

[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.  
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Related U.S. Application Data

- [63] Continuation-in-part of Ser. No. 623,393, Jun. 22, 1984,  
abandoned.  
[51] Int. Cl.<sup>4</sup> ..... 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

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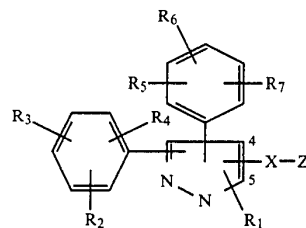
Primary Examiner—Richard A. Schwartz

Assistant Examiner—Kurt G. Briscoe

Attorney, Agent, or Firm—Gerald D. Sharkin; Richard  
E. Vila; Melvyn M. Kassenoff

[57] ABSTRACT

Compounds of the formula

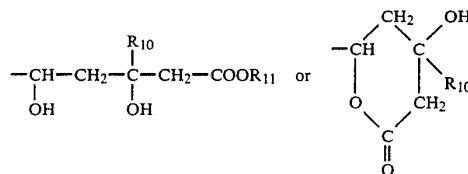


wherein

R<sub>1</sub> is C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom,  
each of R<sub>2</sub> and R<sub>5</sub> is independently hydrogen, C<sub>1-3</sub>alkyl, n-butyl, i-butyl, t-butyl, C<sub>1-3</sub>alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy, phenoxy or benzyloxy,  
each of R<sub>3</sub> and R<sub>6</sub> is independently hydrogen, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,  
each of R<sub>4</sub> and R<sub>7</sub> is independently hydrogen, C<sub>1-2</sub>alkyl, C<sub>1-2</sub>alkoxy, fluoro or chloro, with the provisos that not more than one of R<sub>2</sub> and R<sub>3</sub> is trifluoromethyl, not more than one of R<sub>2</sub> and R<sub>3</sub> is phenoxy, not more than one of R<sub>5</sub> and R<sub>6</sub> is trifluoromethyl, not more than one of R<sub>5</sub> and R<sub>6</sub> is phenoxy, and not more than one of R<sub>5</sub> and R<sub>6</sub> is benzyloxy,

X is —(CH<sub>2</sub>)<sub>m</sub>—, —CH=CH—, —CH=CH—CH<sub>2</sub>— or —CH<sub>2</sub>—CH=CH—, wherein m is 0, 1, 2 or 3, and

Z is



wherein R<sub>10</sub> is hydrogen or C<sub>1-3</sub>alkyl, wherein R<sub>11</sub> 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<sub>1</sub> group and the—X—Z group are ortho to each other,

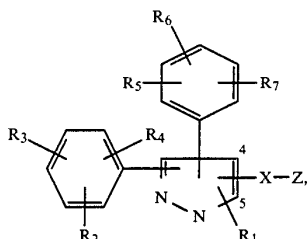
the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

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



wherein

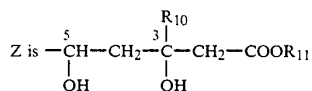
R<sub>1</sub> is C<sub>1-6</sub>alkyl not containing an asymmetric carbon atom,

each of R<sub>2</sub> and R<sub>5</sub> is independently hydrogen, C<sub>1-3</sub>alkyl, n-butyl, i-butyl, t-butyl, C<sub>1-3</sub>alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenyl, phenoxy or benzyloxy,

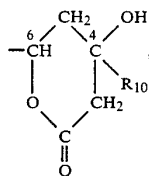
each of R<sub>3</sub> and R<sub>6</sub> is independently hydrogen, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

each of R<sub>4</sub> and R<sub>7</sub> is independently hydrogen, C<sub>1-2</sub>alkyl, C<sub>1-2</sub>alkoxy, fluoro or chloro, with the provisos that not more than one of R<sub>2</sub> and R<sub>3</sub> is trifluoromethyl, not more than one of R<sub>2</sub> and R<sub>3</sub> is phenoxy, not more than one of R<sub>2</sub> and R<sub>3</sub> is benzyloxy, not more than one of R<sub>5</sub> and R<sub>6</sub> is trifluoromethyl, not more than one of R<sub>5</sub> and R<sub>6</sub> is phenoxy, and not more than one of R<sub>5</sub> and R<sub>6</sub> 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



or



wherein R<sub>10</sub> is hydrogen or C<sub>1-3</sub>alkyl, and R<sub>11</sub> is hydrogen, R<sub>12</sub> or M, wherein

