

FORM 1

644846

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

F.Hoffmann-La Roche AG, of 124 Grenzacherstrasse, CH-4002, Basel, SWITZERLAND, hereby apply for the grant of a standard patent for an invention entitled:

Process for the Preparation of Oxetanones

which is described in the accompanying complete specification.

Details of basic application(s):-

<u>Basic Applic. No:</u>	<u>Country:</u>	<u>Application Date:</u>
589/90	CH	23 February 1990
3925/90	CH	12 December 1990

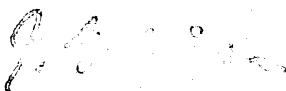
The address for service is:-

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Patent Attorneys
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31 Market Street
Sydney New South Wales Australia

DATED this FIFTEENTH day of FEBRUARY 1991

F.Hoffmann-La Roche AG

By:



Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 153364
S&F CODE: 55541

REPRINT OF RECEIPT

8020025 18/02/91

5845/2

COMMONWEALTH OF AUSTRALIA

THE PATENTS ACT 1952

DECLARATION IN SUPPORT OF A
CONVENTION APPLICATION FOR A PATENTAUSTRALIA
CONVENTION
STANDARD
& PETTY PATENT
DECLARATIONIn support of the Convention Application made for a
patent for an invention entitled:~~RAN 4039/56~~

Title of Invention-

Process for the preparation of oxetanones

Full name(s) and
address(es) of
Declarant(s)

I Roland Borer

of 10 Stockackerstrasse, CH-4153 Reinach, Switzerland

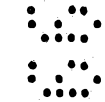
do solemnly and sincerely declare as follows:-

Full name(s) of
Applicant(s)

1. I am authorised by

F. HOFFMANN-LA ROCHE AG

of 124 Grenzacherstrasse, CH-4002 Basle, Switzerland



Basic Country(ies)

the applicant(s) for the patent to make this declaration on
its/~~their~~ behalf.2. The basic application(s) as defined by Section 141 of the
Act ~~was~~/were made

in Switzerland

Priority Date(s)

on February 23, 1990 and on December 12, 1990

Basic Applicant(s)

by ☒ F. HOFFMANN-LA ROCHE AG☐ the inventor(s) cited in paragraph 3.Full name(s) and
address(es) of
inventor(s)

3.

Martin Karpf
4 In der Haselmatte
CH-4153 Reinach, SwitzerlandUlrich Zutter
33 Socinstrasse
CH-4051 Basle, Switzerland

(respectively)

is/are the actual inventor(s) of the invention and the facts upon
which the applicant(s) is/~~are~~ entitled to make the application are
as follows:() the inventor(s) have assigned the invention to
Hoffmann-La Roche Inc., Nutley, USA,
who have re-assigned all their rights for Australia
to the Applicant.(X) the Applicant is the assignee of the invention from
the inventor(s).4. The basic application(s) referred to in paragraph 2 of this
Declaration ~~was~~/were the first application(s) made in a Convention
country in respect of the invention(s) the subject of the application.Set out how Applicant(s)
derive title from actual
inventor(s) e.g. The
Applicant(s) is/are the
assignee(s) of the
invention from the
inventor(s)

Declared at Basle this 14th day of January 1991

To:

The Commissioner of Patents,
COMMONWEALTH OF AUSTRALIA

Signature of Declarant(s)

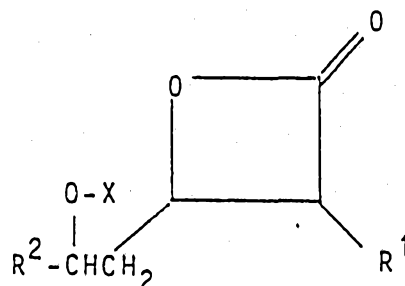


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(12) PATENT ABRIDGMENT (11) Document No. AU-B-71166/91
 (19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 644846

- (54) Title
PROCESS FOR THE PREPARATION OF OXETANONES
- International Patent Classification(s)
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- (21) Application No. : 71166/91 (22) Application Date : 18.02.91
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- (43) Publication Date : 29.08.91
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- (71) Applicant(s)
 F.HOFFMANN-LA ROCHE AG
- (72) Inventor(s)
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- (74) Attorney or Agent
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- (56) Prior Art Documents
 AU 619533 32382/89 C07D 309/32
 AU 71228/91 C07D 305/12
 US 4983746
- (57) Claim

1. A process for the manufacture of oxetanones of the formula



I

wherein

R¹ and R²

are alkyl with up to 17 C atoms optionally interrupted by an O atom in a position other than the α- or β-position; or benzyl optionally ring-substituted by 1 to 3 C₁₋₆-alkyl or C₁₋₆-alkoxy groups,

X

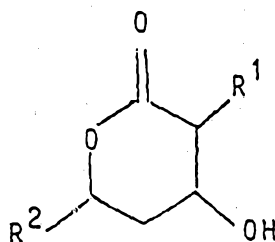
is hydrogen or a group of the formula (R³, R⁴)NCH(R⁵)(CH₂)_n-CO-,

R³

is hydrogen, C₁₋₃-alkyl or C₁₋₃-alkanoyl.

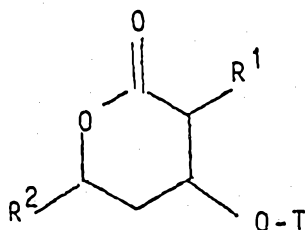
.../2

- R^4 is hydrogen or C_{1-3} -alkyl and
 R^5 is hydrogen, a group Ar or Ar- C_{1-3} -alkyl or C_{1-7} -alkyl optionally interrupted by Y and optionally substituted by Z or
 R^4 with R^5 form together with the N atom to which they are attached a 4- to 6-membered saturated ring,
Y is oxygen, sulphur or a group $N(R^6)$, $C(O)N(R^6)$ or $N(R^6)C(O)$,
Z is a group $-(O \text{ or } S)-R^7$, $-N(R^7, R^8)$, $-C(O)N(R^7, R^8)$ or $-N(R^7)C(O)R^8$,
n is the number 1 or 0, whereby R^5 is hydrogen when n is the number 1,
Ar is phenyl substituted by 1 to 3 groups R^9 or OR^9 and
 R^6 to R^9 are hydrogen or C_{1-3} -alkyl,
and of salts of the oxetanones of formula I in which X is not hydrogen with weak acids, which process comprises
a) etherifying a β -hydroxy- δ -lactone of the formula



II.

- b) opening the resulting ether of the formula



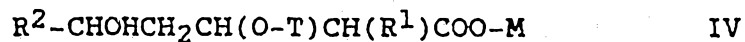
III

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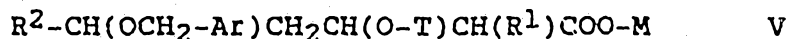
wherein T is a readily cleavable ether group,
with a base,

c) reacting the resulting salt of the formula



wherein M is an alkali metal or alkaline earth metal,
in optional sequence with an arylmethyl halide and a base
and

d) selectively cleaving the resulting diether of the
formula



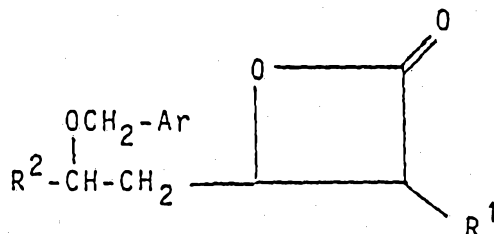
with an acid,

e) cyclizing the resulting β -hydroxyacid of the formula



optionally after resolution into its enantiomers,

f) cleaving the resulting β -lactone ether of the formula



VII

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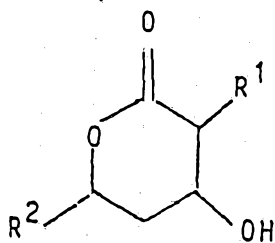
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and

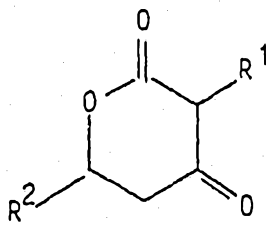
g) if desired, esterifying the resulting β -lactone alcohol of formula I in which X is hydrogen with an agent which introduces the group X and

h) if desired, isolating the ester obtained in the form of a salt with a weak acid.

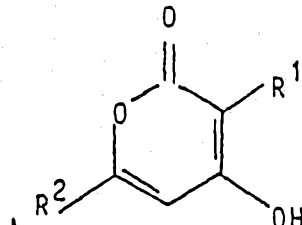
12. The β -hydroxy- δ -lactones, β -keto- δ -lactones and pyrones of formulae II, XII and, respectively, XVI



II



XII



XVI

from the following group:

rac-(2RS,3RS,5SR)-2-Hexyl-3-hydroxy-5-undecyl- δ -valeriolactone,

rac-(2RS,3RS,5SR)-2-ethyl-5-heptadecyl-3-hydroxy- δ -valeriolactone,

(2S,3S,5R)-2-ethyl-5-heptadecyl-3-hydroxy- δ -valeriolactone and

rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-pentyl- δ -valeriolactone;

rac-5,6-dihydro-3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one,

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- 5 -

(R)-3-ethyl-5,6-dihydro-6-heptadecyl-4-hydroxy-2H-
-pyran-2-one and
rac-5,6-dihydro-3-hexyl-4-hydroxy-6-pentyl-2H-pyran-
-2-one;
3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one,
3-ethyl-6-heptadecyl-4-hydroxy-2H-pyran-2-one and
3-hexyl-4-hydroxy-6-pentyl-2H-pyran-2-one.

14. (R)-5,6-Dihydro-6-undecyl-2H-pyran-2,4(3H)-dione and (R)-5,6-dihydro-6-heptadecyl-2H-pyran-2,4(3H)-dione.

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

644846

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

Name and Address
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Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

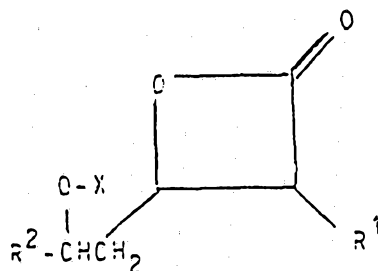
Process for the Preparation of Oxetanones

The following statement is a full description of this invention, including the best method of performing it known to me/us

RAN 4039/56

Abstract

The invention is concerned with a novel process for the manufacture of oxetanones of the formula



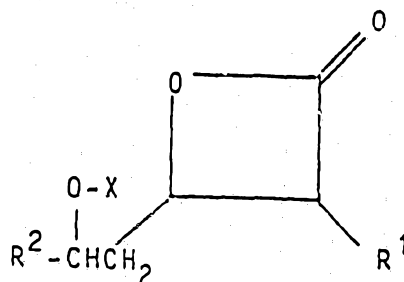
I

wherein R¹, R² and X have the significance given in the description, via corresponding β -keto- and β -hydroxy- δ -lactones, as well as novel intermediates which occur in this process.

