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(54) Titre : COMPOSES DE PHOSPHONATE PRESENTANT UNE ACTIVITE IMMUNOMODULATRICE
(54) Title: IMMUNOMODULATOR PHOSPHONATE CONJUGATES

(57) Abrégé/Abstract:
The invention is related to phosphonate substituted compounds having immuno-modulatory activity, compositions containing such compounds, and therapeutic methods that include the administration of such compounds, as well as to processes and intermediates useful for preparing such compounds.

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2003/08/15 (60/495,533) US; 2003/08/15 (60/495,529) US; 2003/08/15 (60/495,427) US; 2003/08/15 (60/495,456) US;
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[Continued on next page]

(54) Title: IMMUNOMODULATOR PHOSPHONATE CONJUGATES

(57) Abstract: The invention is related to phosphonate substituted compounds having immuno-modulatory activity, compositions containing such compounds, and therapeutic methods that include the administration of such compounds, as well as to processes and intermediates useful for preparing such compounds.

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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JUMBO APPLICATIONS/PATENTS

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CONTAINING PAGES	1	TO	359

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NOM DU FICHIER / FILE NAME :

NOTE POUR LE TOME / VOLUME NOTE:

PHOSPHONATE COMPOUNDS HAVING IMMUNO-MODULATORY ACTIVITY

This non-provisional application claims the benefit of priority under 35 U.S.C. § 119(e) from U.S. Provisional Patent Application Serial Nos. 60/465424, 60/465373, 60/465420, 60/465380, 60/465433, 60/465481, 60/465377, 60/465581, 60/465532, 60/465844, 60/465531, and 60/465574, all filed April 25, 2003; and to U.S. Provisional Patent Application Serial Nos. 60/493303, 60/493310, 60/493309, and 60/493302, all filed August 7, 2003; and to U.S. Provisional Patent Application Serial Nos. 60/495533, 60/495529, 60/495455, 60/495537, 60/495456, 60/495398, 60/495425, 60/495427, 60/495661, 60/495393, 60/495416, 60/495614, and 60/495417, all filed August 15, 2003; and to U.S. Provisional Patent Application Serial Nos. 60/514054, 60/513971, 60/514394, 60/513975, 60/514453, 60/514202, 60/513948, 60/514424, 60/514280, 60/514144, 60/513979, 60/514075, 60/513946, 60/514051, 60/514161, 60/514325, 60/514044, 60/514201, 60/514522, 60/514140, 60/514175, 60/514113, 60/513562, 60/513592, 60/513563, 60/513579, 60/513561, 60/513589, 60/513593, 60/513588, 60/514258, 60/514021, and 60/514298, all filed October 24, 2003; and to U.S. Provisional Patent Application Serial Nos. 60/532230, 60/531960, 60/532160, 60/531940, and 60/531932, all filed December 1, 2003; and to U.S. Provisional Patent Application Serial No. 60/532591, filed December 23, 2003; and to U.S. Provisional Patent Application Serial No. 60/536005, filed January 12, 2004. The entirety of all Provisional Applications listed above are incorporated herein by reference.

FIELD OF THE INVENTION

The invention relates generally to compounds with immuno-modulatory (*e.g.*, immunosuppressant) activity.

BACKGROUND OF THE INVENTION

Improving the delivery of drugs and other agents to target cells and tissues has been the focus of considerable research for many years. Though many attempts have been made to develop effective methods for importing biologically active molecules into cells, both *in vivo* and *in vitro*, none has proved to be entirely satisfactory. Optimizing the association of the inhibitory drug with its intracellular target, while minimizing intercellular redistribution of the drug, e.g., to neighboring cells, is often difficult or inefficient.

Most agents currently administered to a patient parenterally are not targeted, resulting in systemic delivery of the agent to cells and tissues of the body where it is unnecessary, and often undesirable. This may result in adverse drug side effects, and often limits the dose of a drug (e.g., glucocorticoids and other anti-inflammatory drugs) that can be administered. By comparison, although oral administration of drugs is generally recognized as a convenient and economical method of administration, oral administration can result in either (a) uptake of the drug through the cellular and tissue barriers, e.g., blood/brain, epithelial, cell membrane, resulting in undesirable systemic distribution, or (b) temporary residence of the drug within the gastrointestinal tract. Accordingly, a major goal has been to develop methods for specifically targeting agents to cells and tissues. Benefits of such treatment includes avoiding the general physiological effects of inappropriate delivery of such agents to other cells and tissues, such as uninfected cells.

Autoimmune diseases and transplantation rejection remain major public health problems worldwide. Although drugs with immunosuppressive activity are in wide use and have shown effectiveness, there clinical usefulness has been limited due to their toxicity and other side effects. Currrently tthere is a need for new immunosuppressant agents, i.e. drugs, having improved immunosuppressant activity and pharmacokinetic properties, improved oral bioavailability, greater potency, and extended effective half-life *in vivo*. New immunosuppressant agents should have fewer side effects, less complicated dosing schedules, and/or be orally active.

SUMMARY OF THE INVENTION

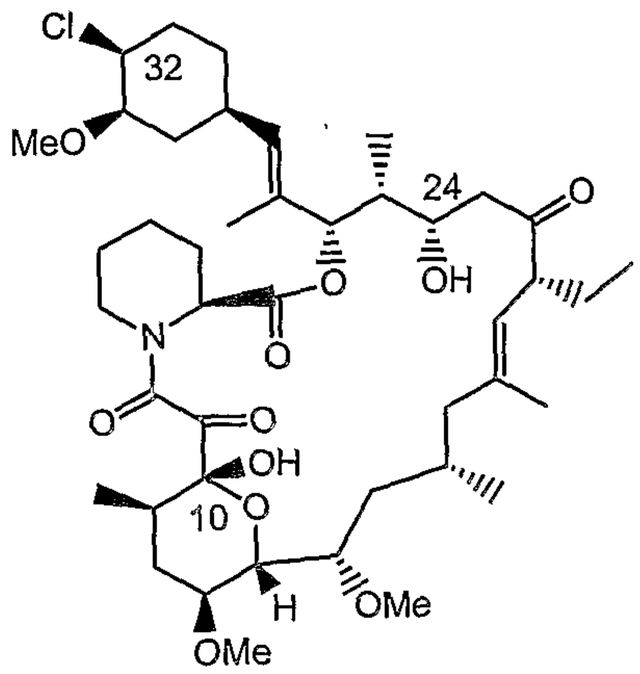
Intracellular targeting may be achieved by methods and compositions that allow accumulation or retention of biologically active agents inside cells. The present invention provides novel phosphonate containing analogs of immuno-modulatory (*e.g.*, immunosuppressant) compounds. These compounds possess the utilities of the related immuno-modulatory compounds, but due to the presence of the phosphonate group(s) they typically provide cellular accumulation of the phosphonate compound. Thus, compounds of the invention may demonstrate improved immuno-modulatory properties, pharmacokinetic properties, oral bioavailability, potency, or extended effective half-life *in vivo,* or a combination thereof. The compounds of the invention may also have distinct resistance profiles, fewer side effects, less complicated dosing schedules, or have increased oral activity.

The present invention relates generally to the accumulation or retention of therapeutic compounds inside cells. The invention is more particularly related to attaining high concentrations of phosphonate-containing molecules in target cells. Such effective targeting may be applicable to a variety of therapeutic formulations and procedures.

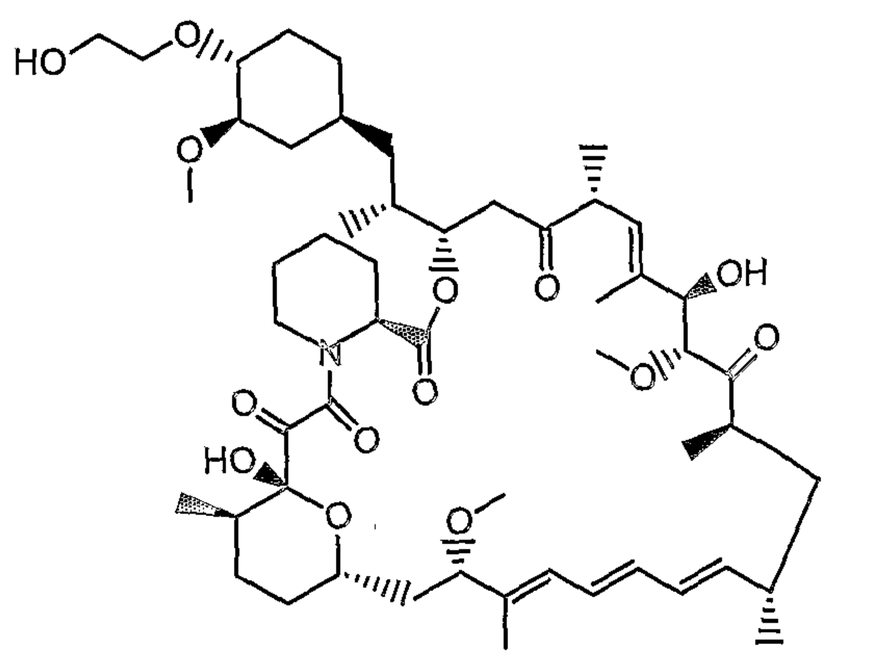
Accordingly, in one embodiment the invention provides a compound of the invention which is a conjugate comprising an immuno-modulatory compound (*e.g.*, an immunosuppressant compound) linked to one or more phosphonate groups.

Compositions of the invention include immuno-modulatory compounds having at least one phosphonate group. Accordingly, in one embodiment the invention provides a conjugate comprising an immuno-modulatory compound (*e.g.*, an immunosuppressant compound) linked to one or more phosphonate groups or a pharmaceutically acceptable salt thereof.

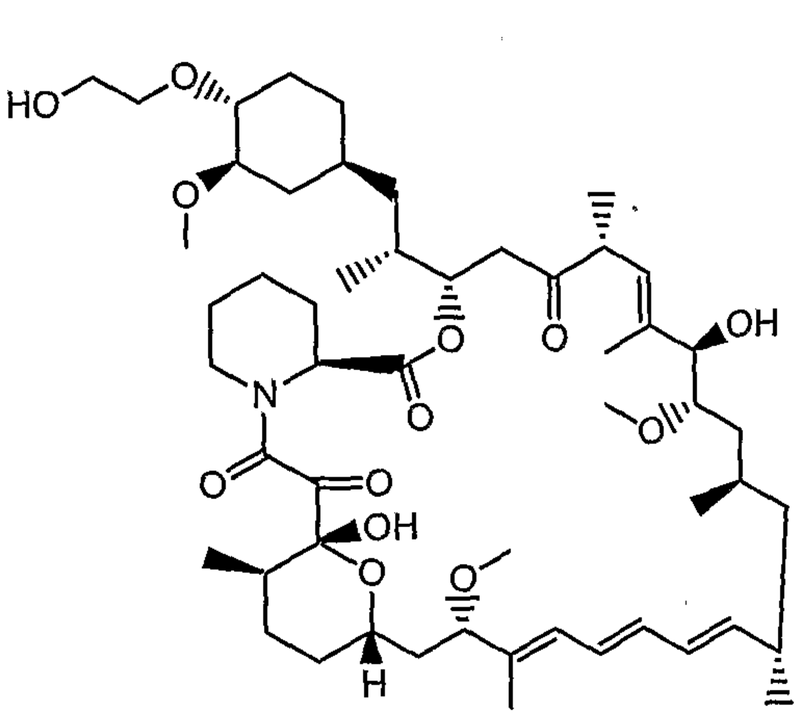
In another embodiment the invention provides a compound of any one of formulae **500-547:**



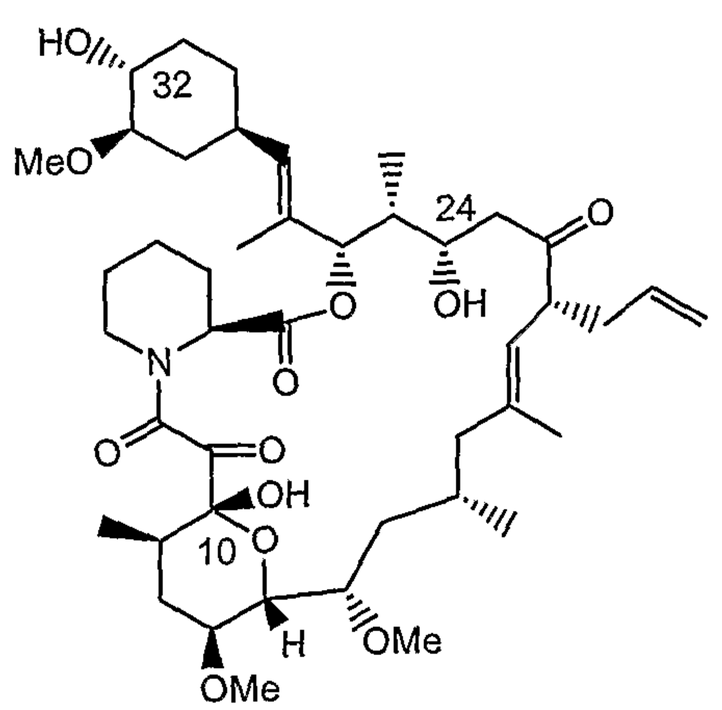
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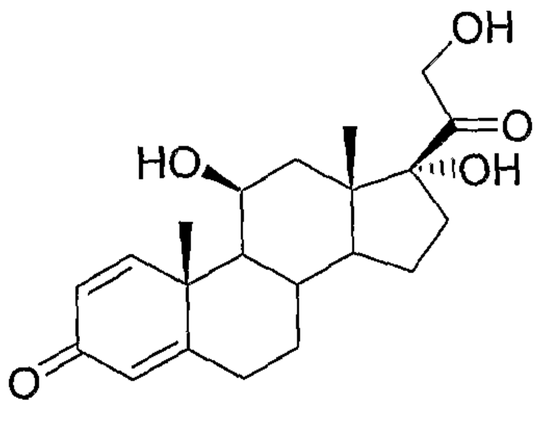


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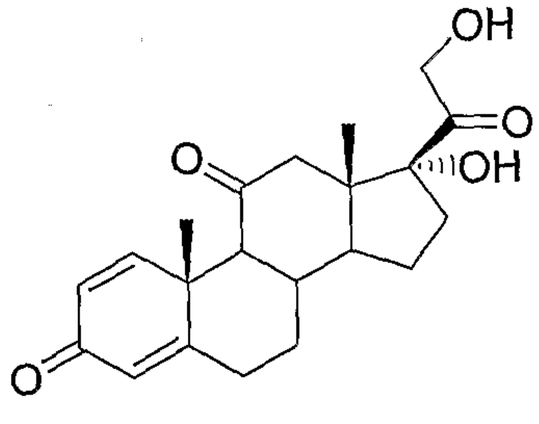


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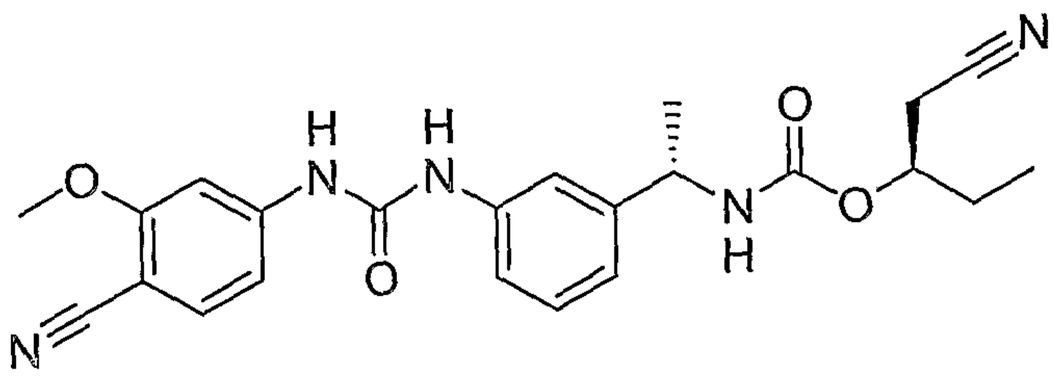
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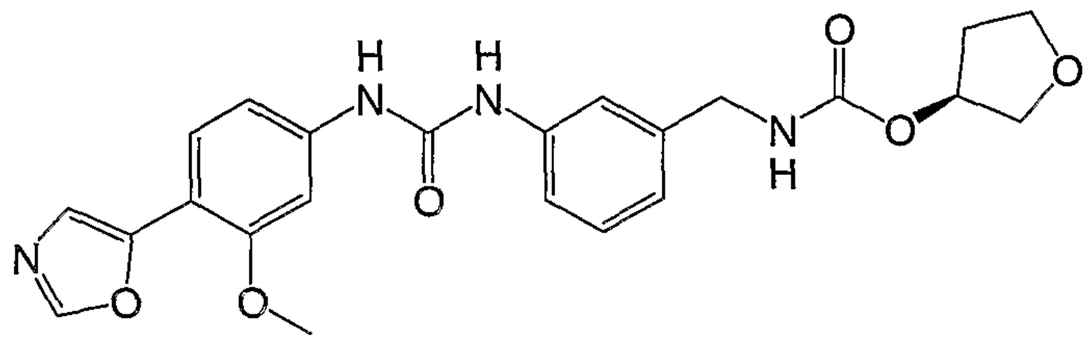


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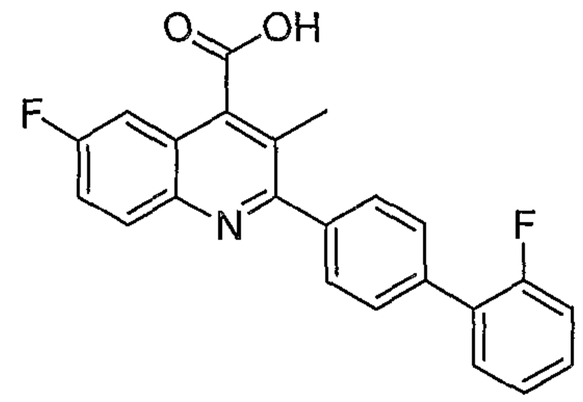


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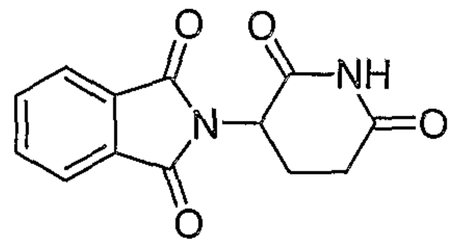
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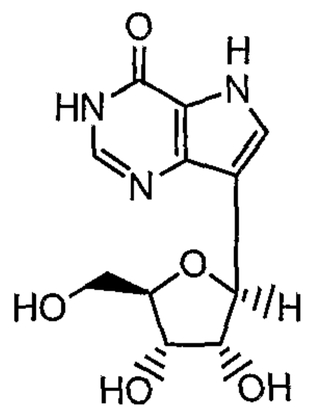
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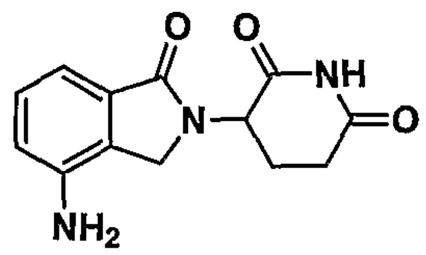
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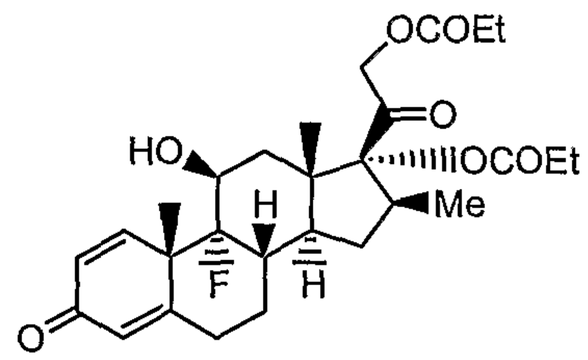
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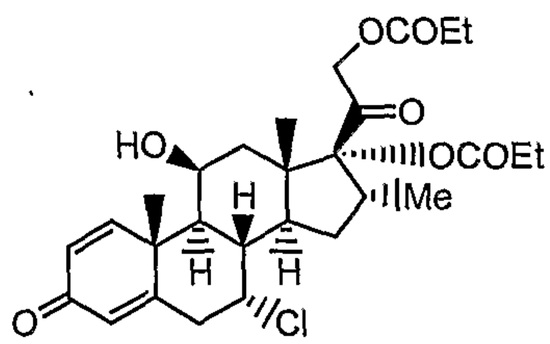
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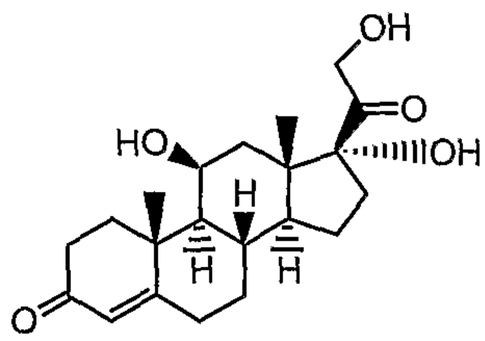
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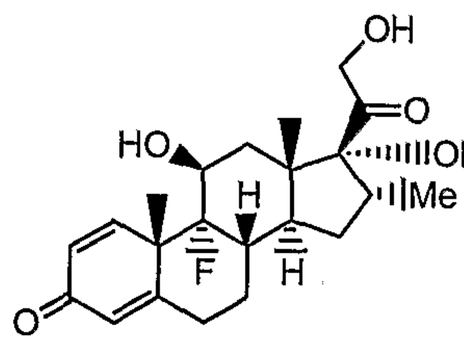
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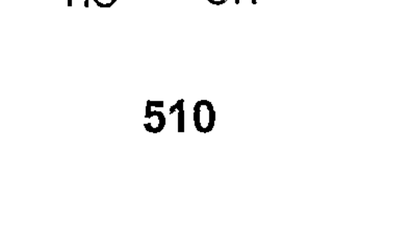
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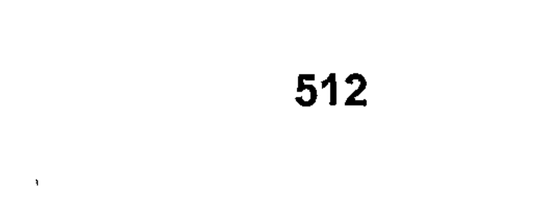
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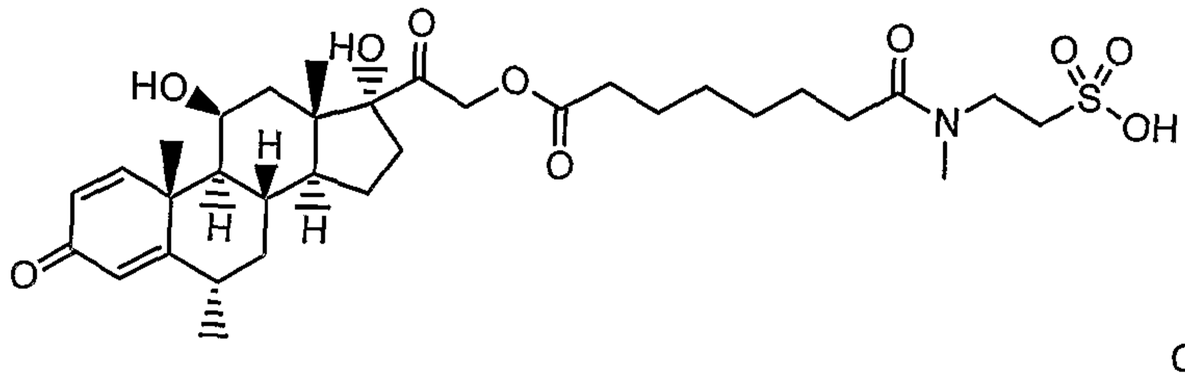
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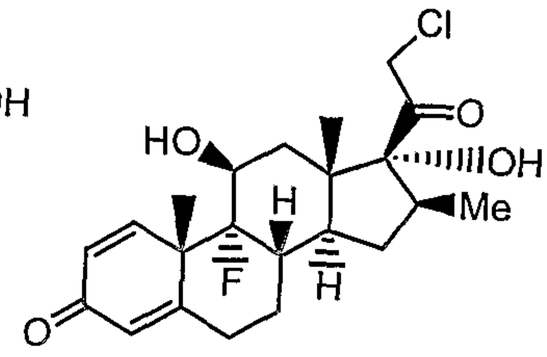
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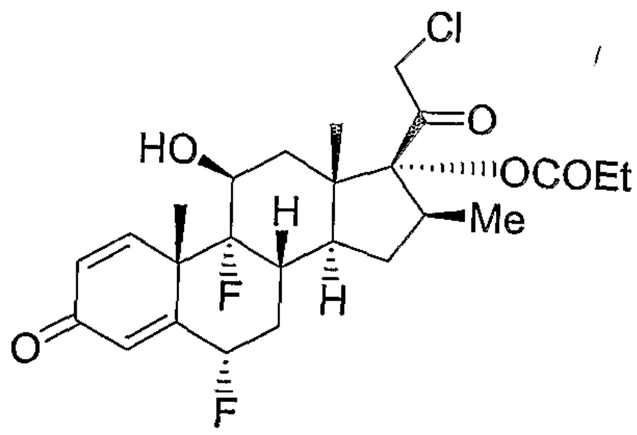
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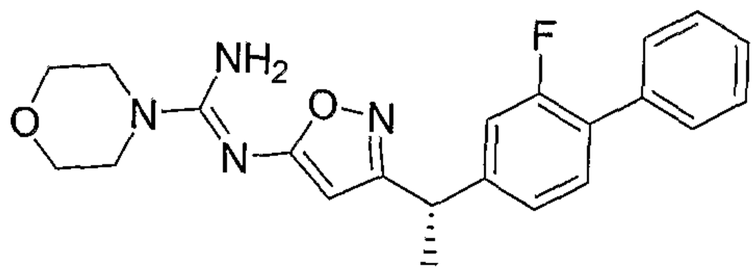
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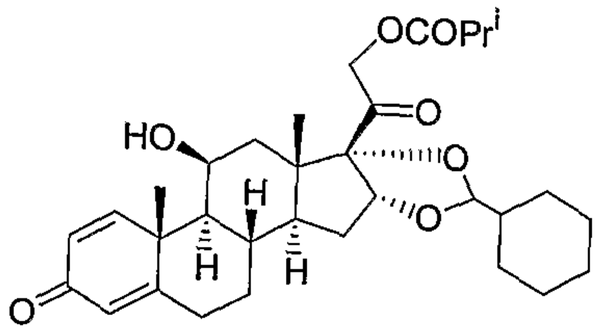
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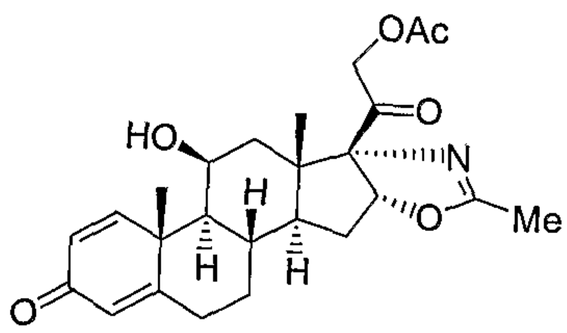
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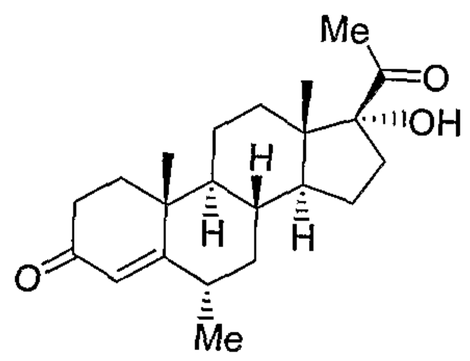
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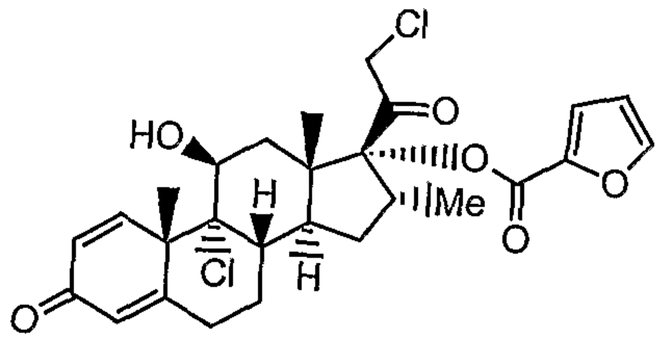
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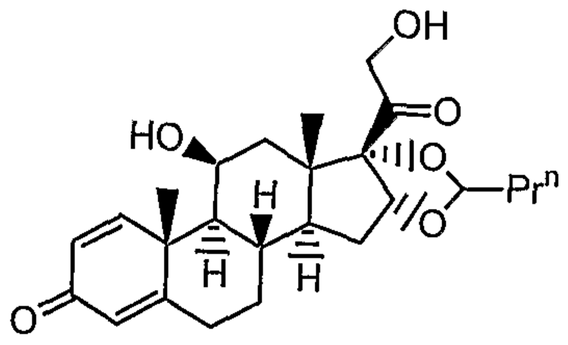
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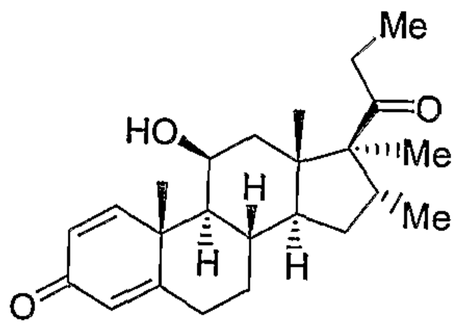
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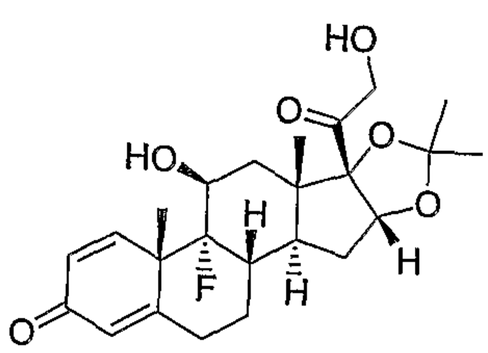
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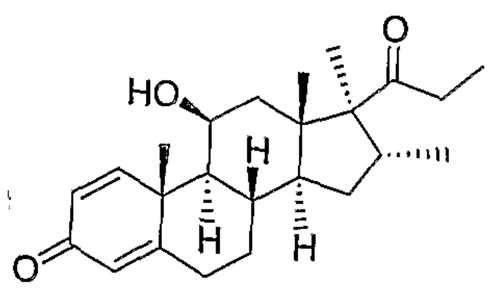
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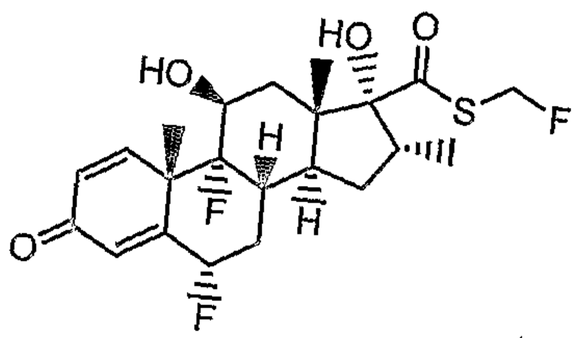
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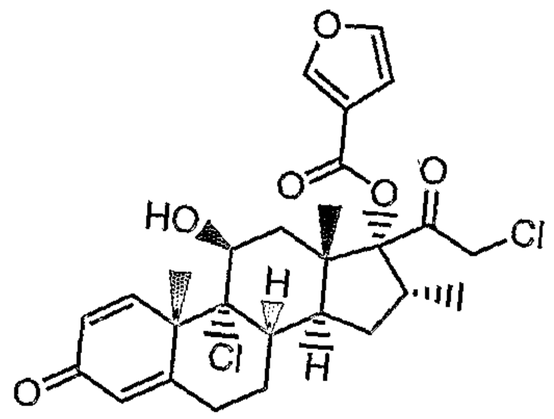
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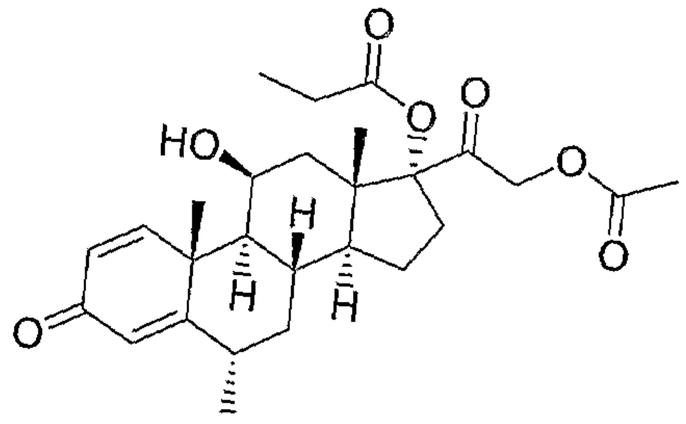
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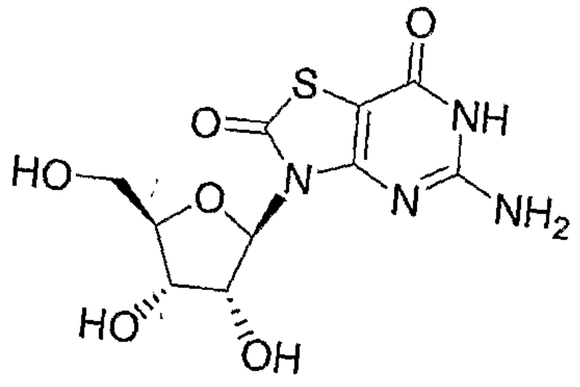
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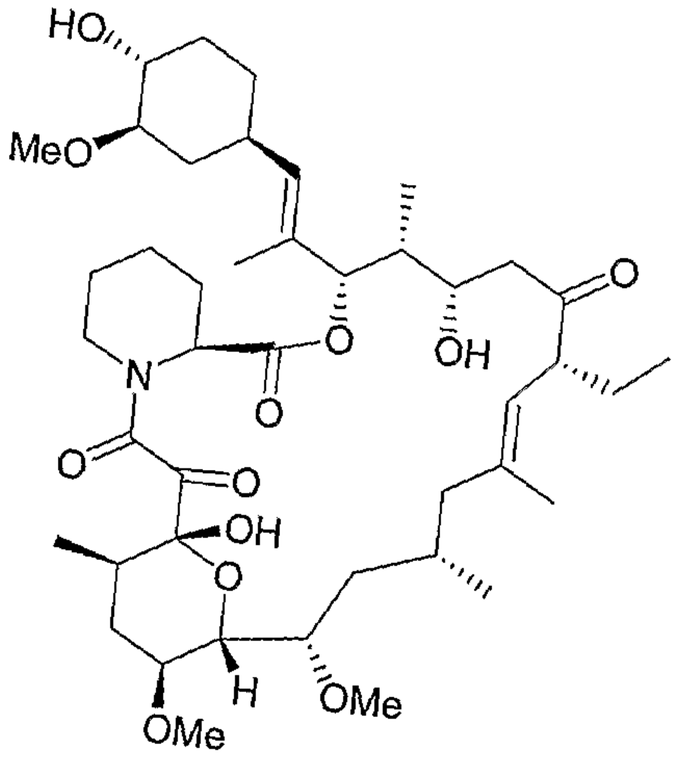
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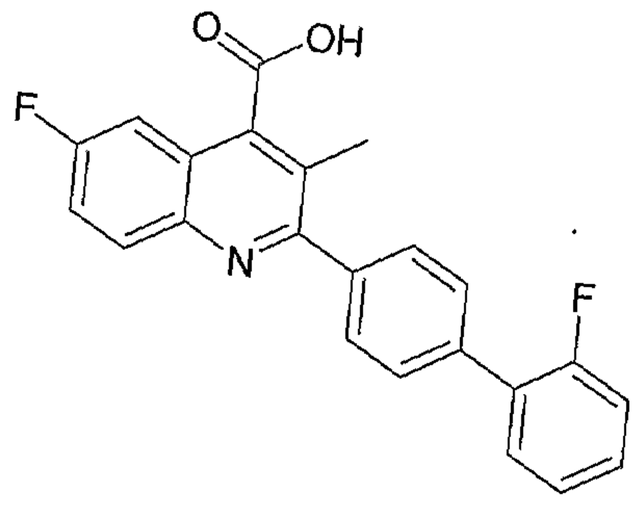
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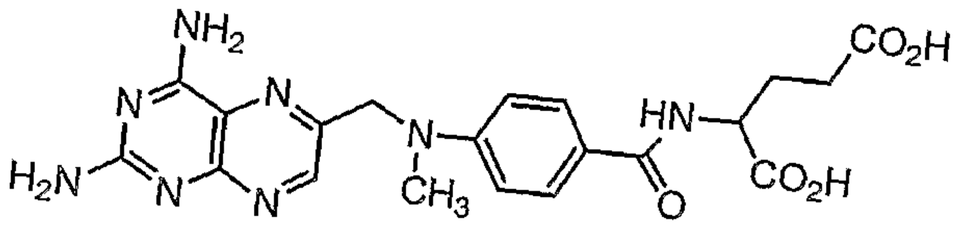
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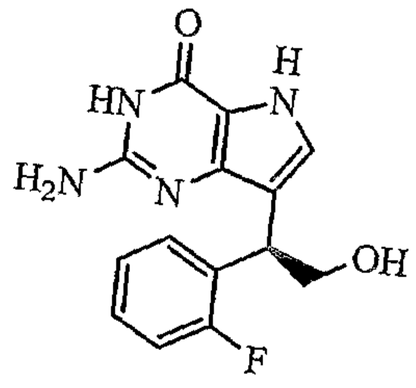
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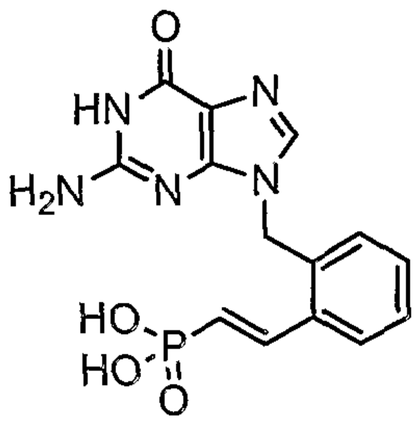
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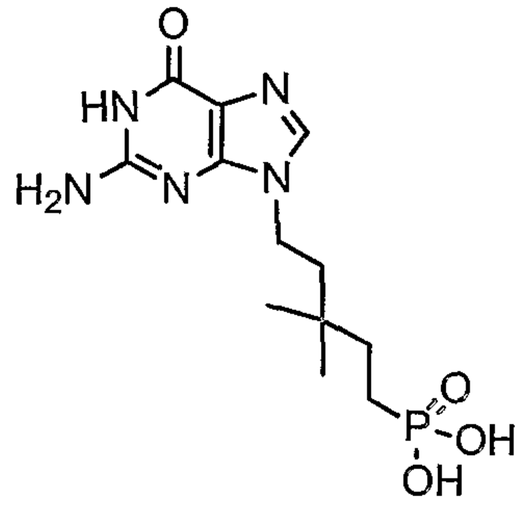
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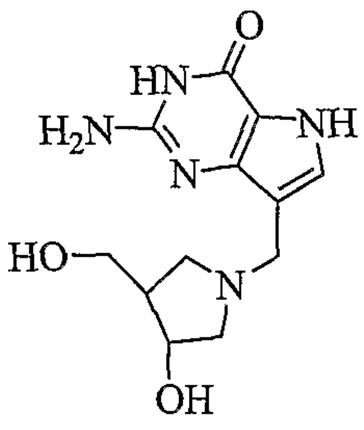
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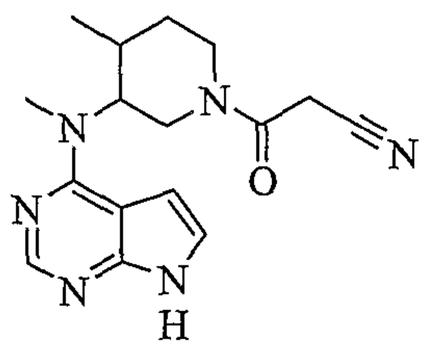
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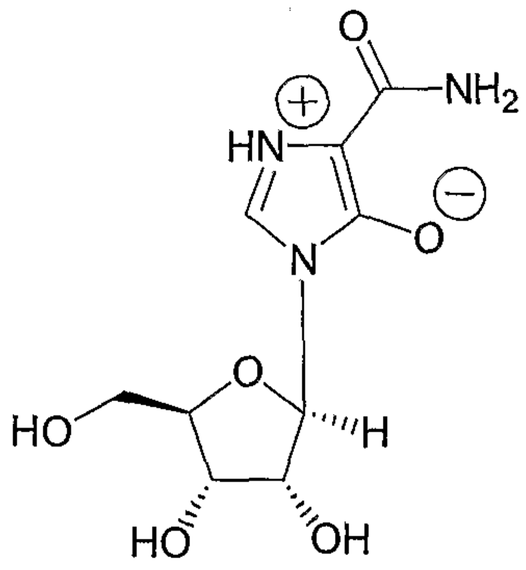
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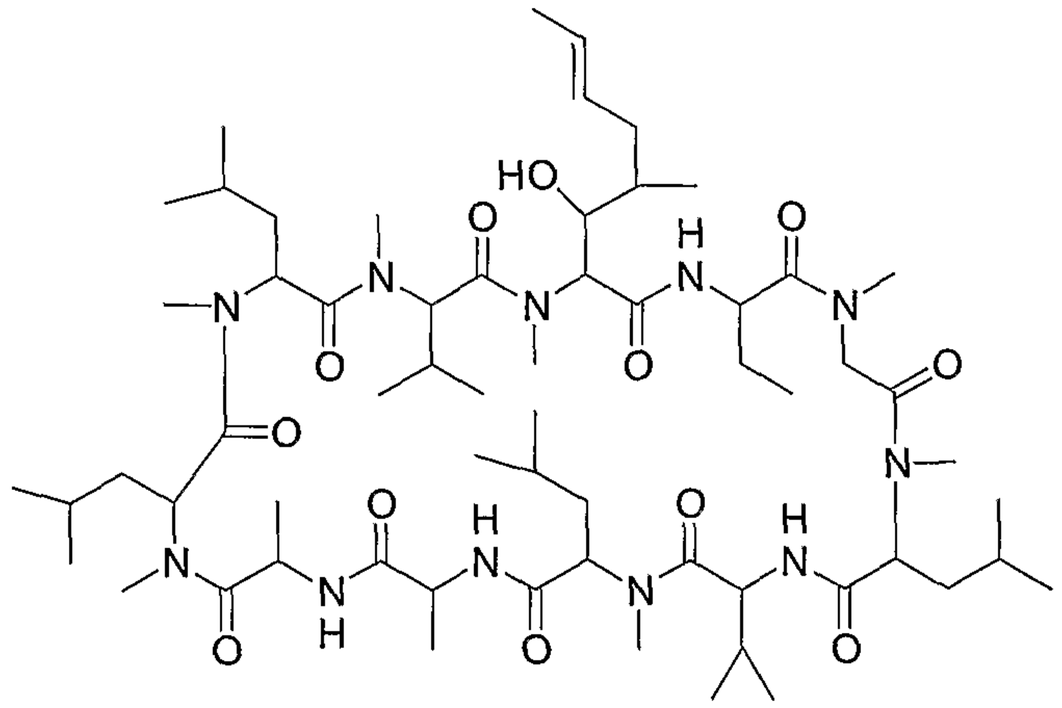
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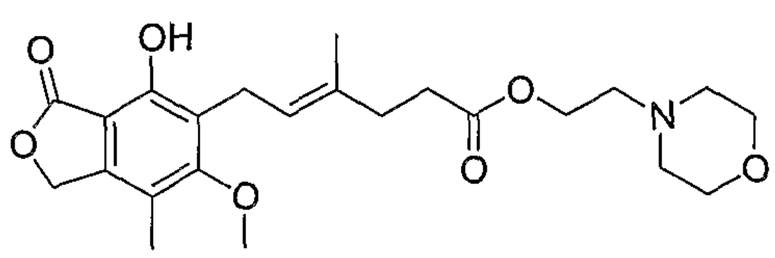
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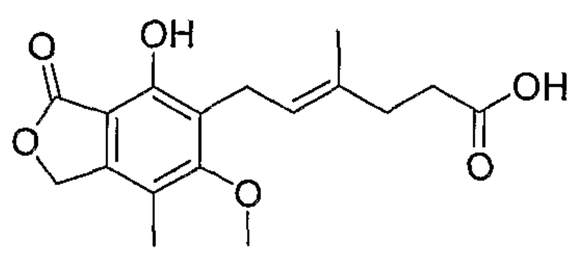
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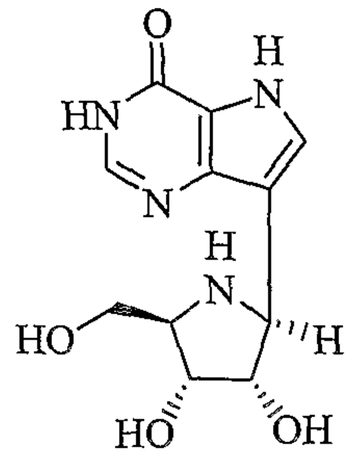
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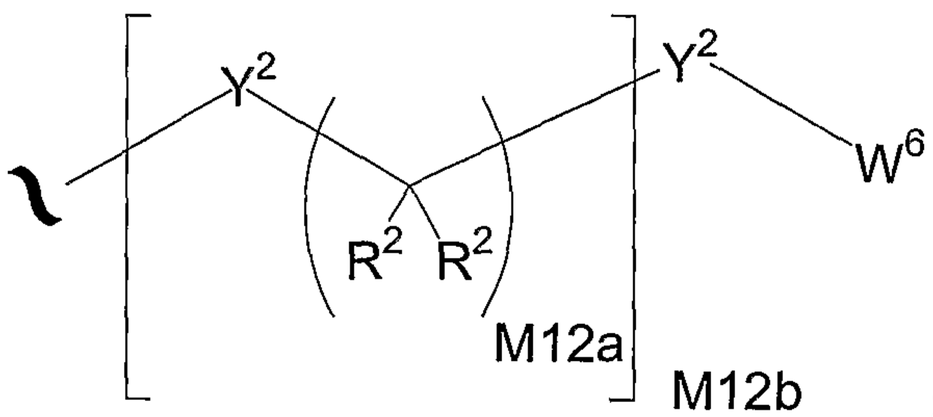


547

that is substituted with one or more phosphonate groups either directly or indirectly through a linker; and that is optionally substituted with one or more groups A^0; or a pharmaceutically acceptable salt thereof, wherein:

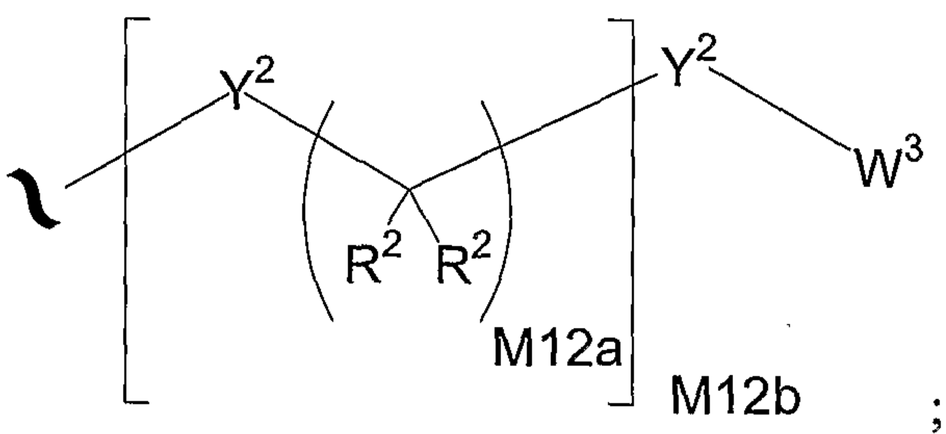
A^0 is A^1, A^2 or W^3 with the proviso that the conjugate includes at least one A^1;

A^1 is:



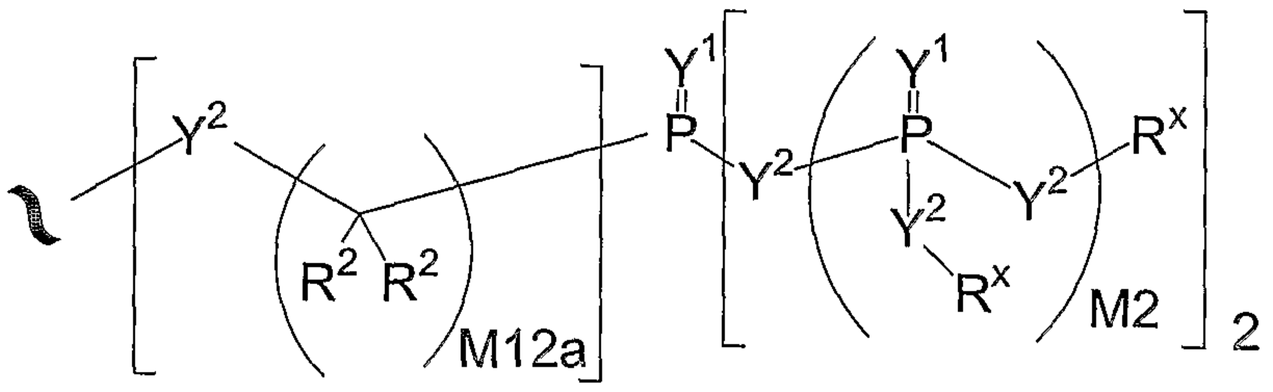
;

A^2 is:



;

A^3 is:

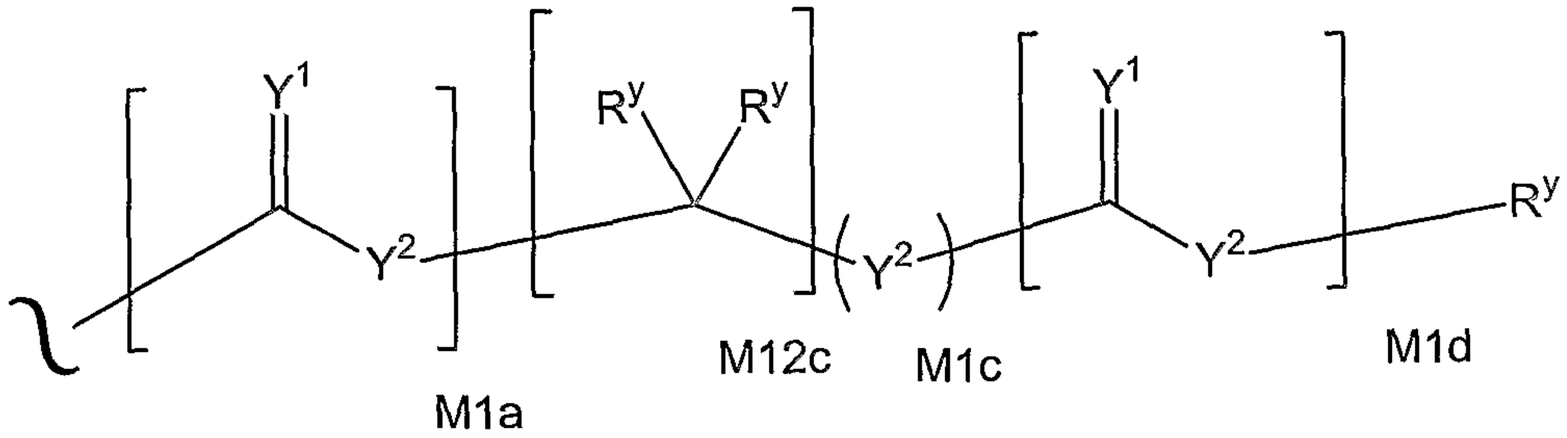


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^1, R^2, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another embodiment the invention provides a compound of the formula:

$$[DRUG]\text{-}(A^0)_{nn}$$

or a pharmaceutically acceptable salt thereof wherein;

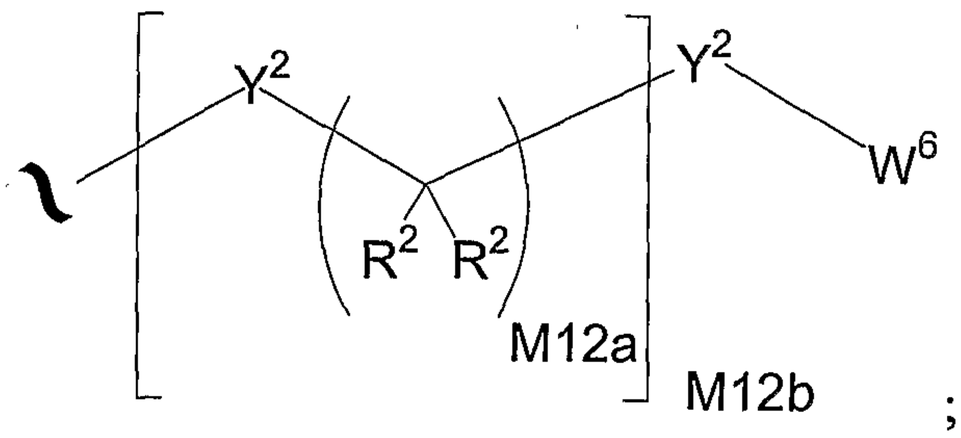
DRUG is a compound of any one of formulae **500-547**;

nn is 1, 2, or 3;

wherein:

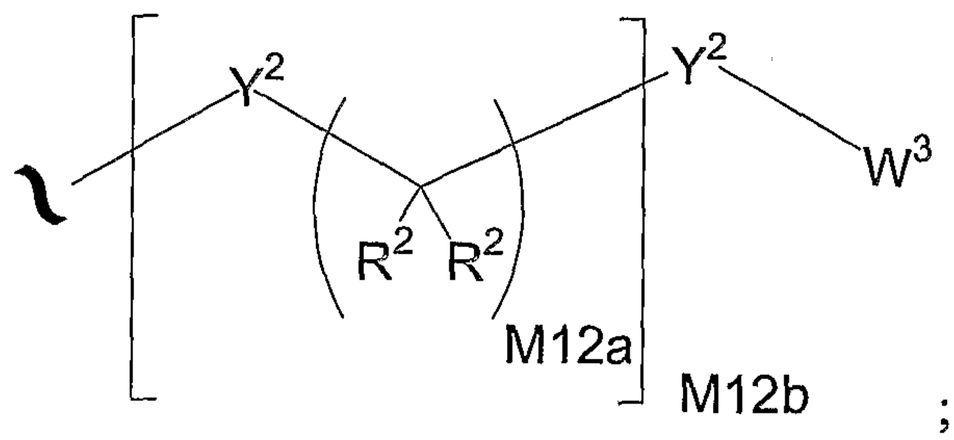
A^0 is A^1, A^2 or W^3 with the proviso that the conjugate includes at least one A^1;

A^1 is:



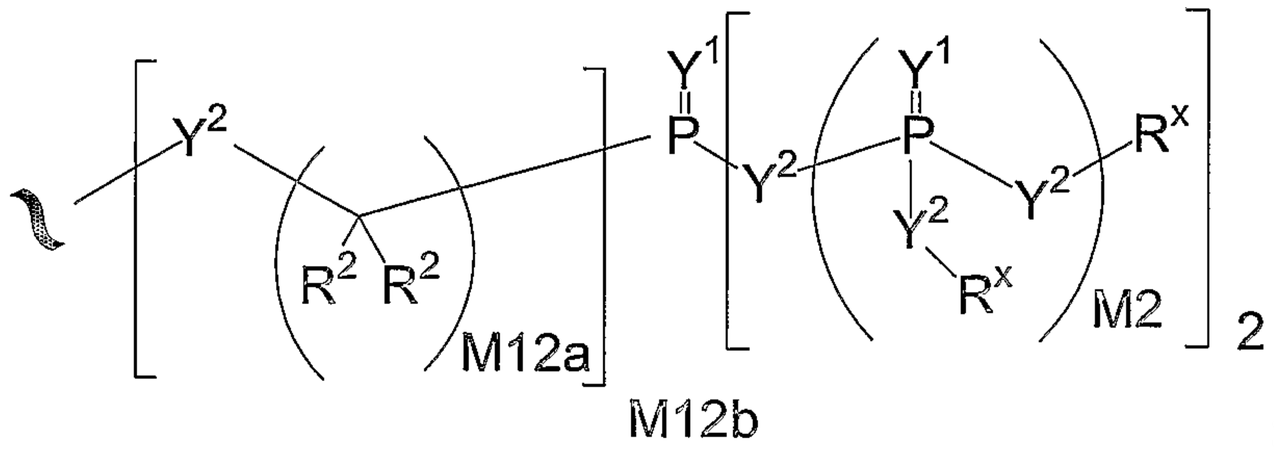
;

A^2 is:



;

A^3 is:

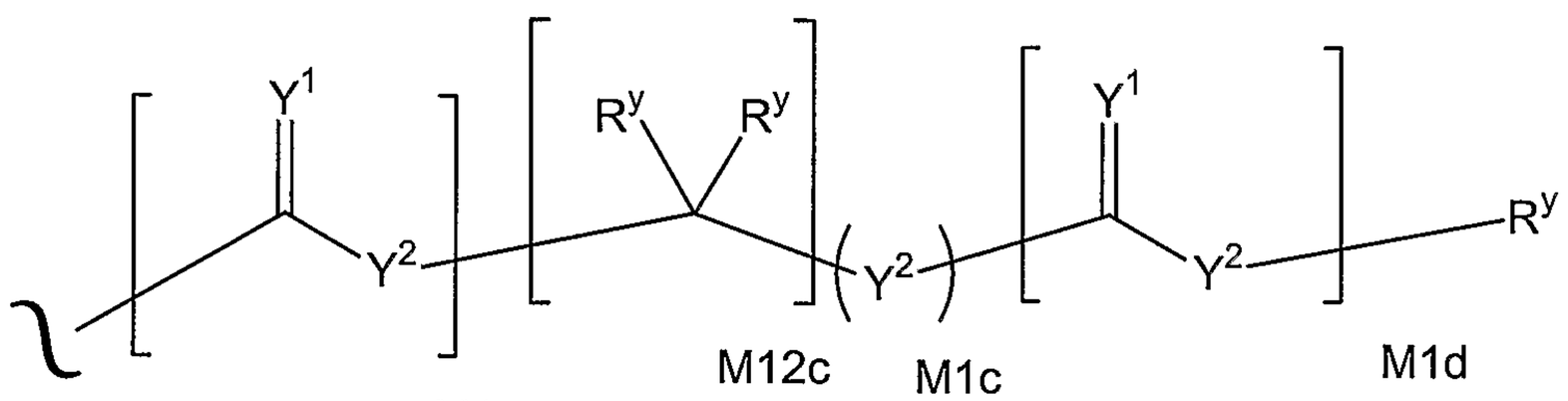


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^1, R^2, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

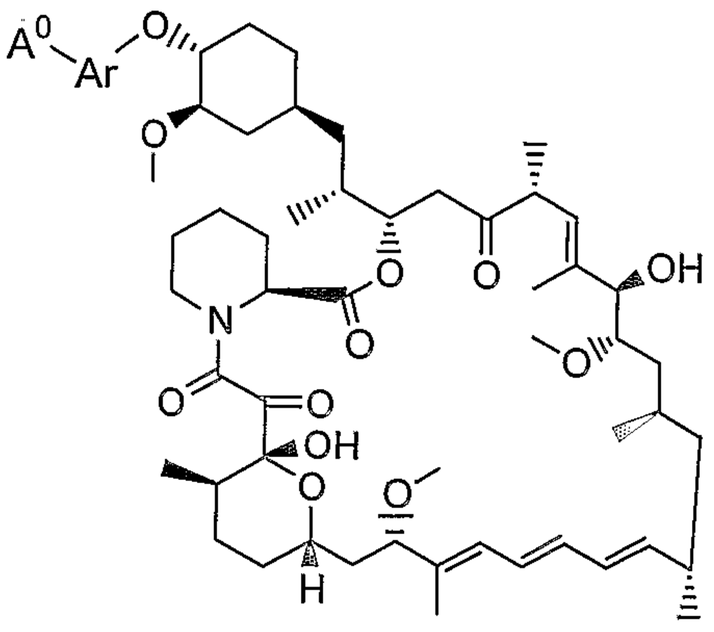
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

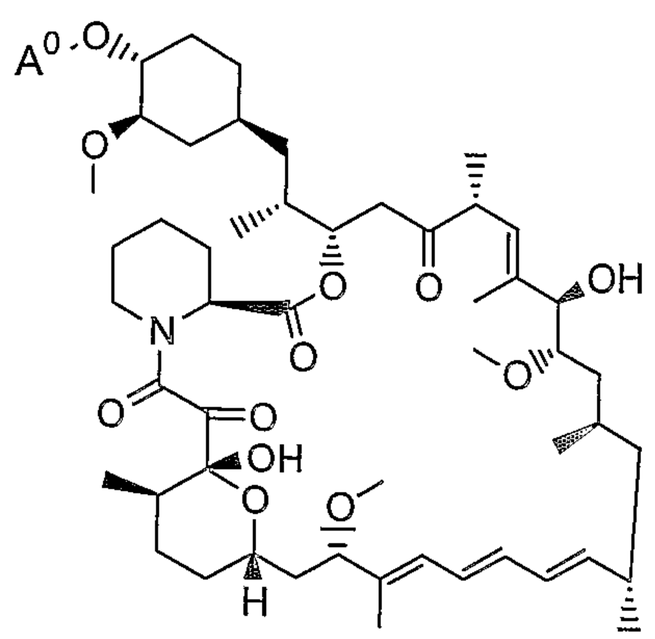
M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

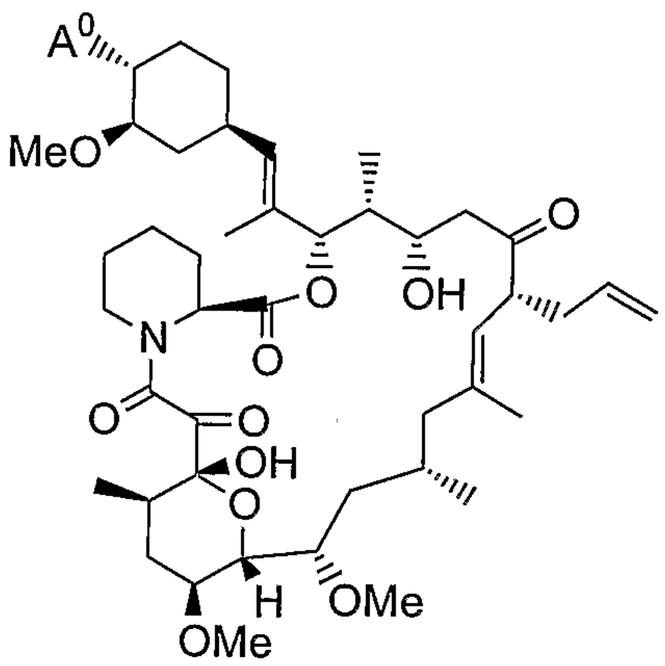
In another embodiment the invention provides a compound of any one of formulae **1-151:**



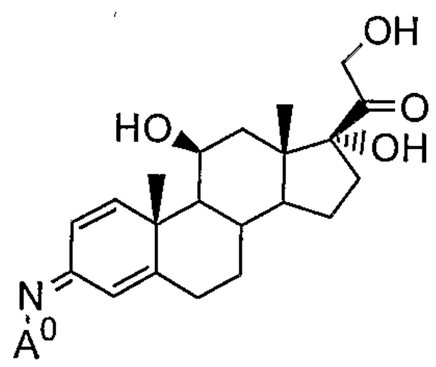
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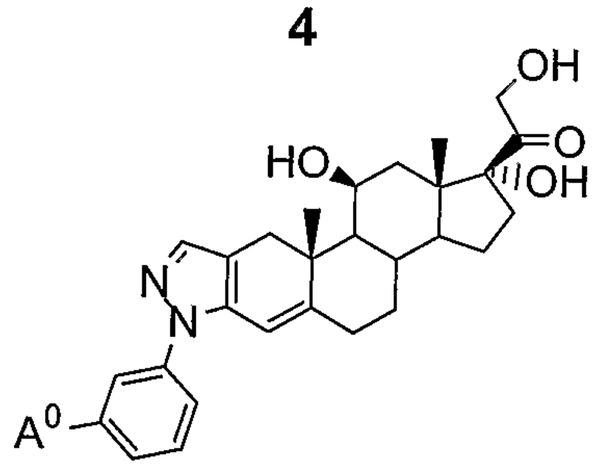
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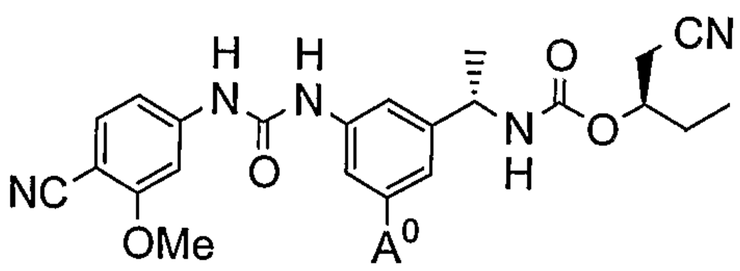
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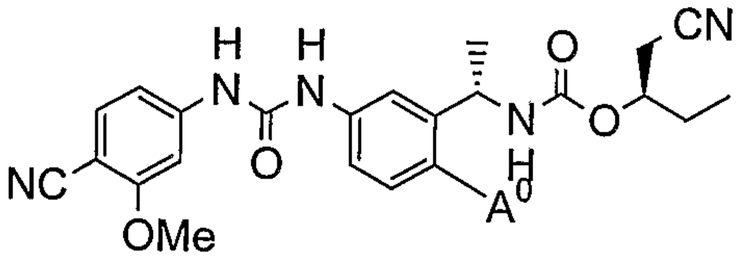
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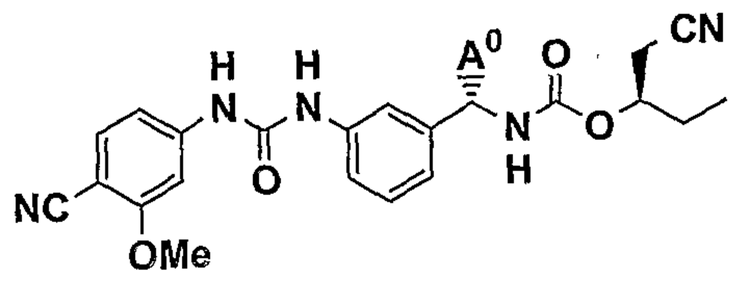
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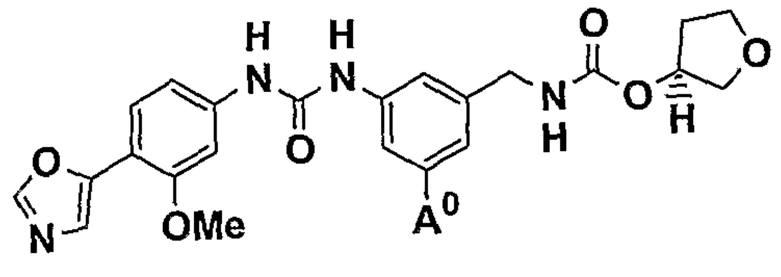
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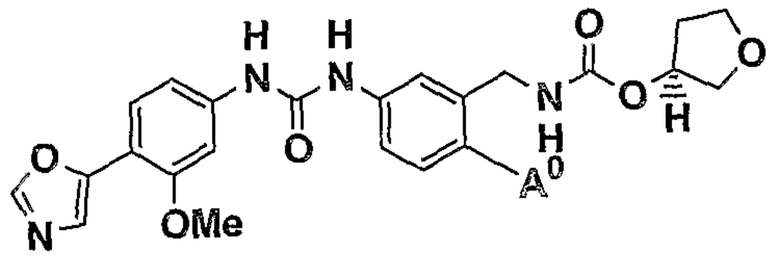
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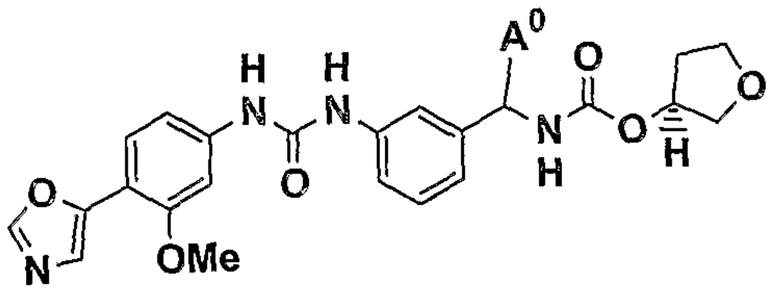
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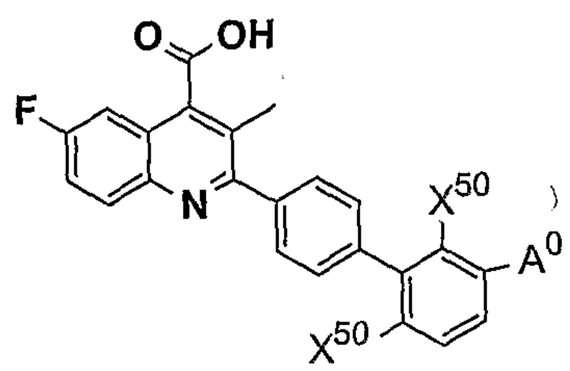
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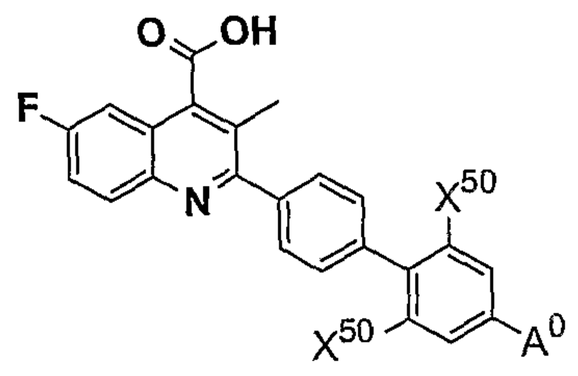
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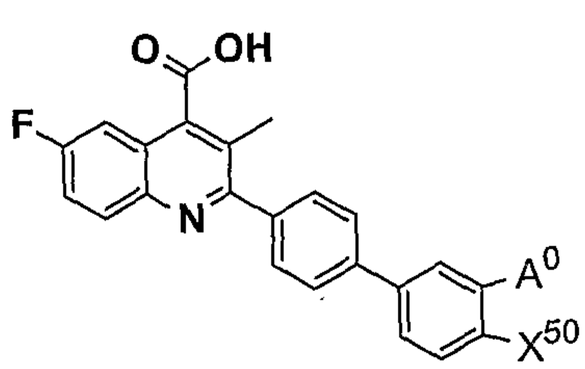
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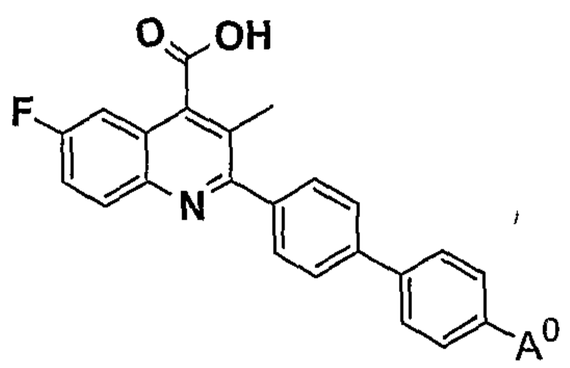
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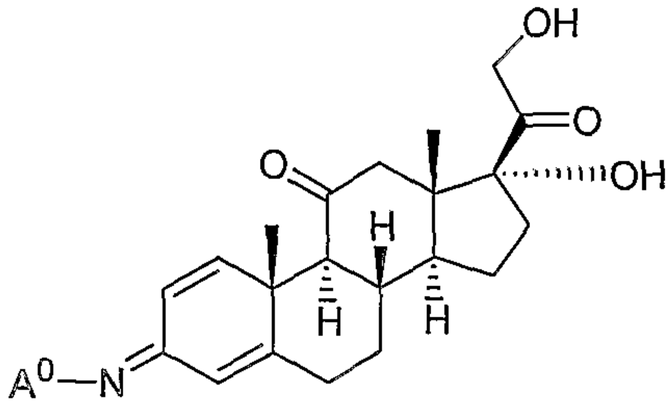
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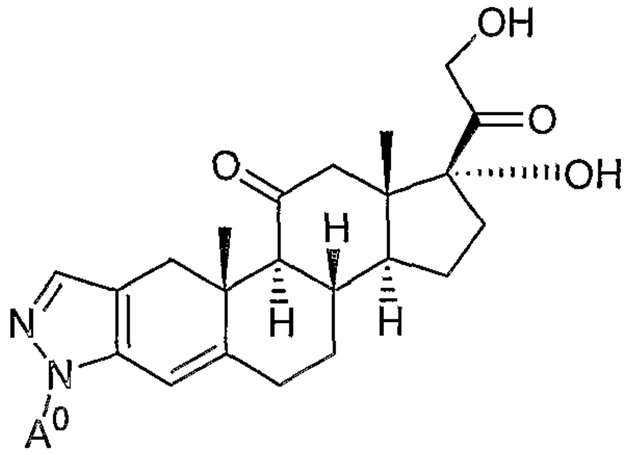
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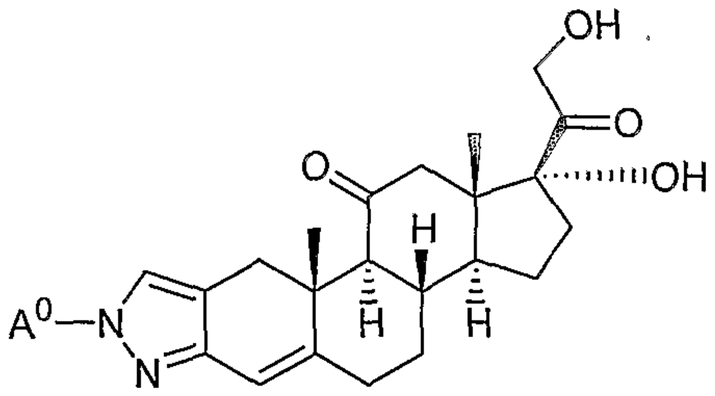
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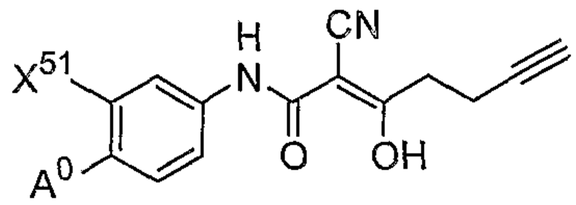
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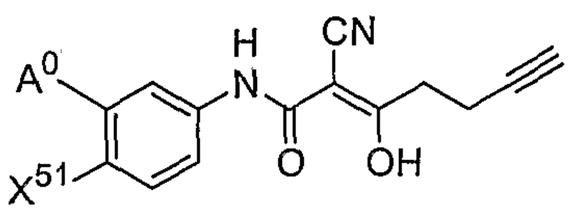
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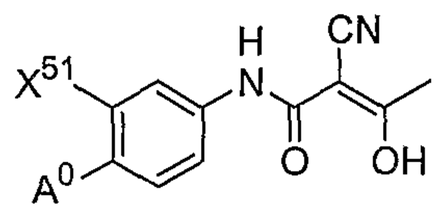
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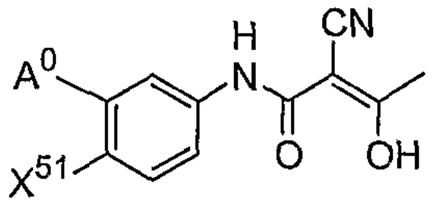
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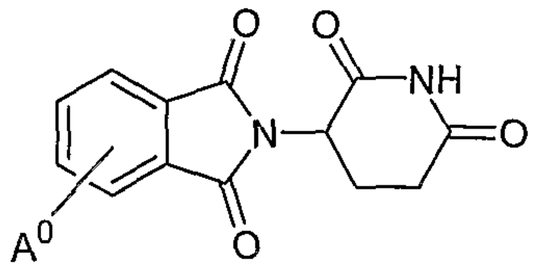
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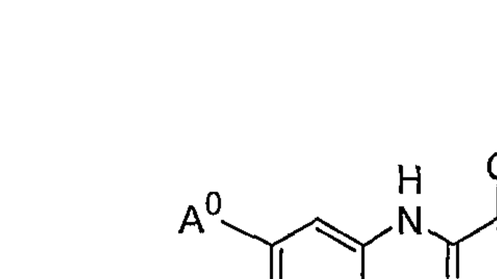
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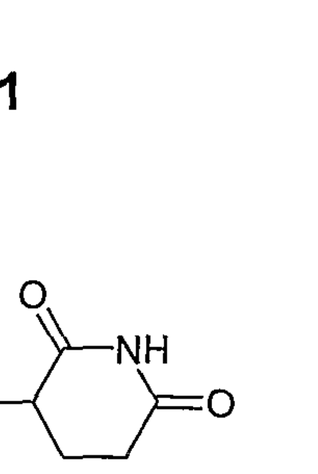
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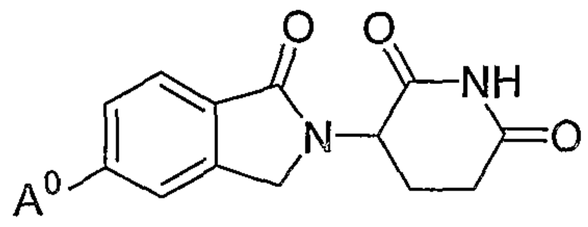
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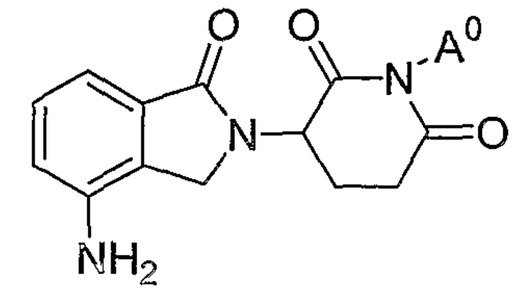
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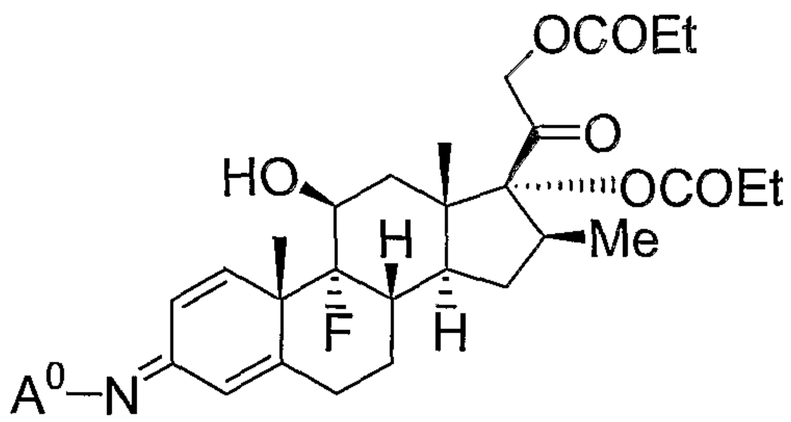
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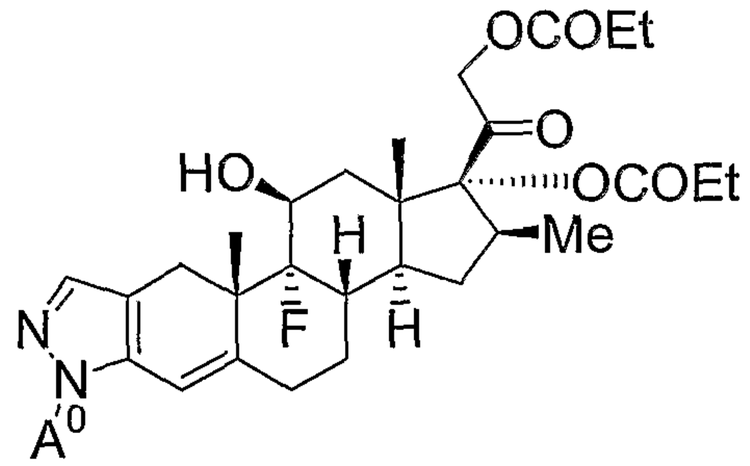
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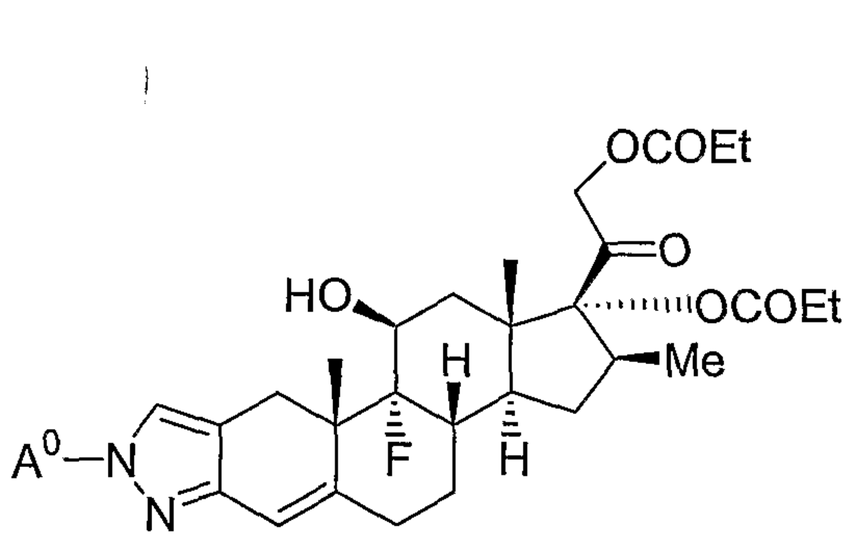
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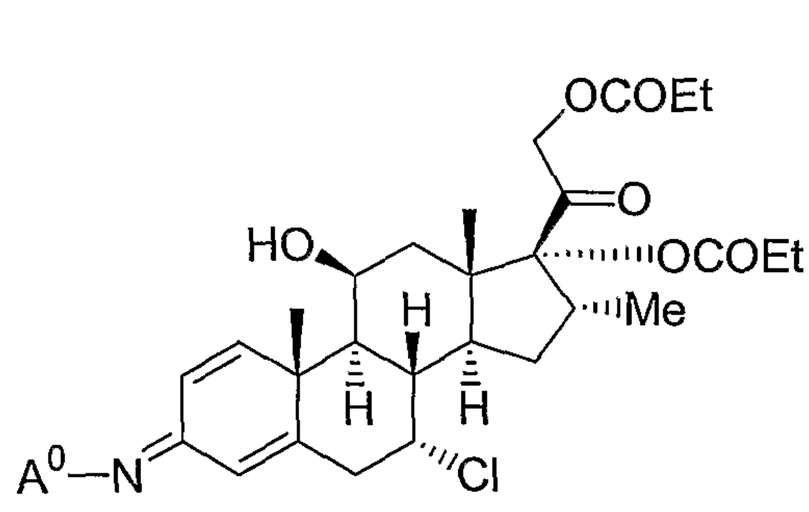
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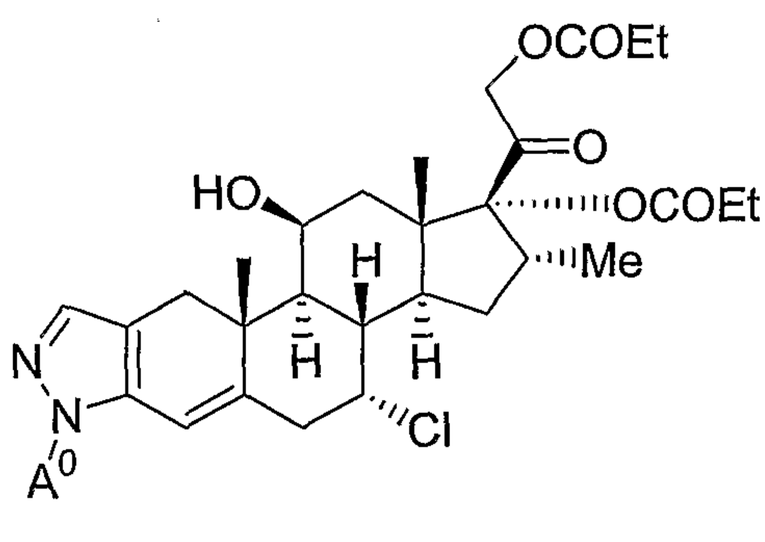
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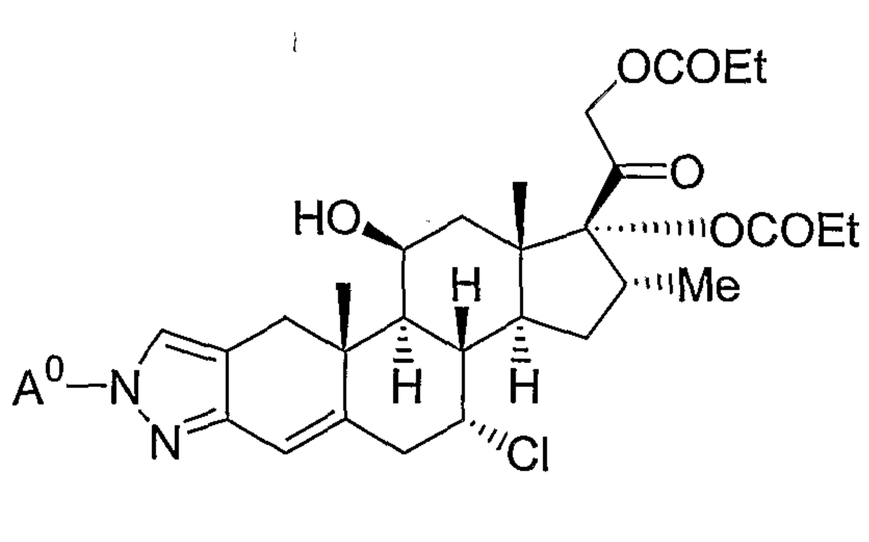
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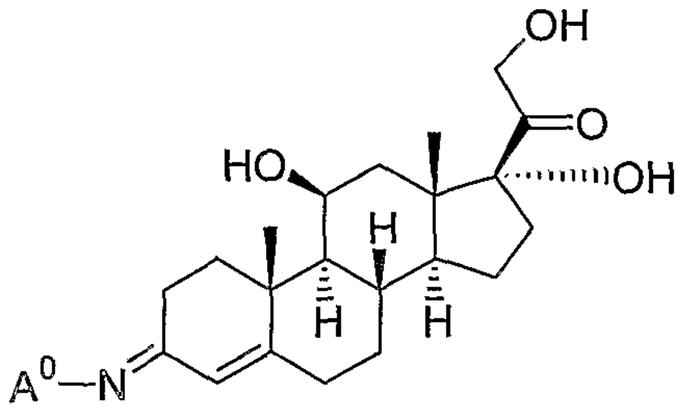
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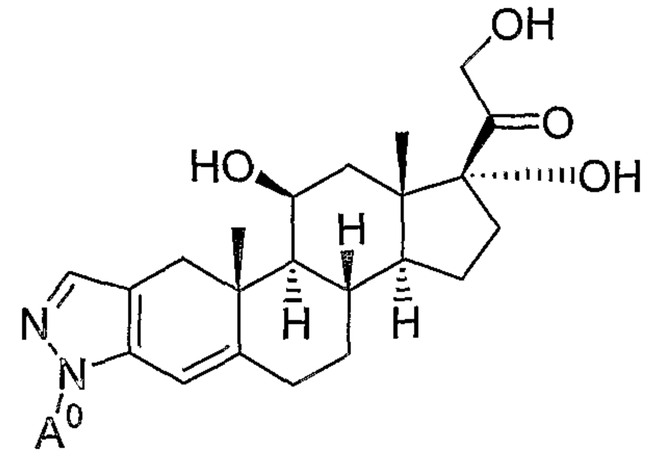
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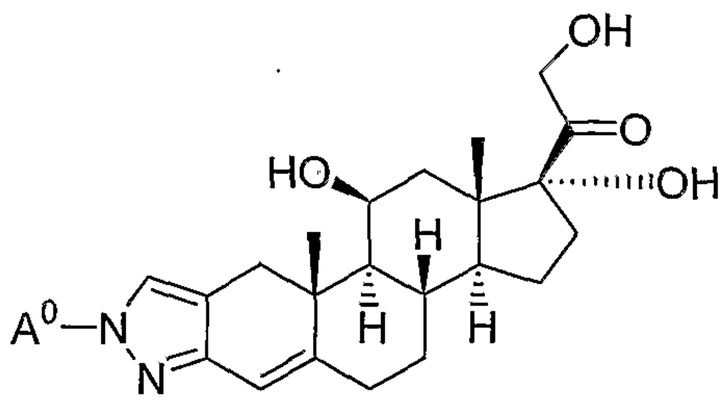
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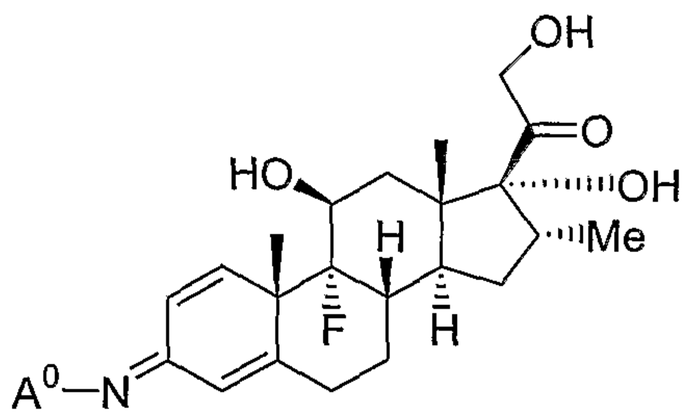
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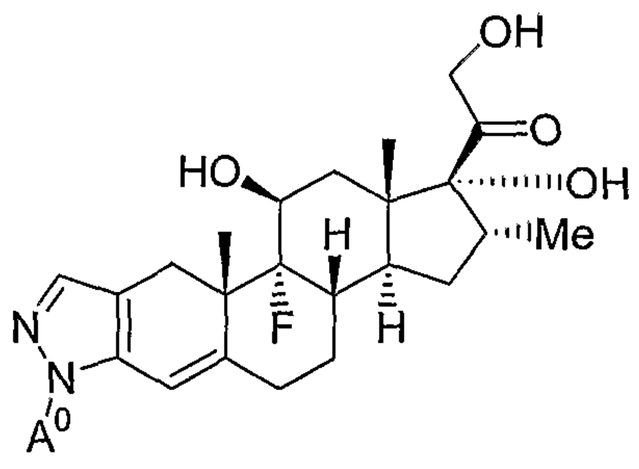


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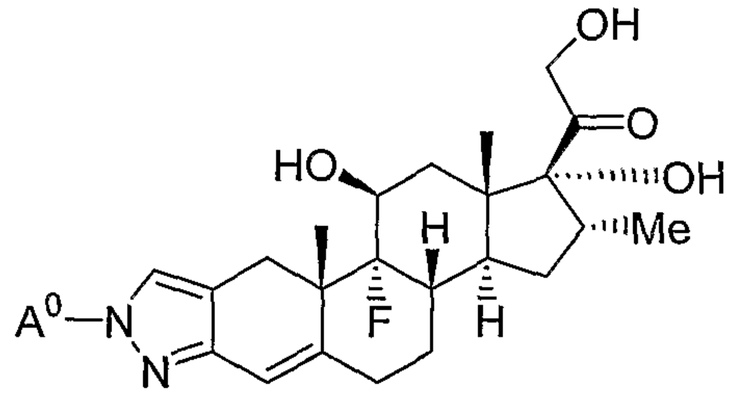


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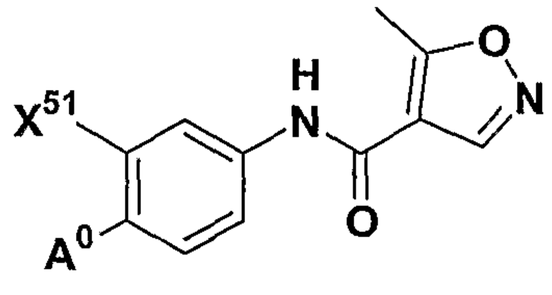
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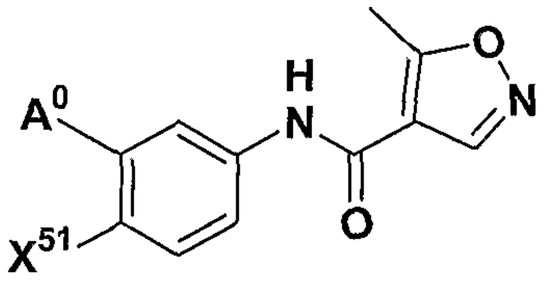
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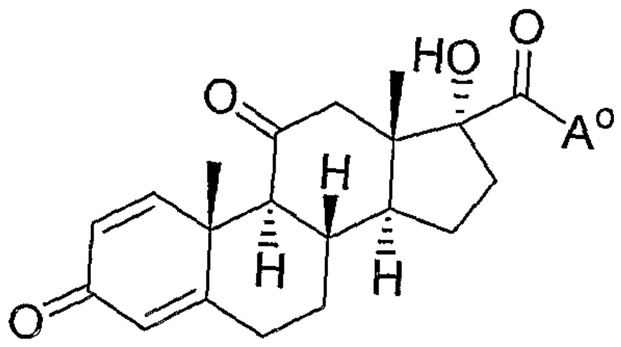


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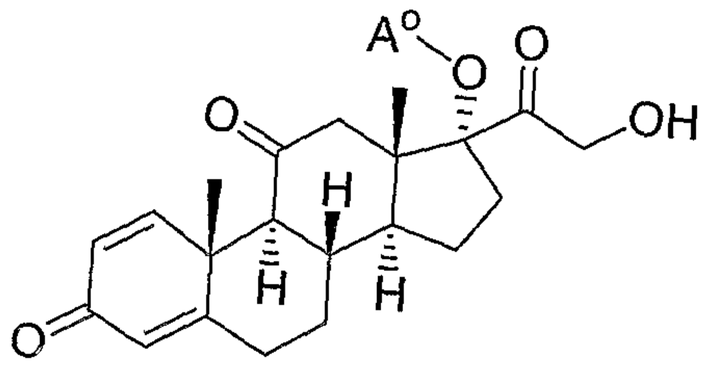


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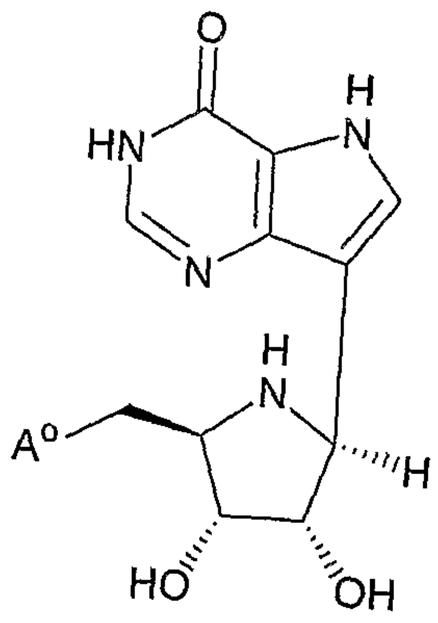
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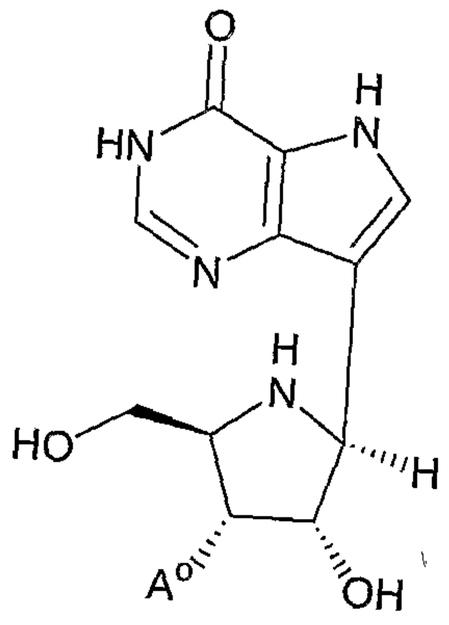
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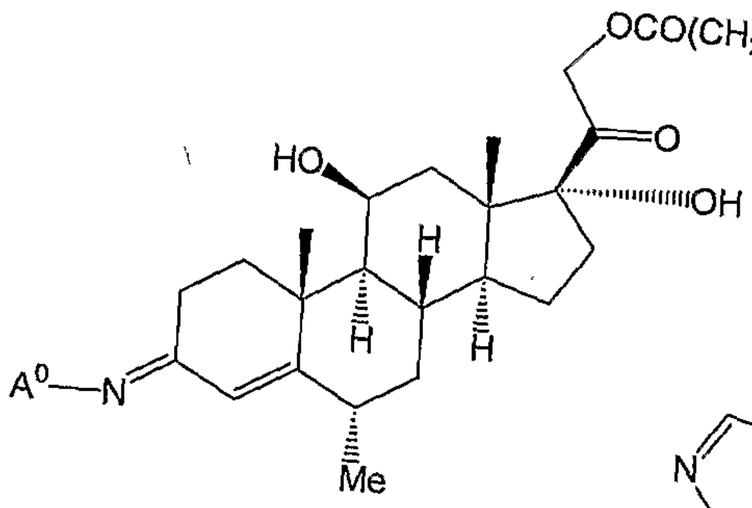
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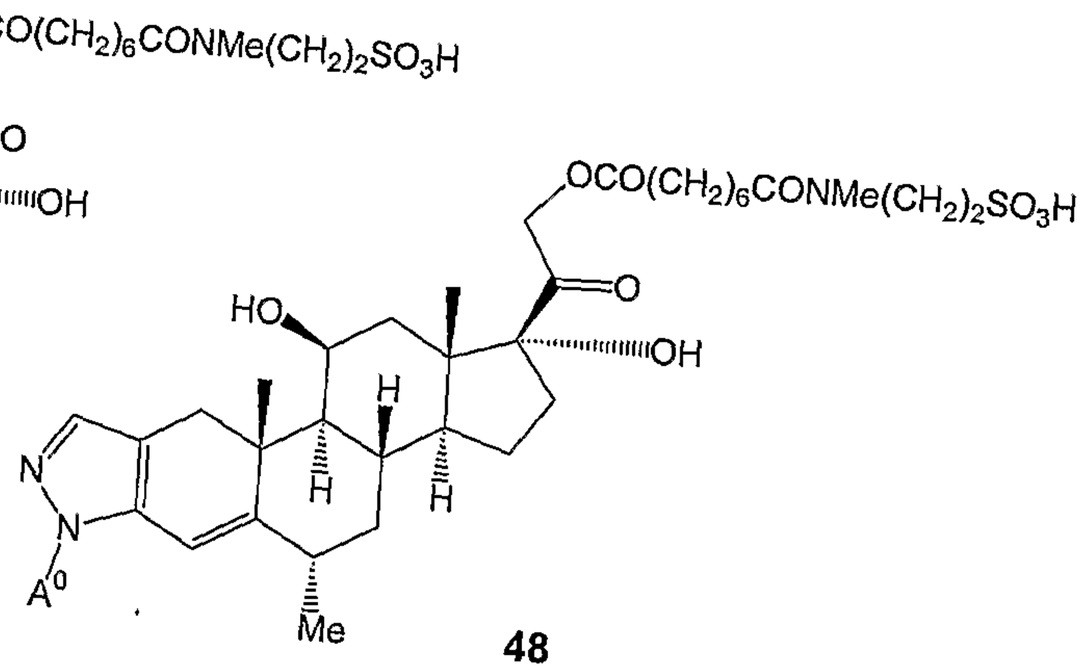
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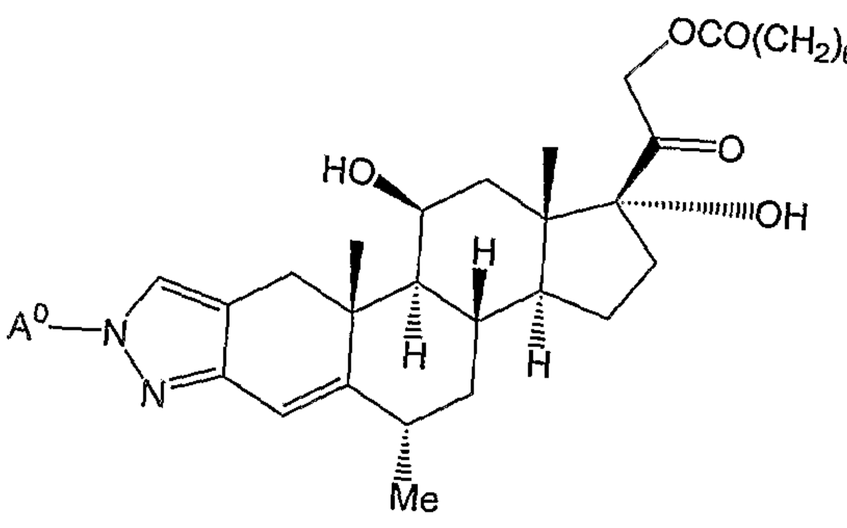
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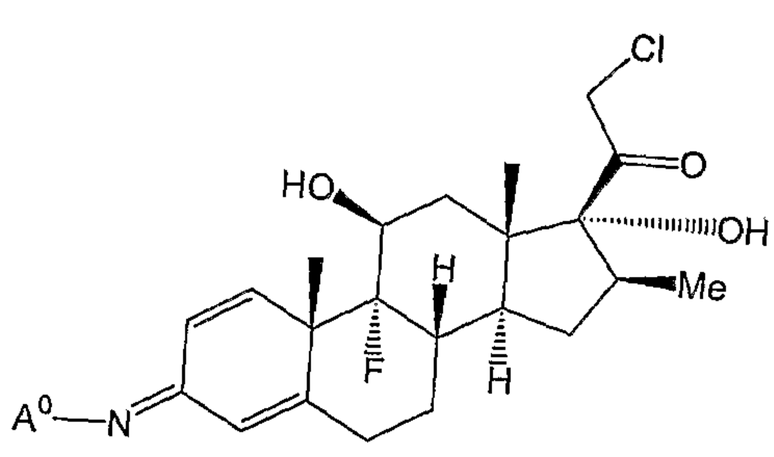
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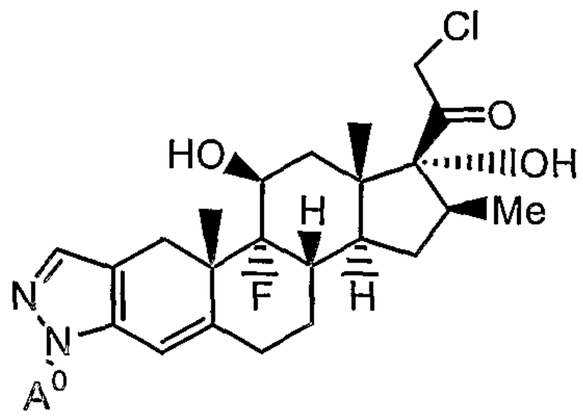
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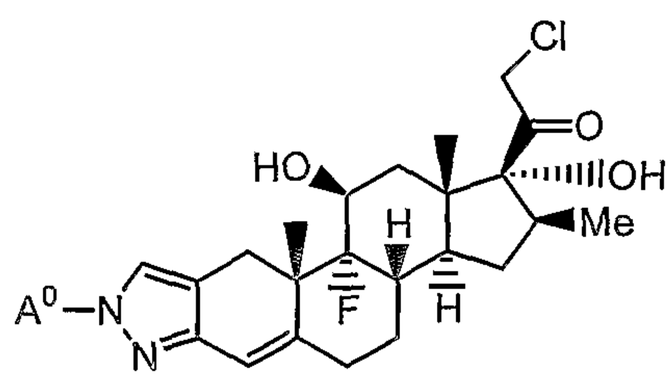
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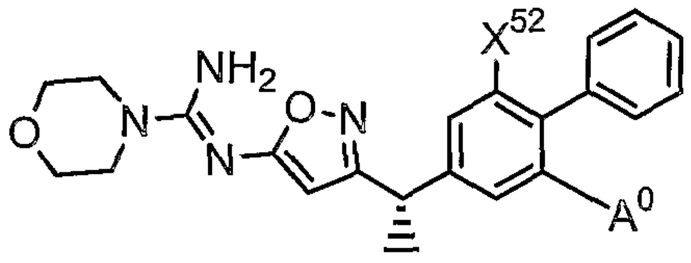
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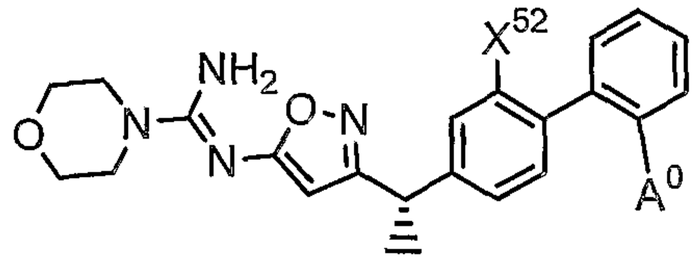
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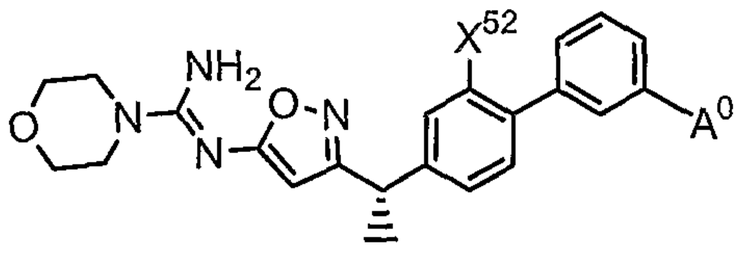
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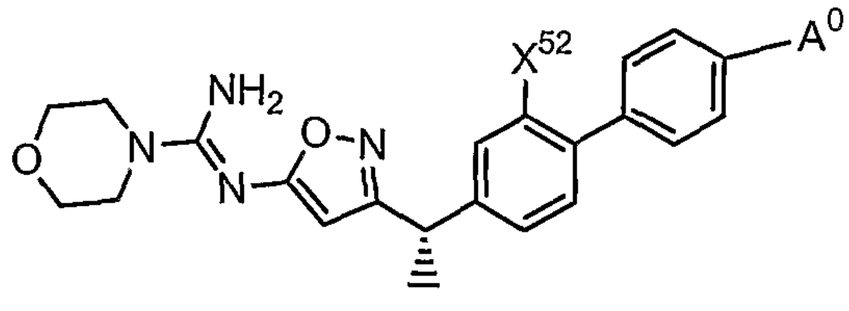
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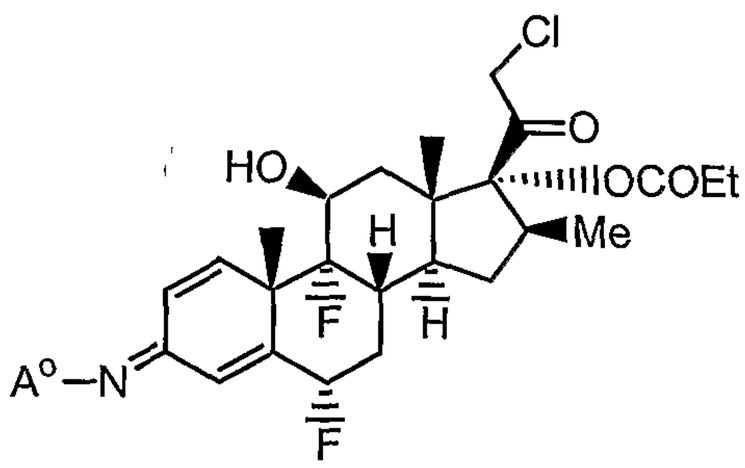
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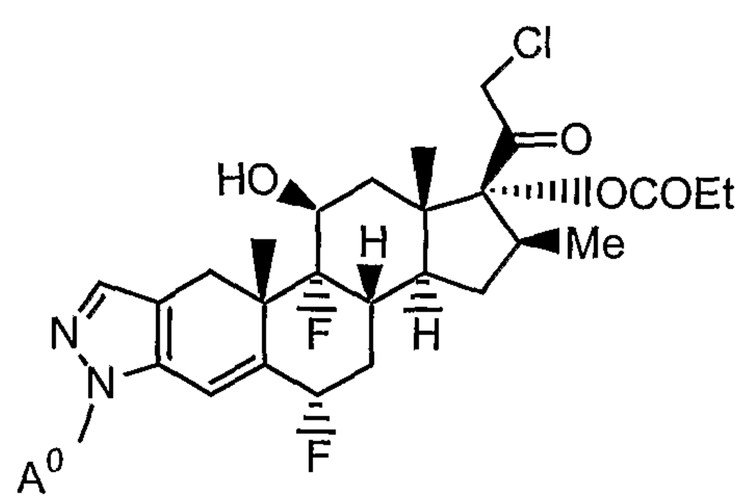
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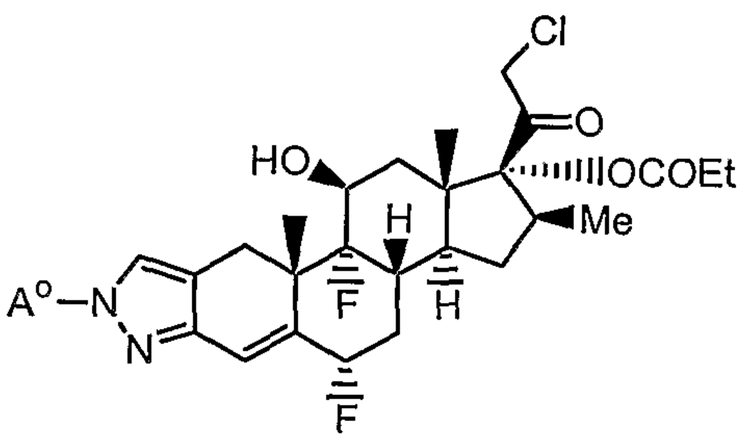
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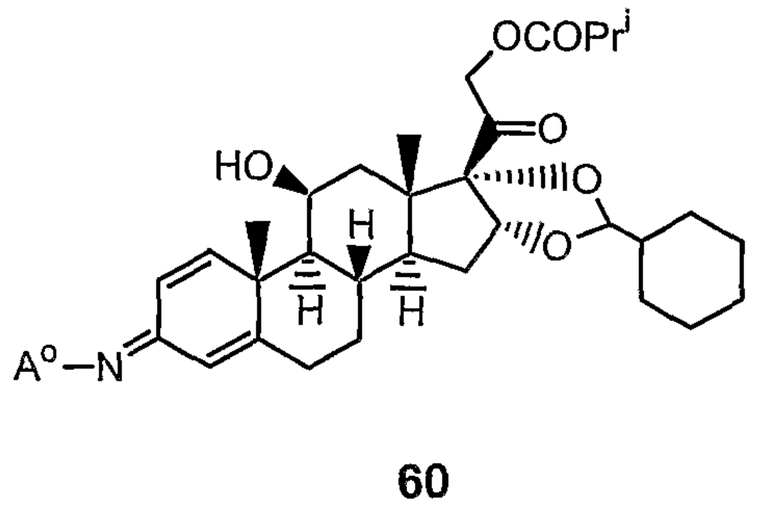
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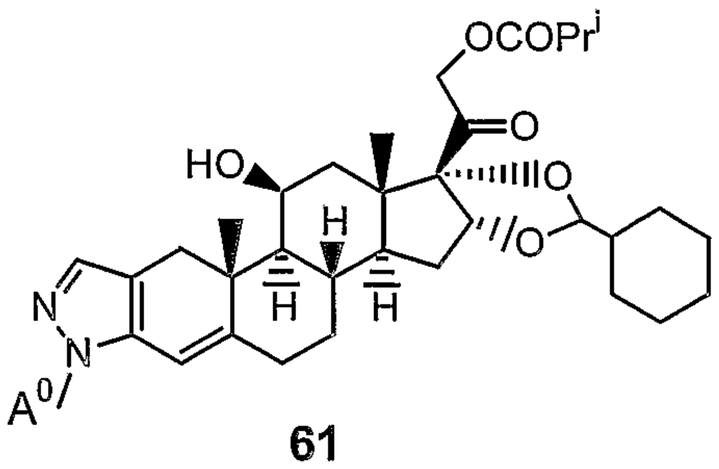
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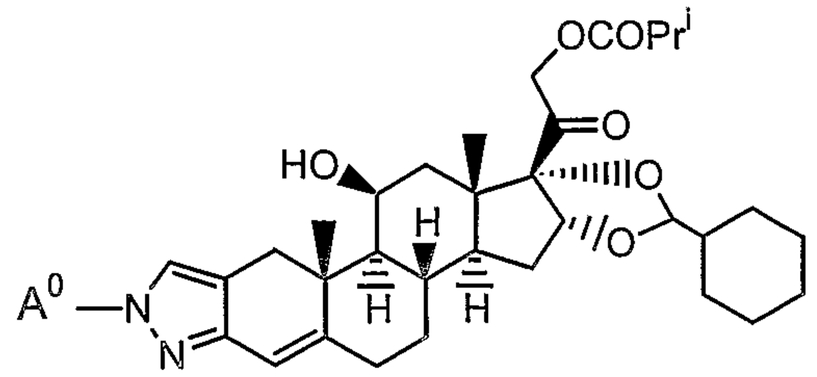
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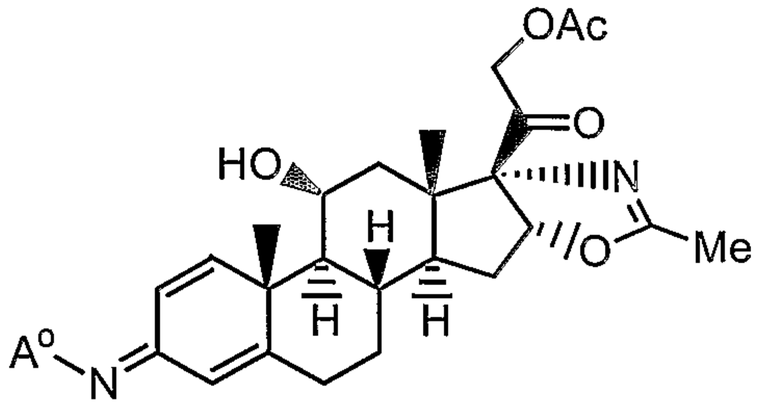
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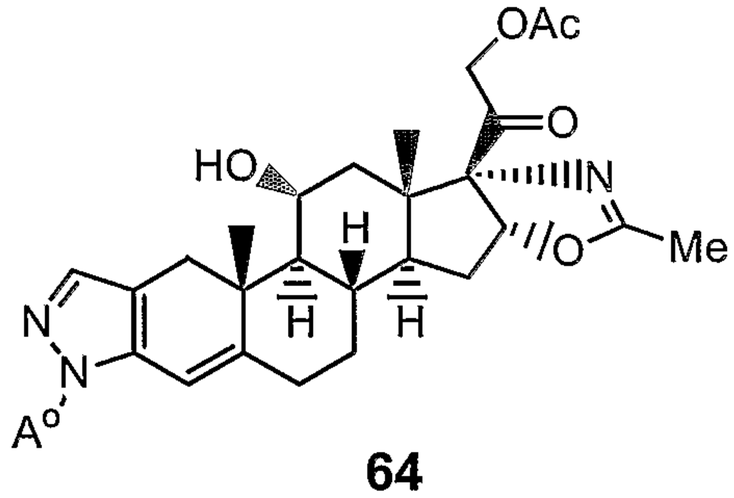
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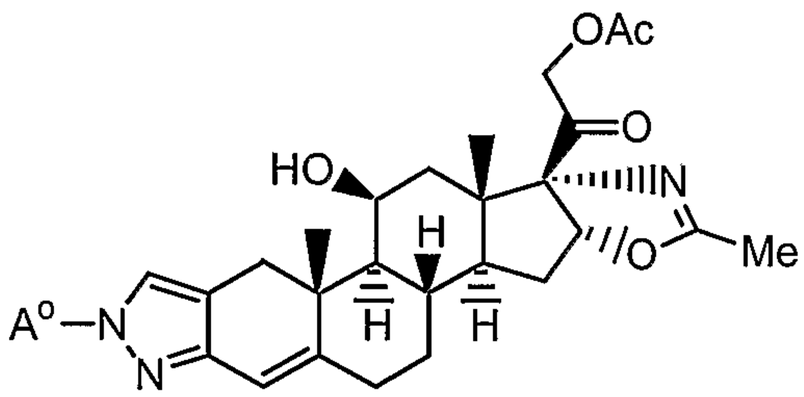
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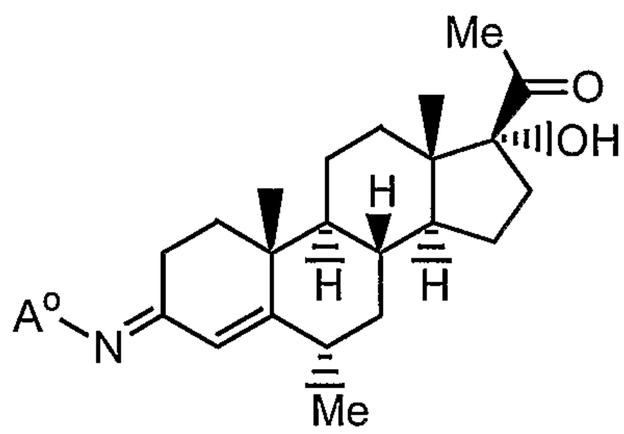
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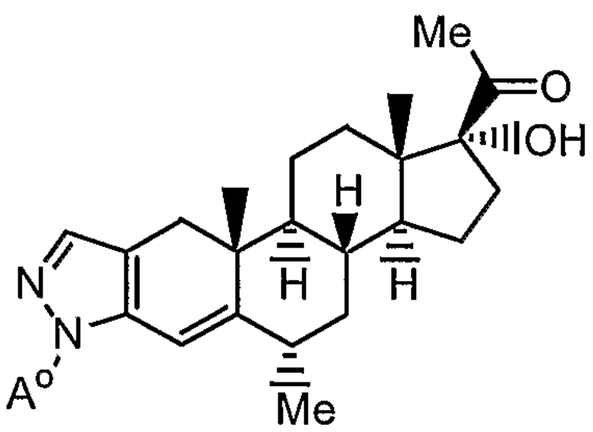
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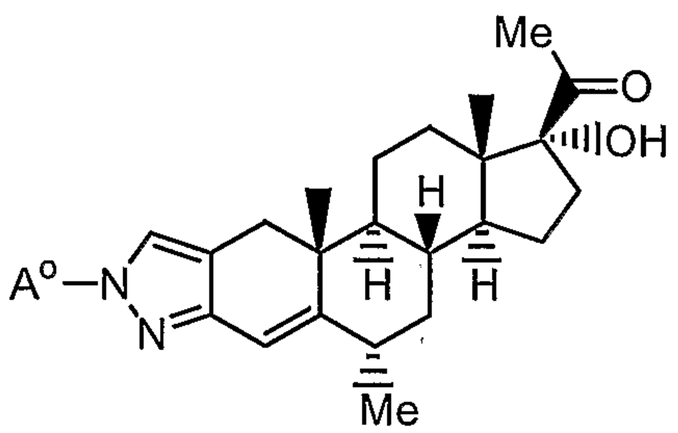
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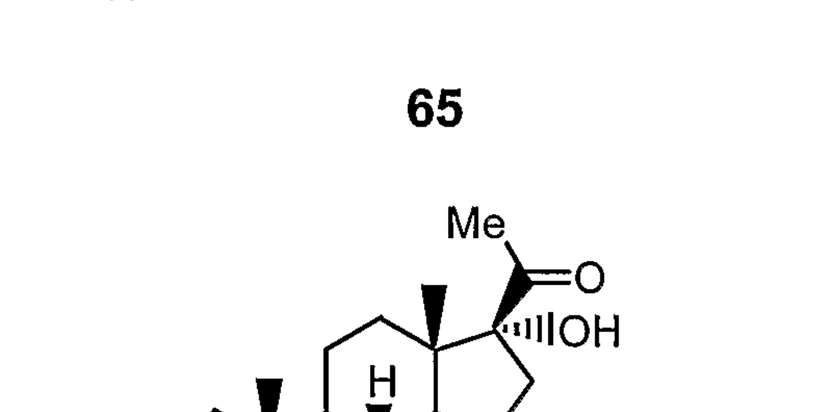
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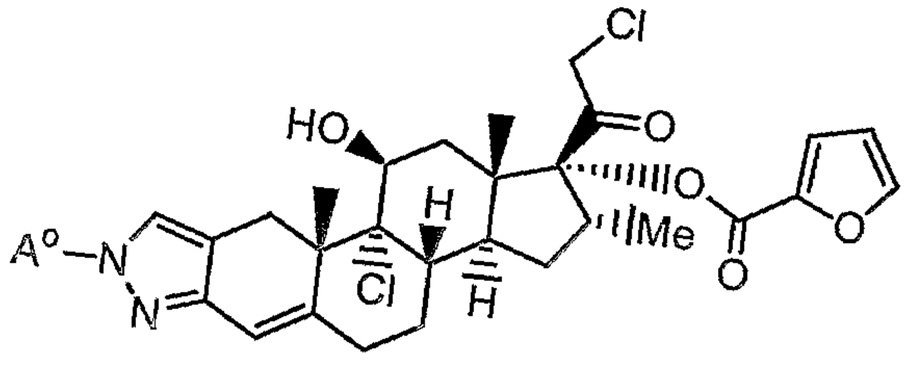


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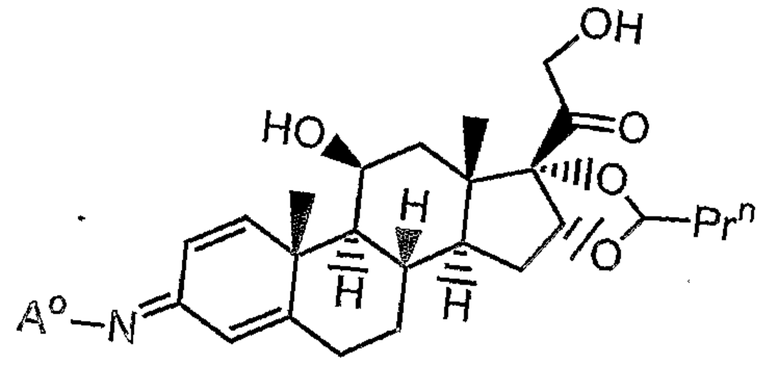


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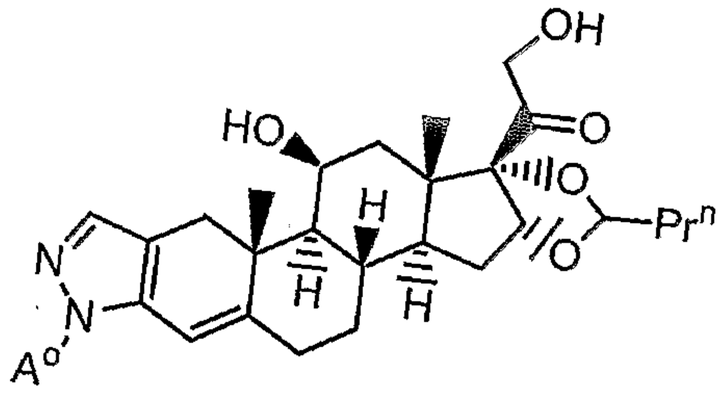
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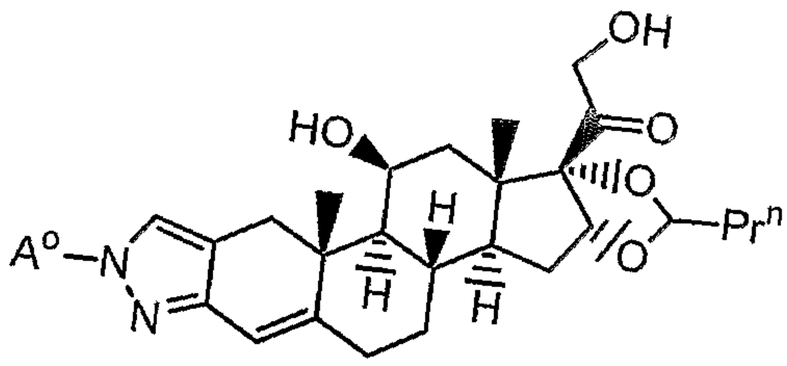
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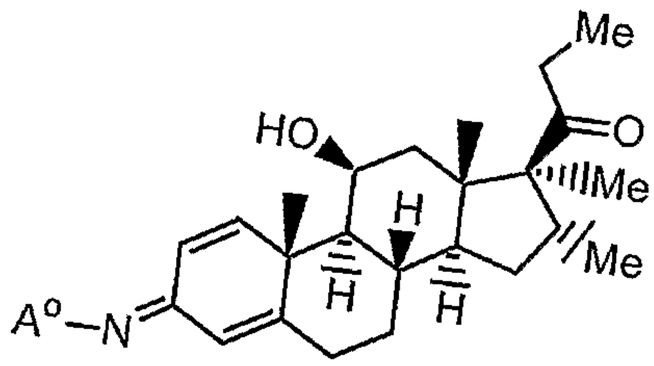
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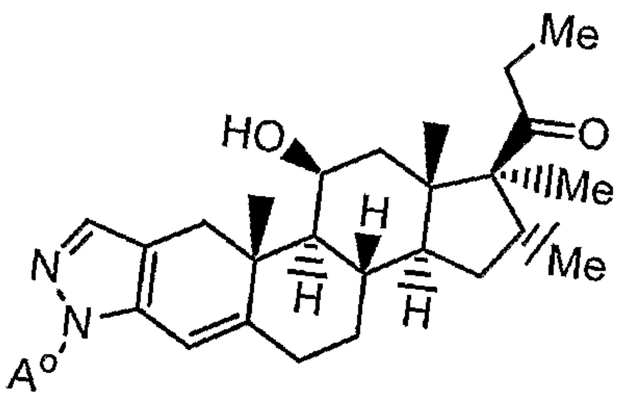
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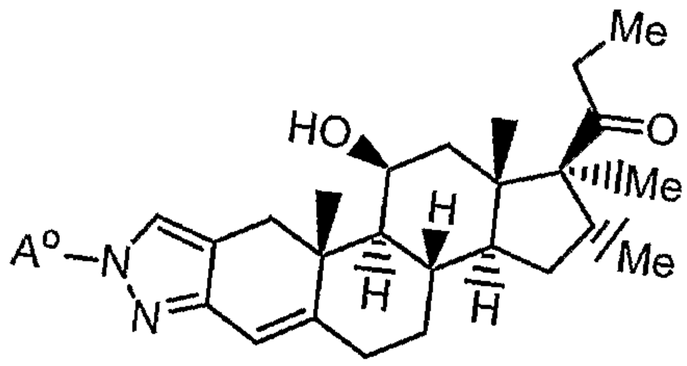
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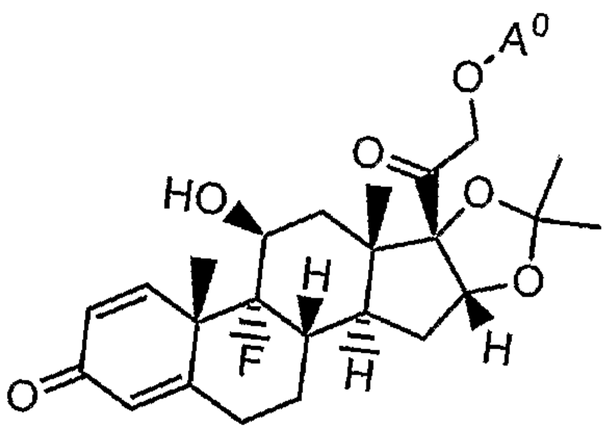
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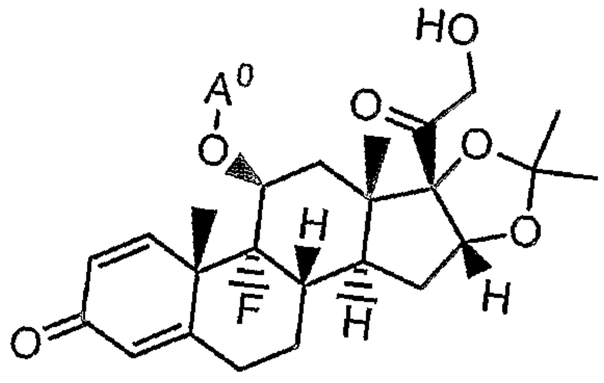
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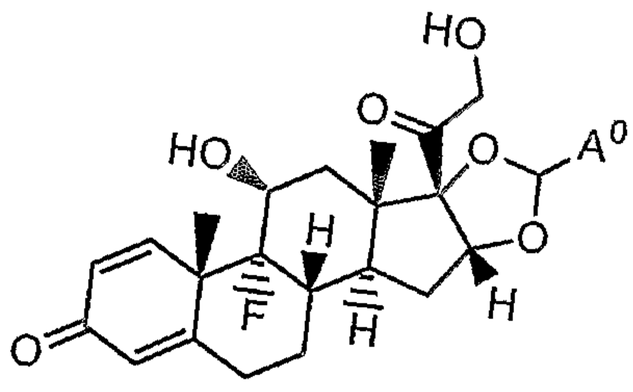
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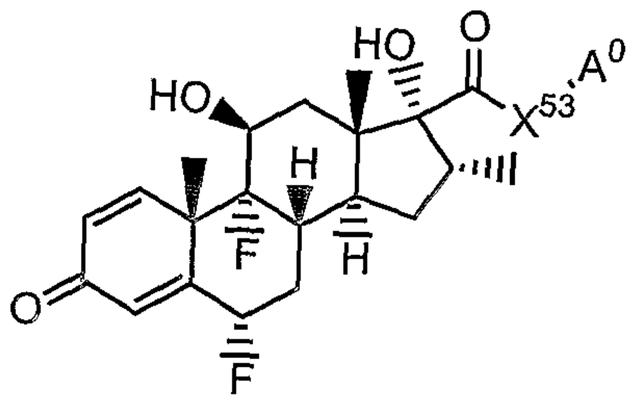
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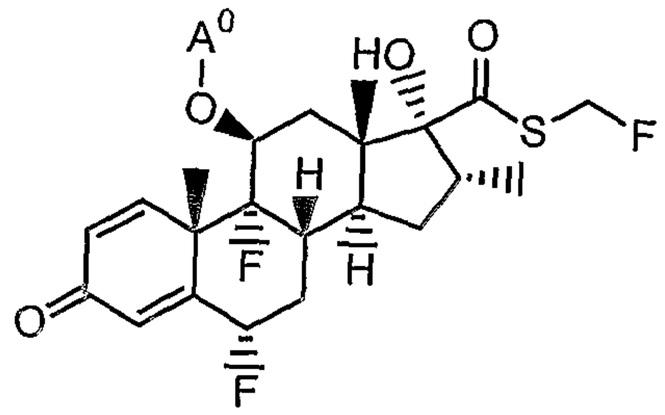
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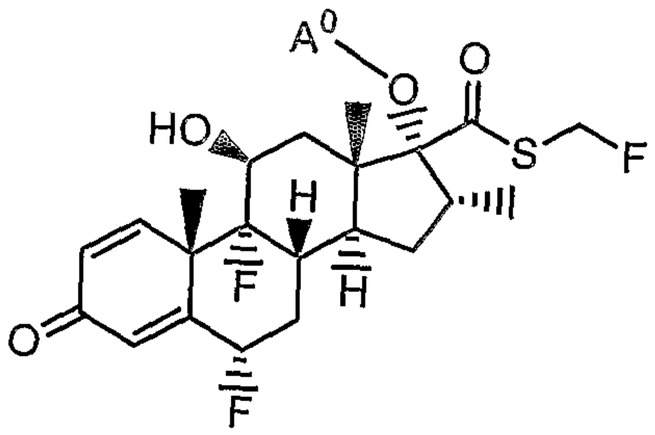
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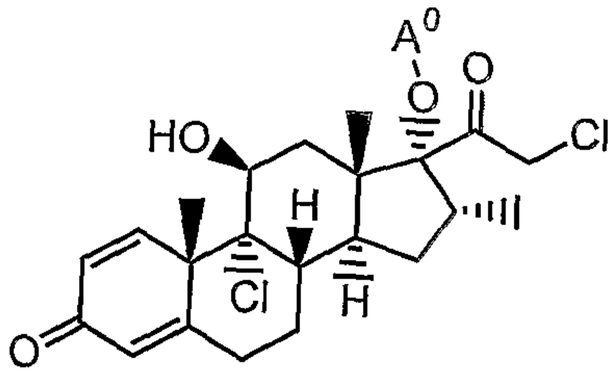
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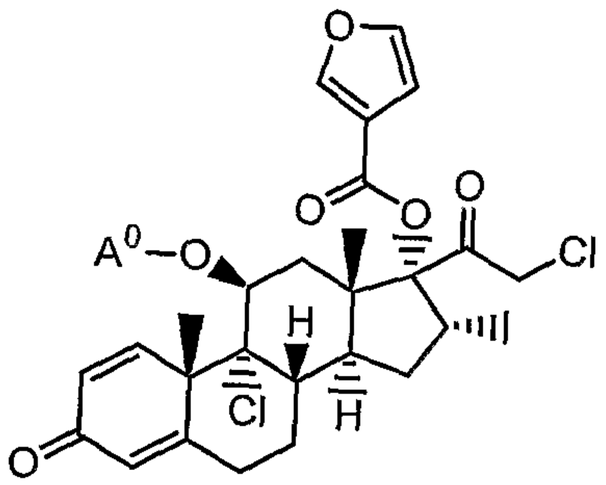
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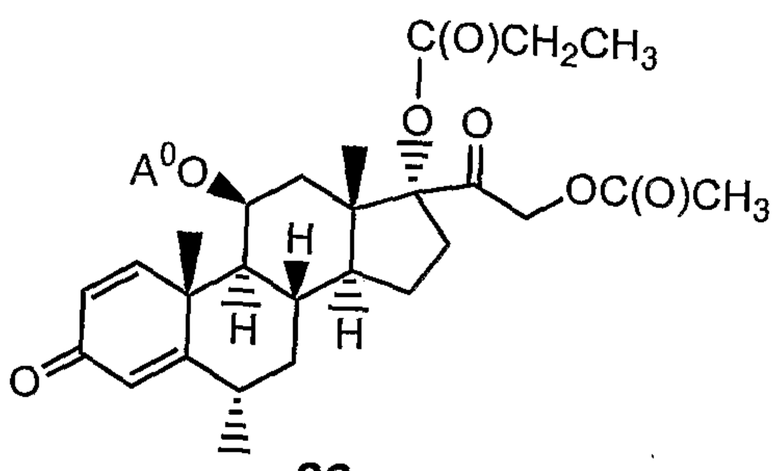
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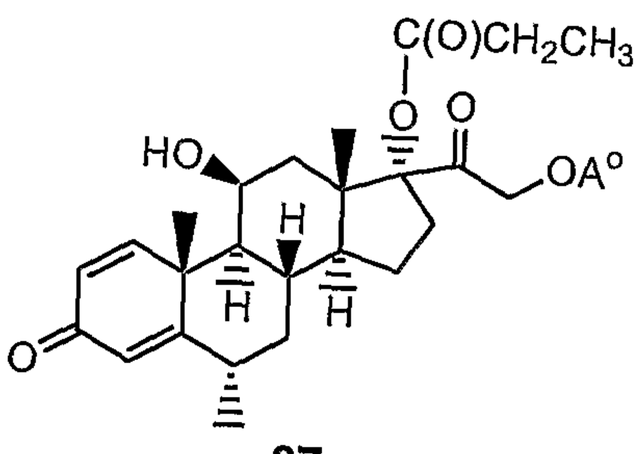
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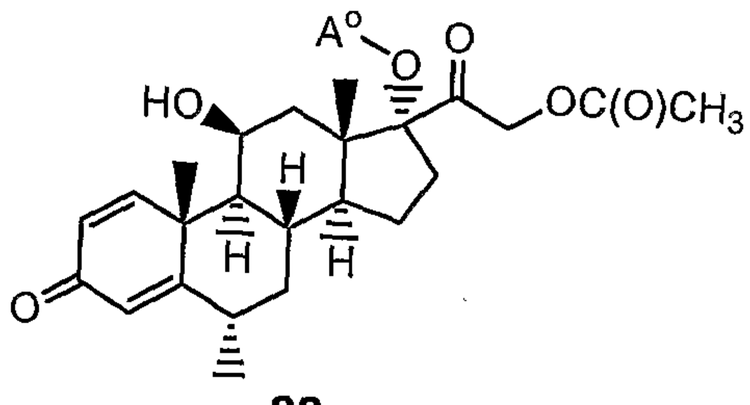
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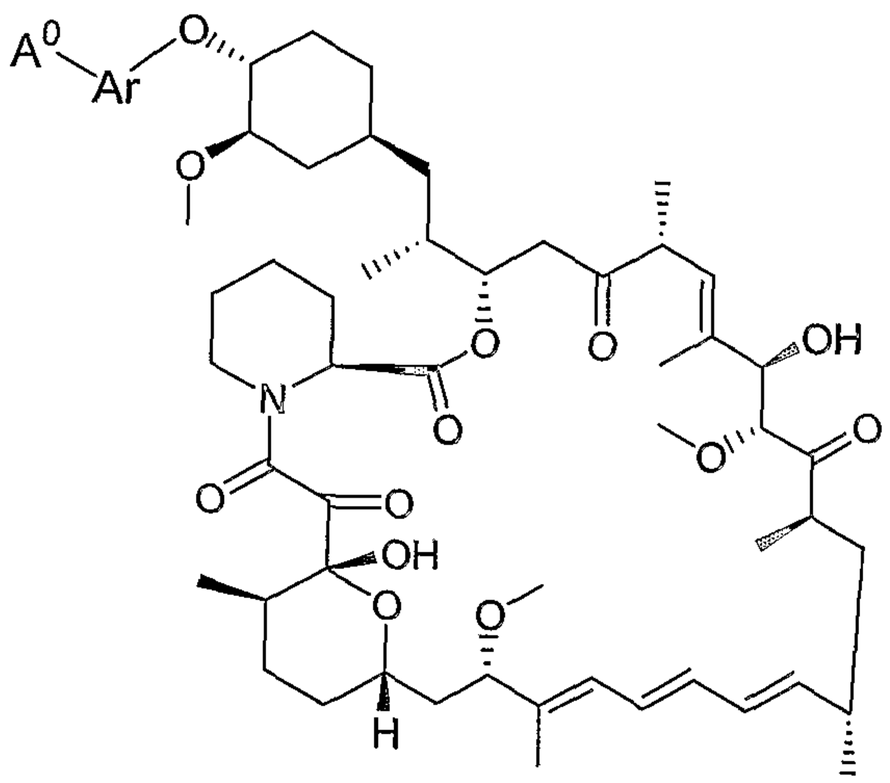
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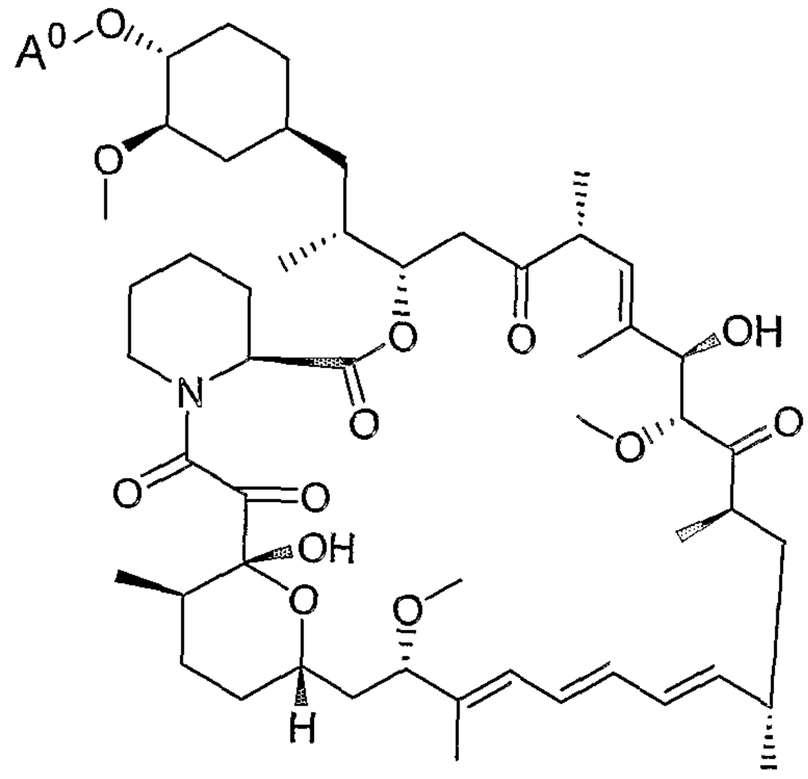
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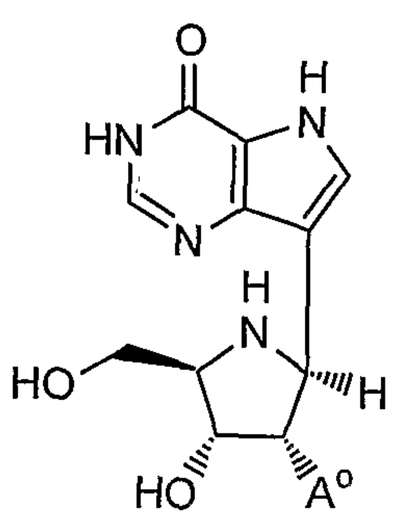
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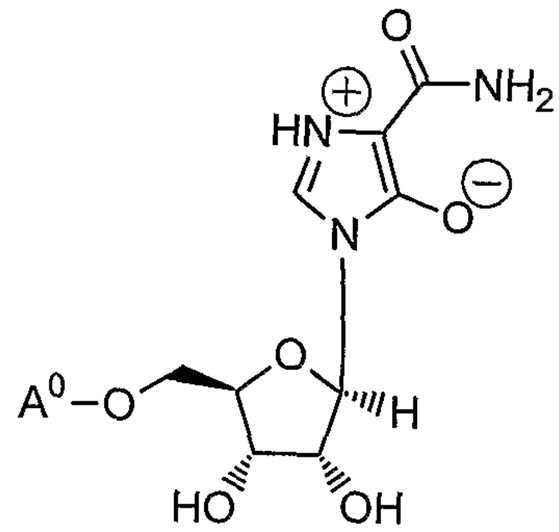
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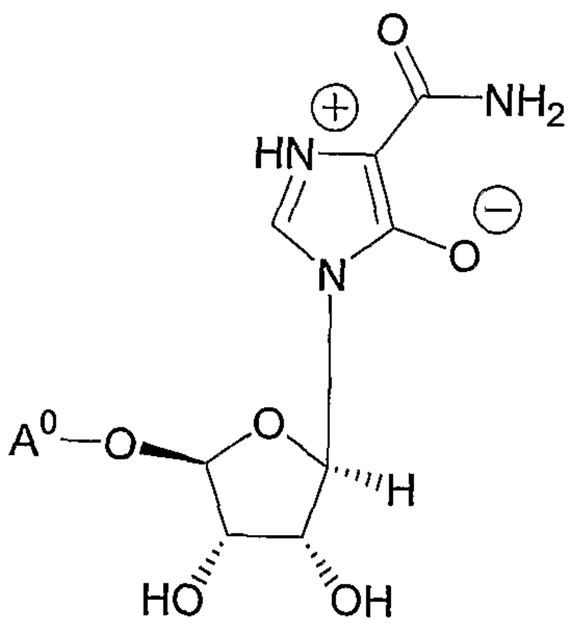
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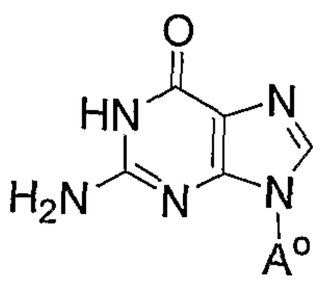
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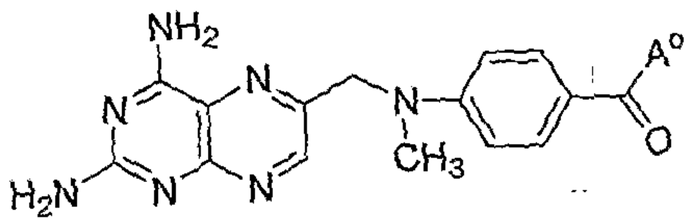
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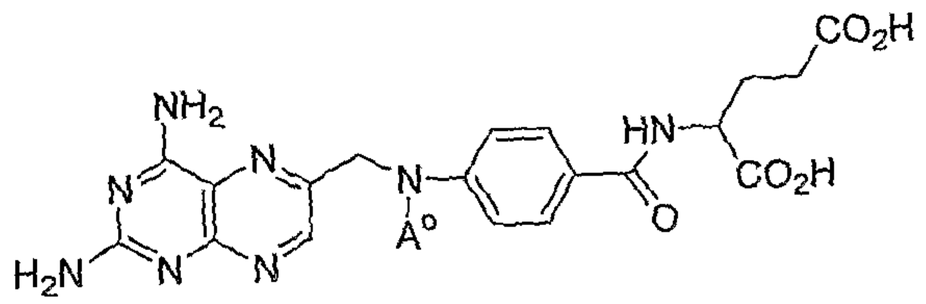
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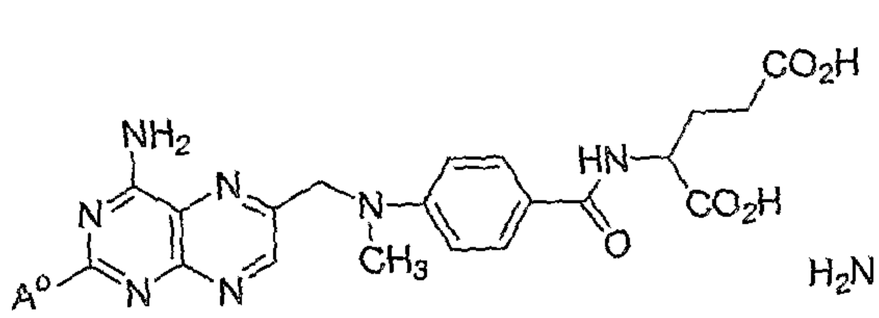
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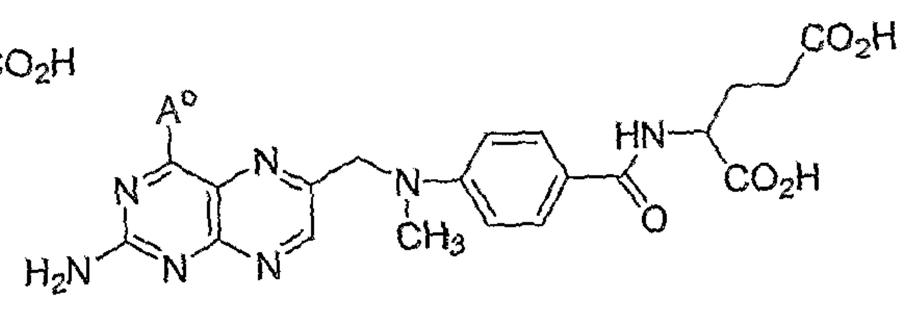
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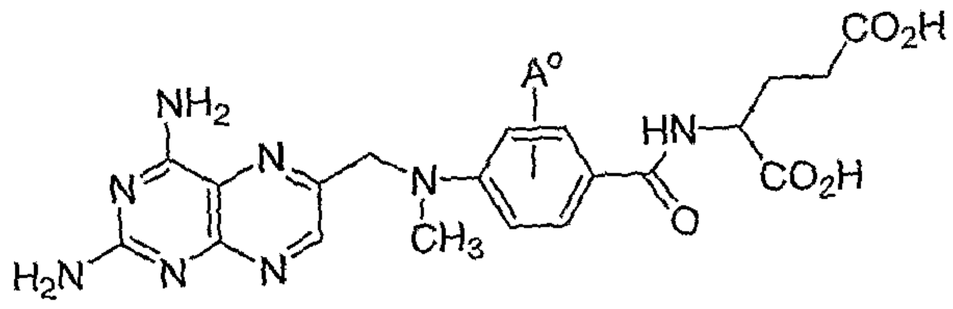
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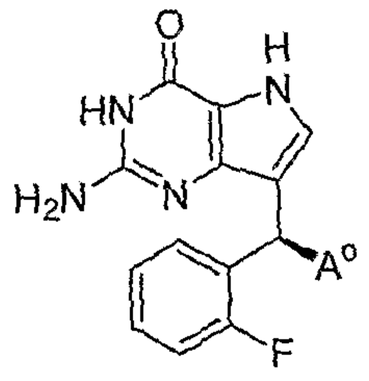
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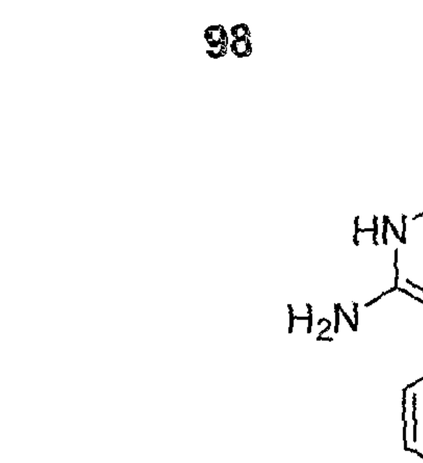


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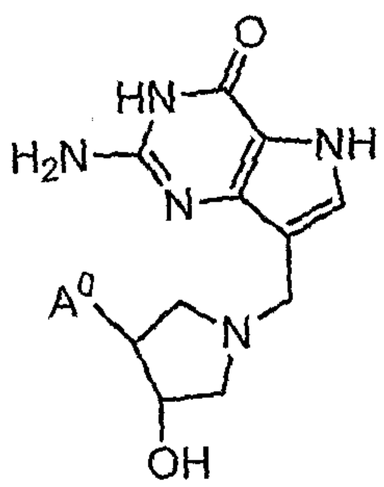


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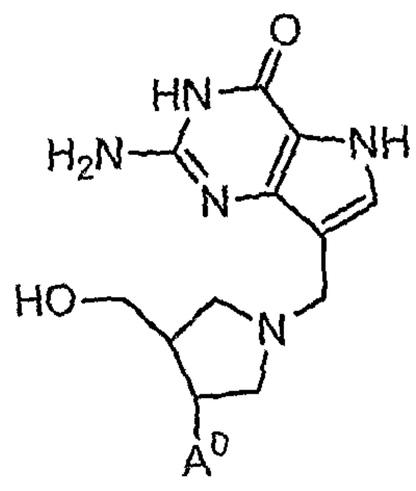
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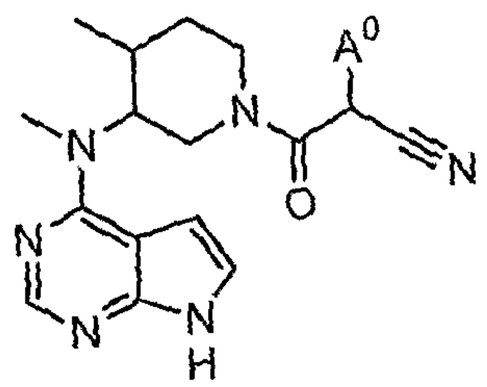
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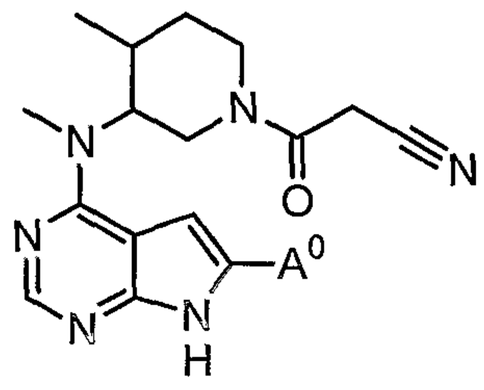
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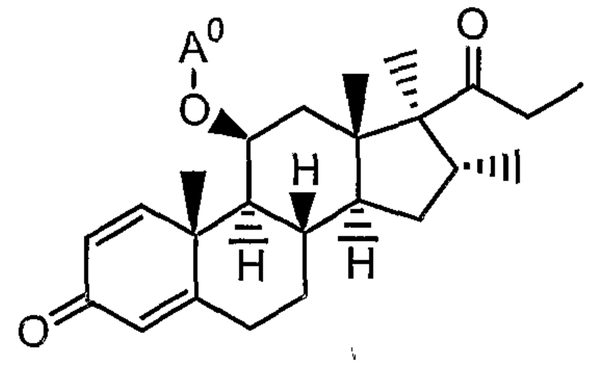
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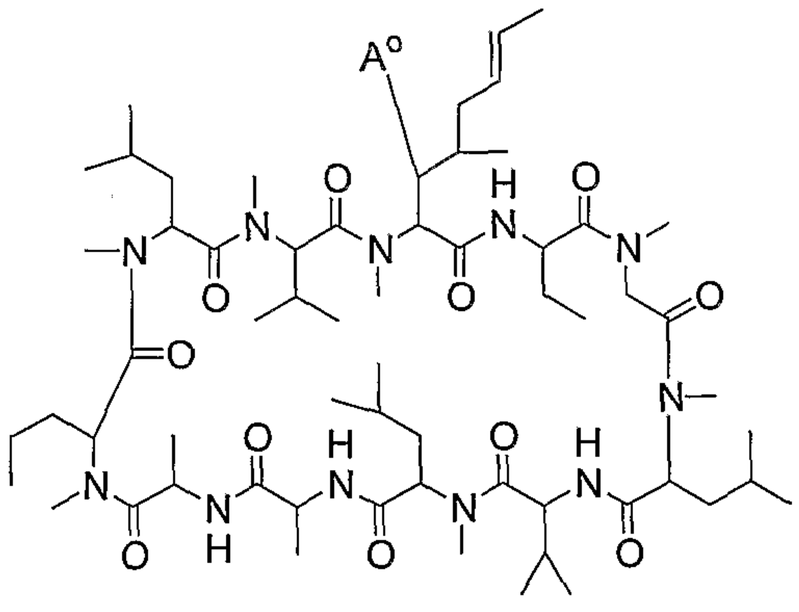
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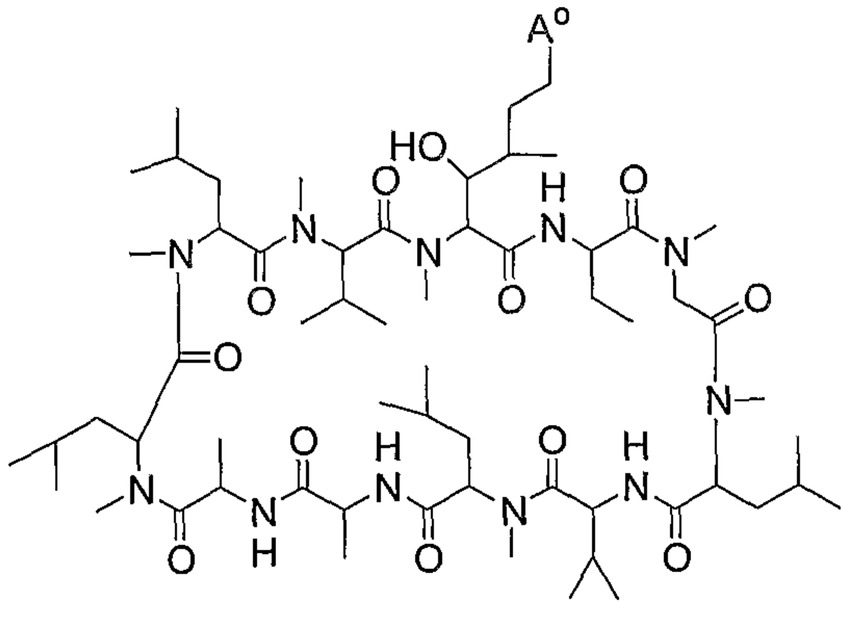
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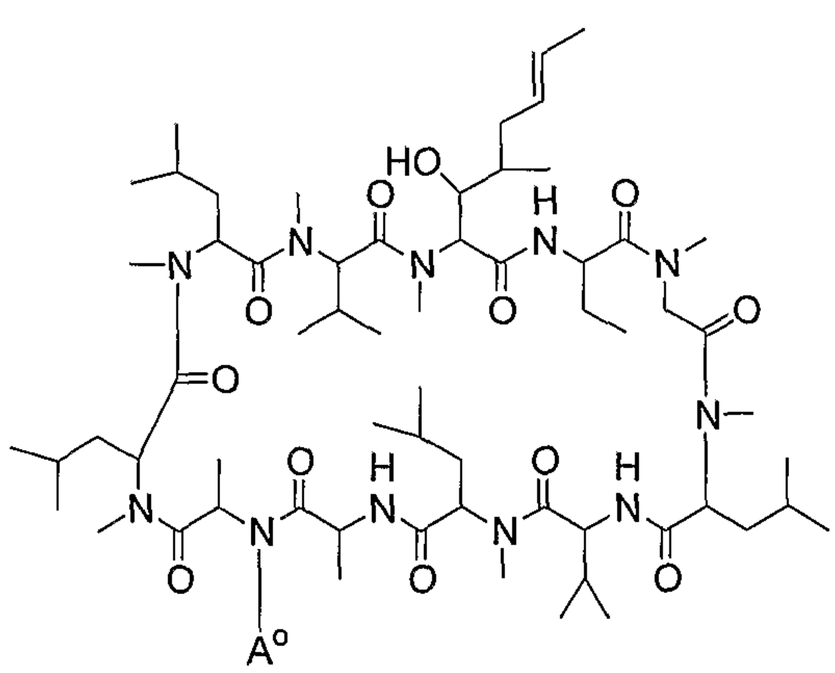
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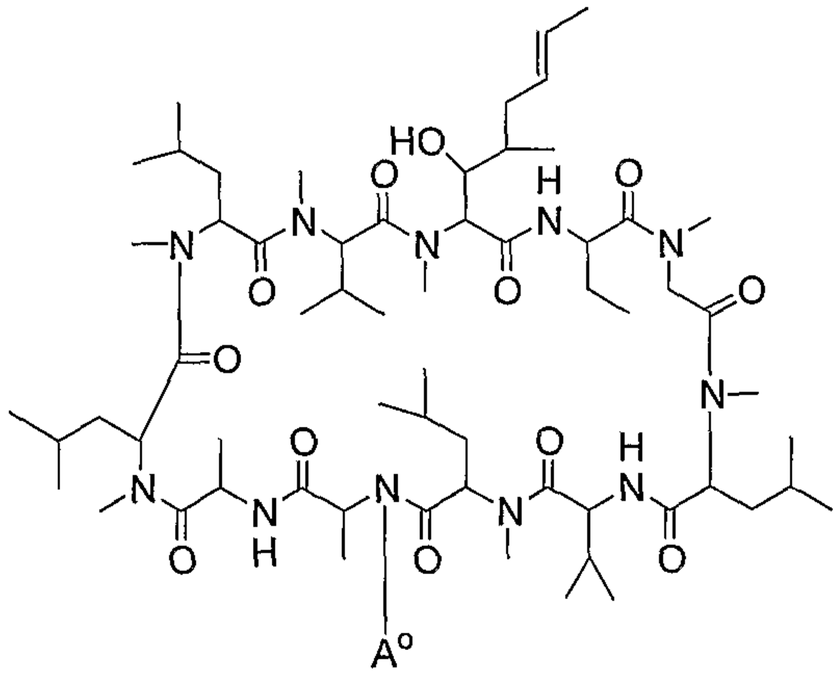
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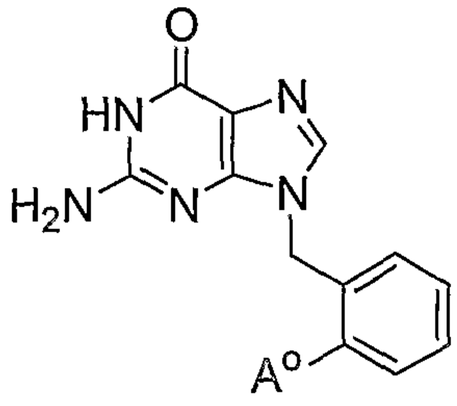
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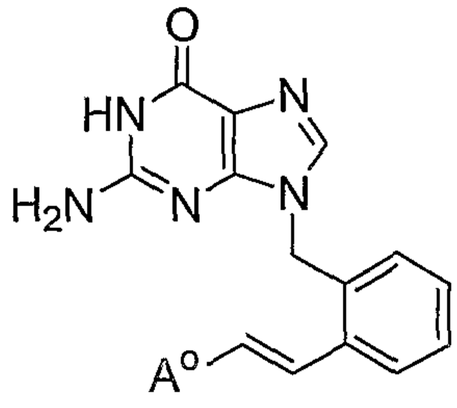
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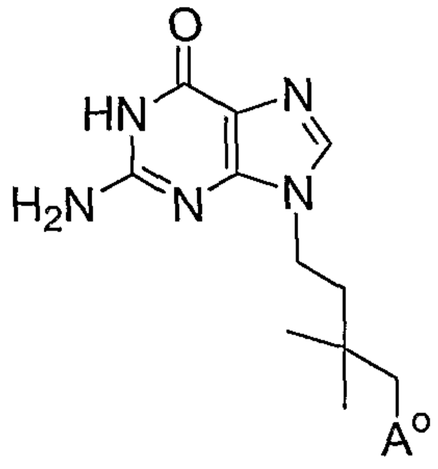
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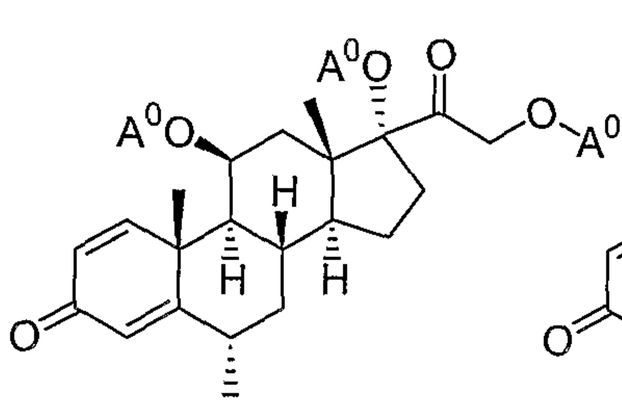
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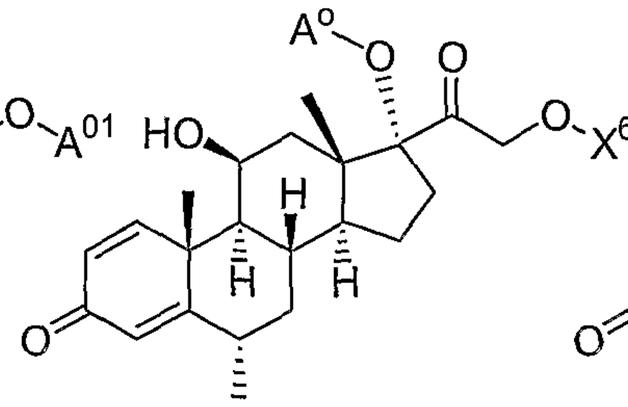
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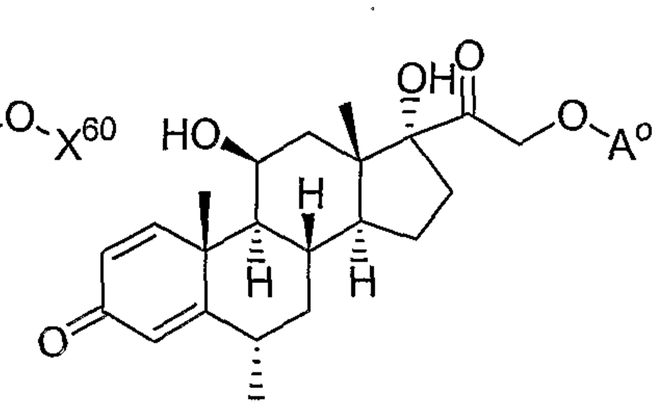
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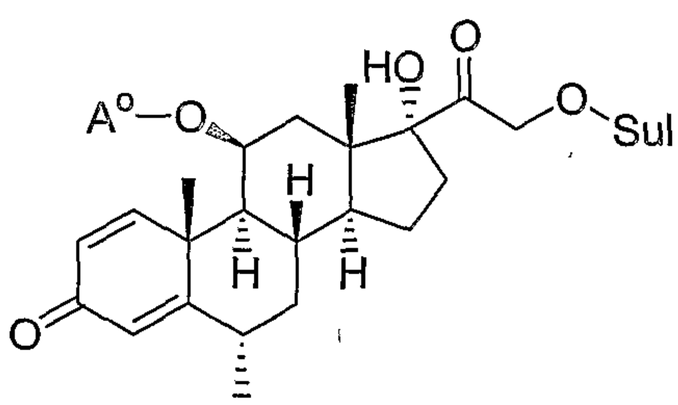
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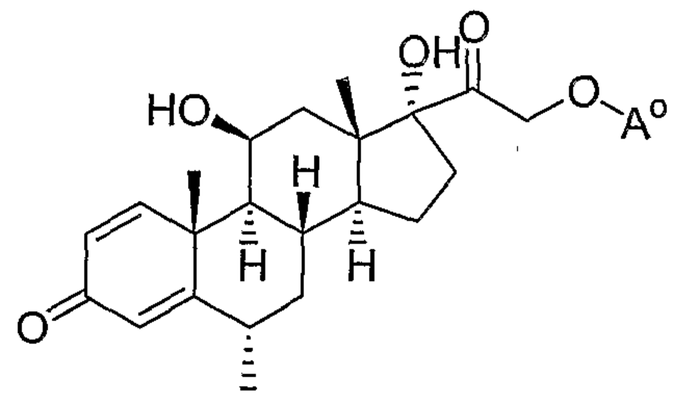


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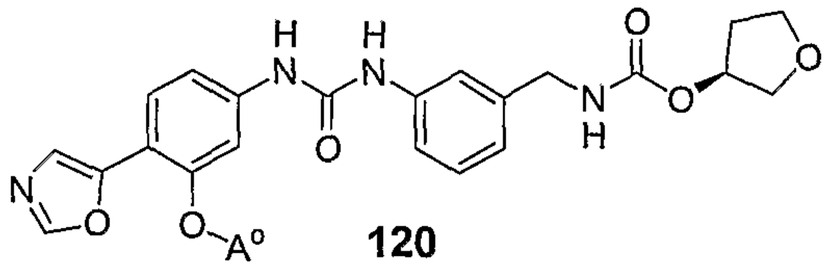


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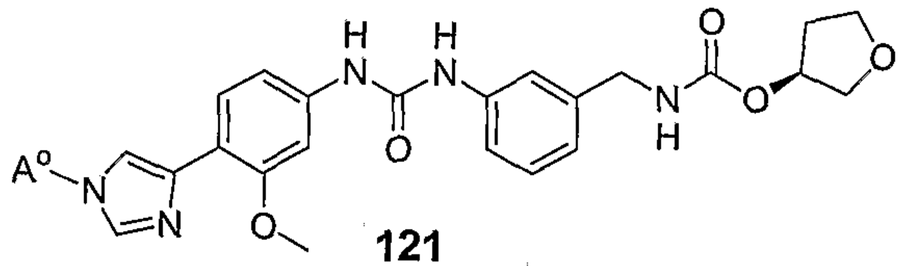
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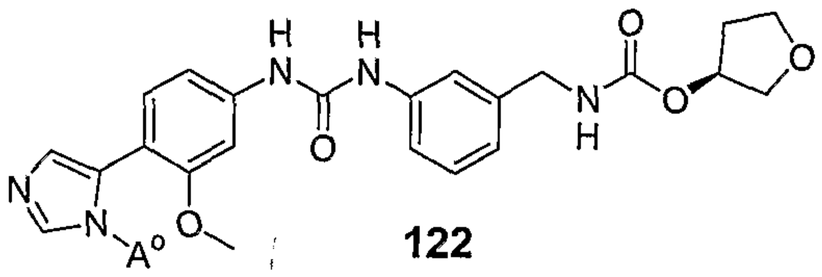
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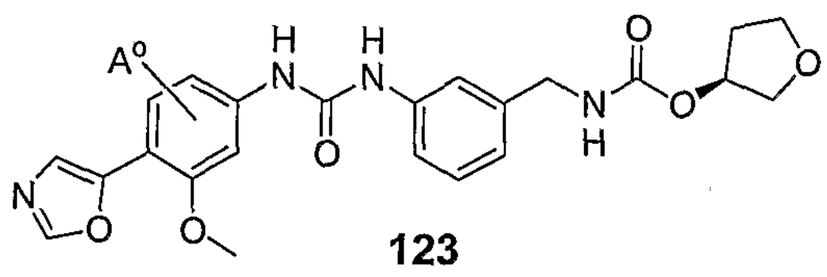
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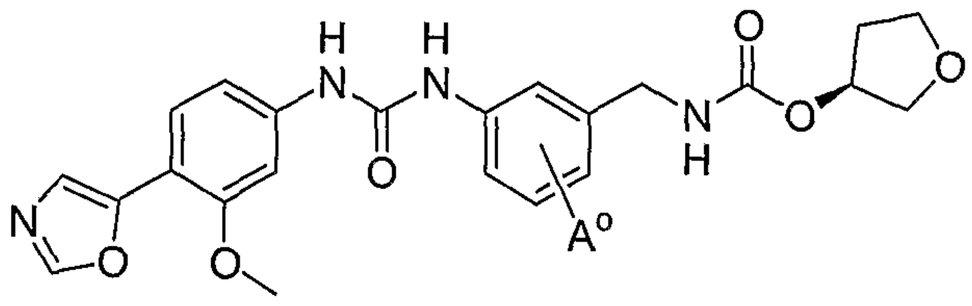
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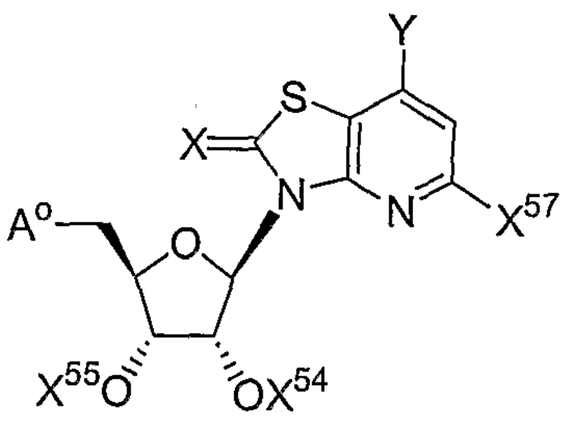
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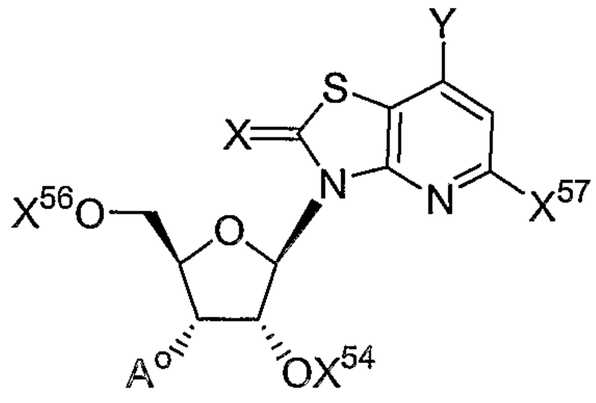
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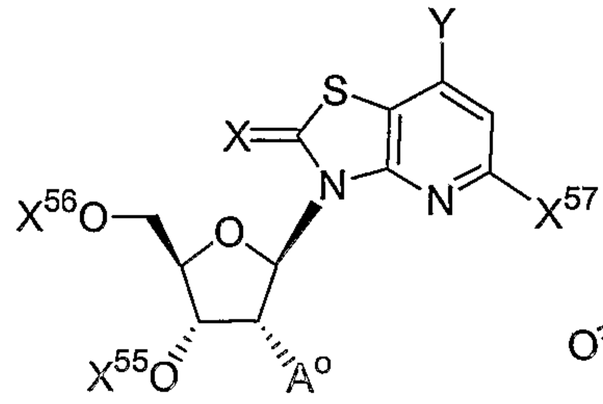
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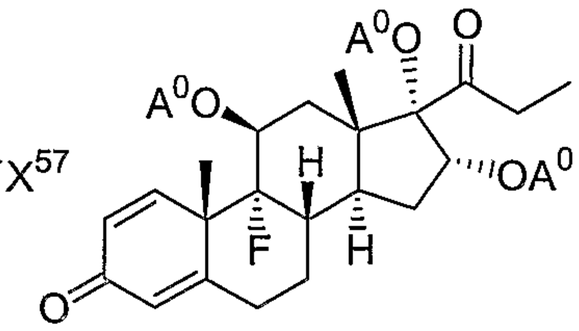
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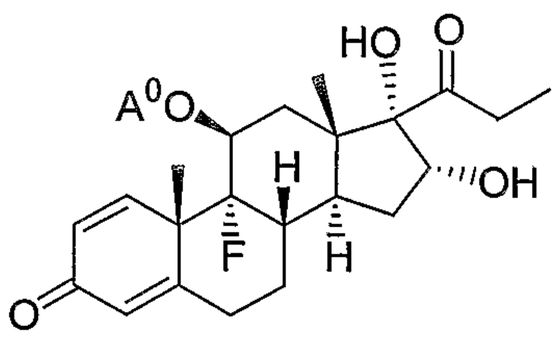
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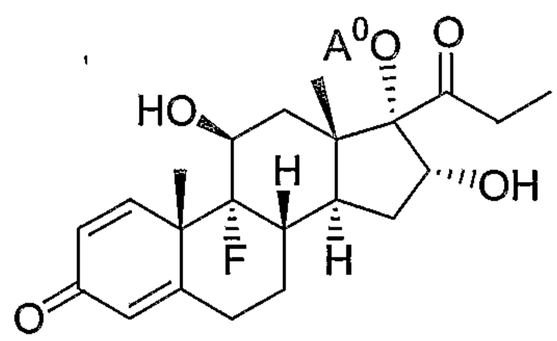
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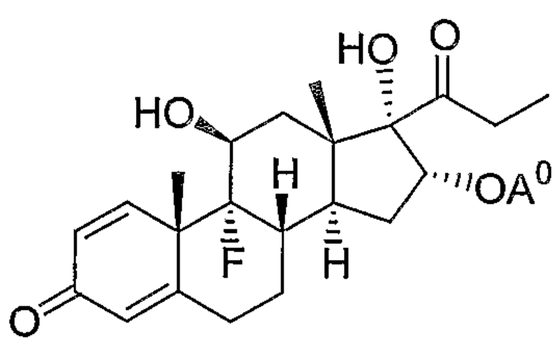
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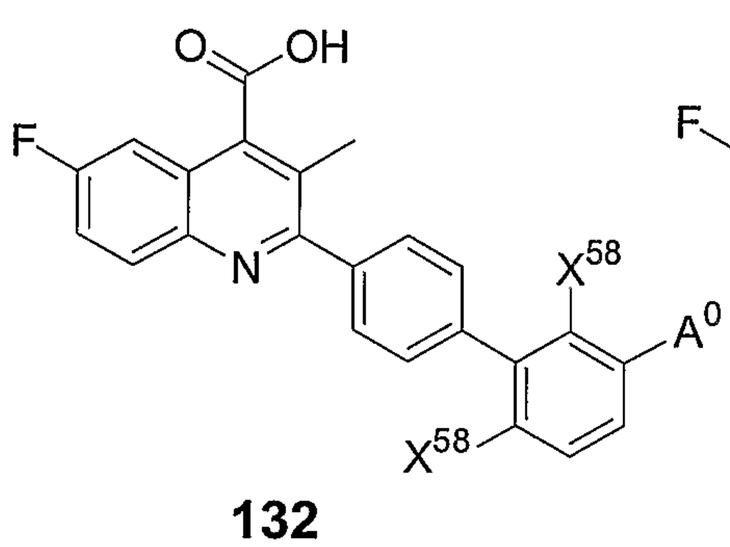
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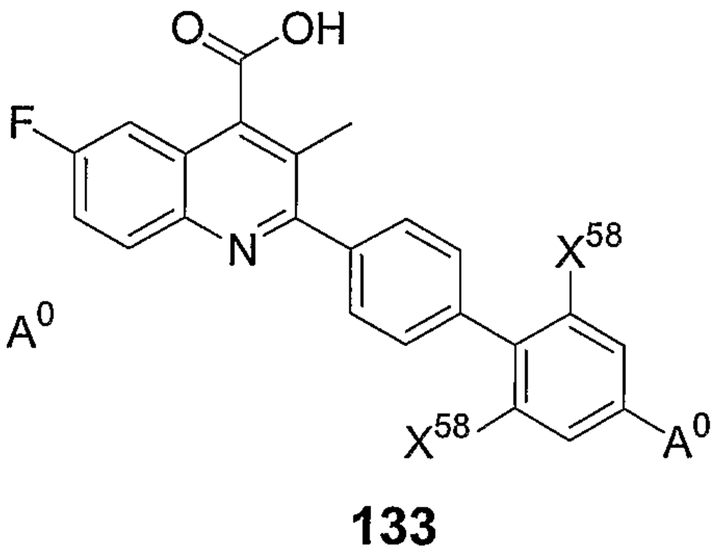
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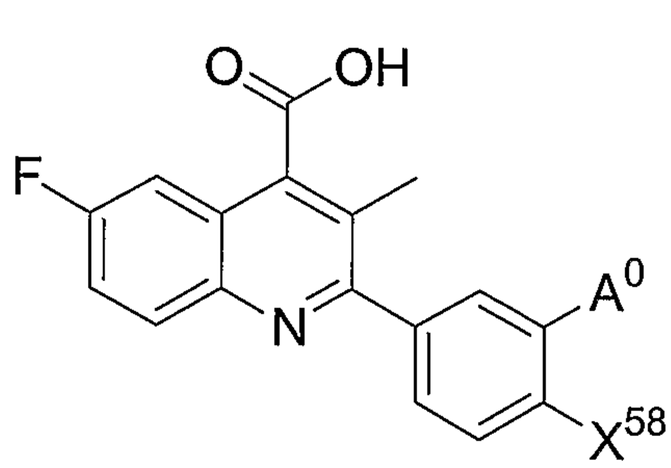
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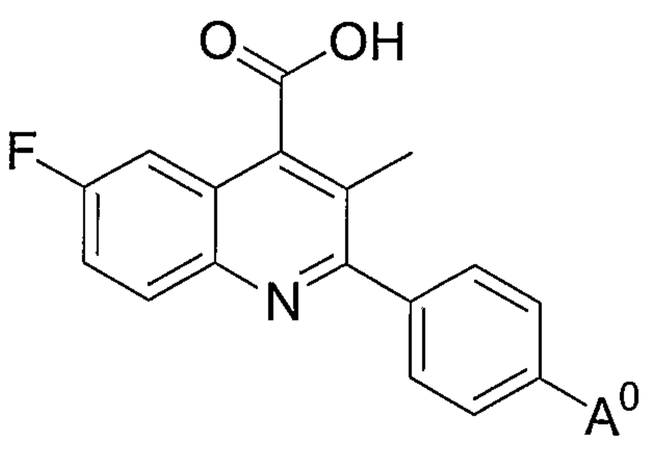
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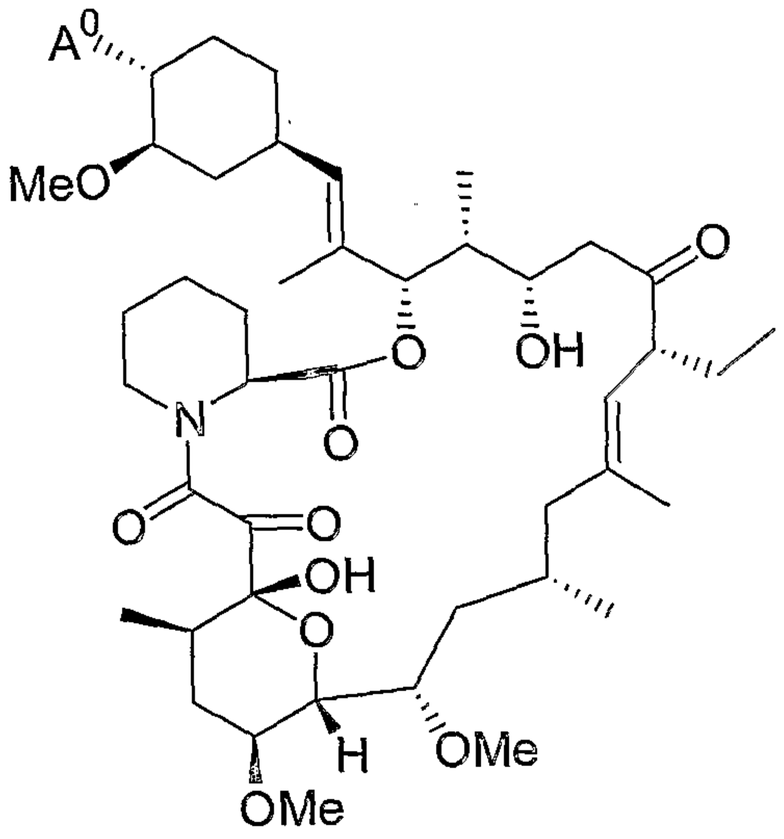
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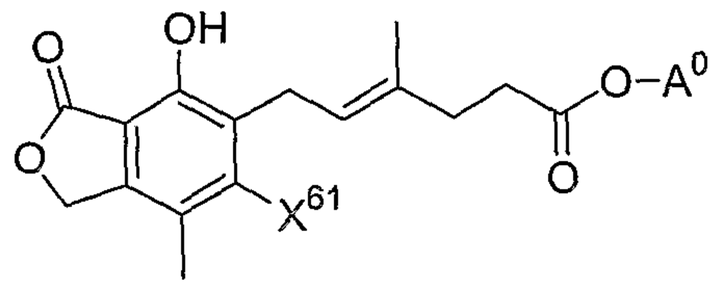
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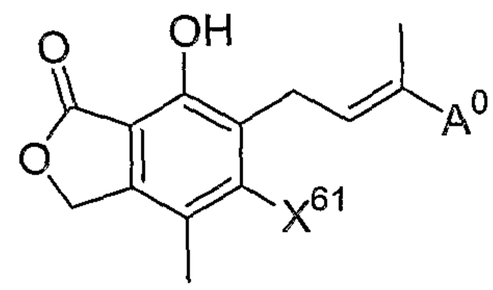
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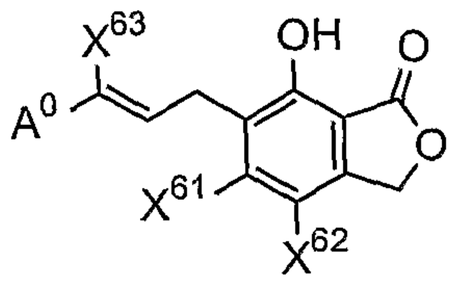
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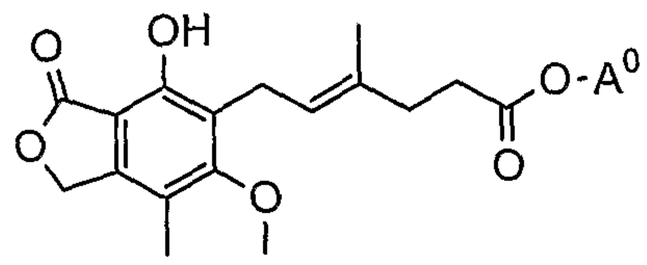
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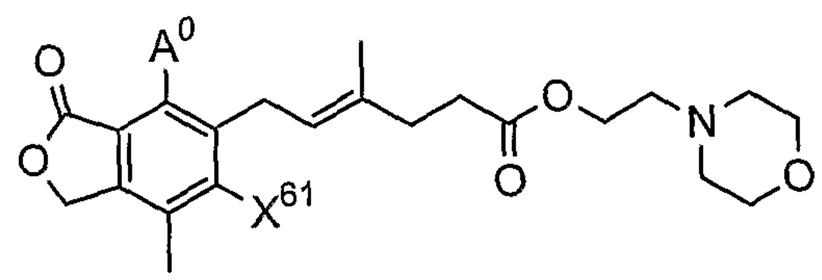
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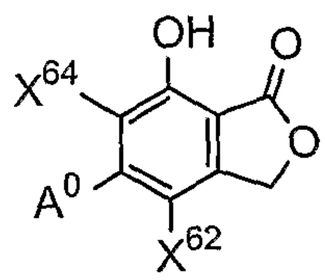
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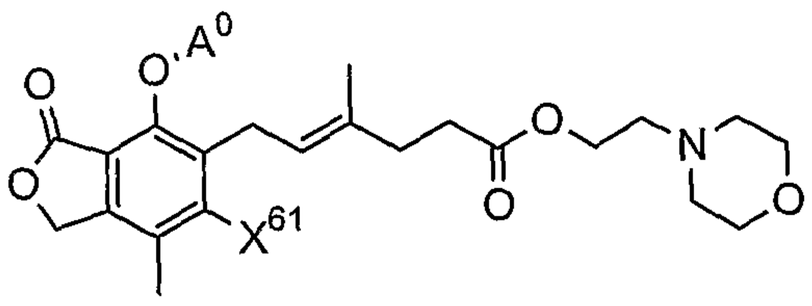
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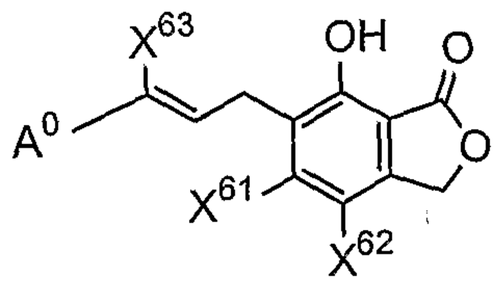
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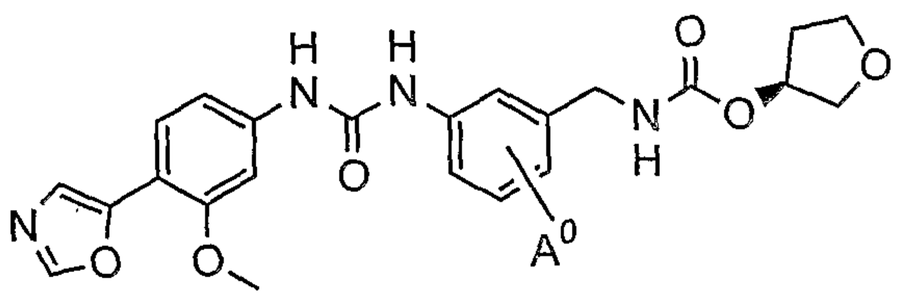
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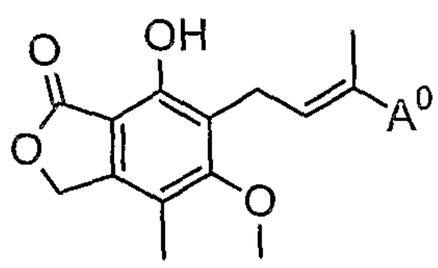
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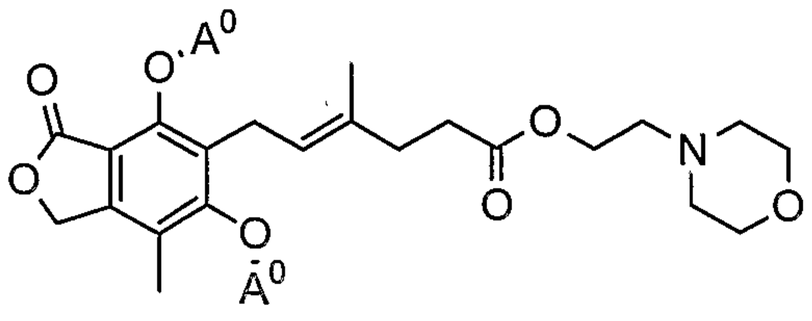
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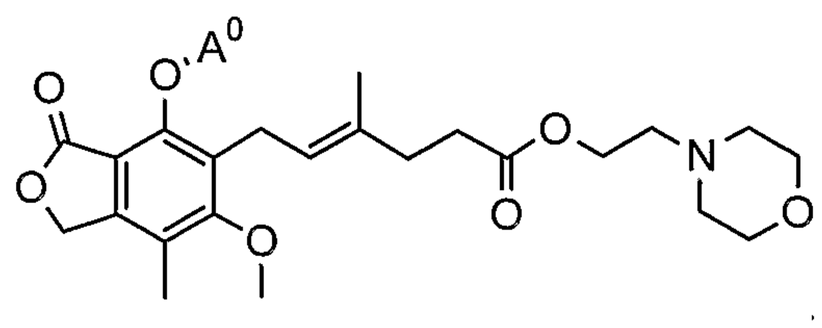
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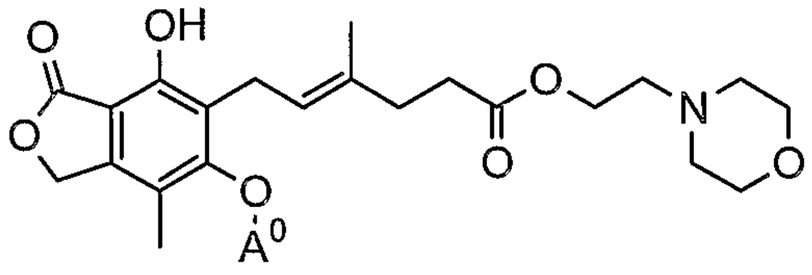
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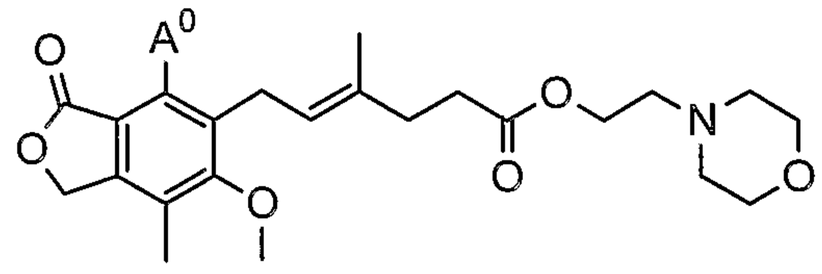
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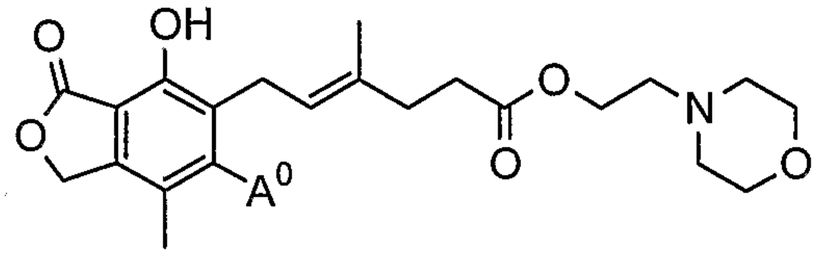
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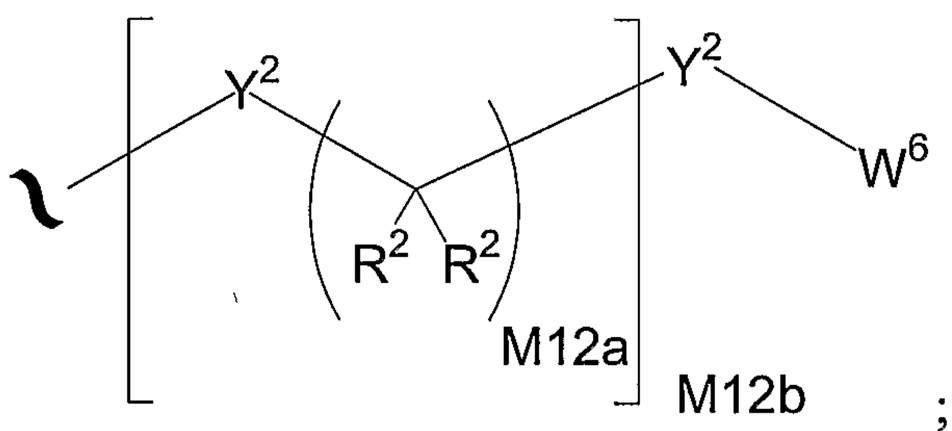


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wherein:

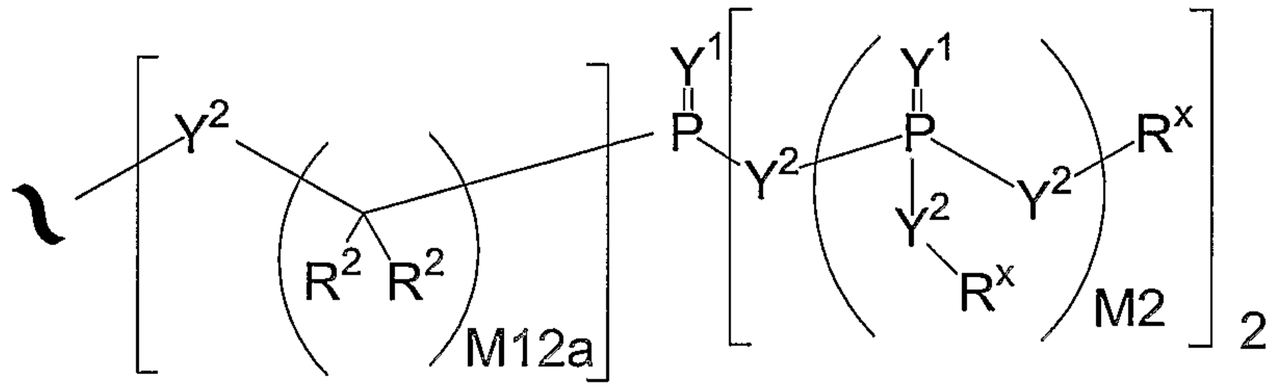
A^0 is A^1;

A^1 is:



;

A^3 is:

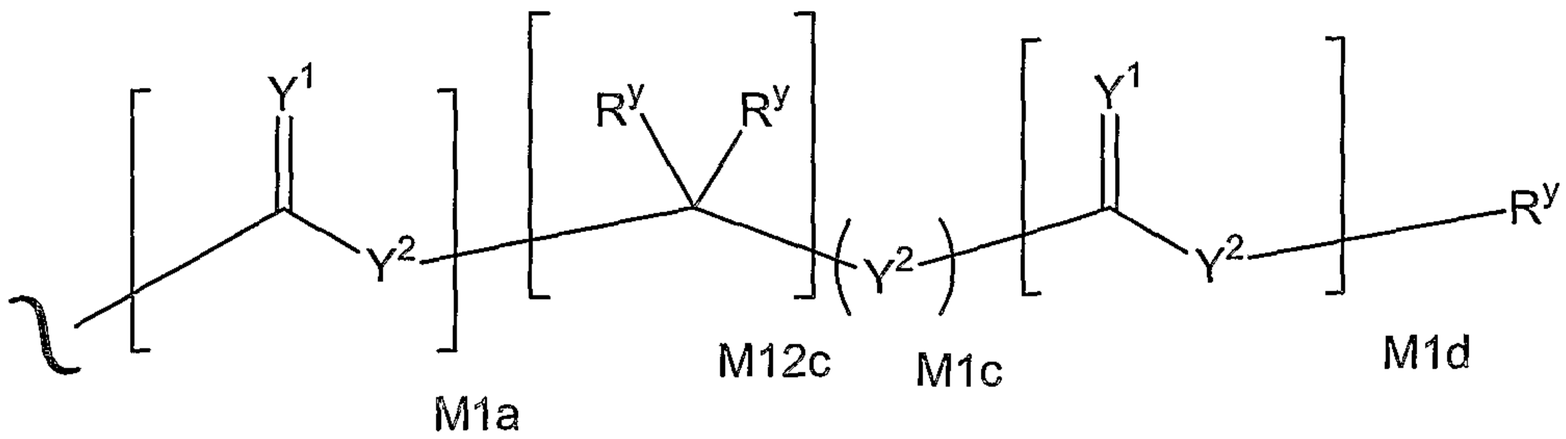


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^2, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

each X^{50} is independently hydrogen, F, Cl, CF_3, CN, methyl, or *tert*-butyl;

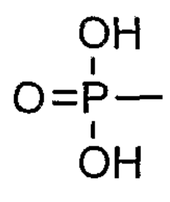
X^{51} is hydrogen, halo, trifluoromethyl, (C1-C3)alkyl, cyano, or (C1-C3)alkoxy;

X^{52} is hydrogen, fluoro, chloro, bromo, methyl, or trifluoromethyl;

X^{53} is -O-, or -S-;

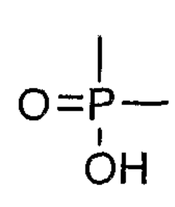
X^{54} and X^{55} are independently selected from hydrogen or a C_1-C_{18} acyl;

X^{56} is hydrogen, a C_1-C_{18} acyl, or



;

or X^{54} is hydrogen and together X^{55} and X^{56} are



;

X^{57} is H, amino, hydroxy, or a halogen selected from Cl and Br;

X^{58} is hydrogen, F, Cl, CF3, cyano, methyl, or t-butyl;

X^{59} is hydrogen, CH_2OH;

X^{60} is $CO(CH_2)_6CONMe(CH_2)2_SO_3H$;

X^{62} is methyl, chloro, or trifluoromethyl;

X^{63} is H, methyl, ethyl, cyclopropyl, vinyl, or trifluoromethyl;

X^{64} is H, methyl, ethyl, cyclopropyl, chloro, vinyl, allyl, 3-methyl-1-buten-1-yl;

X^{65} is hydrogen or F; and

Ar is aryl or heteroaryl.

