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Kathawala

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[54] **INTERMEDIATES IN THE SYNTHESIS OF INDOLE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF**

[75] Inventor: **Faizulla G. Kathawala**, Mountain Lakes, N.J.

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

[21] Appl. No.: **707,854**

[22] Filed: **Mar. 4, 1985**

Related U.S. Application Data

[63] Continuation of Ser. No. 548,850, Nov. 4, 1983, which is a continuation-in-part of Ser. No. 443,668, Nov. 22, 1982.

[51] **Int. Cl.**[4] **C07D 405/06**; C07D 209/12

[52] **U.S. Cl.** **548/406**; 548/414; 548/494

[58] **Field of Search** 548/465, 467, 494, 468, 548/414, 406

[56] **References Cited**

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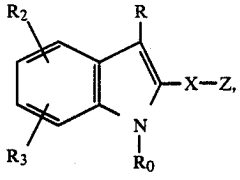
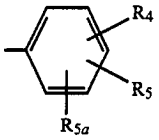
Primary Examiner—Donald G. Daus
Assistant Examiner—William A. Teoli, Jr.
Attorney, Agent, or Firm—Gerald D. Sharkin; Richard E. Vila; Melvyn M. Kassenoff

[57] **ABSTRACT**

Compounds of the formula



wherein one of R and R_o is



and the other is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-6}cycloalkyl or phenyl$(CH_2)_m$—, wherein

R_4 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and

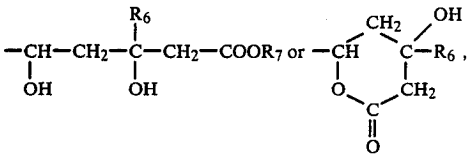
m is 1, 2 or 3, with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy, and not more than one of R_4 and R_5 is benzyloxy,

R_2 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{3-6}cycloalkyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,

X is $—(CH_2)_n—$ or —CH=CH—, wherein n is 0, 1, 2 or 3, and

Z is



wherein

R_6 is hydrogen or C_{1-3}alkyl, and

R_7 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, benzyl or M, wherein M is a pharmaceutically acceptable cation,

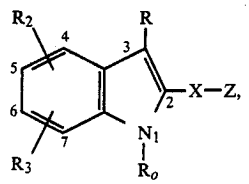
the use thereof for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level, and, therefore, in the treatment of hyperlipoproteinemia and atherosclerosis, pharmaceutical compositions comprising such compounds and processes for and intermediates in the synthesis of such compounds.

20 Claims, No Drawings

INTERMEDIATES IN THE SYNTHESIS OF INDOLE ANALOGS OF MEVALONOLACTONE AND DERIVATIVES THEREOF

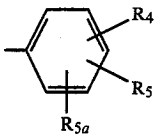
This application is a division of application Ser. No. 06/548,850, filed Nov. 4, 1983 and now abandoned, which in turn is a continuation-in-part of application Ser. No. 06/443,668, filed Nov. 22, 1982 and now abandoned.

This invention relates to compounds of the formula



(I)

wherein one of R and R_o is



and the other is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$—, wherein

R_4 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_5 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_{5a} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and

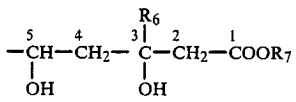
m is 1, 2 or 3, with the provisos that both R_5 and R_{5a} must be hydrogen when R_4 is hydrogen, R_{5a} must be hydrogen when R_5 is hydrogen, not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy, and not more than one of R_4 and R_5 is benzyloxy,

R_2 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{3-6}cycloalkyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that R_3 must be hydrogen when R_2 is hydrogen, not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more than one of R_2 and R_3 is benzyloxy,

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

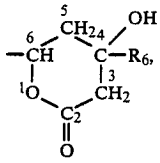
Z is



(II)

or

-continued



(III)

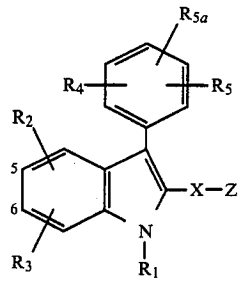
wherein

R_6 is hydrogen or C_{1-3}alkyl, and

R_7 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, benzyl or M, wherein M is a pharmaceutically acceptable cation,

