United States Patent [19]

Wareing

[11] **Patent Number: 4,613,610**

[45] **Date of Patent: Sep. 23, 1986**

[54] **CHOLESTEROL BIOSYNTHESIS INHIBITING PYRAZOLE ANALOGS OF MEVALONOLACTONE AND ITS DERIVATIVES**

[75] Inventor: **James R. Wareing**, Randolph, N.J.

[73] Assignee: **Sandoz Pharmaceuticals Corp.**, E. Hanover, N.J.

[21] Appl. No.: **741,903**

[22] Filed: **Jun. 6, 1985**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 623,393, Jun. 22, 1984, abandoned.

[51] **Int. Cl.**[4] **A61K 31/415**; C07D 231/12; C07D 405/06

[52] **U.S. Cl.** **514/406**; 548/374; 548/378

[58] **Field of Search** 548/374, 378; 514/406

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,198,425	4/1980	Mitsui et al.	549/292
4,248,889	2/1981	Oka et al.	560/56
4,255,444	3/1981	Oka et al.	549/292
4,308,378	12/1981	Stokker	549/292
4,351,844	9/1982	Patchett et al.	549/292
4,361,515	11/1982	Terahara et al.	549/292
4,375,475	3/1983	Willard et al.	549/292
4,376,863	3/1983	Lam	549/292
4,387,242	6/1983	Lam	560/119
4,440,927	4/1984	Prugh	549/292
4,474,971	10/1984	Wareing	549/214
4,503,072	3/1985	Hoffman et al.	514/529

FOREIGN PATENT DOCUMENTS

895445	4/1983	Belgium	549/292
38061	10/1981	European Pat. Off.	549/292
68038	1/1983	European Pat. Off.	549/292
56-7775	1/1981	Japan	549/292
WO84/02131	6/1984	PCT Int'l Appl.	548/467
WO84/02903	8/1984	PCT Int'l Appl.	549/292

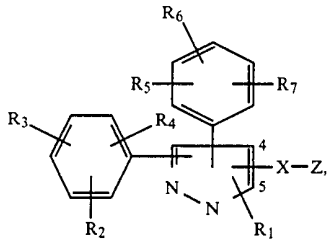
OTHER PUBLICATIONS

Hulcher, Arch. Biochem. Biophys. 146, 422–427 (1971).
Sato et al., Chem. Pharm. Bull. 28, 1509–1525 (1980).
Singer et al., Proc. Soc. Exp. Biol. Med. 102, 370–373 (1959).

Primary Examiner—Richard A. Schwartz
Assistant Examiner—Kurt G. Briscoe
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] **ABSTRACT**

Compounds of the formula



wherein

R_1 is C_{1-6}alkyl not containing an asymmetric carbon atom,

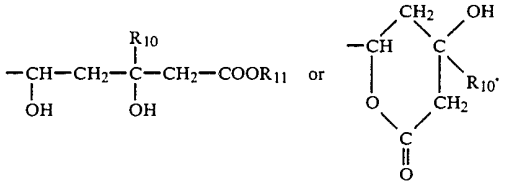
each of R_2 and R_5 is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenyl, phenoxy or benzyloxy,

each of R_3 and R_6 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

each of R_4 and R_7 is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, with the provisos that not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, not more than one of R_2 and R_3 is benzyloxy, not more than one of R_5 and R_6 is trifluoromethyl, not more than one of R_5 and R_6 is phenoxy, and not more than one of R_5 and R_6 is benzyloxy,

X is $-(CH_2)_m-$, $-CH=CH-$, $-CH=CH-CH_2-$ or $-CH_2-CH=CH-$, wherein m is 0, 1, 2 or 3, and

Z is



wherein R_{10} is hydrogen or C_{1-3}alkyl, wherein

R_{12} is a physiologically acceptable and hydrolyzable ester group, and

M is a pharmaceutically acceptable cation,

with the provisos that (i) the—X—Z group is in the 4- or 5-position of the pyrazole ring, and (ii) the R_1 group and the —X—Z group are ortho to each other,

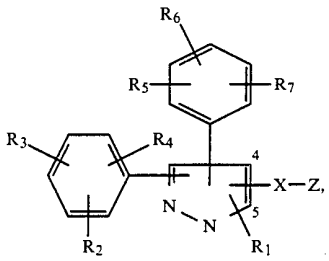
the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

27 Claims, No Drawings

CHOLESTEROL BIOSYNTHESIS INHIBITING PYRAZOLE ANALOGS OF MEVALONOLACTONE AND ITS DERIVATIVES

This application is a continuation-in-part of application Ser. No. 623,393, filed June 22, 1984 and now abandoned.

