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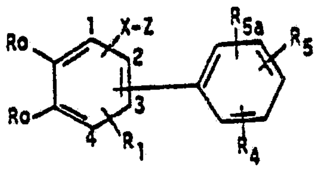

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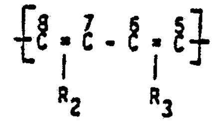

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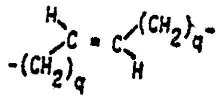

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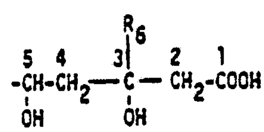

(IV)

(57) Abstract

Compounds of formula (I), wherein the two groups Ro together form a radical of formula (II) or $-(CH_2)_4-$, wherein R_2 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, (except t-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 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 that one of R_2 and R_3 is benzyloxy, R_1 is hydrogen, C_{1-6} alkyl, fluoro, chloro or benzyloxy, R_4 is hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, (except t-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 with the provisos that 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, is $-(CH_2)_n-$, formula (III), wherein n is 0, 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1, Z is formula (IV), wherein R_6 is hydrogen or C_{1-3} alkyl, with the general proviso that -X-Z and the R_4 bearing phenyl group are ortho to each other; in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester of a δ lactone thereof or in salt form. The compounds possess pharmacological properties and are indicated for use as pharmaceuticals, e.g. in inhibiting cholesterol biosynthesis or treating atherosclerosis.

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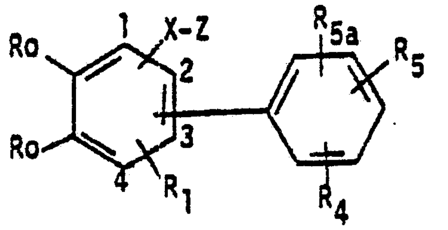
Mevalonolactone analogs, their preparation and pharmaceutical compositions.

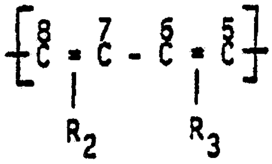
The invention concerns naphthalene and tetrahydronaphthalene analogs of mevalonolactone and derivatives thereof, processes for their production, pharmaceutical compositions containing them and their use as pharmaceuticals in particular as hypolipoproteinemic and anti-atherosclerotic agents.

The invention is especially concerned with compounds of formula I



I

wherein the two groups Ro together form a radical of formula

 or $-(CH_2)_4-$,

wherein R_2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-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 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 that one of R_2 and R_3 is benzyloxy,

R_1 is hydrogen, C_{1-6}alkyl, fluoro, chloro or benzyloxy,

R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-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

with the provisos that 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,

X is $-(CH_2)_n-$, $-(CH_2)_q-C(H)=C(H)-(CH_2)_q-$

wherein n is 0, 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1

Z is

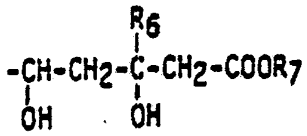
$$\overset{5}{-\underset{\displaystyle OH}{CH}}-\overset{4}{CH_2}-\overset{3}{\underset{\displaystyle OH}{\overset{\displaystyle R_6}{C}}}-\overset{2}{CH_2}-\overset{1}{COOH} \qquad II$$

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

with the general proviso that -X-Z and the R_4 bearing phenyl group are ortho to each other;

in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a δ lactone thereof or in salt form.

By the term "physiologically-hydrolysable and -acceptable ester" is meant an ester of a compound in accordance with the invention in which the carboxyl moiety is esterified, and which is hydrolysable under physiological conditions to yield an alcohol which is itself physiologically acceptable, e.g. non-toxic at desired dosage levels. Preferred such esters as Z can be represented together with the free acid by formula IIa

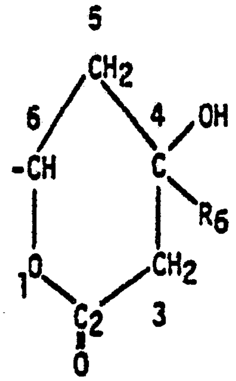


IIa

wherein R_7 is hydrogen, C_{1-4}alkyl or benzyl preferably hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl and R_6 is as defined above.

When in salt form R_7 represents a cation.

When Z is in lactone form it forms a δ-lactone of formula IIb



IIb

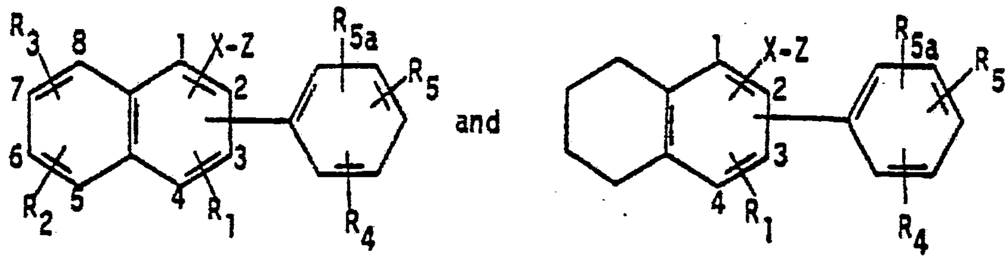
and references to "lactone" hereinafter refer to δ-lactones.

Salts of the compounds of the invention, e.g. of the compounds of formula I, include in particular their pharmaceutically acceptable salts. Such pharmaceutically acceptable salts include e.g. alkali metal salts such as the sodium and potassium salts and ammonium salts.

X-Z, R_1 and the R_4-bearing phenyl ring occupy any of positions 1 to 4 subject to the proviso that X-Z and the R_4-bearing phenyl group are <u>ortho</u> to each other. R_2 and R_3 occupy any of positions 5 to 8.

References to compounds of formula I, II and sub-species thereof are intended to cover all forms unless otherwise stated.

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



(IA) (IB)

wherein R_1 to R_{5a}, X and Z are as defined above.

The compounds of formula IA may be divided into two sub-groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IAa) and those wherein Z is a group of formula IIb(Group IAb). Likewise, the compounds of formula IB may be divided into two sub-groups, the compounds wherein Z is a group of formula II in other than lactone form (Group IBa) and those wherein Z is a group of formula IIb (Group IBb).

Each of those four sub-groups may be further divided into three further sub-groups, viz., the compounds wherein the -X-Z group is in the 1-position and the R_4-bearing phenyl group is in the 2-position (Groups IAa1, IAb1, IBa1 and IBb1), the compounds wherein the -X-Z group is in the 2-position and the R_4-bearing phenyl group is in the 1-position (Groups IAa2, IAb2, IBa2, IBb2) and the compounds wherein the -X-Z group is in the 2-position and the R_4-bearing phenyl group is in the 3-position (Groups IAa3, IAb3, IBa3 and IBb3).

As is self-evident to those in the art, each compound of formula I (and every sub-scope and species thereof) has at least two centers of asymmetry (e.g. the two carbon atoms bearing the hydroxy groups in the group of formula IIa and the carbon atom bearing the hydroxy group and the carbon atom having the free valence in the group of formula IIb) and these lead (e.g. with two centers) to four stereoisomeric forms (enantiomers) of each compound (two racemates or pairs of diastereoisomers). In the preferred compounds having only two such centers of asymmetry these 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. Depending on the nature of substituents further asymmetric carbon atoms may be present and the resulting isomers and mixtures thereof also form part of the invention. Compounds containing only two centers of asymmetry (four mentioned stereoisomers) are preferred.

R_1 is preferably R_1', where R_1' is hydrogen, C_{1-6}alkyl not containing an asymmetric carbon atom or chloro, more preferably R_1'', where R_1'' is hydrogen or C_{1-3}alkyl, and most preferably R_1''', where R_1''' is hydrogen, C_{1-2}alkyl or isopropyl.

Preferably, R_1 (R_1' etc.), when other than hydrogen, is in the 3-position in compounds of Groups IAa2, IAb2, IBa2 and IBb2 and in

Alkyl as R_2 is preferably C_{1-3} or n-, i- or t-butyl and alkoxy C_{1-3} or n- or i-butoxy.

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, methyl, methoxy, fluoro or chloro, 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, more preferably R_3'', where R_3'' is hydrogen, methyl, methoxy, fluoro or chloro, and most preferably hydrogen.

Preferably, when both R_2 and R_3 are other than hydrogen, at least one of them is in the 6- or 7-position and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy.

Alkyl as R_4 is preferably C_{1-3} or n-, i- or t-butyl and alkoxy C_{1-3} or n- or i-butoxy.

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 or fluoro, especially hydrogen 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 hydrogen.

R_{5a} is preferably R_{5a}', where R_5' is hydrogen or methyl and most preferably 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', 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.

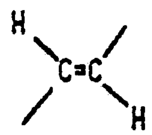
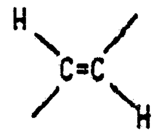
Preferably, when each of R_4 (R_4', etc.), R_5 (R_5', etc.) and R_{5a} (R_{5a}', etc.) is other than hydrogen, at least two of them (more preferably all three) are in meta or para positions, and not more than one of them is a member of the group consisting of t-butyl, trifluoromethyl, phenoxy and benzyloxy;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

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 or C_{1-3}alkyl more preferably R_7'' is hydrogen or C_{1-2}alkyl.

Compounds of formula I wherein Z is of formula II or IIa are most preferably in salt form. Preferred salt-forming cations are those free from centers of asymmetry especially e.g. sodium, potassium or ammonium most preferably sodium.

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


, wherein m is 1, 2 or 3, especially

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Z is preferably a group of formula IIa wherein R_6 is R_6' and R_7 is R_7' or a group of formula IIb wherein R_6 is R_6', more preferably a group of formula IIa wherein R_6 is R_6'' and R_7 is R_7'' or a group of formula IIb wherein R_6 is R_6'' and most preferably a group of formula IIa wherein R_6 is hydrogen and R_7 is R_7'' or a group of formula IIb wherein R_6 is hydrogen, especially a group of formula IIa in sodium salt form wherein R_6 is hydrogen or a group of formula IIb wherein R_6 is hydrogen.

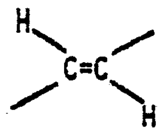
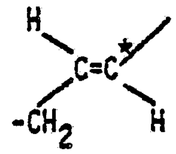
n is preferably m, where m is 1, 2 or 3, preferably 2 or 3 and most preferably 2.

Insofar as the compounds of Groups IAa and IBa and each of the sub-groups 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 II and IIa).

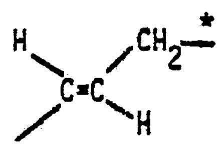
As between otherwise identical compounds of formula I, free acid, salt and ester forms are generally preferred to lactone forms.

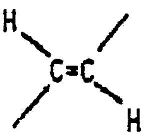
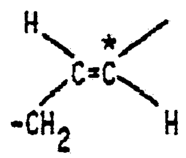
The trans lactones are generally preferred over the cis lactones, cis and trans referring to the relative positions of R_6 and the hydrogen atom in the 6-position of the group of formula IIb.

The preferred stereoisomers of the compounds of formula I having only two centers of asymmetry wherein X is a direct bond,

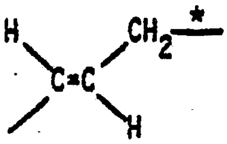
 or , wherein the * denotes the bond to the Z group, and Z is in other than lactone form are the 3R,5S and 3R,5R isomers and the racemate of which each is a constituent, i.e., the 3R,5S-3S,5R (erythro) and 3R,5R-3S,5S (threo) racemates, with the 3R,5S isomer and the racemate of which it is a constituent being more preferred and the 3R,5S isomer being most preferred.

The preferred stereoisomers of the compounds of formula I having only two centers of asymmetry wherein X is

$-(CH_2)_m-$ or , and Z is in other than lactone form 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 having only two centers of asymmetry wherein X is a direct bond,  or , wherein the * denotes the bond to the Z group, and Z is a group of Formula IIb 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 having only two centers of asymmetry wherein X is $-(CH_2)_m-$ or



, and Z is a group of formula IIb 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.

The preferences set forth in the preceding four 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.

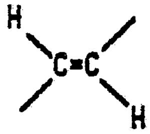
Each of the preferences set forth above applies not only to the compounds of formula I, but also to the compounds of formulae IA and IB and those of Groups IAa, IAb, IBa, IBb, IAa1, IAa2, IAa3, IAb1, IAb2, IAb3, IBa1, IBa2, IBa3, IBb1, IBb2 and IBb3 as well as to every other subgroup thereof set forth infra, e.g. Groups (i) et seq., unless otherwise indicated. When any preference contains a variable, the preferred significances of that variable apply to the preference in question, unless otherwise indicated.

Preferred groups of compounds of formula I include the compounds

(i) of Group IAa1 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 both R_2' and R_3' are other than hydrogen, at least of of them is in the 6- or 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' and R_{5a}' 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 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 hydrogen, R_6 is R_6'', especially hydrogen, R_7 is R_7'' and X is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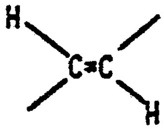
(vii) of (i) wherein R_1 is R_1''', R_2 is hydrogen, R_3 is hydrogen, R_4 is R_4''', R_5 is hydrogen, R_{5a} is hydrogen, R_6 is hydrogen, R_7 is R_7'', and X is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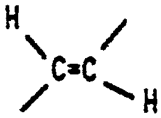
(viii)-(xiii) of (i)-(vi) wherein any salt form is preferably a sodium, potassium or ammonium, especially a sodium salt form.

(xiv) of Group IAbl 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',

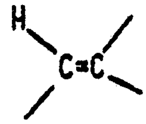
(xv) of (xiv) wherein when both R_2' and R_3' are other than hydrogen, at least one of them is in the 6- or 7-position, when both R_4' and R_5' are other than hydrogen and R_{5a}' is hydrogen, at least one of R_4' and R_5' is in a <u>meta</u> or <u>para</u> position; and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in <u>meta</u> or <u>para</u> 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 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 hydrogen, R_6 is R_6'', especially hydrogen, and X is


,

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



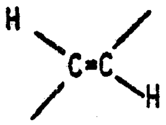
,

(xxi) of Group IBa1 wherein R_1 is R_1', R_4 is R_4', R_5 is R_5', R_{5a}, R_6 is R_6', R_7 is R_7', and X is X',

(xxii) of (xxi) wherein 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 <u>meta</u> or <u>para</u> position, and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in <u>meta</u> or <u>para</u> positions,

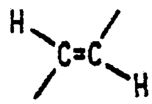
(xxiii)-(xxiv) of (xxi) and (xxii) wherein R_6 is R_6'', especially hydrogen,

(xxv)-(xxvi) of (xxi) and (xxii) wherein R_1 is R_1'', R_4 is R_4'', R_5 is R_5'', R_{5a} is hydrogen, R_6 is R_6'', especially hydrogen, R_7 is R_7'', and X is



,

(xxvii) of (xxi) wherein R_1 is R_1''', R_4 is R_4''', R_5 is hydrogen, R_{5a} is hydrogen, R_6 is hydrogen, R_7 is R_7'', and X is



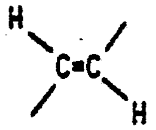
,

(xxviii)-(xxxiii) of (xxi)-(xxvi) wherein any salt form is preferably a sodium, potassium or ammonium, especially a sodium salt form.

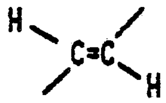
(xxxiv) of Group IBb1 wherein R_1 is R_1', R_4 is R_4', R_5 is R_5', R_{5a} is R_{5a}', R_6 is R_6', and X is X',

(xxxv) of (xxxiv) wherein 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 <u>meta</u> or <u>para</u> position, and when each of R_4', R_5' and R_{5a}' is other than hydrogen, at least two of them are in <u>meta</u> or <u>para</u> positions,

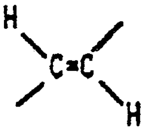
(xxxvi)-(xxxvii) of (xxxiv) and (xxxv) wherein R_6 is R_6'', especially hydrogen, (xxxviii)-(xxxix) of (xxxiv) and (xxxv) wherein R_1 is R_1", R_4 is R_4", R_5 is R_5", R_{5a} is hydrogen, R_6 is R_6", especially hydrogen, and X is

,

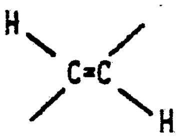
(xl) of (xxxiv) wherein R_1 is R_1"', R_4 is R_4"', R_5 is hydrogen, R_{5a} is hydrogen, R_6 is hydrogen, and X is

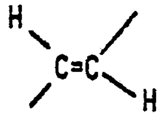
,

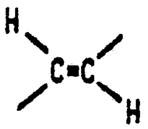
(xli)-(lxvi) of (i)-(xiii) and (xxi)-(xxxiii) wherein the hydroxy groups in the 3- and 5-positions (of the group of formula IIa) have the erythro configuration,

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

(xciii)-(cvi) of (xiv)-xx) and (xxxiv)-(xl) wherein the hydroxy group on the lactone ring is trans to X (the trans lactones) and

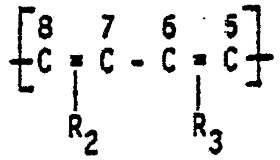
(cvii)-(cxx) the 4R,6S enantiomers of the compounds of (xciii)-(cvi) wherein X is  and the 4R,6R enantiomers of the compounds of these groups wherein X is $-(CH_2)_m-$.

Groups of (xli)-(lxvi) 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 (xciii)-(cvi) 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).

Insofar as Groups IAa2, IAb2, IBa2, IBb2, IAa3, IAb3, IBa3 and IBb3 are concerned, the preferred sub-groups are those that correspond to Groups (i)-(cxx). As should be evident, the preferred groups of compounds of Groups IAa2 and IAa3 are those that correspond to Groups (i)-(xiii), (xli)-(liii) and (lxvii)-(lxxix), the preferred groups of compounds of Groups IAb2 and IAb3 are those that correspond to Groups (xiv)-(xx), (xciii)-(xcix) and (cvii)-(cxiii), the preferred groups of compounds of Groups IBa2 and IBa3 are those that correspond to Groups (xxi)-(xxxiii), (liv)-(lxvi) and (lxxx)-(xcii) and the preferred groups of compounds of Groups IBb2 and IBb3 are those that correspond to Groups (xxxiv)-(xl), (c)-(cvi) and (cxiv)-(cxiv)-(cxx). It is as if each of these additional groups were set forth herein in its entirety.

