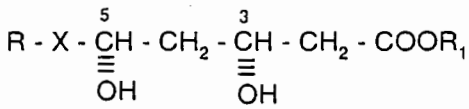
7-SUBSTITUTED-HEPT-6-ENOIC AND -HEPTANOIC ACIDS AND DERIVATIVES THEREOF

The invention relates to the preparation of 7-substituted-hept-6-enoic and -heptanoic acids and derivatives and intermediates thereof.

1. Object

The invention concerns a process for the preparation of a compound of formula I



(I)

wherein

X is $-CH_2CH_2-$ or $-CH=CH-$;

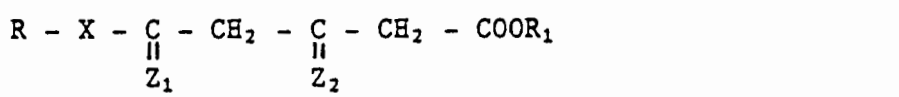
R_1 is an ester group inert to the reaction conditions; and

R is an organic radical having groups which are inert under reducing conditions, with the proviso that, when R is triphenylmethyl, then R_1 additionally includes allyl and X is $-OCH_2-$.

It also comprises a process for the preparation of earlier intermediates (of formulae Va and VII, see below).

The common feature linking these various process steps is that they all lead to improvements at various stages in the preparation of 7-substituted-hept-6-enoic and -heptanoic acid end products and derivatives thereof which are cholesterol biosynthesis inhibitors. This link is illustrated hereunder with a specific embodiment concerning the preparation of one specific cholesterol biosynthesis inhibitor, namely erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoic acid in racemic or optically pure form; in free acid, salt, ester or δ-lactone, i.e. internal ester, form.

The process of the invention for the preparation of a compound of formula I comprises stereoselectively reducing a racemic or optically pure compound of formula II



(II)

wherein

R, R_1 and X are as defined above and

one of Z_1 and Z_2 is oxygen and the other is hydroxy and hydrogen,

to produce a corresponding compound of formula I.

As appears from formula I the compounds have the syn, i.e. the erythro configuration.

The symbol (E)- appearing at the beginning of a formula or in a name indicates that a double bond is in the trans configuration.

The invention also comprises a compound of formula I as defined above in a state of optical purity such that the proportion of erythro to threo isomer is 99.1 : 0.9 or higher, preferably 99.5 : 0.5 or higher, especially 99.7 : 0.3 or higher.

The compounds of formula I, which are esters, and the corresponding free acids, salts and cyclic esters (δ-lactones) are pharmaceuticals, in particular HMG-CoA reductase inhibitors, i.e. cholesterol biosynthesis inhibitors and, therefore, they are indicated for use for the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

2. Preferred significances

An ester group R_1 preferably is a physiologically acceptable and hydrolyzable ester group when the desired end product is an ester.

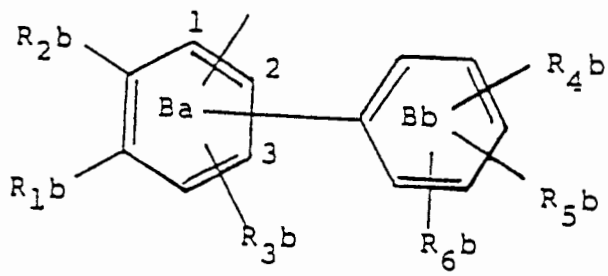
By the term "physiologically acceptable and hydrolyzable ester group" is meant a group which, together with the -COO- radical to which it is attached, forms an ester group which is physiologically acceptable and hydrolyzable under physiological conditions to yield the corresponding carboxylic acid of the compound of formula I (i.e. wherein R_1 is replaced by hydrogen) and an alcohol which itself is physiologically acceptable, i.e. non-toxic at the desired dosage level, particularly a group which is free of centers of asymmetry.

R_1 is preferably R_2 where R_2 is C_{1-4}alkyl or benzyl, especially R_2' where R_2' is C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl, e.g. ethyl, preferably isopropyl or t-butyl, especially t-butyl.

X preferably is X' where X' is -CH=CH-, preferably (E)-CH=CH-.

R preferably is selected from a group A, B, C, D, Ea, Eb, Ec, F, G, H, J, K, L, M or N as follows:

A phenyl trisubstituted by R_{1a}, R_{2a} and R_{3a} wherein R_{1a}, R_{2a} and R_{3a} are independently hydrogen; halo; C_{1-4}alkyl; C_{1-4}haloalkyl; phenyl; phenyl substituted by halo, C_{1-4}alkoxy, C_{2-8}alkanoyloxy, C_{1-4}alkyl or C_{1-4}haloalkyl; or $-OR_{4a}$ wherein R_{4a} is hydrogen, C_{2-8}alkanoyl, benzoyl, phenyl, halophenyl, phenyl(C_{1-3}alkyl), C_{1-9}alkyl, cinnamyl, C_{1-4}haloalkyl, allyl, cycloalkyl(C_{1-3}alkyl), adamantyl(C_{1-3}alkyl) or substituted phenyl(C_{1-3}alkyl) each substituent of which is selected from halo, C_{1-4}alkoxy, C_{1-4}alkyl and C_{1-4}haloalkyl; whereby the halogen atoms are fluoro or chloro and cycloalkyl includes cyclohexyl;

B 

wherein R_1b and R_2b together form a radical of formula:

a) $-C^{8}(R_7b)=C^{7}-C^{6}(R_8b)=C^{5}-$ or b) $-CH_2-CH_2-CH_2-CH_2-$

wherein

R_3b is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

R_4b 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_5b 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_4b and R_5b is trifluoromethyl, not more than one of R_4b and R_5b is phenoxy, and not more than one of R_4b and R_5b is benzyloxy;

R_6b is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro;

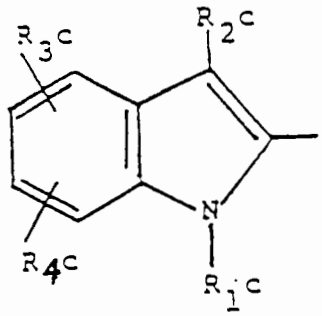
R_7b is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, C_{1-3}alkoxy, n-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

R_8b 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_7b and R_8b is trifluoromethyl, not more than one of R_7b and R_8b is phenoxy, and not more than one of R_7b and R_8b is benzyloxy;

with the further proviso that the free valences on rings Ba and Bb are ortho to each other;

C



wherein

one of R_1c and R_2c is phenyl substituted by R_5c, R_6c and R_7c and the other is C_{1-3}alkyl, n-butyl or i-butyl,

R_3c is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_4c 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_3c and R_4c is trifluoromethyl, not more than one of R_3c and R_4c is phenoxy and not more than one of R_3c and R_4c is benzyloxy,

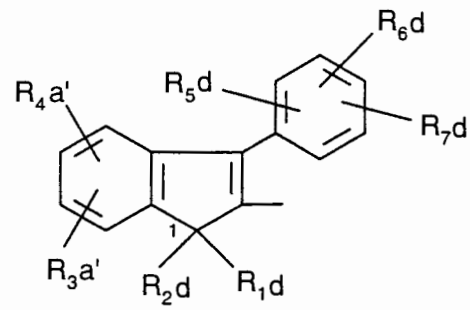
R_5c is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_6c 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_5c and R_6c is trifluoromethyl, not more than one of R_5c and R_6c is phenoxy and not more than one of R_5c and R_6c is benzyloxy, and

R_7c is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro;

D



wherein

R_1d is hydrogen or primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom and

R_2d is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom or

R_1d and R_2d taken together are $-(CH_2)_m-$ or (Z)-CH_2-CH=CH-CH_2- wherein m is 2, 3, 4, 5 or 6;

R_3d is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_4d 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_2d and R_3d is trifluoromethyl, not more than one of R_2d and R_3d is phenoxy and not more than one of R_2d and R_3d is benzyloxy,

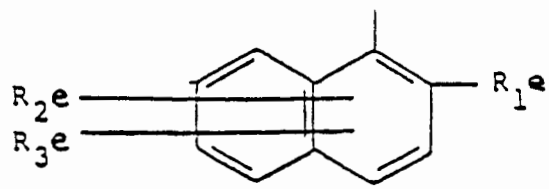
R_5d is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

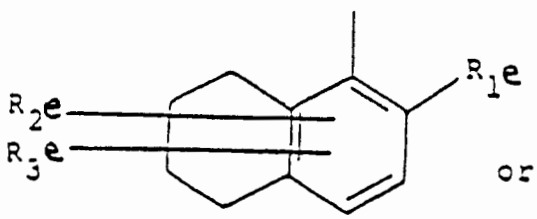
R_6d is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

with the provisos that not more than one of R_5d and R_6d is trifluoromethyl, not more than one of R_5d and R_6d is phenoxy and not more than one of R_5d and R_6d is benzyloxy,

R_7d is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro;

Ea





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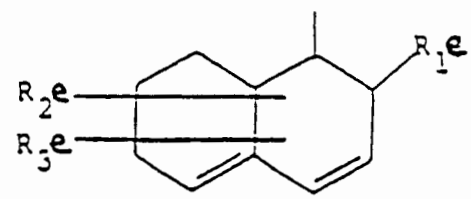
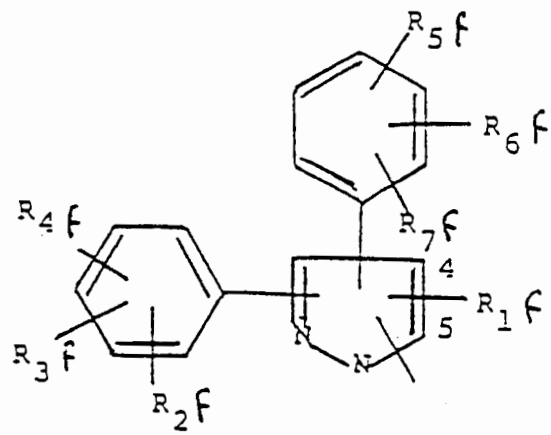


Eb Ec

wherein

each of R_1e, R_2e and R_3e is independently fluoro, chloro, hydrogen or C_{1-4} alkyl, R_1e preferably being methyl;

F



wherein

R_1f is C_{1-6}alkyl not containing an asymmetric carbon atom,

each of R_2f and R_5f is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenyl, phenoxy or benzyloxy,

each of R_3f and R_6f is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy and

each of R_4f and R_7f is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

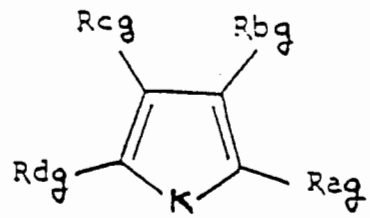
with the provisos that not more than one of R_2f and R_3f is trifluoromethyl, not more than one of R_2f and R_3f is phenoxy, not more than one of R_2f and R_3f is benzyloxy, not more than one of R_5f and R_6f is trifluoromethyl, not more than one of R_5f and R_6f is phenoxy and not more than one of R_5f and R_6f is benzyloxy;

with the provisos that

(i) the free valence of the pyrazole ring is in the 4- or 5- position, and

(ii) the R_1f group and the free valence are ortho to each other;

G



wherein

Rag is a single bond to X, Rbg is R_2g, Rcg is R_3g, Rdg is R_4g and K is $-\underset{\underset{R_1g}{|}}{N}-$; or

Rag is R_1g, Rbg is a single bond to X, Rcg is R_2g, Rdg is R_3g, and K is O, S or $-\underset{\underset{R_4g}{|}}{N}-$;

R_1g, R_2g, R_3g and R_4g independently are C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl or phenyl substituted by R_5g, R_6g and R_7g, or in the case of R_3g and R_4g additionally hydrogen, or for R_3g when K is O or S and X is X′ additionally Ga, and

Ga is $-C(R_{17}g)=C(R_{18}g)R_{19}g$ wherein

$R_{17}g$ is hydrogen or C_{1-3}alkyl and

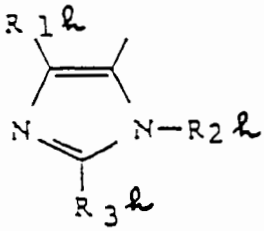
$R_{18}g$ and $R_{19}g$ are independently hydrogen, C_{1-3}alkyl or phenyl,

each R_5g is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy;

each R_6g is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, bromo, phenoxy or benzyloxy; and

each R_7g is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

with the proviso that there may only be one each of trifluoromethyl, phenoxy and benzyloxy on each phenyl ring substituted by R_5g, R_6g and R_7g;

H 

wherein

R_1h is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl, adamantyl-1 or phenyl substituted by R_4h, R_5h and R_6h;

R_2h is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl, adamantyl-1 or phenyl substituted by R_7h, R_8h and R_9h;

R_3h is hydrogen, C_{1-6} alkyl not containing an asymmetric carbon atom, C_{3-7}cycloalkyl, adamantyl-1, styryl or phenyl substituted by $R_{10}h$, $R_{11}h$ and $R_{12}h$;

each of R_4h, R_7h and $R_{10}h$ is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy,

each of R_5h, R_8h and $R_{11}h$ is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, bromo, $-COOR_{17}h$, $-N(R_{19}h)_2$, phenoxy or benzyloxy, wherein

$R_{17}h$ is hydrogen, $R_{18}h$ or M, wherein

$R_{18}h$ is C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl, and

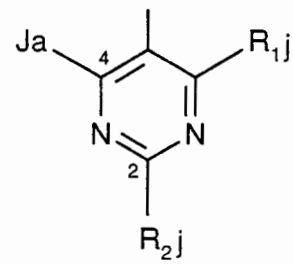
M is as defined above, and

each $R_{19}h$ is independently C_{1-6}alkyl not containing an asymmetric carbon atom, and

each of R_6h, R_9h and $R_{12}h$ is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

with the provisos that not more than one substituent on each phenyl ring independently is trifluoromethyl, not more than one substituent on each phenyl ring independently is phenoxy, and not more than one substituent on each phenyl ring independently is benzyloxy;

J



wherein

each of R_1j and R_2j is independently C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$- wherein m is 0, 1, 2 or 3 and the phenyl group is unsubstituted or substituted by any of R_3j, R_4j and R_5j wherein R_3j, R_4j and R_5j are as defined below; or