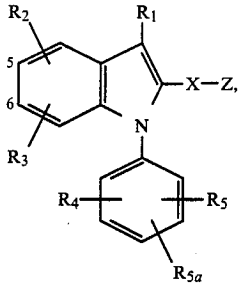
processes for and intermediates in the synthesis thereof, pharmaceutical compositions comprising a compound of Formula I and the use of the compounds of Formula I for inhibiting cholesterol biosynthesis and lowering the blood cholesterol level and, therefore, in the treatment of hyperlipoproteinemia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

The compounds of Formula I may be divided into two groups, the compounds of Formula IA and those of Formula IB:



(IA)

and



(IB)

wherein

R_1 is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, l-ethylpropyl, neopentyl and n-hexyl), C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$—, and

R_2–R_{5a}, X, Z and m are as defined above.

The compounds of Formula IA may be divided into two subgroups, the compounds wherein Z is a group of Formula II (Group IAa) and those wherein Z is a group of Formula III (Group IAb). Likewise, the compounds of Formula IB may be divided into two subgroups, the compounds wherein Z is a group of Formula II (Group IBa) and those wherein Z is a group of Formula III (Group IBb).

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 II

and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of Fromula III) and, therefore, there are four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers), provided that M 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.

R_1 is preferably R_1', where R_1' is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom, more preferably C_{1-3}alkyl and most preferably methyl, ethyl or i-propyl, especially i-propyl.

R_2 is preferably R_2', where R_2' is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_2'', where R_2'' is hydrogen, C_{1-3}alkyl, methoxy, fluoro, chloro or 4-, 5- or 6-benzyloxy, and most preferably R_2''', where R_2''' is hydrogen, C_{1-3}alkyl or 4- or 6-benzyloxy, especially hydrogen or methyl and most especially hydrogen.

R_3 is preferably R_3', where R_3' is hydrogen, C_{1-3}alkyl, C_{1-2}alkoxy, fluoro or chloro, more preferably R_3'', where R_3'' is hydrogen or C_{1-3}alkyl, and most preferably R_3''', where R_3''' is hydrogen or methyl, especially hydrogen. R_3 (R_3', etc.) must be hydrogen when R_2 (R_2', etc.) is hydrogen.

Preferably, when R_2 (R_2', R_2'', etc.) is other than hydrogen and R_3 (R_3', R_3'', etc.) is hydrogen, R_2 (R_2', etc.) is in the 4-, 5- or 6-position.

Preferably, when both R_2 (R_2', R_2'', etc.) and R_3 (R_3', R_3'', etc.) are other than hydrogen, at least one of them is in the 5- or 6-position, neither of them is in the 7-position, and not more than one of them is a member of the group consisting of t-butyl, C_{3-6}cycloalkyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, they are not ortho to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. Most preferably, one is in the 4-position and the other is in the 6-position.

Except where otherwise indicated: (a) Any C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or C_{3-6}cycloalkyl group as R_2, R_2', R_3, R_3', etc. is more preferably in the 4- or 6-position. (b) Any C_{1-3}alkoxy, n-butoxy, i-butoxy, fluoro or chloro substituent as R_2, R_2', R_3, R_3', etc. is more preferably in the 5-position. (c) Any benzyloxy as R_2, R_2', R_3, R_3', etc. is more preferably in the 4-, 5- or 6-position and most preferably in the 4- or 6-position, especially the 6-position.

R_4 is preferably R_4', where R_4' is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, more preferably R_4'', where R_4'' is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_4''', where R_4''' is hydrogen, methyl or fluoro, especially R_4'''', where R_4'''' is hydrogen, 3- or 4-methyl or 4-fluoro and most especially 4-fluoro.

R_5 is preferably R_5', where R_5' is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, more preferably R_5'', where R_5'' is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably R_5''', where R_5''' is hydrogen or methyl, especially hydrogen. R_5 (R_5', R_5'', etc.) must be hydrogen when R_4 (R_4', R_4'', etc.) is hydrogen.

