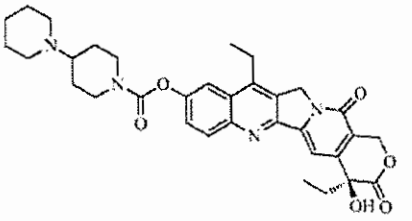

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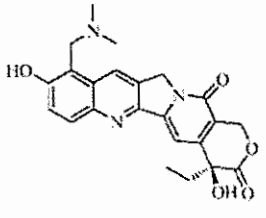

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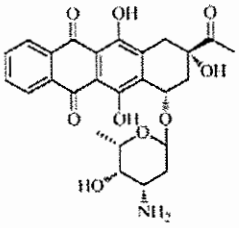

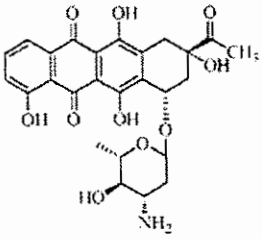

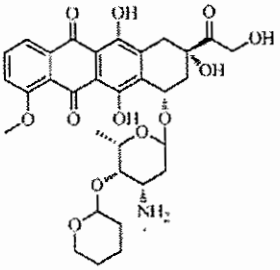

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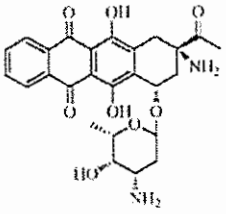

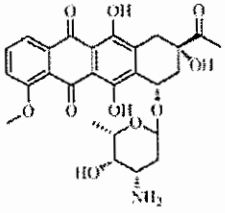

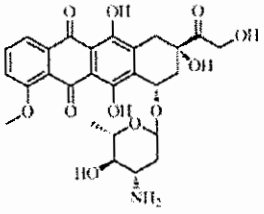

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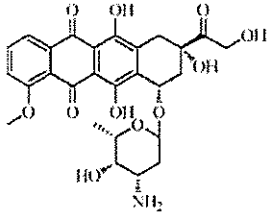

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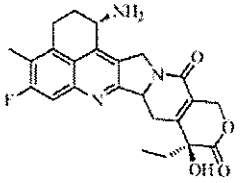

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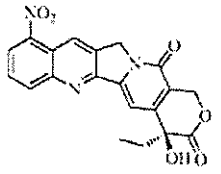

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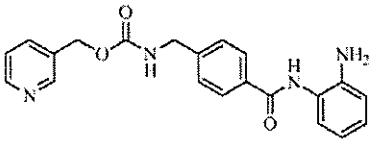

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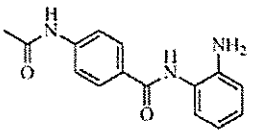

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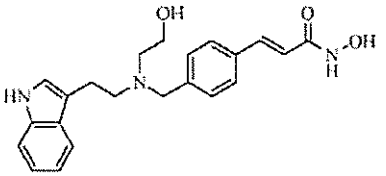

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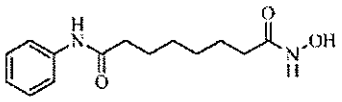

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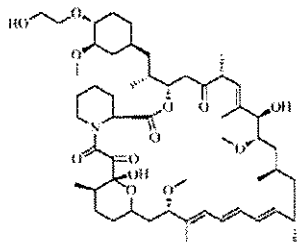

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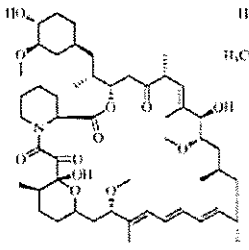

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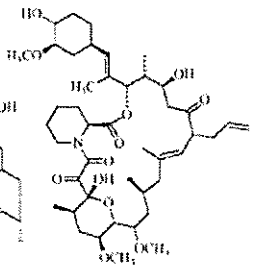

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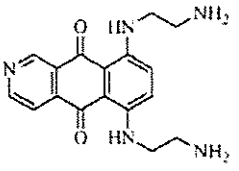

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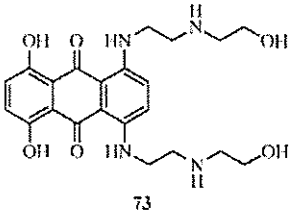