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The present invention is concerned with a novel process for the manufacture of oxetanones of the formula

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wherein
R¹ and R²

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are alkyl with up to 17 C atoms optionally interrupted by an O atom in a position other than the α - or β -position; or benzyl optionally ring-substituted by 1 to 3 C₁₋₆-alkyl or C₁₋₆-alkoxy groups,

X

is hydrogen or a group of the formula (R³, R⁴)NCH(R⁵)(CH₂)_n-CO-,

25

R³

is hydrogen, C₁₋₃-alkyl or C₁₋₃-alkanoyl,

R⁴

is hydrogen or C₁₋₃-alkyl and

R⁵

is hydrogen, a group Ar or Ar-C₁₋₃-alkyl or C₁₋₇-alkyl optionally interrupted by Y and optionally substituted by Z or

30

R⁴ with R⁵

form together with the N atom to which they are attached a 4- to 6-membered saturated ring

Y

is oxygen, sulphur or a group N(R⁶), C(O)N(R⁶) or N(R⁶)C(O),

35

Z

is a group -(O or S)-R⁷, -N(R⁷, R⁸), -C(O)N(R⁷, R⁸) or -N(R⁷)C(O)R⁸,

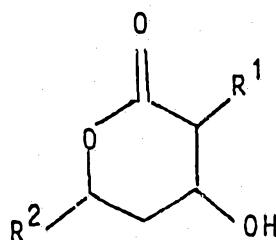
n is the number 1 or 0, whereby R^5 is hydrogen when n is the number 1,
Ar is phenyl substituted by 1 to 3 groups R^9 or OR^9 and
 R^6 to R^9 are hydrogen or C_{1-3} -alkyl,
and of salts of the oxetanones of formula I in which X is not hydrogen with weak acids.

Further, the invention is concerned with novel intermediates which occur in the said process.

Compounds of formula I are known, e.g. from EP 185 359A2. They possess valuable pharmacological properties. In particular, they inhibit pancreas lipase and can accordingly be used for the control or prevention of illnesses, especially of obesity, hyperlipemia, atherosclerosis and arteriosclerosis.

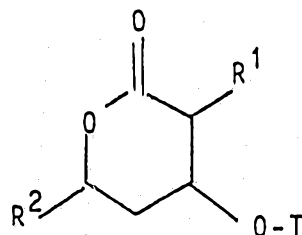
The process in accordance with the invention comprises

a) etherifying a β -hydroxy- δ -lactone of the formula



II,

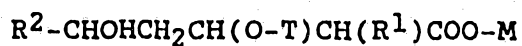
b) opening the resulting ether of the formula



III

wherein T is a readily cleavable ether group,
with a base,

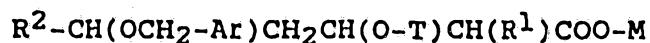
c) reacting the resulting salt of the formula



IV

wherein M is an alkali metal or alkaline earth metal,
in optional sequence with an arylmethyl halide and a base
and

d) selectively cleaving the resulting diether of the
formula



V

with an acid,

e) cyclizing the resulting β -hydroxyacid of the formula



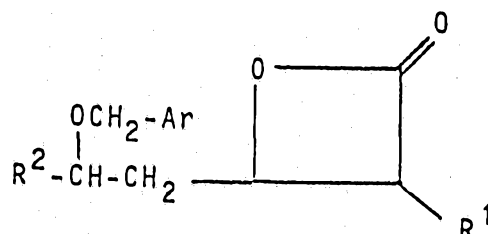
VI.

optionally after resolution into its enantiomers,

f) cleaving the resulting β -lactone ether of the formula

5

10



and

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g) if desired, esterifying the resulting β -lactone alcohol of formula I in which X is hydrogen with an agent which introduces the group X and

20

h) if desired, isolating the ester obtained in the form of a salt with a weak acid.

Alkyl groups are straight-chain or branched hydrocarbon residues such as methyl, ethyl, propyl, isopropyl, butyl isobutyl, pentyl, hexyl, undecyl, hexadecyl and heptadecyl. Phenyl, tolyl and xyllyl are examples of aryl groups. Pyrrolidinyl and pyridinyl are examples of 4- to 6-membered saturated rings.

30

Examples of weak acids which can form salts with the compounds of formula I are p-toluenesulphonic acid, methanesulphonic acid, oxalic acid, ascorbic acid, fumaric acid, maleic acid, malic acid, citric acid and phosphoric acid.

35

Examples of readily cleavable ether groups are tetrahydro-2H-pyran-2-yl (THP), 1-ethoxyethyl or silyl ether

groups such as tri- C_{1-4} -alkyl- or mono-(aryl- C_{1-4} -alkyl)-di-(C_{1-4} -alkyl)-silyl groups, e.g. t-butyl-dimethylsilyl.

5

10 A THP ether of formula III can be prepared by reacting a β -hydroxy- δ -lactone of formula II with 3,4-dihydro-2H-pyran at about 50°C in a solvent such as t-butyl methyl ether (TBME), tetrahydrofuran (THF) or toluene in the presence of catalytic amounts of acid such as pyridinium p-toluenesulphonate or p-toluenesulphonic acid. The THP ether III can subsequently be opened using sodium hydroxide or potassium hydroxide.

15

A silyl ether III can be prepared by reacting the β -hydroxy- δ -lactone II with a silyl halide such as t-butyldimethylsilyl chloride in the presence of a base such as ethyldiisopropylamine in a solvent such as dimethylformamide (DMF) while heating, e.g. to 50-100°C. The opening of a silyl ether III can be performed with an alkaline or alkaline earth base such as potassium hydroxide in a solvent such as dioxan.

20

25 An alkali metal hydride such as NaH or, preferably, an alkali metal t-butyrate, conveniently Na t-butyrate, can be used as the base in the etherification of the alkali metal or alkaline earth metal salt of formula IV to the diether V. This etherification can be performed by treating the salt IV with e.g. benzyl bromide and NaH or Na t-butyrate in a solvent such as THF or TBME.

30

35 A diether V can be selectively cleaved with an acid such as hydrochloric acid in the case of a THP ether or acetic acid in the case of a silyl ether at a temperature up to 60°C.

The optional resolution of a racemic β -hydroxyacid VI

can be effected using a chiral amine such as (R)-(+)- or (S)-(-)- α -methylbenzylamine in a solvent such as an ester, e.g. methyl acetate or ethyl acetate.

5

A β -hydroxyacid VI can be cyclized with an arylsulphonyl halide such as benzenesulphonyl chloride in a solvent such as pyridine while cooling to -10°C .

10

The cleavage of the β -lactone ether VII can be carried out by hydrogenation in a solvent such as a hydrocarbon or halogenated hydrocarbon, e.g. hexane or methylene chloride, an ester or ether, e.g. ethyl acetate or THF, over a catalyst such as palladium-on-charcoal (Pd/C) at a temperature up to about 40°C .

15

The optional esterification of a β -lactone alcohol of formula I in which X is hydrogen with an acid of the formula $(\text{R}^3, \text{R}^4)\text{NCH}(\text{R}^5)(\text{CH}_2)_n\text{-COOH}$ can be performed in the presence of triphenylphosphine and of diethyl azodicarboxylate in a solvent such as an ether, e.g. THF, at a temperature up to about -15°C .

20

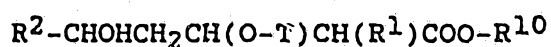
A β -hydroxyacid of formula VI above can also be prepared by

25

a) esterifying a salt of formula IV above with a halide of the formula $\text{R}^{10}\text{-Hal}$, wherein R^{10} is C_{1-4} -alkyl or aryl- C_{1-4} -alkyl,

30

b) etherifying the resulting ester of the formula



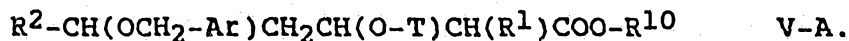
IV-A

35

and

c) in optional sequence saponifying and cleaving in the β -position the resulting diether of the formula

5



10 The esterification of a salt IV with a halide $R^{10}-Hal$, e.g. with benzyl bromide, can be carried out in a solvent such as THF.

15 The etherification of the alcohol ester IV-A can be effected with a chloride of the formula $Ar-CH_2OC(NH)CCl_3$, e.g. with benzyl 2,2,2-trichloroacetimidate, in the presence of an acid such as trifluoromethanesulphonic acid in a solvent such as cyclohexane, hexane or methylene chloride.

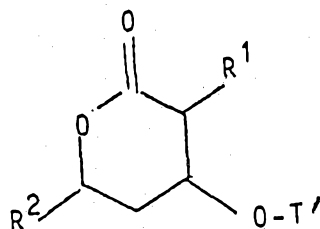
20 A diether V-A can firstly be treated with an acid such as aqueous acetic acid in the case of a silyl ether or such as hydrochloric acid in the case of a THP ether in a solvent such as dioxan at a temperature up to the reflux temperature of the reaction mixture and subsequently saponified in a solvent such as an alkanol, e.g. methanol, using a strong base such as an alkali metal or alkaline earth metal hydroxide, e.g. potassium hydroxide, at a temperature up to about 70°C.

30 It is also possible to prepare a β -hydroxyacid VI by

a) esterifying a β -hydroxy- δ -lactone II,

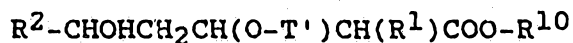
b) opening the resulting ester of the formula

35



III'

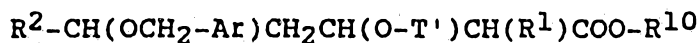
wherein T' is aroyl,
by acidic catalysis in the presence of an alcohol of the
formula $R^{10}-OH$ to give an ester of the formula



IV-B,

c) etherifying the ester of formula IV-B and

d) doubly-saponifying the resulting ether diester of the
formula



V-B.

The esterification of the β -hydroxy- δ -lactone of
formula II can be carried out e.g. with a functional
derivative of an acid of the formula $Ar-COOH$, e.g. an acid
halide or acid anhydride such as benzoic anhydride, and a
strong acid such as perchloric acid or a base such as
dimethylaminopyridine as the catalyst in a solvent such as
toluene and the subsequent opening of the ester III' can
be carried out by acidic catalysis e.g. in the presence of
an acid such as sulphuric acid or hydrochloric acid with
an alcohol of the formula $R^{10}-OH$, e.g. a lower alkanol
such as methanol, optionally in a solvent such as toluene,

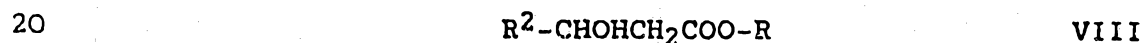
at a temperature up to 60°C.

5 The etherification of the alcohol ester IV-B can be performed in analogy to the etherification of the alcohol ester IV-A described above.

10 The saponification of an ether diester V-B can be carried out in a solvent such as an alkanol, e.g. methanol, using a strong base such as an alkali metal or alkaline earth metal hydroxide, e.g. potassium hydroxide, at a temperature up to about 70°C.

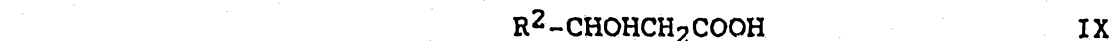
15 The β -hydroxy- δ -lactones of formula II can be prepared by

a) saponifying a β -hydroxyester of the formula



wherein R is C_{1-4} -alkyl.

25 b) reacting the imidazolidine of the resulting β -hydroxy-acid of the formula

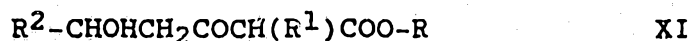


with the Mg salt of the malonic acid ester derivative of the formula



c) cyclizing the resulting δ -hydroxy- β -ketoester of the formula

5

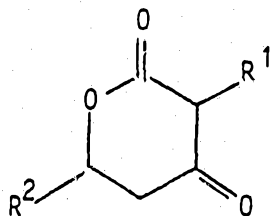


and

10

d) catalytically hydrogenating the resulting β -keto- δ -lactone of the formula

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XII.

20

The saponification of the β -hydroxyester of formula VIII can be carried out in a solvent such as dioxan with a base such as sodium hydroxide in a solvent such as methanol.