The invention provides a pharmaceutical composition comprising an effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable diluent or carrier.

This invention pertains to a method of increasing cellular accumulation and retention of drug compounds, thus improving their therapeutic and diagnostic value, comprising linking the compound to one or more phosphonate groups.

The invention also provides a method for the maintenance of immunosuppression, for example, following transplant surgery, comprising administering to an animal (e.g. a mammal) an effective amount of a compound of the invention.

The invention also provides a method for modulating an immune response *in vitro* or *in vivo* comprising contacting a sample in need of such treatment with a compound of the invention.

The invention also provides a method of inhibiting an immune response in an animal (e.g. a mammal), comprising administering an effective amount of a compound of the invention to the animal.

The invention also provides a method of treating the symptoms or effects of an autoimmune disease (e.g. psoriasis, rheumatoid arthritis, lupus erythematosus, multiple sclerosis, diabetes, Chron's disease, etc.) in an animal (e.g. a mammal), comprising administering an effective amount of a compound of the invention to the animal.

The invention also provides a method of treating the symptoms or effects of transplant rejection in an animal (e.g. a mammal), comprising administering an effective amount of a compound of the invention to the animal.

The invention also provides a method for inhibiting the proliferation of human T cells and/or downregulating the production of Th1 or Th2 type cytokines in an animal (e.g. a mammal) comprising administering a compound of the invention to the animal.

The invention also provides a method for treating atopic dermatitis in an animal (e.g. a mammal), comprising administering an effective amount of a compound of the invention to the animal.

The invention also provides a method for inhibiting one or more T-lymphocyte functions in an animal (e.g. a mammal), comprising administering an effective amount of a compound of the invention to the animal.

The invention also provides a method for inhibiting dihydroorotate dehydrogenase in an animal (e.g. a mammal), comprising administering an effective amount of a compound of the invention to the animal.

The invention also provides a compound of the invention for use in medical therapy (preferably for use in the maintenance of immunosuppression following transplant surgery, inhibiting an immune response, treating an autoimmune disease, treating atopic dermatitis, inhibiting the proliferation of human T cells, or downregulating the production of Th1 or Th2 type cytokines), as well as the use of a compound of the invention for the manufacture of a medicament useful for maintenance of immunosuppression following transplant surgery in an animal (e.g. a mammal). The invention also provides the use of a compound of the invention for the manufacture of a medicament useful for inhibiting an immune response in an animal (e.g. a mammal). The invention also provides the use of a compound of the invention for the manufacture of a medicament useful for treating an autoimmune disease in an animal (e.g. a mammal). The invention also provides the use of a compound of the invention for the manufacture of a medicament useful for inhibiting the proliferation of human T cells or downregulating the production of Th1 or Th2 type cytokines in an animal.

The invention also provides a method for the maintenance of immunosuppression, for example, following transplant surgery, comprising administering to an animal (*e.g.*, a mammal) an effective amount of a compound of the invention.

The invention also provides processes and novel intermediates disclosed herein which are useful for preparing compounds of the invention. Some of the compounds of the invention are useful to prepare other compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made in detail to certain claims of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated claims, it will be understood that they are not intended to limit the invention to those claims. On the contrary, the invention is intended to cover all alternatives,

modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

DEFINITIONS

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When tradenames are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

"Bioavailability" is the degree to which the pharmaceutically active agent becomes available to the target tissue after the agent's introduction into the body. Enhancement of the bioavailability of a pharmaceutically active agent can provide a more efficient and effective treatment for patients because, for a given dose, more of the pharmaceutically active agent will be available at the targeted tissue sites.

The terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to a heteroatom , 3) single-bonded to a heteroatom, and 4) single-bonded to another heteroatom, wherein each heteroatom can be the same or different. The terms "phosphonate" and "phosphonate group" also include functional groups or moieties that comprise a phosphorous in the same oxidation state as the phosphorous described above, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having the characteristics described above. For example, the terms "phosphonate" and "phosphonate group" include phosphonic acid, phosphonic monoester, phosphonic diester, phosphonamidate, and phosphonthioate functional groups. In one specific embodiment of the invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen, and 4) single-bonded to another oxygen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteristics. In another specific embodiment of the

invention, the terms "phosphonate" and "phosphonate group" include functional groups or moieties within a molecule that comprises a phosphorous that is 1) single-bonded to a carbon, 2) double-bonded to an oxygen, 3) single-bonded to an oxygen or nitrogen, and 4) single-bonded to another oxygen or nitrogen, as well as functional groups or moieties that comprise a prodrug moiety that can separate from a compound so that the compound retains a phosphorous having such characteristics.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e. active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically-active compound.

"Prodrug moiety" refers to a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphotases. Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-CH_2OC(=O)R^9$ and acyloxymethyl carbonates $-CH_2OC(=O)OR^9$ where R^9 is C_1-C_6 alkyl, C_1-C_6 substituted alkyl, C_6-C_{20} aryl or C_6-C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral

bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-CH_2OC(=O)C(CH_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-CH_2OC(=O)OC(CH_3)_3$.

The phosphonate group may be a phosphonate prodrug moiety. The prodrug moiety may be sensitive to hydrolysis, such as, but not limited to a pivaloyloxymethyl carbonate (POC) or POM group. Alternatively, the prodrug moiety may be sensitive to enzymatic potentiated cleavage, such as a lactate ester or a phosphonamidate-ester group.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (De Lombaert et al. (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to the phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate the parent phosphonic acid. In some cases, substituents at the *ortho*-or *para*-position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, e.g., esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate the phosphoric acid and the quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al. (1992) *J. Chem. Soc. Perkin Trans. II* 2345; Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al. (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al. (1996) *J. Med. Chem.* 39: 4958). Cyclic phosphonate esters have also been described as prodrugs of phosphorus-containing compounds (Erion et al., US Patent No. 6312662).

"Protecting group" refers to a moiety of a compound that masks or alters the properties of a functional group or the properties of the compound as a whole. Chemical protecting groups and strategies for protection/deprotection are well known in the art. *See e.g.*, Protective Groups in Organic Chemistry, Theodora W. Greene, John Wiley & Sons, Inc., New York, 1991. Protecting groups are often utilized to mask the reactivity of certain functional groups, to assist in the efficiency of desired chemical reactions, e.g., making and breaking chemical bonds in an ordered and planned fashion. Protection of functional groups of a compound alters other physical properties besides the reactivity of the protected functional group, such as the polarity, lipophilicity (hydrophobicity), and other properties which can be measured by common analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro,* in the instance of chemical intermediates, or *in vivo*, in the case of prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, e.g., alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Any reference to any of the compounds of the invention also includes a reference to a physiologically acceptable salt thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_1–C_4 alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic,

fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound of an hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NX_4^+ (wherein X is independently selected from H or a C_1–C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention will be physiologically acceptable, i.e. they will be salts derived from a physiologically acceptable acid or base. However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived form a physiologically acceptable acid or base, are within the scope of the present invention.

"Alkyl" is C_1-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. Examples are methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -$C(CH_3)_3$), 1-pentyl (n-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$.

"Alkenyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon,

sp^2 double bond. Examples include, but are not limited to, ethylene or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), cyclopentenyl (-C_5H_7), and 5-hexenyl (-CH_2 $CH_2CH_2CH_2$CH=CH_2).

"Alkynyl" is C_2-C_{18} hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, i.e. a carbon-carbon, *sp* triple bond. Examples include, but are not limited to, acetylenic (-C≡CH) and propargyl (-CH_2C≡CH),

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical of 1-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. Typical alkylene radicals include, but are not limited to, methylene (-CH_2-) 1,2-ethyl (-CH_2CH_2-), 1,3-propyl (-$CH_2CH_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical of 2-18 carbon atoms, and having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡CH-).

"Aryl" means a monovalent aromatic hydrocarbon radical of 6-20 carbon atoms derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from benzene, substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, , naphthylmethyl, 2-naphthylethan-1-

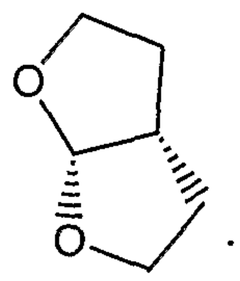
yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group comprises 6 to 20 carbon atoms, e.g., the alkyl moiety, including alkanyl, alkenyl or alkynyl groups, of the arylalkyl group is 1 to 6 carbon atoms and the aryl moiety is 5 to 14 carbon atoms.

"Substituted alkyl", "substituted aryl", and "substituted arylalkyl" mean alkyl, aryl, and arylalkyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R, $-O^-$, -OR, -SR, $-S^-$, $-NR_2$, $-NR_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, NC(=O)R, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)O_2RR$, $-P(=O)O_2RR$ $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)X, -C(S)R, -C(O)OR, $-C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently -H, alkyl, aryl, heterocycle, protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted.

"Heterocycle" as used herein includes by way of example and not limitation these heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (e.g. 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (e.g. O, N, or S).

Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-

thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-

pyrazolyl, and 1-piperidinyl.

"Carbocycle" refers to a saturated, unsaturated or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, phenyl, spiryl and naphthyl.

"Linker" or "link" refers to a chemical moiety comprising a covalent bond or a chain or group of atoms that covalently attaches a phosphonate group to a drug. Linkers include portions of substituents A^1 and A^3, which include moieties such as: repeating units of alkyloxy (e.g., polyethylenoxy, PEG, polymethyleneoxy) and alkylamino (e.g., polyethyleneamino, Jeffamine™); and diacid ester and amides including succinate, succinamide, diglycolate, malonate, and caproamide.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g., melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

The term "treatment" or "treating," to the extent it relates to a disease or condition includes preventing the disease or condition from occurring, inhibiting the disease or condition, eliminating the disease or condition, and/or relieving one or more symptoms of the disease or condition.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, i.e. routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (e.g., acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PG groups do not need to be, and generally are not, the same if

the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

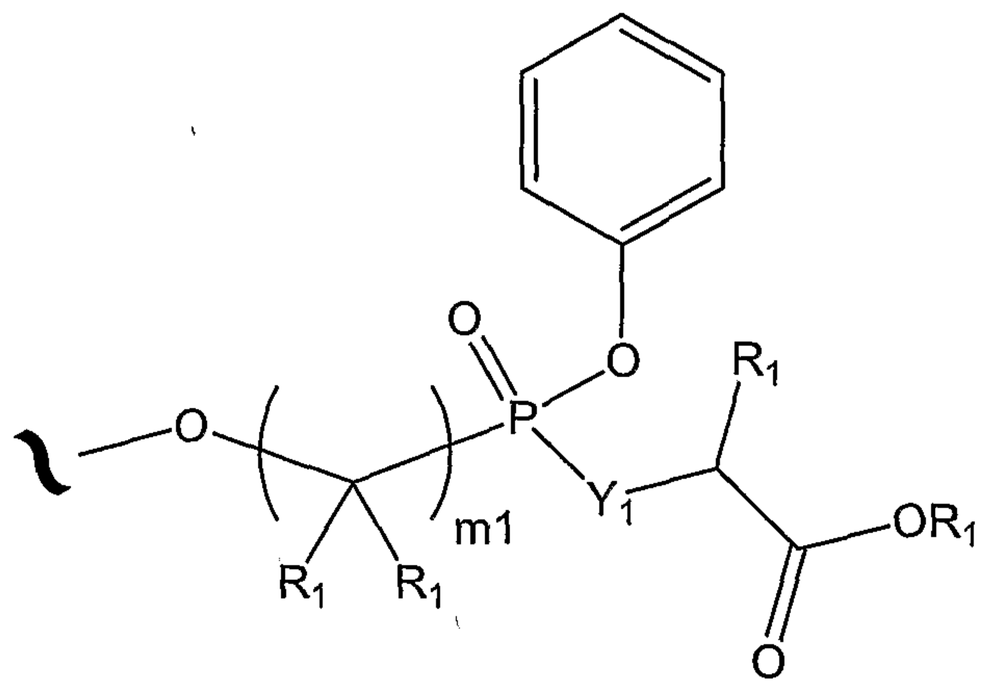
A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The phosphonate moieties of the compounds of the invention may or may not be prodrug moieties, i.e. they may or may not be susceptible to hydrolytic or enzymatic cleavage or modification. Certain phosphonate moieties are stable under most or nearly all metabolic conditions. For example, a dialkylphosphonate, where the alkyl groups are two or more carbons, may have appreciable stability *in vivo* due to a slow rate of hydrolysis.

Within the context of phosphonate prodrug moieties, a large number of structurally-diverse prodrugs have been described for phosphonic acids (Freeman and Ross in Progress in Medicinal Chemistry 34: 112-147 (1997)) and are included within the scope of the present invention. An exemplary phosphonate ester-forming group is the phenyl carbocycle in substructure A_3 having the formula:



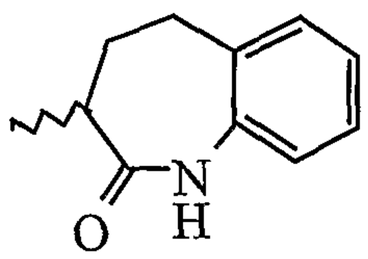
wherein R_1 may be H or C_1–C_{12} alkyl; m1 is 1, 2, 3, 4, 5, 6, 7 or 8, and the phenyl carbocycle is substituted with 0 to 3 R_2 groups. Where Y_1 is O, a lactate ester is formed, and where Y_1 is $N(R_2)$, $N(OR_2)$ or $N(N(R_2)_2$, a phosphonamidate ester results.

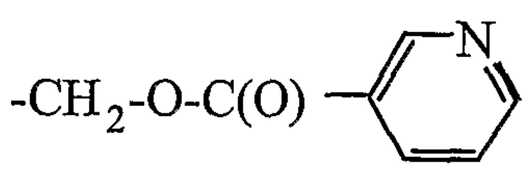
In its ester-forming role, a protecting group typically is bound to any acidic group such as, by way of example and not limitation, a $-CO_2H$ or –C(S)OH group, thereby resulting in $-CO_2R^x$ where R^x is defined herein. Also, R^x for example includes the enumerated ester groups of WO 95/07920.

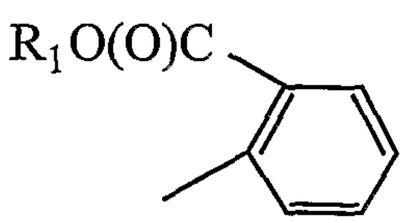
Examples of protecting groups include:

C_3–C_{12} heterocycle (described above) or aryl. These aromatic groups optionally are polycyclic or monocyclic. Examples include phenyl, spiryl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-

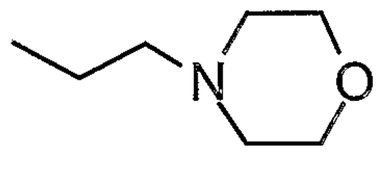
pyrazolyl, 1-, 2-, 3- and 4-pyridinyl, and 1-, 2-, 4- and 5-pyrimidinyl, C_3-C_{12} heterocycle or aryl substituted with halo, R^1, R^1-O-C_1-C_{12} alkylene, C_1-C_{12} alkoxy, CN, NO_2, OH, carboxy, carboxyester, thiol, thioester, C_1-C_{12} haloalkyl (1-6 halogen atoms), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl. Such groups include 2-, 3- and 4-alkoxyphenyl (C_1-C_{12} alkyl), 2-, 3- and 4-methoxyphenyl, 2-, 3- and 4-ethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-diethoxyphenyl, 2- and 3-carboethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-4-hydroxyphenyl, 2- and 3-ethoxy-5-hydroxyphenyl, 2- and 3-ethoxy-6-hydroxyphenyl, 2-, 3- and 4-O-acetylphenyl, 2-, 3- and 4-dimethylaminophenyl, 2-, 3- and 4-methylmercaptophenyl, 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl and 2-, 3- and 4-chlorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-biscarboxyethylphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dimethoxyphenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 3,5-difluorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylphenyl), 2-, 3- and 4-cyanophenyl, 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C_1-C_{12} alkyl including 4-trifluoromethylbenzyl and 2-, 3- and 4-trichloromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 4-N-methylpiperidinyl, 3-N-methylpiperidinyl, 1-ethylpiperazinyl, benzyl, alkylsalicylphenyl (C_1-C_4 alkyl, including 2-, 3- and 4-ethylsalicylphenyl), 2-,3- and 4-acetylphenyl, 1,8-dihydroxynaphthyl (-$C_{10}H_6$-OH) and aryloxy ethyl [C_6-C_9 aryl (including phenoxy ethyl)], 2,2'-dihydroxybiphenyl, 2-, 3- and 4-N,N-dialkylaminophenol, -$C_6H_4CH_2$-$N(CH_3)_2$, trimethoxybenzyl, triethoxybenzyl, 2-alkyl pyridinyl (C_{1-4} alkyl);



;


;


; C_4 - C_8 esters of 2-carboxyphenyl; and C_1-C_4 alkylene-C_3-C_6 aryl (including benzyl, -CH_2-pyrrolyl, -CH_2-thienyl, -CH_2-imidazolyl, -CH_2-oxazolyl, -CH_2-isoxazolyl, -CH_2-thiazolyl, -CH_2-isothiazolyl, -CH_2-pyrazolyl, -CH_2-pyridinyl and -CH_2-pyrimidinyl) substituted in the aryl moiety by 3 to 5 halogen atoms or 1 to 2 atoms or groups selected from halogen, C_1-C_{12} alkoxy (including methoxy and

ethoxy), cyano, nitro, OH, C_1-C_{12} haloalkyl (1 to 6 halogen atoms; including -CH_2CCl_3), C_1-C_{12} alkyl (including methyl and ethyl), C_2-C_{12} alkenyl or C_2-C_{12} alkynyl; alkoxy ethyl [C_1-C_6 alkyl including -CH_2-CH_2-O-CH_3 (methoxy ethyl)]; alkyl substituted by any of the groups set forth above for aryl, in particular OH or by 1 to 3 halo atoms (including -CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -CH_2CH_3, -$(CH_2)_2CH_3$, -$(CH_2)_3CH_3$, -$(CH_2)_4CH_3$, -$(CH_2)_5CH_3$, -CH_2CH_2F, -CH_2CH_2Cl, -CH_2CF_3, and -CH_2CCl_3);  ; -N-2-propylmorpholino, 2,3-dihydro-6-hydroxyindene, sesamol, catechol monoester, -CH_2-C(O)-N(R^1)$_2$, -CH_2-S(O)(R^1), -CH_2-S(O)$_2$(R^1), -CH_2-CH(OC(O)CH_2R^1)-CH_2(OC(O)CH_2R^1), cholesteryl, enolpyruvate (HOOC-C(=CH_2)-), glycerol;

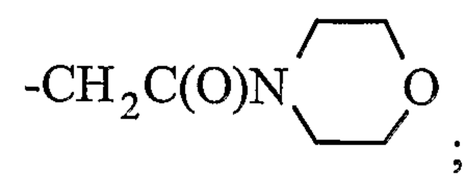
a 5 or 6 carbon monosaccharide, disaccharide or oligosaccharide (3 to 9 monosaccharide residues);

triglycerides such as α-D-β-diglycerides (wherein the fatty acids composing glyceride lipids generally are naturally occurring saturated or unsaturated C_{6-26}, C_{6-18} or C_{6-10} fatty acids such as linoleic, lauric, myristic, palmitic, stearic, oleic, palmitoleic, linolenic and the like fatty acids) linked to acyl of the parental compounds herein through a glyceryl oxygen of the triglyceride;

phospholipids linked to the carboxyl group through the phosphate of the phospholipid;

phthalidyl (shown in Fig. 1 of Clayton et al., *Antimicrob. Agents Chemo.* (1974) 5(6):670-671);

cyclic carbonates such as (5-R_d-2-oxo-1,3-dioxolen-4-yl) methyl esters (Sakamoto et al., *Chem. Pharm. Bull.* (1984) 32(6)2241-2248) where R_d is R_1, R_4 or aryl; and

 ;

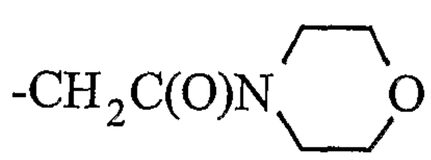
The hydroxyl groups of the compounds of this invention optionally are substituted with one of groups III, IV or V disclosed in WO 94/21604, or with isopropyl.

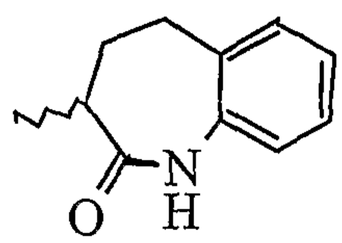
Table A lists examples of protecting group ester moieties that for example

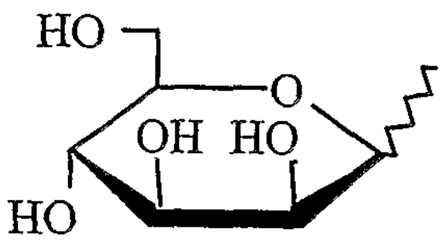
can be bonded via oxygen to -C(O)O- and -P(O)(O-)$_2$ groups. Several amidates also are shown, which are bound directly to -C(O)- or -P(O)$_2$. Esters of structures 1-5, 8-10 and 16, 17, 19-22 are synthesized by reacting the compound herein having a free hydroxyl with the corresponding halide (chloride or acyl chloride and the like) and N ,N-dicyclohexyl-N-morpholine carboxamidine (or another base such as DBU, triethylamine, $CsCO_3$, N,N-dimethylaniline and the like) in DMF (or other solvent such as acetonitrile or N-methylpyrrolidone). When the compound to be protected is a phosphonate, the esters of structures 5-7, 11, 12, 21, and 23-26 are synthesized by reaction of the alcohol or alkoxide salt (or the corresponding amines in the case of compounds such as 13, 14 and 15) with the monochlorophosphonate or dichlorophosphonate (or another activated phosphonate).

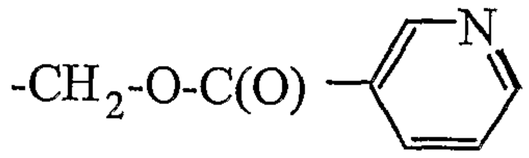
TABLE A

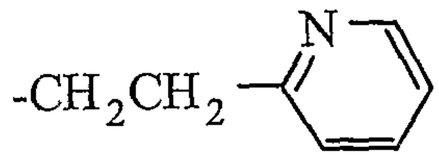
1. -CH_2-C(O)-N(R_1)$_2$ *
2. -CH_2-S(O)(R_1)
3. -CH_2-S(O)$_2$(R_1)
4. -CH_2-O-C(O)-CH_2-C_6H_5
5. 3-cholesteryl
6. 3-pyridyl
7. N-ethylmorpholino
8. -CH_2-O-C(O)-C_6H_5
9. -CH_2-O-C(O)-CH_2CH_3
10. -CH_2-O-C(O)-$C(CH_3)_3$
11. -CH_2-CCl_3
12. -C_6H_5
13. -NH-CH_2-C(O)O-CH_2CH_3
14. -N(CH_3)-CH_2-C(O)O-CH_2CH_3
15. -NHR_1
16. -CH_2-O-C(O)-$C_{10}H_{15}$
17. -CH_2-O-C(O)-$CH(CH_3)_2$
18. -CH_2-C*H(OC(O)CH_2R_1)-CH_2-(OC(O)CH_2R_1)*

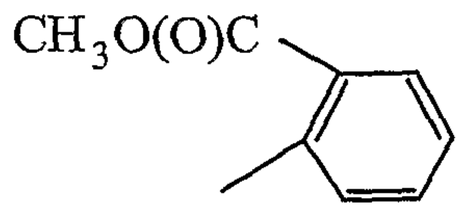
19. 

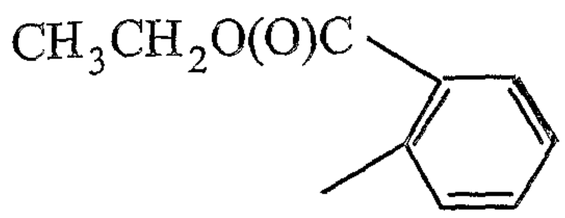
20. 

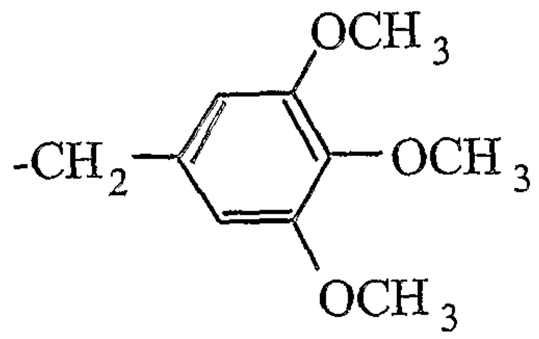
21. 

22. 

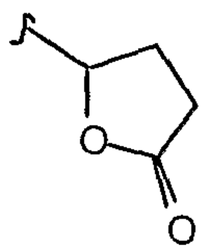
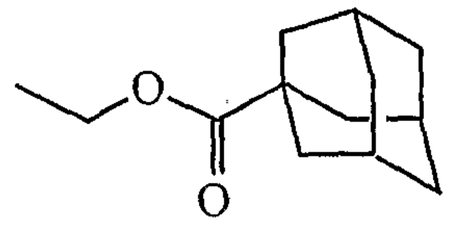
23. 

24. 

25. 

26. 

- chiral center is (R), (S) or racemate.

Other esters that are suitable for use herein are described in EP 632048. Protecting groups also includes "double ester" forming profunctionalities such as $-CH_2OC(O)OCH_3$,  $-CH_2SCOCH_3$, $-CH_2OCON(CH_3)_2$, or alkyl- or aryl-acyloxyalkyl groups of the structure $-CH(R^1 \text{ or } W^5)O((CO)R^{37})$ or $-CH(R^1 \text{ or } W^5)((CO)OR^{38})$ (linked to oxygen of the acidic group) wherein R^{37} and R^{38} are alkyl, aryl, or alkylaryl groups (see U.S. Patent No. 4968788). Frequently R^{37} and R^{38} are bulky groups such as branched alkyl, ortho-substituted aryl, meta-substituted aryl, or combinations thereof, including normal, secondary, iso- and tertiary alkyls of 1-6 carbon atoms. An example is the pivaloyloxymethyl group. These are of particular use with prodrugs for oral administration. Examples of such useful protecting groups are alkylacyloxymethyl esters and their derivatives, including -  ; - $CH_2OC(O)C_{10}H_{15}$, $-CH_2OC(O)C(CH_3)_3$, $-CH(CH_2OCH_3)OC(O)C(CH_3)_3$, - $CH(CH(CH_3)_2)OC(O)C(CH_3)_3$, $-CH_2OC(O)CH_2CH(CH_3)_2$, - $CH_2OC(O)C_6H_{11}$, $-CH_2OC(O)C_6H_5$, $-CH_2OC(O)C_{10}H_{15}$, - $CH_2OC(O)CH_2CH_3$, $-CH_2OC(O)CH(CH_3)_2$, $-CH_2OC(O)C(CH_3)_3$ and - $CH_2OC(O)CH_2C_6H_5$.

In some claims the protected acidic group is an ester of the acidic group and is the residue of a hydroxyl-containing functionality. In other claims, an amino compound is used to protect the acid functionality. The residues of suitable hydroxyl or amino-containing functionalities are set forth above or are found in WO 95/07920. Of particular interest are the residues of amino acids, amino acid esters, polypeptides, or aryl alcohols. Typical amino acid, polypeptide and carboxyl-esterified amino acid residues are described on pages 11-18 and related text of WO 95/07920 as groups L1 or L2. WO 95/07920 expressly teaches the amidates of phosphonic acids, but it will be understood that such amidates are formed with any of the acid groups set forth herein and the amino acid residues set forth in WO 95/07920.

Typical esters for protecting acidic functionalities are also described in WO 95/07920, again understanding that the same esters can be formed with the acidic groups herein as with the phosphonate of the '920 publication. Typical ester groups are defined at least on WO 95/07920 pages 89-93 (under R^{31} or R^{35}), the table on page 105, and pages 21-23 (as R). Of particular interest are esters of unsubstituted aryl such as phenyl or arylalkyl such benzyl, or hydroxy-, halo-, alkoxy-, carboxy- and/or alkylestercarboxy-substituted aryl or alkylaryl, especially phenyl, ortho-ethoxyphenyl, or C_1-C_4 alkylestercarboxyphenyl (salicylate C_1-C_{12} alkylesters).

The protected acidic groups, particularly when using the esters or amides of WO 95/07920, are useful as prodrugs for oral administration. However, it is not essential that the acidic group be protected in order for the compounds of this invention to be effectively administered by the oral route. When the compounds of the invention having protected groups, in particular amino acid amidates or substituted and unsubstituted aryl esters are administered systemically or orally they are capable of hydrolytic cleavage *in vivo* to yield the free acid.

One or more of the acidic hydroxyls are protected. If more than one acidic hydroxyl is protected then the same or a different protecting group is employed, e.g., the esters may be different or the same, or a mixed amidate and ester may be used.

Typical hydroxy protecting groups described in Greene (pages 14-118) include substituted methyl and alkyl ethers, substituted benzyl ethers, silyl

ethers, esters including sulfonic acid esters, and carbonates. For example:

- Ethers (methyl, *t*-butyl, allyl);
- Substituted Methyl Ethers (Methoxymethyl, Methylthiomethyl, *t*-Butylthiomethyl, (Phenyldimethylsilyl)methoxymethyl, Benzyloxymethyl, *p*-Methoxybenzyloxymethyl, (4-Methoxyphenoxy)methyl, Guaiacolmethyl, *t*-Butoxymethyl, 4-Pentenyloxymethyl, Siloxymethyl, 2-Methoxyethoxymethyl, 2,2,2-Trichloroethoxymethyl, Bis(2-chloroethoxy)methyl, 2-(Trimethylsilyl)ethoxymethyl, Tetrahydropyranyl, 3-Bromotetrahydropyranyl, Tetrahydropthiopyranyl, 1-Methoxycyclohexyl, 4-Methoxytetrahydropyranyl, 4-Methoxytetrahydrothiopyranyl, 4-Methoxytetrahydropthiopyranyl *S,S*-Dioxido, 1-[(2-Chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl, 1,4-Dioxan-2-yl, Tetrahydrofuranyl, Tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl));
- Substituted Ethyl Ethers (1-Ethoxyethyl, 1-(2-Chloroethoxy)ethyl, 1-Methyl-1-methoxyethyl, 1-Methyl-1-benzyloxyethyl, 1-Methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-Trichloroethyl, 2-Trimethylsilylethyl, 2-(Phenylselenyl)ethyl,
- *p*-Chlorophenyl, *p*-Methoxyphenyl, 2,4-Dinitrophenyl, Benzyl);
- Substituted Benzyl Ethers (*p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *p*-Halobenzyl, 2,6-Dichlorobenzyl, *p*-Cyanobenzyl, *p*-Phenylbenzyl, 2- and 4-Picolyl, 3-Methyl-2-picolyl *N*-Oxido, Diphenylmethyl, *p,p*'-Dinitrobenzhydryl, 5-Dibenzosuberyl, Triphenylmethyl, α-Naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, Di(*p*-methoxyphenyl)phenylmethyl, Tri(*p*-methoxyphenyl)methyl, 4-(4'-Bromophenacyloxy)phenyldiphenylmethyl, 4,4',4''-Tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-Tris(levulinoyloxyphenyl)methyl, 4,4',4''-Tris(benzoyloxyphenyl)methyl, 3-(Imidazol-1-ylmethyl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-Bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-Anthryl, 9-(9-Phenyl)xanthenyl, 9-(9-Phenyl-10-oxo)anthryl, 1,3-Benzodithiolan-2-yl, Benzisothiazolyl *S,S*-Dioxido);
- Silyl Ethers (Trimethylsilyl, Triethylsilyl, Triisopropylsilyl,

Dimethylisopropylsilyl, Diethylisopropylsilyl, Dimethylthexylsilyl, *t*-Butyldimethylsilyl, *t*-Butyldiphenylsilyl, Tribenzylsilyl, Tri-*p*-xylylsilyl, Triphenylsilyl, Diphenylmethylsilyl, *t*-Butylmethoxyphenylsilyl);

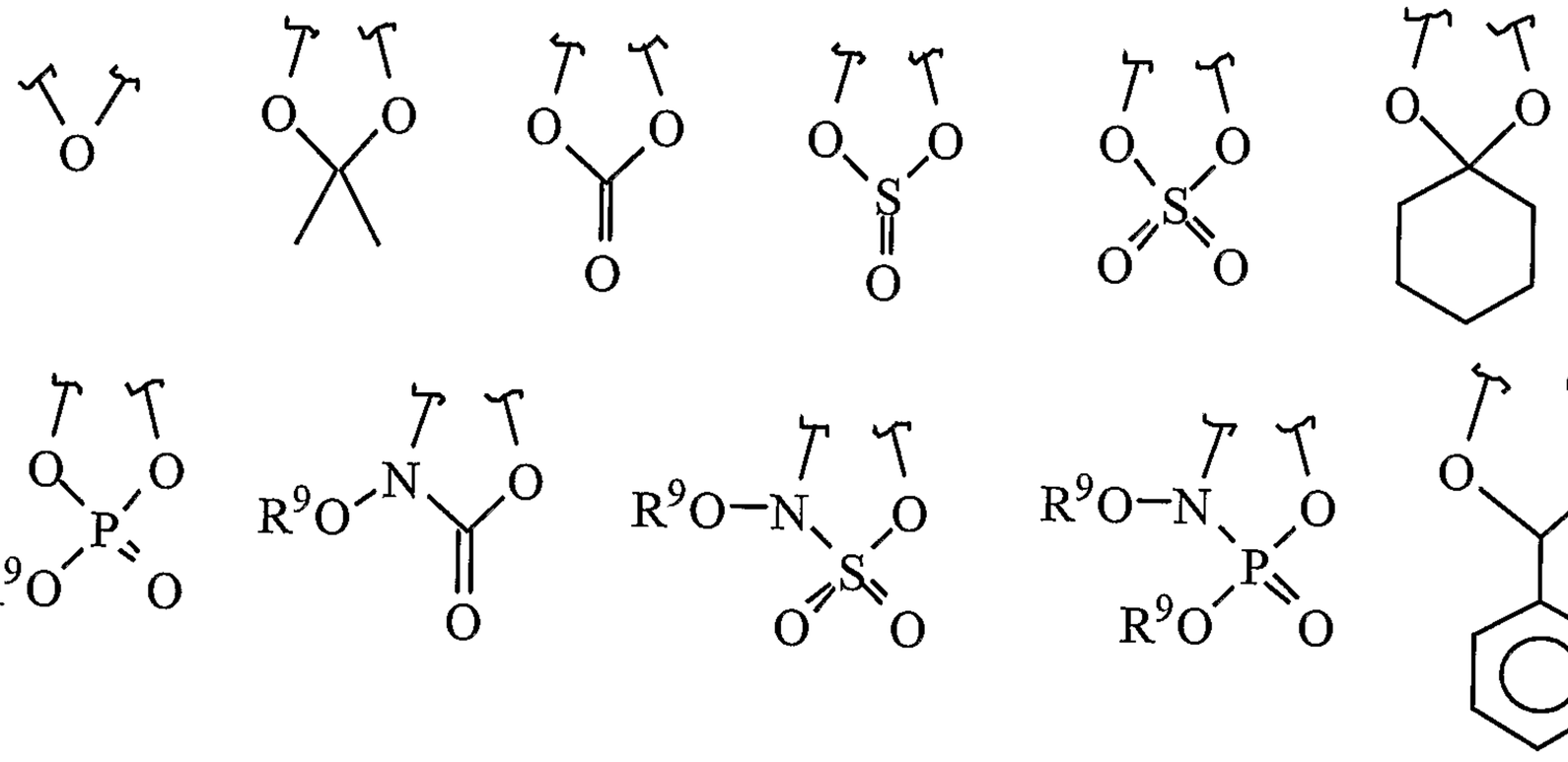
- Esters (Formate, Benzoylformate, Acetate, Choroacetate, Dichloroacetate, Trichloroacetate, Trifluoroacetate, Methoxyacetate, Triphenylmethoxyacetate, Phenoxyacetate, *p*-Chlorophenoxyacetate, *p*-poly-Phenylacetate, 3-Phenylpropionate, 4-Oxopentanoate (Levulinate), 4,4-(Ethylenedithio)pentanoate, Pivaloate, Adamantoate, Crotonate, 4-Methoxycrotonate, Benzoate, *p*-Phenylbenzoate, 2,4,6-Trimethylbenzoate (Mesitoate));
- Carbonates (Methyl, 9-Fluorenylmethyl, Ethyl, 2,2,2-Trichloroethyl, 2-(Trimethylsilyl)ethyl, 2-(Phenylsulfonyl)ethyl, 2-(Triphenylphosphonio)ethyl, Isobutyl, Vinyl, Allyl, *p*-Nitrophenyl, Benzyl, *p*-Methoxybenzyl, 3,4-Dimethoxybenzyl, *o*-Nitrobenzyl, *p*-Nitrobenzyl, *S*-Benzyl Thiocarbonate, 4-Ethoxy-1-naphthyl, Methyl Dithiocarbonate);
- Groups With Assisted Cleavage (2-Iodobenzoate, 4-Azidobutyrate, 4-Nitro-4-methylpentanoate, *o*-(Dibromomethyl)benzoate, 2-Formylbenzenesulfonate, 2-(Methylthiomethoxy)ethyl Carbonate, 4-(Methylthiomethoxy)butyrate, 2-(Methylthiomethoxymethyl)benzoate);
- Miscellaneous Esters (2,6-Dichloro-4-methylphenoxyacetate, 2,6-Dichloro-4-(1,1,3,3 tetramethylbutyl)phenoxyacetate, 2,4-Bis(1,1-dimethylpropyl)phenoxyacetate, Chlorodiphenylacetate, Isobutyrate, Monosuccinate, (*E*)-2-Methyl-2-butenoate (Tigloate), *o*-(Methoxycarbonyl)benzoate, *p*-poly-Benzoate, α-Naphthoate, Nitrate, Alkyl *N,N,N',N'*-Tetramethylphosphorodiamidate, *N*-Phenylcarbamate, Borate, Dimethylphosphinothioyl, 2,4-Dinitrophenylsulfenate); and
- Sulfonates (Sulfate, Methanesulfonate (Mesylate), Benzylsulfonate, Tosylate).

Typical 1,2-diol protecting groups (thus, generally where two OH groups are taken together with the protecting functionality) are described in Greene at pages 118-142 and include Cyclic Acetals and Ketals (Methylene, Ethylidene, 1-*t*-Butylethylidene, 1-Phenylethylidene, (4-Methoxyphenyl)ethylidene, 2,2,2-Trichloroethylidene, Acetonide (Isopropylidene), Cyclopentylidene,

Cyclohexylidene, Cycloheptylidene, Benzylidene, *p*-Methoxybenzylidene, 2,4-Dimethoxybenzylidene, 3,4-Dimethoxybenzylidene, 2-Nitrobenzylidene); Cyclic Ortho Esters (Methoxymethylene, Ethoxymethylene, Dimethoxymethylene, 1-Methoxyethylidene, 1-Ethoxyethylidine, 1,2-Dimethoxyethylidene, α-Methoxybenzylidene, 1-(*N,N*-Dimethylamino)ethylidene Derivative, α-(*N,N*-Dimethylamino)benzylidene Derivative, 2-Oxacyclopentylidene); Silyl Derivatives (Di-*t*-butylsilylene Group, 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene), and Tetra-*t*-butoxydisiloxane-1,3-diylidene), Cyclic Carbonates, Cyclic Boronates, Ethyl Boronate and Phenyl Boronate.

More typically, 1,2-diol protecting groups include those shown in Table B, still more typically, epoxides, acetonides, cyclic ketals and aryl acetals.

Table B



wherein R^9 is C_1-C_6 alkyl.

Amino protecting groups

Another set of protecting groups include any of the typical amino protecting groups described by Greene at pages 315-385. They include:

- Carbamates: (methyl and ethyl, 9-fluorenylmethyl, 9(2-sulfo)fluorenylmethyl, 9-(2,7-dibromo)fluorenylmethyl, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl, 4-methoxyphenacyl);
- Substituted Ethyl: (2,2,2-trichoroethyl, 2-trimethylsilylethyl, 2-phenylethyl, 1-(1-adamantyl)-1-methylethyl, 1,1-dimethyl-2-haloethyl, 1,1-dimethyl-2,2-

dibromoethyl, 1,1-dimethyl-2,2,2-trichloroethyl, 1-methyl-1-(4-biphenylyl)ethyl, 1-(3,5-di-*t*-butylphenyl)-1-methylethyl, 2-(2'- and 4'-pyridyl)ethyl, 2-(*N,N*-dicyclohexylcarboxamido)ethyl, *t*-butyl, 1-adamantyl, vinyl, allyl, 1-isopropylallyl, cinnamyl, 4-nitrocinnamyl, 8-quinolyl, *N*-hydroxypiperidinyl, alkyldithio, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, *p*-bromobenzyl, *p*-chlorobenzyl, 2,4-dichlorobenzyl, 4-methylsulfinylbenzyl, 9-anthrylmethyl, diphenylmethyl);

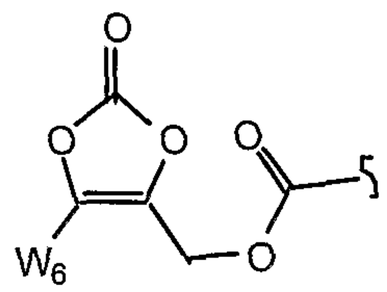
- Groups With Assisted Cleavage: (2-methylthioethyl, 2-methylsulfonylethyl, 2-(*p*-toluenesulfonyl)ethyl, [2-(1,3-dithianyl)]methyl, 4-methylthiophenyl, 2,4-dimethylthiophenyl, 2-phosphonioethyl, 2-triphenylphosphonioisopropyl, 1,1-dimethyl-2-cyanoethyl, *m*-choro-*p*-acyloxybenzyl, *p*-(dihydroxyboryl)benzyl, 5-benzisoxazolylmethyl, 2-(trifluoromethyl)-6-chromonylmethyl);
- Groups Capable of Photolytic Cleavage: (*m*-nitrophenyl, 3,5-dimethoxybenzyl, *o*-nitrobenzyl, 3,4-dimethoxy-6-nitrobenzyl, phenyl(*o*-nitrophenyl)methyl); Urea-Type Derivatives (phenothiazinyl-(10)-carbonyl, *N'*-*p*-toluenesulfonylaminocarbonyl, *N'*-phenylaminothiocarbonyl);
- Miscellaneous Carbamates: (*t*-amyl, *S*-benzyl thiocarbamate, *p*-cyanobenzyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropylmethyl, *p*-decyloxybenzyl, diisopropylmethyl, 2,2-dimethoxycarbonylvinyl, *o*-(*N,N*-dimethylcarboxamido)benzyl, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl, 1,1-dimethylpropynyl, di(2-pyridyl)methyl, 2-furanylmethyl, 2-Iodoethyl, Isobornyl, Isobutyl, Isonicotinyl, *p*-(*p'*-Methoxyphenylazo)benzyl, 1-methylcyclobutyl, 1-methylcyclohexyl, 1-methyl-1-cyclopropylmethyl, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl, 1-methyl-1-(*p*-phenylazophenyl)ethyl, 1-methyl-1-phenylethyl, 1-methyl-1-(4-pyridyl)ethyl, phenyl, *p*-(phenylazo)benzyl, 2,4,6-tri-*t*-butylphenyl, 4-(trimethylammonium)benzyl, 2,4,6-trimethylbenzyl);
- Amides: (*N*-formyl, *N*-acetyl, *N*-choroacetyl, *N*-trichoroacetyl, *N*-trifluoroacetyl, *N*-phenylacetyl, *N*-3-phenylpropionyl, *N*-picolinoyl, *N*-3-pyridylcarboxamide, *N*-benzoylphenylalanyl, *N*-benzoyl, *N-p*-phenylbenzoyl);
- Amides With Assisted Cleavage: (*N*-*o*-nitrophenylacetyl, *N*-*o*-

nitrophenoxyacetyl, *N*-acetoacetyl, (*N'*-dithiobenzyloxycarbonylamino)acetyl, *N*-3-(*p*-hydroxyphenyl)propionyl, *N*-3-(*o*-nitrophenyl)propionyl, *N*-2-methyl-2-(*o*-nitrophenoxy)propionyl, *N*-2-methyl-2-(*o*-phenylazophenoxy)propionyl, *N*-4-chlorobutyryl, *N*-3-methyl-3-nitrobutyryl, *N*-*o*-nitrocinnamoyl, *N*-acetylmethionine, *N*-*o*-nitrobenzoyl, *N*-*o*-(benzoyloxymethyl)benzoyl, 4,5-diphenyl-3-oxazolin-2-one);

- Cyclic Imide Derivatives: (*N*-phthalimide, *N*-dithiasuccinoyl, *N*-2,3-diphenylmaleoyl, *N*-2,5-dimethylpyrrolyl, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct, 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3-5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridonyl);
- *N*-Alkyl and *N*-Aryl Amines: (*N*-methyl, *N*-allyl, *N*-[2-(trimethylsilyl)ethoxy]methyl, *N*-3-acetoxypropyl, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl), Quaternary Ammonium Salts, *N*-benzyl, *N*-di(4-methoxyphenyl)methyl, *N*-5-dibenzosuberyl, *N*-triphenylmethyl, *N*-(4-methoxyphenyl)diphenylmethyl, *N*-9-phenylfluorenyl, *N*-2,7-dichloro-9-fluorenylmethylene, *N*-ferrocenylmethyl, *N*-2-picolylamine *N'*-oxide);
- Imine Derivatives: (*N*-1,1-dimethylthiomethylene, *N*-benzylidene, *N*-*p*-methoxybenylidene, *N*-diphenylmethylene, *N*-[(2-pyridyl)mesityl]methylene, *N*,(*N'*,*N'*-dimethylaminomethylene, *N*,*N'*-isopropylidene, *N*-*p*-nitrobenzylidene, *N*-salicylidene, *N*-5-chlorosalicylidene, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylene, *N*-cyclohexylidene);
- Enamine Derivatives: (*N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl));
- *N*-Metal Derivatives (*N*-borane derivatives, *N*-diphenylborinic acid derivatives, *N*-[phenyl(pentacarbonylchromium- or -tungsten)]carbenyl, *N*-copper or *N*-zinc chelate);
- N-N Derivatives: (*N*-nitro, *N*-nitroso, *N*-oxide);
- N-P Derivatives: (*N*-diphenylphosphinyl, *N*-dimethylthiophosphinyl, *N*-diphenylthiophosphinyl, *N*-dialkyl phosphoryl, *N*-dibenzyl phosphoryl, *N*-diphenyl phosphoryl);
- N-Si Derivatives, N-S Derivatives, and N-Sulfenyl Derivatives: (*N*-benzenesulfenyl, *N*-*o*-nitrobenzenesulfenyl, *N*-2,4-dinitrobenzenesulfenyl, *N*-pentachlorobenzenesulfenyl, *N*-2-nitro-4-methoxybenzenesulfenyl, *N*-

triphenylmethylsulfenyl, *N*-3-nitropyridinesulfenyl); and *N*-sulfonyl Derivatives (*N*-*p*-toluenesulfonyl, *N*-benzenesulfonyl, *N*-2,3,6-trimethyl-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethoxybenzenesulfonyl, *N*-2,6-dimethyl-4-methoxybenzenesulfonyl, *N*-pentamethylbenzenesulfonyl, *N*-2,3,5,6,-tetramethyl-4-methoxybenzenesulfonyl, *N*-4-methoxybenzenesulfonyl, *N*-2,4,6-trimethylbenzenesulfonyl, *N*-2,6-dimethoxy-4-methylbenzenesulfonyl, *N*-2,2,5,7,8-pentamethylchroman-6-sulfonyl, *N*-methanesulfonyl, *N*-β-trimethylsilyethanesulfonyl, *N*-9-anthracenesulfonyl, *N*-4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonyl, *N*-benzylsulfonyl, *N*-trifluoromethylsulfonyl, *N*-phenacylsulfonyl).

More typically, protected amino groups include carbamates and amides, still more typically, $-NHC(O)R^1$ or $-N=CR^1N(R^1)_2$. Another protecting group, also useful as a prodrug for amino or $-NH(R^5)$, is:



See for example Alexander, J. et al. (1996) *J. Med. Chem.* 39:480-486.

Amino acid and polypeptide protecting group and conjugates

An amino acid or polypeptide protecting group of a compound of the invention has the structure $R^{15}NHCH(R^{16})C(O)-$, where R^{15} is H, an amino acid or polypeptide residue, or R^5, and R^{16} is defined below.

R^{16} is lower alkyl or lower alkyl (C_1-C_6) substituted with amino, carboxyl, amide, carboxyl ester, hydroxyl, C_6-C_7 aryl, guanidinyl, imidazolyl, indolyl, sulfhydryl, sulfoxide, and/or alkylphosphate. R^{10} also is taken together with the amino acid α N to form a proline residue (R^{10} = $-CH_2)_3-$). However, R^{10} is generally the side group of a naturally-occurring amino acid such as H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH(CH_3)_2$, $-CHCH_3-CH_2-CH_3$, $-CH_2-C_6H_5$, $-CH_2CH_2-S-CH_3$, $-CH_2OH$, $-CH(OH)-CH_3$, $-CH_2-SH$, $-CH_2-C_6H_4OH$, $-CH_2-CO-NH_2$, $-CH_2-CH_2-CO-NH_2$, $-CH_2-COOH$, $-CH_2-CH_2-COOH$, $-(CH_2)_4-NH_2$ and $-(CH_2)_3-NH-C(NH_2)-NH_2$. R_{10} also includes 1-guanidinoprop-3-yl, benzyl, 4-hydroxybenzyl, imidazol-4-yl, indol-3-yl, methoxyphenyl and ethoxyphenyl.

Another set of protecting groups include the residue of an amino-containing compound, in particular an amino acid, a polypeptide, a protecting group, $-NHSO_2R$, $NHC(O)R$, $-N(R)_2$, NH_2 or $-NH(R)(H)$, whereby for example a carboxylic acid is reacted, i.e. coupled, with the amine to form an amide, as in $C(O)NR_2$. A phosphonic acid may be reacted with the amine to form a phosphonamidate, as in $-P(O)(OR)(NR_2)$.

In general, amino acids have the structure $R^{17}C(O)CH(R^{16})NH-$, where R^{17} is -OH, -OR, an amino acid or a polypeptide residue. Amino acids are low molecular weight compounds, on the order of less than about 1000 MW and which contain at least one amino or imino group and at least one carboxyl group. Generally the amino acids will be found in nature, i.e., can be detected in biological material such as bacteria or other microbes, plants, animals or man. Suitable amino acids typically are alpha amino acids, i.e. compounds characterized by one amino or imino nitrogen atom separated from the carbon atom of one carboxyl group by a single substituted or unsubstituted alpha carbon atom. Of particular interest are hydrophobic residues such as mono-or di-alkyl or aryl amino acids, cycloalkylamino acids and the like. These residues contribute to cell permeability by increasing the partition coefficient of the parental drug. Typically, the residue does not contain a sulfhydryl or guanidino substituent.

Naturally-occurring amino acid residues are those residues found naturally in plants, animals or microbes, especially proteins thereof. Polypeptides most typically will be substantially composed of such naturally-occurring amino acid residues. These amino acids are glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, methionine, glutamic acid, aspartic acid, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, asparagine, glutamine and hydroxyproline. Additionally, unnatural amino acids, for example, valanine, phenylglycine and homoarginine are also included. Commonly encountered amino acids that are not gene-encoded may also be used in the present invention. All of the amino acids used in the present invention may be either the D- or L- optical isomer. In addition, other peptidomimetics are also useful in the present invention. For a general review, see Spatola, A. F., in Chemistry and Biochemistry of Amino Acids,

Peptides and Proteins, B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983).

When protecting groups are single amino acid residues or polypeptides they optionally are substituted at R^3 of substituents A^1, A^2 or A^3 in Formula I. These conjugates are produced by forming an amide bond between a carboxyl group of the amino acid (or C-terminal amino acid of a polypeptide for example). Similarly, conjugates are formed between R^3 (Formula I) and an amino group of an amino acid or polypeptide. Generally, only one of any site in the parental molecule is amidated with an amino acid as described herein, although it is within the scope of this invention to introduce amino acids at more than one permitted site. Usually, a carboxyl group of R^3 is amidated with an amino acid. In general, the α-amino or α-carboxyl group of the amino acid or the terminal amino or carboxyl group of a polypeptide are bonded to the parental functionalities, i.e., carboxyl or amino groups in the amino acid side chains generally are not used to form the amide bonds with the parental compound (although these groups may need to be protected during synthesis of the conjugates as described further below).

With respect to the carboxyl-containing side chains of amino acids or polypeptides it will be understood that the carboxyl group optionally will be blocked, e.g., by R^1, esterified with R^5 or amidated. Similarly, the amino side chains R^{16} optionally will be blocked with R^1 or substituted with R^5.

Such ester or amide bonds with side chain amino or carboxyl groups, like the esters or amides with the parental molecule, optionally are hydrolyzable *in vivo* or *in vitro* under acidic (pH <3) or basic (pH >10) conditions. Alternatively, they are substantially stable in the gastrointestinal tract of humans but are hydrolyzed enzymatically in blood or in intracellular environments. The esters or amino acid or polypeptide amidates also are useful as intermediates for the preparation of the parental molecule containing free amino or carboxyl groups. The free acid or base of the parental compound, for example, is readily formed from the esters or amino acid or polypeptide conjugates of this invention by conventional hydrolysis procedures.

When an amino acid residue contains one or more chiral centers, any of the D, L, meso, threo or erythro (as appropriate) racemates, scalemates or

mixtures thereof may be used. In general, if the intermediates are to be hydrolyzed non-enzymatically (as would be the case where the amides are used as chemical intermediates for the free acids or free amines), D isomers are useful. On the other hand, L isomers are more versatile since they can be susceptible to both non-enzymatic and enzymatic hydrolysis, and are more efficiently transported by amino acid or dipeptidyl transport systems in the gastrointestinal tract.

Examples of suitable amino acids whose residues are represented by R^x or R^y include the following:

Glycine;

Aminopolycarboxylic acids, e.g., aspartic acid, β-hydroxyaspartic acid, glutamic acid, β -hydroxyglutamic acid, β-methylaspartic acid, β-methylglutamic acid, β, β-dimethylaspartic acid, γ-hydroxyglutamic acid, β, γ-dihydroxyglutamic acid, β -phenylglutamic acid, γ-methyleneglutamic acid, 3-aminoadipic acid, 2-aminopimelic acid, 2-aminosuberic acid and 2-aminosebacic acid;

Amino acid amides such as glutamine and asparagine;

Polyamino- or polybasic-monocarboxylic acids such as arginine, lysine, β -aminoalanine, γ -aminobutyrine, ornithine, citruline, homoarginine, homocitrulline, hydroxylysine, allohydroxylsine and diaminobutyric acid;

Other basic amino acid residues such as histidine;

Diaminodicarboxylic acids such as α, α'-diaminosuccinic acid, α, α'-diaminoglutaric acid, α, α'-diaminoadipic acid, α, α'-diaminopimelic acid, α, α'-diamino- β-hydroxypimelic acid, α, α'-diaminosuberic acid, α, α'-diaminoazelaic acid, and α, α'-diaminosebacic acid;

Imino acids such as proline, hydroxyproline, allohydroxyproline, γ-methylproline, pipecolic acid, 5-hydroxypipecolic acid, and azetidine-2-carboxylic acid;

A mono- or di-alkyl (typically C_1-C_8 branched or normal) amino acid such as alanine, valine, leucine, allylglycine, butyrine, norvaline, norleucine, heptyline, α-methylserine, α-amino-α-methyl-γ-hydroxyvaleric acid, α-amino- α-methyl-δ-hydroxyvaleric acid, α-amino- α-methyl-ϵ-hydroxycaproic acid, isovaline, α-methylglutamic acid, α-aminoisobutyric acid, α-aminodiethylacetic acid, α-aminodiisopropylacetic acid, α-aminodi-n-propylacetic acid, α-

aminodiisobutylacetic acid, α-aminodi-n-butylacetic acid, α-aminoethylisopropylacetic acid, α-amino-n-propylacetic acid, α-aminodiisoamyacetic acid, α-methylaspartic acid, α-methylglutamic acid, 1-aminocyclopropane-1-carboxylic acid, isoleucine, alloisoleucine, *tert*-leucine, β-methyltryptophan and α-amino- β-ethyl-β-phenylpropionic acid;

β-phenylserinyl;

Aliphatic α-amino-β-hydroxy acids such as serine, β-hydroxyleucine, β-hydroxynorleucine, β -hydroxynorvaline, and α-amino-β-hydroxystearic acid;

α-Amino, α-, γ-, δ- or ϵ-hydroxy acids such as homoserine, δ -hydroxynorvaline, γ-hydroxynorvaline and ϵ-hydroxynorleucine residues; canavine and canaline; γ -hydroxyornithine;

2-hexosaminic acids such as D-glucosaminic acid or D-galactosaminic acid;

α-Amino-β-thiols such as penicillamine, β-thiolnorvaline or β-thiolbutyrine;

Other sulfur containing amino acid residues including cysteine; homocystine, β-phenylmethionine, methionine, S-allyl-L-cysteine sulfoxide, 2-thiolhistidine, cystathionine, and thiol ethers of cysteine or homocysteine;

Phenylalanine, tryptophan and ring-substituted α-amino acids such as the phenyl- or cyclohexylamino acids α-aminophenylacetic acid, α-aminocyclohexylacetic acid and α-amino-β-cyclohexylpropionic acid; phenylalanine analogues and derivatives comprising aryl, lower alkyl, hydroxy, guanidino, oxyalkylether, nitro, sulfur or halo-substituted phenyl (e.g., tyrosine, methyltyrosine and o-chloro-, p-chloro-, 3,4-dichloro, *o*-, *m*- or *p*-methyl-, 2,4,6-trimethyl-, 2-ethoxy-5-nitro-, 2-hydroxy-5-nitro- and p-nitro-phenylalanine); furyl-, thienyl-, pyridyl-, pyrimidinyl-, purinyl- or naphthyl-alanines; and tryptophan analogues and derivatives including kynurenine, 3-hydroxykynurenine, 2-hydroxytryptophan and 4-carboxytryptophan;

α-Amino substituted amino acids including sarcosine (N-methylglycine), N-benzylglycine, N-methylalanine, N-benzylalanine, N-methylphenylalanine, N-benzylphenylalanine, N-methylvaline and N-benzylvaline; and

α-Hydroxy and substituted α -hydroxy amino acids including serine, threonine, allothreonine, phosphoserine and phosphothreonine.

Polypeptides are polymers of amino acids in which a carboxyl group of one amino acid monomer is bonded to an amino or imino group of the next amino acid monomer by an amide bond. Polypeptides include dipeptides, low molecular weight polypeptides (about 1500-5000 MW) and proteins. Proteins optionally contain 3, 5, 10, 50, 75, 100 or more residues, and suitably are substantially sequence-homologous with human, animal, plant or microbial proteins. They include enzymes (e.g., hydrogen peroxidase) as well as immunogens such as KLH, or antibodies or proteins of any type against which one wishes to raise an immune response. The nature and identity of the polypeptide may vary widely.

The polypeptide amidates are useful as immunogens in raising antibodies against either the polypeptide (if it is not immunogenic in the animal to which it is administered) or against the epitopes on the remainder of the compound of this invention.

Antibodies capable of binding to the parental non-peptidyl compound are used to separate the parental compound from mixtures, for example in diagnosis or manufacturing of the parental compound. The conjugates of parental compound and polypeptide generally are more immunogenic than the polypeptides in closely homologous animals, and therefore make the polypeptide more immunogenic for facilitating raising antibodies against it. Accordingly, the polypeptide or protein may not need to be immunogenic in an animal typically used to raise antibodies, e.g., rabbit, mouse, horse, or rat, but the final product conjugate should be immunogenic in at least one of such animals. The polypeptide optionally contains a peptidolytic enzyme cleavage site at the peptide bond between the first and second residues adjacent to the acidic heteroatom. Such cleavage sites are flanked by enzymatic recognition structures, e.g., a particular sequence of residues recognized by a peptidolytic enzyme.

Peptidolytic enzymes for cleaving the polypeptide conjugates of this invention are well known, and in particular include carboxypeptidases. Carboxypeptidases digest polypeptides by removing C-terminal residues, and are specific in many instances for particular C-terminal sequences. Such enzymes and their substrate requirements in general are well known. For example, a

dipeptide (having a given pair of residues and a free carboxyl terminus) is covalently bonded through its α-amino group to the phosphorus or carbon atoms of the compounds herein. In claims where W_1 is phosphonate it is expected that this peptide will be cleaved by the appropriate peptidolytic enzyme, leaving the carboxyl of the proximal amino acid residue to autocatalytically cleave the phosphonoamidate bond.

Suitable dipeptidyl groups (designated by their single letter code) are AA, AR, AN, AD, AC, AE, AQ, AG, AH, AI, AL, AK, AM, AF, AP, AS, AT, AW, AY, AV, RA, RR, RN, RD, RC, RE, RQ, RG, RH, RI, RL, RK, RM, RF, RP, RS, RT, RW, RY, RV, NA, NR, NN, ND, NC, NE, NQ, NG, NH, NI, NL, NK, NM, NF, NP, NS, NT, NW, NY, NV, DA, DR, DN, DD, DC, DE, DQ, DG, DH, DI, DL, DK, DM, DF, DP, DS, DT, DW, DY, DV, CA, CR, CN, CD, CC, CE, CQ, CG, CH, CI, CL, CK, CM, CF, CP, CS, CT, CW, CY, CV, EA, ER, EN, ED, EC, EE, EQ, EG, EH, EI, EL, EK, EM, EF, EP, ES, ET, EW, EY, EV, QA, QR, QN, QD, QC, QE, QQ, QG, QH, QI, QL, QK, QM, QF, QP, QS, QT, QW, QY, QV, GA, GR, GN, GD, GC, GE, GQ, GG, GH, GI, GL, GK, GM, GF, GP, GS, GT, GW, GY, GV, HA, HR, HN, HD, HC, HE, HQ, HG, HH, HI, HL, HK, HM, HF, HP, HS, HT, HW, HY, HV, IA, IR, IN, ID, IC, IE, IQ, IG, IH, II, IL, IK, IM, IF, IP, IS, IT, IW, IY, IV, LA, LR, LN, LD, LC, LE, LQ, LG, LH, LI, LL, LK, LM, LF, LP, LS, LT, LW, LY, LV, KA, KR, KN, KD, KC, KE, KQ, KG, KH, KI, KL, KK, KM, KF, KP, KS, KT, KW, KY, KV, MA, MR, MN, MD, MC, ME, MQ, MG, MH, MI, ML, MK, MM, MF, MP, MS, MT, MW, MY, MV, FA, FR, FN, FD, FC, FE, FQ, FG, FH, FI, FL, FK, FM, FF, FP, FS, FT, FW, FY, FV, PA, PR, PN, PD, PC, PE, PQ, PG, PH, PI, PL, PK, PM, PF, PP, PS, PT, PW, PY, PV, SA, SR, SN, SD, SC, SE, SQ, SG, SH, SI, SL, SK, SM, SF, SP, SS, ST, SW, SY, SV, TA, TR, TN, TD, TC, TE, TQ, TG, TH, TI, TL, TK, TM, TF, TP, TS, TT, TW, TY, TV, WA, WR, WN, WD, WC, WE, WQ, WG, WH, WI, WL, WK, WM, WF, WP, WS, WT, WW, WY, WV, YA, YR, YN, YD, YC, YE, YQ, YG, YH, YI, YL, YK, YM, YF, YP, YS, YT, YW, YY, YV, VA, VR, VN, VD, VC, VE, VQ, VG, VH, VI, VL, VK, VM, VF, VP, VS, VT, VW, VY and VV.

Tripeptide residues are also useful as protecting groups. When a phosphonate is to be protected, the sequence -X^4-pro-X^5- (where X^4 is any amino

acid residue and X^5 is an amino acid residue, a carboxyl ester of proline, or hydrogen) will be cleaved by luminal carboxypeptidase to yield X^4 with a free carboxyl, which in turn is expected to autocatalytically cleave the phosphonoamidate bond. The carboxy group of X^5 optionally is esterified with benzyl.

Dipeptide or tripeptide species can be selected on the basis of known transport properties and/or susceptibility to peptidases that can affect transport to intestinal mucosal or other cell types. Dipeptides and tripeptides lacking an α-amino group are transport substrates for the peptide transporter found in brush border membrane of intestinal mucosal cells (Bai, J.P.F., (1992) *Pharm Res.* 9:969-978). Transport competent peptides can thus be used to enhance bioavailability of the amidate compounds. Di- or tripeptides having one or more amino acids in the D configuration are also compatible with peptide transport and can be utilized in the amidate compounds of this invention. Amino acids in the D configuration can be used to reduce the susceptibility of a di- or tripeptide to hydrolysis by proteases common to the brush border such as aminopeptidase N. In addition, di- or tripeptides alternatively are selected on the basis of their relative resistance to hydrolysis by proteases found in the lumen of the intestine. For example, tripeptides or polypeptides lacking asp and/or glu are poor substrates for aminopeptidase A, di- or tripeptides lacking amino acid residues on the N-terminal side of hydrophobic amino acids (leu, tyr, phe, val, trp) are poor substrates for endopeptidase, and peptides lacking a pro residue at the penultimate position at a free carboxyl terminus are poor substrates for carboxypeptidase P. Similar considerations can also be applied to the selection of peptides that are either relatively resistant or relatively susceptible to hydrolysis by cytosolic, renal, hepatic, serum or other peptidases. Such poorly cleaved polypeptide amidates are immunogens or are useful for bonding to proteins in order to prepare immunogens.

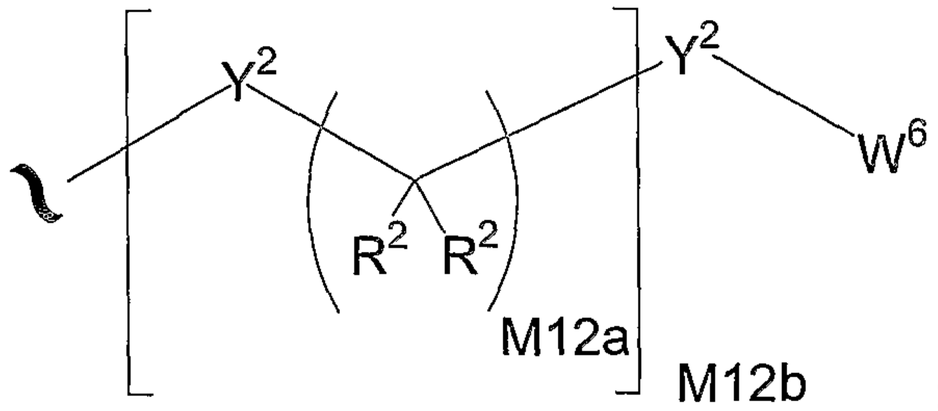
Specific Embodiments of the Invention

Specific values described for radicals, substituents, and ranges, as well as specific embodiments of the invention described herein, are for illustration only; they do not exclude other defined values or other values within defined ranges.

In one specific embodiment of the invention, the conjugate is a compound that is substituted with one or more phosphonate groups either directly or indirectly through a linker; and that is optionally substituted with one or more groups A^0; or a pharmaceutically acceptable salt thereof, wherein:

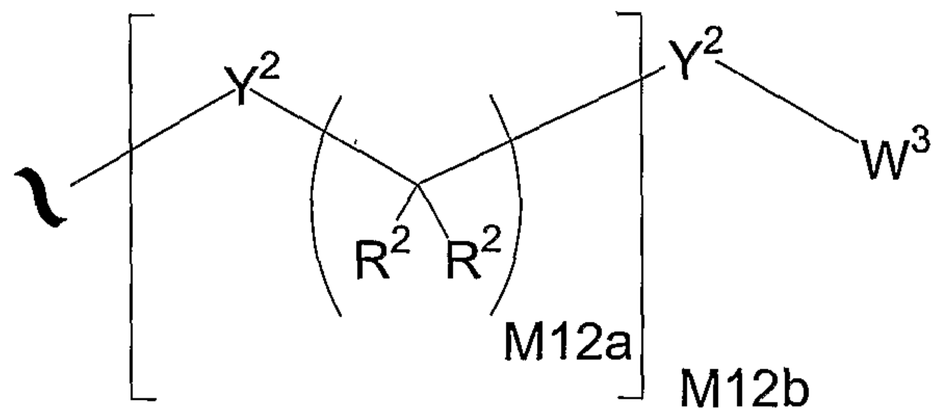
A^0 is A^1, A^2 or W^3;

A^1 is:



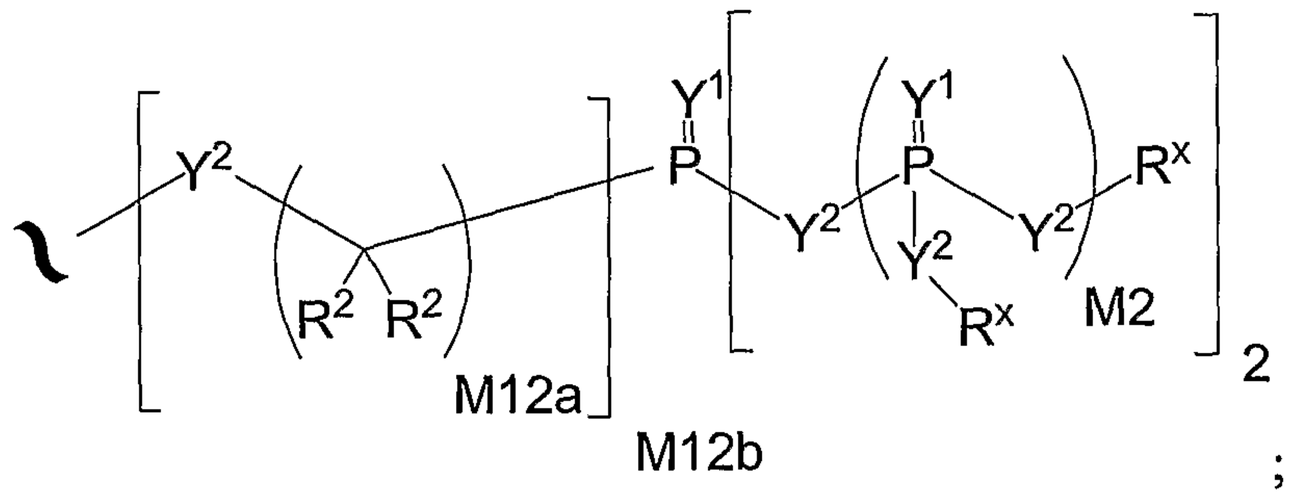
;

A^2 is:



;

A^3 is:

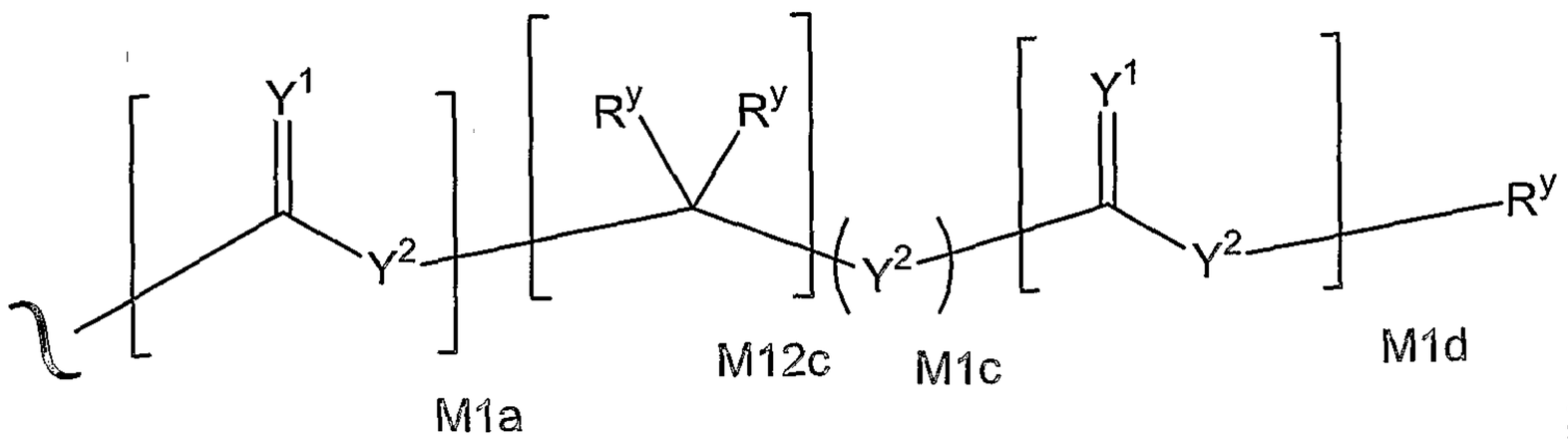


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

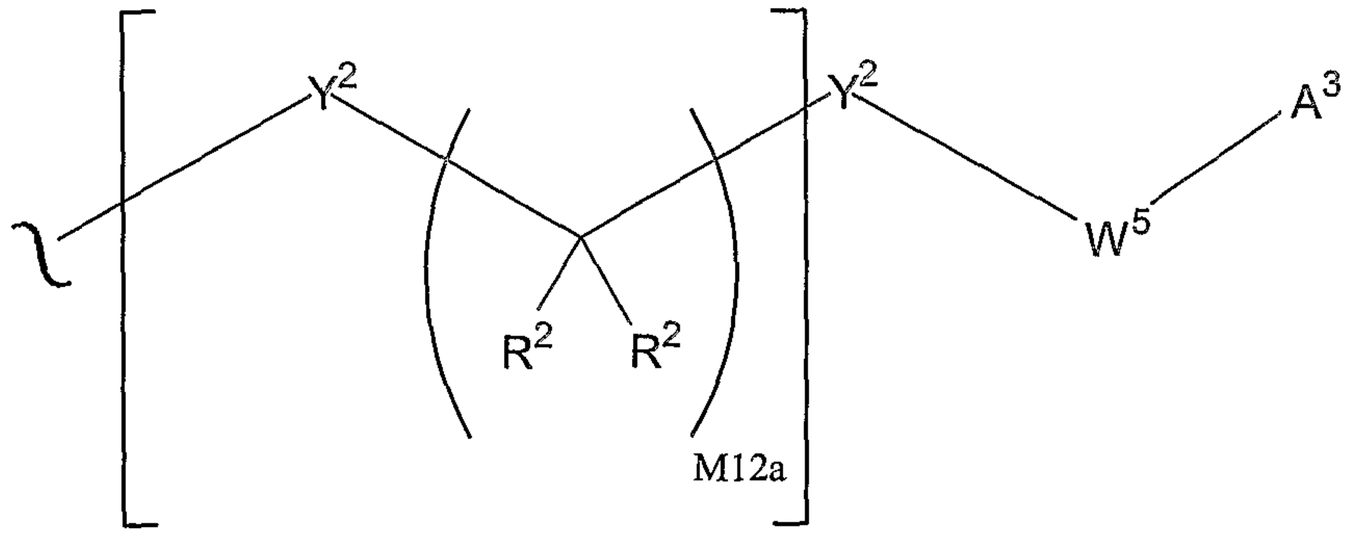
M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

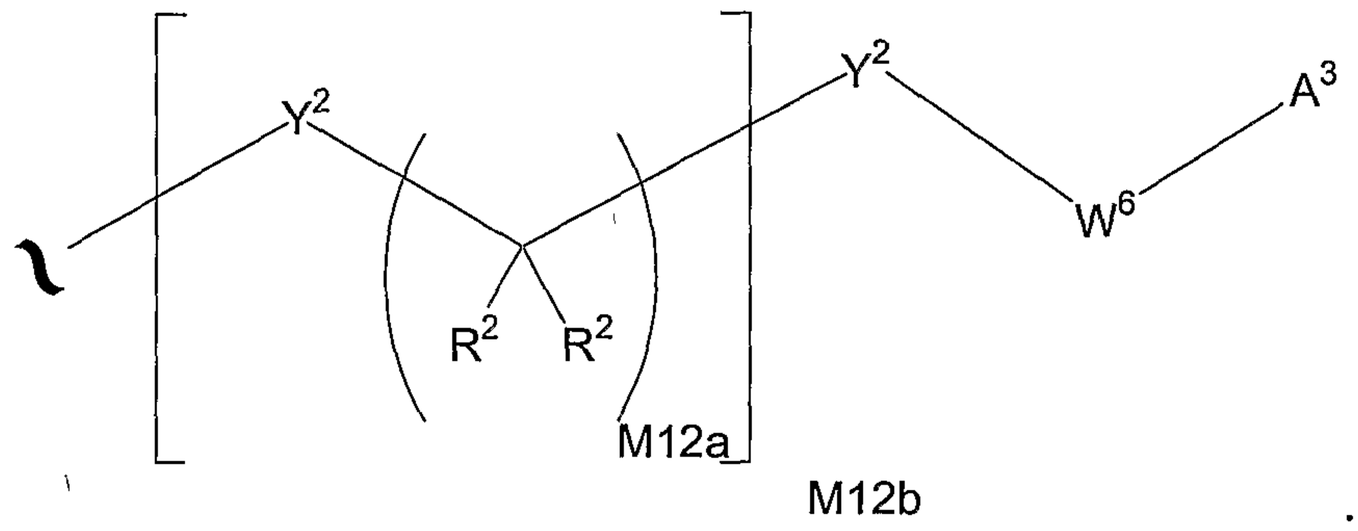
M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

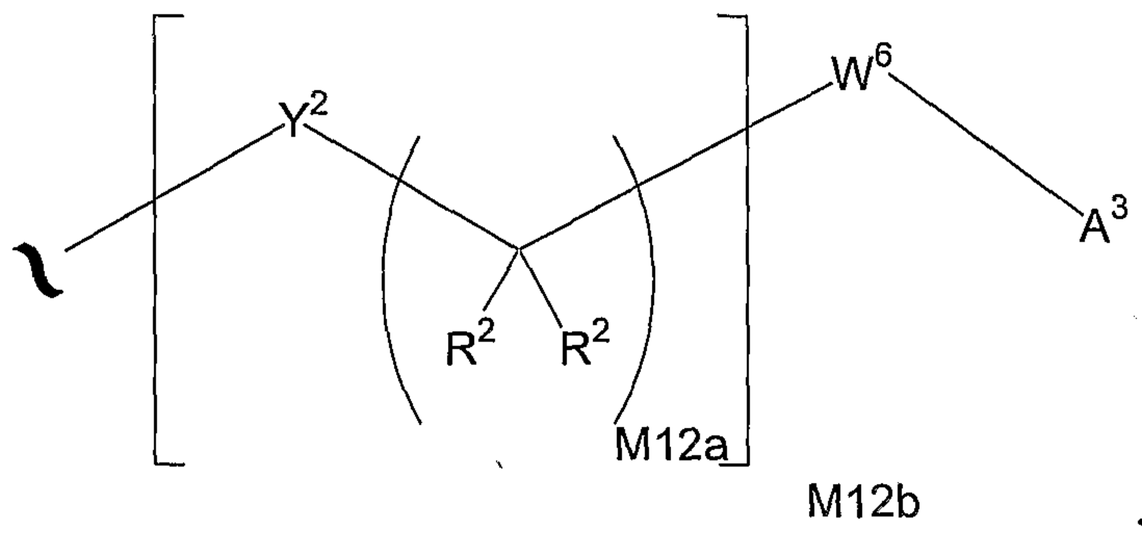
In another specific embodiment of the invention A^1 is of the formula:



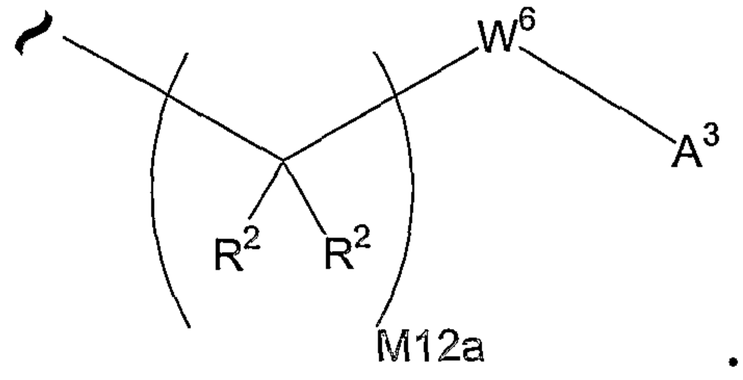
In another specific embodiment of the invention A^1 is of the formula:



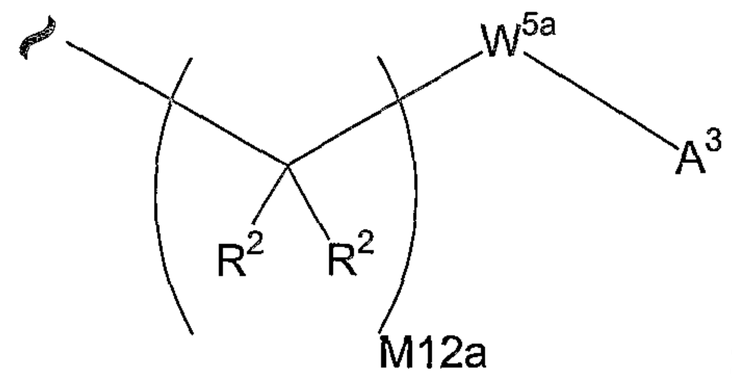
In another specific embodiment of the invention A^1 is of the formula:



In another specific embodiment of the invention A^1 is of the formula:



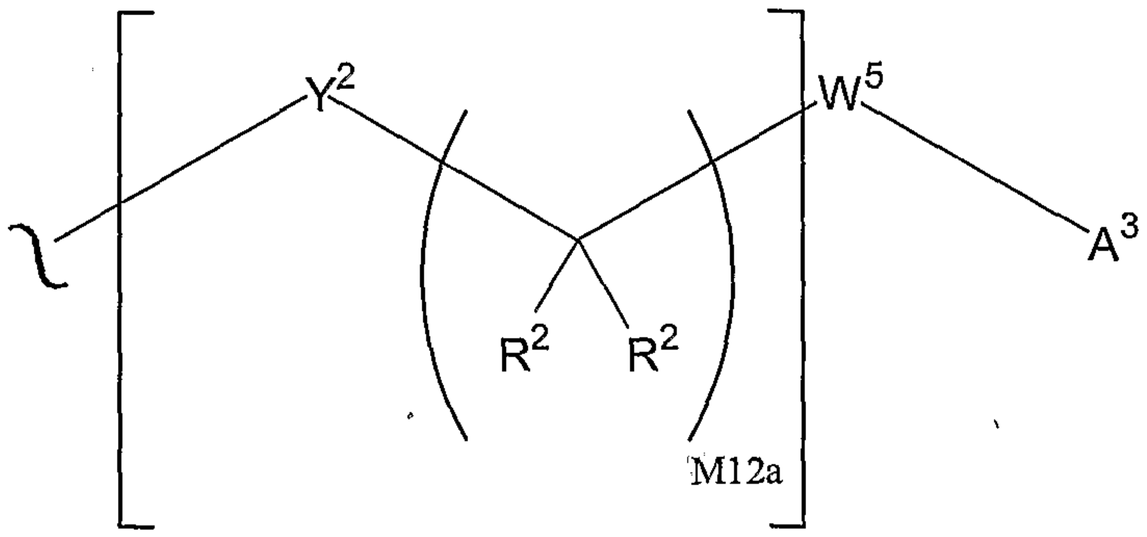
In another specific embodiment of the invention A^1 is of the formula:



;

and W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups. A specific velue for M12a is 1.

In another specific embodiment of the invention A^1 is of the formula:

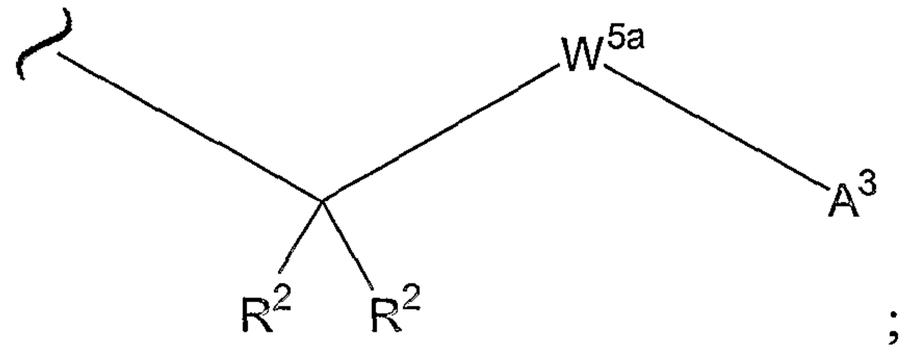


M12b .

In another specific embodiment of the invention A^1 is of the formula:

.

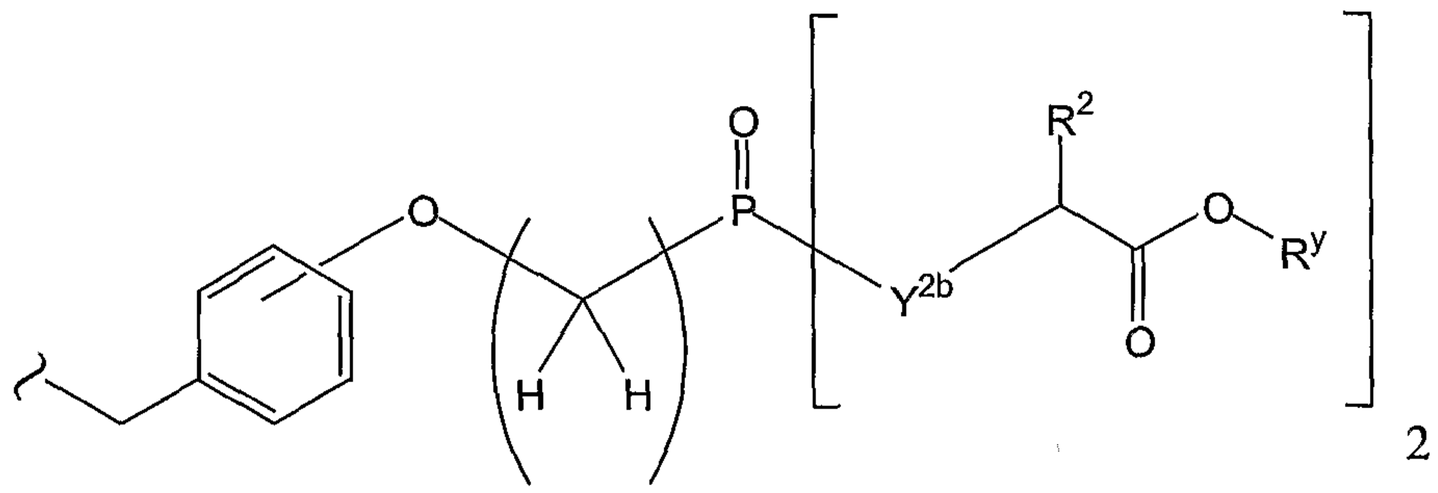
In another specific embodiment of the invention A^1 is of the formula:



;

wherein W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

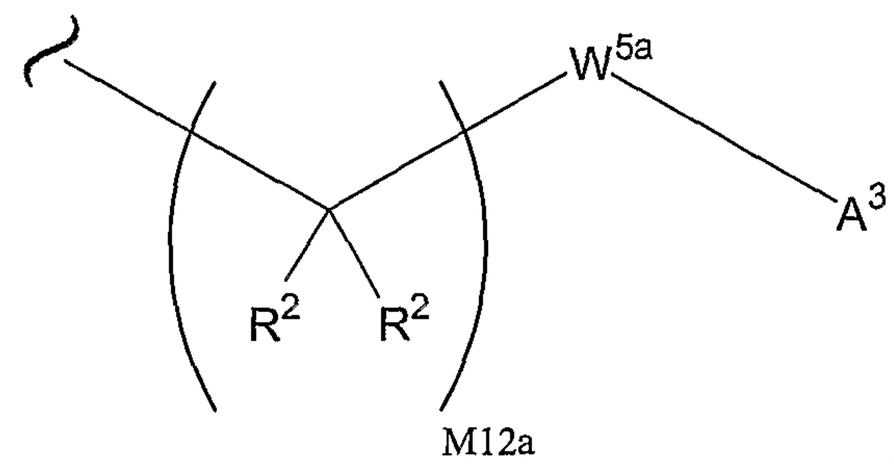
In another specific embodiment of the invention A^1 is of the formula:



M12d

wherein Y^{2b} is O or N(R^2); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

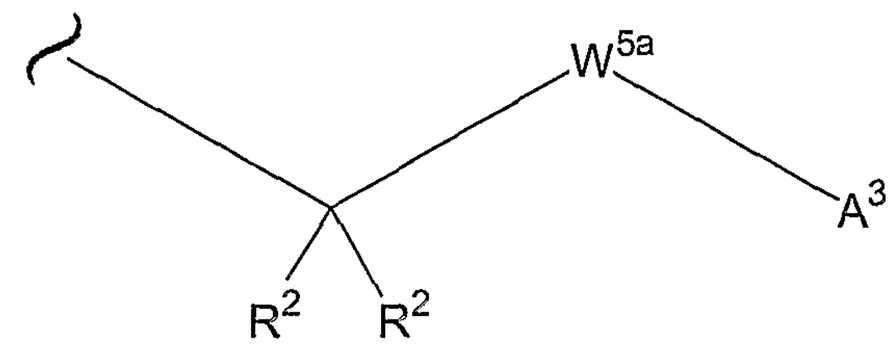
In another specific embodiment of the invention A^1 is of the formula:



M12a ;

wherein W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups;

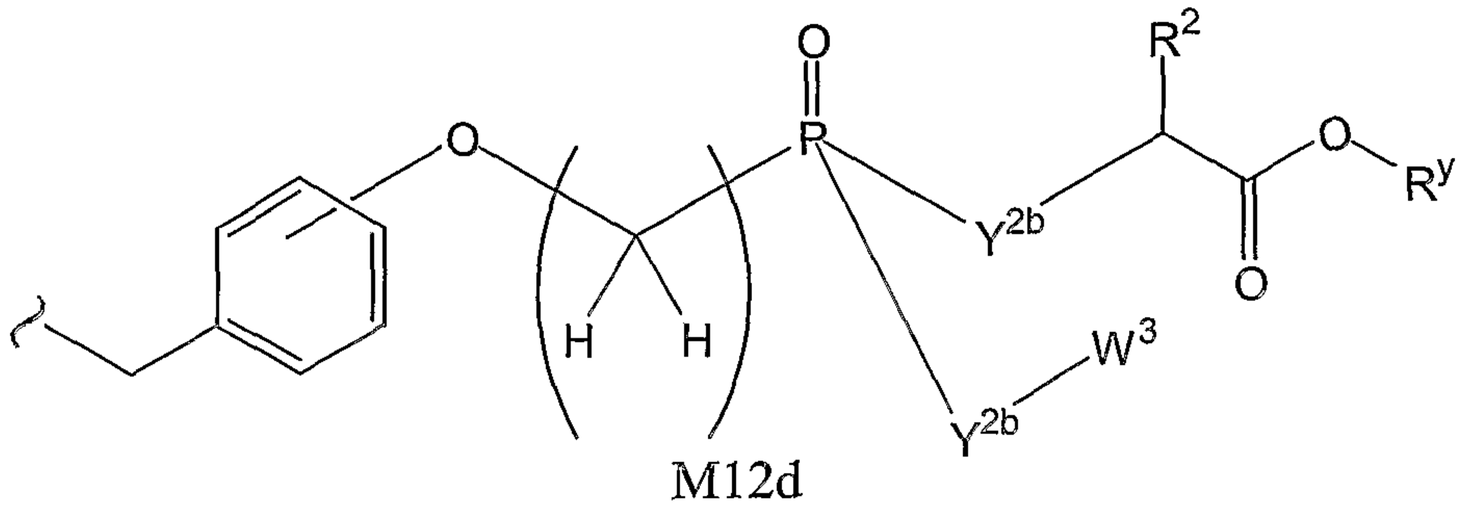
In another specific embodiment of the invention A^1 is of the formula:



;

wherein W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

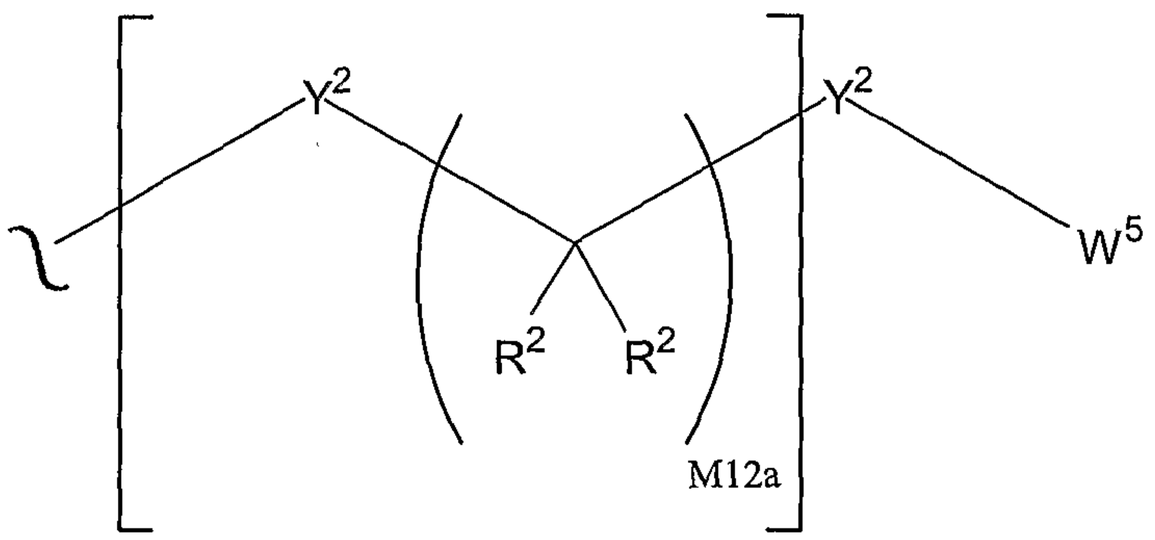
In another specific embodiment of the invention A^1 is of the formula:



M12d

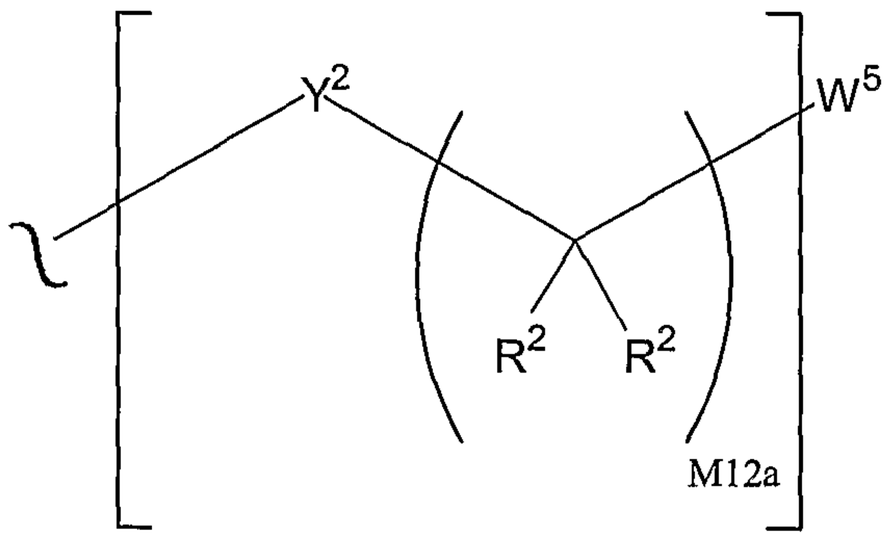
wherein Y^{2b} is O or $N(R^2)$; and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In a specific embodiment of the invention A^2 is of the formula:



M12b

In another specific embodiment of the invention A^2 is of the formula:

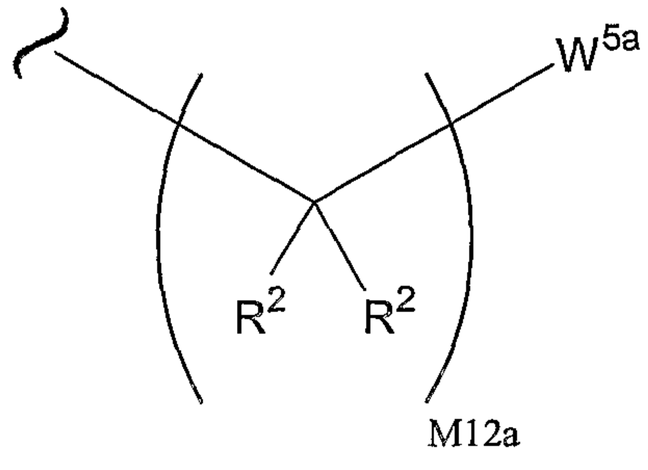


M12b.

In another specific embodiment of the invention M12b is 1.

In another specific embodiment of the invention e M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^2 is of the formula:



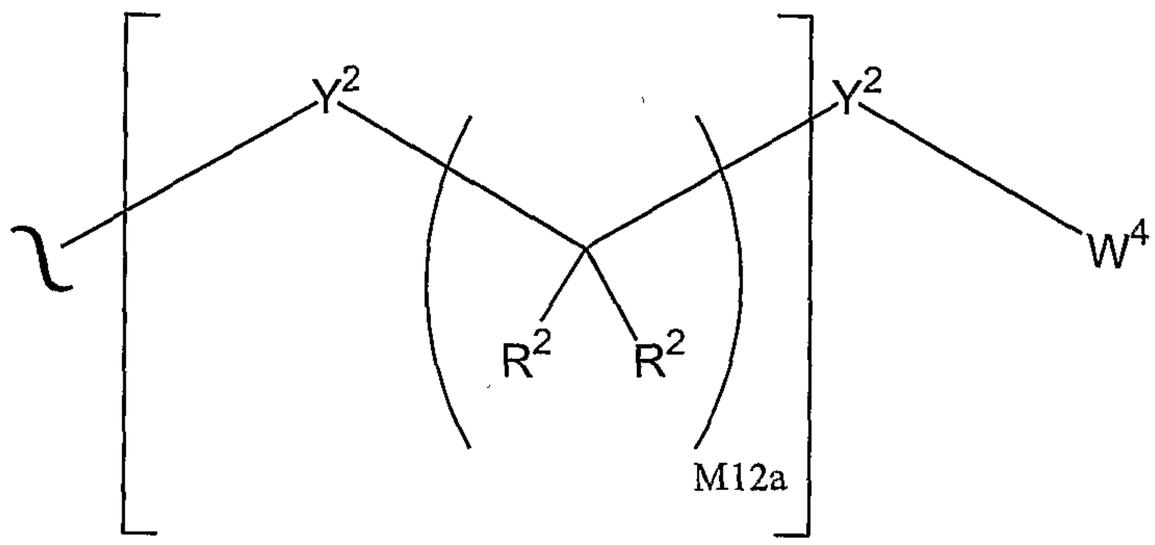
;

wherein W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

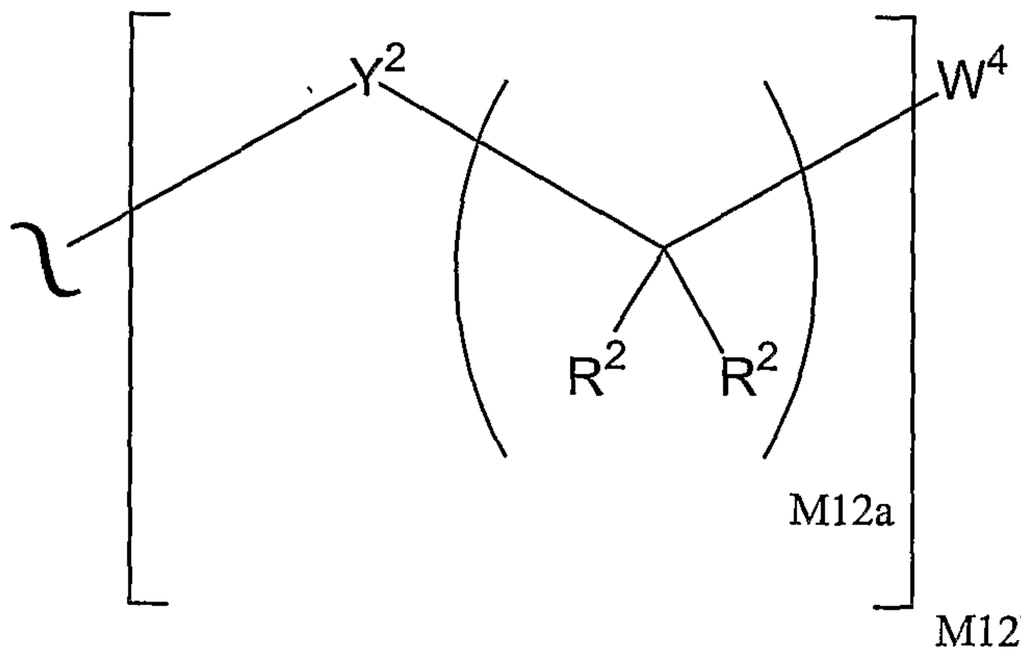
In another specific embodiment of the invention M12a is 1.

In another specific embodiment of the invention A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

In another specific embodiment of the invention A^2 is of the formula:

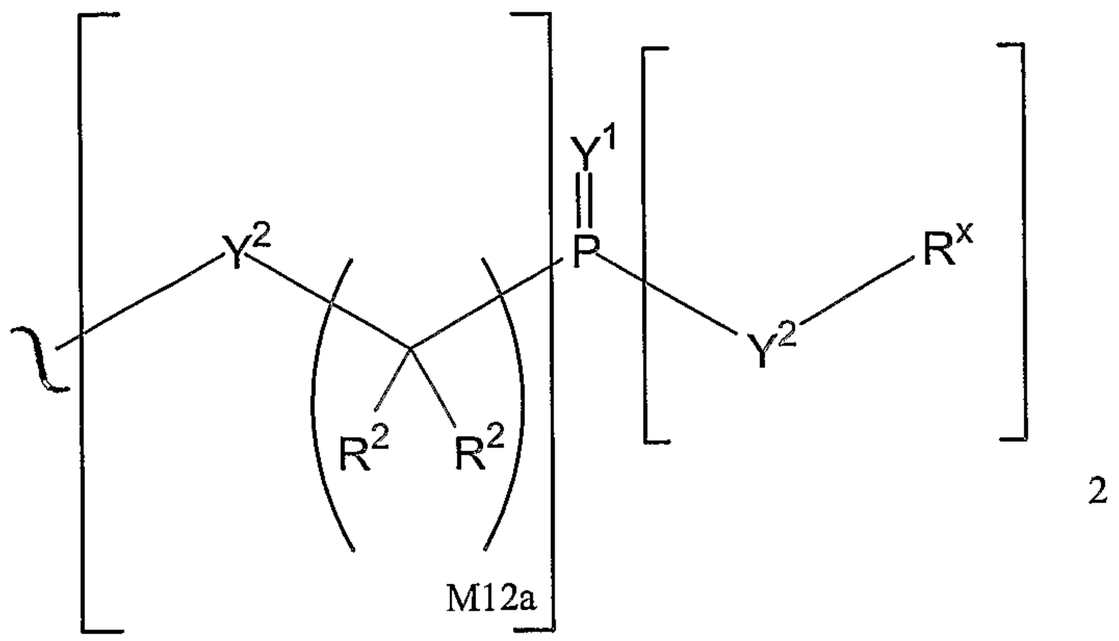


In another specific embodiment of the invention A^2 is of the formula:



In another specific embodiment of the invention M12b is 1.

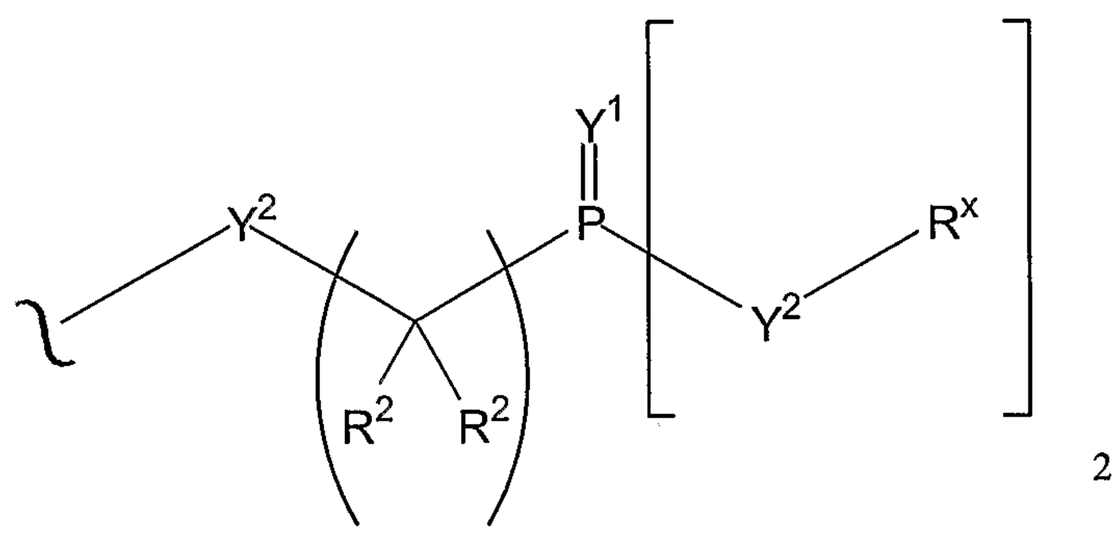
In a specific embodiment of the invention A^3 is of the formula:



M12a

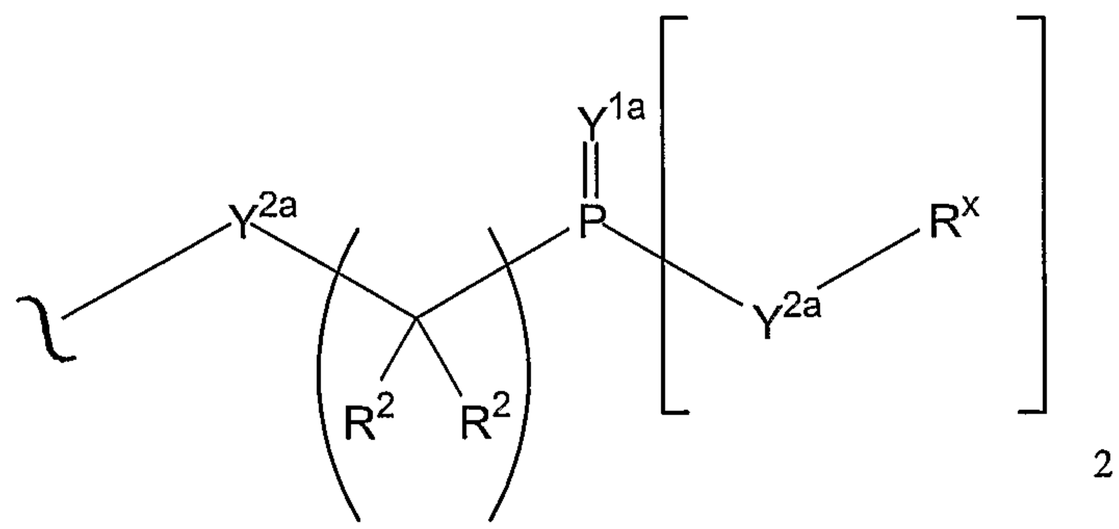
M12b

In another specific embodiment of the invention A^3 is of the formula:



M12a

In another specific embodiment of the invention A^3 is of the formula:

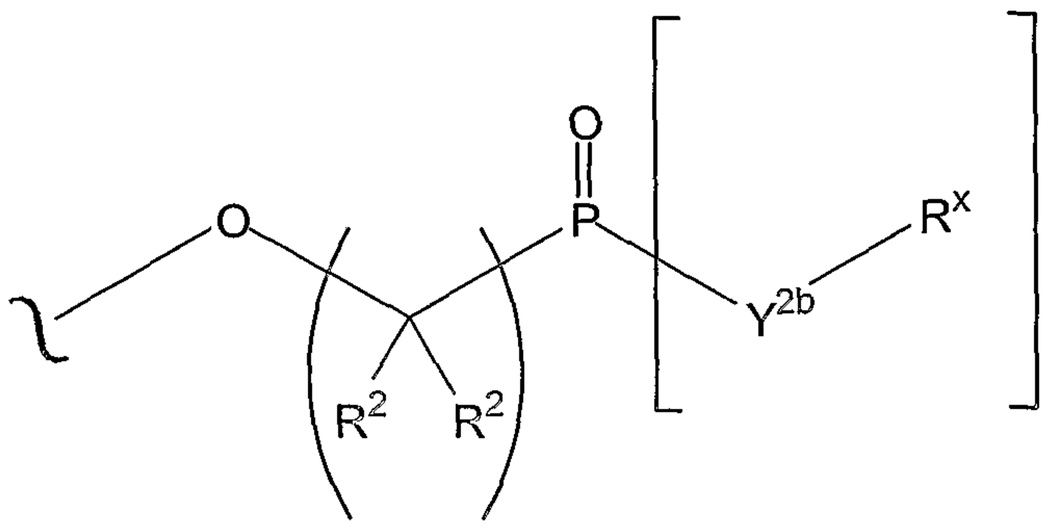


M12a

;

wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^x) or S.

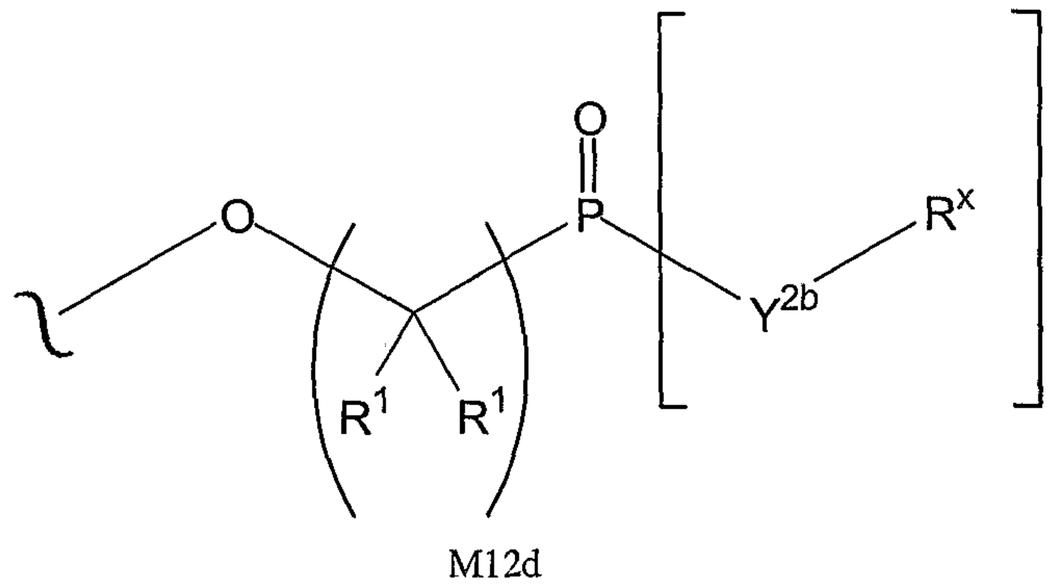
In another specific embodiment of the invention A^3 is of the formula:



M12a ;

wherein Y^{2b} is O or N(R^x).

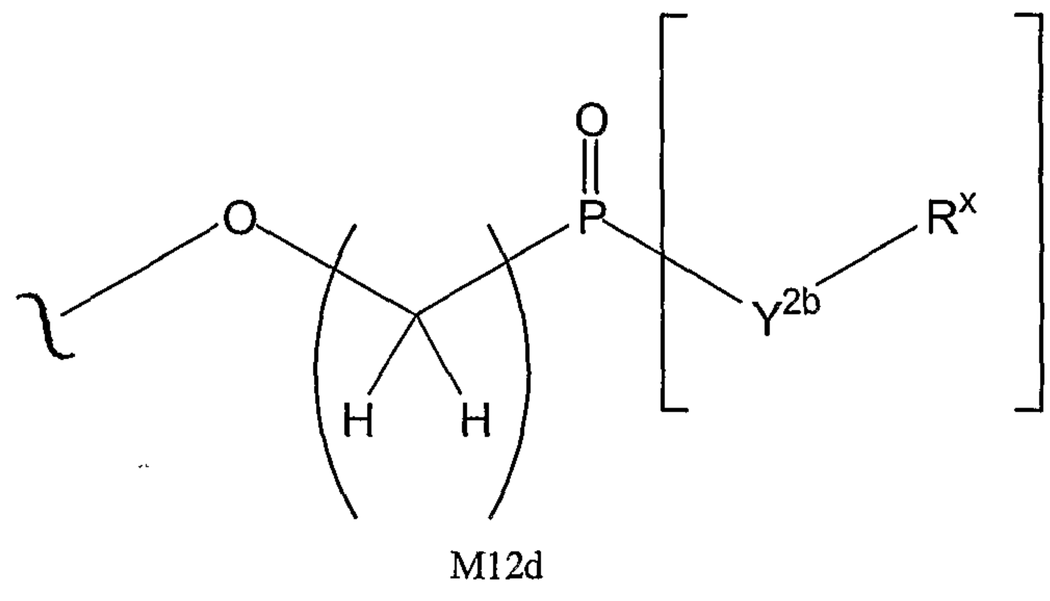
In another specific embodiment of the invention A^3 is of the formula:



M12d ;

wherein Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:

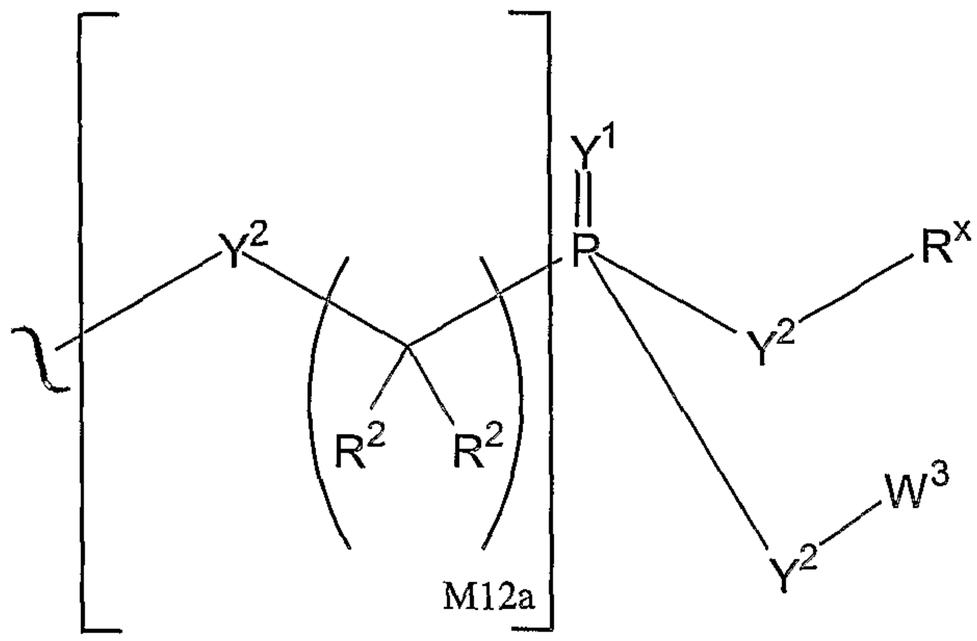


M12d ;

wherein Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

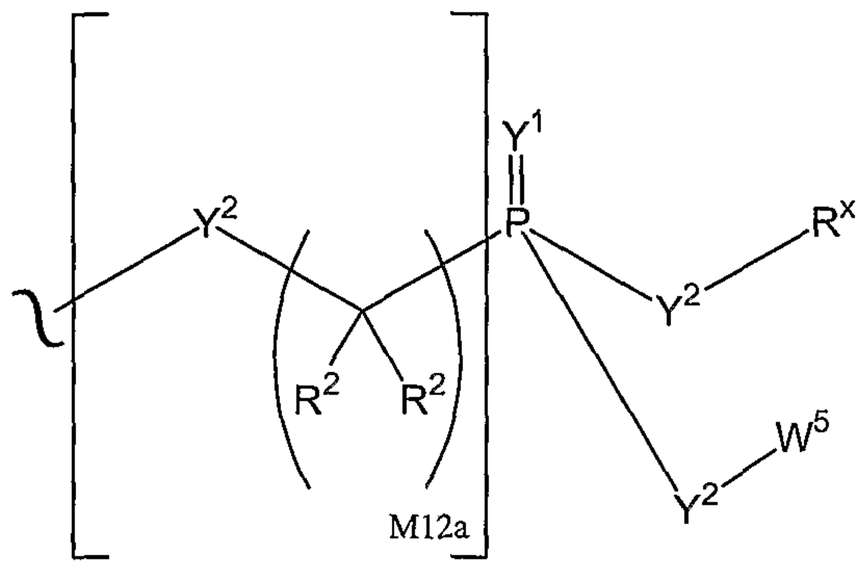
In another specific embodiment of the invention M12d is 1.

In another specific embodiment of the invention A^3 is of the formula:



M12b

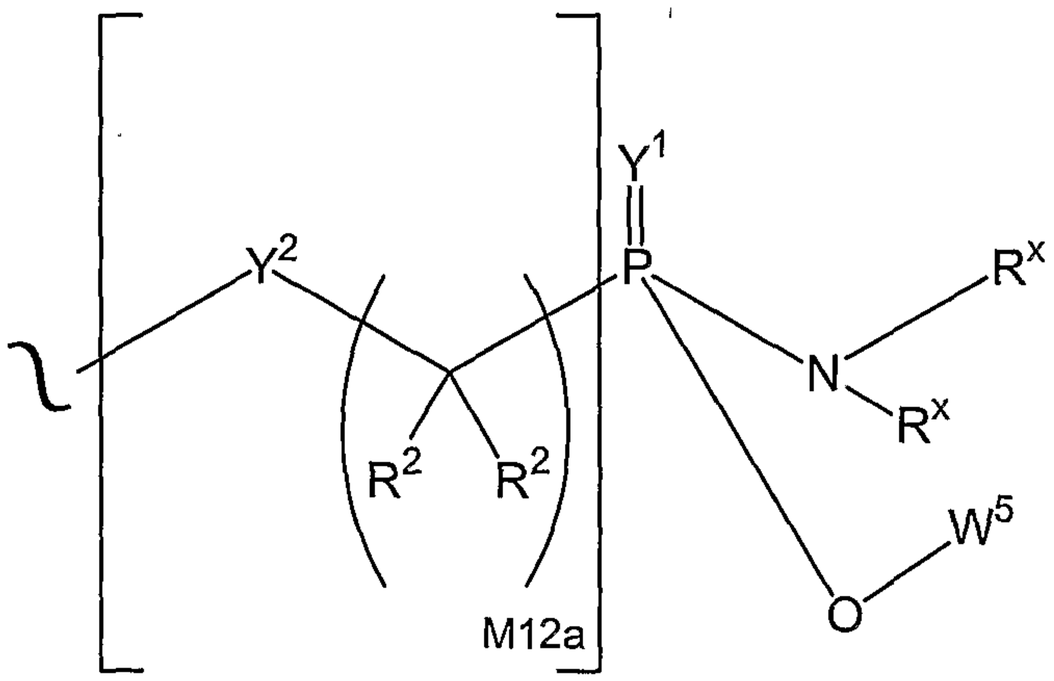
In another specific embodiment of the invention A^3 is of the formula:



M12b

In another specific embodiment of the invention W^5 is a carbocycle.

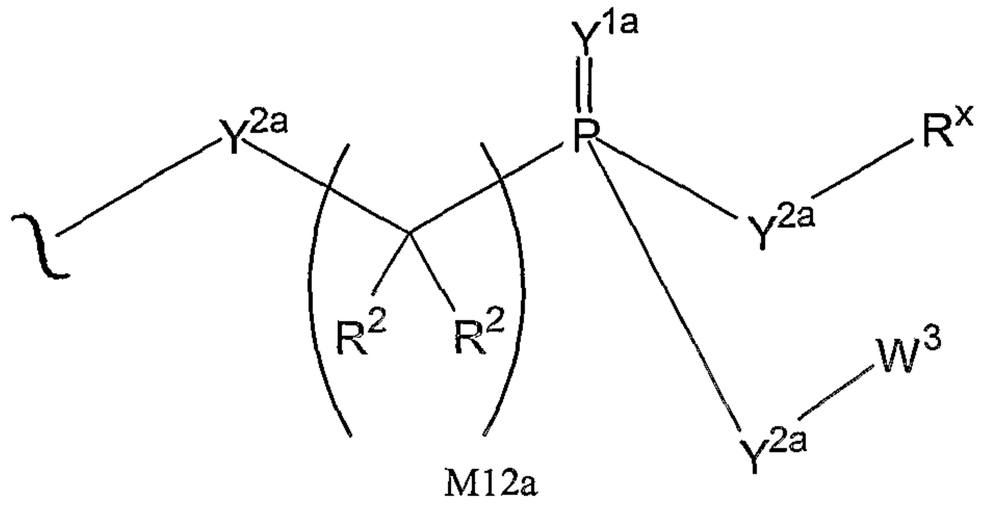
In another specific embodiment of the invention A^3 is of the formula:



M12b

In another specific embodiment of the invention W^5 is phenyl.

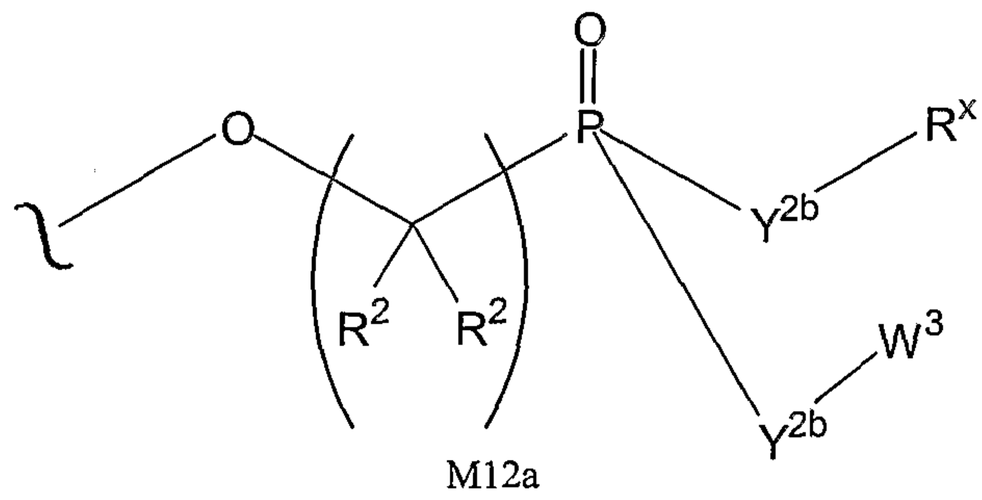
In another specific embodiment of the invention A^3 is of the formula:



;

wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^x) or S.

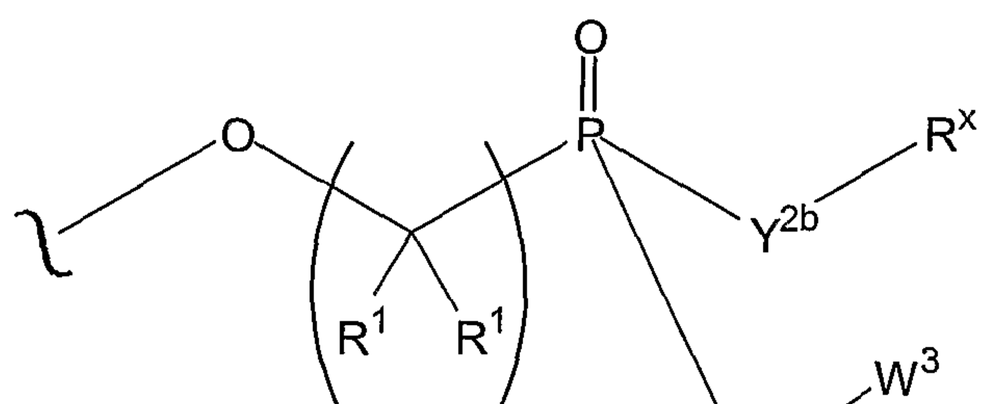
In another specific embodiment of the invention A^3 is of the formula:



;

wherein Y^{2b} is O or N(R^x).

In another specific embodiment of the invention A^3 is of the formula:

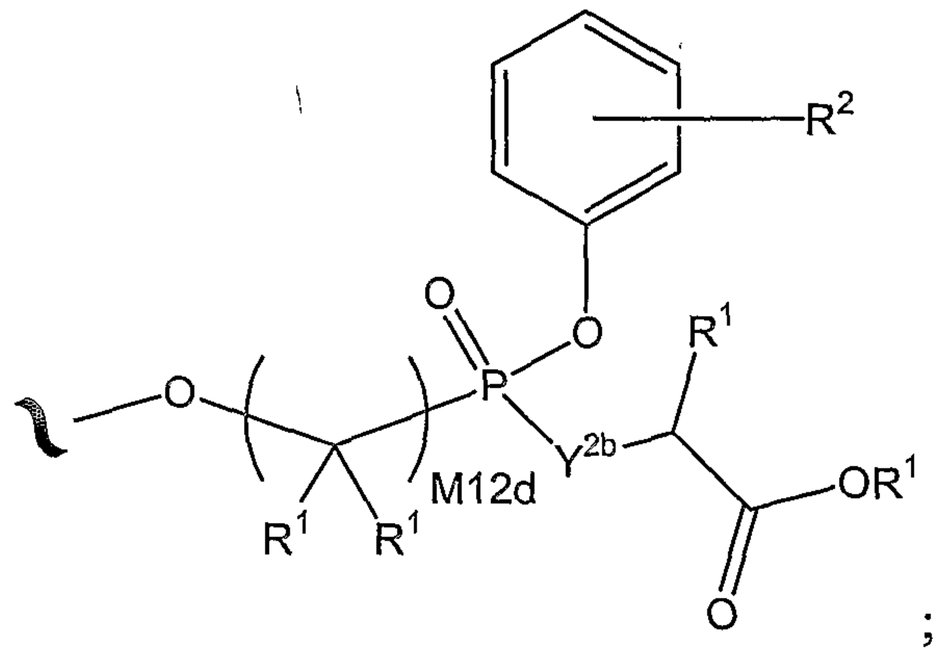


;

wherein Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention R^1 is H.

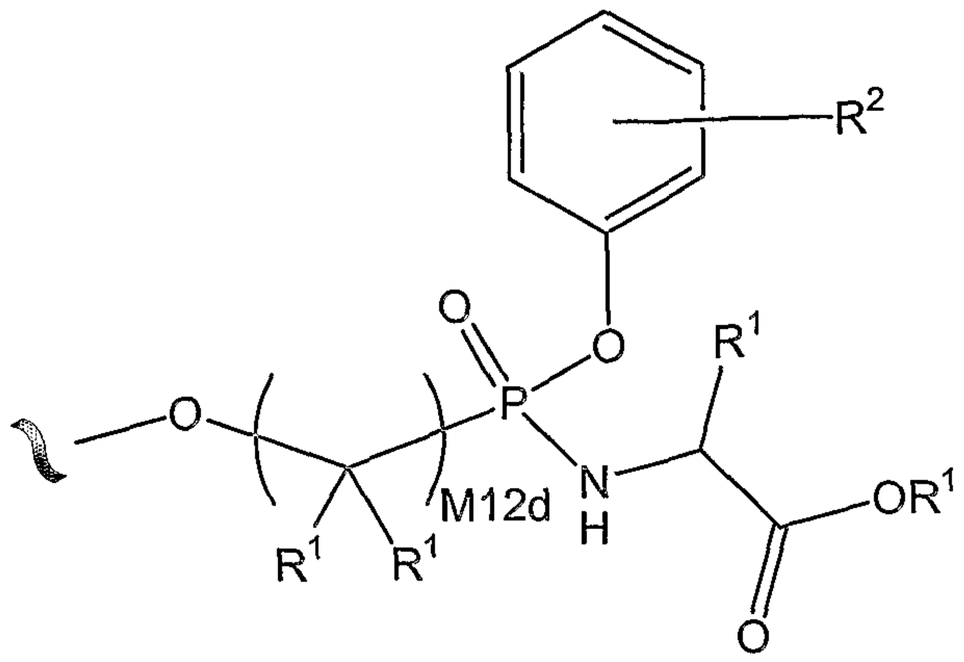
In another specific embodiment of the invention A^3 is of the formula:



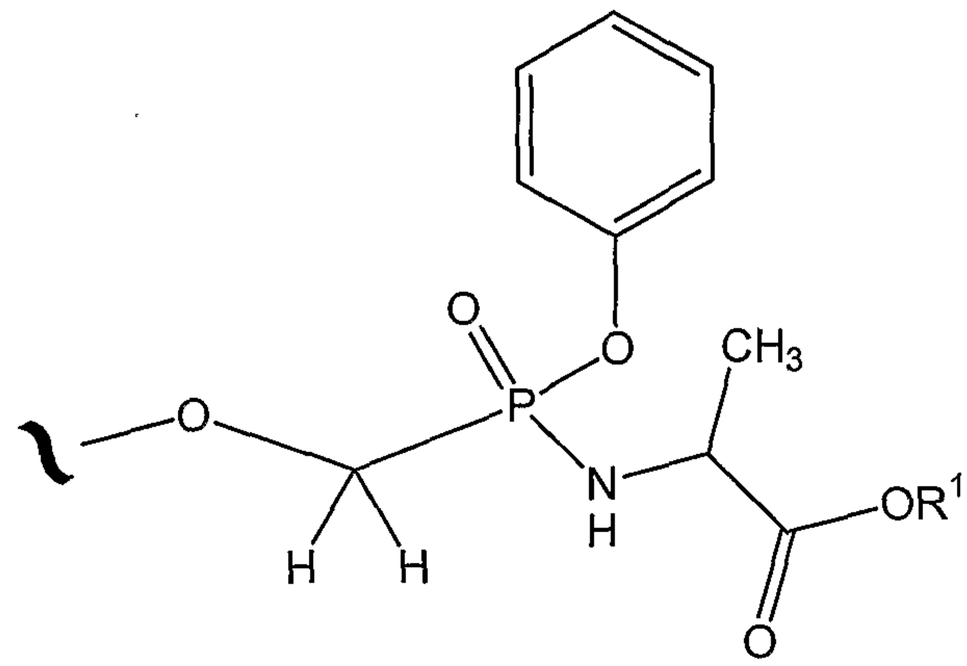
;

wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

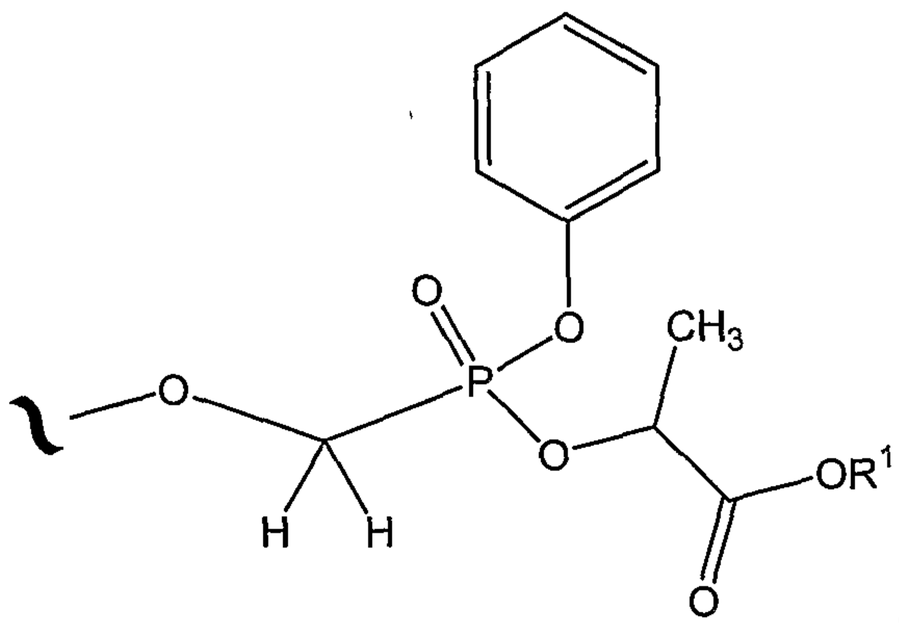
In another specific embodiment of the invention A^3 is of the formula:



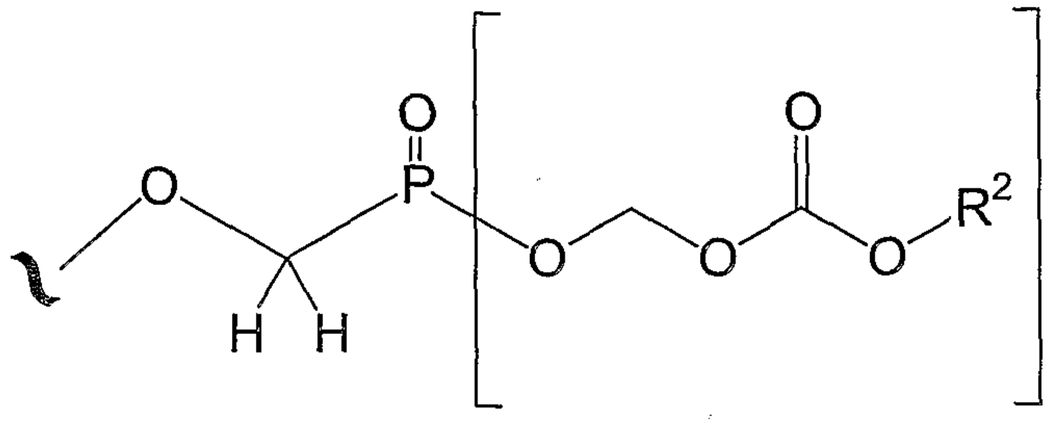
In another specific embodiment of the invention A^3 is of the formula:



In another specific embodiment of the invention A^3 is of the formula:

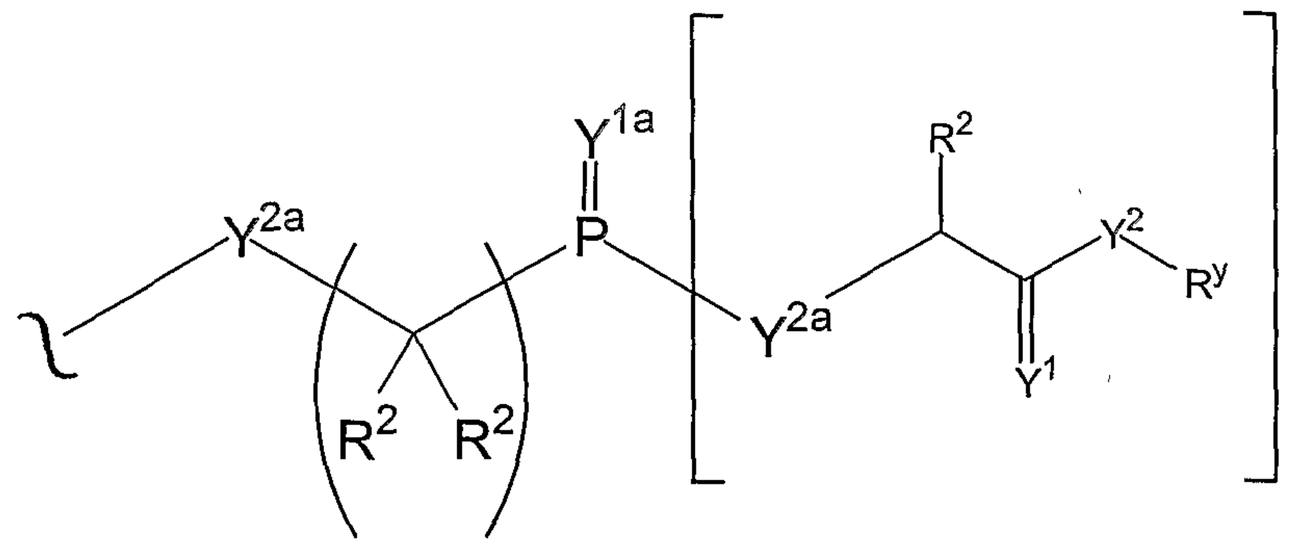


In another specific embodiment of the invention A^3 is of the formula:



2 .

In another specific embodiment of the invention A^3 is of the formula:

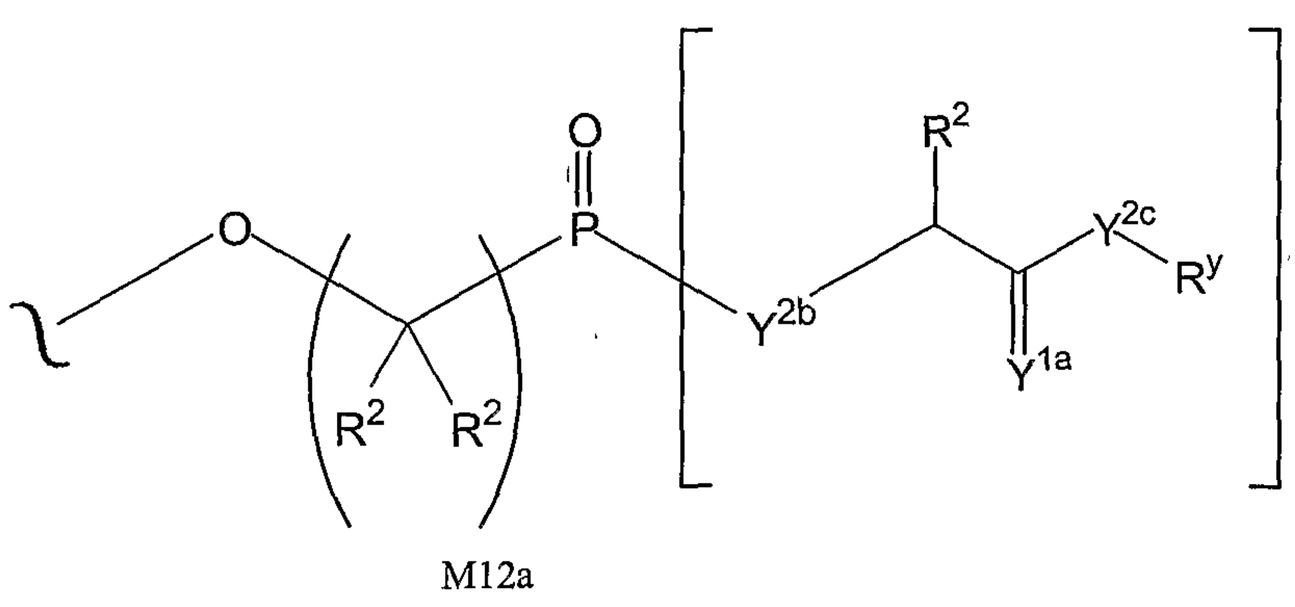


M12a

2 ;

wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^2) or S.

In another specific embodiment of the invention A^3 is of the formula:

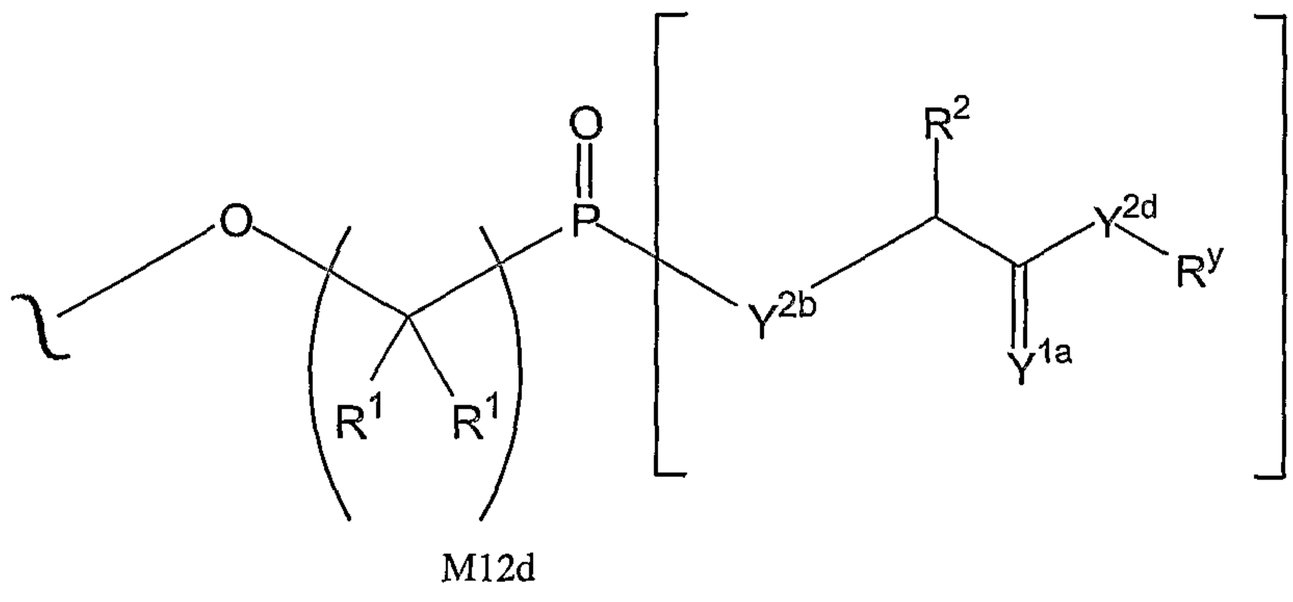


M12a

2 ;

wherein Y^{1a} is O or S; Y^{2b} is O or N(R^2); and Y^{2c} is O, N(R^y) or S.

In another specific embodiment of the invention A^3 is of the formula:

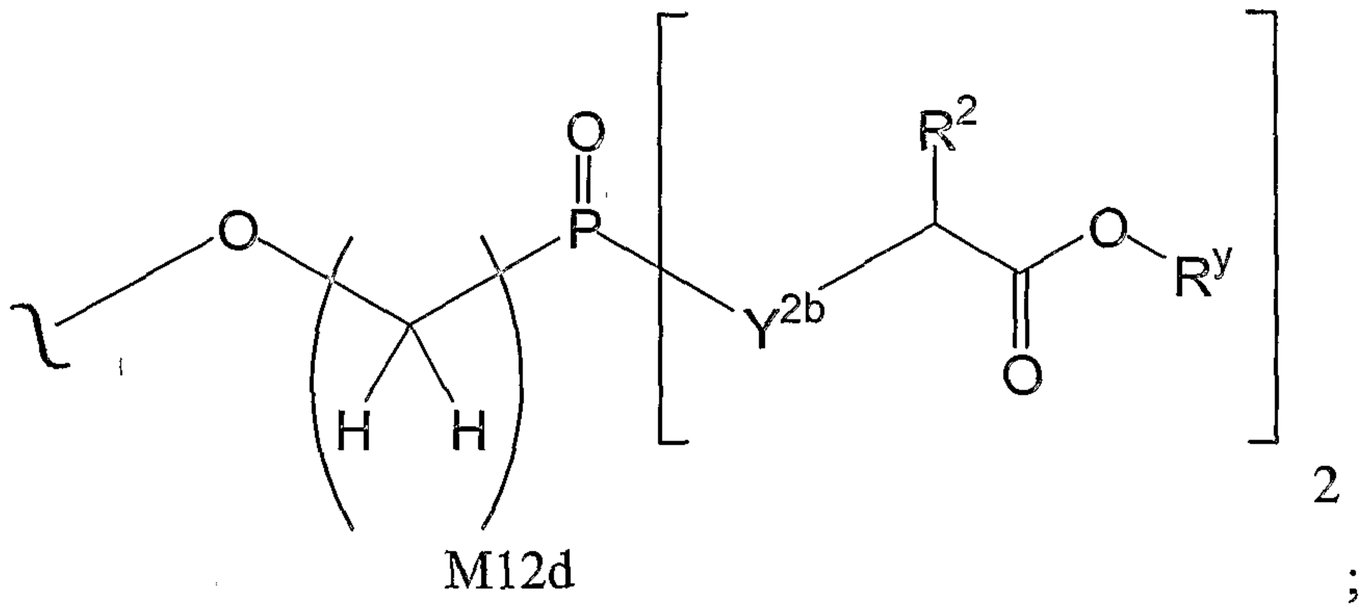


M12d

2 ;

wheren Y^{1a} is O or S; Y^{2b} is O or N(R^2); Y^{2d} is O or N(R^y); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

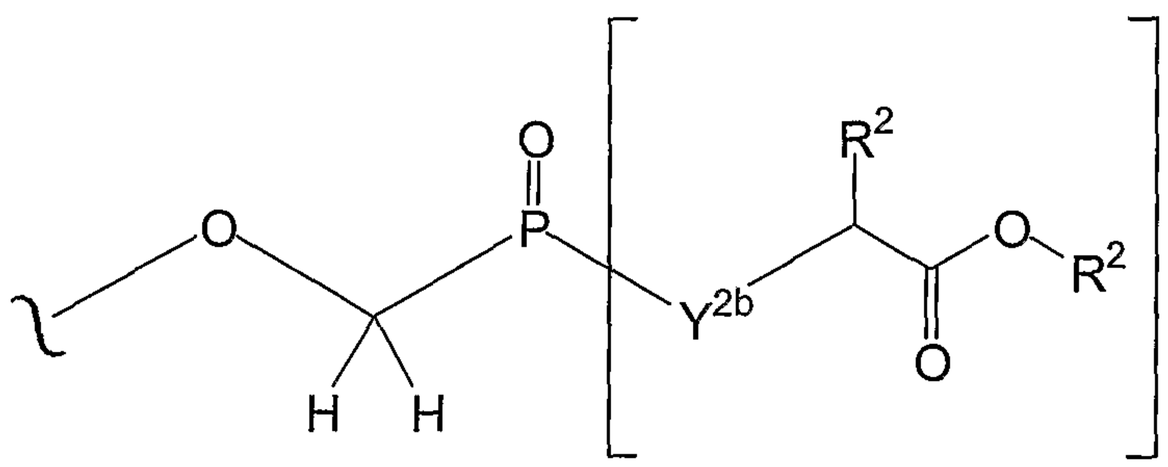
In another specific embodiment of the invention A^3 is of the formula:



M12d

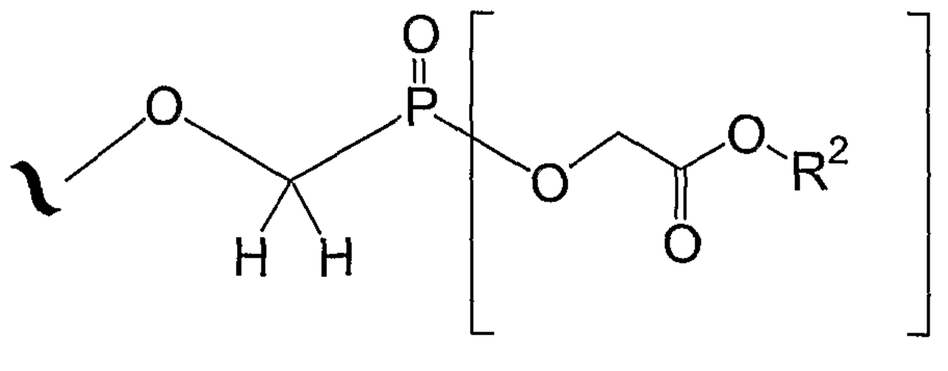
wherein Y^{2b} is O or N(R^2); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:

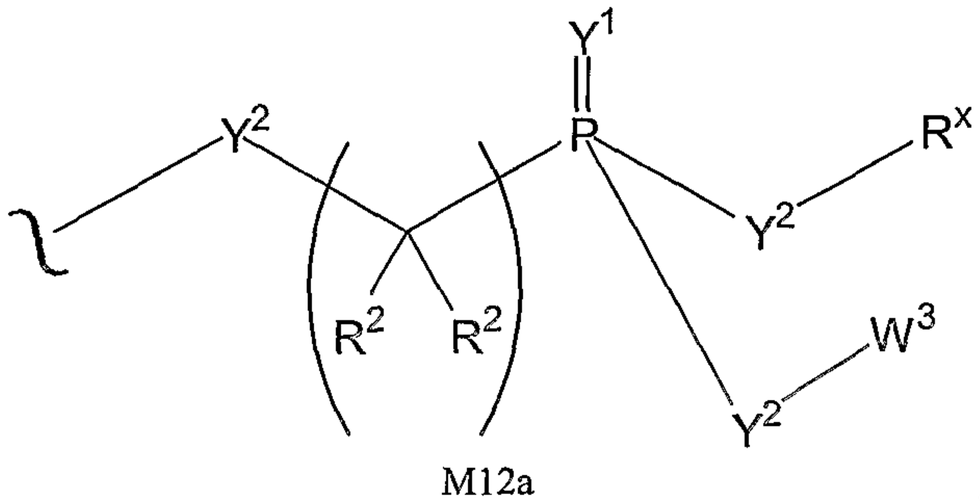


wherein Y^{2b} is O or N(R^2).

In another specific embodiment of the invention A^3 is of the formula:

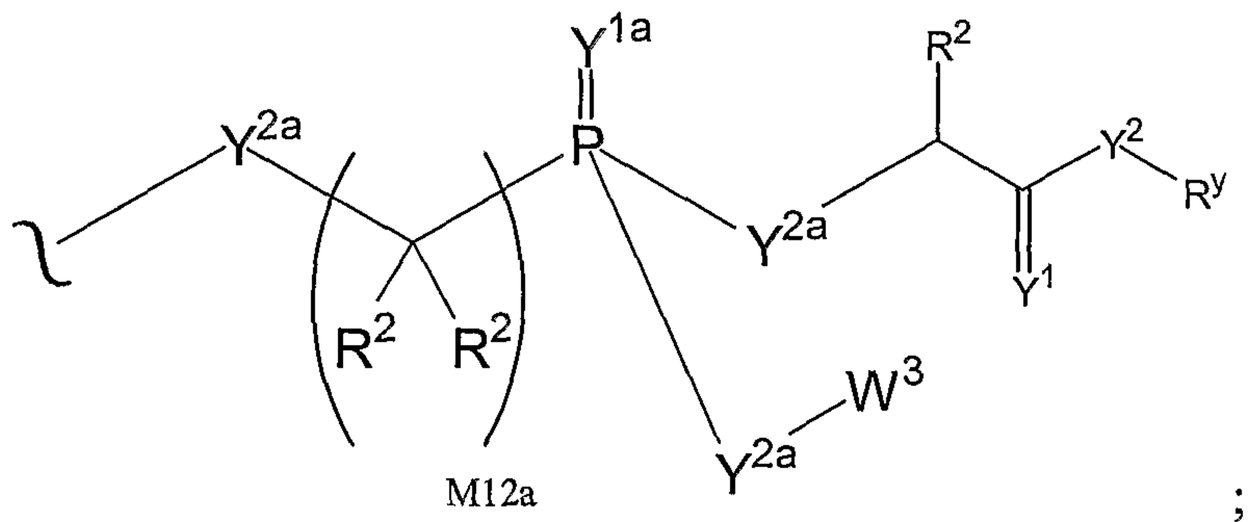


In another specific embodiment of the invention A^3 is of the formula:



M12a

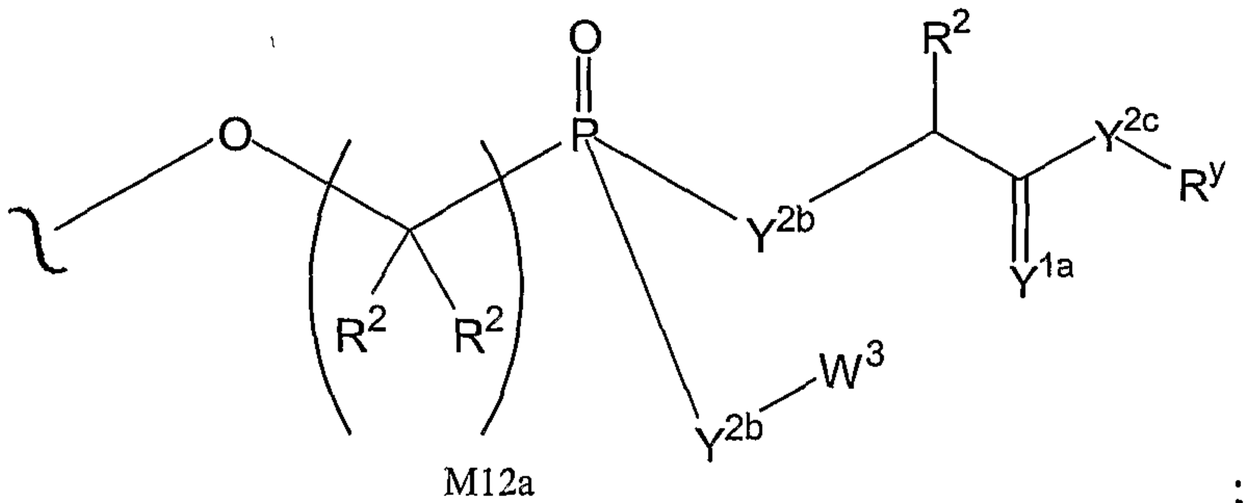
In another specific embodiment of the invention A^3 is of the formula:



M12a ;

wherein Y^{1a} is O or S; and Y^{2a} is O, N(R^2) or S.

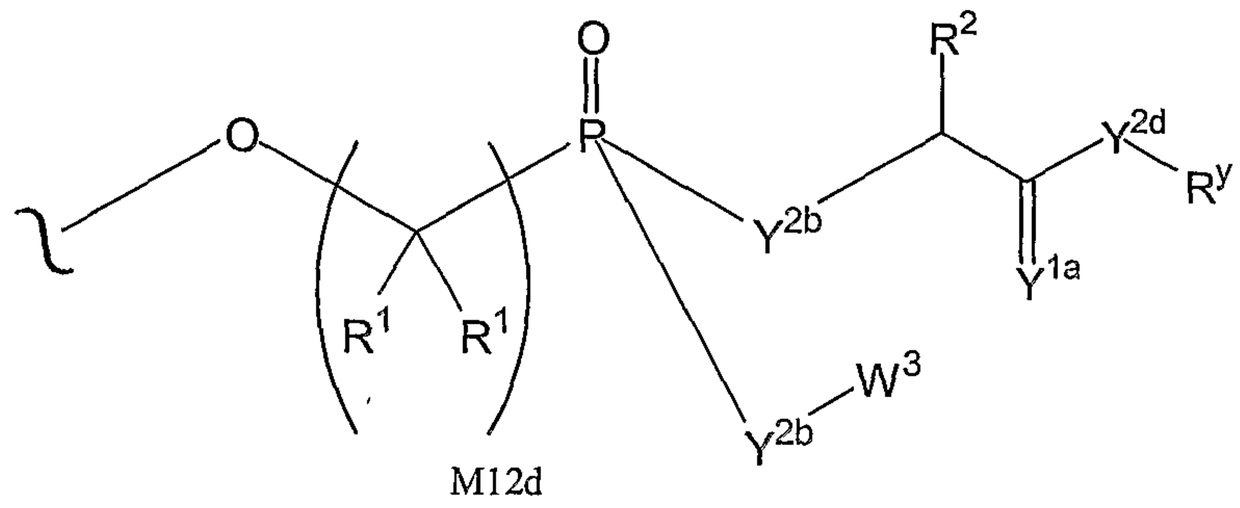
In another specific embodiment of the invention A^3 is of the formula:



M12a ;

wherein Y^{1a} is O or S; Y^{2b} is O or N(R^2); and Y^{2c} is O, N(R^y) or S.

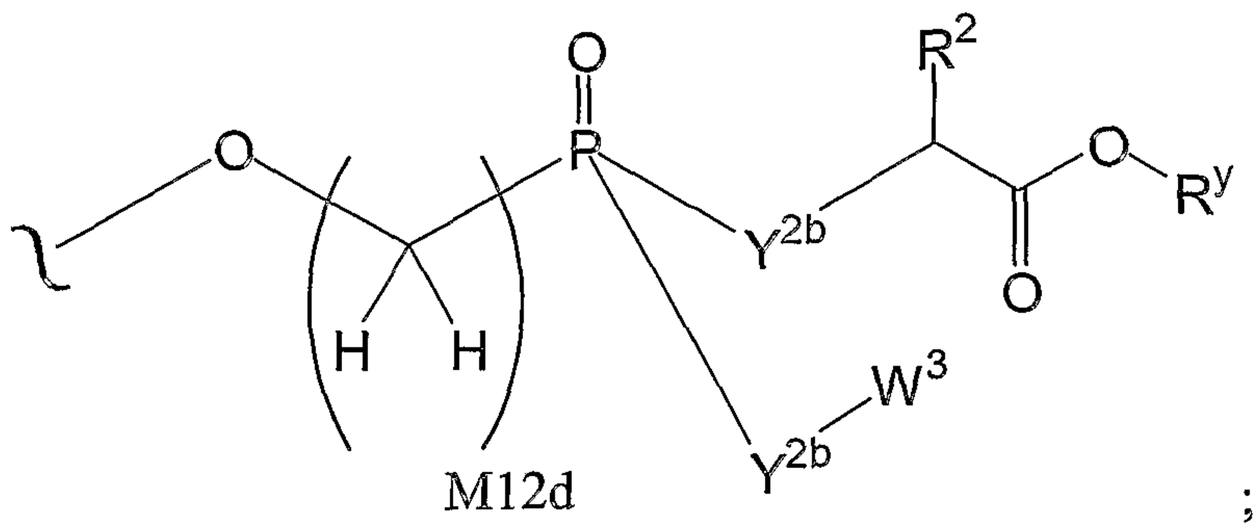
In another specific embodiment of the invention A^3 is of the formula:



M12d

wherein Y^{1a} is O or S; Y^{2b} is O or N(R^2); Y^{2d} is O or N(R^y); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

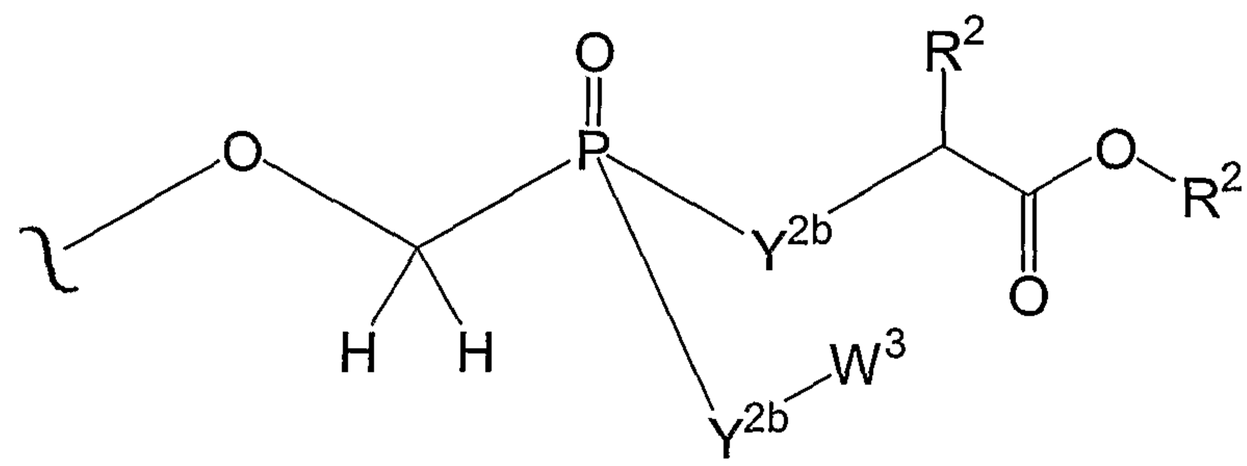
In another specific embodiment of the invention A^3 is of the formula:



;

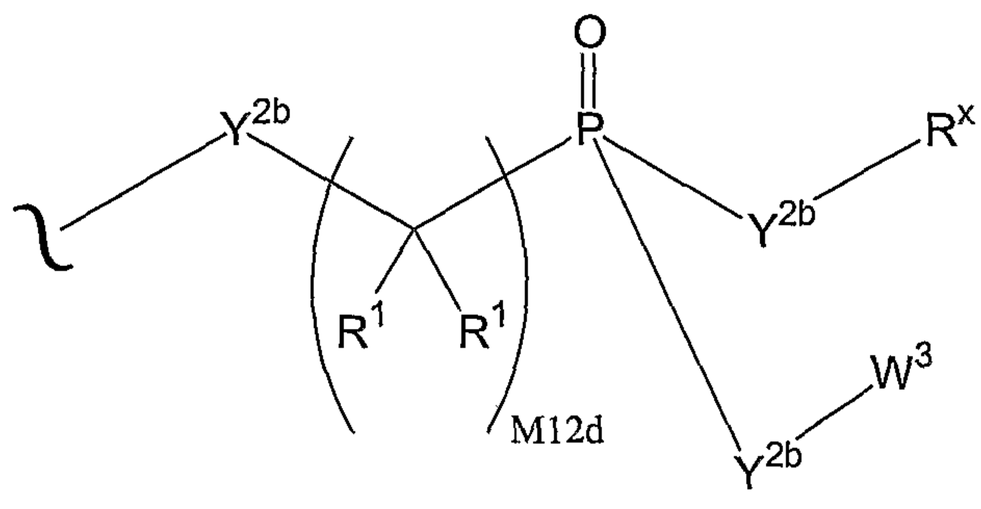
wherein Y^{2b} is O or N(R^2); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:



wherein Y^{2b} is O or N(R^2).

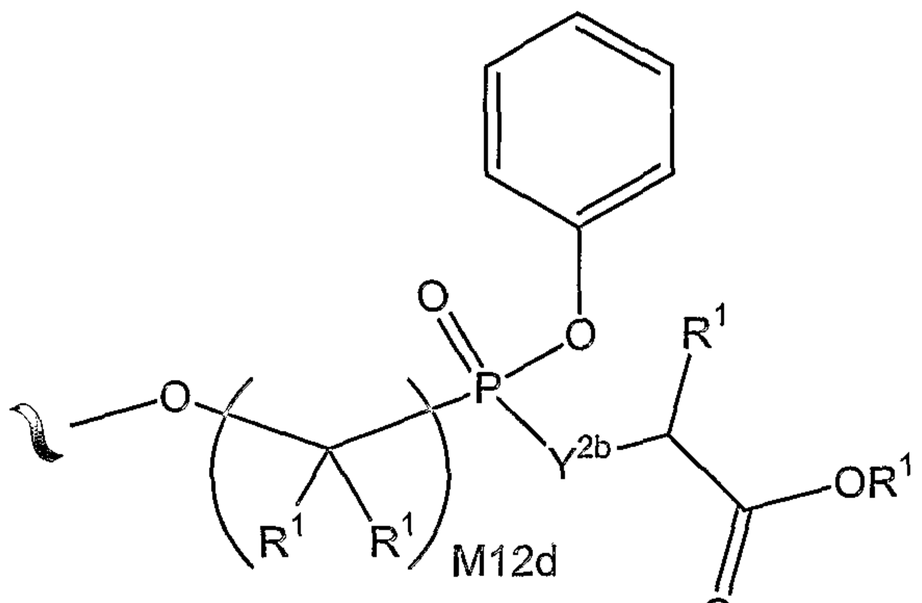
In another specific embodiment of the invention A^3 is of the formula:



;

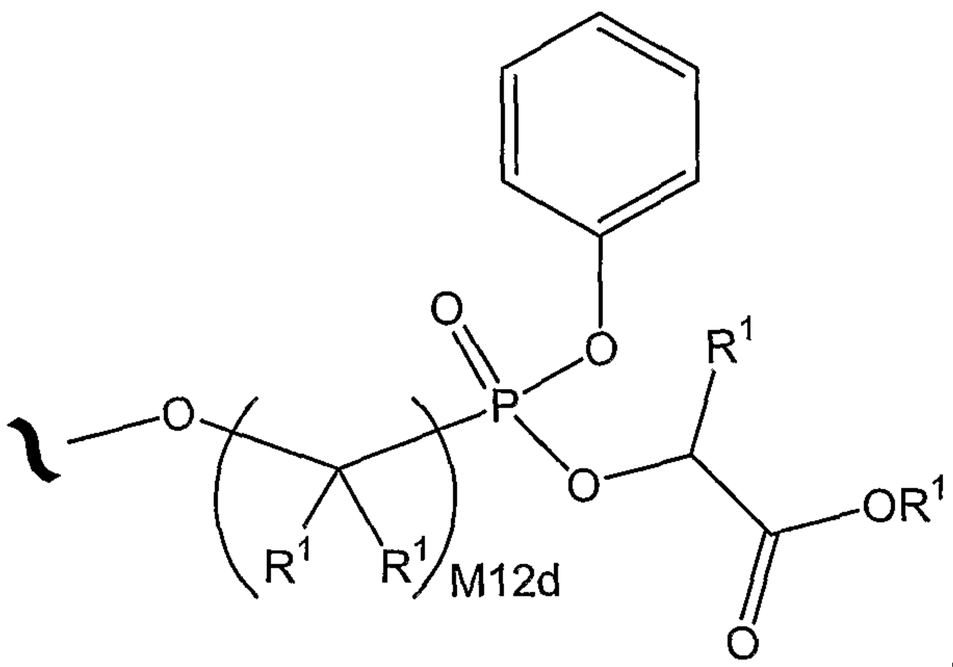
wherein: Y^{2b} is O or N(R^x); and M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

In another specific embodiment of the invention A^3 is of the formula:



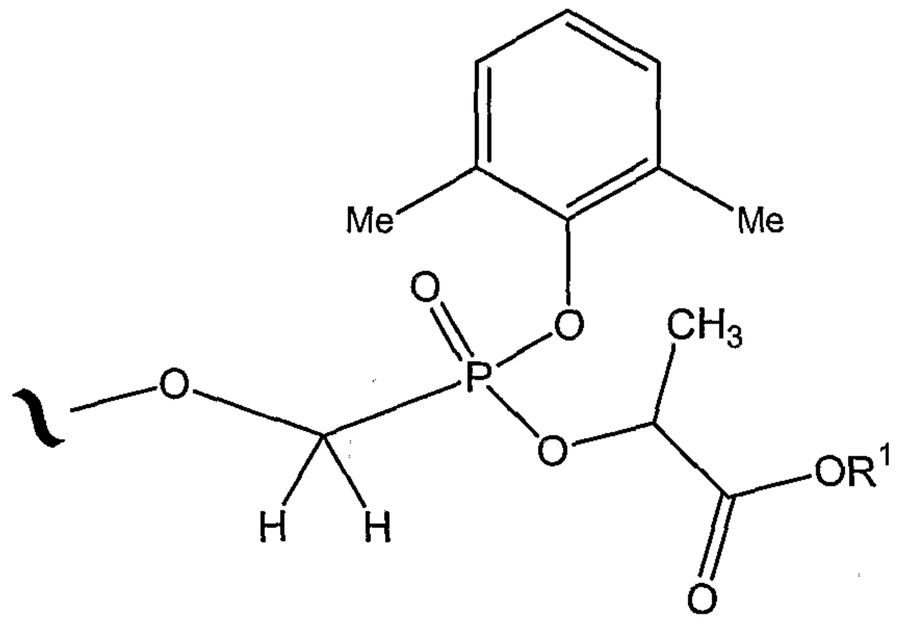
wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^3 is of the formula:

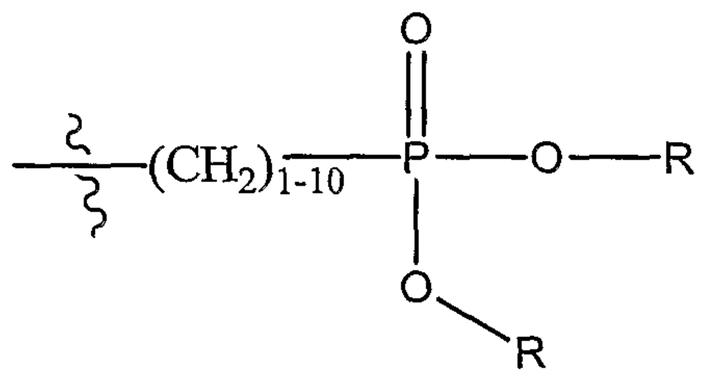


wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

In another specific embodiment of the invention A^3 is of the formula:

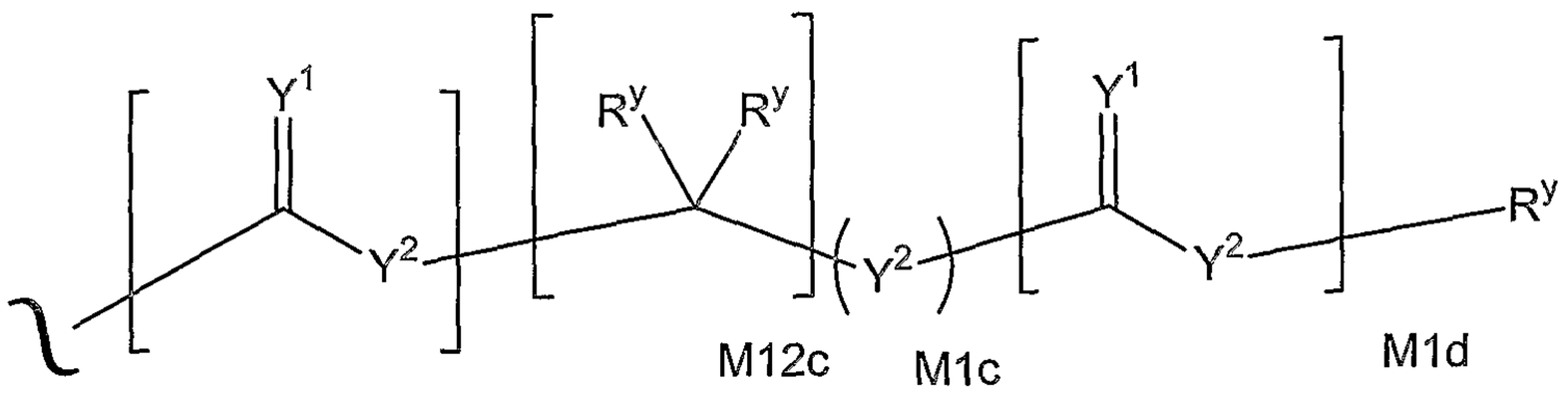


In a specific embodiment of the invention A^0 is of the formula:



wherein each R is independently $(C_1\text{-}C_6)$alkyl.

In a specific embodiment of the invention R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

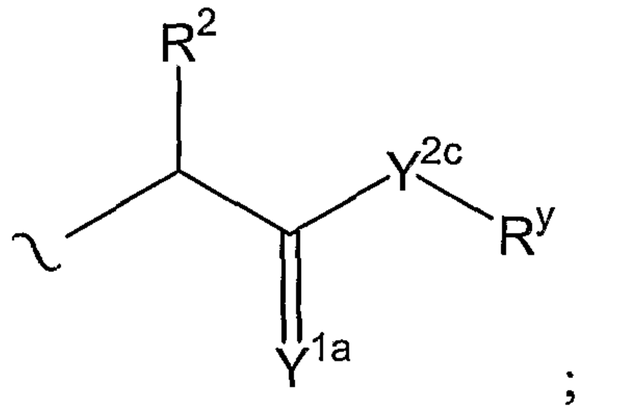
wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

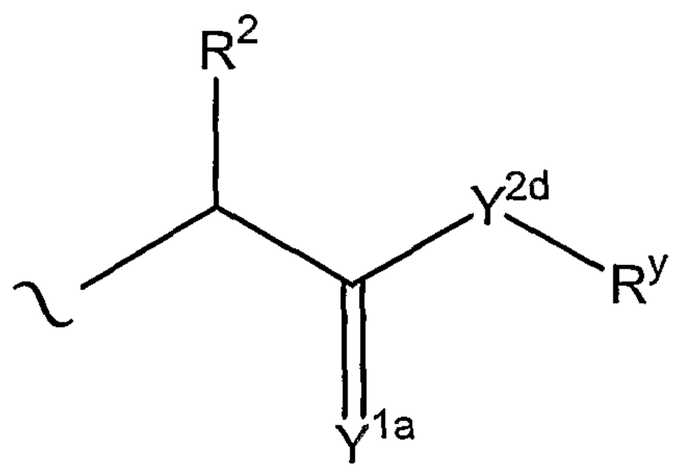
In a specific embodiment of the invention R^x is of the formula:



;

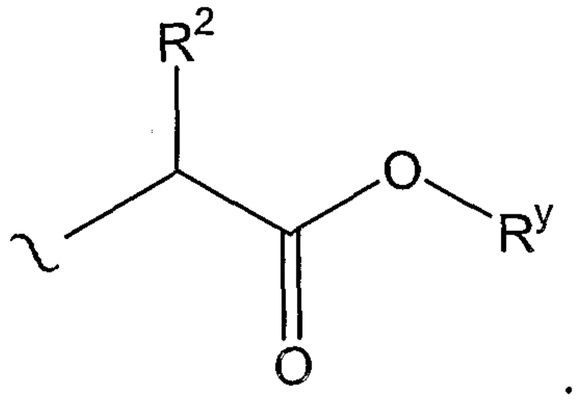
wherein Y^{1a} is O or S; and Y^{2c} is O, $N(R^y)$ or S.

In a specific embodiment of the invention R^x is of the formula:



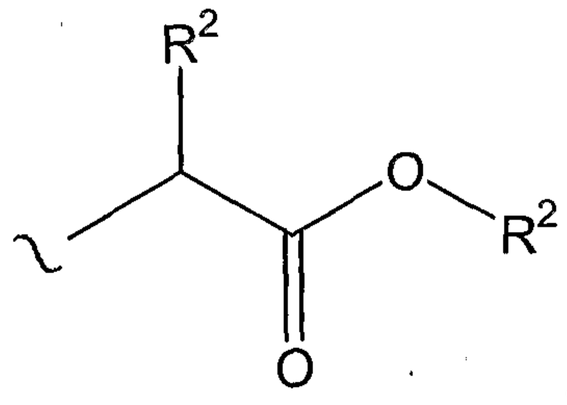
;

In a specific embodiment of the invention R^x is of the formula:

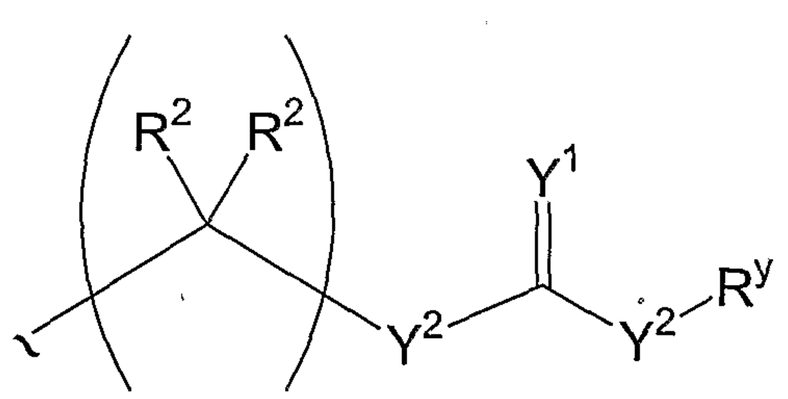


In a specific embodiment of the invention R^y is hydrogen or alkyl of 1 to 10 carbons.

In a specific embodiment of the invention R^x is of the formula:

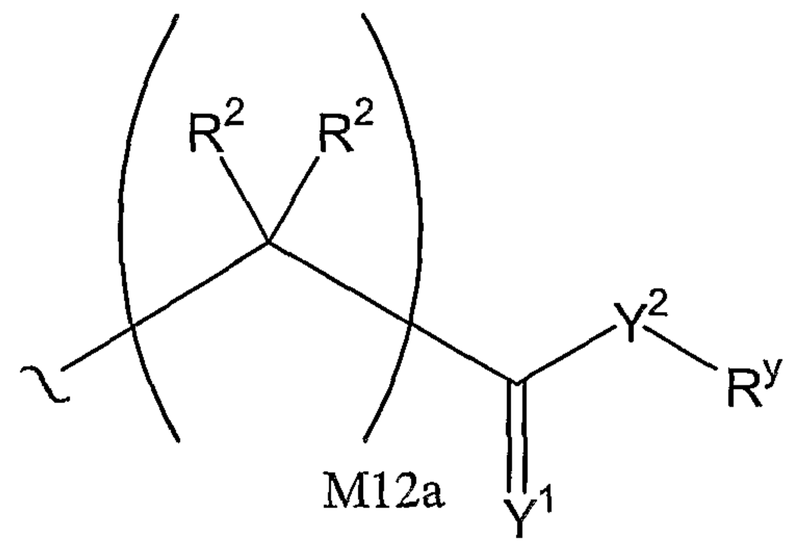


In a specific embodiment of the invention R^x is of the formula:



M12a

In a specific embodiment of the invention R^x is of the formula:

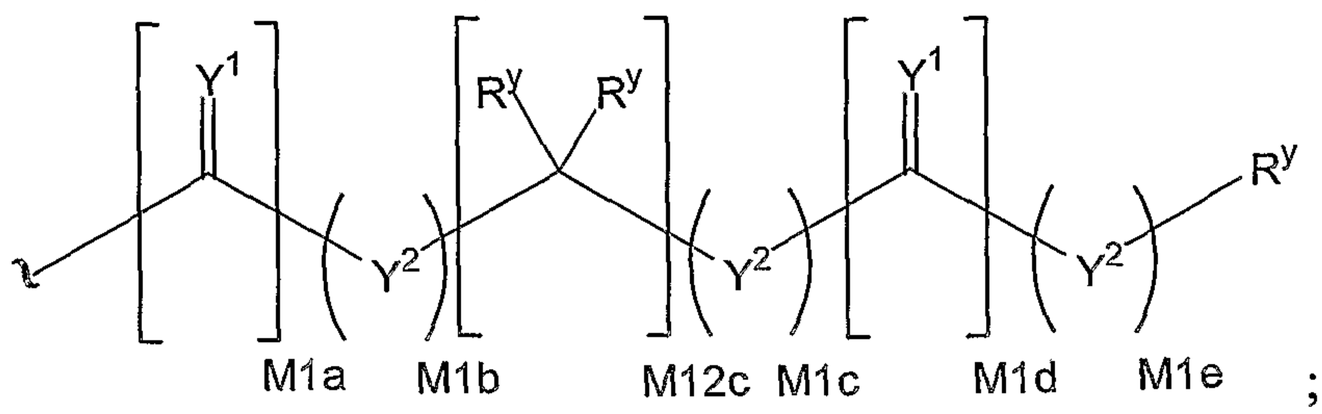


M12a

In a specific embodiment of the invention Y^1 is O or S.

In a specific embodiment of the invention Y^2 is O, $N(R^y)$ or S.

In one specific embodiment of the invention R^x is a group of the formula:



;

wherein:

m1a, m1b, m1c, m1d and m1e are independently 0 or 1;

m12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

R^y is H, W^3, R^2 or a protecting group;

provided that:

if m1a, m12c, and m1d are 0, then m1b, m1c and m1e are 0;

if m1a and m12c are 0 and m1d is not 0, then m1b and m1c are 0;

if m1a and m1d are 0 and m12c is not 0, then m1b and at least one of m1c and m1e are 0;

if m1a is 0 and m12c and m1d are not 0, then m1b is 0;

if m12c and m1d are 0 and m1a is not 0, then at least two of m1b, m1c and m1e are 0;

if m12c is 0 and m1a and m1d are not 0, then at least one of m1b and m1c are 0; and

if m1d is 0 and m1a and m12c are not 0, then at least one of m1c and m1e are 0.

In another specific embodiment, the invention provides a compound of the formula:

$$[DRUG]\text{-}(A^0)_{nn}$$

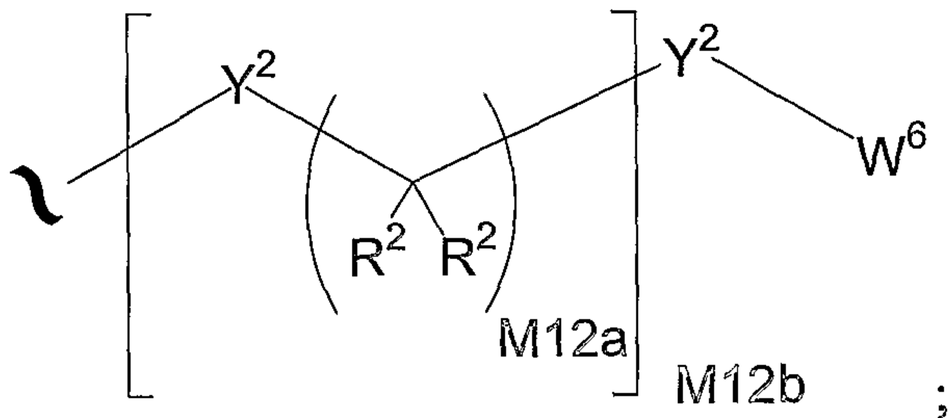
or a pharmaceutically acceptable salt thereof wherein,

DRUG is a compound of any one of formulae **500-547**;

nn is 1, 2, or 3;

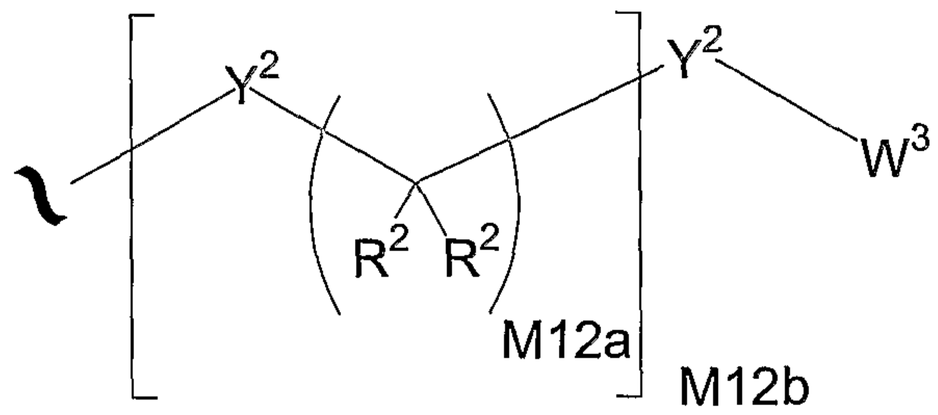
A^0 is A^1, A^2 or W^3 with the proviso that the compound includes at least one A^1;

A^1 is:



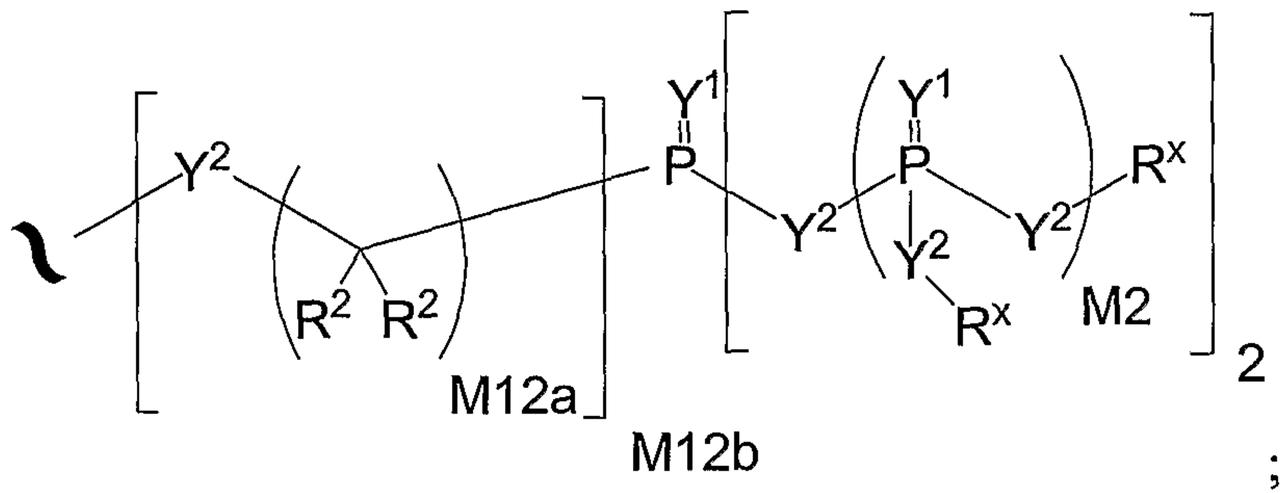
;

A^2 is:



;

A^3 is:

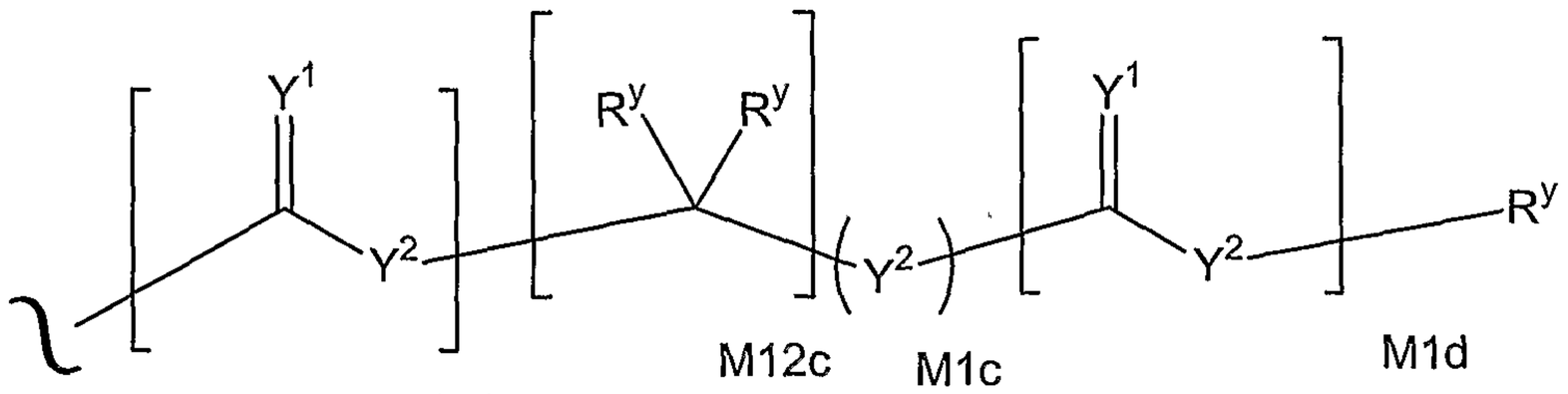


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^1, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

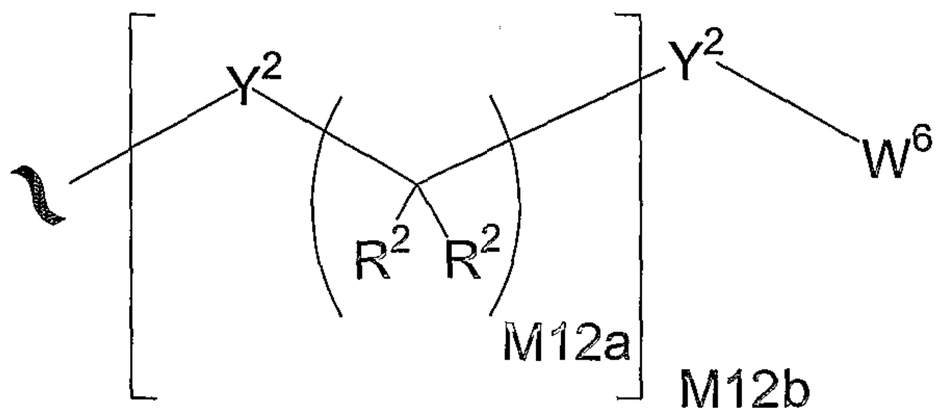
M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another embodiment, the invention provides a compound of any one of formulae **1-151** wherein:

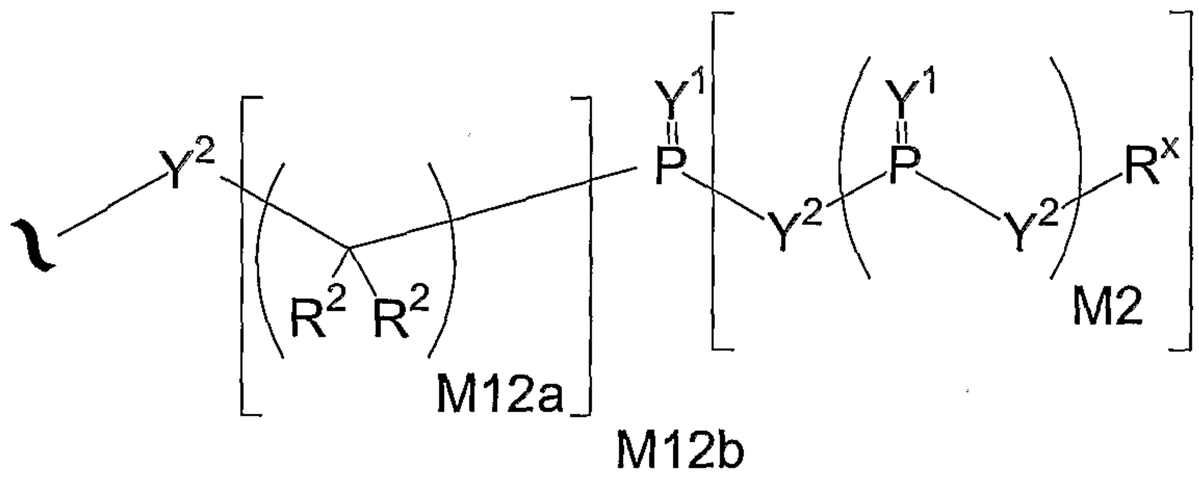
A^0 is A^1;

A^1 is:



;

A^3 is:

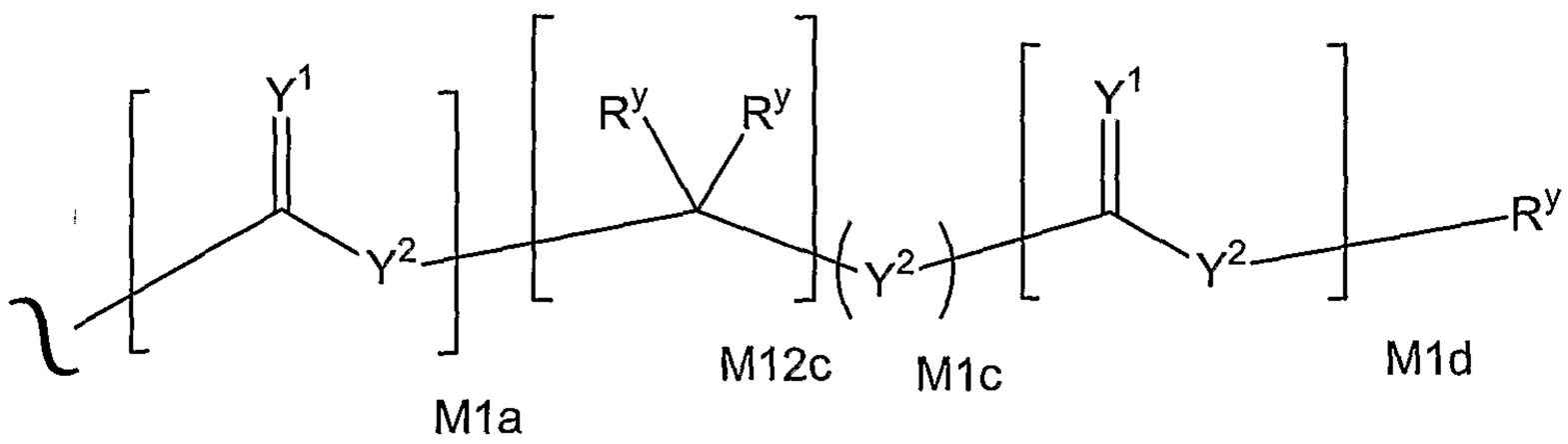


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, -

$SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

R^{5a} is independently alkylene of 1 to 18 carbon atoms, alkenylene of 2 to 18 carbon atoms, or alkynylene of 2-18 carbon atoms any one of which alkylene, alkenylene or alkynylene is substituted with 0-3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In another specific embodiment, the invention provides a compound of the formula:

$$[DRUG]\text{-}[L\text{-}P(=Y^1)\text{-}Y^2\text{-}R^x]_{nn}$$

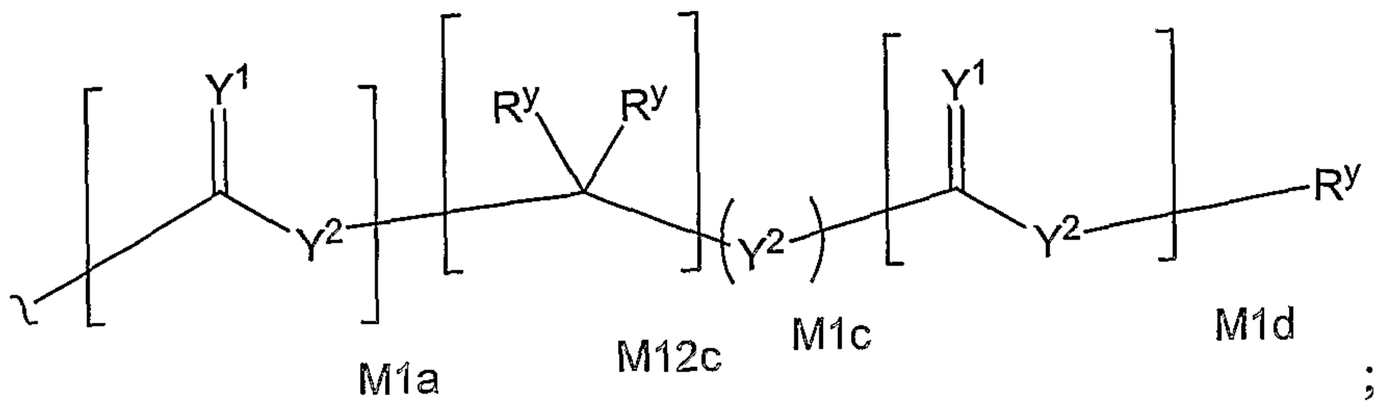
or a pharmaceutically acceptable salt thereof wherein,

DRUG is a compound of any one of formulae **500-547**;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 1, 2, or 3;

M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

nn is 1, 2, or 3; and

L is a linking group.

