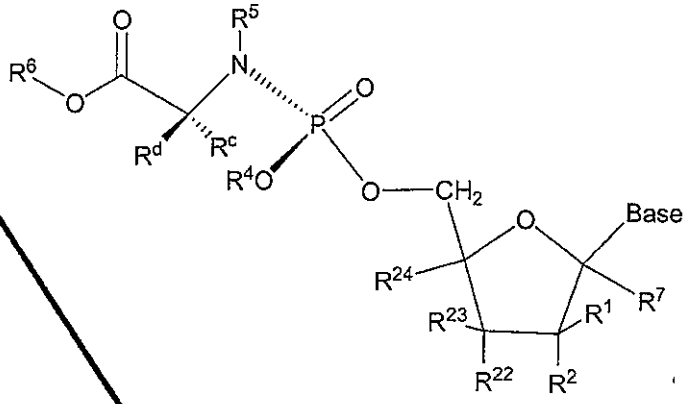
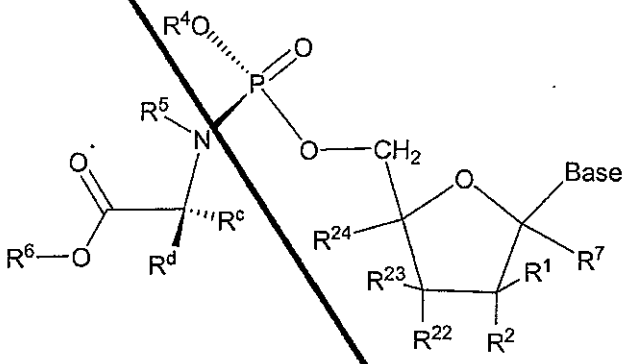
What is claimed is

1. A method for preparing a compound of Formula Ia or Ib:



Formula Ia



Formula Ib;

or a pharmaceutically acceptable salt or acid thereof;

wherein:

each R^1, R^2, R^7, R^{22}, R^{23} or R^{24} is independently H, OR^{11}, $NR^{11}R^{12}$, $C(O)NR^{11}R^{12}$, $-OC(O)NR^{11}R^{12}$, $C(O)OR^{11}$, $OC(O)OR^{11}$, $S(O)_nR^a$, $S(O)_2NR^{11}R^{12}$, N_3, CN, halogen, $(C_1–C_8)$alkyl, (C_3-C_8)carbocyclyl, $(C_4–C_8)$carbocyclylalkyl, $(C_2–C_8)$alkenyl, $(C_2–C_8)$alkynyl or aryl(C_1-C_8)alkyl;

or any two R^1, R^2, R^7, R^{22}, R^{23} or R^{24} on adjacent carbon atoms when taken together are $–O(CO)O-$ or $-O(CR^{11}R^{12})O-$ or when taken together with the ring carbon atoms to which they are attached form a double bond;

each Base is independently a naturally occurring or modified purine or pyrimidine base linked to the furanose ring through a carbon or nitrogen atom;

provided that Base is not uracil;

each n is independently 0, 1, or 2;

each R^a, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

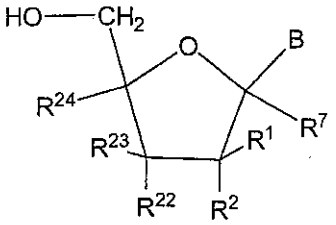
each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

each R^{11} or R^{12} is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl, heteroaryl, -C(=O)$(C_1$-$C_8)$alkyl, -S(O)$_n(C_1$-$C_8)$alkyl or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, -S(O)$_n$- or –NR^a-; and

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^1, R^2, R^{22}, R^{23}, R^{24}, R^4, R^5, R^6, R^7, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, NO_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a:

said method comprising :

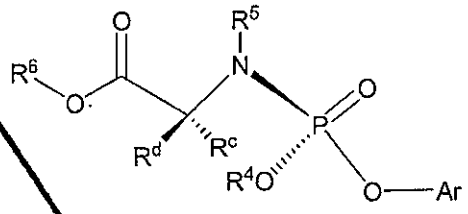
(a) providing a compound of Formula II



Formula II

and

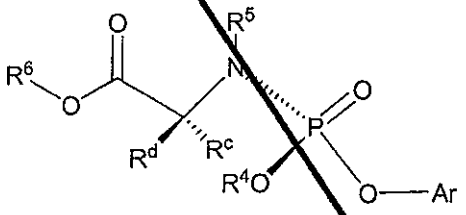
(b) treating the compound of Formula II with a compound of Formula IIIa and a base



Formula IIIa

thereby forming a compound of Formula Ia or

(c) treating the compound of Formula II with a compound of Formula IIIb and a base



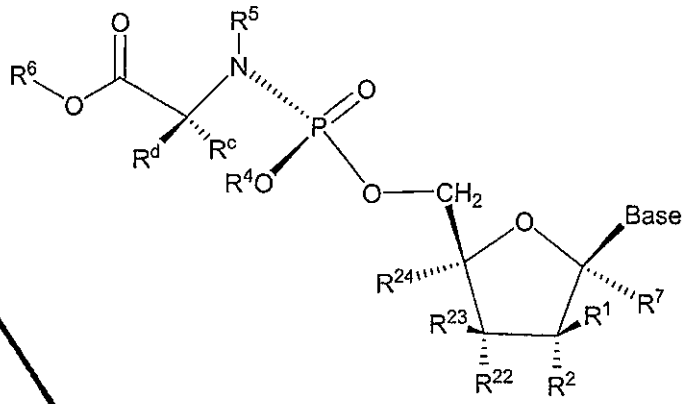
Formula IIIb

thereby forming a compound of Formula Ib;

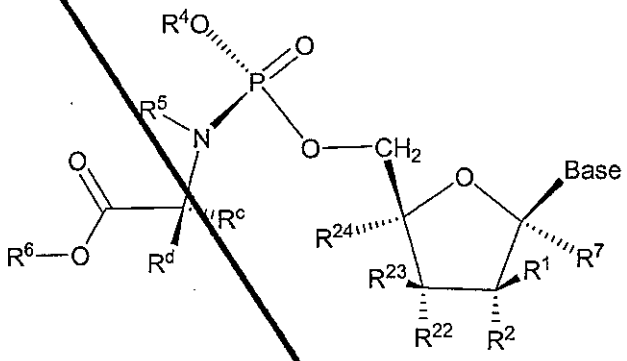
wherein:

each Ar is a (C_6–C_{20}) aryl or heteroaryl wherein said (C_6–C_{20}) aryl or heteroaryl is substituted with one or more halogen, NO_2, or (C_1-C_8)haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4.

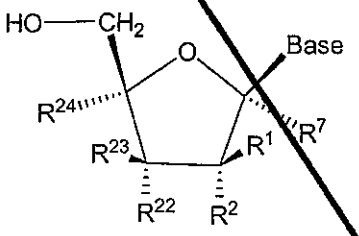
2. The method of claim 1 wherein Formula Ia is Formula IVa, Formula Ib is Formula IVb and Formula II is Formula V:



Formula IVa

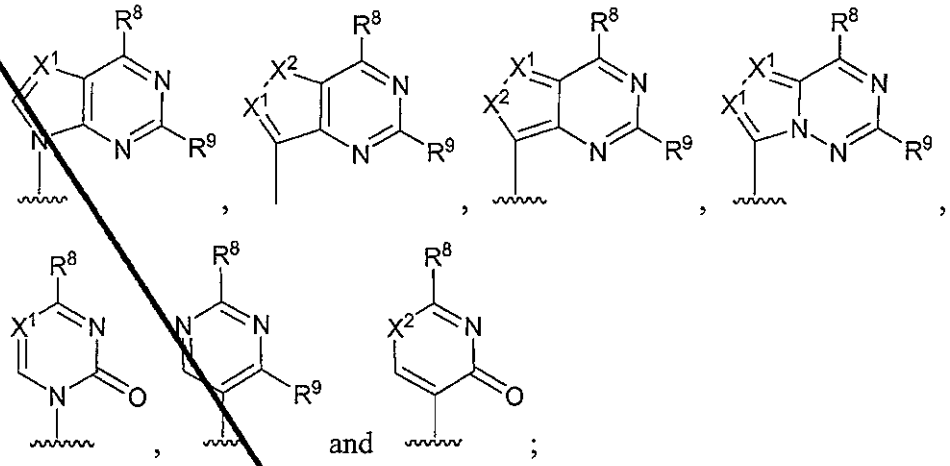


Formula IVb



Formula V

3. The method of claim 1 or 2 wherein Base is selected from the group consisting of:



wherein:

each X^1 is independently N or CR^{10};

each X^2 is independently NR^{11}, O, or $S(O)_n$;

each R^8 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, $-CH(=NR^{11})$, $-CH=NNHR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_4$–$C_8)$carbocyclylalkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl, heteroaryl, $-C(=O)(C_1$-$C_8)$alkyl, $-S(O)_n(C_1$-$C_8)$alkyl, aryl$(C_1$-$C_8)$alkyl, OR^{11} or SR^{11};

each n is independently 0, 1, or 2;

each R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, $-CH(=NR^{11})$, $-CH=NHNR^{11}$, $-CH=N(OR^{11})$, $-CH(OR^{11})_2$, $-C(=O)NR^{11}R^{12}$, $-C(=S)NR^{11}R^{12}$, $-C(=O)OR^{11}$, R^{11}, OR^{11} or SR^{11};