R<sub>12</sub> is a physiologically acceptable and hydrolyzable ester group, and

M is a pharmaceutically acceptable cation,

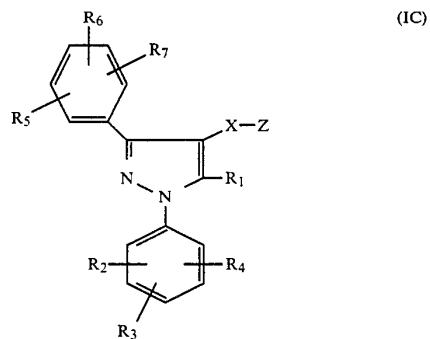
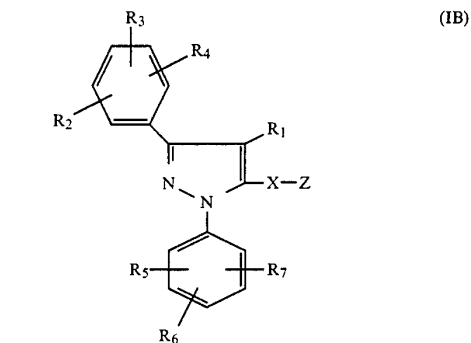
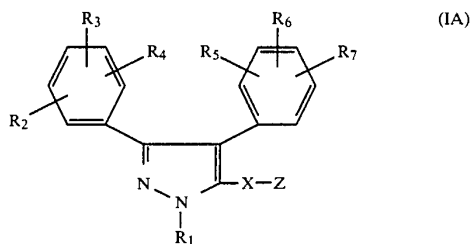
with the provisos that (i) the  $-X-Z$  group is in the 4- or 5-position of the pyrazole ring, and (ii) the R<sub>1</sub> group and the  $-X-Z$  group are ortho to each other, processes for and intermediates in the synthesis thereof, pharmaceutical compositions comprising a compound

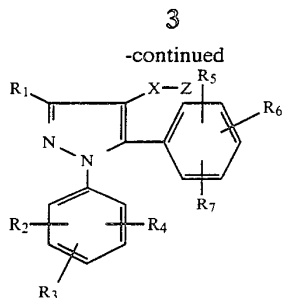
of Formula I and the use of the compounds of Formula I for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis.

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<sub>11</sub> 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<sub>1-3</sub>alkyl, n-butyl, i-butyl, t-butyl and benzyl, collectively referred to as R<sub>12</sub>'.

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:





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<sub>11</sub> 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<sub>11</sub> contains one or more centers of asymmetry, there are eight or more stereoisomers. Since it is preferred that R<sub>11</sub> 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<sub>11</sub> usually will be ignored, it being assumed that R<sub>11</sub> is free of centers of asymmetry.

R<sub>1</sub> is preferably R<sub>1</sub>' where R<sub>1</sub>' is C<sub>1-3</sub>alkyl, n-butyl or i-butyl, more preferably R<sub>1</sub>'' where R<sub>1</sub>'' is C<sub>1-3</sub>alkyl, and most preferably isopropyl.

R<sub>2</sub> is preferably R<sub>2</sub>' where R<sub>2</sub>' is hydrogen, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, trifluoromethyl, fluoro or chloro, more preferably R<sub>2</sub>'' where R<sub>2</sub>'' is hydrogen or fluoro, and most preferably hydrogen.

R<sub>3</sub> is preferably R<sub>3</sub>' where R<sub>3</sub>' is hydrogen, C<sub>1-2</sub>alkyl, C<sub>1-2</sub>alkoxy, fluoro or chloro, and most preferably hydrogen.

R<sub>4</sub> is preferably R<sub>4</sub>' where R<sub>4</sub>' is hydrogen or methyl, and most preferably hydrogen.

The R<sub>2</sub>-bearing phenyl group is preferably unsubstituted.

R<sub>5</sub> is preferably R<sub>5</sub>' where R<sub>5</sub>' is hydrogen, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, trifluoromethyl, fluoro or chloro, more preferably R<sub>5</sub>'' where R<sub>5</sub>'' is hydrogen or fluoro, and most preferably fluoro.

R<sub>6</sub> is preferably R<sub>6</sub>' where R<sub>6</sub>' is hydrogen, C<sub>1-2</sub>alkyl, C<sub>1-2</sub>alkoxy, fluoro or chloro, more preferably R<sub>6</sub>''

where R<sub>6</sub>'' is hydrogen or methyl, and most preferably hydrogen.

R<sub>7</sub> is preferably R<sub>7</sub>' where R<sub>7</sub>' is hydrogen or methyl, and most preferably hydrogen.

5 Preferably, when two of R<sub>5</sub> (R<sub>5</sub>', etc.), R<sub>6</sub> (R<sub>6</sub>', etc.) and R<sub>7</sub> (R<sub>7</sub>', 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.