R_{5a} is preferably R_{5a}', where R_{5a}' is hydrogen or methyl, and most preferably hydrogen. R_{5a} (R_{5a}', etc.) must be hydrogen when at least one of R_4 (R_4', R_4'', etc.) and R_5 (R_5', R_5'', etc.) is hydrogen.

Preferably, when R_4 (R_4', R_4'', etc.) is other than hydrogen and R_5 (R_5', R_5'', etc.) and R_{5a} (R_{5a}', etc.) are both hydrogen, R_4 (R_4', etc.) is in a meta or para position, more preferably the para position. The most preferred monosubstituted phenyl group is 4-fluorophenyl.

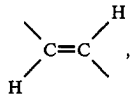
Preferably, when both R_4 (R_4', R_4'', etc.) and R_5 (R_5', R_5'', etc.) are other than hydrogen and R_{5a} (R_{5a}', etc.) is hydrogen, at least one of R_4 (R_4', etc.) and R_5 (R_5', etc.) is in a meta or para position (more preferably both are), and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy; more preferably, R_4 (R_4', etc.) and R_5 (R_5', etc.) are not ortho to each other when neither of them is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred disubstituted phenyl groups are 3,4- and 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl, especially 3,5-dimethylphenyl and 4-fluoro-3-methylphenyl.

Preferably, when each of R_4 (R_4', etc.), R_5 (R_5', etc.) and R_{5a} (R_{5a}', etc.) is other than hydrogen, at least two of them (more preferably all three) are in meta or para positions, and not more than one of them is a member of the group consisting of t-butyl trifluoromethyl, phenoxy and benzyloxy; more preferably, no two of them are ortho to each other unless at least one member of the or each pair of substituents that are ortho to each other is a member of the group consisting of methyl, methoxy, fluoro and chloro. The most preferred trisubstituted phenyl group is 3,5-dimethyl-4-fluorophenyl.

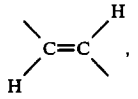
R_6 is preferably R_6', where R_6' is hydrogen or C_{1-2}alkyl, more preferably R_6'', where R_6'' is hydrogen or methyl, and most preferably hydrogen.

R_7 is preferably R_7', where R_7' is hydrogen, C_{1-3}alkyl or M, more preferably R_7'', where R_7'' is hydrogen, C_{1-2}alkyl or M, and most preferably M, especially sodium. M is preferably M' and more preferably sodium.

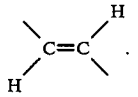
X is preferably X', where X' is $-(CH_2)_m-$ or



more preferably X'', where X'' is $-CH_2CH_2-$ or



especially



Z is preferably a group of Formula II wherein R_6 is R_6' and R_7 is R_7' or a group of Formula III wherein R_6 is R_6'; more preferably a group of Formula II wherein R_6 is R_6'' and R_7 is R_7'' or a group of Formula III wherein R_6 is R_6'' and most preferably a group of Formula II wherein R_6 is hydrogen and R_7 is R_7'' or a group of Formula III wherein R_6 is hydrogen, especially a group of Formula II wherein R_6 is hydrogen and R_7 is M, especially M' and most especially sodium, or a group of Formula III wherein R_6 is hydrogen.

n is preferably m, where m is 1, 2 or 3, preferably 2 or 3 and most preferably 2.

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

Insofar as the compounds of Groups IAa and IBa are concerned, the erythro isomers are generally 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 II).

As between compounds of Formula I having identical R, R_o, R_2, R_3, R_6 and X groups, those wherein Z is a group of Formula II are generally preferred over those wherein Z is a group of Formula III.

The preferred stereoisomers of the compounds of Formula I wherein X is a direct bond or —CH=CH—, and Z is a group of Formula II are the 3R,5S and 3R,5R isomers and the racemate of which each is a constituent, i.e., the 3R,5S-3S,5R (erythro) and 3R,5R-3S,5S (threo) racemates, with the 3R,5S isomer and the racemate of which it is a constituent being more preferred and the 3R,5S isomer being most preferred.