A particular compound group covers those of formula I wherein the two Ro groups together form a radical of the formula

 or $-CH_2CH_2CH_2CH_2-$,

wherein 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_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

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, and not more than one of R_2 and R_3 is benzyloxy,

R_1 is hydrogen, C_{1-3}alkyl, fluoro, chloro or benzyloxy,

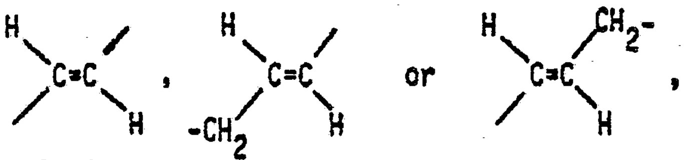
R_4 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

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

R_{5a} is hydrogen,

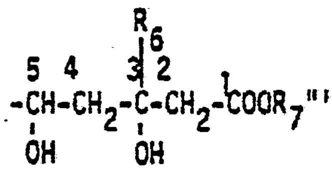
with the proviso that not more than one of R_4 and R_5 is trifluoromethyl, not more than one of R_4 and R_5 is phenoxy, and not more than one of R_4 and R_5 is benzyloxy,

X is $-(CH_2)_n-$,

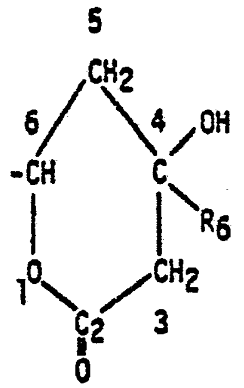


wherein n is 0, 1, 2 or 3, and

Z is



or



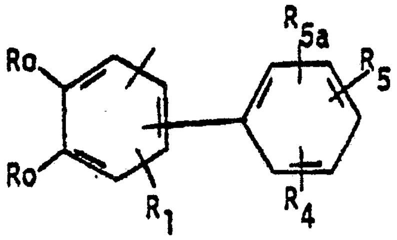
IIb ,

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,

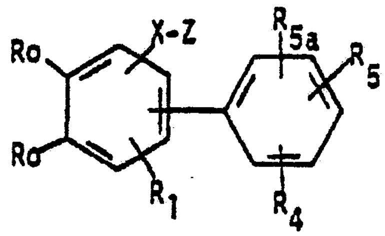
with the proviso that the -X-Z group and the R_4-bearing phenyl group are ortho to each other.

The compounds of formula I can be prepared by the following methods whereby

(BR) represents the basic ring structure

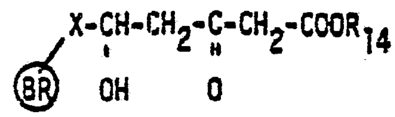


Ro, R_1, R_4, R_{5a} and R_5 as defined above. [Thus (BR)-X-Z stands for



]

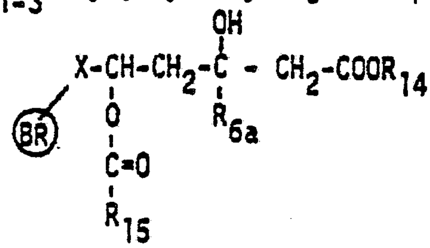
a) When R_6 is hydrogen reducing a compound of formula VI



VI

wherein R_{14} is a radical forming a physiologically-hydrolysable and acceptable ester and X, is as defined above,

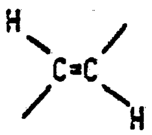
b) when R_6 = C_{1-3}alkyl, hydrolysing a compound of formula XVII



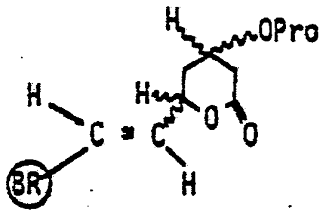
XVII

wherein R_{6a} is C_{1-3}alkyl, R_{15} is part of an ester forming group and X and R_{14} are as defined above,

c) when X is



deprotecting a compound of formula LIX



LVIII

wherein Pro is a protecting group

d) hydrolysing a compound of formula I in the form of a physiologically-hydrolysable ester or a lactone or

e) esterifying or lactonising a compound of formula I in free acid form, and when a free carboxyl group is present, recovering the compound obtained in free acid form or in the form of a salt. In processes a) and b) R_{14} is preferably C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl more preferably C_{1-3}alkyl, most preferably C_{1-2}alkyl and R_{15} is preferably C_{1-2}alkyl, in particular methyl.

It will readily be appreciated that the various forms of the compounds of formula I may interconverted as indicated in d) and e) above.

In the same way compounds obtained according to a), b), and c) may be hydrolysed to free acid forms and free acid forms may be esterified or lactonised to produce a desired end-product. The invention thus also provides a process for preparing a compound of formula I which comprises hydrolysing a compound of formula I in ester or lactone form or esterifying or lactonising a compound of formula I in free acid form and when a free carboxyl group is present recovering the compound obtained in free acid form or in the form of a salt.

Unless otherwise stated reactions are performed in a manner conventional for the type of reaction involved. Molar ratios and reaction times are as a rule conventional and non-critical and are chosen according to principles well established in the art on the basis of reactants and conditions employed.

Solvents, alone or as mixtures, are generally chosen which remain inert and liquid during the reaction in question.

Examples of inert atmospheres are carbon dioxide (some reactions) and more usually nitrogen or a nobel gas, nitrogen being preferred. Most reactions, including those wherein use of an inert atmosphere is not mentioned, are carried out under such for convenience.

Reduction according to a) is preferably carried out using a mild reducing agent such as sodium borohydride or, a complex of t-butylamine and borane in an inert organic solvent such as a lower alkanol, preferably ethanol, conveniently at a temperature of -10° to 30°C, under an inert atmopshere.

Use of an optically pure starting material will lead to only two optical isomers (diastereoisomers) of the resulting end product. However, if stereospecificity is desired it is preferred to utilize a stereoselective reduction in order to maximize production of a mixture of the erythro stereoisomers (racemate) of which the preferred stereoisomer (as set forth above) is a constituent. Stereoselective reduction is carried out in three steps. For example in the first step, the ketoester of formula V is treated with a tri(primary or secondary C_{2-4}alkyl)borane, preferably tri-n-butylborane, and air to form a complex. The reaction temperature is suitably 0° to 50°C, preferably 20° to 30°C. The first step is carried out in an anhydrous inert organic solvent, preferably an ether solvent such as tetrahydrofuran, diethyl ether, 1,2-dimethoxyethane or 1,2-diethoxyethane, with tetrahydrofuran, being the most preferred solvent. In the second step, for example, the complex is reduced with sodium borohydride, preferably in the same solvent as utilized for the first step, at -80° to -40°C, preferably -80° to -70°C. In the third step, the product of the second step is, for example, treated with, aqueous e.g. 30% H_2O_2, an aqueous buffer, preferably a phosphate buffer, to maintain a pH of 7.0 to 7.2, and a lower alkanol preferably methanol. The H_2O_2 is in large molar excess e.g. 50 to 70 moles per mole of VI. The reactants are added slowly to the mixture from step 2 at e.g. -80° to -40°C preferably -80° to -70°C with subsequent warming to 20° to 30°C.

Hydrolysis according to b) or d) is carried out in a manner conventional for such reactions e.g. employing an inorganic hydroxide such as NaOH or KOH with, if desired subsequent acidification to give the free acid form. Suitable solvents are mixtures of water and water miscible solvents such as lower alkanols e.g. methanol or ethanol and reaction conveniently takes place at temperatures from 20°C to reflux preferably not more than 80°C. most preferably 20° to 30°C. If it is desired to recover the compound in a salt form corresponding to the cation of the hydroxide employed then slightly less than equivalent amounts of the latter may be employed. In b) R_{12} will conveniently be the same as R_{15} e.g. C_{1-3}alkyl, especially C_{1-2}alkyl, preferably methyl.

Lactonisation according to e) is carried out in conventional manner e.g. by heating the corresponding acid in an anhydrous inert organic solvent e.g. a hydrocarbon such as benzene, toluene or a xylene or mixtures thereof, preferably at temperatures of 75°C to reflux although more preferably not above 150°C.

As is evident to those in the art, a racemic *threo* 3,5-dihydroxycarboxylic acid yields a racemic *cis* lactone and a racemic *erythro* 3,5-dihydroxycarboxylic acid yields a racemic *trans* lactone. Use of a mixture of *threo* and *erythro* 3,5-dicarboxylic acid yields a mixture of *cis* and *trans* lactones (all four possible diastereoisomers). Likewise if a single enantiomer of the 3,5-dihydroxycarboxylic acid is utilized, a single enantiomer of the lactone is obtained. For example, lactonisation of a 3R,5S *erythro* dihydroxycarboxylic acid yields a 4R,6S lactone.

Esterification according to e) is conventional employing e.g. a large excess of a compound R_{14}OH wherein R_{14} is as defined above at 20°C to 40°C optionally in a solvent (especially when R_{14}OH is not liquid) and in the presence of a catalytic amount of an acid such as *p*-toluenesulfonic acid. Where methyl esters are required these can also be obtained e.g. using diazomethane in an anhydrous inert ether solvent such as tetrahydrofuran, 1,2-dimethoxyethane or 1,2-diethoxyethane and especially diethylether at e.g. 0° to 30°C preferably 20° to 30°C.

Examples of protecting groups in reaction c) are diphenyl-t-butylsilyl, tri-isopropylsilyl or dimethyl-t-butylsilyl, C_{1-6}n-alkyl, benzyl, triphenylmethyl, tetrahydrofuran-2-yl, tetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, C_{1-6}n-alkanoyloxy. Especially preferred are trisubstituted silyl radicals in particular diphenyl-t-butylsilyl.

Deprotection is carried out in conventional manner e.g. by cleavage under mild conditions such as employing e.g. for removal of a silyl containing group such as diphenyl-t-butylsilyl a fluoride reagent e.g. tetra-n-butyl- ammonium fluoride in an anhydrous inert organic medium preferably tetrahydrofuran containing glacial acetic acid at temperagures of 20° to 60°C especially 20° to 30°C. Preferably 1-5 moles of fluoride are used per mole of silyl group with 1.2 to 1.8 moles of glacial acetic acid to each mole of fluoride.

The required starting materials may be prepared for example as illustrated in the following reaction schemes. The symbols used are defined as follows

R, R_0, R_1, R_2, R_3, R_4, R_5, R_{5a}, R_6, R_{6a}, R_{11}, R_{12}, X, (BR)* = as defined above,

M_2 = a cation preferably Na or K

R_{13} = C_{1-6}alkyl preferably C_{1-2}alkyl

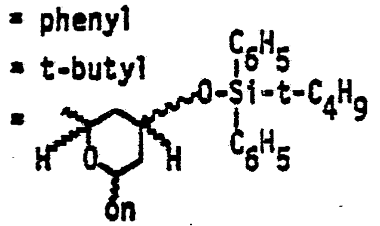
Y = chloro or bromo

Ac = acetyl

ϕ = phenyl

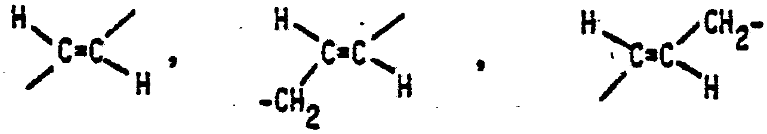
+ = t-butyl

1ac =

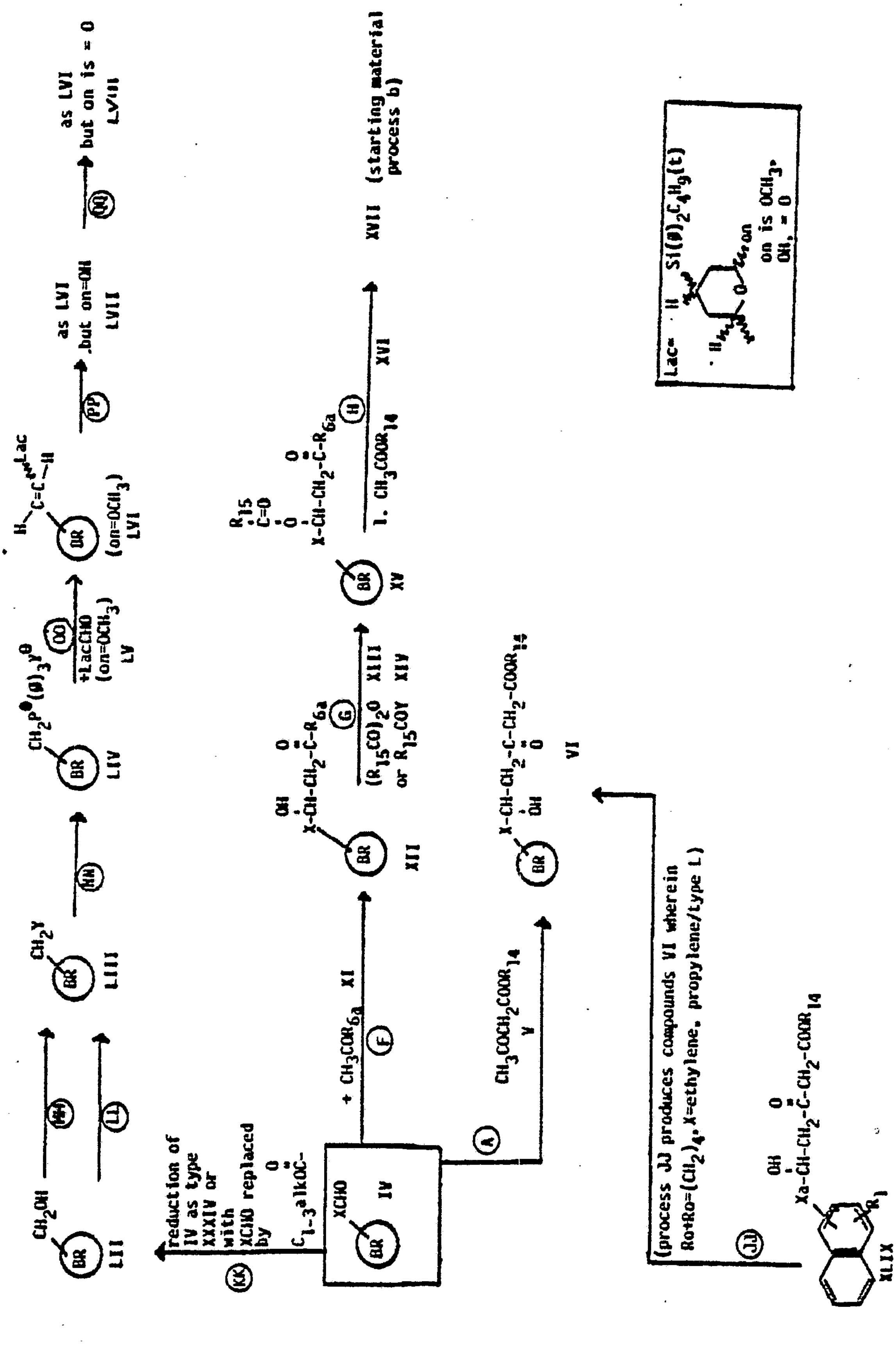


[on = OCH_3 (LVI), OH (LVII) or = O (LVIII)]

Xa =



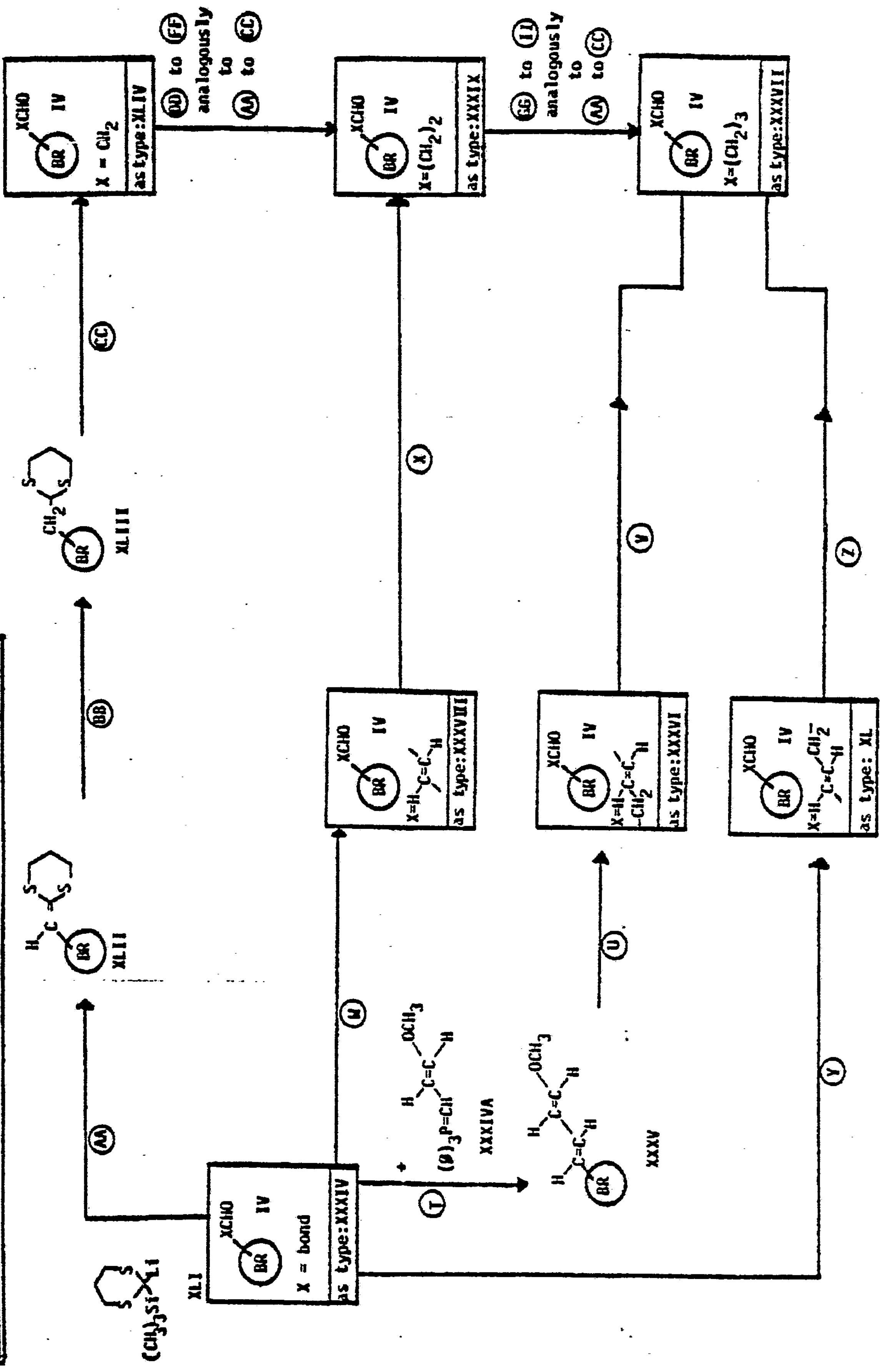
* = these substituents are ortho to each other.

