US005712396A

United States Patent [19]

Magnin et al.

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[45] Date of Patent: Jan. 27, 1998

[54] **α-PHOSPHONOSULFONATE SQUALENE SYNTHETASE INHIBITORS**

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[21] Appl. No.: **266,888**

[22] Filed: **Jul. 5, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 109,762, Aug. 20, 1993, abandoned, which is a continuation-in-part of Ser. No. 967,904, Oct. 28, 1992, abandoned.

[51] **Int. Cl.**[6] **C07F 9/38**; C07F 9/553; C07F 9/6506; C07F 9/6512; A61K 31/66

[52] **U.S. Cl.** **546/22**; 514/94; 514/114; 514/127; 514/79; 514/80; 514/81; 514/86; 514/89; 514/92; 544/232; 544/243; 544/244; 546/23; 540/450; 540/471; 540/474; 540/542; 548/112; 548/113; 558/45; 562/17; 562/21; 562/23; 562/35

[58] **Field of Search** 558/45; 562/17, 562/21, 23, 35; 546/22, 23; 548/112, 113; 544/232, 243, 244; 540/450, 471, 474, 542; 514/27, 80, 81, 86, 89, 92, 94, 114, 127

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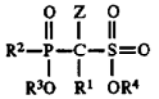
Primary Examiner—Floyd D. Higel

Attorney, Agent, or Firm—Burton Rodney

[57] **ABSTRACT**

α-Phosphonosulfonate compounds are provided which inhibit the enzyme squalene synthetase and thereby inhibit cholesterol biosynthesis. These compounds have the formula



wherein R^2 is OR^5 or R^{5a}; R^3 and R^5 are independently H, alkyl, arylalkyl, aryl or cycloalkyl; R^{5a} is H, alkyl, arylalkyl or aryl; R4 is H, alkyl, aryl, arylalkyl, or cycloalkyl;, Z is H, halogen, lower alkyl or lower alkenyl; and R^1 is a lipophilic group which contains at least 7 carbons and is alkyl, alkenyl, alkynyl, mixed alkenyl-alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl; as further defined above; including pharmaceutically acceptable salts and or prodrug esters of the phosphonic (phosphinic) and/or sulfonic acids.

26 Claims, No Drawings

α-PHOSPHONOSULFONATE SQUALENE SYNTHETASE INHIBITORS

This is a continuation of application Ser. No. 109,762, filed Aug. 20, 1993, now abandoned, which is a continuation-in-part of application Ser. No. 967,904, filed Oct. 28, 1992, now abandoned.

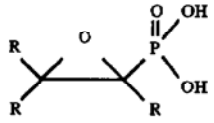
FIELD OF THE INVENTION

The present invention relates to new α-phosphonosulfonate compounds which are useful in inhibiting cholesterol biosynthesis by inhibiting de novo squalene production, to hypocholesterolemic and antiatherosclerotic compositions containing such compounds and to a method of using such compounds for inhibiting cholesterol biosynthesis and atherosclerosis.

BACKGROUND OF THE INVENTION

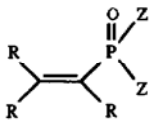
Squalene synthetase is a microsomal enzyme which catalyzes the reductive dimerization of two molecules of farnesyl pyrophosphate (FPP) in the presence of nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) to form squalene (Poulter, C. D.; Rilling, H. C., in "Biosynthesis of Isoprenoid Compounds", Vol. I, Chapter 8, pp. 413–441, J. Wiley and Sons, 1981, and references therein). This enzyme is the first committed step of the de novo cholesterol biosynthetic pathway. The selective inhibition of this step should allow the essential pathways to isopentenyl tRNA, ubiquinone, and dolichol to proceed unimpeded. Squalene synthetase along with HMG-CoA reductase have been shown to be down-regulated by receptor mediated LDL uptake (Faust, J. R.; Goldstein, J. L.; Brown, M. S. *Proc. Nat. Acad. Sci. U.S.A.* 1979, 76, 5018–5022), lending credence to the proposal that inhibiting squalene synthetase will lead to an up-regulation of LDL receptor levels, as has been demonstrated for HMG-CoA reductase, and thus ultimately should be useful for the treatment and prevention of hypercholesterolemia and atherosclerosis.

U.S. Pat. No. 3,657,282 (Merck) (Division U.S. Pat. No. 3,822,296) discloses antibiotics of the structure



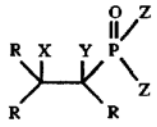
wherein R=SO_3H, SO_2R*, H, hydrocarbyl other than alkyl (eg. alkenyl, alkynyl, phenyl and naphthyl), substituted hydrocarbyl, CO_2H, CO_2R*, SO_3NR_2, heterocycle*, amino*, OH, OR, SH, SR, CHO, halogen, NO_2, CN, PO_3H_2, AsO_3H_2, acyl, —CHR^1R^3 where R^1=H, Me; R^3=R as above, preferably at least one R not =H, R preferably contains 1–10 carbons. *=optionally substituted.

Starting materials employed to prepare the above antibiotics include



via epoxidation

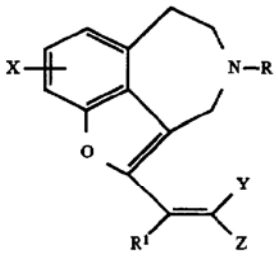
-continued



via ring closure

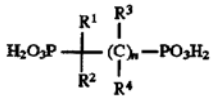
wherein R can be SO_3H, and X and Y are hydroxy or functional equivalent precursor to epoxide: eg. OH, halo, azide, RCO_2—, RSO_2O—, R_2S^+—, R_3N^+—, ArO—, R_2PO_2—, RSO_2NR^1—. One of X and Y must be an oxygen radical.

EP 89/0-344-980 (Smith Kline) discloses α-antagonists of the structure



wherein Y or Z may be —SO_2R, —P(R)O(OR), —PR_2O, —$PO(OR)_2$, and amides.

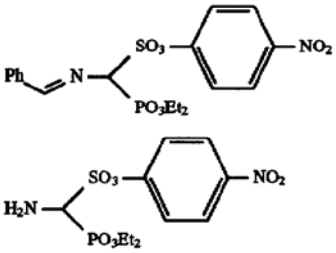
WO 88/00061 (Amersham) discloses Technetium-99 complexes for bone scanning having the structure



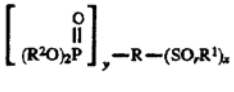
wherein R^1 and R^3=H, SO_3H or alkyl substituted with SO_3H and optionally one or more heteroatoms; R^4 can also be SO_3H or OH, NH_2, NHMe, NMe_2, lower alkyl substituted with a polar group;

R^2=same as R^4 except not SO_3H and n=0, 1.

U.S. Pat. No. 4,032,521 (Merck) discloses inter-mediates, in cephalosporin synthesis, of the structures



WO 90/07513 (Gas Research Institue) discloses electrolytes for fuel cells of the structure



wherein R=organic radicals with 1 or more F atoms;

R^1=H, alkali metal, Zn, Cd;

R^2=H, lower alkyl;

r=2, 3; and x, y=1, 2, 3.

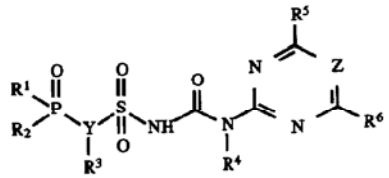
U.S. Pat. No. 4,254,215 (Ciba Geigy AG) discloses a process for photographic developers wherein one component of a developer solution is:

wherein n=1 to 4.

D=optionally substituted, saturated or unsaturated aliphatic radical (<40 carbons), can be interrupted by heteroatoms such as O, SO_2, NH, NR.

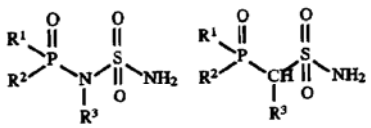
W=PO_3R_2, SO_3R, SO_2R, —NY—SO_3R, —SO_2NR_2, —SSO_3R, CO_2R, OH, NR_3^+, NR_2, $CONR_2$.

DE 89/3739691-A (Hoechst) (Derwent #89-173507/24) discloses herbicides and plant growth regulators of the structure

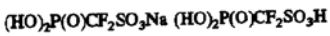


wherein Y=CH, N; X=O, S; Z=CH, N; R^1, R^2=C1–C6 alkyl or alkoxy; R^3=H, C1–C6 alkyl or alkoxy, C2–C6 alkenyl, alkynyl, alkenyloxy, alkynyloxy; all optionally substituted with one or more halogens; and R^4=H, C1–C4 alkyl or physiologically acceptable cation.

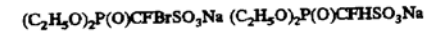
New intermediates are disclosed of the structures

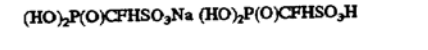


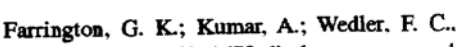
Burton, D. J., J. Am. Chem. Soc. 1989, 111, 1773–1776 discloses electrolytes and chelators of the structures



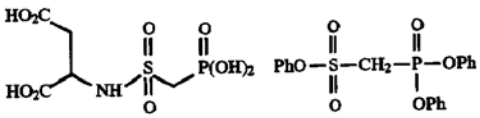
Su, D.; Cen. W.; Kirchmeier, R. L.; Shreeve, J. M., Can. J. Chem. 1989, 67, 1795–1799, disclose electrolytes and chelators of the structures





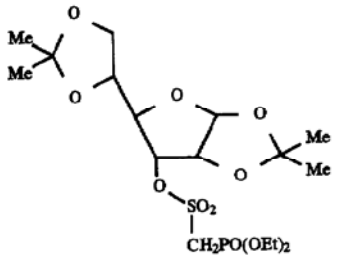


Farrington, G. K.; Kumar, A.; Wedler, F. C., J. Med. Chem. 1985, 28, 1668–1673 discloses compound 10 as an inhibitor of aspartate transcarbamylase. Compound 24 is a synthetic intermediate.



10 24

Musicki, B.; Widlanski, T. S. Tetrahedron Lett. 1991, 32, 1267–1270 discloses compound 4 as a synthetic intermediate.

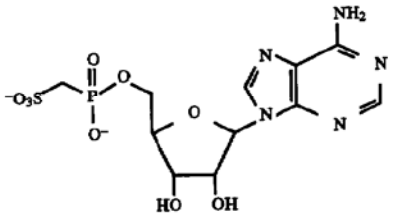


Carretero, J. C.; Demillequand, M.; Ghosez, L., Tetrahedron 1987, 43, 5125–5134 discloses

1a X = Et
1b X = i-Pr
2a X = Li
2b X = n-Bu_4N

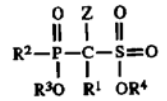
for use in the synthesis of vinyl phosphonates via a Horner-Emmons reaction.

Callahan, L.; Ng, K.; Geller, D. H.; Agarwal, K.; Schwartz, N. B., Analytical Biochemistry 1989, 177, 67–71 discloses an analog of ADP (adenosine diphosphate) of the structure



DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided α-phosphonosulfonate compounds which inhibit cholesterol biosynthesis, and thus are useful as hypocholesterolemic and antiatherosclerotic agents and have the following structure I.



I

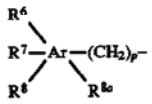
wherein R^2 is OR^5 or R^{5a}, R^3 and R^5 are the same or different and are H, alkyl, arylalkyl, aryl, cycloalkyl, a metal ion or other pharmaceutically acceptable cations as defined below, or a prodrug ester;

R^{5a} is H, alkyl, arylalkyl or aryl;

R^4 is H, alkyl, cycloalkyl, aryl, aryl-alkyl, metal ion or other pharmaceutically acceptable cations as defined below, or a prodrug ester;

Z is H, halogen, lower alkyl or lower alkenyl;

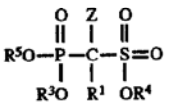
R^1 a lipophilic group containing at least 7 carbons and is alkyl containing 7 to 25 carbons in the chain; alkenyl containing from 7 to 25 carbon atoms in the chain and from 1 to 6 double bonds; alkynyl containing 1 to 6 triple bonds; mixed alkenyl-alkynyl containing 1 to 5 double bonds and 1 to 5 triple bonds; and where in the above groups alkenyl and/or alkynyl may be substituted or unsubstituted; cycloalkyl; cycloheteroalkyl linked through a carbon on the ring or a heteroatom; aryl; heteroaryl; heteroarylalkyl; cycloalkylalkyl; cycloheteroalkylalkyl; or a group of the structure



wherein Ar is aryl (such as phenyl or naphthyl), heteroaryl (5 or 6 membered) and may include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl) and wherein $(CH_2)_p$ contains from 1 to 15 carbons, preferably 2 to 12 carbons, in the chain and may include 0, 1, 2 or 3 double bonds and/or 0, 1, 2 or 3 triple bonds in the normal chain, and may contain an ether or amino function in the chain, and/or may include 0, 1, 2 or 3 substituents as defined below for R^6; and R^6, R^7, R^8 and R^{8a} are the same or different and are H, alkyl containing 1 to 40 carbons, preferably from 3 to 25 carbons, alkoxy containing 1 to 40 carbons, preferably from 3 to 25 carbons, alkenyl containing 2 to 40 carbons, preferably from 3 to 25 carbons, alkenyloxy containing 2 to 40 carbons, preferably from 3 to 25 carbons, alkynyl containing 2 to 40 carbons, preferably from 3 to 25 carbons, alkynyloxy containing 2 to 40 carbons, preferably from 3 to 25 carbons, cycloheteroalkyl, cycloheteroalkylalkyl, heteroaryl, cycloalkyl, cycloalkylalkyl, Ar-alkyl, (such as arylalkyl), ArO (such as aryloxy), Ar-amino (such as arylamino), hydroxy, halogen, nitro, Ar (such as aryl), amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, alkenyl, aryl or any of the Ar groups mentioned above), thiol, alkylthio, Ar-thio (such as arylthio), alkylsulfinyl, Ar-sulfinyl (such as arylsulfinyl), alkylsulfonyl, Ar-sulfonyl (such as arylsulfonyl), carboxy, cyano, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, Ar-carbonyloxy (such as arylcarbonyloxy), Ar-carbonylamino (such as arylcarbonylamino) or alkylcarbonylamino, as well as any of the Ar groups as defined above, and preferably wherein the total number of carbons in the substituted Ar—$(CH_2)_p$— group exceeds 10 carbons; including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other FDA approved cations such as ammonium, choline, diethanolamine, ethylenediamine, and salts of naturally occuring amino acids such as arginine, lysine, alanine and the like.

The $(CH_2)_p$ group may contain 1, 2, 3 or more alkyl, alkoxy, alkenyl, alkynyl, hydroxy and/or halogen substituents as well as any of the substituents defined for R^6.

Thus, the compounds of the invention include the following sub-genuses:



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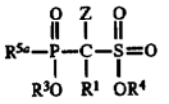
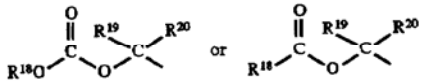
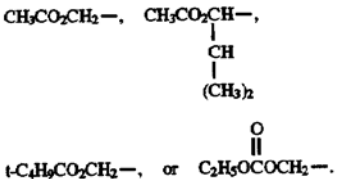


IB

The term "prodrug esters" as employed herein includes prodrug esters which are known in the art for both phosphorus and carboxylic acids. Examples include the following groups: (1-alkanoyloxy)alkyl such as,

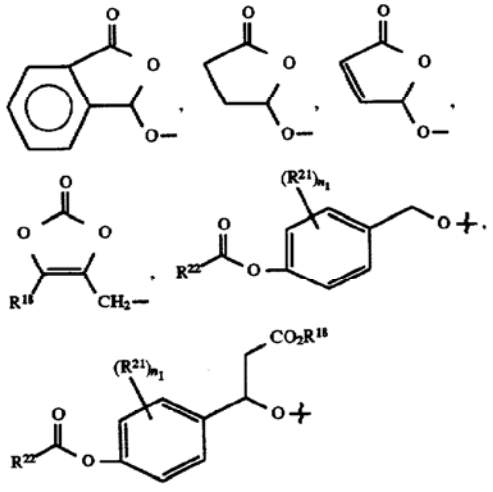


wherein R^{18}, R^{19} and R^{20} are H, alkyl, aryl or aryl-alkyl; however $R^{18}O$ cannot be HO. Examples of such prodrug esters include

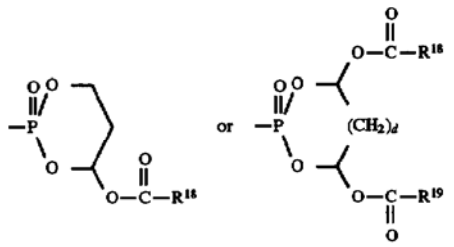


(preferred)

Other examples of suitable prodrug esters include



wherein R^{18} can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^{21} is H, alkyl, halogen or alkoxy, R^{22} is alkyl, aryl, arylalkyl or alkoxyl, and n_1 is 0, 1 or 2; or R^3 and R^5 can be linked together as in



(d is 0 to 3)

Unless otherwise indicated, the term "lower alkyl" or "alkyl" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, in the normal chain, more preferably 1 to 12 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as F, Br, Cl or I or CF_3, alkoxy, aryl, arylalkyl, alkenyl, cycloalkyl, amino, hydroxy, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated cyclic hydrocarbon groups containing 3 to 12 carbons, preferably 3 to 8 carbons, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl, any of which groups may be substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

Unless otherwise indicated, the term "aryl" as employed herein refers to monocyclic or bicyclic aromatic groups containing from 6 to 10 carbons in the ring portion, such as phenyl, naphthyl, or phenyl or naphthyl substituted with 1 to 4 substituents such as alkyl, halogen (Cl, Br or F), alkoxy, hydroxy, amino, alkanoylamino, arylcarbonylamino, aryl, arylalkyl, cycloalkyl, alkylamido, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

The term "aralkyl", "aryl-alkyl" or "aryl-lower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, alkyl, aralkyl or aryl groups linked to a sulfur atom.

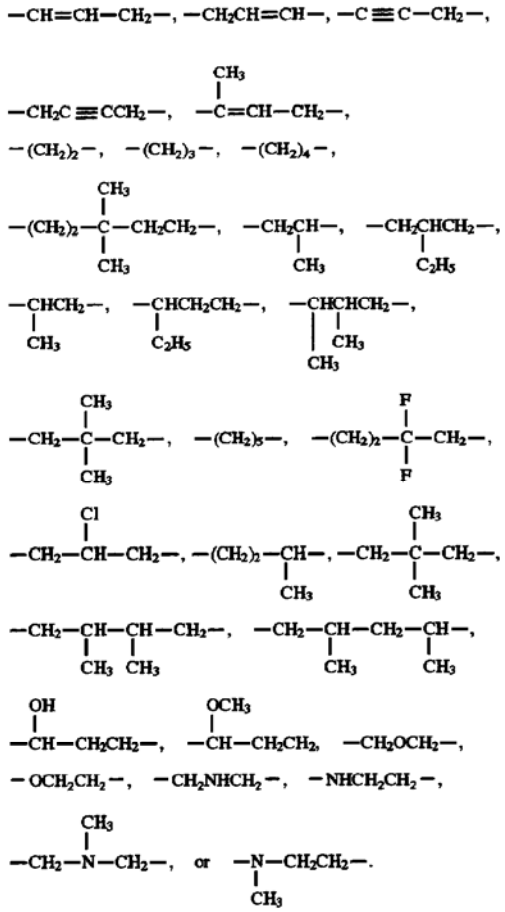
The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 40 carbons, preferably 3 to 30 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^6.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 40 carbons, preferably 2 to 20 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, as well as any of the other substituents as defined for R^6.

Examples of suitable $(CH_2)_p$ groups include



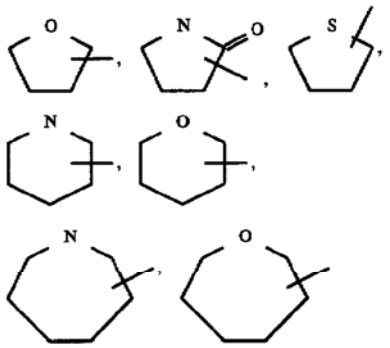
The term "halogen" or "halo" as used herein refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

The term "amino" as used herein refers to unsubstituted amino as well as monosubstituted amino or disubstituted amino wherein the substituents may be alkyl and/or aryl.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

The term "cycloheteroalkyl" as used herein as an R^1 substituent refers to a 5-, 6- or 7-membered saturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked to the carbon "C" of

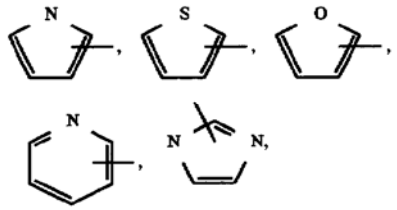
through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



and the like. The above groups may include 1 to 3 substituents such as any of the R^6 groups as defined above. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term "heteroaryl" as an R^1 substituent refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, which is linked to the carbon "C" of

through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



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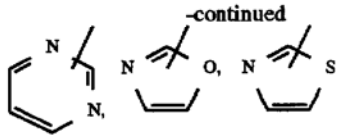


and the like. The above groups may include 1 to 3 substituents such as any of the R^6 groups as defined above. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term cycloheteroalkylalkyl" as defined by R^1 refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to the "C" of

group through a $(CH_2)_p$ chain wherein p is preferably 1 to 8.

The term "heteroarylalkyl" as defined by R^1 refers to a heteroaryl group as defined above linked through a C atom or heteroatom to the "C" of

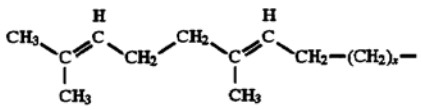
through a $-(CH_2)_p-$ chain as defined above, where p is preferably 1 to 8.

