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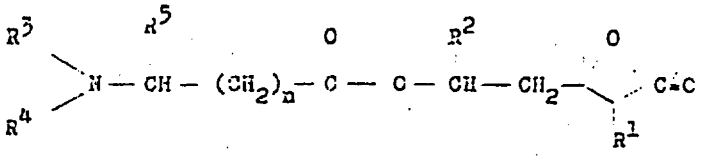
ABSTRACT

Novel pancreas lipase-inhibiting oxetanone ethyl esters of the formula



I

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Abstract

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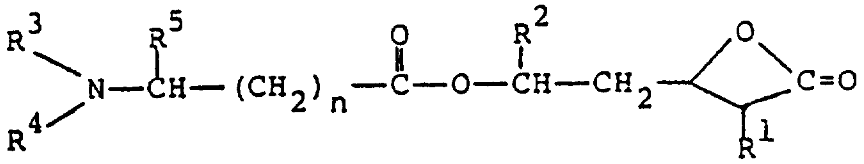

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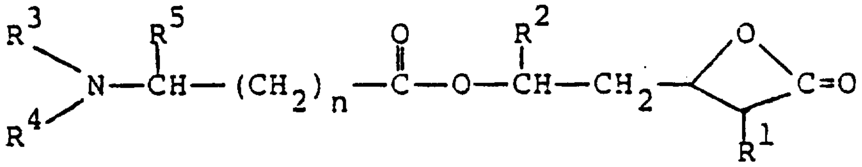
The present invention is concerned with novel oxetanones, a process for their manufacture, novel intermediates which are usable in this process as well as medicaments based on the said oxetanones or based on precusors thereof.

These oxetanones are compounds of the formula



I

wherein

R^1 and R^2 are C_{1-17}-alkyl optionally interrupted by up to 8 double or triple bonds and optionally interrupted by a O or S atom which is present in a position other than the α-position to an unsaturated C-atom; or phenyl, benzyl or $-C_6H_4-X-C_6H_5$ ring-substituted by 0 to 3 C_{1-6}-alkyl-$(O \text{ or } S)_{1 \text{ or } 0}$,

X is oxygen, sulphur or $(CH_2)_{0-3}$,

R^3 is hydrogen, C_{1-3}-alkyl or C_{1-3}-alkanoyl,

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 forms with R^5 a 4- to 6-membered saturated ring,

Y is oxygen, sulphur or a group $N(R^6)$, $C(O)N(R^6)$ or $N(R^6)C(O)$,

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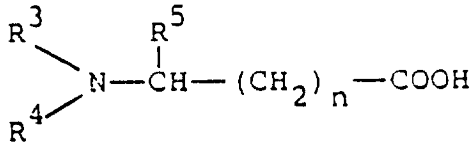
Z	is a group -(O or S)-R^7, -N(R^7,R^8), -C(O)N(R^7,R^8) or -N(R^7)C(O)R^8,
n	is the number 1 or 0, with the proviso that R^5 is hydrogen when n is the number 1,
Ar	is phenyl substituted by 0 to 3 groups R^9 or OR^9, and
R^6 to	R^9 are hydrogen or C_{1-3}-alkyl,

with the proviso that R^4 has a significance other than hydrogen when R^3 is formyl and R^5 is isobutyl or R^3 is acetyl and R^5 is carbamoylmethyl, and simultaneously R^2 is undecyl or 2,5-undecadienyl and R^1 is n-hexyl, and salts of these oxetanones with weak acids.

With weak acids the oxetanones of formula I form salts which are likewise an object of the invention. Examples of such acids are p-toluenesulphonic acid, methanesulphonic acid, oxalic acid, ascorbic acid, fumaric acid, maleic acid, malic acid, citric acid and phosphoric acid.

The oxetanones of formula I can be manufactured by

a) esterifying an acid of the formula



$$(R^3)(R^4)N-CH(R^5)-(CH_2)_n-COOH$$

II

or a functional derivative thereof with an alcohol of the formula

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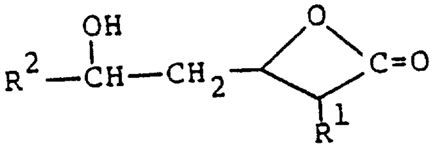
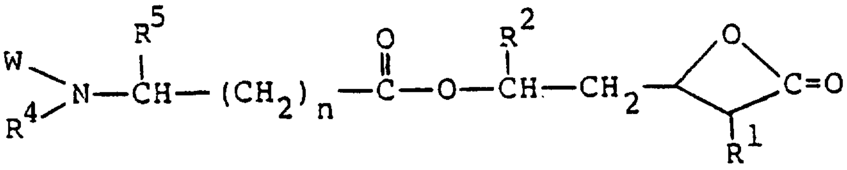


III

wherein R^1-R^5 and n have the above significance,

b) cleaving off the amino protecting group W in an oxetanone of the formula



I'

wherein R^1, R^2, R^4, R^5 and n have the above significance,

c) if desired, catalytically hydrogenating unsaturated residues R^1 and R^2,

d) if desired, C_{1-3}-alkanoylating oxetanones of formula I obtained in which at least one of R^3 and R^4 is hydrogen and an amino group Y or Z which may be present in R^5 is tertiary, and

e) if desired, isolating oxetanones of formula I obtained in the form of their salts with weak acids.

The oxetanones of formula I contain as least 3 asymmetric C atoms and the oxetanones of formula III can contain one or more asymmetric C atoms. They can accordingly be present as optically active enantiomers, as diastereomers or as mixtures, e.g. as racemic mixtures.

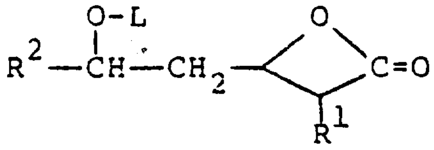
The esterification a) can be carried out in a solvent, e.g. an ether such as tetrahydrofuran (THF), in the presence of triphenylphosphine and diethyl azodicarboxylate, preferably at about room temperature. The corresponding anhydride can be used as the function derivative of an acid of formula II.

Benzyloxycarbonyl and p-nitrobenzyloxycarbonyl can be mentioned as examples of an amino protecting group W in an oxetanone starting material I'. The cleavage reaction b) can be carried out by hydrogenation in a solvent, e.g. an ether such as THF, in the presence of a hydrogenation catalyst such as palladium-on-carbon (Pd/C), preferably at room temperature.

The optional hydrogenation (c) can be carried out under analogous conditions to the above-described cleavage reaction b).

The optional C_{1-3}-alkanoylation d) can be carried out in the presence of an acid anhydride, e.g. a mixed acid anhydride such as formic acid/acetic acid anhydride, in a solvent, e.g. an ether such as THF, preferably at room temperature.

The alcohols III can be prepared by cleaving off the ether protecting group L in an ether of the formula



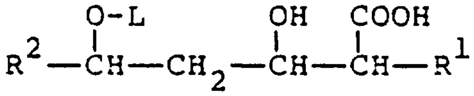
IV

wherein R^1 and R^2 have the above significance.

Tetrahydro-2H-pyran-2-yl, 1-ethoxyethyl, benzyl and t-butyldimethylsilyl are examples of ether protecting groups L.

The cleavage of the ether protecting group L can be carried out in a solvent, e.g. an alcohol such as ethanol, in the presence of pyridinium-4-toluenesulphonate while heating, e.g. to 50-65°C.

The ethers IV can be prepared by cyclizing the acids of the formula



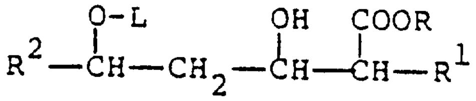
$$R^2-\overset{O-L}{\overset{|}{C}H}-CH_2-\overset{OH}{\overset{|}{C}H}-\overset{COOH}{\overset{|}{C}H}-R^1$$

V.

This reaction can be carried out in a solvent such as pyridine while cooling, e.g. to 0°C, in the presence of benzenesulphonyl chloride.

The acids V can be prepared either

a) by saponifying a corresponding ester of the formula



$$R^2-\overset{O-L}{\overset{|}{C}H}-CH_2-\overset{OH}{\overset{|}{C}H}-\overset{COOR}{\overset{|}{C}H}-R^1 \qquad VI$$

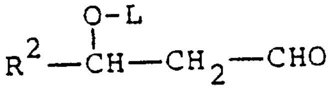
wherein R is C_{1-4}-alkyl and L, R^1 and R^2 have the above significance,

or

b) by condensing an acid of the formula

$$R^1-CH_2-COOH \qquad VII$$

with an aldehyde of the formula



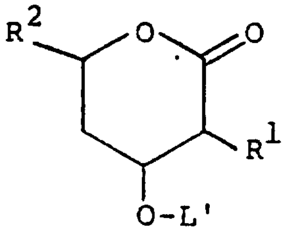
$$R^2-\overset{O-L}{\overset{|}{C}H}-CH_2-CHO \qquad VIII.$$

Methyl, ethyl and t-butyl are examples of alkyl residues R. The saponification a) of an ester VI can be carried out with an alcoholic alkali metal or alkaline earth metal hydroxide solution such as a methanolic potassium hydroxide solution by heating at a temperature up to the reflux temperature of the reaction mixture.

The condensation b) of an acid VII with an aldehyde VIII can be carried out in a solvent such as THF in the presence of diisopropylamine and butyl lithium while cooling, e.g. to -50°C.

The acids V, which are present in the (5R)- or (5S)-form, can be converted in the following manner into the (2S,3S,5R)- or (2R,3R,5S)-stereoisomers:

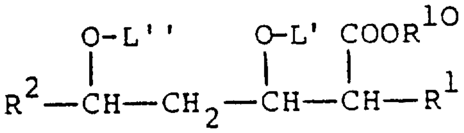
A (5R)- or (5S)-acid of formula V is cyclized, e.g. by means of toluene-4-sulphonic acid monohydrate while heating to 50-60°C in ethanol, to the corresponding (6R)- or (6S)-pyranolone of the formula



V-A

wherein L' stands for hydrogen and R^1 and R^2 have the above significance.

This (6R)- or (6S)-pyranolone is then oxidized, e.g. in acetone by means of Jones' reagent at a temperature below 25°C, to the corresponding pyran-2,4-dione and the latter is stereospecifically hydrogenated, e.g. in ethyl acetate in the presence of platinum oxide, to the (3S,4S,6R)- or (3R,4R,6S)-pyranolone of formula V-A in which L' is hydrogen. This pyranolone is converted into a compound of formula V-A in which L' stands for an ether protecting group such as t-butyldimethylsilyl, e.g. by means of t-butyldimethylchlorosilane in dimethylformamide. The cyclic (3S,4S,6R)- or (3R,4R,6S)-ether obtained is cleaved, e.g. by reaction with an aqueous potassium hydroxide solution in dioxan, and the resulting compound is converted in situ into a (2S,3S,5R)- or (2R,3R,5S)-ether of the formula



$$R^2\text{—}\underset{\displaystyle |}{\overset{\text{O-L}''}{\text{CH}}}\text{—CH}_2\text{—}\overset{\text{O-L}'}{\text{CH}}\text{—}\overset{\text{COOR}^{10}}{\text{CH}}\text{—}R^1$$

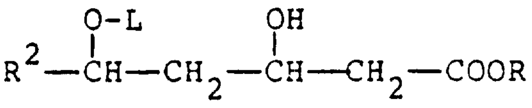
V-B

wherein L" stands for hydrogen, L' is the same ether protecting group as in the ether V-A, R^{10} is benzyl or p-nitrobenzyl and R^1 and R^2 have the above significance.

The ether V-B obtained is then converted into a diethyl of the same formula in which L" stands for an ether protecting group such as tetrahydro-2H-pyran-2-yl. After cleaving off firstly the ether protecting group L', e.g. with tetrabutylammonium fluoride trihydrate in THF, and then the group R^{10}, e.g. by hydrogenation in THF in the presence of Pd/C, there is obtained the desired (2S,3S,5R)- or (2R,3R,5S)-acid of formula V.

The esters VI can be prepared either

a) by alkylating a corresponding ester of the formula

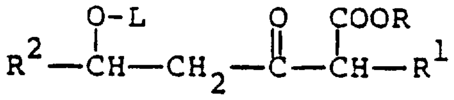


$$R^2\text{—}\overset{\text{O-L}}{\text{CH}}\text{—CH}_2\text{—}\overset{\text{OH}}{\text{CH}}\text{—CH}_2\text{—COOR}$$

IX

or

b) by reducing a ß-ketoester of the formula



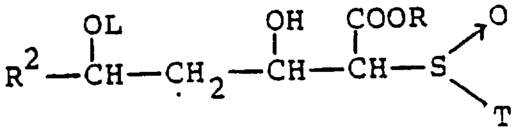
$$R^2-\overset{\text{O-L}}{\overset{|}{\text{CH}}}-\text{CH}_2-\overset{\text{O}}{\overset{\|}{\text{C}}}-\overset{\text{COOR}}{\overset{|}{\text{CH}}}-R^1$$

X.