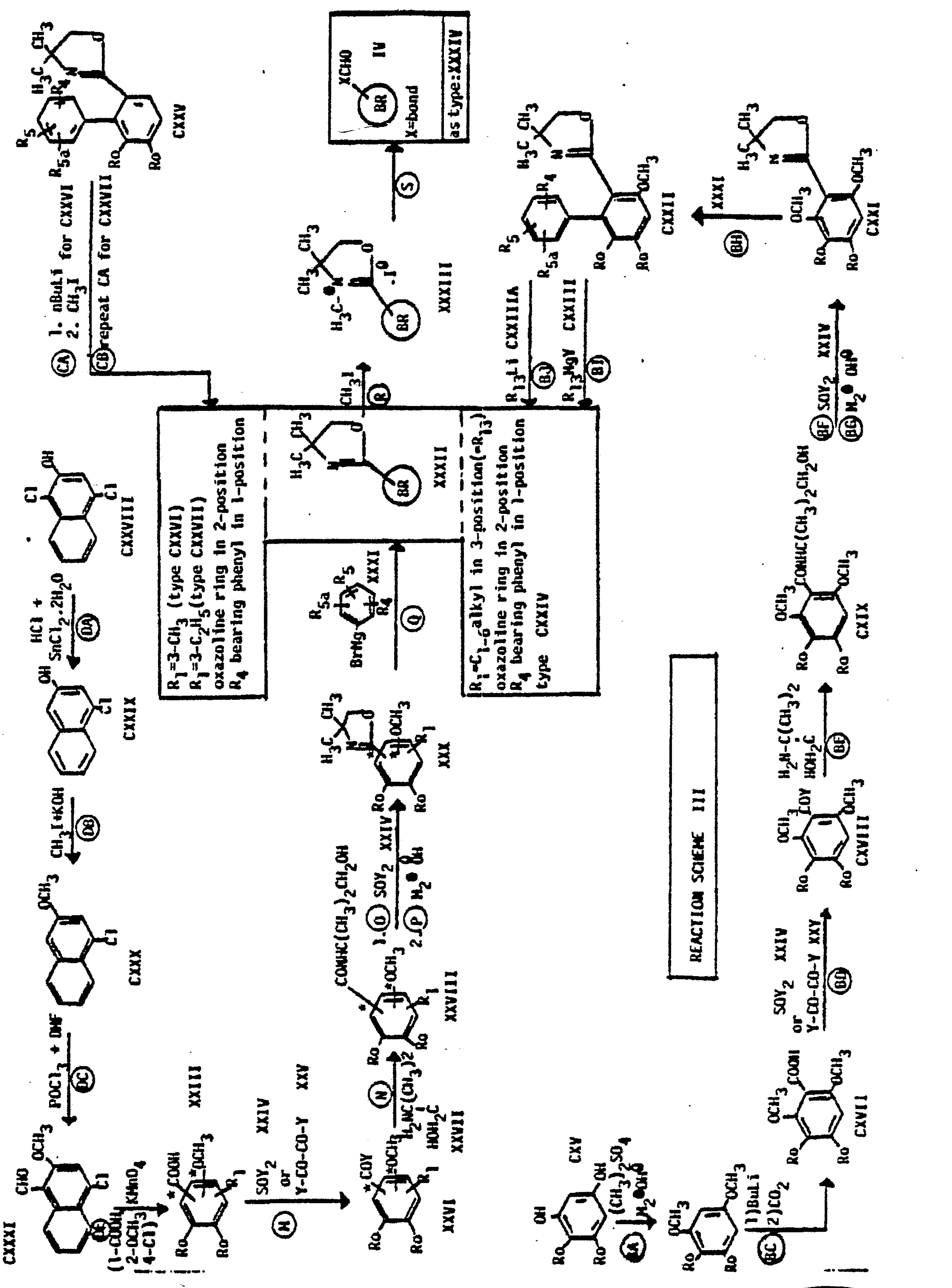


REACTION SCHEME I

REACTION SCHEME II

Interconversion of compounds IV

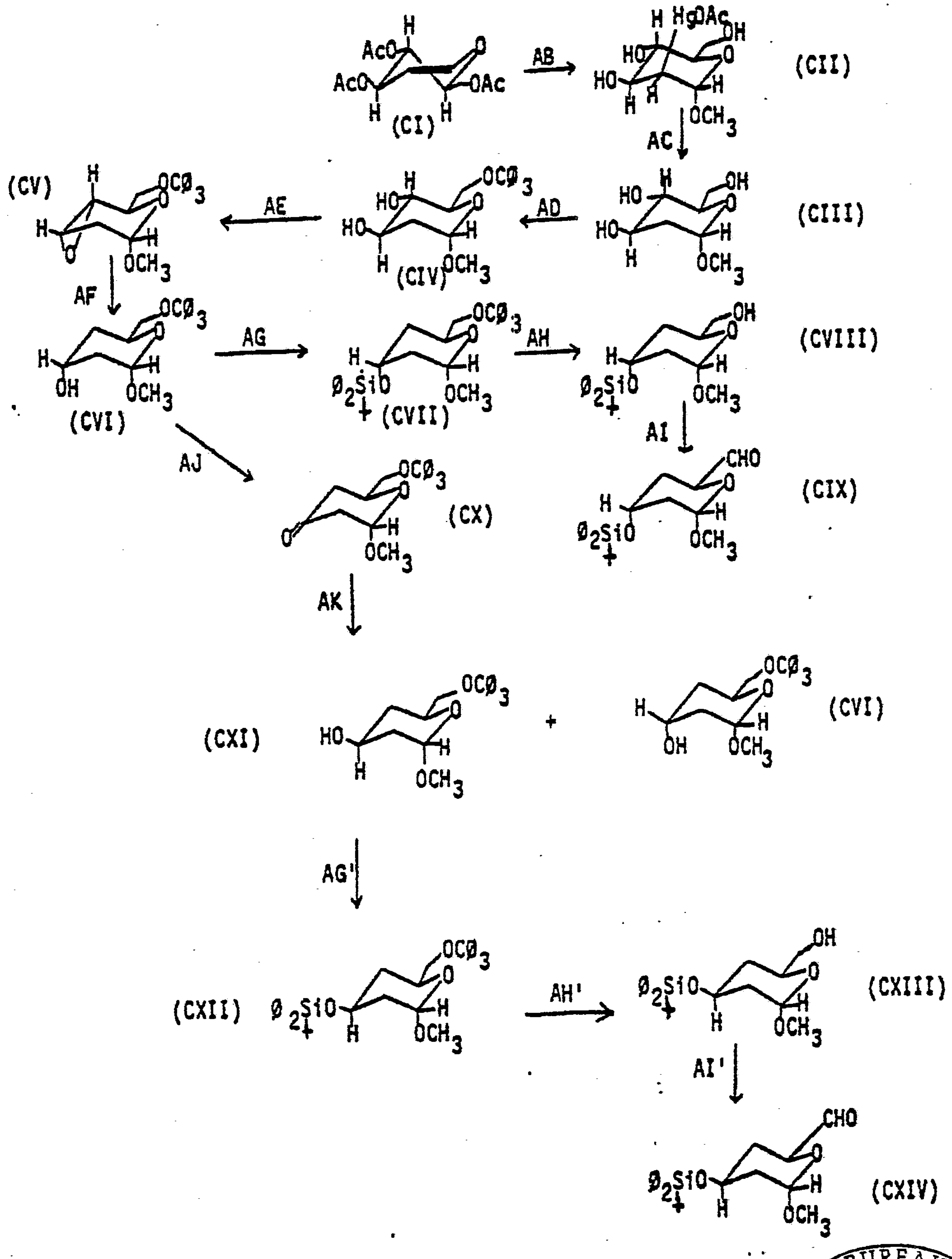




REACTION SCHEME III

Reaction Scheme IV

Two isomers of the compound of formula XXV may be synthesized by the following series of reactions:



Unless otherwise stated reactions are performed in a manner conventional for the type of reaction involved. Mol ratios and reaction times are as a rule conventional and non-critical and are chosen according to principles well established in the art on the basis of reactants and conditions employed.

Solvents, alone or as mixtures, are generally chosen which remain inert and liquid during the reaction in question.

Examples of inert atmospheres are carbon dioxide (some reactions) and more usually nitrogen or a noble gas, nitrogen being preferred. Most reactions, including those wherein use of an inert atmosphere is not mentioned, are carried out under such for convenince.

The following tables give examples of typical reaction conditions. In the reaction schemes temperatures are in degrees centigrade.

Abbreviations

THF (tetrahydrofuran)
DMF (dimethylformamide)
LDA (lithium diisopropylamide)
DEA (diethylacetamide)
BuLi (n-butyllithium)
TsOH (p-toluenesulfonic acid)
NCS (N-chlorosuccinimide)
NBS (N-bromosuccinimide)
DIBAH (diisobutylaluminium hydride)
DMSO (dimethylsulfoxide)

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
(A)	1. V + strong base 2. add IV	1. Strong base e.g. n-butyl lithium, lithium diisopropyl amide (LDA) and NaH (latter for generation of mono-anion only). Pref. LDA (generated in situ cf. Examples)	1. -50° to 10° esp. -5° to 5° 2. -80° to -20° esp. -50° to -20° pref. -40° to -30°	inert	Anhydrous e.g. THF, diethylether, 1,2-dimethoxy ethane, 1,2-diethoxy ethane Preferred THF
(F)	1. XI + strong base 2. add IV	1. Strong base e.g. LDA 2. Mol ratio XI to IV esp. 3:1	-80° to -40°	inert	as (A)
(G)	Esterification	base e.g. pyridine, triethylamine	20° to 50°		excess pyridine
(H)	1. XVI + strong base 2. add XV	1. Strong base e.g. LDA 2. Mol ratio XVI to XV esp. 3:1	1. -80° to 0° 2. -80° to -40° esp. -80° to -70°	inert	as (A) pref. THF
(K)	Halogenation	XXIV or XXV pref. in excess	50° to reflux pref. < 150°		Anhydrous hydrocarbon e.g. benzene toluene, xylene or mixture thereof
(N)	Amidation	XXVII pref. in excess	20° to 50° esp. 20° to 30°		Anhydrous e.g. halo carbon esp. CH_2CH_2
(O)	Cyclisation	XXIV pref. $SOCl_2$ in excess	0° to 75° esp. 20° to 30°		neat or more usually as (A) or CH_2Cl_2, $CHCl_3$ or CCl_4 esp. CH_2Cl_2

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
Ⓟ	Liberation	as hydroxide e.g. NaOH, KOH pref. in excess. Can be run directly from crude hydrohalide of Ⓞ	0° to 40° esp. 20° to 30°		H_2O or H_2O + e.g. CH_3OH or C_2H_5OH
Ⓠ	Grignard		10° to reflux esp. < 75° pref. 20° to 50°	inert	as Ⓐ pref. THF
Ⓡ	N-methylation	CH_3I pref. in large excess.	20° to reflux esp. < 100° pref. 55° to 90°		Anhydrous polar e.g. THF, 1,2-dimethoxyethane, 1,2-diethoxyethane, DMA, DEA pref. nitromethane
Ⓢ	Ring cleavage 1. Mild reducing agent 2. $H^{\oplus}$	1) $NaBH_4$ (1-1.1 mole), $LiBH_4$ (1.8-2.1 mole), 2) dil. aq. acid e.g. 2N HCl pref. in large excess	1) -40° to 10°C esp. 0° to 10° ($NaBH_4$) -40° to -20° ($LiBH_4$) 2) 0° to 100° esp. 20° to 100°		1) Anhydrous alkanol e.g. abs. C_2H_5OH optionally ether e.g. THF 2) e.g. as 1)
Ⓣ	Wittig	XXXIVA pref. generated form 3-methoxypropen-2-yl-tri-phenylphosphonium bromide + e.g. nBuLi	2) -80° to -30° esp. -60° to -40° with warming to 20° to 30°	inert	as Ⓐ pref. THF
Ⓤ	ether-cleavage $H^{\oplus}$	dil. acid e.g. 1N HCl in excess on crude solution from Ⓣ	reflux		as Ⓣ

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
(V) (X)	Hydrogenation	excess H_2 under pressure + Pd/C(pref. 5%) + $FeCl_2.4H_2O$ Termination after 1 mole H_2 taken up	20° to 30°C esp. 25°		1. alkanol e.g. CH_3OH
(W)	1. cis-1-Li-2-ethoxyethylene* 2) pTsOH *prepared e.g. as described in the examples.	1) pref. isolate prior to 2) 2) pTsOH in catalytic amounts.	1) -80° to -40° esp. -80° to -70° 2) 20° to 40° esp. 20°-30°	inert	anhydrous THF 2. H_2O + THF
(Y)	1. trans-2-methoxy cyclopropyl lithium 2. Methanesulfonyl-chloride 3. Hydrolysis	1) 2. tertiaryamine e.g. $N(C_2H_5)_3$ 3. e.g. ammonium hydrogen oxalate + oxalic acid (pref. 2 moles of each)	1) -80° to 25° (esp. start -78° and warm to 25°) 2) -60° to -20° esp. -40° 3) -50° to -30° esp. -40°	inert	1. Anhydrous e.g. THF, 1,2-dimethoxyethane, 1,2-diethoxyethane or pref. diethyl ether 2. Anhydrous e.g. halocarbon e.g. CH_2Cl_2 3. e.g. excess acetone and water
(Z)	Hydrogenation	excess H_2 under pressure + Pd/C (pref. 5%) Termination as V	20°-30°		Anhydrous ℓ. alkanol e.g. ethanol

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
(AA)	2-Li-2-trimethyl-silyl-1,3-dithiane*	*Prepared from 2-trimethylsilyl-1,3-dithiane and n-BuLi/n-hexane	-10° to 30°	inert	as (A) esp. THF
(BB)		anhydrous CF_3COOH + $(C_2H_5)_3SiH$	0° to 50° esp. 20° to 30°		as (N)
(CC)		N-chlorosuccinimide of (NBS) or pref. N-bromosuccinimide (NCS) in excess	0° to 50° esp. 20° to 30°		H_2O + acetonitrile
(JJ)	Hydrogenation	excess H_2 under pressure + PtO_2 until 3 moles taken up	20° to 30°		glacial CH_3COOH
(KK)	Reduction	a) $NaBH_4$ (type XXXIV) pref. 2-4 moles; b) $LiAlH_4$; DIBAH (alkoxy-carbonyl type) at least 2 equivalents	a) 0° to 30° esp. 20° to 30° b) -80° to reflux pref. <70° esp. -80° to 25°	inert	a) ℓ. alkanol e.g. CH_3OH, C_2H_5OH b) as (A) pref. THF
(LL)	Halogenation	phosphorous trihalide, thionyl halide (halide = Y) e.g. PCl_3 or PBr_3 or $SOCl_2$ or $SOBr_2$	20° to 35°		diethylether or THF (for PY_3) or halo-carbon e.g. CH_2Cl_2 (for SOY_2)

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
(MM)	Halogenation	triphenylphosphine $+CY_4$ (e.g. CCl_4 or CBr_4)	-10° to reflux pref. < 120°		neat, excess CY_4, diethylether, THF, benzene, toluen
(NN)		triphenylphosphine	60° to reflux pref. < 150°	inert	as (M)
(OO)	Wittig 1. strong base 2. LV	1. e.g. NaH, nBuLi (esp. nBuLi)	1. -10° to 5° 2. -60° to 80° esp. -55° to 25° (pref. -55° to -50° rising to 20° to 25°)	inert	e.g. THF, benzene, toluene
(PP)	Hydrolysis	e.g. 10% HCl in THF or pref. CH_3COOH, H_2O, THF (e.g. 3:2:4)	10° to 100° esp. 20° to 30° (HCl); 60° to 65° (CH_3COOH)		e.g. THF + H_2O
(QQ)	oxidation	a) mild conditions e.g. pyridinium chlorochromate pref. in excess, or b) Swern's oxidation oxalylchloride, DMSO, triethylamine	a) 10° to 80° esp. 20° to 30° b) -60° to -40° esp. -50°		Halocarbon e.g. CH_2Cl_2
(BA)		pref. hydroxide is NaOH	0°-30° (start 0° to 10° rising to 20°-30°)		water plus alkanol e.g. ethanol

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
(BC)	Two step carboxylation	1. Strong base e.g. n.BuLi 2. CO_2 pref. in excess	1. 0°-25° (start 0° to 5° rising to 20°-25°) 2. 10°-25°, pref. 20°-25°		as (A) pref. diethylether
(BD) to (BG)	as (M) to (P)	as (M) to (P)	as (M) to (P)		as (M) to (P)
(BH)	Grignard		10° to 40° esp. 20° to 30° (low temp. maximises selective displacement of OCH_3 <u>ortho</u> to Ro	inert	as (Q)
(BI)	Grignard — pref. when R_{13} is primary or secondary	Pref. 6-12 moles esp. 6 moles of CXXIII per mole of CXXII	60° to 90° pref. 70-80°	inert	pref. anhydrous THF + toluene
(BJ)	Alkylation [pref. when R_{13} is tertiary]	Pref. large molar excess of CXXIIIA, esp. 4.4 moles (1.1 at beginning, 2.2 after 3 hrs., 1.1 after further 2 hrs.)	-80° to -20° pref. -50° to -40°	inert	as (A) esp. THF
(CA)	Two step methylation	1. strong base e.g. n-BuLi 2. CH_3I	1. 0°-25° pref. 20°-25° 2. 0°-30° pref. 20°-25° (commence 0° rise to 20°-25°)	inert "	1. as A esp. diethylether 2. "

Reaction	Type/Steps	Special conditions/ Reagents	Temperatures	Atmosphere	Solvents
(CB)	as (CA)	as (CA)	1. -10° to 0° pref. -50 2. as (CA)	as (CA)	as (CA)
(DA)-(DC), (DE)	see examples				

CI is the commercially available compound tri- o-acetyl-D-glucal.