Preferred are compounds of formula I and IA wherein R^2 is OR^5 and R^5 is a metal ion such as Na or K, or H or a pharmaceutically acceptable salt or more preferably a pro-drug ester;

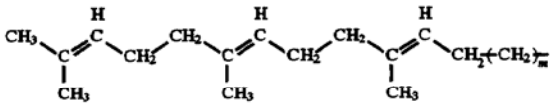
R^3 is H, a metal ion such as Na or K;

R^4 is a metal ion such as Na or K;

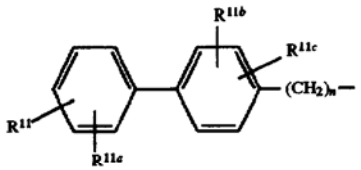
R^1 is alkenyl such as



wherein $(CH_2)_x$ is defined as $(CH_2)_p$ above and x is preferably 2 to 8,

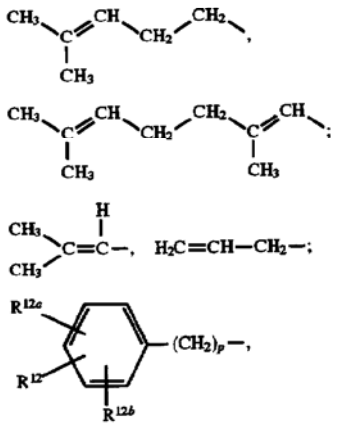


m is 1 to 5;

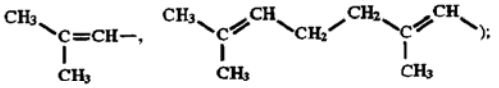


n=1 to 15;

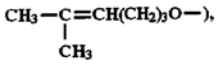
R^{11}, R^{11a}, R^{11b}, and R^{11c} are independently selected from H, alkyl such as propyl, alkoxy, such as methoxy or propyloxy, alkenyl such as



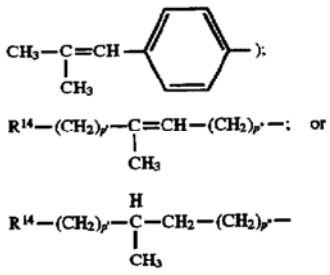
wherein R^{12}, R^{12a} and R^{12b} are independently selected from H, aryl (such as phenyl or naphthyl), alkylphenyl (such as p-propylphenyl, p-pentylphenyl), alkyl containing 1 to 20 carbons (such as p-heptyl), halo, alkoxy (such as methoxy or propyloxy), alkenyl (such as



arylalkyloxy (such as phenethyloxy), alkenyloxy (such as



aryloxy (such as phenoxy), phenylalkyl (such as benzyl, phenylpropyl), alkylphenoxy (such as orthobutylphenoxy), alkenylphenyl (such as



wherein R^{14} is aryl, heteroaryl, aryloxy, heteroaryloxy, cycloalkyl, heterocycloalkyl, and $(CH_2)_{p'}$ and $(CH_2)_{p''}$ are as defined above for $-(CH_2)_p-$. Preferred p' and p" are independently 1 to 4;

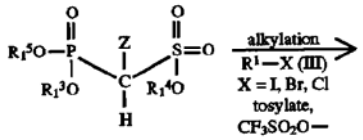
wherein Ar^1 and Ar^2 are independently selected from any of the Ar groups defined hereinbefore, and $(CH_2)_p$ is as defined hereinbefore.

The compounds of the invention may be prepared according to the following reaction sequences.

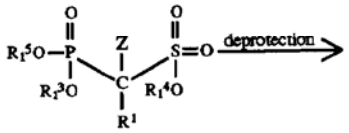
Schemes I, IA and II

General Schemes for the Preparation of α-Phosphonosulfonates

Scheme I

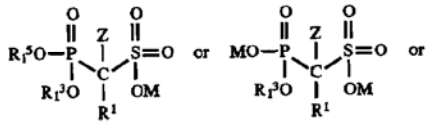


II

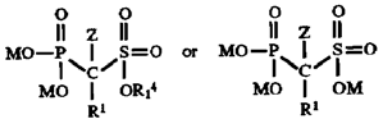


IC

(R_1^3, R_1^4, R_1^5 are independently alkyl, aryl, arylalkyl or cycloalkyl)



ID IE

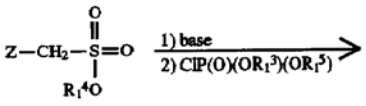


IF IG

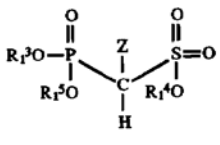
M = H, metal ion, or other pharmaceutically acceptable cation.

Scheme IA

Preparation of Starting Phosphonosulfonate II



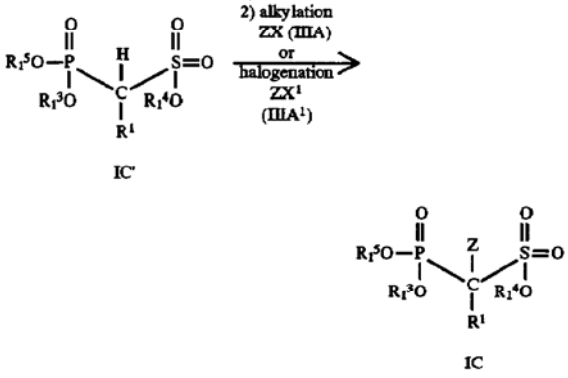
IIA IIB



II

Procedure employed is similar to that described by Carretrero, J.C.; Demillequand, M.; Ghosez, L., Tetrahedron, Vol. 43, 1987, pp 5125–5134.

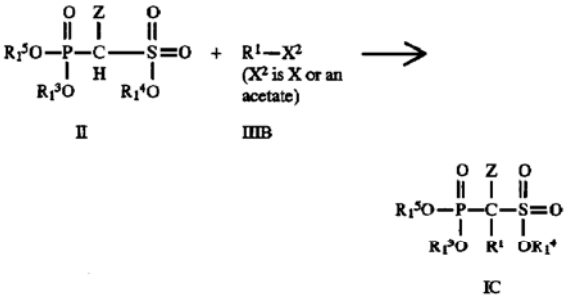
Scheme II
Alternatively, Z can be added after R^1
(where Z = lower alkyl or halogen).



IC'

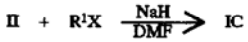
IC

Scheme III - Alkylation Reaction of Electrophiles
III with Phosphonosulfonates II to Yield Triesters IC

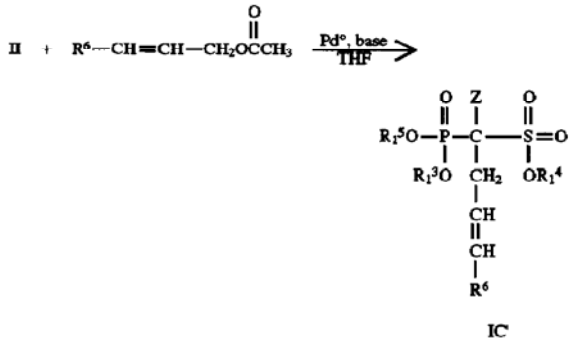


II IIIB IC

Part A.



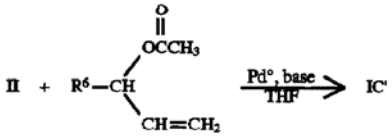
Part B.



(allylic acetate - Type 1)

or

Part C.



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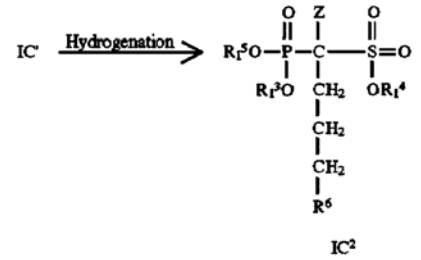
Scheme III - Alkylation Reaction of Electrophiles
III with Phosphonosulfonates II to Yield Triesters IC

(allylic acetate - Type 2)

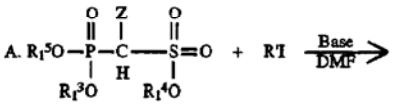
Part D.



IC^2

(where R^1 is $R^6-CH=CH-CH_2-$)

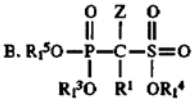
Scheme IV - Preparation of (Dialkoxyphosphinyl)methanesulfonic Monoacid Salts



II IIIA

ID

(R_4^1 = ethyl or other 1°alkyl) M = K, Na



IC

Part B(1) R_1^4 = alkyl, cycloalkyl, arylalkyl

(ICa)

Deprotection
1) a) NH_3/CH_3OH, or
b) $MHCO_3$ or pyridine, or MOAc in CH_3OH or CF_3CH_2OH, opt. H_2O or
c) MI, DMF or
d) MI, 18-crown-6, THF
2) MOH (optional), room temp.

ID

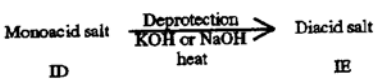
Part B(2) R_1^4 = aryl

MOH
R.T. to 80° C.

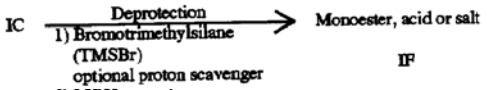
(ICb)

ID

Scheme V - Preparation of (Hydroxyalkoxyphosphinyl)methanesulfonic Diacid Salts IE

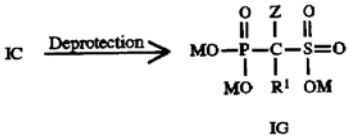


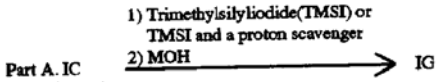
Scheme VI - Preparation of (Dihydroxyphosphinyl)methanesulfonic Acid Monoesters IF

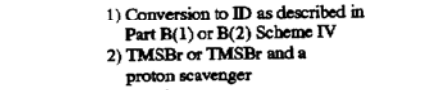


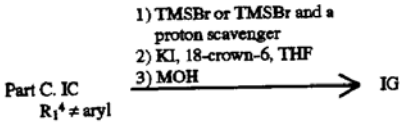
R_1^5, R_1^3 = alkyl, cycloalkyl, arylalkyl

Scheme VII - Preparation of (Dihydroxyphosphinyl)methanesulfonic Acids IG



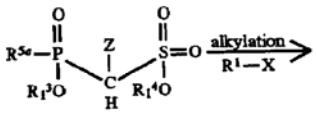


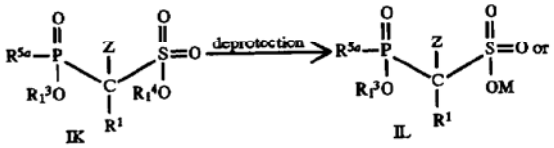




Schemes VIII, IX, IXA and X—General Schemes for the Preparation of α-(Alkyl-or Aryl-hydroxyphosphinyl)sulfonates

Scheme VIII





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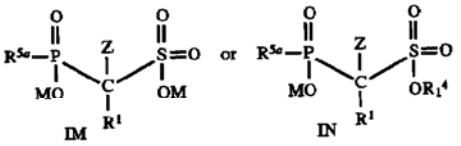
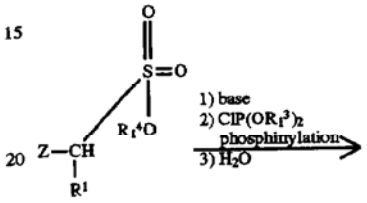
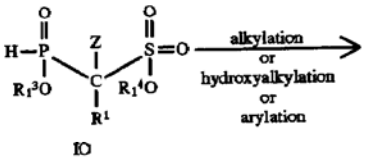
Scheme VIII

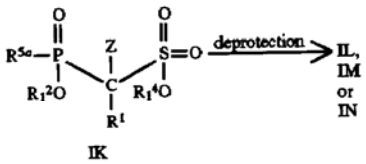


R_1^3, R_1^4 = alkyl, aryl, arylalkyl, cycloalkyl

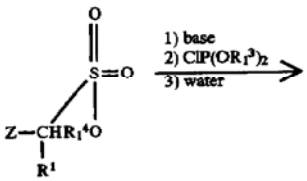
Scheme IX

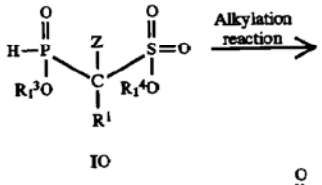


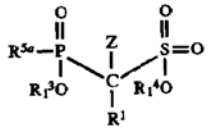




Scheme IXA





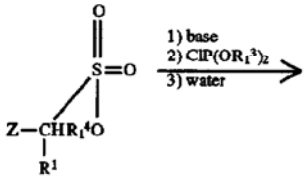


Alkylation Reaction Methodology

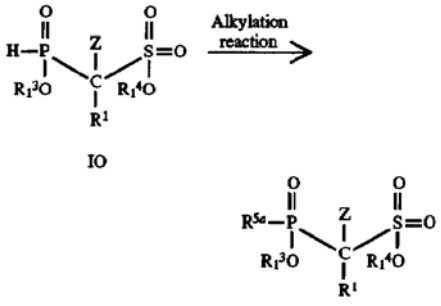
A. A. I) ≧1 eq. of base R^{5a} ≠ Aryl
2) R^{5a}-Hal (Hal = I or Br)

-continued

Scheme IXA



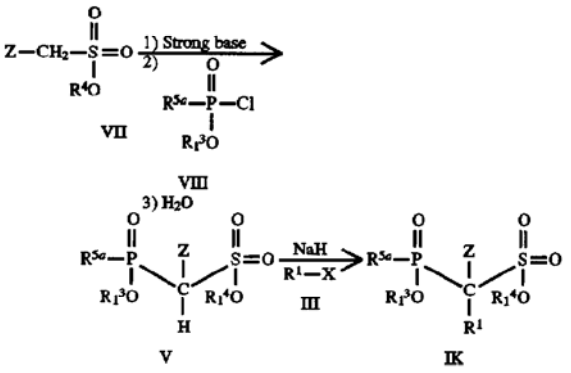
IID or VI



IO IK

Alkylation Reaction Methodology	product IK
VIB B. B. 1) Chlortrimethylsilane (TMSCl) Et_3N 2) R^{5a}-Hal	$R^{5a} \neq$ Aryl
VIB C. C. 1) base 2) aldehyde R^7 = aryl, alkyl or H or 1) TMSCl, $(C_2H_5)_3N$ 2) aldehyde	$R^{5a} = R^7CHOH$
D. D. 1) base 2) aryl halide, $Pd[P(C_6H_5)_3]_4$ or $Ni[P(C_6H_5)_3]_4$	R^{5a} = aryl

Scheme X



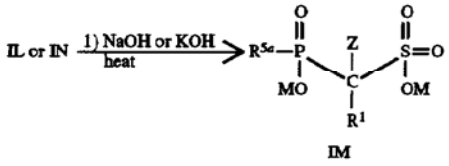
VII VIII IK V

Scheme XI - Preparation of (Hydroxphosphinyl)methanesulfonic Acids

The diesters IL or IM are deprotected by treatment with aqueous alkali as shown below to yield the product IM.

-continued

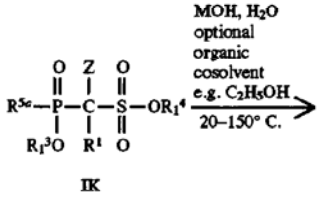
Scheme XI - Preparation of (Hydroxphosphinyl)methanesulfonic Acids



IM

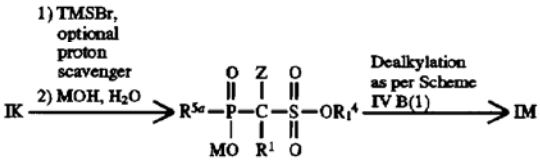
Scheme XIA - Preparation of (Hydroxyphosphinyl)methanesulfonic Acids.

Part A.



IK IM

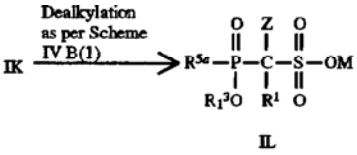
Part B.



IN

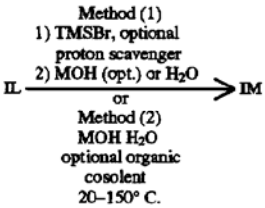
(R_1^4 = alkyl, arylalkyl, cycloalkyl)

Part C.

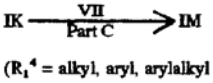


IL

(R_1^4 = alkyl, arylalkyl, cycloalkyl)

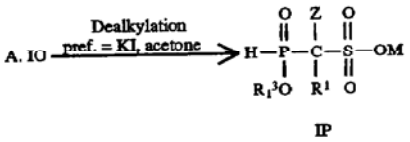


Part D.

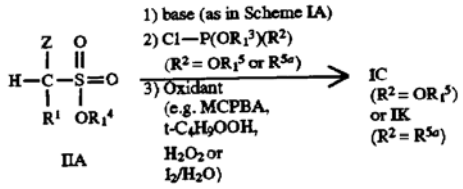


(R_1^4 = alkyl, aryl, arylalkyl

Scheme XII - Preparation of α-Hydroxyphosphinyl methanesulfonic Acids (phosphonous acids)

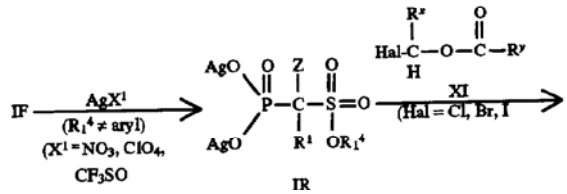


Scheme XIII - Alternative Route to IC or IK



Scheme XIV - Preparation of Prodrugs

Part A



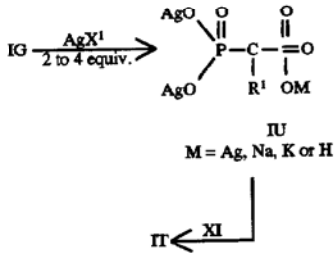
(Rʸ = aryl, aralkyl, alkyl or alkoxy)

Rˣ = aryl, aralkyl, alkyl or H)

-continued

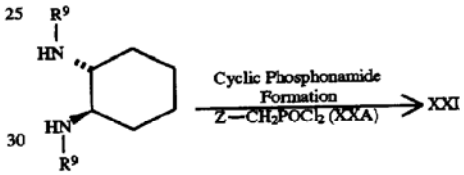
Scheme XIV - Preparation of Prodrugs

Part B

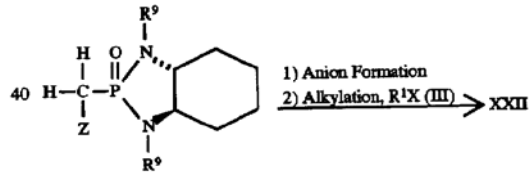


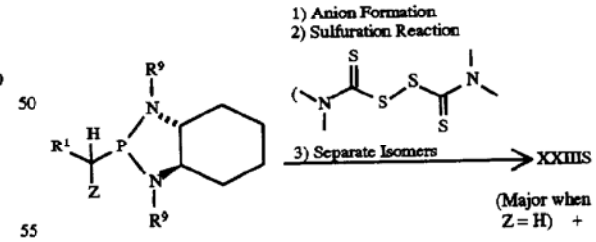
Scheme XV - Preparation of Individual Enantiomers of Formula I Compounds

Part A



(R, R)-Diamine XXR (or (S, S)-Diamine XXS) (R⁹ = alkyl or arylalkyl)

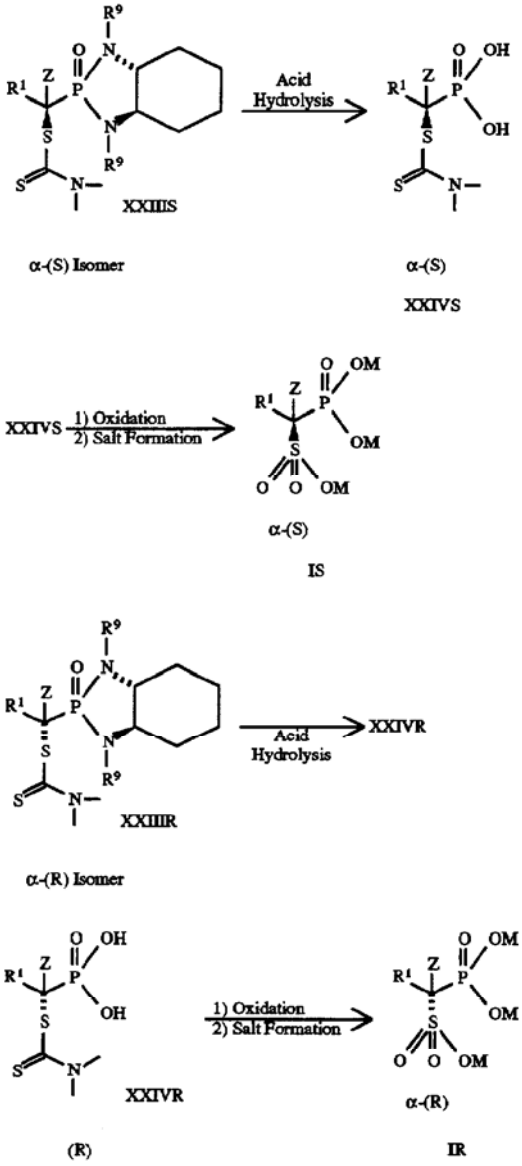




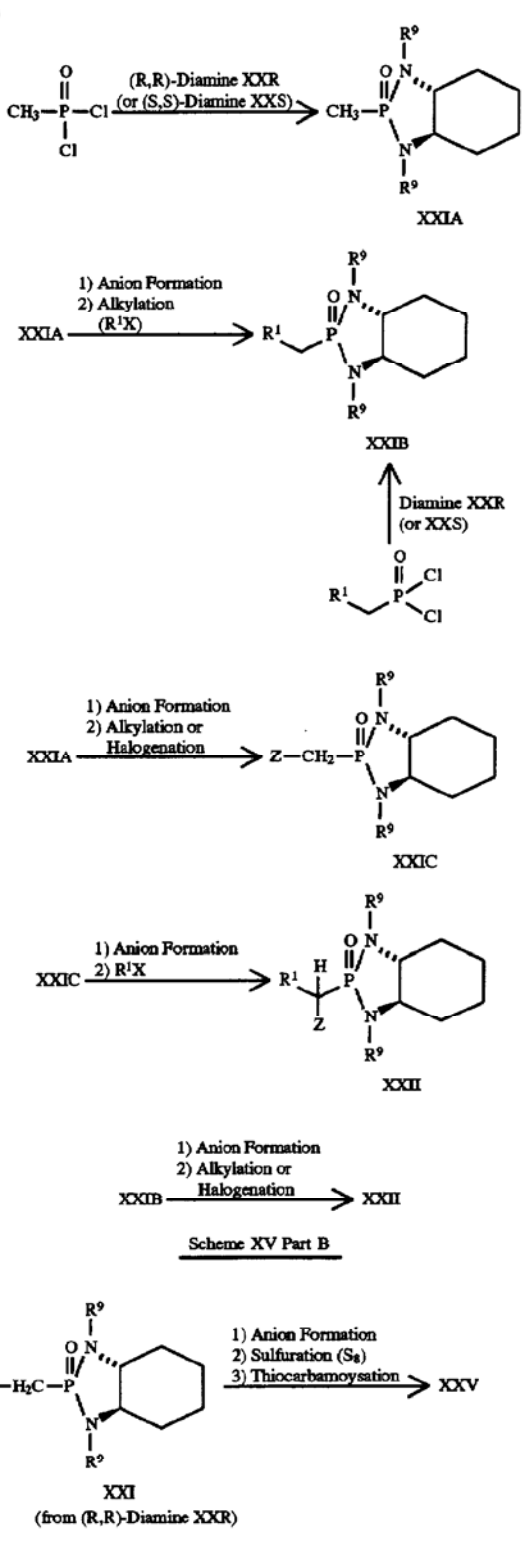
When (S, S)-Diamine XXS is used as starting material, α-(R) is Major Isomer where (Z = H) and α-(S) is Minor Isomer (Z = H)

-continued

Scheme XV - Preparation of Individual Enantiomers of Formula I Compounds



Scheme XV Part A(1) - Alternate Routes to XXII (Used in Scheme XV, Part A)



Scheme XV Part B

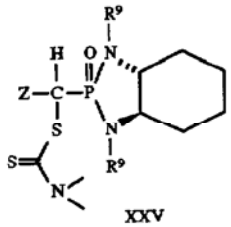
References on asymmetric reaction of chiral phosphonates

Hanessian, S., Delorme, D., Beaudoin, S., LeBlanc (1984) Chemica Scripta 25, 5–11.