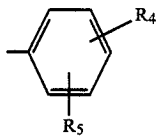
The preferred stereoisomers of the compounds of Formula I wherein X is $—(CH_2)_m—$, and Z is a group of Formula II are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, i.e., the 3R,5R-3S,5S (erythro) and 3R,5S-3S,5R (threo) racemates, with the 3R,5R isomer and the racemate of which it is a constituent being more preferred and the 3R,5R isomer being most preferred.

The preferred stereoisomers of the compounds of Formula I wherein X is a direct bond or —CH=CH—, and Z is a group of Formula III 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.

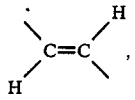
The preferred stereoisomers of the compounds of Formula I wherein X is $—(CH_2)_m—$, and Z is a group of Formula III are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, i.e., the 4R,6R-4S,6S (trans lactone) and 4R,6S-4S,6R (cis lactone) racemates, with the 4R,6R isomer and 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 and IB and those of Groups IAa, IAb, IBa and IBb as well as to every other subgroup thereof set forth infra, e.g., Groups (i)–(cxiv), unless otherwise indicated. When any preference contains a variable, the preferred significances of that variable apply to the preference in question, unless otherwise indicated.

Representative groups of compounds of Formulae I, Ia and Ib and of Groups IAa, IAb, IBa and IBb include those of each of these seven groups wherein one of R and R_o is



and the other is C_{1-3}alkyl, n-butyl or i-butyl, R_1 is C_{1-3}alkyl, n-butyl or i-butyl, R_2 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, R_4 is other than t-butyl, R_{5a} is hydrogen, and X is $—(CH_2)_n—$ or



each of the other variables being as defined above.

Preferred groups of compounds of Formula I include the compounds

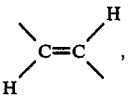
(i) of Group IAa wherein R_1 is R_1', R_2 is R_2', R_3 is R_3', R_4 is R_4', R_5 is R_5', R_{5a} is R_{5a}', R_6 is R_6', R_7 is R_7', and X is X′,

(ii) of (i) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a meta or para position; and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

(iii)–(iv) of (i) and (ii) wherein R_6 is R_6'', especially hydrogen,

(v)–(vi) of (i) and (ii) wherein R_1 is C_{1-3}alkyl, 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'', especially hydrogen, R_7 is R_7'', and X is X″,

(vii) of (i) wherein R_1 is C_{1-3}alkyl, R_2 is R_2''', R_3 is R_3''', R_4 is R_4''', R_5 is R_5''', R_{5a} is hydrogen, R_6 is hydrogen, R_7 is R_7'', and X is



(viii)–(xiii) of (i)–(vi) wherein any M is M′,

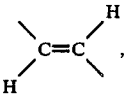
(xiv) of Group IAb wherein R_1 is R_1', R_2 is R_2', R_3 is R_3', R_4 is R_4', R_5 is R_5', R_{5a} is R_{5a}', R_6 is R_6', and X is X′,

(xv) of (xiv) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a meta or para position; and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

(xvi)–(xvii) of (xiv) and (xv) wherein R_6 is R_6'', especially hydrogen,

(xviii)–(xix) of (xiv) and (xv) wherein R_1 is C_{1-3}alkyl, 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'', especially hydrogen, and X is X″,

(xx) of (xiv) wherein R_1 is C_{1-3}alkyl, R_2 is R_2'', 'R_3 is R_3''', R_4 is R_4''', R_5 is R_5''', R_{5a} is hydrogen, R_6 is hydrogen, and X is



(xxi) of Group IBa 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_{5a} is R_{5a}', R_6 is R_6', R_7 is R_7', and X is X',

(xxii) of (xxi) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both R_2' and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a meta or para position; and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

(xxiii)–(xxiv) of (xxi) and (xxii) wherein R_6 is R_6'', especially hydrogen,

(xxv)–(xxvi) of (xxi) and (xxii) wherein R_1 is C_{1-3}alkyl, 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'', especially hydrogen, R_7 is R_7'', and X is X'',