25

The magnesium salt of a malonic acid ester derivative of formula X can be prepared by reacting the malonic acid diester of the formula $CH_2(COOR)_2$ with a solution of sodium methylate in methanol and with a halide of the formula R^1-Hal , e.g. the bromide, at a temperature up to the reflux temperature of the solvent. The resulting malonic acid diester derivative of the formula $R^1-CH(COOR)_2$ is then hydrolyzed with an alkali metal hydroxide, e.g. potassium hydroxide, in a lower-alkanol $R-OH$ such as methanol to the monoester of formula X and the latter is converted into the desired magnesium salt

30

35

with magnesium chloride in THF in the presence of triethylamine at 0°C.

5 The imidazolidine of the β -hydroxyacid of formula IX can be prepared by reacting this in THF with 1,1'-carbonyl-diimidazole.

10 The magnesium salt of the monoester of formula X can be reacted at room temperature with the imidazolidine of the β -hydroxyacid of formula IX to give the δ -hydroxy- β -ketoester of formula XI.

15 The latter can be cyclized to the β -keto- δ -lactone of formula XII in a solvent such as ethyl acetate with an acid such as hydrochloric acid or a base such as sodium hydroxide.

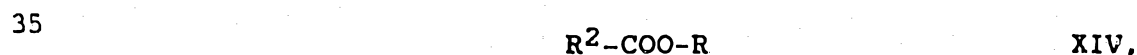
20 The catalytic hydrogenation of this lactone to the β -hydroxy- δ -lactone of formula II can be carried out in a solvent such as ethyl acetate or an ether such as THF in the presence of Raney-nickel.

The β -hydroxy- δ -lactones of formula II can also be
25 prepared by

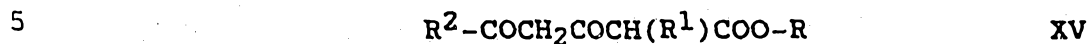
a) reacting a β -ketoester of the formula



with an ester of the formula

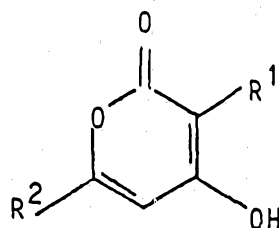


b) cyclizing the resulting diketoester of the formula



and

10 c) catalytically hydrogenating the resulting pyrone of the formula



XVI.

20 A β -ketoester of formula XIII can be prepared by alkylating the corresponding β -ketoester of the formula CH_3COCH_2COOR with a halide of the formula R^1-Hal , e.g. the bromide, in a methanolic sodium methylate solution at a temperature up to the reflux temperature of the reaction mixture.

25 The reaction of the β -ketoester of formula XIII with an ester of formula XIV can be carried out in the presence of sodium hydride in a solvent such as THF and in the presence of butyllithium in hexane while cooling, e.g. at -10°C.

30 The cyclization to a pyrone of formula XVI can be performed in a solvent such as toluene in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene(1,5,5) (DBU).

The pyrone of formula XVI can be hydrogenated to the β -hydroxy- δ -lactone of formula II in the same manner as described above for the catalytic hydrogenation of the β -keto- δ -lactone of formula XII.

A β -keto- δ -lactone of formula XII can also be prepared by

a) reacting a β -ketoester of the formula



with an aldehyde of the formula



and

b) cyclizing the resulting δ -hydroxy- β -ketoester of formula XI.

The reaction of the β -ketoester of formula XIII with the aldehyde of formula XVII can be carried out in the same manner as the reaction with the ester of formula XIV described above.

The cyclization of the δ -hydroxy- β -ketoester of formula XI to the β -keto- δ -lactone of formula XII can be performed with water, conveniently at room temperature.

Further, a β -keto- δ -lactone of formula XII can be prepared by

a) etherifying a β -hydroxyester of the formula

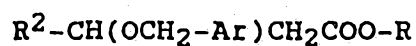
5



VIII,

b) saponifying the resulting ether of the formula

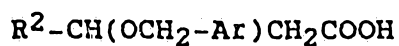
10



XVIII,

c) halogenating the resulting ether acid of the formula

15



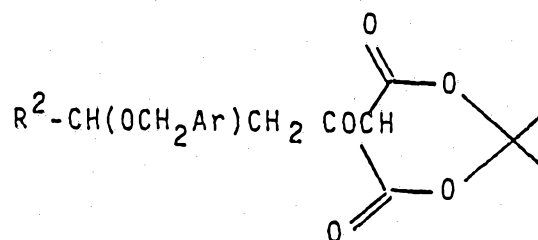
XIX,

d) reacting the resulting acid halide with Meldrum acid,

20

e) hydrogenolyzing the resulting compound of the formula

25

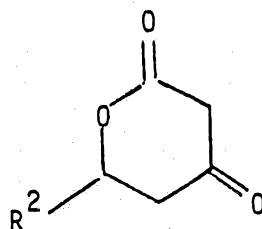


XX

30

and cyclizing to a β -keto- δ -lactone of the formula

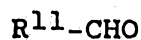
35



XXI

and

f) reacting the β -keto- δ -lactone of formula XXI above with an aldehyde which introduces the group R^1 or $-\text{CH}_2-\text{R}^{11}$ and which has the formula



XXII

wherein R^{11} together with the methylene group represents the group R^1 , to give a β -keto- δ -lactone of formula XII above.

The etherification of the β -hydroxyester of formula VIII to give the ether of formula XVIII can be carried out in a solvent such as cyclohexane, e.g. with benzyl trichloroacetimidate in the presence of trifluoromethanesulphonic acid at a temperature up to 30°C .

The saponification of the ether of formula XVIII to give the ether acid of formula XIX can be performed with an alkali metal hydroxide such as potassium hydroxide in a solvent such as methanol.

The halogenation of the ether acid of formula XIX can be carried out e.g. with oxalyl chloride in a solvent such

as methylene chloride at a temperature up to about 25°C.

5 The reaction of the resulting acid halide with Meldrum acid can be carried out in a solvent such as methylene chloride in the presence of a base such as pyridine while cooling to -10°C.

10 The hydrogenolysis and cyclization of the compound of formula XX to give the β -keto- δ -lactone of formula XXI can be effected in a solvent such as ethyl acetate using a catalyst such as Pd/C.

15 The reaction of the β -keto- δ -lactone of formula XXI with the aldehyde of the formula R^{11} -CHO to give the β -keto- δ -lactone of formula XII is effected e.g. with a boranamine complex such as borane-triethylamine, borane-trimethylamine or borane-morpholine in a solvent such as methanol at a temperature up to 50°C.

20 A β -keto- δ -lactone of formula XXI can also be prepared by

25 a) reacting the imidazolidine of the β -hydroxyacid of the above formula

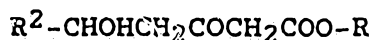


IX

30 with the Mg salt of a mono-lower alkyl malonate and

b) cyclizing the resulting δ -hydroxy- β -ketoester of the formula

35



XXIII

5

to give the β -keto- δ -lactone of formula XXI above.

10

The preparation of the Mg salt of a mono-lower alkyl malonate, the reaction of this salt with the imidazolidine of the β -hydroxyacid of formula IX to give the δ -hydroxy- β -ketoester of formula XXIII and its cyclization to give the β -keto- δ -lactone of formula XXI can be carried out as described above for the preparation of the β -hydroxy- δ -lactone of formula II via the imidazolidine of the β -hydroxyacid of formula IX and the Mg salt of the malonic acid ester derivative of formula X.

15

20

A preferred embodiment of the process of the present invention comprises reacting a β -ketoester XIII with an aldehyde XVII, cyclizing the resulting δ -hydroxy- β -ketoester XI to the β -keto- δ -lactone XII, catalytically hydrogenation the latter and converting the resulting β -hydroxy- δ -lactone II into an ester I via the compounds of formulae III to VII according to the procedure described above.

25

30

The manufacture of the ester of formula I in which R^1 is n-hexyl and R^2 is undecyl is especially preferred.

35

The following β -hydroxy- δ -lactones, β -keto- δ -lactones and pyrones, which fall under formulae II, XII or XVI as the case may be, are novel and as such are objects of the present invention:

rac-(2RS,3RS,5SR)-2-Hexyl-3-hydroxy-5-undecyl- δ -

-valeriolactone,

rac-(2RS,3RS,5SR)-2-ethyl-5-heptadecyl-3-hydroxy- δ -
-valeriolactone,

5 (2S,3S,5R)-2-ethyl-5-heptadecyl-3-hydroxy- δ -valerio-
lactone and

rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-pentyl- δ -
-valeriolactone;

10 rac-5,6-dihydro-3-hexyl-4-hydroxy-6-undecyl-2H-pyran-
-2-one,

(R)-3-ethyl-5,6-dihydro-6-heptadecyl-4-hydroxy-2H-
-pyran-2-one and

rac-5,6-dihydro-3-hexyl-4-hydroxy-6-pentyl-2H-pyran-2-
-one;

15 3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one,

3-ethyl-6-heptadecyl-4-hydroxy-2H-pyran-2-one and

3-hexyl-4-hydroxy-6-pentyl-2H-pyran-2-one.

The β -keto- δ -lactones of formula XXI in which R²
20 has the significance given above, but the number of
C atoms in the alkyl group R² amounts to more than 9,
especially the following:

(R)-5,6-dihydro-6-undecyl-2H-pyran-2,4(3H)-dione and

25 (R)-5,6-dihydro-6-heptadecyl-2H-pyran-2,4(3H)-dione,

are also novel and are an object of the invention.

Example 1

30 a) 465 g of methyl acetoacetate are added dropwise under
nitrogen and while stirring to 720 g of 30% sodium
methylate solution in 1200 ml of methanol. Then, 727 g of
1-bromohexane are added and the reaction mixture is boiled
35 at reflux for 20 hours. The majority of the methanol is
distilled off and the residue is poured on to ice-water.
The mixture is extracted with n-hexane and then with

water. The organic phases are combined and dried over sodium sulphate. The solvent is evaporated and the crude ester is distilled. There are obtained 499.4 g of methyl 2-acetyloctanoate, b.p. 124-128°/15 Torr.

b) 200.3 g of methyl 2-acetyloctanoate are added to a suspension of 26.4 g of sodium hydride in 1250 ml of THF. After stirring at 0-5° for 1 hour the mixture is cooled to -10°. 675 ml of 1.56M butyllithium in hexane are added at this temperature. After stirring at -10° for 30 minutes 107.2 g of methyl laurate are added dropwise. The mixture is stirred at -10° for a further 1 hour. The reaction solution is added under argon to 250 ml of 37% hydrochloric acid and 300 g of ice. The mixture is extracted with hexane and water. The combined organic phases are dried, filtered and evaporated.

The residue (290.5 g) is dissolved in 1250 ml of toluene, treated with 76.1 g of DBU and boiled at reflux under argon for 30 minutes. The reaction solution is extracted in toluene with 3N hydrochloric acid and water. The combined toluene phases are evaporated at 40°. The product is dissolved in hexane and cooled to room temperature while stirring. After stirring at -10° for 17 hours the crystallizate is filtered off under suction, washed with hexane and dried. 123.9 g (70.7%) of 3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one, m.p. 83-84°, result.

c) 100 g of Raney-nickel and 2000 ml of ethyl acetate are added to 100 g of the pyrone from b). After hydrogenating for 17 hours while stirring at 30° the catalyst is filtered off under suction and washed with ethyl acetate. The filtrate is concentrated and stirred at -10° overnight. The crystallizate is filtered off under suction, washed with ethyl acetate and then dried. 90.7 g (89.7%) of rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-undecyl-δ-

-valerolactone, m.p. 98-99°, result.