The preferred reactions conditions for Reactions AB-AI are:

AB: (1) sodium, methanol, 20°C, 15 minutes; (2) mercuric acetate, 25°C.

AC: sodium chloride, sodium borohydride, methanol + isopropanol, 20°C.

AD: triphenylmethyl chloride, pyridine, 35°C.

AE: (1) sodium hydride, tetrahydrofuran, 20°C, (2) 1-(2',4',6'-triisopropylbenzenesulfonyl)imidazole, -30°rising to -20°C

AF: lithium aluminium hydride, methyl t-butyl ether, -10°C.

AG: t-butyldiphenylchlorosilane, imidazole, N,N,dimethylformamide, 20°C.

AH: 70% aqueous trifluoroacetic acid, methylene chloride, -80° to -50°C especially -55°C rising over 1 hour to -10° to +10° -10° to +10° and keeping at latter for 3-5 hours Epimerisation can be minimized by employing low temperatures and/or short times and terminating the reaction before completion.

AI: pyridinium chlorochromate or especially chromium trioxide (e.g. as Collins oxidation) in molar excess (e.g. 8 mole per mole of CVIII)/pyridine, pyridine, methylene chloride, 20°-25°C.

AJ: oxidation cf. AI.

AK: reduction cf. a) and (S) above especially $NaBH_4$.

Resulting compounds may be conventionally separated (e.g. HPLC or column chromatography) or directly further reacted.

The compounds of formulae V, XI, XIII, XIV, XVI, XX, XXIII-XXV, XXVII, XXXI, XXXIVA, XLI, CI, CXV, CXXIII, CXXIIIA and CXXVIII and the reagents not designated by a Roman numeral are known or, if unknown, may be synthesized by processes analogous to those described in the literature for similar known compounds. As for the compound of formula LV, one isomer is disclosed in Yang et al., Tetrahedron Letters 23, 4305-4308 (1982) and the synthesis of the other isomers is disclosed in Reaction Scheme IV.

The isomer of Yang et al. and the isomer disclosed in Reaction Scheme IV yield lactones having the 4R,6S configuration. Lactones having the 4S,6S configuration may be obtained from the other isomer whose synthesis is disclosed in Reaction Scheme IV.

The availability of these intermediates enables synthesis of optically pure end products.

Reaction products both intermediale and final can be isolated and purified in conventional mannr whereby intermediates can where appropriately be employed directly in a subsequent reaction

Mixtures of stereoisomers (cis, trans and optical) may be separated by conventional means at whatever stage of synthesis is appropriate. Such methods include re-crystalisation, chromatography, formation of esters with optically pure acids and alcohols or of amides and salts (cf also Sommer et al. J.A.C.S. 80, 3271 (1958)) with subsequent reconversion under retention of optical purity. For example diastereoisomeric (-)-α-naphthylphenylmethylsilyl derivatives of a lactone type end product of formula I may be separated by conventional means.

Salts may be prepared in conventional manner from free acids, lactones and esters and vice-versa. Whilst all salts are covered by the invention pharmaceutically acceptable salts especially sodium, potassium and ammonium particularly sodium salts are preferred.

The various forms of the compounds of formula I are by virtue of their interconvertability useful as intermediates in addition to the use set out below.

Also within the scope of this invention are the intermediates of formulae VI, XII, XV, XVII, XXVIII-XXX, XXXII, XXXIII,

XXXV-XL, XLII-L, LII-LIV, LVI-LVIII, CXIX-CXXII, CXXIV-CXXVII, CXXXI and CXXXII. The preferences for each variable are the same as those set forth for the compounds of formula I, with the preferred groups of such compounds including those that correspond to Groups (i)-(xiii), (xxi)-(XXXiii) and (xli-xcii) (for formulae VI, XII, XV, XVII, XXVIII-XXX, XXXII, XXXIII, XXXV-XL, XLII-L, LII-LIV, CXIX-CXXII and CXXIV-CXXVII) and Groups (xiv)-(xx), (xxxiv)-(xl) and (xciii)-(cxx) (for formula LVI-LVIII), to the extent consistent therewith, and the corresponding groups for the compounds of Groups IAa2, IAb2, IBa2, IBb2, IAa3, IAb3, IBa3 and IBb3.

The compounds of formula I possess pharmacological activity in particular they are inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase and as a consequence inhibitors of cholesterol biosynthesis as demonstrated in the following three tests.

Test A: In Vitro Microsomal Assay of HMG-CoA Reductase Inhibition:

200 ul. aliquots (1.08-1.50 mg./ml.) of rat liver microsomal suspensions, freshly prepard from male Spargue-Dawley rats (150-225 g. body weight), in Buffer A with 10 mmol. dithiothreitol are incubated with 10 ul. test substance dissolved in dimethylacetamide and assayed for HMG-CoA reductase activity as described by Ackerman et al., J. Lipid Res. 18, 408-413 (1977). In the assay the microsomes are the source of the HMG-CoA reductase enzyme which catalyses the reduction of HMG-CoA to mevalonate. The assay employs a chloroform extraction to separate the product, [^{14}C]mevalonolactone, formed by the HMG-CoA reductase reaction from the substrate, [^{14}C]HMG-CoA. [^{3}H]mevalono-lactone is added as an internal reference. Inhibition of HMG-CoA reductase is calculated from the decrease in specific activity [^{14}C/^{3}H]mevalonate) of test groups compared to controls.

Test 8: In Vitro Cell Culture Cholesterol Biosynthesis Screen:

The cell culture is prepared as follows: Stock monolayer cultures of the Fu5AH rat hepatoma cell line (originally obtained from G. Rothblat; see Rothblat, Lipids 9, 526-535 (1974) are routinely maintained in Eagle's Minimum Essential Medium (EMEM) supplemented with 10% fetal bovine serum (FBS) in 75 cm^2 tissue culture flasks. For these studies, when the cultures reach confluence, they are removed by mild enzymatic treatment with 0.25% trypsin in Hanks' balanced salt solution (without calcium and magnesium). After centrifugation of the cell suspension and aspiration of the enzymatic solution, a cell pellet is resuspended in an appropriate volume of media for seeding into 60 mm. tissue culture dishes. The cultures are incubated at 37°C in an atmosphere of high humidity and 5% carbon dioxide. When the cultures are confluent (approximately 5 days), they are ready for use. The culture media is aspirated from the dishes and replaced with 3 ml of EMEM suplemented with 5 mg/ml of dilipidized serum protein (DLSP) prepared by the method of Rothblat et al., In Vitro 12, 554-557 (1976). Replacement of the FBS with DLSP has been shown to stimulate the incorporation of [^{14}C]acetate into sterol by removing the exogenous sterol supplied by the FBS, thereby requiring the cells to synthesized sterol. Enthanced 3-hydroxy-3-methylglutaryl Coenzyme A reductase (HMG-CoA reductase) activity is measurable in the cells in response to the lack of exogenous sterol. Following approximately 24 hours incubation at 37°C in the DLSP supplemented media, the assay is initiated by the addition of 3μCi of [^{14}C]acetate and the test substances solubilized in dimethylsulfoxide (DMSO) or distilled water. Solvent controls and compactin-treated controls are always prepared. Triplicate 60mm. tissue culture dishes are run for each group. After 3 hours incubation at 37°C, the cultures are examined microscopically using an inverted phase contrast microscope. Notations are made of any morphological changes which may have occurred in the cultures. The media is aspirated and the cell layer is gently washed twice with 0.9% sodium chloride solution (saline). The cell layer is then harvested in 3 ml. of 0.9% saline by gentle scraping with a rubber policeman and transferred to a clean glass tube with Teflon lined cap. The dishes are rinsed with 3 ml. of 0.9% saline and rescraped, and the cells are combined with the first harvest. The tubes are centrifuged at 1500 r.p.m. for 10 minutes in an IEC PR-J centrifuge, and the supernatant is asperated.

The cells are then extracted as follows: One ml. of 100% ethanol is added to the cell pellet followed by sonication for 10 seconds with a "LO" setting of 50 on a Bronwell Biosonik IV. One hundred µl. are taken for protein determination. One ml. of 15% potassium hydroxide (KOH) is added, and the samples are thoroughly vortexed. Saponification is accomplished by heating the ethanol-KOH treated samples at 60°C for 60 minutes in a water bath. Following dilution of the samples with 2ml. of distilled water, they are extracted three times with 7 ml. of petroleum ether. The petroleum ether extracts are then washed three times with 2 ml. of distilled water and finally taken to dryness under a stream of nitrogen.

The obtained samples are then analyzed by thin layer chromatography (TLC) as follows: Residues from the petroleum ether extraction are taken up in a small volume of hexane and spotted on silica gel 60 TLC plates (E. Merck). Development of the plates is carried out in a 150 parts by volume hexane: 50 parts by volume diethyl ether: 5 parts by volume galcial acetic acid solvent system using a three phase development procedure. Visualization is accomplished in an iodine vapor chamber. The plates are divided into five sections such that each section contains the molecules having the following approximate Rf values: section 1- 0-0.4, section 2- 0.4-0.55, section 3- 0.55-0.7, section 4- 0.7-0.9 and section 5- 0.9-1.0. Section 2 contains the non-saponifiable sterols. The five sections of the TLC plates are scraped into scintillation vials. Blanks are also prepared from scrapings of chromatographed non-labelled standards. ACS® scintillation cocktail is added, and the radioactivity is determined in a liquid scintillation spectrometer. [^{14}C]hexadecane standards are used to determine counting efficiencies. The total protein content of the samples is determined employing the Bio-Rad Protein Assay System.

The results are reported as disintegrations per minute per mg protein (d.p.m./mg protein) for each of the live TLC sections. Mean d.p.m./mg protein $\pm$ standard error of the mean are compared for percentage change (%Δ) and statistical significance with solvent control means. TLC section 2 data is taken as a measure of HMG-CoA reductase activity inhibition.

Test C: In Vivo Cholesterol Biosynthesis Inhibition Tests: In vivo studies utilize male Wistar Royal Hart rats weighing 150$\pm$20 g which have been kept for 7-10 days on an altered light cycle (6:30 a.m. - 6:30 p.m. dark) housed two per cage and fed powdered Purina Rat Chow and water ad libitum. Three hours before the diurnal maximum of cholesterol synthesis at mid-dark, the rats are administered the test substances dissolved or as a suspension in 0.5% carboxymethylcellulose in a volume of 1 ml/100 g body weight. Controls receive vehicle alone. One hour after receiving the test substance, the rats are injected intraperitoneally with about 25 µCi/100 g body weight of sodium [1-^{14}C]acetate 1-3 mCi/mmol. Two hours after mid-dark, blood samples are obtained under sodium hexobarbitol anesthesia and the serum separated by centrifugation.

Serum samples are saponified and neutralized, and the 3ß-hydroxy sterols are precipiated with digitonin basically as described by Sperry et al., J. Biol. Chem. 187, 97 (1950). The [^{14}C]digitonides are then counted by liquid scintillation spectrometry. After correcting for efficiencies, the results are calculated in nCi (nanocuries) of sterol formed per 100 ml of serum. Inhibition of sterol synthesis is calculated from the reduction in the nCi of sterols formed from test groups compared to controls.

The compounds are thus indicated for use as hypolipoproteinemic and anti-atherosclerotic agents.

An indicated suitable daily dosage for use in the treatment of pyperlipoproteinemia and athersclerosis is from about 4 to 2000 mg suitably 4-200 e.g. 10 to 100 for the more active compounds suitably administered in divided dosages of 1 to 1000 mg suitably 0.5 to 50 mg two to four times daily or in retard form.

The compounds of formula I may be administered in similar manner as known compounds suggested for use in such indications e.g. Compactin. The suitable daily dosage for a particular compound will depend on a number of factors such as its relative potency of activity. It has, for example been determined that the preferred compound (compound no. 11) obtained an IC_{50} of 0.1 μ-molar in test A compared with 0.5 μ-molar for Compactin. It is therefore indicated that the compounds may be administered at similar or lower dosages than conventionally proposed for Compactin e.g. 25-150 mg/day..

They may be administered in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form.

The invention therefore also concerns a method of treating hyperliproproteinemia or atherosclerosis by administration of a compound of formula I in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceuticals e.g. as hypolipoproteinemic and anti-atherosclerotic agents.

The compounds may be administered alone, or in admixture with a pharmaceutically acceptable diluent or carrier, and, optionally other excipients, and administered orally in such forms as tablets, elixirs, capsules or suspensions or parenterally in such forms as injectable solutions or suspensions.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules.

Such compositions also form part of the invention.

The following examples, in which all temperatures are in °C illustrate the invention.

Example 1

Ethyl erythro-(E)-3,5-dihydroxy-7-(2'-[4"-fluorophenyl]naphth-1'-yl)-hept-6-enoate (compound no. 1)

Step 1 : 2-Methoxy-1-naphthoyl chloride (Reaction M; compound XXVIa)

6.06 g of 2-methoxy-1-naphthoic acid and 7.62 ml of oxalyl chloride are added to 50 ml of anhydrous toluene, and the obtained reaction mixture is refluxed for 2 hours and evaporated to dryness at reduced pressure to obtain the crude product.

Step 2 : 2-Methoxy-1-naphthoic acid N-1,1-dimethyl-2-hydroxyethylamide (Reaction N; compound XXVIIIa)

50 ml of methylene chloride (dried over molecular sieves) and 5.4 g of 2-amino-2-methyl-1-propanol are added to the crude 2-methoxy-1-naphthoyl chloride produced in Step 1 while cooling in an ice bath. The reaction mixture is stirred at room temperature overnight, 50 ml of methylene chloride is added, and the reaction mixture is quenched with water. The methylene chloride phase is separated, washed twice with 10% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated at reduced pressure to near dryness. Diethyl ether is added to the residue, and the precipitate is dried under vacuum to obtain the colourless product, m.p. 160°-163°C.

When this reaction is scaled up, the yield is improved if one adds a solution of 2-methoxy-1-naphthoyl chloride in methylene chloride to a solution of 2-amino-2-methyl-1-propanol in methylene chloride stirred at 0°-5°C.

Step 3 : 4,4-Dimethyl-2-(2'-methoxynaphth-1'-yl)-2-oxazoline.hydrochloride (Reaction O; compound XXIXa)

4.8 ml of thionyl chloride is slowly added to 6.0 g of Compound XXVIIIa, the obtained suspension is stirred under nitrogen at room temperature for 4 hours, 10 ml of methylene chloride dried over molecular sieves is added, and the reaction mixture is stirred overnight under nitrogen. 50 ml of diethyl ether is added, and the precipitated solid is washed with diethyl ether and dried under vacuum to obtain the colourless product, m.p. 168°-171°C.

Step 4 : 4,4-Dimethyl-2-(2'-methoxynaphth-1'-yl)-2-oxazoline (Reaction P; compound XXXa)

75 ml of 20% aqueous sodium hydroxide is added to 13 g of Compound XXIXa and the reaction mixture is extracted four times with diethyl ether. The diethyl ether extracts are combined, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure, and the residue is triturated with diethyl ether/petroleum ether. The resulting solid is dried under vacuum to obtain the colourless product, m.p. 98°-101°C.

Step 5 : 4,4-Dimethyl-2-(2'-[4"-fluorophenyl]naphth-1'-yl)-2-oxazoline (Reaction Q; compound XXXIIa)

A Grignard reagent prepared from 4.2 g of p-bromo-fluorobenzene and 0.583 g of magnesium turnings in 20 ml of dry tetrahydrofuran (distilled over sodium) is slowly added to a solution of 5.1 g of Compound XXXa in 30 ml of dry tetrahydrofuran stirred at room temperature under nitrogen. The reaction mixture is stirred overnight at room temperature under nitrogen and, while slightly cooling, is quenched with 20 ml of saturated ammonium chloride solution. The reaction mixture is extracted with diethyl ether, and the diethyl ether extract is dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The residue is triturated with diethyl ether/petroleum ether, and the precipitate is dried under vacuum to obtain the colourless product, m.p. 115°-117°C.

Step 6 : 2-(2'-[4"-Fluorophenyl]naphth-1'-yl)-3,4,4-trimethyl-2-oxazolinium iodide (Reaction R; compound XXXIIIa)

7 ml of methyl iodide is added to a solution of 4.34 of Compound XXXIIa in 30 ml of nitromethane, and the reaction mixture is stirred at 80°-90°C under nitrogen overnight. The reaction mixture is cooled to room temperature, and 200 ml of diethyl ether is added; the resulting gummy precipitate solidifies on standing. The solid is washed with diethyl ether, dried under vacuum and recrystallised from acetonitrile/ether to obtain the yellow product, m.p. 220°-222°C.

Step 7 : 2-(4'-Fluorophenyl)-1-naphthaldehyde (Reaction S; compound IVa)

0.936 g of sodium borohydride is added portion-wise over a 2 minute period to a suspension of 11.36 g of Compound XXXIIIa in 120 ml of absolute ethanol stirred at about 0°C. The reaction mixture is stirred at about 0°C under nitrogen for 2 hours, and 200 ml of 2N.hydrochloric acid is added, cooling being maintained during the addition. The reaction mixture is stirred at room temperature under nitrogen for 40 hours, concentrated at reduced pressure and extracted three times with diethyl ether. The diethyl ether extracts are combined, washed twice with 3% aqueous sodium thiosulfate, washed once with water, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The residue is dissolved in methylene chloride, and the solution is treated with charcoal, filtered and evaporated at reduced pressure to a small volume. A small amount of isopropanol is added, and the solution is evaporated under vacuum without heating. The precipitated colourless solid is washed with cold isopropanol, washed with petroleum ether and dried under vacuum to obtain the product, m.p. 78°-80°C.