The alkylation a) can be carried out by reacting an ester IX in a solvent such as THF with a solution of n-butyl lithium in a solvent such as n-hexane in the presence of diisopropylamine at about 50°C and subsequently reacting with a solution of an alkyl halide (R^1-Hal), e.g. a bromide, in hexamethylphosphoric acid triamide at a temperature of about 0 to 10°C.

The reduction b) of a ß-ketoester X can be carried out in an inert gas such as argon in a solvent such as THF with a complex metal hydride such as sodium borohydride ($NaBH_4$) at a temperature below 0°C.

The esters IX can be prepared by reductively removing the sulphoxide group in a sulphoxide of the formula



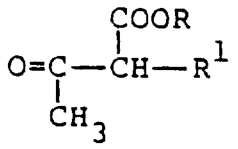
$$R^2-\overset{\text{OL}}{\overset{|}{\text{CH}}}-\text{CH}_2-\overset{\text{OH}}{\overset{|}{\text{CH}}}-\overset{\text{COOR}}{\overset{|}{\text{CH}}}-\text{S}\begin{matrix}\nearrow \text{O}\\ \searrow \text{T}\end{matrix}$$

XI

wherein T is p-tolyl and L, R and R^2 have the above significance.

This reaction can be carried out e.g. by means of aluminium amalgam in a solvent such as THF.

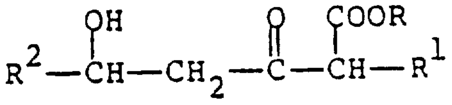
The ß-ketoesters X can be prepared by reacting an aldehyde of the formula R^2-CHO with a ß-ketoester of the formula



$$O{=}\underset{CH_3}{\underset{|}{C}}-\overset{COOR}{\overset{|}{C}H}-R^1$$

XII

and etherifying the resulting alcohol of the formula



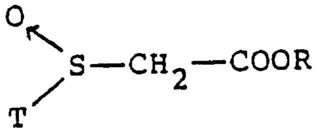
$$R^2-\overset{OH}{\overset{|}{C}H}-CH_2-\overset{O}{\overset{\|}{C}}-\overset{COOR}{\overset{|}{C}H}-R^1$$

XIII.

The preparation of an alcohol XIII and its etherification can be carried out as described e.g. in the following Examples H) and J)e), respectively.

Unsaturated residues R^1 and R^2 which are present in the intermediates of formulae I', III-VI, V-B, X and XIII can be hydrogenated if desired, e.g. under the conditions described above in connection with the hydrogenolytic cleavage of a group W or R^{10}.

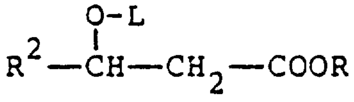
The sulphoxides XI can be prepared by condensing an aldehyde of formula VIII above with an ester of the formula



XIV

e.g. as described in Example G).

The aldehydes VIII can be prepared by reducing an ester of the formula

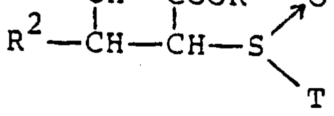


XV

$$R^2-\overset{\displaystyle O-L}{\overset{|}{C}H}-CH_2-COOR$$

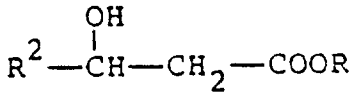
e.g. with a di-(C_{1-4}-alkyl)-aluminium hydride such as diisobutylaluminium hydride in a solvent such as toluene at a temperature of about -60 to -80°C.

The esters of formula XV can be prepared starting from the aldehydes of the formula R^2-CHO via the sulphoxides of the formula



XVI

and the esters of the formula

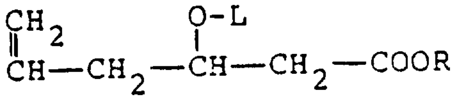


$$R^2-\overset{OH}{\overset{|}{C}}H-CH_2-COOR$$

XVII

e.g. as described in paragraphs F)a), d) and f); G)b), d) and f) and J)b), d) and f) hereinafter.

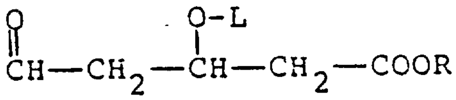
Further, an ester of formula XV in which R^2 is 3-alkenyl can be prepared by the ozonolysis of an ester of the formula



$$\overset{CH_2}{\overset{\|}{CH}}-CH_2-\overset{O-L}{\overset{|}{C}}H-CH_2-COOR$$

XVIII

and a Wittig reaction with the resulting aldehyde of the formula



$$\overset{O}{\overset{\|}{CH}}-CH_2-\overset{O-L}{\overset{|}{C}}H-CH_2-COOR$$

XIX

e.g. as described in Examples K) and L).

(R)-α-(Hydroxydiphenylmethyl)benzyl acetate can be used in place of a sulphinyl ester XIV for the conversion of an aldehyde of formula VIII or of an aldehyde of the formula R^2-CHO into the corresponding ester of formula IX or XVII, respectively. In this case there is obtained as an intermediate in place of a sulphoxide of formula XI or XVI the (R)-2-hydroxy-1,2,2-triphenylethyl ester corresponding to the alkyl esters of formula IX or XVII.

The oxetanones of formula I' can be prepared in the same manner as the oxetanones of formula I, e.g. as described in Example 2.15) hereinafter by esterifying an acid of formula II in which W is present in place of R^3 with an alcohol of formula III. In this esterification there can be used instead of the aforementioned acid the acid anhydride obtained by reaction with N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride or preferably with dicyclohexylcarbodiimide, which can be carried out as described in Example 10 B.1).

The preparation of intermediates of formulae IV to XIX is described in more detail in the following paragraphs A) to M).

A) <u>Preparation of the ethers of formula IV</u>

A)a) 0.57 g of a diastereomer mixture which consists, inter alia, of (2S,3S,5R,13Z,16Z)-2-hexyl -3-hydroxy-5-[(tetrahydro-2H-pyran -2-yl)oxy]-13,16-docosadienoic acid is dissolved in 10 ml of pyridine and cooled to 0°C. After the dropwise addition of 0.28 ml of benzenesulphonyl chloride the mixture is stirred at 0°C for a long time. The reaction mixture is poured into 120 ml of 10 percent aqueous sodium chloride solution and extracted three times with 30 ml of diethyl ether. The combined extracts are dried, filtered and evaporated. After chromatography over silica gel there is obtained a diastereomer mixture of 3-hexyl-4-[(10Z,13Z)-2-[(tetrahydro -2H-pyran-2-yl)oxy]-

-10,13-nonadecadienyl]-2-oxetanones as a colourless oil, IR: 1815 cm^{-1}.

In an analogous manner,

A)b) 3-Ethyl-4-[(10Z,13Z) -2-[(tetrahydro-2H-pyran-2-yl)-oxy]-10,13-nonadecadienyl] -2-oxetanone, IR: 1820 cm^{-1}, is obtained

from (13Z,16Z)-2-ethyl-3-hydroxy -5-[(tetrahydro-2H--pyran-2-yl)oxy]-13,16-docosadienoic acid;

A)c) (3S,4S)-3-ethyl-4-[(R,Z)-2-[(tetrahydro -2H-pyran-2--yl)oxy]-10-nonadecenyl-2-oxetanone is obtained

from (2S,3S,5R,Z)-2-ethyl-3-hydroxy -5-[(tetrahydro--2H-pyran-2-yl)oxy]-13-docosenoic acid;

A)d) (3-benzyl-4-[(10Z,13Z)-2-[(tetrahydro -2H-pyran-2--yl)oxy]-10,13-nonadecadienyl]-2-oxetanone, IR: 1818 cm^{-1}, is obtained

from (13Z,16Z)-2-benzyl-3-hydroxy -5-[(tetrahydro-2H--pyran-2-yl)oxy]-13,16-docosadienoic acid;

A)e) (3S,4S)-3-ethyl-4-[(S)-p-phenoxy -ß-[(tetrahydro-2H--pyran-2-yl)oxy]phenethyl]-2-oxetanone is obtained

from (2S,3S,5S)-2-ethyl-3-hydroxy-5 -(p-phenoxy-phenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]valeric acid;

A)f) (3S,4S)-3-hexyl-4[(S)-p-phenoxy -ß-[(tetrahydro-2H--pyran-2-yl)oxy]phenethyl-2-oxetanone, IR: 1815 cm^{-1}, is obtained

from (2S,3S,5S)-2-hexyl-3-hydroxy-5 -(p-phenoxyphenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]valeric acid;

A)g) 3-hexyl-4-[2-[(tetrahydro -2H-pyran-2-yl)oxy]tridecyl]-2-oxetanone is obtained

from 2-hexyl-3-hydroxy-5[(tetrahydro-2H-pyran -2-yl)-oxy]hexadecanoic acid;

A)h) 3-hexyl-4-[(R)-2-[(tetrahydro-2H-pyran -2-yl)oxy]tridecyl]-2-oxetanone is obtained

from 2-hexyl-3-hydroxy-(R)-5[(tetrahydro -2H-pyran-2--yl)oxy]hexadecanoic acid;

A)i) 3-ethyl-4-[2-[(tetrahydro-2H-pyran -2-yl)oxy]tridecyl]-2-oxetanone is obtained

from 2-ethyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)-oxy]hexadecanoic acid;

A)j) 3-methyl-4-[(R)-2-[(tetrahydro-2H-pyran -2-yl)oxy]-tridecyl]-2-oxetanone is obtained

from 2-methyl-3-hydroxy(R)-5-[(tetrahydro -2H-pyran-2--yl)oxy]hexadecanoic acid;

A)k) 3-allyl-4-[2-[(tetrahydro-2H-pyran -2-yl)oxy]tridecyl]-2-oxetanone is obtained

from 2-allyl-3-hydroxy-5-[(tetrahydro-2H-pyran -2-yl)-oxy]hexadecanoic acid;

A)l) 3-hexyl-4-[(R)-2-[(tetrahydro-2H-pyran -2-yl)oxy]-propyl]-2-oxetanone is obtained

from 2-hexyl-3-hydroxy(R)-5-[(tetrahydro -2H-pyran-2-

-yl)oxy]hexanoic acid;

A)m) 3-hexadecyl-4-[2-[(tetrahydro-2H-pyran -2-yl)oxy]-propyl]-2-oxetanone is obtained

from 2-hexadecyl-3-hydroxy(R) -5-[(tetrahydro-2H--pyran-2-yl)oxy]hexanoic acid;

A)n) 3-hexyl-4-[(2-[(tetrahydro-2H-pyran -2-yl)oxy]-5-hexenyl]-2-oxetanone is obtained

from 2-hexyl-3-hydroxy-5-[(tetrahydro -2H-pyran-2-yl)-oxy]nonenoic acid;

A)o) 3-decyl-4-(R)-2-[(tetrahydro -2H-pyran-2-yl)oxy]-5--hexenyl]-2-oxetanone is obtained

from 2-decyl-3-hydroxy(R)-5-[(tetrahydro -2H-pyran-2--yl)oxy]nonenoic acid;

A)p) 3-hexyl-4-[(R)-2-[(tetrahydro-2H-pyran -2-yl)oxy]-5--tridecenyl-2-oxetanone is obtained

from 2-hexyl-3-hydroxy(R)-5-[tetrahydro -2H-pyran-2--yl)oxy]hexadecenoic acid;

A)q) 3-hexyl-4-[(R)-2-[(tetrahydro-2H-pyran -2-yl)oxy]-5--hexenyl]-2-oxetanone is obtained

from 2-hexyl-3-hydroxy-(R) -5-[(tetrahydro-2H-pyran-2--yl)oxy]nonenoic acid.

B) <u>Preparation of the acids of formula V</u>

B)a) 1.0 g of the crude diastereomer mixture t-butyl (13Z,16Z)-2-hexyl-3-hydroxy-5-[(tetrahydro -2H-pyran-2-

-yl)oxy]-13,16-docosadienoate is heated to reflux in 17 ml of a 2N methanolic potassium hydroxide solution until the starting material has disappeared. The reaction mixture is cooled and poured on to 60 ml of ice-water. The mixture is adjusted to pH 1 by the dropwise addition of 1M aqueous hydrochloric acid and thereupon exhaustively extracted with ether. The combined ether phases are dried, filtered and evaporated. The oil is chromatographed on silica gel, whereby a diastereomer mixture of (13Z,16Z)-2-hexyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]-13,16-docosadienoic acid is obtained as an oil, IR: 3350, 1709, 1132, 1078, 1023 cm^{-1}.