15 Preferably, when each of R<sub>5</sub> (R<sub>5</sub>', etc.), R<sub>6</sub> (R<sub>6</sub>', etc.) and R<sub>7</sub> (R<sub>7</sub>', 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.

25 The R<sub>5</sub>-bearing phenyl group is preferably 4-fluorophenyl or 3,5-dimethylphenyl, preferably the former.

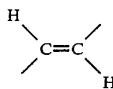
R<sub>10</sub> is preferably R<sub>10</sub>' where R<sub>10</sub>' is hydrogen or methyl, and most preferably hydrogen.

30 R<sub>11</sub> is preferably R<sub>11</sub>' where R<sub>11</sub>' is hydrogen, R<sub>12</sub>' or M, more preferably R<sub>11</sub>'' where R<sub>11</sub>'' is hydrogen, C<sub>1-3</sub>alkyl or M, even more preferably R<sub>11</sub>''' where R<sub>11</sub>''' is hydrogen, C<sub>1-2</sub>alkyl or M, and most preferably M, especially sodium.

35 R<sub>12</sub> is preferably R<sub>12</sub>' where R<sub>12</sub>' is C<sub>1-3</sub>alkyl, n-butyl, i-butyl, t-butyl or benzyl, more preferably C<sub>1-3</sub>alkyl, and most preferably C<sub>1-2</sub>alkyl, especially ethyl.

40 Any —CH=CH—, —CH=CH—CH<sub>2</sub>— or —CH<sub>2</sub>—CH=CH— as X is preferably trans, i.e., (E).

X is preferably X' where X' is —CH<sub>2</sub>CH<sub>2</sub>— or —CH=CH—, more preferably —CH=CH—, and most preferably



(i.e., (E)—CH=CH—).

50 Z is preferably a group of Formula a wherein R<sub>10</sub> is R<sub>10</sub>' (especially hydrogen), and R<sub>11</sub> is R<sub>11</sub>' or a group of Formula b, more preferably a group of Formula a wherein R<sub>10</sub> is hydrogen, and R<sub>11</sub> is R<sub>11</sub>'' or a group of Formula b, even more preferably a group of Formula a wherein R<sub>10</sub> is hydrogen, and R<sub>11</sub> is R<sub>11</sub>''' or a group of Formula b, and most preferably a group of Formula a wherein R<sub>10</sub> is hydrogen, and R<sub>11</sub> is M (especially sodium).

60 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<sub>10</sub> 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<sub>2</sub>—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<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>— or —CH=CH—CH<sub>2</sub>—, 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<sub>2</sub>—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<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>—, —CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>— or —CH=CH—CH<sub>2</sub>—, 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<sub>1</sub> is R<sub>1</sub>', R<sub>2</sub> is R<sub>2</sub>', R<sub>3</sub> is R<sub>3</sub>', R<sub>4</sub> is R<sub>4</sub>', R<sub>5</sub> is R<sub>5</sub>', R<sub>6</sub> is R<sub>6</sub>', R<sub>7</sub> is R<sub>7</sub>', R<sub>10</sub> is R<sub>10</sub>', R<sub>11</sub> is R<sub>11</sub>', and X is X',

(ii) of (i) wherein R<sub>2</sub> is R<sub>2</sub>'', R<sub>3</sub> is hydrogen, R<sub>4</sub> is hydrogen, R<sub>5</sub> is R<sub>5</sub>'', R<sub>6</sub> is R<sub>6</sub>'', R<sub>10</sub> is hydrogen, R<sub>11</sub> is R<sub>11</sub>'', and X is (E)—CH=CH—,

(iii) of (ii) wherein R<sub>1</sub> is R<sub>1</sub>'',

(iv)–(vi) of (i)–(iii) wherein R<sub>11</sub> 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<sub>2</sub>CH<sub>2</sub>—,

(xix) of Group IAb wherein R<sub>1</sub> is R<sub>1</sub>', R<sub>2</sub> is R<sub>2</sub>', R<sub>3</sub> is R<sub>3</sub>', R<sub>4</sub> is R<sub>4</sub>', R<sub>5</sub> is R<sub>5</sub>', R<sub>6</sub> is R<sub>6</sub>', R<sub>7</sub> is R<sub>7</sub>', R<sub>10</sub> is R<sub>10</sub>', and X is X',

(xx) of (xix) wherein R<sub>2</sub> is R<sub>2</sub>'', R<sub>3</sub> is hydrogen, R<sub>4</sub> is hydrogen, R<sub>5</sub> is R<sub>5</sub>'', R<sub>6</sub> is R<sub>6</sub>'', R<sub>10</sub> is hydrogen, and X is (E)—CH=CH—,

(xxi) of (xx) wherein R<sub>1</sub> is R<sub>1</sub>'',

(xxii)–(xxiv) of (xix)–(xxi) wherein R<sub>10</sub> 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<sub>2</sub>CH<sub>2</sub>—.