R_2j is -Yj-benzyl, $-N(R_8j)_2$ or Ja wherein

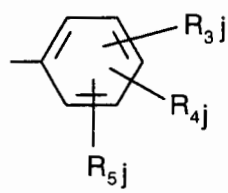
Yj is -O- or -S-;

each R_8j is independently C_{1-4}alkyl not containing an asymmetric carbon atom or may form part of a 5-, 6-, or 7-membered ring Jb, ring Jb being substituted or unsubstituted and optionally also containing one or more heteroatoms; and

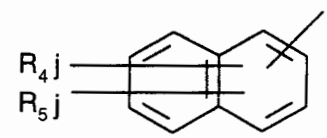
Ja is Ja' or Ja" wherein

Ja' is a heterocyclic group which is unsubstituted or substituted by one or two C_{1-2}alkyl or C_{1-2}alkoxy groups and

Ja" is Ja"a or Ja"b



Ja"a



Ja"b

wherein

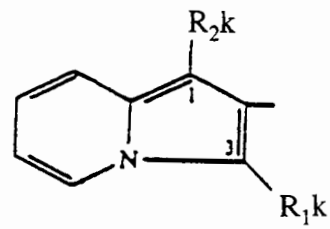
R_3j is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy,

R_4j is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy and

R_5j is hydrogen, C_{1-2}alkyl, C_{1-3}alkoxy, fluoro or chloro;

with the provisos that not more than one of R_3j and R_4j is trifluoromethyl, not more than one of R_3j and R_4l is phenoxy and not more than one of R_3j and R_4j is benzyloxy;

K



wherein

each of R_1k and R_2k is independently

(a) phenyl substituted by R_5k, R_6k and R_7k wherein

R_5k is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

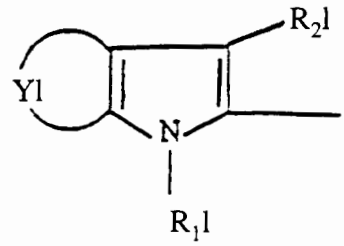
R_6k is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, fluoro, or chloro; and

R_7k is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro;

(b) hydrogen or a primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom;

(c) C_{3-6}cycloalkyl; or

(d) phenyl-$(CH_2)_m$- wherein m is 1, 2 or 3;

L 

wherein Yl is -CH=CH-CH=N-, -CH=CH-N=CH-, -CH=N-CH=CH- or -N=CH-CH=CH-,

R_1l is primary C_{1-6}alkyl not containing an asymmetric carbon atom; or isopropyl;

R_2l is:

a) phenyl substituted by R_5l, R_6l and R_7l wherein R_5l is t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

R_6l 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_5l and R_6l is trifluoromethyl, not more than one of R_5l and R_6l is phenoxy, and not more than one of R_5l and R_6l is benzyloxy,

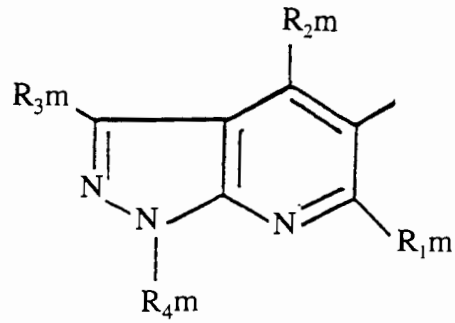
R_7l is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

b) a primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom,

c) C_{3-6}cycloalkyl or

d) phenyl-$(CH_2)_m$- wherein m is 1, 2 or 3;

M



wherein

R_1m is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{5-7}cycloalkyl, (C_{5-7}cycloalkyl)methyl, phenyl-$(CH_2)_m$-, pyridyl-2, pyridyl-3, pyridyl-4, thienyl-2, thienyl-3 or phenyl substituted by R_5m, R_6m and R_7m;

R_2m is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{5-7}cycloalkyl, (C_{5-7}cycloalkyl)methyl, phenyl-$(CH_2)_m$-, pyridyl-2, pyridyl-3, pyridyl-4, thienyl-2, thienyl-3 or phenyl substituted by R_8m, R_9m and $R_{10}m$,

with the proviso that not more than one of R_1m and R_2m is a member of the group consisting of pyridyl-2, pyridyl-3, pyridyl-4, thienyl-2, thienyl-3, phenyl substituted by R_5m, R_6m and R_7m and phenyl substituted by R_8m, R_9m and $R_{10}m$;

R_3m is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{5-7}cycloalkyl or phenyl substituted by $R_{11}m$, $R_{12}m$ and $R_{13}m$;

R_4m is C_{1-6}alkyl not containing an asymmetric carbon atom, C_{5-7}cycloalkyl or phenyl substituted by $R_{14}m$, $R_{15}m$ and $R_{16}m$

wherein

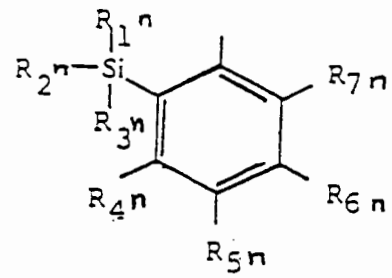
each of R_5m, R_8m, $R_{11}m$ and $R_{14}m$ is independently hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, bromo, phenyl, phenoxy or benzyloxy,

each of R_6m, R_9q, $R_{12}m$ and $R_{15}m$ is independently hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy, and

each of R_7m, $R_{10}m$, $R_{13}m$ and $R_{16}m$ is independently hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro,

with the provisos that not more than one substituent on each phenyl ring independently is trifluoromethyl, not more than one substituent on each phenyl ring independently is phenoxy, and not more than one substituent on each phenyl ring independently is benzyloxy;

N



wherein

each of R_1n, R_2n and R_3n is independently alkyl of 1 to 4 carbon atoms; or phenyl which may be unsubstituted or substituted either by one or two alkyl or alkoxy groups of 1 to 3 carbon atoms, or chloro; or by one fluoro, bromo or trifluoromethyl substituent;

R_4n is hydrogen or alkyl of 1 to 3 carbon atoms, e.g. methyl;

R_5n is hydrogen, lower alkyl or alkoxy; halo, trifluoromethyl; or phenyl, benzyl, or benzyloxy, wherein the aromatic portion may be unsubstituted or substituted by up to two groups, one of which may be fluoro, bromo or trifluoromethyl; or one or two of which may be lower alkyl or alkoxy, or chloro;

R_6n is hydrogen, lower alkyl or alkoxy, halo, or trifluoromethyl; and

R_7n is hydrogen, lower alkyl or alkoxy, halo or trifluoromethyl; and

any of $R_4n + R_5n$, $R_5n + R_6n$, or $R_6n + R_7n$ may constitute either a $-CH=CH-CH=CH-$ or a $-(CH_2)_4-$ radical to form a ring which is substituted by R_8n which is hydrogen; halo, or lower alkyl or alkoxy;

provided that there be no more than one trifluoromethyl group and no more than two bromo substituents present on the molecule.

The compounds of formula I may be divided into thirteen groups, i.e., groups IA to IN, depending upon the significance of R, i.e.:

IA when R = A,

IB when R = B,

IC when R = C,

ID when R = D,

IE when R = Ea, Eb or Ec,

IF when R = F,

IG when R = G,

IH when R = H,

IJ when R = J,

IK when R = K,

IL when R = L,

IM when R = M and

IN when R = N.

3. Stereochemistry

Generally, when a hydroxy-keto compound of formula II is reduced to a dihydroxy compound of formula I, an additional center of asymmetry is generated. Consequently, when a racemic compound of formula II is utilized, four stereoisomers (comprising two pairs of enantiomers, i.e. a pair of erythro and a pair of threo enantiomers) of the resulting compound of formula I are formed. Alternatively, when an optically pure compound of formula II is utilized, two diastereoisomers (i.e. one erythro and one threo isomer) of the compound of formula I are formed, e.g., the 3R,5S and 3S,5S diastereoisomers which result from the reduction of the 5S hydroxy compound. Diastereoisomers may be separated by conventional means, such as by fractional crystallization, column chromatography, preparative thin layer chromatography or HPLC. The proportion of erythro to threo isomer obtained by these methods is usually variable and can be e.g. up to about 98 : 1.

With the stereoselective process of the present invention, when a racemic compound of formula II is utilized, only two stereoisomers (comprising the erythro pair of enantiomers) of the resulting compound of formula I are formed almost exclusively. Alternatively, when an optically pure compound of formula II is utilized, only one enantiomer of the compound of formula I is formed almost exclusively, and this enantiomer is the corresponding erythro enantiomer. For example, the 3R,5S enantiomer results from the reduction of the 5S hydroxy compound wherein X is -CH=CH-.

The proportion of erythro to threo isomer obtained with the process of the present invention is about 99.1 : 0.9 or higher, particularly about 99.5 : 0.5 or higher, especially about 99.7 : 0.3 or higher.

The term "stereoselective" as used herein thus means that the proportion of the erythro to the threo form is 99.1 : 0.9 or higher.

The stereoisomers of the compounds of formula I wherein X is -CH=CH- according to the present invention are the 3R,5S and the 3S,5R isomer and the racemate consisting of both of them, of which the 3R,5S isomer and the racemate are preferred.

The stereoisomers of the compounds of formula I wherein X is $-CH_2CH_2-$ according to the present invention are the 3R,5R and the 3S,5S isomer and the racemate consisting of both of them, of which the 3R,5R isomer and the racemate are preferred.

4. State of the art

Conventional processes for reducing the keto group of a compound of formula II have employed mild reducing agents such as sodium borohydride or a complex of t-butylamine and borane, in an inert organic solvent such as a lower alkanol, to yield a mixture of diastereomeric forms from the optically pure starting compound, or alternatively, the racemic diastereoisomers from the racemic starting material.

A three-step, partly stereoselective reduction process has been used to obtain predominantly the erythro racemate from the racemic starting material. In the first step, a compound of formula II is contacted either with a trialkylborane compound or a compound of formula III:

$$R_4O\text{-}B\text{-}(R_3)_2 \qquad \text{(III)}$$

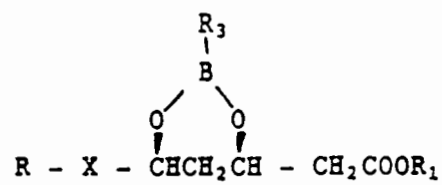
in which R_4 is allyl or lower alkyl having from 1 to 4 carbon atoms, preferably not tertiary, and R_3 is a primary or secondary alkyl having 2 to 4 carbon atoms, preferably not tertiary, in a reaction medium comprising an alcohol and tetrahydrofuran (THF). In the second step of such processes, sodium borohydride ($NaBH_4$) is added to the reaction medium, and reaction proceeds with the reduction of the keto group, and in turn to the formation of the cyclic boronate or a borane complex of the compound of formula I. In the third step, the reaction mixture containing the boron complex and/or cyclic boronate ester is azeotroped with methanol or ethanol, or alternatively, is treated in an organic solvent with aqueous peroxy compound, such as a peroxide, e.g. hydrogen peroxide, or a perborate, e.g. sodium perborate, to yield the resulting compounds of formula I. The aforementioned process is said to provide the erythro racemate with, e.g., about 98 % selectivity relative to the threo isomers (Chen et al., Tetrahedron Letters 28, 155 [1987]).

5. Detailed description

The process of the present invention comprises a method for stereoselectively reducing racemic and optically pure compounds of formula II to obtain almost exclusively the erythro isomers of formula I. Advantageously, the reduction of the keto group of the compound of formula II occurs virtually instantaneously. The compounds of formula I, i.e. the erythro isomers, are, additionally, provided in increased chemical purity and may be further enriched to above 99 % chemical purity by simple recrystallization.

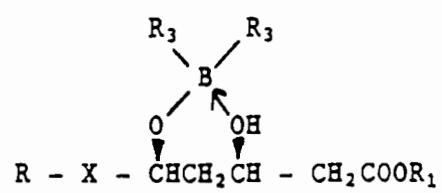
According to a first step of the process of the present invention [step (a)], a compound of formula III is mixed with sodium borohydride $NABH_4$ in a reaction medium comprising an alcohol and tetrahydrofuran.

In a second step [step (b)], a compound of formula II is treated with the mixture obtained in step (a) under conditions suitable to obtain a mixture containing a cyclic boronate compound of formula IV(a)



[IV(a)]

and/or a boron complex of formula IV(b)



[IV(b)]

wherein R, R_1, R_3 and X are as defined above. The latter predominates prior to quenching. However, quenching converts the boron complex into boronate ester.

In a third step [step (c)], the product obtained in step (b) is cleaved to obtain a corresponding compound of formula I.

Step (a) is preferably carried out under essentially anhydrous conditions, preferably in an inert atmosphere, at from about -100° to about +30°C, preferably at from about -80° to about -60 °C, especially at from about -78° to about -70°C. The reaction medium employed in step (a) comprises a mixture of alcohol and tetrahydrofuran wherein the alcohol is of formula AlkOH, in which Alk is alkyl of 1 to 4 carbon atoms, e.g. methyl or ethyl, preferably not tertiary.

One of the products of step (a) may be R_4OH, derived from the compound of formula III employed. However, it is not necessary that all or part of Alk be the same as R_4. The sodium borohydride should generally be present in at least equimolar amount with the compound of formula II, and more preferably in slight excess, such as e.g. from about 1.1 : 1 to about 1.5 : 1 moles $NaBH_4$ per mole of ketone. The molar ratio of the compound of formula III to the compound of formula II is at least about 0.5 : 1, and more preferably from about 0.7 : 1 to about 1.5 : 1 moles of borane compound per mole of ketone.

Step (b) is also preferably carried out at reduced temperatures, the internal temperature being maintained at about -100° to about -40°C, especially from about -78° to about -70°C. The compound of formula II is preferably in a solvent such as alcohol/THF or THF. Preferably the reaction medium of step (a) and the solvent of the compound of formula II which is added in step (b) are selected to make up a combined medium wherein the ratio (v/v) of alcohol to tetrahydrofuran is from about 1:3 to about 1:6 of alcohol to THF, especially from about 1:3 to about 1:4. Reduction of the keto group is exothermic and occurs rapidly, and therefore, addition of the keto compound is desirably staged in order to maintain an internal temperature in the range of from about -78° to about -70°C. The

reduction is almost instantaneous and the reaction mixture is then quenched by adding, e.g., aqueous sodium bicarbonate, ammonium chloride or acetic acid, and a mixture of the desired cyclic boronate intermediate is obtained.