In an analogous manner,

B)b) (13Z,16Z)-2-ethyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy-13,16-docosadienoic acid is obtained

from t-butyl (13Z,16Z)-2-ethyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]-13,16-docosadienoate;

B)c) (2S,3S,5R,Z)-2-ethyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]-13-docosenoic acid is obtained

from t-butyl (2S,3S,5R,Z)-2-ethyl-3-hydroxy-5-[(tetrahydro-2H -pyran-8-yl)oxy]-13-docosenoate;

B)d) (13Z,16Z)-2-benzyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]-13,16-docosadienoic acid, MS: 458 (M$^+$-dihydropyran); IR: 3008, 1709, 1160, 1134, 1115 cm^{-1}, is obtained

from t-butyl (13Z,16Z)-2-benzyl-3-hydroxy-5-[(tetrahydro-2H -pyran-2-yl)oxy]-13,16-docosadienoate;

B)e) (2S,3S,5S)-2-ethyl-3-hydroxy-5 -(p-phenoxyphenyl)-5-

-[(tetrahydro-2H-pyran-2-yl)oxy]valeric acid is obtained

from t-butyl (2S,3S,5S)-2-ethyl-3-hydroxy-5-(p-phenoxyphenyl)-5 -[(tetrahydro-2H-pyran-2-yl)oxy]valerate;

B)f) (2S,3S,5R)-2-hexyl-3-hydroxy-5 -(p-phenoxyphenyl)-5--[(tetrahydro-2H-pyran-2-yl)oxy]valerate is obtained

from t-butyl (2S,3S,5R)-2-hexyl-3-hydroxy-5-(p-phenoxyphenyl)-5 -[(tetrahydro-2H-pyran-2-yl)oxy]valerate;

B)g) 2-hexyl-3-hydroxy-(R)-5 -[(tetrahydro-2H-pyran-2-yl)-oxy]hexadecanoic acid is obtained

from t-butyl 2-hexyl-3-hydroxy-(R)-5 -[(tetrahydro-2H--pyran-2-yl)oxy]hexadecanoate;

B)h) 2-hexyl-3-hydroxy-5 -[(tetrahydro-2H-pyran-2-yl)oxy]-hexadecanoic acid is obtained

from methyl 2-hexyl-3-hydroxy-5 -[(tetrahydro-2H--pyran-2-yl)oxy]hexadecanoate.

C) <u>Preparation of the acids V (variant)</u>

C)a) 2 ml of diisopropylamine in 30 ml of dry THF are cooled to -20°C and thereupon 9.68 ml of butyl lithium (1.6M/hexane) are added dropwise in such a manner that the temperature does not exceed -20°C. The mixture is subsequently stirred for 15 minutes and then cooled to -50°C. Thereafter, 0.720 ml of 4-pentenoic acid in 10 ml of THF is added dropwise and the mixture is stirred at 50°C for a further 10 minutes. The mixture is stirred at room temperature for 1 hour and subsequently again cooled to -50°C. 2 g of rac-3-[(tetrahydro-2H-pyran-2-yl)oxy]tetradecanal in 10 ml of THF are now added dropwise and the mixture is stirred at -50°C for a further 30 minutes, then at room temperature for 72 hours. After hydrolysis with 2N hydrochloric acid the reaction mixture is evaporated. The residue is extracted with ether. The organic phase is dried over sodium sulphate, filtered and evaporated. The material obtained is filtered through a column of silica gel. There is obtained crude 2-allyl-3-hydroxy-5-[(tetrahydro-2H-pyran -2-yl)oxy]hexadecanoic acid.

In an analogous manner,

C)b) 2-ethyl-3-hydroxy-5-[(tetrahydro-2H-pyran -2-yl)oxy]-hexadecanoic acid is obtained

from rac-3-[(tetrahydro-2H-pyran-2-yl)oxy]tetradecanal and butanoic acid;

C)c) 2-methyl-3-hydroxy(R)-5-[(tetrahydro-2H-pyran -2-yl)-oxy]hexadecanoic acid is obtained

from (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy]tetradecanal and propionic acid;

C)d) 2-hexyl-3-hydroxy(R)-5-[(tetrahydro-2H-pyran -2-yl)-oxy]hexanoic acid is obtained

from (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy]butanal and octanoic acid;

C)e) 2-hexadecyl-3-hydroxy-5-[(tetrahydro-2H-pyran -2-yl)-oxy]hexanoic acid is obtained

from 3-[tetrahydro-2H-pyran-2-yl)oxy]butanal and octadecanoic acid;

C)f) 2-hexyl-3-hydroxy-(R)-5[(tetrahydro-2H-pyran -2-yl)-

oxy]-8-nonenoic acid is obtained

from (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-6-heptenal and octanoic acid;

C)g) 2-decyl-3-hydroxy-(R)-5[(tetrahydro-2H-pyran -2-yl)-oxy]-8-nonenoic acid is obtained

from (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-6-heptenal and dodecanoic acid;

C)h) 2-hexyl-3-hydroxy-(R)-5[(tetrahydro -2H-pyran-2-yl)-oxy]-8-pentadecenoic acid is obtained

from (R)-3-[(tetrahydro-2H-pyran-2 -yl)oxy]-6-tetradecenal and octanoic acid;

C)i) 2-hexyl-3-hydroxy-5[(tetrahydro-2H-pyran-2-yl)oxy]-8- -nonenoic acid is obtained

from 3-[(tetrahydro-2H-pyran-2-yl)oxy]-6-heptenal and octanoic acid.

D) Preparation of the esters of formula VI

D)a) 3.1 ml of diisopropylamine are cooled to -5°C under argon and treated dropwise with 14 ml of about 1.6M n-butyl lithium solution in n-hexane. Thereafter, the mixture is stirred for 10 minutes. After cooling to -50°C the cooling bath is removed and a solution of 5.08 g of a diastereomer mixture of butyl (13Z,16Z)-3-hydroxy-5-[(tetrahydro-2H-pyran -2-yl)oxy]-13,16-docosadienoate in 5 ml of THF is added dropwise. In so doing the temperature rises to -20°C. The mixture is left to warm to 0°C and is stirred for 10 minutes. A solution of 2.1 ml of 1-bromohexane in 2.5 ml of hexamethylphosphoric acid triamide is then added, whereby the temperature rises to 9°C. Thereafter, the mixture is left to warm to room temperature and is stirred for 2 1/2 hours. The solution is poured on to 200 ml of ice-water and saturated with sodium chloride. The mixture is extracted with ether. The combined extracts are dried, filtered and evaporated. The residual oil is chromatographed on silica gel. There is obtained a diastereomer mixture of t-butyl (13Z,16Z)-2-hexyl-3-hydroxy-5-[(tetrahydro-2H-pyran -2-yl)oxy]-13,16-docosadienoate, MS: 519 $(M^{+}-(CH_3)_3CO.)$; IR: 3503, 1728, 1709, 1153.

In an analogous manner,

D)b) t-butyl (13Z,16Z)-2-ethyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]-13,16-docosadienoate, MS: 396 (M^{+}-dihydropyran-isobutylene): IR: 3510, 1728, 1153, 1137 cm^{-1}, is obtained

from t-butyl (13Z,16Z)-3-hydroxy-5-[(tetrahydro -2H-pyran-2-yl)oxy]-13,16-docosadienoate and ethyl iodide;

D)c) t-butyl (13Z,16Z)-2-benzyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]-13,16-docosadienoate, MS: 525 $(M^{+}-(H_3C)_3\ CO.)$ IR: 3498, 1725, 1604, 1585, 1496, 1150 cm^{-1}, is obtained

from t-butyl (13Z,16Z)-3-hydroxy-5-[(tetrahydro -2H-pyran-2-yl)oxy]-13,16-docosadienoate and benzyl bromide;

D)d) t-butyl (2S,3S,5R,Z)-2-ethyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]docosenoate, MS: 465 $(M^{+}-(H_3C)_3CO.)$; IR: 3499, 1729, 1155, 1137, 1116 cm^{-1}, is obtained

from t-butyl (3S,5R,Z)-3-hydroxy -5-[(tetrahydro-2H-

-pyran-2-yl)oxy]-13-docosenoate and ethyl iodide;

D)e) t-butyl (2S,3S,5R)-2-ethyl-3-hydroxy -5-(p-phenoxyphenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]valerate is obtained

from t-butyl (3S,5R)-3-hydroxy -5-(p-phenoxyphenyl)-5--[(tetrahydro-2H-pyran-2-yl)oxy]valerate and ethyl iodide;

D)f) t-butyl (2S,3S,5R)-2-hexyl-3-hydroxy -5-(p-phenoxyphenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]valerate is obtained

from t-butyl (3S,5R)-3-hydroxy -5-(p-phenoxyphenyl)-5--[(tetrahydro-2H-pyran-2-yl)oxy]valerate and 1-bromohexane;

D)g) t-butyl 2-hexyl-3-hydroxy(R) -5-[(tetrahydro-2H--pyran-2-yl)oxy]hexadecanoate, D.C. silica gel, hexane-diethyl ether 1:1, Rf = 0.65, is obtained

from t-butyl 3-hydroxy(R) -5-[(tetrahydro-2H-pyran-2--yl)oxy]hexadecanoate and 1-bromohexane.

E) <u>Preparation of the esters of formula VI (variant)</u>

7.76 g of methyl 2-hexyl-3-oxo -5-[(tetrahydro-2H--pyran-2-yl)oxy]hexadecanoate (0.017 mol) are dissolved in 500 ml of THF while gassing with argon, treated with 20 ml of MeOH and cooled to -5°C. 5.3 g of sodium borohydride (0.14 mol) are added portionwise while stirring in such a manner that the temperature does not exceed 0°C. After stirring for 3 hours the excess sodium borohydride is filtered off, the reaction mixture is hydrolyzed (to pH 6) with 2N hydrochloric acid in the cold and the solvent is evaporated off. The residue is extracted with ether and the ethereal phase is dried and evaporated. There are obtained 7.71 g of methyl 2-hexyl-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]hexadecanoate.

F) Preparation of the esters of formulae XVII and IX

F)a) 147.6 g of a diastereomer mixture of t-butyl (11Z,14Z)-3-hydroxy -2-[(R)-o-tolylsulphinyl]-11,14-eicosadienoate are dissolved in 5500 ml of THF and then treated within 6 hours with 190 g of amalgamated aluminium foil. In so doing the temperature is held between 15 and 20°C. After completion of the addition the mixture is stirred until the reaction has finished. The insoluble material is filtered off under suction and washed firstly with 1 l of THF, then with 2 l of THF. The filter cake is taken up in 2 l of diethyl ether, stirred and again filtered off under suction. This procedure is repeated once. The combined organic phases are evaporated and the oily residue is purified by chromatography on silica gel, whereby there is obtained an enantiomer mixture which consists to 80% of

t-butyl (R,11Z,14Z)-3-hydroxy-11,14-eicosadienoate, MS: 324 (M^+-isobutylene); IR: 3452, 1715, 1154 cm^{-1}.