In another specific embodiment, the invention provides a compound of which is a compound of the formula:

$$[DRUG]\text{-}(A^0)_{nn}$$

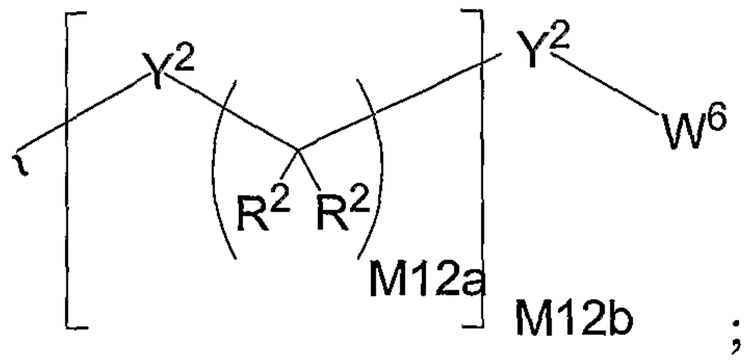
or a pharmaceutically acceptable salt thereof wherein,

DRUG is a compound of any one of formulae **500-547**;

nn is 1, 2, or 3;

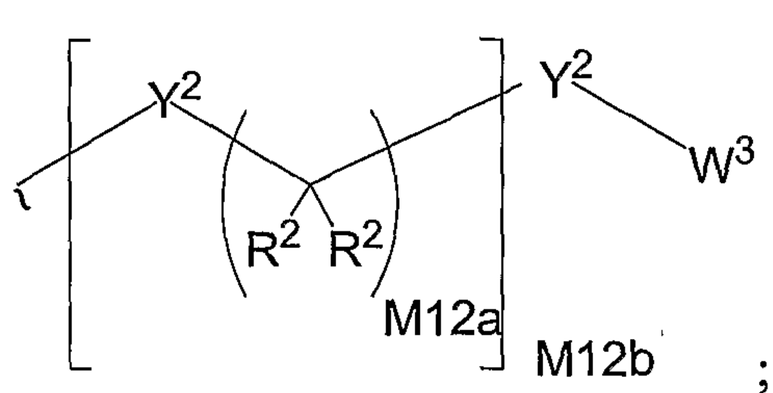
A^0 is A^1, A^2, or W^3 with the proviso that the compound includes at least one A^1;

A^1 is:



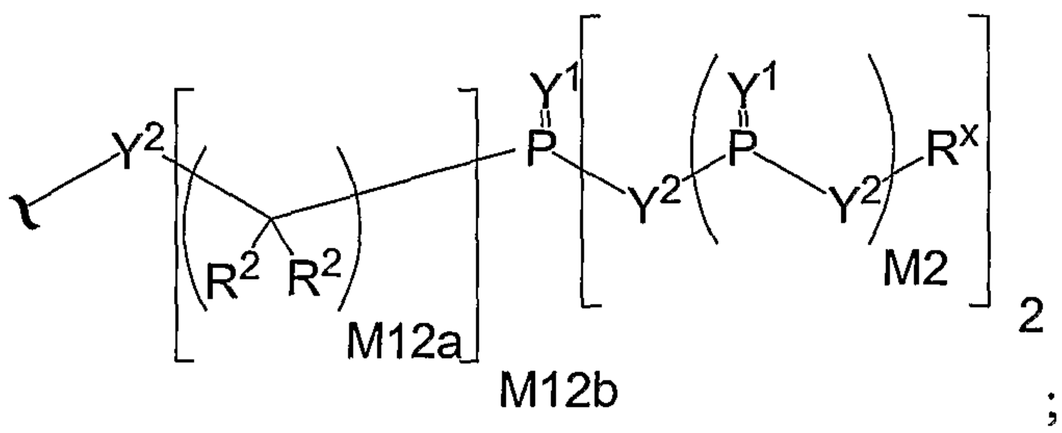
;

A^2 is:



;

A^3 is:

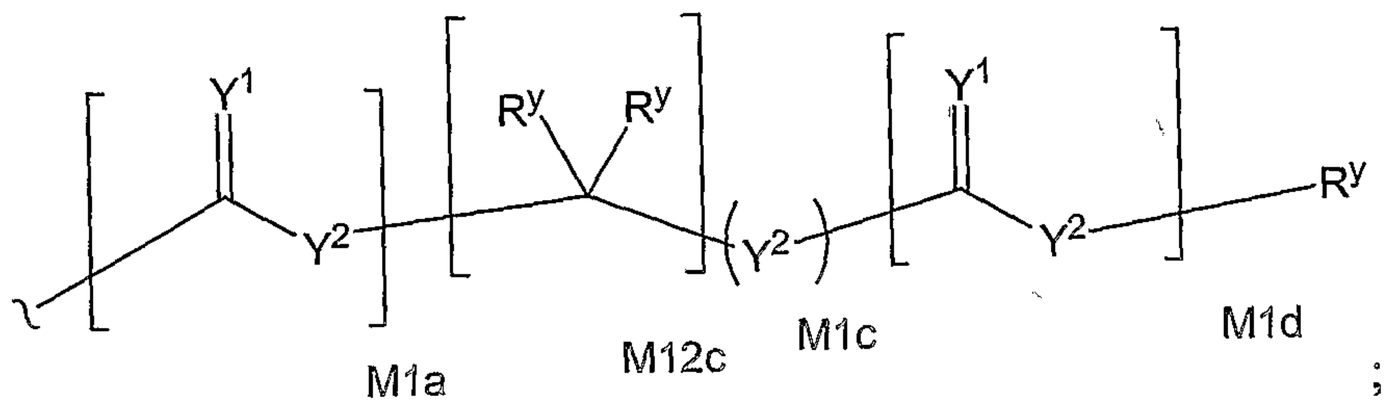


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

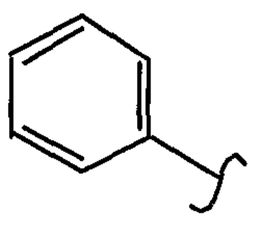
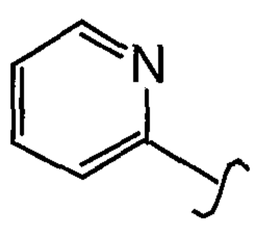
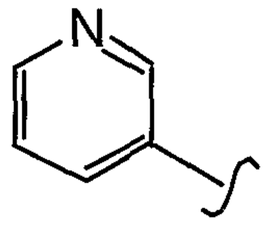
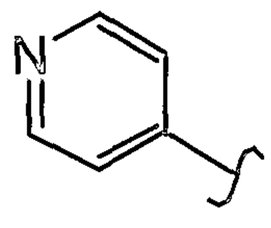
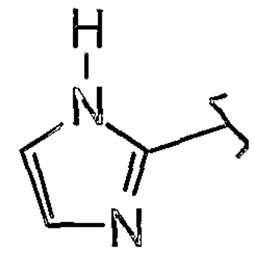
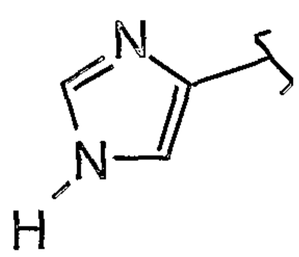
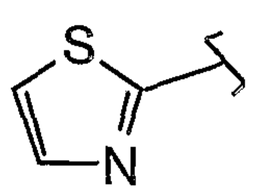
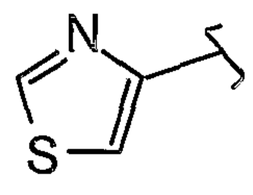
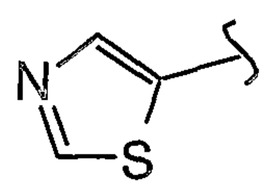
M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

In compounds of the invention W^5 carbocycles and W^5 heterocycles may

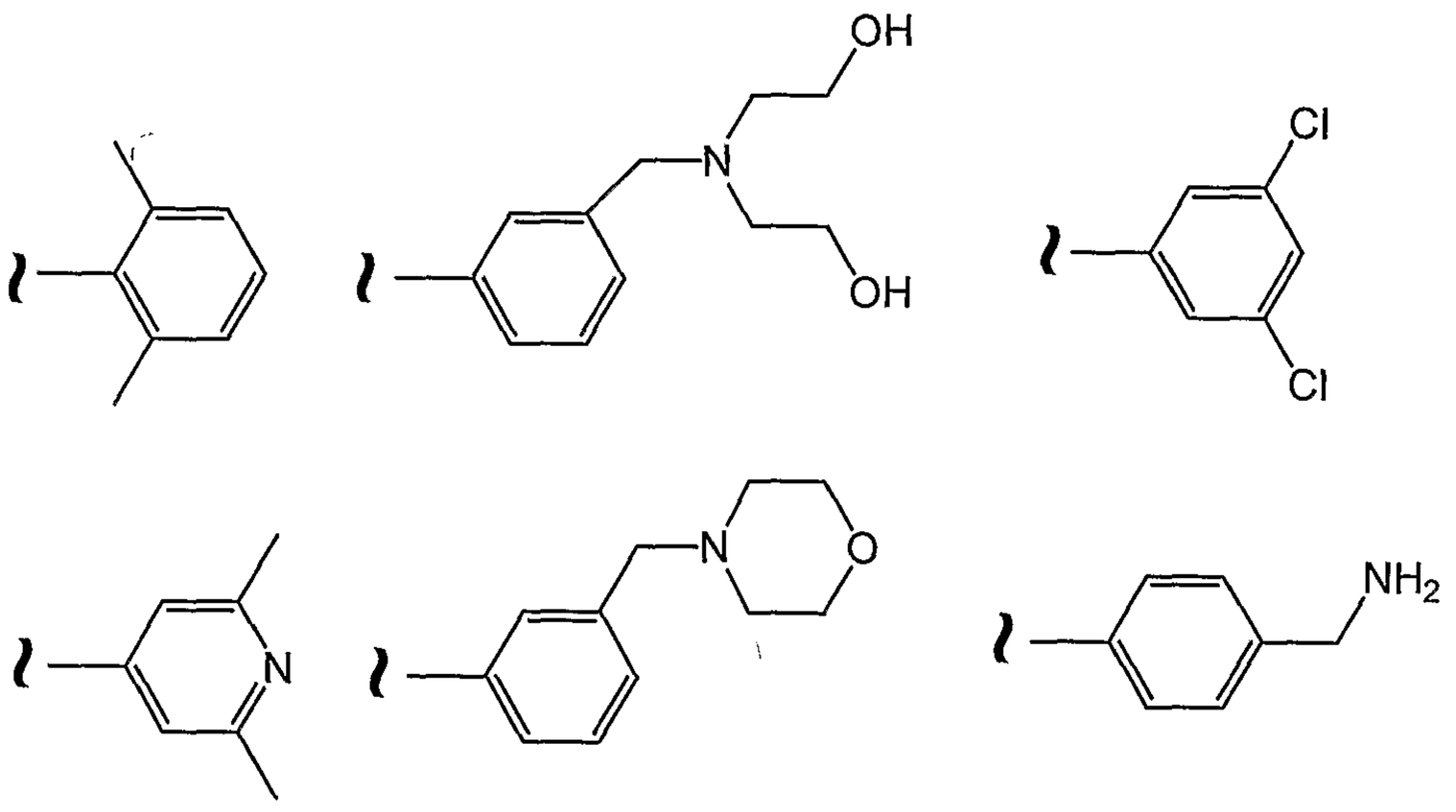
be independently substituted with 0 to 3 R^2 groups. W^5 may be a saturated, unsaturated or aromatic ring comprising a mono- or bicyclic carbocycle or heterocycle. W^5 may have 3 to 10 ring atoms, e.g., 3 to 7 ring atoms. The W^5 rings are saturated when containing 3 ring atoms, saturated or mono-unsaturated when containing 4 ring atoms, saturated, or mono- or di-unsaturated when containing 5 ring atoms, and saturated, mono- or di-unsaturated, or aromatic when containing 6 ring atoms.

A W^5 heterocycle may be a monocycle having 3 to 7 ring members (2 to 6 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S) or a bicycle having 7 to 10 ring members (4 to 9 carbon atoms and 1 to 3 heteroatoms selected from N, O, P, and S). W^5 heterocyclic monocycles may have 3 to 6 ring atoms (2 to 5 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S); or 5 or 6 ring atoms (3 to 5 carbon atoms and 1 to 2 heteroatoms selected from N and S). W^5 heterocyclic bicycles have 7 to 10 ring atoms (6 to 9 carbon atoms and 1 to 2 heteroatoms selected from N, O, and S) arranged as a bicyclo [4,5], [5,5], [5,6], or [6,6] system; or 9 to 10 ring atoms (8 to 9 carbon atoms and 1 to 2 hetero atoms selected from N and S) arranged as a bicyclo [5,6] or [6,6] system. The W^5 heterocycle may be bonded to Y^2 through a carbon, nitrogen, sulfur or other atom by a stable covalent bond.

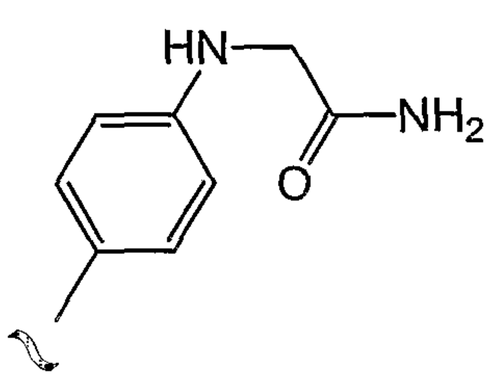
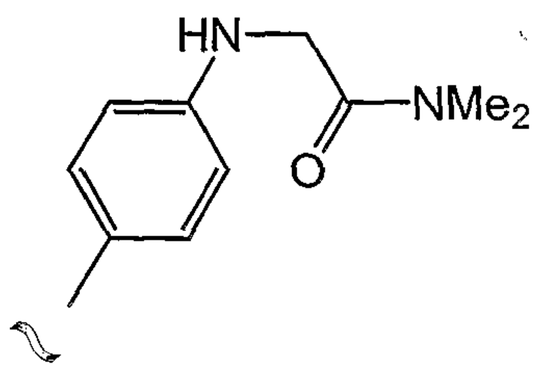
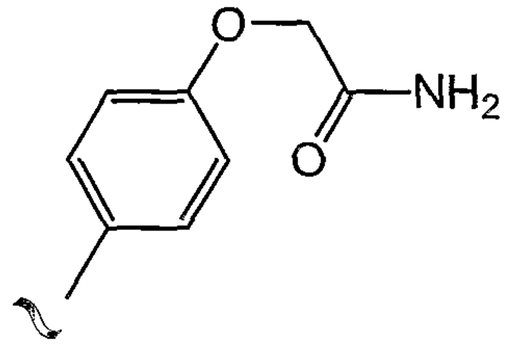
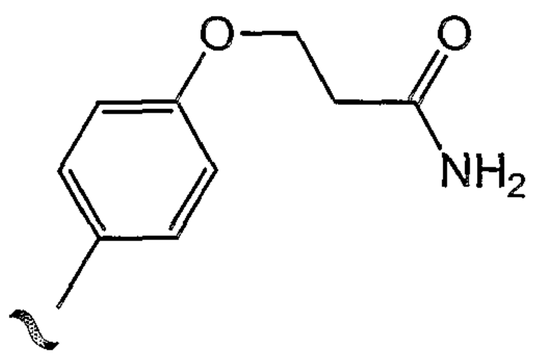
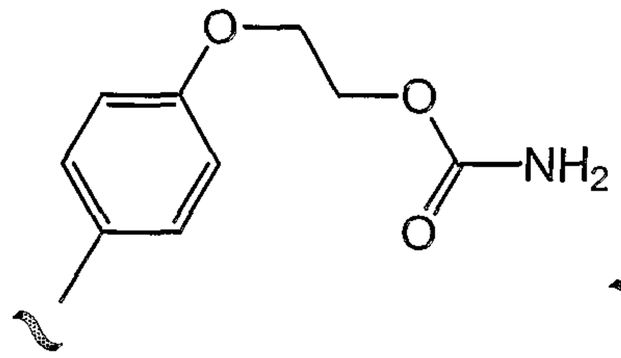
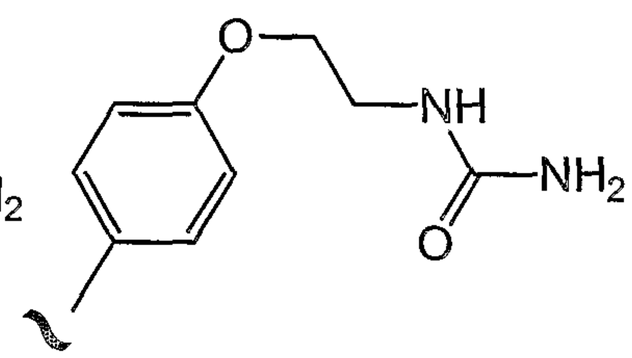
W^5 heterocycles include for example, pyridyl, dihydropyridyl isomers, piperidine, pyridazinyl, pyrimidinyl, pyrazinyl, s-triazinyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, furanyl, thiofuranyl, thienyl, and pyrrolyl. W^5 also includes, but is not limited to, examples such as:


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W^5 carbocycles and heterocycles may be independently substituted with 0 to 3 R^2 groups, as defined above. For example, substituted W^5 carbocycles include:



Examples of substituted phenyl carbocycles include:

Linking Groups and Linkers

The invention provides conjugates that comprise an immuno-modulatory compound that is linked to one or more phosphonate groups either directly (e.g. through a covalent bond) or through a linking group (i.e. a linker). The nature of the linker is not critical provided it does not interfere with the ability of the phosphonate containing compound to function as a therapeutic agent. The phosphonate or the linker can be linked to the compound (e.g. a compound of Formulae **500-547**) at any synthetically feasible position on the compound by removing a hydrogen or any portion of the compound to provide an open valence for attachment of the phosphonate or the linker.

In one embodiment of the invention the linking group or linker (which can be designated "L") can include all or a portions of the group A^0, A^1, A^2, or W^3 described herein.

In another embodiment of the invention the linking group or linker has a molecular weight of from about 20 daltons to about 400 daltons.

In another embodiment of the invention the linking group or linker has a length of about 5 angstroms to about 300 angstroms.

In another embodiment of the invention the linking group or linker separates the DRUG and a $P(=Y^1)$ residue by about 5 angstroms to about 200 angstroms, inclusive, in length.

In another embodiment of the invention the linking group or linker is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more (e.g. 1, 2, 3, or 4) of the

carbon atoms is optionally replaced by (-O-), and wherein the chain is optionally substituted on carbon with one or more (e.g. 1, 2, 3, or 4) substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

In another embodiment of the invention the linking group or linker is of the formula W-A wherein A is (C_1-C_{24})alkyl, (C_2-C_{24})alkenyl, (C_2-C_{24})alkynyl, (C_3-C_8)cycloalkyl, (C_6-C_{10})aryl or a combination thereof, wherein W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -$S(O)_2$-, -N(R)-, -C(=O)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

In another embodiment of the invention the linking group or linker is a divalent radical formed from a peptide.

In another embodiment of the invention the linking group or linker is a divalent radical formed from an amino acid.

In another embodiment of the invention the linking group or linker is a divalent radical formed from poly-L-glutamic acid, poly-L-aspartic acid, poly-L-histidine, poly-L-ornithine, poly-L-serine, poly-L-threonine, poly-L-tyrosine, poly-L-leucine, poly-L-lysine-L-phenylalanine, poly-L-lysine or poly-L-lysine-L-tyrosine.

In another embodiment of the invention the linking group or linker is of the formula W-$(CH_2)_n$ wherein, n is between about 1 and about 10; and W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -$S(O)_2$-, -C(=O)-, -N(R)-, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

In another embodiment of the invention the linking group or linker is methylene, ethylene, or propylene.

In another embodiment of the invention the linking group or linker is attached to the phosphonate group through a carbon atom of the linker.

Compounds

The compounds of the invention include those with immuno-modulatory activity. The compounds of the inventions bear one or more (e.g. 1, 2, 3, or 4)

phosphonate groups, which may be a prodrug moiety.

Typically, compounds of the invention have a molecular weight of from about 400 amu to about 10,000 amu; in a specific embodiment of the invention, compounds have a molecular weight of less than about 5000 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 2500 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 1000 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 800 amu; in another specific embodiment of the invention, compounds have a molecular weight of less than about 600 amu; and in another specific embodiment of the invention, compounds have a molecular weight of less than about 600 amu and a molecular weight of greater than about 400 amu.

The compounds of the invention also typically have a logD(polarity) less than about 5. In one embodiment the invention provides compounds having a logD less than about 4; in another one embodiment the invention provides compounds having a logD less than about 3; in another one embodiment the invention provides compounds having a logD greater than about -5; in another one embodiment the invention provides compounds having a logD greater than about -3; and in another one embodiment the invention provides compounds having a logD greater than about 0 and less than about 3.

Selected substituents within the compounds of the invention are present to a recursive degree. In this context, "recursive substituent" means that a substituent may recite another instance of itself. Because of the recursive nature of such substituents, theoretically, a large number may be present in any given claim. For example, R^x contains a R^y substituent. R^y can be R^2, which in turn can be R^3. If R^3 is selected to be R^{3c}, then a second instance of R^x can be selected. One of ordinary skill in the art of medicinal chemistry understands that the total number of such substituents is reasonably limited by the desired properties of the compound intended. Such properties include, by of example and not limitation, physical properties such as molecular weight, solubility or log P, application properties such as activity against the intended target, and practical properties such as ease of synthesis.

By way of example and not limitation, W^3, R^y and R^3 are all recursive substituents in certain claims. Typically, each of these may independently occur 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, or 0, times in a given claim. More typically, each of these may independently occur 12 or fewer times in a given claim. More typically yet, W^3 will occur 0 to 8 times, R^y will occur 0 to 6 times and R^3 will occur 0 to 10 times in a given claim. Even more typically, W^3 will occur 0 to 6 times, R^y will occur 0 to 4 times and R^3 will occur 0 to 8 times in a given claim.

Recursive substituents are an intended aspect of the invention. One of ordinary skill in the art of medicinal chemistry understands the versatility of such substituents. To the degree that recursive substituents are present in an claim of the invention, the total number will be determined as set forth above.

Whenever a compound described herein is substituted with more than one of the same designated group, e.g., "R^1" or "R^{6a}", then it will be understood that the groups may be the same or different, i.e., each group is independently selected. Wavy lines indicate the site of covalent bond attachments to the adjoining groups, moieties, or atoms.

The term immuno-modulatory compound also includes pimecrolimus, everolimus, sirolimus, tacrolimus, prednisolone, VX-148, merimepodib, brequinar, thalidomide, BCX-1777, revimid, diprolene, aclometasone dipropionate, hydrocortisone, dexamethasone, leflunomide, methylprednisolone suleptanate, prednisone, clobetasol, MNA-715 (FK778), SMP-114, teriflunomide, halobetasol, ciclesonide, deflazacort, medroxyprogesterone, budesonide, rimexolone, triamcinolone acetonide, fluticasone, mometasone furoate, methylprednisolone aceponate, cyclosporin A, tacrolimus, mycophenolate, ANA-245, immunosuppressive macrolide, methotrexate, PNP-405, MDL-74428, 9-(3,3-dimethyl-5-phosphonopentyl) guanine, DADMe-IMMG, CP-690,550, mycophenate, cyclosporin, and mizoribine.

In one embodiment of the invention, the compound is in isolated and purified form. Generally, the term "isolated and purified" means that the compound is significantly free of biological materials (e.g. blood, cells, etc.). In one specific embodiment of the invention, the term means that the compound or conjugate of the invention is at least about 50% pure by weight in a mixture; in

another specific embodiment, the term means that the compound or conjugate of the invention is at least about 75% pure by weight in a mixture; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 90% pure by weight in a mixture; in another specific embodiment, the term means that the compound or conjugate of the invention is at least about 98% pure by weight in a mixture; and in another embodiment, the term means that the compound or conjugate of the invention is at least about 99% pure by weight in a mixture. In another specific embodiment, the invention provides a compound or conjugate of the invention that has been synthetically prepared (e.g. prepared *ex vivo*).

Intracellular Targeting

The phosphonate group of the compounds of the invention may cleave *in vivo* in stages after they have reached the desired site of action, i.e. inside a cell. One mechanism of action inside a cell may entail a first cleavage, e.g. by esterase, to provide a negatively-charged "locked-in" intermediate. Cleavage of a terminal ester grouping in a compound of the invention thus affords an unstable intermediate which releases a negatively charged "locked in" intermediate.

After passage inside a cell, intracellular enzymatic cleavage or modification of the phosphonate or prodrug compound may result in an intracellular accumulation of the cleaved or modified compound by a “trapping” mechanism. The cleaved or modified compound may then be “locked-in” the cell by a significant change in charge, polarity, or other physical property change which decreases the rate at which the cleaved or modified compound can exit the cell, relative to the rate at which it entered as the phosphonate prodrug. Other mechanisms by which a therapeutic effect are achieved may be operative as well. Enzymes which are capable of an enzymatic activation mechanism with the phosphonate prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

From the foregoing, it will be apparent that many different drugs can be derivatized in accord with the present invention. Numerous such drugs are specifically mentioned herein. However, it should be understood that the

discussion of drug families and their specific members for derivatization according to this invention is not intended to be exhaustive, but merely illustrative.

In one embodiment of the invention, the compound is not an antiviral agent compound. In another embodiment the compound is not a nucleoside compound. In another embodiment the compound is not an IMPDH inhibitor compound. In another embodiment the compound is not an antimetabolite compound. In another embodiment the compound is not a PNP inhibitor. In another embodiment the compound is not a substituted compound of any one of formulae **500-533**, **535-541**, or **543-547**. In another embodiment the compound is not a substituted compound of any one of one of formulae **1-104**, **107-124**, or **128-151**.

Stereoisomers

The compounds of the invention may have chiral centers, e.g., chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention include enriched or resolved optical isomers at any or all asymmetric, chiral atoms. In other words, the chiral centers apparent from the depictions are provided as the chiral isomers or racemic mixtures. Both racemic and diastereomeric mixtures, as well as the individual optical isomers isolated or synthesized, substantially free of their enantiomeric or diastereomeric partners, are all within the scope of the invention. The racemic mixtures are separated into their individual, substantially optically pure isomers through well-known techniques such as, for example, the separation of diastereomeric salts formed with optically active adjuncts, e.g., acids or bases followed by conversion back to the optically active substances. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

The compounds of the invention can also exist as tautomeric isomers in certain cases. All though only one delocalized resonance structure may be depicted, all such forms are contemplated within the scope of the invention. For

example, ene-amine tautomers can exist for purine, pyrimidine, imidazole, guanidine, amidine, and tetrazole systems and all their possible tautomeric forms are within the scope of the invention.

Salts and Hydrates

The compositions of this invention optionally comprise salts of the compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na^+, Li^+, K^+, Ca^{+2} and Mg^{+2}. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. Monovalent salts are preferred if a water soluble salt is desired.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. Examples of metal salts which are prepared in this way are salts containing Li^+, Na^+, and K^+. A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound.

In addition, salts may be formed from acid addition of certain organic and inorganic acids, e.g., HCl, HBr, H_2SO_4, H_3PO_4 or organic sulfonic acids, to basic centers, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the amino acids described above are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

Methods of Inhibition of Immuno-Modulation

Another aspect of the invention relates to methods of inhibiting the activity of immuno-modulators comprising the step of treating a sample suspected of containing an immuno-modulator with a composition of the

invention.

Compositions of the invention may act as inhibitors of immune-modulation, as intermediates for such inhibitors or have other utilities as described below. The inhibitors will bind to locations on the surface or in a cavity of an immuno-modulator having a geometry unique to immuno-modulators. Compositions binding immuno-modulators may bind with varying degrees of reversibility. Those compounds binding substantially irreversibly are ideal candidates for use in this method of the invention. Once labeled, the substantially irreversibly binding compositions are useful as probes for the detection of immune-modulation. Accordingly, the invention relates to methods of detecting immune-modulation in a sample suspected of containing an immuno-modulator comprising the steps of: treating a sample suspected of containing an immuno-modulator with a composition comprising a compound of the invention bound to a label; and observing the effect of the sample on the activity of the label. Suitable labels are well known in the diagnostics field and include stable free radicals, fluorophores, radioisotopes, enzymes, chemiluminescent groups and chromogens. The compounds herein are labeled in conventional fashion using functional groups such as hydroxyl or amino.

Within the context of the invention samples suspected of containing an immuno-modulator include natural or man-made materials such as living organisms; tissue or cell cultures; biological samples such as biological material samples (blood, serum, urine, cerebrospinal fluid, tears, sputum, saliva, tissue samples, and the like); laboratory samples; food, water, or air samples; bioproduct samples such as extracts of cells, particularly recombinant cells synthesizing a desired glycoprotein; and the like. Typically the sample will be suspected of containing an immuno-modulator. Samples can be contained in any medium including water and organic solvent/water mixtures. Samples include living organisms such as humans, and man made materials such as cell cultures.

The treating step of the invention comprises adding the composition of the invention to the sample or it comprises adding a precursor of the composition to the sample. The addition step comprises any method of administration as described above.

If desired, the activity of an immuno-modulator, after application of the

composition, can be observed by any method including direct and indirect methods of detecting immuno-modulator activity. Quantitative, qualitative, and semiquantitative methods of determining immuno-modulation activity are all contemplated. Typically one of the screening methods described above are applied, however, any other method such as observation of the physiological properties of a living organism are also applicable.

However, in screening compounds capable of inhibiting immuno-modulation it should be kept in mind that the results of enzyme assays may not correlate with cell culture assays. Thus, a cell based assay should be the primary screening tool.

Screens for Immuno-Modulating Inhibitors

Compositions of the invention are screened for inhibitory activity against immuno-modulators by any of the conventional techniques for evaluating enzyme activity. Within the context of the invention, typically compositions are first screened for inhibition of immuno-modulators *in vitro* and compositions showing inhibitory activity are then screened for activity *in vivo*. Compositions having *in vitro* Ki (inhibitory constants) of less then about 5×10^{-6} M, typically less than about 1×10^{-7} M and preferably less than about 5×10^{-8} M are preferred for *in vivo* use.

Useful *in vitro* screens have been described in detail and will not be elaborated here. However, the examples describe suitable *in vitro* assays.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily

about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the invention comprise at least one active ingredient, as above defined, together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active

ingredient therefrom.

For administration to the eye or other external tissues e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a

non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For

example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of infections as described below.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which

may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

Effective dose of active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active infection, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. It can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about

.01 to about 5 mg/kg body weight per day. More typically, from about .05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

Active ingredients of the invention are also used in combination with other active ingredients. Such combinations are selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination.

It is also possible to combine any compound of the invention with one or more other active ingredients in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

The combination therapy may provide "synergy" and "synergistic effect", i.e. the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a

synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, i.e. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the *in vivo* metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g., C^{14} or H^3) compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found *in vivo*, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no immuno-modulation inhibitory activity of their own.

Recipes and methods for determining stability of compounds in surrogate gastrointestinal secretions are known. Compounds are defined herein as stable in the gastrointestinal tract where less than about 50 mole percent of the protected groups are deprotected in surrogate intestinal or gastric juice upon

incubation for 1 hour at 37 °C. Simply because the compounds are stable to the gastrointestinal tract does not mean that they cannot be hydrolyzed *in vivo*. The phosphonate prodrugs of the invention typically will be stable in the digestive system but are substantially hydrolyzed to the parental drug in the digestive lumen, liver or other metabolic organ, or within cells in general.

Exemplary Methods of Making the Compounds of the Invention.

The invention also relates to methods of making the compositions of the invention. The compositions are prepared by any of the applicable techniques of organic synthesis. Many such techniques are well known in the art. However, many of the known techniques are elaborated in Compendium of Organic Synthetic Methods (John Wiley & Sons, New York), Vol. 1, Ian T. Harrison and Shuyen Harrison, 1971; Vol. 2, Ian T. Harrison and Shuyen Harrison, 1974; Vol. 3, Louis S. Hegedus and Leroy Wade, 1977; Vol. 4, Leroy G. Wade, jr., 1980; Vol. 5, Leroy G. Wade, Jr., 1984; and Vol. 6, Michael B. Smith; as well as March, J., Advanced Organic Chemistry, Third Edition, (John Wiley & Sons, New York, 1985), Comprehensive Organic Synthesis. Selectivity, Strategy & Efficiency in Modern Organic Chemistry. In 9 Volumes, Barry M. Trost, Editor-in-Chief (Pergamon Press, New York, 1993 printing).

A number of exemplary methods for the preparation of the compositions of the invention are provided below. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20 °C), although for metal hydride

reductions frequently the temperature is reduced to 0 °C to -100 °C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0 °C to -100 °C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic (common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g., inert gas environments) are common in the art and will be applied when applicable.

Schemes and Examples

General aspects of these exemplary methods are described below and in the Examples. Each of the products of the following processes is optionally separated, isolated, and/or purified prior to its use in subsequent processes.

Generally, the reaction conditions such as temperature, reaction time, solvents, work-up procedures, and the like, will be those common in the art for the particular reaction to be performed. The cited reference material, together with material cited therein, contains detailed descriptions of such conditions. Typically the temperatures will be -100°C to 200°C, solvents will be aprotic or protic, and reaction times will be 10 seconds to 10 days. Work-up typically consists of quenching any unreacted reagents followed by partition between a water/organic layer system (extraction) and separating the layer containing the product.

Oxidation and reduction reactions are typically carried out at temperatures near room temperature (about 20 °C), although for metal hydride reductions frequently the temperature is reduced to 0 °C to -100 °C, solvents are typically aprotic for reductions and may be either protic or aprotic for oxidations. Reaction times are adjusted to achieve desired conversions.

Condensation reactions are typically carried out at temperatures near room temperature, although for non-equilibrating, kinetically controlled condensations reduced temperatures (0 °C to -100 °C) are also common. Solvents can be either protic (common in equilibrating reactions) or aprotic

(common in kinetically controlled reactions).

Standard synthetic techniques such as azeotropic removal of reaction by-products and use of anhydrous reaction conditions (e.g., inert gas environments) are common in the art and will be applied when applicable.

The terms "treated", "treating", "treatment", and the like, when used in connection with a chemical synthetic operation, mean contacting, mixing, reacting, allowing to react, bringing into contact, and other terms common in the art for indicating that one or more chemical entities is treated in such a manner as to convert it to one or more other chemical entities. This means that "treating compound one with compound two" is synonymous with "allowing compound one to react with compound two", "contacting compound one with compound two", "reacting compound one with compound two", and other expressions common in the art of organic synthesis for reasonably indicating that compound one was "treated", "reacted", "allowed to react", etc., with compound two. For example, treating indicates the reasonable and usual manner in which organic chemicals are allowed to react. Normal concentrations (0.01M to 10M, typically 0.1M to 1M), temperatures (-100 °C to 250 °C, typically -78 °C to 150 °C, more typically -78 °C to 100 °C, still more typically 0 °C to 100 °C), reaction vessels (typically glass, plastic, metal), solvents, pressures, atmospheres (typically air for oxygen and water insensitive reactions or nitrogen or argon for oxygen or water sensitive), etc., are intended unless otherwise indicated. The knowledge of similar reactions known in the art of organic synthesis are used in selecting the conditions and apparatus for "treating" in a given process. In particular, one of ordinary skill in the art of organic synthesis selects conditions and apparatus reasonably expected to successfully carry out the chemical reactions of the described processes based on the knowledge in the art.

Modifications of each of the exemplary schemes and in the examples (hereafter "exemplary schemes") leads to various analogs of the specific exemplary materials produce. The above-cited citations describing suitable methods of organic synthesis are applicable to such modifications.

In each of the exemplary schemes it may be advantageous to separate reaction products from one another and/or from starting materials. The desired products of each step or series of steps is separated and/or purified (hereinafter

separated) to the desired degree of homogeneity by the techniques common in the art. Typically such separations involve multiphase extraction, crystallization from a solvent or solvent mixture, distillation, sublimation, or chromatography. Chromatography can involve any number of methods including, for example: reverse-phase and normal phase; size exclusion; ion exchange; high, medium, and low pressure liquid chromatography methods and apparatus; small scale analytical; simulated moving bed (SMB) and preparative thin or thick layer chromatography, as well as techniques of small scale thin layer and flash chromatography.

Another class of separation methods involves treatment of a mixture with a reagent selected to bind to or render otherwise separable a desired product, unreacted starting material, reaction by product, or the like. Such reagents include adsorbents or absorbents such as activated carbon, molecular sieves, ion exchange media, or the like. Alternatively, the reagents can be acids in the case of a basic material, bases in the case of an acidic material, binding reagents such as antibodies, binding proteins, selective chelators such as crown ethers, liquid/liquid ion extraction reagents (LIX), or the like.

Selection of appropriate methods of separation depends on the nature of the materials involved. For example, boiling point, and molecular weight in distillation and sublimation, presence or absence of polar functional groups in chromatography, stability of materials in acidic and basic media in multiphase extraction, and the like. One skilled in the art will apply techniques most likely to achieve the desired separation.

A single stereoisomer, e.g., an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Stereochemistry of Carbon Compounds, (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) *J. Chromatogr.*, 113:(3) 283-302). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and

(3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions.

Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, α-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts.

Alternatively, by method (2), the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g., (-) menthyl chloroformate in the presence of base, or Mosher ester, α-methoxy-α-(trifluoromethyl)phenyl acetate (Jacob III. (1982) *J. Org. Chem.* 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO 96/15111). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (Chiral Liquid Chromatography (1989) W. J. Lough, Ed. Chapman and Hall, New York; Okamoto, (1990) *J. of Chromatogr.* 513:375-378). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

Examples General Section

A number of exemplary methods for the preparation of compounds of the invention are provided herein, for example, in the Examples hereinbelow.. These methods are intended to illustrate the nature of such preparations are not intended to limit the scope of applicable methods. Certain compounds of the invention can be used as intermediates for the preparation of other compounds of the invention. For example, the interconversion of various phosphonate compounds of the invention is illustrated below.

INTERCONVERSIONS OF THE PHOSPHONATES R-LINK-P(O)$(OR^1)_2$, R-LINK-P(O)(OR^1)(OH) AND R-LINK-P(O)$(OH)_2$.

The following schemes **32-38** described the preparation of phosphonate esters of the general structure R-link-P(O)$(OR^1)_2$, in which the groups R^1 may be the same or different. The R^1 groups attached to a phosphonate ester, or to precursors thereto, may be changed using established chemical transformations. The interconversion reactions of phosphonates are illustrated in Scheme **S32.** The group R in Scheme **32** represents the substructure, i.e. the drug "scaffold, to which the substituent link-P(O)$(OR^1)_2$ is attached, either in the compounds of the invention, or in precursors thereto. At the point in the synthetic route of conducting a phosphonate interconversion, certain functional groups in R may be protected. The methods employed for a given phosphonate transformation depend on the nature of the substituent R^1, and of the substrate to which the phosphonate group is attached. The preparation and hydrolysis of phosphonate esters is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 9ff.

In general, synthesis of phosphonate esters is achieved by coupling a nucleophile amine or alcohol with the corresponding activated phosphonate electrophilic precursor. For example, chlorophosphonate addition on to 5'-hydroxy of nucleoside is a well known method for preparation of nucleoside phosphate monoesters. The activated precursor can be prepared by several well known methods. Chlorophosphonates useful for synthesis of the prodrugs are prepared from the substituted-1,3-propanediol (Wissner, et al, (1992) *J. Med Chem*. 35:1650). Chlorophosphonates are made by oxidation of the

corresponding chlorophospholanes (Anderson, et al, (1984) *J. Org. Chem.* 49:1304) which are obtained by reaction of the substituted diol with phosphorus trichloride. Alternatively, the chlorophosphonate agent is made by treating substituted-1,3-diols with phosphorusoxychloride (Patois, et al, (1990) *J. Chem. Soc. Perkin Trans. I*, 1577). Chlorophosphonate species may also be generated in situ from corresponding cyclic phosphites (Silverburg, et al., (1996) *Tetrahedron lett.*, 37:771-774), which in turn can be either made from chlorophospholane or phosphoramidate intermediate. Phosphoroflouridate intermediate prepared either from pyrophosphate or phosphoric acid may also act as precursor in preparation of cyclic prodrugs (Watanabe et al., (1988) *Tetrahedron lett.*, 29:5763-66).

Phosphonate prodrugs of the present invention may also be prepared from the free acid by Mitsunobu reactions (Mitsunobu, (1981) *Synthesis*, 1; Campbell, (1992) *J. Org. Chem.* 57:6331), and other acid coupling reagents including, but not limited to, carbodiimides (Alexander, et al, (1994) *Collect. Czech. Chem. Commun.* 59:1853; Casara et al, (1992) *Bioorg. Med. Chem. Lett.* 2:145; Ohashi et al, (1988) *Tetrahedron Lett.*, 29:1189), and benzotriazolyloxytris-(dimethylamino)phosphonium salts (Campagne et al (1993) *Tetrahedron Lett.* 34:6743).

Aryl halides undergo Ni^{+2} catalyzed reaction with phosphite derivatives to give aryl phosphonate containing compounds (Balthazar, et al (1980) *J. Org. Chem.* 45:5425). Phosphonates may also be prepared from the chlorophosphonate in the presence of a palladium catalyst using aromatic triflates (Petrakis et al (1987) *J. Am. Chem. Soc.* 109:2831; Lu et al (1987) *Synthesis* 726). In another method, aryl phosphonate esters are prepared from aryl phosphates under anionic rearrangement conditions (Melvin (1981) *Tetrahedron Lett.* 22:3375; Casteel et al (1991) *Synthesis*, 691). N-Alkoxy aryl salts with alkali met al derivatives of cyclic alkyl phosphonate provide general synthesis for heteroaryl-2-phosphonate linkers (Redmore (1970) *J. Org. Chem.* 35:4114). These above mentioned methods can also be extended to compounds where the W^5 group is a heterocycle. Cyclic-1,3-propanyl prodrugs of phosphonates are also synthesized from phosphonic diacids and substituted propane-1,3-diols using a coupling reagent such as 1,3-dicyclohexylcarbodiimide (DCC) in presence of a base (e.g., pyridine). Other

carbodiimide based coupling agents like 1,3-disopropylcarbodiimide or water soluble reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) can also be utilized for the synthesis of cyclic phosphonate prodrugs.

The conversion of a phosphonate diester **S32.1** into the corresponding phosphonate monoester **S32.2** (Scheme **32**, Reaction **1**) is accomplished by a number of methods. For example, the ester **S32.1** in which R^1 is an aralkyl group such as benzyl, is converted into the monoester compound **S32.2** by reaction with a tertiary organic base such as diazabicyclooctane (DABCO) or quinuclidine, as described in *J. Org. Chem.* (1995) 60:2946. The reaction is performed in an inert hydrocarbon solvent such as toluene or xylene, at about 110 °C. The conversion of the diester **S32.1** in which R^1 is an aryl group such as phenyl, or an alkenyl group such as allyl, into the monoester **S32.2** is effected by treatment of the ester **S32.1** with a base such as aqueous sodium hydroxide in acetonitrile or lithium hydroxide in aqueous tetrahydrofuran. Phosphonate diesters **S32.1** in which one of the groups R^1 is aralkyl, such as benzyl, and the other is alkyl, is converted into the monoesters **S32.2** in which R^1 is alkyl by hydrogenation, for example using a palladium on carbon catalyst. Phosphonate diesters in which both of the groups R^1 are alkenyl, such as allyl, is converted into the monoester **S32.2** in which R^1 is alkenyl, by treatment with chlorotris(triphenylphosphine)rhodium (Wilkinson's catalyst) in aqueous ethanol at reflux, optionally in the presence of diazabicyclooctane, for example by using the procedure described in *J. Org. Chem.* (1973) 38:3224, for the cleavage of allyl carboxylates.

The conversion of a phosphonate diester **S32.1** or a phosphonate monoester **S32.2** into the corresponding phosphonic acid **S32.3** (Scheme **32**, Reactions **2** and **3**) can be effected by reaction of the diester or the monoester with trimethylsilyl bromide, as described in *J. Chem. Soc., Chem. Comm.*, (1979) 739. The reaction is conducted in an inert solvent such as, for example, dichloromethane, optionally in the presence of a silylating agent such as bis(trimethylsilyl)trifluoroacetamide, at ambient temperature. A phosphonate monoester **S32.2** in which R^1 is aralkyl such as benzyl, is converted into the corresponding phosphonic acid **S32.3** by hydrogenation over a palladium catalyst, or by treatment with hydrogen chloride in an ethereal solvent such as

dioxane. A phosphonate monoester **S32.2** in which R^1 is alkenyl such as, for example, allyl, is converted into the phosphonic acid **S32.3** by reaction with Wilkinson's catalyst in an aqueous organic solvent, for example in 15% aqueous acetonitrile, or in aqueous ethanol, for example using the procedure described in *Helv. Chim. Acta*. (1985) 68:618. Palladium catalyzed hydrogenolysis of phosphonate esters **S32.1** in which R^1 is benzyl is described in *J. Org. Chem.* (1959) 24:434. Platinum-catalyzed hydrogenolysis of phosphonate esters **S32.1** in which R^1 is phenyl is described in *J. Am. Chem. Soc.* (1956) 78:2336.

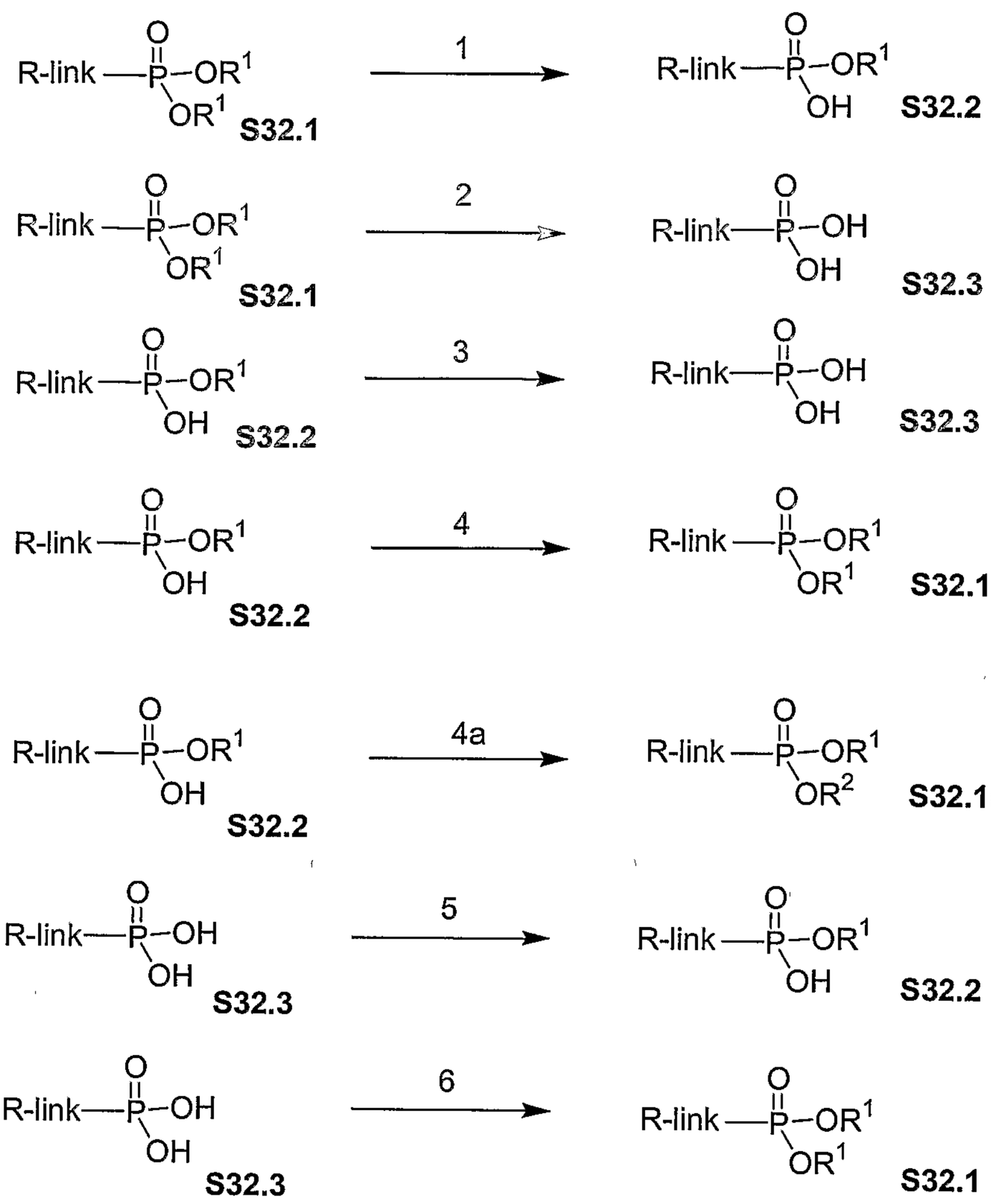
The conversion of a phosphonate monoester **S32.2** into a phosphonate diester **S32.1** (Scheme **32**, Reaction **4**) in which the newly introduced R^1 group is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl is effected by a number of reactions in which the substrate **S32.2** is reacted with a hydroxy compound R^1OH, in the presence of a coupling agent. Typically, the second phosphonate ester group is different than the first introduced phosphonate ester group, i.e. R^1 is followed by the introduction of R^2 where each of R^1 and R^2 is alkyl, aralkyl, haloalkyl such as chloroethyl, or aralkyl (Scheme **32**, Reaction **4a**) whereby **S32.2** is converted to **S32.1a**. Suitable coupling agents are those employed for the preparation of carboxylate esters, and include a carbodiimide such as dicyclohexylcarbodiimide, in which case the reaction is preferably conducted in a basic organic solvent such as pyridine, or (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PYBOP, Sigma), in which case the reaction is performed in a polar solvent such as dimethylformamide, in the presence of a tertiary organic base such as diisopropylethylamine, or Aldrithiol-2 (Aldrich) in which case the reaction is conducted in a basic solvent such as pyridine, in the presence of a triaryl phosphine such as triphenylphosphine. Alternatively, the conversion of the phosphonate monoester **S32.2** to the diester **S32.1** is effected by the use of the Mitsunobu reaction, as described above. The substrate is reacted with the hydroxy compound R^1OH, in the presence of diethyl azodicarboxylate and a triarylphosphine such as triphenyl phosphine. Alternatively, the phosphonate monoester **S32.2** is transformed into the phosphonate diester **S32.1**, in which the introduced R^1 group is alkenyl or aralkyl, by reaction of the monoester with the halide R^1Br, in which R^1 is as alkenyl or aralkyl. The alkylation reaction is

conducted in a polar organic solvent such as dimethylformamide or acetonitrile, in the presence of a base such as cesium carbonate. Alternatively, the phosphonate monoester is transformed into the phosphonate diester in a two step procedure. In the first step, the phosphonate monoester **S32.2** is transformed into the chloro analog $RP(O)(OR^1)Cl$ by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17, and the thus-obtained product $RP(O)(OR^1)Cl$ is then reacted with the hydroxy compound R^1OH, in the presence of a base such as triethylamine, to afford the phosphonate diester **S32.1**.

A phosphonic acid R-link-$P(O)(OH)_2$ is transformed into a phosphonate monoester $RP(O)(OR^1)(OH)$ (Scheme **32**, Reaction **5**) by means of the methods described above of for the preparation of the phosphonate diester R-link-$P(O)(OR^1)_2$ **S32.1**, except that only one molar proportion of the component R^1OH or R^1Br is employed. Dialkyl phosphonates may be prepared according to the methods of: Quast et al (1974) *Synthesis* 490; Stowell et al (1990) *Tetrahedron Lett.* 3261; US 5663159.

A phosphonic acid R-link-$P(O)(OH)_2$ **S32.3** is transformed into a phosphonate diester R-link-$P(O)(OR^1)_2$ **S32.1** (Scheme **32**, Reaction **6**) by a coupling reaction with the hydroxy compound R^1OH, in the presence of a coupling agent such as Aldrithiol-2 (Aldrich) and triphenylphosphine. The reaction is conducted in a basic solvent such as pyridine. Alternatively, phosphonic acids **S32.3** are transformed into phosphonic esters **S32.1** in which R^1 is aryl, by means of a coupling reaction employing, for example, dicyclohexylcarbodiimide in pyridine at ca 70 °C. Alternatively, phosphonic acids **S32.3** are transformed into phosphonic esters **S32.1** in which R^1 is alkenyl, by means of an alkylation reaction. The phosphonic acid is reacted with the alkenyl bromide R^1Br in a polar organic solvent such as acetonitrile solution at reflux temperature, the presence of a base such as cesium carbonate, to afford the phosphonic ester **S32.1**.

Scheme 32



Preparation of phosphonate carbamates.

Phosphonate esters may contain a carbamate linkage. The preparation of carbamates is described in Comprehensive Organic Functional Group Transformations, A. R. Katritzky, ed., Pergamon, 1995, Vol. 6, p. 416ff, and in Organic Functional Group Preparations, by S. R. Sandler and W. Karo, Academic Press, 1986, p. 260ff. The carbamoyl group may be formed by reaction of a hydroxy group according to the methods known in the art, including the teachings of Ellis, US 2002/0103378 A1 and Hajima, US 6018049.

Scheme **33** illustrates various methods by which the carbamate linkage is synthesized. As shown in Scheme **33**, in the general reaction generating carbamates, an alcohol **S33.1**, is converted into the activated derivative **S33.2** in which Lv is a leaving group such as halo, imidazolyl, benztriazolyl and the like, as described herein. The activated derivative **S33.2** is then reacted with an amine

S33.3, to afford the carbamate product **S33.4**. Examples **1** – **7** in Scheme **33** depict methods by which the general reaction is effected. Examples **8 - 10** illustrate alternative methods for the preparation of carbamates.

Scheme **33**, Example **1** illustrates the preparation of carbamates employing a chloroformyl derivative of the alcohol **S33.5**. In this procedure, the alcohol **S33.5** is reacted with phosgene, in an inert solvent such as toluene, at about 0 °C, as described in Org. Syn. Coll. Vol. 3, 167, 1965, or with an equivalent reagent such as trichloromethoxy chloroformate, as described in Org. Syn. Coll. Vol. 6, 715, 1988, to afford the chloroformate **S33.6**. The latter compound is then reacted with the amine component **S33.3**, in the presence of an organic or inorganic base, to afford the carbamate **S33.7**. For example, the chloroformyl compound **S33.6** is reacted with the amine **S33.3** in a water-miscible solvent such as tetrahydrofuran, in the presence of aqueous sodium hydroxide, as described in Org. Syn. Coll. Vol. 3, 167, 1965, to yield the carbamate **S33.7**. Alternatively, the reaction is performed in dichloromethane in the presence of an organic base such as diisopropylethylamine or dimethylaminopyridine.

Scheme **33**, Example **2** depicts the reaction of the chloroformate compound **S33.6** with imidazole to produce the imidazolide **S33.8**. The imidazolide product is then reacted with the amine **S33.3** to yield the carbamate **S33.7**. The preparation of the imidazolide is performed in an aprotic solvent such as dichloromethane at 0°, and the preparation of the carbamate is conducted in a similar solvent at ambient temperature, optionally in the presence of a base such as dimethylaminopyridine, as described in *J. Med. Chem.*, 1989, 32, 357.

Scheme **33** Example **3**, depicts the reaction of the chloroformate **S33.6** with an activated hydroxyl compound R"OH, to yield the mixed carbonate ester **S33.10**. The reaction is conducted in an inert organic solvent such as ether or dichloromethane, in the presence of a base such as dicyclohexylamine or triethylamine. The hydroxyl component R"OH is selected from the group of compounds **S33.19** - **S33.24** shown in Scheme **33**, and similar compounds. For example, if the component R"OH is hydroxybenztriazole **S33.19**, N-hydroxysuccinimide **S33.20**, or pentachlorophenol, **S33.21**, the mixed carbonate **S33.10** is obtained by the reaction of the chloroformate with the hydroxyl

compound in an ethereal solvent in the presence of dicyclohexylamine, as described in *Can. J. Chem.*, 1982, 60, 976. A similar reaction in which the component R"OH is pentafluorophenol **S33.22** or 2-hydroxypyridine **S33.23** is performed in an ethereal solvent in the presence of triethylamine, as described in *Syn.*, 1986, 303, and *Chem. Ber.* 118, 468, 1985.

Scheme **33** Example **4** illustrates the preparation of carbamates in which an alkyloxycarbonylimidazole **S33.8** is employed. In this procedure, an alcohol **S33.5** is reacted with an equimolar amount of carbonyl diimidazole **S33.11** to prepare the intermediate **S33.8**. The reaction is conducted in an aprotic organic solvent such as dichloromethane or tetrahydrofuran. The acyloxyimidazole **S33.8** is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **S33.7**. The reaction is performed in an aprotic organic solvent such as dichloromethane, as described in *Tet. Lett.*, 42, 2001, 5227, to afford the carbamate **S33.7**.

Scheme **33**, Example **5** illustrates the preparation of carbamates by means of an intermediate alkoxycarbonylbenztriazole **S33.13**. In this procedure, an alcohol ROH is reacted at ambient temperature with an equimolar amount of benztriazole carbonyl chloride **S33.12**, to afford the alkoxycarbonyl product **S33.13**. The reaction is performed in an organic solvent such as benzene or toluene, in the presence of a tertiary organic amine such as triethylamine, as described in *Synthesis.*, 1977, 704. The product is then reacted with the amine $R'NH_2$ to afford the carbamate **S33.7**. The reaction is conducted in toluene or ethanol, at from ambient temperature to about 80 °C as described in *Synthesis.*, 1977, 704.

Scheme **33**, Example **6** illustrates the preparation of carbamates in which a carbonate $(R"O)_2CO$, **S33.14**, is reacted with an alcohol **S33.5** to afford the intermediate alkyloxycarbonyl intermediate **S33.15**. The latter reagent is then reacted with the amine $R'NH_2$ to afford the carbamate **S33.7**. The procedure in which the reagent **S33.15** is derived from hydroxybenztriazole **S33.19** is described in *Synthesis*, 1993, 908; the procedure in which the reagent **S33.15** is derived from N-hydroxysuccinimide **S33.20 is** described in *Tet. Lett.*, 1992, 2781; the procedure in which the reagent **S33.15** is derived from 2-hydroxypyridine **S33.23** is described in *Tet. Lett.*, 1991, 4251; the procedure in

which the reagent **S33.15** is derived from 4-nitrophenol **S33.24** is described in *Synthesis*. 1993, 103. The reaction between equimolar amounts of the alcohol ROH and the carbonate **S33.14** is conducted in an inert organic solvent at ambient temperature.

Scheme 33, Example 7 illustrates the preparation of carbamates from alkoxycarbonyl azides **S33.16**. In this procedure, an alkyl chloroformate **S33.6** is reacted with an azide, for example sodium azide, to afford the alkoxycarbonyl azide **S33.16**. The latter compound is then reacted with an equimolar amount of the amine $R'NH_2$ to afford the carbamate **S33.7**. The reaction is conducted at ambient temperature in a polar aprotic solvent such as dimethylsulfoxide, for example as described in *Synthesis*., 1982, 404.

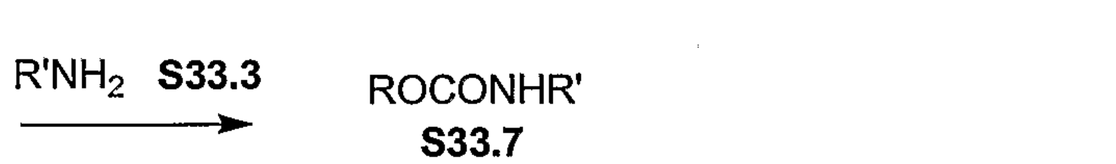
Scheme **33**, Example **8** illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and the chloroformyl derivative of an amine **S33.17**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 647, the reactants are combined at ambient temperature in an aprotic solvent such as acetonitrile, in the presence of a base such as triethylamine, to afford the carbamate **S33.7**.

Scheme **33**, Example **9** illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and an isocyanate **S33.18**. In this procedure, which is described in Synthetic Organic Chemistry, R. B. Wagner, H. D. Zook, Wiley, 1953, p. 645, the reactants are combined at ambient temperature in an aprotic solvent such as ether or dichloromethane and the like, to afford the carbamate **S33.7**.

Scheme **33**, Example **10** illustrates the preparation of carbamates by means of the reaction between an alcohol ROH and an amine $R'NH_2$. In this procedure, which is described in *Chem. Lett.* 1972, 373, the reactants are combined at ambient temperature in an aprotic organic solvent such as tetrahydrofuran, in the presence of a tertiary base such as triethylamine, and selenium. Carbon monoxide is passed through the solution and the reaction proceeds to afford the carbamate **S33.7**.

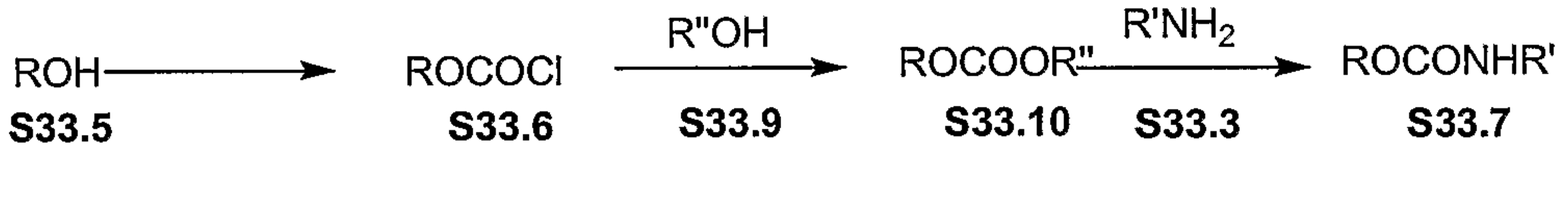
Scheme 33. Preparation of carbamates.

General reaction

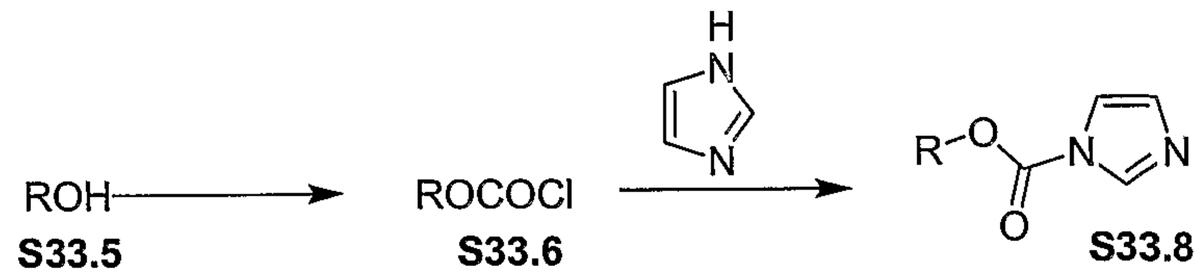


Examples

(1)

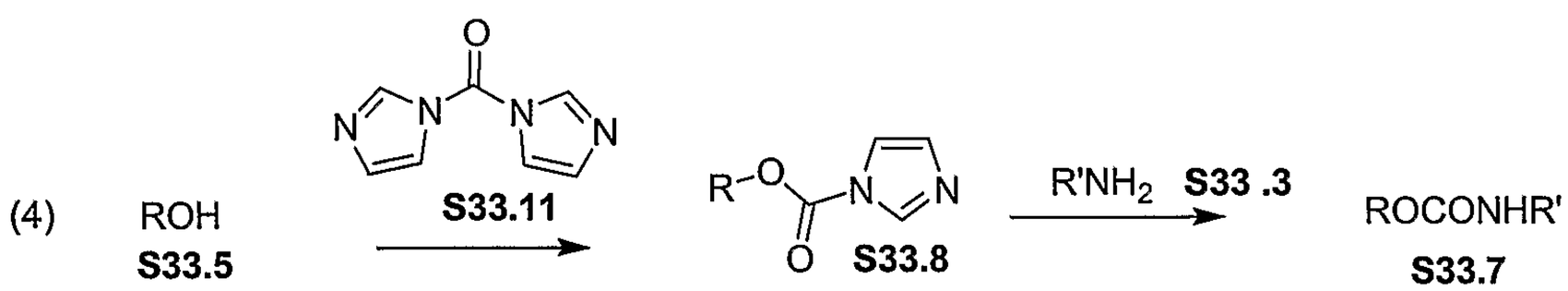


(2)

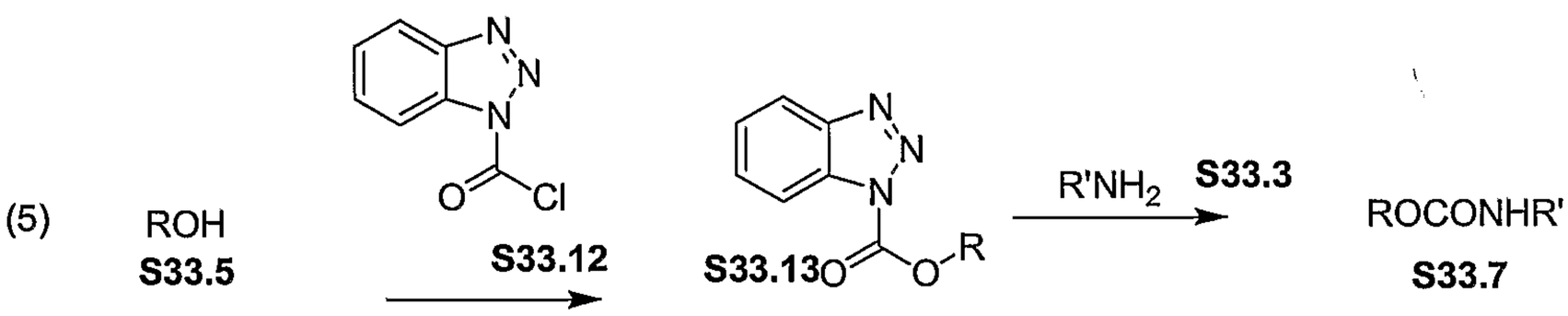


(3)

(4)



(5)



(6) ROH (S33.5) → [$(R''O_2)C=O$, S33.14] → ROCOR'' (S33.15) → [$R'NH_2$, S33.3] → ROCONHR' (S33.7)

(7) ROH (S33.5) → ROCOCl (S33.6) → $ROCON_3$ (S33.16)

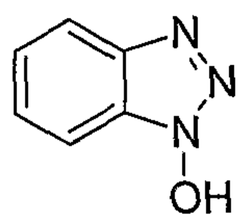
$R'NH_2$ 33.3 → ROCONHR' 33.7

(8) ROH (S33.5) → [R'NHCOCl, S33.17] → ROCONHR' (S33.7)

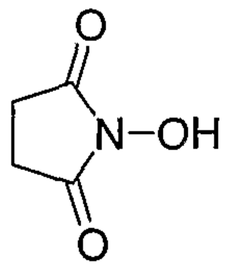
(9) ROH (S33.5) → [R'NCO, S33.18] → ROCONHR' (S33.7)

(10) ROH (S33.5) → [$R'NH_2$, S33.3] → ROCONHR' (S33.7)

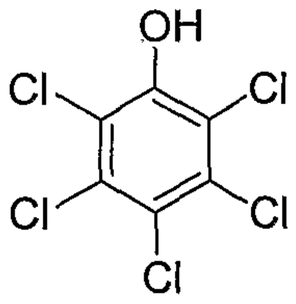
R''OH =



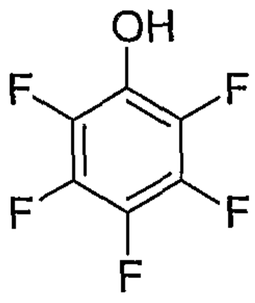
S33.19



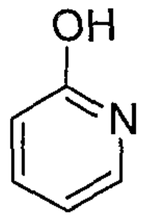
S33.20



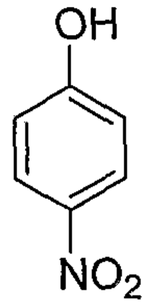
S33.21



S33.22



S33.23



S33.24

PREPARATION OF CARBOALKOXY-SUBSTITUTED PHOSPHONATE BISAMIDATES, MONOAMIDATES, DIESTERS AND MONOESTERS.

A number of methods are available for the conversion of phosphonic acids into amidates and esters. In one group of methods, the phosphonic acid is either converted into an isolated activated intermediate such as a phosphoryl

chloride, or the phosphonic acid is activated in situ for reaction with an amine or a hydroxy compound.

The conversion of phosphonic acids into phosphoryl chlorides is accomplished by reaction with thionyl chloride, for example as described in *J. Gen. Chem. USSR*, 1983, 53, 480, *Zh. Obschei Khim.*, 1958, 28, 1063, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with oxalyl chloride, as described in *J. Am. Chem. Soc.*, 1994, 116, 3251, or *J. Org. Chem.*, 1994, 59, 6144, or by reaction with phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or in *J. Med. Chem.*, 1995, 38, 1372. The resultant phosphoryl chlorides are then reacted with amines or hydroxy compounds in the presence of a base to afford the amidate or ester products.

Phosphonic acids are converted into activated imidazolyl derivatives by reaction with carbonyl diimidazole, as described in *J. Chem. Soc., Chem. Comm.* (1991) 312, or *Nucleosides & Nucleotides* (2000) 19:1885. Activated sulfonyloxy derivatives are obtained by the reaction of phosphonic acids with trichloromethylsulfonyl chloride or with triisopropylbenzenesulfonyl chloride, as described in *Tet. Lett.* (1996) 7857, or *Bioorg. Med. Chem. Lett.* (1998) 8:663. The activated sulfonyloxy derivatives are then reacted with amines or hydroxy compounds to afford amidates or esters.

Alternatively, the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a diimide coupling agent. The preparation of phosphonic amidates and esters by means of coupling reactions in the presence of dicyclohexyl carbodiimide is described, for example, in *J. Chem. Soc., Chem. Comm.* (1991) 312 or *Coll. Czech. Chem. Comm.* (1987) 52:2792. The use of ethyl dimethylaminopropyl carbodiimide for activation and coupling of phosphonic acids is described in *Tet. Lett.*, (2001) 42:8841, or *Nucleosides & Nucleotides* (2000) 19:1885.

A number of additional coupling reagents have been described for the preparation of amidates and esters from phosphonic acids. The agents include Aldrithiol-2, and PYBOP and BOP, as described in *J. Org. Chem.*, 1995, 60, 5214, and *J. Med. Chem.* (1997) 40:3842, mesitylene-2-sulfonyl-3-nitro-1,2,4-triazole (MSNT), as described in *J. Med. Chem.* (1996) 39:4958, diphenylphosphoryl azide, as described in *J. Org. Chem.* (1984) 49:1158, 1-

(2,4,6-triisopropylbenzenesulfonyl-3-nitro-1,2,4-triazole (TPSNT) as described in *Bioorg. Med. Chem. Lett.* (1998) 8:1013, bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), as described in *Tet. Lett.*, (1996) 37:3997, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphinane, as described in *Nucleosides Nucleotides* 1995, 14, 871, and diphenyl chlorophosphate, as described in *J. Med. Chem.*, 1988, 31, 1305.

Phosphonic acids are converted into amidates and esters by means of the Mitsunobu reaction, in which the phosphonic acid and the amine or hydroxy reactant are combined in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The procedure is described in *Org. Lett.,* 2001, 3, 643, or *J. Med. Chem.*, 1997, 40, 3842.

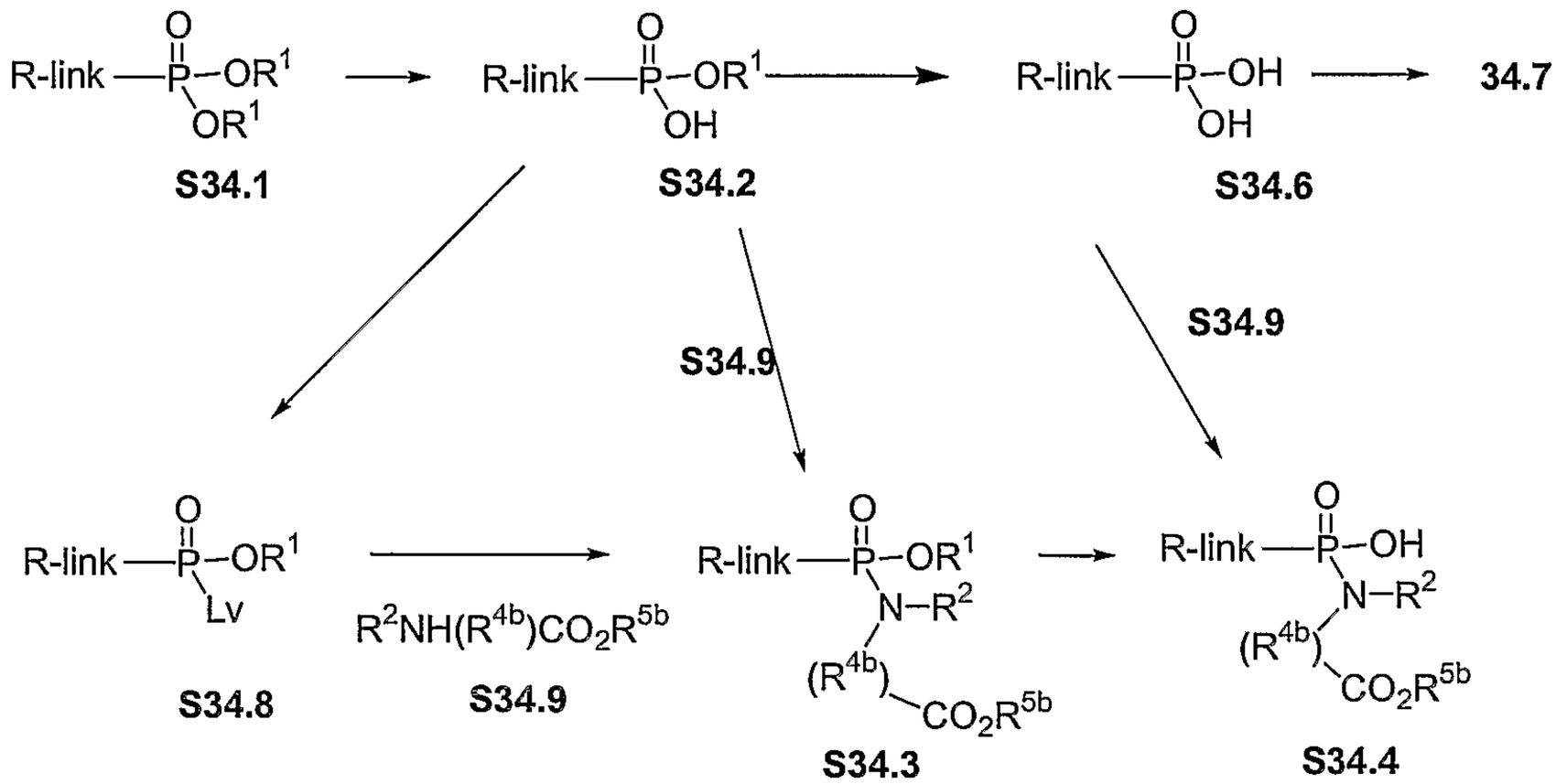
Phosphonic esters are also obtained by the reaction between phosphonic acids and halo compounds, in the presence of a suitable base. The method is described, for example, in *Anal. Chem.*, 1987, 59, 1056, or *J. Chem. Soc. Perkin Trans., I,* 1993, 19, 2303, or *J. Med. Chem.,* 1995, 38, 1372, or *Tet. Lett.*, 2002, 43, 1161.

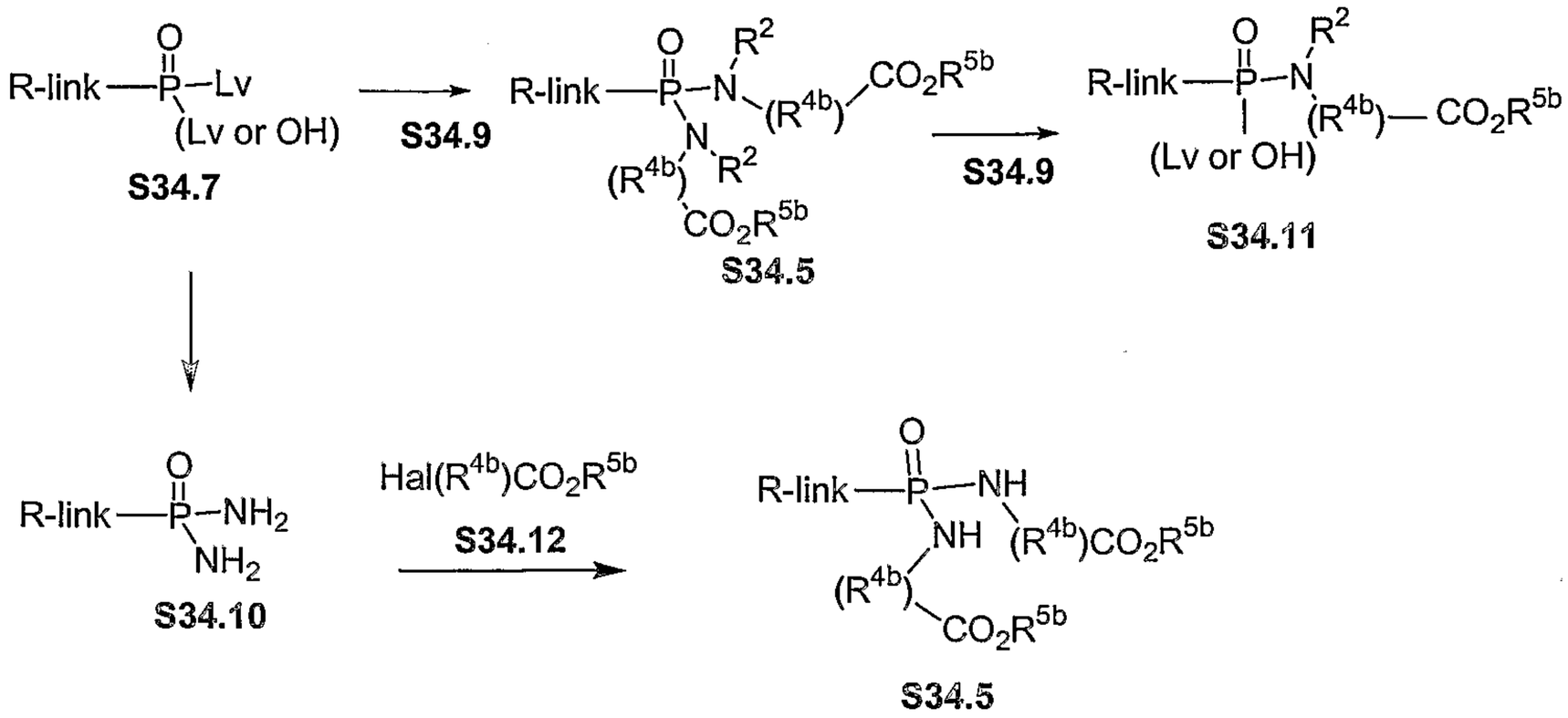
Schemes **34-37** illustrate the conversion of phosphonate esters and phosphonic acids into carboalkoxy-substituted phosphonbisamidates (Scheme **34**), phosphonamidates (Scheme **35**), phosphonate monoesters (Scheme **36**) and phosphonate diesters, (Scheme **37**). Scheme 38 illustrates synthesis of gem-dialkyl amino phosphonate reagents.

Scheme **34** illustrates various methods for the conversion of phosphonate diesters **S34.1** into phosphonbisamidates **S34.5**. The diester **S34.1**, prepared as described previously, is hydrolyzed, either to the monoester **S34.2** or to the phosphonic acid **S34.6**. The methods employed for these transformations are described above. The monoester **S34.2** is converted into the monoamidate **S34.3** by reaction with an aminoester **S34.9**, in which the group R^2 is H or alkyl; the group R^{4b} is a divalent alkylene moiety such as, for example, $CHCH_3$, $CHCH_2CH_3$, $CH(CH(CH_3)_2)$, $CH(CH_2Ph)$, and the like, or a side chain group present in natural or modified aminoacids; and the group R^{5b} is C_1–C_{12} alkyl, such as methyl, ethyl, propyl, isopropyl, or isobutyl; C_6–C_{20} aryl, such as phenyl or substituted phenyl; or C_6–C_{20} arylalkyl, such as benzyl or benzyhydryl. The reactants are combined in the presence of a coupling agent such as a

carbodiimide, for example dicyclohexyl carbodiimide, as described in *J. Am. Chem. Soc.*, (1957) 79:3575, optionally in the presence of an activating agent such as hydroxybenztriazole, to yield the amidate product **S34.3**. The amidate-forming reaction is also effected in the presence of coupling agents such as BOP, as described in *J. Org. Chem.* (1995) 60:5214, Aldrithiol, PYBOP and similar coupling agents used for the preparation of amides and esters. Alternatively, the reactants **S34.2** and **S34.9** are transformed into the monoamidate **S34.3** by means of a Mitsunobu reaction. The preparation of amidates by means of the Mitsunobu reaction is described in *J. Med. Chem.* (1995) 38:2742. Equimolar amounts of the reactants are combined in an inert solvent such as tetrahydrofuran in the presence of a triaryl phosphine and a dialkyl azodicarboxylate. The thus-obtained monoamidate ester **S34.3** is then transformed into amidate phosphonic acid **S34.4**. The conditions used for the hydrolysis reaction depend on the nature of the R^1 group, as described previously. The phosphonic acid amidate **S34.4** is then reacted with an aminoester **S34.9**, as described above, to yield the bisamidate product **S34.5**, in which the amino substituents are the same or different. Alternatively, the phosphonic acid **S34.6** may be treated with two different amino ester reagents simulataneously, i.e. **S34.9** where R^2, R^{4b} or R^{5b} are different. The resulting mixture of bisamidate products **S34.5** may then be separable, e.g. by chromatography.

Scheme 34





An example of this procedure is shown in Scheme **34**, Example **1**. In this procedure, a dibenzyl phosphonate **S34.14** is reacted with diazabicyclooctane (DABCO) in toluene at reflux, as described in *J. Org. Chem.*, 1995, 60, 2946, to afford the monobenzyl phosphonate **S34.15**. The product is then reacted with equimolar amounts of ethyl alaninate **S34.16** and dicyclohexyl carbodiimide in pyridine, to yield the amidate product **S34.17**. The benzyl group is then removed, for example by hydrogenolysis over a palladium catalyst, to give the monoacid product **S34.18** which may be unstable according to J. Med. Chem. (1997) 40(23):3842. This compound **S34.18** is then reacted in a Mitsunobu reaction with ethyl leucinate **S34.19**, triphenyl phosphine and diethylazodicarboxylate, as described in *J. Med. Chem.*, 1995, 38, 2742, to produce the bisamidate product **S34.20**.

Using the above procedures, but employing in place of ethyl leucinate **S34.19** or ethyl alaninate **S34.16**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

Alternatively, the phosphonic acid **S34.6** is converted into the bisamidate **S34.5** by use of the coupling reactions described above. The reaction is performed in one step, in which case the nitrogen-related substituents present in the product **S34.5** are the same, or in two steps, in which case the nitrogen-related substituents can be different.

An example of the method is shown in Scheme 34, Example 2. In this procedure, a phosphonic acid **S34.6** is reacted in pyridine solution with excess ethyl phenylalaninate **S34.21** and dicyclohexylcarbodiimide, for example as

described in *J. Chem. Soc., Chem. Comm.*, 1991, 1063, to give the bisamidate product **S34.22**.

Using the above procedures, but employing, in place of ethyl phenylalaninate, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

As a further alternative, the phosphonic acid **S34.6** is converted into the mono or bis-activated derivative **S34.7**, in which Lv is a leaving group such as chloro, imidazolyl, triisopropylbenzenesulfonyloxy etc. The conversion of phosphonic acids into chlorides **S34.7** (Lv = Cl) is effected by reaction with thionyl chloride or oxalyl chloride and the like, as described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976, p. 17. The conversion of phosphonic acids into monoimidazolides **S34.7** (Lv = imidazolyl) is described in *J. Med. Chem.*, 2002, 45, 1284 and in *J. Chem. Soc. Chem. Comm.*, 1991, 312. Alternatively, the phosphonic acid is activated by reaction with triisopropylbenzenesulfonyl chloride, as described in *Nucleosides and Nucleotides*, 2000, 10, 1885. The activated product is then reacted with the aminoester **S34.9**, in the presence of a base, to give the bisamidate **S34.5**. The reaction is performed in one step, in which case the nitrogen substituents present in the product **S34.5** are the same, or in two steps, via the intermediate **S34.11**, in which case the nitrogen substituents can be different.

Examples of these methods are shown in Scheme 34, Examples 3 and 5. In the procedure illustrated in Scheme 34, Example 3, a phosphonic acid **S34.6** is reacted with ten molar equivalents of thionyl chloride, as described in *Zh. Obschei Khim.*, 1958, 28, 1063, to give the dichloro compound **S34.23**. The product is then reacted at reflux temperature in a polar aprotic solvent such as acetonitrile, and in the presence of a base such as triethylamine, with butyl serinate **S34.24** to afford the bisamidate product **S34.25**.

Using the above procedures, but employing, in place of butyl serinate **S34.24**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

In the procedure illustrated in Scheme 34, Example 5, the phosphonic acid **S34.6** is reacted, as described in *J. Chem. Soc. Chem. Comm.*, 1991, 312, with carbonyl diimidazole to give the imidazolide **S34.S32.** The product is then

reacted in acetonitrile solution at ambient temperature, with one molar equivalent of ethyl alaninate **S34.33** to yield the monodisplacement product **S34.S34.** The latter compound is then reacted with carbonyl diimidazole to produce the activated intermediate **S34.35**, and the product is then reacted, under the same conditions, with ethyl N-methylalaninate **S34.33a** to give the bisamidate product **S34.36**.

Using the above procedures, but employing, in place of ethyl alaninate **S34.33** or ethyl N-methylalaninate **S34.33a**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

The intermediate monoamidate **S34.3** is also prepared from the monoester **S34.2** by first converting the monoester into the activated derivative **S34.8** in which Lv is a leaving group such as halo, imidazolyl etc, using the procedures described above. The product **S34.8** is then reacted with an aminoester **S34.9** in the presence of a base such as pyridine, to give an intermediate monoamidate product **S34.3**. The latter compound is then converted, by removal of the R^1 group and coupling of the product with the aminoester **S34.9**, as described above, into the bisamidate **S34.5**.

An example of this procedure, in which the phosphonic acid is activated by conversion to the chloro derivative **S34.26**, is shown in Scheme 34, Example 4. In this procedure, the phosphonic monobenzyl ester **S34.15** is reacted, in dichloromethane, with thionyl chloride, as described in *Tet. Letters*., 1994, 35, 4097, to afford the phosphoryl chloride **S34.26**. The product is then reacted in acetonitrile solution at ambient temperature with one molar equivalent of ethyl 3-amino-2-methylpropionate **S34.27** to yield the monoamidate product **S34.28**. The latter compound is hydrogenated in ethylacetate over a 5% palladium on carbon catalyst to produce the monoacid product **S34.29**. The product is subjected to a Mitsunobu coupling procedure, with equimolar amounts of butyl alaninate **S34.30**, triphenyl phosphine, diethylazodicarboxylate and triethylamine in tetrahydrofuran, to give the bisamidate product **S34.31**.

Using the above procedures, but employing, in place of ethyl 3-amino-2-methylpropionate **S34.27** or butyl alaninate **S34.30**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained.

The activated phosphonic acid derivative **S34.7** is also converted into the bisamidate **S34.5** via the diamino compound **S34.10**. The conversion of activated phosphonic acid derivatives such as phosphoryl chlorides into the corresponding amino analogs **S34.10**, by reaction with ammonia, is described in Organic Phosphorus Compounds, G. M. Kosolapoff, L. Maeir, eds, Wiley, 1976. The bisamino compound **S34.10** is then reacted at elevated temperature with a haloester **S34.12** (Hal = halogen, i.e. F, Cl, Br, I), in a polar organic solvent such as dimethylformamide, in the presence of a base such as 4, 4-dimethylaminopyridine (DMAP) or potassium carbonate, to yield the bisamidate **S34.5**. Alternatively, **S34.6** may be treated with two different amino ester reagents simulataneously, i.e. **S34.12** where R^{4b} or R^{5b} are different. The resulting mixture of bisamidate products **S34.5** may then be separable, e.g. by chromatography.

An example of this procedure is shown in Scheme 34, Example 6. In this method, a dichlorophosphonate **S34.23** is reacted with ammonia to afford the diamide **S34.37**. The reaction is performed in aqueous, aqueous alcoholic or alcoholic solution, at reflux temperature. The resulting diamino compound is then reacted with two molar equivalents of ethyl 2-bromo-3-methylbutyrate **S34.38**, in a polar organic solvent such as N-methylpyrrolidinone at ca. 150 °C, in the presence of a base such as potassium carbonate, and optionally in the presence of a catalytic amount of potassium iodide, to afford the bisamidate product **S34.39**.

Using the above procedures, but employing, in place of ethyl 2-bromo-3-methylbutyrate **S34.38**, different haloesters **S34.12** the corresponding products **S34.5** are obtained.

The procedures shown in Scheme 34 are also applicable to the preparation of bisamidates in which the aminoester moiety incorporates different functional groups. Scheme 34, Example **7** illustrates the preparation of bisamidates derived from tyrosine. In this procedure, the monoimidazolide **S34.32** is reacted with propyl tyrosinate **S34.40**, as described in Example **5**, to yield the monoamidate **S34.41**. The product is reacted with carbonyl diimidazole to give the imidazolide **S34.42**, and this material is reacted with a further molar equivalent of propyl tyrosinate to produce the bisamidate product **S34.43**.

Using the above procedures, but employing, in place of propyl tyrosinate **S34.40**, different aminoesters **S34.9**, the corresponding products **S34.5** are obtained. The aminoesters employed in the two stages of the above procedure can be the same or different, so that bisamidates with the same or different amino substituents are prepared.

Scheme 35 illustrates methods for the preparation of phosphonate monoamidates.

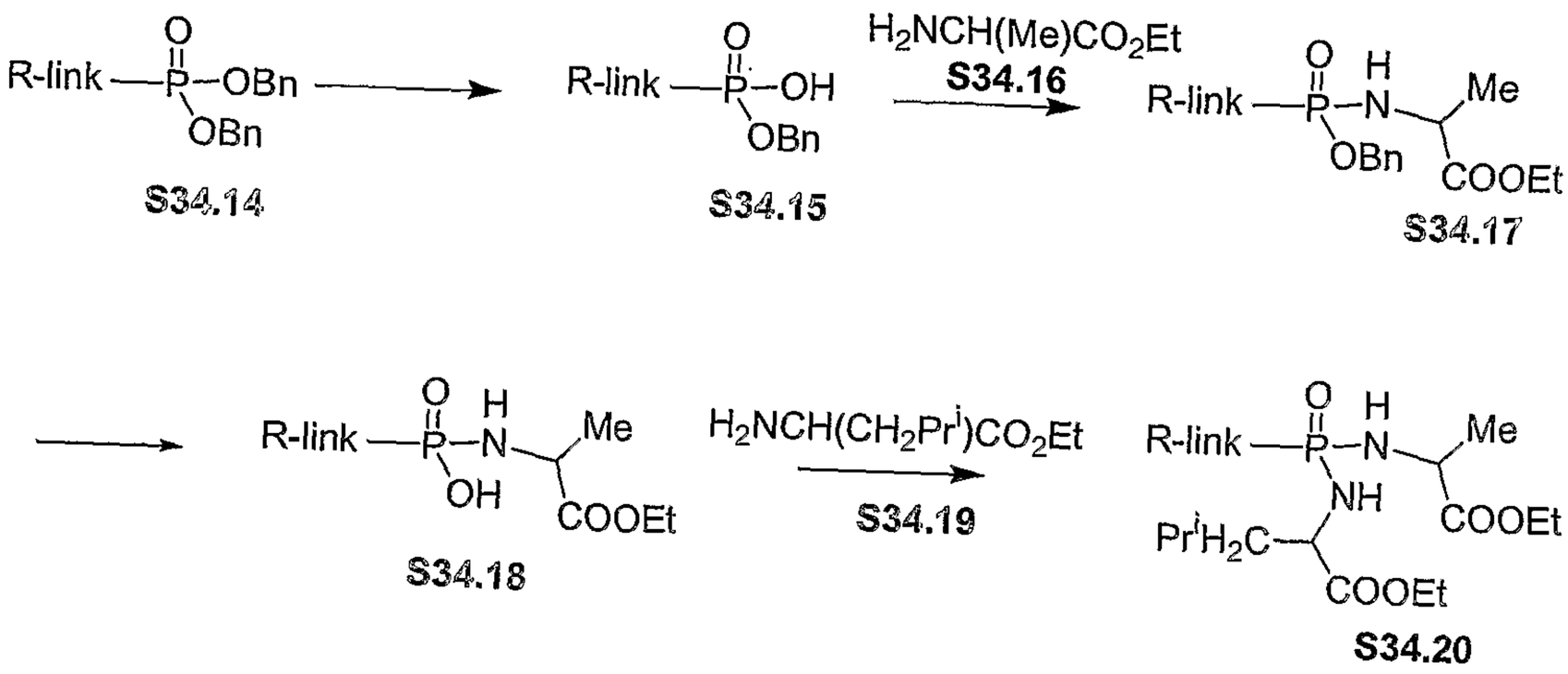
In one procedure, a phosphonate monoester **S34.1** is converted, as described in Scheme 34, into the activated derivative **S34.8**. This compound is then reacted, as described above, with an aminoester **S34.9**, in the presence of a base, to afford the monoamidate product **S35.1**.

The procedure is illustrated in Scheme 35, Example 1. In this method, a monophenyl phosphonate **S35.7** is reacted with, for example, thionyl chloride, as described in *J. Gen. Chem.* USSR., 1983, 32, 367, to give the chloro product **S35.8**. The product is then reacted, as described in Scheme 34, with ethyl alaninate, **S3**, to yield the amidate **S35.10**.

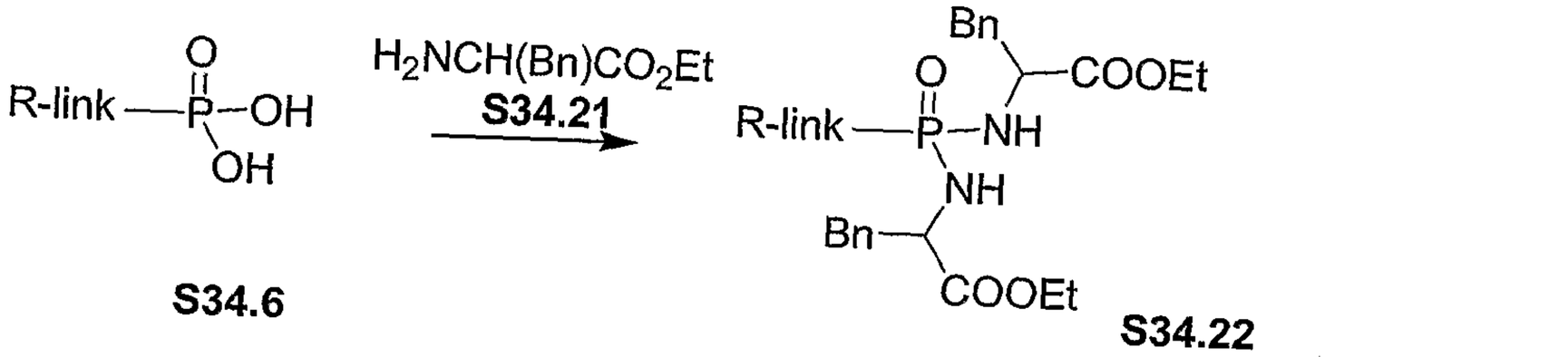
Using the above procedures, but employing, in place of ethyl alaninate **S35.9**, different aminoesters **S34.9**, the corresponding products **S35.1** are obtained.

Alternatively, the phosphonate monoester **S34.1** is coupled, as described in Scheme 34, with an aminoester **S34.9** to produce the amidate, **S335.1**. If necessary, the R^1 substituent is then altered, by initial cleavage to afford the phosphonic acid **S35.2**. The procedures for this transformation depend on the nature of the R^1 group, and are described above. The phosphonic acid is then transformed into the ester amidate product **S35.3**, by reaction with the hydroxy compound R^3OH, in which the group R^3 is aryl, heterocycle, alkyl, cycloalkyl, haloalkyl etc, using the same coupling procedures (carbodiimide, Aldrithiol-2, PYBOP, Mitsunobu reaction etc) described in Scheme 34 for the coupling of amines and phosphonic acids.

Scheme 34 Example 1

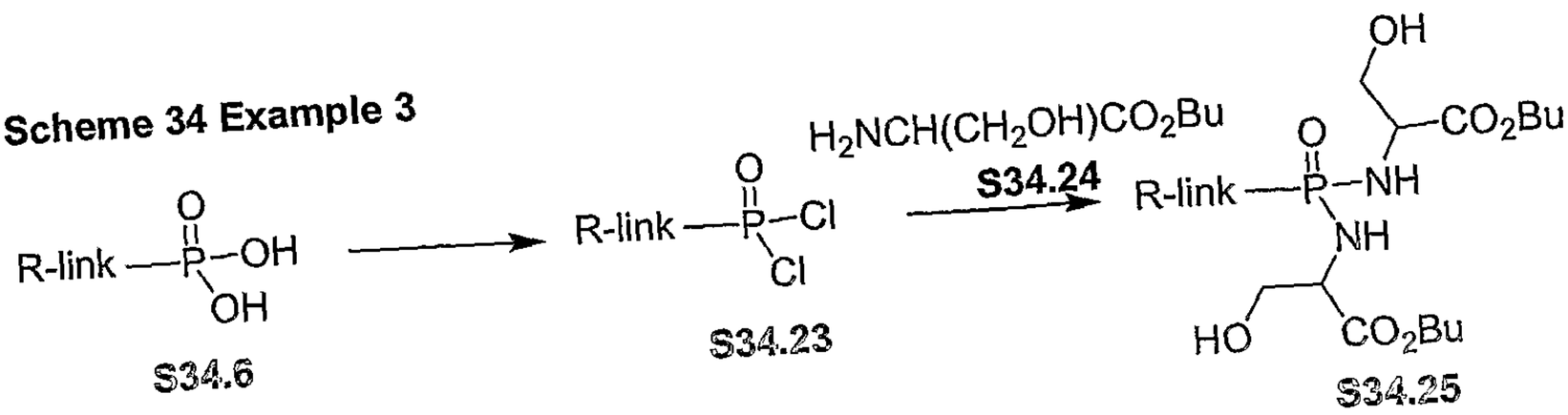


Scheme 34 Example 2

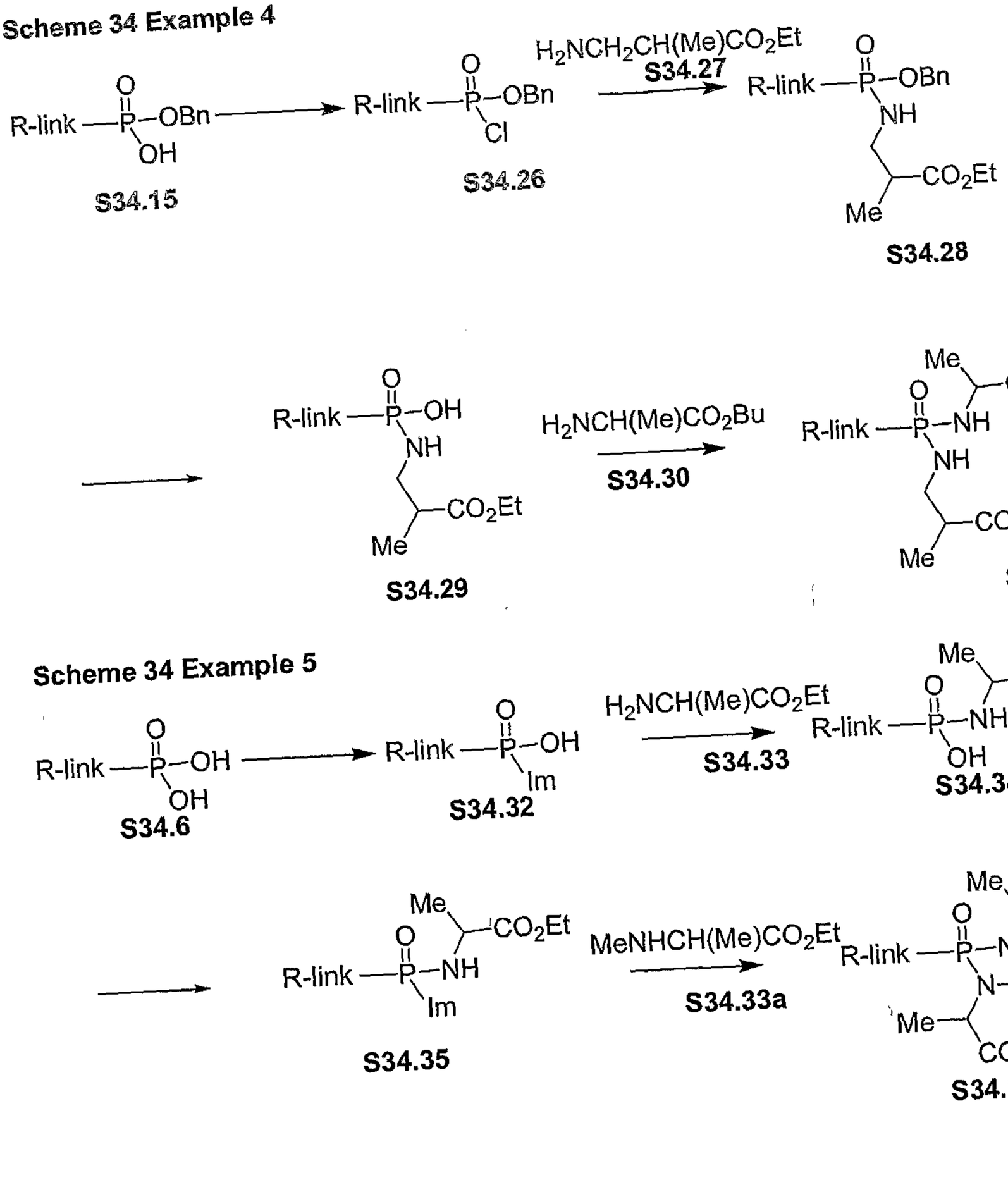


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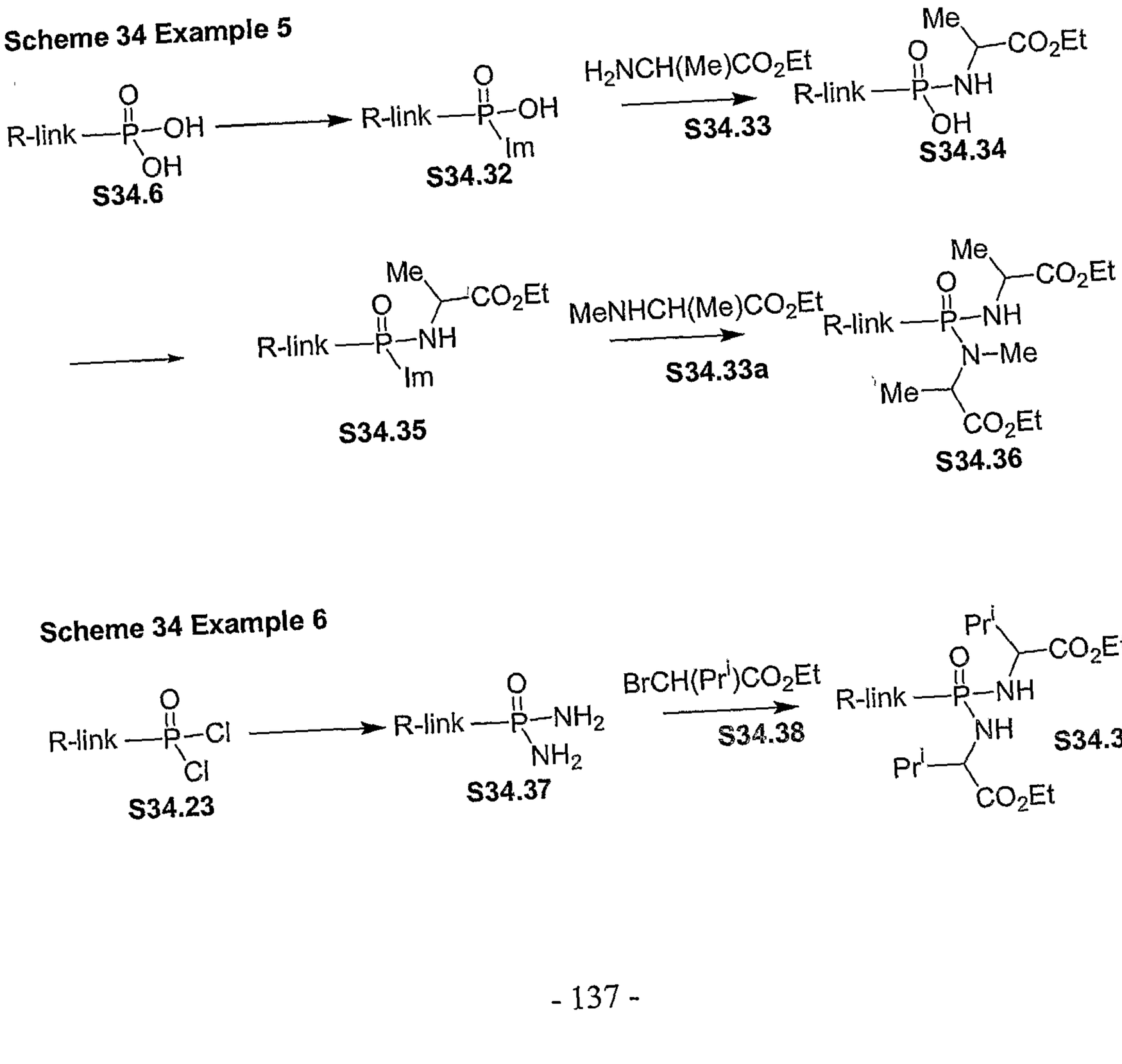
Scheme 34 Example 3



Scheme 34 Example 4

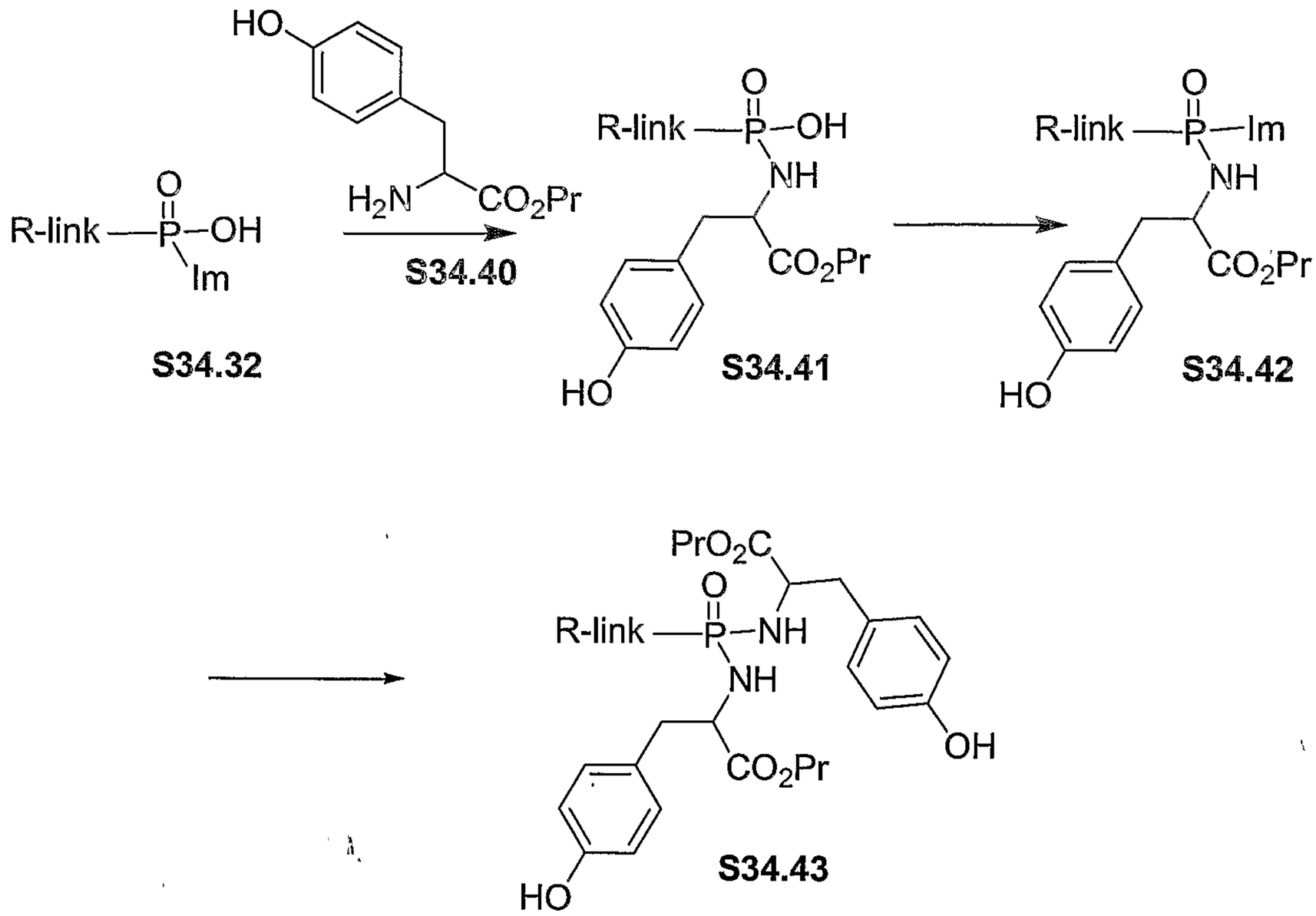


Scheme 34 Example 5



Scheme 34 Example 6

Scheme 34 Example 7



Examples of this method are shown in Scheme 35, Examples and 2 and 3. In the sequence shown in Example 2, a monobenzyl phosphonate **S35.11** is transformed by reaction with ethyl alaninate, using one of the methods described above, into the monoamidate **S35.12**. The benzyl group is then removed by catalytic hydrogenation in ethylacetate solution over a 5% palladium on carbon catalyst, to afford the phosphonic acid amidate **S35.13**. The product is then reacted in dichloromethane solution at ambient temperature with equimolar amounts of 1-(dimethylaminopropyl)-3-ethylcarbodiimide and trifluoroethanol **S35.14**, for example as described in *Tet. Lett.*, 2001, 42, 8841, to yield the amidate ester **S35.15**.

In the sequence shown in Scheme 35, Example 3, the monoamidate **S35.13** is coupled, in tetrahydrofuran solution at ambient temperature, with equimolar amounts of dicyclohexyl carbodiimide and 4-hydroxy-N-methylpiperidine **S35.16**, to produce the amidate ester product **S35.17**.

Using the above procedures, but employing, in place of the ethyl alaninate product **S35.12** different monoacids **S35.2**, and in place of

trifluoroethanol **S35.14** or 4-hydroxy-N-methylpiperidine **S35.16**, different hydroxy compounds R^3OH, the corresponding products **S35.3** are obtained.

Alternatively, the activated phosphonate ester **S34.8** is reacted with ammonia to yield the amidate **S35.4**. The product is then reacted, as described in Scheme 34, with a haloester **S35.5**, in the presence of a base, to produce the amidate product **S35.6**. If appropriate, the nature of the R^1 group is changed, using the procedures described above, to give the product **S35.3**. The method is illustrated in Scheme 35, Example **4**. In this sequence, the monophenyl phosphoryl chloride **S35.18** is reacted, as described in Scheme **34**, with ammonia, to yield the amino product **S35.19**. This material is then reacted in N-methylpyrrolidinone solution at 170° with butyl 2-bromo-3-phenylpropionate **S35.20** and potassium carbonate, to afford the amidate product **S35.21**.

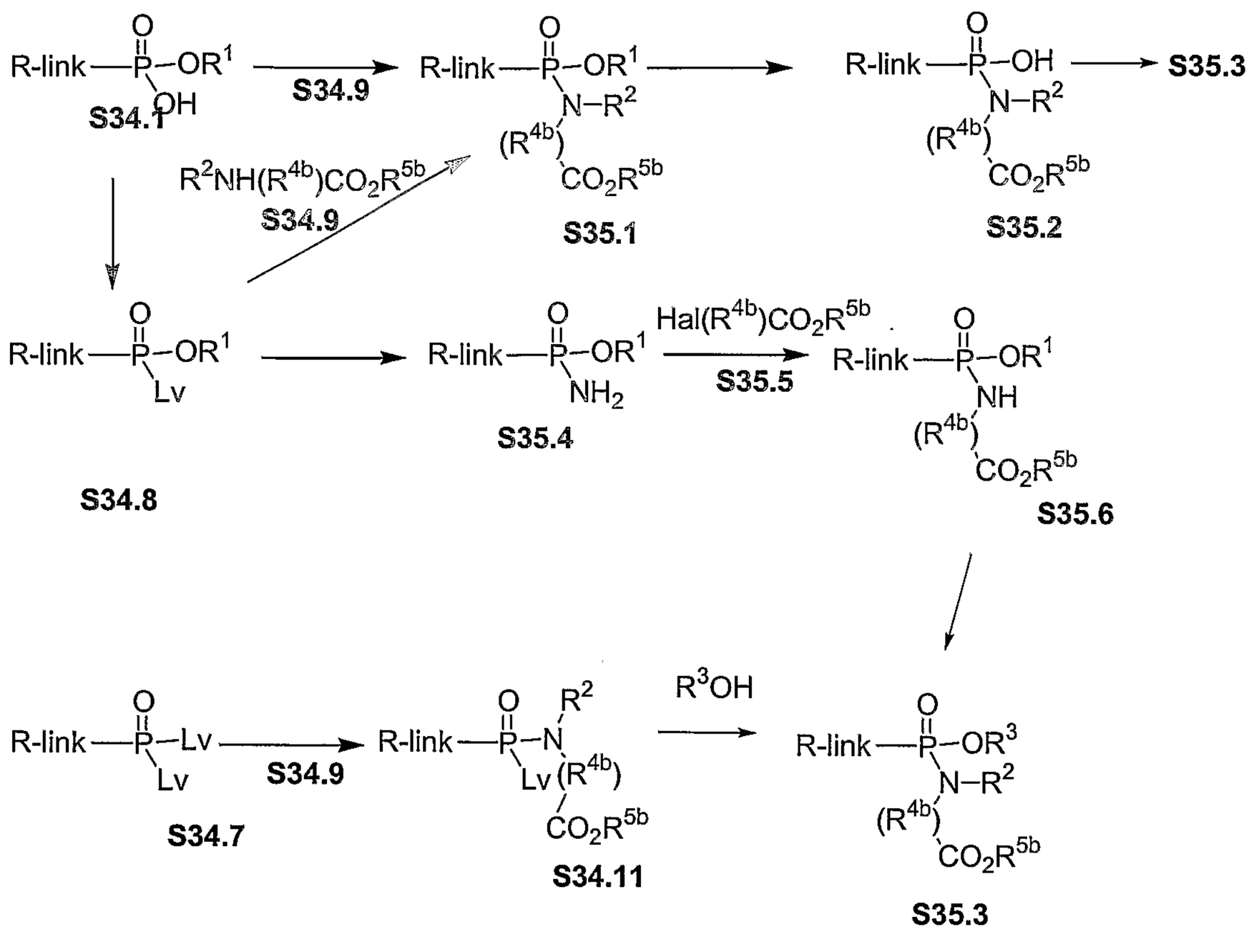
Using these procedures, but employing, in place of butyl 2-bromo-3-phenylpropionate **S35.20**, different haloesters **S35.5**, the corresponding products **S35.6** are obtained.

The monoamidate products **S35.3** are also prepared from the doubly activated phosphonate derivatives **S34.7**. In this procedure, examples of which are described in *Synlett*., 1998, 1, 73, the intermediate **S34.7** is reacted with a limited amount of the aminoester **S34.9** to give the mono-displacement product **S34.11**. The latter compound is then reacted with the hydroxy compound R^3OH in a polar organic solvent such as dimethylformamide, in the presence of a base such as diisopropylethylamine, to yield the monoamidate ester **S35.3**.

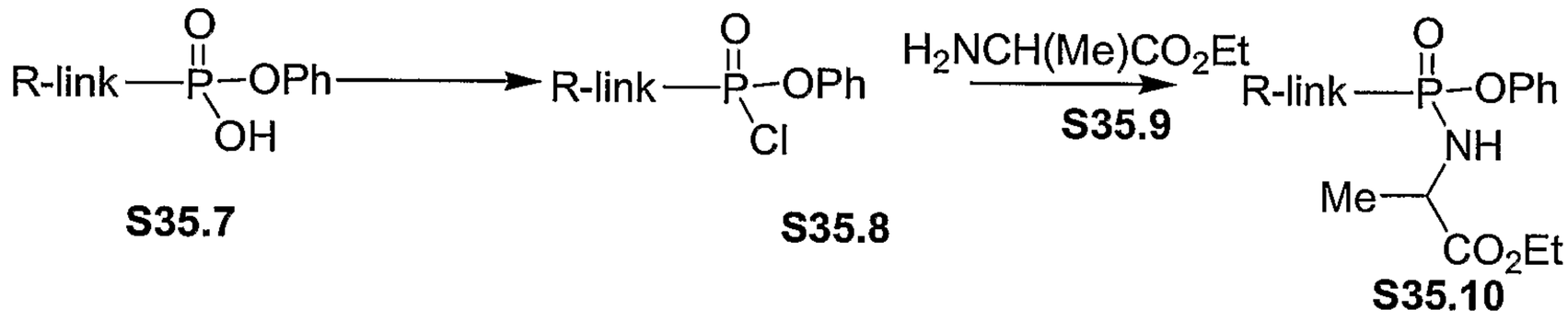
The method is illustrated in Scheme 35, Example 5. In this method, the phosphoryl dichloride **S35.22** is reacted in dichloromethane solution with one molar equivalent of ethyl N-methyl tyrosinate **S35.23** and dimethylaminopyridine, to generate the monoamidate **S35.24**. The product is then reacted with phenol **S35.25** in dimethylformamide containing potassium carbonate, to yield the ester amidate product **S35.26**.

Using these procedures, but employing, in place of ethyl N-methyl tyrosinate **S35.23** or phenol **S35.25**, the aminoesters **34.9** and/or the hydroxy compounds R^3OH, the corresponding products **S35.3** are obtained.

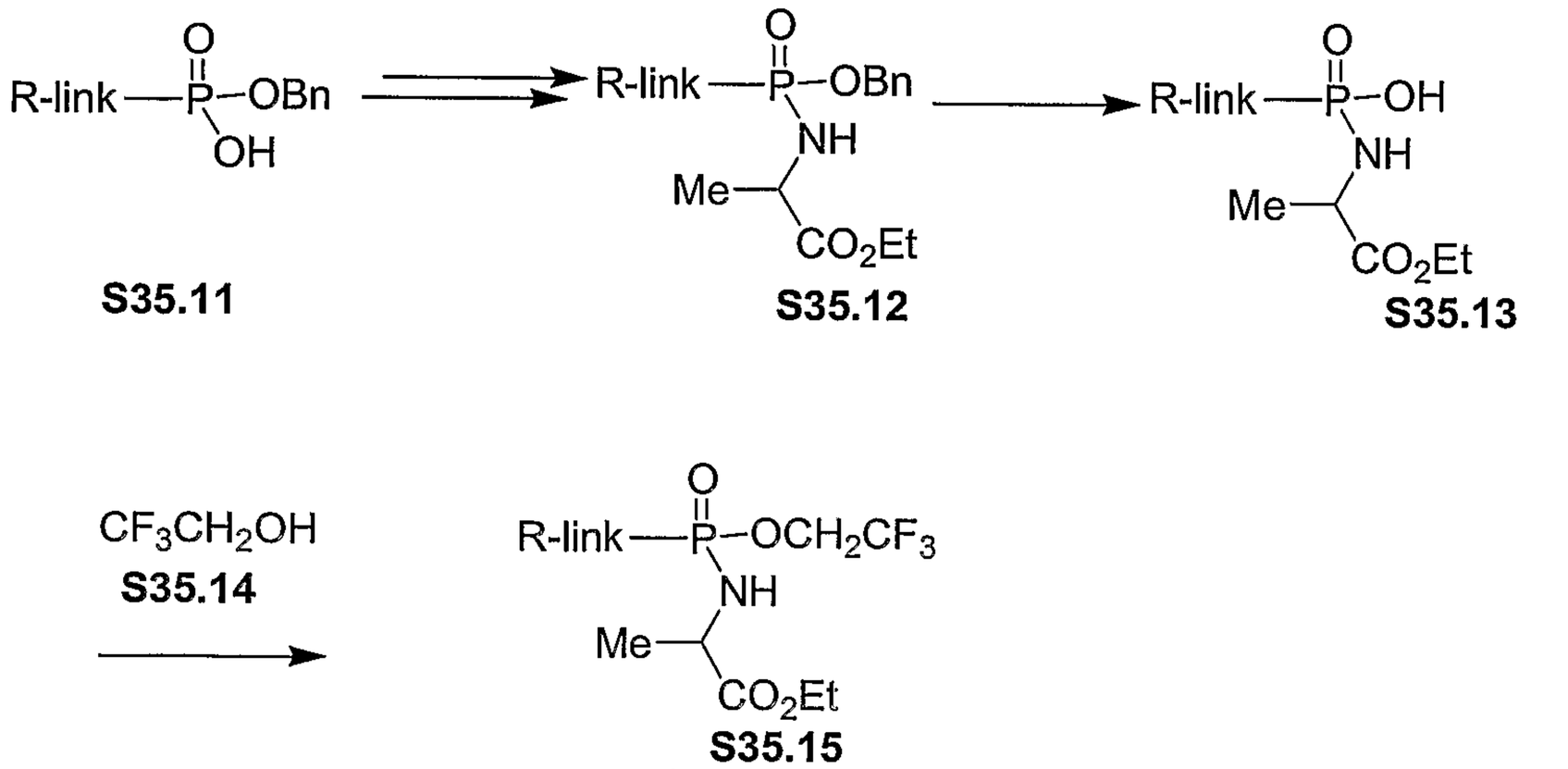
Scheme 35



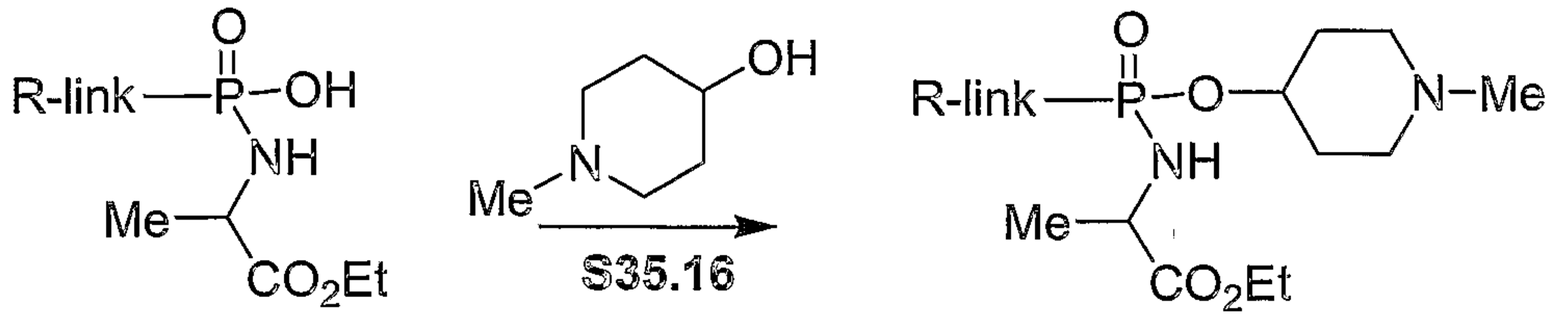
Scheme 35 Example 1



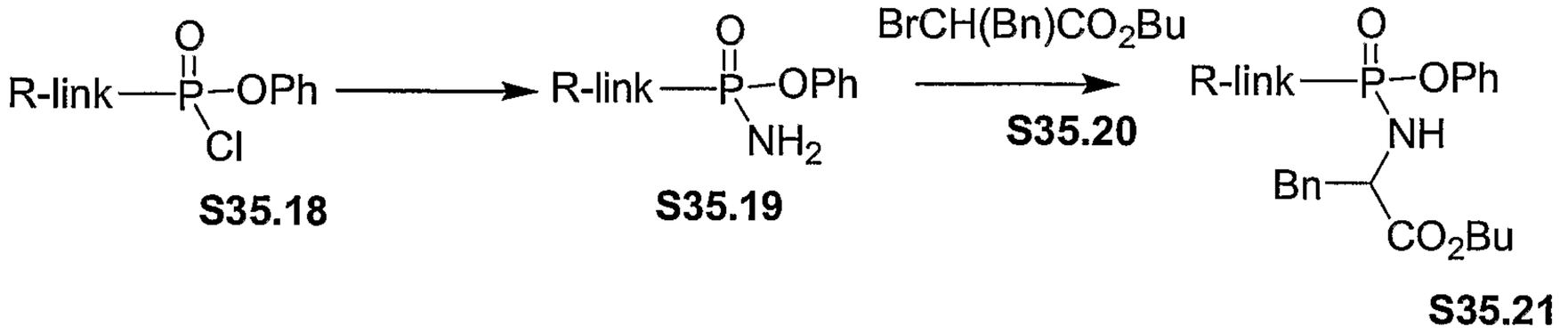
Scheme 35 Example 2



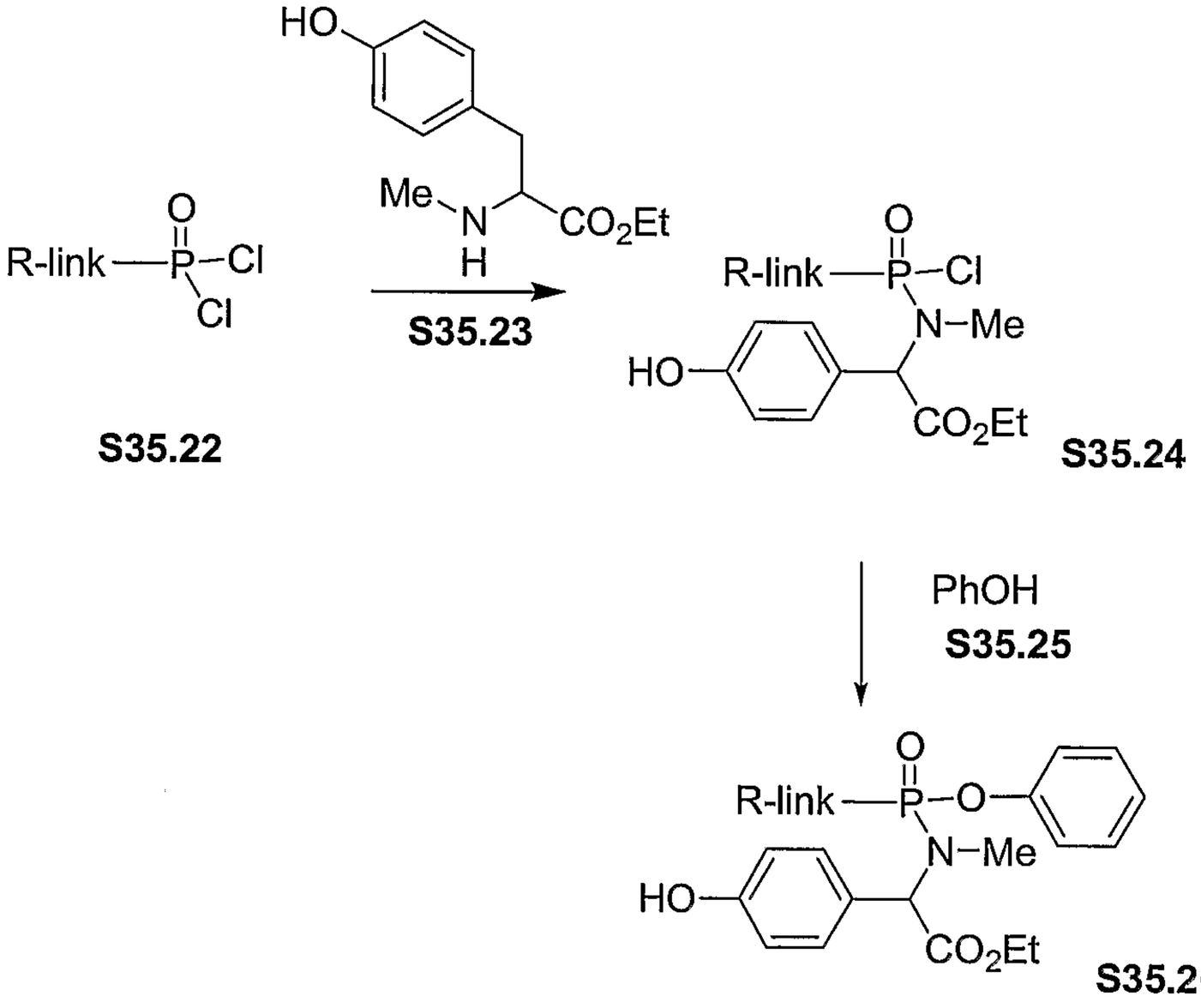
Scheme 35 Example 3



Scheme 35 Example 4



Scheme 35 Example 5



Scheme 36 illustrates methods for the preparation of carboalkoxy-substituted phosphonate diesters in which one of the ester groups incorporates a carboalkoxy substituent.

In one procedure, a phosphonate monoester **S34.1**, prepared as described above, is coupled, using one of the methods described above, with a hydroxyester **S36.1**, in which the groups R^{4b} and R^{5b} are as described in Scheme 34. For example, equimolar amounts of the reactants are coupled in the presence of a carbodiimide such as dicyclohexyl carbodiimide, as described in *Aust. J. Chem.*, 1963, 609, optionally in the presence of dimethylaminopyridine, as described in *Tet.*, 1999, 55, 12997. The reaction is conducted in an inert solvent at ambient temperature.

The procedure is illustrated in Scheme 36, Example 1. In this method, a monophenyl phosphonate **S36.9** is coupled, in dichloromethane solution in the presence of dicyclohexyl carbodiimide, with ethyl 3-hydroxy-2-methylpropionate **S36.10** to yield the phosphonate mixed diester **S36.11**.

Using this procedure, but employing, in place of ethyl 3-hydroxy-2-methylpropionate **S36.10**, different hydroxyesters **S33.1**, the corresponding products **S33.2** are obtained.

The conversion of a phosphonate monoester **S34.1** into a mixed diester **S36.2** is also accomplished by means of a Mitsunobu coupling reaction with the hydroxyester **S36.1**, as described in *Org. Lett.*, 2001, 643. In this method, the reactants **34.1** and **S36.1** are combined in a polar solvent such as tetrahydrofuran, in the presence of a triarylphosphine and a dialkyl azodicarboxylate, to give the mixed diester **S36.2**. The R^1 substituent is varied by cleavage, using the methods described previously, to afford the monoacid product **S36.3**. The product is then coupled, for example using methods described above, with the hydroxy compound R^3OH, to give the diester product **S36.4**.

The procedure is illustrated in Scheme 36, Example 2. In this method, a monoallyl phosphonate **S36.12** is coupled in tetrahydrofuran solution, in the presence of triphenylphosphine and diethylazodicarboxylate, with ethyl lactate **S36.13** to give the mixed diester **S36.14**. The product is reacted with tris(triphenylphosphine) rhodium chloride (Wilkinson catalyst) in acetonitrile, as described previously, to remove the allyl group and produce the monoacid product **S36.15**. The latter compound is then coupled, in pyridine solution at ambient temperature, in the presence of dicyclohexyl carbodiimide, with one molar equivalent of 3-hydroxypyridine **S36.16** to yield the mixed diester **S36.17**.

Using the above procedures, but employing, in place of the ethyl lactate **S36.13** or 3-hydroxypyridine, a different hydroxyester **S36.1** and/or a different hydroxy compound R^3OH, the corresponding products **S36.4** are obtained.

The mixed diesters **S36.2** are also obtained from the monoesters **S34.1** via the intermediacy of the activated monoesters **S36.5**. In this procedure, the monoester **S34.1** is converted into the activated compound **S36.5** by reaction with, for example, phosphorus pentachloride, as described in *J. Org. Chem.*, 2001, 66, 329, or with thionyl chloride or oxalyl chloride (Lv = Cl), or with triisopropylbenzenesulfonyl chloride in pyridine, as described in *Nucleosides and Nucleotides*, 2000, 19, 1885, or with carbonyl diimidazole, as described in *J. Med. Chem.*, 2002, 45, 1284. The resultant activated monoester is then reacted with the hydroxyester **S36.1**, as described above, to yield the mixed diester **S36.2**.

The procedure is illustrated in Scheme 36, Example 3. In this sequence, a monophenyl phosphonate **S36.9** is reacted, in acetonitrile solution at 70 °C, with ten equivalents of thionyl chloride, so as to produce the phosphoryl chloride **S36.19**. The product is then reacted with ethyl 4-carbamoyl-2-hydroxybutyrate **S36.20** in dichloromethane containing triethylamine, to give the mixed diester **S36.21**.

Using the above procedures, but employing, in place of ethyl 4-carbamoyl-2-hydroxybutyrate **S36.20**, different hydroxyesters **S36.1**, the corresponding products **S36.2** are obtained.

The mixed phosphonate diesters are also obtained by an alternative route for incorporation of the R^3O group into intermediates **S36.3** in which the hydroxyester moiety is already incorporated. In this procedure, the monoacid intermediate **S36.3** is converted into the activated derivative **S36.6** in which Lv is a leaving group such as chloro, imidazole, and the like, as previously described. The activated intermediate is then reacted with the hydroxy compound R^3OH, in the presence of a base, to yield the mixed diester product **S36.4**.

The method is illustrated in Scheme 36, Example 4. In this sequence, the phosphonate monoacid **S36.22** is reacted with trichloromethanesulfonyl chloride in tetrahydrofuran containing collidine, as described in *J. Med. Chem.*, 1995, 38,

4648, to produce the trichloromethanesulfonyloxy product **S36.23**. This compound is reacted with 3-(morpholinomethyl)phenol **S36.24** in dichloromethane containing triethylamine, to yield the mixed diester product **S36.25**.

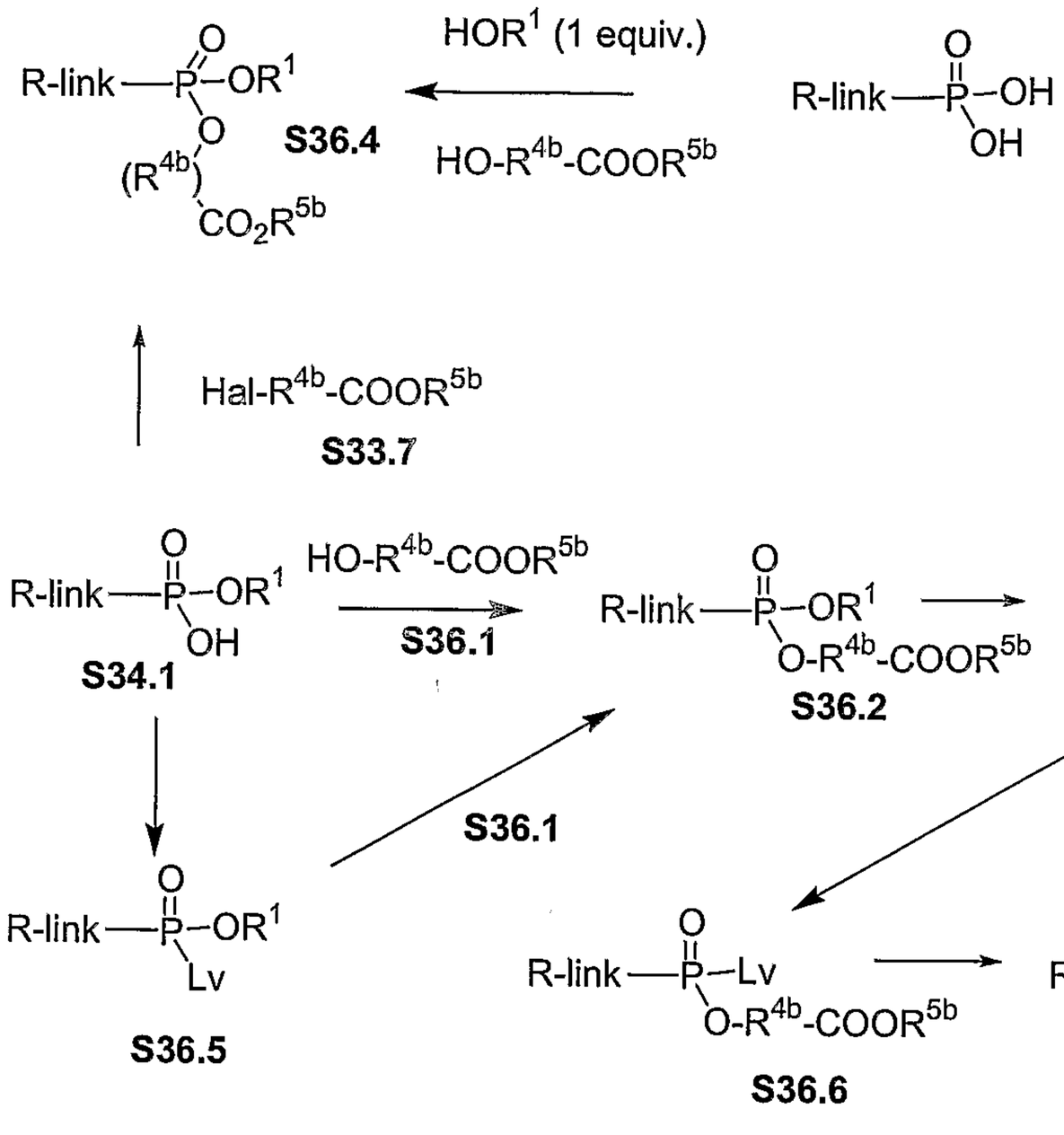
Using the above procedures, but employing, in place of with 3-(morpholinomethyl)phenol **S36.24**, different alcohols R^3OH, the corresponding products **S36.4** are obtained.

The phosphonate esters **S36.4** are also obtained by means of alkylation reactions performed on the monoesters **S34.1**. The reaction between the monoacid **S34.1** and the haloester **S36.7** is performed in a polar solvent in the presence of a base such as diisopropylethylamine, as described in *Anal. Chem.*, 1987, 59, 1056, or triethylamine, as described in *J. Med. Chem.*, 1995, 38, 1372, or in a non-polar solvent such as benzene, in the presence of 18-crown-6, as described in *Syn. Comm.*, 1995, 25, 3565.

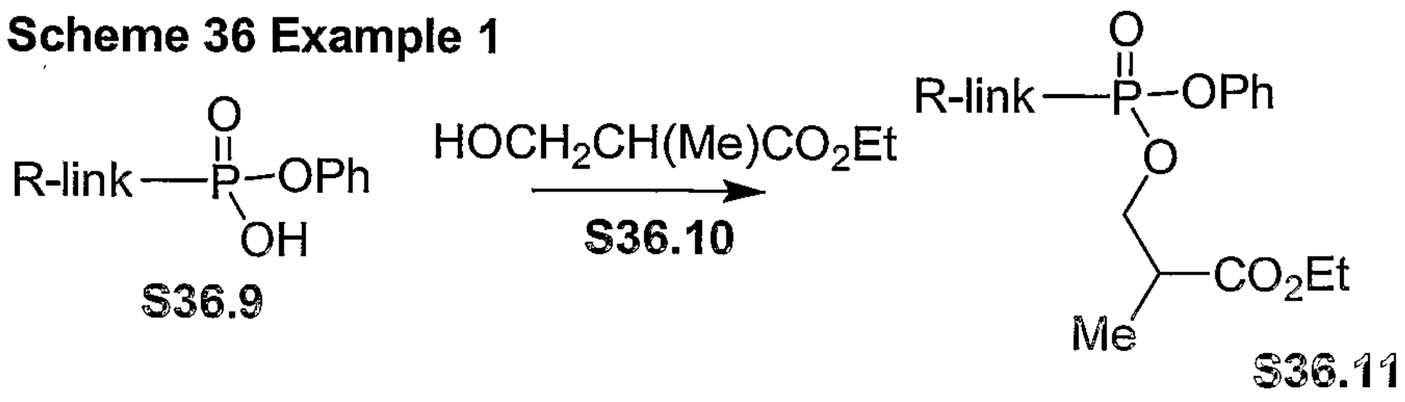
The method is illustrated in Scheme 36, Example 5. In this procedure, the monoacid **S36.26** is reacted with ethyl 2-bromo-3-phenylpropionate **S36.27** and diisopropylethylamine in dimethylformamide at 80 °C to afford the mixed diester product **S36.28**.

Using the above procedure, but employing, in place of ethyl 2-bromo-3-phenylpropionate **S36.27**, different haloesters **S36.7**, the corresponding products **S36.4** are obtained.

Scheme 36

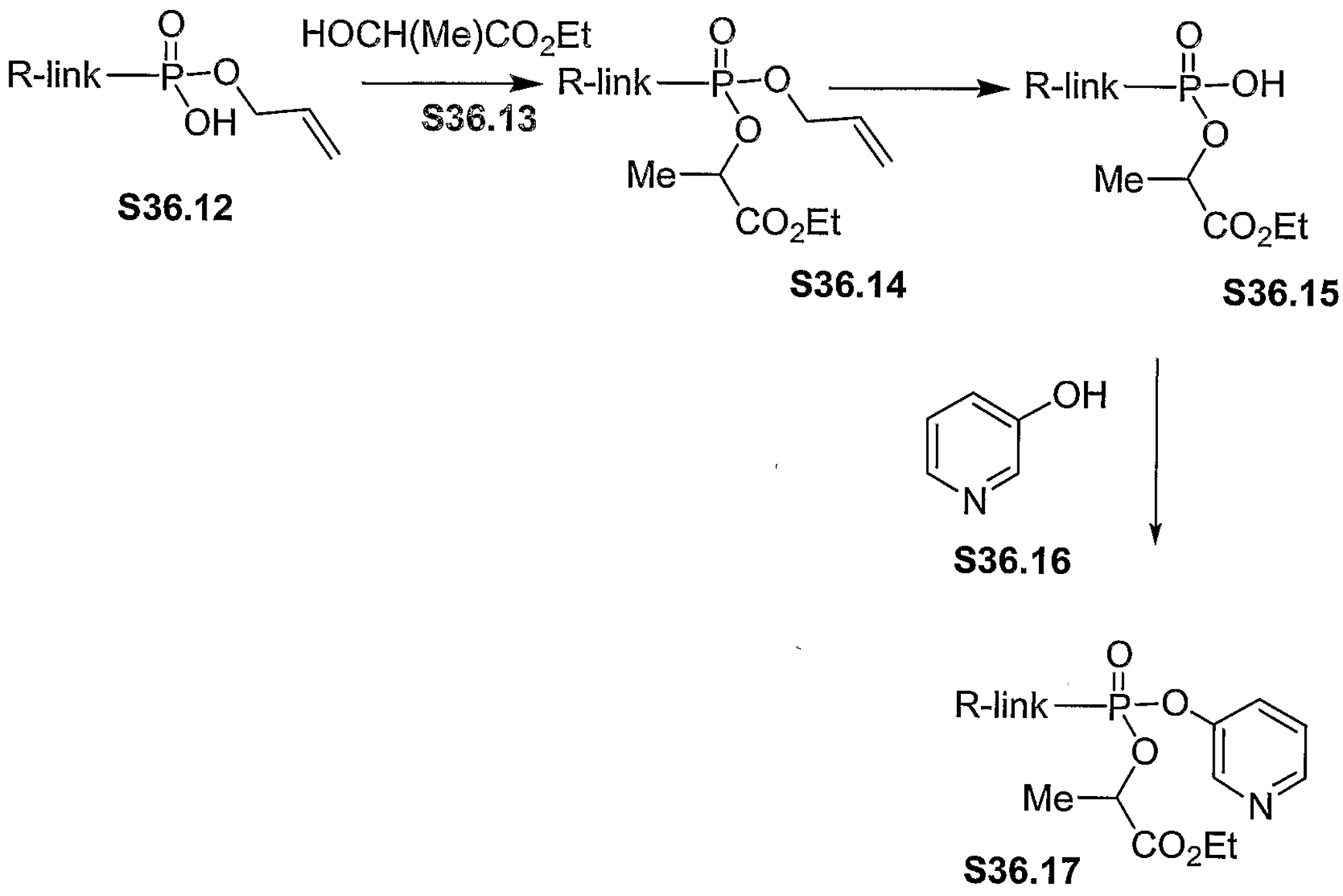

R-link—P(=O)(OR1)(O(R4b)CO2R5b)
S36.4
HOR1 (1 equiv.)
HO-R4b-COOR5b
R-link—P(=O)(OH)2
Hal-R4b-COOR5b
S33.7
R-link—P(=O)(OR1)OH
S34.1
HO-R4b-COOR5b
S36.1
R-link—P(=O)(OR1)(O-R4b-COOR5b)
S36.2
R-link—P(=O)(OH)(O-R4b-COOR5b)
S36.3
S36.1
R-link—P(=O)(OR1)Lv
S36.5
R-link—P(=O)(Lv)(O-R4b-COOR5b)
S36.6
R-link—P(=O)(OR3)(O-R4b-COOR5b)
S36.4

Scheme 36 Example 1



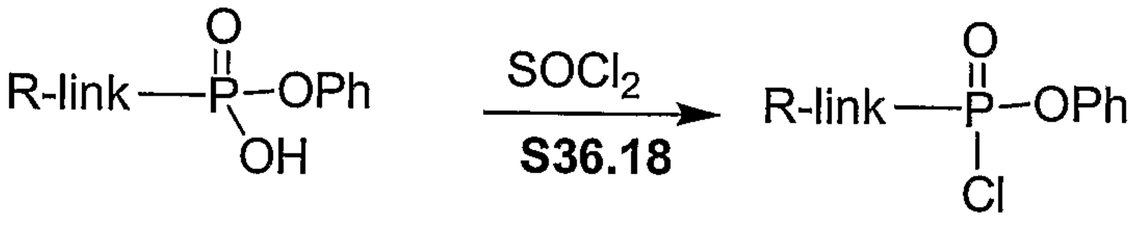
S36.9 S36.11

Scheme 36 Example 2

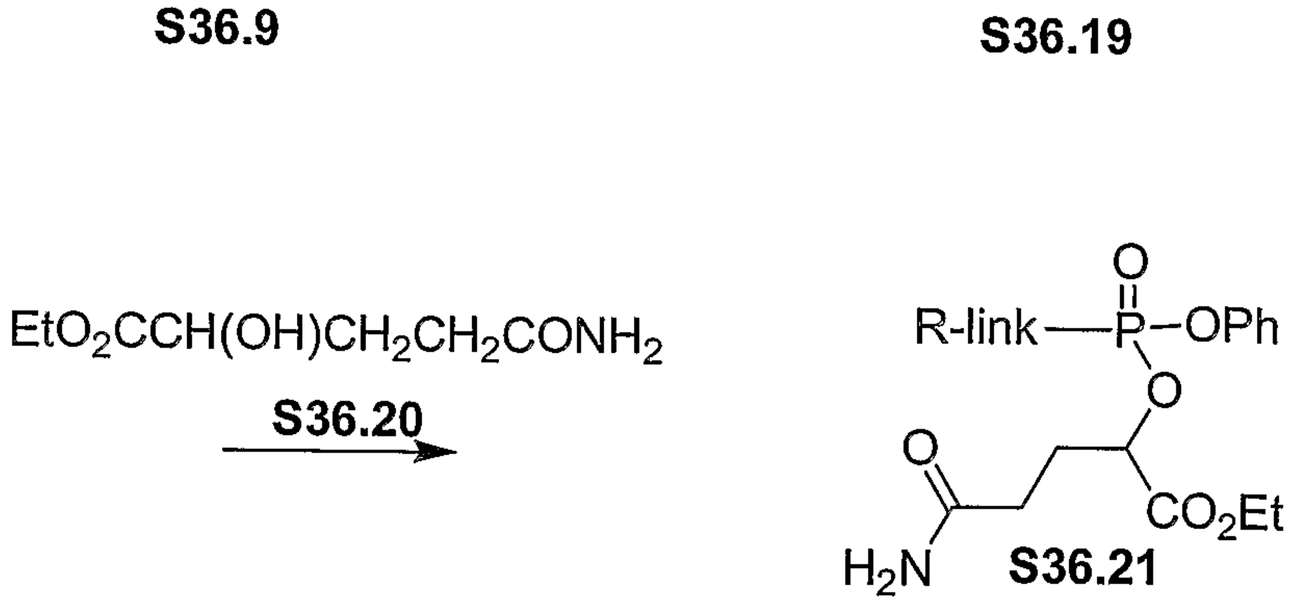


S36.12 S36.14 S36.15 S36.16 S36.17

Scheme 36 Example 3

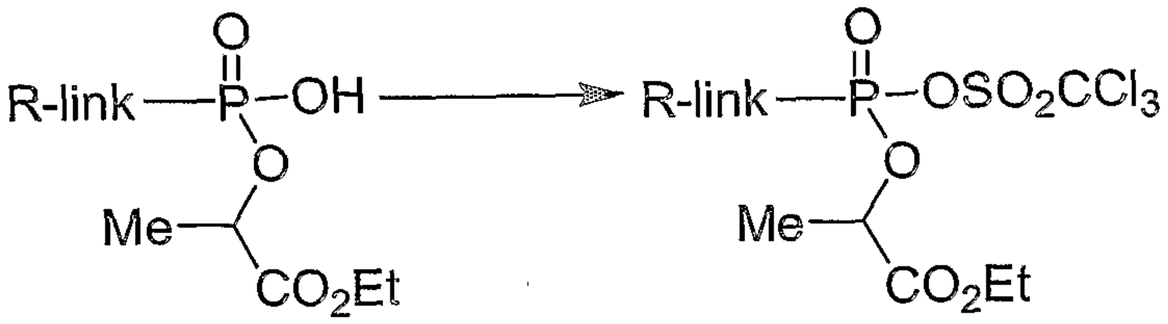


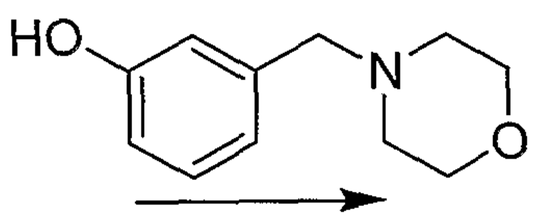
S36.9 S36.19

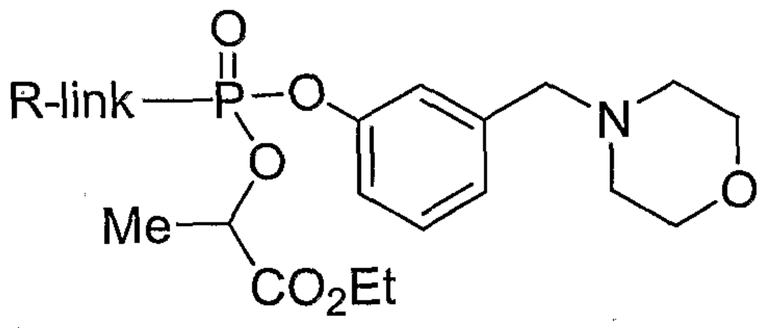


S36.21

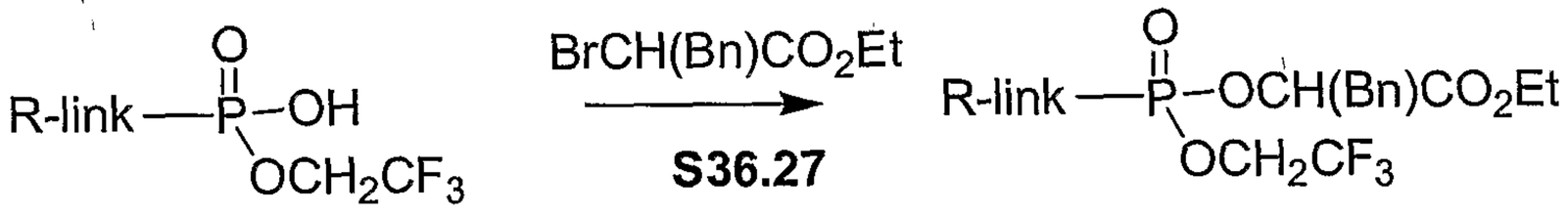
Scheme 36 Example 4







Scheme 36 Example 5



Scheme 37 illustrates methods for the preparation of phosphonate diesters in which both the ester substituents incorporate carboalkoxy groups.

The compounds are prepared directly or indirectly from the phosphonic acids **S34.6**. In one alternative, the phosphonic acid is coupled with the hydroxyester **S37.2**, using the conditions described previously in Schemes 34-36, such as coupling reactions using dicyclohexyl carbodiimide or similar reagents, or under the conditions of the Mitsunobu reaction, to afford the diester product **S37.3** in which the ester substituents are identical.

This method is illustrated in Scheme 37, Example 1. In this procedure, the phosphonic acid **S34.6** is reacted with three molar equivalents of butyl lactate

S37.5 in the presence of Aldrithiol-2 and triphenyl phosphine in pyridine at ca. 70 °C, to afford the diester **S37.6**.

Using the above procedure, but employing, in place of butyl lactate **S37.5**, different hydroxyesters **S37.2**, the corresponding products **S37.3** are obtained.

Alternatively, the diesters **S37.3** are obtained by alkylation of the phosphonic acid **S34.6** with a haloester **S37.1**. The alkylation reaction is performed as described in Scheme 36 for the preparation of the esters **S36.4**.

This method is illustrated in Scheme 37, Example 2. In this procedure, the phosphonic acid **S34.6** is reacted with excess ethyl 3-bromo-2-methylpropionate **S37.7** and diisopropylethylamine in dimethylformamide at ca. 80 °C, as described in *Anal. Chem.*, 1987, 59, 1056, to produce the diester **S37.8**.

Using the above procedure, but employing, in place of ethyl 3-bromo-2-methylpropionate **S37.7**, different haloesters **S37.1**, the corresponding products **S37.3** are obtained.

The diesters **S37.3** are also obtained by displacement reactions of activated derivatives **S34.7** of the phosphonic acid with the hydroxyesters **S37.2**. The displacement reaction is performed in a polar solvent in the presence of a suitable base, as described in Scheme 36. The displacement reaction is performed in the presence of an excess of the hydroxyester, to afford the diester product **S37.3** in which the ester substituents are identical, or sequentially with limited amounts of different hydroxyesters, to prepare diesters **S37.3** in which the ester substituents are different.

The methods are illustrated in Scheme 37, Examples 3 and 4. As shown in Example 3, the phosphoryl dichloride **S35.22** is reacted with three molar equivalents of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **S37.9** in tetrahydrofuran containing potassium carbonate, to obtain the diester product **S37.10**.

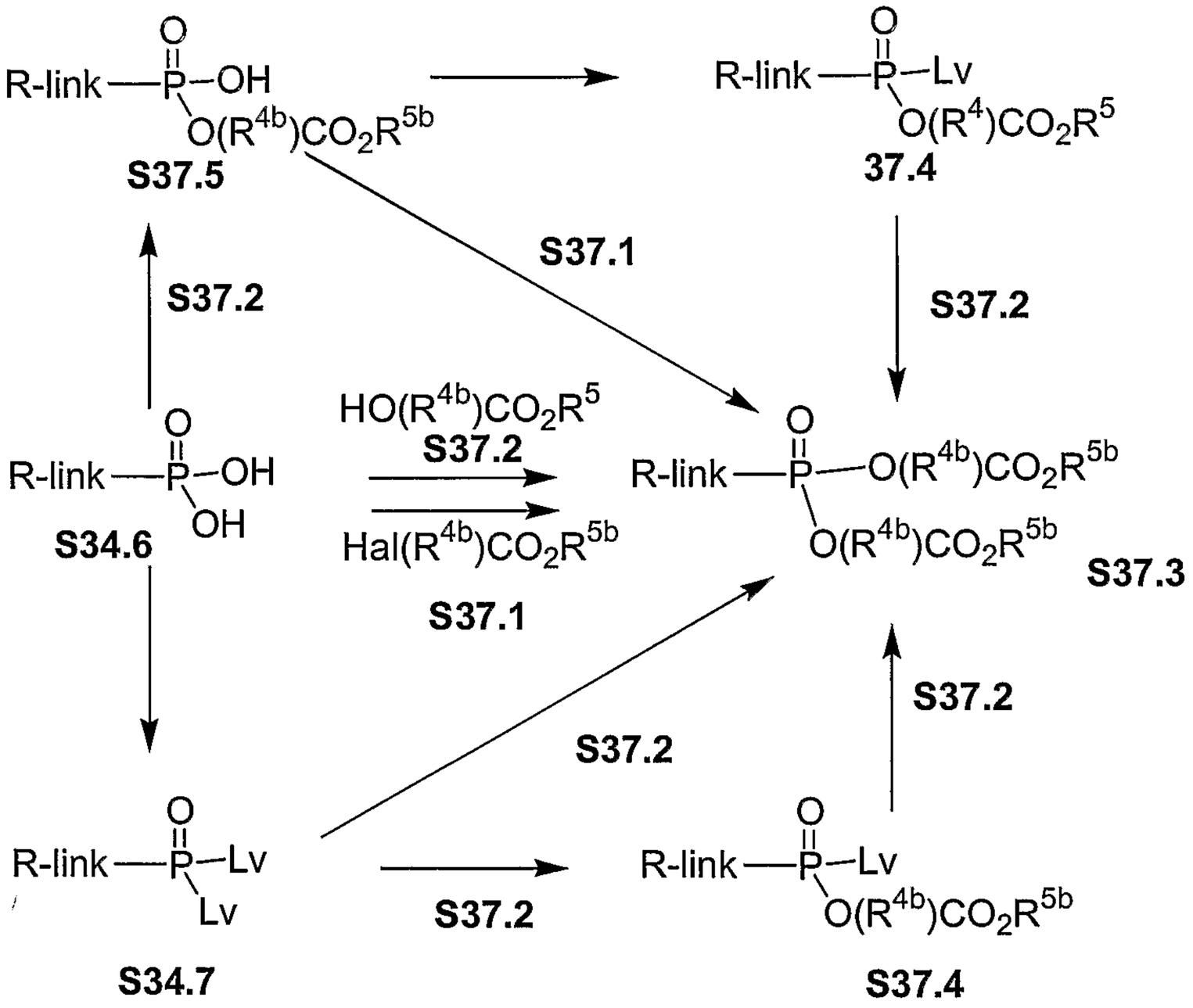
Using the above procedure, but employing, in place of ethyl 3-hydroxy-2-(hydroxymethyl)propionate **S37.9**, different hydroxyesters **S37.2**, the corresponding products **S37.3** are obtained.

Scheme 37, Example 4 depicts the displacement reaction between equimolar amounts of the phosphoryl dichloride **S35.22** and ethyl 2-methyl-3-

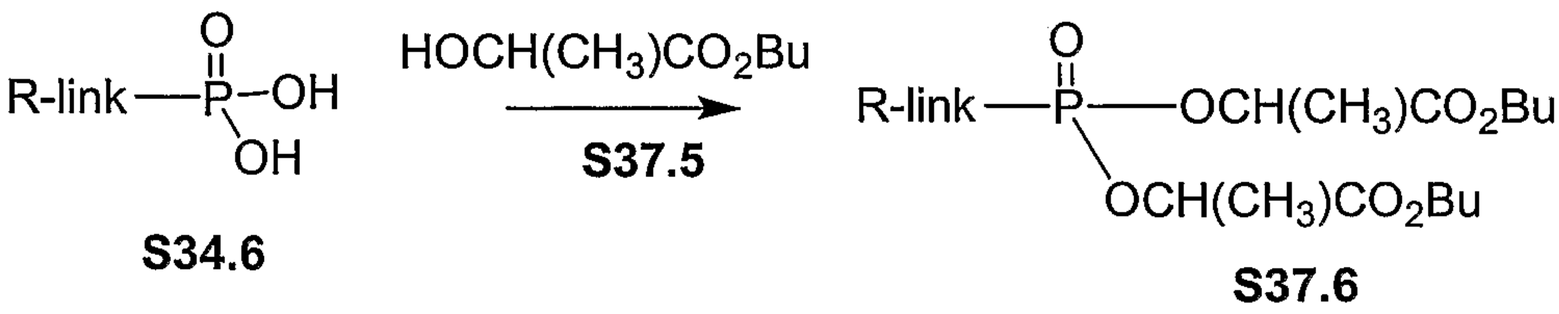
hydroxypropionate **S37.11**, to yield the monoester product **S37.12**. The reaction is conducted in acetonitrile at 70° in the presence of diisopropylethylamine. The product **S37.12** is then reacted, under the same conditions, with one molar equivalent of ethyl lactate **S37.13**, to give the diester product **S37.14**.

Using the above procedures, but employing, in place of ethyl 2-methyl-3-hydroxypropionate **S37.11** and ethyl lactate **S37.13**, sequential reactions with different hydroxyesters **S37.2**, the corresponding products **S37.3** are obtained.

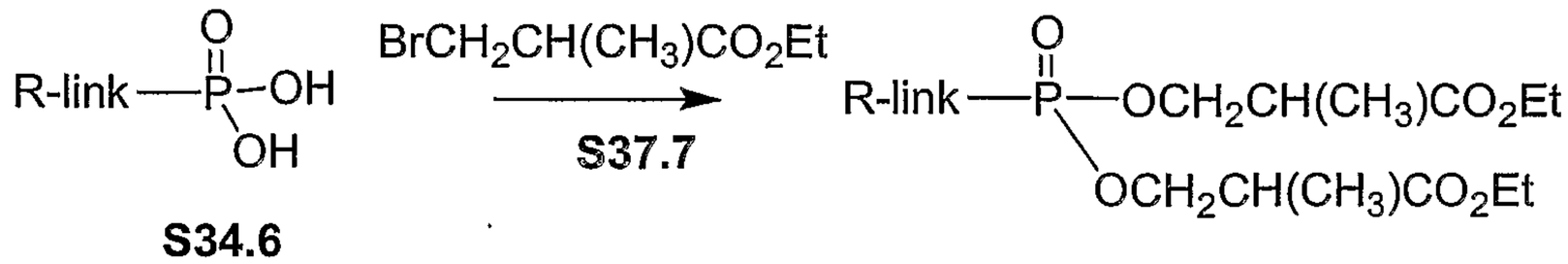
Scheme 37



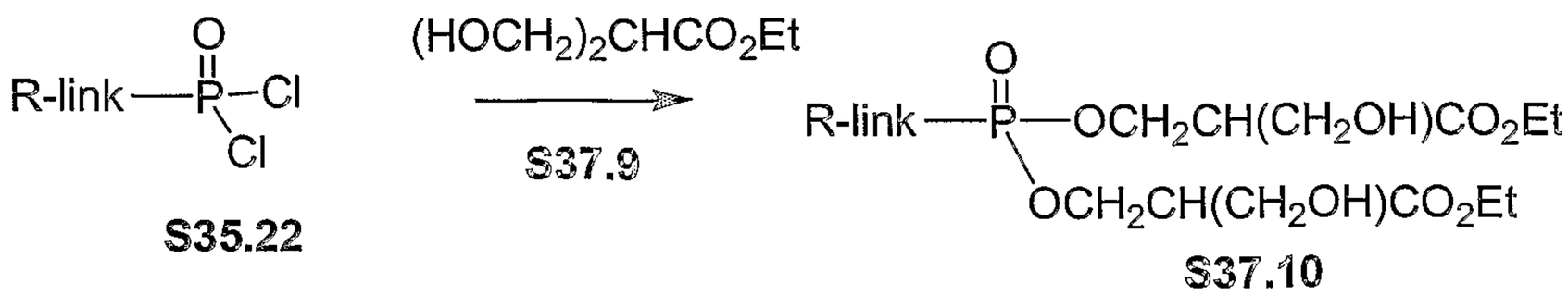
Scheme 37 Example 1



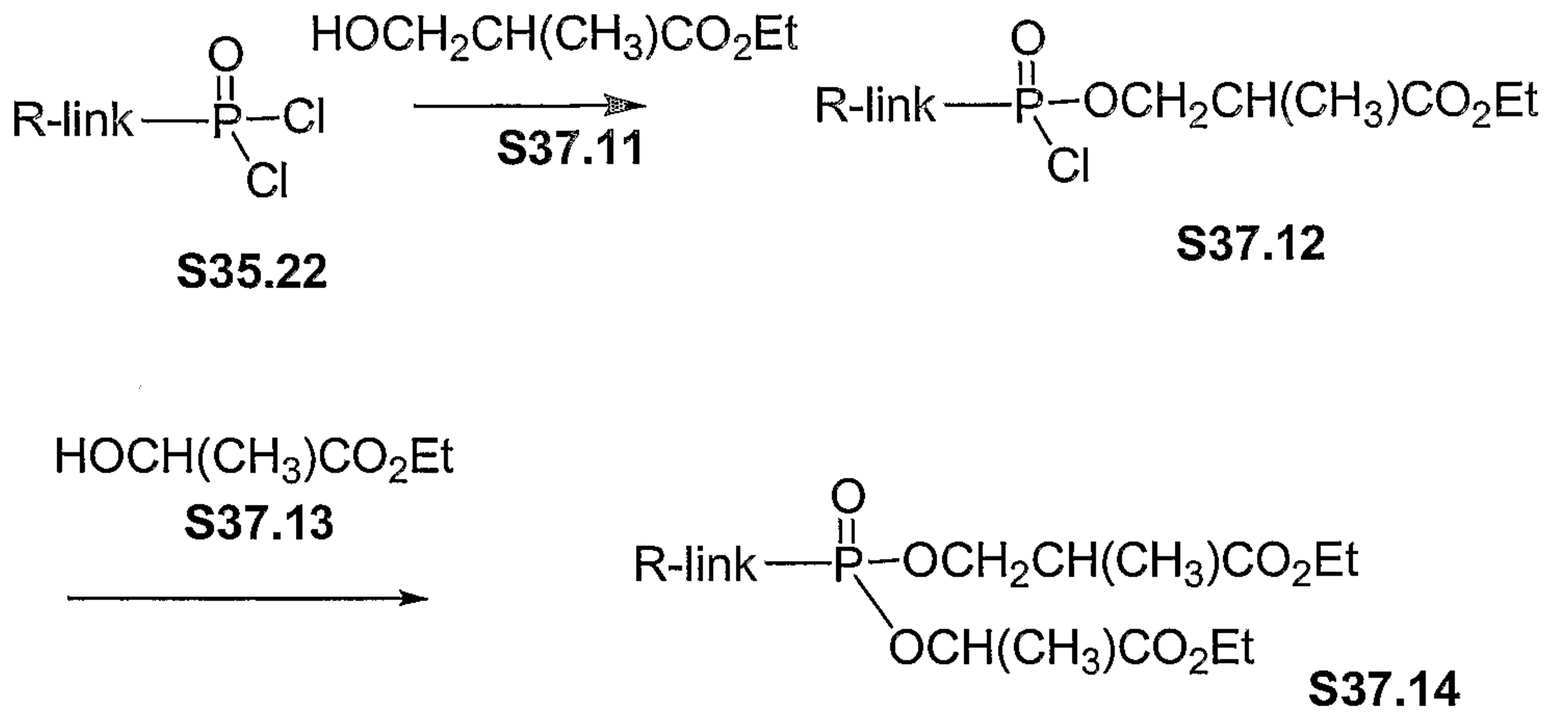
Scheme 37 Example 2



Scheme 37 Example 3

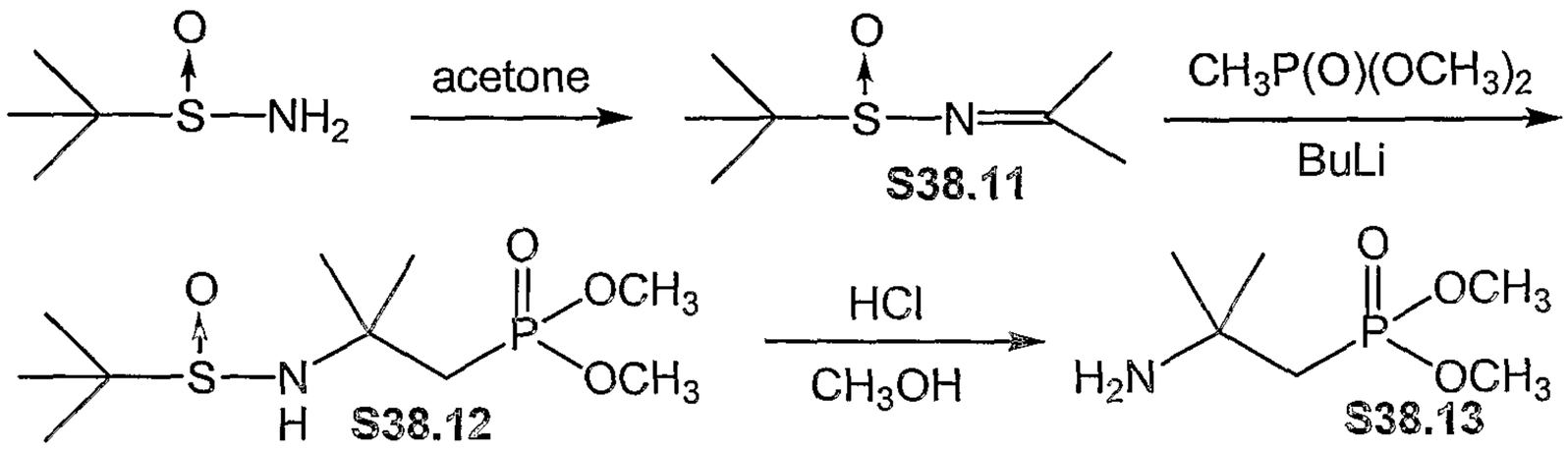


Scheme 37 Example 4

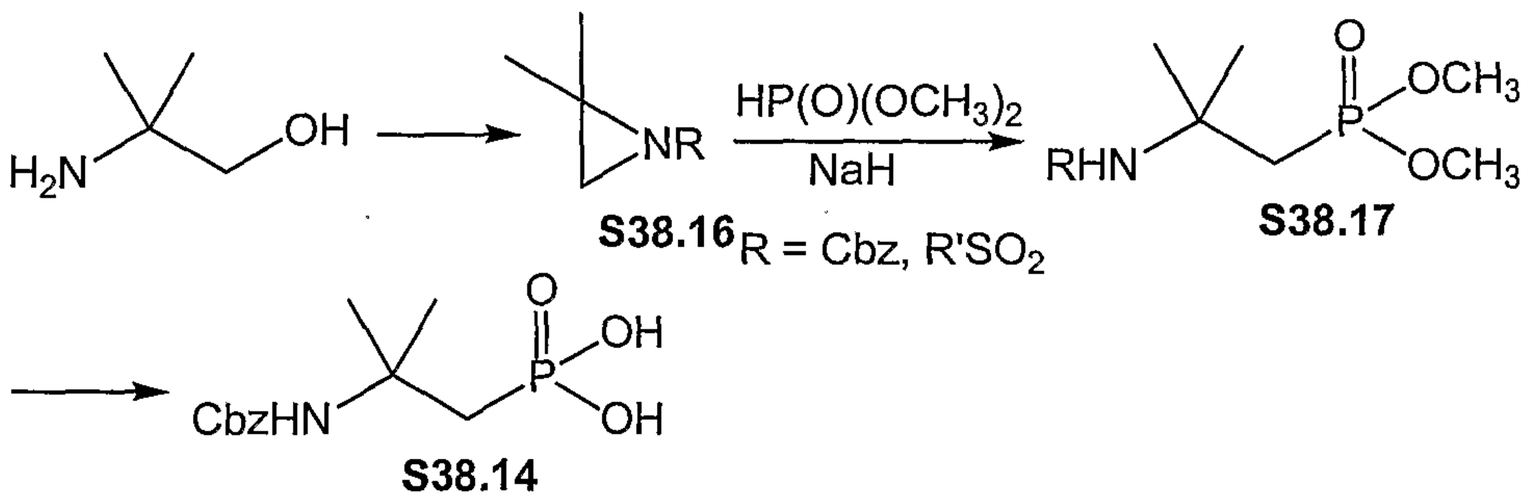


2,2-Dimethyl-2-aminoethylphosphonic acid intermediates can be prepared by the route in Scheme 5. Condensation of 2-methyl-2-propanesulfinamide with acetone give sulfinyl imine **S38.11** (*J. Org. Chem.* **1999**, *64*, 12). Addition of dimethyl methylphosphonate lithium to **S38.11** afford **S38.12**. Acidic methanolysis of **S38.12** provide amine **S38.13**. Protection of amine with Cbz group and removal of methyl groups yield phosphonic acid **S38.14**, which can be converted to desired **S38.15** (Scheme 38a) using methods reported earlier on. An alternative synthesis of compound **S38.14** is also shown in Scheme 38b. Commercially available 2-amino-2-methyl-1-propanol is converted to aziridines **S38.16** according to literature methods (*J. Org. Chem.* **1992**, *57*, 5813; *Syn. Lett.* **1997**, *8*, 893). Aziridine opening with phosphite give **S38.17** (*Tetrahedron Lett.* **1980**, *21*, 1623). Reprotection) of **S38.17** affords **S38.14**.

Scheme 38a



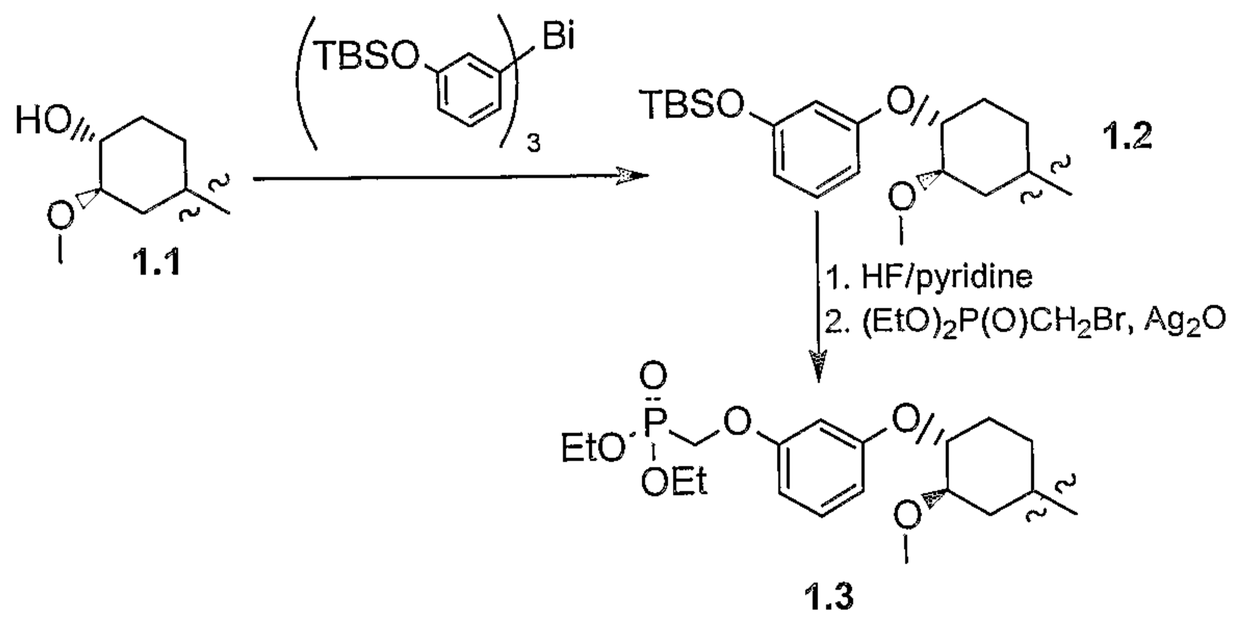
Scheme 38b



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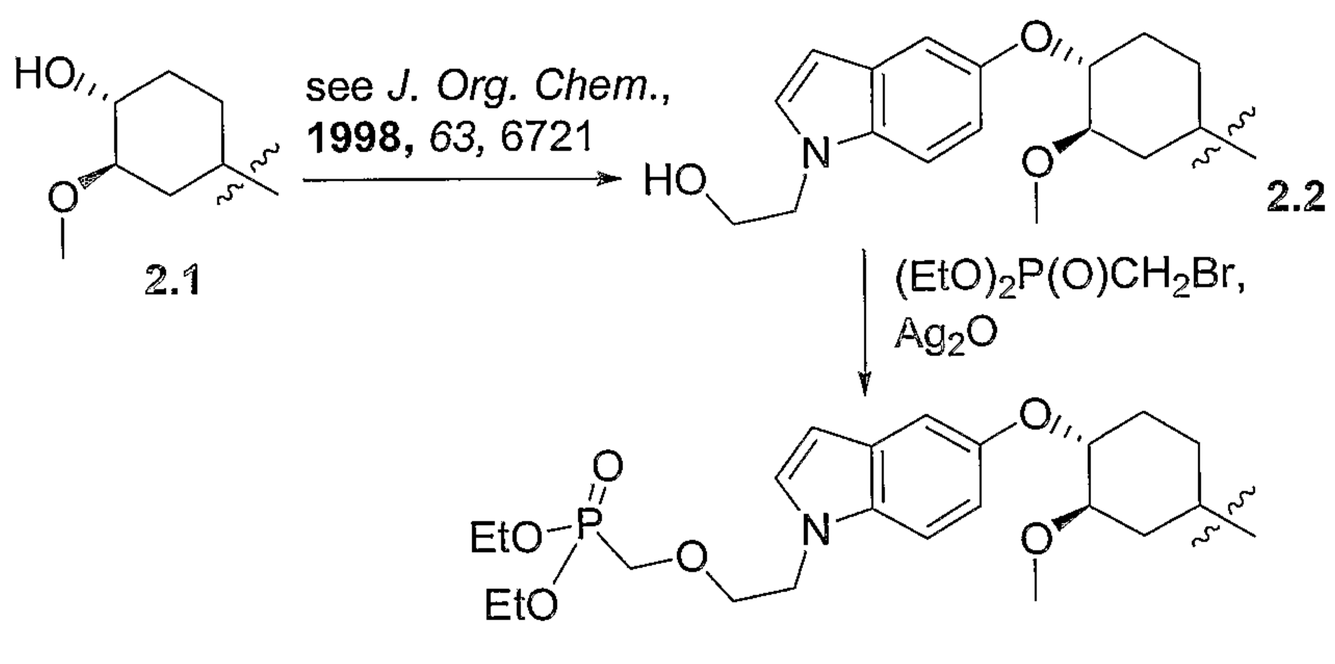
The invention will now be illustrated by the following non-limiting Examples.

Example 1



Rapamycin (compound, **1.1**, wherein the remaining portion of the rapamycin structure is not shown), a synthetic precursor of everolimus, is *O*-arylated as shown above using an appropriate aryl bismuth reagent according to a procedure such as that reported in *Bioorg. Med. Chem. Lett*, **1995**, *5*, 1035. 3-(Dimethyl-t-butylsilyloxy)bromobenzene is treated either with magnesium in diethyl ether or with butyllithium in tetrahydrofuran, and the resulting organometallic reagent is reacted with bismuth trichloride to generate the triarybismuthine. After treating with 1 – 1.2 equivalents of peracetic acid, the bismuth(V) reagent is mixed with rapamycin and copper(II) acetate. The reaction is allowed to proceed for a day at room temperature or, if necessary, at reflux, affording the desired 3-(dimethyl-t-butylsilyloxy)phenyl ether, **1.2**. After removal of the dimethyl-t-butylsilyl protecting group, *O*-akylation is achieved with diethyl (bromomethyl)phosphonate in the presence of silver oxide, affording the desired everolimus analog containing the diethylphosphonate, **1.3**. Silver ion-assisted reactions have been used to mediate *O*-alkylations on an immunosuppresive macrolide structurally similar to rapamycin: see *J. Med. Chem.*, **1998**, *41*, 1764.

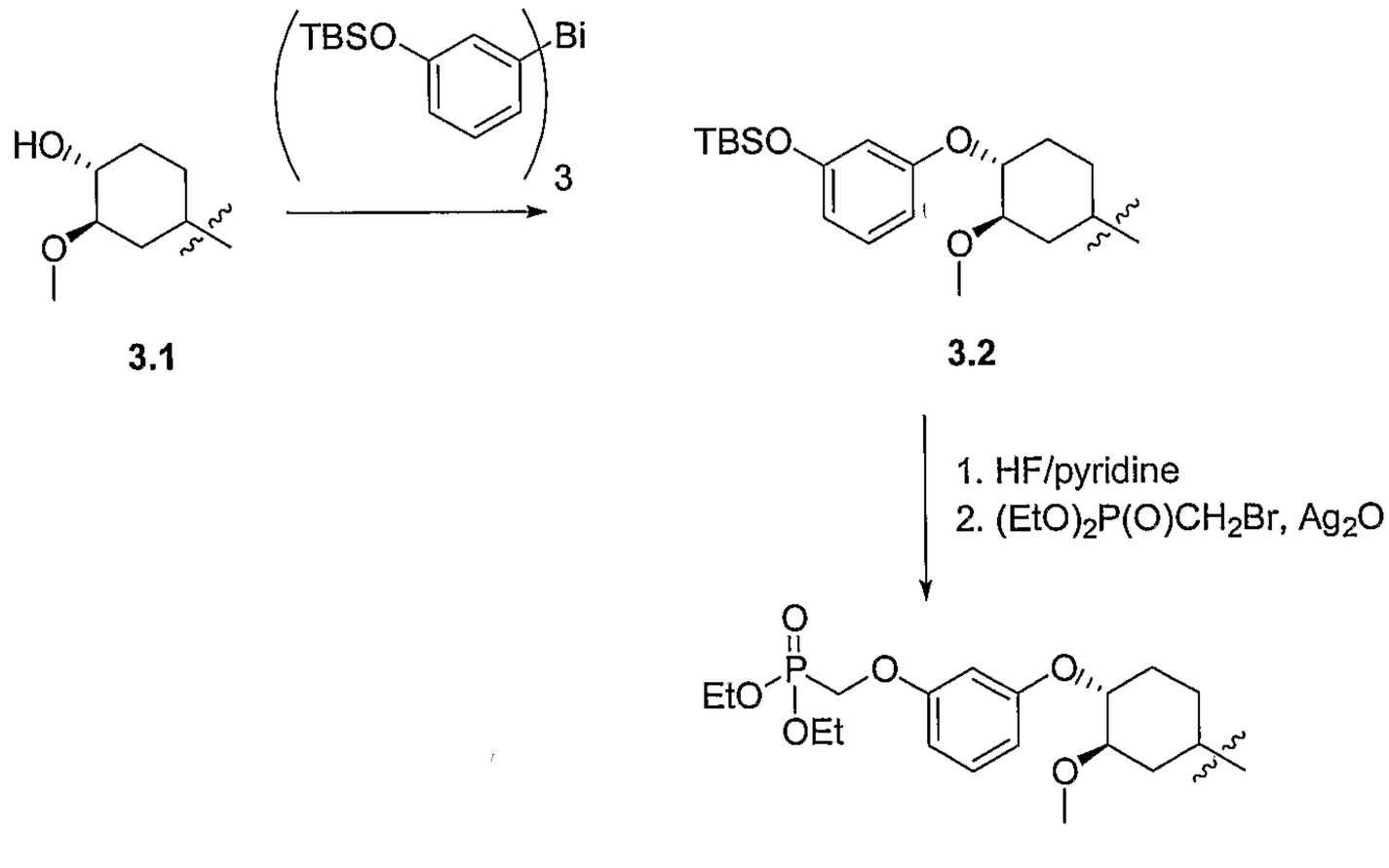
Example 2



2.3

A phosphonate derivative of everolimus indolyl ether is prepared from rapamycin (formula, **2.1**, wherein the remaining portion of the rapamycin structure is not shown) in a similar manner to that described in Example 1, with the exception that the key triindolylbismuthine intermediate is obtained from 5-bromoindole following the procedure described in *J. Org. Chem.* **1998**, *63*, 6721.

Example 3

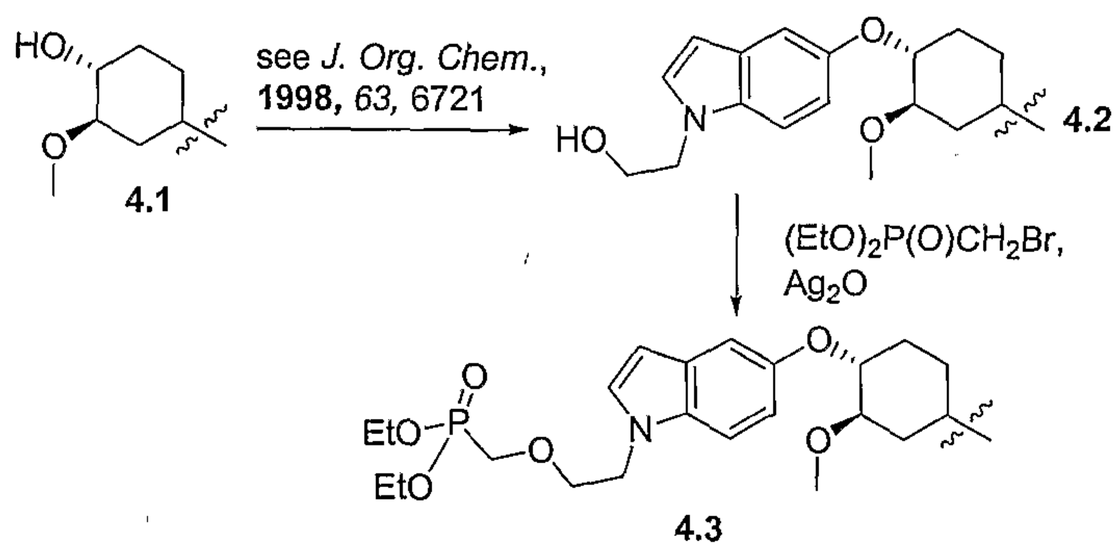


3.3

Tacrolimus (compound, **3.1**, wherein the remaining portion of the tacrolimus molecule is not shown) is *O*-arylated as shown above using an appropriate aryl bismuth reagent according to a procedure such as that reported in *Bioorg. Med. Chem. Lett*, **1995**, *5*, 1035. 3-(Dimethyl-t-butylsilyloxy)-bromobenzene is treated either with magnesium in diethyl ether or with

butyllithium in tetrahydrofuran, and the resulting organometallic reagent is reacted with bismuth trichloride to generate the triarybismuthine. After treating with 1 – 1.2 equivalents of peracetic acid, the bismuth(V) reagent is mixed with tacrolimus, **3.1**, and copper(II) acetate. The reaction is allowed to proceed for a day at room temperature or, if necessary, at reflux, affording the desired 3-(dimethyl-t-butylsilyloxy)phenyl ether. After removal of the dimethyl-t-butylsilyl protecting group with HF, *O*-akylation is achieved with diethyl (bromomethyl)phosphonate in the presence of silver oxide, affording the desired tacrolimus analog containing the diethylphosphonate, **3.3**. Silver ion-assisted reactions have been used to mediate *O*-alkylations on an immunosuppresive macrolide structurally similar to tacrolimus. (See *J.* Med. Chem., 1998, 41, 1764.)

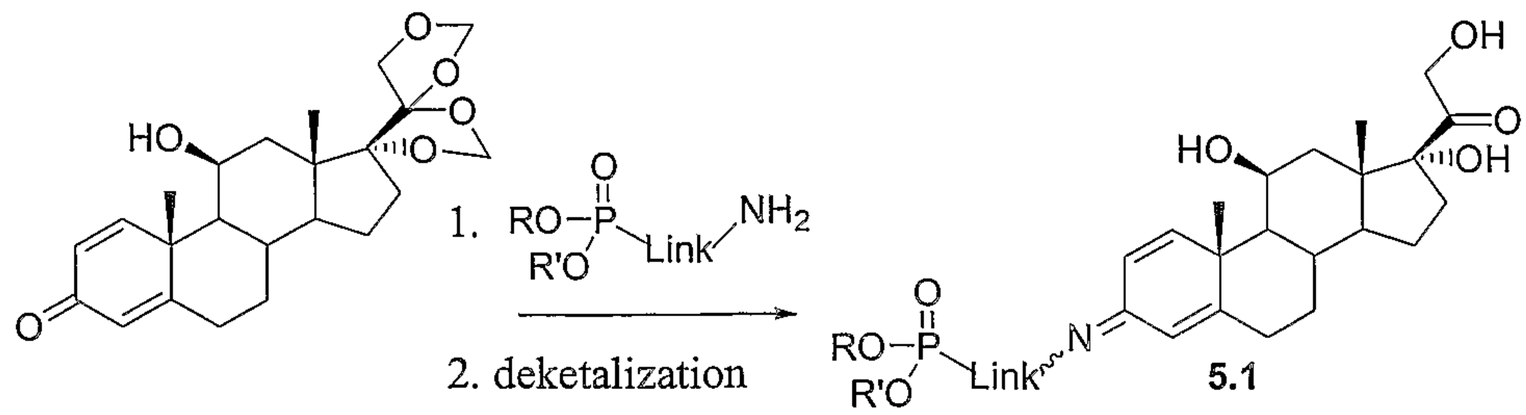
Example 4

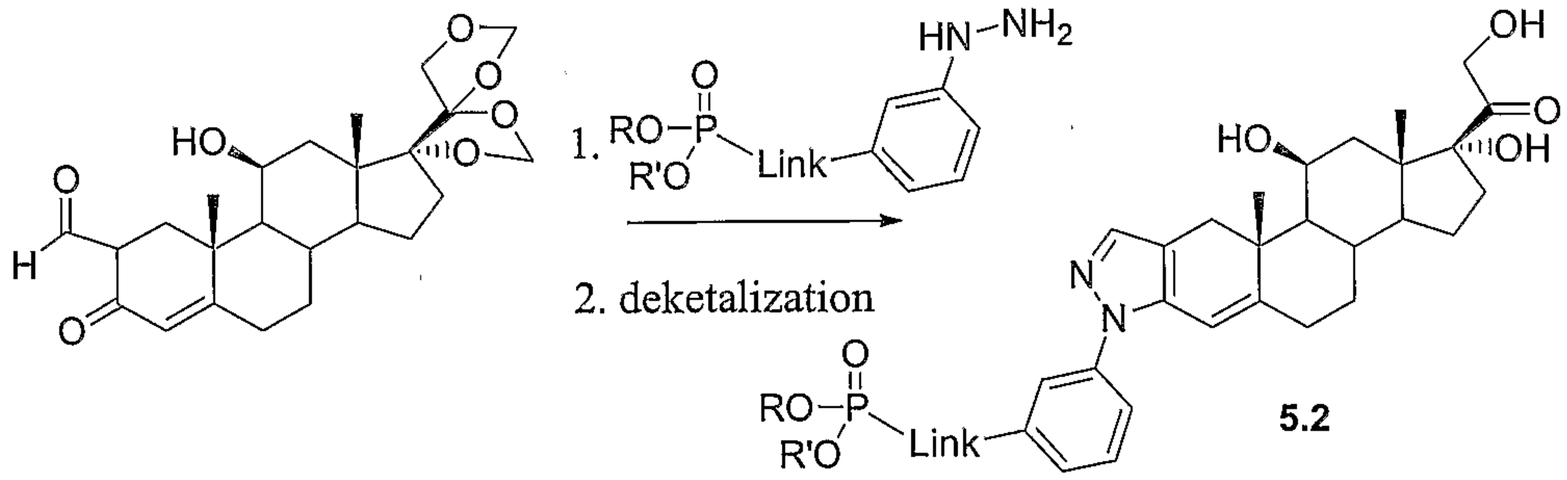


A phosphonate derivative of, **4.3**, tacrolimus indolyl ether is prepared from tacrolimus (compound, **4.1**, wherein the remaining portion of the tacrolimus molecule is not shown) in a similar manner to that described in Example 3 with the exception that the key triindolylbismuthine intermediate is obtained from 5-bromoindole following the procedure described in *J. Org. Chem.* **1998**, *63*, 6721.

Example 5

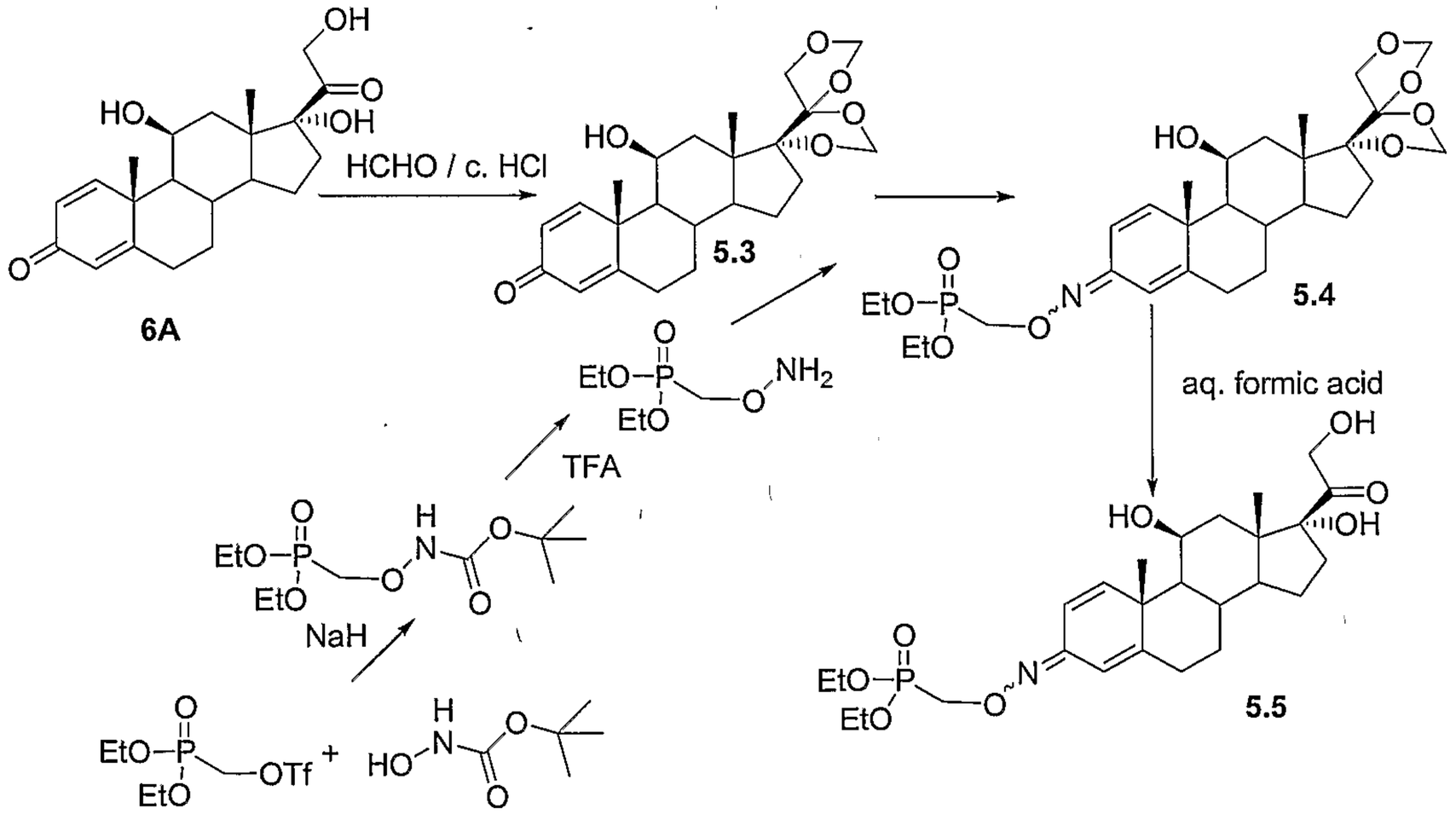
Representative compounds of the invention can be made by procedures such as those described by Boer, et al, *J. Mass Spectrom.* **1995**, *30*, 497-504 and Hoyte, et al, *J. Med. Chem.* **2002**, *45*, 5397-5405; they can also be made according to the following general routes.





Compounds of formulae, **5.1** and **5.2**, wherein "Link" have any of the values defined herein for a linking group or a linker, are representative compounds of the invention.

Example 6

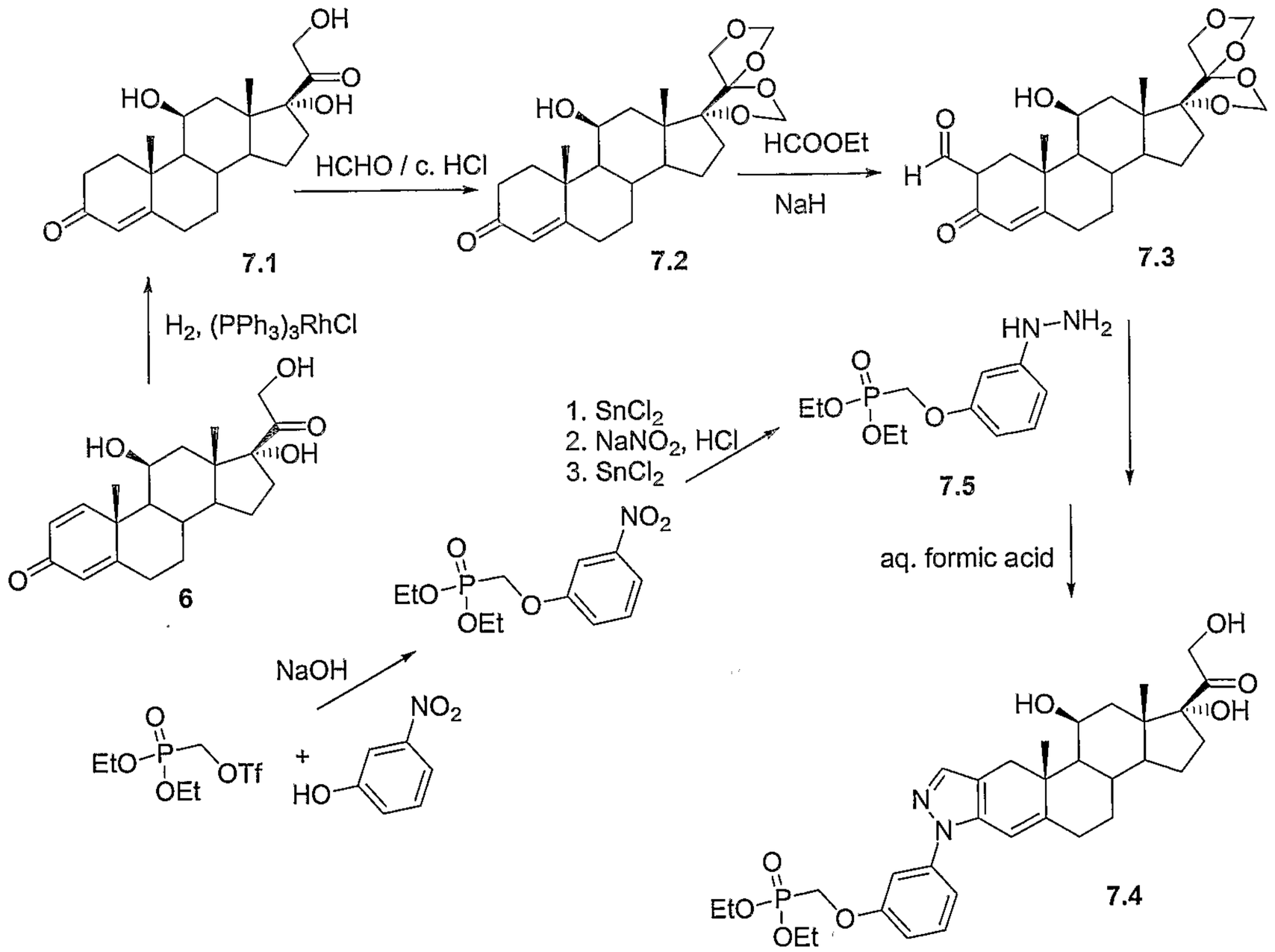


Prednisolone, **6A**, is treated in a solvent, such as chloroform, with formaldehyde in the presence of an acid, such as concentrated hydrochloric acid. After stirring for several hours (preferably 7 to 10 hours) at room temperature, the layers are separated and the organic layer is concentrated to afford the bis-(methylenedioxy) intermediate, **5.3** (Hirschmann, R. et al, *J. Am. Chem. Soc.*

1964, *86*, 1520-1527). This intermediate is treated with diethyl (amino-oxymethyl)phosphonate in a solvent such as pyridine to afford the oxime, **5.4**. The oxime is treated with aqueous acid to remove the bis-(methylenedioxy) protecting group. For example, the oxime is treated with 60% aqueous formic acid and heated at 90 °C for 10 min., cooled and concentrated using portions of ethanol to assist in removing formic acid. Chromatographic purification and/or crystallization of the residue yield the phosphonate oxime analog, **5.5**, of prednisolone.

A key precursor of this synthesis, diethyl (aminooxymethyl)phosphonate, can be obtained from diethyl (trifluoromethyl-sulfonyloxymethyl)phosphonate and N-(t-butoxycarbonyl)-hydroxylamine. Accordingly, N-(t-butoxycarbonyl)-hydroxylamine is dissolved in a solvent such as THF and treated with sodium hydride. When bubbling ceases, diethyl (trifluoromethylsulfonyloxymethyl)-phosphonate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) is added. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the N-Boc protected diethyl (aminooxymethyl)phosphonate is isolated by chromatography. The N-Boc protecting group is then removed by treatment of trifluoroacetic acid, affording the desired diethyl (aminooxymethyl)phosphonate.