5 d) 177.3 g of the δ -lactone from c) are suspended in
1250 ml of toluene while stirring. After the addition of
138.6 g of benzoic anhydride the mixture is stirred for
10 minutes. Then, 2.5 ml of perchloric acid are added. The
10 mixture is stirred for a further 2.5 hours. The reaction
solution is extracted in toluene with 1N sodium hydroxide
solution and then with water. The combined toluene phases
are dried, the drying agent is filtered off under suction
and washed with toluene. Evaporation of the solvent gives
237.2 g (103.4%) of rac-(2RS,3RS,5SR)-3-benzoyloxy-2-
15 -hexyl-5-undecyl- δ -valerolactone, which was used in the
next step without purification.

20 e) 236 g of the benzoate from d) in 1250 ml of methanol
are treated under argon while stirring with 2.5 ml of
conc. sulphuric acid and stirred for a further 18 hours.
Subsequently, the pH of the reaction solution is adjusted
to 9 with triethylamine and the methanol is evaporated.
The residue is taken up in hexane, washed with water and
the aqueous phase is extracted with hexane. After drying
the combined hexane phases are filtered. The filtrate is
25 freed from hexane. There result 259 g (105.5%) of methyl
rac-(2RS,3RS,5SR)-3-benzoyloxy-2-hexyl-5-hydroxyhexa-
decanoate, which is used in the next step without
purification.

30 f) 258 g of the hydroxyester from e) in 1250 ml of hexane
are treated under argon while stirring with 152 g of
benzyl 2,2,2-trichloroacetimidate. Then, 3.2 ml of
trifluoromethanesulphonic acid are added. After stirring
for 17 hours the precipitate is filtered off under suction
35 and washed with hexane. The filtrate is extracted with 5%
sodium bicarbonate solution and then with water. The
hexane phase is dried, filtered and evaporated. 320 g

(110%) of methyl rac-(2RS,3RS,5SR)-3-benzoyloxy-5-benzyl-oxy-2-hexylhexadecanoate result.

- 5 g) 319 g of the benzyl ether from f) in 1125 ml of methanol are treated under argon with a solution of 140 g of potassium hydroxide in 125 ml of water. The reaction mixture is stirred at 40° for 17 hours and subsequently concentrated. The suspension, together with n-hexane, is
10 extracted with 10% sodium chloride solution and then 1N hydrochloric acid. The combined organic phases are dried with sodium sulphate, the drying agent is filtered off under suction and washed with hexane. The filtrate is concentrated to 1000 ml and held at -20° for 1 day. The
15 crystallizate is filtered off under suction, washed with n-hexane and discarded. After evaporation the filtrate gives 169 g (73%) of rac-(2RS,3RS,5SR)-5-benzoyloxy-2-hexyl-3-hydroxyhexadecanoic acid.
- 20 h) 39.4 g of (S)-(-)- α -methylbenzylamine are added dropwise under argon while stirring to 169 g of the δ -hydroxyacid from g) in 1250 ml of methyl acetate. The solution is seeded with phenethylamine salt and then cooled to -10°. After 17 hours at -10° the crystal slurry
25 is filtered off under suction, washed with methyl acetate, sucked off and dried. After two additional crystallizations from methyl acetate there are obtained 56.5 g (19.4%) of the phenethylamine salt of (2S,3S,5R)-5-benzyl-oxy-2-hexyl-3-hydroxyhexadecanoic acid, m.p. 104-105°.
- 30 i) 56.5 g of the phenethylamine salt from h) are treated with 565 ml of hexane and 120 ml of 1N hydrochloric acid while stirring. The organic phase is washed with water, dried and concentrated. There are obtained 44.2 g (98.8%;
35 19.1% based on the δ -lactone from c)) of (2S,3S,5R)-5-benzoyloxy-2-hexyl-3-hydroxyhexadecanoic acid.

j) 231.5 g of the β -hydroxyacid from i) are dissolved in 2500 ml of pyridine while stirring and cooled to 0°. Now, 176.6 g of benzenesulphonyl chloride are added dropwise. The solution is stirred at 0° for a further 20 hours. Thereafter, water is added and the mixture is stirred at room temperature for 30 minutes. The pyridine is evaporated. The crystal slurry, together with hexane, is extracted in succession with 2N hydrochloric acid, 5% sodium bicarbonate solution and 10% sodium chloride solution. The hexane phases are combined and concentrated. After drying active charcoal is added, the mixture is stirred for 1 hour, suction filtered, washed with hexane and evaporated. There result 222.1 g (99.9%) of (3S,4S)-4-
-[(R)-2-benzyloxytridecyl]-3-hexyl-2-oxetanone, which is used in the next step without purification.

k) 222 g of the β -lactone from j) are dissolved in 2500 ml of THF and hydrogenated on 11 g of Pd/C 10% for 18 hours. The solution is filtered and washed with THF. The filtrate is evaporated. The crystals obtained are dissolved in hexane. After stirring at 5° for 18 hours the crystallizate is filtered off under suction, washed with hexane and dried. 150.5 g (84.9%) of (3S,4S)-3-hexyl-4-
-[(R)-2-hydroxytridecyl]-2-oxetanone, m.p. 61-62°C, are obtained.

Example 2

88.6 g of the hydroxy- β -lactone from Example 1k), 51.7 g of N-formyl-(S)-leucine and 98.4 g of triphenylphosphine are dissolved in 1000 ml of THF while stirring. A solution of 72.6 g of diethyl azodicarboxylate in 250 ml of THF is added dropwise to the solution which is cooled to -10°C. The reaction solution is stirred at -10°C for 15 hours. Subsequently, the solvent is evaporated. The crystal slurry is partitioned several times between hexane

and 70% methanol/water while stirring. The combined hexane phases are dried over sodium sulphate, the drying agent is filtered off under suction and washed with hexane. After distillation of the hexane the crude product is dissolved in hexane and cooled slowly to 5°. The crystallize is filtered off under suction, washed with hexane and dried. 98.0 g of N-benzyl-L-leucine (S)-1-[[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-dodecyl ester, m.p. 44-45°C, are obtained.

Example 3

- a) A suspension of 206.7 g of methyl (R)-3-hydroxytetradecanoate in 1000 ml of cyclohexane is treated under nitrogen and while stirring with 214.2 g of benzyl trichloroacetimidate and dissolved at 20°. 10 ml of trifluoromethanesulphonic acid are added dropwise while cooling in an ice/water bath in such a manner that the temperature remains between 20-23°. The resulting suspension is stirred at 25-30°. The precipitate is filtered off, the filter cake is washed with cyclohexane, the filtrates are extracted with sat. NaHCO_3 solution, water and sat. NaCl solution. The organic phase is dried over magnesium sulphate, filtered, the filter cake is washed with cyclohexane and the filtrates are evaporated. 314.5 g of methyl (R)-3-(benzyloxy)-tetradecanoate are obtained.
- b) 314.0 g of the methyl ester from a) are added to a solution of 89.8 g of potassium hydroxide in 680 ml of methanol. After stirring at room temperature for 18.5 hours the resulting suspension is poured on to 680 g of ice and adjusted to pH 1 with 200 ml of 25 percent aqueous HCl solution while cooling at 0-7°. The resulting emulsion is extracted with methylene chloride. The organic phase is dried over magnesium sulphate, filtered, the

filter cake is washed with methylene chloride and the filtrates are evaporated. 277.3 g of (R)-3-benzyloxytetradecanoic acid are obtained.

5

c) 82.5 ml of oxalyl chloride are added dropwise to a solution of 276.5 g of the acid from b) in 1400 ml of methylene chloride. After stirring for 3.5 hours the resulting solution of (R)-3-benzyloxytetradecanoyl chloride is concentrated to 450 ml.

10

d) 164 ml of pyridine are added dropwise at -6 to 0° to a solution of 122.8 g of Meldrum acid in 900 ml of methylene chloride. After stirring at -3 to -1° for 10 minutes the solution of the acid chloride from c) is added dropwise. The resulting suspension is stirred at 0° for 3 hours, then poured into a mixture of 400 g of ice and 1300 ml of hydrochloric acid, stirred for 10 minutes, the organic phase is separated and extracted with 300 ml of 3N hydrochloric acid. The acidic-aqueous phases are extracted with 500 ml of methylene chloride, the combined organic phases are dried over magnesium sulphate, filtered, the filter cake is washed with methylene chloride and the filtrates are concentrated. The solution is treated with silica gel and stirred. The silica gel is filtered off and washed with methylene chloride. The filtrates are concentrated. 382.2 g of 5-[(R)-3-benzyloxy-1-hydroxytetradecylidene]-2,2-dimethyl-m-dioxane-4,6-dione are obtained.

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e) 33.1 g of 5% Pd/C are added to a solution of 381.5 g of the product from d) in 2500 ml of ethyl acetate. The mixture is hydrogenated for 3.5 hours. The suspension is filtered, the filter cake is washed with ethyl acetate and the filtrates are concentrated. The solution obtained is boiled at 79-80°, cooled to room temperature, evaporated and dried. The product is suspended in n-hexane, filtered and the filter cake is washed with n-hexane and the

crystals are dried. The mother liquor is concentrated, dissolved in n-hexane and left to stand at 4° for 72 hours. The precipitated crystals are filtered, washed with n-hexane and dried. The two crystallizates are combined, suspended in water, stirred, filtered, the filter cake is washed with water and the crystals are dried. 62.1 g of (R)-5,6-dihydro-6-undecyl-2H-pyran-2,4(3H)-dione, m.p. 82-85°, are obtained.

f) 100.65 g of the pyrandione from e) are added under nitrogen to a solution of 43.14 g of borane-triethylamine complex in 1000 ml of methanol. The mixture is warmed to 40°. 75.12 g of capronaldehyde are added dropwise to the solution. The solution is stirred at 41° for 70 minutes, then cooled to room temperature and poured on to ice/water. The suspension is treated with 120 ml of 3N hydrochloric acid while stirring and stirred for 30 minutes. The crystals are filtered off under suction, washed with water and then dried. The product is suspended in n-hexane, stirred for 30 minutes, filtered off under suction, washed with n-hexane and dried. There are obtained 112.5 g (85%) of (R)-5,6-dihydro-3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one, m.p. 106-108°, $[\alpha]_D^{20} = -45.6^\circ$ (c = 1% in dioxan).

g) 30.0 g of the pyranone from f) are dissolved in 750 ml of ethyl acetate and, after the addition of 30 g of Raney-nickel, hydrogenated at room temperature for 24.5 hours. The catalyst is filtered, washed with ethyl acetate and the filtrate is concentrated. The product is dissolved in ethyl acetate at 45°, cooled to 20° within 2 hours, then to -10° within 3 hours and stirred at this temperature for 16 hours and then filtered. The crystals are washed with ethyl acetate and then dried. There are obtained 25.5 g (85%) of (2S,3S,5R)-2-hexyl-3-hydroxy-5-undecyl- δ -valerolactone, m.p. 103-104.5°, $[\alpha]_D^{20} = +47.4^\circ$ (c

= 1% in CHCl_3).