In an analogous manner,

F)b) t-butyl (13Z,16Z)-3-hydroxy-5-[(tetrahydro-2H-pyran--2-yl)oxy]-13,16-docosadienoate, IR: 3481, 1730, 1153, 1075, 1014 cm^{-1}, is obtained

from t-butyl (13Z,16Z)-3-hydroxy-5-[(tetrahydro-2H--pyran-2-yl)oxy] -2-[(S)-p-tolylsulphinyl]-13,14-docosadienoate;

F)c) t-butyl (3S,5R,Z)-3-hydroxy-5-[(tetrahydro-2H-pyran--2-yl)oxy]-13-docosenoate, MS: 437 (M^+-$(H_3C)_3CO$);

IR: 3484, 1730, 1655, 1153, 1075, 1024 cm^{-1}, is obtained

from t-butyl (3S,5R,Z)-3-hydroxy -5-[(tetrahydro-2H-pyran-2-yl)oxy]-2-[(S)-p-tolylsulphinyl]-13-docosenoate;

F)d) t-butyl (R,Z)-3-hydroxy-11-eicosenoate, IR: 3445, 1716, 1154 cm^{-1}, is obtained

from t-butyl (R,Z)-3-hydroxy-2-[(R)-p-tolylsulphinyl]-11-eicosenoate;

F)e) t-butyl (3S,5S)-3-hydroxy-5-(p-phenoxyphenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]valerate, MS: 357 (M$^+$-tetrahydropyranyl); IR: 3446, 1727, 1590, 1505, 1489, 1152, 1133, 1118, 1074, 1022 cm^{-1}, is obtained

from t-butyl (3S,5S)-3-hydroxy -5-(p-phenoxyphenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy] -2-[(S)-o-tolylsulphinyl]valerate;

F)f) t-butyl [(S)-α-hydroxy-p-phenoxybenzyl]acetate, m.p. 64-65°C (from n-hexane), MS: 314 (M$^+$); IR: 3440, 1713, 1590, 1506, 1491, 1158, is obtained

from t-butyl (ßS)-ß-hydroxy-p-phenoxy -α-[(R)-p-tolylsulphinyl-hydrocinnamate;

F)g) t-butyl 3-hydroxy-(R)-5-[(tetrahydro-2H-pyran -2-yl)-oxy]hexadecanoate is obtained

from t-butyl 3-hydroxy-(R)-5-tetrahydro -2H-pyran-2-yl)oxy]-2-[(S)-p-tolylsulphinyl]hexadecanoate.

G) <u>Preparation of the sulphoxides of formulae XI and XVI</u>

G)a) 16.5 g of t-butyl [(S)-p-tolylsulphinyl]acetate are dissolved in a mixture of 600 ml of ether and 60 ml of THF and cooled to -78°C. 43 ml of t-butylmagnesium bromide are then added dropwise in such as manner that the temperature remains below -70°C. After stirring at -78°C for 1 hour 13.4 g of (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-tetradecanal in 100 ml of THF are added dropwise. After 2 hours at -78°C the reaction mixture is hydrolyzed with 2N hydrochloric acid and the solvent is evaporated off. The reaction mixture remaining behind is extracted with ether and the ethereal phase is dried and evaporated. After chromatography on silica gel there are obtained 14.9 g of t-butyl 3-hydroxy-(R)-5-[(tetrahydro -2H-pyran-2-yl)oxy]-2-[(S)-p-tolylsulphinyl]-hexadecanoate (67% yield). m.p. 97-98°C.

In an analogous manner,

G)b) t-butyl (3R,11Z,14Z)-3-hydroxy-2-[(R)-p-tolylsulphinyl] -11,14-eicosadienoate, IR: 3400, 1727, 1653, 1596, 1494, 1279, 1258, 1145, 1085, 1045 cm^{-1}, is obtained

from 9,12-octadienal and t-butyl (R)-p-tolylsulphinyl-acetate;

G)c) t-butyl (13Z,16Z)-3-hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]-2-[(S)-p-tolylsulphinyl]-13,16-docosadienoate is obtained

from t-butyl (11Z,14Z)-3-[(tetrahydro -2H-pyran-2-yl)-oxy]-11,14-eicosadienal and t-butyl (S)-p-tolylsulphinyl-acetate;

G)d) t-butyl (R,Z)-3-hydroxy-2-[(R) -p-tolylsulphinyl]-11-eicosenoate, MS: 464 (M^+-isobutylene), IR: 3403, 1727, 1596, 1494, 1145, 1043 cm^{-1}, is obtained from 9-octenal and t-butyl (R)-p-tolylsulphinyl-acetate;

G)e) t-butyl (3S,5R,Z)-3-hydroxy-5-[(tetrahydro -2H-pyran--2-yl)-oxy]-2-[(S)-p-tolylsulphinyl-13-docosenoate is obtained

from t-butyl (R,Z)-3-[(tetrahydro-2H-pyran -2-yl)oxy]--11-eicosenal and (S)-p-tolylsulphinyl-acetate;

G)f) t-butyl (ßS)-ß-hydroxy-p-phenoxy -α-[(R)-p-tolylsulphinyl]-hydrocinnamate, m.p. 126-128°C (from n-hexane), is obtained

from t-butyl p-phenoxy-benzaldehyde and (R)-p-tolylsulphinyl-acetate;

G)g) t-butyl (3S,5S)-3-hydroxy -5-(p-phenoxyphenyl)-5--[(tetrahydro-2H-pyran-2-yl)oxy] -2-[(S)-p-tolylsulphinyl]valerate, m.p. 140-145°C, is obtained

from t-butyl (ßS)-p-phenoxy-ß-[(tetrahydro -2H--pyranyl)oxy]-hydrocinnamaldehyde and t-butyl (S)-p-tolylsulphinyl-acetate.

H) <u>Preparation of the alcohols of formula XIII</u>

5 g of a 55% sodium hydride dispersion are washed with hexane and treated with 600 ml of THF. 18.9 g of methyl 2--acetyloctanoate dissoved in 80 ml of THF are added dropwise while cooling. After stirring for 2 hours the mixture is cooled to -10°C and treated while cooling with 65 ml of butyl lithium (1.6M hexane). After 1 hour at -10°C a solution of 19.7 g of dodecanal in 80 ml of THF is added dropwise. The mixture is left to warm to room temperature and stirred for a further 2 hours. The reaction mixture is

hydrolyzed with 100 ml of 2N hydrochloric acid and evaporated. The residue is extracted with ether and the ethereal phase is dried and evaporated. After chromatography on silica gel there is obtained methyl 2-hexyl-5-hydroxy-3-oxohexadecanoate, m.p. 38-39°C.

I) Preparation of the aldehydes of formula VIII

I)a) 9.2 g of t-butyl (R)-3-[(tetrahydro-2H-pyran-2-yl)-oxy]tetradecanoate are dissolved in 115 ml of toluene while gassing with argon and with the exclusion of moisture and cooled to -75°C. 26.5 ml of a 1.2M solution of diisobutylaluminium hydride in toluene are then added dropwise in such a manner that the temperature does not exceed -70°C. After stirring at -75°C for 1 hour there are added dropwise 7.4 ml of saturated aqueous ammonium chloride solution and subsequently 15.5 ml of 1N hydrochloric acid at -70°C. The mixture is then left to warm to room temperature. After stirring for 1 hour the organic phase is dried, filtered and evaporated. The material obtained is chromatographed on silica gel. There is obtained (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy]tetradecanal as a colourless oil.

In an analogous manner,

I)b) rac-3-[(tetrahydro-2H-pyran-2-yl)oxy]tetradecanal is obtained

from methyl rac-3-[(tetrahydro-2H-pyran-2-yl)oxy]-tetradecanoate;

I)c) (11Z,14Z)-3-[(tetrahydro -2H-pyran-2-yl)oxy]-11,14-eicosadienal, MS: 291 (M^+-2-tetrahydropyranyloxy), 290 (M^+-tetrahydro-2-pyranol), IR: 2729, 1726, 1132, 1118, 1077 cm^{-1}, is obtained from t-butyl (11Z,14Z)-3-[(tetrahydro-2H-pyran-2-yl)-oxy] -11,14-eicosadienoate;

I)d) (R,Z)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-11-eicosanal, MS: 292 (M^+-tetrahydro-2-pyranol); IR: 2722, 1726, 1132, 1118, 1077 cm^{-1}, is obtained

from t-butyl (R,Z)-3-[(tetrahydro -2H-pyran-2-yl)oxy]-11-eicosanoate;

I)e) (βS)-p-phenoxy-β-[(tetrahydro -2H-pyran-2-yl)oxy]-hydrocinnamaldehyde is obtained

from t-butyl [(S)-p-phenoxy-α-[(tetrahydro -2H-pyran-2-yl)oxy]benzyl]acetate;

I)f) (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-6Z-tetradecenal is obtained

from ethyl (R)-3-[(tetrahydro-2H-pyran -2-yl)oxy]-6H-tetradecenoate.

J) <u>Preparation of the esters of formula XV</u>

J)a) 66.5 g of t-butyl (R,11Z,14Z)-3-hydroxy-11,14-eicosadienoate, which contains about 20% of the (S)-isomer, and 32 ml of freshly distilled 3,4-dihydro-2H-pyran are dissolved in 650 ml of methylene chloride and cooled to 3°C. Thereafter, 640 mg of p-toluenesulphonic acid monohydrate are added, whereby the temperature rises to 8°C. The mixture is stirred until the reaction has finished. Thereupon, the solution is washed with a mixture of 250 ml of saturated aqueous sodium chloride solution, 250 ml of saturated aqueous sodium hydrogen carbonate solution and 500 ml of water. After drying the mixture is filtered and the solvent is removed. The oily residue is purified by chromatography on silica gel. There is obtained a diastereomer mixture of t-butyl (11Z,14Z)-3-[(tetrahydro -2H--pyran-2-yl)oxy]-11,14-eicosadienoate, MS: 324 (M^+-dihydropyran-isobutylene); IR: 1731, 1158, 1024 cm^{-1}.

In an analogous manner,

J)b) t-butyl (R,Z)-3-[(tetrahydro -2H-pyran-2-yl)oxy]-11--eicosenoate, MS: 326 (M^+-dihydropyran-isobutylene), IR: 1731, 1158, 1134, 1118 cm^{-1}, is obtained

from t-butyl (R,Z)-3-hydroxy-11-eicosenoate and dihydropyran;

J)c) t-butyl [(S)-p-phenoxy-α-[(tetrahydro -2H-pyran-2--yl)oxy]benzyl]acetate, MS: 313 (M^+-tetrahydropyranyl); IR: 1730, 1590, 1506, 1489, 1391, 1367, 1201, 1149, 1118 cm^{-1}, is obtained

from t-butyl [(S)-α-hydroxy-p-phenoxybenzyl]acetate and dihydropyran;

J)d) methyl rac-3-[(tetrahydro-2H-pyran -2-yl)oxy]tetradecanoate, D.C. silica gel, hexane ether 3:1, Rf = 0.67, is obtained

from methyl rac-3-hydroxytetradecanoate and dihydropyran;

J)e) methyl 2-hexyl-3-oxo-5-[(tetrahydro -2H-pyran-2-yl)-oxy]hexadecanoate, m.p. 37-38°C, is obtained

from methyl 2-hexyl-5-hydroxy-3-oxo-hexadecanoate and dihydropyran.

K) Preparation of an ester of formula XV (variant)

K)a) A solution of 0.51 g of diisopropylamine in 20 ml of THF is treated at 0°C with 3.13 ml of a 1.6 molar solution of butyl lithium in hexane. The mixture is then cooled to -78°C and 2.3 g of heptyltriphenylphosphonium bromide are added thereto and the mixture is left at this temperature for 5 minutes. A solution of ethyl 5-formyl-(R)-3-[(tetrahydro-2H-pyran -2-yl)oxy]pentanecarboxylate in 10 ml of THF is subsequently added dropwise. The mixture is left to stir at room temperature overnight. The reaction mixture is treated with water, extracted with ether, dried and evaporated in vacuo. The residue is chromatographed over silica gel with toluene-ethyl acetate (9:1) and there is obtained 0.5 g of ethyl (R)-3-[(tetrahydro-2H-pyran-2--yl)oxy] -6Z-tetradecenecarboxylate.

K)b) In an analogous manner there is obtained:

Ethyl (R)-3-[(tetrahydro-2H-pyran-2-yl)oxy] -6Z-eicosenecarboxylate.

L) Preparation of an aldehyde of formula XIX

A solution of 2.56 g of methyl (R)-3-[(tetrahydro-2H--pyran-2-yl)oxy]-6-heptenoate in 40 ml of ethyl acetate is treated with ozone at -75°C. After completion of the reaction 0.1 g of Pd-on-carbon is added thereto and the mixture is hydrogenated at room temperature. After the hydrogen uptake has finished the catalyst is filtered off and washed with ethyl acetate and the filtrate and washings are evaporated in vacuo. There is obtained crude methyl 5-formyl-(R)-3-[(tetrahydro -2H-pyran-2-yl)oxy]--pentanecarboxylate.

M) Separation of the acids of formula V into their stereoisomers

M)a) 15.4 g of a diastereomer mixture of 2-hexyl-3-hydroxy-(R)-5-[(tetrahydro-2H -pyran-2-yl)oxy]hexadecanoic acid are dissolved in 160 ml of ethanol and 800 mg of toluene-4-sulphonic acid monohydrate are added. The reaction mixture is heated to 55-60°C until the reaction has finished. The solvent is removed in vacuo and the residue is dissolved in 160 ml of dichloromethane. The solution is stirred at room temperature for 1 hour. The reaction mixture is evaporated. The material obtained is chromatographed on silica gel. There is obtained tetrahydro-3-hexyl-4-hydroxy-(R)-6-undecyl-2H-pyran-2-one, m.p. 95-96°C.