Hanessian, S., Bennani, Y. L., Delorme, D. (1990) Tetrahedron Lett. 45, 6461–6464.

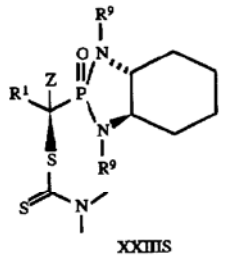
Hanessian, S., Bennani, Y. L. (1990) Tetrahedron Lett. 45, 6465–6468.

-continued

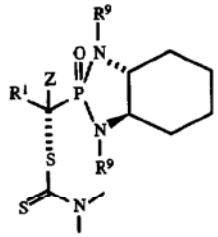


XXV

1) anion formation
2) alkylation
R^1Hal



XXIIIS



XXIIIR

(Minor Isomer
α-(S) when Z = H)

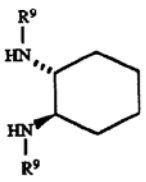
(Major Isomer
α-(R) when Z = H)

When (S,S)-Diamine XXS is the starting material, the α-(S) isomer XXIIIS is obtained as the major product when Z = H.

XXIIIS → Continue as in Scheme XV Part A → IS

XXIIIR → Continue as in Scheme XV Part A → IR

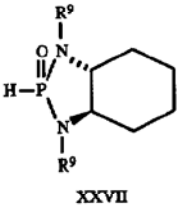
Scheme XV Part C



XXR

(R,R)-Diamine
(or (S,S)-Diamine (XXS))

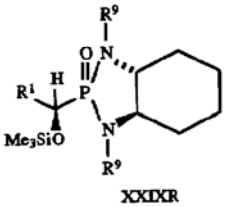
Phosphorous Diamide Formation



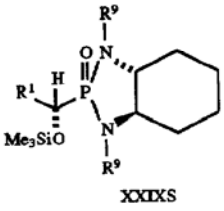
XXVII

1) Condensation Reaction
R^1CHO (XXVIII)
Silylating Agent
2) Separate Isomers

XXVII → XXIXS + XXIXR



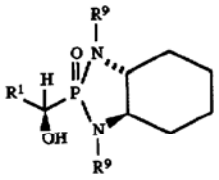
XXIXR



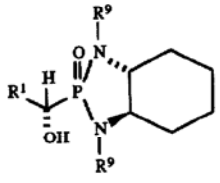
XXIXS

Fluoride Source

-continued



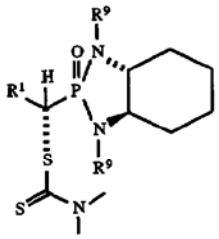
XXXR



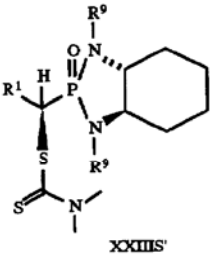
XXXS

Alternatively, isomers can be separated at the alcohol stage, that is, XXR and XXS.

XXXR → Mitsunobu Displacement* → XXXS



XXIIIR'



XXIIIS'

XXIIIR' → α-(R) → Continue as in Scheme XV Part A → IR

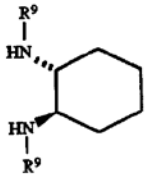
XXIIIS' → α-(S) → Continue as in Scheme XV Part A → IS

*P. Rollin, Tetrahedron Lett. 1986, 27, 4169–4170

Part C (1)

XXVII → 1) Condensation Reaction R^1CHO (XXVIII), Various Bases including Fluoride, 2) Separate Isomers → XXXR + XXXS

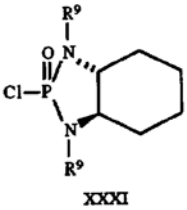
Scheme XVI - Alternate Preparation of Individual Enantiomers of Formula I Compounds



XXR

(R,R)-Diamine
(or S,S-Diamine XXS)

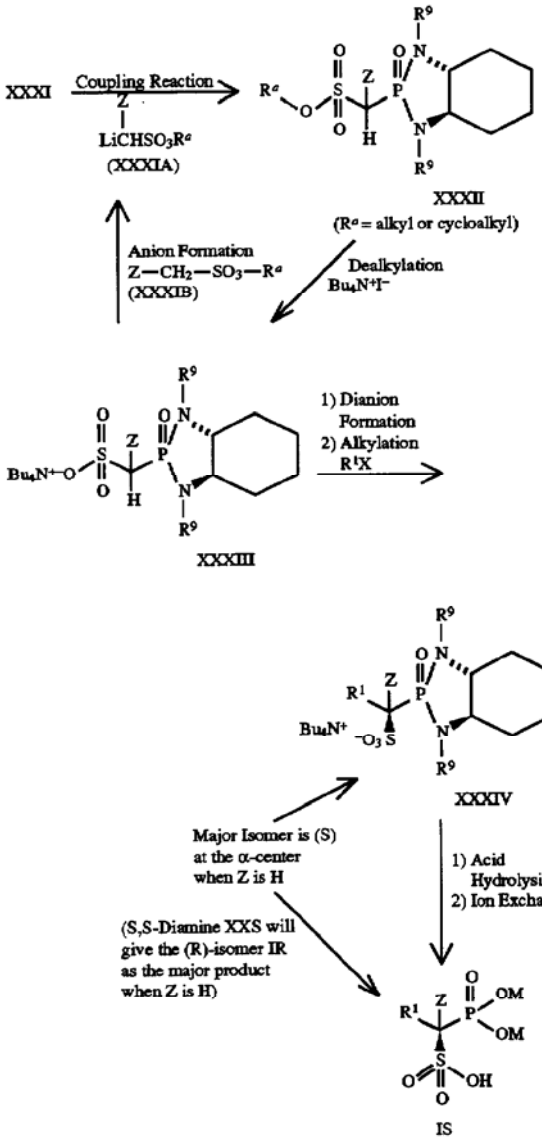
Acid Cl Formation
$POCl_3$



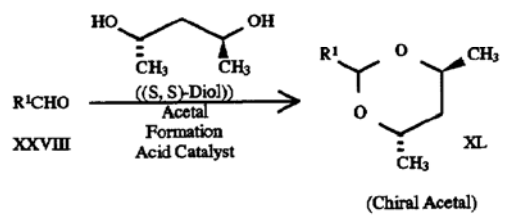
XXXI

-continued

Scheme XVI - Alternate Preparation of Individual Enantiomers of Formula I Compounds



Scheme XVII - Preparation of Individual Enantiomer



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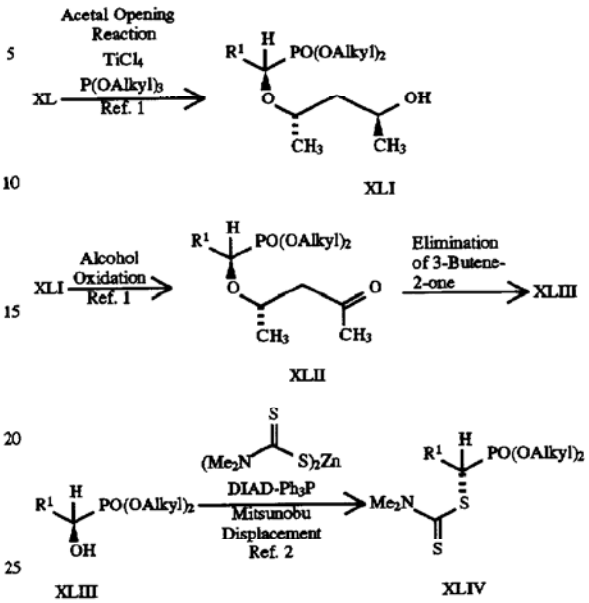
Scheme XVII - Preparation of Individual Enantiomer



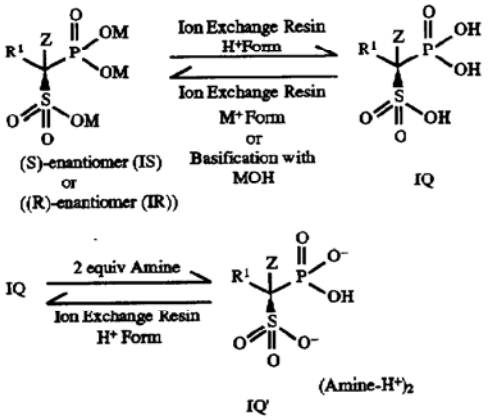
Use (R, R)-diol to obtain (S)-enantiomer (IS)

References:

(1) Yokomatsu T.; Shibuya, S., Tetrahedron Asymmetry 1992, 3, 377–378

(2) P. Rollin, Tetrahedron Lett. 1986, 27, 4169–4170

Scheme XVIII - Purification of Desired Enantiomer



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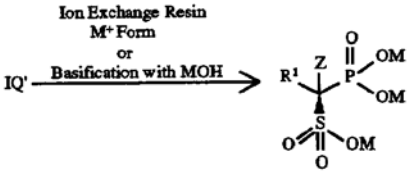
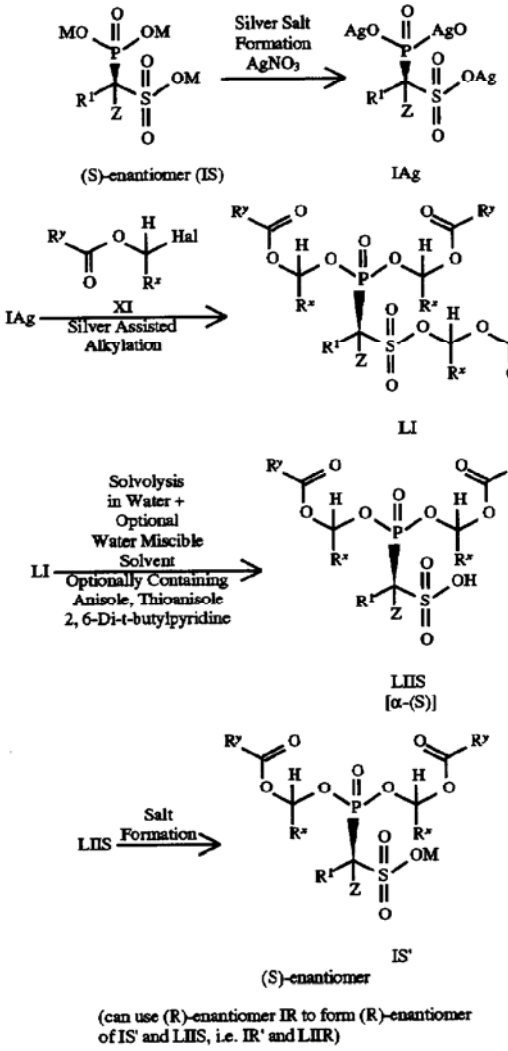
Scheme XVIII - Purification of Desired Enantiomer

Diamine Salts (IQ') are useful for purification and improvement of enantiomeric excess, especially by recrystallization



Scheme XIX - Preparation of Prodrug of Desired Enantiomer



Referring to "General Reaction" Scheme I, compounds of the invention IC may be prepared by alkylating the phosphonosulfonate II by reacting II with compound III in the presence of an appropriate base and an inert organic solvent under an inert atmosphere to form IC, followed by deprotection to the various acid forms ID, IE, IF and IG.

In carrying out the above reaction, the phosphonosulfonate II is employed in a molar ratio to compound III of within the range of from about 5:1 to about 0.8:1, and preferably from about 3:1 to about 1.2:1. The reaction is carried out under an inert atmosphere, such as argon, initially preferably at a reduced temperature of within the range of from about −78° to about 80° C., and more preferably from about 0° to about 50° C., although the reaction may be completed at room temperature.

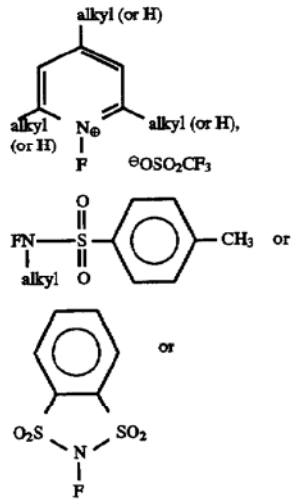
Examples of inert organic solvents suitable for use herein include, but are not limited to dimethylformamide (DMF), tetrahydrofuran (THF), dimethylsulfoxide (DMSO), hexamethylphosphoramide (HMPA) or diethyl ether (Et_2O), or mixtures thereof.

Examples of bases suitable for use in carrying out the above reaction include, but are not limited to, alkali metal hydrides, such as sodium hydride (which is preferred), potassium hydride, lithium-, sodium- or potassium bis (trimethylsilyl)amide, lithium diisopropylamide or butyllithium.

Referring to Scheme IA, starting compounds of formula IIC wherein R_1^2, R_1^3, and R_1^4 of II as defined in Scheme I may be prepared by reacting starting sulfonate IIA with a strong base such as any of those used in Scheme I, in the presence of or followed by chlorophosphate IIB, and an inert organic solvent such as used in Scheme I, to form IIC.

In carrying out the reaction of Scheme IA, chlorophosphate IIB will be employed in a molar ratio to sulfonate IIA of within the range of from about 3:1 to about 1:2, and preferably from about 2.0:1 to about 1:1. The reaction is carried out at a temperature of within the range of from about −100° to about 30° C., and preferably from about −90° to about 0° C.

Referring to Scheme II, compounds of the invention IC may be prepared by alkylating the phosphonosulfonate IC' with an alkylhalide, ZX (IIIA) (Z is alkyl and X is as defined in Scheme I), or with a halogenating agent ZX^1 (where Z is halogen except F and X^1 is succinimido, Cl, Br or I, or OH; when Z is F, ZX^1 is XeF_2),



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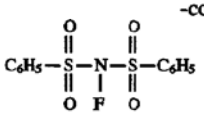


The above reactions are carried out in the presence of appropriate inert organic solvent as described above, under an inert atmosphere, to form IC.

In carrying out the above reaction, the phosphonosulfonate IC' is employed in a molar ratio, to compound IIIA or IIIA' of within the range of from about 2:1 to about 0.2:1, and preferably from about 1.5:1 to about 0.7:1. The reaction is carried out under an inert atmosphere, such as argon, initially preferably at a reduced temperature of within the range of from about −78° to about 80° C., and more preferably from about 0° C. to about 50° C., although the reaction may be completed at room temperature. Bases and solvents appropriate for this reaction are as described for Scheme I.

Referring to Scheme III Part A, compounds of the invention IC may be prepared by alkylating the phosphonosulfonate II with compound III in the presence of an appropriate base and an inert organic solvent (as described hereinbefore with respect to Scheme I) preferably dimethylformamide (DMF), under an inert atmosphere to form IC.

In carrying out the above reaction, the phosphonosulfonate II is employed in a molar ratio to compound III of within the range of from about 5:1 to about 0.8:1, and preferably from about 3:1 to about 1.5:1. The reaction is carried out under an inert atmosphere, such as argon, initially preferably at a reduced temperature of within the range of from about −78° to about 80° C., and more preferably from about 0° to about 50° C., although the reaction may be completed at room temperature.

Referring to Schemes III PartB and III Part C, compounds of the invention IC' may be prepared through the palladium catalyzed base promoted coupling of allylic acetates (Types 1 or 2) with the phosphonosulfonate II to provide the coupled product of the invention IC'. Either allylic isomer serves as a substrate in the reaction.

In carrying out the above reactions, the phosphonosulfonate II is employed in a molar ratio to allylic acetate of within the range of from about 5:1 to about 0.8:1, and preferably from about 3:1 to about 1.5:1. The reaction is carried out under an inert atmosphere, such as argon, initially preferably at a reduced temperature of within the range of from about −78° to about 110° C., and more preferably from about 0° to about 80° C., although the reaction may be completed at room temperature.

The above reactions are carried out in the presence of a suitable inert organic solvent as described hereinbefore with respect to Scheme I, preferably employing tetrahydrofuran (THF) or dimethylformamide (DMF). Suitable bases are sodium hydride and sodium bis(trimethylsilyl)amide, and preferably bis(trimethylsilyl)acetamide (BSA) in the presence of palladium (O) catalyst such as $Pd[P(C_6H_5)_3]_4$.

The base or BSA is employed in a molar ratio to allylic acetate within the range of from about 4:1 to about 1:1, while the Pd(O) is employed in a molar ratio to allylic acetate of within the range of from about 0.005:1 to about 0.5:1.

Referring to Scheme IV, Part A, the coupling reaction is carried out with (dialkoxyphosphinyl)methane sulfonate ethyl ester II to yield the sulfonate salt ID directly from the reaction. The product emerges by means of a concomitant iodide promoted dealkylation of the sulfonate ester.

The Scheme IV Part A, reaction is carried out in a manner similar to Scheme I.

The sulfonate salt ID may also be formed as shown in Scheme IV, Part B(1) and (2). Part B(1) depicts the dealkylation of the sulfonate ester ICa to yield ID, using various reagents as shown in the reaction sequence set out hereinbefore, while B(2) shows the cleavage of an aryl methanesulfonate ester ICb by aqueous alkali containing from about 5 to about 20% by weight base) and heating at a temperature within the range of from about 40° to about 100° C., to give ID.

Referring to Scheme V, the diacid salt IE is prepared by the further hydrolysis of monoacid ID employing aqueous alkali (containing from about 5° to about 20% by weight base) optionally in the presence of a cosolvent, such as dimethoxyethane, dioxane or THF, and heating at a temperature within the range of from about 40 to about 100° C.

Referring to Scheme VI, the (dihydroxyphosphinyl) methanesulfonic acid monoester IF is prepared by the cleavage of the phosphorous ester IC (wherein R_1^2 and R_1^3 are each lower alkyl, arylalkyl, cycloalkyl and R_1^4 is lower alkyl, arylalkyl, cycloalkyl or aryl) with bromotrimethylsilane (TMSBr), optionally in the presence of a proton scavenger such as 2,4,6-collidine, hexamethyl disilazane, alkyl, trimethylsilane, bis(trimethylsilyl)trifluoroacetamide, pyridine or triethylamine, followed by aqueous alkali (as described above except that elevated temperatures are not necessary) or water wherein the TMSBr is employed in a molar ratio to IC of within the range of from about 2:1 to about 15:1, preferably from about 2: to about 5:1.

Scheme VII Parts A, B and C sets out the chemical processes employed for the deprotection of phosphonosulfonate triester IC to phosphonosulfonic acid IG.

In Scheme VII, Part A shows the direct deprotection of the ester IC through the agency of trimethylsilyl iodide (TMSI) (employs a molar ratio of TMSI:IC of within the range of from about 3:1 to about 20:1, preferably from about 3.5:1 to about 5:1) optionally in the presence of a proton scavenger as defined above, and followed by aqueous alkali (as described above) or water at a temperature of within the range of from about 0° to about 50° C.

In Scheme VII Part B, phosphonosulfonic triacid IG is formed via a two step process where in the first step, the sulfonate ester is removed as described in Part B, Scheme IV and in the second step treatment with bromotrimethylsilane optionally in the presence of a proton scavenger as defined above, yields the silyl esters which are then hydrolyzed via aqueous alkali (as described hereinbefore) or water.

In Scheme VII Part C, the phosphonate esters are removed (from IC) first with bromotrimethylsilane (TMSBr) (employing a molar ratio of TMSBr:IC of within the range of from about 2:1 to about 20:1, preferably from about 2.5:1 to about 5:1) optionally in the presence of a proton scavenger as defined above, to provide the intermediate bis(silyl) esters. Subsequent cleavage of the sulfonate ester with potassium iodide (18-crown-6, THF) and hydrolysis (MOH and H_2O) yields the phosphonosulfonic triacid IG.

Schemes VIII, IX, IXA and X relate to the preparation of α-(alkyl- or aryl-hydroxyphosphinyl)sulfonates.

Schemes VIII and IX depict the general chemical process for the formation of diesters IK, and their deprotection to form IL and IO, respectively.

Scheme IXA depicts the P-H route to diester IK. Starting sulfonate VI is treated with a strong base followed by dialkyl chlorophosphite (employing a molar ratio of dialkyl chlorophosphite:VI of within the range of from 1:1 to about 10:1), followed by hydrolysis with water under acidic conditions, to form alkoxyphosphinyl sulfonate IO which serves as an intermediate for the synthesis of substituted (alkyl- or aryl-alkoxyphosphinyl)methylsulfonate diesters

via alkylation of IO. The alkylation methods are shown in Parts A, B, C and D.

In Scheme IXA Part A, diester IK where $R^{5a} \neq$ aryl is formed by selective alkylation of IO by treating IO with base such as NaH, KH, LDA, butyllithium, Li-, Na- or K-bis (trimethylsilyl)amide and a halide VIB of the structure

VIB R^5Hal

wherein Hal is I or Br, as described with respect to Scheme I.

In Scheme IXA Part B, diester IN where $R^5 \neq$ aryl is formed by treatment of IO with chlorotrimethylsilane (TMSCl) and organic base such as triethylamine (Et_3N) in the presence of alkylating agent VIB. In carrying out this alkylation, the silane compound is employed in a molar ratio to IO of within the range of from about 1:1 to about 5:1, preferably from about 1:1 to about 3:1 while VIB is employed in a molar ratio to IO of within the range of from about 0.8:1 to about 10:1.

In Scheme IXA Part C, IK where R^{5a} is R^7CHOH (and R^7 is H, aryl or alkyl) is prepared by treating IO with base followed by aldehyde R^7CHO, carried out by employing a molar ratio of R^7CHO to IO of from about 1:1 to about 10:1. Alternatively, IO can be treated with $(CH_3)_3SiCl$ and an organic base (such as triethylamine) followed by an aldehyde, followed subsequently with a standard desilylation reaction (such as tetrabutylammonium fluoride in THF) to provide IK with $R^5=R^7CHOH$.

In Scheme IXA, Part D IO is reacted with an aryl halide in the presence of a base such as triethylamine and $Pd[P(C_6H_5)_3]_4$, $Ni[P(C_6H_5)_3]_4$ or other nickel and palladium catalysts, to yield IK when R^{5a} is aryl.

Scheme X depicts the preparation of (hydroxyphospinyl) methanesulfonic acid diester IN by alkylation of diester V by treatment of V with base, such as NaH, and alkylating agent III as described hereinbefore in Scheme I. The intermediate V may be prepared via a coupling reaction of the alkylsulfonate VII with phosphonic acid chloride VIII employing a molar ratio of VII:VIII of within the range of from about 0.5:1 to about 10:1, preferably from about 1.5:1 to about 3:1, similar to that described in Scheme IA, for the conversion of IIA to IIC.

Schemes XI and XIA depict various routes (A, B and C) for the deprotection of diesters IK to yield IM.

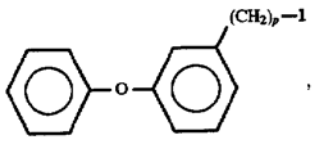
Scheme XII Part A depicts the preparation of salts IQ by dealkylating IO using techniques as described hereinbefore, preferably with KI and acetone, to form monoester IP and then subjecting IP to hydrolysis to form salt IQ.