(xxvii)–(xxxii) of (xxi)–(xxvi) wherein any M is M',

(xxxiii) of Group IBb 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_{5a} is R_{5a}', R_6 is R_6', and X is X',

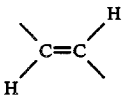
(xxxiv) of (xxxiii) wherein when R_2' is other than hydrogen and R_3' is hydrogen, R_2' is in the 4-, 5- or 6-position; when both $R_2'$and R_3' are other than hydrogen, at least one of them is in the 5- or 6-position and neither of them is in the 7-position; when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a meta or para position; and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in meta or para positions,

(xxxv)–(xxxxvi) of (xxxiii) and (xxxiv) wherein R_6 is R_6'', especially hydrogen,

(xxxvii)–(xxxviii) of (xxxiii) and (xxxiv) wherein R_1 is C_{1-3}alkyl, 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'', especially hydrogen, and X is X'',

(xxxix)–(lxiii) of (i)–(xiii) and (xxi)–(xxxii) wherein the hydroxy groups in the 3- and 5-positions (of the group of Formula II) have the erythro configuration,

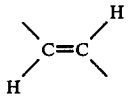
(lxiv)–(lxxxviii) the 3R,5S enantiomers of the compounds of (xxxix)-(lxiii) wherein X is



and the 3R,5R enantiomers of the compounds of these groups wherein X is $-(CH_2)_m-$,

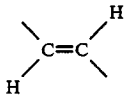
(lxxxix)–(ci) of (xiv)–(xx) and (xxxiii)–(xxxviii) wherein the hydroxy group on the lactone ring is trans to X (i.e., the trans lactones), and

(cii)–(cxiv) the 4R,6S enantiomers of the compounds of (lxxxix)–(ci) wherein X is



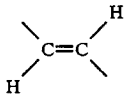
and the 4R,6R enantiomers of the compounds of these groups wherein X is $-(CH_2)_m-$.

Groups (xxxix)–(lxiii) embrace the 3R,5S-3S,5R racemate and the 3R,5S and 3S,5R enantiomers of the compounds wherein X is



(the 3S,5R enantiomer being least preferred) and the 3R,5R-3S,5S racemate and the 3R,5R and 3S,5S enantiomers of the compounds wherein X is $-(CH_2)_m-$ (the 3S,5S enantiomer being least preferred).

Groups (1xxxix)–(ci) embrace the 4R,6S-4S,6R racemate and the 4R,6S and 4S,6R enantiomers of the compounds wherein X is

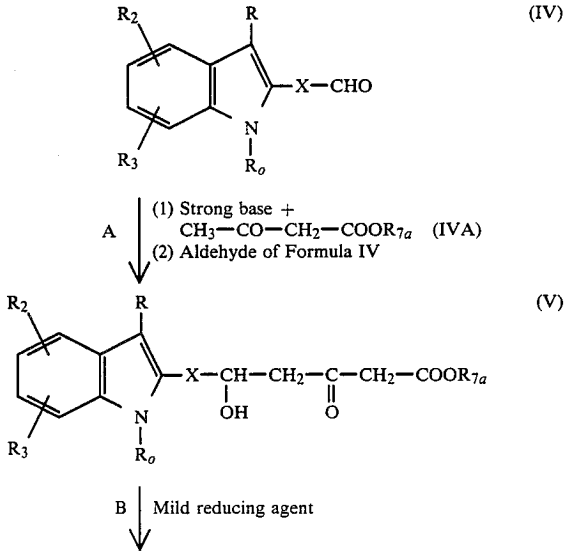


(the 4S,6R enantiomer being least preferred) and the 4R,6R-4S,6S racemate and the 4R,6R and 4S,6S enantiomers of the compounds wherein X is $-(CH_2)_m-$ (the 4S,6S enantiomer being least preferred).

The compounds of Formula I may be synthesized as follows:

REACTION SCHEME I

The compounds of Formula I wherein R_6 is hydrogen may be synthesized by the following series of reactions:



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