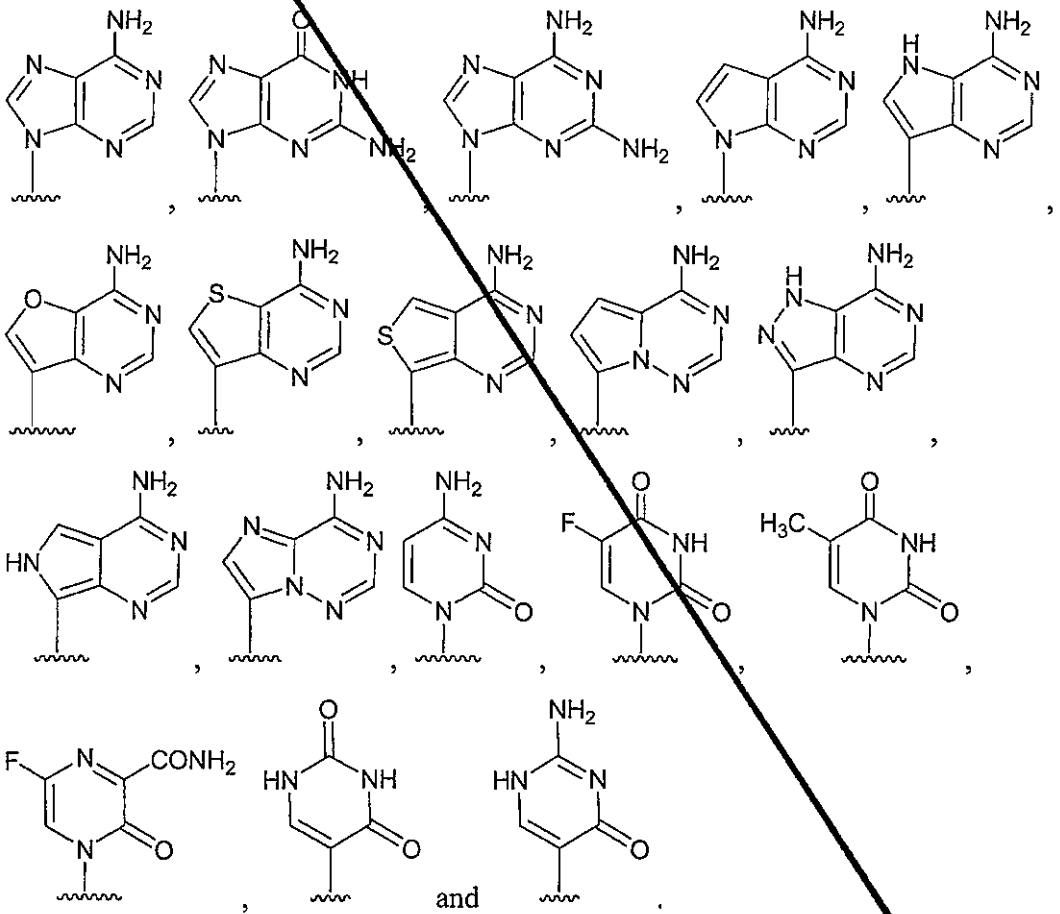
each R^{11} or R^{12} is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl, heteroaryl, $-C(=O)(C_1$-$C_8)$alkyl, $-S(O)_n(C_1$-$C_8)$alkyl or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with -O-, $-S(O)_n$- or $-NR^a$-;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl,

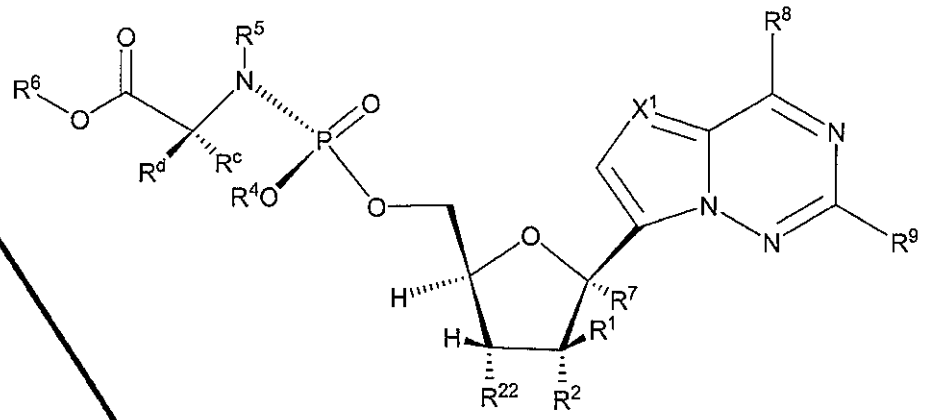
(C_6–C_{20})aryl, (C_2–C_{20})heterocyclyl or heteroaryl of each R^c, R^d, R^1, R^2, R^{22}, R^{23}, R^{24}, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, NO_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

provided that Base is not uracil.

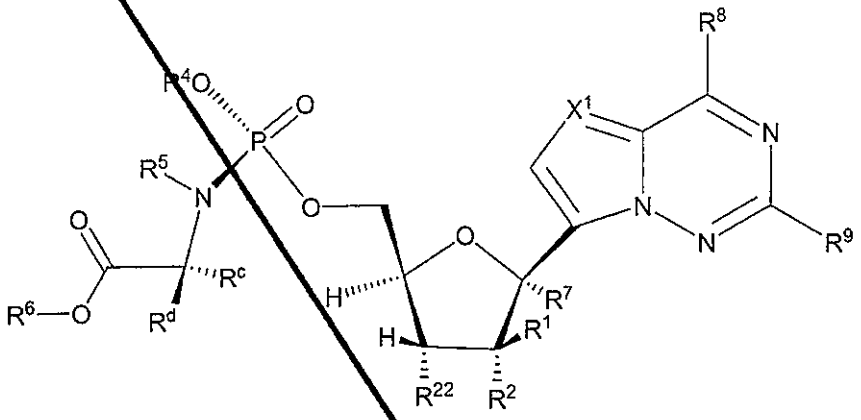
4. The method of any one of claims 1-3 wherein Base is selected from the group consisting of:



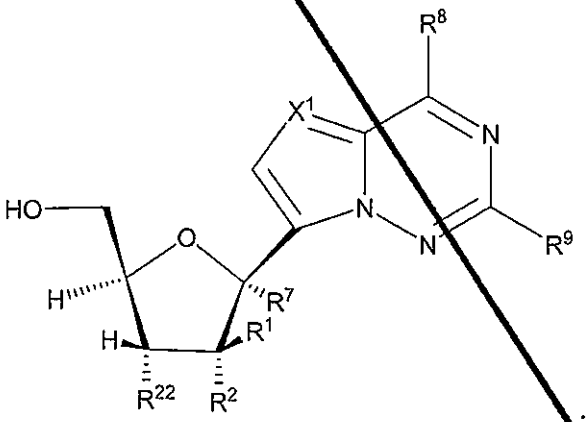
5. The method of any one of claims 1-3 wherein Formula Ia is Formula VIa, Formula Ib is Formula VIb and Formula II is Formula VII:



Formula VIa

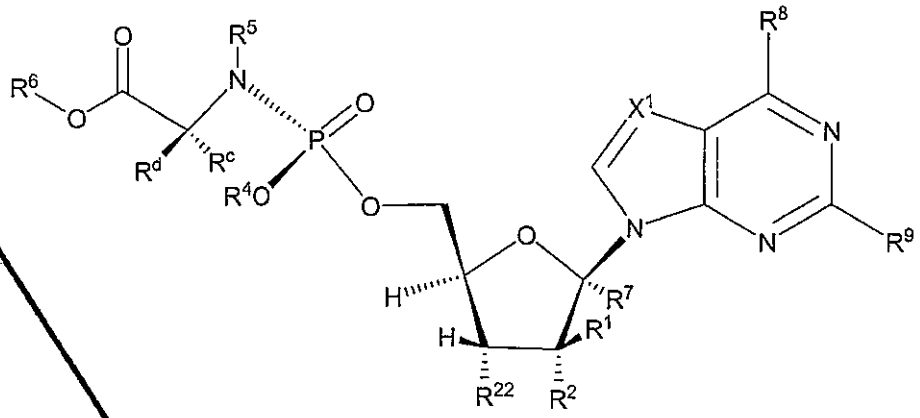


Formula VIb

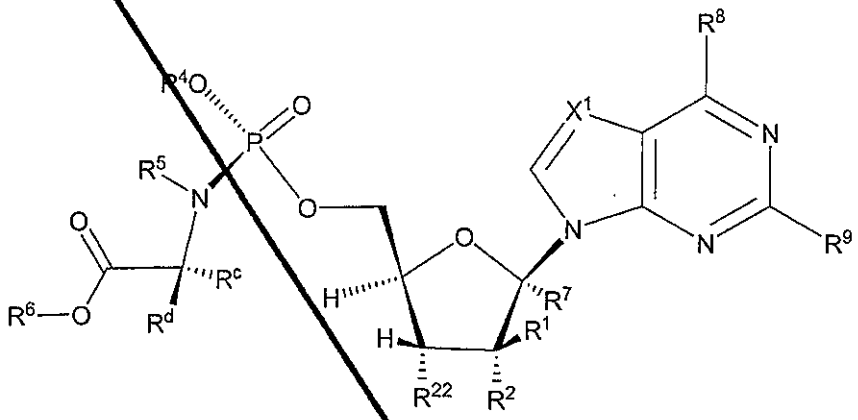


Formula VII

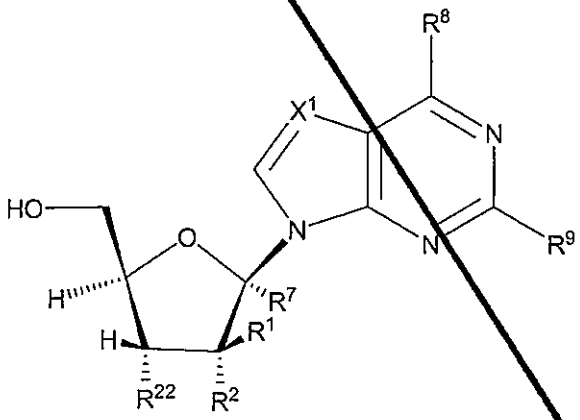
6. The method of any one of claims 1-3 wherein Formula Ia is Formula XIa, Formula Ib is Formula XIb and Formula II is Formula XII:



Formula XIa



Formula XIb



Formula XII

wherein:

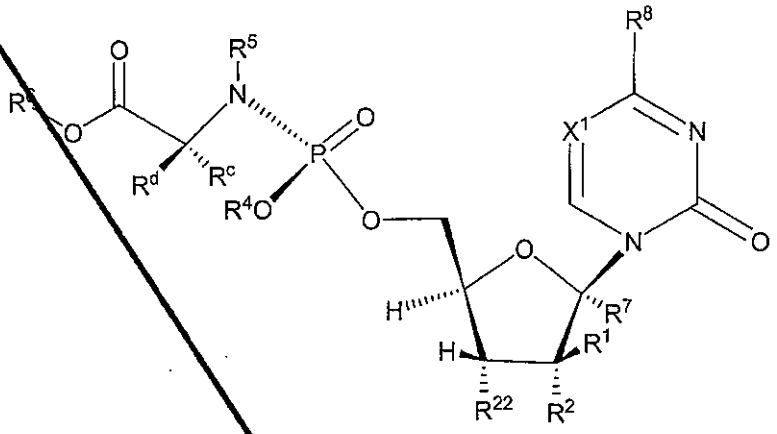
each R^1 is independently H, halogen, optionally substituted $(C_1–C_8)$alkyl, optionally substituted $(C_2–C_8)$alkenyl or optionally substituted $(C_2–C_8)$alkynyl;

each R^2 is independently halogen or OR^{11};

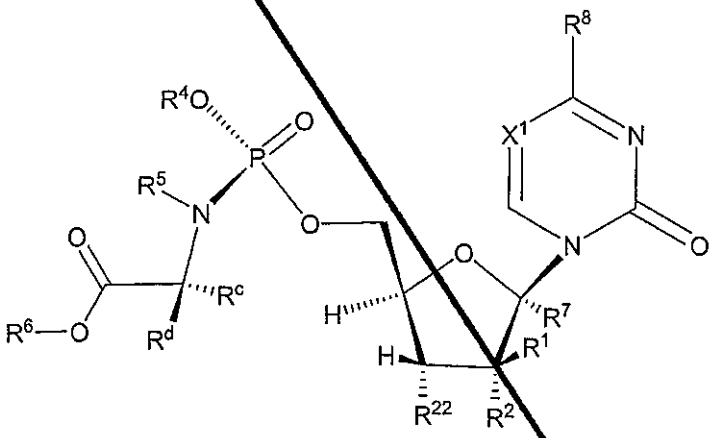
each R^5 is H; and

each R^{22} is OR^{11}.

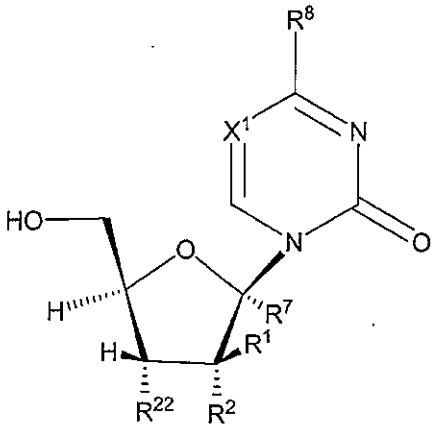
7. The method of any one of claims 1-3 wherein Formula Ia is Formula XIIIa, Formula Ib is Formula XIIIb and Formula II is Formula XIV:



Formula XIIIa



Formula XIIIb



Formula XIV

wherein:

each R^1 is independently H, halogen, optionally substituted (C_1–C_8)alkyl, optionally substituted (C_2–C_8)alkenyl or optionally substituted (C_2–C_8)alkynyl;

each R^2 is independently halogen or OR^{11};

each R^5 is H; and

each R^{22} is OR^{11}.

8. The method of any one of claims 1-7 wherein R^1 is H, halogen, optionally substituted (C_1–C_8)alkyl, optionally substituted (C_2–C_8)alkenyl or optionally substituted (C_2–C_8)alkynyl.

9. The method of any one of claims 1-8 wherein R^1 is H, CH_3 or F.

10. The method of any one of claims 1-9 wherein each R^{21}, R^{23} and R^{24} is H.

11. The method of any one of claims 1-10 wherein one of R^c or R^d is H and the other of R^c or R^d is optionally substituted (C_1-C_8)alkyl.

12. The method of any one of claims 1-11 wherein R^6 is optionally substituted (C_1–C_8)alkyl.

13. The method of any one of claims 1-12 wherein R^8 is $NR^{11}R^{12}$ or OR^{11}.

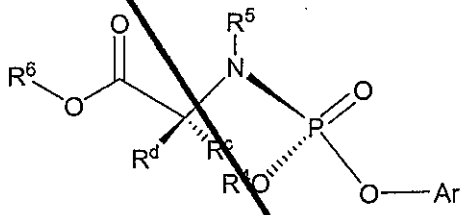
14. The method of any one of claims 1-13 wherein R^9 is H or $NR^{11}R^{12}$.

15. The method of any one of claims 1-14 wherein when R^8 or R^9 is OR^{11} or $NR^{11}R^{12}$ then each R^{11} and R^{12} of said OR^{11} or $NR^{11}R^{12}$ is H.

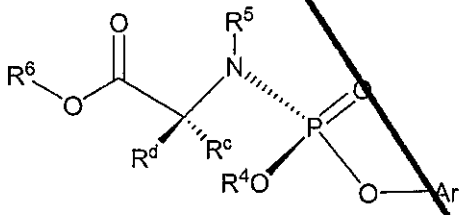
16. The method of any one of claims 1-15 wherein R^8 is NH_2 and R^9 is H.