Step 8 : (E)-3-(2'-[4"-Fluorophenyl]naphth-1'-yl)prop-2-enal (Reaction W; compound IVb)

3.16 ml of 1.3M n-butyllithium/n-hexane is added dropwise to a solution of 1.414 g of cis-1-ethoxy-2-tri-n-butylstannylethylene in 40 ml of dry tetrahydrofuran (distilled over sodium) stirred at -78°C under nitrogen, stirring is maintained for 2 hours nder the same conditions, and a solution of 0.888 g of Compound IVa in 10 ml of dry tetrahydrofuran (distilled over sodium) is added. The reaction mixture is stirred at -78°C under nitrogen for 1.5 hours and allowed to warm to room temperature. 5 ml of saturated aqueous sodium bicarbonate is added followed by 50 ml of water. The reaction mixture is extracted twice with 50 ml portions of diethyl ether, and the diethyl ether extracts are combined, washed twice with 50 ml portions of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The residue is distributed between acetonitrile and n-hexane. The acetonitrile layer is extracted twice with n-hexane and evporated to dryness at reduced pressure to obtain a dark green gum. 30 ml of 80% aqueous tetrahydrofuran and 5 mg of p-toluenesulfonic acid monohydrate are added, and the reaction mixture is stirred at room temperature for 4 hours. Water and 0.5 g of solid sodium bicarbonate are added, and the reaction mixture is extracted with ethyl acetate. The ethyl acetate extract is dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure to obtain a yellow sticky solid. The solid is triturated with diethyl ether/petroleum ether to obtain the colourless product, m.p. 119°-122°C.

Step 9 : Ethyl (E)-7-(2'-[4"-fluorophenyl]naphth-1'-yl)-5-hydroxy-3-oxohept-6-enoate (Reaction A; compound VIa)

29.1 ml of 1.7 M n-butyllithium/n-hexane is slowly added to a solution of 6.9 ml of diisopropylamine in 140 ml of dry tetrahydrofuran stirred at 0°C under nitrogen. The reaction mixture is stirred at 0°C under nitrogen for 20 minutes, 3.14 ml of ethyl acetoacetate is slowly added, and the reaction mixture is stirred under the same conditions for 1 hour and cooled to -40° to -30°C. A solution of 3.4 g of Compound IVb in 75 ml of dry tetrahydrofuran is slowly added to the reaction mixture stirred at -40° to -30°C under nitrogen. The reaction mixture is stirred for an additional 45 minutes under the same conditions, quenched with 150 ml of saturated aqueous ammonium chloride and allowed to warm to room temperature overnight. Water is added to the reaction mixture, and the reaction mixture is extracted with ethyl acetate. The ethyl acetate extract is washed with water, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The gummy residue is triturated with a small amount of diethyl ether, and the precipitated colourless solid is washed with cold 1:1 (by volume) diethyl ether/petroleum ether and dried under vacuum to obtain the product, m.p. 84°-86°C.

The product is a racemate that may be resolved into its R and S components.

Step 10 : Ethyl erythro-(E)-3,5-dihydroxy-7-(2'-[4"-fluorophenyl]naphth-1'-yl)hept-6-enoate (process a); compound no. 1)

6.52 ml of 1M tri-n-butylborane/tetrahydrofuran is added to a solution of 2.42 g of Compound VIa in 200 ml of dry tetrahydrofuran stirred at room temperature, and 34 ml of air (at 25°C and 760 mm Hg) is slowly bubbled in. The reaction mixture is stirred at room temperature for 2 hours and cooled to -78° to -75°C, and 0.248 g of sodium borohydride is added portion-wise. The reaction mixture is stirred at -78° to -75°C under nitrogen for 3 hours, and a solution of 33.8 ml of 30% aqueous hydrogen peroxide, 67.6 ml of an aqueous phosphate buffer having a pH of 7.2 (0.047M. sodium phosphate/0.024M. potassium phsophate/0.054M. sodium hydroxide) and 67.6 ml of methanol is slowly added, the aforementioned temperature being maintained during the addition. The reaction mixture is allowed to warm to room temperature overnight, water is added, and the reaction mixture is extracted three times with methylene chloride. The methylene chloride extracts are combined, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. Methanol is added to the residue, it is heated at 40° to 45°C for 30 seconds, and the methanol is evaporated at reduced pressure at room temperature; this procedure is repeated twice. The residue is triturated with a small amount of diethyl ether while being cooled. The precipitated colourless solid is washed with diethyl ether/petroleum ether and dried under vacuum to obtain the product, m.p. 114°-116°C.

The product is a racemic mixture which may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The use of a non-stereoselective reduction, a t-butylamine-borane complex in abs. C_2H_5OH at 0° for 1 hour, affords a mixture of all four enatiomers (compound no. 12).

Example 2 : Erythro-(E)-3,5-dihydroxy-7-(2'-[4"-fluorophenyl]naphth-1'-yl)-hept-6-enoic acid and its sodium salt (process d); compound nos. 2 and 3)

A mixture of 0.30 g of Compound 1, 10 ml of ethanol and 0.88 ml of 1N. aqueous sodium hydroxide is stirred at room temperature for 1.5 hours, water is added and the reaction mixture is extracted with diethyl ether. The aqueous phase, which contains racemic sodium salt can either be evaporated to dryness, m.p. 210°-220°C (decomp.) (compound 3) or acidified with 2N. hydrochloric acid, to yield a gummy precipitate which is extracted with ethyl acetate. The ethyl acetate extract is dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure to obtain the crude free acid as a sticky pale yellow foam, m.p. 43°-102°C (compound 2).

The products are racemic mixtures which may be resolved into optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred.

Example 3 : (E)-Trans-6-(2'-[2"-(4"'-fluorophenyl)naphth-1"-yl]ethenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (process e); compound no. 4)

A solution of 0.223 g of Compound 2 in 40 ml of dry toluene is refluxed for 5 hours, the water formed being removed by the use of a Dean-Starke apparatus. The reaction mixture is cooled and extracted with 10% aqueous sodium bicarbonate and with water. The toluene solution is dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The residue is dissolved in diethyl ether and evaporated at reduced pressure and room temperature until precipitation commences. The solution is cooled, and the precipitated pale yellow solid is washed with petroleum ether and dried under vacuum to obtain the product, m.p. 152-154°C.

The product is a racemate that may be resolved by conventional means into two optically pure enantiomers, the 4R,6S and 4S,6R isomers, of which the former is preferred. The product contains about 1% of the corresponding cis racemate, which may be separated from the trans racemate by, for example, column chromatography. The cis racemate may be resolved by conventional means into two optically pure enantiomers, the 4R,6R and 4S,6S isomers. The cis racemate results from a small amount of the threo isomer of Compound 1 formed in Step 10 of Example 1 and not separated therefrom which is carried through process d) (Example 2) and process e) (this example). A sample of the trans lactone free of any detectable cis lactone melted at 153° to 150°C.

Example 4 : Ethyl erythro-3,5-dihydroxy-7-('-[4"-fluorophenyl]-5',6',7',8'-tetrahydronaphth-1'-yl)heptanoate (compound no. 5)

Step 1 : Ethyl 7-(2'-[4"-fluorophenyl]-5',6',7',8'-tetrahydronaphth-1'-yl-5-hydroxy-3-oxoheptanoate (reaction JJ; compound VIb)

A solution of 406 mg (1mmole) of Compound VIa in 20 ml of glacial acetic acid is contacted with a large excess of hydrogen at an initial pressure of 50 p.s.i. at room temperature in the presence of 40 mg of platinum dioxide until 3 mmoles of hydrogen (7.5 p.s.i.) are taken up. The platinum dioxide is removed by filtration, and the filtrate is evaporated to dryness at reduced pressure. The residue (397 mg) is dissolved in a small amount of methylene chloride and applied to silica gel preparative thin layer chromatography plates; methylene chloride is used as the chromatography solvent. The bands containing the product are eluted with ethyl acetate. The ethyl acetate is evaporated at reduced pressure to obtain the crude product as a yellow gum.

The product is a racemate that may be resolved into its R and S components.

Step 2 : Ethyl erythro-3,5-dihydroxy-7-(2'-[4"-fluorophenyl]-5',6',7',8'-tetrahydronaphth-1'-yl)heptanoate (process a); compound no. 5)

Analogous to Example 1. Step 10 starting from VIb.
Product (compound no. 5) is obtained as a yellow gum.

The product is a racemate that may be resolved into two optically pure enantiomers, the 3R,5R and 3S,5S isomers, of which the former is preferred.

Example 5 : Ethyl erythro-(E)-7-(4'-chloro-2'-[4"-fluorophenyl]naphth-1'-yl-3,5-dihydroxyhept-6-enoate (compound no. 6)

Step 1 : 4-Chloro-2-naphthol (reaction DA; compound no. cxxix)

A solution of 406 mg (1 mmole) of Compound VIa in 20 ml of glacial acetic acid is contracted with a large excess of hydrogen at an initial pressure of 50 p.s.i. at room temperature in the presence of 40 mg of platinum dioxide until 3 mmoles of hydrogen (7.5 p.s.i.) are taken up. The platinum dioxide is removed by filtration, and the filtrate is evaporated to dryness at reduced pressure. The residue (397 mg) is dissolved in a small amount of methylene chloride and applied to silica gel preparative thin layer chromatography plates; methylene chloride is used as the chromatography solvent. The bands containing the product are eluted with ethyl acetate. The ethyl acetate is evaporated at reduced pressure to obtain the crude product as a yellow gum.

The product is a racemate that may be resolved into its R and S components.

<u>Step 2</u> : Ethyl <u>erythro</u>-3,5-dihydroxy-7-(2'-[4"-fluorophenyl]-5',6',7',8'-<u>tetrahydronaphth-1'-yl)heptanoate (process a); compound no. 5)</u>

Analogous to Example 1, Step 10 starting from VIb.

Product (compound 5) is obtained as a yellow gum.

The product is a racemate that may be resolved into two optically pure enantiomers, the 3R,5R and 3S,5S isomers, of which the former is preferred.

Example 5 : Ethyl erythro-(E)-7-(4'-chloro-2'-[4"-fluorophenyl]naphth-1'-yl-3,5-dihydroxy)hept-6-enoate (compound no. 6)

Step 1 : 4-Chloro-2-naphthol (Reaction DA; compound CXXIX)

A mixture of 90 g (0.42 mole) of 1,4-dichloro-2-naphthol, 420 g of stannous chloride.dihydrate and 1.5 liters of glacial acetic acid is refluxed for about 80 hours, gaseous hydrogen chloride being slowly bubbled in throughout. The reaction mixture is added to 9 liters of ice water, the resulting mixture is stirred for 1 hour,.and the product is collected by filtration, washed with 4 liters of water, washed with 2 liters of petroleum ether, air dried and dried at 40°C under high vacuum for 5 hours, m.p. 93°-95°C.

Step 2 : 1-Chloro-3-methoxynaphthalene (Reaction DB; compound CXXX)

23.2 g (0.414 mole) of ground potassium hydroxide is added to a mixture of 65.4 (0.366 mole) of 4-chloro-2-naphthol and 370 ml of dimethylformamide stirred at 0°-5°C. The reaction mixture is stirred at 0°-5°C for 3 hours, 58.8 g (0.414 mole) of methyl iodide is added over a 5 minute period, and the reaction mixture is allowed to warm to 20° to 25°C and is stirred at that temperature for 16 hours. 2 Liters of water is added, and the mixture is extracted with diethyl ether. The diethyl ethyl is evaporated at reduced pressure until the onset of turbidity, and petroleum ether is added to obtain the solid product, m.p. 35°-39°C.

Step 3 : 4-Chloro-2-methoxy-1-naphthaldehyde (Reaction DC; compound CXXXI)

50 g (0.326 mole) of phosphorus oxychloride is slowly added to a mixture of 24 g (0.125 mole) of 1-chloro-3-methoxynaphthalene and 30 g (0.411 mole) of dimethylformamdie stirred at 20°-25°C. The reaction mixture is stirred at 80°C for 16 hours, cooled in an ice bath and made basic by the dropwise addition of 10% aqueous sodium hydroxide solution with vigorous stirring. The precipitate is collected by filtration, washed with water, washed with petroleum ether and air dried to obtain the crude product, m.p. 145°-160°C (dec.) (shrinks at 105°-145°C).

An analytical sample may be obtained by (a) dissolving the crude product in ethyl acetate, (b) adding petroleum ether, (c) decanting the solution from the insoluble tar, (d) repeating (b) and (c) until no more tar results and (e) adding additional petroleum ether to obtain the pure product, m.p. 154°-157°C.

Step 4 : 4-Chloro-2-methoxy-1-naphthoic acid (Reaction DE, compound XXIIIa)

18.6 g (0.175 mole) of sodium carbonate is added to a mixture of 37.2 g (0.169 mole) of crude 4-chloro-2-methoxy-1-naphthaldehyde, 450 ml of acetone and 92 ml of water stirred at 20°-25°C. 27.9 g (0.177 mole) of potassium permanganate is added over a 2.5 hour period with stirring at 40°-45°C. The reaction mixture is stirred at room temperature for 16 hours, 400 ml of water is added, and the reaction mixture is filtered through Celite, acidified with 2N. hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract is extracted, three times with 10% aqueous sodium carbonate solution, and the combined aqueous extracts are carefully acidified with 2N hydrochloric acid. The obtained product is washed with water and washed with petroleum ether, m.p. 199.5°-202°C.

Step 5 to 14

Proceed analogously to Steps 1 to 10 of Example 1 through the intermediates listed hereafter.

Step 5 : 4-Chloro-2-methoxy-1-naphthoyl chloride (Reaction M; compound XXVIb), oil)

Step 6 : 4-Chloro-2-methoxy-1-naphthoic acid N-1,1-dimethyl-2-hydroxy-ethylamide (Reaction N; compound XXVIIIb), m.p. 142° to 146°

Step 7 and 8 : 2-(4'-Chloro-2'-methoxynaphth-1'-yl)-4,4-dimethyl-2-oxazoline and its hydrochloride salt (Reactions O and P; compound XXXb and XXIXb), m.p. 91-94° (XXXb)

Step 9 : 2-(4'-Chloro-2'-[4"-fluorophenyl]naphth-1'-yl)-4,4-dimethyl-2-oxazoline (Reaction Q; compound XXXIIb), m.p. 150°-152°
Gringard reagent cf. Example 10.7.

Step 10: 2-(4'-Chloro-2'-[4"-fluorophenyl]naphth-1'-yl)-3,4,4-trimethyl-2-oxazolinium iodide (Reaction R; compound XXXIIIb), m.p. 224°-226°

Step 11 : 4-Chloro-2-(4'-fluorophenyl)-1-naphthaldehyde (Reaction S; compound IVc), m.p. 137°-139°

Step 12 : (E)-3-(4'-Chloro-2'-[4"-fluorophenyl]naphth-1'-yl)prop-2-enal (Reaction W; compound IVd), m.p. 143-147°

Step 13 : Ethyl (E)-7-(4'-chloro-2'-[4"-fluorophenyl]naphth-1'-yl)-5-hydroxy-3-oxohept-6-enoate (Reaction A; compound VIc), m.p. m.p. 87°-89°

Step 14 : Ethyl erthro (E)-7-(4'-chloro-2'-[4"-fluorophenyl]naphth-1'-yl-3,5-dihydroxyhept-6-enoate (process a); compound no. 6), m.p. 121-124°

The principal (erythro) product is a racemate that may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The threo minor product is a racemate that may be resolved into the 3R,5R and 3S,5S isomers, of which the former is preferred. The use of a non-stereoselective reduction would afford all four stereoisomers in approximately equal amounts.

The crude reaction mixture of Step 14 also contains threo isomer.

Example 6 : Erythro-(E)-7-(4'-chloro-2'-[4"-fluorophenyl]naphth-1'-yl)-3,5-dihydroxyhept-6-enoic acid and its sodium salt (process d); compounds 7 and 8)

Analogous to Example 2 starting from compound 6, m.p. 201°-204° (dec.) for salt. Free acid as crude oil containing a small amount of threo compound.

The principal (erythro) product is a racemate which may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The minor (threo) product is also a resolvable racemate, the two enantiomers being the 3R,5R and 3S,5S isomers, of which the former is preferred.

Example 7 : (E)-Trans-6-(2'-[4"-chloro-2"-(4"'-fluorophenyl)naphth-1"-yl]-ethenyl-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (Process e); compound 9)

Analogous to Example 3 starting from Compound 7, m.p. of product 131°-134°.

Example 8 : (E)-Trans-6S-2'-[2"-(4"'-fluorophenyl)naphth-1"-yl]ethenyl)-4R-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (compound no. 10)

Step 1 : 2-(4'-fluorophenyl)-1-naphthalenemethanol (Reaction KK, compound LIIa)

75 g (1.94 moles) of powdered sodium borohydride is added to a mixture of 497 g (1.988 moles) of 2-(4'-fluorophenyl)-1-naphthaldehyde and 6.6 liters of absolute ethanol stirred at 20°-25°. The reaction mixture is stirred at this temperature for 16 hours, suction filtered through 1 kg. of silica gel (EM-60, 230-240 mesh ASTM) and evaporated at reduced pressure to obtain a crystalline residue. The solids are collected by filtration, washed with 100 ml of cold (0°) methylene chloride and taken up in 1 liter of diethyl ether. The insoluble residue is removed by filtration, and the filtrate is evaporated to dryness at reduced pressure. The residue is dissolved in 500 ml of methylene chloride, and the solution is cooled to 0° to obtain the product, m.p. 91-93°.

Step 2 : 1-Chloromethyl-2-(4'-fluorophenyl)naphthalene (Reaction LL; compound LIIIa)

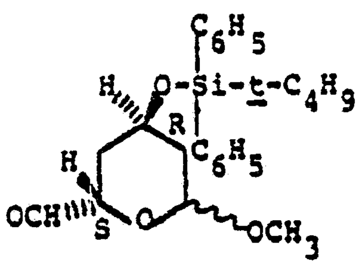
A solution of 45 g (0.378 mole) of thionyl chloride in 500 ml of methylene chloride is added over a 20 minute period to a mixture of 237 g (0.94 mole) of 2-(4'-fluorophenyl)-1-naphthalenemethanol and 3 liters of methylene chloride stirred at 20°-25° under nitrogen, and the reaction mixture is stirred at this temperature for 16 hours. An additional 25 g (0.31 mole) of thionyl chloride is added, the reaction mixture is stirred at 20°-25° for 2 hours and cooled to 0°. 1 liter of 10% aqueous sodium bicarbonate solution is cautiously added, the organic layer is separated, and the aqueous phase is extracted with 500 ml of methylene chloride. The two organic phases are combined, washed with 1 liter of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, filtered through 1 kg of silica gel (EM-60, 230-400 mesh ASTM) and concentrated at reduced pressure to obtain the crystalline product, m.p. 93-95°.