Example 7



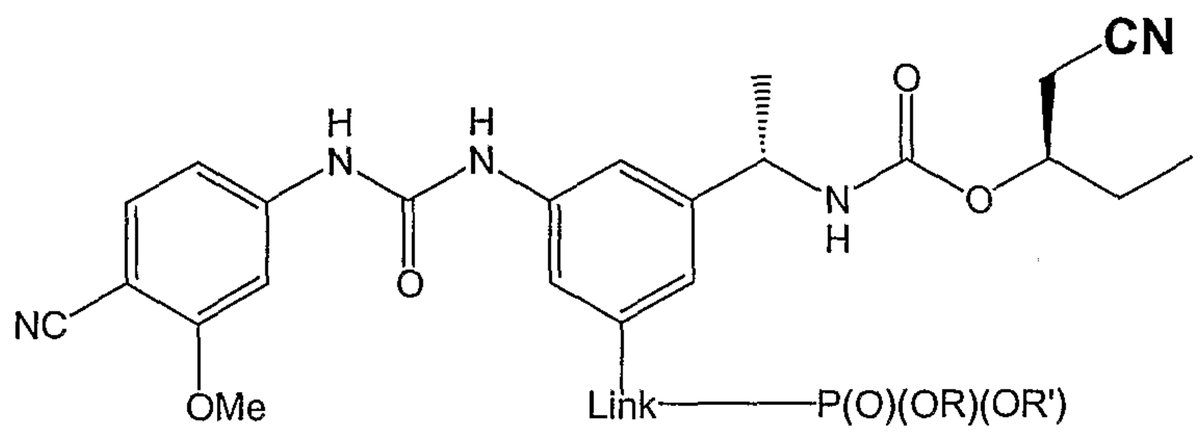
Prednisolone, **6A**, is reduced to 1,2-dihydroprednisolone, **7.1**, using a rhodium catalysis such as tris(triphenylphosphine)rhodium(I) chloride under hydrogen according to a procedure such as that reported by Procopiou, P. et al, *J. Med. Chem.*, **2001**, *44*, 602-612. The dihydroxy ketone group on the D ring of the steroid is then protected using the method described in Example 6, before formylation at the C-2 position. For example, the bis-(methylenedioxy) intermediate, **7.2**, is treated with freshly distilled ethyl formate and sodium hydride in a solvent such as toluene. The reaction is quenched with aqueous solution of a weak base such as potassium dihydrogen phosphate. The crude product is purified by a general method such as crystallization, affording the 2-formyl intermediate, **7.3**. This 2-formyl compound is condensed with a phosphonate-substituted phenylhydrazine to yield, after removal of the bis-(methylenedioxy) protecting group, the desired phosphonate pyrazole analog, **7.4**, of prednisolone.

A key precursor, 3-[(diethylphosphono)-methoxy]phenylhydrazine, **7.5**, can be made starting from diethyl (trifluoromethylsulfonyloxymethyl)-phosphonate and 3-nitrophenol. 3-Nitrophenol is treated with a base such as

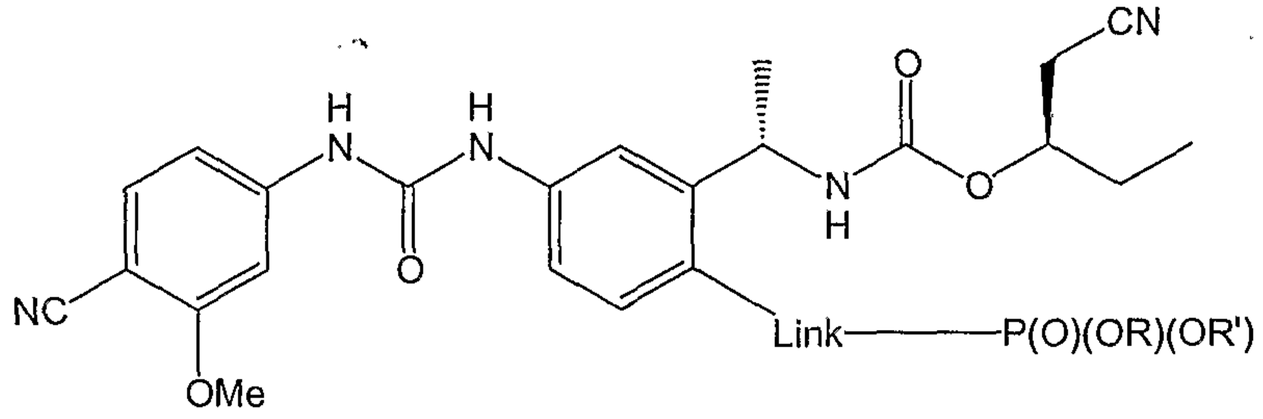
sodium hydroxide and then *O*-alkylated with diethyl (trifluoromethylsulfonyl-oxymethyl)phosphonate. The nitro group is reduced with tin(II) chloride and subsequently converted to the aryl hydrazine by diazotization and reduction with sodium sulfite (*Chem. Ber.*, **1960**, *93*, 540) or tin(II) chloride (*J. Med. Chem.*, **2001**, *44*, 4031).

Examples 8-13

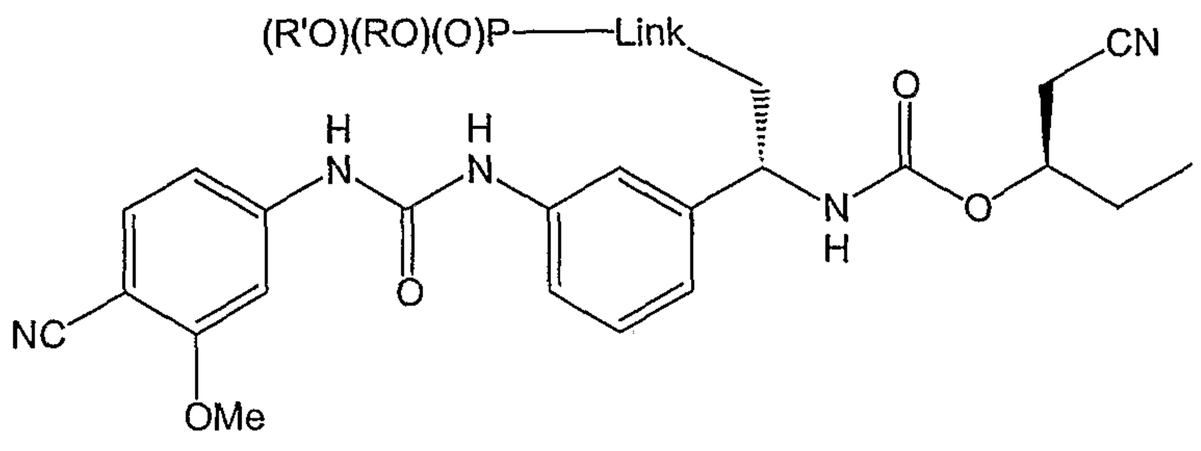
Synthetic methodologies and intermediate compounds that can be used to prepare VX-148 analogs of formulae A, B, or C are described in Examples **8-13**. The below compounds are representative examples of compounds of Formulae **6**, **7**, and **8**.



A



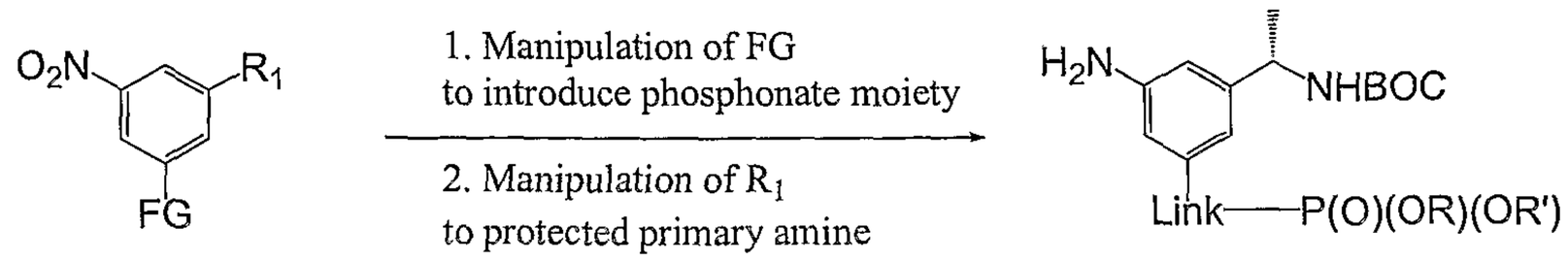
B



C

Link includes 0-8 atoms; 2 - 6 is preferred.

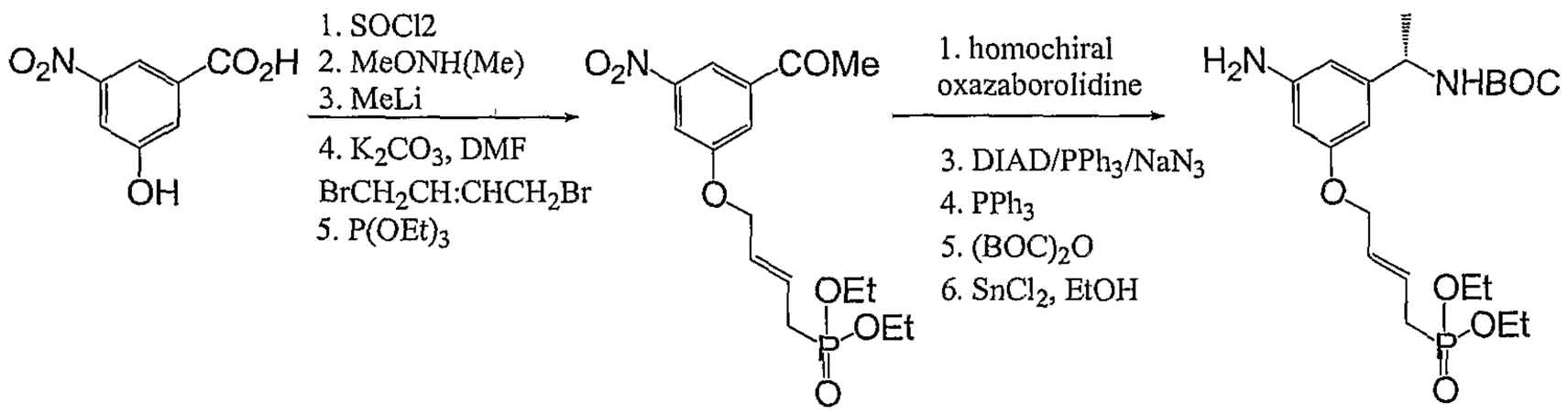
Example 8



R_1 = 1-carbon substituent;
FG = functional group

A general scheme that is useful for converting a 3,5-difunctionalized nitrobenzene derivative to an aniline that can be used to prepare a VX-148 analog of the invention is illustrated above.

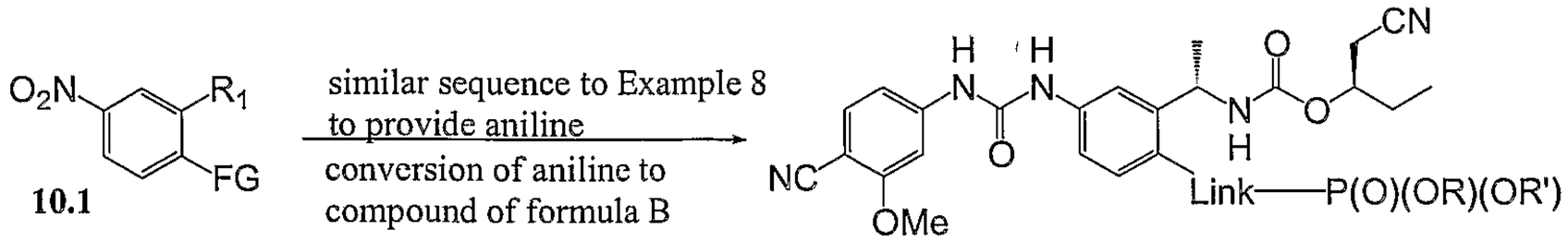
Example 9



3-Hydroxy-5-nitro-benzoic acid is heated briefly in thionyl chloride to generate the acid chloride. The acid chloride is condensed with O,N-dimethyl-hydroxylamine in the presence of a base such as triethylamine to produce the Weinreb amide which, upon reaction with methyl lithium, provides the acetophenone derivative. The acetophenone derivative is treated with a base such as potassium carbonate in a dipolar aprotic solvent such as dimethyl-formamide, in the presence of an excess of *E*-1,4-dibromobutene. The monobromide is isolated by chromatography and then subjected to treatment with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, **1988**) to generate the desired phosphonate diethyl ester. Thereafter, the carbonyl of the acetophenone is reduced enantioselectively using an appropriate homochiral oxazaborolidine such as that described by Corey (*J. Am. Chem. Soc.*, **1987**, *109*, 5551), and the resulting alcohol is displaced by azide using a method such as that described by Mitsunobu (*Bull. Chem. Soc. Japan.*, **1971**, *44*, 3427). The azide is reduced to the amine under Staudinger conditions (*Helv. Chim. Act.*, **1919**, *2*, 635) and protected as the t-butyl carbonate. Finally, the desired aniline

intermediate is generated by tin (II)-mediated reduction of the nitrobenzene. The aniline is converted to a compound of Formula **A** (also Formula **6**) using coupling reactions similar to those described in U.S. Patent No. 6,054,472 and U.S. Patent No. 6,344,465.

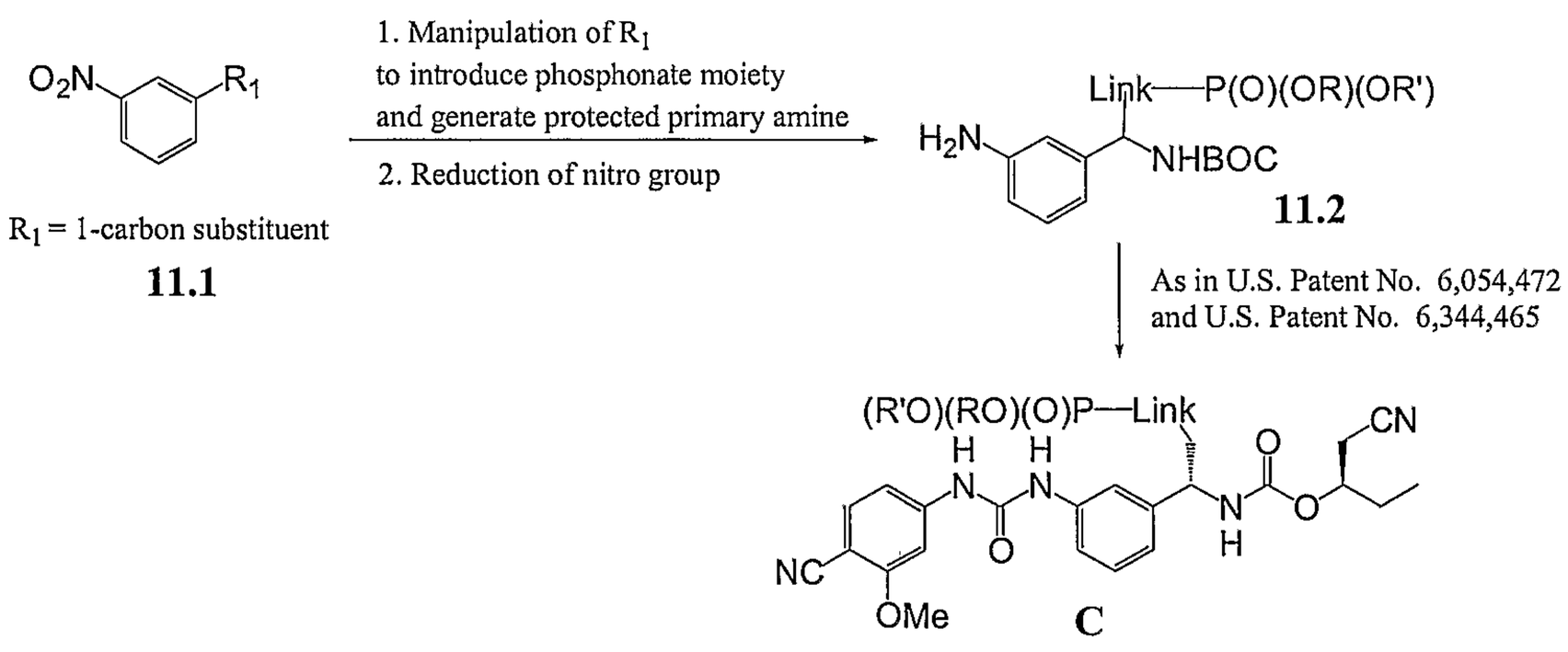
Example 10



R_1 = 1-carbon substituent;
FG = functional group

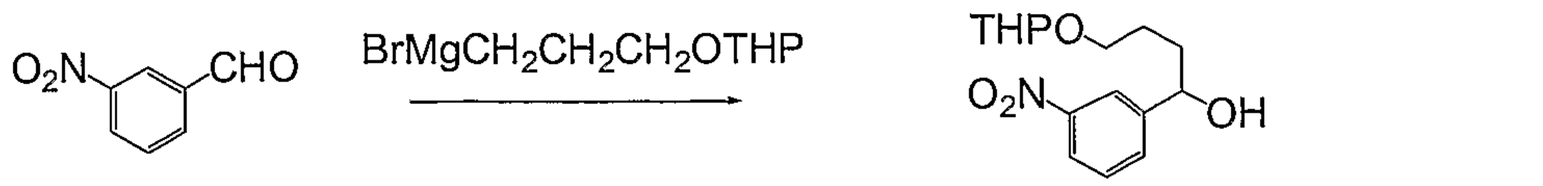
A general scheme that is useful for converting a 3,4-difunctionalized nitrobenzene derivative, **10.1**, to an aniline, which can be converted to a compound of Formula **B** (also Formula 7) using coupling reactions similar to those described in U.S. Patent No. 6,054,472 and U.S. Patent No. 6,344,465, is illustrated above.

Example 11

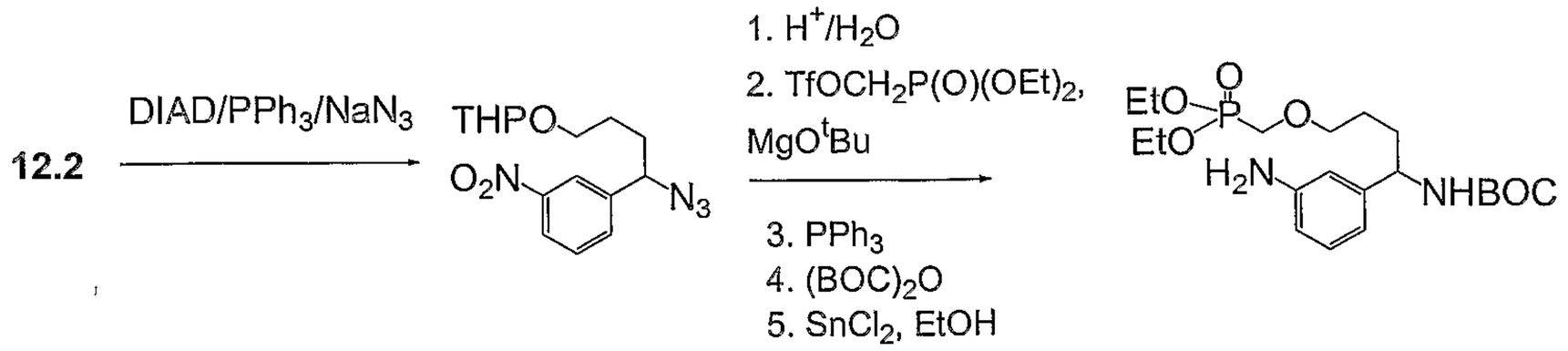


Manipulation of a 3-substituted nitrobenzene, **11.1,** provides aniline, **11.2,** which can be converted to a compound of formula **C** (also Formula **8**) using coupling reactions similar to those described in U.S. Patent No. 6,054,472 and U.S. Patent No. 6,344,465.

Example 12

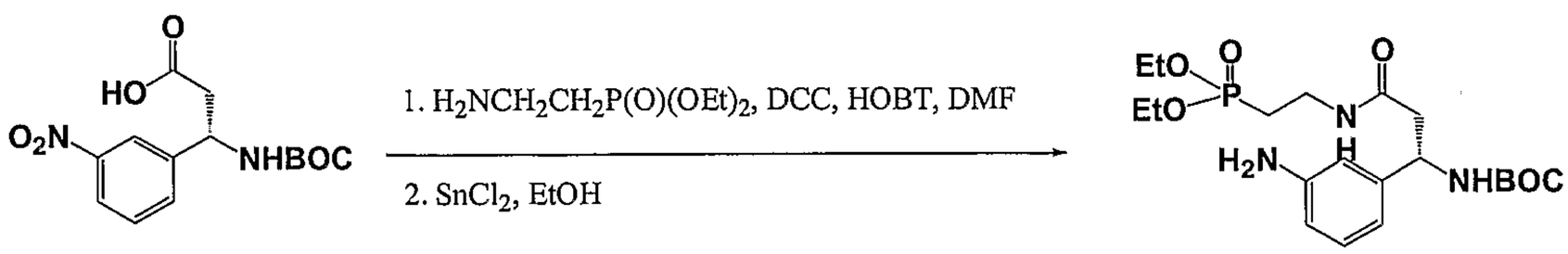


12.1 **12.2**



3-Nitrobenzaldehyde, **12.1**, reacts with a Grignard reagent to introduce a tether bearing a protected alcohol and simultaneously to generate a benzylic alcohol, as shown. The alcohol, **12.2**, is displaced by an azide in a manner similar to that described for Example 9. After deprotection, the liberated alcohol is alkylated with diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) using a base such as magnesium tert-butoxide in a solvent such as tetrahydrofuran. Subsequent transformations of the azide and nitro groups proceed in a fashion similar to that described in Example 9. See Batt et al, *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 1549.

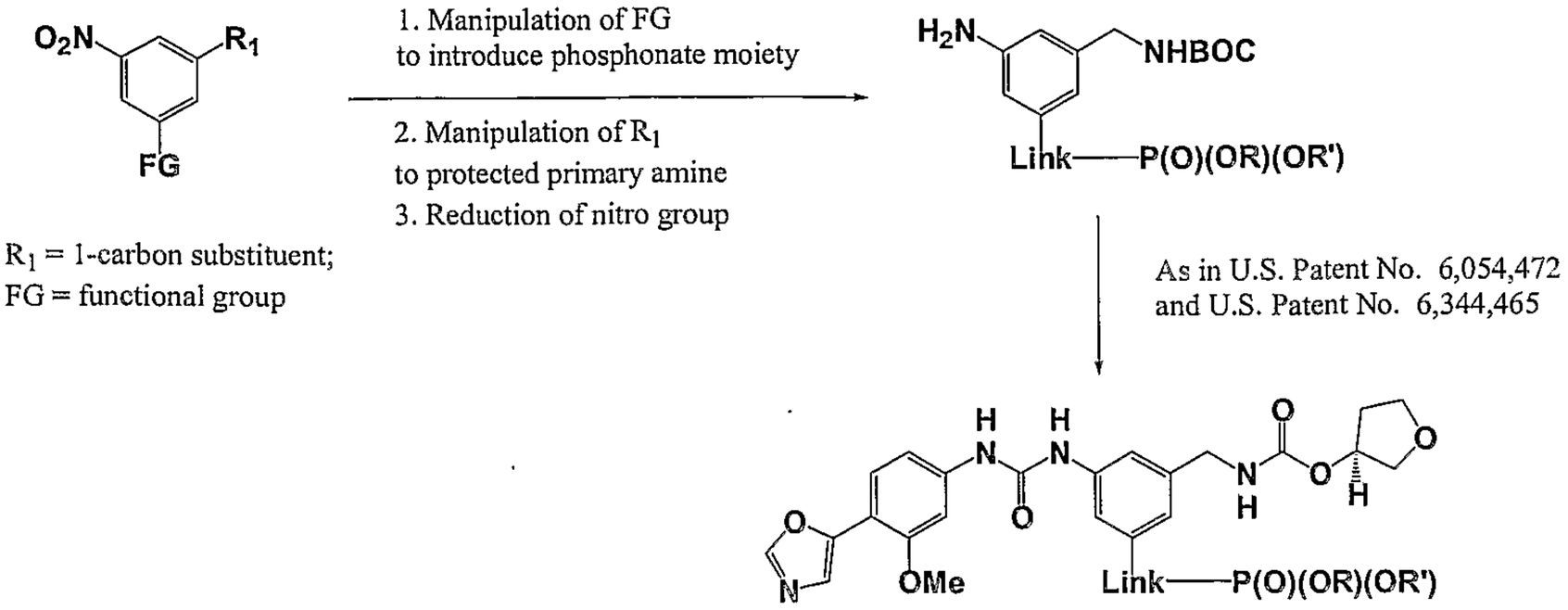
Example 13



13.1

3-*tert*-Butoxycarbonylamino-3-(3-nitro-phenyl)-propionic acid, **13.1**, (commercially available) is coupled with 2-aminoethylphosphonic acid diethyl ester (commercially available) using standard reagents for the formation of a secondary amide such as dicyclohexylcarbodiimide (DCC) and hydroxy-benztriazole (HOBT), in a solvent such as dimethylformamide. Subsequent reduction of the nitro group proceeds in a fashion similar to that described in Example 9.

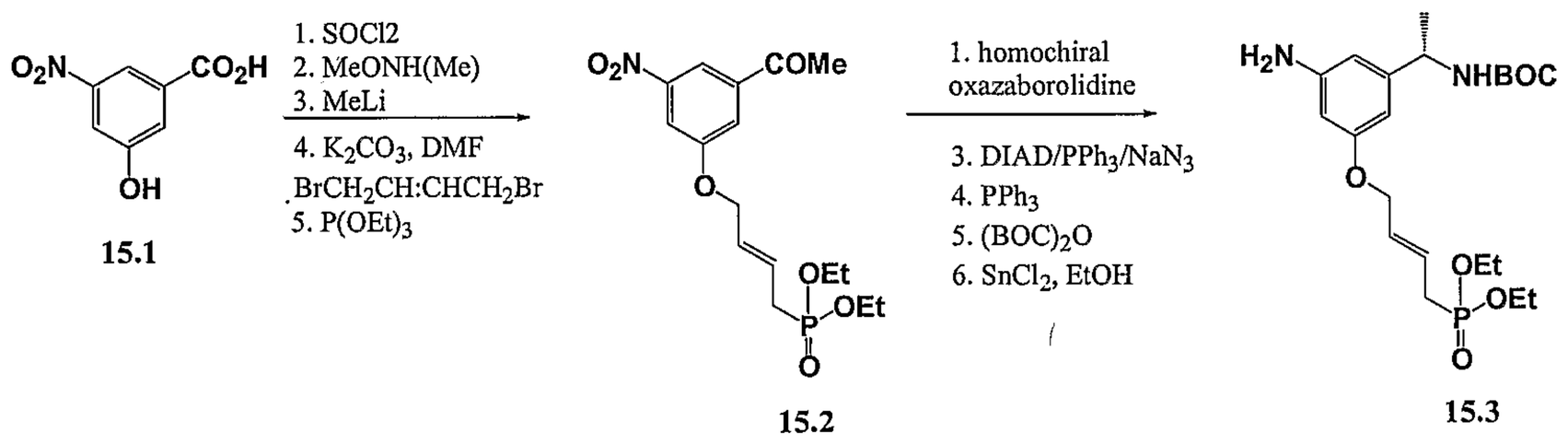
Examle 14



R1 = 1-carbon substituent;
FG = functional group

The above scheme illustrates a general route that can be used to prepare compounds of Formula **9**.

Example 15

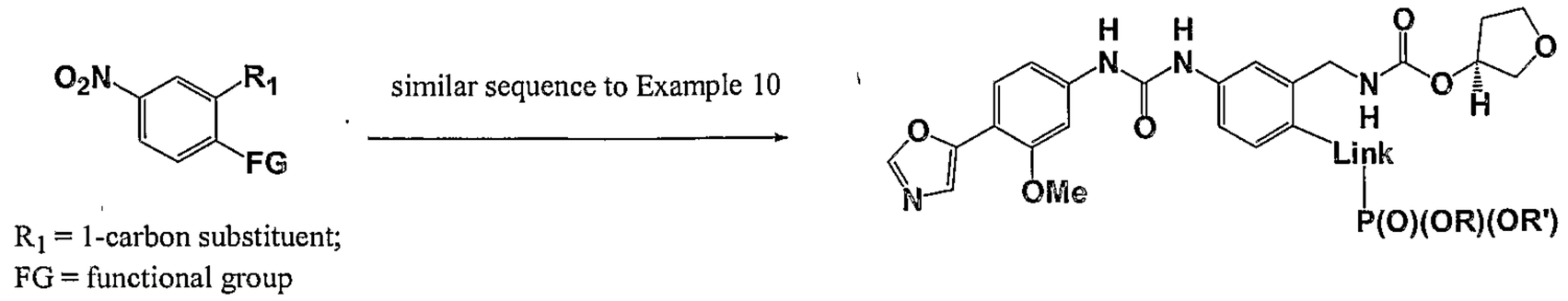


15.1 **15.2** **15.3**

3-Hydroxy-5-nitro-benzoic acid, **15.1**, is heated briefly in thionyl chloride to generate the acid chloride. This is then condensed with O,N-dimethyl-hydroxylamine in the presence of a base such as triethylamine to produce the Weinreb amide which, upon reaction with methyl lithium, gives the acetophenone derivative. This is then treated with a base such as potassium carbonate in a dipolar aprotic solvent such as dimethyl-formamide, in the presence of an excess of *E*-1,4-dibromobutene. The monobromide is isolated by chromatography and then subjected to treatment with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, **1988**) to generate the desired phosphonate diethyl ester, **15.2**. Thereafter, the carbonyl of the acetophenone is reduced enantioselectively using an appropriate homochiral oxazaborolidine such as that described by Corey (*J. Am. Chem. Soc.*, **1987**, *109*, 5551), and the resulting alcohol is displaced by azide using a method such as that described by Mitsunobu (*Bull. Chem. Soc. Japan.*, **1971**, *44*, 3427). The azide is

reduced to the amine under Staudinger conditions (*Helv. Chim. Act.*, **1919**, *2*, 635) and protected as the t-butyl carbonate. Finally, the desired aniline intermediate, **15.3**, is generated by tin (II)-mediated reduction of the nitrobenzene.

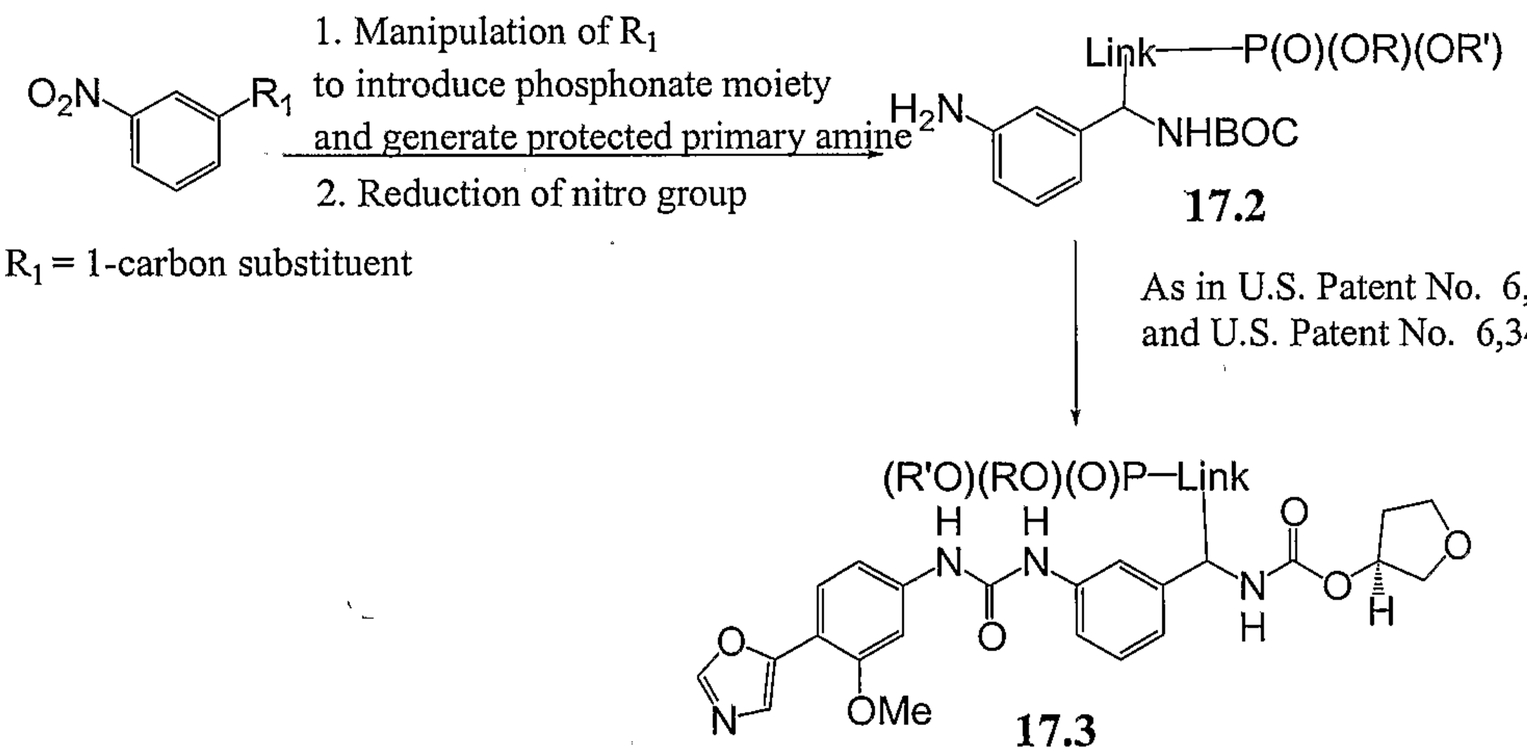
Example 16



R_1 = 1-carbon substituent;
FG = functional group

Reagents suitable for use in the synthesis of representative compounds of Formula **10** may be made by routes analogous to that shown in Example 10, starting from 2-hydroxy-5-nitro-benzoic acid.

Example 17

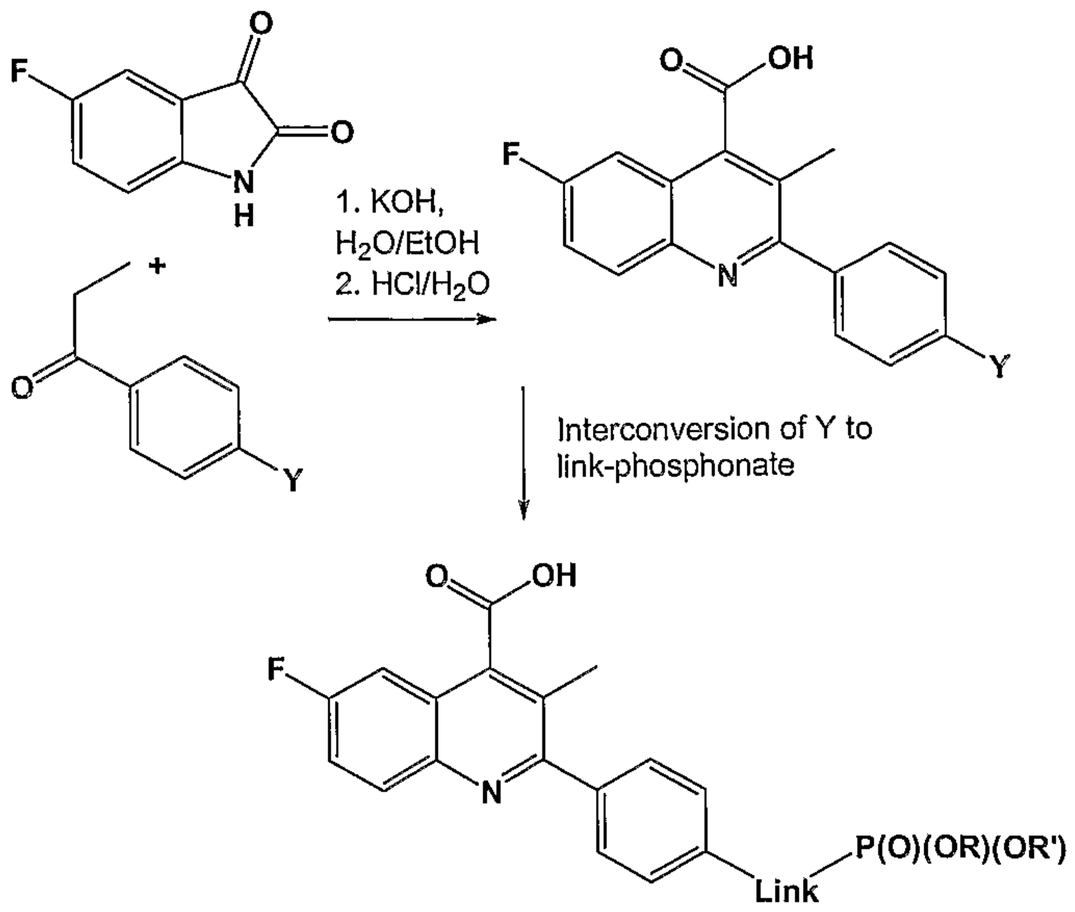


R_1 = 1-carbon substituent

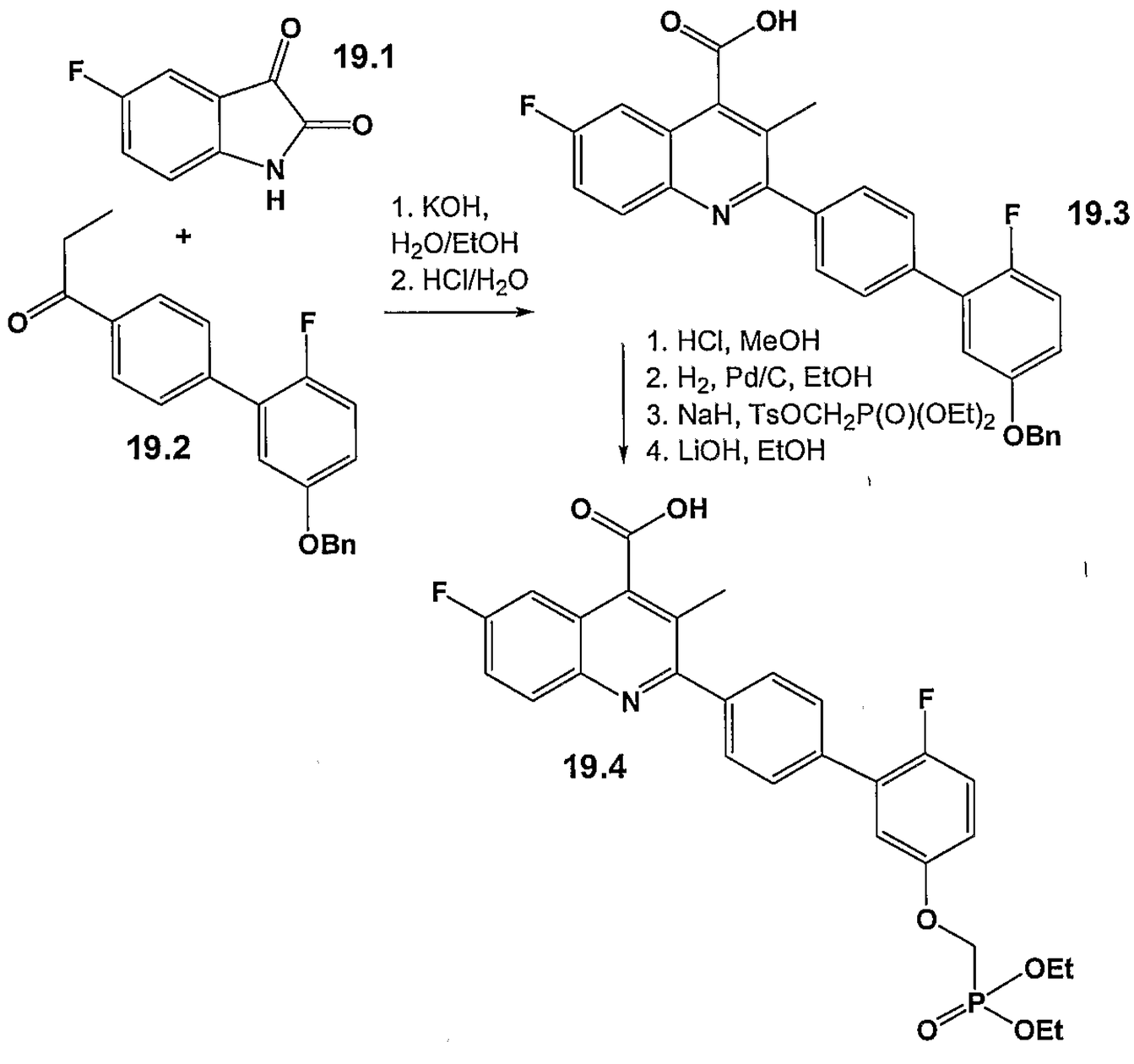
Representative compounds of Formula **11** can be prepared as illustrated in Examples 11-13, above. The preparation of anilines of formula, **17.2**, is illustrated in Examples 11-13 above. Anilines of formula, **17.2**, can be converted to compounds of Formula **11** using procedures similar to those described in U.S. Patent No. 6,054,472 and U.S. Patent No. 6,344,465.

Example 18

The following is a general route that can be used to prepare compounds of Formula **15**.



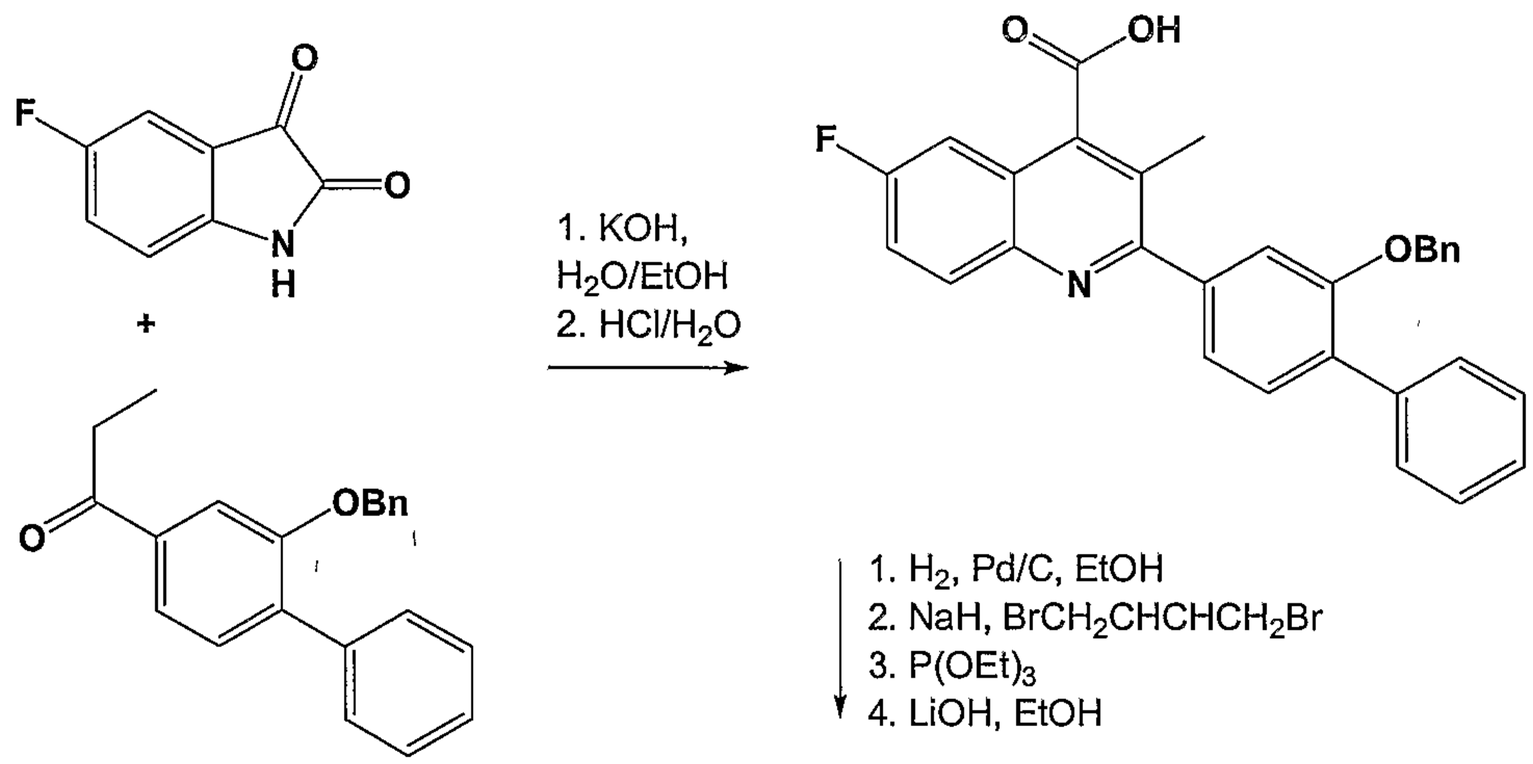
Example 19

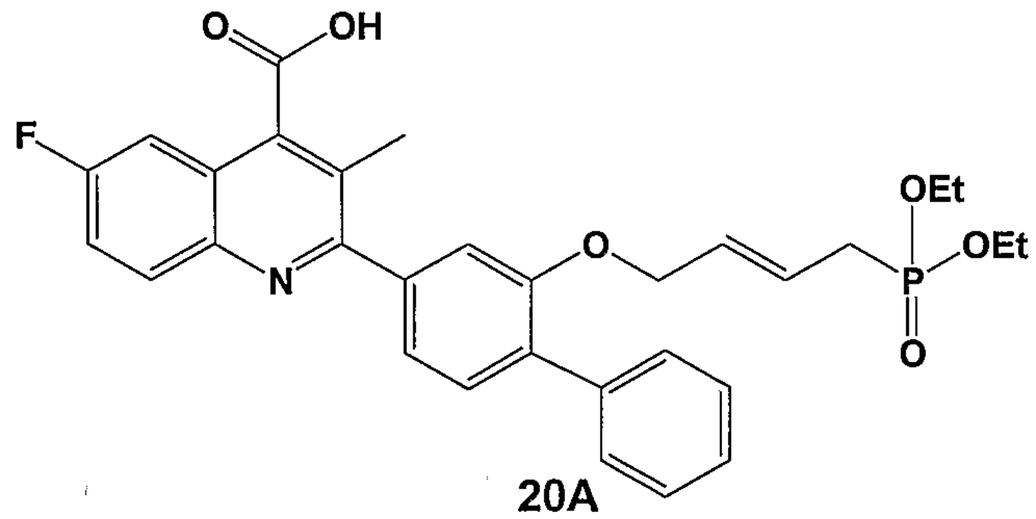


The initial Pfitzinger condensation of compound **19.1** and compound **19.2** is achieved in a single step using potassium hydroxide with acidic work-up, as shown. Alternatively, the initial aldol condensation may be performed using diethylamine in ethanol, and the quinoline ring may be formed in a second step mediated by an acid such as hydrochloric acid in a solvent such as 1,4-dioxane. Following removal of the benzyl protecting group via hydrogenation, the phenol

can be treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyltriflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) is added, yielding the desired phosphonate diester. The carboxylate is deprotected by treatment with lithium hydroxide in ethanol to provide compound **19.4** (which is a compound of Formula **12**).

Example 20



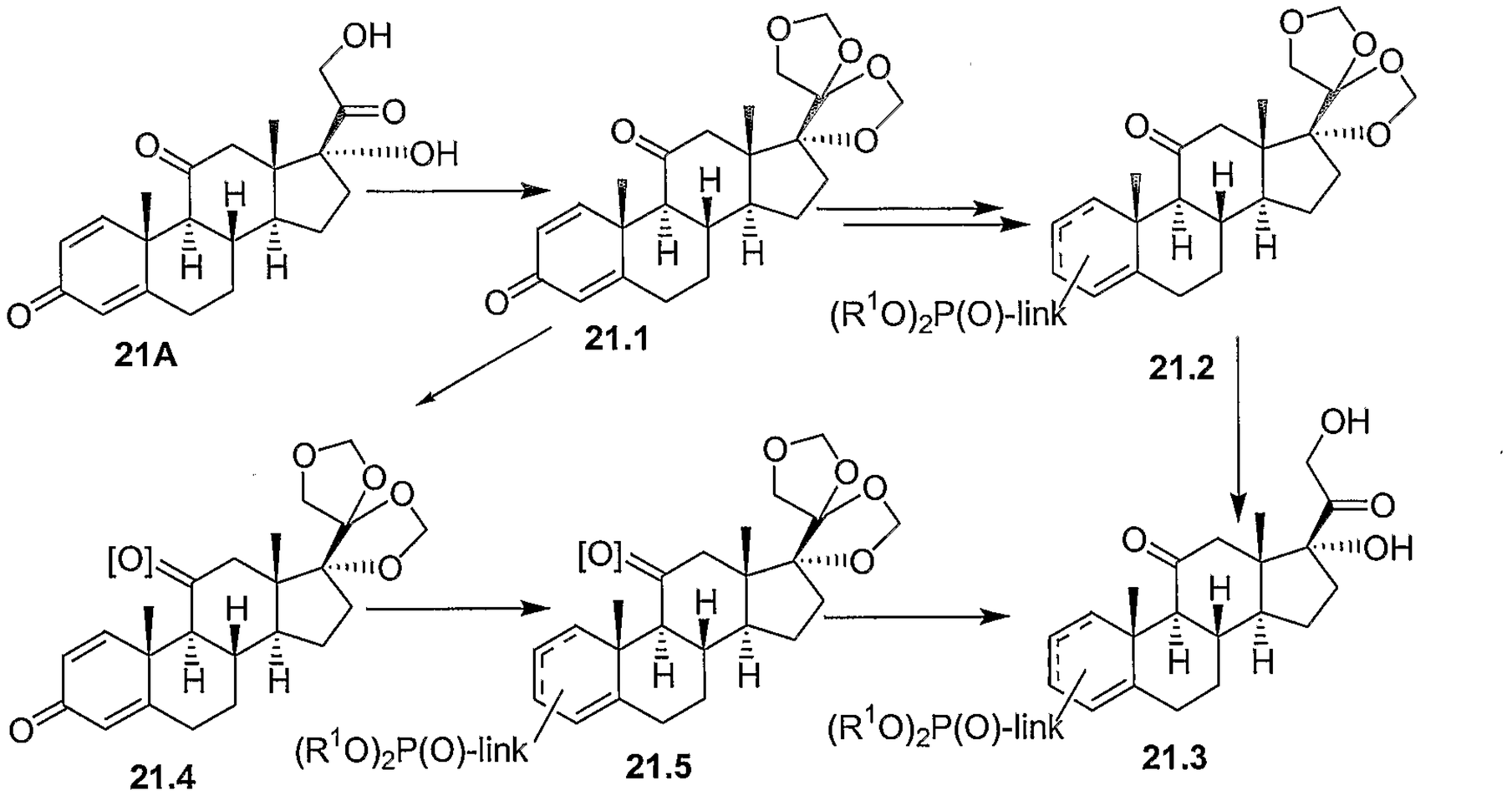


20A

The synthesis is similar to that depicted in Example 19 except that, following deprotonation of the phenol, *E*-1,4-dibromobutene is added in excess. After quenching the reaction with aqueous ammonium chloride and extracting the product with an organic solvent such as ethyl acetate, the mono-alkylated product is isolated by chromatography. The resulting bromide is heated with triethylphosphite in a solvent such as toluene to generate the diethyl ester of the desired phosphonic acid, and the carboxylic acid is deprotected as before to provide compound **20A** (which is a compound of Formula **12**).

Example 21

The structures of Prednisone, **21A** (U.S. Patent No. 2,897,464), and representative phosphonate esters are shown below, in which the substituent R^1 is H, alkyl, alkenyl, aryl or aralkyl. The phosphonate compounds incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link."



For example, the above scheme depicts a protection-deprotection sequence in which the steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety. In this sequence, Prednisone, **21A**, is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **21.1**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester, **21.2**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the triol, **21.3** (which is a compound of Formula **23**).

Optionally, depending on the nature of the reactions employed, the 11-ketone group in the BMD compound, **21.1**, is protected before introduction of the phosphonate group. The ketone is protected, for example, as the cyclic

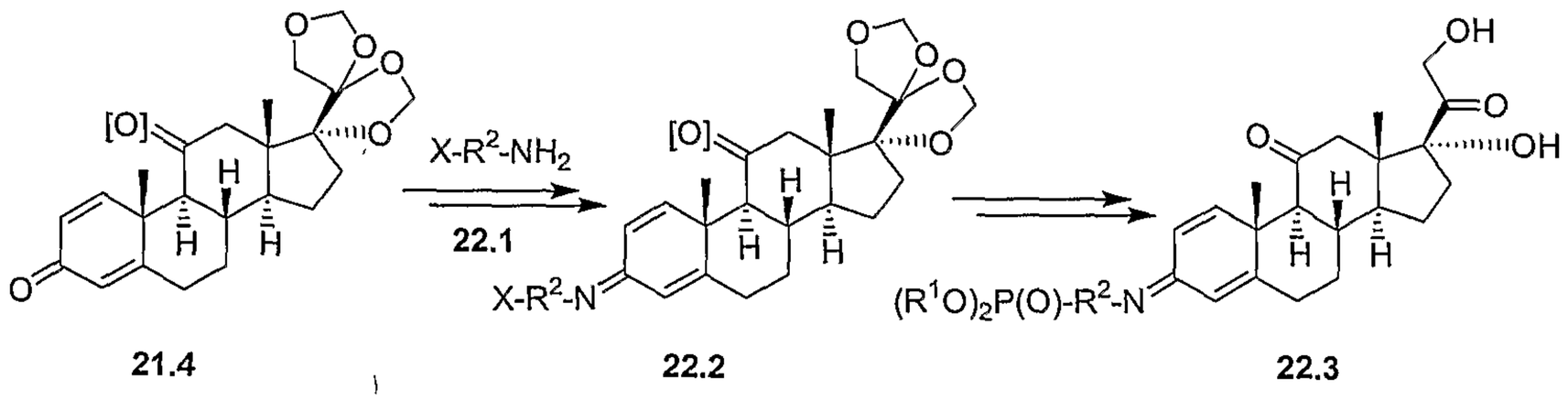
ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, **1955**, *77*, 1904. Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc., Chem. Comm.*, 1351, 1987.

Alternatively, the 11-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone, **21.1**, with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.*, **1970**, *50*, 102. The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, **1979**, *101*, 5841.

Alternatively, the 11-ketone is protected as the diethylamine adduct. In this procedure, the substrate, **21.1**, is reacted with titanium tetrakis-(diethylamide), as described in *J. Chem. Soc., Chem. Comm.*, 406, 1983, to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The 11-protected BMD compound, **21.4**, is then converted, using the procedures described below, into the phosphonate, **21.5**. Deprotection then yields the 11-keto diol, **21.3**.

Example 22

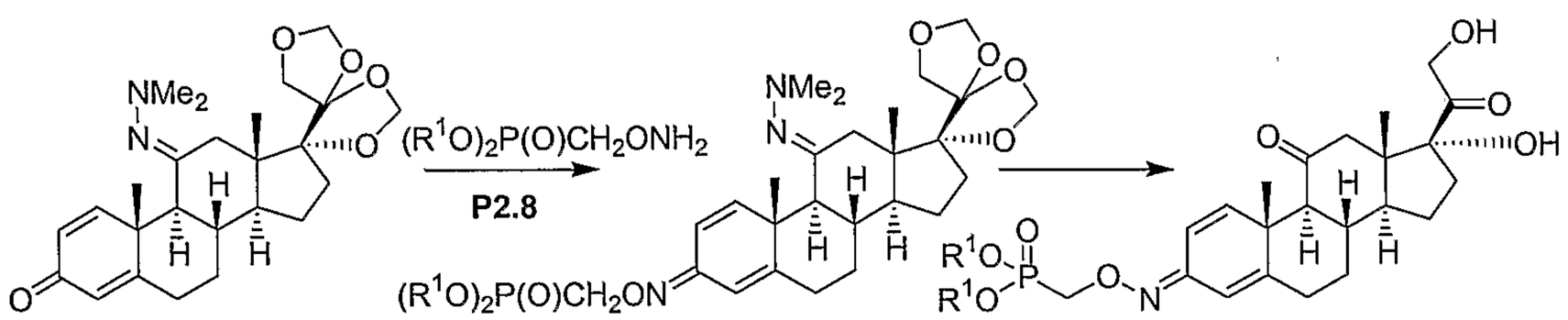


The preparation of phosphonates, **22.3**, in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain are depicted above. In this procedure, the doubly-protected derivative, **21.4**, is reacted with an amine or hydroxylamine, **22.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally

incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent.

For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The protecting groups are then removed to afford the ketodiol, **22.3** (which is a compound of Formula **16**).

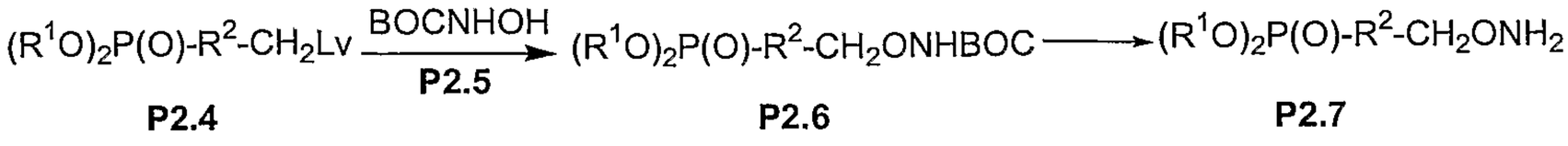
Example 23



23.1 **P2.9** **P2.10**

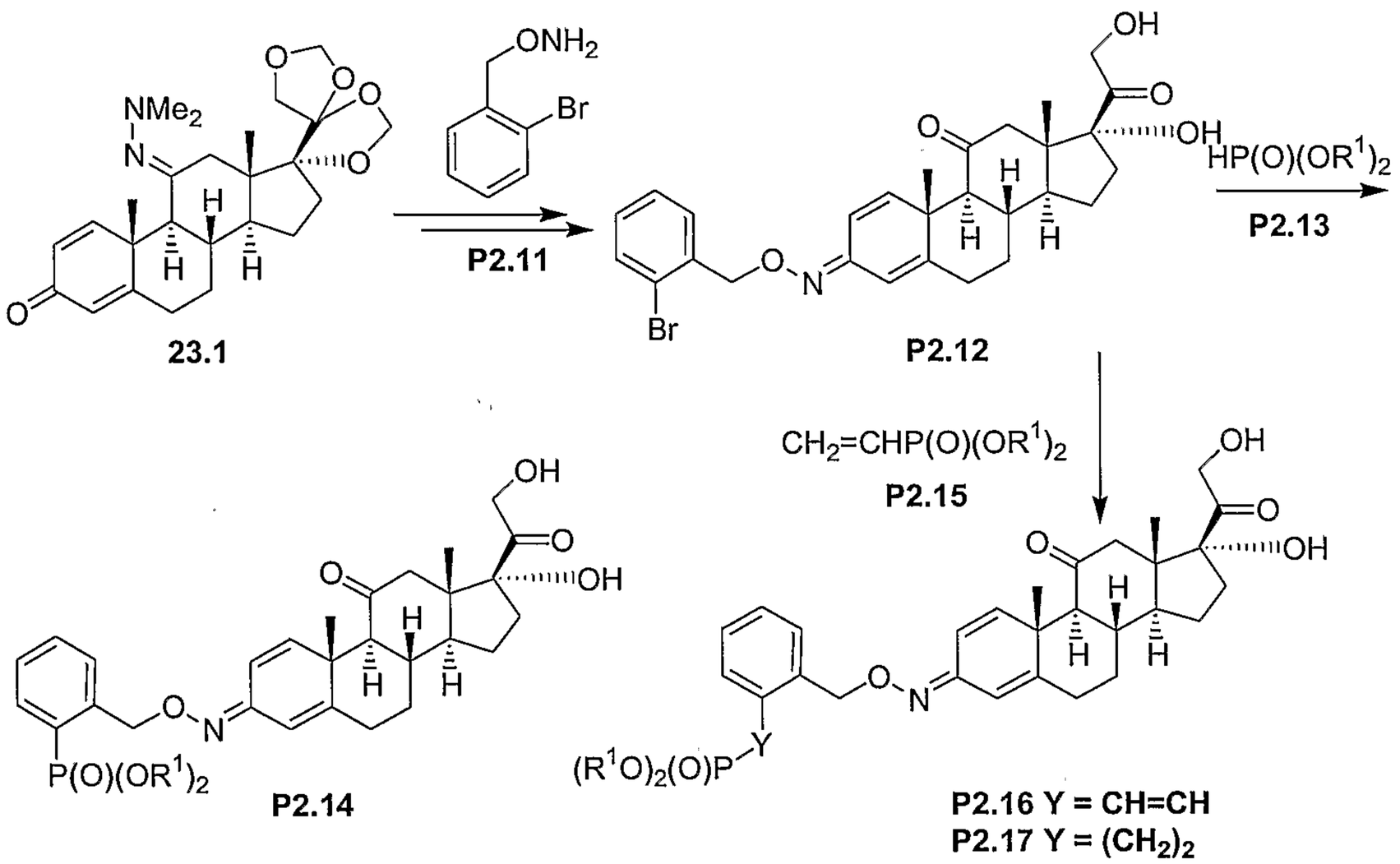
The preparation of phosphonates, **P2.10**, in which the phosphonate is attached by means of an iminoxy group, is illustrated above. The substrate, **23.1**, a compound of Formula **23.1**, in which the 11-ketone is protected as the dimethyl hydrazone, is reacted with a dialkyl phosphonomethyl hydroxylamine, **P2.8**, prepared from a dialkyl trifluoromethyl-sulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **P2.9**, which is deprotected by reaction with 50% aqueous acetic acid, to afford the diol, **P2.10**. The oxime forming reaction is typically performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

The intermediate dialkyl phosphonomethyl hydroxylamine, **P2.8**, (compound, **2.7**, wherein R^2 is a bond) can be prepared as follows.



A phosphonate, **P2.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **P2.5**, (Aldrich) to produce the ether, **P2.6**. The reaction is typically conducted between equimolar amounts of the reactants in a polar solvent such as dimethyl-formamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example, by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **P2.7**.

Example 24

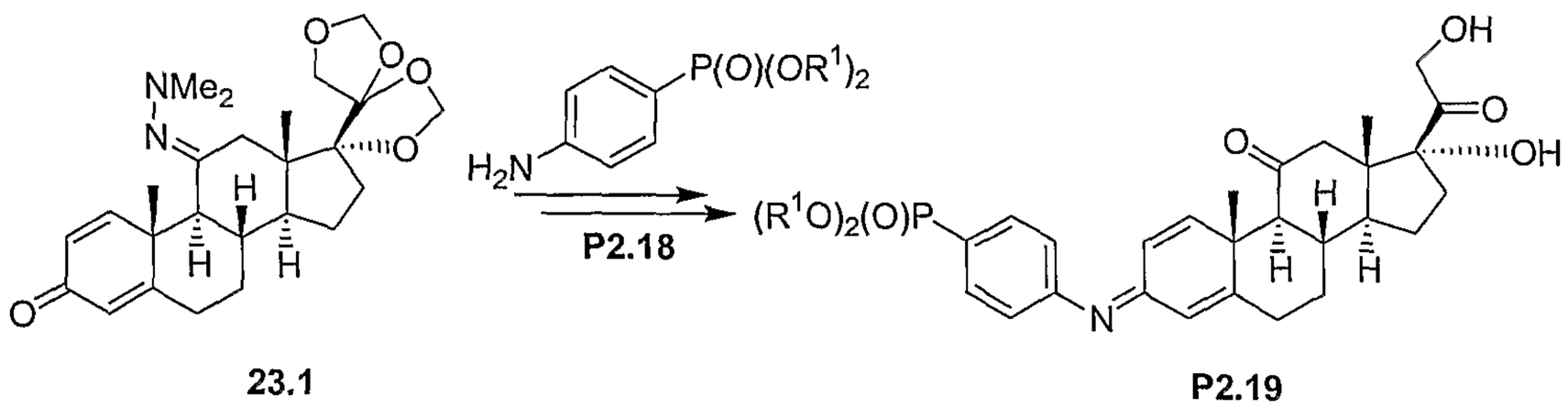


The dienone, **23.1**, is reacted, as described in Example 23, with O-(2-bromobenzyl)hydroxylamine, **P2.11**, prepared from 2-bromobenzyl bromide, to give, after deprotection, the oxime, **P2.12**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **P2.13**, to afford the phosphonate, **P2.14**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is typically performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound, **P2.12**, is coupled with a dialkyl vinylphosphonate, **P2.15** (Aldrich), to afford the phosphonate, **P2.16**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethyl-formamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **P2.16**, is reduced, for example by reaction with diimide, to produce the saturated analog, **P2.17**. The reduction of olefinic bonds is described in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the benzyloxy reagent, **P2.11**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **P2.14**, **P2.16** and **P2.17** are obtained.

Example 25

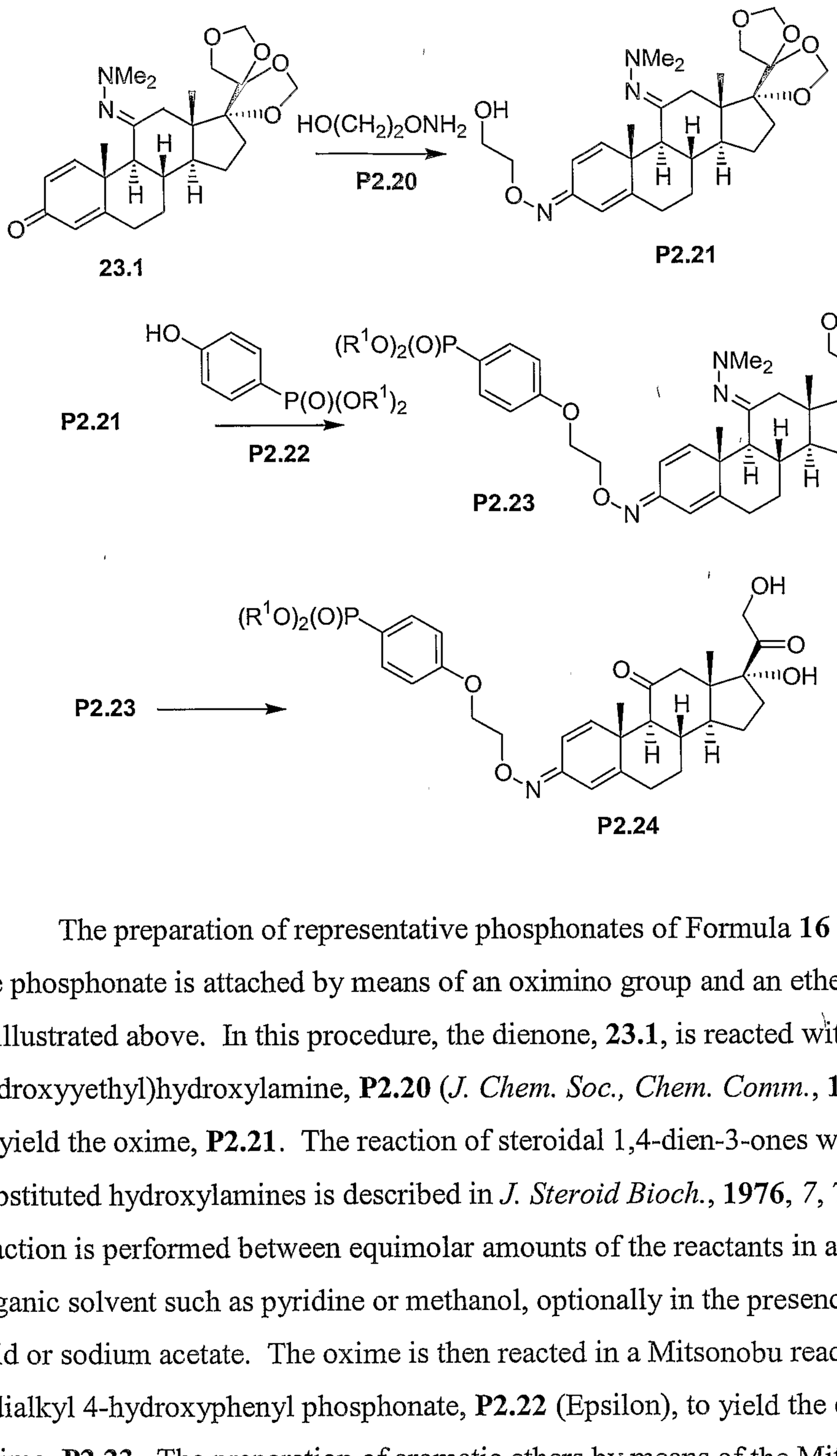


23.1 **P2.19**

The preparation of phosphonates of Formula **16** wherein the phosphonate is attached by means of an imino group is illustrated above. The substrate, **23.1**, is reacted with a dialkyl 4-aminophenyl phosphonate, **P2.18** (Epsilon), to give, after deprotection, the imine product, **P2.19**. The reaction is typically conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the

presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Example 26

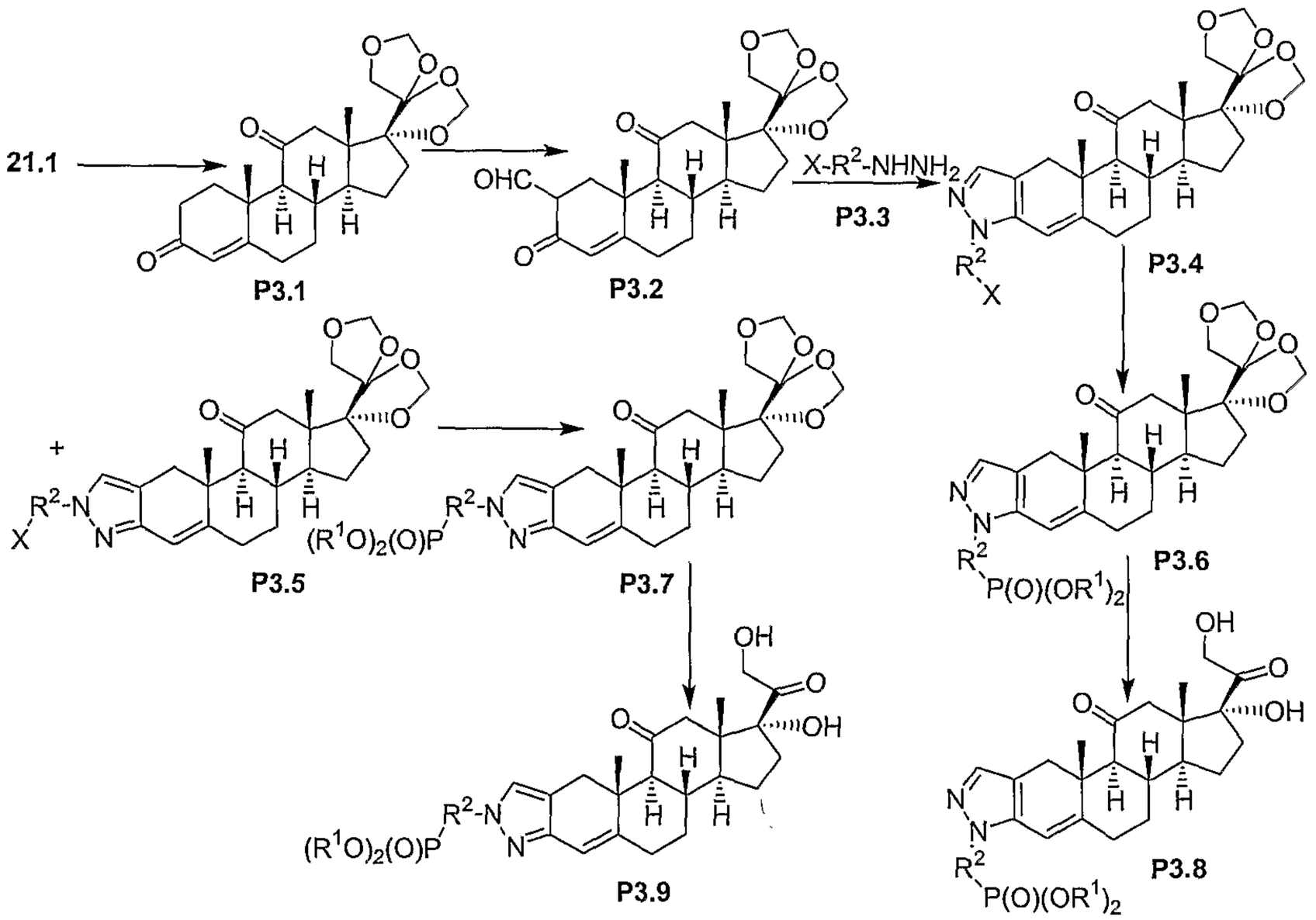


The preparation of representative phosphonates of Formula **16** wherein the phosphonate is attached by means of an oximino group and an ether linkage is illustrated above. In this procedure, the dienone, **23.1**, is reacted with O-(2-hydroxyyethyl)hydroxylamine, **P2.20** (*J. Chem. Soc., Chem. Comm.*, **1986**, 903), to yield the oxime, **P2.21**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795. The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then reacted in a Mitsonobu reaction with a dialkyl 4-hydroxyphenyl phosphonate, **P2.22** (Epsilon), to yield the ether oxime, **P2.23**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in "Comprehensive Organic

Transformations," by R. C. Larock, VCH, **1989**, p. 448, and in "Advanced Organic Chemistry," Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p. 153-4 and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656. The ether product, **P2.23**. is then converted into the ketodiol, **P2.24** (which is a compound of Formula **16**).

Using the above procedures, but employing, in place of the hydroxylamine, **P2.20**, different hydroxy-substituted hydroxylamines, and/or different hydroxy-substituted aryl phosphonates, the products analogous to **P2.24** are obtained.

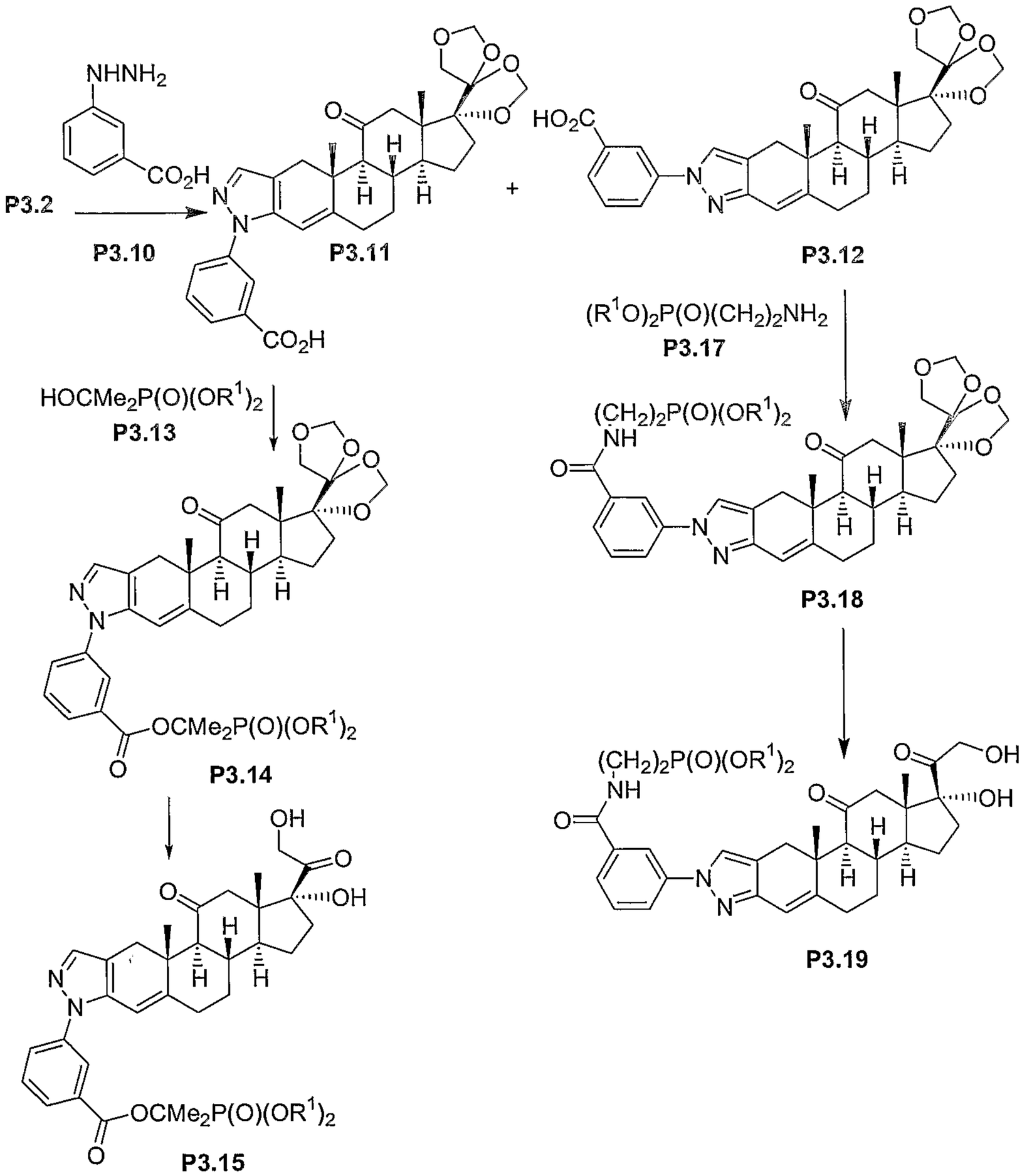
Example 27



The preparation of the phosphonate esters of Formulae **17** and **18** in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain. In this procedure, the BMD-protected dienone, **21.1**, is reduced to afford the 1,2-dihydro product, **P3.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride,

for example as described in *J. Med. Chem.*, **2001**, *44*, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **P3.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **P3.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **P3.4** and **P3.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **P3.4** and **P3.5**, are then transformed via the BMD-protected intermediates, **P3.6** and **P3.7**, into the phosphonates, **P3.8** and **P3.9**, which are compounds of Formulae **17** and **18** respectively.

Example 28



The preparation of phosphonates in which the phosphonate is attached by means of a phenyl ring and an ester or an amide linkage are illustrated above. The ketoaldehyde, **P3.2**, is reacted with 3-carboxyphenylhydrazine, **P3.10** (Apin), to give the pyrazoles, **P3.11** and **P3.12**. The 2'-substituted isomer, **P3.11**, is then reacted in dichloromethane solution at ambient temperature with one molar equivalent of a dialkyl 2-hydroxy-2-methylpropyl phosphonate, **P3.13** (French Patent No. 2,462,440), and dicyclohexylcarbodiimide, to yield the ester, **P3.14**. The protecting groups are then removed to yield the diol, **P3.15**, which is a compound of Formula **18**.

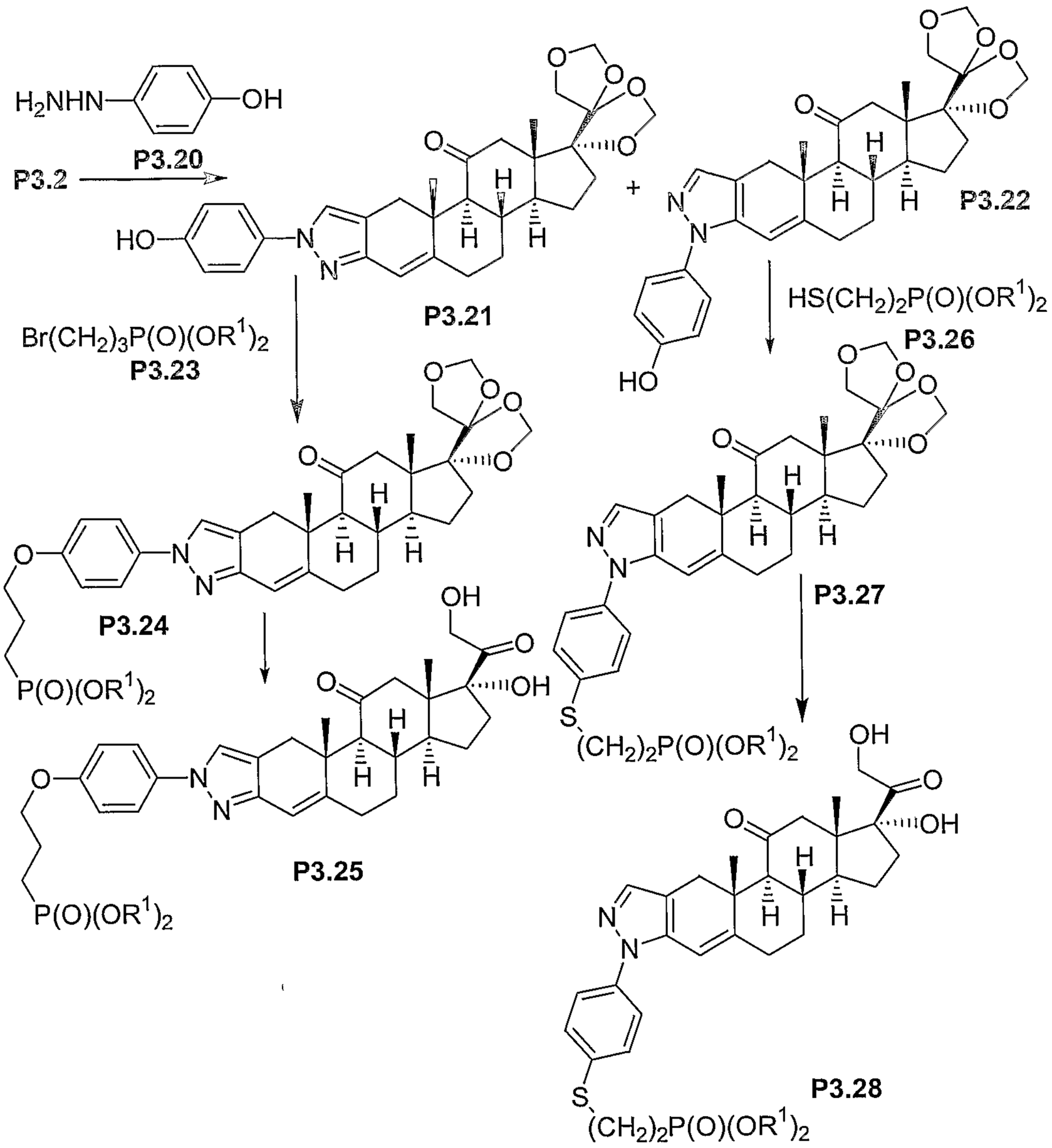
Alternatively, the 1'-substituted pyrazole, **P3.12**, is coupled with a dialkyl 2-aminoethyl phosphonate, **P3.17** (Aurora), to afford the amide, **P3.18**. The

preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R.Sandler and W. Karo, Academic Press, **1968**, p. 274, and "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxy-succinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. The product, **P3.18**, is then deprotected to give the diol, **P3.19** (which is a compound of Formula **17**).

Using the above procedures, but employing different amino or hydroxyl-substituted phosphonates, and/or different carboxy-substituted hydrazines, the products analogous to **P3.15** and **P3.19** are obtained. The functionalization procedures are interchangeable between the pyrazole substrates, **P3.11** and **P3.12**.

Example 29



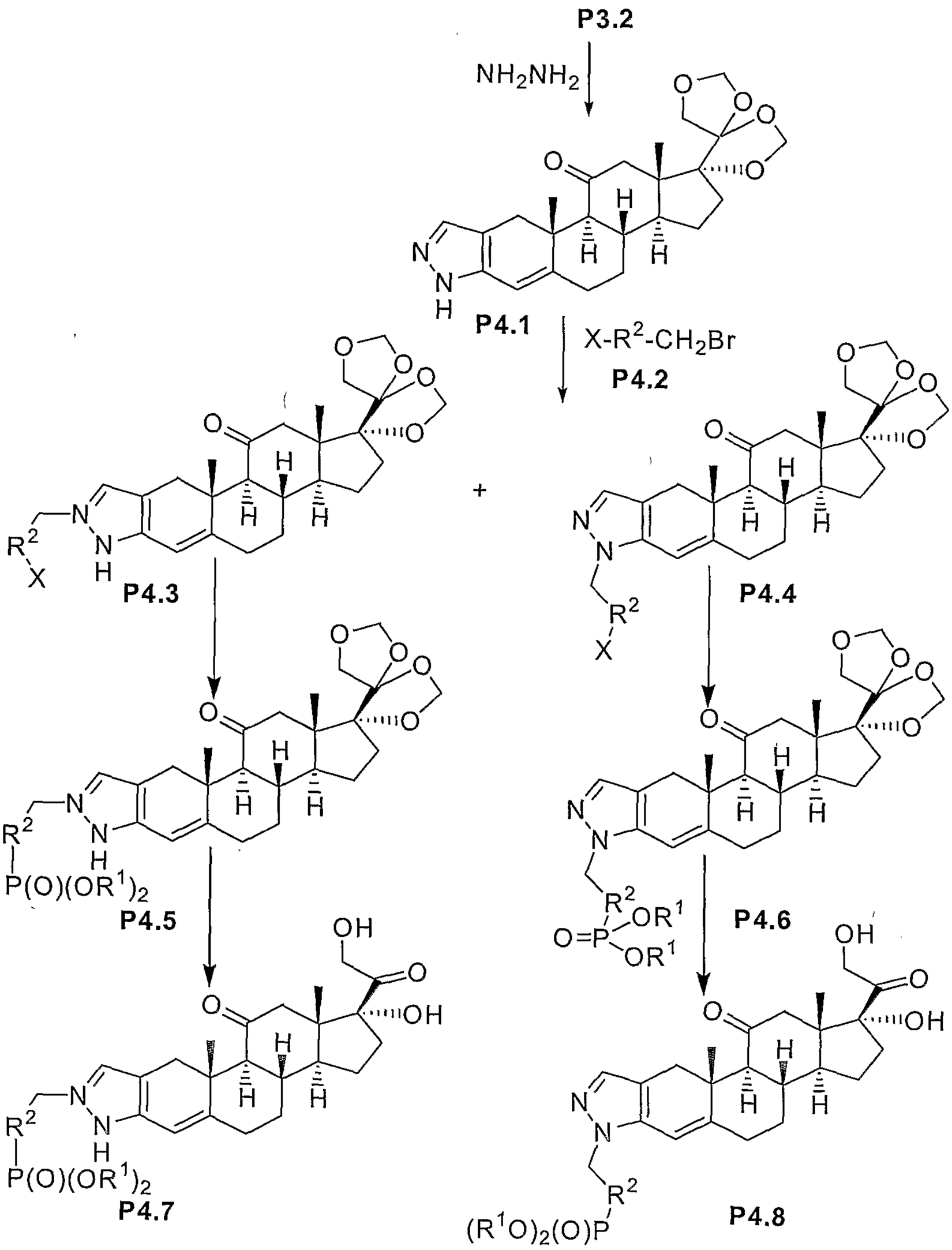
The preparation of the phosphonates of Formulae **17** and **18** wherein the phosphonate group is attached by means of a phenyl group and an alkoxy or alkylthio carbon chain is illustrated above. In this procedure, the ketoaldehyde, **P3.2**, is reacted with 4-hydroxyphenyl hydrazine, **P3.20** (EP 437 105), to produce the pyrazoles, **P3.21** and **P3.22**. The 1'-substituted isomer, **P3.21**, is reacted, in dimethylformamide solution at 70°, with a dialkyl bromopropyl phosphonate, **P3.23** (*J. Amer. Chem. Soc.*, **2000**, *122*, 1554), and potassium carbonate, to give the phosphonate, **P3.24**. The product is then deprotected to afford the diol, **P3.25**.

Alternatively, the 2'-substituted pyrazole, **P3.22**, is reacted in a Mitsonobu reaction, as described above, with a dialkyl mercaptoethyl

phosphonate, **P3.26** (*Zh. Obschei. Khim.*, **1973**, *43*, 2364), to prepare the thioether phosphonate, **P3.27**, which is deprotected to give the diol, **P3.28**.

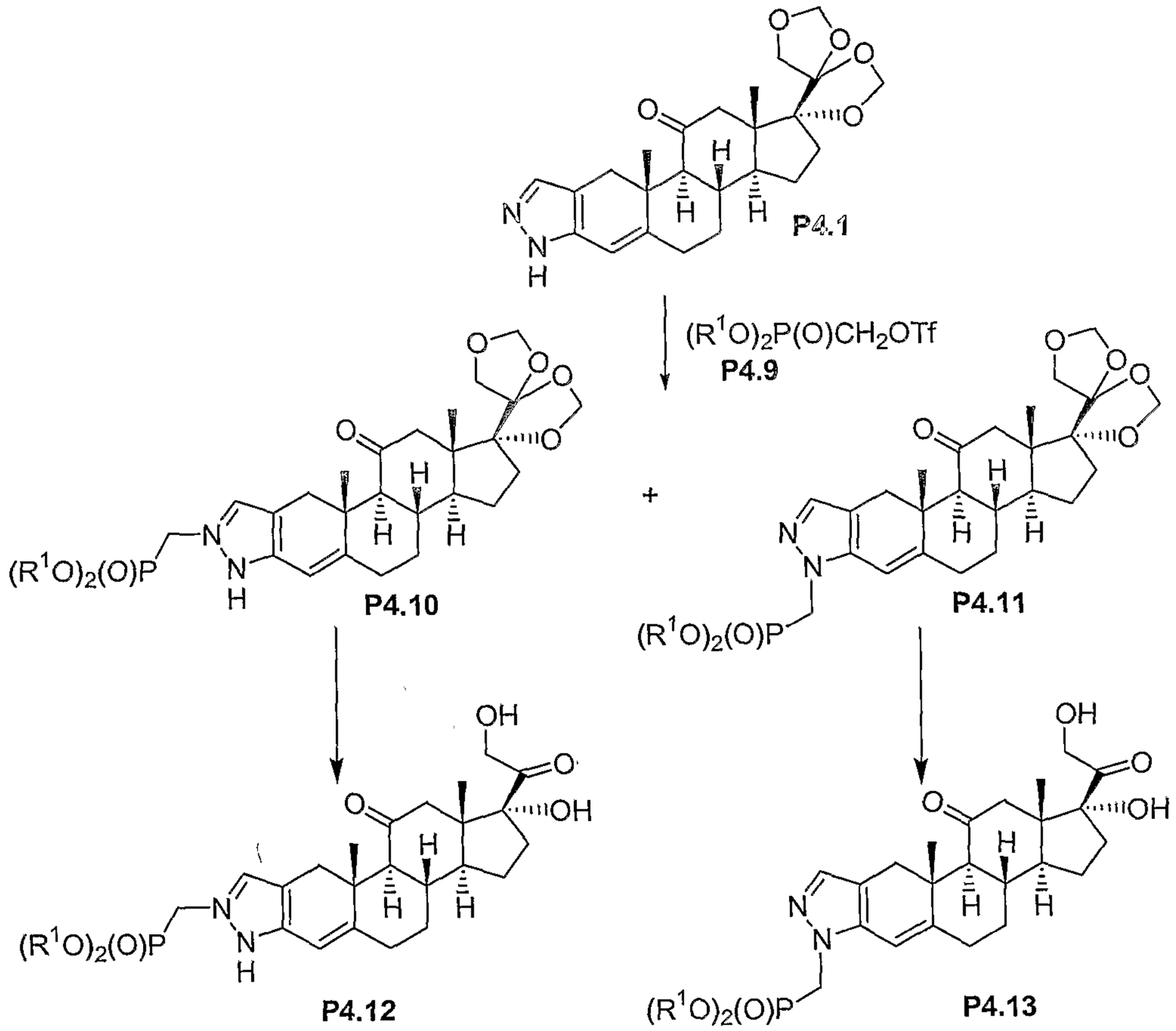
Using the above procedures, but employing, in place of the hydroxyphenyl reagent, **P3.20**, different hydroxy-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl bromo or mercapto-substituted phosphonates, the products analogous to the compounds, **P3.25** and **P3.28** are obtained.

Example 30



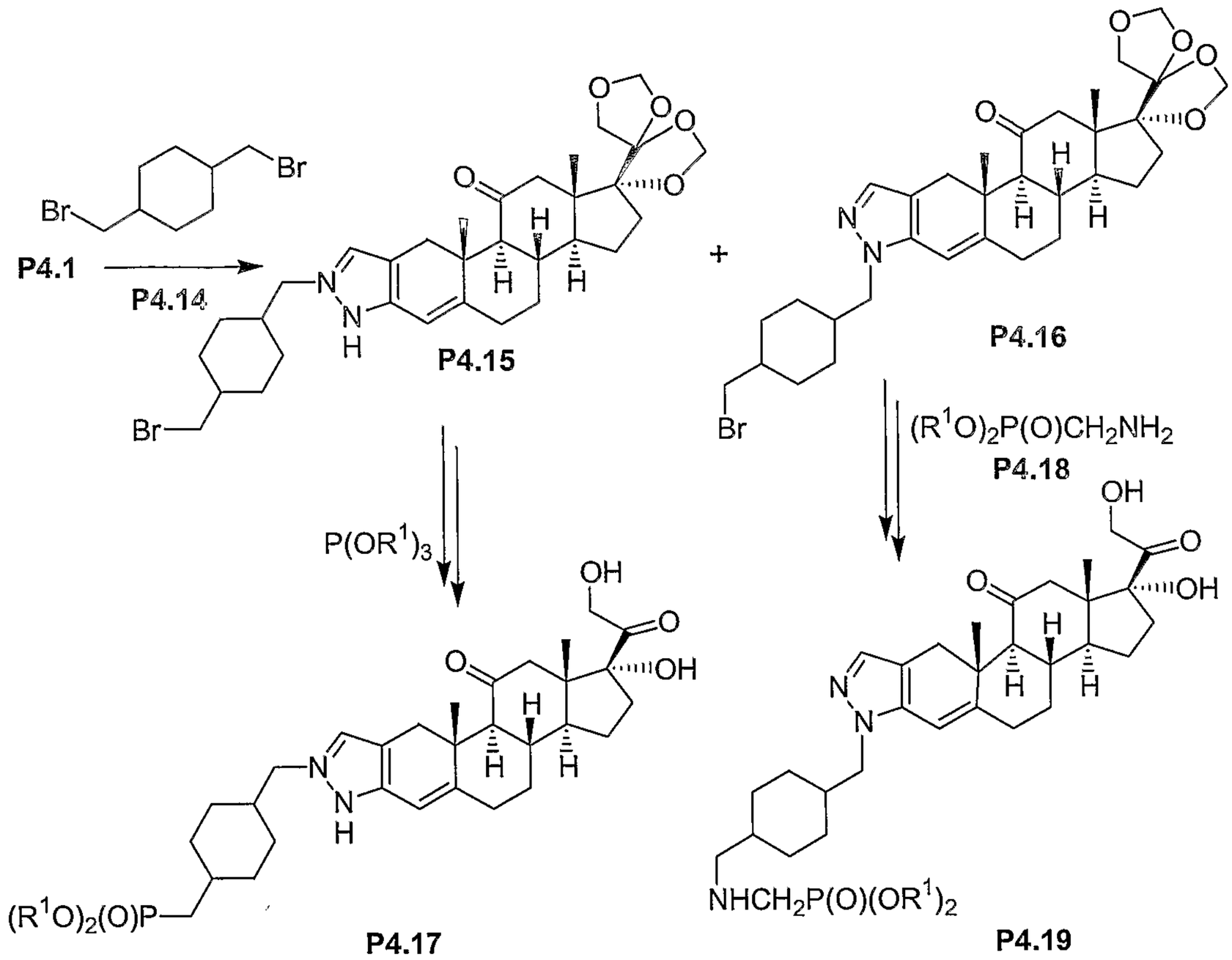
The preparation of phosphonate esters of Formulae **17** and **18** wherein the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **P3.2**, is reacted with hydrazine to afford the pyrazole derivative, **P4.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **P4.2**, to yield the alkylation products, **P4.3** and **P4.4**. The alkylation of substituted pyrazoles is described, for example, in "Heterocyclic Chemistry," by T. L. Gilchrist, Longman, **1992**, p. 309. The reaction is typically performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **P4.3** and **P4.4**, are, except in cases where X is dialkylphosphono, converted into the phosphonates, **P4.5** and **P4.6**, using the procedures described herein. Deprotection affords the diols, **P4.7** and **P4.8** (which are compounds of Formulae **18** and **17**, respectively).

Example 31



As illustrated above, the pyrazole, **P4.1**, is reacted with one molar equivalent of a dialkyl trifluoromethanesulfonyloxy phosphonate, **P4.9**, as described above to give the alkylated pyrazoles, **P4.10** and **P4.11**. Deprotection yields the diols, **P4.12** and **P4.13** (which are compounds of Formulae **18** and **17** respectively).

Example 32



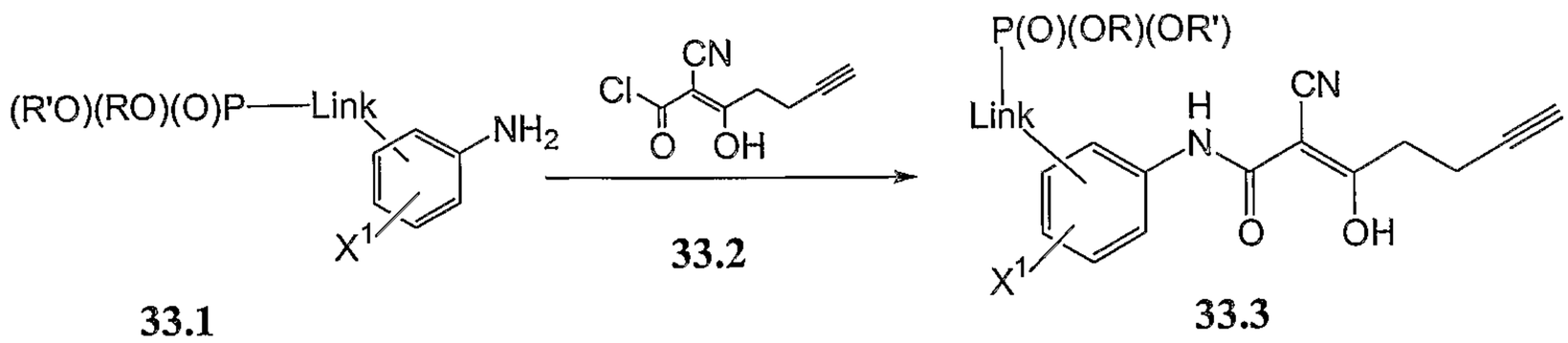
As illustrated above, the pyrazole, **P4.1**, is reacted, as described above, with 1,4-bis(bromomethyl)cyclohexane, **P4.14** (Salor), to give the pyrazoles, **P4.15** and **P4.16**. The product, **P4.15**, is subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite to prepare, after deprotection of the side chain, the phosphonate, **P4.17**, (which is a compound of Formula **18**).

The pyrazole, **P4.16**, is reacted in dimethylformamide with potassium carbonate and a dialkyl aminomethyl phosphonate, **P4.18**, (Interchim) to give after deprotection the amino phosphonate, **P4.19**, which is a compound of Formula **17**.

Using the above procedures, but employing, in place of the dibromide, **P4.14**, different dibromides, and/or different amino-substituted phosphonates, the products analogous to **P4.17** and **P4.19** are obtained.

Example 33

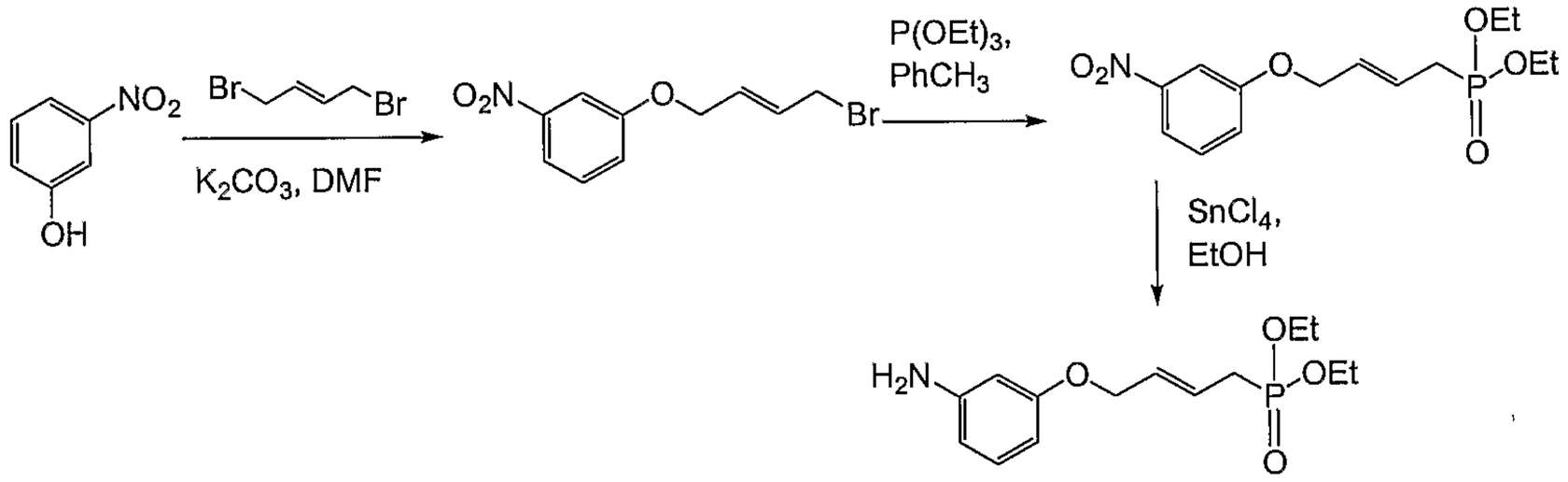
Representative compounds of the invention can be prepared as generally described by Westwood et al, *J. Med. Chem.*, **1996**, *39*, 4608-4621, and according to the following general route.



33.1 **33.2** **33.3**

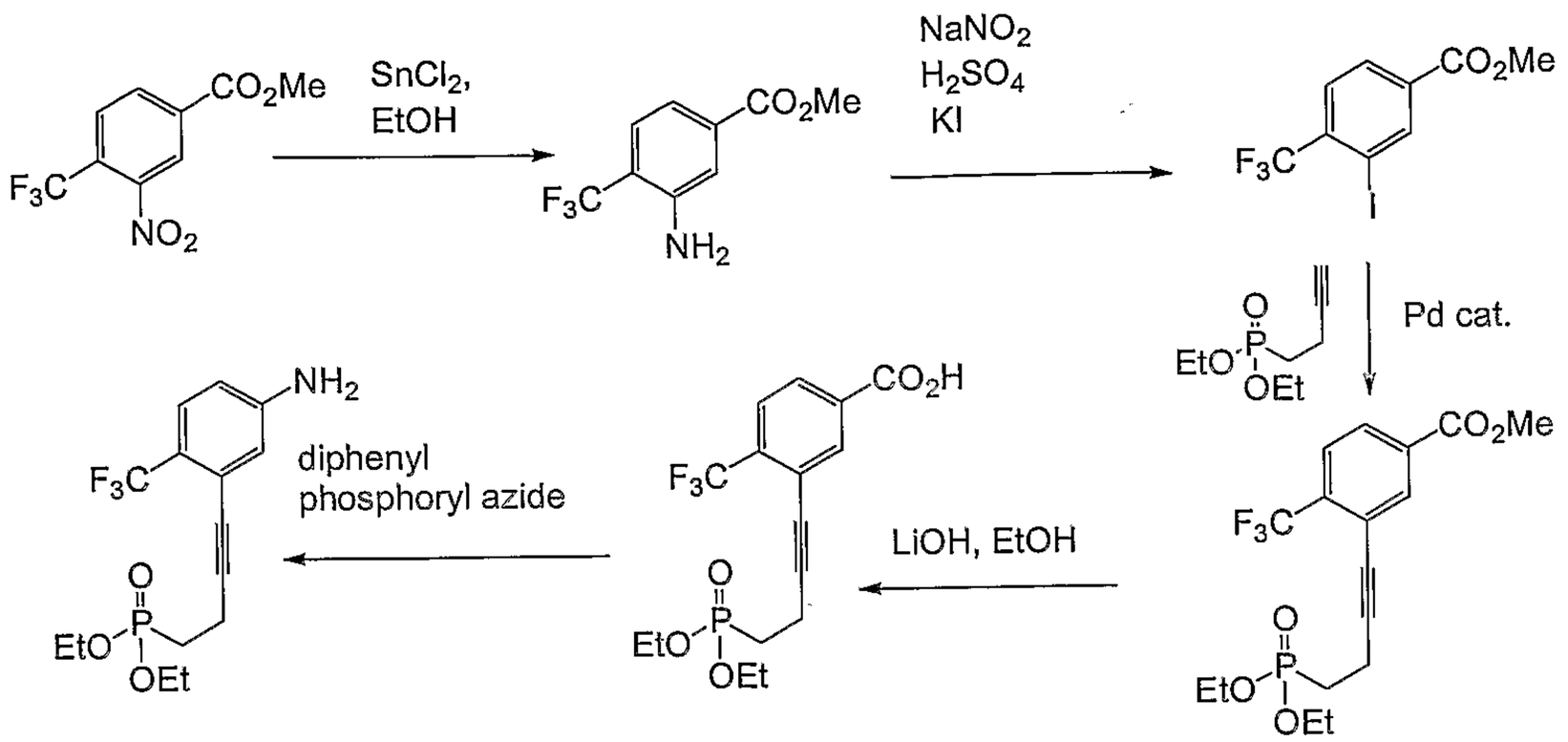
Coupling of a suitable aniline, **33.1**, wherein X^1 is hydrogen, halo, trifluoromethyl, (C_1-C_3)alkyl, cyano, or (C_1-C_3)alkoxy, with acid chloride, **33.2**, provides compound, **33.3** (which is a representative compound of Formula **19** or **20**).

The synthesis of two suitable anilines that can be employed in the above reaction is outlined below.



33.4

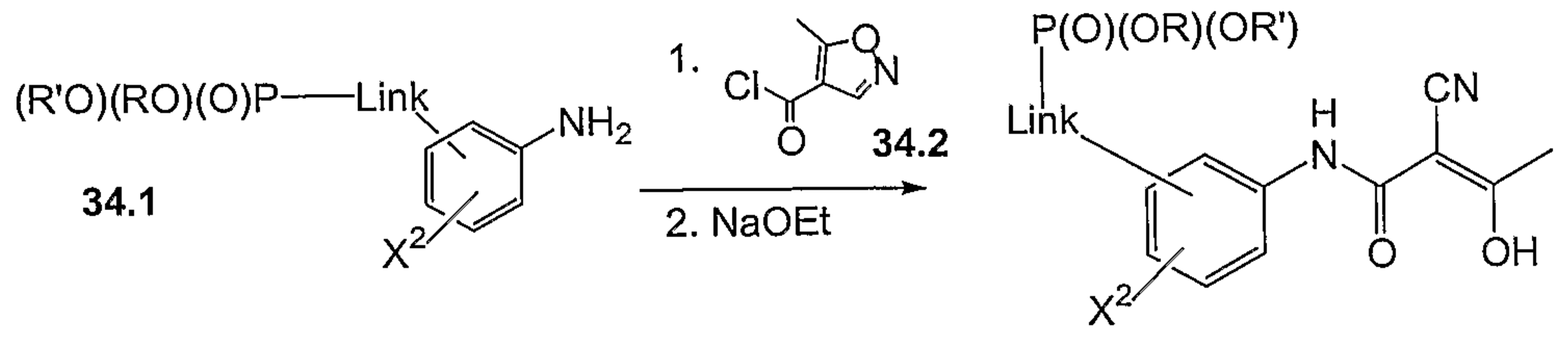
3-Nitrophenol is alkylated with *E*-1,4-dibromobutene and the resulting monobromide is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions to generate the diethyl ester of the desired phosphonic acid, **33.4**. (See Engel, R., "Synthesis of Carbon-phosphorus Bonds," CRC press, **1988**). Finally, the desired aniline is generated by tin (II)-mediated reduction of the nitrobenzene.



The methyl ester of 3-nitro-4-trifluoromethylbenzoic acid is treated with tin (II) chloride to produce the corresponding aniline. The 3-iodobenzoic acid is generated by diazotization and treatment with potassium iodide. A diethylphosphonate ester is attached via an acetylene linker using palladium catalysis, and after saponification of the benzoate ester, Curtius rearrangement of the acyl azide provides an aniline suitable for incorporation into representative MNA-715 analogs of the invention.

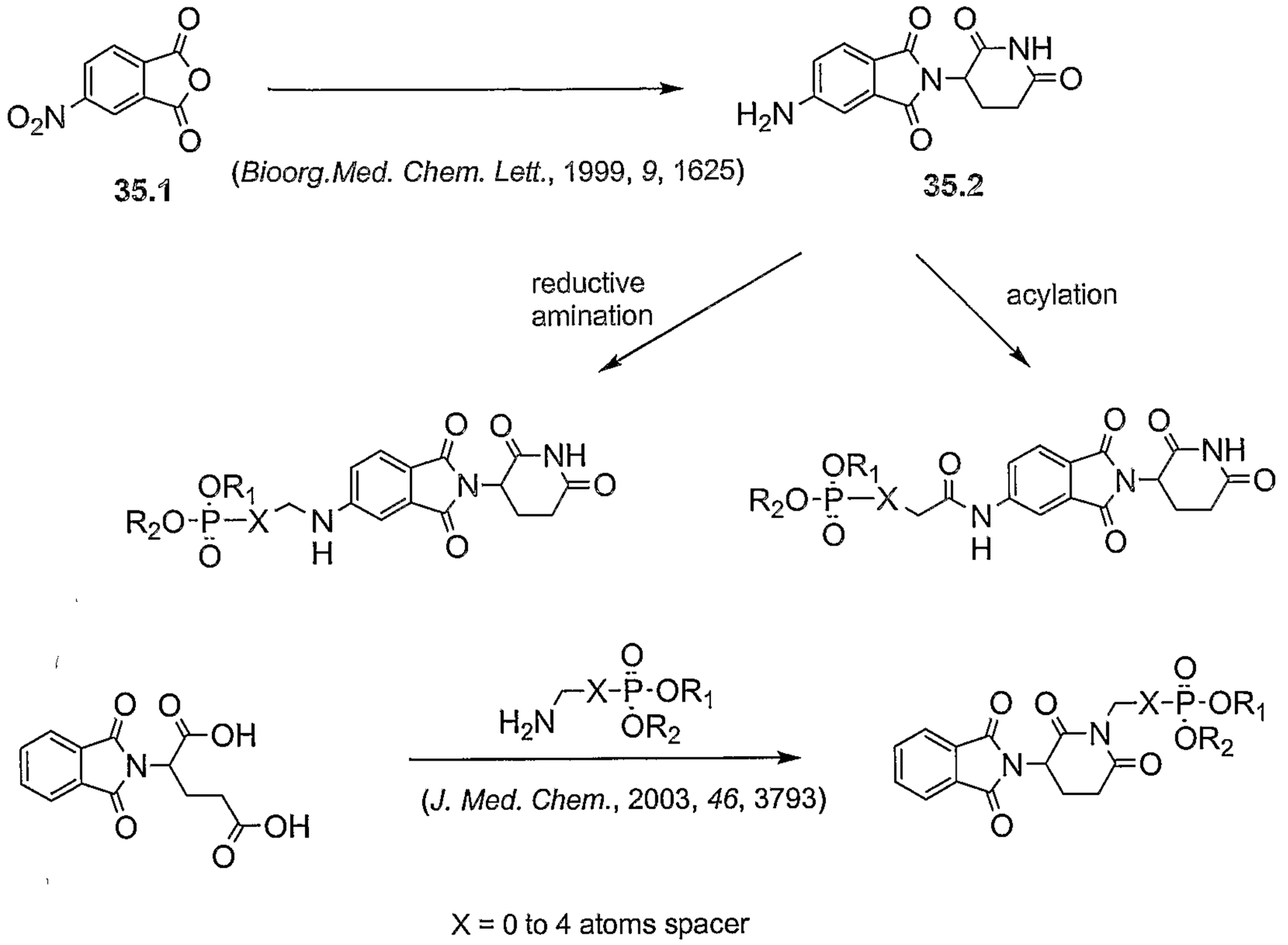
Example 34

Representative compounds of Formulae **21** and **22** can be prepared as generally described by Westwood et al, *J. Med. Chem.*, **1996**, *39*, 4608-4621, and according to the following general route.

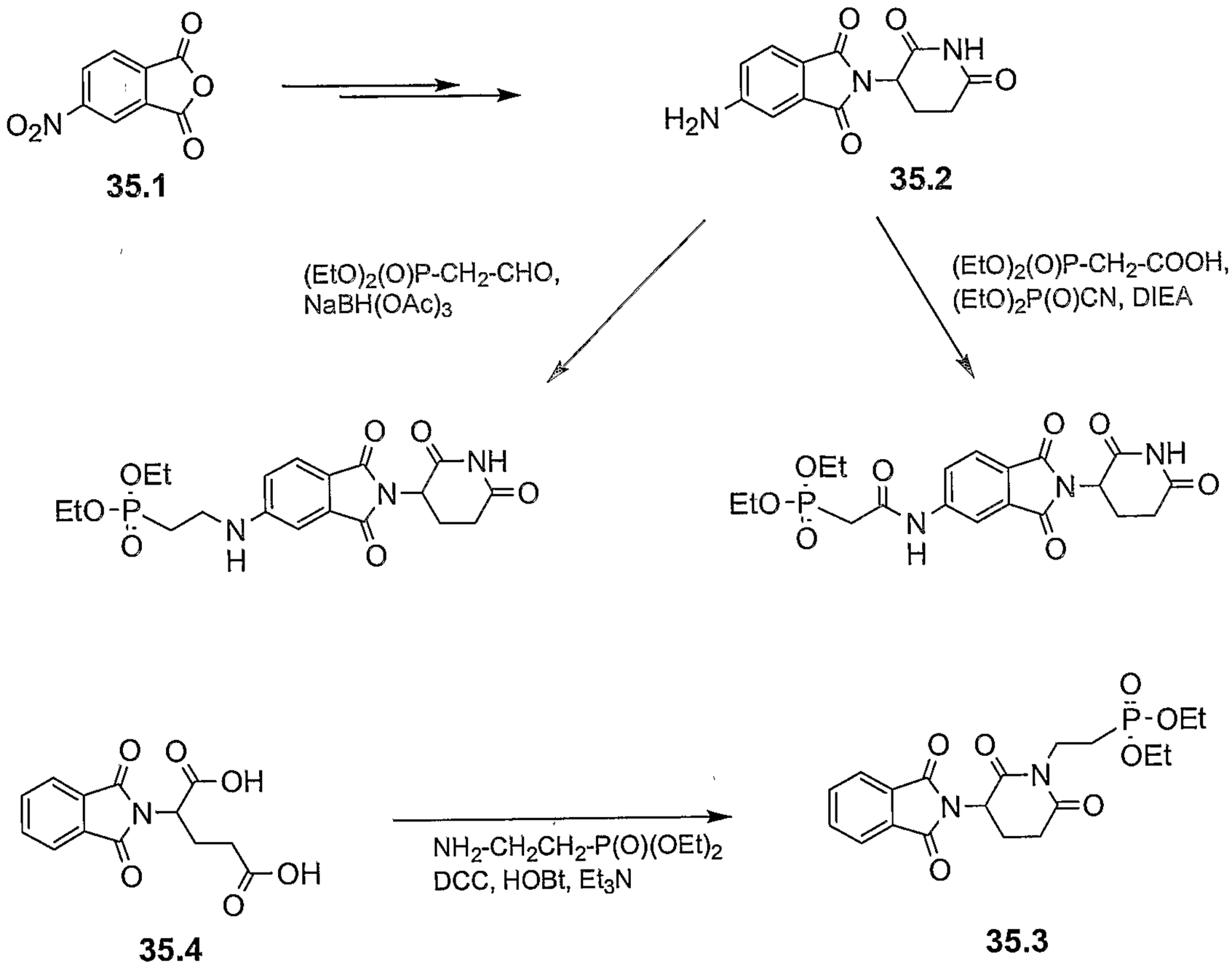


Coupling of a suitable aniline, **34.1**, wherein X^2 is hydrogen, halo, trifluoromethyl, cyano, or methyl with acid chloride, **34.2**, provides a representative compound of Formulae **21** and **22**. Anilines prepared as described in Example 33 and elsewhere herein can be incorporated into this synthesis.

Example 35

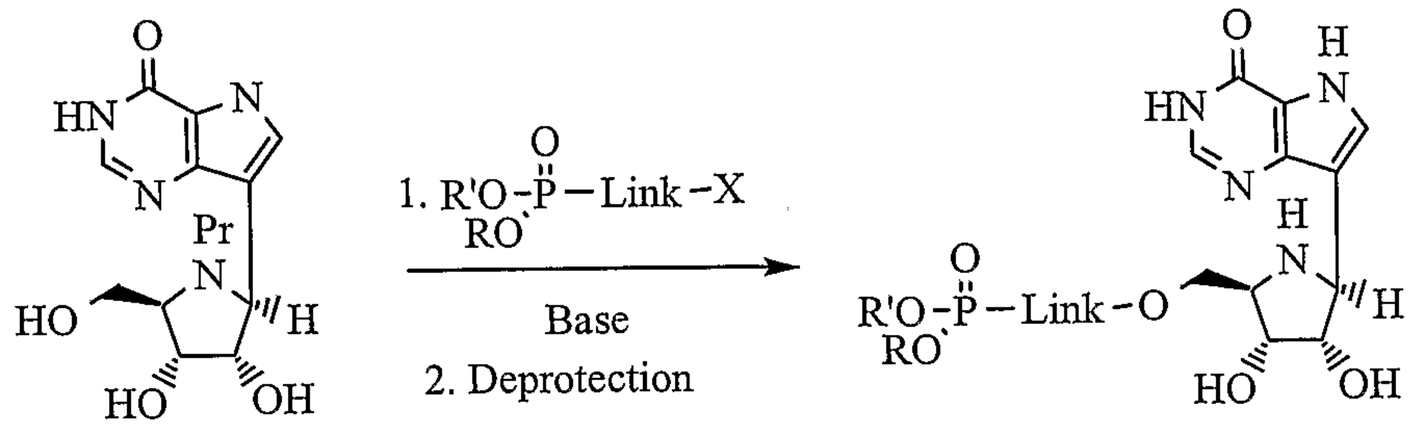


5-Nitro-isobenzofuran-1,3-dione, **35.1**, (commercially available), is converted to 5-amino-2-(2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione, **35.2**, following the procedures reported in *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1625. This amine intermediate is subjected to a reductive amination with diethyl-phosphonoacetaldehyde (obtained from ozonolysis of diethyl allyphosphonate) in the presence of a reducing agent such as sodium triacetoxyborohydride to generate the desired amine linker analog (*J. Org. Chem.*, **1996**, *61*, 3849). Alternatively, the amine is acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, **1982**, *25*, 960 and *J. Med. Chem.*, **1984**, *27*, 600. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature. A specific example where X is CH_2 is illustrated below.

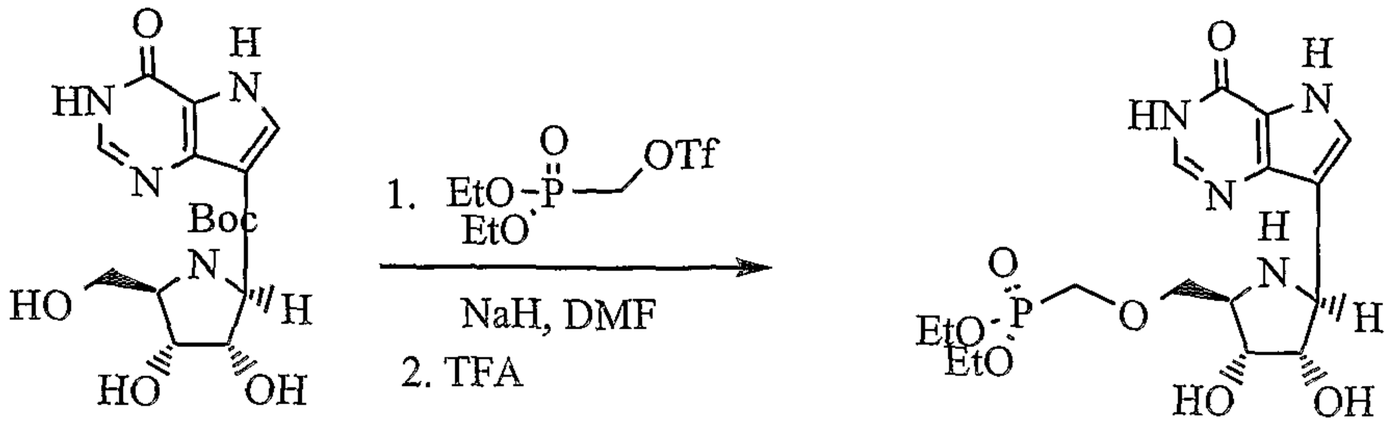


Alternatively, 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanedioic acid, **35.4**, (commercially available) is treated in a solvent such as acetonitrile with triethylamine, 1-hydroxybenzotriazole, 4-methoxybenzylamine, and 1,3-dicyclo-hexylcarbodiimide. After the reaction is complete, the solvent is removed and the residue is purified by chromatography to generate the desired analog, **35.3**, according to a procedure such as that reported in *J. Med. Chem.*, **2003**, *46*, 3793.

Example 36



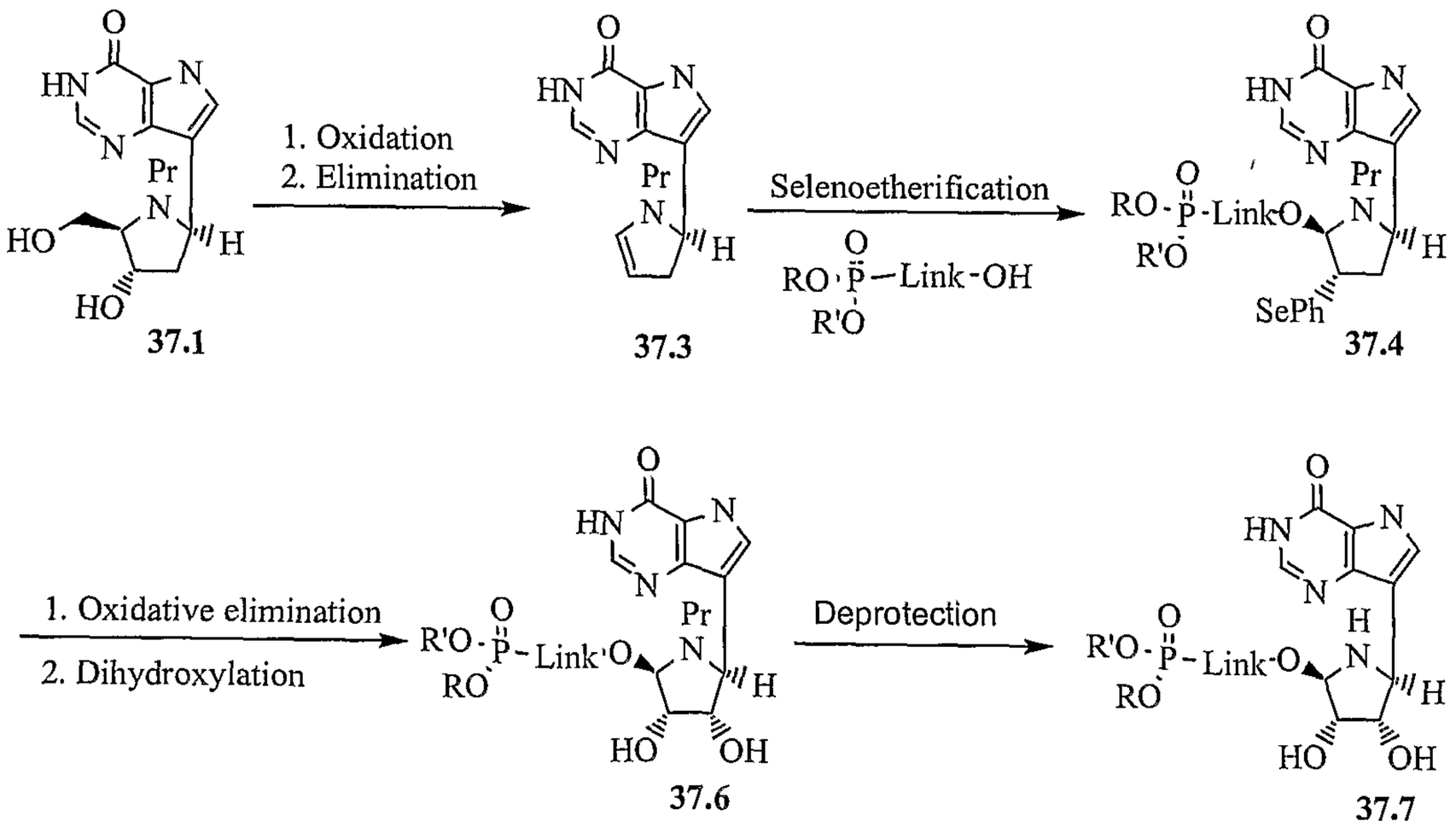
36.1 **36.2**



36.3 36.4

The Boc-protected (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol, compound, **36.3**, is prepared by stirring the (1S)-1-(9-deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol (WO 99/19338 and Evans, G. B. et al., *Tetrahedron*, **2000**, *56*, 3053, also reported in Evans, G. B. et al., *J. Med. Chem.* **2003**, *46*, 3412) with BOC anhydride as described in Greene, T., "Protective groups in organic synthesis," Wiley-Interscience, **1999**. Compound, **36.3**, is then treated in a solvent such as tetrahydrofuran or dimethylformamide with a base such as sodium hydride. When bubbling ceases, diethyl phosphonomethyl-triflate (prepared according to *Tetrahedron Lett.*, **1986**, *27*, 1477) is added, yielding the desired phosphonate diester, **36.4**, after deprotection of the BOC group using trifluoroacetic acid (TFA) (which is a compound of Formula **25**).

Example 37

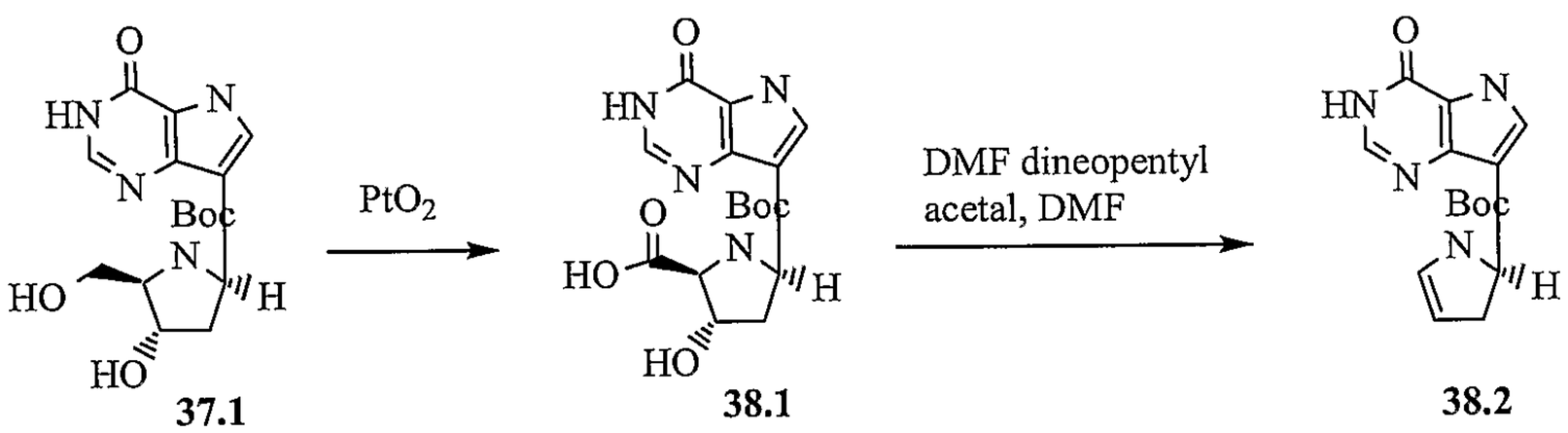


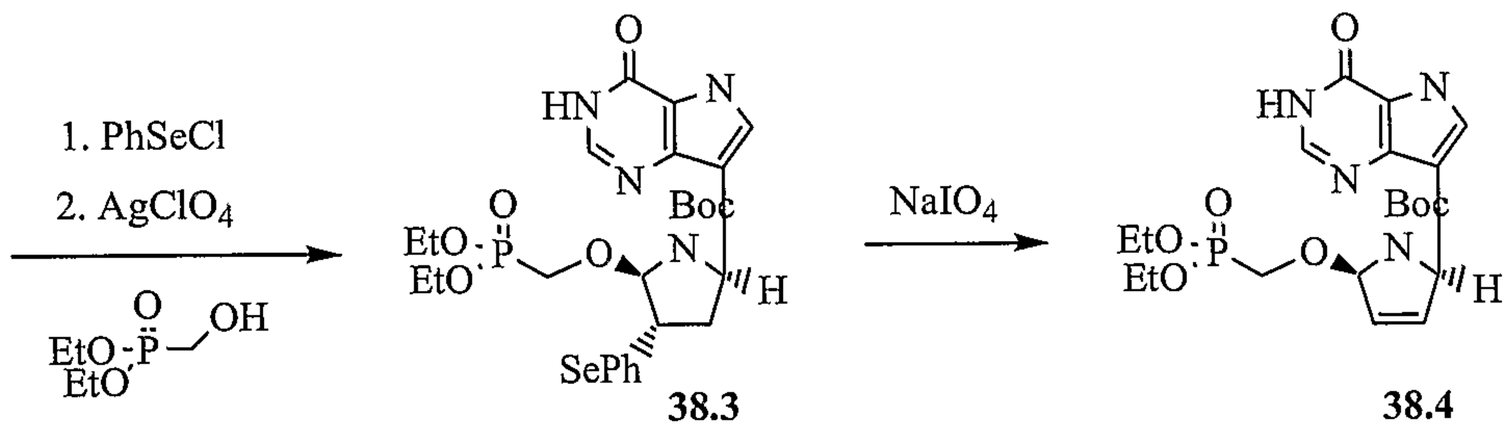
37.1 37.3 37.4 37.6 37.7

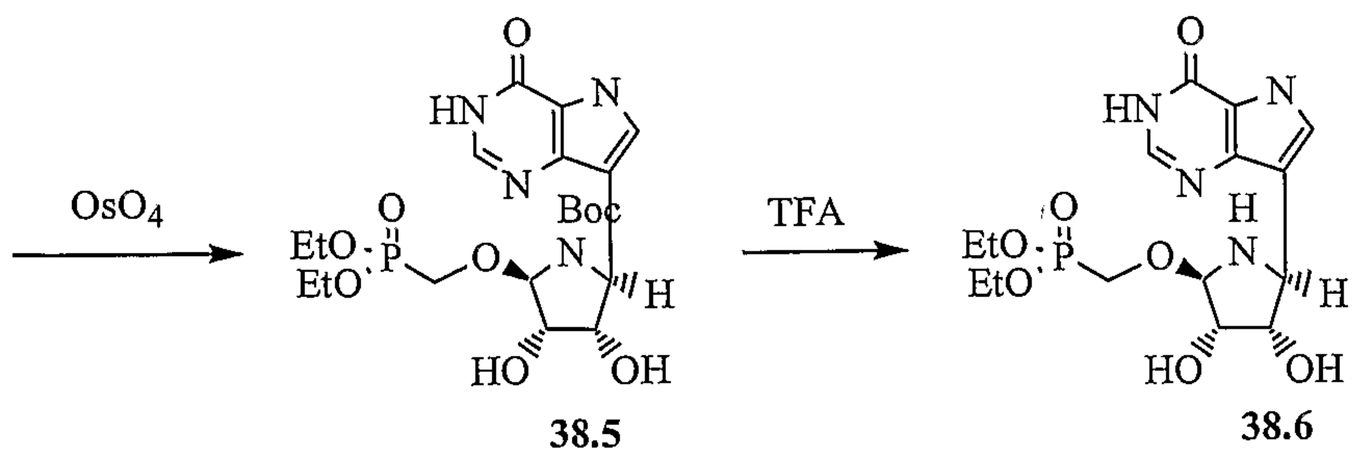
Protected compound, **37.1**, ((1*R*)-1-(9-deazahypoxanthin-9-yl)-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol, as the hydrochloride salt) is prepared as described in Evans, G. B. et al., *Tetrahedron*, **2000**, *56*, 3053, using di-*t*-butyl

dicarbonate in dichloromethane. Oxidation of the 5'-OH followed by elimination provides glycal, **37.3** (see the procedure of Zemlicka J. et al., *J. Am. Chem. Soc.*, **1972**, *94*, 9, 3213). Selenoetherification provides the protected phosphonate, **37.4** (Kim, C. et al., *J. Org. Chem.*, **1991**, *56*, 2642). Oxidative elimination of the phenylselenide (as described in Kim, C. et al., *J. Org. Chem.*, **1991**, *56*, 2642) followed by stereoselective dihydroxylation provides the desired diol, **37.6**. Finally, the protecting group is removed to provide a compound, **37.7**, compound of Formula **26**.

Example 38





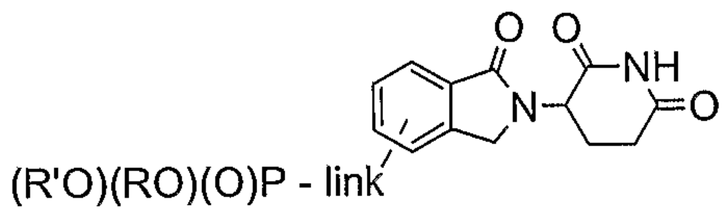


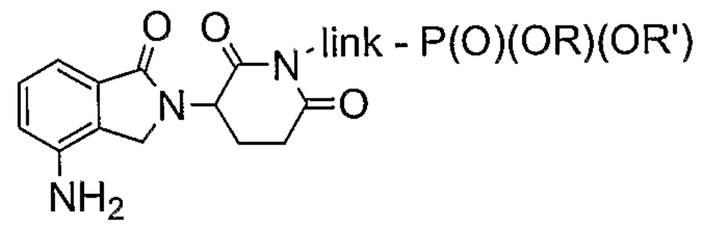
(1R)-1-(9-Deazahypoxanthin-9-yl)-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol, prepared as the HCl salt as described in Evans, G. B. et al., *Tetrahedron*, **2000**, *56*, 3053, is first protected and then oxidized with PtO_2 to provide carboxylic acid, **38.1**. Decarboxylative elimination is achieved using dimethylformamide dineopentyl acetal in dimethylformamide at high temperature (Zemlicka J. et al., *J. Am. Chem. Soc.*, **1972**, *94*, 9, 3213).

Selenoetherification followed by treatment of the protected glycal with silver perchlorate in the presence of diethyl(hydroxylmethyl)phosphonate (Phillion, D. et al., *Tetrahedron Lett.*, **1986**, *27*, 1477) provides the phosphonate, **38.3** (Kim, C. et al., *J. Org. Chem.*, **1991**, *56*, 2642). Oxidative elimination of the selenide followed by dihydroxylation using osmium tetraoxide provides diol, **38.5**. Removal of the amine protecting group, according to the procedure of Greene, T., "Protective groups in organic synthesis," Wiley-Interscience, **1999**, provides compound **38.6**.

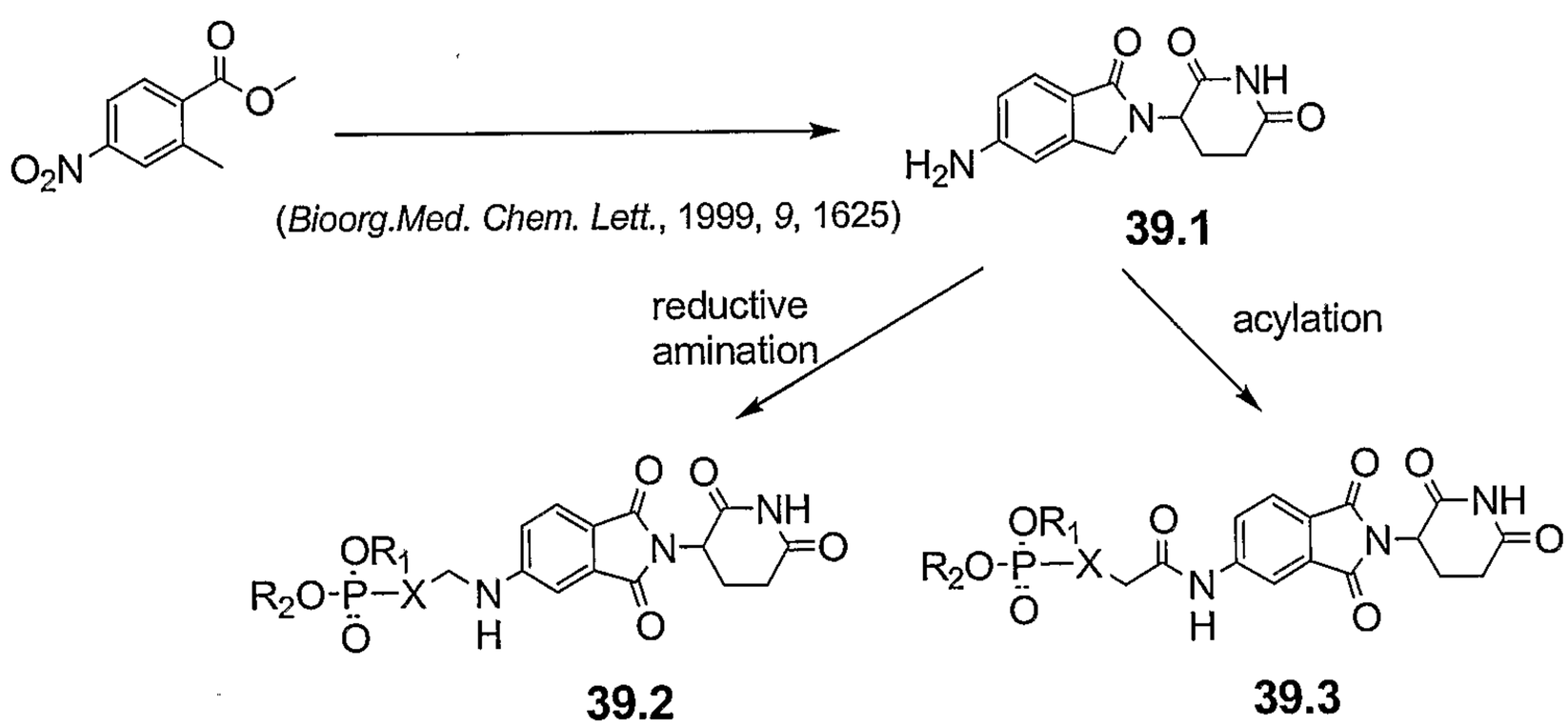
Example 39

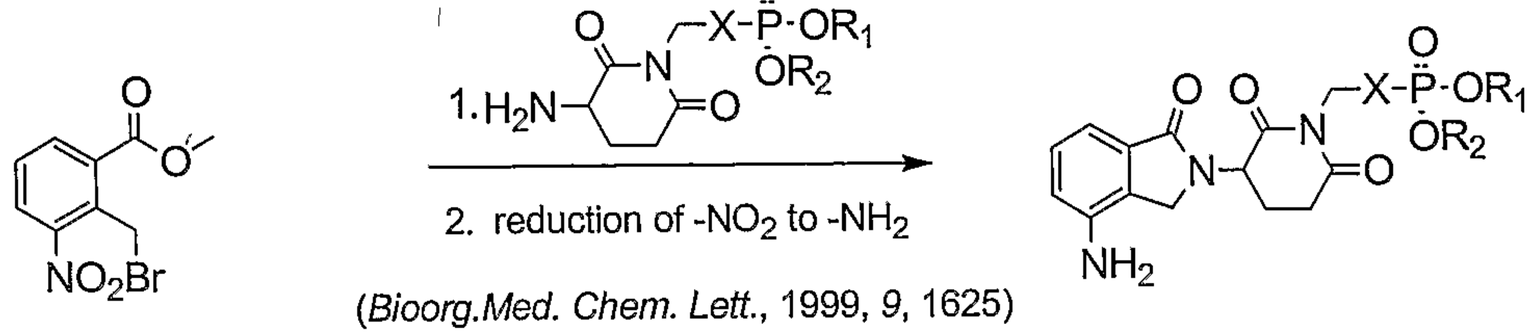
Synthetic methodologies and intermediate compounds that can be used to prepare pro-drugs of analogs of thalidomide are described below.





link includes 1 or more atoms; 2 or more is preferred





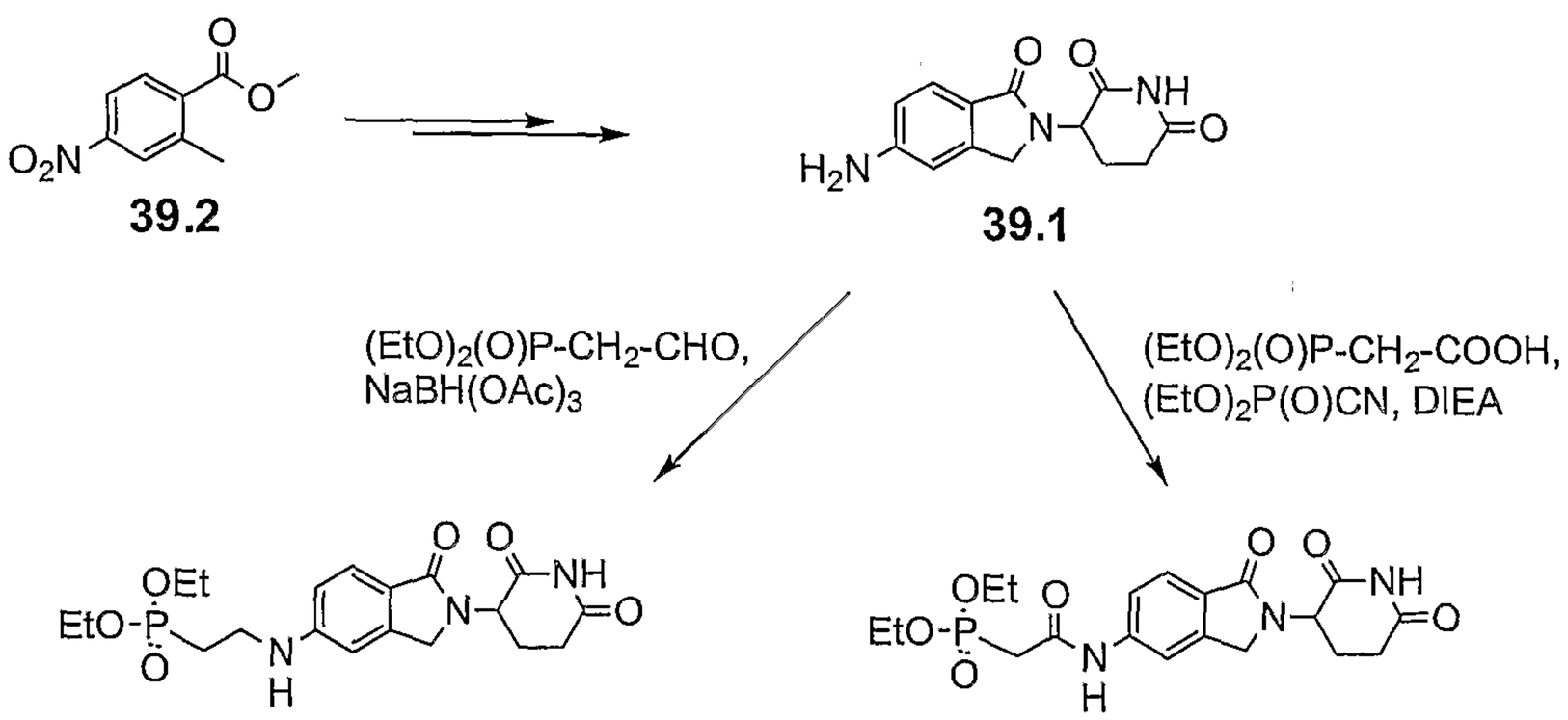
39.4

X = 0 to 4 atoms spacer

2-Methyl-4-nitrobenzoic acid methyl ester (commercially available) is converted to 3-(5-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, **39.1**, following the procedures reported in *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1625. This amine intermediate is subjected to a reductive amination with diethylphosphonoacetaldehyde (obtained from ozonolysis of diethyl allyphosphonate) in the presence of a reducing agent such as sodium triacetoxyborohydride to generate the desired amine linker analog, **39.2** (*J. Org. Chem.*, **1996**, *61*, 3849). Alternatively, the amine is acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, **39.3**, according to a procedure such as those reported in *J. Med. Chem.*, **1982**, *25*, 960 and *J. Med. Chem.*, **1984**, *27*, 600. The activated diethylphosphono-acetic acid can be obtained by treatment, in a solvent such as dimethylform-amide, with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

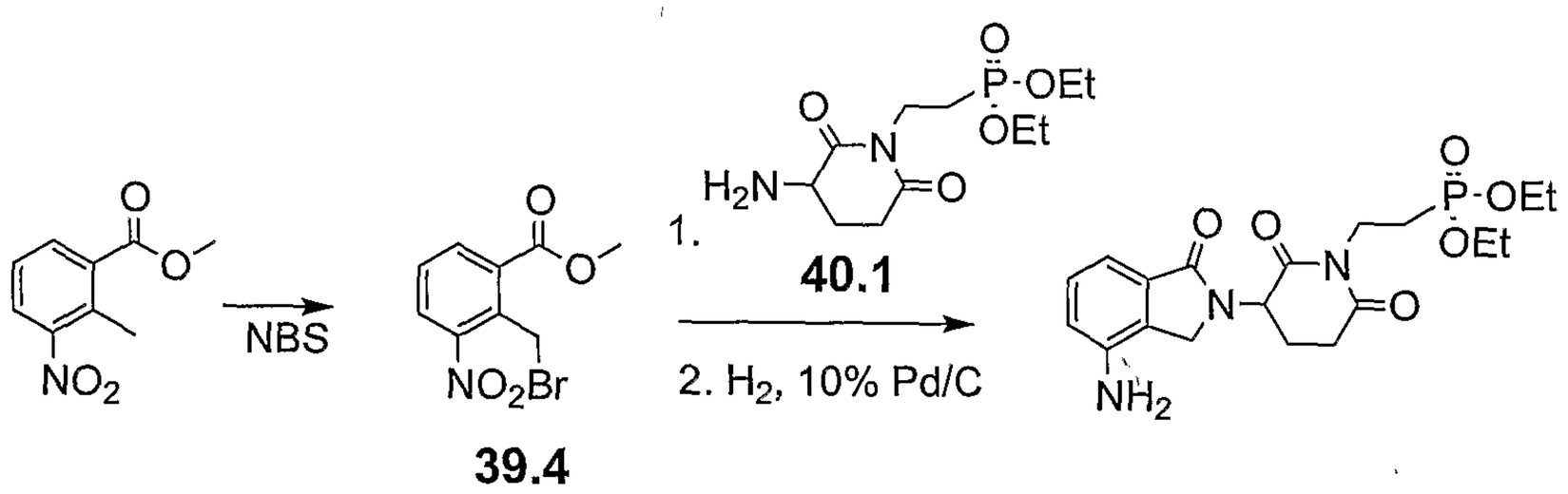
2-Methyl-3-nitrobenzoic acid methyl ester (commercially available) is treated in a solvent such as carbon tetrachloride with N-boromosuccinimide under light to produce 2-bromomethyl-3-nitrobenzoic acid methyl ester, **39.4**. The benzylic bromide is treated in a solvent such as dimethylformamide with [2-(3-amino-2,6-dioxo-piperidin-1-yl)-ethyl]-phosphonic acid diethyl ester (for the preparation of this compound, see Example 40, below) in the presence of a base such as triethylamine. The coupled product is then reduced by hydrogenation (*Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1625) to afford the desired analog.

Example 40



2-Methyl-4-nitrobenzoic acid methyl ester, **39.2** (commercially available), is converted to 3-(5-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione, following the procedures reported in *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1625. This amine intermediate is subjected to a reductive amination with diethylphosphonoacetaldehyde (obtained from ozonolysis of diethyl allyphosphonate) in the presence of a reducing agent such as sodium triacetoxyborohydride to generate the desired amine linker analog (*J. Org. Chem.*, **1996**, *61*, 3849). Alternatively, the amine is acylated with an activated diethylphosphonoacetic acid to provide the desired amide linker compound, according to a procedure such as those reported in *J. Med. Chem.*, **1982**, *25*, 960 and *J. Med. Chem.*, **1984**, *27*, 600. The activated diethylphosphonoacetic acid can be obtained by treatment in a solvent such as dimethylformamide with a coupling reagent such as diethyl cyanophosphonate and a base such as diisopropylethylamine at room temperature.

Example 40A



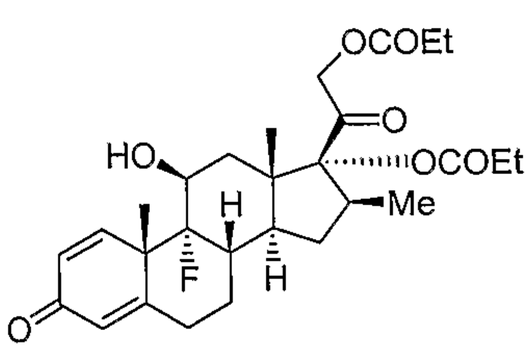
2-Methyl-3-nitrobenzoic acid methyl ester, **39.2** (commercially available) is treated in a solvent such as carbon tetrachloride with N-boromosuccinimide under light to produce 2-bromomethyl-3-nitrobenzoic acid methyl ester, **39.4**. This benzylic bromide is treated in a solvent such as dimethylformamide with [2-(3-amino-2,6-dioxo-piperidin-1-yl)-ethyl]-phosphonic acid diethyl ester (for the preparation of this compound , see below) in the presence of a base such as triethylamine. The coupled product is then reduced by hydrogenation (*Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1625) to afford the desired analog.

[2-(3-amino-2,6-dioxo-piperidin-1-yl)-ethyl]-phosphonic acid diethyl ester, **40.1**, is obtained according to a procedure such as that reported in *J. Med.*

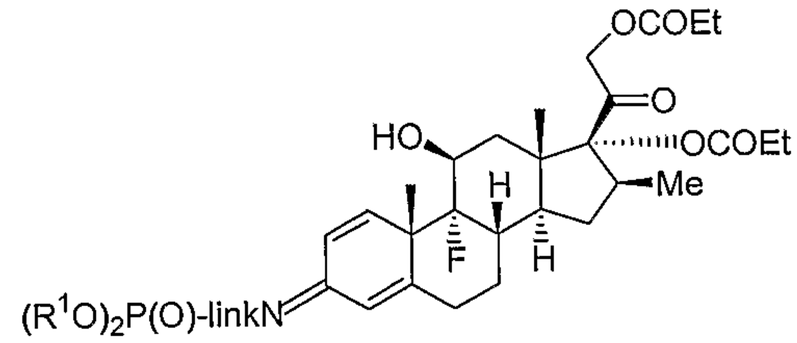
Chem., **2003**, *46*, 3793. Accordingly, benzyloxycarbonyl-protected glutaric acid is treated in a solvent such as acetonitrile with triethylamine, 1-hydroxybenzotriazole, diethyl 2-aminoethylphosphonate and 1,3-dicyclohexylcarbodiimide. After the reaction is complete, the solvent is removed and the residue is purified by chromatography to generate the cyclic product, which is subjected to hydrogen in the presence of palladium catalysis to afford the desired intermediate.

Further manipulations can be performed on the phosphonate moiety prior to the final deprotection. These types of transformations are more extensively described herein.

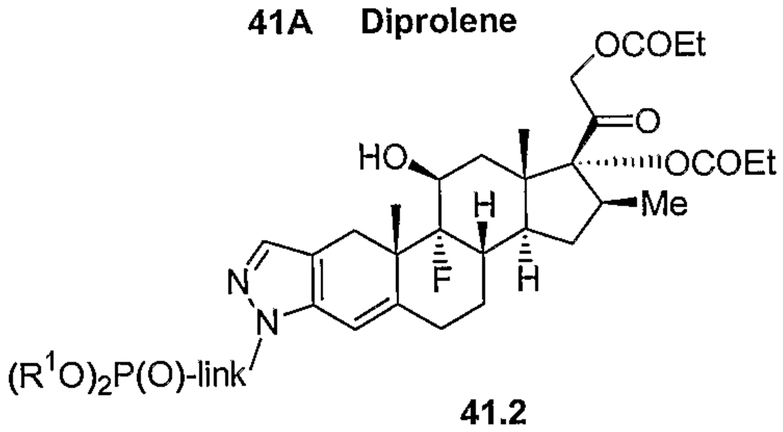
Example 41



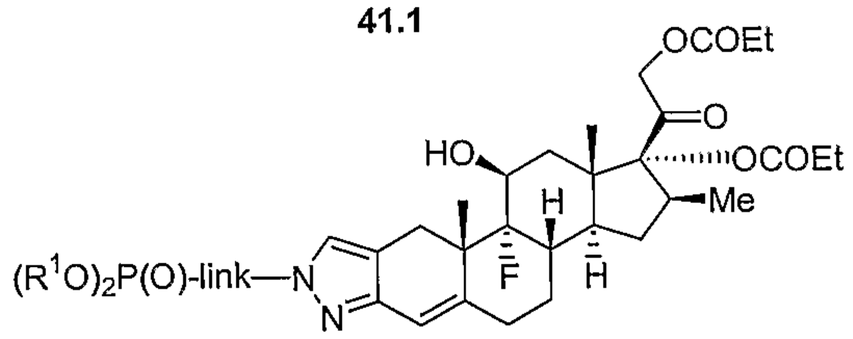
41A Diprolene



41.1



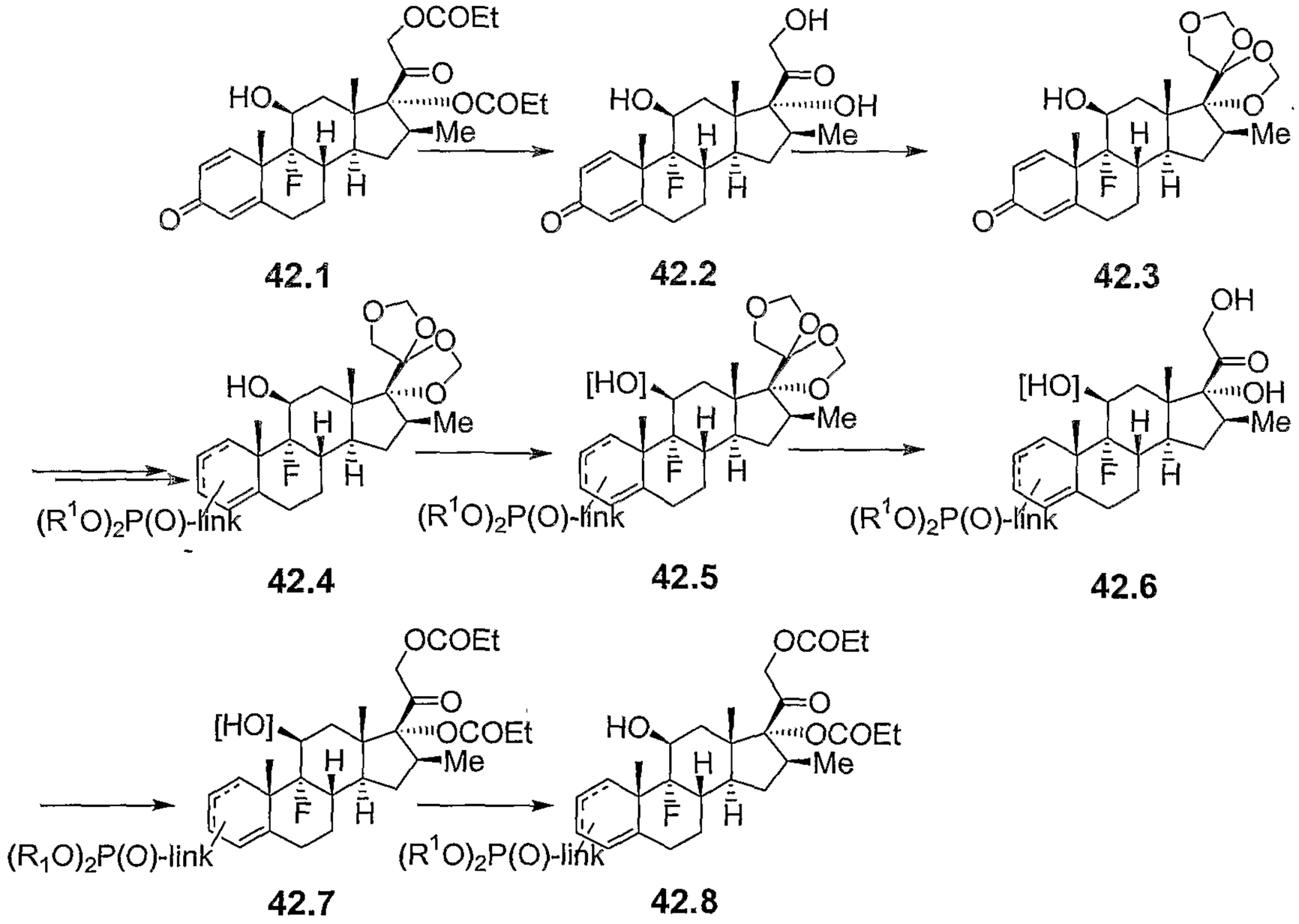
41.2



41.3

The structures of Diprolene, **41A** (German Patent DE 2905674), and the esters, **41.1 – 41.3**, are shown below, in which the substituent R^1 is H, alkyl, alkenyl, aryl or aralkyl. The compounds, **41.1 - 41.3**, incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.

Example 42



A protection-deprotection sequence in which the steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety is shown above. The propionate ester groups of compound, **42.1**, are hydrolyzed, for example by reaction with two molar equivalents of lithium hydroxide in aqueous dimethoxyethane solution at ambient temperature, to give the diol, **42.2**. The product is then reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **42.3**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester, **42.4**. Prior to hydrolysis of the BMD protecting group, the 11-hydroxyl group is protected. The protecting group is selected so that it is stable to the conditions required for removal of the BMD group, and so that it is removable without affecting the subsequently introduced 17, 21-diester moiety.

For example, the 11-hydroxyl group is protected by conversion to the 4-azidobutyrate ester, by reaction with 4-azidobutyryl chloride in pyridine. The 11-azidobutyrate group is then removed from the diester, **42.7**, by reaction with triphenylphosphine, as described in *Bull. Soc. Chem. Jpn.*, **1986**, *59*, 1296.

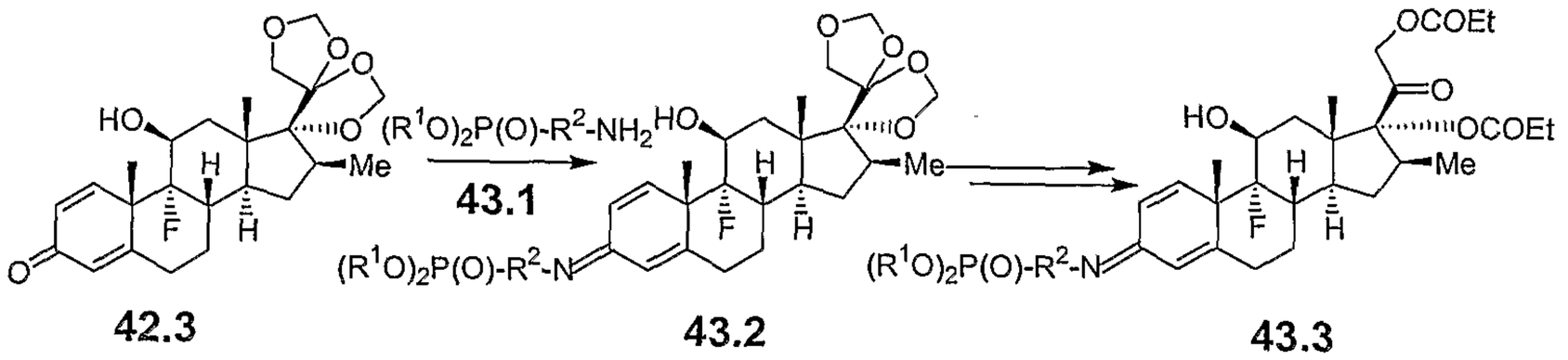
Alternatively, the 11-hydroxyl group is protected by conversion to the 2-(trimethylsilyl)ethyl carbonate, by reaction with 2-(trimethylsilyl)ethyl carbonyl chloride and pyridine. The 2-(trimethylsilyl) carbonate is removed from the diester, **42.7**, by reaction with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in *Tet. Lett.*, **1981**, *22*, 969.

Alternatively, the 11-hydroxyl group is protected by conversion to the trichloroacetyl ester, by reaction with trichloroacetyl chloride in dimethylformamide-pyridine. The trichloroacetyl ester is removed by reaction with ethanolic ammonia at ambient temperature, as described in *Coll. Czech. Chem. Commun.*, **1962**, *27*, 2567.

The BMD moiety in the protected product, **42.5**, is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the diol, **42.6**. The diol compound is then acylated, for example by reaction with propionic acid and dicyclohexyl carbodiimide in dimethylformamide at ambient temperature, or by reaction with propionyl chloride and triethylamine in dichloromethane, to produce the dipropionate, **42.7**. Deprotection of the 11-hydroxyl group, as described above, then affords the diester, **42.8**.

Alternatively, the 20-ketone group is protected as the diethylamine adduct by reaction with titanium tetrakis(diethylamide), as described in Protective Groups in Organic Synthesis, by T.W. Greene and P.G.M Wuts, Wiley, Second Edition 1990, p. 219.

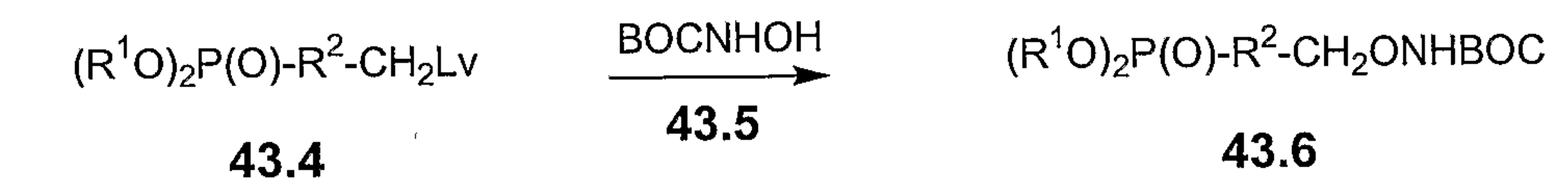
Example 43



42.3 **43.2** **43.3**

The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative, **42.3**, is reacted with an amine or hydroxylamine, **43.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or

cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, to afford the imine or iminoxy product, **43.2**. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The BMD-protected compound, **43.2**, is then converted, as described above, into the diester, **43.3**.

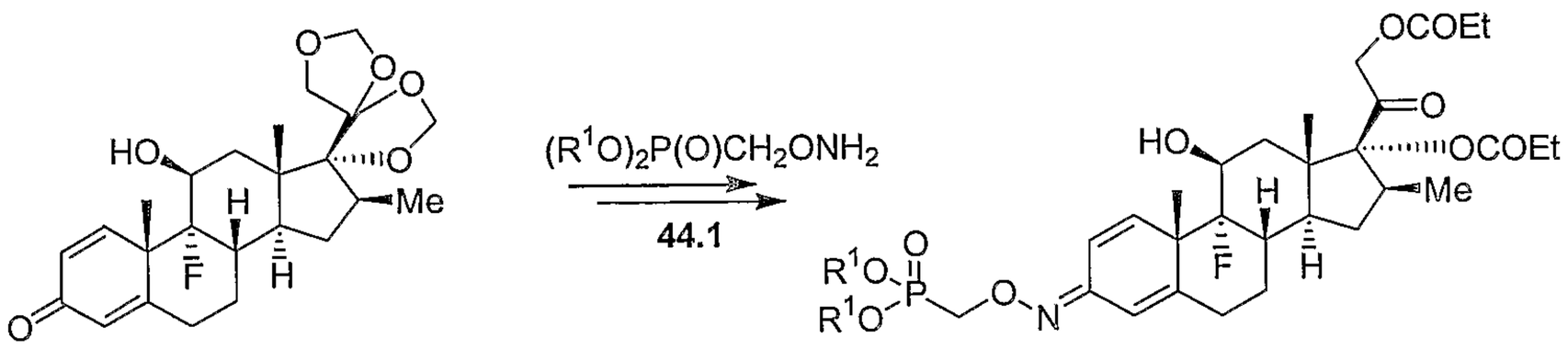


43.4 **43.5** **43.6**

43.6 **43.7**

The preparation of hydroxylamine ethers incorporating a phosphonate group is shown above. In this procedure, a phosphonate, **43.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **43.5** (Aldrich), to produce the ether, **43.6**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine, to give the product, **43.6**. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **43.7**.

Example 44

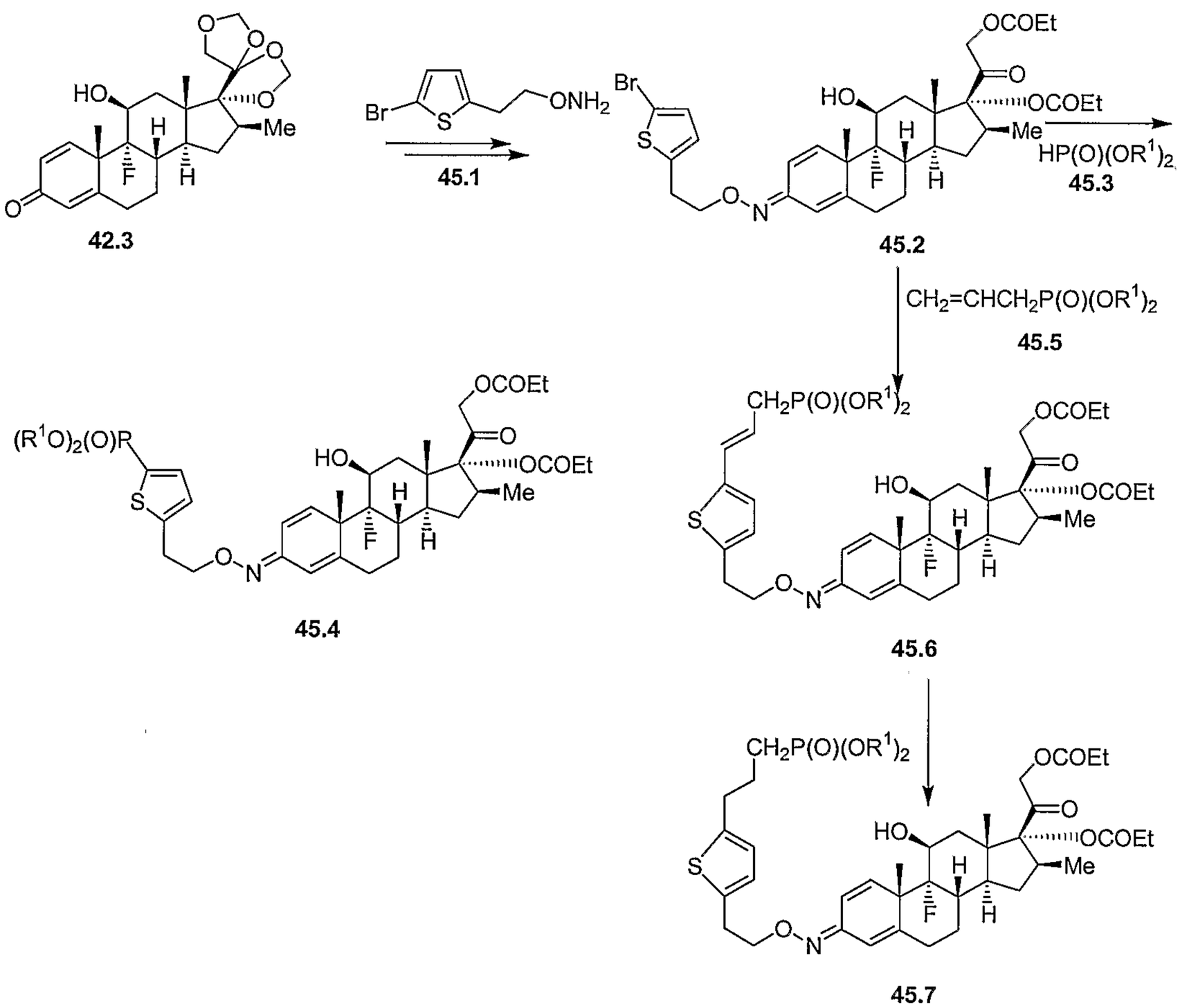


42.3 **44.1** **44.2**

The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate, **42.3**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **44.1**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford, after deprotection and side chain acylation, the oxime ether, **44.2**. The oxime forming reaction is performed at ambient temperature in pyridine solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the oxime ether, **44.1**, different oxime ethers, **43.7**, the corresponding products, **43.3** are obtained.

Example 45



The preparation of phosphonates incorporating an iminoxy group, by means of the reaction between the substrate the substrate, **42.3**, and O-2-(5-bromo-2-thienyl)ethoxyhydroxylamine, **45.1**, prepared as described above from 2-(5-bromo-2-thienyl)ethyl bromide (*J. Chem. Soc., Perkin Trans. Phys. Org. Chem.*, **1975**, 821), is illustrated above. The resultant oxime ether is converted,

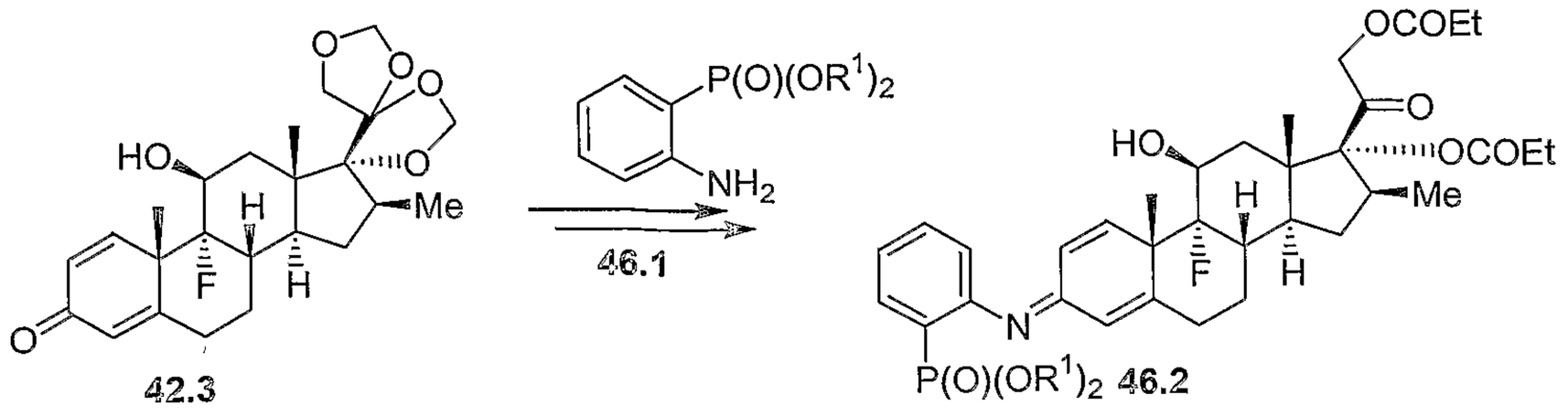
by deprotection and side chain acylation, into the compound, **45.2**, which is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **45.3**, to afford the phosphonate, **45.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo-substituted product, **45.2**, is coupled, in a palladium-catalyzed Heck reaction, with a dialkyl propenyl phosphonate, **45.5**, (Acros) to give the unsaturated phosphonate, **45.6**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)-palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate.

Optionally, the styrenoid double bond present in the product, **45.6**, is reduced, for example by reaction with diimide, to produce the saturated analog, **45.7**. The reduction of olefinic bonds is described in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen, or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromothienyl reagent, **45.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds **45.4**, **45.6** and **45.7** are obtained.

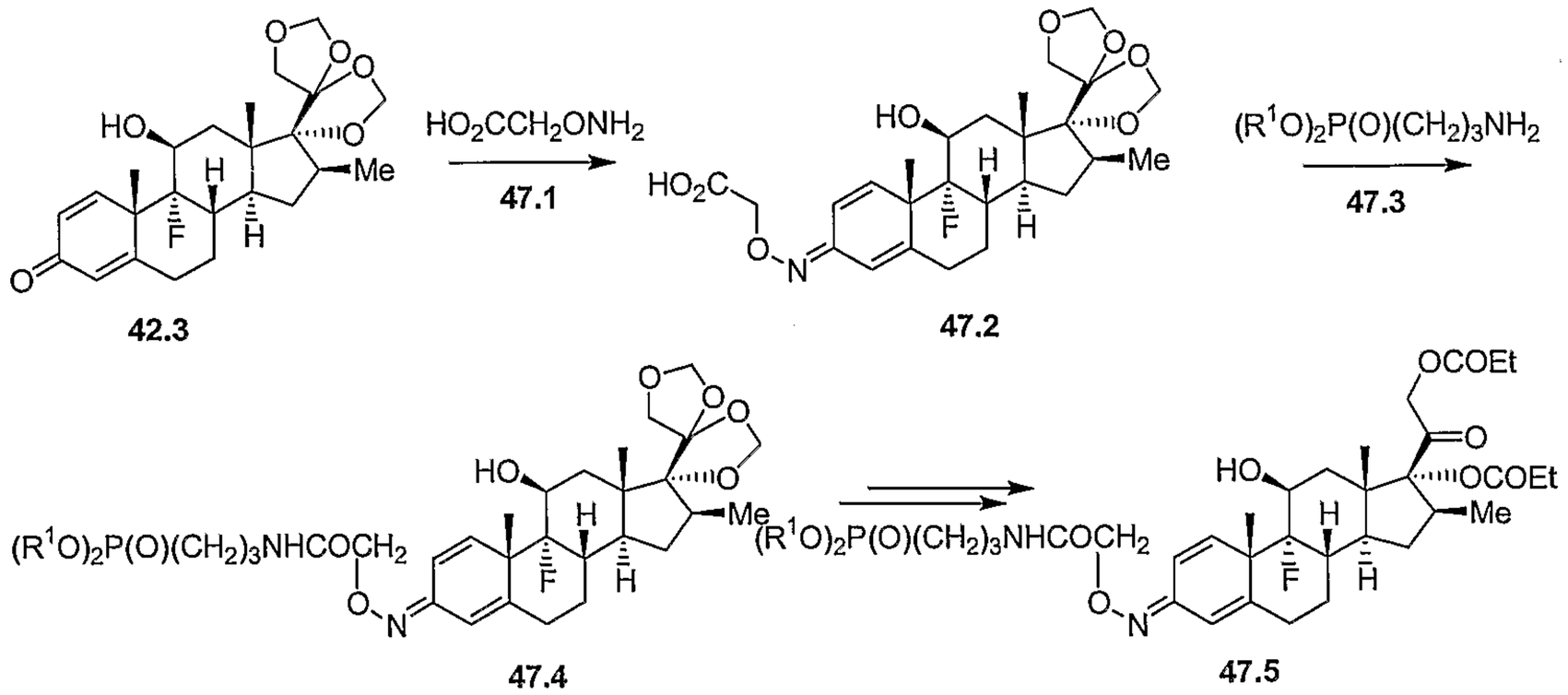
Example 46



The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate, **42.3**, which is reacted with a dialkyl 2-aminophenyl phosphonate, **46.1** (Aurora), to give, after deprotection and side chain acylation, the imine product, **46.2**. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions, to give the product, **46.2**.

Using the above procedures, but employing, in place of the 2-amino-phenyl phosphonate, **46.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **46.2** are obtained.

Example 47

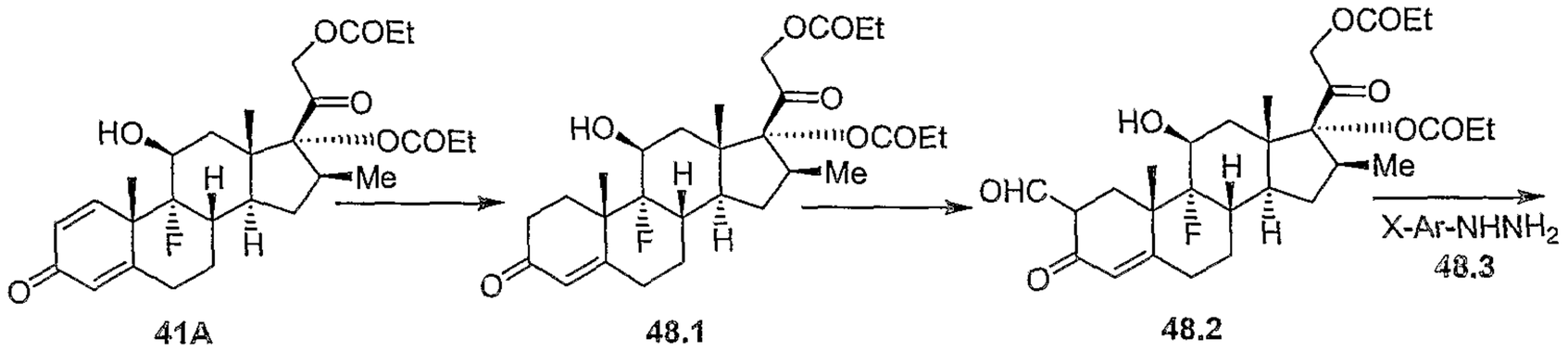


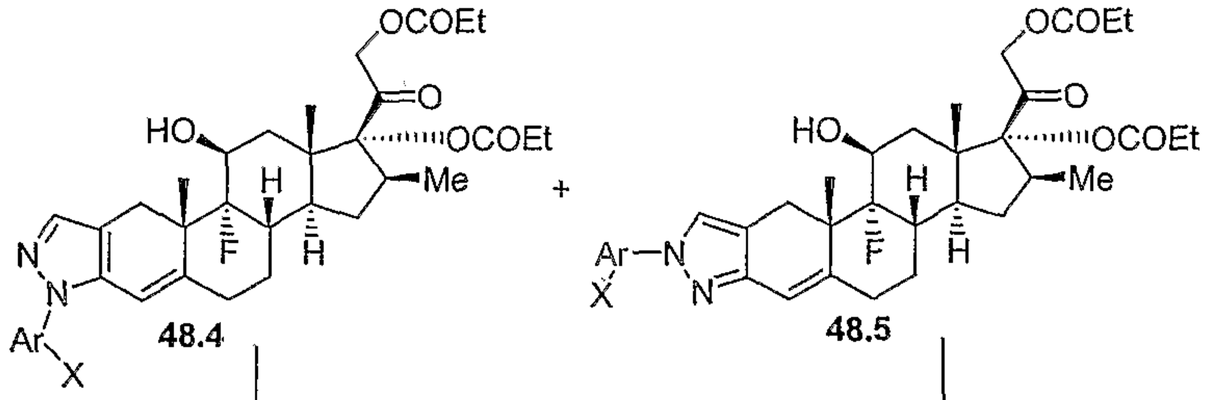
An alternative method for the preparation of phosphonates in which the phosphonate is attached by means of an oximino group is illustrated above. In this procedure, the dienone, **42.3**, is reacted with O-(carboxymethyl)hydroxyl-amine, **47.1** (Interchim), to yield, after deprotection and side chain acylation, the

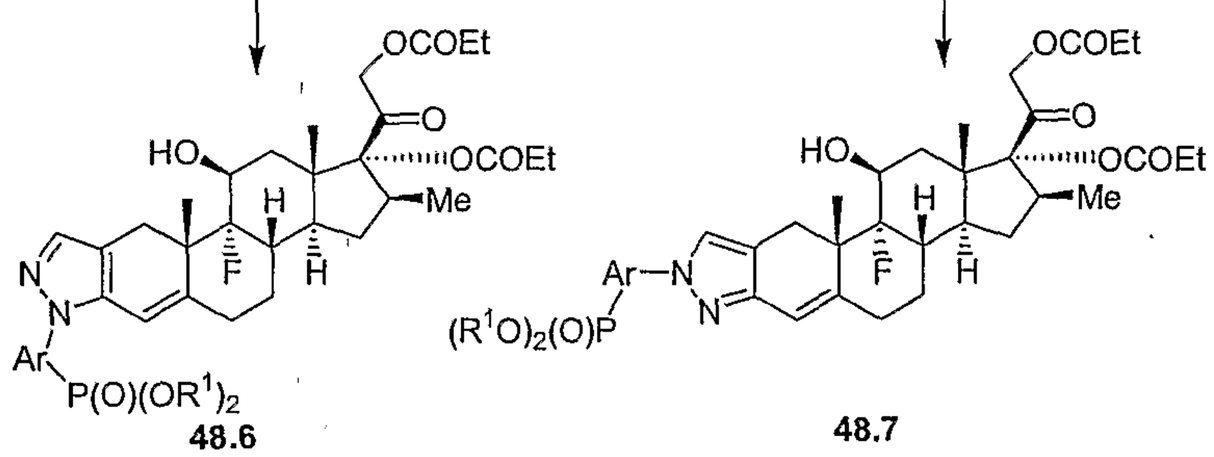
oxime, **47.2**. The reaction of steroidal 1,4-dien-3-ones with hydroxylamine is described in *J. Steroid Bioch.*, **1976**, *7*, 795. The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime, **47.2**, is then reacted with a dialkyl 3-hydroxyphenyl phosphonate, **47.3** (Epsilon), in a Mitsonobu reaction, to yield the substituted oxime, **47.4**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 448, and in "Advanced Organic Chemistry," Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p. 153-4 and in *Org. React.*, **1992**, *42*, 335. The phenol and the hydroxy or mercapto component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656. The product, **47.4**, is then transformed, by deprotection and acylation, into the diester, **47.5**.

Using the above procedures, but employing, in place of the phosphonate, **47.3**, different dialkyl hydroxy-substituted aryl or heteroaryl phosphonates, the products analogous to **47.5** are obtained.

Example 48





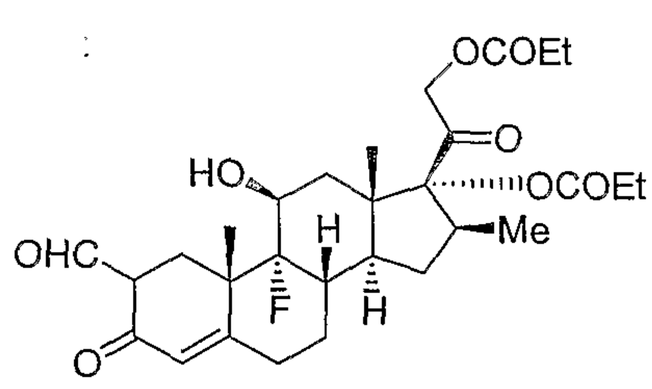


The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, Diprolene, **41A**, is reduced to afford the 1,2-dihydro product, **48.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in Australian Patent Application 275950409, to afford the 2-formyl product, **48.2**.

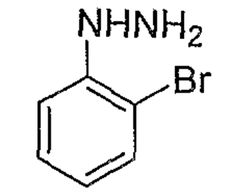
Optionally, the substrate, **41A**, is protected, for example as described in Example 42, above, prior to the formylation reaction, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The 2-formyl product is then reacted with an aryl or heteroaryl hydrazine, **48.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **48.4** and **48.5**. The ring-forming reaction is performed between

equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **48.4** and **48.5** are then transformed, for example by the procedures described in Examples **49-50**, respectively into the phosphonates, **48.6** and **48.7**.

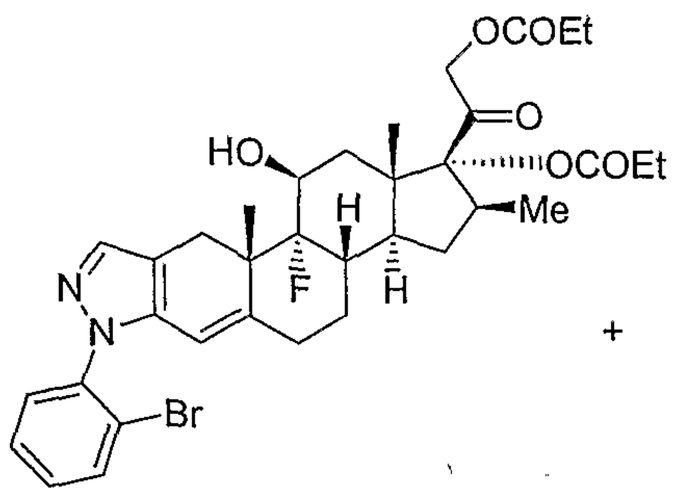
Example 49



48.2

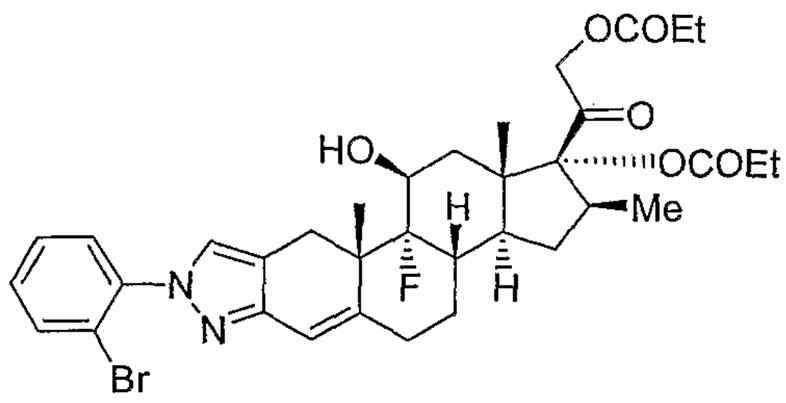


49.1

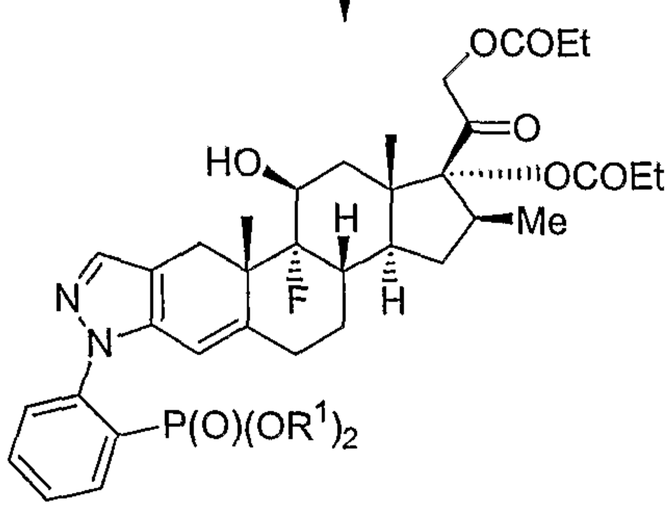


49.2

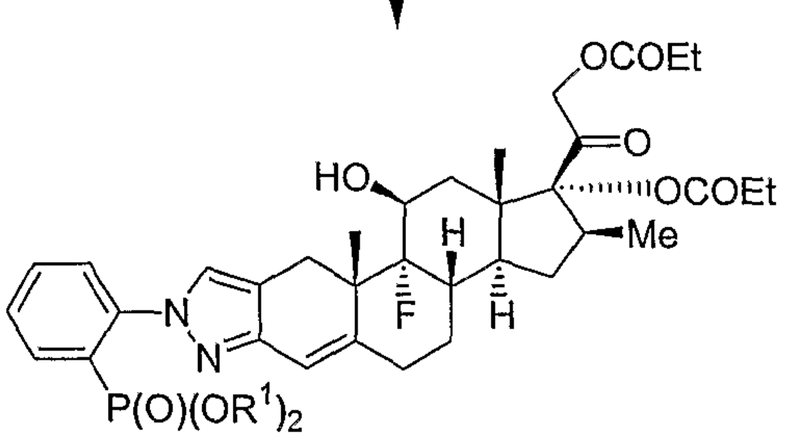
+



49.3



49.4

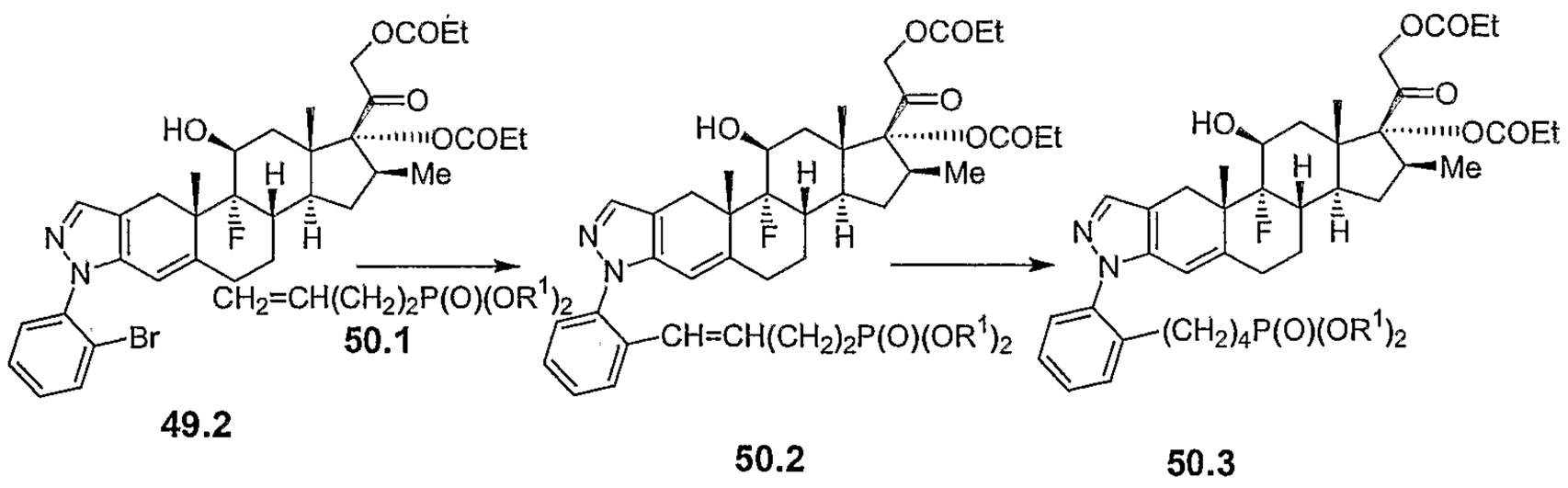


49.5

The preparation of phosphonates in which the phosphonate is attached by means of a phenyl group is illustrated above. In this sequence, the ketoaldehyde, **48.2**, is reacted, as described above, with 2-bromophenylhydrazine, **49.1** (Fluka), to give the isomeric pyrazole products, **49.2** and **49.3**. The products are then

reacted, as described herein, with a dialkyl phosphite $HP(O)(OR^1)_2$ and a palladium catalyst, to afford respectively the phosphonates, **49.4** and **49.5**. Using the above procedures, but employing, in place of 2-bromophenyl hydrazine, different bromoaryl or bromoheteroaryl hydrazines, **48.3**, the products, **48.6** and **48.7** are obtained.

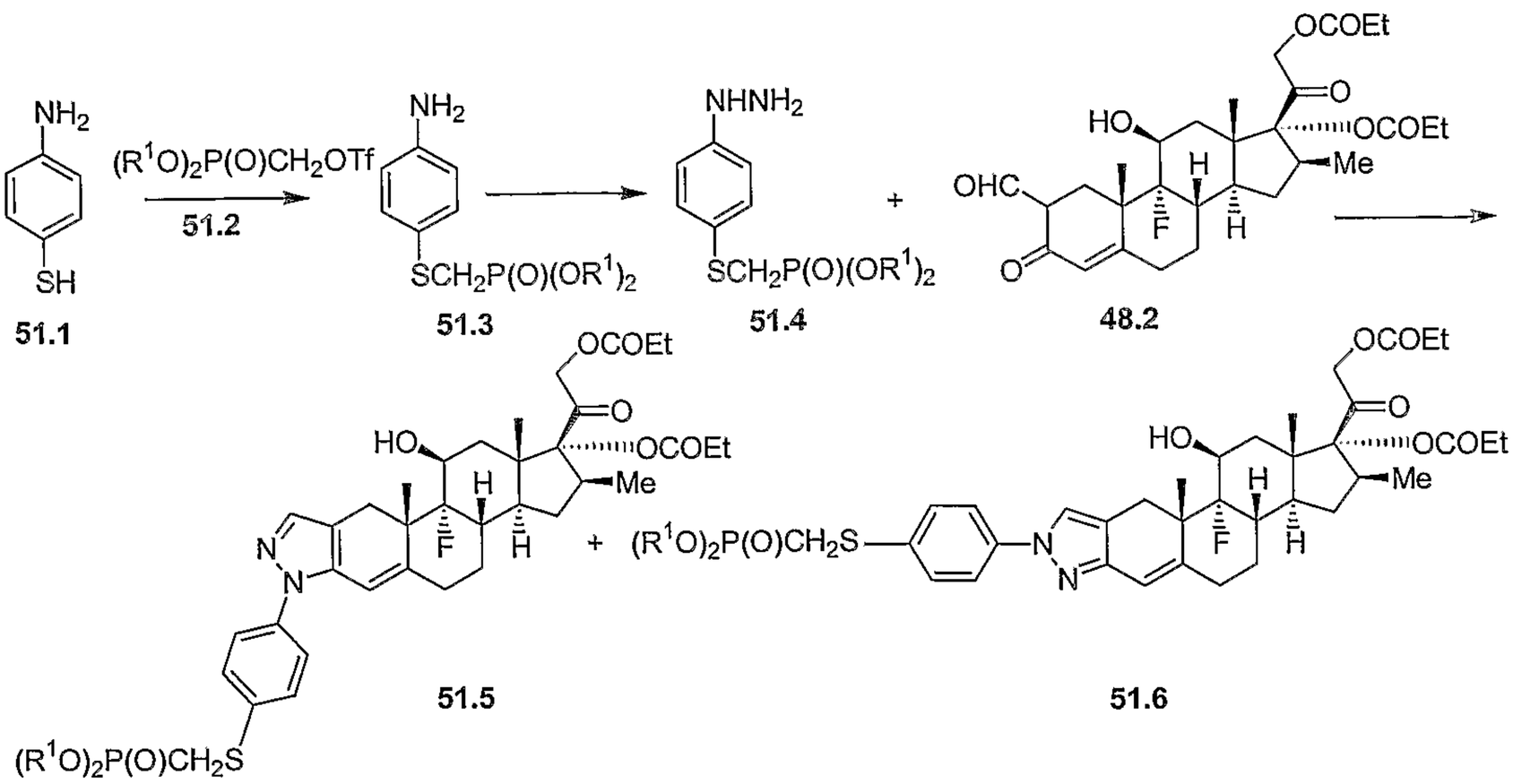
Example 50



49.2 **50.2** **50.3**

The preparation of phosphonates in which the phosphonate is attached by means of an aromatic or heteroaromatic group and a saturated or unsaturated alkyl chain is illustrated above. In this procedure, the bromophenyl-substituted pyrazole, **49.2**, is coupled in a Heck reaction, as described above, with, for example a dialkyl butenyl phosphonate, **50.1**, (*Org. Lett.*, **2001**, *3*, 217) to give the unsaturated phosphonate product, **50.2**. Optionally, the product is reduced, as described above, to give the saturated analog, **50.3**. Application of the above procedures to the isomeric bromophenyl pyrazole, **49.3**, affords the products isomeric with, **50.2** and **50.3**. Using the above procedures, but employing, in place of the phosphonate, **50.1**, different dialkyl alkenyl phosphonates, and/or different bromoaryl or heteroaryl pyrazoles, **48.4** or **48.5**, the products analogous to **50.2** and **50.3** are obtained.