M)b) 3 g of a diastereomer mixture of tetrahydro-3-hexyl-4-hydroxy-(R)-6-undecyl-2H-pyran-2-one are dissolved in 300 ml of acetone. 3 ml of Jones' reagent are added dropwise while stirring in such a manner that the temperature does not exceed 25°C. After 3 hours the reaction mixture is poured into 700 ml of H_2O. The lactone precipitates out and is filtered off. After recrystallization in ether/n-hexane there are obtained 1.7 g of tetrahydro-3-hexyl-4-oxo-(R)-6-undecyl-2H-pyran-2-one, m.p. 112.5-113.5°C.

M)c) 8 g of an isomer mixture of tetrahydro-3-hexyl-4-oxo-(R)-6-undecyl-2H-pyran-2-one are dissolved in 2 l of ethyl acetate and 3 g of PtO_2 are added. The mixture is then hydrogenated (50 bar) for 12 hours. The catalyst is filtered off and the solution is evaporated. After recrystallization there are obtained 7 g of (3S,4S,6R)-tetrahydro-3-hexyl-4 -hydroxy-6-undecyl-2H-pyran-2-one, m.p 108-109°C.

M)d) 1.5 g of (3S,4S,6R)-tetrahydro-3-hexyl-4-hydroxy-6-undecyl-2H-pyran-2-one are dissolved in 8 ml of DMF. 0.85 g of t-butyldimethylchlorosilane in 4 ml of DMF are then added dropwise. The mixture is stirred for 48 hours. The reaction mixture is poured in to 100 ml of ether and washed with 1N hydrochloric acid. The organic phase is dried, filtered and evaporated. The material obtained is chromatographed on silica gel. There are obtained 1.26 g of (3S,4S,6R)-tetrahydro-3-hexyl-4-[(t-butyldimethylsilyl)oxy]-6-undecyl-2H-pyran-2-one, MS: 411 (M^+-t-butyl).

M)e) 0.3 g of (3S,4S,6R)-tetrahydro-3-hexyl-4-[(t-butyldimethylsilyl)oxy]-6-undecyl-2H-pyran-2-one is dissolved in mixture of 12 ml of dioxan and 0.64 ml of 1N aqueous potassium hydroxide. The mixture is stirred overnight. The reaction mixture is then evaporated and the residue is dissolved in 10 ml of hexamethylphosphortriamide. 0.35 ml of benzyl bromide is added. The mixture is stirred for 2 days. The reaction mixture is poured into water and extracted with ether. The ether phase is dried, filtered and evaporated. The oil is chromatographed on silica gel. There are obtained 330 mg of benzyl (2S,3S,5R)-2-hexyl-3-[(t-butyldimethylsilyl)oxy]-5-hydroxyhexadecanoate, MS: 519 (M^+-t-butyl).

M)f) 350 mg of benzyl (2S,3S,5R)-2-hexyl-3-[(t-butyldimethylsilyl)oxy]-5-hydroxyhexadecanoate and 0.5 ml of freshly distilled 3,4-dihydro-2H-pyran are dissolved in 10 ml of methylene chloride and cooled to -15°C. A crystal of p-toluenesulphonic acid monohydrate is added thereto. The mixture is stirred until the reaction has finished. Thereupon, the solution is evaporated and the residue is chromatographed on silica gel. There are obtained 330 mg of benzyl (2S,3S,5R)-2-hexyl-3-[(t-butyldimethylsilyl)-oxy]-5-[(tetrahydro-2H-pyran-2-yl)oxy]hexadecanoate, MS:

603 (M^+-t-butyl).

M)g) 480 mg of benzyl (2S,3S,5R)-2-hexyl-3-[(t-butyldimethylsilyl)oxy]-5 -[(tetrahydro-2H-pyran-2-yl)oxy]hexadecanoate and 350 mg of tetrabutylammonium fluoride trihydrate are dissolved in 8 ml of THF and stirred for 12 hours. After evaporation the residue is dissolved in 50 ml of ether and washed with water. The ethereal phase is dried and evaporated. The crude product is chromatographed on silica gel. There are obtained 240 mg of benzyl (2S,3S,5R)-2-hexyl-3-hydroxy-5 -[(tetrahydro-2H-pyran-2--yl)oxy] hexadecanoate, MS: 463 [$(M+H)^+$-dihydro-2H--pyran-2-yl].

M)h) 430 mg of benzyl (2S,3S,5R)-2-hexyl-3-hydroxy-5--[(tetrahydro-2H -pyran-2-yl)oxy]hexadecanoate in 10 ml of THF are treated with Pd/C 10% and hydrogenated for 3 hours. The catalyst is filtered off and, after evaporation of the filtrate, the crude product is chromatographed on silica gel. There is obtained (2S,3S,5R)-2--hexyl-3-hydroxy-5-[(tetrahydro-2H -pyran-2-yl)oxy]hexadecanoic acid.

The alcohols of formula III in which R^1 and R^2 have the above significance, with the proviso that when R^1 is n-hexyl and R^2 is undecyl or 2Z,5Z-undecadienyl, at least one of the asymmetric C-atoms present in the oxetanone ring and in the ß-position to the latter has the R-configuration, are novel.

Preferred oxetanones of formulae I and III are those in which R^1 is methyl, propyl, hexyl, decyl, hexadecyl, allyl, benzyl or especially ethyl; R^2 is methyl, undecyl, 3-butenyl, 3-undecenyl, 8,11-heptadecadienyl, phenoxyphenyl or especially heptadecyl; R^3 is acetyl or especially formyl; R^4 is methyl or especially hydrogen and R^5 is hydrogen, methyl, 2-butyl, benzyl, methylthio-ethyl or especially i-butyl, or R^4 and R^5 together form a pyrrolidinyl residue.

Examples of such compounds are:

N-Formyl-L-leucine 1-[(trans-3-ethyl-4-oxo-2--oxetanyl)methyl]dodecyl ester

N-formyl-L-leucine 1-[(trans-3-allyl-4-oxo-2--oxetanyl)methyl]dodecyl ester

N-formyl-(S)-leucine (S,9Z,12Z)-1-[(2S,3S)-3-ethyl-4--oxo-2-oxetanyl]methyl]-9,12 -octadecadienyl ester

N-formyl-(S)-leucine (S,Z)-1-[[(2S,3S)-3-ethyl-4-oxo--2-oxetanyl]methyl]-9 -octadecenyl ester and

N-formyl-(S)-leucine (R)-α-[[(2S,3S)-3-ethyl-4-oxo--2-oxetanyl]methyl]-p -phenoxybenzyl ester.

N-Formyl-(S)-leucine (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2--oxetanyl]methyl]octadecyl ester is especially preferred.

The oxetanones of formulae I and III have valuable pharmacological properties. In particular, they inhibit pancreas lipase and can accordingly be used in the control or prevention of obesity, hyperlipaemia, athersclerosis or arteriosclerosis

The inhibition of pancreas lipase by the oxetanones of formulae I and III can be demonstrated experimentally by registering titrimetrically the oleic acid liberated in the cleavage of triolein by pig pancreas lipase. To an emulsion which contains 1 mM of taurodeoxycholate, 9 mM of taurocholeate, 0.1 mM of cholesterol, 1 mM of egg lecithin, 15 mg/ml of BSA, 2 mM of Tris HCl, 100 mM of sodium chloride, 1 mM of calcium chloride and triolein as the substrate is added the compound of formula I dissolved in ethanol or dimethyl sulphoxide (10% of the emulsion volume) and the reaction is started by the addition of

100 µg (175 U) of pig pancreas lipase. The pH is held at 8 during the reaction by the addition of sodium hydroxide solution. The IC_{50} is calculated from the consumption of sodium hydroxide solution determined during 10 minutes. The IC_{50} is that concentration at which the lipase activity is inhibited to half of the maximum. The following Table contains the IC_{50} values determined for the compounds of formula I and data concerning the acute toxcity (toxcity after single oral administration to mice).

Table

Test compound in:	IC_{50} in µg/ml	Toxcity in mg/kg p.o.
Example 1b)	19	
Example 2, 13)a)	0.007	
Example 2, 14)	0.015	5000
Example 2, 21)	0.02	
Example 2, 23)a)	0.035	2000
Example 2, 25)a)	0.01	
Example 2, 34)	0.13	4000
Example 4, 1)	0.011	
Example 5	0.20	
Example 6, 2)	1.0	
Example 7	15	
Example 9 F.2.	85	

The oxetanones of formulae I and III can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelatine capsules, solutions, emulsions or suspensions.

For the manufacture of pharmaceutical preparations the products in accordance with the invention can be processed with pharmaceutically inert, inorganic or organic carriers. As such carriers there can be used for tablets, coated tablets, dragees and hard gelatine capsules, for example, lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, generally required in the case of soft gelatine capsules. Suitable carriers for the manufacture of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose and the like.

Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, colouring agents, flavouring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing an oxetanone of formula I or III are likewise an object of the present invention as is a process for the manufacture of such medicaments, which process comprises bringing an oxetanone of formula I or III and, if desired, one or more other therapeutically valuble substances into a galenical administration form. As mentioned, the compounds of formula I can be used in the control or prevention of illnesses, especially in the control or prevention of obesity, hyperlipaemia, atherosclerosis and arteriosclerosis. The dosage can vary within wide limits and is, of course, fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 100 mg/kg body weight should be appropriate.

The oxetanones of formula I or III can also be added to industrially-produced foodstuffs, whereby fats, oils, butter, margarine, chocolate and other confectionery goods especially come into consideration. Such industrially-produced foodstuffs, which can contain about 0.1 to 5 wt% of an oxetanone of formula I or III, and their manufacture are likewise objects of the present invention.

The following Examples are intended to illustrate the present invention in more detail, but they are not intended to limit its extent in any manner. All temperatures are given in degrees Celsius.

Example 1

44.3 ml of diethyl azodicarboxylate are added dropwise while stirring to a solution of 100 mg of rac-3-hexyl-4-(2-hydroxytridecyl)-2 -oxetanone(2R,3S,4S:2S,3R,4R), 74 mg of triphenylphosphine and 45 mg of N-formyl-D-leucine in 2 ml of THF. After stirring overnight the organic phase is evaporated in vacuo and the residue is purified by chromatography on silica gel with toluene-ethyl acetate (9:1). There are obtained

1.a) N-formyl-D-leucine (R)-1-[[(2R,3R)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester and

1.b) N-formyl-D-leucine (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester.

Example 2

Analogously to Example 1,

2.1) by esterifying rac-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone(2R,3R,4R:2S,3S,4S) with N-formyl-D-leucine there are obtained

2.1)a) N-formyl-D-leucine (S)-1-[[(2R,3R)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester and

2.1)b) N-formyl-D-leucine (R)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester;

2.2) by esterifying rac-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone(2S,3R,4R:2R,3S,4S) with N-formyl-L-leucine there is obtained

N-formyl-L-leucine (R)-1-[[(2R,3R)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester, $[\alpha]_D^{25}$ = -2.2° (methanol, c = 0.9%);

2.3) by esterifying rac-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone(2S,3S,4S:2R,3R,4R) or (3R,4R)-3-hexyl-4-[(R)-2-hydroxytridecyl]-2-oxetanone with N-formyl-L-leucine there are obtained

2.3)a) N-formyl-L-leucine (R)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester, $[\alpha]_D^{25}$ = -19.4° (methanol, c = 0.35%), and

2.3)b) N-formyl-L-leucine (S)-1-[[(2R,3R)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester, $[\alpha]_D^{25}$ = -2.87° (methanol, c = 0.8%);

2.4) by esterifying rac-cis-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone (enantiomer pair A) with N-formyl-L-leucine there are obtained

2.4)a) N-formyl-L-leucine 1-[(cis-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel; toluene-ethyl acetate 2:1, Rf = 0.55, and

2.4)b) N-formyl-L-leucine 1-[(cis-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel; toluene-ethyl acetate 2:1, Rf = 0.47;

2.5) by esterifying rac-cis-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone (enantiomer pair B) with N-formyl-L-leucine there are obtained

2.5)a) N-formyl-L-leucine 1-[(cis-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel; toluene-ethyl acetate 2:1, Rf = 0.53, and

2.5)b) N-formyl-L-leucine 1-[(cis-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel; toluene-ethyl acetate 2:1, Rf = 0.50;

2.6) by esterifying (3S,4S)-3-hexyl-4-[(R)-2-hydroxytridecyl]-2-oxetanone with N-formylglycine there is obtained