17. The method of any one of claims 1-16 wherein R^4 is optionally substituted $(C_6–C_{20})$aryl.

18. The method of any one of claims 1-17 further comprising a method of preparing a compound of Formula IIIa or Formula IIIb



Formula IIIa



Formula IIIb

wherein:

each R^a, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4–C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6–C_{20})$aryl, $(C_2–C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

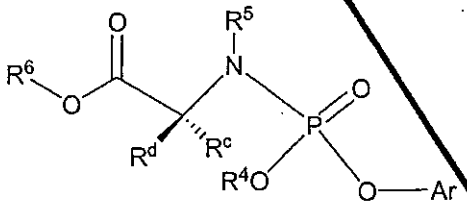
each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^4, R^5 or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a $(C_6$–$C_{20})$ aryl or heteroaryl wherein said $(C_6$–$C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4;

said method comprising:

(d) providing a diastereomeric compound of Formula VIII



Formula VIII

and

(e) dissolving the compound of Formula VIII in a suitable solvent and inducing crystallization by addition of a C_5-C_8 hydrocarbon or C_5-C_8 cyclic hydrocarbon;

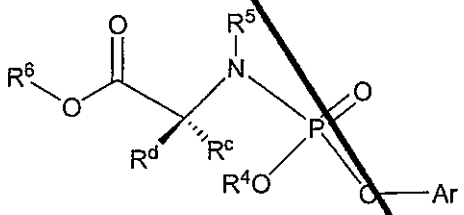
thereby forming a pure diasteromer of Formula IIIa or Formula IIIb.

19. The method of claim 18 wherein the compound of Formula VIII is dissolved in an ether solvent and the crystallization is induced by addition of a C_5-C_8 hydrocarbon.

20. The method of claim 18 or 19 wherein the compound of Formula VIII is dissolved in diethyl ether or methyl-t-butyl ether and crystallization is induced by the addition of hexane.

21. The method of any one of claims 18-20 wherein the compound of Formula VIII is dissolved in diethyl ether and crystallization is induced by the addition of hexane.

22. The method of any one of claims 18-21 further comprising a method of preparing a compound of Formula VIII



Formula VIII

wherein:

each R^a, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

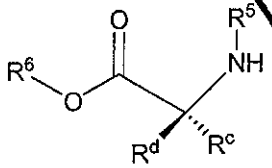
each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^4, R^5 or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a $(C_6$–$C_{20})$ aryl or heteroaryl wherein said $(C_6$–$C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4;

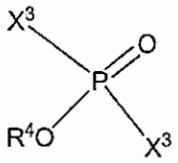
said method comprising:

(f) providing a chirally pure amino acid ester of Formula IX or a salt thereof



Formula IX

(g) treating the compound of Formula IX with a compound of Formula X in the presence of a base



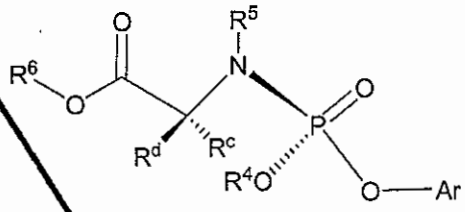
Formula X

wherein each X^3 is halogen; and

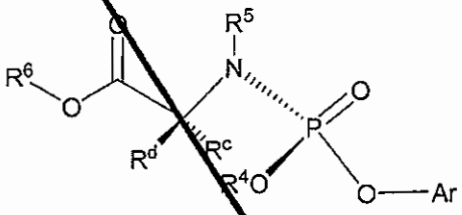
(h) treating the resulting mixture with ArOH;

thereby forming a compound of Formula VIII.

23. A method of preparing a compound of Formula IIIa or Formula IIIb



Formula IIIa



Formula IIIb

or a salt or ester thereof,

wherein:

each R^a, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

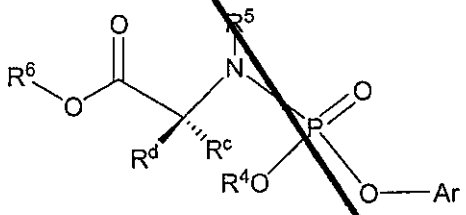
each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^4, R^5 or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a $(C_6$–$C_{20})$ aryl or heteroaryl wherein said $(C_6$–$C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4;

said method comprising:

(d) providing a diastereomeric compound of Formula VIII



Formula VIII

and

(e) dissolving the compound of Formula VIII in a suitable solvent and inducing crystallization by addition of a C_5-C_8 hydrocarbon or C_5-C_8 cyclic hydrocarbon;

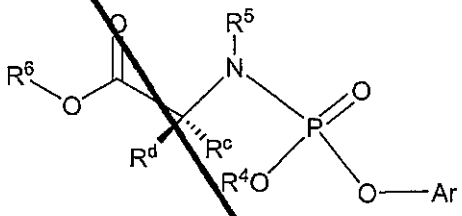
thereby forming a pure diasteromer of Formula IIIa or Formula IIIb.

24. The method of claim 23 wherein the compound of Formula VIII is dissolved in an ether solvent and the crystallization is induced by addition of a C_5-C_8 hydrocarbon.

25. The method of claim 23 or 24 wherein the compound of Formula VIII is dissolved in diethyl ether or methyl-t-butyl ether and crystallization is induced by the addition of hexane.

26. The method of any one of claims 23-25 wherein the compound of Formula VIII is dissolved in diethyl ether and crystallization is induced by the addition of hexane.

27. The method of any one of claims 23-26 further comprising a method of preparing a compound of Formula VIII



Formula VIII

or a salt or ester thereof,

wherein

each R^a, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

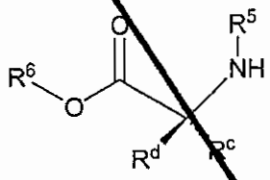
each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$–$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$–$C_{20})$aryl, $(C_2$–$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^4, R^5 or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a $(C_6$–$C_{20})$ aryl or heteroaryl wherein said $(C_6$–$C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4;

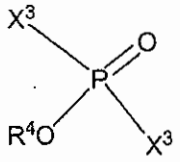
said method comprising:

(f) providing a chirally pure amino acid ester of Formula IX or a salt thereof



Formula IX

(g) treating the compound of Formula IX with a compound of Formula X in the presence of a base



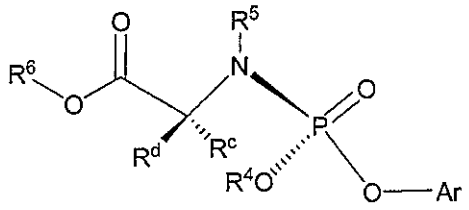
Formula X

wherein each X^3 is halogen; and

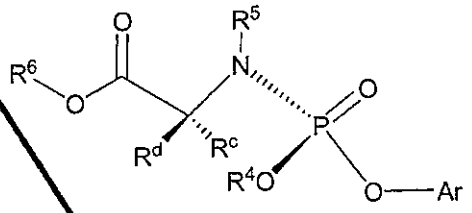
(h) treating the resulting mixture with ArOH;

thereby forming a compound of Formula VIII.

28. The method of any one of claims 18-27 wherein the compound Formula IIIa or Formula IIIb is



Formula IIIa



Formula IIIb

or a salt or ester thereof;

wherein:

each R^a, R^4 or R^6 is independently (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl;

each R^c or R^d is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

each R^5 is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl;

wherein each (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl of each R^c, R^d, R^4, R^5 or R^6 is

independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a $(C_6–C_{20})$ aryl or heteroaryl wherein said $(C_6–C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4.

29. The method of any one of claims 18-28 wherein R^5 is H and one of R^c or R^d is H.

30. The method of any one of claims 18-29 wherein R^6 is optionally substituted $(C_1$-$C_8)$alkyl and R^4 is optionally substituted $(C_6–C_{20})$aryl.