This invention relates to compounds of the formula


(I)

wherein

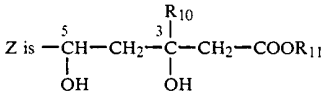
R_1 is C_{1-6}alkyl not containing an asymmetric carbon atom,

each of R_2 and R_5 is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenyl, phenoxy or benzyloxy,

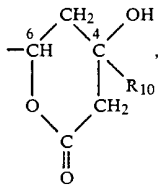
each of R_3 and R_6 is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

each of R_4 and R_7 is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, with the provisos that not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, not more than one of R_2 and R_3 is benzyloxy, not more than one of R_5 and R_6 is trifluoromethyl, not more than one of R_5 and R_6 is phenoxy, and not more than one of R_5 and R_6 is benzyloxy,

X is $-(CH_2)_m-$, $-CH=CH-$, $-CH=CH-CH_2-$ or $-CH_2-CH=CH-$, wherein m is 0, 1, 2 or 3, and


(a)

or


(b)

wherein R_{10} is hydrogen or C_{1-3}alkyl, and R_{11} is hydrogen, R_{12} or M, wherein

R_{12} is a physiologically acceptable and hydrolyzable ester group, and

M is a pharmaceutically acceptable cation,

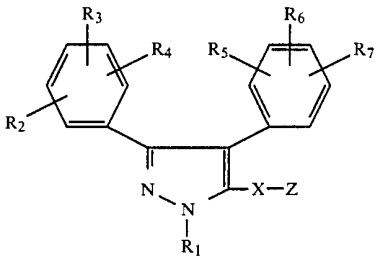
with the provisos that (i) the —X—Z group is in the 4- or 5-position of the pyrazole ring, and (ii) the R_1 group and the —X—Z group are ortho to each other,

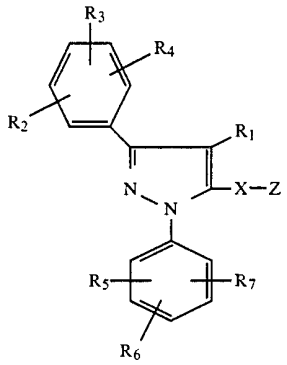
processes for and intermediates in the synthesis thereof, pharmaceutical compositions comprising a compound of Formula I and the use of the compounds of Formula I for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis.

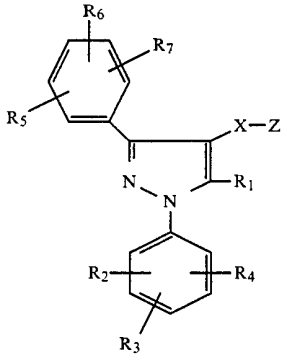
By the term "physiologically acceptable and hydrolyzable ester group" is meant a group which, together with the —COO— radical to which it is attached, forms an ester group which is physiologically acceptable and hydrolyzable under physiological conditions to yield a compound of Formula I wherein R_{11} is hydrogen and an alcohol which itself is physiologically acceptable, i.e., non-toxic at the desired dosage level, and which, preferably, is free of centers of asymmetry. Examples of such groups are C_{1-3}alkyl, n-butyl, i-butyl, t-butyl and benzyl, collectively referred to as R_{12}'.

For the avoidance of doubt, throughout this application it is the right-hand side of the X radical that is attached to the Z group.