N-formylglycine (S)-1-(2S,3S)-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, $[\alpha]_D^{25} = -22°$ ($CHCl_3$, c = 0.88);

2.7) by esterifying trans-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone with N-formylglycine there is obtained

N-formylglycine 1-[(trans-3-hexyl-4-oxo-2-oxetanyl)-methyl]dodecyl ester, D.C. silica gel, diethyl ether-hexane 9:1, Rf = 0.34;

2.8) by esterifying rac-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone(2R,3S,4S:2S,3R,4R) with N-acetyl-L-leucine there is obtained

N-acetyl-L-leucine 1-[(trans-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel; $CHCl_3$: hexane:dioxan 1:3:0.25, Rf = 0.36;

2.9) by esterifying (3S,4S)-3-hexyl-4-[(R)-2-hydroxytridecyl]-2-oxetanone with N-formyl-ß-alanine there is obtained

N-formyl-ß-alanine (S)-1-(2S,3S)-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel; toluene-ethyl acetate 2:1, Rf = 0.39;

2.10) by esterifying trans-3-hexyl-[(S)-2-hydroxypropyl]-2-oxetanone(3S,4S:3R,4R) with N-formyl-L-leucine there is obtained

N-formyl-L-leucine (S)-1-[(3-hexyl-4-oxo-2-oxetanyl)-methyl] ester, D.C. silica gel, toluene-ethyl acetate 2:1, Rf = 0.27;

2.11) by esterifying 3-methyl-4-[(R)-2-hydroxytridecyl]-2-oxetanone(3R,4R:3S,4S) with N-formyl-L-leucine there is obtained

N-formyl-L-leucine (S)-1-[(3-methyl-4-oxo-2-oxetanyl)-methyl]dodecyl ester, D.C. silica gel, toluene-ethyl acetate 2:1, Rf = 0.34;

2.12) by esterifying rac-trans-3-hexadecyl-4-(2-hydroxypropyl)-2-oxetanone with N-formyl-L-leucine there is obtained

N-formyl-L-leucine 1-[(trans-3-hexadecyl-4-oxo-2-oxetanyl)methyl]ethyl ester, M.S.: 496 (M^+; D.C. silica gel, toluene-ethyl acetate 2:1, Rf = 0.44;

2.13) by esterifying rac-trans-3-ethyl-4-(2-hydroxytridecyl)-2-oxetanone with N-formyl-L-leucine there are obtained

2.13)a) N-formyl-L-leucine 1-[(trans-3-ethyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel, toluene-ethyl acetate 2:1, Rf = 0.62, and

2.13)b) N-formyl-L-leucine 1-[(trans-3-ethyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, D.C. silica gel, toluene-ethyl acetate 2:1, Rf = 0.55;

2.14) by esterifying rac-trans-3-allyl-4-(2-hydroxytridecyl)-2-oxetanone with N-formyl-leucine there is obtained

N-formyl-L-leucine 1-[(trans-3-allyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, I.R.: 1825, 1739, 1688; D.C. silica gel, toluene-ethyl acetate 2:1. Rf = 0.58;

2.15) by esterifying rac-trans-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone with N-benzylcarbamoyl-leucine there is obtained

N-benzylcarbamoyl-leucine 1-[(trans-3-hexyl-4-oxo-2--oxetanyl)methyl]dodecyl ester, D.C. silica gel, hexane--diethyl ether 1:1, Rf = 0.64;

2.16) by esterifying (3S,4S)-3-hexyl-4-[(R,10Z,13Z)-2--hydroxy-10,13-nonadecadienyl)-2-oxetanone with formyl--(S)-leucine there is obtained

N-formyl-(S)-leucine(S,9Z,12Z)-1-[[(2S,3S)-3-hexyl-4--oxo-2-oxetanyl]methyl]-9,12-octadienyl ester, M.S.: 575 (M^+); I.R.: 1824, 1739, 1675 cm^{-1};

2.17) by esterifying rac-trans-3-hexyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone(2R,3R,4R:2S,3S,4S) with N-formyl-(S)-leucine there is obtained

N-formyl-(S)-leucine (9Z,12Z)-1-(trans-3-hexyl)-4-oxo-2-oxetanyl)methyl]octadecadienyl ester (2 diastereomers), M.S.: 575 (M^+): I.R.: 1824, 1740, 1687 cm^{-1};

2.18) by esterifying cis-3-hexyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone (diastereomer mixture) with N-formyl-(S)-leucine there are obtained

2.18)a) N-formyl-(S)-leucine (9Z,12Z)-1-[(cis-3-hexyl-4-oxo-2-oxetanyl)methyl]-9,12-octadienyl ester (diastereomer mixture I), M.S.: 575 (M^+); I.R.: 1823, 1739, 1674 cm^{-1}, and

2.18)b) N-formyl-(S)-leucine (9Z,12Z)-1-[(cis-3-hexyl-4-oxo-2-oxetanyl)methyl]-9,12-octadienyl ester (diastereomer mixture II), M.S.: 372 (M^+-N-formyl-leucine-CO_2); I.R.: 1822, 1739, 1684 cm^{-1};

2.19) by esterifying (3S,4S)-3-benzyl-4-[(R,10Z,13Z)-2-hydroxy-10,13-nonadecadienyl)]-2-oxetanone with N-formyl-(S)-leucine there is obtained

N-formyl-(S)-leucine (S,9Z,12Z)-1-[[(2S,3S)-3-benzyl-4-oxo-2-oxetanyl]methyl]-9,12-octadienyl ester, M.S.: 581 (M^+); I.R.: 1825, 1739, 1683 cm^{-1};

2.20) by esterifying rac-trans-3-benzyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone(2R,3R,4S:2S,3S,4S) with N-formyl-(S)-leucine there are obtained

2.20)a) N-formyl-(S)-leucine (9Z,12Z)-1-[(trans-3-benzyl-4-oxo-2-oxetanyl)methyl]-9,12-octadecadienyl ester (diastereomer I), M.S.: 581 (M^+); I.R.: 1825, 1739, 1676 cm^{-1}, and

2.20)b) N-formyl-(S)-leucine (9Z,12Z)-1-[(trans-3-benzyl-4-oxo-2-oxetanyl)methyl]-9,12-octadecadienyl ester (diastereomer II), M.S.: 581 (M^{+}); I.R.: 1824, 1740, 1687 cm^{-1};

2.21) by esterifying trans-3-ethyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone (diastereomer mixture) with N-formyl-(S)-leucine there is obtained

N-formyl-(S)-leucine (S,9Z,12Z)-1-[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-9,12-octadecadienyl ester, M.S.: 519 (M^{+}); I.R.: 1825, 1739, 1684 cm^{-1};

2.22) by esterifying cis-3-ethyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone with N-formyl-(S)-leucine (enantiomer mixture B) there is obtained

N-formyl-(S)-leucine (9Z,12Z)-1-[[cis-3-ethyl-4-oxo-2-oxetanyl]methyl]-9,12-octadecadienyl ester (diastereomer mixture), M.S.: 316 (M^{+}-N-formyl-leucine-CO$_2$); I.R.: 1825, 1739, 1677 cm^{-1};

2.23) by esterifying (3S,4S)-3-ethyl-4-[(R,Z)-2-hydroxy-10-nonadecenyl]-2-oxetanone with N-formyl-S-leucine there are obtained

2.23)a) N-formyl-(S)-leucine (S,Z)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-9-octadecenyl ester (diasteromer I), M.S.: 521 (M^{+}); I.R.: 1825, 1739, 1673 cm^{-1}, and

2.23)b) N-formyl-(S)-leucine (Z)-1-[(trans-3-ethyl-4-oxo-2-oxetanyl)methyl]-9-octadecenyl ester;

2.24) by esterifying (3S,4S)-3-hexyl-4-[(S)-β-hydroxy-p-

-phenoxyphenethyl]-2-oxetanone with N-formyl-(S)-leucine there is obtained

N-formyl-(S)-leucine α-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-p-phenoxybenzyl ester (diastereomer mixture), M.S.: 509 (M^+); I.R.: 1821, 1742, 1686 cm^{-1};

2.25) by esterifying (3S,4S)-3-ethyl-4-[(S)-ß-hydroxy-p-phenoxyphenethyl]-2-oxetanone with N-formyl-(S)-leucine there are obtained

2.25)a) N-formyl-(S)-leucine (R)-α-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-p-phenoxybenzyl ester, M.S.: 453 (M^+); I.R.: 1824, 1742, 1686 cm^{-1}, and

2.25)b) N-formyl-(S)-leucine (S)-α-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-p-phenoxybenzyl ester, M.S.: 453 (M^+); I.R.: 1823, 1743, 1686 cm^{-1};

2.26) by esterifying rac-trans-3-hexyl-4-(2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-L-leucine there is obtained

N-formyl-L-leucine 1-[(trans-3-hexyl-4-oxo-2-oxetanyl)methyl]-4-pentenyl ester (mixture of 2 diastereomers);

2.27) by esterifying (S)-3-hexyl-(S)-4-[(R)-2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-L-leucine there is obtained

N-formyl-L-leucine (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-4-pentenyl ester;

2.28) by esterifying (S)-3-hexyl-(S)-4-[(R)-2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-(S)-valine there is obtained

N-formyl-(S)-valine 1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-4-pentenyl ester;

2.29) by esterifying (S)-3-hexyl-(S)-4-[(R)-2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-L-isoleucine there is obtained

N-formyl-L-isoleucine (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-4-pentenyl ester;

2.30) by esterifying (S)-3-hexyl-(S)-4-[(R)-2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-L-phenylalanine there is obtained

N-formyl-phenylalanine (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl)methyl[-4-pentenyl ester;

2.31) by esterifying (S)-3-hexyl-(S)-4-[(R)-2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-L-alanine there is obtained

N-formyl-L-alanine (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl)-4-pentenyl ester;

2.32) by etherifying (S)-3-hexyl-(S)-4-[(R)-2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-L-proline there is obtained

N-formyl-L-proline (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl)methyl]-4-pentenyl ester;

2.33) by esterifying (S)-3-hexyl-(S)-4-[(R,Z)-2-hydroxy-5-tridecenyl)-2-oxetanone with N-formyl-L-leucine there is obtained

N-formyl-L-leucine (S,Z)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-4-dodecenyl ester;

2.34) by esterifying (S)-3-decyl-(S)-4-[(R)-2-hydroxy-5-hexenyl)-2-oxetanone with N-formyl-L-leucine there is obtained

N-formyl-L-leucine (S)-1-[[(2S,3S)-3-decyl-4-oxo-2-oxetanyl]methyl]-4-pentenyl ester;

2.35) by esterifying (S)-3-hexyl-(S)-4-[(R)-2-hydroxy-5-hexenyl]-2-oxetanone with N-formyl-L-methionine there is obtained

N-formyl-L-methionine (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl)methyl]-4-pentenyl ester;

2.36) by esterifying 3-ethyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl)-2-oxetanone with N-formyl-N-methyl-L-leucine there is obtained

N-formyl-N-methyl-L-leucine (9Z,12Z)-1-[(3-ethyl-4-oxo-2-oxetanyl)methyl]-9,12-octadienyl ester.

Example 3

A solution of 27 mg of N-formyl-(S)-leucine (S,9Z,12Z)-1-[(2S,3S)-3-hexyl-4-oxo-2 -oxetanyl]methyl]-9,12-octadienyl ester in 1 ml of THF are added to 4.4 mg of 10% Pd/C. The mixture is hydrogenated at room temperature until the reaction has finished. The catalyst is filtered off and the solvent is removed in vacuo. After drying in vacuo there is obtained N-formyl-(S)-leucine (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyloctadecyl ester as white crystals, m.p. 64-65°C.

Example 4

Analogously to Example 3,

4.1) from N-formyl-(S)-leucine (S,9Z,12Z)-1-[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-9,12-octadecadienyl ester there is obtained

N-formyl-(S)-leucine (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester as white crystals, m.p. 48-53°C;

Claim 9

4.2) from N-formyl-L-leucine 1-[(trans-3-allyl-4-oxo-2-oxetanyl]methyl]dodecyl ester there is obtained

N-formyl-L-leucine 1-[(trans-3-propyl-4-oxo-2-oxetanyl]methyl]dodecyl ester.

Example 5

A solution of 10 mg of N-formyl-L-leucine 1-[(trans-3-hexyl-4-oxo-2-oxetanyl)methyl]-4-pentenyl ester in 0.5 ml of THF is treated with 2.5 mg of 5% Pd/C and hydrogenated. After the hydrogen uptake has finished the catalyst is filtered off and the filtrate is evaporated in vacuo. The residue is chromatographed over silica gel with toluene/ethyl acetate (8:2) and there is obtained amorphous N-formyl-L-leucine 1-[(trans-3-hexyl-4-oxo-2-oxetanyl]methyl]pentyl ester as a mixture of 2 diastereomers.