31. The method of any one of claims 18-30 wherein R^4 is optionally substituted phenyl.

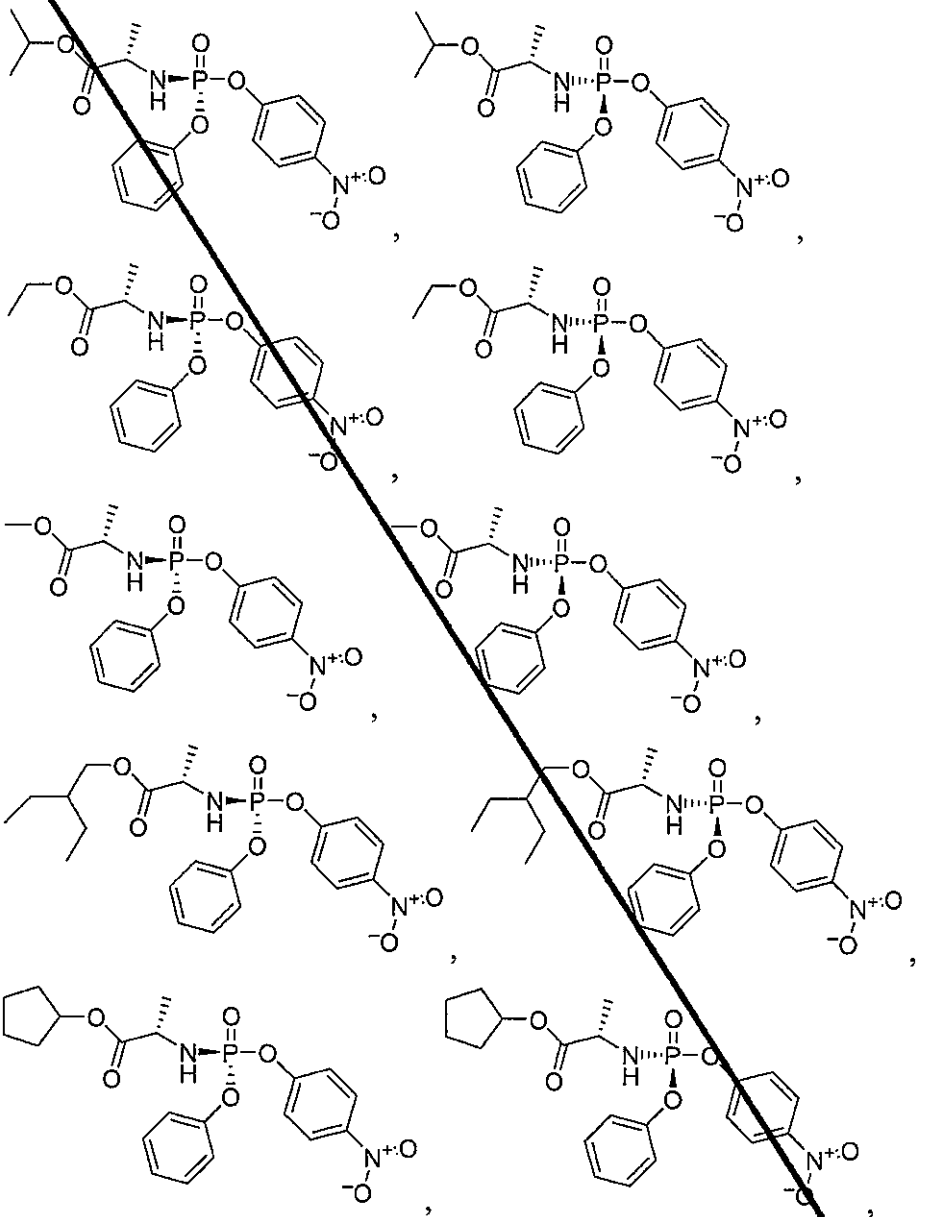
32. The method of any one of claims 18-31 wherein one of R^c or R^d is H and the other of R^c or R^d is CH_3.

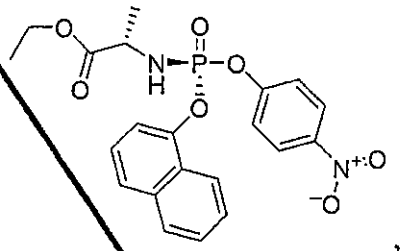
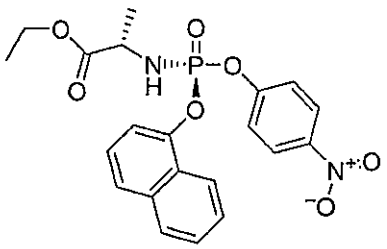
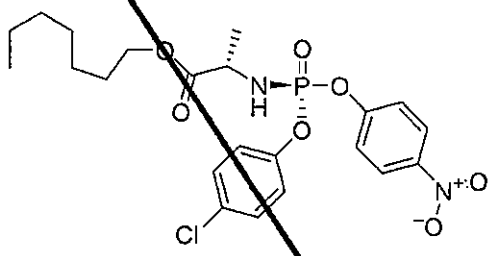
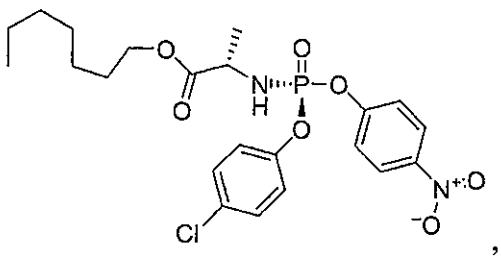
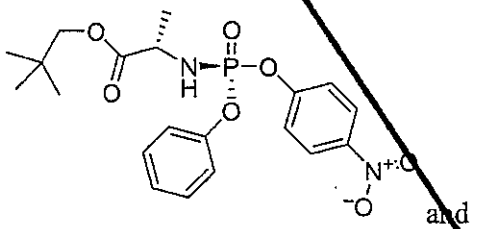
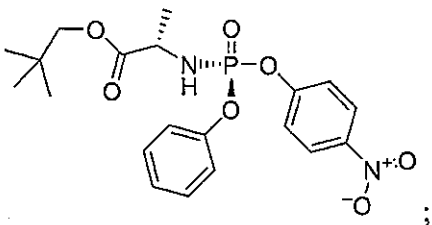
33. The method of any one of claims 18-32 wherein Ar is optionally substituted *para*-nitrophenyl.

34. The method of any one of claims 18-33 wherein the chirality at the carbon directly attached to R^c and R^d is *S*.

35. The method of any one of claims 18-34 wherein the chirality at the carbon directly attached to R^c and R^d is *R*.

36. The method of any one of claims 18-35 wherein the compound is selected from the group consisting of



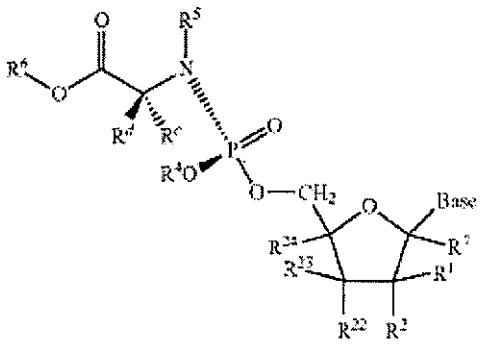

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and

; or salts or esters thereof.

CLAIMS

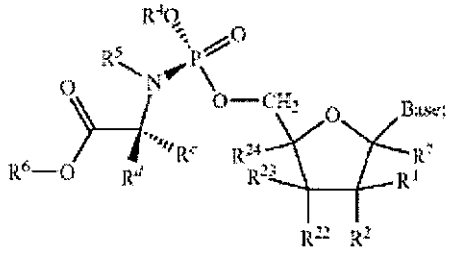
What is claimed is:

1. A method for preparing a compound of Formula Ia or Ib:

Formula Ia



Formula Ib



or a pharmaceutically acceptable salt or acid thereof;

wherein:

each R^1, R^2, R^7, R^{22}, R^{23} or R^{24} is independently H, OR^{11}, $NR^{11}R^{12}$, $C(O)NR^{11}R^{12}$, $—OC(O)NR^{11}R^{12}$, $C(O)OR^{11}$, $OC(O)OR^{11}$, $S(O)_nR^a$, $S(O)_2NR^{11}R^{12}$, N_3, CN, halogen, $(C_1$-$C_8)$alkyl, $(C_3$-$C_8)$carbocyclyl, $(C_2$-$C_8)$carbocyclylalkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl or aryl $(C_1$-$C_8)$alkyl;

or any two R^1, R^2, R^7, R^{22}, R^{23} or R^{24} on adjacent carbon atoms when taken together are —O(CO)O— or —$O(CR^{11}R^{12})$O— or when taken together with the ring carbon atoms to which they are attached form a double bond;

each Base is independently a naturally occurring or modified purine or pyrimidine base linked to the furanose ring through a carbon or nitrogen atom;

provided that Base is not uracil;

each n is independently 0, 1, or 2;

each R^a, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_6)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_6)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

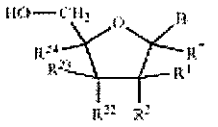
each R^{11} or R^{12} is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_6)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl, heteroaryl, —C(=O)$(C_1$-$C_8)$alkyl, —S(O)$_2(C_1$-$C_8)$alkyl or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with —O—, —S(O)$_n$— or —NR^a—; and

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_6)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^1, R^2, R^{22}, R^{23}, R^{24}, R^4, R^5, R^6, R^7, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, N(R^a)$_2$, NH(R^a), NH_2, NO_2, C(O)N(R^a)$_2$, C(O)NH(R^a), C(O)NH_2, OC(O)N(R^a)$_2$, OC(O)NH(R^a), OC(O)NH_2, C(O)OR^a, OC(O)OR^a, C(O)R^a, OC(O)R^a, S(O)$_n$R^a, S(O)$_2$N(R^a)$_2$, S(O)$_2$NH(R^a), S(O)$_2$$NH_2$, OR^a or R^a;

said method comprising:

(a) providing a compound of Formula II

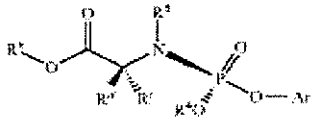
Formula II



and

(b) treating the compound of Formula II with a compound of Formula IIIa and a base

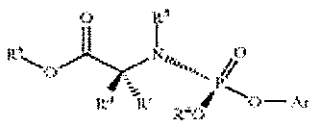
Formula IIIa



thereby forming a compound of Formula Ia or

(c) treating the compound of Formula II with a compound of Formula IIIb and a base

Formula IIIb

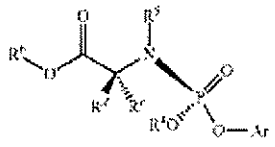


thereby forming a compound of Formula Ib:

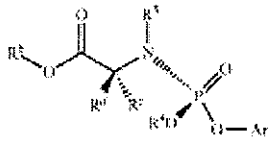
wherein:

each Ar is a $(C_6$-$C_{20})$ aryl or heteroaryl wherein said $(C_6$-$C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4, the method further comprising a method of preparing a compound of Formula IIIa or Formula IIIb

Formula IIIa



Formula IIIb



wherein:

each R^a, R^b or R^c is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$ alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$ carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$ alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-(C_8)carbocyclyl, $(C_4$-$C_8)$ carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

each R^4 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

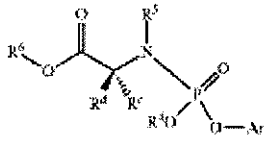
wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl $(C_1$-$C_8)$alkyl, heterocyclyl $(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl of each R^a, R^b, R^c, R^d or R^e is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^aS(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a $(C_6$-$C_{20})$ aryl or heteroaryl wherein said $(C_6$-$C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^aS(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4.

said method comprising:

(d) providing a diastereomeric compound of Formula VIII

Formula VIII



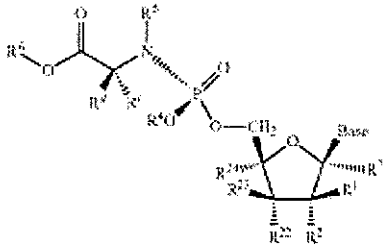
and

(e) dissolving the compound of Formula VIII in a suitable solvent and inducing crystallization by addition of a C_5-C_6 hydrocarbon or C_5-C_8 cyclic hydrocarbon;

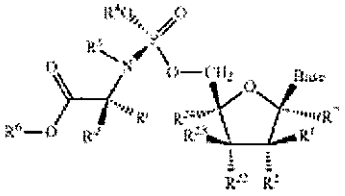
thereby forming a pure diastereomer of Formula IIIa or Formula IIIb.

2. The method of claim 1 wherein Formula Ia is Formula IVa, Formula Ib is Formula IVb and Formula II is Formula V:

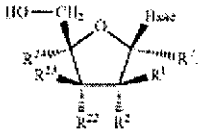
Formula IVa



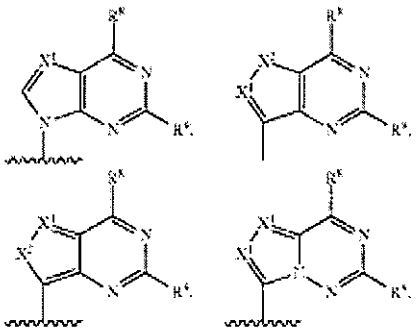
Formula IVb



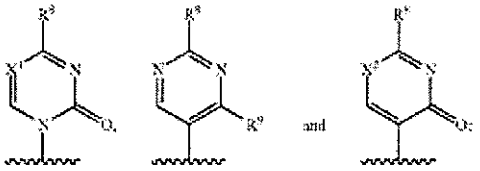
Formula V



3. The method of claim 1 wherein Base is selected from the group consisting of:



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wherein:

each X^1 is independently N or CR^{10};

each X^2 is independently NR^{11}, O, or $S(O)_n$;

each R^5 is independently halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, —CH(=NR^{11}), —CH=$NNHR^{11}$, —CH=$N(OR^{11})$, —CH$(OR^{11})_2$, —C(=O)$NR^{11}R^{12}$, —C(=S)$NR^{11}R^{12}$, —C(=O)OR^{11}, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclylalkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl, heteroaryl, —C(=O)(C_1-C_6)alkyl, —$S(O)_n$(C_1-C_8)alkyl, aryl(C_1-C_8)alkyl, OR^{11} or SR^{11};

each n is independently 0, 1, or 2;

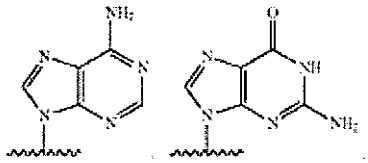
each R^9 or R^{10} is independently H, halogen, $NR^{11}R^{12}$, $N(R^{11})OR^{11}$, $NR^{11}NR^{11}R^{12}$, N_3, NO, NO_2, CHO, CN, —CH(=NR^{11}), —CH=$NHNR^{11}$, —CH=$N(OR^{11})$, —CH$(OR^{11})_2$, —C(=O)$NR^{11}R^{12}$, —C(=S)$NR^{11}R^{12}$, —C(=O)OR^{11}, R^{11}, OR^{11} or SR^{11};

each R^{11} or R^{12} is independently H, (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl, heteraryl, —C(=O)(C_1-C_8)alkyl, —$S(O)_n$(C_1-C_8)alkyl or R^{11} and R^{12} taken together with a nitrogen to which they are both attached form a 3 to 7 membered heterocyclic ring wherein any one carbon atom of said heterocyclic ring can optionally be replaced with —O—, —$S(O)_n$— or —NR^a—;

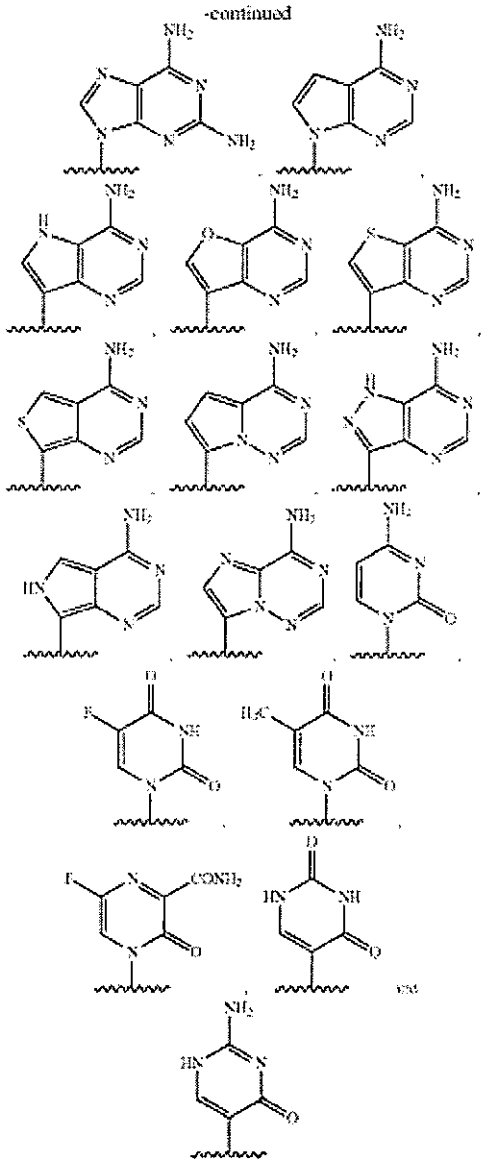
wherein each (C_1-C_8)alkyl, (C_2-C_8)alkenyl, (C_2-C_8)alkynyl, (C_3-C_8)carbocyclyl, (C_4-C_8)carbocyclylalkyl, aryl(C_1-C_8)alkyl, heterocyclyl(C_1-C_8)alkyl, (C_6-C_{20})aryl, (C_2-C_{20})heterocyclyl or heteroaryl of each R^a, R^d, R^2, R^{22}, R^{23}, R^{24}, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} or R^{12} is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, NO_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

provided that Base is not uracil.