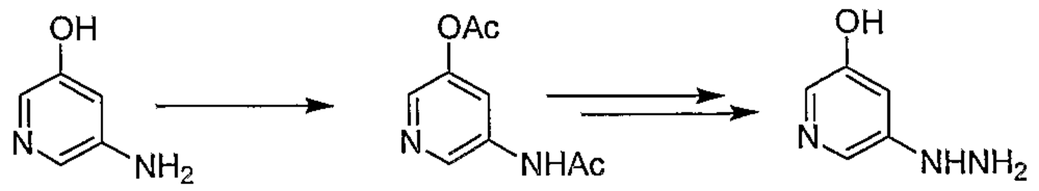
Example 51



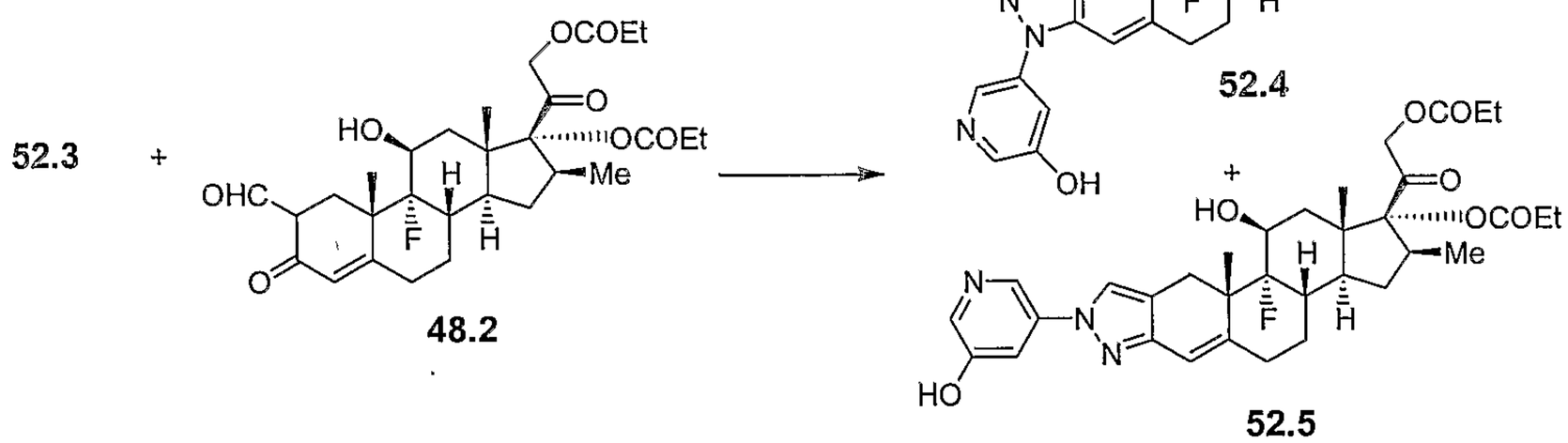
The preparation of phosphonates, **51.5** and **51.6**, in which the phosphonate is attached by means of an aryl or heteroaryl group and an alkoxy chain is illustrated above. In this procedure, 4-Aminothiophenol, **51.1**, is reacted in dimethylformamide solution at ambient temperature with a dialkyl trifluoro-methanesulfonyloxymethyl phosphonate, **51.2** (*Tetrahedron Lett.*, **1986**, *27*, 1477), and potassium carbonate to give the thioether, **51.3**. The product is then converted into the corresponding hydrazine, **51.4**, by means of a diazotization reaction in aqueous ethanolic hydrochloric acid, followed by reduction of the diazonium chloride with tin(II) chloride, as described in *J. Med. Chem.*, **2001**, *44*, 4031. The hydrazine is then reacted, as described above, with the ketoaldehyde, **48.2**, to form the isomeric pyrazoles, **51.5** and **51.6**.

Using the above procedures, but employing, in place of the triflate, **51.2**, different dialkylphosphono alkyl bromides or triflates, and/or different aromatic or heteroaromatic mercapto or hydroxyamines, the products analogous to **51.5** and **51.6** are obtained.

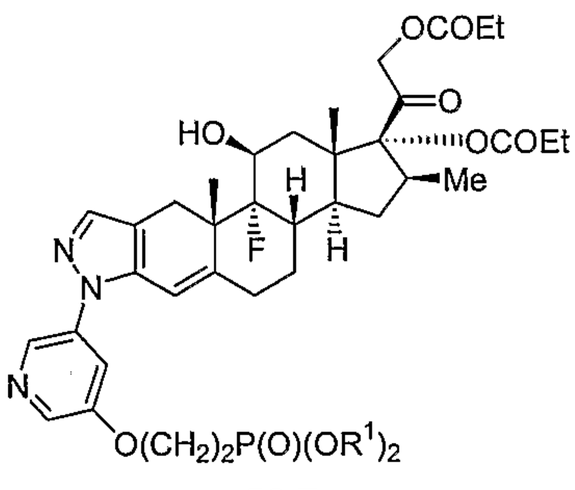
Example 52



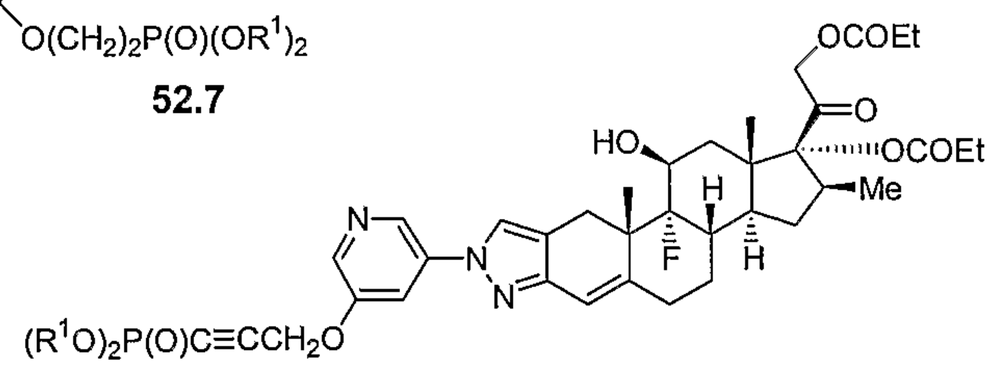
52.1 52.2 52.3



52.3 + 48.2 → 52.4 + 52.5



52.4 → 52.6 → 52.7

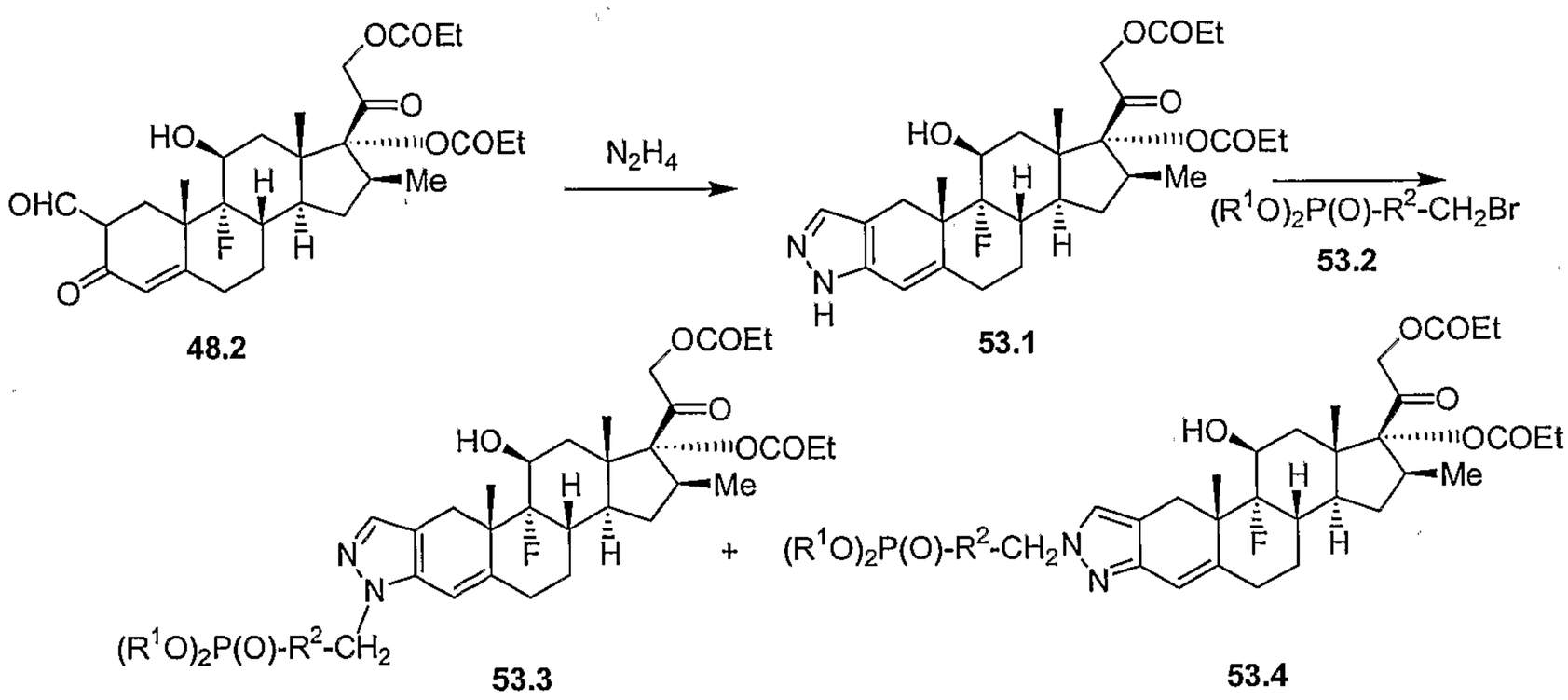


52.5 → 52.8 → 52.9

The preparation of phosphonates in which the phosphonate is attached by means of a pyridyl group a heteroatom and a variable carbon chain is illustrated above. In this procedure, 3-amino-5-hydroxypyridine, **52.1**, is converted, by reaction with acetic anhydride, into the diacetyl analog, **52.2**. The product is then transformed by diazotization and reduction, as described above, into the hydrazine, **52.3**. The hydrazine, **52.3**, is then reacted with the ketoaldehyde, **48.2**, to give the isomeric pyrazoles, **52.4** and **52.5**. The 2'-pyridyl product, **52.4**, is reacted in a Mitsonobu reaction, as described above, with a dialkyl hydroxyethyl phosphonate, **52.6** (*Zh. Obschei. Khim.*, **1973**, *43*, 2364), to afford the ether, **52.7**. Application of this procedure to the isomeric phenol, **52.5**, affords the product isomeric to compound, **52.7**.

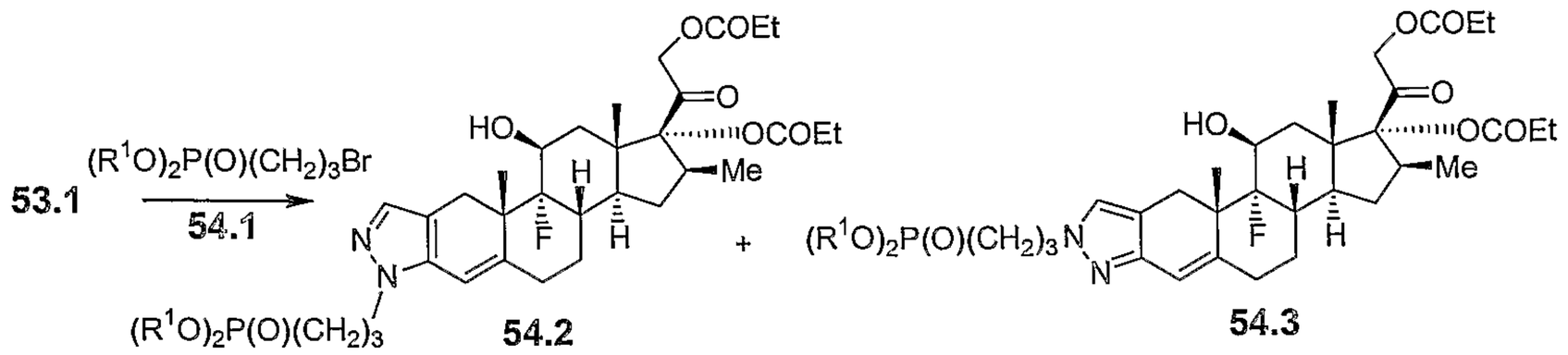
Alternatively, the isomeric phenol, **52.5**, is reacted, in dimethyl-formamide solution at about 80°, with one molar equivalent of a dialkyl bromopropynyl phosphonate, **52.8** (*Bioorg. Med. Chem. Lett.*, **1994**, *4*, 273), and cesium carbonate, to prepare the phosphonate, **52.9**. Application of this procedure to the isomeric phenol, **52.4**, affords the product isomeric with compound, **52.4**. Using the above procedures, but employing, in place of the carbinol, **52.6**, or the bromide, **52.8**, different thiols, alcohols or bromides, and/or different phenols, **48.4** or **48.5**, in which X is OH, the corresponding products analogous to **52.7** and **52.9** are obtained.

Example 53

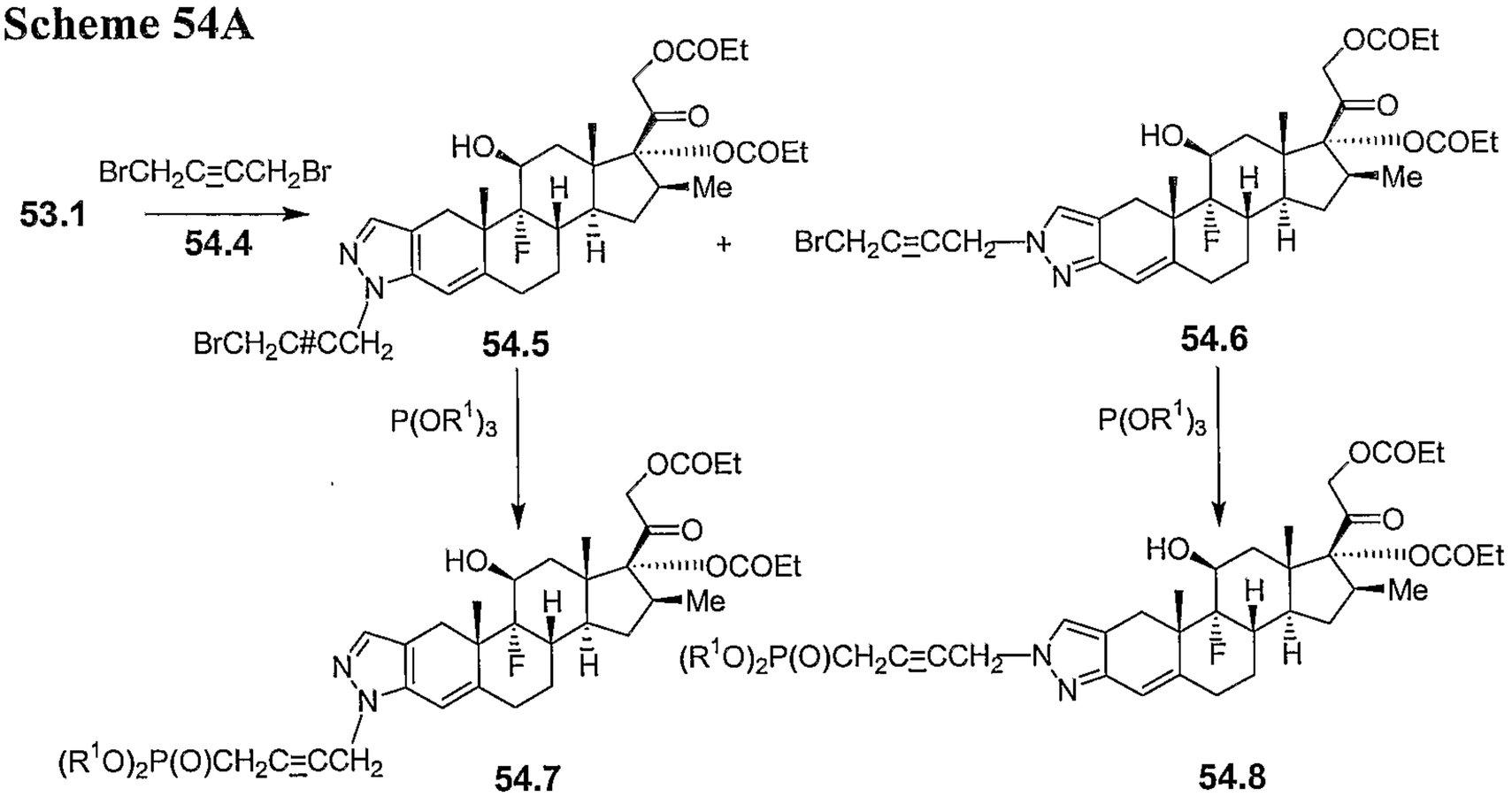


The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **48.2**, is reacted with hydrazine, to afford the pyrazole derivative, **53.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The resulting pyrazole is then reacted with a dialkyl bromomethyl phosphonate, **53.2**, in which R^2 is as defined above, to produce the isomeric 2' and 1' alkylation products, **53.3** and **53.4**, respectively. The alkylation of substituted pyrazoles is described, for example, in "Heterocyclic Chemistry," by T. L. Gilchrist, Longman, **1992**, p. 309.

Example 54



Scheme 54A



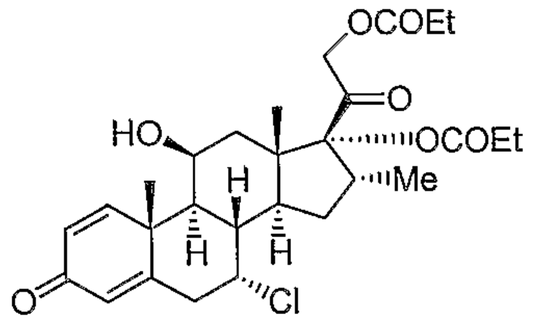
Pyrazole, **53.1**, is reacted, in dimethylformamide solution at ca. 90°, with a dialkyl bromopropyl phosphonate, **54.1** (Aldrich), and a base such as dimethylaminopyridine or lithium hexamethyldisilazide, to yield the isomeric alkylation products, **54.2** and **54.3**.

As shown in Scheme **54A**, the pyrazole, **53.1**, is reacted in dimethyl-formamide solution at ambient temperature with one molar equivalent of 1,4-dibromobut-2-yne, **54.4** (Narchem),and potassium carbonate, to afford the alkylation products, **54.5** and **54.6**. The products are then heated at 120° with a trialkyl phosphite in an Arbuzov reaction, to yield the phosphonates, **54.7** and **54.8**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115-72. Using the above procedures, but employing, in place of the dibromide, **54.4**, different alkyl, alkenyl or alkynyl dibromides, the products analogous to **54.7** and **54.8** are obtained.

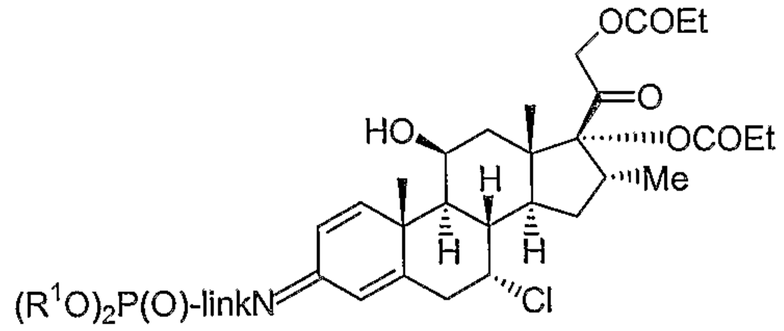
Example 55

The structures of Aclometasone dipropionate, **55/A** (*J. Med. Chem.*, **1980**, *23*, 430; U.S. Patent No. 4,124,707), and the esters, **55A – 55C**, are shown

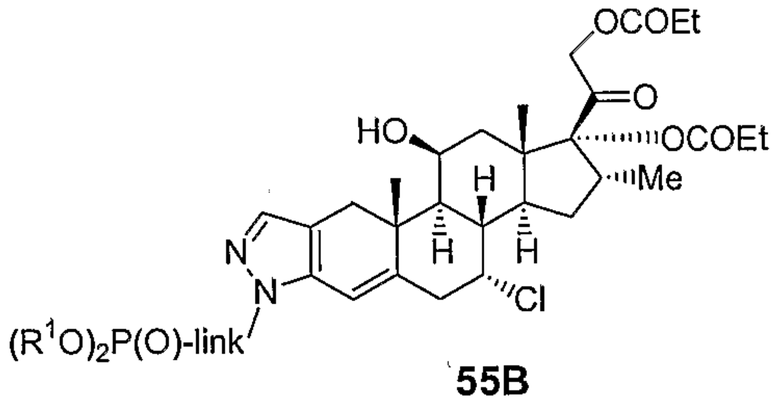
below, in which the substituent R^1 is H, alkyl, alkenyl, aryl or aralkyl. The compounds, **55A – 55C**, incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.



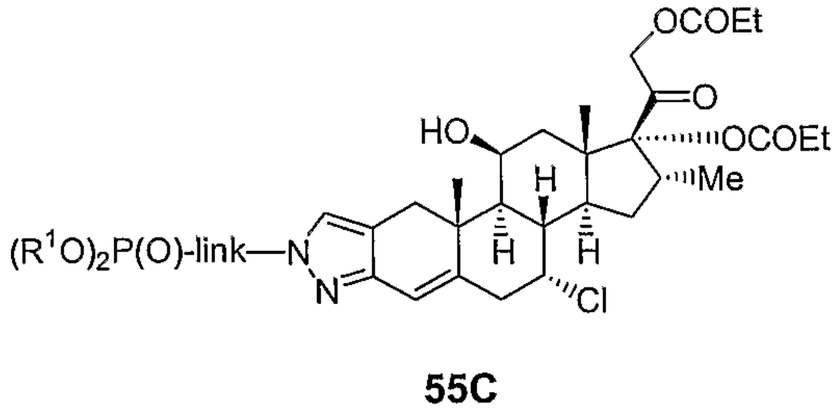
55/A
Aclometasone Dipropionate



55A

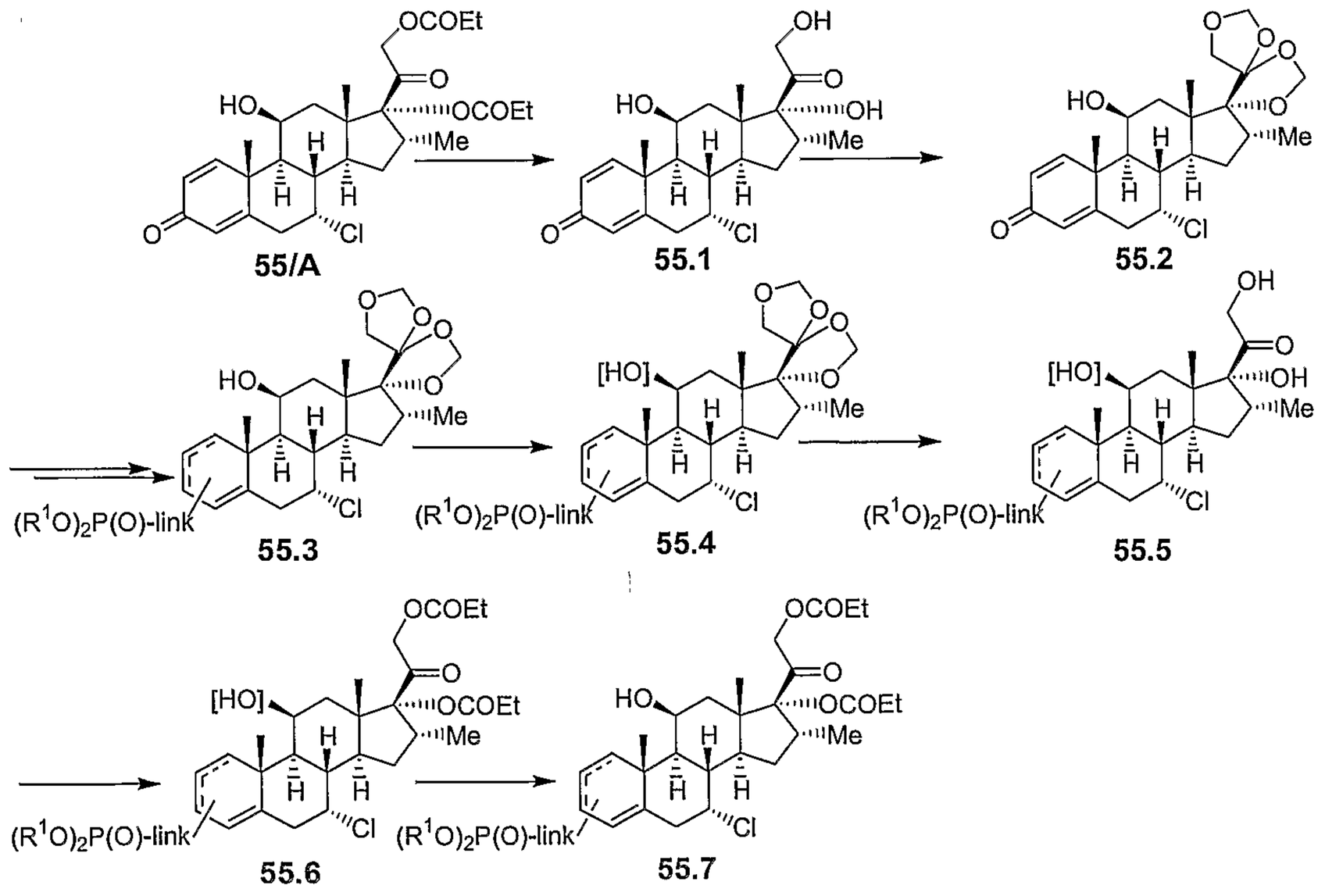


55B



55C

Scheme 55A



The steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety, as illustrated in Scheme 55A. In this sequence, the propionate esters are hydrolyzed, for example by reaction with two molar equivalents of lithium hydroxide in aqueous dimethoxyethane solution at ambient temperature, to give

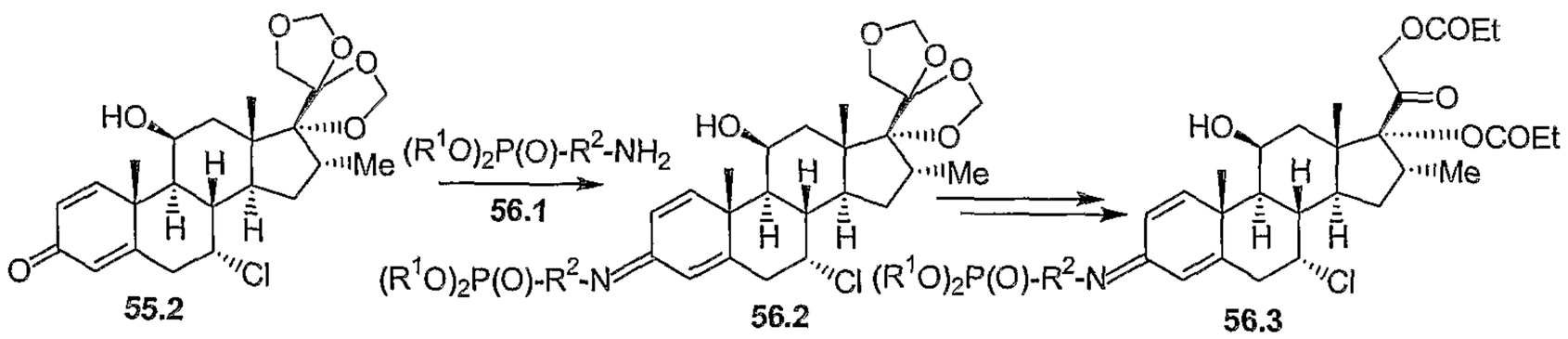
the diol, **55.1**. The product is then reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **55.2**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester, **55.3**. Prior to hydrolysis of the BMD protecting group, the 11-hydroxyl group is protected. The protecting group is selected so that it is stable to the conditions required for removal of the BMD group, and so that it is removable without affecting the subsequently introduced 17, 21-diester moiety. For example, the 11-hydroxyl group is protected by conversion to the 4-azido-butyrate ester, by reaction with 4-azidobutyryl chloride in pyridine. The 11-azidobutyrate group is then removed from the diester, **55.6**, by reaction with triphenylphosphine, as described in *Bull. Soc. Chem. Jpn.*, **1986**, *59*, 1296. Alternatively, the 11-hydroxyl group is protected by conversion to the 2-(trimethylsilyl)ethyl carbonate, by reaction with 2-(trimethylsilyl)ethyl carbonyl chloride and pyridine. The 2-(trimethylsilyl) carbonate is removed from the diester, **55.6**, by reaction with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, as described in *Tet. Lett.*, **1981**, *22*, 969.

Alternatively, the 11-hydroxyl group is protected by conversion to the trichloroacetyl ester, by reaction with trichloroacetyl chloride in dimethyl-formamidepyridine. The trichloroacetyl ester is removed by reaction with ethanolic ammonia at ambient temperature, as described in *Coll. Czech. Chem. Commun.*, **1962**, *27*, 2567. The BMD moiety in the protected product, **55.4**, is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the diol, **55.5**. The diol, **55.5**, is acylated, for example by reaction with propionic acid and dicyclohexyl carbodiimide in dimethylformamide at ambient temperature, or by reaction with propionyl chloride and triethylamine in dichloromethane, to produce the dipropionate, **55.6**. Deprotection of the 11-hydroxyl group, as described above, then affords the diester, **55.7**.

Alternatively, the 20-ketone group is protected as the diethylamine adduct by reaction with titanium tetrakis(diethylamide), as described in

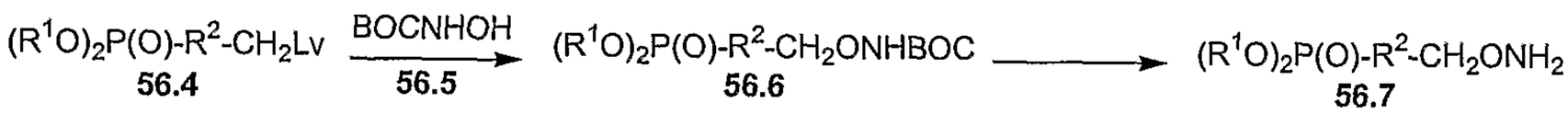
"Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M Wuts, Wiley, Second Edition **1990**, p. 219.

Example 56



The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative, **55.2**, is reacted with an amine or hydroxylamine, **56.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, to afford the imine or iminoxy product, **56.2**. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The BMD-protected side-chain compound, **56.2**, is then converted into the diester, **56.3**.

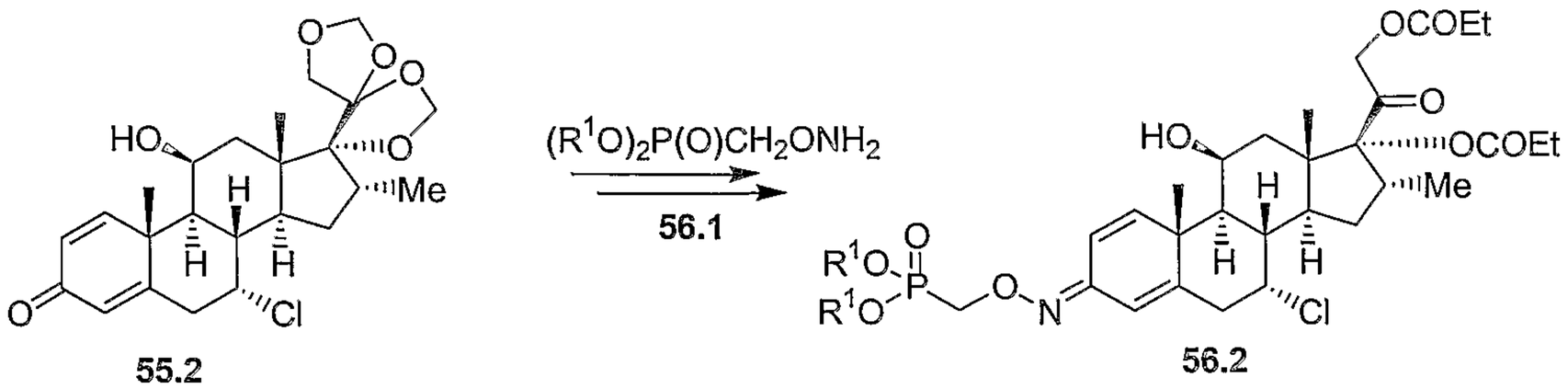
Example 56A



Also illustrated is the preparation of hydroxylamine ethers incorporating a phosphonate group. A phosphonate, **56.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **56.5** (Aldrich), to produce the ether, **56.6**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethyl-formamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine, to give the product, **56.6**. Deprotection,

for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **56.7**.

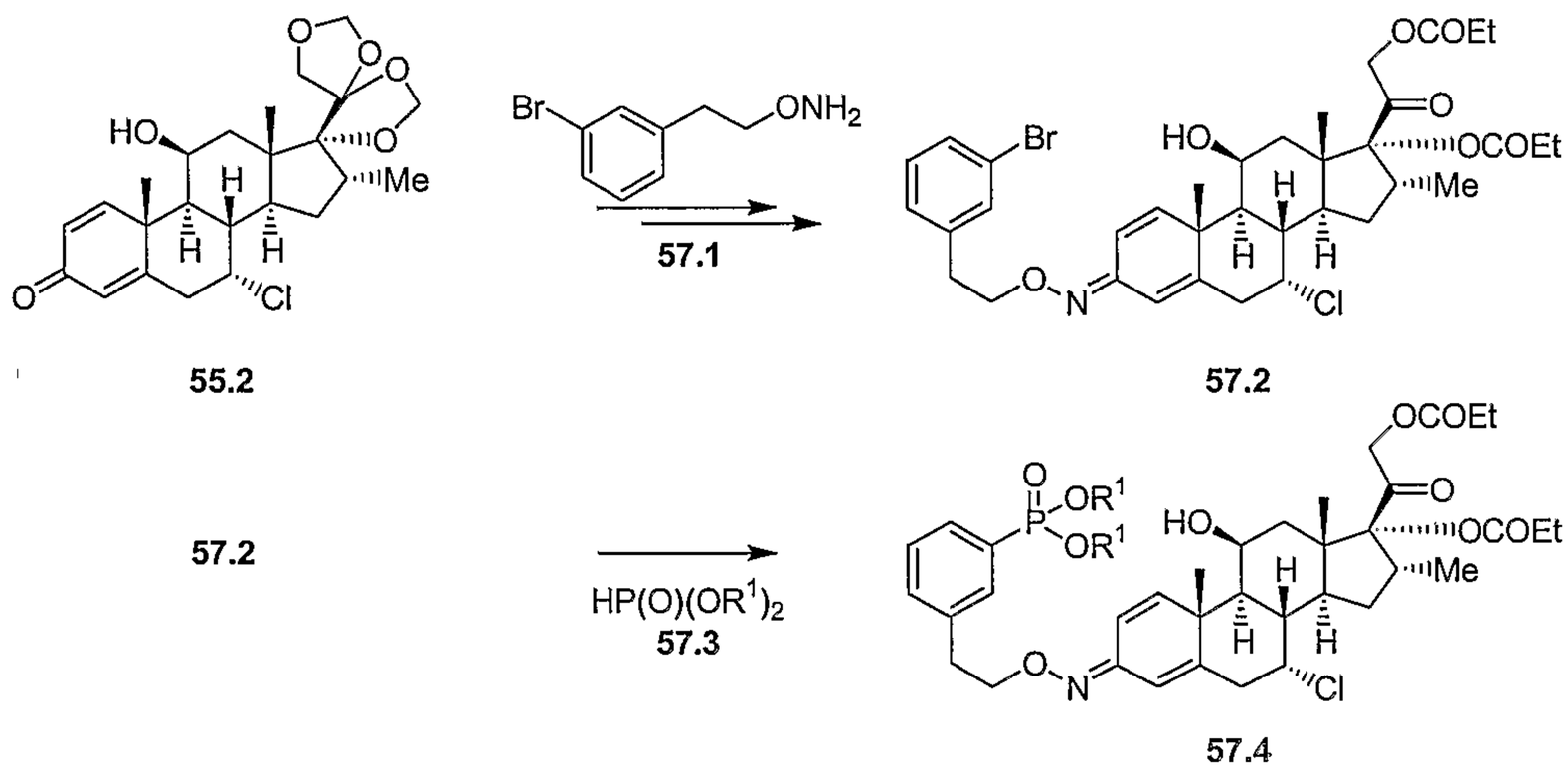
Example 56B



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate, **55.2**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **56.1**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford, after deprotection and side chain acylation, the oxime ether, **56.2**. The oxime forming reaction is performed at ambient temperature in pyridine solution between equimolar amounts of the reactants.

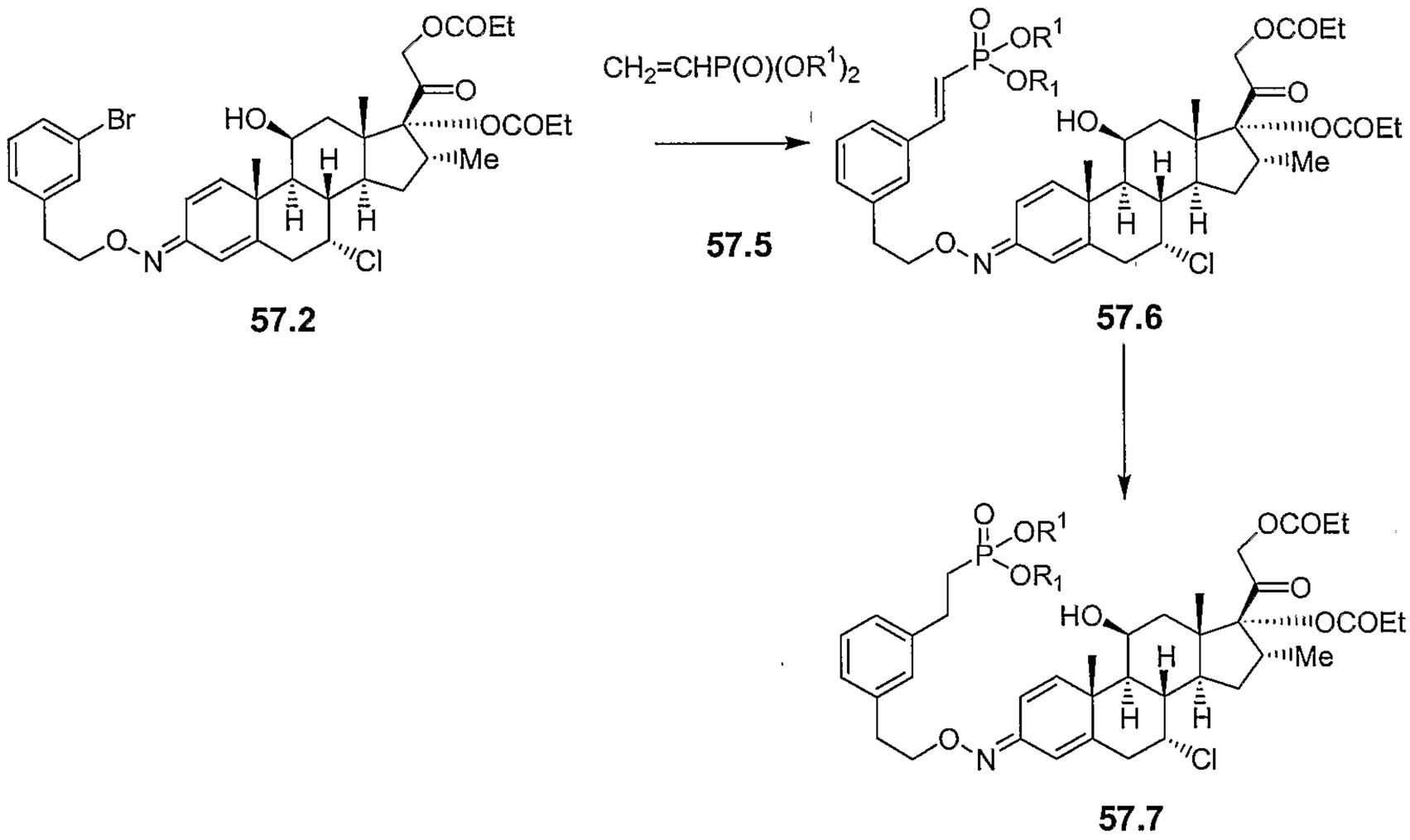
Using the above procedures, but employing, in place of the oxime ether, **56.1**, different oxime ethers, **56.7**, the corresponding products, **56.2** are obtained.

Example 57



The preparation of phosphonates incorporating an iminoxy group, by means of the reaction between the substrate, **55.2**, and O-2-(3-bromophenyl)-ethylhydroxylamine, **57.1**, prepared as described above from compound, **55.1**,

and 2-(3-bromophenyl)ethyl bromide, respectively. The resultant oxime ether is converted, by deprotection and side chain acylation, into the compound, **57.2**, which is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **57.3**, to afford the phosphonate, **57.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0).

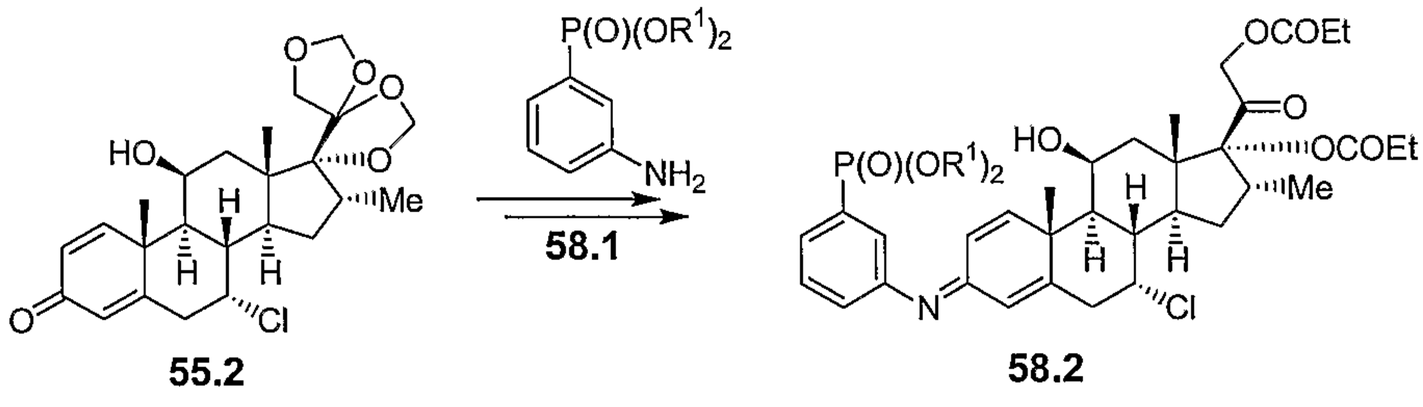


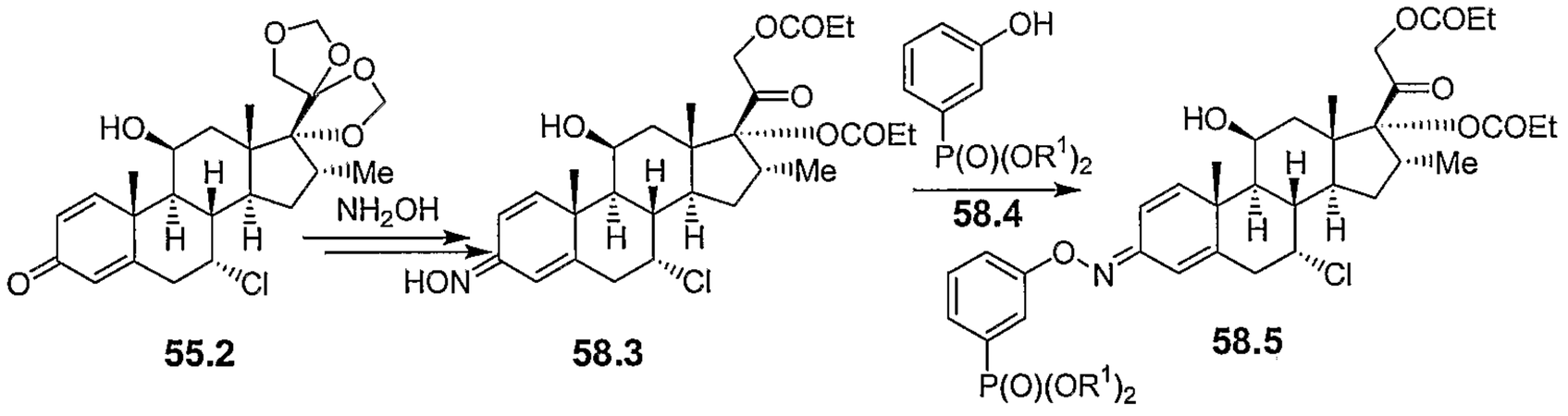
Alternatively, the bromo-substituted product, **57.2**, is coupled, in a palladium-catalyzed Heck reaction, with a dialkyl vinyl phosphonate, **57.5** (Aldrich), to give the unsaturated phosphonate, **57.6.** The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)-palladium(0) or a palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **57.6**, is reduced, for example by reaction with diimide, to produce the saturated analog, **57.7**. The reduction of olefinic bonds is described in "Comprehensive Organic

Transformations," by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromophenyl reagent, **57.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **57.4**, **57.6** and **57.7** are obtained.

Example 58





The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate, **55.2**, is reacted with a dialkyl 3-aminophenyl phosphonate, **58.1** (*J. Med. Chem.*, **1984**, *27*, 654), to give, after deprotection and side chain acylation, the imine product, **58.2**. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions, to give the product, **58.2**.

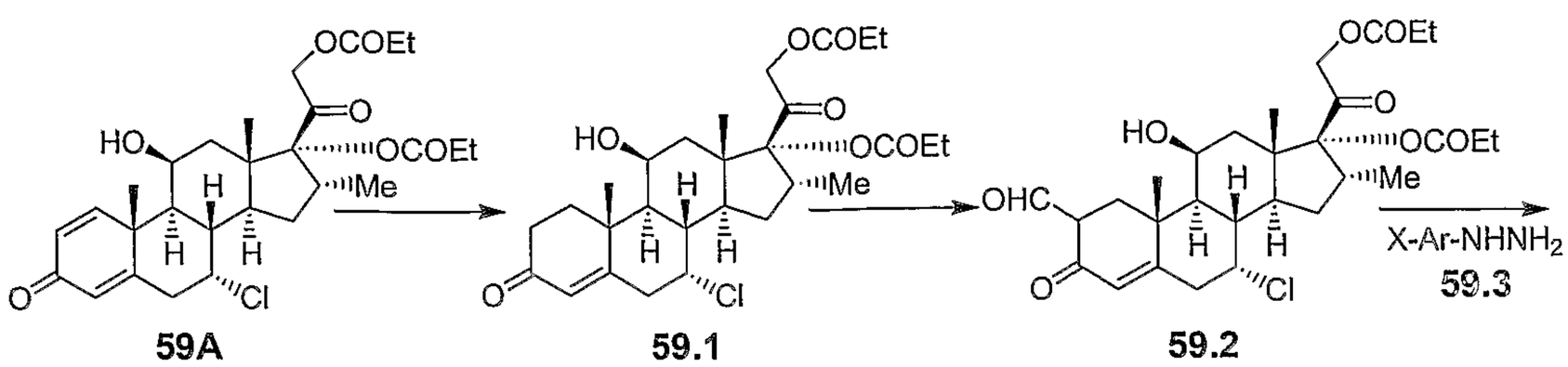
Using the above procedures, but employing, in place of the 3-aminophenyl phosphonate, **58.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **58.2** are obtained.

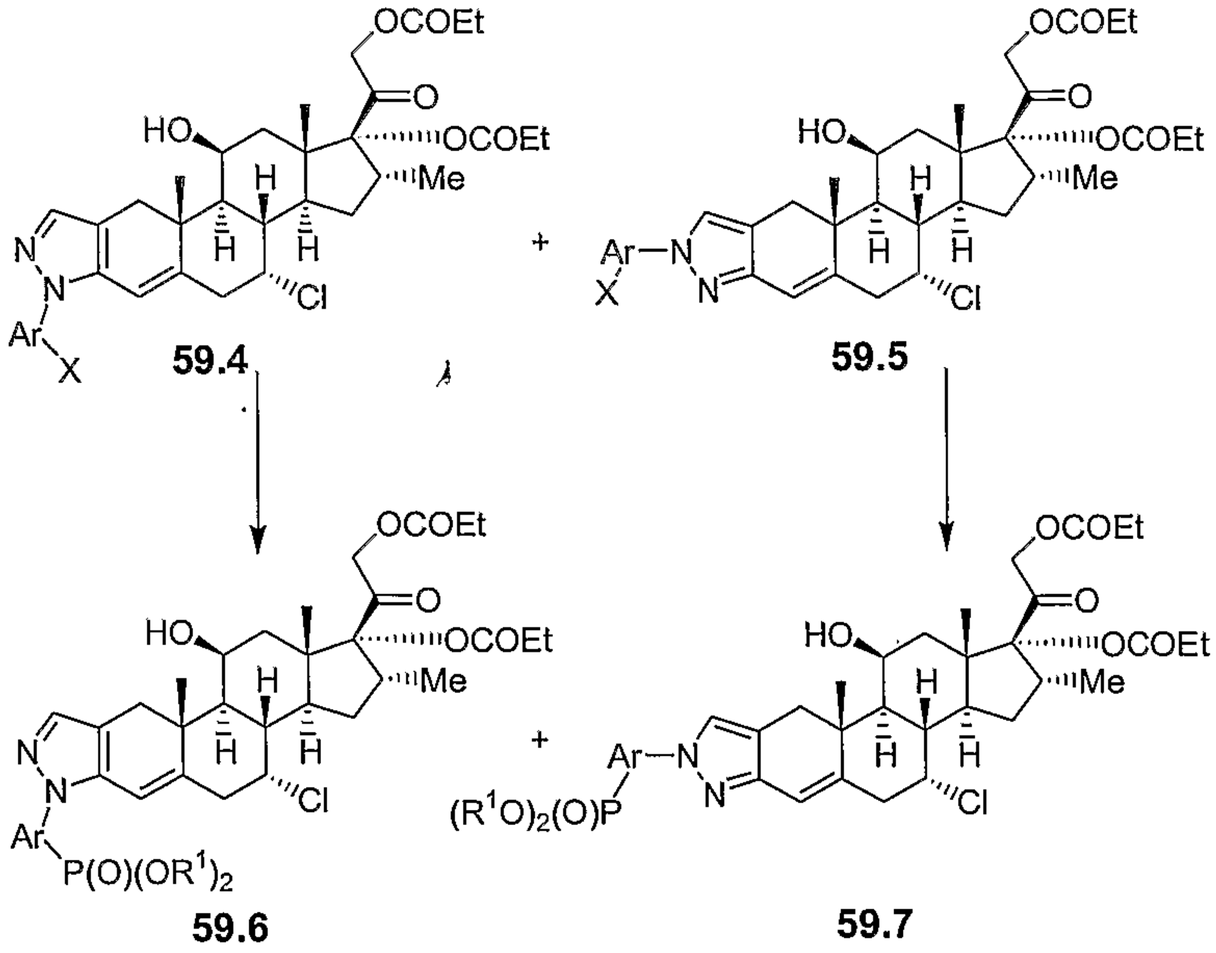
An alternative method for the preparation of phosphonates, **58.3**, where the phosphonate is attached by means of an oximino group starts with the

dienone, **55.2**, is illustrated above. The dienone is reacted with hydroxylamine to yield, after deprotection and side chain acylation, the oxime, **58.3**. The reaction of steroidal 1,4-dien-3-ones with hydroxylamine is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then reacted with a dialkyl 3-hydroxyphenyl phosphonate, **58.4** (Epsilon), in a Mitsonobu reaction, to yield the substituted oxime, **58.5**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 448, and in "Advanced Organic Chemistry," Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p. 153-4 and in *Org. React.*, **1992**, *42*, 335. The phenol and the hydroxy or mercapto component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656.

Using the above procedures, but employing, in place of the phosphonate, **58.4**, different dialkyl hydroxy-substituted aryl or heteroaryl phosphonates, the products analogous to **58.5** are obtained.

Example 59

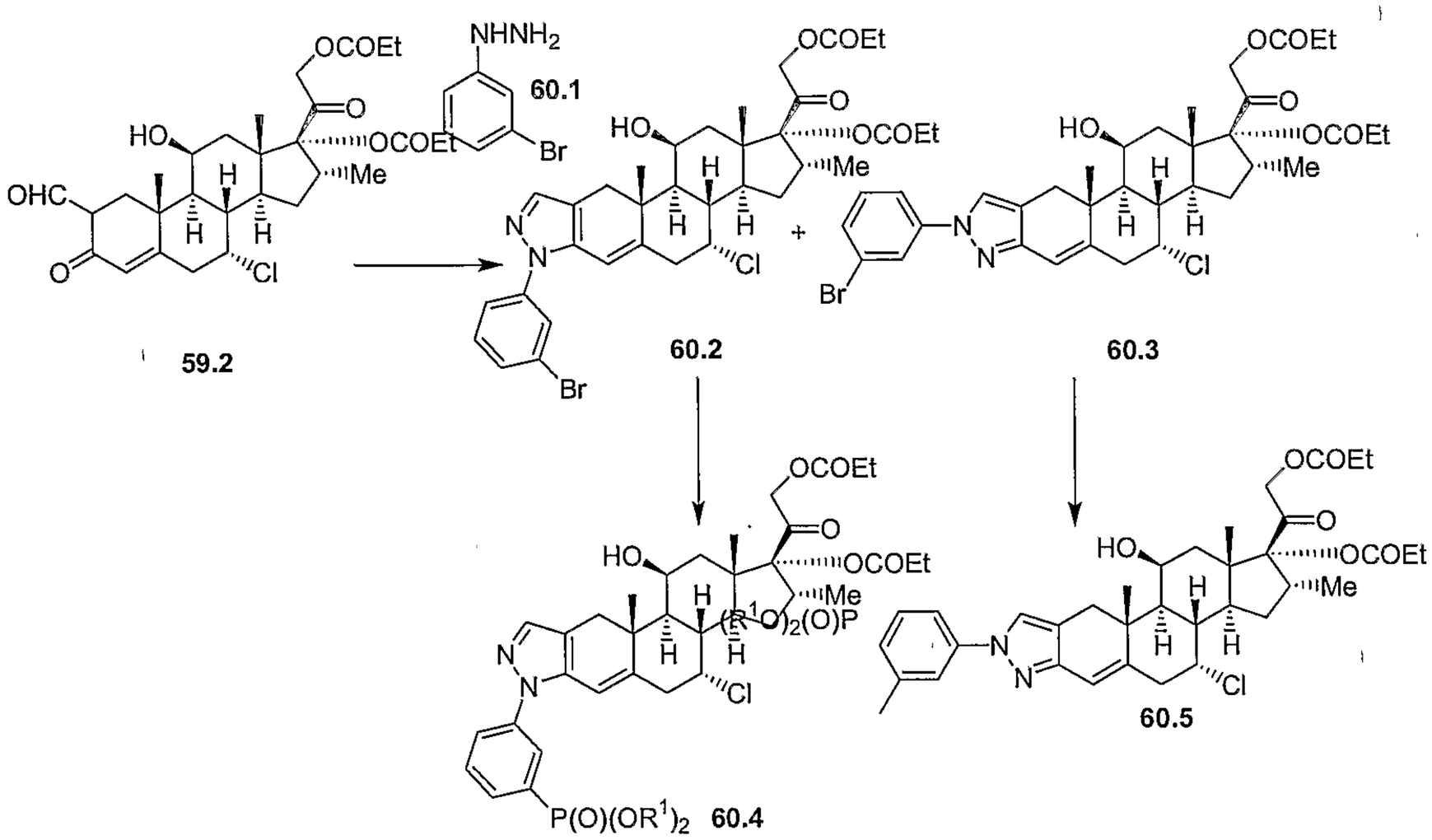




The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is shown above. In this procedure, Aclometasone dipropionate, **59A**, is reduced to afford the 1,2-dihydro product, **59.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in Australian Patent Application 275950409, to afford the 2-formyl product, **59.2**. Optionally, the substrate, **59A**, is protected, for example, as described above in Example 55, prior to the formylation reaction, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The 2-formyl product is then reacted with an aryl or heteroaryl hydrazine, **59.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **59.4** and **59.5**. The

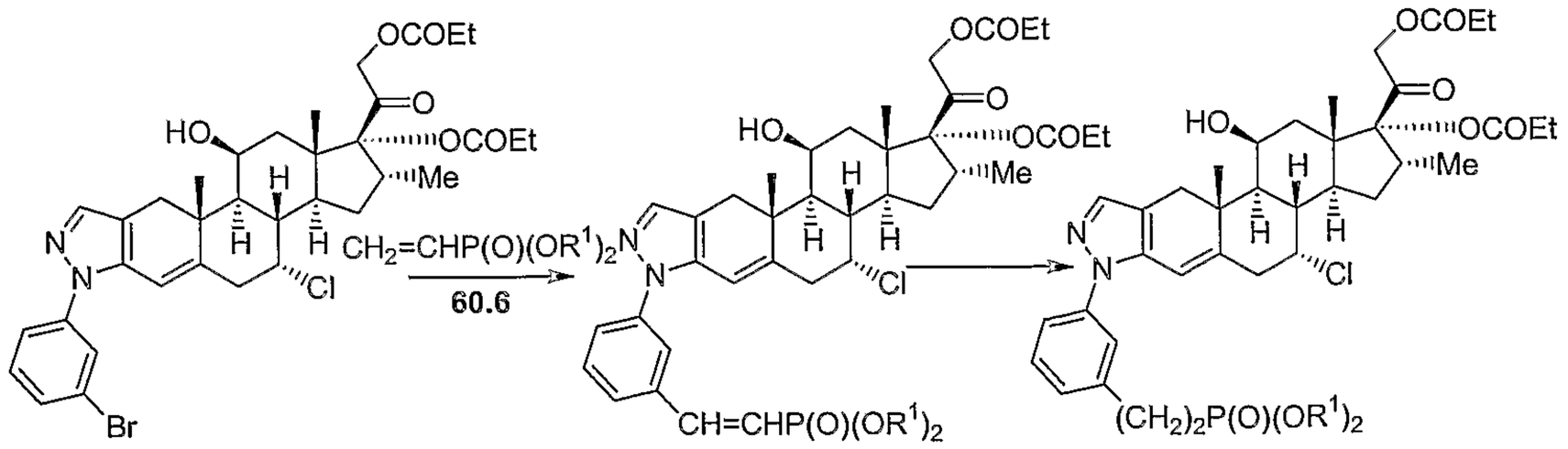
ring-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **59.4** and **59.5**, are then transformed, for example by the procedures described in Examples 60 - 65, respectively into the phosphonates, **59.6** and **59.7**.

Example 60



The preparation of phosphonates in which the phosphonate is attached by means of a phenyl group is illustrated above. In this sequence, the ketoaldehyde, **59.2**, is reacted, as described above, with 3-bromophenylhydrazine, **60.1** (Fluka), to give the isomeric pyrazole products, **60.2** and **60.3**. The products are then reacted, as described above, with a dialkyl phosphite $HP(O)(OR^1)_2$ and a palladium catalyst, to afford respectively the phosphonates, **60.4** and **60.5**. Using the above procedures, but employing, in place of 3-bromophenyl hydrazine, different bromoaryl or bromoheteroaryl hydrazines, **59.3**, the corresponding products, **59.6** and **59.7** are obtained.

Example 60A

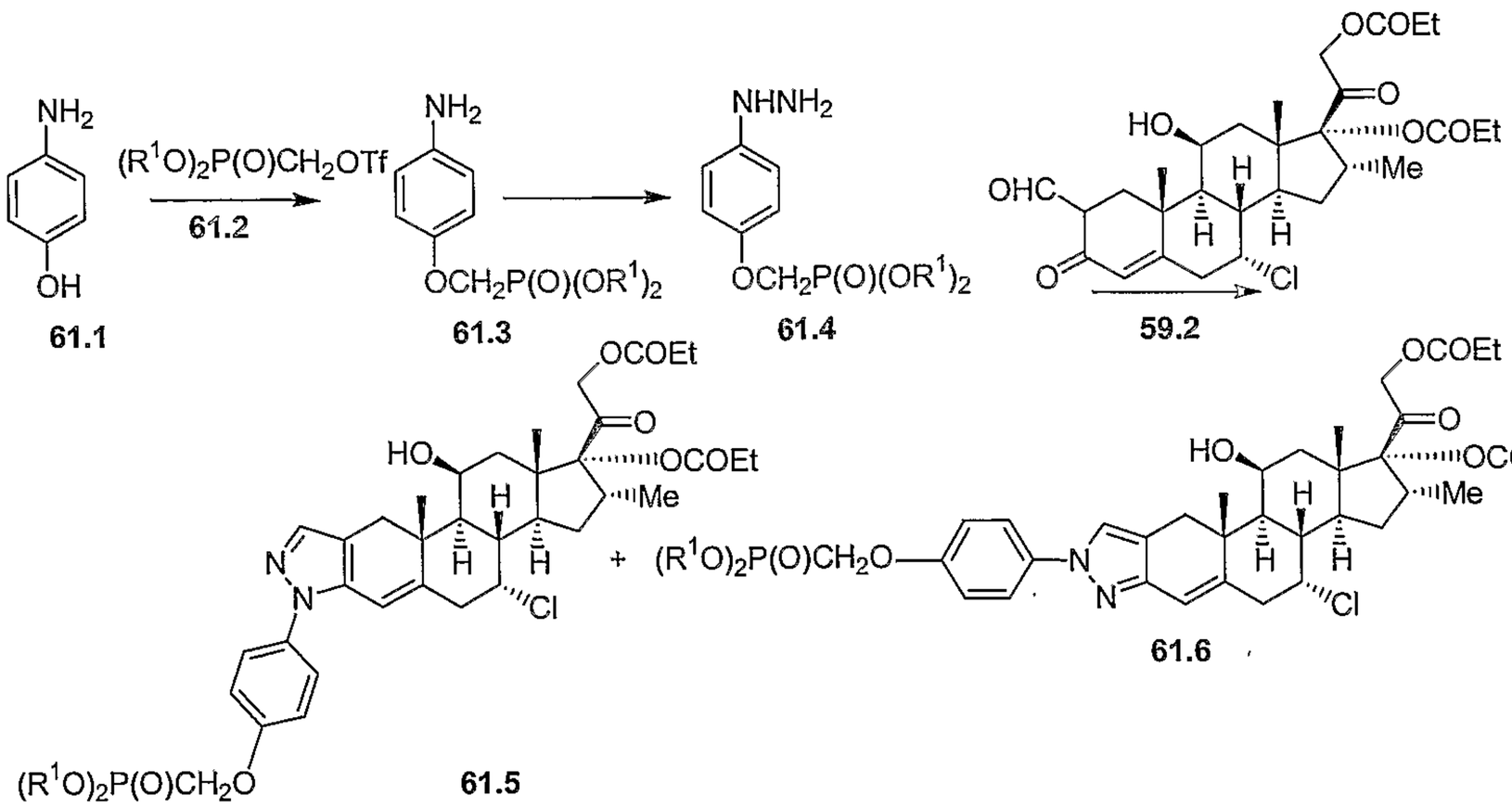


60.2 60.7 60.8

The preparation of phosphonates in which the phosphonate is attached by means of an aromatic or heteroaromatic group and a saturated or unsaturated alkyl chain is illustrated above. In this procedure, the bromophenyl-substituted pyrazole, **60.2**, is coupled in a Heck reaction, as described above, with, for example a dialkyl vinyl phosphonate, **60.6** (Aldrich), to give the unsaturated phosphonate product, **60.7**. Optionally, the product is reduced, as described above, to give the saturated analog, **60.8**. Application of the above procedures to the isomeric bromophenyl pyrazole, **60.3**, affords the products isomeric with, **60.7** and **60.8**.

Using the above procedures, but employing, in place of the phosphonate, **60.6**, different dialkyl alkenyl phosphonates, and/or different bromoaryl or heteroaryl pyrazoles, **59.4** or **59.5** (X = Br), the products analogous to **60.7** and **60.8** are obtained.

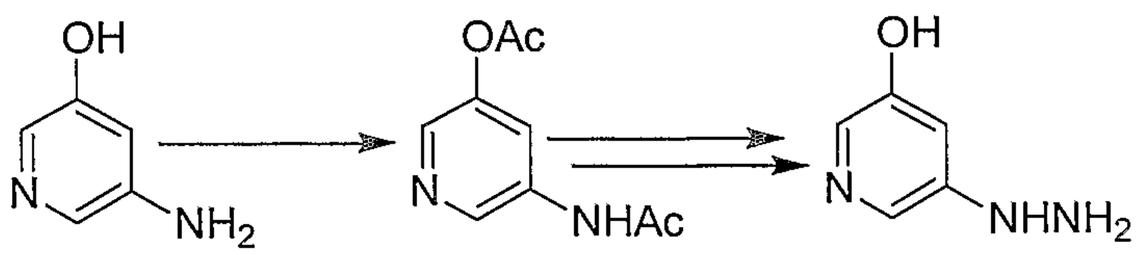
Example 61



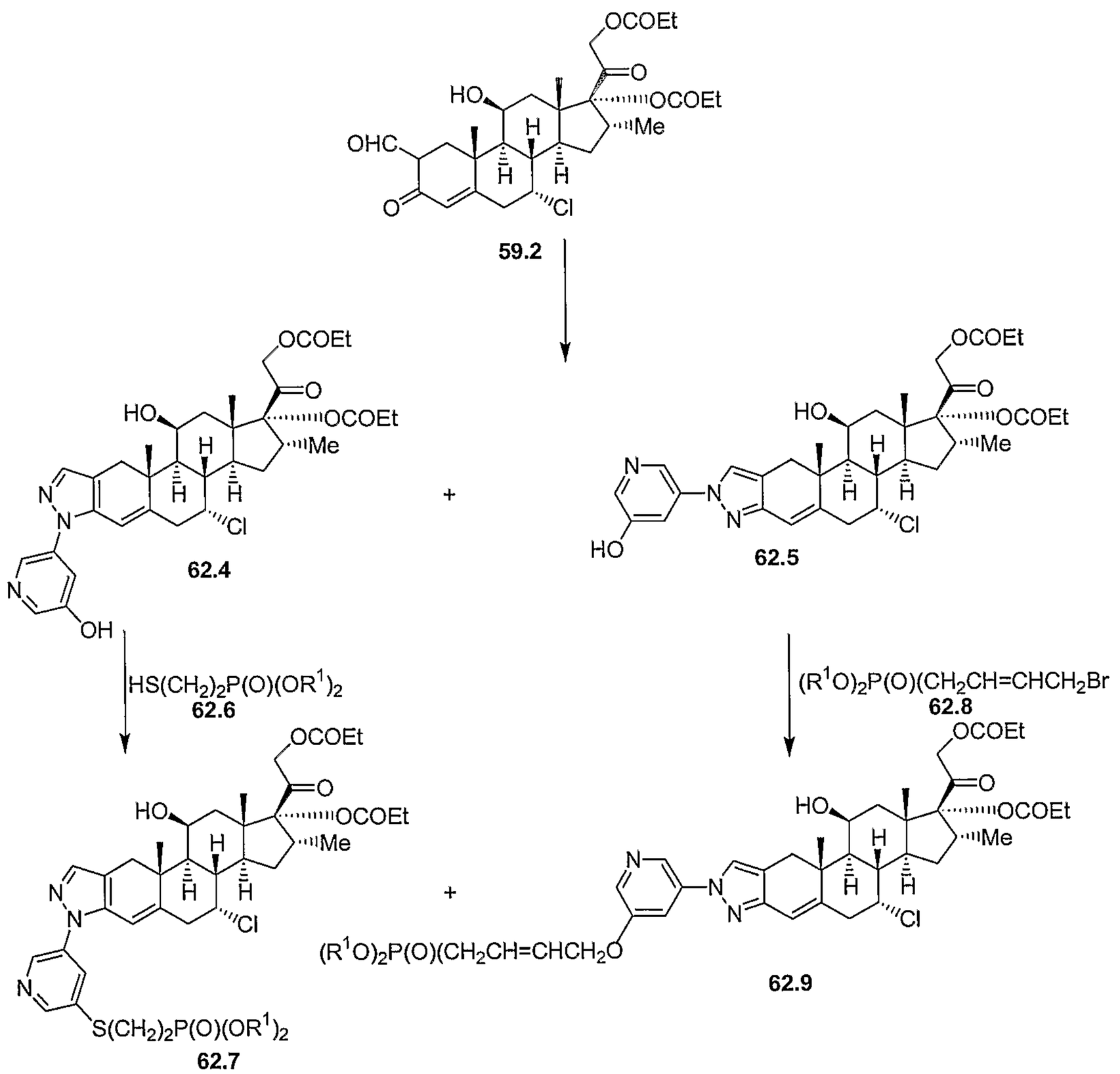
The preparation of phosphonates in which the phosphonate is attached by means of an aryl or heteroaryl group and an alkoxy chain is illustrated above. In this procedure, 4-aminophenol, **61.1**, is reacted in dimethylformamide solution at ambient temperature with a dialkyl trifluoromethanesulfonyloxymethyl phosphonate, **61.2** (*Tetrahedron Lett.*, **1986**, *27*, 1477), and potassium carbonate to give the ether, **61.3**. The product is then converted into the corresponding hydrazine, **61.4**, by means of a diazotization reaction in aqueous ethanolic hydrochloric acid, followed by reduction of the diazonium chloride with tin(II) chloride, as described in *J. Med. Chem.*, **2001**, *44*, 4031. The hydrazine is then reacted, as described above, with the ketoaldehyde, **59.2**, to form the isomeric pyrazoles, **61.5** and **61.6**.

Using the above procedures, but employing, in place of the triflate, **61.2**, different dialkylphosphono alkyl bromides or triflates, and/or different aromatic or heteroaromatic hydroxyamines, the products analogous to **61.5** and **61.6** are obtained.

Example 62



The preparation of phosphonates in which the phosphonate is attached by means of a pyridyl group, a heteroatom, and a variable carbon chain is shown herein. In this procedure, 3-amino-5-hydroxypyridine, **62.1**, is converted, by reaction with acetic anhydride, into the diacetyl analog, **62.2**. The product is then transformed by diazotization and reduction, as described above, into the hydrazine, **62.3**.



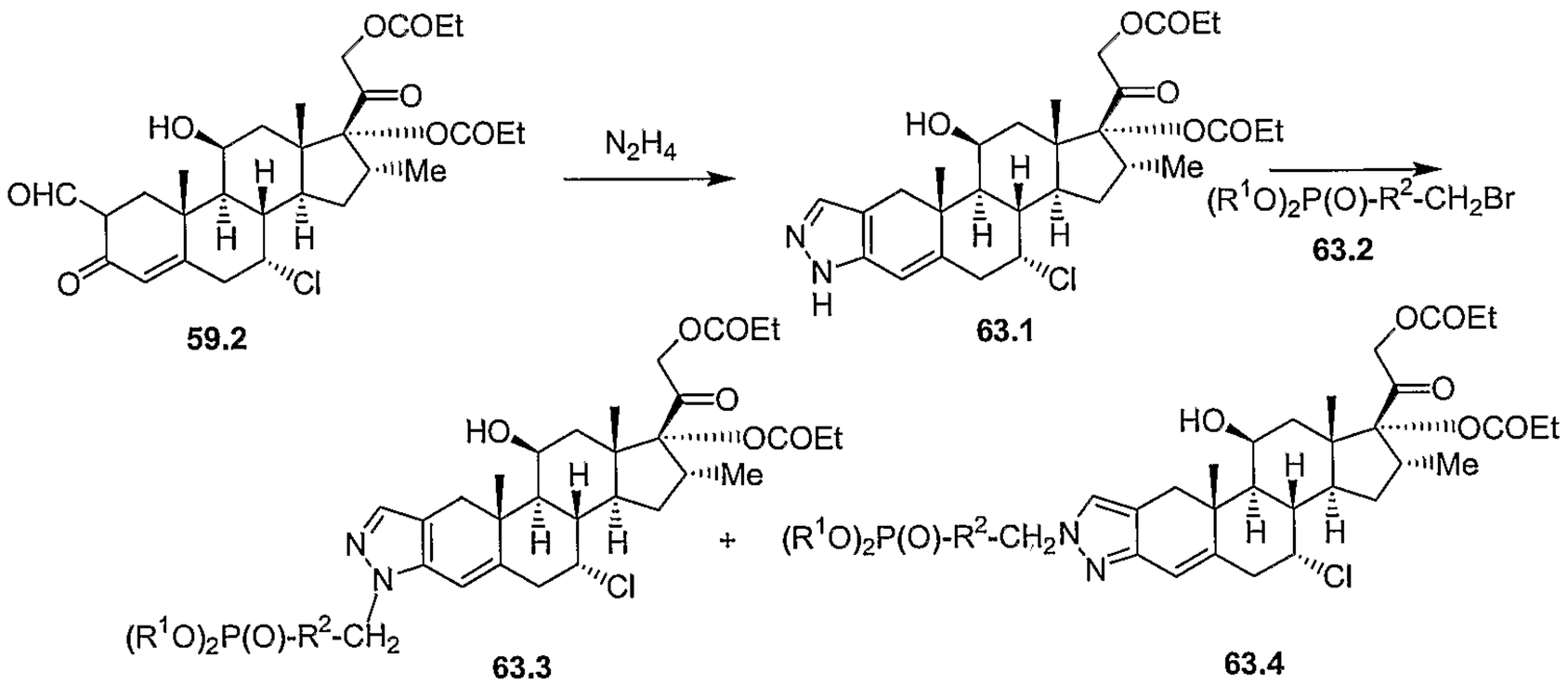
The hydrazine, **62.3**, is then reacted with the ketoaldehyde, **59.2**, to give the isomeric pyrazoles, **62.4** and **62.5**. The 2'-pyridyl product, **62.4**, is reacted in a Mitsonobu reaction, as described above, with a dialkyl mercaptoethyl phosphonate, **62.6** (*Zh. Obschei. Khim.*, **1973**, *43*, 2364), to afford the thioether, **62.7**. Application of this procedure to the isomeric phenol, **62.5**, affords the product isomeric to, **62.7**.

Alternatively, the isomeric phenol, **62.5**, is reacted, in dimethyl-formamide solution at ca. 80°, with one molar equivalent of a dialkyl bromo-

butenyl phosphonate, **62.8** (*J. Med. Chem.*, **1992**, *35*, 1371), and cesium carbonate, to prepare the phosphonate, **62.9**. Application of this procedure to the isomeric phenol, **62.4**, affords the product isomeric with, **62.9**.

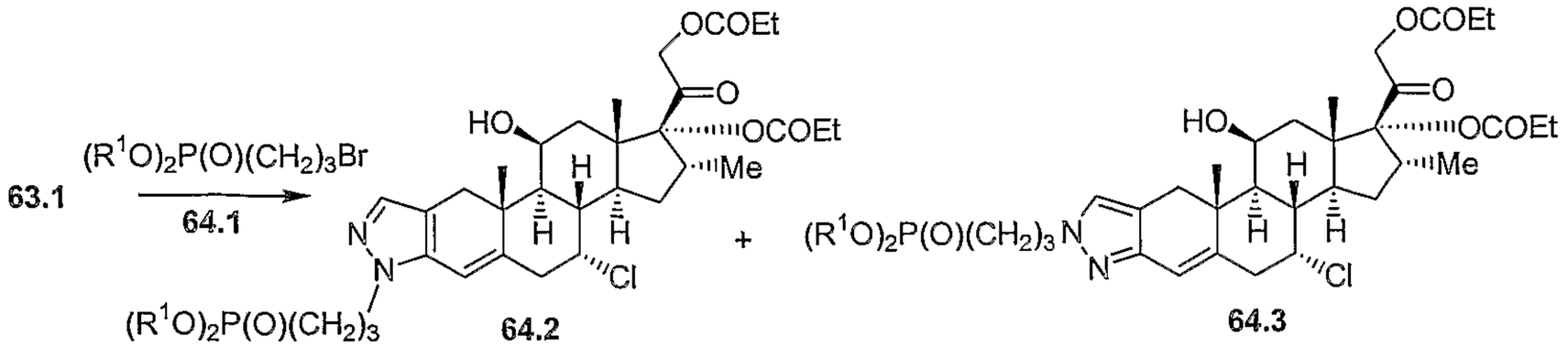
Using the above procedures, but employing, in place of the thiol, **62.6**, or the bromide, **62.8**, different thiols, alcohols or bromides, and/or different phenols, **59.4** or **59.5**, in which X is OH, the corresponding products analogous to **62.7** and **62.9** are obtained.

Example 63



The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **59.2**, is reacted with hydrazine, to afford the pyrazole derivative, **63.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The resulting pyrazole is then reacted with a dialkyl bromomethyl phosphonate, **63.2**, in which R^2 is as defined above, to produce the isomeric 2' and 1' alkylation products, **63.3** and **63.4**, respectively. The alkylation of substituted pyrazoles is described, for example, in "Heterocyclic Chemistry," by T. L. Gilchrist, Longman, **1992**, p. 309.

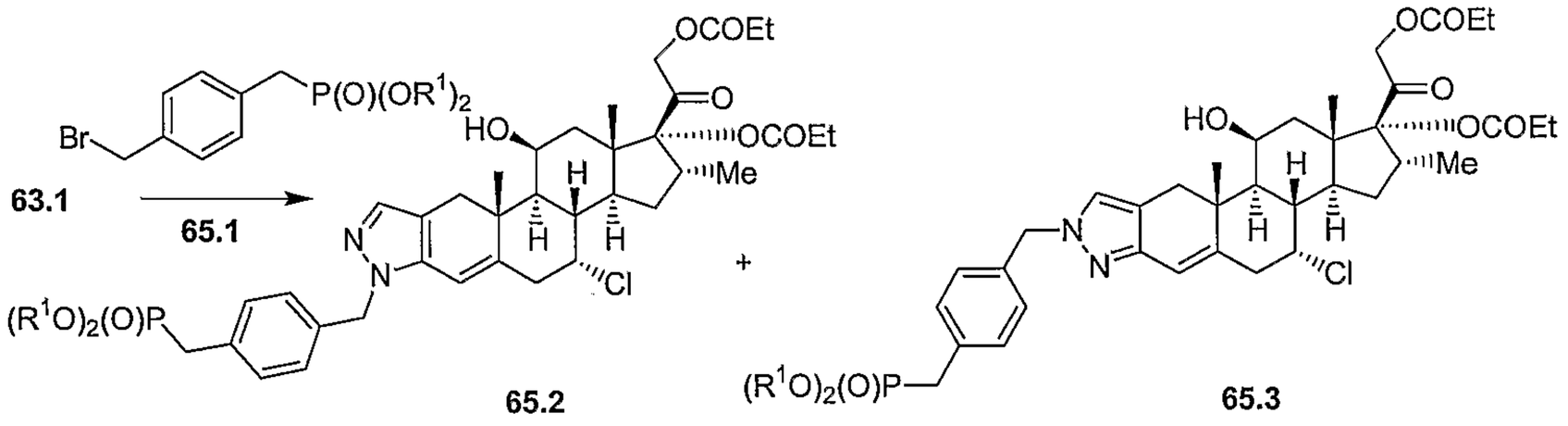
Example 64



The pyrazole, **63.1**, is reacted, in dimethylformamide solution at ca. 90°, with a dialkyl bromopropyl phosphonate, **64.1** (Aldrich), and a base such as dimethylaminopyridine or lithium hexamethyldisilazide, to yield the isomeric alkylation products, **64.2** and **64.3**.

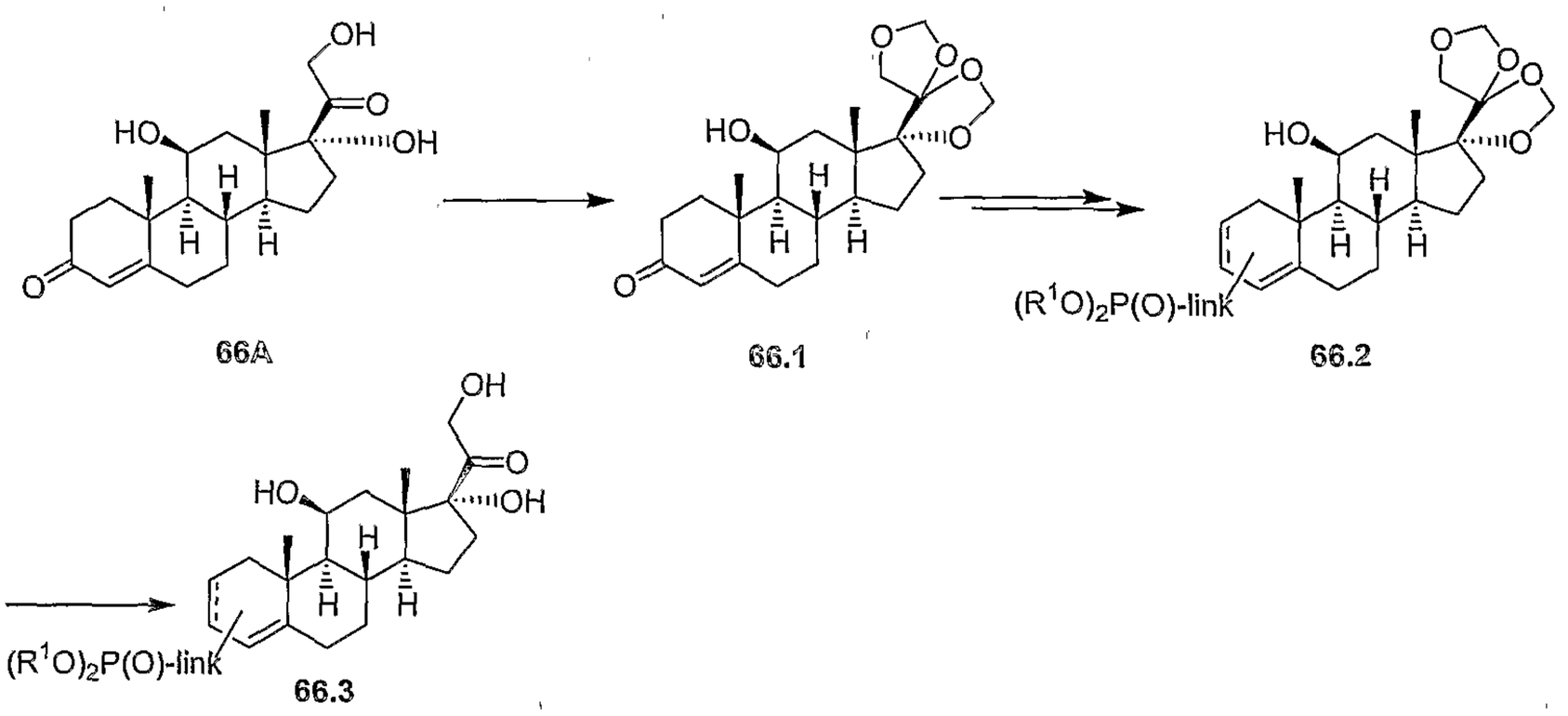
Example 65

Pyrazole, **63.1**, is reacted, as described above, with a dialkyl 4-bromomethyl benzyl phosphonate, **65.1** (*Tet.*, **1998**, *54*, 9341), to give the products, **65.2** and **65.3**.



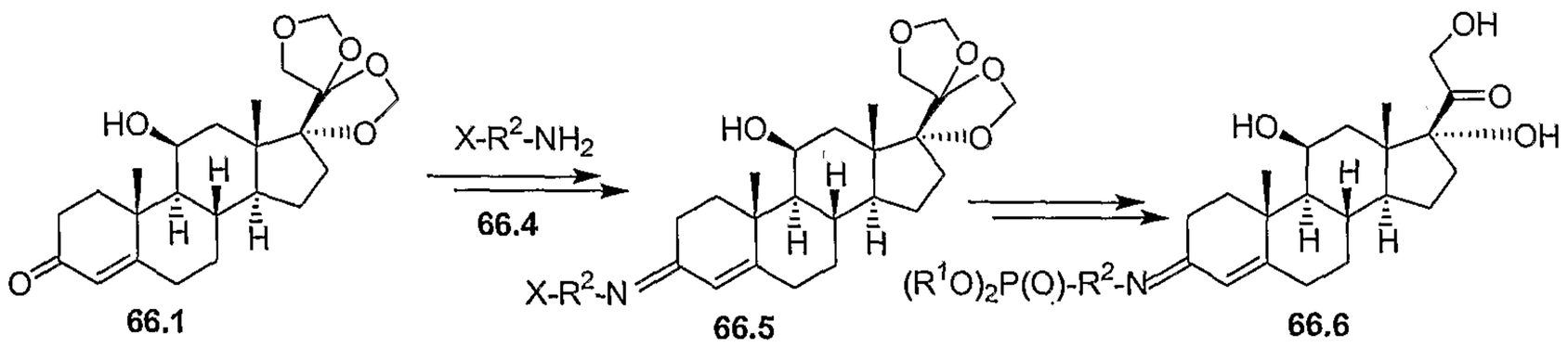
Example 66

The structures of Hydrocortisone, **66A** (U.S. Patent No. 2,602,769) and the phosphonate esters are shown below, in which the substituent R^1 is H, alkyl, alkenyl, aryl or aralkyl. These compounds incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. A general protection-deprotection sequence in which the steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety is shown below.



Hydrocortisone, **66A**, is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **66.1**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester, **66.2**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the triol, **66.3**

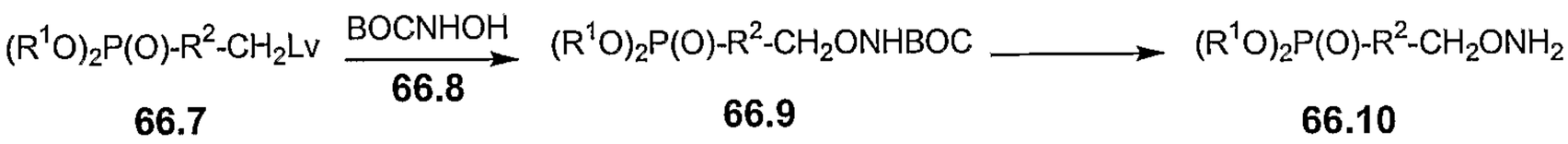
Example 66A



The BMD-protected derivative, **66.1**, is reacted with an amine or hydroxylamine, **66.4**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The

reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime, **66.5**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. In cases in which X is not dialkylphosphono, the substituent X is converted, using the methods described below; into a phosphonate-containing substituent; the BMD-protected side-chain is then removed to afford the triol, **66.6**.

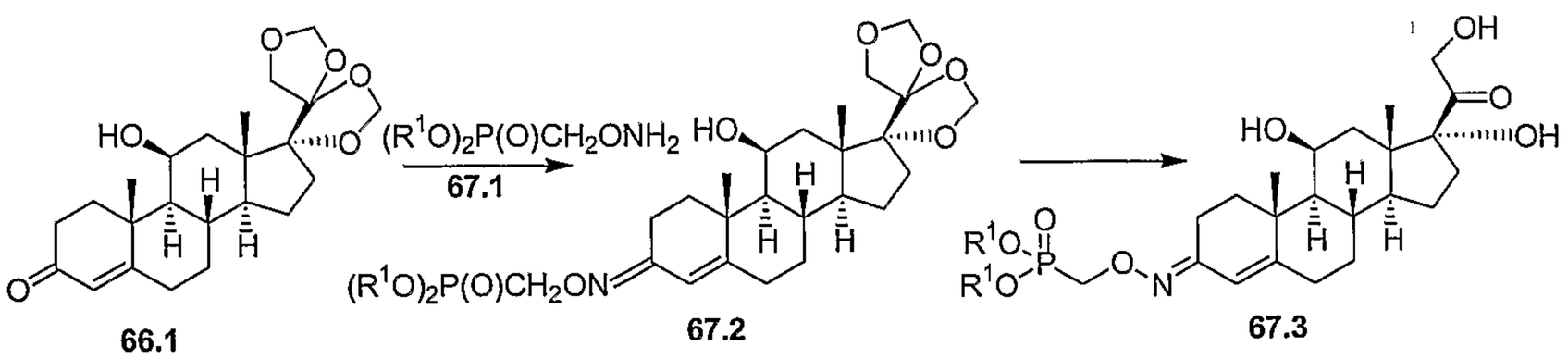
Example 66B



66.7 **66.8** **66.9** **66.10**

The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated above. In this procedure, a phosphonate, **66.7**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **66.8** (Aldrich), to produce the ether, **66.9**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **66.10**.

Example 67

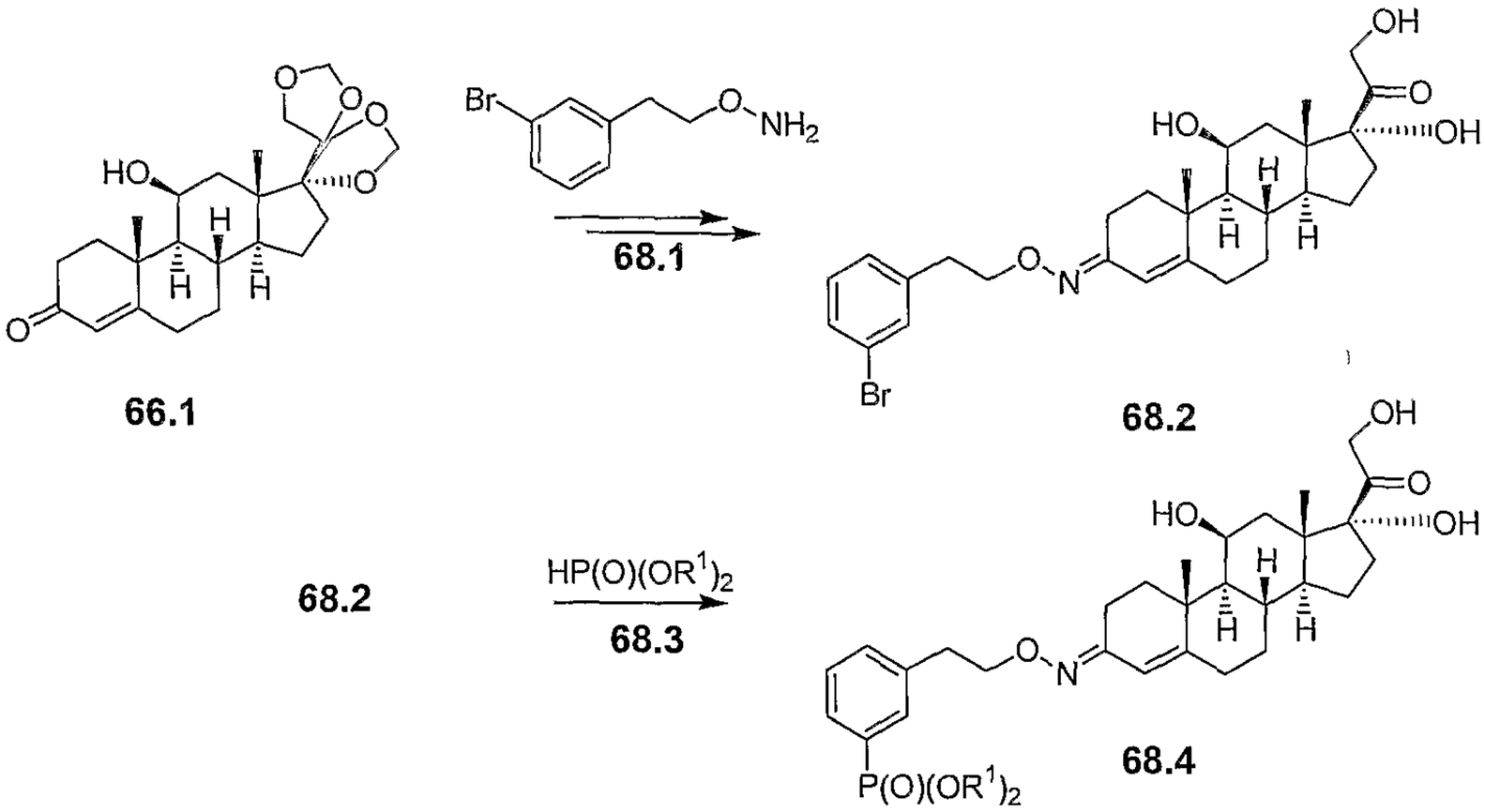


66.1 **67.2** **67.3**

The substrate, **66.1**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **67.1**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **67.2**, which is deprotected to afford the triol, **67.3**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants. Using

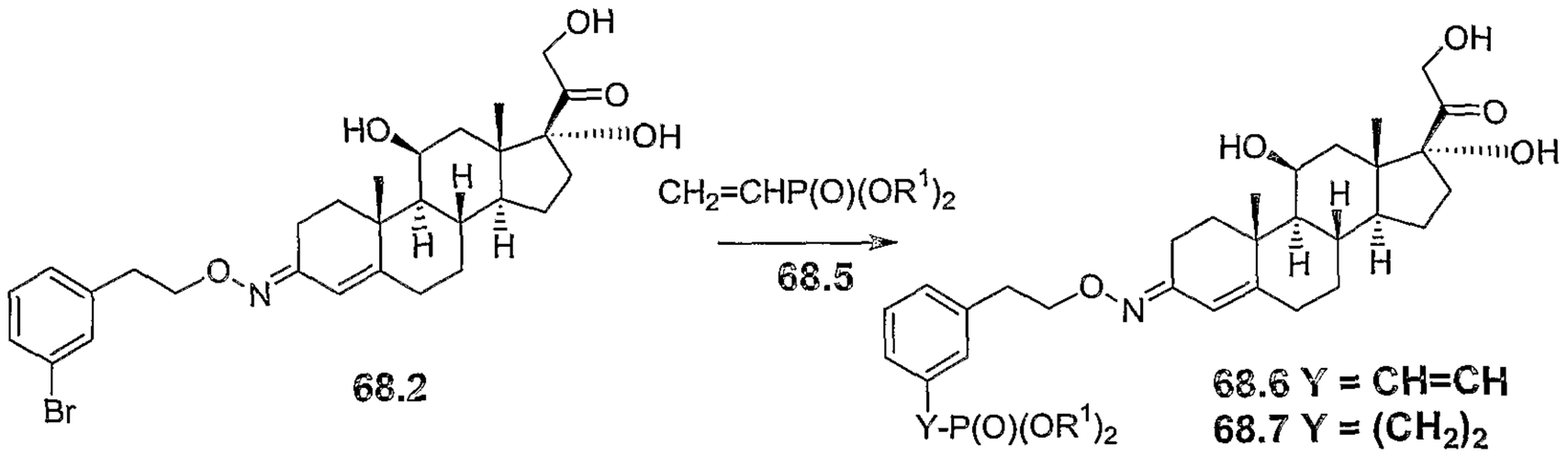
the above procedures, but employing, in place of the hydroxylamine ether, **67.1**, different oxime ethers, **66.10**, the corresponding products, **66.6** are obtained.

Example 68



The preparation of compounds in which the phosphonate group is attached by means of a phenyl ethoxy group is illustrated above. In this procedure, the enone, **66.1**, is reacted, as described above, with O-(3-bromophenyl)ethyl hydroxylamine, **68.1**, prepared as described above from 2-(3-bromophenyl)ethyl bromide (French Patent FR 1,481,052), to give, after deprotection of the side-chain, the oxime, **68.2**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **68.3**, to afford the phosphonate, **68.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed in an inert solvent such as toluene, in the presence of a base, such as triethylamine, and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Example 68A

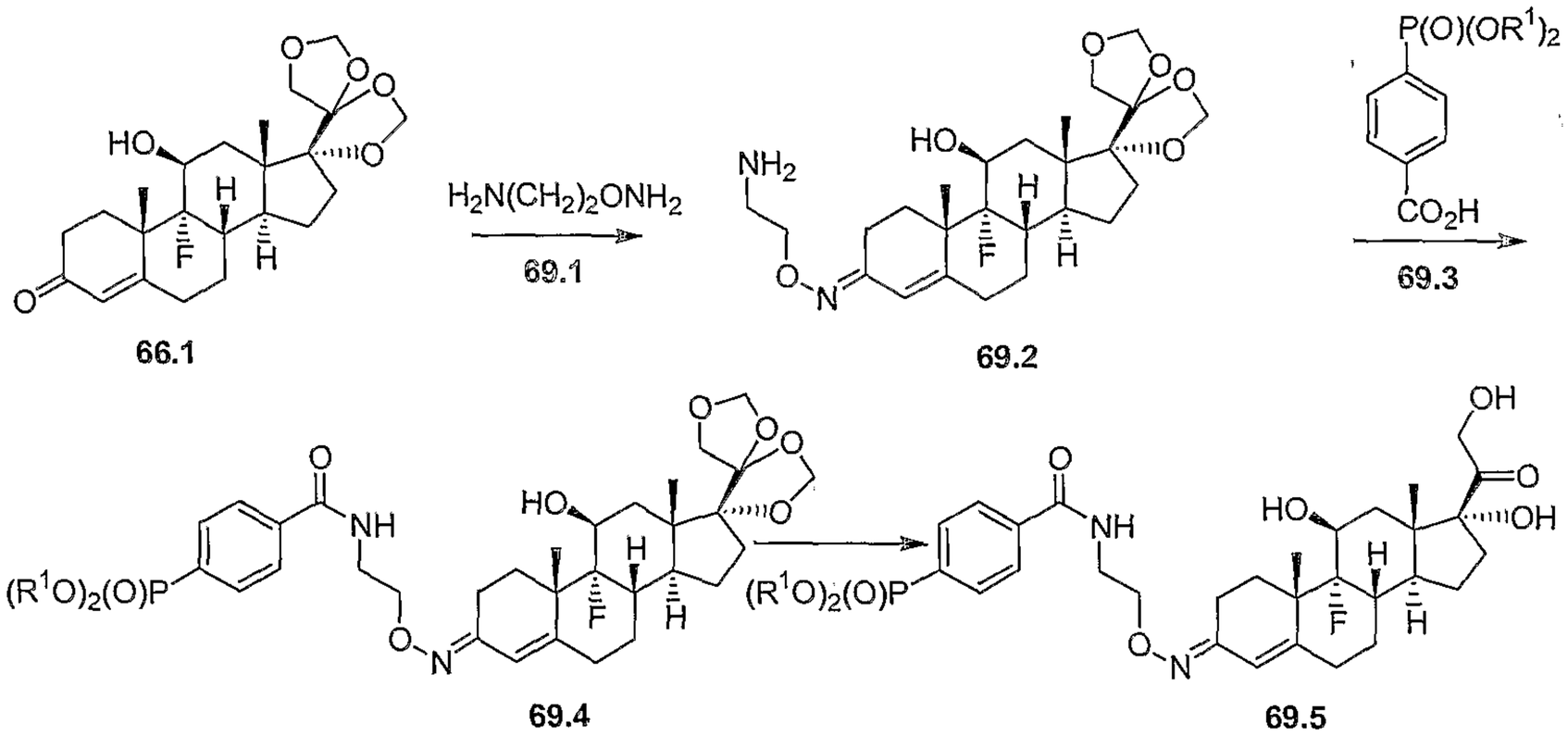


Alternatively, the bromo compound, **68.2**, is coupled with a dialkyl vinylphosphonate, **68.5** (Aldrich), to afford the phosphonate, **68.6**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146.

The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product **68.6** is reduced, for example by reaction with diimide, to produce the saturated analog, **68.7**. The reduction of olefinic bonds is described in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromophenyl ethoxy reagent, **68.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **68.4**, **68.6** and **68.7** are obtained.

Example 69



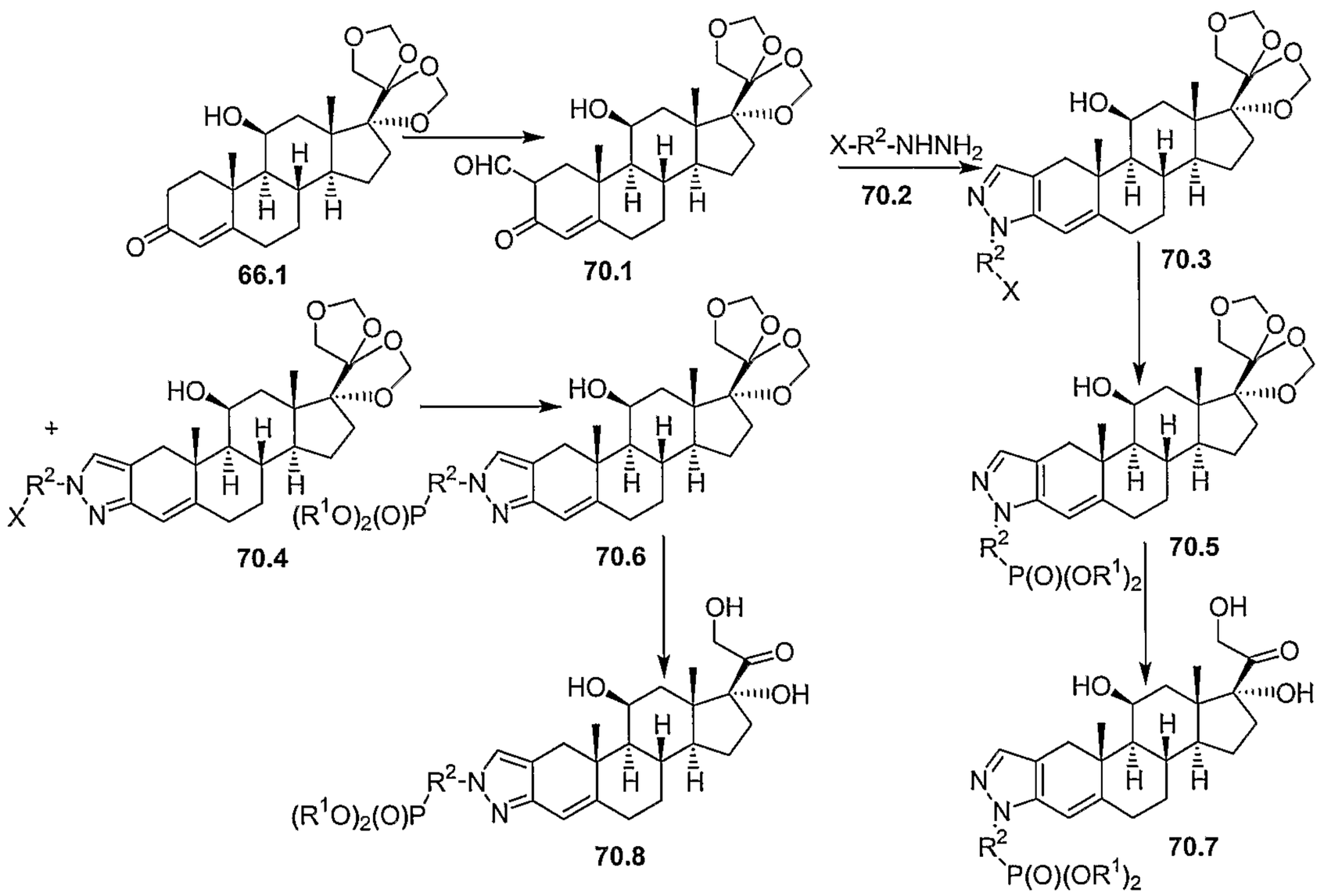
The enone, **66.1**, is reacted with O-(2-aminoethyl)hydroxylamine, **69.1**, (*Pol. J. Chem.*, **1981**, *55*, 1163) to yield the oxime, **69.2**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795. The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then coupled with a dialkyl 4-carboxyphenyl phosphonate, **69.3** (Epsilon), to yield the amide oxime, **69.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in Organic Functional Group Preparations, by S.R.Sandler and W. Karo, Academic Press, 1968, p. 274, and Comprehensive Organic Transformations, by R. C. Larock, VCH, 1989, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid (*e.g.*, dialkyl 4-carboxyphenyl phosphonate, **69.3**) is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a

reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. The amide product, **69.4**, is then converted, as described herein, into the triol, **69.5**.

Using the above procedures, but employing, in place of the hydroxylamine, **69.1**, different amino-substituted hydroxylamines, and/or different carboxy-substituted phosphonates, the products analogous to **69.5** are obtained.

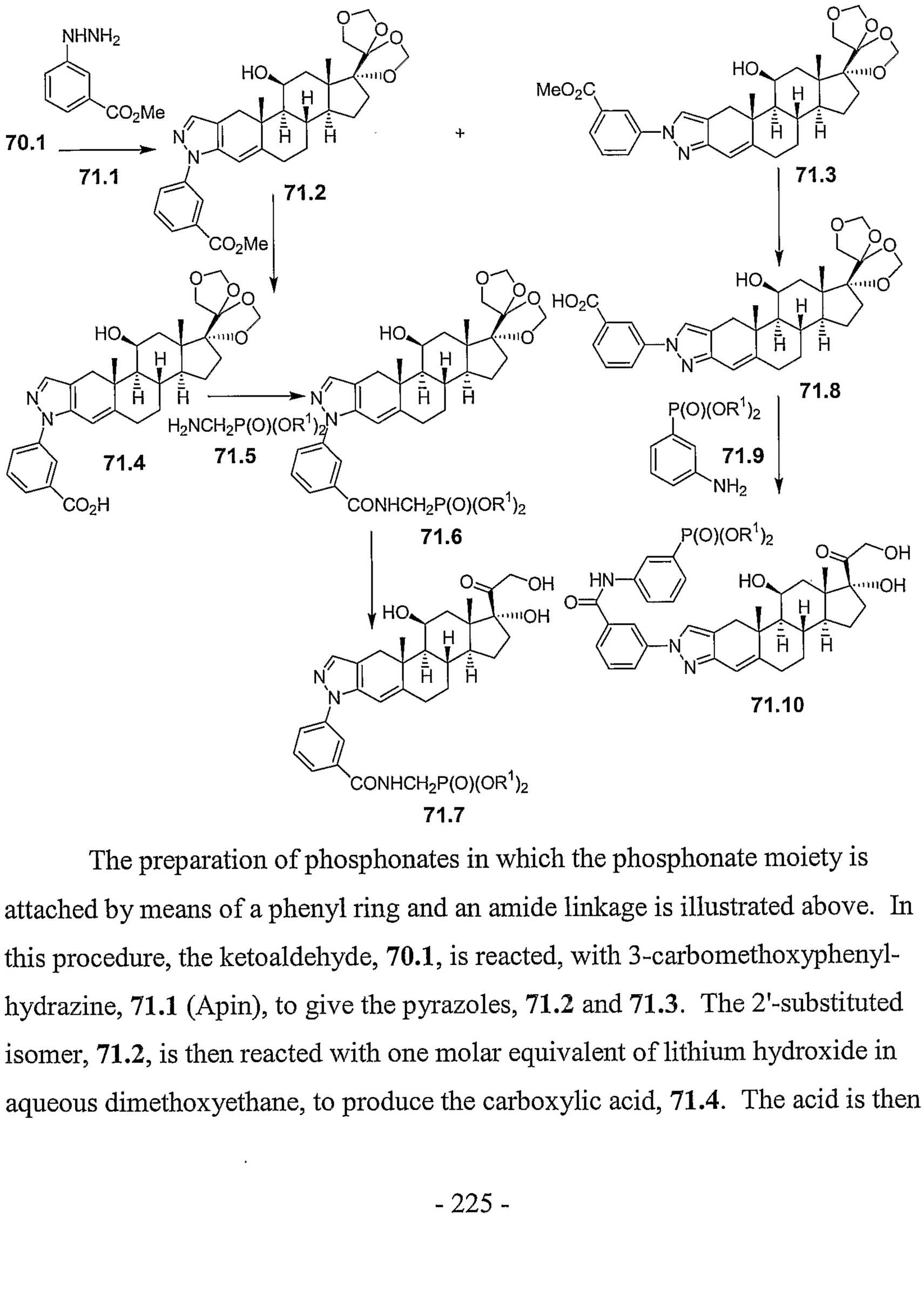
Example 70



The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of a variable carbon chain is illustrated above. In this procedure, the BMD-protected enone, **66.1**, is reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **70.1**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **70.2**, wherein R^2 is alkyl, aralkyl, aryl, or heteroaryl, and in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is

dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **70.3** and **70.4**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **70.3** and **70.4**, are then transformed, for example, using procedures described herein, via the BMD-protected intermediates, **70.5** and **70.6**, into the phosphonates, **70.7** and **70.8**.

Example 71

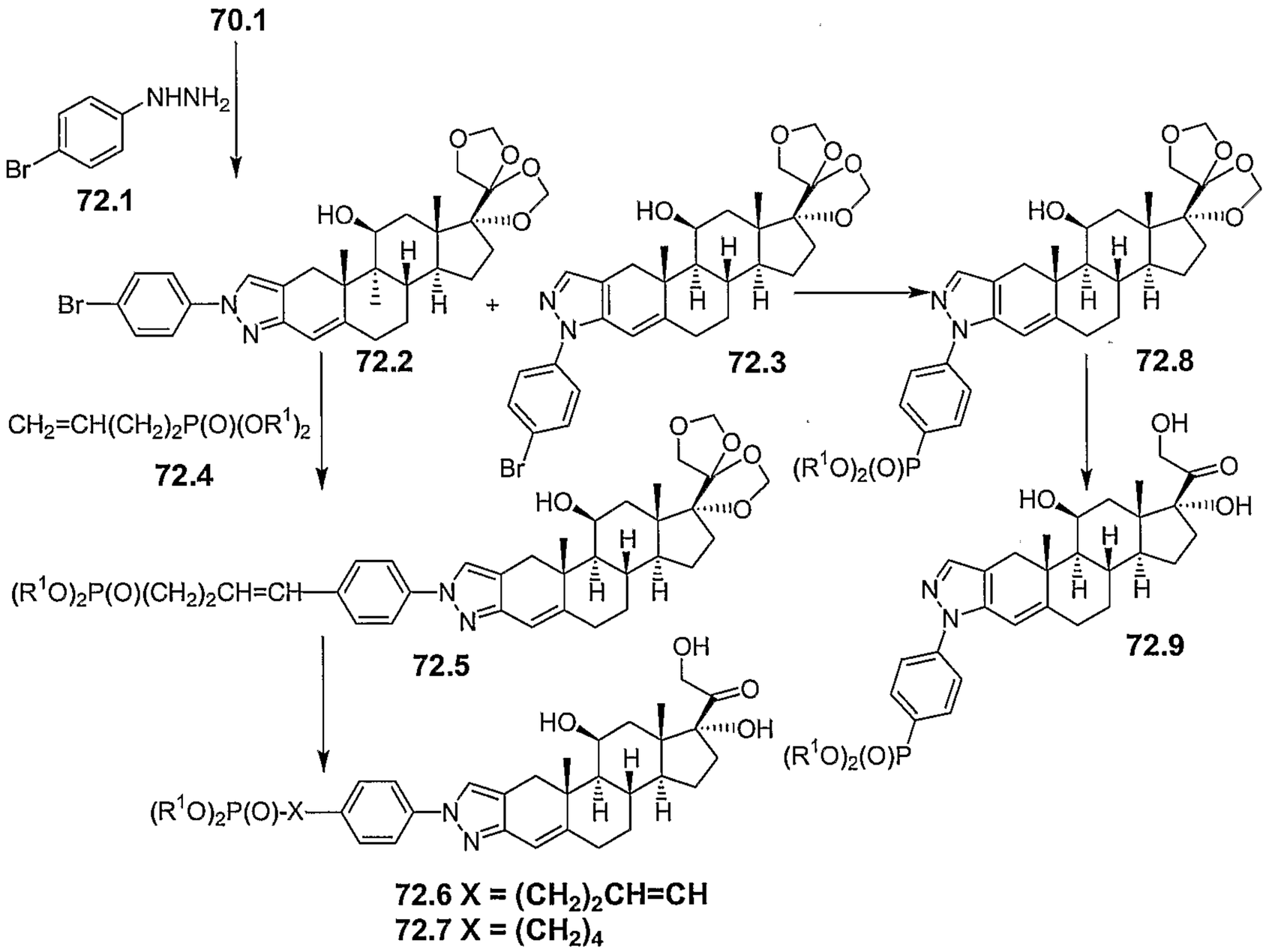


The preparation of phosphonates in which the phosphonate moiety is attached by means of a phenyl ring and an amide linkage is illustrated above. In this procedure, the ketoaldehyde, **70.1**, is reacted, with 3-carbomethoxyphenyl-hydrazine, **71.1** (Apin), to give the pyrazoles, **71.2** and **71.3**. The 2'-substituted isomer, **71.2**, is then reacted with one molar equivalent of lithium hydroxide in aqueous dimethoxyethane, to produce the carboxylic acid, **71.4**. The acid is then

coupled, as described above, with a dialkyl aminomethyl phosphonate, **71.5**, (Interchim) to give the amide, **71.6**, deprotection then affords the triol, **71.7**. Alternatively, the 1'-substituted pyrazole, **71.3**, is hydrolyzed, as described above, to the carboxylic acid, **71.8**. The product is then coupled with a dialkyl 3-aminophenyl phosphonate, **71.9** (*J. Med. Chem.*, **1984**, *27*, 654), to yield after deprotection the triol amide, **71.10**.

Using the above procedures, but employing, in place of the carbomethoxyphenyl hydrazine, **71.1**, different carbomethoxy-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl amino-substituted phosphonates, the products analogous to the compounds, **71.7** and **71.10** are obtained.

Example 72



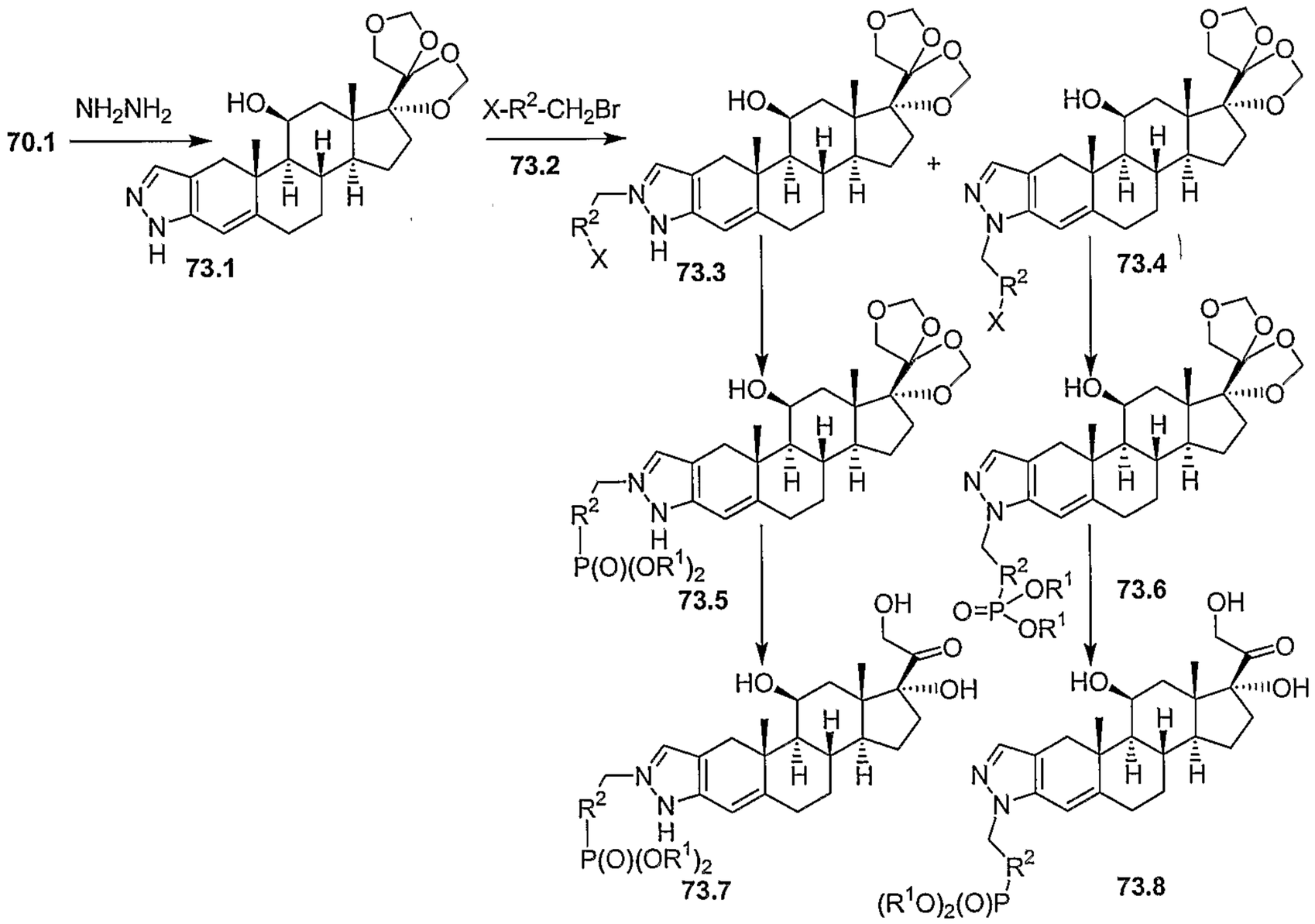
The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **70.1**, is reacted, as described above, with 4-bromophenyl hydrazine, **72.1** (*J. Organomet. Chem.*, **1999**, *62*, 581), to produce the pyrazoles, **72.2** and **73.3**. The 1'-substituted isomer, **72.2**, is coupled, as described herein, in the presence of a palladium catalyst, with a dialkyl butenyl

phosphonate, **72.4** (*Org. Lett.*, **2001**, *3*, 217), to give the phosphonate, **72.5**. The product is then deprotected to afford the triol, **72.6**. Optionally, the styrenoid double bond present in the product, **72.6**, is reduced, as described above, to produce the saturated analog, **72.7**.

Alternatively, the 2'-substituted pyrazole, **72.3**, is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite to prepare the phosphonate, **72.8**, which is deprotected to give the triol, **72.9**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and tetrakis(triphenylphosphine)-palladium(0).

Using the above procedures, but employing, in place of the bromophenyl hydrazine, **72.1**, different bromo-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **72.6**, **72.7** and **72.9** are obtained.

Example 73

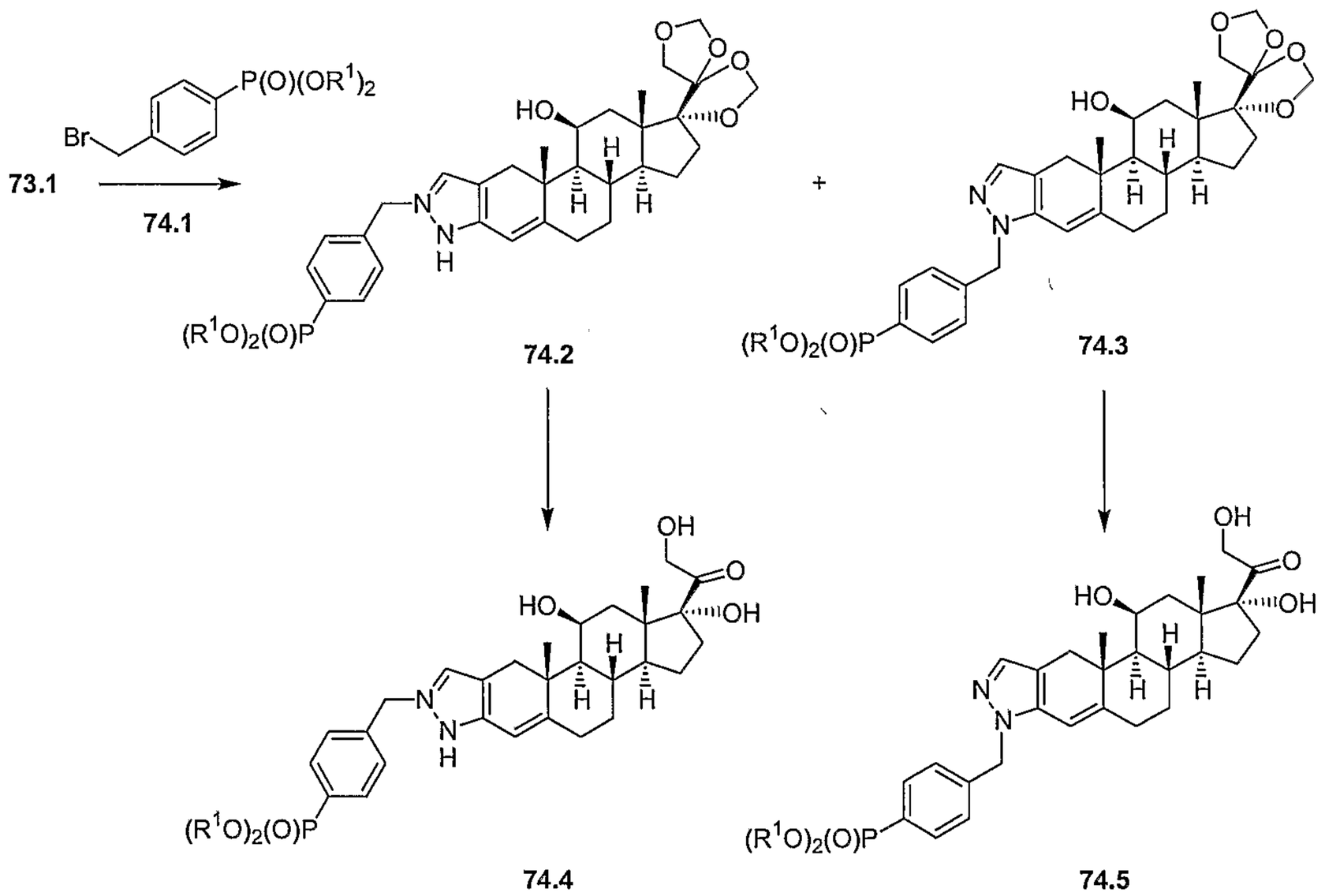


The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **70.1**, is reacted with hydrazine, to afford the

pyrazole derivative, **73.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, 86, 1520. The reaction is performed in ethanol at reflux temperature. The pyrazole product is then reacted with a bromomethyl compound, **73.2**, in which R^2 and X are as defined above, to yield the alkylation products, **73.3** and **73.4**. The alkylation of substituted pyrazoles is described, for example, in "Heterocyclic Chemistry," by T. L. Gilchrist, Longman, **1992**, p. 309.

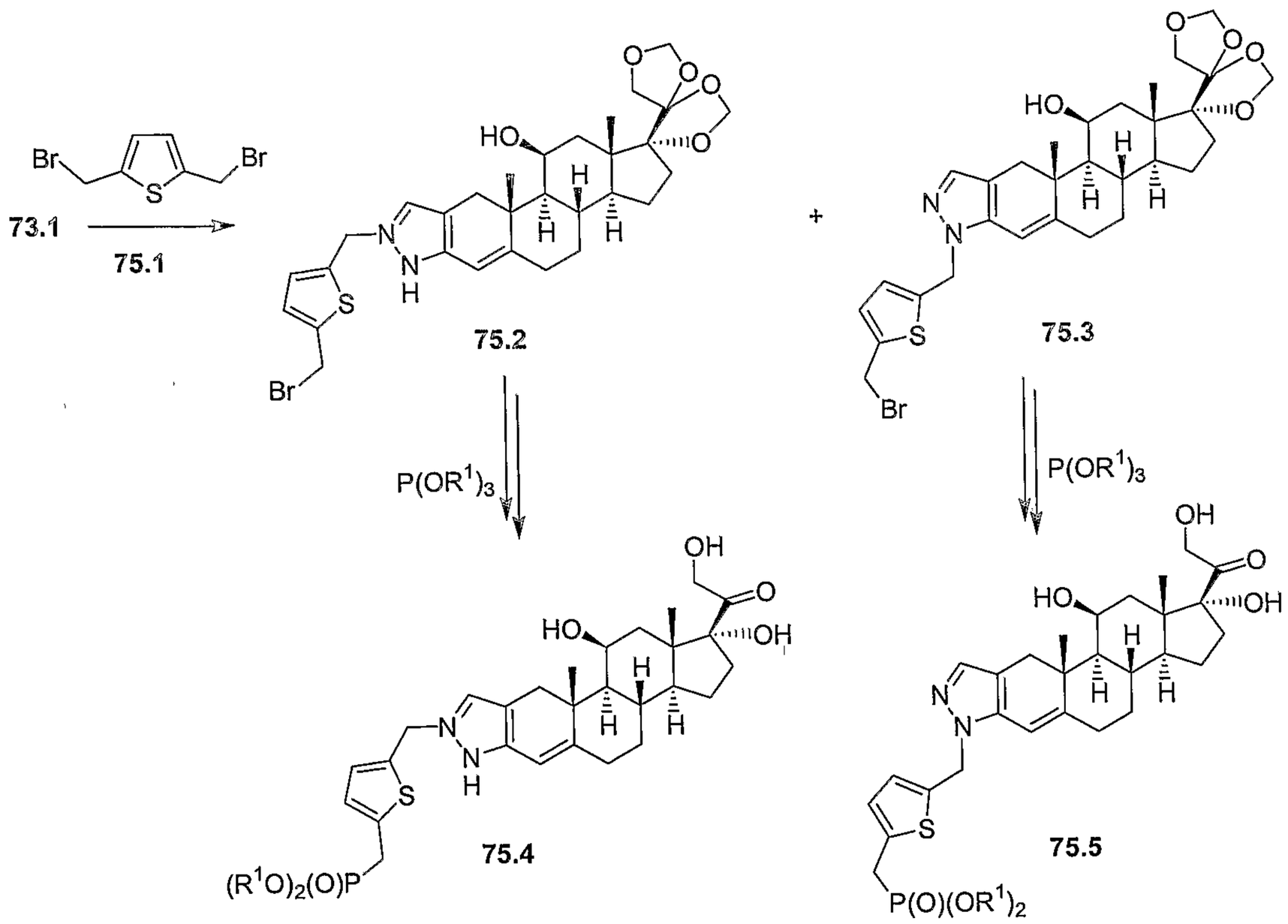
The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **73.3** and **73.4**, are converted into the phosphonates, **73.5** and **73.6**, except in cases where X is dialkylphosphono, using the procedures described herein. Deprotection affords the triols, **73.7** and **73.8**.

Example 74



The pyrazole, **73.1**, is reacted, as described above, with one molar equivalent of a dialkyl 4-(bromomethyl)phenyl phosphonate, **74.1** (WO 2003/042150), to give the alkylated pyrazoles, **74.2** and **74.3**. Deprotection then yields the triols, **74.4** and **74.5**.

Example 75



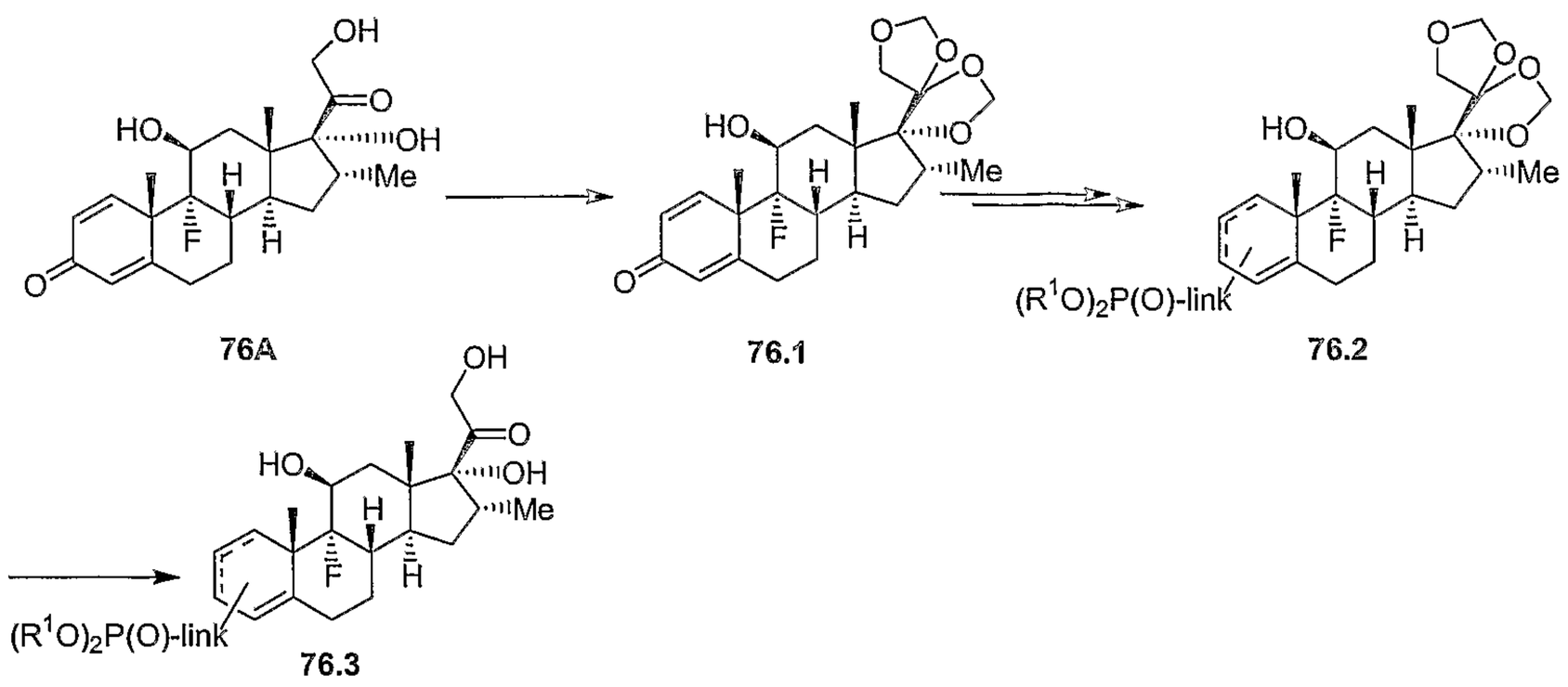
The pyrazole, **73.1**, is reacted, as described above, with 2,5-bis(bromomethyl)thiophene, **75.1** (*Tet.*, **1999**, *55*, 4709), to give the pyrazoles, **75.2** and **75.3**. The products are subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain, the phosphonates, **75.4** and **75.5**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115-72. In the procedure, the substrate is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite.

Using the above procedures, but employing, in place of the dibromide, **75.1**, different dibromides, the products analogous to **75.4** and **75.5** are obtained.

Example 76

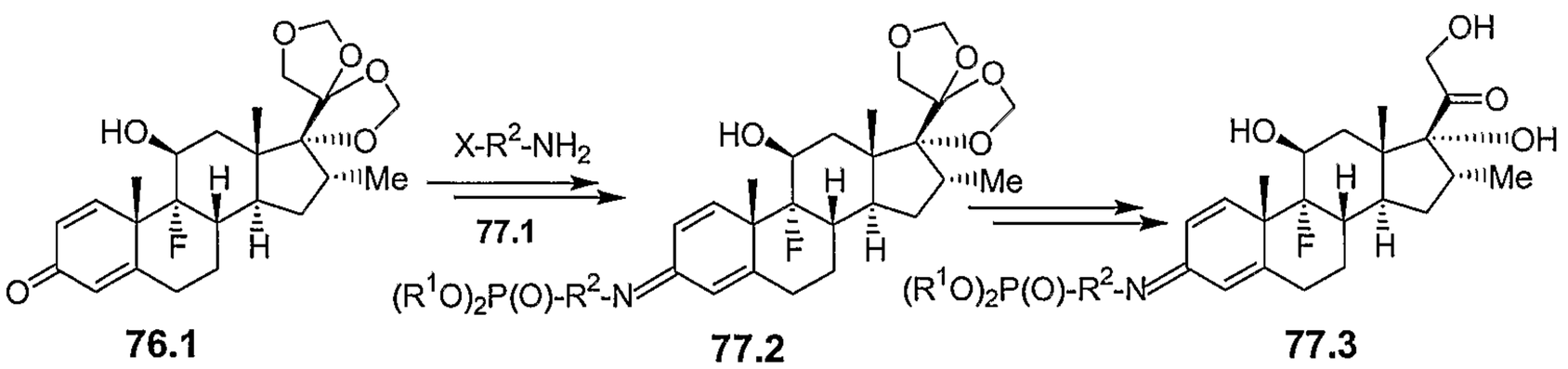
Dexamethasone, **76A**, (U.S. Patent No. 3,007,923) analogs where the substituent R^1 is H, alkyl, alkenyl, aryl or aralkyl are prepared by the procedures below. The compounds **76.1 – 76.3** incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.

Scheme M1



Dexamethasone, **76A**, is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **76.1**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester, **76.2**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the triol, **76.3**.

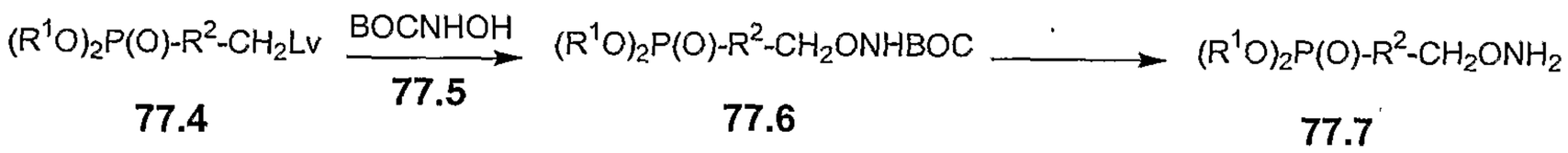
Example 77



The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative, **76.1**, is reacted with an amine or hydroxylamine, **77.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating

a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The BMD-protected side-chain compound, **77.2**, is then converted, as described in Scheme **M1** in Example 76, into the triol, **77.3**.

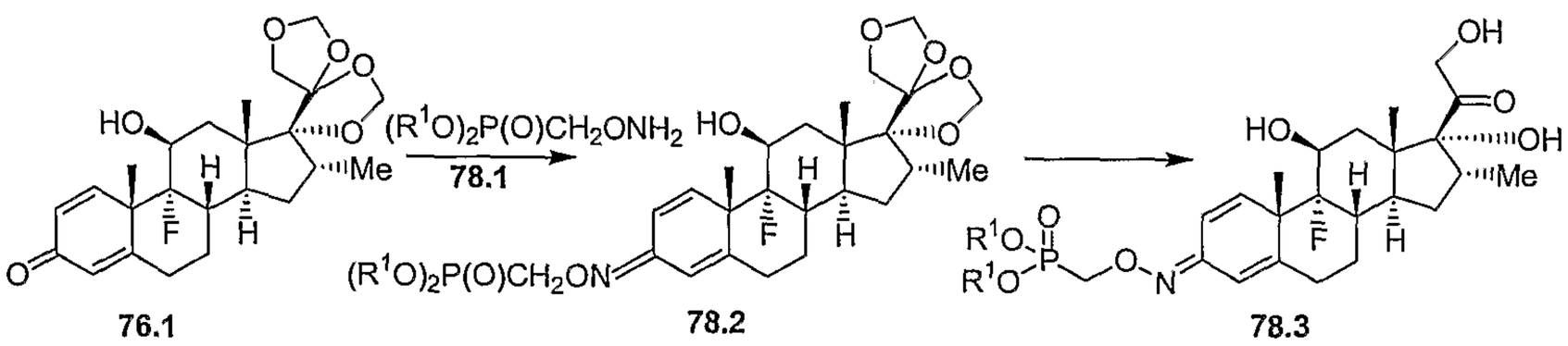
Example 77A



77.4 **77.5** **77.6** **77.7**

The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated above. In this procedure, a phosphonate, **77.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **77.5** (Aldrich), to produce the ether, **77.6**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **77.7**.

Example 78



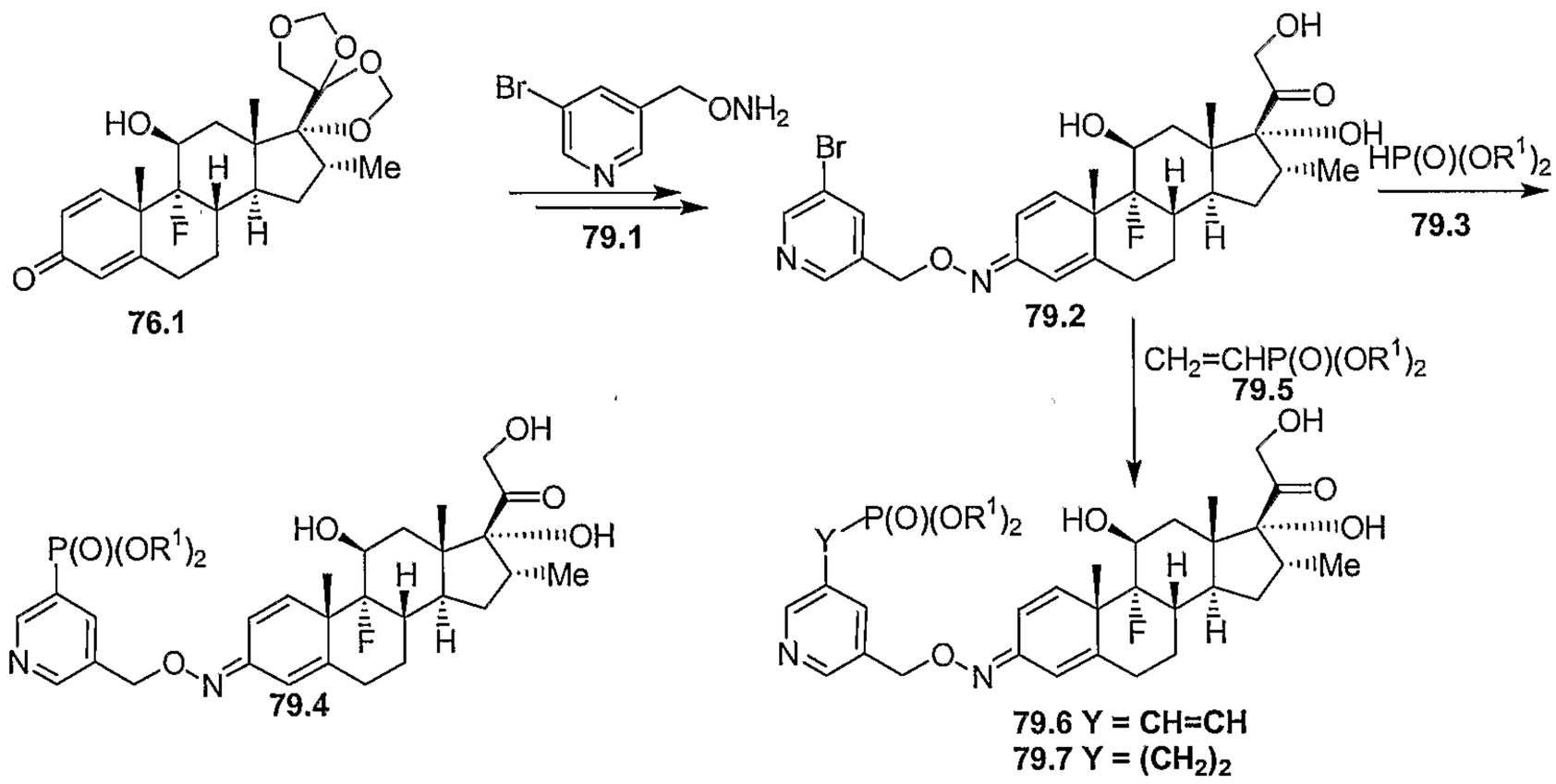
76.1 **78.2** **78.3**

The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group. In this procedure, the substrate, **76.1**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **78.1**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the

oxime, **78.2**, which is deprotected to afford the triol, **78.3**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **78.1**, different oxime ethers, **77.1**, the corresponding products, **77.3** are obtained.

Example 79



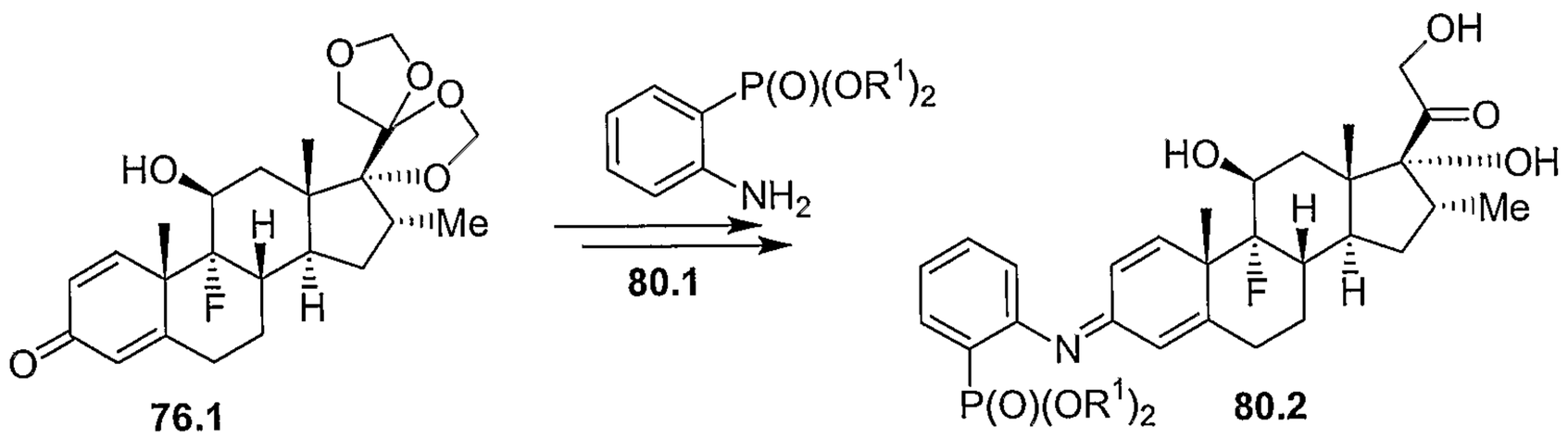
The preparation of compounds in which the phosphonate group is attached by means of a pyridyl methoxy group is illustrated above. In this procedure, the dienone, **76.1**, is reacted, as described above, with O-(3-bromo-5-pyridylmethyl)hydroxylamine, **79.1**, prepared as described above from 3-bromo-5-bromomethylpyridine (WO 95/28400), to give, after deprotection of the side-chain, the oxime, **79.2**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **79.3**, to afford the phosphonate, **79.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis-(triphenylphosphine)palladium(0).

Alternatively, the bromo compound, **79.2**, is coupled with a dialkyl vinylphosphonate, **79.5** (Aldrich), to afford the phosphonate, **79.6**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg,

Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenyl-phosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **79.6**, is reduced, for example by reaction with diimide, to produce the saturated analog, **79.7**. The reduction of olefinic bonds is described in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromopyridyloxy reagent, **79.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **79.4**, **79.6** and **79.7** are obtained.

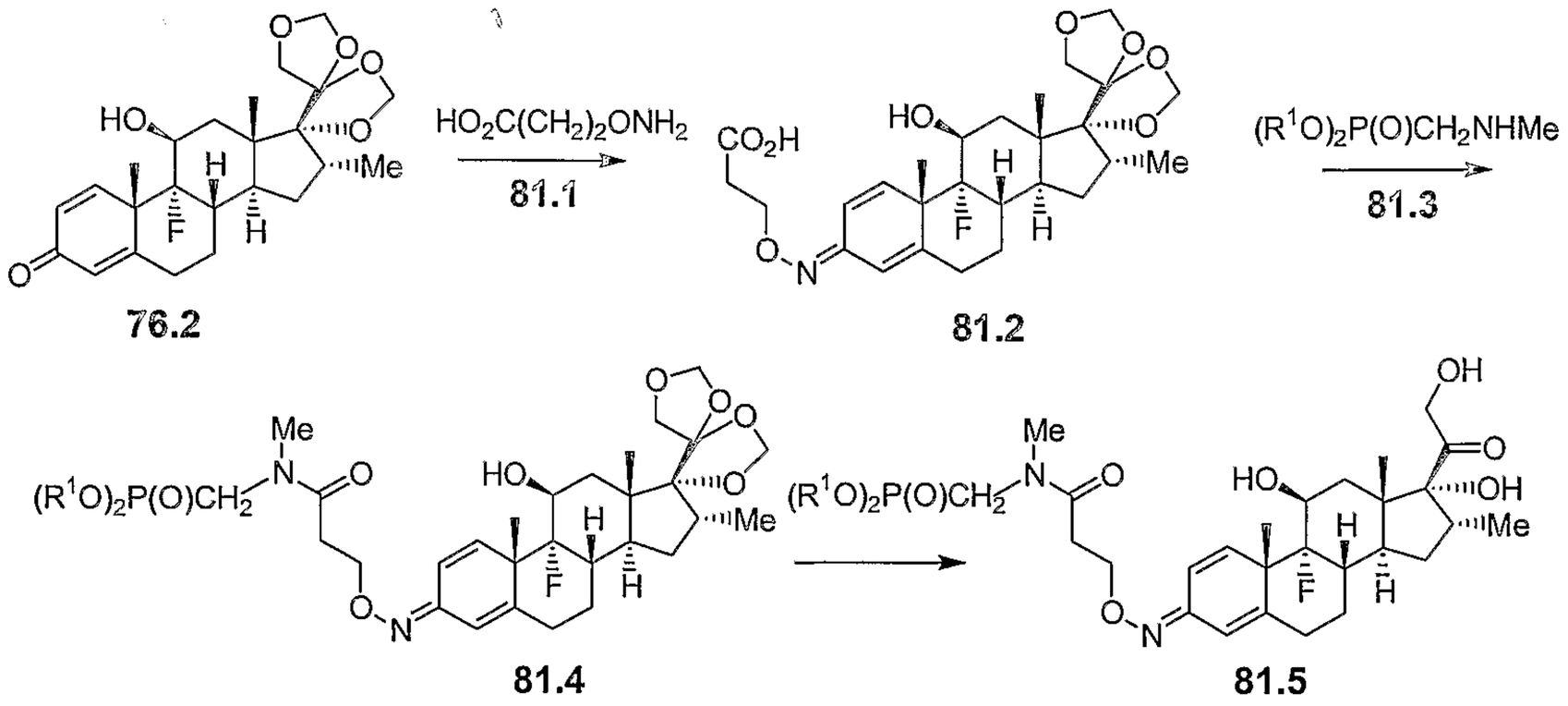
Example 80



76.1 **80.2**

The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate, **76.1**, is reacted with a dialkyl 2-aminophenyl phosphonate, **80.1**, (*Syn.*, **1999**, 1368) to give, after deprotection, the imine product, **80.2**. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. Using the above procedures, but employing, in place of the 2-aminophenyl phosphonate, **80.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **80.2** are obtained.

Example 81



The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and an amide linkage is illustrated above. In this procedure, the dienone, **76.2**, is reacted with O-(2-carboxyethyl)hydroxylamine, **81.1**, (*J. Med. Chem.*, **1990**, *33*, 1423) to yield the oxime, **81.2**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then reacted with a dialkyl methylaminomethyl phosphonate, **81.3**, to yield the amide oxime, **81.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R. Sandler and W. Karo, Academic Press, **1968**, p. 274, and "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

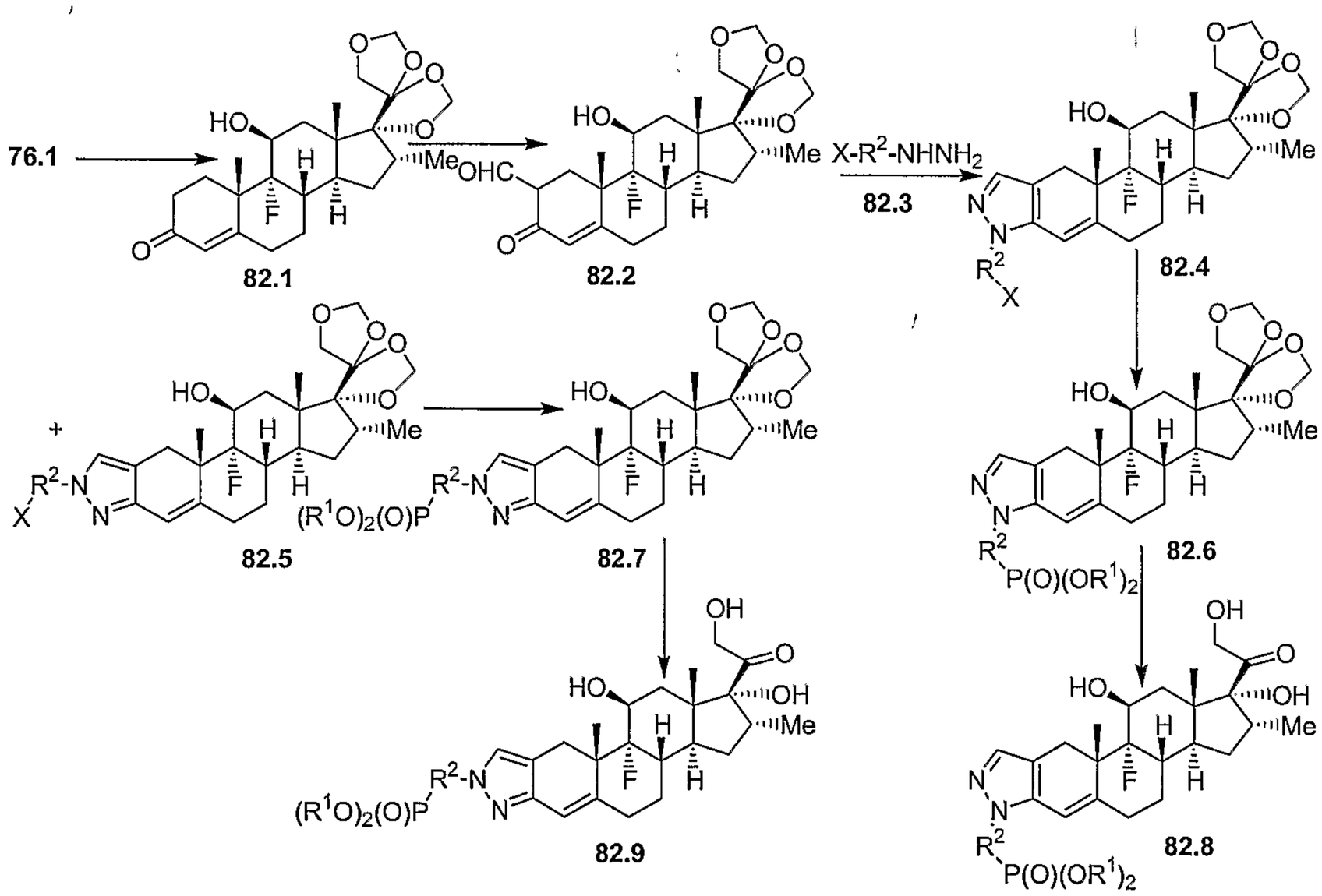
Alternatively, the carboxylic acid is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base

such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The amide product, **81.4**, is then converted, as described herein, into the triol, **81.5**.

Using the above procedures, but employing, in place of the hydroxylamine, **81.3**, different carboxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to **81.5** are obtained.

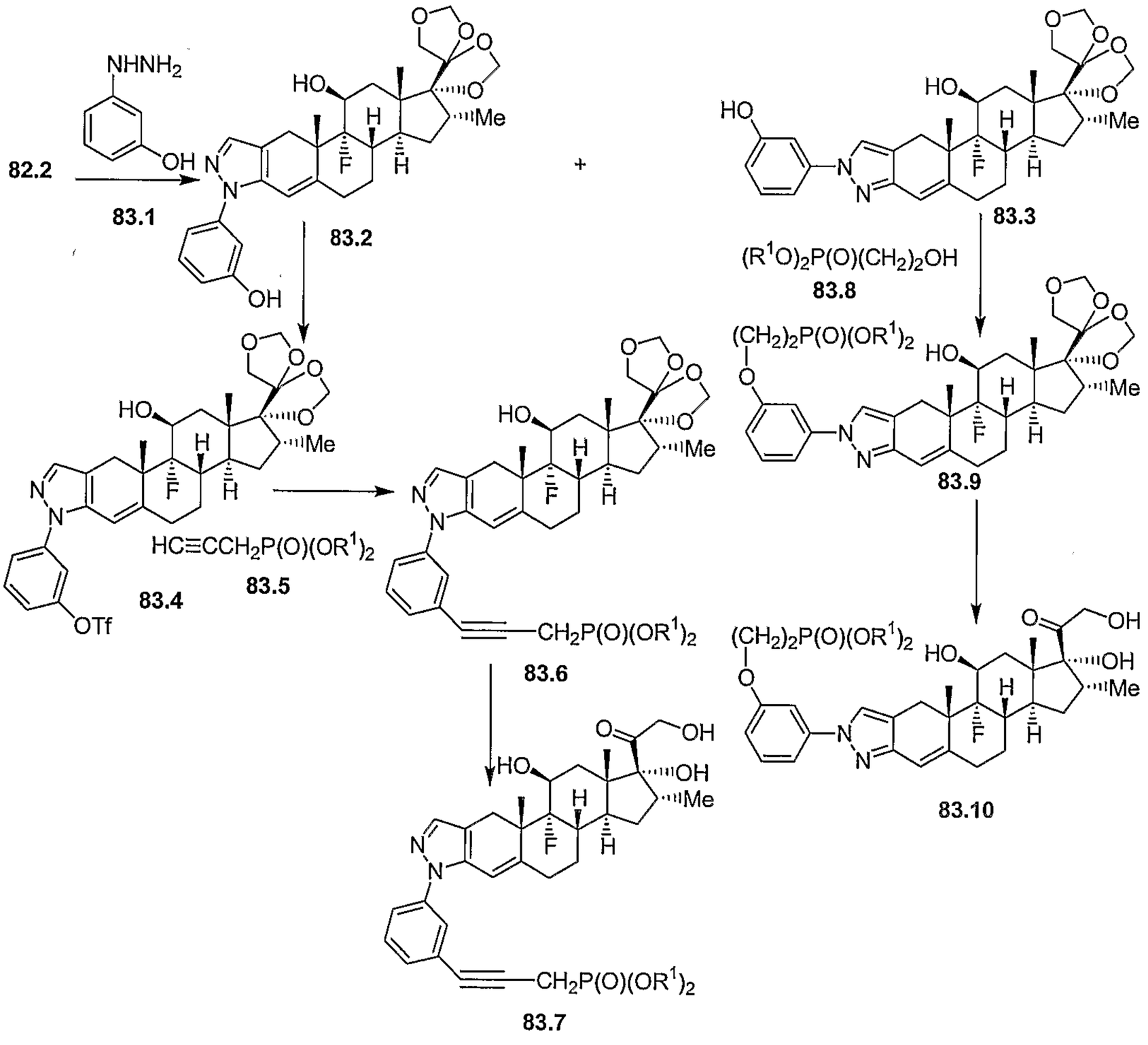
Example 82



The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, the BMD-protected dienone, **76.1**, is reduced to afford the 1,2-dihydro product, **82.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, 44, 602. The product is then

reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **82.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **82.3**, wherein R^2 is alkyl, aralkyl, aryl or heteroaryl and in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **82.4** and **82.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **82.4** and **82.5**, are then transformed, for example by the procedures described herein, via the BMD-protected intermediates, **82.6** and **82.7**, into the phosphonates, **82.8** and **82.9**.

Example 83

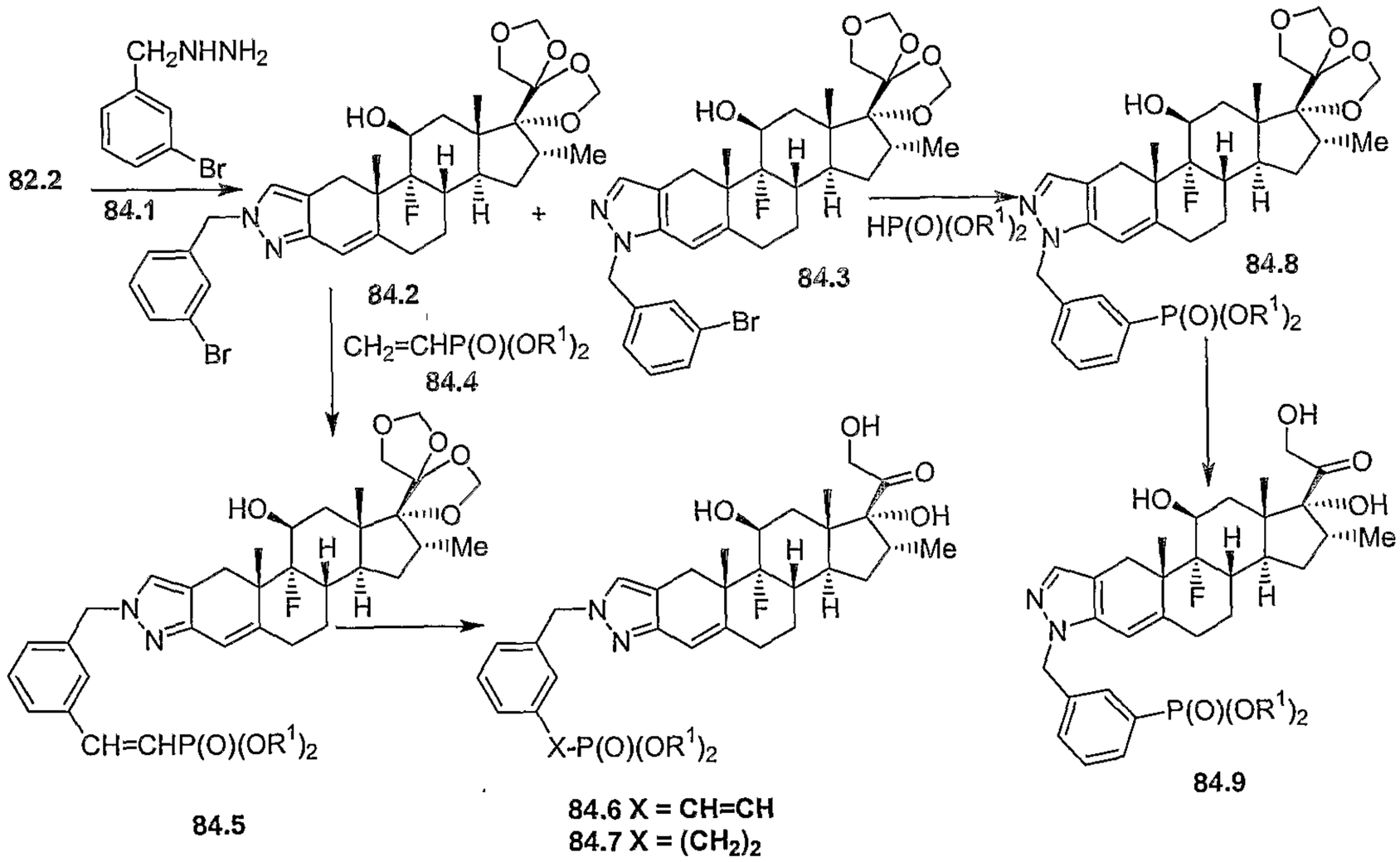


The preparation of phosphonates in which the phosphonate is attached by means of a phenyl ring and an alkoxy or an acetylenic linkage is illustrated above. In this procedure, the ketoaldehyde, **82.2**, is reacted, as described above, with 3-hydroxyphenylhydrazine, **83.1** (Japanese Patent No. JP 03011081), to give the pyrazoles, **83.2** and **83.3**. The 2'-substituted isomer, **83.2**, is then reacted in dichloromethane solution at ambient temperature with one molar equivalent of trifluoromethylsulfonyl chloride and dimethylaminopyridine, to yield the triflate, **83.4**. The product is then reacted in toluene solution with a dialkyl propynyl phosphonate, **83.5** (*Syn.*, **1999**, 2027), triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium (0), to give the acetylenic product, **83.6**. The palladium-catalyzed coupling reaction of aryl triflates with terminal acetylenes is described in WO 02/30930. The BMD protecting group is then removed to yield the triol, **83.7**.

Alternatively, the 1'-substituted pyrazole, **83.3**, is reacted, in a Mitsonobu reaction, with a dialkyl 2-hydroxyethyl phosphonate, **83.8** (Epsilon), to afford the ether, **83.9**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 448, and in "Advanced Organic Chemistry," Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p. 153-4 and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656. The product, **83.9**, is then deprotected to give the triol, **83.10**.

Using the above procedures, but employing different acetylenic or hydroxyl-substituted phosphonates, the products analogous to **83.7** and **83.10** are obtained. The functionalization procedures are interchangeable between the pyrazole substrates, **83.2** and **83.3**.

Example 84



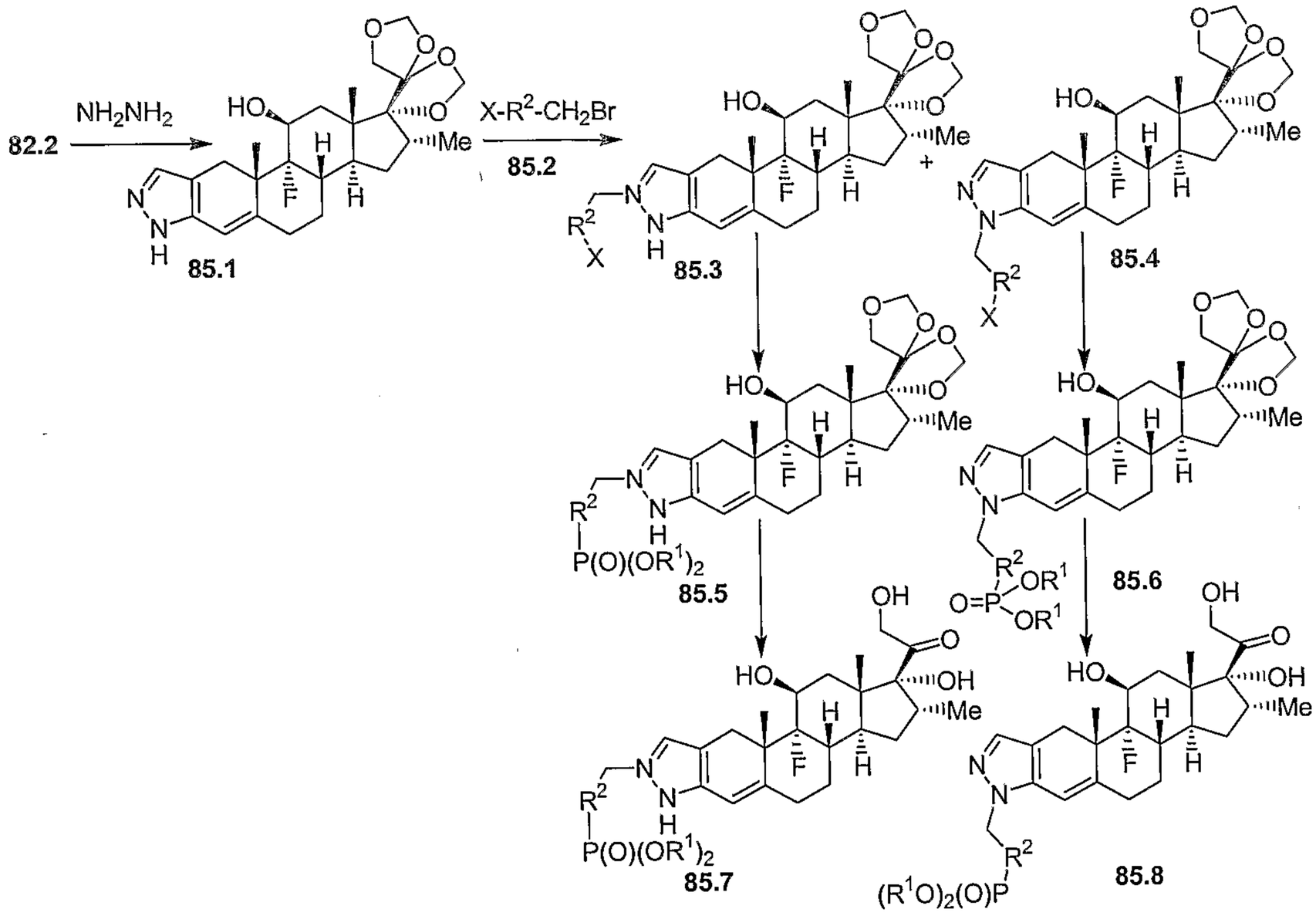
The preparation of the phosphonates in which the phosphonate group is attached by means of a benzyl group and a saturated or unsaturated carbon chain is illustrated above. In this procedure, the ketoaldehyde, **82.2**, is reacted, as described above, with 3-bromobenzyl hydrazine, **84.1** (U.S. Patent No. 4,370,339), to produce the pyrazoles, **84.2** and **84.3**. The 1'-substituted isomer **84.2** is coupled, in the presence of a palladium catalyst, with a dialkyl vinylphosphonate, **84.4** (Aldrich), to give the phosphonate, **84.5**. The product is then deprotected to afford the triol, **84.6**. Optionally, the styrenoid double bond present in the product, **84.6**, is reduced, as described above, to produce the saturated analog, **84.7**.

Alternatively, the 2'-substituted pyrazole, **84.3**, is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite to prepare the phosphonate, **84.8**, which is deprotected to give the triol, **84.9**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and tetrakis(triphenylphosphine)palladium(0).

Using the above procedures, but employing, in place of the bromobenzyl reagent, **84.1**, different bromo-substituted aralkyl, aryl or heteroaryl alkoxy

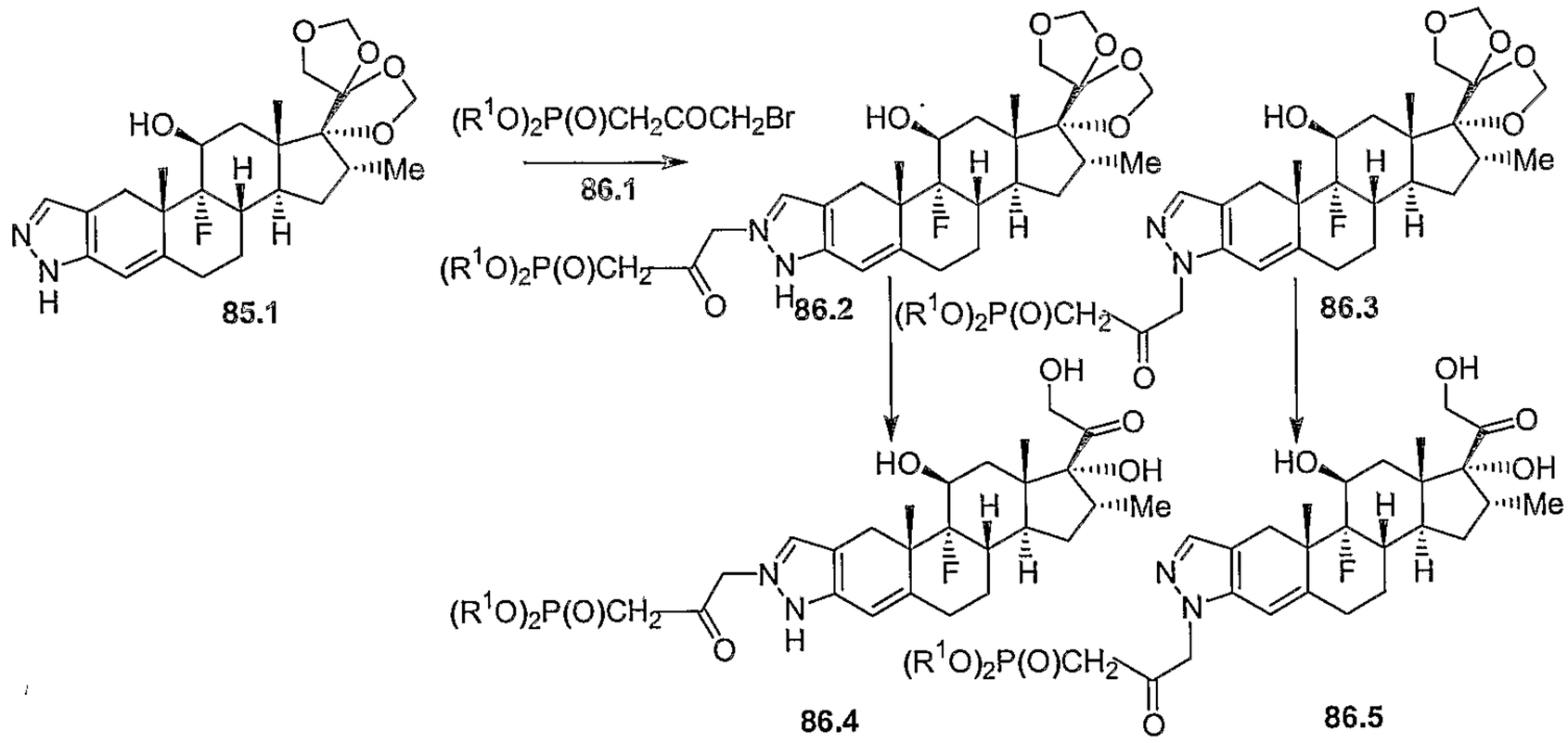
hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **84.6**, **84.7** and **84.9** are obtained.

Example 85



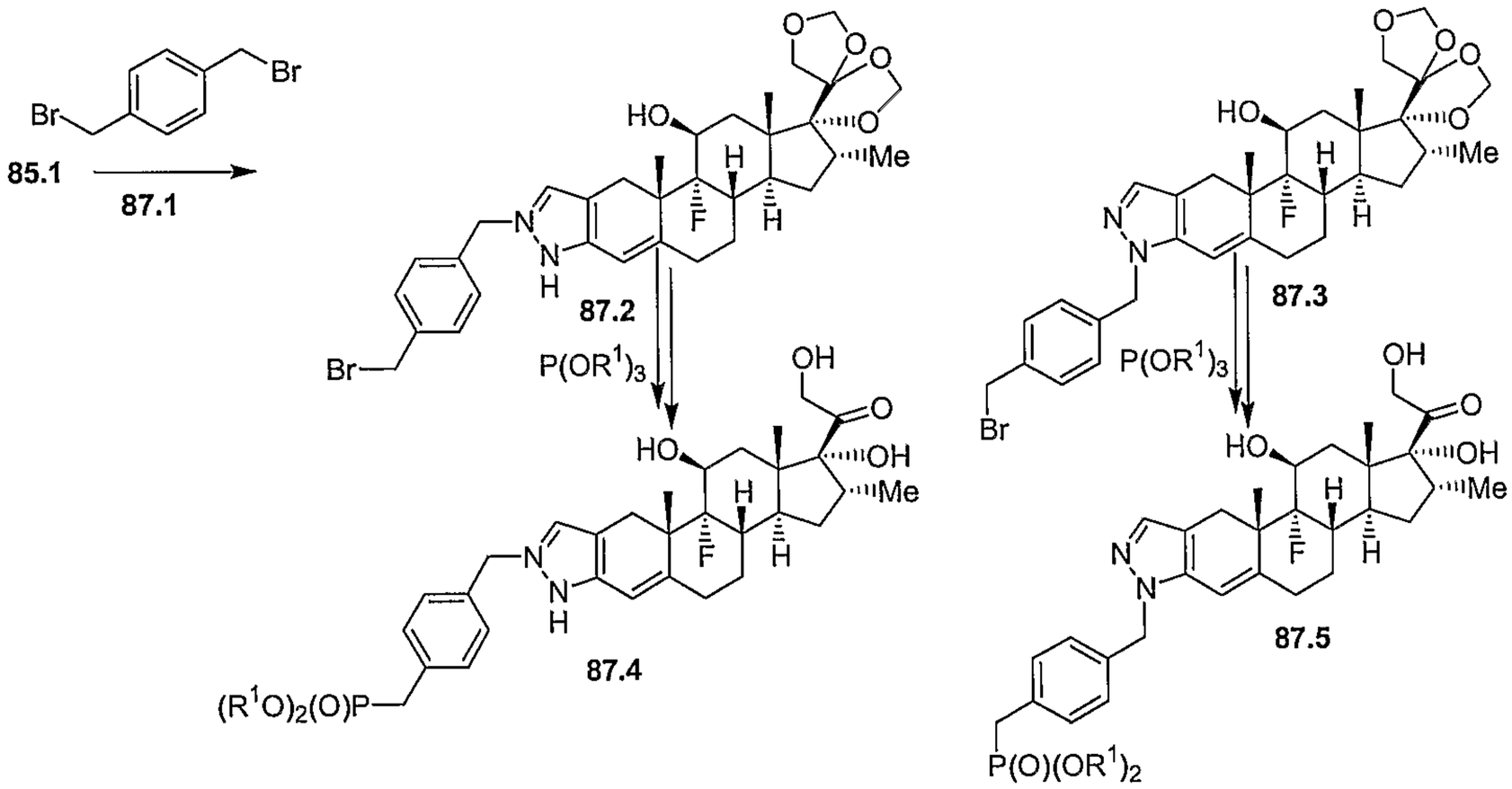
The preparation of the phosphonate esters, **85.7** and **85.8**, in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **82.2**, is reacted with hydrazine, to afford the pyrazole derivative, **85.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **85.2**, in which R^2 and X are as defined above, to yield the alkylation products, **85.3** and **85.4**. The alkylation of substituted pyrazoles is described, for example, in "Heterocyclic Chemistry," by T. L. Gilchrist, Longman, **1992**, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **85.3** and **85.4**, are, except in cases where X is dialkylphosphono, converted into the phosphonates, **85.5** and **85.6**, using the procedures described herein, and deprotection then affords the triols, **85.7** and **85.8**.

Example 86



The pyrazole, **85.1**, is reacted, as described above, with one molar equivalent of a dialkyl bromoacetonyl phosphonate, **86.1** (*Tet.*, **1978**, *34*, 649), to give the alkylated pyrazoles, **86.2** and **86.3**. Deprotection then yields the triols, **86.4** and **86.5**.

Example 87



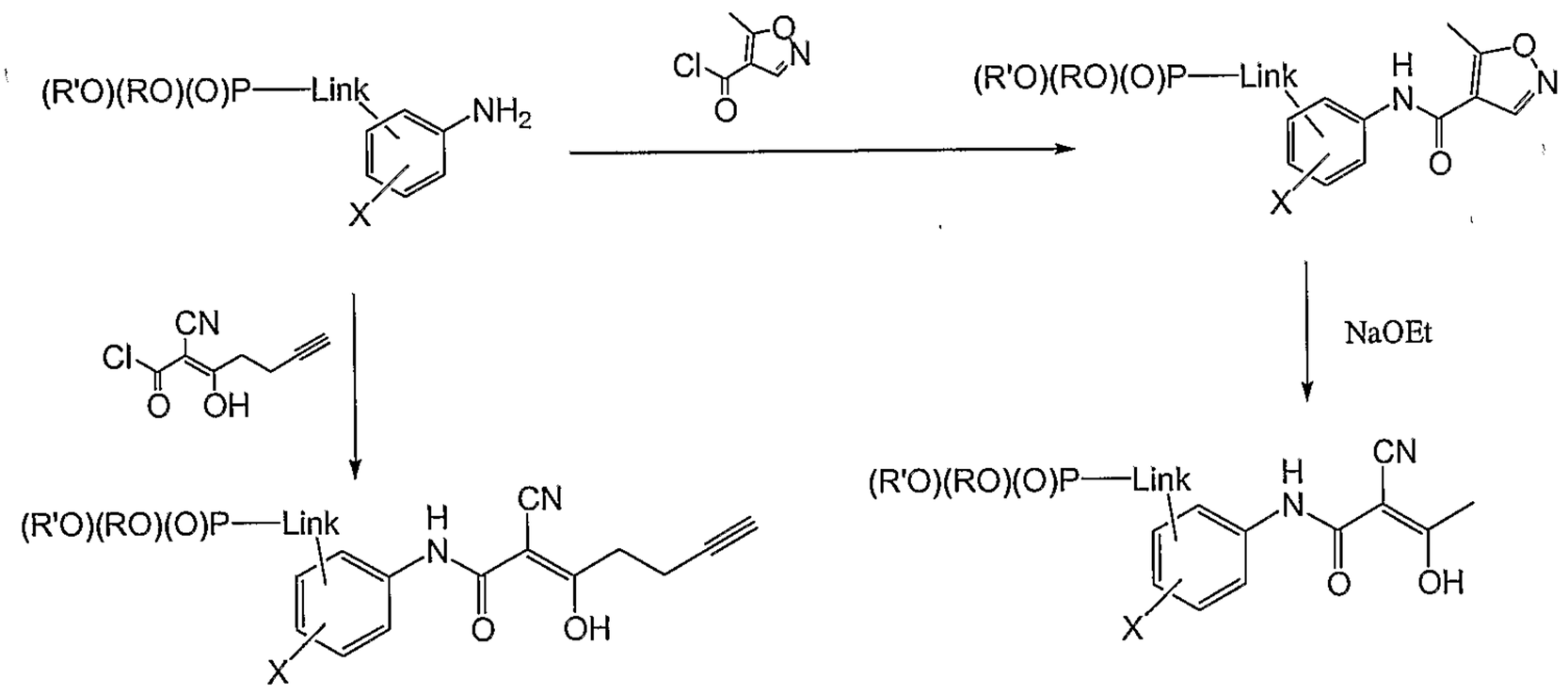
The pyrazole, **85.1**, is reacted, as described above, with 1,4-bis(bromomethyl)benzene, **87.1**, to give the pyrazoles, **87.2** and **87.3**. The products are subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain, the phosphonates, **87.4** and **87.5**. The Arbuzov reaction is described in *Handb.*

Organophosphorus Chem., **1992**, 115-72. In the procedure, the substrate is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite.

Using the above procedures, but employing, in place of the dibromide, **87.1**, different dibromides, the products analogous to **87.4** and **87.5** are obtained.

Example 88

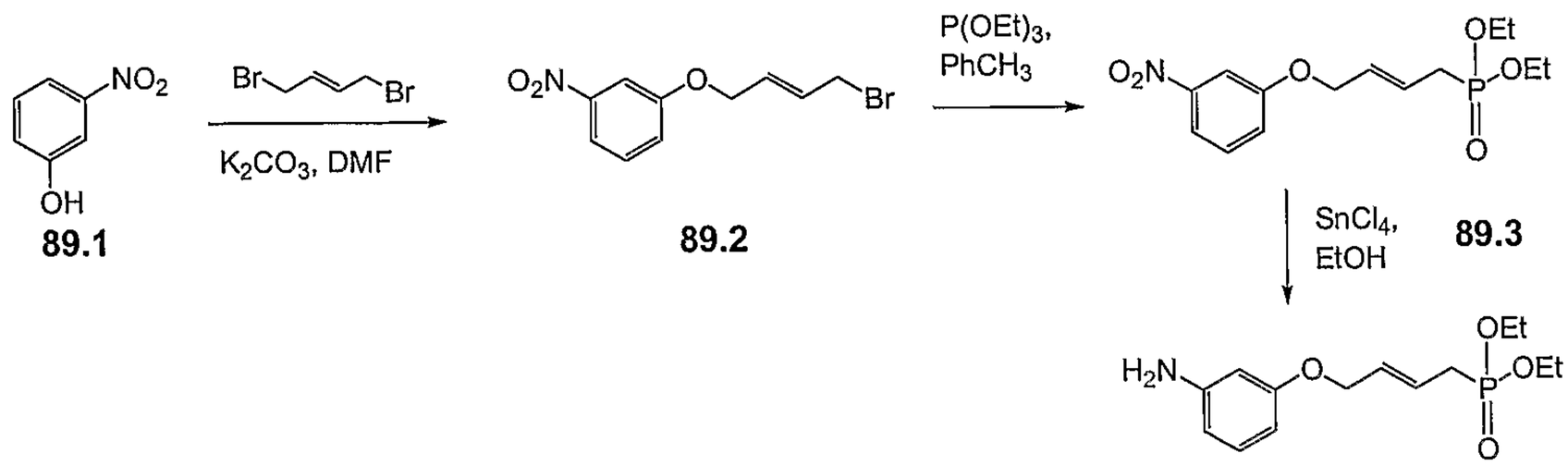
A synthetic methodology towards the preparation of phosphonate compounds of Formulae **88.1** and **88.2** is described by Westwood et al, *J. Med. Chem.*, **1996**, *39*, 4608-4621, according to the general routes outlined below.



88.1 **88.2**

Example 89

The preparation of compounds of the invention having phosphonate groups and intermediate compounds useful for their synthesis are illustrated below.

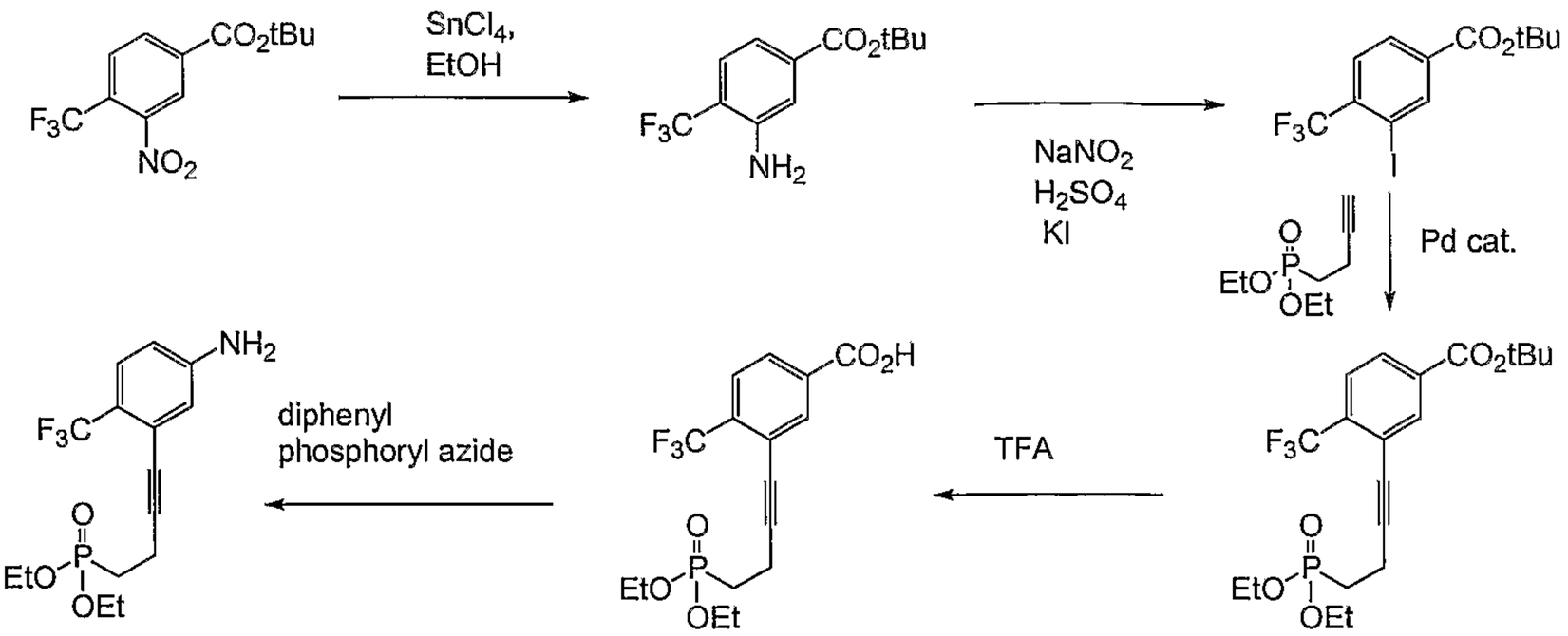


89.1 **89.2** **89.3**

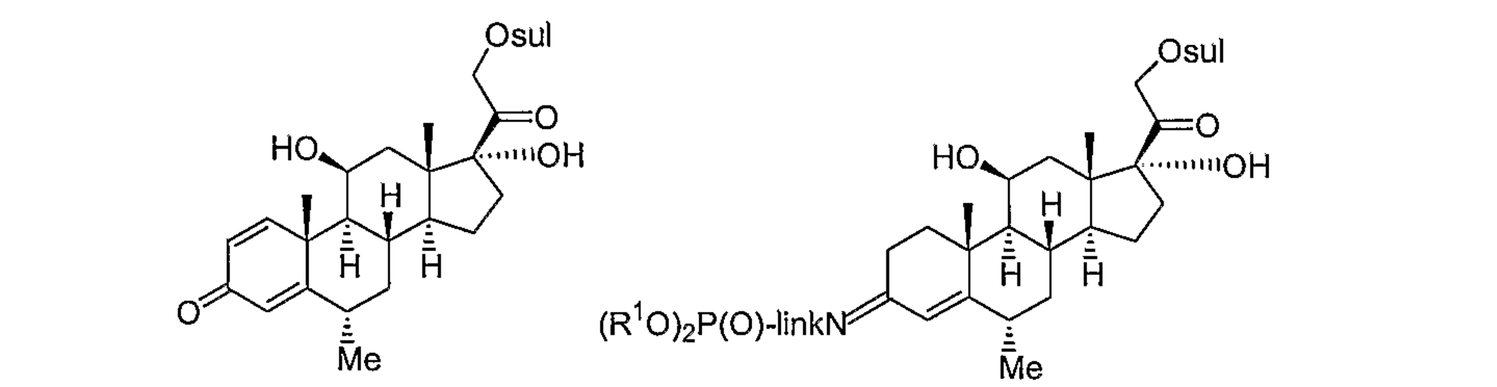
89.4

Example 90

The preparation of compounds of the invention having phosphonate groups and intermediate compounds useful for their synthesis are illustrated below.

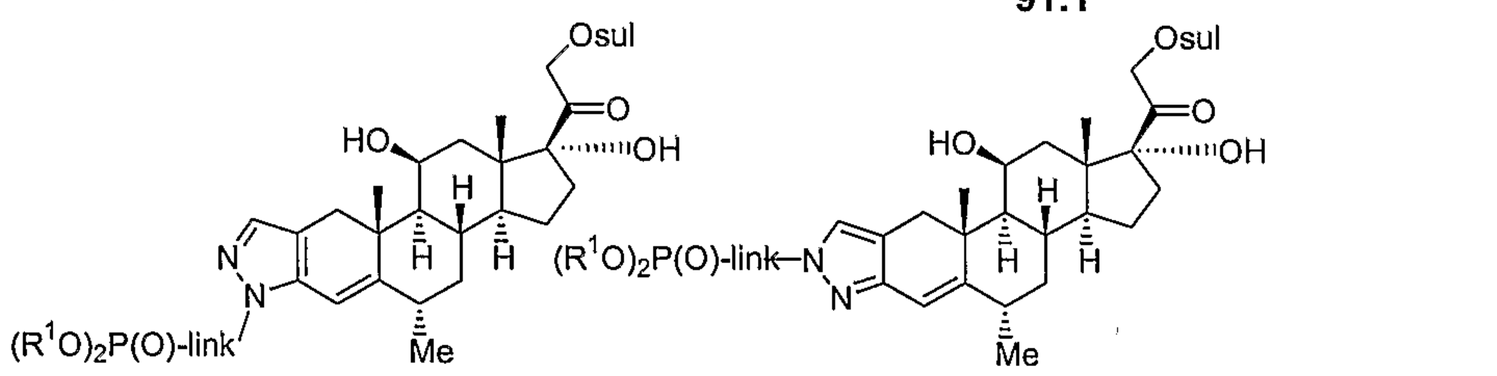


Example 91

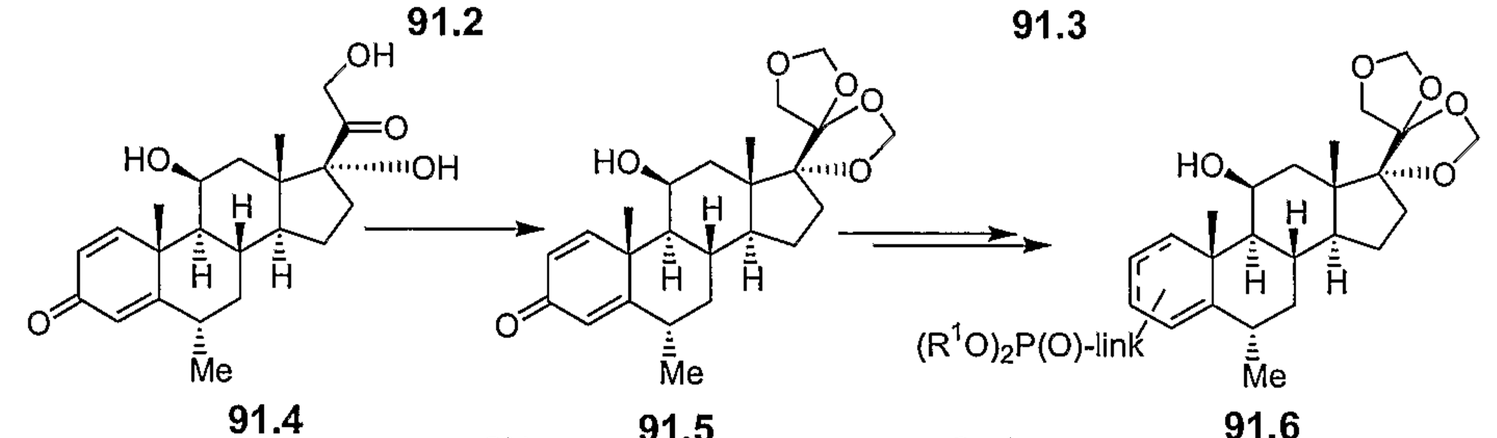


Methylprednisolone suleptanate **91A**

91.1



91.2

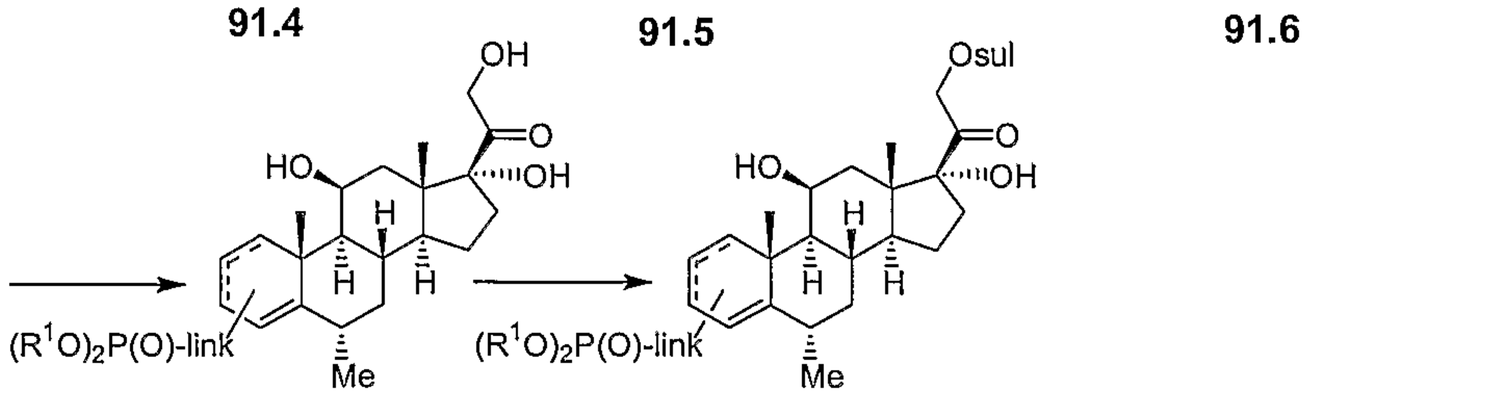


91.3

91.4

91.5

91.6

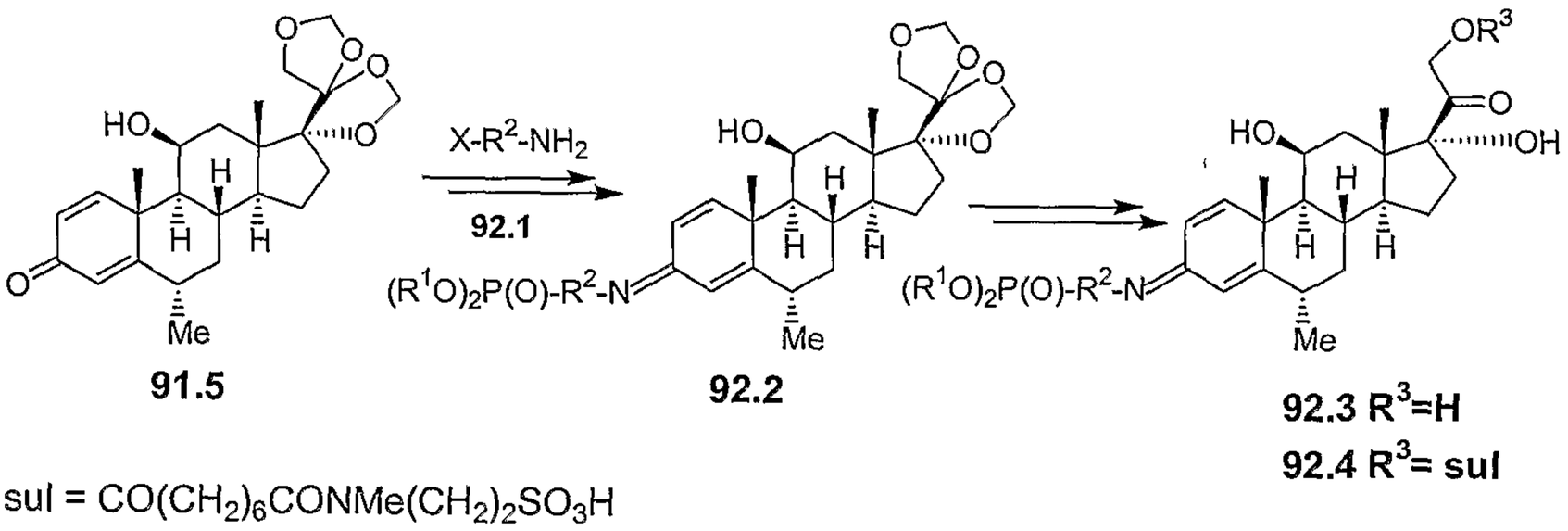


91.7 **91.8** sul = $CO(CH_2)_6CONMe(CH_2)_2SO_3H$

The structures of Methylprednisolone suleptanate, **91A** (WO 89/00558), and the phosphonate esters, **91.1 – 91.3**, are shown above in Example **91**, in which the substituent R^1 is H, alkyl, alkenyl, aryl or aralkyl. The compounds, **91.1 – 91.3**, incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures. The syntheses of the phosphonate compounds of this invention, **91.1 – 91.3**, and of the intermediate compounds necessary for their synthesis are set forth below.

Methylprednisolone, **91.4**, is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **91.5**. The phosphonate moiety is then introduced, using the procedures described herein, to produce the phosphonate ester, **91.6**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the triol, **91.7**. The triol is then converted into the 21-suleptanate ester as described in WO 89/00558. In this procedure, a mixed anhydride prepared by reacting suleptanic acid with pivaloyl chloride, in the presence of a base such as triethylamine, is reacted with the 21-hydroxy steroid, **91.7**, to prepare the 21-suleptanate ester, **91.8**.

Example 92

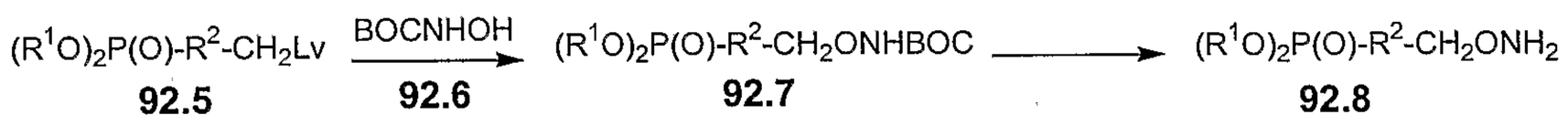


sul = $CO(CH_2)_6CONMe(CH_2)_2SO_3H$

The preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is illustrated above. In this procedure, the BMD-protected derivative, **91.5**, is reacted with an

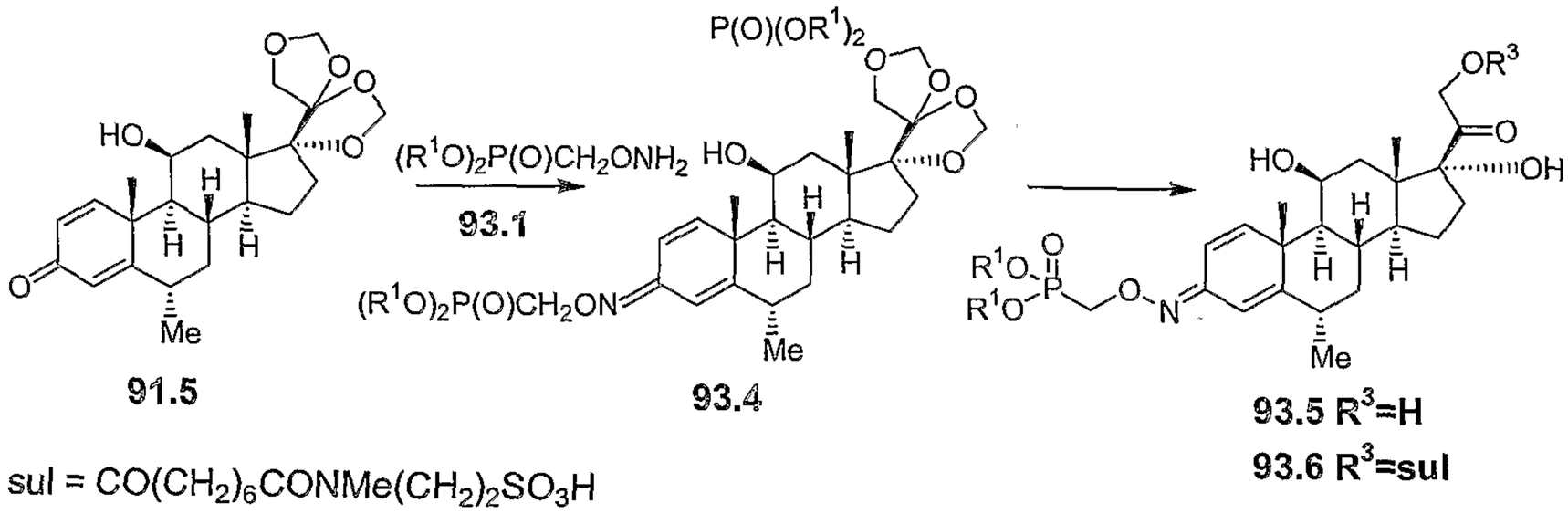
amine or hydroxylamine, **92.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The BMD-protected side-chain compound, **92.2**, is then converted into the triol, **92.3**, and then to the suleptanate, **92.4**, as described above in Example **91**.

Example 92A



The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated above. In this procedure, a phosphonate, **92.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy. The phosphonate is reacted with BOC-hydroxylamine, **92.6** (Aldrich), to produce the ether, **92.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **92.8**.