In Scheme XII Part B, the ester IP is treated with aldehyde (R^7CHO) in the presence of organic base such as triethylamine, diisopropylethylamine or 1,8-diazabicyclo [5.4.0]undec-7-ene, to form IK where R^{5a} is R^7CHOH. In this reaction, the aldehyde is employed in a molar ratio to IP of within the range of from about 1:1 to about 10:1, preferably from about 1:1 to about 5:1.

Scheme XIII depicts an alternate route to IC where IIA is treated with base (as per Scheme IA) and chlorophosphite (as described hereinbefore) and an oxidant such as m-chloroperbenzoic acid (MCPBA), $t\text{-}C_4H_9COOH$, hydrogen peroxide or I_2/H_2O to form IC.

Scheme XIV (Parts A and B) depict the preparation of prodrug esters.

Referring to Scheme XV, the individual isomers or enantiomers of the formula I compounds of the invention may be prepared, in accordance with the present invention, by treating the (R,R)-diamine XXR (or (S,S)-diamine XXS) where R^a is alkyl or aralkyl, with an alkyl phosphonic dihalide XXA, such as methylphosphonic dichloride, in the presence of a tertiary amine base and an aprotic solvent such as benzene, toluene, dichloromethane or diethyl ether, to form the alkylphosphondiamide XXI which is metalated with a base such as n-butyllithium, sec-butyllithium, t-butyllithium or lithium diisopropylamide, to form the lithium anion of XXI which is then alkylated by treatment the halide R^1X (IIIa) such as the iodide XXIB



in the presence of an inert organic solvent such as tetrahydrofuran (THF), diethyl ether or dimethoxyethane or mixtures thereof, at a temperature within the range of from about −90° to about 25° C., preferably from about −80° to about 0° C., to form XXII. Compound XXII is reacted with a base as above to form the lithium anion of XXII which is sulfurated with tetramethylthiuram disulfide or the corresponding tetraethyl derivative at a temperature within the range of from about −100° to about 0° C., preferably from about −90° to about −60° C., to form a mixture of isomers XXIIIR and XXIIIS (which are novel compounds in accordance with the present invention).

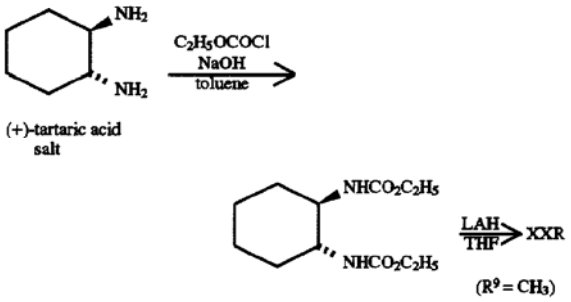
Where the sulfuration is carried out at below about 0° C., preferably at about −60° C. to about −100° C., and the starting diamine is the (R,R)-diamine XXR and Z is H, a mixture of major XXIIIS (α-(S)) and minor XXIIIR (α-(R)) thiocarbamate isomers (about 3:1 mixture at −90° C.) is obtained.

It should be noted that in the above and following discussions and schemes α-(R) and α-(S) refer to the enantiomeric configuration at the chiral carbon center adjacent to the phosphorus and sulfur moieties.

It will be appreciated that where the (S,S)-diamine XXS is employed in place of (R,R)-diamine XXR and Z is H, the major isomer obtained will be the α-(R)-isomer XXIIIR.

The thiocarbamate isomers XXIIIS and XXIIIR can be separated by chromatography on silica gel, crystallization or HPLC. The individual and separate diastereomers (XXIIIS and XXIIIR) are then separately subjected to acid hydrolysis (such as treatment with aqueous acid such as HCl), to form compound XXIVR or XXIVS (which are novel compounds in accordance with the present invention) which are separately subjected to oxidation (such as reaction with H_2O_2 in the presence of formic acid, acetic acid or mixtures of formic and acetic acids) and salt formation by base treatment or ion exchange chromatography, to form the individual enantiomers IS and IR of the invention.

In carrying out the reactions of Scheme XV, the starting (R,R)-diamine with R^9=methyl is prepared by a two-step reductive methylation of the L-(+)-tartaric acid salt (available from racmeic 1,2-trans-cyclohexanediamine, Gasbol, F. et al (1972) Acta. Chem. Scand. 26, 3605 and Onuma, K. et al, (1980) Bull. Chem. Soc. Jap. 53, 2012) as follows:



Other examples of XXR and XXS where R^9 is alkyl or aralkyl are prepared as reported in the prior art as follows: Alexakis, A. et al, *J. Org. Chem.*, 1992, 57, 1224–1237; Denmark, S. et al, *J. Org. Chem.*, 1991, 56, 5063–5079; Hanessian, S. et al, *Tetrahedron*, 1992, 33, 7659–7662; and Koeller, K. J. et al, *Tetrahedron Lett.*, 1991, 32, 6297–6300.

The (R,R)-diamine XXR (or XXS) is employed in a molar ratio to the alkylphosphonic dichloride XXA of within the range of from about 0.5:1 to about 3:1, preferably from about 0.9:1 to about 1.5:1. The amine base, such as triethylamine, pyridine, diisopropylethylamine will be employed in a molar ratio to the alkylphosphonic dichloride XXIA of within the range of from about 1:1 to about 5:1, preferably from 1.5:1 to about 3:1.

The metalation (anion formation) of XXI is carried out at a temperature within the range of from about −90° to about 0° C., preferably from about −80° to about −60° C., employing a molar ratio of base compound to alkylphosphondiamide XXI of within the range of from about 0.8:1 to about 2:1, preferably from about 0.9:1 to about 1.3:1. The alkylating agent R^1X (III) where X is preferably iodide, but may be Cl or Br as well, will be employed in a molar ratio to alkylphosphondiamide XXI of within the range of from about 1:1 to about 4:1, preferably from about 1:1 to about 2:1.

As seen in Scheme XVI Part A(1), compound XXII may be prepared by a variety of routes which will be apparent to those skilled in the art.

The metalation of XXII is carried out at a temperature within the range of from about −100° C. to about 0° C., preferably from about −60° C. to about −80° C. employing a molar ratio of base to XXII of within the range of from about 2:1 to about 0.8:1, preferably from about 1.4:1 to about 0.9:1.

The lithium anion of XXII is then sulfurated employing a molar ratio of tetramethylthiuram disulfide: lithium anion of XXII of within the range of from about 3:1 to about 1:1, preferably from abut 2:1 to about 1:1.

The acid hydrolysis of the individual isomer XXIIIS and XXIIIR to the corresponding thiocarbamate XxIVS and XXIVR, respectively, is carried out by employing aqueous strong acid, such as aqueous HCl, formic acid or sulfuric acid, optionally in the presence of acetonitrile, dioxane or other inert organic solvent. The thiocarbamates XXIVS and XXIVR may be oxidized by conventional techniques, for example, by reaction with hydrogen peroxide in the presence of acetic acid or formic acid, or mixtures thereof or peracids such as peracetic in acetic acid or metachloroperbenzoic acids in dichloromethane or diethyl ether, or using Oxone in alcoholic solvents, to the sulfonic acid which is treated with alkali metal hydroxide, such as KOH, NaOH, or LiOH or an ion exchange resin to form the triacid salt, IS or IR.

Referring to Scheme XV Part B, in accordance with the present invention, in an alternate synthesis of the Part A method, alkylphosphondiamide XXI (or (S,S)-isomer) is metalated by reaction with a base as described above, such as n-butyllithium, sec-butyllithium, t-butyllithium or lithium diisopropylamide in the presence of an inert organic solvent such as hexane, tetrahydrofuran or diethylether to form the lithium anion of XXI which is sulfurated by treatment with sulfur and subjected to thiocarbamoylation with a dialkyl thiocarbamoyl halide to form XXV (a novel compound in accordance with the present invention). Compound XXV is then metalated by treatment with a base as described above, alkylated by treatment with R^1Hal and the resulting mixture of isomers XXIIIS and XXIIIR are separated as described hereinbefore. Isomers XXIIIS and XXIIIR may then be subjected to acid hydrolysis and oxidation and salt formation as described with respect to XXIIIS and XXIIIR in Part A, to form IR and IS.

In carrying out the Scheme XV Part B method, the base, preferably n-butyllithium, is reacted with alkylphosphondiamine XXI under an inert atmosphere such as argon or nitrogen at a temperature within the range of from about −100° to about 0° C., preferably from about −60° to about −80° C., employing a molar ratio of alkyllithium:XXI of within the range of from about 0.8:1 to about 2:1, preferably from about 1.2:1 to about 1:1.

The sulfuration reaction of lithiated XXI (with sulfur) is carried out at a temperature within the range of from about −90° to about 0° C., preferably from about −80° to about −40° C., employing a molar ratio of sulfur:lithiated XXI of within the range of from about 4:1 to about 1:1, preferably from about 2:1 to about 1:1.

Thiocarbamoylaton of the sulfurated XXI with the dialkylthiocarbamoyl halide, preferably, dimethyl- or diethylthiocarbamoyl chloride is carried out at a temperature within the range of from about −60° to about 25° C., preferably from about −30° to about 0° C., employing a molar ratio of dialkylthiocarbomoyl halide:sulfurated XXI of within the range of from about 4:1 to about 1:1, preferably from about 2:1 to about 1:1. The thiocarbamoylation reaction is optionally carried out in the presence of a weak organic base, such as triethylamine or pyridine.

The thiocarbamoylated compound XXV is metalated with a base, as described above, preferably n-butyllithium, at a temperature within the range of from about −90° to about −60° C., preferably from about −80° to about −70° C., under an inert atmosphere such as argon or nitrogen, employing a molar ratio of alkyllithium: thiocarbamoylated compound XXV of within the range of from about 2:1 to about 0.8:1, preferably from about 1.4:1 to about 0.9:1.

Alkylation of the lithiated XXV is carried out at a temperature within the range of from about −90° to about 0° C., preferably from about −80° to about −40° C., employing a molar ratio of R^1Hal:lithiated XXV of within the range of from about 4:1 to about 0.8:1, preferably from about 1.5:1 to about 0.9:1. The alkylation is preferably carried out in the presence of a weak base such as hexamethylphosphoramide (HMPA), or tetramethylethylene diamine.

Still another alternative method for preparing the desired enantiomers of formula I compounds, in accordance with the present invention, is shown in Scheme XV Part C wherein starting (R,R)-diamine XXR (or the corresponding (S,S-)-diamine XXS) is made to undergo a phosphorous diamide formation by treating a solution of XXR and weak organic base such as triethylamine or pyridine, in an inert organic solvent such as THF, dichloromethane or toluene, with phosphorus trichloride under an inert atmosphere such as argon or nitrogen, and then treating the resulting filtrate (chilled), under an inert atmosphere, such as argon, with water, and a tertiary amine base, to form the phosphorous

diamide XXVII. The diamide XXVII may then be subjected to a condensation reaction with the aldehyde XXVIII

R^1CHO

and a silylating agent such as, for example, bis (trimethylsilyl) acetamide, bis(trimethylsilyl) trifluoroacetamide or hexamethyl disilazane in the presence of an inert organic solvent, such as methylene chloride, toluene or THF, under an inert atmosphere, such as argon or nitrogen, to form a mixture of protected isomers XXIXR (α-(R)isomer) and XXIXS (α-(S)isomer).

The isomers XXIXR and XXIXS are separated by chromatography or other conventional means such as crystallization and each of the α-(R) isomer XXIXR and α-(S) isomer XXIXS in solution in an inert organic solvent such as THF, diethyl ether, acetonitrile or dichloromethane, is separately treated with a fluoride source such as tetrabutylammonium fluoride, aqueous hydrofluoric acid or lithium tetrafluoroborate, to form the compounds XXXR and XXXS.

Each of the isomers XXXR and XXXS can then be separately made to undergo a Mitsunobu displacement (Rollin, P., Tetrahedron Lett. 1986, 27, 4169–4170) wherein each of XXXR and XXXS is separately treated with dimethyl (or diethyl) dithiocarbamic acid, zinc salt, and triphenylphosphine, tributylphosphine, triethylphosphite and diethyl diazodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD), in the presence of an inert organic solvent such as THF, toluene, or dichloromethane, under an inert atmosphere such as argon or nitrogen, to form the separate isomers XXIIIS' and XXIIIR' which may be converted to the IS and IR isomers, respectively, as described in Scheme XV Part A. Alternatively, the isomer separation can be carried out at the stage of XXXR and XXXS.

If desired, the phosphorous diamide XXVII may be converted directly into the alcohols XXXR and XXXS by subjecting XXVII to a condensation reaction with aldehyde XXVIII in the presence of a base such as 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), triethylamine, basic alumina or a fluoride source such as described above or potassium or cesium fluoride, to form a mixture of XXXR and XXXS.

In carrying out the Scheme XV Part C method, the diamine XXR (or XXS) is reacted with phosphorus trichloride at a temperature of within the range of from about 50° C. to about −80° C., preferably from about 0° C. to about −80° C., employing a molar ratio of trichloride:XXR of within the range of from about 3:1 to about 0.8:1, preferably from about 1.5:1 to about 1:1.

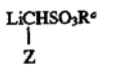
The condensation reaction of the phosphorus diamide XXVII with the aldehyde XXVIII is carried out employing a molar ratio of diamide XXVII:aldehyde XXVIII of within the range of from about 2:1 to about 0.8:1, preferably from about 1.5:1 to about 1:1, and a molar ratio of silyl protecting compound:XXVII of within the range of from abut 3:1 to about 1:1, preferably from about 1.5:1 to about 1:1.

Reaction of the individual isomers XXIXS and XXIXR with the fluoride source is carried out employing a molar ratio of fluoride source to XXIxS or XXIXR of within the range of from about 4:1 to about 1:1, preferably from about 2:1 to about 1.1:1.

Where the phosphorus diamide XXVII is converted directly to the isomers XXXR and XXXS (see Scheme XV Part C(1)), the condensation reaction of XXVII with the aldehyde XXVIII and base or fluoride source as described above will be carried out essentially under similar conditions previously described for formation of XXIXS and XXIXR, and XXXS and XXXR.

The Mitsunobu displacement of XXXR and XXXS is carried out employing a molar ratio of dimethyldithiocarbamic acid or diethyl derivative, zinc salt or equivalent: XXXS or XXXR of within the range of from about 2:1 to about 0.5:1, preferably from about 1.5:1 to about 0.6:1, and a molar ratio of triphenylphosphine or equivalent:XXXR or XXXS of within the range of from about 4:1 to about 1:1, preferably from about 2:1 to about 1:1.

A preferred method for forming the desired enantiomers of formula I is shown in Scheme XVI wherein a solution of the (R,R)-diamine XXR (or the corresponding (S,S)-diamine XXS where the α-(R) product is desired) in an aprotic solvent such as toluene, benzene, dichloromethane or THF, and weak organic base such as triethylamine, pyridine or diisopropylethylamine is treated with phosphorus oxychloride to form the acid chloride XXXI which in solution with an inert organic solvent such as THF, diethylether or dimethoxyethane is subjected to a coupling reaction with



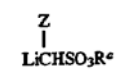
(XXXIA)

(prepared by reaction of an alkylmethanesulfonate XXXIB with alkyllithium) to form the sulfonate XXXII (which is a novel intermediate in accordance with the present invention). Sulfonate XXXII is dealkylated by treatment with a dealkylating agent such as tetrabutylammonium iodide, in the presence of an inert organic solvent such as THF, diethylether or acetone, to form sulfonate XXXIII (which is a novel intermediate in accordance with the present invention) which is made to undergo dianion formation by reaction with a metalating agent such as n-butyllithium, sec-butyllithium, t-butyllithium or lithium diisopropylamide, under an inert atmosphere such as argon or nitrogen, in the presence of an inert organic solvent such as hexane, THF or diethyl ether, and is then treated with alkylating agent R^1Hal in an inert organic solvent such as THF, diethyl ether or hexane to form XXXIV (which is a novel intermediate in accordance with the present invention) optionally in the presence of hexamethyl phosphoramide (HMPA) or tetramethyl ethylenediamine (TMEDA). XXXIV may be subjected to acid hydrolysis and ion exchange to form the individual enantiomer IS, when Z is H.

As indicated, where the starting diamine XX is the (S,S)-enantiomer XXS, the final product will be the IR (R)-enantiomer, when Z is H.

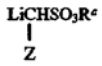
In carrying out the Scheme XVI method, the phosphorus oxychloride will be employed in a molar ratio to the diamine XXR of within the range of from about 1.5:1 to about 0.8:1, preferably from about 1.1:1 to about 0.9:1. The reaction will be carried out at a temperature within the range of from about −20° to about 40° C., preferably from about 0° to about 25° C.

In forming



(XXXIA) (where alkyl is preferably ethyl or cyclohexyl) the alkylmethanesulfonate XXXIB is reacted with the alkyllithium or other strong base at a temperature within the range of from about −90° to about 0° C., employing a molar ratio of alkyllithium:sulfonate XXXIB of within the range of from about 1.2:1 to about 0.8:1, preferably from about 1.1:1 to about 0.9:1.

The



compound XXXIA will be reacted with the acid chloride XXXI at a temperature within the range of from about −90° to about 0° C., preferably from about −80° to about −30° C., employing a molar ratio of Li compound XXXIA to XXXI of within the range of from about 4:1 to about 1:1, preferably from about 2.5:1 to about 1.5:1.

The dealkylation of sulfonate XXXII is carried out employing a molar ratio of iodide:XXXII of within the range of from about 1.5:1 to about 0.9:1, preferably about 1:1.

In the dianion formation, sulfonate XXXIII is treated with the base at a temperature within the range of from about −100° to about 0° C., preferably from about −90° to about −60° C., employing a molar ratio of base:XXXIII of within the range of from about 2:1 to about 0.8:1, preferably from about 1.5:1 to about 1:1.

The lithiated XXXIII compound is alkylated with R^1Hal at a temperature within the range of from about −100° to about 0° C., preferably from about −90° to about −60° C., employing a molar ratio of R^1Hal:lithiated halide of within the range of from about 2:1 to about 1:1, preferably from about 1.5:1 to about 1.1:1.

The alkylated sulfonate XXXIV is made to undergo acid hydrolysis by treating XXXIV with strong aqueous acid, such as HCl, sulfuric or formic acids, and then with base such as KOH, NaOH or LiOH to form the major isomer IS where (S) is at the α-center when Z is H. As indicated, where the starting (S,S)-diamine XXS is employed, the major isomer obtained is IR where (R) is at the α-center when Z is H.

An alternative preferred method for forming the desired enantiomers of the invention is shown in Scheme XVII. The starting aldehyde XXVIII (can be prepared by reaction of the alcohol R^1CH_2OH with methylsulfoxide, and oxalyl chloride in the presence of weak organic base such as triethylamine, that is the Swern oxidation or other standard alcohol oxidations), is treated with (2S,4S)-(+)-pentanediol (or the corresponding (2R,4R)-isomer) and p-toluenesulfonic acid in the presence of an inert solvent such as benzene, toluene or dichloroethane, to form the chiral acetal XL. Chiral acetal XL is subjected to an acetal opening reaction wherein acetal XL is reacted with a trialkylphosphite, such as triethylphosphite, in the presence of titanium (IV) chloride, and an inert organic solvent such as methylene chloride, toluene or benzene, under an inert atmosphere such as argon or nitrogen, to form the alcohol XLI which is oxidized via the Swern oxidation, pyridinium chlorochromate (PCC) or Jones reagent under standard conditions, to form XLII. The 3-butene-2-one portion of XLII is eliminated by treating XLII with p-toluenesulfonic acid or methanesulfonic acid in the presence of dioxane, or acetonitrile and water to form the diester XLIII which is subjected to a Mitsunobu displacement under the same conditions as described for the conversion of XXXS/R to XXIIIS'/R' See P. Rollin, supra, to form XLIV. Compound XLIV is dealkylated by reaction with a dealkylating agent such as bromotrimethylsilane or iodotrimethylsilane in the presence of an inert organic solvent such as methylene chloride, benzene or toluene, under an inert atmosphere such as argon or nitrogen, to form the diacid XLV which is oxidized by treatment with hydrogen peroxide in formic acid, acetic acid or mixtures thereof or other oxidants as described for Scheme XV, and then treated with alkali metal hydroxide such as KOH, NaOH or LiOH, or ion exchange resin as described hereinbefore to form the (R)-enantiomer IR.

It will be appreciated that in carrying out the above method, where the aldehyde XXVIII is reacted with the (R,R)-diol, the final product obtained will be the α-(S)-enantiomer IS.

In carrying out the method of Scheme XVII, the (2S,4S)-(+)-pentanediol will be reacted with the starting aldehyde XXVIII at a temperature within the range of from about 25° to about 100° C., preferably from about 60° to about 90° C., employing a molar ratio of diol:XXVII of within the range of from about 4:1 to about 0.8:1, preferably from about 2:1 to about 1:1. The resulting chiral acetal XL is reacted with the trialkylphosphite and titanium(IV)chloride or equivalent at a temperature within the range of from about −90° to about −20° C., preferably from about −80° to about −40° C., employing a molar ratio of phosphite:xL of within the range of from about 5:1 to about 1:1, preferably from about 3:1 to about 2:1, and a molar ratio of phosphite:titanium tetrachloride of within the range of from about 3:1 to about 1:1, preferably from about 1.2:1 to about 1.6:1, to form alcohol XLI.

The oxidation of alcohol XLI is carried out at a temperature within the range of from about −80° to about 0° C., and the elimination reaction involving XLII is carried out at a temperature within the range of from about 30° to about 150° C., preferably from about 80° to about 120° C., employing a molar ratio of p-toluenesulfonic acid or equivalent:XLII of within the range of from about 0.5:1 to about 0.005:1, preferably from about 0.1:1 to about 0.05:1.

The Mitsunobu displacement reaction is as described previously for Scheme XV Part C.

Dealkylation of XLIV is carried out employing a molar ratio of dealkylating agent:XLIV of within the range of from about 10:1 to about 2:1, preferably from about 6:1 to about 4:1.

Scheme XVIII sets out a purification procedure wherein the desired individual enantiomers (salt thereof) is subjected to ion exchange (H^+ form) such as by treatment with AG 50-X8 ion exchange resin, to form the free triacid IQ which is treated with an amine such as adamantanamine or (S)-(−)-α-methylbenzylamine (under an inert atmosphere such as argon where the latter amine is employed), in a molar ratio of amine:IQ within the range of from about 2.2:1 to about 1.9:1, preferably about 2:1, to form the corresponding bis-amine salt IQ' which is separated out by recrystallization. The so-formed diamine salt IQ' may be treated with ion exchange resin (M^+ form) such as Ag50-X8 (K^+ form) or basified with MOH (where M is K, Li or Na) to form the purified enantiomer. Amine salts IQ' of chiral amines and racemic triacid I may be used to resolve the racemate into α-(R) and (α)-S isomers by recrystallization.

If desired, the diamine salt IQ' may be treated with ion exchange resin (H^+ form) to form the triacid IQ which may be treated with ion exchange resin (M^+ form) or basified with MOH to form the purified enantiomers, IS or IR.