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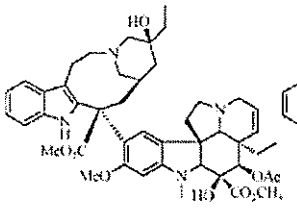

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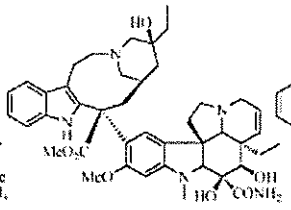

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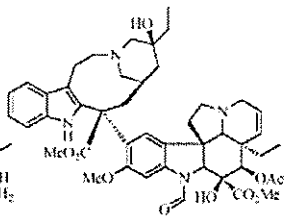

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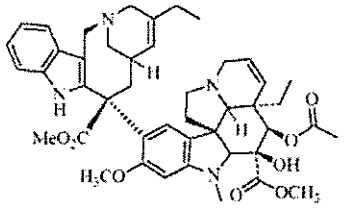

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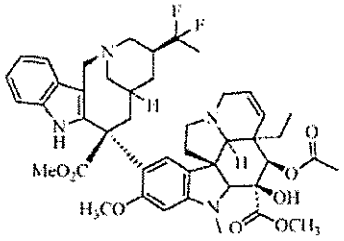

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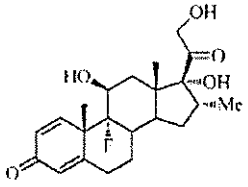

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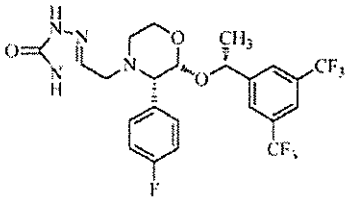

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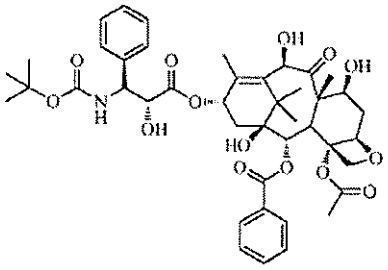

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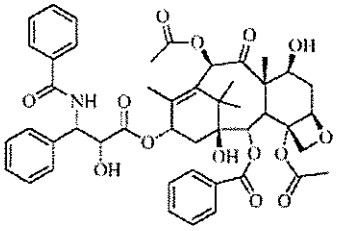

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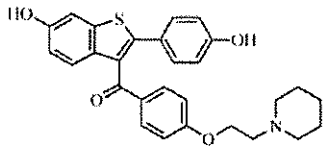

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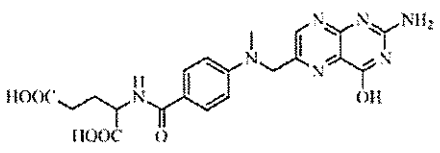

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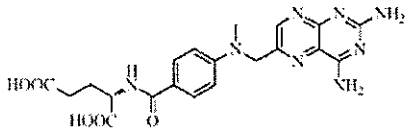

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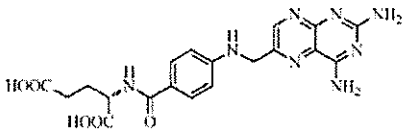

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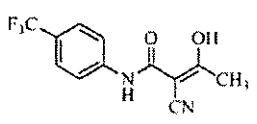

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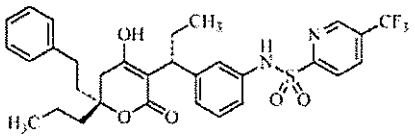

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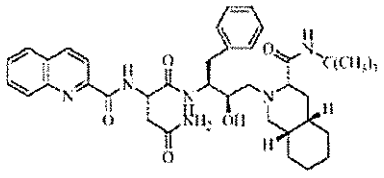

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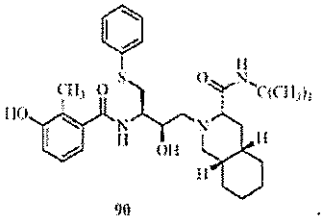