In step (c) the reaction product of step (b) may be azeotroped with methanol or ethanol, at, e.g., from about 60° to about 80°C, under essentially anhydrous conditions. Alternatively and preferably, particularly where X is -CH=CH-, the product having been neutralized by addition of sodium bicarbonate ($NaHCO_3$) is dissolved in an organic solvent, e.g., ethyl acetate, and treated with aqueous (e.g. 30 %) hydrogen peroxide or aqueous sodium perborate ($NaBO_3.4H_2O$), initially at reduced temperature, e.g. about +10°C, and then allowed to warm to a moderate temperature, e.g. about 20° to about 30°C, to obtain the corresponding compound of formula I.

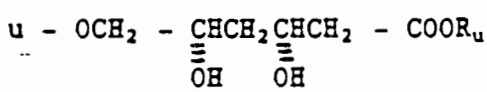
Alternatively, the cyclic boronate ester from step (b) may be extracted with an organic solvent such as ethyl acetate and then treated directly with an aqueous solution of a peroxy compound such as 30 % aqueous hydrogen peroxide or aqueous sodium perborate solution to obtain the corresponding compound of formula I.

Since reducing conditions occur in practicing the invention, it is understood that any substituents or functions on the radical employed as R will be inert, i.e. that it will be free of substituents or functions which would be reactive or susceptible of alteration under such conditions, e.g. by known methods of masking or protecting such functions or introducing them at a later stage.

The compounds of formula I, the corresponding δ-lactones, free acids and salts, processes for converting a compound of formula I wherein R_1 has one significance into the corresponding compound wherein it has a different significance and/or into the corresponding δ-lactone or free acid or salts are known.

The compounds of formula I may if desired be converted by conventional means into corresponding free acid or salt forms, i.e. wherein R_1 is replaced by hydrogen or a cation, such as an alkali metal cation or ammonium, preferably sodium or potassium and especially sodium, into other ester forms, or into the corresponding δ-lactones, i.e. internal esters.

As mentioned above the compounds of formula I obtained according to the process of the invention are pharmaceuticals. In a further embodiment, however, the process of the invention may also be applied to the preparation of chiral intermediates, of e.g. formula Iu



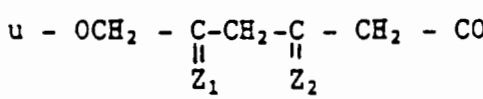
(Iu)

wherein

u is triphenylmethyl (trityl) and

R_u is allyl or a radical forming an ester inert under the reaction conditions, preferably allyl or C_{1-3}alkyl, n-butyl, i-butyl, t-butyl or benzyl, especially t-butyl,

by stereoselectively reducing a racemic or optically pure compound of formula IIu



(IIu)

wherein u, R_u, Z_1 and Z_2 are as defined above.

Such chiral intermediates are disclosed in e.g. EP 244364. They are indicated for use in preparing pharmaceuticals.

6. Starting materials

The (primary or secondary C_{1-4}alkoxy or allyloxy)-di-(primary C_{2-4}alkyl)boranes of formula III used as starting materials in the process of the present invention are known [Koster et al, Ann. (1975), 352; Chen et al., Tetrahedron Letters 28, 155 (1987); and Chen et al, Chemistry Letters (1987), 1923-1926]. However, they may be prepared in situ from the corresponding tri-(primary or secondary C_{2-4}alkyl)boranes by reaction with a primary or secondary C_{1-4}alkanol or allyl alcohol, the concentration of the former in the latter preferably being from about 0.2 M to about 1.2 M, especially about 0.5 M.

The compounds of formula II are known or may be prepared analogously to known compounds of formula II, e.g. as described in USP 4 739 073 (e.g. for Z_2 = oxygen) or in EP 216 785 (e.g. for Z_1 = oxygen).

Thus the compounds of formula II wherein Z_2 is oxygen are normally prepared by reaction of a compound of formula V

$$R - X - CHO \qquad (V)$$

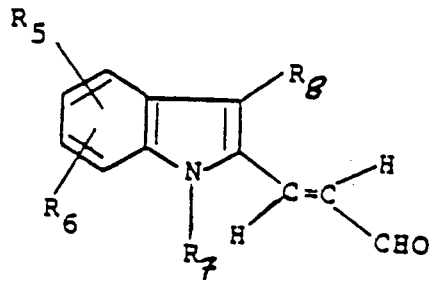
wherein R and X are as defined above,
with the dianion of a compound of formula VI

$$CH_3 - CO - CH_2 - COOR_1 \qquad (VI)$$

wherein R_1 is as defined above.

7. Further embodiments concerning earlier intermediates

The compounds of formula V and VI are also known. In further embodiments, however, the present invention also comprises a novel process for the preparation of a subgroup of compounds of formula V, namely the compounds of formula Va



(Va)

wherein

R_5 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{3-6}cycloalkyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

R_6 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_5 and R_6 is trifluoromethyl, not more than one of R_5 and R_6 is phenoxy, and not more than one of R_5 and R_6 is benzyloxy;

one of R_7 and R_8 is phenyl trisubstituted by R_9, R_{10} and R_{11} and the other is primary or secondary C_{1-6}alkyl not containing an asymmetric carbon atom, C_{3-6}cycloalkyl or phenyl-$(CH_2)_m$-, wherein

R_9 is hydrogen, C_{1-3}alkyl, n-butyl, i-butyl, t-butyl, C_{1-3}alkoxy, n-butoxy, i-butoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

R_{10} is hydrogen, C_{1-3}alkyl, C_{1-3}alkoxy, trifluoromethyl, fluoro, chloro, phenoxy or benzyloxy;

R_{11} is hydrogen, C_{1-2}alkyl, C_{1-2}alkoxy, fluoro or chloro, and m is 1, 2 or 3;

with the provisos that not more than one of R_9 and R_{10} is trifluoromethyl, not more than one of R_9 and R_{10} is phenoxy, and not more than one of R_9 and R_{10} is benzyloxy;

starting from a subgroup of compounds of formula VII

$$(E) - OHC - CH=CH - N(R_{12})R_{13} \qquad (VII)$$

wherein

R_{12} is C_{1-3}alkyl, phenyl or phenyl substituted by 1 to 3 substituents each of which is independently C_{1-3}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or nitro with a maximum of two nitro groups; and

R_{13} independently has the significance indicated above for R_{12},

as well as a novel process for the preparation of the compounds of formula VII themselves.

The process for the preparation of the compounds of formula VII is hereinafter designated as "process A" and the process for the preparation of the compounds of formula Va is hereinafter designated as "process B".

The compounds of formulae Va, VII and XVII (see under 7.2.) are known from i.a. USP 4 739 073 which discloses the compounds of formula VII wherein R_{12} is C_{1-3}alkyl and their use for the synthesis of the compounds of formula Va, the compounds of formula XVII, and the use of the compounds of formula Va for the synthesis of indole analogs of mevalonolactone and derivatives thereof which are indicated for use as HMG-CoA reductase inhibitors. Since they inhibit cholesterol synthesis, they lower the blood cholesterol level and are therefore indicated for use in the treatment of hypercholesterolemia, hyperlipoproteinemia and atherosclerosis.

Compounds of formula VII and their synthesis are also disclosed in British Patent Specification No. 945 536 and Czechoslovakian Patent No. 90 045. However, the processes disclosed therein differ from process A with respect to, for example, the use of phosgene or phosphorus trichloride, pentachloride or oxychloride rather than an oxalic acid derivative.

7.1. Process A (preparation of the compounds of formula VII)

The process for the preparation of the compounds of formula VII (process A) comprises

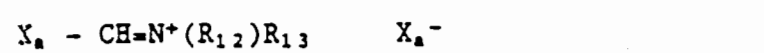
(i) reacting a compound of formula VIII

(VIII)

wherein R_{12} and R_{13} are as defined above,
with a compound of formula IX

(IX)

wherein X_a is a monovalent leaving group,
optionally in an inert anhydrous organic medium, to form the corresponding compound of formula X



(X)

wherein X_a, R_{12} and R_{13} are as defined above,

(ii) reacting that compound of formula X
with a compound of formula XI

(XI)

wherein R_{14} is a monovalent group that does not deactivate the oxygen atom to which it is attached,
optionally in an inert anhydrous organic medium,

to form a corresponding compound of formula XII

$$(E) - R_{14}O - CH{=}CH - CH{=}N^{+}(R_{12})R_{13} \quad X_a^- \qquad (XII)$$

wherein R_{12}, R_{13}, R_{14} and X_a are as defined above, and

(iii) hydrolyzing that compound of formula XII to obtain a corresponding compound of formula VII in free base or acid addition salt form and, if in acid addition salt form, neutralizing the acid addition salt with base.

In a variant of process A step (iii) may be dispensed with and a compound of formula XII used directly in, e.g., process B.

Steps (i) and (ii) may be carried out simultaneously or step (ii) may follow step (i); step (iii) follows step (ii) and step (iv) (see hereafter), when employed, follows step (iii).

R_{12} is R_{12a}, where R_{12a} is C_{1-3}alkyl; or R_{12b}, where R_{12b} with the exception of C_{1-3}alkyl has the significance indicated above for R_{12} (i.e. it is phenyl or phenyl substituted by 1 to 3 substituents each of which is independently C_{1-3}alkyl, C_{1-3}alkoxy, fluoro, chloro, bromo or nitro with a maximum of two nitro groups).

R_{12a} is preferably C_{1-2}alkyl and most preferably methyl.

R_{12b} is preferably R_{12b}' where R_{12b}' is phenyl or phenyl substituted by 1 or 2 substituents each of which is independently C_{1-3}alkyl, C_{1-2}alkoxy or chloro, more preferably R_{12b}'' where R_{12b}'' is phenyl or phenyl substituted by 1 or 2 methyl groups, and most preferably phenyl.

R_{13} is preferably C_{1-2}alkyl and most preferably methyl.

R_{14} is preferably C_{1-6}alkyl, preferably primary or secondary C_{2-4}alkyl, more preferably n-C_{2-4}alkyl and most preferably ethyl or n-butyl.

Each X_a is preferably chloro or bromo, especially chloro. Each X_a^- is preferably chloride or bromide, especially chloride. The base utilized in the hydrolysis or neutralization of step (iii) is preferably an inorganic base such as sodium carbonate, potassium carbonate, sodium hydroxide or potassium hydroxide and more preferably is sodium carbonate or potassium carbonate.

Preferred reaction conditions for process A are as follows:

Step (i) [when carried out prior to Step (ii)]:

Temperature: -20° to +50°C

Time: 1.5 to 5 hours

Reaction medium: liquid halogenated lower alkane, e.g. 1,2-dichloroethane and methylene chloride; or acetonitrile; methylene chloride and acetonitrile being most preferred

Molar ratio of reactants: 1 to 1.5 moles IX per mole VIII

Step (ii) [when carried out subsequent to step (i)]:

Temperature: 10° to 60°C, 10° to 40°C being more preferred

Time: 0.5 to 3 hours

Reaction medium: same as step (i)

Molar ratio of reactants: 1 to 1.5 moles XI per mole VIII utilized in step (i)

Steps (i) and (ii) [when carried out simultaneously]:

Temperature: -15° to +35°C

Time: 2 to 6 hours

Reaction medium: same as step (i) when carried out prior to step (ii)

Molar ratio of reactants: 1 to 1.5 moles IX and 1 to 1.5 moles XI per mole VIII

Step (iii):

Temperature: 0° to 65°C

Time: 0.5 to 3 hours

Reaction medium: water or mixture of water and reaction medium utilized in step (ii)

Molar ratio of reactants: 2 to 4 equivalents base per mole IX utilized in step (i)

It is preferred to effect the hydrolysis of step (iii) with base.

The reaction medium for steps (i) and (ii) may, alternatively and preferably, consist of the neat reagents, i.e. the reagents in the absence of any solvent, i.e. for step (i) the compounds of formulae VIII and IX and for step (ii) the compounds of formulae X and XI. This is very advantageous from e.g. an ecological point of view since the presence of solvents such as acetonitrile in waste water or the emission of vapours of e.g.methylene chloride into the atmosphere is avoided thereby. The compounds of formulae VIII and IX or, respectively, X and XI can be brought to react in the absence of solvent because they do not form a solid block when mixed together but, surprisingly, form a suspension.

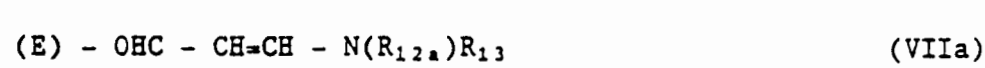
Process A may be divided into two subprocesses depending upon the significances of R_{12} and R_{13}:
(1) R_{12} and R_{13} independently are C_{1-3}alkyl (**subprocess Aa**) and
(2) at least one of R_{12} and R_{13} is other than C_{1-3}alkyl (**subprocess Ab**).

The product of step (iii) of **subprocess Aa** often contains an appreciable amount of the compound of formula XIII

(E) - OHC - CH=CH - OR_{14} (XIII)

wherein R_{14} is as defined above,
corresponding to the obtained compound of formula VII, the molar ratio of the compound of formula VII to the compound of Formula XIII typically being about 2:1. While it is, of course, possible to separate the compound of formula VII from that of formula XIII by conventional means of separation, it is preferable to subject the product of step (iii), i.e. the crude compound of formula VII (a mixture of the compound of formula VII with the corresponding compound of formula XIII), to step (iv), i.e.:

(iv) treating the crude mixture containing the compound of formula VIIa



(E) - OHC - CH=CH - $N(R_{12a})R_{13}$ (VIIa)

wherein R_{12a} and R_{13} are as defined above,
with a corresponding compound of formula XIV

H - $N(R_{12a})R_{13}$ (XIV)

wherein R_{12a} and R_{13} are as defined above,
to convert any compound of formula XIII present therein into additional compound of formula VIIa.

Preferred reactants in subprocess Aa are those

(a) wherein R_{12a} is C_{1-2}alkyl, R_{13} is C_{1-2}alkyl, R_{14} is primary or secondary C_{2-4}alkyl, each X_a is chloro, and each X_a^- is chloride;

(b) as (a) but wherein R_{14} is n-C_{2-4}alkyl;

(c) as (b) but wherein R_{12a} is methyl, R_{13} is methyl, and R_{14} is ethyl;

(d)-(f) as (a)-(c) but wherein the base utilized in step (iii) is sodium carbonate or potassium carbonate; and

(g)-(i) as (d)-(f) but wherein the base utilized in step (iii) is potassium carbonate.