4. The method of claim 3 wherein Base is selected from the group consisting of:

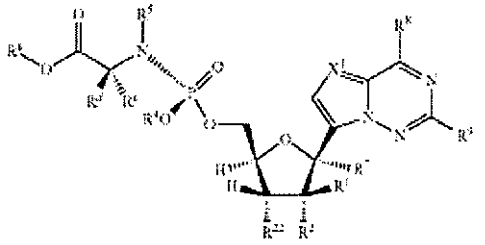


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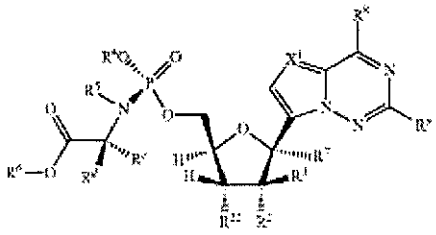
5. The method of claim 1 wherein Formula Ia is Formula VIa, Formula Ib is Formula VIb and Formula II is Formula VII:

Formula VIa

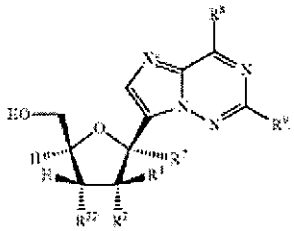


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Formula VIb

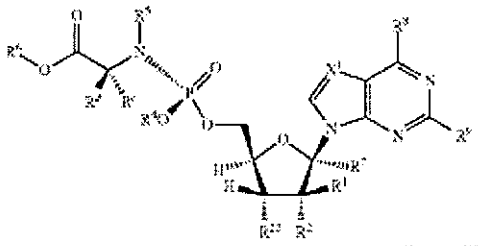


Formula VII

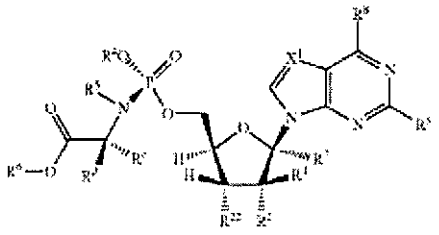


6. The method of claim 1 wherein Formula Ia is Formula XIa, Formula Ib is Formula XIb and Formula II is Formula XII:

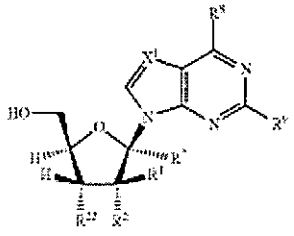
Formula XIa



Formula XIb



Formula XII



wherein:

each R^1 is independently H, halogen, optionally substituted (C_1-C_8)alkyl, optionally substituted (C_2-C_8)alkenyl or optionally substituted (C_2-C_8)alkynyl;

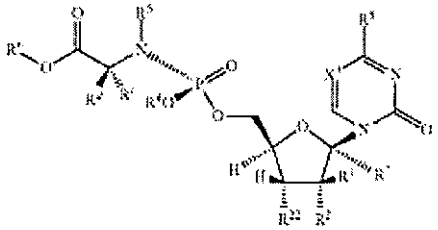
each R^2 is independently halogen or OR^{11};

each R^5 is H; and

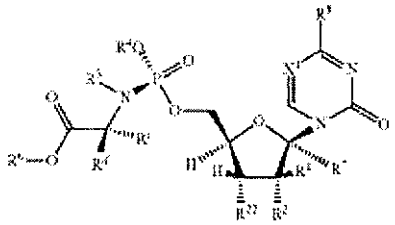
each R^{22} is OR^{11}.

7. The method of claim 1 wherein Formula Ia is Formula XIIIa, Formula Ib is Formula XIIIb and Formula II is Formula XIV:

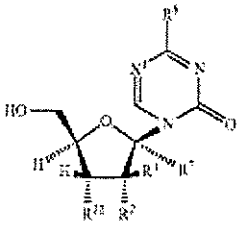
Formula XIIIa



Formula XIIIb



Formula XIV



wherein:

each R^1 is independently H, halogen, optionally substituted (C_1-C_8)alkyl, optionally substituted (C_2-C_8)alkenyl or optionally substituted (C_2-C_8)alkynyl;

each R^2 is independently halogen or OR^{11};

each R^5 is H; and

each R^{22} is OR^{11}.

8. The method of claim 1 wherein R^1 is H, halogen, optionally substituted (C_1-C_8)alkyl, optionally substituted (C_2-C_8)alkenyl or optionally substituted (C_2-C_8)alkynyl.

9. The method of claim 8 wherein R^1 is H, CH_3, or F.

10. The method of claim 1 wherein each R^5, R^{23} and R^{22} is H.

11. The method of claim 1 wherein one of R^c or R^d is H and the other of R^c or R^d is optionally substituted (C_1-C_8)alkyl.

12. The method of claim 1 wherein R^6 is optionally substituted (C_1-C_8)alkyl.

13. The method of claim 1 wherein R^A is $NR^{11}R^{12}$ or OR^{11}.

14. The method of claim 13 wherein R^A is H or $NR^{11}R^{12}$.

15. The method of claim 1 wherein when R^9 or R^9 is OR^{11} or $NR^{11}R^{12}$ then each R^{11} and R^{12} of said OR^{11} or $NR^{11}R^{12}$ is H.

16. The method of claim 14 wherein R^9 is NH_2 and R^9 is H.

17. The method of claim 1 wherein R^4 is optionally substituted $(C_6$-$C_{20})$aryl.

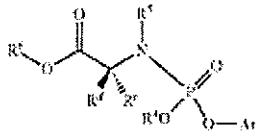
18. The method of claim 1 wherein the compound of Formula VIII is dissolved in an ether solvent and the crystallization is induced by addition of a C_5-C_8 hydrocarbon.

19. The method of claim 1 wherein the compound of Formula VIII is dissolved in diethyl ether or methyl-t-butyl ether and crystallization is induced by the addition of hexane.

20. The method of claim 19 wherein the compound of Formula VIII is dissolved in diethyl ether and crystallization is induced by the addition of hexane.

21. The method of claim 1 further comprising a method of preparing a compound of Formula VIII

Formula VIII



wherein:

each R^6, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

each R^7 or R^8 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl provided that R^7 and R^8 are not the same;

each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocylylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

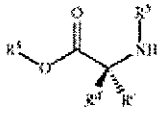
wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl $(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl of each R^6, R^4, R^7, R^8 or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a $(C_6$-$C_{20})$ aryl or heteroaryl wherein said $(C_6$-$C_{20})$ aryl or heteroaryl is substituted with one or more halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4;

said method comprising:

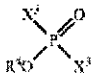
(f) providing a chirally pure amino acid ester of Formula IX or a salt thereof

Formula IX



(g) treating the compound of Formula IX with a compound of Formula X in the presence of a base

Formula X



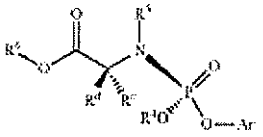
wherein each X^3 is halogen; and

(h) treating the resulting mixture with ArOH;

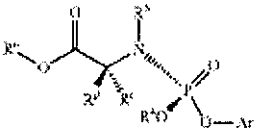
thereby forming a compound of Formula VIII.

22. A method of preparing a compound of Formula IIIa or Formula IIIb

Formula IIIa



Formula IIIb



or a salt or ester thereof,

wherein:

each R^a, R^2 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl $(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^4, R^5 or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^a)_2$, $NH(R^a)$, NH_2, $C(O)N(R^a)_2$, $C(O)NH(R^a)$, $C(O)NH_2$, $OC(O)N(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_qR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

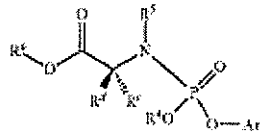
each Ar is a $(C_6$-$C_{20})$ aryl or heteroaryl wherein said $(C_6$-$C_{20})$ aryl or heteroaryl is substituted with one or more

halogen, NO_2, or $(C_1$-$C_8)$haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^n)_2$, $C(O)N(R^n)_2$, $OC(O)N(R^n)_2$, $C(O)OR^n$, $OC(O)OR^n$, $C(O)R^n$, $OC(O)R^n$, $S(O)_nR^n$, $S(O)_2N(R^n)_2$, OR^n or R^4 with the proviso that Ar is different from R^4;

said method comprising:

(d) providing a diastereomeric compound of Formula VIII

Formula VIII



and

(e) dissolving the compound of Formula VIII in a suitable solvent and inducing crystallization by addition of a C_5-C_{10} hydrocarbon or C_5-C_8 cyclic hydrocarbon;

thereby forming a pure diastereomer of Formula IIIa or Formula IIIb.

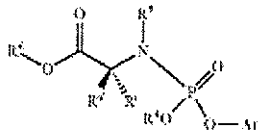
23. The method of claim **22** wherein the compound of Formula VIII is dissolved in an ether solvent and the crystallization is induced by addition of a C_5-C_8 hydrocarbon.