Scheme XIX set out a reaction sequence for preparing prodrugs of the desired enantiomer. As seen, the starting enantiomer IS (or IR) is treated with a silver salt such as silver nitrate to form the silver salt IAg which is alkylated by treatment of IAg (optionally in the presence of 4A molecular sieves, anisole, thioanisole, 2,6-di-t-butylpyridine and mixtures thereof) with alkylating agent XI to form triester LI.

The triester LI is subjected to solvolysis in water, or optionally a water-miscible solvent such as ethanol, methanol, 2,2,2-trifluoroethanol, acetonitrile or mixtures of water and the organic solvent, at 0° C. to 60° C., to form the

diester LII which is made to undergo salt formation by treatment of LII with an alkali metal phosphate buffer, such as potassium phosphate buffer, or ion exchange, to form the salt

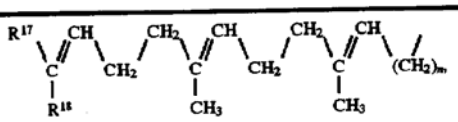
The various acid and salt forms of the invention ID, IE, IF, IG, IL, IM, IN, IO, IP, IQ, IR, IS, IR', IS', LIIR, LIIS, IT and IU can be interconverted by standard means, including ion exchange chromatography. It should be understood that all acids can be isolated either as salts (M=pharmaceutically acceptable cations such as Li^+, Na^+, K^+, NH_4^+), or free acids (M=H).

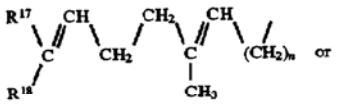
Examples of starting alkylating agents that is R^1X or R^1Hal suitable for use herein include the following which are either known in the literature or are simple derivatives of known compounds prepared by employing conventional procedures.

It will be appreciated that the R^1X compounds listed in the following table represent all possible stereoisomers.

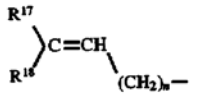
R^1Hal where Hal is Cl, Br or I, or Otosyl or OSO_2CF_3 is as follows in A. through F.

A.





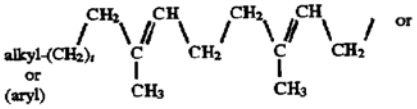
or



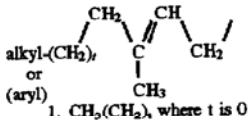
n is 1 to 8

R^{17}	R^{18}
1. C_2H_5	CH_3
2. CH_3	C_2H_5
3. n-C_3H_7	CH_3
4. CH_3	n-C_4H_9
5. t-C_4H_9	CH_3
	$-(CH_2)_{s'}-$ s' = 4 to 6
7. H	H
8. F	F
9. Cl	Cl
10. CH_2F	CH_3
11. $-CH=CH_2$	H
12. $CF_3(CH_2)_t$	H
	t = 0 to 8

B.

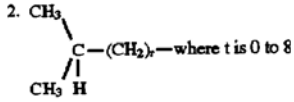


or

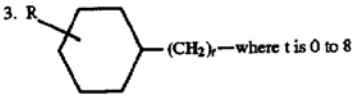


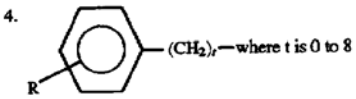
(n is 1 to 8)

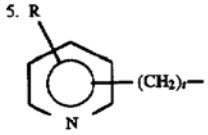
1. $CH_3(CH_2)_t$ where t is 0 to 8

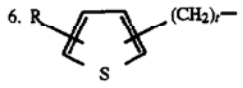
2. 

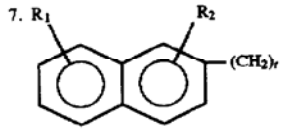
C. Miscellaneous

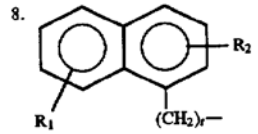
3. 

4. 

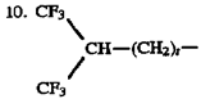
5. 

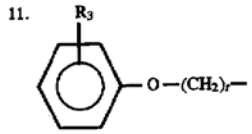
6. 

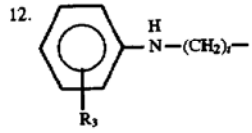
7. 

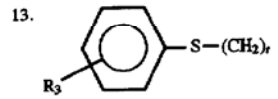
8. 

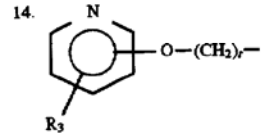
9. $CF_3(CH_2)_t-$

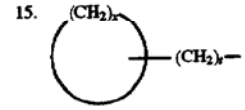
10. 

11. 

12. 

13. 

14. 

15. 

Examples 5 to 10

t=0 to 8

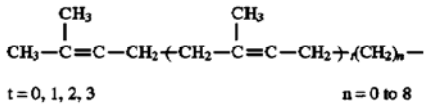
R_1, R_2 and R_3 may be the same or different and can be any of the radicals included in R^6.

Examples 11 to 15

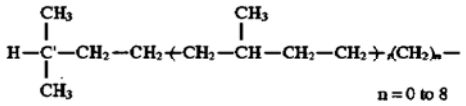
t=1 to 8

x=3 to 8

C.



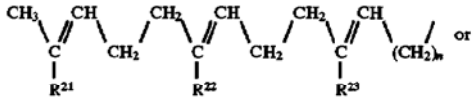
t = 0, 1, 2, 3 n = 0 to 8



n = 0 to 8

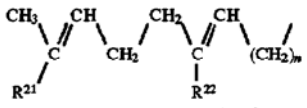
t = 0, 1, 2, 3

D.



or

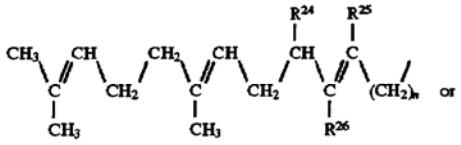
n = 1 to 8



n = 1 to 8

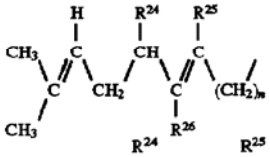
	R^{21}	R^{23}	R^{22}
1.	C_2H_5	C_2H_5	CH_3
2.	CH_3	CH_3	C_2H_5
3.	CH_3	C_2H_5	C_2H_5
4.	C_2H_5	C_2H_5	C_2H_5
5.	CH_3	C_2H_5	CH_3
6.	CH_3	H	CH_3
7.	CH_3	CH_3	H
8.	H	H	H
9.	CF_3	CH_3	CH_3
10.	CH_3	CF_3	CH_3
11.	CH_3	CH_3	CF_3
12.	CF_3	CF_3	CH_3
13.	CF_3	CF_3	CF_3

E.



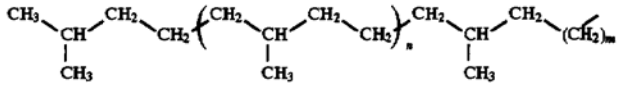
or

n = 1 to 8

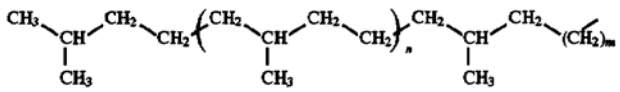


	R^{24}	R^{25}	R^{26}
1.	H	I	H
2.	H	H	I
3.	H	CH_3	CH_3
4.	CH_3S	CH_3	H
5.	F	CH_3	H
6.	CH_3	CH_3	H
7.	H	CH_3	CH_3
8.	H	CH_3	Cl
9.	H	CF_3	H
10.	H	Cl	H
11.	H	CH_3	$(CH_3)_3Si$
12.	H.	CH_3	F
13.	H	CF_3	CH_3
14.	H	CH_3	CF_3

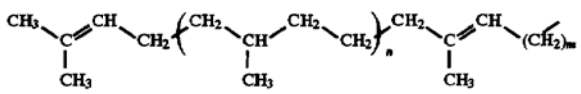
F. Other examples of R^1 include the following

1. 

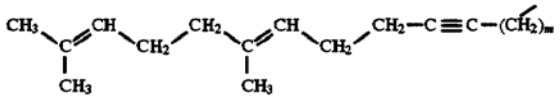
(n is 0, 1)

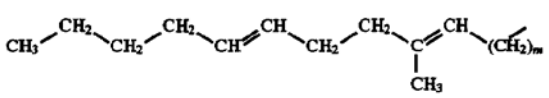
2. 

(n is 0, 1)

3. 

(n is 0, 1)

4. 

5. 

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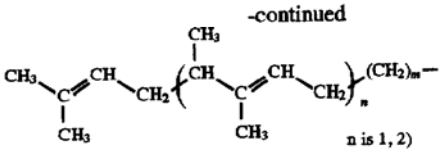
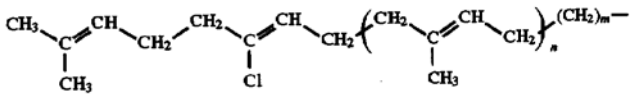
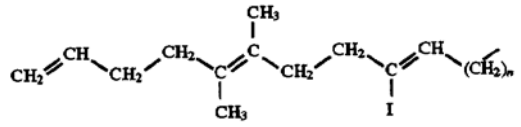
6. 

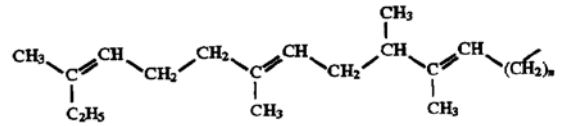
n is 1, 2)

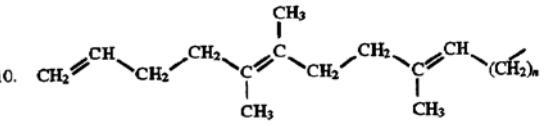
7. 

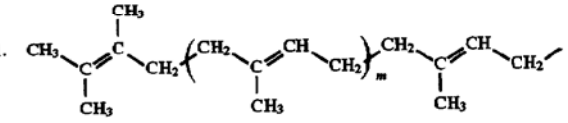
(n is 0, 1)

In Examples 1 to 5, m is 1 to 8.
In Examples 6 and 7, m is 0 to 8.

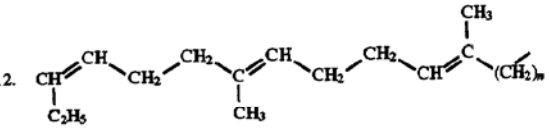
8. 

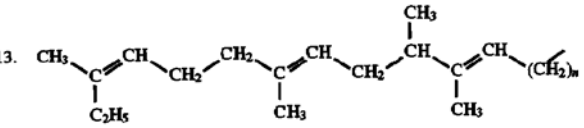
9. 

10. 

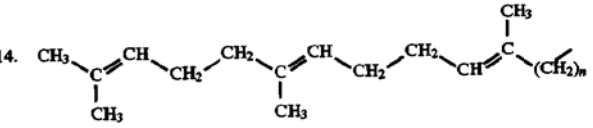
11. 

(m is 1, 2)

12. 

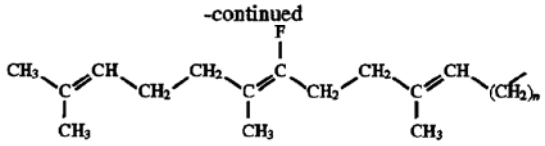
13. 

In Examples 8 to 13, n is 1 to 8.

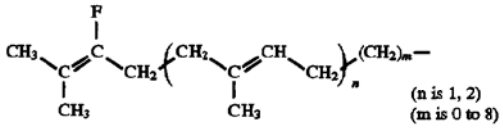
14. 

(n is 1 to 8)

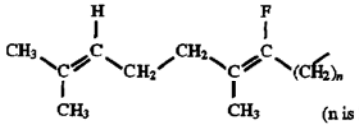
-continued

15. 

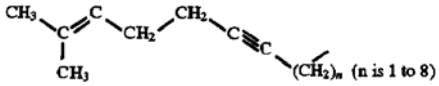
(n is 1 to 8)

16. 

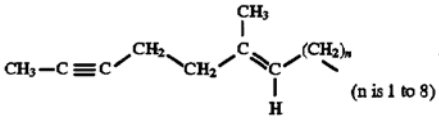
(n is 1, 2)
(m is 0 to 8)

17. 

(n is 1 to 8)

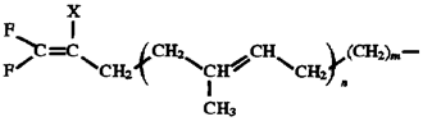
18. 

(n is 1 to 8)

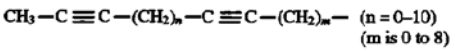
19. 

(n is 1 to 8)

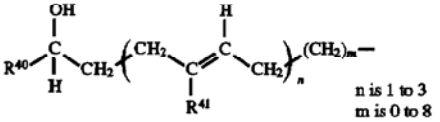
20. $CH_3-C\equiv C-(CH_2)_n-$ (n = 4–12)

21. 

X=H, F, CH_3
n is 1 or 2
m is 0 to 8

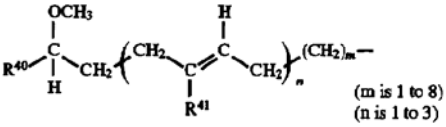
22. 

(n = 0–10)
(m is 0 to 8)

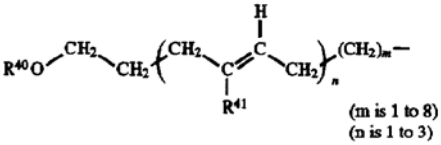
23. 

n is 1 to 3
m is 0 to 8

R^{40}=H, alkyl, cycloalkyl, or aryl such as methyl, ethyl, isopropyl, pentyl, phenyl and cyclopentyl
R^{41}=alkyl such as methyl, ethyl or halo such as Cl or F

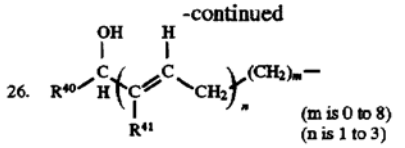
24. 

(m is 1 to 8)
(n is 1 to 3)

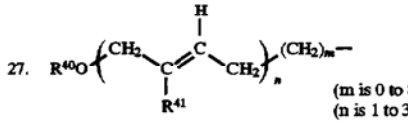
25. 

(m is 1 to 8)
(n is 1 to 3)

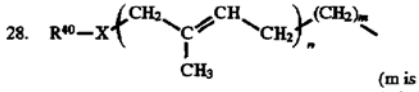
-continued

26. 

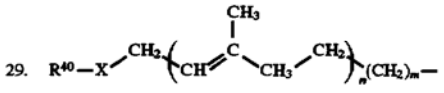
(m is 0 to 8)
(n is 1 to 3)

27. 

(m is 0 to 8)
(n is 1 to 3)

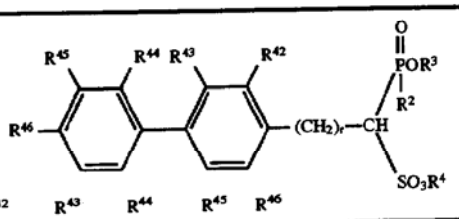
28. 

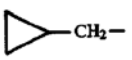
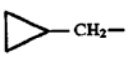
(m is 0 to 8)
(n is 1 to 3)
(X is O, S, NH)

29. 

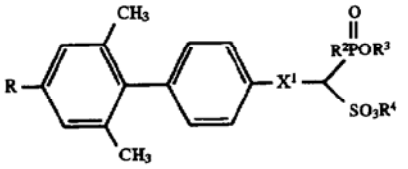
X is O, S, NH, CH_2)
(m is 0 to 8)
(n is 1 to 3)

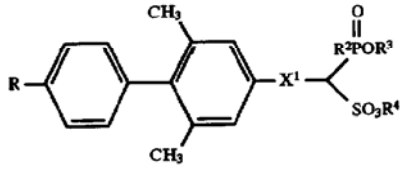
Additional compounds within the scope of the present invention are set out below.



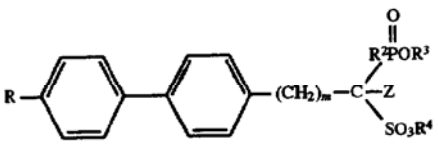
	R^{42}	R^{43}	R^{44}	R^{45}	R^{46}	t
30)	H	H	H	H	n-C_3H_7	3
31)	H	H	H	H	n-C_4H_9	3
32)	H	H	H	H	$(CH_3)_2-C=CH-$	4
33)	H	H	H	H	$(CH_3)_2-C=CH-CH_2-$	2
34)	CH_3	H	CH_3	H		3
35)	H	H	CH_3	H	$(CH_3)_2-CH-CH_2-O-$	3
36)	H	CH_3	CH_3	H	n-C_3H_7	3
37)	CH_3O	H	H	H	n-C_4H_9	3
38)	H	H	H	H	$(CH_3)_2-C=CH-$	3
39)	H	H	H	H	$(CH_3)_2-C=CH-CH_2-$	4
40)	CH_3	H	H	H		5
41)	F	H	CH_3	H	n-C_3H_7	3
42)	CH_3	H	F	H	n-C_4H_9	3
43)	H	CH_3	H	CH_3	$(CH_3)_2-C=CH-$	3
44)	H	H	H	CF_3	$(CH_3)_2-C=CH-CH_2-$	3
45)	H	H	H	F		3
46)	H	Cl	Cl	H	$CH_2=CH-CH_2-$	3
47)	CH_3	H	H	H	C_4H_9	3
48)	H	H	OH	H	C_3H_7	3
49)	H	H	OCH_3	H	C_3H_7	4
50)	H	H	CH_3	H	C_3H_7	3
51)	H	OH	H	H	C_3H_7	3
52)	H	OCH_3	H	H	C_3H_7	4
53)	H	CH_3	H	H	C_3H_7	3

R^2=H, OMetal, alkyl, aryl
R^3=H, metal ion or alkyl
R^4=H, metal ion or alkyl

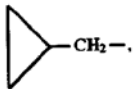




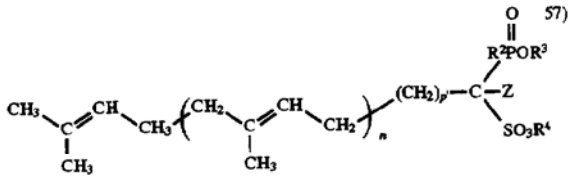
X^1= $-(CH_2)_n-$, $-CH=CH-CH_2-$
n = 1 to 6



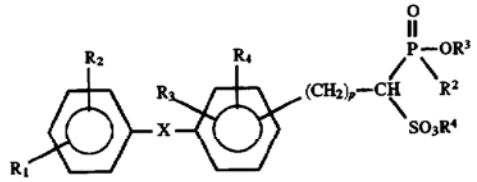
Re 54) to 56)
R is n-C_3H_7, n-C_4H_9, $(CH_3)_2-C=CH-$, $CH_3-CH=CH-CH_2-$, $(CH_3)_2-CH=CH-CH_2-$, $CH_2=CH-CH_2O-$, $(CH_3)_2-CH-O-$, $(CH_3)_2CHCH_2O-$,



$CH_2=CH-CH_2-$, $CH_2=CH-CH_2CH_2-$, phenyl, pyridyl

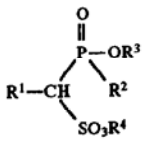


Z=Cl, F, alkyl such as methyl, ethyl, propyl or allyl
n=0, 1, 2
p^1=0–8
m=2–8
In compounds 49) to 52)
R^3=H, metal ion or alkyl
R^4=H, metal ion, alkyl or aryl
R^2=H, Ometal, alkyl, aryl

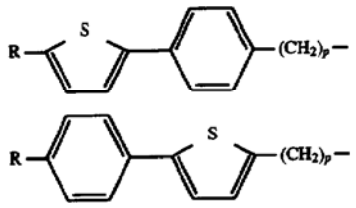


X is O, S NH, SO, SO_2, CR^5R^6, C=O R_1, R_2, R_3, R_4, R^5 and R^6 are independently H, halogen, C_1–C_5alkyl, C_1–C_5alkenyl, C_1–C_5alkoxy, aryl, arylalkyl, aryloxy; for R^5 and R^6, halogen can be fluorine only.

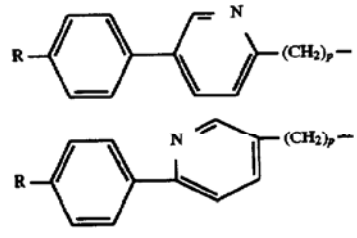
54)



55)



56)



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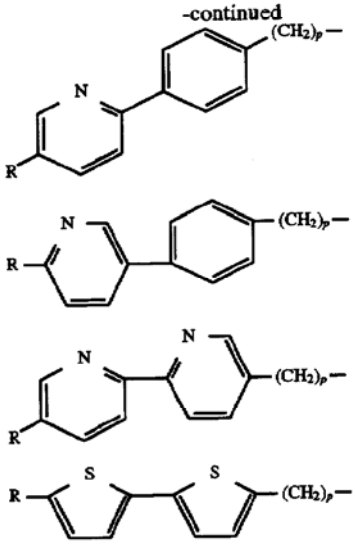
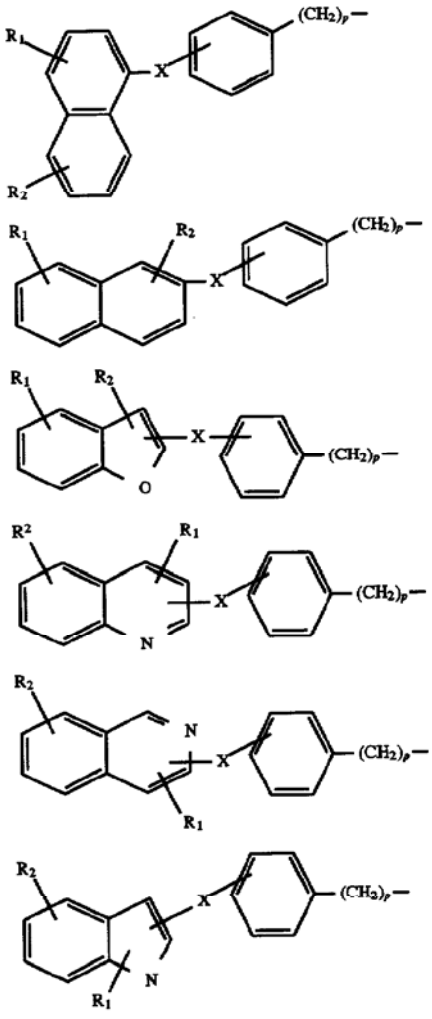


R is as defined for 54) to 56).



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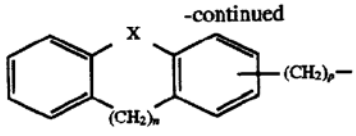
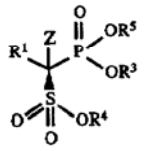


X=bond, 0, NH, S, CH_2, CR^5R^6

p=1 to 8

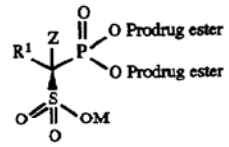
n=0 to 4; R_1, R_2, R^5 and R^6 are independently halogen, alkyl, alkenyl, alkoxy, aryl, H, aryloxy; for R^5 and R^6 halogen can be fluorine only.