Preferred reaction conditions for subprocess Aa, particularly when the reactants are those of subgroups (a), (d) and (g), more particularly when they are those of subgroups (b), (e) and (h) and especially when they are those of subgroups (c), (f) and (i), are:

Step (i):

Temperature: 0° to 20°C, 0° to 15°C being more preferred and 5° to 15°C being even more preferred

Time: 1.5 to 4 hours

Reaction medium: liquid halogenated lower alkane or acetonitrile, or the neat reagents; methylene chloride or the neat reagents being most preferred

Molar ratio of reactants: 1 to 1.2 moles IX per mole VIII
1.1 to 1.2 moles IX per mole VIII being more preferred;

Step (ii):

Temperature: 25° to 40°C

Time: 0.7 to 2.5 hours

Reaction medium: same as step (i)

Molar ratio of reactants: 1 to 1.2 moles XI per mole VIII utilized in step (i), 1.1 to 1.2 moles IX per mole VIII being more preferred;

Step (iii):

Temperature: 20° to 65°C, 20° to 30°C being more preferred

Time: 0.75 to 2 hours

Reaction medium: aqueous

Molar ratio of reactants: 2 to 4 equivalents base per mole IX utilized in step (i);

Step (iv):

Temperature: 0° to 20°C, 10° to 20°C being more preferred

Time: 0.3 to 1 hour

Reaction medium: C_{1-4}alkanol, methanol being most preferred

Molar ratio of reactants: 0.15 to 1 mole XIV per mole VIII utilized in step (i), 0.15 to 0.4 mole XIV per mole VIII being more preferred.

In subprocess Aa step (ii) is preferably carried out after step (i).

Preferably, subprocess Aa comprises

(i) reacting N,N-dimethylformamide (compound of formula VIII wherein R_{12} and R_{13} are methyl) with oxalyl chloride (compound of formula IX wherein X_a is chloro) neat or in methylene chloride at a temperature of 0° to 15°C to form the compound of formula Xa

$$Cl - CH{=}N^{+}(CH_3)_2 \quad Cl^{-} \qquad (Xa)$$

(ii) reacting the compound of formula Xa with ethyl vinyl ether (compound of formula XI wherein R_{14} is ethyl) neat or in methylene chloride at a temperature of 25° to 40°C to form the compound of formula XIIa

$$(E) - C_2H_5O - CH{=}CH{-}CH{=}N^{+}(CH_3)_2 \quad Cl^{-} \qquad (XIIa)$$

(iii) hydrolyzing the compound of formula XIIa with potassium carbonate in an aqueous medium at a temperature of 20° to 30°C to form a mixture of the compounds of formula VIIaa

$$(E) - OHC - CH{=}CH - N(CH_3)_2 \qquad (VIIaa)$$

and of formula XIIIa

$$(E) - OHC - CH{=}CH - OC_2H_5 \qquad (XIIIa)$$

(iv) treating the mixture of compounds of formulae VIIaa and XIIIa with dimethylamine (compound of formula XIV wherein R_{12a} and R_{13} are methyl) in methanol at a temperature of 10° to 20°C to convert the compound of formula XIIIa into additional compound of formula VIIaa.

More preferably, in subprocess Aa

(1) the molar ratio of oxalyl chloride to N,N-dimethylformamide in step (i) is from 1:1 to 1.2:1, and step (i) is carried out by adding oxalyl chloride to N,N-dimethylformamide neat or in solution in methylene chloride over a period of 1.5 to 4 hours at a rate such that the temperature is maintained at 5° to 15°C;

(2) in step (ii) the molar ratio of ethyl vinyl ether to the N,N-dimethylformamide utilized in step (i) is from 1:1 to 1.2:1, and step (ii) is carried out by adding ethyl vinyl ether to the reaction mixture over a period of 0.4 to 1.5 hours at a rate such that the temperature does not exceed 30°C and, upon completion of the addition, refluxing the reaction mixture at 35° to 40°C for 0.3 to 1 hour and if indicated recovering as much methylene chloride as possible at a temperature not in excess of 45°C;

(3) in step (iii) the molar ratio of potassium carbonate to the oxalyl chloride utilized in step (i) is from 1:1 to 2:1, and step (iii) is carried out by adding water to the product of step (ii) stirred at 20° to 30°C, allowing the temperature to rise to 45° to 60°C, maintaining this temperature during the balance of the addition of the water and for an additional 0.3 to 1 hour, cooling the reaction mixture to 15° to 25°C, adding an aqueous solution of potassium carbonate over a period of 0.3 to 1.25 hours at this temperature, extracting the mixture with methylene chloride and distilling as much methylene chloride as possible at a temperature not in excess of 45°C; and

(4) in step (iv) the molar ratio of dimethylamine to the N,N-dimethylformamide utilized in step (i) is from 0.15:1 to 0.4:1, and step (iv) is carried out by adding anhydrous dimethylamine to a solution of the product of step (iii) in methanol stirred at 10° to 20°C at a rate such that the temperature does not exceed 20°C and distilling the solvent and any excess dimethylamine at a temperature not in excess of 120°C.

Preferred reactants in subprocess Ab are those

(a) wherein R_{12b} is R_{12b}', R_{13} is C_{1-2}alkyl, R_{14} is primary or secondary C_{2-4}alkyl, each X_a is chloro, and each X_a^- is chloride;

(b) as (a) but wherein R_{12b} is R_{12b}'', and R_{14} is n-C_{2-4}alkyl;

(c) as (b) but wherein R_{12b} is phenyl, R_{13} is methyl, and R_{14} is ethyl or n-butyl, especially n-butyl;

(d)-(f) as (a)-(c) but wherein the base utilized in step (iii) is sodium carbonate or potassium carbonate, and

(g)-(i) as (d)-(f) but wherein the base utilized in step (iii) is sodium carbonate.

Preferred reaction conditions for subprocess Ab, particularly when the reactants are those of subgroups (a), (d) and (g), more particularly when they are those of subgroups (b), (e) and (h) and especially when they are those of subgroups (c), (f) and (i), are:

Step (i) [when carried out prior to step (ii)]:

Temperature: -20° to +45°C

Time: 1.5 to 5 hours

Reaction medium: liquid halogenated lower alkane or acetonitrile, methylene chloride and acetonitrile being more preferred and acetonitrile being most preferred; or, most preferably, the neat reagents;

Molar ratio of reactants: 1 to 1.2 moles IX per mole VIII, 1.1 to 1.2 moles IX per mole VIII being more preferred;

Step (ii) [when carried out subsequent to step (i)]:

Temperature: 10° to 40°C

Time: 0.5 to 3 hours

Reaction medium: same as step (i)

Molar ratio of reactants: 1 to 1.3 moles XI per mole VIII utilized in step (i), 1.1 to 1.25 moles XI per mole VIII being more preferred;

Steps (i) and (ii) [when carried out simultaneously]:

Temperature: -15° to +35°C

Time: 2 to 6 hours

Reaction medium: same as step (i) when carried out prior to step (ii)

Molar ratio of reactants: 1 to 1.5 moles IX and 1 to 1.5 moles XI per mole VIII;

Step (iii):

Temperature: 0° to 35°C, 0° to 30°C being more preferred

Time: 0.5 to 1.5 hours

Reaction medium: mixture of water and reaction medium of step (ii)

Molar ratio of reactants: 2 to 4 equivalents base per mole IX utilized in step (i).

There are three preferred variants of subprocess Ab, namely variants Ab1, Ab2 and Ab3. In variant Ab1 R_{14} is ethyl and the reaction medium for steps (i) and (ii) is methylene chloride or, preferably, the neat reagents, and in variants Ab2 and Ab3 R_{14} is n-butyl and the reaction medium for steps (i) and (ii) is acetonitrile or, preferably, the neat reagents. In variants Ab1 and Ab2, step (ii) is carried out after step (i) and in variant Ab3 steps (i) and (ii) are carried out simultaneously; in each variant, step (iii) follows steps (i) and (ii).

Variant Ab1 of subprocess Ab preferably comprises

(i) reacting N-methylformanilide (compound of formula VIII wherein R_{12} is phenyl and R_{13} is methyl) with oxalyl chloride (compound of formula IX wherein X_a is chloro) neat or in methylene chloride at a temperature of 15° to 45°C to form the compound of formula Xb

$$Cl - CH{=}N^{+}(C_6H_5)CH_3 \quad Cl^{-} \qquad (Xb)$$

(ii) reacting the compound of formula Xb with ethyl vinyl ether (compound of formula XI wherein R_{14} is ethyl) neat or in methylene chloride at a temperature of 15° to 40°C to form the compound of formula XIIb1

$$(E) - C_2H_5O - CH{=}CH{-}CH{=}N^{+}(C_6H_5)CH_3 \quad Cl^{-} \qquad (XIIb1)$$

(iii) hydrolyzing the compound of formula XIIb1 with sodium carbonate in a mixture of methylene chloride and water at a temperature of 20° to 30°C to obtain the compound of formula VIIb

$$(E) - OHC - CH{=}CH{-}N(C_6H_5)CH_3 \qquad (VIIb)$$

More preferably, in variant Ab1 of subprocess Ab,

(1) the molar ratio of oxalyl chloride to N-methylformanilide in step (i) is from 1:1 to 1.2:1, and step (i) is carried out by adding oxalyl chloride to N-methylformanilide neat or in solution in methylene chloride at 15° to 20°C over a period of 1 to 2 hours and, upon completion of the addition, gradually raising the temperature of the reaction mixture to 40° to 45°C over a period of 0.75 to 1.25 hours and then refluxing it for 0.75 to 1.25 hours;

(2) in step (ii) the molar ratio of ethyl vinyl ether to the N-methylformanilide utilized in step (i) is 1 to 1.3:1, and step (ii) is carried out by cooling the product of step (i) to 15° to 20°C, adding ethyl vinyl ether over a period of 0.5 to 1.5 hours at a rate such that the temperature does not exceed 30°C, and, upon completion of the addition, refluxing the reaction mixture for 0.3 to 0.7 hour; and

(3) in step (iii) the molar ratio of sodium carbonate to the oxalyl chloride utilized in step (i) is from 1:1 to 1.2:1, and step (iii) is carried out by cooling the product of step (ii) to 15° to 20°C, adding, over a period of 0.5 to 1 hour, an aqueous solution of sodium carbonate at a rate such that the temperature of the reaction mixture is 20° to 30°C and, upon completion of the addition, stirring the mixture at 20° to 30°C for 0.2 to 0.5 hour, allowing the mixture to separate into two phases, separating the two phases and recovering the product from the organic phase.

Variant Ab2 of subprocess Ab preferably comprises

(i) reacting N-methylformanilide with oxalyl chloride neat or in acetonitrile at a temperature of from -20° to +20°C to form the compound of formula Xb

(ii) reacting the compound of formula Xb with n-butyl vinyl ether (compound of formula XI wherein R_{14} is n-butyl) neat or in acetonitrile at a temperature of 10° to 40°C to form the compound of formula XIIb2

$$(E) - n\text{-}C_4H_9O - CH{=}CH{-}CH{=}N^+(C_6H_5)CH_3 \quad Cl^- \qquad \text{(XIIb2)}$$

and

(iii) hydrolyzing the compound of formula XIIb2 with sodium carbonate in a mixture of acetonitrile and water at a temperature of 0° to 25°C to obtain the compound of formula VIIb.

More preferably, in variant Ab2 of subprocess Ab,

(1) the molar ratio of oxalyl chloride to N-methylformanilide in step (i) is from 1:1 to 1.2:1, and step (i) is carried out by adding oxalyl chloride to N-methylformanilide neat or in solution in acetonitrile at -18° to +8°C over a period of 1 to 2 hours and, upon completion of the addition, gradually raising the temperature of the reaction mixture to 12° to 20°C over a period of 0.4 to 0.75 hour and then stirring it for 0.2 to 0.4 hour at this temperature;

(2) in step (ii) the molar ratio of n-butyl vinyl ether to the N-methylformanilide utilized in step (i) is from 1:1 to 1.2:1, and step (ii) is carried out by adding n-butyl vinyl ether to the product of step (i) stirred at 12° to 20°C over a period of 0.5 to 1.5 hours at a rate such that the temperature does not exceed 30°C, and, upon completion of the addition, stirring the reaction mixture for 0.3 to 0.7 hour at 25° to 35°C; and

(3) in step (iii) the molar ratio of sodium carbonate to the oxalyl chloride utilized in step (i) is from 1:1 to 1.3:1, and step (iii) is carried out by cooling the product of step (ii) to 0° to 5°C, adding, over a period of 0.5 to 1.2 hours, an aqueous solution of sodium carbonate at a rate such that the temperature of the reaction mixture is 5° to 12°C and, upon completion of the addition, adding toluene, stirring the mixture at 15° to 25°C for 0.2 to 0.5 hour, allowing the mixture to separate into two phases, separating the two phases and recovering the product from the organic phase.

Variant Ab3 of subprocess Ab preferably comprises(i) and (ii) reacting N-methylformanilide with oxalyl chloride neat or in acetonitrile at -10° to +30°C in the presence of n-butyl vinyl ether to form the compound of formula Xb,

which compound then reacts with the n-butyl vinyl ether in the reaction mixture to form the compound of formula XIIb2, and

(iii) hydrolyzing the compound of formula XIIb2 with sodium carbonate in a mixture of acetonitrile and water at a temperature of 0° to 25°C to obtain the compound of formula VIIb.