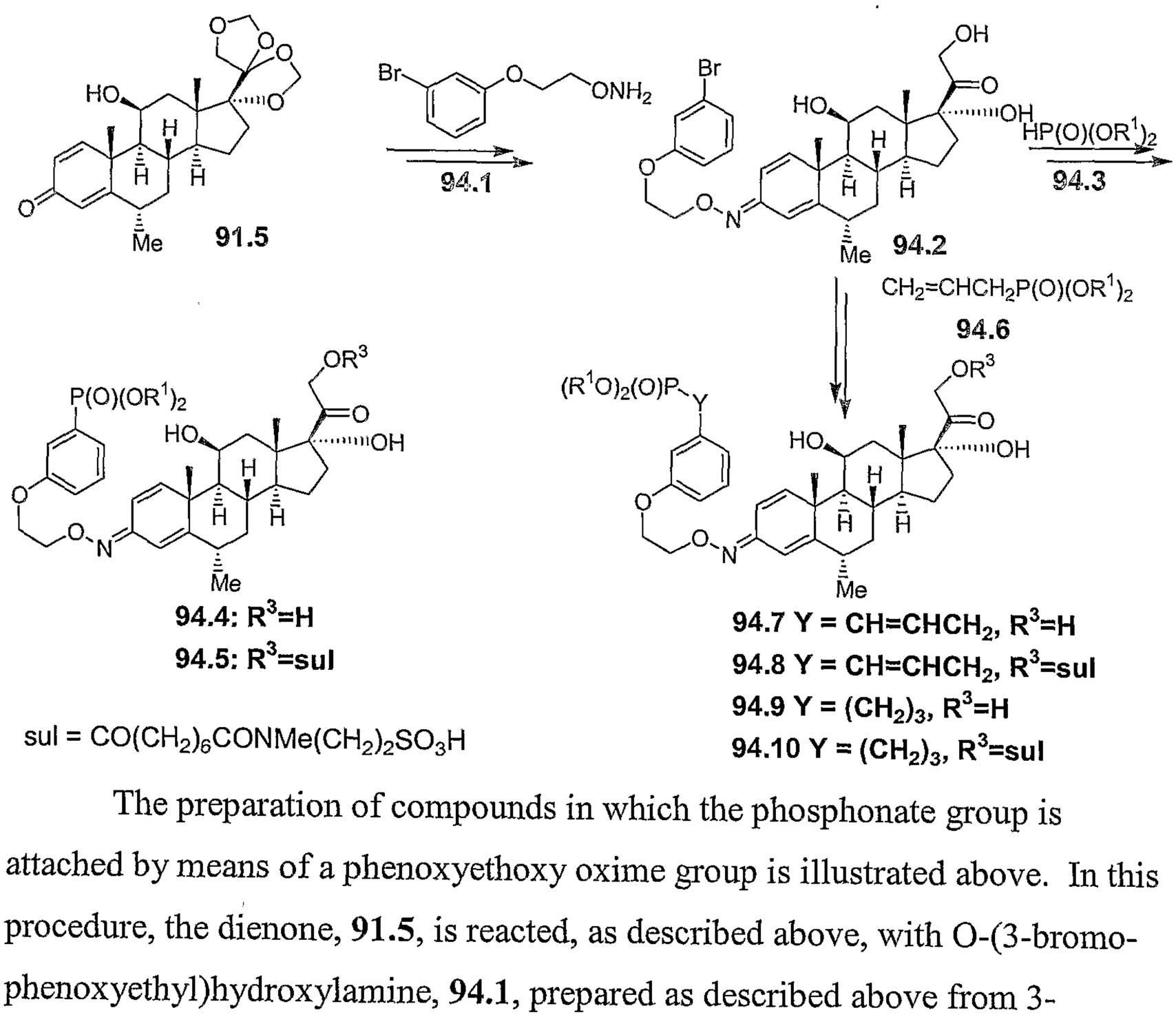
Example 93



The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group is illustrated above. In this procedure, the substrate, **91.5**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **93.1**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **93.4**, which is deprotected to afford the triol, **93.5**, from which the suleptanate ester, **93.6**, is prepared. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **93.1**, different oxime ethers, **92.1**, the corresponding products, **92.4** are obtained.

Example 94



94.4: R^3=H

94.5: R^3=sul

sul = $CO(CH_2)_6CONMe(CH_2)_2SO_3H$

94.7 Y = $CH=CHCH_2$, R^3=H

94.8 Y = $CH=CHCH_2$, R^3=sul

94.9 Y = $(CH_2)_3$, R^3=H

94.10 Y = $(CH_2)_3$, R^3=sul

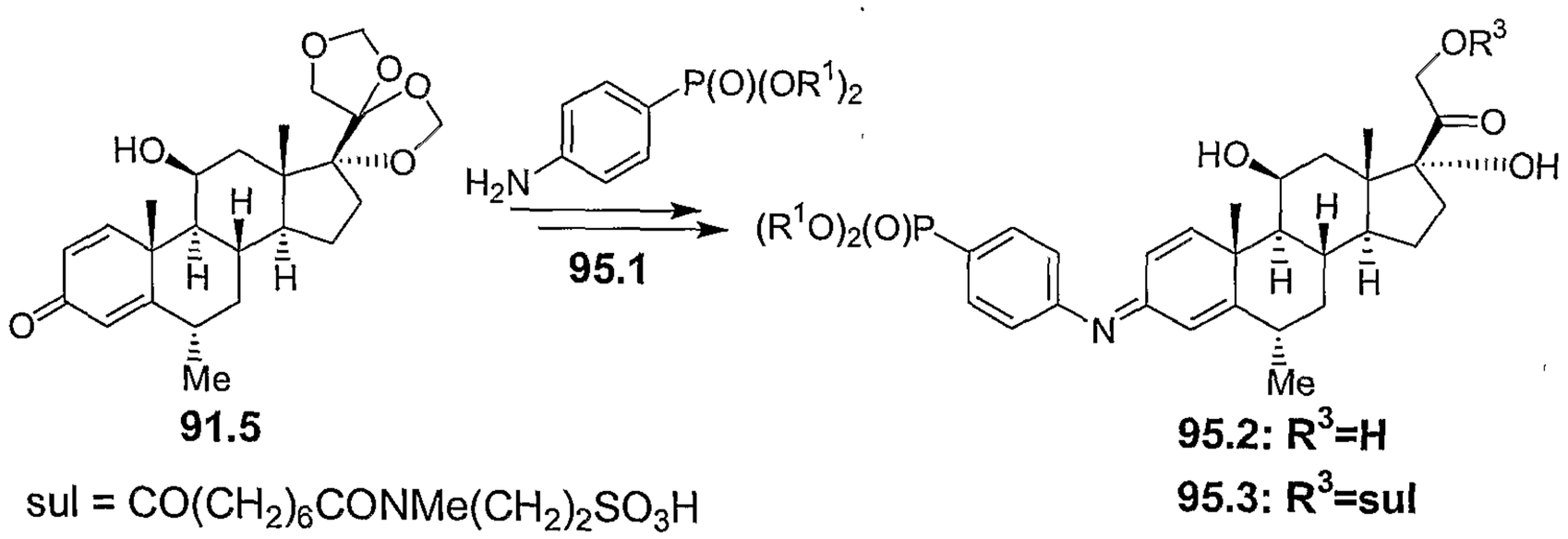
The preparation of compounds in which the phosphonate group is attached by means of a phenoxyethoxy oxime group is illustrated above. In this procedure, the dienone, **91.5**, is reacted, as described above, with O-(3-bromophenoxyethyl)hydroxylamine, **94.1**, prepared as described above from 3-bromophenoxyethyl bromide (FR 1,481,052) and BOC-protected hydroxylamine, to give, after deprotection of the side-chain, the oxime, **94.2**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **94.3**, to afford the phosphonate, **94.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0). The 21-hydroxy group is then converted into the 21-suleptanate product, **94.5**.

Alternatively, the bromo compound, **94.2**, is coupled with a dialkyl propenylphosphonate, **94.6** (Aldrich), to afford the phosphonate, **94.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by F. A. Carey and R. J. Sundberg, Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as

tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **94.7**, is reduced, for example by reaction with diimide, to produce the saturated analog, **94.9**. The reduction of olefinic bonds is described in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane. The products, **94.7** and **94.9**, are then converted into the suleptanate esters, **94.8** and **94.10**.

Using the above procedures, but employing, in place of the bromo-phenoxyethoxy reagent, **94.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **94.5**, **94.8** and **94.10** are obtained.

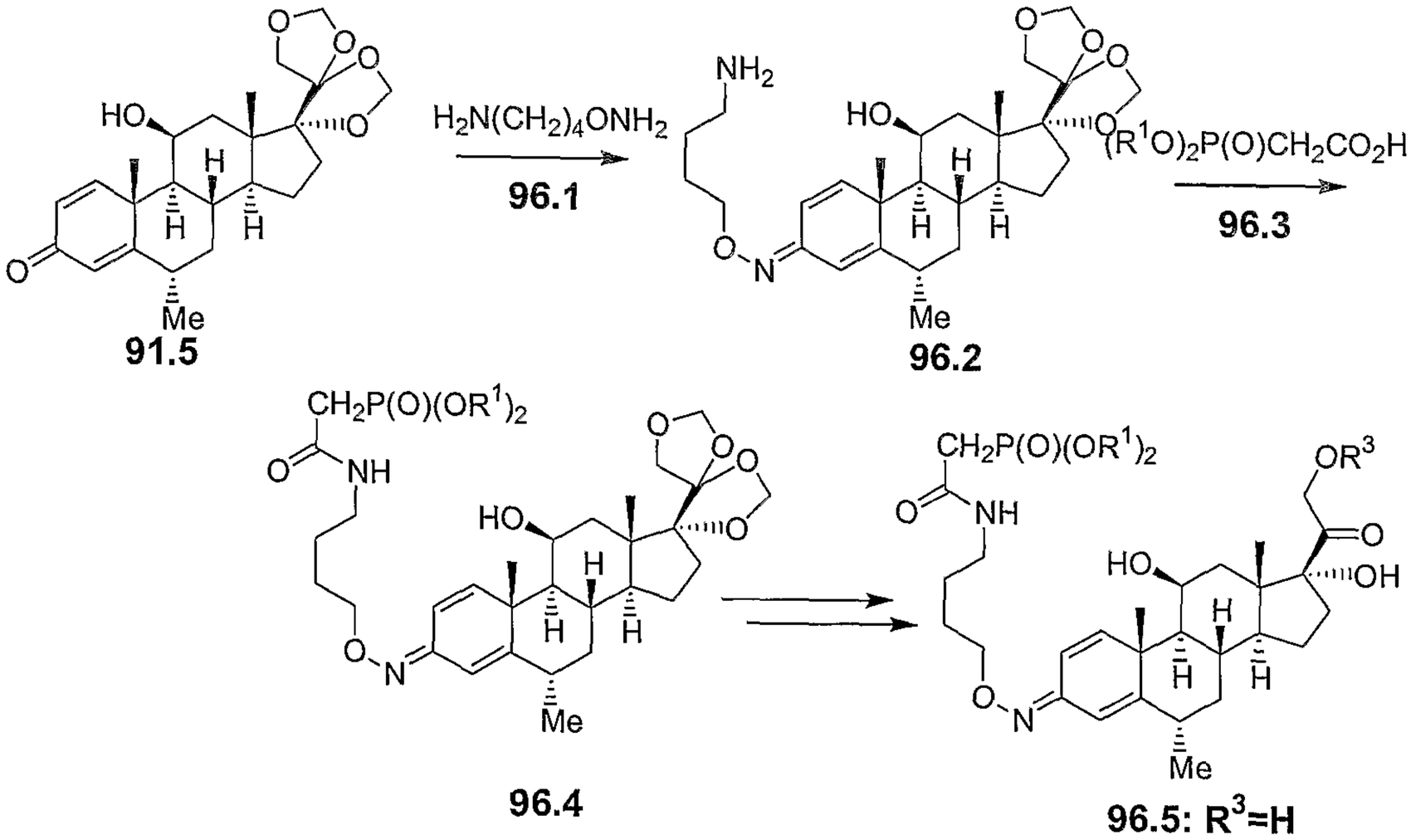
Example 95



The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, compound, **91.5**, is reacted with a dialkyl 4-aminophenyl phosphonate, **95.1** (Epsilon), to give, after deprotection, the imine product, **95.2**. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. The product is then converted into the suleptanate ester, **95.3**.

Using the above procedures, but employing, in place of the 4-aminophenyl phosphonate, **95.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **95.3** are obtained.

Example 96



The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and an amide linkage is illustrated above. In this procedure, the dienone, **91.5**, is reacted with O-(4-aminobutyl)hydroxylamine, **96.1** (*Pol. J. Chem.*, **1981**, *55*, 1163), to yield the oxime, **96.2**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795. The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The oxime is then coupled with a dialkyl phosphonoacetic acid, **96.3** (Aldrich), to yield the amide oxime, **96.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R.Sandler and W. Karo, Academic Press, **1968**, p. 274, and "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-

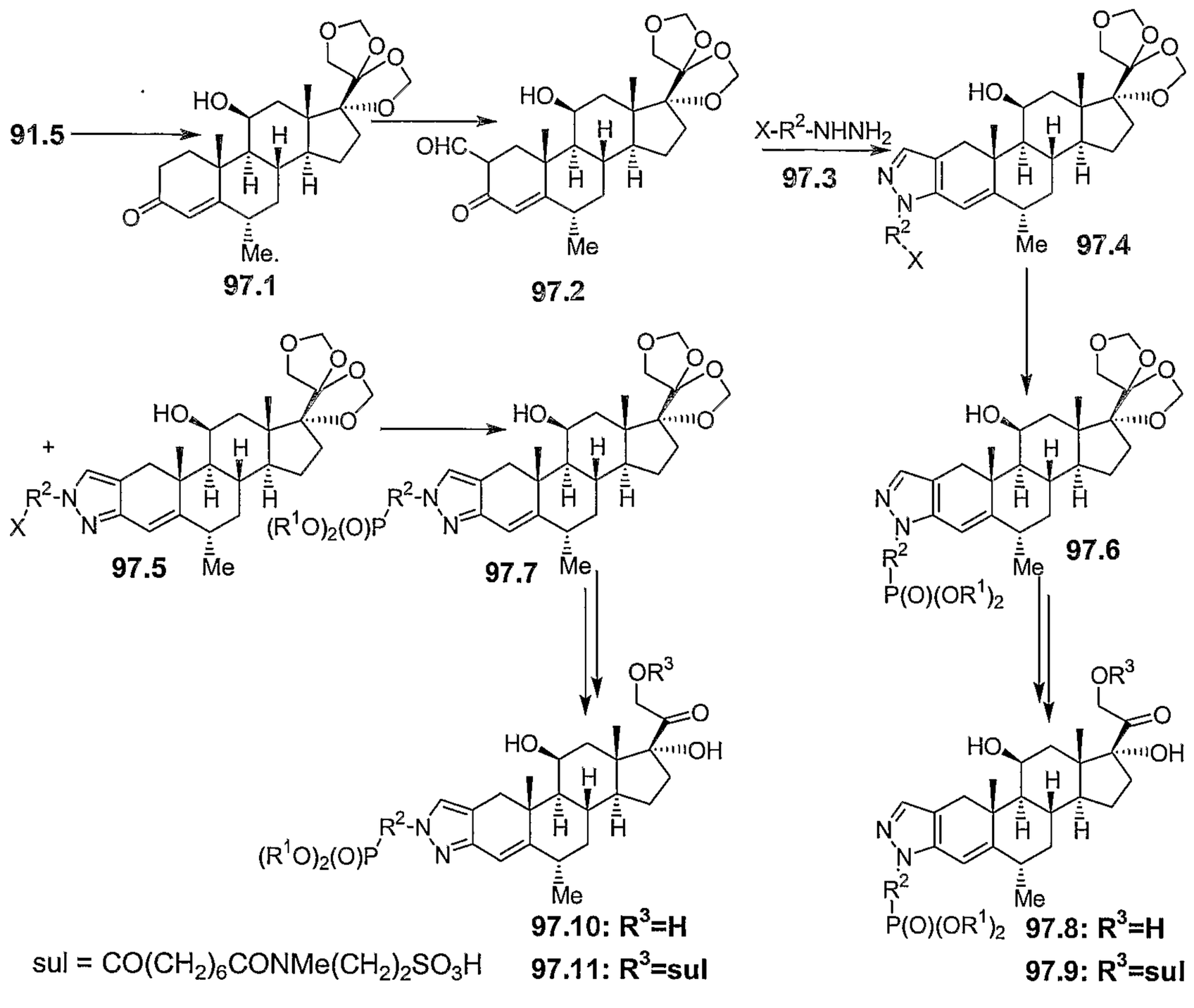
hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid is first converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide. The conversion of a carboxylic acid into the corresponding acid chloride is effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The amide product, **96.4**, is then converted, as described herein, into the suleptanate, **96.6**.

Using the above procedures, but employing, in place of the hydroxylamine, **96.1**, different amino-substituted hydroxylamines, and/or different carboxy-substituted phosphonates, the products analogous to **96.6** are obtained.

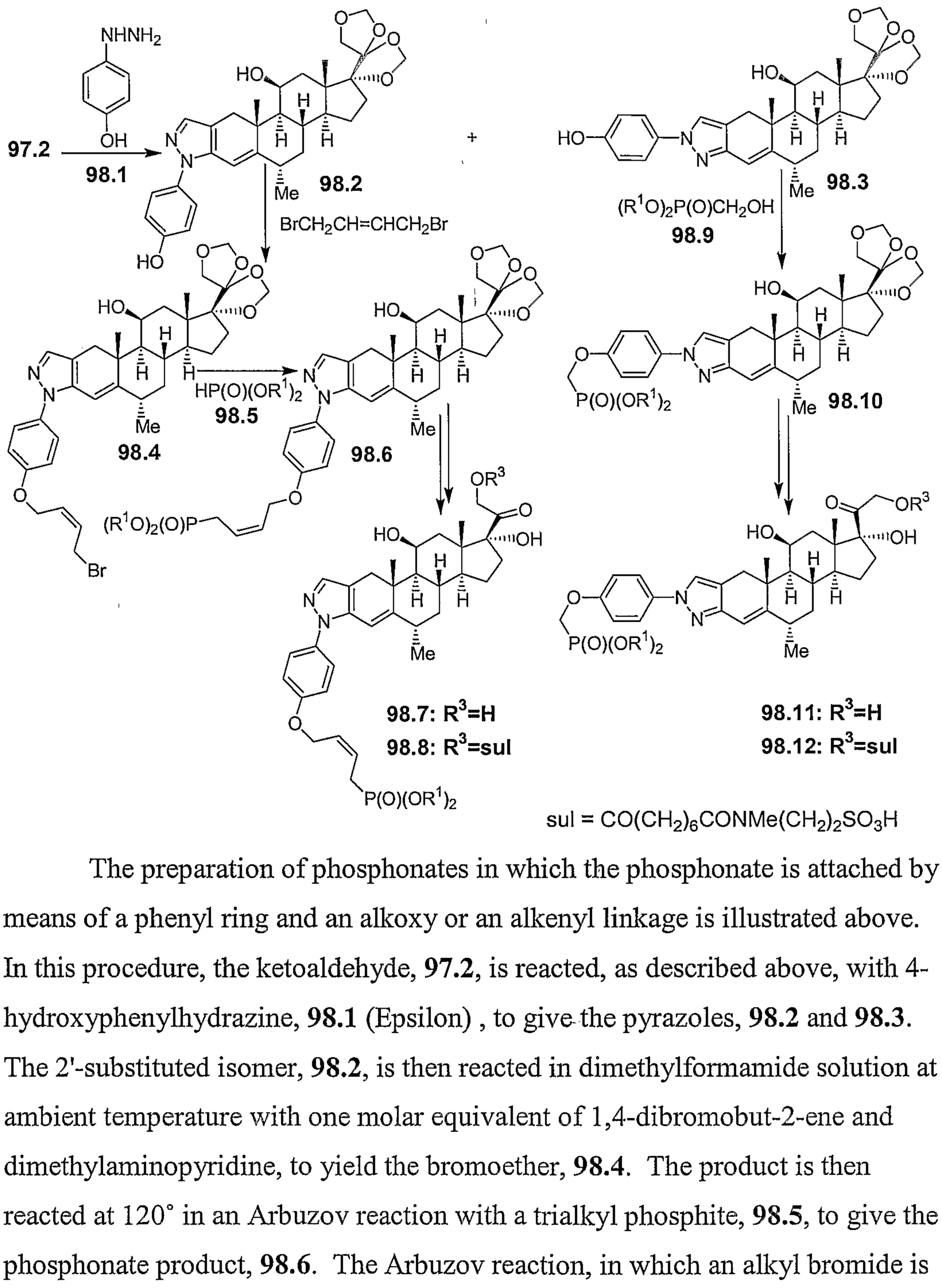
Example 97



The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, the BMD-protected dienone, **91.5**, is reduced to afford the 1,2-dihydro product, **97.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **97.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **97.3**, wherein R^2 is alkyl, aralkyl, aryl or heteroaryl and in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **97.4** and **97.5**. The pyrazole-forming reaction is performed between

equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **97.4** and **97.5**, are then transformed, for example by the procedures described in Examples **98** and **99**, via the BMD-protected intermediates, **97.6** and **97.7**, into the phosphonate suleptanates, **97.9** and **97.11**.

Example 98



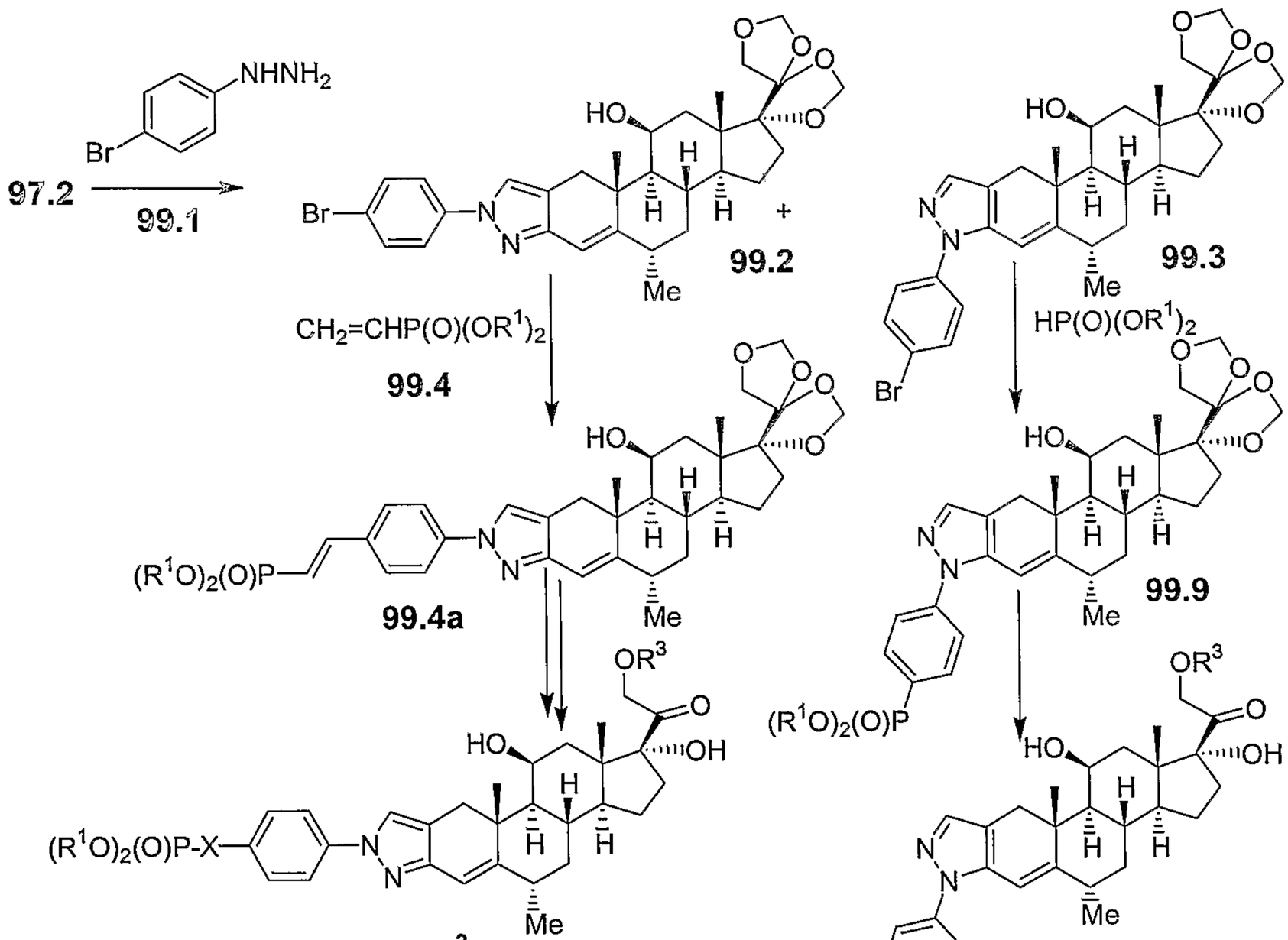
The preparation of phosphonates in which the phosphonate is attached by means of a phenyl ring and an alkoxy or an alkenyl linkage is illustrated above. In this procedure, the ketoaldehyde, **97.2**, is reacted, as described above, with 4-hydroxyphenylhydrazine, **98.1** (Epsilon) , to give the pyrazoles, **98.2** and **98.3**. The 2'-substituted isomer, **98.2**, is then reacted in dimethylformamide solution at ambient temperature with one molar equivalent of 1,4-dibromobut-2-ene and dimethylaminopyridine, to yield the bromoether, **98.4**. The product is then reacted at 120° in an Arbuzov reaction with a trialkyl phosphite, **98.5**, to give the phosphonate product, **98.6**. The Arbuzov reaction, in which an alkyl bromide is

transformed into the corresponding phosphonate, by heating at from 60°to about 150° with a trialkyl phosphite, is described in *Handb. Organophosphorus Chem.*, **1992**, 115-72. The BMD protecting group is then removed and the product is acylated to yield the suleptanate ester triol, **98.8**.

Alternatively, the 1'-substituted pyrazole, **98.3**, is reacted, in a Mitsonobu reaction, with a dialkyl 2-hydroxymethyl phosphonate, **98.9** (Aldrich), to afford the ether, **98.10**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 448, and in "Advanced Organic Chemistry," Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p. 153-4 and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triaryl-phosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335. The product, **98.10**, is then deprotected to give the triol, **98.11**, and the latter compound is acylated to afford the suleptanate, **98.12**.

Using the above procedures, but employing different dibromides or hydroxyl-substituted phosphonates, the products analogous to **98.8** and **98.12** are obtained. The functionalization procedures are interchangeable between the pyrazole substrates, **98.2** and **98.3**.

Example 99



sul = $CO(CH_2)_6CONMe(CH_2)_2SO_3H$

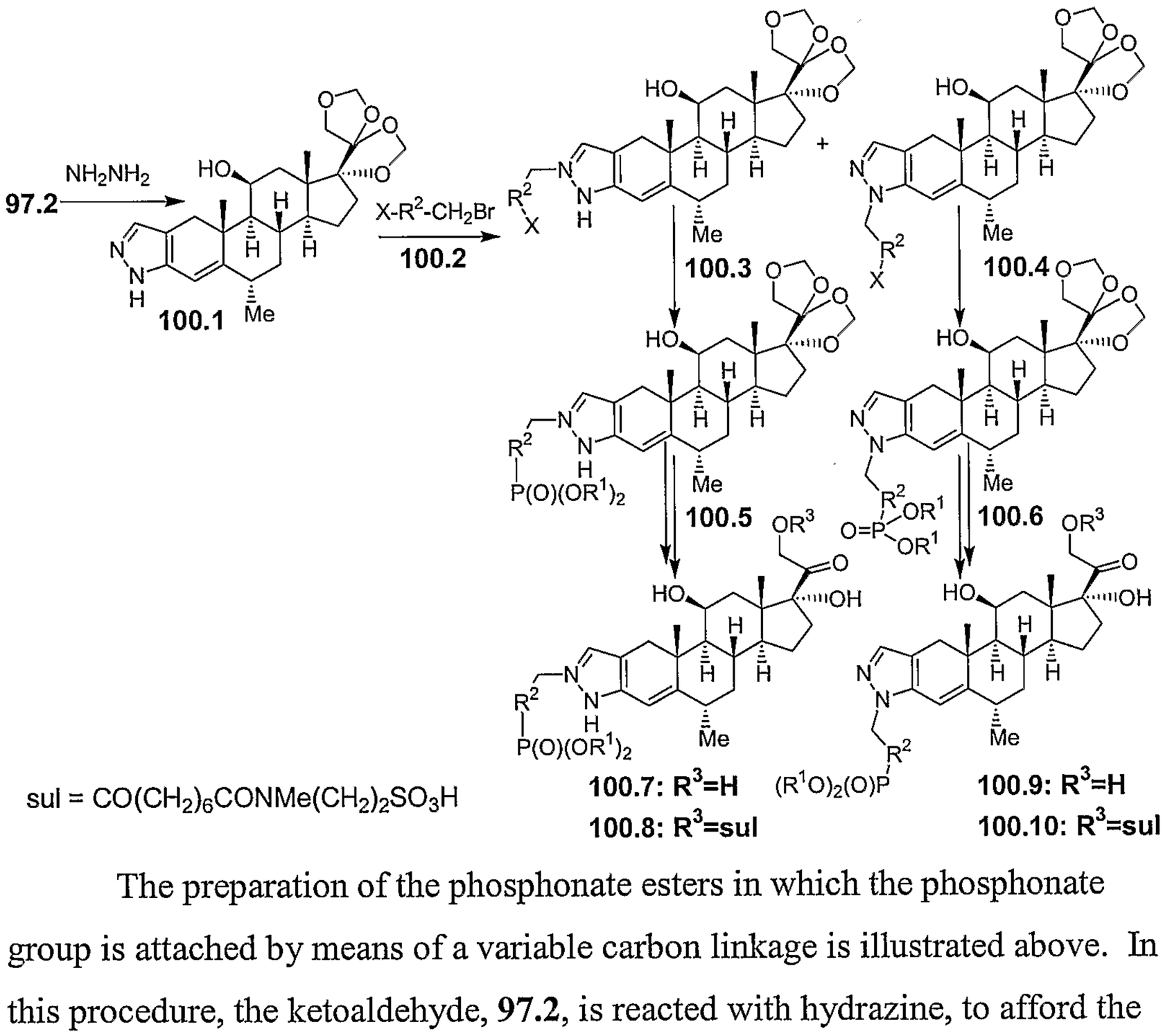
The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl ring or a phenyl ring and a saturated or unsaturated carbon chain is illustrated above. In this procedure, the keto-aldehyde, **97.2**, is reacted, as described above, with 4-bromophenyl hydrazine, **99.1** (*J. Organomet. Chem.*, **1999**, *62*, 581), to produce the pyrazoles, **99.2** and **99.3**. The 1'-substituted isomer, **99.2**, is coupled, in the presence of a palladium catalyst, with a dialkyl vinylphosphonate, **99.4** (Aldrich), to give the phosphonate, **99.4a**. The product is then deprotected to afford the triol, **99.5**, which is converted into the suleptanate, **99.6**. Optionally, the styrenoid double bond present in the product, **99.6**, is reduced, as described above, to produce the saturated analog, **99.8**.

Alternatively, the 2'-substituted pyrazole, **99.3**, is coupled, in the presence of a palladium catalyst, with a dialkyl phosphite to prepare the phosphonate, **99.9**, which is deprotected, and the product is acylated to give the

suleptanate ester, **99.11**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. This reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and tetrakis-(triphenylphosphine)palladium(0).

Using the above procedures, but employing, in place of the bromophenyl hydrazine, **99.1**, different bromo-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **99.6**, **99.8** and **99.11** are obtained.

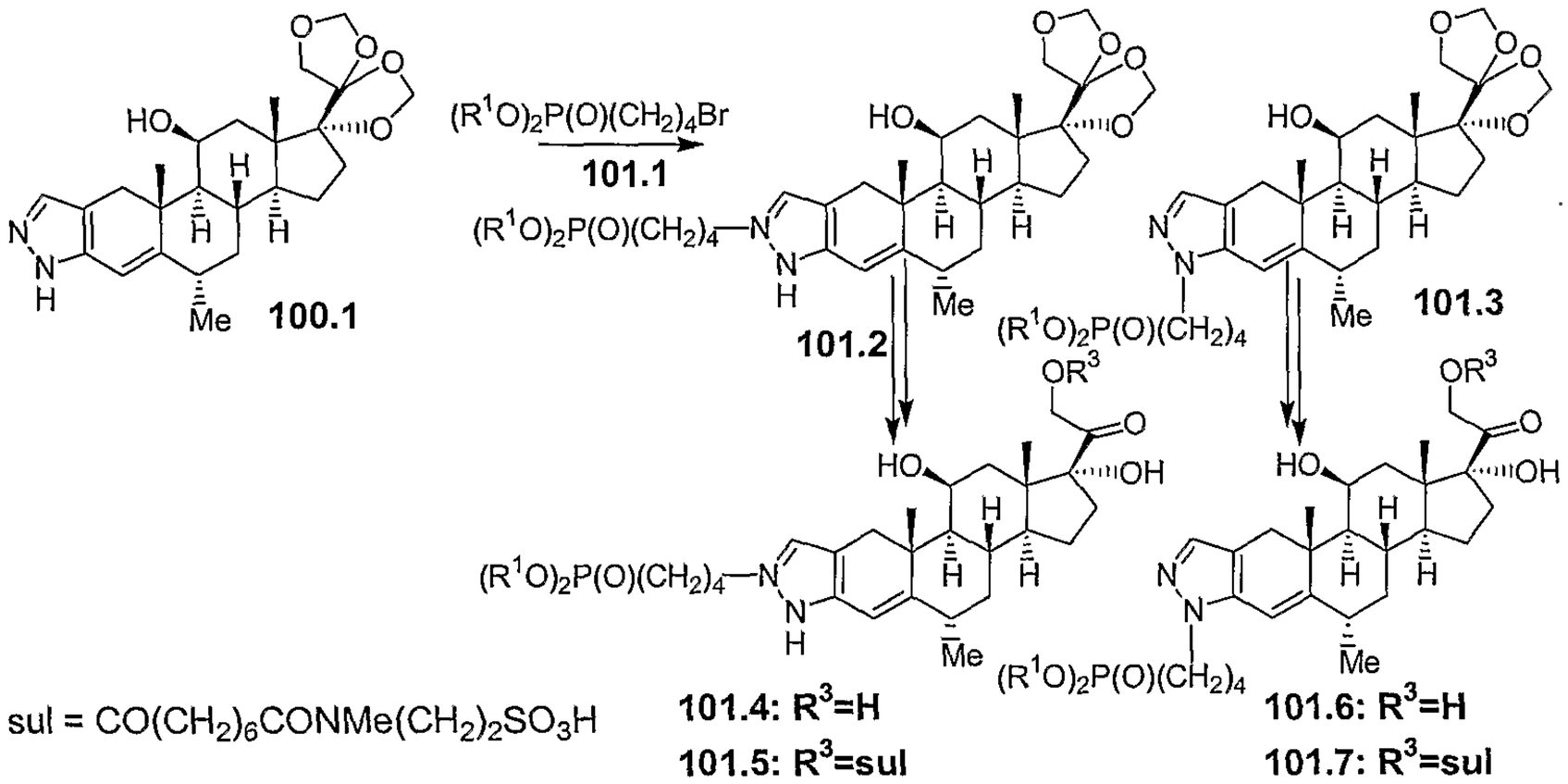
Example 100



The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **97.2**, is reacted with hydrazine, to afford the pyrazole derivative, **100.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **100.2**, in which R^2 and X are as defined above, to yield the alkylation products, **100.3** and **100.4**. The alkylation of

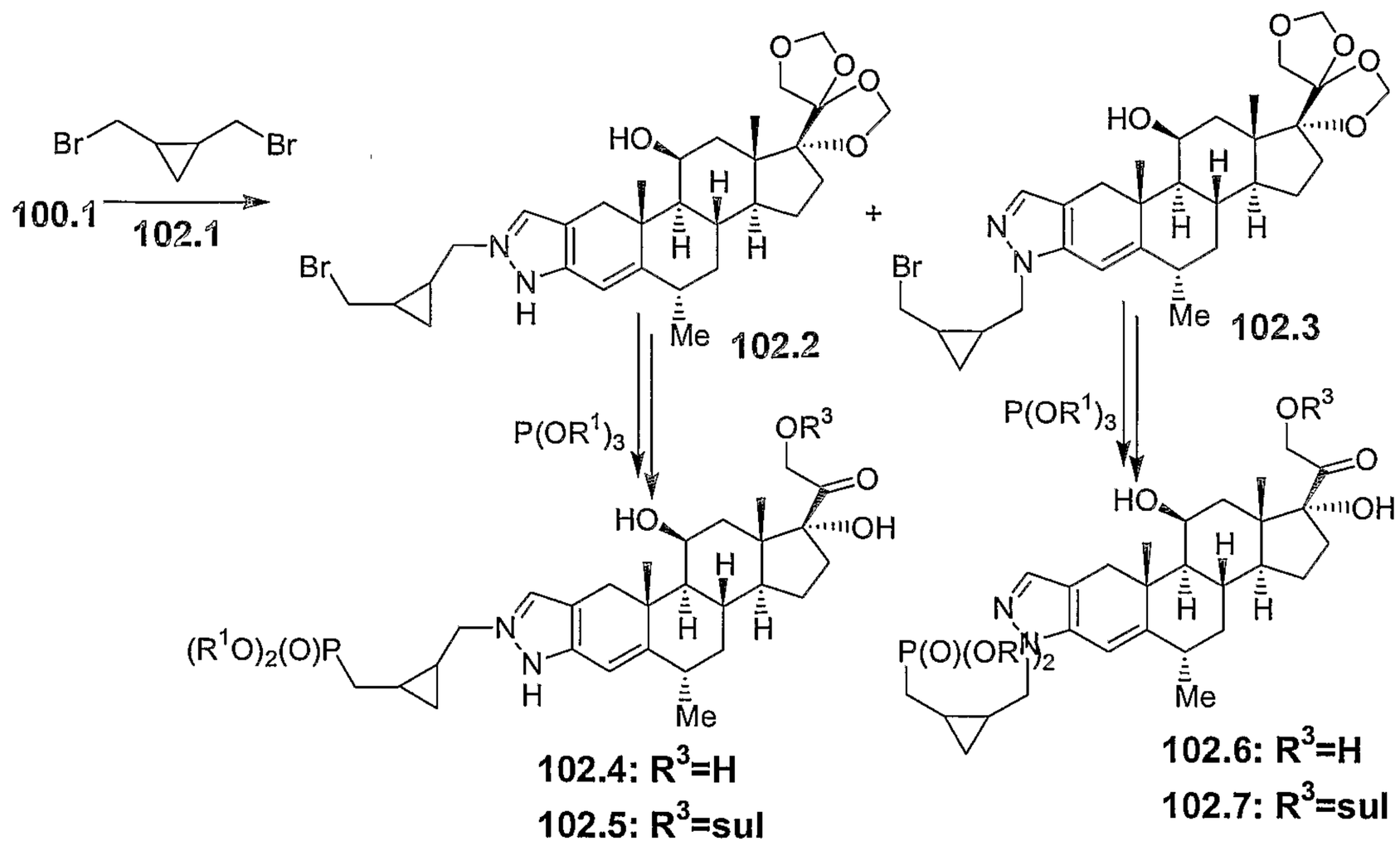
substituted pyrazoles is described, for example, in "Heterocyclic Chemistry," by T. L. Gilchrist, Longman, **1992**, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **100.3** and **100.4** are, except in cases where X is dialkylphosphono, converted into the phosphonates, **100.5** and **100.6**, using the procedures described herein, and deprotection/acylation then affords the suleptanate esters, **100.8** and **100.10**.

Example 101



The pyrazole, **100.1**, is reacted in tetrahydrofuran solution, as described above, with one molar equivalent of a dialkyl bromobutyl phosphonate, **101.1**, (*Synthesis*, **1994**, *9*, 909) and lithium hexamethyldisilazide to give the alkylated pyrazoles, **101.2** and **101.3**. Deprotection/acylation then yields the suleptanates, **101.5** and **101.7**.

Example 102

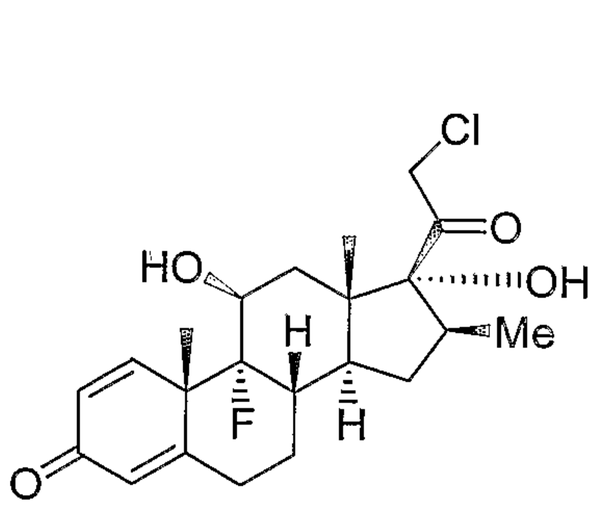


sul = $CO(CH_2)_6CONMe(CH_2)_2SO_3H$

The pyrazole, **100.1**, is reacted in tetrahydrofuran solution, as described above, with 1,2-bis(bromomethyl)cyclopropane, **102.1** (*Tet.*, **1997**, *53*, 10459), to give the pyrazoles, **102.2** and **102.3**. The products are subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after deprotection of the side chain and acylation, the suleptanate phosphonates, **102.5** and **102.7**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115-72. In the procedure, the substrate is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite.

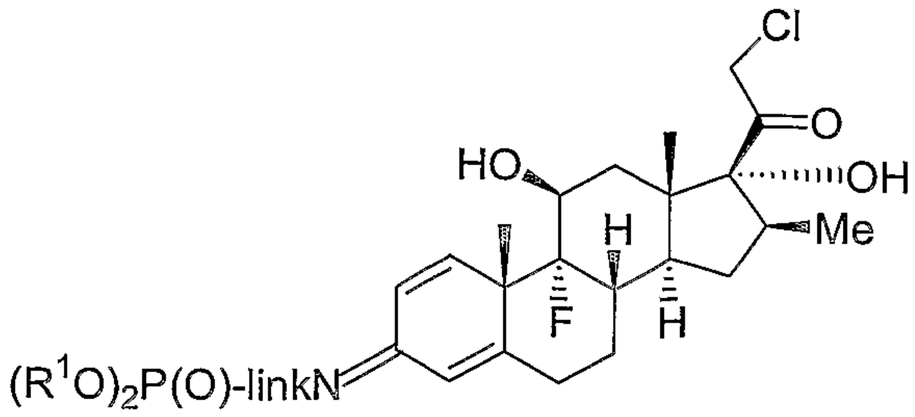
Using the above procedures, but employing, in place of the dibromide, **102.1**, different dibromides, the products analogous to **102.5** and **102.7** are obtained.

Example 103

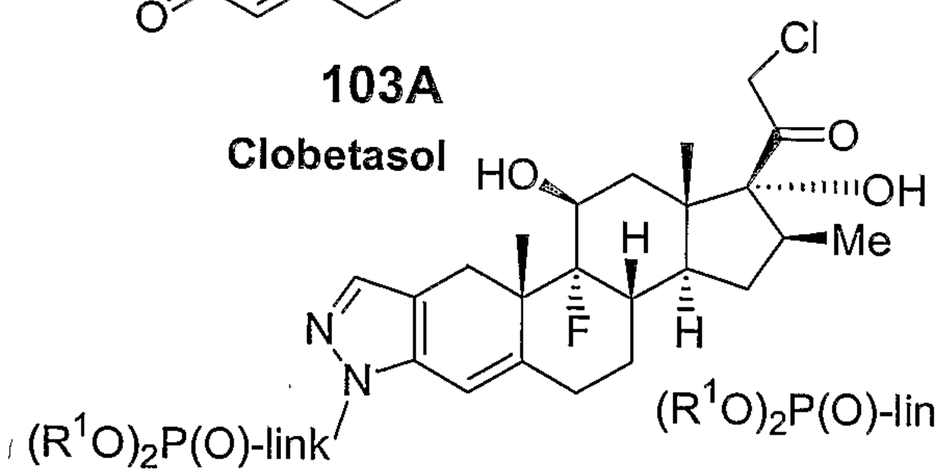


103A

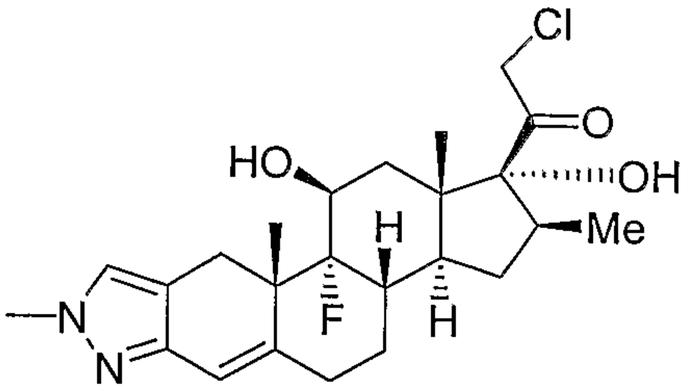
Clobetasol



103.1

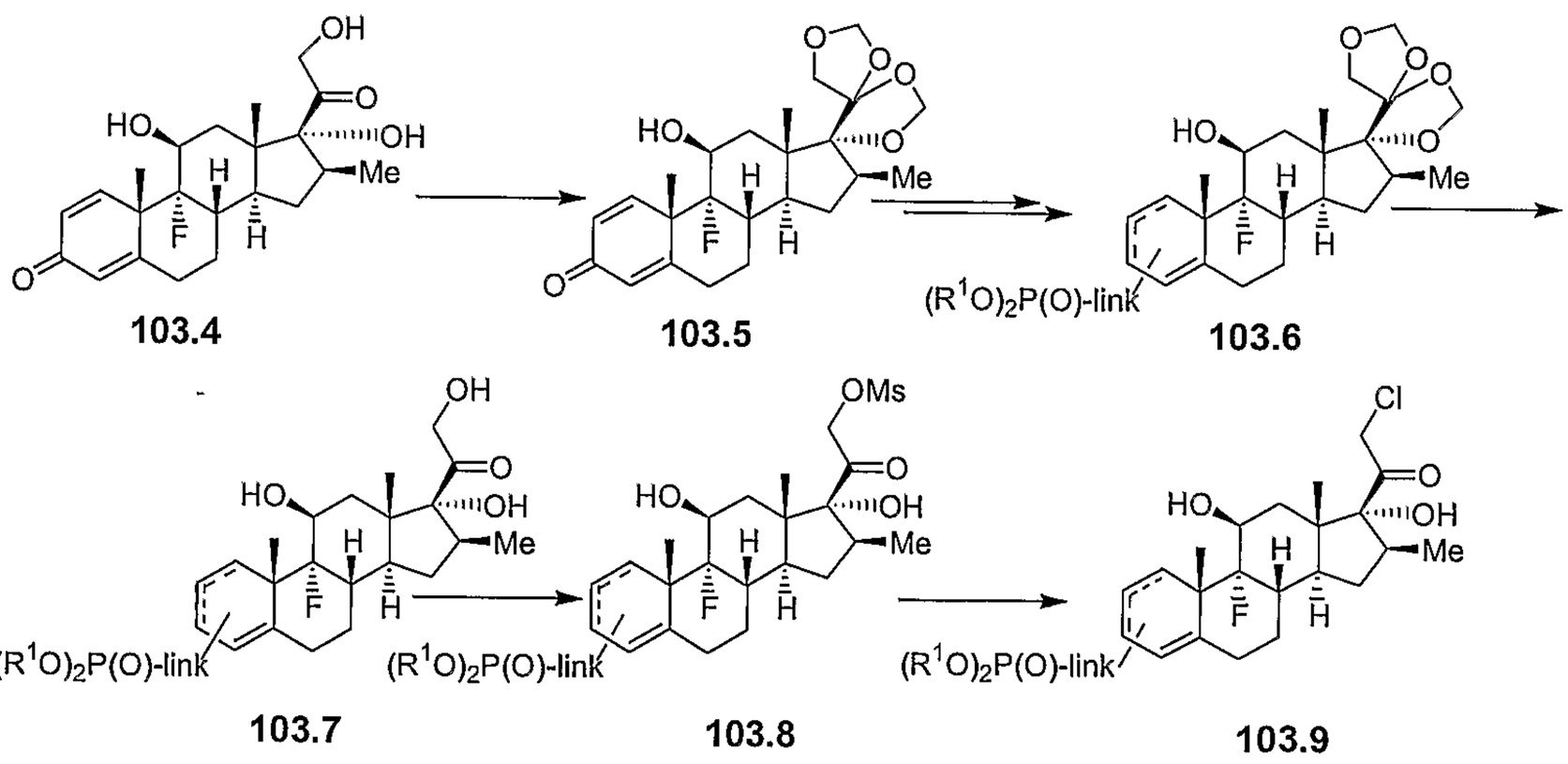


103.2



103.3

The structures of Clobetasol, **103A** (U.S. Patent No. 3,721,687), and the phosphonate esters, **103.1** – **103.3**, are shown above. The compounds, **103.1** – **103.3**, incorporate a phosphonate moiety $(R^1O)_2P(O)$ connected to the nucleus by means of a variable linking group, designated as "link" in the attached structures.



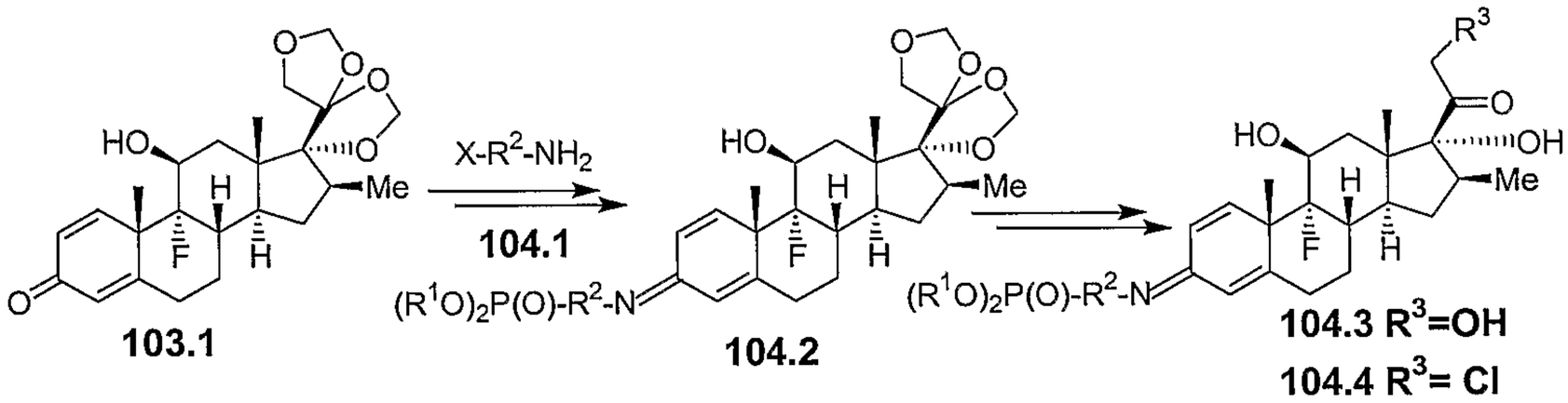
103.4 **103.5** **103.6**

103.7 **103.8** **103.9**

A protection-deprotection sequence in which the steroid side-chain is protected as a bis-methylenedioxy (BMD) moiety is illustrated above. In this sequence, 9α-fluoro-16β-methyl-11β,17α,21-trihydroxypregn-1,4-dien-3,21-dione, **103.4** (U.S. Patent No. 3,721,687), is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in "Protective Groups in

Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **103.5**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester, **103.6**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the triol, **103.7**. The 21-hydroxy group is then converted into the 21-chloro group as described in U.S. Patent No. 3,721,687, *Chimia*, **1992**, *46*, 338, or *J. Med. Chem.*, **1987**, *30*, 1581. In this procedure, the 21-hydroxy substrate is reacted at about 0° with one molar equivalent of methanesulfonyl chloride in a basic solvent such as pyridine, to afford the 21-mesylate, **103.8**. The product is then reacted, in dimethylformamide solution at about 70°, with ca. five molar equivalents of lithium chloride, to yield the 21-chloro product, **103.9**.

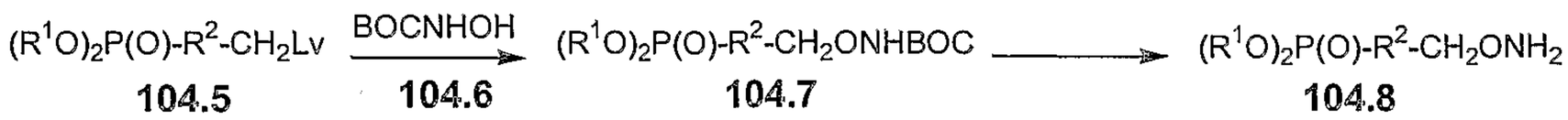
Example 104



The the preparation of phosphonates in which the phosphonate is attached by means of an imino or iminoxy group and a variable carbon chain is described herein. In this procedure, the BMD-protected derivative, **103.1**, is reacted with an amine or hydroxylamine, **104.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic

solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The BMD-protected side-chain compound, **104.2**, is then converted into the triol, **104.3**, and then to the 21-chloro product, **104.4**, as described herein.

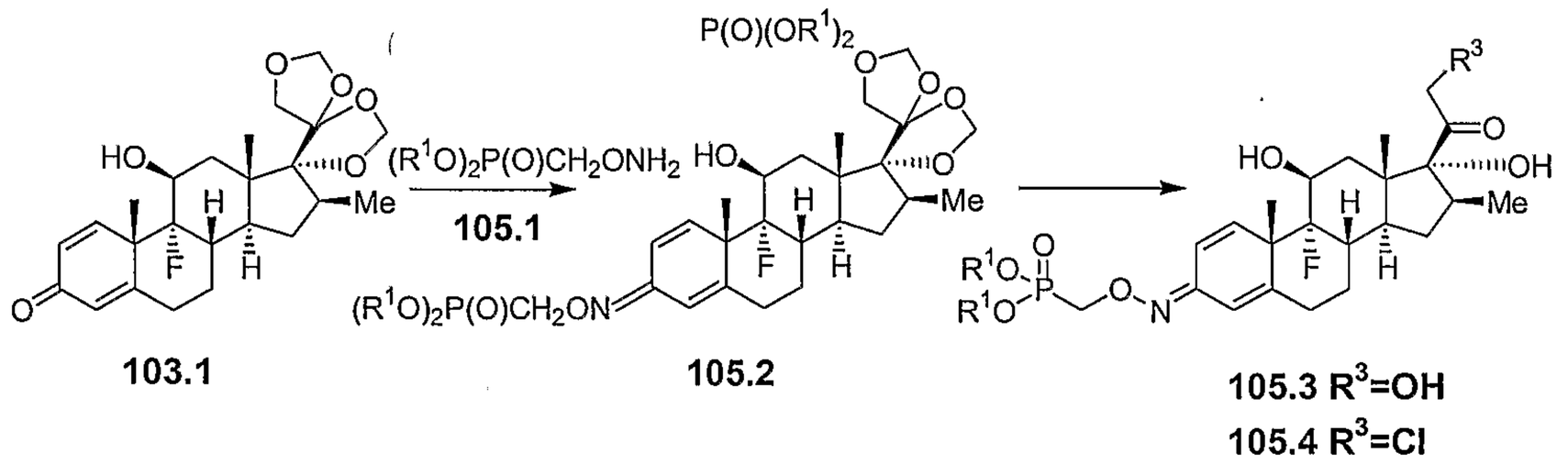
Example 104A



104.5 **104.6** **104.7** **104.8**

The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated above. In this procedure, a phosphonate, **104.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **104.6** (Aldrich), to produce the ether, **104.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **104.8**.

Example 105

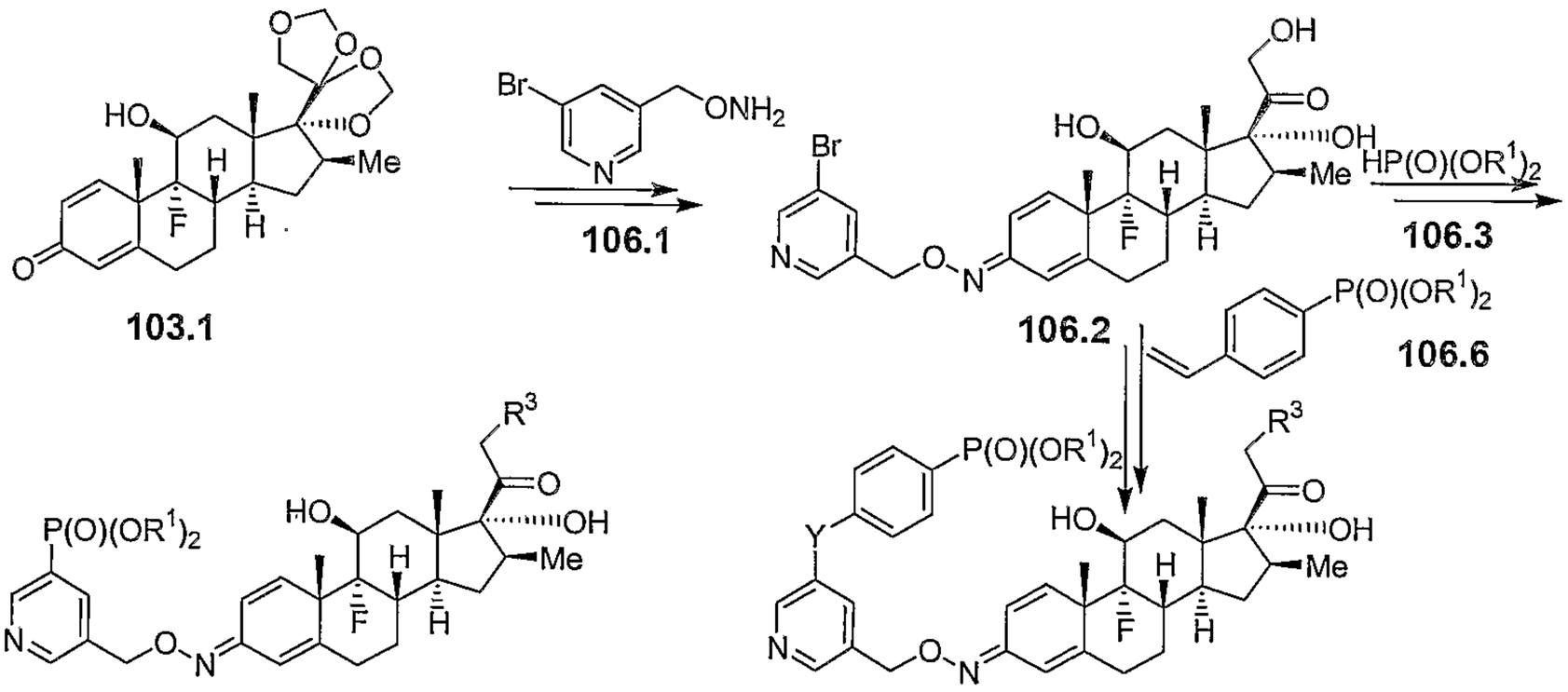


103.1 **105.2** **105.3 R^3=OH** **105.4 R^3=Cl**

The preparation of phosphonates in which the phosphonate is attached by means of an iminoxy group. In this procedure, the substrate, **103.1**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **105.1**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **105.2**. Deprotection then affords the triol, **105.3**, from which the 21-chloro compound, **105.4**, is prepared. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants. Using the above procedures, but employing, in place

of the hydroxylamine ether, **105.1**, different oxime ethers, **104.1**, the corresponding products, **105.4** are obtained.

Example 106

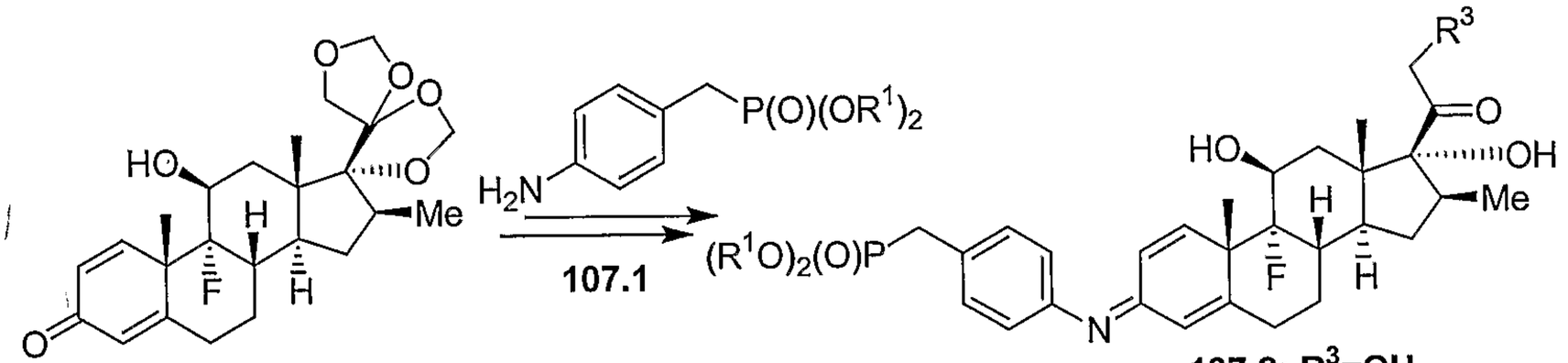


The preparation of compounds in which the phosphonate group is attached by means of a 3-pyridylmethoxy oxime group described herein. In this procedure, the dienone, **103.1**, is reacted, as described above, with O-(5-bromo-3-pyridylmethoxy)hydroxylamine, **106.1**, prepared as described above from 5-bromo-3-bromomethylpyridine (WO 95/28400) and BOC-protected hydroxylamine, to give, after deprotection of the side-chain, the oxime, **106.2**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **106.3**, to afford the phosphonate, **106.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0). The 21-hydroxy group is then converted into the 21-chloro derivative, **106.5**.

Alternatively, the bromo compound, **106.2**, is coupled with a dialkyl 4-vinylphenyl phosphonate, **106.6** (*Macromolecules*, **1998**, *31*, 2918), to afford the phosphonate, **106.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in "Advanced Organic Chemistry," by

F. A. Carey and R. J. Sundberg, Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **106.7**, is reduced, for example by reaction with diimide, to produce the saturated analog, **106.9**. The reduction of olefinic bonds is described in "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane. The products, **106.7** and **106.9**, are then converted into the 21-chloro analogs, **106.8** and **106.10**.
Using the above procedures, but employing, in place of the bromopyridylmethoxy reagent, **106.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **106.5**, **106.8** and **106.10** are obtained.

Example 107



103.1

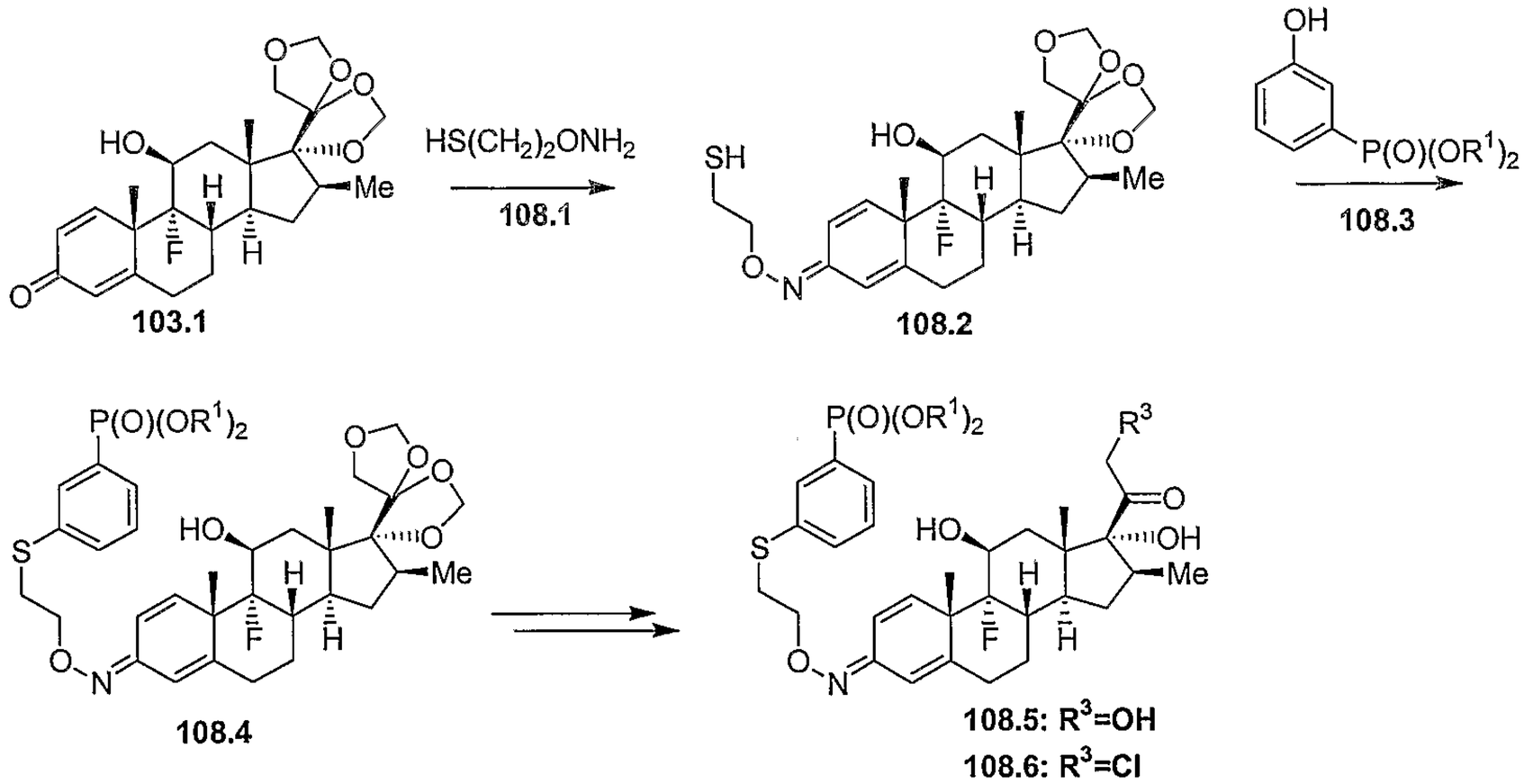
107.2: R^3=OH

107.3: R^3=Cl

The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated above. In this procedure, the substrate, **103.1**, is reacted with a dialkyl 4-aminobenzyl phosphonate, **107.1**, (Fluka) to give, after deprotection, the imine product, **107.2**. The reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. The product is then converted into the 21-chloro compound, **107.3**.

Using the above procedures, but employing, in place of the 4-aminobenzyl phosphonate, **107.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **107.3** are obtained.

Example 108

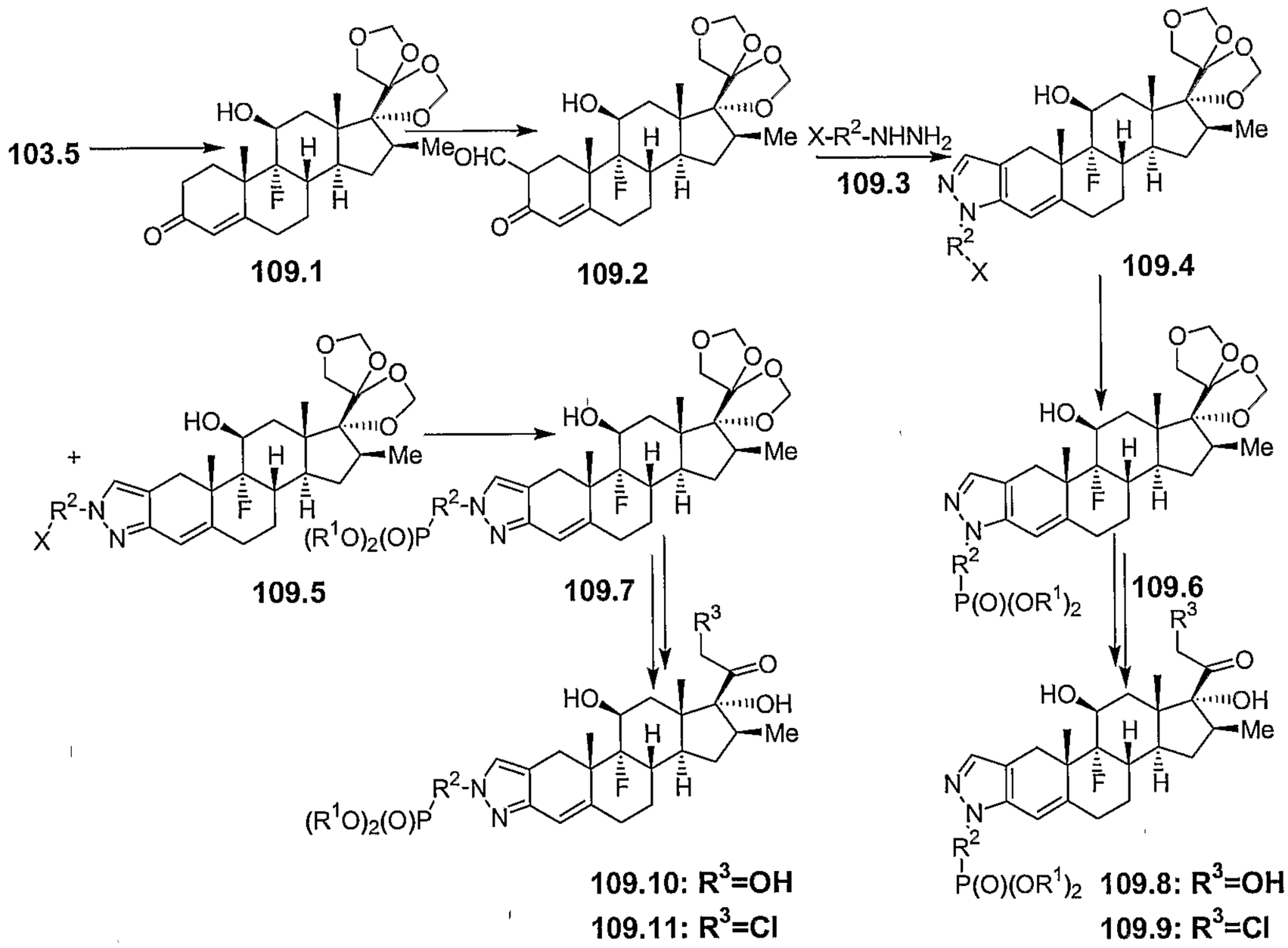


The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and a thioether linkage is illustrated above. In this procedure, the dienone, **103.1**, is reacted with O-(2-mercaptoethyl)hydroxyl-amine, **108.1** (*Bioorganicheskaya Khim.*, **1986**, *12*, 1662), to yield the oxime, **108.2**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxyl-amines is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product is then coupled, in a Mitsonobu reaction, with a dialkyl 3-hydroxy-phenyl phosphonate, **108.3** (Aurora), to yield the thioether oxime, **108.4**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in "Comprehensive Organic Transformations", by R. C. Larock, VCH, **1989**, p. 448, and in "Advanced Organic Chemistry," Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p. 153-4 and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656.

The thioether product, **108.4**, is then hydrolyzed and converted into the 21-chloro product, **108.6**, as described in Example 103.

Using the above procedures, but employing, in place of the hydroxyl-amine, **108.3**, different hydroxy or mercapto-substituted hydroxylamines, and/or different hydroxyaryl-substituted phosphonates, the products analogous to **108.6** are obtained.

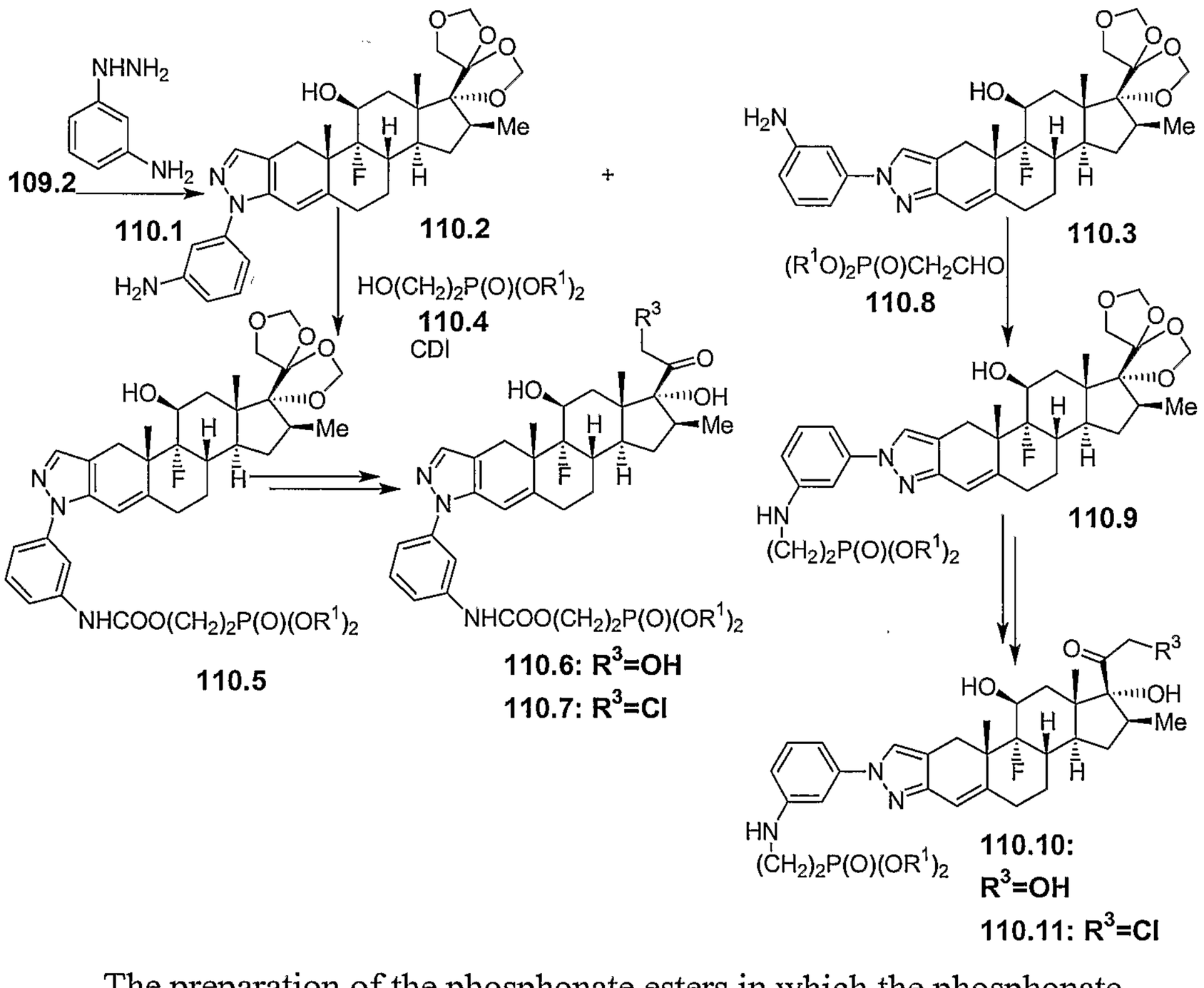
Example 109



The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of an aromatic or heteroaromatic group, a heteroatom and a variable carbon chain is illustrated above. In this procedure, the BMD-protected dienone, **103.5**, is reduced to afford the 1,2-dihydro product, **109.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, 44, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **109.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **109.3**, wherein R2 is alkyl,

aralkyl, aryl or heteroaryl and in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **109.4** and **109.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **109.4** and **109.5**, are then transformed, for example by the procedures described in Examples 110 and 111, via the BMD-protected intermediates, **109.6** and **109.7**, into the 21-chloro phosphonates, **109.9** and **109.11**.

Example 110



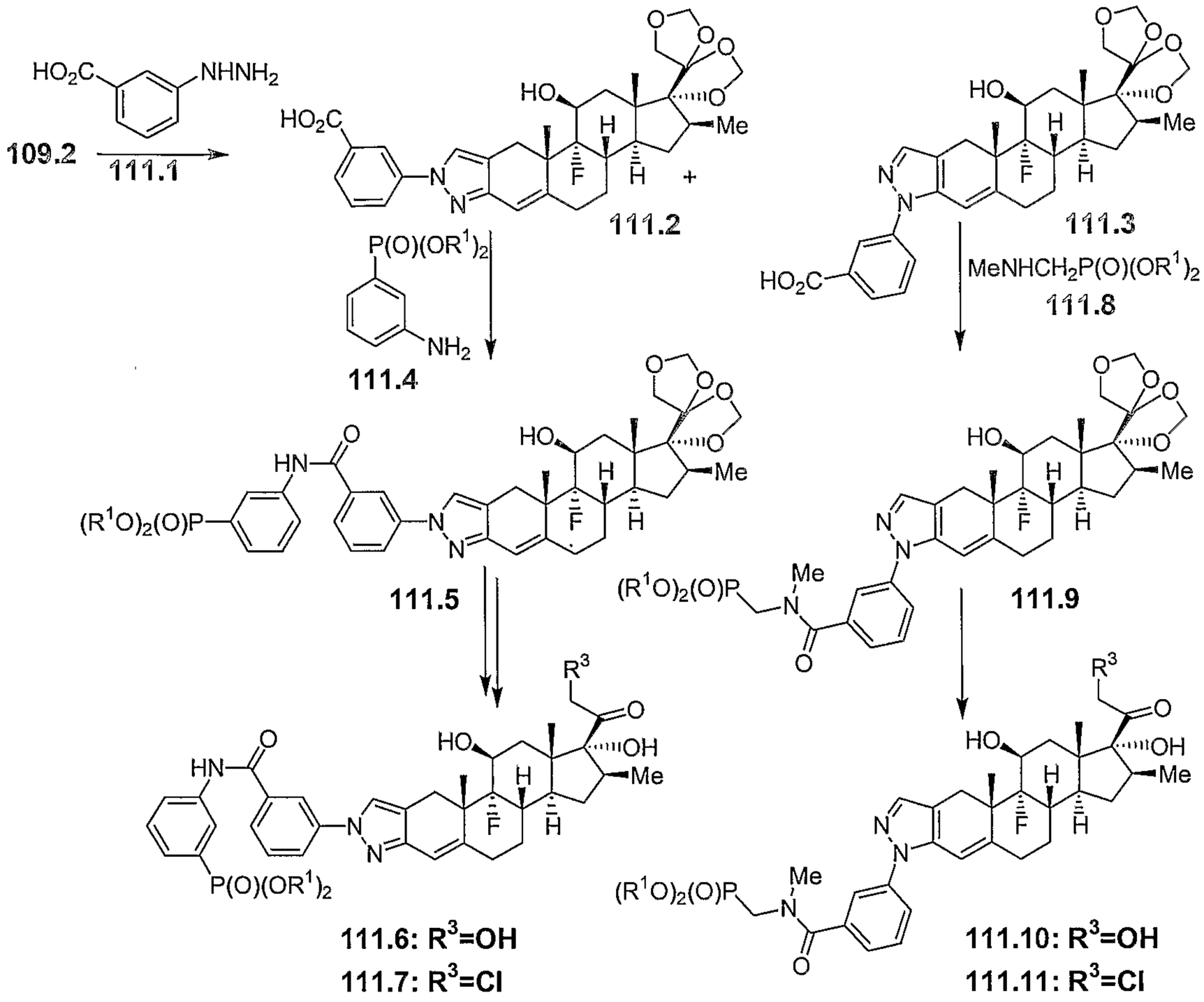
The preparation of the phosphonate esters in which the phosphonate group is attached to the 1' or 2' position of the pyrazole ring, by means of a carbamate or an amino linkage is illustrated above. In this procedure, the ketoaldehyde, **109.2**, is reacted, as described above, with 3-aminophenyl-hydrazine **110.1** (EP 437105) to give the pyrazoles **110.2** and **110.3**. The 2'-substituted isomer **110.2** is then reacted in dimethylformamide solution at

ambient temperature with one molar equivalent of a dialkyl 2-hydroxyethyl phosphonate, **110.4** (Epsilon), and carbonyl diimidazole, to yield the carbamate, **110.5**. The preparation of carbamates is described in "Comprehensive Organic Functional Group Transformations," A. R. Katritzky, ed., Pergamon, **1995**, Vol. *6*, p 416ff, and in "Organic Functional Group Preparations," by S. R. Sandler and W. Karo, Academic Press, **1986**, p. 260ff. In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate. The BMD protecting group is then removed and the product is converted into the 21-chloro product, **110.7**.

Alternatively, the 1'-substituted pyrazole, **110.3**, is reacted, in a reductive amination reaction, with a dialkyl formylmethyl phosphonate, **110.8** (*Zh. Obschei. Khim.*, **1987**, *57*, 2793), and sodium triacetoxyborohydride, to afford the amine, **110.9**. The preparation of amines by means of reductive amination procedures is described, for example, in "Comprehensive Organic Transformations," by R. C. Larock, VCH, p 421, and in "Advanced Organic Chemistry," Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p 269. In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, **1990**, *55*, 2552. The product, **110.9**, is then deprotected to give the triol, **110.10**, and the latter compound is transformed into the 21-chloro analog, **110.11**.

Using the above procedures, but employing different formyl or hydroxyl-substituted phosphonates, and/or different amino-substituted hydrazines, the products analogous to **110.7** and **110.11** are obtained. The functionalization procedures are interchangeable between the pyrazole substrates, **110.2** and **110.3**.

Example 111



The preparation of the phosphonates in which the phosphonate group is attached by means of a phenyl ring and an amide linkage is illustrated above. In this procedure, the ketoaldehyde, **109.2**, is reacted, as described above, with 3-carboxyphenyl hydrazine, **111.1** (Apin), to produce the pyrazoles, **111.2** and **111.3**. The 1'-substituted isomer, **111.1**, is coupled, in the presence of dicyclohexylcarbodiimide, with a dialkyl 3-aminophenyl phosphonate, **111.4** (Aurora), to give the amide, **111.5**. The preparation of amides from carboxylic acids and derivatives is described, for example, in "Organic Functional Group Preparations," by S.R.Sandler and W. Karo, Academic Press, **1968**, p. 274, and "Comprehensive Organic Transformations," by R. C. Larock, VCH, **1989**, p. 972ff. The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-

protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

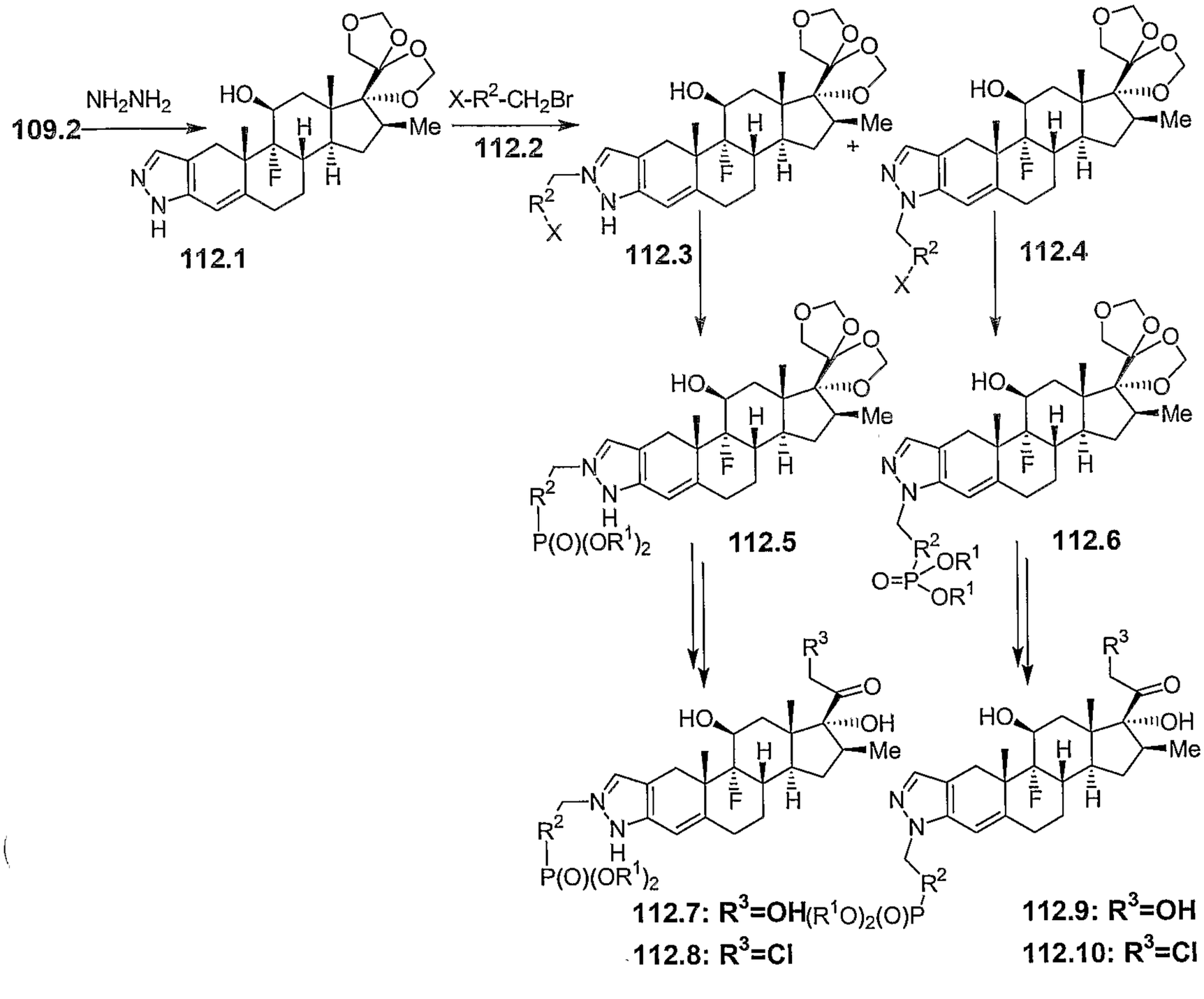
The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The product is then deprotected to afford the triol, **111.6**, which is converted into the 21-chloro compound, **111.7**.

Alternatively, the 2'-substituted pyrazole, **111.3**, is coupled, as described above, with a dialkyl methylaminomethyl phosphonate, **111.8**, to prepare the amide phosphonate 111.9 which is deprotected, and the product is converted into the 21-chloro analog, **111.11**.

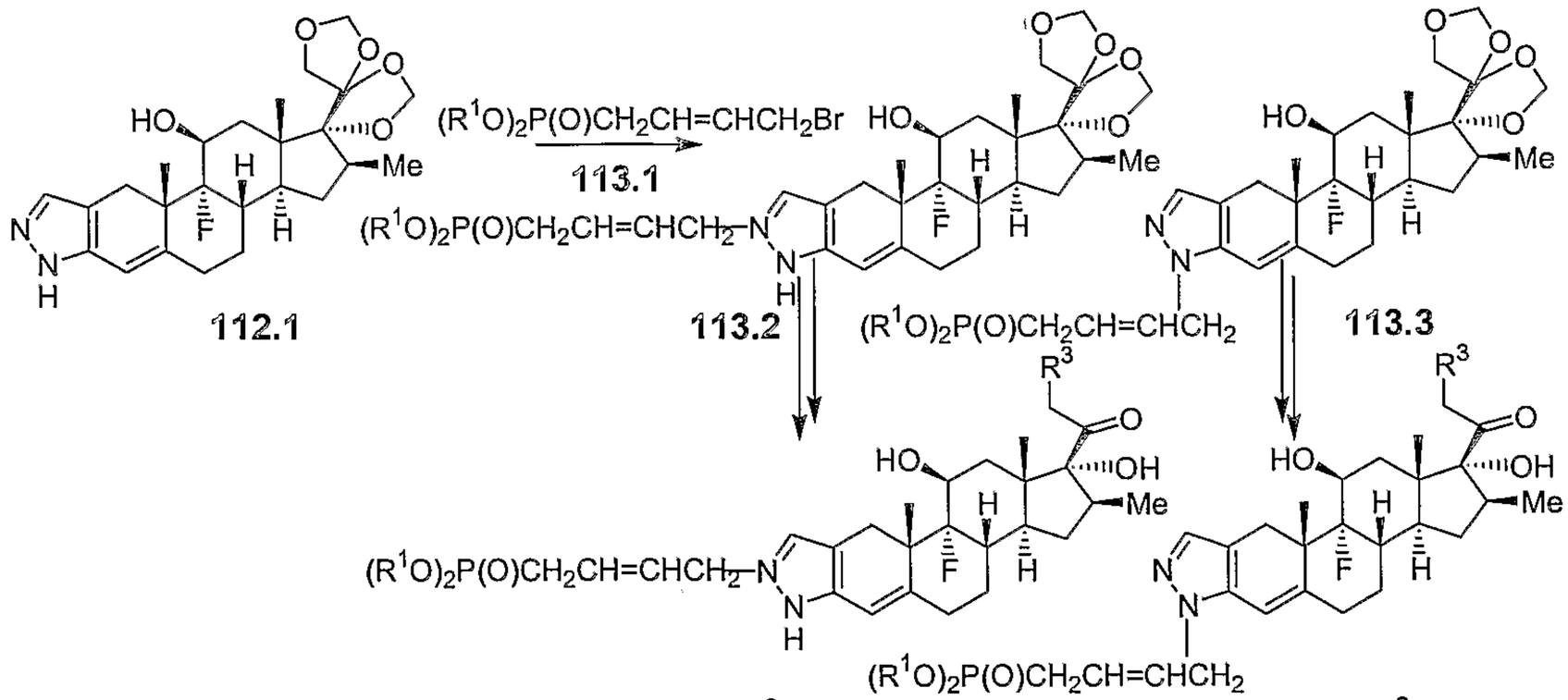
Using the above procedures, but employing, in place of the carboxyphenyl hydrazine, **111.1**, different carboxy-substituted aralkyl, aryl or heteroaryl alkoxy hydrazines, and/or different dialkyl amino-substituted phosphonates, the products analogous to the compounds, **111.7** and **111.11** are obtained.

Example 112



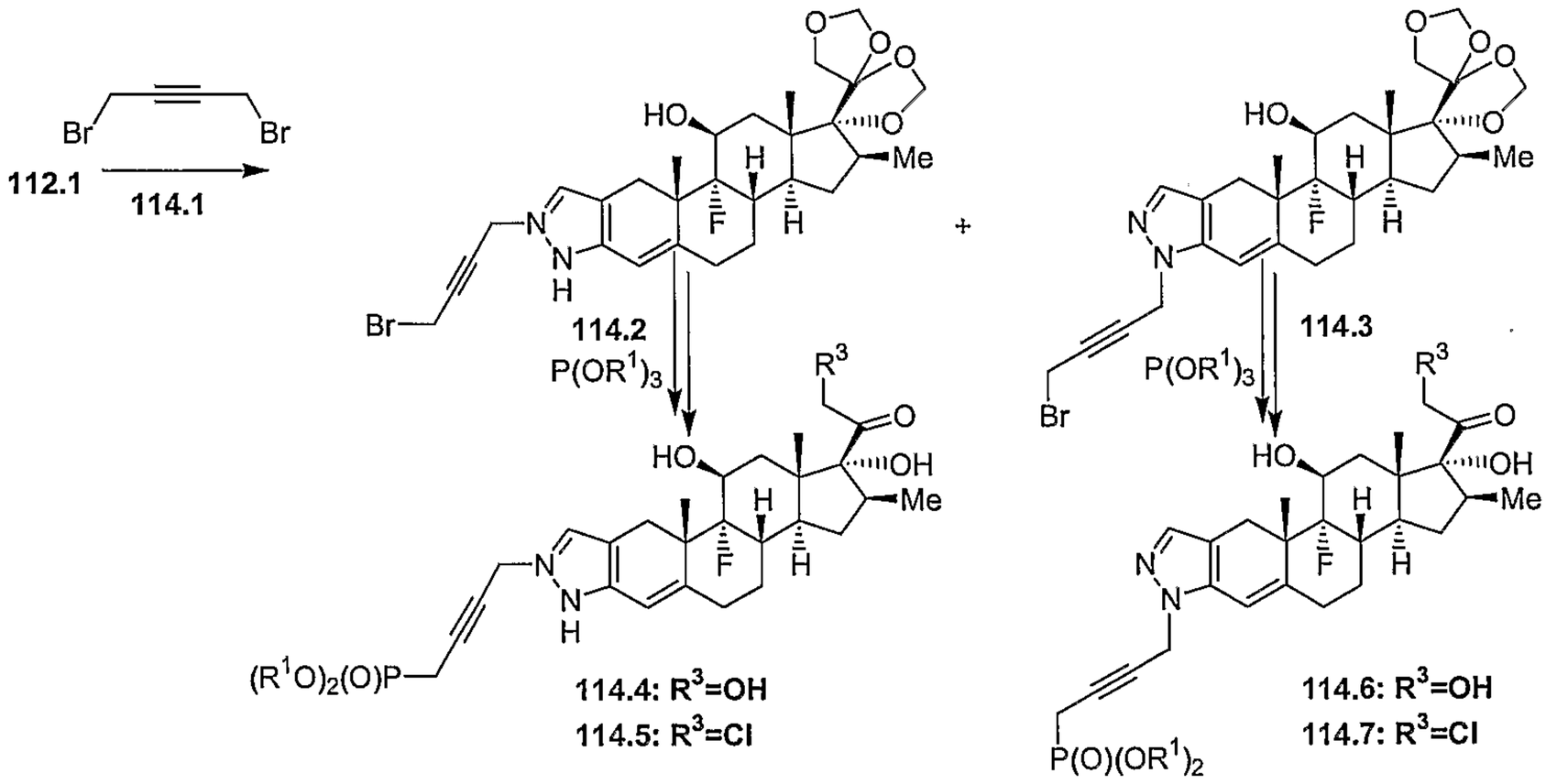
The preparation of the phosphonate esters in which the phosphonate group is attached by means of a variable carbon linkage is illustrated above. In this procedure, the ketoaldehyde, **109.2**, is reacted with hydrazine, to afford the pyrazole derivative, **112.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, 86, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **112.2**, in which R^2 and X are as defined above, to yield the alkylation products, **112.3** and **112.4**. The alkylation of substituted pyrazoles is described, for example, in "Heterocyclic Chemistry," by T. L. Gilchrist, Longman, **1992**, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **112.3** and **112.4**, are, except in cases where X is dialkylphosphono, converted into the phosphonates, **112.5** and **112.6**, using the procedures described herein, and deprotection/ acylation then affords the 21-chloro compounds, **112.8** and **112.10**.

Example 113



The pyrazole, **112.1**, is reacted in tetrahydrofuran solution, as described above, with one molar equivalent of a dialkyl bromobutenyl phosphonate, **113.1** (*J. Med. Chem.*, **1992**, *35*, 1371), and lithium hexamethyldisilazide to give the alkylated pyrazoles, **113.2** and **113.3**. Deprotection followed by chlorination yields the 21-chloro products, **113.5** and **113.7**.

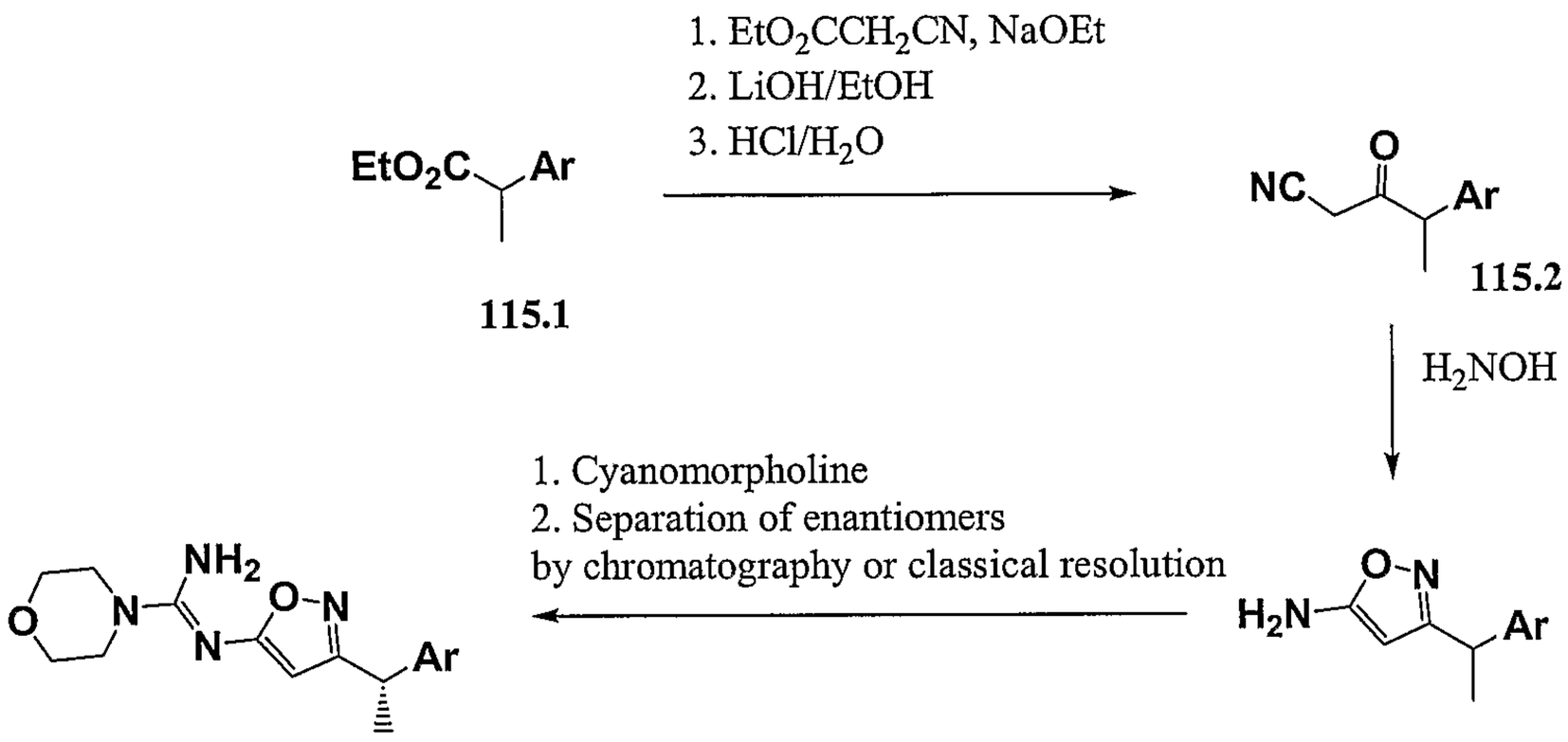
Example 114



The pyrazole, **112.1**, is reacted in tetrahydrofuran solution, as described above, with 1,4-dibromobut-2-yne, **114.1** (Aldrich), to give the pyrazoles, **114.2** and **114.3**. The products are subjected to an Arbuzov reaction, in which the bromomethyl substituent is converted into the dialkyl phosphonomethyl substituent, by reaction with a trialkyl phosphite at 120°, to prepare, after

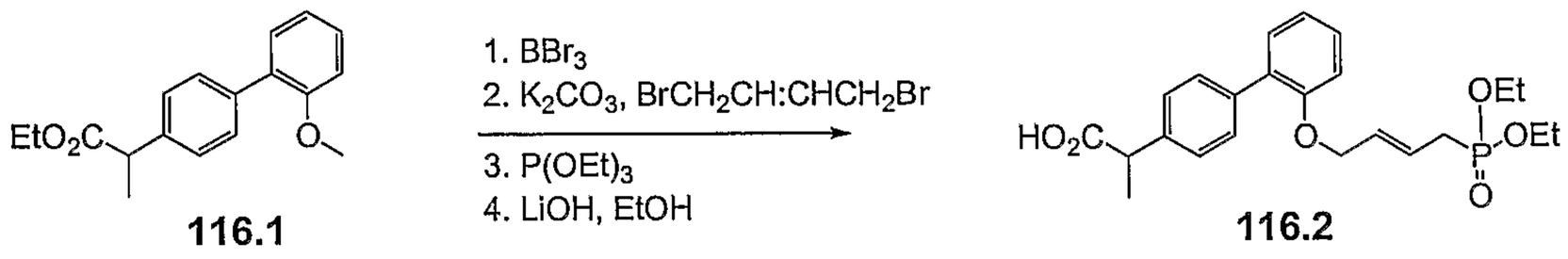
deprotection of the side chain and chlorination, the 21-chloro phosphonates, **114.5** and **114.7**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115-72. In the procedure, the substrate is heated at from 60° to about 160° with a five to fifty-fold molar excess of the trialkyl phosphite. Using the above procedures, but employing, in place of the dibromide, **114.1**, different dibromides, the products analogous to **114.5** and **114.7** are obtained.

Example 115



The preparation of compounds of the invention having phosphonate groups and intermediate compounds useful for their synthesis are illustrated herein. A β-ketonitrile, **115.2**, is generated from a phenylacetic acid, **115.1**, by condensation with a malononitrile ester under Claisen conditions. Reaction with hydroxylamine provides the 5-amino-1,2-oxazole which, upon condensation with cyanomorpholine provides the desired SMP-114 analogs.

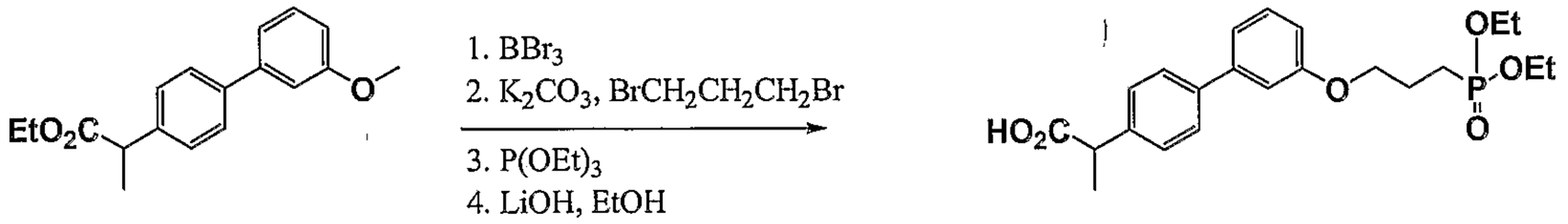
Example 116



The anisole derivative, **116.1**, is demethylated by treatment with a Lewis acid such as boron tribromide. The resulting phenol is alkylated with *E*-1,4-dibromobutene and the resulting monobromide is heated with triethylphosphite in a solvent such as toluene (or other Arbuzov reaction conditions: see Engel, R.,

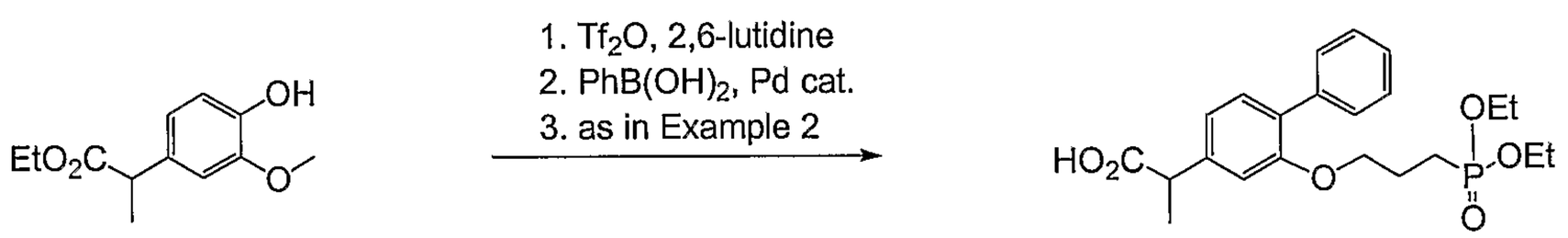
"Synthesis of Carbon-phosphorus Bonds," CRC press, **1988**) to generate the diethyl ester of the desired phosphonic acid, **116.2**. Saponification of the carboxylate ester gives the phenylacetic acid ready for incorporation into the synthesis of SMP-114 analogs.

Example 117



The preparation of compounds of the invention having phosphonate groups can be prepared the procedure of Example 116 and substituting 1,3-dibromopropane in place of the 1,4-dibromobutene.

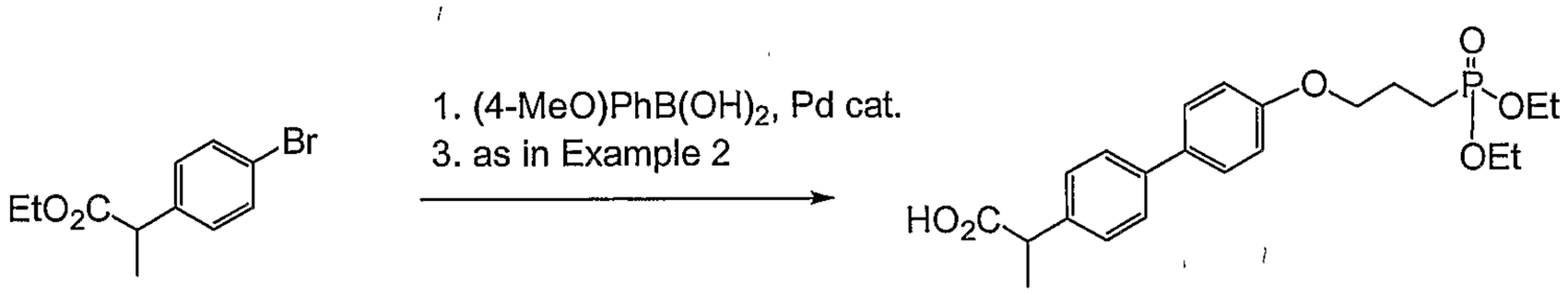
Example 118



118.1

The free phenol in ethyl homovanillate, **118.1**, is converted to the aryl triflate, and the biphenyl motif is generated by Suzuki coupling with phenyl-boronic acid (see *Chem. Rev.*, **1995**, *95*, 2457). The remaining steps are analogous to those described in Example **116**.

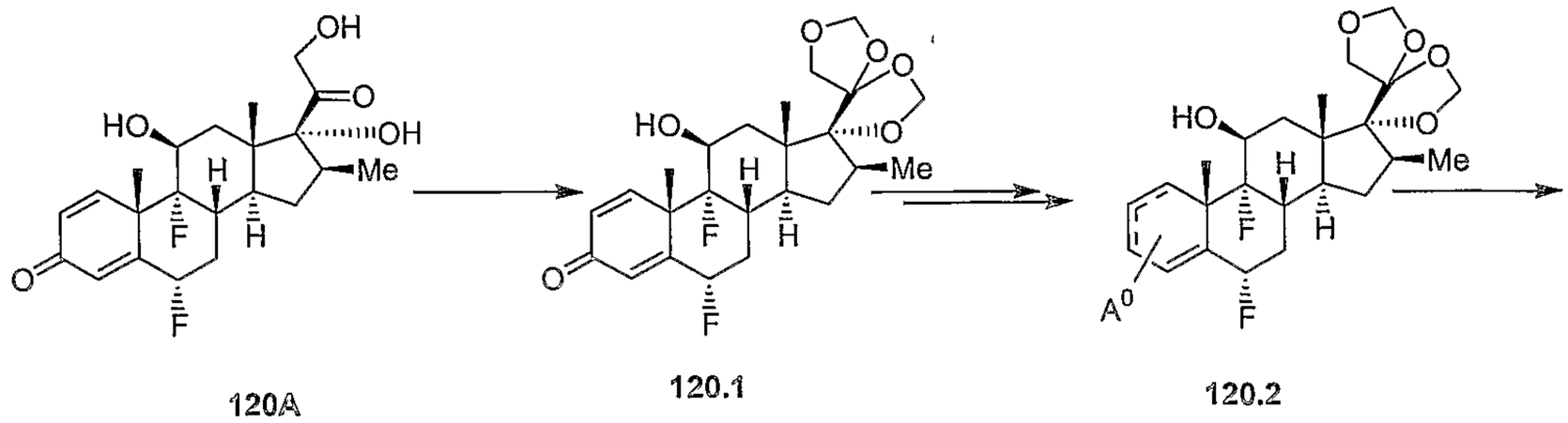
Example 119

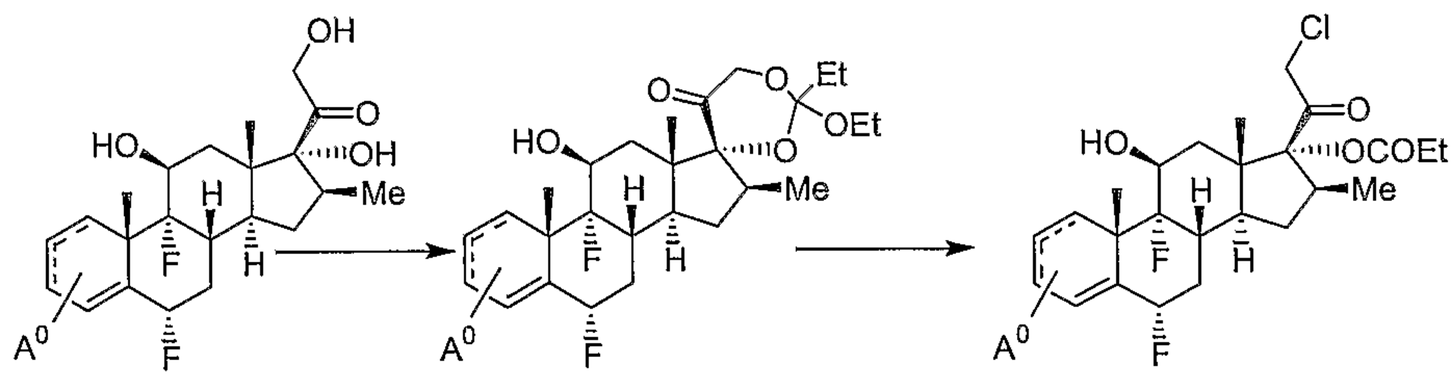


119.1

Ethyl 4-bromophenylacetate, **119.1**, is coupled with 4-methoxyphenyl-boronic acid using the Suzuki method (see above). The remaining steps are analogous to those described in Example **116**.

Example 120



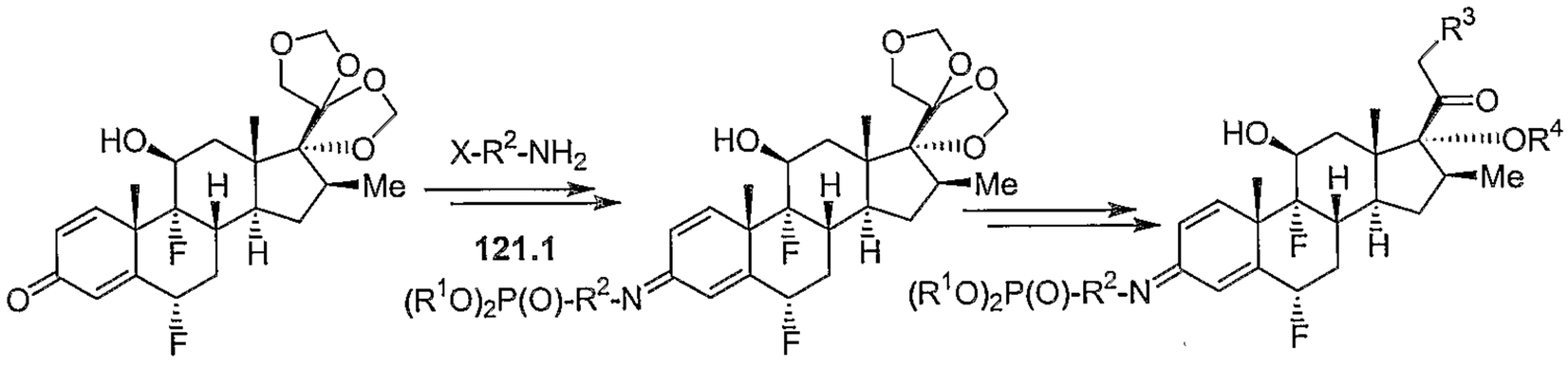


6α,9α-Difluoro-16β-methyl-11β,17α,21-trihydroxypregn-1,4-dien-3,21-dione, **120A**, (U.S. Patent No. 4,619,921) is reacted with paraformaldehyde and an acid catalyst such as hydrochloric acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **120.1**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester **120.2**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in "Protective Groups in Organic Synthesis," by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the triol, **120.3**. The latter compound is then converted into the 17,21-cyclic orthoester, **120.4**, using the procedure described in *Chem. Pharm. Bull.*, **1986**, *34*, 1613. The substrate is reacted in dimethylformamide at 70°C with two molar equivalents of triethyl orthopropionate and a catalytic amount of p-toluenesulfonic acid. The product is then reacted with an excess of trimethylsilyl chloride in dimethylformamide at ambient temperature to produce the 21-chloro 17-propionate product, **120.5**.

Alternatively, the substrate, **120.3**, is converted into the product, **120.5**, by means of the method described in *J. Med. Chem.*, **1987**, *30*: 1581. In this procedure, the 21-hydroxy group is activated by conversion to the 21-mesylate, by reaction with mesyl chloride in pyridine; the mesylate group is then displaced to yield the 21-chloro intermediate, by reaction with lithium chloride in dimethylformamide, and the 17-hydroxyl group is esterified to give the 21-

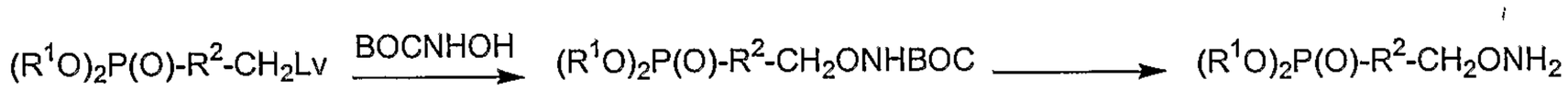
chloro-17-propionate derivative, **120.5**. The selective acylation of the 17α hydroxyl group in the presence of an 11β hydroxyl group is described in *J. Med. Chem.*, **1987**, *30*: 1581.

Example 121



120.1 **121.2** **121.3 R^3=OH, R^4=H**
121.4 R^3= Cl, R^4=COEt

The BMD-protected derivative, **120.1**, is reacted with an amine or hydroxylamine, **121.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The BMD-protected side-chain compound, **121.2**, is then converted into the triol, **121.3**, and then to the 21-chloro 17 propionate product, **121.4**, as described above.

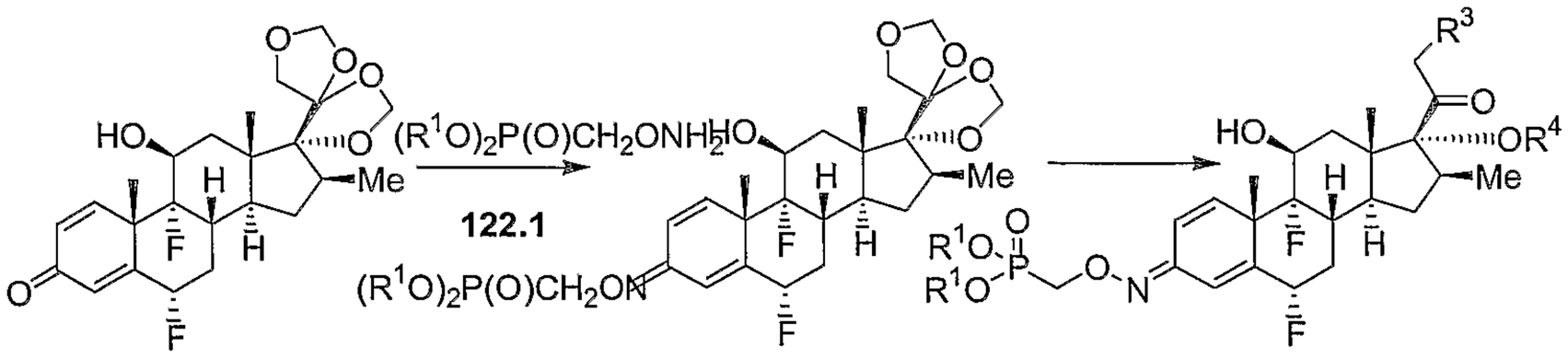


121.5 **121.7** **121.8**

The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated above. A phosphonate, **121.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **121.6**, (Aldrich) to produce the ether, **121.7**. The reaction is

conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **121.8**.

Example 122

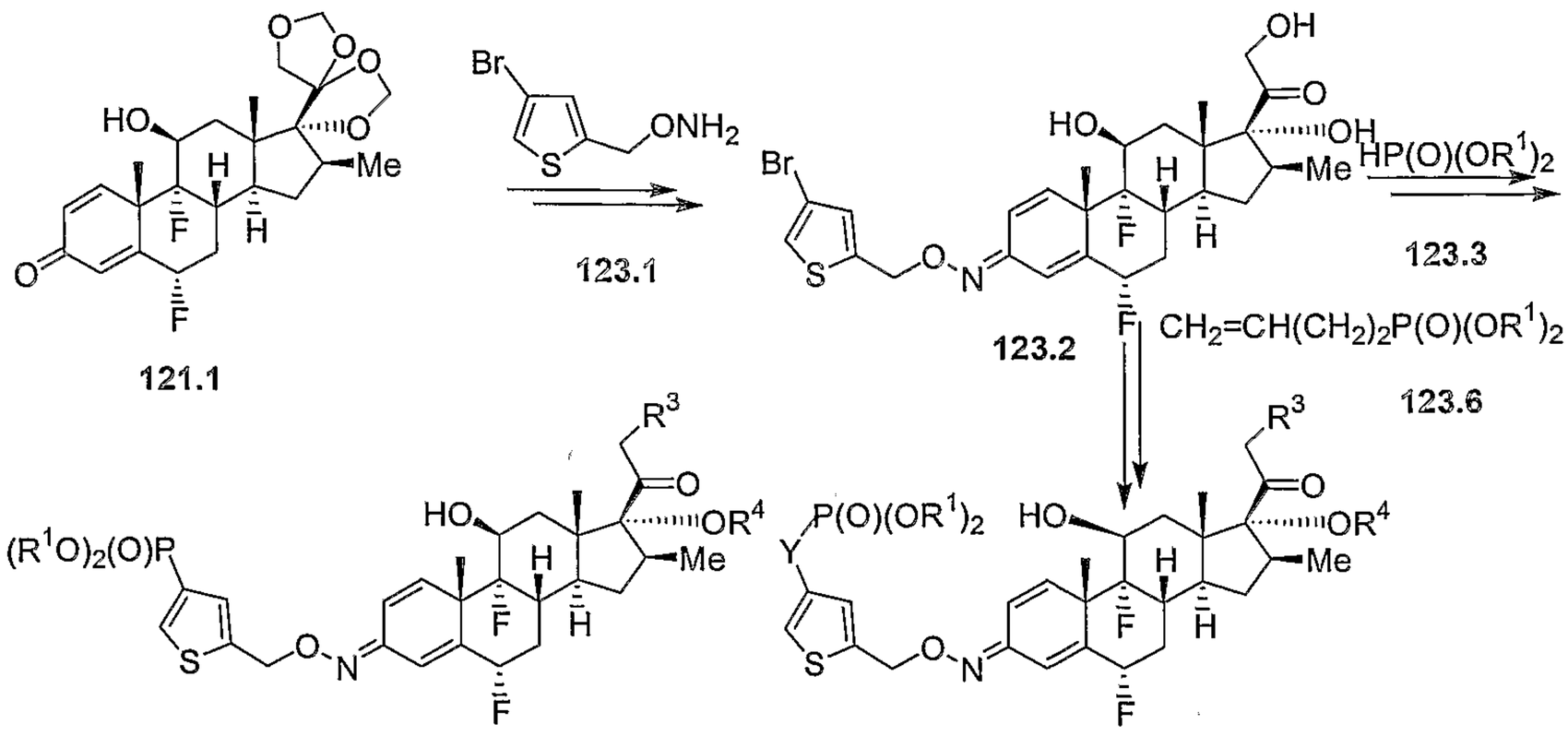


120.1 **122.2** **122.3 R^3=OH, R^4=H**
122.4 R^3= Cl, R^4=COEt

The substrate, **120.1**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **122.1**, prepared as described above from a dialkyl trifluoro-ethylsulfonyloxymethyl phosphonate (*Tet. Lett.*, **1986**, *27*:1477) and BOC-hydroxylamine, to afford the oxime, **122.2**. Deprotection then affords the triol, **122.3**, from which the 21-chloro 17-propionate compound, **122.4**, is prepared. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **122.1**, different oxime ethers, **121.1**, the corresponding products, **121.4** are obtained.

Example 123



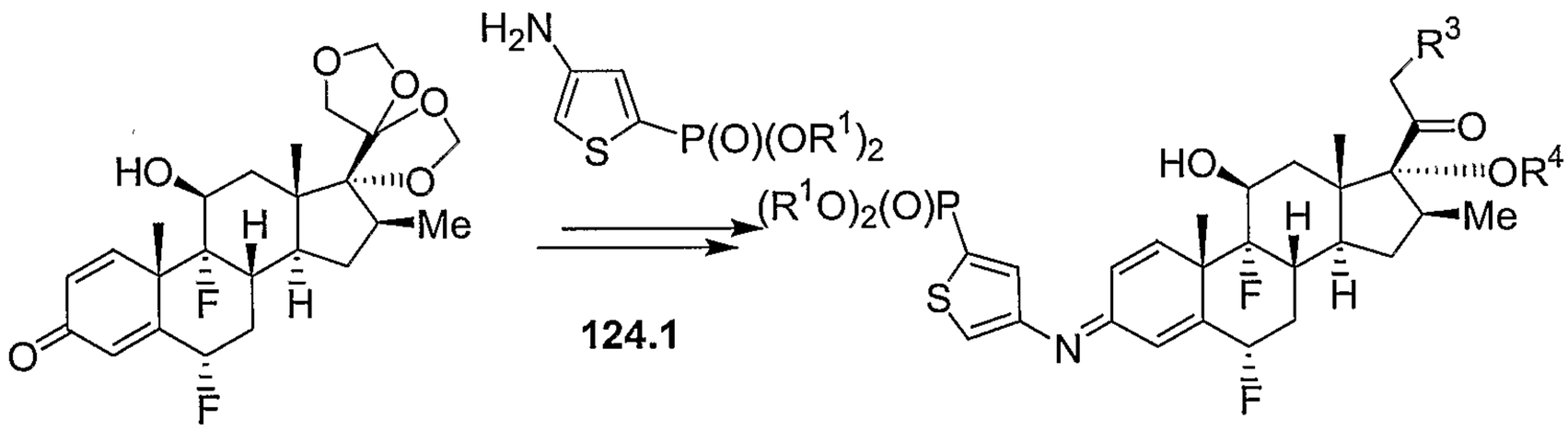
The dienone, **121.1**, is reacted, as described above, with O-(4-bromo-2-thienylmethoxy)hydroxylamine, **123.1**, prepared as described above from 4-bromo-2-bromomethylthiophene (WO 94/20456) and BOC-protected hydroxylamine, to give, after deprotection of the side-chain, the oxime, **123.2**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphate, **123.3**, to afford the phosphonate, **123.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.* **1992**, *35*, 1371. The reaction is performed in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0). The 21-hydroxy compound, **123.4**, is then converted, as described herein, into the 21-chloro 17-propionate derivative, **123.5**.

Alternatively, the bromo compound, **123.2**, is coupled with a dialkyl butenyl phosphonate, **123.6**, (*Org. Lett.*, **2001**, *3*, 217) to afford the phosphonate, **123.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, 503ff (Plenum, **2001**) and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as

palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the double bond present in the product, **123.7**, is reduced, for example by reaction with diimide, to produce the saturated analog, **123.9**. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations*, 6ff (VCH **1989**). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane. The products, **123.7** and **123.9**, are then converted into the 21-chloro 17-propionate analogs, **123.8** and **123.10**.

Using the above procedures, but employing, in place of the bromothienylmethoxy reagent, **123.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **123.5**, **123.8** and **123.10** are obtained.

Example 124

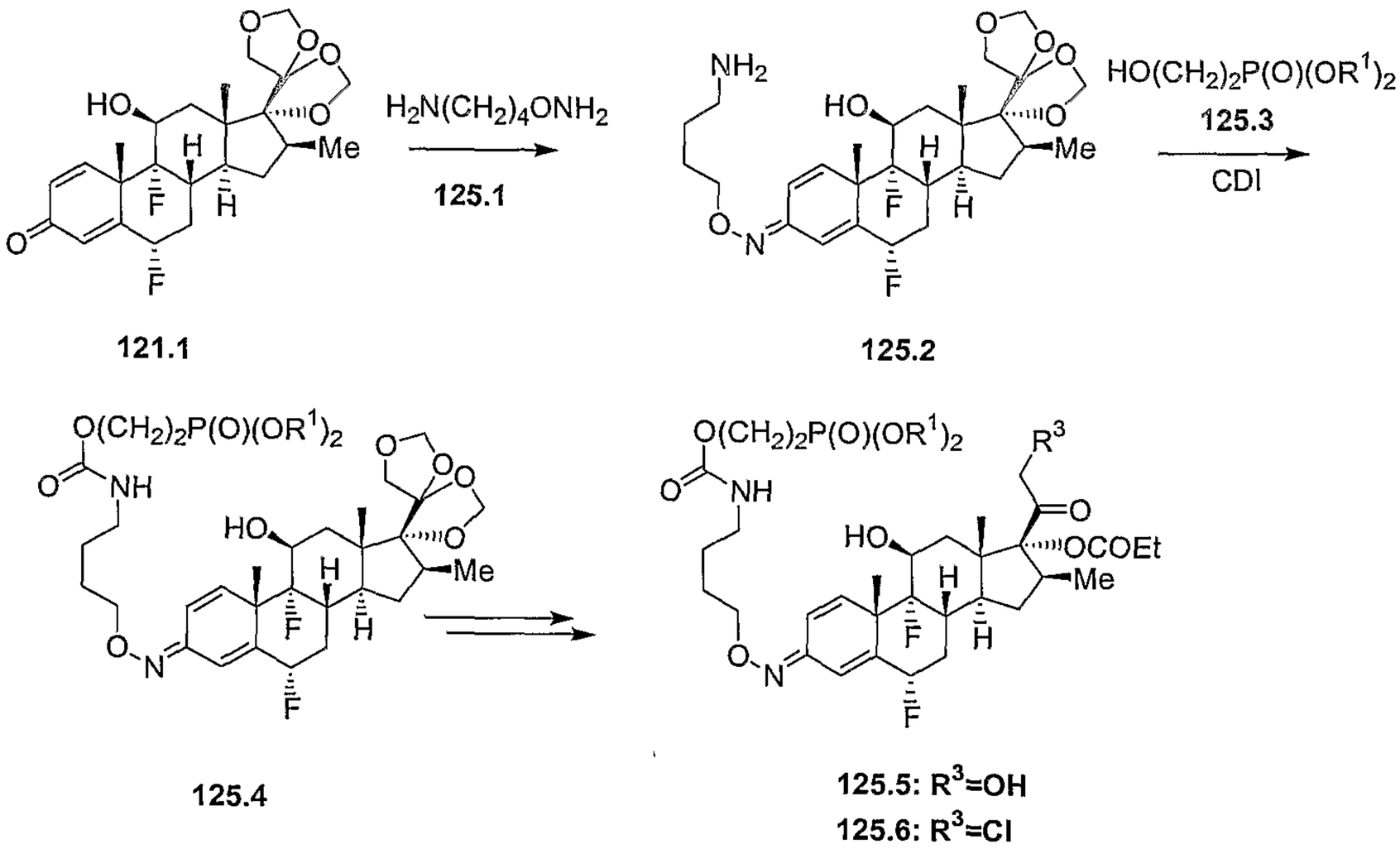


The substrate, **121.1**, is reacted with a dialkyl 4-amino-2-thienyl phosphonate, **124.1**, prepared by the palladium-catalyzed coupling, as described above, between 4-amino-2-bromothiophene (*Tet.*, **1987**, *43*, 3295) and a dialkyl phosphite, to give, after deprotection, the imine product, **124.2**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic

conditions. The product is then converted into the 21-chloro 17-propionate compound, **124.3**.

Using the above procedures, but employing, in place of the 4-aminothienyl phosphonate, **124.1** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **124.3** are obtained.

Example 125



121.1 **125.2**

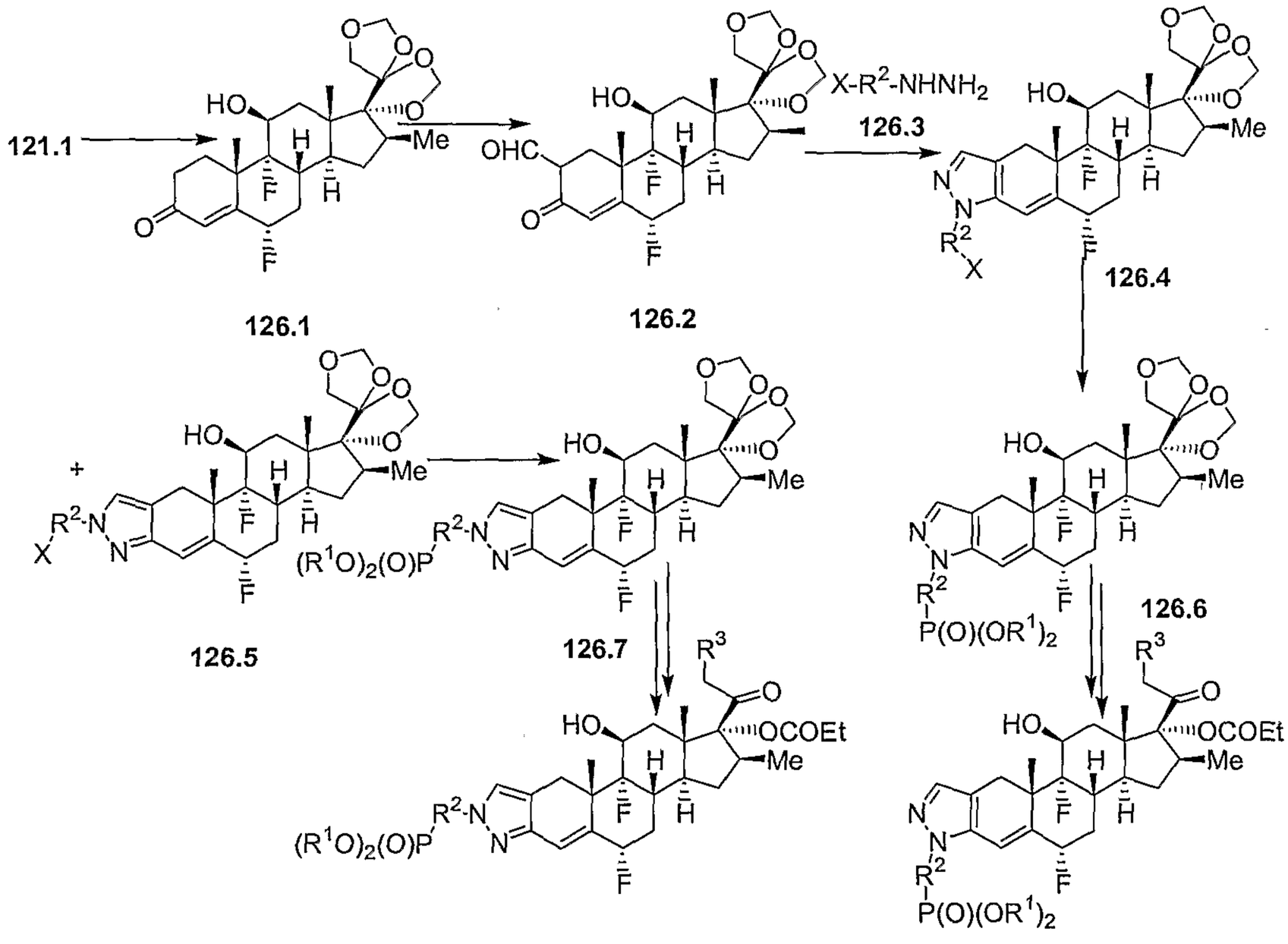
125.4 **125.5: R^3=OH**
125.6: R^3=Cl

The dienone, **121.1**, is reacted with O-(4-aminobutyl)hydroxylamine, **125.1**, (*Pol. J. Chem.*, **1981**, *55*, 1163) to yield the oxime, **125.2**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product is then coupled with a dialkyl 2-hydroxyethyl phosphonate, **125.3**, (Epsilon) and carbonyl diimidazole, to yield the carbamate oxime, **125.4**. The preparation of carbamates is described in A. R. Katritzky, *Comprehensive Organic Functional Group Transformations*, *6*, 416ff (Pergamon, **1995**), and in S. R. Sandler and W. Karo, *Organic Functional Group Preparations*, 260ff (Academic Press, **1986**). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate

and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate. The carbamate product, **125.4**, is then converted, as described herein, into the 21-chloro 17-propionate product, **125.6**.

Using the above procedures, but employing, in place of the hydroxylamine, **125.3**, different amino-substituted hydroxylamines, and/or different hydroxy-substituted phosphonates, the products analogous to **125.6** are obtained.

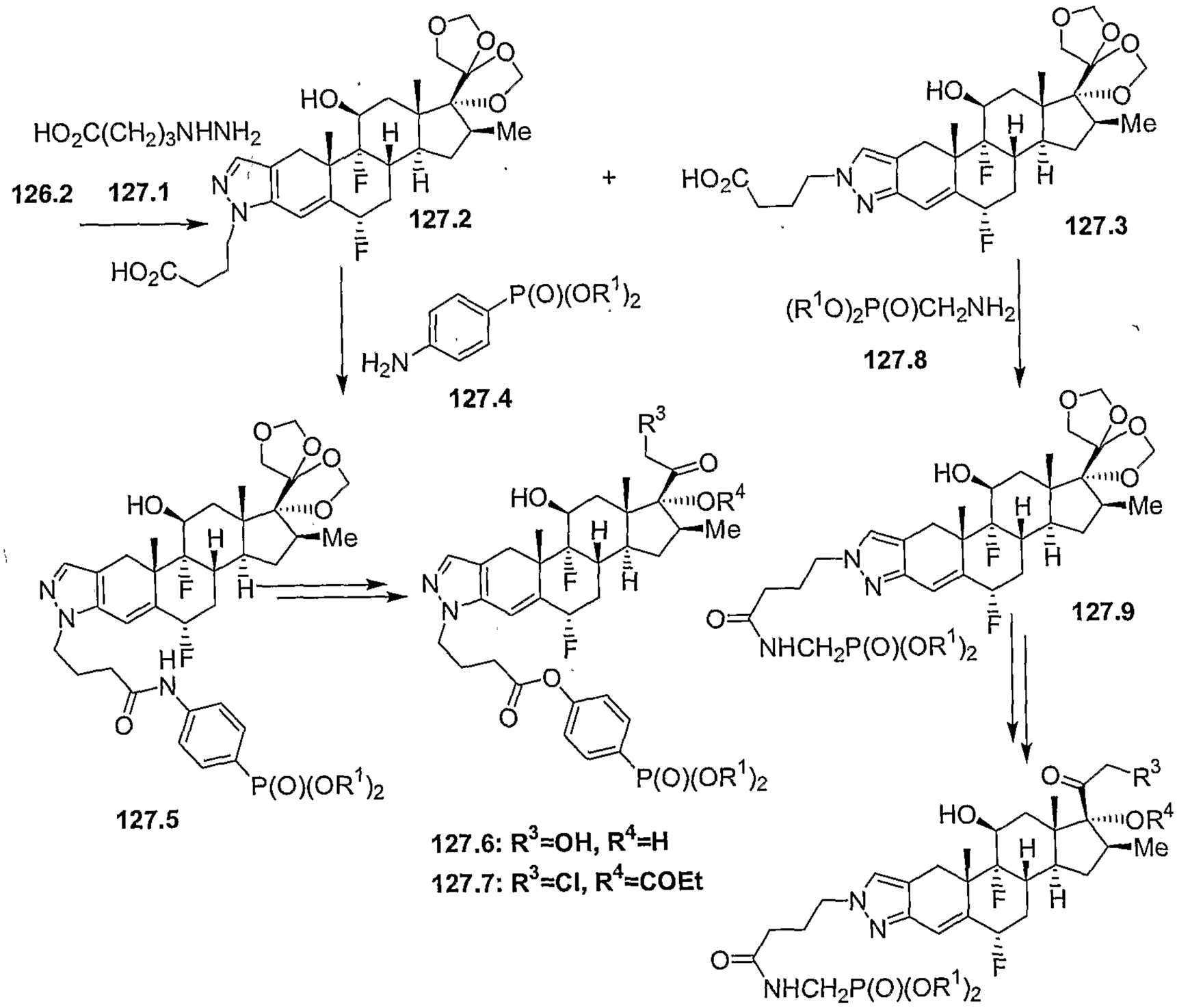
Example 126



The BMD-protected dienone, **121.1**, is reduced to afford the 1,2-dihydro product, **126.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, *44*, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **126.2**. This compound is then reacted with an alkyl,

aralkyl, aryl or heteroaryl hydrazine, **126.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **126.4** and **126.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **126.4** and **126.5**, are then transformed, for example by the procedures described in Examples 122 and 123, via the BMD-protected intermediates, **126.6** and **126.7**, into the 21-chloro 17-propionate phosphonates, **126.9** and **126.11**.

Example 127



The ketoaldehyde, **126.2**, is reacted, as described above, with 3-carboxypropyl hydrazine, **127.1**, (*Ind. J. Exp. Biol.*, **1994**, *32*, 218) to give the

pyrazoles, **127.2** and **127.3**. The 2'-substituted isomer, **127.2**, is then reacted in dimethylformamide solution at ambient temperature with one molar equivalent of a dialkyl 4-aminophenyl phosphonate, **127.4**, (Epsilon) and dicyclohexyl carbodiimide, to yield the amide, **127.5**. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R. Sandler and W. Karo, *Organic Functional Group Preparations*, 274 (Academic Press, **1968**), and R. C. Larock, *Comprehensive Organic Transformations*, 972ff (VCH, **1989**). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

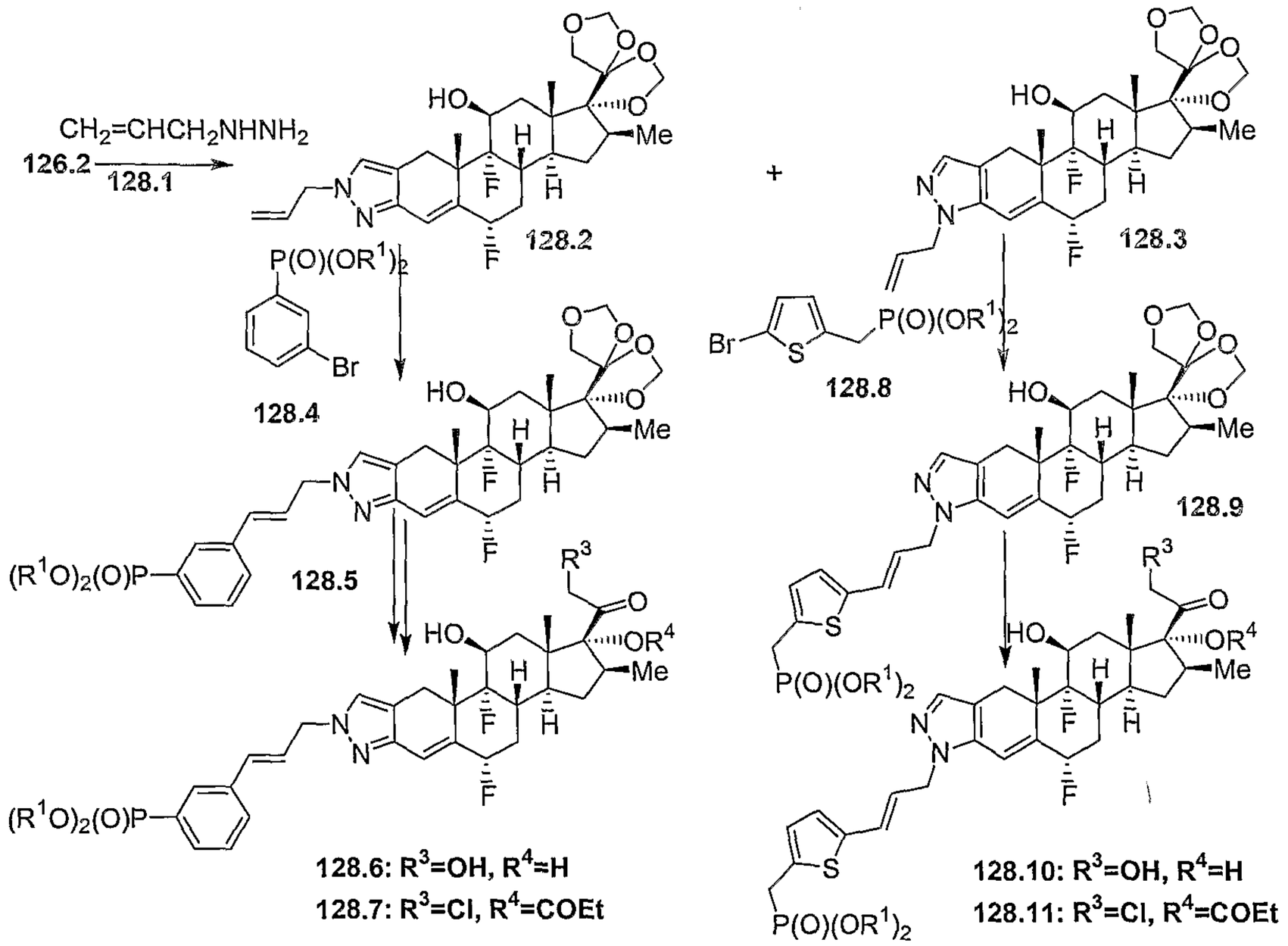
Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide. The BMD protecting group is then removed and the product is converted into the 21-chloro 17-propionate product, **127.7**.

The 1'-substituted pyrazole, **127.3**, is coupled, as described above, with a dialkyl aminomethyl phosphonate, **127.8** (Interchim), to afford the amide, **127.9**. The product, **127.9**, is then deprotected to give the triol, **127.10**, and the latter compound is transformed into the 21-chloro 17-propionate, **127.11**.

Using the above procedures, but employing different amino-substituted phosphonates, and/or different carboxy-substituted hydrazines, the products analogous to **127.7** and **127.11** are obtained. The functionalization procedures are interchangeable between the pyrazole substrates, **127.2** and **127.3**.

Example 128

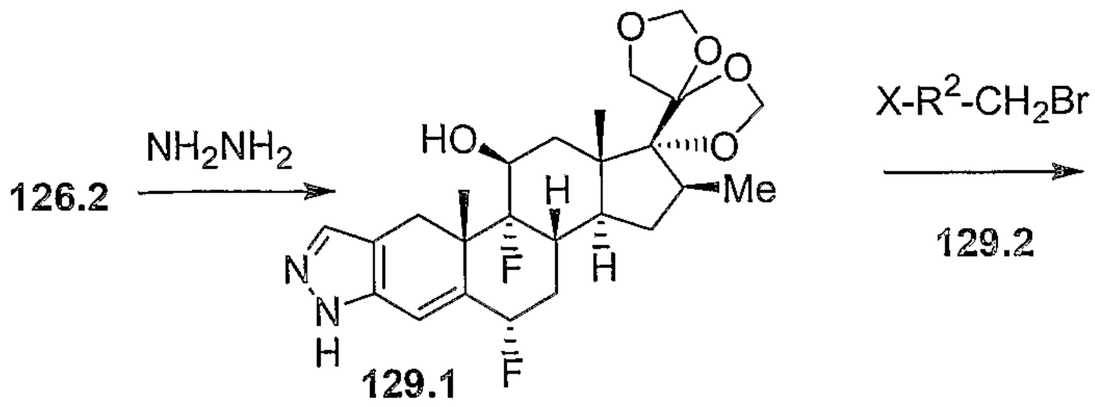


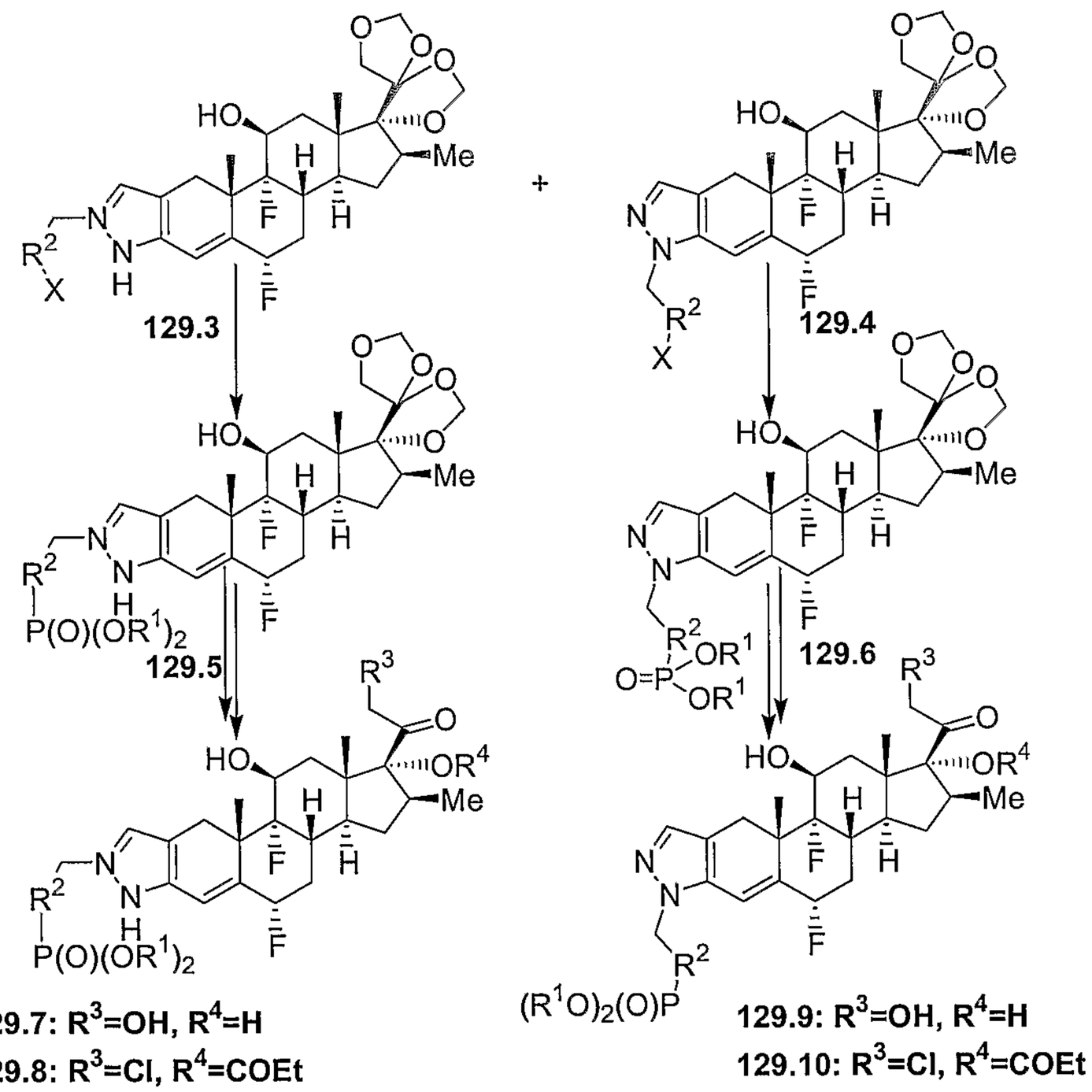
The ketoaldehyde, **126.2**, is reacted, as described above, with allyl hydrazine, **128.1**, (*Zh. Org. Khim.*, **1967**, *3*, 983) to produce the pyrazoles, **128.2** and **128.3**. The 1'-substituted isomer, **128.2**, is coupled, as described herein, with a dialkyl 3-bromophenyl phosphonate, **128.4**, (Epsilon) to give the phosphonate, **128.5**. The product is then deprotected to afford the triol, **128.6**, which is converted into the 21-chloro 17-propionate compound, **128.7**.

The 2'-substituted pyrazole, **128.3**, is coupled, as described above, with a dialkyl 5-bromo-2-thienyl phosphonate, **128.8**, (*Syn.*, **2003**, 455) to prepare the phosphonate, **128.9**, which is deprotected, and the product is converted into the 21-chloro 17-propionate analog, **128.11**.

Using the above procedures, but employing, in place of the propenyl hydrazine, **128.1**, different alkenyl hydrazines, and/or different dialkyl bromo-substituted phosphonates, the products analogous to the compounds, **128.7** and **128.11** are obtained.

Example 129

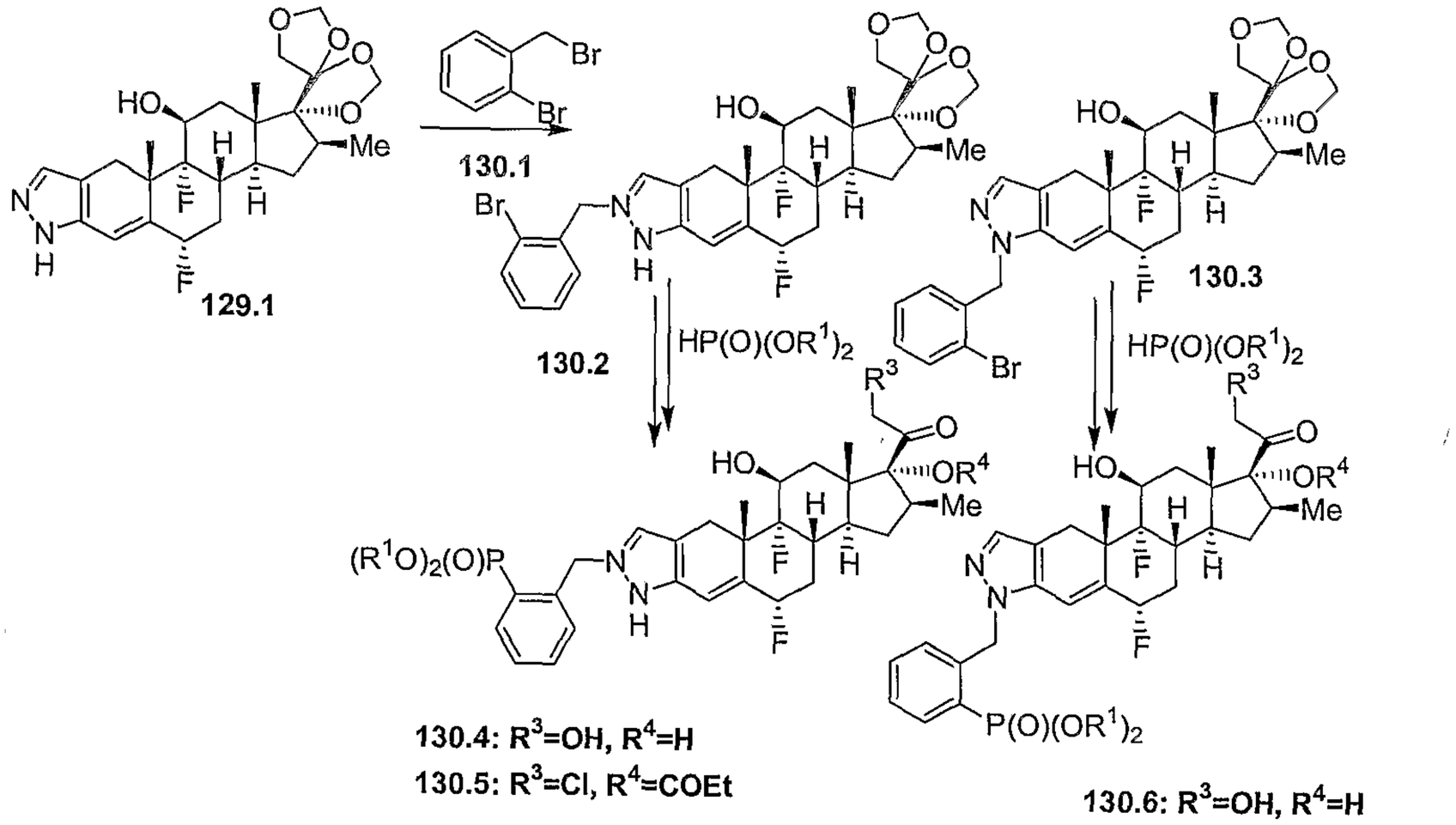




The ketoaldehyde, **126.2**, is reacted with hydrazine, to afford the pyrazole derivative, **129.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **129.2**, in which R^2 and X are as defined above, to yield the alkylation products, **129.3** and **129.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry*, 309 (Longman, **1992**). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **129.3** and **129.4**, are,

except in cases where X is dialkylphosphono, converted into the phosphonates, **129.5** and **129.6**, using the procedures described herein, and deprotection/chlorination/acylation then affords the 21-chloro 17-propionate compounds, **129.8** and **129.10**.

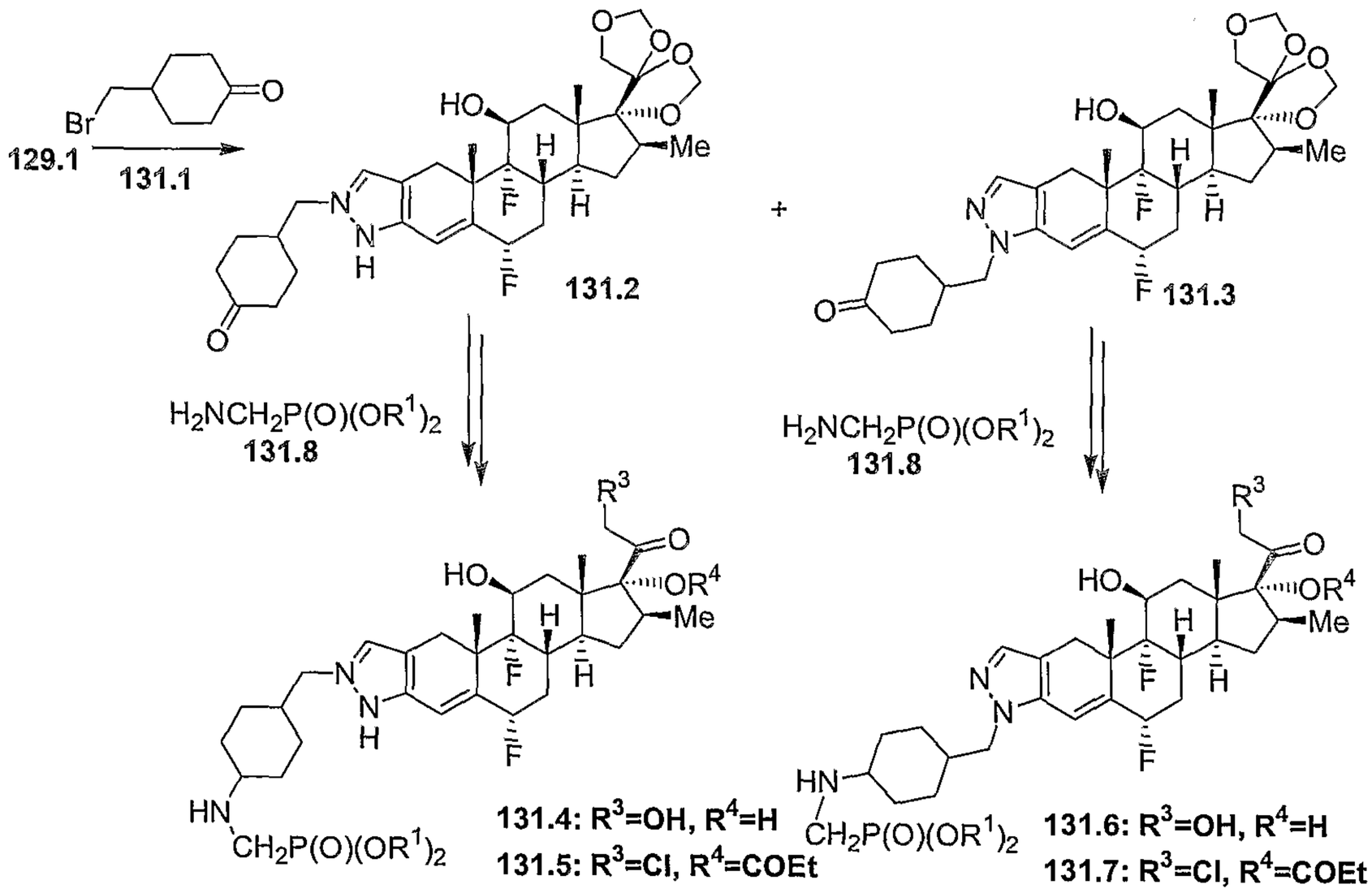
Example 130



130.4: R^3=OH, R^4=H
130.5: R^3=Cl, R^4=COEt
130.6: R^3=OH, R^4=H
130.7: R^3=Cl, R^4=COEt

Following the procedure described in Example **129**, the pyrazole, **129.1**, is reacted with 2-bromobenzyl bromide, **130.1**, to give the pyrazoles, **130.2** and **130.3**. The products are then coupled, as described above, with a dialkyl phosphite, to afford, after side-chain deprotection and modification, as described herein, the 21-chloro 17 propionates, **130.5** and **130.7**.

Example 131



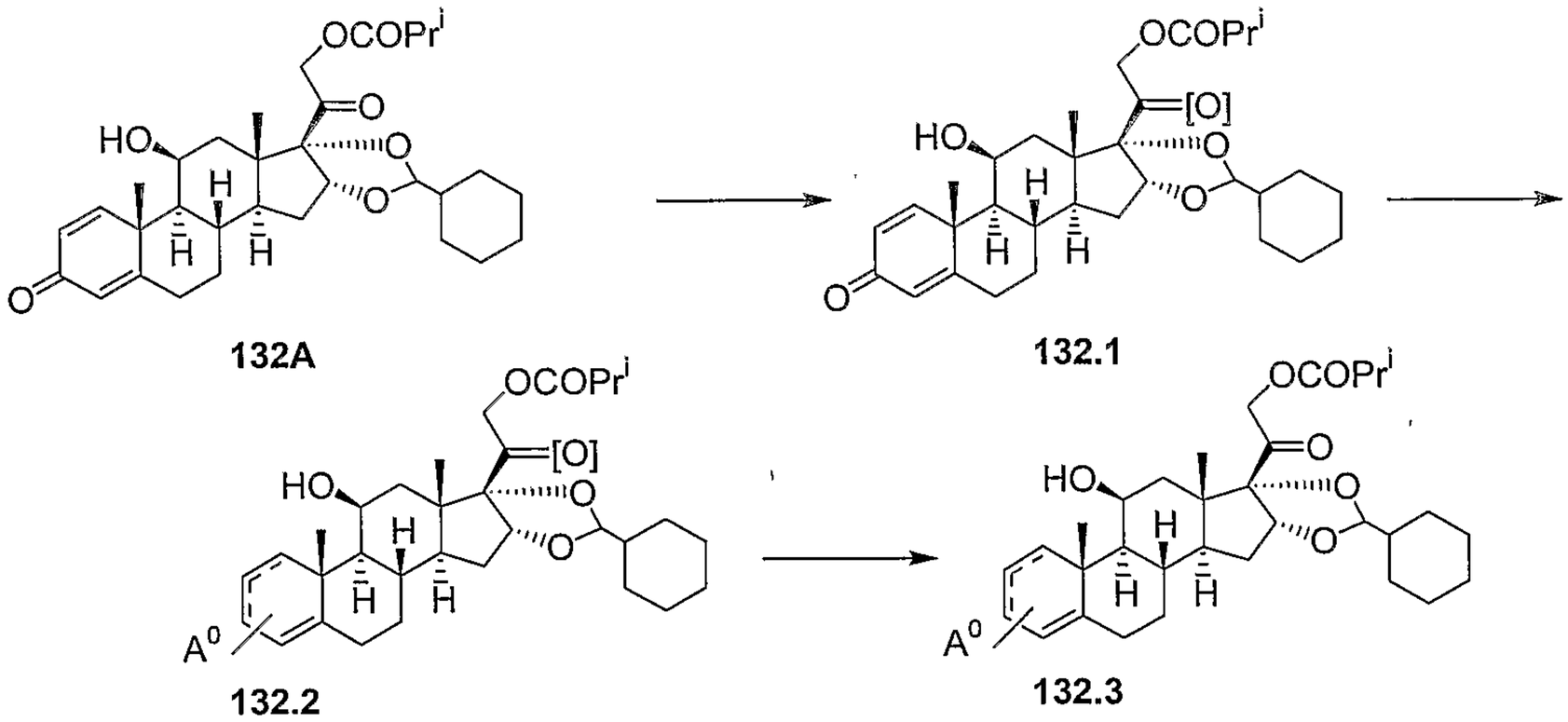
Following the procedure described in Example **129**, the pyrazole, **129.1**, is reacted in tetrahydrofuran solution with 4-bromomethyl cyclohexanone, **131.1**, (WO 97/37959) to give the alkylation products, **131.2** and **131.3**. The 1'-substituted isomer, **131.2**, is then reacted, in a reductive amination reaction, with a dialkyl aminomethyl phosphonate, **131.8**, (Interchim) and sodium cyanoborohydride, to yield, after deprotection and side-chain modification, the 21-chloro 17-propionate, **131.5**.

The preparation of amines by means of reductive amination procedures is described, for example, in R. C. Larock, *Comprehensive Organic Transformations*, 421 (VCH, **1989**), and in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Part B, 269 (Plenum, **2001**). In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, **1990**, *55*, 2552.

The 2'-substituted pyrazole, **131.3**, is subjected to the same series of reaction to give the amine phosphonate, **131.7**.

Using the above procedures, but employing different bromomethyl-substituted aldehydes or ketones, and/or different amino-substituted phosphonates, the products analogous to **131.5** and **131.7** are obtained.

Example 132



132A **132.1** **132.2** **132.3**

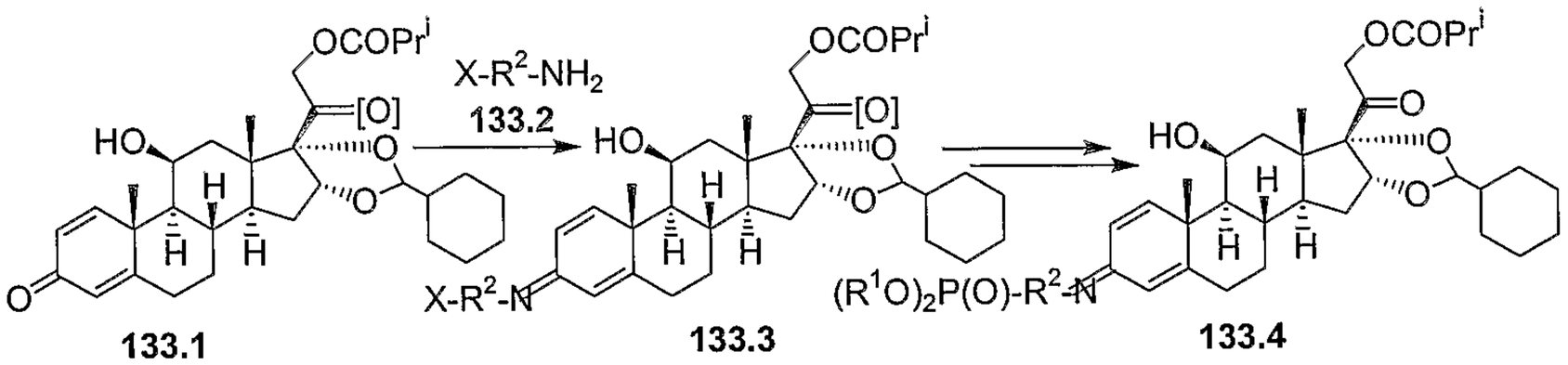
A protection-deprotection sequence in which the 20-ketone group of Ciclesonide, **132A**, (U.S. Patent No. 5,482,934) is protected to afford the derivative, **132.1**. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, **1955**, *77*, 1904. Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.*, **1987**, 1351.

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone, **132A**, with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.*, **1970**, *50*, 102. The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, **1979**, *101*, 5841.

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate, **132A**, is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc. Chem. Comm.*, **1983**, 406, to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The protected compound, **132.1**, is then converted into the phosphonate-containing analog, **132.2**, using the procedures described below, and the protecting group is then removed, as described above, to give the phosphonate, **132.3**.

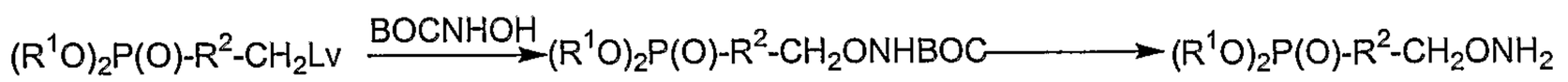
Example 133



133.1 **133.3** **133.4**

The protected derivative, **133.1**, is reacted with an amine or hydroxylamine, **133.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime, **133.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The protecting group is then removed, as described herein, to afford the 20-keto phosphonate product, **133.4**.

Example 133A

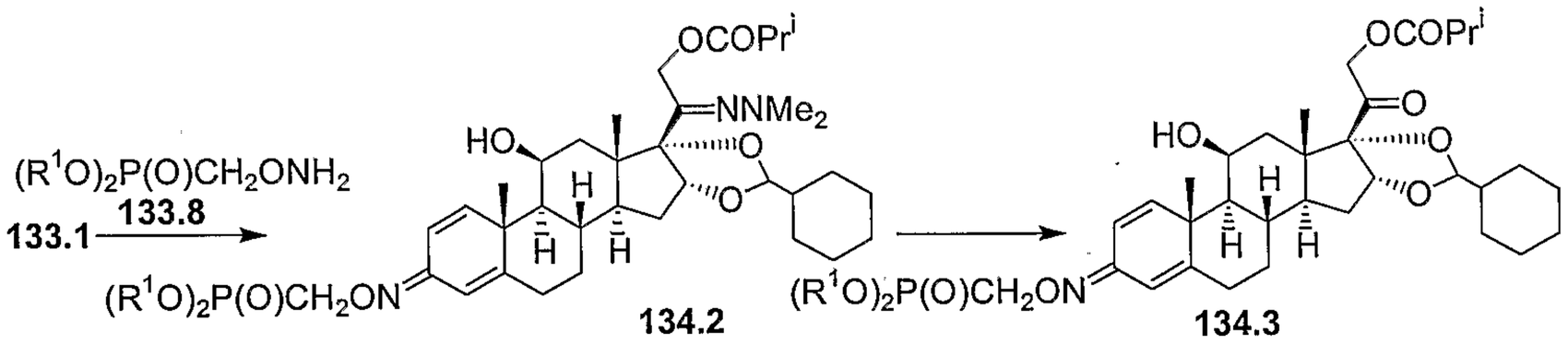


133.5 **133.6** **133.7** **133.8**

The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated herein. In this procedure, a phosphonate, **133.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **133.6**, (Aldrich) to produce the ether, **133.7**. The reaction

is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **133.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.

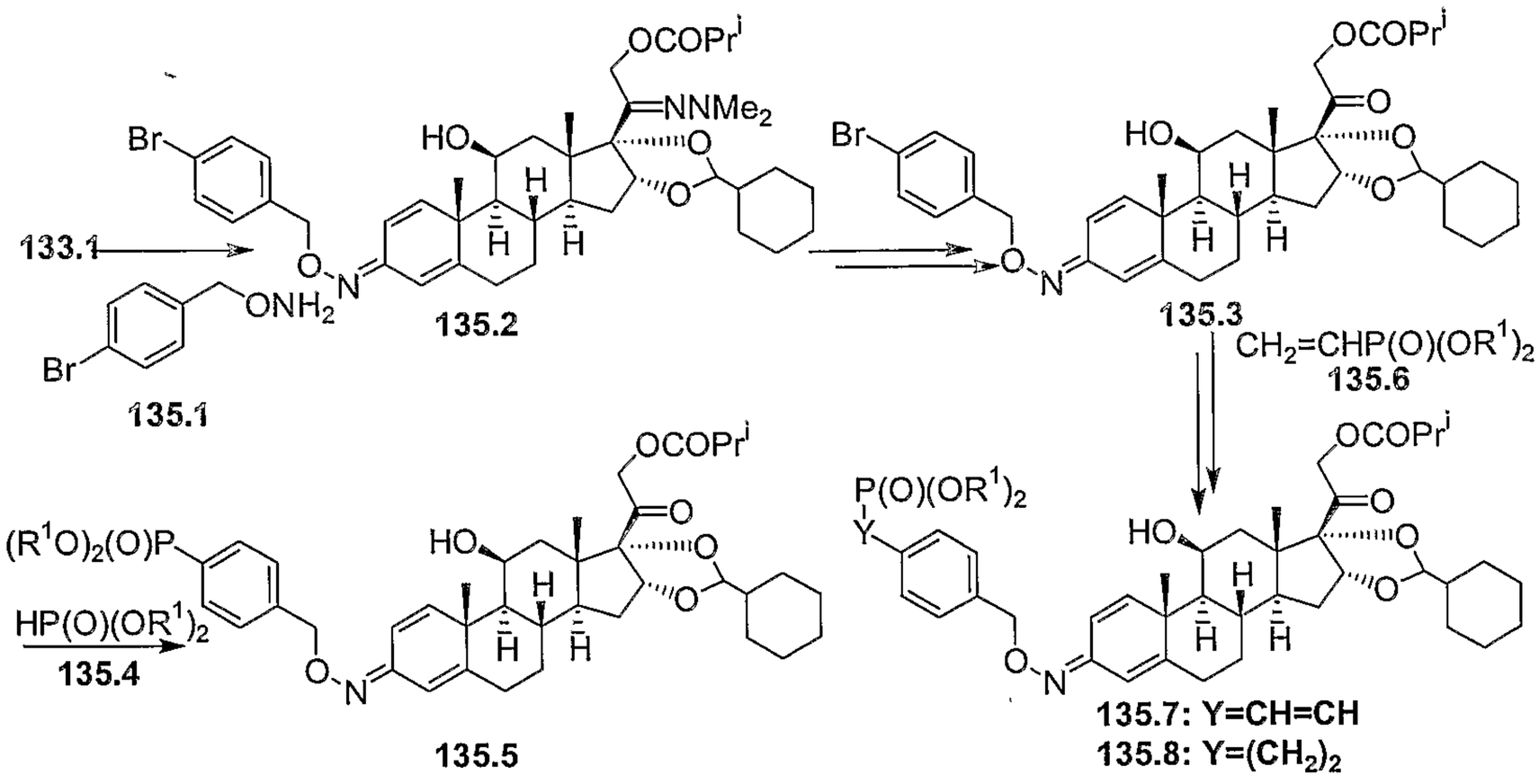
Example 134



The substrate, **133.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine, **133.8**, prepared as described above from a dialkyl trifluoromethylsulfonyl-oxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **134.2**. Deprotection, as described in Example **132**, then affords the 20-keto phosphonate, **134.3**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **133.8**, different oxime ethers, **133.2**, the corresponding products, **133.4** are obtained.

Example 135



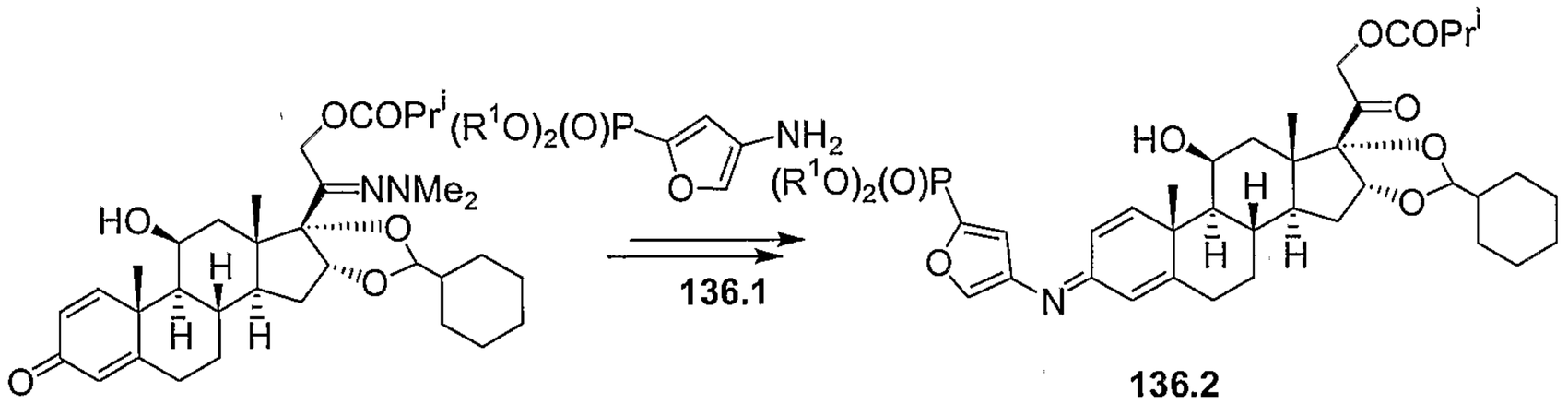
The dienone, **133.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(4-bromobenzyloxy)-hydroxylamine, **135.1**, prepared as described above from 4-bromobenzyl bromide and BOC-protected hydroxylamine, **133.6**, to give the oxime, **135.2**. The protecting group is then removed to yield the 20-keto product, **135.3**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphate, **135.4**, to afford the phosphonate, **135.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenyl-phosphine)palladium(0).

Alternatively, the bromo compound, **135.3**, is coupled with a dialkyl vinyl phosphonate, **135.6**, (Aldrich) to afford the phosphonate, **135.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, **2001**) and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenyl-phosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **135.7**,

is reduced, for example by reaction with diimide, to produce the saturated analog, **135.8**. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations* 6ff (VCH **1989**). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromobenzyl-oxy reagent, **135.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, products analogous to the compounds, **135.5**, **135.7** and **135.8** are obtained.

Example 136

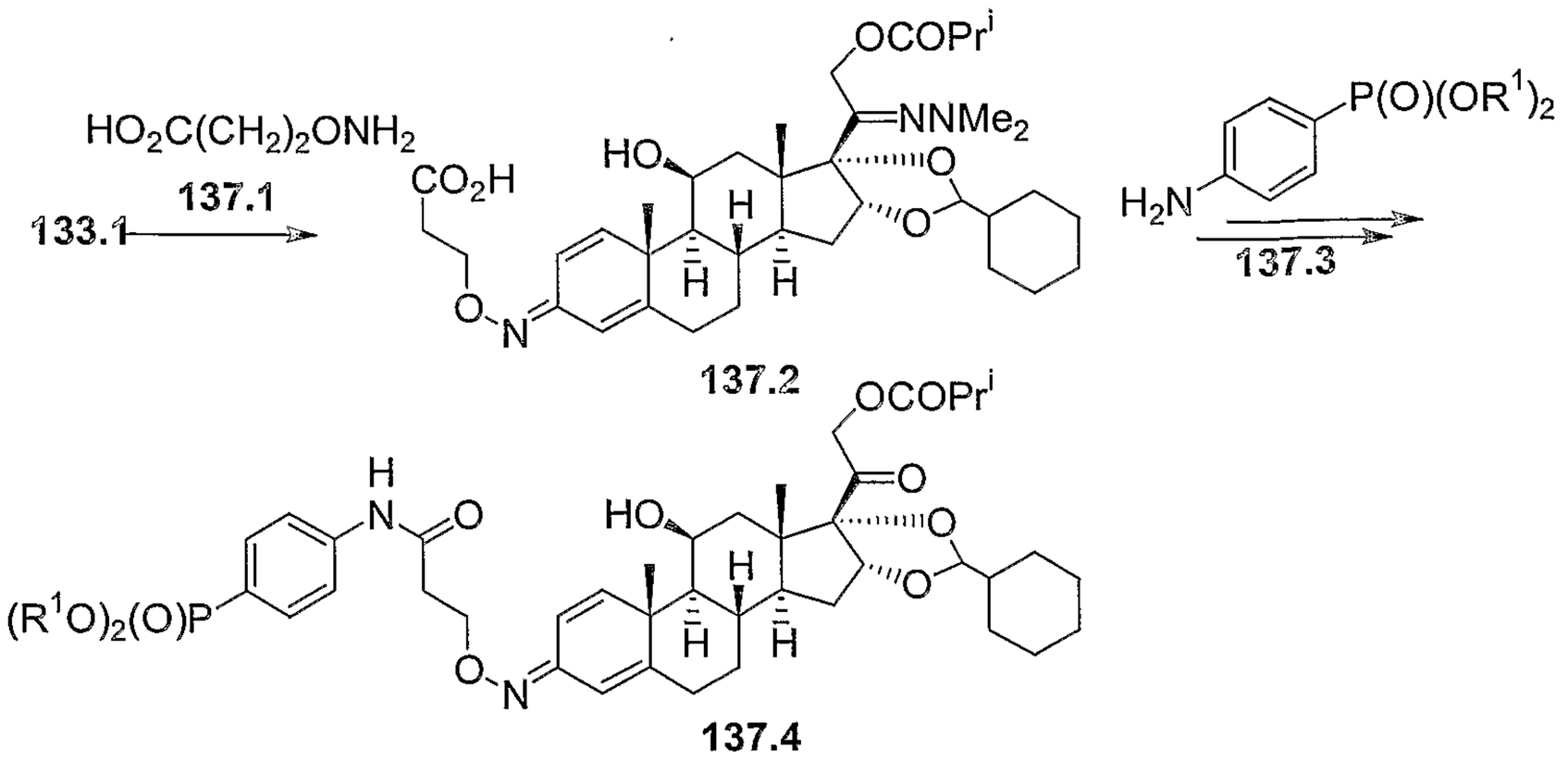


133.1 **136.2**

The substrate, **133.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 4-amino-2-furyl phosphonate, **136.1**, prepared by the palladium catalyzed coupling reaction, as described above, between 4-amino-2-bromofuran (*Tetrahedron Lett.*, **1987**, *43*, 3295) and a dialkyl phosphite, to give, after deprotection, the imine product, **136.2**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-amino-2-furyl phosphonate, **136.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **136.2** are obtained.

Example 137



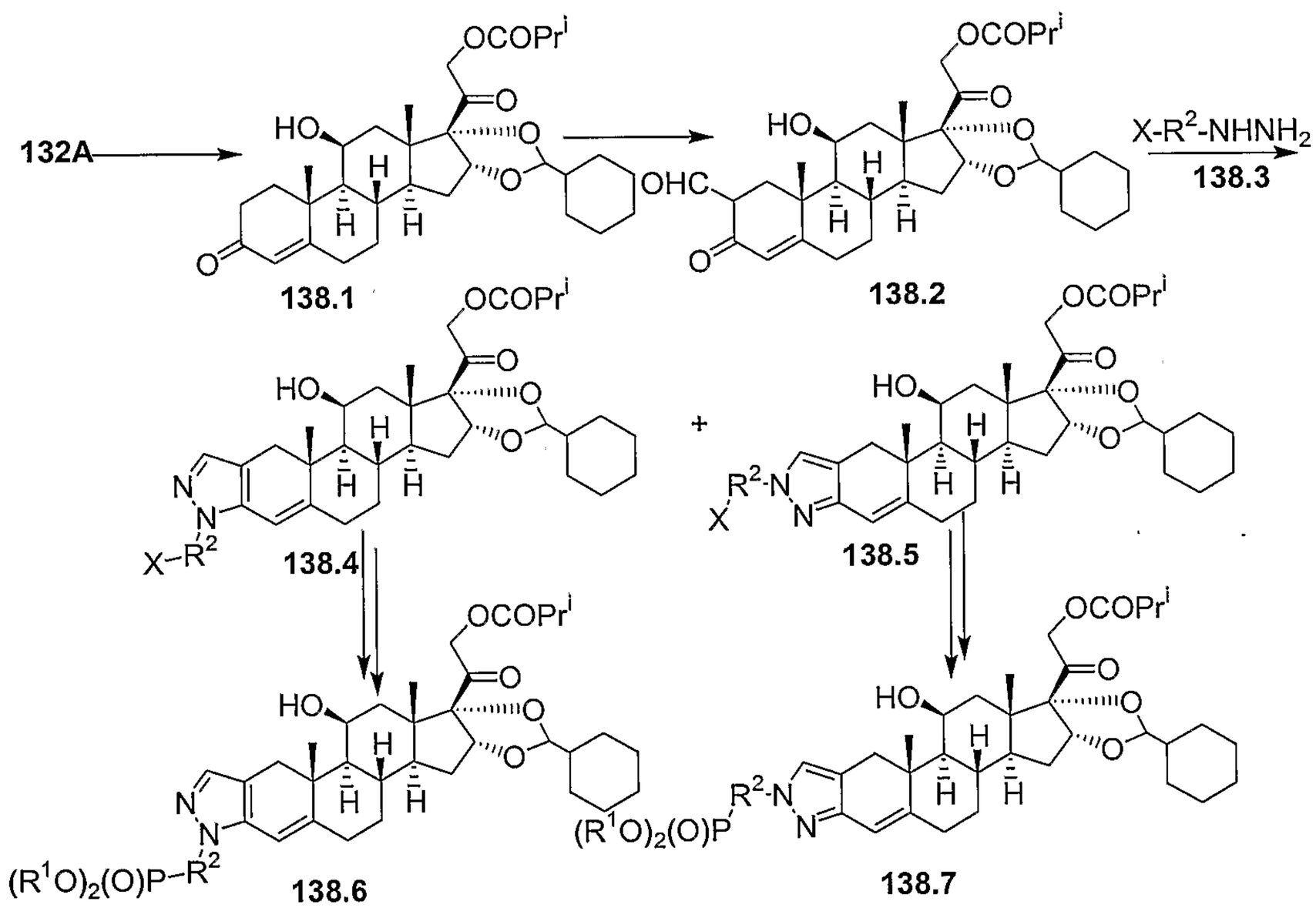
The dienone, **133.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with O-(2-carboxyethyl)hydroxylamine, **137.1**, (*J. Med. Chem.*, **1990**, *33*, 1423) to yield the oxime, **137.2**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product, **137.2**, is then coupled with a dialkyl 4-aminophenyl phosphonate, **137.3**, (Epsilon) and dicyclohexylcarbodiimide, to yield, after deprotection the amide oxime, **137.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R. Sandler and W. Karo, *Organic Functional Group Preparations* 274 (Academic Press, **1968**) and R. C. Larock, *Comprehensive Organic Transformations* 972ff (VCH, **1989**). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

Using the above procedures, but employing, in place of the carboxy-substituted hydroxylamine, **137.1**, different carboxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, products analogous to **137.4** are obtained.

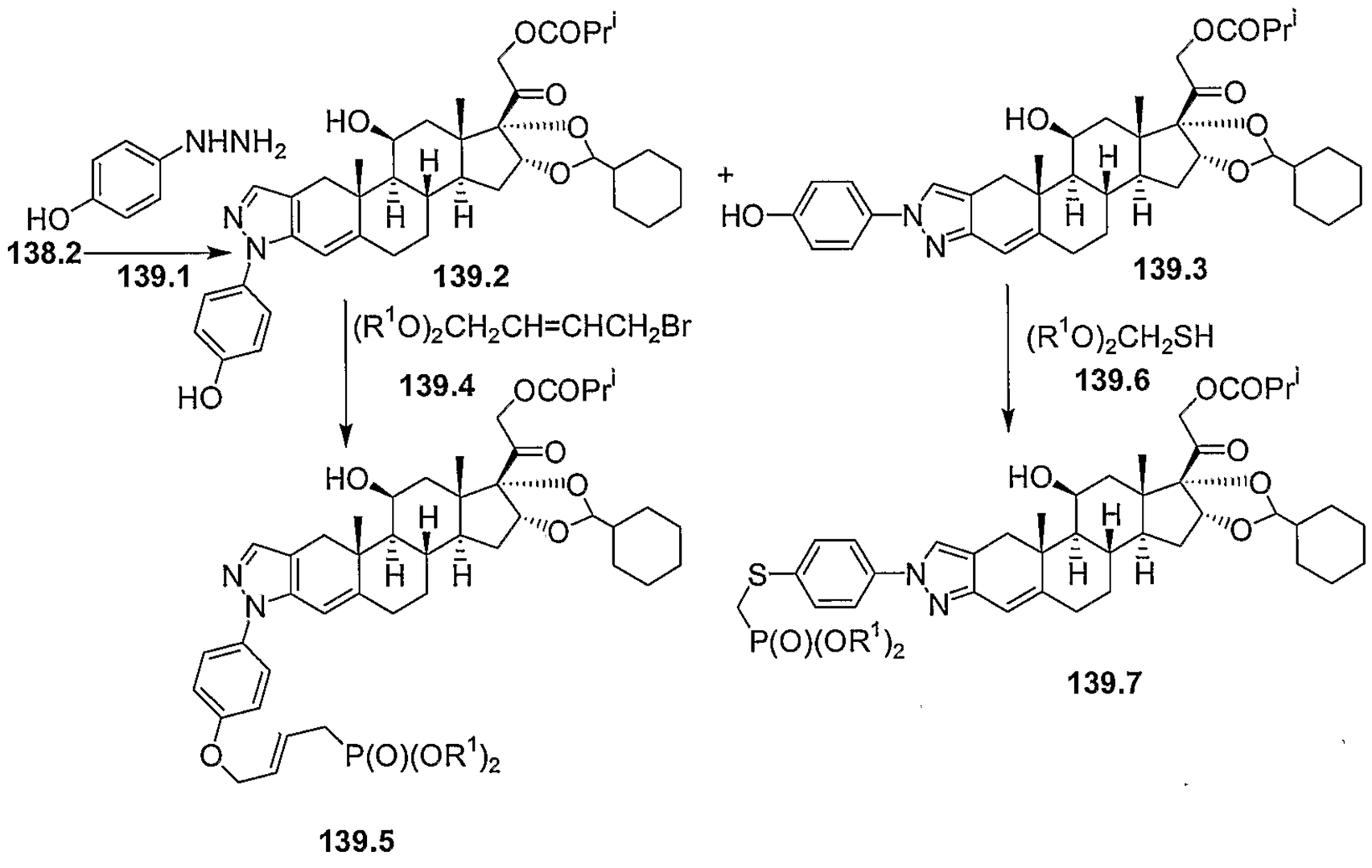
Example 138



The dienone, **132A**, is reduced to afford the 1,2-dihydro product, **138.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenyl-phosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, *44*, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **138.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl

hydrazine, **138.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **138.4** and **138.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **138.4** and **13.5**, are then transformed, for example by the procedures described in Examples **139** and **140**, into the phosphonates, **138.6** and **138.7**.

Example 139



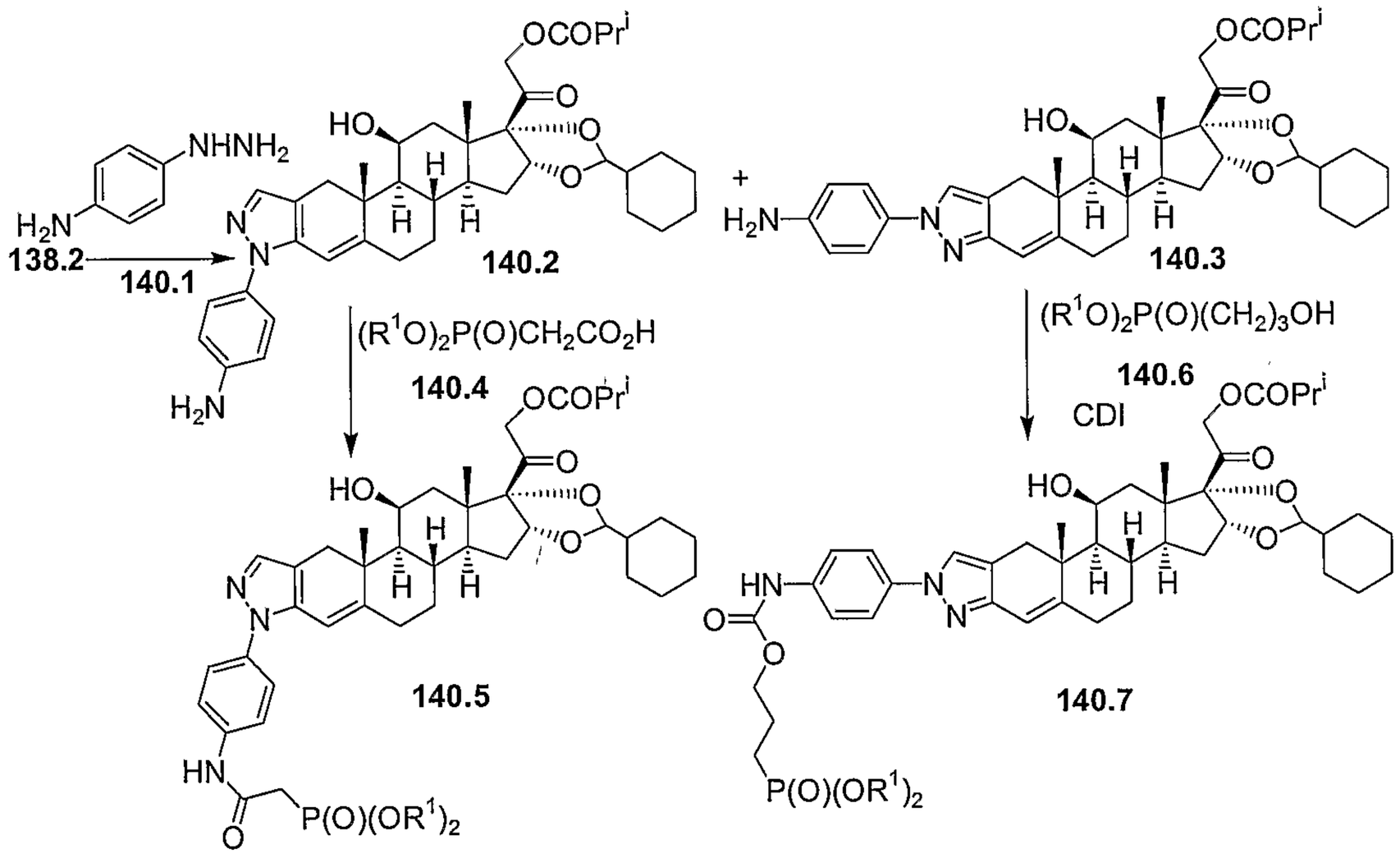
The ketoaldehyde, **138.2**, is reacted, as described above, with 4-hydroxy-phenyl hydrazine, **139.1**, (EP 437105) to give the pyrazoles, **139.2** and **139.3**. The 2'-substituted isomer, **139.2**, is then reacted in dimethylformamide solution at ca. 70°C with a dialkyl bromobutenyl phosphonate, **139.4**, (*J. Med. Chem.*, **1992**, *35*, 1371) and potassium carbonate, to yield the ether phosphonate, **139.5**.

The isomeric pyrazole, **139.3**, is reacted, in a Mitsonobu reaction, with a dialkyl mercaptomethyl phosphonate, **139.6**, (*J. Med. Chem.*, **1985**, *26*, 1688) to yield the thioether phosphonate, **139.7**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in R. C. Larock, *Comprehensive Organic Transformations* 448 (VCH, **1989**), in F.A.

Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Part B 153-4 (Plenum, **2001**), and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656.

Using the above procedures, but employing different hydroxy-substituted hydrazines, and/or different bromo- or mercapto-substituted phosphonates, products analogous to **139.5** and **139.7** are obtained.

Example 140



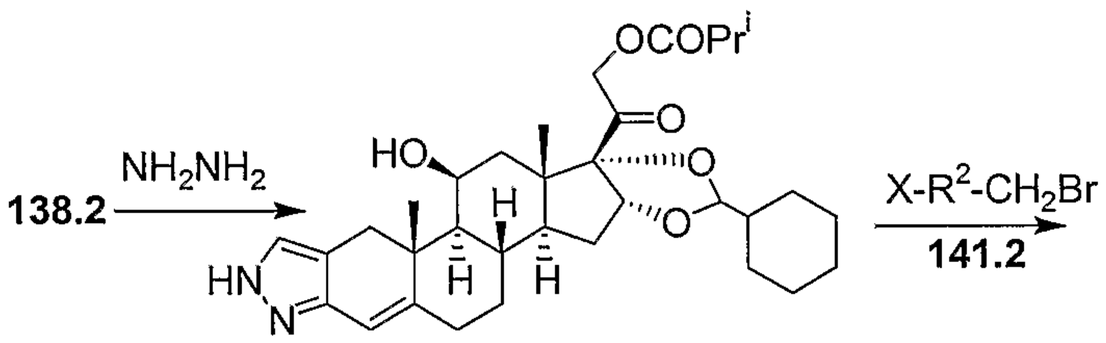
The ketoaldehyde, **138.2**, is reacted, as described above, with 4-aminophenyl hydrazine, **140.1**, (Epsilon) to produce the pyrazoles, **140.2** and **140.3**. The 2'-substituted isomer, **140.2**, is coupled, as described above, with a dialkyl phosphonoacetic acid, **140.4**, (Aldrich) and dicyclohexyl carbodiimide, to give the amide phosphonate, **140.5**.

Alternatively, the 1'-substituted pyrazole, **140.3**, is reacted with a dialkyl 3-hydroxypropyl phosphonate, **140.6**, (*Zh. Obschei. Khim.*, **1973**, *43*, 2364), and carbonyl diimidazole to prepare the carbamate phosphonate, **140.7**. The preparation of carbamates is described in *Comprehensive Organic Functional*

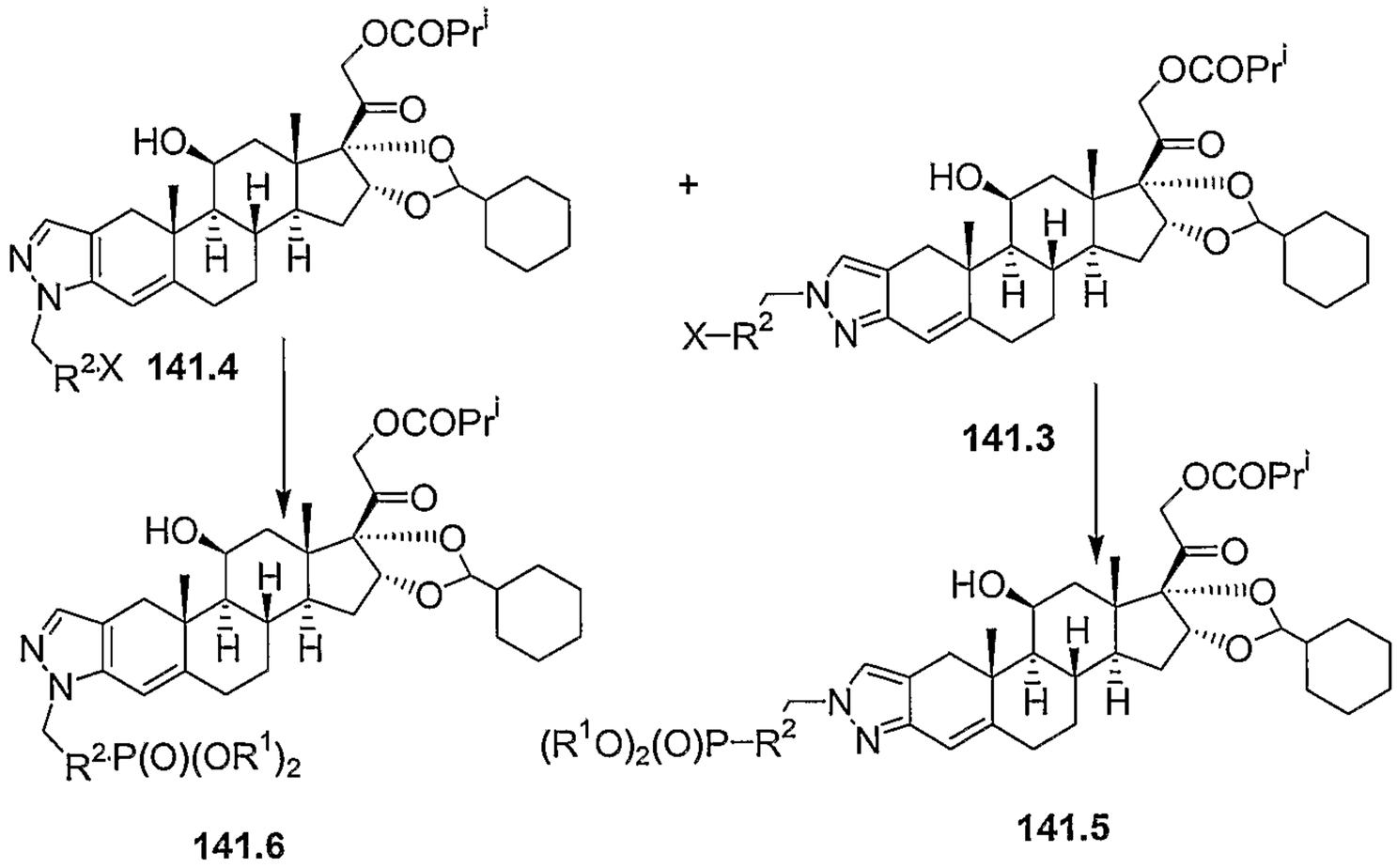
Group Transformations, *Vol. 6*, 416ff (A. R. Katritzky, ed., Pergamon, **1995**) and in S. R. Sandler and W. Karo, *Organic Functional Group Preparations* 260ff (Academic Press, **1986**). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

Using the above procedures, but employing, in place of the 4-amino-phenyl hydrazine, **140.1**, different amino-substituted hydrazines, and/or different dialkyl carboxy or hydroxy-substituted phosphonates, products analogous to the compounds, **140.5** and **140.7** are obtained.