Step 3 : [(2-[4'-Fluorophenyl]-1-naphthalenyl)methyl]triphenylphosphonium chloride (Reaction NN; compound LIVa)

A mixture of 218 g (0.81 mole) of 1-chloromethyl-2-(4'-fluorophenyl)-naphthalene, 214 g (0.81 mole) of triphenylphosphine and 4 liters of toluene is refluxed under nitrogen for 16 hours, cooled, concentrated at reduced pressure, to about $^1/_3$ of its original volume, filtered through 1 kg of silica gel (EM-60, 230-400 mesh ASTM) and evaporated to dryness at reduced pressure. 500 ml of anhydrous diethyl ether is added to the crystalline residue, the mixture is cooled to 0°, and the precipitate is collected by filtration, washed twice with a total of 500 ml of anhydrous diethyl ether and vacuum dried at 70° for 5 hours to obtain the product as a colourless solid, m.p. >250°.

Step 4 : (E)-4βR-(1',1'-Dimethylethyl-diphenylsilyloxy)-6αS-(2'-[2"-(4"'-fluorophenyl)naphth-1"-yl]ethenyl)-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (Reaction OO; compound LVIa)

115.6 ml of 1.65M. n-butyllithium/n-hexane (0.191 mole) is added over a period of 5 minutes to a mixture of 100 g (0.188 mole) of Compound LIVa in 1.5 liters of dry tetrahydrofuran stirred at -15° under nitrogen. The reaction mixture is stirred at about 0° for 1 hour and cooled to -55°, a solution of 71.5 g (0.179 mole) of Compound LVa



LVa

in 600 ml of dry tetrahydrofuran is added over a period of about 20 minutes, the temperature of the reaction mixture being -55° to -50° during the addition, and the reaction mixture is allowed to slowly warm to 20°-25° over a 16 hour period, stirring under nitrogen being maintained throughout. The reaction mixture is cooled to 0°, quenched with 1 liter of saturated aqueous ammonium chloride solution and filtered through Celite. The organic phase is separated, and the aqueous phase is extracted twice with 750 ml portions of diethyl ether. The three organic phases are combined, washed with 1 liter of saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure to obtain an oil. The oil is dissolved in 150 ml of 2:1 (by volume) methylene chloride/n-hexane and flash chromatographed on a column packed with 1 kg of silica gel (EM-60, 230-400 mesh ASTM) utilizing the same solvent as the eluant. The fractions containing the product (as determined by thin layer chromatography) are combined and evaporate to dryness at reduced pressure to obtain the product as a gummy solid, $[\alpha]_D^{26}$ = +24.51° (CH_2Cl_2, c = 0.01).

Step 5 : (E)-4βR-(1',1'-Dimethylethyl-diphenylsilyloxy)-6αS-(2'-[2"-(4"'-fluorophenyl)naphth-1"-yl]ethenyl)-2-hydroxy-3,4,5,6-tetrahydro-2H-pyran (Reaction PP; compound LVIIa)

A mixture of 121 g (0.196 mole) of Compound LVIa and 2 liters of 3:2:4 (by volume) acetic acid/water/tetrahydrofuran is heated to 65° with stirring, stirred at 65° for 16 hours and cooled to 20°-25°, and 1.5 liter of methylene chloride is added. With stirring and cooling, the mixture is carefully washed with saturated aqueous sodium carbonate solution until slightly basic. The organic phase is separated, and the aqueous phase is extracted with 1 liter of methylene chloride. The organic phases are combined, washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated at reduced pressure to obtain a light brown oil. The oil is dissolved in 1:1 (by volume) diethyl ether/petroleum ether and flash chromatographed on a column packed with 1 kg of silica gel (EM-60, 230-400 mesh ASTM) utilizing the same solvent as the eluant. The fractions containing the product and little or nothing else (as determined by thin layer chromatography) are combined and evaporated at reduced pressure to obtain the product as a gummy solid, $[\alpha]_D^{26}$ = +5.00° (CH_2Cl_2, c = 0.01).

Step 6 : (E)-4βR-(1',1'-Dimethylethyl-diphenylsilyloxy)-6αS-(2'-[2"-(4"'-fluorophenyl)naphth-1"-yl]ethenyl)-3,4,5,6-tetrahydro-2H-pyran-2-one (Reaction QQ; compound LVIIIa)

A mixture of 89 g (0.147 mole) of Compound LVIIa, 2 liters of methylene chloride, 64 g (0.317 mole) of pyridinium chlorochromate and 60 g of #3A molecular sieves is stirred at 20°-25° under nitrogen for 16 hours and filtered through Celite and about 100 g of neutral aluminium oxide. The Celite and aluminium oxide are washed several times with methylene chloride and the filtrate and washings are combined and evaporated at reduced pressure to obtain an oil. The oil is dissolved in 100 ml of methylene chloride and flash chromatographed on a column packed with 800 g of silica gel (EM-60, 230-400 mesh ASTM) utilizing methylene chloride as the eluant. The fractions containing the product and little or nothing else (as determined by thin layer chromatography) are combined and evaporated at reduced pressure to obtain the product as an oil, $[\alpha]_D^{26}$ = +12.32° (CH_3OH, c = 0.0215).

Step 7 : (E)-Trans-6S-(2'-[2"-(4"-fluorophenyl)naphth-1"-yl]ethenyl)-4R-hydroxy-3,4,5,6-tetrahydropyran-2H-one (process c); compound no. 10)

26.3 ml (0.46 mole) of glacial acetic acid is added with stirring to a mixture of 63 g (0.105 mole) of Compound LVIIIa in 2.3 liters of dry tetrahydrofuran stirred at 20°-25°. 425 ml of 1M. tetra-n-butylammonium fluoride/tetrahydrofuran (0.425 mole) is added, and the reaction mixture is stirred at 20°-25° for 2 hours. 157 g of solid sodium bicarbonate is added, and the reaction mixture is stirred for 30 minutes and filtered through 800 g of silica gel (EM-60, 230-400 mesh ASTM). The silica gel is washed twice with 500 ml portions of diethyl ether, and the washings are combined with the filtrate. The combined filtrate and washings are evaporated to dryness at reduced pressure, 200 ml of diethyl ether is added, and the mixture is cooled to 0°. The waxy crystals are collected by filtration, washed twice with 100 ml portions of diethyl ether and dissolved in 300 ml of ethyl acetate. The ethyl acetate solution is washed twice with 500 ml portions of saturated aqueous sodium bicarbonate solution and once with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated at reduced pressure to about 1/3 of its original volume. 100 ml of diethyl ether is added, the mixture is cooled to 0°, and the obtained solids are collected by filtration and washed twice with diethyl ether to obtain the product, m.p. 184°-186°, $[\alpha]_D^{26}$ = +44.31° (CH_2Cl_2, c = 0.0058).

Example 9 : Sodium erythro-(E)-3R,5S-dihydroxy-7-(2'-[4"-fluorophenyl]-naphth-1'-yl)hept-6-enoate (process d); compound no. 11)

5.06 ml of 1N. aqueous sodium hydroxide solution (5.06 mmoles) is added to a solution of 2.0 g (5.52 mmoles) of Compound 10 in 160 ml of absolute ethanol, and the reaction mixture is stirred at 20°-25° for 2 hours. 50 g of sodium sulfate is added, and the mixture is stirred for 1 hour and filtered. The salt is washed three times with 100 ml portions of diethyl ether, and the washings are combined with the ethanolic filtrate. The combined washings and filtrate are evaporated to dryness at reduced pressure, and the crystalline residue is dissolved in chloroform. The chloroform is evaporated at reduced pressure, 300 ml of petroleum is evaporated at reduced pressure, 300 ml of petroleum ether is added to the residue, and the mixture is stirred for about 60 hours. The solid product is collected by filtration and washed twice with petroleum ether, m.p. 215°-220° (dec.) $[\alpha]_D^{28}$ = +26.283° (CH_3OH, c = 0.0047).

Example 10 : Ethyl erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-[1"-methylethyl]naphth-2'-yl)hept-6-enoate (Compound no. 13)

Step 1 : 1,3-Dimethoxynaphthalene (Reaction BA; compound CXVIa)

A solution of 32.1 g (0.801 mole) of sodium hydroxide in 80.3 ml of water and 96 g (0.763 mole) of dimethyl sulfate are simultaneously added over a period of 30-45 minutes to 50 g (0.312 mole) of 1,3-dihydroxynaphthalene in 250 ml of absolute ethanol stirred at -5° - 0°C, the former being added slightly faster than the latter. The reaction mixture is allowed to gradually warm to 20° - 25°C with stirring over a 16 hour period. Most of the ethanol is evaporated at reduced pressure, water is added, and the mixture is extracted three times with methyl _t_-butyl ether. The extracts are combined, washed with 2N. aqueous sodium carbonate solution, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure to obtain an oil. The oil is chromatographed on a Waters Prep-500 high pressure liquid chromatography apparatus having a silica gel column and utilizing 5% ethyl acetate/_n_-hexane as the eluant. The fractions containing the product are combined and evaporated at reduced pressure to obtain the product as a yellow oil.

Step 2 : 1,3-Dimethoxy-2-naphthoic acid (Reaction BC; compound CXVIIa)

62 ml of 1.55M. _n_-butyllithium/_n_-hexane (96 mmoles) is slowly added to 15.04 g (80 mmoles) of 1,3-dimethoxynaphthalene in 250 ml of anhydrous diethyl ether stirred at 0°C under nitrogen. The reaction mixture is allowed to warm to 20°-25°C and is stirred at this temperature for 20 hours, the reaction mixture being stirred under nitrogen throughout. Excess anhydrous carbon dioxide is bubbled in for 30 minutes. The reaction mixture is stirred at 20°-25°C for 4 hours, quenched with water and extracted thoroughly with ethyl acetate. The alkaline aqueous phase is acidified with 2N. hydrochloric acid (to a pH of 1-2) and extracted with ethyl acetate. This ethyl acetate extract is dried over anhydrous sodium sulfate and evaporated to dryness. The residue is dried under high vacuum to obtain the product, m.p. 119°-123°C.

Step 3 : 1,3-Dimethoxy-2-naphthoyl chloride (Reaction BD; compound CXVIIIa)

Analogous to Example 1, Step 1.

Step 4 : 1,3-Dimethoxy-2-naphthoic acid N-1,1-dimethyl-2-hydroxyethylamide (Reaction BE; compound CXIXa)

Analogous to Example 1, Step 2.

Steps 5 and 6 : 2-(1',3'-dimethoxynaphth-2'-yl)-4,4-dimethyl-2-oxazoline and its hydrochloride salt (Reactions BF and BG; compound CXXIa + HCl salt

Analogous to Example 1, Steps 3 and 4.

Step 7 : 4,4-Dimethyl-2-(1'-[4"-fluorophenyl]-3'-methoxynaphth-2'-yl)-2-oxazoline (Reaction BH; compound CXXIIa)

A Grignard reagent is prepared by the dropwise addition of 7.7 g (0.044 mole) of p-bromofluorobenzene to a mixture of 1.1 g (0.045 mole) of magnesium turnings, one crystal of iodine and 40 ml of dry tetrahydrofuran stirred at 65°C under nitrogen, the addition being at a rate sufficient to maintain reflux without external heating. Upon completion of the addition (30-45 minutes), the reaction mixture is refluxed under nitrogen for 1.5 hours and cooled to obtain a solution of the Grignard reagent.

18 ml of a IM. solution of the Grignard reagent is slowly added to 4.25 g (14.9 mmoles) of Compound CXXIa in 80 ml of dry tetrahydrofuran (distilled from sodium) stirred at 20°-25°C under nitrogen, and the reaction mixture is stirred at 20°-25°C under nitrogen for 16 hours and quenched with ice and saturated aqueous ammonium chloride solution. The mixture is extracted with ethyl acetate, and the ethyl acetate extract is dried over anhydrous sodium sulfate and evaporated to a small volume at reduced pressure to obtain the product. The product is collected by filtration, washed with a small amount of diethyl ether, washed with a small amount of petroleum ether and dried under high vacuum, m.p. 169°-171°C.

Step 8 : 4,4-Dimethyl-2-(1'-[4"-fluorophenyl]-3'-[1"-methylethyl]naphth-2'-yl)-2-oxazoline (Reaction BI; compound CXXIVa)

13.25 ml of 2M. isopropylmagnesium chloride/diethyl ether (26.5 mmoles) is slowly added to 1.54 g (4.41 mmoles) of Compound CXXIIa in 90 ml of dry tetrahydrofuran (distilled from sodium) and 22 ml of dry toluene (dried over molecular sieves) stirred at 20°-25°C, the reaction mixture is stirred at 20°-25°C for 30 minutes and at 70°-80°C for 18 hours, an additional 13.25 ml of 2M. isopropylmagnesium chloride/diethyl ether (26.5 mmoles) is added, and the reaction mixture is stirred at 70°-80°C for an additional 20 hours, the reaction mixture being maintained under nitrogen throughout. The reaction mixture is quenched with ice and saturated aqueous ammonium chloride solution and extracted with ethyl acetate. The ethyl acetate extract is dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The residue is dissolved in methylene chloride, and the solution is dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The obtained gum is dissolved in about 10 ml of methylene chloride, a small amount of charcoal is added, and the solution is filtered through a silica gel column utilizing methylene chloride as the eluant. The fractions containing the product as determined by thin layer chromatography are combined and evaporated to dryness at reduced pressure to obtain the product as an amber-green gum.

Step 9 : 2-(1'-[4"-Fluorophenyl]-3-'-[1"-methylethyl]naphth-2'-yl)-3,4,4-trimethyl-2-oxazolinium iodide (Reaction R; cmpd. XXXIIIc)

Analogous to Example 1, Step 6: m.p. 233°-243°C (dec.).

Step 10 : 1-(4-Fluorophenyl)-3-(1'-methylethyl)-2-naphthaldehyde (Reaction S; compound IVe)

205 mg (9.37 mmoles) of lithium borohydride is added to 2.35 g (4.67 mmoles) of Compound XXXIIIc stirred in 105 ml of dry tetrahydrofuran (distilled from sodium) and 42 ml of absolute ethanol (dried over molecular sieves) at -30°C under nitrogen. The reaction mixture is stirred at -40° to -30°C under nitrogen for 2 hours and allowed to warm to 0° to 5°C, and 62 ml of 2N. hydrochloric acid is slowly added. The reaction mixture is stirred at 70°-80°C for 2 hours, cooled to 20°-25°C, quenched with water and thoroughly extracted with diethyl ether. The diethyl ether extract is washed with saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate and evaporated to dryness at reduced pressure. The residue is triturated with diethyl ether and then petroleum ether. The insoluble solids are removed by filtration, and the filtrate is evaporated to dryness at reduced pressure to obtain the crude product as a light orange-yellow sticky solid, m.p. 80°-90°C.

Step 11 : (E)-3-(1'-[4"-Fluorophenyl]-3'-(1"-methylethyl)naphth-2'-yl)-prop-2-enal (Reaction W; compound IVF)

Analogous to Example 1, Step 8: m.p. 102°-105°C.

Step 12 : Ethyl (E)-7-(1'-[4"-fluorophenyl]-3'-[1"-methylethyl]naphth-1'-yl)-5-hydroxy-3-oxohept-6-enoate (Reaction A; cmpd. VId)

Analogous to Example 1, Step 9: m.p. 73-76°C.

Step 13 : Ethyl erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-[1"-methylethyl]naphth-2'-yl)hept-6-enoate (Process a); cmpd. no. 13)

Analogous to Example 1, Step 10: yellow gummy foam.

The principal (erythro) product is a racemate that may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The threo minor product (about 8%) is a racemate that may be resolved into the 3R,5R and 3S,5S isomers, of which the former is preferred. The use of a non-stereoselective reduction would afford all four stereoisomers in approximately equal amounts.

Example 11 : Erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-[1"-methylethyl]naphth-2'-yl)hept-6-enoic acid and its sodium salt (Process d, cmpds. nos. 14 (acid) and 15 (salt)

Analogous to Example 2 (without isolation of intermediate sodium salt).

The principal (erythro) product is a racemate which may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The minor (threo) product is also a resolvable racemate, the two enantiomers being the 3R,5R and 3S,5S isomers, of which the former is preferred.

Example 12 : (E)-Trans-6-(2'-[4"'-fluorophenyl)-3"-(1"'-methylethyl)-naphth-2"-yl]ethenyl)-4-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (Process e); compound no. 16)

Analogous to Example 3.

The crude product is purified by preparative thin layer chromatography on silica gel plates utilizing 2% methanol/methylene chloride as the solvent and ethyl acetate to elute the product from the plates. Evaporation of the ethyl acetate at reduced pressure yields the product as a pale yellow foam.

Separation of isomers cf. Example 3.

Example 13 : Sodium erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-[1"-methylethyl]naphth-2'-yl)hept-6-enoate (Process d); compound no. 15)

0.19 ml of 1N. aqueous sodium hydroxide solution is added to 80 mg (0.2 mmole) of Compound no. 16 in 5 ml of absolute ethanol. The reaction mixture is stirred at 20°-25°C for 1 hour and evaporated to dryness at reduced pressure. The residue is dissolved in chloroform, the obtained solution is dried over anhydrous sodium sulfate and evaporated to dryness, and the residue is dried under high vacuum to obtain the product as a pale yellow foam.

The principal product is the erythro racemate which may be resolved to obtain the 3R,5S and 3S,5R enantiomers, of which the former is preferred. A very small amount of the threo racemate is present; it may be resolved to obtain the 3R,5R and 3S,5S enantiomers, of which the former is preferred.

Example 14 : Ethyl erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-methylnaphth-2'-yl)hept-6-enoate (Compound no. 17)

Step 1/2 : 1-Methoxy-2-naphthoic acid (Compound no. XXIIIb)

1-Hydroxy-2-naphthoic acid is dimethylated substantially as described in Example 5, Step 2 and the resulting Ethyl-1-methoxy-2-naphthoate hydrolysed substantially according to Example 2: m.p. of product 126°-128°C.