The compounds of Formula I may be divided into four groups, viz., those of Formulae IA, IB, IC and ID:

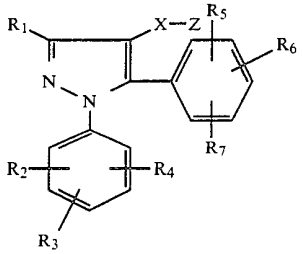

(IA)


(IB)


(IC)

-continued

(ID)



The compounds of each of Groups IA–ID may be divided into two subgroups based upon the significance of Z, viz., Group IAa (the compounds of Group IA wherein Z is a group of Formula a), Group IAb (the compounds of Group IA wherein Z is a group of Formula b), Group IBa (the compounds of Group IB wherein Z is a group of Formula a), Group IBb (the compounds of Group IB wherein Z is a group of Formula b), Group ICa (the compounds of Group IC wherein Z is a group of Formula a), Group ICb (the compounds of Group IC wherein Z is a group of Formula b), Group IDa (the compounds of Group ID wherein Z is a group of Formula a) and Group IDb (the compounds of Group ID wherein Z is a group of Formula b).

As is self-evident to those in the art, each compound of Formula I (and every subscope and species thereof) has two centers of asymmetry (the two carbon atoms bearing the hydroxy groups in the group of Formula a and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of Formula b) and, therefore, there are four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers), provided that R_{11} does not contain any center of asymmetry. The four stereoisomers may be designated as the R,R, R,S, S,R and S,S enantiomers, all four stereoisomers being within the scope of this invention. When R_{11} contains one or more centers of asymmetry, there are eight or more stereoisomers. Since it is preferred that R_{11} not contain a center of asymmetry and for reasons of simplicity any additional stereoisomers resulting from the presence of one or more centers of asymmetry in R_{11} usually will be ignored, it being assumed that R_{11} is free of centers of asymmetry.

R_1 is preferably R_1', where R_1' is C_{1-3}alkyl, n-butyl or i-butyl, more preferably R_1'', where R_1'' is C_{1-3}alkyl, and most preferably isopropyl.

R_2 is preferably R_2', where R_2' is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro or chloro, more preferably R_2'', where R_2'' is hydrogen or fluoro, and most preferably hydrogen.

R_3 is preferably R_3', where R_3' is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and most preferably hydrogen.

R_4 is preferably R_4', where R_4' Is hydrogen or methyl, and most preferably hydrogen.

The R_2-bearing phenyl group is preferably unsubstituted.

R_5 is preferably R_5', where R_5' is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro or chloro, more preferably R_5'', where R_5'' is hydrogen or fluoro, and most preferably fluoro.

R_6 is preferably R_6', where R_6' is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, more preferably R_6'', where R_6'' is hydrogen or methyl, and most preferably hydrogen.

R_7 is preferably R_7', where R_7' is hydrogen or methyl, and most preferably hydrogen.

Preferably, when two of R_5 (R_5', etc.), R_6 (R_6', etc.) and R_7 (R_7', etc.) are other than hydrogen and one is hydrogen, at least one of the two that are other than hydrogen is in a meta or para position and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenyl, phenoxy and benzyloxy; more preferably, the two that are other than hydrogen are not ortho to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro.

Preferably, when each of R_5 (R_5', etc.), R_6 (R_6', etc.) and R_7 (R_7', etc.) is other than hydrogen, at least two of them are in meta or para positions, and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenyl, phenoxy and benzyloxy; more preferably, no two of them are ortho to each other unless at least one member of each pair of substituents that are ortho to each other is a member of the group consisting of methyl, methoxy, fluoro and chloro.

The R_5-bearing phenyl group is preferably 4-fluorophenyl or 3,5-dimethylphenyl, preferably the former.

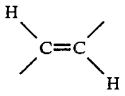
R_{10} is preferably R_{10}', where R_{10}' is hydrogen or methyl, and most preferably hydrogen.

R_{11} is preferably R_{11}', where R_{11}' is hydrogen, R_{12}' or M, more preferably R_{11}'', where R_{11}'' is hydrogen, C_{1-3}alkyl or M, even more preferably R_{11}''', where R_{11}''' is hydrogen, C_{1-2}alkyl or M, and most preferably M, especially sodium.