More preferably, in variant Ab3 of subprocess Ab,

(1) in steps (i) and (ii), the molar ratio of each of oxalyl chloride and n-butyl vinyl ether to N-methylformanilide is from 1:1 to 1.2:1, and steps (i) and (ii) are carried out by adding a solution of N-methylformanilide and n-butyl vinyl ether neat or in acetonitrile to oxalyl chloride neat or in solution in acetonitrile stirred at -10° to +10°C over a period of 2 to 3 hours and, upon completion of the addition, gradually raising the temperature of the reaction mixture to 20 to 30°C over a period of 0.4 to 1.5 hours and then stirring the reaction mixture at this temperature for 0.5 to 1.5 hours; and

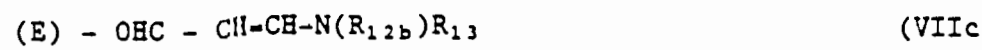
(2) in step (iii), the molar ratio of sodium carbonate to the oxalyl chloride utilized in step (i) is from 1:1 to 1.3:1, and step (iii) is carried out by cooling the product of step (ii) to 0° to 5°C, adding, over a period of 0.5 to 1.2 hours, an aqueous solution of sodium carbonate at a rate such that the temperature of the reaction mixture is 0° to 12°C and, upon completion of the addition, adding toluene, stirring the mixture at 15° to 25°C for 0.2 to 0.5 hour, allowing the mixture to separate into two phases, separating the two phases and recovering the product from the organic phase.

The product of step (iii) of subprocess Ab may be subjected to a step (iv) analogous to step (iv) of subprocess Aa. However, there is usually no reason to do so since the product usually contains little or no compound of formula XIII.

7.2. Process B (preparation of the compounds of formula Va from the compounds of formula VIIc)

The process for the preparation of the compounds of formula Va (process B) comprises

(i) reacting a compound of formula VIIc



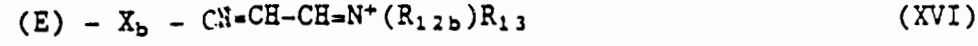
(VIIc)

wherein R_{12b} and R_{13} are as defined above,
with a compound of formula XV

(XV)

wherein X_b is chloro or bromo, or
with a compound selected from oxalyl chloride or bromide; phosgene or carbonyl bromide; phosphorus trichloride or tribromide; phosphorus pentachloride or pentabromide; and an alkyl- or arylsulfonyl chloride or bromide, such as p-toluenesulfonyl chloride or bromide or methanesulfonyl chloride or bromide;

to form the corresponding compound of formula XVI

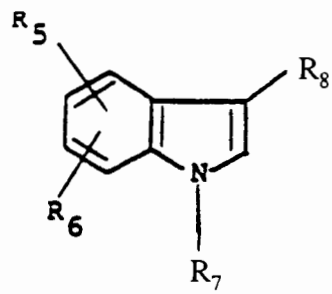


(XVI)

and the corresponding anion, e.g. $^{-}PO_2(X_b)_2$,
wherein X_b, R_{12b} and R_{13} are as defined above,

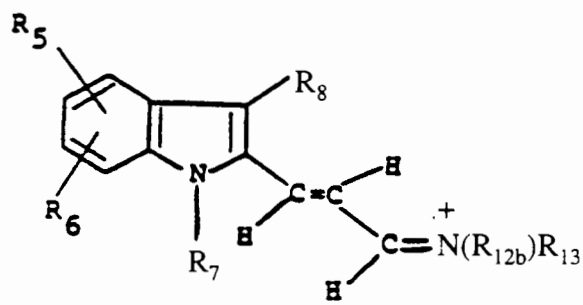
(ii) reacting that compound of formula XVI

with a compound of formula XVII



(XVII)

wherein R_5, R_6, R_7 and R_8 are as defined above, to form a corresponding compound of formula XVIII



(XVIII)

and the corresponding anion, e.g. $^{-}PO_2(X_b)_2$,

wherein R_5, R_6, R_7, R_8, R_{12b}, R_{13} and X_b are as defined above,

and

(iii) hydrolyzing that compound of formula XVIII to obtain a corresponding compound of formula Va.

As mentioned above for process A, in a variant, in step (i) a compound of formula XII obtained according to process A may be used directly in place of a compound of formula VIIc.

The preferred significances for R_{12b} and R_{13} are set forth above, and the preferences for R_5, R_6, R_7 and R_8 are those set forth for R_o, R, R_2 and R_3, respectively, in USP 4 739 073. X_b preferably is chloro.

A compound of formula VIIc preferably is reacted with a compound of formula XV.

Steps (i) and (ii) preferably are effected in an inert anhydrous organic medium.

Preferred reactants (and final products) are

(a)-(d) those wherein R_{12b} is R_{12b}', R_{13} is C_{1-2}alkyl, each X_b is chloro, and R_5 to R_8 have the significances of the corresponding variables of Groups (i), (ii), (xxi) and (xxii) of USP 4 739 073;

(e)-(h) those of (a)-(d) wherein R_{12b} is R_{12b}'', and R_5 to R_8 have the significances of the corresponding variables of Groups (v), (vi), (xxv) and (xxvi) of USP 4 739 073;

(i) and (j) those of (e) and (f) wherein R_7 is C_{1-3}alkyl, R_8 is phenyl, methylphenyl, fluorophenyl, dimethylphenyl or methyl-fluorophenyl, R_5 is hydrogen, C_{1-3}alkyl or 4- or 6-benzyloxy, and R_6 is hydrogen or methyl;

(k) and (l) those of (g) and (h) wherein R_7 is phenyl, methylphenyl, fluorophenyl, dimethylphenyl or methyl-fluorophenyl, R_8 is C_{1-3}alkyl, R_5 is hydrogen, C_{1-3}alkyl or 4- or 6-benzyloxy, and R_6 is hydrogen or methyl;

(m)-(p) those of (i)-(l) wherein R_5 is hydrogen, and R_6 is hydrogen;

(q)-(t) those of (m)-(p) wherein R_{12b} is phenyl, and R_{13} is methyl;

(u) that of (q) wherein R_7 is 1-methylethyl, and R_8 is 4-fluorophenyl; and

(v) that of (s) wherein R_7 is 4-fluorophenyl, and R_8 is 1-methylethyl.

Most preferably, R_5 and R_6 are hydrogen, R_7 is 1-methylethyl and R_8 is para-fluorophenyl.

The compounds of formula VIIc used for step (i) may be in free base form or, preferably, in acid addition salt form, e.g. in hydrochloride acid addition salt form.

The preferred bases for step (iii) are inorganic hydroxides such as sodium hydroxide and potassium hydroxide, especially the former. However, as set forth infra, it is most preferred not to employ any base in step (iii).

Preferred reaction conditions for process B are:

Step (i):

Temperature: -10° to +25°C, -10° to +10°C being more preferred

Time: 0.1 to 1.2 hours, 0.5 to 1 hour being more preferred

Reaction medium: lower alkyl nitrile, acetonitrile being most preferred

Molar ratio of reactants: 1 to 1.5 moles XV per mole VIIc, 1.1 to 1.3 moles XV per mole VIIc being more preferred

Step (ii):

Temperature: 60° to 100°C, 65° to 85°C being more preferred

Time: 2 to 30 hours, 3 to 24 hours being more preferred

Reaction medium: same as step (i)

Molar ratio of reactants: 1 to 5 moles XVI per mole XVII, 2 to 3 moles XVI per mole XVII being more preferred (100% yield in step (i) assumed in each case)

Step (iii):

Temperature: 10° to 40°C when base is employed and 35° to 60°C when it is not

Time: 0.1 to 1 hour when base is employed and 2 to 4 hours when it is not

Solvent: mixture of water and reaction medium of step (ii)

Molar ratio of reactants: when base is employed, 4 to 8 equivalents base, preferably sodium hydroxide or potassium hydroxide, per mole XV utilized in step (i).

Even more preferred reaction conditions for process B, particularly when the reactants and final products are those of subgroups (a)-(v), especially of subgroups (i), (j), (m), (n), (q), (r) and (u), are:

Step (i):

Temperature: -10° to +10°C

Time: 0.75 to 1 hour

Reaction medium: acetonitrile

Molar ratio of reactants: 1.1 to 1.3 moles XV per mole VIIc

Step (ii):

Temperature: 65° to 85°C, 80° to 83°C being more preferred

Time: 3 to 16 hours, 3 to 10 hours being more preferred

Reaction medium: acetonitrile

Molar ratio of reactants: 2 to 3 moles XVI per mole XVII, 2.1 to 2.5 moles XVI per mole XVII being more preferred (100% yield in step (i) assumed in each case)

Step (iii):

Temperature: 20° to 55°C; 25° to 35°C being preferred when base is employed, and 35° to 55°C when it is not

Time: 0.3 to 0.7 hour when base is employed and 2 to 3 hours when it is not

Reaction medium: mixture of water and reaction medium of step (ii)

Molar ratio of reactants: when base is employed, 4 to 6 equivalents base, preferably sodium hydroxide, per mole XV utilized in step (i).

It is most preferred not to employ base in step (iii).

8. General conditions applicable to all processes

Most of the molar amounts (ratios) recited herein are merely exemplary and may be varied, as is evident to one of ordinary skill in the art.

Steps (i) and (ii) of process A (including subprocesses Aa and Ab and the variants thereof), steps (i) and (ii) of process B and, preferably, step (iv) of subprocess Aa are preferably carried out under anhydrous conditions and an inert atmosphere, preferably dry helium, argon or nitrogen, or a mixture thereof, usually dry nitrogen. Step (iii) of process A (including subprocesses Aa and Ab and the variants thereof) and process B are often, but need not be, carried out under an inert atmosphere.

Likewise, most of the temperature ranges given above are merely exemplary. All temperatures are internal temperatures, unless otherwise indicated. As utilized above, the term "reaction medium" embraces mixtures of liquids and implies that the reaction medium is a liquid at the desired reaction temperature. It should, therefore, be understood that not all of the liquids listed for a particular step may be utilized for the entire recited temperature range. It should also be understood that the reaction medium must be at least substantially inert to the reactants employed, intermediates generated and end products under the reaction conditions utilized. It should be understood that the reaction temperature may exceed the boiling point of a reactant or the reaction medium if a condenser or a closed system (reaction bomb) is utilized.

The reaction times set forth above are also merely exemplary and may be varied.

It will also be understood that conventional work-up procedures may be employed. The term "solvent", as utilized herein, embraces mixtures of solvents and implies that the reaction medium is a liquid at the desired reaction temperature. Unless indicated otherwise all solvent mixtures are by volume. The term "inert atmosphere" means an atmosphere that does not react with any of the reactants, intermediates or end products or otherwise interfere with the reaction.

The product of each process may, if desired, be purified by conventional techniques such as recrystallization, chromatography or fractional distillation.

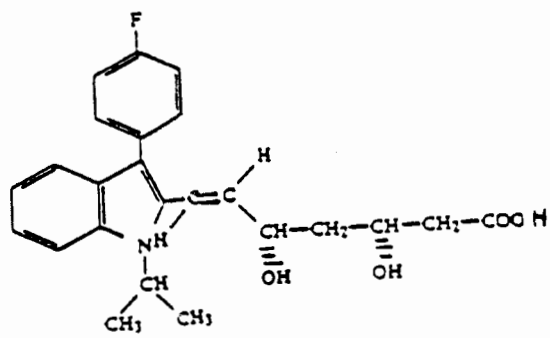
All temperatures are in degrees Centigrade and room temperature is 20° to 30°C, usually 20° to 25°C unless otherwise indicated; evaporations are done under vacuum employing minimal heating, drying of organic phases is done over anhydrous magnesium sulfate, and unless otherwise indicated, silica gel is utilized for all column chromatographies.

It will be appreciated that the process variants disclosed with the present invention are improvements over known similar processes; they may be used to obtain the desired end products, i.e. 7-substituted-hept-6-enoic and -heptanoic acids and derivatives thereof, e.g. more easily, or in e.g. a greater state of chemical or optical purity than can be achieved with conventional methods.

The above process variants may each be used either separately together with conventional processes or, if desired or indicated, in combination, to arrive at the desired end products.

9. Specific embodiment

A specific illustration of the general inventive concept underlying the above process variants concerns the preparation of erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-hept-6-enoic acid of formula Ia



(Ia)

in racemic or optically pure form; in free acid, salt, ester or δ-lactone, i.e. internal ester, form,

in a multistep process using all the above process variants, namely processes A, B and the stereoselective reduction of a compound of formula II, and comprising:

- according to process A:
a) reacting a compound of formula VIIIa

$$OHC - N(R_{12b})R_{13} \qquad \text{(VIIIa)}$$

wherein R_{12b} and R_{13} are as defined above,

with a compound of formula IX, optionally in an inert anhydrous organic medium, to form a corresponding compound of formula Xc

X_a - $CH=N^+(R_{12b})R_{13}$ X_a- (Xc)

wherein X_a, R_{12b} and R_{13} are as defined above;

b) reacting that compound of formula Xc
with a compound of formula XI, optionally in an inert anhydrous organic medium, to form a corresponding compound of formula XIIc

(E) - $R_{14}O$ - $CH=CH-CH=N^+(R_{12b})R_{13}$ X_a- (XIIc)

wherein R_{12b}, R_{13}, R_{14} and X_a are as defined above;

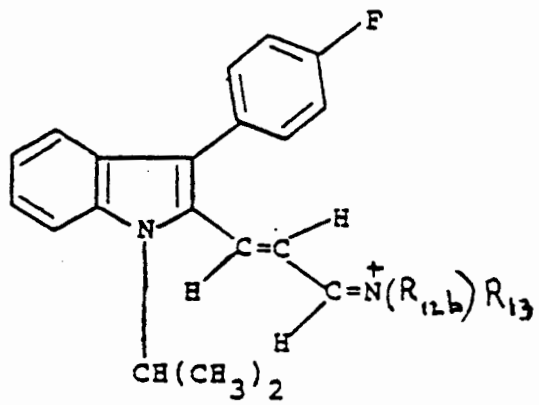
c) hydrolyzing that compound of formula XIIc to obtain a corresponding compound of formula VIIc in free base or acid addition salt form and, if in acid addition salt form, neutralizing the acid addition salt with base;

according to process B:

d) reacting that compound of formula VIIc
with a compound of formula XV or
with a compound selected from oxalyl chloride or bromide;
phosgene or carbonyl bromide; phosphorus trichloride or tribromide;
phosphorus pentachloride or pentabromide; and an alkyl- or arylsulfonyl chloride or bromide, such as p-toluenesulfonyl chloride or bromide or methanesulfonyl chloride or bromide;

to form a corresponding compound of formula XVI and the corresponding anion, e.g. $^-P0_2(X_b)_2$;

e) reacting that compound of formula XVI with
3-(4'-fluorophenyl)-1-(1'-methylethyl)-1H-indole (the compound of formula XVII wherein R_5 and R_6 are hydrogen, R_7 is 1-methylethyl and R_8 is p-fluorophenyl)
to form a corresponding compound of formula XVIIIa