Steps 3 to 7 : 4,4-Dimethyl-2-(1'-[4"-fluorophenyl]naphth-2'-yl)-2-oxazoline (Reactions M - Q; compound XXXIIc)

Analogous to to Example 1, Steps 1 to 5:
m.p. Step 4 product = 95°-97°
m.p. Step 6 product = 75°-78°
m.p. Step 7 product (XXXIIc) = 96°-98°

Step 8 : 4,4-Dimethyl-2-(1'-[4"-fluorophenyl]-3'-methylnaphth-2'-yl)-2-oxazoline (Reaction CA; compound XXXIId)

16.16 ml of 1.7M. n-butyllithium/n-hexane (27.5 mmoles) is added dropwise to 7.9 g (24.8 mmoles) of Compound XXXIIc in 185 ml of anhydrous diethyl ether stirred at 0°C under nitrogen. The reaction mixture is stirred at 0°C for 30 minutes, 3.9. g (27.5 mmoles) of methyl iodide is added and the reaction mixture is allowed to warm to 20°-25°C and stirred at this temperature for 20 hours, the reaction mixture being maintained under nitrogen throughout. Saturated aqueous sodium chloride solution and additional diethyl ether are added. The diethyl ether phase is separated, dried over anhydrous sodium sulfate and evaporated at reduced pressure until the onset of turbidity, and petroleum ether is added. The precipitate is washed with petroleum ether and dried under high vacuum, m.p. 125°-129°C.

Steps 9 to 13 : Ethyl erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-methylnaphth-2'-yl)hept-6-enoate (Compound no. 17)

Analogous to Example 1, Step 6; Example 10, Step 10; Example 1, Steps 8 to 10.

m.p. product of Step 10 first reaction isolated, 115°-118°
m.p. product of step 10 second reaction, 104-107°
m.p. product of Step 11. 143°-147°
m.p. product of Step 12, 89°-92°
m.p. product of Step 13 (compound no. 17), 121°-124°.

The product, the erythro racemate, may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. It contains a small amount (less than about 5%) of the corresponding threo compound, a racemate that may be resolved into the 3R,5R and 3S,5S isomers, of which the former is preferred. The use of a non-stereoselective reduction would afford all four stereoisomers in approximately equal amounts.

Example 15 : Sodium erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-methylnaphth-2'-yl)hept-6-enoate (Process d); compound no. 18)

Analogous to Example 2 with isolation of sodium salt; m.p. 222°-226° (dec.).

The erythro component of the product, the erythro racemate, may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The product contains a small amount (less than about 5%) of the corresponding threo, compound also a resolvable racemate, the two enantiomers being the 3R,5R and 3S,5S isomers, of which the former is preferred.

Example 16 : Ethyl erythro-(E)-3,5-dihydroxy-7-(3'-ethyl-1'-[4"-fluorophenyl]naphth-2'-yl)hept-6-enoate (Compound no. 19)

Step 1 : 2-(3'-Ethyl-1'-[4"-fluorophenyl]naphth-2'-yl)-4,4-dimethyl-2-oxazoline (Reaction CB; compound XXXIIe)

Analogous to Example 14, Step 8 starting from XXXIId; m.p. product 106°-109°.

Step 2 to 6 : Ethyl erythro-(E)-3,5-dihydroxy-7-(3'-ethyl-1'-[4"-fluorophenyl]naphth-2'-yl)hept-6-enoate (Compound no. 19)

Analogous to Example 1, Step 6; Example 10, Step 10; Example 1, Steps 8 to 10.

m.p. product of Step 2 = 200° (dec.)
m.p. product of Step 5 = 92°-98°
m.p. product of Step 6 = (compound no. 19) = 101°-106°.

The principal component of the product, the erythro racemate, may be resolved into two optically pure enantiomers, the 3R,5S and 3S,5R isomers, of which the former is preferred. The use of a non-stereoselective reduction would afford all four stereoisomers in approximately equal amounts.

Example 17 : Erythro-(E)-3,5-dihydroxy-7-(3'-ethyl-1'-[4"-fluorophenyl]-naphth-2'-yl)hept-6-enoic acid and its sodium salt (Process d); compound nos. 20 and 21)

Analogous to Example 2 (without isolation of intermediate sodium salt); separation of isomers as Example 16.

Example 18 : (E)-Trans-6-(2'-[3"-ethyl-1"-(4"'-fluorophenyl)naphth-2"-yl)-ethenyl)-4-hydroxy-3,4,5,6-tetrahydropyran-2-one (process e); compound no. 22)

Analogous to Examples 3 and 12; m.p. 118°-122°; separation of isomers cf. Example 3 (about 9% of cis racemate).

Example 19 : Sodium erythro-(E)-3,5-dihydroxy-7-(3'-ethyl-1'-[4"-fluorophenyl]naphth-2'-yl)hept-6-enoate (process d) compound no. 21)

Analogous to Example 13 starting from compound no. 22.

The principal component of the product is the erythro racemate which may be resolved to obtain the 3R,5S and 3S,5R enantiomers, of which the former is preferred. The product contains a small amount of the corresponding threo racemate, which may be resolved to obtain the 3R,5R and 3S,5S enantiomers, of which the former is preferred.

TABLE I

The following compounds of Groups IAa1-IAa3 may be synthesized by the processes set forth above:

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
1	H	H	H	4-F	H	2	(E)CH=CH	1	H	C_2H_5	E	114-116°
12	H	H	H	4-F	H	2	"	1	H	C_2H_5	4 enantiomers	gum
2	H	H	H	4-F	H	2	"	1	H	H	E	43-102°
3	H	H	H	4-F	H	2	"	1	H	Na	E	210-220° (dec.)
6	4-Cl	H	H	4-F	H	2	"	1	H	C_2H_5	E	121-124°

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
7	4-Cl	H	H	4-F	H	2	(E)CH=CH	1	H	H	E	oil
8	4-Cl	H	H	4-F	H	2	"	1	H	Na	E	201-204°(dec.
11	H	H	H	4-F	H	2	"	1	H	Na	E(3R,5S)	215-220°(dec.
13	3-iC_3H_7	H	H	4-F	H	1	"	2	H	C_2H_5	E	gummy foam
14	3-iC_3H_7	H	H	4-F	H	1	"	2	H	H	E	

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
15	3-iC_3H_7	H	H	4-F	H	1	(E)CH=CH	2	H	Na	E	fpa.
17	3-CH_3	H	H	4-F	H	1	"	2	H	C_2H_5	E	121-124°
18	3-CH_3	H	H	4-F	H	1	"	2	H	Na	E	222-226°(dec.)
19	3-C_2H_5	H	H	4-F	H	1	"	2	H	C_2H_5	E	101-106°
20	3-C_2H_5	H	H	4-F	H	1	"	2	H	H	E	oil

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
21	3-C_2H_5	H	H	4-F	H	1	(E)CH=CH	2	H	Na	E	230°(dec.)
23	H	H	H	4-F	H	2	$-CH_2CH_2-$	1	H	C_2H_5	E	Gum
24	H	H	H	4-F	H	2	"	1	H	Na	E	180-190°
25	H	H	H	4-F	H	2	"	1	H	H	E	Solid foam
26	4-Cl	H	H	4-F	H	2	(E)CH=CH	1	H	K	E	
27	4-CH_3	H	H	4-F	H	2	"	1	H	C_2H_5	E	

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
28	4-CH_3	H	H	4-F	H	2	(E)CH=CH	1	H	Na	E	
29	4-CH_3	H	H	4-F	H	2	"	1	H	H	E	
30	3-CH_3	H	H	4-F	H	1	"	2	H	K	E	
31	3-CH_3	H	H	4-F	H	1	"	2	H	H	E	
32	3-CH_3	H	H	4-F	H	1	-CH_2CH_2-	2	H	C_2H_5	E	

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_1-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
33	3-CH_3	H	H	4-F	H	1	$-CH_2CH_2-$	2	H	Na	E	
34	3-CH_3	H	H	4-F	H	1	$-CH_2CH_2-$	2	H	H	E	
35	1-CH_3	H	H	4-F	H	3	(E)CH=CH	2	H	C_2H_5	E	
36	1-CH_3	H	H	4-F	H	3	"	2	H	K	E	
37	1-CH_3	H	H	4-F	H	3	"	2	H	H	E	
38	1-CH_3	H	H	4-F	H	3	$-CH_2CH_2-$	2	H	CH_3	E	

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
39	1-CH_3	H	H	4-F	H	3	$-CH_2CH_2-$	2	H	Na	E	
40	1-CH_3	H	H	4-F	H	3	$-CH_2CH_2-$	2	H	H	E	
41	H	H	H	H	H	2	(E)CH=CH	1	H	C_2H_5	E	
42	H	H	H	H	H	2	"	1	H	K	E	
43	H	H	H	H	H	2	"	1	H	H	E	

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
44	H	6-OC_6H_5	7-CH_3	3-CF_3	H	2	$-CH_2-$	1	CH_3	CH_3	E	
45	H	6-OC_6H_5	7-CH_3	3-CF_3	H	2	$-CH_2-$	1	CH_3	Na	E	
46	H	6-OC_6H_5	7-CH_3	3-CF_3	H	2	$-CH_2-$	1	CH_3	H	E	
47	H	H	H	4-F	H	1	(E)CH=CH	2	H	C_2H_5	E	Oil
48	H	H	H	4-F	H	1	"	2	H	Na	E	>220°C. (dec.)
49	H	H	H	4-F	H	1	$-CH_2CH_2-$	2	H	C_2H_5	E	Oil

pd. .	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
[illegible]	H	H	H	4-F	H	1	$-CH_2CH_2-$	2	H	Na	E	>190°C. (dec.)
[illegible]	H	H	H	4-F	H	3	(E)CH=CH	2	H	C_2H_5	E	Gum
[illegible]	H	H	H	4-F	H	3	"	2	H	H	E	Solid foam
[illegible]	H	H	H	4-F	H	3	"	2	H	Na	E	225°-230°((d .)

TABLE II

The following compounds of Groups IAb1-IAb3 may be synthesized by the processes set forth above:

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	Isomer	m.p.
4	H	H	H	4-F	H	2	(E)CH=CH	1	H	trans	152-154° (no detectable cis 153-156°)
9	4-Cl	H	H	4-F	H	2	"	1	H	trans	131-134°
10	H	H	H	4-F	H	2	"	1	H	trans (6S,4R)	184-186°
16	3-iC_3H_7	H	H	4-F	H	1	"	2	H	trans	foam
22	3-C_2H_5	H	H	4-F	H	1	"	2	H	trans	110-122°

-74-

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	Isomer	m.p.
54	H	H	H	4-F	H	2	$-CH_2CH_2-$	1	H	<u>trans</u>	Solid foam
55	$4-CH_3$	H	H	4-F	H	2	(E)CH=CH	1	H	<u>trans</u>	
56	$3-CH_3$	H	H	4-F	H	1	"	2	H	<u>trans</u>	
57	$3-CH_3$	H	H	4-F	H	1	$-CH_2CH_2-$	2	H	<u>trans</u>	
58	$1-CH_3$	H	H	4-F	H	3	(E)CH=CH	2	H	<u>trans</u>	
59	$1-CH_3$	H	H	4-F	H	3	$-CH_2CH_2-$	2	H	<u>trans</u>	

Cmpd. No.	R_1	R_2	R_3	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	Isomer	m.p.
60	H	H	H	H	H	2	(E)CH=CH	1	H	<u>trans</u>	
61	H	6-OC_6H_5	7-CH_3	3-CF_3	H	2	$-CH_2-$	1	H	<u>trans</u>	
62	H	H	H	4-F	H	2	(E)CH=CH	1	H	<u>cis</u>	143°-146°C.
63	H	H	H	4-F	H	2	"	1	H	mixture: ~53% <u>cis</u> ~47% <u>trans</u>	134°-137°C.
64	H	H	H	4-F	H	1	$-CH_2CH_2-$	2	H	<u>trans</u>	Oil
65	H	H	H	4-F	H	3	(E)CH=CH	2	H	<u>trans</u>	Solid foam

Table III

The following compounds of Groups IBa1-IBa3 may be synthesized by the processes set forth above:

Cmpd. No.	R_1	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
5	H	4-F	H	2	(E)CH=CH	1	H	C_2H_5	E	Gum
66	H	4-F	H	2	$-CH_2CH_2-$	1	H	K	E	
67	H	4-F	H	2	$-CH_2CH_2-$	1	H	H	E	
68	H	4-F	H	2	(E)CH=CH	1	H	C_2H_5	E	Gum
69	H	4-F	H	2	"	1	H	Na	E	220°-22[illegible]°C. (dec..
70	H	4-F	H	2	"	1	H	H	E	
71	4-Cl	4-F	H	2	"	1	H	C_2H_5	E	

Cmpd. No.	R_1	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
72	4-Cl	4-F	H	2	(E)CH=CH	1	H	K	E	
73	4-Cl	4-F	H	2	"	1	H	H	E	
74	4-CH_3	4-F	H	2	"	1	H	C_2H_5	E	
75	4-CH_3	4-F	H	2	"	1	H	Na	E	
76	4-CH_3	4-F	H	2	"	1	H	H	E	
77	3-CH_3	4-F	H	1	"	2	H	C_2H_5	E	

Cmpd. No.	R_1	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
78	3-CH_3	4-F	H	1	(E)CH=CH	2	H	K	E	
79	3-CH_3	4-F	H	1	"	2	H	H	E	
80	3-CH_3	4-F	H	1	-CH_2CH_2-	2	H	C_2H_5	E	
81	3-CH_3	4-F	H	1	-CH_2CH_2-	2	H	Na	E	
82	3-CH_3	4-F	H	1	-CH_2CH_2-	2	H	H	E	
83	1-CH_3	4-F	H	3	(E)CH=CH	2	H	C_2H_5	E	
84	1-CH_3	4-F	H	3	"	2	H	K	E	

Cmpd. No.	R_1	R_4	R_5 R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
85	1-CH_3	4-F	H	3	$-C(H)=C(H)-$	2	H	H	E	
86	1-CH_3	4-F	H	3	$-CH_2CH_2-$	2	H	C_2H_5	E	
87	1-CH_3	4-F	H	3	$-CH_2CH_2-$	2	H	Na	E	
88	1-CH_3	4-F	H	3	$-CH_2CH_2-$	2	H	H	E	
89	H	H	H	2	$-C(H)=C(H)-$	1	H	C_2H_5	E	
90	H	H	H	2	$-C(H)=C(H)-$	1	H	K	E	
91	H	H	H	2	$-C(H)=C(H)-$	1	H	H	E	

Cmpd. No.	R_1	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	R_7	Isomer	m.p.
92	H	3-CH_3	4-OCH_3	2	-CH_2-	1	CH_3	CH_3	E	
93	H	3-CH_3	4-OCH_3	2	-CH_2-	1	CH_3	Na	E	
94	H	3-CH_3	4-OCH_3	2	-CH_2-	1	CH_3	H	E	
95	H	4-F	H	3	(E)CH=CH	2	H	C_2H_5	E	Gum
96	H	4-F	H	3	"	2	H	H	E	Solid foam
97	H	4-F	H	3	"	2	H	Na	E	215°-230°C. (dec.)

Table IV

The following compounds of Groups IBb1-IBb3 may be synthesized by the processes set forth above:

Cmpd. No.	R_1	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	Isomer	m.p.
98	H	4-F	H	2	$-CH_2CH_2-$	1	H	<u>trans</u>	188°-191°C.
99	H	4-F	H	2	H–C=C–H (trans)	1	H	<u>trans</u>	
100	4-Cl	4-F	H	2	H–C=C–H (trans)	1	H	<u>trans</u>	
101	$4-CH_3$	4-F	H	2	H–C=C–H (trans)	1	H	<u>trans</u>	
102	$3-CH_3$	4-F	H	1	H–C=C–H (trans)	2	H	<u>trans</u>	
103	$3-CH_3$	4-F	H	1	$-CH_2CH_2-$	2	H	<u>trans</u>	
104	$1-CH_3$	4-F	H	3	H–C=C–H (trans)	2	H	<u>trans</u>	

Cmpd. No.	R_1	R_4	R_5, R_{5a}	Position of R_4-bearing Phenyl Group	-X-	Position of -X-Z Group	R_6	Isomer	m.p.
105	1-CH_3	4-F	H	3	$-CH_2CH_2-$	2	H	<u>trans</u>	
106	H	H	H	2	(E)CH=CH	1	H	<u>trans</u>	
107	H	3-CH_3	4-OCH_3	2	$-CH_2-$	1	CH_3	<u>trans</u>	
108	H	4-F	H	2	(E)CH=CH	1	H	<u>cis</u>	
109	H	4-F	H	3	"	2	H	<u>trans</u>	Solid foam
110	H	4-F	H	2	"	1	H	<u>trans</u>	168°-172°C.

In Tables I and III,

E = <u>erythro</u> racemate (two stereoisomers unless otherwise stated)

In Tables II and IV,

<u>cis</u> and <u>trans</u> refer to the relative positions of the R_6 group in the 4-position and the hydrogen atom in the 6-position of the lactone ring (racemates unless otherwise stated)

The principal component of each of Compounds 23-25, 32-34, 38-40, 44-46, 49, 50, 66, 67, 80-82, 86-88, 92-94 is the <u>erythro</u> racemate which may be resolved, the two enantiomers being the 3R,5R and 3S,5S isomers. The minor component (usually about 1-15%) of each example is the corresponding <u>threo</u> racemate which may be separated therefrom and resolved to obtain the 3R,5S and 3S,5R isomers. If, however, a non-stereoselective process were utilized in process a) to reduce the 3-oxo group to the 3-hydroxy group, a resolvable mixture containing approximately equal amounts of the four stereoisomers would be obtained. Preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, <u>viz</u>., the 3R,5R-3S,5S and 3R,5S-3S,5R racemates, with the 3R,5R isomer and the 3R,5R-3S,5S racemate being more preferred.