R_{12} is preferably R_{12}', where R_{12}' is C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl, more preferably C_{1-3}alkyl, and most preferably C_{1-2}alkyl, especially ethyl.

Any —CH=CH—, —CH=CH—CH_2— or —CH_2—CH=CH— as X is preferably trans, i.e., (E).

X is preferably X', where X' is —CH_2CH_2— or —CH=CH—, more preferably —CH=CH—, and most preferably



(i.e., (E)—CH=CH—).

Z is preferably a group of Formula a wherein R_{10} is R_{10}' (especially hydrogen), and R_{11} is R_{11}' or a group of Formula b, more preferably a group of Formula a wherein R_{10} is hydrogen, and R_{11} is R_{11}'' or a group of Formula b, even more preferably a group of Formula a wherein R_{10} is hydrogen, and R_{11} is R_{11}''' or a group of Formula b, and most preferably a group of Formula a wherein R_{10} is hydrogen, and R_{11} is M (especially sodium).

m is preferably m', where m' is 2 or 3, most preferably 2.

M is preferably free from centers of asymmetry and is more preferably M', i.e., sodium, potassium or ammonium, and most preferably sodium. For simplicity, each formula in which M appears has been written as if M were monovalent and, preferably, it is. However, it may also be divalent or trivalent and, when it is, balances the charge of two or three carboxy groups, respectively.

Thus, Formula I and every other formula containing an M embraces compounds wherein M is divalent or trivalent, i.e., compounds containing two or three carboxylate-containing anions per cation M.

As between otherwise identical compounds of Formula I, those wherein Z is a group of Formula a are generally preferred over those wherein Z is a group of Formula b.

Insofar as the compounds of Groups IAa, IBa, ICa and IDa and each of the subgroups thereof are concerned, the erythro isomers are preferred over the threo isomers, erythro and threo referring to the relative positions of the hydroxy groups in the 3- and 5-positions of the group of Formula a.

Insofar as the compounds of Groups IAb, IBb, ICb and IDb and each of the subgroups thereof are concerned, the trans lactones are generally preferred over the cis lactones, cis and trans referring to the relative positions of R_{10} and the hydrogen atom in the 6-position of the group of Formula b.

The preferred stereoisomers of the compounds of Formula I having only two centers of asymmetry wherein X is a direct bond, —CH=CH— or —CH_2—CH=CH—, and Z is a group of Formula a are the 3R,5S isomer and the racemate of which it is a constituent, i.e., the 3R,5S-3S,5R (erythro) racemate.

The preferred stereoisomers of the compounds of Formula I having only two centers of asymmetry wherein X is —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$— or —CH=CH—CH_2—, and Z is a group of Formula a are the 3R,5R isomer and the racemate of which it is a constituent, i.e., the 3R,5R-3S,5S (erythro) racemate.

The preferences set forth in the preceding two paragraphs also apply to the compounds of Formula I having more than two centers of asymmetry and represent the preferred configurations of the indicated positions.

The preferred stereoisomers of the compounds of Formula I wherein X is a direct bond, —CH=CH— or —CH_2—CH=CH—, and Z is a group of Formula b are the 4R,6S and 4R,6R isomers and the racemate of which each is a constituent, i.e., the 4R,6S-4S,6R (trans lactone) and 4R,6R-4S,6S (cis lactone) racemates, with the 4R,6S isomer and the racemate of which it is a constituent being more preferred and the 4R,6S isomer being most preferred.

The preferred stereoisomers of the compounds of Formula I wherein X is —CH_2—, —CH_2CH_2—, —$CH_2CH_2CH_2$— or —CH=CH—CH_2—, and Z is a group of Formula b are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, i.e., the 4R,6R-4S,6S (trans lactone) and 4R,6S-4S,6R (cis lactone) racemates, with the 4R,6R isomer and the racemate of which it is a constituent being more preferred and the 4R,6R isomer being most preferred.