24. The method of claim **23** wherein the compound of Formula VIII is dissolved in diethyl ether or methyl-t-butyl ether and crystallization is induced by the addition of hexane.

25. The method of claim **24** wherein the compound of Formula VIII is dissolved in diethyl ether and crystallization is induced by the addition of hexane.

26. The method of claim **22** further comprising a method of preparing a compound of Formula VIII

Formula VIII



or a salt or ester thereof,

wherein

each R^a, R^4 or R^6 is independently $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

each R^c or R^d is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl provided that R^c and R^d are not the same;

each R^5 is independently H, $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl$(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl;

wherein each $(C_1$-$C_8)$alkyl, $(C_2$-$C_8)$alkenyl, $(C_2$-$C_8)$alkynyl, $(C_3$-$C_8)$carbocyclyl, $(C_4$-$C_8)$carbocyclylalkyl, aryl $(C_1$-$C_8)$alkyl, heterocyclyl$(C_1$-$C_8)$alkyl, $(C_6$-$C_{20})$aryl, $(C_2$-$C_{20})$heterocyclyl or heteroaryl of each R^c, R^d, R^4, R^5 or R^6 is, independently, optionally substituted with one or more halo, hydroxy, CN, N_3, $N(R^n)_2$, $NH(R^n)$, NH_2, $C(O)N(R^n)_2$, $C(O)NH(R^n)$, $C(O)NH_2$, $OC(O)N$

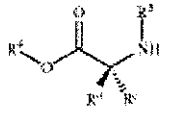
$(R^a)_2$, $OC(O)NH(R^a)$, $OC(O)NH_2$, $C(O)OR^a$, $OC(O)OR^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, $S(O)_2NH(R^a)$, $S(O)_2NH_2$, OR^a or R^a; and

each Ar is a (C_6-C_{20}) aryl or heteroaryl wherein said (C_6-C_{20}) aryl or heteroaryl is substituted with one or more halogen, NO_2, or (C_1-C_6)haloalkyl and optionally substituted with with one or more CN, N_3, $N(R^a)_2$, $C(O)N(R^a)_2$, $OC(O)N(R^a)_2$, $C(O)OR^a$, $OC(O)OR^a$, $C(O)R^a$, $OC(O)R^a$, $S(O)_nR^a$, $S(O)_2N(R^a)_2$, OR^a or R^a with the proviso that Ar is different from R^4;

said method comprising:

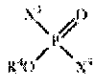
(f) providing a chirally pure amino acid ester of Formula IX or a salt thereof

Formula IX



(g) treating the compound of Formula IX with a compound of Formula X in the presence of a base

Formula X



wherein each X^1 is halogen; and

(h) treating the resulting mixture with ArOH;

thereby forming a compound of Formula VIII.

27. The method of claim **22** wherein R^5 is H and one of R^c or R^d is H.

28. The method of claim **22** wherein R^6 is optionally substituted (C_1-C_8)alkyl and R^4 is optionally substituted (C_6-C_{20})aryl.

29. The method of claim **22** wherein R^4 is optionally substituted phenyl.

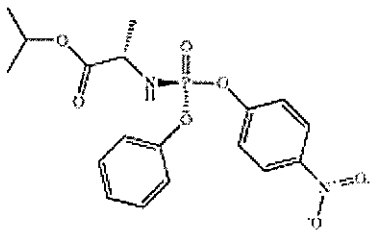
30. The method of claim **22** wherein one of R^c or R^d is H and the other of R^c or R^d is CH_3.

31. The method of claim **22** wherein Ar is optionally substituted para-nitrophenyl.

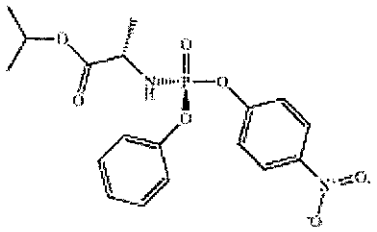
32. The method of claim **22** wherein the chirality at the carbon directly attached to R^c and R^d is S.

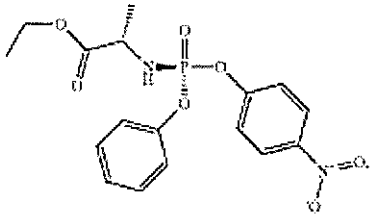
33. The method of claim **22** wherein the chirality at the carbon directly attached to R^c and R^d is R.

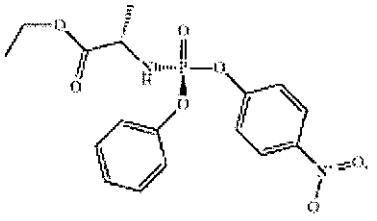
34. The method of claim **22** wherein the compound is selected from the group consisting of

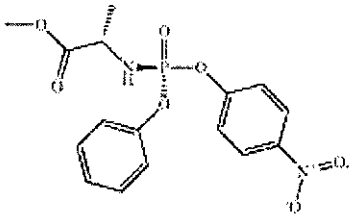


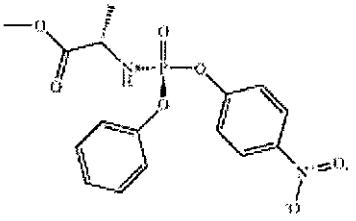
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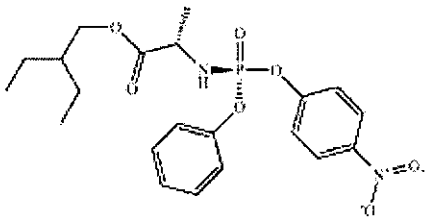




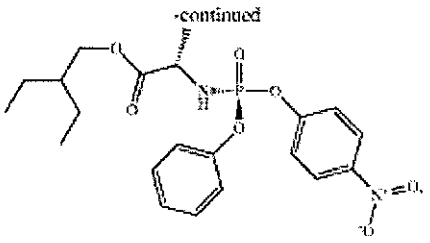


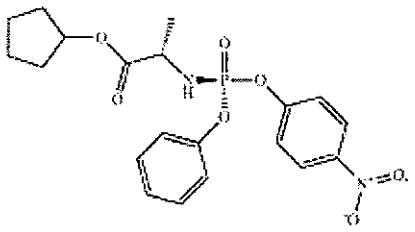


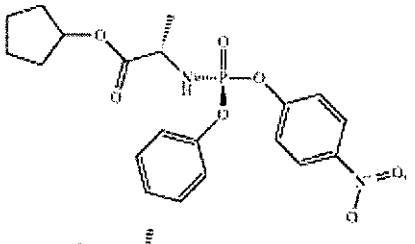


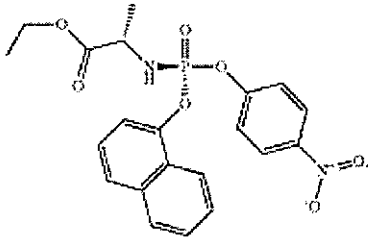


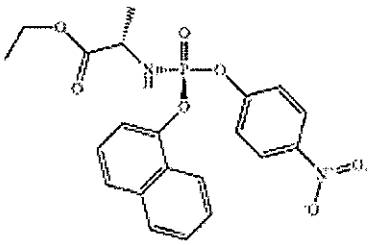
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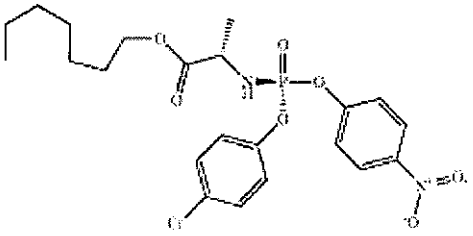




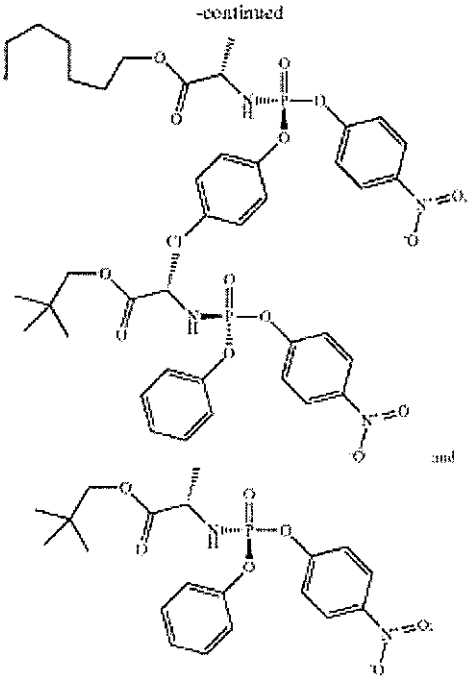








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and

or salts or esters thereof.

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