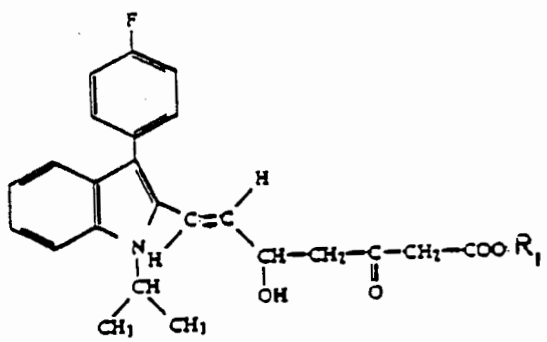


(XVIIIa)

and the corresponding anion, e.g. $^-PO_2(X_b)_2$,
wherein R_{12b}, R_{13} and X_a are as defined above;

f) hydrolyzing that compound of formula XVIIIa to obtain (E)-3-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)-1H-indol-2'-yl]-prop-2-enal (the compound of formula Va wherein R_5 and R_6 are hydrogen, R_7 is 1-methylethyl and R_8 is p-fluorophenyl);

g) reacting that compound of formula Va with the dianion of an acetoacetic ester of formula $CH_3COCH_2COOR_1$ wherein R_1 is as defined above,
to obtain a corresponding compound of formula IIa



(IIa)

wherein R_1 is as defined above; in racemic or optically pure form;

- according to the stereoselective reduction process:

h) stereoselectively reducing the racemic or optically pure compound of formula IIa by,

in a **first step** [= step (a) under 5. above], mixing a compound of formula III with sodium borohydride ($NaBH_4$) in a reaction medium comprising an alcohol and tetrahydrofuran;

in a **second step** [= step (b) under 5. above], treating a compound of formula IIa in racemic or optically pure form with the resultant mixture under conditions suitable to obtain a mixture containing a cyclic boronate compound of formula IV(a) and/or a boron complex of formula IV(b) wherein
R is [3-(4'-fluorophenyl)-1-(1'-methylethyl)-1H-indol]-2-yl,
X is -CH=CH- and
R_2 and R_3 are as defined above; and

in a **third step** [= step (c) under 5. above], cleaving the product obtained in the second step to obtain the compound of formula Ia in ester form; in racemic or optically pure form; and

i) if desired, converting the compound of formula Ia in ester form by conventional means into the free acid form, a salt form, a further ester form or the δ-lactone, i.e. internal ester, form.

The compound of formula Ia may be in free acid, salt, ester or δ-lactone, i.e. internal ester, form. It preferably is in free acid or salt, preferably alkaline salt, especially sodium salt form. It preferably is in racemic or, alternatively, optically pure (3R,5S) enantiomeric form, it especially is in racemic form. As appears from formula Ia that form is the erythro form.

It will be appreciated that the specific embodiment illustrated under 9. is effected either in accordance with the procedures disclosed with this invention or, for some of the steps, in accordance with procedures known in the art.

Thus

- steps a), b) and c) are effected as described above under 7.1. for subprocess Ab, especially steps i), ii) and, respectively, iii) thereof, e.g. according to variants Ab1, Ab2 and/or Ab3 of subprocess Ab; steps a) and b) may thus e.g. be carried out simultaneously as described above for process A:
- steps d), e) and f) are effected as described above under 7.2. for process B, especially steps i), ii) and, respectively, iii) thereof;
- step g) is effected according to procedures published, e.g. in USP 4 739 073, especially in Reaction Scheme I on column 8 and in Example 5, Step_5 on column 47 thereof;
- step h) is effected as described above under 5.;
- step i) is effected in conventional manner, e.g. as described in USP 4 739 073, especially in Reaction Schemes I (Reactions C, D and E) on column 9; Reaction Scheme II (Reaction L) on column 11; Reaction Scheme VIII (Reaction EE) on column 16; and in Examples 6(a), 6(b), 6(c), 8 and 9 on columns 49 and 50 and 52 and 53 thereof, whereby THF may advantageously be replaced by ethanol.

In the second part of the above stereoselective reduction step h), preferably a compound of formula IIa is used wherein R_1 is isopropyl or, especially, t-butyl, which facilitates the isolation of a relatively more pure compound of formula I than with a group R_1 such as methyl. Further, surprisingly, the compound of formula I obtained thereby is completely colourless, whereas it has always been obtained pale yellow in earlier syntheses.

As mentioned previously, the stereoselective reduction according to step h) above may be effected with a racemic or an optically pure compound of formula IIa. An optically pure compound of formula IIa is obtained e.g. by chromatographic resolution of a racemic compound of formula IIa obtained in step g) or, preferably, by an asymmetrical synthesis. Alternatively, resolution may be effected on a subsequent step, or on the racemic end product.

The starting materials for this specific embodiment of the invention are also known or may be prepared in accordance with known procedures. The preparation of 3-(4'-fluorophenyl)-1-(1'-methylethyl)-1H-indole [a compound of formula XVII, see step e) above] is disclosed in USP 4 739 073 as Example 5, Steps 1 to 3 on columns 44 and 45, starting from fluorobenzene.

The invention, of course, also concerns the above processes A, B and the stereospecific reduction process individually, when applied to the preparation of the compound of formula Ia in combination with conventional procedures not specifically described above.

10. Examples

The following Examples are illustrative of the invention. All temperatures are in degrees Centigrade. The optical purity is expressed in percentage terms and thus e.g. "99.9 % pure erythro isomer" means that there is at most 0.9 % threo form in the compound obtained.

10.1. Examples for the stereoselective reduction of a compound of formula II to obtain a compound of formula I

Example 1: (±)-Erythro-(E)-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-3,5-dihydroxyhept-6-enoic acid tert-butyl ester

[Formula I: R = 3-(4'-fluorophenyl)-1-(1'-methylethyl)indol-2-yl; X = (E)-CH=CH-; R_1 = t-butyl; in racemic form]

(a) 47.67 g (1.26 moles) of sodium borohydride are added to a solvent comprising 1.32 l of dry tetrahydrofuran (THF) and 356 ml of methanol under nitrogen at about -77°. To the resulting solution is added 102 ml of 50% (4.09 M) diethylmethoxyborane in THF over a 15 minute period, and the formed mixture is stirred for an additional 10 minutes.

(b) 300.5 g (0.464 mole) of 71.88 % pure (±)-(E)-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-5-hydroxy-3-oxohept-6-enoic acid tert-butyl ester in 104 ml THF and 26 ml of methanol at a temperature of from about -74° to -77°C are added dropwise over to the mixture formed in (a) over a period of 1.5 hours, and the resulting mixture is stirred for an additional 30 minutes. 720 ml of saturated sodium bicarbonate solution and 1.75 l of heptane are added to quench

the reaction. 500 ml of ethyl acetate is then added and the resulting mixture is diluted with 3.5 l of water with stirring for 15 minutes, the temperature of the mixture being about 10°. The top organic layer is separated and washed several times with a total of 2.4 l of saturated sodium chloride solution, pH 7.5, and the organic layer is concentrated at 20-30 mm Hg at a maximum external temperature of about 45°. To the organic residue is added 375 ml of toluene, and the solvent is distilled at 20-30 mm Hg at a maximum external temperature of about 45°.

(c) 3.73 l of ethyl acetate is added to the obtained thick oil (the predominantly cyclic boronate). 500 ml of 30% hydrogen peroxide solution (4.41 moles) is then added to the ethyl acetate solution while maintaining an internal temperature of from 25 to 30° (the addition initially being exothermic), and the reaction mixture is stirred at 20 to 25° for about 2 hours until thin layer chromatography shows no boronate present. The top organic layer is washed twice with a total of 2.22 l of saturated sodium chloride solution, pH 7.5. The top organic layer is then separated, washed three times with a total of 2.61 l of 10% sodium sulfite solution (until the organic layer is free of peroxide) while maintaining an internal temperature of 25°. The top organic layer is then washed twice with a total of 1.72 l of saturated sodium chloride solution, pH 7.5 and the solvent is distilled at 20-30 mm Hg and a maximum external temperature of about 45°. The residue is dissolved in 1.17 l of refluxing ethyl acetate, the mixture is filtered while hot, and the filtrate is stirred at 20 to 25° for 18 hours. The solids are collected by filtration, dried under reduced pressure (about 20-30 mm Hg) at 25°C, washed with 550 ml of ethyl acetate/heptane (1:4), redissolved in 880 ml of ethyl acetate and stirred at ambient temperature for 18 hours. The solids are collected by filtration and washed with 480 ml of ethyl acetate/heptane (1:2). The solids are dried under reduced pressure to give a product of 114.5 g (M.P. 135-137°).

A second crop is obtained from the mother liquors, to give a total yield of 149.5 g. The product has a chemical purity of 99.44% and is 99.67% pure erythro isomer. It may be resolved into two optically active enantiomers, the 3R, 5S and 3S,5R, of which the former is preferred.

Alternatively and preferably in step (a) one half of the indicated amount of sodium borohydride may be used.

Alternatively in step (c) aqueous sodium perborate solution may be used in place of 30 % hydrogen peroxide solution .

Example 2: (±)-Erythro-(E)-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)-indol-2'-yl]-3,5-dihydroxyhept-6-enoic acid methyl ester

[Formula I: R, X = as for Example 1; R_1 = methyl; in racemic form]

(a) Sodium borohydride is treated in a manner analogous to Example 1, step (a), but using 15 % diethylmethoxyborane in THF.

(b) 118.5 g (0.28 mole) of (±)-(E)-[7-(3'-(4"- fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-5-hydroxy-3-oxohept-6-enoic acid methyl ester is treated analogously to Example 1, step (b) but dilution is effected with 1.42 l of water and 1.185 l of heptane, instead of 3.5 l of water alone.

(c) To the organic residue (the predominantly cyclic boronate) is added 2.375 l of ethyl acetate and the mixture is treated with 264 ml of 30 % hydrogen peroxide solution (2.328 moles) and worked up as described in Example 1, step (c). The residue is then dissolved in 130 ml of isopropanol. The mixture is heated to refluxing temperature. While hot, 14 g of boric are added and refluxing is continued for 15 minutes. The mixture is then filtered and the filtrate is stirred at 20° to 25° for 18 hours. The solids are collected by filtration, washed with 100 ml of isopropanol, and dried under reduced pressure to give a product of 110 g (80 % yield). The product is redissolved in methanol and recrystallized [M.P. 124-126°]. The product is 99.07 % pure erythro racemate, which may be resolved into two optical enantiomers, the 3R,5S and 3S,5R, of which the former is preferred.

Example 3: (+)-Erythro-(E)-3,5-dihydroxy-7-[1'-(4"-fluorophenyl)--4'-(1"-methylethyl)-2'-phenyl-1H-imidazol-5'-yl]-hept-6-enoic acid tert-butyl ester

[Formula I: R = 1-(4'-fluorophenyl)-4-(1'-methylethyl)-2-phenyl-1H-imidazol-5-yl;
X = (E)-CH=CH-; R_1 = tert-butyl;
in (3R,5S)-enantiomeric form]

(a) 10.27 g (0.27 mole) of sodium borohydride are added to a solvent comprising 1.67 liter of dry THF and 513 ml of methanol under nitrogen at about -76°. To the resulting solution is added 387 ml of 15 % diethylmethoxyborane in THF over a 30 minute period, while maintaining the internal temperature below -77.5°, and the formed mixture is stirred for an additional 5 minutes.

(b) 110 g (0.223 mole) of (5S)-(E)-7-[1'-(4"-fluorophenyl)-4'-(1"-methylethyl)-2'-phenyl-1H-imidazol-5'-yl]-5-hydroxy-3-oxohept-6-enoic acid tert-butyl ester in 304 ml of THF and 76 ml of methanol at a temperature of about -74° to -77° are added dropwise to the mixture formed in (a) over a period of two hours. The resulting yellow solution is stirred at -76.5° for six hours. 425 ml of saturated ammonium chloride is then added to quench the reaction, the temperature being maintained at about -65°. 950 ml of ethyl acetate, 950 ml of hexane and 1.13 liter of water are added, the temperature of the mixture being about 5°, and the mixture is stirred for 15 minutes, the resulting temperature of the mixture being about 5°. The top organic layer is separated and washed successively with a total of 1.4 l of saturated sodium chloride solution (pH 7.5), and the solvent is distilled at 20 to 30 mm Hg at a maximum external temperature of about 45°.

(c) 3.25 liter of ethyl acetate is added to the obtained oil (the predominantly cyclic boronate). 340 ml of 30 % hydrogen peroxide solution (3 moles) is then slowly added so as to maintain an internal temperature of 20° to 25°, and the reaction mixture is stirred at 20° to 25° for about 3 hours until thin layer chromatography shows no boronate present. The top organic layer is washed twice with a total of 1.6 l of saturated sodium chloride solution, pH 7.5. The top organic layer is then separated, washed three times (for ten minutes each time) with a total of 1.5 l of 10 % sodium sulfite solution (until the organic layer is free of peroxide) while maintaining an internal temperature of 25°. The top organic layer is washed with 600 ml of saturated sodium chloride solution (pH 7.5). The solvent is distilled at 20 to 30 mm Hg at a maximum external temperature of about 45°. 106 g of crude material is obtained. Purification of 0.68 g of the crude dihydroxy ester is done by column chromatography using ethyl acetate/hexane (1:2) as the eluant, yielding 490 mg (M.P. 143-145°), which is shown by NMR analysis to contain the <u>erythro</u> isomer in 98.78% purity (there being no threo isomer present); $[\alpha]_D^{20}$ = + 6.49° (c = 0.77, CH_2Cl_2).

Example 4: (3R,5S)-Erythro-dihydroxy-6-trityloxyhexanoic acid tert-butyl ester

[Formula Iu: u = trityl; R_u = t-butyl; in (-)-enantiomeric form]

(a) 5.61 g (148.4 mmoles) of sodium borohydride are added to a solvent comprising 990 ml of dry THF and 280 ml of methanol under nitrogen at about -76°. The temperature increases to about -74°. To the resulting solution is added 129.7 ml of 15 % diethylmethoxyborane in THF dropwise over a 20 minute period, and the formed mixture is stirred for an additional 10 minutes at from -77° to -76°.