- 5 h) A solution of 12.0 g of the lactone from g) in 70 ml of DMF is treated with 6.77 g of ethyl diisopropylamine and, after the addition of 7.64 g of t-butyldimethylsilyl chloride, heated to 80° for 13 hours while stirring. The reaction mixture is concentrated, taken up in 120 ml of hexane, filtered and the filter cake is washed with 50 ml of hexane. The combined filtrates are extracted with 3N hydrochloric acid and the organic phase is dried. After filtration and concentration there are obtained 15.7 g of (2S,3S,5R)-3-t-butyldimethylsiloxy-2-hexyl-5-undecyl- δ -valerolactone.
- 10
- 15 i) A solution of 42.2 g of the lactone from h) in 570 ml of dioxan is stirred for 5.5 hours after the addition of 90 ml of 1N potassium hydroxide solution. The reaction mixture is concentrated and dried azeotropically by the addition of toluene and distillation. The residue is dissolved in 250 ml of THF and, after the addition of 23.1 g of benzyl bromide and 4.75 g of 18-crown-6, stirred for 4 hours. The reaction mixture is concentrated, treated with n-hexane and extracted with 3N hydrochloric acid. The organic phase is dried, filtered and concentrated, whereby 61.7 g of benzyl (2S,3S,5R)-3-t-butyldimethylsiloxy-2-hexyl-5-hydroxyhexadecanoate separate.
- 20
- 25
- 30 j) A solution of 60.6 g of the product from i) in 130 ml of methylene chloride and 260 ml of cyclohexane is treated with 33.5 g of benzyl trichloroacetimidate and, after the addition of 0.53 ml of trifluoromethanesulphonic acid, stirred for 5 hours. The suspension is filtered, the filter cake is washed with hexane and the combined filtrates are washed in sequence with 3N hydrochloric acid, 3N sodium hydroxide solution, 3N hydrochloric acid and water. The organic phase is dried, filtered and
- 35

concentrated, whereby 74.8 g of benzyl (2S,3S,5R)-5-benzyloxy-3-t-butyldimethylsiloxy-2-hexylhexadecanoate separate.

5

10 k) A mixture of 20 g of the ester from j), 48 ml of glacial acetic acid, 16 ml of water and 16 ml of dioxan is heated at reflux for 3.5 hours and subsequently freed from the acetic acid by azeotropic distillation with the addition of 120 ml of dioxan and concentrated. The residue is dissolved in hexane and stored at -25° for 14 hours. The crystals formed are filtered, the filtrate is concentrated and the residue, dissolved in methanol, is mixed thoroughly for 24 hours with an aqueous solution of
15 potassium hydroxide. The reaction solution is evaporated, the residue is taken up in hexane and washed with 1N hydrochloric acid and 10% sodium chloride solution and concentrated. The residue is dissolved in methyl acetate and treated with 2.6 g of benzylamine. By crystallization
20 there can be obtained 6.0 g of (2S,3S,5R)-5-benzyloxy-3-hydroxy-2-hexylhexadecanoic acid (the product of Example 1h) as the benzylamine salt of m.p. 57-60° and a further 1.4 g of m.p. 61-64°.

25

Example 4

28 a) Under nitrogen and while stirring there are added dropwise to a solution of 129.2 g of methyl (R)-3-hydroxy-tetradecanoate, 1033 ml of dioxan and 122.9 g of
30 28 percent sodium hydroxide solution. 77.5 ml of methanol are added dropwise to the solution. After stirring for a further 1.5 hours the resulting suspension is filtered and the filter cake is washed with 1000 ml of dioxan and filtered off. The filter cake is adjusted to pH 0 by the
35 addition of 650 ml of 1.5N hydrochloric acid. The suspension is stirred, filtered, the filter cake is washed with 3000 ml of water and the crystals are dried. 119.64 g

(98%) of (R)-3-hydroxytetradecanoic acid, m.p. 70.6-71.4°, are obtained.

- 5 b) 5.11 g of magnesium chloride are suspended in 50 ml of THF under nitrogen and cooled to 0°. A solution of 11.33 g of monomethyl malonate in 70 ml of THF and subsequently 10.7 g of triethylamine are added dropwise. The suspension is stirred at 0°.
- 10 c) 6.81 g of 1,1'-carbonyldiimidazole are added under nitrogen and while stirring to a solution of 7.33 g of (R)-3-hydroxytetradecanoic acid.
- 15 d) The reaction solution obtained under c) is added to the suspension previously prepared under b) and stirred for 5 hours. The suspension is concentrated. The resin obtained is taken up in 200 ml of ethyl acetate and extracted with 3N hydrochloric acid. The ethyl acetate
- 20 phase is treated with 3N sodium hydroxide solution and, after the addition of ice-water, the aqueous phase is separated. The ethyl acetate phase is again mixed thoroughly with 3N sodium hydroxide solution, diluted with ice-water and extracted. The combined aqueous phases are
- 25 cooled to 0° and adjusted to pH 1 with 25 percent hydrochloric acid. The resulting suspension is extracted with ethyl acetate. The combined organic phases are dried and filtered. The filter cake is washed with ethyl acetate. The combined filtrates are concentrated. The product is
- 30 suspended in ice-water, stirred and filtered. The filter cake is washed with water and the crystals are dried. There are obtained 4.63 g (57.6%) of (R)-5,6-dihydro-6-undecyl-2H-pyran-2,4(3H)-dione, m.p. 84.1-84.8°, the product of Example 3e).

Example 5

5 a) 350.1 g of 30 percent sodium methylate solution in
methanol are diluted with 550 ml of methanol under
nitrogen and while stirring. 264.2 g of dimethyl malonate
are added dropwise. After warming the suspension to 40°
321.0 g of 1-bromohexane are added dropwise. After
10 stirring at 40° for 1 hour, under reflux for 2 hours, at
65-69° for 2.5 hours and cooling the suspension to room
temperature water is added and the mixture is stirred. The
organic phase is separated. The aqueous phase is extracted
with methylene chloride, the combined organic extracts are
dried and filtered, the filter cake is washed with
15 methylene chloride and the combined filtrates are
concentrated. After distillation of the product there are
obtained 329.3 g (78.3%) of dimethyl n-hexylmalonate.

20 b) A solution of 40.1 g of KOH in 150 ml of methanol is
added dropwise under nitrogen and while stirring to
129.78 g of the ester from a). The reaction mixture is
stirred for 2 hours, then poured on to ice-water and
extracted with methylene chloride. The aqueous phase is
adjusted to pH 2 by the addition of 3N hydrochloric acid
25 and extracted with methylene chloride. The organic phases
are dried and filtered, the filter residue is washed with
methylene chloride and the combined filtrates are
concentrated. 113.9 g (94%) of monomethyl n-hexylmalonate
are obtained.

30 c) A solution of 21.57 g of the ester from b) in 70 ml of
THF and subsequently 10.7 g of triethylamine are added
dropwise under nitrogen and while stirring to a suspension
of 5.11 g of magnesium chloride in 50 ml of THF at 0° and
35 the resulting suspension of monomethyl n-hexylmalonate
magnesium salt is stirred at 0° for 75 minutes.

d) 6.81 g of 1,1'-carbonyldiimidazole are added under nitrogen and while stirring to a solution of 7.33 g of (R)-3-hydroxytetradecanoic acid (Example 4a) in 60 ml of THF. After stirring the reaction solution is added to the suspension of monomethyl n-hexylmalonate magnesium salt and the mixture is stirred at room temperature for 22 hours. The suspension is concentrated, whereby 60.35 g of resin remain behind. This is taken up in 200 ml of ethyl acetate, extracted with 200 ml of 3N hydrochloric acid and with 600 ml of 5 percent NaHCO_3 solution. The ethyl acetate phase is separated and treated with 100 ml of 25 percent hydrochloric acid while stirring at 10-15°. The mixture is stirred at 25° for 1.5 hours. The resulting, homogeneous phase is left to stand at room temperature for 16 hours. The suspension is stored at -20° for 4 hours, filtered, the filter cake is washed with water and the crystals are dried. There are obtained 3.63 g (34.3%) of (R)-5,6-dihydro-3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one, m.p. 104.8-106.2°, the product of Example 3f).

Example 6

- a) 465 g of methyl acetoacetate and then 458 g of ethyl bromide are added under nitrogen to 720 g of 30% sodium methylate solution in 1200 ml of methanol. The reaction mixture is subsequently boiled at reflux. After distillation of the methanol the residue is poured on to ice-water. It is then extracted with n-hexane and water. The organic phases are combined and dried. After evaporation of the solvent and distillation there are obtained 328 g (56.9%) of methyl 2-acetylbutyrate, b.p. 77-79°/15 Torr.
- b) 144.17 g of the methyl ester from a) are added under argon at 0-5° to a suspension of 26.4 g of sodium hydride in 1250 ml of THF. After stirring at 0-5° for 1.5 hours

the mixture is cooled to -10° . 675 ml of 1.56M butyllithium in hexane are added at this temperature. After stirring at -10° for 30 minutes a solution of 149.3 g of methyl stearate in 250 ml of THF is added dropwise. After stirring at -10° for 1.5 hours the reaction solution is added under argon to 250 ml of 37% hydrochloric acid and 300 g of ice. The mixture is extracted with hexane and water. The combined organic phases are dried, filtered and evaporated.

The residue is dissolved in 2500 ml of THF, treated with 76.1 g of DBU and boiled at reflux under argon. The cooled reaction solution is extracted with 37% hydrochloric acid and then with saturated sodium chloride solution. The combined organic phases are dried and evaporated. The product is dissolved in ethyl acetate. The solution is cooled to room temperature and stirred at 25° overnight. The crystallizate is filtered off under suction, washed with ethyl acetate and dried. 122.5 g (64.7%) of 3-ethyl-6-heptadecyl-4-hydroxy-2H-pyran-2-one, m.p. $101-102^{\circ}$, result.

c) 100 g of Raney-nickel and 2000 ml of THF are added to 100 g of the pyrone from b). After hydrogenation at 25° for 3 days the catalyst is filtered off under suction and washed with THF. The filtrate is evaporated to dryness. The residue is dissolved in ethyl acetate and stirred at 10° for 17 hours. The crystallizate is filtered off under suction, washed with -10° cold ethyl acetate and dried at 40° for 17 hours. 90.54 g (89.6%) of rac-(2RS,3RS,5SR)-2-ethyl-5-heptadecyl-3-hydroxy- δ -valerolactone, m.p. $101-102^{\circ}$, result.

d) 138.5 g of benzoic anhydride and subsequently 2.5 ml of perchloric acid 70% are added to a suspension of 191.3 g of the δ -lactone from c) in 1250 ml of toluene.

After stirring for 2.5 hours the reaction mixture in toluene is extracted with 1N sodium hydroxide solution in 20% sodium chloride solution and then with saturated sodium chloride solution. The organic phases are combined, dried and evaporated. 243.4 g (100.0%) of rac-(2RS,3RS,5SR)-3-benzoyloxy-2-ethyl-5-heptadecyl- δ -valerolactone, m.p. 64.5-66°, result.

10 e) 243 g of the benzoate from d) are dissolved in 450 ml of toluene at 40° under argon. 1000 ml of methanol and thereafter 2.5 ml of conc. sulphuric acid are added and the reaction mixture is stirred at 25° for 20 hours. After neutralization of the sulphuric acid with triethylamine
15 the solvent is evaporated. The residue is dissolved in butyl methyl ether and washed with water. The aqueous phase is extracted with t-butyl methyl ether and the organic phases are combined and dried over sodium sulphate. the drying agent is filtered off under suction
20 and washed with t-butyl methyl ether and subsequently evaporated. 257 g (99.1%) of methyl rac-(2RS,3RS,5SR)-3-benzoyloxy-2-ethyl-5-hydroxydocosanoate result.