The principal component of each of Compounds 26-31, 35-37, 41-43, 47, 48, 51-53, 68-79, 83-85, 89-91, 95-97 is likewise ther <u>erythro</u> racemate which may be resolved into two optically pure enantiomers, <u>viz</u>., the 3R,5S and 3S,5R isomers. The minor component (usually about 1-15%) of each example is the corresponding <u>threo</u> racemate which may be separated therefrom and resolved to obtain the 3R,5R and 3S,5S isomers. If, however, a non-stereoselective process were utilized in process a) to reduce the 3-oxo group to the 3-hydroxy group, a resolvable mixture containing approximately equal amounts of the four stereoisomers would be obtained. Preferred are the 3R,5R and 3R,5S isomers and the racemate of which each is a constituent, <u>viz</u>., the 3R,5R-3S,5S and 3R,5S-3S,5R racemates, with the 3R,5S isomer and the 3R,5S-3S,5R racemate being more preferred.

The principal component of each of Compounds 54, 57, 59, 61, 64, 98, 103, 105 and 107 is the <u>trans</u> racemate which may be resolved into two optically pure enantiomers, <u>viz</u>., the 4R,6R and 4S,6S isomers. The minor component (usually about 1-15%) of each example is the corresponding <u>cis</u> racemate which may be separated therefrom and resolved to obtain the 4R,6S and 4S,6R isomers. The use in process e) of a mixture containing approximately equal amounts of the four stereoisomeric carboxylic acids would yield a mixture containing approximately equal amounts of the four stereoisomeric lactones. Preferred are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, with the 4R,6R isomer and the 4R,6R-4S,6S racemate being more preferred.

The principal component of each of Compounds 55, 56, 58, 60, 65, 99-102, 104, 106, 109, 110 is the trans racemate which may be resolved into two optically pure enantiomers, viz., the 4R,6S and 4S,6R isomers. The minor component (usually about 1-15%) of each example is the corresponding cis racemate which may be separated therefrom and resolved to obtain the 4R,6R and 4S,6S isomers. The use in process e) of a mixture containing approximately equal amounts of the four stereoisomeric carboxylic acids would yield a mixture containing approximately equal amounts of the four stereoisomeric lactones as in Compound 63. Preferred are the 4R,6R and 4R,6S isomers and the racemate of which each is a constituent, with the 4R,6S isomer and the 4R,6S-4S,6R racemate being more preferred.

The principal component of each of Compounds 62 and 108 is the cis racemate which may be resolved into two optically pure enantiomers, viz., the 4R,6R and 4S,6S isomers. The minor component (usually about 1-15%) of each example is the corresponding trans racemate which may be separated therefrom and resolved to obtain the 4R,6S and 4S,6R isomers. The preferred isomers are ad indicated in the preceding paragraph.

Each of the compounds of the examples wherein R_7 is a cation may be converted into the corresponding free acid and into the corresponding compounds wherein R_7 is a different M by conventional means.

Throughout the examples, the term "reduced pressure" denotes aspirator pressure, and where no solvent is specified in connection with a solution, the solvent is water. All solvent mixtures are by volume.

The following data were obtained for the preceding compounds. Unless otherwise stated the data are NMR spectra measured at 200 mHz. Shifts are in ppm. relative to tetramethylsilane.

Abbreviations:

s = singlet
d = doublet
dd = doublet of a doublet
t = triplet
q = quartet
m = multiplet
br = broad
bm = broad multiplet
bs = broad singlet

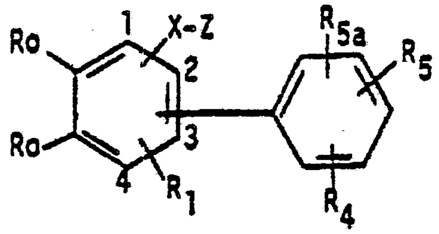
Cmpd. No.	
2	$CDCl_3$: (90mHz); 1.59(m,2H); 2.53(d,2H,J=2.5Hz); 4.24(m,1H); 4.52(m,1H); 5.62(m,1H); 6.83(m,1H); 7.23(m,7H); 7.79(m,2H); 8.13(m,1H).
5	$CDCl_3$: 1.23(t,3H,J=1.5Hz); 1.42(m,6H); 1.8(m,2H); 2.4(m,2H); 2.8(m,4H); 3.12(m,2H); 3.78(m,2H); 4.16(q,2H,J=1.5Hz); 7.15(m,4H); 7.52(m,1H); 7.82(m,1H).
12	$CDCl_3$: 1.28(t,3H,J=1.5Hz); 1.6(m,2H); 2.43(m,2H); 2.95(br,2H); 4.2(q,2H,J=1.5Hz); 4.2(br,1H); 4.51(br,1H); 5.65(m,1H); 6.9(dd,1H,J=3 and 3 Hz); 7.07 (t,2H,J=1.5Hz); 7.41(m,5H); 7.82 (m,2H); 8.17(m.1H).
13	$CDCl_3$: 1.31(m,11H); 2.41(m,2H); 2.88(s,1H); 3.32(m,1H); 3.61(s,1H); 4.09(m,1H); 4.19(q,2H,J=1Hz); 4.33 (m,1H); 5.28(m,1H); 6.54(d,1H,J=2Hz); 7.23(m,7H); 7.77(m,2H).
14	$CDCl_3$: 1.3 (m,8H); 2.49(d,2H); 3.3(m,1H); 3.57(bm,1H); 4.12(bm,2H); 4.36(m,1H); 5.3(dd,1H,J=1.5Hz); 6.56(d,1H,J=3Hz); 7.25(m,8H); 7.78(m,2H).
15	D_2O: 0.9(m,7H); 1.27(m,1H); 2.03(m,2H); 3.0(m,1H); 3.43(m,1H); 3.97(m,1H); 4.9(m,1H); 6.29(d,1H,J=2Hz); 6.72(m,7H); 7.26(m,2H);
16	$CDCl_3$: 1.3(m,6H); 1.45(bm,2H); 1.82(bs,1H); 2.61(m,2H); 3.3(m,1H); 4.12(m,1H); 5.1(m,1H); 5.31(dd.1H,J=1Hz); 6.64(d,1H,J=2.5Hz); 7.25(m,7H); 7.78(m,2H).
18	CD_3SOCD_3: 1.1(m,2H); 1.85(m,2H); 2.5(s,3H); 3.5(m,1H); 4.1(m,1H); 5.4(q,1H,J=1.25Hz); 6.3(d,1H,J=3.5Hz); 7.3(m,7H); 7.83(m,2H).
21	$CDCl_3$ + CD_3OD: 1.25(m,2H); 1.35(t,3H,J=1.5Hz); 2.25(m,2H); 2.89(q,2H,J=1.5Hz); 3.88(m,1H); 4.27(m,1H); 5.39(q,1H,J=1.5Hz); 6.52(d,1H,J=3Hz); 7.25(m,5H); 7.72(m,4H).

Cmpd. No.	
23	$CDCl_3$: 1.29(t,3H,J=1.5Hz); 1.80(m,4H); 2.43(m,2H); 3.13(m,2H); 3.92(m,2H); 4.20(q,2,J=1.5Hz); 7.25(m,5H); 7.56(t,2H,J=1.5Hz); 7.75(d,1H,J=1.5Hz); 7.90(d,1H,J=1.5Hz); 8.17(m,1H).
25	$CDCl_3$: 1.45(m,2H); 1.80(m,2H); 2.45(m,2H); 3.10(m,2H); 3.95(bm,2H); 7.6(bm,10H).
47	$CDCl_3$: 1.26(t,3H,J=1.5Hz); 1.75(m,2H); 2.49(d,2H,J=1.33Hz); 3.13(d,1H,J=0.5Hz); 3.66(d,1H,J=0.5Hz); 4.17(q,2H,J=1.5Hz); 4.25(m,1H); 4.45(m,1H); 6.23(dd,1H,J=1.5 and 2 Hz); 6.47(d,1H,J=3.5Hz); 7.25(m,4H); 7.4(m,3H); 7.8(m,3H).
49	$CDCl_3$: 1.23(t,3H,J=1.5Hz); 1.40(m,2H); 1.65(m,2H); 2.41(d,2H, J=1.5Hz); 2.60(m,2H); 3.25(d,1H,J=0.5Hz); 3.70(d,1H,J=0.5Hz); 3.75(m,1H); 4.15(q,2H,J=1.5Hz); 4.2(m,1H); 7.3(m,8H); 7.83(m,2H).
51	$CDCl_3$; 1.27(t,3H,J=1.5Hz); 1.72(m,2H); 2.5(d,2H,J=1.5Hz); 3.22(s,1H); 3.69(s,1H); 4.15(q,2H,J=1.5Hz); 4.27(m,1H); 4.51(m,1H); 6.22(dd,1H,J=3 and 1.5 Hz); 6.61(d,1H,J=3Hz); 7.11(t,2H,J=2Hz); 7.38(m,4H); 7.67(s,1H); 7.78(m,2H); 7.97(s,1H).
52	$CDCl_3$: 1.73(m,2H); 2.55(d,2H,J=1.5Hz); 4.3(m,1H); 4.5(m,1H); 6.2(dd,1H,J=3 and 1.5 Hz); 6.6(d,1H,J=3Hz); 7.1(m,2H); 7.4(m,4H); 7.66(s,1H); 7.78(m,2H); 7.97(s,1H).
54	$CDCl_3$: 1.82(m,4H); 2.67(m,2H); 3.05(m,1H); 3.26(m,1H); 4.32(m,1H); 4.61(m,1H); 7.10(m,2H); 7.28(m,3H); 7.51(m,2H); 7.72(d,1H,J=1.5Hz); 7.86(m,1H); 8.11(d,1H,J=1.5Hz).
64	$CDCl_3$: 1.7(m,2H); 1.7(m,2H); 1.75(s,1H); 2.7(m,2H); 2,7(m,2H); 4.35(m,1H); 4.56(m,1H); 7.3(m,8H); 7.85(d,2H).

Cmpd.No.	
65	$CDCl_3$: 2.0(m,2H); 2.71(m,2H); 4.41(m,1H); 5.29(m,1H); 6.23(dd,1H,J=3 and 1.5 Hz); 6.7(d,1H,J=3Hz); 7.13(m,2H); 7.41(m,4H); 7.68(s,1H); 7.79(m,2H); 7.98(s,1H).
68	$CDCl_3$: 1.3(t,3H,J=1.5Hz); 1.75(m,6H); 2.43(m,2H); 2.78(m,4H); 4.18(m,3H); 4.37(m,1H); 5.25(dd,1H,J=3 and 1.5 Hz); 6.5(d,1H,J=3Hz); 7.02(m,3H); 7.22(m,3H).
95	$CDCl_3$: 1.24(t,3H,J=1.5Hz); 1.76(m,6H); 2.5(m,2H); 2.8(m,4H); 4.17(m,3H); 4.14(m,1H); 6.06(dd,1H,J=3 and 1.5 Hz); 6.5(d,1H,J=3Hz); 7.1(m,6H).
96	$CDCl_3$: 1.83(m,6H); 2.69(m,6H); 4.26(m,1H); 4.43(m,1H); 6.06(m,1H); 6.52(m,1H); 7.12(m,6H).
109	$CDCl_3$: 1.96(m,6H); 2.73(m,6H); 4.4(m,1H); 5.22(m,1H); 6.1(dd,1H,J=3 and 1.5 Hz); 6.57(d,1H,J=3Hz); 7.17(m,6H).

Claims:

1. A compound of formula I



I

wherein the two groups Ro together form a radical of formula

$$-\left[\underset{R_2}{\overset{8}{C}}=\overset{7}{C}-\overset{6}{C}=\underset{R_3}{\overset{5}{C}}\right]- \quad \text{or} \quad -(CH_2)_4- ,$$

wherein R_2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

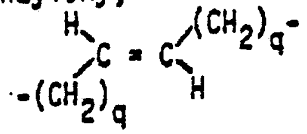
R_3 is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, with the provisos that not more than one of R_2 and R_3 is trifluoromethyl, not more than one of R_2 and R_3 is phenoxy, and not more that one of R_2 and R_3 is benzyloxy,

R_1 is hydrogen, C_{1-6}alkyl, fluoro, chloro or benzyloxy,

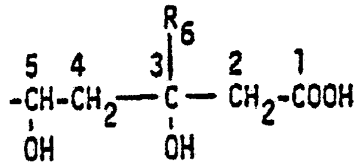
R_4 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, (except t-butoxy), trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

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 with the provisos that 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,

X is $-(CH_2)_n-$, 

wherein n is 0, 1, 2 or 3 and both q's are 0 or one is 0 and the other is 1

Z is  II

wherein R_6 is hydrogen or C_{1-3}alkyl, with the general proviso that -X-Z and the R_4 bearing phenyl group are ortho to each other;

in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a δ lactone thereof or in salt form.

2. A compound according to Claim 1 wherein Ro, R_1, R_2, R_3, R_4, R_5, R_{5a}, X and Z have meanings selected from those hereinbefore defined in Groups (i) to (cxx).

3. Erythro-(E)-3R,5S,dihydroxy-7-(2'-[4"-fluorophenyl]naphth-1'-yl)hept-6-enoate or a salt thereof.

4. Erythro-(E)-3,5-dihydroxy-7-(1'-[4"-fluorophenyl]-3'-[1'-methylethyl]naphth-2'-yl)hept-6-enoate or a salt thereof.

5. (E)-Trans-6-(2'-[3"-ethyl-1"-(4"'-fluorophenyl)naphth-2"-yl]-ethenyl)-4-hydroxy-3,4,5,6-tetrahydropyran-2-one.

6. A compound according to Claim 3 or 4 in sodium salt form.

7. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 6 as appropriate in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form, together with a pharmaceutically acceptable diluent or carrier.

8. A method of inhibiting chlolesterol biosynthesis or treating atherosclerosis by administering to a subject in need of such treatment an effective amount of a compound according to any one of Claims 1 to 6 as appropriate in free acid form or in the form of a physiologicallyhydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form.

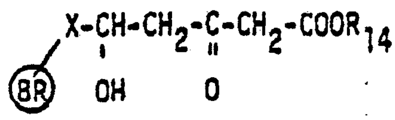
9. The use of a compound according to any one of Claims 1 to 6 as appropriate in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form in inhibiting cholesterol biosynthesis or treating atherosclerosis.

10. A compound according to any one of Claims 1 to 6 as appropriate in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use as a pharmaceutical.

11. A compound according to any one of Claims 1 to 6 as appropriate in free acid form or in the form of a physiologically-hydrolysable and -acceptable ester or a lactone thereof or in pharmaceutically acceptable salt form for use in inhibiting cholesterol biosynthesis or treating atherosclerosis.

12. A process for preparing a compound according to Claim 1 which comprises

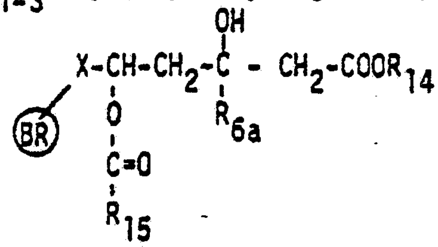
a) When R_6 is hydrogen reducing a compound of formula VI



VI

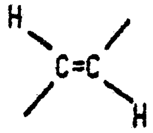
wherein R_{14} is a radical forming a physiologically-hydrolysable and acceptable ester and X, is as defined above,

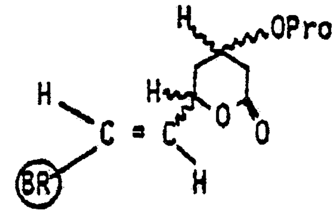
b) when R_6 = C_{1-3}alkyl, hydrolysing a compound of formula XVII



XVII

wherein R_{6a} is C_{1-3}alkyl, R_{15} is part of an ester forming group and X and R_{14} are as defined above,

c) when X is  deprotecting a compound of formula LIX



LVIII

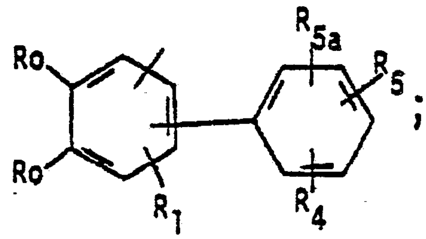
wherein Pro is a protecting group

d) hydrolysing a compound of formula I in the form of a physiologically-hydrolysable ester or a lactone or

e) esterifying or lactonising a compound of formula I in free acid form,

and when a free carboxyl group is present, recovering the compound obtained in free acid form or in the form of a salt, whereby

(BR) represents the basic ring structure



; Ro, R_1, R_4, R_{5a}, R_5, X and Z

as defined in Claim 1.

13. A process for preparing a compound of formula I which comprises hydrolysing a compound of formula I in ester or lactone form or esterifying or lactonising a compound of formula I in free acid form and when a free carboxyl group is present recovering the compound obtained in free acid form or in the form of a salt.

14. A compound of formula VI, XII, XV, XVII, XXVIII-XXX, XXXII, XXXIII, XXXV-XL, XLII-L, LII-LIV, LVI-LVIII, CXIX-CXXII, CXXIV-CXXVII, CXXXI or CXXXII as hereinbefore defined.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 84/00018

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC^3: C 07 C 59/56; 69/732; 103/38; C 07 D 261/08; C 07 C 47/546; C 07 D 309/10; C 07 C 39/367; 43/29; 59/64; 33/46; ./.

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC^3	C 07 C 59/00; C 07 C 69/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	EP, A, 0011928 (SANKYO COMPANY LTD.) 11 June 1980 see claims 1-4,8,9; page 4, lines 3-15 ------	1,7

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
13th April 1984	17 MAI 1984
International Searching Authority [1]	**Signature of Authorized Officer** [20]
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 84/00018 -2-

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3]: 25/18; C 07 F 9/54; 7/18; C 07 C 43/164; A 61 K 31/19; 31/215; 31/365; 31/42.

II. FIELDS SEARCHED

Minimum Documentation Searched[4]

Classification System	Classification Symbols
IPC[3]	

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[14]

Category *	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No.[18]

* Special categories of cited documents:[15]

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search[2]	Date of Mailing of this International Search Report[2]
International Searching Authority[1]	**Signature of Authorized Officer**[20]
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

Form PCT/ISA/210 (second sheet) (October 1981)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 84/00018 (SA 6432)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/05/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0011928	11/06/80	US-A- 4248889	03/02/81
		JP-A- 55059140	02/05/80
		AT-A- 910	15/05/82

For more details about this annex :
see Official Journal of the European Patent Office, No. 12/82