Example 6

Analogously to Example 5,

6.1) from N-formyl-L-alanine (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-4-pentenyl ester there is obtained

N-formyl-L-alanine (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]pentenyl ester;

6.2) from N-formyl-L-phenylalanine (S)-1-[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-4-pentyl ester there is obtained

N-formyl-L-phenylalanine (S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]-4-pentyl ester;

6.3) from N-formyl-L-leucine (S)-1-[[(2S,3S)-3-decyl-4-oxo-2-oxetanyl]methyl]-4-pentenyl ester there is obtained

N-formyl-L-leucine (S)-1-[[(2S,3S)-3-decyl-4-oxo-2-oxetanyl]methyl]pentyl ester.

Example 7

A solution of 67 mg of N-benzylcarbamoyl-leucine 1-[(trans-3-hexyl-4-oxo-2-oxetanyl)methyldodecyl ester in 15 ml of THF is hydrogenated in the presence of 10% Pd/C at room temperature under a H_2 atmosphere (normal pressure) until the reaction has finished. The product obtained after filtration and evaporation is chromatographed on silica gel. There is obtained pure leucine 1-[(trans-3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester m.p. 27-30°C.

Example 8

265 mg of a diastereomer mixture of 3-hexyl-4-[(10Z,13Z)-2-[tetrahydro-2H-pyran -2-yl)oxy]-10,13-nonadecadienyl]-2-oxetanone are dissolved in 2.5 ml of ethanol and 13 mg of pyridinium-4-toluenesulphonate are added. The reaction mixture is heated to 55-60°C until the reaction has finished. The solvent is removed in vacuo and the residue is taken up in ether, whereby there separate

crystals which are removed by filtration. The solvent is evaporated off in vacuo and the residue is chromatographed on silica gel, whereby the products listed below are eluted in the sequence given. The products, which are to some extent still impure, can be purified by repeating the chromatography. In this manner there are obtained:

8.1) ((3S,4S)-4-Hexyl-4-[(R,10Z,13Z) -2-hydroxy-10,13--nonadecadienyl]-2-oxetanone (diastereomer I) as a colourless oil, MS: M^+ (434); IR: 3420, 1820, 1120 cm^{-1},

8.2) rac-trans-3-hexyl-4-[(10Z,13Z) -2-hydroxy-10,13-nonadecadienyl]-2-oxetanone (diastereomer II) as a colourless oil, MS: M^+ (434); IR: 3448, 1820, 1122 cm^{-1} and

8.3) cis-3-hexyl-4-[(10Z,13Z) -2-hydroxy-10,13-nonadecadienyl]-2-oxetanone (diastereomer III) as a colourless oil, MS: M^+ (434): IR: 3374, 1822, 1117 cm^{-1}.

Example 9

Analogously to Example 8,

9.A.1) trans-3-ethyl-4-[(10Z,13Z) -2-hydroxy-10,13-nonadecadienyl]-2-oxetanone, MS: 360 (M^+-H_2O), 334 (M^+-CO_2), 316 (M^+-H_2O-W_2), IR: 3446, 1823, 1122 cm^{-1},

9.A.2) cis-3-ethyl-4-[(10Z,13Z) -2-hydroxy-10,13-nonadecadienyl]-2-oxetanone (enantiomer mixture A), MS: 378/M^+): IR: 3445, 1822, 1116 cm^{-1} and

9.A.3) cis-3-ethyl-4-[(10Z,13Z) -2-hydroxy-10,13-nonadecadienyl]-2-oxetanone (enantiomer mixture B), MS: (chemical induction with NH_3): 396 (M + NH_4^+, 374 (M + H^+): IR: 3415, 1823, 1115 cm^{-1}, were obtained from a cis, trans mixture of 3-ethyl-4-[(R,10Z,13Z)-2-[tetrahydro-2H-pyran-2-yl)oxy]-10,13-nonadecadienyl]-2-oxetanone;

9.B. 3-ethyl-4-[(Z)-2-hydroxy-10-nonadecenyl]-2-oxetanone, MS: 362 (M^+-H_2O), 318 (M^+-H_2O-$1O_2$); IR: 3435, 1823, 1119 cm^{-1}, was obtained

from 3-ethyl-4-[(Z)-2-[(tetrahydro-2H-pyran-2-yl)-oxy]-10-nonadecenyl-2-oxetanone;

9.C.1) (3S,4S)-3-benzyl-4-[(R,10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone, MS: 440 (M^+); IR: 3430, 1822, 1120 cm^{-1},

9.C.2). rac-trans-3-benzyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone, MS: 440 (M^+); IR: 3512, 1822, 1123 cm^{-1} and

9.C.3) cis-3-benzyl-4-[(10Z,13Z)-2-hydroxy-10,13-nonadecadienyl]-2-oxetanone (2 diastereomers), MS: 378 (M^+-CO_2-H_2O), 287 (M^+-H_2O-CO_2-benzyl); IR: 3420, 1822, 1134 cm^{-1}, were obtained

from a diastereomer mixture of 3-benzyl-4-[(R,10Z,13Z)-2-[tetrahydro-2H-pyran-2-yl)oxy]-10,13-nonadecadienyl]-2-oxetanone;

9.D. (3S,4S)-3-hexyl-4-[(S)-ß-hydroxy-p-phenoxyphenethyl]-2-oxetanone, m.p. 51-54°C, MS: 368 (M^+); IR: 3486, 1793, 1245, 1141, was obtained

from (3S,4S)-3-hexyl-4-[(S)-p-phenoxy-ß-[(tetrahydro-2H-pyran-2-yl)oxy]phenethyl]-2-oxetanone;

9.E. (3S,4S)-3-ethyl-4-[(S)-ß-hydroxy-p-phenoxyphenethyl]-2-oxetanone, m.p. 67-70°C, MS: 312 (M^+); IR: 3416, 1835, 1250, 1108, was obtained

from (3S,4S)-3-ethyl-4-[(S)-p-phenoxy-β-[(tetrahydro-2H-pyran -2-yl)oxy]phenethyl]-2-oxetanone.

9.F.1. rac-trans-3-hexyl-4-(2-hydroxytridecyl) -2-oxetanone(2R,3S,4S:2S,3R,4R), m.p. 44.5-46°,

9.F.2. rac-trans-3-hexyl-4-(2-hydroxytridecyl) -2-oxetanone(2S,3S,4S:2R,3R,4R), m.p. 45.5-47°C,

9.F.3. rac-cis-3-hexyl-4-(2-hydroxytridecyl) -2-oxetanone (enantiomer pair A), D.C. silica gel, hexane-ethyl acetate 9:1, Rf = 0.49, and

9.F.4. rac-cis-3-hexyl-4-(2-hydroxytridecyl) -2-oxetanone (enantiomer pair B), D.C. silica gel, hexane-ethyl acetate 9:1, Rf = 0.46, were obtained

from 3-hexyl-4-[2-[(tetrahydro -2H-pyran-2-yl)oxy]tridecyl]-2-oxetanone;

9.G.1. (3S,4S)-3-hexyl-4-[(R)-2-hydroxytridecyl] -2-oxetanone, m.p. 46-46.5°C, and

9.G.2. (3R,4R)-3-hexyl-4-[(R)-2-hydroxytridecyl] -2-oxetanone, m.p. 46-47°; $[\alpha]_D^{20}$ = +12°C ($CHCl_3$, c = 1.5), were obtained

from 3-hexyl-4-[(R)-2-[(tetrahydro-2H-pyran -2-yl)-oxy]tridecyl]-2-oxetanone;

9.H. rac-trans-3-ethyl-4-(2-hydroxytridecyl) -2-oxetanone, m.p. 35.5-36°C, was obtained from 3-ethyl-4-[2-[(tetrahydro-2H-pyran -2-yl]oxy]tridecyl]-2-oxetanone;

9.I. trans-3-methyl-4-[(R)-2-hydroxytridecyl]-2-oxetanone, D.C. silica gel, hexane-ether 1:3, Rf = 0.49, was obtained

from 3-methyl-4-[(R)-2-[(tetrahydro -2H-pyran-2--yl]oxy]tridecyl]-2-oxetanone;

9.J. rac-trans-3-allyl -4-[2-hydroxytridecyl]-2-oxetanone, D.C. silica gel, hexane-ethyl 1:1, Rf = 0.39, was obtained

from 3-allyl-4-[2-(tetrahydro -2H-pyran-2-yl]oxy]tridecyl]-2-oxetanone;

9.K. trans-3-hexyl-4-[(R) -2-hydroxypropyl]-2-oxetanone, D.C. silica gel, hexane-ether 1:3, Rf = 0.36, was obtzined

from 3-hexyl-4-[(R)-2-[(tetrahydro -2H-pyran-2-yl]-oxy]propyl]-2-oxetanone;

9.L. rac-trans-3-hexadecyl -4-(2-hydroxypropyl)-2-oxetanone, m.p. 37-38°C, was obtained

from 3-hexadecyl-4-[2-[(tetrahydro -2H-pyran-2-yl]-oxy]propyl]-2-oxetanone;

9.M. rac-trans-3-hexyl -4-[-2-hydroxy-5-hexenyl]-2--oxetanone(2R,3S,4S:2S,3R,4R) was obtained

from trans-3-hexyl-4-[-2-[(tetrahydro -2H-pyran-2-yl)-oxy]-5-hexenyl]-2-oxetanone;

9.N. trans-3-decyl-4-[(R) -2-hydroxy-5-hexenyl-2-oxetanone was obtained from trans-3-decyl-4-[(R)-2-[(tetrahydro -2H-pyran-2--yl)oxy]hexenyl]-2-oxetanone;

9.O. trans-3-hexyl-4-((R) -2-hydroxy-5-tridecenyl)-2--oxetanone was obtained

from trans-3-hexyl-4-[(R)-2-[(tetrahydro -2H-pyran-2--yl]oxy]tridecenyl-2-oxetanone;

9.P. (S)-3-hexyl-(S)-4[(R) -2-hydroxy-5-hexenyl]-2--oxetanone was obtained

from 3-hexyl-4-[[(R)-2-[(tetrahydro-2H-pyran -2-yl)-oxy]hexenyl]-2-oxetanone;

9.Q. trans-3-hexyl-4-(2-hydroxytridecyl)-2-oxetanone (diastereomer mixture) was obtained

from 3-hexyl-4-[2-[tetrahydro-2H-pyran -2-yl)oxy]tridecyl]-2-oxetanone.

Example 10

10.A. Manufacture of the product

565 mg of N-[(benzyloxy)carbonyl]-L-leucine (S)-1--[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester are dissolved in 12 ml of THF. The mixture is hydrogenated at room temperature in the presence of 40 mg of 10% Pd/C. After the reaction has finished the catalyst is filtered off and the filtrate is evaporated. The residue is taken up in 9 ml of THF and 71 µl of formic acid/acetic acid anhydride are added dropwise. The mixture is diluted with 5 ml of diethyl ether and washed twice with 2% sodium hydrogen carbonate solution and then with water. After drying over sodium sulphate it is filtered and evaporated.

By chromatography on silica gel and recrystallization from n-pentane there is obtained N-formyl-(S)-leucine (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester of m.p. 60-61°C.

10.B. <u>Preparation of the starting material</u>

10.B.a) As described in paragraph 10.B.e) hereinafter, a diastereomer mixture which consists to 85-90% of (R)-2-hydroxy-1,2,2-triphenylethyl (S,Z)-3-hydroxy-11-eicosenoate, m.p. 112-114°C, is obtained

from oleyl aldehyde and (R)-α-(hydroxydiphenylmethyl)benzyl acetate.

10.B.b) As described in paragraph 10.B.f) hereinafter, methyl (S,Z)-3-hydroxy-11-eicosenoate is obtained as a colourless oil

from (R)-2-hydroxy-1,2,2-triphenylethyl (S,Z)-3-hydroxy-11-eicosenoate.

10.B.c) As described in paragraph J)a) above for the preparation of the esters of formula XV, methyl (S,Z)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-11-eicosenoate, which contains 10-15% of the (R)-isomer, is obtained

from methyl (S,Z)-3-hydroxy-11-eicosenoate.

10.B.d) As described in paragraph I)a) above for the preparation of the aldehydes of formula VIII, (S,Z)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-11-eicosenal, which contains 10-15% of the corresponding (R)-isomer, is obtained

from methyl (S,Z)-3-[(tetrahydro-2H-pyran-2-yl)oxy]-

-11-eicosenoate.