Preferred are enantiomers of compounds of formula I in the (S) configuration of the above preferred compounds, that is

IS 

wherein Z is H, R^1 is preferably $Ar^1—O—Ar^2—(CH_2)_p—$, R^3, R^5 and R^4 are an alkali metal such as K or Na.

More preferred are prodrug (P.D.) esters of the (S)-enantiomer (IS), that is

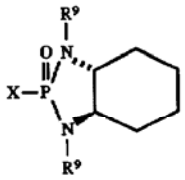
IS (P.D.) 

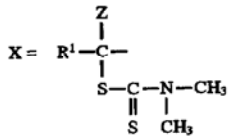
Most preferred are compounds of formula IS where R^1 is

$Ar^1—O—Ar^2—(CH_2)_p$

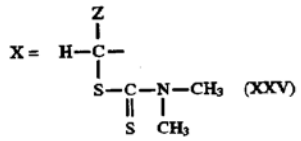
R^4 is an alkali metal such as K or Na Z is H and Prodrug ester is bis(pivaloyloxymethyl) ester.

In addition, in accordance with the present invention new intermediates are provided which are prepared as described above, and have the following formulae:

a) 



(XXIIIS or XXIIIR, XXIIIS' or XXIIIR')



(XXV)

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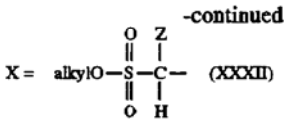
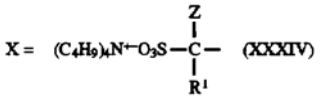
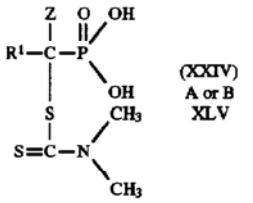


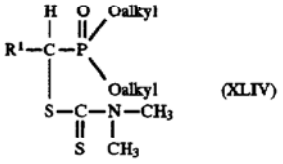
(XXXII)



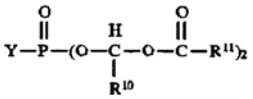
(XXXIV)

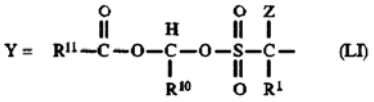


(XXIV)
A or B
XLV

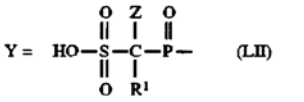


(XLIV)

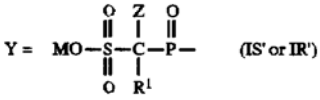




(LI)



(LII)



(IS' or IR')

The compounds of Formula I of the invention inhibit cholesterol biosynthesis by inhibition of de novo squalene production. These compounds inhibit the squalene synthetase enzyme and, in addition, some of the compounds of Formula I of the invention inhibit other enzymes in the pathway from isopentenyl diphosphate to squalene, that is, farnesyl diphosphate synthetase and isopentenyl diphosphate-dimethylallyl diphosphate isomerase.

The compounds of the invention are useful in treating hyperlipoproteinemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, combined hypercholesterolemia and hypertriglyceridemia, and/or in preventing development of and/or treating atherosclerosis. Thus, the compounds of the invention may be used to treat diseases such as chylomicronemia syndrome, Type I hyperlipoproteinemia, familial combined hyperlipoproteinemia, familial hypertriglyceridemia, mixed hyperlipoproteinemia, familial hypercholesterolemia and Type III hyperlipoproteinemia and/or atherosclerosis.

In addition, the compounds of the invention may increase plasma high density lipoprotein cholesterol levels.

The compounds of the invention may also be useful in inhibiting formation of gallstones, treating hepatitis D (by virtue of protein prenyltransferase inhibition, Glenn et al, Science, Vol. 256, pp. 1331–1333, May 29, 1992), treating tumors, lowering blood pressure, lowering blood sugar, treating diabetes mellitus, treating inflammation, as a diuretic, as an inotropic agent, as an anti-arthritic (antirheumatic) agent, in treating other diseases of calcium and phosphate metabolism including treatment of bone resorption, Paget's disease, osteoporosis, calcification of joints, implants and metastasis, as antitartar and anticalculus agents in toothpastes and mouthwashes, treating various stones and calculi, treating sickle cell anemia, treating b) hypoxia and ischemic tissue, and as an anti-ameobal agent, as well as for use in complexes with technetium-99m and radioiodinated derivatives for use as diagnostics.

U.S. application Ser. No. 774,957, filed Oct. 11, 1991, now abandoned, discloses that post-translational modification of CAAX box containing proteins may be inhibited by administering a protein-prenyl transferase inhibitor which inhibits the transfer of the prenyl group [such as farnesyl (in the case of ras oncogene products), geranyl or c) geranylgeranyl] to the cysteine of the CAAX box by the protein-prenyl transferase enzyme. The protein-prenyl transferase inhibitor will block the protein-prenyl transferase enzyme from catalyzing the transfer of the prenyl group (for example, farnesyl, geranyl or geranyl-geranyl) from the prenyl pyrophosphate to the cys residue of the CAAX box, such as the ras p21 cys, or to the CAAX box cysteine of d) other CAAX box containing proteins. In the case of ras p21 oncogene products, inasmuch as the cys is not farnesylated, in the presence of the protein prenyl transferase inhibitor, it cannot effect interaction of the ras protein with the membrane so that neoplastic transformation of the cell will be prevented. In this manner protein-prenyl transferase inhibitors prevent neoplastic transformation of the cell, thereby acting as an anti-cancer agent for the treatment of and/or prevention of ras-related tumors.

Examples of CAAX box containing proteins which have been demonstrated or are believed to undergo prenylation include, but are not limited to, ras, nuclear lamins, α or γ subunits of heterotrimeric G-proteins, γ-subunits of retinal transducin, G25K and K-rev p21, and protein families including rho, rap, rac, ral, and rab.

The present invention includes a method for blocking or preventing the prenylation of CAAX box containing proteins such as ras oncogene products, and thereby inhibit disease promoting effects of the CAAX box containing protein or more specifically prevent and/or treat ras-related tumors, by administering to a patient in need of treatment a therapeutic amount of a compound of Formula I of the invention which serves as a protein-prenyl transferase inhibitor.

The Formula I protein-prenyl transferase inhibitors, unlike HMG CoA reductase inhibitors, will interfere with prenylation of the ras oncogene products and inhibit their transforming activity, yet may or may not interfere with the synthesis of FPP, a precursor in the synthesis of ubiquinones, dolichols and Haem A.

The compounds of the invention may also be employed in combination with an antihyperlipoproteinemic agent, hypocholesterolemic agent, and/or hypotriglyceridemic agent, and/or antiatherosclerotic agent such as one or more HMG CoA reductase inhibitors, for example, pravastatin, lovastatin, simvastatin, velostatin, fluvastatin, rivastatin, compactin, SDZ-63,370 (Sandoz), CI-981 (W-L), HR-780, L-645,164, CL-274,471, dalvastatin, α-, β-, and γ-tocotrienol, (3R,5S,6E)-9,9-bis(4-fluorophenyl)-3,5-dihydroxy-8-(1-methyl-1H-tetrazol-5-yl)-6,8-nonadienoic acid, L-arginine salt, (S)-4-[[2-[4-(4-fluorophenyl)-5-methyl-2-(1-methylethyl)-6-phenyl-3-pyridinyl]ethenyl]

hydroxyphosphinyl]-3-hydroxybutanoic acid, disodium salt, BB-476, (British Biotechnology), dihydrocompactin, [4R-[4α,6β(E)]]-6-[2-[5-(4-fluorophenyl)-3-(1-methylethyl)-1-(2-pyridinyl)-1H-pyrazol-4-yl]ethenyl]tetrahydro-4-hydroxy-2H-pyran-2-one, and/or 1H-pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]calcium salt[R-(R*, R*)]; one or more fibric acid derivatives such as clofibrate, bezafibrate, Lopid(gemfibrozil) one or more other cholesterol biosynthesis inhibitors, such as NB-598, N-(1-oxododecyl)-4α,10-dimethyl-8-aza-trans-decal-3β-ol, 2,4-undecadienoic acid, 11-[3-(hydroxymethyl)-4-oxo-2-oxetanyl]-3,5,7-trimethyl-, [2R-[2α(2E,4E,7R*),3β]]; one or more bile acid sequestrants, for example, cholestyramine, colestipol, polidexide (DEAE-Sephadex); one or more antioxidants, for example probucol and Vitamin E; and/or one or more other lipid lowering and/or antiatherosclerotic agents, for example nicotinic acid or derivatives thereof, neomycin, p-aminosalicylic acid, probucol, hydroxypropylmethylcellulose, LS-2904, ethanol, 2-[[1-methyl-2-[3-(trifluoromethyl)phenyl]ethyl]amino]benzoate (ester).

The above compounds to be employed in combination with the squalene synthetase inhibitor of the invention will be used in amounts as indicated in the Physicians' Desk Reference (PDR).

The compounds of the invention may also be employed with sodium lauryl sulfate of other pharmaceutically acceptable detergents to enhance oral bioavailability of such compounds.

Inhibition of squalene synthetase may be measured by the following procedure.

Rat liver microsomal squalene synthetase activity is measured using farnesyl diphosphate as substrate and quantitating squalene synthesis using gas chromatographic analysis. The assay was developed by modifying conditions originally described by Agnew (Methods in Enzymology 110:357, 1985).

A further aspect of the present invention is a pharmaceutical composition consisting of at least one of the compounds of the invention, such as Formula I, in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc., by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations. The dose for adults is preferably between 200 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1–4 times per day.

A typical capsule for oral administration contains active ingredient (250 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectible preparation is produced by aseptically placing 250 mg of sterile active ingredient into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectible preparation.

The following Examples represent preferred embodiments of the present invention.

Introduction to Experimental

All temperatures are reported in degress Centigrade.

^1H and ^{13}C chemical shifts are reported as δ-values with respect to Me_4Si (δ=0). ^{31}P spectra were obtained using 85% H_3PO_4 as an external reference (δ=0). Coupling constants J are reported in Hz. For mass spectra (mass spec or MS) the value utilized for the parent M is that of the salt form which was prepared and tested.

All reactions were carried out under an atmosphere of dry argon or nitrogen. The following reagents and solvents were distilled prior to use from the indicated drying agents, where applicable: CH_2Cl_2, 2,4,6-collidine, and diisopropylamine (CaH_2); THF and diethyl ether (K, benzophenone); N,N-diethyltrimethylsilylamine and oxalyl chloride. Benzene was passed through neutral alumina (activity I) and stored over 4A-molecular sieves. Lithium bromide was dried at 100° C. over P_2O_5. (E,E)-Farnesol was purchased from Aldrich Chemical Company.

TLC was performed on E. Merck Silica Gel 60 F-254 plates (0.25 mm) or E. Merck Cellulose F plates (0.1 mm). Flash chromatography was carried out using E. Merck Kieselgel 60 (230–400 mesh).

Reverse-phase chromatographic purification of salts or mixed ester salts was carried on CHP20P gel or SP207SS gel, highly porous, polystyrenedivinyl benzene copolymers available from Mitsubishi Chemical Industries. The indicated general procedure was followed: An FMI Model RP-SY pump was utilized for solvent delivery. A column of CHP20P or SP207SS (2.5 cm diameter, 12–22 cm height) ws slurry packed and washed with water (500–1000 mL), and a basic, aqueous solution of the crude salt was applied to the top of the column. Typically, the column was eluted with water, followed by a gradient composed of increasing concentrations of acetonitrile or methanol in water. The gradient was created by placing the tip of a tightly stoppered separatory funnel containing 300–500 mL of the organic solvent, or an aqueous-organic mixture, just beneath the surface of a reservoir containing 300–500 mL of pure water. To start the gradient, the stopcock of the separatory funnel was opened, so that as the solvent was withdrawn by the pump from the reservoir, it was replaced with the solvent from the separatory funnel. HPLC-grade solvents were employed. Fractions were collected (10–15 mL each) at a flow rate of 5–10 mL per minute. Those fractions that contained pure product as judged by TLC or HPLC were pooled, the organic solvents were evaporated and the aqueous residue was lyophilized to dryness.

EXAMPLE 1

(E,E)-(6,10,14-Trimethyl-2-phosphono-5,9,13-pentadecatriene-1-sulfonic acid, trisodium salt

A. Bishomofarnesol

(1) (E,E)-3,7,11,-Trimethyl-2,6,10-dodecatrienyl bromide (farnesyl bromide)

A solution of 1.00 g (4.5 mmol) of (E,E)-farnesol (Aldrich, further purified by flash chromatography) in 10 mL of distilled ether at 0° C. under argon in the dark was treated dropwise with a solution of 195 μL (2.05 mmol, 0.45 eq.) of PBr_3 in 2 mL of diethyl ether (ether). The resultant mixture was stirred at 0° C. for one hour, then quenched with water and separated. The organic phase was washed with 5 mL of H_2O, 5 mL of saturated $NaHCO_3$, and 5 mL of brine, dried over Na_2SO_4 and evaporated to give 1.26 g (98%) of crude bromide as a clear oil.

TLC Silica (2:8 ethyl acetate:hexane) Rf=0.69.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.52 (t, 1H, J=8.5 Hz), 5.08 (m, 2H), 4.01 (d, 2H, J=8.5 Hz), 2.20–1.90 (m, 8H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H) ppm.

(2) (E,E)-5,9,13-Trimethyl-4,8,12-tetradecatrienoic acid, 1,1-dimethylethyl ester

To a solution of 9.60 mL (68.5 mmol, 1.5 eq.) of diisopropylamine in 100 mL of tetrahydrofuran (THF) at −78° C. under argon was added 28.2 mL (45.0 mmol, 1.0 eq.) of 1.6 M n-butyllithium in hexanes over 20 minutes. After warming to 0° C. for 15 minutes, the solution was recooled to −78° C. and 6.05 mL (45 mmol, 1.0 eq.) of t-butyl acetate was added over 20 minutes. After an additional 15 minutes, 16.0 mL (92 mmol, 2.05 eq.) of hexamethylphosphoramide (HMPA) was added, followed by a solution of 12.53 g (45.0 mmol) of Part A(1) farnesyl bromide in 100 mL of THF over 20 minutes. The reaction was stirred at −78° C. for 2.5 hours, quenched with saturated NH_4Cl and allowed to warm to room temperature. After diluting with 400 mL of ethyl acetate, the mixture was washed with four 100 mL portions of water, and 200 mL of brine, dried over $MgSO_4$ and evaporated to provide 12.96 g of crude product as a yellow oil. Purification by flash chromatography on 1 kg of silica gel, eluted with 1:9 ethyl acetate:petroleum ether afforded 9.39 g (65%) of title compound as a pale yellow oil.

TLC Silica gel (2:98 ethyl acetate:hexane) R_f=0.16.

IR(neat) 2977, 2925, 2857, 1733, 1452, 1368, 1258, 1149 cm^{-1}.

^{1}H NMR($CDCl_3$, 270 MHz): δ5.10 (m, 3H), 2.25 (m, 4H), 2.10–1.90 (m, 8H), 1.68 (s, 3H), 1.62 (s, 3H), 1.59 (s, 6H), 1.44 (s, 9H) ppm.

Mass spec. (CI-CH_4/N_2O) (+ions) m/e 165 (M+H−C_4H_8), 247, 183,137, 68, 67. (−ions) m/e 319 (M−H), 279, 2510 100.

(3) Bishomofarnesol

To a stirred solution of 5.00 g (15.6 mmol) of Part (2) compound in 45 mL of dry diethyl ether at 0° C. under argon was added 592 mg (15.6 mmol, 1 mol-eq.) of lithium aluminum hydride, and the resulting suspension was stirred at room temperature for 20 hours. After cooling to 0° C., the reaction was quenched by treating with 5 mL of H_2O, 5 mL of 15% NaOH, and 15 mn of H_2O and stirring the suspension for ½ hour. After adding Na_2SO_4, the slurry was filtered through Celite, washing well with diethyl ether and evaporated to obtain 3.62 g of crude product. Purification by flash chromatography on 300 g of silica gel, eluted with 1:9 ethyl acetate:petroleum ether provided 3.516 g (90%) of bishomofarnesol as a colorless liquid.

TLC Silica gel (2:8 ethyl acetate (EtOAc):hexane) R_f=0.19.

IR(neat) 3330, 2964, 2926, 2873, 2958, 1448, 1384, 1107, 1059, 401 cm^{-1}.

^{1}H NMR($CDCl_3$, 270 MHz): δ5.10 (m, 3H), 3.63 (t, 2H, J=6.5 Hz), 2.20–1.90 (m, 10H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s+m, 8H) ppm.

Mass Spec (CI-CH_4/N_2O, +ions) m/e 251 (M+H), 249 (M+H−H_2), 137, 123, 109, 69.

A^1. Bishomofarnesol (alternative preparation)

(1) (E,E)-(3,7,11-Trimethyl-2,6,10-undecadienyl) propanedicarboxylic acid, diethyl ester

To a suspension of 1.62 g (40.5 mmol, 3 eq.) of a 60% suspension of sodium hydride in mineral oil (washed three times with pentane) in 150 mL of tetrahydrofuran at room temperature under argon was slowly added 6.15 mL (40.5 mmol, 3 eq.) of diethyl malonate. The resulting solution was stirred for 0.5 hours, then treated with a solution of 3.83 g (13.5 mmol) of farnesyl bromide in 10 mL of tetrahydrofuran. After stirring for 6 hours, the reaction was quenched with saturated NH_4Cl and diluted with 300 mL of diethyl ether. The organic layer was washed with two 100 mL portions of water and 100 mL of brine, dried over $MgSO_4$ and evaporated and the bulk of the diethyl malonate removed by spinning under high vacuum to afford 4.29 g (87%) of crude title product.

TLC Silica gel (ethyl acetate:hexane 1:9) R_f=0.37.

(TLC shows slight amount of diethyl malonate and a second by-product.)

(2) (E,E)-5,9,13-Trimethyl-4,8,12-tetradecatrienoic acid, ethyl ester

A mixture of 4.103 g (11.2 mmol) of Part A^1 (1) diester, 200 μL (11.2 mmol, 1 eq.) of water and 950 mg (22.4 mmol, 2 eq.) of lithium chloride in 20 mL of dimethyl sulfoxide was heated at reflux (~190° C.) for four hours. After cooling, the reaction mixture was diluted with 180 mL of a 1:1 mixture of diethyl ether: petroleum ether and washed with five 50 mL portions of water and 50 mL of brine, dried over $MgSO_4$ and evaporated to yield 3.623 g of crude product as a yellow-orange oil. Kugelrohr distillation at 180° C. (meter setting) and 0.025 mm allowed the collection of 2.100 g of a pale yellow oil, which was, however, still contaminated (by TLC). The distillation, therefore, is unnecessary and should not be performed. Flash chromatography on 180 g of silica gel, eluted with 3:97 ethyl acetate:petroleum ether provided 1.844 g (56%) of desired title product as a pale yellow oil.

TLC Silica gel (ethyl acetate:hexane 5:95) R_f=0.27.

^{1}H-NMR ($CDCl_3$, 270 MHz): δ5.08 (m, 3H), 4.12 (q, 2H, J=6.7 Hz), 2.31 (m, 4H), 2.10–1.90 (m, 8H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 6H), 1.25 (t, 3H, J=6.7 Hz), ppm.

(3) Bishomofarnesol

A solution of 7.05 g (24 mmol) of Part A^1 (2) monoester in 65 mL of dry diethyl ether at 0° C. under argon was treated in portions with 915 mg (24 mmol) of lithium aluminum hydride and stirred at room temperature for three hours. After cooling to 0° C., the reaction was quenched with 7 mL of water, 7 mL of 15% NaOH, then stirred for 15 minutes. Additional 21 mL of water was added, and the reaction was stirred 0.5 hours, then dried with Na_2SO_4. The mixture was filtered through Celite, washing well with diethyl ether, and evaporated to give 5.665 g of a colorless oil. Purification by flash chromatography on silic gel eluted with 15:85, ethyl acetate:petroleum ether provided 5.23 g (87%) of title compound as a colorless oil.

TLC Silica gel (2:8 ethyl acetate:hexanes) R_f=0.21.

IR(neat) 3330, 2964, 2926, 2873, 2858, 1448, 1384, 1107, 1059, 401 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 270 MHz): δ5.10 (m, 3H), 3.63 (t, 2H, J=6.5 Hz), 2.20–1.90 (m, 10H), 1.68 (s, 3H), 1.62 (s, 3H), 1.60 (s+m, 8H), ppm.

Mass Spec (CI-CH_4/N_2O, +ions) m/e 251 (M+H), 249 (M+H−H_2), 137, 123, 109, 69.

B. (E,E)-5,9,13-Trimethyl-4,8,12-tetradecatrien-1-ol, methanesulfonate ester

To a stirred solution of 2.02 g (8.07 mmol) of bishomofarnesol (prepared as described in Example 1, Part A) in 20 mL of dichloromethane at 0° C. was added 2.2 mL (16.1 mmol) of triethylamine followed by 0.69 mL (8.90 mmol) of methanesulfonyl chloride, dropwise over 15 mintues. After stirring for 1.5 hours at 0° C., the reaction was diluted with dichloromethane, washed with 20 mL each of 10% HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give 2.71 g (100%) of the crude title mesylate as a colorless oil.

TLC Silica gel (CH_2Cl_2) R_f=0.46.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.09 (t, 3H, J=6.5 Hz), 4.21 (t, 2H, J=7.0 Hz), 2.99 (s, 3H), 2.20–1.90 (m, 10H), 1.78 (quint, 2H, J=7.0 Hz), 1.65 (s, 3H), 1.61 (s, 3H), 1.60 (s, 6H),

C. (E,E)-14-Iodo-2,6,10-trimethyl-2,6,10-tetradecatriene

The crude Example 1, Part B mesylate prepared from 441.1 mg (1.76 mmol) of the corresponding alcohol according to the procedure of Example 1, Part B, was dissolved in 5 mL of acetone and treated with 530 mg (3.52 mmol) of sodium iodide. The reaction was allowed to stir for 16 hours at room temperature followed by 5 hours at reflux. The suspension was diluted with hexane and stirred with dilute aqueous sodium bisulfite to discharge to yellow color. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to provide 577 mg of crude product. Flash chromatography on 35 g of silica gel eluted with hexane gave 550.9 mg (87%) of title iodide as a colorless liquid.

TLC Silica gel (hexane) R_f=0.31.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.09 (m, 3H), 3.16 (t, 2H, J=7.0 Hz), 2.20–1.90 (m, 10H), 1.85 (quint., 2H, J=6.5 Hz), 1.67 (s, 3H), 1.63 (s, 3H), 1.59 (s, 6H) ppm.

Mass Spec (CI-CH_4/N_2O, +ions) m/e 361, 359 (M+H), 137.