Example 141



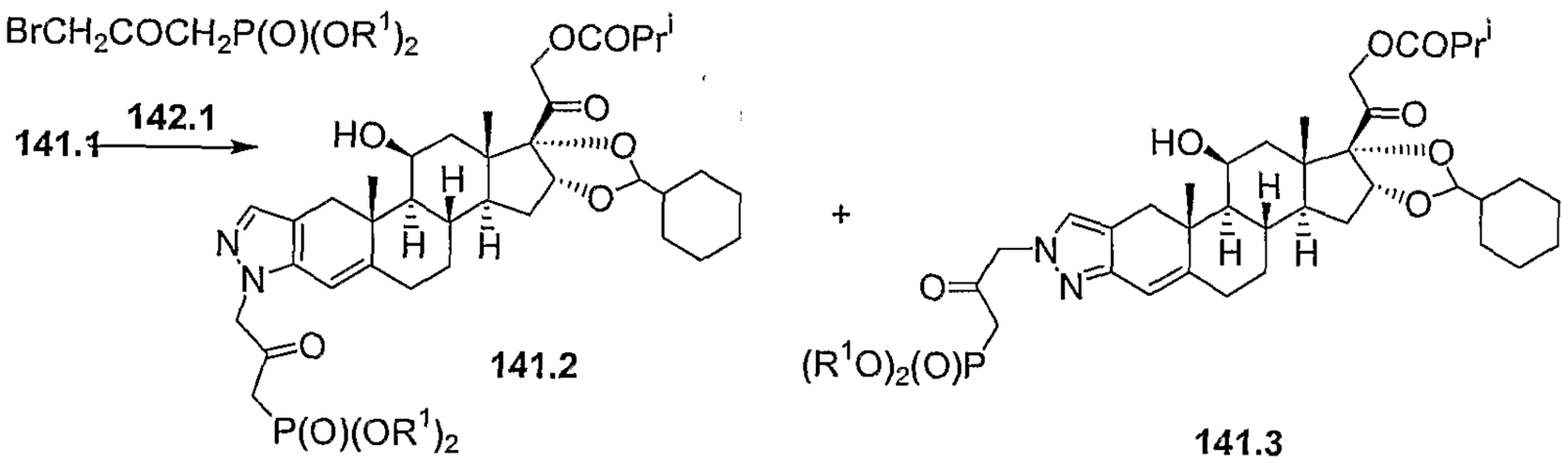
141.1



The ketoaldehyde, **138.2**, is reacted with hydrazine, to afford the pyrazole derivative, **141.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then

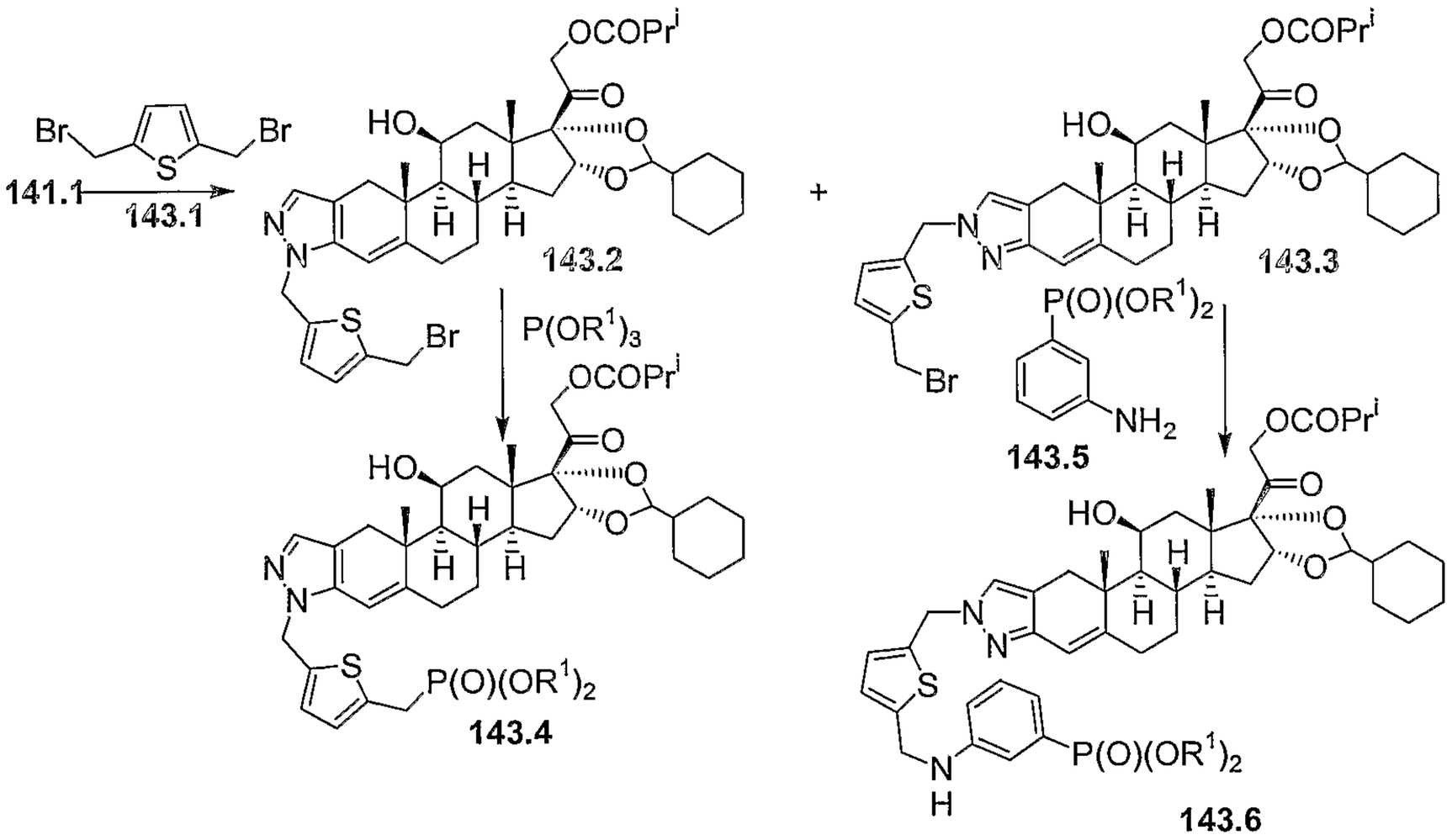
reacted with a bromomethyl compound, **141.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products, **141.3** and **141.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry* 309 (Longman, **1992**). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **141.3** and **141.4**, are, except in cases where X is dialkyl-phosphono, converted into the phosphonates, **141.5** and **141.6**, using the procedures described herein.

Example 142



The pyrazole, **141.1**, is reacted, as described above, with a dialkyl acetonyl phosphonate, **142.1**, (*Tetrehedron Lett.*, **1978**, *34*, 649) to give the pyrazoles, **141.2** and **141.3**.

Example 143

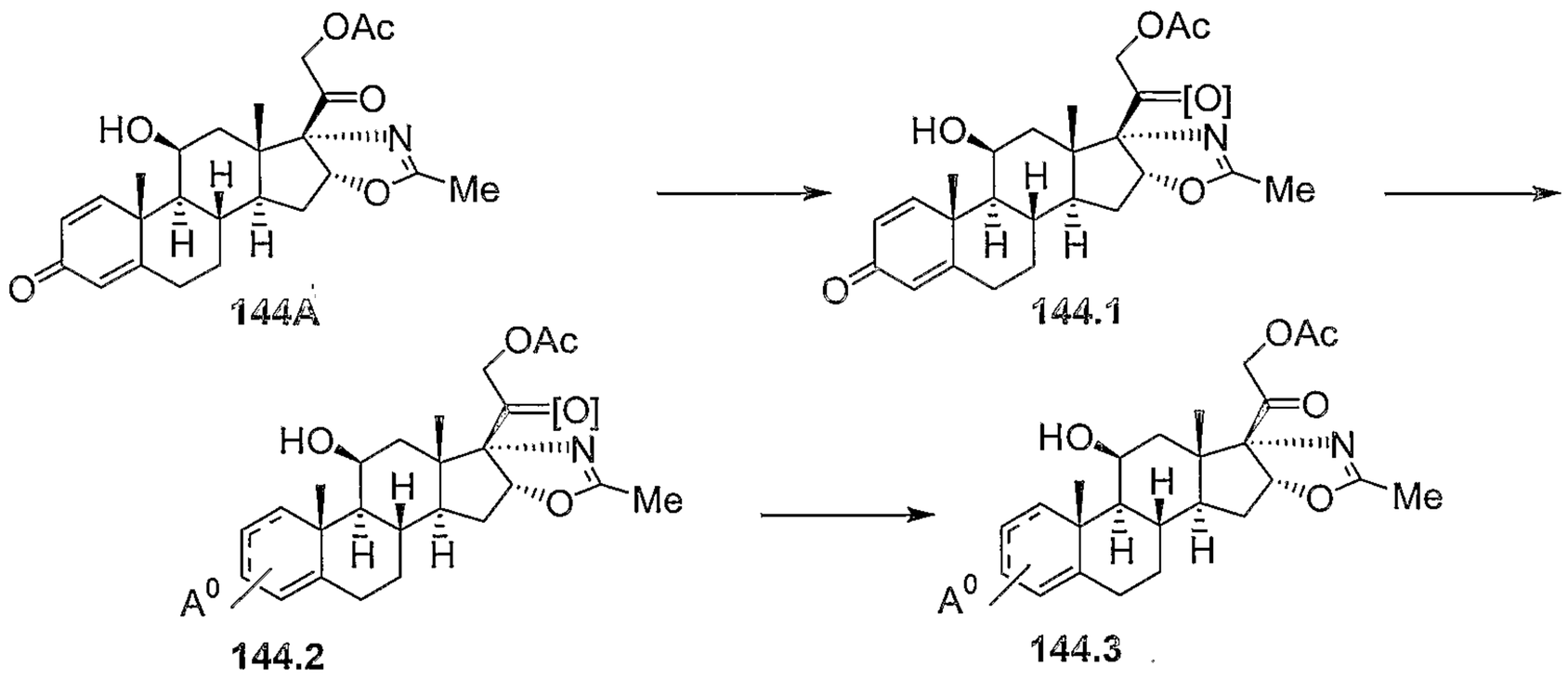


The pyrazole, **141.1**, is reacted in tetrahydrofuran solution, with 2,5-bis(bromomethyl)thiophene, **143.1**, (*Tetrahedron Lett.*, **1999**, *55*, 4709) and potassium hexamethyl disilazide, to give the alkylation products, **143.2** and **143.3**. The 2'-substituted isomer, **143.2**, is then reacted, in a Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate, **143.4**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, 1992, 115. In this procedure, in which a bromo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60°C to about 160°C with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole, **143.3**, is reacted at 70°C in dimethylformamide solution with one molar equivalent of a dialkyl 3-aminophenyl phosphonate, **143.5**, and cesium carbonate, to give the amine phosphonate, **143.6**.

Using the above procedures, but employing different dibromides, and/or different amino-substituted phosphonates, products analogous to **143.4** and **143.6** are obtained.

Example 144



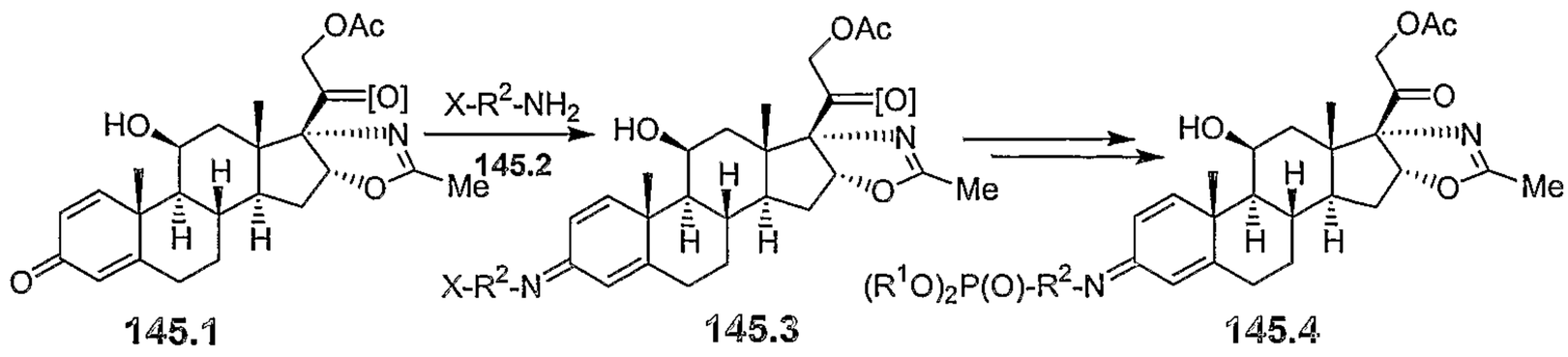
A protection-deprotection sequence in which the 20-ketone group of Deflazacort, **144A**, (U.S. Patent No. 3,436,389) is protected to afford the derivative, **144.1**, as shown. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, **1955**, 77, 1904. Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.*, **1987**, 1351.

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone, **144A**, with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.*, **1970**, *50*, 102. The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, **1979**, *101*, 5841.

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate, **144A**, is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc. Chem. Comm.*, **1983**, 406, to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

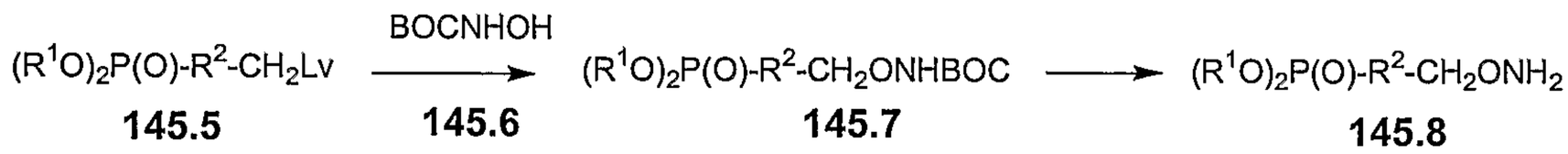
The protected compound, **144.1**, is then converted into the phosphonate-containing analog, **144.2**, using the procedures described below, and the protecting group is then removed, as described above, to give the phosphonate, **144.3**.

Example 145



The protected derivative, **145.1**, is reacted with an amine or hydroxylamine, **145.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime, **145.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The protecting group is then removed, as described herein, to afford the 20-keto phosphonate product, **145.4**.

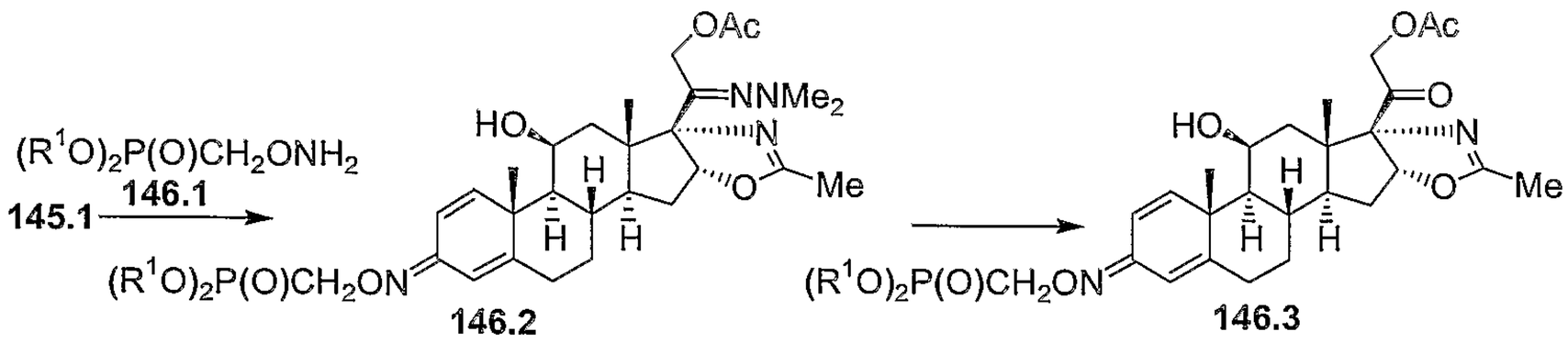
Example 145A



The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated herein. In this procedure, a phosphonate, **145.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **145.6**, (Aldrich) to produce the ether, **145.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **145.8**.

The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.

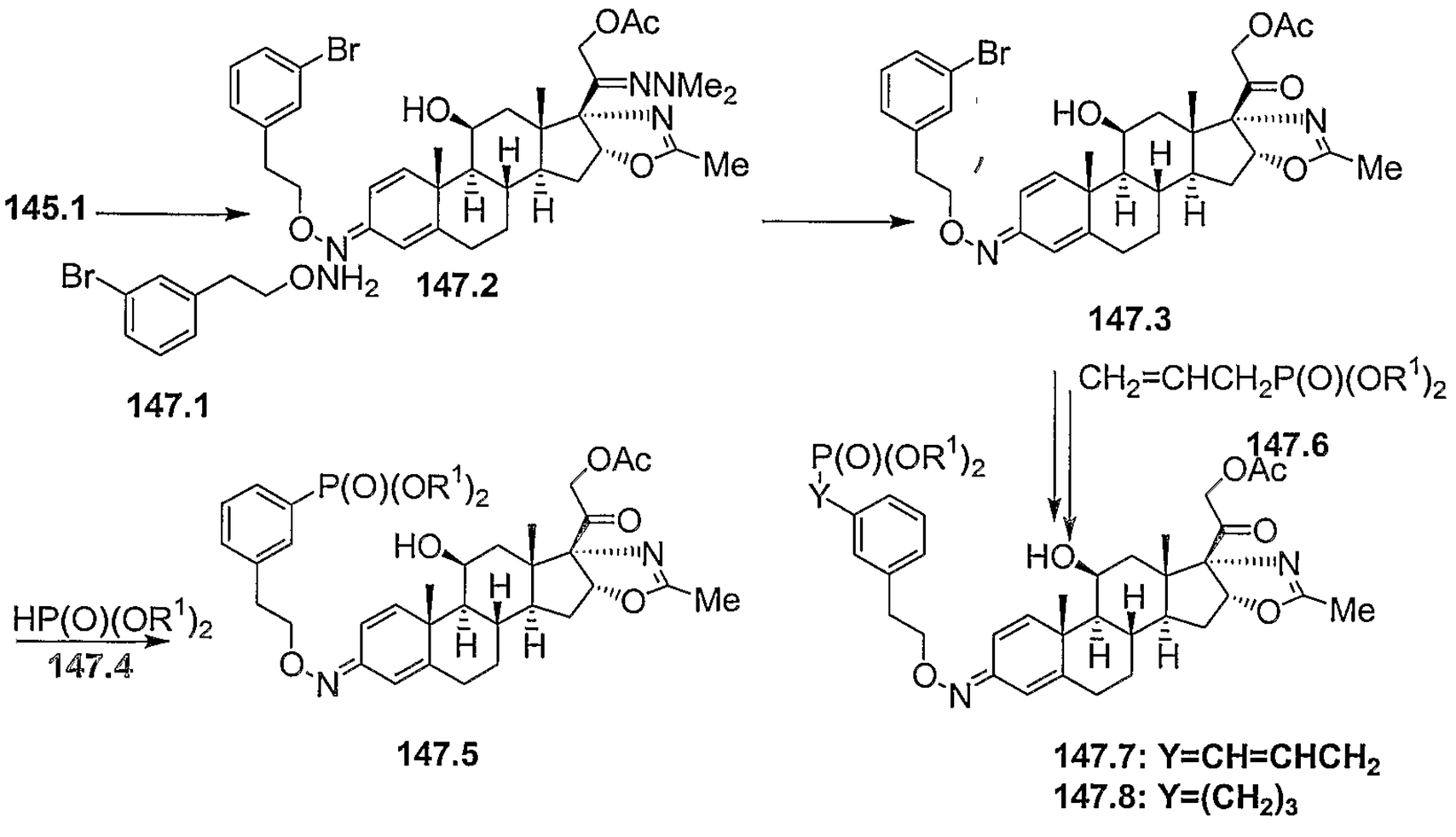
Example 146



The substrate, **145.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine, **146.1**, prepared as described above from a dialkyl trifluoromethylsulfonyl-oxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **146.2**. Deprotection, as described in Example **144**, then affords the 20-keto phosphonate, **146.3**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **146.1**, different oxime ethers, **145.2**, the corresponding products, **145.4** are obtained.

Example 147

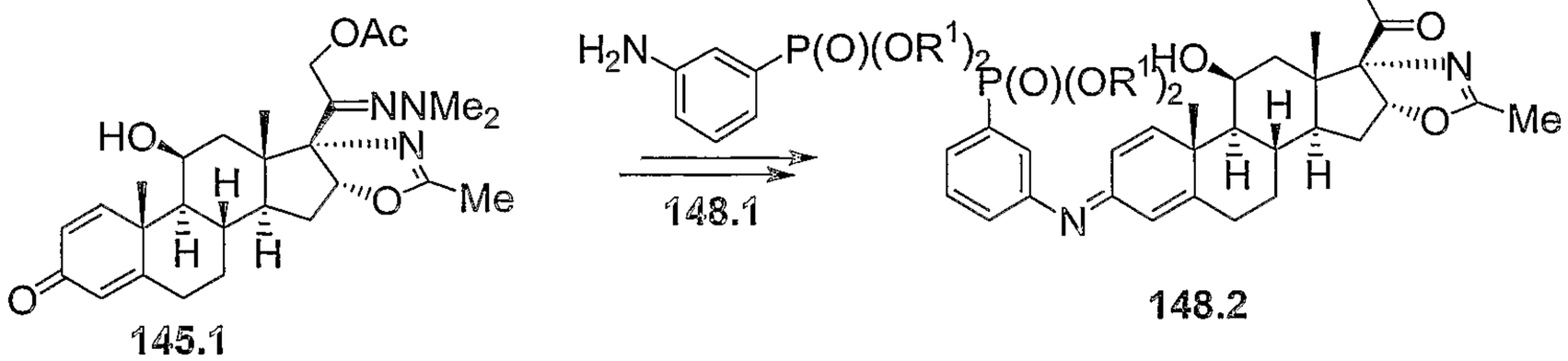


The dienone, **145.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(3-bromophenylethoxy)-hydroxylamine, **147.1**, prepared as described above from 3-bromophenylethyl bromide (French Patent FR 1481052), and BOC-protected hydroxylamine, **145.6**, to give the oxime, **147.2**. The protecting group is then removed to yield the 20-keto product, **147.3**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphate, **147.4**, to afford the phosphonate, **147.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound, **147.3**, is coupled with a dialkyl propenyl phosphonate, **147.6**, (Aldrich) to afford the phosphonate, **147.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, **2001**) and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenyl-phosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **147.7**, is reduced, for example by reaction with diimide, to produce the saturated analog, **147.8**. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations* 6ff (VCH **1989**). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromophenylethyl reagent, **147.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, products analogous to the compounds, **147.5**, **147.7** and **147.8** are obtained.

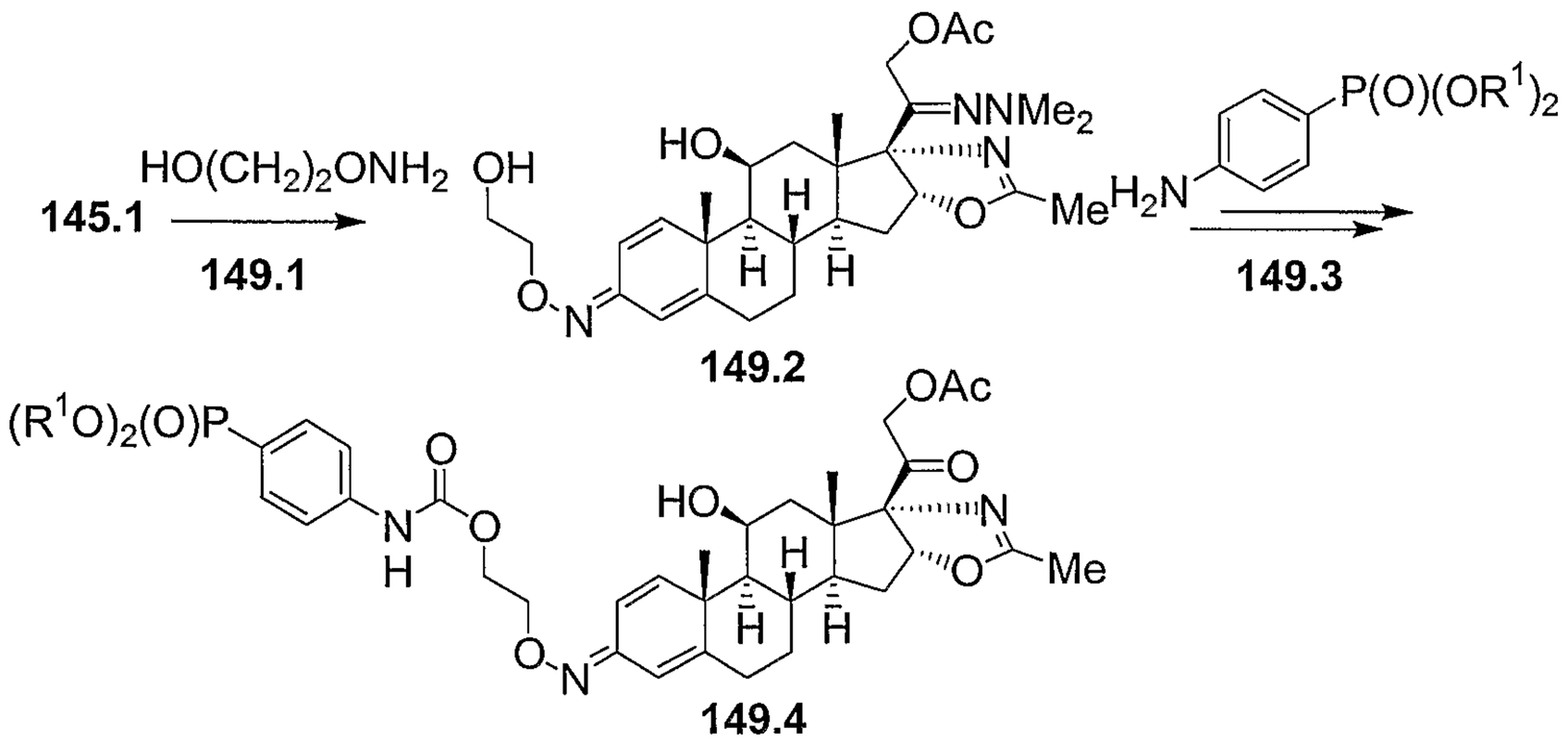
Example 148



The substrate, **145.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 3-aminophenyl phosphonate, **148.1**, (*J. Med. Chem.*, **1984**, *27*, 654), to give, after deprotection, the imine product, **148.2**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 3-aminophenyl phosphonate, **148.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **148.2** are obtained.

Example 149

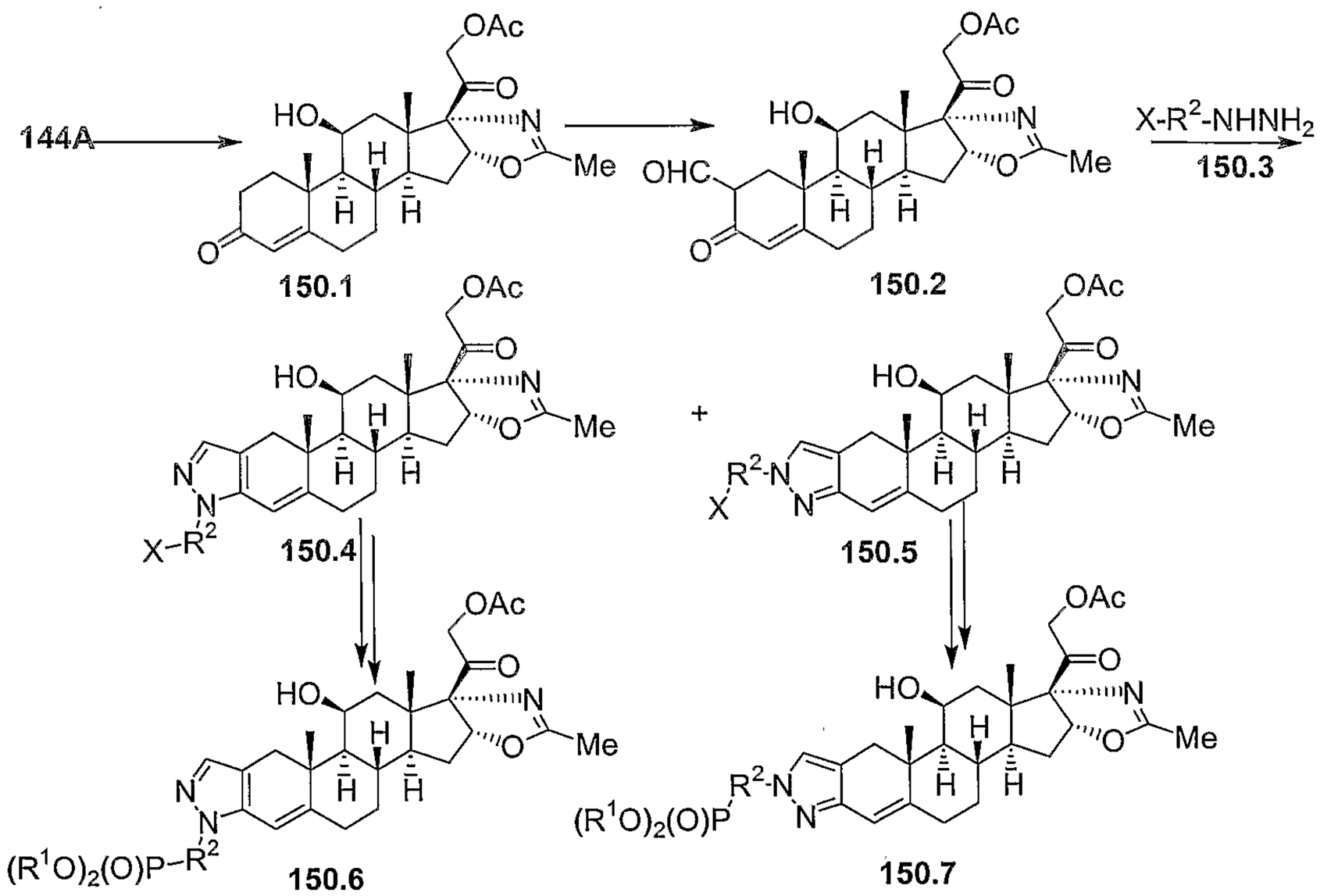


The dienone, **145.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with O-(2-hydroxyethyl)hydroxylamine, **149.1**, (*J. Chem. Soc. Chem. Comm.*, **1986**, 903) to yield the oxime, **149.2**. The reaction of

steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product, **149.2**, is then coupled with a dialkyl 4-aminophenyl phosphonate, **149.3**, (Epsilon) and carbonyl diimidazole, to yield, after deprotection, the carbamate oxime, **149.4**. The preparation of carbamates is described in *Comprehensive Organic Functional Group Transformations*, *Vol. 6*, 416ff (A. R. Katritzky, ed., Pergamon, **1995**) and in S. R. Sandler and W. Karo, *Organic Functional Group Preparations* 260ff (Academic Press, **1986**). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

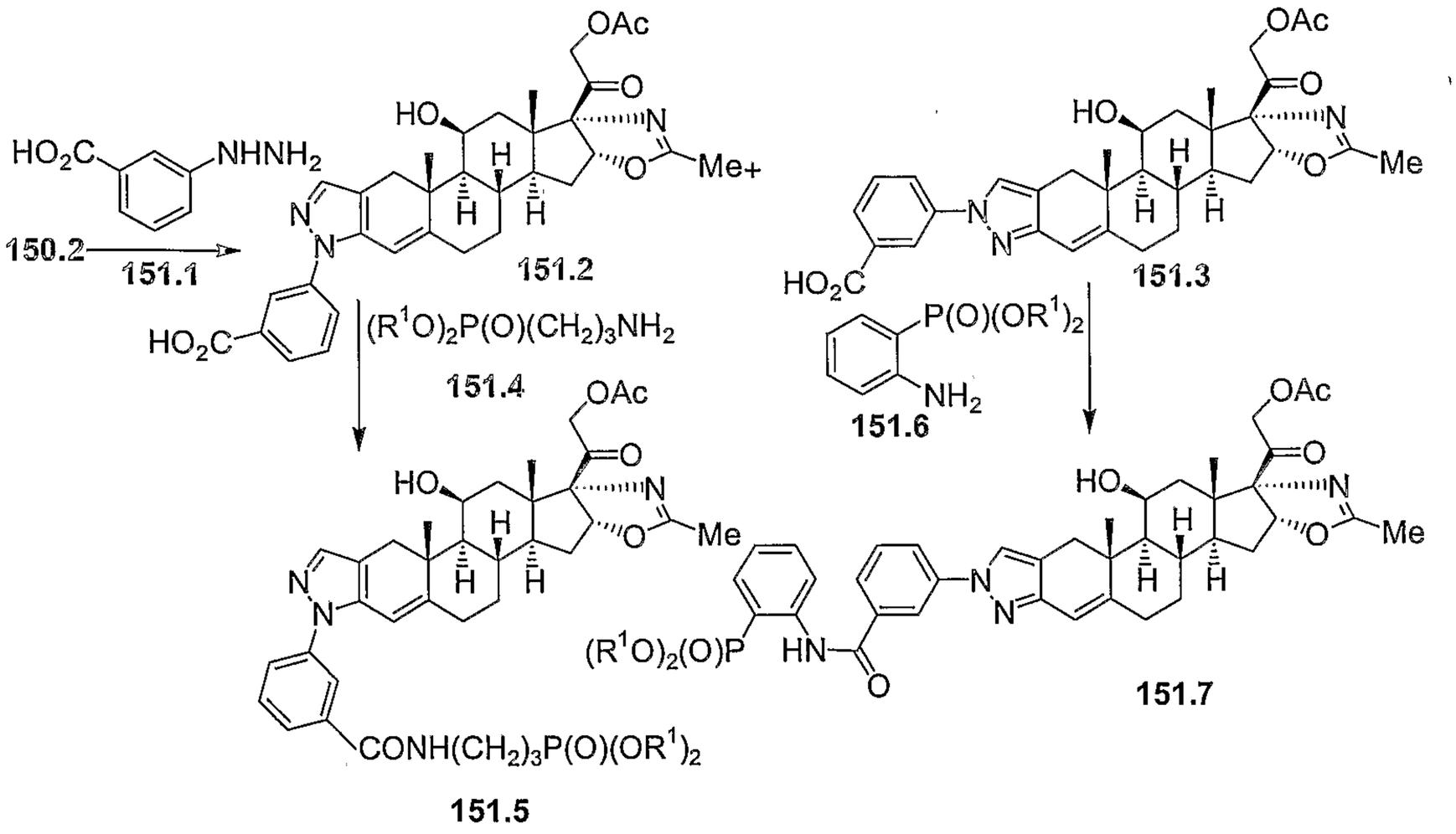
Using the above procedures, but employing, in place of the hydroxy-substituted hydroxylamine, **149.1**, different hydroxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to **149.4** are obtained.

Example 150



The dienone, **144A**, is reduced to afford the 1,2-dihydro product, **150.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenyl-phosphine)rhodium (I) chloride, for example, as described in *J. Med. Chem.*, **2001**, *44*, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **150.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **150.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **150.4** and **150.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **150.4** and **150.5**, are then transformed, for example by the procedures described herein, into the phosphonates, **150.6** and **150.7**.

Example 151



The ketoaldehyde, **150.2**, is reacted, as described above, with 3-carboxyphenyl hydrazine, **151.1**, (Apin) to give the pyrazoles, **151.2** and **151.3**. The 2'-substituted isomer, **151.2**, is then coupled in dimethylformamide solution at ambient temperature with a dialkyl 3-aminopropyl phosphonate, **151.4**, (Acros) and dicyclohexyl carbodiimide, to yield the amide phosphonate, **151.5**. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R. Sandler and W. Karo, *Organic Functional Group Preparations* 274 (Academic Press, **1986**), and R. C. Larock, *Comprehensive Organic Transformations* 972ff (VCH, **1989**). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexyl-carbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

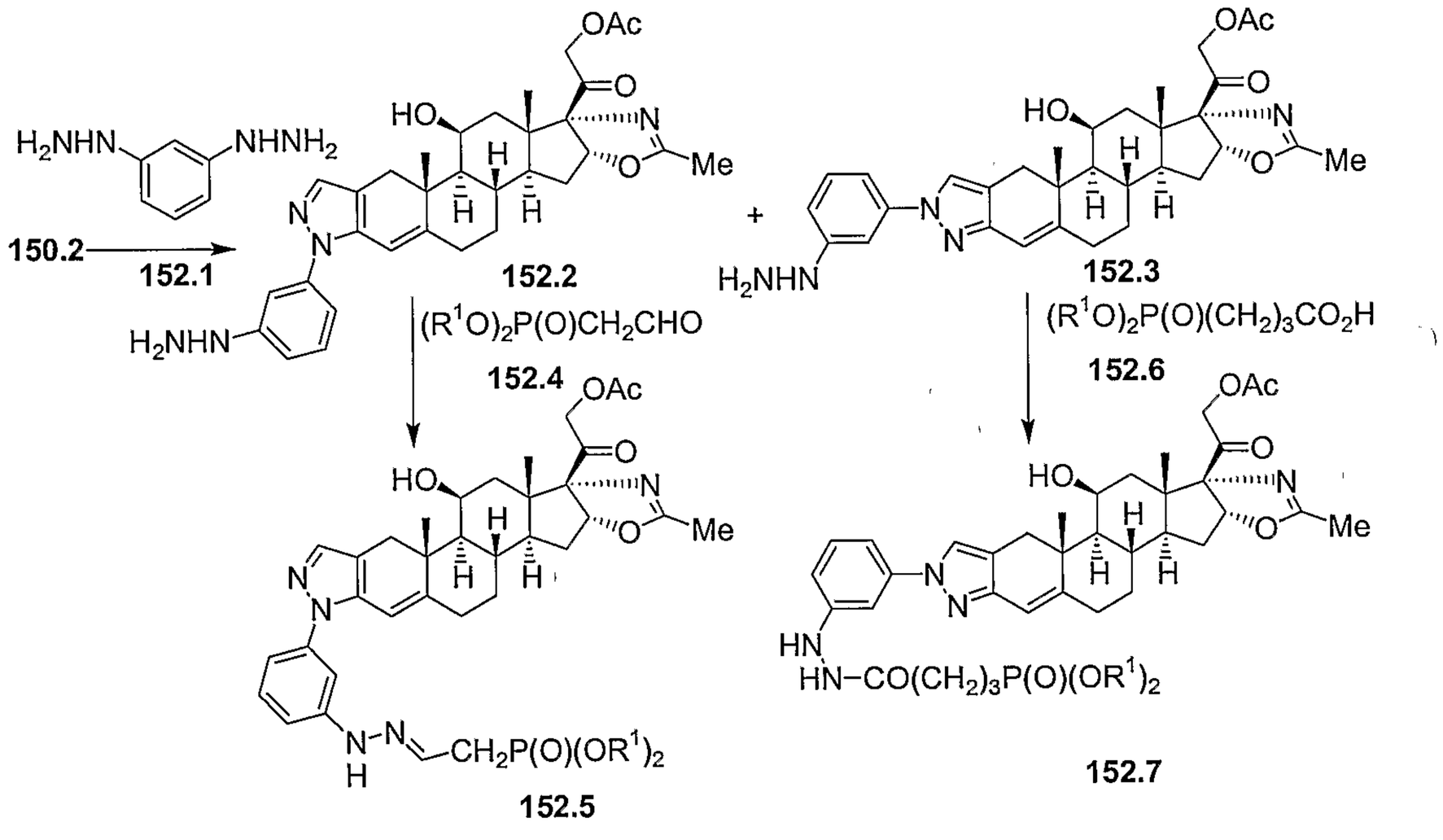
The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for

example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The isomeric pyrazole, **151.3**, is reacted, as described above, with a dialkyl 2-aminophenyl phosphonate, **151.6**, (Acros) to yield the amide phosphonate, **151.7.**

Using the above procedures, but employing different carboxy-substituted hydrazines, and/or different amino-substituted phosphonates, the products analogous to **151.5** and **151.7** are obtained.

Example 152

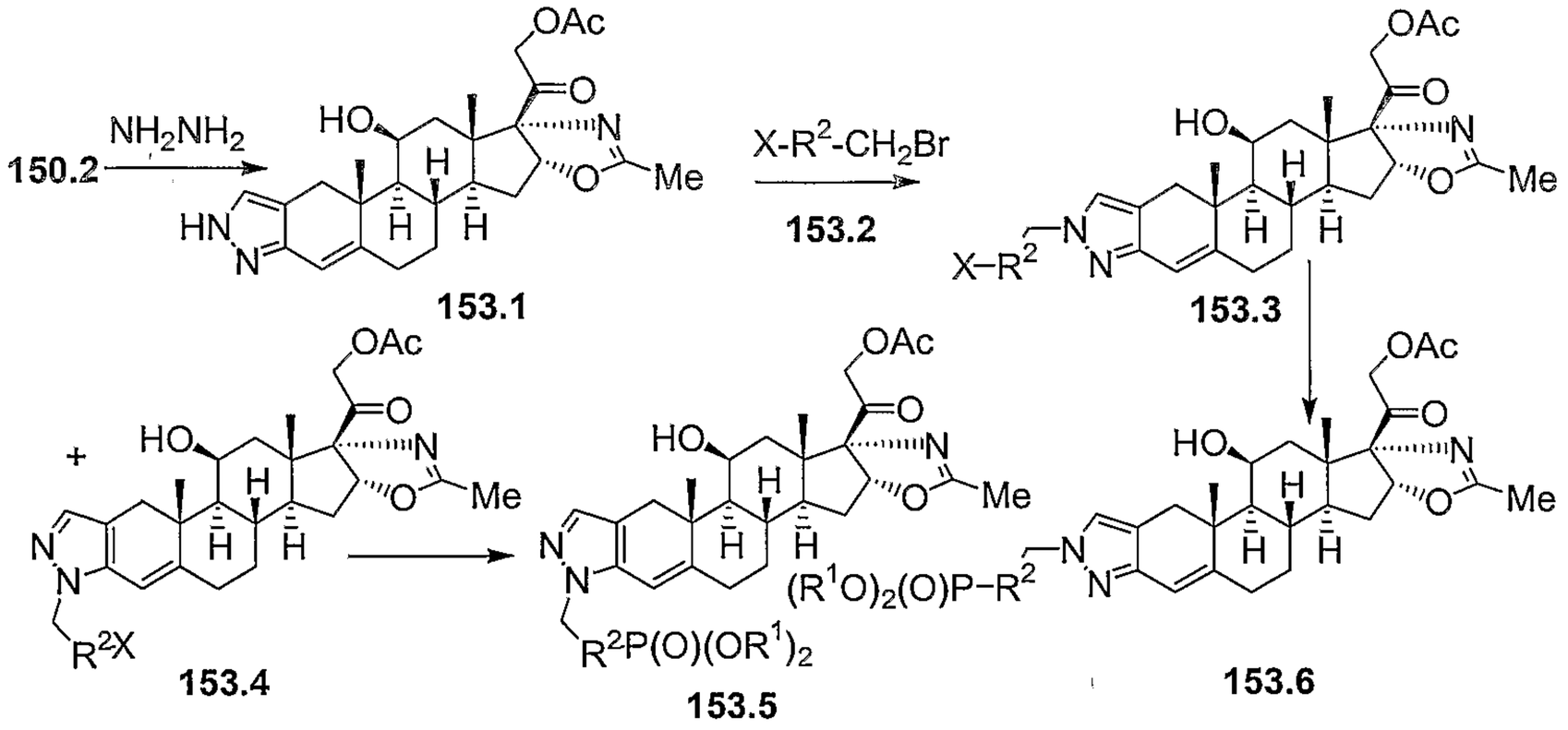


The ketoaldehyde, **150.2**, is reacted, as described above, with 1,3-bis(hydrazino)benzene, **152.1**, (*Bull. Soc. Chim. Fr.*, **1975**, 1371) to produce the pyrazoles, **152.2** and **152.3**. The 2'-substituted isomer, **152.2**, is reacted in tetrahydrofuran solution at ambient temperature with one molar equivalent of a dialkylphosphono acetaldehyde (Aurora), to give the hydrazone phosphonate, **152.5**.

Alternatively, the 1'-substituted pyrazole, **152.3**, is coupled, as described above, with a dialkylphosphono butyric acid, **152.6**, (Epsilon) and dicyclohexyl carbodiimide to prepare the phosphonate, **152.7**.

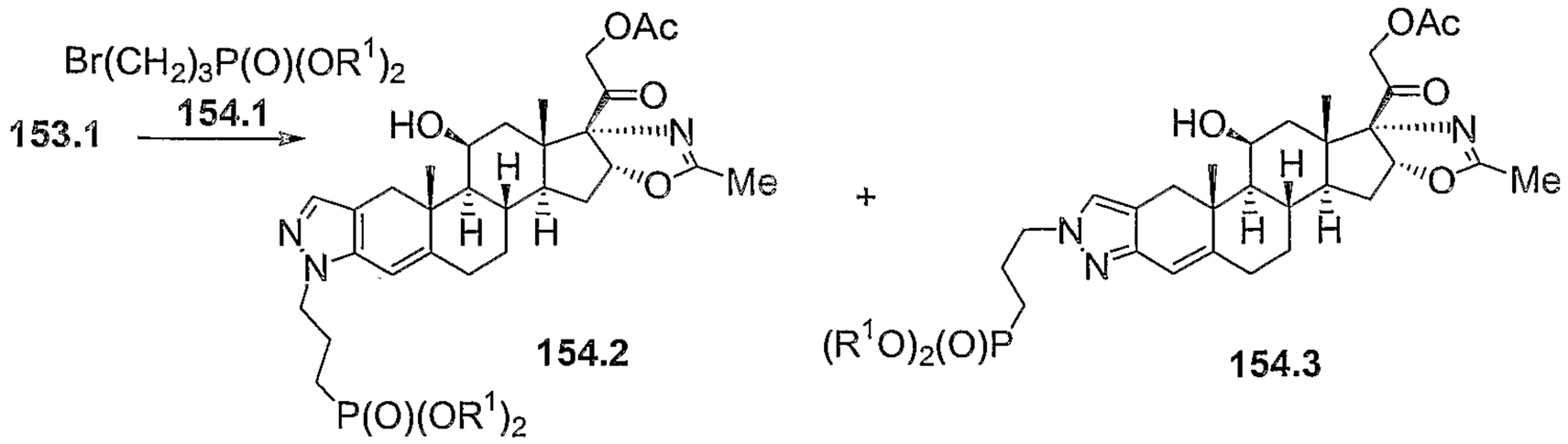
Using the above procedures, but employing, in place of the 1,3-bis(hydrazino)phenyl hydrazine, **152.1**, different bis hydrazines, and/or different dialkyl formyl or carboxy-substituted phosphonates, the products analogous to the compounds, **152.5** and **152.7** are obtained.

Example 153



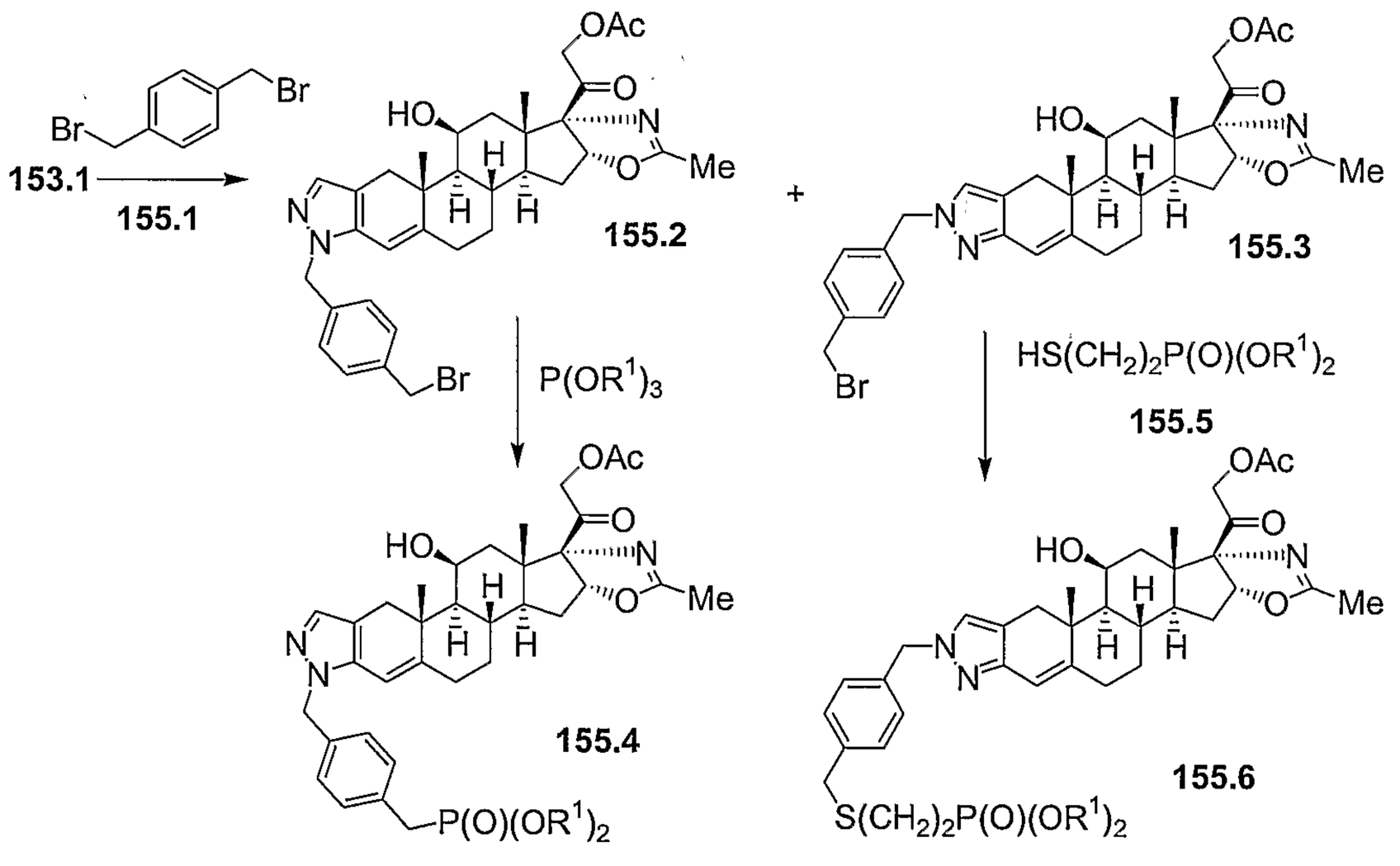
The ketoaldehyde, **150.2**, is reacted with hydrazine to afford the pyrazole derivative, **153.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound **153.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products, **153.3** and **153.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry* 309 (Longman, **1992**). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **153.3** and **153.4**, are, except in cases where X is dialkylphosphono, converted into the phosphonates, **153.5** and **153.6**, using the procedures described herein.

Example 154



The pyrazole, **153.1**, is reacted in dimethylformamide solution at 70°C with one molar equivalent of a dialkyl bromopropyl phosphonate, **154.1**, (Synthelec) and cesium carbonate, to give the pyrazoles, **154.2** and **154.3**.

Example 155



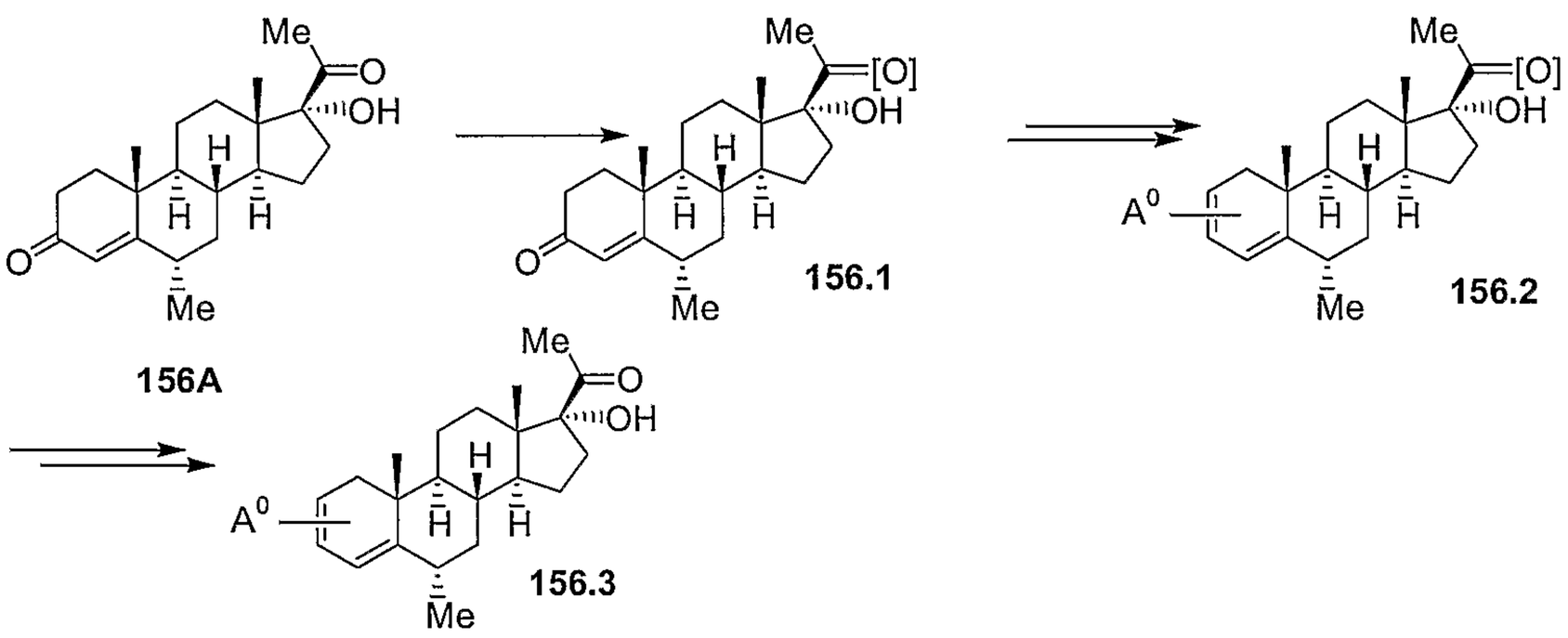
The pyrazole, **153.1**, is reacted in tetrahydrofuran solution with 1,4-bis(bromomethyl)benzene, **155.1**, and potassium hexamethyl disilazide, to give the alkylation products, **155.2** and **155.3**. The 2'-substituted isomer, **155.2**, is then reacted, in an Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate, **155.4**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115. In this procedure, in which a bromo substituent is converted into the corresponding phosphonate, the substrate is

heated at from about 60°C to about 160°C with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole, **155.3**, is reacted at 70°C in dimethyl-formamide solution with one molar equivalent of a dialkyl mercaptoethyl phosphonate, **155.5**, (*Zh. Obschei. Khim.*, **1973**, *43*, 2364) and cesium carbonate, to give the thioether phosphonate, **155.6**.

Using the above procedures, but employing different dibromides, and/or different mercapto-substituted phosphonates, products analogous to **155.4** and **155.6** are obtained.

Example 156



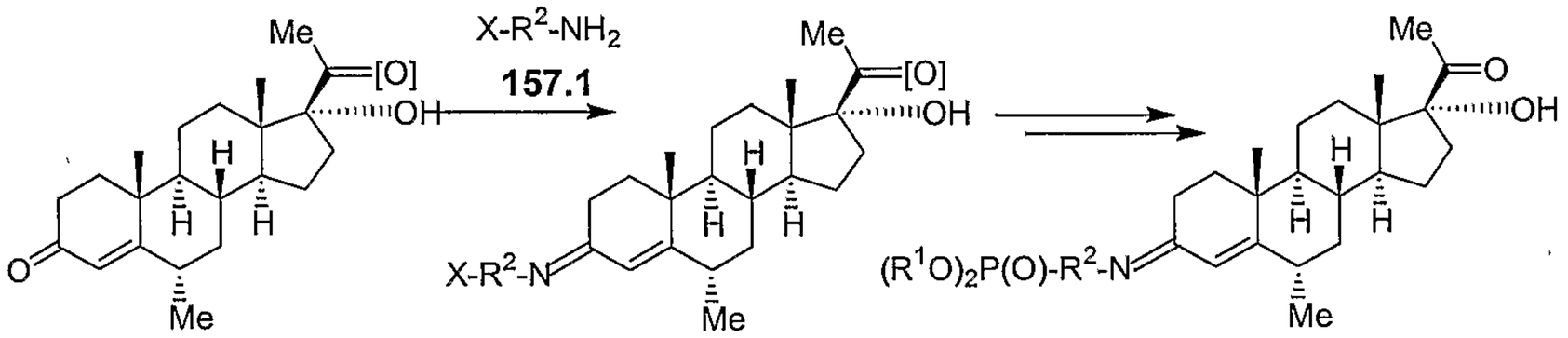
Medroxyprogesterone, **156A**, (U.S. Patent Nos. 3,043,832, 3,061,616, and 3,377,364) is protected to afford the derivative, **156.1**. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, **1955**, *77*, 1904. Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in as described in *J. Chem. Soc. Chem. Comm.*, **1987**, 1351.

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone, **156A**, with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.*, **1970**, *50*, 102. The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, **1979**, *101*, 5841.

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate, **156A**, is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc. Chem. Comm.*, **1983**, 406, to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The protected compound, **156.1**, is then converted into the phosphonate-containing analog, **156.2**, using the procedures described below, and the protecting group or groups are then removed, as described above, to give the phosphonate, **156.3**.

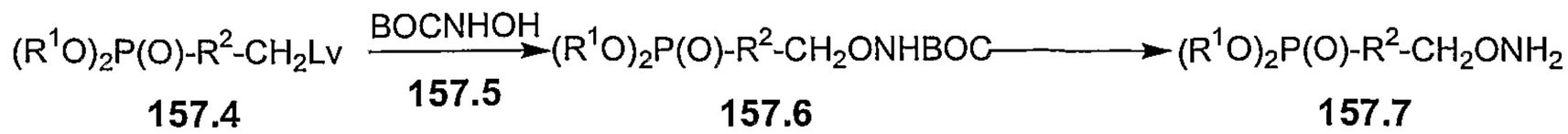
Example 157



156.1 **157.2** **157.3**

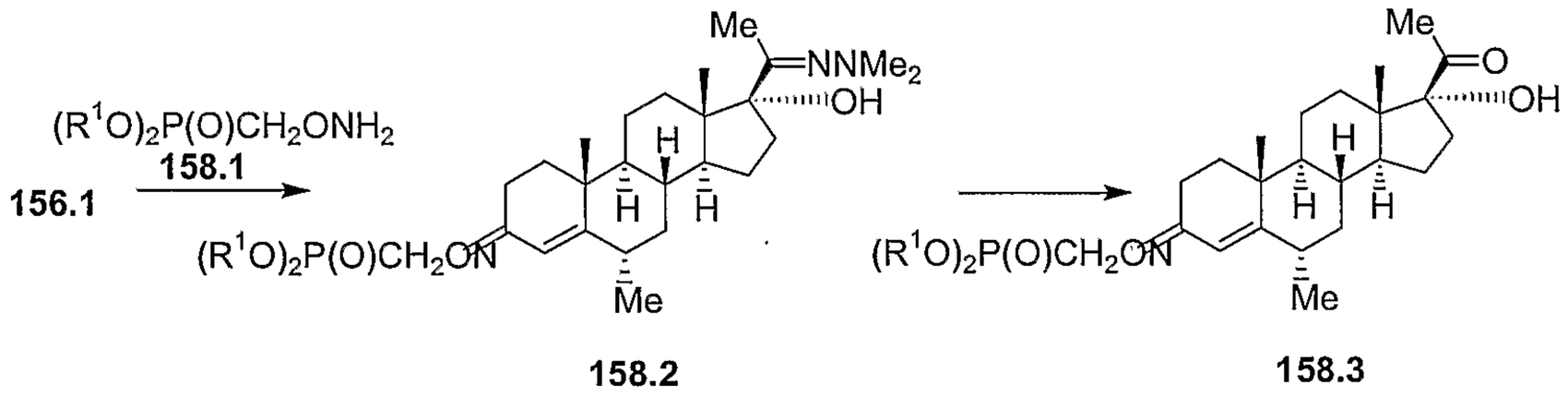
The ketone-protected derivative, **156.1**, is reacted with a hydroxylamine or amine, **157.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone, etc., or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the oxime, **157.2**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.* **1978**, *86*, 133 and in *J. Mass. Spectrom.* **1995**, *30*, 497. The protecting group is then removed, as described in Example **156**, to afford the 20-keto phosphonate product, **157.3**.

Example 157A



The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated herein. A phosphonate, **157.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **157.5**, (Aldrich) to produce the ether, **157.6**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **157.7**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.

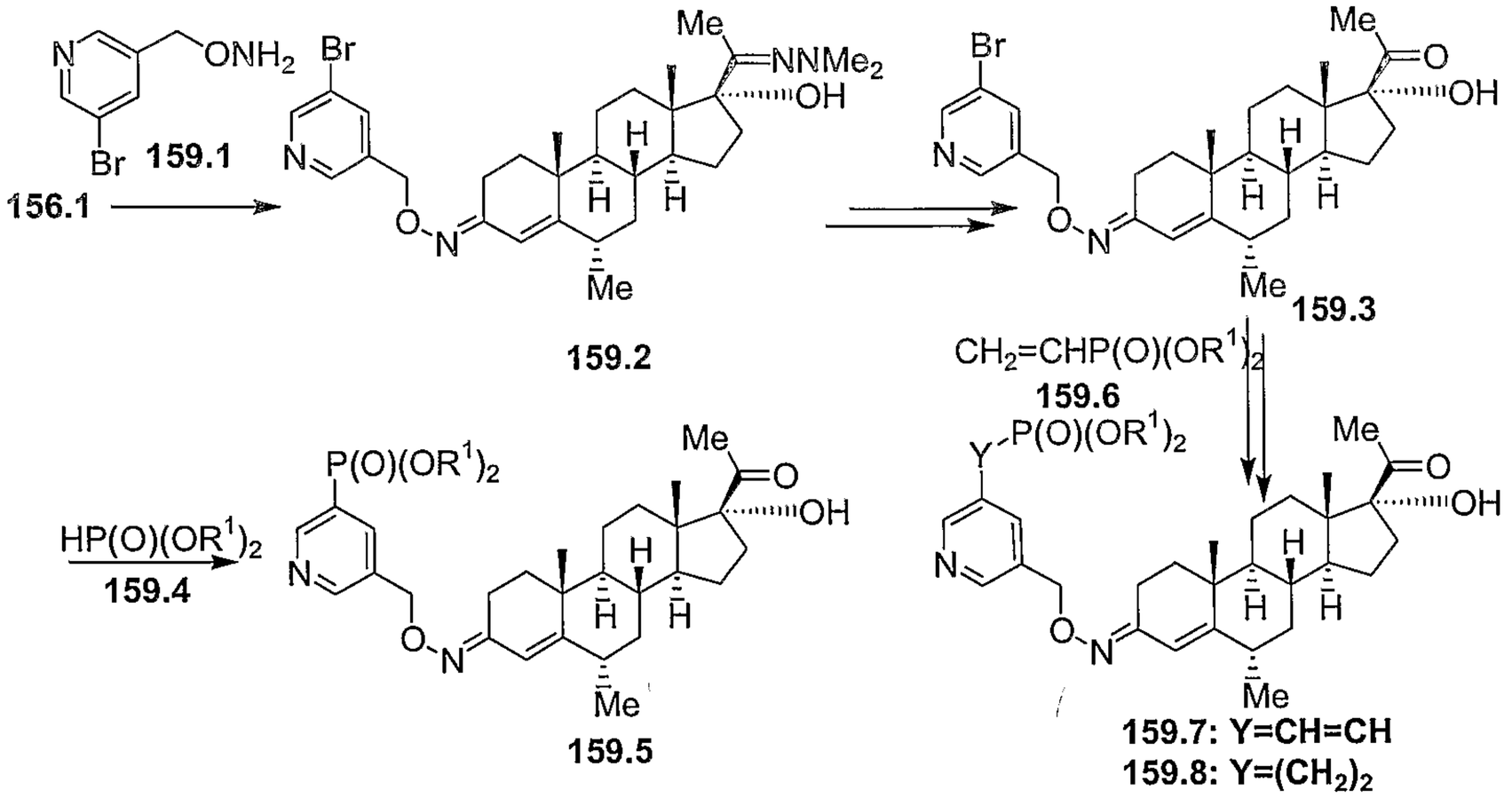
Example 158



The preparation of phosphonates, in which the phosphonate is attached by means of an iminoxy group is illustrated herein. In this procedure, the substrate, **156.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine, **158.1**, prepared as described above from a dialkyl trifluoromethylsulfonyloxymethyl phosphonate (*Tetrahedron Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **158.2**. Deprotection, as described in Example **156**, then affords the 20-keto phosphonate, **158.3**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **158.1**, different oxime ethers, **157.1**, the corresponding products, **157.3** are obtained.

Example 159



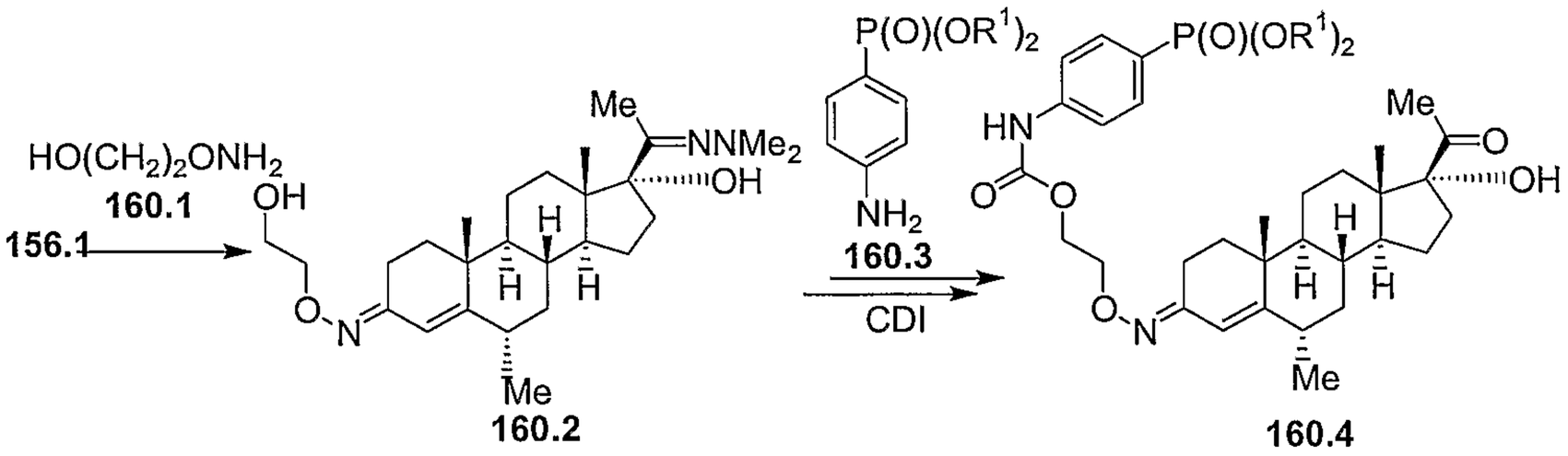
The dienone, **156.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(5-bromo-3-pyridylmethoxy)-hydroxylamine, **159.1**, prepared as described above from 5-bromo-3-bromo-methylpyridine (WO 95/28400) and BOC-protected hydroxylamine, **157.5**, to give the oxime, **159.2**. The protecting group is then removed to yield the 20-keto product, **159.3**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **159.4**, to afford the phosphonate, **159.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound, **159.3**, is coupled with a dialkyl vinylphosphonate, **159.6**, (Aldrich) to afford the phosphonate, **159.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry* 503ff (Plenum, **2001**) and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide

and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenyl-phosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **159.7**, is reduced, for example by reaction with diimide, to produce the saturated analog, **159.8**. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations* 6ff (VCH **1989**). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromopyridyl reagent, **159.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, products analogous to the compounds, **159.5**, **159.7** and **159.8** are obtained.

Example 160

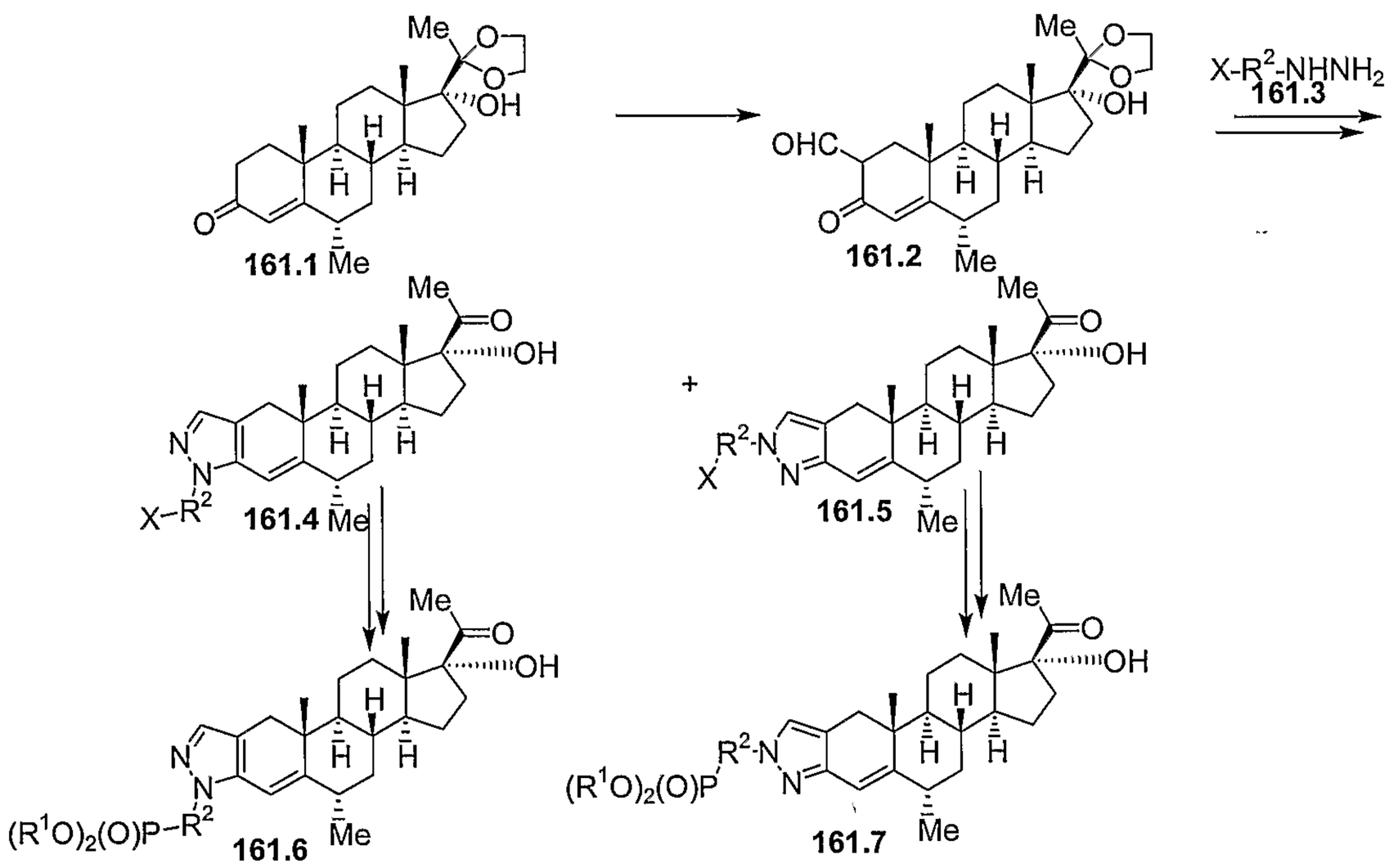


The dienone, **156.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with 2-hydroxyethyl hydroxylamine, **160.1**, (*J. Chem. Soc. Chem. Comm.*, **1986**, 903) to yield the oxime, **160.2**. The reaction of unsaturated steroidal ketones with hydroxylamines is described in *J. Steroid Bioch.* **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product, **160.2**, is then coupled with a dialkyl 4-aminophenyl phosphonate, **160.3**, (Epsilon) and carbonyl diimidazole, to yield, after deprotection, the carbamate oxime, **160.4**. The preparation of carbamates is described in *Comprehensive Organic*

Functional Group Transformations, *Vol. 6*, 416ff (A. R. Katritzky, ed., Pergamon, **1995**) and in S. R. Sandler and W. Karo, *Organic Functional Group Preparations* 260ff (Academic Press, **1986**). In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

Using the above procedures, but employing, in place of the hydroxy-substituted hydroxylamine, **160.1**, different hydroxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to **160.4** are obtained.

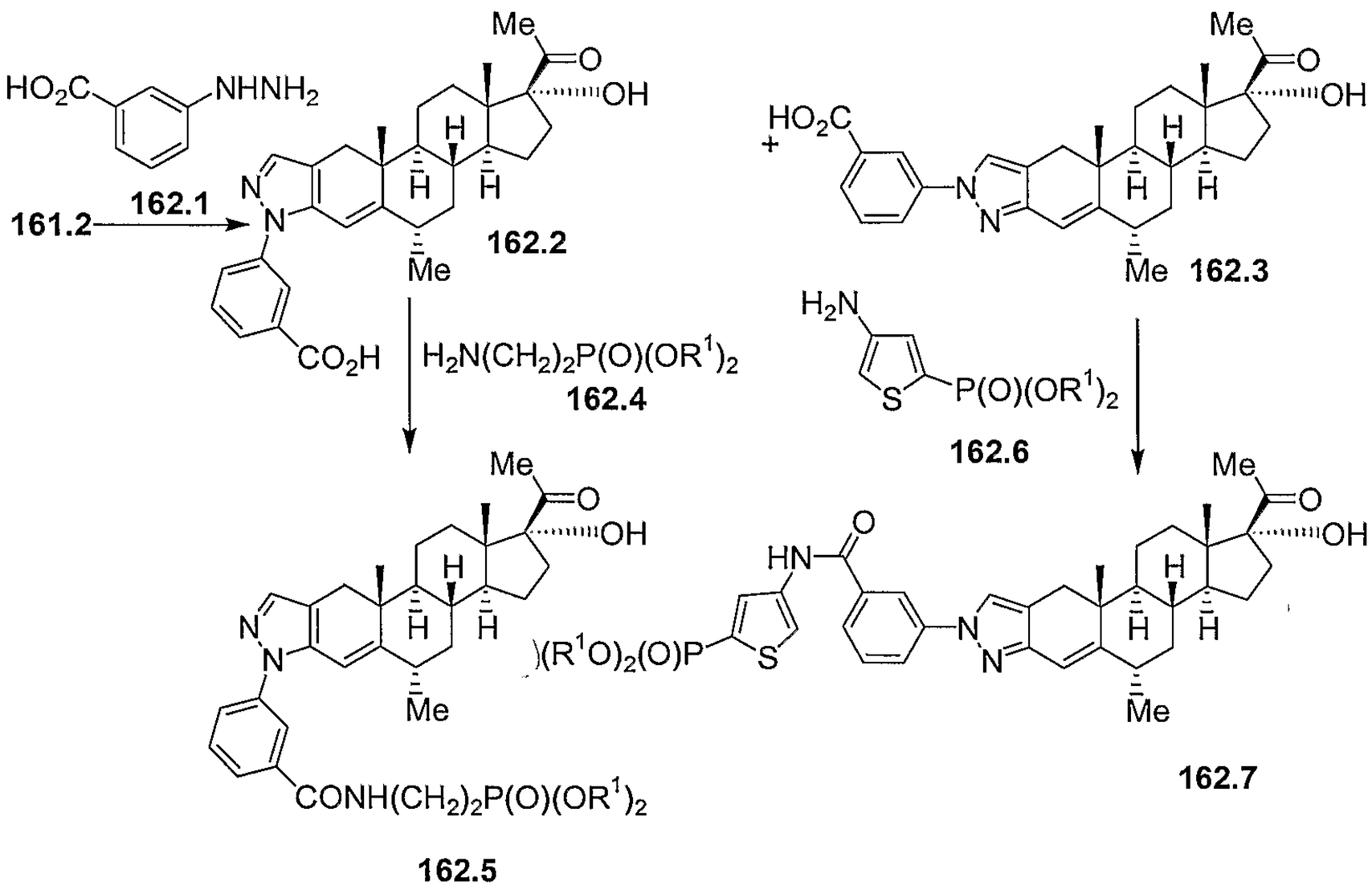
Example 161



The enone, **161.1**, in which the 20-ketone is protected as the cyclic ethylene ketal, is reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.* 86:1520 (1964), to afford the 2-formyl product, **161.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **161.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For

example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields, after deprotection of the 20-ketone, the isomeric 2'- and 1'-aryl pyrazoles, **161.4** and **161.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **161.4** and **161.5**, are then transformed, for example by the procedures described herein, into the phosphonates, **161.6** and **161.7**.

Example 162



The ketoaldehyde, **161.2**, is reacted, as described above, with 3-carboxyphenyl hydrazine, **162.1**, (Apin) to give the pyrazoles, **162.2** and **162.3**. The 2'-substituted isomer, **162.2**, is then reacted in dimethylformamide solution at ambient temperature with one molar equivalent of a dialkyl 2-aminoethyl phosphonate, **162.4**, (Aldrich) and dicyclohexyl carbodiimide, to give the amide phosphonate, **162.5**. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R. Sandler and W. Karo, *Organic Functional Group Preparations* 274 (Academic Press, **1968**) and R. C. Larock, *Comprehensive Organic Transformations* 972ff (VCH, **1989**). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-

hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

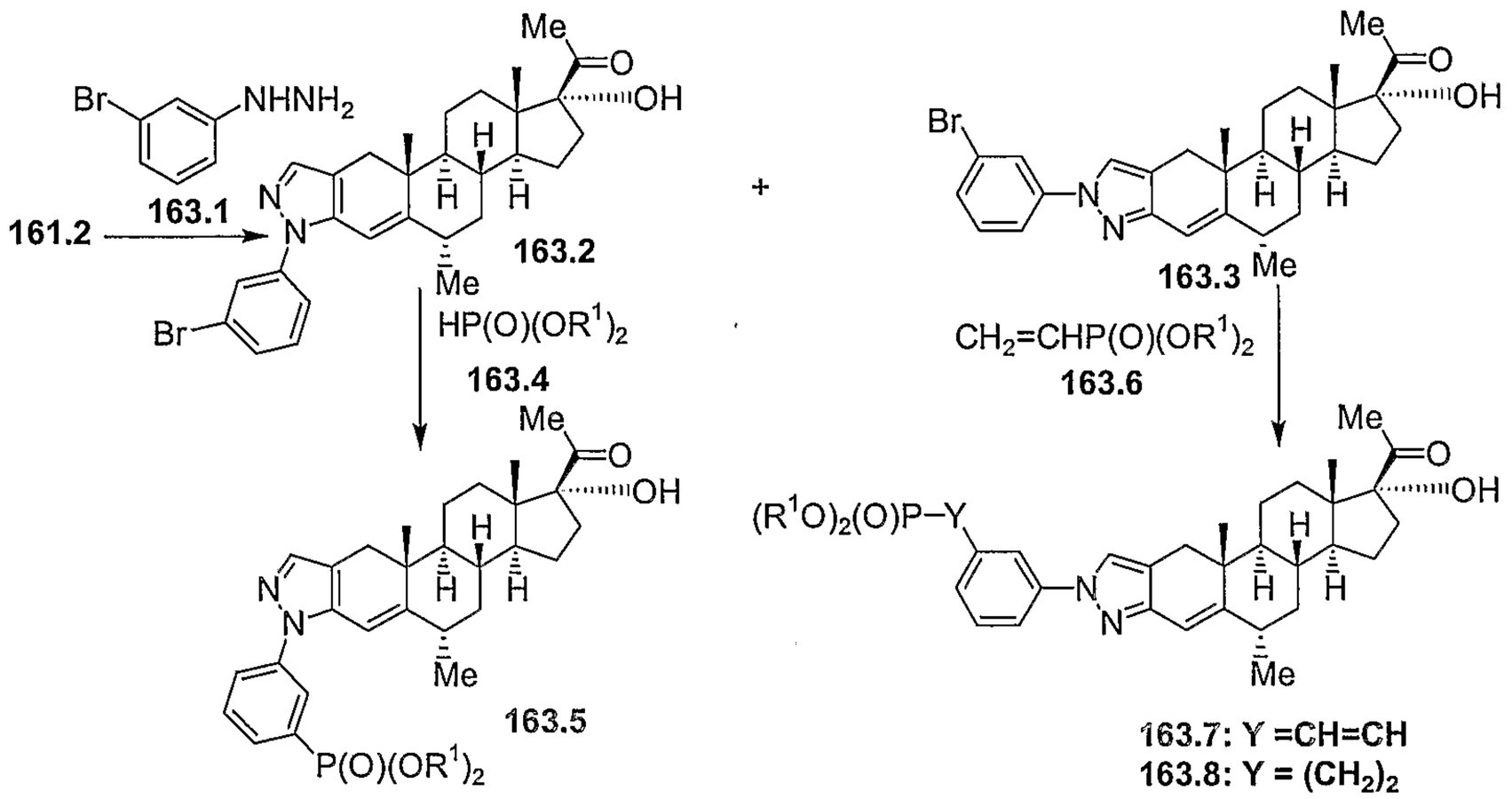
Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

The isomeric pyrazole, **162.3**, is reacted, as described above, with one molar equivalent of a dialkyl 4-amino-2-thienyl phosphonate, **162.6**, prepared by the palladium catalyzed coupling reaction, as described above, between 4-amino-2-bromothiophene (*Tetrahedron Lett.*, **1987**, *43*, 3295) and a dialkyl phosphite, to give the amide phosphonate, **162.7**.

Using the above procedures, but employing different carboxy-substituted hydrazines, and/or different amino-substituted phosphonates, the products analogous to **162.5** and **162.7** are obtained.

Example 163

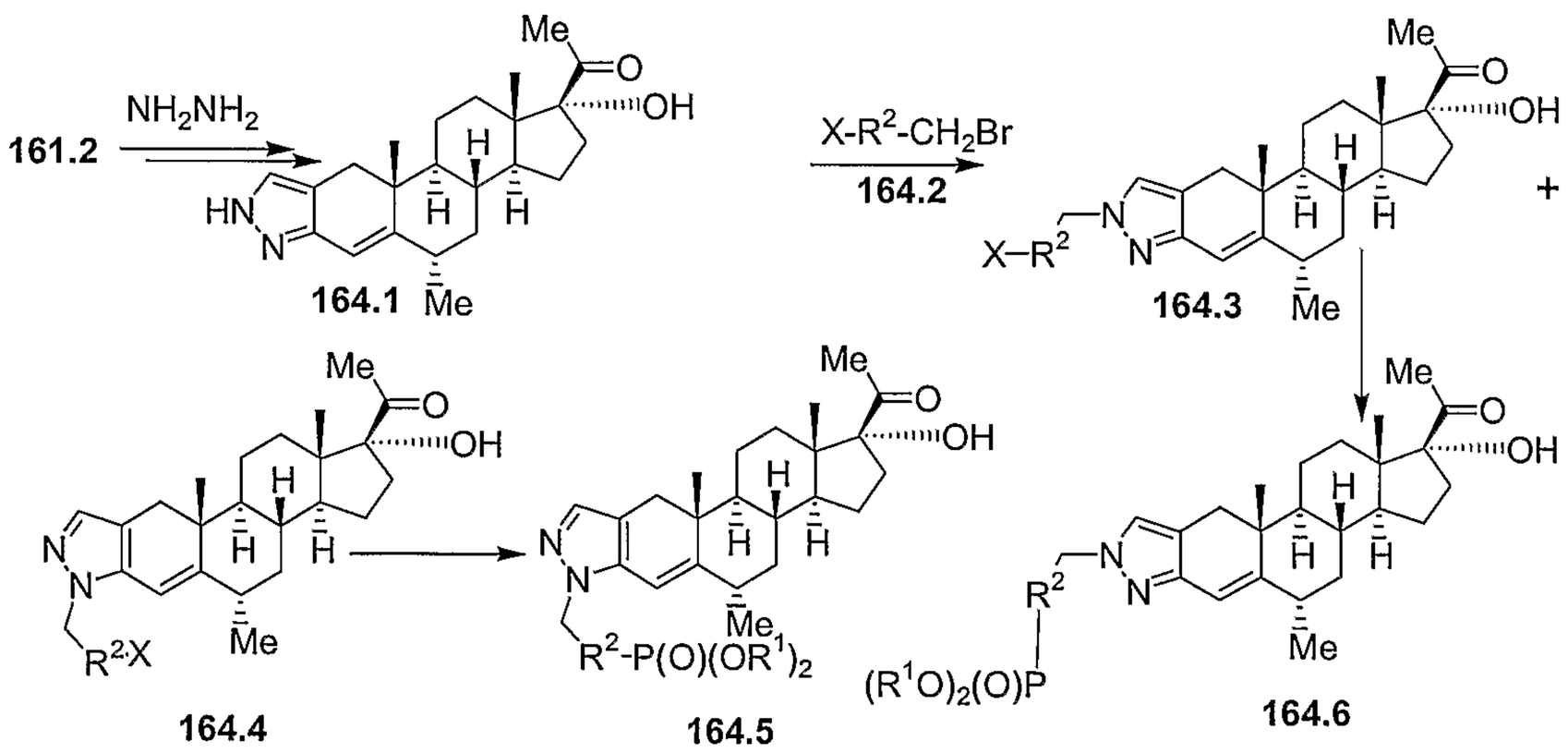


The ketoaldehyde, **161.2**, is reacted, as described above, with 3-bromophenyl hydrazine, **163.1**, (Fluka) to produce the pyrazoles, **163.2** and **163.3**. The 2'-substituted isomer, **163.2**, is then coupled, as described above, with a dialkyl phosphite, **163.4**, to afford the phosphonate, **163.5**.

Alternatively, the 1'-substituted pyrazole, **163.3**, is coupled, as described above, with a dialkyl vinylphosphonate, **163.6**, (Aldrich) and a palladium catalyst to prepare the vinyl phosphonate, **163.7**. Optionally, the product is reduced, as described above, to give the analog, **163.8**.

Using the above procedures, but employing, in place of the bromophenyl hydrazine, **163.1**, different bromo-substituted hydrazines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **163.5** and **163.7, 163.8** are obtained.

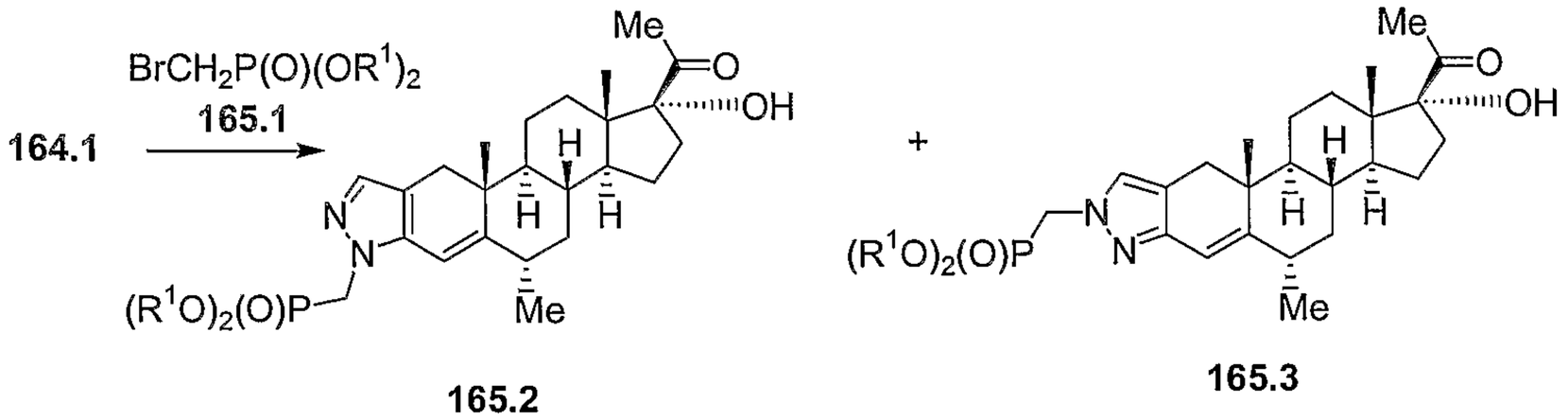
Example 164



The ketoaldehyde, **161.2**, is reacted with hydrazine to afford, after deprotection of the 20-ketone, the pyrazole derivative, **164.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **164.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products, **164.3** and **164.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry*, 309 (Longman, **1992**). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or

tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **164.3** and **164.4**, are, except in cases where X is dialkylphosphono, converted into the phosphonates, **164.5** and **164.6**, using the procedures described herein.

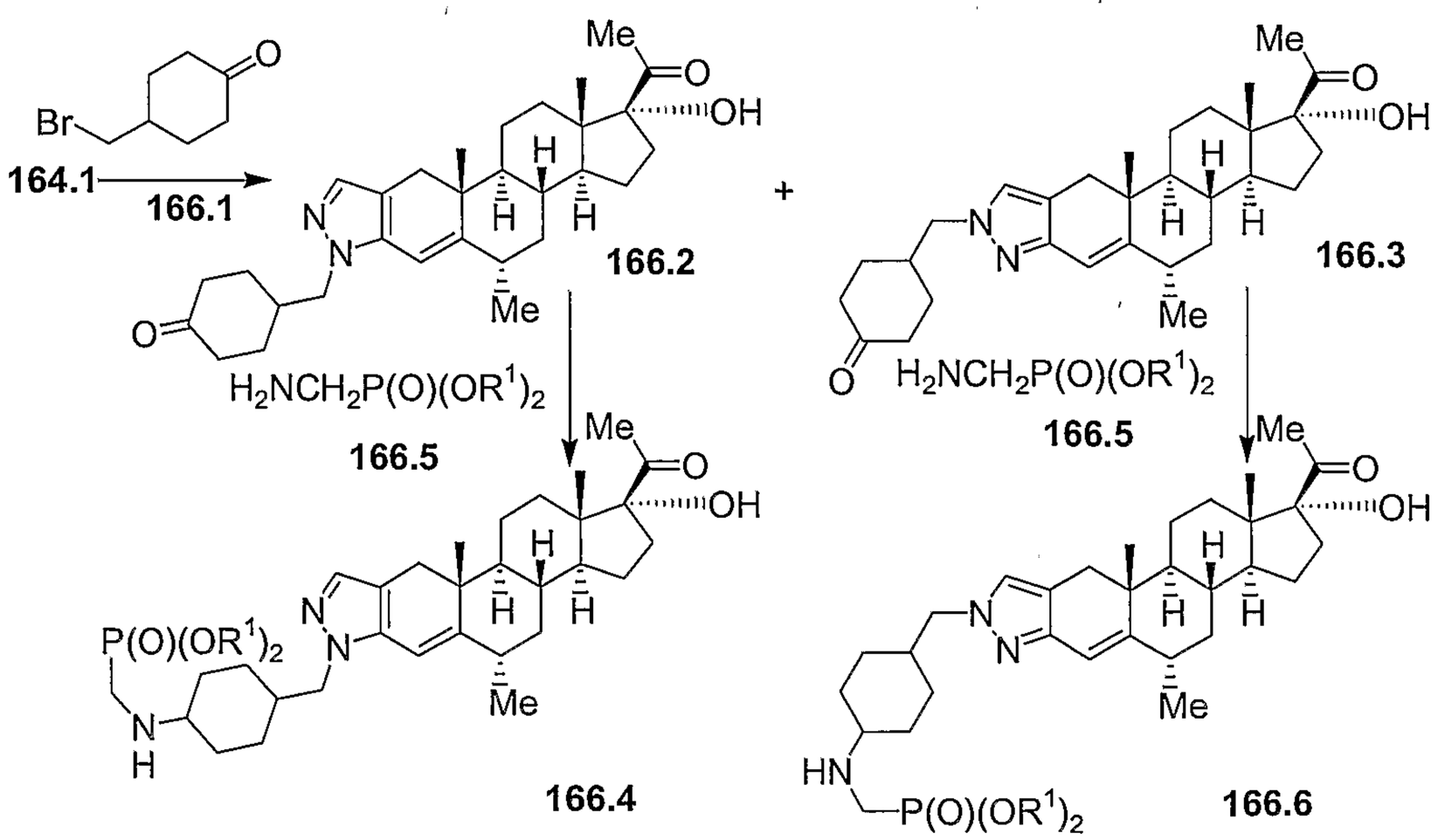
Example 165



The pyrazole, **164.1**, is reacted in dimethylformamide solution at 70°C with one molar equivalent of a dialkyl 4-bromomethyl phosphonate, **165.1**, (Lancaster) and lithium hexamethyl disilazide, to give the pyrazoles, **165.2** and **165.3**.

Using the above procedures, but employing different bromo-substituted phosphonates, the products analogous to **165.2** and **165.3** are obtained.

Example 166

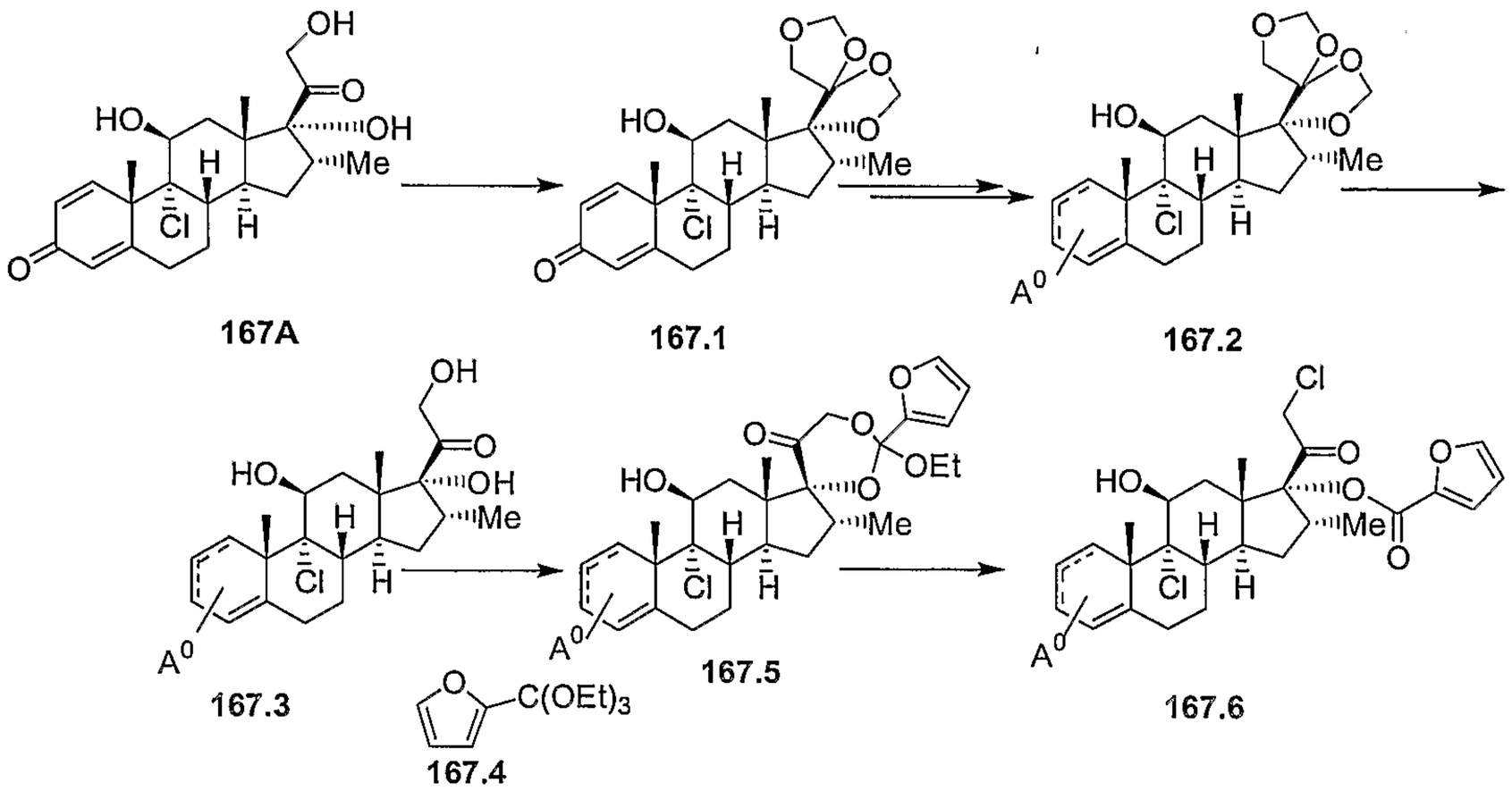


The pyrazole, **164.1**, is reacted in tetrahydrofuran solution with 4-bromomethyl cyclohexanone, **166.1**, (WO 97/37959) and potassium hexamethyl disilazide, to give the alkylation products, **166.2** and **166.3**. The 2'-substituted isomer, **166.2**, is then reacted, in a reductive amination reaction, with a dialkyl aminomethyl phosphonate, **166.5**, (Interchim) and sodium triacetoxy borohydride, to yield the amine phosphonate, **166.4**. The preparation of amines by means of reductive amination procedures is described, for example, in R. C. Larock, *Comprehensive Organic Transformations* 421 (VCH) and in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Part B, 269 (Plenum, **2001**). In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, **1990**, *55*, 2552.

The 1'-substituted pyrazole, **166.3**, is converted by the same reaction into the isomeric amine phosphonate, **166.6**.

Using the above procedures, but employing different bromo-substituted aldehydes and ketones, and/or different amino-substituted phosphonates, products analogous to **166.4** and **166.6** are obtained.

Example 167

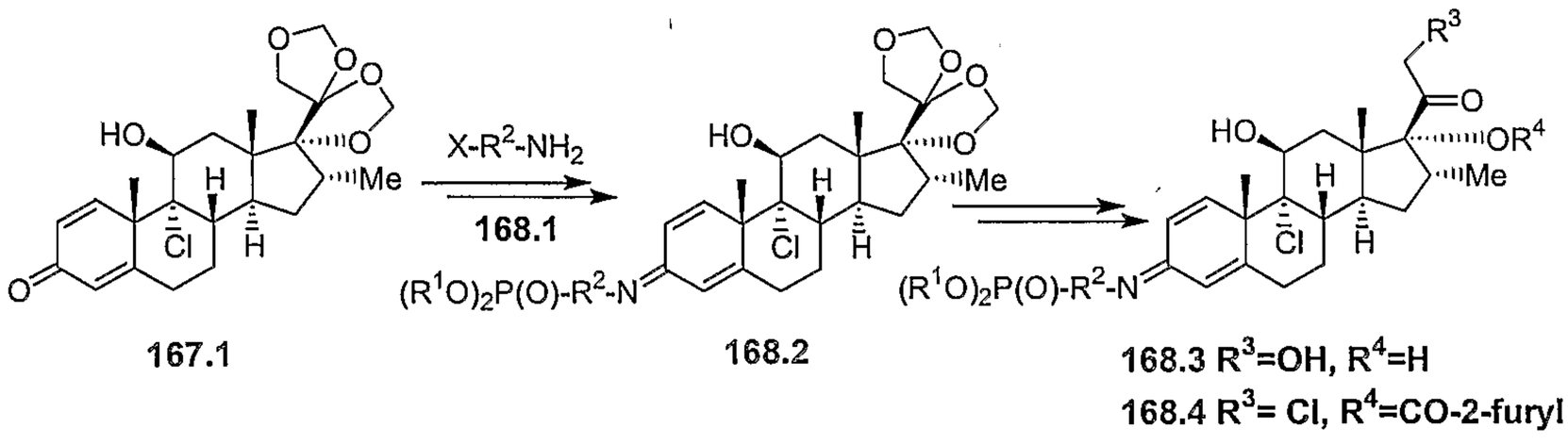


9α-Chloro-16α-methyl-11β,17α,21-trihydroxypregn-1,4-dien-3,21-dione, **167A**, (U.S. Patent No. 4,472,393) is reacted with paraformaldehyde and an acid

catalyst such as hydrochloric acid, as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to yield the BMD derivative, **167.1**. The phosphonate moiety is then introduced, using the procedures described below, to produce the phosphonate ester, **167.2**. The BMD moiety is then hydrolyzed, for example by treatment with 50% aqueous acetic acid, as described in *Protective Groups in Organic Synthesis*, by T.W. Greene and P.G.M. Wuts, Wiley, Second Edition **1990**, p. 223, to afford the triol, **167.3**. The latter compound is then converted into the 17,21-cyclic orthoester, **167.5**, using the procedure described in *Chem. Pharm. Bull.*, **1986**, *34*, 1613. The substrate is reacted in dimethylformamide at 70°C with two molar equivalents of triethyl ortho-2-furoate, **165.4**, (*Zh. Org. Khim.*, **1980**, *50*, 1348) and a catalytic amount of p-toluenesulfonic acid. The product is then reacted with an excess of trimethylsilyl chloride in dimethylformamide at ambient temperature to produce the 21-chloro 17-(2-furoate) product, **167.6**.

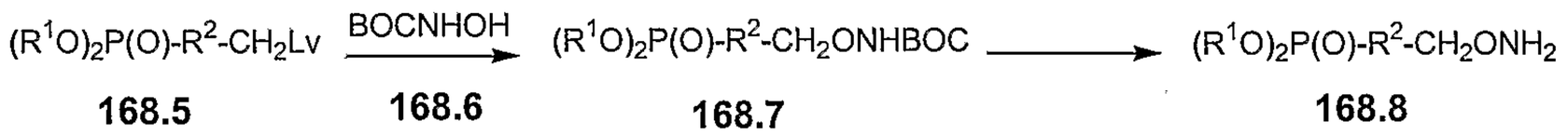
Alternatively, the substrate, **167.3**, is converted into the product, **167.6**, by means of the method described in *J. Med. Chem.*, **1987**, *30*, 1581. In this procedure, the 21-hydroxy group is activated by conversion to the 21-mesylate, by reaction with mesyl chloride in pyridine; the mesylate group is then displaced to yield the 21-chloro intermediate, by reaction with lithium chloride in dimethylformamide, and the 17-hydroxyl group is esterified to give the 21-chloro-17-(2-furoate) derivative, **167.6**. The selective acylation of the 17α-hydroxyl group in the presence of an 11β hydroxyl group is described in *J. Med. Chem.*, **1987**, *30*, 1581.

Example 168



The BMD-protected derivative, **167.1**, is reacted with an amine or hydroxylamine, **168.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or

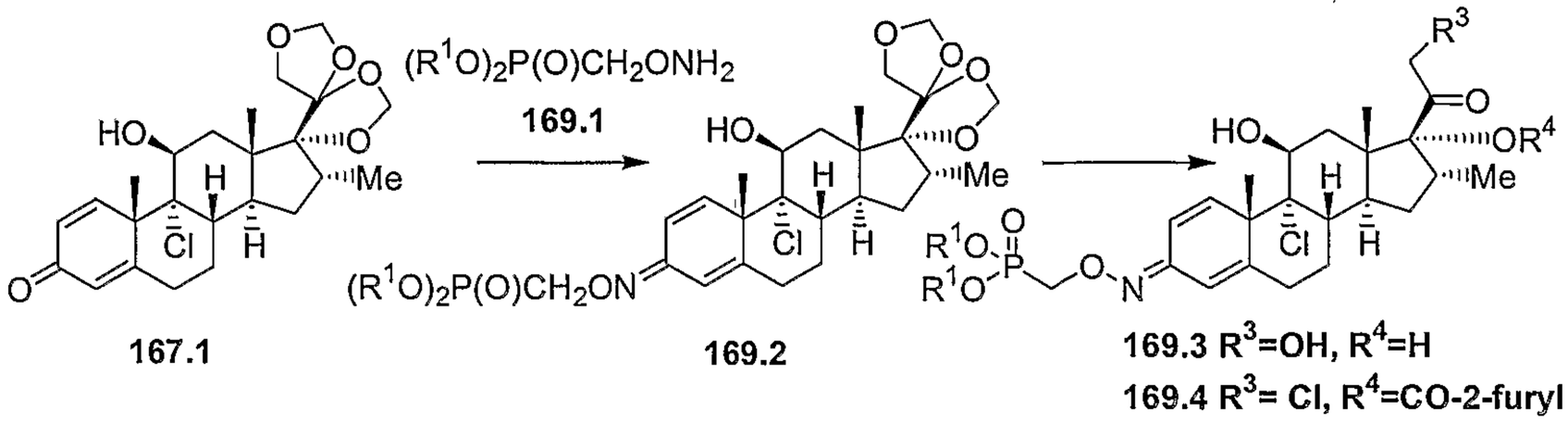
cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The BMD-protected side-chain compound, **168.2**, is then converted into the triol, **168.3**, and then to the 21-chloro 17-(2-furoate) product, **168.4**, as described herein.



168.5 **168.6** **168.7** **168.8**

The preparation of hydroxylamine ethers incorporating a phosphonate group is illustrated herein. In this procedure, a phosphonate, **168.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **168.6**, (Aldrich) to produce the ether, **168.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **168.8**.

Example 169



167.1 **169.2**

169.3 R^3=OH, R^4=H

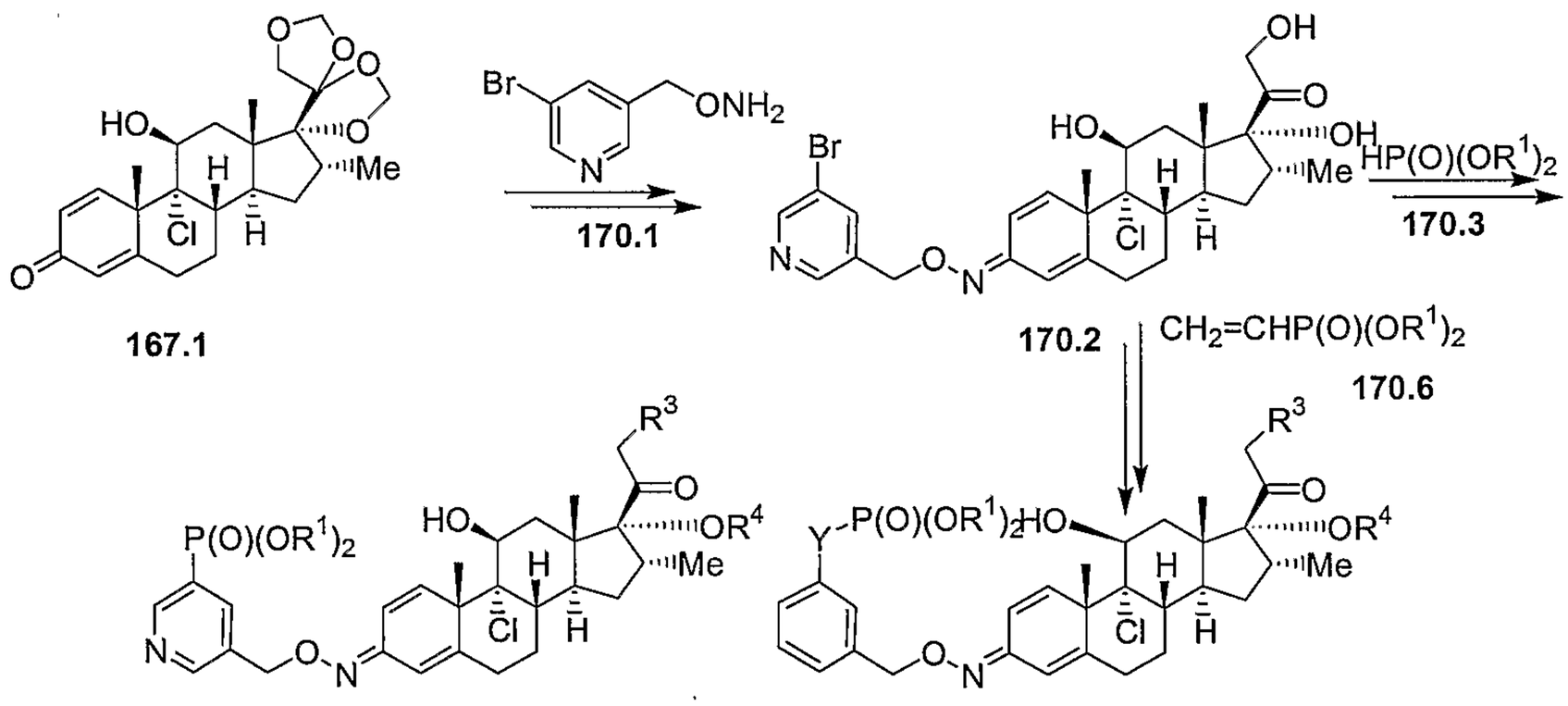
169.4 R^3= Cl, R^4=CO-2-furyl

The substrate, **167.1**, is reacted with a dialkyl phosphonomethyl hydroxylamine, **169.1**, prepared as described above from a dialkyl

trifluoromethylsulfonyloxymethyl phosphonate (*Tet. Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **169.2**. Deprotection then affords the triol, **169.3**, from which the 21-chloro 17-(2-furoate) compound, **169.4**, is prepared, using the procedures described in Example **167**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **169.1**, different oxime ethers, **167.1**, the corresponding products, **169.4** are obtained.

Example 170



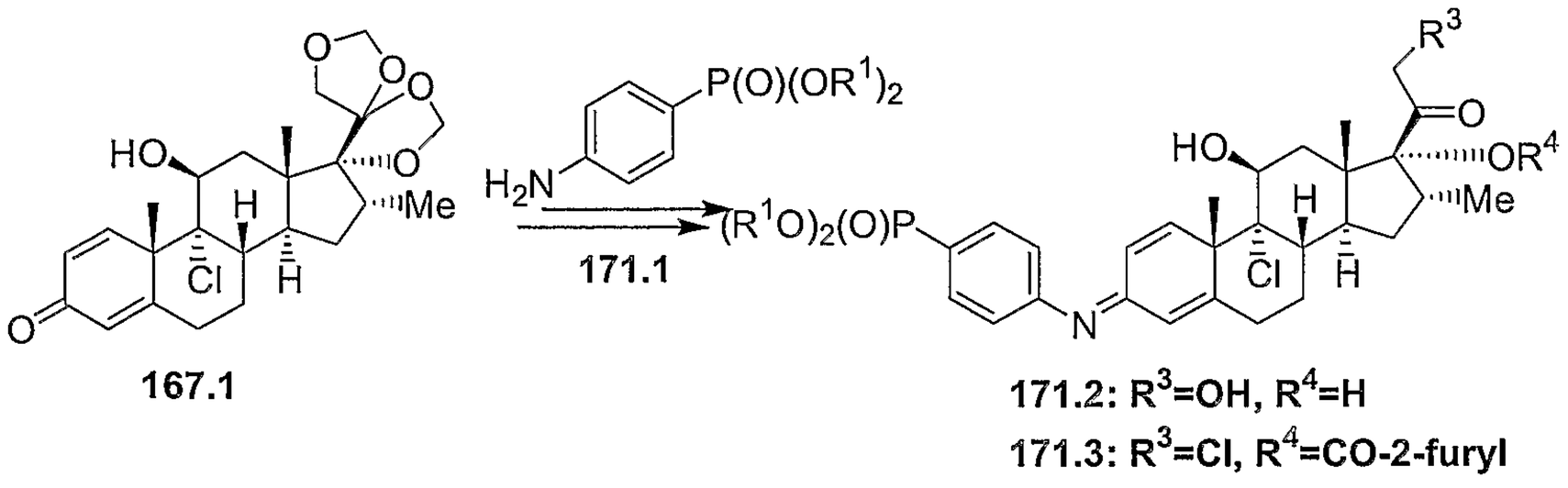
The dienone, **167.1**, is reacted, as described above, with O-(5-bromo-3-pyridylmethoxy)hydroxylamine, **170.1**, prepared as described above from 5-bromo-3-bromomethylpyridine (EP 511865) and BOC-protected hydroxylamine, **168.6**, to give, after deprotection of the side-chain, the oxime, **170.2**. The product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **170.3**, to afford the phosphonate, **170.4**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenyl-

phosphine)palladium(0). The 21-hydroxy compound, **170.4**, is then converted, as described in Example **167**, into the 21-chloro 17-(2-furoate) derivative, **170.5**.

Alternatively, the bromo compound, **170.2**, is coupled with a dialkyl vinyl phosphonate, **170.6**, (Aldrich) to afford the phosphonate, **170.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, 503ff (Plenum, **2001**) and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenyl-phosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the double bond present in the product, **170.7**, is reduced, for example by reaction with diimide, to produce the saturated analog, **170.9**. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations*, 6ff (VCH, **1989**). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane. The products, **170.7** and **170.9**, are then converted into the 21-chloro 17-(2-furoate) analogs, **170.8** and **170.10**.

Using the above procedures, but employing, in place of the bromopyridylmethoxy reagent, **170.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **170.5**, **170.8** and **170.10** are obtained.

Example 171



167.1

171.1

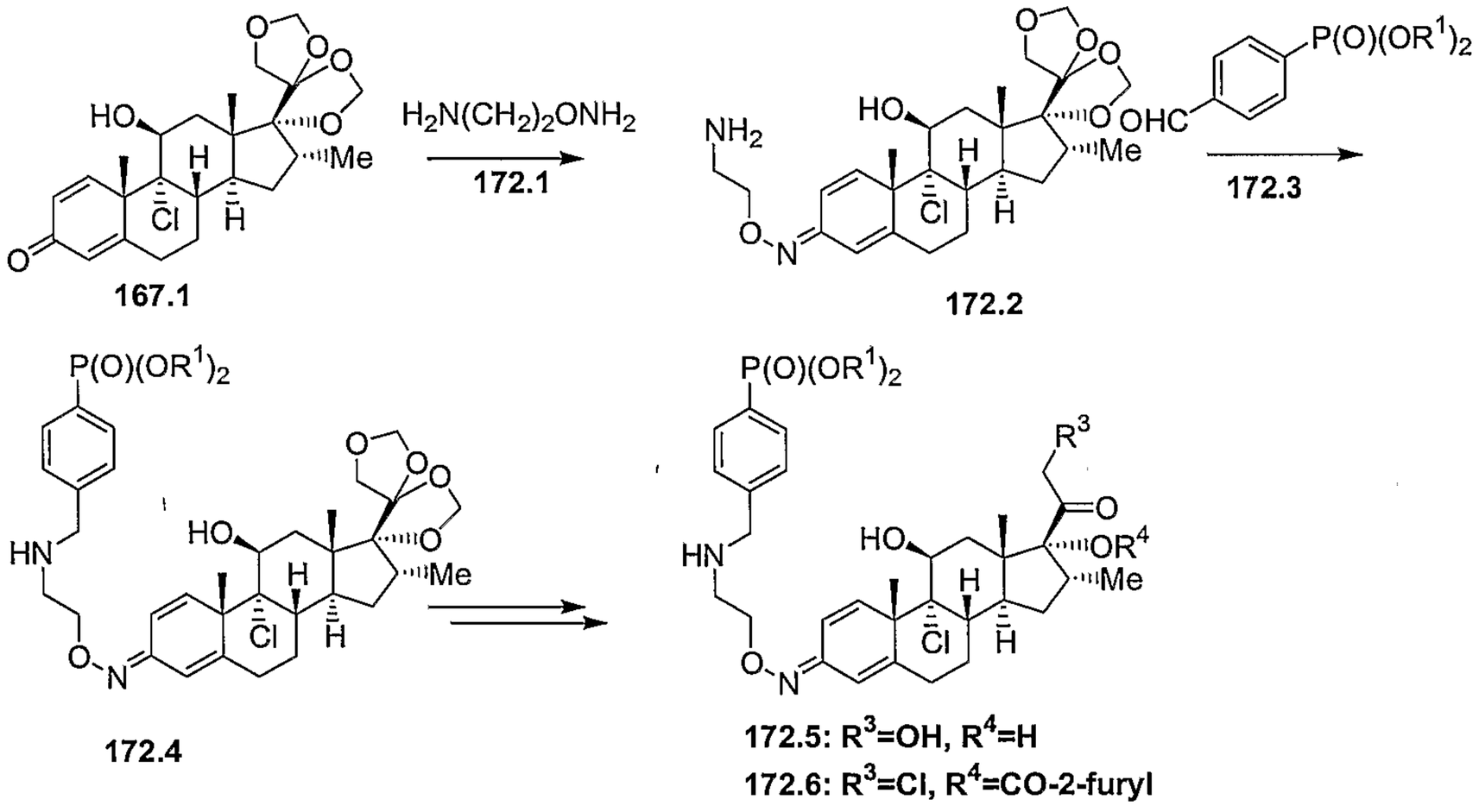
171.2: R^3=OH, R^4=H

171.3: R^3=Cl, R^4=CO-2-furyl

The preparation of phosphonates in which the phosphonate is attached by means of an imino group is illustrated herein. In this procedure, the substrate, **167.1**, is reacted with a dialkyl 4-aminophenyl phosphonate, **171.1**, (Epsilon) to give, after deprotection, the imine product, **171.2**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions. The product is then converted into the 21-chloro 17-(2-furoate) compound, **171.3**.

Using the above procedures, but employing, in place of the 4-aminophenyl phosphonate, **171.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **171.3** are obtained.

Example 172



167.1 **172.2** **172.4**

172.5: R^3=OH, R^4=H
172.6: R^3=Cl, R^4=CO-2-furyl

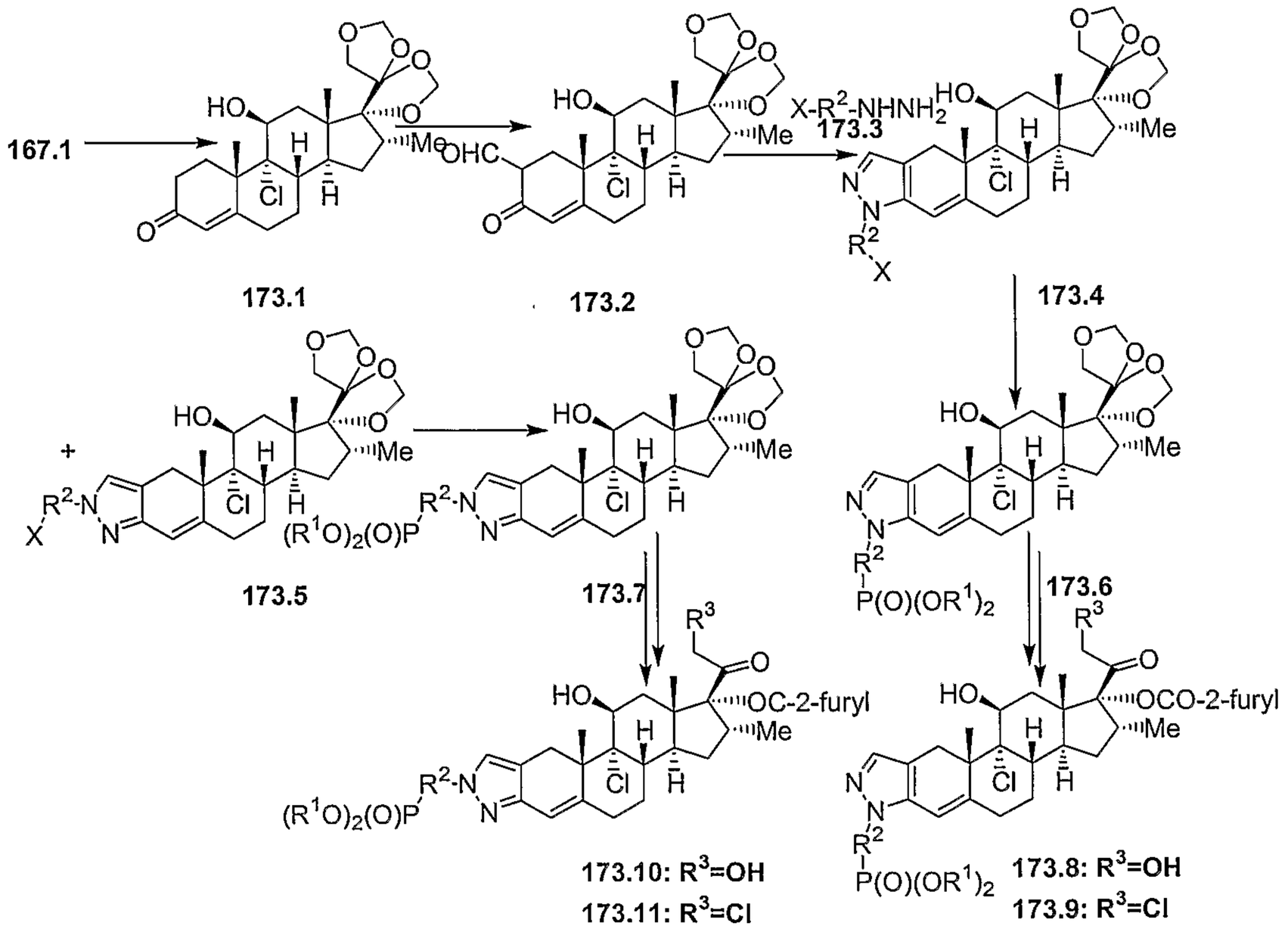
The dienone, **167.1**, is reacted with O-(2-aminoethyl)hydroxylamine, **172.1**, (*Pol. J. Chem.*, **1981**, *55*, 1163) to yield the oxime, **172.2**. The reaction of steroidal 1,4-dien-3-ones with substituted hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product is then reacted, in a reductive amination procedure, with a dialkyl 4-formylphenyl phosphonate, **172.3**, (Epsilon) and sodium triacetoxyborohydride, to yield the

amine oxime **172.4**. The preparation of amines by means of reductive amination procedures is described, for example, in R. C. Larock, *Comprehensive Organic Transformations*, 421 (VCH), and in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Part B, 269 (Plenum, **2001**). In this procedure, the amine component and the aldehyde or ketone component are reacted together in the presence of a reducing agent such as, for example, borane, sodium cyanoborohydride, sodium triacetoxyborohydride or diisobutylaluminum hydride, optionally in the presence of a Lewis acid, such as titanium tetraisopropoxide, as described in *J. Org. Chem.*, **1990**, *55*, 2552.

The amine product, **172.4**, is then converted, as described herein, into the 21-chloro 17-(2-furoate) product, **171.6**.

Using the above procedures, but employing, in place of the hydroxylamine, **172.3**, different amino-substituted hydroxylamines, and/or different formyl-substituted phosphonates, the products analogous to **177.6** are obtained.

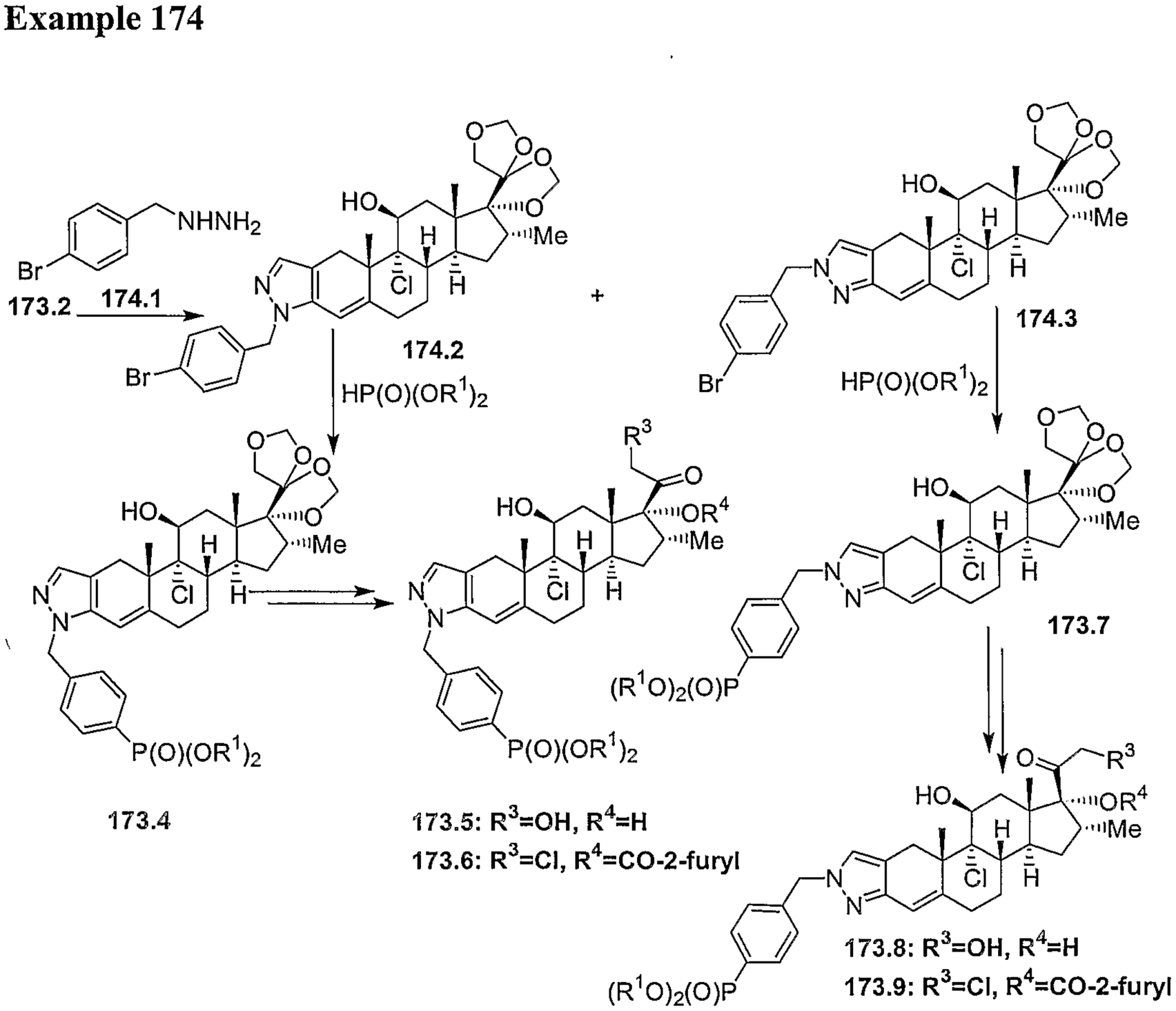
Example 173



The BMD-protected dienone, **167.1**, is reduced to afford the 1,2-dihydro product, **173.1**. The catalytic hydrogenation reaction is effected by the use of

tris(triphenylphosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, *44*, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **173.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **173.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **173.4** and **173.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **173.4** and **173.5**, are then transformed, for example by the procedures described herein, via the BMD-protected intermediates, **173.6** and **173.7**, into the 21-chloro 17-(2-furoate) phosphonates, **173.9** and **173.11**.

Example 174

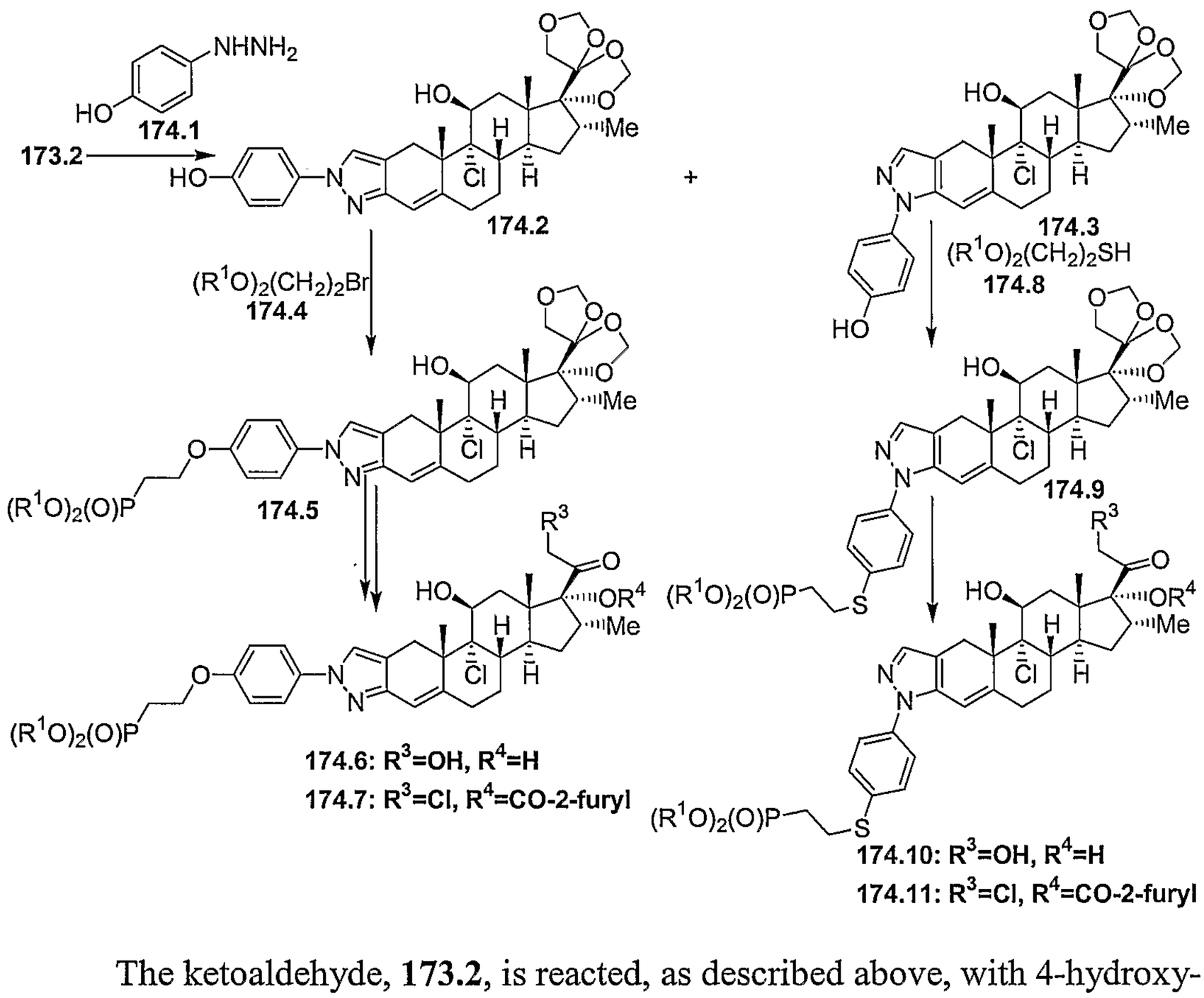


The ketoaldehyde, **173.2**, is reacted, as described above, with 4-bromo-benzyl hydrazine, **174.1**, (*Ann.*, **1968**, *717*, 104) to give the pyrazoles, **174.2** and **174.3**. The 2'-substituted isomer, **174.2**, is then coupled, as described in Example **170**, with a dialkyl phosphite, to yield the phosphonate, **173.4**. The BMD protecting group is then removed and the product is converted into the 21-chloro 17-(2-furoate) product, **173.6**.

The isomeric pyrazole, **174.3**, is subjected to the same series of reactions to afford the isomeric product, **173.9**.

Using the above procedures, but employing different bromo-substituted hydrazines, the products analogous to **173.6** and **173.9** are obtained.

Example 174



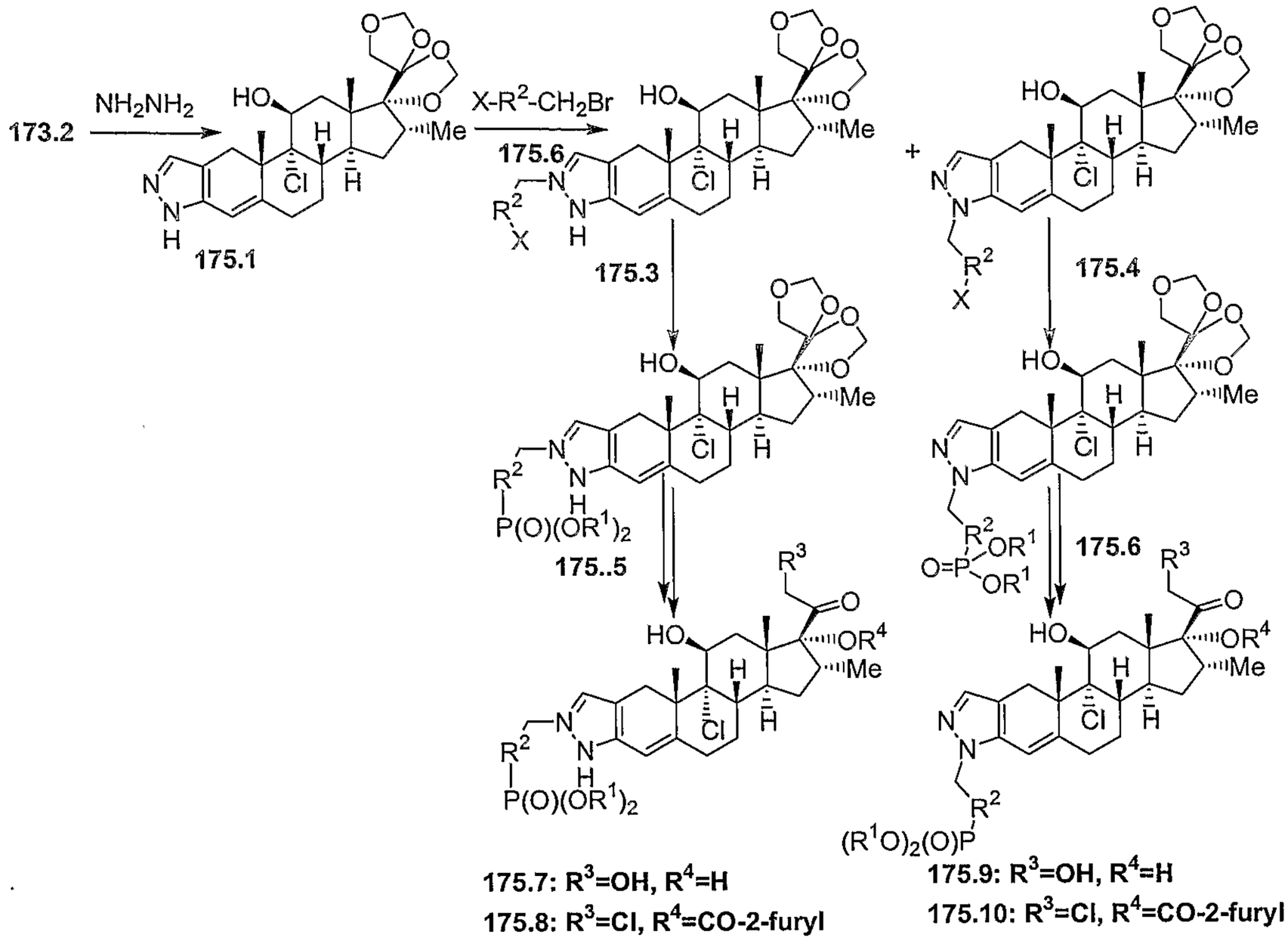
The ketoaldehyde, **173.2**, is reacted, as described above, with 4-hydroxy-phenyl hydrazine, **174.1**, (EP 437105) to produce the pyrazoles, **174.2** and **174.3**. The 1'-substituted isomer, **174.2**, is reacted in dimethylformamide at 70°C, with a dialkyl 2-bromoethyl phosphonate, **174.4**, (Aldrich) and potassium carbonate, to give the ether phosphonate, **174.5**. The product is then deprotected to afford

the triol, **174.6**, which is converted into the 21-chloro 17-(2-furoate) compound, **174.7**.

Alternatively, the 2'-substituted pyrazole, **174.3**, is coupled, in a Mitsonobu reaction, with a dialkyl 2-mercaptoethyl phosphonate, **174.8**, (*Zh. Obschei. Khim.*, **1973**, *43*, 2364) to prepare the thioether phosphonate, **174.9**, which is deprotected, and the product is converted into the 21-chloro 17-(2-furoate) analog, **174.11**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in R. C. Larock, *Comprehensive Organic Transformations*, 448 (VCH, **1989**), and in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Part B, 153-4 (Plenum, **2001**) and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triaryl-phosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656.

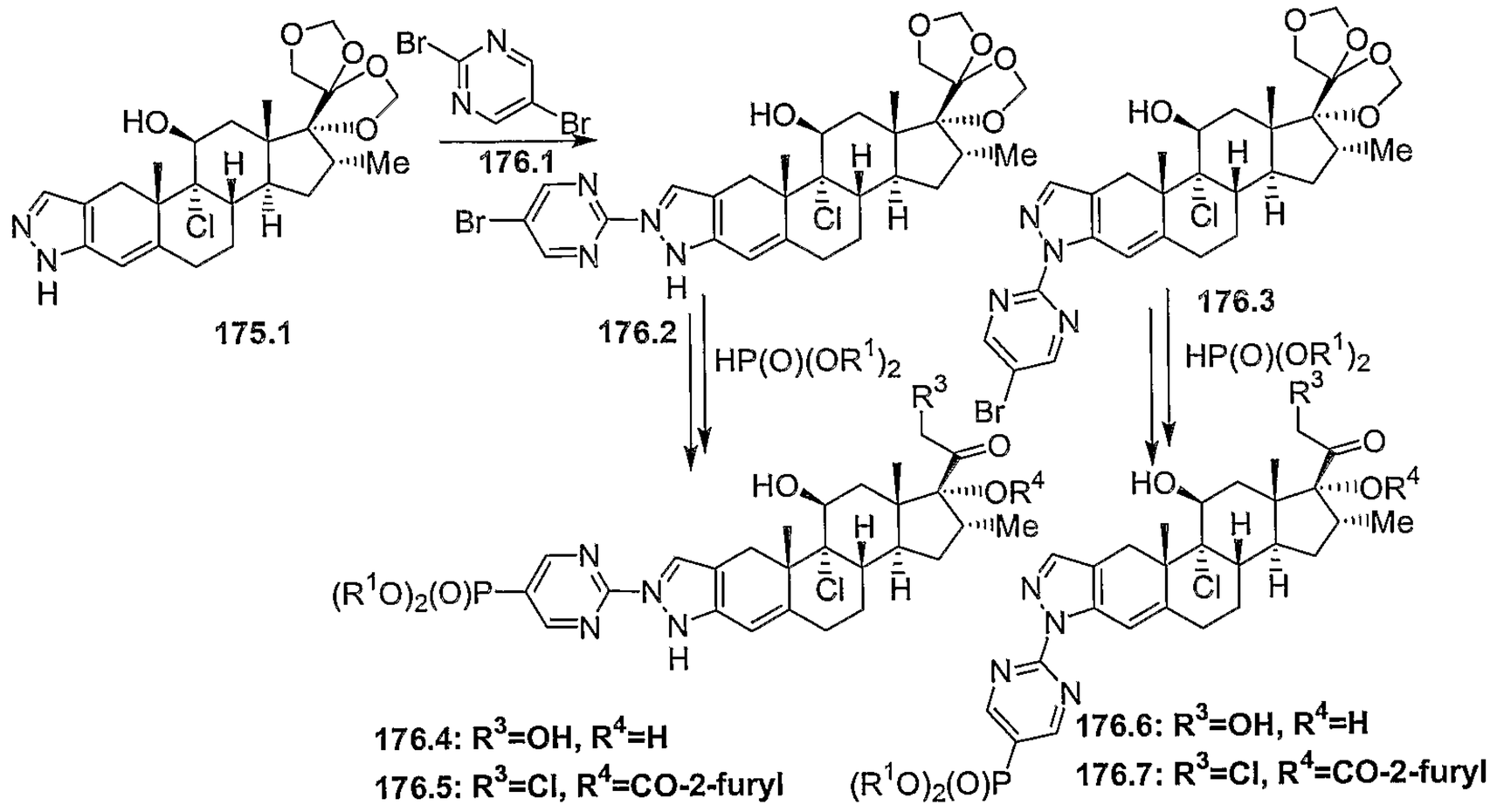
Using the above procedures, but employing, in place of the 4-hydroxy-phenyl hydrazine, **174.1**, different hydroxy-substituted hydrazines, and/or different dialkyl bromo- or mercapto-substituted phosphonates, the products analogous to the compounds, **174.7** and **174.11** are obtained.

Example 175



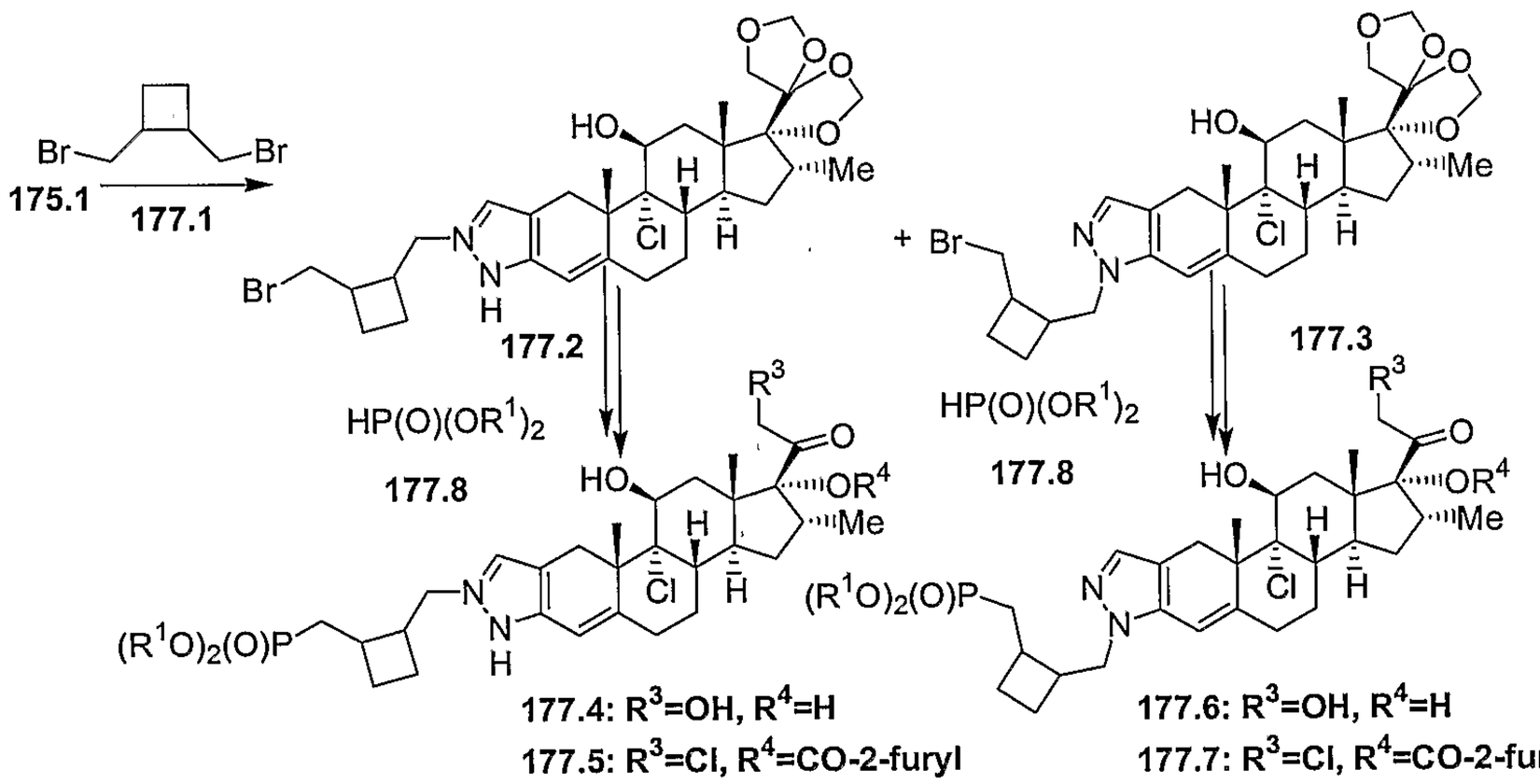
The ketoaldehyde, **173.2**, is reacted with hydrazine, to afford the pyrazole derivative, **175.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **175.6**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products, **175.3** and **175.4**. The alkylation of substituted pyrazoles is described, for example, in T. L. Gilchrist, *Heterocyclic Chemistry*, 309 (Longman, **1992**). The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **175.3** and **175.4**, are, except in cases where X is dialkyl-phosphono, converted into the phosphonates, **175.5** and **175.6**, using the procedures described herein, and deprotection/chlorination/acylation then affords the 21-chloro 17-(2-furoate) compounds, **175.8** and **175.10**.

Example 176



The pyrazole, **175.1**, is reacted with 2,5-dibromopyrimidine, **176.1**, (*Chem. Lett.*, **1992**, 583) to give the pyrazoles, **176.2** and **176.3**. The products are then coupled, as described above, with a dialkyl phosphite, to afford after side-chain deprotection and modification, as described above, the 21-chloro 17-(2-furoates), **176.5** and **176.7**.

Example 177



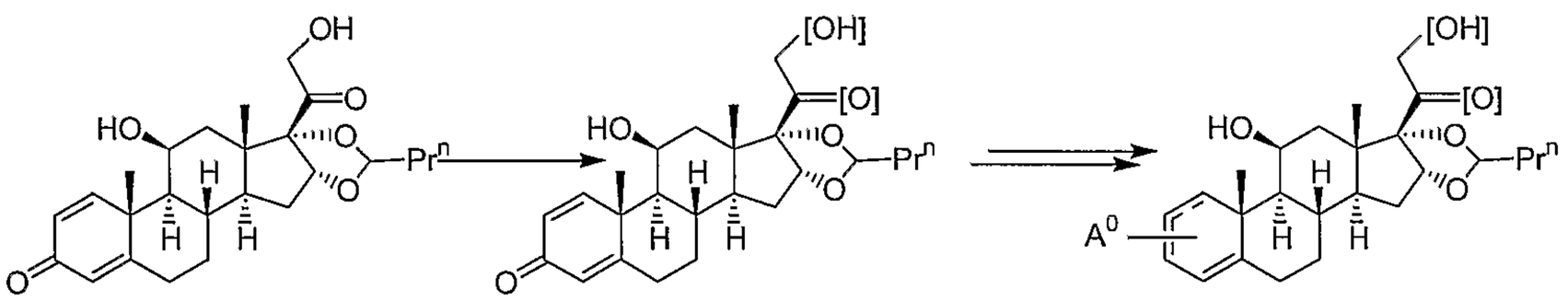
The pyrazole, **175.1**, is reacted in tetrahydrofuran solution, with 1,2-bis(bromomethyl)cyclobutane, **177.1** (*J. Org. Chem.*, **1981**, *46*, 3530) and potassium hexamethyl disilazide, to give the alkylation products, **177.1** and **177.2**. The 1'-substituted isomer, **177.2**, is then reacted, in an Arbuzov reaction, with a trialkyl phosphite to yield, after deprotection and side-chain modification,

the 21-chloro 17-(2-furoate), **177.5**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115. In this procedure, in which a bromo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60°C to about 160°C with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole, **177.3**, is subjected to the same series of reaction to give the amine phosphonate, **177.7**.

Using the above procedures, but employing different dibromides, the products analogous to **177.5** and **177.7** are obtained.

Example 178



178A **178.1** **178.2** **178.3**

A protection-deprotection sequence in which the 20-ketone group and/or the 21-hydroxyl group of Budesonide, **178A**, are protected to afford the derivative, **178.1**. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, **1955**, *77*, 1904. Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc. Chem. Comm.*, **1987**, 1351.

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone, **178A**, with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.*, **1970**, *50*, 102. The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, **1979**, *101*, 5841.

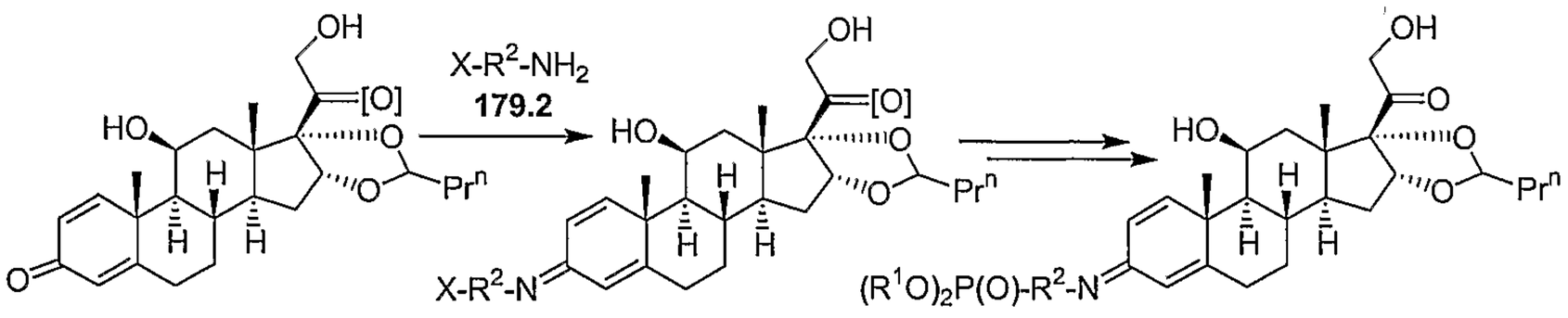
Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate, **178A**, is reacted with titanium tetrakis(diethylamide), as described in *J. Chem. Soc., Chem. Comm.*, **1983**, 406, to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

The 21-hydroxyl group is protected, for example, by conversion to the acetate ester, by reaction with one molar equivalent of acetyl chloride in dichloromethane/pyridine. The 21-acetoxy group is removed by reaction with one molar equivalent of lithium hydroxide in aqueous dimethoxyethane.

Alternatively, the 21-hydroxyl group is protected by conversion to the tert. butyl dimethylsilyl ether, by reaction in dimethylformamide solution with one molar equivalent of tert. butylchlorodimethylsilane and imidazole, as described in *J. Am. Chem. Soc.*, **1972**, *94*, 6190. The silyl ether is removed by reaction with tetrabutylammonium fluoride in tetrahydrofuran solution, as described in *J. Am. Chem. Soc.*, **1972**, *94*, 6190.

The protected compound, **178.1**, is then converted into the phosphonate-containing analog, **178.2**, using the procedures described below, and the protecting group or groups are then removed, as described above, to give the phosphonate, **178.3**.

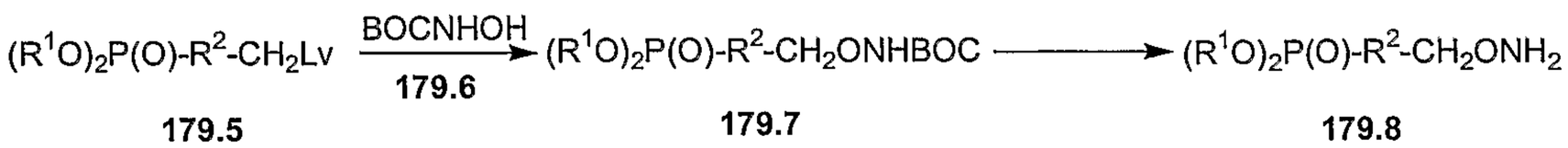
Example 179



The ketone-protected derivative, **179.1**, is reacted with an amine or hydroxylamine, **179.2**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The

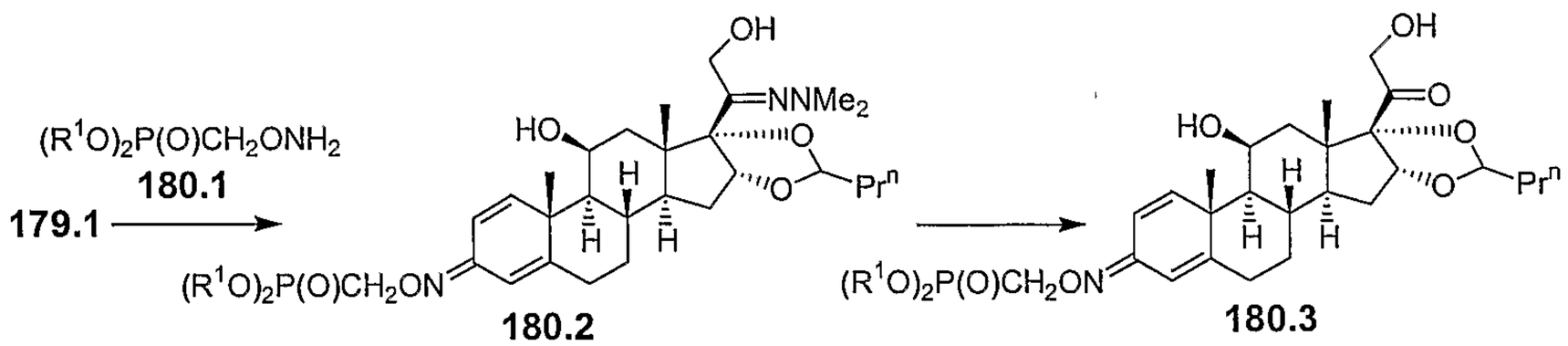
reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime, **179.3**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The protecting group is then removed, as described herein, to afford the 20-keto phosphonate product, **179.4**.

Example 179A



The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated. In this procedure, a phosphonate, **179.5**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **179.6**, (Aldrich) to produce the ether, **179.7**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **179.8**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.

Example 180

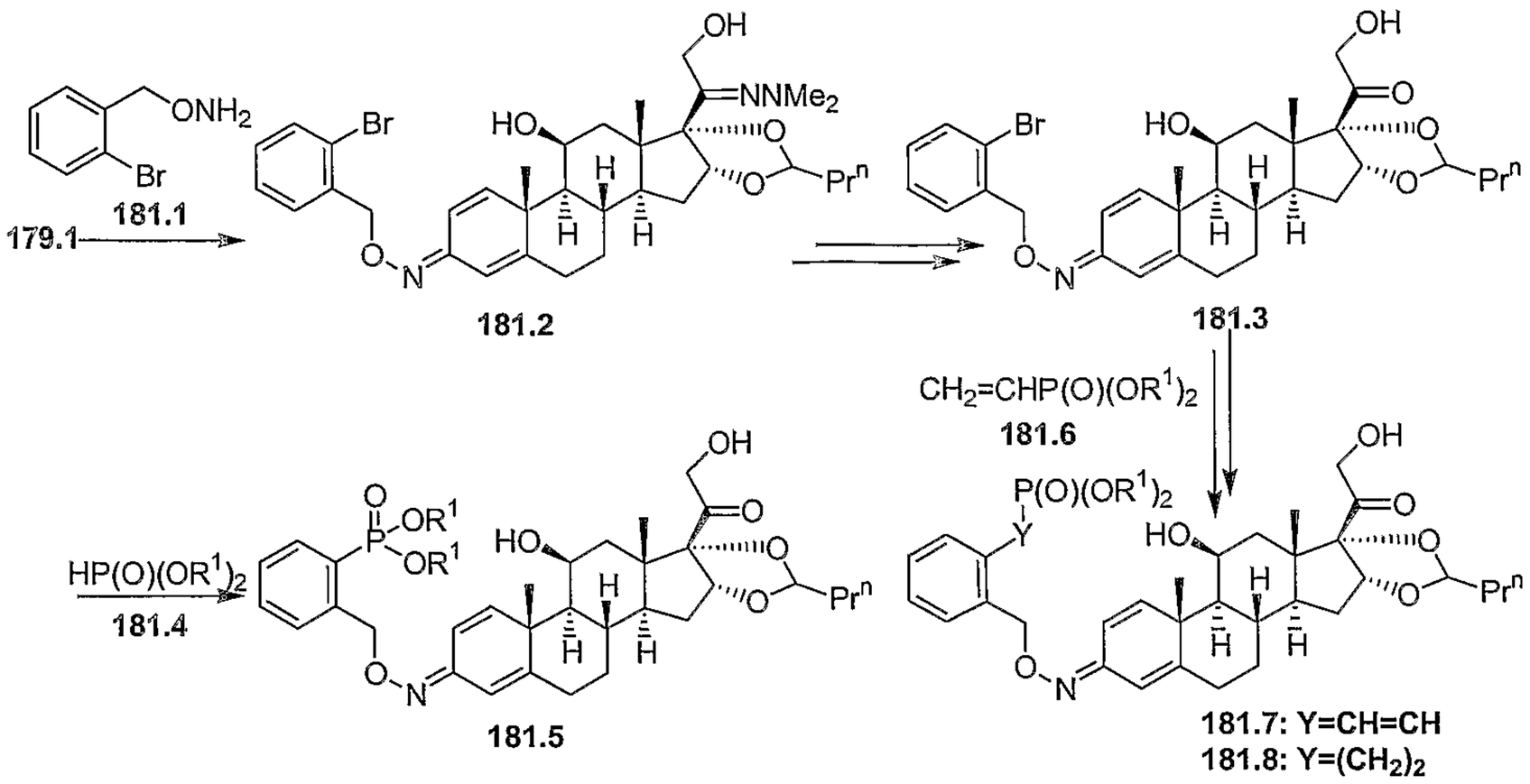


The substrate, **179.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine, **180.1**, prepared as described above from a dialkyl trifluoromethylsulfonyl-oxymethyl phosphonate (*Tet. Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **180.2**. Deprotection, as described in Example **179**, affords the

20-keto phosphonate, **180.3**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxylamine ether, **180.1**, different oxime ethers, **179.2**, the corresponding products, **179.4** are obtained.

Example 181



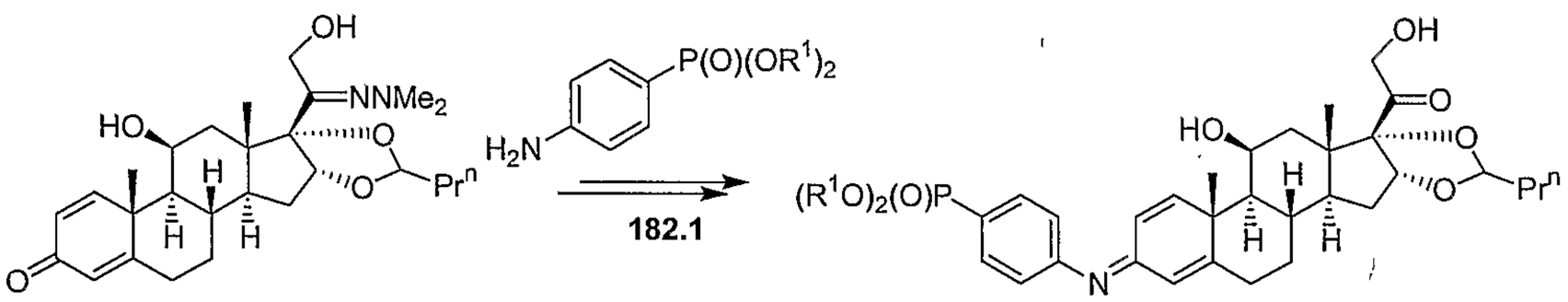
The preparation of compounds, **179.1**, in which the phosphonate group is attached by means of a benzyloxy oxime group is illustrated above. In this procedure, the dienone, **179.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(2-bromobenzyl)hydroxylamine, **181.1**, prepared as described above from 2-bromobenzyl bromide and BOC-protected hydroxylamine, **179.6**, to give the oxime, **181.2**. The protecting group is then removed to yield the 20-keto product, **181.3**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphite, **181.4**, to afford the phosphonate, **181.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed at ca. 100° in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)palladium(0).

Alternatively, the bromo compound, **181.3**, is coupled with a dialkyl vinylphosphonate, **181.6**, (Aldrich) to afford the phosphonate, **181.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in *Advanced Organic Chemistry*, by F. A. Carey and R. J. Sundberg, Plenum, **2001**, p. 503ff and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethyl-formamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenylphosphine)palladium(0) or palladium(II) catalyst such as

palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **181.7**, is reduced, for example by reaction with diimide, to produce the saturated analog, **181.8**. The reduction of olefinic bonds is described in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, **1989**, p. 6ff. The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromobenzyl reagent, **181.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxylamines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **181.5**, **181.7** and **181.8** are obtained.

Example 182

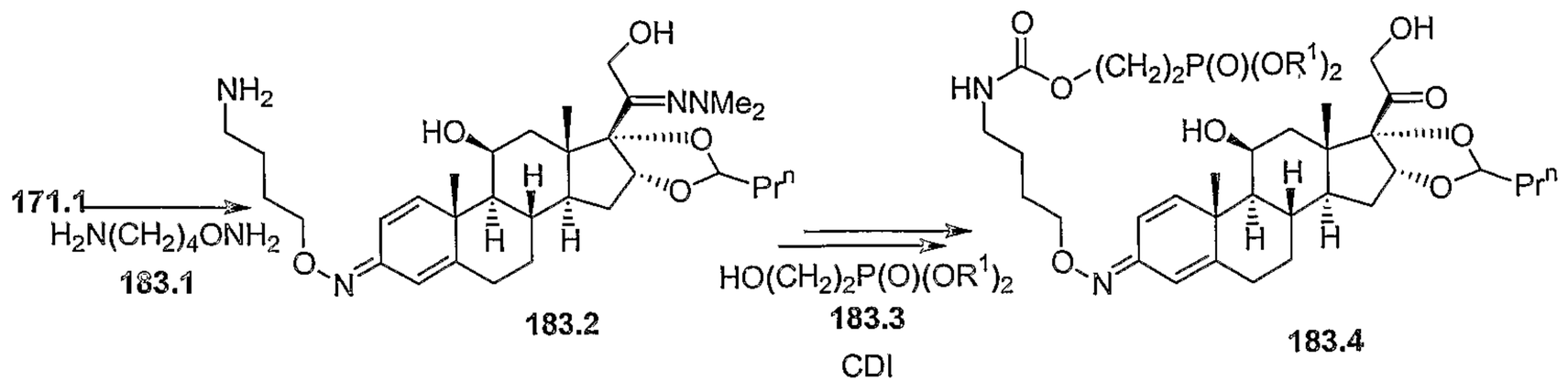


171.1 182.2

The substrate, **171.1**, in which the 20-ketone is protected as the dimethyl-hydrazone, is reacted with a dialkyl 4-aminophenyl phosphonate, **182.1**, (Epsilon), to give, after deprotection, the imine product, **182.2**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-amino-phenyl phosphonate, **182.1** different amino-substituted aryl or heteroaryl phosphonates, products analogous to **182.2** are obtained.

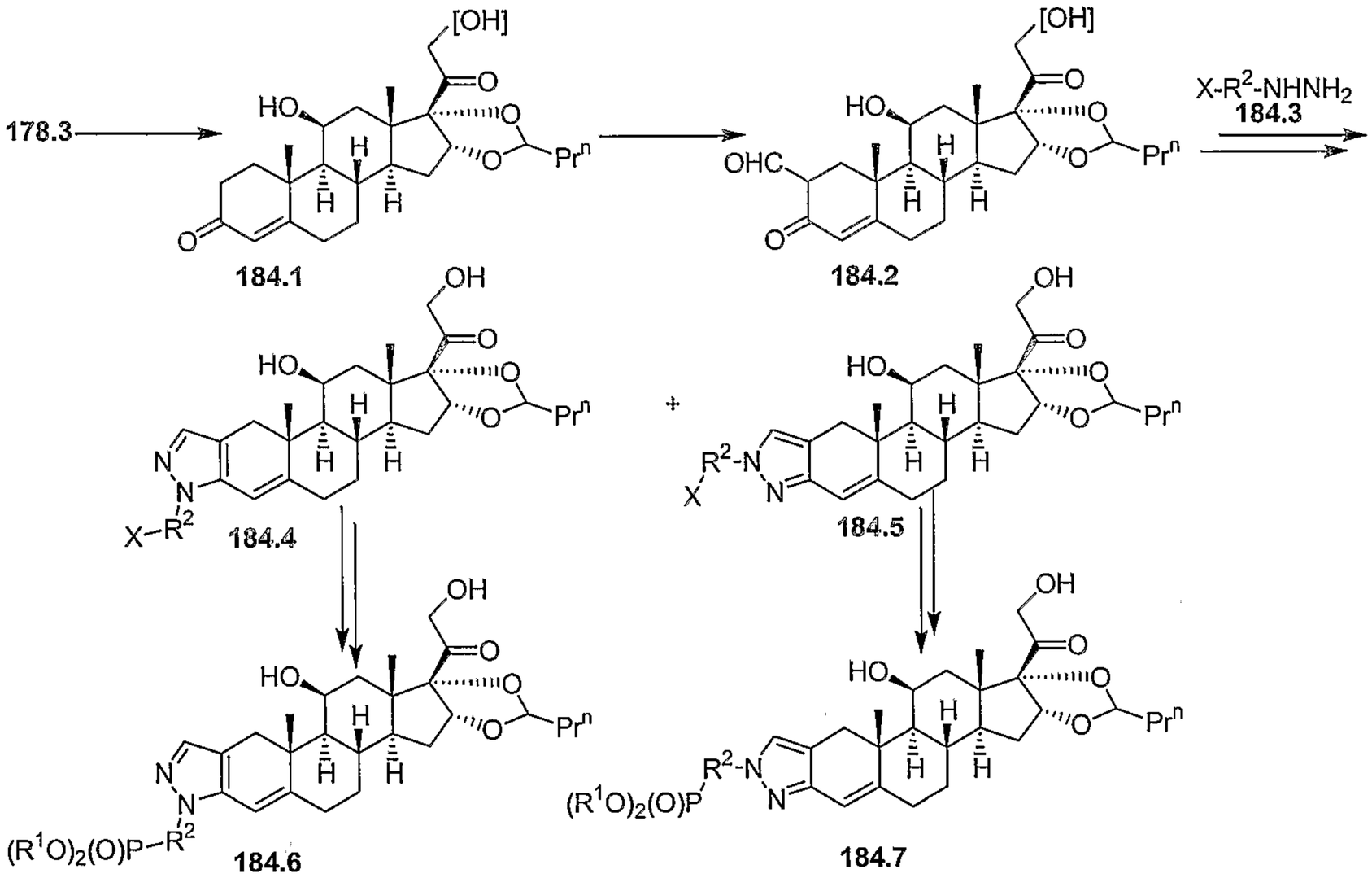
Example 183



The preparation of phosphonates in which the phosphonate is attached by means of an oximino group and a carbamate linkage is illustrated herein. In this procedure, the dienone, **171.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with 4-aminobutyl hydroxylamine, **183.1**, (*Pol. J. Chem.*, **1981**, *55*, 1163) to yield the oxime, **183.2**. (The reaction of steroidal 1,4-dien-3-ones with hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795.) The reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product, **183.2**, is then coupled with a dialkyl 2-hydroxyethyl phosphonate, **183.3**, (Epsilon) and carbonyl diimidazole (CDI), to yield, after deprotection, the carbamate oxime, **183.4**. The preparation of carbamates is described in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, ed., Pergamon, **1995**, Vol. *6*, p 416ff, and in *Organic Functional Group Preparations*, by S. R. Sandler and W. Karo, Academic Press, **1986**, p. 260ff. In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

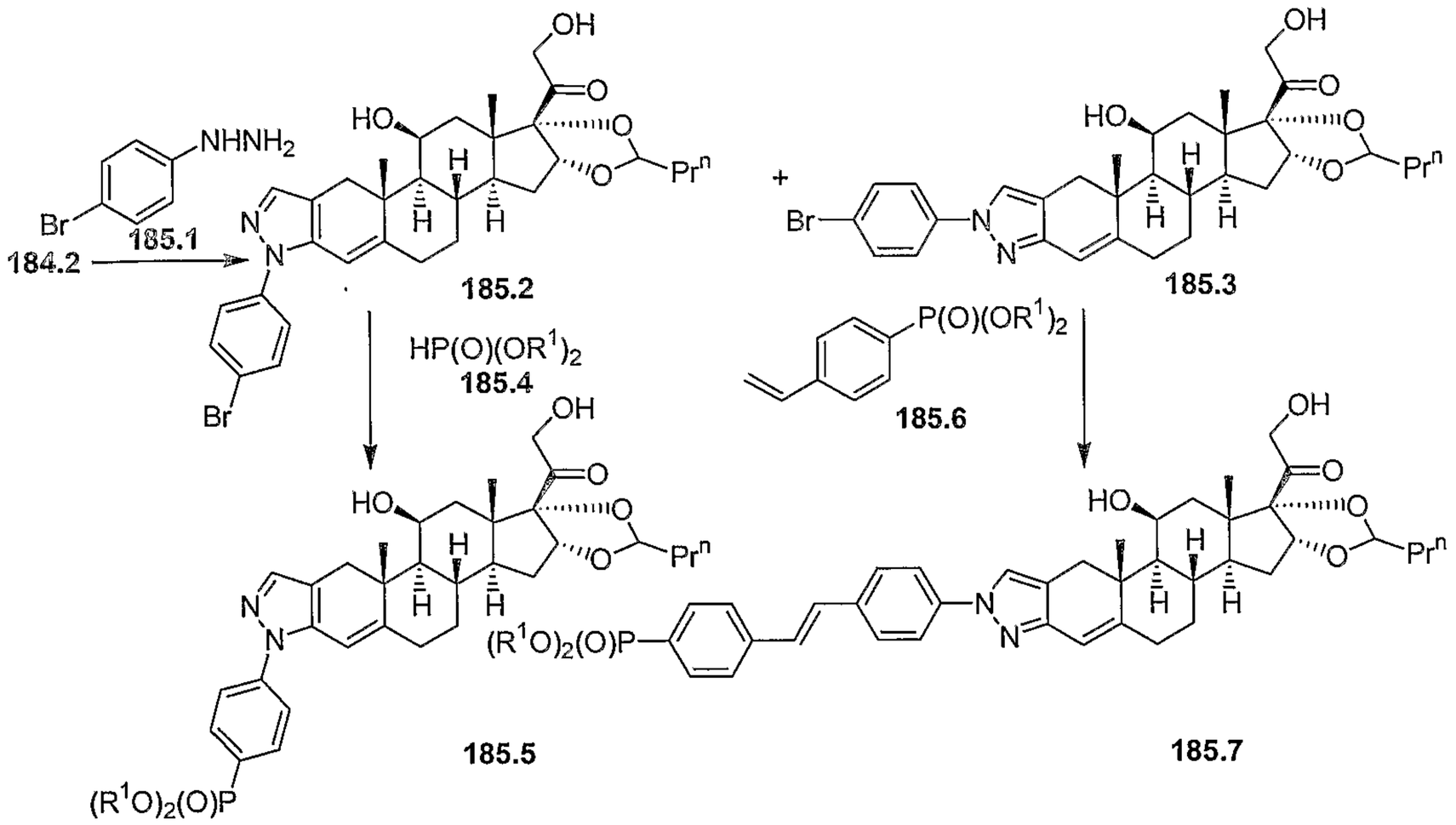
Using the above procedures, but employing, in place of the amino-substituted hydrazine, **183.1**, different amino-substituted hydrazines, and/or different hydroxy-substituted phosphonates, the products analogous to **183.4** are obtained.

Example 184



The dienone, **178.3**, in which the 21-hydroxyl group is protected as described in Example **178** is reduced to afford the 1,2-dihydro product, **184.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenyl-phosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, *44*, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **184.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **184.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields, after deprotection of the 21-hydroxyl group, the isomeric 2'- and 1'-aryl pyrazoles, **184.4** and **184.5**. The pyrazole-forming reaction is performed between equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The pyrazoles, **184.4** and **184.5**, are then transformed, for example by the procedures described in Examples **180** and **181**, into the phosphonates, **184.6** and **184.7**.

Example 185

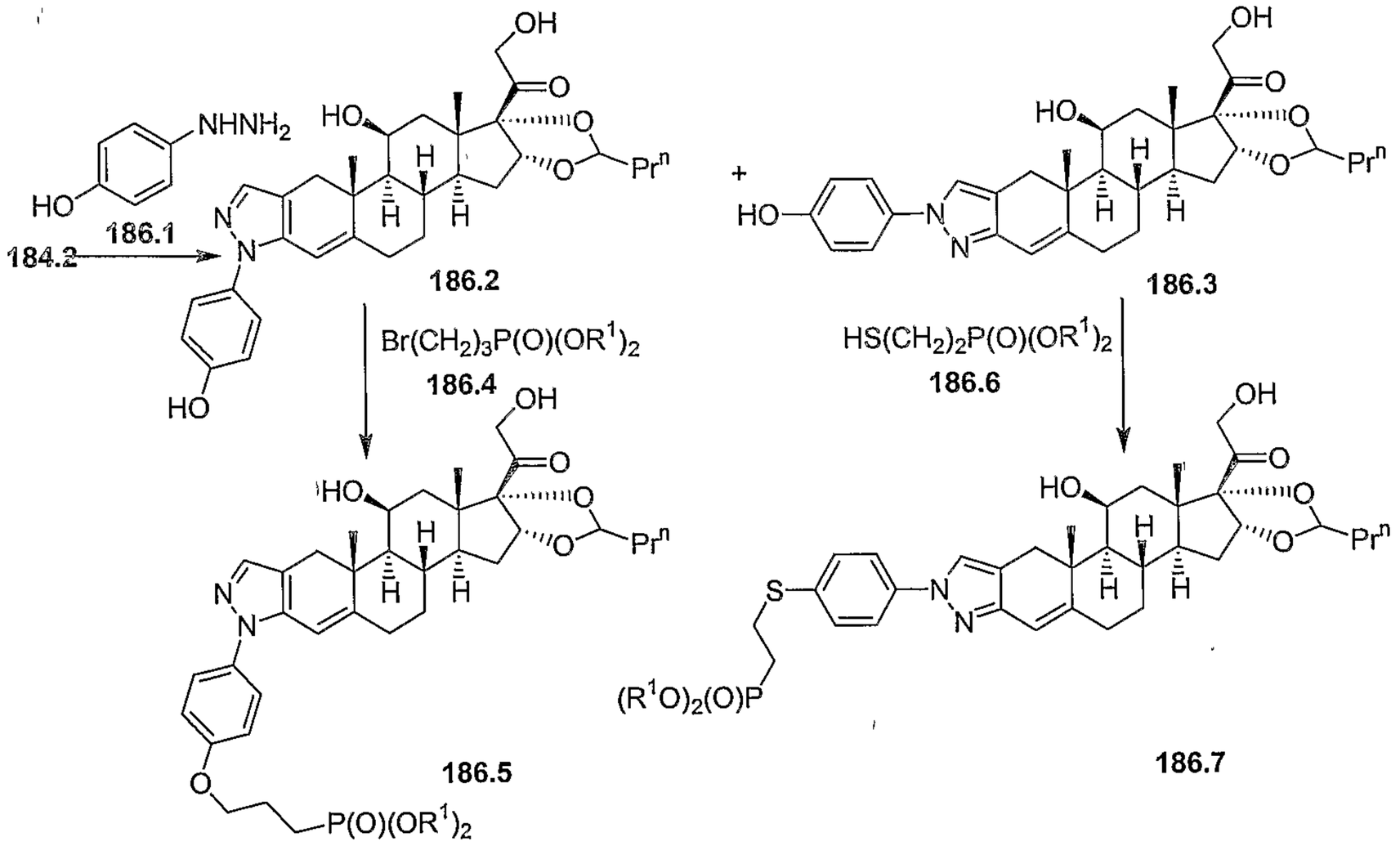


The ketoaldehyde, **184.2**, is reacted, as described above, with 4-bromophenyl hydrazine, **185.1**, (*J. Organomet. Chem.*, **1999**, *62*, 581) to give the pyrazoles, **185.2** and **185.3**. The 2'-substituted isomer **185.2** is then reacted, as described above, with a dialkyl phosphate, **184.4**, to give the phosphonate, **185.5**.

The isomeric pyrazole, **185.3**, is reacted in a Heck reaction, as described above, with one molar equivalent of a dialkyl 4-vinylphenyl phosphonate, **185.6**, (*Macromolecules*, **1998**, *31*, 2918) to yield the phosphonate, **185.7**.

Using the above procedures, but employing different bromo-substituted hydrazines, and/or different alkenyl-substituted phosphonates, the products analogous to **185.5** and **185.7** are obtained.

Example 186



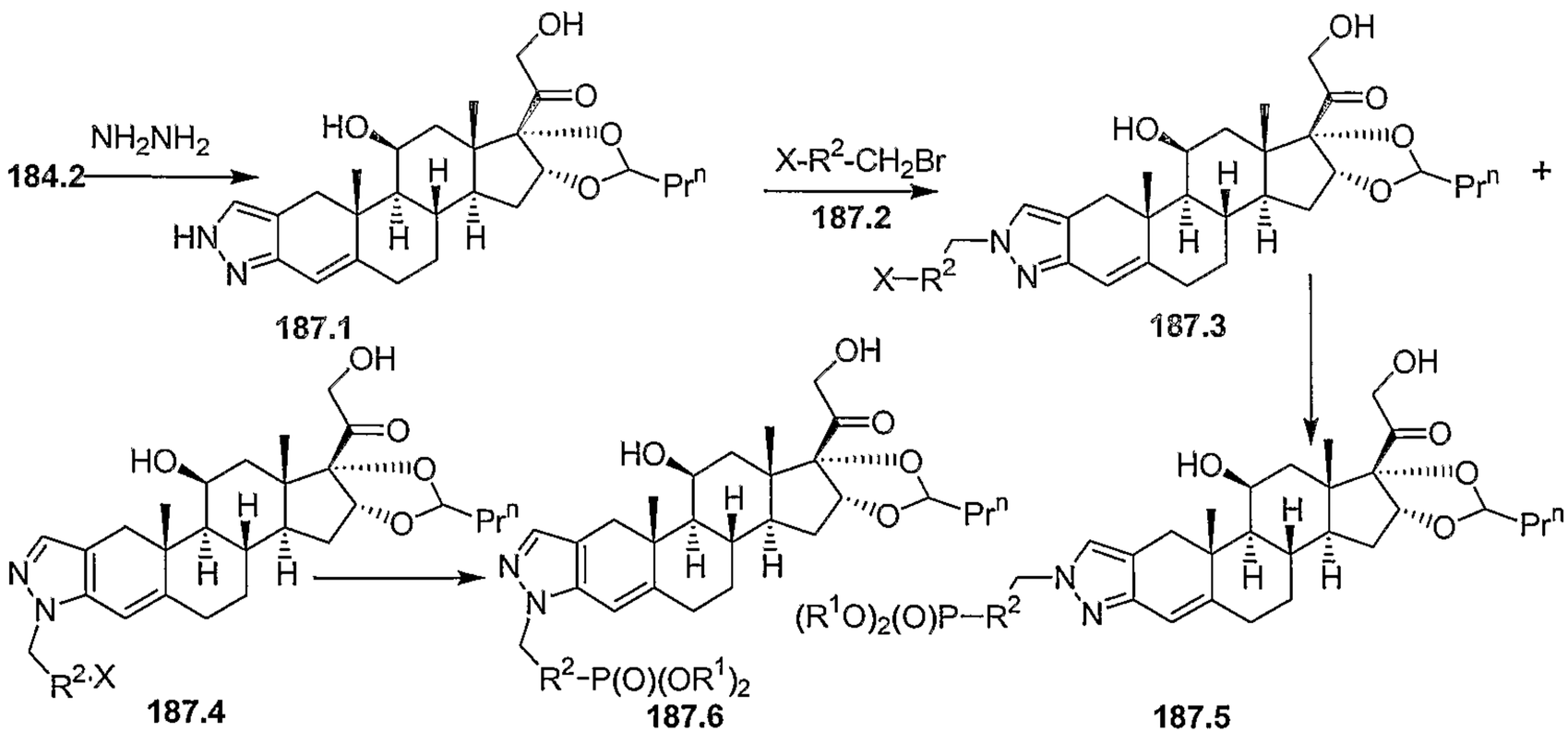
The ketoaldehyde, **184.2**, is reacted, as described above, with 4-hydroxyphenyl hydrazine, **186.1**, (EP 437105) to produce the pyrazoles, **186.2** and **186.3**. The 2'-substituted isomer, **186.2**, is then reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl bromopropyl phosphonate, **186.4**, (*J. Amer. Chem. Soc.*, **2000**, *122*, 1554) and cesium carbonate, to give the ether phosphonate, **186.5**.

Alternatively, the 1'-substituted pyrazole, **186.3**, is coupled in a Mitsonobu reaction, with a dialkyl 2-mercaptoethyl phosphonate, **186.6**, (*Zh. Obschei. Khim.*, **1973**, *43*, 2364) to prepare the thioether phosphonate, **186.7**. The preparation of aromatic ethers and thioethers by means of the Mitsonobu reaction is described, for example, in *Comprehensive Organic Transformations*, by R. C. Larock, VCH, **1989**, p. 448, and in *Advanced Organic Chemistry*, Part B, by F.A. Carey and R. J. Sundberg, Plenum, **2001**, p. 153-4 and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656.

Using the above procedures, but employing, in place of the hydroxylphenyl hydrazine, **186.1**, different hydroxyaryl hydrazines, and/or different

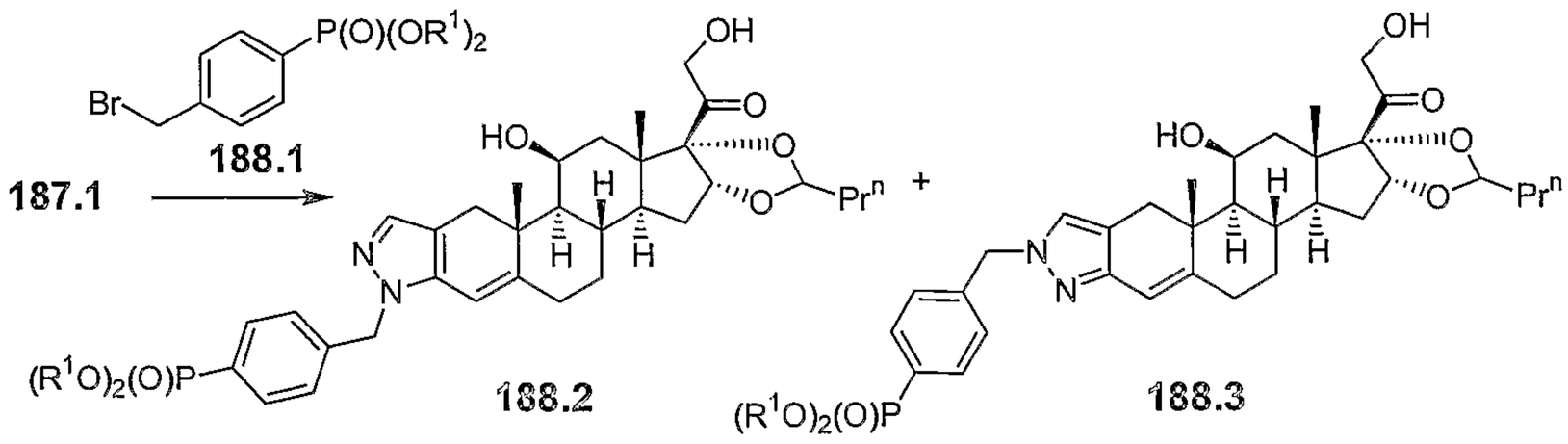
dialkyl bromo- or mercapto-substituted phosphonates, the products analogous to the compounds, **186.5** and **186.7** are obtained.

Example 187



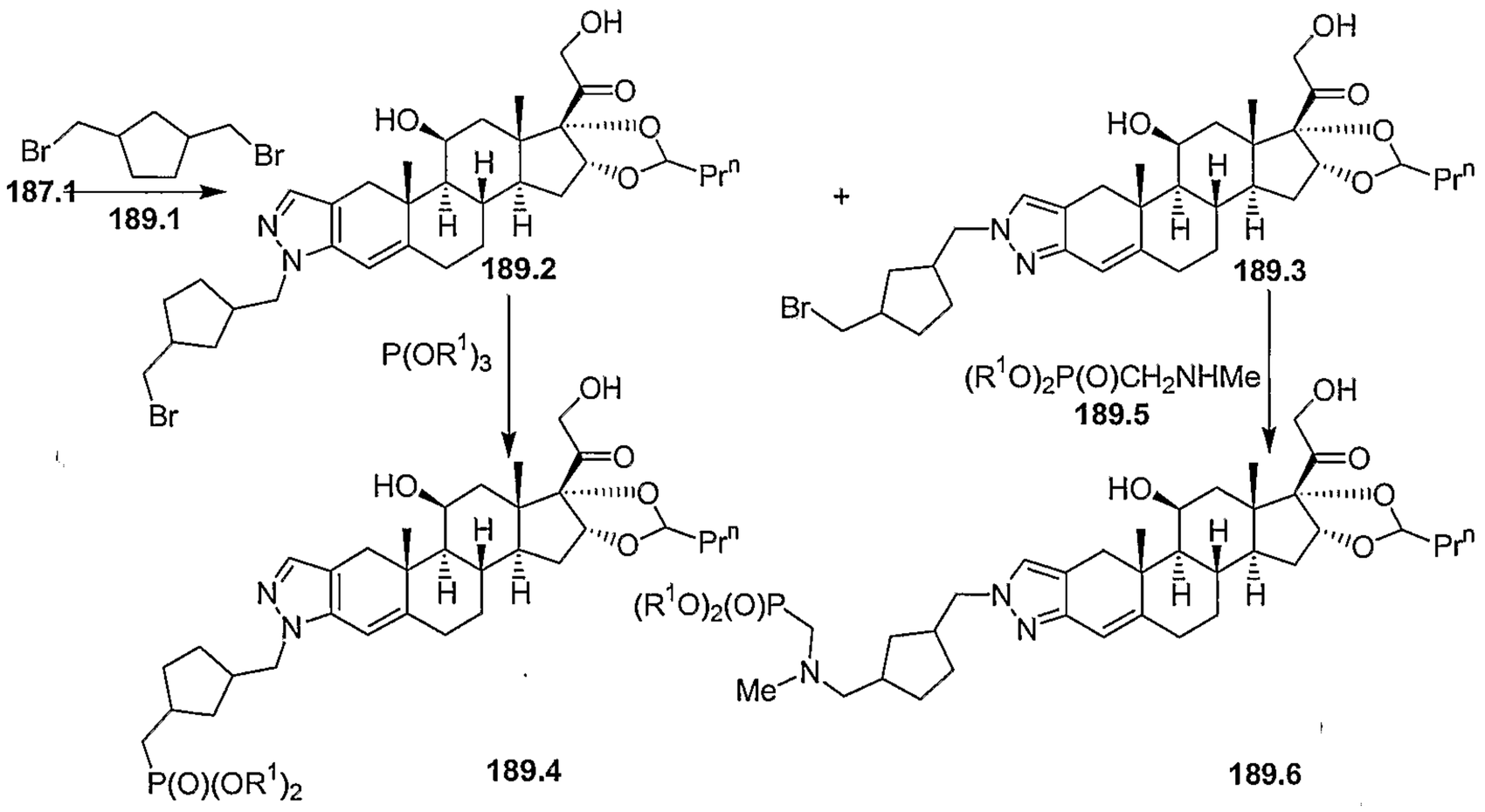
The ketoaldehyde, **184.2**, is reacted with hydrazine to afford the pyrazole derivative, **187.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **187.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products, **187.3** and **187.4**. The alkylation of substituted pyrazoles is described, for example, in *Heterocyclic Chemistry*, by T. L. Gilchrist, Longman, **1992**, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **187.3** and **187.4**, are, except in cases where X is dialkylphosphono, converted into the phosphonates, **187.5** and **187.6**, using the procedures described herein.

Example 188



The pyrazole, **187.1**, is reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl 4-bromomethylphenyl phosphonate, **188.1**, (*Tet.*, **1998**, *54*, 9341) and lithium hexamethyl disilazide, to give the pyrazoles, **188.2** and **188.3**. Using the above procedures, but employing different bromomethyl-substituted phosphonates, the products analogous to **188.2** and **188.3** are obtained.

Example 189



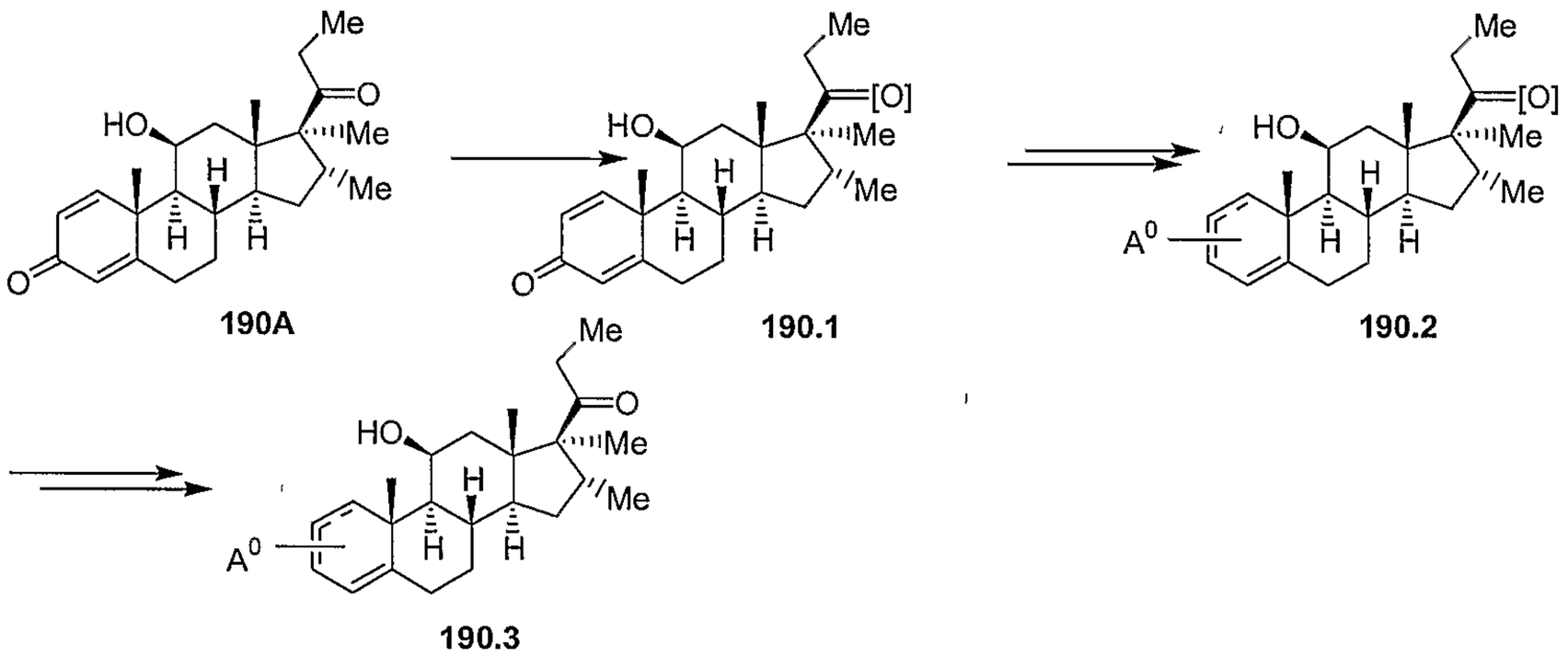
The pyrazole, **187.1**, is reacted in tetrahydrofuran solution with 1,3-bis(bromomethyl)cyclopentane, **189.1**, (*Bull. Soc. Chim. Fr.*, **1975**, 1295) and sodium hydride, to give the alkylation products, **189.2** and **189.3**. The 2'-substituted isomer, **189.2**, is then reacted, in a Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate, **189.4**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115. In this procedure, in which a bromo substituent is converted into the corresponding phosphonate, the substrate

is heated at from about 60° to about 160° with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 2'-substituted pyrazole, **189.3**, is reacted at 70° in dimethyl-formamide solution with one molar equivalent of a dialkyl methylaminomethyl phosphonate, **189.5**, and cesium carbonate, to give the amine phosphonate, **189.6**.

Using the above procedures, but employing different dihalides, and/or different amino-substituted phosphonates, the products analogous to **189.4** and **189.6** are obtained.

Example 190



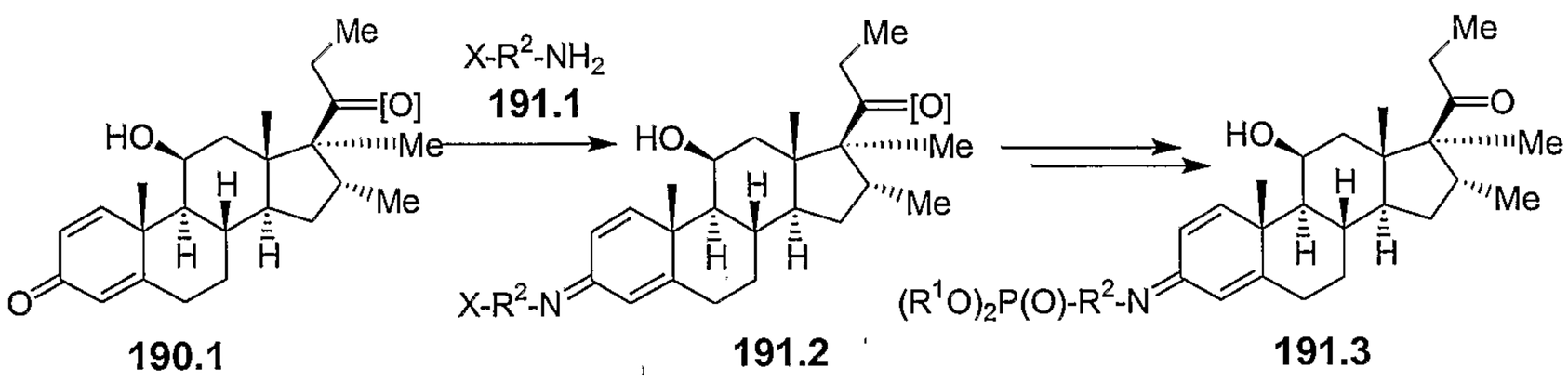
A protection-deprotection sequence in which the 20-ketone group of Rimexolone, **190A**, is protected to afford the derivative, **190.1**. The ketone is protected, for example, by conversion to the cyclic ethylene ketal, by reaction in toluene solution at reflux temperature with ethylene glycol and an acid catalyst, as described in *J. Am. Chem. Soc.*, **1955**, *77*, 1904. Deprotection is effected by reaction with pyridinium tosylate in aqueous acetone, as described in *J. Chem. Soc., Chem. Comm.*, **1987**, 1351.

Alternatively, the 20-ketone is protected by conversion to the N, N-dimethylhydrazone. The dimethyl hydrazone is prepared by the reaction of the ketone, **190A**, with N,N-dimethylhydrazine in ethanol-acetic acid, as described in *Org. Syn.*, **1970**, *50*, 102. The group is removed by treatment with sodium acetate and acetic acid in aqueous tetrahydrofuran, as described in *J. Am. Chem. Soc.*, **1979**, *101*, 5841.

Alternatively, the 20-ketone is protected as the diethylamine adduct. In this procedure, the substrate, **190.1**, is reacted with titanium tetrakis-(diethylamide), as described in *J. Chem. Soc., Chem. Comm.*, **1983**, 406, to afford the adduct. The ketone is deprotected by reaction with water in an aqueous organic solvent.

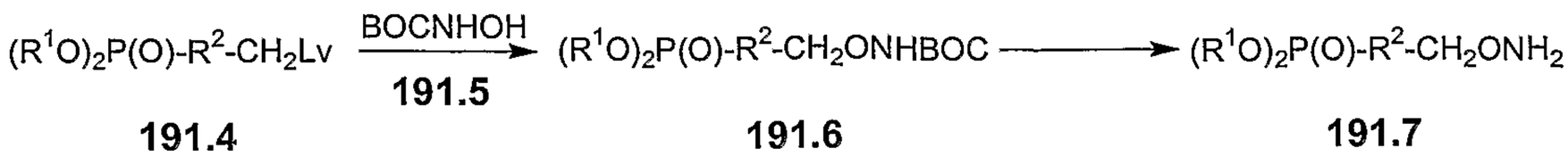
The protected compound, **190.2**, is then converted into the phosphonate-containing analog, **190.3**, using the procedures described below, and the protecting group or groups are then removed, as described above, to give the phosphonate, **190.3**.

Example 191



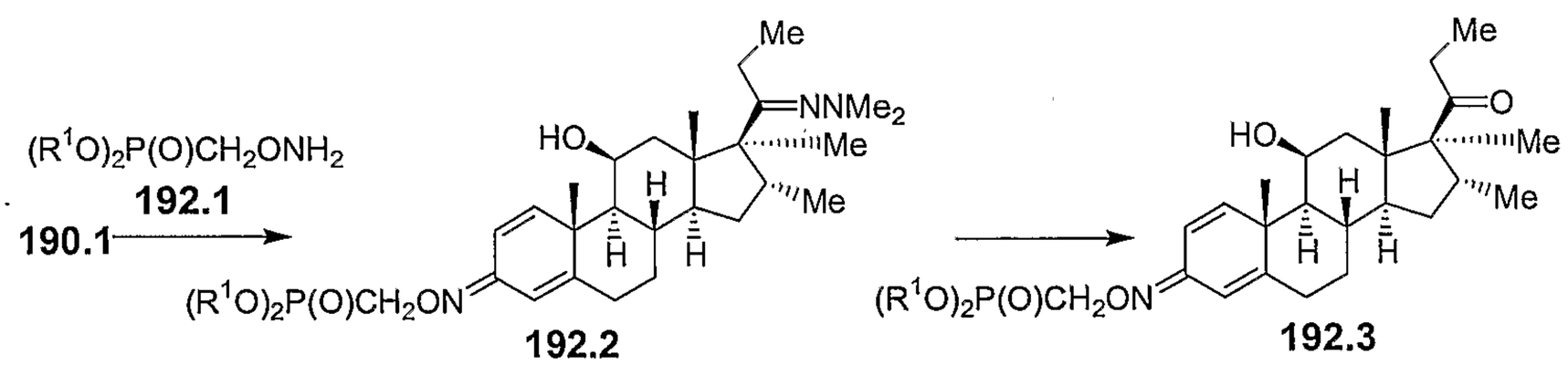
The ketone-protected derivative, **190.1**, is reacted with an amine or hydroxylamine, **191.1**, in which R^2 is an alkyl, alkenyl, cycloalkyl or cycloalkenyl group, optionally incorporating a heteroatom O, S or N, or a functional group such as an amide, ester, oxime, sulfoxide or sulfone etc, or an optionally substituted aryl, heteroaryl or aralkyl group, optionally incorporating a heteroatom O, S or N, and X is either a phosphonate group or a group which is subsequently converted into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxy and the like. The reaction is conducted between equimolar amounts of the reactants in an aprotic solvent such as pyridine or xylene, or in an alcoholic solvent such as ethanol, optionally in the presence of an acid catalyst, to give the imine or oxime, **191.2**. The preparation of oximes of steroidal 3-ketones is described in *Anal. Bioch.*, **1978**, *86*, 133 and in *J. Mass. Spectrom.*, **1995**, *30*, 497. The protecting group is then removed, as described in Example **190**, to afford the 20-keto phosphonate product, **191.3**.