10.B.e) 7.7 g of (R)-α-(hydroxydiphenylmethyl)benzyl acetate are suspended in 75 ml of THF under argon and cooled to about -75°C. This suspension is treated dropwise with a two-fold amount of a lithium diisopropylamide solution. The mixture is left to warm to 0°C and stirred at this temperature for 10 minutes. The solution is then cooled to -113 to -117°C and treated during the cooling with 230 ml of diethyl ether. A solution of (S,Z)-3--[(tetrahydro-2H-pyran-2-yl)oxy]-11-eicosenal in 20 ml of diethyl ether is added dropwise to the solution and the mixture is stirred for a further 30 minutes. The mixture is treated dropwise with 20 ml of saturated ammonium chloride solution. The mixture is left to warm to room temperature. The aqueous phase is separated and the organic phase is washed three times with 80 ml of water and once with saturated sodium chloride solution. After two-fold washing with 100 ml of saturated ammonium chloride solution the organic phase is dried over sodium sulphate, filtered and evaporated. By repeated recrystallization from methanol there is obtained a diastereomer mixture which consists mainly of (R)-2--hydroxy-1,2,2-triphenylethyl (3S,5S,13Z)-3-hydroxy-5--[(tetrahydro-2H-pyran-2-yl)- oxy]-13-docosenoate, m.p. 91-93°C.

10.B.f) 12.75 g of (R)-2-hydroxy-1,2,2-triphenylethyl (3S,5S,13Z)-3-hydroxy-5 -[(tetrahydro-2H-pyran-2-yl)oxy]--13-docosenoate are suspended in 130 ml of methanol and treated with 17.5 ml of 1N methanolic sodium methylate solution. After the reaction has finished the mixture is poured into 650 ml of saturated ammonium chloride solution and extracted several times with diethyl ether. After drying over sodium sulphate the organic phase is filtered and evaporated, the residue is taken up in 70 ml of n-hexane and stirred for 1 hour while cooling in an ice-

-bath. The white crystals are filtered off under suction and washed with n-hexane. The filtrate is evaporated and the residue is chromatographed on silica gel. There is obtained a diastereomer mixture which consists chiefly of methyl (3S,5S,13Z)-3-hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]-13-docosenoate, IR: 3473, 1739, 1076, 1024 cm^{-1}.

10.B.g) As described in paragraph D)a) above for the preparation of the esters of formula VI, a diastereomer mixture, which contains chiefly methyl (2S,3S,5S,13Z)-2-ethyl-3-hydroxy-5 -[(tetrahydro-2H-pyran-2-yl)oxy]-13-docosenoate, is obtained as a colourless oil

from methyl (3S,5S,13Z)-3-hydroxy-5 -[(tetrahydro-2H-pyran-2-yl)oxy]-13-docosenoate and ethyl iodide.

10.B.h) In analogy to Example 3 above, a diastereomer mixture, which contains chiefly methyl (2S,3S,5S)-2-ethyl-3-hydroxy-5-[(tetrahydro-2H-pyran-2 -yl)oxy]docosanoate, IR: 1738, 1199, 1167, 1132, 1115, 1176, 1023 cm^{-1}, is obtained

from a diastereomer mixture which consists chiefly of methyl (2S,3S,5S,13Z)-2-ethyl-3-hydroxy-5 -[(tetrahydro-2H-pyran-2-yl)oxy]-13-docosenoate.

10.B.i) 0.12 g of a diastereomer mixture, which consists chiefly of methyl (2S,3S,5S)-2-ethyl-3-hydroxy-5-[(tetrahydro-2H-pyran-2 -yl)oxy]docosanoate, is stirred at room temperature in 2.5 ml of 2N methanolic potassium hydroxide solution until the reaction has finished. The turbid solution is poured into 10 ml of water and adjusted to pH 2 with 2N hydrochloric acid. After extraction with diethyl ether the extract is dried over sodium sulphate, filtered and evaporated. Chromatography on silica gel gives a diastereomer mixture which consists chiefly of (2S,3S,5S)-2-

-ethyl-3-hydroxy-5-[(tetrahydro-2H-pyran-2 -yl)oxy]docosanoic acid as a colourless oil, IR: 1709 cm^{-1}.

10.B.j) As described in paragraph A.a) above for the preparation of the ethers of formula IV, (3S,4S)-3-ethyl-4--[(S)-2-[(tetrahydro-2H-pyran-2 -yl)oxy]nonadecyl]-2-oxetanone is obtained as the main component of a diasteromer mixture as a colourless oil, IR: 1826 cm^{-1},

from a diastereomer mixture which consists chiefly of (2S,3S,5S)-2-ethyl-3-hydroxy-5 -[(tetrahydro-2H-pyran-2--yl)oxy]docosanoic acid.

10.B.k) In analogy to Example 8, (3S,4S)-3-ethyl-4-[(S)--2-hydroxynonadecyl]-2-oxetanone, m.p. 82-84°C (MeOH), is obtained

from (3S,4S)-3-ethyl-4-[(S)-2-[(tetrahydro -2H-pyran--2-yl)oxy]nonadecyl]-2-oxetanone.

10.B.l) 796 mg of N-[(benzyloxy)carbonyl]-L-leucine are dissolved in 10 ml of methylene chloride, the solution is cooled to 2-3°C and 309 mg of dicyclohexylcarbodiimide are added. After 15 minutes the white crystals are filtered off under suction and washed with methylene chloride. The filtrate is evaporated at RT in vacuo and the residue is dissolved in 7 ml of N,N-dimethylformamide (DMF). This solution is added to 574 mg of (3S,4S)-3-ethyl-4-[(S)-2--hydroxynonadecyl]-2-oxetanone and 22 mg of 4-dimethylamino-pyridine in 6 ml of DMF. The mixture is stirred for 30 minutes. The mixture is poured on to 100 ml of ice--water and extracted three times with 20 ml of diethyl ether. The combined organic phases are dried over sodium sulphate, filtered and evaporated. After chromatography on silica gel there is obtained N-[(benzyloxy)carbonyl]-L--leucine (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-

octadecyl ester as white crystals of m.p. 44-47°C.

Example A

Manufacture of soft gelatine capsules of the following composition:

	Amount per capsule
An oxetanone of formula I or III	50 mg
NEOBEE M-5	450 µl

The solution of the active substance in NEOBEE M-5 is filled into soft gelatine capsules of suitable size.

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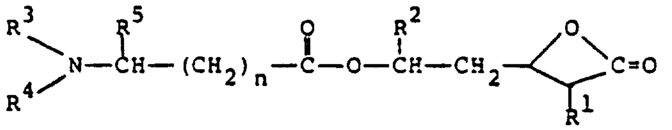
Patent Claims

"1. Oxetanones of the formula



I

$$R^3R^4N-\overset{R^5}{CH}-(CH_2)_n-\overset{O}{\overset{\|}{C}}-O-\overset{R^2}{CH}-CH_2-\text{(oxetan-2-one ring bearing } R^1\text{)}$$

wherein

R^1 and R^2 are C_{1-17} alkyl optionally interrupted by up to 8 double or triple bonds and optionally interrupted by a O or S atom which is present in a position other than the α-position to an unsaturated C-atom; or phenyl, benzyl or C_6H_4-O-C_6H_5 ring-substituted by 0 to 3 C_{1-6} alkyl - (O or S)$_{1 \text{ or } 0}$.

R^3 is hydrogen, or C_{1-3}-alkanoyl,

R^4 is hydrogen or C_{1-3}-alkyl, and

R^5 is hydrogen, phenyl, or phenyl C_{1-3}-alkyl or C_{1-7}-alkyl optionally interrupted by S or

R^4 forms with R^5 a C_{2-4}-alkylene chain;

n is the number 1 or 0, with the proviso that R^5 is hydrogen when n is the number 1, with the proviso that R^4 has a significance other than hydrogen when R^3 is formyl and R^5 is isobutyl or R^3 is acetyl and R^5 is carbamoylmethyl and R^2 is undecyl or 2,5-undecadienyl, and R^1 is n-hexyl, and salts of these oxetanones with weak acids."

W

R

X

R^3

R^4

R^5

~~C_{1-7}-alkyl optionally interrupted by Y and optionally substituted by Z, or~~

~~R^4 forms with R^5 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 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, with the proviso that R^5 is hydrogen when n is the number 1,~~

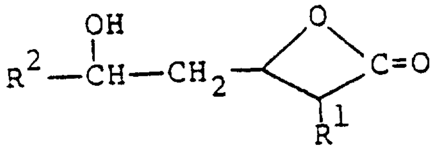
~~Ar is phenyl substituted by 0 to 3 groups R^9 or OR^9, and~~

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

~~with the proviso that R^4 has a significance other than~~

hydrogen when R^3 is formyl ~~and R^5~~ is isobutyl or R^3 is acetyl and R^5 ~~is~~ carbamoylmethyl and simultaneously R^2 is undecyl or 2,5-undecadienyl, and R^1 is n-hexyl, ~~and salts of these oxetanones with weak acids~~.

(2) Oxetanones of the formula



III

wherein

R^1 and R^2 are C_{1-17}-alkyl optionally interrupted by up to 8 double or triple bonds and optionally interrupted by a O or S atom which is present in a position other than the α-position to an unsaturated C atom; or phenyl, benzyl or -C_6H_4-O-C_6H_5 ring substituted by 0 to 3 C_{1-6}-alkyl-(O or S)$_1$ or $_0$, and

~~X is oxygen, sulphur or $(CH_2)_{0-3}$.~~

with the proviso that when R^1 is n-hexyl and R^2 is undecyl or 2Z,5Z-undecadienyl, ~~at least~~ one of the asymmetric C-atoms present in the oxetanone ring and in the β-position to the latter has the R-configuration.

(3.) Oxetanones according to claim 1 or 2, wherein R^1 is methyl, propyl, hexyl, decyl, hexadecyl, allyl, benzyl or ~~especially~~ ethyl; R^2 is methyl, undecyl, 3-butenyl, 3-undecenyl, 8,11-heptadecadienyl, phenoxyphenyl or ~~especially~~ heptadecyl; R^3 is acetyl or ~~especially~~ formyl; R^4 is methyl or ~~especially~~ hydrogen and R^5 is hydrogen, methyl, 2-butyl, benzyl, methylthioethyl or ~~especially~~ i-butyl, or R^4 and R^5

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together form a pyrrolidinyl residue.

~~4. N-Formyl-(S)-leucine (S)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]octadecyl ester.~~

a

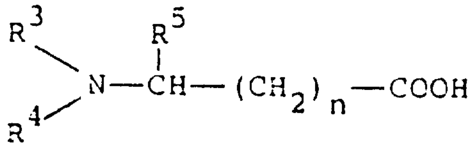
~~5. An oxetanone selected from the following group:~~

~~N-Formyl-L-leucine 1-[(trans-3-ethyl-4-oxo-2-oxetanyl)methyl]dodecyl ester,~~
~~N-formyl-L-leucine 1-[(trans-3-allyl-4-oxo-2-oxetanyl)methyl]dodecyl ester,~~
~~N-formyl-(S)-leucine (S,9Z,12Z)-1-[((2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-9,12-octadecadienyl ester,~~
~~N-formyl-(S)-leucine (S,Z)-1-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-9-octadecenyl ester and~~
~~N-formyl-(S)-leucine (R)-α-[[(2S,3S)-3-ethyl-4-oxo-2-oxetanyl]methyl]-p-phenoxybenzyl ester.~~

~~6. An oxetanone in accordance with any one of claims 1-5 for~~ use as a therapeutically active ~~substance.~~ particularly for inhibiting pancreas lipase.

7. A process for the manufacture of an oxetanone of formula I, which process comprises

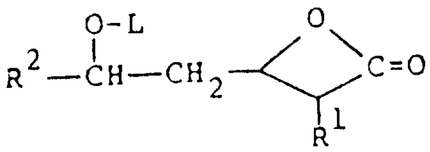
a) esterifying an acid of the formula



$$\begin{matrix}R^3 \\ & \searrow \\ & & N-\underset{|}{\overset{R^5}{}}CH-(CH_2)_n-COOH \\ & \nearrow \\ R^4\end{matrix}$$

II

formula III, which process comprises cleaving off the ether protecting group L in an ether of the formula



IV

wherein L, R^1 and R^2 have the above significance.

⑤9. A pharmaceutical composition containing a compound in accordance with claim 1 and a therapeutically inert carrier material."

ma~~terial~~.