D. (Diethoxyphosphinyl)methanesulfonic acid, ethyl ester

A solution of ethyl methanesulfonate (4.27 mL, 40.3 mmol) in 100 mL of dry THF was treated at −78° C. with 19.3 mL (44.4 mmol) of n-BuLi in hexane. After 15 min. diethyl chlorophosphate (3.30 ml, 22.2 mmol) was added. The solution was kept at −78° C. for 0.5 h and allowed to stay at −50° C. for 1 h. Saturated ammonium chloride (75 mL) was added to the solution and the mixture warmed to room temperature. The mixture was concentrated (THF removed), diluted with water and extracted with methylene chloride (3×70 mL). The combined organic fractions were dried ($MgSO_4$), concentrated and purified by distillation to yield 3.86 g (70%) of title compound.

b.p. 120°–130° C., 1 mm Hg.

^{1}H NMR (270 MHz, $CDCl_3$) δ4.40 (q, 2H, J=7.0 Hz) 4.20 (m, 4H) 3.80 (d, 2H, J=17.2 Hz) 1.40 (t, 3H, J=7.1 Hz) 1.25 (t, 6H, J=7.0 Hz).

Ref. Carretero, J. C.; Demillequ, M.; Ghosez, L. Tetrahedron Vol. 43, 1987, pp 5125.

E. (E,E)-1-(Diethoxyphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, sodium salt

To a suspension of 192 mg (8.00 mmol) of NaH in 6 mL of dry DMF at 0° C. under argon was added 2.16 g (8.33 mmol) of Part D sulfonate over 15 min. to give a yellow solution. The reaction was allowed to warm to room temperature and stir for 0.5 h when 1.00 g (2.77 mmol) of Part C iodide was added in one portion. The reaction mixture was stirred for 18 h when it was quenched with 10 mL of saturated NaCl solution and diluted with 50 mL of ethyl acetate. The layers were separated, the organics dried (Na_2SO_4) and evaporated to provide a crude glass. The glass was dissolved with 2.0 mL of 1M NaOH solution and purified by MPLC on a column of CHP20P gel (2.5 cm diam.×15 cm height) eluting with water (150 mL), followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 250 mL of water. Approximately 8 mL fractions were collected. The aqueous solution was concentrated and lyophilized to provide 0.78 g (57%) of title compound as a glass.

TLC Silica gel (8:1:1 propanol/conc. NH_3/water) R_f=0.75.

IR (film) 3476 2921, 1664, 1444, 1383, 1241, 1029, 968, 815 cm^{-1}.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.10 (m, 3H) 4.10 (m, 4H) 3.40 (dr, 1H, J=19.5, 6.0 Hz) 2.10–1.80 (m, 12H) 1.65 (s, 3H) 1.60 (m, 2H) 1.55 (s, 9H) 1.30 (t, 6H, J=6.0 Hz) ppm.

Mass Spec (FAB, +ions) m/e 510 (M+Na).

F. (E,E)-6,10,14-Trimethyl-1-phosphono-5,9,13-pentadecatriene-1-sulfonic acid, trisodium salt

To a stirred solution of 0.75 g (1.50 mmol) of Part E salt in 8 mL of dichloromethane at room temperature was added 0.54 g (4.50 mmol) of 2,4,6-collidine followed by 0.82 g (5.35 mmol) of bromotrimethylsilane. The reaction was allowed to stir at room temperature for 14 h when the solvent was evaporated and the semisolid residue pumped (≈1 mm pressure) for 0.5 h. The residue was dissolved by adding 6.6 mL (6.60 mmol), of 1M NaOH solution then diluting with 15 mL of water. The solution was freeze dried to provide an off white solid. The solid was purified by MPLC on a column of CHP20P gel (2.5 cm diam.×15 cm height) eluting with water (150 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 250 mL of water. Approximately 10 mL fractions were collected. The acetonitrile was removed under reduced pressure and the aqueous solution was lyophilized to provide 0.34 g (46.5%) of the title compound as a white lyophilate.

TLC Silica gel (5:4:1 n-propanol/conc. ammonia/water) R_f=0.75.

IR (KBr) 3438, 2966, 2926, 2859, 1636, 1449, 1206, 1137, 1110, 976 cm^{-1}.

^{1}H NMR (D_2O, 400 MHz): δ5.15 (t, 1H, J=7.0 Hz) 5.06 (q, 2H, J=7.0 Hz) 2.77 (ddd, 1H, J=18.2, 7.0, 4.7 Hz) 2.10–1.80 (m, 12H) 1.54 (S, 3H) 1.49 (s, 3H) 1.47 (s, 6H) 1.50 (m, 2H) ppm.

Mass Spec (FAB, +ions) m/e 475 (M+H), 453 (M−Na+2H).

Anal. Calc'd for $C_{18}H_{30}O_6Na_3PS$+1.70 H_2O: C, 42.80; H, 6.67; P, 6.13; S, 6.35 Found: C, 42.80; H, 7.01; P, 6.24; S, 6.56.

EXAMPLE 1A

(E,E)-6,10,14-Trimethyl-1-phosphono-5,9,13-Dentadecatriene-1-sulfonic acid, trisodium salt

A. Methanesulfonic acid, cyclohexyl ester

To a stirred solution of 25.0 g (0.25 mol) of cyclohexanol (purchased from the Aldrich Chemical Company and used without purification) and 27.3 g (0.27 mol) of triethylamine in 500 mL of ether at −15° C. was added 28.6 g (0.25 mol) of methanesulfonyl chloride in 50 mL of ether dropwise over 35 min. The reaction was warmed to 0° C. and stirred for 1 h when the mixture was diluted water and washed with aqueous solutions of 1N HCl and brine. The organics were dried ($MgSO_4$) and concentrated under reduced pressure to provide 43.0 g, 96% yield of title mesylate as a colorless oil. The mesylate was used without further purification.

B. (Diethoxyphosphinyl)methanesulfonic acid, cyclohexyl ester

To a rapidly stirred, nitrogen-purged [Note 1] solution of 24.4 g (137 mmol) of Part A mesylate in 600 mL of THF under nitrogen at −78° C. was added 55 mL (137.5 mmol, 2.5M in hexanes) of n-butyl-lithium over 35 min. The temperature was not allowed to rise above −70° C. [NOTE 2]. After an additional 10 min, 11.8 g (68.5 mmol) of freshly distilled diethyl chlorophosphate was added to the resulting slightly turbid solution at a rate to keep the temperature below −70° C. The reaction mixture was stirred for 45 min and then a solution of 8.30 g (138 mmol) of glacial acetic acid in 25 mL of THF was added over 5 minutes. The reaction mass was warmed to room temperature and evaporated at 30° C. at reduced pressure. The residue was partitioned between 250 mL of dichloromethane and 75 mL of water and extracted twice with dichloromethane. The extracts were combined, dried over $MgSO_4$ and evaporated.

The crude product was purified by flash chromatography [NOTE 3] {8×50 cm column, 2 L of dichloromethane, then 4 L of 11:89 ether/dichloromethane, then 2 L of 1:4 ether/dichloromethane) to give title compound as a colorless oil, 11.4 g, 53%.

TLC Silica gel, (11:89 ether/dichloromethane) R_f=0.20.

^{1}H NMR ($CDCl_3$, 400 MHz) δ4.83 (m, 1H) 4.26 (m, 4H) 3.72 (d, 2H, J=7.1 Hz) 2.01 (m, 2H) 1.80–1.30 (m, 8H) 1.39 (t, 6H, J=7.3 Hz) ppm.

NOTE 1. The reaction is run under a rapid nitrogen stream in an attempt to rigorously exclude oxygen from the system.

NOTE 2. Efficient and rapid mechanical stirring is essential to prevent formation of the impurities sometimes seen in this reaction.

NOTE 3. In an independent experiment, a 15.5 g sample of crude material was chromatographed on 850 g of silica gel eluted with 20:80 isopropanol/hexane, collecting 50 mL fractions. Fractions 61–85 were combined to provide 13.8 g (73 yield of pure triester.

C. (E,E)-1-(Diethoxyphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, cyclohexyl ester

To a suspension of 0.57 g (23.7 mmol, 1.9 eq.) of NaH in 50 mL of dry DMF at −20° C. under argon was added 9.00 g (28.7 mmol, 2.3 eq.) of Part B sulfonate over 15 min. to give a yellow solution. The reaction was allowed to warm to room temperature and stir for 0.5 h when 4.48 g (12.46 mmol, 1 eq.) of Example 1 Part C iodide was added in one portion. The reaction mixture was stirred for 12 h when it was quenched with 100 mL of saturated NaCl solution and diluted with 250 mL of ether. The layers were separated, the organics dried (Na_2SO_4) and evaporated to provide a crude oil. Flash chromatography was performed on 500 g of silica gel eluting with 3:7 ethyl acetate/hexane to provide 5.20 g (76%) of title compound in the form of a pale yellow oil.

TLC Silica gel (1:1 ethyl acetate/hexanes) R_f=0.60.

IR (film) 2934, 2861, 1449, 1352, 1260, 1173, 1053, 1024, 930 cm^{-1}.

^{1}H NMR ($CDCl_3$, 270 MHz) δ5.05 (m, 3H) 4.75 (m, 1H) 4.15 (m, 4H) 3.40 (dr, 1H, J=19.3, 6.4 Hz) 2.10–1.80 (m, 14H) 1.65–1.25 (m, 6H) 1.60 (s, 3H) 1.53 (s, 9H) 1.30 (t, 6H, J=7.3 Hz) ppm.

Mass Spec. (CI, +ions)m/e 564 ($M+NH_4$), 547 (M+H), ($M+NH_4-C_6H_{10}$), 465 ($M+H-C_6H_{10}$).

D. (E,E)-6,10,14-Trimethyl-1-phosphono-5,9,13-pentadecatriene-1-sulfonic acid, trisodium salt

To a solution of 1.00 g (1.82 mmol) of Part C compound and 20 mL of methanol in a sealable tube at 0° C. was added NH_3 (g) until the solution was saturated. The tube was sealed and placed in an oil bath at 75° C. for 16 h, at which point the tube was opened and the volatiles removed under reduced pressure. The remainder was dissolved in dry toluene and evaporated two times (2×7.0 mL) leaving an amber oil. The oil was dissolved in 10 mL of dry methylene chloride and treated with 2.40 mL (9.0 mmol) of bis (trimethylsilyl)trifluoroacetamide (BSTFA) for 0.5 h, followed by 0.79 mL (6.0 mmol) of bromotrimethylsilane. The reaction mixture was stirred for 18 h when the solvent was evaporated and the residue pumped (≈0.5 mm pressure) for 0.5 h. The remainder was dissolved by adding 50 mL (10 mmol) of 0.2M NaOH solution and stirring vigorously for ten min. The soapy solution was freeze dried to provide a white solid. The solid was purified by MPLC on a column of CHP20P gel (0.30 L) eluting with water (0.5 L) followed by isocratic elution with 15% acetonitrile in water. Approximately 25 mL fractions were collected. Pure fractions were pooled and the aqueous solution lyophilized to provide 0.80 g (91%) of title salt as a white lyophilate. The lyophilate was diluted with 0.6 mL of water and the mixture mashed to a gummy white solid. The solid was repeatedly washed and mashed with acetone (3×4 mL) until a granular solid resulted. The granular solid was dried under vacuum for 10 h and collected to yield 0.75 g (85%) of title salt as a fine white powder.

TLC Silica gel (6:3:1 n-propanol/conc. ammonia/water) R_f=0.35.

IR (KBr) 3434, 2924, 2857, 1667, 1449, 1209, 1136, 1109, 976 cm^{-1}.

^{1}H NMR (D2O, 400 MHz) δ5.35 (t, 1H, J=7.0 Hz) 5.23 (q, 2H, J=7.0 Hz) 2.93 (ddd, 1H, J=18.2, 7.0, 4.7 Hz) 2.20–1.80 (m, 12H) 1.74 (s, 3H) 1.65 (s, 3H) 1.60 (s, 6H) 1.63 (m, 2H) ppm.

Mass Spec (FAB, +ions) m/e 497 (M+Na), 475 (M+H).

Anal. Calc'd for $C_{18}H_{30}O_6Na_3PS$+0.81 H_2O: C, 44.20; H, 6.52; P, 6.33; S, 6.55 Found: C, 43.83; H, 6.93; P, 6.02; S, 6.69.

EXAMPLE 1B

(E,E)-6,10,14-Trimethyl-1-phosphono-5,9,13-pentadecatriene-1-sulfonic acid, tripotassium salt

To a solution of 11.11 g (20.3 mmol) of Example 1A, Part C compound and 120 mL of methanol in a sealable tube at 0° C. was added NH_3 (g) until the solution was saturated. The tube was sealed and placed in an oil bath at 65° C. for 24 h, at which point the tube was opened and the volatiles removed under reduced pressure. The remainder was dissolved in a 1:1 mixture of dry toluene/hexamethyl disilazane (HMDS) and evaporated two times (2×60 mL), leaving an amber oil. The oil was dissolved in 70 mL of dry methylene chloride and treated with 21.4 mL (101.6 mmol) of HMDS for 0.5 h at RT. The mixture was then treated with 16.0 mL (121.9 mmol) of bromotrimethylsilane. The reaction was allowed to stir at RT for 45 h when the solvent was evaporated and the residue pumped (≈0.5 mm pressure, 35° C.) for 0.5 h. The remainder was dissolved by adding 120 mL (120 mmol) of 1M KOH solution and stirring vigorously for ten min. The soapy solution was freeze dried to provide a white solid. The solid was purified by MPLC on a column of CHP20P gel (1 L) eluting with water (2 L) followed by a stepwise gradient created by the addition of: 1:9 acetonitrile/water (1.5 L), 1.5:8.5 acetonitrile/water (1.5 L), 2:8 acetonitrile/water (1 L) and finally 2.5:7.5 acetonitrile/water (1 L). Approximately 50 mL fractions were collected. Fractions 52 to 83 were pooled, the acetonitrile was removed under reduced pressure and the aqueous solution lyophilized to provide 8.11 g (78%) of title compound as a white lyophilate which was 98.5% pure by HPLC. The lyophilate was dissolved with 16 mL of water, and 40 mg (0.5 mol %) of Trolox was added. The product was precipitated with 16 mL acetone, and the precipitate was repeatedly washed (2×8 mL) and mashed with acetone until a solid resulted. The solid was dried under vacuum for 24 h and collected to yield 7.58 g (72%) of title compound as a fine white powder.

TLC Silica gel (6:3:1 n-propanol/conc. ammonia/water) R_f=0.35.

IR (KBr) 3435, 2924, 2857, 1632, 1449, 1204, 1140, 1109, 974 cm^{-1}.

^{1}H NMR (D_2O, 400 MHz) δ5.15 (t, 1H, J=7.0 Hz) 5.06 (q, 2H, J=7.0 Hz) 2.77 (ddd, 1H, J=18.2, 7.0, 4.7 Hz) 2.10–1.80 (m, 12H) 1.54 (s, 3H) 1.50 (m, 2H) 1.49 (s, 3H 1.47 (s, 6H) ppm.

Mass Spec (FAB, +ions) m/e 561 (M+K), 523 (M+H), 485 (M−K+2H).

Anal. Calc'd for $C_{18}H_{30}O_6K_3PS+0.59\ H_2O$: C, 40.53; H, 5.89; P, 5.81; S, 6.13 Found: C, 40.50; H, 6.20; P, 5.67; S, 5.91.

EXAMPLE 2

(E)-6,10-Dimethyl-1-phosphono-5,9-undecadiene-1-sulfonic acid, trisodium salt

A. (E)-8-Chloro-2,6-dimethyl-2,6-octadiene

To a stirred solution of 30.0 g (0.194 mol) of (E)-3,7-dimethyl-2,6-octadien-1-ol and 28.27 mL (0.213 mol) of 2,4,6-collidine under argon at room temperature was added dropwise 8.23 g (0.194 mol) of lithium chloride in 100 mL of DMF. The mixture was cooled to 0° C. and treated with 16.56 mL (0.213 mol) of methanesulfonyl chloride dropwise over 10 minutes. The reaction was stirred at 0° C. for 1.5 hours (solid present), then was poured into 500 mL of ice/water. The aqueous solution was washed three times with 200 mL portions of hexane, the organic layers were combined and washed with 5% $KHSO_4$, water, $NaHCO_3$, brine, dried ($MgSO_4$) and evaporated to provide 29.95 g of a pale yellow oil. Rapid flash chromatography was performed on 400 g of silica gel, eluting with 3:9 EtOAc/hexane. Pure product fractions were combined and evaporated to provide 25.20 g (75%) of title compound as a pale yellow oil.

TLC Silica gel (8:1 hexane/EtOAc) R_f=0.68.

^{1}H-NMR ($CDCl_3$, 270 MHz): δ5.44 (m, 1H), 5.08 (m, 1H), 4.09 (d, 2H, J=8.2 Hz), 2.08 (m, 4H), 1.73 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H) ppm.

B. (E)-(3,7-Dimethyl-2,6-octadienyl)propanedioic acid, diethyl ester

To a stirred solution of 14.68 g (0.611 mol) of NaH (100%) in 400 mL of THF at 0° C. under argon was added dropwise 92.76 mL (0.611 mol) of diethyl malonate in 100 mL of THF over 0.5 hours. This solution was stirred for 0.5 hours at 0° C., at which time 35.20 g (0.204 mol) of Part A chloride in 50 mL of THF was added dropwise over 15 minutes. The reaction gradually warmed to room temperature, stirred for 18 hours then was quenched with 250 mL of saturated NH_4Cl and diluted with 250 mL of ether. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated to remove solvent and provide 100 g of an oil. The excess diethyl malonate was removed by distillation at 75° C. (1.5 mm) to provide 65 g of title compound also containing some dialkylated product and diethyl malonate.

TLC Silica gel (1:1 Hexane/Ethyl acetate) R_f=0.37.

IR (CCl_4) 2982, 2926, 2854, 1751, 1734, 1446, 1369, 1332, 1269, 1236, 1209, 1149, 1111, 1095, 1035, 860 cm^{-1}.

^{1}H NMR ($CDCl_3$, 270MHz): δ5.07 (q, 2H, J=7.1 Hz), 4.18 (q, 2H, J=7.0 Hz), 3.33 (t, 1H, J=7.6 Hz), 2.60 (t, 2H, J=7.3 Hz), 2.04–1.98 (m, 4H), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.26 (t, 6H, J=7.0 Hz) ppm.

MS (CI-NH_3, +ions) m/e 314 ($M+NH_4$), 297 (M+H).

C. (E)-5,9-Dimethyl-4,8-decadienoic acid, ethyl ester

To a solution of 65 g of the crude Part B diester described above, 5.40 mL (0.30 mol) of water and 25.0 g (0.60 mol) of lithium chloride in 250 mL of DMSO was heated to 190° C. and stirred for 9 hours. The reaction was treated with a 1:1 solution of hexane/ether and then washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to provide 34.6 g of title compound in the form of a yellow oil. No further purification was performed; the sample was carried on to the next step.

TLC Silica gel (95:5 Hexane/Ethyl acetate) R_f=0.30.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.00 (m, 2H), 4.04 (q, 2H, J=7.0 Hz), 2.23 (m, 4H), 1.99–1.87 (m, 4H), 1.59 (S, 3H), 1.54 (s, 3H), 1.51 (s, 3H), 1.17 (t, 3H, J=7.0 Hz) ppm.

MS (CI-NH_3, +ions) m/e 242 ($M+NH_4$), 225 (M+H).

D. (E)-5,9-Dimethyl-4,8-decadien-1-ol

To a stirred solution of 5.84 g (0.154 mol) of lithium aluminum hydride in 700 mL of ether at 0° C. under argon was added dropwise 34.50 g of crude Part C ester over 20 minutes. The mixture was stirred for 1.5 hours at which time it was quenched by the following: 5.8 mL (0.324 mol) of water, 5.8 mL of 15% NaOH in water and then 17.5 mL (0.973 mol) of water. The granular mixture was stirred and dried ($MgSO_4$) for 0.5 hours at which time the mixture was filtered through a celite cake and washed with ether followed by dichloromethane. The filtrate was evaporated to provide 28.16 g of an oil that was distilled using a short-path apparatus (bp 95°–96° C., 0.3 mm) to provide 20.5 g (55% overall from Part A chloride) of title alcohol as a colorless oil.

TLC Silica gel (Dichloromethane) R_f=0.11.

IR (CCl_4) 3620, 3340, 2966, 2924, 2877, 2856, 2729, 1670, 1446, 1377, 1350, 1278, 1199, 1155, 1107, 1057, 985, 829, 814, 792 cm^{-1}.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.10 (m, 2H), 3.62 (t, 2H, J=6.5 Hz), 2.11–1.94 (m, 7H), 1.67–1.58 (m, 2H), 1.67 (s, 3H), 1.61 (s, 6H) ppm.

MS (CI-NH_3, +ions) m/e 200 ($M+NH_4$), 183 (M+H).

E. (E)-5,9-Dimethyl-4,8-decadien-1-ol, methanesulfonate ester

To a stirred solution of 12.0 g (65.93 mmol) of Part D alcohol in 200 mL of dichloromethane at 0° C. under argon was added 11.95 mL (85.71 mmol) of triethylamine and 6.12 mL (79.12 mmol) of methanesulfonyl chloride. The reaction was stirred for 1 hour then was diluted with ether and washed with 5% $KHSO_4$, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and evaporated to provide 16.91 g (98%) of title compound as a pale yellow oil.

TLC Silica gel (Dichloromethane) R_f=0.53.

IR (CCl_4) 2963, 2927, 2922, 2882, 2875, 2856, 1455, 1450, 1381, 1363, 1347, 1178, 1007, 969, 957, 929,793,785, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.09 (m, 2H), 4.21 (t, 2H, J=6.5 Hz), 2.98 (s, 3H), 2.13–1.99 (m, 6H), 1.79 (quint., 2H, J=6.7 Hz), 1.68 (s,3H), 1.61 (s, 3H), 1.60 (s, 3H) ppm.

MS (CI-NH_3, +ions)m/e 278 ($M+NH_4$).

F. (E)-5,9-Dimethyl-4,8-decadien-1-yl iodide

To a stirred solution of 16.91 g (65.04 mmol) of Part E methanesulfonate in 500 mL of acetone at room temperature under argon was added 39.00 g (260.16 mmol) of sodium iodide. The reaction mixture was refluxed for 3.5 hours, then diluted with 400 mL of a 1:1 mixture of water/hexane. The organic layer was washed with saturated sodium sulfite, dried ($MgSO_4$) and evaporated to provide 17.57 g of a pale yellow oil. The oil residue was filtered through 400 g of silica gel eluting with hexane. The pure product fractions were combined and evaporated to provide 16.86 g (89%) of title iodide as a colorless oil.

TLC Silica gel (Hexane) R_f=0.37.

IR (CCl_4) 2962, 2924, 2852, 1444, 1375, 1342, 1261, 1226, 1201, 1163, 1107, 983, 873,835, 819, 761, 742 cm^{-1}.

^{1}H NMR ($CDCl_3$, 270 MHz): δ5.07 (t, 2H, J=7.0 Hz), 3.18 (t, 2H, J=7.0 Hz), 2.14–1.96 (m, 6H), 1.86 (quint., 2H, J=7.0 Hz), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H) ppm.