25 f) 257 g of the hydroxyester from e) in 1250 ml of n-hexane are treated under argon with 152 g of benzyl 2,2,2-trichloroacetimidate. Then, 3.2 ml of trifluoromethanesulphonic acid are added. After stirring at room temperature for 18 hours the precipitate is filtered off under suction and washed with n-hexane. The filtrate is
30 extracted with 5% sodium bicarbonate solution and water. The combined hexane phases are dried, filtered and concentrated. After stirring at -20° for 20 hours the crystallizate is filtered off under suction, washed with n-hexane and discarded. The filtrate is evaporated. There
35 result 239.6 g (78.7%) of methyl rac-(2RS,3RS,5SR)-3-benzoyloxy-5-benzoyloxy-2-ethyldocosanoate, which are used in the next step without purification.

g) 239.6 g of the benzyl ether from f) are treated under argon with a solution of 140 g of potassium hydroxide in 1250 ml of 95% (v/v) methanol/water and stirred at 40° for 17 hours. Subsequently, the mixture is concentrated at 40°. The suspension is taken up in t-butyl methyl ether and washed in sequence with 10% sodium chloride solution, 1N hydrochloric acid and again with 10% sodium chloride solution. The organic phase is dried with sodium sulphate, the drying agent is filtered off under suction and washed with t-butyl methyl ether. The filtrate is evaporated.

82.1 g (74.2%) of rac-(2RS,3RS,5SR)-5-benzyloxy-2-ethyl-3-hydroxydocosanoic acid result.

h) 33.3 g of (S)-(-)- α -methylbenzylamine are added dropwise to a solution of 182.1 g of the β -hydroxyacid from g) in 1250 ml of methyl acetate. The solution is seeded with 50 mg of the phenethylamine salt of (2S,3S,5R)-5-benzyloxy-2-ethyl-3-hydroxydocosanoic acid and left to stand for 20 hours. The crystallizate is filtered off under suction, washed with -20° cold methyl acetate and then dried. This 1st crystallizate is dissolved in hot methyl acetate, cooled to 45° and seeded with 50 mg of the phenethylamine salt of (2S,3S,5R)-5-benzyloxy-2-ethyl-3-hydroxydocosanoic acid. The solution is left to stand at room temperature for 20 hours. The crystallizate is filtered off under suction, washed with -20° cold methyl acetate and dried. The same procedure as with the 1st crystallizate is repeated with the 2nd crystallizate. 39.4 g (12.9%) of the phenethylamine salt of (2S,3S,5R)-5-benzyloxy-2-ethyl-3-hydroxydocosanoic acid, m.p. 92-95°, result.

i) 39.4 g of the phenethylamine salt from h) are treated with 400 ml of t-butyl methyl ether and 80 ml of 1N hydrochloric acid and dissolved while stirring. The organic phase is washed with water, dried, filtered and

concentrated. 31.4 g (99.4%; 12.8% based on the
δ-lactone from c) of (2S,3S,5R)-5-benzyloxy-2-ethyl-3-
-hydroxydocosanoic acid, m.p. 62-63.5°, result.

5
j) 17.6 g of benzenesulphonyl chloride are added dropwise
under argon to a solution of 24.5 g of the β-hydroxyacid
from i) in 250 ml of pyridine at 0°. After stirring at 0°
for 20 hours 5 ml of water are added dropwise to the
10 solution. The mixture is stirred at room temperature for
1 hour. The pyridine is evaporated. The crystal slurry is
taken up in t-butyl methyl ether and washed in succession
with 2N hydrochloric acid, 5% sodium bicarbonate solution
and 10% sodium chloride solution. The organic phase is
15 dried over sodium sulphate and thereafter triturated with
active charcoal. Drying agent and active charcoal are
filtered off under suction and the filtrate is evaporated.
23.4 g (99%) of (3S,4S)-4-[(R)-2-benzyloxynonadecyl]-3-
-ethyl-2-oxetanone result.

20
k) A solution of 23.4 g of the oxetanone from j) in
250 ml of THF is treated with 2.3 g of Pd/C 10%. After
hydrogenation for 5 hours the hydrogenation solution is
suction filtered. After washing with THF the filtrate is
25 evaporated, the residue is dissolved in n-hexane and
seeded with (3S,4S)-3-ethyl-4-[(R)-2-hydroxynonadecenyl]-
-oxetanone. After 18 hours the crystallizate is filtered
off under suction, washed with hexane and dried. 16.1 g
(64.1%) of (3S,4S)-3-ethyl-4-[(R)-2-hydroxynonadecyl]-2-
30 -oxetanone, m.p. 66.5-68°, result.

Example 7

19.13 g of the hydroxy-β-lactone from Example 6k),
35 10.34 g of N-formyl-(S)-leucine and 19.70 g of triphenyl-
phosphine are dissolved in 400 ml of THF under argon while
stirring. The mixture is cooled to 0° and a solution of

14.5 g of diethyl azodicarboxylate in 50 ml of THF is added dropwise. The reaction solution is stirred at 0° for 4 hours. Subsequently, the solvent is evaporated. The crystal slurry is partitioned several times between hexane and 70% methanol/water. The combined hexane phases are dried over sodium sulphate, the drying agent is filtered off under suction and washed with hexane. After distillation of the hexane the product is dissolved in hexane and, after 20 hours, the crystallizate is filtered off under suction, washed with hexane and dried. 20.74 g (79.2%) of N-formyl-L-leucine (S)-1-[[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester, m.p. 61-62°, result.

Example 8

a) To a suspension of 177.3 g of (2S,3S,5R)-2-hexyl-3-hydroxy-5-undecyl-δ-valerolactone in 1250 ml of toluene under argon are added 135.7 g of benzoic anhydride and, after stirring at room temperature for 10 minutes, 2.5 ml of 70% perchloric acid. After stirring for 4 hours the reaction solution in toluene is extracted with 1N sodium hydroxide solution and water. The combined toluene phases are dried over sodium sulphate, the drying agent is filtered off under suction and washed with toluene. Evaporation of the solvent gives 249.9 g (109%) of (2S,3S,5R)-3-benzoyloxy-2-hexyl-5-undecyl-δ-valerolactone, which is used in the next step without purification.

b) 249.8 g of the benzoate from a) in 1250 ml of methanol are treated under argon while stirring with 2.5 ml of conc. sulphuric acid and stirred at 35° for 18 hours. Subsequently, the pH value of the reaction solution is adjusted to 9 with triethylamine and the methanol is evaporated. The residue is taken up in hexane, washed with

water and the aqueous phase is extracted with hexane. After drying the combined hexane phases they are filtered and the filtrate is freed from hexane. There result
5 246.5 g (100.5%) of methyl (2S,3S,5R)-3-benzoyloxy-2-hexyl-5-hydroxyhexadecanoate, which is used in the next step without purification.

10 c) 246.5 g of the hydroxyester from b) in 1250 ml of hexane are treated under argon while stirring with 152 g of benzyl 2,2,2-trichloroacetimidate. Then, 3.2 ml of trifluoromethanesulphonic acid are added. After stirring at room temperature for 17 hours the precipitate is filtered off under suction and washed with hexane. The
15 filtrate is extracted with 5% sodium bicarbonate solution and then with water. The combined hexane phases are dried, filtered and evaporated. There result 308 g (104.2%) of methyl (2S,3S,5R)-3-benzoyloxy-5-benzyloxy-2-hexylhexadecanoate, which is used in the next step without purification.
20

25 d) 308.5 g of the benzyl ether from c) in 1125 ml of methanol are treated under argon with a solution of 140 g of potassium hydroxide in 125 ml of water. The reaction mixture is stirred at 40° for 17 hours and subsequently concentrated. The suspension is taken up in hexane and washed in sequence with 10% sodium chloride solution, 1N hydrochloric acid and 10% sodium chloride solution. The organic phase is dried with sodium sulphate, the drying
30 agent is filtered off under suction and washed with hexane. The filtrate is concentrated to 1000 ml and stirred at -20°. The crystallizate is filtered off under suction, washed with hexane and discarded. After evaporation of the solvent the filtrate gives a product
35 which is dissolved in methyl acetate and treated with benzylamine while stirring. The solution is seeded with the benzylamine salt of (2S,3S,5R)-5-benzyloxy-2-hexyl-3-

-hydroxyhexadecanoic acid and subsequently cooled to -5° . Then, it is crystallized at -10° for 17 hours. The crystallizate is filtered off under suction, washed with methyl acetate and thereafter dried. 116.7 g (41% based on the starting valerolactone of a) of the benzylamine salt of (2S,3S,5R)-5-benzyloxy-2-hexyl-3-hydroxyhexadecanoic acid, m.p. $66-68^{\circ}$, result.

- 5
10 e) 116.7 g of the benzylamine salt from d) are treated with 1000 ml of hexane and 250 ml of 1N hydrochloric acid while stirring. The organic phase is washed with water, dried and evaporated. There are obtained 95.4 g (100.6%; 41.2% based on the starting valerolactone of a) of
15 (2S,3S,5R)-5-benzyloxy-2-hexyl-3-hydroxyhexadecanoic acid, the product of Example 1i).

Example 9

- 20 a) 110.2 g of methyl 2-acetyloctanoate (the product of Example 1a) are added dropwise under argon and while stirring at $0-5^{\circ}$ to a suspension of 14.4 g of sodium hydride 97% in 750 ml of THF. The mixture is stirred at room temperature for 1 hour and subsequently cooled to
25 -12° . 370 ml of 1.56M butyllithium in hexane are added within 1 hour at -12 to -10° . The mixture is stirred at -12° for 1 hour. 92.2 g of lauric aldehyde are added dropwise at -10° to the solution obtained. The mixture is stirred at this temperature for a further 1 hour. The
30 reaction solution is added to 600 ml of water within 5 minutes while stirring. The mixture is stirred at room temperature for a further 1 hour and subsequently neutralized with 100 ml of 37% hydrochloric acid. After separating the aqueous phase the organic phase is washed
35 with 300 ml of saturated sodium chloride solution, dried over sodium sulphate and the drying agent is filtered off under suction. After evaporation of the solvent the

product is triturated with hexane. The crystallize is filtered off under suction, washed with hexane and dried. 130.61 g (74.1%) of rac-5,6-dihydro-3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one, m.p. 121.5-122.5°, result.

5

b) 1000 ml of ethyl acetate and 12.5 g of Raney-nickel are added to 50 g of the dihydropyrone from a) while stirring. After hydrogenating for 17 hours while stirring at 30° the catalyst is filtered off under suction and washed with ethyl acetate. The filtrate is concentrated and stirred at -10°. The crystallize is filtered off under suction, washed with ethyl acetate and dried. There result 45.4 g (90.3%) of rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-undecyl-δ-valerolactone, m.p. 98.5-99.5°, the product of Example 1c).

15

Example 10

a) To a solution of 117 g of Meldrum acid and 131 ml of pyridine in 1.5 l of methylene chloride, 270 ml of stearic acid chloride are added dropwise at a maximum temperature of 15°C. After stirring, the reaction mixture is washed with 4N hydrochloric acid, the aqueous phase is extracted with methylene chloride, the methylene chloride phase is dried and concentrated. The residue is taken up in methanol and stirred under reflux. After cooling, the precipitated crystals are filtered off, dissolved in methylene chloride and chromatographed on silica gel with methylene chloride to give 175 g of methyl-3-oxo-eicosanoate, m.p. 52-54°C.