Example 191A



The preparation of hydroxylamine ethers incorporating a phosphonate group is also illustrated. In this procedure, a phosphonate, **191.4**, in which Lv is a leaving group such as bromo or trifluoromethylsulfonyloxy, is reacted with BOC-hydroxylamine, **191.5**, (Aldrich) to produce the ether, **191.6**. The reaction is conducted between equimolar amounts of the reactants in a polar solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as potassium hydroxide or dimethylaminopyridine. Deprotection, for example by treatment with trifluoroacetic acid, then gives the hydroxylamine ether, **191.7**. The above procedure is also employed for the preparation of substituted hydroxylamines which are precursors to phosphonates.

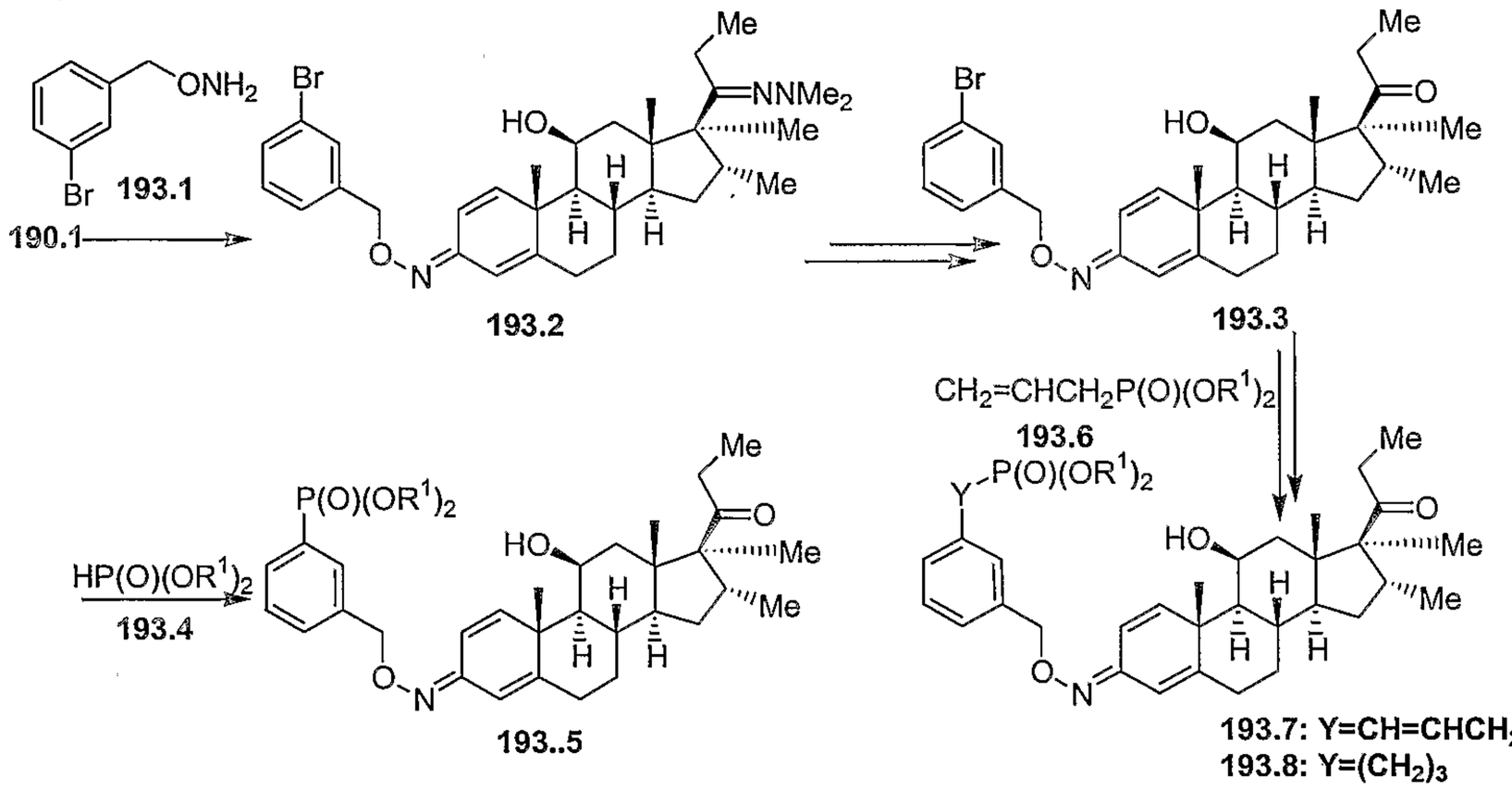
Example 192



The substrate, **190.1**, in which the 20-ketone is protected as the dimethyl hydrazone derivative, is reacted with a dialkyl phosphonomethyl hydroxylamine, **192.1**, prepared as described above from a dialkyl trifluoromethyl-sulfonyl-oxymethyl phosphonate (*Tet. Lett.*, **1986**, *27*, 1477) and BOC-hydroxylamine, to afford the oxime, **192.2**. Deprotection, as described in Example **191**, then affords the 20-keto phosphonate, **192.3**. The oxime forming reaction is performed at ambient temperature in ethanol-acetic acid solution between equimolar amounts of the reactants.

Using the above procedures, but employing, in place of the hydroxyl-amine ether, **192.1**, different oxime ethers, **191.1**, the corresponding products, **191.3** are obtained.

Example 193



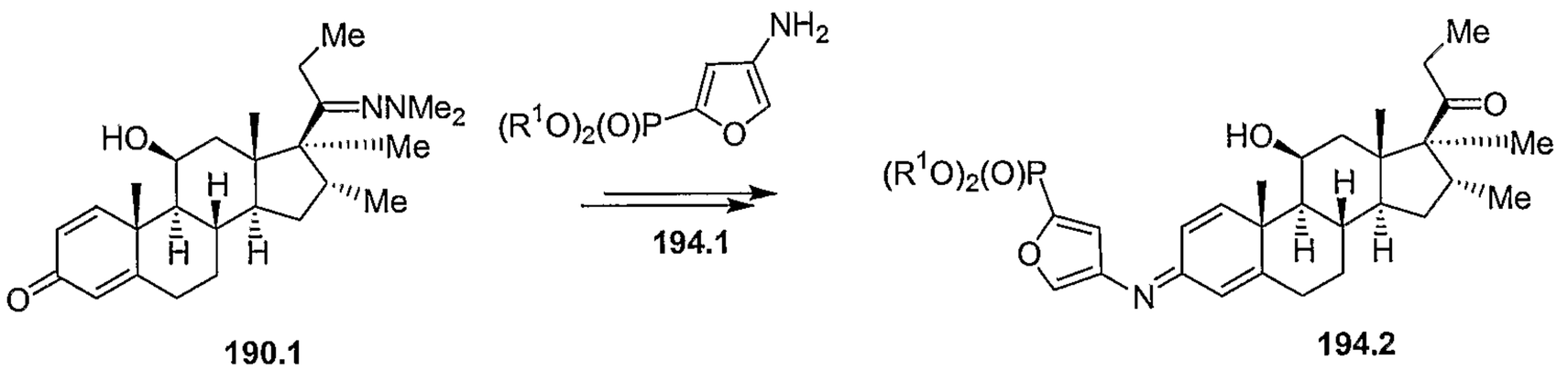
The dienone, **190.1**, in which the 20-ketone is protected as the dimethyl hydrazone, is reacted, as described above, with O-(3-bromobenzyl)hydroxyl-amine, **193.1**, prepared as described above from 3-bromobenzyl bromide and BOC-protected hydroxylamine, **191.5**, to give the oxime, **193.2**. The protecting group is then removed to yield the 20-keto product **193.3**. The latter product is then reacted, in the presence of a palladium catalyst, with a dialkyl phosphate, **193.4**, to afford the phosphonate, **193.5**. The preparation of arylphosphonates by means of a coupling reaction between aryl bromides and dialkyl phosphites is described in *J. Med. Chem.*, **1992**, *35*, 1371. The reaction is performed at ca. 100°C in an inert solvent such as toluene, in the presence of a base such as triethylamine and a catalytic amount of tetrakis(triphenylphosphine)-palladium(0).

Alternatively, the bromo compound, **193.3**, is coupled with a dialkyl propenylphosphonate, **193.6**, (Aldrich) to afford the phosphonate, **193.7**. The coupling of aryl halides with olefins by means of the Heck reaction is described, for example, in F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, 503ff (Plenum, **2001**) and in *Acc. Chem. Res.*, **1979**, *12*, 146. The aryl bromide and the olefin are coupled in a polar solvent such as dimethylformamide or dioxan, in the presence of a palladium(0) catalyst such as tetrakis(triphenyl-phosphine)palladium(0) or palladium(II) catalyst such as palladium(II) acetate, and optionally in the presence of a base such as triethylamine or potassium carbonate. Optionally, the styrenoid double bond present in the product, **193.7**,

is reduced, for example by reaction with diimide, to produce the saturated analog, **193.8**. The reduction of olefinic bonds is described in R. C. Larock, *Comprehensive Organic Transformations*, 6ff (VCH, **1989**). The transformation is effected by means of catalytic hydrogenation, for example using a palladium on carbon catalyst and hydrogen or a hydrogen donor, or by the use of diimide or diborane.

Using the above procedures, but employing, in place of the bromobenzyl reagent, **193.1**, different bromo-substituted aryl or heteroaryl alkoxy hydroxyl-amines, and/or different dialkyl alkenyl phosphonates, the products analogous to the compounds, **193.5**, **193.7** and **193.8** are obtained.

Example 194

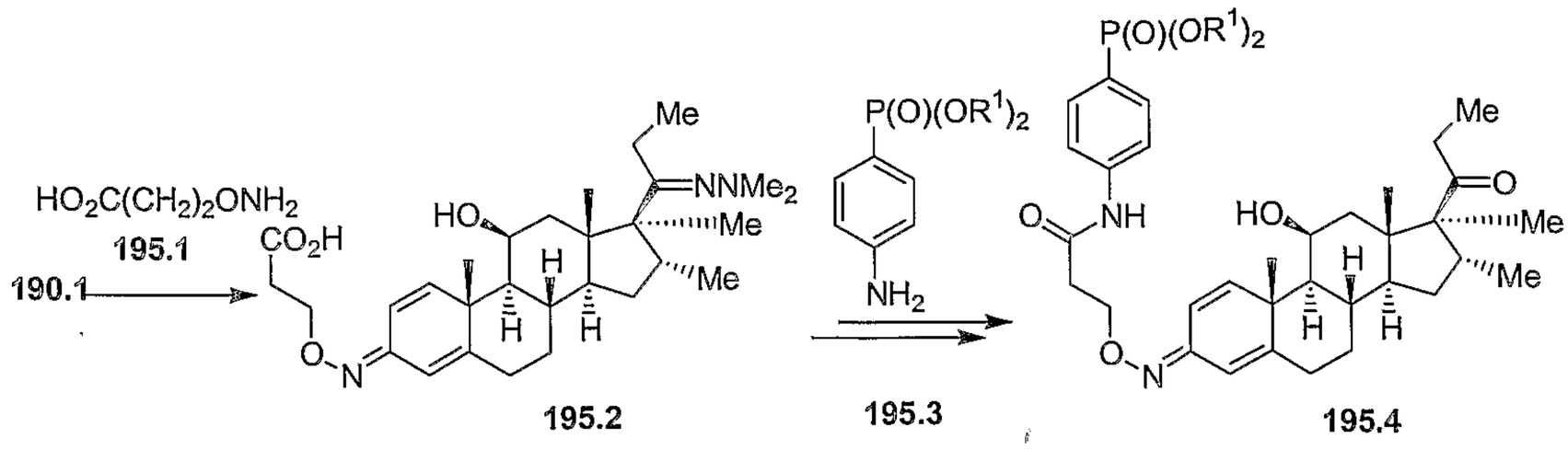


190.1 **194.2**

The substrate, **190.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with a dialkyl 4-amino-2-furyl phosphonate, **194.1**, prepared by the palladium catalyzed coupling reaction, as described above, between 4-amino-2-bromofuran (*Tet.*, **1987**, *43*, 3295) and a dialkyl phosphite, to give, after deprotection, the imine product, **194.2**. The imine forming reaction is conducted in a hydrocarbon solvent such as toluene or xylene, at reflux temperature, in the presence of a basic catalyst such as sodium methoxide, or an acid catalyst such as p-toluenesulfonic acid, under azeotropic conditions.

Using the above procedures, but employing, in place of the 4-aminofuryl phosphonate, **194.1**, different amino-substituted aryl or heteroaryl phosphonates, products analogous to **194.2** are obtained.

Example 195



The dienone, **190.1**, in which the 20-ketone is protected as the dimethylhydrazone, is reacted with 2-carboxyethyl hydroxylamine, **195.1**, (*J. Med. Chem.*, **1990**, *33*, 1423) to yield the oxime, **195.2**. The reaction of steroidal 1,4-dien-3-ones with hydroxylamines is described in *J. Steroid Bioch.*, **1976**, *7*, 795; the reaction is performed between equimolar amounts of the reactants in a polar organic solvent such as pyridine or methanol, optionally in the presence of acetic acid or sodium acetate. The product, **195.2**, is then coupled with a dialkyl 4-aminophenyl phosphonate, **195.3**, (Epsilon) and dicyclohexyl carbodiimide, to yield, after deprotection, the amide oxime, **195.4**. The preparation of amides from carboxylic acids and derivatives is described, for example, in S.R. Sandler and W. Karo, *Organic Functional Group Preparations*, 274 (Academic Press, **1968**), and R. C. Larock, *Comprehensive Organic Transformations*, 972ff (VCH, **1989**). The carboxylic acid is reacted with the amine in the presence of an activating agent, such as, for example, dicyclohexylcarbodiimide or diisopropylcarbodiimide, optionally in the presence of, for example, hydroxybenztriazole, N-hydroxysuccinimide or N-hydroxypyridone, in a non-protic solvent such as, for example, pyridine, DMF or dichloromethane, to afford the amide.

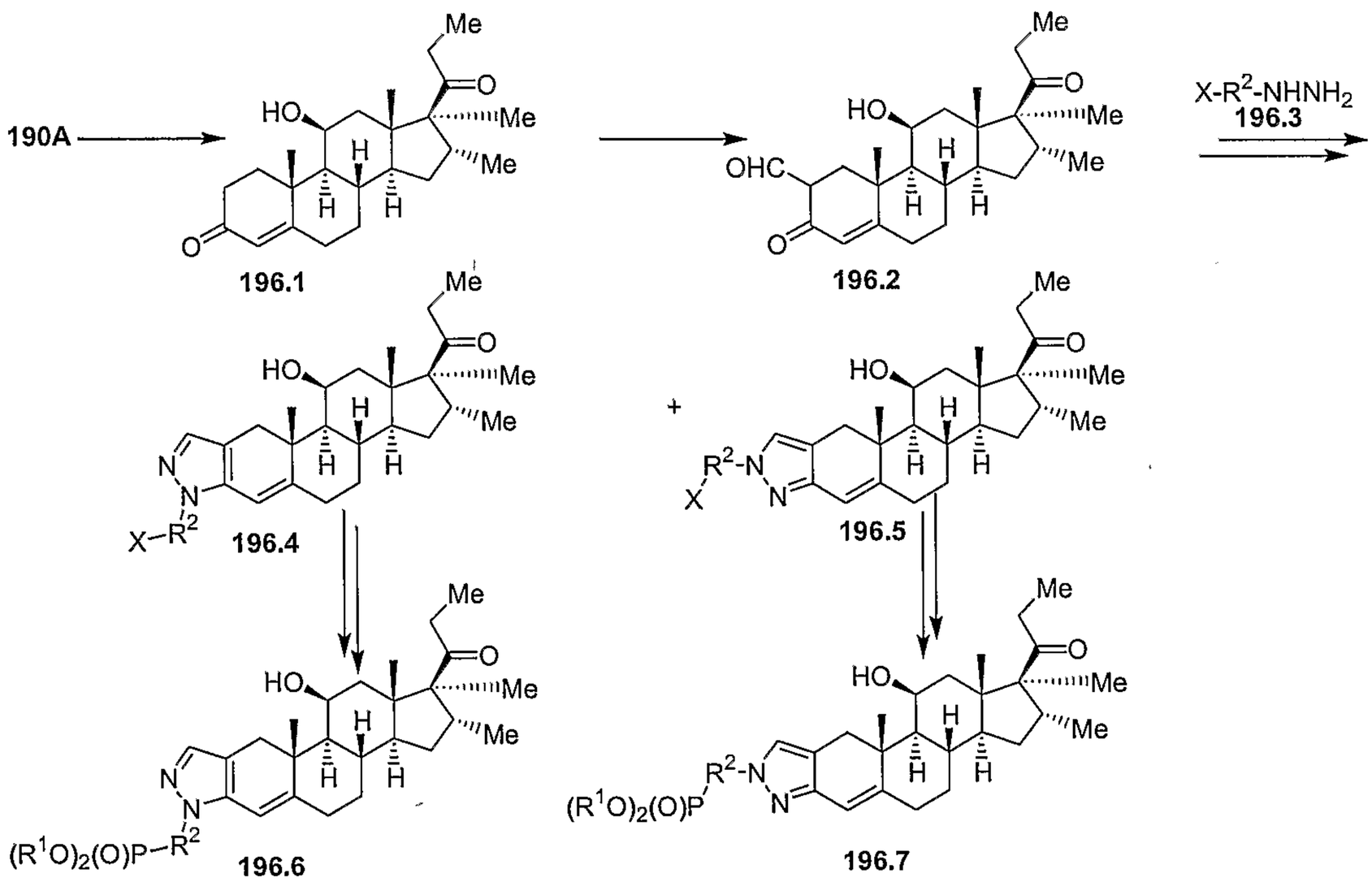
Alternatively, the carboxylic acid may first be converted into an activated derivative such as the acid chloride, anhydride, mixed anhydride, imidazolide and the like, and then reacted with the amine, in the presence of an organic base such as, for example, pyridine, to afford the amide.

The conversion of a carboxylic acid into the corresponding acid chloride can be effected by treatment of the carboxylic acid with a reagent such as, for example, thionyl chloride or oxalyl chloride in an inert organic solvent such as

dichloromethane, optionally in the presence of a catalytic amount of dimethylformamide.

Using the above procedures, but employing, in place of the carboxy-substituted hydroxylamine, **195.1**, different carboxy-substituted hydroxylamines, and/or different amino-substituted phosphonates, the products analogous to **195.4** are obtained.

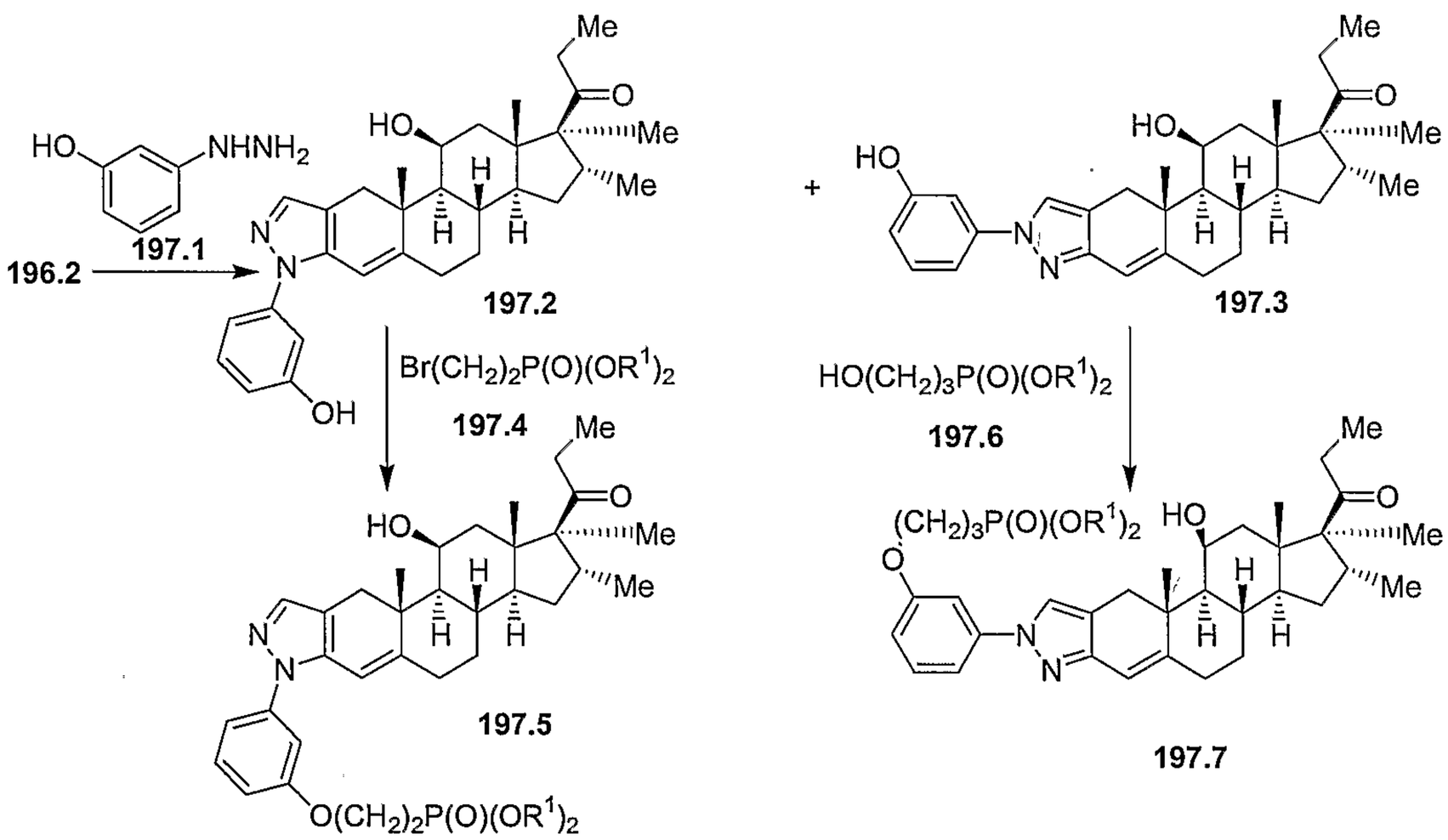
Example 196



The dienone, **190A**, is reduced to afford the 1,2-dihydro product, **196.1**. The catalytic hydrogenation reaction is effected by the use of tris(triphenyl-phosphine)rhodium (I) chloride, for example as described in *J. Med. Chem.*, **2001**, *44*:, 602. The product is then reacted with ethyl formate and a base such as sodium hydride, in an inert solvent such as toluene or dimethylformamide, as described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520, to afford the 2-formyl product, **196.2**. This compound is then reacted with an alkyl, aralkyl, aryl or heteroaryl hydrazine, **196.3**, in which the substituent X is either a phosphonate group or a group which is subsequently transformed into a phosphonate-containing substituent. For example, X is dialkylphosphono, bromo, hydroxy, amino, carboxyl and the like. The reaction yields the isomeric 2'- and 1'-aryl pyrazoles, **196.4** and **196.5**. The pyrazole-forming reaction is performed between

equimolar amounts of the reactants in an acidic solvent such as acetic acid, as described in *J. Am. Chem. Soc.*, **1964,** *86*, 1520. The pyrazoles, **196.4** and **196.5**, are then transformed, for example, by the procedures described in Examples **192** and **193**, into the phosphonates, **196.6** and **196.7**. Optionally, the reduction and formylation reactions are performed on the substrate, **190.1**, in which the 20-ketone is protected as the cyclic ethylene ketal.

Example 197



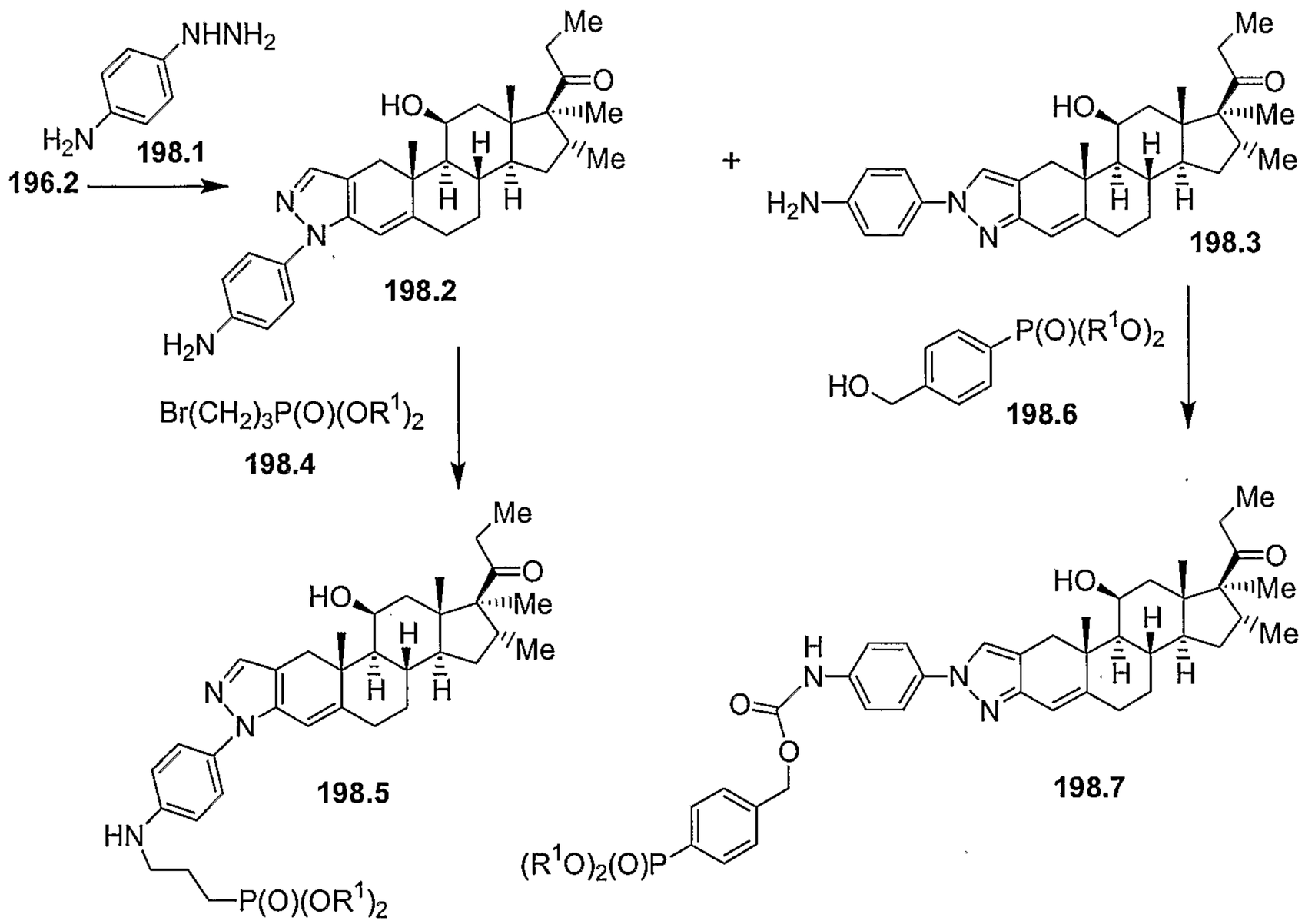
The ketoaldehyde, **196.2**, is reacted, as described above, with 3-hydroxy-phenyl hydrazine, **197.1**, (JP 03011081) to give the pyrazoles, **197.2** and **197.3**. The 2'-substituted isomer, **197.2**, is then reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl 2-bromoethyl phosphonate, **197.4**, (Aldrich) and potassium carbonate, to give the ethoxy phosphonate, **197.5**.

The isomeric pyrazole, **197.3**, is reacted in a Mitsonobu with one molar equivalent of a dialkyl 3-hydroxypropyl phosphonate, **197.6**, (*Zh. Obschei. Khim.*, **1974**, *44*, 1834) to yield the phosphonate, **197.7**. The preparation of aromatic ethers by means of the Mitsonobu reaction is described, for example, in R. C. Larock, *Comprehensive Organic Transformations*, 448 (VCH, **1989**), and in F.A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Part B, 153-4 (Plenum, **2001**) and in *Org. React.*, **1992**, *42*, 335. The phenol and the alcohol or thiol component are reacted together in an aprotic solvent such as, for

example, tetrahydrofuran, in the presence of a dialkyl azodicarboxylate and a triarylphosphine, to afford the ether or thioether products. The procedure is also described in *Org. React.*, **1992**, *42*, 335-656.

Using the above procedures, but employing different hydroxy-substituted hydrazines, and/or different bromo or hydroxy-substituted phosphonates, the products analogous to **195.5** and **197.6** are obtained.

Example 198



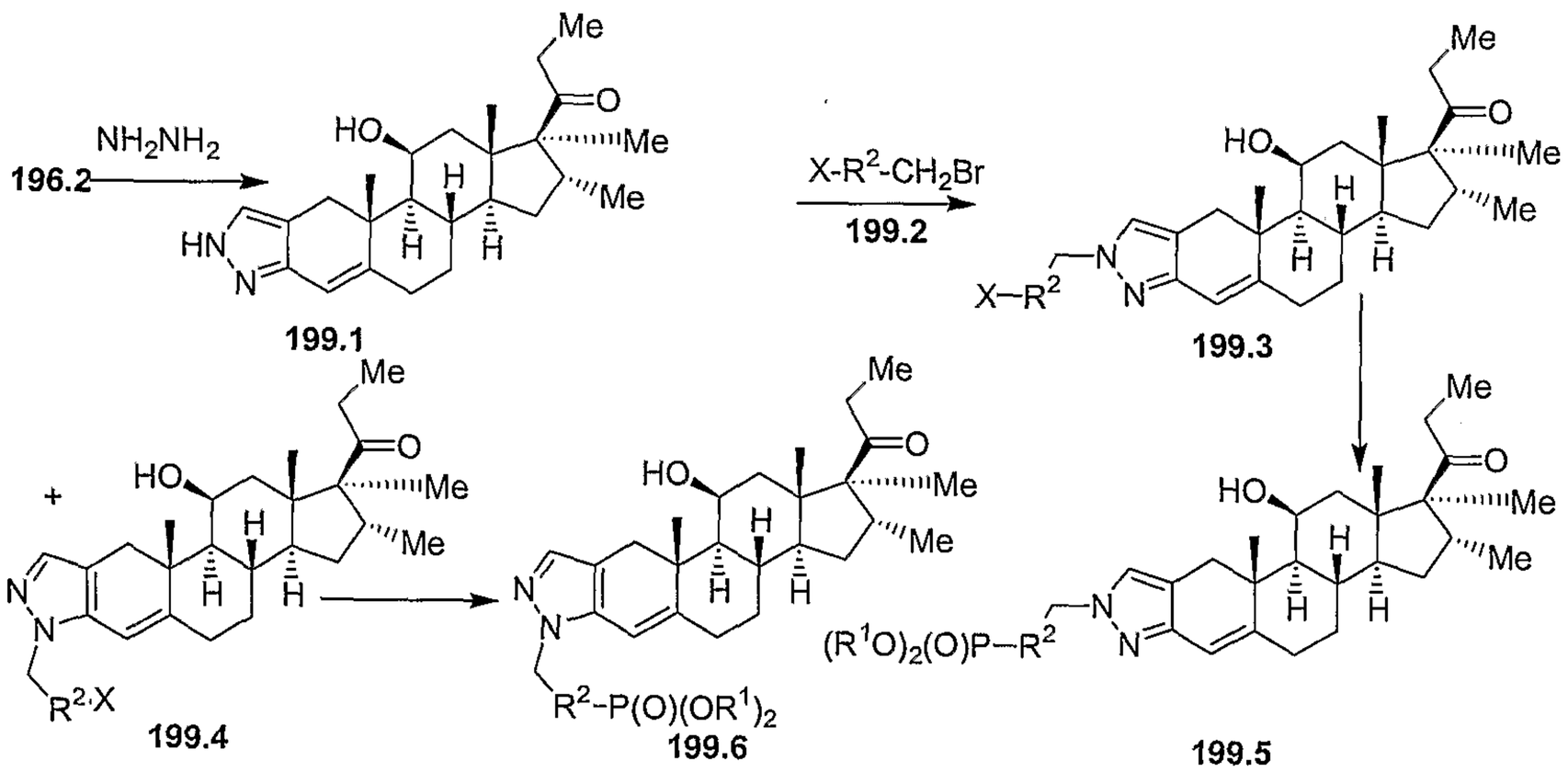
The ketoaldehyde, **196.2**, is reacted, as described above, with 4-amino-phenyl hydrazine, **198.1**, (*Syn. Comm.*, **1974**, *4*, 57) to produce the pyrazoles, **198.2** and **198.3**. The 2'-substituted isomer, **198.2**, is then reacted in dimethylformamide solution at 70° with one molar equivalent of a dialkyl 3-bromopropyl phosphonate, **198.4**, (*J. Amer. Chem. Soc.*, **2000**, *122*, 1554) and cesium carbonate, to give the amine phosphonate, **198.5**.

Alternatively, the 1'-substituted pyrazole, **198.3**, is coupled with a dialkyl 4-hydroxymethylphenyl phosphonate, **198.6**, (U.S. Patent No. 5,569,664) and carbonyl diimidazole to prepare the carbamate phosphonate, **198.7**. The preparation of carbamates is described in *Comprehensive Organic Functional*

Group Transformations, A. R. Katritzky, ed., Pergamon, **1995**, Vol. *6*, p 416ff, and in *Organic Functional Group Preparations*, by S. R. Sandler and W. Karo, Academic Press, **1986**, p. 260ff. In the procedure, the amine is reacted in an inert aprotic solvent such as dichloromethane or tetrahydrofuran, with phosgene or a functional equivalent thereof, such as carbonyl diimidazole, triphosgene, pentafluorophenyl carbonate and the like, to afford the corresponding activated acylamine. The latter compound is then reacted with an alcohol to yield the carbamate.

Using the above procedures, but employing, in place of the aminophenyl hydrazine, **198.1**, different amino-substituted hydrazines, and/or different dialkyl bromo or hydroxy-substituted phosphonates, the products analogous to the compounds, **198.5** and **198.7** are obtained.

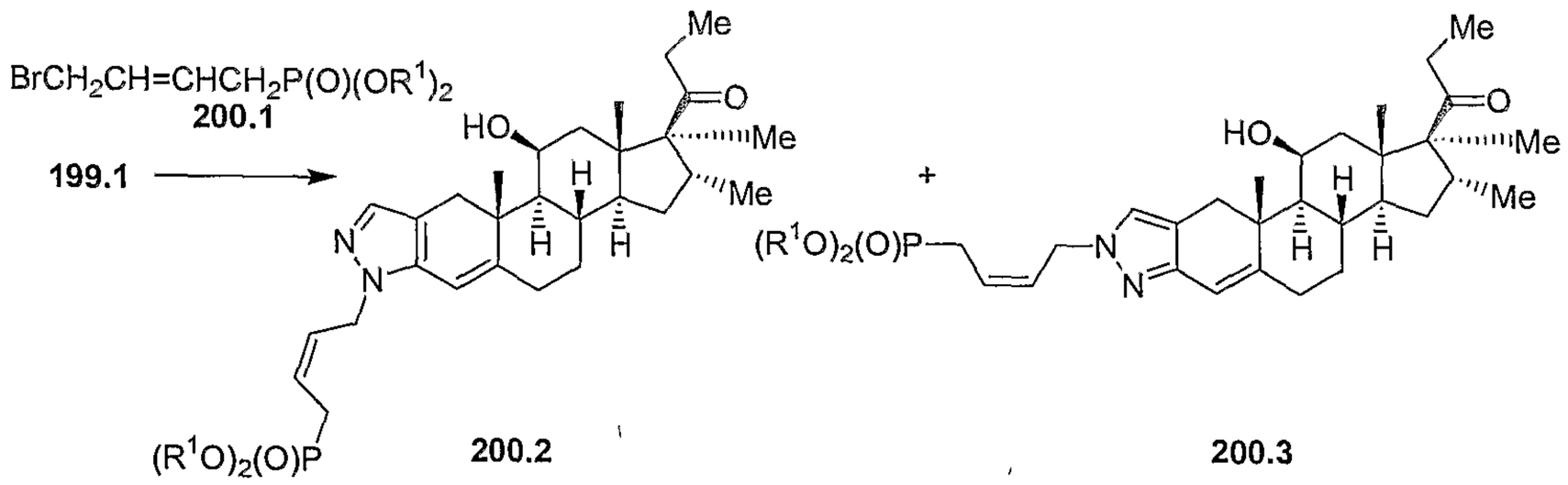
Example 199



The ketoaldehyde, **196.2**, is reacted with hydrazine to afford the pyrazole derivative, **199.1**. The reaction of steroidal 2-formyl-3-ketones with hydrazine is described in *J. Am. Chem. Soc.*, **1964**, *86*, 1520. The reaction is performed in acetic acid at ambient temperature. The pyrazole product is then reacted with a bromomethyl compound, **199.2**, in which R^2 and X are as defined above, or a reactive bromoheteroaromatic reagent, to yield the alkylation products, **199.3** and **199.4**. The alkylation of substituted pyrazoles is described, for example, in *Heterocyclic Chemistry*, by T. L. Gilchrist, Longman, **1992**, p. 309. The reaction is performed between equimolar amounts of the substrates in a polar

solvent such as dimethylformamide or tetrahydrofuran, in the presence of a base such as dimethylaminopyridine, lithium hexamethyldisilazide and the like. The products, **199.3** and **199.4**, are, except in cases where X is dialkylphosphono, converted into the phosphonates, **199.5** and **199.6**, using the procedures described herein.

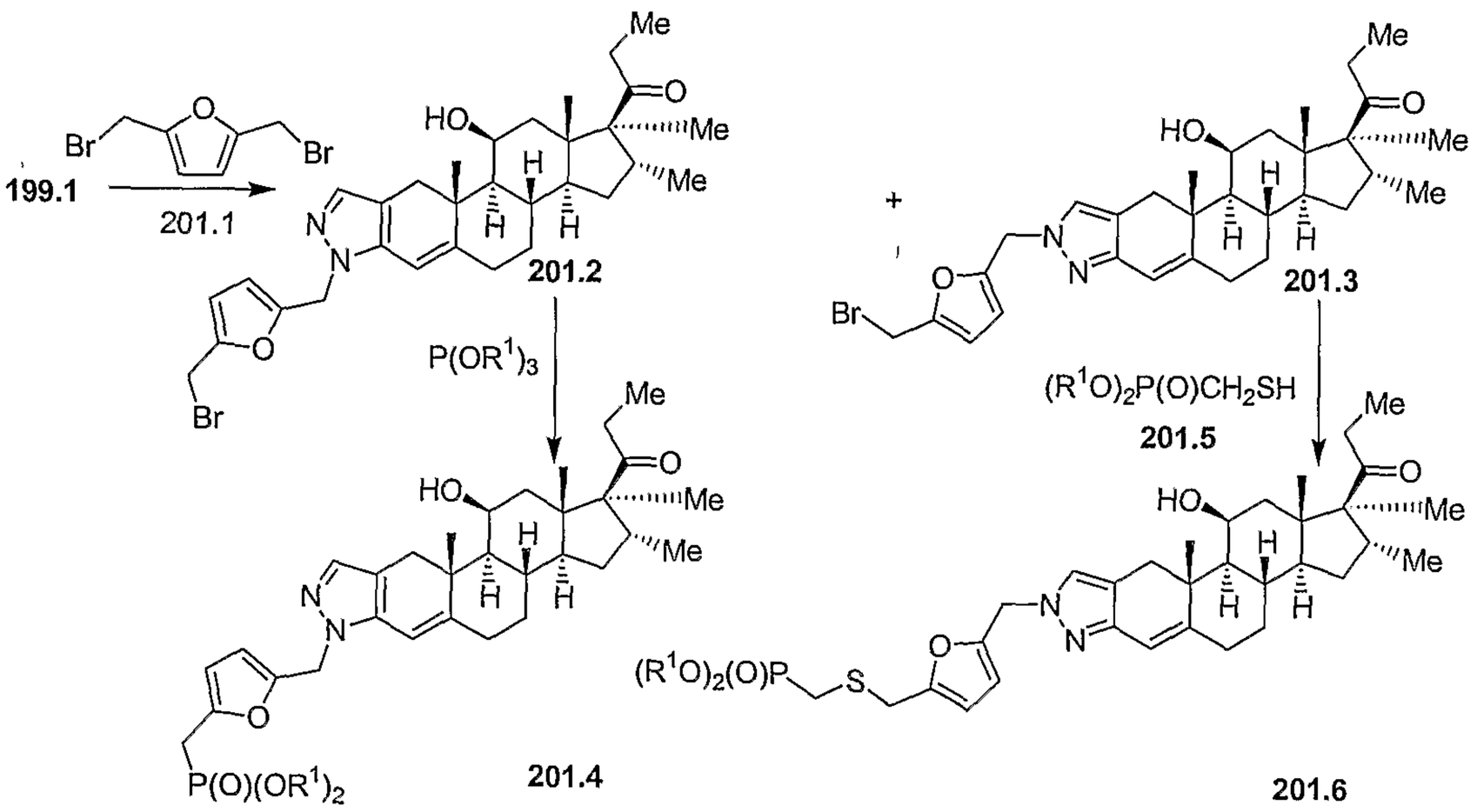
Example 200



The pyrazole, **199.1**, is reacted in dimethylformamide solution at 70°C with one molar equivalent of a dialkyl 4-bromobutenyl phosphonate, **200.1**, (*J. Med. Chem.*, **1992**, *35*, 1371) and lithium hexamethyl disilazide, to give the pyrazoles, **200.2** and **200.3**.

Using the above procedures, but employing different bromo-substituted phosphonates, the products analogous to **200.2** and **200.3** are obtained.

Example 201

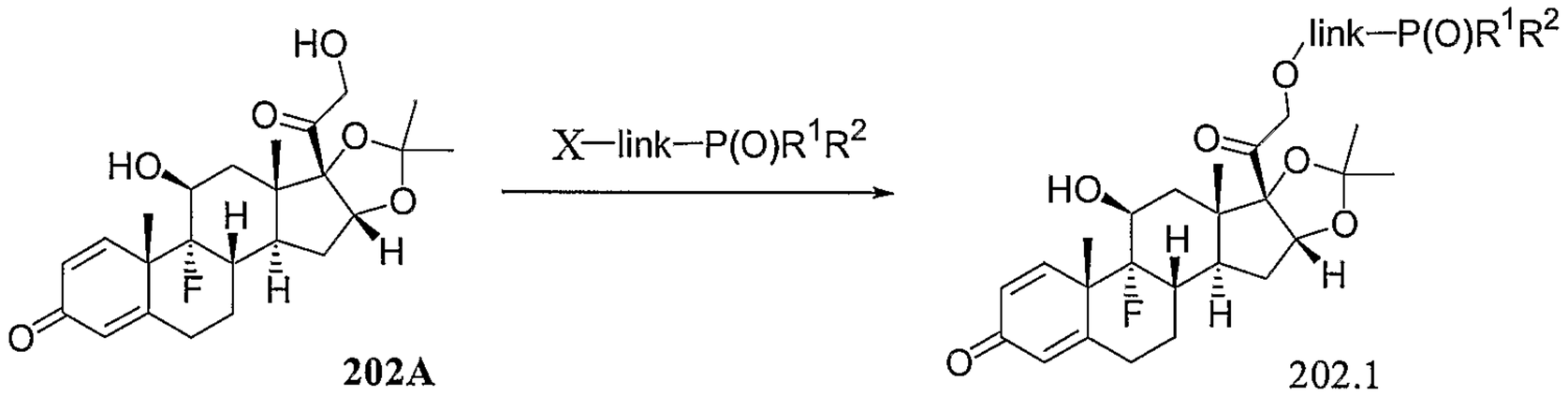


The pyrazole, **199.1**, is reacted in tetrahydrofuran solution with 2,5-bis(bromomethyl)furan, **201.1**, (*Tet.*, **1999**, *55*, 4709) and potassium hexamethyl disilazide, to give the alkylation products, **201.2** and **201.3**. The 2'-substituted isomer, **201.2**, is then reacted, in a Arbuzov reaction, with a trialkyl phosphite to yield the phosphonate, **201.4**. The Arbuzov reaction is described in *Handb. Organophosphorus Chem.*, **1992**, 115. In this procedure, in which a bromo substituent is converted into the corresponding phosphonate, the substrate is heated at from about 60° to about 160° with a five to fifty-fold molar excess of a trialkyl phosphite, to effect the transformation.

The 1'-substituted pyrazole, **201.3**, is reacted at ambient temperature in dimethylformamide solution with one molar equivalent of a dialkyl mercapto-methyl phosphonate, **201.5**, (*J. Med. Chem.*, **1985**, *26*, 1688) and cesium carbonate, to give the thioether phosphonate, **201.6**.

Using the above procedures, but employing different dihalides, and/or different mercapto-substituted phosphonates, the products analogous to **201.4** and **201.6** are obtained.

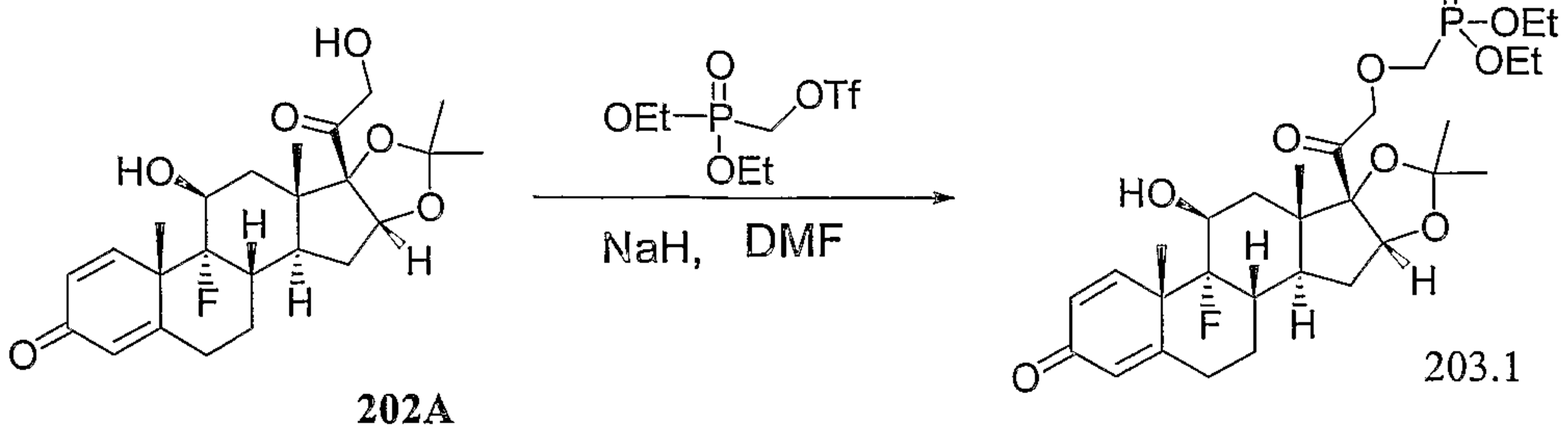
Example 202



202A 202.1

Derivatives of the C-21 primary hydroxy group of the type, **202.1**, are readily prepared by alkylating triamcinolone acetonide, **202A**, with the appropriate phosphonate as shown.

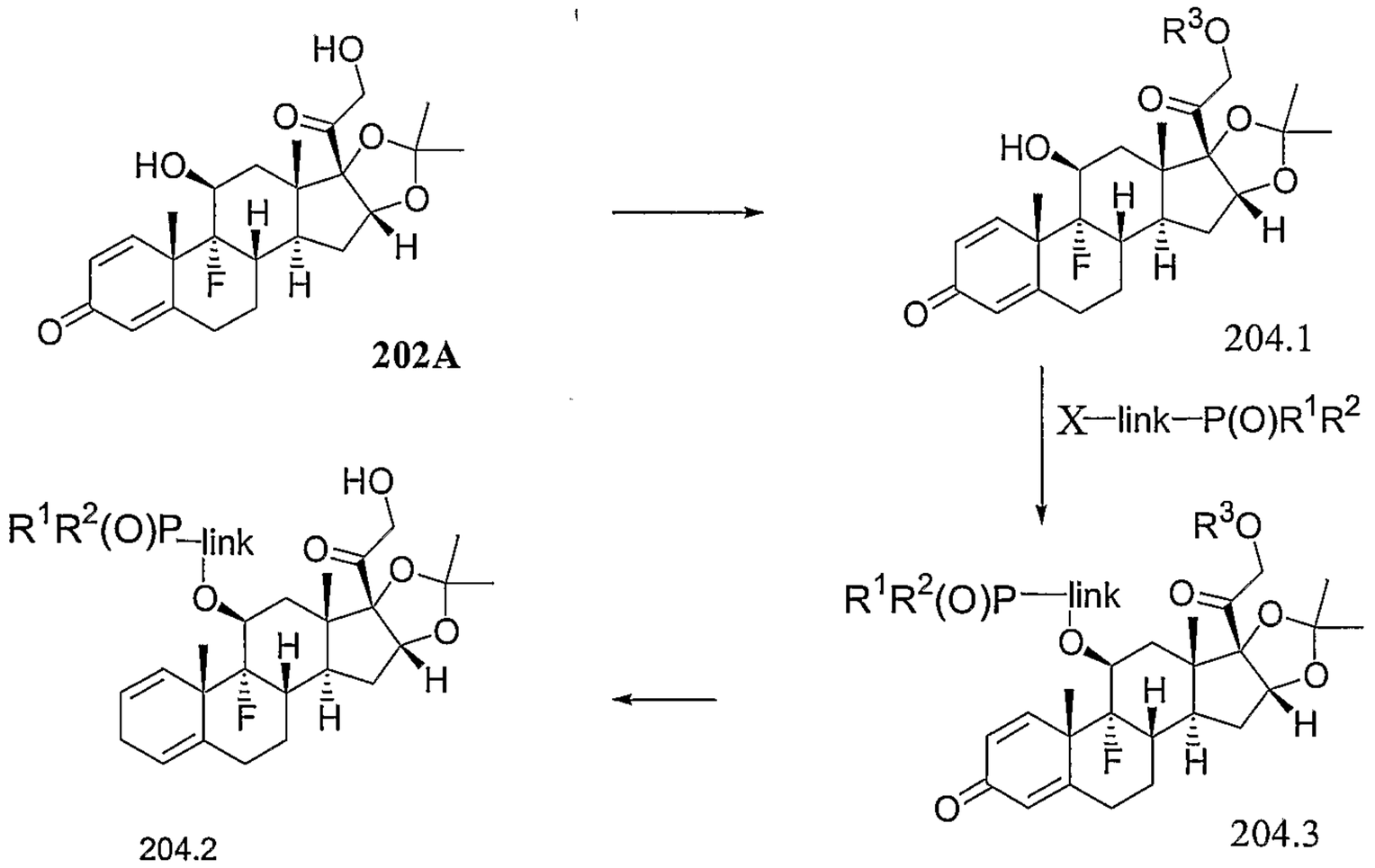
Example 203



202A 203.1

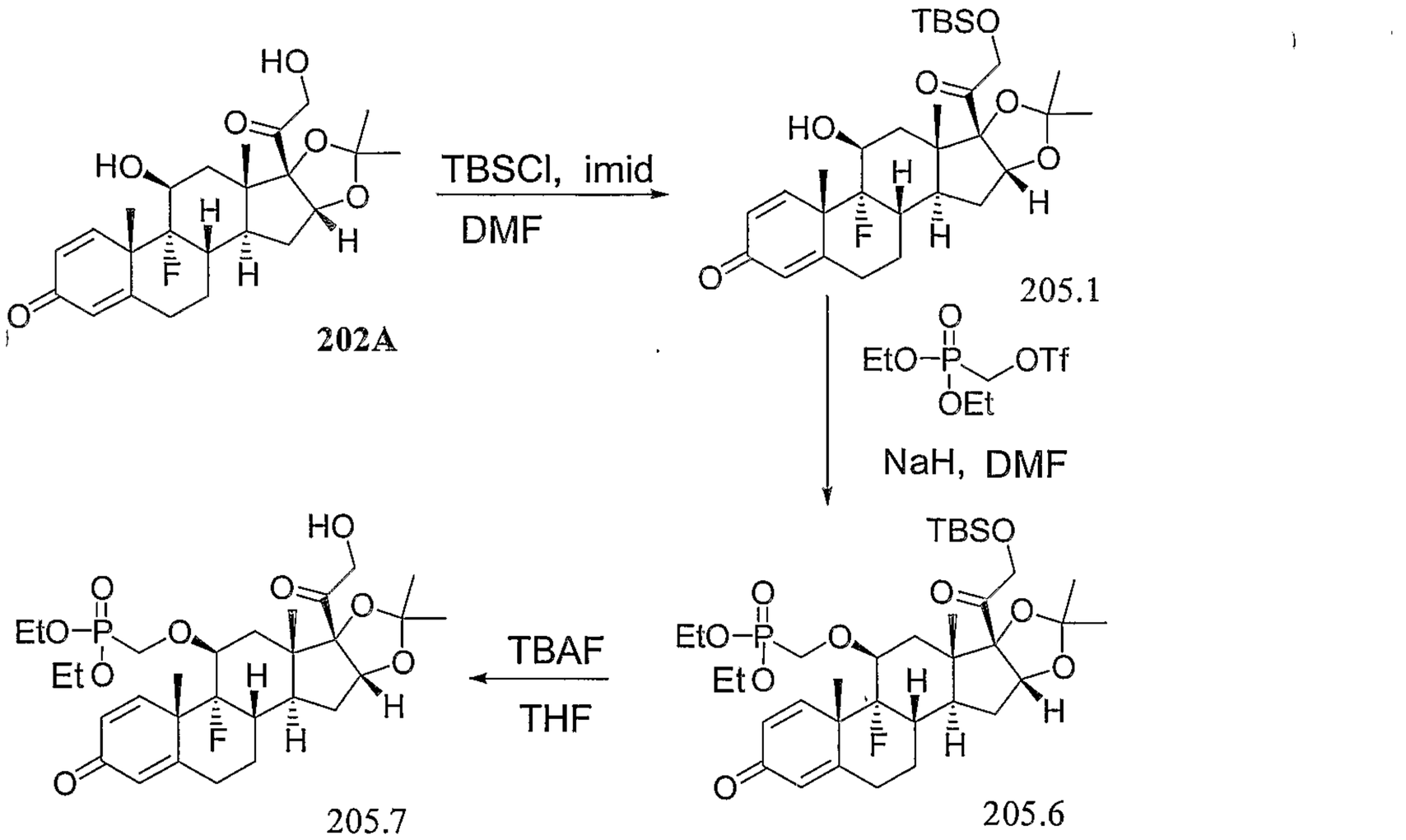
After chemoselective extraction of the primary hydroxy proton of compound, **202A**, using one equivalent of sodium hydride, the phosphonate triflate is added to provide the ether, **203.1**.

Example 204



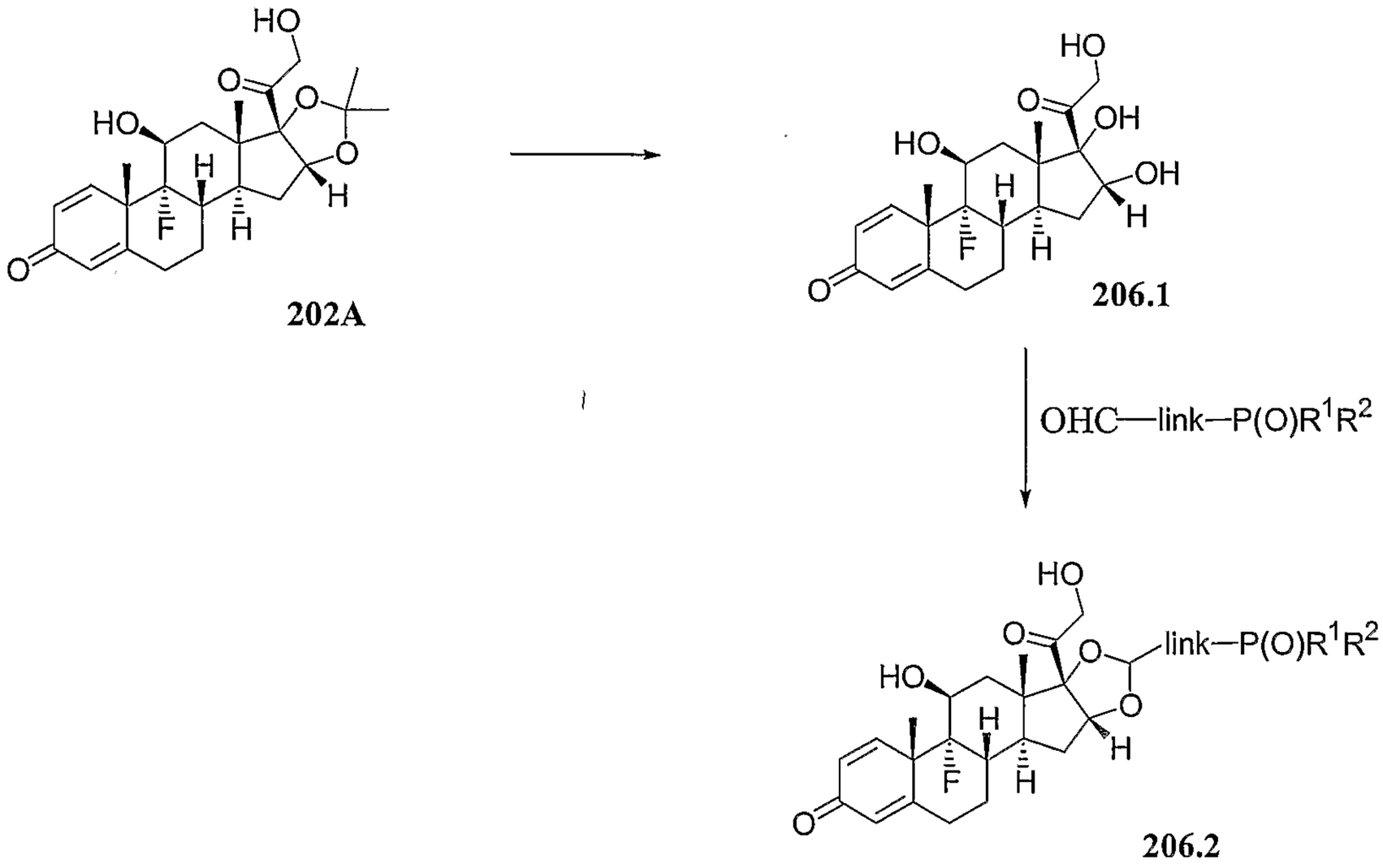
The primary hydroxy group is masked by an appropriate protecting group. After alkylation at the secondary hydroxy moiety of, **204.1**, with a leaving group-attached phosphonate and subsequent deprotection, desired analog, **204.2,** is obtained.

Example 205



Triamcinolone acetonide, **202A**, is chemoselectively protected as its silyl ether using the standard TBSCl and imidazole conditions (*J. Am. Chem. Soc.* **1972**, *94*, 6190). Alkylation at the exposed secondary hydroxy group with sodium hydride and the phosphonate triflate furnishes the intermediate, **205.6**. Final TBAF deprotection of the silyl ether affords the desired product, **205.7**.

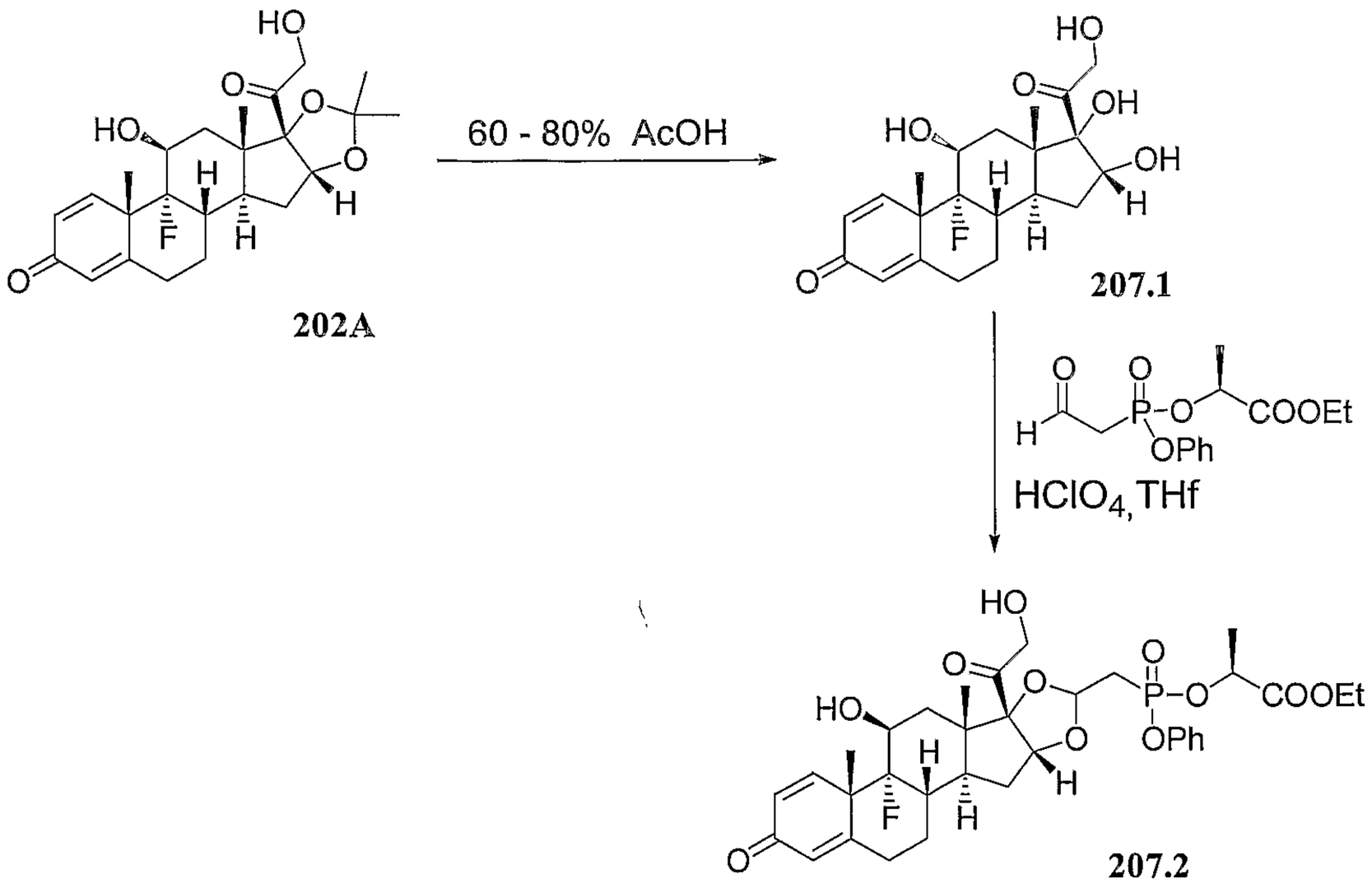
Example 206



Phosphonate derivatives of the acetal are readily prepared from acidic hydrolysis of triamcinolone acetonide, **202A**, to the diol, **206.1**, as illustrated in

Scheme **3.1**. Acetylization of the diol with a phosphonate aldehyde furnishes the desired acetal, **206.2**.

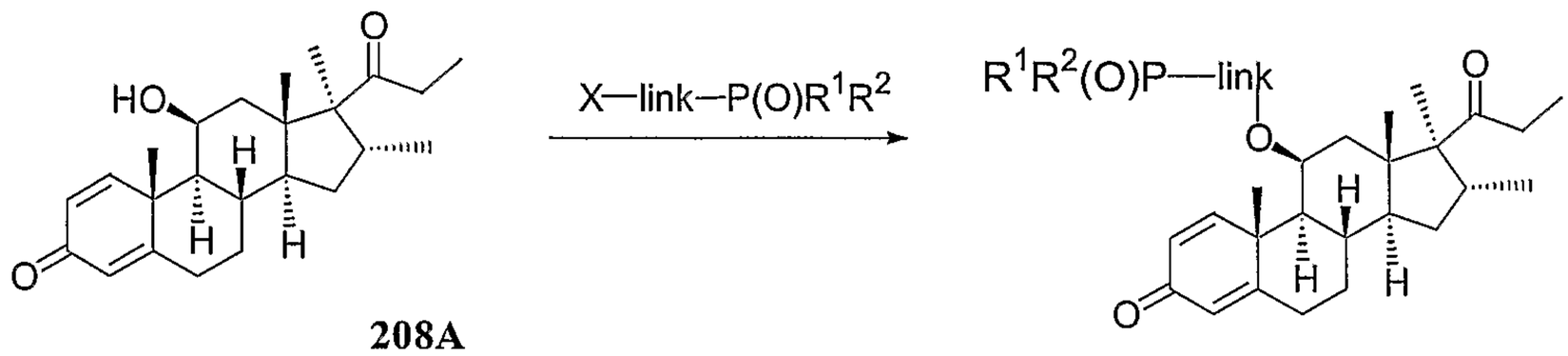
Example 207



202A

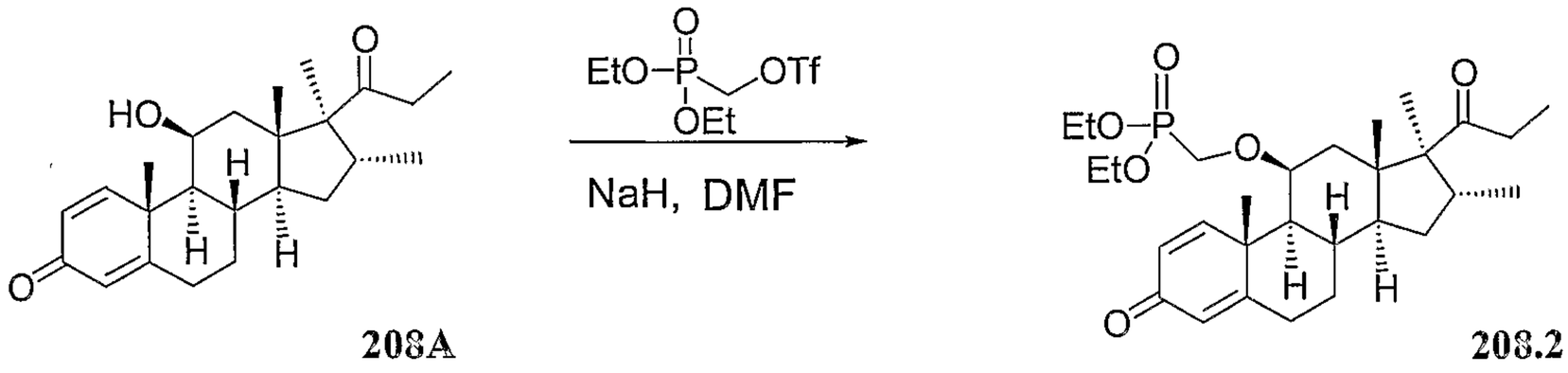
Triamcinolone acetonide, **202A**, is first hydrolized in aqueous acetic acid. (*Can. J. Chem.* **1983**, *61*, 634) The resulting diol, **207.1**, is acetalized with the phosphonate aldehyde and perchloric acid, affording the acetal, **207.2** (*J. Med. Chem.* **1996**, *39*, 4888-4896).

Example 208



208A **208.1**

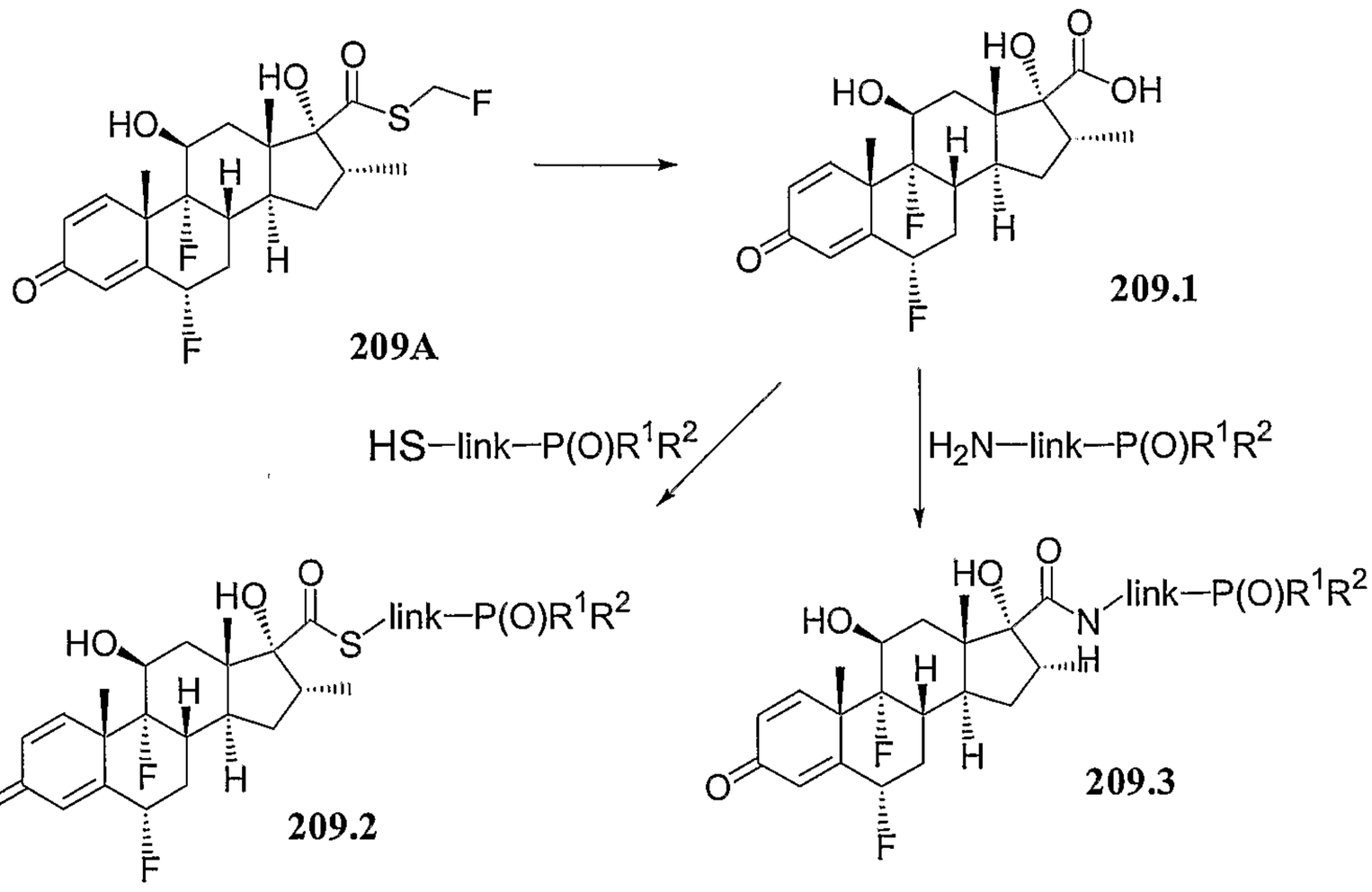
Derivatization at the C-11 hydroxy group is accomplished through alkylation of rimexolone, **208A**, with the appropriate phosphonate, furnishing analogs of the type, **208.1**.



208A **208.2**

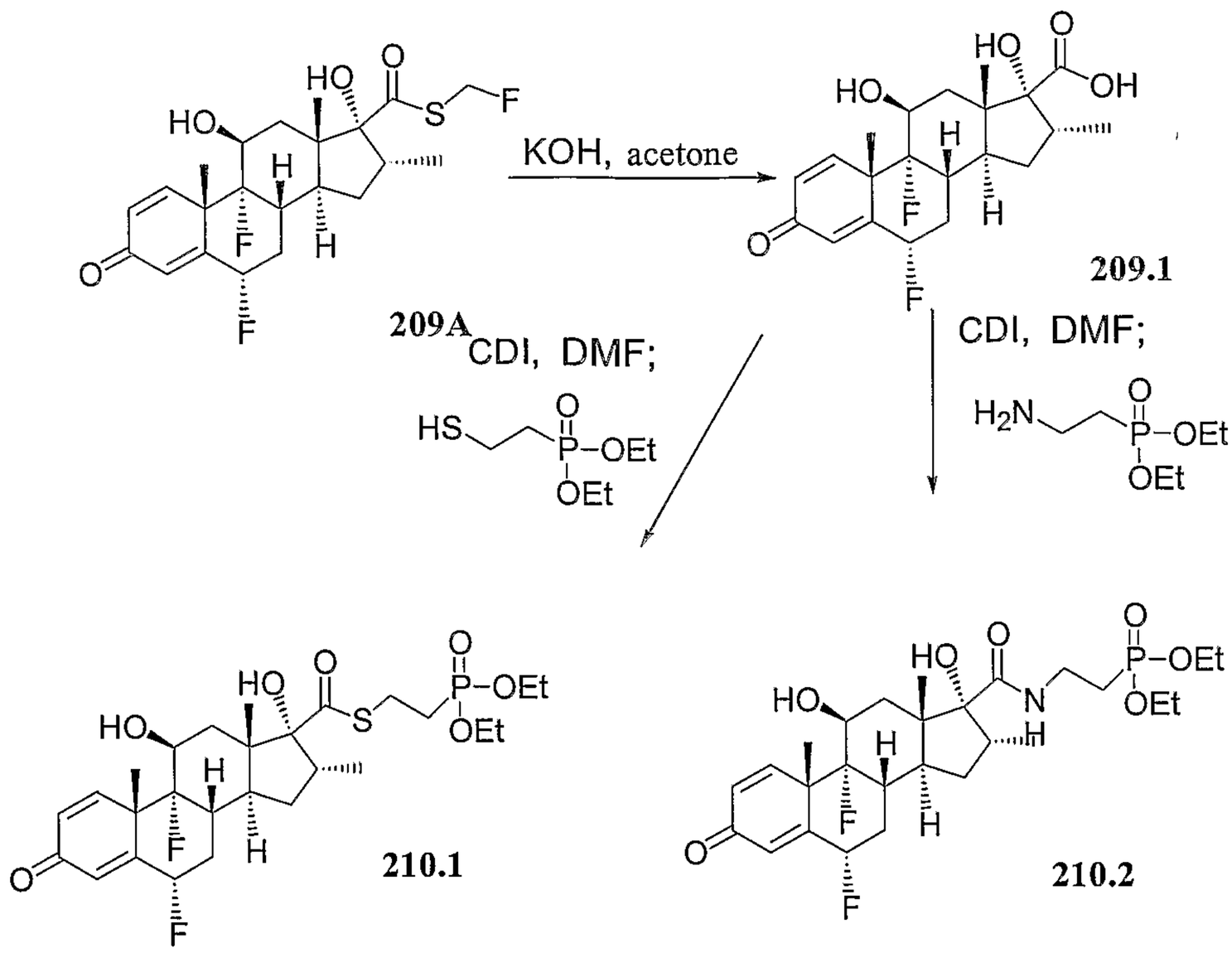
After sodium hydride extraction of the hydroxy proton in, **208A**, diethyl phosphonate triflate is added to afford ether, **208.2**.

Example 209



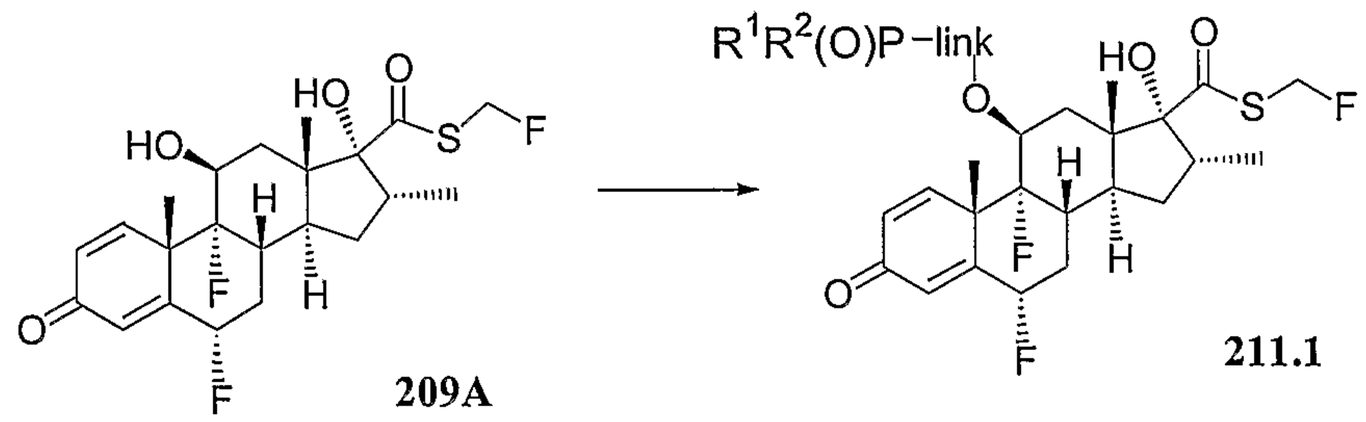
Derivatives of the carbonyl at C-17 are readily prepared from saponification of fluticasone, **209A**, to the carboxylic acid, **209.1**. Activation of the carboxylic acid, followed by reaction with thiophosphonate or aminophosphonate nucleophile furnishes the desired thioester, **209.2**, and amide, **209.3**, respectively.

Example 210



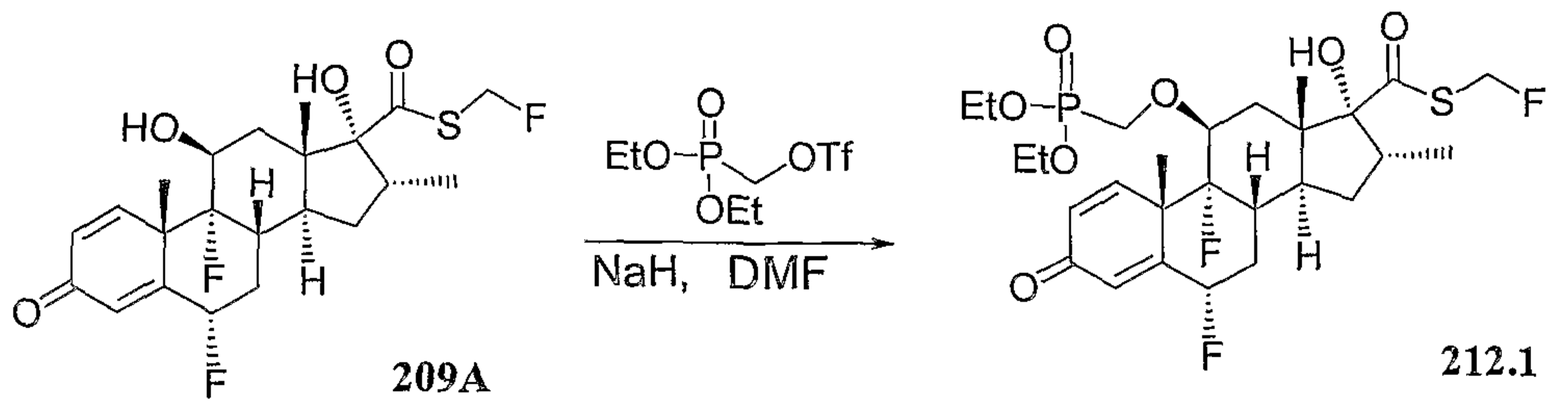
Fluticasone, **209A**, is first saponified with potassium hydroxide in acetone. (*Synthesis*, **2002**, 921-927) The resulting carboxylic acid, **209.1**, is activated to the carboxylic acid imidazole by the addition of 1,1'-carbonyldiimidazole (CDI) (*J. Med. Chem.* **1994**, *37*, 3717-3729). Treatment with the thiophosphonate affords thioester, **210.1**. Magnesium ethoxide may be added to help enhance the reactivity (*Tetrahedron Lett.* **1981**, *22*, 3245-3246). Alternatively, the carboimidazole intermediate derived from, **209.1**, can be reacted with the aminophosphonate to produce amide, **210.2**.

Example 211



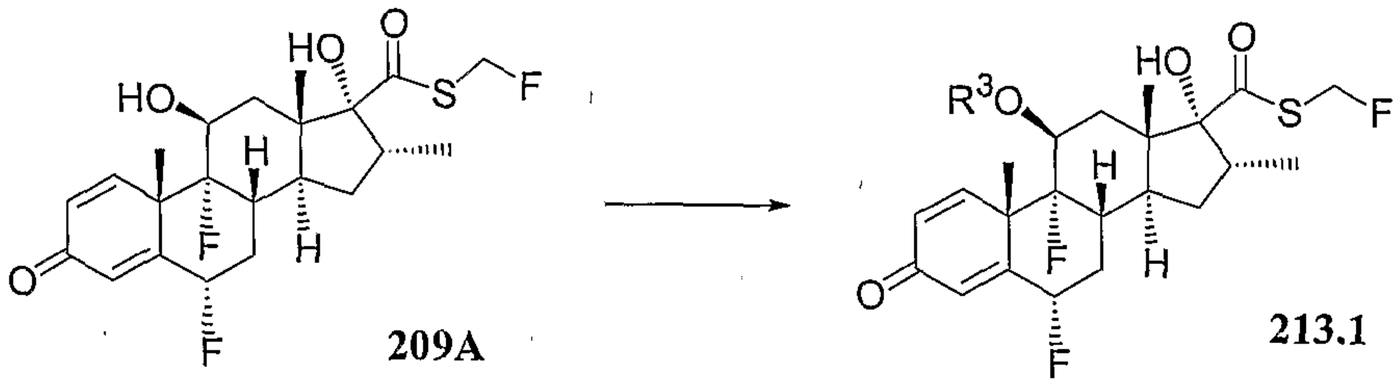
The less sterically hindered C-11 hydroxy group is selectively alkylated with the appropriate phosponate to give analogs of formula, **211.1**.

Example 212



After regioselective extraction of the C-11 hydroxy proton in, **209A**, using one equivalent of sodium hydride, the phosphonate triflate is added to provide the ether, **212.1**.

Example 213



The C-11 hydroxy group is masked by an appropriate protecting group. After alkylation at the C-17 hydroxy moiety of, **213.1**, with a leaving group-attached phosphonate and subsequent deprotection, desired analog, **213.3**, is obtained.

DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

CECI EST LE TOME	1	DE	3
CONTENANT LES PAGES	1	À	359

NOTE : Pour les tomes additionels, veuillez contacter le Bureau canadien des brevets

JUMBO APPLICATIONS/PATENTS

THIS SECTION OF THE APPLICATION/PATENT CONTAINS MORE THAN ONE VOLUME

THIS IS VOLUME	1	OF	3
CONTAINING PAGES	1	TO	359

NOTE: For additional volumes, please contact the Canadian Patent Office

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Claims

We claim:

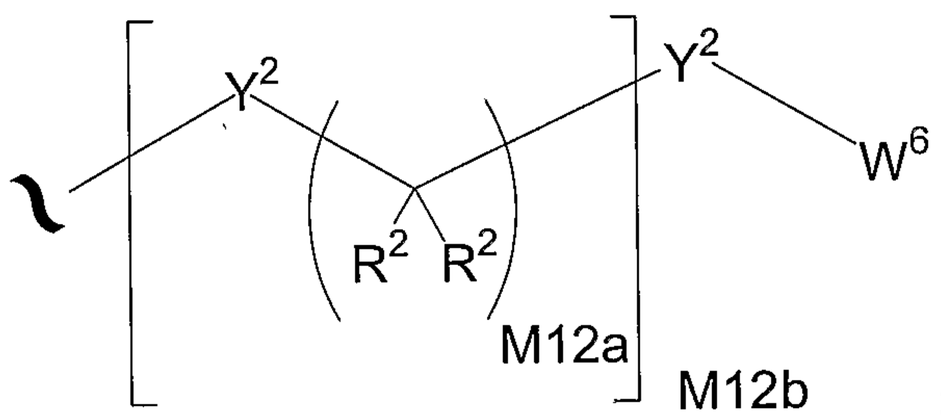
1. A conjugate comprising an immuno-modulatory compound linked to one or more phosphonate groups; or a pharmaceutically acceptable salt or solvate thereof.

2. The conjugate of claim 1, or a pharmaceutically acceptable salt or solvate thereof, that is a compound of any one of formulae **500-547** substituted with one or more groups A^0,

wherein:

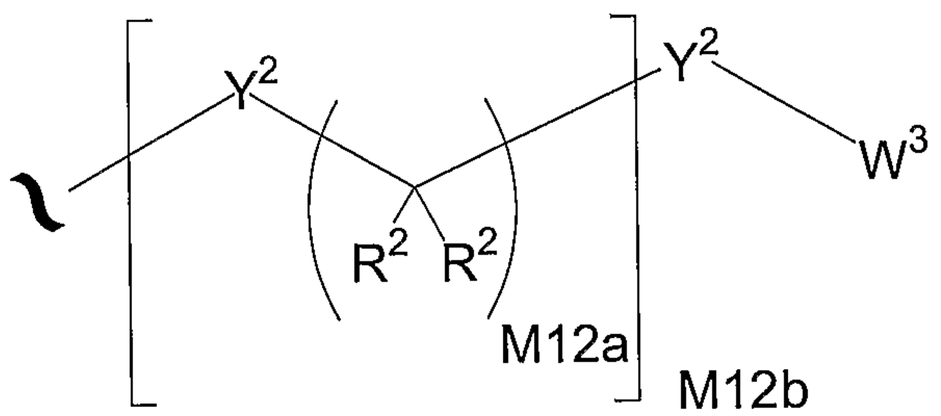
A^0 is A^1, A^2 or W^3 with the proviso that the conjugate includes at least one A^1;

A^1 is:



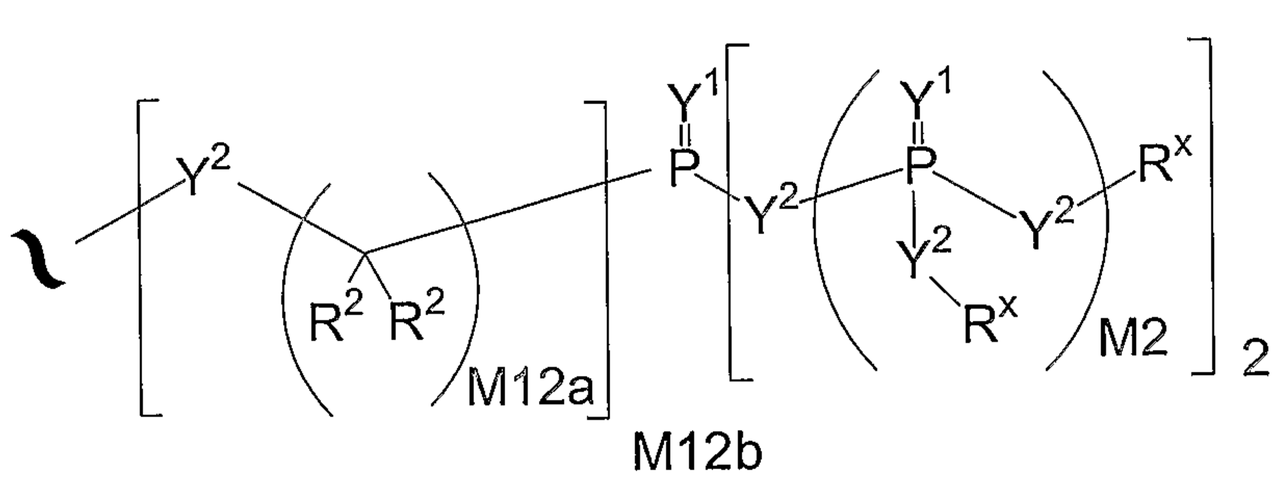
;

A^2 is:



;

A^3 is:

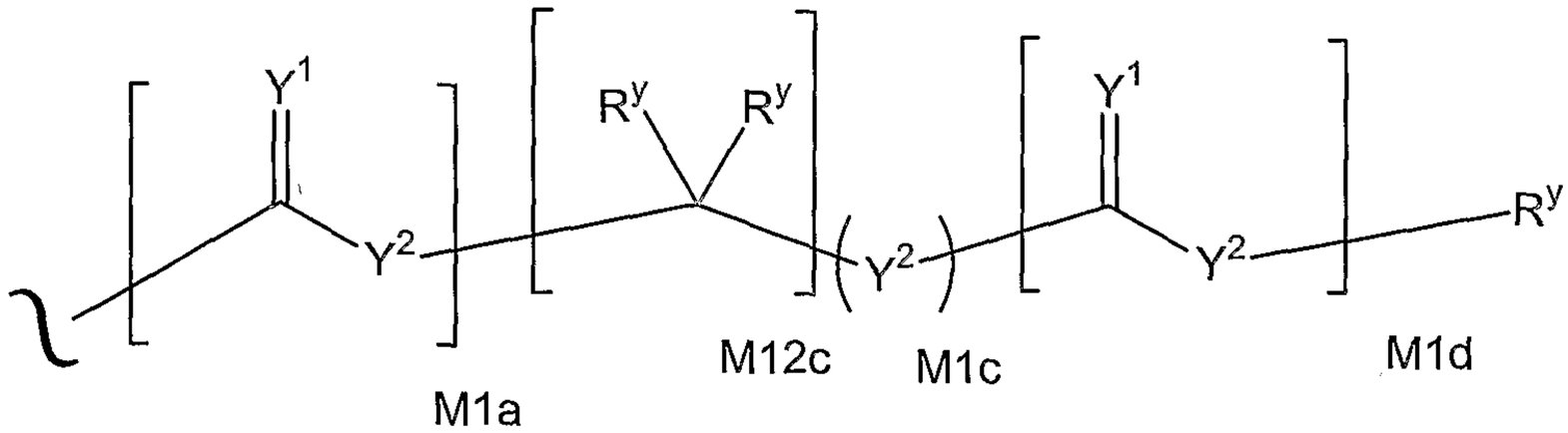


;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$; and when Y^2 joins two phosphorous atoms Y^2 can also be $C(R^2)(R^2)$;

R^x is independently H, R^1, R^2, W^3, a protecting group, or the formula:



;

wherein:

R^y is independently H, W^3, R^2 or a protecting group;

R^1 is independently H or alkyl of 1 to 18 carbon atoms;

R^2 is independently H, R^1, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups or taken together at a carbon atom, two R^2 groups form a ring of 3 to 8 carbons and the ring may be substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_{M2}R^5$, or $-SO_{M2}W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

W^6 is W^3 independently substituted with 1, 2, or 3 A^3 groups;

M2 is 0, 1 or 2;

M12a is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M12b is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

M1a, M1c, and M1d are independently 0 or 1; and

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12.

3. The conjugate of claim 2, or a pharmaceutically acceptable salt or solvate thereof, which has the formula:

$$[DRUG]\text{-}(A^0)_{nn}$$

wherein:

DRUG is a compound of any one of formulae **500-547**; and

nn is 1, 2, or 3.

4. The conjugate of claim 2 which has any one of formulae **1-151** wherein:

one A^0 is A^1; each X^{50} is independently hydrogen, F, Cl, CF_3, CN, methyl, or *tert*-butyl;

X^{51} is hydrogen, halo, trifluoromethyl, (C1-C3)alkyl, cyano, or (C1-C3)alkoxy;

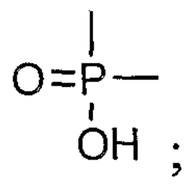
X^{52} is hydrogen, fluoro, chloro, bromo, methyl, or trifluoromethyl;

X^{53} is -O-, or -S-;

X^{54} and X^{55} are independently selected from hydrogen or a C_1-C_{18} acyl;

X^{56} is hydrogen, a C_1-C_{18} acyl, or

or X^{54} is hydrogen and together X^{55} and X^{56} are



X^{57} is H, amino, hydroxy, or a halogen selected from Cl and Br;

X^{58} is hydrogen, F, Cl, CF3, cyano, methyl, or t-butyl;

X^{59} is hydrogen, CH_2OH;

X^{60} is $CO(CH_2)_6CONMe(CH_2)2_SO_3H$;

X^{62} is methyl, chloro, or trifluoromethyl;

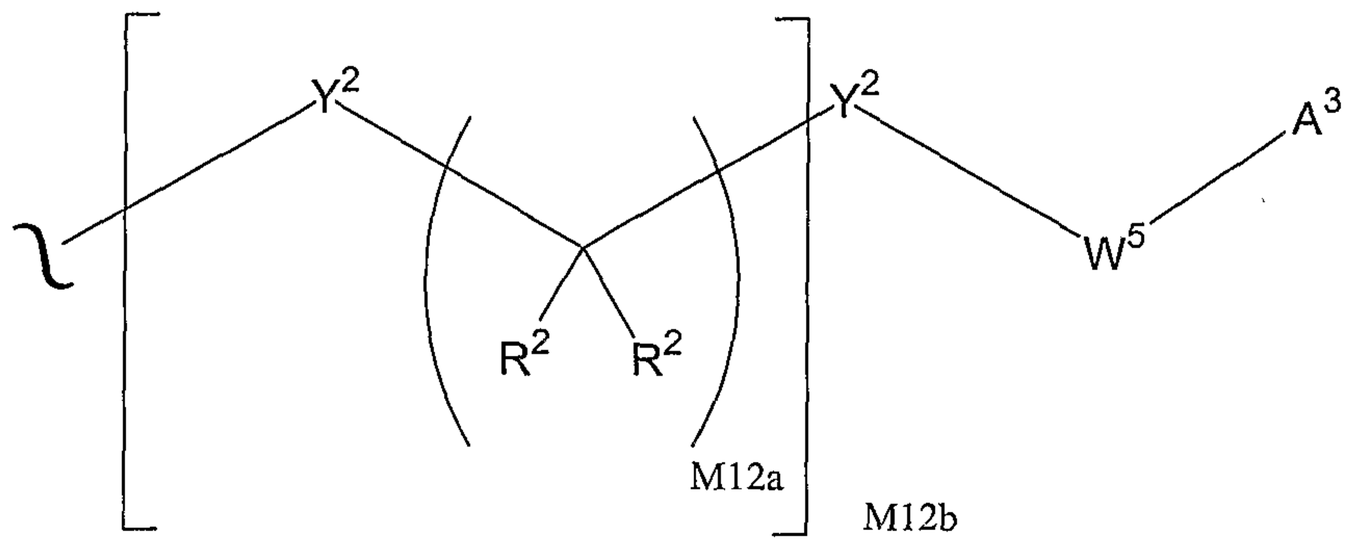
X^{63} is H, methyl, ethyl, cyclopropyl, vinyl, or trifluoromethyl;

X^{64} is H, methyl, ethyl, cyclopropyl, chloro, vinyl, allyl, 3-methyl-1-buten-1-yl;

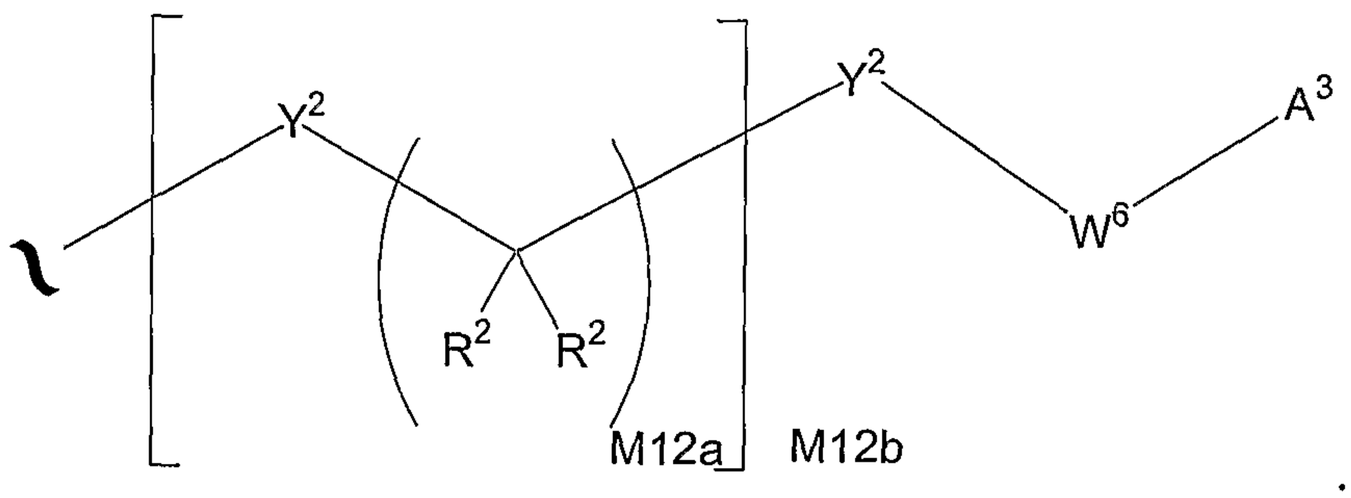
X^{65} is hydrogen or F; and

Ar is aryl or heteroaryl.

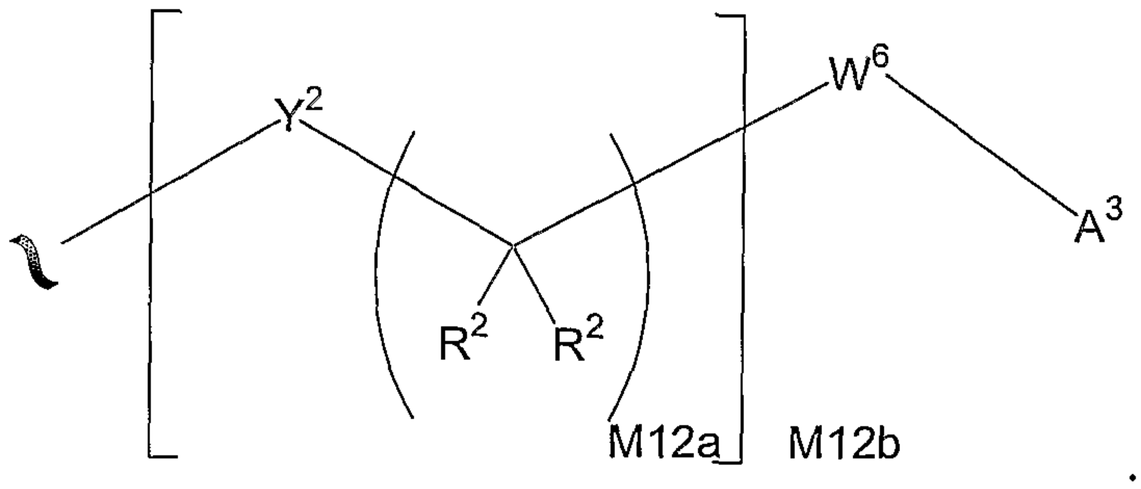
5. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



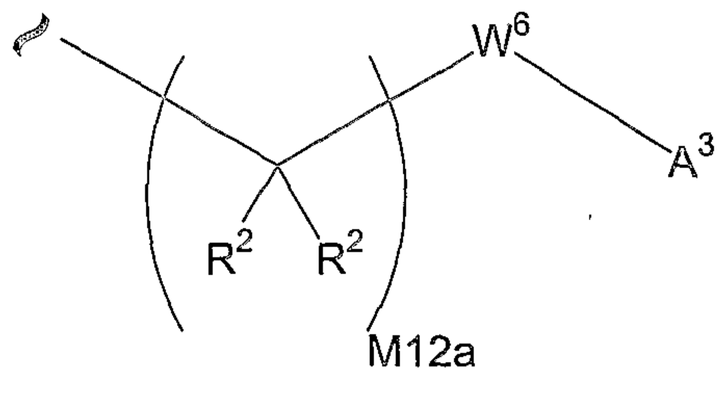
6. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



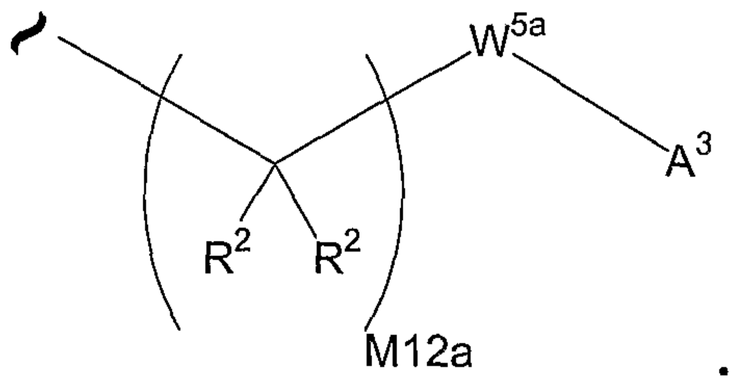
7. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



8. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



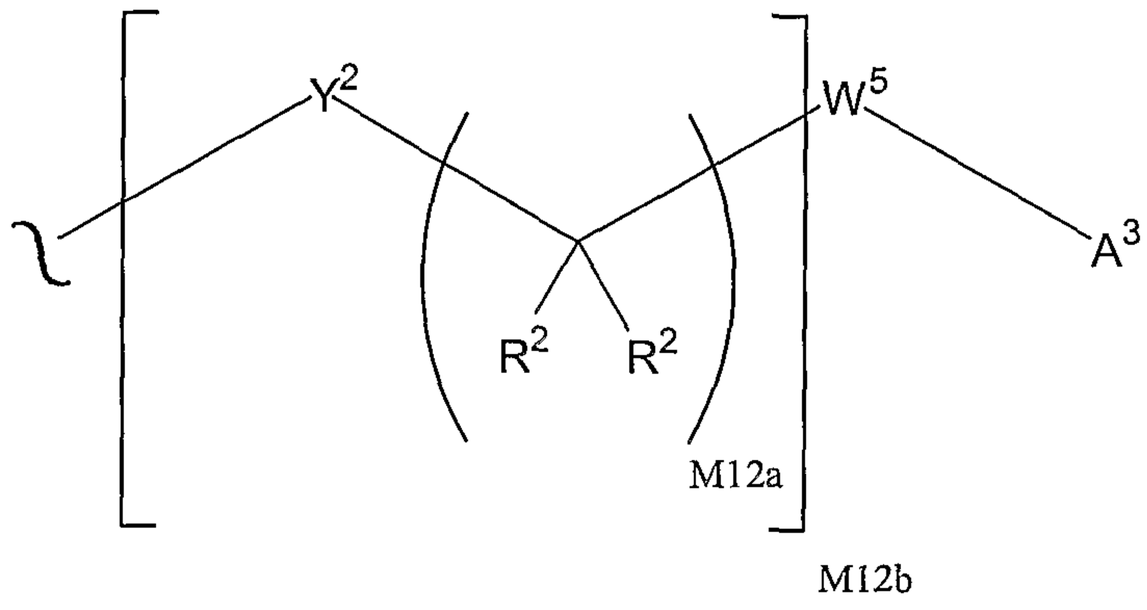
9. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



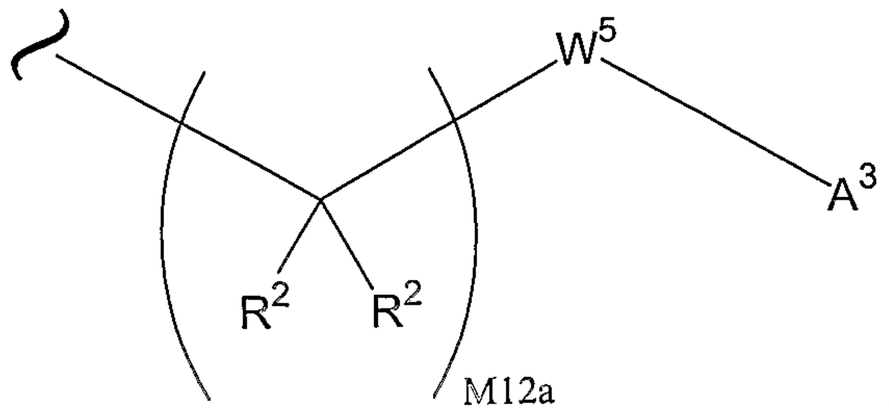
wherein: W^{5a} is a carbocycle or a heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

10. The conjugate of any one of claims 2-4, wherein M12a is 1.

11. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:

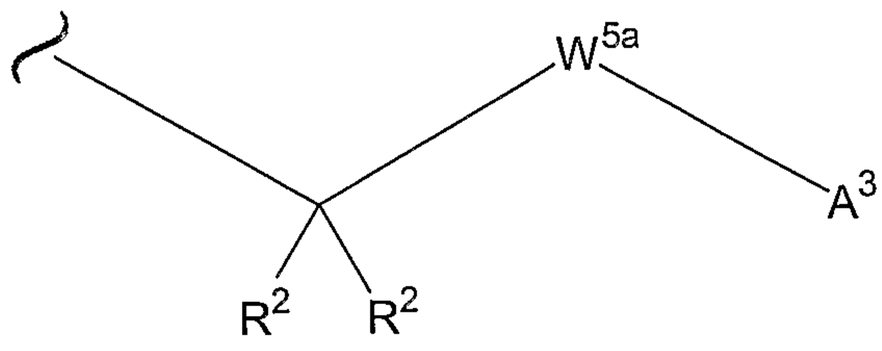


12. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



M12a .

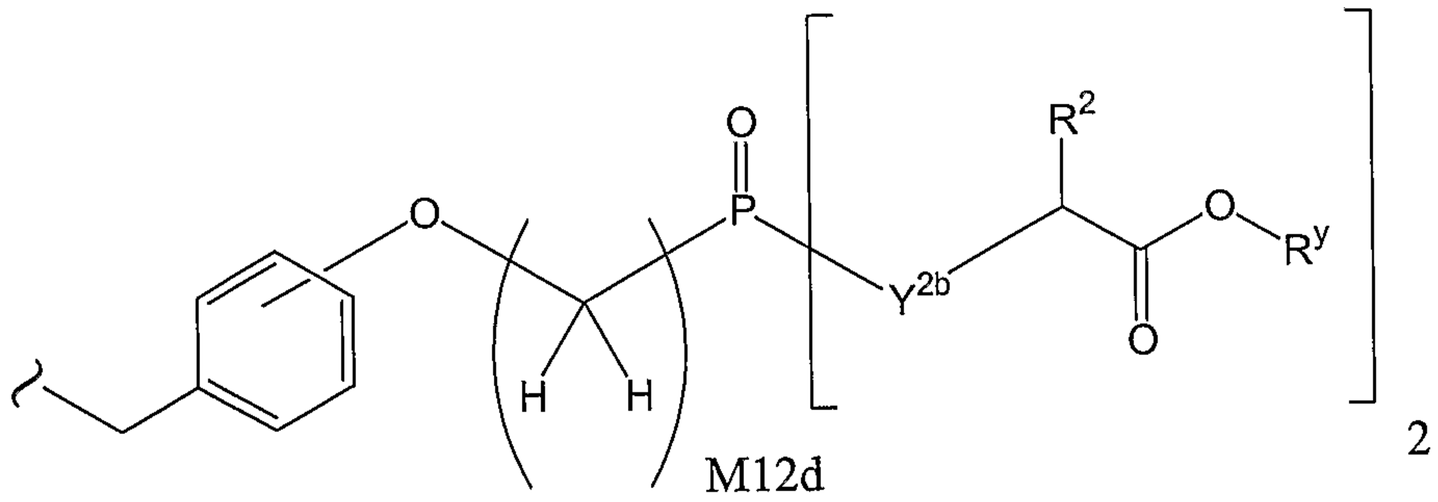
13. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



;

wherein: W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups.

14. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



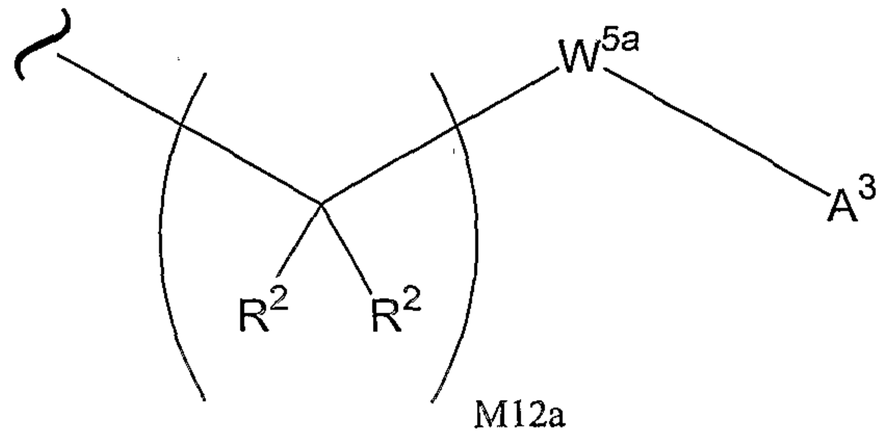
M12d

wherein:

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

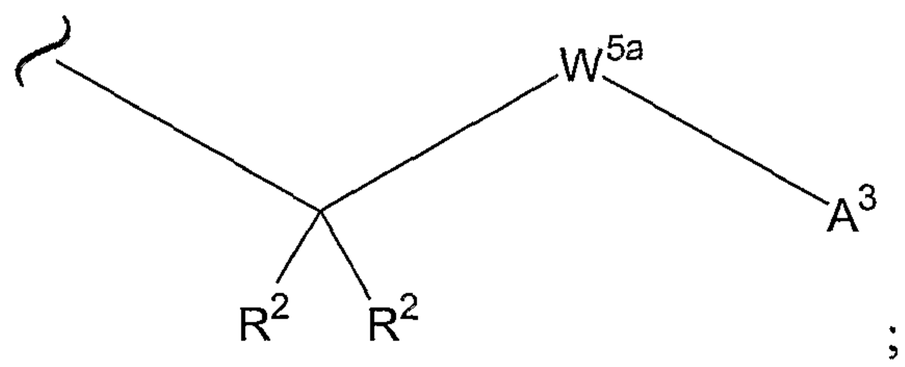
15. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



M12a ;

wherein: W^{5a} is a carbocycle independently substituted with 0 or 1 R^2 groups.

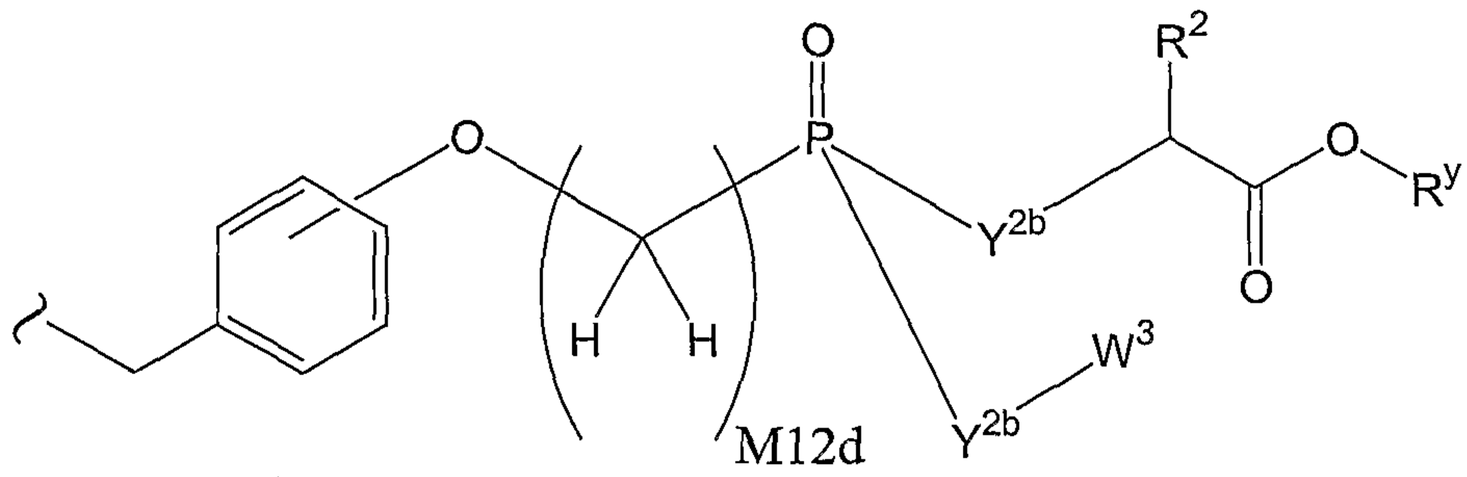
16. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



;

wherein: W^{5a} is a carbocycle or heterocycle where W^{5a} is independently substituted with 0 or 1 R^2 groups.

17. The conjugate of any one of claims 2-4, wherein each A^1 is of the formula:



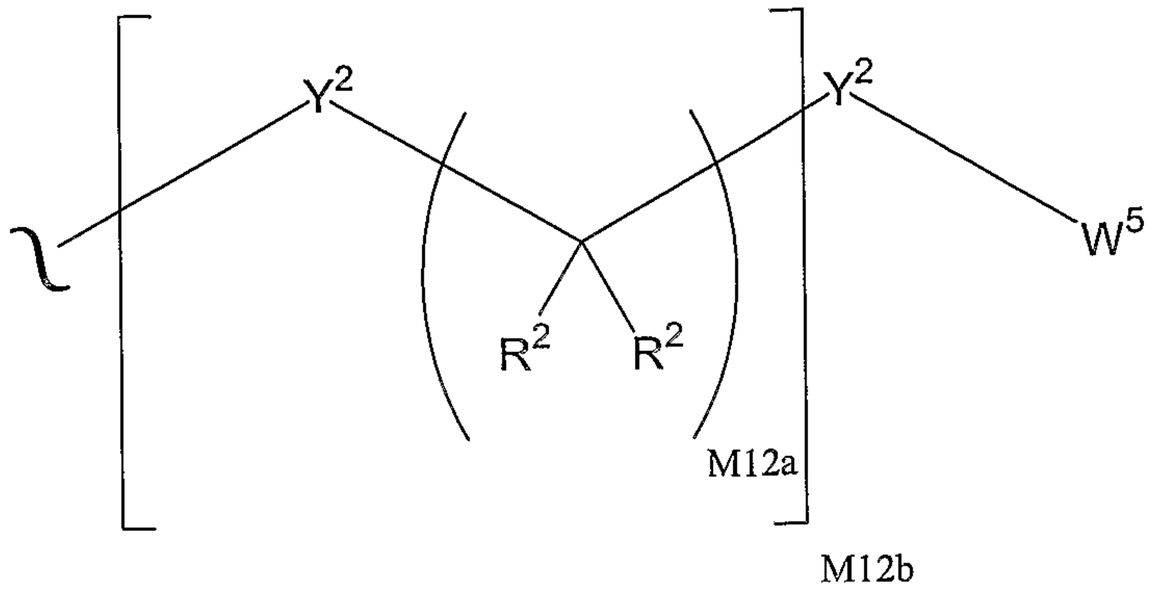
M12d

wherein:

Y^{2b} is O or $N(R^2)$; and

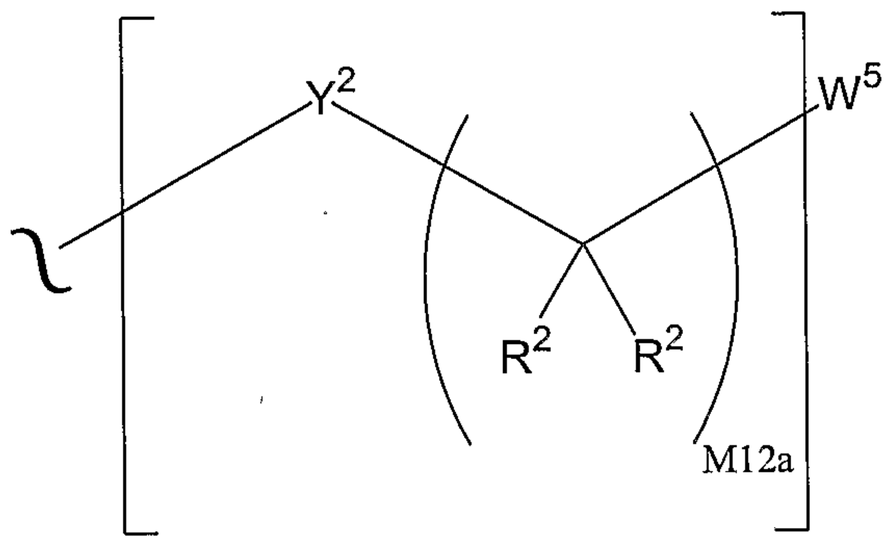
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

18. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:



M12b .

19. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:

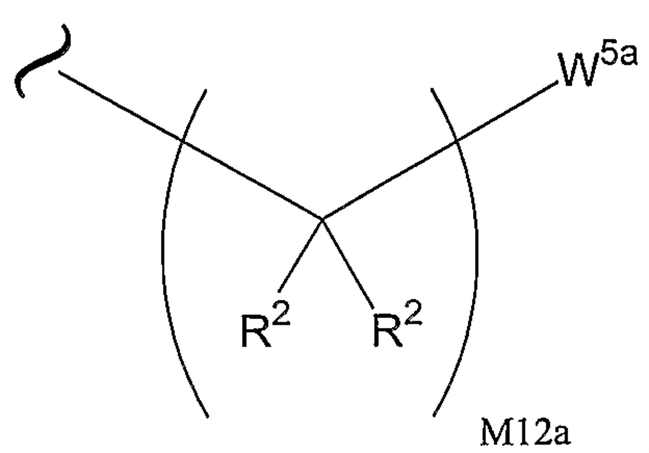


M12b .

20. The conjugate of any one of claims 2-17 wherein each M12b is 1.

21. The conjugate of claim 20 where M12b is 0, Y^2 is a bond and W^5 is a carbocycle or heterocycle where W^5 is optionally and independently substituted with 1, 2, or 3 R^2 groups.

22. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:



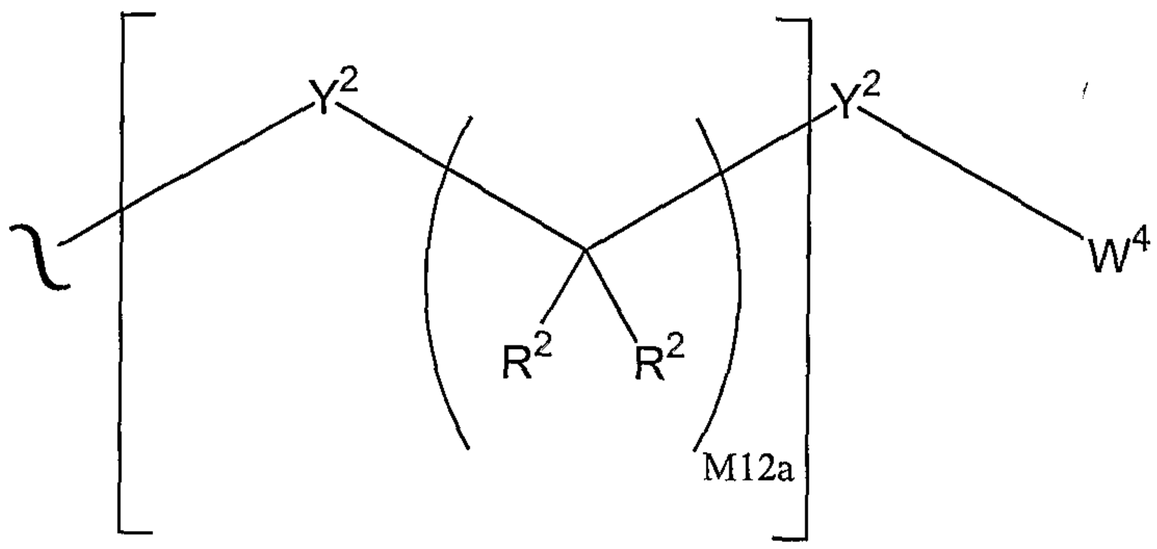
;

wherein: W^{5a} is a carbocycle or heterocycle where W^{5a} is optionally and independently substituted with 1, 2, or 3 R^2 groups.

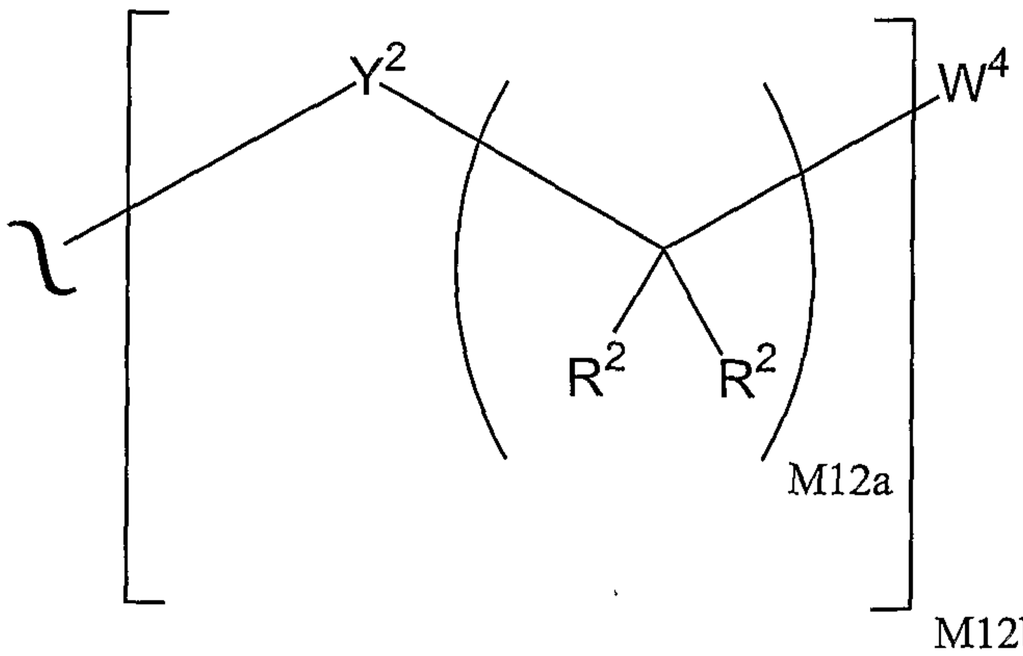
23. The conjugate of claim 22 wherein M12a is 1.

24. The conjugate of any one of claims 2-17 wherein each A^2 is selected from phenyl, substituted phenyl, benzyl, substituted benzyl, pyridyl and substituted pyridyl.

25. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:

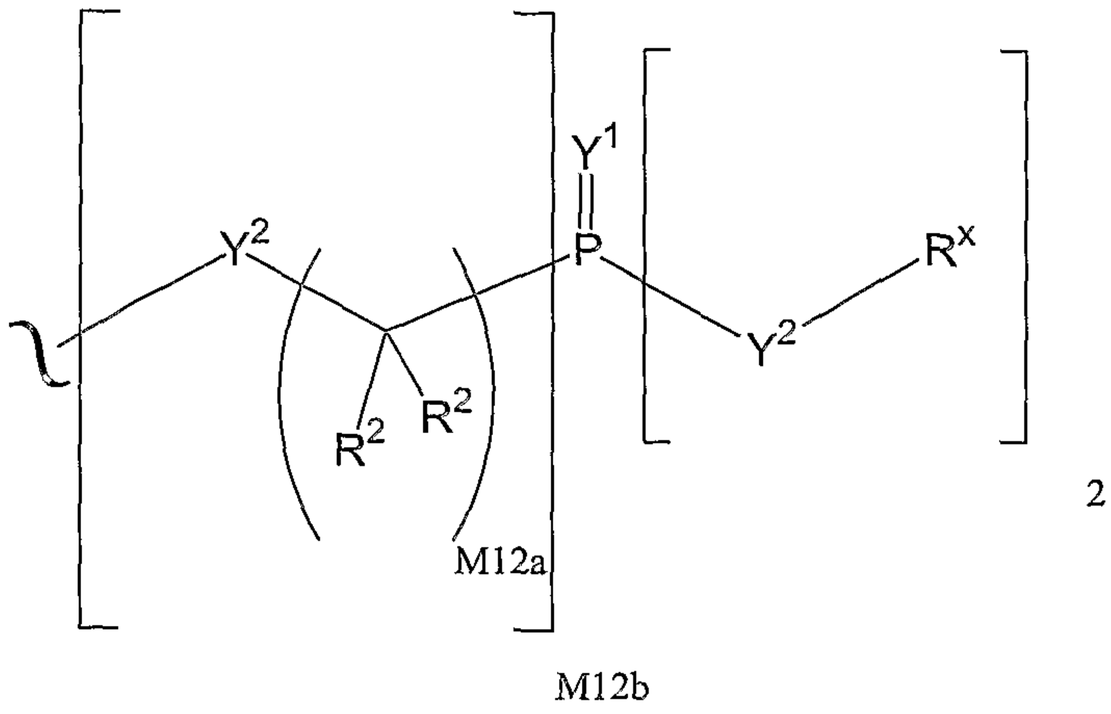


26. The conjugate of any one of claims 2-17 wherein each A^2 is of the formula:



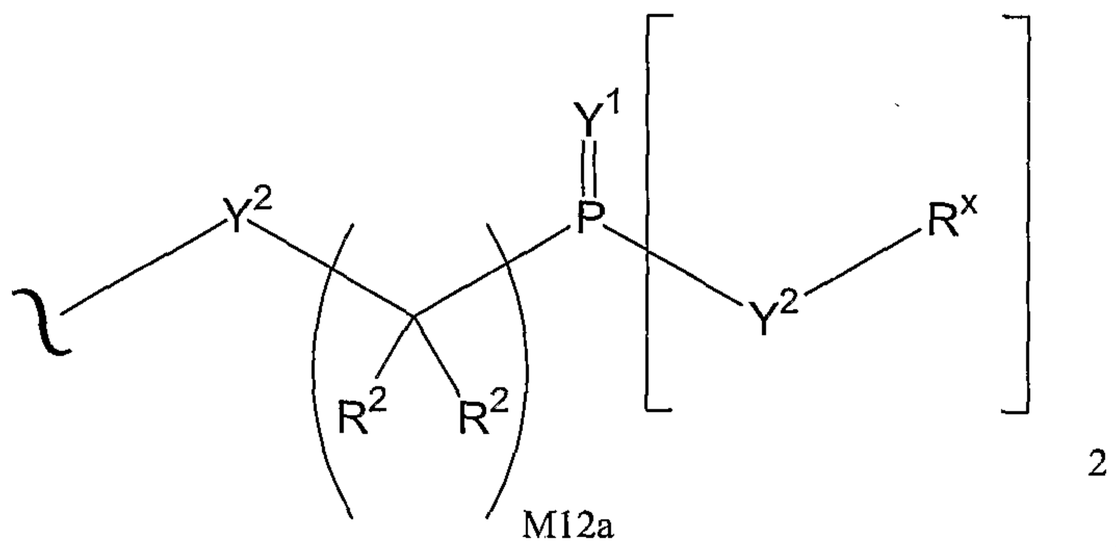
27. The conjugate of claim 26 wherein M12b is 1.

28. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

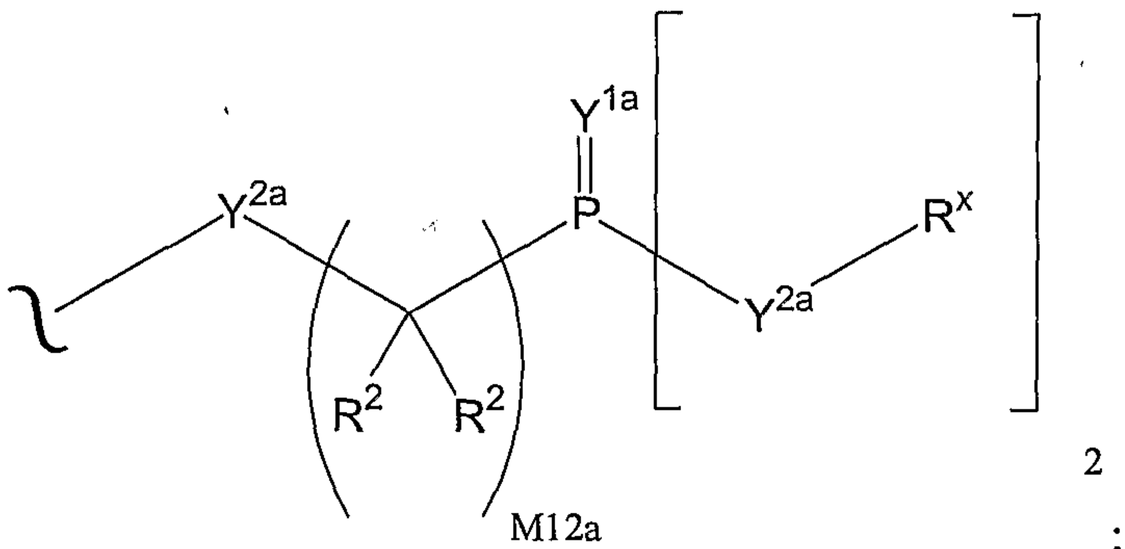


M12b

29. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



30. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



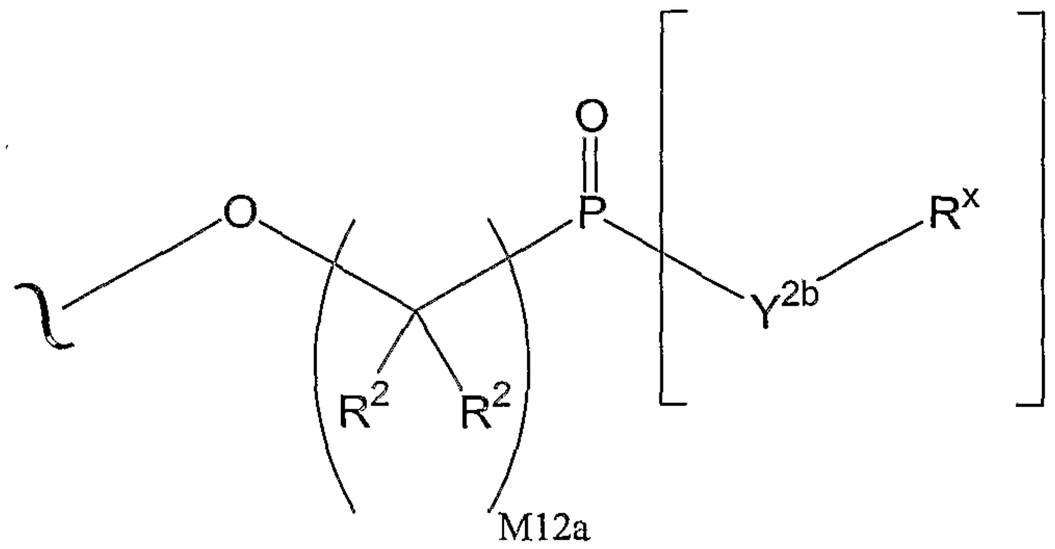
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, N(R^x) or S.

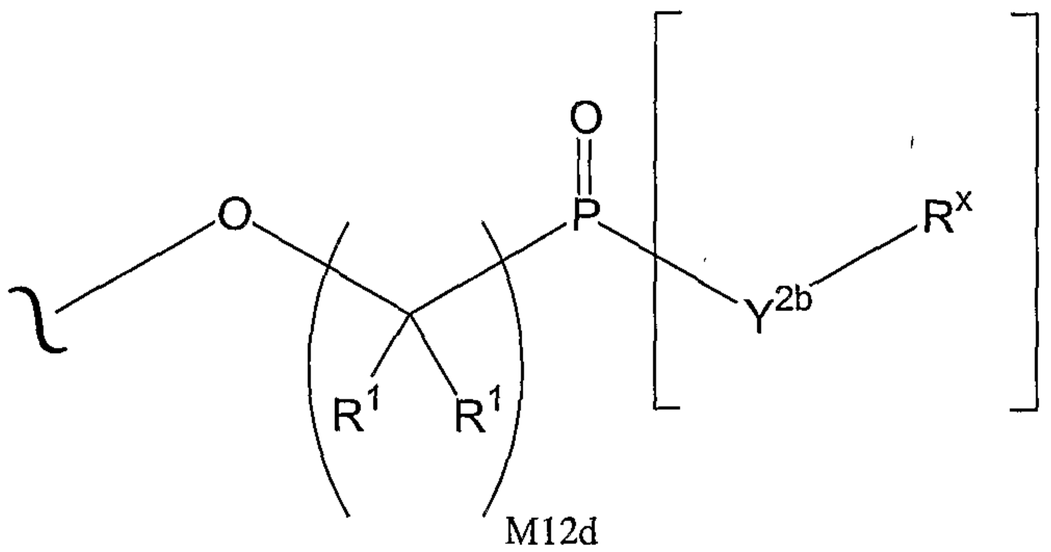
31. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



;

wherein Y^{2b} is O or $N(R^x)$.

32. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



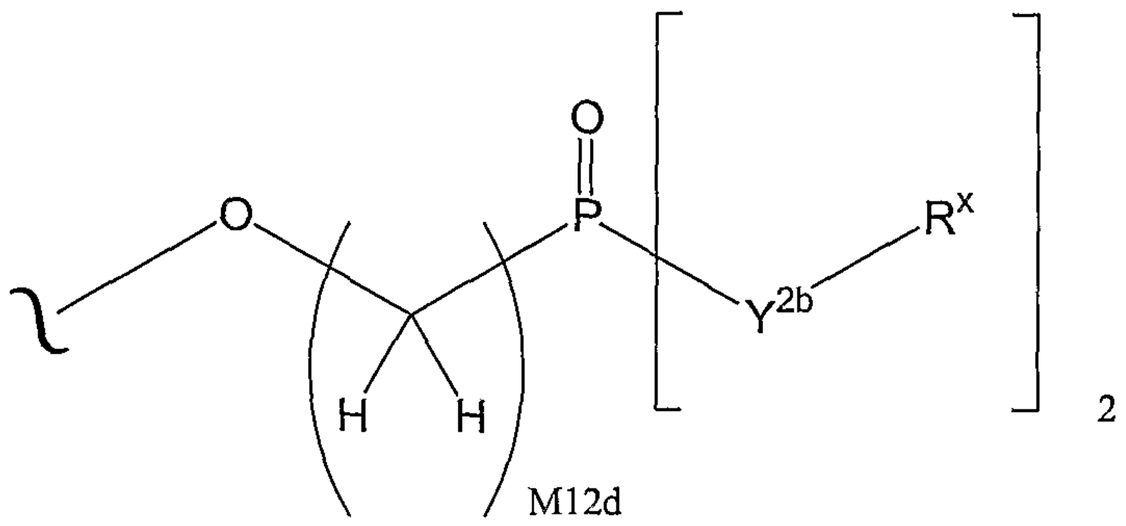
;

wherein:

Y^{2b} is O or $N(R^x)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

33. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



;

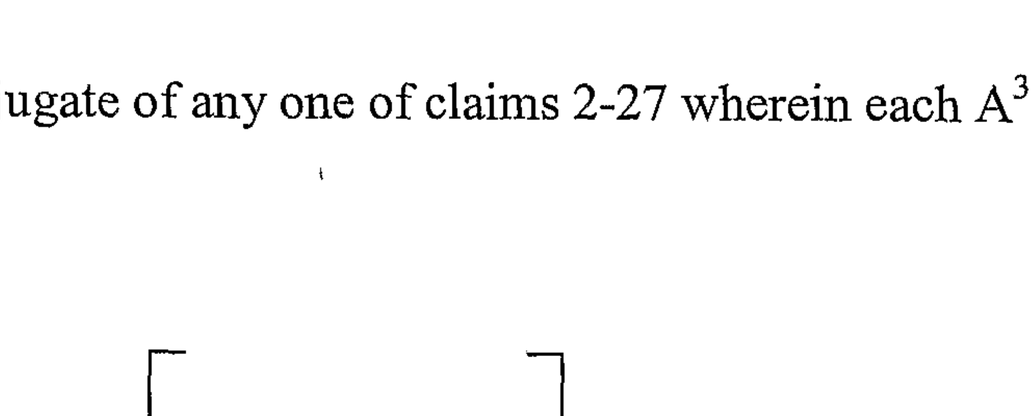
wherein:

Y^{2b} is O or $N(R^x)$; and

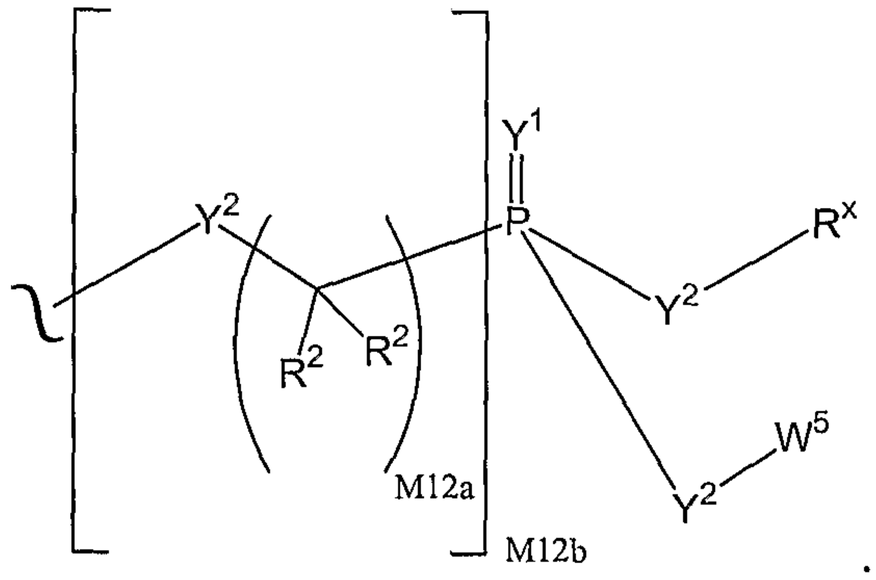
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

34. The conjugate of claim 33 wherein M12d is 1.

35. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

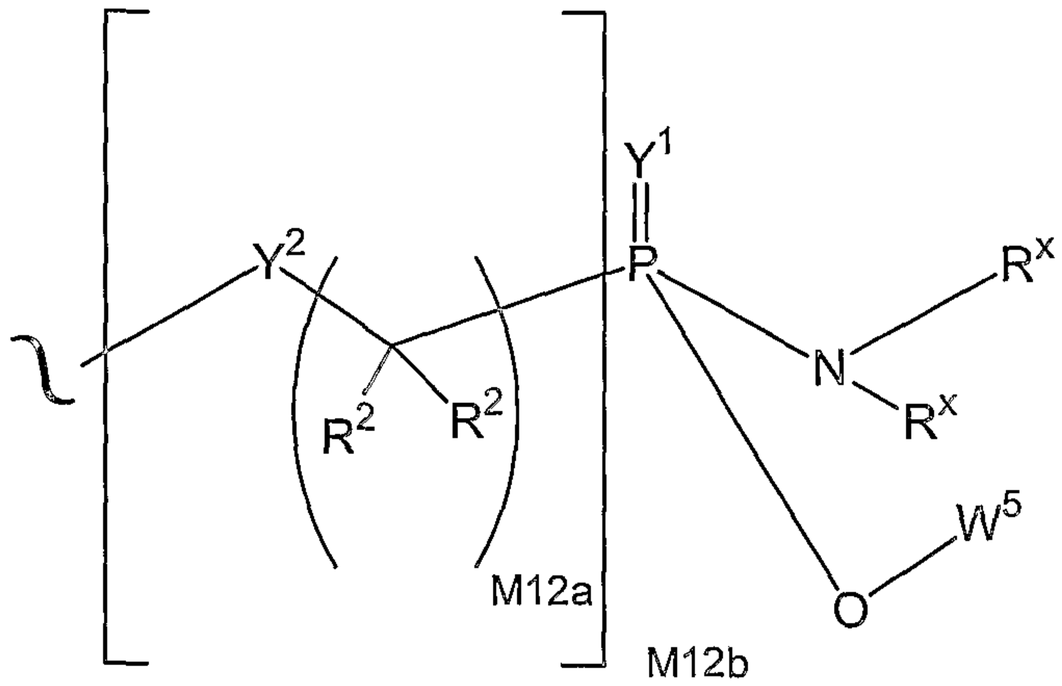


36. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



37. The conjugate of claim 36 wherein W^5 is a carbocycle.

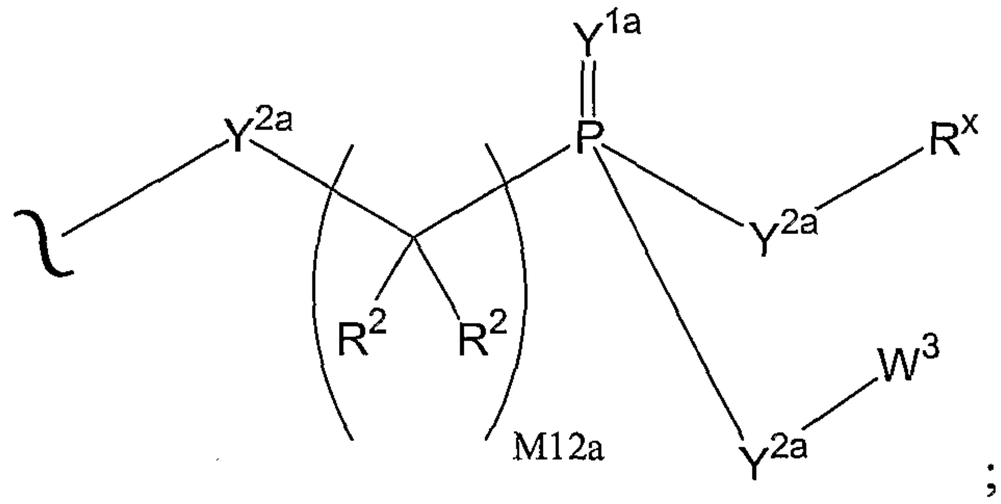
38. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



39. The conjugate of claim 38 wherein W^5 is phenyl.

40. The conjugate of claim 39 wherein M12b is 1.

41. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



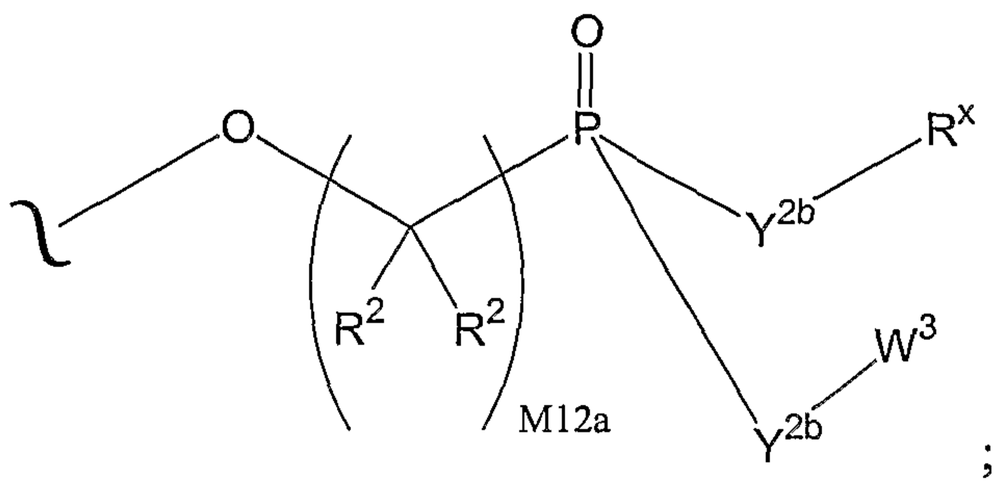
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, N(R^x) or S.

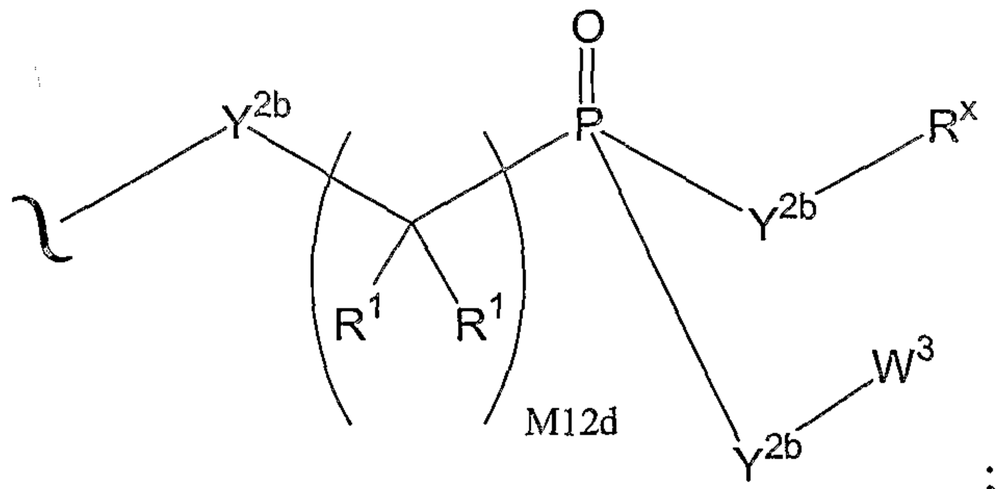
42. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



;

wherein Y^{2b} is O or N(R^x).

43. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



wherein:

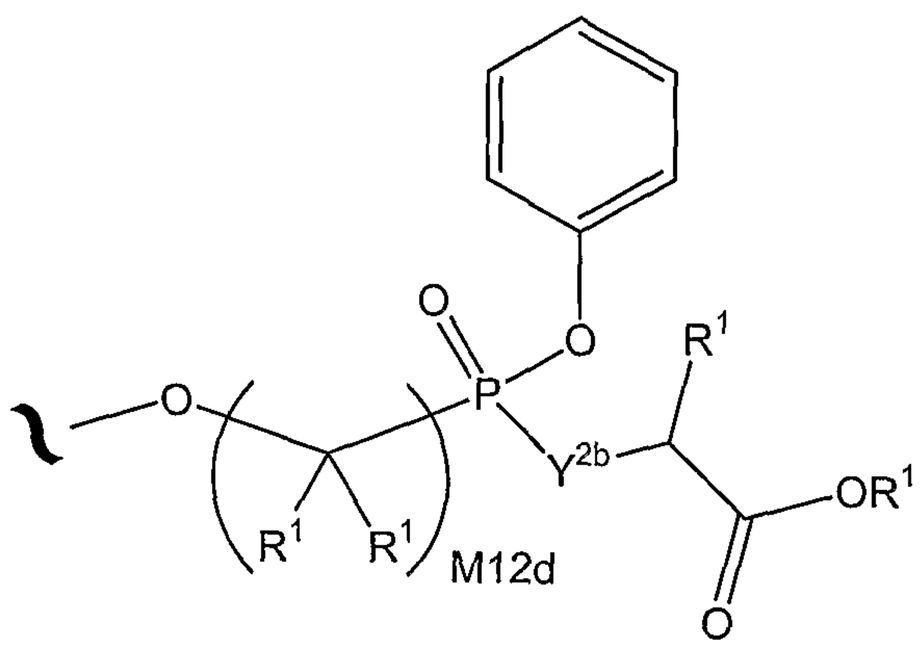
Y^{2b} is O or N(R^x); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

44. The conjugate of claim 43 wherein R^1 is H.

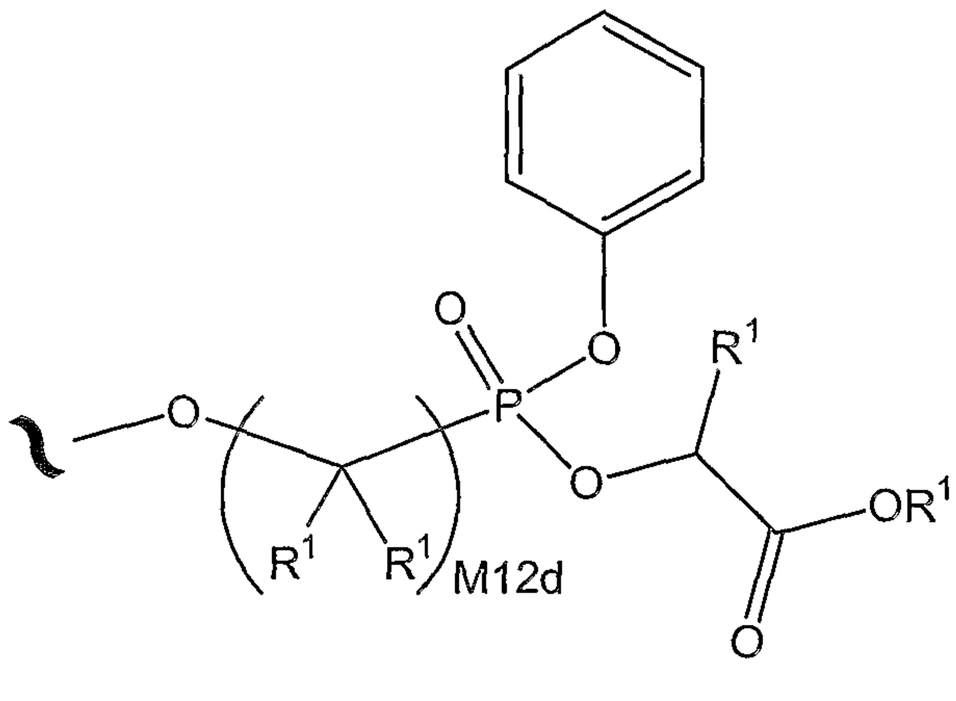
45. The conjugate of claim 44 wherein M12d is 1.

46. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



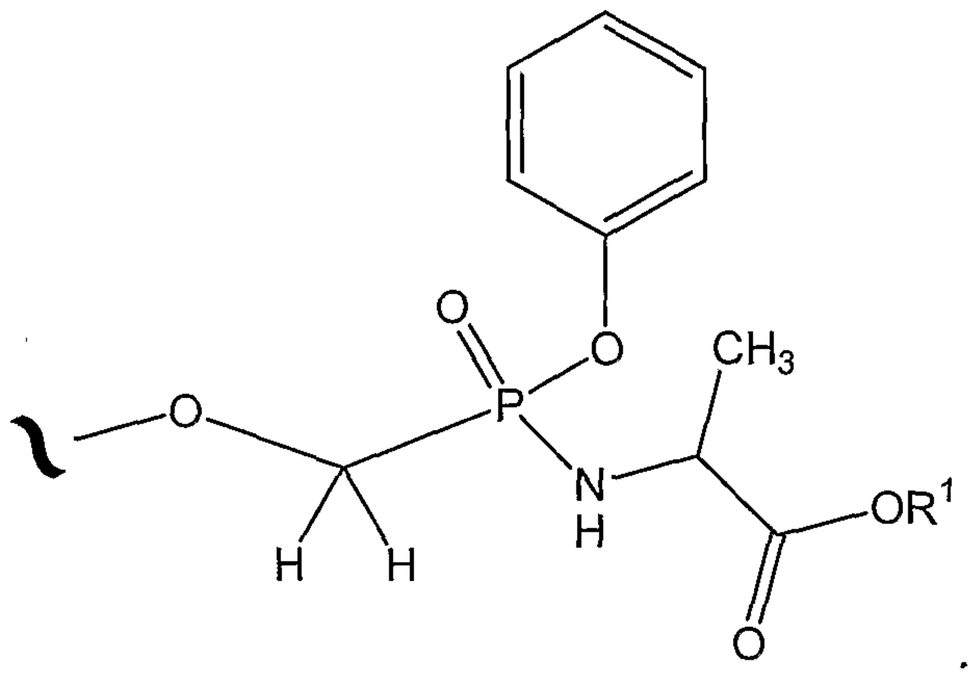
wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

47. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

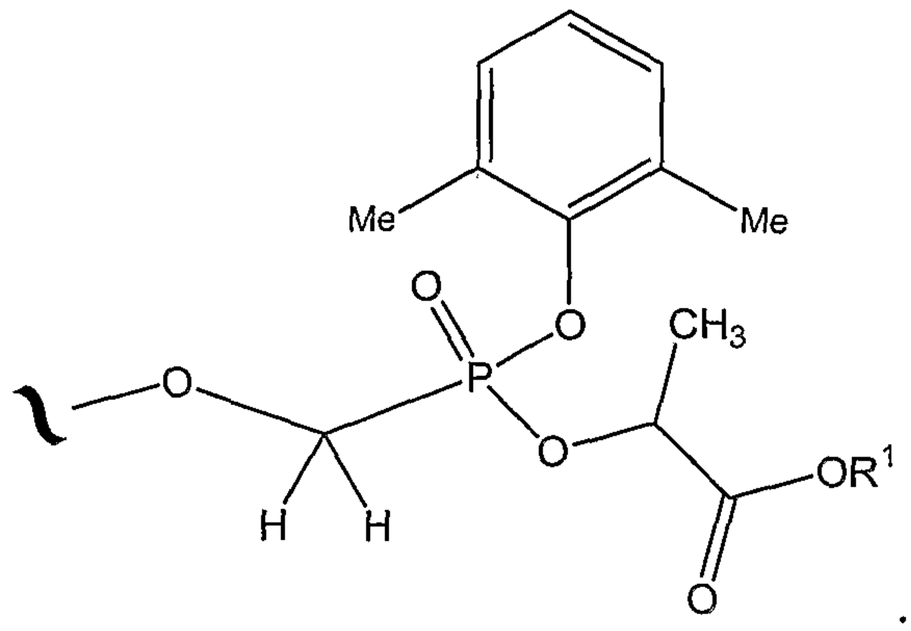


wherein the phenyl carbocycle is substituted with 0, 1, 2, or 3 R^2 groups.

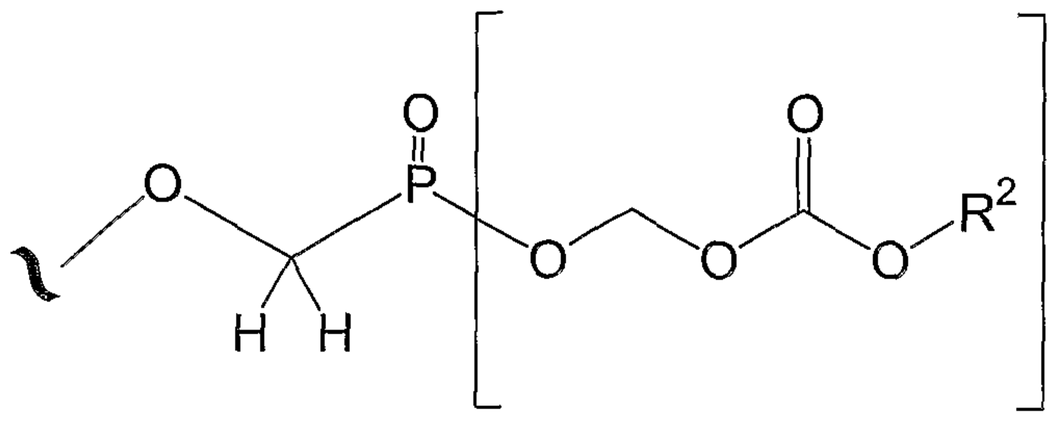
48. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



49. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:

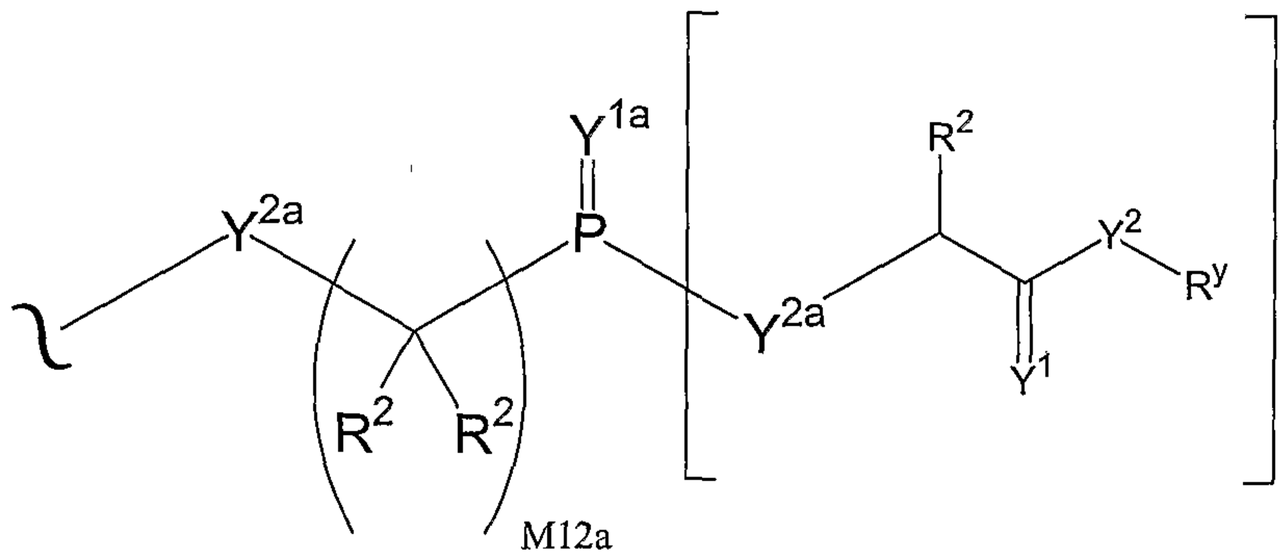


50. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



.

51. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



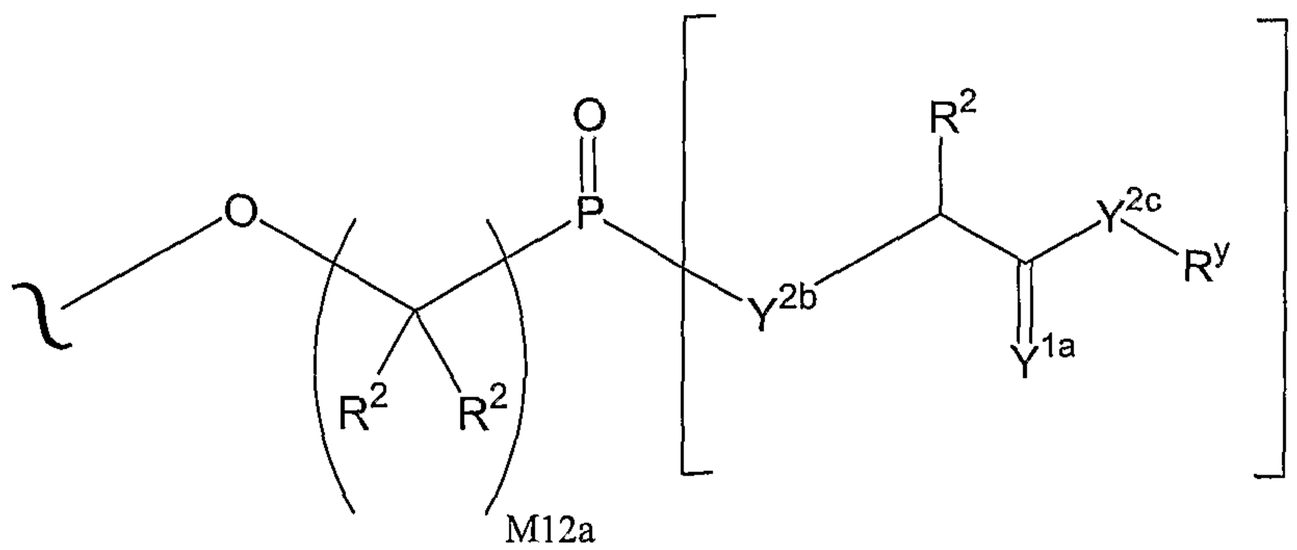
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, $N(R^2)$ or S.

52. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



;

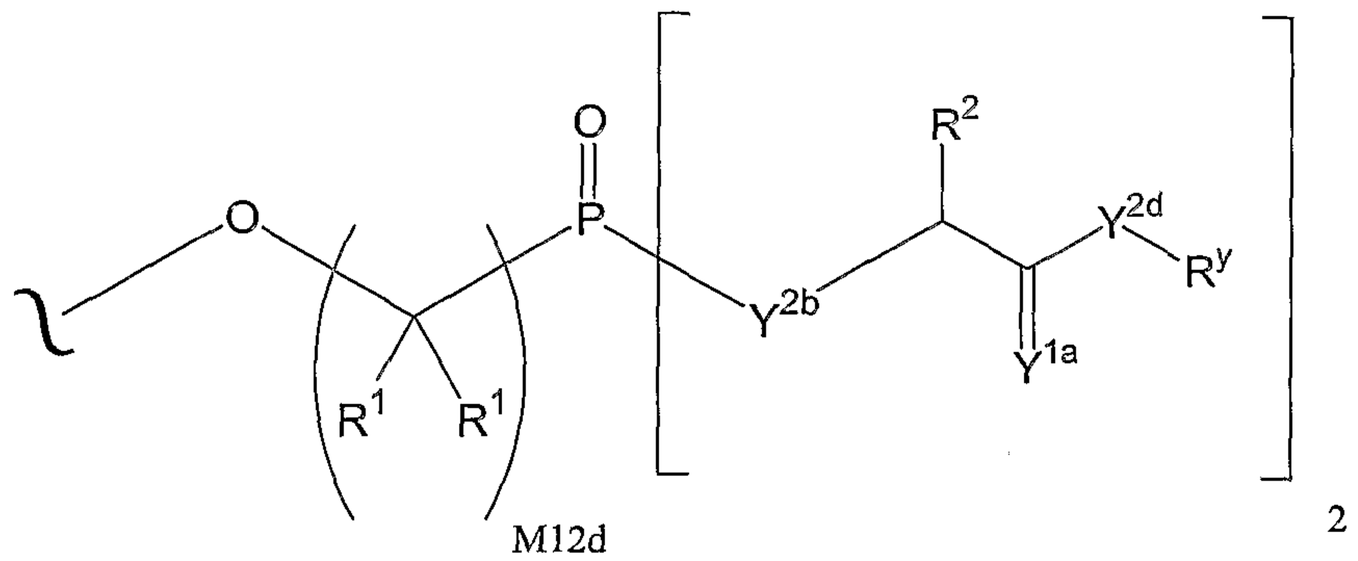
wherein:

Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$; and

Y^{2c} is O, $N(R^y)$ or S.

53. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



wherein:

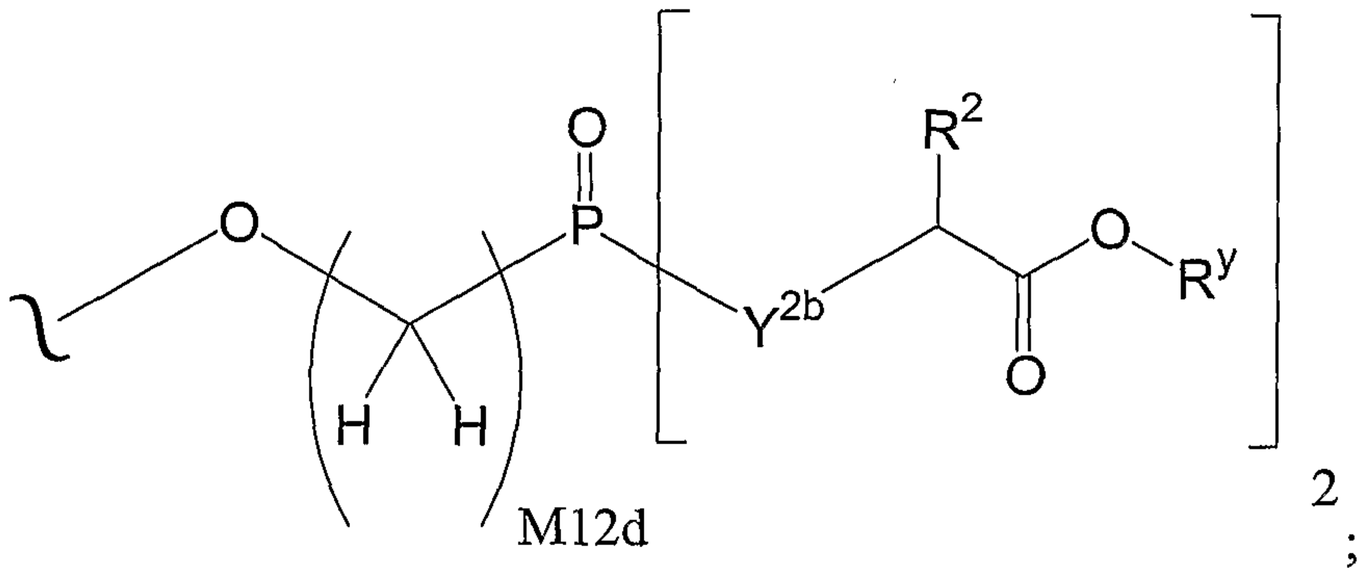
Y^{1a} is O or S;

Y^{2b} is O or $N(R^2)$;

Y^{2d} is O or $N(R^y)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

54. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



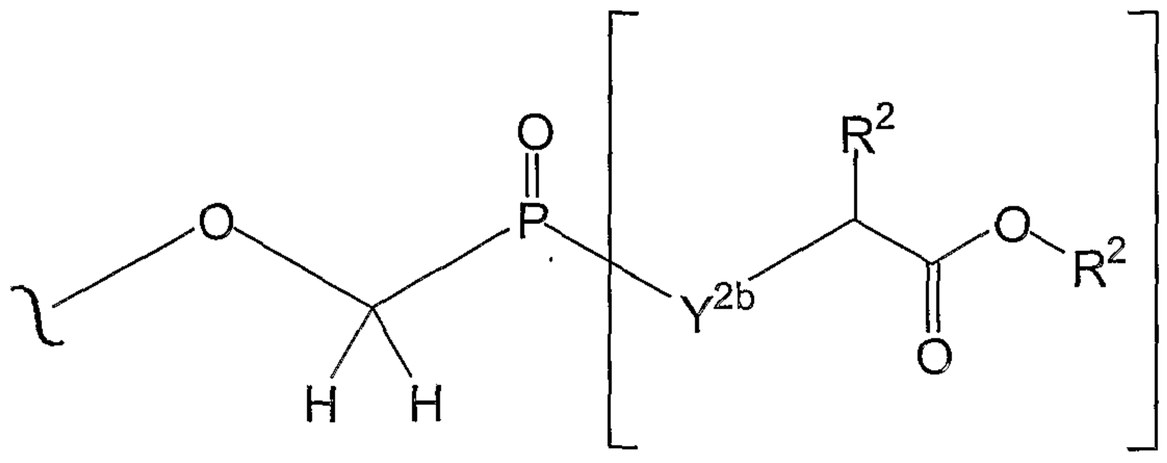
;

wherein:

Y^{2b} is O or $N(R^2)$; and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

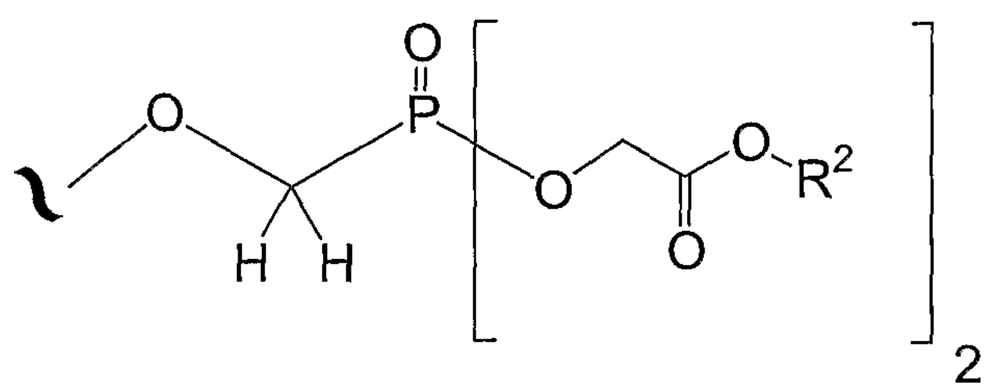
55. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



2

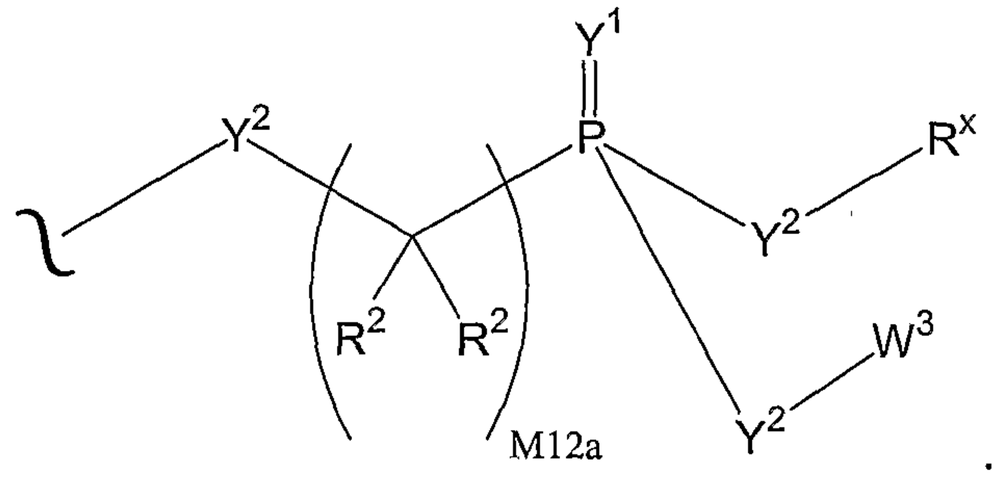
wherein Y^{2b} is O or $N(R^2)$.

56. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



2 .

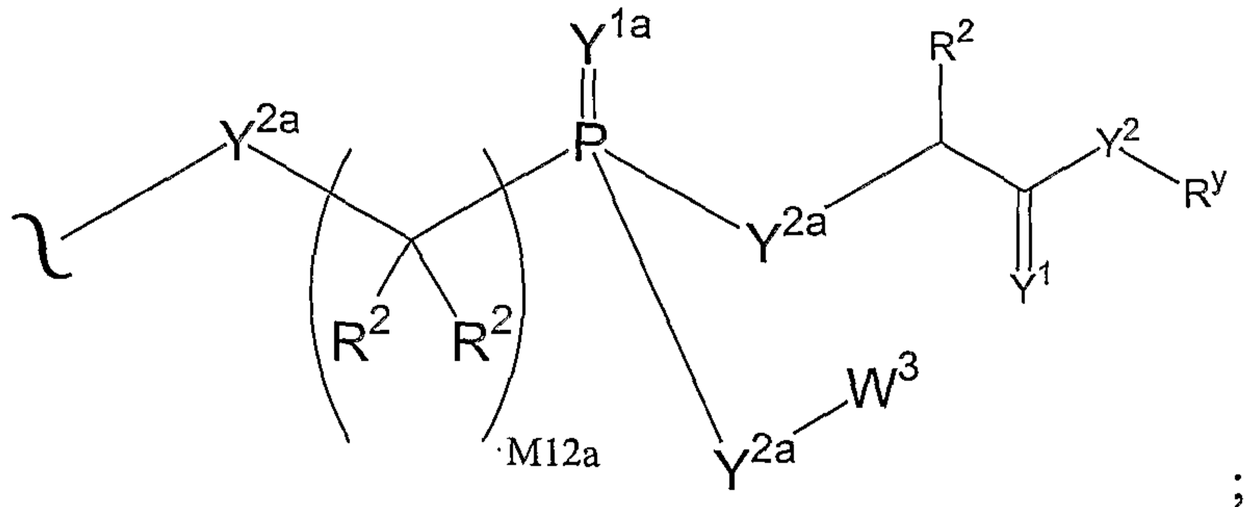
57. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12a

.

58. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



M12a

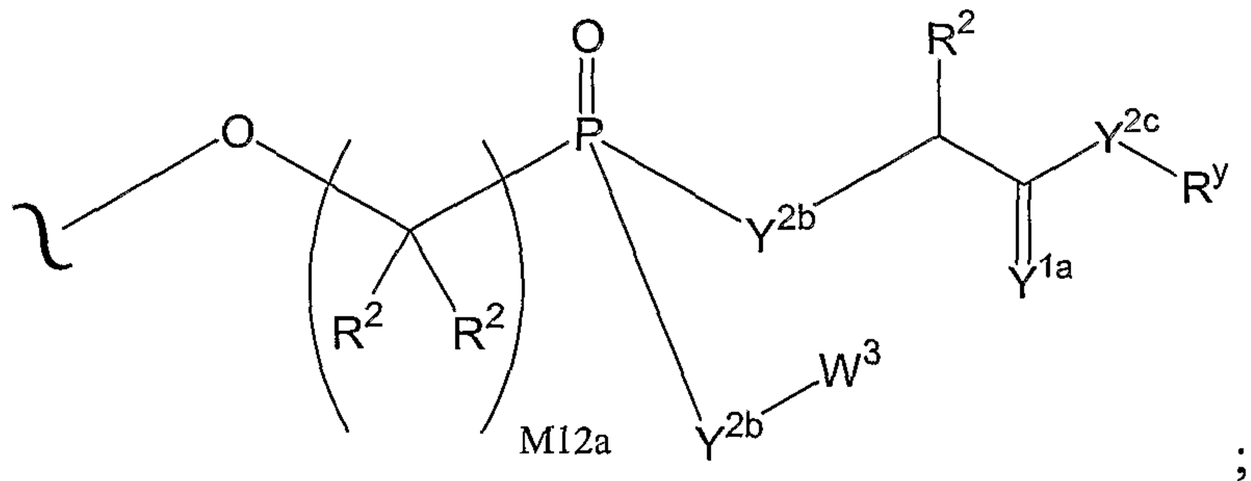
;

wherein:

Y^{1a} is O or S; and

Y^{2a} is O, N(R^2) or S.

59. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



;

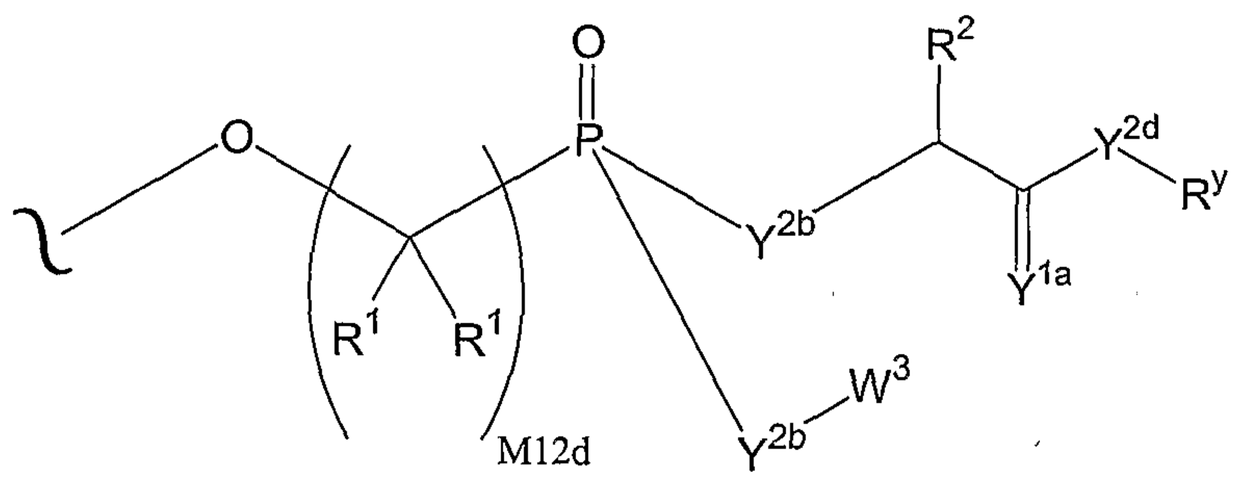
wherein:

Y^{1a} is O or S;

Y^{2b} is O or N(R^2); and

Y^{2c} is O, N(R^y) or S.

60. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



wherein:

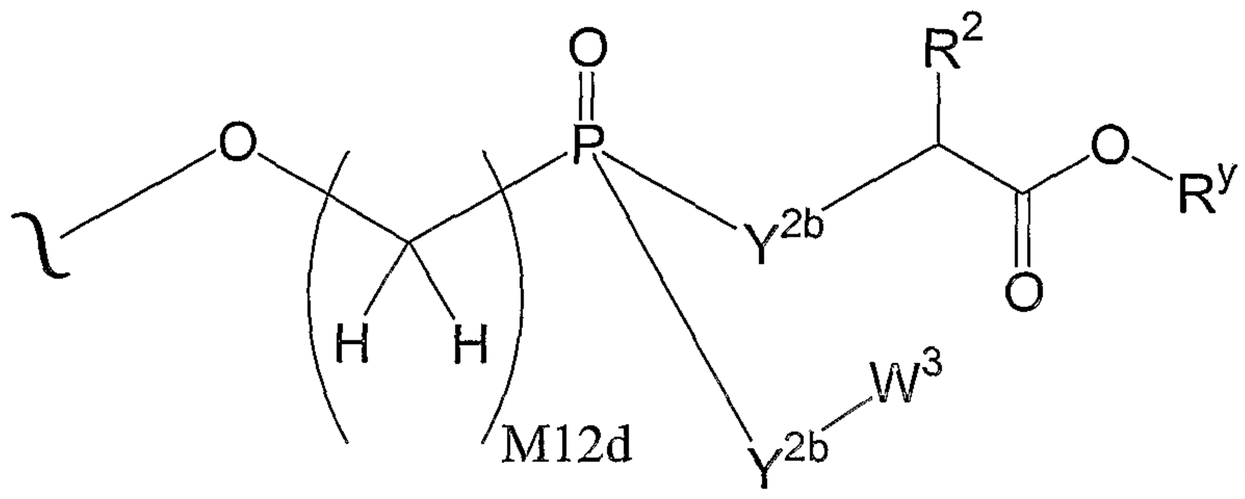
Y^{1a} is O or S;

Y^{2b} is O or N(R^2);

Y^{2d} is O or N(R^y); and

M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

61. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



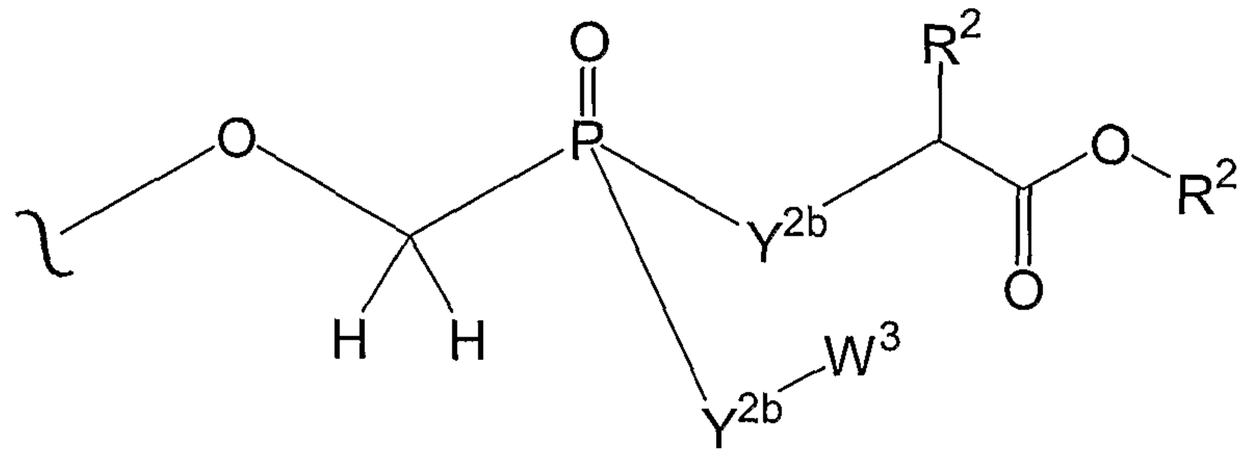
;

wherein:

Y^{2b} is O or $N(R^2)$; and

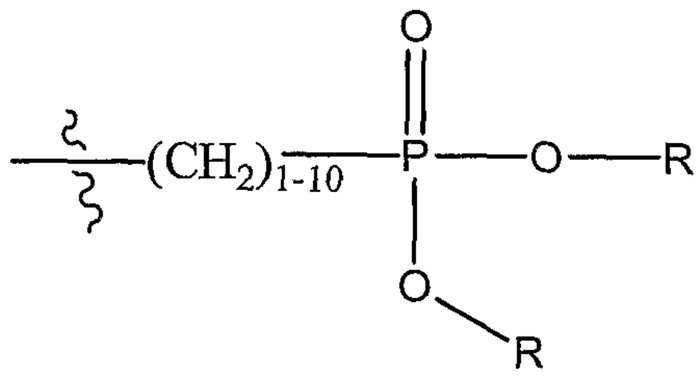
M12d is 1, 2, 3, 4, 5, 6, 7 or 8.

62. The conjugate of any one of claims 2-27 wherein each A^3 is of the formula:



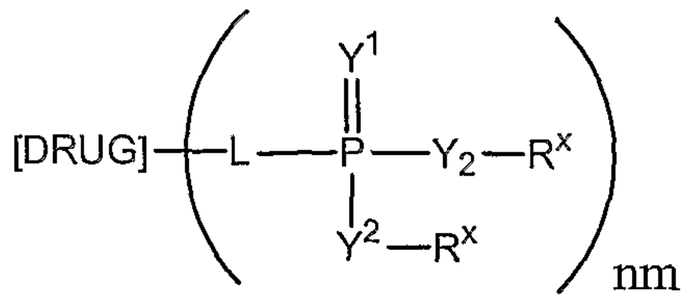
wherein Y^{2b} is O or $N(R^2)$.

63. The conjugate of claim 3 wherein A^0 is of the formula:



wherein each R is independently alkyl.

64. The conjugate of claim 1, 2, 3, or 4 which has the formula:



or a pharmaceutically acceptable salt or solvate thereof,

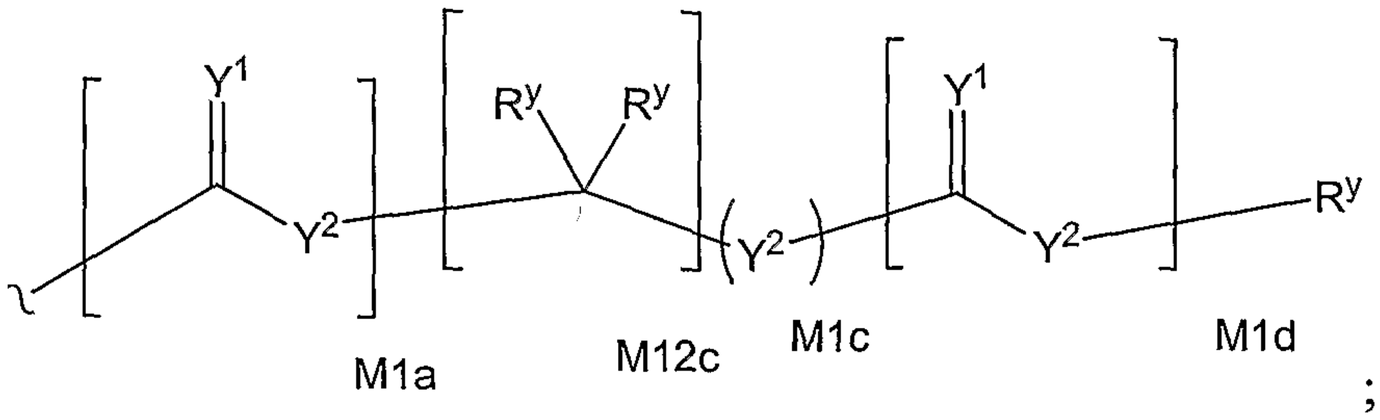
wherein:

DRUG is an with immuno-modulatory compound;

Y^1 is independently O, S, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, or $N(N(R^x)(R^x))$;

Y^2 is independently a bond, O, $N(R^x)$, $N(O)(R^x)$, $N(OR^x)$, $N(O)(OR^x)$, $N(N(R^x)(R^x))$, $-S(O)_{M2}-$, or $-S(O)_{M2}-S(O)_{M2}-$;

R^x is independently H, R^2, W^3, a protecting group, or the formula:



;

R^y is independently H, W^3, R^2 or a protecting group;

R^2 is independently H, R^3 or R^4 wherein each R^4 is independently substituted with 0 to 3 R^3 groups;

R^3 is R^{3a}, R^{3b}, R^{3c} or R^{3d}, provided that when R^3 is bound to a heteroatom, then R^3 is R^{3c} or R^{3d};

R^{3a} is F, Cl, Br, I, -CN, N_3 or $-NO_2$;

R^{3b} is Y^1;

R^{3c} is $-R^x$, $-N(R^x)(R^x)$, $-SR^x$, $-S(O)R^x$, $-S(O)_2R^x$, $-S(O)(OR^x)$, $-S(O)_2(OR^x)$, $-OC(Y^1)R^x$, $-OC(Y^1)OR^x$, $-OC(Y^1)(N(R^x)(R^x))$, $-SC(Y^1)R^x$, $-SC(Y^1)OR^x$, $-SC(Y^1)(N(R^x)(R^x))$, $-N(R^x)C(Y^1)R^x$, $-N(R^x)C(Y^1)OR^x$, or $-N(R^x)C(Y^1)(N(R^x)(R^x))$;

R^{3d} is $-C(Y^1)R^x$, $-C(Y^1)OR^x$ or $-C(Y^1)(N(R^x)(R^x))$;

R^4 is an alkyl of 1 to 18 carbon atoms, alkenyl of 2 to 18 carbon atoms, or alkynyl of 2 to 18 carbon atoms;

R^5 is R^4 wherein each R^4 is substituted with 0 to 3 R^3 groups;

W^3 is W^4 or W^5;

W^4 is R^5, $-C(Y^1)R^5$, $-C(Y^1)W^5$, $-SO_2R^5$, or $-SO_2W^5$;

W^5 is carbocycle or heterocycle wherein W^5 is independently substituted with 0 to 3 R^2 groups;

M2 is 1, 2, or 3;

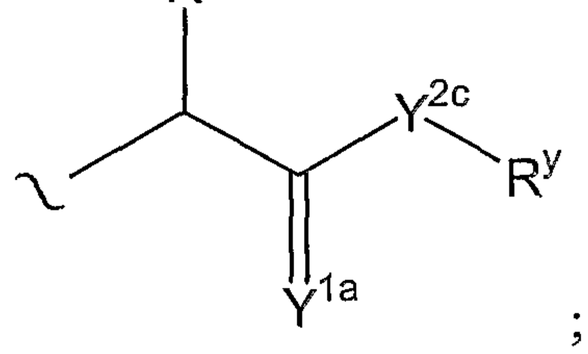
M1a, M1c, and M1d are independently 0 or 1;

M12c is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12;

nn is 1, 2, or 3; and

L is a direct bond or a linking group.

65. The conjugate of claim 64 wherein each R^x is of the formula:

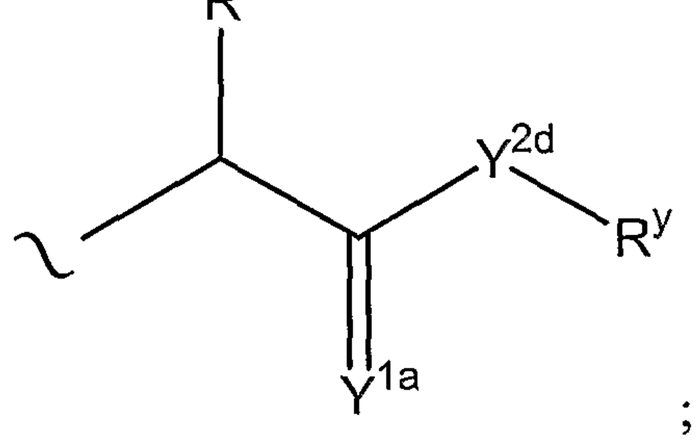


;

Y^{1a} is O or S; and

Y^{2c} is O, $N(R^y)$ or S.

66. The conjugate of claim 64 wherein each R^x is of the formula:

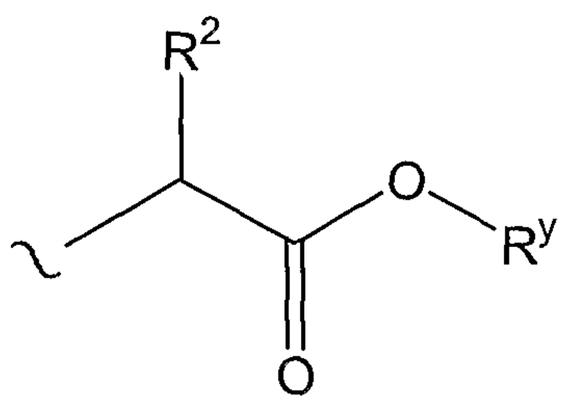


;

Y^{1a} is O or S; and

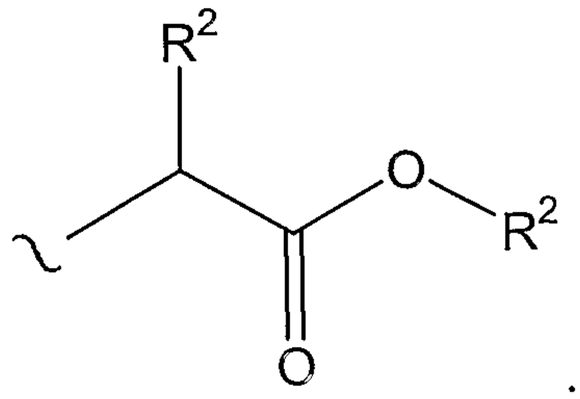
Y^{2d} is O or $N(R^y)$.

67. The conjugate of claim 64 wherein each R^x is of the formula:

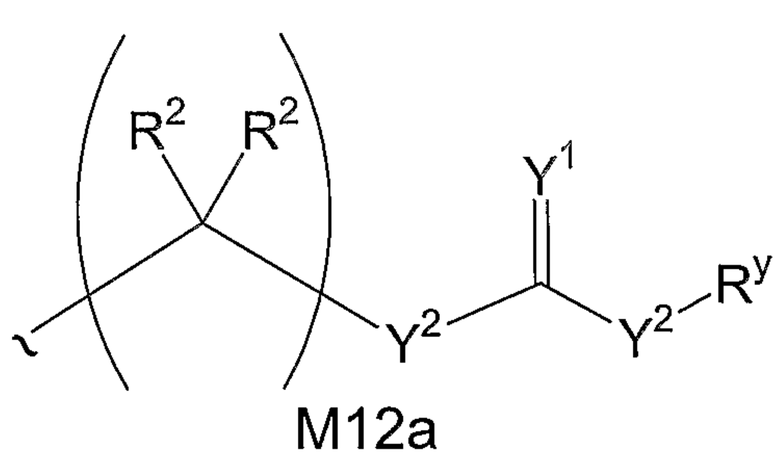


68. The conjugate of any one of claims 65-67 wherein each R^y is independently H or alkyl of 1 to 10 carbons.

69. The conjugate of claim 64 wherein each R^x is of the formula:

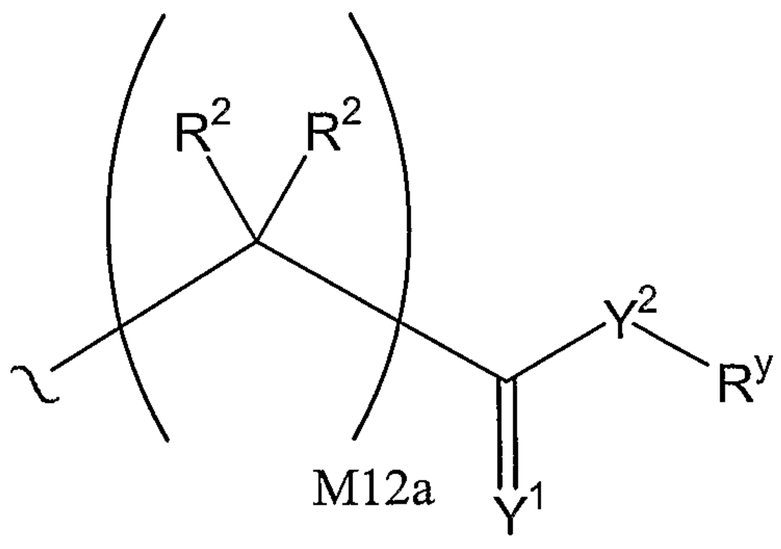


70. The conjugate of claim 64 wherein each R^x is of the formula:



M12a

71. The conjugate of claim 64 wherein each R^x is of the formula:



M12a

72. The conjugate of claim 64 wherein each Y^1 is O or S.

73. The conjugate of claim 64 wherein each Y^2 is O, N(R^y) or S.

74. The conjugate of any one of claims 64-73 wherein nn is 1.

75. The conjugate of any one of claims 64-73 wherein nn is 2.

76. The conjugate of any one of claims 64-73 wherein nn is 3.

77. The conjugate of claim 64 wherein the kinase inhibiting compound is a compound of any one of formulae **500-547**.

78. The conjugate of claim 77 wherein each L has a molecular weight of from about 20 daltons to about 400 daltons.

79. The conjugate of claim 77 wherein each L has a length of about 5 angstroms to about 300 angstroms.

80. The conjugate of claim 77 wherein each L separates the compound of any one of formulae **500-547** and the phosphorous of the phosphonate group by about 5 angstroms to about 200 angstroms, inclusive.

81. The conjugate of claim 77 wherein each L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 2 to 25 carbon atoms, wherein one or more of the carbon atoms is optionally replaced by (-O-), and wherein the chain is optionally substituted on carbon with one or more substituents selected from (C_1-C_6)alkoxy, (C_3-C_6)cycloalkyl, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, azido, cyano, nitro, halo, hydroxy, oxo (=O), carboxy, aryl, aryloxy, heteroaryl, and heteroaryloxy.

82. The conjugate of claim 77 wherein each L is of the formula W-A wherein A is (C_1-C_{24})alkylene, (C_2-C_{24})alkenylene, (C_2-C_{24})alkynylene, (C_3-C_8)cycloalkylene, (C_6-C_{10})aryl or a combination thereof, wherein each W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, -$S(O)_2$-, -N(R)-, -C(=O)-, -N(R)C=N(R)-N(R)-, -C(R)=N(R)-, -$S(O)_{M2}$-N(R)-, -N(R)-$S(O)_{M2}$-, or a direct bond; wherein each R is independently H or alkyl of 1 to 10 carbons.

83. The conjugate of claim 82 wherein each A is alkylene of 1 to 10 carbons.

84. The conjugate of claim 77 wherein each L is a divalent radical formed from a peptide.

85. The conjugate of claim 77 wherein each L is a divalent radical formed from an amino acid.

86. The conjugate of claim 77 wherein each L is a divalent radical formed from poly-L-glutamic acid, poly-L-aspartic acid, poly-L-histidine, poly-L-ornithine, poly-L-serine, poly-L-threonine, poly-L-tyrosine, poly-L-leucine, poly-L-lysine-L-phenylalanine, poly-L-lysine or poly-L-lysine-L-tyrosine.

87. The conjugate of claim 77 wherein each L is of the formula $W-(CH_2)_n$ wherein, n is between about 1 and about 10; and W is -N(R)C(=O)-, -C(=O)N(R)-, -OC(=O)-, -C(=O)O-, -O-, -S-, -S(O)-, $-S(O)_2-$, -C(=O)-, -N(R)-, -N(R)C=N(R)-N(R)-, -C(R)=N(R)-, $-S(O)_{M2}-N(R)-$, $-N(R)-S(O)_{M2}-$, or a direct bond; wherein each R is independently H or (C_1-C_6)alkyl.

88. The conjugate of claim 77 wherein each L is methylene, ethylene, or propylene.

89. The conjugate of claim 77 wherein each L is linked to P at a carbon atom of L.

90. The conjugate as described in any one of claims 1-89, which is isolated and purified.

91. The conjugate of any one of claims 1-90 which is not an anti-inflammatory compound.

92. The conjugate of any one of claims 1-91 which is not an anti-infective.

93. The conjugate of any one of claims 1-92 which is not a compound that is not a kinase inhibitor.

94. The conjugate of any one of claims 1-93 which is not a compound that is active against metabolic diseases.

95. The conjugate of any one of claims 1-94 which is not an antiviral agent.

96. The conjugate of any one of claims 1-95 which is not a nucleoside.

97. The conjugate of any one of claims 1-96 which is not a IMPDH inhibitor.

98. The conjugate of any one of claims 1-97 which is not an antimetabolite.

99. The conjugate of any one of claims 1-98 which is not a PNP inhibitor.

100. The conjugate of any one of claims 2-99 which is not a substituted compound of any one of formulae **500-533**, **535-541**, or **543-547**.

101. The conjugate of any one of claims 2-100 which is not a substituted compound of formula **534** or **542**.

102. The conjugate of any one of claims 4-101 which is not a compound of any one of formulae **1-104**, **107-124**, or **128-151**.

103. The conjugate of any one of claims 4-102 which is not a compound of formula **105-106**, or **125-127**.

104. A kinase inhibitor conjugate as described herein.

105. A compound of the formula MBF.

106. A compound of claim 105 selected from Table 100.

107. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a conjugate as described in any one of claims 1-89 and 91-104 or a compound as described in claim 105 or 106.

108. A unit dosage form comprising a conjugate as described in any one of claims 1-89 and 91-104 or a compound as described in claim 105 or 106 and a pharmaceutically acceptable excipient.

109. A method for inhibiting an immune response *in vitro* or *in vivo* comprising contacting a sample in need of such treatment with a conjugate as described in any one of claims 1-89 and 91-104 or a compound as described in claim 105 or 106.

110. The method of claim 109 wherein the contacting is *in vivo*.

111. The invention also provides a method of modulating an immune response in a mammal, comprising administering a compound as described in any one of claims 1-89 and 91-104 or a compound as described in claim 105 or 106 to the mammal.

112. The method of claim 111 wherein the compound is formulated with a pharmaceutically acceptable carrier.

113. The method of claim 112 wherein the formulation further comprises a second active ingredient.

114. The method of claim 111 or 112 wherein an immune response is suppressed.

115. A conjugate as described in any one of claims 1-89 and 91-104 or a compound as described in claim 105 or 106 for use in medical therapy.

116. The use of a conjugate as described in any one of claims 1-89 and 91-104 or a compound as described in claim 105 or 106 to prepare a medicament for modulating an immune response in an animal.

117. A phosphonate substituted immuno-modulatory conjugate as described herein.

118. A method for preparing a conjugate as described in the schemes and examples herein.