Each of the preferences set forth above applies, not only to the compounds of Formula I, but also to the compounds of Formulae IA, IB, IC and ID and those of Groups IAa, IAb, IBa, IBb, ICa, ICb, IDa and IDb as well as to every other subgroup thereof set forth in the specification, e.g., Groups (i) et seq., unless otherwise indicated. When any preference or group contains a variable, the preferred significances of that variable apply to the preference in question, unless otherwise indicated.

Preferred groups of compounds of Formulae IAa and IAb include the compounds

(i) of Group IAa wherein R_1 is R_1', R_2 is R_2', R_3 is R_3', R_4 is R_4', R_5 is R_5', R_6 is R_6', R_7 is R_7', R_{10} is R_{10}', R_{11} is R_{11}', and X is X',

(ii) of (i) wherein R_2 is R_2'', R_3 is hydrogen, R_4 is hydrogen, R_5 is R_5'', R_6 is R_6'', R_{10} is hydrogen, R_{11} is R_{11}'', and X is (E)—CH=CH—,

(iii) of (ii) wherein R_1 is R_1'',

(iv)-(vi) of (i)-(iii) wherein R_{11} is M, especially sodium,

(vii)-(xii) of (i)-(vi) wherein the hydrogen groups in the 3- and 5-positions of the group of Formula a have the erythro configuration.

(xiii)-(xviii) the 3R,5S enantiomers of the compounds of (vii)-(xii) wherein X is —CH=CH— and the 3R,5R enantiomers of those wherein X is —CH_2CH_2—,

(xix) of Group IAb wherein R_1 is R_1', R_2 is R_2', R_3 is R_3', R_4 is R_4', R_5 is R_5', R_6 is R_6', R_7 is R_7', R_{10} is R_{10}', and X is X',

(xx) of (xix) wherein R_2 is R_2'', R_3 is hydrogen, R_4 is hydrogen, R_5 is R_5'', R_6 is R_6'', R_{10} is hydrogen, and X is (E)—CH=CH—,

(xxi) of (xx) wherein R_1 is R_1'',

(xxii)-(xxiv) of (xix)-(xxi) wherein R_{10} and the hydrogen atom in the 6-position of the group of Formula b are trans to each other (i.e., the trans lactones), and

(xxv)-(xxvii) the 4R,6S enantiomers of the compounds of (xxii)-(xxiv) wherein X is —CH=CH— and the 4R,6R enantiomers of those wherein X is —CH_2CH_2—.

Groups (viii)-(xii) embrace the 3R,5S-3S,5R racemate and the 3R,5S and 3S,5R enantiomers, the 3S,5R enantiomer being least preferred.

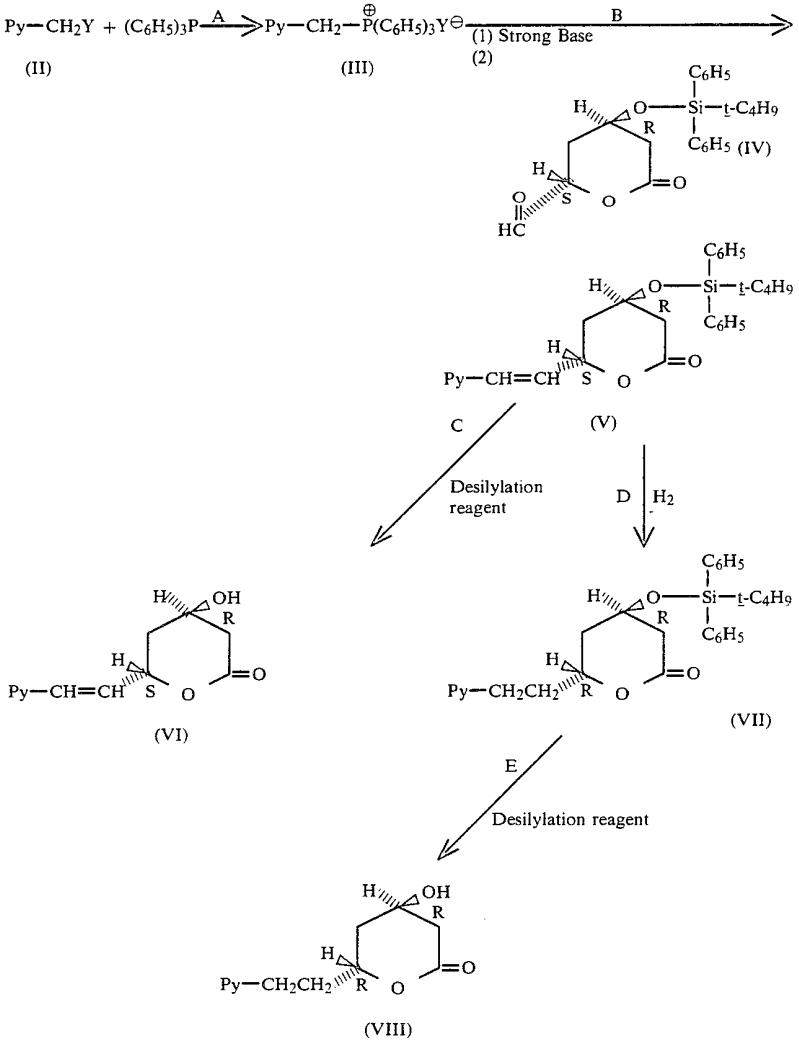
Groups (xxiii) and (xxiv) embrace the 4R,6S-4S,6R racemate and the 4R,6S and 4S,6R enantiomers, the 4S,6R enantiomer being least preferred.