30

b) To a solution of 9.1 mg of [(R)-2,2'-bis(diphenylphosphino)-6,6'-dimethylbiphenyl]ruthenium-diacetate in 20 ml of methylene chloride, are added 1.84 mg of acetyl chloride in 1.84 ml of methanol. The obtained solution is hydrogenated at 60°C under 35 bar of hydrogen together with 39.8 mg of the ketoester of (a) and 170 ml of

35

methanol. After adding methylene chloride, the mixture is evaporated to dryness. Chromatography on silica gel with diethyl ether and recrystallization from n-hexane give 35.7 g of methyl (R)-3-hydroxyeicosanoate, m.p. 64-64.5°C.

5

c) Analogously to Example 4, from methyl (R)-3-hydroxyeicosanoate via (R)-3-hydroxyeicosanoic acid of m.p. 89° there is prepared (R)-5,6-dihydro-6-heptadecyl-2H-pyran-2,4(3H)-dione of m.p. 97°.

10

Analogously to Example 3f) and g), the above pyran-dione is converted with acetaldehyde via (R)-3-ethyl-5,6-dihydro-6-heptadecyl-4-hydroxy-2H-pyran-2-one of m.p. 110.5-112.5° into 2S,3S,5R-2-ethyl-5-heptadecyl-3-hydroxy- δ -valerolactone, $[\alpha]_D^{20} = -39.8^\circ$ (c = 1 in CHCl_3).

15

Analogously to Example 2h) to k), the above pyranone can be converted via (3S,4S,6R)-4-(t-butyldimethylsiloxy)-3-ethyl-3,4,5,6-tetrahydro-6-heptadecyl-2H-pyran-2-one,

20

benzyl (2S,3S,5R)-3-(t-butyldimethylsiloxy)-2-ethyl-5-hydroxydocosanoate and

25

benzyl (2S,3S,5R)-5-benzyloxy-3-(t-butyldimethylsiloxy)-2-ethyldocosanoate

into (2S,3S,5R)-5-benzyloxy-3-hydroxy-2-ethyldocosanoic acid (the product of Example 6h) as the benzylamine salt.

30

Example 11

a) Analogously to Example 1b), methyl 2-acetyloctanoate (Example 1a) is converted with methyl hexanoate into 3-hexyl-4-hydroxy-6-pentyl-2H-pyran-2-one, m.p. 110.8-111.7°.

35

b) Analogously to Example 9a), methyl 2-acetyloctanoate is converted with hexanal into rac-5,6-dihydro-3-hexyl-4-hydroxy-6-pentyl-2H-pyran-2-one, m.p. 137-139°.

- 5 c) Hydrogenation of the pyranone from a) or b) analogously to Example 1c) or 9c) leads to rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-pentyl-δ-valerolactone, m.p. 117-118°.
- 10 d) Analogously to Example 1d) to k), the lactone from Example 11c) is converted via rac-(2RS,3RS,5SR)-3-benzoyloxy-2-hexyl-5-pentyl-δ-valerolactone,

15 methyl rac-(2RS,3RS,5SR)-3-benzoyloxy-2-hexyl-5-hydroxy-decanoate,

methyl rac-(2RS,3RS,5SR)-3-benzoyloxy-5-benzyloxy-2-hexyl-decanoate,

20 methyl rac-(2RS,3RS,5SR)-5-benzyloxy-2-hexyl-3-hydroxy-decanoate,

(2S,3S,5R)-5-benzyloxy-2-hexyl-3-hydroxydecanoic acid
(S)-α-methylbenzylamine salt, m.p. 116-117°,

25 (2S,3S,5R)-5-benzyloxy-2-hexyl-3-hydroxydecanoic acid,
[α]_D²⁰ = -31.5° (c = 0.635 in CHCl₃), and

30 (3S,4S)-4-[(R)-2-benzyloxyheptyl]-3-hexyl-2-oxetanone,
[α]_D²⁰ = 63.1° (c = 1 in CHCl₃),

into (3S,4S)-3-hexyl-4-[(R)-2-hydroxyheptyl]-2-oxetanone,
[α]_D²⁰ = -51.9° (c = 1 in CHCl₃).

- 35 e) The latter is esterified analogously to Example 2 to N-formyl-L-valine (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-

-oxetanyl]methyl]hexyl ester (valilactone), m.p.
57.0-57.3°,

or to N-formyl-L-leucine (S)-1-[[[(2S,3S)-3-hexyl-4-oxo-2-
5 -oxetanyl]methyl]hexyl ester, m.p. 50-50.5°.

Example 12

a) 3.55 g of rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-
10 -undecyl-δ-valerolactone (Example 1c), 30 ml of TBME,
12.6 mg of pyridinium p-toluenesulphonate and 2.66 g of
95% 3,4-dihydro-2H-pyran are stirred at 50° for 20 hours.
The solution is washed with aqueous NaCl solution and then
dried. Evaporation of the solvent and drying give 4.41 g
15 (100.5%) of (2RS,3RS,5SR)-2-hexyl-3- -(tetrahydro-2H-
-pyran-2-yloxy)-5-undecyl-δ-valerio- lactone, m.p.
39-41°.

b) A solution of 4.41 g of the ether from a) in 30 ml of
20 t-butyl methyl ether is treated with 10 ml of 2N sodium
hydroxide solution and stirred for 20 hours. After
separating the aqueous phase the organic phase is washed
with 10 ml of 10%, aqueous NaCl solution and evaporated at
55°. The residue is dissolved in 30 ml of TBME and the
25 solvent is again evaporated. A solution of the residue in
30 ml of THF is firstly evaporated and then dried. 4.81 g
(100.5%) of the sodium salt of (2RS,3RS, 5SR)-2-hexyl-5-
-hydroxy-3-(tetrahydro-2H-pyran-2-yloxy)hexadecanoic acid
result.

30 c) 4.80 g of the sodium salt from b) are treated under
argon with 50 ml of THF, 2.57 g of benzyl bromide and
0.495 g of sodium hydride and stirred at 50° for 24 hours.
The suspension is hydrolyzed to pH 0 with 10 ml of 2N
35 hydrochloric acid, stirred at 50° for 2 hours and then the
aqueous phase is separated. After washing with aqueous
NaCl solution the organic phase is evaporated. There

result 5.42 g of rac-(2RS,3RS,5SR)-5-benzyloxy-2-hexyl-3-hydroxyhexadecanoic acid, the product of Example 1g), which is resolved into its antipodes as in Example 1h).

5

Example 13

10 a) 177.3 mg of rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-undecyl- δ -valerolactone (Example 1c), 750 ml of TBME, 86.7 g of 97% 3,4-dihydro-2H-pyran and 0.314 g of pyridinium p-toluenesulphate are stirred at 50° under argon for 20 hours. 500 ml of 2N sodium hydroxide solution are added to the reaction solution. After stirring at 50° for 2.5 hours the aqueous phase is separated and the organic phase is washed with 500 ml of 10% sodium chloride solution.

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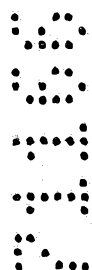
20 b) After boiling on a water separator for 24 hours the sodium salt slurry is cooled, treated under argon in succession with 152.7 g of benzyl bromide and 99.1 g of Na t-butyrate and stirred at room temperature for 24 hours. After adding 750 ml of 2N hydrochloric acid and stirring at 50° for 22 hours the mixture is cooled, the aqueous phase is separated and the organic phase is washed with sodium chloride solution, dried and filtered. After 25 evaporation of the solvent there are obtained 349.8 g of rac-(2RS,3RS,5SR)-5-benzyloxy-2-hexyl-3-hydroxy-decanoic acid (the product of Examples 1g and 12c).

30 c) In a variant of b), the product of a) is boiled on a water separator for 17 hours. The solvent is then distilled off. After drying there are obtained 253.4 g of the sodium salt of (2RS,3RS,5SR)-2 hexyl-5-hydroxy-3-(tetrahydro-2H-pyran-2-yloxy)hexadecanoic acid.

35 d) A solution of the product from c) in 2 l of THF is added to a suspension of 24.7 g of 97% NaH in 500 ml of THF and 131 g of benzyl bromide at 50° while stirring.

After stirring for 22 hours 500 ml of 2N hydrochloric acid are added. After cooling the aqueous phase is separated and washed with sodium chloride solution. The resulting solution of the racemic hydroxyacid, rac-(2RS,3RS,5SR)-5-
5 -benzyloxy-2-hexyl-3-hydroxycecanoic acid (Example 13b), is used for the racemate resolution (Example 1h).

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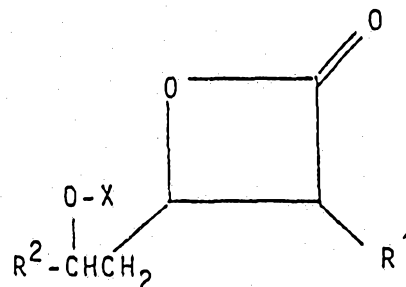
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~~Claims~~

The claims defining the invention are as follows:

1. A process for the manufacture of oxetanones of the formula



I

wherein
R¹ and R²

are alkyl with up to 17 C atoms optionally interrupted by an O atom in a position other than the α- or β-position; or benzyl optionally ring-substituted by 1 to 3 C₁₋₆-alkyl or C₁₋₆-alkoxy groups, is hydrogen or a group of the formula (R³, R⁴)NCH(R⁵)(CH₂)_n-CO-, is hydrogen, C₁₋₃-alkyl or C₁₋₃-alkanoyl, is hydrogen or C₁₋₃-alkyl and is hydrogen, a group Ar or Ar-C₁₋₃-alkyl or C₁₋₇-alkyl optionally interrupted by Y and optionally substituted by Z or form together with the N atom to which they are attached a 4- to 6-membered saturated ring,

X

R³

R⁴
R⁵

R¹ with R⁵

Y

Z

35

n

is oxygen, sulphur or a group N(R⁶), C(O)N(R⁶) or N(R⁶)C(O), is a group -(O or S)-R⁷, -N(R⁷, R⁸), -C(O)N(R⁷, R⁸) or -N(R⁷)C(O)R⁸, is the number 1 or 0, whereby R⁵ is hydrogen when n is the number 1,

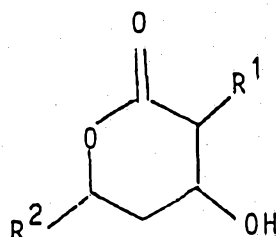
Ar is phenyl substituted by 1 to 3 groups R^9 or OR^9 and

R^6 to R^9 are hydrogen or C_{1-3} -alkyl,

and of salts of the oxetanones of formula I in which X is not hydrogen with weak acids, which process comprises

a) etherifying a β -hydroxy- δ -lactone of the formula

10

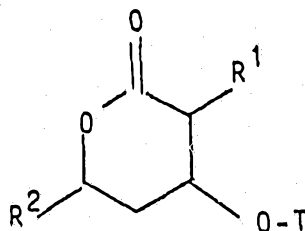


II.