90

wherein W is an aryl or $-(CH_2)_nSC(O)C(CH_3)_m(CH_2OH)_{3-m}$;

wherein n is 2 or 3 and m is 0, 1, 2, or 3;

wherein LG is selected from the group consisting of halogen, tosylate, mesylate, triflate, acetate, trifluoromethylacetate, camphorsulfonate, 2-thioxobenzo[d]thiazol-3(2H)-yl, aryloxide, and aryloxide substituted with at least one electron withdrawing group;

wherein R is a substituted or unsubstituted C_{1-30} alkyl, a substituted or unsubstituted C_{3-10} cycloalkyl, a substituted or unsubstituted C_{1-30} alkylaryl, a substituted or unsubstituted C_{2-10} alkenyl, a substituted or unsubstituted $-OC_{1-30}$ alkyl, a substituted or unsubstituted C_{6-12} aryl; and

wherein R' is a substituted or unsubstituted C_{1-30} alkyl, a substituted or unsubstituted cycloalkyl, a substituted or unsubstituted C_{1-30} alkylaryl, or a substituted or unsubstituted C_{6-12} aryl; and

(b) optionally deprotecting the compound obtained in step (a) to obtain the enantiomerically- or diastereomerically-enriched phosphorous-containing active, salt, or pharmaceutically acceptable salt thereof of formula I-1,

wherein the enatiomerically- or diastereomerically-enriched compound of formula II-1 is obtained by crystallization from a composition comprising:

i. a first composition;

ii. a leaving group precursor;

iii. a non-nucleophilic base; and

iv. a liquid composition;

wherein the first composition comprises Rp-II-1 and Sp-II-1; and

wherein the leaving group precursor is 2,4-dinitrophenol, 4-nitrophenol, 2-nitrophenol, 2-chloro-4-nitrophenol, 2,4-dichlorophenol, or pentafluorophenol.

2. The process of claim 1, wherein the Active is a nucleoside.

3. The process of claim 1, wherein R' is a C_{1-6}alkyl or C_{3-7}cycloalkyl.

4. The process of claim 1, wherein R is methyl or isopropyl and R' is a C_{1-6}alkyl or C_{3-7} cycloalkyl.

5. The process of claim 1, wherein LG is an aryloxide substituted with at least one electron withdrawing group.

6. The process of claim 1, wherein LG is selected from among 2-nitrophenoxide, 4-nitrophenoxide, 2,4-dinitrophenoxide, pentafluorophenoxide, 2-chloro-4-nitrophenoxide, 2,4-dichlorophenoxide, and 2,4,6-trichlorophenoxide.

7. The process of claim 1, wherein the Active is a nucleoside analog.

8. The process of claim 1, wherein the Active is a non-nucleoside.

9. The process of claim 1, wherein the enantiomerically- or diastereomerically enriched phosphorous-containing active, salt, or pharmaceutically acceptable salt thereof of formula I-1 has at least 90 mol% of one enantiomer or diastereomer and at most about 10 mol% of the other enantiomer or diastereomer.

10. The process of claim 9, wherein no chiral purification technique is used.

11. The process of claim 1, wherein the enantiomerically- or diastereomerically enriched phosphorous-containing active, salt, or pharmaceutically acceptable salt thereof of formula I-1 has at least 95 mol% of one enantiomer or diastereomer and at most about 5 mol% of the other enantiomer or diastereomer.

12. The process of claim 1, wherein LG is 2,4-dinitrophenoxide, 4- nitrophenoxide, 2-nitrophenoxide, 2-chloro-4-nitrophenoxide, 2,4-dichlorophenoxide, or pentafluorophenoxide.

13. The process of claim 12, wherein LG is 4-nitrophenoxide or pentafluorophenoxide.

14. The process of claim 12, wherein the non-nucleophilic base is triethylamine.

15. The process of claim 1, wherein the crystallization occurs at a temperature between about -10°C and about 40°C.

16. The process of claim 1, wherein the non-nucleophilic base is potassium carbonate, cesium carbonate, di-isopropropylamine, di-isopropylethylamine, triethylamine, quinuclidine, napthalene-1,8-diamine, 2,2,6,6-tetramethylpiperidine, 1,8-diazabicycloundec- 7-ene, 4-dimethylamino-pyridine, pyridine, a 2,6-di-C_{1-6}-alkyl-pyridine, a 2,4,6-tri-C_{1-6}-alkyl-pyridine, or a mixture thereof.