Insofar as Groups IBa, IBb, ICa, ICb, IDa and IDb are concerned, the preferred subgroups are those that correspond to Groups (i)-(xxvii). As should be self-evident, the preferred groups of compounds of Groups IBa, ICa and IDa are those that correspond to Groups (i)-(xviii), i.e., Groups (xxviii)-(xlv), (lv)-(lxxii) and (lxxxii)-(xcix), respectively, and the preferred groups of compounds of Groups IBb, ICb and IDb are those that correspond to Groups (xix)-(xxvii), i.e., Groups (xlvi)-(liv), (lxxiii)-(lxxxi) and (c)-(cviii), respectively.

The compounds of Formula I may be synthesized as follows:

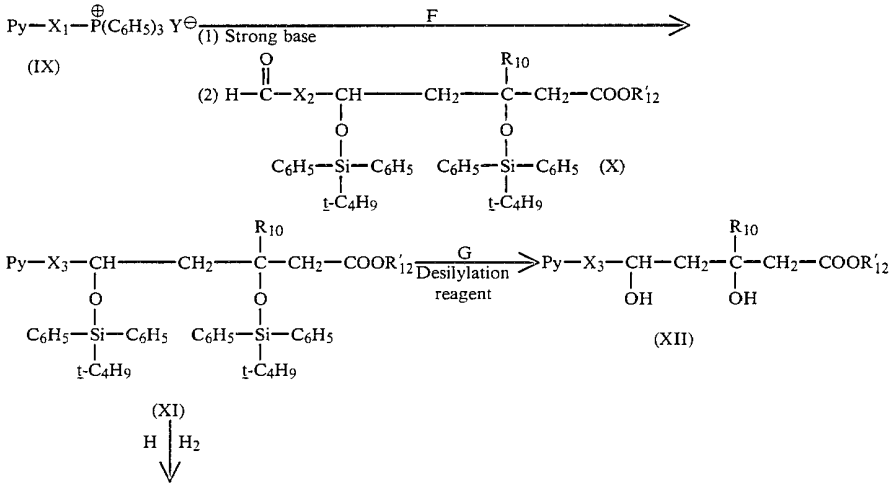
Reaction Scheme I

The compounds of Formula I wherein X is —CH=CH— and Z is a group of Formula b having the 4R,6S configuration or X is —CH_2CH_2— and Z is a group of Formula b having the 4R,6R configuration may be synthesized by the following series of reactions:



Reaction Scheme II

The compounds of Formula I wherein X is $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-$, $-CH=CH-CH_2-$ or $-CH_2-CH=CH-$, and Z is a group of Formula a wherein R_{11} is R_{12}' may be synthesized by the following series of reactions:



DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.