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b) opening the resulting ether of the formula

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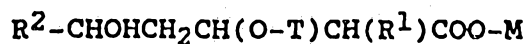
III

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wherein T is a readily cleavable ether group, with a base,

30

c) reacting the resulting salt of the formula



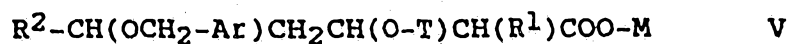
IV

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wherein M is an alkali metal or alkaline earth metal, in optional sequence with an arylmethyl halide and a base

and

- 5 d) selectively cleaving the resulting diether of the formula



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with an acid,

- e) cyclizing the resulting β -hydroxyacid of the formula

15

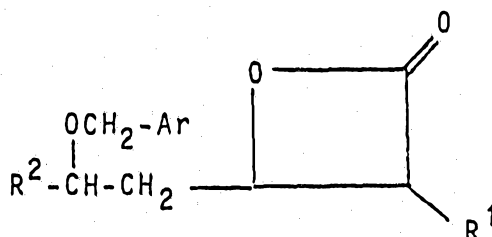


optionally after resolution into its enantiomers,

20

- f) cleaving the resulting β -lactone ether of the formula

25



VII

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and

- g) if desired, esterifying the resulting β -lactone alcohol of formula I in which X is hydrogen with an agent which introduces the group X and

35

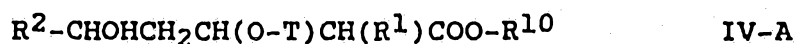
- h) if desired, isolating the ester obtained in the form of a salt with a weak acid.

2. A process according to claim 1, wherein an alkali metal hydride is used as the base in step c).

5 3. A process for the preparation of a β -hydroxyacid of formula VI according to claim 1, which process comprises

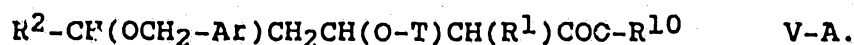
10 a) esterifying a salt of formula IV according to claim 1 with a halide of the formula R^{10} -Hal, wherein R^{10} is C_{1-4} -alkyl or aryl- C_{1-4} -alkyl,

b) etherifying the resulting ester of the formula



and

20 c) in optional sequence saponifying and cleaving in the β -position the resulting diether of the formula

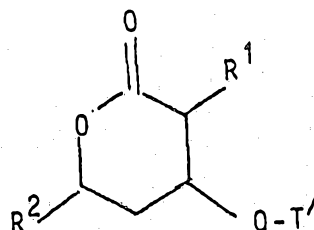


4. A process for the preparation of a β -hydroxyacid of formula VI according to claim 1, which process comprises

30 a) esterifying a β -hydroxy- δ -lactone of formula II according to claim 1,

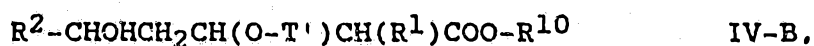
b) opening the resulting ester of the formula

35



III'

wherein T' is aroyl,
by acidic catalysis in the presence of an alcohol of the
formula $R^{10}-OH$ to give an ester of the formula



c) etherifying the ester of formula IV-B and

d) doubly-saponifying the resulting ether diester of the
formula



5. A process for the preparation of the β -hydroxy-
- δ -lactones of formula I according to claim 1, which
process comprises

a) saponifying a β -hydroxyester of the formula



wherein R is C_{1-4} -alkyl.

b) reacting the imidazolidine of the resulting β -hydroxy-acid of the formula

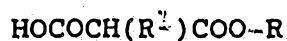
5



IX

with the Mg salt of the malonic acid ester derivative of the formula

10



X.

15

c) cyclizing the resulting δ -hydroxy- β -ketoester of the formula



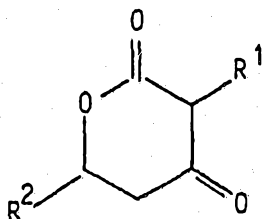
XI

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and

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d) catalytically hydrogenating the resulting β -keto- δ -lactone of the formula



XII.

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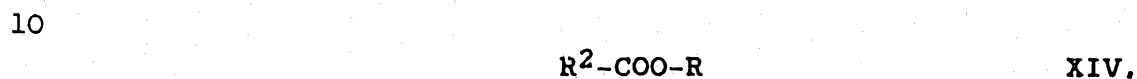
35

6. A process for the preparation of the β -hydroxy- δ -lactones of formula II according to claim 1, which process comprises

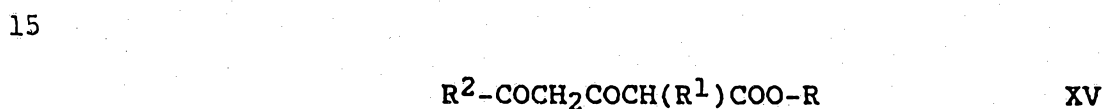
a) reacting a β -ketoester of the formula



with an ester of the formula

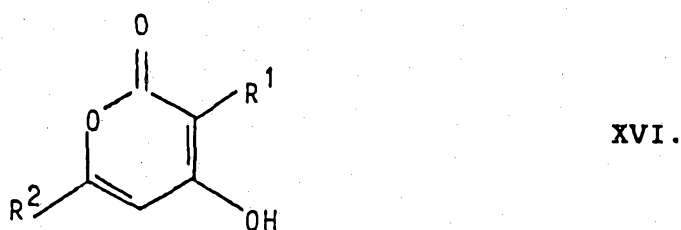


b) cyclizing the resulting diketoe~~ster~~ of the formula



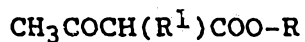
and

20 c) catalytically hydrogenating the resulting pyrone of the formula



30 7. A process for the preparation of the β -keto- δ -lactones of formula XII according to claim 5, which process comprises

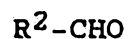
35 a) reacting a β -ketoester of the formula



XIII

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with an aldehyde of the formula



XVII

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and

b) cyclizing the resulting δ -hydroxy- β -ketoester of the formula XI.

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8. A process for the preparation of the β -keto- δ -lactones of formula XII according to claim 5, which process comprises

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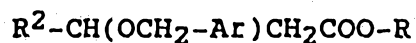
a) etherifying a β -hydroxyester of the above formula



VIII,

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b) saponifying the resulting ether of the formula

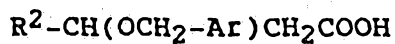


XVIII,

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c) halogenating the resulting ether acid of the formula

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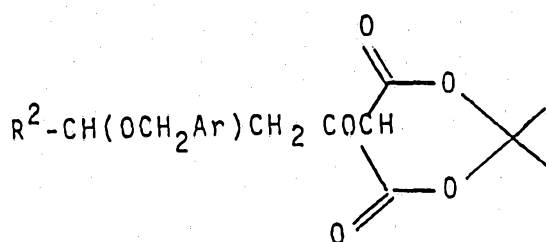
XIX.

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d) reacting the resulting acid halide with Meldrum acid,

e) hydrogenolyzing the resulting compound of the formula

10

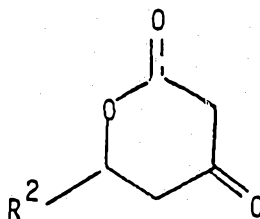


XX

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and cyclizing to a β -keto- δ -lactone of the formula

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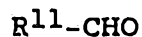
XXI

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and

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f) reacting the β -keto- δ -lactone of formula XXI above with an aldehyde which introduces the group R^1 or $-CH_2-R^{11}$ and which has the formula



XXII

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wherein R^{11} together with the methylene group represents the group R^1 ,
to give a β -keto- δ -lactone of formula XII above.

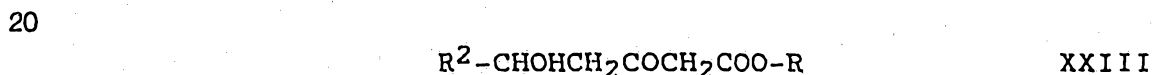
5 9. A process for the preparation of the β -keto- δ -
-lactones of formula XXI according to claim 8, which
process comprises

a) reacting the imidazolidine of the β -hydroxyacid of the
10 formula



15 with the Mg salt of a mono-lower alkyl malonate and

b) cyclizing the resulting δ -hydroxy- β -ketoester of the
formula

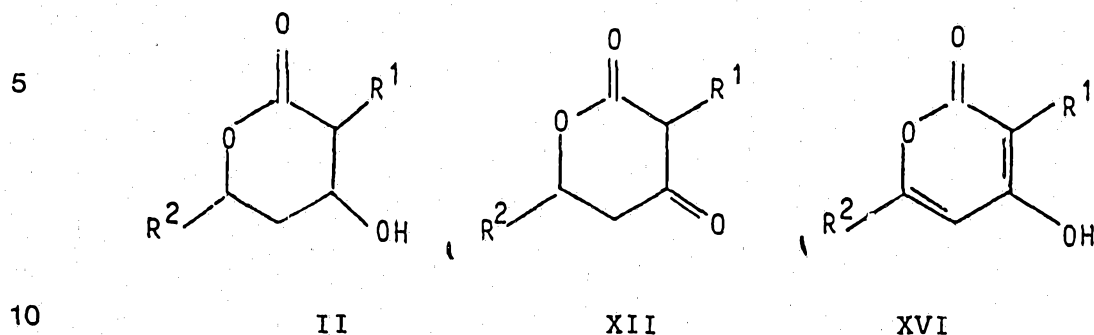


to give the β -keto- δ -lactone of formula XXI above.

25 10. A process according to claim 1,2,5 and 7 for the
manufacture of esters of formula I, which process
comprises reacting a β -ketoester XIII with an aldehyde
XVII, cyclizing the resulting δ -hydroxy- β -ketoester XI to
the β -keto- δ -lactone XII, catalytically hydrogenating
30 the latter and converting the resulting β -hydroxy- δ -
-lactone II into an ester I via the compounds of formulae
III to VII according to the process of claim 1 or 2.

35 11. A process according to claim 10, wherein R^1 is
n-hexyl and R^2 is undecyl.

12. The β -hydroxy- δ -lactones, β -keto- δ -lactones and pyrones of formulae II, XII and, respectively, XVI



from the following group:

- 15 rac-(2RS,3RS,5SR)-2-Hexyl-3-hydroxy-5-undecyl- δ -
-valeriolactone,
rac-(2RS,3RS,5SR)-2-ethyl-5-heptadecyl-3-hydroxy- δ -
-valeriolactone,
(2S,3S,5R)-2-ethyl-5-heptadecyl-3-hydroxy- δ -valerio-
lactone and
20 rac-(2RS,3RS,5SR)-2-hexyl-3-hydroxy-5-pentyl- δ -
-valeriolactone;
rac-5,6-dihydro-3-hexyl-4-hydroxy-6-undecyl-2H-pyran-
-2-one,
(R)-3-ethyl-5,6-dihydro-6-heptadecyl-4-hydroxy-2H-
25 -pyran-2-one and
rac-5,6-dihydro-3-hexyl-4-hydroxy-6-pentyl-2H-pyran-
-2-one;
3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one,
3-ethyl-6-heptadecyl-4-hydroxy-2H-pyran-2-one and
30 3-hexyl-4-hydroxy-6-pentyl-2H-pyran-2-one.

13. The β -keto- δ -lactones of formula XXI in claim 8 in which R² has the significance given in claim 1, but

the number of C atoms in the alkyl group R² amounts to more than 9.

14. (R)-5,6-Dihydro-6-undecyl-2H-pyran-2,4(3H)-dione and (R)-5,6-dihydro-6-heptdecyl-2H-pyran-2,4(3H)-dione.

15. The compounds of formula I in claim 1 and of formulae II, XII, XVI and XXI in claims 12 and 13, whenever prepared by the process of claims 1, 2 and 5-11 or by an obvious chemical equivalent thereof.

16. A process for the manufacture of oxetanones of the formula I, as set out in claim 1, said process substantially as hereinbefore described with reference to any one of the Examples.

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Dated 21 October, 1993
F.Hoffmann-La Roche AG

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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