(b) 56 g (0.122 mmole) of (S)-5-hydroxy-6-trityloxy-3-oxo-hexanoic acid t-butyl ester in 165 ml of THF and 41 ml of methanol at a temperature of from about -77° to -75° are added dropwise to the mixture formed in (a) over a period of 40 minutes, and the resulting mixture is stirred for an additional two hours at from -77° to -75°. 156 ml of saturated ammonium chloride solution is added to quench the reaction. 500 ml of ethyl acetate, 500 ml of heptane and 600 ml of water are then added. The top organic layer is separated and washed successively with a total of 600 ml of saturated sodium chloride solution, pH 7.5, and the organic layer is concentrated at 20 to 30 mm Hg at a maximum external temperature of about 45°.

(c) 793 ml of ethyl acetate is added to the obtained organic residue (containing predominantly the cyclic boronate). 79 ml of 30 % hydrogen peroxide solution (0.7 moles) is then slowly added, and the reaction mixture is stirred for about 3 hours until thin layer chromatography shows no boronate present. The top organic layer is washed twice with a total of 400 ml of saturated sodium chloride solution, pH 7.5. The top organic layer is then separated, washed three times (for ten minutes each time) with a total of 576 ml of 10% sodium sulfite solution (until the organic layer is free of

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peroxide) while maintaining an internal temperature of 25°. The top organic layer is then washed successively with a total of 200 ml of saturated sodium chloride solution, pH 7.5, and the solvent is distilled at 20-30 mm Hg and a maximum external temperature of about 45°. 54.3 g of the crude dihydroxy compound (M.P. 84-86°) are obtained, which is indicated to contain 99.19 % erythro isomer; $[\alpha]_D^{20}$ = - 5.59° (c = 1.6, CH_2Cl_2).

10.2. Examples for the preparation of intermediates of formula VII by process A

Example 5: 3-(N,N-Dimethylamino)acrolein

[= (E)-3-(N,N-Dimethylamino)prop-2-enal]

[Formula VII: R_{12}, R_{13} = methyl]
[Subprocess Aa]

Step (i): A 12 l four-neck round bottom flask equipped with a stirrer, brine-filled condenser, thermometer, caustic scrubber, addition funnel and cooling bath is charged, under a blanket of nitrogen, with 4.0 l of methylene chloride and 438 g (5.99 moles) of N,N-dimethylformamide. The solution is cooled to 7°, and 860 g (6.8 moles) of oxalyl chloride is added over a period of 2.5 hours at a rate such that little or no solvent and/or reagent is swept into the condenser, while maintaining the temperature of the reaction mixture at 5° to 10°. A white solid forms.

Step (ii): 483 g (6.7 moles) of ethyl vinyl ether is added over a period of 30 to 60 minutes while maintaining a maximum temperature of 25° to 28°, the addition being very exothermic. A brown-red solution results. The reaction mixture is heated at 37° to 38° for 30 minutes, refluxing taking place. As much methylene chloride as possible is recovered by distillation at 30 to 40 mm Hg and 45° and, after the distillation ceases, the reaction mixture is maintained at 30 mm Hg and 45° for 30 minutes to obtain a dark brown stirrable oil.

Step (iii): The reaction mixture is cooled to 20°, and 450 ml of water is added over a period of about 30 minutes; the exotherm is allowed to raise the temperature to 60°, and this temperature is maintained for the balance of the addition. The mixture is stirred at 50° to 60° for 30 minutes and cooled to 20°. A solution of 1.71 kg

(12.35 moles) of anhydrous potassium carbonate in 3.6 l of water is added over a period of 30 to 45 minutes while maintaining the temperature at 20° to 22°. The aqueous layer is extracted with 4 l of methylene chloride, the bottom methylene chloride layer is separated, and the top aqueous layer is extracted four times with 1 l portions of methylene chloride. The five methylene chloride phases are combined, dried over 500 g of anhydrous sodium sulfate and filtered, and the solid is washed twice with 250 ml portions of methylene chloride. The washings and filtrate are combined and as much methylene chloride as possible is recovered by distillation at 20 to 40 mm Hg and 45° to obtain a thick stirrable oil.

Step (iv): The oil is cooled to 20°, 500 ml of methanol is added, the mixture is cooled to 10°, and 60 g (1.33 moles) of anhydrous dimethylamine is added while maintaining a maximum temperature of 20°. As much solvent as possible is recovered by distillation at 20 to 30 mm Hg and 70°, the pressure is lowered to 3 to 4 mm Hg, and distillation is continued while gradually raising the temperature until it reaches 120° and the vapor temperature reaches 115° to obtain the 89.7 % pure product as an oil [412 g; yield 62 %; B.P. of pure product 271°-272.8°).

Example 6: 3-(N-Methyl-N-phenylamino)acrolein

[= (E)-3-(N-Methyl-N-phenylamino)prop-2-enal]

[Formula VII: R_{12} = phenyl; R_{13} = methyl]
[Subprocess Ab, variant Ab1]

Step (i): A 12 l four-neck round bottom flask equipped with a stirrer, brine-filled condenser, thermometer, caustic scrubber, addition funnel and cooling bath is charged, under a blanket of nitrogen, with 3.0 l of methylene chloride and 1.02 kg (7.4 moles) of N-methylformanilide. The solution is cooled to 15°, and 1.10 kg (8.67 moles) of oxalyl chloride is added over a period of 1.5 hours at a rate such that little or no solvent and/or reagent is swept into the bottom of the brine-filled condenser, while maintaining a temperature of 15° to 17° under gentle refluxing. The reaction mixture is slowly warmed to 43° over a period of 1 hour, refluxed for 1 hour at 43° to 45° to obtain a clear yellow solution and cooled to 15°.

Step (ii): 648 g (8.99 moles) of ethyl vinyl ether is added over a period of 40 to 60 minutes while maintaining a maximum temperature of 28° to 29°, the reaction being very exothermic. The resulting brown-red solution is heated at 38° to 39° for 30 minutes, refluxing taking place, and is cooled to 15°.

Step (iii): A solution of 960 g (9.05 moles) of anhydrous sodium carbonate in 4.5 l of water is added over a period of 45 to 60 minutes while maintaining a temperature of 22° to 30°, the addition being very exothermic. The mixture is stirred at 22° to 25° for 15 minutes and allowed to stand for 15 minutes to permit separation into two phases. The organic phase is separated, and the aqueous phase is extracted with 1.25 l of methylene chloride. The methylene chloride extract is

combined with the previous organic phase, and the combined solution is extracted with 1 l of water. The aqueous extract is back extracted with 250 ml of methylene chloride and this methylene chloride extract is combined with the previous organic phase. As much methylene chloride as possible is recovered by distillation at 20 to 40 mm Hg and 60°, and the residual oil is heated at 20 to 30 mm Hg and 60° to 65° for 4 hours to obtain the 83.5 % pure product as an oil [1.295 kg; yield 90.7 %; B.P. of pure product 244° (dec.); M.P. of pure product 46-47° from isopropanol/hexane 1:1].

Example 7: 3-(N-Methyl-N-phenylamino)acrolein

[= (E)-3-(N-Methyl-N-phenylamino)prop-2-enal]

[Formula VII: R_{12}, R_{13} = as for Example 6]
[Subprocess Ab, variant Ab2]

Step (i): A 5 l four-neck round bottom flask equipped with a stirrer, brine-filled condenser, thermometer, caustic scrubber, addition funnel and cooling bath is charged, under a blanket of nitrogen, with 350 ml of acetonitrile and 425 g (3.8 moles) of N-methylformanilide. The solution is cooled to -15°, and 440 g (3.46 moles) of oxalyl chloride is added over a period of 1.5 hours at a rate such that little or no solvent and/or reagent is swept into the bottom of the brine-filled condenser maintained at -25° to -20°, while maintaining a temperature of -15° to -10° under gentle refluxing. The reaction mixture is slowly warmed to 15° over a period of 30 minutes and stirred for 15 minutes at 15° to 18°.

Step (ii): 339.5 g (3.39 moles) of n-butyl vinyl ether is added over a period of 45 minutes while maintaining a maximum temperature of 28° to 30°, the reaction being very exothermic. The reaction mixture is stirred at 30° to 35° for 30 minutes to obtain a red-brown solution and is cooled to 0°.

Step (iii): A solution of 395 g (3.73 moles) of anhydrous sodium carbonate in 1.75 l of water is added over a period of 40 to 60 minutes while maintaining a temperature of 8° to 10°, the addition being very exothermic. 1.75 l of toluene is added, and the mixture is stirred at 20° to 22° for 15 minutes and allowed to stand for 15 minutes to permit separation into two phases. The organic phase is separated and washed twice with 150 ml portions of water. As much toluene as possible is recovered by distillation at 20 to 80 mm Hg and

60° to 90°, and the residual oil is heated at 20 to 30 mm Hg and 89° to 90° for 30 minutes to obtain the 86.6 % pure product as an oil [492 g; yield 85.7 %; B.P. of pure product 244° (dec.); M.P. of pure product 46-47° from isopropanol/hexane 1:1].

If the reaction mixture is stirred at 28° to 30° for 30 minutes instead of at 30° to 35°, a 90.7 % yield of a 92.3 % pure product is obtained.

Example 7a: 3-(N-Methyl-N-phenylamino)acrolein

[= (E)-3-(N-Methyl-N-phenylamino)prop-2-enal]

[Formula VII: R_{12}, R_{13} = as for Example 6]
[Subprocess Ab, variant Ab2, neat reagents]

Step (i): A 2.5 l four-neck flask equipped as in Example 7, step (i) is charged, under an atmosphere of nitrogen, with 223.2 ml (1.81 moles) of N-methylformanilide. The solution is cooled to 15° and 177.6 ml (2.07 moles) of oxalyl chloride is added over a period of 20 minutes while maintaining the same temperature. A spontaneous gas evolution occurs and an orange, homogeneous solution forms.

Step (ii): 278.4 ml (2.16 moles) of n-butyl vinyl ether is added over a period of 45 minutes while maintaining an internal temperature of 25° to 30°, the reaction being exothermic. The orange suspension is stirred at 40° to 45° for 30 minutes and is cooled to 0°.

Step (iii): To the product of step (ii) is added slowly during about 90 minutes 4N NaOH solution so that the temperature does not exceed 5°. The mixture is warmed up to room temperature and stirred for a further 60 minutes. The organic layer is separated in a 3 l funnel and the aqueous phase is extracted with 100 ml of n-butanol. The combined organic layers are washed twice with 200 ml of brine and the solvent distilled off at 80°/15 Torr over 2 hours to give a thick, brown-black oil [295 g; yield 92 %; chemical purity > 98 %; B.P. of pure product 244° (dec.); M.P. of pure product 46-47° from isopropanol/hexane 1:1].

Example 8: 3-(N-Methyl-N-phenylamino)acrolein

[= (E)-3-(N-Methyl-N-phenylamino)prop-2-enal]
[Formula VII: R_{12}, R_{13} = as for Example 6]
[Subprocess Ab, variant Ab3]

Steps (i) and (ii): A 12 l four-neck round bottom flask equipped with a stirrer, brine-filled condenser, thermometer, caustic scrubber, addition funnel and cooling bath is charged, under a blanket of nitrogen, with 1.056 kg (8.15 moles) of oxalyl chloride and 480 ml of acetonitrile. The solution is cooled to -10°, and a mixture of 1.02 kg (7.395 moles) of N-methylformanilide, 816 g (7.98 moles) of n-butyl vinyl ether and 360 ml of acetonitrile is added over a period of 2.5 hours at a rate such that little or no solvent and/or reagent is swept into the bottom of the brine-filled condenser (maintained at -25° to -20°), while maintaining a temperature of -10° to -5° under gentle refluxing. The resulting homogeneous orange reaction mixture is slowly warmed to 20° over a period of 30 minutes; a slight exotherm raises the temperature to 28° over a period of 30 minutes. The reaction mixture is stirred at 28° to 30° for 1 hour to obtain a brown homogeneous mixture and is cooled to 0°

Step (iii): A solution of 948 g (8.94 moles) of anhydrous sodium carbonate in 4.20 l of water is added over a period of 45 to 60 minutes while maintaining a temperature of 8° to 10°, the addition initially being very exothermic. 3.60 l of toluene is added, and the mixture is stirred at 20° to 22° for 15 minutes and allowed to stand for 15 minutes to permit separation into two phases. The organic phase is separated and washed twice with 360 ml portions of water. As much toluene as possible is recovered by distillation at 20 to 80 mm Hg and 60° to 90°, and the residual oil is heated at 20 to 30 mm Hg and 89° to 90° for 30 minutes to obtain the 89.1 % pure product as an oil [1.16 kg; yield 86.6 %; B.P. of pure product 244°C. (dec.); M.P. of pure product 46-47° from isopropanol/hexane 1:1].

10.3. Examples for the preparation of intermediates of formula Va by process B

Example 9: (E)-3-[3'-(4"-Fluorophenyl)-1'-(1"-methylethyl)-1H-indol-2'-yl]prop-2-enal

[Formula Va: R_5, R_6 = H; R_7 = 1-methylethyl; R_8 = 4-fluorophenyl]
[Process B]

(i) A 5 l four-neck round bottom flask equipped with a stirrer, condenser, thermometer, addition funnel and cooling bath is charged, under a blanket of dry nitrogen, with 100 ml of dry acetonitrile and 174.4 g (1.14 moles) of phosphorus oxychloride, the mixture is cooled to -5°, and a solution of 184 g (0.96 mole) of 83.5 % pure 3-(N-methyl-N-phenylamino)acrolein (product of Examples 6 to 8) in 156 ml of dry acetonitrile is added over a period of 45 minutes while maintaining a temperature of -5° to +5°. The reaction mixture is stirred at 0° to 5° for 10 minutes.

(ii) 115.2 g (0.45 mole) of 3-(4'-fluorophenyl)-1-(1'-methylethyl)-1H-indole (compound of formula XVII) is added over a period of 20 minutes while maintaining a temperature of about 5°. The reaction mixture is refluxed at 83° for 9 hours and cooled to 10°.

(iii) A solution of 228 g (5.7 moles) of sodium hydroxide in 2.0 l of water is slowly added over a period of 30 minutes while maintaining a temperature of 25° to 30°, the addition being very exothermic. 1.6 l of toluene is added, the mixture is stirred at 25° for 30 minutes and filtered through a filter pad. The filter cake is washed with 100 ml of toluene, and the washing is combined with the previous filtrate.