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.

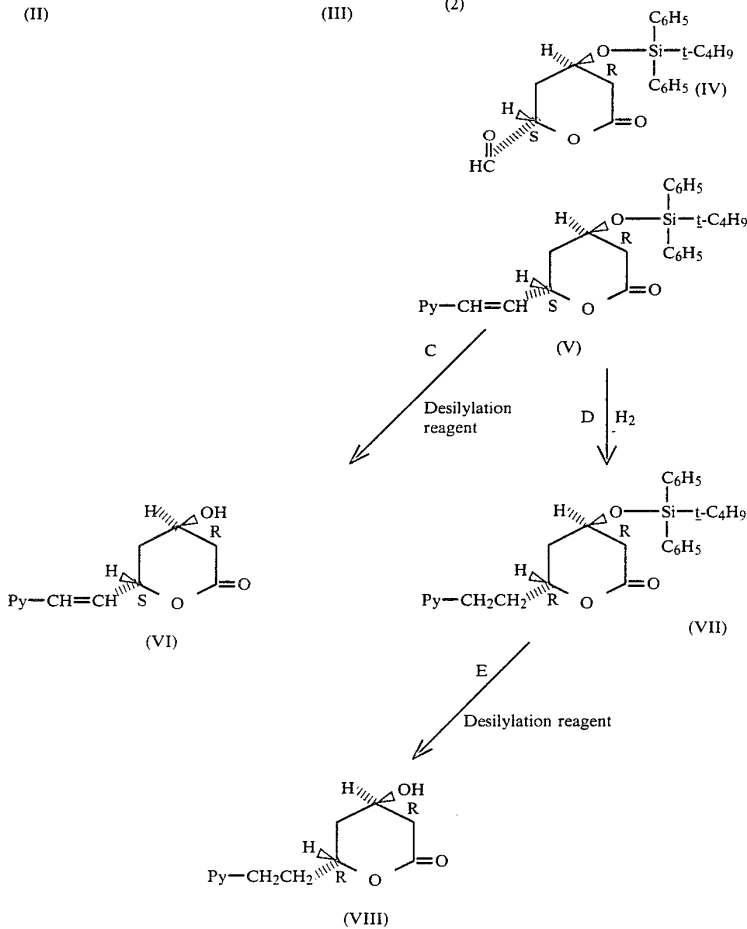
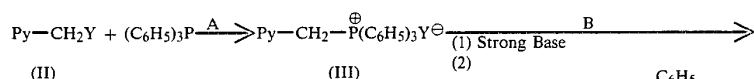
Groups (xxiii) and (xxiv) embrace the 4R,6S-4S,6R racemate and the 4R,6S and 4S,6R enantiomers, the 4S,6R enantiomer being least preferred.

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.

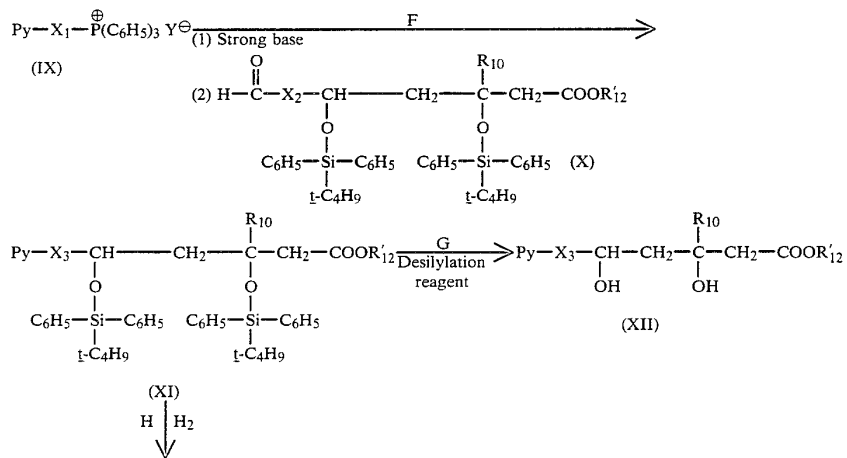
The compounds of Formula I may be synthesized as follows:

#### 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<sub>2</sub>CH<sub>2</sub>— and Z is a group of Formula b having the 4R,6R configuration may be synthesized by the following series of reactions:



45  $\text{CH}-\text{CH}_2-$  or  $-\text{CH}_2-\text{CH}=\text{CH}-$ , and Z is a group of Formula a wherein  $\text{R}_{11}$  is  $\text{R}_{12}'$  may be synthesized by the following series of reactions:



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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.