G. (E)-1-(Diethyoxyphosphinyl)-5,9-undecadiene-1-sulfonic acid, sodium salt

To a suspension of 153 mg (6.40 mmol) of NaH in 10 mL of dry DMF at 0° C. under argon was added 1.66 g (6.40 mmol) of Example 1 Part D sulfonate over 15 min. to give a yellow solution. The reaction was allowed to warm to room temperature and stir for 0.5 h when 0.75 g (2.56 mmol)

of Part F iodide was added in one portion. The reaction mixture was stirred for 18 h when it was quenched with 15 mL of saturated aq NH_4Cl solution and diluted with 100 ml of ethyl acetate. The fractions were separated and the organic layer washed with brine, dried (Na_2SO_4) and evaporated to provide a crude glass. The glass was diluted with 2.5 ml (2.5 mmol) of 1M NaOH solution and purified by MPLC on a column of CHP20P gel (2.5 cm diam.×15 cm height) eluting with water (150 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 250 mL of water. Approximately 10 mL fractions were collected. The acetonitrile was removed under reduced pressure and the aqueous solution was lyophilized to provide 0.63 g (59%) of title salt as a white lyophilate.

TLC Silica gel (8:1:1 propanol/conc. NH_3/water) R_f=0.65.

IR (film) 3468, 2972, 2926, 1664, 1444, 1376, 1241, 1036, 968, 812 cm^{-1}.

^1H NMR (CD_3OD, 270 MHz) δ5.10 (t, 1H, J=6.9 Hz) 5.05 (t, 1H, J=6.0 Hz) 4.10 (m, 4H) 3.15 (dr, 1H, J=20.0, 6.5 Hz) 2.10–1.80 (m, 8H) 1.67 (m, 2H) 1.60 (s, 3H) 1.55 (s, 3H) 1.53 (s, 3H) 1.25 (t, 6H, J=7.1 Hz) ppm.

H. (E)-6,10-Dimethyl-1-phosphono-5,9-undecadiene-1-sulfonic acid, trisodium salt

To a stirred solution of 0.63 g (1.50 mmol) of Part G salt in 8 mL of dichloromethane at RT was added 0.36 g (3.00 mmol) of 2,4,6-collidine followed by 1.14 g (7.50 mmol) of bromotrimethylsilane. The reaction was allowed to stir at RT for 14 h when the solvent was evaporated and the semisolid residue pumped (≈1 mm pressure) for 0.5 h. The residue was dissolved by adding 7.0 mL of 1M NaOH solution (7.0 mmol), then diluting with 15 mL of water. The solution was freeze dried to provide off white solids. The solids were purified by MPLC on a column of CHP20P gel (2.5 cm diam.×15 cm height) eluting with water (150 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 250 mL of water. Approximately 10 mL fractions were collected. The acetonitrile was removed under reduced pressure and the aqueous solution was lyophilized to provide 0.40 g (65%) of title compound as a white lyophilate.

TLC Silica gel (5:4:1 n-propanol/conc. ammonia/water) R_f=0.45.

IR (KBr) 3425, 2964, 2926, 2858, 1641, 1450, 1203, 1099, 1053, 974 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ5.15 (t, 1H, J=7.0 Hz) 5.06 (t, 1H, J=7.0 Hz) 2.77 (ddd, 1H, J=18.7, 6.7, 4.4 Hz) 2.10–1.80 (m, 8H) 1.55 (s, 3H) 1.50 (m, 2H) 1.49 (s, 3H) 1.48 (s, 3H) ppm.

Mass Spec (FAB, +ions) m/e 429 (M+Na), 407 (M+H), 385 (M–Na+2H).

Anal. Calc'd for $C_{13}H_{22}O_6Na_3PS$+1.58 H_2O: C, 35.92; H, 5.83; P, 7.13; S, 7.38 Found: C, 35.92; H, 5.99; P, 7.24; S, 7.28.

EXAMPLE 3

α-Phosphono-[1,1'-biphenyl]-4-butanesulfonic acid, trisodium salt

A. [1,1'-Biphenyl]-4-propanoic acid, 1,1-dimethylethyl ester

To a stirred solution of 2.07 mL (14.80 mmol) of diisopropylamine in 15 mL of THF was added 6.2 mL (9.87 mmol) of 1.6M butyllithium in hexanes to give a pale yellow solution. The solution was warmed to 0° C. for 15 min and then cooled to –78° C. when 1.33 mL (9.87 mmol) of t-butyl acetate was added neat over 10 min. After 15 min, 3.5 mL (20.2 mmol) of HMPA was added and then 2.0 g (9.87 mmol) of 4-chloromethyl [1,1'-biphenyl] (Aldrich) was added in 20 mL of THF over 10 min. After 2 h at –78° C., the reaction was diluted with ether and quenched with saturated NH_4Cl. The organic layer was washed with water and brine, dried ($MgSO_4$) and evaporated to provide 3.8 g of a clear oil. The crude product was filtered through a pad of silica gel eluting with 500 mL each of pentane, CH_2Cl_2 and EtOAC. The latter two filtrates were combined and evaporated to provide 1.97 g of an oil. Further purification by flash chromatography on 200 g of silica gel packed in 3:1 pentane/CH_2Cl_2 and eluted with 2:1 pentane/CH_2Cl_2 gave 1.27 g (45%) of title ester as a clear, colorless oil.

IR (CCl_4) 2980, 2932, 1732, 1487, 1368, 1148, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ7.50, 7.56 (two dm, 2H each J=7 Hz) 7.42 (tm, 2H, J=7 Hz) 7.20–7.40 (m, 3H, H_3, H_5) 2.94 (t, 2H, J=7.6 Hz) 2.58 (t, 2H, J=7.6 Hz) 1.43 (s, 9H) ppm.

MS (CI-NH_3, +ions) m/z 300 (M+NH_4), 283 (M+H).

Anal. Calc'd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85 Found: C, 81.10; H, 7.88.

B. 4-(3-Hydroxypropyl)[1,1'-biphenyl]

To a suspension of 250 mg (6.58 mmol) of LAH in 15 mL of ether at 0° C. under argon was added 1.24 g (4.39 mmol) of Part A ester in 20 mL of ether over 10 min. After 0.5 h at 0° C., the reaction was carefully quenched by the sequential addition of 0.26 mL of water, 0.26 mL of 15% NaOH, and 0.79 mL of water. The mixture was stirred for 0.5 h, Na_2SO_4 was added and after an additional 1 h of stirring, the solids were removed by filtration through a pad of Celite. The solids were washed with ether, the filtrate was evaporated and the residue was purified by flash chromatography on 90 g of silica gel eluted with CH_2Cl_2 to provide 857 mg (92%) of title alcohol as a white solid, mp 72°–74° C.

IR (CCl_4) 3639, 3550 (br) 3029, 2939, 2875, 1602, 1487, 1041, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ7.50, 7.55 (two dm, 2H each, J=7 Hz) 7.40 (tm, 2H, J=7 Hz) 7.29 (tm, 1H, J=7 Hz) 7.24 (d, 2H, J=7.6 Hz) 3.68 (t, 2H, J=6.3 Hz) 2.72 (t, 2H, J=7.6 Hz) 1.90 (tt, 2H, J=6.3, 7.6 Hz) 1.83 (br s, 1H, 0[) ppm.

MS (CI-NH_3, +ions) m/z 230 (M+NH_4), 212 (M+H).

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.87; H, 7.60 Found: C, 84.95; H, 7.67.

C. 4-(3-Iodopropyl)[1,1'-biphenyl]

To a stirred solution of 857 mg (4.04 mmol) of Part B alcohol, 1.16 g (4.44 mmol) of triphenylphosphine and 577 mg (8.48 mmol) of imidazole in 30 mL of dry THF under argon at room temperature was added 1.13 g (4.44 mmol) of iodine in 25 mL of THF dropwise over 40 min. After 1 h, the reaction was diluted with ether and washed with water, saturated $Na_2S_2O_3$ and brine, dried ($MgSO_4$) and evaporated to provide an oily, white solid. Flash chromatography on 65 g of silica gel eluted with CH_2Cl_2 provided mg (62%) of title iodide as a white solid, mp 42°–43° C.

^1H NMR ($CDCl_3$, 270 MHz): δ7.50, 7.55 (two dm, 2H each, J=7 Hz) 7.41 (tm, 2H, J=7 Hz) 7.31 (tm, 1H, J=7 Hz) 7.25 (d, 2H, J=7.6 Hz) 3.18 (t, 2H, J=7 Hz) 2.75 (t, 2H, J=7 Hz) 2.14 (quint, 2H, J=7 Hz) ppm.

MS (CI-NH_3, +ions) m/z 340 (M+NH_4), 322 (M+H).

Anal. Calc'd for $C_{15}H_{15}I$: C, 55.92; H, 4.69; I, 39.39 Found: C, 56.04; H, 4.70; I, 39.37.

D. (E,E)-1-(Dicthoxyphosphinyl)-[1,1,-biphenyl-4-butanesulfonic acid, sodium salt

To a suspension of 223 mg (9.30 mmol) of NaH in 7 mL of dry DMF at 0° C. under argon was added 2.41 g (9.30 mmol) of Example 1 Part D sulfonate over 15 min. to give a yellow solution. The reaction was allowed to warm to

room temperature and stir for 0.5 h when 1.00 g (3.10 mmol) of Part C iodide was added in 3 mL of DMF over 2 min. The reaction mixture was stirred for 18 h when it was quenched with 10 mL of saturated aq NaCl solution and diluted with 100 ml of ethyl acetate. The fractions were separated and the organic layer washed with brine, dried (Na_2SO_4) and evaporated to provide a crude glass. The glass was diluted with 2.5 ml of 1M NaOH solution and purified by MPLC on a column of CHP20P gel (2.5 cm diam.×15 cm height) eluting with water (150 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 250 mL of water. Approximately 10 mL fractions were collected. The acetonitrile was removed under reduced pressure and the aqueous solution was lyophilized to provide 1.10 g (79%) of title salt as a viscous glass.

TLC Silica gel (7:2:1 propanol/conc. NH_3/water) R_f=0.55.

IR (film) 3466, 2984, 2932, 1614, 1485, 1444, 1392, 1368, 1240, 1069, 1035, 970, 794 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz) δ7.40–7.10 (m 9H) 4.10 (m, 4H) 3.15 (m, 1H) 2.65 (m, 2H) 2.30 (m, 1H) 2.00 (m, 3H) 1.25 (t, 6H, J=7.1 Hz) ppm.

Mass Spec (FAB, +ions) m/e 471 (M+Na), 449 (M+H).

E. α-Phosphono-[1,1'-biphenyl]-4-butanesulfonic acid, trisodium salt

To a stirred solution of 1.10 g (2.45 mmol) of Part D salt in 8 mL of dichloromethane at RT was added 1.49 g (9.80 mmol) of bromotrimethylsilane. The reaction was allowed to stir at RT for 14 h when the solvent was evaporated and the semisolid residue pumped (≈1 mm pressure) for 0.5 h. The residue was dissolved by adding 10 mL of 1M NaOH solution (10 mmol). The solution was purified by MPLC on a column of CHP20P gel (2.5 cm diam.×15 cm height) eluting with water (150 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 250 mL of water. Approximately 10 mL fractions were collected. Pure fractions were combined and the acetonitrile was removed under reduced pressure. The aqueous solution was lyophilized to provide 0.27 g (25%) of title salt as a white lyophilate.

TLC Silica gel (5:4:1 n-propanol/conc. ammonia/water) R_f=0.45.

IR (KBr) 3433, 3029, 2931, 1636, 1487, 1450, 1202, 1094, 1053, 973 cm^{-1}.

^1H NMR (D_2O, 270 MHz) δ

7.70, 7.55, 7.45 (3m, 9H) 2.97 (ddd, 1H, J=15.8, 6.5, 4.7 Hz) 2.75 (m, 2H) 2.00 (m, 4H)

Mass Spec (FAB, +ions) m/e 459 (M+Na), 437 (M+H), 415 (M-Na+2H).

Anal. Calc'd for $C_{16}H_{16}O_6Na_3PS$+2.00 H_2O: C, 40.69; H, 4.27; P, 6.56; S, 6.79 Found: C, 40.90; H, 4.39; P, 6.43; S, 6.89.

EXAMPLE 4

(E)-4-(4-Heptylphenyl)-1-phosphono-3-butene-1-sulfonic acid, tripotassium salt

A. 4-Heptylbenzaldehyde

To a stirred solution of 6.60 g (30 mmol) of 4-heptylbenzoic acid (obtained from Aldrich Chemical Company (#23,064-2) and used without purification) in 50 mL of dichloromethane at room temperature under nitrogen was added 4.0 mL (45 mmol, 1.5 equivalents) of oxalyl chloride and then 0.1 mL (1.3 mmol) of DMF. The resulting vigorously bubbling solution was stirred for 1 h and then evaporated. The semi-solid residue was dissolved in 40 mL of benzene under argon and 350 mg (0.31 mmol) of tetrakis (triphenylphosphine)palladium was added. To this stirring solution at room temperature was added 11.1 mL (34 mmol) of tributyltin hydride over 20 min. The solution turns yellow and warms autogenously to 40° C. After 1 h, the reaction was treated with 100 mL of 10% aqueous potassium fluoride and stirred vigorously for 30 min. The reaction mass was filtered, the filtrate diluted with ether, washed with water, and the organic layer separated, dried ($MgSO_4$) and evaporated onto 10 g of silica gel. Purification by flash chromatography (5×20 cm column, 3:7 dichloromethane/hexanes as elutent) gave 5.95 g, 97% yield, of title compound as a colorless oil.

B. α-Ethenyl-4-heptylbenzenemethanol, acetate ester

To a stirred slurry of 42.0 mL (42.0 mmol, 1M in THF) of vinyl magnesium bromide in 40 mL of THF at −40° C. under argon was added a solution of 5.85 g (28.6 mmol) of Part A compound in 10 mL of THF over 20 min. The resulting pale yellow solution was warmed to room temperature, stirred for 2 h and then quenched with saturated ammonium chloride solution. The reaction mixture was extracted twice with ether. The extracts were combined, dried ($MgSO_4$) and evaporated. The resulting yellow oil was dissolved in 50 mL of dichloromethane at room temperature under nitrogen and 5.6 mL (40 mmol) of triethylamine and 3.8 mL (40 mmol) of acetic anhydride were added, followed by 100 mg (0.4 mmol) of 4-dimethylaminopyridine (DMAP). After 30 minutes, the reaction mixture was diluted with ether, washed twice with 10% citric acid, once wtih brine and once with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated onto 10 g of silica gel. Purification by flash chromatography (5×25 cm column, 35:65 dichloromethane/hexanes as elutent) gave 7.12 g, 91%, of title compound.

C. (E)-1-(Diethoxyphosphinyl)-4-(4-heptylphenyl)-3-butenesulfonic acid, 1-methylethyl ester

To a stirred solution of 2.75 g (10.0 mmol) of Part B compound, 6.7 mL (27 mmol, 2.2 equiv.) of bis (trimethylsilyl)acetamide, 3.45 g (12.6 mmol, 1.26 equiv.) of Example 1A, Part B sulfonate and 270 mg (1 mmol) of triphenyl-phosphine in 30 mL of THF under argon was added 600 mg (0.54 mmol) of tetrakis(triphenylphosphine) -palladium. The resulting mixture was heated to reflux for 1 hour. The reaction was cooled, evaporated, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column) eluted with 1:19 ether/dichloromethane gave title compound as a colorless oil, 3.10 g, 67% yield.

D. (E)-4-(4-Heptylphenyl)-1-phosphono-3-butene-1-sulfonic acid, triootassium salt

To a stirred solution of 458 mg (1.0 mmol) of Part C compound, in 5 mL of dichloromethane under argon at room temperature was added 420 mL (2.0 mmol) of bis (trimethylsilyl)trifluoroacetamide and then 530 mL (4.0 mmol) of bromotrimethylsilane. After 16 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 5 mL of THF. To this stirred solution was added 200 mg (1.2 mmol) of dried, finely ground potassium iodide and 5 mg (0.02 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24 h, evaporated and then stirred for 1 h with 6 mL (3 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads HP-20 resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 2:1 acetonitrile/water). Fractions 23–25 were collected and lyophilized to give title salt as a white solid, 485 mg, 89% yield.

IR (KBr pellet) 3414, 2924, 2853, 1653, 1198, 1154, 1092, 972 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ23 (d, 2H, J=7.1 Hz) 7.06 (d, 2H, J=7.1 Hz) 6.35 (m, 2H) 2.91 (dm, 1H, J=14.5 Hz) 2.79 (t, 1H, J=13.6 Hz) 2.64 (m, 1H) 2.79 (t, 1H, J=13.6 Hz) 2.43 (t, 2H, J=6.6 Hz) 1.42 (m, 2H) 1.12 (m, 8H) 0.68 (t, 3H, J=6.0 Hz) ppm.

Anal. Calc'd for $C_{17}H_{24}K_3O_6PS.2.25\ H_2O$: C, 37.45; H, 5.27; P, 5.68; S, 5.88 Found: C, 37.09; H, 5.43; P, 6.08; S, 6.12.

MS (FAB, +ions) m/e 543 (M+K), 505 (M+H), 423 (M−2K−3H).

EXAMPLE 5

4-Heptyl-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. α-(Diethoxyphosphinyl)-4-heptylbenzenebutanesulfonic acid, 1-methylethyl ester

To an argon-purged solution of 675 mg (1.38 mmol) of Example 4 Part C compound and 100 mg of 10% palladium-on-carbon in 20 mL of ethyl acetate in a 500 mL one-neck round bottom flask was attached a hydrogen-filled rubber bladder of approximately 1 L capacity. The reaction mixture was vigorously stirred for 16 h, purged with nitrogen, filtered through Celite and the filtrate evaporated. The oily residue was redissolved in dichlormethane, filtered through a 0.75 m filter and re-evaporated to give title compound as a colorless oil, 640 mg, 94% yield. The product was used without further purification.

B. 4-Heptyl-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

To a stirred solution of 620 mg (1.26 mmol) of Part A compound in 5 mL of dichloromethane under argon at room temperature was added 660 mL (5 mmol) of bromotrimethylsilane. After 24 h, the resulting clear solution was evaporated at 25 ° C. and the residue dissolved in 5 mL of THF. To this stirred solution was added 225 mg (1.4 mmol) of dried, finely ground potassium iodide and 3 mg (0.01 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24 h, evaporated and then stirred for 1 h with 4 mL (4 mmol) of 1.0M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads HP-20 resin): 11.5 mL fractions, mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 2:1 acetonitrile/water). Fractions 36–41 were collected and lyophilized to give title compound as a white solid, 550 mg, 84% yield.

IR (KBr pellet) 3434, 2926, 2855, 1649, 1460, 1200, 1084, 1049, 966 cm^{-1}.

^1H NMR (D_2O, 270 MHz) δ7.08 (d, 2H, J=7.6 Hz) 7.02 (d, 2H, J=7.6 Hz) 2.81 (dm, 1H, J=17 Hz) 2.47 (m, 2H) 2.41 (t, 2H, J=7.9 Hz) 1.78 (m, 4H) 1.41 (m, 2H) 0.69 (t, 3H, J=6.4 Hz) ppm.

Anal. Calc'd for $C_{17}H_{26}K_3O_6PS.0.75\ H_2O$: C, 39.25; H, 5.33; P, 5.95; S, 6.16 Found: C, 39.45; H, 5.72; P, 5.71; S, 5.83.

MS (FAB, +ions) m/e 545 (M+K), 507 (M+H), 469 (M−K+2H).

EXAMPLE 6

(E)-4-(4'-Propyl[1,1'-biphenyl]-4-yl)-1-phosphono-3-butene-1-sulfonic acid, tripotassium salt

A. (E)-(4'-Propyl[1,1'-biphenyl]-4-yl)-2-propen-1-ol, acetate ester

A(1). (E)-(4'-Propyl[1,1'-biphenyl]-4-yl)-2-propenoic acid, n-butyl ester

A stirred solution of 4.13 g (15 mmol) of 4-bromo-4'-n-propylbiphenyl, 106 mg (0.35 mmol) of tri-p-tolylphosphine, 2.7 mL (19 mmol) of n-butyl acrylate, 7.4 mL (30.8 mmol) of tributylamine and 10 mg (0.1 mmol) of hydroquinone was purged with a stream of nitrogen gas for 20 min at room temperature. To this mixture was added 4 mg (0.018 mmol) of palladium acetate. The reaction was heated to 150 ° C. for 18 h under argon and then cooled to room temperature. The resulting slurry was diluted with ether, extracted twice with 50 mL of 1M hydrochloric acid, once with brine and once with saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated. The crude product (4.5 g) was purified by flash chromatography on silica gel (5×25 cm column) eluted with 1 L of hexanes and then 1:1 dichloromethane/hexanes to give 4.08 g (81%) of title ester as a colorless oil.

A(2). (E)-(4'-Propyl[1,1'-biphenyl]-4-yl)-2-propen-1-ol, acetate ester

To a stirred solution of 3.22 g (10.0 mmol) of Part A(1) ester in 50 mL of dichloromethane at 0° C. under nitrogen was added a solution of 22 mL (22 mmol, 1M in hexanes) of diisobutylaluminum hydride over 5 min. The resulting pale yellow solution was stirred for 2 h and then quenched with 2 mL of methanol. The solution was then treated with 150 mL of 1M potassium sodium tartrate. A gel formed which dissolved within 5 min. The reaction mixture was extracted twice with ether. The extracts were combined, dried (Na_2SO_4) and evaporated. The resulting oil (2.6 g) was dissolved in 25 mL of THF, cooled to 0° C. under nitrogen and 4.6 mL (25 mmol) of diisopropylethylamine and 2.4 mL (25 mmol) of acetic anhydride was added. After 1 h, the reaction mixture was diluted with ether, washed twice with 1M hydrochloric acid once with brine and once with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated onto 10 g of silica gel. Purification by flash chromatography on silica gel (5×20 cm column) eluted with 9:11 dichloromethane:hexane to give title compound as a colorless oil, 2.21 g, 88% from Part A(1) ester.

B. (E)-1-(Diethoxyphosphinyl)-4-(4'-propyl[1,1'-biphenyl]-4-yl)-3-butene-1-sulfonic acid, cyclohexyl ester

To a stirred solution of 1.91 g (6.50 mmol) of Part A compound, 2.5 mL (10 mmol, 1.5 equiv.) of bis(trimethylsilyl)acetamide, 3.00 g (9.5 mmol, 1.46 equiv.) of Example 1A, Part B sulfonate and 180 mg (0.7 mmol) of triphenylphosphine in 10 mL of THF under argon was added 400 mg (0.35 mmol) of tetrakis(tri-phenylphosphine) palladium. The resulting mixture was heated to reflux for 1 hour. The reaction was cooled, evaporated, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column) eluted with 3:97 ether/dichloromethane gave title compound as a colorless oil, 2.32 g, 65% yield.

C. (E)-4-(4'-Propyl[1,1'-biphenyl]-4-yl)-1-phosphono-3-butene-1-sulfonic acid, tripotassium salt

To a stirred solution of 578 mg (1.05 mmol) of Part B compound in 5 mL of dichloromethane under argon at room temperature was added 560 mL (2.1 mmol) of bis (trimethylsilyl)trifluoroacetamide and then 560 mL (4.2