The organic layer is separated, and a mixture of 93.4 g of concentrated hydrochloric acid and 2 l of water is added followed by 400 ml of saturated sodium chloride solution. The mixture is stirred at 25° for 30 minutes, and the resulting slurry is filtered through a filter pad. The tars are washed with 100 ml of toluene, and the washing is combined with the filtrate. The organic layer is separated, washed twice with 2 l portions of deionized water and filtered through a filter pad. As much toluene as possible is recovered by distillation at 30-50 mm Hg and an external temperature of 60° to 65° to obtain a thick stirrable oil. 100 ml of 95 % ethanol is added, as much ethanol as possible is recovered by distillation at 30 to 80 mm Hg and 60° to 65°, and this is repeated twice. 180 ml of 95 % ethanol is added, and the mixture is refluxed at 78° for 15 minutes and slowly cooled to 20° over a period of 2 hours, crystallization commencing at about 55°. The slurry is slowly cooled to 0° to 5° over a period of 30 minutes, maintained at 0° to 2° for 1 hour and filtered. The filter cake is washed three times with 50 ml portions of cold (0° to 5°) 95 % ethanol and vacuum dried at 60° to 65° for 16 hours to constant weight to obtain the 98.7 % pure product (101 g; yield 71.3 %; M.P. 127°-128°).

In a variant isopropanol is used in place of 95 % ethanol.

Example 10: (E)-3-[3'-(4"-Fluorophenyl)-1'-(1"-methylethyl)-1H-indol-2'-yl]prop-2-enal

[Formula Va: R_5, R_6, R_7, R_8 = as for Example 9]
[Process B, alternative procedure]

i) A 5 l four-neck round bottom flask equipped with a stirrer, condenser, thermometer, addition funnel and cooling bath is charged, under a blanket of dry nitrogen, with 263 ml of dry acetonitrile and 454 g (2.96 moles) of phosphorus oxychloride, the mixture is cooled to -5°, and a solution of 471.6 g (2.49 moles) of 85.5 % pure 3-(N-methyl-N-phenylamino)acrolein in 406 ml of dry acetonitrile is added over a period of 45 minutes while maintaining a temperature of 5° to 7°. The reaction mixture is stirred at 5° to 7° for 10 minutes.

ii) 300 g (1.18 moles) of 3-(4'-fluorophenyl)-1-(1'-methylethyl)-1H-indole (compound of formula XVII) is added over a period of 10 minutes while maintaining a temperature of about 7°. The reaction mixture is refluxed at 83° for 3 hours and cooled to 22°.

iii) 2.7 l of water is slowly added over a period of 15 minutes while maintaining a temperature of 22° to 35°, the addition being exothermic. The reaction mixture is stirred at 35° to 50° for 30 minutes, heated at 50° to 55° for 1.5 hours (a longer period of heating may be necessary for complete hydrolysis), cooled to 22°, maintained at 22° for 15 minutes and filtered. The filter cake is washed three times with 600 ml portions of water and suction dried at aspirator pressure for 6 to 16 hours (N-methylaniline may be recovered from the combined aqueous layer and washings). The wet filter cake is transferred to the original 5 l flask, 2.5 l of toluene and 180 g of 20 µ powdered cellulose are added, and the mixture is heated at 50° to 55° for 1.5 hours, cooled to 22°, maintained at 22° for 15 minutes and optionally filtered through a pad of 91 g of 70-230 mesh A.S.T.M.

silica gel covered with a filter cloth. The cellulose and silica gel pad are washed three times with 200 ml portions of toluene. The toluene filtrate and washings are combined and as much toluene as possible is recovered by distillation at 30 to 50 mm Hg and 50° to 65° (external). 280 ml of 95 % ethanol is added to the residual thick oil, the ethanol is distilled at 20 to 30 mm Hg and 60° to 65°, 280 ml of 95 % ethanol is added, and as much ethanol as possible is distilled at 30 to 80 mm Hg and 60° to 65°. 700 ml of 95 % ethanol is added, and the mixture is refluxed at 78° for 15 minutes and slowly cooled to 20° over a period of 1 hour, crystallization commencing at about 55°. The resulting slurry is cooled to 0° to 5° over a period of 30 minutes and maintained at 0° to 2° for 30 minutes, and the solids are collected by filtration, washed three times with 120 ml portions of cold (0° to 5°) 95 % ethanol and vacuum dried at 60° to 65° for 16 hours to constant weight to obtain the 99.4 % pure product (276.6 g; yield 75.5 %; M.P. 129°-130°).

In a variant isopropanol is used in place of 95 % ethanol.

It is preferred to omit the pad of silica gel, i.e. the powdered cellulose-containing liquid is subjected to a simple filtration, and it is the residue therefrom that is washed three times with 200 ml portions of toluene.

Example 10a: (E)-3-[3'-(4"-Fluorophenyl)-1'-(1"-methylethyl)-1H-indol-2'-yl]prop-2-enal

[Formula Va: R_5, R_6, R_7, R_8 = as for Example 9]
[Process B, alternative procedure]

(i) A 1.5 l flask equipped as described in Example 10, step (i) is charged, under a blanket of dry nitrogen, with 170 ml of dry acetonitrile and 105.3 g 3-(N-methyl-N-phenylamino)acrolein hydrochloride salt at room temperature. To the mixture is added over 5 minutes 96.6 g of phosphorus oxychloride. A dark solution is obtained.

(ii) 90 g of 3-(4'-fluorophenyl)-1-(1'-methylethyl)-1H-indole (compound of formula XVII) is added at 30°. The mixture is heated to reflux for 4.5 hours at 75° to 83°, then cooled to 22°.

(iii) 250 ml of water at 5° are added, followed by 500 ml of water at room temperature over 15 minutes. The mixture is stirred at 35° to 50° for 30 minutes, then heated at 50° to 55° for 1.5 hour. A dark slurry is obtained. The mixture is cooled to 30°, maintained at 30° for 15 minutes, and the brown slurry is filtered. The filter cake is washed three times with a total of 540 ml of water. The filter cake is suction dried under vacuum for about 4 hours. The solids are transferred into the original 1.5 l flask, 750 ml of toluene and 54 g of 20 µ powdered cellulose are added, and the subsequent working-up is effected as described in Example 10, step (iii) to obtain the product (89 g; yield 81 %; M.P. 123-129°).

10.4. Examples for the specific embodiment

Example 11: (±)-Erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoic acid sodium salt

[Formula Ia: in racemic form; sodium salt form]

Steps (a), (b) and (c): N-Methylformanilide is reacted with oxalyl chloride and ethyl or n-butyl vinyl ether according to process A, subprocess Ab to produce 3-(N-methyl-N-phenylamino)acrolein as described in Examples 6, 7, 7a or 8 [steps (i), (ii) and (iii)].

Step (d): The above product, 3-(N-methyl-N-phenylamino)acrolein, is reacted with phosphorus oxychloride as described in Example 9, 10 or 10a, step (i) to produce the compound of formula XVI wherein X_a is chloro, R_{12b} is phenyl and R_{13} is methyl.

Step (e): The above compound of formula XVI is reacted with 3-(4'-fluorophenyl)-1-(1'-methylethyl)-1H-indole as described in Example 9, 10 or 10a, step (ii) to produce the compound of formula XVIIIa wherein X_a is chloro, R_{12b} is phenyl and R_{13} is methyl.

Step (f): The above compound of formula XVIIIa is hydrolyzed as described in Example 9, 10 or 10a, Step (iii) to produce (E)-3-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)-1H-indol-2'-yl]prop-2-enal.

Step (g): Under a nitrogen atmosphere a reactor is charged with 0.5 l of tetrahydrofuran, the solution is cooled to -10°, 60 g sodium hydride (60 % dispersion in mineral oil) are added carefully. Then 237.3 g t-butyl acetoacetate in 250 ml of THF are added carefully over 45 minutes while maintaining the temperature below 2°. The resultant solution is stirred at -10° to 20° for 1 hour. The mixture is cooled to -10° and 938 ml of a 1.6 M solution of n-butyllithium in hexane is added at a rate such that the temperature does not exceed 0° (over about 60 minutes). The mixture is stirred for 10 minutes at that temperature, then cooled to -10°, and a solution of 230 g of product of step f) above in 650 ml of THF is added at a rate such that the temperature does not exceed 0° (over about 70 minutes). The reaction mixture is stirred at 0° for 15 minutes and poured onto a mixture of 248 ml of conc. hydrochloric acid and 2.5 kg of ice under vigourous stirring over 5 to 10 minutes. The mixture is vigourously stirred for a further 15 minutes, the organic phase is separated, washed twice with 500 ml portions of saturated NaCl solution and concentrated under reduced pressure (about 25 mm Hg). To the residue is added 200 ml of toluene and the solution is concentrated again. The obtained crude (±)-(E)-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-5-hydroxy-3-oxohept-6-enoic acid t-butyl ester (compound of formula IIa wherein R_1 is t-butyl, in racemic form) (503.6 g; 70.04 % pure) is used in the next step without further purification.

Step (h): The above crude product is stereoselectively reduced as described in Example 1, steps (a), (b) and (c) to produce (±)-erythro-(E)-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]-3,5-dihydroxy-hept-6-enoic acid t-butyl ester.

Step (i): To 42.5 g of the ester obtained under step (h) above in 275 ml of THF is added over 5 minutes 90 ml of 1 N sodium hydroxide while maintaining the temperature below 10°. The solution is stirred for 1 hour at room temperature, 275 ml of methanol are added, the mixture is concentrated at 25 mm Hg and 45°, then 300 ml of deionized water are added, distillation is continued to a remaining volume of 140 ml, then 380 ml of deionized water are added again and the solution is washed with a total of 640 ml of t-butyl methyl ether in 3 portions. The aqueous layer is concentrated at 25 mm Hg and 45° to a volume of about 300 ml, 220 ml of deionized water are added, and the clear aqueous solution is lyophilized over 3 days. The title compound is obtained (35.9 g; 91 % yield; chemical purity 98.9 %; 99.9 % pure erythro isomer; boron concentration below detection limit).

Alternative procedure for step (i): To 35.0 g of the ester obtained under step (h) above in 175 ml of ethanol is added over 5 minutes under stirring 74 ml of 1 N sodium hydroxide solution while maintaining the temperature below 12°. The solution is stirred for 1 hour, the mixture is concentrated at 25 mm Hg and 45°, then 250 ml of deionized water are added, distillation is continued to a remaining volume of 115 ml, then 315 ml of deionized water are added and the solution is washed with a total of 525 ml of tert-butyl methyl ether in 3 portions. The aqueous layer is concentrated at 25 mm Hg and 45° to a volume of about 245 ml, 185 ml of deionized water are added, and the clear aqueous solution is lyophylized over 3 days. The title compound is obtained (29.75 g; colour pure white; 91 % yield; M.P. 204-207° (dec.); chemical purity 100 %; 99.61 % pure erythro isomer; boron concentration 3.96 ppm).

Example 12: (±)-Erythro-(E)-3,5-dihydroxy-7-[3'-(4"-fluorophenyl)-1'-(1"-methylethyl)indol-2'-yl]hept-6-enoic acid sodium salt

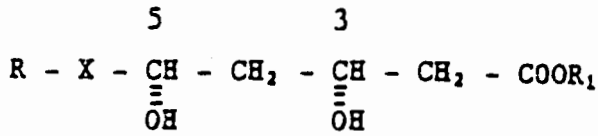
[Formula Ia: in racemic form; sodium salt form]

The title compound is obtained in a manner analogous to Example 11, except that

- in step (g) the methyl ester is produced, by reaction with the dianion of methyl acetoacetate instead of with t-butyl acetoacetate;
- step (h) is effected as described in Example 2, steps (a), (b) and (c);
- step (i) is effected by hydrolyzing the methyl ester obtained in step (h), as described in USP 4 739 073, Example 6(b) on column 50.

CLAIMS:

1. A combination comprising erythro form a compound of formula I and threo form of a compound of formula I



(I)

wherein

X is $-CH_2CH_2-$ or $-CH=CH$;

R_1 is an ester group inert to the reaction conditions; and

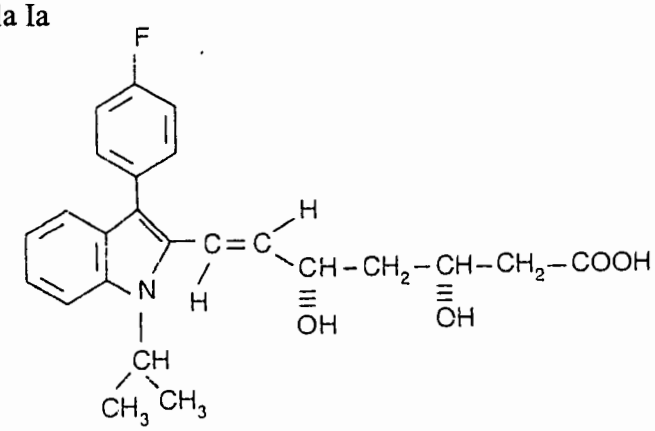
R is an organic radical having groups which are inert under reducing conditions, with the proviso that, when R is triphenylmethyl, then R_1 additionally includes allyl and X is $-OCH_2-$, or the free acid or a salt form or a further ester form or the δ-lactone, i.e. internal ester form thereof,

in a state of purity such that the proportion of erythro form to threo form is in a range of from 99.1 : 0.9 to 99.9 : 0.1,

2. Combination according to claim 1, in a state of purity such that the proportion of erythro form to threo form is 99.5 : 0.5 to 99.9 : 0.1

3. Combination as defined in claim 1, in a state of purity such that the proportion of erythro form to threo form is 99.7 : 0.3 to 99.9 : 0.1

4. Combination according to claim 1, wherein the compound of formula I is the compound of formula Ia



(Ia)

5. Combination according to claim 4, wherein the compound of formula Ia is in racemic or optically pure form; in free acid, salt, ester or δ-lactone, i.e. internal ester, form, in a state of purity such that the proportion of erythro form to threo form is 99.1 :0.9 to 99.9 : 0.1.

6. Combination according to claim 4, in a state of purity such that the proportion of erythro form to threo form is 99.9 : 0.1.